Towards the Synthesis

of

Indole Alkaloids

A thesis submitted by Stephen Hilton in partial fulfilment

of the requirements for the degree of Doctor of Philosophy at

Kingston University.

June 2002

Declaration

The research described in this thesis, is to the best of my knowledge, original except where due reference is made to other authors and has not been submitted in any part at this or any other university.

This thesis is dedicated to

my grandparents, my parents, my wife Sophie

and our daughter Claire.

Acknowledgements

I would like to thank my supervisor Prof. Keith Jones for the opportunity to carry out this PhD. and for his friendship, enthusiasm, humour and help throughout. I would also like to thank my second supervisor Dr. John Storey for his friendship, help and encouragement.

Special thanks go to my wife Sophie and my parents for their help in proof reading this thesis. I would also like to thank everyone who worked in lab WB69 for making it such a fun and enjoyable working environment namely Dr. Sophie Hilton, Andrea Fiumana, Dr. Arfan Ashraf, Dr. Jean-Marie Peron, Emma McGrane, Dr. Carmen Escolano, Dr. Cristina Visintin, Mitesh Ladwa, Jackie Allen and Dr. Ed Gravett. I would also like to thank everyone who worked in lab 702 at King's College, London University at the start of my PhD especially Dr. Quyen Ong and Dr. Sharon Rossiter.

I would also like to thank the technicians at King's College, London University and at Kingston University for all their invaluable help. Special thanks go to Bert Bunby for all his glassblowing and friendship.

Abstract

Radical chemistry and, in particular, tandem radical chemistry has rarely been used in the synthesis of the *Strychnos* and *Aspidosperma* alkaloids. These two classes of compounds are structurally complex, possess a range of biological activity and present a synthetic challenge. Previous routes to these molecules are reviewed in the first section of this thesis. The utility of radical chemistry, tandem radical chemistry and 1,5-hydrogen atom abstraction towards the syntheses of complex molecules is outlined with examples that demonstrate the potential of radical chemistry.

A new synthetic approach towards the spiropyrrolidinyl oxindole alkaloids is presented, which utilises tandem radical chemistry. The radical sequence involves an initial 1,5-hydrogen atom abstraction, followed by a 5-*exo*-trig cyclisation onto the indole C-3 position. This is governed by the directing effect of a cyano group at the C-2 position of indole. The tricyclic core of the oxindole alkaloids can be readily obtained following an oxidative decyanation. In the course of these studies a novel product was observed during the cyclisation of the *N*-isopropyl precursor. Modification of the cyclisation precursor to incorporate the *N*-pentenyl group resulted in the formation of the tetracyclic core of the *Strychnos* and *Aspidosperma* alkaloids. This arose from a subsequent 6-*exo*-trig cyclisation after formation of the tricyclic core. Cyclisation of the *N*-pentynyl radical precursor led to the expected cyclised product along with an unexpected pentacyclic structure, which arose from an unprecedented further 1,5-hydrogen atom abstraction followed by a 4-*exo*-dig cyclisation.

The second approach involves the addition of alkyl radicals onto the indole C-3 position to generate the tricyclic core of the spiropyrrolidinyl oxindole alkaloids. This approach is directed towards a total synthesis of the oxindole alkaloids, horsfiline and coerulescine. However, this approach led instead to rearrangement before cyclisation followed by intramolecular transfer of the cyano group from the indole C-2 to C-3 position.

A novel approach to the formation of 3-substituted 2-cyanoindoles is also presented which negates the need for protection of the indole nitrogen allowing for a flexible approach to the tandem radical cyclisation precursors. The experimental conditions for the synthesis of all new compounds prepared during this work along with characterisation data are presented.

Contents

Abbreviations

^{13}C NMR = carbon 13 nuclear magnetic resonance

^{1}H NMR = hydrogen (proton) nuclear magnetic resonance

AIBN = azo-bis-isobutyronitrile

CBZ = benzyloxycarbonyl

CBZCl = Benzyl chloroformate

DCC = dicyclohexylcarbodiimide

DEAD = diethyl azodicarboxylate

DMAP = *N,N*-4-dimethylaminopyridine

EI = electron impact

ESI = ElectroSpray Ionisation

FAB = fast atom bombardment

KHMDS = Potassium bis(trimethylsilyl)amide

LiHMDS = Lithium bis(trimethylsilyl)amide

NADPH = nicotinamide adenine dinucleotide phosphate

NMP = *N*-methyl pyrrolidinone

nOe = nuclear Overhauser enhancement

R_f = retention factor = distance moved by product spot/ distance moved by solvent front

SEM = trimethylsilylethoxymethyl

*t*BOC = tertiary butoxycarbonyl

TLC = thin layer chromatography

TMSCl = Chlorotrimethylsilane

TPPT = triphenylphosphine thiocyanogen

TTF = Tetrathiafulvalene

Chapter 1

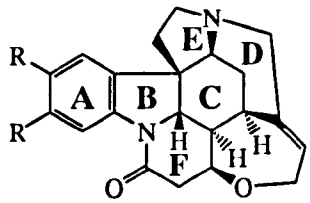
The *Strychnos* and *Aspidosperma* Alkaloids

1.1 Introduction

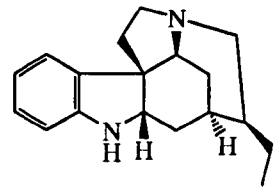
Of all the alkaloid classes found in nature, the monoterpenoid indole alkaloids are perhaps the best known and most widely found. They are derived from two precursors: tryptophan and a monoterpene unit. Two sub-groups are the *Strychnos* and *Aspidosperma* alkaloids, which contain a large number of molecules.

1.2 The *Strychnos* Alkaloids

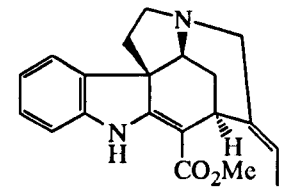
The *Strychnos* alkaloids are a structurally complex group of natural products, which possess powerful pharmacological and toxic properties.[1] They occur in plants of the *Apocynaceae* and *Loganiaceae* families, which are found throughout the southern hemisphere.[1] A common feature of the *Strychnos* alkaloids is a pentacyclic ring with an exocyclic functionality on ring D that in several cases is also unsaturated.



(1) Strychnine R = H
(2) Brucine R = OMe



(3) Tubifolidine



(4) Akuamicine

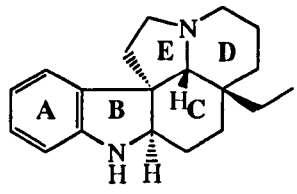
Figure 1

Perhaps the best-known member of this class of natural products is strychnine (**1**), which was first isolated in 1818.[2] Its notoriety stems principally from its extremely toxic properties and it can be found in the seeds of plants of the *Loganiaceae* family, in particular *Strychnos nux-vomica* and *Strychnos ignatii Bergius* where it can reach concentrations of between two and three percent by weight.[2] It acts as a CNS (central nervous system) stimulant with extreme toxicity; typically less than 50 mg is enough to kill an adult.[1] It functions by blocking postsynaptic inhibition in the spinal cord, which

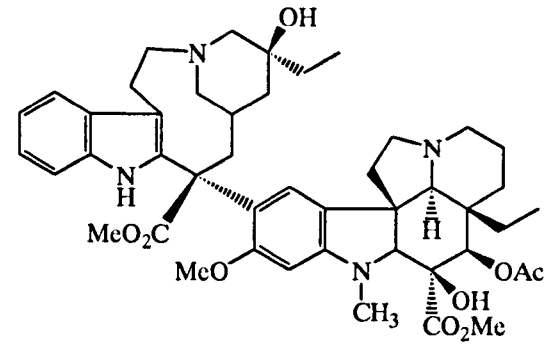
thereby removes the confining influences on nerve impulses resulting in enhanced outgoing activity leading to exaggerated reflexes.[1] As a result of this activity, strychnine has become a useful compound in experimental pharmacology.

1.3 The *Aspidosperma* Alkaloids

The *Aspidosperma* alkaloids possess a pentacyclic skeleton with the C and D rings joined in a different position to that of the *Strychnos* alkaloids. The absolute stereochemistry is also opposite to that of the *Strychnos* alkaloids. The *Aspidosperma* group forms the largest of the indole alkaloid groups and is composed of several sub-groupings.[2] The largest of these is that which contains compounds based on the aspidospermidine backbone. Aspidospermidine (**5**) is the main alkaloid of *Aspidosperma quebrachoblanco* and was the first of this group to be isolated. The *Aspidosperma* alkaloids are found in plants of the *Plumerioideae* family, a subgroup of the *Apocynaceae* family. The *Aspidosperma* alkaloids are of interest due to the use of the dimeric alkaloids vincristine and vinblastine (**6**) as chemotherapy for leukaemia.[1]



Aspidospermidine (**5**)

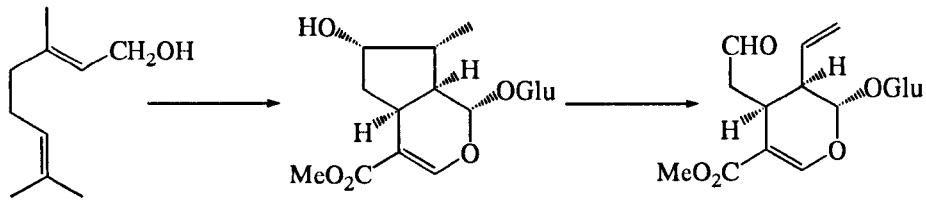


Vinblastine (**6**)

Figure 2

1.4 Biosynthesis of the Indole Alkaloids

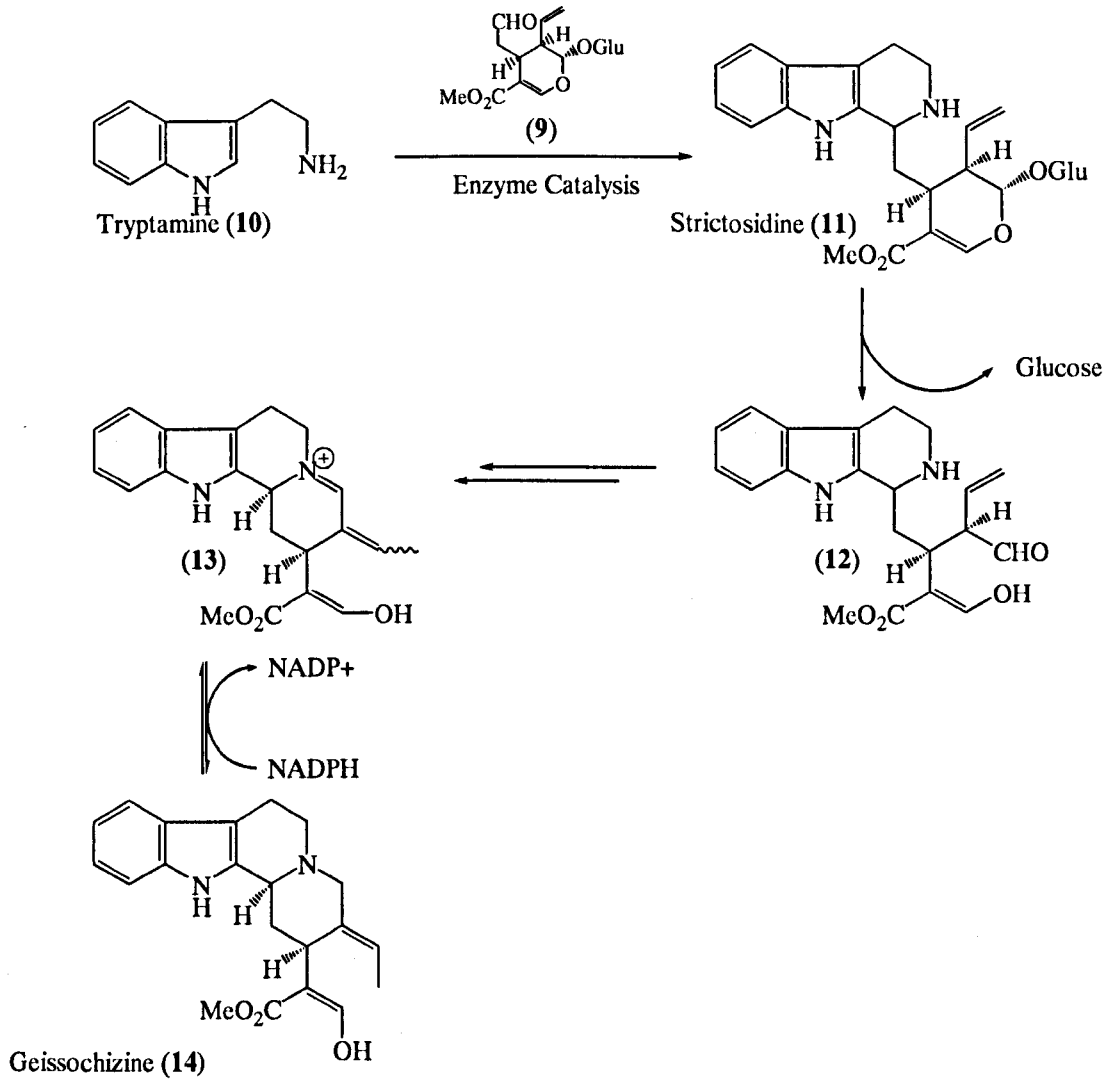
Both the *Strychnos* and *Aspidosperma* alkaloids are derived from the same origin. It was demonstrated that they are formed from a condensation between tryptamine and secologanin (**9**) that is itself derived from geraniol (**7**) *via* loganin (**8**) (scheme 1).[2] The large variation in alkaloid structure comes from this monoterpenoid fragment and in a few cases from the tryptamine fragment.[3,4]



Geraniol (**7**) Loganin (**8**) Secologanin (**9**)

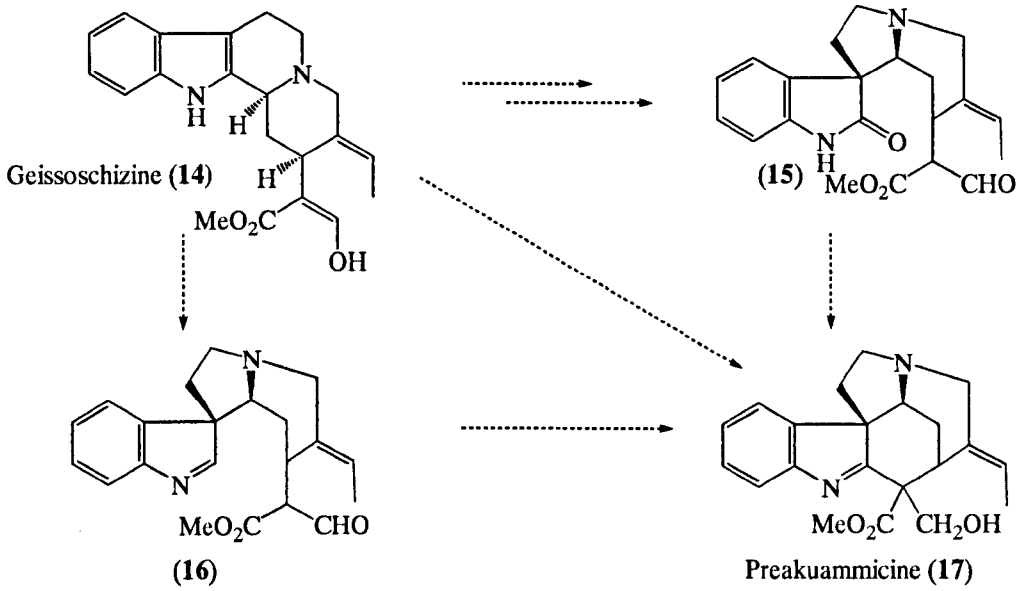
Scheme 1

Condensation of tryptamine (**10**) and secologanin (**9**) by an enzyme-catalysed Pictet-Spengler reaction, gives strictosidine (**11**). Loss of the glucose moiety gives the aldehyde (**12**), which then reacts with the secondary amine to give the iminium ion. This undergoes a rearrangement to an intermediate (**13**), which in the presence of NADPH is converted to geissochizine (**14**).[2]



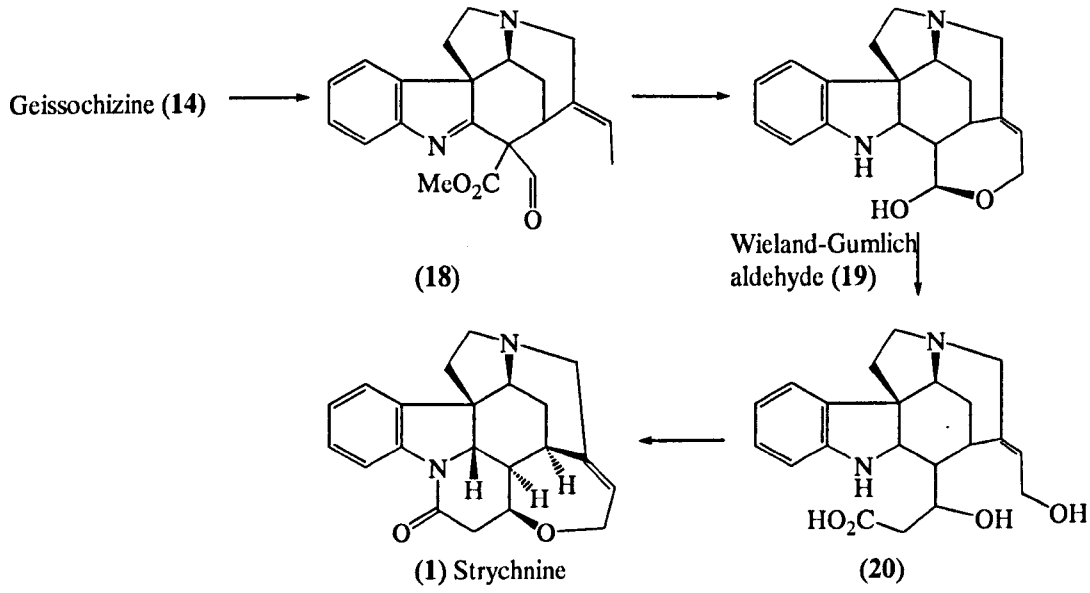
Scheme 2

The conversion of geissochizine (**14**) to the *Strychnos* skeleton has been suggested to proceed *via* a simple 1,2-rearrangement through (**16**) or *via* an oxindole intermediate (**15**) (scheme 3).[5,6] Recent synthetic work by Martin has also indicated a possible mechanistic route for this key interconversion, which will be discussed in detail later.[7] Rearrangement and functionalisation of preakuammicine (**17**) leads to the *Strychnos* alkaloids that are exemplified by akuamicine (**4**) (figure 1).



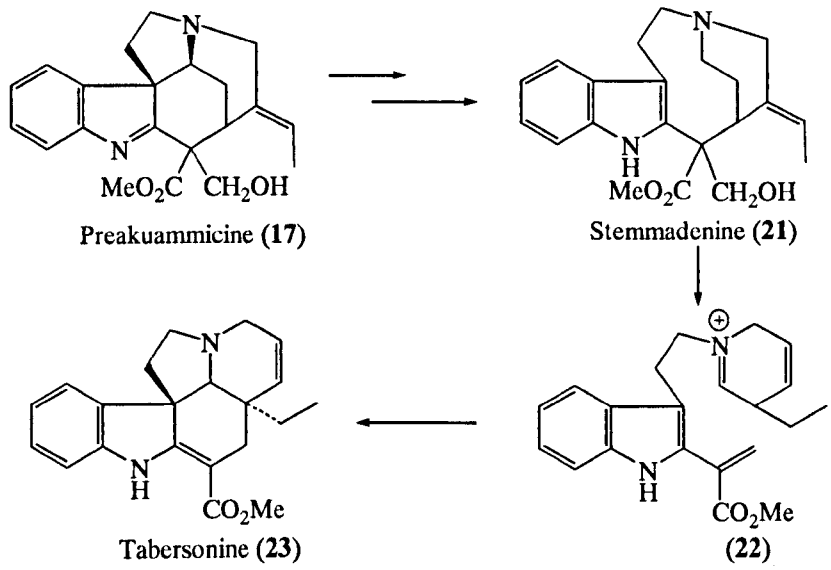
Scheme 3

Strychnine (**1**) has an additional C-2 unit, which is derived from acetate.[8] The biosynthetic pathway probably proceeds *via* the Wieland-Gumlich aldehyde (**19**) and the ring-opened intermediate (**20**) gives the final structure (**1**).[9]



Scheme 4

Preakuammicine (**17**) is also purported to be an intermediate involved in the biosynthesis of the *Aspidosperma* alkaloids.[2] Its rearrangement to the ring-opened stemmadenine (**21**) is followed by fragmentation to the ring-opened enamine (**22**), which then rearranges to tabersonine (**23**).[4] Kuehne has utilised this approach in his biomimetic synthesis of the *Aspidosperma* alkaloids.[10]



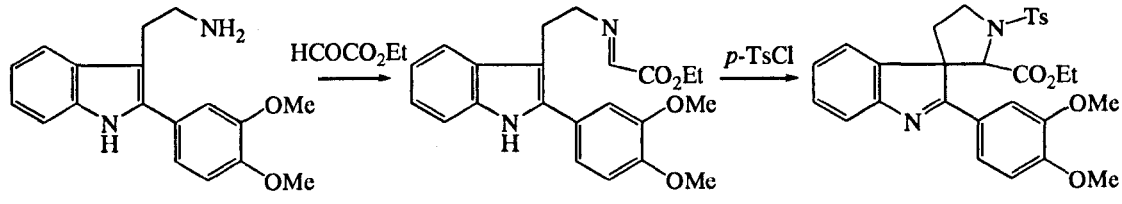
Scheme 5

1.5 Synthetic Approaches to Strychnine

Strychnine (**1**) has long fascinated organic chemists as a result of its structural complexity based on 24 skeletal atoms comprising seven rings and six contiguous chiral centres. As a result of these features and its pharmacological properties, strychnine was and remains a challenging synthetic target.

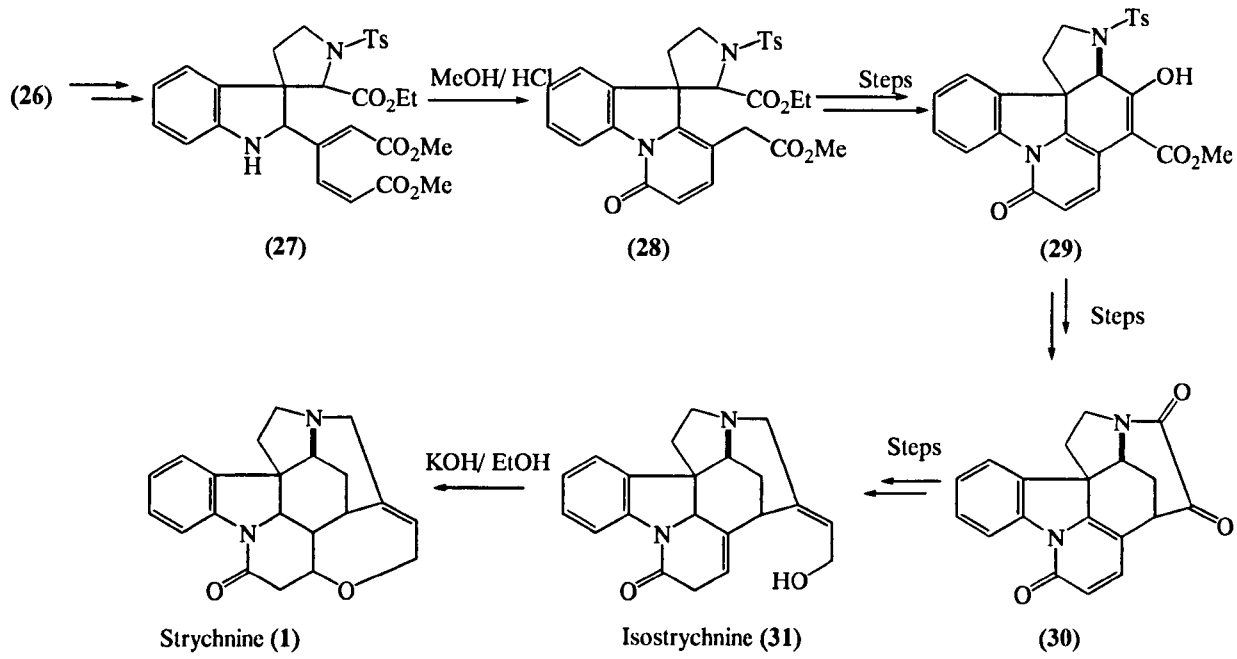
The first total synthesis of strychnine (**1**) by Woodward in 1954 represents an outstanding achievement in synthetic organic chemistry.[11,12] It was not until nearly forty years later, that other research groups finally achieved the total synthesis of strychnine (**1**). Since Woodward, several research groups have reported syntheses of racemic strychnine: Magnus, Stork, Kuehne, Rawal, Martin and Eichberg and Vollhardt. Overman, Kuehne and Bonjoch and Bosch have also achieved syntheses of single enantiomers of strychnine.

Woodward's approach in 1954 involved the use of three relay compounds to aid structural analysis and was completed in twenty-eight overall steps. He synthesised 2-veratryltryptamine (**24**) starting from 2-veratrylindole. Generation of the Schiff Base (**25**) and treatment with tosyl chloride enabled formation of the ABE ring containing indolenine (**26**) (scheme 6). The veratryl group had blocked reaction at the two position of indole and was then cleaved by ozonolysis to give the muconic ester (**27**), which enabled formation of ring F (**28**) (scheme 7). Construction of ring C *via* a Dieckmann condensation reaction gave the pentacyclic compound (**29**), which was then converted by subsequent synthetic steps to the relay compound (**30**). Conversion of the relay compound (**30**) to isostrychnine (**31**) and treatment of (**31**) with ethanolic potassium hydroxide gave strychnine (**1**) (scheme 7).



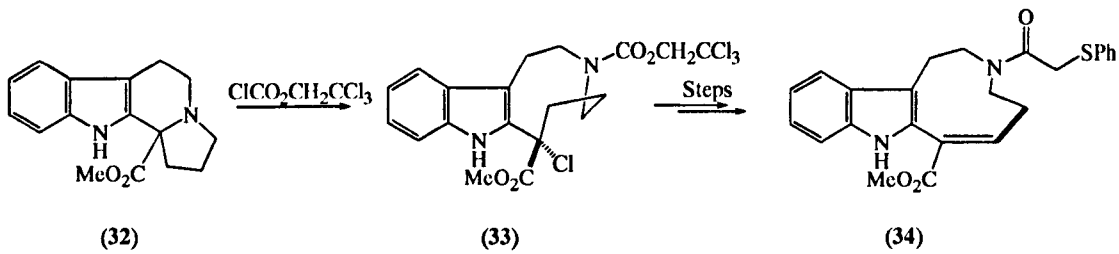
(**24**) (**25**) (**26**)

Scheme 6

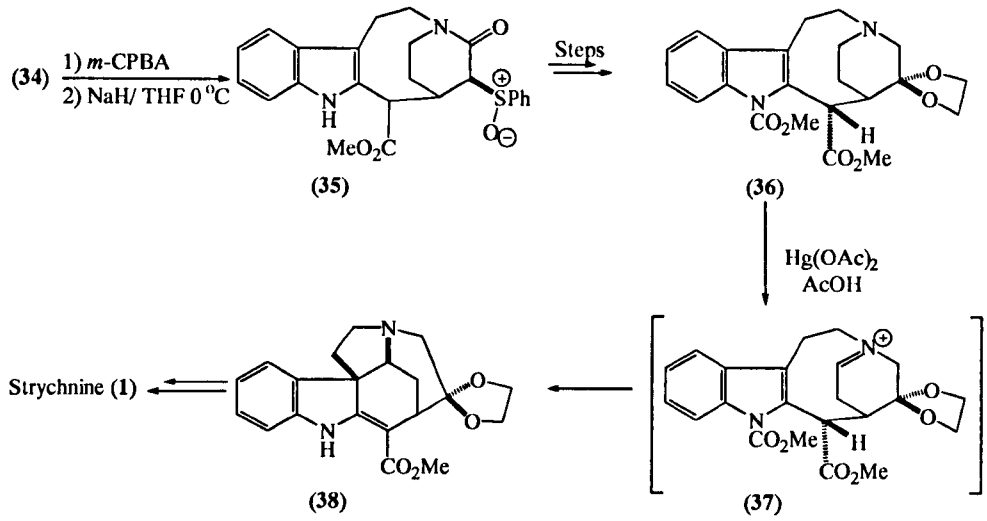


Scheme 7

In 1992, Magnus reported the first total synthesis of the Wieland-Gumlich aldehyde (**19**), which was used to synthesise strychnine (**1**) following a biomimetic approach.[13,14] Treatment of the tetracyclic amine (**32**) with β,β,β-trichloroethyl chloroformate gave the ring expanded tricyclic amine (**33**). This was then converted to the protected compound (**34**), which under basic conditions underwent conjugate addition to give the tetracyclic lactam (**35**). Conversion of this lactam (**35**) *via* a Pummerer-type reaction gave the protected ketone (**36**). The key step involved oxidation of (**36**) with mercuric acetate in acetic acid to enable a transannular cyclisation to give compound (**38**). Conversion of the pentacyclic (**38**) to the Wieland-Gumlich aldehyde (**19**) was followed by treatment with sodium acetate and acetic acid to give strychnine (**1**) in 27 overall steps (scheme 9).

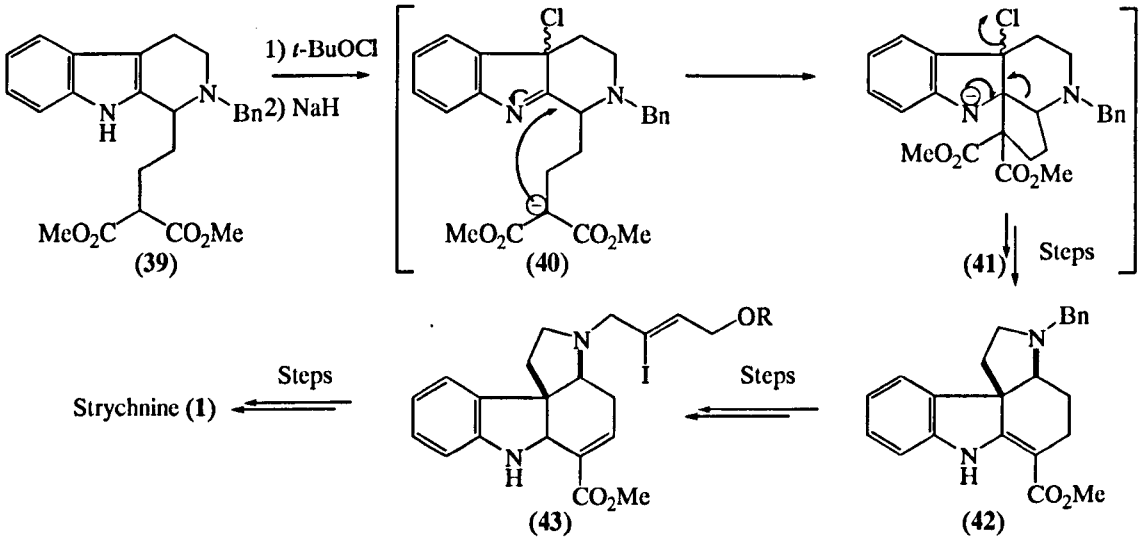


Scheme 8



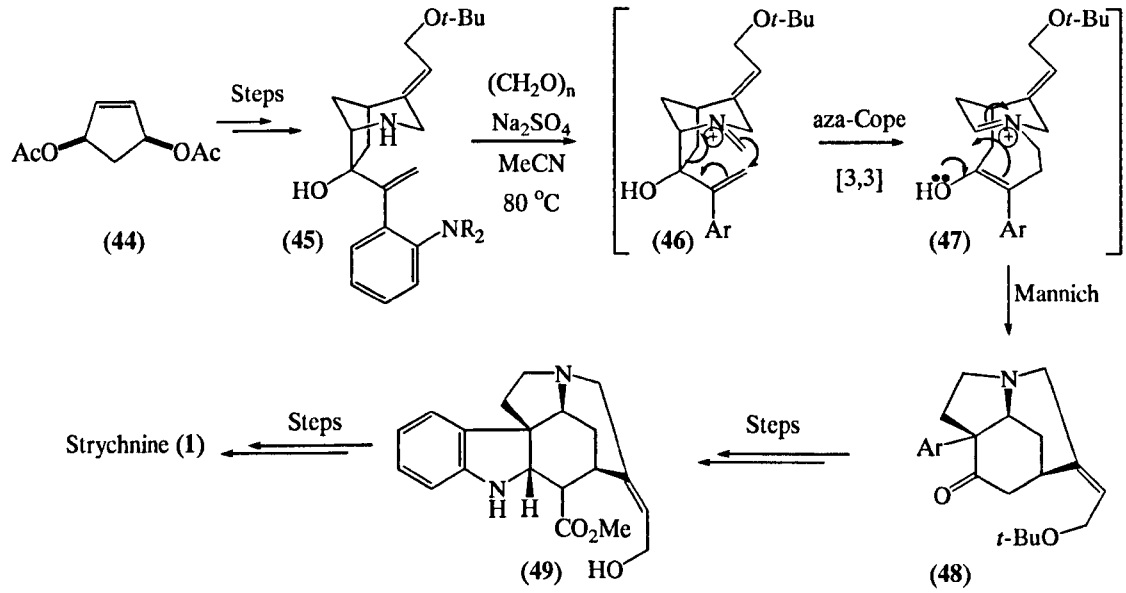
Scheme 9

Stork reported the third total synthesis of strychnine in 1992.[15] His approach started with the preparation of the diester (**39**) *via* a Pictet-Spengler condensation of *N*-benzyltryptamine with the appropriate aldehyde to give the tetrahydro-β-carboline (**39**). Treatment with *t*-BuOCl gave the chloroindolenine (**40**), which on reaction with sodium hydride gave the tetracycle (**42**) *via* skeletal rearrangement involving bond migration and elimination of chloride. Conversion to the vinylic iodide (**43**) enabled a *t*-BuLi mediated conjugate addition to the acrylate ester. Further elaboration of this resultant moiety to the Wieland-Gumlich aldehyde (**19**) enabled formation of strychnine (**1**) (scheme 10).



Scheme 10

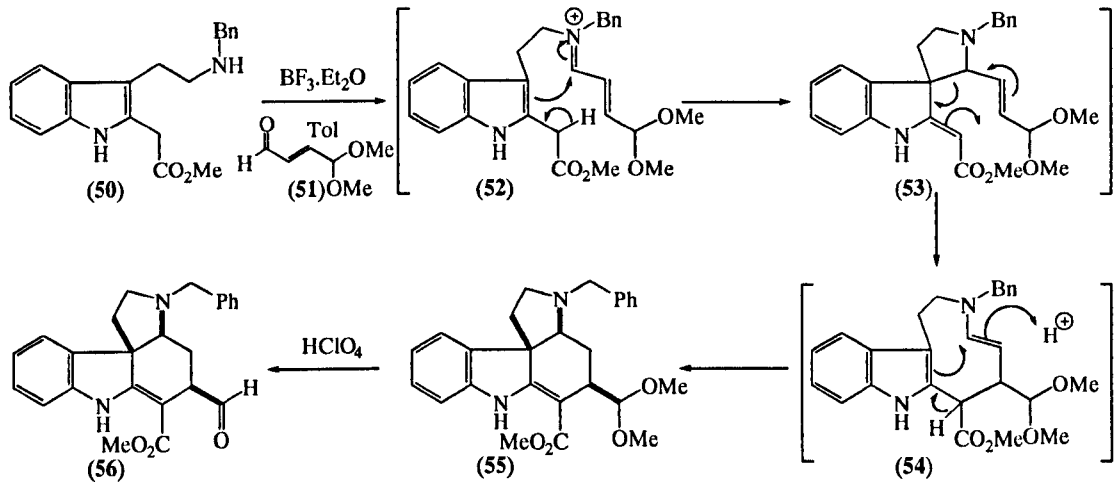
Overman's approach to strychnine (**1**) in 1993 was the first enantioselective total synthesis of (-)-strychnine.[16,17] Overman's route required the synthesis of the unsaturated azabicyclo[3.2.1]octane (**45**) as a single enantiomer which was obtained in 15 steps starting from the *meso* compound *cis*-1,4-diacetoxycyclopent-2-ene (**44**). *Meso*-desymmetrisation under enzymatic conditions furnished the mono-acetate in high enantiomeric purity. The key step in Overman's synthesis is the aza-Cope-Mannich rearrangement, which enables formation of the tetracyclic structure (**48**) (scheme11).



Scheme 11

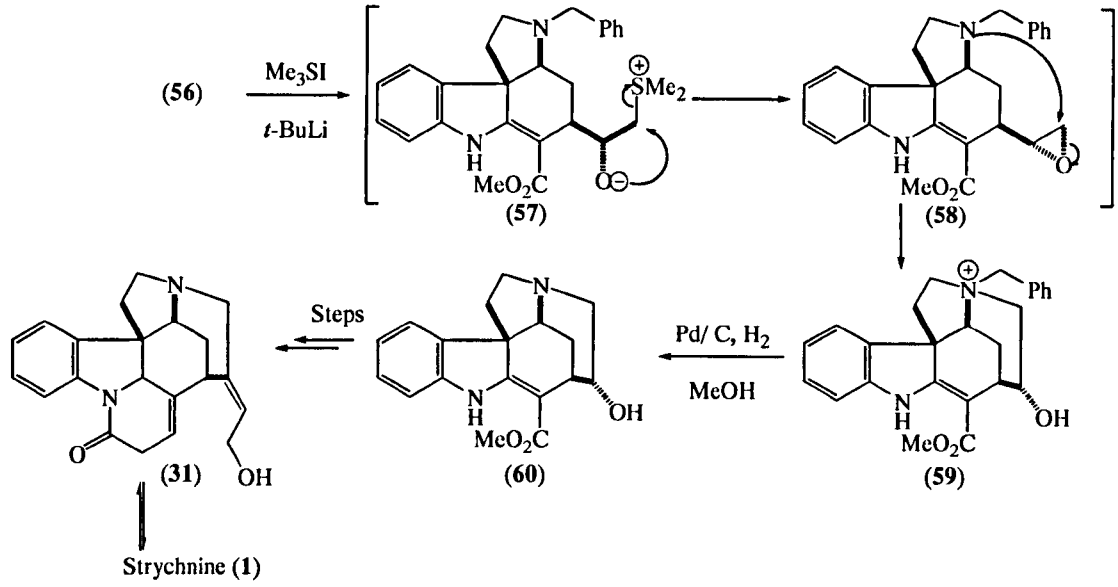
Overman's approach to the C-3 spirocyclic centre of strychnine (**1**) using the cationic tandem aza-Cope-Mannich reaction was based on earlier work in his previous synthesis of akuamicine (**4**).[18] Heating of (**45**) in acetonitrile with excess paraformaldehyde and anhydrous sodium sulfate led to the tetracyclic structure (**48**) in almost quantitative yield. Reaction of the secondary amine (**45**) with formaldehyde generated *in situ*, resulted in the formation of the iminium ion (**46**), which underwent a [3,3] sigmatropic rearrangement to give (**47**). The intermediate (**47**) underwent a Mannich reaction to give the tetracyclic compound (**48**). Transformation of this intermediate into the pentacyclic structure (**49**) was achieved in three steps by acylation with methyl cyanoformate and cleavage of the both the aryl amine and alcohol protecting groups followed by dehydration to give the pentacyclic structure (**49**) (scheme 11). Conversion of this to the Wieland-Gumlich aldehyde (**19**) enabled formation of enantiomerically pure strychnine (**1**).

Kuehne first published a racemic approach to strychnine (**1**) in 1993 based on the synthesis of the ABCE-tetracyclic core of strychnine (**1**) *via* a tandem sequence to form pyrrolocarbazole derivatives (scheme 12). His final step in the synthesis was based on the conversion of isostrychnine (**31**) to strychnine (**1**), but suffered from a poor equilibration between these two on treatment with potassium hydroxide in ethanol.[19] Kuehne's enantioselective second approach in 1998 was directed towards the Wieland-Gumlich aldehyde (**19**) to avoid this problem.[20]



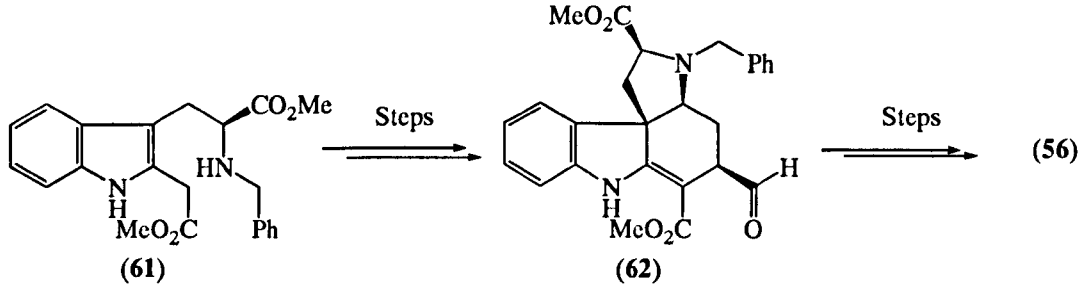
Scheme 12

Condensation of the *N*-benzyltryptamine derivative (**50**) with aldehyde (**51**) in the presence of boron trifluoride-etherate led to the tetracyclic acetal (**55**). Formation of the conjugated enamine (**52**) enabled a [3,3]-sigmatropic Cope rearrangement to take place to generate the ABCE-tetracyclic structure (**55**). Hydrolysis of the acetal with perchloric acid gave the aldehyde (**56**). Formation of ring D was achieved by generation of the epoxide *in situ* using trimethylsulfonium iodide/*n*-butyl lithium methodology. Thermodynamically-controlled opening of the epoxide in the presence of DBU gave the pentacyclic structure (**59**), which was further elaborated to isostrychnine (**31**) (scheme 13).



Scheme 13

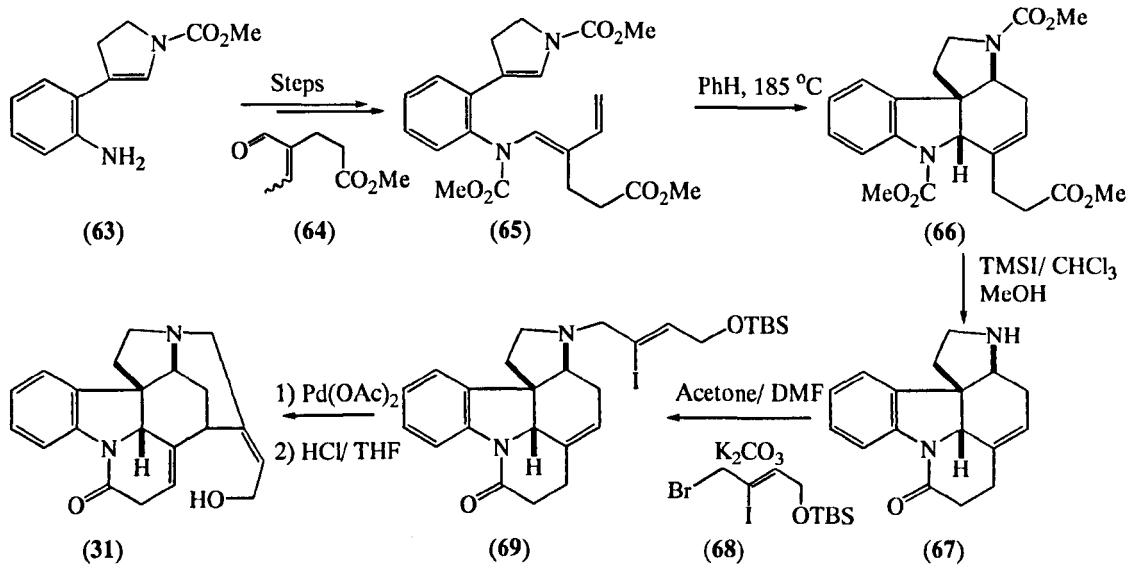
Kuehne's enantioselective approach followed a very similar route but utilised an enantioselective synthesis of the tetracyclic aldehyde (**56**). Utilisation of the inherent chirality in the L-tryptophan derivative (**61**) and removal of the ester after formation of the tetracycle (**62**) enabled enantioselective generation of the tetracyclic aldehyde (**56**) (scheme 14).[20]



Scheme 14

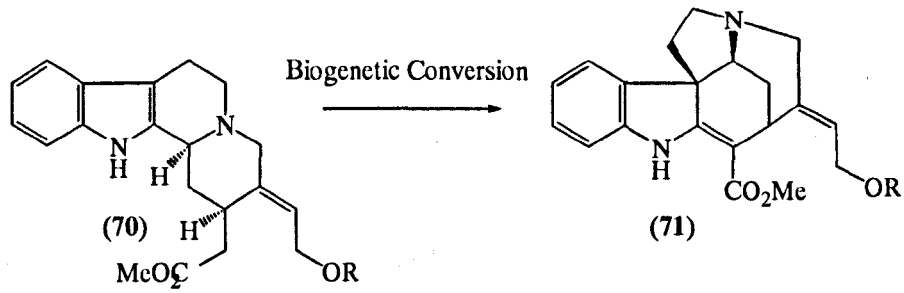
Rawal's approach was based on the synthesis of the key 3-anilinopyrroline (**63**) and its use in the formation of an intramolecular Diels-Alder cyclisation precursor (**65**) (scheme 15). The starting pyrroline was prepared in five steps from *o*-nitrophenylacetonitrile.[21,22,23,24] Intramolecular cycloaddition of the diene-carbamate (**65**) was achieved quantitatively and with complete stereocontrol following heating in benzene under sealed tube conditions. Cleavage of the protecting groups followed by intramolecular amide formation resulted in the generation of the pentacycle (**67**).

Alkylation of the pentacycle with allylic bromide (**68**) followed by an intramolecular Heck cyclisation resulted in isostrychnine (**31**). Interconversion of isostrychnine (**31**) and strychnine (**1**) was again hampered by the poor yield obtained by earlier groups (scheme 15).[19]



Scheme 15

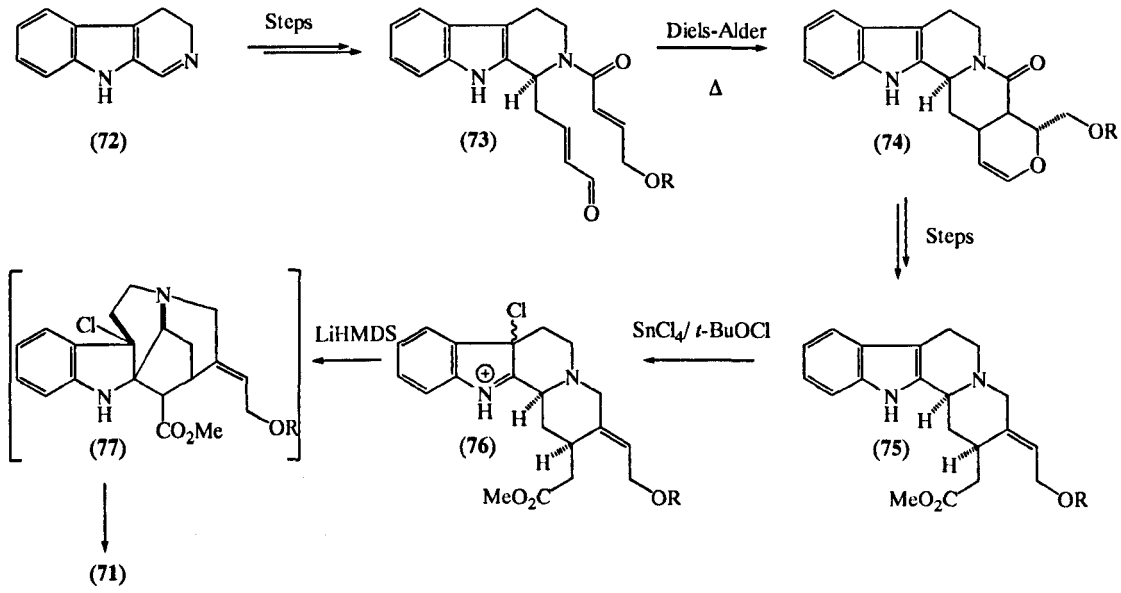
Martin's biomimetic approach to the *Strychnos* alkaloids in 1996 was based on a concise route to akuamicine (**4**) and strychnine (**1**).[7] The final product is an intermediate in Overman's synthesis.[16,17] His route was developed from the proposed biogenetic conversion of indole alkaloids containing the *Corynantheoid* skeleton such as (**70**) into the core structure of the *Strychnos* alkaloids (**71**) (scheme 16).



Scheme 16

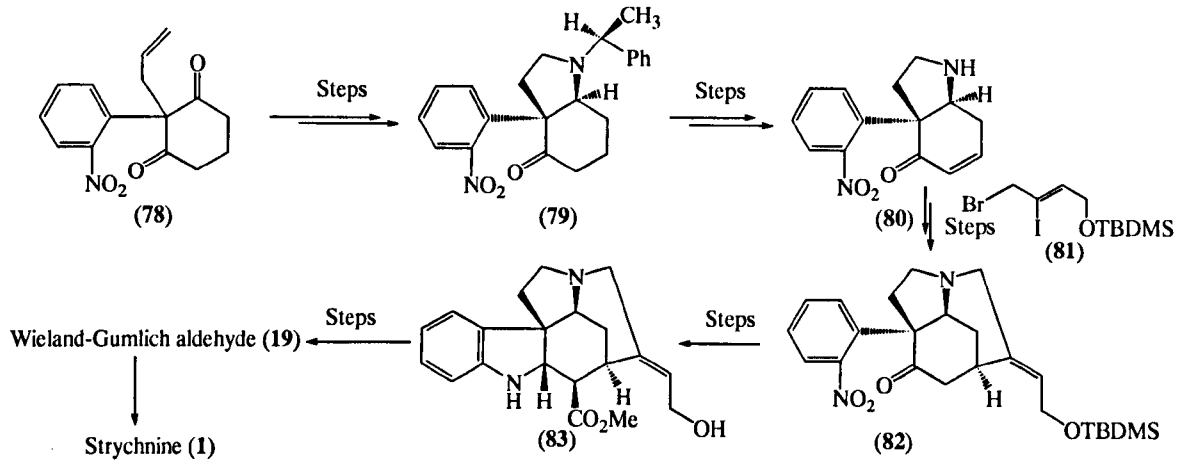
Martin's route started from dihydro-β-carboline (**72**), which was prepared using a Bischler-Napieralski reaction between tryptamine (**10**) and formic acid. Generation of

intermediate (**73**) followed by a hetero-Diels-Alder cyclisation gave the pentacyclic adduct (**74**).[7] Conversion to the *Corynantheoid* intermediate (**75**) was achieved in seven steps to give the biomimetic precursor, similar to Stork's version.[15] Treatment of (**75**) with *t*-butylhypochlorite in the presence of tin tetrachloride resulted in a mixture of epimeric chloroindolenines (**76**), which afforded the pentacyclic intermediate (**77**) on treatment with lithium hexamethyldisilazide. This then rearranged to give (**71**), which had previously been converted into strychnine (**1**) by Overman in four steps.[16,17]



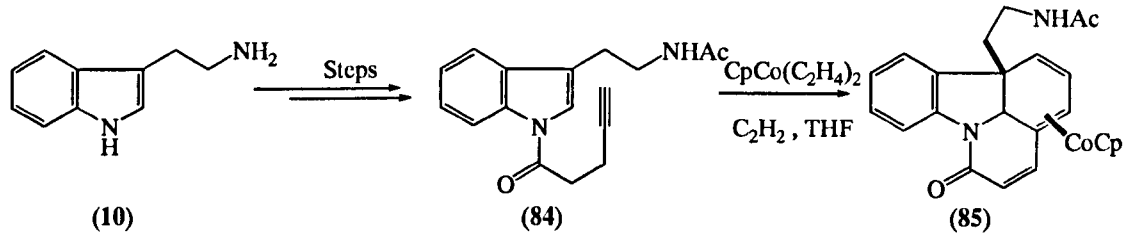
Scheme 17

Bosch and Bonjoch's enantioselective approach to the *Strychnos* alkaloids is derived from the formation of the C-3 spirocyclic centre early in the synthesis. The CD- and E-rings are generated before formation of ring B.[25,26] The starting prochiral dione (**78**) was readily obtained from 1,3-cyclohexanedione *via* direct arylation, *O*-allylation and an intramolecular Claisen rearrangement. Chirality was introduced *via* a double reductive amination with α-(*S*)-methylbenzylamine to give the pyrrolidine ring (**79**). Removal of the methylbenzyl group along with the introduction of the double bond generated the conjugated ketone (**80**). Alkylation with the allylic bromide (**81**) as used by several previous groups was followed by an intramolecular Heck reaction, which gave stereoselective incorporation of the exocyclic *E*-double bond to give the tricyclic core structure (**82**). Methoxycarbonylation followed by reductive cyclisation generated the pentacyclic structure (**83**). This was then converted to the Wieland-Gumlich aldehyde (**19**) and hence to strychnine (**1**) (scheme 18).



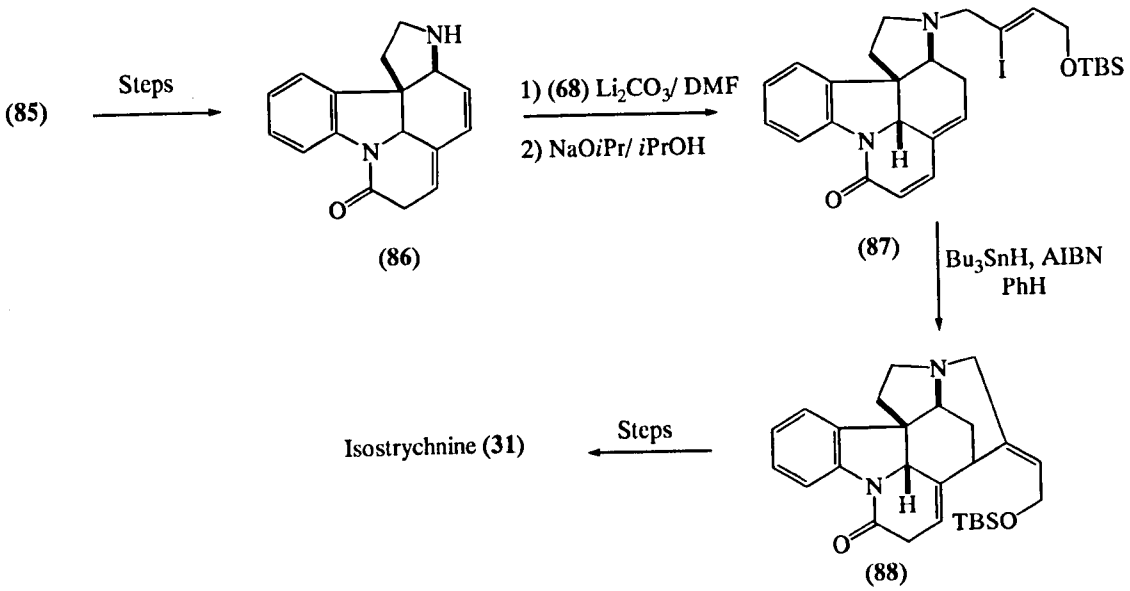
Scheme 18

The recent synthesis by Vollhardt and Eichberg in 2000 was based on the formation of the core ABC ring structure of strychnine *via* a cobalt mediated [2+2+2] cycloaddition reaction.[27] This synthesis also involves the isostrychnine-strychnine interconversion as carried out by previous groups and as such is low yielding in the final step. Conversion of tryptamine (**10**) to the cobalt cyclisation precursor indole acetylene (**84**) enabled cyclisation to be carried out in the presence of acetylene and $CpCo(C_2H_4)_2$. The tetracyclic product (**85**) was obtained as a single diastereoisomer (scheme 19).



Scheme 19

Deprotection of the exocyclic nitrogen in the organometallic intermediate with potassium hydroxide in methanol-water followed by oxidative demetalation with iron (III) afforded the pentacycle (**86**). The exocyclic amine added in a [1,8]-conjugate addition to the unsaturated lactam. Alkylation of the pyrrolidine nitrogen with the allylic bromide (**68**) used by Rawal followed by radical cyclisation gave the hexacyclic structure (**88**). The hexacycle (**88**) was then converted to isostrychnine (**31**) and then to strychnine (**1**) (scheme 20).

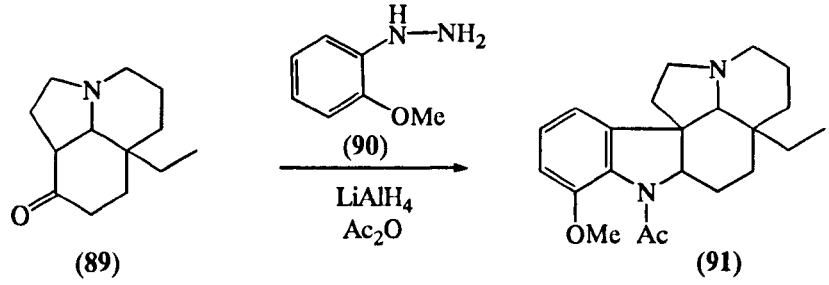

(85)
Steps
NH
N
O
(86)
1) (68) Li_2CO_3/ DMF
2) NaO*i*Pr/ *i*PrOH
N
I
OTBS
N
H
O
(87)
Bu_3SnH, AIBN
PhH
N
N
H
O
TBSO
(88)
Steps
Isostrychnine (31)

Scheme 20

1.6 Synthetic Approaches Towards Aspidospermidine

Aspidospermidine (**5**) (figure 2), the core parent structure of the *Aspidosperma* alkaloids, along with others of its class, has attracted a large amount of research effort. The interest in these compounds is a result of the pharmacological activity of the bisindole alkaloids. Although aspidospermidine (**5**) itself is not biologically active, the lack of functionality means that it has become an attractive synthetic target in the development of novel routes towards these classes of compounds.

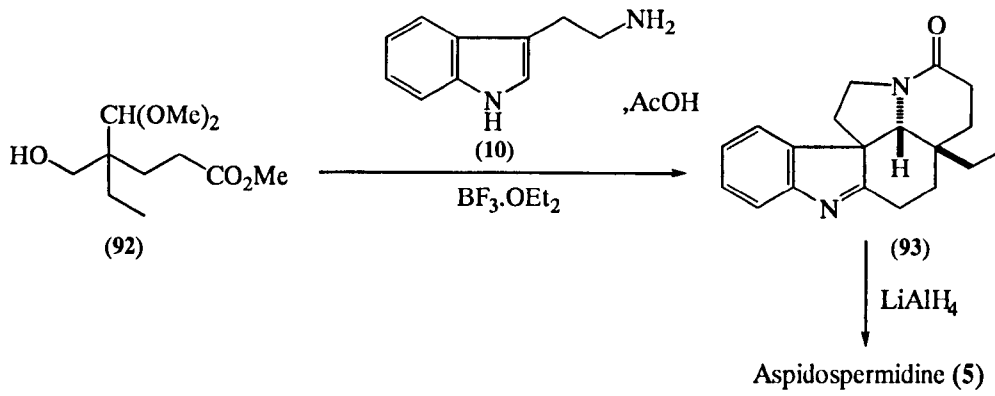
Stork and Dolfini first carried out the initial synthetic approaches to this class of alkaloids, in 1963,[28] three years after the publication of its X-ray crystal structure. Aspidospermine (**91**) possesses the same skeletal structure as aspidospermidine (**5**), but contains a 7-methoxy substituent on the indole ring and an acetate group on the indole nitrogen. Stork and Dolfini's synthesis relied on a key Fisher indole cyclisation to generate aspidospermine (**91**). Formation and reaction of the key tricyclic keto-amine (**89**) with *o*-methoxyphenyl-hydrazine (**90**), followed by reduction of the imine intermediate and acetylation gave aspidospermine (**91**) (scheme 21).[28] The synthetic usefulness of this approach is demonstrated by the fact that other groups such as Ban,[29] Kuehne,[30] Stevens[31,32] and Meyers[33] have applied this approach in their syntheses of aspidospermidine (**5**). More recently, Aubè has used the same methodology in his enantioselective total synthesis of (+)-aspidospermidine (**5**).[34]



Scheme 21

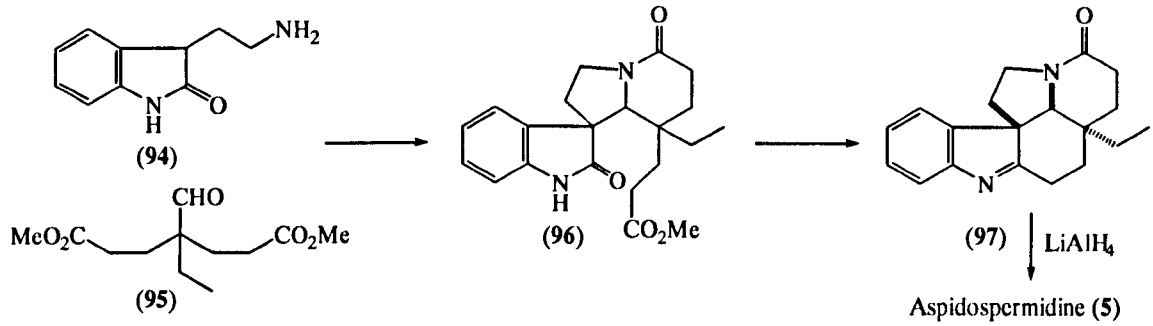
Harley-Mason's short synthesis of aspidospermidine (**5**) concentrated on the reaction of tryptamine (**10**) with the readily prepared hydroxy ester (**92**) to form the indole-lactam (**93**) after treatment with sulphuric acid or boron trifluoride etherate.[35] Reduction with lithium aluminium hydride furnished aspidospermidine (**5**) in 20-25% overall yield

based on tryptamine (**10**) (scheme 22). Fuji has also applied Harley-Mason's methodology to synthesise (-)-aspidospermidine (**5**).[36,37,38] Schultz has also used similar methodology to Fuji in his synthesis of (-)-aspidospermidine (**5**).[39]



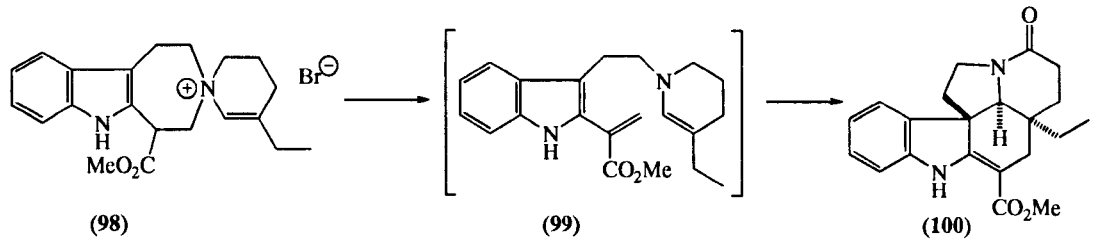
Scheme 22

Spiropyrrolidinyl-oxindole intermediates have been used by Ban[40] in the syntheses of the aspidospermine skeleton and by Le Men in the synthesis of aspidospermidine (**5**).[41] Generation of the spiro-intermediate (**96**) *via* a Mannich reaction with 2-hydroxytryptamine (**94**) and aldehyde (**95**) followed by treatment with polyphosphoric acid generated the pentacyclic compound (**97**). Reduction of this compound generated aspidospermidine (**5**) (scheme 23).



Scheme 23

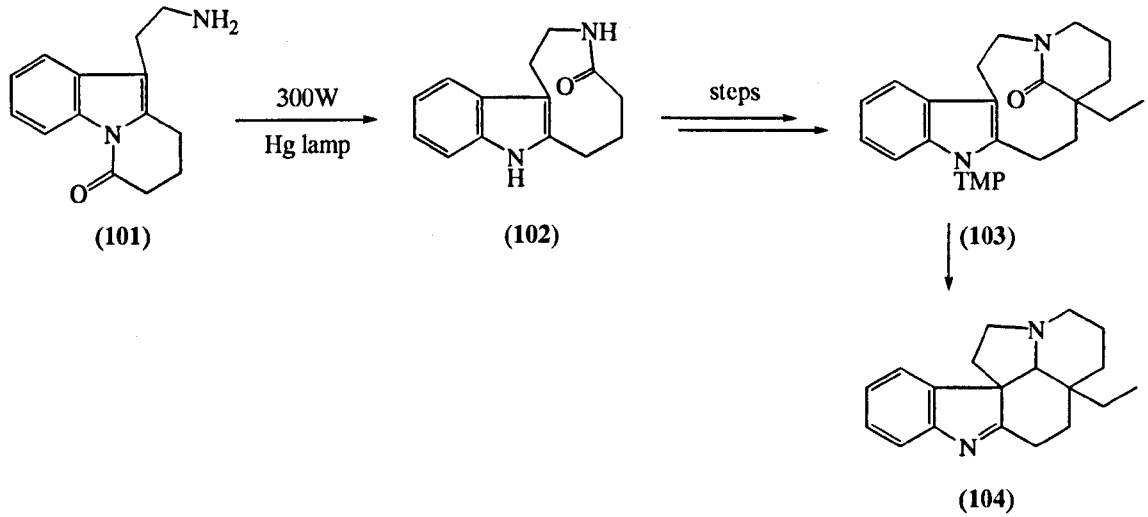
Kuehne's biomimetic approach to the *Aspidosperma* alkaloids is based on the purported biosynthetic link between preakuammicine (**17**) and its conversion to stemmadenine (**21**).[42] Generation of the spiroammonium salt (**98**) followed by fragmentation to the secodine intermediate (**99**) led to vincadiformine (**100**) in yields of up to 70% (scheme 24).



(98) (99) (100)

Scheme 24

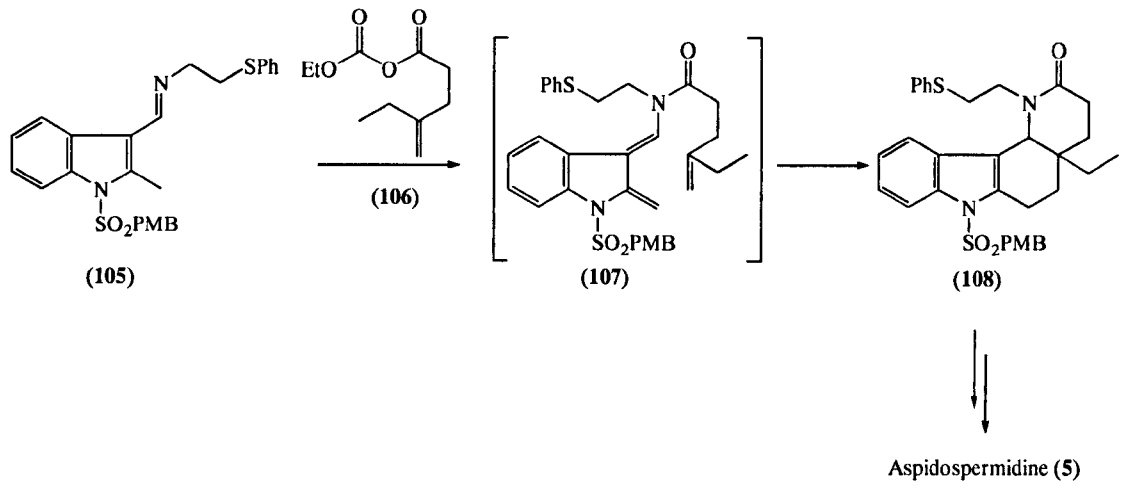
Following his initial approach to the *Aspidosperma* alkaloids, Ban also applied photoisomerisation in his synthesis of the *Aspidosperma* alkaloids.[43,44] Generation of the amine (**101**) followed by treatment with a 300W high-pressure mercury lamp furnished the ring expanded nine-membered lactam in 80% yield. Conversion to the lactam (**103**) followed by reduction and treatment with acid gave rise to dehydroaspidospermidine (**104**) (scheme 25).



(101) (102) (103) (104)

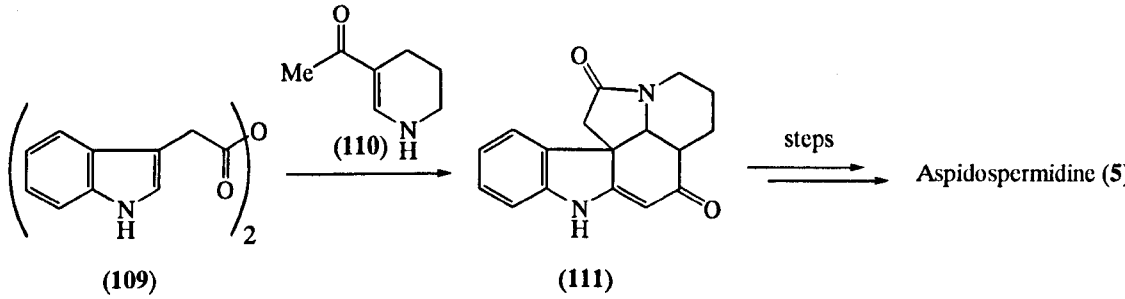
Scheme 25

Magnus' novel approach to aspidospermidine (**5**) was based on the Diels-Alder reaction of an indole-2,3-quinodimethane intermediate (**107**) to give the tetracyclic core of aspidospermidine.[45,46,47] Condensation of 3-formyl-2-methylindole with 2-(phenylthio)ethylamine generated imine (**105**), which on reaction with the mixed anhydride (**106**) gave the tetracyclic compound (**108**) presumably *via* the indole-2,3-quinodimethane intermediate (**107**). Oxidation of (**108**) to the sulfoxide followed an intramolecular Pummerer reaction and reduction of the amidic carbonyl generated aspidospermidine (**5**) in 12% overall yield (scheme 26).



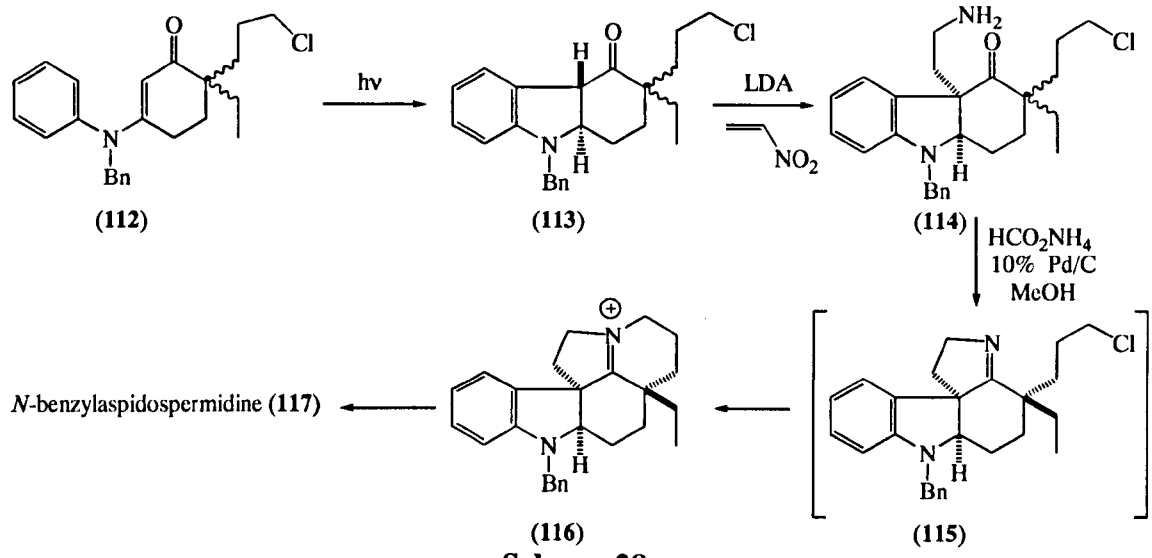
Scheme 26

Wenkert disclosed a very short synthesis of aspidospermidine (**5**) in 1991 based on the reaction of indoleacetic anhydride (**109**) and 3-acetyl-1,4,5,6-tetrahydropyridine (**110**) to give the pentacyclic lactam (**111**).[48,49,50,51,52] Alkylation of the protected lactam followed by reduction of the two carbonyl groups and hydrogenation generated aspidospermidine in four steps following generation of pentacycle (**111**) (scheme 27).



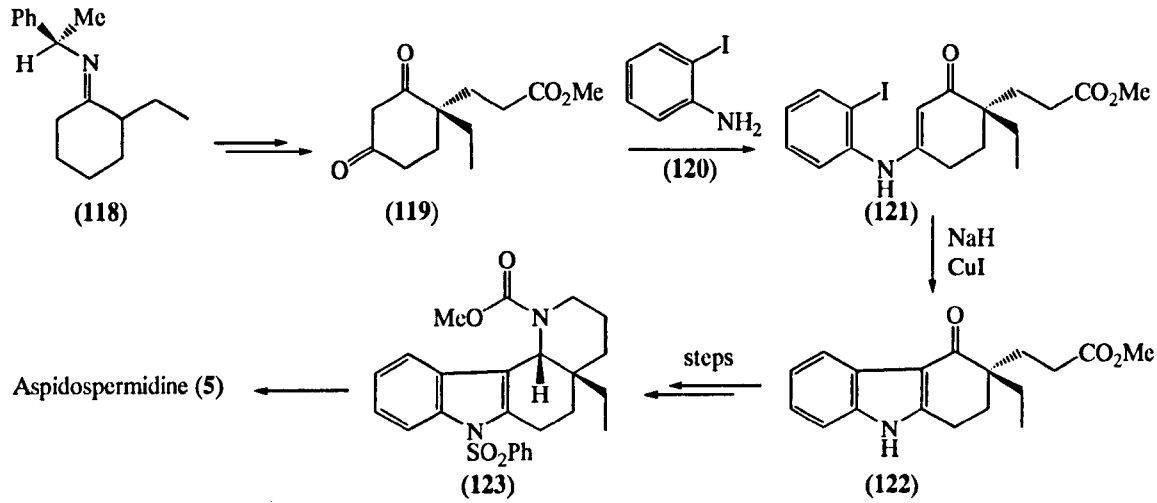
Scheme 27

The approach used by Dugat in the synthesis of *N*-benzyl aspidospermidine (**117**) was based on a photocyclisation to give ring B, followed by consecutive cyclisations to give rings D and E of aspidospermidine.[53,54] The enamine (**112**) was prepared in three steps from *N*-benzylaniline and treatment with a 400W medium pressure mercury lamp in a non-oxidative photocyclisation generated the hexahydrocarbazolone (**113**). Generation of the C-3 quaternary centre was achieved *via* a Michael reaction with nitroethylene to give a 1:1 mixture of isomers. Reductive cyclisation generated the iminium chloride (**115**), which was then reduced *via* catalytic hydrogenation to give *N*-benzylaspidospermidine (**117**) (scheme 28).



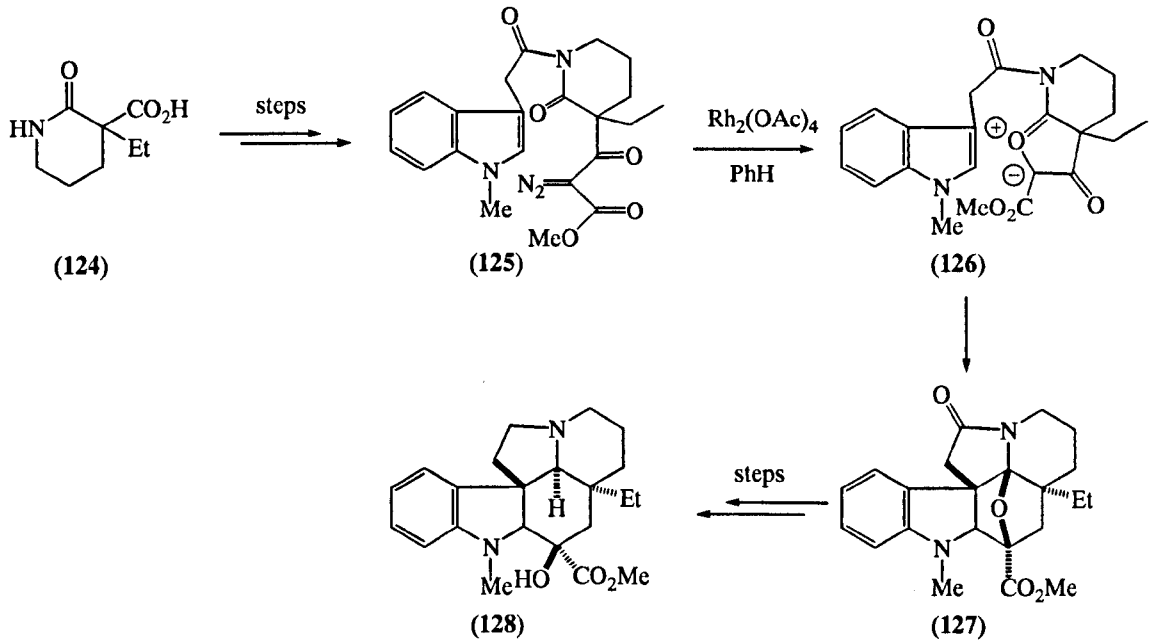
Scheme 28

D'Angelo's enantioselective synthesis of (+)-aspidospermidine (**5**) is similar to Dugat's in that a cyclisation step is used to construct ring B.[55] D'Angelo's approach was to synthesise the enantiomerically pure dione (**119**) from imine (**118**) utilising an enantioselective Michael addition with methyl acrylate. Condensation of the dione (**119**) with 2-iodoaniline (**120**) followed by cyclisation of the enaminone (**121**) generated the carbazolone (**122**). Reduction of the ester to the alcohol was followed by conversion to the azide, which led to the tetracyclic compound (**123**) (scheme 29). The construction of ring E followed Magnus' Pummerer rearrangement strategy (Scheme 26).[46,47] Rodriguez has also applied D'Angelo's approach in his synthesis of the *Aspidosperma* alkaloids.[56,57]



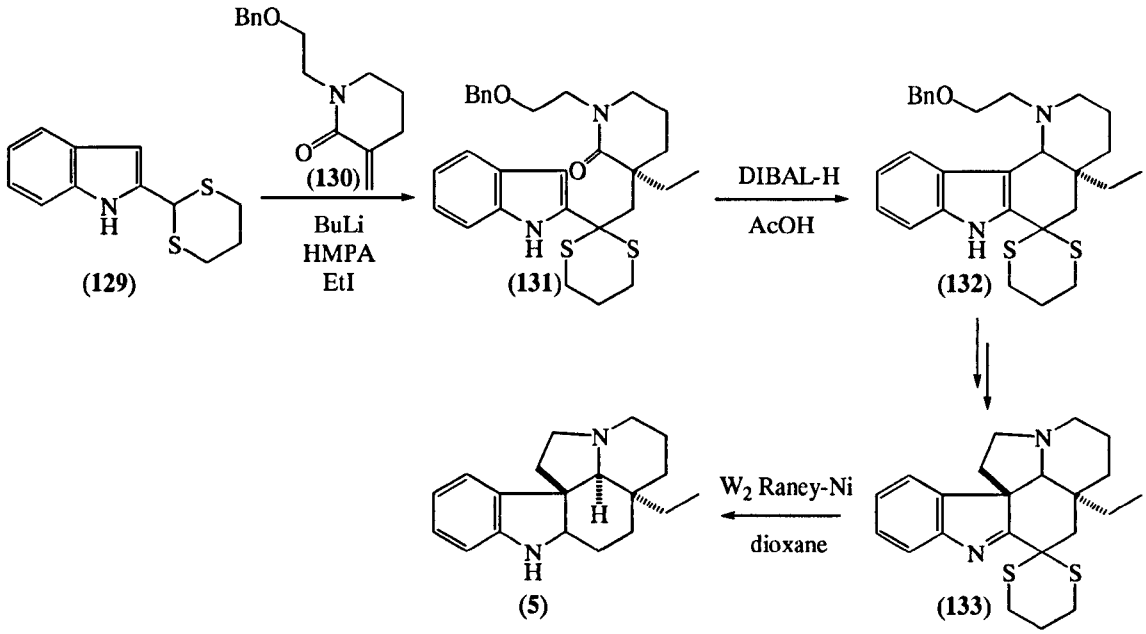
Scheme 29

Padwa's use of rhodium carbenoids in a tandem cyclisation-cycloaddition approach to the *Aspidosperma* alkaloids is another rapid way of generating highly functionalised alkaloids in a short number of steps.[58] Treatment of the diazo imide (**125**), prepared from 3-carboxy-3-ethyl-2-piperidone (**124**), with rhodium acetate in benzene, generated the cycloadduct (**127**) as a single diastereoisomer. His use of the 1,3-dipolar cycloaddition reaction enabled the construction of five chiral centres in one step. The cycloadduct was then converted to the core structure of the *Aspidosperma* alkaloids (**128**) in three steps (scheme 30).



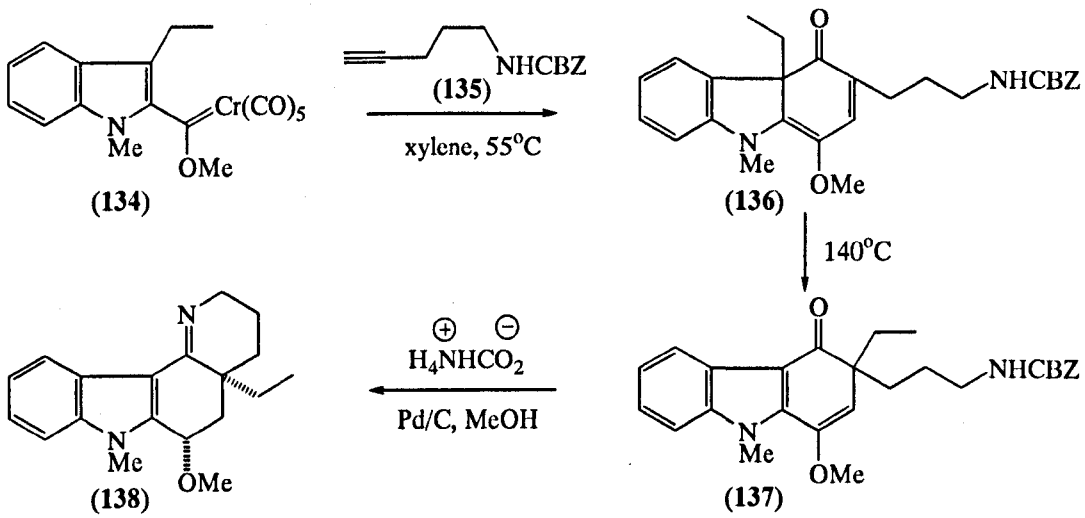
Scheme 30

Rubiralta constructed the ABCD-ring structure of aspidospermidine (**5**) in three steps from indolyldithiane (**129**).[59] Treatment with base followed by a tandem Michael addition-alkylation reaction generated the lactam (**131**). Reduction of lactam (**131**) with DIBAL-H followed by treatment with acetic acid generated the tetracycle (**132**). Deprotection of the alcohol followed by tosylation and elimination resulted in the construction of ring E to give the pentacycle (**133**). Reduction of the pentacycle (**133**) yielded aspidospermidine (**5**) (scheme 31).



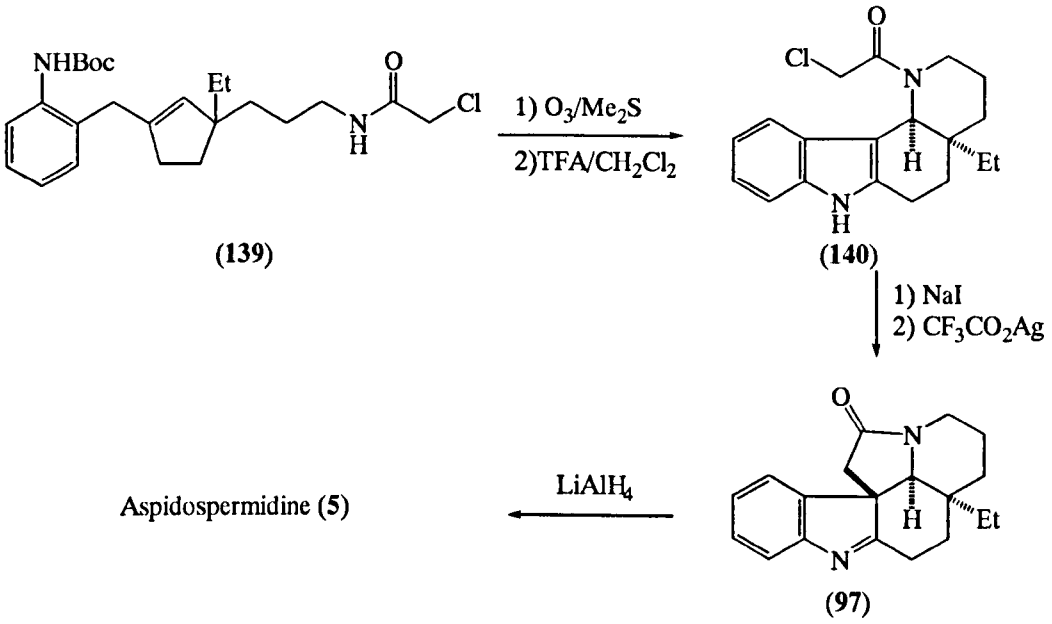
Scheme 31

Wulff has employed a novel approach to the synthesis of aspidospermidine in his use of the chromium carbene (**134**) and a [1,5] sigmatropic rearrangement.[60] Generation of the 1,3-disubstituted-indol-2-yl carbene complex (**134**), followed by cyclohexadienone annulation with alkyne (**135**) yielded the carbazol-4-one (**136**). Heating of the carbazol-4-one at 140°C effected a [1,5] sigmatropic shift of the ethyl group. Cleavage of the protecting group and a reductive amination resulted in the ABCD-core structure (**138**) of the *Aspidosperma* alkaloids (scheme 32).



Scheme 32

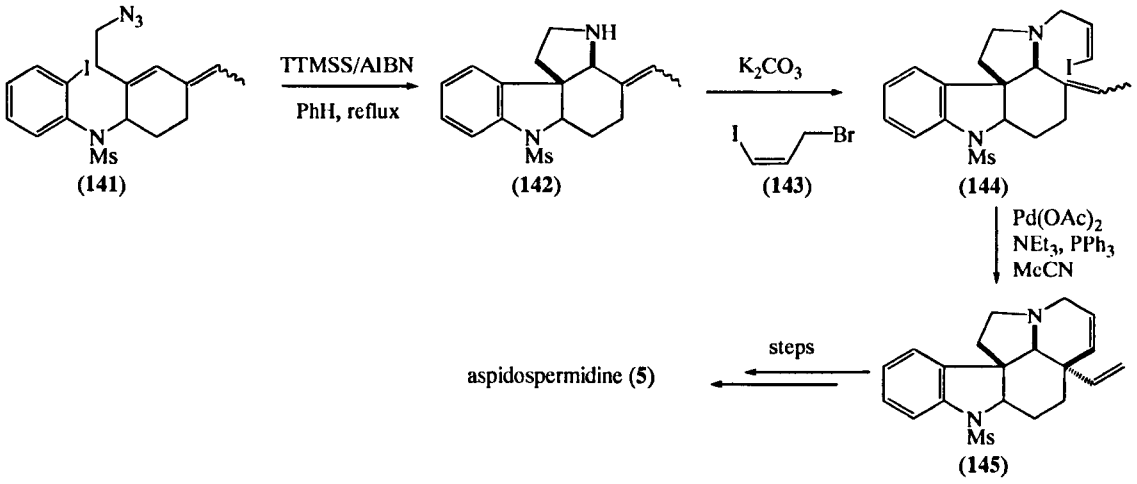
Heathcock's approach to aspidospermidine (**5**) was based on an intramolecular cascade reaction, which resulted in the formation of the B, C and D rings of aspidospermidine (**5**).[61] Formation of the cyclopentene amide (**139**) followed by ozonolysis and treatment with TFA yielded the tetracyclic amide (**140**). Treatment of the chloride (**140**) with sodium iodide in a Finkelstein reaction followed by reaction with silver trifluoroacetate generated the E-ring of aspidospermidine (**5**). Reduction of the amidic carbonyl and the indolenine yielded aspidospermidine (**5**) (scheme 33).



(**139**) (**140**) (**97**)

Scheme 33

A recent tandem radical approach to aspidospermidine (**5**) has been developed by Murphy.[62,63,64,65,66] His use of the tetrathiafulvalene-mediated radical-polar crossover reaction enabled the synthesis of the B and E rings of aspidospermidine in one reaction. Formation of the cyclisation precursor (**141**) followed by treatment with tetrathiafulvalene and AIBN in benzene at reflux generated the tetracycle (**142**). Alkylation with (*Z*)-3-bromo-1-iodopropene (**143**) generated the vinyl iodide (**144**). Ring closure of the *Z*-iodoalkene generated the pentacyclic structure (**145**). Hydrogenation followed by cleavage of the mesyl protecting group yielded aspidospermidine (**5**) (scheme 34).



Scheme 34

There have been a variety of synthetic methods used in the synthesis of the *Aspidosperma* and *Strychnos* alkaloids. However, only a small number of these syntheses have incorporated radical chemistry in the construction of these polycyclic systems. An increasing number of research groups have incorporated tandem processes in their syntheses and the synthetic potential of these can clearly be observed. Murphy's tandem radical process elegantly demonstrates the potential of a combination of both tandem and radical synthetic methodology and this is discussed in detail in the next chapter.

Chapter 2

Radical Chemistry

2.1 Introduction

Gomberg first proposed the initial evidence for the existence of radical containing species in 1900 when investigating the reaction of triphenylmethyl bromide with silver.[67,68] He postulated that the highly reactive white solid, which in solution turned yellow, was due to the triphenylmethyl radical, which existed in equilibrium with the solid hexaphenylethane. However, it took mechanistic work by Waters and Hey[69] in 1937 and Karasch[70] to show that radicals were indeed intermediates in chemical reactions. Since then, the potential uses of radicals in synthesis have grown from polymer production in the 1940's and 1950's through to the 1970's and beyond where more radical reactions have been developed and have become important synthetic tools in the synthesis of complex natural products.[71]

2.1.1 Radicals

Radicals are generally highly reactive species which contain at least one unpaired electron and unlike their other reactive counterparts; anionic and cationic species, can react with themselves, are neutral and are not solvated. They are formed by homolysis of chemical bonds.

2.1.2 Carbon-Centred Radicals

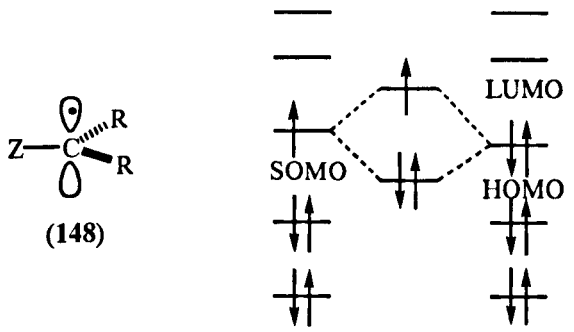
Carbon radicals can be either planar or pyramidal in structure.[72] Planar radicals (**146**) are sp^2 hybridised and pyramidal radicals (**147**) are sp^3 hybridised with greater stabilisation of the planar radical due to reduced repulsion of the three R-groups. The pyramidal radical (**147**) has also been shown to possess higher energy than the ground state planar radical (**146**) and as such, the planar structure (**146**) is often preferred (figure 3).[73,72]

(146) (147)

Figure 3

As a result of the preferred planar structure, the radical or unpaired electron resides in a 2*p*-orbital. The frontier orbital of this radical is the singly occupied molecular orbital (SOMO), which can then interact with the highest occupied molecular orbital (HOMO), or lowest unoccupied molecular orbital (LUMO) of another molecule to achieve a net reduction in energy (figures 4 & 5).

Substituents on the radical centre affect the nature of carbon-centred radicals. An electron-withdrawing group on the radical centre (e.g. C=O, C=N), lowers the energy of the SOMO by an interaction with the orbitals of the Z-group (**148**) making it electrophilic in nature.[74]

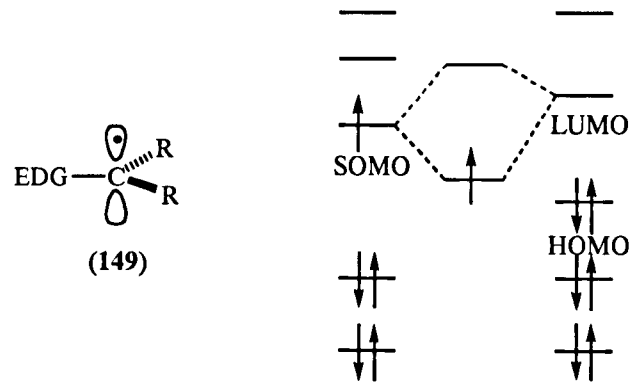


(148)

Figure 4

This electrophilic radical will react preferentially with a molecule possessing a high energy HOMO, such as an electron rich alkene where the SOMO-HOMO interaction will dominate (figure 4).

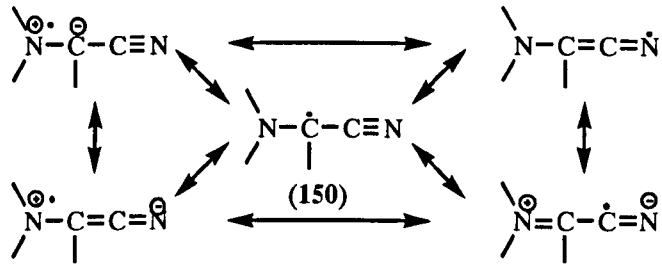
An electron-donating group (EDG) on the radical centre (e.g. N, O, Ph) also stabilises the radical *via* a net overall stabilisation (**149**). However, this raises the energy of the SOMO making it nucleophilic in nature and thus the SOMO-LUMO interaction will dominate (figure 5).[74]



(149)

Figure 5

If both electron withdrawing and electron donating groups are present, then the radical can be stabilised by both these substituents (**150**). This combination is known as the captodative effect and results in enhanced stabilisation.[75,76] This is different from the stable radical observed by Gomberg, which was persistent as a result of steric effects.[67] Captodative radicals are stabilised thermodynamically and thus have a lower energy ground state. Captodative radicals can be thought of as being stabilised by conjugation, whereby the push-pull of electron density allows delocalisation of the radical (figure 6).[75]

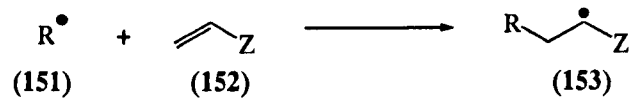


(150)

Figure 6

2.1.3 Reactivity of Radicals

As mentioned previously, both electron-donating and electron-withdrawing groups stabilize radicals. However, they also affect the reactivity of the resultant radical (**153**) as a result of the change in the energy of the SOMO. Their reaction with either an electron rich or electron poor alkene (**152**) is therefore governed by the energy of the starting radical (**151**) (scheme 35) (figure 7).



(151) (152) (153)

Scheme 35

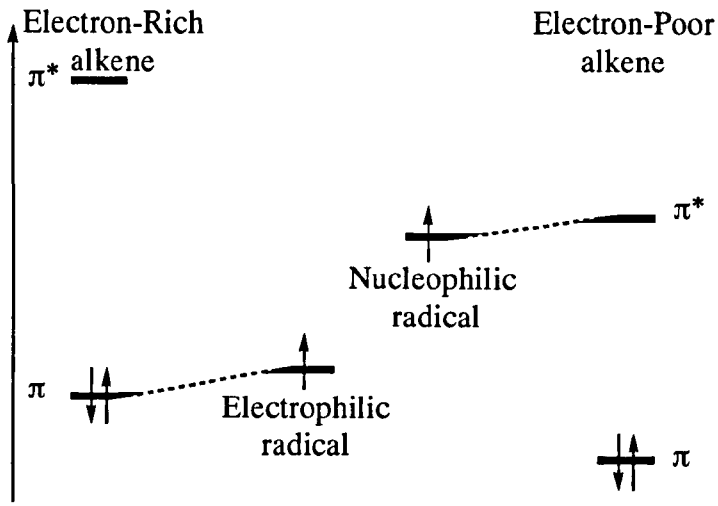
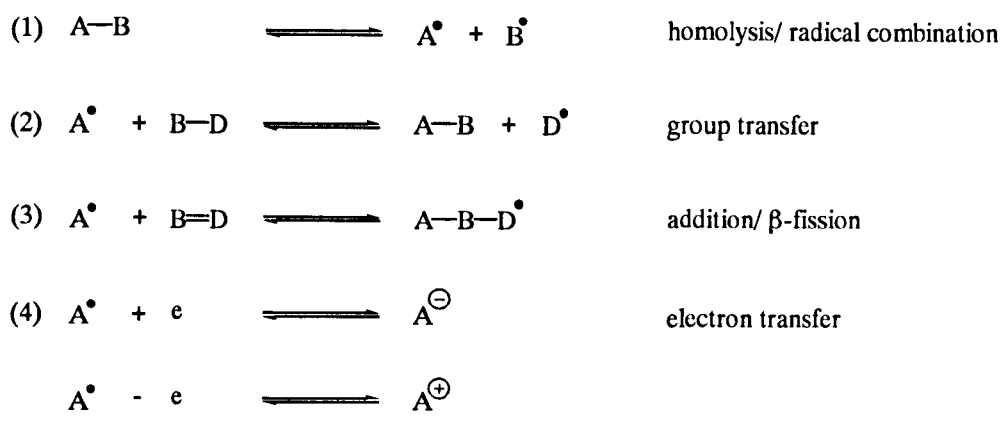


Figure 7

As shown in the preceding diagram (figure 7), the SOMO of an electrophilic radical is closer in energy to the HOMO of an electron-rich alkene and will react preferentially with electron-rich alkenes. Alternatively the SOMO of a nucleophilic radical is closer in terms of energy to the LUMO of an electron-poor alkene and reacts preferentially with electron-deficient alkenes. Thus in general, radicals with low energy SOMO's demonstrate electrophilic properties whilst those with high energy SOMO's will demonstrate nucleophilic properties.[77]

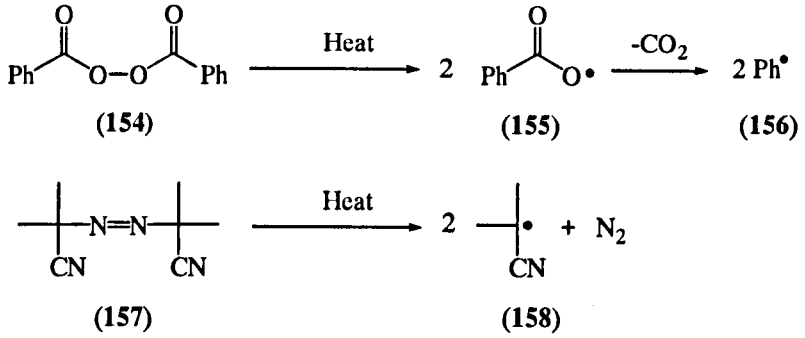
2.2 Radical Reactions

There are a variety of mechanistic pathways available to free radicals; homolysis and its reverse reaction of radical combination (equation 1), radical abstraction or group transfer (S_H2) (equation 2), addition and its reverse reaction of β-fission (elimination) (equation 3), and electron transfer (equation 4) (scheme 36).[78,79]



Scheme 36

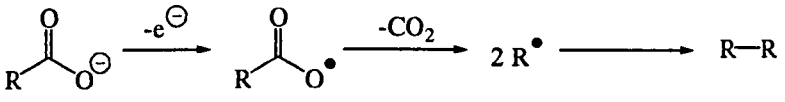
All radicals are generated by homolytic cleavage, usually by thermolysis or photolysis of a molecule to give two radicals. The rate of cleavage of A-B is dependent on the stability of the two resultant radicals. Therefore increasing the temperature will also result in higher concentrations of radicals A· and B·. Compounds that undergo homolytic cleavage are peroxides (R-O-O-R) and azo-compounds (RN=NR). These are the most common means of generating radicals in organic reactions. Two reagents used in radical chemistry are benzoyl peroxide (**154**) and azo-bis-isobutyronitrile (AIBN) (**157**) which both decompose upon thermolysis (scheme 37). Thermolysis of AIBN leads to two 2-cyanopropyl radicals (**158**). Thermolysis of benzoyl peroxide (**154**) results in the formation of two benzoic acid radicals (**155**) that extrude carbon dioxide to generate two phenyl radicals (**156**).[72]



Scheme 37

The reverse reaction in equation one (scheme 36), that of recombination, is known as a termination reaction. Typically, it is rare that recombination follows homolysis as radicals are highly reactive species and are generated in low concentrations which means that they are more likely to come into contact with another molecule than another

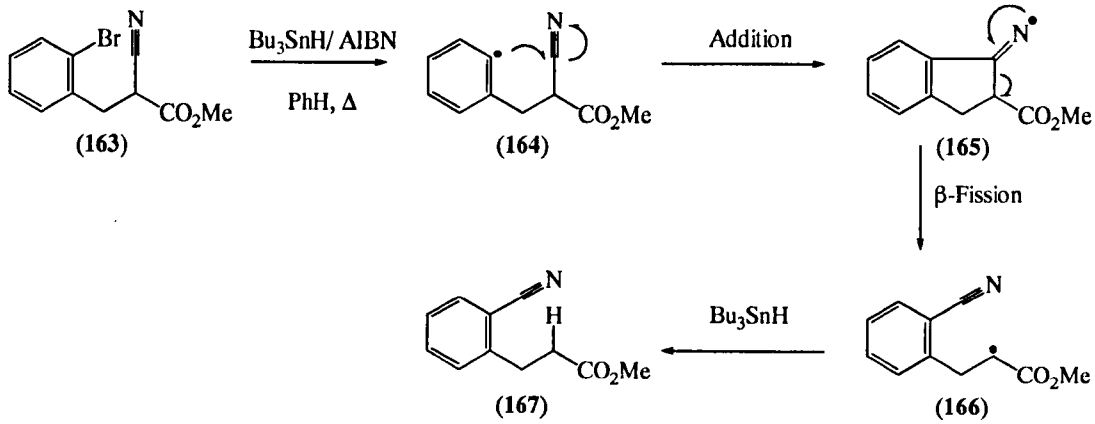
radical.[80] An example where radical-radical recombinations are used in synthesis is the Kolbe electrolytic synthesis.[81] Anodic oxidation of the carboxylate anion (**159**) of a carboxylate salt results in the generation of an alkane (**162**). The carboxylate radical (**160**) that is generated undergoes decarboxylation to generate an alkyl radical (**161**). Combination of these two alkyl radicals results in the formation of an alkane (**162**) (scheme 38). Unlike the use of benzoyl peroxide, the Kolbe reaction generates radicals in high localised concentrations and as a result two radicals can come into contact and recombine. A mixture of two carboxylate salts can also be used in the formation of unsymmetrical products.[82] The Kolbe reaction is also an example of electron transfer in radical reactions (equation 4, scheme 36).



(159) (160) (161) (162)

Scheme 38

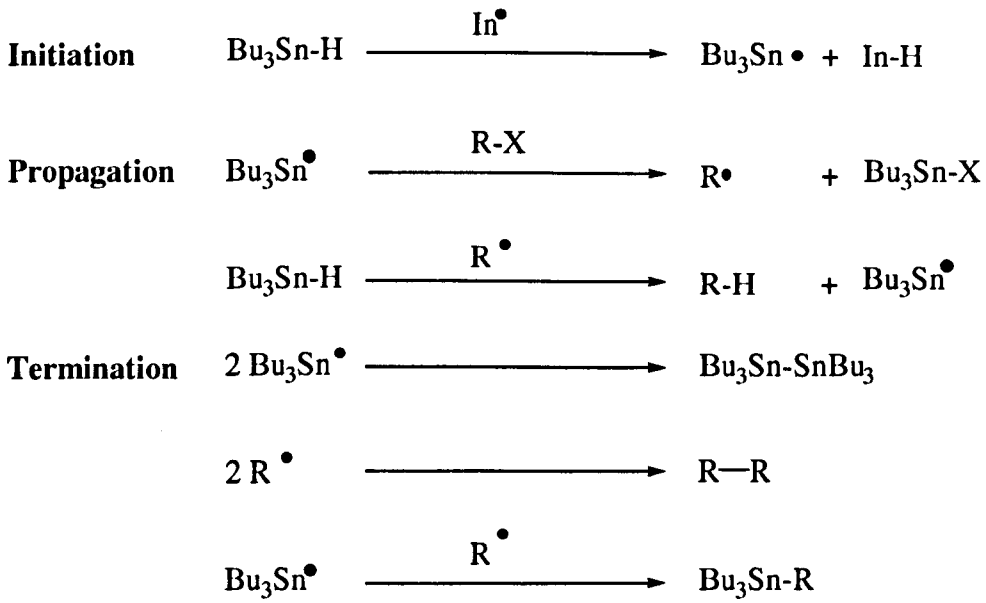
Perhaps the two most important reactions carried out by free radicals are group transfer (equation 2) and addition reactions (equation 3) (scheme 36). In a group transfer reaction, S_H2 reaction, a radical abstracts an atom or group from another molecule to generate a new radical D· at the site of abstraction. Hydrogen atoms and halogens are the most commonly abstracted atoms, although phenylthio and selenophenyl groups are also abstracted. Hart has used the abstraction of the phenylthio group in his synthesis of swainsonine.[83] Alkyl,[84] vinyl[85] and aryl radicals[86] abstract hydrogen atoms from tri-*n*-butyltin hydride at the rates of 2×10^6 $M^{-1}s^{-1}$, 1×10^8 $M^{-1}s^{-1}$ and 7.8×10^8 $M^{-1}s^{-1}$ respectively. Beckwith has used group migration reactions to transfer both cyano and acyl groups onto an aromatic ring by consecutive homolytic addition and β-fission reactions.[87,88] Generation of the aryl radical (**164**) from (**163**) results in radical addition to the cyano group to give the imine radical (**165**). This imine radical (**165**) then undergoes a β-fission reaction to transfer the cyano group to the aromatic ring and generate the acyl radical (**166**) that subsequently undergoes a hydrogen atom transfer with tri-*n*-butyltin hydride (scheme 39).



Scheme 39

2.3 Tin in Radical Chemistry

Following the initial report in 1959 on the reduction of alkyl halides with organotin hydrides,[89] their use in organic synthesis has increased dramatically.[90] Perhaps the best-known and most commonly used organotin reagent is tri-*n*-butyltin hydride.[91] It reacts *via* a free-radical chain mechanism involving initiation, propagation and termination (scheme 40).

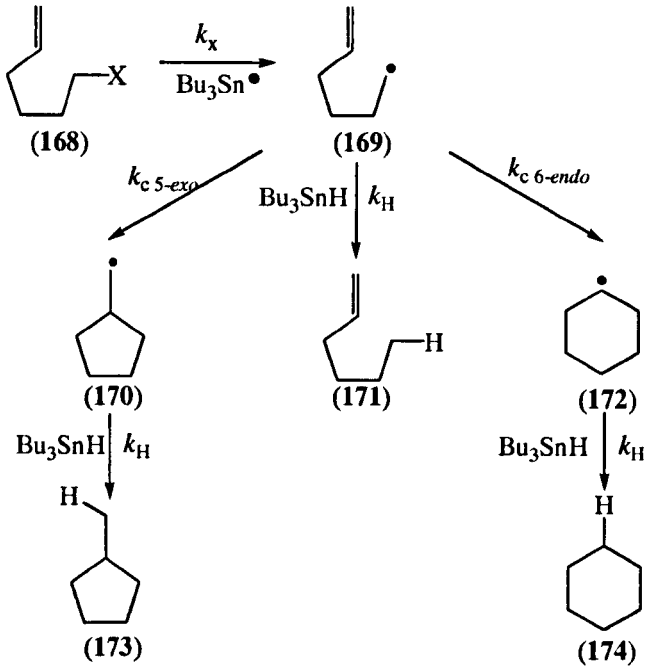


Scheme 40

The initiation of the radical sequence arises from the abstraction of hydrogen from tri-*n*-butyltin hydride by an initiator (In˙) such as the 2-cyanopropyl radical, which is derived

from AIBN (scheme 37). The next step is propagation whereby the resultant alkyl tin radical abstracts a halogen from the alkyl halide to generate an alkyl radical and tri-*n*-butyltin halide. The alkyl radical can then abstract a hydrogen atom from another molecule of tri-*n*-butyltin hydride to yield the reduced product and regenerate another alkyl tin radical. The use of tin hydride in this reaction is essential and arises as a result of the disparity in the relative bond strengths. The tin-hydrogen bond is weaker than the C-H bond. The overall reaction is thus driven by this exchange to generate stronger bonds on each of the two reacting counterparts.[92] It is for this reason perhaps, that the usefulness of tin has not been superseded in radical chemistry by other compounds. In addition to simple reductions (scheme 40), the carbon centred radical R$^{\cdot}$ can also undergo reactions other than straightforward reduction with tri-*n*-butyltin hydride. If the carbon radical generated in the propagation step (scheme 40) is not reduced immediately, it has the opportunity to react with other species. The most common reactions are intramolecular, as they do not rely on diffusion for reaction.[93] The rate of the first propagation step is important in the reaction as it should be fast enough to maintain reaction and enable propagation of the chain. The rate of transfer of various atoms and groups to the tri-*n*-butylstannyl radical is in the order of I > Br > SePh ≈ OC(S)SMe > Cl > SPh. The reactivity of a range of R$^{\cdot}$ groups toward tri-*n*-butyltin hydride is aryl ≈ vinyl > alkyl > allyl ≈ benzyl.[92]

As mentioned previously, (equation 3, scheme 36), the intramolecular addition reaction of radicals to double bonds is perhaps the most commonly used reaction in synthetic organic radical chemistry. Following its discovery, the cyclisation of the 5-hexenyl radical has been extensively investigated.[94,95] Cyclisation of the 5-hexenyl radical (**169**) results in predominantly the cyclopentylmethyl radical (**170**), rather than the more thermodynamically stable cyclohexyl radical (**172**) (scheme 41).

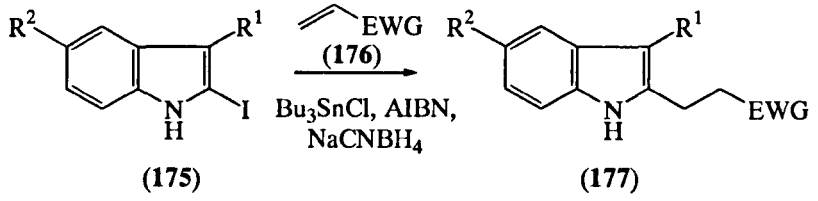


Scheme 41

The possible reaction pathways open to a 5-hexenyl radical are shown above (scheme 41) and are governed by kinetics and the concentration of the reactants. Once generated, the 5-hexenyl radical (**169**) can undergo one of three different reactions. Firstly, it can carry out a 5-*exo*-trig cyclisation ($k_{c(5\text{-}exo)} \sim 2.3 \times 10^5\ s^{-1}$) onto the terminal double bond to give the kinetic product (**170**). Secondly it can undergo a 6-*endo*-trig cyclisation ($k_{c(6\text{-}endo)} \sim 4.1 \times 10^3\ s^{-1}$) to give the thermodynamic product (**172**) and thirdly it can abstract a hydrogen atom from tri-*n*-butyltin hydride to give the reduced product (**171**).[95] Once the cyclised products are generated these can also abstract a hydrogen atom to give the reduced products (**173** and **174**).

If the concentration of tri-*n*-butyltin hydride is low, then the intramolecular reactions should predominate. There are two main methods of maintaining a low concentration of tri-*n*-butyltin hydride. The first method is the use of a syringe pump for delivery of tri-*n*-butyltin hydride and a sub-stoichiometric amount of the radical initiator to a solution of the radical precursor at reflux over a period of time. This allows the concentration of the tri-*n*-butyltin hydride to remain low throughout the course of the reaction. The second method used is to add a catalytic amount of tri-*n*-butyltin hydride or tri-*n*-butyltin chloride to the reaction along with a stoichiometric amount of sodium borohydride or sodium cyanoborohydride. [96,97,98,99,100] Jones and Fiumana have used

the catalytic tin methodology in their synthesis of 2-substituted indoles. Reaction of 2-iodoindoles (**175**) with a range of electron deficient alkenes (**176**) resulted in 2-substituted indoles (**177**) in yields of up to 40% (scheme 42). Use of standard tin conditions only gave reduced product.[101]



Scheme 42

The terms "*exo*" and "*endo*" refer to the external (exocyclic) position and internal position of the double bond in the ring-forming step respectively and are based on Baldwin's rules, which give good predictability of radical reactions.[102]

The regioselectivity observed in the cyclisation of the 5-hexenyl radical cyclisation results in the formation of the less thermodynamically stable cyclopentylmethyl radical (**170**) in preference to the more stable secondary cyclohexyl radical (**172**) in a ratio of 50: 1.[79] Thermochemical criteria would normally have predicted that the more stable secondary radical (**172**) would be preferentially formed. The cyclisation is therefore governed by kinetic factors. Homolytic addition to a double bond is purported to proceed *via* an overlap of a semi-occupied 2p orbital with one lobe of the vacant π^* orbital as shown below (figure 8).[103,104] The preferred *exo*-cyclisation of the 5-hexenyl radical arises as a result of the strain involved in incorporation of the reactive centres within the transition structure for the 6-*endo* cyclisation.

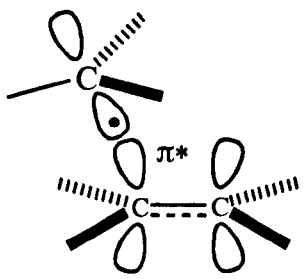
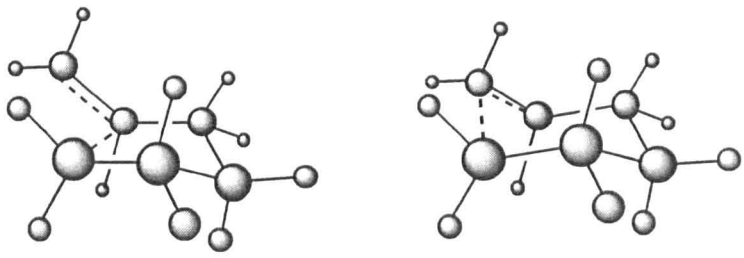


Figure 8

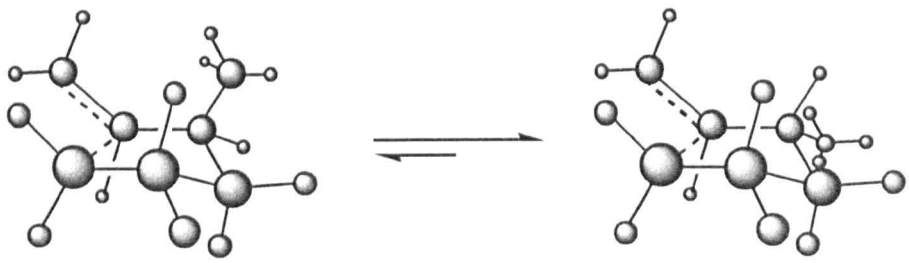
The two calculated transition structures for the ring-closure of the 5-hexenyl radical represent a distorted chair forms of cyclohexane (figure 9). The 6-*endo*-trig transition structure (**179**) was determined to be ~11 $KJmol^{-1}$ higher in energy than the 5-*exo*-trig transition structure (**178**).[78]



(**178**)-*exo* (**179**)-*endo*

Figure 9

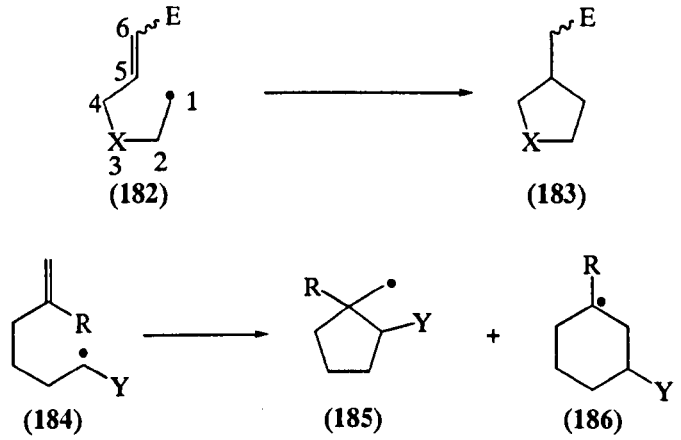
Beckwith and Houk have also explored the addition of a substituent onto the 5-hexenyl radical system in order to rationalise the stereochemical outcome of cyclisation. For the 4-methylhexenyl radical, there are two possible diastereoisomeric products, which arise from the transition structures (figure 10). In a 5-*exo*-trig cyclisation, the methyl group can be either pseudo-axial (**180**) or pseudo-equatorial (**181**). Beckwith's calculations showed that the pseudo-equatorial possesses the lower energy, which confirms the experimental stereochemical results. Thus 5-*exo*-trig cyclisation of the 4-methylhexenyl radical results in mainly the *trans*-product.[105,78] Beckwith demonstrated experimentally that 1,5-ring closure of 1- or 3-substituted hexenyl radicals results in mainly the *cis*-disubstituted products, whereas 2- or 4-substituted hexenyl radicals afford mainly the *trans*-products.[106]



(**180**) pseudo-axial (**181**) pseudo-equatorial

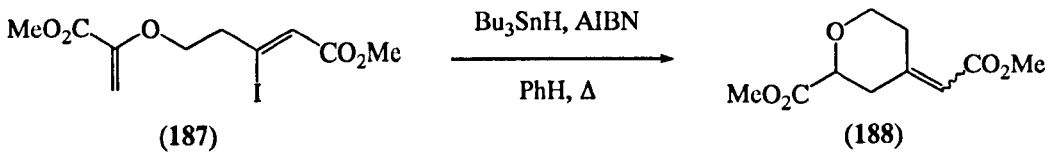
Figure 10

As mentioned previously, there are several factors that affect intramolecular cyclisation. Substituents on the radical centre also have a significant effect on the cyclisation reaction.[106,93] Addition of electron-donating groups on the 1-position of the radical and electron-withdrawing groups on the alkene bond can increase the yield of cyclised products.[107] The incorporation of a nitrogen or oxygen atom at the 3-position (scheme 43) also accelerates the rate of ring closure. Incorporation of a substituent at the 5-position retards the rate of the 5-*exo*-cyclisation and allows the 6-*endo*-cyclisation to become significant. Cyclisation is also impeded by the incorporation of radical-stabilising groups (C=O, C=C, heteroatom) at the 1-position.[93]



Scheme 43

Incorporation of an electron-withdrawing group at the 5-position can also favour 6-*endo*-cyclisation over the 5-*exo*-cyclisation. Radical cyclisation of **(187)** resulted in 70% of the 6-*endo*-cyclised product **(188)** in contrast to the 5-*exo*.[108,109] The ester group favoured a Michael addition of the radical to the 6-position over the expected 5-*exo* addition (scheme 44).

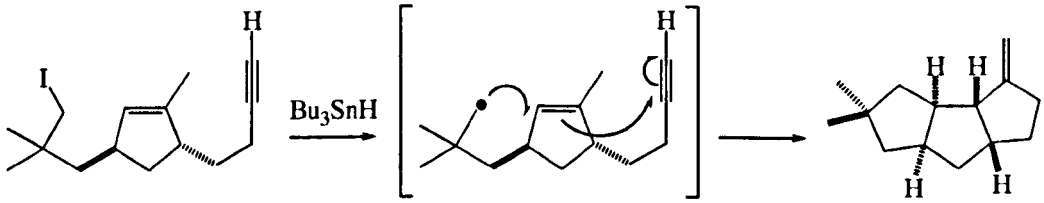


Scheme 44

2.4 Tandem Radical Reactions in Synthesis

Tandem, cascade, zip and domino reactions are multiple step chemical transformations carried out in one pot. Tandem radical chemistry involves two or more radical reactions, which can be connected in a radical sequence. The applicability of radical chemistry to this field is a result of the fact that radicals are self-propagating, i.e. the addition of one radical to a double bond results in the generation of a new radical, which can then carry out a subsequent radical reaction.[110,111,112]

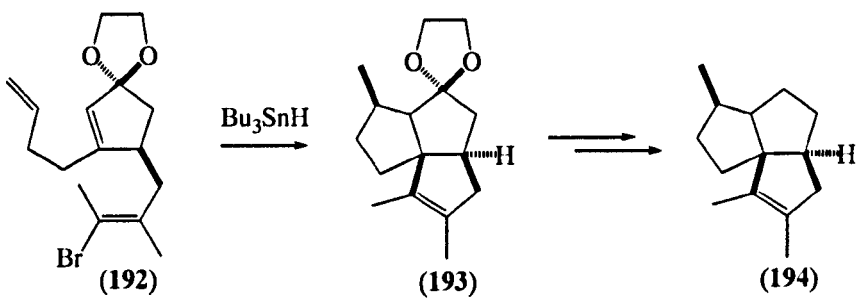
Curran's synthesis of the linear triquinane hirsutene **(191)** is based on a sequence of 5-exo cyclisations and is a good demonstration of the synthetic utility of tandem radical cyclisations.[113] Treatment of the cyclisation precursor **(189)** under standard radical conditions generated (±)-hirsutene **(191)** in one single step in 65% yield (scheme 45). Using similar methodology, Curran has also synthesised $\Delta^{9(12)}$-cappneline, a related linear triquinane.[114]



(189) **(190)** **(191)**

Scheme 45

The angular triquinanes are also accessible using the same methodology, which is exemplified in Curran's synthesis of (±)-silphiperfolene. Radical cyclisation of the precursor **(192)** generated silphiperfolene **(194)** and its diastereoisomer in 66% yield in a 3:1 ratio (scheme 46).[115,116]

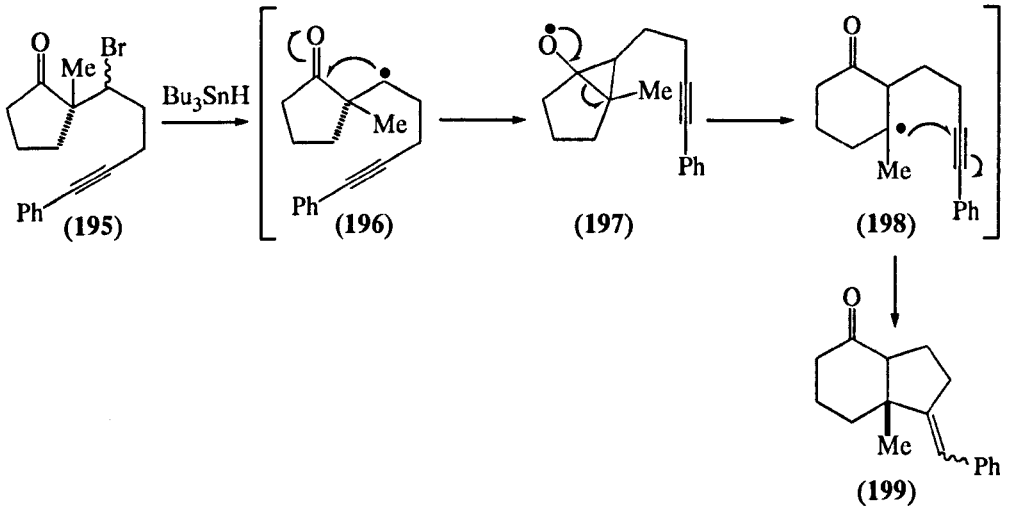


(192) **(193)** **(194)**

Scheme 46

Other groups have also applied tandem radical methodology in the synthesis of a range of carbacycles. Stork has applied tandem methodology in his synthesis of a butenolide[117,118] as has Kilburn, in the synthesis of isoiridomyrmecin.[119] Clive has demonstrated the ability of radicals to generate spiro-fused centres in the synthesis of fredericamycin A[120,121,122,123] and has also used sequential radical addition, β-fission reactions in his synthesis of benzofurans.[124] Sha has also used tandem radical methodology to generate spiro-centres in the synthesis of (+)-paniculatine.[125] Chen's synthesis of (±)-α-cedrene,[126,127] Ziegler's and Parson's approach to the prostaglandins[128,129] and Ishibashi's radical cascade approach to benzo[α]quinolizidines[130] also all use tandem methodology.

Boger has used tandem radical methodology in a ring expansion process to generate fused bicyclic carbocycles.[131] Treatment of the radical precursor (**195**) with tri-*n*-butyltin hydride generated the fused bicyclic ring system (**199**) in 86% yield. The radical generated from (**195**) is purported to add to the carbonyl group in a 3-*exo*-trig addition to give the cyclopropane (**197**), followed by a β-fission to generate the ring expanded radical (**198**) which undergoes a 5-*exo*-dig cyclisation onto the triple bond (scheme 47). Work by Malacria has shown that the cyclopropane intermediates can also be isolated from the reaction.[132]

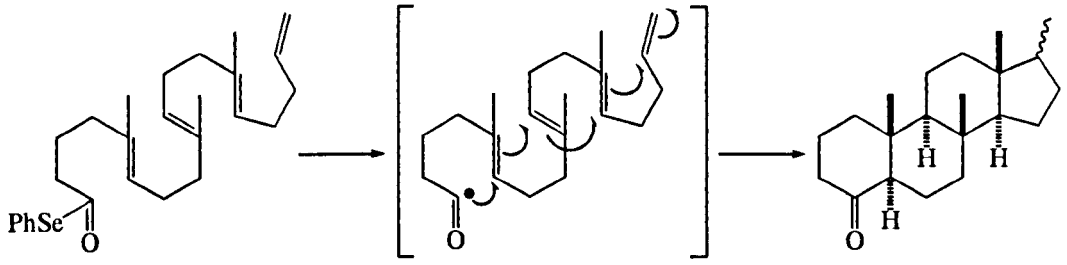


Scheme 47

The incorporation of heteroatoms in tandem radical reactions has been employed by Bowman in his synthesis of indolizidines and pyrrolizidines.[133] Zard has more recently published a synthesis of (±)-γ-lycorane using nitrogen-centred radicals to initiate a

tandem sequence.[134] Motherwell and Harrowven have used tandem sequences in the synthesis of biaryl compounds *via* radical *ipso*-substitution.[135,136,137]

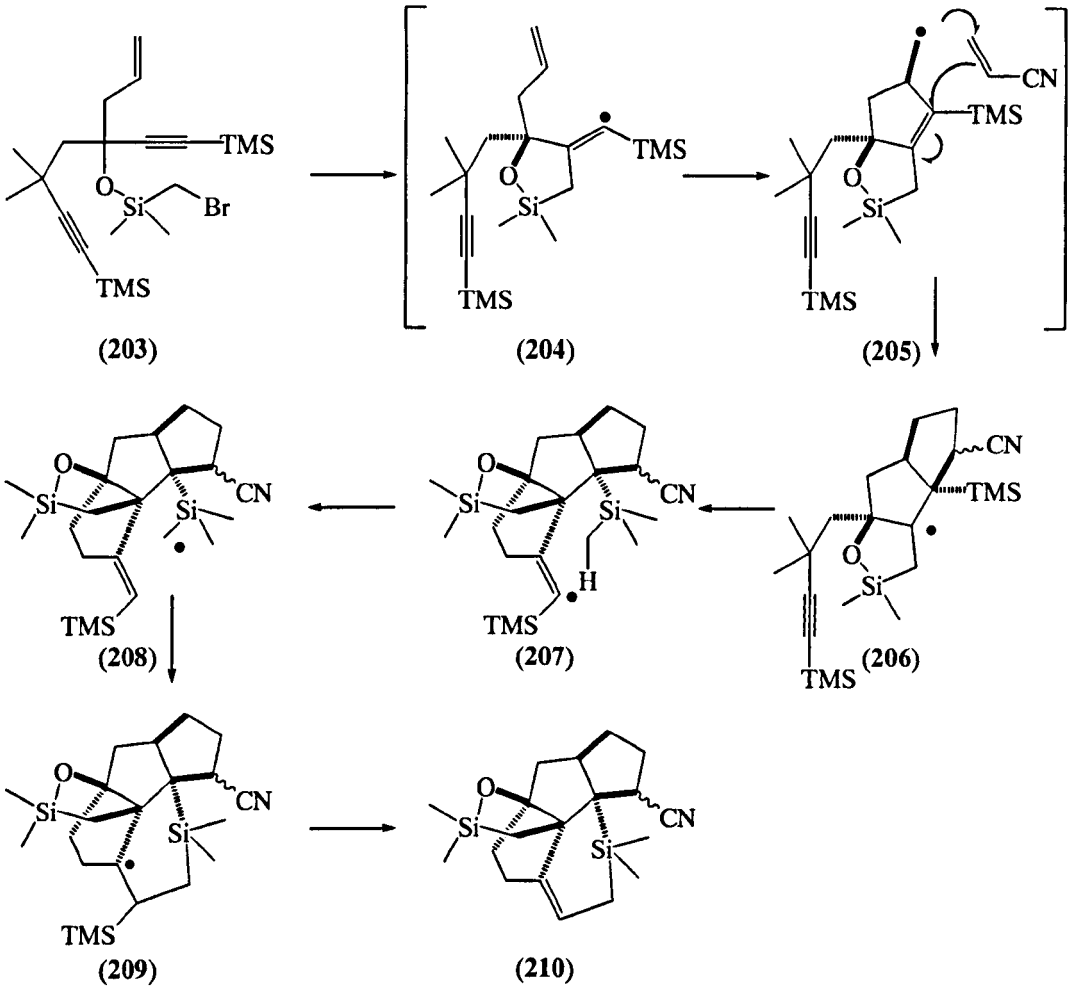
Pattenden, Curran and Takahashi have all applied tandem radical cyclisations in their synthesis of the steroid skeleton structure.[138,139,140,141,142,143] Pattenden's synthesis of the tetraene ester (**200**) followed by treatment with tri-*n*-butyltin hydride generated the ABCD-steroid skeleton (**202**) in 51% yield.[140] Generation of the acyl radical (**201**) followed by three consecutive 6-*endo*-trig radical cyclisations led to the tetracyclic structure (**202**) (scheme 48). Pattenden has also prepared the taxane ring system *via* a tandem radical macrocyclisation.[144]



(200) (201) (202)

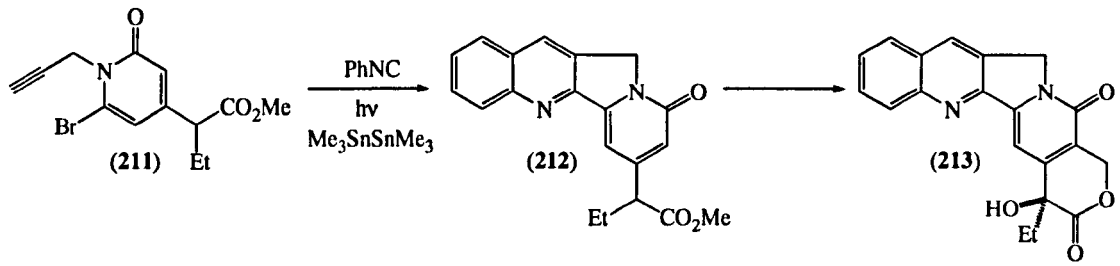
Scheme 48

Malacria's radical cyclisation of bromomethyldimethylsilylpropyl ethers is a very powerful demonstration of the potential of tandem radical cyclisations to generate complex systems very rapidly.[145,146,110] Radical cyclisation of the precursor (**203**) resulted in the formation of the pentacyclic structure (**210**) (scheme 49).



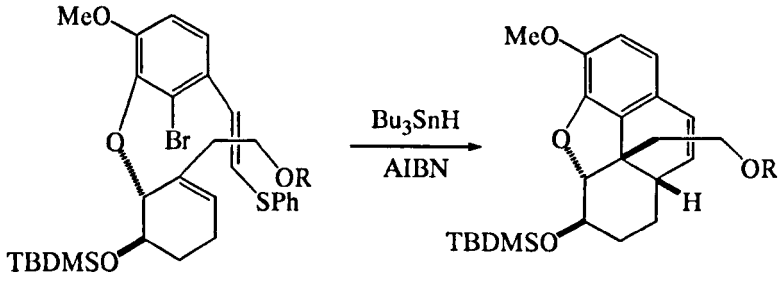
Scheme 49

Curran's synthesis of (±)-campothecin also illustrates the usefulness of tandem radical reactions which incorporate an annulation step.[147,148,149] Radical cyclisation of the precursor **(211)** and phenylisonitrile using hexamethylditin and a sunlamp generated the tetracyclic structure **(212)** in 45% yield. This was then converted to (±)-campothecin **(213)** following Danishefsky's work (scheme 50).[150]



Scheme 50

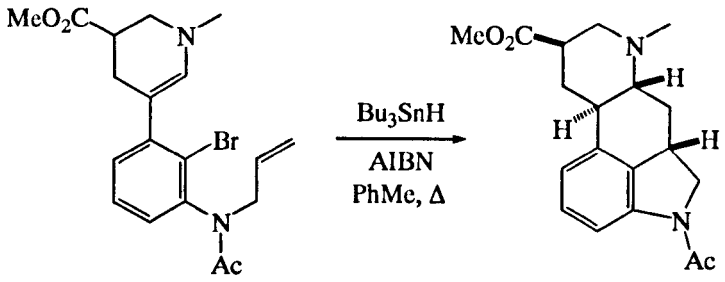
Complex natural products such as morphine and codeine have also been synthesised using tandem radical methodology.[151] Parker's cyclisation of the precursor (**214**) led to the morphine skeleton (**215**) in one single reaction *via* an initial 5-*exo*-trig cyclisation, followed by a 6-*endo*-trig cyclisation and subsequent elimination of the phenylthio radical (scheme 51).[152,153,154,155]



(214) (215)

Scheme 51

Parson's synthesis of the lysergic acid analogue (**217**) is another example of the synthetic utility of tandem radical chemistry.[151,156,157] Cyclisation of the precursor (**216**) resulted in the tetracyclic structure (**217**) possessing the lysergic acid skeleton (scheme 52). Parsons and Penkett have also developed tandem radical approaches to the *Pseudocopsinine* skeleton as well as the *Aspidosperma* alkaloid skeleton.[158,159]

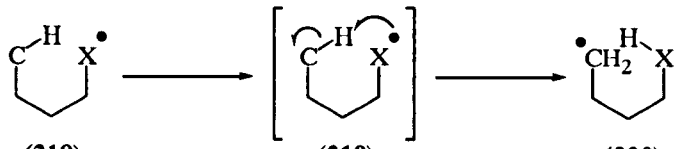


(216) (217)

Scheme 52

2.5 1,5-Hydrogen Atom Abstraction Reactions

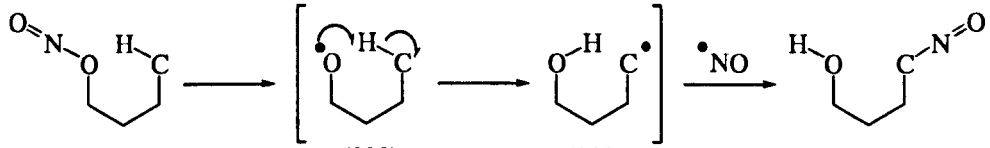
The intramolecular abstraction of hydrogen atoms at remote unactivated sites by a radical is a very powerful reaction in radical chemistry. The most common site of abstraction is five atoms from the initial radical centre (scheme 53). This arises from the need to allow for an X---H---C bond angle of close to 180°.[160]



(218) (219) (220)

Scheme 53

Classic examples of 1,5-hydrogen atom abstraction reactions include the Hoffman-Löffler-Freytag rearrangement of *N*-chloroamines,[161] which has been used for the remote functionalisation of steroid structures.[162] In this reaction, a nitrogen-centred radical is generated by photolysis and abstracts a hydrogen atom, five atoms away. The resultant radical then traps the chlorine radical.[161,162] The Barton photolysis of nitrite esters involves the use of an oxygen-centred radical in the abstraction of a hydrogen atom.[163] Photolysis of the nitrite ester (**221**) cleaves the O-N bond generating the oxygen radical (**222**), which abstracts a hydrogen atom five centres away to generate the carbon-centred radical (**223**), which then can react with nitric oxide to give the nitroso compound (**224**) (scheme 54). If deuterothiophenol is present, then deuterium can be incorporated in place of nitric oxide.[163]

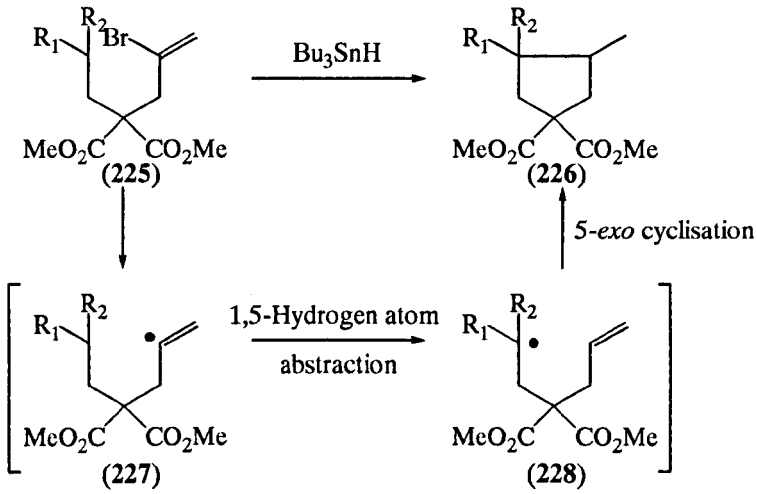


(221) (222) (223) (224)

Scheme 54

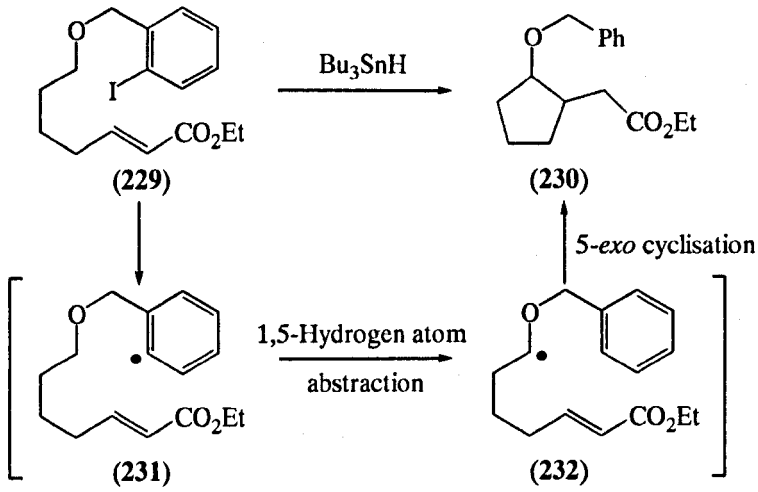
However, it was not until the late 1980's that the usefulness of this reaction was realised. Work by Curran, Čeković and Parsons in 1988, demonstrated that a radical generated after 1,5-hydrogen atom abstraction, could also undergo a further intramolecular addition reaction.[164,165,166] Čeković, following Barton's early work, generated an alkoxy radical, which abstracted a hydrogen atom to give a carbon-centred radical. This underwent a 5-*exo*-trig-cyclisation onto a pendant double bond to generate a cyclic system.[165] Parsons' synthesis of the pyrrolizidine ring system incorporated a 1,5-hydrogen atom abstraction by a vinylic radical, with the resultant radical cyclising back onto the vinylic bond.[164] Curran's report detailed two potential variations on the 1,5-hydrogen atom abstraction reaction.[166] The first was based on the same observations found by Parsons' with the generation of a vinylic radical. Generation of radical (**227**) followed by a 1,5-hydrogen atom abstraction resulted in the stabilised

radical (**228**). Cyclisation back onto the double bond thus resulted in the formation of the cyclised structure (**226**) (scheme 55). Curran investigated a range of substituents R^1 and R^2 to determine the effects of a range of electron-donating and withdrawing groups.[167]



Scheme 55

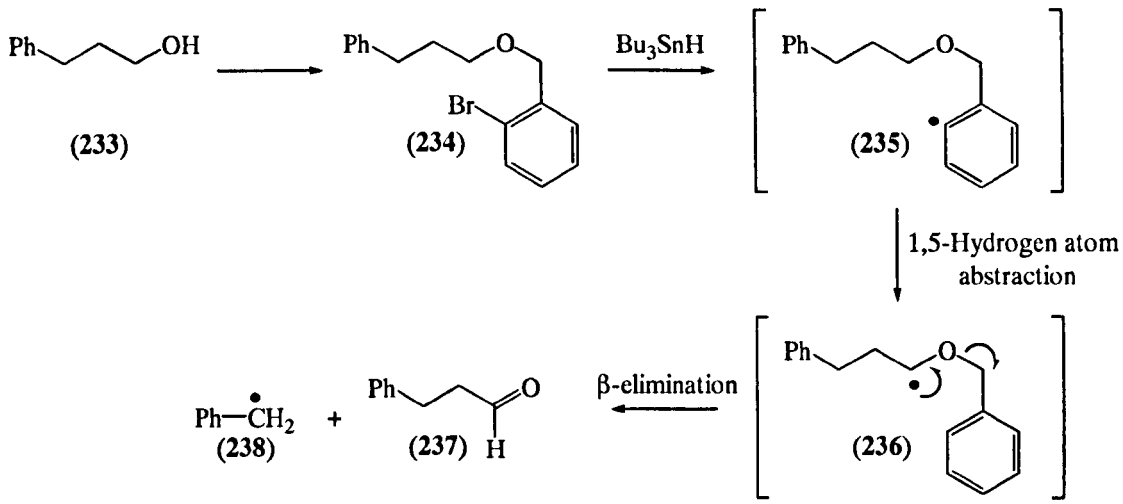
The second variation was based on the generation of a radical on a modified protecting group, which then underwent a 1,5-hydrogen transfer to generate a radical α- to the protected functional group.[167] Generation of the aryl radical (**231**) followed by abstraction of a hydrogen atom resulted in the α-alkoxy radical which can undergo cyclisation onto the double bond to give the cyclised product (**232**) (scheme 56). The benzyl group is left as a protecting group on the alcohol and has functioned as both a protecting group and a radical translocator.



Scheme 56

Incorporation of the *o*-(bromophenyl)dimethylsilyl group in place of the *o*-bromobenzyl group resulted in increased yields of subsequent cyclised products.[167,168] However, further exploration of this protecting-translocating group revealed that 1,7-(and to a lesser extent 1,6-) hydrogen atom transfers compete with 1,5-hydrogen transfers.[168,169]

The 1,5-hydrogen atom abstraction reaction of *o*-bromobenzyl ethers has also been used in a mild self-oxidising manner.[170] Generation of an *o*-bromobenzyl ether (**234**) from an alcohol (**233**) followed by treatment under mild radical conditions resulted in the formation of an aldehyde (**237**) (scheme 57). The 1,5-translocated α-alkoxy radical (**236**) underwent a β-fragmentation to generate the aldehyde (**237**) and the benzyl radical (**238**) (scheme 57).

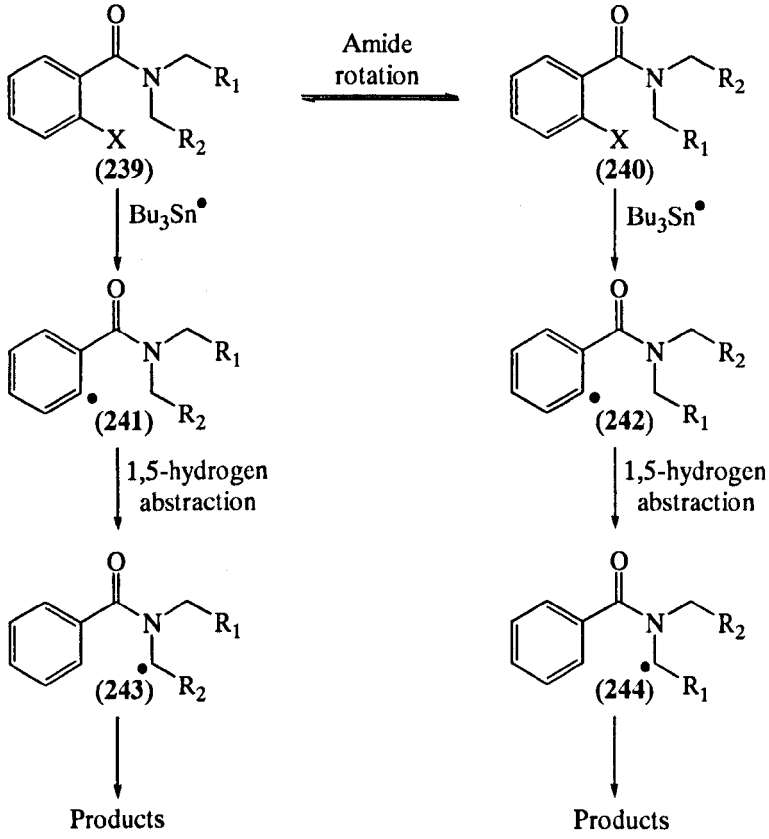


Scheme 57

As well as the *o*-bromobenzyl and *o*-(bromophenyl)dimethylsilyl protecting-radical translocating (PRT) groups, anilides, amines and amides can also be used and have been investigated by Curran.[171,172,173] The benzamide protecting group provides a useful way of generating α-amidoyl radicals which have been used in the synthesis of natural products by Hart in the synthesis of (-)-swainsonine.[83] Hart generated the α-amidoyl radical from a phenylthio amide. Snieckus first observed the generation of α-amidoyl radicals in a failed cyclisation reaction, which demonstrated that the 1,5-hydrogen atom abstraction was faster than a 5-*exo* aryl radical cyclisation. However, Cohen had observed abstraction of a hydrogen atom from benzamides in copper-catalysed decomposition reactions in 1966.[174,175] The Heck reaction has also been shown to fail

when diazo-*N*,*N*-diethyl-*o*-benzamides are used as a result of 1,5-hydrogen atom abstraction.[176]

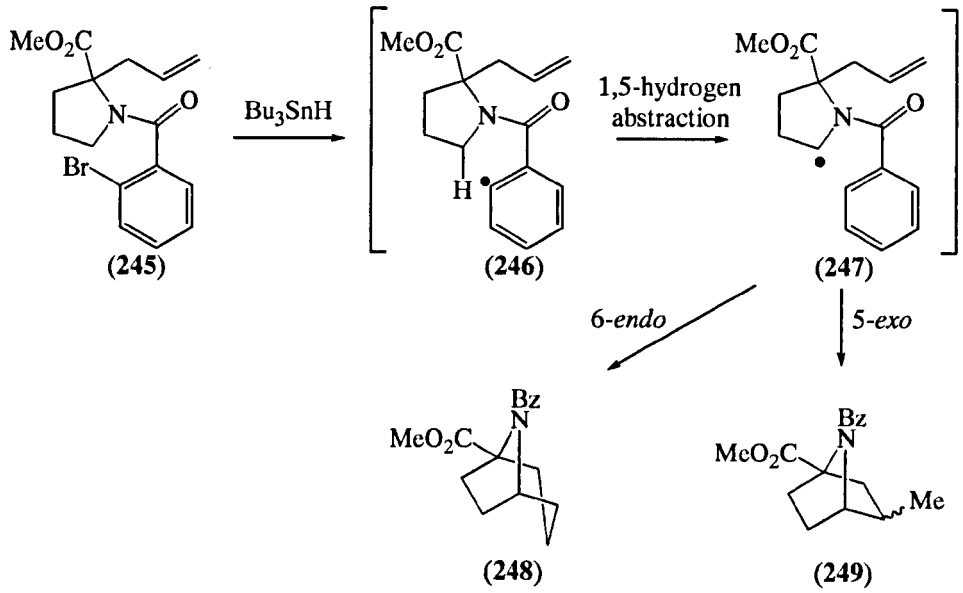
The incorporation of the amide bond in the benzamide PRT group poses a problem as a result of restricted rotation about the amide bond, which leads to two amide rotamers. Amide rotamers interconvert at the rate of 10^{-1} to 10^{-2} s^{-1} and aryl radical solution lifetimes are in the order of 10^{-5} s^{-1}.[173,177,178,179,180,181,182] Therefore the two aryl radicals **(241)** and **(242)** cannot interconvert (scheme 58). Curran showed that the product ratios reflected the ratios of amide rotamers in the starting benzamides.[173]



Scheme 58

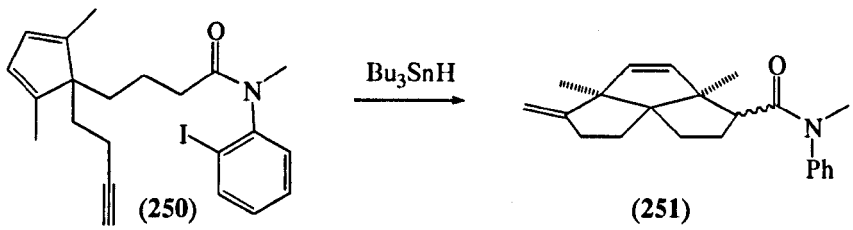
Curran and Snieckus utilised the *o*-iodobenzamide PRT group in a cyclisation reaction to generate pentacyclic structures and found that the products ratio closely reflected the rotamers ratio in the starting *o*-iodobenzamides.[172] Ikeda utilised the *o*-bromobenzamide PRT group to generate bridged azabicyclic compounds.[183] Generation of the aryl radical **(246)** followed by a 1,5-hydrogen atom abstraction resulted in the α-

acylamino radical (**247**) which underwent a cyclisation to give (**249**), the 5-*exo* cyclised product in 30% yield along with 12% of the reduced product (scheme 59).



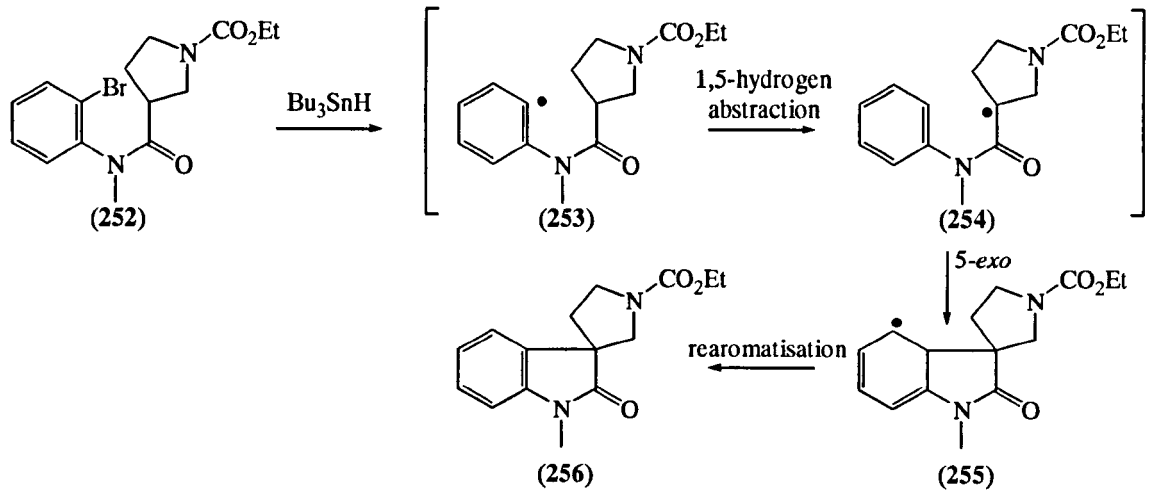
Scheme 59

Curran has used the *o*-iodoanilide PRT groups in the synthesis of tricyclic compounds directed towards the crinipellins.[184,171] Cyclisation of (**250**) resulted in the tricyclic structure (**251**) as a mixture of diastereoisomers in 75% yield (scheme 60).



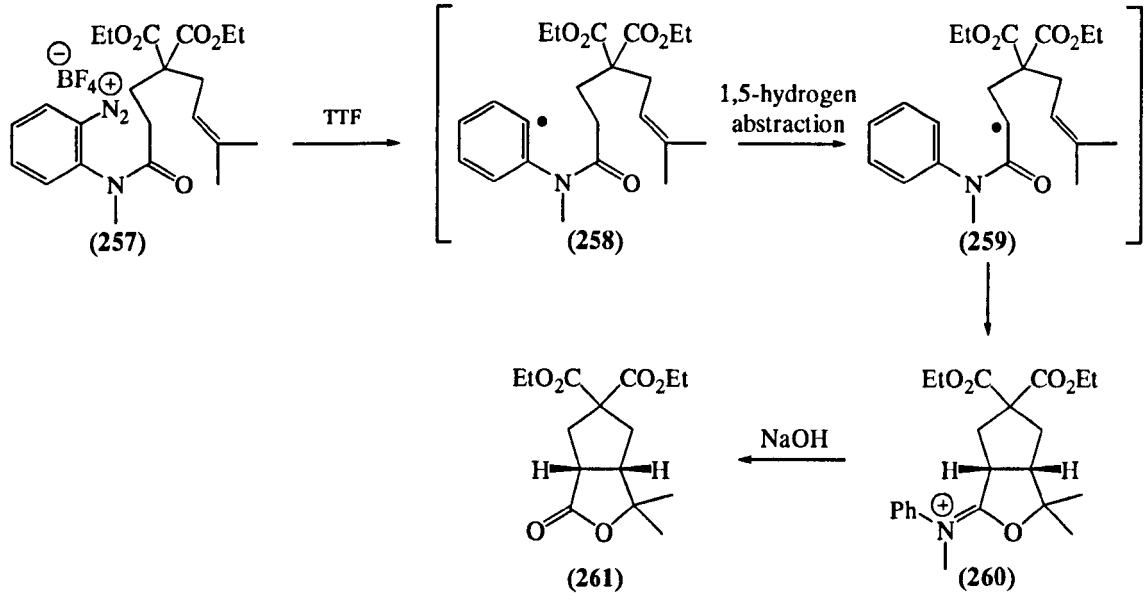
Scheme 60

Beckwith and Storey have utilised the 1,5-abstraction reaction of *o*-bromoanilides in their short synthetic route towards spiropyrrolidinyloxindoles.[185,186] Generation of the aryl radical (**253**) followed by a 1,5-hydrogen atom abstraction resulted in the α-amidoyl radical on the pyrrolidine ring (**254**). This cyclised back into the aromatic ring to generate the oxindole (**256**) (scheme 61).



Scheme 61

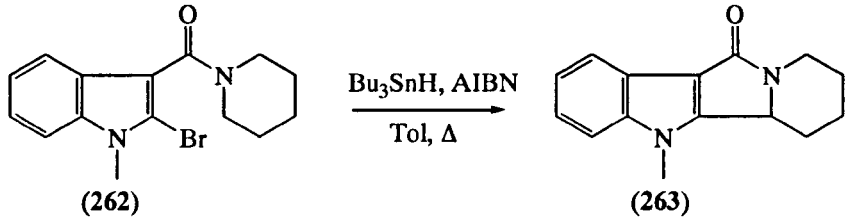
Murphy has utilised *o*-diazoanilide salts in a 1,5-abstraction cyclisation reaction to generate fused bicyclic systems.[187] Treatment of the diazonium salt (**257**) with tetrathiafulvalene generated the aryl radical (**258**), which underwent a 1,5-hydrogen abstraction to give the α-amidoyl radical (**259**) which was followed by two subsequent intramolecular cyclisation steps to generate the iminium salt (**260**). Hydrolysis of this salt furnished the lactone (**261**) in 45% yield (scheme 62).



Scheme 62

Following Jones' work[188] on 1,5-hydrogen atom abstraction starting from indole radicals, Gribble has utilised a 1,5-abstraction/5-*endo* addition route to tetracyclic

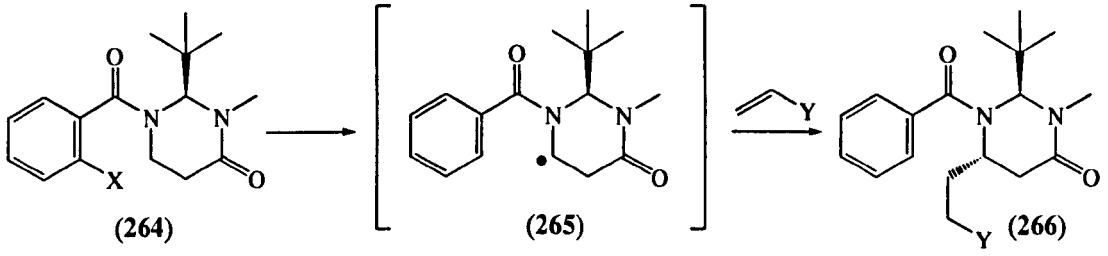
indole-containing compounds.[189] Generation of the indole radical from the 2-bromoindole (**262**) furnished the tetracycle (**263**) in 54% yield (scheme 63).



(262) (263)

Scheme 63

Snieckus has utilised the *o*-halobenzamide PRT group in his synthesis of β-substituted β-amino acid in high enantiopurity.[190] 1,5-Hydrogen atom abstraction from the enantiopure pyrimidone ring (**264**) by the benzamide radical followed by olefin trapping of various Michael acceptors resulted in the substituted products (**266**) in yields of 40-60% (scheme 64). Renaud has also utilised similar methodology to achieve high diastereoselectivity.[191]



(264) (265) (266)

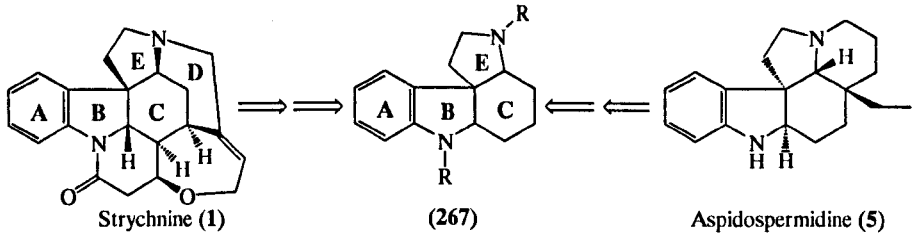
Scheme 64

Chapter 3

Strategic Aim of the Project

The compounds that form the basis of the *Strychnos* and *Aspidosperma* alkaloids present a broad range of both structural complexity and biological activity. The ultimate aim of this project is to develop a novel and flexible approach to these two classes of alkaloid using radical methodology.

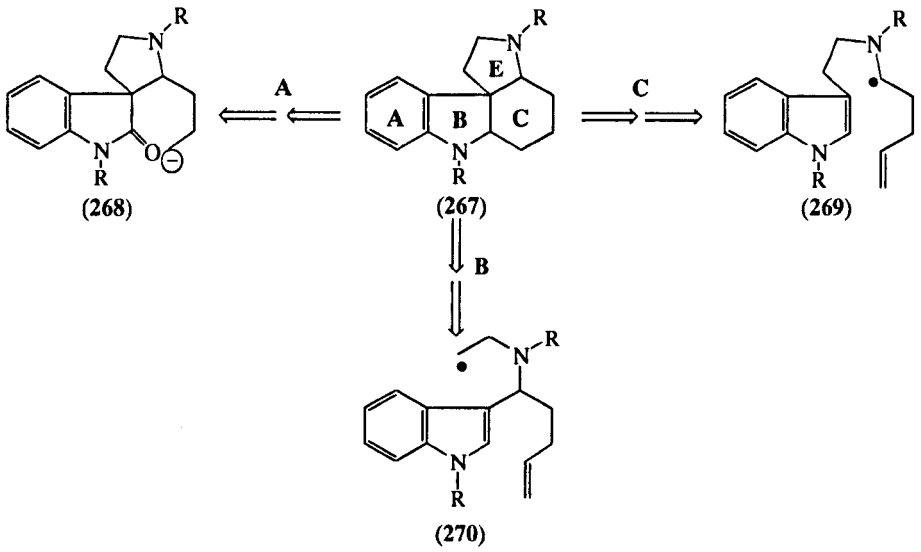
Disconnection of both strychnine (**1**) and aspidospermidine (**5**) leads back to tetracyclic intermediates such as (**267**), (scheme 65) which, with further functionality incorporated into the molecule, would allow the development of rapid synthetic routes to both classes of alkaloid. A key aim of this project is to develop a flexible approach to this tetracyclic core.



Strychnine (**1**) (**267**) Aspidospermidine (**5**)

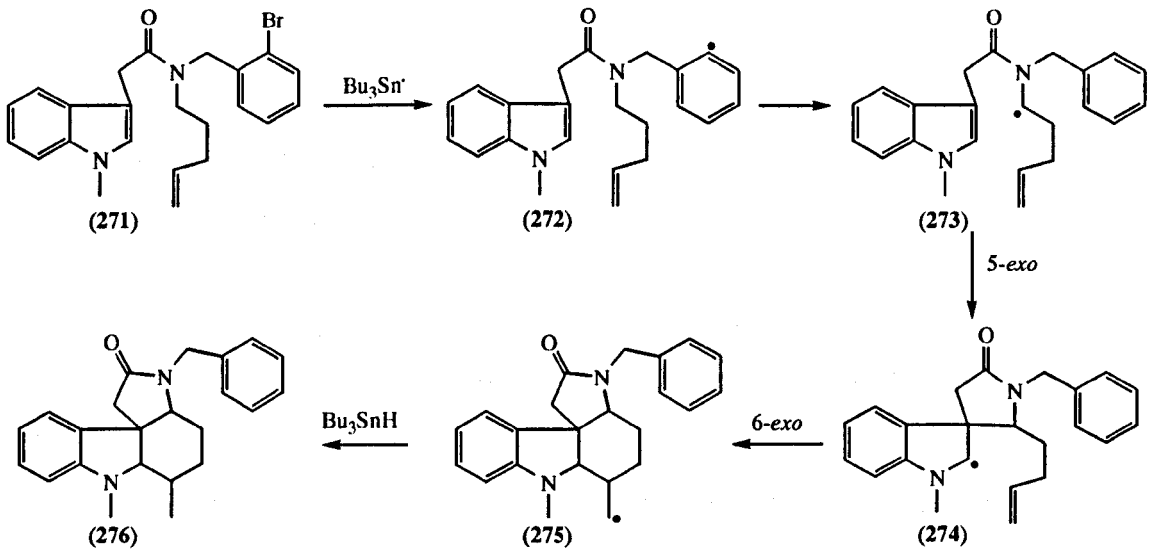
Scheme 65

Our approach to the tetracyclic core was based on maintaining rings A and B intact so that our synthetic routes would involve simple functionalisation of either an indole (disconnections B and C) or an oxindole (disconnection A) (scheme 66).



Scheme 66

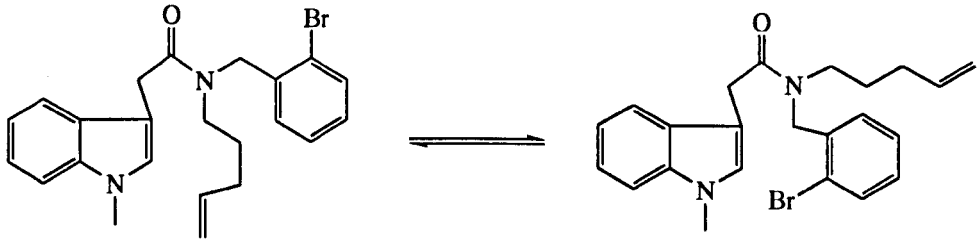
Previous work in the group by Tim Ho had focused on disconnection route C.[192] The aim was to use tandem radical methodology to synthesise the tetracyclic core. Disconnection C gave **(269)** (scheme 66), which is a tandem radical cyclisation precursor. The cyclisation precursor was designed so that construction of rings C and E could be carried out in one step using radical chemistry. The cyclisation precursor contains the 2-bromobenzyl group, which functions both as a radical translocator and as a protecting group. The use of *ortho*-halo benzyl groups has been shown by Curran to be an effective method of 1,5-hydrogen atom abstractions to furnish radicals at remote sites.[167]



Scheme 67

The proposed tandem radical cyclisation sequence is illustrated above (scheme 67). Reaction of (**271**) under standard radical conditions should generate the aryl radical (**272**), which can undergo a rapid 1,5-hydrogen atom abstraction to generate a new α-amidoyl radical (**273**), which is stabilised due to its location α- to the nitrogen. It was hoped that this radical (**273**) would undergo a 5-*exo*-trig cyclisation onto the 3-position of indole to give the spirocyclic intermediate radical (**274**). This resultant radical (**274**) should then undergo a 6-*exo*-trig cyclisation onto the pendant double bond to form ring C and generate an unstable primary radical (**275**). Abstraction of a hydrogen atom from tri-*n*-butyltin hydride would generate the tetracycle (**276**).

The cyclisation precursor was synthesised in seven steps in 58% overall yield and was obtained as a mixture of amide rotamers (**271a**) and (**271b**) in the ratio of 1: 1.2 (scheme 68).[192]



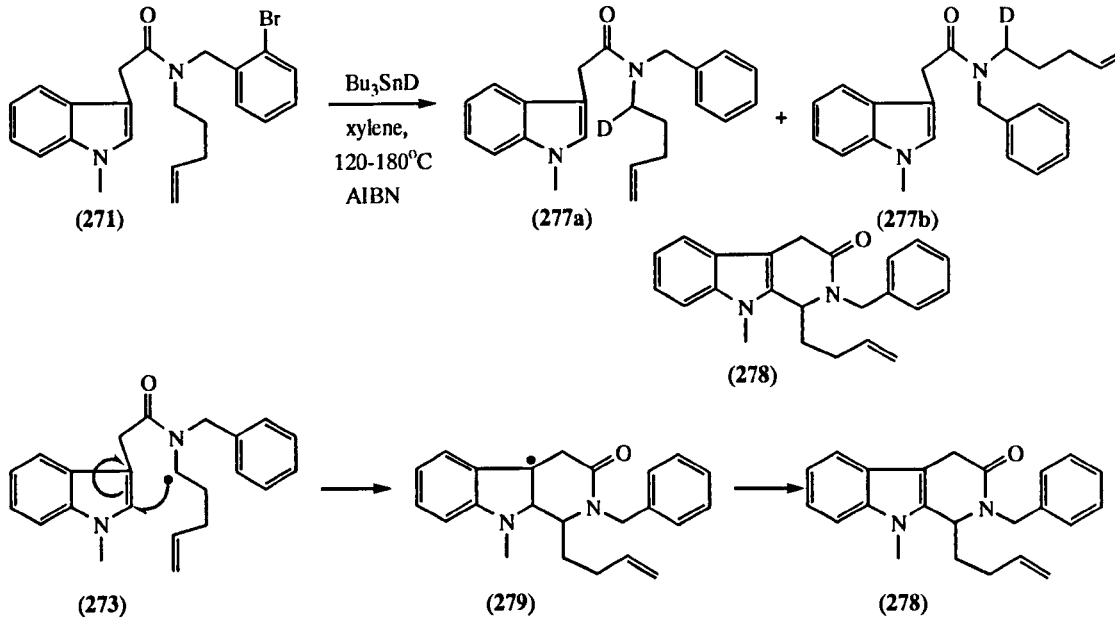
Minor (**271a**) Major (**271b**)

Scheme 68

The minor amide rotamer (**271a**) possesses the correct conformation for radical cyclisation following 1,5-hydrogen atom abstraction. The major rotamer (**271b**) can only lead to reduced product as the radical generated following 1,5-hydrogen atom abstraction is too far away to cyclise into the indole ring and rotation around the amide bond will not occur during the radical lifetime.

As a result of this, the radical cyclisation was carried out in xylene to try and overcome the energy barrier for interconversion of the two amide rotamers (**271a**) and (**271b**). Azo-bis-isobutyronitrile was used as the radical initiator and tri-*n*-butyltin deuteride used in place of tri-*n*-butyltin hydride in order to follow the course of the reaction.

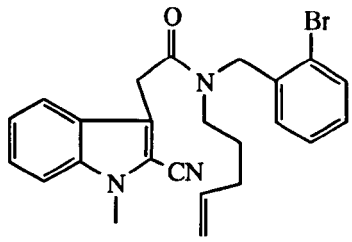
Two products were isolated from the reaction with none of the desired tetracyclic structure (**276**) obtained. The major product (**277**) arose as a result of a 1,5-hydrogen atom transfer, followed by reduction of the resultant radical with tri-*n*-butyltin deuteride and was obtained as a mixture of two amide rotamers. The minor product (**278**) was obtained *via* a 1,5-hydrogen atom abstraction followed by a 6-*endo*-trig cyclisation to give the tricyclic structure (**279**) and subsequent re-aromatisation of the resultant radical (**279**) (scheme 69).[192,193]



Scheme 69

As a result of the failure of the initial cyclisation carried out by Ho, one aim of the project is to solve the problems associated with this cyclisation. We need to be able to distinguish between the C-2 and C-3 positions of the indole ring and direct radical addition exclusively to the C-3, thus favouring the 5-*exo*-trig cyclisation over the observed 6-*endo*-trig cyclisation.

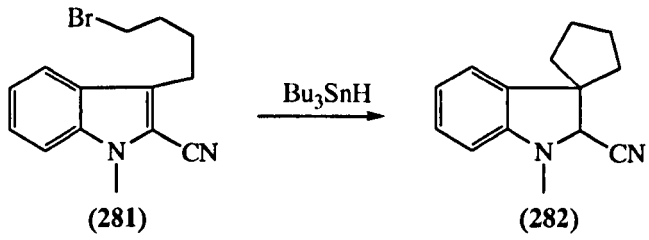
One way to achieve this is to add an electron-withdrawing group at C-2 of the indole (figure 11). This would have three effects: (i) reduce the electron density at C-3 to favour addition of the nucleophilic radical, (ii) stabilise the resulting radical, (iii) sterically block addition to C-2.



(280)

Figure 11

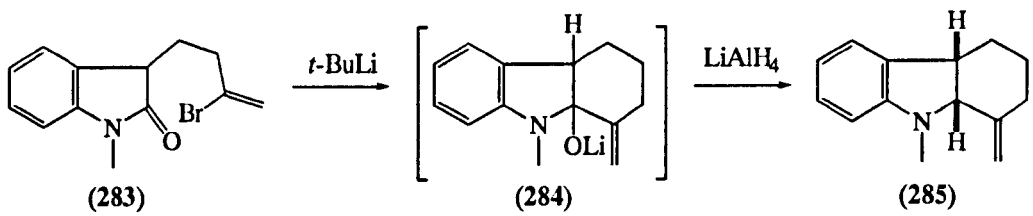
The resultant radical would then be stabilised by both the nitrogen and the cyano group in a captodative manner. This stabilised radical should now undergo the 6-*exo*-trig cyclisation that we require to give the desired tetracyclic structure. Nucleophilic radical cyclisations at the 3-position of 2-cyano-3-substituted indoles (**281**) have been reported by Fang to give spiro-annelated indolines (**282**) as shown below (scheme 70).[194] One aim of this project is therefore to incorporate the cyano group into the 2-position of the previous cyclisation precursor (**271**) and to investigate its effect on the cyclisation.



(281) (282)

Scheme 70

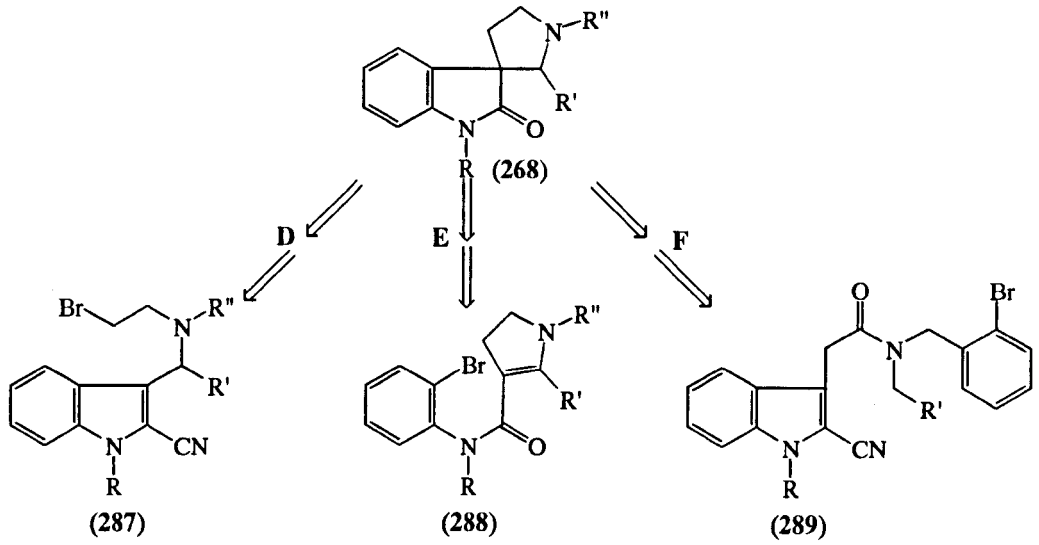
Disconnection A of tetracycle (**267**) (scheme 66) leads back to spirooxindole (**268**) with a pendant substituted alkyl component. Several groups have achieved the conversion of structures such as these to tetracyclic intermediates.[40,41] Within our group, work by McCarthy has shown that intramolecular addition of organolithiums to oxindoles can give rise to the C ring of the tetracycle (**267**). The oxindole bromide (**283**), on treatment with *tert*-butyl lithium followed by lithium aluminium hydride, gave rise to the hexahydrocarbazole (**285**) in 85% yield (scheme 71).[195]



(283) (284) (285)

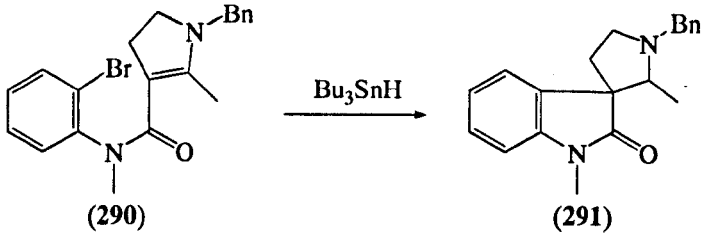
Scheme 71

The spiropyrrolidinyloxindole (**268**) can also be disconnected to give three radical cyclisation precursors (**287**), (**288**) and (**289**) as shown below (scheme 72).



Scheme 72

Disconnection D is an extension and simplification of the cyclisation of radical precursor (**270**) (scheme 66) and is discussed in detail in chapter 7. Disconnection E to give compound (**288**) has been explored within our group previously by McCarthy and Wilkinson.[196,197] Cyclisation of (**290**) only gave low yields of oxindole (**291**) and as a result further investigations were abandoned (scheme 73).[196]



Scheme 73

Disconnection F to give radical cyclisation precursor (**289**) allows the indole ring to remain intact and will allow us to explore the effect of the cyano group in the formation of spiropyrrolidinyl oxindoles. Simple members such as (**289**) would also allow us to gain some insight into the potential disconnection route C (scheme 66) whereby a pendant alkenyl group in place of R would allow us to form the tetracyclic structure in one single step. We aim, therefore, to investigate this cyclisation and extend it towards the spiropyrrolidinyloxindole alkaloids.

Chapter 4

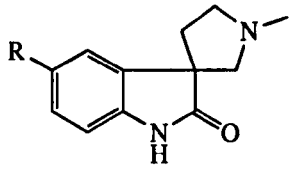
An Approach Towards the Tricyclic Core of the Spiropyrrolidinyl Oxindole Alkaloids (Disconnection F)

4.1 Introduction

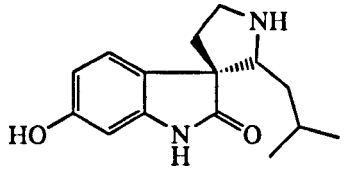
As a result of the failure to form the tetracyclic structure (**276**) (chapter 3, scheme 67), we decided to investigate the cyclisation in a stepwise manner. The essential elements to a successful outcome of the reaction were: (i) 1,5-hydrogen atom abstraction; (ii) 5-*exo*-trig cyclisation and (iii) a 6-*exo*-trig cyclisation.

The initial cyclisation by Ho had shown that 1,5-hydrogen atom abstraction was successful to some degree but the subsequent 5-*exo*-trig cyclisation had failed.[192] We therefore chose to investigate this subsequent step as it would allow us an insight into this reaction and would also allow us to synthesise a range of the core structures of the spiropyrrolidinyl oxindole alkaloids (disconnection F, chapter 3, scheme 72) of which increasing numbers are being discovered.

The spiropyrrolidinyl oxindole alkaloids present a wide range of structural complexity, from the relatively simple members such as horsfiline[198] (**292**), coerulescine[199] (**293**) and elacomine (**294**) (figure 12) through to the more complex structures such as alstonisine (**295**) (figure 13).[200] Spirotryprostatin A (**296**) has been recently isolated and has been shown to inhibit the cell cycle, showing potential as an antineoplastic agent (figure 13).[201] Danishefsky has recently shown that unnatural analogues of spirotryprostatin act as inhibitors of human breast cancer cell lines.[202]

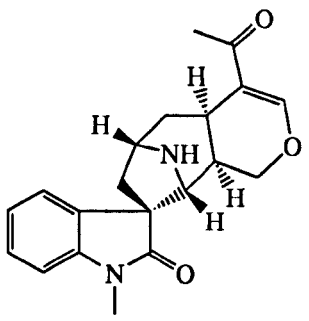


R = OMe Horsfiline (**292**)
R = H Coerulescine (**293**)

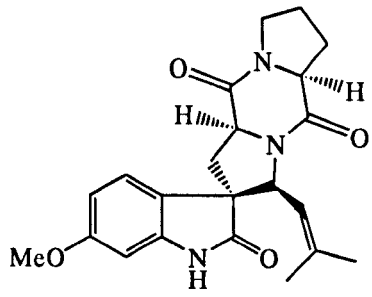


Elacomine (**294**)

Figure 12



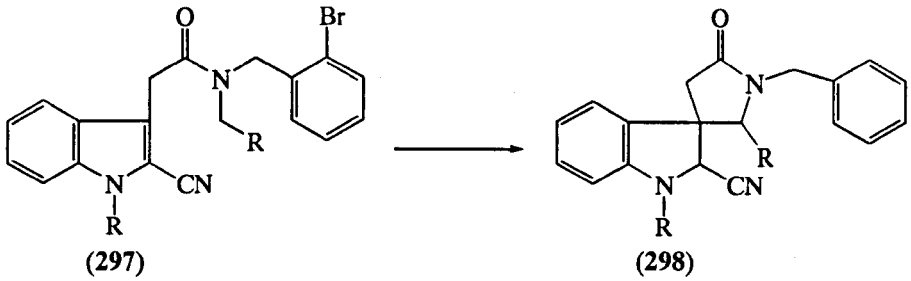
Alstonisine (**295**)



Spirotryprostatin A (**296**)

Figure 13

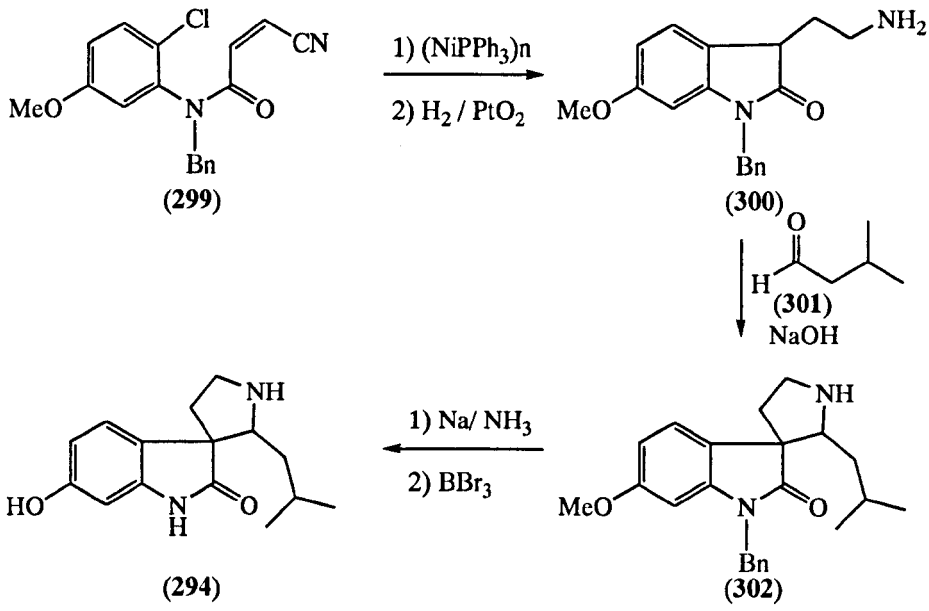
Elacomine (**294**) possesses a simple pendant alkyl group on the pyrrolidine ring and as such would be an ideal target structure for our chemistry. Cyclisation of the radical cyclisation precursor (**297**) would enable formation of the core structure (**298**) of elacomine and would enable formation of various analogues of its structure (scheme 74).



(**297**) (**298**)

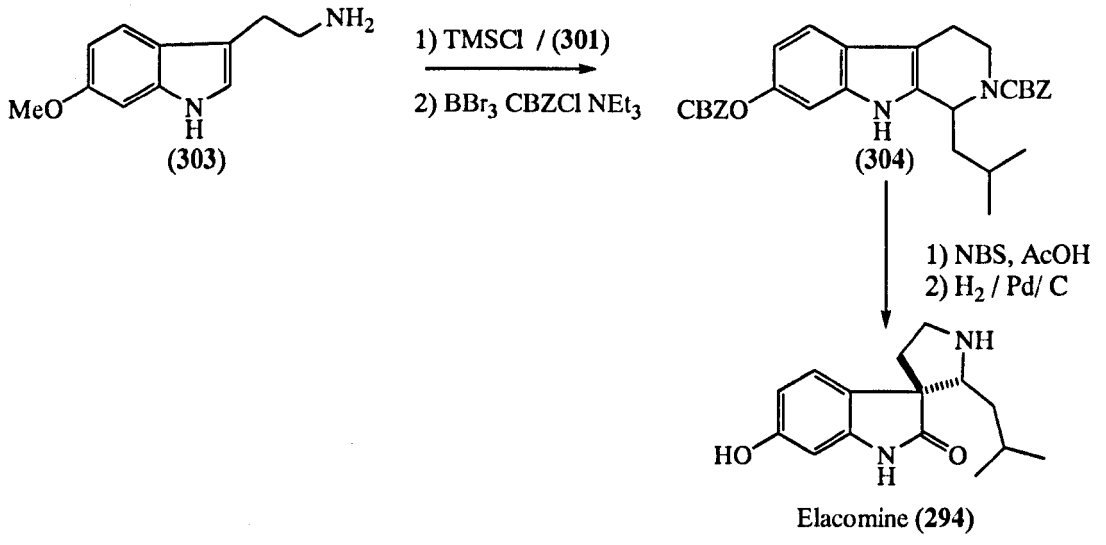
Scheme 74

James and Williams first determined the structure of elacomine in 1972.[203] Since then, there have been only two reported syntheses. The first synthesis, reported by Ban in 1978, focused on a 5-*exo*-trig cyclisation of the unsaturated anilide (**299**) using a nickel (0) complex.[204] Reduction of the resultant nitrile followed by reaction with 3-methyl-butanal (**301**) gave the spiropyrrolidinyl oxindole skeleton (**302**). This was then deprotected following treatment with sodium/liquid ammonia and then boron tribromide to give the natural product (**294**) in 6% overall yield (scheme 75).



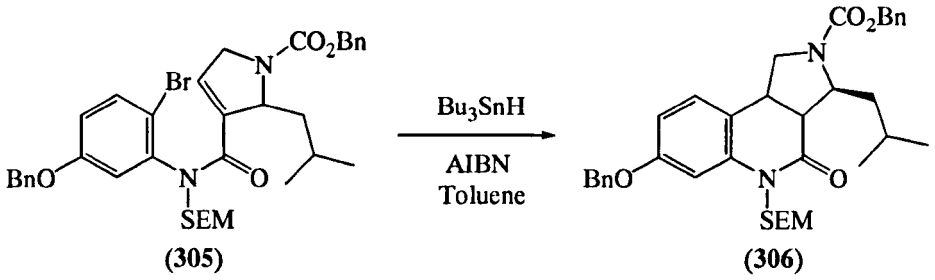
Scheme 75

Borschberg has reported a more recent synthesis of elacomine in five steps starting from 6-methoxytryptamine (**303**).[205] Pictet-Spengler condensation of 6-methoxytryptamine (**303**) and 3-methylbutanal (**301**) gave the racemic β-carboline in 44% yield. Deprotection and re-protection of the ether and piperidine nitrogen gave (**304**) an intermediate, which underwent oxidative rearrangement on treatment with aqueous *N*-bromosuccinimide. Deprotection *via* hydrogenolysis of the two CBZ groups gave elacomine (**294**) and isoelacomine in 16% and 8% overall yields respectively (scheme 76). Borschberg also achieved an enantioselective synthesis of (+)-elacomine (**294**) and (-)-isoelacomine starting from L-tryptophan using an alternative route.



Scheme 76

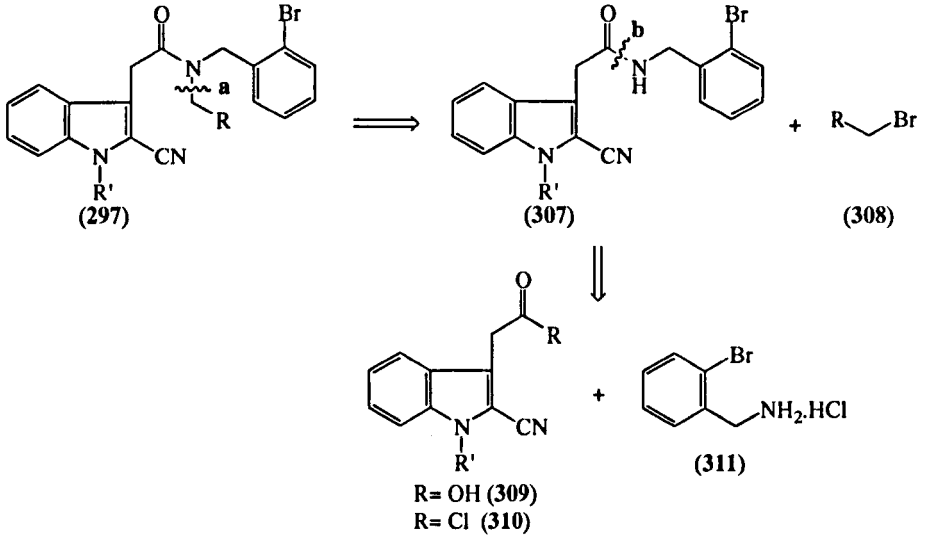
Previous work in our group focused on an aryl radical cyclisation approach to elacomine (**294**). However, attempted cyclisation of radical precursor (**305**) only gave the 6-*endo*-trig cyclisation product (**306**) with none of the expected 5-*exo*-trig product being obtained (scheme 77).[192]



Scheme 77

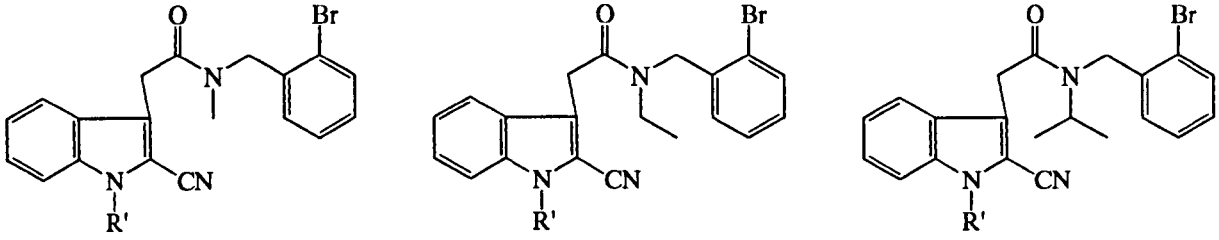
4.2 Synthetic Approach

Our approach to the cyclisation precursor (**297**) to generate alkaloids such as elacomine (**294**) is based on disconnection F (scheme 72, chapter 3) and is outlined below (scheme 78). We believed that the alkyl chain on the amidic nitrogen could be introduced under basic conditions (disconnection a). The secondary amide could be formed from coupling the acid (**309**) or acid chloride (**310**) with 2-bromobenzylamine hydrochloride (**311**) (disconnection b).



Scheme 78

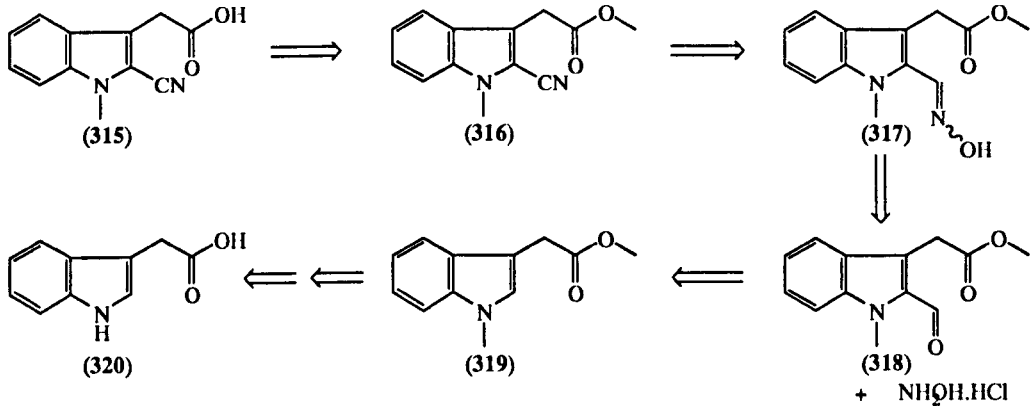
The introduction of the alkyl group on the nitrogen in the last step of the synthesis also allows for an increased diversity of compounds. As we wanted to investigate the nature of the cyclisation step, we chose to incorporate a methyl, ethyl and isopropyl group on the amidic nitrogen to give cyclisation precursors (**312**), (**313**) and (**314**) respectively (figure 14). The use of these groups would allow us to investigate the effect of changing the type of H-atom abstracted. We predicted that increasing the stability of the radical would result in increased yields of cyclised product, as the 1,5-translocation step would be more efficient and the resultant radical would have a longer lifetime.



(312) (313) (314)

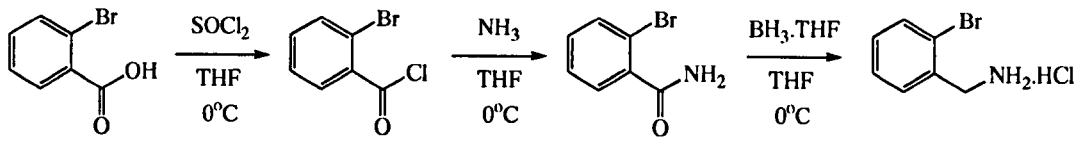
Figure 14

The synthesis of the required acid chloride (**310**) or acid (**309**) posed several problems due to the need to incorporate the cyano group at the 2-position. Our synthetic route is outlined below (scheme 79). The key feature is introduction of the cyano group by formylation at C-2, oxime formation and dehydration.



Scheme 79

The required 2-bromobenzylaminehydrochloride (**311**) was synthesised in three steps from commercially available 2-bromobenzoic acid (**321**) as shown below (scheme 80).

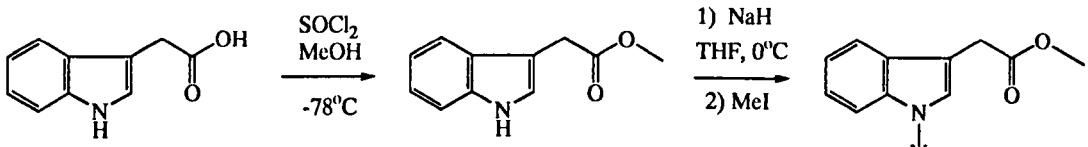


(321) (322) (323) (311)

Scheme 80

Formation of the acid chloride (**322**) proceeded smoothly using thionyl chloride and quenching with concentrated aqueous ammonia in THF gave amide (**323**) in 96% yield. Borane reduction furnished the amine, which was isolated as its hydrochloride salt (**311**) in 65% yield. The melting point was in good agreement with the literature value.

The synthesis of indole ester (**319**) was achieved in two steps, as outlined below (scheme 81), in good yield starting from indole-3-acetic acid (**320**).



(320) (324) (319)

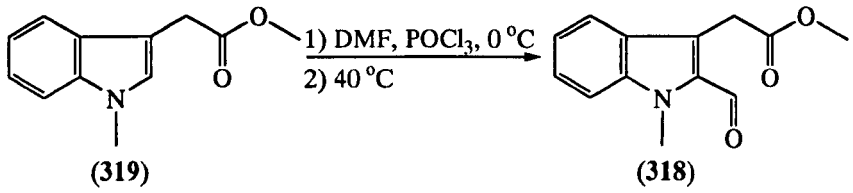
Scheme 81

Addition of thionyl chloride to a solution of indole-3-acetic acid in methanol at –78 °C gave indole-3-acetic acid methyl ester (**324**) in 98% yield. Simple removal of the solvent following the reaction gave a red oil that solidified on standing, which was consistent with the literature. However, careful distillation of this solid at reduced pressure gave a colourless oil which solidified on standing to give a white solid. It was found that the distilled product gave more consistent yields of subsequent reactions even though the crude product was pure by ^{1}H NMR spectroscopy.

Methylation of indole-3-acetic acid methyl ester (**324**) using sodium hydride in tetrahydrofuran with methyl iodide at 0 °C gave *N*-methyl-indole-3-acetic acid methyl ester (**319**) in 92% yield.

The next step of the synthesis was the incorporation of functionality at the 2-position of the protected indole (**319**). Following standard Vilsmeier conditions, a solution of ester (**319**) was added to the pre-prepared Vilsmeier reagent at 0 °C in DMF (scheme 82).

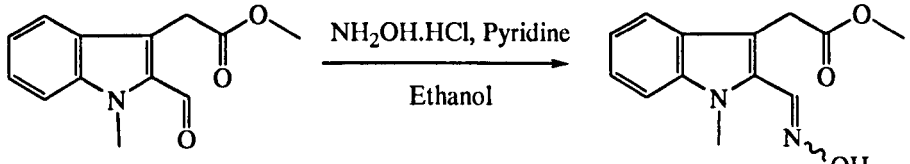
After workup and distillation of the crude product, 48% of the aldehyde (**318**) was obtained. When carried out on a much smaller scale with purification by gradient elution column chromatography, we were able to obtain the product in 67% yield. The formyl group was readily observable as a singlet integrating for one proton at δ 10.17 ppm in the ^{1}H NMR spectrum.



(319) (318)

Scheme 82

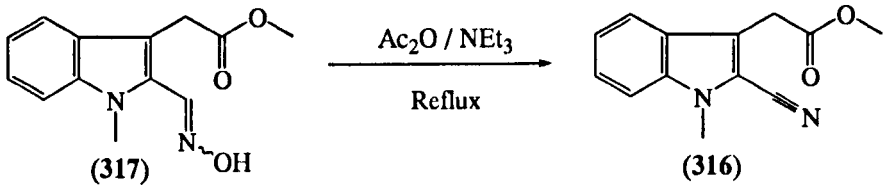
Reaction of the aldehyde (**318**) with hydroxylamine hydrochloride in ethanol and pyridine (scheme 83) gave the oxime (**317**) in 99% yield. The loss of the aldehyde proton and the appearance of a singlet at δ 8.46 ppm along with a broad peak at δ 8.58 ppm confirmed that the aldehyde (**318**) had been successfully converted to the oxime (**317**).



(318) (317)

Scheme 83

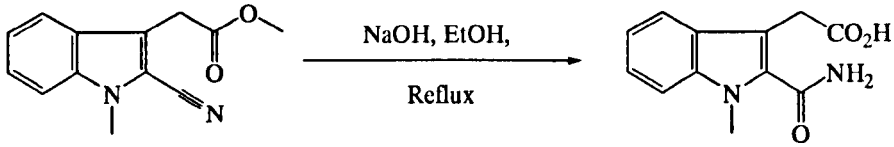
The key 2-cyanoindole ester (**316**) was synthesised in 73% yield by reaction of the oxime (**317**) with excess acetic anhydride and triethylamine (scheme 84). The cyano-group was readily observed in the infrared spectrum of (**316**) at ν_{max} 2220.2 cm^{-1}. The loss of the proton signals for the oxime (**317**) were readily observed, along with the appearance of a signal for a quaternary carbon in the ^{13}C NMR spectrum at δ 112.91 ppm which was assigned to the carbon of the cyano group.



(317) (316)

Scheme 84

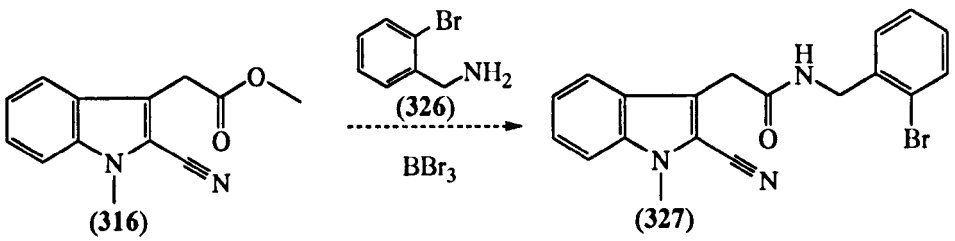
Hydrolysis of the methyl ester proved problematic. Basic hydrolysis using sodium hydroxide in ethanol, followed by an acidic work-up, yielded the amide (**325**) in 63% yield (scheme 85). Hydrolysis of the ester had been achieved, but concomitant hydrolysis of the nitrile to the amide had occurred. The ^{13}C NMR spectrum showed two carbonyl peaks at δ 163.40 and δ 173.27 ppm indicative of the formation of the amide (**325**). We attempted to modify the conditions by carrying out the hydrolysis at room and low temperature, but to no avail. In all cases there was no evidence for the formation of the desired nitrile (**315**).



(316) (325)

Scheme 85

In the light of these problems we next investigated a procedure by Yazawa, whereby he had succeeded in converting carboxylic esters to the corresponding amides after treatment with boron tribromide and an amine.[206] Following Yazawa's procedure, a solution of ester (**316**) was treated with a solution of boron tribromide. The reaction required the free amine (**326**) of 2-bromobenzylamine hydrochloride, which was prepared by addition of 1.1 equivalents of triethylamine to a solution of the hydrochloride salt (**311**). Addition of this solution of 2-bromobenzylamine to the ester (**316**) failed to furnish any of the desired amide (**327**) (scheme 86) and only starting material was recovered.

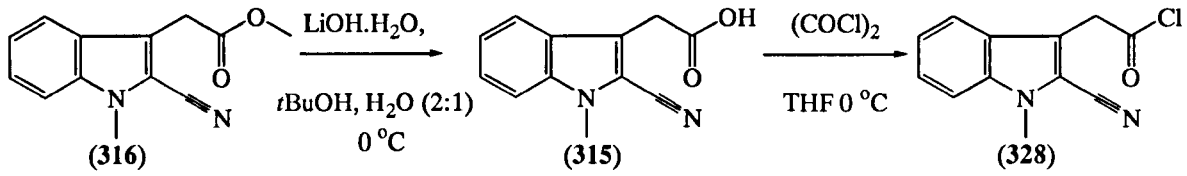


(316) (327)

Scheme 86

As a result of this failure, we decided to repeat our attempts to hydrolyse the ester (**316**), using a very mild procedure published by Boger.[207] Treatment of a suspension of the

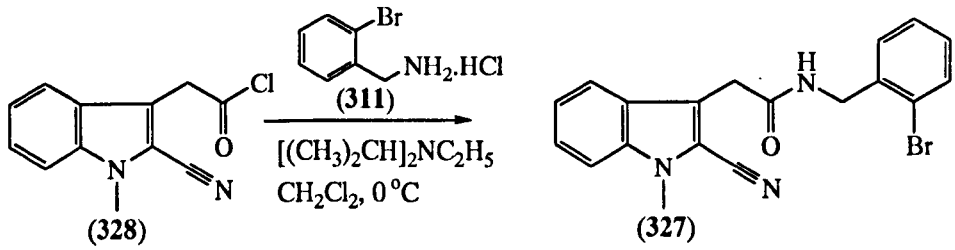
ester (**316**) in a *t*-butanol/ water mixture with lithium hydroxide resulted in the required 2-cyano-indole acetic acid (**315**) in almost quantitative yield with no observed hydrolysis of the nitrile (scheme 87). The quaternary carbon of the nitrile was clearly visible in the ^{13}C NMR spectrum at δ 112.91 ppm.



Scheme 87

Treatment of the resultant acid (**315**) with oxalyl chloride in tetrahydrofuran gave 2-cyano-1-methyl-1*H*-indole-3-acetyl chloride (**328**) (scheme 87), which was used immediately in the reaction with 2-bromobenzylamine hydrochloride (**311**).

Reaction of the acid chloride (**328**) with 2-bromobenzylamine hydrochloride (**311**) in the presence of the non-nucleophilic Hünig's base, resulted in the formation of the desired secondary amide (**327**) in 93% yield (scheme 88). The amidic carbonyl stretch was visible in the infra-red spectrum at ν_{max} 1646.6 cm^{-1} along with the cyano group at ν_{max} 2219.9 cm^{-1}. In the ^1H NMR spectrum, a doublet was observed at δ 4.32 ppm that integrated for two protons and was assigned as the benzylic CH_2. This doublet was clearly coupled to the amidic NH at δ 8.75 ppm, which integrated for one proton.

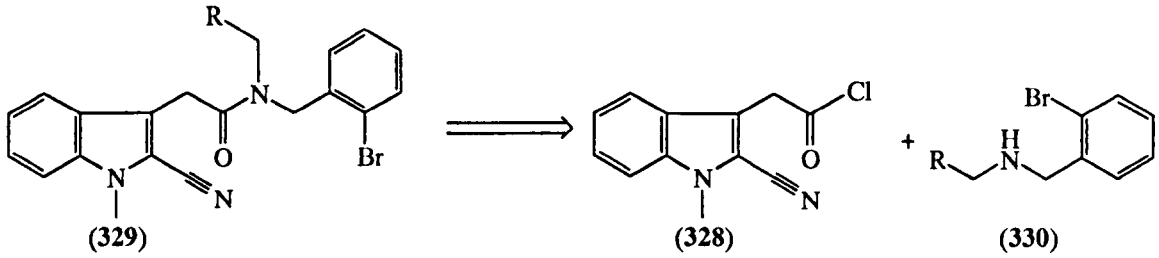


Scheme 88

Incorporation of the alkyl group on the nitrogen was attempted using potassium hydride as a base and methyl iodide as the alkylation agent, at –10 °C in tetrahydrofuran. Unfortunately none of the required tertiary amide could be isolated from the reaction

mixture. The only isolable products appeared not to contain the nitrile functionality and had been alkylated α- to the amidic carbonyl.

As a result of the problems associated with the alkylation of the secondary amide (**327**), an alternative route was required to effect the synthesis of the tertiary amides (figure 14). An alternative disconnection of the tertiary amide (**329**) leads back to the previously prepared acid chloride (**328**) and a secondary amine (**330**) (scheme 89).



Scheme 89

The reaction of a secondary amine (**330**) as opposed to a primary amine (**311**), with the acid chloride (**328**), does not appear to present any problems. However, it reduces the flexibility envisaged in the earlier disconnection (scheme 78) and thus necessitates an efficient approach to the synthesis of the secondary amines that we require.

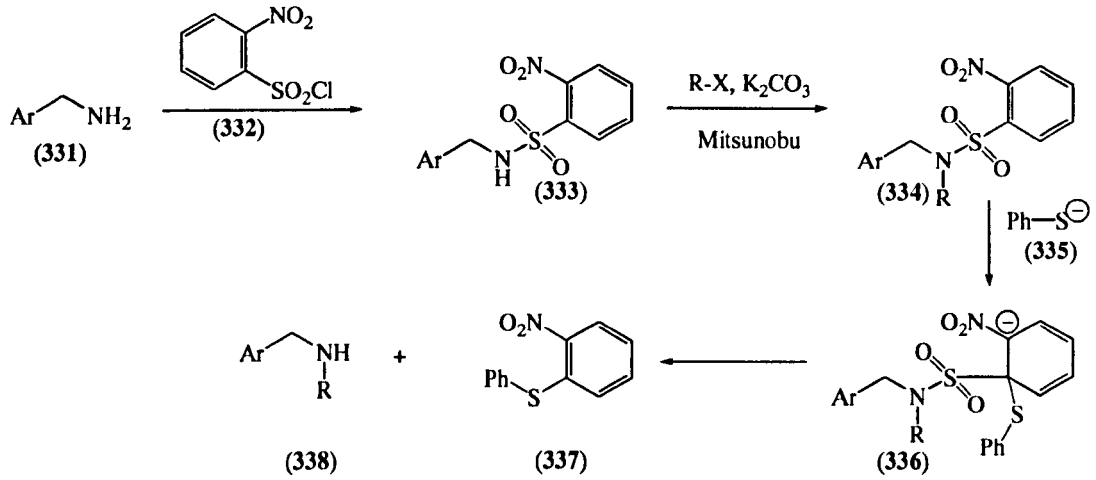
4.2.1 Synthetic Approaches Towards Secondary Amines

The conversion of primary amines to secondary amines is not as straightforward as it would immediately appear. Simple alkylation of primary amines is often a problem as the formation of the tertiary amine and the quaternary ammonium salt accompanies formation of the secondary amine. This indeed proved to be the case. Our attempted alkylation of 2-bromobenzylamine hydrochloride (**311**) resulted in the formation of the secondary amine along with the tertiary amine, which proved troublesome to separate.

Alternative strategies would be to carry out either a reductive amination with the corresponding aldehyde or to synthesise the corresponding amide and reduce the amidic carbonyl group as in the synthesis of 2-bromobenzylamine hydrochloride (**311**). The problem with the first route relates to the availability of the starting materials.

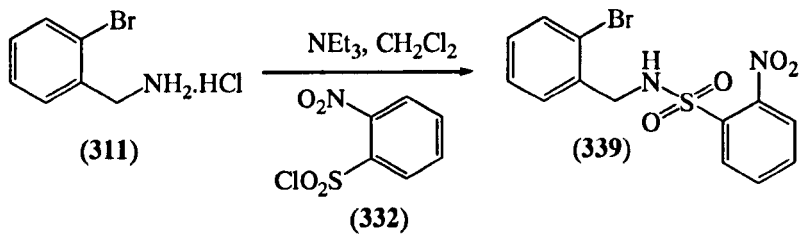
Acylation reactions do not always yield the mono-acylated products and often, double acylation can occur.

However, sulfonamides are readily prepared and readily react with base and a range of alkyl halides. They have also been shown to react under modified Mitsunobu conditions.[208,209,210] The key problem associated with sulfonamides is the removal of the sulfonyl group afterwards. Fukuyama, followed by Bowman, utilised the 2-nitrobenzenesulfonamide protecting group in the formation of a range of secondary amines.[211,212] Fukuyama demonstrated that the primary sulfonamide can be formed in excellent yields and can then be alkylated either under basic or Mitsunobu conditions.[211] He also demonstrated the facile removal of the protecting group using thiophenol and potassium carbonate (scheme 90). Deprotection proceeds *via ipso*-attack of the thiophenol anion in a S_NAr manner with extrusion of sulfur dioxide.



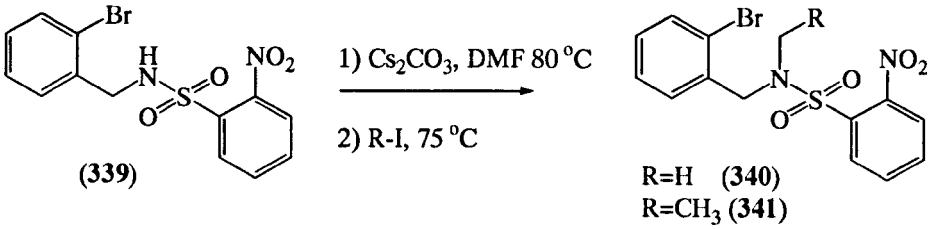
Scheme 90

Following Bowman's procedure,[212] we reacted 2-bromobenzylamine hydrochloride **(311)** with 2-nitrobenzenesulfonyl chloride **(332)** in the presence of three equivalents of triethylamine and obtained *N*-(2-bromobenzyl)-2-nitrobenzenesulfonamide **(339)** as a white crystalline solid in 89% yield (scheme 91). The reaction could be carried out on 100 g of 2-bromobenzylamine hydrochloride **(311)** with no appreciable loss of yield.



Scheme 91

Treatment of the sulfonamide (**339**) with caesium carbonate in DMF at 80 °C, followed by addition of methyl iodide led to the tertiary sulfonamide (**340**) in almost quantitative yield. Similarly, reaction with ethyl iodide also led to an almost quantitative yield of the *N*-ethyl tertiary sulfonamide (**341**) (scheme 92).

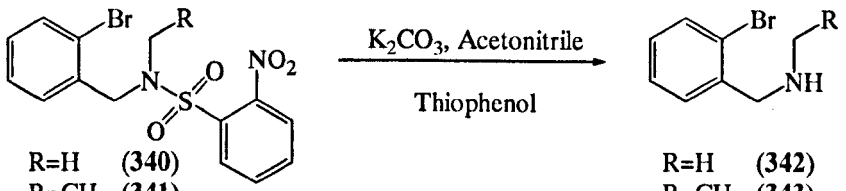


(**339**)

R=H (**340**)
R=CH_3 (**341**)

Scheme 92

Addition of thiophenol to a stirred suspension/ solution of the *N*-methyl tertiary sulfonamide (**340**) and potassium carbonate in acetonitrile, led to a bright yellow solution. Following work up, 2-bromobenzylmethylamine (**342**) was isolated as a colourless oil in 85% yield (scheme 93). Deprotection of the *N*-ethylsulfonamide (**341**) was also successful, with 2-bromobenzylethylamine (**343**) obtained in 77% yield (scheme 93).

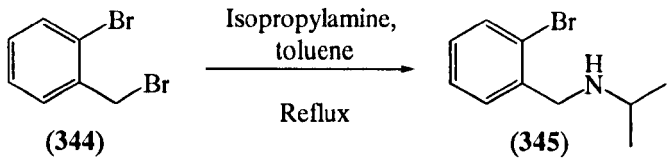


R=H (**340**)
R=CH_3 (**341**)

R=H (**342**)
R=CH_3 (**343**)

Scheme 93

In order to synthesise the secondary amine that was needed to form the cyclisation precursor (**314**), we needed to synthesise 2-bromobenzylisopropylamine (**345**). The secondary amine (**345**) was generated following a procedure by Glover, who reacted a range of amines *via* an S_N2 reaction with 2-bromobenzyl bromide (**344**).[213] Rapid addition of a ten-fold excess of isopropylamine to a solution of 2-bromobenzyl bromide (**344**), led to the formation of 2-bromobenzyl isopropylamine (**345**) in virtually quantitative yield (scheme 94).



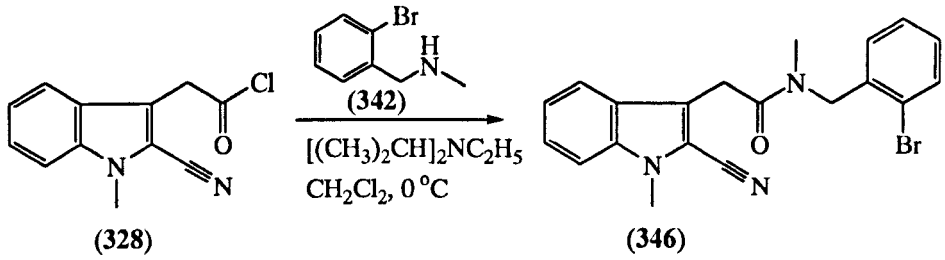
(344) (345)

Scheme 94

Having the desired secondary amines in hand, we were now in a position to react these with the acid chloride (**328**), to generate the three radical cyclisation precursors.

4.3 Synthesis of the Radical Cyclisation Precursors

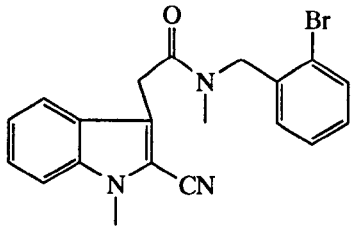
The initial reaction between the acid chloride (**328**) and 2-bromobenzylamine hydrochloride (**311**) was successful. We therefore decided to repeat the reaction using the three secondary amines in place of 2-bromobenzylamine hydrochloride (**311**). Addition of a solution of freshly prepared acid chloride (**328**) to 2-bromobenzylmethylamine (**342**) in the presence of Hünig's base, resulted in the formation of the *N*-methyl cyclisation precursor (**346**) in 84% yield (scheme 95).



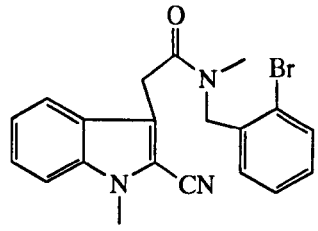
(328) (346)

Scheme 95

The cyclisation precursor was obtained as a 1:1 mixture of amide rotamers (**346a**) and (**346b**). The ratio was determined from the integration of the peaks observed in the ^{1}H NMR spectrum. Two singlets at δ 3.54 and δ 3.69 ppm integrating for three protons each were assigned to the pendant methyl group on the indole nitrogen. The integration of these two was equal (figure 15).



(346a)

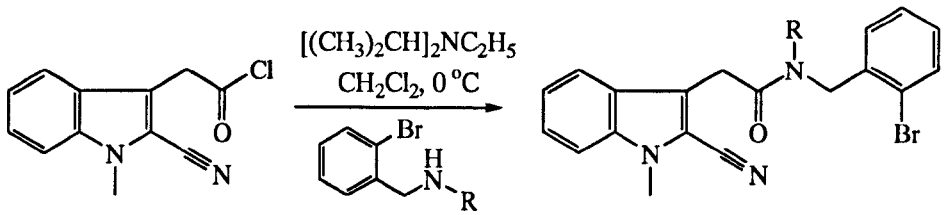


(346b)

Figure 15

In order to determine which amide rotamer is the one that cyclises, it is necessary to look at the signals for the benzylic CH_2 protons and the amidic *N*-methyl protons. The benzylic CH_2 signals appear at δ 4.54 ppm and δ 4.60 ppm, with the amidic *N*-methyl signals at δ 2.88 ppm and δ 2.95 ppm. In the rotamer (**346a**), the benzylic CH_2 protons are *cis* to the amidic carbonyl and will thus be shifted downfield at δ 4.60 ppm when compared to the other amide rotamer (**346b**) at δ 4.54 ppm. Similarly the *N*-methyl protons in (**346a**) are *trans* to the amidic carbonyl and at δ 2.88 ppm are upfield compared to the other amide rotamer (**346b**) where the *cis* amidic *N*-methyl protons are at δ 2.95 ppm.

Repeating the conditions used in the synthesis of the *N*-methyl cyclisation precursor (**346**), the *N*-ethyl (**348**) and *N*-isopropyl (**347**) cyclisation precursors were synthesised in yields of 90% and 65% respectively (scheme 96).



(328)

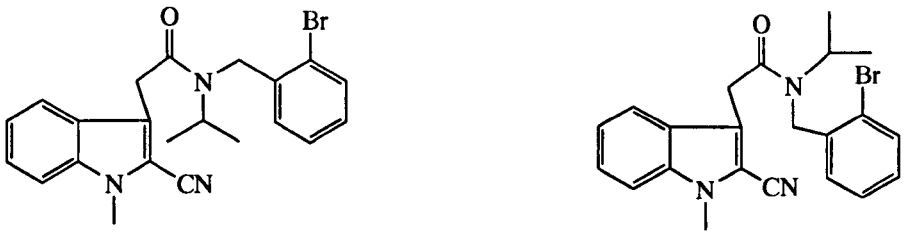
R= *i*Pr (**345**)
R= Et (**343**)

R= *i*Pr (**347**)
R= Et (**348**)

Scheme 96

The *N*-ethyl cyclisation precursor (**348**) was obtained as a 1:1 mixture of amide rotamers, whilst the *N*-isopropyl cyclisation precursor (**347**) was obtained in a 1:1.3 rotamer ratio. The minor *N*-isopropyl amide rotamer (**347a**), is the one that is required

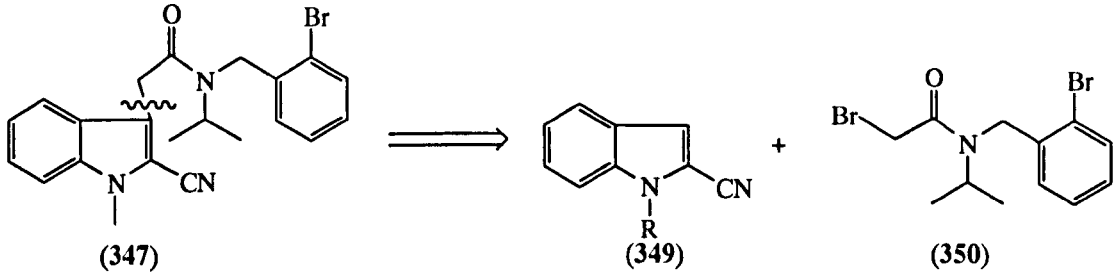
for cyclisation, whilst the major one (**347b**) is in the wrong conformation for cyclisation (figure 16).



Minor (**347a**) Major (**347b**)

Figure 16

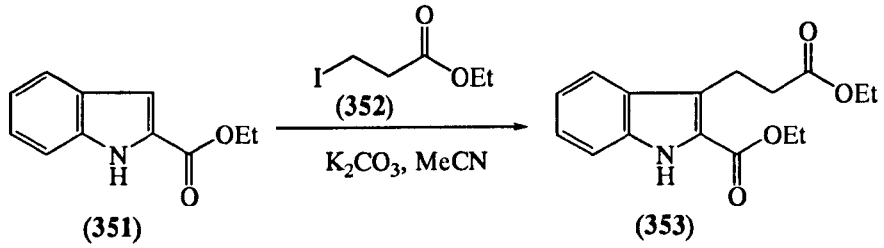
The lower yield obtained in the formation of the *N*-isopropyl cyclisation precursor (**347**) is probably due to the increased steric bulk of the secondary amine (**345**). We therefore decided to investigate an alternative synthetic route to the cyclisation precursor (**347**). An alternative disconnection to the *N*-isopropyl cyclisation precursor (**347**) is outlined below (scheme 97).



(**347**) (**349**) (**350**)

Scheme 97

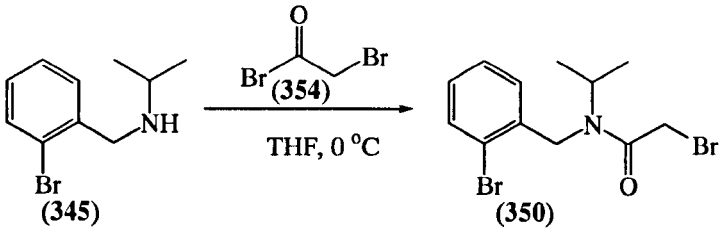
The precedent for this was based on work carried out by Gray.[214] Treatment of ethyl 2-indole carboxylate (**351**) with potassium carbonate and ethyl 3-iodopropanoate (**352**) was reported to generate the 3-alkyl indole (**353**) (scheme 98).



(**351**) (**352**) (**353**)

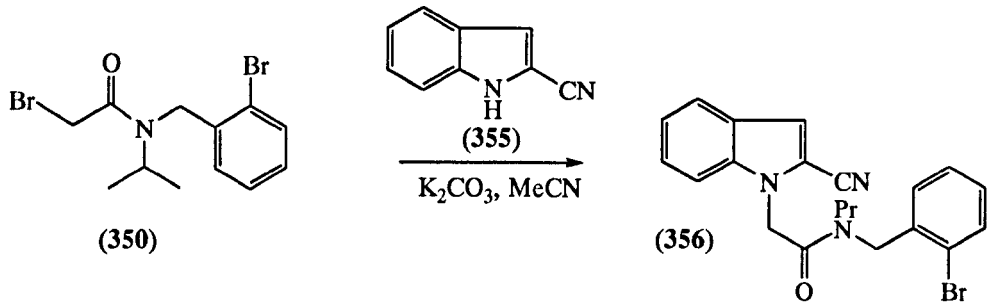
Scheme 98

Following Gray's work, we synthesised *N*-isopropyl-bromoacetamide (**350**) in 87% yield by reaction of 2-bromobenzylisopropylamine (**345**) with bromoacetyl bromide (**354**) in the presence of triethylamine (scheme 99).



Scheme 99

The tertiary amide (**350**) was obtained as 1:1.3 mixture of amide rotamers. We predicted that reaction of 2-cyanoindole (**355**) (chapter 7) in place of ethyl 2-indole carboxylate (**351**) would not pose a problem as both compounds contain electron-withdrawing groups of similar magnitude. Reaction of 2-cyanoindole (**355**) with the tertiary amide (**350**) in the presence of potassium carbonate, resulted in the formation of the *N*-alkylated compound (**356**) in place of the required *C*-alkylated precursor (**347**) (scheme 100). No evidence for *C*-alkylation was observed.



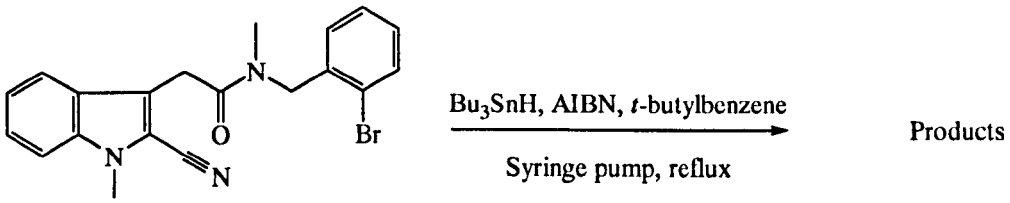
Scheme 100

As a result of this failure, we carefully analysed the data provided by Gray[214] and discovered that he had recorded five protons in the aromatic region, which is consistent with *N*-alkylation as opposed to the claimed *C*-alkylation. This concurs with previous reports in the literature on *N*-versus *C*-alkylation of indole.[215,216,217,218] When potassium is used as the counter ion, the proportion of *N*-alkylation is relatively high.[215] Changing the counter ion to lithium or magnesium bromide and changing the solvent to toluene has been demonstrated to increase the ratio of *C*-alkylation of indole. However, as we

had already prepared the *N*-isopropyl cyclisation precursor (**347**) albeit in a moderate yield, we chose to discontinue this alternative synthetic route.

4.4 Tandem Radical Cyclisation of the *N*-Methyl Cyclisation Precursor

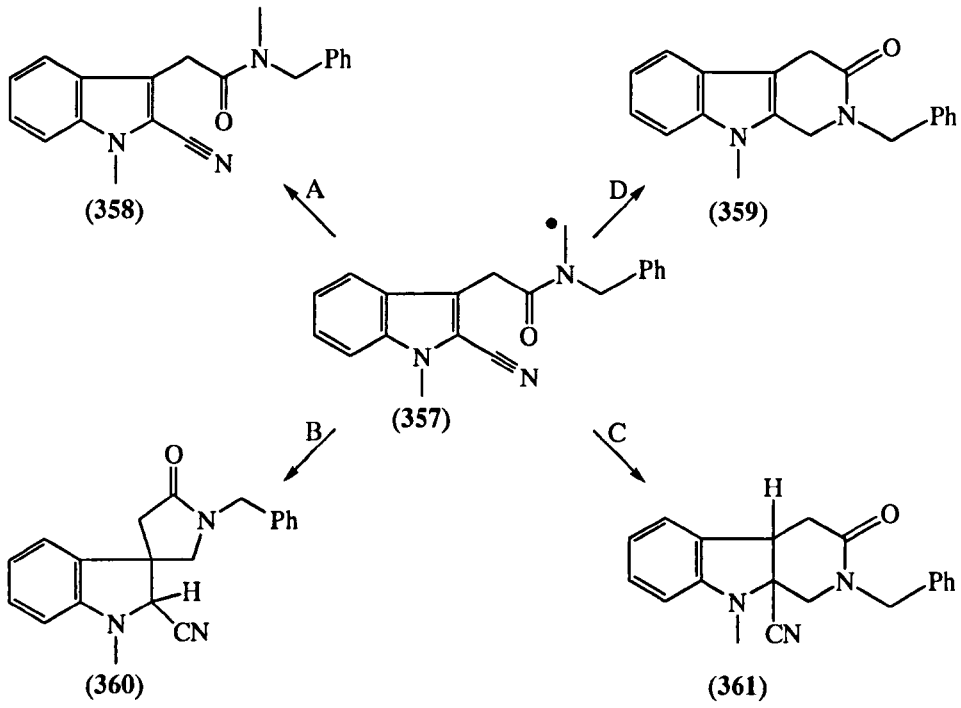
Following the initial work undertaken by Ho,[192] we decided to carry out the radical cyclisations at higher temperatures than is typical for radical reactions, in order to try to overcome the amide rotamer problem. As such, we decided to use *t*-butylbenzene as solvent, which boils at 170 °C. Following syringe pump addition over 3.5 hours of a *t*-butylbenzene solution of tri-*n*-butyltin hydride and a sub-stoichiometric amount of AIBN to a solution of the *N*-methyl cyclisation precursor (**346**) at 170 °C, three products of R_f 0.63, 0.35 and 0.26 (1: 1, hexane: ethyl acetate) were isolated (scheme 101).



(**346**)

Scheme 101

We had identified four potential products following tandem radical cyclisation of the *N*-methyl precursor (**346**) (scheme 102).



Scheme 102

The aryl radical generated from (**346**) should have undergone 1,5-hydrogen atom abstraction, as determined from the previous studies. The α-amidoyl radical (**357**) so formed could:

1) Abstract a hydrogen atom from tri-*n*-butyltin hydride to give the reduced product (**358**). (Route A)

2) Cyclise in a reductive 5-*exo*-trig manner to generate the desired cyclised product (**360**) as a mixture of two diastereoisomers. (Route B)

3) Cyclise in a reductive 6-*endo*-trig manner to give the tricyclic product (**361**). (Route C)

4) Cyclise in an oxidative 6-*endo*-trig manner to give the tricyclic indole (**359**) following elimination of H-CN. (Route D)

The product of R_f 0.63 appeared strikingly similar in appearance to the starting material in its ^{1}H NMR and ^{13}C NMR spectra. There were clearly two amide rotamers from the ^{1}H NMR in a 1: 1 rotamer ratio. In the ^{1}H NMR spectrum the amidic *N*-methyl could be seen at δ 2.86 ppm and δ 2.90 ppm. The cyano group was visible as a strong peak at

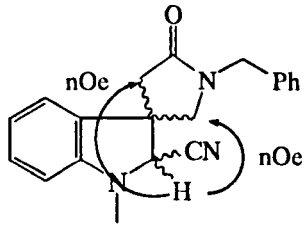
ν_{max} 2217.5 cm^{-1} in the infra-red. In the mass spectrum (ESI), the parent ion of 318.1606 was determined to be the M^++H ion, which, with the above data, indicated that this was the reduced product (**358**) (scheme 102). Confirmation that the compound was indeed reduced, came from the fact that there were nine aromatic hydrogens present in the ^1H NMR. The reduced product had therefore been formed in 62% yield.

The second product of R_f 0.35 was isolated in 44 mg quantity. In the ^1H NMR spectrum in the aliphatic region, there were three AB quartets integrating for two protons each. There was also a singlet at δ 2.77 ppm integrating for three protons, and at δ 4.01 ppm, which integrated for one proton. In the aromatic region, there were two triplets at δ 6.75 ppm and δ 7.12 ppm integrating for one proton each, along with two doublets, integrating for one proton each. There was also a multiplet at δ 7.17-7.26 ppm integrating for five protons. On the basis of this data, the product could be either the desired spirocyclic compound (**360**), arising from 5-*exo*-trig addition of the α-amidoyl radical, or it could be the product (**361**) arising from a 6-*endo*-trig addition of the α-amidoyl radical. However, the hydrogen β- to the cyano group in the 6-*endo*-trig product (**361**) would be expected to couple to the CH_2 next to the carbonyl. This was clearly not the case, indicating that we had indeed formed one of the diastereoisomers of our required cyclised product (**360**). Confirmation came from the ^{13}C NMR spectrum with a quaternary carbon at δ 48.13 ppm, which was assigned to the spirocyclic centre. The quaternary carbon for the nitrile was present at δ 115.47 ppm. The mass spectrum (ESI) showed a parent ion of 340.1424, indicative of M^++Na.

The third product of R_f 0.26 was isolated in 44 mg. The spectral features were very similar to the second product, in that there were three AB quartets and two singlets, one integrating for three protons and the other for one proton. The aromatic signals were also similar to the second compound. In the ^{13}C NMR spectrum, a quaternary carbon was again observed at δ 48.03 ppm, which was assigned as the spirocyclic C-3 centre of our required tricyclic product. The mass spectrum (ESI) of the compound showed a parent ion of 340.1424, indicative of the molecular ion plus sodium as for the previous compound.

The two products of R_f 0.35 and 0.26 appeared to be the two diastereoisomers of the cyclised product (**360**). They were also present in equal amounts. The indole aromatic protons had also shifted upfield in both compounds, which is indicative of cyclisation into indole having taken place. The two singlets integrating for one proton were assigned as the C-H next to the cyano group for each compound. The three AB quartets found in each molecule were also indicative of the formation of the spiropyrrolidinyl ring system.

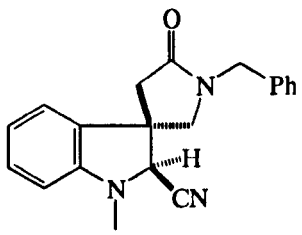
In order to determine the relative stereochemistry of each diastereoisomer, we decided to conduct nOe difference studies of each product. Irradiation of the methine proton next to the cyano group should provide an enhancement of either the methylene next to the carbonyl or the CH_2 next to the nitrogen (figure 17).



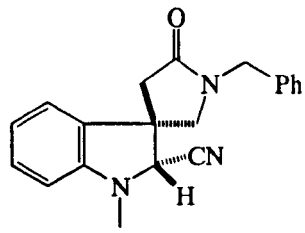
(360)

Figure 17

Irradiation of the ^1H NMR singlet at δ 4.01 ppm of the compound of R_f 0.35 under nOe difference conditions, brought about an enhancement of one half of the AB quartet of the CH_2 next to the nitrogen. We were therefore able to assign structure (**360a**) to the compound of R_f 0.35 (figure 18).



(360a)



(360b)

Figure 18

Irradiation of the C-H singlet at δ 4.07 ppm in the ^{1}H NMR spectrum of the compound of R_f 0.26 brought about an enhancement of one half of the AB quartet that was assigned to the CH_2 next to the carbonyl group. This must be the other diastereoisomer (**360b**).

In order to confirm the structures of the cyclised products and the nOe results, we were able to carry out a slow crystallisation of the diastereoisomer of R_f 0.35 (**360a**). An X-ray structure of this compound was obtained (figure 19) which confirmed that we had indeed formed the spiropyrrolidinyl ring system. The X-ray structure also confirmed the results of the nOe studies.

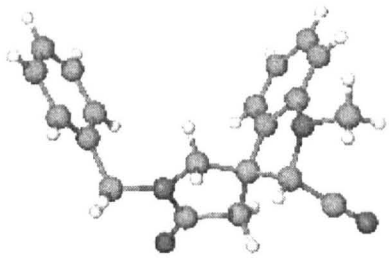
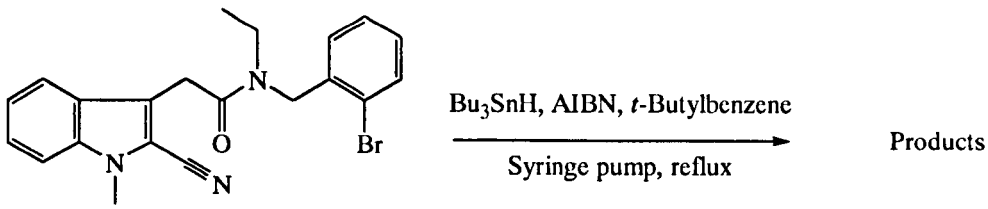


Figure 19

In summary, cyclisation of the *N*-methyl precursor (**346**) generated the 5-*exo*-trig cyclised products in 30% yield. These were obtained *via* a 1,5-hydrogen atom abstraction, 5-*exo*-addition, and subsequent reduction of the captodatively stabilised radical. There was no evidence of any 6-*endo*-cyclised products, which indicated that by incorporating the cyano group into our radical cyclisation precursor (**346**), we had solved the problem of distinguishing between the C-2 and C-3 positions of indole for radical addition.

4.5 Tandem Radical Cyclisation of the *N*-Ethyl Cyclisation Precursor

The tandem radical cyclisation of the *N*-methyl precursor (**346**) had shown that the cyano group directed radical addition to the indole C-3 position. We therefore applied the same conditions used in the previous cyclisation of the *N*-methyl precursor to the *N*-ethyl precursor (**348**) (scheme 103).



(348)

Scheme 103

From the cyclisation of the *N*-methyl precursor (**346**), we predicted that cyclisation of the *N*-ethyl precursor (**348**) would result in the formation of up to four diastereoisomers as a result of the three chiral centres formed. The formation of a more stable secondary α-amidoyl radical should also increase the yield of cyclised products as a result of the increased stability of the radical following 1,5-hydrogen atom abstraction.

After reaction of the *N*-ethyl precursor (**348**) with tri-*n*-butyltin hydride in *t*-butylbenzene under reflux, five products of R_f 0.63, 0.50, 0.43, 0.42 and 0.24 were isolated.

The least polar product of R_f 0.63 existed as a mixture of amide rotamers in a 1: 1.2 ratio and was isolated in 110 mg. In the infra-red spectrum the nitrile was visible at ν_{max} 2218.3 cm^{-1}. In the ^1H NMR spectrum there were nine aromatic protons visible along with the two triplets at δ 1.15 ppm and δ 1.20 ppm. These were assigned as the CH_3 groups on both of the amidic *N*-ethyl amide rotamers. In the mass spectrum (ESI), a parent ion of 332.1767 was found, which equated with the M^++H ion. The above ^1H NMR data, along with the ^{13}C NMR spectrum data, indicated that this was the reduced product, which was isolated in 45% yield.

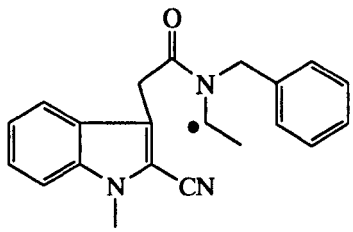
The product of R_f 0.50 contained an AB quartet in the ^1H NMR spectrum at δ 2.97 ppm and δ 3.07 ppm, with a coupling constant at 17.5 Hz. Two doublets at δ 3.87 ppm and δ 5.12 ppm also contained large coupling constants of 14.8 Hz. These were separated by a singlet at δ 3.99 ppm, which integrated for one proton. The two doublets were clearly part of an AB system from the observed coupling constant. A doublet at δ 0.85 ppm integrating for three protons was coupled to a quartet at δ 3.59 ppm integrating for one

proton. In the ^{13}C NMR spectrum, the characteristic spirocyclic quaternary carbon was visible at δ 52.78 ppm, indicative, along with the above date, for the formation of one of the diastereoisomers (**363**).

The products of R_f 0.43 and 0.42 proved hard to separate by column chromatography. From the ^1H and ^{13}C NMR spectra of the combined products, it was clear that these two products were two of the diastereoisomers of the cyclised product (**363**). Two quaternary carbons were visible in the ^{13}C NMR spectrum at δ 51.69 ppm and δ 51.39 ppm, which is indicative of the spiropyrrolidinyl ring system. Crystallisation of the mixture of diastereoisomers (hexane/ ethyl acetate) resulted in the isolation of a single diastereoisomer of R_f 0.43. The benzylic protons at δ 4.22 and δ 4.67 in the ^1H NMR spectrum were present as an AB quartet with a coupling constant of 15.1 Hz. A singlet at δ 3.94 ppm integrating for one proton was assigned as the C-H next to the cyano group of one of the diastereoisomers. Both the mixture of two diastereoisomers and the single diastereoisomer gave high resolution mass spectra confirming their formula.

The product of R_f 0.24 was obtained in 17 mg. The ^1H NMR spectrum contained two AB systems for the benzylic CH_2 and the CH_2 next to the carbonyl. The singlet for the C-H next to the cyano group overlapped with the benzylic AB quartet. The spirocyclic quaternary carbon was also clearly visible in the ^{13}C NMR spectrum at δ 52.25 ppm. An accurate mass spectrum confirmed that the product formed was indeed the fourth diastereoisomer.

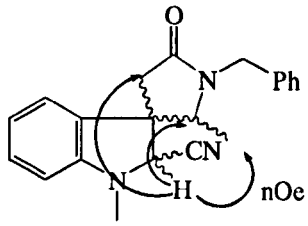
The four diastereoisomers (figure 21) were obtained in 52% overall yield, which was higher than in the previous cyclisation (scheme 101). This was probably a result of the increased stability of the intermediate α-amidoyl radical (**362**) (figure 20).



(362)

Figure 20

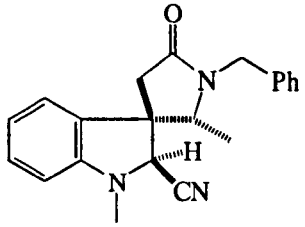
In order to determine the relative stereochemistry of the four diastereoisomers, we carried out a range of nOe studies of the three pure diastereoisomers of R_f 0.50, 0.43 and 0.24. As per the cyclised products (**360**) of the *N*-methyl precursor (**346**), we decided to irradiate the C-H next to the CN in each diastereoisomer (figure 21).



(**363**)

Figure 21

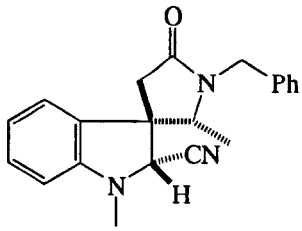
Irradiation of the C-H of the diastereoisomer of R_f 0.50 brought about an enhancement of the C-H next to the CH_3. Irradiation of the doublet at δ 0.85 ppm brought about an enhancement of the C-H next to the CH_3 as well as a small enhancement of a doublet in the aromatic region at δ 7.08 ppm. From this data, we can assign the structure below (**363a**) (figure 22) to the diastereoisomer.



(**363a**)

Figure 22

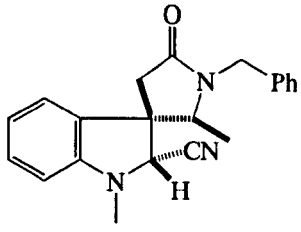
Irradiation of the C-H of the second diastereoisomer (R_f 0.43) brought about an enhancement of one half of the CH_2 next to the carbonyl. Irradiation of the doublet at δ 0.75 ppm enhanced the CH next to the CH_3 along with the doublet at δ 7.08 ppm in the aromatic region. As a result of this information, we can assign the structure below (**363b**) (figure 23) to the diastereoisomer of R_f 0.43.



(363b)

Figure 23

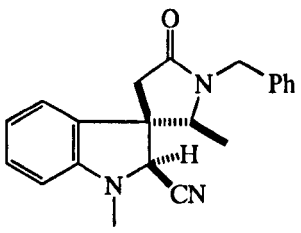
Irradiation of the C-H of the fourth diastereoisomer (R_f 0.24) enhanced one half of the CH_2 next to the carbonyl along with the CH_3 of the methyl group on the pyrrolidinone ring. This was probably due to the benzylic CH_2, which overlapped the C-H singlet. There was no enhancement of the CH next to the CH_3. Irradiation of the CH_3 doublet at δ 1.43 ppm brought about an enhancement of the C-H next to the exocyclic CH_3 as well as one half of the benzylic CH_2, which overlapped with the C-H next to the CN. On this basis it is difficult to fully assign the relative stereochemistry of this diastereoisomer. However, the initial nOe of the first diastereoisomer (**363a**) allows us to assign the structure (**363d**) below (figure 24).



(363d)

Figure 24

The relative stereochemistry of the final diastereoisomer (R_f 0.42) was determined *via* a process of elimination of the other three diastereoisomers. The proposed structure (**363c**) is shown below (figure 25).



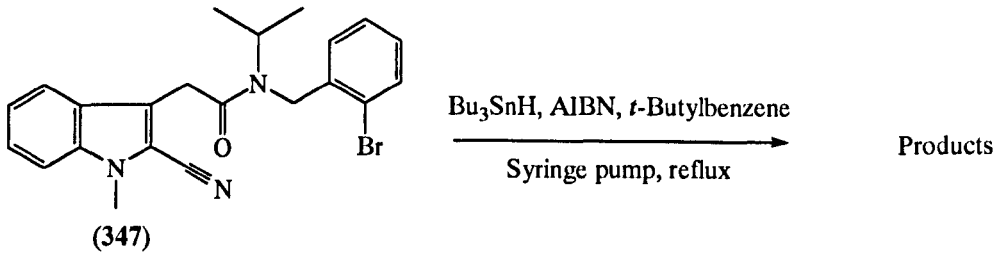
(363c)

Figure 25

In summary, cyclisation of the *N*-ethyl cyclisation precursor (**348**) resulted in a 52% yield of four diastereoisomers in a ratio of 9: 26: 10: 7, which correspond to the diastereoisomers of R_f 0.50, 0.43, 0.42 and 0.26 respectively. The increased yield, when compared to the *N*-methyl cyclisation (scheme 101), is presumably because of the enhanced stability of a secondary radical over a primary radical. Thus the radical generated following 1,5-hydrogen atom abstraction has a longer solution lifetime and hence an increased chance of cyclising into indole.

4.6 Tandem Radical Cyclisation of the *N*-Isopropyl Cyclisation Precursor

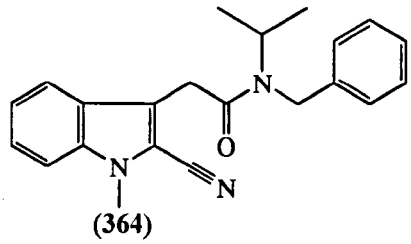
Changing from a primary to a secondary α-amidoyl radical had resulted in increased yields of the respective cyclised products. We therefore anticipated that this would also be the case on generation of the tertiary α-amidoyl radical. The resultant radical should be more stable and should therefore have an increased likelihood of cyclisation. Following the same conditions as for the two previous cyclisations (scheme 104), four products of R_f 0.61, 0.40, 0.31 and 0.21 were isolated.



(347)

Scheme 104

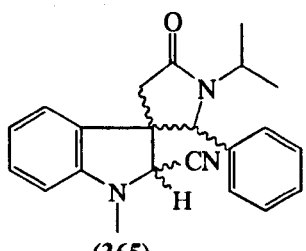
The product of R_f 0.61 was isolated in 320 mg in 54% yield, and was determined to be the reduced product (**364**) (figure 26). The product existed as a 1: 1.4 mixture of amide rotamers, which was determined from the ^1H NMR spectrum. The ratio was determined from the benzylic CH_2 at δ 4.57 ppm and δ 4.64 ppm. Confirmation that this was indeed the reduced product came from the mass spectrum, which showed a parent ion of 346.1919 (ESI), which equates as the molecular ion plus hydrogen.



(364)

Figure 26

The product of R_f 0.40 was isolated in 80 mg and appeared to have cyclised into the indole ring as a result of the appearance of the characteristic quaternary carbon in the ^{13}C NMR spectrum at δ 53.94 ppm. However, the ^1H NMR spectrum did not present any of the expected characteristics. An isopropyl group was clearly present, from the two doublets at δ 1.06 ppm and δ 1.35 ppm, which integrated for three protons each. These were coupled to a septet at δ 4.25 ppm, which integrated for one proton. On the basis of this data alone, this could not be the expected cyclised product, as the isopropyl group was still intact. Two doublets at δ 2.56 ppm and δ 3.17 ppm with a coupling constant of 17.5 Hz were assigned as the CH_2 next to the carbonyl, which indicated that we had formed the spiropyrrolidinyl ring system. The benzylic CH_2 was not readily observable as its predicted AB quartet. A singlet at δ 5.15 ppm integrating for one proton appeared to account for the benzylic system. A singlet at δ 3.96 ppm integrating for one proton appeared to be the expected C-H next to the cyano group. A ^1H COSY analysis of the molecule showed the AB quartet analysis to be correct, as well as confirming the presence of the isopropyl group. On the basis of the ^1H NMR data we assigned the structure below **(365)** (figure 27) to this compound. A high resolution mass spectrum (ESI) of the compound confirmed that the molecular weight was correct.

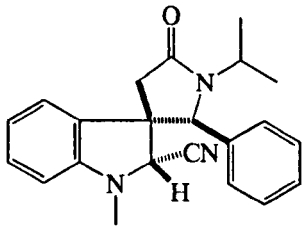


(365)

Figure 27

The aromatic hydrogens also posed some problems in the ^1H NMR spectrum. A doublet at δ 5.83 ppm was coupling with the rest of the aromatic protons, which ranged

from δ 6.37 ppm to δ 7.36 ppm. The expected pattern for the cyclised products was not apparent. Previously, the phenyl protons appeared as a multiplet at around δ 7.0 ppm. In the molecule of R_f 0.40, they were clearly distinguishable in terms of their couplings. In order to confirm the structure of this molecule, we carried out nOe irradiation of the C-H singlet next to the CN, and the benzylic CH singlet. Irradiation of the C-H next to the CN brought about an enhancement of one half of the CH_2 next to the carbonyl. However, irradiation of the proposed benzylic hydrogen caused a small increase in one of the aromatic doublets at δ 6.61 ppm. On the basis of these results, we have assigned the relative stereochemistry as shown below **(365)** (figure 28).



(365)

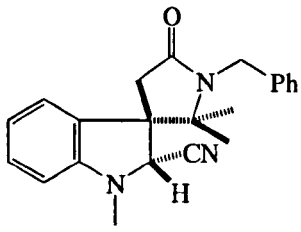
Figure 28

The structure shown above (figure 28), places the cyano group near to the aromatic ring. This may account for the shift of the aromatic protons at the unusually upfield positions. The product of R_f 0.40 was isolated in 15% overall yield.

The material of R_f 0.31 was isolated in 70 mg and was a mixture of products. In the ^1H NMR spectrum between δ 5 ppm and δ 5.2 ppm, two singlets were visible, which was similar to that of the previous product of R_f 0.40. Between δ 0.6 ppm and δ 1.2 ppm, there appeared to be doublets reminiscent of the exocyclic isopropyl group of the previous cyclised product. However, we were unable to separate these products further. They appeared to be similar to the previous product and may be the other diastereoisomers of this product.

The final product of R_f 0.21 was isolated in 40 mg and contained the spirocyclic centre at δ 56.58 ppm in the ^{13}C NMR spectrum. The benzylic CH_2 was evident as an AB quartet at δ 4.37 ppm and δ 4.79 ppm in the ^1H NMR spectrum. A singlet at δ 4.15 ppm integrating for one proton was assigned as the C-H next to the cyano group. The

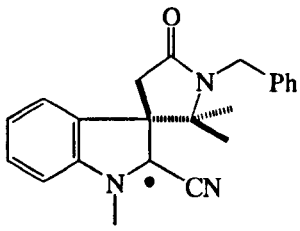
isopropyl group was incorporated into the spiropyrrolidinyl ring on the basis of the absence of the isopropyl group and the appearance of a singlet at δ 1.40 ppm, which integrated for six hydrogens. An accurate mass spectrum confirmed the molecular weight of the cyclised product. Irradiation of the C-H next to the cyano group brought about an enhancement of one half of the CH_2 next to the carbonyl. We therefore assigned the relative stereochemistry shown below (**366**) (figure 29) to this compound.



(**366**)

Figure 29

The product of R_f 0.21 was isolated in 7% yield and as a single diastereoisomer. No evidence for the formation of the other diastereoisomer could be found from the NMR spectrum. Presumably there is some steric strain involved in the final reduction step of the resultant captodatively stabilised radical (**367**) (figure 30). The dimethyl group may hinder addition of hydrogen from tri-*n*-butyltin hydride on one face of the molecule, favouring the isolated diastereoisomer (**366**).



(**367**)

Figure 30

The fact that the predicted product of cyclisation (**366**) was only formed in 7% yield is somewhat surprising. We had expected that the yield would be higher than for the *N*-ethyl cyclised products. The low yield may be a result of the increased steric strain resulting from the formation of two quaternary centres next to each other. The

dimethyl-stabilised radical may be too bulky to add efficiently to indole, which may account for the low yield obtained.

The mechanism for the formation of the unexpected product (**365**) is not entirely clear. From the previous cyclisations we had determined that 1,5-hydrogen atom abstraction was successful. Therefore, we would have predicted that the product of 1,5-hydrogen atom abstraction would preferentially be formed. The yield of this product was 15%, which is slightly more than double that of the expected product. The other isolated products of R_f 0.31 may also be other diastereoisomers of the unexpected product (**365**). This would bring the yield of this cyclised product up to 27%. The possible explanations for the formation of the formation of this product are:

1) 1,3-hydrogen atom abstraction.

2) 1,6-hydrogen atom abstraction, followed by a 1,4-hydrogen atom abstraction.

3) 1,5-hydrogen atom abstraction, followed by a 1,3-hydrogen atom abstraction.

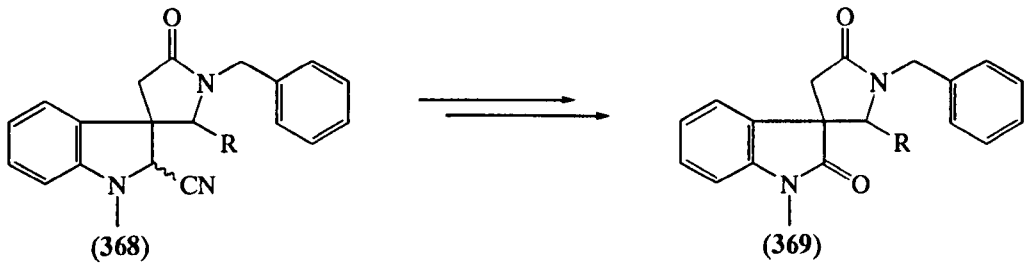
4) 1,5-hydrogen atom abstraction, followed by an intermolecular hydrogen abstraction of one of the benzylic hydrogens.

Of the possible explanations, direct 1,3-hydrogen atom abstraction *via* the aryl radical is unlikely. The second possibility, that of 1,6-hydrogen atom abstraction is known, but is relatively rare. More rare however, is 1,4-hydrogen abstraction and it was thought unlikely in this case. The other possibility that of 1,5-hydrogen abstraction, followed by a 1,3-hydrogen abstraction is also unlikely leaving the fourth option as offering the most likely mechanistic route to this compound (**365**).

In summary, cyclisation of the *N*-isopropyl precursor (**347**), gave rise to the expected product (**366**) in low yield and also led to the unexpected unknown compound (**365**). This is probably a result of increased steric constraints following the generation of a tertiary α-amidoyl radical.

4.7 Synthesis of Spirooxindoles

The ultimate aim of this section of the project is to synthesise the spiropyrrolidinyl oxindole alkaloids, such as elacomine (**294**) (figure 12). We therefore need to be able to convert the cyclised products such as the one represented below (**368**), from the α-cyano compounds into amides (**369**) (scheme 105).



Scheme 105

There are numerous reports of base catalysed conversions of nitriles into ketones in the literature.[219,220,221,222] The conversion of α-aminonitriles is however less common.[223,224,225,226,227] Work by Fang however, has focused on this reaction with reported yields of between 70% and 95%.[228]

The *N*-ethyl cyclised products (**363**) possess a pendant methyl group on the pyrrolidinone ring, which is similar in structure to that of elacomine (**294**). Replacement of the *N*-ethyl group in the cyclisation precursor (**348**) with a pendant alkyl group as in (**370**) would allow us access to the basic structure of elacomine (**294**) (figure 31).

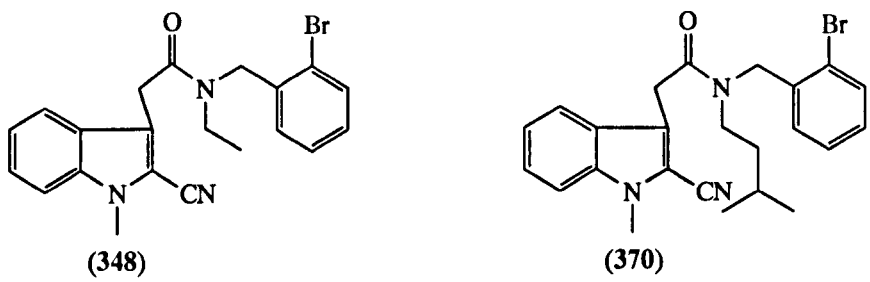
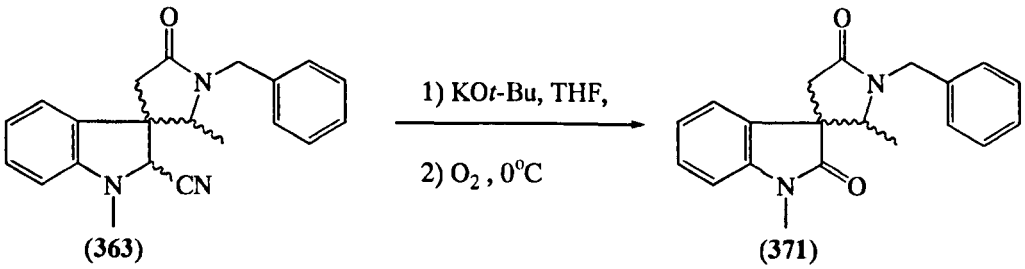


Figure 31

We therefore chose to investigate the oxidative decyanation of the *N*-ethyl cyclised products, as we believed that this would behave as a suitable model compound for the construction of the amidic carbonyl.

Treatment of a mixture of the four diastereoisomers of the *N*-ethyl cyclised products (**363**) with freshly sublimed potassium *t*-butoxide, followed by oxygen, as in the procedure by Fang,[228] resulted in a 40% yield of the oxindoles (**371**) as a 1: 1.2 ratio of diastereoisomers (scheme 106).



Scheme 106

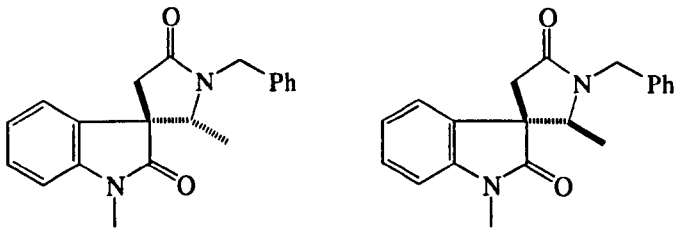
As a result of the low yield we attempted to modify the conditions used by Fang. Using potassium hexamethyldisilazide in place of potassium *t*-butoxide did not increase the yield, but enabled a more rapid deprotonation of the α-aminonitrile. However, in all cases, we were unable to improve upon the yield obtained.

During the nOe studies of the *N*-ethyl cyclised products (**363**), it became apparent that they decomposed over a period of time. After a couple of months, a doublet appeared at δ 0.71 ppm in the ^{1}H NMR spectrum of the product of R_f 0.50. The integration of the C-H next to the cyano group also decreased in size. From GCMS analysis of this compound, it was apparent that the product of decomposition was in fact the oxindole. The second diastereoisomer of R_f 0.43 also produced the same oxindole spectra. The *N*-ethyl cyclised product of R_f 0.24 decomposed to the oxindole diastereoisomer of R_f 0.26 with the appearance of a doublet at δ 1.04 ppm.

The conversion of the diastereoisomers of the *N*-ethyl cyclised products to the oxindoles appears to possibly occur *via* an acid-catalysed mechanism. This is probably due to their storage in a solution of $CDCl_3$, which is slightly acidic. The conversion of these

compounds into the oxindoles also appears to avoid the decomposition problems associated with the base mediated oxidative decyanation reaction. This is based on the observation that no other products were observed in the ^{1}H NMR spectrum apart from the *N*-ethyl cyclised products and the oxindoles. On the basis of this information, we can also assign the relative stereochemistry of each diastereoisomer of the oxindoles.

The diastereoisomer of R_f 0.34 **(371a)** is derived from the *N*-ethyl cyclised products of R_f 0.50 and 0.43. We can therefore assign the structure below to the diastereoisomer **(371a)** (figure 32). The other diastereoisomer **(371b)** must therefore arise from the *N*-ethyl diastereoisomers of R_f 0.42 and 0.24. This was confirmed from the ^{1}H NMR spectrum of the diastereoisomer of R_f 0.24. This confirms the structure of the oxindole diastereoisomer of R_f 0.26 (figure 32).



(371a) **(371b)**

Figure 32

4.8 Conclusions

In conclusion, the results from the cyclisation reactions have shown that the incorporation of the cyano group at the C-2 position of indole is essential for successful cyclisation. We have succeeded in developing a novel route to the spiropyrrolidinyl oxindoles. We have also observed a highly unusual hydrogen atom translocation reaction in the formation of the novel structure (**365**). However we do not appear to have increased the yield of cyclised product by raising the reaction temperature by the use of *t*-butylbenzene as solvent. We therefore need to increase the temperature of future cyclisations to hopefully overcome the amide rotamer problem.

By careful observation, we have also outlined a potentially more convenient route towards oxidative decyanation of α-aminonitriles using acid catalysis. This contrasts with the standard base promoted reactions used previously.

Chapter 5

Incorporation of the Benzyl Protecting Group in the Cyclisation Precursors

5.1 Introduction

During the synthesis of the tricyclic oxindoles, we had used the *N*-methyl group to protect the indole nitrogen. Whilst this simplified the NMR spectra of the cyclisation precursors, it posed a problem due to the difficulty of its removal following cyclisation. In addition to the previous work, we thus chose to investigate the use of an alternative protecting group that could be more readily removed and which did not pose a problem for the cyclisation. We chose the benzyl group as a replacement for the methyl group as we believed that it should be removable following cyclisation and oxindole formation.[229]

In order to investigate the effects of the benzyl group on the cyclisations, we chose to synthesise the *N*-methyl (**372**) and *N*-isopropyl (**373**) benzyl protected cyclisation precursors (figure 33). The products following cyclisation of these two should each consist of two diastereoisomers, which should produce less complex NMR data as opposed to the *N*-ethyl benzyl protected cyclisation precursor, which would generate up to four diastereoisomers.

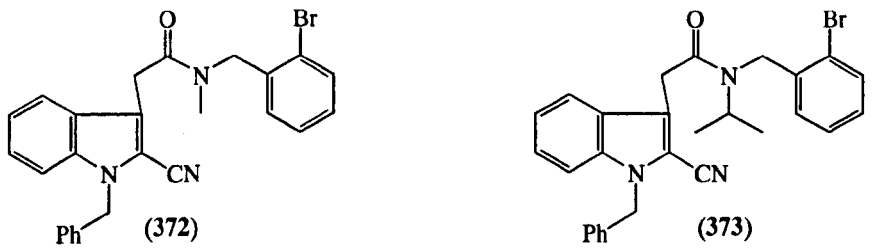
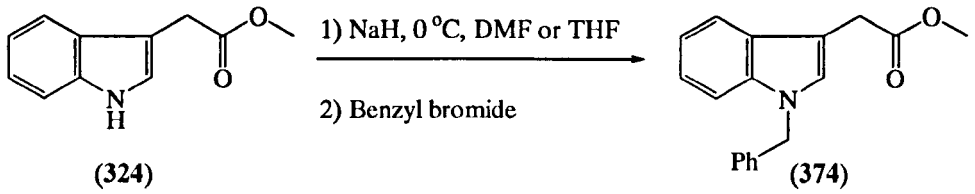


Figure 33

5.2 Synthetic Approach

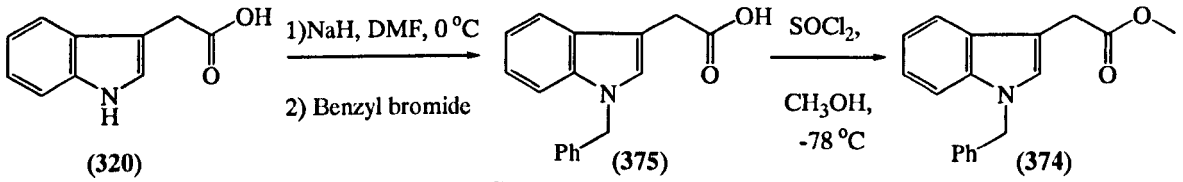
We utilised the same synthetic approach as in the synthesis of the previous cyclisation precursors. Reaction of indole-3-acetic acid methyl ester (**324**) with sodium hydride in THF, followed by addition of benzyl bromide, led to a 20% yield of the *N*-benzyl

protected indole (**374**). Changing the solvent to DMF brought the yield up to 75% (scheme 107). The problem with this alkylation step appeared to relate to *N*-versus *C*-alkylation. In both reactions, the product required extensive purification to remove the by-product from the reaction.



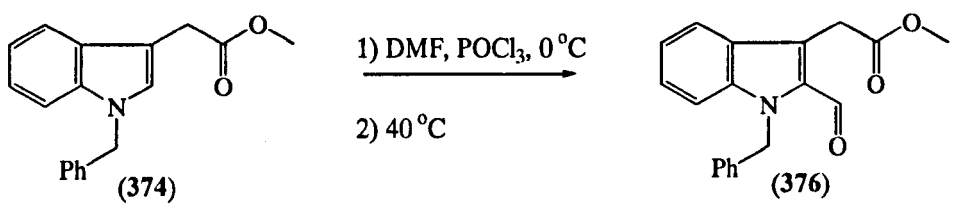
Scheme 107

To solve this problem, we decided to reverse the order of *N*-protection and methyl ester formation (scheme 108). Reaction of indole-3-acetic acid (**320**) with two equivalents of sodium hydride in DMF, followed by benzyl bromide, resulted in the formation of the *N*-benzyl protected indole-3-acetic acid (**375**) in 81% yield, with no evidence of any by-products. Treatment of a suspension of this resultant acid with thionyl chloride in methanol gave the *N*-benzyl protected indole-3-acetic acid methyl ester (**374**) in 86% yield (scheme 108).



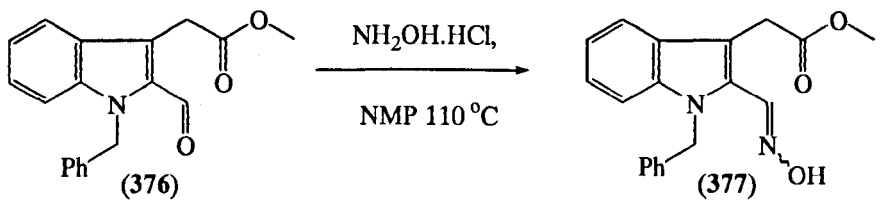
Scheme 108

Vilsmeier formylation of the *N*-benzyl protected indole-3-acetic acid methyl ester (**374**), gave the 2-formylindole (**376**) in 49% yield. The purification of this product posed some problems as a result of additional formylated products in the crude reaction mixture. Gradient elution of the product eventually gave a clean yield of product (**376**) (scheme 109).



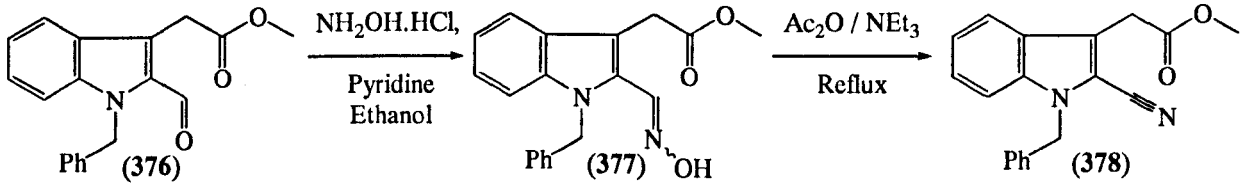
Scheme 109

We attempted to increase the yield of this step by utilisation of the conditions used by other groups.[230,231,232] However, we were unable to improve the yield of the reaction under all the conditions that were tried. A report in the literature by Kumar[233] on the conversion of aldehydes to nitriles in one pot appeared to offer the opportunity to reduce the number of overall steps in the synthesis. We therefore duly followed Kumar's conditions, whereby the aldehyde (**376**) was heated with hydroxylamine hydrochloride in *N*-methyl pyrrolidinone (NMP) at 110°C. However, we only obtained the oxime (**377**) (scheme 110). No evidence for nitrile formation was observed at all. Changing from dry to wet NMP resulted in a reduction in yield of the oxime (**377**).



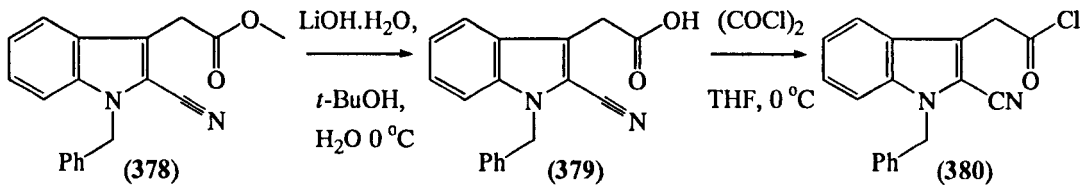
Scheme 110

Reaction of the aldehyde under the previous conditions, with hydroxylamine hydrochloride in ethanol and pyridine, led to the oxime (**377**) in 94% yield (scheme 111). This was then converted to the nitrile (**378**) in 90% yield following reaction with acetic anhydride and triethylamine (scheme 111).



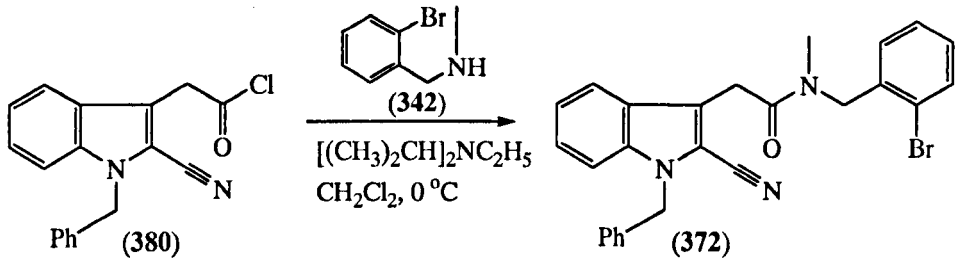
Scheme 111

Reaction of the methyl ester (**378**) with lithium hydroxide in a *t*-butanol: water mixture gave the acid (**379**) in almost quantitative yield. This was then converted to the acid chloride (**380**) following subsequent treatment with oxalyl chloride (scheme 112).



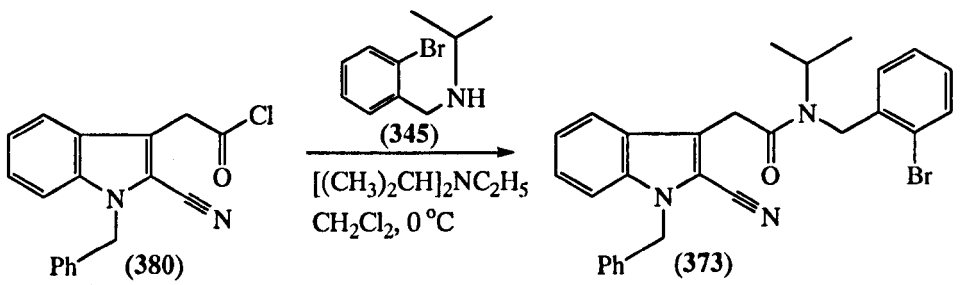
Scheme 112

Addition of a solution of the acid chloride (**380**) to a solution of (2-bromobenzyl) methylamine (**342**) in the presence of Hünig's base, gave the *N*-benzyl protected *N*-methyl cyclisation precursor (**372**) in 90% yield as a 1: 1.3 mixture of amide rotamers (scheme 113). The ratio of the two amide rotamers was determined from the two benzylic signals at δ 5.32 ppm and δ 5.45 ppm in the ^{1}H NMR spectrum, which were assigned as the benzylic CH_2 protons next to the indole nitrogen.



Scheme 113

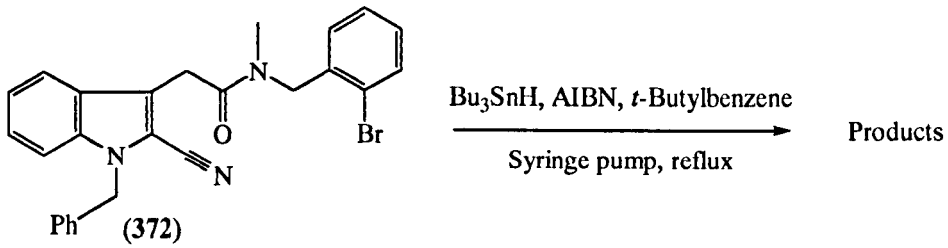
Following addition of a solution of acid chloride (**380**) to a solution of (2-bromobenzyl)isopropylamine (**345**) (scheme 114), the *N*-benzyl protected isopropyl cyclisation precursor (**373**) was isolated in 82% yield and as a 1: 1.2 mixture of amide rotamers. The ratio was determined from the indole *N*-benzylic signals at δ 5.38 ppm and δ 5.48 ppm in the ^{1}H NMR spectrum.



Scheme 114

5.3 Radical Cyclisation

With the formation of the two benzyl protected cyclisation precursors (**372**) and (**373**), we next investigated the cyclisation of these. We chose the same radical cyclisation conditions as before, in order to compare the results obtained. Syringe pump addition of a solution of tri-*n*-butyltin hydride and AIBN in *t*-butylbenzene to a solution of the *N*-benzyl protected *N*-methyl precursor (**372**) in *t*-butylbenzene at reflux, two products were isolated from the reaction mixture of R_f 0.40 and 0.28 (scheme 115).



Scheme 115

The product of R_f 0.40 was isolated in 134 mg and was clearly composed of two amide rotamers in a 1: 1.1 ratio. This product was assigned as the reduced product as a result of the fourteen aromatic protons in the ^{1}H NMR spectrum. An accurate mass spectrum also confirmed that this was indeed the reduced product (**381**) (figure 34), which had been isolated in 32% yield.

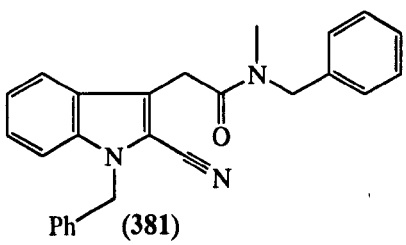
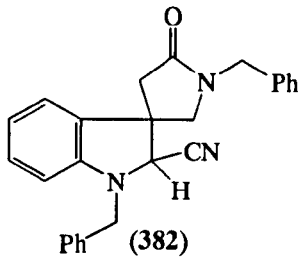


Figure 34

The reduced product was obtained in a total yield of 50%. An extra 18% yield of this product was isolated from the hexane used to remove the tin residues.

The second product of R_f 0.28 was isolated in 134 mg and contained two products that were inseparable by column chromatography. From the ^{1}H NMR spectrum there were

two singlets at δ 4.02 ppm and δ 4.09 ppm, which each integrated for one proton. The ratio of these two were equal from their integration. The ^{1}H NMR spectrum also contained several AB quartets, indicative of the desired cyclised product (**382**) (figure 35).



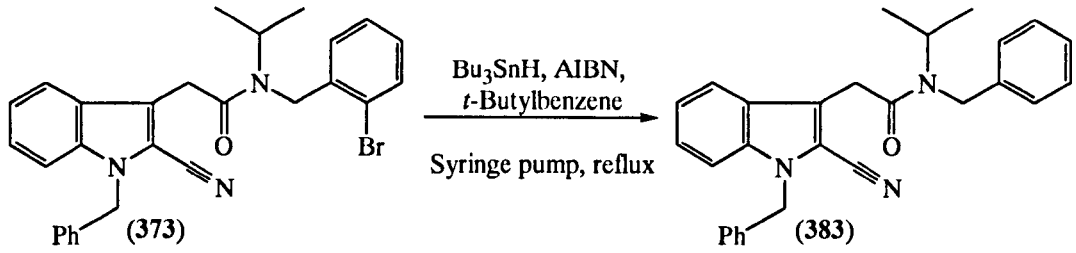
(**382**)

Figure 35

The two quaternary carbons at δ 48.09 ppm and δ 47.81 ppm were readily observable in the ^{13}C NMR spectrum, indicative of the cyclised product. A high resolution mass spectrum confirmed the formation of these two compounds, which had been isolated in 34% yield.

We were able to isolate one of the diastereoisomers using slow recrystallisation (hexane/ethyl acetate). This enabled us to assign the spectra of each diastereoisomer. In the ^{1}H NMR spectrum of this separated compound, four AB quartets were readily observable, along with the distinct aromatic protons, indicative of successful cyclisation into indole. The singlet at δ 4.09 ppm was assigned as the C-H next to the cyano group.

We used the same conditions for the cyclisation of the *N*-benzyl protected isopropyl cyclisation precursor (**373**). However, following cyclisation, we were only able to isolate the reduced product (**383**) (scheme 116) in 54% yield as a 1: 1.1 ratio of amide rotamers. The remainder of the reaction mixture was composed of two isolable groups of compounds of R_f 0.31 and 0.27. We were unable to purify these further to determine their composition. We believe that this confirms the earlier problems and observations encountered with the *N*-methyl protected *N*-isopropyl cyclisation. The 1,5-abstracted α-amidoyl radical can abstract other hydrogen atoms either intra- or possibly inter-molecularly, leading to a complex distribution of products.



Scheme 116

5.4 Conclusions

Cyclisation of the *N*-benzyl protected *N*-methyl cyclisation precursor (**372**) generated the expected cyclised products, with no appreciable loss of yield when compared to the *N*-methyl protected *N*-methyl cyclisation precursor (**346**) (figure 36).

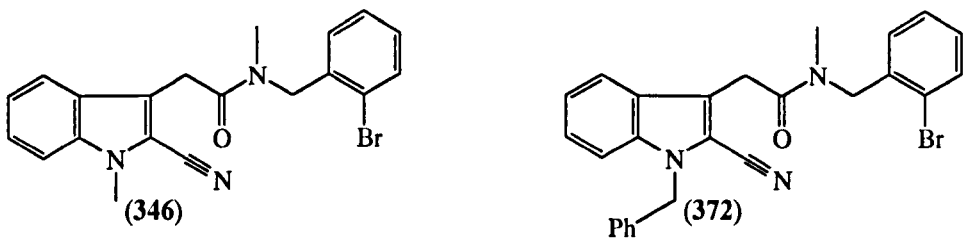


Figure 36

The cyclisation of the *N*-benzyl protected *N*-isopropyl precursor (**383**) confirms the previous observations encountered in the corresponding methyl protected cyclisation precursor (**347**). With a removable indole nitrogen-protecting group, a route is now opened up towards the synthesis of *N*-unsubstituted spirooxindole alkaloids.

Chapter 6

An Approach Towards the Tetracyclic Core of the *Strychnos* and *Aspidosperma* Skeleton

Disconnection C

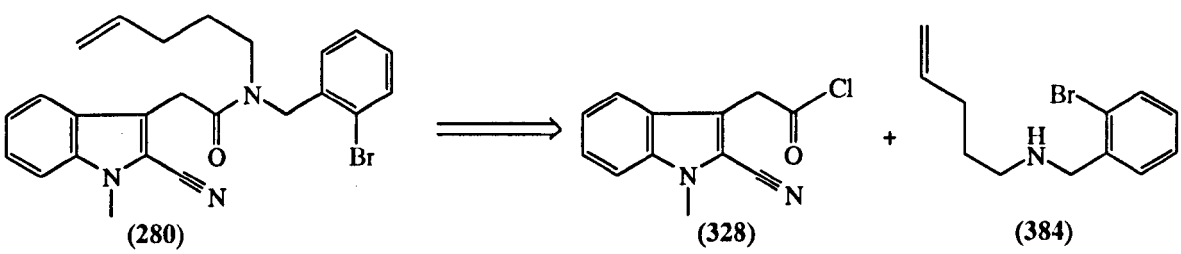
6.1 Introduction

In the preceding chapters, we have shown that incorporation of a cyano group at the C-2 position of indole facilitated the addition of an α-amidoyl radical to the C-3 position. The generation of these key spirocyclic tricyclic structures allowed us to synthesise the required spiropyrrolidinyl oxindole skeleton.[234]

The success of this initial work has enabled us to extend this chemistry towards disconnection C (scheme 66). By incorporation of a suitable pendant alkenyl group into the cyclisation precursor, we should be able to generate the tetracyclic core of the *Strychnos* and *Aspidosperma* alkaloids.

6.2 Synthetic Approach

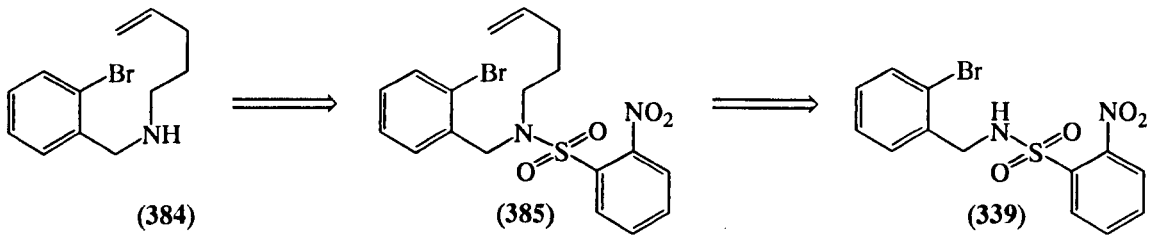
The synthetic approach to the tandem radical cyclisation precursor (**280**) is outlined below (scheme 117). From the previous chapter, we had shown that the synthesis of the tricyclic precursors (figure 14) occurred *via* reaction of the 2-cyano acid chloride with a secondary amine (scheme 117). Our disconnection of the cyclisation precursor is, therefore, based on this approach (scheme 117). Disconnection of the cyclisation precursor (**280**) leads back to the previously prepared acid chloride (**328**) and the secondary amine (**384**).



(280) (328) (384)

Scheme 117

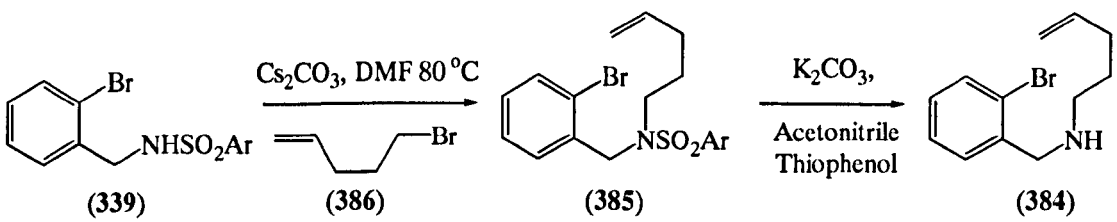
We envisaged that the secondary amine (**384**) could be prepared by the previously used method. Alkylation of the sulfonamide (**339**) with 5-bromo-1-pentene (**386**) should generate the tertiary sulfonamide (**385**), which should undergo deprotection to give the secondary amine (**384**) (scheme 118).



(384) (385) (339)

Scheme 118

Following the above approach, treatment of the sulfonamide (**339**) with caesium carbonate in DMF at 80°C, followed by addition of 5-bromo-1-pentene (**386**), resulted in the formation of the tertiary sulfonamide (**385**) in almost quantitative yield (scheme 119).

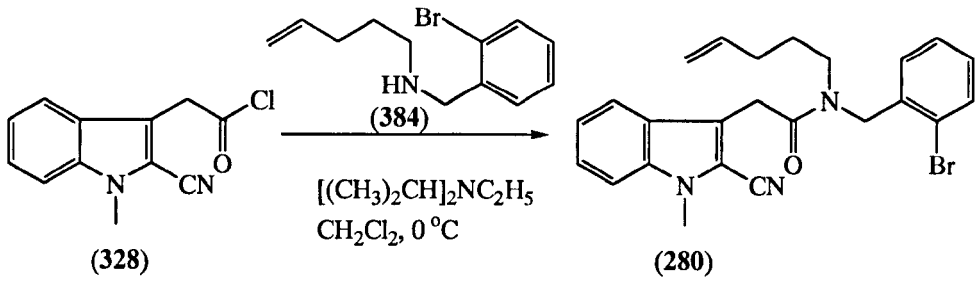


(339) (386) (385) (384)

Scheme 119

Treatment of the tertiary sulfonamide (**385**) with thiophenol in the presence of the potassium carbonate led to (2-bromobenzyl)pent-4-enylamine (**384**) in 86% yield (scheme 119).

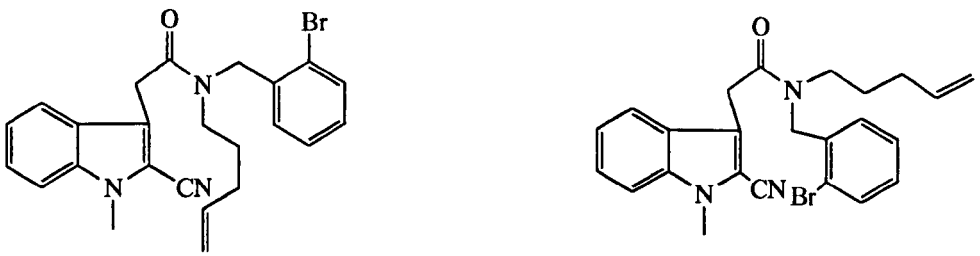
Following the successful formation of the tertiary amides in the previous chapter, the secondary amine (**384**) was reacted with the acid chloride (**328**) (scheme 120).



(328) (280)

Scheme 120

The cyclisation precursor was obtained in 83% yield as a 1:1.2 mixture of amide rotamers. The ratio was determined from the integration of the benzylic CH_2 peaks in the ^1H NMR spectrum at δ 4.65 ppm and δ 4.73 ppm. The two rotamers are shown below (figure 37). The minor rotamer **(280a)** possesses the right conformation for cyclisation, whilst the major rotamer **(280b)** is not in the right conformation for cyclisation.



(280a) (280b)

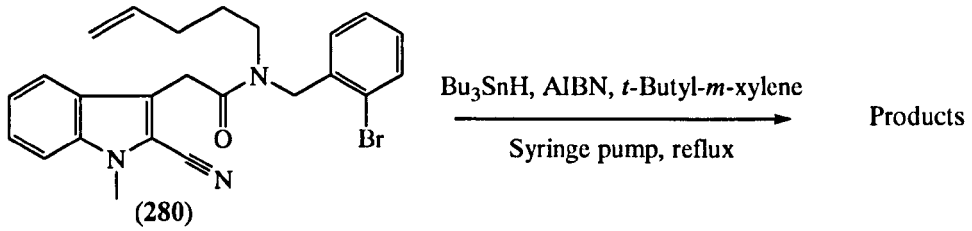
Figure 37

We also looked at the reaction of the acid **(315)** with the secondary amine **(384)** under DCC coupling conditions but only obtained a 28% yield of the cyclisation precursor **(280)**.

6.3 Tandem Radical Cyclisation of the *N*-pentenyl Cyclisation Precursor

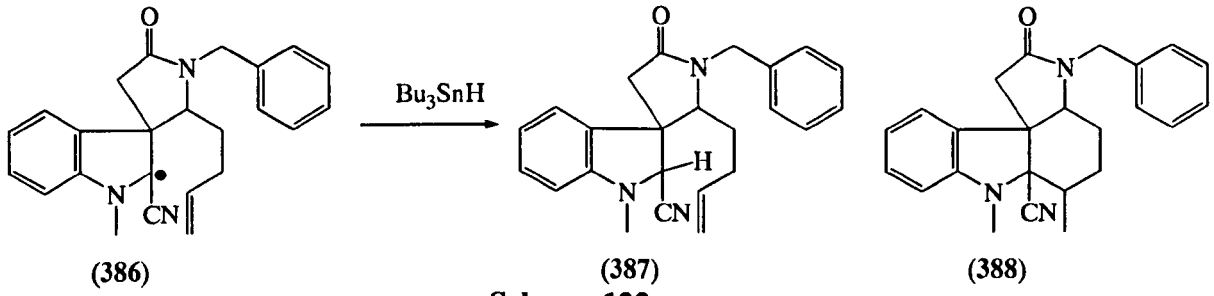
On the basis of the previous results we decided to apply the same conditions in the radical reaction of the *N*-pentenyl cyclisation precursor. We also decided to increase the temperature of the cyclisations from 170 °C to around 200 °C by changing to *t*-butyl-*m*-xylene as solvent. We hoped that this would alleviate the problems associated with the amide rotamers, which we had not appeared to have solved with the use of *t*-butylbenzene.

The tertiary amide (**280**) was therefore reacted with a solution of tri-*n*-butyltin hydride and sub-stoichiometric amounts of AIBN *via* syringe pump in *t*-butyl-*m*-xylene under reflux. Following work-up of the reaction, five products of R_f 0.72, 0.47, 0.39, 0.39 and 0.25 were isolated (scheme 121).



Scheme 121

From the previous cyclisations, we knew that the 5-*exo*-trig cyclisation should be successful. However, we were unsure as to whether the final 6-*exo*-trig cyclisation would occur. We anticipated that the resultant captodatively-stabilised radical (**386**) might undergo cyclisation to give the tetracyclic product (**388**) or it might be reduced by tri-*n*-butyltin hydride to give the reduced product (**387**) (scheme 122).



Scheme 122

The product of R_f 0.72 was isolated in 110 mg and as a 1:1.2 mixture of amide rotamers. There were nine aromatic hydrogens in the ^1H NMR spectrum, which is indicative of the reduced product. The pendant alkene group was also clearly visible in the ^{13}C NMR spectrum at δ 115.14 ppm and δ 115.85 ppm. The mass spectrum also confirmed the formation of the reduced product (**389**), which was obtained in 45% yield (figure 38).

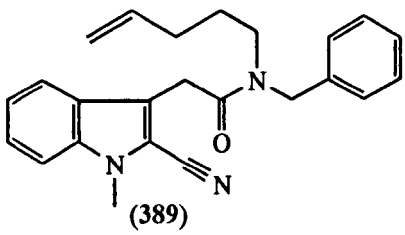
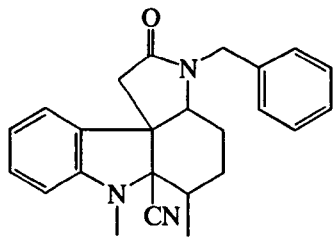


Figure 38

Crude ^{1}H NMR and ^{13}C NMR spectra of the remaining four products were very complex. What was apparent, however, was that there was no alkene chain present in any of the four products. This was evident from the crude ^{13}C NMR spectrum, which clearly showed that there was no CH_2 at around δ 115 ppm. This was a very strong indication of having generated the desired tetracyclic structures.

The four cyclised products proved difficult to separate *via* column chromatography and their ratios were therefore determined *via* GCMS of the crude cyclised products. They were obtained in a ratio of 8:3:2:1 and in 130 mg yield.

The product of R_f 0.47 was isolated in 9 mg as a pale yellow oil. There were no signs of any vinylic protons in the ^{1}H NMR spectrum. There was a clear doublet at δ 1.30 ppm integrating for three protons. There were two AB quartets in the ^{1}H NMR, which were assigned as the CH_2 next to the carbonyl and the benzylic CH_2. In the aromatic region, cyclisation into indole had definitely taken place, with the characteristic aromatic splitting pattern from δ 6.44 ppm to δ 7.36 ppm. The doublet at δ 1.30 ppm was assigned as the exocyclic methyl group on the C ring of the tetracyclic product. This was indicative that the expected cyclised product (**388**) (figure 39) had formed. The product of R_f 0.47, therefore, constituted one of the diastereoisomers of the cyclised product and was obtained in 3% yield. A high resolution mass spectrum confirmed the formation of the tetracyclic structure.



(388)

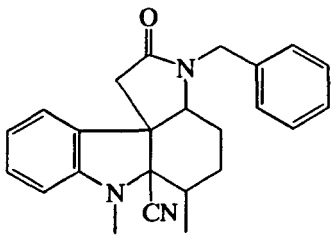
Figure 39

The next products to be isolated were obtained as an inseparable mixture of diastereoisomers of R_f 0.39. Slow recrystallisation of the oil (hexane/ dichloromethane) resulted in the formation of crystals of the major diastereoisomer. From the ratio of products obtained from the GCMS, this crystalline product was obtained in 74 mg.

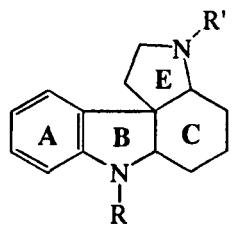
From the ^{13}C and ^{1}H NMR spectra, it was apparent that we had formed this diastereoisomer of the tetracyclic product (**388**) (figure 39) in 24% yield. A ^{1}H COSY analysis of this diastereoisomer also aided analysis of the other diastereoisomers. The benzylic CH_2 was present as a clear AB quartet and the exocyclic methyl group was present as a doublet at δ 1.41 ppm in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum the spirocyclic centre was readily visible at δ 50.97 ppm. The second ring junction quaternary carbon was present at δ 75.63 ppm. This data confirmed that we had indeed formed the tetracyclic product. A high resolution mass spectrum also confirmed the formation of this compound.

The other two diastereoisomers of R_f 0.39 and 0.25 presented very similar spectra to the two previous diastereoisomers, and were in good agreement with these.

In summary, cyclisation of the *N*-pentenyl tandem radical cyclisation precursor (**280**) generated the tetracyclic structure (**388**), which is the core of the *Strychnos* and *Aspidosperma* alkaloids in an overall yield of 43%. This follows a 1,5-hydrogen atom abstraction, 5-*exo*-trig cyclisation and a 6-*exo*-trig cyclisation to give the ABCE core structure (**267**) (figure 40).



(388)



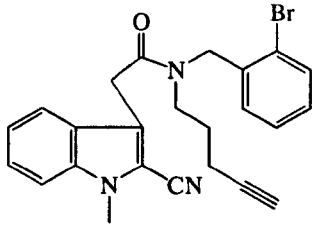
(267)

Figure 40

6.4 Incorporation of Additional Functionality

In order to undertake a synthesis of either the *Strychnos* or *Aspidosperma* alkaloids, we need to incorporate additional functionality into our tetracyclic intermediates. The preceding synthesis of the tetracyclic core had shown that our tandem radical cyclisation approach is a feasible way of synthesising such molecules. However, the functionality in the tetracyclic compound (**388**) is minimal. We therefore embarked on

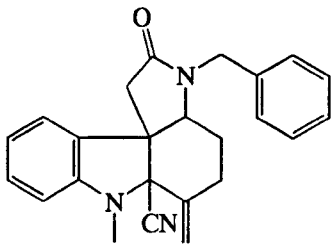
a synthesis of a cyclisation precursor which, after cyclisation, would enable us to access suitable intermediates towards the *Strychnos* and *Aspidosperma* alkaloids. The proposed cyclisation precursor is shown below (**390**) (figure 41).



(390)

Figure 41

Cyclisation of the above compound (**390**) should provide an exocyclic double bond on the tetracyclic product (**391**) (figure 42) shown below. This would allow further elaboration of such molecules towards natural products.



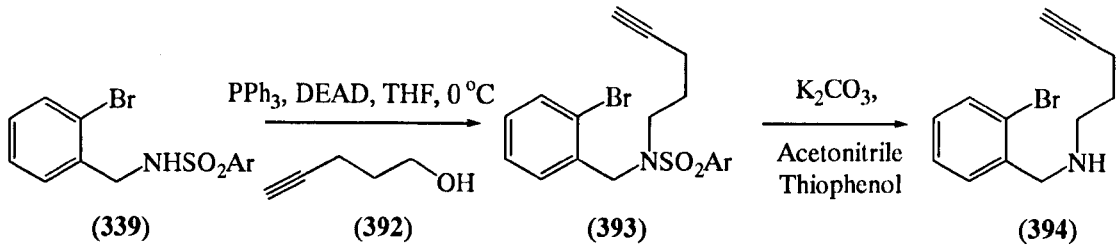
(391)

Figure 42

6.4.1 Synthesis of the Cyclisation Precursor

Our synthetic approach to the *N*-pentynyl precursor is based on that used in the previous syntheses. Reaction of the acid chloride (**328**) with the respective amine (**394**), should generate the required compound (**390**).

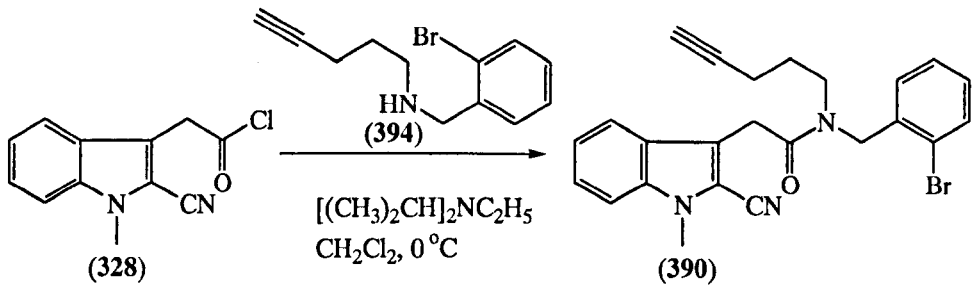
In order to synthesise the secondary amine (**394**) the previous approach was used (scheme 123). We were unable to use the base promoted reaction between sulfonamide (**339**) and the respective alkyl halide, as 5-bromopentyne is not available. We therefore carried out alkylation of the sulfonamide (**339**) with 4-pentynol (**392**) under Mitsunobu conditions (scheme 123),[235] which gave the tertiary sulfonamide (**393**) in 96% yield.



(339) (392) (393) (394)

Scheme 123

Deprotection of the tertiary sulfonamide (**393**) using potassium carbonate and thiophenol gave the secondary amine (**394**) in 75% yield (scheme 123). Reaction of this with the acid chloride (**328**) in the presence of Hünig's base gave the *N*-pentynyl cyclisation precursor (**390**) in 86% yield (scheme 124).

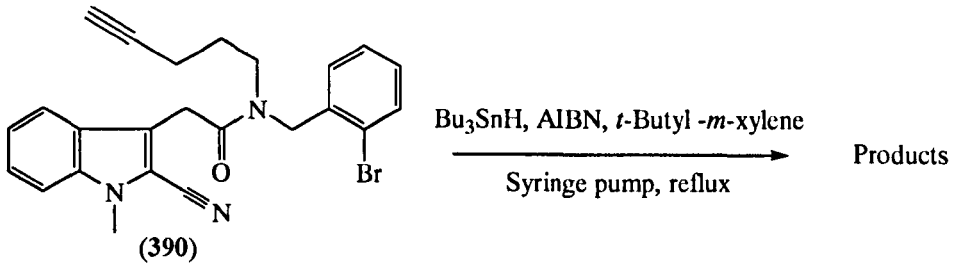


Scheme 124

The *N*-pentynyl cyclisation precursor (**390**) was obtained as a 1: 1.3 mixture of amide rotamers. The ratio of amide rotamers was determined from the ratio of the benzylic CH_2 protons in the ^1H NMR spectrum at δ 4.82 ppm and δ 4.88 ppm.

6.5 Tandem Radical Cyclisation of the *N*-Pentynyl Precursor

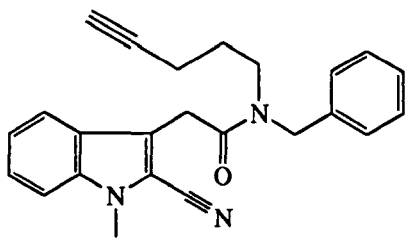
Following the successful cyclisation of the *N*-pentenyl precursor (**280**), we decided to use the same conditions for cyclisation of the *N*-pentynyl precursor (**390**). Treatment of a solution of the tertiary amide (**390**) in *t*-butyl-*m*-xylene under reflux with syringe pump addition of a solution of tri-*n*-butyltin hydride and AIBN in *t*-butyl-*m*-xylene resulted in the formation of three isolable products of R_f 0.71, 0.63 and 0.28 (scheme 125).



(390)

Scheme 125

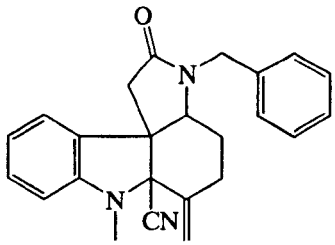
The product of R_f 0.71 was isolated in 380 mg and as a 1:1 ratio of amide rotamers. There were nine aromatic protons in the ^1H NMR spectrum, which is indicative of the reduced product (**395**) (figure 43). An accurate mass spectrum confirmed the formation of the reduced product in 45% yield.



(395)

Figure 43

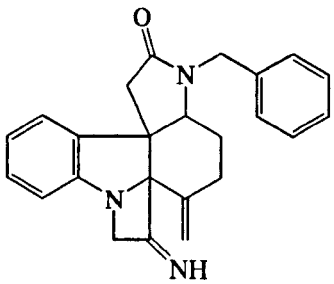
The second product of R_f 0.63 was isolated in 140 mg as a colourless oil. From the ^1H NMR and ^{13}C NMR spectra, it was clear that this was the expected cyclised product. One singlet at δ 5.63 ppm and a doublet at δ 6.67 ppm in the ^1H NMR spectrum were indicative of the exocyclic double bond. This was confirmed from the ^{13}C NMR spectrum with the appearance of a CH_2 at δ 119.43 ppm. There were two AB quartets in the ^1H NMR spectrum for the CH_2 next to the carbonyl and the benzylic CH_2. The cyano group was present at δ 116.90 ppm in the ^{13}C NMR spectrum and at ν_{max} 2218.2 cm^{-1} in the infra-red spectrum. The spirocyclic centre of the molecule was present at δ 53.84 ppm in the ^{13}C NMR spectrum. An accurate mass spectrum confirmed the formation of the required tetracyclic compound (**391**) in 16% yield (figure 44).



(391)

Figure 44

The third isolable product of R_f 0.28 was obtained in 130 mg as a white solid. The ^1H NMR spectrum contained three AB quartets as opposed to the usual two. What was immediately apparent was the absence of the *N*-methyl signal at around δ 3 ppm. A broad singlet at δ 4.19 ppm was also unprecedented in the ^1H NMR spectrum. The exocyclic double bond was also readily visible at δ 5.31 ppm and δ 5.62 ppm in the ^1H NMR spectrum and at δ 116.99 ppm in the ^{13}C NMR spectrum. There were also five CH_2 signals, excluding the exocyclic double bond in the ^{13}C NMR spectrum. Eight quaternary carbons were observed in the ^{13}C NMR spectrum with no evidence for the cyano group at its expected position. On the basis of this evidence, we have assigned the pentacyclic structure (**396**) (figure 45) to this compound. A high resolution mass spectrum confirmed the molecular formula of this compound.

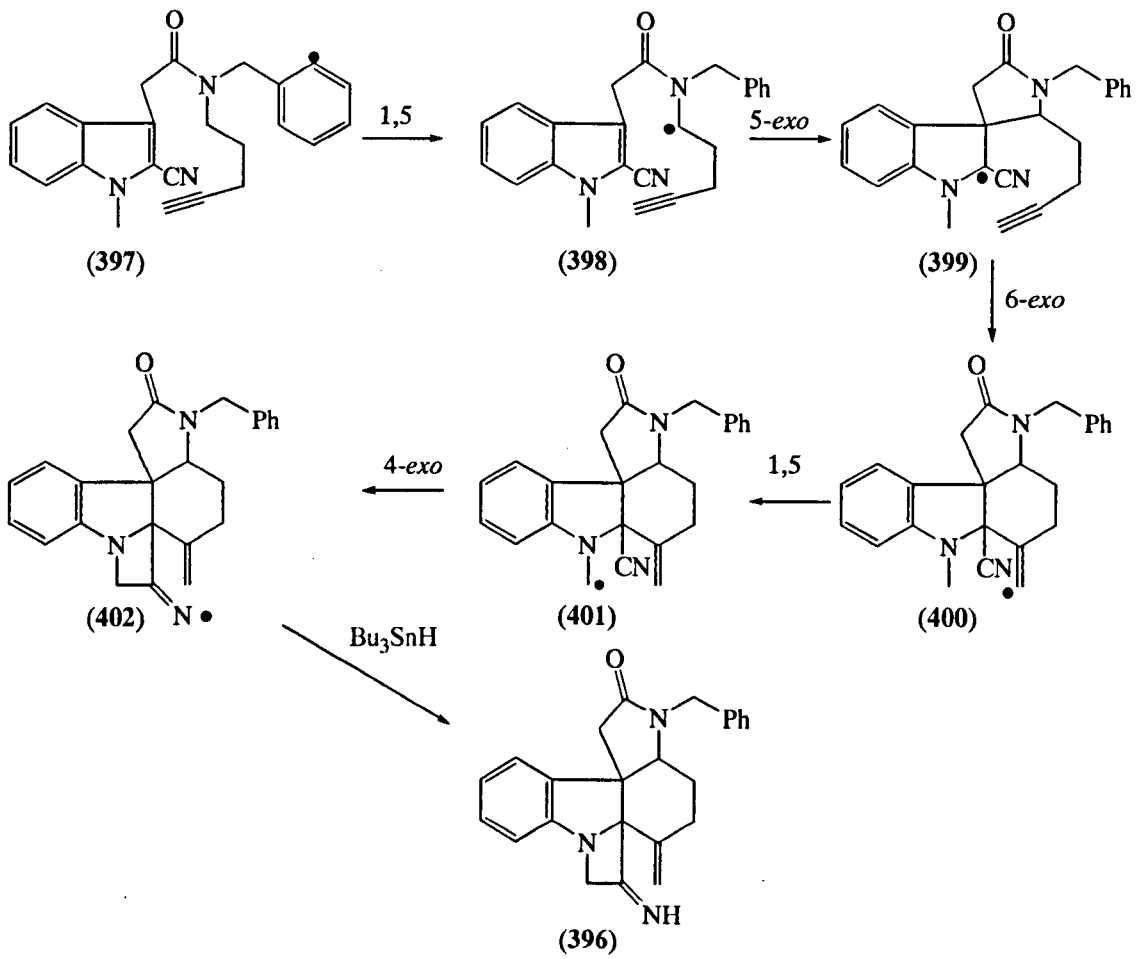


(396)

Figure 45

The product was thus isolated in 15% yield on the basis of this information. The broad singlet at δ 4.19 ppm in the ^1H NMR spectrum was assigned to the NH in the above structure (**396**) (figure 45). One of the three AB quartets was assigned to the CH_2 attached to the indole nitrogen, which accounted for the absence of the indole CH_3 group. The rest of the data was consistent with the previous product (**391**), indicative of the remainder of the structure. The formation of this unexpected product is believed to have occurred from an additional 1,5-hydrogen atom abstraction by the vinylic radical

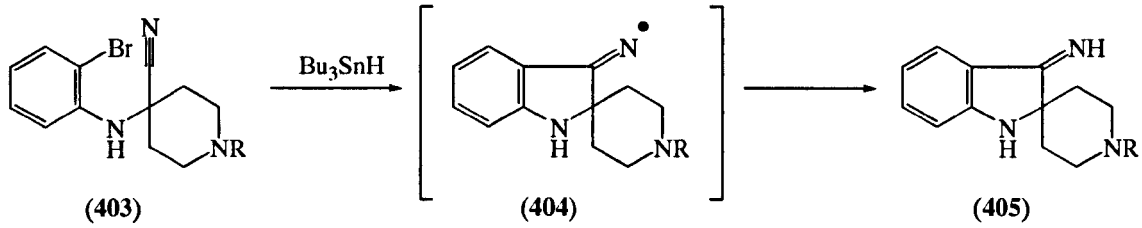
(**400**) from the pendant methyl group on the indole (scheme 126). The resultant primary radical then underwent a 4-*exo*-dig cyclisation on to the cyano group to give the resultant iminyl radical (**402**), which was reduced by tri-*n*-butyltin hydride to give the final compound (**396**). The full mechanism is shown below (scheme 126).



Scheme 126

The formation of this product is surprising. Whilst 1, 5-hydrogen atom abstraction by a vinylic radical, followed by cyclisation back on to the vinyl double bond has been widely used by various groups,[167,165,164,166] cyclisation onto cyano-groups has been mostly limited to their transfer on to an aromatic ring as reported by Cossy and other groups.[87,88,236] A report by Bowman detailed radical cyclisation on to nitriles,[237] with the resultant iminyl radical undergoing a range of further intramolecular cyclisations. He also observed formation of the imine itself, which was isolated as the ketone.[237] Work by Sulsky, in direct contrast to the work of Cossy, however, has shown that radical cyclisation of the aryl radical onto the nitrile (**403**) can result in the formation

and isolation of the imine (**405**) (scheme 127).[238] Using similar reactions and conditions to Cossy, Sulsky isolated the imine intermediates in good yields.



(403) (404) (405)

Scheme 127

Sulsky's work shows that radical cyclisation on to nitriles can produce the resultant imine and provides support for our structural assignment (**396**).

In summary, cyclisation of the *N*-pentynyl precursor (**390**) results in the formation of the reduced product in 45% yield as well as the expected cyclised product (**391**) in 16% yield, along with a novel pentacyclic structure (**396**), which has undergone an 4-*exo*-dig cyclisation which is supposed to be disallowed under Baldwin's rules.[102]

6.6 Conclusions

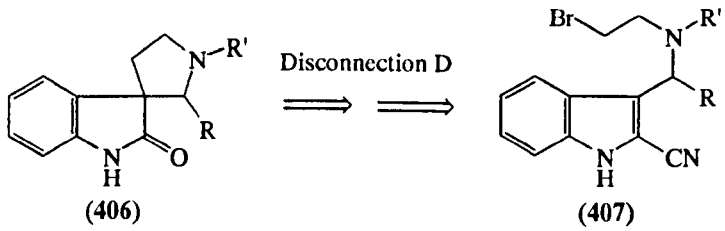
The tandem radical cyclisations of the *N*-pentenyl (**280**) and *N*-pentynyl (**390**) precursors have been achieved. We have succeeded in generating the tetracyclic core of the *Aspidosperma* and *Strychnos* alkaloids using tandem radical methodology. The captodatively stabilised radical generated after formation of the tricyclic structure can undergo a further cyclisation to give tetracyclic structures. We have also shown that the incorporation of additional functionality in the tetracyclic structures can be carried out using a slight modification of the radical cyclisation precursor. This has also led to the isolation of a novel pentacyclic structure (**396**).

Chapter 7

An Approach Towards the Synthesis of the Spirooxindole Alkaloids Horsfiline and Coerulescine (Disconnection D)

7.1 Introduction

We have demonstrated in the preceding chapters that radical cyclisation into indole is facilitated by the incorporation of a cyano group at the 2-position. Consequently, we chose to investigate disconnection D, in order to gain more insight into direct radical addition onto the 3-position of indole (scheme 128). As target molecules for this study, the simple oxindole alkaloids horsfiline (**292**) and coerulescine (**293**) were chosen.

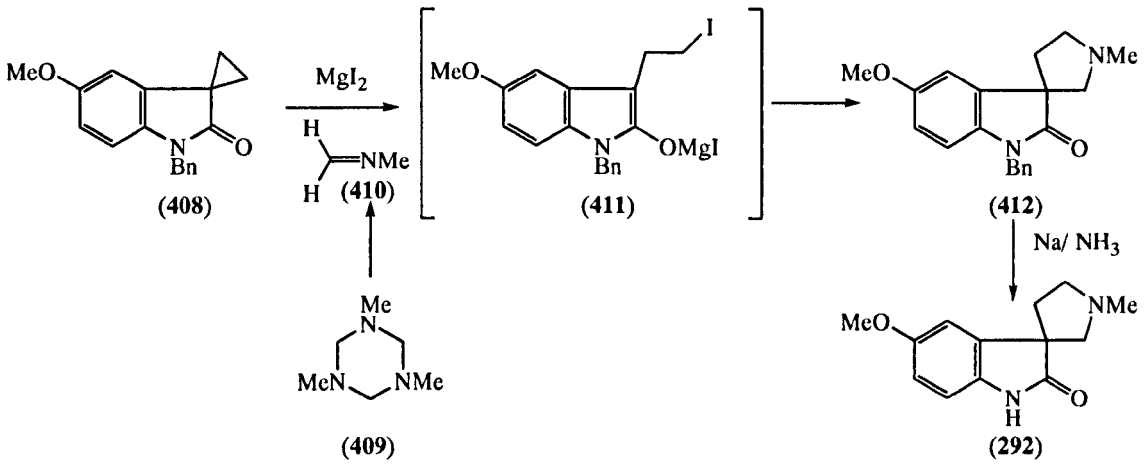


(406) (407)

Scheme 128

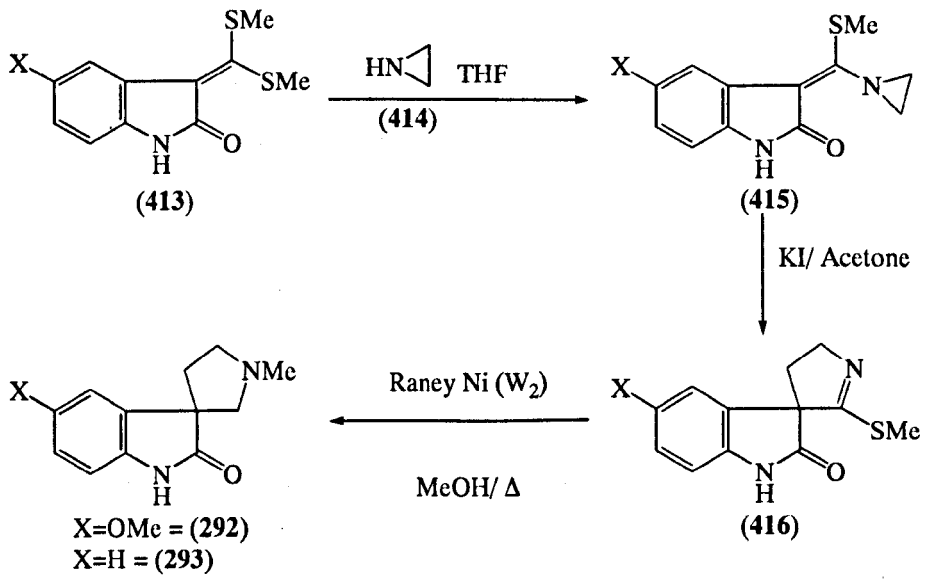
Horsfiline (**292**) was first isolated from *Horsfieldia superba*, a small tree from Malaysia, which is sometimes used as a medicinal plant.[198] Coerulescine (**293**) was first isolated in 1998 from *Phalaris coerulescens*, and has been linked to neurotoxic and cardiotoxic effects in animals eating the grasses of *Phalaris*.[199,239] Previous syntheses of horsfiline (**292**) and coerulescine (**293**) have focused on the oxidative rearrangement of β-carbolines.[240,10,241,242] Kornet and Bascop have used an intramolecular Mannich reaction to form coerulescine and horsfiline.[243,244] Fuji has also used the intramolecular Mannich reaction in his synthesis of (-)-horsfiline (**292**), following asymmetric nitroolefination.[245] Brown has used a cycloaddition approach to the pyrrolidine core of (±)-horsfiline (**292**),[246] as has Palmisano in his synthesis of (-)-horsfiline.[247,248] Carreira has introduced a novel MgI_2 catalysed ring expansion of a spiro[cyclopropane-1,3'-indol]-2'-one (**408**) (scheme 129).[229] Treatment of the cyclopropane (**408**) with a catalytic amount of magnesium iodide and a stoichiometric amount of the imine (**410**), itself derived from 1,3,5-trimethyl-1,3,5-triazinane (**409**), resulted in the formation of

the benzyl-protected horsfiline (**412**) in 83% yield (scheme 129). This was readily deprotected following treatment with sodium in ammonia.



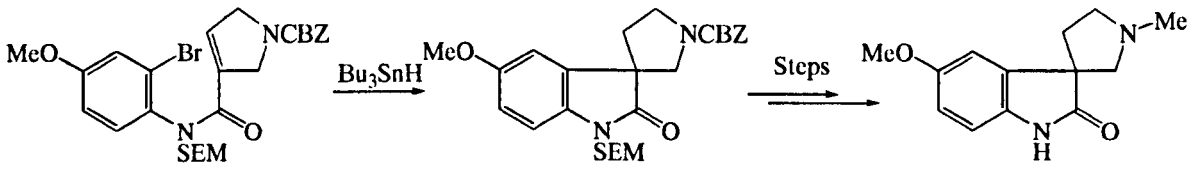
Scheme 129

More recently, Junjappa has utilised a similar approach to horsfiline and coerulescine *via* an iodide ion mediated rearrangement of [(*N*-aziridinomethylthio)methylene]-2-oxindoles.[249] Reaction of the α-oxoketene dithioacetal (**413**) with the aziridine (**414**) generated the oxindole (**415**). Treatment of this oxindole (**415**) with potassium iodide resulted in the formation of the pyrroline (**416**). Reductive dethiomethylation of this pyrroline (**416**) gave either horsfiline (**292**) or coerulescine (**293**) (scheme 130).



Scheme 130

There have been relatively few syntheses of horsfiline (**292**) using radical chemistry. Jones' work in the field of aryl radical cyclisations has led to a synthesis of horsfiline (**292**).[250] Generation of the aryl radical from the cyclisation precursor (**417**), followed by a 5-*exo*-trig radical cyclisation, resulted in the formation of the spirocyclic oxindole (**418**) This was then deprotected and converted into horsfiline (**292**) in three steps (scheme 131). Cossy has followed Jones' work in a synthesis of the core structure of coerulescine (**293**).[251] More recently, Murphy has completed a total synthesis of horsfiline (**292**) using an aryl iodoazide tandem cyclisation, based on his earlier approaches towards aspidospermidine.[252]

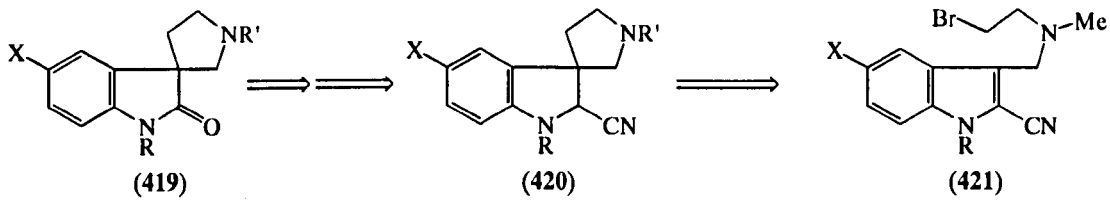


(417) (418) (292)

Scheme 131

7.2 Retrosynthesis of Horsfiline (292) and Coerulescine (293)

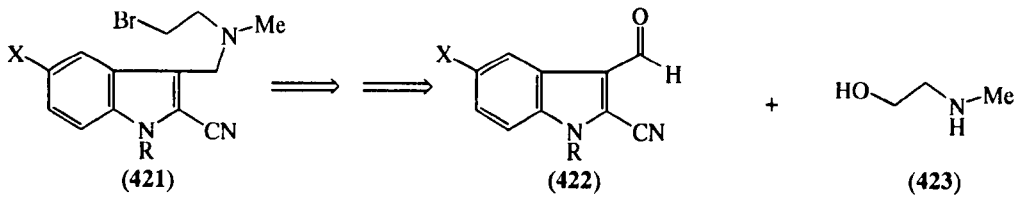
Our synthetic approach is based on disconnection D as previously outlined in Chapter 3. The key step is radical cyclisation of the precursor (**421**), to generate the tricyclic spirocyclic compound (**420**) (scheme 132).



(419) (420) (421)

Scheme 132

We envisaged that the tricyclic compound (**421**) could be formed *via* a reductive amination of the appropriate aldehyde (**422**) with *N*-methylethanolamine (**423**), or the protected alcohol (scheme 133). The bromo compound (**421**) should be readily accessible from the alcohol.



(421) (422) (423)

Scheme 133

The synthesis of the desired 3-formyl-2-cyano indoles (**422**) presented the problem related to the incorporation of two electron-withdrawing groups next to each other. However, reports in the literature on the formylation of 2-cyanoindole by Fang seemed to indicate that this would not pose a problem.[253,254]

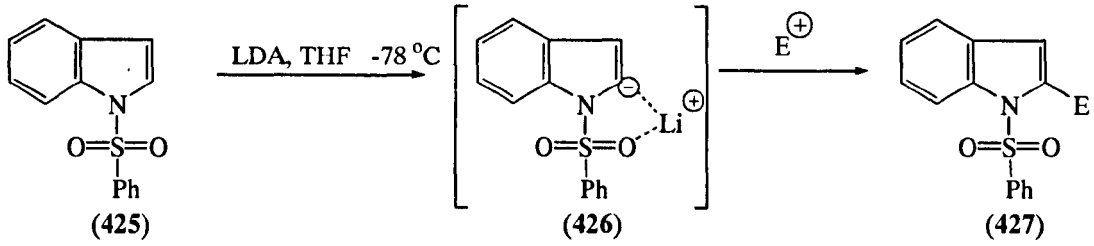
7.3 Attempted Synthesis of 2-Cyano-3-Formylindoles (422)

Our synthetic approach to the formation of the 3-formyl-2-cyanoindole was based on the formylation of 2-cyanoindoles. We therefore set out to synthesise 2-cyanoindole (**355**) and 2-cyano-5-methoxyindole (**424**) (figure 46).

(424) (355)

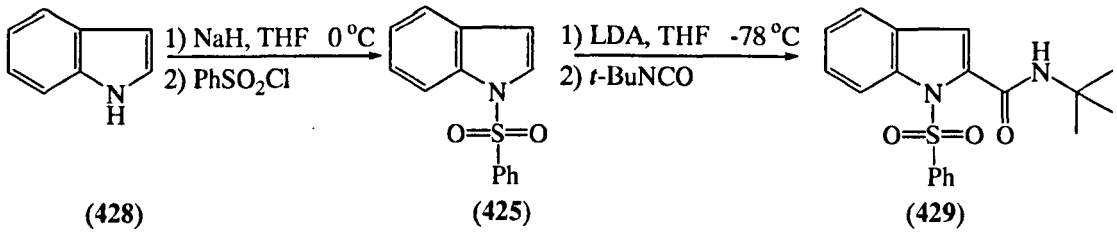
Figure 46

The literature contains many examples of the formation of cyano-substituted indoles. However, we required a general synthesis of 2-cyanoindoles, which would also allow us to synthesise 5-methoxy-2-cyanoindole (**424**). Work by Gribble has shown that 2-lithiaton of indoles can be achieved selectively by deprotonation of 1-phenylsulfonylindole (**425**) with lithium diisopropylamide (LDA). This can then be reacted with a range of electrophiles to give 2-substituted indoles (scheme 134).[255,256] The reaction can also be carried out with 5-methoxy-1-phenylsulfonylindole.[256]



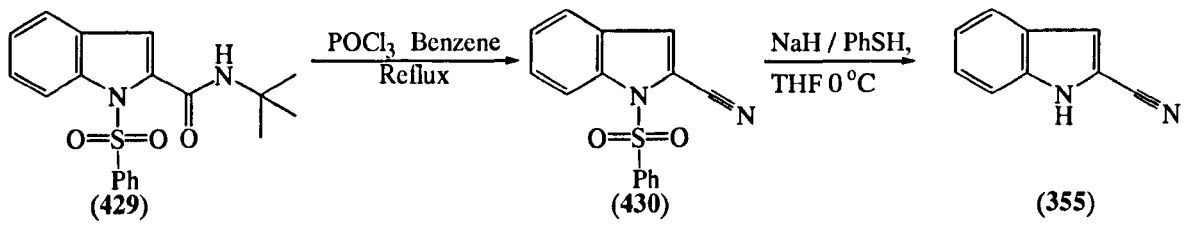
Scheme 134

We therefore reacted indole (**428**) with sodium hydride followed by phenylsulfonyl chloride to give 1-benzenesulfonyl-1*H*-indole (**425**) in 82% yield (scheme 134). Reaction of this protected indole (**425**) with LDA, followed by quenching with *t*-butylisocyanate, gave the 2-substituted indole (**429**) in 54% yield (scheme 135). We were unable to obtain the same yields recorded by Gribble in his synthesis.[257]



Scheme 135

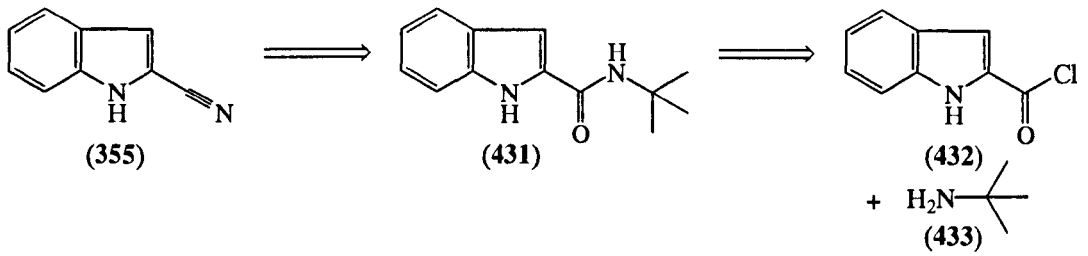
Treatment of this amide (**429**) with phosphorus oxychloride led to formation of the protected 2-cyanoindole (**430**) in 83% yield (scheme 136).[257] In order to remove the phenylsulfonyl group, we utilised a procedure by Fang,[254] whereby treatment of 1-benzenesulfonyl-1*H*-indole-2-carbonitrile (**430**) with freshly prepared sodium thiophenoxide gave 2-cyanoindole (**355**) in 93% yield (scheme 136).



Scheme 136

In the synthesis of 2-cyanoindole (**355**) thus far, the overall yield was relatively low. We also had to incorporate protection and deprotection steps in the synthesis, which

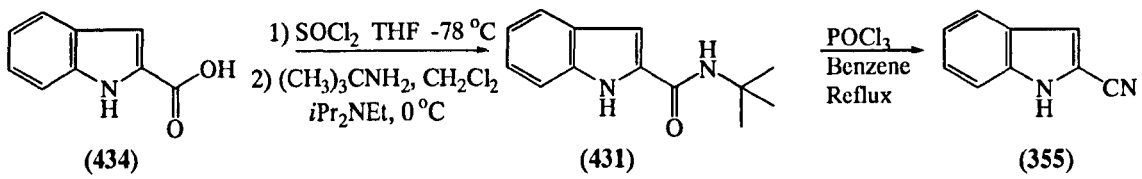
was costly in terms of material and in the number of steps. In order to avoid the use of protection and deprotection, we employed a different route to 2-cyanoindole (**355**) and 5-methoxy-2-cyanoindole (**424**). Functional group interchange of 2-cyanoindole (**355**) leads back to the amide (**431**). This can then be further disconnected to give the acid chloride (**432**) and *t*-butylamine (**433**) (scheme 137).



Scheme 137

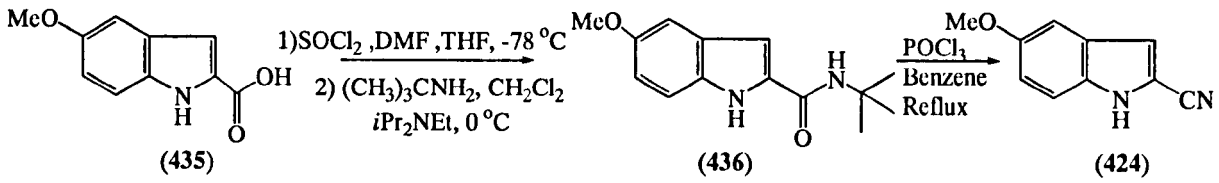
Formation of amides (**431**) from the acid chlorides should provide a shorter synthesis as both indole-2-carboxylic acid (**434**) and 5-methoxyindole-2-carboxylic acid (**435**) are commercially available. The synthesis of the respective 2-cyano compounds was therefore potentially better, as the total number of steps is limited to three.

Following a procedure of Reed,[258] indole-2-carboxylic acid (**434**) was treated with thionyl chloride and a catalytic amount of DMF (scheme 138). The acid chloride was reacted immediately with *t*-butylamine in the presence of Hünig's base to give the amide (**431**) in 96% yield (scheme 138). Treatment of the amide (**431**) with phosphorus oxychloride resulted in a 91% yield of 2-cyanoindole (**355**) (scheme 138).



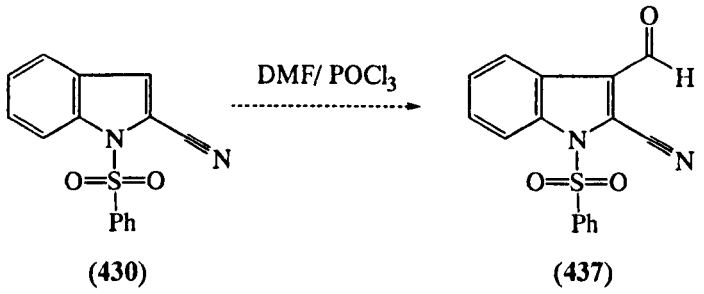
Scheme 138

As a result of the successful formation of 2-cyanoindole (**355**) in high yield, we next repeated the sequence of reactions for 5-methoxyindole-2-carboxylic acid (**435**). Modification of the procedure by Roques[259] for the synthesis of the acid chloride by addition of a catalytic amount of DMF, followed by reaction with *t*-butylamine, gave the amide (**436**) in 70% yield (scheme 139). Treatment with phosphorus oxychloride gave the nitrile (**424**) in 70% yield.



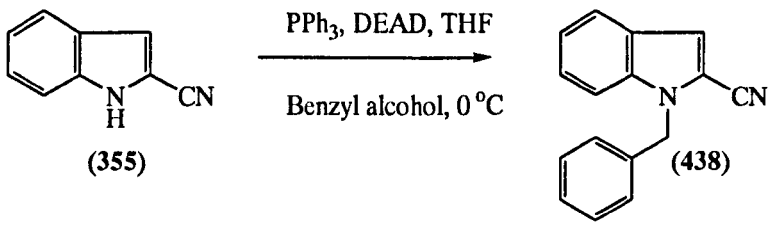
Scheme 139

Having prepared the required 2-cyanoindoles in good yield, we attempted a range of formylation reactions in order to synthesise the required 2-cyano-3-formylindoles. Attempted Vilsmeier formylation of 1-phenylsulfonyl-2-cyanoindole (**430**) using the same conditions as in previous chapters did not yield any of the expected product (**437**) (scheme 140). Unexpectedly, small amounts of 2-cyanoindole (**355**) were formed from the reaction.



Scheme 140

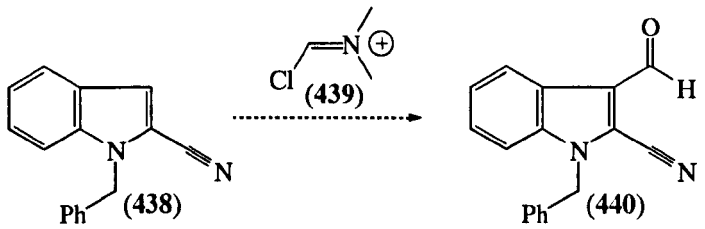
Repetition of the reaction with 2-cyanoindole (**355**), in place of 1-phenylsulfonyl-2-cyanoindole (**430**), also failed to yield the desired product. A number of formylated products were isolated from the reaction mixture, leading us to conclude that we needed to protect the indole nitrogen. The reaction of 2-cyanoindole (**355**) and benzyl alcohol under Mitsunobu conditions[235] gave a 96% yield of the benzyl protected 2-cyanoindole (**438**) (scheme 141).



Scheme 141

Attempted formylation using the same conditions as before failed to yield any product. At this stage, we believed that we needed a different formylation approach. The

conditions we had used previously, did not lead to clean formation of the Vilsmeier reagent. We therefore utilised a procedure by Bergman, whereby the Vilsmeier reagent was prepared very cleanly.[260,261] Formation of *N,N*-dimethylchloromethaniminium chloride (**439**), followed by addition of 1-benzyl-2-cyanoindole (**438**), did not lead to any of the desired product (**440**) (scheme 142).

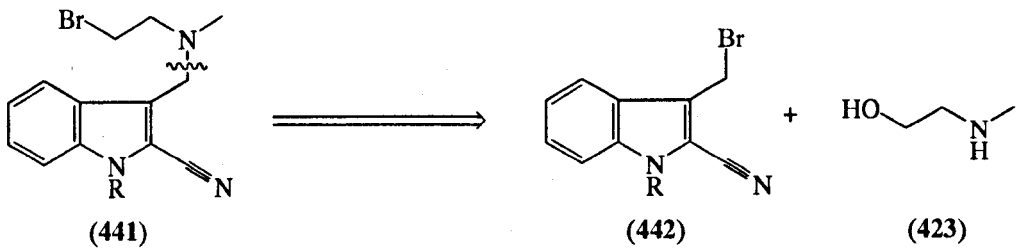


Scheme 142

Use of the conditions employed by Kempf and also Lachance also failed to yield the formylated product (**440**),[262,263] whereby *N*-methylformanilide was used in place of DMF. None of the cyanoindoles prepared could be cleanly formylated under any conditions explored.

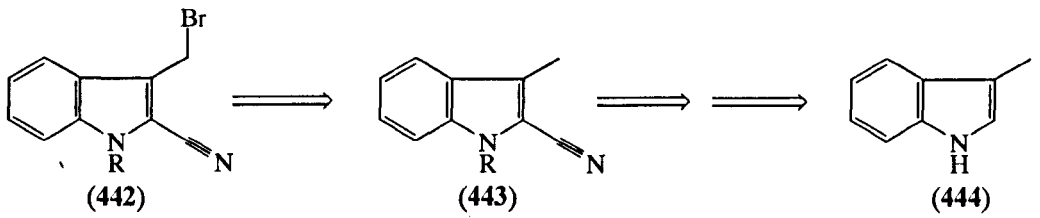
7.4 Second Retrosynthesis of Coerulescine (293)

The failure to incorporate a formyl group at the 3-position of 2-cyanoindole (**355**) led to an alternative approach to the tertiary amine (**441**) (scheme 143). Disconnection of the benzylic C-*N* bond leads back to the benzylic bromide (**442**) and *N*-methylethanolamine (**423**).



Scheme 143

We envisaged that the bromine could be incorporated *via* a benzylic bromination (scheme 145). The synthesis of the 3-methyl-2-cyanoindole (**443**) could again be approached using the chemistry of Gribble,[257] starting from 3-methyl indole (**444**).

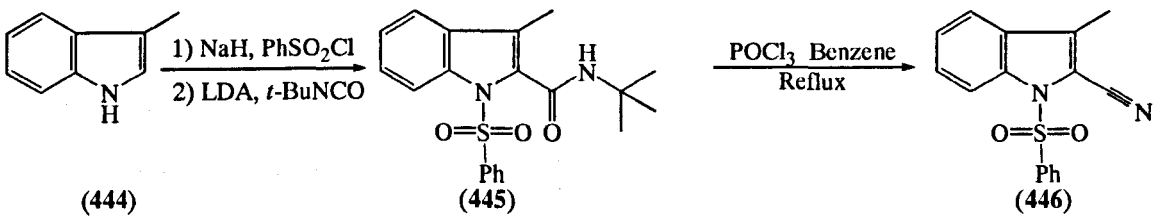


Scheme 144

Our synthesis was limited as a result of this disconnection. Only 3-methylindole (**444**) is commercially available, which would give rise to coerulescine (**293**).

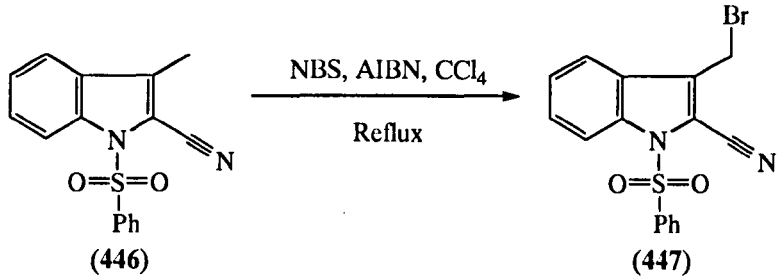
7.5 Synthetic Approach

Treatment of 3-methylindole (**444**) with sodium hydride, followed by addition of phenylsulfonyl chloride, generated 1-benzenesulfonyl-3-methylindole in 85% yield (scheme 145).[264,265] Addition of the protected indole to a solution of LDA, followed by addition of *t*-butylisocyanate, led to the amide (**445**) in 68% yield (scheme 145). Addition of phosphorus oxychloride to a solution of this amide (**445**) gave 1-benzenesulfonyl-3-methylindole-2-carbonitrile (**446**) in 83% yield (scheme 145).



Scheme 145

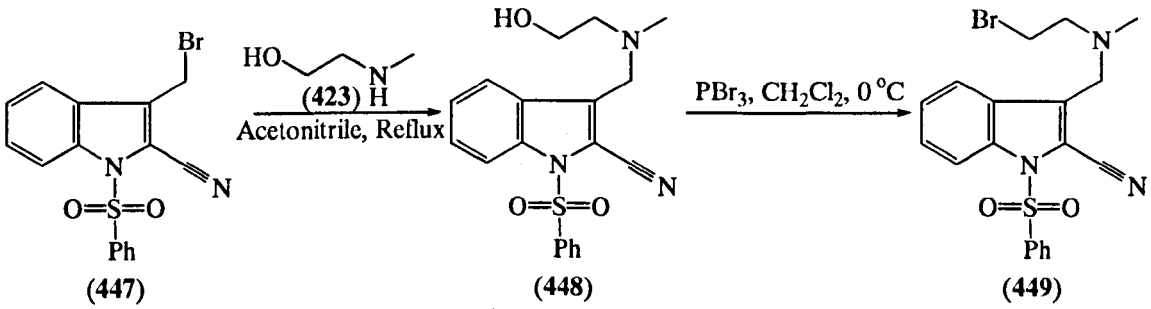
Using Cook's procedure for the regiospecific bromination of 3-methylindoles,[266,267] we carried out a radical benzylic bromination of our protected 3-methyl-2-cyanoindole (**446**) (scheme 146). Reaction with *N*-bromo succinimide and AIBN in carbon tetrachloride gave the brominated indole (**447**) in 86% yield (scheme 146). We also observed that heptane could be used in place of carbon tetrachloride, with no appreciable loss of yield.



(446) (447)

Scheme 146

Reaction of a solution of the benzylic bromide (**447**) with *N*-methylethanolamine in dry acetonitrile gave the tertiary amine (**448**) in 78% yield. Using toluene in place of acetonitrile reduced the yield to 68% (scheme 147). Treatment of the resultant alcohol (**448**) with a solution of phosphorus tribromide in dichloromethane, gave the bromo-compound (**449**) in 57% yield (scheme 147). We had now obtained the radical cyclisation precursor that we required to synthesise the core of coerulescine (**293**).

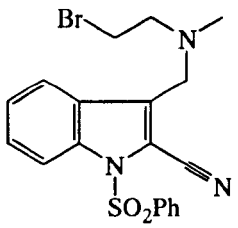


(447) (448) (449)

Scheme 147

7.6 Radical Cyclisation of the Precursor (449)

We chose toluene as solvent in the radical cyclisation of the precursor (**449**). We did not need the high temperatures used in previous examples, as there was no problem associated with amide rotamers. Syringe pump addition of a solution of tri-*n*-butyltin hydride and AIBN in toluene to a solution of the cyclisation precursor, led to the formation of a product of R_f 0.08 and a white solid.



(449)

Bu_3SnH, AIBN, toluene

Syringe pump, reflux

Products

Scheme 148

The product of R_f 0.08 was isolated in 18 mg as a mixture of products, and was heavily contaminated by tin-containing by-products, which proved difficult to separate. It was immediately evident that this was not the desired cyclised product from the pattern of the aromatic protons in the ^1H NMR spectrum. No aromatic protons below δ 7.0 ppm were observed, which would have been indicative of cyclisation into indole.

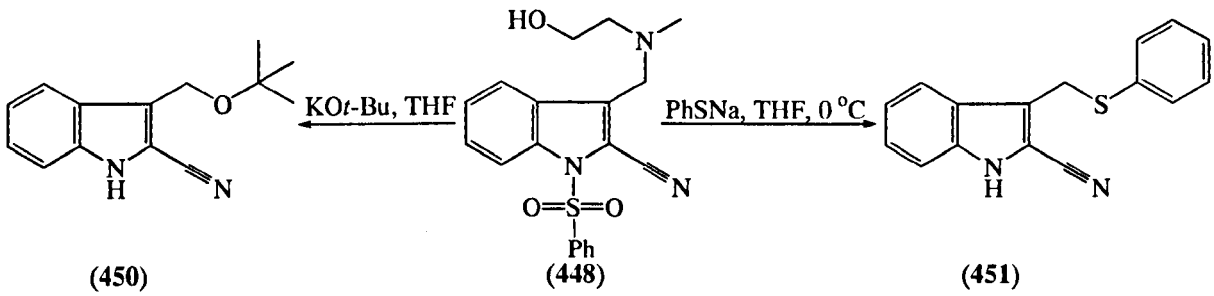
Approximately 80 mg of the insoluble product was isolated and was evidently not the cyclised product. No aromatic protons were observed below δ 7.0 ppm. It was also clear that the benzylic CH_2 was no longer present. A singlet for the *N*-methyl integrating for three protons at δ 3.26 ppm showed that this was still present. The ethyl group was still present and substituted at either end, on the basis of the two triplets at δ 3.10 ppm and δ 3.80 ppm which each integrated for two protons. This was confirmed in the ^{13}C NMR spectrum with two signals corresponding to two CH_2 groups at δ 20.73 ppm and δ 52.77 ppm. The methyl group was also present at δ 38.19 ppm. The compound also readily decomposed and we were unable to obtain an accurate mass spectrum for this compound. From the ^1H and ^{13}C NMR spectra it is difficult to assign a structure to this compound as no further evidence is available. We believe that the ethyl and the *N*-methyl signals indicate that the amine has formed the aziridinium salt, which may account for the insolubility of this compound.

7.7 Synthesis of an Alternative Radical Cyclisation Precursor

The radical cyclisation of the phenylsulfonyl-protected precursor (**449**) generated results that were difficult to interpret on the evidence that we obtained. The phenylsulfonyl group had also been observed to cause problems in other radical cyclisations by other members within our group. The trimethylsilylethoxymethyl

(SEM) group had been used by Ho in his radical approach to elacomine.[192] We therefore chose to incorporate this into our cyclisation precursor in place of the phenylsulfonyl group.

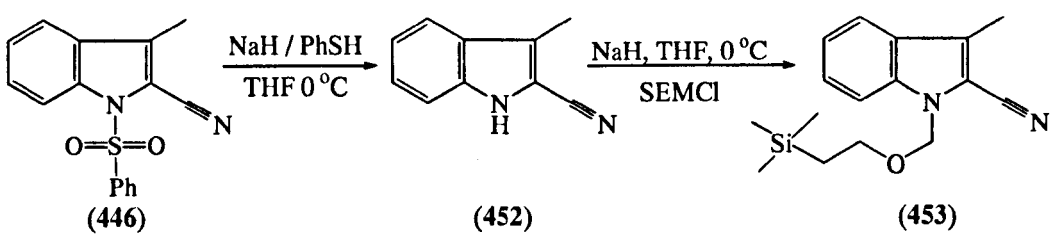
We attempted to remove the *N*-phenylsulfonyl group from the alcohol (**448**), following a procedure by Husson.[268] Treatment of a solution of the alcohol (**448**) with a five-fold excess of potassium *t*-butoxide resulted in the rapid decomposition of the starting material (**448**). The only isolable product was the *t*-butoxyether (**450**) in 16% yield (scheme 149).



(450) (448) (451)

Scheme 149

The phenylsulfonyl group had been removed and the amine displaced by *t*-butoxide to give the ether (**450**). We next attempted to use a milder method, opting for sodium thiophenoxide in place of potassium *t*-butoxide. However, we obtained the sulfenyl compound (**451**) in 86% yield. The attempted deprotections showed that we needed to deprotect the protected 3-methyl-2-cyanoindole (**446**) and not the preceding benzylic bromide (**447**). Addition of a solution of 1-benzenesulfonyl-3-methylindole-2-carbonitrile (**446**) to a freshly prepared solution of sodium thiophenoxide gave 3-methylindole-2-carbonitrile (**452**) in 72% yield (scheme 150).

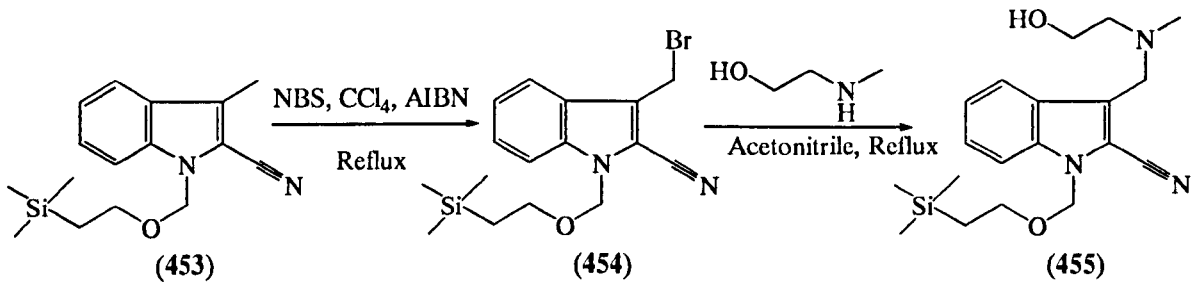


(446) (452) (453)

Scheme 150

Deprotonation of 3-methylindole-2-carbonitrile (**452**) with sodium hydride, followed by addition of (trimethylsilyl)ethoxymethyl chloride (SEMCl), gave the SEM-protected product (**452**) in 94% yield (scheme 150).

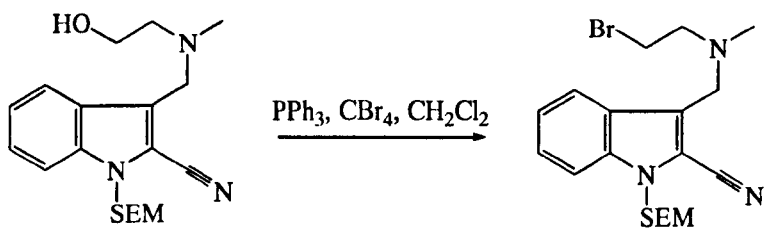
Benzylic bromination using the same conditions as before (scheme 151), gave the bromo SEM-protected bromoindole (**454**) in 77% yield. Addition of a solution of *N*-methylethanolamine to the bromoindole (**454**) led to the tertiary amine (**455**) in 96% yield (scheme 151).



(453) (454) (455)

Scheme 151

Conversion of the alcohol (**455**) to the bromo cyclisation precursor (**456**) proved troublesome. Use of phosphorus tribromide resulted in rapid decomposition of the starting material, with loss of the SEM protecting group. Application of the conditions used by Thomas,[269] whereby addition of a solution of triphenylphosphine to a solution of the alcohol (**455**) and carbon tetrabromide, gave the cyclisation precursor (**456**) in 80% yield (scheme 152). Little or no decomposition of the starting material was observed using these conditions.

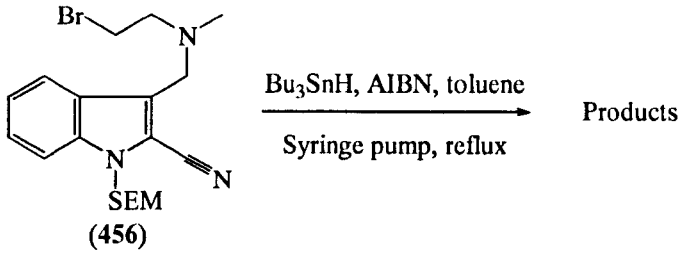


(455) (456)

Scheme 152

7.8 Radical Cyclisation of the SEM Protected Precursor (456)

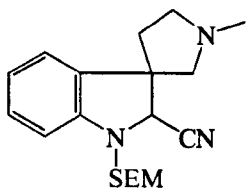
Radical cyclisation of a solution of the precursor (**456**) using syringe pump addition of a solution of tri-*n*-butyltin hydride and AIBN gave a light yellow oil in 140 mg (scheme 153).



(456)

Scheme 153

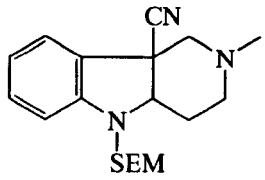
It was apparent from the ^1H NMR spectrum that radical cyclisation into indole had taken place from the shift upfield in the aromatic protons. An AB quartet for the benzylic CH_2 was apparent at δ 2.49 ppm and δ 2.83 ppm as expected. There was no evidence, however, of the C-H singlet next to the cyano group at around δ 4.00 ppm, which we would also have expected. A triplet at δ 3.56 ppm appeared to account for this. This was not the expected cyclised product (**457**) (figure 47).



(457)

Figure 47

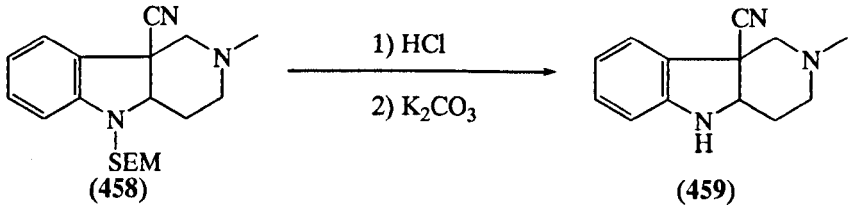
In the ^{13}C NMR spectrum a signal for a C-H at δ 44.19 ppm was evident along with the *N*-methyl at δ 46.06 ppm. A quaternary carbon at δ 64.80 ppm indicated that a tetrasubstituted centre had been formed either at the C-2 or C-3 position. There were four quaternary carbon atoms in total in the ^{13}C NMR spectrum, indicating that the cyano group was still present. On the basis of the NMR data that we obtained, we have assigned the structure (**458**) shown below to the compound that we obtained (figure 48).



(458)

Figure 48

The evidence for this compound was strengthened following removal of the SEM group by acid treatment of the unknown compound (**458**). This removed the SEM group and also removed the last traces of tin by-products from the NMR spectra (scheme 154).

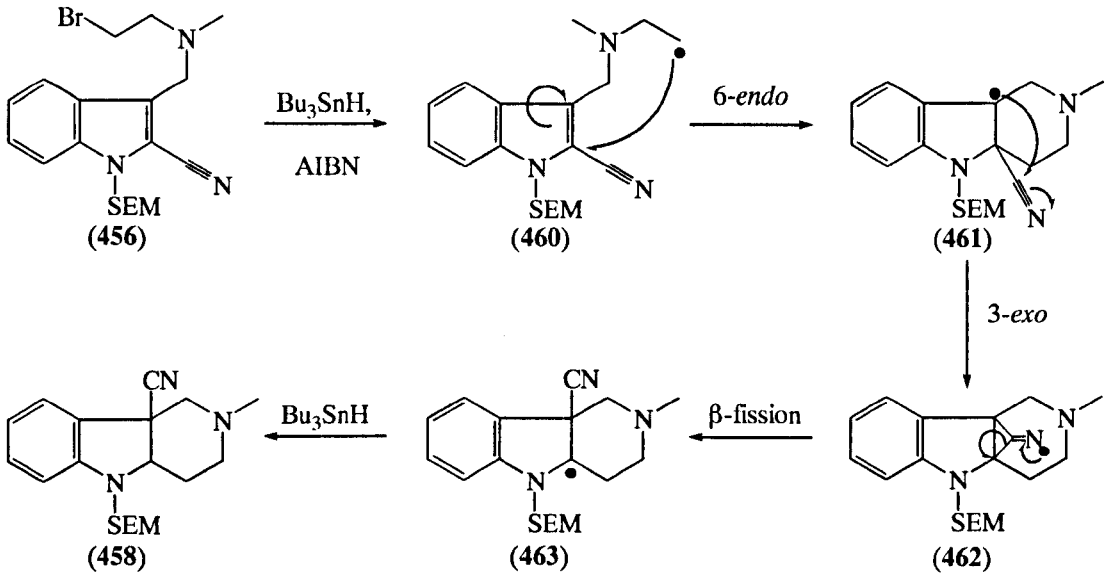


(458) (459)

Scheme 154

Removal of the SEM group helped to clarify the aliphatic region of the ^1H NMR spectrum. ^1H COSY analysis of the deprotected compound (**459**) showed that the triplet at δ 3.41 ppm was indeed coupling to the ethyl part of the molecule at around δ 2.00 ppm. The AB quartet at δ 2.54 ppm and δ 2.70 ppm was clearly isolated and not coupled to anything else. We were therefore more confident about our original structural assignment of this compound (**458**). An accurate mass spectrum of both the protected and deprotected compounds helped to confirm the formation of these compounds. However, the mechanism for the formation of these structures is not immediately apparent. What is probable is that aziridine formation is a major problem in this precursor (**456**) and the previous (**449**) cyclisation precursor. From the literature it appears that aziridine formation occurs readily and under mild conditions.[270]

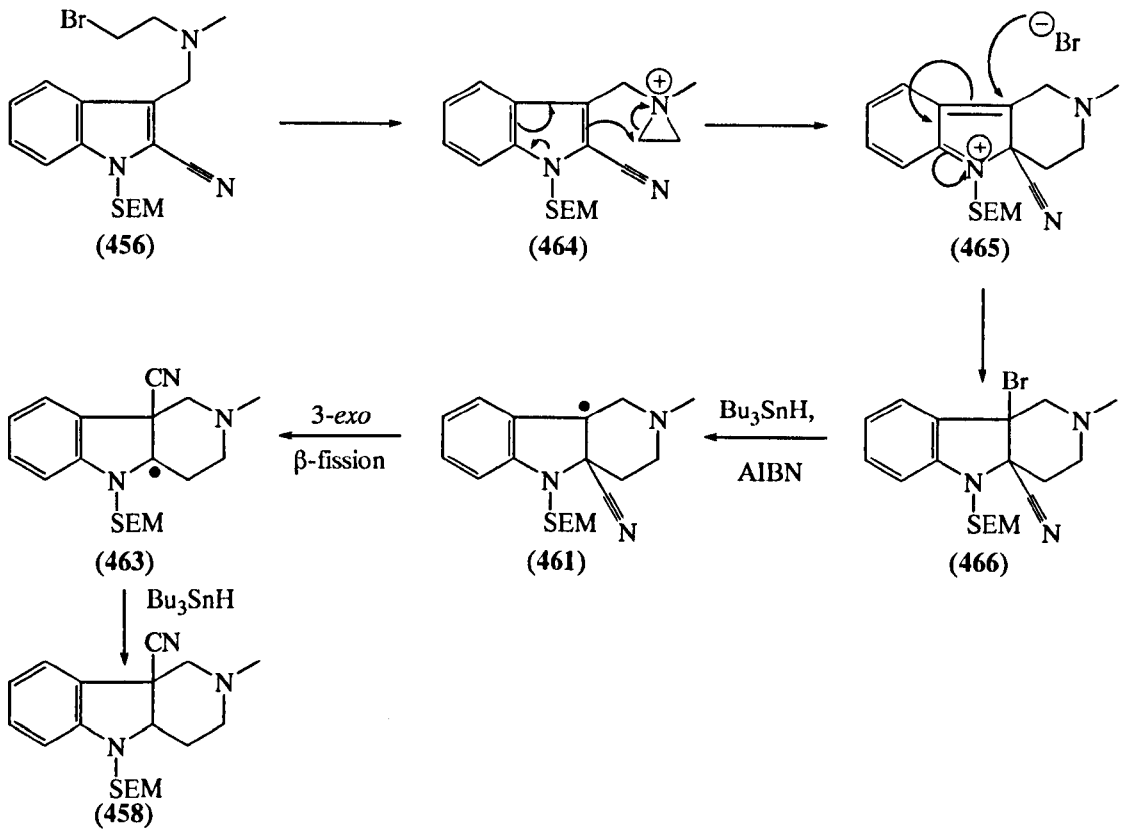
There are two possible mechanistic routes for the formation of the tricyclic structure (**458**). The first involves 6-*endo*-trig addition of the primary radical (**460**). The resultant radical (**461**) then undergoes a 3-*exo*-dig addition/ β-fission reaction to give the α-amino radical (**463**), which is then reduced by tri-*n*-butyltin hydride (scheme 155).



Scheme 155

This mechanism seems unlikely on the basis of previous work where no evidence of 6-*endo* cyclisation into indole was observed.

The next mechanism (scheme 156), involves initial formation of the aziridine (**464**), followed by ring opening by the indole C-2 position to give tricyclic structure (**465**). The bromide anion presumably attacks this structure to allow re-aromatisation to give the bromo compound (**466**). This, on treatment with tri-*n*-butyltin hydride, generates the benzylic radical (**461**) which undergoes the previous 3-*exo*-dig addition, followed by a β-fission reaction to give the α-amino radical (**463**) which is reduced by tri-*n*-butyltin hydride to give the reduced product (**458**) (scheme 156).



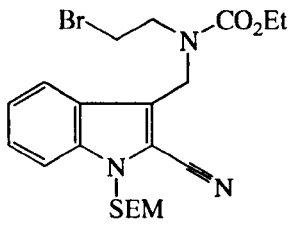
Scheme 156

Of the two mechanisms, the latter is perhaps the most probable on the basis of the previous results. However, in order to determine if this is indeed the correct mechanism, we would need to repeat the cyclisation without tri-*n*-butyltin hydride or AIBN. Therefore, simple heating of the reactants in toluene should enable us to observe the formation of the tricyclic structure **(466)**.

7.9 Conclusions and Future Work

In previous chapters, we have shown that radical cyclisations into indole were successful when a cyano group was incorporated at the indole C-2 position. Unfortunately, the simple approach in this chapter has failed to realise similar results. The probable mechanistic pathways involve decomposition and rearrangement in preference to radical cyclisation.

One way of avoiding the rearrangement problems associated with the cyclisation precursors is to synthesise the cyclisation precursor shown below (figure 49).



(467)

Figure 49

The ester group on the nitrogen should stop formation of the aziridine and so allow successful cyclisation into indole. This would also allow us to direct our efforts towards a synthesis of analogues of the spirotryprostatins, which possess an amidic nitrogen at the same position as this potential cyclisation precursor.

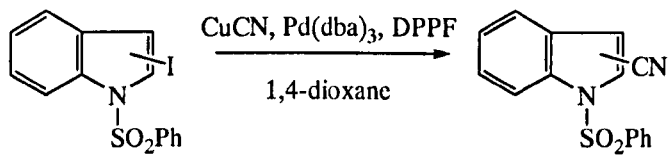
Chapter 8

Synthesis of 3-Substituted 2-Cyanoindoles

8.1 Synthetic Approach

In order to improve our route to the tetracyclic alkaloid precursor (**267**) (page 49) we need to overcome the lengthy and low-yielding incorporation of the 2-cyano group presented in chapter 4.

Reports in the literature suggested that palladium-catalysed cyanation of the corresponding 2-haloindoles would give the desired 2-cyano indoles.[271,272] Sakamoto converted both 2- and 3- iodo-*N*-phenylsulfonylindoles (**468**) to the corresponding cyanoindoles (**469**) using copper cyanide in the presence of a palladium catalyst in 1,4-dioxane in good yields (scheme 157).[271]

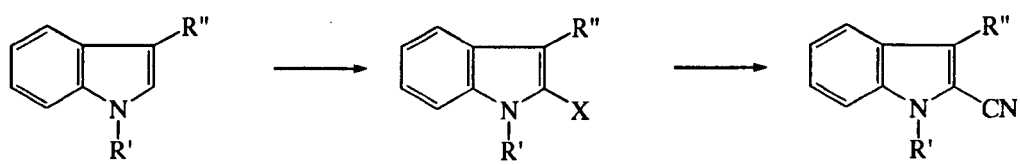


(**468**) (**469**)

Scheme 157

Fukuyama has also succeeded in generating 2-cyano-3-substituted indoles following earlier work by Okamoto.[273,274] Treatment of the aryl halide with potassium cyanide in the presence of $Pd(PPh_3)_4$ gave the aryl-cyano compounds in good yields.

Our synthetic plan was to use the same methodology as Fukuyama and convert the 2-haloindole (**471**) to the corresponding nitrile (**472**). This would reduce the overall number of steps in the synthesis and also allow late stage introduction of a protecting group on the indole nitrogen.

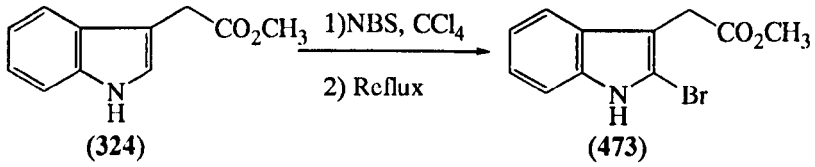


(**470**) (**471**) (**472**)

Scheme 158

Initial attempts at bromination of indole-3-acetic acid methyl ester (**324**) focused on the use of NBS in the presence of silica gel in a range of chlorinated solvents.[275] However, yields from this reaction were poor (~45 %) with recovery of starting material. Reactions with 3-methylindole (**444**) were carried out in the dark, due to the sensitivity of the product to light. Three products were evident from TLC of the crude reaction, with starting material constituting one of these.

As a result of the light-sensitivity of 2-bromo-3-methylindole we decided to focus on the reaction of the indole ester (**324**). Reaction of (**324**) with NBS in CCl_4 at room temperature for $1^1/_2$ hours followed by heating at reflux for 2 hours furnished the corresponding 2-bromoindole (**473**) compound in 87 % yield (scheme 159).[276]



(**324**) (**473**)

Scheme 159

Following the procedure of Fukuyama, treatment of the 2-bromoindole (**473**) with KCN and $Pd(PPh_3)_4$ in THF, gave only starting material. Heating the reaction also failed to give any product. Changing to copper cyanide and using 1,4-dioxane as reported also failed to give any product even after heating for several days. This prompted us to explore alternative older examples in the literature. Rapaport reported that treatment of 5-bromoindole with copper cyanide in *N*-methyl pyrrolidinone at reflux gave the corresponding cyano-derivative.[277] However in our case, none of the desired product could be isolated.

Owing to the apparent lack of reactivity of the 2-bromoindole, we attempted to synthesise the corresponding 2-iodoindole, as it should be more reactive towards palladium insertion. Treatment of indole ester (**324**) with chloramine-T and potassium iodide following the method of Vitale gave a complex mixture of products, presumably due to the reactivity of the corresponding 2-iodoindole ester.[278] Similarly carrying out the reaction with NIS in place of NBS also gave a complex mixture of products.

As a result of the failure of the palladium-catalysed cyanide insertion reaction, we decided to look at the mechanism of the reaction.

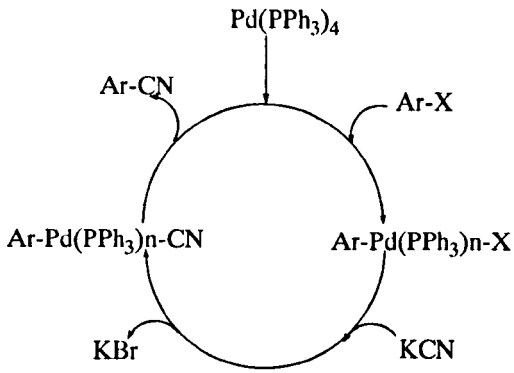
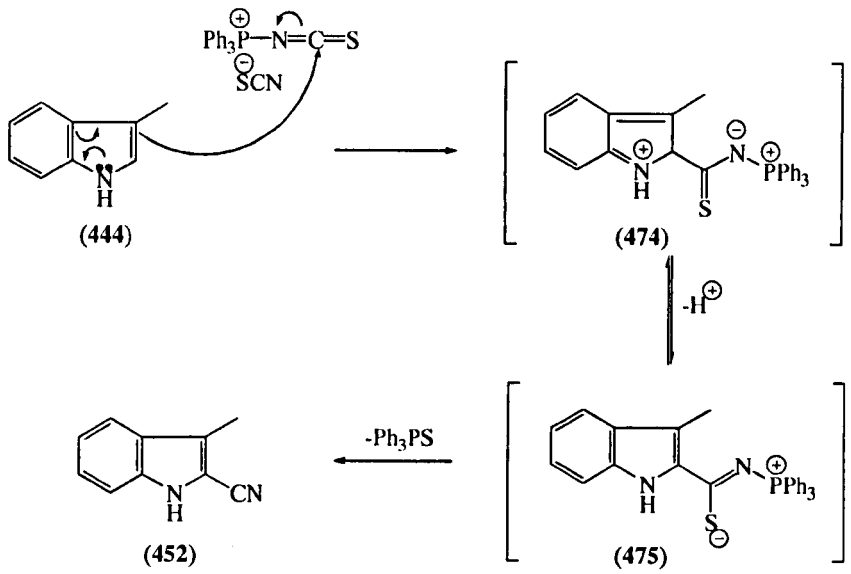


Figure 50

The initial step of the mechanism is insertion of palladium into the aryl/halogen bond followed by displacement of the halogen with cyanide and reductive elimination to form the aryl cyanide. In all cases, we recovered starting material from the reaction, which indicated that the initial reaction is a problem. This could be due to the fact that the C-2 position of the indole ester (**473**) is electron rich. This makes it harder for palladium to insert into the aryl/ halogen bond. In order to overcome this, it would be necessary to use either the iodo-derivative as used by Fukuyama or protect the indole nitrogen with an electron-withdrawing group as carried out by Sakamoto. Protection of the indole nitrogen with a phenyl sulfonyl group is not practical, as we have found it can cause problems in radical cyclisation reactions. Use of such a group would necessitate a further two steps, lengthening the synthesis still further and as a result is impractical for our requirements.

Tamura has developed an alternative cyanation reaction, with the use of triphenylphosphine-thiocyanogen (TPPT).[279] Reaction of a range of substituted indoles, including 3-methylindole, with TPPT gave the corresponding cyanoindoles. The proposed mechanism is shown below (Scheme 160).

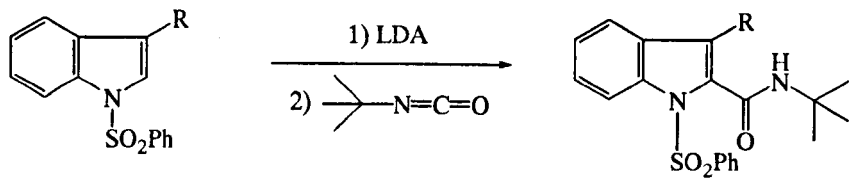


Scheme 160

Following the same procedure as Tamura, we carried out the reaction using the same conditions with 3-methyl indole (**444**).[279] However, none of the desired product was detected even by GCMS, with starting material recovered quantitatively. The reaction was repeated several times but in all cases, no product could be obtained.

As we had already shown that electrophilic brominations at the 2-position were high yielding, we believed cyanation could be achieved using a suitable source of $^{\oplus}CN$. The problem lay with the need to use an electron-withdrawing group on the indole nitrogen. As a result of this, we undertook a literature investigation into potential sources of electrophilic cyanation reagents, but found that there were few examples. We believed that with the right reagent and conditions, similar high yields to electrophilic brominations could be obtained.

In conjunction with this work, we were attempting to synthesise multi-gram quantities of 2-cyano and 2-cyano-3-methyl indole. The synthetic route used was based on work carried out by Gribble.[255,256] The synthesis of these compounds has been discussed previously (chapter 7) but the key step was reaction of an anion at the 2-position of a protected indole with *t*-butyl isocyanate (scheme 161). The product was then dehydrated to give 2-cyano indoles.



R= H = (425)
R=CH_3 = (476)

R= H = (429)
R=CH_3 = (445)

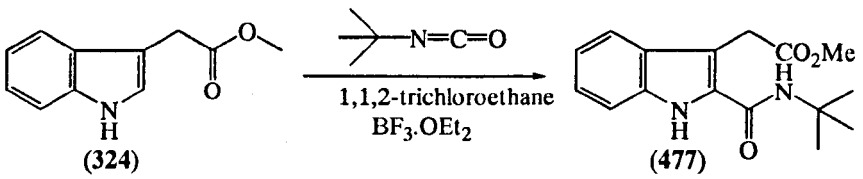
Scheme 161

Clearly the use of an *N*-phenylsulfonyl group is undesirable in our case. However, we thought that the electron-rich *N*-H indole might react directly with *t*-butyl isocyanate without the need for anion formation.

Both Gribble and Katritzky have used anion chemistry to activate indole.[255,280] Activation of both reactants or activation of *t*-butyl isocyanate has to our knowledge, not been investigated. We therefore decided to carry out reactions between *t*-butyl isocyanate and 3-substituted indoles.

Indole-3-acetic acid methyl ester (**324**) was initially reacted with *t*-butyl isocyanate in 1,1,2-trichloroethane and the resulting mixture heated at 110-115 °C for several days with no sign of product formation. This indicated that *t*-butyl isocyanate is not a powerful enough electrophile in itself and therefore activation is necessary. One possible means of activation of the isocyanate is to use a different group to *t*-butyl. Although chlorosulfonyl isocyanate has been used to prepare 2-cyanoindoles, both the reagent and conditions are unsuitable as *N*-protection is often required. Another possible means of activating *t*-butyl isocyanate is to use a Lewis acid to increase its electrophilicity.

We initially chose boron trifluoride etherate ($BF_3.OEt_2$) as the Lewis acid because of its moderate reactivity and its versatility. Addition of 1.2 equivalents of $BF_3.OEt_2$ to the solution of indole-3-acetic acid methyl ester (**324**) and isocyanate in 1,1,2-trichloroethane resulted in rapid formation of the 2-carboxamide (**477**) in approximately 62% yield at room temperature.



(**324**) (**477**)

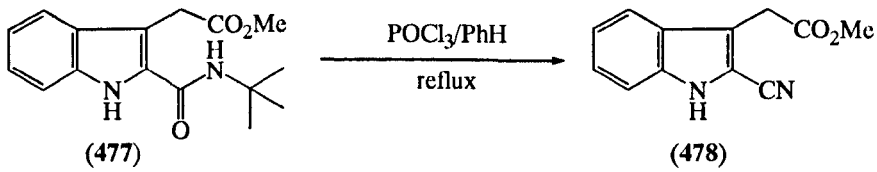
Scheme 162

In the ^1H NMR spectrum, loss of the C-2 hydrogen at δ 7.02 ppm was clearly observed along with formation of a singlet at δ 1.91 ppm that integrated for 9 hydrogens. The two NH hydrogens were also readily visible as broad singlets at δ 8.13 and δ 10.68 ppm.

Following this initial success, we attempted to optimise the reaction by increasing the amount of Lewis acid and also changing to a more common solvent in order to increase the flexibility of the reaction. Increasing the quantity of Lewis acid used to two equivalents and carrying out the reaction in dichloromethane resulted in a 97% yield of the amide (**477**).

Owing to the exothermic nature of the reaction on addition of $BF_3.OEt_2$, it was found that cooling was necessary when carrying out the reaction on amounts greater than 30 grammes. Therefore, subsequent reactions were carried out at 0 °C with slow addition of the Lewis acid.

With the amide (**477**) in hand, we next carried out the conversion to the cyano group following Gribble's chemistry. Treatment of the indole (**477**) with phosphorus oxychloride in benzene at reflux gave a 77% yield of the 2-cyanoindole acetic acid methyl ester (**478**) (scheme 163).



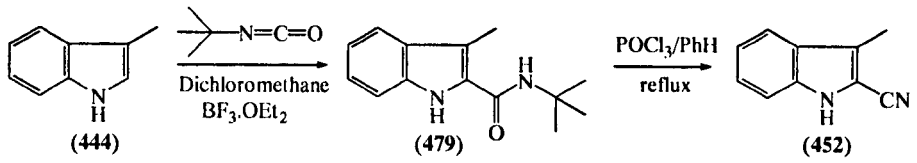
(**477**) (**478**)

Scheme 163

In addition to a clear infra-red peak for the cyano group (2224 cm^{-1}), the product contained a quaternary carbon resonance in the ^{13}C NMR spectrum at δ 113.75 ppm which was consistent with the cyano-carbon in previously prepared compounds.

Following the successful application of this new route, we next looked at the formation of 3-methyl-2-cyanoindole (**452**) using our new methodology. Treatment of 3-methylindole (**444**) with *t*-butyl isocyanate and $BF_3.OEt_2$ gave the amide (**479**) in 79%

yield, which was then converted to the nitrile (**452**) with phosphorus oxychloride in good yield (scheme 164).

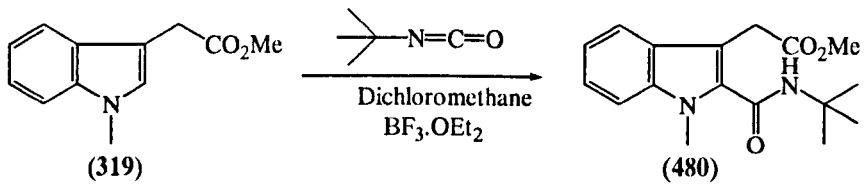


(444) (479) (452)

Scheme 164

The synthesis of 3-methyl-2-cyanoindole (**452**) in two steps was a great improvement on our previous route, which required four steps including a protection and a deprotection using harsh conditions.

We next looked at the reaction of *N*-protected indole-3-acetic acid methyl ester (**319**) using the previous conditions as shown below (scheme 165).

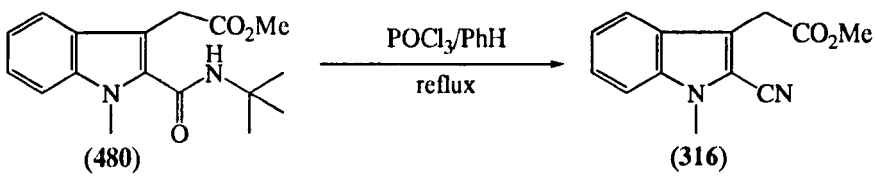


(319) (480)

Scheme 165

The reaction was carried out using 2 equivalents of Lewis acid, but only 60% of the amide (**480**) was obtained. Presumably, protection of the nitrogen reduces the reactivity of the indole C-2 position. ^{1}H NMR spectrum analysis revealed the appearance of an N-H as a broad singlet at δ 7.86 ppm, along with the disappearance of the signal for the C-2 hydrogen of the starting ester (**319**).

The amide (**480**) was then converted to the 2-cyanoindole (**316**) in 88% yield by treatment using standard conditions of phosphorus oxychloride in benzene at reflux.



(480) (316)

Scheme 166

The spectral and analytical data were in agreement with previous data (see chapters 4 and 7).

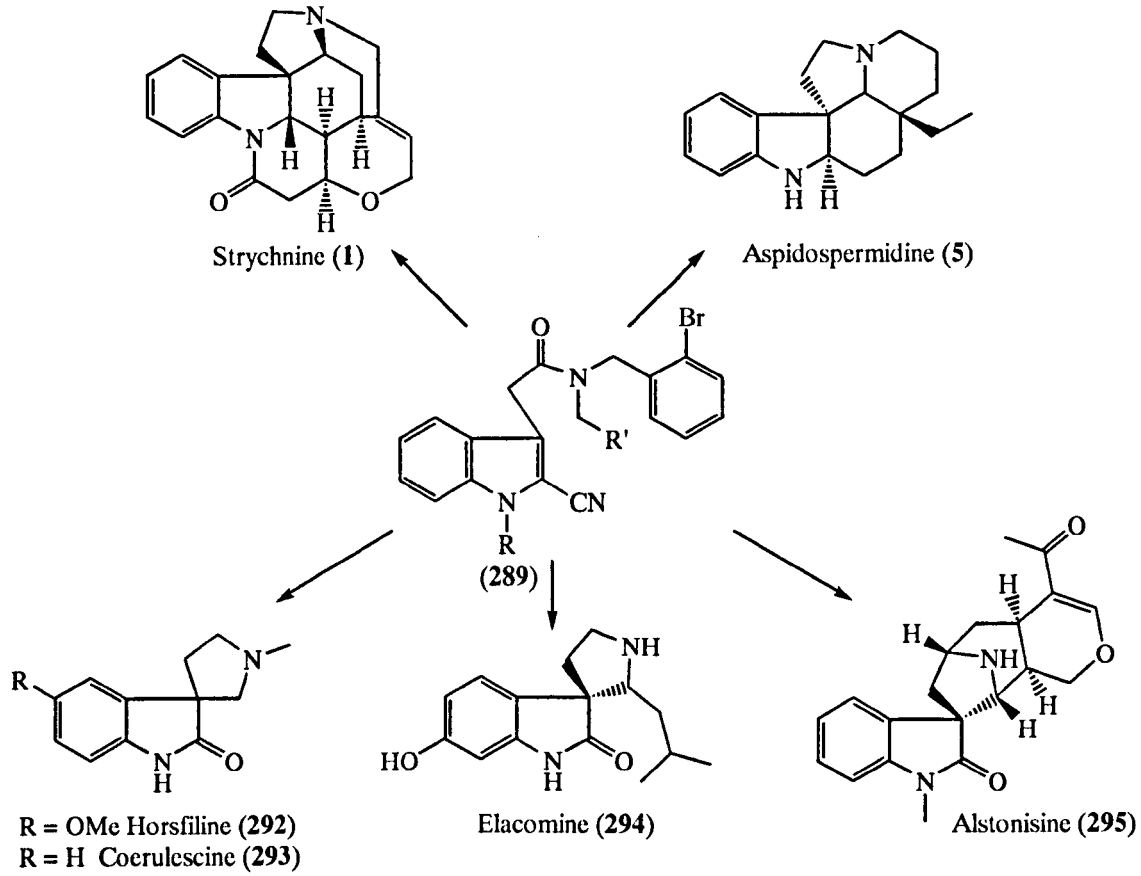
8.2 Summary

We have succeeded in developing a convenient route to 2-cyano-3-substituted indoles, which obviates the need for protection of the indole nitrogen. The use of $BF_3.OEt_2$ is sufficient to activate *t*-butyl isocyanate, which was previously used under anionic conditions. The synthesis of 2-cyano-3-substituted indoles can be conducted on relatively large scales (approximately 100 g for indole-3-acetic acid methyl ester) and without the need for extensive chromatography, which was required following the formylation step (chapter 4). The overall yield of the cyclised spirooxindole products has also been raised by this route.

Chapter 9

Future Work

Incorporation of the cyano group into the tandem radical cyclisation precursor has enabled us to form advanced intermediates towards the spirooxindoles and dihydroindole alkaloids. Simple variation of the R' group on the cyclisation precursor **(289)** has therefore enabled us to access the core structures of all the compounds shown below (scheme 167).



Scheme 167

Unfortunately there were two key limitations that restricted multi-gram formation of these compounds. The first problem was the synthesis of the 2-cyanoester **(478)** (figure 51).

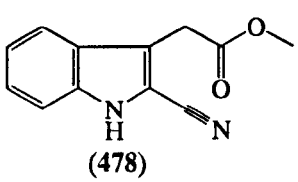
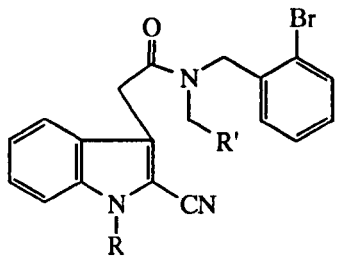


Figure 51

The initial low overall yield of this compound and the high number of steps limited our synthetic approach to the dihydroindole and oxindole synthetic targets. The problem stemmed principally from the incorporation of the cyano-group into the molecule. The formylation step was low yielding and required protection of the indole nitrogen. However, we have developed a convenient route to this compound, which is now readily available in multi-gram quantities in a short number of steps and has been covered in detail in chapter 8.

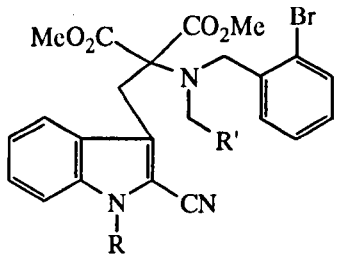
The second limitation is the incorporation of the amide bond in the cyclisation precursor **(289)** (figure 52).



(289)

Figure 52

Despite our attempts at increasing the yields of the cyclised products by raising the reaction temperature, we did not appear to have greatly increased the ratio of cyclised to reduced product by much more than the amide rotamer ratios. To increase the ratio of cyclised product, we need to remove the amide bond from the molecule to enable free rotation of the amine. One possible way of doing this is to make the amide acetal. Unfortunately there are relatively few easy examples of these compounds in the literature. Simple removal of the amidic carbonyl would allow free rotation, but would also generate another site suitable for 1,5-hydrogen atom abstraction by the benzylic radical. This would therefore effectively limit the yield of the cyclisation to 50%. Another option is to substitute the amidic carbonyl for another group. The amidic position must be blocked by two groups in order to stop 1,5-hydrogen atom abstraction from this position. A potential tandem radical cyclisation precursor is therefore outlined below **(481)** (figure 53).

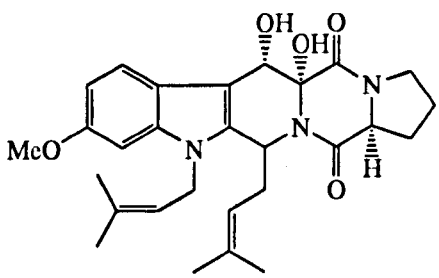


(481)

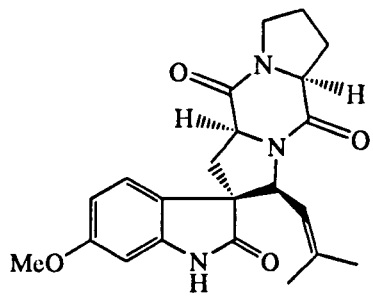
Figure 53

The two ester groups in place of the amidic carbonyl, solve the problem of 1,5-hydrogen atom abstraction from this position. They should also allow free rotation of the amine, which should increase the ratio of cyclised to reduced product. The two ester groups also have the added advantage of potentially increasing the rate of 5-*exo*-trig addition.[167]

Nagarathnam has achieved the synthesis of similar compounds,[281] as has Harrison in his synthetic approach towards the fumitremorgins.[282] These are very closely structurally related to the spirotryprostatins (figure 54).



Fumitrimorgin B (**482**)



Spirotryprostatin A (**296**)

Figure 54

Chapter 10 Experimental

General Details

All reactions requiring the use of dry conditions were carried out under an atmosphere of nitrogen and all glassware predried in an oven (110 °C) or flame dried and cooled under nitrogen prior to use. Stirring was by internal magnetic follower unless otherwise stated. All reactions were followed by TLC and organic phases extracted were dried with anhydrous magnesium sulfate.

Diethyl ether, tetrahydrofuran and toluene were distilled from sodium with benzophenone ketyl as indicator immediately before use. Dichloromethane, *N*-methylpyrrolidinone, pyridine and triethylamine were all distilled from calcium hydride before use. Methanol and ethanol were distilled from magnesium turnings and iodine under nitrogen, either directly into the reaction vessel, or stored and kept for later use over activated 3Å molecular sieves. Dimethylformamide was distilled from calcium hydride under reduced pressure and stored over activated 3Å molecular sieves prior to use. Acetonitrile was stirred over phosphorus pentoxide and distilled, followed by stirring over potassium carbonate and a second distillation before use. Acetic anhydride, benzyl bromide, benzyl alcohol, phosphorus oxychloride and *t*-butyl isocyanate were all freshly distilled immediately prior to use. Sodium hydride was washed with hexane at least three times prior to use. Triphenylphosphine was recrystallised from hexane and kept under an atmosphere of argon prior to use. *N*-Bromosuccinimide was recrystallised from water and dried in a drying pistol over phosphorus pentoxide before use.

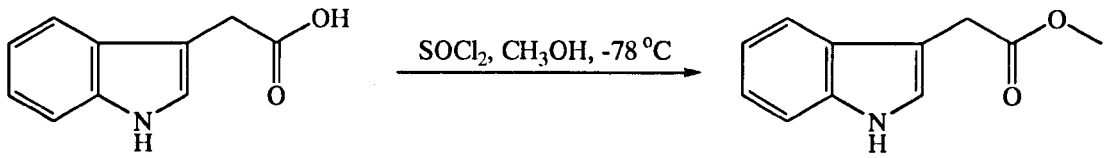
Purification was carried out by column chromatography using the flash column chromatography technique reported by Still.[283] The silica gel used was Merck 60 (230-400 mesh). Thin layer chromatographic analysis was carried out using Merck aluminium-backed plates coated with silica gel 60 F_{254}. Components were visualised using combinations of ultraviolet light, iodine and ceric ammonium molybdate stain.

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1605 FT-IR spectrophotometer using NaCl plates. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AM300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon.

Chemical shifts (δ_H and δ_C) are quoted as parts per million downfield from 0. The multiplicity of a ^{1}H NMR signal is designated by one of the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, br = broad and m = multiplet. Coupling constants (*J*) are expressed in Hertz.

High resolution mass spectra were carried out at King's College, London University or at Kingston University. Mass spectra carried out at King's College using either a Kratos MS89MS with Kratos DS90 software or a Jeol AX505W with Jeol complement data system. Samples were ionised electronically (EI), with an accelerating voltage of ~6kV or by low resolution fast atom bombardment (FAB) in a thioglycerol matrix. High resolution fast atom bombardment was carried out at the ULIRS mass spectrometry facility at the School of Pharmacy, University of London. Mass spectra carried out at Kingston University were recorded using a Micromass LCT time of flight mass spectrometer equipped with an ElectroSpray Ionisation (ESI) ion source. Elemental analyses of compounds were carried out at the Chemistry Department, University College, London University.

Indole-3-acetic acid methyl ester (324)

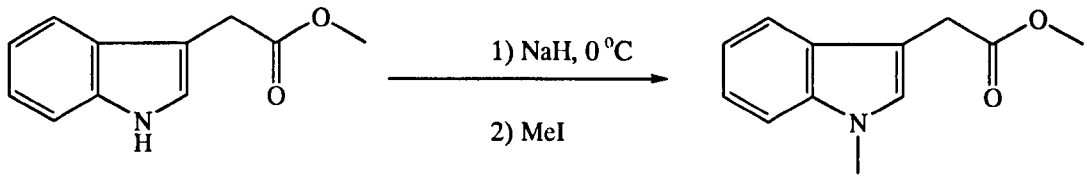


$C_{10}H_9NO_2$
Mol. Wt.: 175.18

$C_{11}H_{11}NO_2$
Mol. Wt.: 189.21

Thionyl chloride (5.0 cm^3, 8.14 g, 68.4 mmol) was added dropwise to a stirred solution of indole-3-acetic acid (**320**) (10.0 g, 57.0 mmol) in dry methanol (180 cm^3) at –78 °C under nitrogen. The solution was stirred at below –50 °C for two hours and then allowed to warm to room temperature and stirred overnight. Organic solvent and excess thionyl chloride were removed under reduced pressure and the crude product purified by distillation (168-170 °C / 2 mmHg) to give a colourless oil which solidified on standing to give the title compound (**324**) as a white solid (10.60 g, 98%); m.p. 49–51 °C (Lit.[284] 49-50.5 °C); R_f (2: 1, hexane: ethyl acetate) 0.41; (Found M^+, 189.0787, $C_{11}H_{11}NO_2$ requires M^+ 189.0790); ν_{max} /cm^{-1} 3408.3 (N-H), 1731.9 (CO_2CH_3); δ_H(300 MHz; $CDCl_3$) 3.75 (3H, s, OCH_3), 3.84 (2H, s, CH_2), 7.02 (1H, br s, C-2*H*), 7.19 – 7.31 (3H, m, C-5*H*, C-6*H*, C-7*H*), 7.67 (1H, dd, *J* 8.2 & 1.2, C-4*H*), 8.20 (1H, br s, N-*H*); δ_C(75 MHz; $CDCl_3$) 31.21 (CH_2), 52.09 (OCH_3), 108.04 (**C**-3), 111.43 (**C**-7), 118.79 (Ar-**C**-H), 119.66 (Ar-**C**-H), 122.14 (Ar-**C**-H), 123.41 (Ar-**C**-H), 127.19 (**C**-3a), 136.18 (**C**-7a), 172.96 (CO_2CH_3); *m/z* 189.08 (34.9%, M^+), 130.07 (100.0), 103.06 (10.4), 77.03 (16.9).

(1-Methyl-1*H*-indol-3-yl)-acetic acid methyl ester (319)

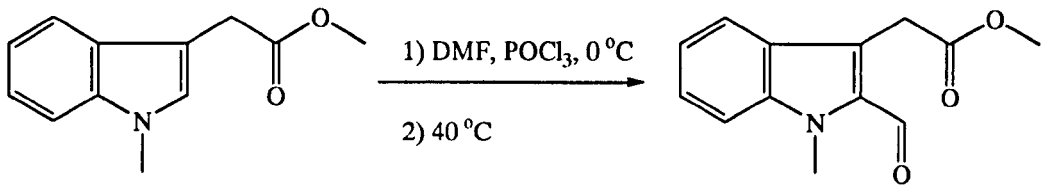


$C_{11}H_{11}NO_2$
Mol. Wt.: 189.21

$C_{12}H_{13}NO_2$
Mol. Wt.: 203.24

Indole-3-acetic acid methyl ester (**324**) (7.07 g, 37.4 mmol) in THF (50 cm^3) was added dropwise to a stirred suspension of sodium hydride (1.50 g of a 60% dispersion in mineral oil, hexane washed, 37.4 mmol) in THF (100 cm^3) at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred until the evolution of hydrogen had ceased. Methyl iodide (9.30 cm^3, 21.20 g, 149.5 mmol) was added dropwise and the resulting solution left to stir for 15 hours at room temperature. Water (70 cm^3) was added to quench the reaction and organic solvent was removed under reduced pressure. The resulting aqueous residue was extracted with diethyl ether (3 x 100 cm^3) and the combined organic extracts washed with brine (200 cm^3), dried ($MgSO_4$), filtered and solvent removed under reduced pressure to give a dark yellow oil. The crude product was purified by distillation under reduced pressure (148-150 °C / 2 mmHg) to give the title compound (**319**) as a light yellow oil (7.00 g, 92%); R_f (2: 1, hexane: ethyl acetate) 0.52; (Found M^+, 203.0942, $C_{12}H_{13}NO_2$ requires M^+ 203.0946); ν_{max} /cm^{-1} 1736.4 (CO_2CH_3); δ_H(300 MHz; $CDCl_3$) 3.76 (3H, s, O*CH*$_3$), 3.81 (3H, s, N*CH*$_3$), 3.89 (2H, s, *CH*$_2$), 7.09 (1H, s, C-2*H*), 7.27 (1H, m, C-5*H*), 7.37 (2H, m, C-6*H* & C-7*H*), 7.75 (1H, d, *J* 7.9, C-4*H*); δ_C(75 MHz; $CDCl_3$) 31.13 (CH_2), 32.69 (NCH_3), 52.02 (OCH_3), 106.81 (C-3), 109.38 (C-7), 119.01 (Ar-C-H), 119.32 (Ar-C-H), 121.84 (C-5), 127.74 (C-3a), 127.83 (C-2), 136.97 (C-7a), 172.62 (CO_2CH_3); *m/z* 204.09 (41.1%), 203.09 (79.0, M^+), 169.08 (68.4), 145.08 (66.4), 144.08 (100.0), 143.07 (65.0), 115.05 (51.7), 102.04 (55.7), 77.04 (51.5).

(2-Formyl-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (318)

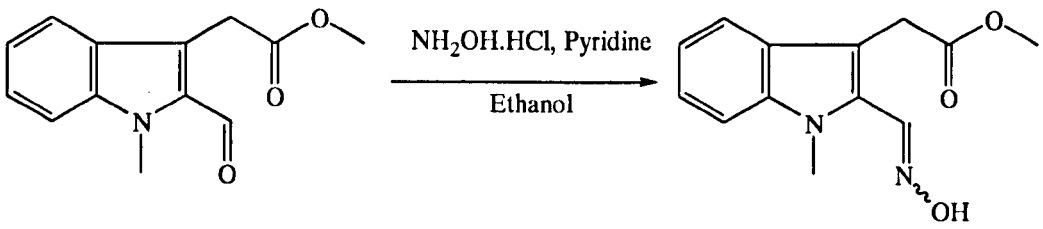


$C_{12}H_{13}NO_2$
Mol. Wt.: 203.24

$C_{13}H_{13}NO_3$
Mol. Wt.: 231.25

To a mixture of phosphorus oxychloride (7.17 cm^3, 11.80 g, 77 mmol), and dry dimethylformamide (2.88 g, 3.00 cm^3, 38.5 mmol) was added a solution of *N*-methylindole-3-acetic acid methyl ester (**319**) (7.82 g, 38.5 mmol) in dry dimethylformamide (3.0 cm^3) at room temperature. The resulting solution was heated at 40 °C for 4 hours, allowed to cool to room temperature and left to stir for 48 hours. Water (100 cm^3) and diethyl ether (100 cm^3) were added and the resulting solution made basic by the addition of saturated sodium hydrogen carbonate solution. The organic layer was separated and the aqueous phase extracted with diethyl ether (3 x 200 cm^3). The combined organic extracts were washed with brine (200 cm^3), dried ($MgSO_4$) filtered and organic solvent removed under reduced pressure to give the crude product which was purified by distillation under reduced pressure (186–188 °C / 2 mmHg) to give the title compound (**318**) as a white crystalline solid (4.25 g, 48%); m.p. 90.5–91.5 °C; R_f (3: 1, hexane: ethyl acetate) 0.40; (Found M^+, 231.0895, $C_{13}H_{13}NO_3$ requires M^+ 231.0895); ν_{max} /cm^{-1} 1664.8 (CHO), 1737.1 (CO_2CH_3); δ_H(300 MHz; $CDCl_3$) 3.69 (3H, s, OCH_3), 4.04 (3H, s, NCH_3), 4.08 (2H, s, CH_2), 7.18 (1H, td, *J* 8.0 & 1.0, C-5*H*), 7.33 (1H, d, *J* 8.0, C-7*H*), 7.42 (1H, td, *J* 8.0 & 1.0, C-6*H*), 7.72 (1H, d, *J* 8.0, C-4*H*), 10.17 (1H, s, C*H*O); δ_C(75 MHz; $CDCl_3$) 29.66 (CH_2), 31.52 (NCH_3), 52.34 (OCH_3), 110.38 (C-7), 120.89 (Ar-C-H), 121.14 (Ar-C-H), 126.26 (quaternary C), 127.26 (Ar-C-H), 131.60 (quaternary C), 139.44 (C-7a), 170.97 (CO_2CH_3), 181.72 (CHO); *m/z* 231.09 (49.5%, M^+), 199.06 (31.8), 172.07 (100.0), 144.07 (46.3), 143.07 (34.3), 103.05 (30.1), 77.04 (31.8).

[2-(Hydroxyimino-methyl)-1-methyl-1*H*-indol-3-yl]-acetic acid methyl ester (317)

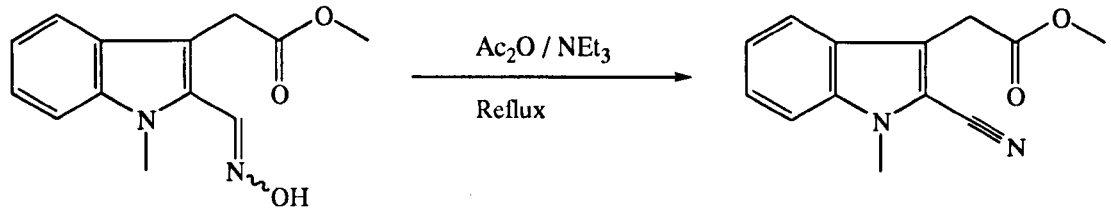


$C_{13}H_{13}NO_3$
Mol. Wt.: 231.25

$C_{13}H_{14}N_2O_3$
Mol. Wt.: 246.26

A solution of (2-formyl-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (**318**) (4.25 g, 18.4 mmol) and hydroxylamine hydrochloride (1.28 g, 18.4 mmol) in ethanol (60 cm^3) and pyridine (15 cm^3) were heated under reflux for 4 hours. The reaction mixture was allowed to cool to room temperature and left to stir for a further 14 hours. Organic solvent was removed under reduced pressure and water (60 cm^3) added. The aqueous residue was extracted with diethyl ether (4 x 100 cm^3) and the combined extracts washed with brine (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the title compound (**317**) as a white solid (4.57 g, 99%); m.p. 109-111 °C; R_f (3: 1, hexane: ethyl acetate) 0.31; (Found M^+, 246.1001, $C_{13}H_{14}N_2O_2$ requires M^+ 246.1004); ν_{max} /cm^{-1} 3398.0 (OH), 1732.9 (CO_2CH_3); δ_H(300 MHz; $CDCl_3$) 3.70 (3H, s, OCH_3), 3.89 (3H, s, NCH_3), 3.95 (2H, s, CH_2), 7.17 (1H, m, C-5*H*), 7.30 (2H, m, C-6*H* & C-7*H*), 7.64 (1H, d, *J* 8.0, C-4*H*), 8.46 (1H, s, C*H*NOH), 8.58 (1H, s, O*H*); δ_C(75 MHz; $CDCl_3$) 30.51 (CH_2), 31.78 (NCH_3), 52.32 (OCH_3), 109.63 (C-7), 111.14 (C-3), 119.48 (Ar-C-H), 120.12 (Ar-C-H), 123.97 (Ar-C-H), 127.14 (quaternary C), 128.45 (quaternary C), 138.41 (C-7a), 142.52 (CHNOH), 172.22 (CO_2CH_3); *m/z* 246.10 (50.3%, M^+), 187.09 (48.8), 183.09 (30.8), 170.09 (48.8), 169.08 (100.0), 130.07 (30.5).

(2-Cyano-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (316)

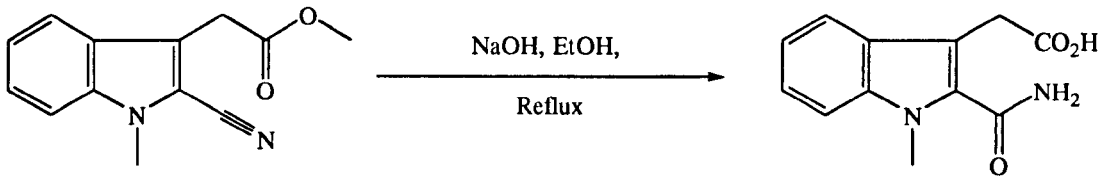


$C_{13}H_{14}N_2O_3$
Mol. Wt.: 246.26

$C_{13}H_{12}N_2O_2$
Mol. Wt.: 228.25

[2-(Hydroxyimino-methyl)-1-methyl-1*H*-indol-3-yl]-acetic acid methyl ester (**317**) (4.57 g, 18.6 mmol) in acetic anhydride (120 cm^3) and triethylamine (30 cm^3) was heated under reflux for 4 hours, allowed to cool to room temperature and left to stir for 15 hours. The reaction mixture was poured into water (150 cm^3) and extracted with diethyl ether (4 x 200 cm^3). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (3 x 300 cm^3), brine (200 cm^3), dried ($MgSO_4$) filtered and organic solvent removed under reduced pressure to give a crude product which was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the title compound (**316**) as a white crystalline solid (3.07 g, 73%); m.p. 102.5 – 104 °C; R_f (3: 1, hexane: ethyl acetate) 0.49; (Found: C, 68.80; H, 5.21; N, 11.97. $C_{13}H_{12}N_2O_2$ requires C, 68.41; H, 5.30; N, 12.27%); (Found M^+, 228.0907, $C_{13}H_{12}N_2O_2$ requires M^+ 228.0899); ν_{max} /cm^{-1} 3020.3, 2953.6 (Ar-H), 2220.2 (CN), 1739.8 (CO_2CH_3); δ_H(300 MHz; $CDCl_3$) 3.72 (3H, s, OCH_3), 3.85 (3H, s, NCH_3), 3.93 (2H, s, CH_2), 7.22 (1H, td, *J* 8.0 & 1.0, C-5*H*), 7.32 (1H, d, *J* 8.0, C-7*H*), 7.42 (1H, td, *J* 8.0 & 1.0, C-6*H*), 7.64 (1H, d, *J* 8.0, C-4*H*); δ_C(75 MHz; $CDCl_3$) 30.85 (CH_2), 31.57 (NCH_3), 52.33 (OCH_3), 110.10 (C-3), 110.22 (C-7), 112.91 (CN), 119.19 (C-2), 120.66 (Ar-C-H), 121.28 (Ar-C-H), 125.72 (C-3a), 126.16 (C-5), 137.95 (C-7a), 170.43 (CO_2CH_3); *m/z* 228.09 (32.3%, M^+), 183.09 (10.9), 170.08 (16.2), 169.08 (100.0).

(2-Carbamoyl-1-methyl-1*H*-indol-3-yl)-acetic acid (325)

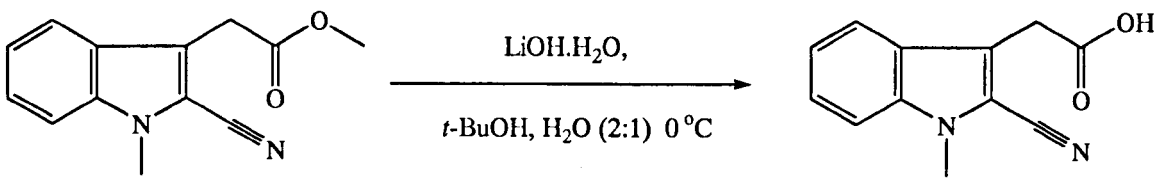


$C_{13}H_{12}N_2O_2$
Mol. Wt.: 228.25

$C_{12}H_{12}N_2O_3$
Mol. Wt.: 232.24

A solution of (2-cyano-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (**316**) (0.29 g, 1.3 mmol) in ethanol (30 cm^3) and aqueous sodium hydroxide (10 cm^3 of a 1.0 M solution) was heated under reflux conditions for 2 hours. The reaction mixture was reduced in volume under reduced pressure and the residue taken up in water (100 cm^3) and acidified with hydrochloric acid (2M solution). The aqueous residue was extracted with diethyl ether (3 x 100 cm^3) and the combined extracts washed with brine (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9: 1, dichloromethane: methanol) to give the title compound (**325**) as a yellow white solid (0.19 g, 63%); m.p. ~170 °C (decomp.); R_f (9: 1, dichloromethane: methanol) 0.58; (Found M^+, 232.0842, $C_{12}H_{12}N_2O_3$ requires M^+ 232.0848); ν_{max} /cm^{-1} 3393.2 ($CONH_2$), 1688.8 (CO_2H), 1626.3 ($CONH_2$); δ_H(300 MHz; DMSO-d_6) 3.84 (3H, s, NC*H*$_3$), 3.87 (2H, s, C*H*$_2$), 7.11 (1H, td, *J* 8.0 & 1.0, C-5*H*), 7.28 (1H, td, *J* 8.0 & 1.0, C-6*H*), 7.49 (1H, d, *J* 8.0, C-7*H*), 7.62 (1H, d, *J* 8.0, C-4*H*), 7.86 (2H, br d, *J* 16, N*H*$_2$), 12.60 (1H, br s, COO*H*); δ_C(75 MHz; DMSO d_6) 30.44 (CH_2), 31.05 (NCH_3), 108.90 (C-3), 110.17 (C-7), 119.62 (C-6 & C-4), 123.34 (C-5), 126.16 (quaternary C), 132.30 (quaternary C), 136.83 (C-7a), 163.40 ($CONH_2$), 173.27 (COOH); *m/z* 232.08 (30.3%, M^+), 214.07 (100.0), 188.09 (58.0), 187.09 (43.4), 169.08 (73.9), 143.07 (93.8).

2-Cyano-1-methyl-1*H*-indole-3-acetic acid (315)

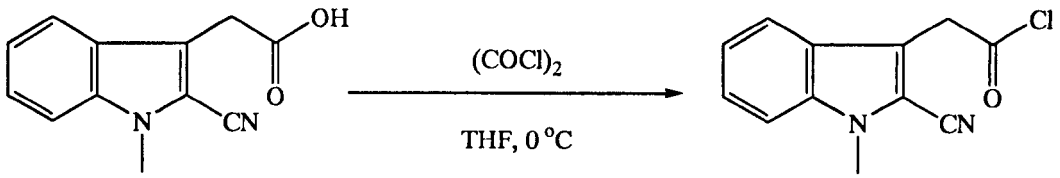


$C_{13}H_{12}N_2O_2$
Mol. Wt.: 228.25

$C_{12}H_{10}N_2O_2$
Mol. Wt.: 214.22

Lithium hydroxide.H_2O (1.09 g, 26.0 mmol) was added to a suspension of 2-cyano-1-methyl-1*H*-indole-3-acetic acid methyl ester (**316**) (2.97 g, 13.0 mmol) in *t*-butanol / H_2O (100 cm^3 of a 2:1 solution) at 0 °C. The resulting solution was allowed to warm to room temperature and left to stir for 16 hours overnight. The reaction mixture was neutralised by the dropwise addition of dilute hydrochloric acid (0.5 M) and evaporated to dryness under reduced pressure. Water (50 cm^3) was added to the resulting residue and the pH of the solution adjusted to ~5 by the dropwise addition of a solution of citric acid (15% w/v) at 0 °C. The resulting solution was extracted with ethyl acetate (3 x 100 cm^3) and the combined organic extracts were washed with water (100 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the title compound (**315**) as a pale yellow solid (2.69 g, 97%); m.p. 175-177 °C; (Found M^+, 214.0752, $C_{12}H_{10}N_2O_2$ requires M^+ 214.0742); ν_{max} /cm^{-1} 2221.0 (CN), 1707.5 (CO_2H); δ_H(300 MHz; DMSO-d_6) 3.83 (3H, s, N-C*H*$_3$), 3.87 (2H, s, C*H*$_2$), 7.19 (1H, t, *J* 8.0, C-5*H*), 7.41 (1H, t, *J* 8.0, C-6*H*), 7.55 (1H, d, *J* 8.0, C-7*H*), 7.69 (1H, d, *J* 8.0, C-4*H*), 12.65 (1H, br s, O*H*); δ_C(75 MHz; DMSO d_6) 30.30 (CH_2), 31.32 (N-CH_3), 109.09 (C-3), 110.78 (C-7), 112.91 (CN), 119.95 (quaternary C), 120.54 & 120.66 (C-4 & C-6), 125.20 (quaternary C), 125.75 (C-5), 137.40 (C-7a), 171.19 (C=O); *m/z* 214.08 (47.7%, M^+), 183.09 (35.4), 169.08 (100.0).

2-Cyano-1-methyl-1*H*-indole-3-acetyl chloride (328)

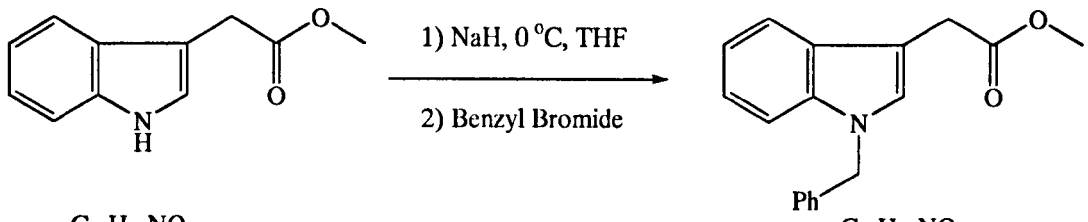


$C_{12}H_{10}N_2O_2$
Mol. Wt.: 214.22

$C_{12}H_9ClN_2O$
Mol. Wt.: 232.67

N-Methyl-2-cyano-indole-3-acetic acid (**315**) (1.02 g, 4.8 mmol) was dissolved and THF (20 cm^3) and added dropwise to a stirred solution of oxalyl chloride (2.5 cm^3, 3.63 g, 28.65 mmol) in THF (30 cm^3) at 0 °C under nitrogen. The resulting solution was allowed to warm to room temperature and stirred for 20 hours. The solvent and excess oxalyl chloride, were removed under reduced pressure to give the title compound (**328**) as a light red solid which was used immediately without further purification.

(1-Benzyl-1*H*-indol-3-yl)-acetic acid methyl ester (374)

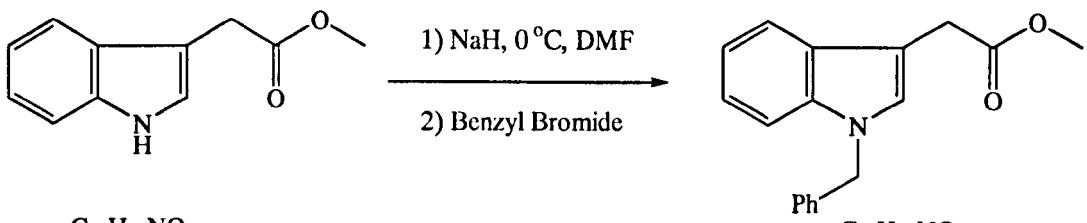


$C_{11}H_{11}NO_2$
Mol. Wt.: 189.21

$C_{18}H_{17}NO_2$
Mol. Wt.: 279.33

Indole-3-acetic acid methyl ester (**324**) (0.46 g, 2.4 mmol) in THF (15 cm^3) was added dropwise to a stirred suspension of sodium hydride (0.10 g of a 60% dispersion in mineral oil, hexane washed, 2.4 mmol) i THF (30 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred until the evolution of hydrogen had ceased. Benzyl bromide (0.35 cm^3, 0.50 g, 2.9 mmol) was added dropwise and the resulting solution left to stir for 16 hours at ambient temperature. Water (40 cm^3) was added and organic solvent removed under reduced pressure. The resulting aqueous residue was extracted with diethyl ether (4 x 50 cm^3) and the combined extracts washed with saturated sodium hydrogen carbonate solution (100 cm^3), water (100 cm^3), brine (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The dark yellow oil obtained was purified by flash column chromatography (4: 1, hexane: ethyl acetate) to give the title compound (**374**) as a yellow oil (0.12 g, 20%); R_f (4: 1, hexane: ethyl acetate) 0.44; (Found M^+, 279.1254, $C_{18}H_{17}NO_2$ requires M^+ 279.1259); ν_{max} /cm^{-1} 3030.0, 2950.0 (Ar-H), 1736.2 (CO_2CH_3), 741.2, 699.9 (C_6H_5); δ_H(300 MHz; $CDCl_3$) 3.79 (3H, s, OCH_3), 3.90 (2H, s, $CH_2CO_2CH_3$), 5.31 (2H, s, $PhCH_2$), 7.19 – 7.37 (9H, m, Ar-*H*), 7.75 (1H, dd, *J* 8.2 & 1.6, C-4*H*); δ_C(75 MHz; $CDCl_3$) 31.25 ($CH_2CO_2CH_3$), 50.04 ($PhCH_2$), 52.08 (CO_2CH_3), 107.62 (C-3), 109.94 (C-7), 119.23 (Ar-C-H), 119.60 (Ar-C-H), 122.11 (Ar-C-H), 126.98 (C-3' & C-5'), 127.30 (Ar-C-H), 127.73 (quaternary C), 128.07 (quaternary C), 128.87 (C-2' & C-6'), 136.64 (quaternary C), 137.56 (C-7a), 172.60 (CO_2CH_3).

(1-Benzyl-1*H*-indol-3-yl)-acetic acid methyl ester (374)

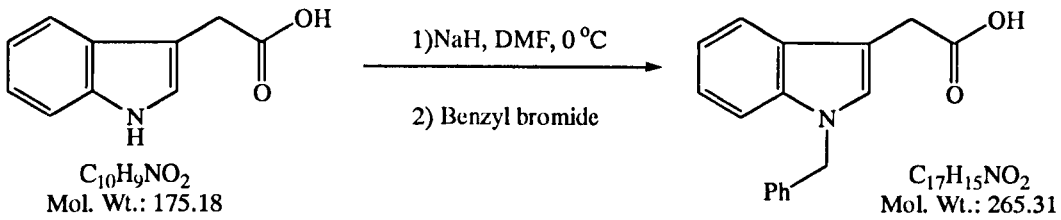


$C_{11}H_{11}NO_2$
Mol. Wt.: 189.21

$C_{18}H_{17}NO_2$
Mol. Wt.: 279.33

Indole-3-acetic acid methyl ester (**324**) (0.18 g, 1.0 mmol) in DMF (10 cm^3) was added dropwise to a stirred suspension of sodium hydride (0.03 g of a 60% dispersion in mineral oil, hexane washed, 1.0 mmol) in DMF (30 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred until the evolution of hydrogen had ceased. Benzyl bromide (0.12 cm^3, 0.18 g, 1.1 mmol) was added dropwise and the resulting solution left to stir for 16 hours at ambient temperature. Water (30 cm^3) was added and organic solvent removed under reduced pressure. The resulting aqueous residue was extracted with diethyl ether (4 x 50 cm^3) and the combined organic extracts washed with saturated sodium hydrogen carbonate solution (100 cm^3), water (100 cm^3), brine (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The dark yellow oil obtained was purified by flash column chromatography (4: 1, hexane: ethyl acetate) to give the title compound (**374**) as a yellow oil (0.20 g, 75%); identical spectroscopic data to that obtained previously.

(1-Benzyl-1*H*-indol-3-yl)-acetic acid (375)

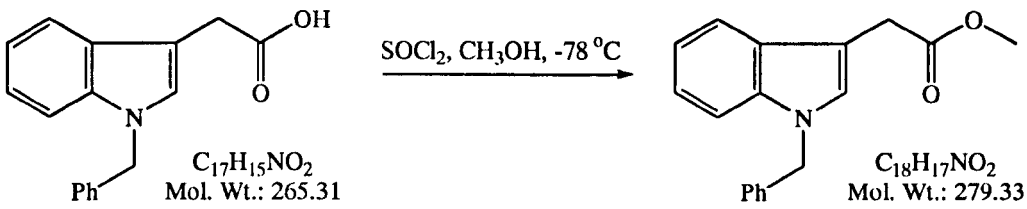


$C_{10}H_9NO_2$
Mol. Wt.: 175.18

$C_{17}H_{15}NO_2$
Mol. Wt.: 265.31

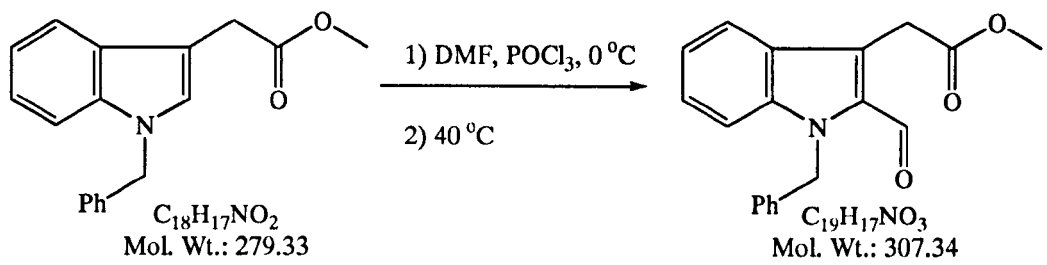
To a solution of indole-3-acetic acid (**320**) (18.72 g, 106.8 mmol) in DMF (200 cm^3) was added portionwise, sodium hydride (10.26 g of a 60% dispersion in mineral oil, 256.45 mmol) at 0 °C. The resulting mixture was stirred for ½ hour at 0 °C followed by dropwise addition of benzyl bromide (15.3 cm^3, 21.90 g, 128.2 mmol). Stirring was continued for 1 hour and the reaction mixture poured into water (200 cm^3). Acidification of the mixture with dilute hydrochloric acid (2M) gave a light tan solid which was purified by recrystallisation (ethyl acetate/ hexane) to give (1-benzyl-1*H*-indol-3-yl)-acetic acid (**375**) as a white crystalline solid (23.10 g, 81%); m.p. 152-154 °C (Lit.[285] 154-156 °C); (Found M^+, 265.1112, $C_{17}H_{15}NO_2$ requires M^+ 265.1103); ν_{max} /cm^{-1} 1703.9 (CO_2H); δ_H(300 MHz; $CDCl_3$) 3.81 (2H, s, CH_2CO_2H), 5.29 (2H, s, NCH_2), 7.12–7.30 (9H, m, Ar-*H*), 7.62 (1H, dd, *J* 6.9 & 1.2, C-4*H*), 9.01 (1H, br s, CO_2H); δ_C(75 MHz; $CDCl_3$) 31.07 (CH_2CO_2H), 50.04 (NCH_2), 106.89 (C-3), 109.86 (C-7), 119.09 (Ar-C-H), 119.57 (Ar-C-H), 122.11 (Ar-C-H), 126.87 (C-3' & C-5'), 127.33 (Ar-C-H), 127.67 (quaternary C), 127.83 (quaternary C), 128.80 (C-2' & C-6'), 136.51 (quaternary C), 137.34 (C-7a), 177.75 (CO_2H).

(1-Benzyl-1*H*-indol-3-yl)-acetic acid methyl ester (374)



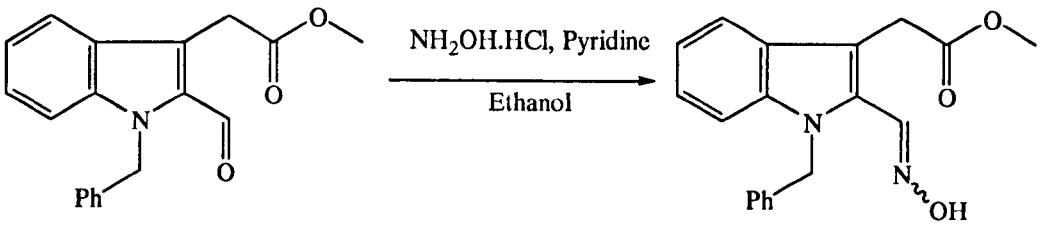
Thionyl chloride (6.6 cm^3, 10.8 g, 90.4 mmol) was added dropwise to a stirred suspension of (1-benzyl-1*H*-indol-3-yl)-acetic acid (**375**) (20.00 g, 75.3 mmol) in dry methanol (500 cm^3) at –78 °C. The resulting mixture was stirred for 2 hours at below –50 °C and then allowed to warm to room temperature and stirred overnight. Organic solvent was removed under reduced pressure and the crude residue taken up in diethyl ether (200 cm^3), filtered and the solvent removed under reduced pressure. Purification by distillation under reduced pressure (184-186 °C / 0.4 mmHg) gave (1-benzyl-1*H*-indol-3-yl)-acetic acid methyl ester (**374**) as a yellow oil (18.00 g, 86%); identical spectroscopic data to that obtained previously.

(1-Benzyl-2-formyl-1*H*-indol-3-yl)-acetic acid methyl ester (376)



To a mixture of phosphorus oxychloride (6.7 cm^3, 10.96 g, 71.5 mmol), and dry dimethylformamide (30 cm^3) was added a solution of (1-benzyl-1*H*-indol-3-yl)-acetic acid methyl ester (**374**) (8.00 g, 28.6 mmol) in dry dimethylformamide (20 cm^3) at room temperature. The resulting solution was heated at 50 °C for 16 hours, water (100 cm^3) added and the resulting solution made basic by the addition of saturated sodium hydrogen carbonate solution. The aqueous phase was extracted with dichloromethane (4 x 200 cm^3) and the combined organic extracts washed with brine (200 cm^3), dried ($MgSO_4$) filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography using gradient elution (hexane: ethyl acetate) to give the title compound (**376**) as a yellow oil (4.30 g, 49%); R_f (3: 1, hexane: ethyl acetate) 0.29; (Found M^+, 307.1219, $C_{19}H_{17}NO_3$ requires M^+ 307.1208); ν_{max} /cm^{-1} 3031.7 & 2951.6 (Ar-H), 1739.6 (CO_2CH_3), 1660.2 (CHO), 746.5 & 698.0 (C_6H_5); δ_H(300 MHz; $CDCl_3$) 3.73 (3H, s, CO_2CH_3), 4.16 (2H, s, $CH_2CO_2CH_3$), 5.81 (2H, s, CH_2Ar), 7.11 (1H, td, *J* 8.0 & 1.0, C-5*H*), 7.20 – 7.27 (6H, m, Ar-*H*), 7.40 (1H, td, *J* 8.0 & 1.0, C-6*H*), 7.81 (1H, d, *J* 8.0, C-4*H*), 10.20 (1H, s, C*H*O); δ_C(75 MHz; $CDCl_3$) 29.79 ($CH_2CO_2CH_3$), 47.87 ($ArCH_2$), 52.49 (OCH_3), 111.05 (C-7), 110.05 (C-3), 121.27 (Ar-C-H), 121.36 (Ar-C-H), 121.85 (quaternary C), 126.56 (C-3' & C-5'), 127.42 (Ar-C-H), 127.66 (Ar-C-H), 128.69 (C-2' & C-6'), 131.20 (quaternary C), 137.79 (quaternary C), 139.30 (C-7a), 170.97 (CO_2CH_3), 181.59 (CHO).

[1-Benzyl-2-(hydroxyimino-methyl)-1*H*-indol-3-yl]-acetic acid methyl ester (377)

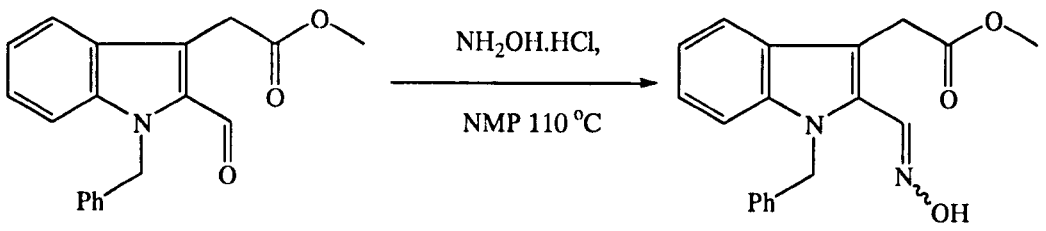


$C_{19}H_{17}NO_3$
Mol. Wt.: 307.34

$C_{19}H_{18}N_2O_3$
Mol. Wt.: 322.36

A solution of (1-benzyl-2-formyl-1*H*-indol-3-yl)-acetic acid methyl ester (**376**) (2.26 g, 7.4 mmol) and hydroxylamine hydrochloride (0.56 g, 8.1 mmol) in ethanol (30 cm^3) and pyridine (10 cm^3) was heated under reflux for 4 hours. The reaction mixture was allowed to cool to room temperature and left to stir for 14 hours. Organic solvent was removed under reduced pressure and water (60 cm^3) added. The aqueous residue was extracted with diethyl ether (4 x 100 cm^3), washed with brine (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude compound was purified by flash column chromatography on silica gel (3: 1, hexane: ethyl acetate) to give the title compound (**377**) as a white solid (2.20 g, 94%); m.p. 128.5-130 °C; R_f (3: 1, hexane: ethyl acetate) 0.25; (Found M^+, 322.1308, $C_{19}H_{18}N_2O_3$ requires M^+ 322.1317); ν_{max} /cm^{-1} 3403.9 (OH), 1732.3 (CO_2CH_3); δ_H(300 MHz; $CDCl_3$) 3.55 (3H, s, CO_2CH_3), 3.83 (2H, s, $CH_2CO_2CH_3$), 5.48 (2H, s, NCH_2), 6.87 – 6.90 (2H, m, C-5*H* & C-6*H*), 7.02 – 7.14 (6H, m, Ar-*H*), 7.54 (1H, dd, *J* 7.4 & 1.0, C-4*H*), 8.14 (1H, br s, O*H*), 8.26 (1H, s, C*H*NOH); δ_C(75 MHz; $CDCl_3$) 30.60 (CO_2CH_3), 48.11 (NCH_2), 52.35 (CO_2CH_3), 110.17 (C-7), 111.77 (C-3), 119.61 (Ar-C-H), 120.45 (Ar-C-H), 124.24 (Ar-C-H), 126.17 (C-3' & C-5'), 127.29 (Ar-C-H), 127.51 (quaternary C), 128.42 (quaternary C), 128.71 (C-2' & C-6'), 137.83 (quaternary C), 138.27 (C-7a), 142.26 (CHNOH), 172.20 (CO_2CH_3); *m/z* 323.14 (33.8%), 322.13 (95.8, M^+), 30.14 (38.1), 305.13 (96.3), 304.13 (44.4), 263.12 (39.0), 246.11 (39.8), 245.10 (81.0), 92.40 (32.5), 91.40 (100.0), 65.46 (34.9).

[1-Benzyl-2-(hydroxyimino-methyl)-1*H*-indol-3-yl]-acetic acid methyl ester (377)

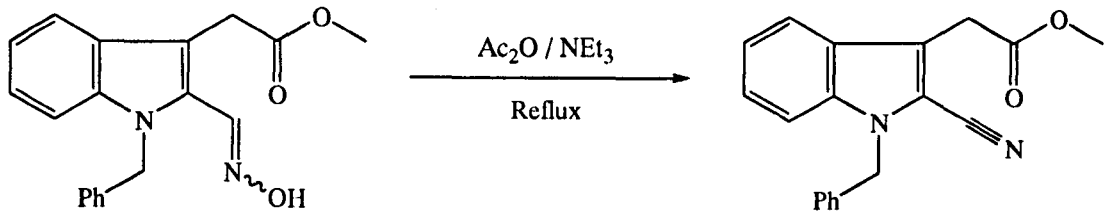


$C_{19}H_{17}NO_3$
Mol. Wt.: 307.34

$C_{19}H_{18}N_2O_3$
Mol. Wt.: 322.36

A solution of (1-benzyl-2-formyl-1*H*-indol-3-yl)-acetic acid methyl ester (**376**) (0.14 g, 0.5 mmol) and hydroxylamine hydrochloride (0.04 g, 0.6 mmol) in *N*-methylpyrrolidinone (10 cm^3) was heated at 110 °C for 4 hours. The resulting solution was poured into water (20 cm^3) and extracted with ethyl acetate (3 x 30 cm^3). The combined organic extracts were washed with brine (2 x 30 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the title compound (**377**) as a white solid (0.10 g, 69%); identical spectroscopic data to that obtained previously.

(1-Benzyl-2-cyano-1*H*-indol-3-yl)-acetic acid methyl ester (378)

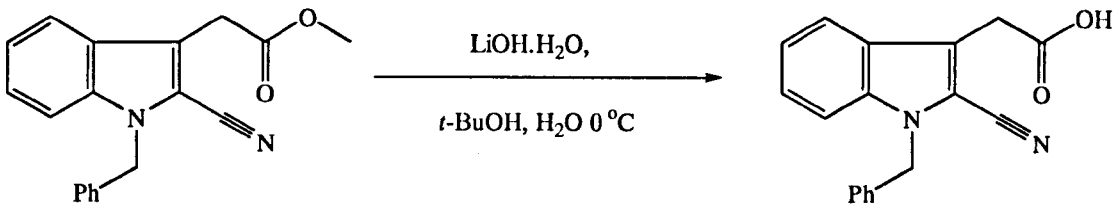


$C_{19}H_{18}N_2O_3$
Mol. Wt.: 322.36

$C_{19}H_{16}N_2O_2$
Mol. Wt.: 304.34

[1-Benzyl-2-(hydroxyimino-methyl)-1*H*-indol-3-yl]-acetic acid methyl ester (**377**) (2.00 g, 6.2 mmol) in acetic anhydride (40 cm^3) and triethylamine (10 cm^3) was heated under reflux for 4 hours. The reaction mixture was allowed to cool and left to stir for 15 hours at room temperature. The reaction mixture was poured into water (50 cm^3) and extracted with diethyl ether (4 x 100 cm^3). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (3 x 100 cm^3), brine (200 cm^3), dried ($MgSO_4$) filtered and organic solvent removed under reduced pressure to give the crude product. Purification by flash column chromatography (3: 1, hexane: ethyl acetate) gave the title compound (**378**) as a white crystalline solid (1.70 g, 90%); m.p. 133.5–134.5 °C; R_f (3: 1, hexane: ethyl acetate) 0.45; (Found M^+, 304.1199, $C_{19}H_{16}N_2O_2$ requires M^+ 304.1212); ν_{max} /cm^{-1} 3020.4, 2954.7 (C-H), 2220.9 (CN), 1740.1 (CO_2Me); δ_H(300 MHz; $CDCl_3$) 3.74 (3H, s, OCH_3), 3.98 (2H, s, $CH_2CO_2CH_3$), 5.44 (2H, s, NCH_2), 7.17 – 7.40 (8H, m, Ar-*H*), 7.69 (1H, d, *J* 8.1, C-4*H*); δ_C(75 MHz; $CDCl_3$) 30.96 ($CH_2CO_2CH_3$), 49.12 (NCH_2), 52.41 (CO_2CH_3), 109.86 (**C**-3), 110.84 (**C**-7), 113.02 (**C**N), 120.86 (Ar-**C**-H), 121.52 (Ar-**C**-H), 126.06 (quaternary **C**), 126.41 (Ar-**C**-H), 126.89 (**C**-3' & **C**-5'), 128.13 (Ar-**C**-H), 128.99 (**C**-2' & **C**-6'), 135.98 (quaternary **C**), 137.53 (**C**-7a), 170.38 (CO_2CH_3); *m/z* 304.12 (54.7%, M^+), 245.11 (23.4), 91.40 (100.0). (Missing one quaternary **C**).

(1-Benzyl-2-cyano-1*H*-indol-3-yl)-acetic acid (379)

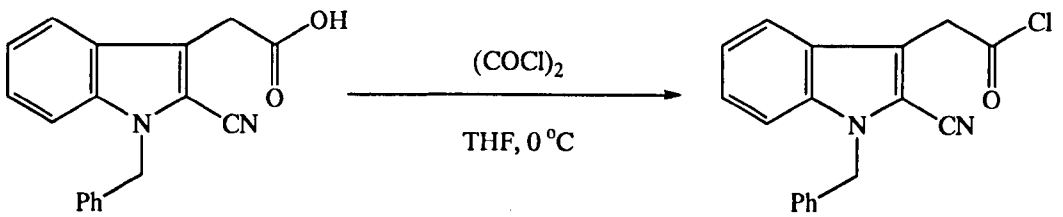


$C_{19}H_{16}N_2O_2$
Mol. Wt.: 304.34

$C_{18}H_{14}N_2O_2$
Mol. Wt.: 290.32

Lithium hydroxide.H_2O (0.42 g, 9.9 mmol) was added to a suspension of (1-benzyl-2-cyano-1*H*-indol-3-yl)-acetic acid methyl ester (**378**) (1.50 g, 5.0 mmol) in *t*-butanol / H_2O (60 cm^3 of a 2:1 solution) at 0 °C. The resulting solution was allowed to warm to room temperature and left to stir for 16 hours overnight. The reaction mixture was neutralised by the dropwise addition of dilute hydrochloric acid (0.5 M) and solvent was removed under reduced pressure. The resulting residue had water added (40 cm^3) and the pH of the solution was adjusted to ~5 by the dropwise addition of a solution of citric acid (15% w/v) at 0 °C. The resulting solution was extracted with ethyl acetate (3 x 100 cm^3) and the combined extracts washed with water (100 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the title compound (**379**) as a pale yellow solid (1.50 g, 99%); m.p. 180.5–183.0 °C; (Found M^+, 290.1052, $C_{18}H_{14}N_2O_2$ requires M^+ 290.1055); ν_{max} /cm^{-1} 2219.5 (CN), 1711.2 (CO_2H); δ_H(300 MHz; DMSO-d_6) 3.94 (2H, s, C*H*$_2$CO$_2$H), 5.55 (2H, s, NC*H*$_2$), 7.18 – 7.44 (7H, m, Ar-*H*), 7.67 (1H, d, *J* 8.0, C-7*H*), 7.76 (1H, d, *J* 8.0, C-4*H*), 12.68 (1H, br s, CO_2H); δ_C(75 MHz; DMSO d_6) 30.43 (CH_2CO_2H), 48.00 (N-CH_2), 108.69 (C-3), 111.13 (C-7), 113.03 (CN), 120.83 (quaternary C), 120.98 (Ar-C-H), 121.15 (Ar-C-H), 125.53 (quaternary C), 126.11 (Ar-C-H), 126.71 (C-3' & C-5'), 127.72 (Ar-C-H), 128.71 (C-2' & C-6'), 136.78 (quaternary C), 137.06 (C-7a), 171.16 (CO_2H); *m/z* 290.10 (60.2%, M^+), 245.09 (12.4), 91.40 (100.0), 65.45 (12.0).

(1-Benzyl-2-cyano-1*H*-indol-3-yl)-acetyl chloride (380)

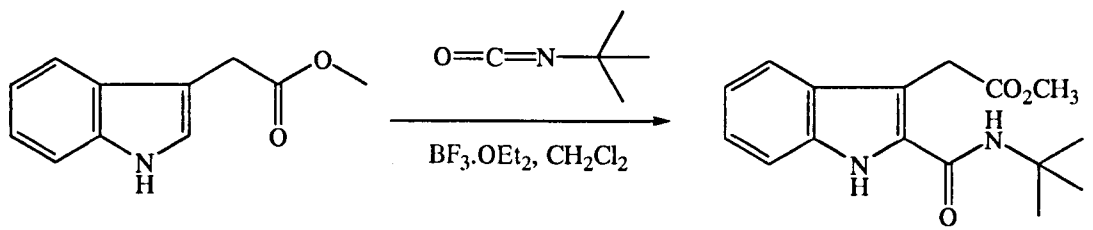


$C_{18}H_{14}N_2O_2$
Mol. Wt.: 290.32

$C_{18}H_{13}ClN_2O$
Mol. Wt.: 308.76

(1-Benzyl-2-cyano-1*H*-indol-3-yl)-acetic acid (**379**) (0.30 g, 0.9 mmol) was dissolved in THF (15 cm^3) and added dropwise to a stirred solution of oxalyl chloride (0.5 cm^3, 0.67 g, 5.2 mmol) in THF (30 cm^3) at 0 °C under nitrogen. The solution was allowed to warm to room temperature and stirred for 20 hours. Solvent and excess oxalyl chloride were removed under reduced pressure to give the title compound (**380**) as a light red solid that was used immediately without further purification.

(2-*t*-Butylcarbamoyl-1*H*-indol-3-yl)-acetic acid methyl ester (477)

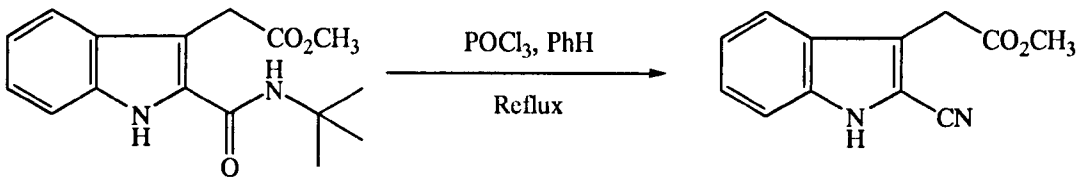


$C_{11}H_{11}NO_2$
Mol. Wt.: 189.21

$C_{16}H_{20}N_2O_3$
Mol. Wt.: 288.34

Boron trifluoride diethyl ether complex (7.2 cm^3, 8.10 g, 57.5 mmol) was added to a stirred solution of indole-3-acetic acid methyl ester (**324**) (5.40 g, 28.8 mmol) and freshly distilled *t*-butyl isocyanate (4.9 cm^3, 4.30 g, 43.1 mmol) in dichloromethane (40 cm^3) at room temperature. The reaction was allowed to stir for 18 hours whereupon organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3) and washed with a solution of saturated ammonium chloride (100 cm^3). The aqueous phase was extracted with dichloromethane (2 x 100 cm^3) and the combined organic extracts washed with brine (200 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the title compound (**477**) as white crystalline needles (8.00 g, 97%); m.p. 159.5–160.5 °C; R_f (3: 1, hexane: ethyl acetate) 0.31; (Found M^+, 288.1473, $C_{16}H_{20}N_2O_3$ requires M^+ 288.1474); ν_{max} /cm^{-1} 3273.1 (NH), 1720.1 (CO_2CH_3), 1638.0 (CONH*t*-Bu); δ_H(300 MHz; $CDCl_3$) 1.91 (9H, s, $C(CH_3)_3$), 3.75 (3H, s, OCH_3), 3.98 (2H, s, $CH_2CO_2CH_3$), 7.17 (1H, td, *J* 8.0 & 1.0, C-5*H*), 7.29 (1H, td, *J* 8.0 & 1.0, C-6*H*), 7.53 (1H, d, *J* 8.0, C-7*H*), 7.70 (1H, d, *J* 8.0, C-4*H*), 8.13 (1H, br s, N*H*), 10.68 (1H, br s, CON*H*); δ_C(75 MHz; $CDCl_3$) 29.04 ($C(CH_3)_3$), 31.05 ($CH_2CO_2CH_3$), 52.17 ($C(CH_3)_3$), 52.68 (CO_2CH_3), 106.86 (C-3), 112.27 (C-7), 119.53 (Ar-C-H), 120.13 (Ar-C-H), 124.15 (Ar-C-H), 127.76 (quaternary C), 131.32 (quaternary C), 135.36 (C-7a), 161.89 (CONH), 173.80 (CO_2CH_3); *m/z* 288.15 (87.6%, M^+), 216.06 (38.9), 215.04 (95.4), 201.06 (34.4), 200.05 (92.1), 188.07 (56.1), 183.03 (62.1), 173.07 (60.5), 156.04 (89.5), 128.05 (100.0), 58.16 (67.4).

(2-Cyano-1*H*-indol-3-yl)-acetic acid methyl ester (478)

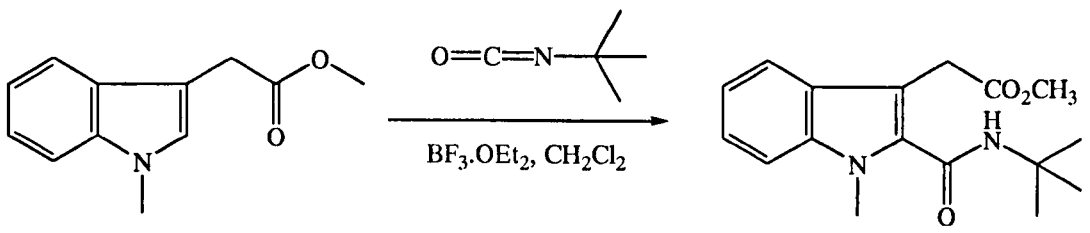


$C_{16}H_{20}N_2O_3$
Mol. Wt.: 288.34

$C_{12}H_{10}N_2O_2$
Mol. Wt.: 214.22

A solution of (2-*t*-butylcarbamoyl-1*H*-indol-3-yl)-acetic acid methyl ester (**477**) (48.90 g, 0.20 mole) and phosphorus oxychloride (50.0 cm^3, 82.30 g, 0.54 mole) in benzene (300 cm^3) was heated under reflux conditions for 7 hours. Organic solvent was removed under reduced pressure and the residue partitioned between dichloromethane (200 cm^3) and a solution of saturated sodium hydrogen carbonate (200 cm^3) and stirred for one hour. The organic layer was separated and the aqueous phase extracted with dichloromethane (3 x 200 cm^3). The combined organic extracts were washed with brine (200 cm^3), dried ($MgSO_4$), filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (5: 1, hexane: ethyl acetate) to give (2-cyano-1*H*-indol-3-yl)-acetic acid methyl ester (**478**) as a white crystalline solid (26.87 g, 77%); m.p. 88.0-89.5 °C (Lit.[286] 81-82 °C); R_f (5: 1, hexane: ethyl acetate) 0.23; (Found M^+, 214.07418, $C_{12}H_{10}N_2O_2$ requires M^+ 214.07423); ν_{max} /cm^{-1} 3322.4 (NH), 2224.6 (CN), 1730.8 (CO_2CH_3); δ_H(300 MHz; $CDCl_3$) 3.77 (3H, s, OCH_3), 3.95 (2H, s, CH_2), 7.14-7.20 (2H, m, C-6*H* & C-7*H*), 7.29 (1H, m, C-5*H*), 7.60 (1H, d, *J* 8.0, C-4*H*), 9.59 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 30.70 (CH_2), 52.66 (OCH_3), 105.92 (C-3), 112.28 (C-7), 113.75 (CN), 120.11 (Ar-C-H), 120.27 (quaternary C), 121.41 (Ar-C-H), 125.59 (quaternary C), 126.26 (C-5), 136.95 (C-7a), 171.40 (CO_2CH_3); *m/z* 214.07 (85.4%, M^+), 156.07 (100.0), 148.93 (34.6), 126.05 (53.6), 127.04 (37.3), 102.05 (39.4), 101.04 (46.8), 77.04 (52.4), 75.02 (36.7).

(2-*t*-Butylcarbamoyl-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (480)

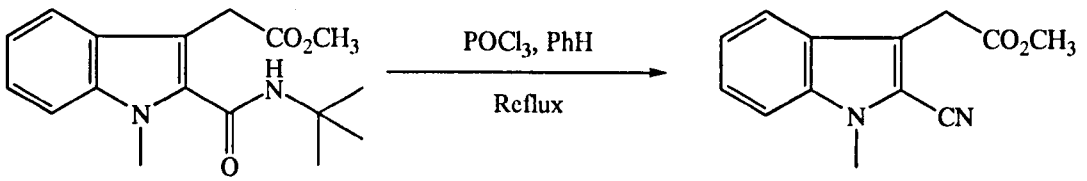


$C_{12}H_{13}NO_2$
Mol. Wt.: 203.24

$C_{17}H_{22}N_2O_3$
Mol. Wt.: 302.37

Boron trifluoride diethyl ether complex (21.7 cm^3, 24.50 g, 94.8 mmol) was added dropwise to a stirred solution of *N*-methylindole-3-acetic acid methyl ester (**319**) (17.50 g, 86.2 mmol) and freshly distilled *t*-butyl isocyanate (10.8 cm^3, 9.40 g, 94.8 mmol) in dichloromethane (200 cm^3) at 0 °C. The reaction was allowed to stir for 18 hours whereupon organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3) and washed with a solution of saturated ammonium chloride (100 cm^3). The aqueous phase was extracted with dichloromethane (2 x 100 cm^3) and the combined organic extracts washed with brine (200 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by recrystallisation (IMS/ water) to give the title compound (**480**) as white crystalline needles (15.50 g, 60%); m.p. 105.0-106.5 °C; R_f (5: 1, hexane: ethyl acetate) 0.39; (Found M^+, 302.16418, $C_{17}H_{22}N_2O_3$ requires M^+ 302.16306); ν_{max} /cm^{-1} 3319.7 (NH), 1718.7 (CO_2CH_3), 1658.9 (CONH*t*-Bu); δ_H(300 MHz; $CDCl_3$) 1.54 (9H, s, $C(CH_3)_3$), 3.73 (3H, s, OCH_3), 3.90 (2H, s, CH_2), 3.91 (3H, s, NCH_3), 7.16 (1H, td, *J* 8.0 & 1.0, C-6*H*), 7.30 (2H, m, C-5*H* & C-7*H*), 7.63 (1H, d, *J* 8.0, C-4*H*), 7.86 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 28.97 ($C(CH_3)_3$), 30.85 (NCH_3), 31.29 (CH_2), 52.12 ($C(CH_3)_3$), 52.58 (CO_2CH_3), 107.08 (C-3), 109.94 (C-7), 119.54 (Ar-C-H), 120.10 (Ar-C-H), 123.81 (C-5), 126.24 (quaternary C), 133.59 (quaternary C), 137.38 (C-7a), 161.55 (CONH*t*-Bu), 173.93 (CO_2CH_3); *m/z* 302.16 (17.3%, M^+), 301.16 (78.5), 229.07 (100.0), 214.07 (82.9), 202.08 (69.1), 187.08 (95.8), 158.23 (52.4), 143.05 (69.2), 142.11 (40.5), 115.05 (48.7), 57.07 (60.3).

(2-Cyano-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (316)

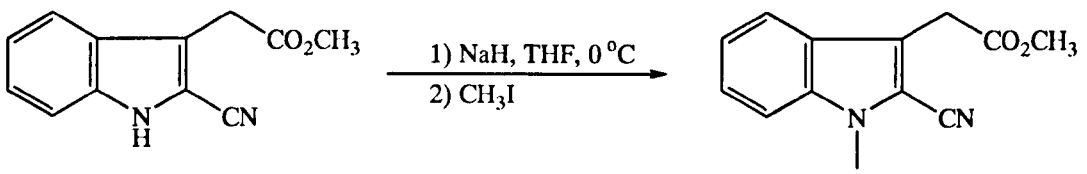


$C_{17}H_{22}N_2O_3$
Mol. Wt.: 302.37

$C_{13}H_{12}N_2O_2$
Mol. Wt.: 228.25

A solution of (2-*t*-butylcarbamoyl-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (**480**) (14.90 g, 49.14 mmol) and phosphorus oxychloride (11.4 cm^3, 18.80 g, 122.9 mmol) in benzene (200 cm^3) was heated under reflux conditions for 16 hours. Organic solvent was removed under reduced pressure and the residue partitioned between dichloromethane (200 cm^3) and a solution of saturated sodium hydrogen carbonate (400 cm^3) and stirred for one hour. The organic layer was separated and the aqueous phase extracted with dichloromethane (3 x 200 cm^3). The combined organic extracts were washed with brine (200 cm^3), dried ($MgSO_4$), filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (4: 1, hexane: ethyl acetate) to give (2-cyano-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (**316**) as a white crystalline solid (9.90 g, 88%); identical spectroscopic data to that obtained previously.

(2-Cyano-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (316)

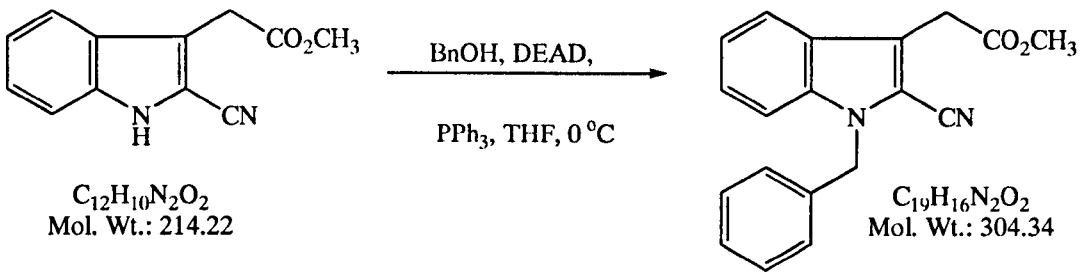


$C_{12}H_{10}N_2O_2$
Mol. Wt.: 214.22

$C_{13}H_{12}N_2O_2$
Mol. Wt.: 228.25

(2-Cyano-1*H*-indol-3-yl)-acetic acid methyl ester (**478**) (16.41 g, 76.6 mmol) in THF (100 cm^3) was added dropwise to a stirred suspension of sodium hydride (3.37 g of a 60% dispersion in mineral oil, hexane washed, 84.3 mmol) in THF (150 cm^3) at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred until the evolution of hydrogen had ceased. Methyl iodide (11.92 cm^3, 27.18 g, 191.5 mmol) was added dropwise and the resulting solution was left to stir for 15 hours at room temperature. Water (100 cm^3) was added to quench the reaction and organic solvent was removed under reduced pressure. The aqueous phase was extracted with diethyl ether (3 x 200 cm^3) and the combined organic extracts were washed with brine (200 cm^3), dried ($MgSO_4$), filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give (2-cyano-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester (**316**) as a white crystalline solid (13.40 g, 77%); identical spectroscopic data to that obtained previously.

(1-Benzyl-2-cyano-1*H*-indol-3-yl)-acetic acid methyl ester (378)

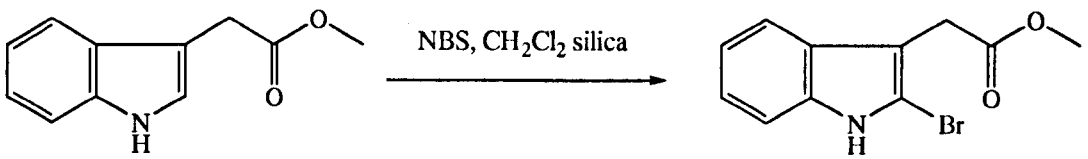


$C_{12}H_{10}N_2O_2$
Mol. Wt.: 214.22

$C_{19}H_{16}N_2O_2$
Mol. Wt.: 304.34

Diethyl azodicarboxylate (9.0 cm^3, 9.95 g, 57.2 mmol) was added dropwise to a solution of (2-cyano-1*H*-indol-3-yl)-acetic acid methyl ester (**478**) (9.39 g, 43.83 mmol), freshly distilled benzyl alcohol (5.5 cm^3, 5.70 g, 52.6 mmol) and triphenylphosphine (14.94 g, 57.0 mmol) in THF (100 cm^3) at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. Organic solvent was removed under reduced pressure and the residue taken up in diethyl ether (70 cm^3). The volume of the solution was reduced and the solution filtered to remove the triphenylphosphine oxide precipitated. Concentration under reduced pressure gave the crude product, which was purified by recrystallisation (hexane/ ethyl acetate). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the title compound (**378**) as a white crystalline solid (12.75 g, 96%); identical spectroscopic data to that obtained previously.

(2-Bromo-1*H*-indol-3-yl)-acetic acid methyl ester (473)

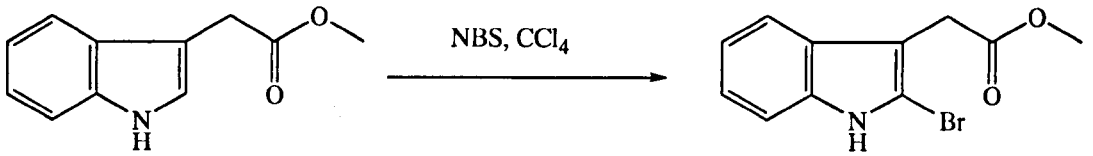


$C_{11}H_{11}NO_2$
Mol. Wt.: 189.21

$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.11

Indole-3-acetic acid methyl ester (**324**) (0.75 g, 4.0 mmol), silica gel (0.71 g) and *N*-bromosuccinimide (0.70 g, 4.0 mmol) in dichloromethane (10 cm^3) were stirred for 24 hours at room temperature followed by heating under reflux for 2 hours. The reaction was filtered and the silica washed with dichloromethane (200 cm^3). Organic solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give (2-bromo-1*H*-indol-3-yl)-acetic acid methyl ester (**473**) as a yellow oil (1.07 g, 46%); R_f (3: 1, hexane: ethyl acetate) 0.46; (Found M^+, 266.9885/ 268.9866, $C_{11}H_{10}BrNO_2$ requires M^+ 266.9895/ 268.9876); ν_{max} /cm^{-1} 3334.2 (NH), 1727.3 (CO_2CH_3); δ_H(300 MHz; $CDCl_3$) 3.58 (3H, s, CO_2CH_3), 3.63 (2H, s, $CH_2CO_2CH_3$), 6.92–7.01 (3H, m, C-5*H*, C-6*H*, C-7*H*), 7.36 (1H, dd, *J* 8.0 & 1.8, C-4*H*), 8.35 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 30.96 (CH_2), 52.33 (CO_2CH_3), 108.14 (quaternary **C**), 109.95 (quaternary **C**), 110.83 (**C**-7), 118.19 (Ar-**C**-H), 120.34 (Ar-**C**-H), 122.43 (Ar-**C**-H), 127.43 (**C**-3a), 136.06 (**C**-7a), 172.06 (CO_2CH_3); *m/z* 268.99 (80.1%, M^+, ^{81}Br), 266.79 (76.4, M^+, ^{79}Br), 210.98 (29.7), 209.97 (97.5), 208.98 (34.7), 207.97 (100.0), 129.17 (55.4), 128.17 (53.2), 102.32 (40.3), 101.32 (41.8), 91.39 (60.2).

(2-Bromo-1*H*-indol-3-yl)-acetic acid methyl ester (473)

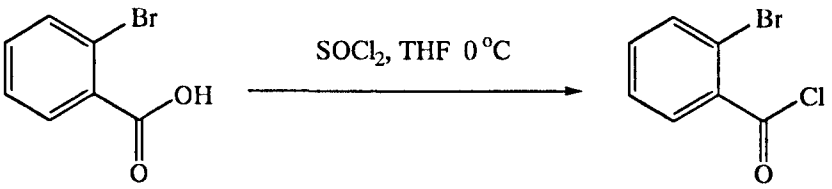


$C_{11}H_{11}NO_2$
Mol. Wt.: 189.21

$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.11

Indole-3-acetic acid methyl ester (**324**) (0.15 g, 0.8 mmol) and *N*-bromosuccinimide (0.16 g, 0.9 mmol) in carbon tetrachloride (10 cm^3) were stirred for 1½ hours at room temperature followed by heating under reflux for 2 hours. The reaction was allowed to cool, filtered and organic solvent removed under reduced pressure. The crude residue was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give (2-bromo-1*H*-indol-3-yl)-acetic acid methyl ester (**473**) as a yellow oil (0.70 g, 87%); identical spectroscopic data to that obtained previously.

2-Bromobenzoyl chloride (322)

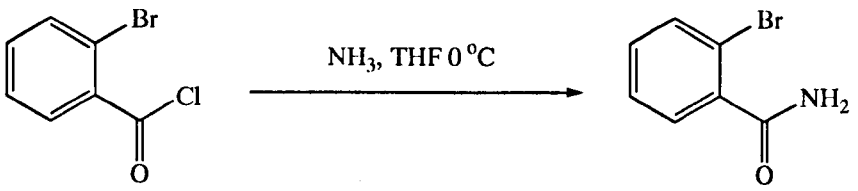


$C_7H_5BrO_2$
Mol. Wt.: 201.02

C_7H_4BrClO
Mol. Wt.: 219.46

2-Bromobenzoic acid (**321**) (20.00 g, 99.5 mmol) in THF (50 cm^3) was added dropwise to a solution of thionyl chloride (30 cm^3) in THF (50 cm^3) at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. Organic solvent was removed under reduced pressure to give 2-bromobenzoyl chloride (**322**) as a light yellow viscous oil that was used immediately without further purification.

2-Bromobenzamide (323)

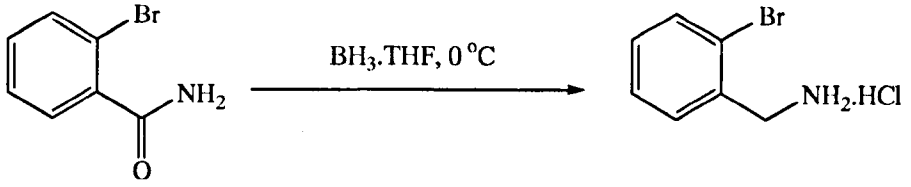


C_7H_4BrClO
Mol. Wt.: 219.46

C_7H_6BrNO
Mol. Wt.: 200.03

2-Bromobenzoyl chloride (**322**) (entire residue from previous reaction, ~99.5 mmol) was dissolved in THF (50 cm^3) and added dropwise to a solution of concentrated ammonia (250 cm^3, excess) at 0 °C. The resulting solution was left to stir for 48 hours before being poured onto crushed ice (400 g). The resulting solution was made neutral by the dropwise addition of dilute hydrochloric acid (30 % solution). The aqueous solution was extracted with ethyl acetate (4 x 200 cm^3) and the combined extracts washed with dilute hydrochloric acid (2 x 200 cm^3 of a 0.5 M solution), dilute sodium hydroxide (2 x 200 cm^3 of a 0.5 M solution), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give 2-bromobenzamide (**323**) as a white crystalline solid (19.20 g, 96%); m.p. 147-151.5 °C (Lit.[287] 160-162 °C); R_f (3: 1, hexane: ethyl acetate) 0.58; (Found M^+, 199.9713/ 201.9692, C_7H_6BrNO requires M^++H 199.9711/ 201.969); ν_{max} /cm^{-1} 3354.2, 3175.6 ($CONH_2$), 1624.7 ($CONH_2$); δ_H(300 MHz; $CDCl_3$ DMSO-d_6) 7.31-7.43 (3H, m, C-3*H*, C-4*H*, C-5*H*), 7.62 (1H, br s, N*H*), 7.64 (1H, d, *J* 8.1, C-6*H*), 7.91 (1H, br s, N*H*); δ_C(75 MHz; DMSO-d_6) 118.55 (**C**-2), 127.39 (**C**-5), 128.47 (**C**-3), 130.55 (**C**-6), 132.62 (**C**-4), 139.22 (**C**-1), 169.03 (**C**O).

2-Bromobenzylamine hydrochloride (311)

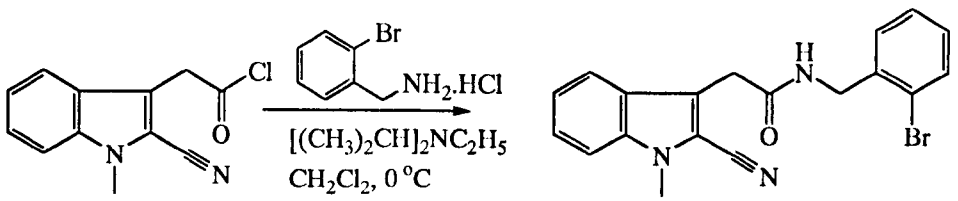


C_7H_6BrNO
Mol. Wt.: 200.03

C_7H_9BrClN
Mol. Wt.: 222.51

A solution of 2-bromobenzamide (**323**) (20.00 g, 100.0 mmol) in THF (150 cm^3) was added dropwise to a stirred solution of borane: THF complex (200 cm^3 of a 1.0 M solution 200.0 mmol) at 0 °C. The resulting solution was heated under reflux for 20 hours, allowed to cool and was quenched by the dropwise addition of dilute hydrochloric acid (30 cm^3 of an 8M solution). The resulting solution was then heated under reflux for 4 hours and cooled to room temperature. Organic solvent was removed under reduced pressure and the aqueous residue made basic by the dropwise addition of aqueous sodium hydroxide (pH > 10). The aqueous phase was extracted with ethyl acetate (4 x 200 cm^3) and the combined extracts washed with brine (200 cm^3) and extracted with hydrochloric acid (4 x 200 cm^3 of a 1 M solution). The hydrochloric acid was removed under reduced pressure to give a white solid, which was dried by azeotropic removal of water with toluene to give 2-bromobenzylamine hydrochloride (**311**) as a white solid (14.40 g, 65%); m.p. 238-240 °C (Lit.[288] 241-242 °C); (Found M^+, 185.9922/ 187.991, C_7H_8BrN requires M^++H 185.9918/ 187.9898); ν_{max} /cm^{-1} 1583.9, 1524.4 (Ar-C-H), 747.5 (*ortho* disubstituted aromatic); δ_H (300 MHz; DMSO-d_6) 4.09 (2H, s, C*H*$_2$), 7.32 (1H, td, *J* 7.8 & 1.1, C-4*H*), 7.46 (1H, td, *J* 7.8 & 1.1, C-5*H*), 7.67-7.70 (2H, overlapping d, *J* 7.8, C-6*H* & C-3*H*), 8.84 (3H, br s, N*H*$_3$); δ_C(75 MHz; DMSO-d_6) 41.79 (**C**H$_2$), 123.17 (**C**-2), 127.90 (**C**-5), 130.32 (**C**-4 & **C**-6), 132.58 (**C**-3), 133.21 (**C**-1).

_N_-(2-Bromobenzyl)-2-(2-cyano-1-methyl-1_H_-indol-3-yl)-acetamide (327)

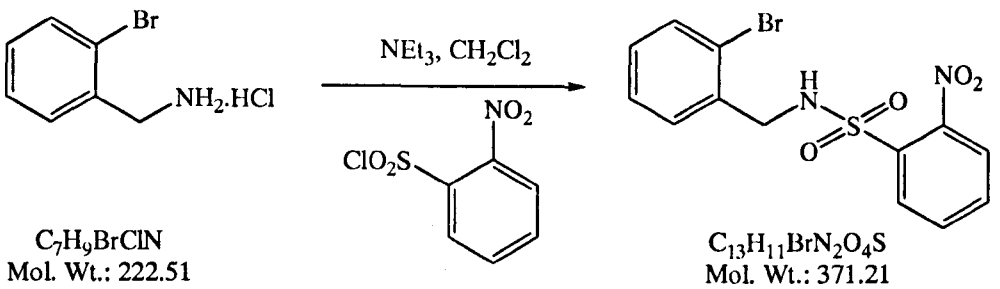


$C_{12}H_9ClN_2O$
Mol. Wt.: 232.67

$C_{19}H_{16}BrN_3O$
Mol. Wt.: 382.25

A solution of 2-cyano-1-methyl-1*H*-indole-3-acetyl chloride (**328**) (0.097 g, 0.4 mmol) in dichloromethane (10 cm^3) was added dropwise to a stirred solution of 2-bromobenzylamine hydrochloride (**311**) (0.10 g, 0.5 mmol) and *N,N*-ethyldiisopropylamine (0.25 cm^3, 0.19 g, 1.5 mmol) in dichloromethane (10 cm^3) at 0 °C. The reaction was stirred for 5 hours and then diluted with dichloromethane (40 cm^3), washed with dilute hydrochloric acid (60 cm^3 of a 0.2 M solution), dilute sodium hydroxide (60 cm^3 of a 0.2 M solution), water (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the title compound (**327**) as a white solid (0.15 g, 93%); R_f (3: 1, hexane: ethyl acetate) 0.42; (Found M^+, 382.0558/ 384.0561, $C_{19}H_{16}BrN_3O$ requires M^++H 382.0555/ 384.0535); ν_{max} /cm^{-1} 3280.1 (NH), 2219.9 (CN), 1646.6 (CONH); δ_H(300 MHz; $CDCl_3$) 3.86 (2H, s, CH_2CO), 3.87 (3H, s, NCH_3), 4.32 (2H, d, *J* 5.7, Ar-CH_2), 7.15-7.24 (2H, m, Ar-*H*), 7.32 (2H, m, Ar-*H*), 7.43 (1H, t, *J* 8.0, Ar-*H*), 7.59 (1H, d, *J* 8.0, Ar-*H*), 7.61 (1H, d, *J* 8.0, Ar-*H*), 7.78 (1H, d, *J* 8.0, Ar-*H*), 8.75 (1H, t, *J* 5.7, NH); δ_C(75 MHz; $CDCl_3$) 31.36 (NCH_3), 31.72 (CH_2CO), 42.75 (CH_2Ar), 109.31 (C-3), 110.81 (C-7), 113.17 (CN), 120.50 (quaternary C), 120.73 (Ar-C-H), 120.87 (Ar-C-H), 122.33 (quaternary C), 125.30 (quaternary C), 125.71 (Ar-C-H), 127.55 (Ar-C-H), 128.81 (Ar-C-H), 128.87 (Ar-C-H), 132.28 (Ar-C-H), 137.53 (C-7a), 168.74 (CO).

N-(2-Bromobenzyl)-2-nitrobenzenesulfonamide (339)

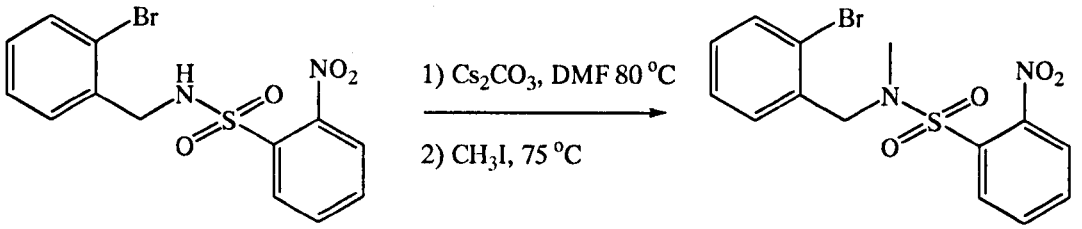


C_7H_9BrClN
Mol. Wt.: 222.51

$C_{13}H_{11}BrN_2O_4S$
Mol. Wt.: 371.21

2-Nitrobenzene sulfonyl chloride (**332**) (25.00 g, 112.3 mmol) in dichloromethane (100 cm^3) was added dropwise to a stirred solution of 2-bromobenzylamine hydrochloride (**311**) (25.00 g, 112.3 mmol) and triethylamine (50.1 cm^3, 36.40 g, 360.0 mmol) in dichloromethane (150 cm^3) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 16 hours. The resulting solution was washed with water (3 x 200 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by recrystallisation (ethyl acetate/ hexane) to give *N*-(2-bromobenzyl)-2-nitrobenzenesulfonamide (**339**) as a white crystalline solid (36.63 g, 89%); m.p. 101-103 °C; R_f (3: 2, hexane: ethyl acetate) 0.57; (Found M^+, 370.9694/ 372.9696, $C_{13}H_{11}BrN_2O_4S$ requires M^++H 370.9701/ 372.9681); ν_{max} /cm^{-1} 3347.8 (NH), 1531.1 (Ar-NO_2), 1162.6 (NSO_2Ar); δ_H(300 MHz; $CDCl_3$) 4.34 (2H, d, *J* 6.3, CH_2), 6.04 (1H, t, *J* 6.3, N*H*), 7.00 (1H, td, *J* 7.8 & 1.6, C-4*H*), 7.13 (1H, td, *J* 7.8 &1.6, C-5*H*), 7.29 (1H, dd, *J* 7.8 & 1.6, C-6*H*), 7.31 (1H, dd, *J* 7.8 & 1.6, C-3*H*), 7.51 (1H, td, *J* 7.6 & 1.6, C-5'*H*), 7.58 (1H, td, *J* 7.6 & 1.6, C-4'*H*), 7.34 (1H, dd, *J* 7.6 & 1.6, C-6'*H*), 7.83 (1H, dd, *J* 7.6 & 1.6, C-3'*H*); δ_C(75 MHz; $CDCl_3$) 48.20 (CH_2), 123.60 (C-2), 125.40 (Ar-C-H), 127.63 (Ar-C-H), 129.80 (Ar-C-H), 130.72 (Ar-C-H), 130.92 (Ar-C-H), 132.80 (Ar-C-H), 132.91 (Ar-C-H), 133.61 (Ar-C-H), 133.86 (quaternary C), 134.93 (quaternary C), 147.48 (C-2').

N-(2-Bromobenzyl)-*N*-methyl-2-nitrobenzenesulfonamide (340)

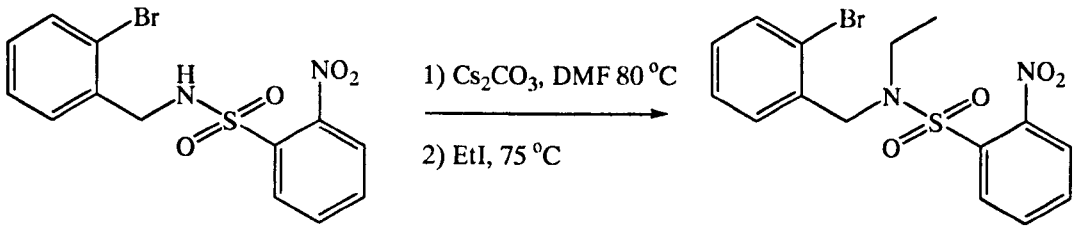


$C_{13}H_{11}BrN_2O_4S$
Mol. Wt.: 371.21

$C_{14}H_{13}BrN_2O_4S$
Mol. Wt.: 385.23

N-(2-Bromobenzyl)-2-nitrobenzenesulfonamide (**339**) (3.17 g, 8.5 mmol) and cesium carbonate (2.78 g, 8.5 mmol) in DMF (80 cm^3) were heated at 80 °C for 1 hour. The reaction was allowed to cool to room temperature and methyl iodide (2.7 cm^3, 6.00 g, 42.7 mmol) was added. The resulting solution was stirred at room temperature for 16 hours. Organic solvent was removed under reduced pressure and the residue dissolved in dichloromethane (100 cm^3) and filtered to remove the cesium carbonate. Purification of the viscous yellow oil by flash column chromatography (3: 2, hexane: ethyl acetate) gave *N*-(2-bromobenzyl)-*N*-methyl-2-nitrobenzenesulfonamide (**340**) as a light yellow oil (3.30 g, 99%); R_f (3: 2, hexane: ethyl acetate) 0.69; (Found M^+, 384.9864/ 386.9844, $C_{14}H_{13}BrN_2O_4S$ requires M^++H 384.9858/ 386.9837); ν_{max} /cm^{-1} 3060.7 (Ar-H), 1545.4 (Ar-NO_2), 1468.2, 1440.2 (NCH_3), 1372.1 (NSO_2Ar); δ_H(300 MHz; $CDCl_3$) 2.87 (3H, s, NCH_3), 4.58 (2H, s, CH_2), 7.16 (1H, td, *J* 7.7 & 1.6, C-4*H*), 7.33 (1H, td, *J* 7.7 & 1.6, C-5*H*), 7.49 (1H, dd, *J* 7.7 & 1.6, C-6*H*), 7.54 (1H, dd, *J* 7.7 & 1.6, C-3*H*), 7.65-7.75 (3H, m, C-4'*H*, C-5'*H*, C-6'*H*), 8.02 (1H, m, C-3'*H*); δ_C(75 MHz; $CDCl_3$) 34.82 (CH_3), 53.60 (CH_2), 123.55 (C-2), 124.29 (Ar-C-H), 128.03 (Ar-C-H), 129.46 (Ar-C-H), 129.58 (Ar-C-H), 130.96 (Ar-C-H), 131.80 (Ar-C-H), 132.12 (Ar-C-H), 132.96 (Ar-C-H), 133.81 (Ar-C-H), 134.59 (C-1'), 148.25 (C-2').

N-(2-Bromobenzyl)-N-ethyl-2-nitrobenzenesulfonamide (341)

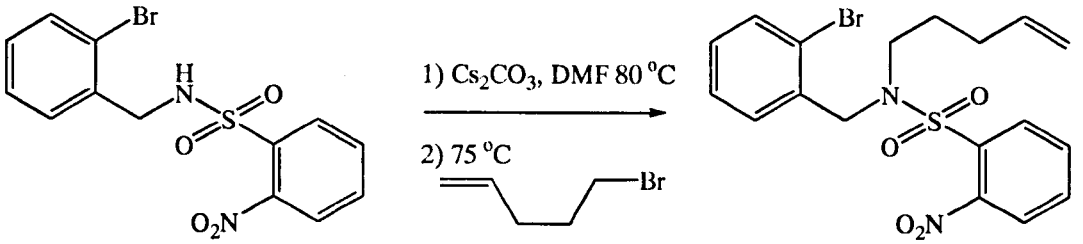


$C_{13}H_{11}BrN_2O_4S$
Mol. Wt.: 371.21

$C_{15}H_{15}BrN_2O_4S$
Mol. Wt.: 399.26

N-(2-Bromobenzyl)-2-nitrobenzenesulfonamide (**339**) (3.10 g, 8.3 mmol) and cesium carbonate (2.71 g, 8.3 mmol) in DMF (80 cm^3) were heated at 80 °C for 1 hour. The reaction was allowed to cool to room temperature and ethyl iodide (3.3 cm^3, 6.50 g, 41.6 mmol) was added. The resulting solution was stirred at room temperature for 16 hours. Organic solvent was removed under reduced pressure and the residue dissolved in dichloromethane (100 cm^3) and filtered to remove the cesium carbonate. Purification of the viscous yellow oil by flash column chromatography (3: 2, hexane: ethyl acetate) gave *N*-(2-bromobenzyl)-*N*-ethyl-2-nitrobenzenesulfonamide (**341**) as a light yellow oil (3.30 g, 99%); R_f (3: 2, hexane: ethyl acetate) 0.5; (Found M^+, 399.0020/ 400.9991, $C_{15}H_{15}BrN_2O_4S$ requires M^++H 399.0014/ 400.9994); ν_{max} /cm^{-1} 3095.8, 2979.3, 2937.4 (Ar-H), 1543.7 (Ar-NO_2), 1358.1 (NSO_2Ar), 1163.2 (NSO_2Ar), 759.9 & 736.5 (*ortho* disubstituted Ar); δ_H(300 MHz; $CDCl_3$) 1.03 (3H, t, *J* 7.1, CH_3), 3.39 (2H, q, *J* 7.1, CH_2CH_3), 4.68 (2H, s, CH_2Ar), 7.12 (1H, td, *J* 7.6 & 1.3, C-4*H*), 7.27 (1H, td, *J* 7.6 & 1.3, C-5*H*), 7.46 (1H, dd, *J* 7.6 & 1.3, C-6*H*), 7.51 (1H, dd, *J* 7.6 & 1.3, C-3*H*), 7.62-7.71 (3H, m, C-4'*H*, C-5'*H* & C-6'*H*), 7.99 (1H, m, C-3'*H*); δ_C(75 MHz; $CDCl_3$) 13.32 (CH_3), 42.87 (CH_2CH_3), 50.54 (CH_2Ar), 123.20 (C-2), 124.28 (Ar-C-H), 127.85 (Ar-C-H), 129.28 (Ar-C-H), 129.65 (Ar-C-H), 130.76 (Ar-C-H), 131.87 (Ar-C-H), 132.87 (Ar-C-H), 133.67 (Ar-C-H), 135.25 (C-1'), 147.92 (C-2').

N-(2-Bromobenzyl)-2-nitro-*N*-pent-4-enylbenzenesulfonamide (385)

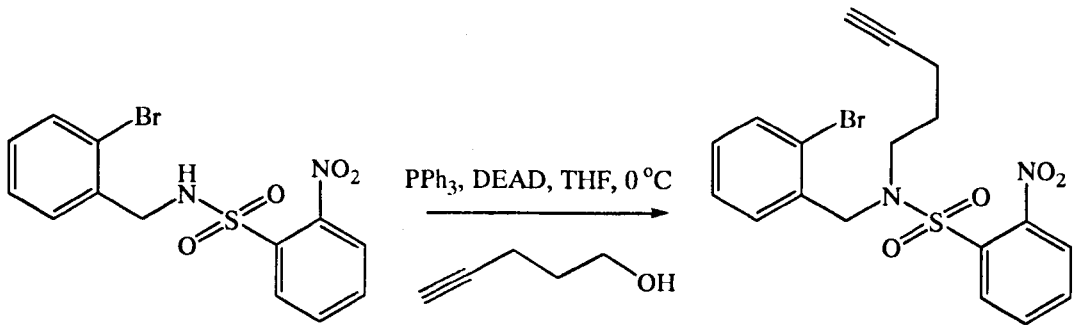


$C_{13}H_{11}BrN_2O_4S$
Mol. Wt.: 371.21

$C_{18}H_{19}BrN_2O_4S$
Mol. Wt.: 439.33

N-(2-Bromobenzyl)-2-nitrobenzenesulfonamide (**339**) (3.85 g, 10.4 mmol) and cesium carbonate (3.38 g, 10.4 mmol) in DMF (80 cm^3) were heated at 80 °C for 1 hour. The reaction was allowed to cool to room temperature and 5-bromo-1-pentene (**386**) (4.9 cm^3, 6.20 g, 41.4 mmol) was added. The resulting solution was heated at 75 °C for 4 hours and then at room temperature for 16 hours. Organic solvent was removed under reduced pressure and the residue dissolved in dichloromethane (100 cm^3) and filtered to remove the cesium carbonate. Purification of the viscous yellow oil by flash column chromatography (3: 2, hexane: ethyl acetate) gave the title compound (**385**) as a light yellow oil (4.60 g, 99%); R_f (3: 2, hexane: ethyl acetate) 0.64; (Found M^+, 439.0341/ 441.0308, $C_{18}H_{19}BrN_2O_4S$ requires M^++H 439.0327/ 441.0307); ν_{max} /cm^{-1} 3055.4, 2986.9 (Ar-H), 1387.0 (NSO_2Ar), 1187.9 (NSO_2Ar), 739.4, 704.9 (*ortho* disubstituted Ar); δ_H(300 MHz; $CDCl_3$) 1.52 (2H, quin, *J* 7.5, NCH_2CH_2), 1.92 (2H, q, *J* 7.5, $NCH_2CH_2CH_2$), 3.31 (2H, t, *J* 7.5, NCH_2CH_2), 4.68 (2H, s, NCH_2Ar), 4.87-4.92 (2H, m, $CH=CH_2$), 5.61 (1H, ddt, *J* 17.5, 9.6 & 7.5, $CH=CH_2$), 7.12 (1H, td, *J* 7.7 & 1.4, C-4*H*), 7.26 (1H, td, *J* 7.7 & 1.4, C-5*H*), 7.45 (1H, dd, *J* 7.7 & 1.4, C-6*H*), 7.50 (1H, dd, *J* 7.7 & 1.4, C-3*H*), 7.62-7.73 (3H, m, Ar-*H*), 7.99 (1H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 27.00 (CH_2), 30.61 (CH_2), 47.83 (CH_2), 51.23 (CH_2), 115.44 ($C=CH_2$), 123.26 (C-2), 124.30 (Ar-C-H), 127.85 (Ar-C-H), 129.34 (Ar-C-H), 129.72 (Ar-C-H), 130.80 (Ar-C-H), 131.87 (Ar-C-H), 132.90 (Ar-C-H), 133.48 (quaternary C), 133.75 (Ar-C-H), 135.16 (quaternary C), 137.08 ($CH=CH_2$), 147.91 (C-2').

_N_-(2-Bromobenzyl)-2-nitro-_N_-pent-4-ynylbenzenesulfonamide (393)

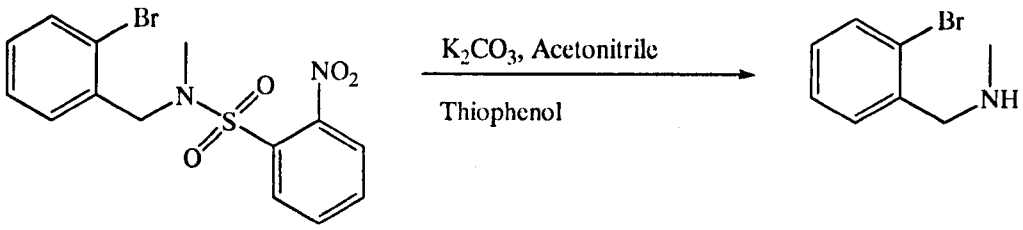


$C_{13}H_{11}BrN_2O_4S$
Mol. Wt.: 371.21

$C_{18}H_{17}BrN_2O_4S$
Mol. Wt.: 437.31

Diethyl azodicarboxylate (11.20 cm^3, 12.38 g, 71.1 mmol) was added dropwise to a solution of *N*-(2-bromobenzyl)-2-nitrobenzenesulfonamide (**339**) (20.30 g, 54.7 mmol), 4-pentyn-1-ol (**392**) (6.1 cm^3, 5.52 g, 65.6 mmol) and triphenylphosphine (18.64 g, 71.1 mmol) in THF (150 cm^3) at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. Organic solvent was removed under reduced pressure and the residue taken up in diethyl ether (70 cm^3). The volume of the solution was reduced and the solution filtered to remove the triphenylphosphine oxide. The filtrate was reduced in volume and the yellow oil purified by flash column chromatography (3: 2, hexane: ethyl acetate) to give the title compound (**393**) as a light yellow oil (22.96 g, 96%); R_f (3: 2, hexane: ethyl acetate) 0.55; (Found M^+, 437.0156/ 439.0169, $C_{18}H_{17}BrN_2O_4S$ requires M^++H 437.0171/ 439.0150); ν_{max} /cm^{-1} 3300.4 (CCH), 3061.0, 2942.5 (Ar-H), 1544.7 (Ar-NO_2), 1371.4 (NSO_2Ar), 1163.8 (NSO_2Ar); δ_H(300 MHz; $CDCl_3$) 1.61 (2H, m, NCH_2CH_2), 1.87 (1H, t, *J* 2.6, CC*H*), 2.04 (2H, td, *J* 7.0 & 2.6, CH_2CH_2CCH), 3.39 (2H, t, *J* 7.6, NCH_2CH_2), 4.66 (2H, s, NCH_2Ar), 7.09 (1H, td, *J* 7.6 & 1.6, C-4*H*), 7.23 (1H, td, *J* 7.6 & 1.6, C-5*H*), 7.42 (1H, dd, *J* 7.6 & 1.6, C-6*H*), 7.47 (1H, dd, *J* 7.6 & 1.6, C-3*H*), 7.60-7.70 (3H, m, Ar-*H*), 7.96 (1H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 15.73 (CH_2), 26.78 (CH_2), 47.28 (NCH_2CH_2), 51.48 (NCH_2Ar), 69.44 (CCH), 82.69 (CCH), 123.32 (C-2), 124.33 (Ar-C-H), 127.91 (Ar-C-H), 129.47 (Ar-C-H), 129.80 (Ar-C-H), 130.86 (Ar-C-H), 132.04 (Ar-C-H), 132.96 (Ar-C-H), 133.09 (C-1), 133.96 (Ar-C-H), 135.02 (C-1'), 147.88 (C-2').

(2-Bromobenzyl)methylamine (342)

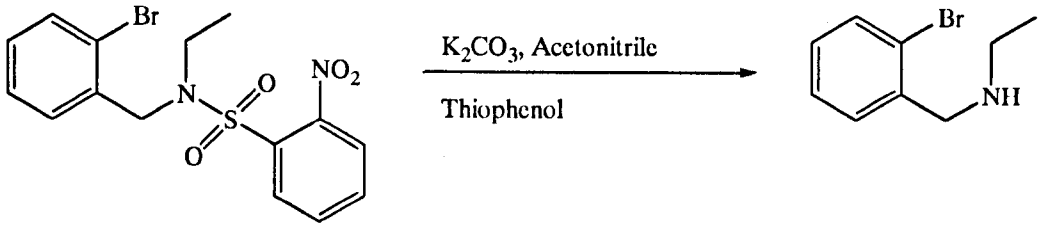


$C_{14}H_{13}BrN_2O_4S$
Mol. Wt.: 385.23

$C_8H_{10}BrN$
Mol. Wt.: 200.08

Thiophenol (0.99 cm^3, 0.92 g, 8.9 mmol) was added to a stirred solution of *N*-(2-nitrophenylsulfonyl)-*N*-(2-bromobenzyl)-methylamine (**340**) (3.15 g, 7.9 mmol) and potassium carbonate (3.67 g, 26.6 mmol) in acetonitrile (100 cm^3) at room temperature. The resulting solution was left to stir overnight at room temperature. Organic solvent was removed under reduced pressure and the residue was taken up in diethyl ether (200 cm^3). Hydrochloric acid (100 cm^3 of a 1.0 M solution) was added and the resulting solution was stirred for ten minutes. The organic layer was separated and washed with dilute hydrochloric acid (100 cm^3 of a 1.0 M solution) and the combined aqueous phases washed with diethyl ether (200 cm^3) and made basic by the addition of solid potassium carbonate. The aqueous solution was extracted with diethyl ether (3 x 150 cm^3) and the combined organic extracts washed with brine (200 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the title compound (**342**) as a pale yellow oil (1.39 g, 85%); R_f (1: 1, hexane: ethyl acetate) 0.33; (Found M^+, 200.0061/ 202.0045, $C_8H_{10}BrN$ requires M^++H 200.0075/ 202.0054); ν_{max} /cm^{-1} 3413.0 (NH), 2947.3, 2798.8 (Ar-H); δ_H(300 MHz; $CDCl_3$), 1.49 (1H, s, N*H*), 2.37 (3H, s, NCH_3), 3.75 (2H, s, Ar-CH_2), 7.03 (1H, td, *J* 7.5 & 1.5, C-4*H*), 7.19 (1H, t, *J* 7.5 , C-5*H*), 7.29 (1H, dd, *J* 7.5 & 1.5, C-6*H*), 7.46 (1H, d, *J* 7.5, C-3*H*); δ_C(75 MHz; $CDCl_3$) 35.84 (CH_3), 52.67 (Ar-CH_2), 123.96 (C-2), 127.32 (C-5), 128.51 (C-4), 130.19 (C-6), 132.71 (C-3), 139.04 (C-1).

(2-Bromobenzyl)ethylamine (343)

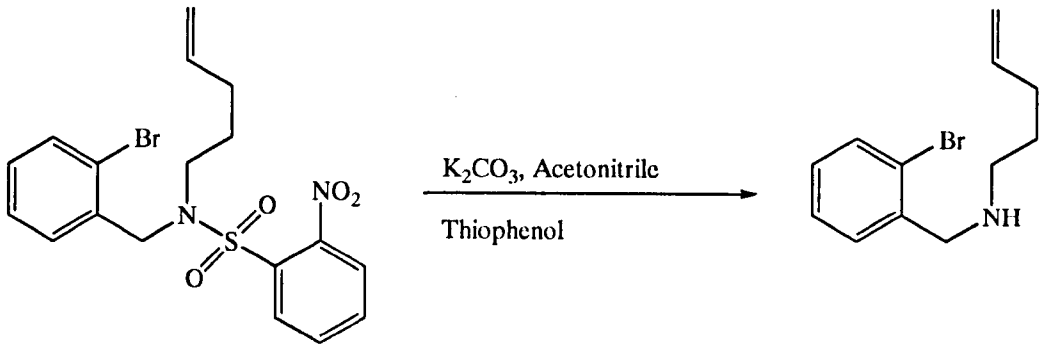


$C_{15}H_{15}BrN_2O_4S$
Mol. Wt.: 399.26

$C_9H_{12}BrN$
Mol. Wt.: 214.10

Thiophenol (0.89 cm^3, 0.96 g, 8.7 mmol) was added to a stirred solution of *N*-(2-nitrophenylsulfonyl)-*N*-(2-bromobenzyl)ethylamine (**341**) (3.15 g, 7.9 mmol) and potassium carbonate (3.55 g, 25.7 mmol) in acetonitrile (100 cm^3) at room temperature. The resulting solution was left to stir overnight at room temperature. Organic solvent was removed under reduced pressure and the residue was taken up in diethyl ether (200 cm^3). Hydrochloric acid (100 cm^3 of a 1.0 M solution) was added and the resulting solution was stirred for ten minutes. The organic layer was separated and washed with dilute hydrochloric acid (100 cm^3 of a 1.0 M solution). The combined aqueous phases were washed with diethyl ether (200 cm^3) and made basic by the addition of solid potassium carbonate. The aqueous solution was extracted with diethyl ether (3 x 150 cm^3) and the combined extracts washed with brine (200 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the title compound (**343**) as a pale yellow oil (1.31 g, 77%); R_f (1: 1, hexane: ethyl acetate) 0.50; (Found M^+, 214.0237/ 216.0218, $C_9H_{12}BrN$ requires M^++H 214.0231/ 216.0211); ν_{max} /cm^{-1} 3406.3 (NH); δ_H(300 MHz; $CDCl_3$) 1.23 (3H, t, *J* 7.1, CH_3), 1.47 (1H, s, N*H*), 2.65 (2H, q, *J* 7.1, NCH_2CH_3), 3.84 (2H, s, Ar-CH_2), 7.08 (1H,td, *J* 7.5 & 1.5, C-4*H*), 7.24 (1H, td, *J* 7.5 & 1.5, C-5*H*), 7.35 (1H, dd, *J* 7.5 & 1.5, C-6*H*), 7.51 (1H, dd, *J* 7.5 & 1.5, C-3*H*); δ_C(75 MHz; $CDCl_3$) 15.35 (CH_3), 43.45 (NCH_2CH_3), 53.68 (Ar-CH_2), 123.95 (**C**-2), 127.39 (**C**-5), 128.49 (**C**-4), 130.22 (**C**-6), 132.73 (**C**-3), 139.37 (**C**-1).

(2-Bromobenzyl)pent-4-enylamine (384)

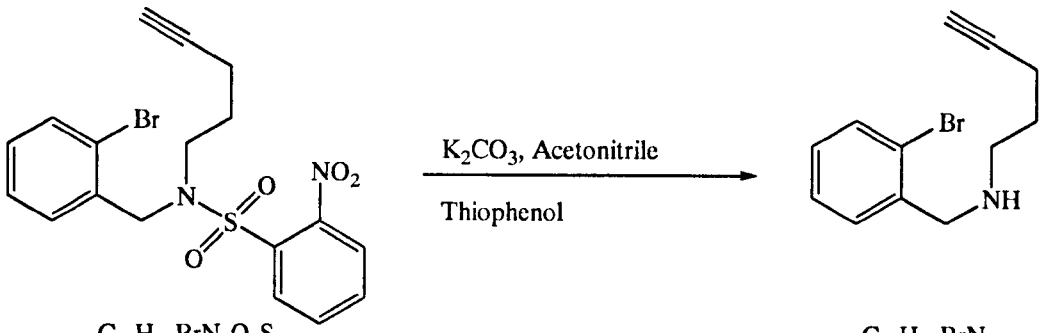


$C_{18}H_{19}BrN_2O_4S$
Mol. Wt.: 439.33

$C_{12}H_{16}BrN$
Mol. Wt.: 254.17

Thiophenol (1.14 cm^3, 1.23 g, 11.1 mmol) was added to a stirred solution of *N*-(2-nitrophenylsulfonyl)-*N*-(2-bromobenzyl)pent-4-enylamine (**385**) (4.44 g, 10.1 mmol) and potassium carbonate (4.54 g, 32.8 mmol) in acetonitrile (100 cm^3) at room temperature and the resulting solution left to stir overnight at room temperature. Organic solvent was removed under reduced pressure and the residue was taken up in diethyl ether (200 cm^3). Hydrochloric acid (100 cm^3 of a 1.0 M solution) was added and the resulting solution was stirred for ten minutes. The organic layer was separated and washed with dilute hydrochloric acid (100 cm^3 of a 1.0 M solution). The combined aqueous phases were washed with diethyl ether (200 cm^3) and made basic by the addition of solid potassium carbonate. The aqueous solution was extracted with diethyl ether (3 x 150 cm^3) and the combined extracts washed with brine (200 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the title compound (**384**) as a pale yellow oil (2.20 g, 86%); R_f (1: 1, hexane: ethyl acetate) 0.51; (Found M^+ (FABMS Matrix), 437.0156 ^{79}Br $C_{12}H_{16}BrN$ requires M^++H 437.0171 ^{79}Br); ν_{max}/ cm^{-1} 3411.7 (NH); δ_H(300 MHz; $CDCl_3$) 1.62 (2H, quin, *J* 7.3, NCH_2CH_2), 1.72 (1H, br s, N*H*), 2.10 (2H, q, *J* 7.3, $NCH_2CH_2CH_2$), 2.63 (2H, t, *J* 7.3, NCH_2CH_2), 3.84 (2H, s, Ar-CH_2), 4.95 (1H, dd, *J* 10.2 & 1.5, CH=CH_{cis}), 5.01 (1H, dd, *J* 17.1 &1.5, CH=CH_{trans}), 5.80 (1H, tdd, *J* 17.1 & 10.2 & 6.7, CH=CH_2), 7.10 (1H, td, *J* 7.5 & 1.0, C-4*H*), 7.26 (1H, td, *J* 7.5 & 1.0, C-5*H*), 7.38 (1H, dd, *J* 7.5 & 1.0, C-6*H*), 7.52 (1H, dd, *J* 7.5 & 1.0, C-3*H*); δ_C(75 MHz; $CDCl_3$) 29.21 (C-2'), 31.53 (C-3'), 48.64 (C-1'), 53.76 (Ar-CH_2), 114.75 (C-5'), 123.97 (C-2), 127.42 (C-5), 128.55 (C-4), 130.27 (C-6), 132.75 (C-3), 138.40 (C-4'), 139.25 (C-1); *m/z* (FBMS Matrix) 256 (82.7%, M^++H, ^{81}Br), 254 (100.0, M^++H, ^{79}Br), 171 (32.3), 169 (34.0).

(2-Bromo-benzyl)pent-4-ynylamine (394)

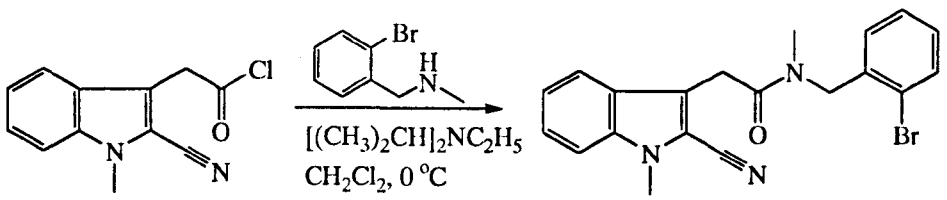


$C_{18}H_{17}BrN_2O_4S$
Mol. Wt.: 437.31

$C_{12}H_{14}BrN$
Mol. Wt.: 252.15

Thiophenol (5.9 cm^3, 6.36 g, 57.8 mmol) was added to a stirred solution of *N*-(2-bromobenzyl)-2-nitro-*N*-pent-4-ynylbenzenesulfonamide (**393**) (22.95 g, 52.5 mmol) and potassium carbonate (23.58 g, 170.6 mmol) in acetonitrile (150 cm^3) at room temperature. The resulting solution was left to stir overnight at room temperature. Organic solvent was removed under reduced pressure and the residue was taken up in diethyl ether (200 cm^3). Hydrochloric acid (2.0 M solution) was added until the solution remained acidic and the resulting solution was stirred for ten minutes. The organic layer was separated and washed with dilute hydrochloric acid (100 cm^3 of a 1.0 M solution). The combined aqueous phases were washed with diethyl ether (200 cm^3) and made basic by the addition of solid potassium carbonate. The aqueous solution was extracted with diethyl ether (4 x 150 cm^3) and the combined extracts washed with brine (200 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the title compound (**394**) as a pale yellow oil (9.94 g, 75%); R_f (3: 2, hexane: ethyl acetate) 0.21; (Found M^+, 252.0377/ 254.0381, $C_{12}H_{14}BrN$ requires M^++H 252.0388/ 254.0367); ν_{max}/ cm^{-1} 3422.5 (NH), 3301.6 (CCH); δ_H(300 MHz; $CDCl_3$) 1.39 (1H, br s, N*H*), 1.64 (2H, quin, *J* 7.0, NHCH2CH_2), 1.86 (1H, t, *J* 2.6, CC*H*), 2.19 (2H, td, *J* 7.0 & 2.6, CH_2CCH), 2.64 (2H, t, *J* 7.0, NCH_2CH_2), 3.76 (2H, s, NCH_2Ar), 7.01 (1H, td, *J* 7.5 & 1.0, C-4*H*), 7.17 (1H, td, *J* 7.5 & 1.0, C-5*H*), 7.29 (1H, dd, *J* 7.5 & 1.0, C-6*H*), 7.43 (1H, dd, *J* 7.5 & 1.0, C-3*H*); δ_C(75 MHz; $CDCl_3$) 16.61 (CH_2), 28.75 (CH_2), 47.92 (NCH_2CH_2), 53.65 (NCH_2Ar), 68.61 (CCH), 84.08 (CCH), 123.94 (C-2), 127.39 (C-5), 128.52 (C-4), 130.19 (C-6), 132.75 (C-3), 139.34 (C-1).

***N*1-(2-bromobenzyl)-*N*1-(methyl)-2-(1-methyl-2-cyano-1*H*-3-indolyl)acetamide (346)**



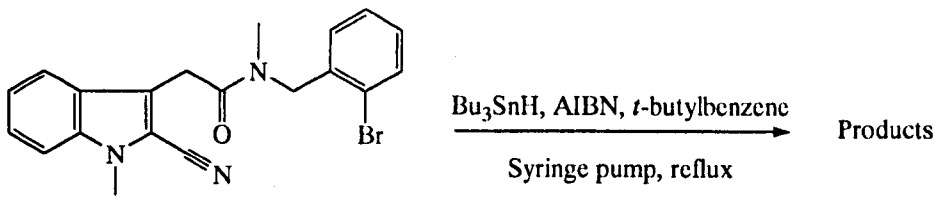
$C_{12}H_9ClN_2O$
Mol. Wt.: 232.67

$C_{20}H_{18}BrN_3O$
Mol. Wt.: 396.28

2-Cyano-1-methyl-1*H*-indole-3-acetyl chloride (**328**) (1.11 g, 4.8 mmol) in dichloromethane (30 cm^3) was added dropwise *via* cannula to a stirred solution of (2-bromobenzyl)methylamine (**342**) (1.05 g, 5.2 mmol) and *N, N*-diisopropylethylamine (2.9 cm^3, 2.17 g, 16.8 mmol) in dichloromethane (30 cm^3) at 0 °C under nitrogen. The resulting mixture was left to stir at 0 °C for one hour, allowed to warm to room temperature and then left to stir overnight at room temperature. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3), washed with HCl (100 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate (100 cm^3) and brine (100 cm^3). The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give a light green solid which was purified by flash column chromatography (1: 1, hexane: ethyl acetate) to give the tertiary amide (**346**) as a light yellow solid and as a 1: 1 mixture of amide rotamers (1.60 g, 84%); m.p. 111.5-113.0 °C; R_f (1: 1, hexane: ethyl acetate) 0.66; (Found M^+, 395.0655/ 397.0630, $C_{20}H_{18}BrN_3O$ requires M^+ 395.06337/ 397.0614); ν_{max}/ cm^{-1} 2218.5 (CN), 1652.1 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 2.88 (1.5H, s, CONC*H*$_3$), 2.95 (1.5H, s, CONC*H*$_3$), 3.54 (1.5H, s, NC*H*$_3$), 3.69 (1.5H, s, NC*H*$_3$), 3.79 (1H, s, C*H*$_2$CO), 3.92 (1H, s, C*H*$_2$CO), 4.54 (1H, s, C*H*$_2$Ar), 4.60 (1H, s, C*H*$_2$Ar), 6.74 (0.5H, m, Ar-*H*), 6.93-7.11 (4H, m, Ar-*H*), 7.18 (0.5H, d, *J* 8.4, Ar-*H*), 7.20 (0.5H, d, *J* 7.3, Ar-*H*), 7.26 (0.5H, m, Ar-*H*), 7.38 (0.5H, dd, *J* 7.4 & 1.1, Ar-*H*), 7.44 (0.5H, m, Ar-*H*), 7.53 (0.5H, d, *J* 8.1, Ar-*H*), 7.66 (0.5H, d, *J* 8.1, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 31.00 (CH_2CO), 31.33 (CH_2CO), 31.55 (indole NCH_3), 31.76 (indole NCH_3), 34.87 ($CONCH_3$), 35.90 ($CONCH_3$), 51.34 (CH_2ArBr), 54.50 (CH_2ArBr), 109.85 (2 x C-3), 110.23 (C-7), 110.30 (C-7), 113.10 (CN), 113.47 (CN), 120.29 (quaternary C), 120.57 (quaternary C), 121.25 (Ar-C-H), 121.63 (Ar-C-H), 122.72 (quaternary C), 123.70

(quaternary **C**), 126.15 (quaternary **C**), 126.24 (Ar-**C**-H), 126.39 (Ar-**C**-H), 127.79 (Ar-**C**-H), 127.80 (Ar-**C**-H), 127.89 (Ar-**C**-H), 129.03 (Ar-**C**-H), 129.12 (Ar-**C**-H), 129.15 (Ar-**C**-H), 132.98 (Ar-**C**-H), 133.19 (Ar-**C**-H), 135.18 (quaternary **C**), 136.06 (quaternary **C**), 138.08 (quaternary **C**), 138.29 (quaternary **C**), 169.57 (**C**O), 170.00 (**C**O); *m/z* 397.06 (12.4%, M^+, ^{81}Br), 395.07 (12.9, M^+, ^{79}Br), 316.14 (52.2), 170.98 (80.0), 170.09 (64.3), 169.92 (100.0), 168.09 (46.2), 154.05 (57.6), 128.05 (36.6), 127.04 (40.3), 115.05 (37.5), 102.04 (45.2), 101.03 (46.5), 91.06 (61.6), 90.05 (73.5), 89.04 (52.0), 77.04 (51.1).

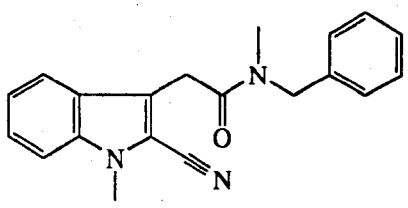
Radical cyclisation of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-methylacetamide (346)



$C_{20}H_{18}BrN_3O$
Mol. Wt.: 396.28

A solution of tri-*n*-butyltin hydride (0.30 cm^3, 0.33 g, 1.12 mmol) and azo-bis-isobutyronitrile (AIBN) (0.030 g, 0.18 mmol) in *t*-butylbenzene (20 cm^3) was added dropwise *via* syringe pump (6.37 cm^3/hour) to a solution of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-methylacetamide **(346)** (0.36 g, 0.92 mmol) in *t*-butylbenzene (25 cm^3) under reflux. Once addition was complete, heating was continued for $1^1/_2$ hours. The reaction was allowed to cool and organic solvent removed under reduced pressure and the residue taken up in diethyl ether (50 cm^3). DBU (0.33 cm^3, 0.33 g, 2.2 mmol) was added and the white precipitate that formed filtered and washed with ethyl acetate. Organic solvent was removed under reduced pressure and the residue purified by multiple flash column chromatography (3: 1, hexane: ethyl acetate) to give three products of R_f= 0.63, 0.35 & 0.26 (1: 1, hexane: ethyl acetate).

Product of R_f = 0.63 (358)

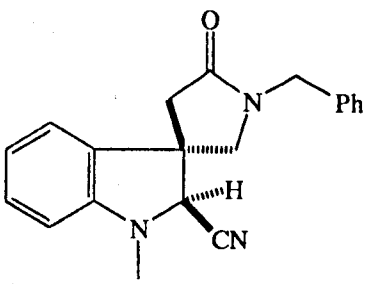


$C_{20}H_{19}N_3O$
Mol. Wt.: 317.38

Pale white solid as a 1: 1 mixture of amide rotamers (0.18 g, 62%); m.p. 100-101 °C; (Found M^+, 318.1594, $C_{20}H_{19}N_3O$ requires M^++H 318.1606); ν_{max} /cm^{-1} 3058.5, 3090.3, 2937.0 (Ar-H), 2217.5 (CN), 1651.2 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 2.86 (1.5H, s, $CONCH_3$), 2.90 (1.5H, s, $CONCH_3$), 3.55 (1.5H, s, indole NCH_3), 3.67 (1.5H, s, indole NCH_3), 3.86 (1H, s, CH_2CO), 3.92 (1H, s, CH_2CO), 4.48 (1H, s, NCH_2Ar), 4.54 (1H, s,

NCH_2Ar), 6.95 (1H, m, Ar-*H*), 6.93-7.30 (7H, m, Ar-*H*), 7.59 (0.5H, d, *J* 8.1, Ar-*H*), 7.66 (0.5H, d, *J* 8.1, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 31.00 (CH_2CO), 31.18 (CH_2CO), 31.39 (indole NCH_3), 31.56 (indole NCH_3), 34.57 ($CONCH_3$), 35.29 ($CONCH_3$), 51.29 (NCH_2Ar), 53.71 (NCH_2Ar), 109.70 (C-3), 110.06 (C-7), 110.12 (C-7), 113.18 (CN), 113.32 (CN), 120.56 (quaternary C), 120.67 (quaternary C), 121.19 (2 x Ar-C-H), 121.32 (Ar-C-H), 121.50 (Ar-C-H), 125.99 (Ar-C-H), 126.07 (Ar-C-H), 126.14 (Ar-C-H), 126.20 (Ar-C-H), 127.43 (Ar-C-H), 127.47 (Ar-C-H), 128.12 (2 x Ar-C-H), 128.62 (2 x Ar-C-H), 128.80 (Ar-C-H), 136.30 (quaternary C), 137.12 (quaternary C), 138.04 (quaternary C), 138.18 (quaternary C), 169.17 (CO), 169.62 (CO), Missing (3 x quaternary C & 1 x Ar-C-H).

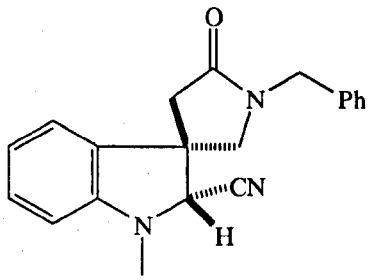
Product of R_f = 0.35 (360a)



$C_{20}H_{19}N_3O$
Mol. Wt.: 317.38

Colourless solid (0.044 g, 15%); m.p. 151-153 °C; (Found M^+, 340.1429, $C_{20}H_{19}N_3O$ requires M^++Na 340.1426); ν_{max} /cm^{-1} 3056.8 & 2226.0 (Ar-H), 2218.0 (CN), 1686.0 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 2.77 (3H, s, NCH_3), 2.82 & 3.02 (2H, ABq, *J* 17.4, CH_2CO), 3.23 & 3.38 (2H, ABq, *J* 10.3, CH_2N), 4.01 (1H, s, *CH*CN), 4.35 & 4.50 (2H, ABq, *J* 14.5, NCH_2Ar), 6.50 (1H, d, *J* 7.4, C-7*H*), 6.75 (1H, td, *J* 7.4 & 1.0, C-6*H*), 6.95 (1H, d, *J* 7.4, C-4*H*), 7.12 (1H, td, *J* 7.4 & 1.0, C-5*H*), 7.17-7.26 (5H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 34.07 (NCH_3), 40.24 (CH_2), 46.72 (CH_2), 48.13 (quaternary C), 56.79 (CH_2), 67.32 (CHCN), 109.04 (C-7), 115.47 (CN), 120.68 (Ar-C-H), 121.79 (Ar-C-H), 127.98 (Ar-C-H), 128.32 (2 x Ar-C-H), 128.91 (2 x Ar-C-H), 129.58 (Ar-C-H), 131.54 (C-1'), 135.77 (C-3a), 149.19 (C-7a), 171.48 (CO).

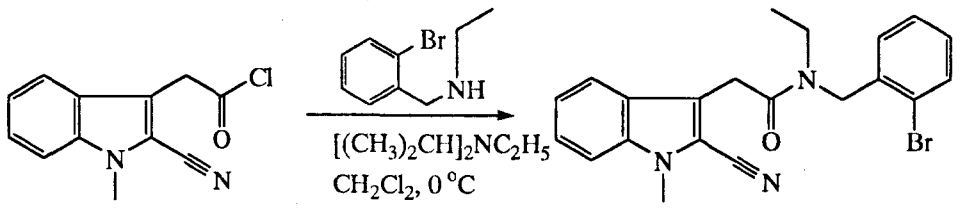
Product of R_f = 0.26 (360b)



$C_{20}H_{19}N_3O$
Mol. Wt.: 317.38

Pale yellow oil (0.044 g, 15%); (Found M^+, 340.1424, $C_{20}H_{19}N_3O$ requires M^++Na 340.1426); ν_{max} /cm^{-1} 3057.3, 2924.5 (Ar-H), 2201.9 (CN), 1692.6 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 2.66 & 2.73 (2H, ABq, *J* 17.0, C*H*$_2$CO), 2.79 (3H, s, NC*H*$_3$), 3.43 & 3.73 (2H, ABq, *J* 10.9, C*H*$_2$N), 4.07 (1H, s, C*H*CN), 4.31 & 4.67 (2H, ABq, *J* 14.5, NC*H*$_2$Ar), 6.50 (1H, d, *J* 7.4, C-7*H*), 6.73 (1H, t, *J* 7.4, C-6*H*), 6.89 (1H, d, *J* 7.4, C-4*H*), 7.12 (1H, td, *J* 7.4 & 1.1, C-5*H*), 7.21-7.31 (5H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 34.20 (NCH_3), 43.34 (CH_2), 46.89 (CH_2), 48.03 (quaternary **C**), 54.48 (CH_2), 67.53 (CHCN), 109.04 (C-7), 115.60 (CN), 120.67 (Ar-C-H), 121.71 (Ar-C-H), 128.01 (Ar-C-H), 128.50 (2 x Ar-C-H), 128.91 (2 x Ar-C-H), 129.57 (Ar-C-H), 131.45 (C-1'), 135.61 (C-3a), 149.20 (C-7a), 171.16 (CO).

***N*-(2-Bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-ethylacetamide (348)**



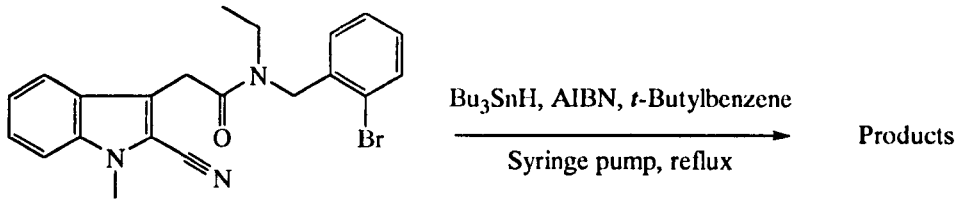
$C_{12}H_9ClN_2O$
Mol. Wt.: 232.67

$C_{21}H_{20}BrN_3O$
Mol. Wt.: 410.31

2-Cyano-1-methyl-1*H*-indole-3-acetyl chloride (**328**) (1.00 g, 4.5 mmol) in dichloromethane (30 cm^3) was added dropwise *via* cannula to a stirred solution of (2-bromobenzyl)ethylamine (**343**) (1.05 g, 4.9 mmol) and *N, N*-diisopropylethylamine (2.7 cm^3, 2.00 g, 15.7 mmol) in dichloromethane (30 cm^3) at 0 °C under nitrogen. The resulting mixture was left to stir at 0 °C for one hour, allowed to warm to room temperature and left to stir overnight. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3), washed with HCl (100 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate (100 cm^3) and brine (100 cm^3). The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give a light green solid which was purified by flash column chromatography (1: 1, hexane: ethyl acetate) to give the tertiary amide (**348**) as a light yellow solid and as a 1: 1 mixture of amide rotamers (1.70 g, 90%); m.p. 127-128.5 °C; R_f (1: 1, hexane: ethyl acetate) 0.83; (Found M^+, 409.0790/ 411.0796, $C_{21}H_{20}BrN_3O$ requires M^+ 409.07902/ 411.07705); ν_{max} /cm^{-1} 3059.3, 2931.8 (Ar-H), 2217.4 (CN), 1650.2 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.69 (1.5H, t, *J* 7.1, CH_2CH_3), 1.23 (1.5H, t, *J* 7.1, CH_2CH_3), 3.46 (2H, overlapping q, *J* 7.1, CH_2CH_3), 3.72 (1.5H, s, NCH_3), 3.87 (1.5H, s, NCH_3), 3.92 (1H, s, CH_2CO), 4.08 (1H, s, CH_2CO), 4.65 (1H, s, CH_2ArBr), 4.74 (1H, s, CH_2ArBr), 6.90 (0.5H, m, Ar-*H*), 7.05-7.26 (4H, m, Ar-*H*), 7.32 (0.5H, d, *J* 8.3, Ar-*H*), 7.33-7.44 (1H, m, Ar-*H*), 7.57 (0.5H, m, Ar-*H*), 7.67 (0.5H, d, *J* 8.1, Ar-*H*), 7.67 (0.5H, d, *J* 8.1, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 12.73 (CH_2CH_3), 14.03 (CH_2CH_3), 30.81 (CH_2CO), 31.27 (CH_2CO), 31.41 (NCH_3), 31.64 (NCH_3), 41.98 (CH_2CH_3), 42.66 (CH_2CH_3), 48.27 (CH_2ArBr), 51.73 (CH_2ArBr), 109.68 (2 x C-3), 110.01 (C-7), 110.09 (C-7), 112.96 (CN), 113.29 (CN), 120.24 (quaternary C), 120.84 (quaternary C), 121.16 (Ar-C-H), 121.20 (Ar-C-H), 121.61 (Ar-C-H), 122.56 (quaternary C), 123.48 (quaternary C), 126.06 (Ar-C-H), 126.26 (Ar-C-H), 126.79 (Ar-C-H), 127.56

(Ar-C-H), 128.74 (Ar-C-H), 128.88 (Ar-C-H), 129.07 (Ar-C-H), 132.70 (Ar-C-H), 132.99 (Ar-C-H), 135.44 (quaternary C), 136.43 (quaternary C), 137.97 (quaternary C), 138.19 (quaternary C), 169.14 (quaternary C), 169.41 (quaternary C); Missing (2 x Ar-C-H) & (2 x quaternary C); *m/z* 411.08 (15.0%, M^+, ^{81}Br), 409.08 (13.2, M^+, ^{79}Br), 330.17 (41.6), 170.98 (86.4), 170.09 (36.7), 169.09 (100.0), 168.09 (15.1), 154.05 (17.9), 91.05 (25.0).

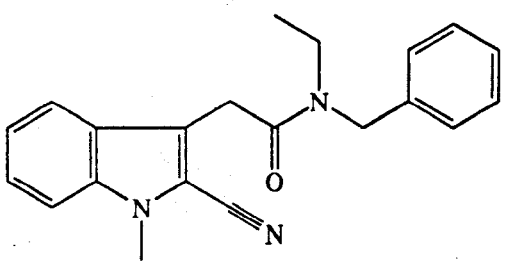
Radical cyclisation of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-ethylacetamide (348)



$C_{21}H_{20}BrN_3O$
Mol. Wt.: 410.31

A solution of tri-*n*-butyltin hydride (0.24 cm^3, 0.26 g, 0.91 mmol) and azo-bis-isobutyronitrile (AIBN) (0.024 g, 0.15 mmol) in *t*-butylbenzene (18 cm^3) were added dropwise *via* syringe pump (6.37 cm^3/hour) to a solution of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-ethylacetamide (**348**) (0.31 g, 0.76 mmol) in *t*-butylbenzene (20 cm^3) under reflux. Once addition was complete, heating was continued for $1^1/_2$ hours. The reaction was allowed to cool and organic solvent removed under reduced pressure and the residue taken up in diethyl ether (50 cm^3). DBU (0.27 cm^3, 0.28 g, 1.8 mmol) was added and the white precipitate that formed filtered and washed with ethyl acetate. Organic solvent was removed under reduced pressure and the residue purified by multiple flash column chromatography (3: 1, hexane: ethyl acetate) to give five products of R_f= 0.63, 0.50, 0.43, 0.42, & 0.24 (1: 1, hexane: ethyl acetate).

Product of R_f = 0.63 (483)

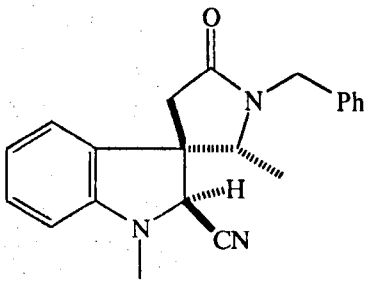


$C_{21}H_{21}N_3O$
Mol. Wt.: 331.41

White solid as a 1: 1.2 mix of amide rotamers (0.11 g, 45%); m.p. 93-95 °C; (Found M^+, 332.1767, $C_{21}H_{21}N_3O$ requires M^++H 332.1763); ν_{max} /cm^{-1} 3055.6, 2978.9 (Ar-H), 2218.3 (CN), 1651.6 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.15 (1.35H, t, *J* 7.1, NCH_2CH_3

(minor)), 1.20 (1.65H, t, *J* 7.1, NCH_2CH_3 (major)), 3.39-3.50 (2H, m, NCH_2CH_3 (major + minor)), 3.61 (1.35H, s, NCH_3 (minor)), 3.73 (1.65H, s, NCH_3 (major)), 3.91 (0.9H, s, CH_2CO (minor)), 3.97 (1.1H, s, CH_2CO (major)), 4.64 (1.1H, s, CH_2Ar (major)), 4.66 (0.9H, s, CH_2Ar (minor)), 7.10-7.42 (8.1H, m, Ar-*H* (major + minor)), 7.70 (0.45H, d, *J* 8.0, Ar-*H* (minor)), 7.79 (0.45H, d, *J* 8.0, Ar-*H* (minor)); δ_C(75 MHz; $CDCl_3$) 12.78 ($CHCH_3$), 13.95 ($CHCH_3$), 30.57 (CH_2CO), 31.19 (CH_2CO), 31.35 (NCH_3), 31.52 (NCH_3), 41.80 (NCH_2CH_3), 42.14 (NCH_2CH_3), 48.32 (CH_2Ar), 51.00 (CH_2Ar), 109.70 (C-3), 109.76 (C-3), 110.13 (C-7), 110.22 (C-7), 113.25 (CN), 113.35 (CN), 120.63 (quaternary C), 121.04 (quaternary C), 121.12 (Ar-C-H), 121.15 (Ar-C-H), 121.28 (Ar-C-H), 121.46 (Ar-C-H), 126.03 (2 x Ar-C-H), 126.08 (Ar-C-H), 126.17 (Ar-C-H), 127.35 (Ar-C-H), 127.42 (Ar-C-H), 128.11 (Ar-C-H), 128.59 (Ar-C-H), 128.79 (Ar-C-H), 136.78 (quaternary C), 137.70 (quaternary C), 137.98 (quaternary C), 138.12 (quaternary C), 168.96 (CO), 169.22 (CO).

Product of R_f = 0.50 (363a)

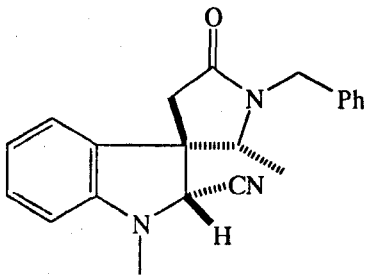


$C_{21}H_{21}N_3O$
Mol. Wt.: 331.41

Pale yellow solid; (0.022 g, 9%); m.p. 165.0-166.5 °C; (Found M^+, 331.16924, $C_{21}H_{21}N_3O$ requires M^+ 331.16846); ν_{max} /cm^{-1} 3056.0, 2977.0, 2933.0 (Ar-H), 2219.0 (CN), 1694.5 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 0.85 (3H, d, *J* 6.5, $CHCH_3$), 2.78 (3H, s, NCH_3), 2.97 & 3.07 (2H, ABq, *J* 17.5, CH_2CO), 3.59 (1H, q, *J* 6.5, $CHCH_3$), 3.87 (1H, d, *J* 14.8, CH_2Ar), 3.99 (1H, s, CHCN), 5.12 (1H, d, *J* 14.8, CH_2Ar), 6.56 (1H, d, *J* 7.5, C-7*H*), 6.85 (1H, td, *J* 7.5 & 1.0, C-6*H*), 7.08 (1H, dd, *J* 7.5 & 1.0, C-4*H*), 7.21 (1H, td, *J* 7.5 & 1.0, C-5*H*), 7.39-7.26 (5H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 15.17 ($CHCH_3$), 33.79 (NCH_3), 38.68 (CH_2CO), 44.33 (CH_2Ar), 52.78 (quaternary C), 59.17 ($CHCH_3$), 67.78 (CHCN), 108.99 (C-7), 115.33 (CN), 120.11 (Ar-C-H), 124.04 (Ar-C-H), 127.94 (Ar-C-H), 128.07 (quaternary C), 128.20 (2 x Ar-C-H), 128.95 (2 x Ar-C-H), 129.76

(Ar-C-H), 136.17 (quaternary C), 150.09 (quaternary C), 171.56 ($CONR_2$); *m/z* 332.17 (30.3%), 331.17 (42.1, M^+), 183.09 (28.2), 170.08 (90.1), 169.08 (100.0), 144.08 (47.3), 91.05 (51.5).

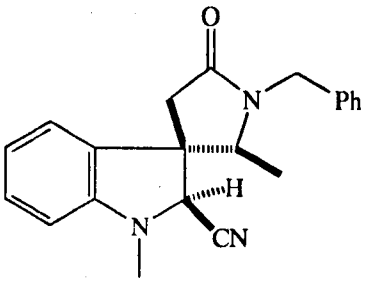
Product of R_f = 0.43 (363b)



$C_{21}H_{21}N_3O$
Mol. Wt.: 331.41

Colourless solid; (0.065 g, 26%); m.p. 123.5-124.5 °C; (Found M^+, 331.1677, $C_{21}H_{21}N_3O$ requires M^+ 331.1685); ν_{max} /cm^{-1} 3055.7, 2979.2 (Ar-H), 2220.1 (CN), 1693.8 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 0.75 (3H, d, *J* 6.5, $CHCH_3$), 2.61 (1H, d, *J* 17.1, CH_2CO), 2.72 (3H, s, NCH_3), 2.82 (1H, d, *J* 17.1, CH_2CO), 3.94 (1H, s, *CH*CN), 4.02 (1H, q, *J* 6.5, $CHCH_3$), 4.22 & 4.67 (2H, ABq, *J* 15.1, CH_2Ar), 6.50 (1H, d, *J* 7.5, C-7*H*), 6.74 (1H, td, *J* 7.5 & 1.0, C-6*H*), 6.96 (1H, dd, *J* 7.5 & 1.0, C-4*H*), 7.12 (1H, td, *J* 7.5 & 1.0, C-5*H*), 7.15-7.26 (5H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 15.49 ($CHCH_3$), 35.13 (NCH_3), 41.51 (CH_2CO), 44.87 (CH_2Ar), 51.69 (quaternary C), 59.30 ($CHCH_3$), 66.39 (CHCN), 109.23 (C-7), 116.14 (CN), 120.44 (Ar-C-H), 123.80 (Ar-C-H), 127.71 (Ar-C-H), 128.19 (2 x Ar-C-H), 128.77 (2 x Ar-C-H), 128.89 (quaternary C), 129.70 (Ar-C-H), 136.37 (quaternary C), 150.21 (quaternary C), 171.66 ($CONR_2$); *m/z* 331.17 (71.2%, M^+), 170.08 (75.1), 169.08 (100.0), 144.08 (39.8), 91.05).

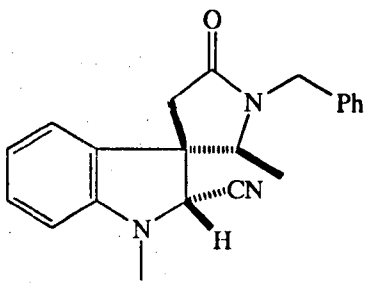
Product of R_f = 0.42 (363c)



$C_{21}H_{21}N_3O$
Mol. Wt.: 331.41

Pale yellow oil; (0.026 g, 10%); Discernible data: (Found M^+, 331.16814, $C_{21}H_{21}N_3O$ requires M^+ 331.16846); δ_H(300 MHz; $CDCl_3$) 1.60 (3H, d, *J* 6.6, $CHCH_3$), 2.79 (3H, s, NCH_3), 3.46 (1H, q, *J* 6.6, $CHCH_3$), 4.92 (1H, d, *J* 14.8, CH_2Ar), 6.47 (1H, d, *J* 7.5, C-7*H*), 6.64 (1H, t, *J* 7.5, C-6*H*), 6.75 (1H, d, *J* 7.5, C-4*H*), 7.08 (1H, t, *J* 7.5, C-5*H*); δ_C(75 MHz; $CDCl_3$) 14.59 ($CHCH_3$), 34.17 (NCH_3), 39.75 (CH_2CO), 44.55 (CH_2Ar), 51.39 (quaternary C), 61.13 ($CHCH_3$), 62.88 (CHCN), 108.95 (C-7), 116.26(CN), 120.45 (Ar-C-H), 121.66 (Ar-C-H), 127.87 (Ar-C-H), 128.50 (2 x Ar-C-H), 129.43 (Ar-C-H), 132.33 (quaternary C), 136.07 (quaternary C), 148.86 (quaternary C), 171.21 ($CONR_2$); *m/z* 331.16 (25.4%, M^+), 320.15 (50.9), 170.08 (41.1), 159.07 (93.1), 134.09 (100.0), 91.05 (95.6), 77.04 (25.0).

Product of R_f = 0.24 (363d)

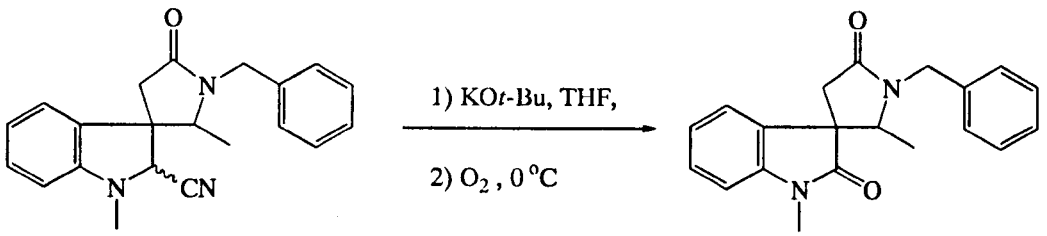


$C_{21}H_{21}N_3O$
Mol. Wt.: 331.41

Colourless solid; (0.017 g, 7%); m.p. 144.5-146.0 °C; (Found M^+, 331.16846, $C_{21}H_{21}N_3O$ requires M^+ 331.16790); ν_{max} /cm^{-1} 3058.8, 2974.5 & 2934.0 (Ar-H), 2218.5 (CN), 1695.6 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.43 (3H, d, *J* 6.5, $CHCH_3$), 2.55 & 2.78 (2H, ABq, *J* 16.4, CH_2CO), 2.85 (3H, s, NCH_3), 3.88 (1H, q, *J* 6.5, $CHCH_3$), 4.07 (1H,

d, *J* 14.5, C*H*$_2$Ar), 4.09 (1H, s, C*H*CN), 5.10 (1H, d, *J* 14.5, C*H*$_2$Ar), 6.53 (1H, d, *J* 7.5, C-7*H*), 6.58 (1H, d, *J* 7.5, C-4*H*), 6.63 (1H, t, *J* 7.5, C-6*H*), 7. 14 (1H, td, *J* 7.5 & 1.0, C-5*H*), 7.34-7.41 (5H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 13.39 (**C**HCH_3), 34.15 (**C**H$_3$), 42.66 (**C**H$_2$CO), 44.49 (**C**H$_2$Ar), 52.25 (quaternary **C**), 58.61 (**C**HCH$_3$), 65.17 (**C**HCN), 109.40 (**C**-7), 115.98 (**C**N), 120.71 (Ar-**C**-H), 121.56 (Ar-**C**-H), 128.15 (Ar-**C**-H), 128.97 (2 x Ar-**C**-H), 129.15 (2 x Ar-**C**-H), 129.30 (Ar-**C**-H), 132.39 (quaternary **C**), 136.12 (quaternary **C**), 148.77 (quaternary **C**), 170.87 (**C**ONR$_2$); *m/z* 331.17 (79.9%, M^+), 183.09 (58.3), 170.08 (83.2), 169.07 (100.0), 134.09 (42.6), 91.05 (86.25).

1'-Benzyl-1,2'-dimethyl-1*H*-spiro[indole-3,3'-pyrrolidine]-2,5'-dione (371)

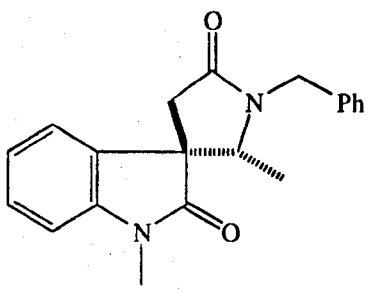


$C_{21}H_{21}N_3O$
Mol. Wt.: 331.41

$C_{20}H_{20}N_2O_2$
Mol. Wt.: 320.39

A solution of a mixture of diastereoisomers of 1'-benzyl-1,2'-dimethyl-5'-oxo-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-2-carbonitrile (**363**) (0.102 g, 0.31 mmol) in THF (20 cm^3) was added *via* cannula to a stirred solution of potassium *t*-butoxide (0.04 g, 0.34 mmol) in THF (20 cm^3) at room temperature and the solution stirred for one hour. Oxygen was bubbled through the reaction mixture for one hour and the reaction stirred for 16 hours. A saturated solution of potassium iodide (50 cm^3) was added and organic solvent removed under reduced pressure. The aqueous residue was extracted with ethyl acetate (3 x 100 cm^3) and the combined organic extracts washed with brine (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The resulting dark yellow oil was purified by flash column chromatography (1: 1, hexane: ethyl acetate) to give the title compound (**371**) as a pale yellow oil and as a 1.2: 1 mixture of diastereoisomers (0.036 g, 38%);

Product of R_f = 0.34 (371a)

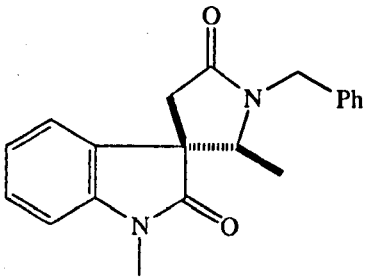


$C_{20}H_{20}N_2O_2$
Mol. Wt.: 320.39

Pale yellow oil; (Found M^+, 321.1616, $C_{20}H_{20}N_2O_2$ requires M^++H 321.1603); ν_{max} /cm^{-1} 3055.9, 2974.2, 2933.0 (Ar-H), 1708.9 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 0.71 (3H, d, *J* 6.6, $CHCH_3$), 2.50 & 3.04 (2H, ABq, *J* 16.6, CH_2CO), 3.14 (3H, s, NCH_3), 3.91 (1H, q,

J 6.6, C*H*CH_3), 4.05 & 4.97 (2H, ABq, *J* 15.1, CH_2Ar), 6.79 (1H, d, *J* 7.7, C-7*H*), 6.99 (1H, td, *J* 7.7 & 0.9, C-6*H*), 7.14 (1H, d, *J* 7.7, C-4*H*), 7.18-7.27 (6H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 14.65 ($CHCH_3$), 26.62 (NCH_3), 41.38 (CH_2), 44.49 (CH_2), 52.52 (quaternary **C**), 59.16 ($CHCH_3$), 108.55 (**C**-7), 122.93 (Ar-**C**-H), 123.83 (Ar-**C**-H), 127.68 (Ar-**C**-H), 127.96 (2 x Ar-**C**-H), 128.81 (2 x Ar-**C**-H), 128.85 (Ar-**C**-H), 129.79 (quaternary **C**), 136.10 (quaternary **C**), 143.12 (quaternary **C**), 172.82 (**C**O), 176.86 (**C**O).

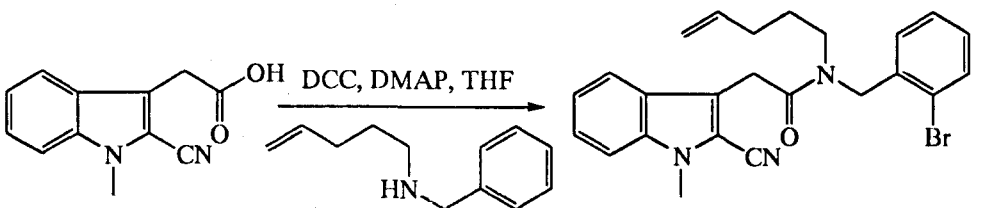
Product of R_f = 0.26 (371b)



$C_{20}H_{20}N_2O_2$
Mol. Wt.: 320.39

Pale yellow oil; (Found M^+, 321.1614, $C_{20}H_{20}N_2O_2$ requires M^++H 321.1603); ν_{max} /cm^{-1} 3057.6, 2927.8 (Ar-H), 1710.3 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.04 (3H, d, *J* 6.6, CHC*H*$_3$), 2.61 & 2.91 (2H, ABq, *J* 16.9, CH_2CO), 3.12 (3H, s, NCH_3), 3.63 (1H, q, *J* 6.6, C*H*CH_3), 4.04 & 4.97 (2H, ABq, *J* 15.0, CH_2Ar), 6.74 (1H, d, *J* 7.6, C-7*H*), 6.91 (1H, td, *J* 7.6 & 0.9, C-6*H*), 6.98 (1H, d, *J* 7.6, C-4*H*), 7.17-7.27 (6H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 14.22 ($CHCH_3$), 26.24 (NCH_3), 40.35 (CH_2), 44.49 (CH_2), 50.82 (quaternary **C**), 60.77 ($CHCH_3$), 108.10 (**C**-7), 122.28 (Ar-**C**-H), 123.03 (Ar-**C**-H), 127.62 (Ar-**C**-H), 128.16 (2 x Ar-**C**-H), 128.73 (2 x Ar-**C**-H), 128.80 (Ar-**C**-H), 131.32 (quaternary **C**), 136.30 (quaternary **C**), 143.16 (quaternary **C**), 171.87 (**C**O), 176.27 (**C**O).

***N*-(2-Bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-pent-4-enylacetamide (280)**



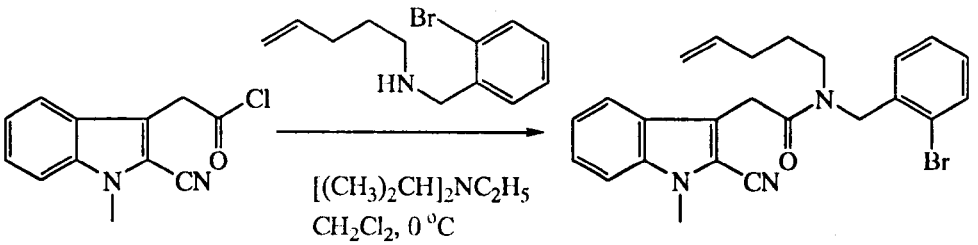
$C_{12}H_{10}N_2O_2$
Mol. Wt.: 214.22

$C_{24}H_{24}BrN_3O$
Mol. Wt.: 450.37

2-Cyano-1-methyl-1*H*-indole-3-acetic acid (**315**) (0.07 g, 0.4 mmol), *N,N'*-dicyclohexylcarbodiimide (0.09 g, 0.5 mmol), triethylamine (0.06 cm^3, 0.045 g, 0.5 mmol), *N,N* 4-dimethylaminopyridine (0.004 g, 0.03 mmol) and (2-bromobenzyl)-pent-4-enylamine (**384**) (0.09 g, 0.4 mmol) in THF (20 cm^3) were stirred at room temperature for 48 hours. Organic solvent was removed under reduced pressure and the solid residue purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the tertiary amide (**280**) as a pale white solid and as a 1: 1.1 ratio of amide rotamers (0.05 g, 28%); m.p. 95.5-96.5 °C; R_f (3: 1, hexane: ethyl acetate) 0.62; (Found: C, 63.83; H, 5.24; N, 9.30. $C_{24}H_{24}BrN_3O$ requires C, 64.00; H, 5.37; N, 9.33%); (Found M^+, 472.0990/ 474.0969, $C_{21}H_{20}BrN_3O$ requires M^++Na 472.1000/ 474.0980); ν_{max} /cm^{-1} 3064.3, 3018.1, 2935.8 (Ar-H), 22192 (CN), 1651.8 ($CONR_2$), 919.1 ($CH=CH_2$); δ_H(300 MHz; $CDCl_3$) 1.70 (2H, quin, *J* 7.5, C-2''H_2 (major + minor)), 2.04 (1.04H, q, *J* 7.5, C-3''H_2 (major)), 2.11 (0.96H, q, *J* 7.5, C-3''H_2 (minor)), 3.36 (0.96H, t, *J* 7.5, C-1''H_2 (minor)), 3.40 (1.04H, t, *J* 7.5, C-1''H_2 (major)), 3.63 (1.56H, s, NCH_3 (major)), 3.77 (1.44H, s, NCH_3 (minor)), 3.84 (1.04H, s, CH_2CO (major)), 4.04 (0.96H, s, CH_2CO (minor)), 4.65 (1.04H, s, NCH_2Ar (major)), 4.73 (0.96H, s, NCH_2Ar (minor)), 4.93-5.08 (2H, m, C-5''H_{cis} & H_{trans} (major + minor)), 5.78 (1H, m, C-4''*H* (major + minor)), 6.92 (0.52H, m, Ar-*H*), 7.02-7.21 (4H, m, Ar-*H*), 7.28 (0.48H, d, *J* 8.0, Ar-*H* (minor)), 7.34 (0.52H, d, *J* 8.0, Ar-*H* (major)), 7.37 (0.48H, m, Ar-*H* (minor)), 7.47 (0.48H, d, *J* 8.0, Ar-*H* (minor)), 7.57 (0.52H, d, *J* 8.0, Ar-*H* (major)), 7.63 (0.52H, d, *J* 8.0, Ar-*H* (major)), 7.78 (0.48H, d, *J* 8.0, Ar-*H* (minor)); δ_C(75 MHz; $CDCl_3$) 26.65 (CH_2), 27.90 (CH_2), 30.88 (CH_2), 31.05 (CH_2), 31.15 (CH_2), 31.44 (NCH_3), 31.64 (NCH_3), 46.95 (CH_2), 47.62 (CH_2), 48.71 (CH_2), 52.34 (CH_2), 109.67 (C-3), 109.79 (C-3), 110.04 (C-7), 110.12 (C-7), 112.96 (CN),

113.32 (**C**N), 115.14 (CH=**C**H_2), 115.85 (CH=**C**H_2), 120.18 (quaternary **C**), 120.72 (quaternary **C**), 121.17 + 121.23 + 121.58 (Ar-**C**-H), 122.56 + 123.48 + 126.00 (quaternary **C**), 126.07 + 126.28 + 126.71 + 127.61 + 127.69 + 128.78 + 128.93 + 129.05 + 132.71 + 133.02 (Ar-**C**-H), 135.36 (quaternary **C**), 136.31 (quaternary **C**), 137.10 (**C**H=CH_2), 137.73 (**C**H=CH_2), 137.95 (quaternary **C**), 138.17 (quaternary **C**), 169.32 (**C**O), 169.68 (**C**O). Missing (1 x **C**H_2, 1 x Ar-**C**-H, 1 x quaternary **C**).

***N*-(2-Bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-pent-4-enylacetamide (280)**

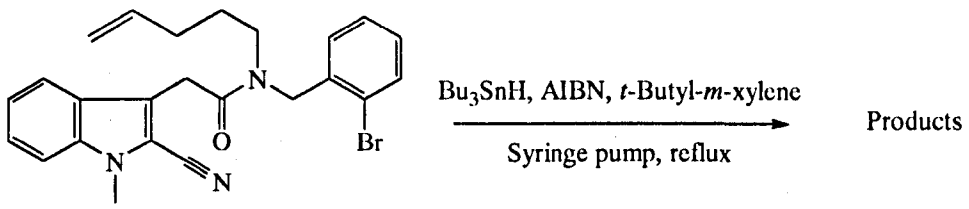


$C_{12}H_9ClN_2O$
Mol. Wt.: 232.67

$C_{24}H_{24}BrN_3O$
Mol. Wt.: 450.37

2-Cyano-1-methyl-1*H*-indole-3-acetyl chloride (**328**) (1.20 g, 5.0 mmol) in dichloromethane (30 cm^3) was added dropwise *via* cannula to a stirred solution of (2-bromobenzyl)-pent-4-enylamine (**384**) (1.40 g, 5.5 mmol) and *N, N*-diisopropylethylamine (3.0 cm^3, 2.3 g, 17.5 mmol) in dichloromethane (30 cm^3) at 0 °C under nitrogen. The resulting mixture was left to stir at 0 °C for one hour, allowed to warm to room temperature and then left to stir overnight. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3), washed with HCl (100 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate (100 cm^3) and brine (100 cm^3). The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give a light green solid which was purified by column chromatography (1: 1, hexane: ethyl acetate) to give the tertiary amide (**280**) as a light yellow solid (1.90 g, 83%); identical spectroscopic data to that obtained previously.

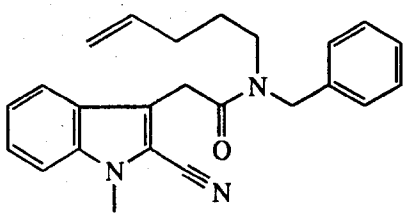
Radical cyclisation of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-pent-4-enylacetamide (280)



$C_{24}H_{24}BrN_3O$
Mol. Wt.: 450.37

A solution of tri-*n*-butyltin hydride (0.27 cm^3, 0.29 g, 1.01 mmol) and azo-bis-isobutyronitrile (AIBN) (0.028 g, 0.17 mmol) in *t*-butyl-*m*-xylene (18 cm^3) were added dropwise *via* syringe pump (6.37 cm^3/ hour) to a solution of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-pent-4-enylacetamide (**280**) (0.38 g, 0.84 mmol) in *t*-butyl-*m*-xylene (20 cm^3) under reflux. Once addition was complete, heating was continued for 2 hours. The reaction was allowed to cool and organic solvent removed under reduced pressure and the residue taken up in diethyl ether (50 cm^3). DBU (0.30 cm^3, 0.31 g, 2.0 mmol) was added and the white precipitate that formed filtered and washed with ethyl acetate. Organic solvent was removed under reduced pressure and the residue purified by multiple flash column chromatography (3: 1, hexane: ethyl acetate) to give five products of R_f= 0.72, 0.47, 0.39, 0.39 & 0.19 (1: 1, hexane: ethyl acetate).

Product of R_f = 0.72 (389)

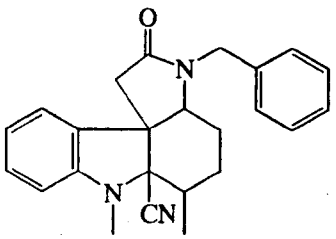


$C_{24}H_{25}N_3O$
Mol. Wt.: 371.47

White solid as a 1: 1.2 mix of amide rotamers (0.16 g, 51%); m.p. 82-84 °C; (Found M^+, 371.19952, $C_{24}H_{25}N_3O$ requires M^+ 371.19977); ν_{max} /cm^{-1} 3061.5, 3029.3, 2931.4 (Ar-H), 2217.0 (CN), 1649.9 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.67 (2H, m, C-3''H_2

(major + minor)), 2.02 (1.1H, q, *J* 7.5, C-3''H_2 (major)), 2.09 (0.9H, q, *J* 7.0, C-3''H_2 (minor)), 3.34 (0.9H, t, *J* 7.5, C-1''H_2 (minor)), 3.41 (1.1H, t, *J* 7.5, C-1''H_2 (major)), 3.73 (1.65H, s, NCH_3 (major)), 3.87 (1.35H, s, NCH_3 (minor)), 3.97 (1.1H, s, CH_2CO (major)), 4.05 (0.9H, s, CH_2CO (minor)), 4.64 (1.1H, s, NCH_2Ar (major)), 4.69 (0.9H, s, NCH_2Ar (minor)), 4.92-5.07 (2H, m, C-5''H_{cis} & H_{trans} (major + minor)), 5.77 (1H, m, C-4''*H* (major + minor)), 7.09 (1H, m, Ar-*H* (major + minor)), 7.17-7.45 (7H, m, Ar-*H*), 7.71 (0.55H, d, *J* 8.1, Ar-*H* (minor)), 7.79 (0.45H, d, *J* 8.1, Ar-*H* (major)); δ_C(75 MHz; $CDCl_3$) 26.61 (**C**H_2), 27.66 (**C**H_2), 30.80 (**C**H_2), 31.00 (**C**H_2), 31.13 (**C**H_2), 31.35 (**C**H_2), 31.43 (N**C**H_3), 31.62 (N**C**H_3), 46.79 (**C**H_2), 46.98 (**C**H_2), 48.58 (**C**H_2), 48.68 (**C**H_2), 51.60 (**C**H_2), 109.67 (**C**-3), 109.74 (**C**-3), 109.98 (**C**-7), 110.08 (**C**-7), 113.22 (**C**N), 113.34 (**C**N), 115.01 (CH=**C**H_2), 115.82 (CH=**C**H_2), 120.61 (quaternary **C**), 120.95 (quaternary **C**), 121.18 (Ar-**C**-H), 121.20 (Ar-**C**-H), 121.39 (Ar-**C**-H), 121.58 (Ar-**C**-H), 125.86 (Ar-**C**-H), 125.91 (Ar-**C**-H), 126.07 (Ar-**C**-H), 126.12 (Ar-**C**-H), 126.23 (Ar-**C**-H), 127.34 (Ar-**C**-H), 127.39 (Ar-**C**-H), 128.08 (Ar-**C**-H), 128.55 (Ar-**C**-H), 128.76 (Ar-**C**-H), 136.58 (**C**H=CH_2), 137.13 (**C**H=CH_2), 137.46 (quaternary **C**), 137.82 (quaternary **C**), 138.03 (quaternary **C**), 138.18 (quaternary **C**), 169.12 (**C**O), 169.50 (**C**O); *m/z* 371.20 (65.4%, M^+), 202.12 (24.6), 170.08 (42.7), 169.08 (100.0), 120.08 (44.1), 91.06 (97.3).

Product of R_f = 0.49 (388a)

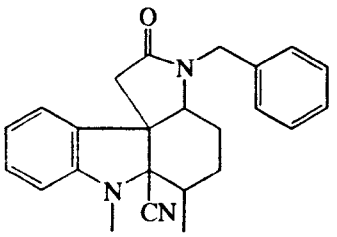


$C_{24}H_{25}N_3O$
Mol. Wt.: 371.47

Pale yellow oil (0.010 g, 3%); Discernible data: (Found M^+, 371.19861, $C_{24}H_{25}N_3O$ requires M^+ 371.19976); ν_{max} /cm^{-1} 2930.6 (Ar-H), 2217.9 (CN), 1662.7 (CONR$_2$); δ_H(300 MHz; $CDCl_3$) 1.30 (3H, d, *J* 6.8, CHCH_3), 1.86-1.95 (2H, m, NCHCH_2CH_2C*H*), 2.22-2.35 (2H, m, NCHCH_2CH_2C*H*), 2.66 & 2.93 (2H, ABq, *J* 15.5, CH_2CO), 2.93 (3H, s, NCH_3), 4.61 & 4.77 (2H, ABq, *J* 14.4, NCH_2Ar), 6.44 (1H, d, *J* 7.5, C-7*H*), 6.75 (1H, t, *J* 7.5, C-5*H*), 6.91 (1H, d, *J* 7.5, C-4*H*), 7.15 (1H, t, *J* 7.5, C-6*H*), 7.30-7.36 (5H, m,

Ar-*H*); *m/z* 371.20 (100.0%, M^+), 234.05 (17.1), 174.13 (23.6), 169.08 (58.1), 126.09 (29.0), 91.03 (46.9).

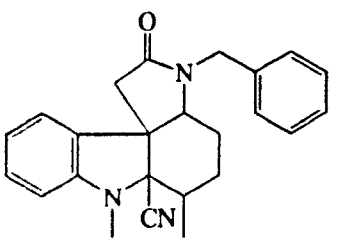
Product of R_f = 0.39 (388b)



$C_{24}H_{25}N_3O$
Mol. Wt.: 371.47

White solid (0.074 g, 24%); m.p. 174-176 °C; (Found M^+, 371.19926, $C_{24}H_{25}N_3O$ requires M^+ 371.19977); ν_{max} /cm^{-1} 3054.5, 2985.1, 2942.0 (Ar-H), 2223.3 (CN), 1689.5 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.18-1.29 (1H, m, NCHC*H*$_2$), 1.41 (3H, d, *J* 7.3, CHC*H*$_3$), 1.46-1.58 (2H, m, NCHCH$_2$C*H*$_2$), 1.96-2.04 (1H, m, NCHC*H*$_2$), 2.06-2.13 (1H, m, C*H*CH$_3$), 2.80 (1H, d, *J* 20.0, C*H*$_2$CO), 2.89 (3H, s, NC*H*$_3$), 2.92 (1H, t, *J* 3.0, NC*H*CH$_2$), 4.06 & 4.82 (2H, ABq, *J* 14.8, NC*H*$_2$Ar), 6.59 (1H, d, *J* 7.5, C-7*H*), 6.78 (1H, td, *J* 7.5 & 0.8, C-5*H*), 7.02 (1H, dd, *J* 7.5 & 0.8, C-4*H*), 7.11-7.21 (6H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 19.03 (CHCH$_3$), 24.61 (CH$_2$), 28.48 (CH$_2$), 35.48 (NCH$_3$), 36.44 (CHCH$_3$), 37.95 (CH$_2$), 44.93 (CH$_2$), 50.97 (quaternary C), 63.17 (CON(CH$_2$Ar)CH), 75.63 (N(CH$_3$)CCN), 109.72 (C-7), 117.43 (CN), 120.63 (Ar-C-H), 121.36 (Ar-C-H), 127.69 (Ar-C-H), 128.42 (2 x Ar-C-H), 128.51 (2 x Ar-C-H), 129.17 (Ar-C-H), 133.58 (quaternary C), 135.81 (quaternary C), 149.58 (quaternary C), 171.07 (CO); *m/z* 371.20 (89.4%, M^+), 344.19 (71.5), 199.11 (43.9), 184.11 (45.5), 169.08 (100.0).

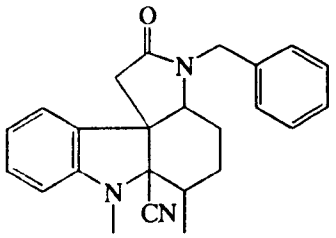
Second Product of R_f = 0.39 (388c)



$C_{24}H_{25}N_3O$
Mol. Wt.: 371.47

Pale yellow oil (0.03 g, 9%); Discernible data: (Found M^+, 371.19998, $C_{24}H_{25}N_3O$ requires M^+ 371.19977); δ_H(300 MHz; $CDCl_3$) 1.23 (1H, m, NCHC*H*$_2$), 1.36 (3H, d, *J* 7.4, CHC*H*$_3$), 1.40-1.80 (3H, m, NCHC*H*$_2$C*H*$_2$), 2.37 (1H, m ,NC*H*CH$_3$), 2.75 (3H, s, NCH$_3$), 2.90-3.15 (3H, m, CH$_2$CO & NC*H*), 4.08 & 4.86 (2H, ABq, *J* 15.2, NC*H*$_2$Ar), 6.57 (1H, d, *J* 8.0, C-7*H*), 6.77 (1H, m, Ar-*H*), 7.00 (1H, m, Ar-*H*), 7.12-7.29 (6H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 16.06 (CHCH$_3$), 21.92 (**C**H$_2$), 23.06 (**C**H$_2$), 29.73 (**C**HCH$_3$), 30.97 (NCH$_3$), 39.76 (**C**H$_2$), 44.91 (**C**H$_2$), 48.51 (quaternary **C**), 63.12 (CON(CH$_2$Ar)**C**H), 75.34 (N(CH$_3$)**C**CN), 109.25 (**C**-7), 117.43 (**C**N), 120.51 (Ar-**C**-H), 121.33 (Ar-**C**-H), 127.71 (Ar-**C**-H), 128.33 (2 x Ar-**C**-H), 128.54 (2 x Ar-**C**-H), 129.07 (Ar-**C**-H), 134.38 (quaternary **C**), 135.87 (quaternary **C**), 148.06 (quaternary **C**), 171.22 (**C**O); *m/z* 371.20 (100.0%, M^+), 344.19 (66.9), 196.09 (46.3), 184.12 (43.9), 169.08 (81.2) 91.05 (64.1).

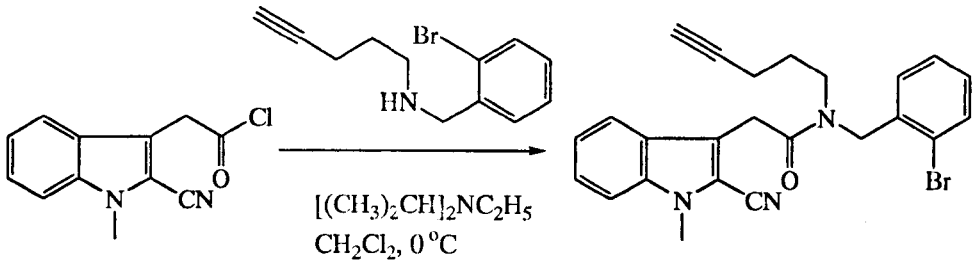
Product of R_f 0.19 (388d)



$C_{24}H_{25}N_3O$
Mol. Wt.: 371.47

Pale yellow oil (0.019 g, 6%); Discernible data: (Found M^+, 371.19963, $C_{24}H_{25}N_3O$ requires M^+ 371.19976); ν_{max} /cm^{-1} 3055.8, 2926.9 & 2854.8 (Ar-H), 2218.0 (CN), 1686.1 (CONR$_2$); δ_H(300 MHz; $CDCl_3$) 1.05 (3H, d, *J* 6.6, CHC*H*$_3$), 1.29-1.43 (2H, m, NCHC*H*$_2$C*H*$_2$CH), 2.77 (3H, s, NCH$_3$), 3.27 & 3.44 (2H, ABq, *J*12.2, C*H*$_2$CO), 4.06 & 5.00 (2H, ABq, *J* 15.2, NC*H*$_2$Ar), 6.49 (1H, d, *J* 7.5, C-7*H*), 6.62 (1H, t, *J* 7.5, C-5*H*), 6.95 (1H, t, *J* 7.5, C-6*H*), 7.03 (1H, d, *J* 7.5, C-4*H*), 7.13-7.28 (5H, m, Ar-*H*); *m/z* 371.20 (100.0%, M^+), 303.14 (11.5), 169.08 (12.9), 91.03 (54.1).

***N*-(2-Bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-pent-4-ynylacetamide (390)**



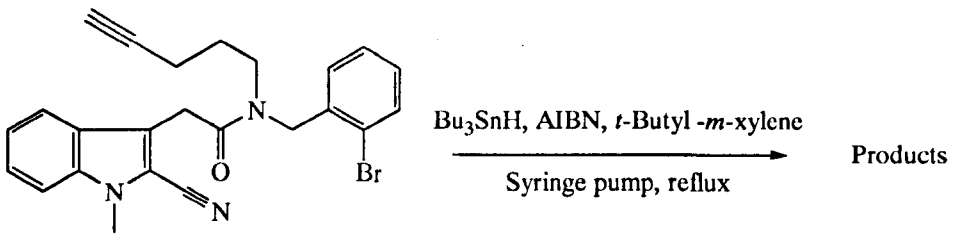
$C_{12}H_9ClN_2O$
Mol. Wt.: 232.67

$C_{24}H_{22}BrN_3O$
Mol. Wt.: 448.36

2-Cyano-1-methyl-1*H*-indole-3-acetyl chloride (**328**) (3.25 g, 14.0 mmol) in dichloromethane (50 cm^3) was added dropwise *via* cannula to a stirred solution of (2-bromobenzyl)-pent-4-ynylamine (**394**) (4.58 g, 18.15 mmol) and *N*, *N*-diisopropylethylamine (8.5 cm^3, 6.31 g, 48.9 mmol) in dichloromethane (100 cm^3) at 0 °C under nitrogen. The resulting mixture was left to stir at 0 °C for one hour, allowed to warm to room temperature and then left to stir overnight. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (200 cm^3), washed with HCl (200 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate (200 cm^3) and brine (200 cm^3). The organic phase was dried ($MgSO_4$), filtered and solvent removed under reduced pressure to give a light green solid which was purified by flash column chromatography (2: 1, hexane: ethyl acetate) to give the tertiary amide (**390**) as a light yellow solid and as a 1: 1.3 ratio of amide rotamers (5.40 g, 86%); m.p. 119-120 °C; R_f (2: 1, hexane: ethyl acetate) 0.83; (Found M^+, 447.0956/ 449.0916, $C_{24}H_{22}BrN_3O$ requires M^+ 447.0947/ 449.0927); ν_{max} /cm^{-1} 3303.1 (CCH), 3012.8 (Ar-H), 2217.6 (CN), 1653.9 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.96 (2H, quin, *J* 6.8, C-2''H_2 (major + minor)), 2.08 (0.4H, t, *J* 2.4, C-5''*H* (minor)), 2.17 (0.6H, t, *J* 2.4, C-5''*H* (major)), 2.34 (1.2H, td, *J* 6.8 & 2.4, C-3''H_2 (major)), 2.40 (0.8H, td, *J* 6.8 & 2.4, C-3''H_2 (minor)), 3.64 (2H, m, C-1''H_2 (major + minor)), 3.83 (1.8H, s, NCH_3 (major)), 3.97 (1.2H, s, NCH_3 (minor)), 4.02 (1.2H, s, CH_2CO (major)), 4.25 (0.8H, s, CH_2CO (minor)), 4.82 (1.2H, s, NCH_2Ar (major)), 4.88 (0.8H, s, NCH_2Ar (minor)), 6.92 (0.4H, m, Ar-*H* (minor)), 7.04-7.42 (5.6H, m, Ar-*H* (major + minor)), 7.49 (0.4H, d, *J* 8.0, Ar-*H* (minor)), 7.70 (0.6H, m, Ar-*H* (major)), 7.76 (0.6H, d, *J* 8.0, Ar-*H* (major)), 7.89 (0.4H, d, *J* 8.0, Ar-*H* (minor)); δ_C(75 MHz; $CDCl_3$) 15.86 (CH_2), 16.17

(CH_2), 26.33 (CH_2), 27.36 (CH_2), 30.76 (CH_2), 31.09 (CH_2), 31.41 (NCH_3), 31.62 (NCH_3), 46.50 (CH_2), 46.78 (CH_2), 48.65 (CH_2), 52.57 (CH_2), 69.12 (C-4''), 70.00 (C-4''), 82.72 (C-5''), 83.40 (C-5''), 109.82 (C-3), 110.06 (C-7), 110.14 (C-7), 112.93 (CN), 113.32 (CN), 120.09 (quaternary C), 120.69 (quaternary C), 121.08 (Ar-C-H), 121.18 (Ar-C-H), 121.43 (Ar-C-H), 122.60 (quaternary C), 123.50 (quaternary C), 126.07 + 126.22 + 126.77 + 127.66 + 127.33 + 128.85 + 128.99 + 129.21 + 132.75 + 133.08 (Ar-C-H), 135.33 (quaternary C), 136.25 (quaternary C), 137.96 (quaternary C), 138.14 (quaternary C), 169.43 (CO), 169.84 (CO); Missing (1 x Ar-C-H, 3 x quaternary C); *m/z* 449.09 (18.8%, M^+ ^{81}Br), 447.10 (20.6, M^+ ^{79}Br), 368.17 (62.9), 183.09 (59.2), 170.99 (91.8), 170.10 (66.6), 169.09 (100.0), 168.08 (43.3), 91.06 (49.9), 90.05 (56.0).

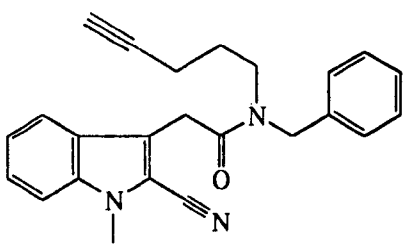
Radical cyclisation of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-pent-4-ynylacetamide (390)



$C_{24}H_{22}BrN_3O$
Mol. Wt.: 448.36

A solution of tri-*n*-butyltin hydride (0.75 cm^3, 0.81 g, 2.78 mmol) and azo-bis-isobutyronitrile (AIBN) (0.048 g, 2.78 mmol) in *t*-butyl-*m*-xylene (30 cm^3) were added dropwise *via* syringe pump (6.37 cm^3/ hour) to a solution of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-pent-4-ynylacetamide (1.039 g, 2.32 mmol) in *t*-butyl-*m*-xylene (90 cm^3) under reflux. Once addition was complete, heating was continued for 2 hours. The reaction was allowed to cool and organic solvent removed under reduced pressure and the residue taken up in acetonitrile (50 cm^3) and extracted with hexane (4 x 50 cm^3). The acetonitrile was removed under reduced pressure and the residue purified by multiple flash column chromatography (3: 1, hexane: ethyl acetate) to give a mixture of four products of R_f= 0.71, 0.63, 0.51 & 0.28 (1: 1, hexane: ethyl acetate).

Product of R_f = 0.71 (395)

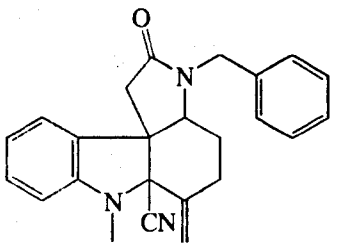


$C_{24}H_{23}N_3O$
Mol. Wt.: 369.46

White solid as a 1: 1 mix of amide rotamers (0.38 g, 45%); m.p. 82-84 °C; (Found M^+, 369.18510, $C_{24}H_{23}N_3O$ requires M^+ 369.18411); ν_{max} /cm^{-1} 3296.7 (CCH), 3059.2, 3030.5, 2938.7 (Ar-H), 2217.5 (CN), 1648.6 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.81 (2H,

quin, *J* 7.0, C-2''H_2), 1.94 (0.5H, t, *J* 2.5, CC*H*), 2.05 (0.5H, t, *J* 2.5, CC*H*), 2.19 (1H, td, *J* 7.0 & 2.5, C-3''H_2), 2.26 (1H, td, *J* 7.0 & 2.5, C-3''H_2), 3.51 (2H, m, C-1''H_2), 3.72 (1.5H, s, NCH_3), 3.85 (1.5H, s, NCH_3), 3.96 (1H, s, CH_2CO), 4.09 (1H, s, CH_2CO), 4.65 (1H, s, CONCH_2Ar), 4.72 (1H, s, CONCH_2Ar), 7.09-7.44 (8H, m, Ar-*H*), 7.69 (0.5H, d, *J* 8.1, Ar-*H*), 7.77 (0.5H, d, *J* 8.1, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 15.80 (CH_2), 16.14 (CH_2), 26.28 (CH_2), 27.15 (CH_2), 30.77 (CH_2), 31.27 (CH_2), 31.44 (NCH_3), 31.62 (NCH_3), 46.15 (CH_2), 46.37 (CH_2), 48.72 (CH_2), 51.91 (CH_2), 69.12 (CCH), 69.94 (CCH), 82.84 (CCH), 83.54 (CCH), 109.76 (C-3), 110.05 (C-7), 110.15 (C-7), 113.21 (CN), 113.38 (CN), 120.48 (quaternary C), 120.91 (quaternary C), 121.20 (Ar-C-H), 121.29 (Ar-C-H), 121.43 (Ar-C-H), 125.93 (Ar-C-H), 126.05 (Ar-C-H), 126.14 (Ar-C-H), 126.20 (Ar-C-H), 127.43 (Ar-C-H), 127.48 (Ar-C-H), 128.18 (Ar-C-H), 128.35 (quaternary C), 128.60 (Ar-C-H), 128.82 (Ar-C-H), 136.53 (quaternary C), 137.39 (quaternary C), 138.02 (quaternary C), 138.15 (quaternary C), 169.27 (CO), 169.71 (CO); *m/z* 369.19 (43.6%, M^+), 321.23 (11.4), 273.13 (77.2), 169.08 (90.9), 168.08 (56.6), 121.06 (79.9), 91.04 (81.4), 77.04 (37.6).

Product of R_f = 0.63 (391)

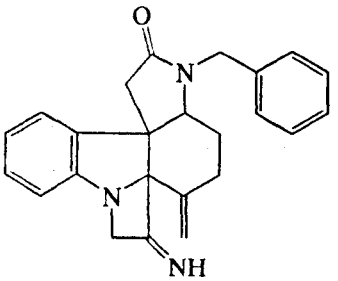


$C_{24}H_{23}N_3O$
Mol. Wt.: 369.46

Colourless oil (0.14 g, 16%); (Found M^+, 369.18666, $C_{24}H_{23}N_3O$ requires M^+ 369.18411); ν_{max} /cm^{-1} 2924.4, 2854.8 (Ar-H), 2218.2 (CN), 1694.1 ($CONR_2$); δ_H(300 MHz; CD_3OD) 1.32 (1H, m, NCHCH_2), 2.16-2.28 (2H, m, NCHCH_2 & NCHCH_2CH_2), 2.39 (1H, m, NCHCH_2CH_2), 2.63 (3H, s, NCH_3), 2.69 & 2.93 (2H, ABq, CH_2CO), 3.13 (1H, dd, *J* 5.4, NC*H*), 4.11 & 4.76 (2H, ABq, *J* 14.7, CONCH_2Ar), 5.49 (1H, d, *J* 1.3, CCH_2), 5.63 (1H, s, CCH_2), 6.67 (1H, d, *J* 7.5, C-7*H*), 6.76 (1H, td, *J* 7.5 & 1.0, C-6*H*), 6.94 (1H, d, *J* 7.4, C-4*H*), 7.16 (1H, td, *J* 7.5 & 1.0, C-5*H*), 7.20 (5H, m, Ar-*H*); δ_C(75 MHz; CD_3OD) 25.53 (CH_2), 29.38 (CH_2), 30.69 (NCH_3), 38.38 (CH_2), 45.77 (CH_2), 53.84 (quaternary C), 65.02 (NCH), 78.91 (quaternary C), 110.57 (C-7), 116.90 (CN),

119.43 (CCH_2), 121.58 (Ar-C-H), 122.59 (Ar-C-H), 128.87 (Ar-C-H), 129.62 (2 x Ar-C-H), 129.69 (2 x Ar-C-H), 130.55 (Ar-C-H), 134.66 (quaternary C), 137.19 (quaternary C), 140.86 (quaternary C), 149.83 (quaternary C), 173.36 (CO); *m/z* 369.19 (100.0%, M^+), 360.95 (16.4), 266.99 (24.4), 169.08 (35.8), 149.02 (32.9), 91.06 (86.6), 83.09 (35.2).

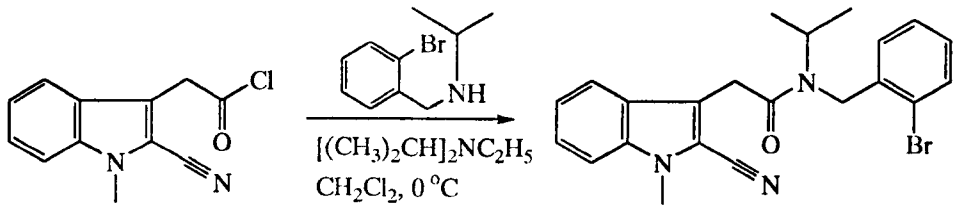
Product of R_f = 0.28 (396)



$C_{24}H_{23}N_3O$
Mol. Wt.: 369.46

White solid (0.13 g, 15%); m.p. 195-197 °C; (Found M^+, 369.18407, $C_{24}H_{23}N_3O$ requires M^+ 369.18411); δ_H(300 MHz; $CDCl_3$) 1.71-1.62 (1H, m, NCHC*H*$_2$), 1.97-1.85 (1H, m, NCHC*H*$_2$), 2.35 (2H, m, NCHCH$_2$C*H*$_2$), 2.84 & 2.98 (2H, ABq, *J* 17.5, C*H*$_2$CO), 3.37 (1H, dd, *J* 12.6 & 3.3, NC*H*$_2$CNH), 3.52 (1H, d, *J* 12.7, NC*H*$_2$CNH), 3.54 (1H, t, *J* 5.3, NC*H*), 4.04 (1H, d, *J* 14.9, CONC*H*$_2$Ar), 4.19 (1H, br s, N*H*), 4.96 (1H, d, *J* 14.9, CONC*H*$_2$Ar), 5.31 (1H, s, CC*H*$_2$), 5.62 (1H, s, CC*H*$_2$), 6.54 (1H, d, *J* 7.5, C-7*H*), 6.69 (1H, td, *J* 7.5 & 1.0, C-5*H*), 7.01-7.07 (2H, m, Ar-*H*), 7.13-7.24 (5H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 24.57 (CH_2), 25.38 (CH_2), 42.91 (CH_2), 43.01 (quaternary C), 44.70 (CH_2), 45.65 (quaternary C), 48.91 (CH_2), 62.13 (NCH), 115.54 (C-7), 116.99 (CCH_2), 119.20 (Ar-C-H), 120.12 (quaternary C), 125.53 (quaternary C), 126.58 (Ar-C-H), 127.75 (Ar-C-H), 128.35 (2 x Ar-C-H), 128.55 (Ar-C-H), 128.62 (2 x Ar-C-H), 135.67 (quaternary C), 140.27 (quaternary C), 140.87 (quaternary C), 172.60 (CO); *m/z* 369.18 (48.0%, M^+), 303.15 (21.7), 266.99 (27.8), 245.11 (29.2), 169.08 (53.2), 91.06 (28.8).

***N*-(2-Bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-isopropylacetamide (347)**



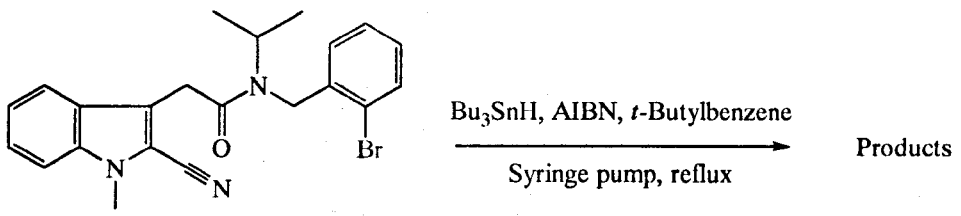
$C_{12}H_9ClN_2O$
Mol. Wt.: 232.67

$C_{22}H_{22}BrN_3O$
Mol. Wt.: 424.33

2-Cyano-1-methyl-1*H*-indole-3-acetyl chloride (**328**) (2.06 g, 8.9 mmol) in dichloromethane (50 cm^3) was added dropwise *via* cannula to a stirred solution of (2-bromobenzyl)isopropylamine (**345**) (2.63 g, 11.5 mmol) and *N, N*-diisopropylethylamine (5.3 cm^3, 4.0 g, 31.0 mmol) in dichloromethane (100 cm^3) at 0 °C under nitrogen. The resulting mixture was left to stir at 0 °C for one hour, allowed to warm to room temperature and left to stir overnight. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3), washed with HCl (100 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate (100 cm^3) and brine (100 cm^3). The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give a light green solid which was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the tertiary amide (**347**) as a light yellow solid and as a 1: 1.3 ratio of amide rotamers (2.43 g, 65%); m.p. 143-144 °C; R_f (2: 1, hexane: ethyl acetate) 0.50; (Found M^+, 424.1070/ 426.1020, $C_{22}H_{22}BrN_3O$ requires M^++H 424.1024/ 426.1004); ν_{max} /cm^{-1} 3055.7, 2980.8, 2924.2 (Ar-H), 2218.7 (CN), 1648.7 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.12 (3.6H, d, *J* 6.7, $NCH(CH_3)_2$ (major)), 1.13 (2.4H, d, *J* 6.7, $NCH(CH_3)_2$ (minor)), 3.73 (1.8H, s, NCH_3 (major)), 3.76 (1.2H, s, CH_2CO (major)), 3.83 (1.2H, s, NCH_3 (minor)), 4.14 (0.8H, s, CH_2CO (minor)), 4.47 (0.4H, sept, *J* 6.7, $NCH(CH_3)_2$ (minor)), 4.57 (2H, s, N(*i*-Pr)CH_2Ar (major + minor)), 4.90 (0.6H, sept, *J* 6.7, $NCH(CH_3)_2$ (major)), 6.93-7.47 (6.6H, m, Ar-*H* (major + minor)), 7.60 (1H, d ,*J* 8.0, Ar-*H* (major + minor)), 7.83 (0.4H, d, *J* 8.1, Ar-*H* (minor)); δ_C(75 MHz; $CDCl_3$) 20.17 ($CH(CH_3)_2$), 21.26 ($CH(CH_3)_2$), 31.47 (CH_2CO), 31.64 (indole NCH_3), 44.43 (N(*i*-Pr)CH_2Ar), 46.50 ($CH(CH_3)_2$), 47.26 (N(*i*-Pr)CH_2Ar), 49.47 ($CH(CH_3)_2$), 109.53 (C-3), 109.88 (C-3), 110.11 (C-7), 113.02 (CN), 113.27 (CN), 120.41 (quaternary C), 120.79 (quaternary

C), 121.04 (Ar-C-H), 121.08 (Ar-C-H), 121.26 (Ar-C-H), 121.71 (Ar-C-H), 122.11 (quaternary C), 122.19 (quaternary C), 125.99 (Ar-C-H), 126.04 (Ar-C-H), 126.32 (Ar-C-H), 127.25 (Ar-C-H), 127.33 (Ar-C-H), 127.71 (Ar-C-H), 127.83 (Ar-C-H), 128.05 (Ar-C-H), 128.89 (Ar-C-H), 132.40 (Ar-C-H), 133.02 (Ar-C-H), 136.77 (quaternary C), 137.31 (quaternary C), 137.95 (quaternary C), 138.18 (quaternary C), 169.27 (CO), 169.88 (CO).

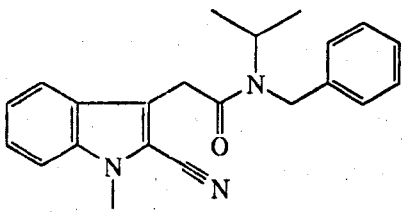
Radical cyclisation of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-isopropylacetamide (347)



$C_{22}H_{22}BrN_3O$
Mol. Wt.: 424.33

A solution of tri-*n*-butyltin hydride (0.55 cm^3, 0.60 g, 2.06 mmol) and azo-bis-isobutyronitrile (AIBN) (0.035 g, 0.34 mmol) in *t*-butylbenzene (30 cm^3) were added dropwise *via* syringe pump (5.7 cm^3/ hour) to a solution of *N*-(2-bromobenzyl)-2-(2-cyano-1-methyl-1*H*-indol-3-yl)-*N*-isopropylacetamide (**347**) (0.73 g, 1.71 mmol) in *t*-butylbenzene (70 cm^3) under reflux. Once addition was complete, heating was continued for $1^1/_2$ hours. The reaction was allowed to cool and organic solvent removed under reduced pressure and the residue taken up in acetonitrile (50 cm^3) and extracted with hexane (4 x 50 cm^3). The acetonitrile was removed under reduced pressure and the residue purified by multiple flash column chromatography (1: 1, hexane: ethyl acetate) to give 4 products of R_f= 0.61, 0.40, 0.31 & 0.21 (1: 1, hexane: ethyl acetate).

Product of R_f = 0.61 (364)

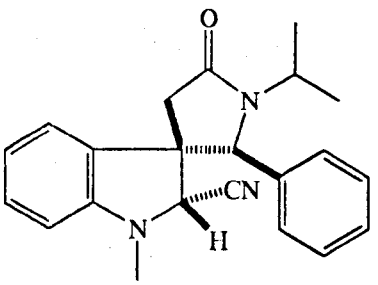


$C_{22}H_{23}N_3O$
Mol. Wt.: 345.44

White semi-solid as a 1: 1.4 mix of amide rotamers (0.32 g, 54%); (Found M^+, 346.1919, $C_{22}H_{23}N_3O$ requires M^++H 346.1919); ν_{max} /cm^{-1} 3057.9, 2977.0 & 2936.2 (Ar-H), 2217.7 (CN), 1646.7 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.15 (6H, d, *J* 6.7, $NCH(CH_3)_2$ (major + minor)), 3.69 (1.8H, s, NCH_3 (major)) 3.79 (1.2H, s, CH_2CO (major)), 3.81 (1.2H, s, NCH_3 (minor)), 4.09 (0.8H, s, CH_2CO (minor)), 4.42 (0.4H,

sept, *J* 6.7, NC*H*$(CH_3)_2$ (minor)), 4.57 (0.8H, s, N(*i*-Pr)CH_2Ar (minor)), 4.64 (1.2H, s, N(*i*-Pr)CH_2Ar (major)), 4.87 (0.6H, sept, *J* 6.7, NC*H*$(CH_3)_2$ (major)), 7.15-7.42 (8H, m, Ar-*H* (major + minor)), 7.63 (0.6H, d, *J* 8.1, Ar-*H* (major)), 7.81 (0.4H, d, *J* 8.1, Ar-*H* (minor)); δ_C(75 MHz; $CDCl_3$) 20.33 (CH(**C**$H_3)_2$), 21.63 (CH(**C**$H_3)_2$), 31.38 (**C**H_2CO), 31.42 (indole NCH_3), 31.58 (**C**H_2CO), 44.12 (N(*i*-Pr)**C**H_2Ar), 46.55 (**C**H$(CH_3)_2$), 46.63 (N(*i*-Pr)**C**H_2Ar), 49.43 (**C**H$(CH_3)_2$), 109.53 (**C**-3), 109.78 (**C**-3), 110.09 (**C**-7), 110.13 (**C**-7), 113.31 (**C**N), 120.92 (quaternary **C**), 121.04 (Ar-**C**-H), 121.10 (quaternary **C**), 121.17 (Ar-**C**-H), 121.23 (Ar-**C**-H), 121.66 (Ar-**C**-H), 125.84 (Ar-**C**-H), 125.99 (Ar-**C**-H), 126.13 (quaternary **C**), 126.22 (Ar-**C**-H), 126.60 (Ar-**C**-H), 127.00 (Ar-**C**-H), 127.25 (Ar-**C**-H), 128.30 (Ar-**C**-H), 128.82 (Ar-**C**-H), 137.97 (quaternary **C**), 138.15 (quaternary **C**), 138.25 (quaternary **C**), 169.15 (**C**O), 169.82 (**C**O).

Product of R_f = 0.40 (365)

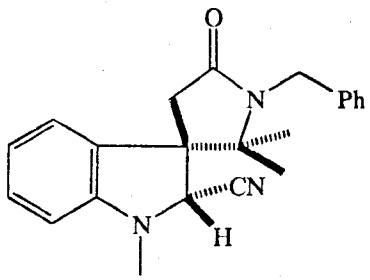


$C_{22}H_{23}N_3O$
Mol. Wt.: 345.44

White solid (0.08 g, 15%); m.p. 202-204 °C; (Found M^+, 346.1913, $C_{22}H_{23}N_3O$ requires M^++H 346.1919); ν_{max} /cm^{-1} 3055.4, 2974.0, 2927.7 (Ar-H), 2217.9 (CN), 1687.0 (CONR$_2$); δ_H(300 MHz; $CDCl_3$) 1.06 (3H, d, *J* 6.8, CH(C$H_3)_2$), 1.35 (3H, d, *J* 6.8, CH(C$H_3)_2$), 2.56 (1H, d, *J* 17.5, CH_2CO), 2.91 (3H, s, NCH_3), 3.17 (1H, d, *J* 17.5, CH_2CO), 3.96 (1H, s, C*H*CN), 4.25 (1H, sept, *J* 6.8, C*H*$(CH_3)_2$), 5.15 (1H, s, N(CH$(CH_3)_2$C*H*Ar), 5.83 (1H, d, *J* 7.5, Ar-*H*), 6.37 (1H, t, *J* 7.5, Ar-*H*), 6.54 (1H, d, *J* 7.5, Ar-*H*), 6.61 (1H, d, *J* 7.5, Ar-*H*), 7.03 (2H, t, *J* 7.5, Ar-*H*), 7.20-7.26 (2H, m, Ar-*H*), 7.36 (1H, t, *J* 7.5, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 19.85 (CH(**C**$H_3)_2$), 21.38 (CH(**C**$H_3)_2$), 34.90 (NCH_3), 40.82 (**C**H_2CO), 46.16 (**C**H$(CH_3)_2$), 53.94 (quaternary **C**), 65.85 (**C**H), 69.10 (**C**H), 108.83 (Ar-**C**-H), 116.57 (**C**N), 119.77 (Ar-**C**-H), 124.18 (Ar-**C**-H), 125.65 (Ar-**C**-H), 127.16 (quaternary **C**), 128.13 (Ar-**C**-H), 128.43 (Ar-**C**-H),

128.46 (Ar-C-H), 128.60 (Ar-C-H), 129.15 (Ar-C-H), 138.11 (quaternary C), 150.21 (quaternary C), 171.97 (CO).

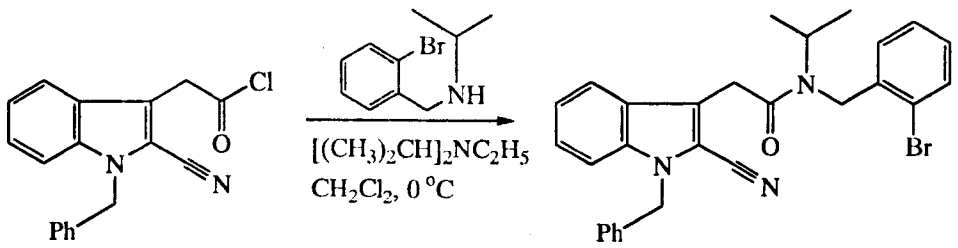
Product of R_f = 0.21 (366)



$C_{22}H_{23}N_3O$
Mol. Wt.: 345.44

Pale yellow oil (0.04 g, 7%); (Found M^+, 346.1919, $C_{22}H_{23}N_3O$ requires M^++H 346.1919); ν_{max} /cm^{-1} 3054.9, 2979.3, 2927.6 (Ar-H), 2218.7 (CN), 1689.4 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.40 (6H, s, $C(CH_3)_2$), 2.60 & 2.82 (2H, ABq, *J* 16.5, CH_2CO), 2.88 (3H, s, NCH_3), 4.15 (1H, s, *CH*CN), 4.37 & 4.79 (2H, ABq, *J* 15.0, NCH_2Ar), 6.61 (1H, d, *J* 7.6, C-7*H*), 6.72 (1H, t, *J* 7.6, C-5*H*), 6.93 (1H, d, *J* 7.6, C-4*H*), 7.18 (1H, t, *J* 7.6, C-6*H*), 7.24-7.49 (5H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 22.29 ($C(CH_3)_2$), 22.56 ($C(CH_3)_2$), 33.68 (NCH_3), 43.24 (CH_2), 43.99 (CH_2), 56.58 (quaternary C), 64.23 (quaternary C), 64.62 (CHCN), 109.51 (C-7), 116.20 (CN), 120.15 (Ar-C-H), 124.10 (Ar-C-H), 127.67 (Ar-C-H), 128.64 (2 x Ar-C-H), 128.64 (2 x Ar-C-H), 129.22 (Ar-C-H), 129.81 (quaternary C), 138.43 (quaternary C), 149.27 (quaternary C), 171.59 (CO).

2-(1-Benzyl-2-cyano-1*H*-indol-3-yl)-*N*-(2-bromobenzyl)-*N*-isopropylacetamide (373)



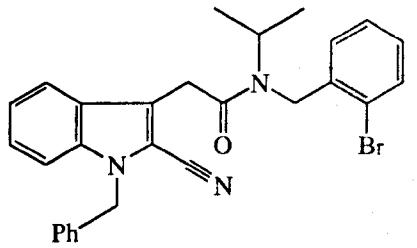
$C_{18}H_{13}ClN_2O$
Mol. Wt.: 308.76

$C_{28}H_{26}BrN_3O$
Mol. Wt.: 500.43

(2-Cyano-1-benzyl-1*H*-indol-3-yl)-acetyl chloride (**380**) (3.43 g, 11.1 mmol) in dichloromethane (50 cm^3) was added dropwise *via* cannula to a stirred solution of (2-bromobenzyl)isopropylamine (**345**) (3.30 g, 14.4 mmol) and *N, N*-diisopropylethylamine (6.7 cm^3, 5.03 g, 38.9 mmol) in dichloromethane (100 cm^3) at 0 °C under nitrogen. The resulting mixture was left to stir at 0 °C for one hour, allowed to warm to room temperature and left to stir overnight. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3), washed with HCl (100 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate (100 cm^3) and brine (100 cm^3). The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give a light green solid which was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the tertiary amide (**373**) as a light yellow solid and as a 1: 1.2 ratio of amide rotamers (4.54 g, 82%); m.p. 133-135 °C; R_f (2: 1, hexane: ethyl acetate) 0.54; (Found M^+, 500.1332/ 502.1301, $C_{28}H_{26}BrN_3O$ requires M^++H 500.1337/ 502.1317); ν_{max} /cm^{-1} 3061.0, 2976.9, 2932.4 (Ar-H), 2217.3 (CN), 1647.5 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.08 (2.4H, d, *J* 6.7, NCH(CH_3)$_2$ (minor)), 1.14 (3.6H, d, *J* 6.7, NCH(CH_3)$_2$ (major)), 3.83 (1.2H, s, CH_2CO (major)), 4.20 (0.8H, s, CH_2CO (minor)), 4.47 (0.4H, sept, *J* 6.7, NC*H*(CH_3)$_2$ (minor)), 4.55 (0.8H, s, N(*i*-Pr)CH_2Ar (minor)), 4.58 (1.2H, s, N(*i*-Pr)CH_2Ar (major)), 4.94 (0.6H, sept, *J* 6.7, NC*H*(CH_3)$_2$ (major)), 5.38 (1.2H, s, indole NCH_2Ar (major)), 5.48 (0.8H, s, indole NCH_2Ar (minor)), 6.87 (0.4H, m, Ar-*H* (minor)), 7.00 (1H, m, Ar-*H* (major + minor)), 7.14-7.49 (5H, m, Ar-*H* (major + minor)), 7.61 (0.6H, d ,*J* 8.0, Ar-*H* (major)), 7.64 (0.6H, d, *J* 8.0, Ar-*H* (major)), 7.91 (0.4H, d, *J* 8.0, Ar-*H* (minor)); δ_C(75 MHz; $CDCl_3$) 20.19 (CH(CH_3)$_2$), 21.12 (CH(CH_3)$_2$), 31.54 (CH_2CO), 31.93 (CH_2CO),

44.42 (N(*i*-Pr)CH_2Ar), 46.46 ($CH(CH_3)_2$), 47.20 (N(*i*-Pr)CH_2Ar), 48.95 (indole NCH_2Ar), 49.03 (indole NCH_2Ar), 49.55 ($CH(CH_3)_2$), 109.13 (C-3), 109.72 (C-3), 110.72 (C-7), 113.14 (CN), 113.31 (CN), 121.24 (Ar-C-H), 121.68 (Ar-C-H), 122.02 (Ar-C-H), 122.15 (quaternary C), 122.24 (quaternary C), 126.24 (Ar-C-H), 126.30 (quaternary C), 126.41 (quaternary C), 126.64 (Ar-C-H), 126.80 (Ar-C-H), 126.91 (Ar-C-H), 127.29 (Ar-C-H), 127.76 (Ar-C-H), 127.83 (Ar-C-H), 128.02 (Ar-C-H), 128.08 (Ar-C-H), 128.12 (Ar-C-H), 128.93 (Ar-C-H), 128.97 (Ar-C-H), 132.43 (Ar-C-H), 133.08 (Ar-C-H), 136.14 (quaternary C), 136.76 (quaternary C), 137.28 (quaternary C), 137.79 (quaternary C), 169.18 (CO), 169.80 (CO).

Radical cyclisation of 2-(1-benzyl-2-cyano-1*H*-indol-3-yl)-*N*-(2-bromo-benzyl)-*N*-isopropyl-acetamide (373)



Bu_3SnH, AIBN, *t*-Butylbenzene

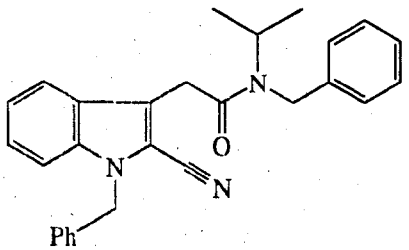
Syringe pump, reflux

Products

$C_{28}H_{26}BrN_3O$
Mol. Wt.: 500.43

A solution of tri-*n*-butyltin hydride (0.43 cm^3, 0.47 g, 1.62 mmol) and azo-bis-isobutyronitrile (AIBN) (0.030 g, 0.30 mmol) in *t*-butylbenzene (30 cm^3) were added dropwise *via* syringe pump (6.37 cm^3/ hour) to a solution of 2-(1-benzyl-2-cyano-1*H*-indol-3-yl)-*N*-(2-bromobenzyl)-*N*-isopropylacetamide **(373)** (0.68 g, 1.35 mmol) in *t*-butylbenzene (50 cm^3) under reflux. Once addition was complete, heating was continued for $1^1/_2$ hours. The reaction was allowed to cool and organic solvent removed under reduced pressure and the residue taken up in acetonitrile (50 cm^3) and extracted with hexane (4 x 50 cm^3). The acetonitrile was removed under reduced pressure and the residue purified by multiple flash column chromatography (2: 1, hexane: ethyl acetate) to give 3 products of R_f= 0.48, 0.31 & 0.27 (2: 1, hexane: ethyl acetate).

Product of R_f = 0.48 (381)

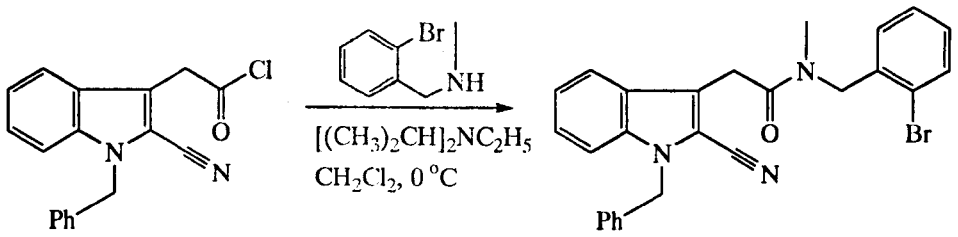


$C_{28}H_{27}N_3O$
Mol. Wt.: 421.53

White solid as a 1: 1.1 mix of amide rotamers (0.31 g, 54%); m.p. 126-128 °C; (Found M^+, 422.2216, $C_{28}H_{27}N_3O$ requires M^++H 422.2232); ν_{max} /cm^{-1} 3061.1, 3031.7, 2975.7, 2933.5 (Ar-H), 2217.3 (CN), 1644.7 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 1.10 (2.7H, d, *J* 6.7, $NCH(CH_3)_2$ (minor)), 1.17 (3.3H, d, *J* 6.7, $NCH(CH_3)_2$ (major)), 3.88 (1.1H, s,

CH_2CO (major)), 4.18 (0.9H, s, CH_2CO (minor)), 4.44 (0.45H, sept, *J* 6.7, $NCH(CH_3)_2$ (minor)), 4.57 (0.9H, s, N(*i*-Pr)CH_2Ar (minor)), 4.67 (1.1H, s, N(*i*-Pr)CH_2Ar (major)), 4.91 (0.55H, sept, *J* 6.7, $NCH(CH_3)_2$ (major)), 5.36 (1.1H, s, indole NCH_2Ar (major)), 5.46 (0.9H, s, indole NCH_2Ar (minor)), 7.13-7.41 (13H, m, Ar-*H* (major + minor)), 7.67 (0.55H, d, *J* 8.1, Ar-*H* (major)), 7.89 (0.45H, d, *J* 8.1, Ar-*H* (minor)); δ_C(75 MHz; $CDCl_3$) 20.34 ($CH(CH_3)_2$), 21.54 ($CH(CH_3)_2$), 31.71 (CH_2CO), 31.94 (CH_2CO), 44.09 (N(*i*-Pr)CH_2Ar), 46.50 ($CH(CH_3)_2$), 46.61 (N(*i*-Pr)CH_2Ar), 48.97 (indole NCH_2Ar), 49.05 (indole NCH_2Ar), 49.52 ($CH(CH_3)_2$), 109.14 (C-3), 109.58 (C-3), 110.62 (C-7), 113.35 (CN), 121.29 (Ar-C-H), 121.47 (Ar-C-H), 121.85 (quaternary C), 121.96 (quaternary C), 122.06 (Ar-C-H), 125.85 (Ar-C-H), 126.23 (Ar-C-H), 126.35 (quaternary C), 126.50 (quaternary C), 126.57 (Ar-C-H), 126.79 (Ar-C-H), 126.84 (Ar-C-H), 126.91 (Ar-C-H), 127.32 (Ar-C-H), 128.01 (Ar-C-H), 128.10 (Ar-C-H), 128.29 (Ar-C-H), 128.89 (Ar-C-H), 128.93 (Ar-C-H), 136.13 (quaternary C), 137.61 (quaternary C), 137.79 (quaternary C), 138.18 (quaternary C), 139.22 (quaternary C), 169.05 (CO), 169.74 (CO);

2-(1-Benzyl-2-cyano-1*H*-indol-3-yl)-*N*-(2-bromobenzyl)-*N*-methylacetamide (372)



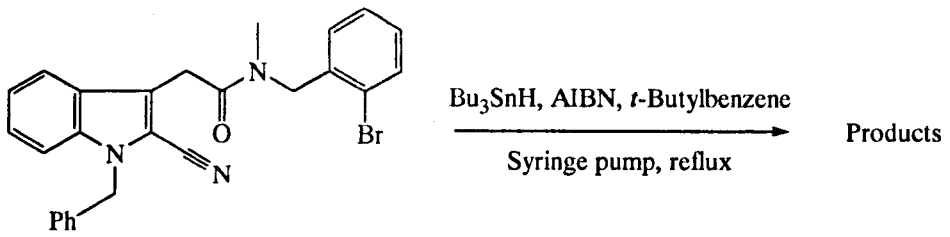
$C_{18}H_{13}ClN_2O$
Mol. Wt.: 308.76

$C_{26}H_{22}BrN_3O$
Mol. Wt.: 472.38

(2-Cyano-1-benzyl-1*H*-indol-3-yl)-acetyl chloride (**380**) (4.79 g, 15.5 mmol) in dichloromethane (50 cm^3) was added dropwise *via* cannula to a stirred solution of (2-bromobenzyl)methylamine (**342**) (4.03 g, 20.15 mmol) and *N, N*-diisopropylethylamine (9.4 cm^3, 7.01 g, 54.3 mmol) in dichloromethane (100 cm^3) at 0 °C under nitrogen. The resulting mixture was left to stir at 0 °C for one hour, allowed to warm to room temperature and left to stir overnight. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3), washed with HCl (100 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate (100 cm^3) and brine (100 cm^3). The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give a light green solid which was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the tertiary amide (**372**) as a light yellow solid and as a 1: 1.3 mix of amide rotamers (6.56 g, 90%); m.p. 131.5-132.5 °C; R_f (2: 1, hexane: ethyl acetate) 0.43; (Found M^+, 472.1014/ 474.0997, $C_{26}H_{22}BrN_3O$ requires M^++H 472.1024/ 474.1004); ν_{max} /cm^{-1} 2926.4 (Ar-H), 2216.8 (CN), 1654.1 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 3.04 (1.2H, s, NC*H*$_3$ (minor)), 3.09 (1.8H, s, NC*H*$_3$ (major)), 4.01 (0.8H, s, C*H*$_2$CO (minor)), 4.12 (1.2H, s, C*H*$_2$CO (major)), 4.71 (0.8H, s, N(CH_3)C*H*$_2$Ar (minor)), 4.76 (1.2H, s, N(CH_3)C*H*$_2$Ar (major)), 5.32 (0.8H, s, indole NC*H*$_2$Ar (minor)), 5.45 (1.2H, s, indole NC*H*$_2$Ar (major)), 6.95 (0.6H, dd, *J* 8.0 & 1.8, Ar-*H* (major)), 7.07-7.40 (10.4H, m, Ar-*H* (major + minor)), 7.53 (0.6H, d, *J* 7.7, Ar-*H* (major)), 7.59 (0.4H, dd, *J* 7.4 & 1.5, Ar-*H* (minor)), 7.72 (0.4H, d, *J* 8.0, Ar-*H* (minor)), 7.86 (0.6H, d, *J* 8.1, Ar-*H* (major)); δ_C(75 MHz; $CDCl_3$) 31.00 (CH_2CO), 31.47 (CH_2CO), 34.75 (NCH_3), 35.80 (NCH_3), 48.99 (N(CH_3)CH_2Ar), 49.09 (N(CH_3)CH_2Ar), 51.22 (indole NCH_2Ar), 54.35 (indole NCH_2Ar), 109.45 (C-3), 109.55 (C-3), 122.66 (quaternary C), 123.60 (quaternary C), 126.35 (Ar-C-H), 126.55

(Ar-C-H), 126.69 (Ar-C-H), 126.79 (Ar-C-H), 126.88 (Ar-C-H), 127.44 (Ar-C-H), 127.79 (Ar-C-H), 128.05 (Ar-C-H), 128.11 (Ar-C-H), 128.89 (Ar-C-H), 128.95 (Ar-C-H), 128.99 (Ar-C-H), 129.08 (Ar-C-H), 132.88 (Ar-C-H), 133.17 (Ar-C-H), 135.02 (quaternary C), 135.89 (quaternary C), 136.00 (quaternary C), 136.07 (quaternary C), 137.59 (quaternary C), 137.80 (quaternary C), 169.34 (CO), 169.80 (CO).

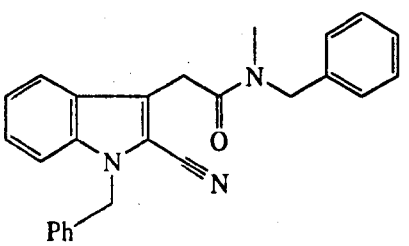
Radical cyclisation of 2-(1-benzyl-2-cyano-1*H*-indol-3-yl)-*N*-(2-bromo-benzyl)-*N*-methyl-acetamide (372)



$C_{26}H_{22}BrN_3O$
Mol. Wt.: 472.38

A solution of tri-*n*-butyltin hydride (0.34 cm^3, 0.37 g, 1.27 mmol) and azo-bis-isobutyronitrile (AIBN) (0.033 g, 0.32 mmol) in *t*-butylbenzene (30 cm^3) were added dropwise *via* syringe pump (6.37 cm^3/ hour) to a solution of 2-(1-benzyl-2-cyano-1*H*-indol-3-yl)-*N*-(2-bromobenzyl)-*N*-methylacetamide (**372**) (0.50 g, 1.06 mmol) in *t*-butylbenzene (40 cm^3) under reflux. Once addition was complete, heating was continued for $1^1/_2$ hours. The reaction was allowed to cool and organic solvent removed under reduced pressure and the residue taken up in acetonitrile (50 cm^3) and extracted with hexane (4 x 50 cm^3). The acetonitrile was removed under reduced pressure and the residue purified by multiple flash column chromatography (2: 1, hexane: ethyl acetate) to give 3 products of R_f= 0.40 & 0.28 (2 overlapping spots, 1: 1 ratio by NMR) (2: 1, hexane: ethyl acetate).

Product of R_f = 0.40 (381)

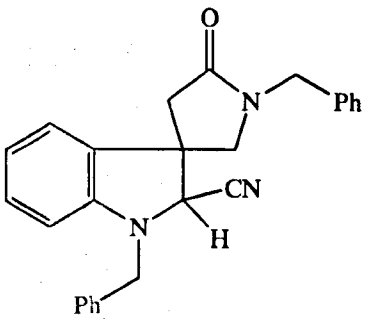


$C_{26}H_{23}N_3O$
Mol. Wt.: 393.48

White solid as a 1: 1.5 mix of amide rotamers (0.134 g, 32%); m.p. 133-134 °C; (Found M^+, 394.1914, $C_{26}H_{23}N_3O$ requires M^++H 394.1919); ν_{max} /cm^{-1} 3061.1, 3031.9, 2926.8 (Ar-H), 2217.3 (CN), 1651.3 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 3.02 (1.2H, s, NCH_3 (minor)), 3.04 (1.8H, s, NCH_3 (major)), 4.07 (0.8H, s, CH_2CO (minor)), 4.08 (1.2H, s,

CH_2CO (major)), 4.65 (1.2H, s, $N(CH_3)CH_2Ar$ (major)), 4.71 (0.8H, s, $N(CH_3)CH_2Ar$ (minor)), 5.33 (0.8H, s, indole NCH_2Ar (minor)), 5.44 (1.2H, s, indole NCH_2Ar (major)), 7.10-7.41 (13H, m, Ar-*H* (major + minor)), 7.79 (0.4H, d, *J* 8.1, Ar-*H* (minor)), 7.87 (0.6H, d, *J* 8.1, Ar-*H* (major)); δ_C(75 MHz; $CDCl_3$) 31.12 (CH_2CO), 31.43 (CH_2CO), 34.56 (NCH_3), 35.35 (NCH_3), 48.99 ($N(CH_3)CH_2Ar$), 49.06 ($N(CH_3)CH_2Ar$), 51.31 (indole NCH_2Ar), 53.77 (indole NCH_2Ar), 109.44 (C-3), 109.47 (C-3), 110.69 (C-7), 110.72 (C-7), 113.30 (CN), 113.44 (CN), 121.49 (Ar-C-H), 121.56 (Ar-C-H), 121.76 (Ar-C-H), 126.14 (Ar-C-H), 126.38 (quaternary C), 126.43 (Ar-C-H), 126.52 (Ar-C-H), 126.83 (Ar-C-H), 127.47 (Ar-C-H), 127.62 (Ar-C-H), 128.06 (quaternary C), 128.11 (Ar-C-H), 128.66 (Ar-C-H), 128.94 (Ar-C-H), 128.97 (Ar-C-H), 128.99 (Ar-C-H), 136.07 (quaternary C), 136.14 (quaternary C), 136.24 (quaternary C), 137.07 (quaternary C), 137.66 (quaternary C), 137.80 (quaternary C), 169.13 (CO), 169.56 (CO).

Product 1 of R_f = 0.28 (382)

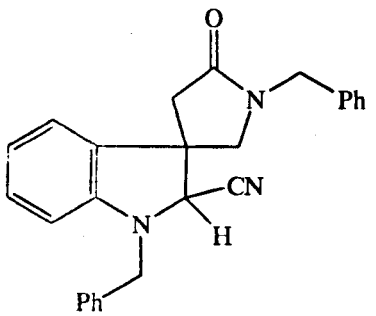


$C_{26}H_{23}N_3O$
Mol. Wt.: 393.48

Inseparable from other diastereoisomer as a light oil (0.07 g, 17%); (Found M^+, 394.1915, $C_{26}H_{23}N_3O$ requires M^++H 394.1919); ν_{max} /cm^{-1} 3059.6, 3031.1, 2924.8 (Ar-H), 2218.2 (CN), 1694.4 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 2.96 &3.05 (2H, ABq, *J* 18.0, CH_2CO), 3.23 & 3.42 (2H, ABq, *J* 10.3, CH_2NCH_2Ar), 4.02 (1H, s, *CH*CN), 4.08 (1H, d, *J* 14.4, $N(CHCN)CH_2Ar$), 4.33 & 4.59 (2H, ABq, *J* 14.6, $CONCH_2Ar$), 4.67 (1H, d, *J* 14.4, $N(CHCN)CH_2Ar$), 6.68 (1H, d, *J* 7.3, C-7*H*), 6.88 (1H, t, *J* 7.3, C-5*H*), 7.10 (1H, d, *J* 7.3, C-4*H*), 7.19-7.39 (11H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 39.72 (CH_2), 46.56 (CH_2), 48.09 (quaternary C), 50.87 (CH_2), 56.81 (CH_2), 64.74 (CHCN), 109.38 (Ar-C-H), 115.53 (CN), 120.94 (Ar-C-H), 122.15 (Ar-C-H), 127.96 (Ar-C-H), 128.12 (Ar-C-

H), 128.19 (2 x Ar-C-H), 128.41 (2 x Ar-C-H), 128.92 (2 x Ar-C-H), 129.03 (2 x Ar-C-H), 129.60 (Ar-C-H), 131.37 (quaternary C), 135.44 (quaternary C), 135.62 (quaternary C), 148.56 (quaternary C), 171.52 (CO).

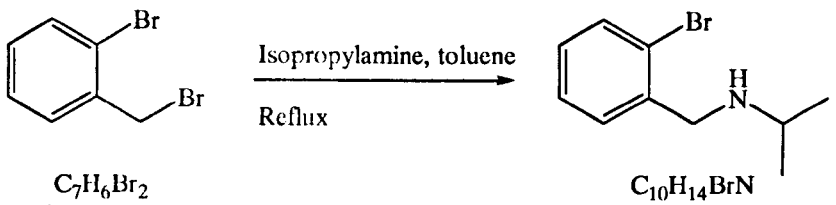
Product 2 of R_f = 0.28 (382)



$C_{26}H_{23}N_3O$
Mol. Wt.: 393.48

White solid (0.07 g, 17%); m.p. 175-176 °C; (Found M^+, 394.1914, $C_{26}H_{23}N_3O$ requires M^++H 394.1919); ν_{max} /cm^{-1} 3030.6, 2923.7, 2850.1 (Ar-H), 2224.2 (CN), 1693.7 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 2.64 & 2.77 (2H, ABq, *J* 17.1, C*H*$_2$CO), 3.64 & 3.75 (2H, ABq, *J* 11.0, C*H*$_2$NCH$_2$Ar), 4.07 (1H, d, *J* 14.0, N(CHCN)C*H*$_2$Ar), 4.09 (1H, s, C*H*CN), 4.36 (1H, d, *J* 14.5, CONC*H*$_2$Ar), 4.70 (1H, d, *J* 14.0, N(CHCN)C*H*$_2$Ar), 4.75 (1H, d, *J* 14.5, CONC*H*$_2$Ar), 6.67 (1H, d, *J* 7.7, C-7*H*), 6.83 (1H, t, *J* 7.7, C-5*H*), 6.97 (1H, d, *J* 7.7, C-4*H*), 7.17 (1H, t, *J* 7.7, C-6*H*), 7.25-7.39 (10H, m Ar-*H*); δ_C(75 MHz; $CDCl_3$) 43.90 (CH_2), 46.88 (CH_2), 47.81 (quaternary C), 50.89 (CH_2), 53.94 (CH_2), 96.43 (CHCN), 109.29 (Ar-C-H), 115.52 (CN), 120.86 (Ar-C-H), 121.94 (Ar-C-H), 128.07 (Ar-C-H), 128.24 (Ar-C-H), 128.42 (2 x Ar-C-H), 128.48 (2 x Ar-C-H), 128.96 (2 x Ar-C-H), 129.06 (2 x Ar-C-H), 129.53 (2 x Ar-C-H), 131.62 (quaternary C), 135.41 (quaternary C), 135.56 (quaternary C), 148.39 (quaternary C), 171.16 (CO).

N-(2-Bromobenzyl)isopropylamine (345)

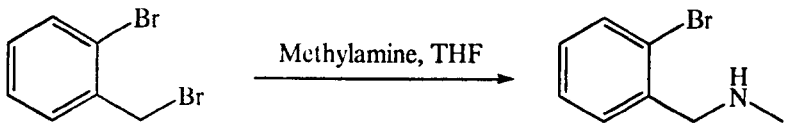


$C_7H_6Br_2$
Mol. Wt.: 249.93

$C_{10}H_{14}BrN$
Mol. Wt.: 228.13

Isopropylamine (14.3 cm^3, 9.90 g, 167.5 mmol) was added to a solution of 2-bromobenzyl bromide (**344**) (4.19 g, 16.8 mmol) in toluene (100 cm^3) and the resulting solution heated under reflux for 24 hours. The reaction mixture was washed with a solution of saturated sodium carbonate (100 cm^3), water (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give *N*-(2-bromobenzyl)isopropylamine (**345**) as a pale yellow oil (3.73 g, 98%); R_f (1: 1, hexane: ethyl acetate) 0.19; (Found M^+, 227.0293/ 229.0299, $C_{10}H_{14}BrN$ requires M^+ 227.03101/ 229.03772); ν_{max} /cm^{-1} 3061.3 (NH), 2930.3 (Ar-H); δ_H(300 MHz; $CDCl_3$) 1.08 (6H, d, *J* 6.2, $CH(CH_3)_2$), 1.44 (1H, br s, N*H*), 2.80 (1H, sept, *J* 6.2, C*H*), 3.8 (2H, s, CH_2), 7.05 (1H, td, *J* 7.5 & 1.5, C-4*H*), 7.23 (1H, td, *J* 7.5 & 1.5, C-5*H*), 7.35 (1H, dd, *J* 7.5 & 1.5, C-6*H*), 7.49 (1H, dd, *J* 7.5 & 1.5, C-3*H*); δ_C(75 MHz; $CDCl_3$) 22.98 ($CH(CH_3)_2$), 47.95 (CH), 51.48 (CH_2), 123.97 (C-2), 127.43 (C-5), 128.48 (C-4), 130.32 (C-6), 132.75 (C-3), 136.60 (C-1); *m/z* 229.03 (9.3%, M^+ ^{81}Br), 227.03 (9.9, M^+ ^{79}Br), 214.00 (89.5), 212.00 (98.0), 170.98 (100.0), 168.99 (97.0), 91.39 (20.8), 90.39 (29.1), 89.39 (23.5).

(2-Bromobenzyl)methylamine (342)

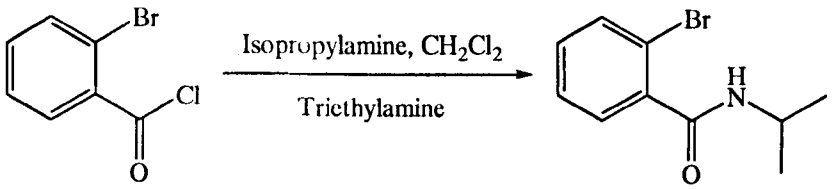


$C_7H_6Br_2$
Mol. Wt.: 249.93

$C_8H_{10}BrN$
Mol. Wt.: 200.08

A solution of 2-bromobenzylbromide (**344**) (25.00 g, 100.0 mmol) in THF (50 cm^3) was added *via* cannula to a stirred solution of methylamine in THF (130 cm^3 of a 2.0M solution, 260 mmol) at room temperature and the resulting solution stirred for 16 hours. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3), washed with saturated sodium hydrogen carbonate solution (150 cm^3), water (100 cm^3), dried ($MgSO_4$), filtered and solvent removed under reduced pressure. The crude product was purified by distillation under reduced pressure (62-63 °C/ 1.5 mmHg) to give (2-bromobenzyl)methylamine (**342**) as a colourless oil (12.10 g, 60%); identical spectroscopic data to that obtained previously.

2-Bromo-*N*-isopropylbenzamide (484)

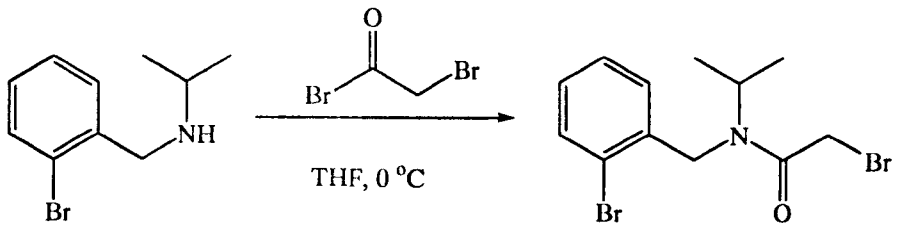


C_7H_4BrClO
Mol. Wt.: 219.46

$C_{10}H_{12}BrNO$
Mol. Wt.: 242.11

2-Bromobenzoyl chloride (**322**) (~99.5 mmol) in dichloromethane (100 cm^3) was added dropwise to a stirred solution of isopropylamine (8.5 cm^3, 5.88 g, 99.5 mmol) and triethylamine (28.0 cm^3, 20.20 g, 199.0 mmol) in dichloromethane (100 cm^3) at 0 °C. The reaction was left to stir at 0 °C for 1 hour and then at room temperature overnight. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3), washed with HCl (100 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate (100 cm^3) and brine (100 cm^3). The organic phase was dried ($MgSO_4$), filtered and solvent removed under reduced pressure to give the crude compound which was purified by recrystallisation (hexane/ ethyl acetate) to give 2-bromo-*N*-isopropylbenzamide (**484**) as a white crystalline solid (17.95 g, 75%); m.p. 148.5-151.5 °C (Lit.[289] 144 °C); R_f (3: 2, hexane: ethyl acetate) 0.45; (Found M^+, 242.0174/ 244.0158, $C_{10}H_{12}BrNO$ requires M^++H 242.0181/ 244.0160); ν_{max} /cm^{-1} 3248.2 (CONH^{i}Pr), 1633.6 (CONH); δ_H(300 MHz; $CDCl_3$) 1.20 (6H, d, *J* 6.6, $CH(CH_3)_2$), 4.19 (1H, sept.d, *J* 6.6 & 1.4, C*H*), 6.02 (1H, br s, N*H*), 7.19 (1H, td, *J* 7.5 & 1.5, C-4*H*), 7.27 (1H, td, *J* 7.5 & 1.5, C-5*H*), 7.39 (1H, dd, *J* 7.5 & 1.5, C-6*H*), 7.49 (1H, dd, *J* 7.5 & 1.5, C-3*H*); δ_C(75 MHz; $CDCl_3$) 22.59 ($CH(CH_3)_2$), 42.15 (CH), 119.25 (C-2), 127.48 (C-5), 129.33 (C-6), 130.96 (C-3), 133.18 (C-4), 138.27 (C-1), 166.86 (CO).

2-Bromo-*N*-(2-bromobenzyl)-*N*-isopropylacetamide (350)

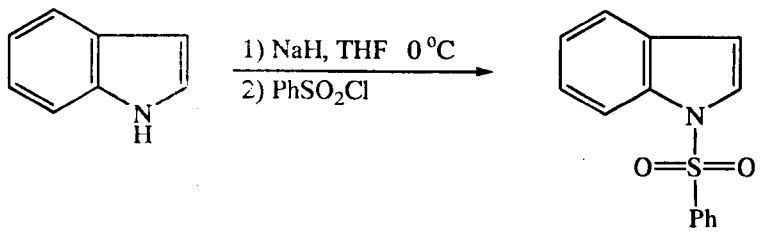


$C_{10}H_{14}BrN$
Mol. Wt.: 228.13

$C_{12}H_{15}Br_2NO$
Mol. Wt.: 349.06

Bromoacetyl bromide (**354**) (0.42 cm^3, 0.98 g, 4.9 mmol) was added dropwise to a stirred solution of (2-bromobenzyl)-isopropylamine (**345**) (1.01 g, 4.4 mmol) and triethylamine (0.49 cm^3, 0.68 g, 4.9 mmol) in THF (10 cm^3) at 0 °C under nitrogen. The reaction was left to stir for 16 hours and poured into water (50 cm^3) and extracted with diethyl ether (3 x 40 cm^3). The combined extracts were washed with brine (50 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give a light yellow oil which was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the title compound (**350**) as a pale yellow oil (1.33 g, 87%); R_f (3: 1, hexane: ethyl acetate) 0.46; ν_{max} /cm^{-1} 3058.6, 2979.4, 2934.3 (Ar-H), 1648.4 ($CONR_2$); δ_H(300 MHz; $CDCl_3$) 0.99 (3H, d, *J* 6.7, $CH(CH_3)_2$ (minor)), 1.07 (3H, d, *J* 6.7, $CH(CH_3)_2$ (major)), 3.55 (2H, s, $COCH_2Br$ (minor)), 3.90 (2H, s, $COCH_2Br$ (major)), 4.15 (1H, sept, *J* 6.7, $CH(CH_3)_2$ (major)), 4.41 (4H, s, $ArCH_2$ (major + minor)), 4.69 (1H, sept, *J* 6.7, $CH(CH_3)_2$ (minor)), 6.95-7.24 (6H, m, Ar-*H* (major + minor)), 7.37 (1H, dd, *J* 8.4 & 0.6, C-3*H* (major)), 7.46 (1H, d, *J* 8.4, C-3*H* (minor)); δ_C(75 MHz; $CDCl_3$) 19.73 ($CH(CH_3)_2$), 21.11 ($CH(CH_3)_2$), 26.75 ($COCH_2Br$), 27.56 ($COCH_2Br$), 44.15 ($ArCH_2$), 46.66 ($CH(CH_3)_2$), 47.28 ($ArCH_2$), 50.25 ($CH(CH_3)_2$), 122.06 (C-2), 122.14 (C-2), 126.81 (Ar-C-H), 127.40 (Ar-C-H), 127.46 (Ar-C-H), 127.87 (Ar-C-H), 128.19 (Ar-C-H), 129.12 (Ar-C-H), 132.40 (Ar-C-H), 133.10 (Ar-C-H), 136.48 (C-1), 136.92 (C-1), 167.00 (CO), 167.32 (CO).

1-Benzenesulfonyl-1*H*-indole (425)

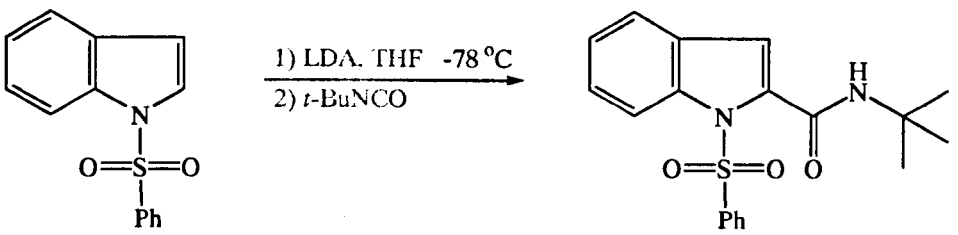


C_8H_7N
Mol. Wt.: 117.15

$C_{14}H_{11}NO_2S$
Mol. Wt.: 257.31

A solution of indole (**428**) (20.00 g, 170.7 mmol) in THF (50 cm^3) was added to a stirred suspension of sodium hydride (7.51 g of a 60% dispersion in mineral oil, hexane washed, 187.8 mmol) in THF (100 cm^3) at 0 ° C. The reaction mixture was allowed to warm to room temperature and left to stir until the evolution of hydrogen had ceased. The reaction mixture was cooled to 0 °C and benzene sulfonyl chloride (44 cm^3, 60.30 g, 341 mmol) was added dropwise and the resulting solution left to stir for 16 hours at room temperature. Water (60 cm^3) was added and organic solvent removed under reduced pressure. The aqueous residue was extracted with diethyl ether (3 x 200 cm^3) and the combined extracts washed with saturated sodium bicarbonate solution (200 cm^3), water (200 cm^3), brine (200 cm^3), dried ($MgSO_4$) filtered and organic solvent removed under reduced pressure to give a light amber oil which was triturated (hexane / diethyl ether, 80 cm^3 of a 2: 1 solution) to give the title compound (**425**) as a white crystalline solid (36.10 g, 82%); m.p. 75-77 °C (Lit.[290] 78-79 °C); R_f (3:1, hexane: ethyl acetate) 0.57; ν_{max} /cm^{-1} 1371.8 & 1175.6 (SO_2Ph); δ_H(300 MHz; $CDCl_3$) 6.69 (1H, d, *J* 3.6, C-3*H*), 7.23-7.62 (7H, m, Ar-*H*), 7.90 (2H, dd, *J* 7.5 & 1.5, C-2'*H* & C-6'*H*), 8.07 (1H,d, *J* 7.5, C-4*H*); δ_C(75 MHz; $CDCl_3$) 109.36 (**C**-3), 113.56 (**C**-7), 121.54 (Ar-**C**-H), 123.48 (Ar-**C**-H), 124.73 (Ar-**C**-H), 126.37 (Ar-**C**-H), 126.76 (**C**-2' & **C**-6'), 129.30 (**C**-3' & **C**-5'), 130.82 (**C**-3a), 133.90 (**C**-4'), 134.88 (**C**-1'), 138.19 (**C**-7a);

1-Benzenesulfonyl-1*H*-indole-2-carboxylic acid *t*-butylamide (429)

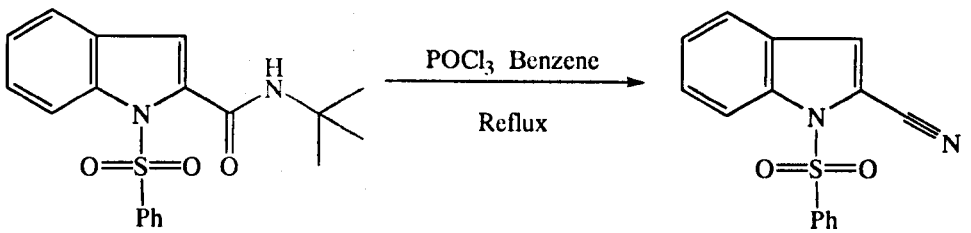


$C_{14}H_{11}NO_2S$
Mol. Wt.: 257.31

$C_{19}H_{20}N_2O_3S$
Mol. Wt.: 356.44

A solution of 1-benzenesulfonyl-1*H*-indole (**425**) (10.00 g, 38.9 mmol) in THF (100 cm^3) was added dropwise to a solution of lithium diisopropylamide (23.3 cm^3 of a 2.0 M solution in THF, 46.6 mmol) in THF (100 cm^3) at –78 °C. Once addition was complete the solution was left to stir for one hour and warmed to –5 °C over 20 minutes and then re-cooled to –78 °C. *t*-Butyl isocyanate (6.7 cm^3, 5.70 g, 58.3 mmol) was added rapidly and the resulting solution left to stir at this temperature for 2 hours and then at ambient temperature for 12 hours. The reaction mixture was poured into saturated ammonium chloride solution (250 cm^3), stirred for 5 minutes and organic solvent removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 x 200 cm^3) and the combined extracts washed with water (200 cm^3), brine (200 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by recrystallisation (hexane/ ethyl acetate) to give the title compound (**429**) as a pale white solid (7.50 g, 54%); m.p. 163.5-165.5 °C (Lit.[257] 162.5-165 °C); R_f (3: 1, hexane: ethyl acetate) 0.45; (Found M^+, 357.1274, $C_{19}H_{20}N_2O_3S$ requires M^++H 357.1273); ν_{max} /cm^{-1} 3389.9 & 3315.4 (NH), 1669.9 (CONH*t*-Bu), 1368.2 & 1176.7 (SO_2Ph); δ_H(300 MHz; $CDCl_3$) 1.52 (9H, s, $C(CH_3)_3$), 6.10 (1H, br s, N*H*), 6.84 (1H, s, C-3*H*), 7.23 (1H, t, *J* 7.5, C-5*H*), 7.31-7.52 (5H, m, Ar-*H*), 8.04 (3H, m, C-4*H*, C-2'*H*, C-6'*H*); δ_C(75 MHz; $CDCl_3$) 28.59 ($C(CH_3)_3$), 52.36 ($C(CH_3)_3$), 113.16 (C-3), 115.28 (C-7), 121.94 (Ar-C-H), 124.21 (Ar-C-H), 126.07 (Ar-C-H), 127.56 (C-2' & C-6'), 128.96 (C-3' & C-5'), 133.98 (C-4'), 136.79 (C-1'), 137.41 (C-7a), 161.05 (CO); Missing (1 x quaternary C).

1-Benzenesulfonyl-1*H*-indole-2-carbonitrile (430)

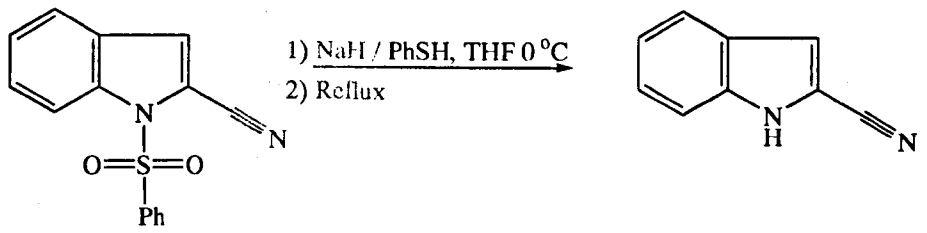


$C_{19}H_{20}N_2O_3S$
Mol. Wt.: 356.44

$C_{15}H_{10}N_2O_2S$
Mol. Wt.: 282.32

Phosphorus oxychloride (9.0 cm^3, 14.80 g, 97.0 mmol) was added to a solution of 1-benzenesulfonyl-1*H*-indole-2-carboxylic acid *t*-butylamide (**429**) (6.91 g, 19.4 mmol) in benzene (150 cm^3) and the resulting solution heated to reflux for 6 hours. Organic solvent was removed under reduced pressure and the residue partitioned between dichloromethane (150 cm^3) and saturated sodium hydrogen carbonate solution (150 cm^3). The resulting solution was stirred until the evolution of gas had ceased and the organic phase separated. The aqueous residue was extracted with dichloromethane (100 cm^3) and the combined organic extracts washed with water (100 cm^3), brine (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give a light yellow solid which was purified by flash column chromatography (4: 1, hexane: ethyl acetate) to give the title compound (**430**) as a white crystalline solid (4.53 g, 83%); m.p. 133.5-134.5 °C (Lit.[257] 127.5-129 °C); R_f (4: 1, hexane: ethyl acetate) 0.57; (Found M^+, 346.0614, $C_{15}H_{10}N_2O_2S$ requires M^++H+MeCN 346.0626); ν_{max} /cm^{-1} 2227.3 (CN), 1382.9 & 1187.2 (SO_2Ph); δ_H(300 MHz; $CDCl_3$) 7.32-7.38 (2H, m, Ar-*H*), 7.47-7.64 (5H, m, Ar-*H*), 8.02 (2H, dd, *J* 7.5 & 1.0, C-4'*H* & C-6'*H*), 8.22 (1H, dd, *J* 7.5 & 1.0, C-4*H*); δ_C(75 MHz; $CDCl_3$) 109.00 (**C**-2), 112.12 (**C**N), 114.61 (**C**-7), 122.65 (**C**-6), 123.32 (**C**-4), 124.89 (**C**-3), 127.11 (**C**-2' & **C**-6'), 127.55 (**C**-3a), 128.80 (**C**-5), 129.69 (**C**-3' & **C**-5'), 134.84 (**C**-4'), 136.66 (**C**-1'), 137.31 (**C**-7a).

1*H*-Indole-2-carbonitrile (355)

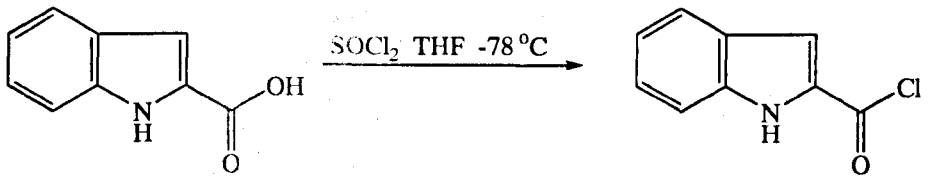


$C_{15}H_{10}N_2O_2S$
Mol. Wt.: 282.32

$C_9H_6N_2$
Mol. Wt.: 142.16

Thiophenol (1.95 cm^3, 2.10 g, 19.1 mmol) was added to a stirred suspension of sodium hydride (0.76 g of a 60% dispersion in mineral oil, hexane washed, 19.1 mmol) in THF (150 cm^3) at 0 °C. The resulting solution was stirred until the evolution of hydrogen had ceased. A solution of 1-benzenesulfonyl-1*H*-indole-2-carbonitrile (**430**) (4.48 g, 15.9 mmol) in THF (50 cm^3) was added *via* cannula and the resulting solution heated at reflux for 72 hours. The reaction mixture was allowed to cool to room temperature and saturated ammonium chloride added (100 cm^3). Organic solvent was removed under reduced pressure and the aqueous residue extracted with dichloromethane (3 x 200 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the crude product which was purified by flash column chromatography (9: 1, hexane: ethyl acetate) to give the title compound (**355**) as a white crystalline solid (2.10 g, 93%); m.p. 98.5-100.5 °C (Lit.[254] 102-103 °C); R_f (9: 1, hexane: ethyl acetate) 0.28; (Found: C, 75.58; H, 4.15; N, 19.65. $C_9H_6N_2$ requires C, 76.04, H, 4.25, N, 19.71%); (Found M^+, 142.05193, $C_9H_6N_2$ requires M^+ 142.05310); ν_{max} /cm^{-1} 3443.0 (N-H), 2228.4 (CN); δ_H(300 MHz; $CDCl_3$) 7.22 (1H, s,C-3*H*), 7.26 (1H, td, *J* 7.5 & 1.5, C-5*H*), 7.42 (2H, m, C-6*H* & C-7*H*), 7.70 (1H, dd, *J* 7.5 & 1.5, C-4*H*), 9.09 (1H, br s, N-*H*); δ_C(75 MHz; $CDCl_3$) 106.02 (**C**-2), 112.00 (**C**-3), 114.54 (**C**-7), 114.65 (**C**N), 121.73 (C-6), 122.12 (**C**-4), 126.19 (**C**-3a), 126.32 (**C**-5), 137.06 (**C**-7a); *m/z* 142.05 (64.5%, M^+), 137.00 (10.8), 115.04 (18.0), 113.01 (100.0), 65.02 (20.2).

1*H*-Indole-2-carbonyl chloride (432)

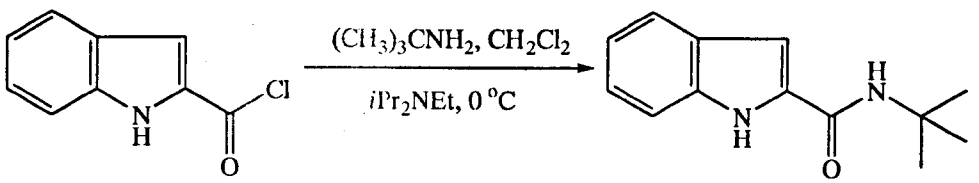


$C_9H_7NO_2$
Mol. Wt.: 161.16

C_9H_6ClNO
Mol. Wt.: 179.60

Thionyl chloride (1.5 cm^3, 2.50 g, 21.2 mmol) and a catalytic amount of dimethyl formamide (8 drops) were added to a suspension of indole-2-carboxylic acid (**434**) (3.41 g, 21.16 mmol) in THF (50 cm^3) at –78 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. Organic solvent was removed under reduced pressure to give the title compound (**432**) as a yellow oil that was used immediately without further purification.

1*H*-Indole-2-carboxylic acid *t*-butylamide (431)

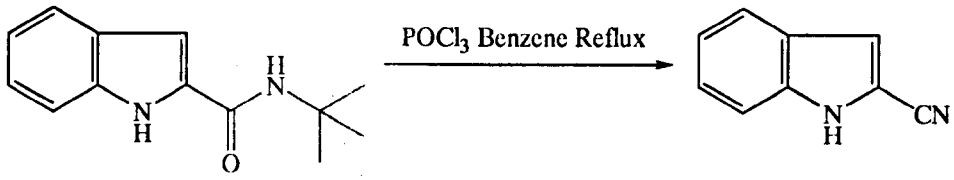


C_9H_6ClNO
Mol. Wt.: 179.60

$C_{13}H_{16}N_2O$
Mol. Wt.:216.28

A solution of indole-2-carbonyl chloride (**432**) (entire residue from previous reaction, ~ 21.16 mmol) in dichloromethane (50 cm^3) was added *via* cannula to a stirred solution of *t*-butylamine (**433**) (2.44 cm^3, 1.70 g, 23.27 mmol) and *N,N*-diisopropylethylamine (11 cm^3, 8.20 g, 63.50 mmol) in dichloromethane (100 cm^3) at 0 °C under nitrogen. The resulting mixture was left to stir at 0 °C for 1 hour and then at room temperature overnight. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (150 cm^3). The organic phase was washed with dilute hydrochloric acid (100 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate solution (100 cm^3), brine (100 cm^3), dried ($MgSO_4$) and filtered. Organic solvent was removed under reduced pressure to give the crude product which was purified by flash column chromatography (1: 1, hexane: ethyl acetate) to give the title compound (**431**) as a yellow crystalline solid (4.41 g, 96%); m.p. 98.5-100.5 °C; R_f (9: 1, hexane: ethyl acetate) 0.28; (Found M^+, 216.12492, $C_{13}H_{16}N_2O$ requires M^+ 216.12627); ν_{max} /cm^{-1} 3271.8 (NH), 1642.7 (CONH*t*-Bu); δ_H(300 MHz; $CDCl_3$) 1.59 (9H, s, C(CH_3)$_3$), 6.17 (1H, br s, CON*H*), 6.82 (1H, d, *J* 1.7, C-3*H*), 7.15 (1H, td, *J* 7.5 & 1.0, C-5*H*), 7.29 (1H, td, *J* 7.5 & 1.0, C-6*H*), 7.57 (1H, dd, *J* 7.5 & 1.0, C-7*H*), 7.65 (1H, d, *J* 7.5, C-4*H*), 10.70 (1H, br s, N-*H*); δ_C(75 MHz; $CDCl_3$) 29.12 (C(CH_3)$_3$), 51.88 (C(CH_3)$_3$), 101.47 (C-3), 112.31 (C-7), 120.38 (Ar-C-H), 121.68 (Ar-C-H), 124.07 (C-5), 127.65 (quaternary C), 131.95 (quaternary C), 136.76 (C-7a), 161.59 (CO); *m/z* 216.13 (99.7%, M^+), 160.6 (78.7), 144.04 (92.5), 143.04 (100.0), 116.05 (35.5), 115.04 (47.8), 89.04 (83.0), 65.02 (39.3), 57.06 (36.9).

1*H*-Indole-2-carbonitrile (355)

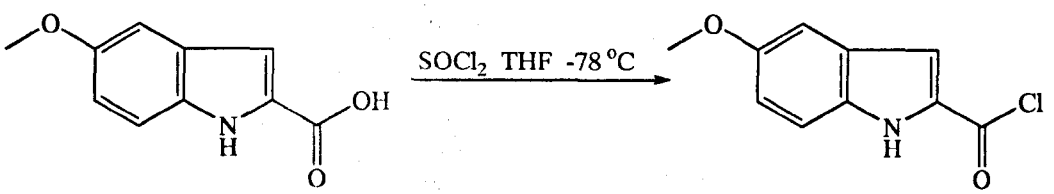


$C_{13}H_{16}N_2O$
Mol. Wt.: 216.28

$C_9H_6N_2$
Mol. Wt.: 142.16

Phosphorus oxychloride (9.00 cm^3, 14.80 g, 96.80 mmol) was added to a suspension of 1*H*-indole-2-carboxylic acid *t*-butylamide (**431**) (4.19 g, 19.40 mmol) in benzene (200 cm^3) and the resulting solution heated at reflux for 8 hours. The reaction mixture was allowed to cool and organic solvent was removed under reduced pressure. The residue was partitioned between dichloromethane (200 cm^3) and saturated sodium hydrogen carbonate solution (150 cm^3) and stirred until the evolution of gas had ceased. Organic solvent was separated and the aqueous layer extracted with dichloromethane (3 x 100 cm^3). The combined organic layers were washed with water (200 cm^3), brine (200 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9: 1, hexane: ethyl acetate) to give the title compound (**355**) as a white crystalline solid (2.50 g, 91%); identical spectroscopic data to that obtained previously.

5-Methoxy-1*H*-indole-2-carbonyl chloride (485)

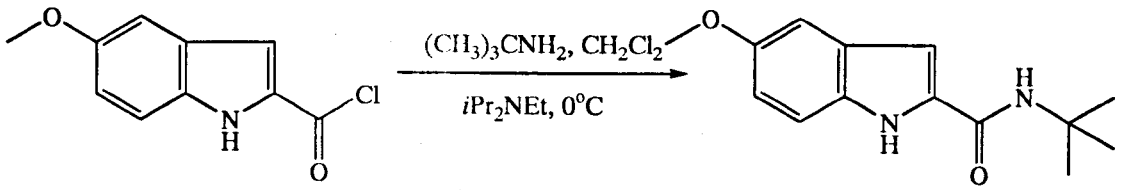


$C_{10}H_9NO_3$
Mol. Wt.: 191.18

$C_{10}H_8ClNO_2$
Mol. Wt.: 209.63

Thionyl chloride (1.98 cm^3, 3.24 g, 27.23 mmol) and a catalytic amount of dimethyl formamide (8 drops) were added to a suspension of 5-methoxy-1*H*-indole-2-carboxylic acid (**435**) (5.21 g, 27.23 mmol) in dichloromethane (100 cm^3) at –78 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. Organic solvent was removed under reduced pressure to give the title compound (**485**) as a yellow oil that was used immediately without further purification.

5-Methoxy-1*H*-indole-2-carboxylic acid *tert*-butylamide (436)

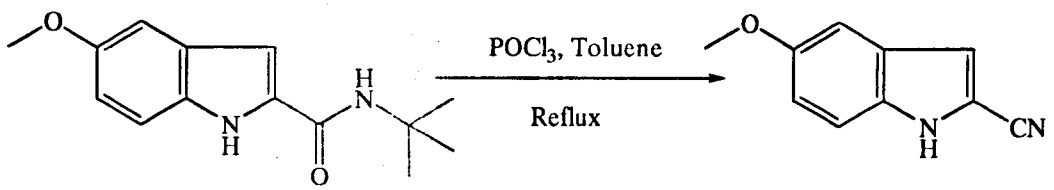


$C_{10}H_8ClNO_2$
Mol. Wt.: 209.63

$C_{14}H_{18}N_2O_2$
Mol. Wt.: 246.31

5-Methoxy-1*H*-indole-2-carbonyl chloride (**485**) (entire residue from previous reaction, ~27.23 mmol) in dichloromethane (50 cm^3) was added *via* cannula to a stirred solution of *t*-butylamine (**433**) (3.2 cm^3, 2.19 g, 29.95 mmol) and *N,N*-diisopropylethylamine (14.2 cm^3, 10.56 g, 81.69 mmol) in dichloromethane (100 cm^3) at 0 °C under nitrogen. The resulting solution was left to stir at 0 °C for 1 hour and then at room temperature overnight. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (150 cm^3). The organic phase was washed with dilute hydrochloric acid (100 cm^3 of a 0.5 M solution), saturated sodium hydrogen carbonate solution (100 cm^3), brine (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give the crude product. Purification by flash column chromatography (1: 1, hexane: ethyl acetate) gave the title compound (**436**) as a yellow crystalline solid (4.70 g, 70%); m.p. 202-204 °C; R_f (1: 1, hexane: ethyl acetate) 0.66; (Found M^+, 269.1257, $C_{14}H_{18}N_2O_2$ requires M^++Na 269.1266); ν_{max} /cm^{-1} 3436.3 & 3418.9 (CONH*t*-Bu), 3271.0 (NH), 1644.3 (CONH), 1265.2 ($ArOCH_3$); δ_H(300 MHz; $CDCl_3$) 1.56 (9H, s, $C(CH_3)_3$), 3.84 (3H, s, OCH_3), 6.14 (1H, br s, CONH), 6.72 (1H, d, *J* 1.7, C-3*H*), 6.94 (1H, dd, *J* 8.9 & 2.4, C-6*H*), 7.02 (1H, d, *J* 2.4, C-4*H*), 7.40 (1H, d, *J* 8.9, C-7*H*), 10.53 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 29.09 ($C(CH_3)_3$), 51.83 ($C(CH_3)_3$), 55.70 (OCH_3), 101.10 (Ar-C-H), 102.13 (Ar-C-H), 113.13 (C-7), 115.27 (C-3), 127.91 (C-2), 132.05 (C-3a), 132.32 (C-7a), 154.44 (C-5), 161.49 (CO).

5-Methoxy-1*H*-indole-2-carbonitrile (424)

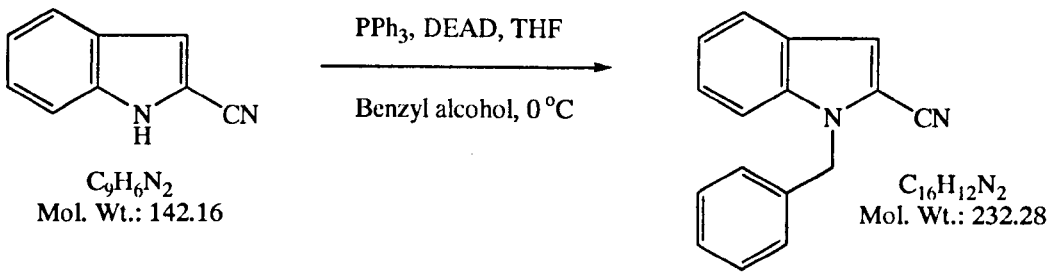


$C_{14}H_{18}N_2O_2$
Mol. Wt.: 246.30

$C_{10}H_8N_2O$
Mol. Wt.: 172.18

Phosphorus oxychloride (6.4 cm^3, 10.56 g, 68.86 mmol) was added to a suspension of 5-methoxy-1*H*-indole-2-carboxylic acid *tert*-butylamide (**436**) (4.24 g, 17.21 mmol) in toluene (200 cm^3) and the resulting solution heated at reflux for 8 hours. The reaction mixture was allowed to cool and organic solvent removed under reduced pressure. The residue was partitioned between dichloromethane (200 cm^3) and saturated sodium hydrogen carbonate solution (150 cm^3) and stirred until the evolution of gas had ceased. Organic solvent was separated and the aqueous layer extracted with dichloromethane (3 x 100 cm^3). The combined organic layers were washed with water (200 cm^3), brine (200 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9: 1, hexane: ethyl acetate) to give the title compound (**424**) as a white crystalline solid (2.08 g, 70%); m.p. 150.0-151.5 °C; R_f (3: 1, hexane: ethyl acetate) 0.41; (Found M^+, 171.0565, $C_{10}H_8N_2O$ requires M^+-H 171.0558); ν_{max} /cm^{-1} 3288.3 (NH), 2226.9 (CN), 1264.5 ($ArOCH_3$); δ_H(300 MHz; $CDCl_3$) 3.86 (3H, s, OCH_3), 7.05-7.08 (2H, m, C-3*H* & C-6*H*), 7.12 (1H, d, *J* 1.3, C-4*H*), 7.31 (1H, dd, *J* 9.6 & 0.7, C-7*H*), 8.68 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 55.69 (OCH_3), 101.90 (C-3), 106.37 (C-2), 112.66 (Ar-C-H), 113.90 (Ar-C-H), 114.35 (CN), 117.98 (C-7), 126.69 (C-3a), 132.15 (C-7a), 155.33 (C-5).

1-Benzyl-1*H*-indole-2carbonitrile (438)

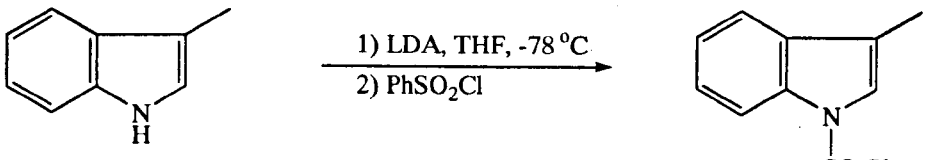


$C_9H_6N_2$
Mol. Wt.: 142.16

$C_{16}H_{12}N_2$
Mol. Wt.: 232.28

Diethyl-azodicarboxylate (3.6 cm^3, 3.98 g, 22.68 mmol) was added dropwise to a stirred solution of 1*H*-indole-2-carbonitrile (**355**) (2.50 g, 17.60 mmol), triphenylphosphine (5.99 g, 22.86 mmol) and benzyl alcohol (2.2 cm^3, 2.3 g, 21.12 mmol) at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred overnight. Organic solvent was removed under reduced pressure and diethyl ether (50 cm^3) added. The volume of the reaction was reduced (~10-15 cm^3) and excess triphenylphosphine oxide was removed by filtration. The filtrate was purified by flash column chromatography (9: 1, hexane: ethyl acetate) to give the title compound (**438**) as a white crystalline solid (3.93 g, 96%); m.p. 93.5-94.5 °C; R_f (9: 1, hexane: ethyl acetate) 0.44; (Found: C, 82.52; H, 5.19; N, 12.10. $C_{16}H_{12}N_2$ requires C, 82.73, H, 5.21, N, 12.06%); (Found M^+, 232.10045, $C_{16}H_{12}N_2$ requires M^+ 232.10005); ν_{max} /cm^{-1} 3061.7, 3034.9 (CH), 2220.5 (CN); δ_H(300 MHz; $CDCl_3$) 5.36 (2H, s, C*H*$_2$), 7.04-7.25 (9H, m, Ar-*H*), 7.58 (1H, d, *J* 8.1, C-4*H*); δ_C(75 MHz; $CDCl_3$) 49.00 (CH_2), 110.03 (C-2), 110.79 (C-3), 113.52 (C-7), 113.77 (CN), 121.61 (Ar-C-H), 122.50 (Ar-C-H), 126.08 (Ar-C-H), 126.42 (quaternary C), 126.82 (C-3' & C-5'), 128.12 (Ar-C-H), 128.99 (C-2' & C-6'), 136.04 (quaternary C), 137.53 (C-7a); *m/z* 232.10 (68.7%, M^+), 142.05 (34.0), 141.05 (54.5), 114.04 (46.5), 92.06 (54.6), 91.06 (100.0), 89.04 (50.2), 75.02 (39.6), 65.03 (90.7), 64.02 (41.5), 63.02 (80.2), 62.00 (38.4).

1-Benzenesulfonyl-3-methyl-1*H*-indole (486)

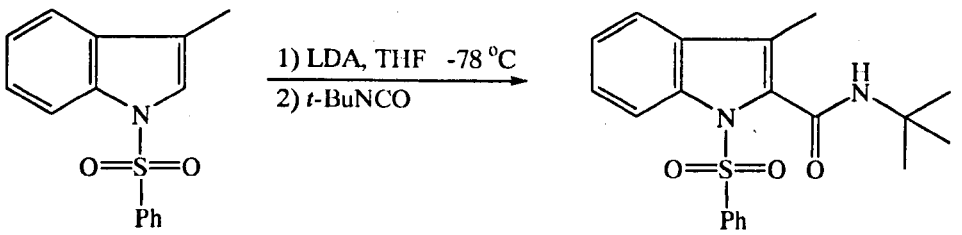


C_9H_9N
Mol. Wt.: 131.18

$C_{15}H_{13}NO_2S$
Mol. Wt.: 271.34

A solution of 3-methylindole (**444**) (8.90 g, 67.7 mmol) in THF (30 cm^3) was added to a stirred solution of lithium diisopropylamide (41.0 cm^3 of a 2.0 M solution in THF, 81.3 mmol) in THF (100 cm^3) at –78 °C under nitrogen. The resulting solution was left to stir for 30 minutes and then warmed to room temperature over 30 minutes. The reaction was stirred for 2 hours and then cooled to –78 °C whereupon phenyl sulfonyl chloride (10.4 cm^3, 4.34 g, 81.0 mmol) was added dropwise. The solution was left to stir at this temperature for 2 hours and then at room temperature for 12 hours. Organic solvent was removed under reduced pressure and a solution of saturated ammonium chloride (200 cm^3) added. The aqueous residue was extracted with dichloromethane (3 x 200 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by recrystallisation (diethyl ether/ hexane) to give the title compound (**486**) as a white solid (needles) (15.63 g, 85%); m.p. 122.0-122.5 °C (Lit.[264] 117.5-119.0 °C); R_f (3:1, hexane: ethyl acetate) 0.19; (Found M^+, 271.0659, $C_{15}H_{13}NO_2S$ requires M^+ 271.0667); ν_{max} /cm^{-1} 1370.4 & 1174.2 (SO_2Ph); δ_H(300 MHz; $CDCl_3$) 2.25 (3H, d, *J* 1.1, C*H*$_3$), 7.25 (1H, td, *J* 7.5 & 1.0, C-5*H*), 7.33 (1H, d, *J* 1.1, C-2*H*), 7.49-7.36 (5H, m, Ar-*H*), 7.88 (2H, dd, *J* 7.5 & 1.0, C-2'*H* & C-6'*H*), 8.02 (1H, d, *J* 7.5, C-4*H*); δ_C(75 MHz; $CDCl_3$) 9.72 (CH_3), 113.66 (C-7), 118.86 (C-3), 119.48 (Ar-C-H), 123.01 (Ar-C-H), 123.12 (Ar-C-H), 124.70 (Ar-C-H), 126.70 (C-2' & C-6'), 129.19 (C-3' & C-5'), 133.65 (quaternary C), 135.27 (quaternary C), 138.29 (C-7a); *m/z* 271.04 (47.1%, M^+), 130.07 (100.0), 77.04 (23.8).

1-Benzenesulfonyl-3-methyl-1*H*-indole-2-carboxylic acid *t*-butylamide (445)

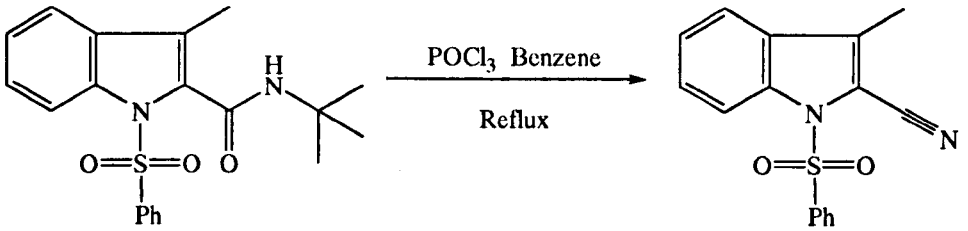


$C_{15}H_{13}NO_2S$
Mol. Wt.: 271.34

$C_{20}H_{22}N_2O_3S$
Mol. Wt.: 370.47

A solution of 1-benzenesulfonyl-3-methyl-1*H*-indole (**486**) (4.35 g, 16.04 mmol) in THF (30 cm^3) was added dropwise to a solution of LDA (8.8 cm^3 of a 2.0 M solution in THF, 17.64 mmol) in THF (100 cm^3) at –78 °C. Once addition was complete the solution was left to stir for one hour and warmed to –5 °C over 20 minutes and then re-cooled to –78 °C. *t*-Butyl isocyanate (3.7 cm^3, 3.18 g, 32.08 mmol) was added rapidly and the resulting solution left to stir at this temperature for 2 hours and then at room temperature for 12 hours. The reaction mixture was poured into saturated ammonium chloride solution (250 cm^3), stirred for 5 minutes and organic solvent removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 x 200 cm^3) and the combined organic extracts washed with water (200 cm^3), brine (200 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (9: 1, hexane: ethyl acetate) to give the title compound (**445**) as a pale white solid (4.02 g, 68%); m.p. 197.5-199.0 °C; R_f (9: 1, hexane: ethyl acetate) 0.15; (Found M^+, 370.1345, $C_{20}H_{22}N_2O_3S$ requires M^+ 370.1351); ν_{max} /cm^{-1} 3385.3 (NH), 1663.7 (CONH), 1271.6 & 1173.9 (SO_2Ph); δ_H(300 MHz; $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 2.17 (3H, s, CH_3), 5.78 (1H, br s, N*H*), 7.15 (1H, t, *J* 7.5, C-5*H*), 7.39-7.23 (5H, m, Ar-*H*), 7.87 (2H, dd, *J* 7.5 & 1.4, C-2'*H* & C-6'*H*), 7.94 (1H, d, *J* 7.5, C-4*H*); δ_C(75 MHz; $CDCl_3$) 9.15 (CH_3), 28.60 ($C(CH_3)_3$), 52.38 ($C(CH_3)_3$), 115.26 (C-7), 119.96 (Ar-C-H), 121.28 (quaternary C), 124.06 (Ar-C), 126.07 (Ar-C-H), 127.47 (C-2' & C-6'), 128.84 (C-3' & C-5'), 130.95 (quaternary C), 132.26 (quaternary C), 133.78 (Ar-C-H), 135.84 (quaternary C), 136.89 (C-7a), 161.40 (CO); *m/z* 370.13 (37.1%, M^+), 298.05 (31.3), 229.13 (33.8), 173.07 (60.2), 157.06 (50.7), 156.06 (100.0), 128.05 (22.3).

1-Benzenesulfonyl-3-methyl-1*H*-indole-2-carbonitrile (446)

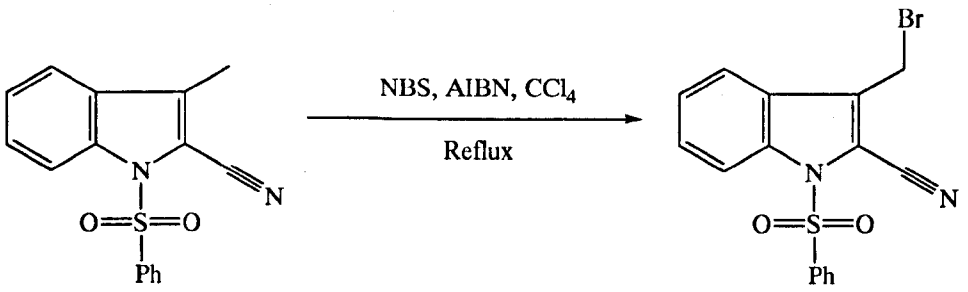


$C_{20}H_{22}N_2O_3S$
Mol. Wt.: 370.47

$C_{16}H_{12}N_2O_2S$
Mol. Wt.: 296.35

Phosphorus oxychloride (4.0 cm^3, 6.65 g, 43.4 mmol) was added to a solution of 1-benzenesulfonyl-3-methyl-1*H*-indole-2-carboxylic acid *t*-butylamide (**445**) (4.02 g, 10.85 mmol) in benzene (150 cm^3) and the resulting solution heated to reflux for 6 hours. Organic solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (150 cm^3) and saturated sodium hydrogen carbonate solution (150 cm^3). The resulting solution was stirred until the evolution of gas had ceased and the organic phase separated. The aqueous residue was washed with dichloromethane (100 cm^3) and the combined organic extracts washed with water (100 cm^3), brine (100 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give a light yellow solid which was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the title compound (**446**) as a white crystalline solid (2.68 g, 83%); m.p. 190-192 °C; R_f (3: 1, hexane: ethyl acetate) 0.33; (Found M^+, 297.0683, $C_{16}H_{12}N_2O_2S$ requires M^++H 297.0698); ν_{max} /cm^{-1} 2223.9 (CN), 1376.8 & 1183.6 (SO_2Ph); δ_H(300 MHz; $CDCl_3$) 2.34 (3H, s, C*H*$_3$), 7.27 (1H, dd, *J* 7.5 & 0.9, C-5*H*), 7.35-7.53 (5H, m, Ar-*H*), 7.89 (2H, dd, *J* 7.5 & 1.0, C-2'*H* & C-6'*H*), 8.10 (1H, dd, *J* 7.5 & 1.0, C-4*H*); δ_C(75 MHz; $CDCl_3$) 10.15 (CH_3), 107.00 (C-3), 112.12 (CN), 114.74 (C-7), 120.81 (Ar-C-H), 124.58 (Ar-C-H), 127.05 (C-2' & C-6'), 128.70 (quaternary C), 128.94 (Ar-C-H), 129.58 (C-3' & C-5'), 134.60 (Ar-C-H), 134.75 (quaternary C), 136.64 (quaternary C), 137.30 (C-7a).

1-Benzenesulfonyl-3-bromomethyl-1*H*-indole-2-carbonitrile (447)

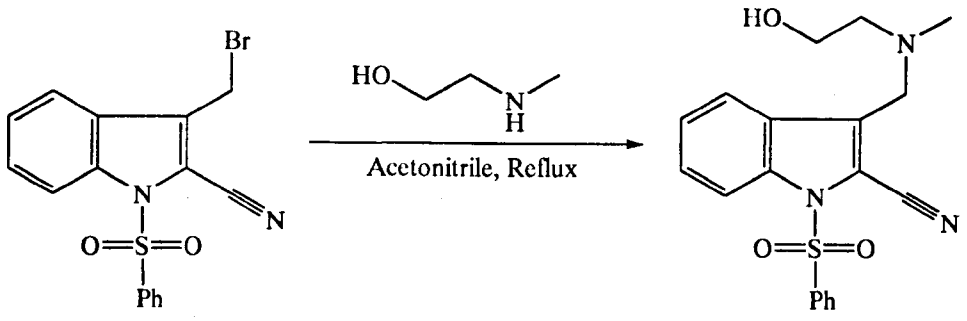


$C_{16}H_{12}N_2O_2S$
Mol. Wt.: 296.35

$C_{16}H_{11}BrN_2O_2S$
Mol. Wt.: 375.24

1-Benzenesulfonyl-3-methyl-1*H*-indole-2-carbonitrile (**446**) (0.95 g, 3.22 mmol) was heated in carbon tetrachloride (20 cm^3) under reflux conditions and *N*-bromosuccinimide (0.63 g, 3.54 mmol) and AIBN (0.029 g, 0.18 mmol) added portionwise over 5 minutes at reflux. After 30 minutes and 60 minutes respectively, more AIBN (*ca.* 10 mg) was added. After 3 hours the reaction was allowed to cool to room temperature and filtered to remove the succinimide, which was washed with dichloromethane (50 cm^3). The filtrate was reduced in volume under reduced pressure and the crude product obtained was purified by flash column chromatography (6: 1, hexane: ethyl acetate) to give the title compound (**447**) as a white solid (1.04 g, 86%); m.p. 156–158 °C; R_f (6: 1, hexane: ethyl acetate) 0.19; (Found: C, 51.50; H, 2.87; N, 7.39. $C_{16}H_{11}N_2$ requires C, 51.21, H, 2.95, N, 7.47%); (Found M^+, 373.9734/ 375.9710, $C_{16}H_{11}BrN_2O_2S$ requires M^+ 373.2725/ 375.9705); ν_{max} /cm^{-1} 2225.0 (CN), 1391.0 & 1188.5 (SO_2Ph); δ_H(300 MHz; $CDCl_3$) 4.55 (2H, s, CH_2), 7.26 – 7.55 (5H, m, Ar-*H*), 7.59 (1H, d, *J* 7.5, C-7*H*), 7.88 (2H, dd, *J* 7.5 & 1.3, C-2'*H* &C-6'*H*), 8.07 (1H, d, *J* 7.5, C-4*H*); δ_C(75 MHz; $CDCl_3$) 19.95 (CH_2), 107.37 (C-3), 110.97 (CN), 114.71 (Ar-C-H), 121.11 (Ar-C-H), 125.03 (Ar-C-H), 126.39 (quaternary C), 127.15 (C-2' & C-6'), 129.64 (Ar-C-H), 129.88 (C-3' & C-5'), 132.70 (quaternary C), 135.14 (Ar-C-H), 136.61 (quaternary C), 137.00 (C-7a); *m/z* 375.97 (20.5%, M^+, ^{81}Br), 373.97 (19.4, M^+, ^{79}Br), 296.06 (64.0), 295.05 (93.1), 155.05 (69.5), 154.05 (99.2), 127.04 (50.6), 102.04 (58.0), 77.04 (100.0), 76.03 (41.2).

1-Benzenesulfonyl-3-{[(2-hydroxy-ethyl)methylamino]-methyl}-1*H*-indole-2-carbonitrile (448)

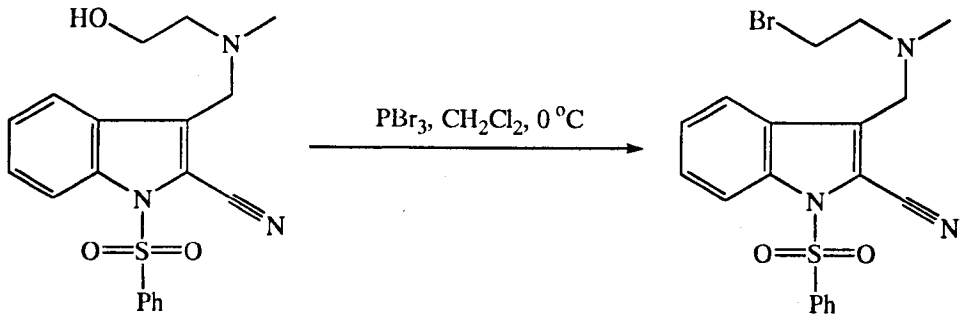


$C_{16}H_{11}BrN_2O_2S$
Mol. Wt.: 375.24

$C_{19}H_{19}N_3O_3S$
Mol. Wt.: 369.44

1-Benzenesulfonyl-3-bromomethyl-1*H*-indole-2-carbonitrile (**447**) (0.30 g, 0.80 mmol) and *N*-methylethanolamine (**423**) (0.06 cm^3, 0.06 g, 0.8 mmol) in toluene were heated under reflux conditions for 5 hours. Organic solvent was removed under reduced pressure and a solution of saturated sodium hydrogen carbonate (20 cm^3) added. The aqueous phase was extracted with dichloromethane (4 x 50 cm^3) and the combined extracts were dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give a light yellow oil which was purified by flash column chromatography (1: 2, hexane: ethyl acetate) to give the title compound (**448**) as a white solid (0.23 g, 78%); m.p. 88.0-89.5 °C; R_f (1: 2, hexane: ethyl acetate) 0.20; (Found M^+, 370.1231, $C_{19}H_{19}N_3O_3S$ requires M^++H 370.1225); ν_{max} /cm^{-1} 3416.2 (OH), 2223.2 (CN), 1376.6 & 1186.8 (SO_2Ph); δ_H(300 MHz; $CDCl_3$) 2.08 (3H, s, C*H*$_2$), 2.50 (2H, t, *J* 5.3, NC*H*$_2$CH$_2$OH), 2.54 (1H, br s, OH), 3.52 (2H, t, *J* 5.3, C*H*$_2$OH), 3.73 (2H, s, C*H*$_2$N(CH$_3$)CH$_2$CH$_2$OH), 7.25 (1H, td, *J* 7.5 & 0.7, C-5*H*), 7.35 – 7.53 (5H, m, Ar-*H*), 7.68 (1H, d, *J* 7.5, C-7*H*), 7.87 (2H, m, C-2'*H* & C-6'*H*), 8.10 (1H, d, *J* 7.5, C-4*H*); δ_C(75 MHz; $CDCl_3$) 41.69 (CH_3), 52.21 ($HOCH_2CH_2NCH_3$), 58.75 (CH_2), 59.01 (CH_2), 108.21 (C-3), 111.99 (CN), 114.82 (C-7), 121.53 (Ar-C-H), 124.92 (Ar-C-H), 126.98 (C-2' & C-6'), 128.00 (quaternary C), 129.13 (Ar-C-H), 129.68 (C-3' & C-5'), 134.84 (Ar-C-H), 135.09 (quaternary C), 136.88 (quaternary C), 137.01 (C-7a).

1-Benzenesulfonyl-3-{[(2-bromo-ethyl)methylamino]-methyl}-1*H*-indole-2-carbonitrile (449)

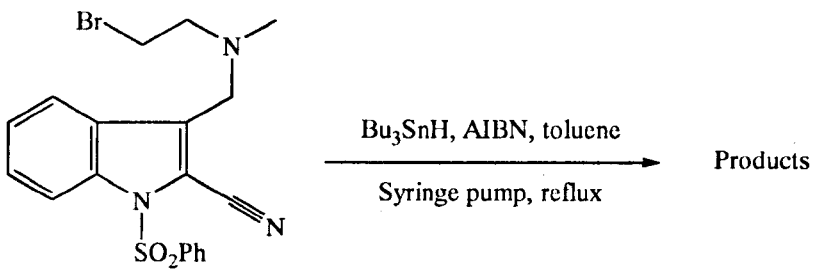


$C_{19}H_{19}N_3O_3S$
Mol. Wt.: 369.44

$C_{19}H_{18}BrN_3O_2S$
Mol. Wt.: 432.34

A solution of 1-benzenesulfonyl-3-{[(2-hydroxyethyl)methylamino]-methyl}-1*H*-indole-2-carbonitrile (**448**) (0.28 g, 0.76 mmol) in dichloromethane (5 cm^3) was added *via* cannula to a stirred solution of phosphorus tribromide (0.05 cm^3, 0.14 g, 0.51 mmol) in dichloromethane (5 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 hours. Ethanol (5 cm^3) was added and the reaction stirred for 15 minutes. Organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (50 cm^3) and washed with saturated sodium hydrogen carbonate solution (50 cm^3). The aqueous phase was extracted with dichloromethane (2 x 50 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (1: 1, hexane: ethyl acetate) to give the title compound (**449**) as a colourless oil (0.19 g, 57%); R_f (1: 1, hexane: ethyl acetate) 0.74; (Found M^+,(FABMS Matrix), 432.0398, $C_{19}H_{18}N_3O_2BrS$ requires M^++H 432.0398); δ_H(300 MHz; $CDCl_3$) 2.10 (3H, s, NC*H*$_3$), 2.76 (2H, t, *J* 6.8, NC*H*$_2$CH$_2$Br), 3.34 (2H, t, *J* 6.8, C*H*$_2$Br), 3.75 (2H, s, C*H*$_2$N(CH$_3$)CH$_2$CH$_2$Br), 7.28 (1H, t, *J* 7.5, C-5*H*), 7.38 – 7.55 (4H, m, Ar-*H*), 7.87 (1H, d, *J* 7.5, C-7*H*), 7.89 – 7.92 (2H, m, C-2'*H* & C-6'*H*), 8.13 (1H, d, *J* 7.5, C-4*H*); δ_C(75 MHz; $CDCl_3$) 29.74 (NCH$_2$CH$_2$Br), 41.79 (CH$_3$), 52.28 (CH$_2$N(CH$_3$)CH$_2$CH$_2$Br), 59.00 (CH$_2$Br), 108.08 (C-3), 111.71 (CN), 114.67 (C-7), 122.51 (Ar-C-H), 124.76 (Ar-C-H), 127.02 (C-2' & C-6'), 127.95 (quaternary C), 129.09 (Ar-C-H), 129.64 (C-3' & C-5'), 134.74 (Ar-C-H), 135.05 (quaternary C), 137.00 (quaternary C), 137.15 (C-7a); *m/z* (FABMS Matrix) 434 (16.5%, M^++H, ^{81}Br), 432 (18.1, M^++H, ^{79}Br), 338 (14.6), 295 (22.0), 155 (30.6), 154 (100.0), 137 (56.3), 136 (71.3).

Radical cyclisation of 1-benzenesulfonyl-3-{[(2-bromo-ethyl)methylamino]-methyl}-1*H*-indole-2-carbonitrile (449)

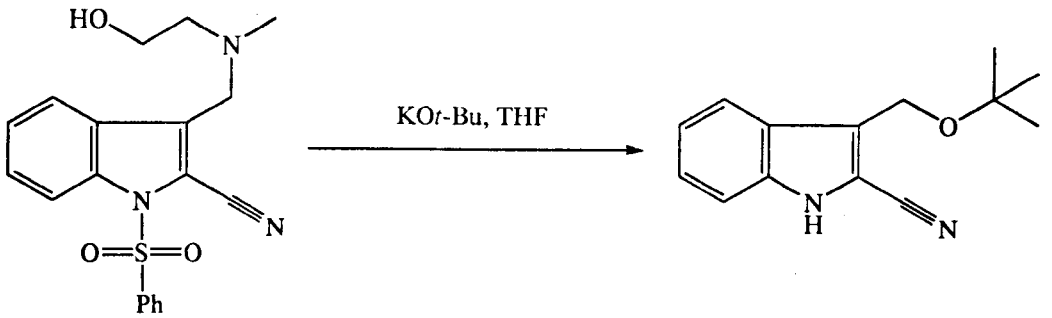


$C_{19}H_{18}BrN_3O_2S$
Mol. Wt.: 432.34

Tri-*n*-butyltin hydride (0.13 cm^3, 0.14 g, 0.48 mmol) and azo-bis-isobutyronitrile (AIBN) (0.008 g, 0.08 mmol) in toluene (10 cm^3) were added dropwise *via* syringe pump (6.37 cm^3/ hour) to a solution of 1-benzenesulfonyl-3-{[(2-bromo-ethyl)methylamino]-methyl}-1*H*-indole-2-carbonitrile (**449**) (0.17 g, 0.40 mmol) in toluene (10 cm^3) under reflux. Once addition was complete, heating was continued for 2 hours. The reaction was allowed to cool and organic solvent removed under reduced pressure and the residue purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give a product of R_f= 0.08 (1: 1, hexane: ethyl acetate) along with a yellow white precipitate which was soluble in methanol.

Pale yellow solid (0.080 g); Discernible data: δ_H(300 MHz; CD_3OD) 3.10 (2H, t, *J* 7.5, C*H*$_2$), 3.26 (3H, s, NC*H*$_3$), 3.80 (2H, t, *J* 7.5, C*H*$_2$), 7.16 (1H, t, *J* 8.0, Ar-*H*), 7.34-7.41 (5H, m, Ar-*H*), 7.48 (1H, d, *J* 8.0, Ar-*H*), 7.65 (1H, d, *J* 8.0, Ar-*H*), 7.82 (1H, m, Ar-*H*); δ_C(75 MHz; CD_3OD) 20.73 (**C**H$_2$), 38.19 (**C**H$_3$), 52.77 (**C**H$_2$), 113.89 (Ar-**C**-H), 121.60 (Ar-**C**-H), 121.88 (quaternary **C**), 122.21 (Ar-**C**-H), 123.19 (quaternary **C**), 125.85 (quaternary **C**), 126.93 (Ar-**C**-H), 128.04 (Ar-**C**-H), 129.33 (Ar-**C**-H), 131.32 (Ar-**C**-H), 140.58 (quaternary **C**), 155.14 (quaternary **C**).

3-*t*-Butoxymethyl-1*H*-indole-2-carbonitrile (450)

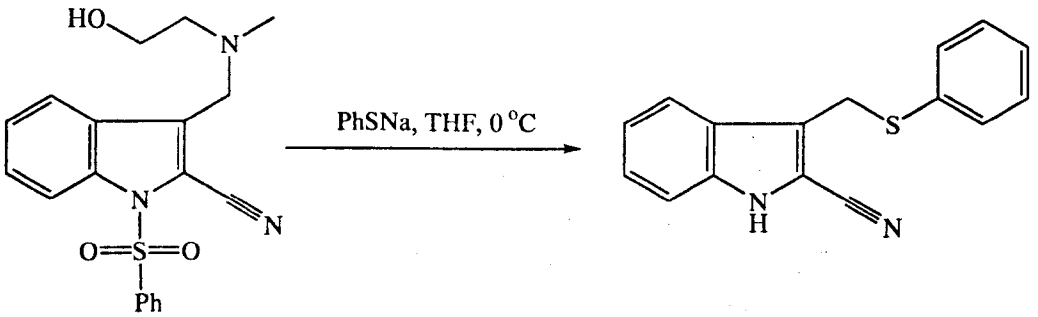


$C_{19}H_{19}N_3O_3S$
Mol. Wt.: 369.44

$C_{14}H_{16}N_2O$
Mol. Wt.: 228.29

Potassium *t*-butoxide (0.36 g, 3.22 mmol) and 11-benzenesulfonyl-3-{[(2-hydroxyethyl)methylamino]-methyl}-1*H*-indole-2-carbonitrile (**448**) (0.24 g, 0.64 mmol) in THF (5 cm^3) were stirred for 15 minutes. Saturated ammonium chloride (20 cm^3) was added and organic solvent removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 x 30 cm^3) and the combined extracts dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give a crude product which was purified by flash column chromatography (2: 1, hexane: ethyl acetate) to give the title compound (**450**) as a white solid (0.024 g, 16%); m.p. 126.5-128.5 °C; R_f (2: 1, hexane: ethyl acetate) 0.73; (Found M^+, 251.1162, $C_{14}H_{16}N_2O$ requires M^++Na 251.1160); ν_{max} /cm^{-1} 3299.9 (NH), 2224.1 (CN), 1187.6 ($CH_2OC(CH_3)_3$); δ_H(300 MHz; $CDCl_3$) 1.39 (9H, s, $C(CH_3)_3$), 4.78 (2H, s, CH_2), 7.20 (1H, td, *J* 7.5 & 1.5, C-5*H*), 7.26 – 7.37 (2H, m ,C-6*H* & C-7*H*), 7.75 (1H, d, *J* 7.5, C-4*H*), 8.75 (1H, br s, NH); δ_C(75 MHz; $CDCl_3$) 27.54 ($C(CH_3)_3$), 55.53 (CH_2), 74.23 ($C(CH_3)_3$), 105.14 (C-3), 111.81 (C-7), 113.71 (CN), 120.90 (Ar-C-H), 121.37 (Ar-C-H), 125.51 (C-2), 126.19 (C-3a), 126.35 (C-5), 137.00 (C-7a).

3-Phenylsulfanylmethyl-1*H*-indole-2-carbonitrile (451)

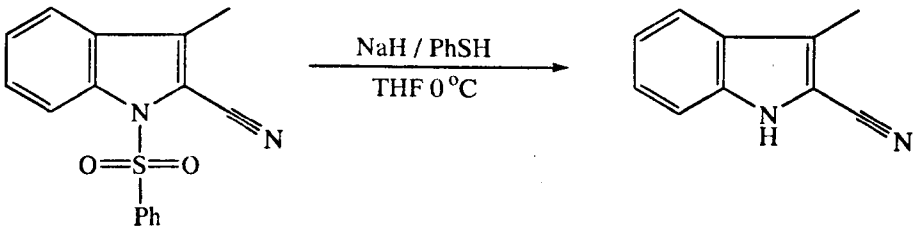


$C_{19}H_{19}N_3O_3S$
Mol. Wt.: 369.44

$C_{16}H_{12}N_2S$
Mol. Wt.: 264.35

Thiophenol (0.10 cm^3, 0.11 g, 0.97 mmol) was added to a stirred suspension of sodium hydride (0.020 g of a 60% dispersion in mineral oil, hexane washed, 0.47 mmol) in THF (10 cm^3) at 0 °C under nitrogen. The resulting solution was stirred at room temperature until the evolution of hydrogen had ceased, whereupon a solution of the alcohol (**448**) (0.15 g, 0.39 mmol) in THF (3 cm^3) was added dropwise *via* cannula. Once addition was complete, the resulting solution was heated to reflux for 72 hours. The reaction mixture was allowed to cool and quenched with water (15 cm^3) and organic solvent removed under reduced pressure and the aqueous residue extracted with dichloromethane (3 x 20 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give the crude compound which was purified by flash column chromatography (4: 1, hexane: ethyl acetate) to give the title compound (**451**) as a white solid (0.089 g, 86%); m.p. 130.0-132.5 °C; R_f (4: 1, hexane: ethyl acetate) 0.32; (Found M^+, 264.0724, $C_{16}H_{12}N_2S$ requires M^+ 264.0721); ν_{max} /cm^{-1}3455.3 (NH), 224.5 (CN); δ_H(300 MHz; $CDCl_3$) 4.28 (2H, s, C*H*$_2$), 7.08 – 7.31 (8H, m, Ar-*H*), 7.65 (1H, d, *J* 8.1, C-4*H*), 8.49 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 29.82 (CH_2), 105.39 (C-3), 112.02 (C-7), 113.45 (CN), 120.90 (Ar-C-H), 121.46 (Ar-C-H), 124.67 (quaternary C), 125.17 (quaternary C), 126.62 (Ar-C-H), 127.42 (Ar-C-H), 129.02 (C-2' & C-6'), 131.83 (C-3' & C-5'), 134.81 (quaternary C), 136.97 (C-7a); *m/z* 264.07 (25.5%, M^+), 155.07 (100.0), 110.23 (13.4).

3-Methyl-1*H*-indole-2-carbonitrile (452)

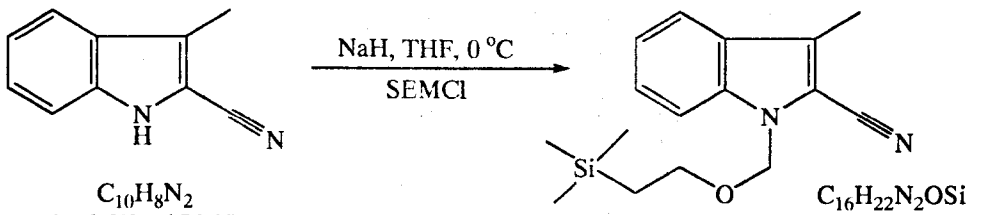


$C_{16}H_{12}N_2O_2S$
Mol. Wt.: 296.35

$C_{10}H_8N_2$
Mol. Wt.: 156.18

Thiophenol (1.11 cm^3, 1.19 g, 10.85 mmol) was added to a stirred suspension of sodium hydride (0.43 g of a 60% dispersion in mineral oil, hexane washed, 10.85 mmol) in THF (100 cm^3) at 0 °C. The resulting solution was stirred until the evolution of hydrogen had ceased. A solution of 1-benzenesulfonyl-3-methyl-1H-indole-2-carbonitrile (**446**) (2.68 g, 9.04 mmol) in THF (50 cm^3) was added *via* cannula and the resulting solution heated at reflux for 72 hours. The reaction mixture was allowed to cool to room temperature and saturated ammonium chloride added (100 cm^3). Organic solvent was removed under reduced pressure and the aqueous residue extracted with dichloromethane (3 x 200 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the crude product which was purified by flash column chromatography (9:1, hexane: ethyl acetate) to give the title compound (**452**) as a white crystalline solid (1.02 g, 72%); m.p. 110.5–112.5 °C (Lit.[291] 102-103.5 C); R_f (4:1, hexane: ethyl acetate) 0.46; (Found M^+, 156.0692, $C_{10}H_8N_2$ requires M^+ 156.0687); ν_{max} /cm^{-1} 3445.5 (NH), 2220.8 (CN); δ_H(300 MHz; $CDCl_3$) 2.32 (3H, s, C*H*$_3$), 7.05 (1H, 2dd, *J* 8.0 & 2.3, C-5*H*), 7.21 – 7.23 (2H, m, C-6*H* & C-7*H*), 7.88 (1H, d, *J* 8.0, C-4*H*), 8.63 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 9.66 (CH_2), 104.56 (C-3), 111.99 (C-7), 114.64 (CN), 120.37 (Ar-C-H), 120.88 (Ar-C-H), 125.53 (C-2), 126.33 (C-5), 126.47 (C-3a), 137.09 (C-7a); *m/z* 156.07 (70.5%, M^+), 155.06 (100.0), 130.07 (15.7), 77.04 (17.8).

3-Methyl-1-(2-trimethylsilanylethoxymethyl)-1*H*-indole-2-carbonitrile (453)

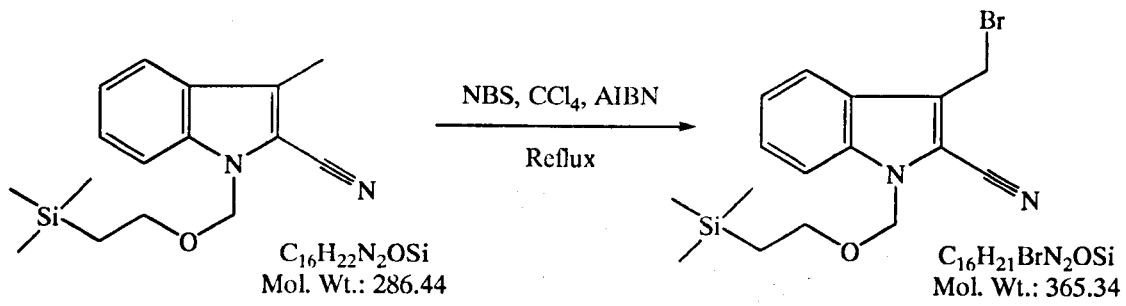


$C_{10}H_8N_2$
Mol. Wt.: 156.18

$C_{16}H_{22}N_2OSi$
Mol. Wt.: 286.44

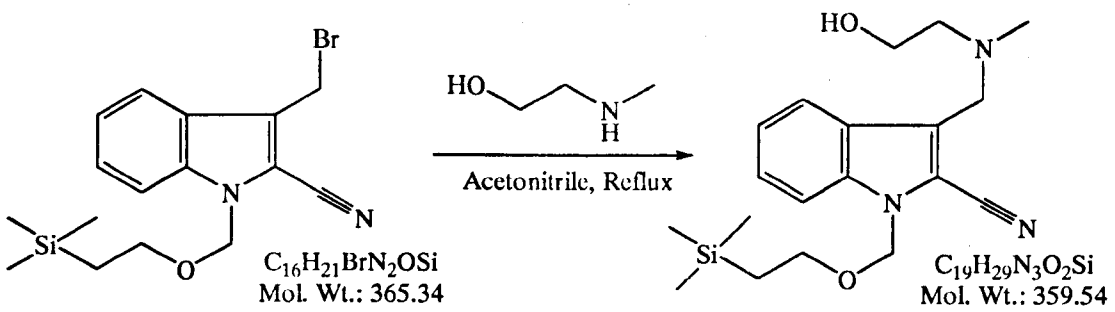
3-Methyl-1*H*-indole-2-carbonitrile (**452**) (0.92 g, 5.88 mmol) in THF (10 cm^3) was added to a stirred suspension of sodium hydride (0.26 g of a 60% dispersion in mineral oil, hexane washed, 6.47 mmol) in THF (30 cm^3) at 0 °C. Once addition was complete, the reaction was allowed to warm to room temperature and stirred for 1 hour. Trimethylsilylethoxymethyl chloride (2.1 cm^3, 1.96 g, 11.77 mmol) was added dropwise and the reaction left to stir overnight at room temperature. Water (20 cm^3) was added and organic solvent removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 x 50 cm^3) and the combined organic extracts washed with brine (50 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure to give a dark oil. Purification by flash column chromatography (9: 1, hexane: ethyl acetate) to give the title compound (**453**) as a colourless oil (1.58 g, 94%); R_f (9: 1, hexane: ethyl acetate) 0.46; (Found M^+, 286.1501, $C_{16}H_{22}N_2OSi$ requires M^+ 286.1501); ν_{max} /cm^{-1} 2216.4 (CN), 1249.2 ($SiCH_3$), 1101.0 (CH_2OCH_2), 860.3 & 836.9 ($SiCH_3$); δ_H(300 MHz; $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.95 (2H, t, *J* 8.2, $CH_2Si(CH_3)_3$), 2.52 (3H, s, CH_3), 3.58 (2H, t, *J* 8.2, $OCH_2CH_2Si(CH_3)_3$), 5.56 (2H, s, NCH_2), 7.26 (1H, td, *J* 7.5 & 1.1, C-5*H*), 7.41 – 7.52 (2H, m, C-7*H* & C-6*H*), 7.63 (2H, d, *J* 7.5, C-4*H*); δ_C(75 MHz; $CDCl_3$) –1.40 ($Si(CH_3)_3$), 9.76 (CH_3), 17.67 ($CH_2Si(CH_3)_3$), 66.27 ($CH_2CH_2Si(CH_3)_3$), 73.86 (NCH_2), 108.58 (C-3), 110.84 (C-7), 113.32 (CN), 120.56 (Ar-C-H), 121.38 (Ar-C-H), 125.23 (C-2), 126.40 (C-5), 127.03 (C-3a), 137.79 (C-7a); *m/z* 286.15 (35.1%, M^+), 228.11 (85.2), 169.08 (63.4), 85.92 (92.2), 83.95 (100.0), 73.05 (99.5).

3-Bromomethyl-1-(2-trimethylsilanylethoxymethyl)-1*H*-indole-2-carbonitrile (454)



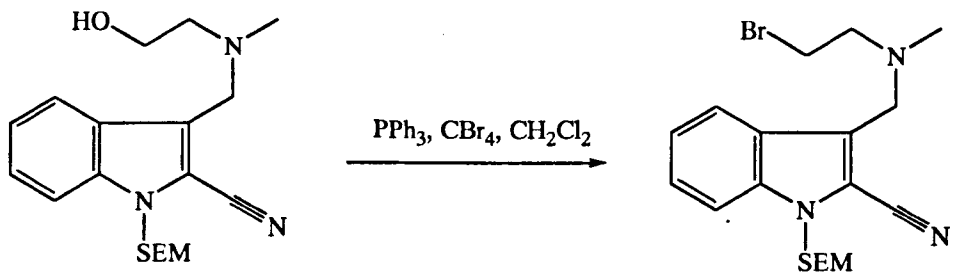
3-Methyl-1-(2-trimethylsilanylethoxymethyl)-1*H*-indole-2-carbonitrile (**453**) (1.45 g, 5.07 mmol) was heated in carbon tetrachloride (30 cm^3) under reflux conditions whereupon *N*-bromo succinimide (0.99 g, 5.57 mmol) and AIBN (0.046 g, 0.28 mmol) were added portion wise over 5 minutes at reflux. After 30 minutes and 60 minutes, more AIBN (*ca.* 10 mg) was added. After 3 hours the reaction was allowed to cool to room temperature and filtered to remove the succinimide, which was washed with dichloromethane (50 cm^3). The filtrate was reduced in volume under reduced pressure and the crude product obtained was purified by flash column chromatography (9: 1, hexane: ethyl acetate) to give the title compound (**454**) as a white solid (1.42 g, 77%); m.p. 88–90 °C; R_f (9: 1, hexane: ethyl acetate) 0.44; (Found M^+, 364.0616/ 366.0585, $C_{16}H_{21}BrN_2OSi$ requires M^+ 364.0607/ 366.0587); ν_{max} /cm^{-1} 2215.5 (CN), 1248.6 ($SiCH_3$), 1083.0 (CH_2OCH_2), 860.2 & 840.1 ($SiCH_3$); δ_H(300 MHz; $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.95 (2H, t, *J* 8.1, $CH_2Si(CH_3)_3$), 3.60 (2H, t, *J* 8.1, $OCH_2CH_2Si(CH_3)_3$), 4.87 (2H, s, CH_2Br), 5.65 (2H, s, NCH_2), 7.38 (1H, td, *J* 7.0 & 1.0, C-5*H*), 7.51 (1H, td, *J* 7.0 & 1.0, C-6*H*), 7.58 (1H, d, *J* 7.0, C-7*H*), 7.84 (1H, d, *J* 7.0, C-4*H*); δ_C(75 MHz; $CDCl_3$) –1.45 ($Si(CH_3)_3$), 17.62 ($CH_2Si(CH_3)_3$), 21.64 (CH_2Br), 66.71 ($CH_2CH_2Si(CH_3)_3$), 74.31 (NCH_2), 109.18 (C-3), 111.33 (C-7), 111.97 (CN), 120.68 (Ar-C-H), 122.46 (Ar-C-H), 124.21 (C-2), 125.36 (C-3a), 127.07 (C-5), 137.85 (C-7a); *m/z* 366.06 (13.5%, M^+, ^{81}Br), 364.06 (14.0, M^+, ^{79}Br), 286.14 (44.8), 285.14 (43.7), 228.10 (80.0), 227.09 (84.5), 169.08 (75.1), 168.07 (57.2), 155.06 (45.1), 154.06 (54.1), 73.05 (100.0), 58.02 (44.8).

3-{[(2-Hydroxyethyl)-methylamino]-methyl}-1-(2-trimethylsilanylethoxymethyl)-1*H*-indole-2-carbonitrile (455)



N-Methylethanolamine (**423**) (0.32 cm^3, 0.30 g, 3.97 mmol) was added to a stirred solution of 3-bromomethyl-1-(2-trimethylsilanylethoxymethyl)-1*H*-indole-2-carbonitrile (**454**) (1.32 g, 3.61 mmol) in dry acetonitrile (40 cm^3) and the resulting solution heated under reflux conditions for 8 hours and then at room temperature for 16 hours. Organic solvent was removed under reduced pressure and a solution of saturated sodium bicarbonate (50 cm^3) was added. The aqueous residue was extracted with dichloromethane (3 x 50 cm^3) and the combined organic extracts dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (1: 1, hexane: ethyl acetate) to give the title compound (**455**) as a colourless oil (1.25 g, 96%); R_f (1: 1, hexane: ethyl acetate) 0.19; (Found M^+, 359.2021, $C_{19}H_{29}N_3O_2Si$ requires M^+ 359.2029); ν_{max} /cm^{-1} 3462.2 (OH), 2219.1 (CN), 1249.3 ($SiCH_3$), 860.1 & 837.3 ($SiCH_3$); δ_H(300 MHz; $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.95 (2H, t, *J* 8.0, $CH_2Si(CH_3)_3$), 2.34 (3H, s, NCH_3), 2.71 (2H, t, *J* 5.3, NCH_2CH_2OH), 2.79 (1H, br s, OH), 3.62 (2H, t, *J* 8.0, $OCH_2CH_2Si(CH_3)_3$), 3.70 (2H, t, *J* 5.3, NCH_2CH_2OH), 3.94 (2H, s, $CH_2N(CH_3)CH_2CH_2OH$), 5.57 (2H, s, $NCH_2OCH_2CH_2Si(CH_3)_3$), 7.27 (1H, t, *J* 7.5, C-5*H*), 7.45 (1H, td, *J* 7.5 & 1.0, C-6*H*), 7.54 (1H, d, *J* 7.5, C-7*H*), 7.82 (1H, d, *J* 7.5, C-4*H*); δ_C(75 MHz; $CDCl_3$) –1.48 ($Si(CH_3)_3$), 17.64 ($CH_2Si(CH_3)_3$), 41.72 (NCH_3), 52.28 ($HOCH_2CH_2NCH_3$), 58.82 (CH_2), 58.90 (CH_2), 66.37 ($OCH_2CH_2Si(CH_3)_3$), 73.93 (NCH_2O), 109.76 (C-3), 111.04 (C-7), 113.11 (CN), 120.99 (Ar-C-H), 121.89 (Ar-C-H), 125.79 (C-2), 126.52 (C-3a), 126.59 (C-5), 137.95 (C-7a); *m/z* 359.20 (15.2%, M^+), 328.18 (67.1), 285.14 (40.4), 242.11 (50.5), 228.10 (55.5), 227.09 (78.9), 85.94 (73.4), 83.94 (81.4), 73.03 (94.1).

3-{[(2-Bromoethyl)-methylamino]-methyl}-1-(2-trimethylsilanylethoxymethyl)-1*H*-indole-2-carbonitrile (456)

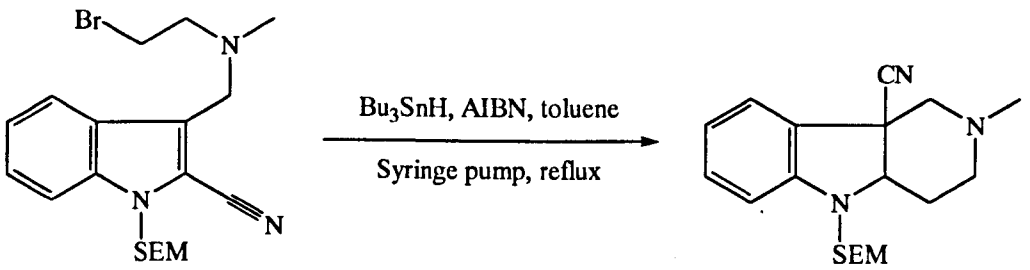


$C_{19}H_{29}N_3O_2Si$
Mol. Wt.: 359.54

$C_{19}H_{28}BrN_3OSi$
Mol. Wt.: 422.43

A solution of triphenyl phosphine (1.0 g, 3.9 mmol) in dichloromethane (5 cm^3) was added to a solution of alcohol (**455**) (1.0 g, 2.8 mmol) and carbon tetrabromide (1.1 g, 3.3 mmol) in dichloromethane (20 cm^3) whilst maintaining the temperature between 0–5 °C. Once addition was complete, the reaction was stirred at 0 °C for 2 hours and organic solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (9: 1, hexane: ethyl acetate) to give the title compound (**456**) as a colourless oil (0.90 g, 80%); R_f (9: 1, hexane: ethyl acetate) 0.16; (Found M^+, 342.1996, $C_{19}H_{28}BrN_3O_2Si$ requires M^+-Br 342.2002); ν_{max} /cm^{-1} 2219.4 (CN), 1249.0 ($SiCH_3$), 859.9 & 837.2 ($SiCH_3$); δ_H(300 MHz; $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.95 (2H, t, *J* 8.0, $CH_2Si(CH_3)_3$), 2.32 (3H, s, NCH_3), 2.92 (2H, t, *J* 7.0, NCH_2CH_2Br), 3.50 (2H, t, *J* 7.0, NCH_2CH_2Br), 3.60 (2H, t, *J* 8.0, $OCH_2CH_2Si(CH_3)_3$), 3.90 (2H, s, $CH_2N(CH_3)CH_2CH_2Br$), 5.60 (2H, s, $NCH_2OCH_2CH_2Si(CH_3)_3$), 7.28 (1H, td, *J* 7.5 & 0.8, C-5*H*), 7.45 (1H, td, *J* 7.5 & 0.8, C-6*H*), 7.53 (1H, d, *J* 7.5, C-7*H*), 7.96 (1H, d, *J* 7.5, C-4*H*); δ_C(75 MHz; $CDCl_3$) –1.32 ($Si(CH_3)_3$), 17.64 ($CH_2Si(CH_3)_3$), 29.96 (CH_2), 41.97 (NCH_3), 52.51 (CH_2), 58.97 (CH_2), 66.37 ($OCH_2CH_2Si(CH_3)_3$), 73.93 (NCH_2O), 109.67 (C-3), 110.92 (C-7), 112.92 (CN), 121.84 (Ar-C-H), 121.87 (Ar-C-H), 125.67 (C-2), 126.54 (C-3a), 126.60 (C-5), 137.97 (C-7a).

Radical cyclisation of 3-{[(2-Bromoethyl)-methylamino]-methyl}-1-(2-trimethylsilanylethoxymethyl)-1*H*-indole-2-carbonitrile (456)

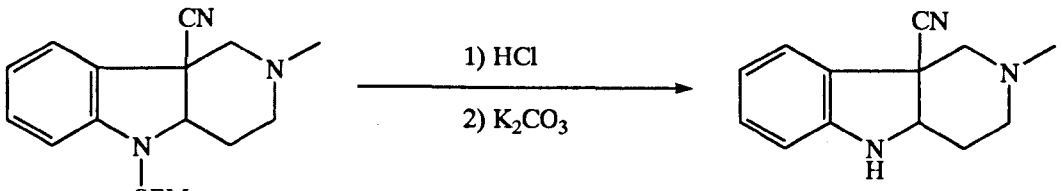


$C_{19}H_{28}BrN_3OSi$
Mol. Wt.: 422.43

$C_{19}H_{29}N_3OSi$
Mol. Wt.: 343.54

Tri-*n*-butyltin hydride (0.49 cm^3, 0.54 g, 1.85 mmol) and azo-bis-isobutyronitrile (AIBN) (0.031 g, 0.30 mmol) in toluene (15 cm^3) were added dropwise *via* syringe pump (6.37 cm^3/ hour) to a solution of 3-{[(2-bromoethyl)-methylamino]-methyl}-1-(2-trimethylsilanylethoxymethyl)-1*H*-indole-2-carbonitrile (**456**) (0.65 g, 1.50 mmol) in toluene (50 cm^3) under reflux. Once addition was complete, heating was continued for 2 hours. The reaction was allowed to cool and organic solvent removed under reduced pressure and the residue taken up in diethyl ether (50 cm^3). DBU (0.53 cm^3, 0.55 g, 3.6 mmol) was added and the white precipitate that formed filtered and washed with ethyl acetate. The crude product was purified by flash column chromatography (3: 1, hexane: ethyl acetate) to give the cyclised product (**458**) as a yellow oil (0.14 g, 27%); R_f (3: 1, hexane: ethyl acetate) 0.25; (Found M^+, 343.20660, $C_{19}H_{29}N_3OSi$ requires M^+ 343.20799); ν_{max} /cm^{-1} 2949.8, 2855.3 & 2800.2 (Ar-H), 2218.3 (CN), 860.5 & 837.3 ($SiCH_3$); δ_H(300 MHz; $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 0.91 (2H, m, $CH_2Si(CH_3)_3$), 2.00-2.24 (3H, m, $N(CH_3)CH_2CH_2$), 2.26 (3H, s, NCH_3), 2.49 (2H, m, $N(CH_3)CH_2CH_2$ & $C(CN)CH_2$), 2.83 (1H, d, *J* 11.8, $C(CN)CH_2$), 3.56 (1H, t, *J* 5.4, $CHCH_2CH_2NCH_3$), 3.65 (2H, m, $OCH_2CH_2Si(CH_3)_3$), 4.80 (2H, ABq, *J* 10.9, NCH_2O), 6.70 (1H, d, *J* 7.6, C-7*H*), 6.83 (1H, t, *J* 7.6, C-5*H*), 7.05 (1H, d, *J* 7.6, C-4*H*), 7.14 (1H, t, *J* 7.6, C-6*H*); δ_C(75 MHz; $CDCl_3$) –1.34 ($Si(CH_3)_3$), 17.98 ($CH_2Si(CH_3)_3$), 24.97 (CH_2), 44.19 (C-H), 46.06 (NCH_3), 51.41 (CH_2), 57.88 (CH_2), 64.80 (quaternary C), 65.48 (CH_2), 75.31 (CH_2), 108.90 (Ar-C-H), 120.18 (Ar-C-H), 120.84 (quaternary C), 123.08 (Ar-C-H), 128.25 (quaternary C), 128.41 (Ar-C-H), 147.37 (quaternary C); *m/z* 343.21 (7.3%, M^+), 316.20 (31.1), 273.15 (34.0), 199.12 (33.4), 156.08 (40.9), 143.07 (35.3), 73.05 (67.8), 58.07 (78.4), 58.06 (100.0).

2-Methyl-1,2,3,4,4a,5-hexahydropyrido[4,3-b]indole-9b-carbonitrile (459)

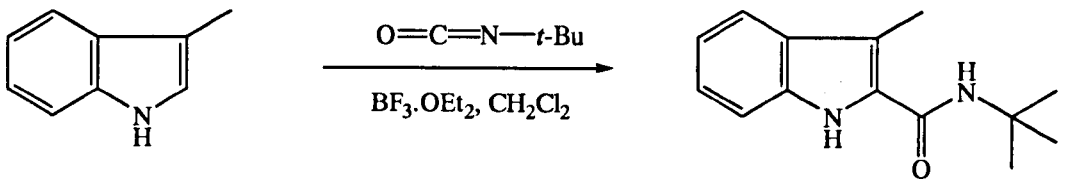


$C_{19}H_{29}N_3OSi$
Mol. Wt.: 343.54

$C_{13}H_{15}N_3$
Mol. Wt.: 213.28

A solution of 2-methyl-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,4,4a,5-hexahydropyrido[4,3-b]indole-9b-carbonitrile (**458**) (0.05 g, 0.14 mmol) in diethyl ether (30 cm^3) was washed with dilute hydrochloric acid (3 x 30 cm^3 of a 2 M solution). The combined aqueous phases were washed with hexane (50 cm^3) and made basic by the addition of solid potassium carbonate. The aqueous solution was extracted with diethyl ether (3 x 50 cm^3) and the combined extracts washed with brine (50 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure to give the title compound (**459**) as a pale yellow oil (0.020 g, 67%); (Found M^+, 213.12642, $C_{13}H_{15}N_3$ requires M^+ 213.12660); ν_{max} /cm^{-1} 3336.3 (NH), 2945.0, 2852.1 & 2799.2 (Ar-H), 2245.2 (CN); δ_H(300 MHz; $CDCl_3$) 1.83-1.94 (1H, m, $CH_2CH_2NCH_3$), 2.06-2.18 (1H, m, $CH_2CH_2NCH_3$), 2.24 (3H, s, NCH_3), 2.26-2.38 (2H, m, $CH_2CH_2NCH_3$), 2.54 & 2.70 (2H, ABq, *J*12.0, $C(CN)CH_2$), 3.41 (1H, t, *J* 6.1, $CHCH_2$), 4.72 (1H, br s, N*H*), 6.66 (1H, d, *J* 7.6, Ar-*H*), 6.80 1H, t, *J* 7.6, Ar-*H*), 7.05 (2H, m, Ar-*H*); δ_C(75 MHz; $CDCl_3$) 20.01 (CH_2), 44.11 (CH), 45.96 (NCH_3), 51.56 (CH_2), 59.73 (CH_2), 61.06 (quaternary C), 111.13 (Ar-C-H), 120.85 (Ar-C-H), 122.36 (quaternary C), 123.50 (Ar-C-H), 128.37 (Ar-C-H), 129.00 (quaternary C), 147.57 (quaternary C); *m/z* 213.13 (20.4%, M^+), 186.11 (100.0), 185.10 (60.6), 144.00 (91.5), 141.99 (68.2), 115.06 (52.5), 71.07 (31.7), 58.07 (46.8).

3-Methyl-1*H*-indole-2-carboxylic acid *t*-butylamide (479)

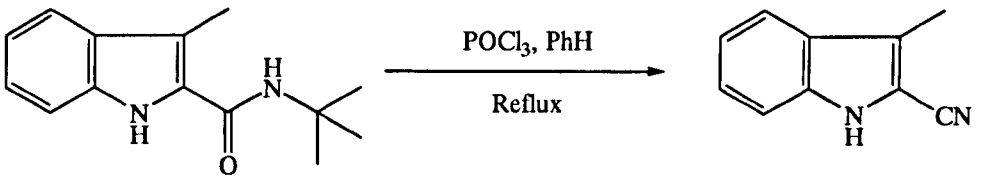


C_9H_9N
Mol. Wt.: 131.17

$C_{14}H_{18}N_2O$
Mol. Wt.: 230.31

Boron trifluoride diethyl ether complex (12.6 cm^3, 14.20 g, 100 mmol) was added to a stirred solution of 3-methyl indole (**444**) (13.13 g, 100.1 mmol) and freshly distilled *t*-butyl isocyanate (13.7 cm^3, 11.91 g, 120.1 mmol) in dichloromethane (100 cm^3) at room temperature. The reaction was allowed to stir for 18 hours whereupon organic solvent was removed under reduced pressure and the residue taken up in dichloromethane (100 cm^3) and washed with saturated ammonium chloride solution (100 cm^3). The aqueous phase was extracted with dichloromethane (2 x 100 cm^3) and the combined organic extracts washed with brine (200 cm^3), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. Purification by recrystallisation (ethanol) gave the title compound (**479**) as white crystalline needles (18.30 g, 79%); m.p. 205-206 °C (Lit.[280] 173.5-174.0 °C); R_f (9: 1, hexane: ethyl acetate) 0.35; (Found M^+, 230.14132, $C_{14}H_{18}N_2O$ requires M^+ 230.14191); ν_{max} /cm^{-1} 3454.1 (NH), 3288.2 (NH), 1638.6 (CONH*t*Bu); δ_H(300 MHz; $CDCl_3$) 1.57 (9H, s, C(CH_3)$_3$), 2.57 (3H ,s, CH_3), 6.00 (1H, br s, CONH), 7.14 (1H, td, *J* 7.5 & 0.8, C-5*H*), 7.27 (1H, td, *J* 7.5 & 1.1, C-6*H*), 7.44 (1H, d, *J* 7.5, C-7*H*), 7.62 (1H, d, *J* 7.5, C-4*H*), 9.88 (1H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 10.34 (CH_3), 29.18 (C(CH_3)$_3$), 51.92 (C(CH_3)$_3$), 110.56 (C-3), 111.87 (C-7), 119.59 (Ar-C-H), 119.87 (Ar-C-H), 124.24 (C-5), 128.48 (quaternary C), 128.74 (quaternary C), 135.21 (C-7a), 162.21 (CO); *m/z* 230.14 (57.7%, M^+), 174.08 (42.1), 158.06 (39.9), 157.05 (100.0), 129.06 (24.1).

3-Methyl-1*H*-indole-2-carbonitrile (452)



$C_{14}H_{18}N_2O$
Mol. Wt.: 230.31

$C_{10}H_8N_2$
Mol. Wt.: 156.18

A solution of 3-methyl-1*H*-indole-2-carboxylic acid *tert*-butylamide (**479**) (16.0 g, 69.47 mmol) and phosphorus oxychloride (19.4 cm^3, 31.96 g, 208.41 mmol) in benzene (200 cm^3) was heated under reflux conditions for 7 hours. Organic solvent was removed under reduced pressure and the residue partitioned between dichloromethane (200 cm^3) and a solution of saturated sodium bicarbonate (200 cm^3) and stirred for one hour. The organic layer was separated and the aqueous phase extracted with dichloromethane (3 x 200 cm^3). The combined organic extracts were washed with brine (200 cm^3), dried ($MgSO_4$), filtered and solvent removed under reduced pressure. The crude product was purified by recrystallisation (hexane) to give 3-methyl-1*H*-indole-2-carbonitrile (**452**) as a white crystalline solid (6.55 g, 60%); identical spectroscopic data to that obtained previously.

Chapter 11

References

(1) W.A. Creasey, *Monoterpenoid Indole Alkaloids, Supplement to Volume 25, Part 4.*, J.E. Saxton, Ed., Wiley: New York, 1994, Chapter 14.

(2) H.P. Husson In *The Monoterpenoid Indole Alkaloids*, J.E. Saxton, Ed.. Wiley: New York, 1988, Chapter 1 and 7.

(3) R. Thomas, *Tetrahedron Lett.*, 1961, **2**, 544.

(4) E. Wenkert, *J. Am. Chem. Soc.*, 1962, **84**, 98.

(5) A.I. Scott, P.C. Cherry, A.A. Qureshi, *J. Am. Chem. Soc.*, 1969, **91**, 4932.

(6) A.I. Scott, *Acc. Chem. Res.*, 1970, **3**, 151.

(7) S.F. Martin, C.W. Clark, M. Ito, M. Mortimore, *J. Am. Chem. Soc.*, 1996, **118**, 9804.

(8) Ch. Schlatter, E.E. Waldner, H. Schmid, W. Maier, D. Groger, *Helv. Chim. Acta*, 1969, **52**, 776.

(9) S.I. Heimberger, A.I. Scott, *J. Chem. Soc., Chem. Commun.*, 1973, 217.

(10) M.E. Kuehne, D.M. Roland, R. Hafter, *J. Org. Chem.*, 1978, **43**, 3705.

(11) R.B. Woodward, M.P. Cava, W.D. Ollis, A. Hunger, H.U. Daeniker, K. Schenker, *J. Am. Chem. Soc.*, 1954, **76**, 4749.

(12) R.B. Woodward, M.P. Cava, W.D. Ollis, A. Hunger, H.U. Daeniker, K. Schenker, *Tetrahedron*, 1963, **19**, 247.

(13) P. Magnus, M. Giles, R. Bonnert, C.S. Kim, L. McGuire, A. Merritt, N. Vicker, *J. Am. Chem. Soc.*, 1992, **114**, 4403.

(14) P. Magnus, M. Giles, R. Bonnert, G. Johnson, M. Deluca, C.S. Kim, L. McGuire, A. Merritt, N. Vicker., *J.Am. Chem. Soc*, 1993, **115**, 8116.

(15) J. Bonjoch, D. Sole, *Chem. Rev.*, 2000, **100**, 3455.

(16) S.D. Knight, L.E. Overman, G. Pairaudeau, *J.Am. Chem. Soc*, 1993, **115**, 9293.

(17) S.D. Knight, L.E. Overman, G. Pairaudeau, *J.Am. Chem. Soc.*, 1995, **117**, 5776.

(18) S.R. Angle, J.M. Fevig, S.D. Knight, R.W. Marquis, L.E. Overman, *J.Am. Chem. Soc.*, 1991, **113**, 5085.

(19) M.E. Kuehne, F. Xu, *J. Org. Chem.*, 1993, **58**, 7490.

(20) M.E. Kuehne, F. Xu, *J. Org. Chem.*, 1998, **63**, 9427.

(21) V.H. Rawal, C. Michoud, *Tetrahedron Lett.*, 1991, **32**, 1695.

(22) V.H. Rawal, C. Michoud, *J. Org. Chem.*, 1993, **58** 5583.

(23) V.H. Rawal, C. Michoud, R.F. Monestel, *J. Am. Chem. Soc.*, 1993, **115**, 3030.

(24) V.H. Rawal, S. Isawa, *J. Org. Chem.*, 1994, **59**, 2685.

(25) D. Sole, J. Bonjoch, S. Garcia-Rubio, E. Peidro, J. Bosch, *Angew. Chem. Int. Ed.*, 1999, **38**, 395.

(26) D. Sole, J. Bonjoch, S. Garcia-Rubio, E. Peidro, J. Bosch, *Chem. Eur. J.*, 2000, **6** 655.

(27) M.J. Eichberg, R.L. Dorta, K. Lamottke, K.P.C. Vollhardt, *Org. Lett.*,2000, **2**, 2479.

(28) G. Stork, J.E. Dolfini, *J. Am. Chem. Soc.*, 1963, **85**, 2872.

(29) Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, Y. kanaoka, *Tetrahedron Lett.*, 1965, 2261.

(30) M.E. Kuehne, C. Bayha, *Tetrahedron Lett.*,1966, **12**, 1311.

(31) R.V. Stevens, R.K. Mehra, R.L. Zimmerman, *J. Chem. Soc., Chem. Commun.*, 1969, 877.

(32) R.V. Stevens, J.M. Fitzpatrick, M. Kaplan, R.I. Zimmerman, *J. Chem. Soc., Chem. Commun.*, 1971, 857.

(33) A.I. Meyers, D. Berney, *J. Org. Chem.*, 1989, **54**, 4673.

(34) R. Iyengar, K. Scildknegt, J. Aube, *Org. Lett.*, 2000, **2** 1625.

(35) J. Harley-Mason, M. Kaplan, *J. Chem. Soc., Chem. Commun.*, 1967, 915.

(36) K. Fuji, M Node, H. Nagasawa, Y. Naniwa, S. Terada, *J. Am. Chem. Soc.*, 1986, **108**, 3855.

(37) M. Node, H. Nagasawa, K. Fuji, *J. Am. Chem. Soc.*, 1987, **109**, 7901.

(38) M. Node, H. Nagasawa, K. Fuji, *J. Org. Chem.*, 1990, **55**, 517.

(39) A.G. Scultz, L. Pettus, *J. Org. Chem.*, 1997, **62**, 6855.

(40) Y. Ban, T. Ohnuma, M. Nagai, Y. Sendo, T. Oishi, *Tetrahedron Lett.*, 1972, **49**, 5023.

(41) J. Laronze, J. Laronze-Fontaine, J. Le Men, *Tetrahedron Lett.*, 1974, **6**, 491.

(42) M.E. Kuehne, T.H. Matsko, J.C. Bohnert, C.L. Kirkemo, *J. Org. Chem.*, 1979, **44**, 1063.

(43) Y. Ban, K. Yoshida, J. Goto, T. Oishi, *J. Am. Chem. Soc.*, 1981, **103**, 6990.

(44) Y. Ban, K. Yoshida, J. Goto, T. Oishi, E. Takeda, , *Tetrahedron*, 1983, **39**, 3657.

(45) T. Gallagher, P. Magnus, *J. Am. Chem. Soc.*, 1982, **104**, 1140.

(46) C. Exon, T. Gallagher, P. Magnus, *J. Am. Chem. Soc.*, 1983, **105**, 4739.

(47) T. Gallagher, P. Magnus, J.C. Huffman, *J. Am. Chem. Soc.*, 1983, **105**, 4750.

(48) E. Wenkert, J.S. Bindra, B. Chauncy, *Synth. Commun.*, 1972, **2**, 285.

(49) E. Wenkert, K. Orito, D.P. Simmons, N. Kunesch, J. Ardisson, J. Poisson, *Tetrahedron*, 1983, **39**, 3719.

(50) E. Wenkert, T. Hudlicky, *J. Org. Chem.*, 1988, **53**, 1953.

(51) P. Le Menez, N. Kunesch, S. Liu, E. Wenkert, *J. Org. Chem.*, 1991, **56**, 2915.

(52) E. Wenkert, S. Liu, *J. Org. Chem.*, 1994, **59**, 7677.

(53) N. Benchekroun-Mounir, D. Dugat, J. Gramain, *Tetrahedron Lett.*, 1992, **33**, 4001.

(54) N. Benchekroun-Mounir, D. Dugat, J. Gramain, H. Husson, *J. Org. Chem.*, 1993, **58**, 6457.

(55) D. Desmaele, J. d'Angelo, *J. Org. Chem.*, 1994, **59**, 2292.

(56) A. Urrutia, J.G. Rodriguez, *Tetrahedron Lett.*, 1998, **39**, 4143.

(57) A. Urrutia, J.G. Rodriguez, *Tetrahedron*, 1999, **55**, 11095.

(58) A. Padwa, A.T. Price, *J. Org. Chem.*, 1995, **60**, 6258.

(59) P. Forns, A. Diez, M. Rubiralta, *J. Org. Chem.*, 1996, **61**, 7882.

(60) J. F. Quinn, M.E. Bos, W.D.Wulff, *Org. Lett.*, 1999, **1**, 161.

(61) M.A. Toczko, C.H. Heathcock, *J. Org. Chem.*, 2000, **65**, 2642.

(62) M. Kizil, J.A. Murphy, *J. Chem. Soc., Chem. Commun.*, 1995, 1409.

(63) O. Callaghan, C. Lampard, A.R. Kennedy, J.A. Murphy, *Tetrahedron Lett.*, 1999, **40**, 161.

(64) M. Kizil, B. Patro, O. Callaghan, J.A. Murphy, M.B. Hursthouse, D. Hibbs, *J. Org. Chem.*, 1999, **64**, 7856.

(65) O. Callaghan, C. Lampard, A.R. Kennedy, J.A. Murphy, *J. Chem. Soc., Perkin Trans 1*, 1999, 995.

(66) B. Patro, J.A. Murphy, *Org. Lett.*, 2000, **2**, 3599.

(67) M. Gomberg, *J. Am. Chem. Soc.*, 1900, **22**, 757.

(68) M. Gomberg, *Chem. Ber.*, 1900, **33**, 3150.

(69) D.H. Hey, W.A. Waters, *Chem. Rev.*, 1937, **21**, 169.

(70) M.S. Karasch, E.T. Margolis, F.R.Mayo, *J. Org. Chem.*, 1937, **2**, 393.

(71) A.F. Parsons In *An Introduction To Free Radical Chemistry*, Blackwell Science, 2000.

(72) M.B. Smith, *Organic Synthesis*, Int. Ed., McGraw-Hill Inc., 1994.

(73) C.L. Kibby, R.E. Weston, *J. Am. Chem. Soc.*, 1968, **90**, 1084.

(74) I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John Wiley and Sons Inc., 1976.

(75) H.G. Viehe, Z. Janousek, R. Merenyi, L.Stella, *Acc. Chem. Res.*, 1985, **18**, 148.

(76) H.G. Viehe, R. Merenyi, L. Stella, Z. Janousek, , *Angew. Chem. Int. Ed.*, 1979, **18**, 917.

(77) J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, 2001.

(78) A.L.J. Beckwith, *Chem. Soc. Rev.*, 1993, 143.

(79) A.L.J. Beckwith, *Tetrahedron*, 1981, **37**, 3073.

(80) J. March, *Advanced Organic Chemistry*, Fourth Ed., Wiley Interscience, 1992.

(81) A.K. Vijh, B.E. Conway, *Chem. Rev.*, 1967, **67**, 623.

(82) W.Seidel, H.J. Schafer, *Chem. Ber.*, 1980, **112**, 451.

(83) J.M. Dener, D.J. Hart, S. Ramesh, *J. Org. Chem.*, 1988, **53**, 6022.

(84) C. Chatgilialoglu, K.U. Ingold, J.C. Scaiano, *J. Am. Chem. Soc.*, 1981, **103**, 7739.

(85) A.N. Abeywickrema, A.L.J. Beckwith, S. Gerba, *J. Org. Chem.*, 1987, **52**, 4072.

(86) S.J. Garden, D.V. Avila, A.L.J. Beckwith, V.W.Bowry, K.U. Ingold, J. Lusztyk, *J. Org. Chem.*, 1996, **61**, 805.

(87) A.L.J.Beckwith, D.M. O'Shea, S. Gerba, S.W. Westwood, *J. Chem. Soc., Chem. Commun.*, 1987, 666.

(88) A.L.J.Beckwith, D.M. O'Shea, S.W. Westwood, , *J. Am. Chem. Soc.*, 1988, **110**, 2565.

(89) G.J.M. van der Kerk, J.G. Noltes, J.G.A. Luijten, *J. Applied Chem.*, 1957, **7**, 356.

(90) M. Pereyre, J. Quintard, A. Rahm, *Tin in Organic Synthesis*, Butterworths, 1986.

(91) W.P. Neumann, *Synthesis*, 1987, 665.

(92) C.P. Jaspere, D.P. Curran, T.L. Fevig, *Chem. Rev.*, 1991, **91**, 1237.

(93) D.P. Curran, *Synthesis*, 1988, 417.

(94) R.C. Lamb, P.W. Ayers, M.K. Toney, *J. Am. Chem. Soc.*, 1963, **85**, 3483.

(95) A.L.J. Beckwith, C.H. Schiesser, *Tetrahedron*, 1985, **41**, 3925.

(96) H.G. Kuivila, L.W. Menapace, *J. Org. Chem.*, 1963, **28**, 2165.

(97) E.J. Corey, J.W. Suggs, *J. Org. Chem.*, 1975, **40**, 2554.

(98) D.B. Gerth, B. Giese, *J. Org. Chem.*, 1986, **51**, 3726.

(99) G. Stork, P.M. Sher, *J. Am. Chem. Soc.*, 1986, **108**, 303.

(100) D.E. Bergbreiter, J.R. Blanton, , *J. Org. Chem.*, 1987, **52**, 473.

(101) A. Fiumana, K. Jones, *J. Chem. Soc., Chem. Commun.*, 1999, 1761.

(102) J.E.Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

(103) M.J.S. Dewar, S. Olivella, *J. Am. Chem. Soc.*, 1978, **100**, 5290.

(104) K.N. Houk, M.N. Paddon-Row, D.C. Spellmeyer, N.R. Rondan, S. Nagase, *J. Org. Chem.*, 1986, **51**, 2874.

(105) A.L.J. Beckwith, C.J. Easton, T. Lawrence, A.K. Serelis, *Aust. J. Chem.*, 1983, **36**, 545.

(106) A.L.J. Beckwith, T. Lawrence, A.K. Serelis, *J. Chem. Soc., Chem. Commun.*, 1980, 484.

(107) W. Zhang, *Tetrahedron*, 2001, **57**, 7237.

(108) R.J. Maguire, S.P. Munt, E.J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2853.

(109) S.P. Munt, E.J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1989, 480.

(110) A.J. McCarroll, J.C. Walton, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3215.

(111) L.F. Tietze, *Chem. Rev.*, 1996, **96**, 115.

(112) I. Ryu, N. Sonoda, , *Chem. Rev.*, 1996, **96**, 177.

(113) D.P. Curran, D.M. Rakiewicz, *Tetrahedron*, 1985, **41**, 3943.

(114) D.P. Curran, M.H. Chen, *Tetrahedron Lett.*, 1985, **26**, 4991.

(115) D.P. Curran, S. Kuo, *Tetrahedron*, 1987, **43**, 5653.

(116) C.E. Schwartz, D.P. Curran, *J. Am. Chem. Soc.*, 1990, **112**, 9272.

(117) G. Stork, R. Mook, *J. Am. Chem. Soc.*, 1983, **105**, 3720.

(118) G. Stork, R. Mook, S.A. Biller, S.D. Rychnovsky, *J. Am. Chem. Soc.*, 1983, **105**, 3741.

(119) J.D. Kilburn, *Tetrahedron Lett.*, 1990, **31**, 2193.

(120) D.L.J. Clive, *Pure Appl. Chem.*, 1988, **60**, 1645.

(121) D.L.J. Clive, A.G. Angoh, S.M. Bennett, *J. Org. Chem.*, 1987, **52**, 1339.

(122) D.L.J. Clive, L. Set, D.R. Cheshire, *J. Chem. Soc., Chem. Commun.*, 1985, 1205.

(123) D.L.J. Clive, S.M. Bennett, *J. Chem. Soc., Chem. Commun.*, 1986, 878.

(124) D.L.J. Clive, S. Daigneault, , *J. Org. Chem.*, 1991, **56**, 5285.

(125) C. Sha, F. Lee, C. Chang, *J. Am. Chem. Soc.*, 1999, **121**, 9875.

(126) Y. Chen, C. Chen, W. Lin, *Tetrahedron Lett.*, 1993, **34**, 2961.

(127) Y. Chen, W. Chang, *J. Org. Chem.*, 1996, **61**, 2536.

(128) F.E. Ziegler, A.K. Petersen, *Tetrahedron Lett.*, 1996, **37**, 809.

(129) P.J, Parsons, M. Penverne, I.L. Pinto, *Synlett*, 1994, 721.

(130) H. Ishibashi, M. Inomata, M. Ohba, M. Ikeda, *Tetrahedron Lett.*, 1999, **40**, 1149.

(131) D.L. Boger, R.J. Mathvink, *J. Org. Chem.*, 1990, **55**, 5442.

(132) M. Journet, M. Malacria, *J. Org. Chem.*, 1994, **59**, 718.

(133) W.R. Bowman, P.T. Stephenson, A.R. Young, *Tetrahedron Lett.*, 1995, **36**, 5623.

(134) X. Cong, B. Quiclet-Sire, S.Z. Zard, *Tetrahedron Lett.*, 1999, **40**, 2125.

(135) D.C. Harowven, M.I.T. Nunn, N.A. Newman, D.R. Fenwick, *Tetrahedron Lett.*, 2001, **42**, 961.

(136) W.B. Motherwell, A. Nakamoto, T. Shimidzu, *J. Chem. Soc., Chem. Commun.*, 1992, 1067.

(137) W.B. Motherwell, A.M.K. Pennell, *J. Chem. Soc., Chem. Commun.*, 1991, 877.

(138) G. Pattenden, A.J. Smithies, D.S. Walter, *Tetrahedron Lett.*, 1994, **35**, 2413.

(139) M.J. Begley, G. Pattenden, A.J. Smithies, D.S. Walter, *Tetrahedron Lett.*, 1994, **35**, 2417.

(140) L.Chen, B. Gill, G. Pattenden, *Tetrahedron Lett.*, 1994, **35**, 2593.

(141) H.M. Boehm, S. Handa, G. Pattenden, L. Roberts, A.J. Blake, W. Li, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3522.

(142) U. Jahn, D.P. Curran, *Tetrahedron Lett.*, 1995, **36**, 8921.

(143) T. Takahashi, S. Tomida, Y. Sakamoto, H. Yamada, *J. Org. Chem.*, 1997, **62**, 1912.

(144) S.A. Hitchcock, G. Pattenden, *Tetrahedron Lett.*, 1992, **33**, 4843.

(145) L. Fensterbank, A. Dhimane, S. Wu, E. Lacote, S. Bogen, M. Malacria, *Tetrahedron*, 1996, **52**, 11405.

(146) M.Journet, E. Lacote, M. Malacria, *J. Chem. Soc., Chem. Commun.*, 1994, 461.

(147) D.P. Curran, H. Liu, H. Josien, S. Ko, *Tetrahedron*, 1996, **52**, 11385.

(148) D.P. Curran, H. Liu, *J. Am. Chem. Soc.*, 1992, **114**, 5863.

(149) D.P. Curran, S. Ko, H. Josien, *Angew. Chem. Int. Ed.*, 1995, **34**, 2683.

(150) R. Volkmann, S. Danishefsky, J. Eggler, D.M. Soloman, *J. Am. Chem. Soc.*, 1971, **93**, 5576.

(151) P.J. Parsons, C.S. Penkett, A.J. Shell, *Chem. Rev.*, 1996, **96**, 195.

(152) K.A. Parker, D. Fokas, *J. Org. Chem.*, 1994, **59**, 3933.

(153) K.A. Parker, D. Fokas, *J. Am. Chem. Soc.*, 1992, **114**, 9688.

(154) K.A. Parker, D.M. Spero, K.C. Inman, *Tetrahedron Lett.*, 1986, **27**, 2833.

(155) K.A. Parker, D.M. Spero, J. Van Epp, *J. Org. Chem.*, 1988, **53**, 4628.

(156) D.E. Cladingboel, P.J. Parsons, *J. Chem. Soc., Chem. Commun.*, 1990, 1543.

(157) Y. Ozlu, D.E. Cladingboel, P.J. Parsons, *Tetrahedron*, 1994, **50**, 2183.

(158) P.J. Parsons, C.S. Penkett, M.C. Cramp, R.I. West, E.S. Warren, *Tetrahedron*, 1996, **52**, 647.

(159) P.J. Parsons, C.S. Penkett, M.C. Cramp, R.I. West, J. Warrington, M.C. Saraiva, *Synlett*, 1995, 507.

(160) J. Robertson, J. Pillai, R.K. Lush, *Chem. Soc. Rev.*, 2001, **30**, 94.

(161) M.E. Wolff, *Chem. Rev.*, 1963, **63**, 55.

(162) J.F. Kerwin, M.E. Wolff, F.F. Owings, B.B. Lewis, B.Blank, A. Magnani, C. Karasch, V. Georgian, *J. Org. Chem.*, 1962, **27**, 3628.

(163) D.H.R. Barton, *Pure Appl. Chem.* 1968, **16**, 1.

(164) D.C. Lathbury, P.J. Parsons, I. Pinto , *J. Chem. Soc., Chem. Commun.*, 1988, 81.

(165) Z. Čeković, D. Ilijev, *Tetrahedron Lett.*, 1988, **29**, 1441.

(166) D.P. Curran, D. Kim, H.T. Liu, W. Shen, *J. Am. Chem. Soc.*, 1988, **110**, 5900.

(167) D.P. Curran, W. Shen, *J. Am. Che. Soc.*, 1993, **115**, 6051.

(168) D.P. Curran, K.V. Somayajula, H. Yu, *Tetrahedron Lett.*, 1992, **33**, 2295.

(169) N. Yamazaki, E. Eichenberger, D.P. Curran, *Tetrahedron Lett.*, 1994, **35**, 6623.

(170) D.P. Curran, H. Yu, *Synthesis*, 1992, 123.

(171) D.P. Curran, H. Yu, H. Liu, *Tetrahedron*, 1994, **50**, 7343.

(172) V. Snieckus, J. Cuevas, C.P. Sloan, H. Liu, D.P. Curran, *J. Am. Chem. Soc.*, 1990, **112**, 896.

(173) D.P. Curran, H. Liu, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1377.

(174) A.H. Lewin, A.H. Dinwoodie, T. Cohen, *Tetrahedron*, 1966, **22**, 1527.

(175) T. Cohen, K.W. Smith, M.D. Swerdloff, *J. Am. Chem. Soc.*, 1971, **93**, 4303.

(176) S. Sengupta, S. Bhattacharyya, *Tetrahedron Lett.*, 2001, **42**, 2035.

(177) W.E. Stewart, T.H. Sidall, *Chem. Rev.*, 1970, **70**, 517.

(178) P.K. Korver, P.J. van der Haak, T.J. de Boer, *Org. Magn. Reson.*, 1971, **3**, 605.

(179) L.M. Jackman, T.E. Kavanagh, R.C. Haddon, *Org. Magn. Reson.*, 1969, **1**, 109.

(180) R.F.C. Brown, L. Radom, S. Sternhell, I.D. Rae, *Can. J. Chem.*, 1968, **46**, 2577.

(181) A.H. Lewin, M. Frucht, K.V.J. Chen, E. Benedetti, B. Di Blasio, *Tetrahedron*, 1975, **31**, 207.

(182) A.H. Lewin, M. Frucht, *Org. Magn. Reson.*, 1975, **7**, 206.

(183) T. Sato, Y. Kugo, E. Nakaumi, H. Ishibashi, M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1801.

(184) D.P. Curran, A.C. Abraham, H. Liu, *J. Org. Chem.*, 1991, **56**, 4335.

(185) A.L. Beckwith, J.M.D. Storey, *J. Chem. Soc., Chem. Commun.*, 1995, 977.

(186) J.M.D. Storey, *Tetrahedron Lett.*, 2000, **41**, 8173.

(187) J.A. Murphy, S.J. Roome, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1349.

(188) A. Fiumana, K. Jones, *Tetrahedron Lett.*, 2000, **41**, 4209.

(189) G.W. Gribble, H.L. Fraser, J.C. Badeock, *J. Chem. Soc., Chem. Commun.*, 2001, 805.

(190) F.Beaulieu, J. Arora, U. Veith, N.J. Taylor, B.J. Chapell, V. Snieckus, *J. Am. Chem. Soc.*, 1996, **118**, 8727.

(191) L. Giraud, P. Renaud, *J. Org. Chem.*, 1998, **63**, 9162.

(192) T.C.T. Ho, Ph.D. Thesis, University of London, 1997.

(193) S.T. Hilton, T.C.T. Ho, G. Pljevaljcic, M. Schulte, K. Jones, *J. Chem. Soc., Chem. Commun.*, 2001, 209.

(194) C.C. Yang, H.T. Chang, J.M. Fang, *J. Org. Chem.*, 1993, **58**, 3100.

(195) C. McCarthy, K. Jones, *J. Chem. Soc., Chem. Commun.*, 1989, 1717.

(196) C. McCarthy, Ph.D. Thesis, University of London, 1990.

(197) J.A. Wilkinson, Ph.D. Thesis, University of London, 1993.

(198) A. Jossang, P. Jossang, H.A. Hadi, T. Sevenet, B. Bodo, *J. Org. Chem.*, 1991, **56**, 6527.

(199) N. Anderton, P.A. Cockrum, S.M. Colegate, *Phytochemistry*, 1998, **48**, 437.

(200) R.C. Elderfield, R.E. Gilman, *Phytochemistry*, 1972, **11**, 339.

(201) C.B. Cui, H. Kakeya, G. Okada, R. Onose, H. Osada, *J. Antibiot.*, 1996, **49**, 527.

(202) S. Edmonson, S.J. Danishefsky, L. Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.*, 1999, **121**, 2147.

(203) M.N.G. James, G.J.B. Williams, *Can. J. Chem.*, 1972, **50**, 2407.

(204) M. Mori, Y. Ban, *Heterocycles*, 1978, **9**, 391.

(205) C. Pellegrini, M. Weber, H. Borschberg, *Helv. Chim. Acta*, 1996, **76**, 151.

(206) H. Yazawa, K. Tanaka, K. karyone, *Tetrahedron Lett.*, 1974, 3995.

(207) D.L. Boger, R.M. Borzilleri, S. Nukui, R.T. Beresis, *J. Org. Chem.*, 1997, **62**, 4721.

(208) J.R. Henry, L.R. Marcin, M.C. McIntosh, P.M. Scola, G.D. Harris, S.M. Weinreb, *Tetrahedron Lett.*, 1989, **30**, 5709.

(209) T. Tsunoda, F. Ozaki, S. Ito, *Tetrahedron Lett.*, 1994, **35**, 5081.

(210) T. Tsunoda, Y. Yamamiya, S. Ito, *Tetrahedron Lett.*, 1993, **34**, 1639.

(211) T. Fukuyama, C. Jow, M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373.

(212) W.R. Bowman, D.C. Coghlan, *Tetrahedron*, 1997, **53**, 15787.

(213) S.A. Glover, J. Warkentin, *J. Org. Chem.*, 1993, **58**, 2115.

(214) N.M. Gray, M.S. Dappen, B.K. Cheng, A.A. Cordi, J.P. Biesterfeldt, W.F. Hodd, J.B. Monahan, *J. Med. Chem.*, 1991, **34**, 1283.

(215) M.G. Reinecke, J.F. Sebastian, H.W. Johnson, C. Pyun, *J. Org. Chem.*, 1972, **37**, 3066.

(216) W.C. Guida, D.J. Mathre, *J. Org. Chem.*, 1980, **45**, 3172.

(217) N. Wang, K. Teo, H.J. Anderson, *Can. J. Chem.*, 1977, **55**, 4112.

(218) B. Cardillo, G. Casnati, A. Pochini, A. Ricca, *Tetrahedron*, 1967, **23**, 3771.

(219) A. Miyashita, K. Obae, Y. Suzuki, E. Oishi, K. Iwamoto, T. Higashino, *Heterocycles*, 1997, **45**, 2159.

(220) S.J. Selikson, D.S. Watt, *J. Org. Chem.*, 1975, **40**, 267.

(221) S.S. Kulp, M.J. McGee, *J. Org. Chem.*, 1983, **48**, 4097.

(222) R.W. Freerksen, S.J. Selikson, R.R. Wroble, K.S. Kyler, D.S. Watt, *J. Org. Chem.*, 1983, **48**, 4087.

(223) H. Ishii, T. Ishikawa, T. Watanabe, Y. Ichikawa, E. Kawanabe, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2283.

(224) H. Ishii, I. Chen, T. Ishikawa, *J. Chem. Soc., Perkin Trans. 1*, 1987, 671.

(225) K. Shiosaki, H. Rappaport, *J. Org. Chem.*, 1985, **50**, 1229.

(226) H. Takahashi, M. Iguchi, M. Onda, *Chem. Pharm. Bull.*, 1985, **33**, 4775.

(227) P. Forns, A. Diez, M. Rubiralta, X. Solans, M. Font-Bardia, *Tetrahedron*, 1996, **52**, 3563.

(228) T. Chuang, C. Yang, C. Chang, J. Fang, *Synlett*, 1990, 733.

(229) C. Fischer, C. Meyers, E.M. Carreira, *Helv. Chim. Acta.*, 2000, **83**, 1175.

(230) P. Van Doren, D. Vanderzande, S. Toppet, G. Hoornaert, *Tetrahedron*, 1989, **45**, 6761.

(231) P.D. Magnus, N.L. Sear, *Tetrahedron*, 1984, **40**, 2795.

(232) A.S. Bailey, P.W. Scott, M.H. Vandrevala, *J. Chem. Soc., Perkin Trans. 1*, 1980, 97.

(233) H.M.S. Kumar, B.V. Reddy, P.T. Reddy, J.S. Yadav, *Synthesis*, 1999, 586.

(234) S.T. Hilton, T.C.T. Ho, G. Pljevaljcic, K. Jones, *Org. Lett.*, 2000, **2**, 2639.

(235) O. Mitsunobu, *Synthesis*, 1981, 1.

(236) J. Cossy, C. Poitevin, D.G. Pardo, J.L. Peglion, *Synthesis*, 1995, 1368.

(237) W.R. Bowman, C.F. Bridge, P. Brookes, *Tetrahedron Lett.*, 2000, **41**, 8989.

(238) R. Sulsky, J.Z. Gougoutas, J. DiMarco, S.A. Biller, *J. Org. Chem.*, 1999, **64**, 5504.

(239) N. Anderton, P.A. Cockrum, S.M. Colegate, J.A. Edgar, K. Flower, *A. C. S. Sym. Ser. 745*, 2000, 140.

(240) C. Pellegrini, C. Strassler, M. Webber, H.J. Borschberg, *Tetrahedron Asymmetry*, 1994, **5**, 1979.

(241) M. Somei, K. Noguchi, R. Yamagami, Y. Kawada, K. Yamada, F. Yamada, *Heterocycles*, 2000, **53**, 7.

(242) S. Ghosal, P.K. Banerjee, *Indian J. Chem.*, 1971, **9**, 289.

(243) M.J. Kornet, A.P. Thio, *J. Med. Chem.*, 1976, **19**, 892.

(244) S. Bascop, J. Sapi, J. Laronze, J. Levy, *Heterocycles*, 1994, **38**, 725.

(245) G. Lakshmaiah, T. Kawabata, M. Shang, K. Fuji, *J. Org. Chem.*, 1999, **64**, 1699.

(246) S.E.V. Bell, R.F.C. Brown, F.W. Eastwood, J.M. Horvath, *Aust. J. Chem.*, 2000, **53**, 183.

(247) G. Palmisano, R. Annunziata, G. Papeo, M. Sisti, *Tetrahedron Asymmetry*, 1996, **7**, 1.

(248) G. Cravotto, G.B. Giovenzana, T. Pilati, M. Sisti, G. Palmisano, *J. Org. Chem.*, 2001, **66**, 8447.

(249) U.K.S. Kumar, H. Ika, H. Junjappa, *Org. Lett.*, 2001, **3**, 4193.

(250) K. Jones, J. Wilkinson, *J. Chem. Soc., Chem. Commun.*, 1992, 1767.

(251) J. Cossy, M. Cases, D.G. Pardo, *Tetrahedron Lett.*, 1998, **39**, 2331.

(252) D. Lizos, R. Tripoli, J.A. Murphy, *J. Chem. Soc., Chem. Commun.*, 2001, 2732.

(253) J. Shiue, J. Fang, *J. Chem. Soc., Chem Commun.*, 1993, 1277.

(254) C. Lin, J. Fang, *J. Chin. Chem. Soc. (Taipei)*, 1993, **40**, 571.

(255) M.G. Saulnier, G.W. Gribble, *J. Org. Chem.*, 1982, **47**, 757.

(256) G.W. Gribble, M.G. Saulnier, J.A. Obaza-Nutaitis, D.M. Ketcha, *J. Org. Chem.*, 1992, **57**, 5891.

(257) G.W. Gribble, T.C. Barden, D.A. Johnson, *Tetrahedron*, 1988, **44**, 3195.

(258) G.E. Wuenschell, C. Tetreau, D. Lavalette, C.A. Reed, *J. Am. Chem. Soc.*, 1992, **114**, 3346.

(259) D. Pelaprat, R. Oberlin, I. Le Guen, B.P. Roques, *J. Med. Chem.*, 1980, **23**, 1330.

(260) E. Desabre, J. Bergman, *J. Chem. Soc., Perkin Trans 1*, 1998, 2009.

(261) T. Fujisawa, T. Sato, *Org. Synth.*, 1987, **66**, 121.

(262) Z.L. Hichman, C.F. Sturino, N. Lachance, *Tetrahedron Lett.*, 2000, **41**, 8217.

(263) D.J. Kempf, S.L. Condon, *J. Org. Chem.*, 1990, **55**, 1390.

(264) G.W. Gribble, D.J. Keavy, D.A. Davis, M.G. Saulnier, B. Pelcman, T.C. Barden, M.P. Sibi, E.R. Olson, J.J. BelBruno, *J. Org. Chem.*, 1992, **57**, 5878.

(265) S. Kano, E. Sugino, S. Shibuya, S. Hibino, *J. Org. Chem.*, 1981, **46**, 2979.

(266) P. Zhang, R. Liu, J.M. Cook, *Tetrahedron Lett.*, 1995, **36**, 3103.

(267) R. Liu, P. Zhang, T. Gan, J.M. Cook, *J. Org. Chem.*, 1997, **62**, 7447.

(268) D.S. Grierson, M. Vuilhorgne, H. Husson, G. Lemoine, *J. Org. Chem.*, 1982, **47**, 4439.

(269) P.G. Steel, E.J. Thomas, *J. Chem. Soc., Perkin Trans 1*, 1997, 371.

(270) B. Ringdahl, D.J. Jenden, *J. Med. Chem.*, 1987, **30**, 852.

(271) T. Sakamoto, K. Ohsawa, *J. Chem. Soc., Perkin Trans 1*, 1999, 2323.

(272) B. A. Anderson, E. C. Bell, F. O. Ginah, N. K. Harn, L. M. Pagh, J. P. Wepsiec, *J. Org. Chem.*, 1998, **63**, 8224.

(273) H. Tokuyama, Y. Kaburagi, X. Chen, T. Fukuyama, *Synthesis*, 2000, **3**, 429.

(274) K. Takagi, T. Okamoto, Y. Sakakibara, A. Ohno, S. Oka, N. Hayama, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 3298.

(275) A. G. Mistry, K. Smith, M. R. Bye, *Tetrahedron Lett.*, 1986, **27**, 1051.

(276) Y. Kobayashi, T. Fujimoto, T. Fukuyama, *J. Am. Chem. Soc.*, 1999, **121**, 6501.

(277) R. Ikan, E. Rapaport, *Tetrahedron*, 1967, **23**, 3823.

(278) J. A. Sintas, A. A. Vitale, *J. Labelled Compd. Radiopharm.*, 1997, 677.

(279) Y. Tamura, M. Adachi, T. Kawasaki, H. Yasuda, Y. Kita, *J. Chem. Soc., Perkin Trans 1*, 1980, 1132.

(280) A. R. Katritzky, K. Akutagawa, R. A. Jones, *Synth. Commun.*, 1988, **18**, 1151.

(281) D. Nagarathnam, *J. Heterocyclic Chem.*, 1992, **29**, 953.

(282) D.M. Harrison, R.B. Sharma, *Tetrahedron*, 1993, **49**, 3165.

(283) W. C. Still, M. Khan and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

(284) A. R. Katritzky, *J. Chem. Soc.*, 1955, 2581.

(285) R. F. Chapman, N. I. J. Phillips, R. S. Ward, *Tetrahedron*, 1985, **41**, 5229.

(286) H. Tokuyama, Y. Kaburagi, X. Chen, T. Fukuyama, *Synthesis*, 2000, **3**, 429.

(287) Aldrich catalogue handbook of fine chemicals, 1999-2000.

(288) R. Bernstein, *Helv. Chim. Acta.*, 1930, **13**, 457.

(289) W. Meese, *Chem. Ber.*, 1977, **110**, 2463.

(290) R. J. Sundberg, J. D. Bloom, *J. Org. Chem.*, 1980, **45**, 3382.

(291) Yoshida, *J. Am. Chem. Soc.*, 1979, **101**, 2116.

Supplementary Information

Contents

X-Ray Structure of 360a

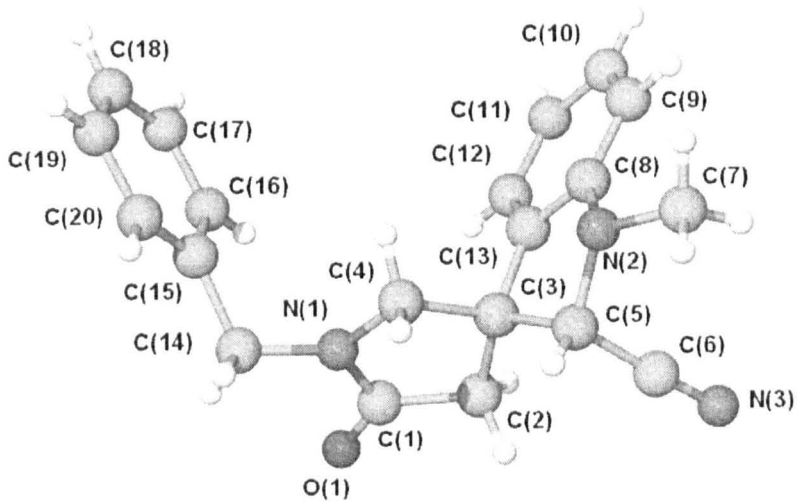


Table 1. Crystal data and structure refinement for shspiro2.

Identification code	shspiro2	
Empirical formula	C20 H19 N3 O	
Formula weight	317.38	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 12.9093(6) Å	α= 90°.
	b = 5.9168(2) Å	β= 97.624(2)°.
	c = 21.8865(9) Å	γ = 90°.
Volume	1656.95(12) $Å^3$	
Z	4	
Density (calculated)	1.272 Mg/m^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	672	
Crystal size	0.50 x 0.40 x 0.35 mm^3	
Theta range for data collection	3.18 to 27.49°.	
Index ranges	-15<=h<=16, -7<=k<=7, -24<=l<=28	
Reflections collected	7227	
Independent reflections	3120 [R(int) = 0.0416]	
Completeness to theta = 27.49°	81.8 %	
Absorption correction	Scalepack	
Max. and min. transmission	0.9724 and 0.9609	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3120 / 0 / 219	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0459, wR2 = 0.0930	
R indices (all data)	R1 = 0.0782, wR2 = 0.1047	
Extinction coefficient	0.015(2)	
Largest diff. peak and hole	0.180 and -0.214 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for shspiro2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1826(1)	8664(2)	1839(1)	39(1)
N(1)	952(1)	5306(2)	1889(1)	24(1)
C(1)	1403(1)	7222(3)	2130(1)	25(1)
N(2)	-126(1)	2898(2)	3607(1)	24(1)
C(2)	1334(1)	7264(3)	2809(1)	25(1)
N(3)	1567(1)	6529(3)	4451(1)	45(1)
C(3)	583(1)	5347(2)	2922(1)	21(1)
C(4)	564(1)	3837(2)	2340(1)	23(1)
C(5)	874(1)	3908(2)	3510(1)	23(1)
C(6)	1284(1)	5393(3)	4038(1)	28(1)
C(7)	-179(2)	1603(3)	4171(1)	36(1)
C(8)	-883(1)	4587(2)	3432(1)	22(1)
C(9)	-1859(1)	4865(3)	3614(1)	30(1)
C(10)	-2457(1)	6709(3)	3378(1)	33(1)
C(11)	-2095(1)	8209(3)	2974(1)	31(1)
C(12)	-1111(1)	7902(3)	2791(1)	25(1)
C(13)	-507(1)	6091(2)	3022(1)	21(1)
C(14)	1011(1)	4526(3)	1262(1)	30(1)
C(15)	-51(1)	4120(3)	894(1)	24(1)
C(16)	-785(1)	5825(3)	809(1)	31(1)
C(17)	-1733(1)	5476(3)	441(1)	34(1)
C(18)	-1956(1)	3415(3)	162(1)	32(1)
C(19)	-1239(1)	1712(3)	250(1)	36(1)
C(20)	-289(1)	2057(3)	616(1)	32(1)

Table 3. Bond lengths [Å] and angles [°] for shspiro2.

O(1)-C(1)	1.2347(19)
N(1)-C(1)	1.3492(19)
N(1)-C(4)	1.454(2)
N(1)-C(14)	1.458(2)
C(1)-C(2)	1.501(2)
N(2)-C(8)	1.4149(19)
N(2)-C(7)	1.463(2)
N(2)-C(5)	1.463(2)
C(2)-C(3)	1.533(2)
N(3)-C(6)	1.146(2)
C(3)-C(13)	1.517(2)
C(3)-C(5)	1.549(2)
C(3)-C(4)	1.553(2)
C(5)-C(6)	1.492(2)
C(8)-C(9)	1.381(2)
C(8)-C(13)	1.395(2)
C(9)-C(10)	1.395(2)
C(10)-C(11)	1.377(2)
C(11)-C(12)	1.394(2)
C(12)-C(13)	1.381(2)
C(14)-C(15)	1.515(2)
C(15)-C(20)	1.379(2)
C(15)-C(16)	1.380(2)
C(16)-C(17)	1.387(2)
C(17)-C(18)	1.378(2)
C(18)-C(19)	1.364(2)
C(19)-C(20)	1.388(2)
C(1)-N(1)-C(4)	113.99(13)
C(1)-N(1)-C(14)	124.06(14)
C(4)-N(1)-C(14)	120.99(12)
O(1)-C(1)-N(1)	125.20(16)
O(1)-C(1)-C(2)	126.01(14)
N(1)-C(1)-C(2)	108.77(14)
C(8)-N(2)-C(7)	119.39(14)
C(8)-N(2)-C(5)	105.29(12)

C(7)-N(2)-C(5)	118.46(12)
C(1)-C(2)-C(3)	105.64(12)
C(13)-C(3)-C(2)	115.28(12)
C(13)-C(3)-C(5)	99.53(13)
C(2)-C(3)-C(5)	116.89(12)
C(13)-C(3)-C(4)	111.84(12)
C(2)-C(3)-C(4)	103.57(13)
C(5)-C(3)-C(4)	109.98(12)
N(1)-C(4)-C(3)	104.10(12)
N(2)-C(5)-C(6)	111.01(14)
N(2)-C(5)-C(3)	102.90(11)
C(6)-C(5)-C(3)	110.05(12)
N(3)-C(6)-C(5)	177.69(19)
C(9)-C(8)-C(13)	121.27(14)
C(9)-C(8)-N(2)	129.04(15)
C(13)-C(8)-N(2)	109.69(14)
C(8)-C(9)-C(10)	117.79(16)
C(11)-C(10)-C(9)	121.62(17)
C(10)-C(11)-C(12)	120.00(15)
C(13)-C(12)-C(11)	119.18(16)
C(12)-C(13)-C(8)	120.14(16)
C(12)-C(13)-C(3)	131.35(15)
C(8)-C(13)-C(3)	108.50(13)
N(1)-C(14)-C(15)	113.24(14)
C(20)-C(15)-C(16)	118.58(15)
C(20)-C(15)-C(14)	120.52(14)
C(16)-C(15)-C(14)	120.85(14)
C(15)-C(16)-C(17)	120.44(15)
C(18)-C(17)-C(16)	120.34(16)
C(19)-C(18)-C(17)	119.56(15)
C(18)-C(19)-C(20)	120.23(15)
C(15)-C(20)-C(19)	120.83(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for shspiro2. The anisotropic

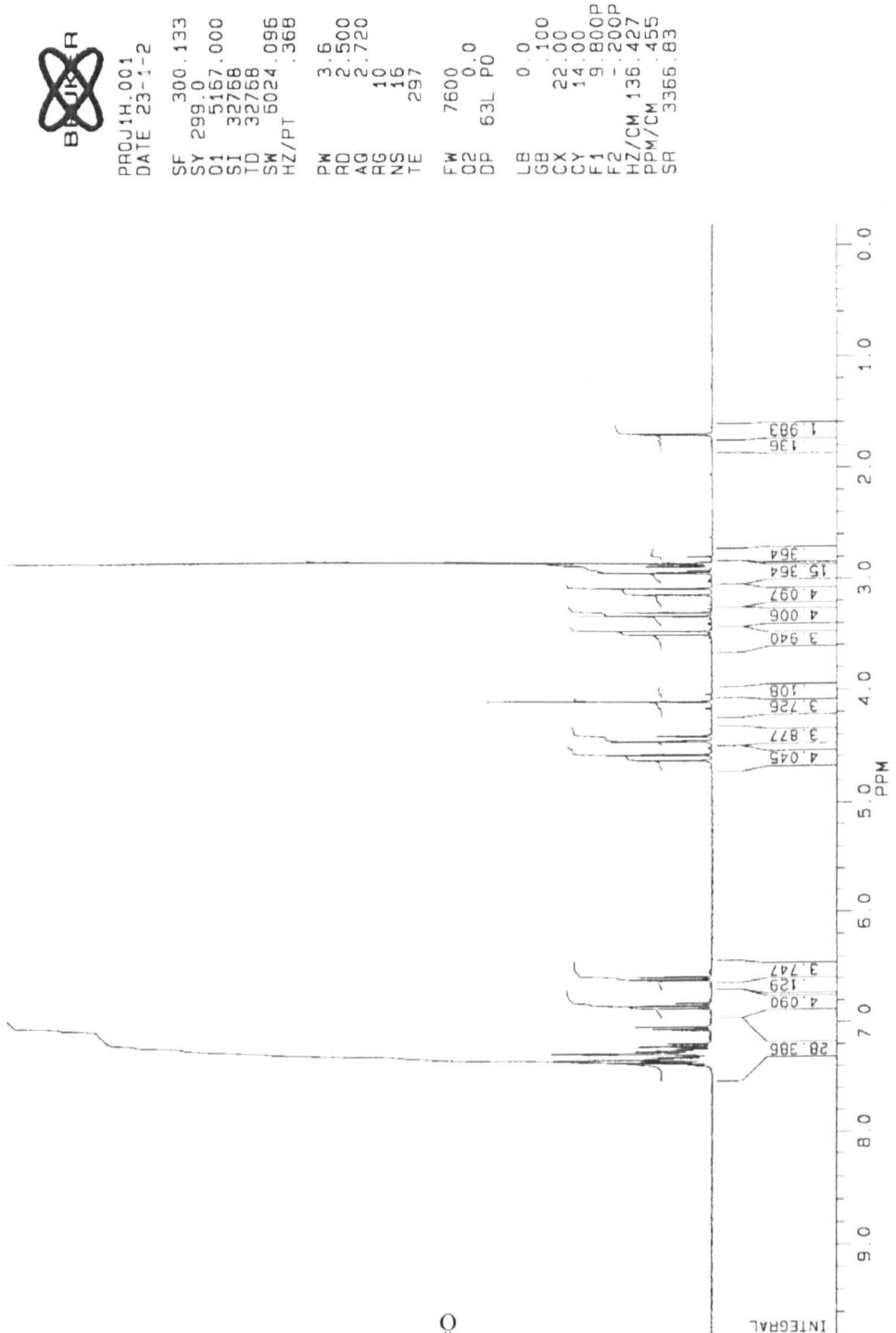
displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

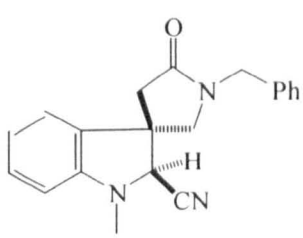
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	36(1)	37(1)	45(1)	10(1)	12(1)	-10(1)
N(1)	24(1)	28(1)	21(1)	3(1)	4(1)	-3(1)
C(1)	16(1)	26(1)	32(1)	4(1)	3(1)	0(1)
N(2)	25(1)	24(1)	24(1)	7(1)	2(1)	0(1)
C(2)	21(1)	23(1)	31(1)	-1(1)	0(1)	-1(1)
N(3)	46(1)	46(1)	39(1)	-8(1)	-11(1)	2(1)
C(3)	20(1)	19(1)	22(1)	-1(1)	2(1)	-1(1)
C(4)	24(1)	22(1)	23(1)	0(1)	5(1)	-2(1)
C(5)	23(1)	22(1)	24(1)	0(1)	1(1)	3(1)
C(6)	27(1)	29(1)	27(1)	3(1)	-4(1)	5(1)
C(7)	41(1)	34(1)	33(1)	11(1)	6(1)	2(1)
C(8)	23(1)	24(1)	20(1)	0(1)	1(1)	1(1)
C(9)	27(1)	42(1)	23(1)	4(1)	7(1)	0(1)
C(10)	23(1)	50(1)	27(1)	-5(1)	4(1)	8(1)
C(11)	27(1)	32(1)	31(1)	-2(1)	-3(1)	8(1)
C(12)	25(1)	24(1)	25(1)	0(1)	-1(1)	1(1)
C(13)	21(1)	21(1)	18(1)	-3(1)	0(1)	-1(1)
C(14)	29(1)	40(1)	23(1)	2(1)	7(1)	1(1)
C(15)	27(1)	28(1)	18(1)	2(1)	7(1)	1(1)
C(16)	38(1)	23(1)	29(1)	-3(1)	-1(1)	2(1)
C(17)	35(1)	36(1)	30(1)	2(1)	-1(1)	10(1)
C(18)	32(1)	43(1)	21(1)	-4(1)	3(1)	-3(1)
C(19)	40(1)	32(1)	36(1)	-11(1)	8(1)	-3(1)
C(20)	35(1)	28(1)	35(1)	-2(1)	9(1)	7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)
for shspiro2.

	x	y	z	U(eq)
H(2A)	1060	8737	2931	30
H(2B)	2030	7011	3048	30
H(4A)	1022	2501	2427	27
H(4B)	-155	3318	2192	27
H(5)	1394	2714	3441	28
H(7A)	-132	2635	4523	54
H(7B)	403	526	4231	54
H(7C)	-842	778	4136	54
H(9)	-2115	3836	3892	36
H(10)	-3130	6935	3498	40
H(11)	-2517	9453	2820	37
H(12)	-858	8925	2510	30
H(14A)	1418	3103	1281	36
H(14B)	1391	5665	1046	36
H(16)	-641	7247	1003	37
H(17)	-2231	6665	382	41
H(18)	-2605	3180	-90	38
H(19)	-1391	284	61	43
H(20)	204	858	676	38

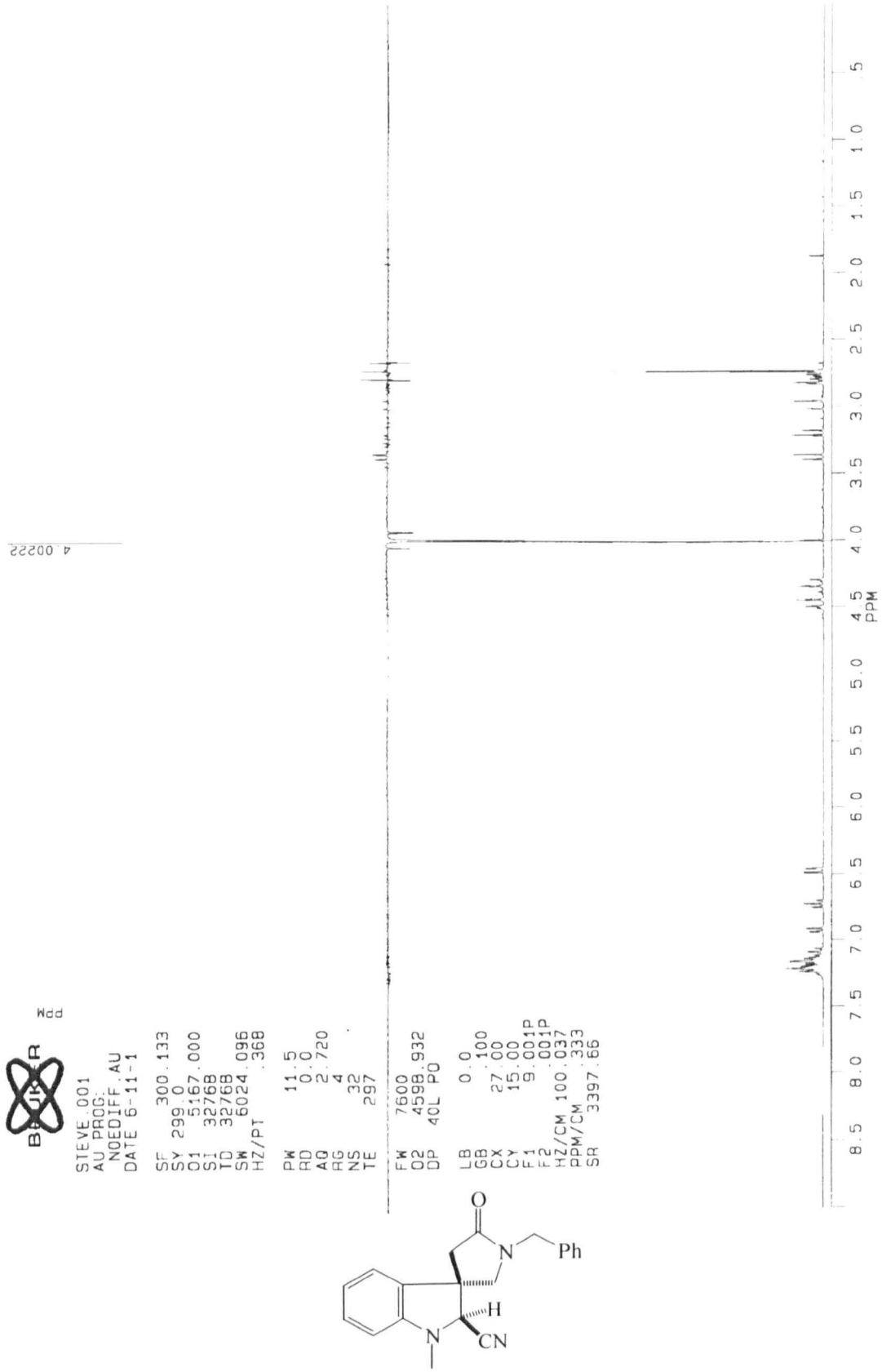
^{1}H NMR spectrum of **360a**





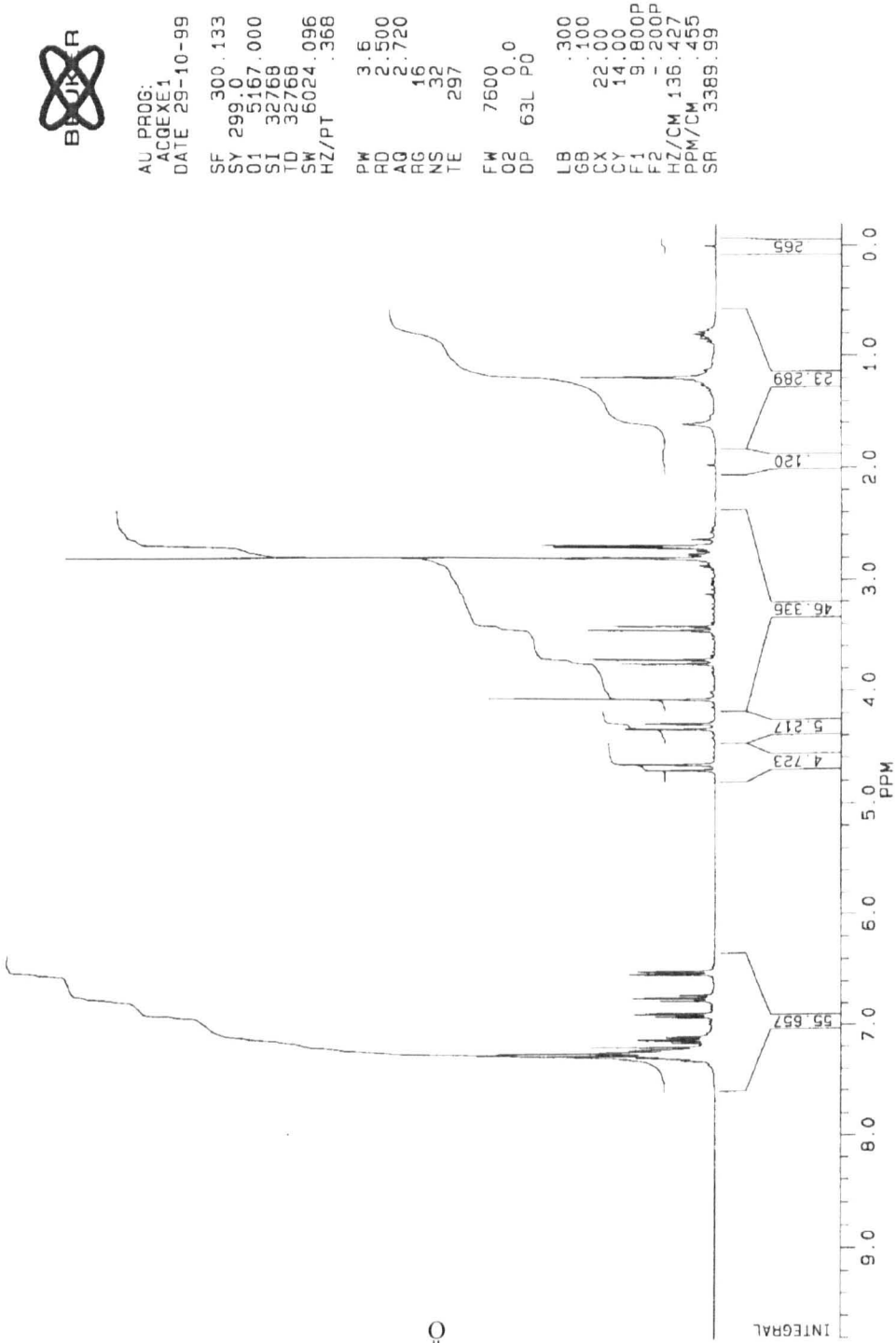
(360a)

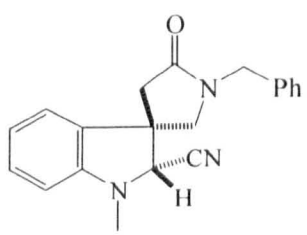
nOe difference spectrum of **360a**



(360a)

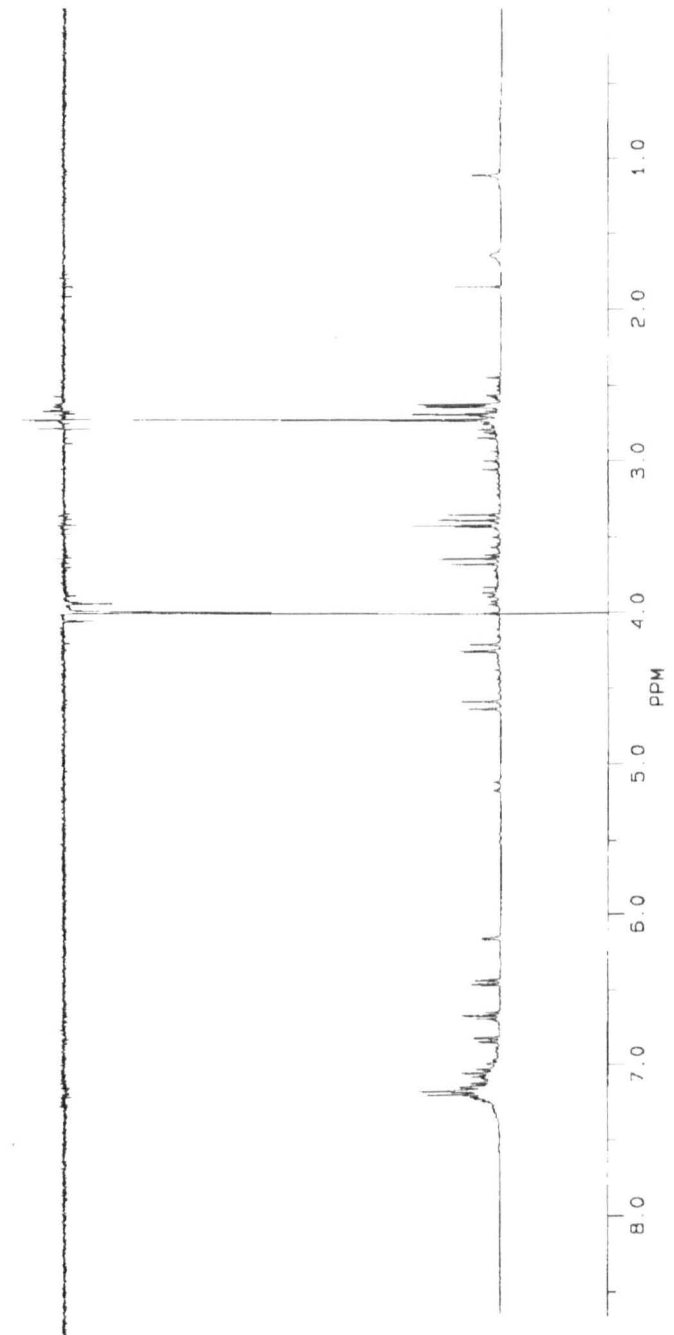
^{1}H NMR spectrum of **360b**

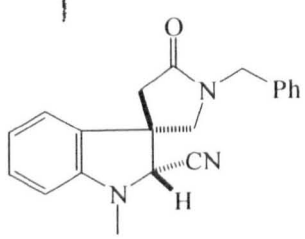




(360b)

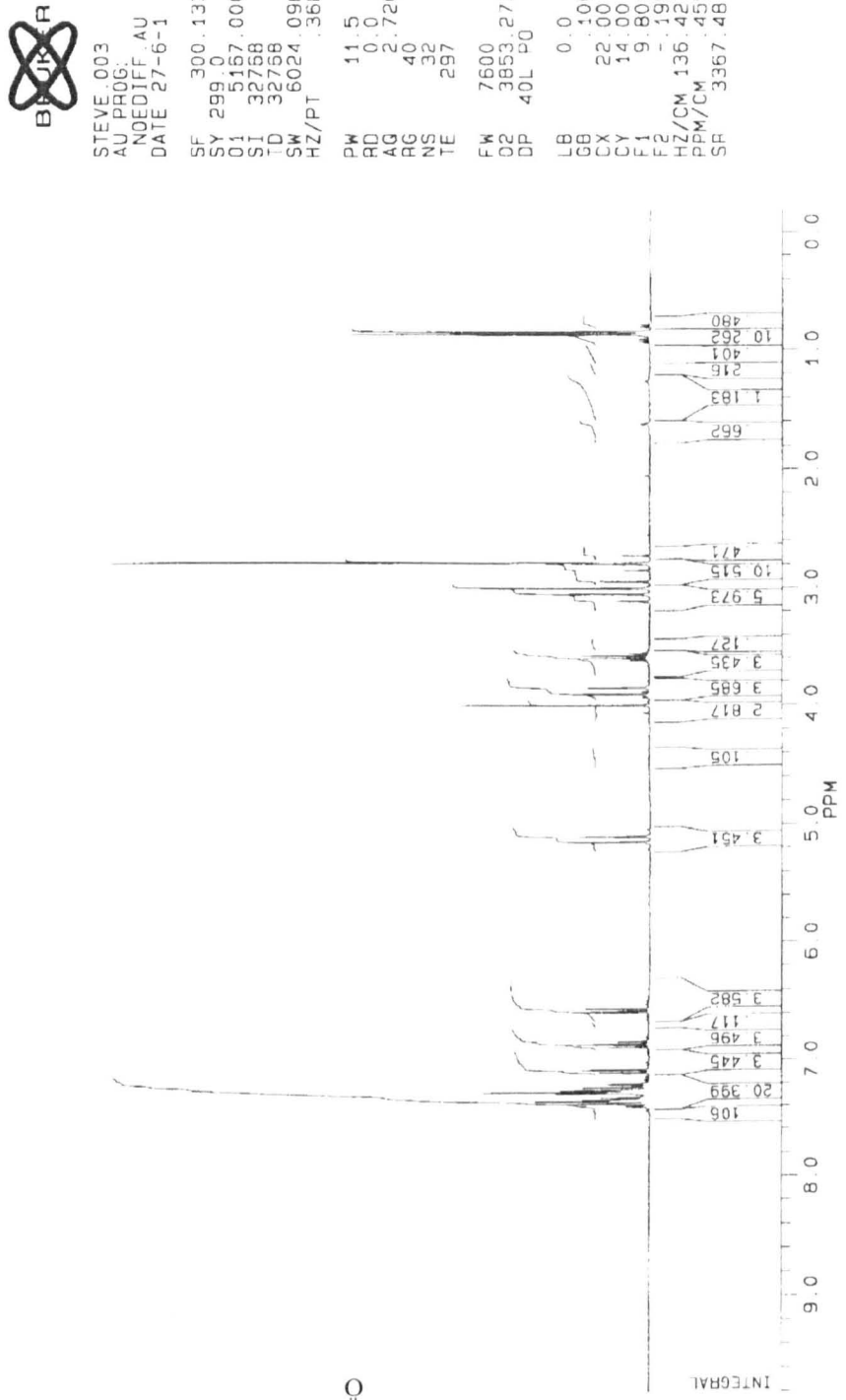
nOe difference spectrum of **360b**

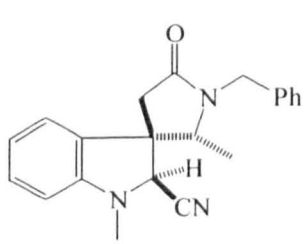




(360b)

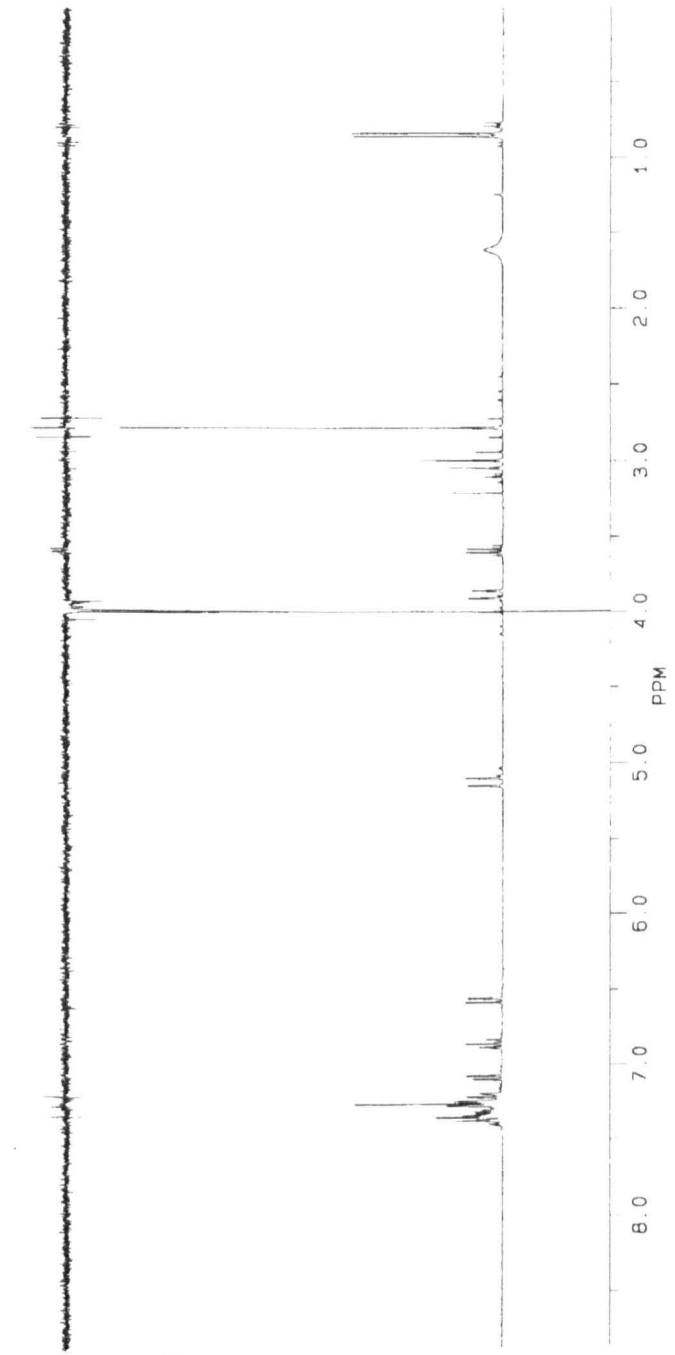
^{1}H NMR spectrum of **363a**

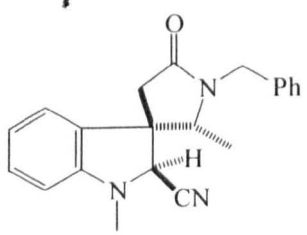




(363a)

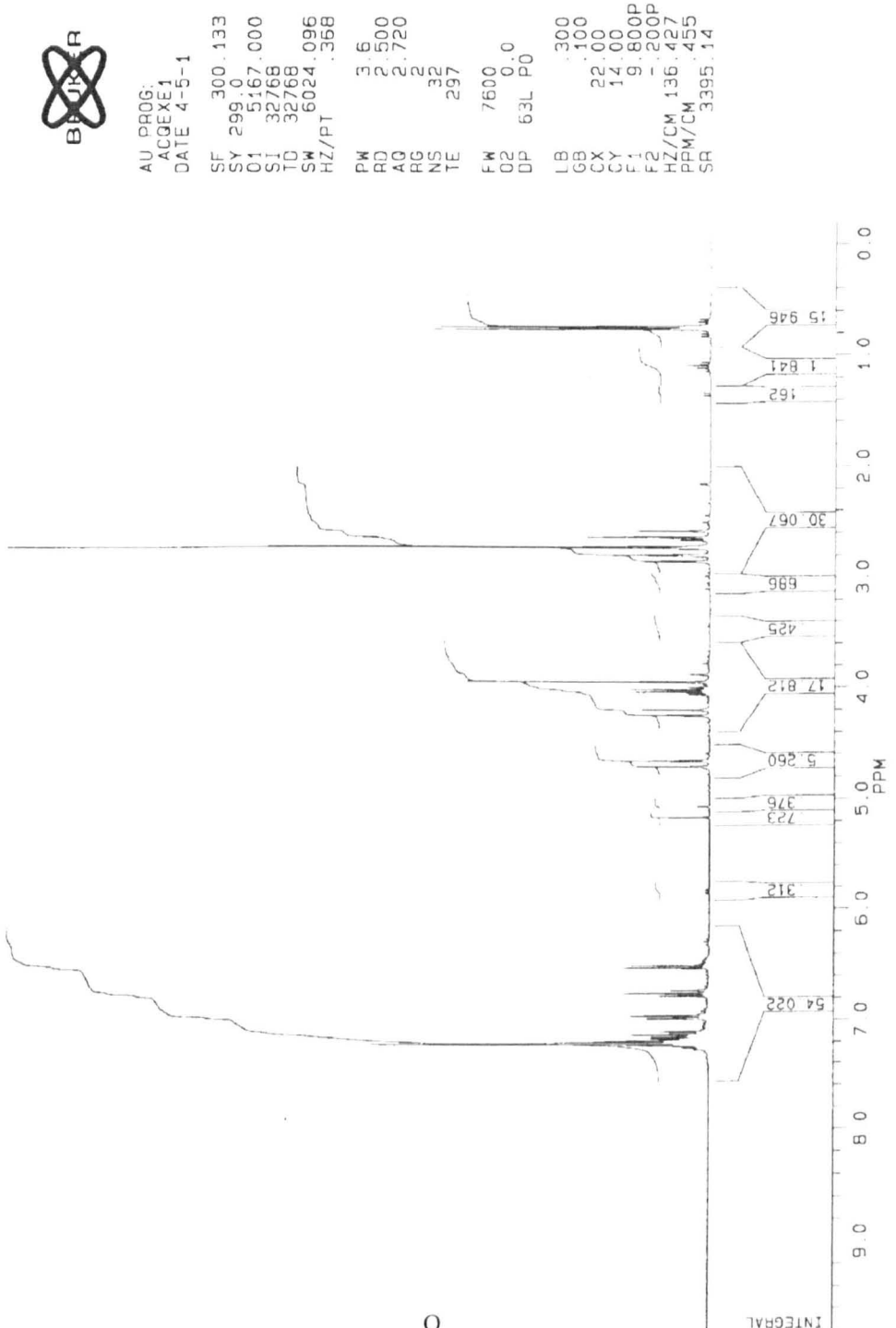
nOe difference spectrum of **363a**

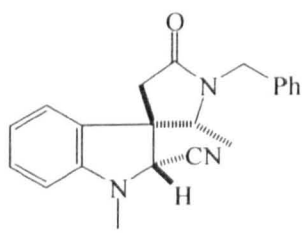




(363a)

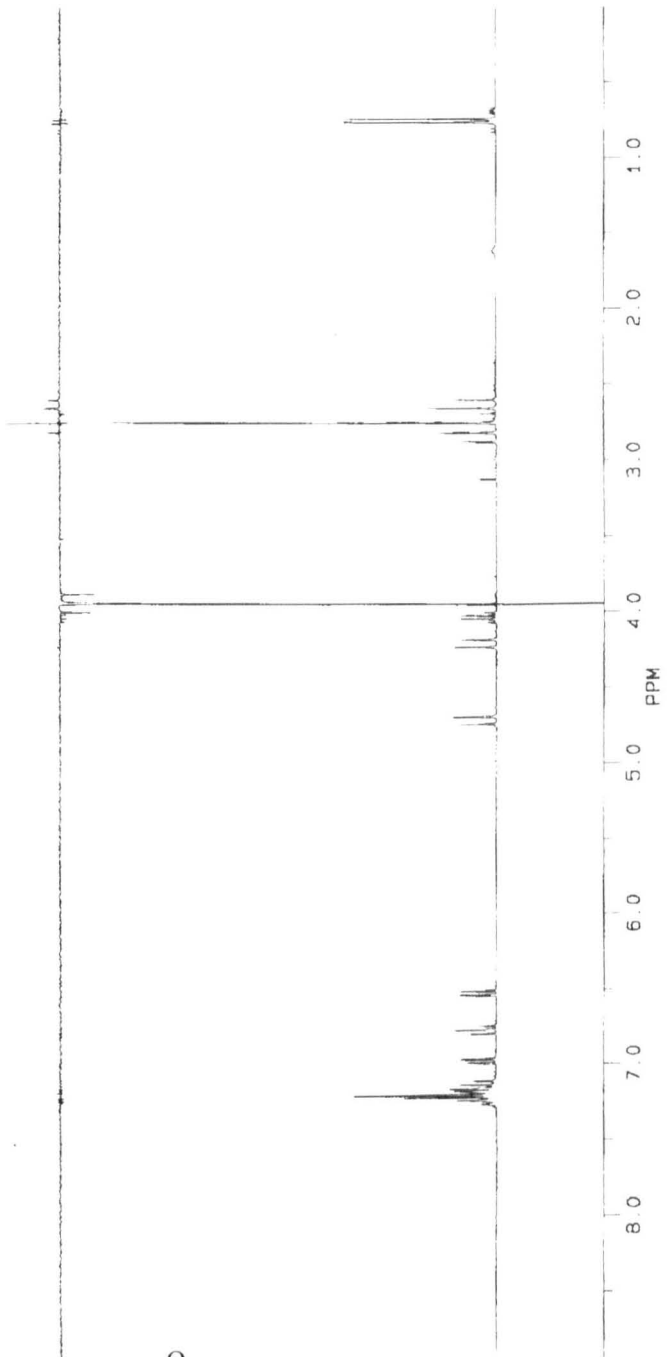
^{1}H NMR spectrum of **363b**

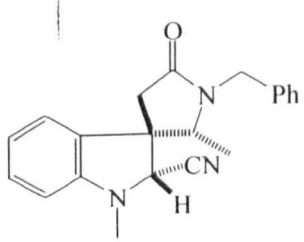




(363b)

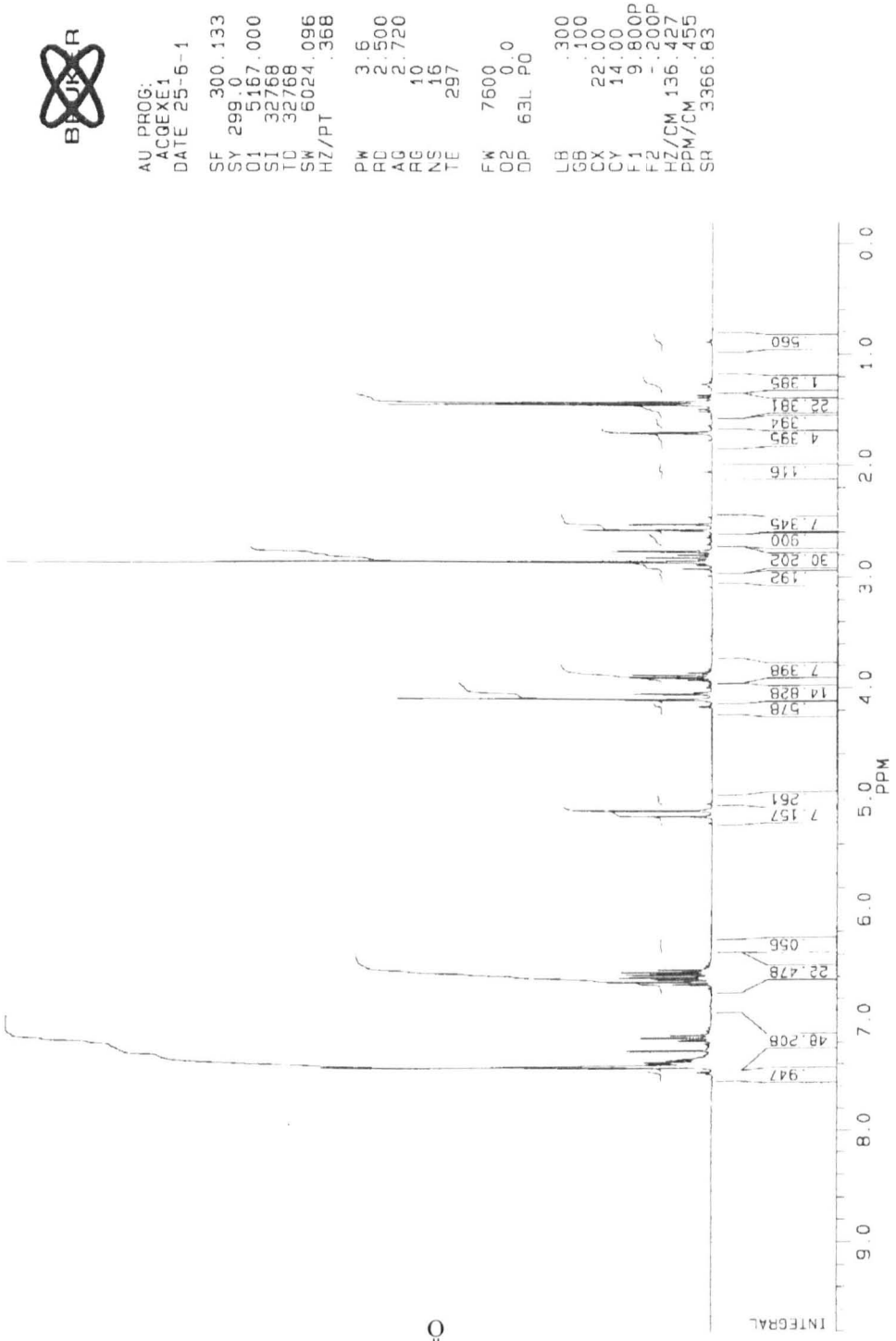
nOe difference spectrum of **363b**





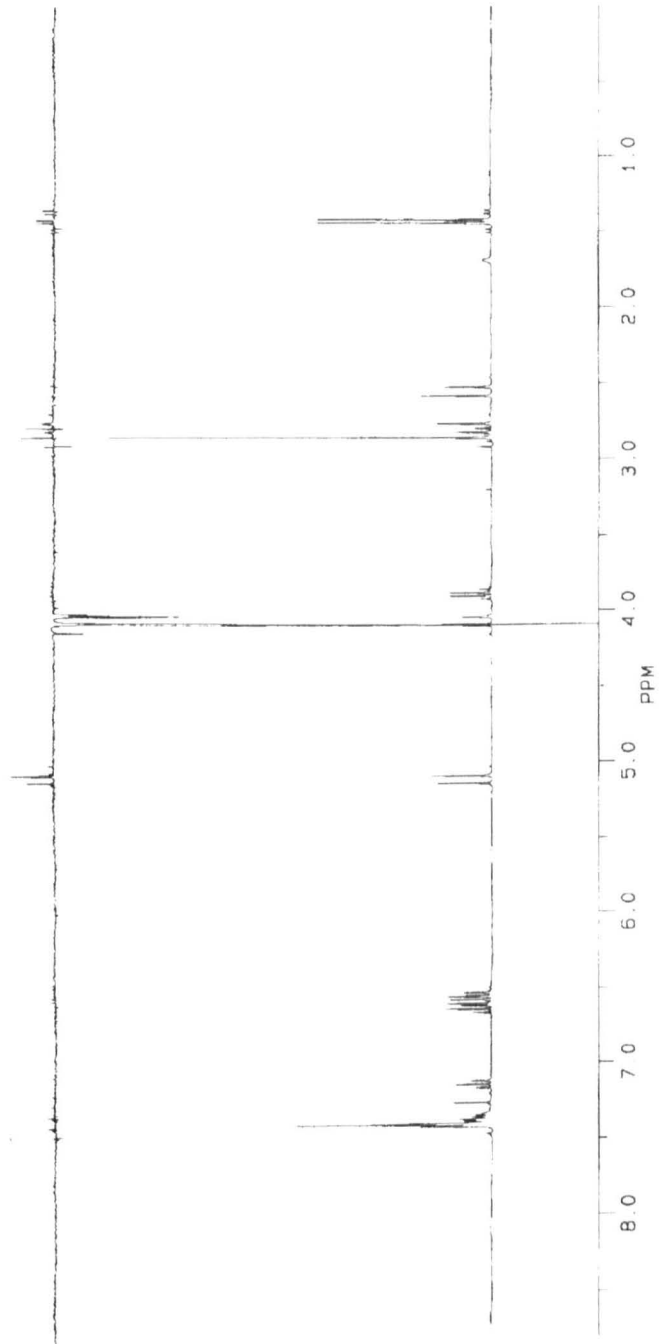
(363b)

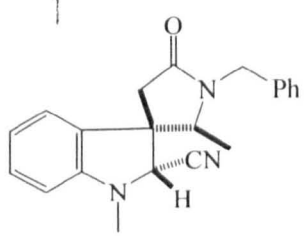
^{1}H NMR spectrum of **363d**



(363d)

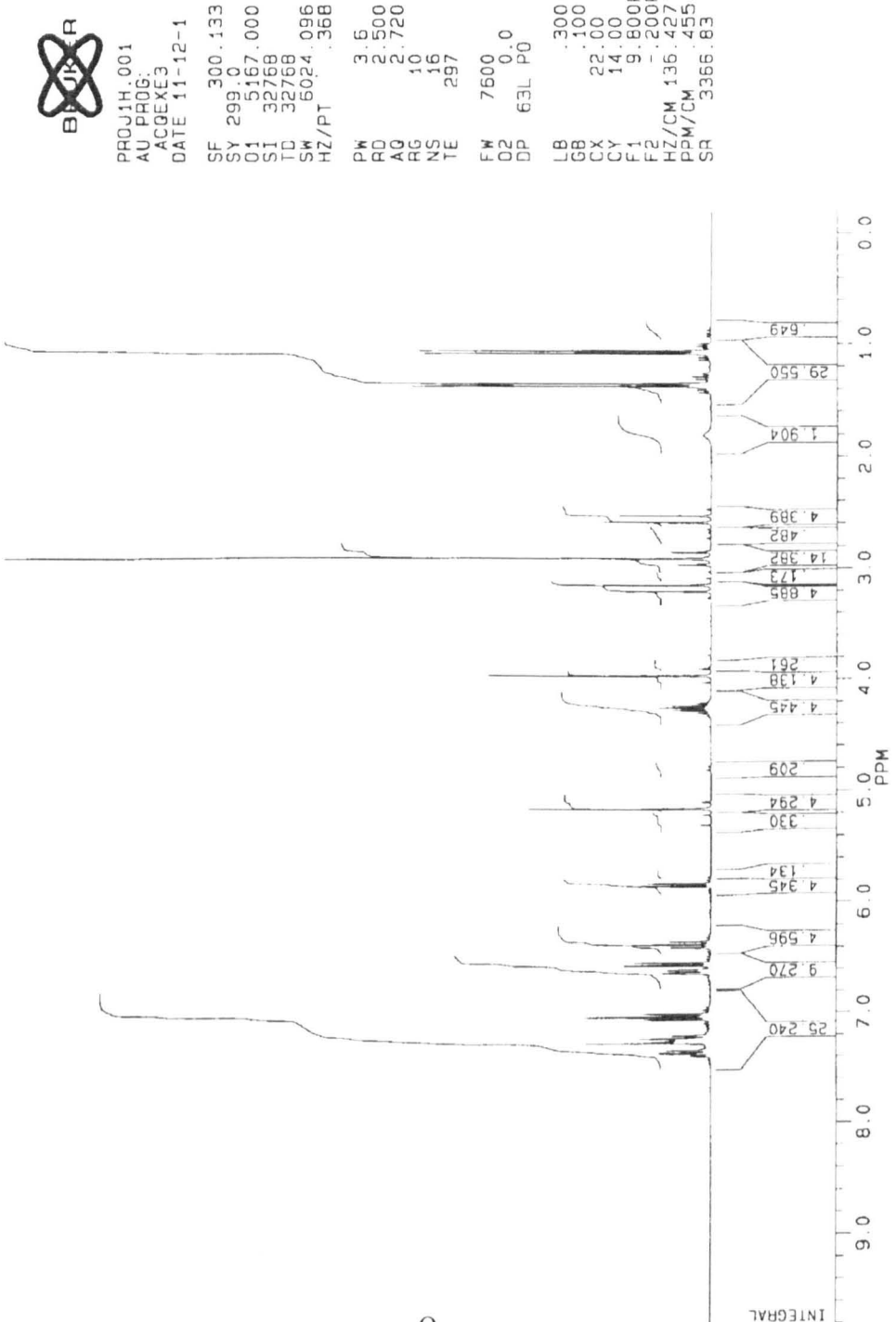
nOe difference spectrum of **363d**

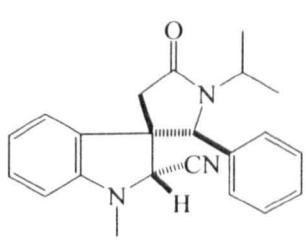




(363d)

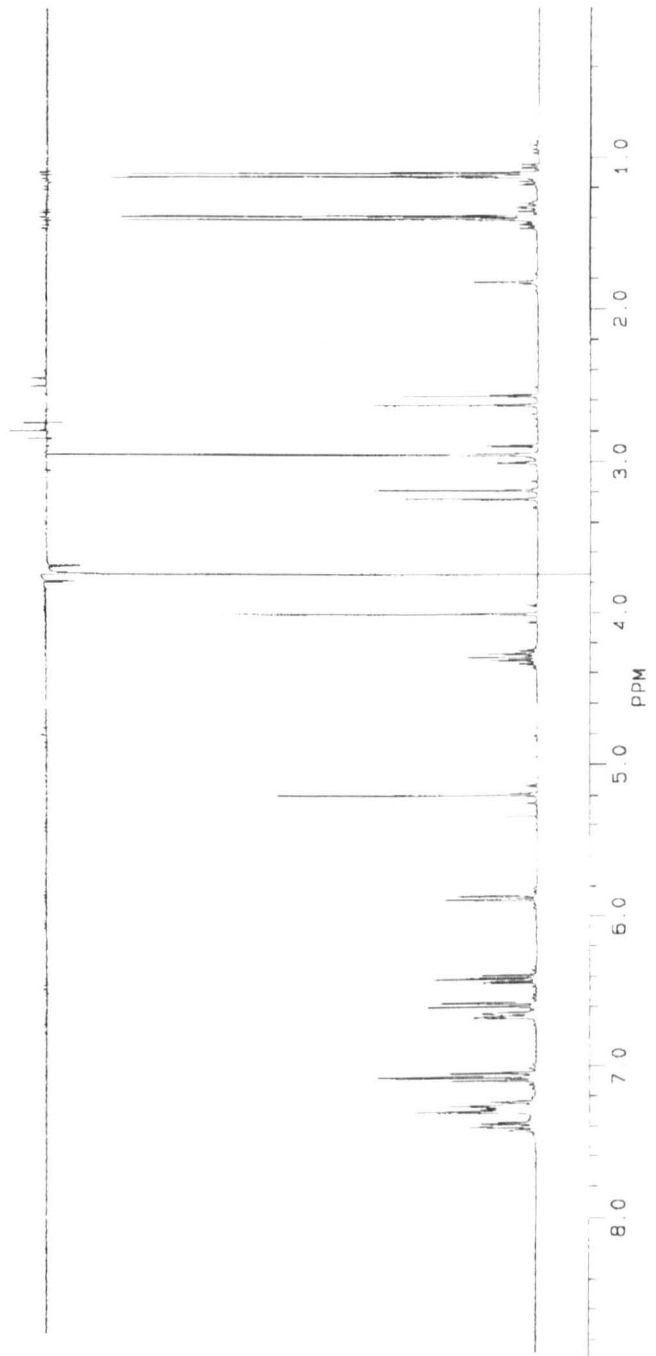
^{1}H NMR spectrum of **365**

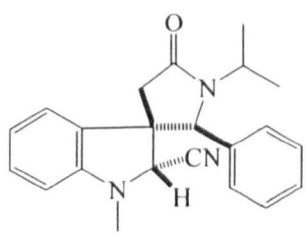




(365)

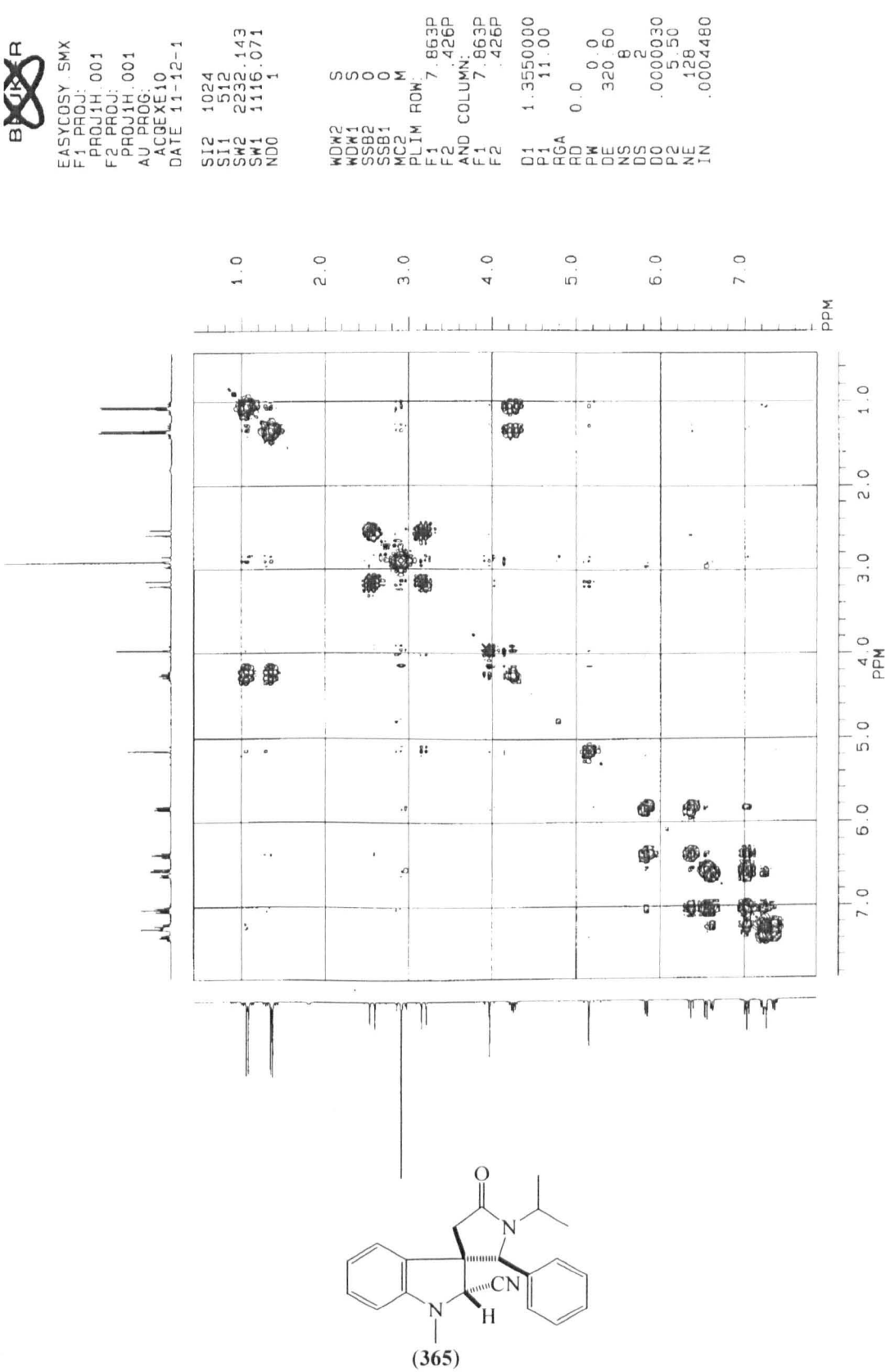
nOe difference spectrum of **365**





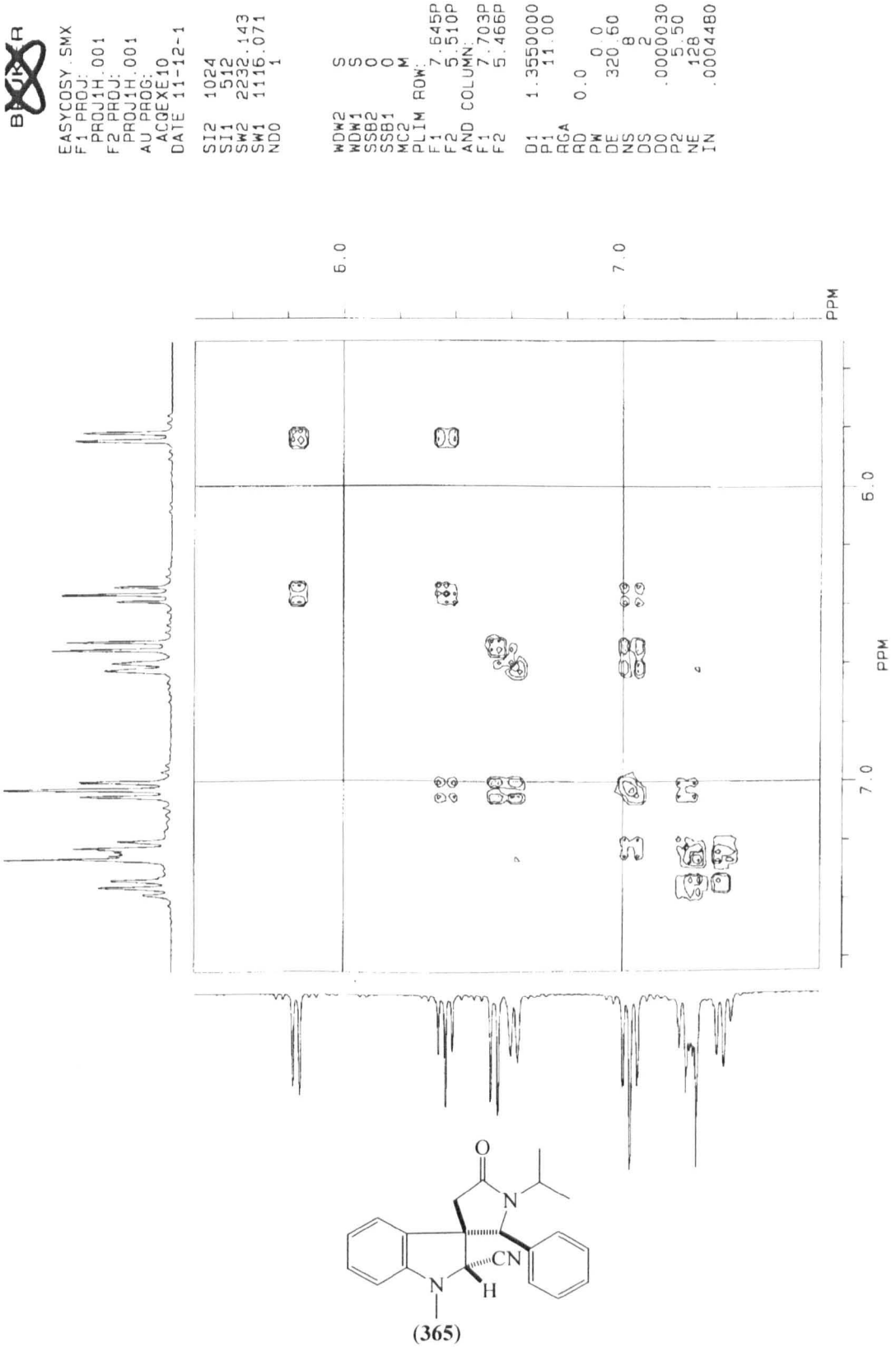
(365)

^{1}H COSY spectrum of **365**



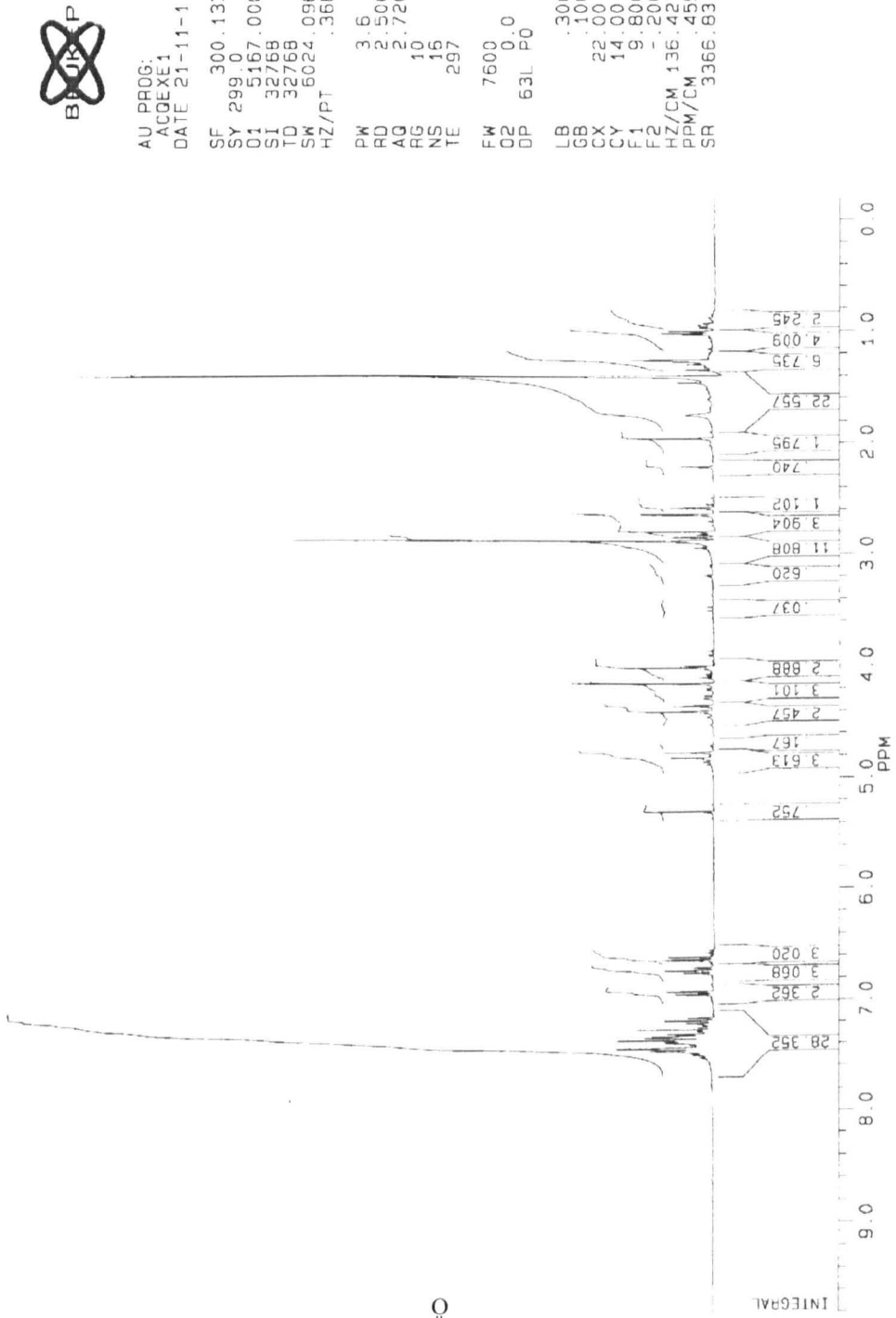
(365)

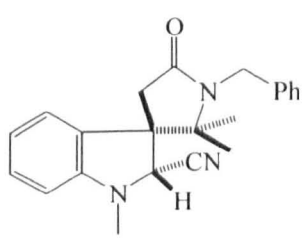
Expanded ^{1}H COSY spectrum of **365**



(365)

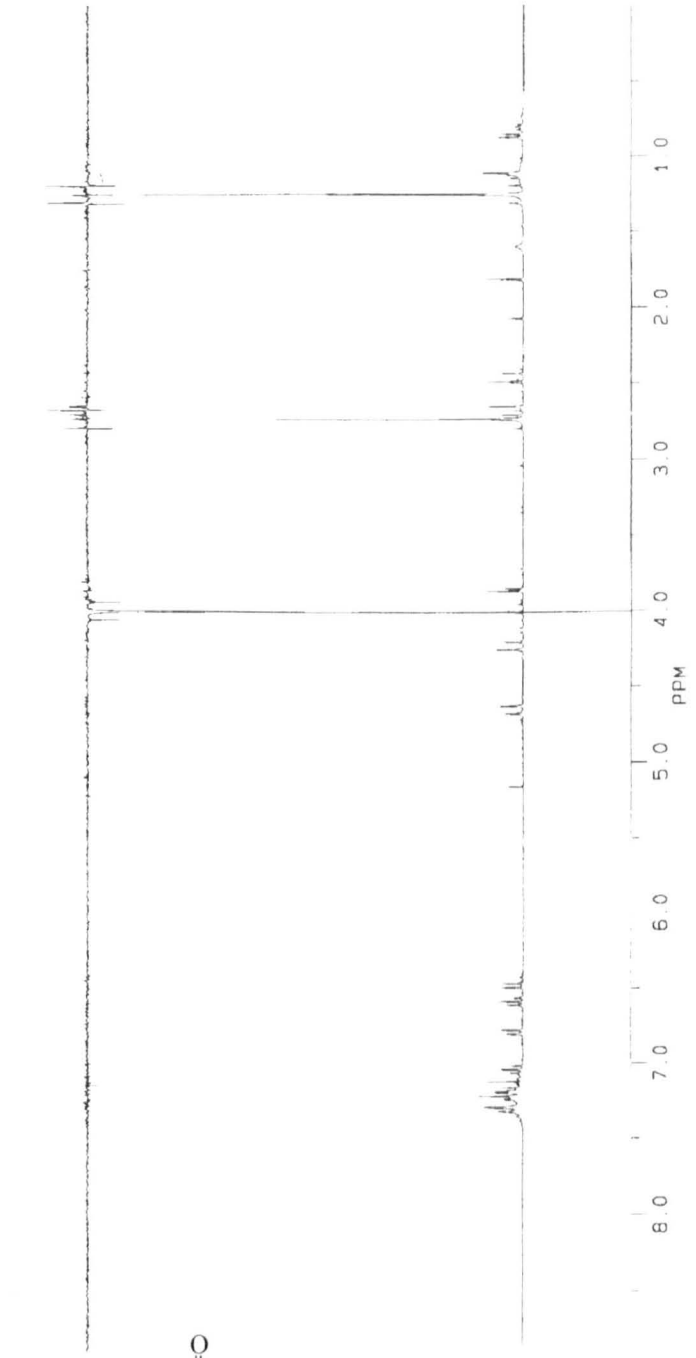
^{1}H NMR spectrum of **366**

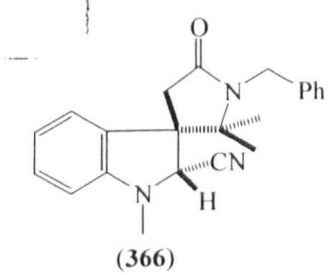




(366)

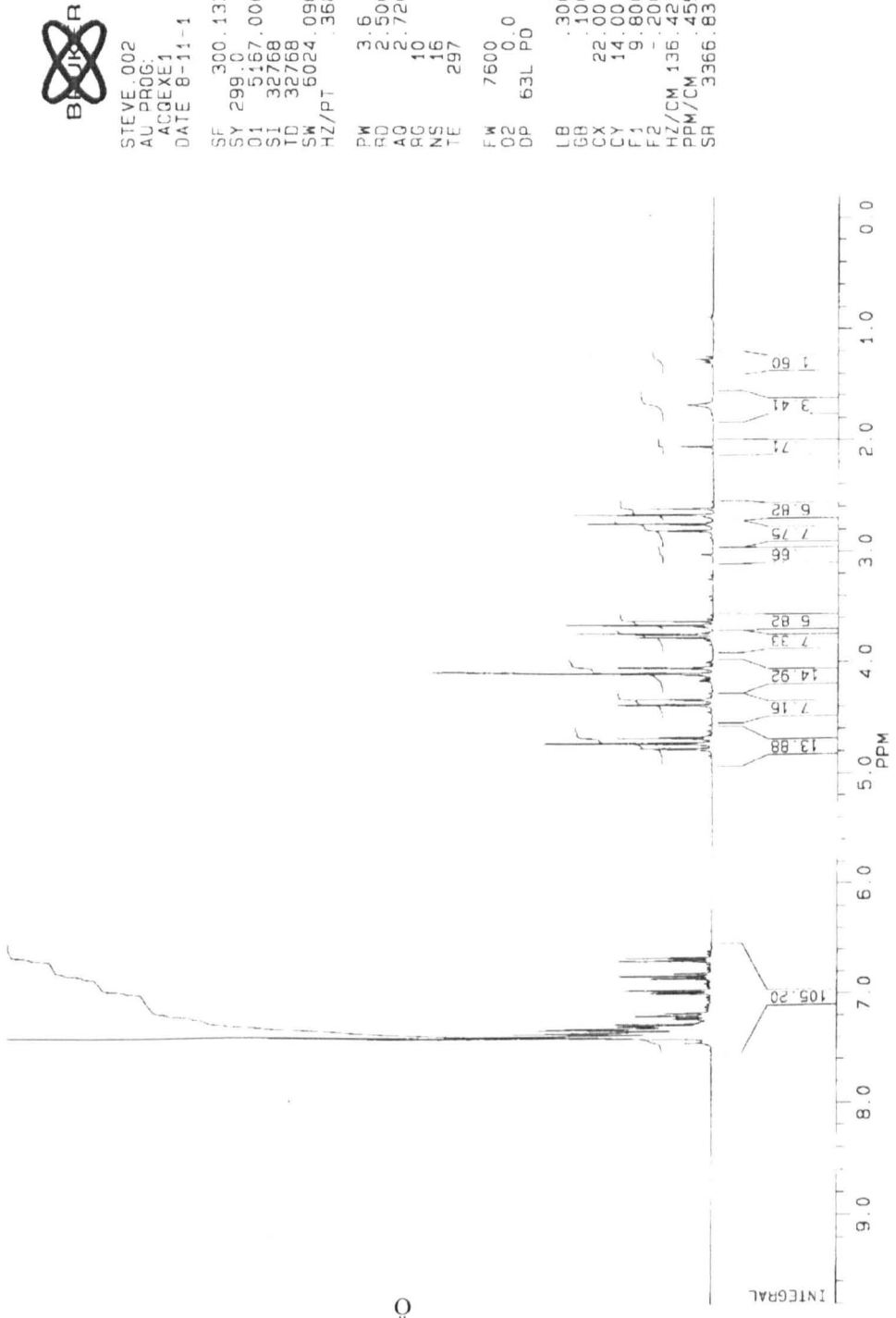
nOe difference spectrum of **366**

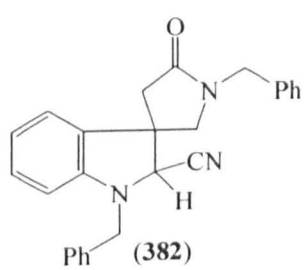




(366)

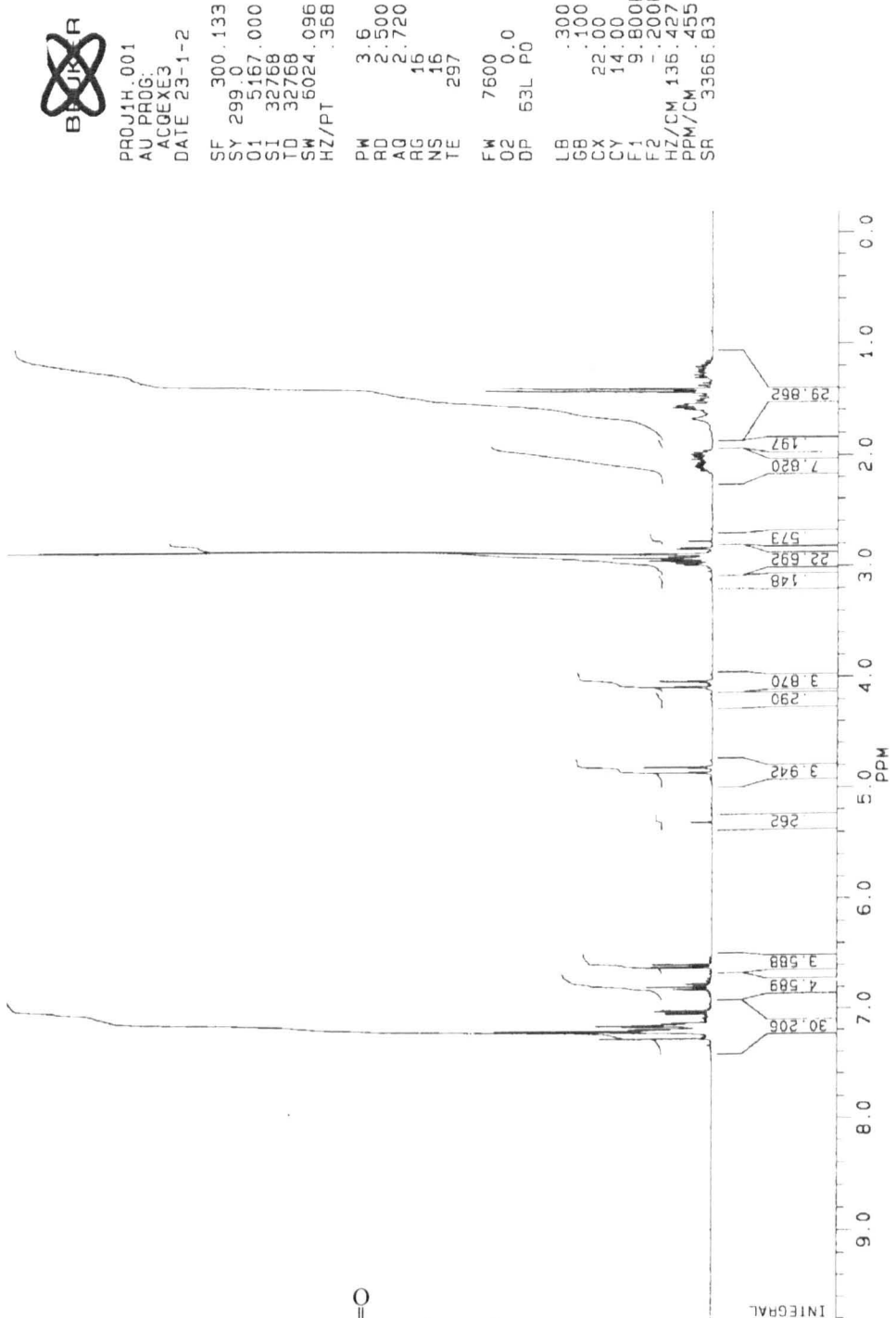
^{1}H NMR spectrum of **382**

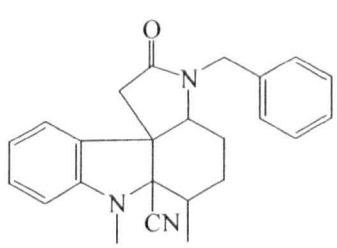




(382)

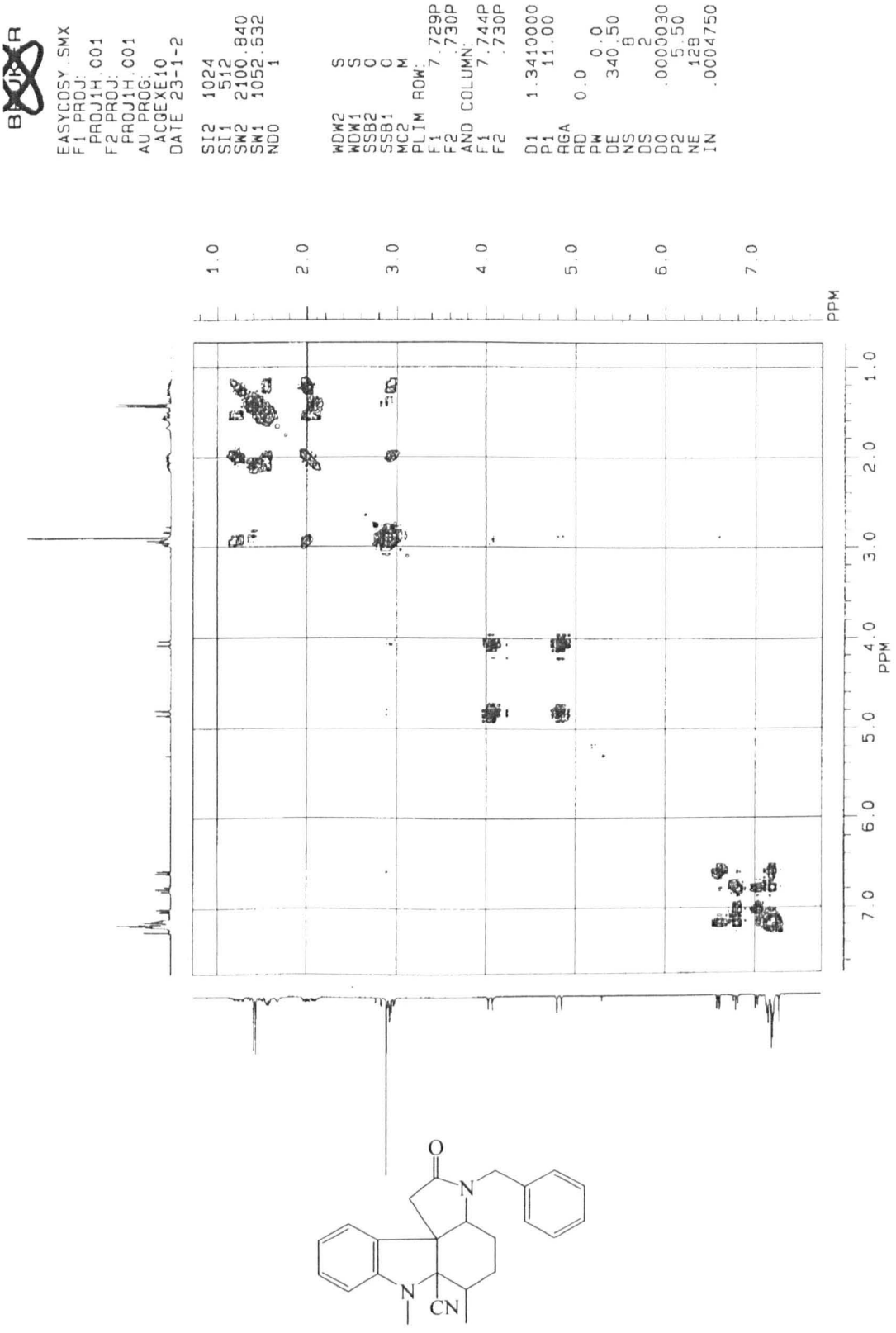
^{1}H NMR spectrum of **388**





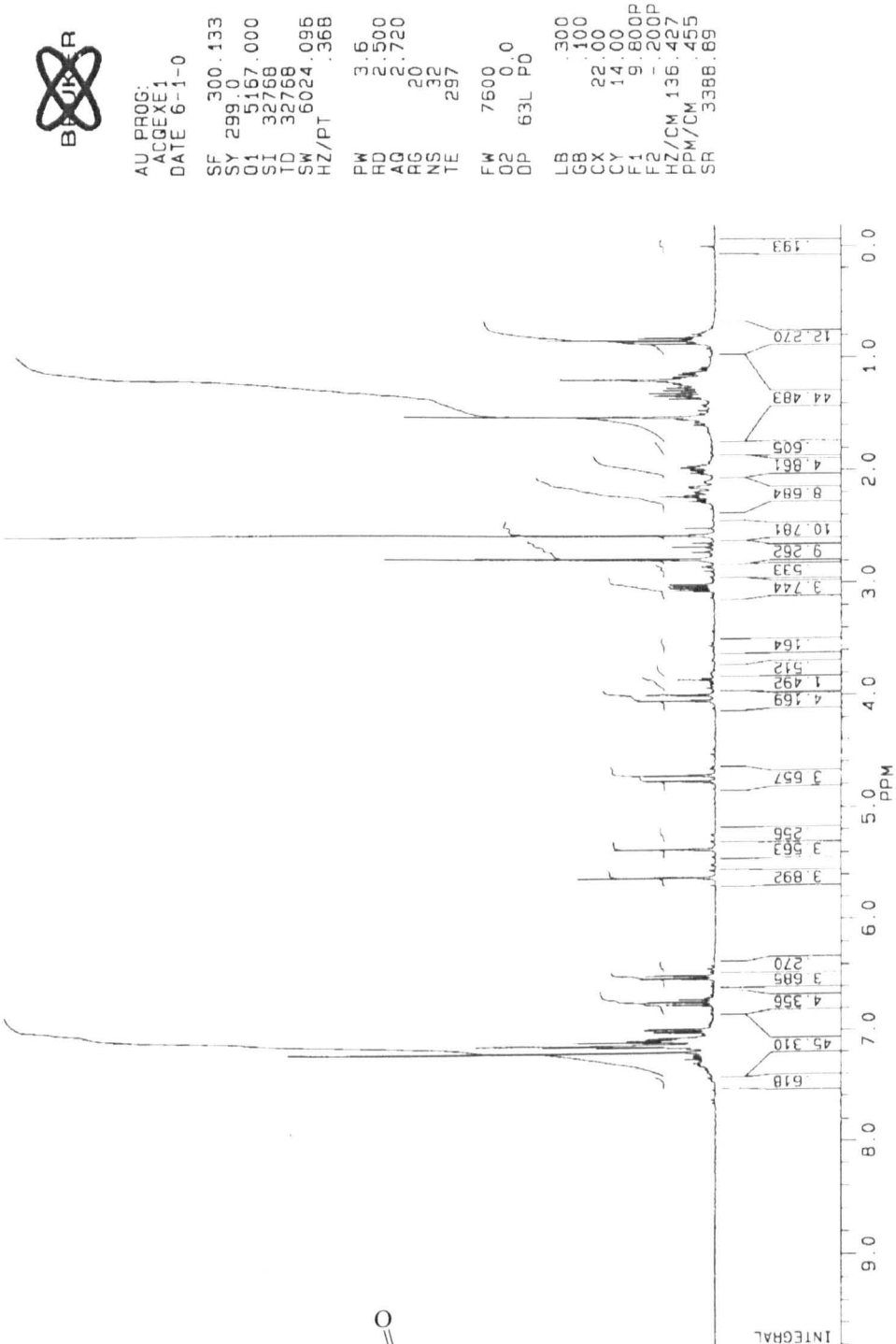
(388)

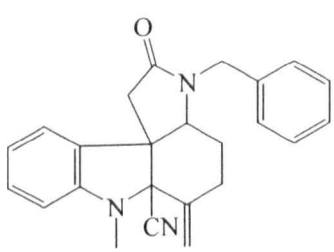
^{1}H COSY spectrum of **388**



(388)

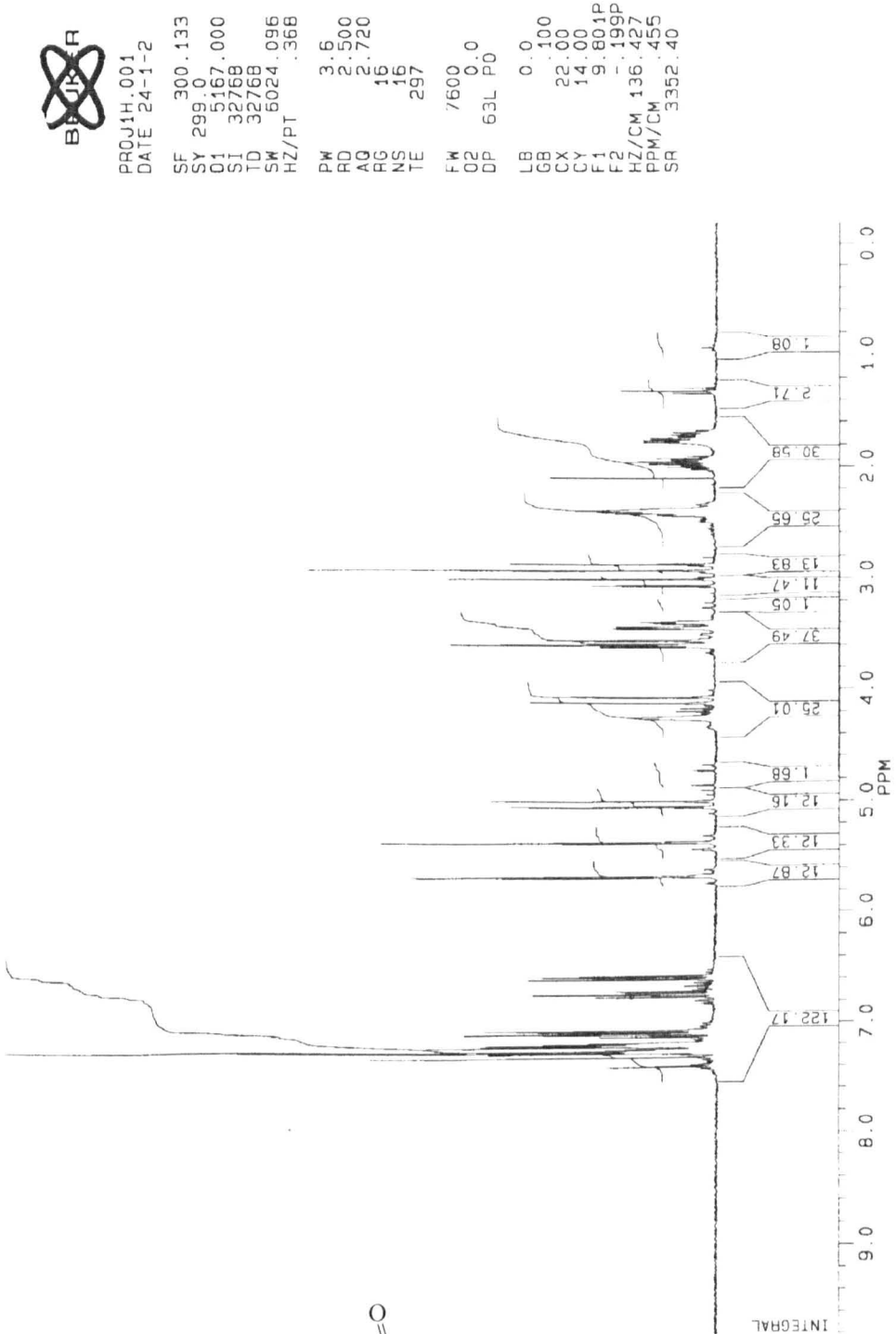
^{1}H NMR spectrum of **391**

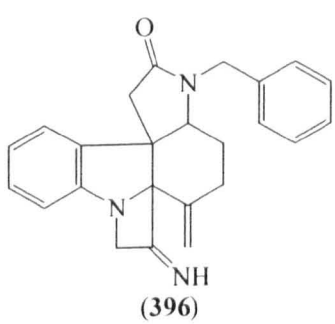




(391)

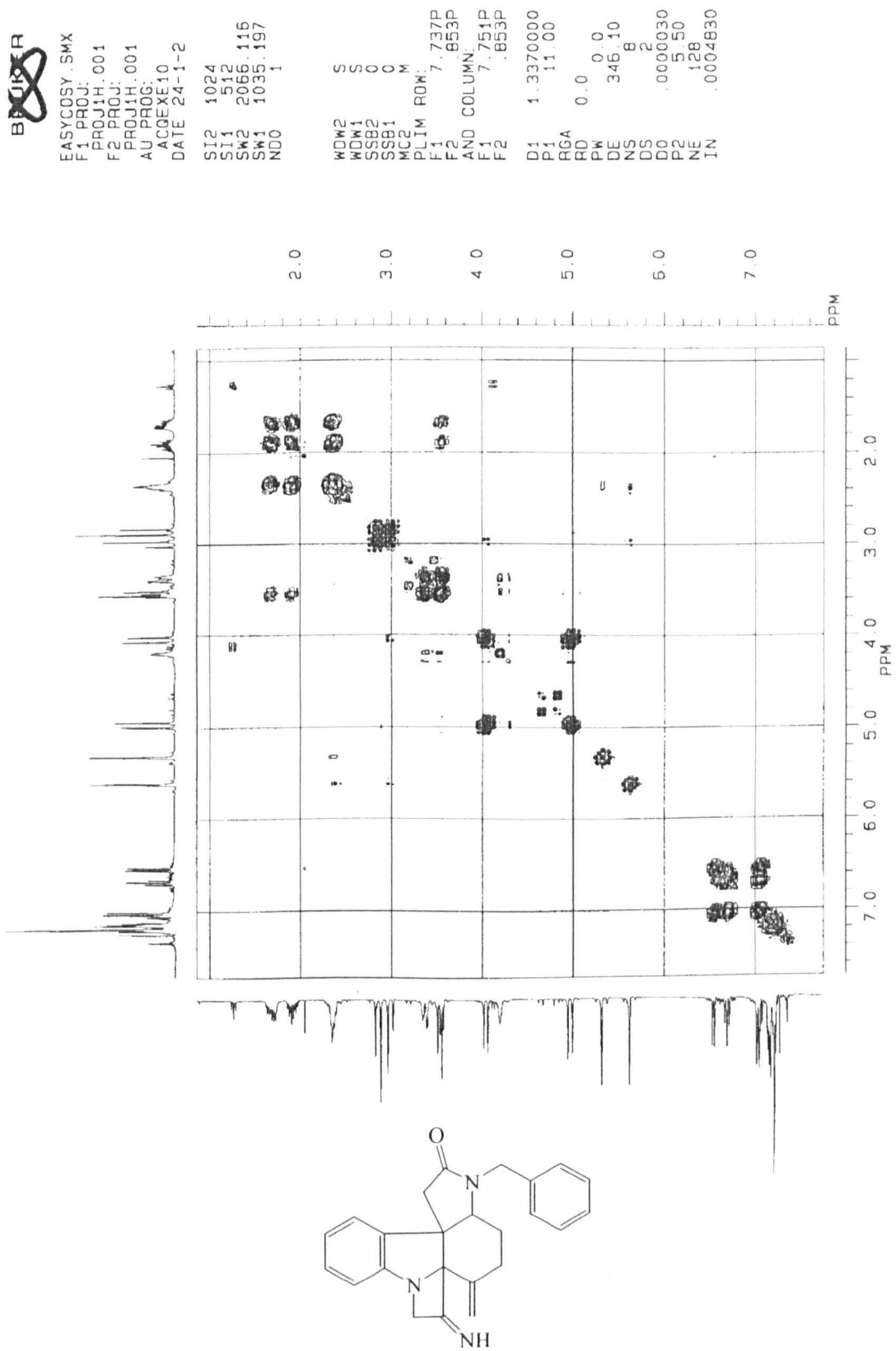
^{1}H NMR spectrum of **396**





(396)

^{1}H COSY spectrum of **396**



(396)