UNIVERSITY OF SOUTHAMPTON

Part I: Solid Phase Radical Reactions
Part II: Studies Towards the Synthesis of Asterriquinone and Petromindole

by

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ABSTRACT

FACULTY OF SCIENCE
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Part I: Solid Phase Radical Reactions
Part II: Studies Towards the Synthesis of
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In Part I, Barton esters were demonstrated to be excellent radical precursors for carbon-carbon bond forming reactions on solid phase. The alkyl radicals were generated photochemically from the corresponding Barton esters and underwent conjugate addition to acrylate immobilized on polystyrene and TentaGel resins. This work was carried out at the Institute of Molecule and Cell Biology, National University of Singapore.

Part II describes synthetic approaches towards several natural products. Two methods for the biomimetic synthesis of polyporic acid by condensation of two molecules of pyruvate are described in Chapter Two. A one-step procedure for the prenylation of indole in high yield under very mild and straightforward reaction conditions is introduced in Chapter Three. This method is also suitable for substituted indoles and alkylations with other allylic, benzylic and tertiary halides. A model study with tryptophan shows that the procedure is also adaptable to the core skeleton of mollenines and other alkaloid natural products. An application of the method of alkylation is shown in the last chapter. ω-Epoxygeranyl, ω-epoxyfarnesyl and ω-epoxygeranylgeranyl groups were attached to the C-3 position of indole under our established alkylation conditions. Epoxide initiated polyene cyclizations using indole as a terminator were extensively studied with these compounds.

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Chapter 2: Synthetic Strategies Towards Asterriquinones

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Chapter 4: Biomimetic Polyene Cyclizations Terminated by Indole

PREFACE

The research work described in this thesis was carried out under the supervision of Dr. A. Ganesan. No part of this thesis has previously been submitted for a degree at this or any other University.

ACKNOWLEDGEMENTS

I sincerely thank my supervisor Dr. A. Ganesan for his guidance, great patience and encouragement during the past few years. Thanks to the Department of Chemistry for a studentship.

Thanks also go to Ganesan's previous group members in Singapore for their help and discussion while I studied there and Ganesan's present group members in Southampton who made me feel at home.

I must also thank the following people without whom my work would have been made much more difficult: Prof. Mike Hursthouse and Dr. Mark Light for X-ray crystallography, Dr. Haishan Wang (Singapore), Ms. Joan Street, Mr. Neil Wells and Mr. Alexander Sylvester Yurek-George for NMR experiments, Dr. John Langley and Ms. Julie Herniman for mass spectral analysis.

Finally, I would like to take this opportunity to thank my parents not just for their genes but mostly for their love, education and bringing me up. Thanks to my husband for his love, understanding and support.

TO MY DAD AND MUM

ABBREVIATIONS

Ac	acetyl
AIBN	α,α'-azobisisobutyronitrile
Ar	aryl
bp	boiling point
t-Bu	*tert*-butyl
calcd	calculated
CI	chemical ionisation (in mass spectrometry)
DABCO	1,4-diazabicyclo[2,2,2]octane
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminum hydride
DIEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EI	electron impact (in mass spectrometry)
ES	electron spray (in mass spectrometry)
GC	gas chromatography
HOBT	*N*-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrum
Hz	hertz
IR	infrared
LDA	lithium diisopropylamide
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
m/z	mass to charge ratio (in mass spectrometry)
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide

NMM	*N*-methyl morpholine
NMR	nuclear magnetic resonance
δ	chemical shift in parts per million downfield from tetramethylsilane
br	broad
d	doublet
J	coupling constant
m	multiplet
ppm	parts per million
s	singlet
t	triplet
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Py	pyridine
rt	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane

Chapter 1: Intermolecular Conjugate Addition of Alkyl Radicals on Solid Phase

1. Introduction

1.1. Free Radical Reactions

Carbon-carbon bond formation is the fundamental means by which organic compounds are built up. The traditional ways to construct carbon-carbon bonds are ionic methods involving carbocations and carbanions, or concerted processes *via* pericyclic reactions. These charged reactive intermediates are very strongly influenced by the nature and polarity of the surrounding functional groups. Changing the solvent can also alter the solvation and hence the reactivity of cations and anions. In contrast, radical reactions, homolytic process involving neutral radicals, are fairly effective in carrying out transformations in molecules which possess many polar carbon-heteroatom bonds. Solvent effects are much less important in radical reactions as radicals are uncharged and usually have little interaction with the solvent. However, radical reactions were not widely used for a long time as they were believed to be prone to undesirable pathways such as premature radical-radical recombination or hydrogen atom abstraction from the solvent. Only in recent years has a deep understanding of the kinetics of radical reactions made radical reactions a powerful synthetic strategy for carbon-carbon bond forming reactions.[1] Efficient and selective radical reactions are also being used as the key steps in the construction of complex molecules.[2]

1.2. Solid Phase Organic Synthesis

Solid phase techniques were developed by Merrifield in the early 1960s to synthesize peptides.[3] These oligomers are comprised of amino acid building blocks linked by the readily synthesized amide bond, and their syntheses involve only carbon-heteroatom bond formation. The nascent peptide chain is immobilized to the solid support, most commonly polystyrene beads. A small cycle of operations (monomer activation, coupling, and deprotection) is repeated during peptide synthesis. Reactions can be driven to completion by a high concentration of reagents, with workup accomplished by simple filtration. Although it did not

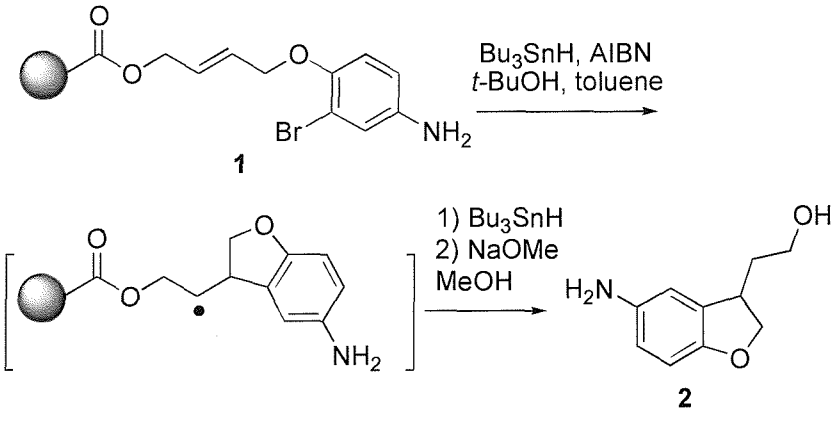
require much time for solid phase synthesis to be adapted to nonpeptidic small molecules,[4] this has come to the fore only in recent years due to the development of high-throughput screening for drug discovery. Simplification of the purification of intermediates in organic synthesis through the solid phase method leads to an increase in synthetic productivity. Parallel synthesis and the split-and-pool strategy of synthesis allow a focused library of related compounds sharing structural features to be synthesized by the variation of building blocks in key fragment coupling steps. Besides amide bond formation, a wide variety of solution phase organic reactions including aromatic substitution, cross-coupling reaction, condensations, cycloadditions, Grignard reactions, Michael additions, olefinations, oxidations, and reductions are being successfully extended to substrates anchored on a polymer support.[5] By comparison, reactions with reactive intermediates such as radicals, carbenes, nitrenes, *etc*. are relatively undeveloped.

1.3. Early Examples of Free Radical Reactions on Solid Phase

A radical reaction often involves multiple elementary steps whose individual rates determine the success of the overall process. In order to form a desired carbon-carbon bond, the solution-phase radical reaction must be conducted in a manner to ensure that the radical generated reacts with a radical acceptor without being terminated. This is normally achieved by using an excess of the acceptor and by kinetics favouring the desired pathway. There are some unique features of solid phase reactions which may be advantageous for radical reactions. The kinetics of solid phase reactions is slower than their solution phase counterparts because of the lower mobility of the gel-phase, and there are also differences in rate between one type of resin and another. This rate deceleration may be useful for radical reactions. Radical reactions may also benefit from the "dilution" due to the low loading on resin (typically $\leq$ 1 mmol/g), preventing radical recombination to some extent. Many reactions, including Merrifield's original peptide syntheses, were done with the substrate attached directly to polystyrene. Today, it is common to include a "linker".[6] The linker can profoundly influence chain mobility as well as the polymer microenvironment where the reaction takes place. Despite these potential benefits, radical reactions were explored on solid phase only very recently, long after solid phase synthesis was applied to small molecules.

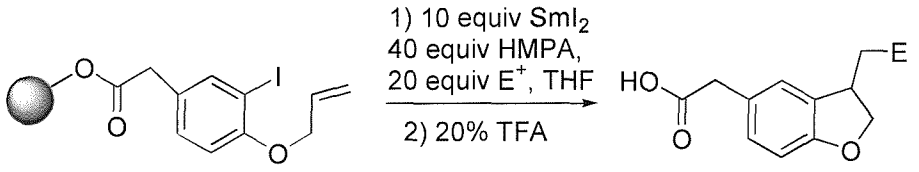
The first example of carbon-carbon bond forming radical reactions on solid phase was reported by Balasubramanian *et al.*[7] at Cambridge who investigated the formation of dihydrobenzofurans from aryl halides with a pendant alkene or alkyne (Scheme 1). The aryl radical generated from (**1**) underwent 5-*exo-trig* cyclization, and further hydrogen abstraction from tributyltin hydride to give dihydrobenzofuran compound (**2**) after cleavage. At least a stoichiometric amount of radical initiator (AIBN) was needed with polystyrene resin, while the reaction was complete within 20 hours using 6 mol% of AIBN on TentaGel resin. This suggests quenching effects from the polystyrene backbone. β-Elimination of the radical intermediate was suppressed by addition of *tert*-butanol. Intramolecular cyclization of an alkyl radical to a triple bond was also achieved on solid phase.

Scheme 1



Du and Armstrong reported similar cyclizations on polystyrene resin by using SmI_2 for radical generation.[8] The organosamarium intermediate was also trapped by an electrophile in solution (Scheme 2), with TentaGel performing better than polystyrene-Rink amide resin.[9] This was attributed to TentaGel's superior swelling properties or anion quenching by the Rink amide proton rather than inherent reactivity of polystyrene.

Scheme 2

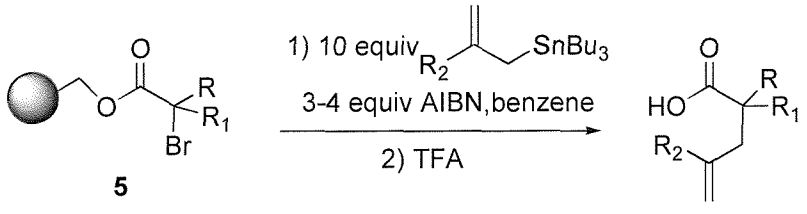


3 **4**

5 examples, 5-33%

The above examples demonstrated the feasibility of well-established solution phase radical reactions of an aryl radical with a double bond to form a dihydrobenzofuran ring. However, they benefit from the tremendous entropic acceleration imposed by intramolecularity, disfavouring undesired bimolecular pathways. Sibi and Chandramouli reported the first intermolecular solid phase reaction, an allylation of α-bromoesters using allyl stannanes (Scheme 3).[10] For a complete reaction, a large excess of both AIBN and allyl stannanes was required. Five secondary and tertiary bromides (**5**) bound on solid support underwent allylation with allyl tributyltin under refluxing conditions, providing acids (**6**) in 58-76% yield after cleavage. The electronic nature of the substituent at the 2-position of the allyl stannane did not impact significantly on the chemical efficiency.

Scheme 3



5

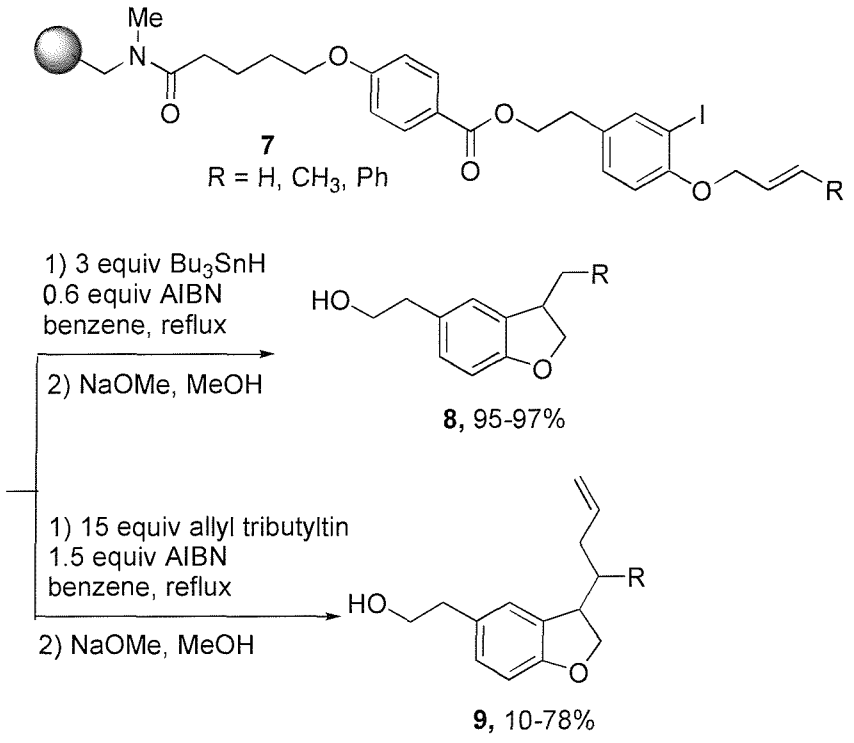
R = H, CH_3
R1= CH_3, *i*-C_3H_7, *n*-C_4H_9
R_2 = H, CH_3, OAc, CO_2CH_3

6, 58-76%

A second example reported by Berteina and De Mesmaeker at Novartis involved the combination of intramolecular halide cyclization followed by intermolecular allylstannane trapping (Scheme 4).[11] Cyclizations of substrates (**7**) to form dihydrobenzofuran rings were realized using 3 equivalents of Bu_3SnH. The products (**8**) were obtained in very high yields. No reduction of the radical before cyclization was observed in these cases, while reduced material is always a major

side product in the presence of high concentrations of tributyltin hydride in solution phase. A more complicated reaction where the cyclized radical is further trapped by an allyltributyltin derivative was investigated. For best results, 15 equivalents of allyltributyltin were required due to the rate of allyl chain transfer being slower than the rate of hydrogen transfer from tributyltin hydride to the radical. The tandem radical cyclizations were satisfactory with the simple allyl ether (**7**, R = H), but not more substituted cases (**7**, R = CH_3, Ph). This type of cyclization was also successful with an alkyne, and *ortho*-iodo benzyl enol ethers and enamines can be efficiently cyclized by radical initiation.[12]

Scheme 4



These successful intra- and intermolecular examples indicate that solid phase radical reactions are feasible and efficient processes. The often problematic removal of tin reagents and tin byproducts from solution reactions is easily accomplished in the solid phase methodology by simple washing of the resin with solvent. There are still some questions which need to be addressed, in particular those of resin compatibility and premature radical termination. The properties of the solid support can have a strong effect on certain radical reactions as seen from the above examples. Two types of resins, polystyrene and TentaGel, are generally used. Polystyrene resin with 1 or 2% divinylbenzene (DVB) cross-linking is very

stable, but not compatible with a wide range of polar solvents. TentaGel resin is a copolymer made by grafting poly(ethylene glycol) onto polystyrene/DVB resin. Although it has a lower loading capacity (typically 0.3 mmol/g) than the polystyrene resin, it swells better in polar solvents like methanol and water.

Our investigation of the compatibility of both polystyrene and TentaGel resins with intermolecular radical reactions was undertaken to determine if they suffer from any limitations on solid phase.

2. Preliminary Investigation of Radical Reactions on Solid Phase

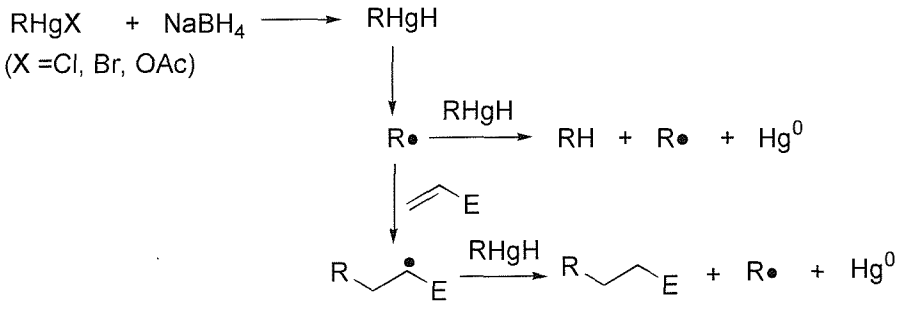
Radical reactions proceed under mild reaction conditions. The radicals are conveniently generated from sources such as organohalides, organosulfides, organoselenides, organomercury compounds and *O*-acyl derivatives of *N*-hydroxy-2-thiopyridone. Preliminary investigation of radical reactions on solid phase with some of these radical precursors was carried out.

2.1. Intermolecular Radical Addition of Organomercurial Halides

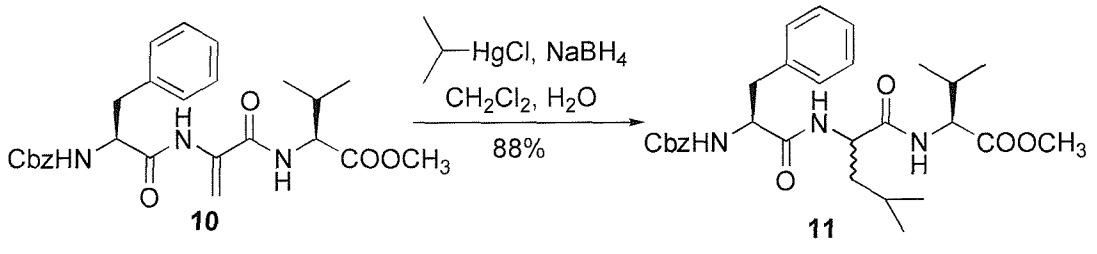
Radical addition reactions conducted by the mercury hydride method were pioneered by Giese.[1,13] Reduction of organomercurial acetates, halides and related derivatives with a variety of hydride sources ($NaBH_4$, $NaCNBH_3$, Bu_3SnH) produces a transient organomercurial hydride, which acts as a source of alkyl radical. The alkyl radical has two competing pathways, addition to an alkene or hydrogen atom abstraction from the alkyl mercurial hydride (Scheme 5). Thus, the alkyl mercurial hydride functions as both radical donor and hydrogen atom donor. This reaction is autoinitiating and proceeds readily at room temperature. There are a wide variety of methods available for the generation of organomercurial halides and acetates.[14] Among them, an alkyl halide being converted into the alkylmercury halide *via* the corresponding Grignard reagent is most often used. An application of

the method to small peptides is shown in Scheme 6.[15] Radical addition to dipeptide (**10**) containing a dehydroalanine residue proceeded smoothly in good yield.

Scheme 5



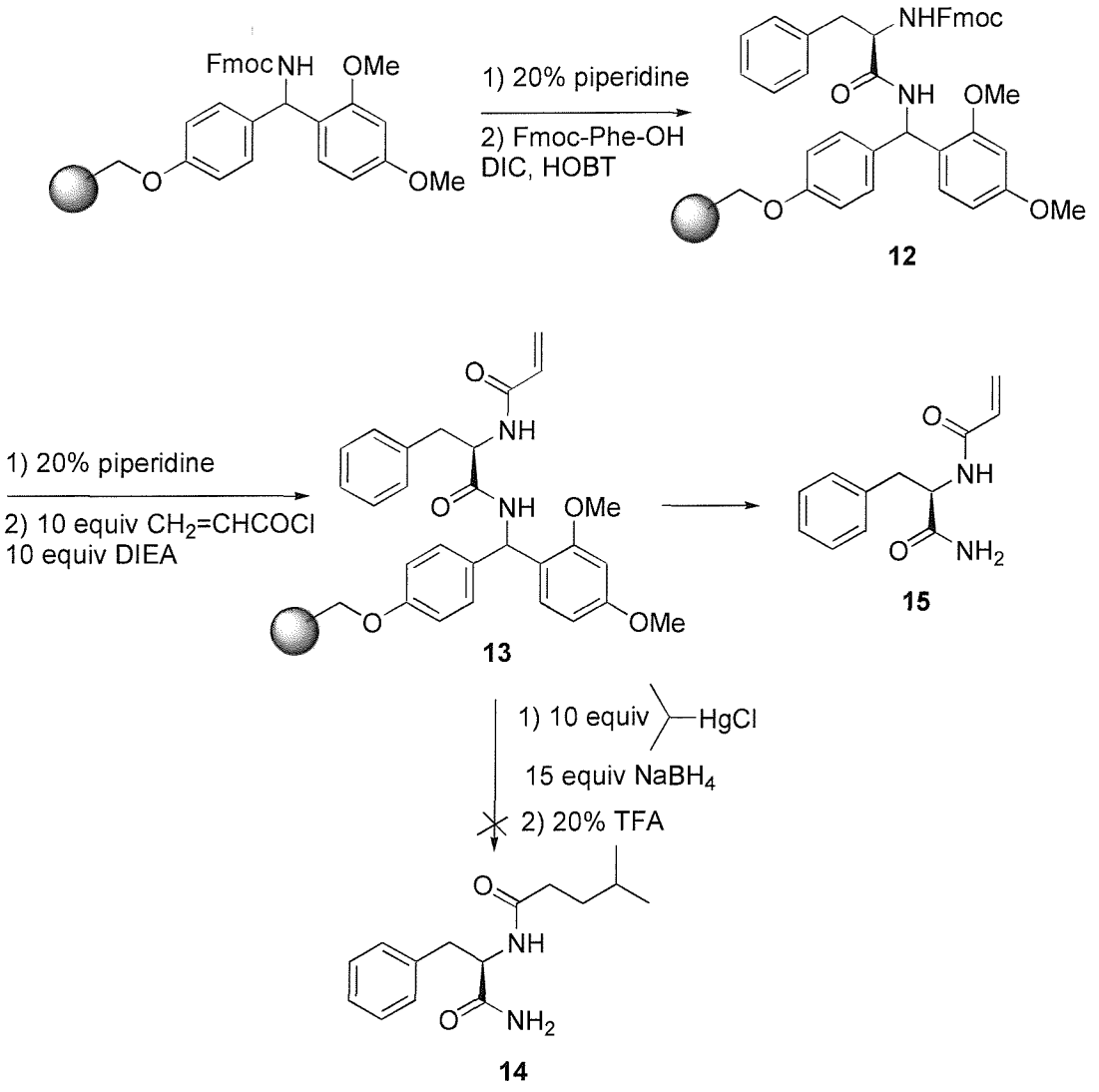
Scheme 6



Radical reactions on solid phase using organomercurial halides as the source of alkyl radical was first tried. The Rink amide resin was treated with 20% piperidine twice to remove the Fmoc protective group, and the resulting free amino group coupled with Fmoc protected phenylalanine to give resin (**12**) (Scheme 7). Removal of Fmoc again generated an amine function on the resin, which was coupled with acryloyl chloride in the presence of *N*,*N*'-diisopropylethylamine (DIEA) to yield functionalised acrylamide (**13**). Resin (**13**) was reacted with 10 equivalents of isopropyl mercury chloride[16] in the presence of sodium borohydride. After cleavage with 20% TFA, a compound isolated in 40% yield based on the initial loading of the resin was identified as (**15**). The desired addition product (**14**) was not observed. Although deposition of mercury was observed in the radical generation step, most likely the radical reaction did not occur on solid phase. The organomercury hydrides are thought to be better hydrogen atom donors than tin hydrides by about one order of magnitude.[17] Thus, the use of highly reactive alkenes is essential to avoid significant amounts of direct reduction products. Our alkene on the solid phase might not be sufficiently reactive, and the isopropyl

radical generated quenched by mercury hydride rather than captured by the alkene loaded on the solid support.

Scheme 7

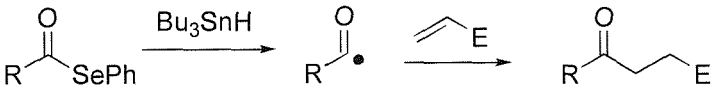


2.2. Intermolecular Radical Addition of Selenoesters

The acyl radicals generated from the corresponding primary alkyl and arylacyl phenyl selenoesters by treatment with tributyltin hydride participate in intermolecular addition with electron deficient alkenes (Scheme 8).[1,18] This provides a practical alternative to the addition of an aldehyde to an alkene. In the case of secondary and tertiary alkylacyl phenyl selenoesters, decarbonylation always occurs. The phenylselenoesters are easily prepared by the reaction of acid

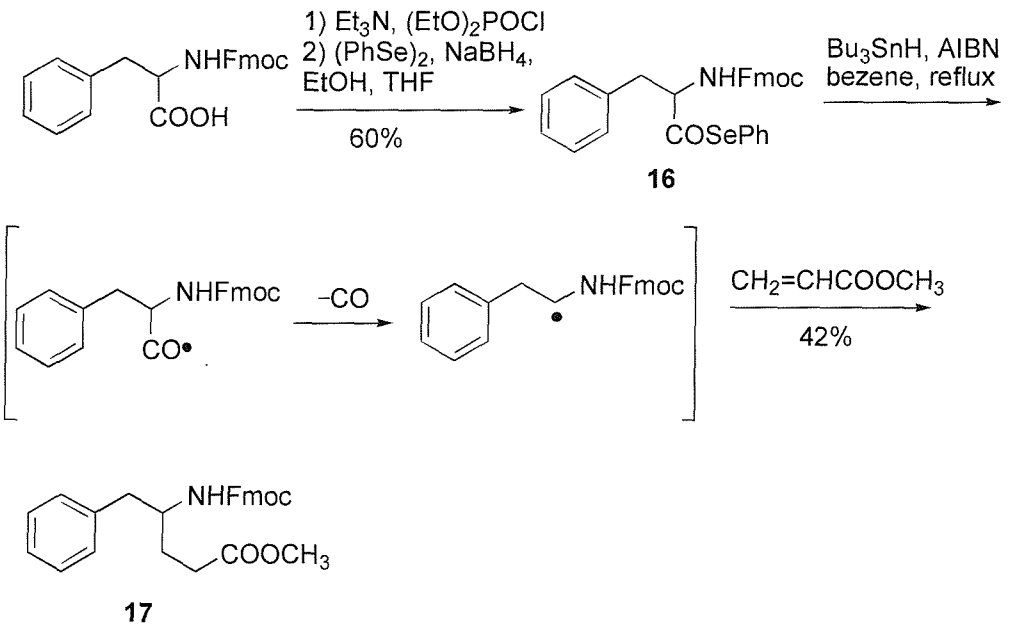
derivatives with sodium phenylselenide or by simply stirring the acid with tributylphosphine and diphenyl diselenide.[18]

Scheme 8

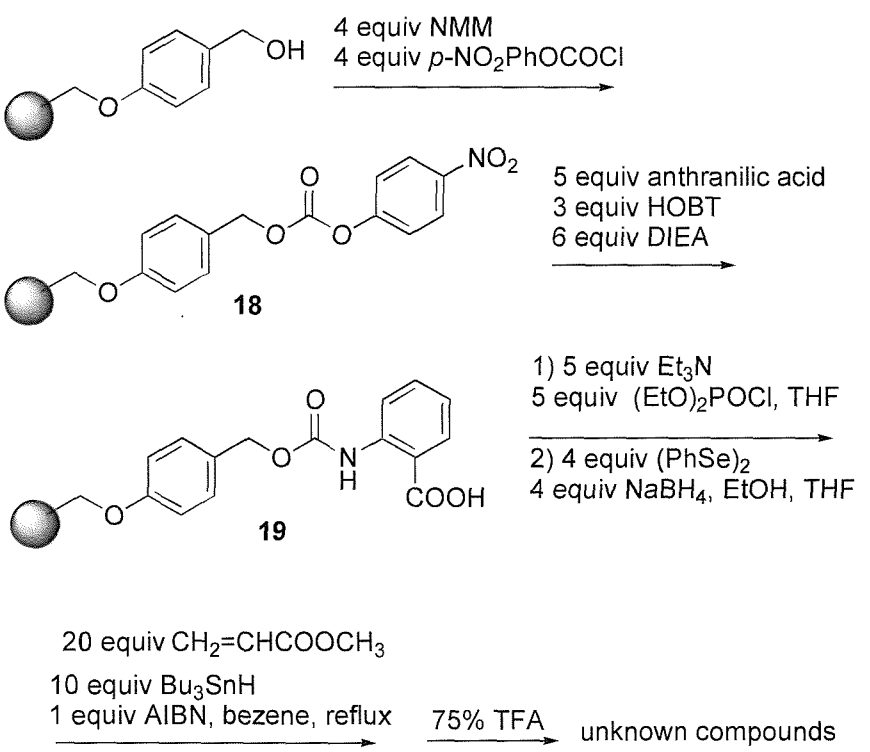


Selenoesters of *N*-protected amino acids were shown to undergo reductive decarboxylation by treatment with tributyltin hydride, the transient 1-amido substituted radicals undergoing further intermolecular carbon-carbon bond forming reactions.[19] This provides a useful method for homologation of an α-amino acid by two carbon atoms leading to a γ-amino acid derivative. It would be useful for peptide synthesis if this could be applied on solid phase. This chemistry was repeated in solution phase first (Scheme 9). Fmoc protected phenylalanine in anhydrous THF was treated sequentially with triethylamine and diethyl chlorophosphate to form an activated anhydride. This was transferred under a nitrogen atmosphere into a reaction flask containing sodium phenylseleno(triethyoxy)borate[20] generated *in situ* by reduction of diphenyl diselenide with sodium borohydride in ethanol to give the selenoester (**16**) in 60% yield. In radical reactions involving tin hydride, simple reduction of the radical precursor by the tin hydride is a competing pathway. In order to overcome this problem, it is usual to add the tin hydride slowly into the reaction mixture containing an excess of the alkene. Thus, tributyltin hydride was added to a mixture of the selenoester (**16**), methyl acrylate and radical initiator AIBN in anhydrous benzene over a short period. Unlike primary alkyl and arylacyl phenyl selenoesters, (**16**) was rapidly decarbonylated by treatment with tin hydride upon heating. The 1-amido radical generated was captured by methyl acrylate to give (**17**) in 42% yield. Our attempt to remove the Fmoc protective group in (**16**) with an aim of attaching the resulting amino phenyl selenoester to the resin failed. A clear solution of (**16**) in dichloromethane turned yellow when exposed to 20% piperidine, indicating that the selenium-carbon bond was cleaved, forming diphenyl diselenide.

Scheme 9



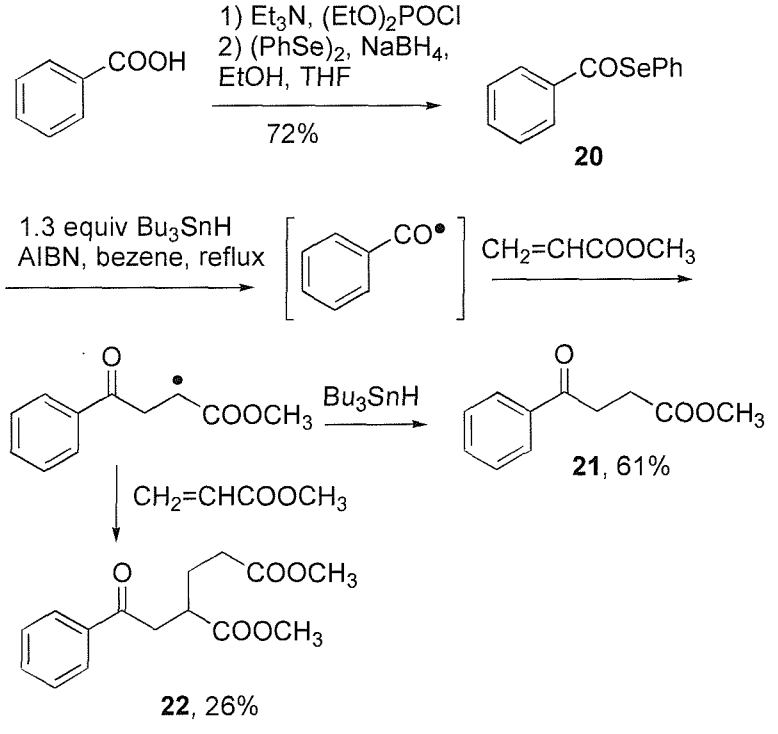
Scheme 10



So it was better to generate the phenyl selenoester on the solid support followed by radical addition. Anthranilic acid was attached to the resin through an activated carbonate resin (Scheme 10).[21] Polystyrene-Wang resin was converted to carbonate resin (**18**) using *N*-methyl morpholine (NMM) and *p*-nitrophenyl chloroformate.

The obtained nitrophenyl carbonate resin (**18**) was reacted with anthranilic acid together with *N*-hydroxybenzotriazole (HOBT) and *N,N'*-diisopropylethylamine in a mixed solvent of DMF and CH_2Cl_2 to give carbamate (**19**). This resin was converted to the phenyl selenoester using the solution phase method. After washing and drying, the assumed polymer bound phenyl selenoester was subjected to radical addition with methyl acrylate and AIBN by slow addition of tributyltin hydride. Several compounds were identified by TLC after cleavage of the resin with 75% TFA, but these could not be characterized. Formation of the selenoester on solid phase was thought to have been unsuccessful.

Scheme 11

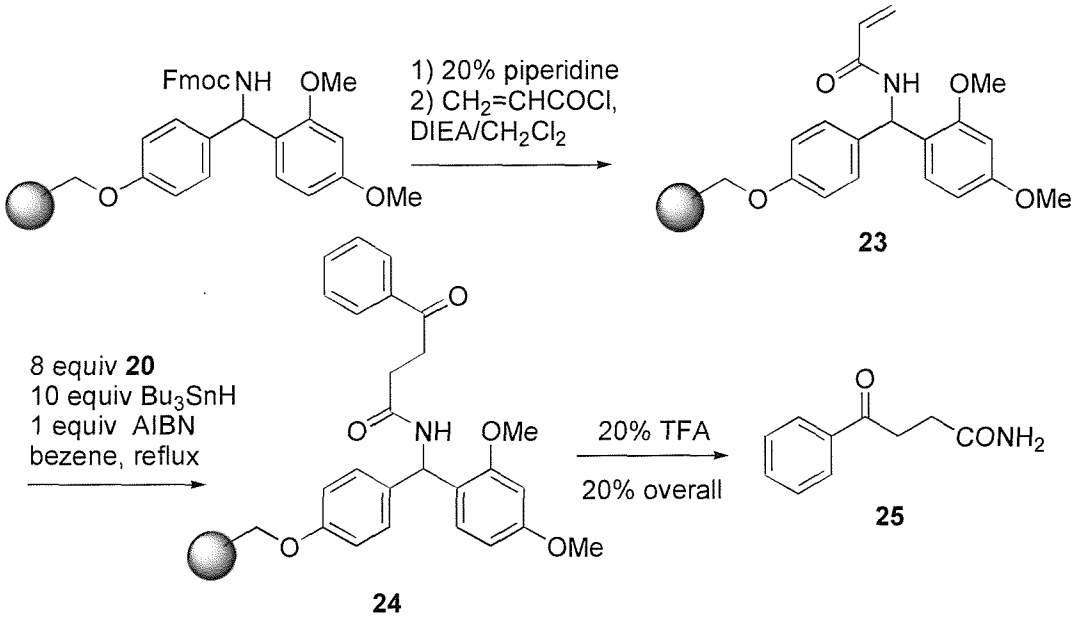


Attention was turned to radical reactions on solid support using a polymer bound radical acceptor to capture the radicals generated in solution. As a model, the reaction of selenoester (**20**) (Scheme 11) with methyl acrylate was carried out, giving 1:1 addition product (**21**) in 61% (58% reported[18a]) yield and 2:1 addition product (**22**) in 26% (16% reported[18a]) yield.

For the solid phase reaction, simple phenyl selenoester (**20**) derived from benzoic acid was chosen as acyl radical precursor. Removal of the Fmoc protective group

in Rink amide resin generated the free amino group, which was coupled with acryloyl chloride in the presence of *N,N'*-diisopropylethylamine to give acrylamide bound resin (**23**). This resin captured acyl radical in solution generated from (**20**) by treatment with tributyltin hydride under refluxing conditions. Cleavage of (**24**) was accomplished with 20% TFA to afford amide (**25**) in 20% isolated yield (Scheme 12). These results suggest that the capture of acyl radicals on solid phase is not very efficient.

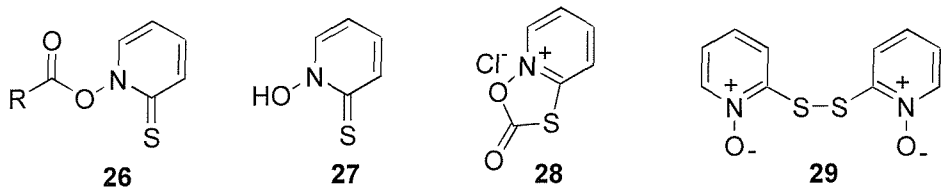
Scheme 12



2.3. Intermolecular Radical Addition of Barton Esters

One of the most important methods of conducting radical addition reactions that do not revolve around the chemistry of the tin radical is Barton's thiohydroxamate method.[1] *O*-Acyl derivatives of *N*-hydroxy-2-thiopyridone (Barton esters or Thiohydroxamate esters, **26**) are readily prepared from the corresponding carboxylic acids through several convenient ways: (a) the use of carbodiimide and *N*-hydroxypyridine-2-thione (**27**), (b) conversion to the acid chloride and coupling with (**27**), (c) the formation of a mixed anhydride with isobutyl chloroformate and coupling with (**27**), (d) the use of the salt (**28**) with loss of carbon dioxide from the intermediate pyrocarbonate, and (e) the use of disulfide (**29**) with tributylphosphine (Figure 1).[22]

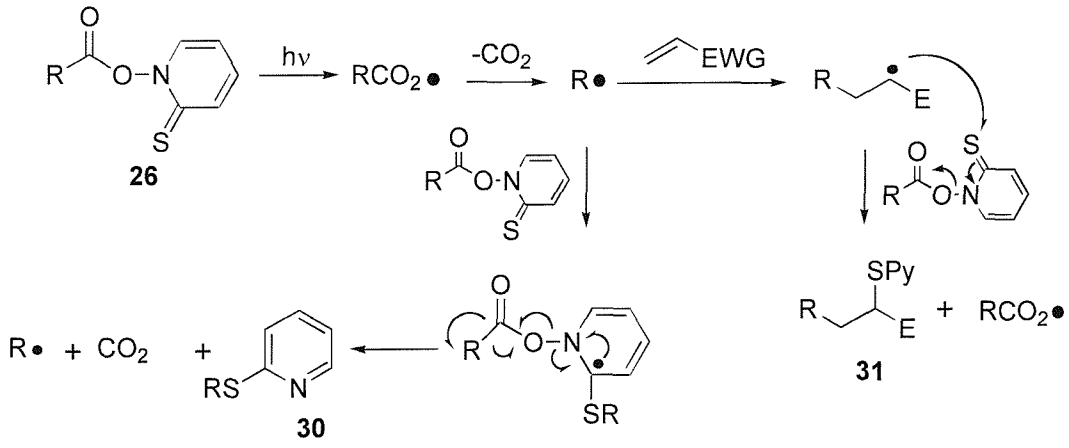
Figure 1



26 **27** **28** **29**

Upon irradiation with an ordinary tungsten lamp or just heating, these esters are rapidly decarboxylated to provide an alkyl radical R•, which is then captured by the precursor Barton ester to afford pyridyl sulfide (**30**). In the presence of an electron deficient alkene acceptor, the nucleophilic alkyl radical R• can be intercepted by addition to the alkene. The resulting radical is now electrophilic in character compared with R•, and preferentially interacts with the electron rich sulphur in the Barton ester to give (**31**), as illustrated in Scheme 13.

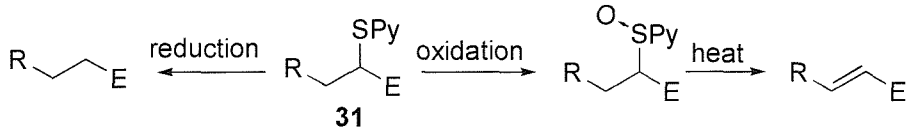
Scheme 13



EWG = electron withdrawing group

Unlike the tin hydride method, the Barton ester itself generates the chain transfer species upon irradiation, and the chain reaction is not terminated by hydride transfer. The doubly functionalised carbon centre in addition products (**31**) makes them particularly attractive from a synthetic point of view. The thiopyridyl group introduced can be transformed to other fuctionalities. It may simply be reductively removed by Raney nickel or tributyltin hydride. Alternatively, controlled oxidation followed by *syn* elimination affords alkenes (Scheme 14).

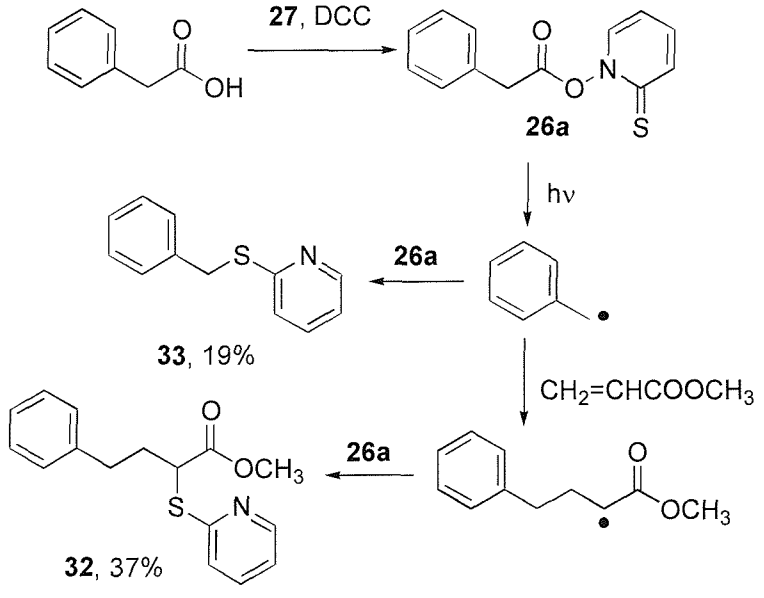
Scheme 14



In solution phase, Barton has shown that the radicals can be efficiently trapped by conjugate addition to acrylate esters,[23] acrylamide,[24] acrylonitriles[25] and vinylsulphone[26] *et al.* Since both the esters and amides can be conveniently linked to resins, these appeared most suitable for study.

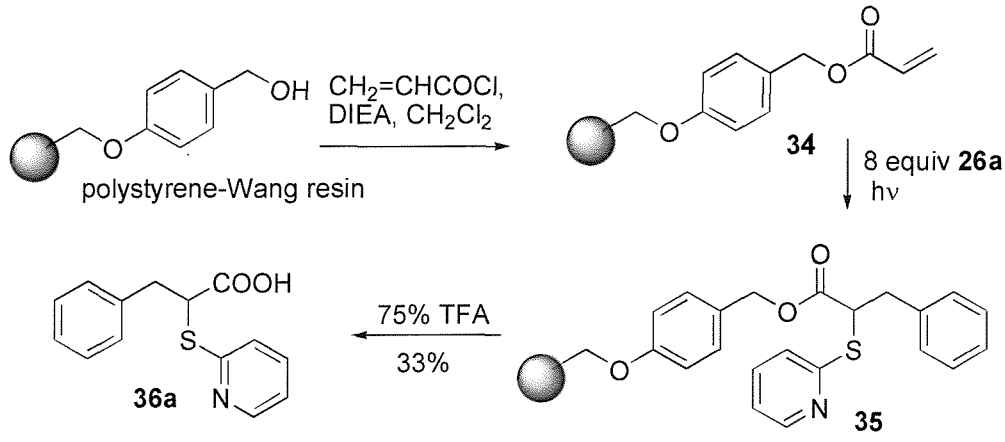
Barton ester (**26a**) (Scheme 15) was prepared from the corresponding phenylacetic acid and (**27**) using the coupling reagent 1,3-dicyclohexylcarbodiimide (DCC). Upon irradiation with two commercial 100 W tungsten lamps in dry dichloromethane for 2 hours at 0 °C, (**26a**) was rapidly decarboxylated to generate the benzyl radical, which underwent addition to methyl acrylate to afford the addition product (**32**) in 37% yield, together with some of premature termination product (**33**). Although the yield was low, this encouraging result showed that the radical generation and the conjugate addition had occurred. In fact, Barton had not prepared such a reaction with the benzyl radical, and the low yields were probably due to the stabilized nature of this radical.

Scheme 15



The Barton chemistry was then adapted to solid phase (Scheme 16). Acrylate bound polystyrene-Wang resin (**34**) was easily prepared from commercially available polystyrene-Wang resin and acryloyl chloride in the presence of *N,N'*-diisopropylethylamine. This was reacted with 8 equivalents of Barton ester (**26a**) under the same photochemical reaction condition as in solution phase. After irradiation for 8 hours and washing, the resin was subjected to 75% TFA in dichloromethane for one hour. The resin was again washed, the filtrate collected and concentrated to give a crude product, which was then purified by preparative TLC. Acid (**36a**) was obtained in 33% yield based on the initial loading of resin. The by-product (**33**) seen in solution phase was not observed, as it would have simply removed by washing the resin prior to cleavage. Although the conditions were not optimised, the yield obtained from this solid phase reaction was almost the same as that in solution phase.

Scheme 16



3. Further Studies of Radical Reactions of Barton Esters with Solid Phase Acceptors

As mentioned earlier, the addition product from the benzyl radical was obtained in moderate yield from both solution phase and solid phase reactions. In Barton's work, the ester (**26b**) derived from hydrocinnamic acid gave the best yield in

addition reactions with methyl acrylate. Barton ester (**26b**) was prepared from the corresponding hydrocinnamic acid and (**27**), and a model study was carried out to establish the photo-radical reaction time on solid phase. The reactions were performed with 10 equivalents of ester (**26b**) and acrylate bound polystyrene-Wang resin in dry dichloromethane cooled in an ice-water bath for different reaction periods (Scheme 17). The products were released from the resin by treatment with 75% TFA in dichloromethane for 1.5 hours (Table 1). Irradiation of acrylate resin and the acid for 2 hours gave the lowest yield, suggesting relatively slow kinetics on solid phase, while the reaction was complete after 4 hours.

Scheme 17

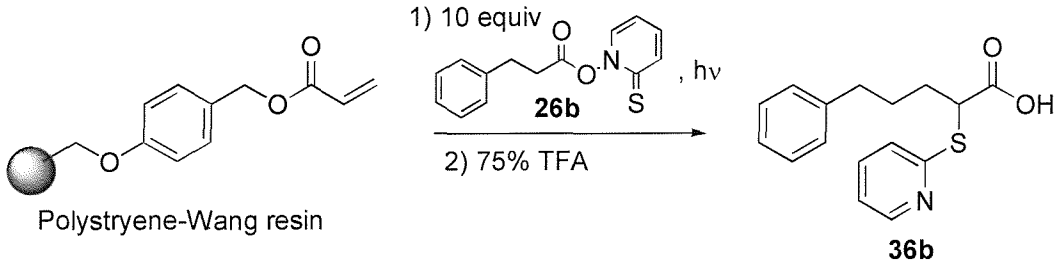


Table 1

Reaction time (hours)	Isolated yield of (**36b**) (%)
overnight (12)	92
8	90
4	94
2	78

Next, the reaction of Barton ester with a bulky adamantyl group (**26c**) on solid phase was investigated. Both polystyrene and TentaGel resins were examined. Acrylate bound TentaGel-Wang resin was easily prepared from commercially available TentaGel HL PHB resin with the same method used for preparing acrylate bound polystyrene resin. 10 equivalents of ester were found to achieve the highest yield for both these resins (Scheme 18, Table 2).

Scheme 18

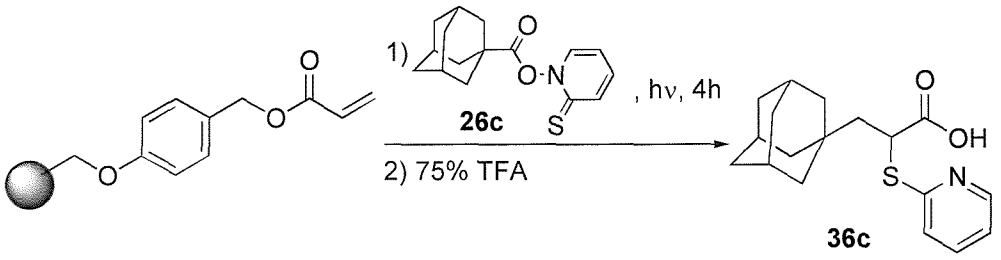
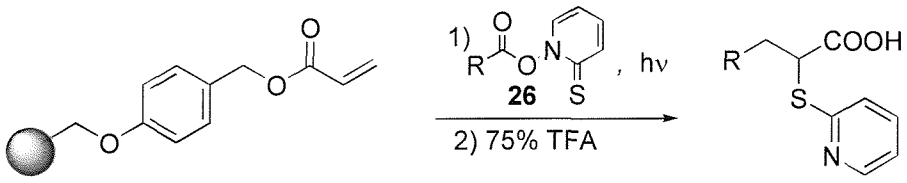


Table 2

	Quantity of ester (**26c**) (molar equivalents)	Isolated Yield of (**36c**) (%)
Polystyrene resin	15	60
	10	63
	5	41
TentaGel resin	10	45
	5	28

Besides phenylacetic acid, hydrocinnamic acid and 1-admantyl carboxylic acid, cyclohexyl carboxylic acid and trimethylacetic acid were also chosen to carry out radical reactions on both acrylate bound polystyrene and TentaGel-Wang resin under the established conditions. Barton esters (**26a-26e**) were all prepared from the corresponding acid just before they were used. The photoreactions were carried out in dry dichloromethane in an ice-water bath with two commercial 100 W tungsten lamps. Upon irradiation, these esters decarboxylated smoothly to the corresponding nucleophilic carbon radicals, which were trapped by the acrylate resins. Finally, cleavage of the resin with 75% trifloroacetic acid in dichloromethane gave the acids (**36a-36e**) (Scheme 19, Table 3).

Scheme 19



a, R = $PhCH_2$-
b, R = $PhCH_2CH_2$-
c, R = 1-adamantyl-
d, R = cyclohexyl-
e, R = $(CH_3)_3C$-

Table 3

Product	Polystyrene-Wang resin (Yield %)[a]	TentaGel-Wang resin (Yield %)[a]
36a	32	17
36b	94	76
36c	63	45
36d	91	76
36e	91	78

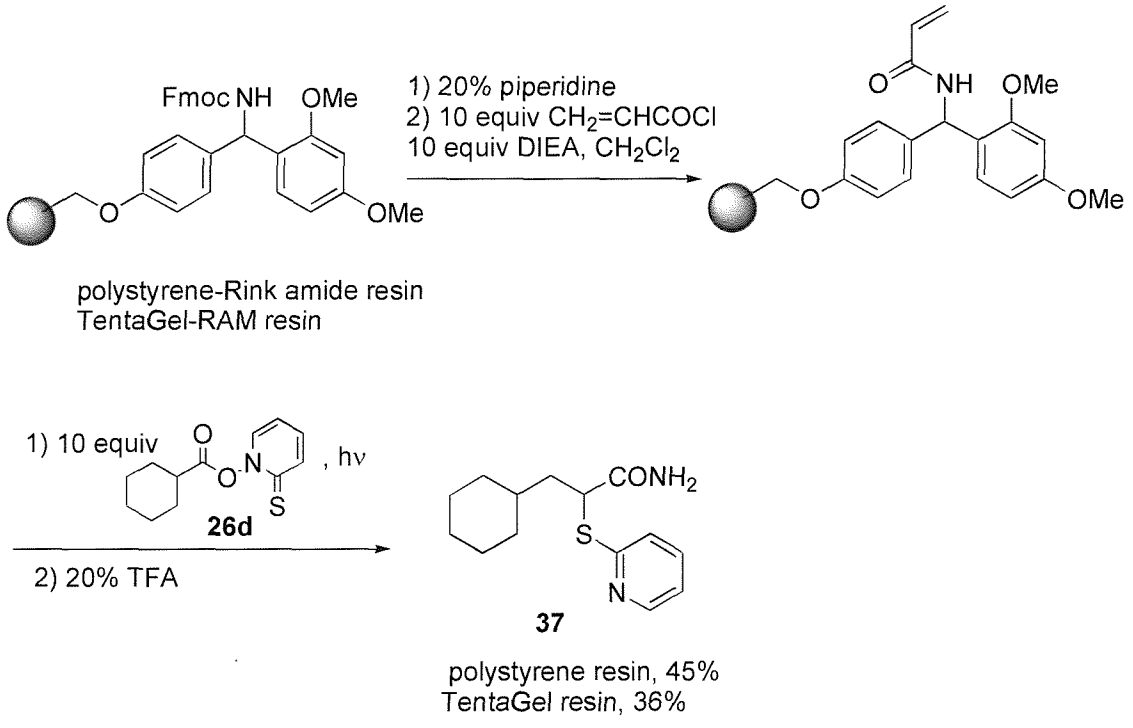
[a] Isolated yields, based on manufacturer's loading of resin.

As seen from Table 3, the conjugate additions of nonstablized radicals give high yields on solid phase. The yields of (**36b**) and (**36d**) are comparable to Barton's results with methyl acrylate, while addition of the 1-adamantyl radical was somewhat less efficient probably because it is much more bulky. The benzyl radical performed poorly under both solid phase and solution phase conditions.

The TentaGel-Wang resin gave consistently lower yields by approximately 15% than polystyrene. It is possible the resins differed in loading efficiency, but this could not be directly compared due to the difficulty of isolating acrylic acid after TFA cleavage of acrylate bound resins. Instead, the two types of resins were reacted with phenylacetyl chloride under the same conditions used for acrylate attachment. After TFA cleavage, ^{1}H NMR with a known amount of *p*-anisaldehyde as internal standard quantified the crude yield of phenylacetic acid. The loading for both resins was found to closely match the manufacturer's specifications. Thus, the

lower yield appears to arise from the radical reaction itself on TentaGel resin. As hydrogen atom abstraction from ethers is well precedented, it is possible that this is due to interference from the poly(ethylene glycol) spacer.[27] Depending on the age of the resin and exposure to oxygen and light, TentaGel resin is also susceptible to peroxide formation, which is likely to be detrimental to these reactions.

Scheme 20



Barton *et al.* also reported the use of acrylamide as a radical trap leading to a convenient synthesis of primary amides from carboxylic acids with two-carbon homologation.[24] The versatile amide function can be converted to other derivatives. In solution phase, addition of alkyl radicals to acrylamide was shown to proceed in 25-30% lower yields than their addition to methyl acrylate due to premature termination or oligomerization of acrylamide. Acrylic acid immobilized on the Rink amide resin was examined. Polystyrene-Rink amide and TentaGel-RAM resins were treated with 20% piperidine twice to remove the Fmoc protecive group and then coupled with acryloyl chloride to give the acrylate bound amide resin. Irradiation of cyclohexyl Barton ester (**26d**) followed by acid cleavage gave the product (**37**). The yields with polystyrene-Rink amide resin and TentaGel-RAM

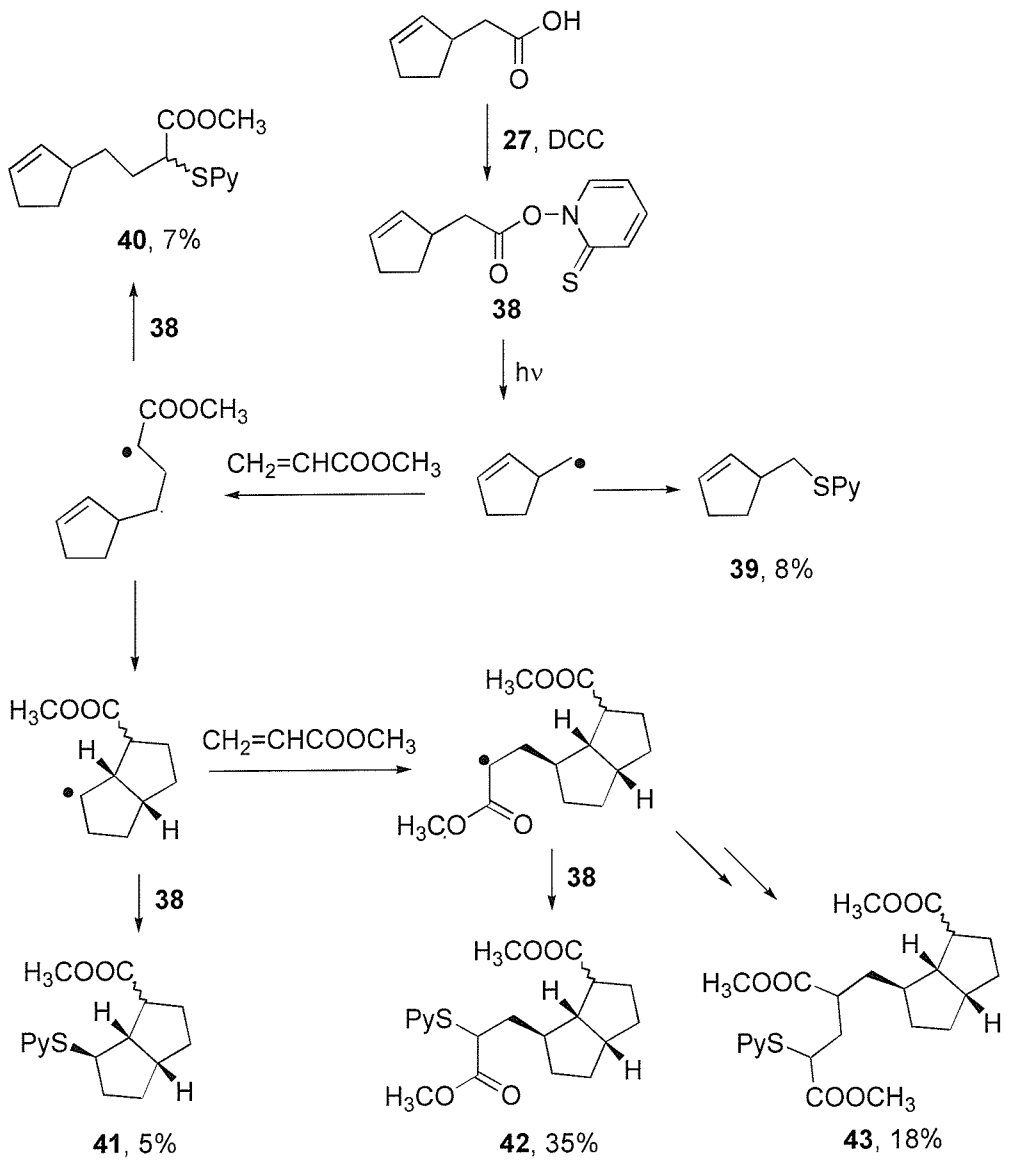
resin were 45% and 36%, respectively (73% reported in solution phase[24]) (Scheme 20).

The loading of the amide resin was also checked. Deprotection of the Fmoc group in polystyrene-Rink amide resin and TentaGel-RAM resin provided an amino function, which was reacted with phenylacetyl chloride. After 20% TFA cleavage, ^{1}H NMR with a known amount of *p*-anisaldehyde as internal standard quantified the crude yield of phenylacetamide. The loading for both resins was also found to match the manufacturer's specifications. These results indicate that the radical addition to acrylamide acceptors is less efficient than with acrylate esters.

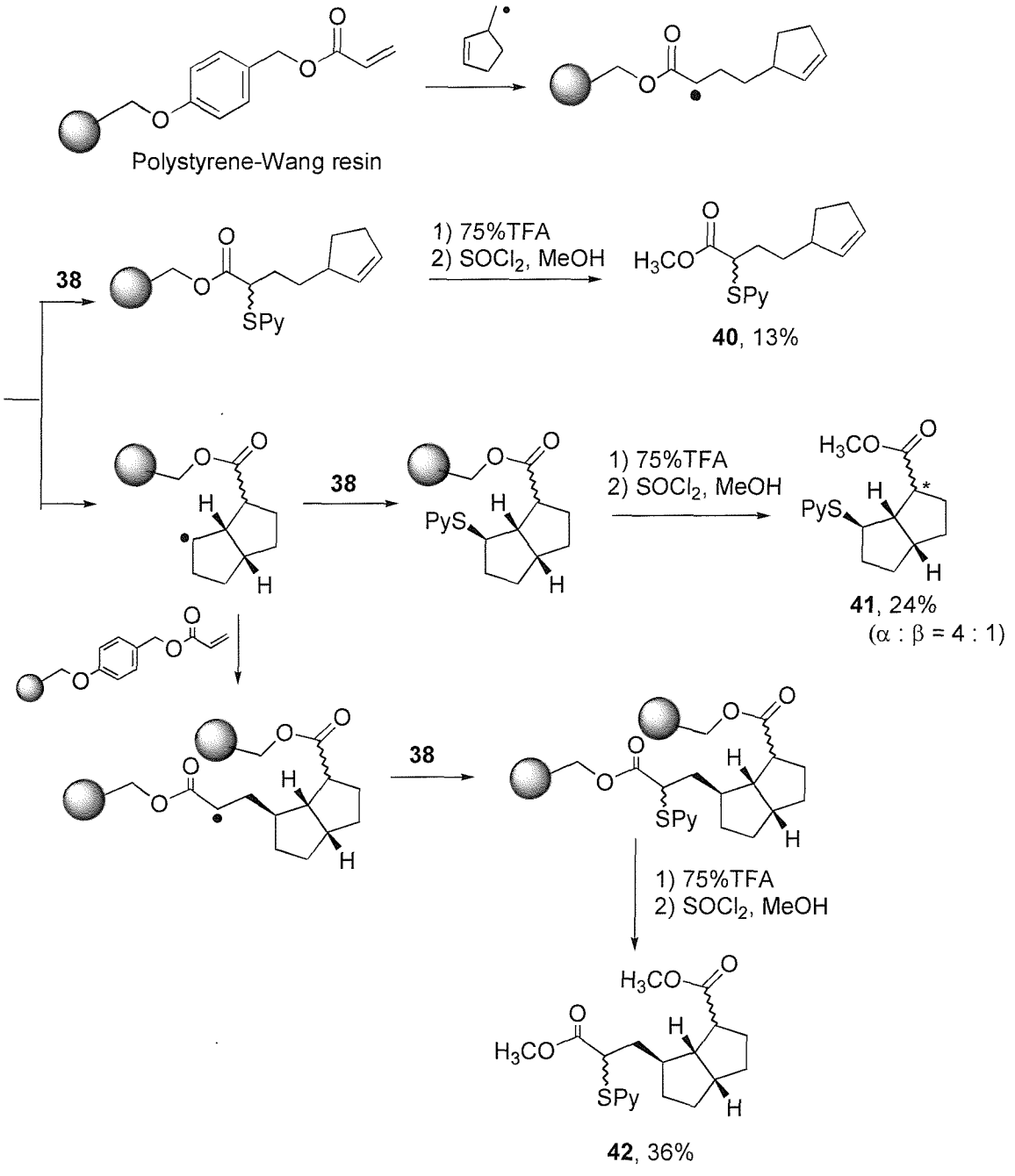
Barton, da Silva, and Zard have demonstrated that the intermediate α-carboxymethyl radical can undergo further reactions.[28] For example, irradiation of the Barton ester (**38**) derived from cyclopent-2-enylacetic acid with methyl acrylate affords the conjugate addition product (**42**) (Scheme 21). Rather than immediate chain transfer to give (**40**), the major reaction pathway of this electrophilic acyl-substituted radical is intramolecular 5-*exo-trig* cyclization to yield a bicyclic radical, as a mixture of epimers. As a nucleophilic alkyl radical, the bicyclic radical is not only capable of chain transfer but a second conjugate addition, leading to oligomers. Despite the complexity of this system, experimentally 2:1 adduct (**42**) of methyl acrylate and cyclopentenylmethyl radical was isolated as the major product in 43% yield (as a mixture of diastereomers) from the reaction.

It was interesting to compare this reaction in solution phase with solid phase conditions, since immobilisation of the acrylate chains might simulate high-dilution conditions and hinder the formation of 2:1 or higher adducts. In our hands (Scheme 21), the solution phase experiment (with limiting Barton ester and 2 equivalents of methyl acrylate) also afforded (**42**) as the major product in 35% yield. In addition, 18% of a 3:1 adduct (**43**), 8% of (**39**), 7% of (**40**), and a trace amount (<5%) of (**41**) were also isolated.

Scheme 21


OH
O
27, DCC
O–N
O
S
38
hν
COOCH3
SPy
40, 7%
38
COOCH3
CH2=CHCOOCH3
SPy
39, 8%
H3COOC
H
H
CH2=CHCOOCH3
H3COOC
H
H3CO
O
H
38
38
H3COOC
H
PyS
H
41, 5%
H3COOC
H
PyS
H3CO
O
H
42, 35%
H3COOC
H
H3COOC
PyS
COOCH3
H
43, 18%

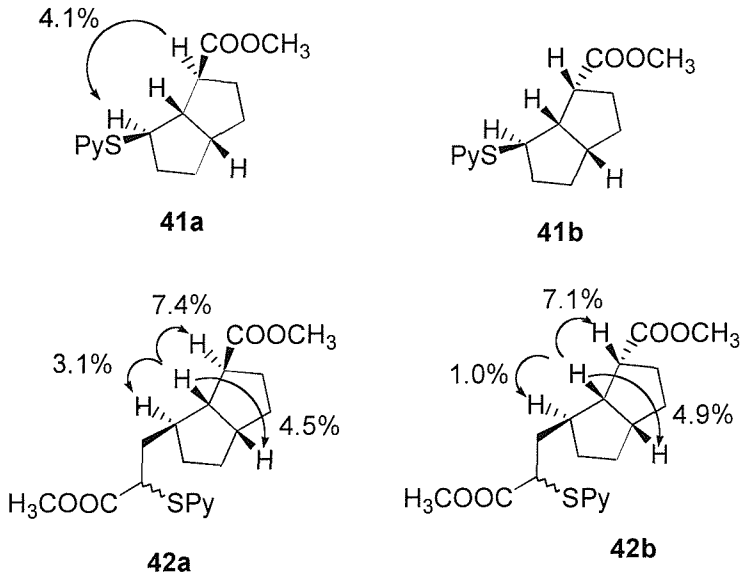
Scheme 22



The reaction of acrylate bound polystyrene-Wang resin with 10 equivalents of Barton ester (**38**) was performed under our solid-phase conditions (Scheme 22). After TFA cleavage, the free carboxylate acids in the crude product mixture were converted to methyl esters by treatment with $SOCl_2$ in dry methanol for ease of purification. The yields were calculated based on the original loading of resin. The 2:1 adduct (**42**) was still the major product. Compound (**40**) (13%) and (**41**) (24%) were also isolated. Both (**41**) (**41a**:**41b** approximately 1:4) and (**42**) (**42a**:**42b**

approximately 1:1) were obtained as a mixture of two diastereoisomers whose structures were assigned on the basis of nuclear Overhauser effect (NOE) experiments (Figure 2) and also supported by epimerisation reactions. In compound (**41a**), a strong NOE was observed between C-2 proton and C-8 proton, suggesting they have a close relationship in space. This was not observed in compound (**41b**), where the two protons are *trans* to each other and about 3.7 Å apart by computer modelling. The major diastereomer (**41b**) could be completely epimerised to (**41a**) with 1.5 equivalents of DBU in refluxing methanol for one day. Epimer (**42b**) was converted to its diastereoisomer (**42a**) partially under the same epimerisation conditions for two days.

Figure 2



Comparing the solution-phase radical cascade reaction with our solid-phase version, a significantly higher amount of (**41**) was formed on solid phase. This could be due to intrinsic differences between the solution- and solid-phase reactions or reflect the concentration of Barton ester (10:1 on solid phase relative to acrylate, compared to the 1:2 ratio on solution phase). It is difficult to distinguish these alternatives on solid phase, as an excess of Barton ester is needed to ensure good yields. Instead, the solution-phase experiment with 10 equivalents of Barton ester (**38**) was repeated. Under these conditions, 13% of (**40**), 43% of (**41**) (approximately 1:4 diastereomeric mixture), and 35% of (**42**) (approximately 1:1 diastereomeric mixture) were isolated. These results show that the fate of

bicyclic radical is mainly determined by the concentration of Barton ester. When it is high, chain transfer resulting in (**41**) effectively competes with further conjugate additions of acrylate. The slower kinetics on solid phase relative to homogeneous conditions is probably responsible for the lower accumulation of (**41**) (24% on solid phase versus 43% in solution phase). Site isolation of the bicyclic radical on solid phase is not significant, enabling relatively free access to a second acrylate chain, leading to (**42**). This is consistent with previous studies[3a] of chain flexibility and cross-linking when two mutually reactive functional groups are on solid phase resins.

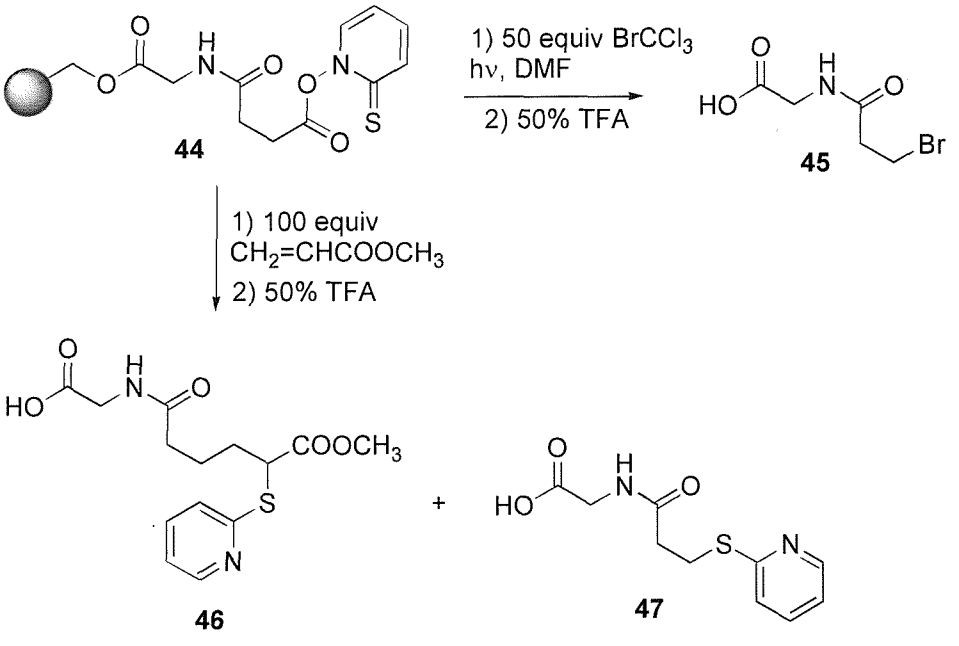
4. Conclusion

Barton esters were demonstrated being excellent radical precursors for carbon-carbon bond forming reactions on solid-phase. The alkyl radicals were generated photochemically from the corresponding Barton esters and underwent conjugate addition to acrylate immobilized on both polystyrene- and TentaGel-Wang resin. With the polystyrene-Wang resins, yields were comparable to Barton's solution-phase results. The lower yields of TentaGel resin are probably due to hydrogen atom abstraction from the polyethylene glycol linker. Another possibility is peroxide formation upon long-term exposure to oxygen and light. The conjugate addition to acrylic acid immobilized by the Rink amide linker was also examined. The yield was lower than with the ester linkage. Finally, the product of conjugate addition was shown to be capable of further intramolecular and intermolecular reactions. This reveals a high degree of site interaction on the resin, with an intermediary radical capable of cross-linking a second acrylate chain. Our results show that radical conjugate addition reaction is a viable synthetic process on solid-phase.

5. Radical Reactions on Solid Phase: Recent Developments

Recently, in connection with their syntheses of unnatural amino acids in solution phase, Attardi and Taddei studied the photochemical decarboxylation of Barton esters on solid phase (Scheme 23).[29] Upon irradiation, Barton ester (**44**) on Wang resin generated a radical which was captured by $BrCCl_3$ to give (**45**) in 72% yield after cleavage, although at least 50 equivalents of $BrCCl_3$ was required. Conjugate addition of the radical to methyl acrylate resulted in a mixture of (**46**) and (**47**), (**47**) being the major product even with 50 equivalents of radical acceptor. Addition products were still contaminated by 10-20% of (**47**) even when using more than 100 equivalents of methyl acrylate. Quenching the radical with $BrCCl_3$ was more synthetically useful, as the halide functional group generated on solid phase could be further displaced by an amine. This provides a route to the synthesis of unnatural amino acids on solid phase.

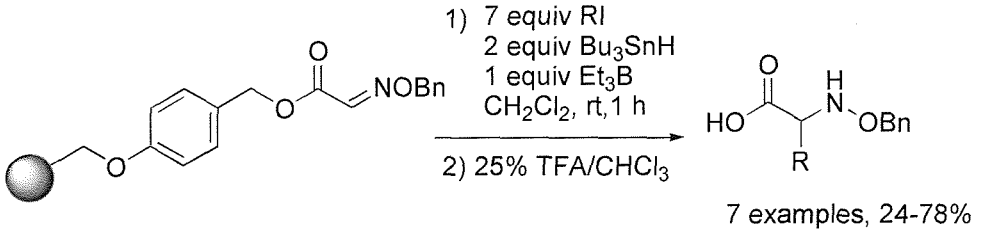
Scheme 23



Oxime ethers are well-known excellent radical acceptors because of the extra stabilization of the intermediate aminyl radical by the adjacent oxygen atom. Naito's group reported the addition of alkyl radicals to glyoxylic oxime ethers anchored on a polymer support with stoichiometric triethylborane as radical

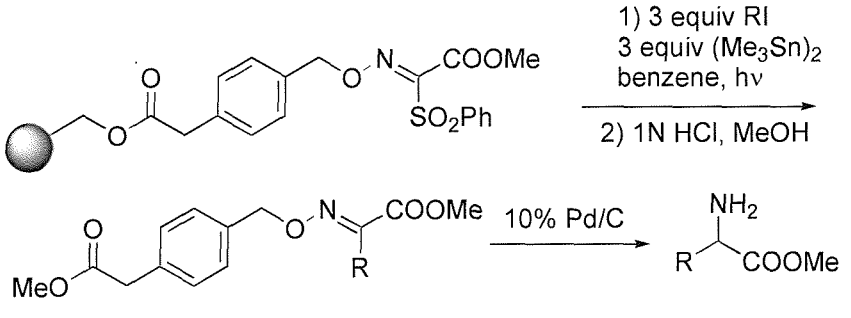
initiator and 2 equivalents of Bu_3SnH (Scheme 24).[30] Polystyrene Wang resin was found to give much better yields than TentaGel. All reactions were run without any special precautions such as drying, degassing, or purification of solvents and reagents and are thus adaptable to parallel syntheses of unnatural α-amino acids. Stereoselective synthesis of amino acids was reported later by the same group using triethylborane or diethylzinc as a radical initiator and Oppolzer's camphorsultam as a chiral auxiliary.[31] Examples given show moderate to good yield and high enantiomeric excess. One example on solid phase gave better result than that obtained in the solution phase radical reaction, probably due to lower reactivity of the oxime ether bound on polymer support. A group in Korea also reported solid phase synthesis of α-amino acids in reasonable yield using alkyl radical addition to resin-bound phenylsulfonyl oxime ether (Scheme 25).[32] Pyrrolidines were also achieved by radical cyclization of oxime ether on solid support.[33,34]

Scheme 24



7 examples, 24-78%

Scheme 25

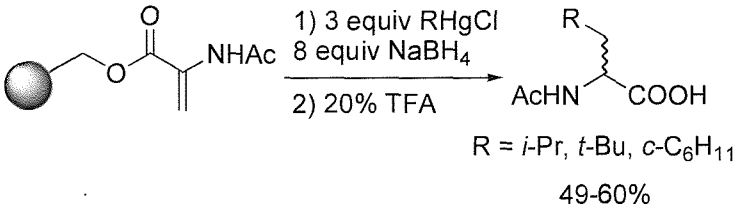


7 examples, 0-50%

The solid phase radical reaction of *N*-acetyl dehydroalanine provided another route to amino acid derivatives (Scheme 26).[35] *N*-Acetyl dehydroalanine was bound to Wang resin employing Mitsunobu chemistry and the resulting resin was then subjected to alkyl radicals generated *in situ* by the addition of sodium

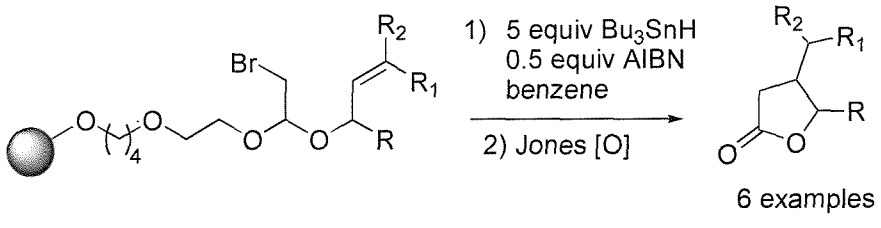
borohydride to the alkylmercury choride in dichloromethane. Conjugate addition of the radicals followed by cleavage from Wang resin afforded the free acids in 49-60% yield.

Scheme 26



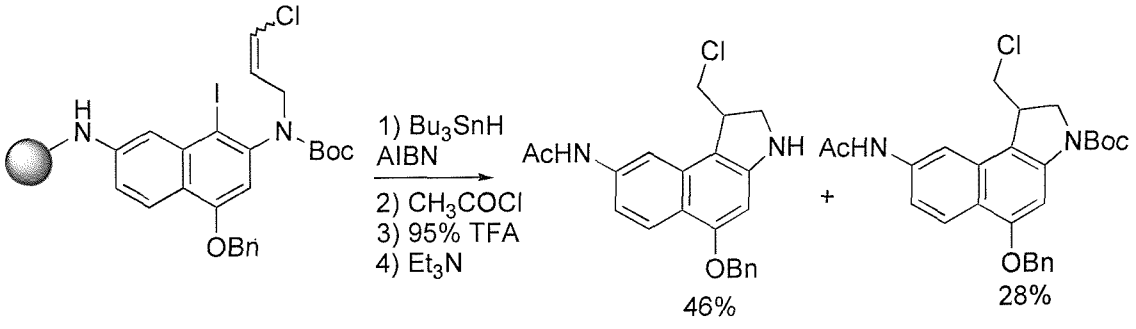
Synthesis of γ-butyrolactones on solid phase was achieved by treatment of polymer supported β-bromoethylacetals with tributyltin hydride in the presence of a catalytic amount of AIBN (Scheme 27).[36] Jones oxidation released the products in 47-93% yield for the radical cyclisation and cleavage steps (23-43% overall based on initial loading of Merrifield resin). A linear spacer separates the polystyrene support from the reaction site due to competitive hydrogen abstraction from the benzylic position of Merrifield resin.

Scheme 27



Intramolecular cyclization of aryl radicals with allyl anilines leads to indoline compounds, as seen in Scheme 28. Its application in the synthesis of *seco*-CBI, related to the pharmacophore of the CC-1065 and duocarmycin class of cyclopropylindole antitumor antibiotics, holds promise for the combinatorial preparation of analogue libraries.[37]

Scheme 28

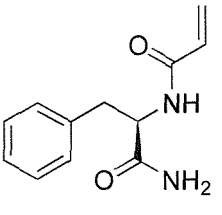


Besides demonstrating the feasibility and compatibility of radical reactions on solid support, a number of polymer-supported reagents and scavenger resins are now available that facilitate radical reactions in parallel, with the potential for considerably simplified workup and purification compared to the original procedures. Radical chemistry is now an important complement to traditional polar processes both in solution phase and on solid phase, and further advances will undoubtedly be made in the near future.[38]

Experimental Section

General. All chemicals obtained commercially were used without futher purification. Dichloromethane was distilled from CaH_2 immediately before use. Wang resin (capacity: 1.08 mmol/g, 100-200 mesh, 1% DVB) and Rink amide resin (capacity: 0.56 mmol/g, 100-200 mesh, 1% DVB) were obtained from Calbiochem-Novabiochem Corp. TentaGel HL PHB (capacity: 0.42 mmol/g) and TentaGel HL RAM (capacity: 0.38 mmol/g) were obtained from Rapp Polymere GmbH. All water- and air-sensitive reactions were performed under nitrogen atmosphere in oven-dried glassware. Analytical TLC was performed on precoated glass plates (Merck, silica gel 60F-254) and visualized with UV light. Preparative TLC was carried out on 20 × 20 cm glass plates precoated with 1 mm silica (Aldrich). Column chromatography was performed with silica (Merck, 70-230 mesh). ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively, in $CDCl_3$ solvent with a Bruker Avance-400 instrument unless stated otherwise. Chemical shifts are expressed in ppm downfield from tetramethylsilane as an internal standard. Mass spectra (EIMS, HRMS) were obtained on a VG7035 analytical spectrometer, and relative intensities of ions are indicated in parentheses. Infrared spectra were recorded on a BIO-RAD Win-IR spectrometer ($CHCl_3$ thin film, KBr liquid cell).

***N*-(1-carbamoyl-2-phenyl-ethyl)-acrylamide (15)**

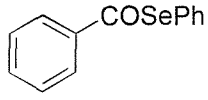


Isolated from cleavage of resin (**13**).

^1H NMR (CD_3OD) δ 2.92 (dd, J = 9.0, 13.9 Hz, 1H), 3.15 (dd, J = 5.7, 13.9 Hz, 1H), 4.70 (dd, J = 5.7, 9.0 Hz, 1H), 5.62 (dd, J = 2.5, 9.8 Hz, 1H), 6.10-6.35 (m, 2H), 7.10-7.30 (m, 5H);

EIMS *m/z* 218 (M^+, 8), 174 (64), 120 (96), 55 (100).

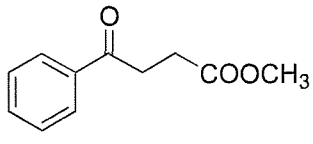
***Se*-Phenyl benzenecarboselenoate (20)**



To a stirred solution of benzoic acid (305 mg, 2.5 mmol) in anhydrous THF (12 mL) was added triethylamine (0.42 mL, 3 mmol) and diethyl chlorophosphate (0.44 mL, 3 mmol) at room temperature. The reaction mixture was stirred for 4 h and filtered under nitrogen atmosphere into a suspension of $Na^{+}[PhSeB(OEt)_3]^{-}$ (3 mmol) [prepared from PhSeSePh (468 mg, 1.5 mmol), $NaBH_4$ (113 mg, 3 mmol) and EtOH (0.53 mL, 9 mmol)] in anhydrous THF (6 mL). The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo*, and partitioned between ether and water. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography afforded (**20**) as an off-white solid (470 mg, 72%). ^{1}H NMR was identical to that reported.[18a]

^{1}H NMR δ 7.40-7.70 (m, 8H), 7.96 (d, J = 7.7 Hz, 2H).

4-Oxo-4-phenyl-butyric acid methyl ester (21)



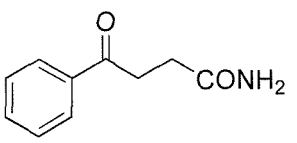
To a refluxed solution of (**20**) (100 mg, 0.38 mmol), methyl acrylate (0.17 mL, 1.9 mmol) and AIBN (6.2 mg, 10 mol %) in anhydrous benzene (2.5 mL) was added a solution of tributyltin hydride (0.13 mL, 0.5 mmol) in benzene (1 mL) over a period of 20 min. The reaction mixture was stirred for another 1 h, cooled down to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography to afford (**21**) as a colourless oil (45 mg, 61%). ^{1}H NMR was identical to that reported.[39]

^{1}H NMR δ 2.77 (t, J = 6.6 Hz, 2H), 3.33 (t, J = 6.6 Hz, 2H), 3.71 (s, 3H), 7.44-7.60 (m, 3H), 7.98 (m, 2H).

Acrylate-functionalized Rink resin (23)

Fmoc-Rink amide resin was treated with 20% piperidine in DMF for 30 min, followed by washing with DMF (3 times), CH_3OH (3 times), CH_2Cl_2 (3 times). This process was repeated to fully remove Fmoc protective group, and the resin then dried *in vacuo*. To the resin in dry dichloromethane was added diisopropylethylamine (10 equivalents) and acryloyl chloride (10 equivalents). The whole reaction mixture was shaken for 4 h at room temperature. The resin was washed with DMF (3 times), CH_3OH (3 times), CH_2Cl_2 (3 times), CH_3OH (2 times) and CH_2Cl_2 (2 times), and dried *in vacuo*.

4-Oxo-benzenebutanamide (25)



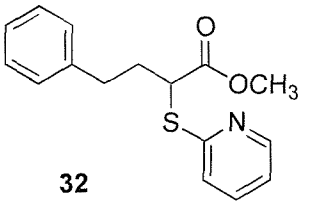
A mixture of acrylate bound Rink amide resin (**23**) (0.28 mmol), compound (**20**) (585 mg, 2.24 mmol) and AIBN (46 mg, 0.28 mmol) in anhydrous benzene (5 mL) was heated to reflux. Tributyltin hydride (0.75 mL, 2.8 mmol) in benzene (1 mL) was added slowly to the reaction mixture over 30 min. The whole reaction mixture was refluxed for 6 h, cooled down and filtered. The resin was washed with DMF (3 × 4 mL), CH_3OH (3 × 4 mL), CH_2Cl_2 (3 × 4 mL), CH_3OH (2 × 4 mL) and CH_2Cl_2 (2 × 4 mL), and dried. Cleavage of the resin was carried out by treatment with TFA/CH_2Cl_2/triethylsilane (5 mL, 20:75:5) for 30 min. The resin was washed with methanol (3 × 5 mL) and dichloromethane (3 × 5 mL) successively. The combined filtrate was evaporated and the crude product purified by preparative TLC with 5% MeOH/CH_2Cl_2 as the developing solvent to afford (**25**) as an oil (10 mg, 20%). NMR spectra data for this commercially available compound could not be found in the literature.

^{1}H NMR (CD_3OD) δ 2.64 (t, J = 6.7 Hz, 2H), 3.33 (t, J = 6.7 Hz, 2H), 7.40-7.60 (m, 3H), 7.98 (m, 2H).

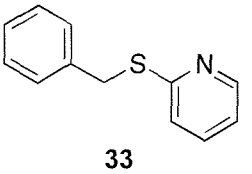
Preparation of Barton Esters

N-Hydroxypyridine-2-thione and *N,N*-dicyclohexylcarbodiimide (1 equivalent) were dissolved in dry CH_2Cl_2 under a nitrogen atmosphere. The solution was protected from light with aluminium foil and cooled to 0 °C, followed by dropwise addition of a carboxylic acid dissolved in dry CH_2Cl_2. The reaction mixture was warmed to room temperature, stirred overnight, and rapidly filtered (again protected from light), and the precipitates were washed with CH_2Cl_2. The combined filtrates were concentrated to give the crude Barton ester, which was purified by quick passage through a short column of silica gel, eluting with CH_2Cl_2/hexanes. The Barton esters were stored in the dark until further use.

Methyl 4-phenyl-2-(2'-thiopyridyl)butanoate (32) and
2-Thiobenzyl pyridine (33)



32



33

To a stirred solution of Barton ester (**26a**) (100 mg, 0.4 mmol) in dry dichloromethane (2 mL) was added methyl acrylate (72 μL, 0.8 mmol) in an ice-water bath under nitrogen. The reaction mixture was irradiated with two 100 W tungsten lamps (25 cm away from the reaction flask) for 1.5 h. Evaporation of solvent and purification of the residue by column chromatography with 30% ethyl acetate in hexanes afforded (**32**) as a yellow oil (42 mg, 37%) and (**33**) as a yellow oil (15 mg, 19%).

Compound (**32**):

^{1}H NMR δ 2.10-2.42 (m, 2H), 2.80 (m, 2H), 3.74 (s, 3H), 4.60 (t, J = 7.2 Hz, 1H), 6.95 (m, 1H), 7.10-7.30 (m, 6H), 7.45 (m, 1H), 8.40 (m, 1H).

Compound (**33**):

^{1}H NMR δ 4.45 (s, 2H), 6.95 (m, 1H), 7.00-7.50 (m, 7H), 8.43 (m, 1H).

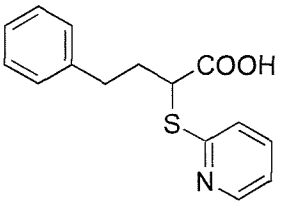
Acrylate-functionalized Wang resin (34)

Diisopropylethylamine (10 equivalents) was added to Wang resin in dry dichloromethane, followed by addition of acryloyl chloride (10 equivalents). The whole reaction mixture was shaken for 4 h at room temperature. The resin was washed with DMF (3 times), CH_3OH (3 times), CH_2Cl_2 (3 times), CH_3OH (2 times) and CH_2Cl_2 (2 times), and dried *in vacuo*.

General Procedure for Radical Reactions with Barton Esters on Solid Phase (36a-36e, 37)

The loaded resins (200 mg for polystyrene resins, 500 mg for TentaGel resins) were agitated in CH_2Cl_2 at 0 °C with 10 equivalents of a Barton ester. Photolysis was initiated by irradiation with two commercial 100 W tungsten lamps. After 4 h, the resin was filtered, washed with DMF (3 × 3 mL), CH_3OH (3 × 3 mL), CH_2Cl_2 (3 × 3 mL), CH_3OH (2 × 3 mL) and CH_2Cl_2 (2 × 3 mL), and dried *in vacuo*. Cleavage of acids from Wang linkers was carried out by treatment with TFA/CH_2Cl_2/triethylsilane (5 mL, 75:20:5) for 90 min. After the resin was washed with CH_3OH (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL), the combined filtrate was evaporated *in vacuo* and the crude product was purified using preparative TLC with ethyl acetate/hexane/acetic acid as the developing solvent. Cleavage of amides from the Rink amide linkers was accomplished by treatment with TFA/CH_2Cl_2/triethylsilane (5 mL, 20:75:5) for 30 min. After the resin was washed with CH_3OH (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL), the combined filtrate was evaporated *in vacuo* and the crude product was purified using preparative TLC with 5% CH_3OH in CH_2Cl_2 as the developing solvent. Yields of compounds (**36a-36e**) and (**37**) were given in the Table 3 and Scheme 20.

4-Phenyl-2-(2-pyridinylthio)butyric acid (36a)



A yellow oil.

IR ν 3020, 2401, 1729, 1589 cm^{-1};

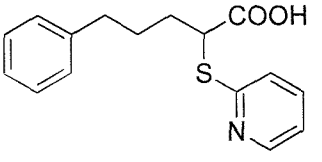
^{1}H NMR δ 2.06-2.11 (m, 1H), 2.40-2.50 (m, 1H), 2.80-2.93 (m, 2H), 3.84 (t, J = 7.4 Hz, 1H), 7.15-7.26 (m, 6 H), 7.43 (d, J = 7.9 Hz, 1H), 7.68 (m, 1H), 8.40 (d, J = 4.7 Hz, 1H);

^{13}C NMR δ 31.7, 33.0, 47.0, 121.3, 124.2, 126.2, 128.5, 128.5, 138.2, 140.5, 147.9, 157.9, 172.7;

EIMS *m/z* 273 (M^+, 16), 255 (40), 229 (44), 182 (100), 164 (77), 138 (80);

HRMS (EI) calcd for $C_{15}H_{15}NO_2S$ 273.08234, found 273.08347.

5-Phenyl-2-(2-pyridinylthio)pentanoic acid(36b)



A yellow oil.

IR ν 3020, 2401, 1732, 1589, 1561 cm^{-1};

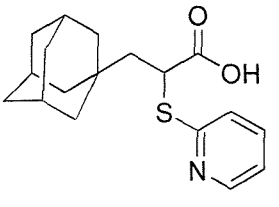
^{1}H NMR δ 1.77-1.92 (m, 3H), 2.18-2.24 (m, 1H), 2.55-2.74 (m, 2H), 3.87 (t, J = 7.0 Hz, 1H), 7.10-7.27 (m, 6 H), 7.40 (d, J = 8.1 Hz, 1H), 7.67 (m, 1H), 8.40 (d, J = 5.0 Hz, 1H);

^{13}C NMR δ 28.8, 29.7, 35.4, 47.8, 121.2, 124.1, 125.9, 128.3, 128.3, 138.1, 141.6, 147.8, 158.0, 172.8;

EIMS *m/z* 287 (M^+, 51), 269 (67), 243 (74), 182 (100), 164 (83);

HRMS (EI) calcd for $C_{16}H_{17}NO_2S$ 287.09799, found 287.09919.

3-(Adamantyl-1-yl)-2-(2-pyridinylthio)propionic acid (36c)



A yellow solid, mp 116-118 °C.

IR ν 3020, 2401, 1728, 1589 cm^{-1};

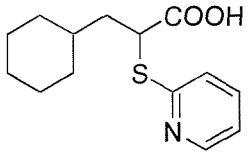
^{1}H NMR δ 1.40-1.93 (m, 16 H), 2.32 (dd, J = 7.0, 14.6 Hz, 1H), 3.99 (t, J = 5.5 Hz, 1H), 7.19 (m, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.67 (m, 1H), 8.44 (d, J = 4.5 Hz, 1H);

^{13}C NMR δ 28.5, 28.7, 33.1, 36.8, 42.1, 44.1, 121.0, 123.8, 138.0, 147.8, 158.5, 173.2;

EIMS *m/z* 317 (M^+, 5), 299 (68), 273 (44), 182 (85), 164 (100), 136 (98);

HRMS (EI) calcd for $C_{18}H_{23}NO_2S$ 317.14496, found 317.14362.

3-Cyclohexyl-2-(2-pyridinylthio)propinoic acid (36d)



A yellow oil.

IR ν 3020, 2401, 1730, 1589 cm^{-1};

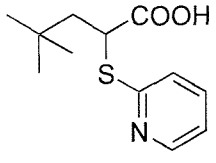
^{1}H NMR δ 0.88-0.96 (m, 2H), 1.10-1.28 (m, 3H), 1.52-1.74 (m, 7H), 2.04 (m, 1H), 3.99 (t, J = 7.5 Hz, 1H), 7.22 (m, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.69 (m, 1H), 8.42 (d, J = 4.5 Hz, 1H);

^{13}C NMR δ 26.0, 26.1, 26.4, 32.7, 33.2, 34.9, 37.3, 45.2, 121.2, 124.1, 138.1, 147.8, 158.3, 172.9;

EIMS *m/z* 265 (M^+, 7), 247 (33), 182 (93), 164 (94), 125 (100);

HRMS (EI) calcd for $C_{14}H_{18}NO_2S$ 265.11365, found 265.11492.

4,4-Dimethyl-2-(2-pyridinylthio)pentanoic acid (36e)



A yellow oil.

IR ν 3020, 2401, 1730, 1588 cm^{-1};

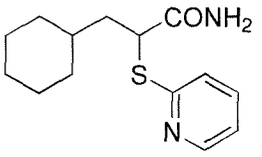
^{1}H NMR δ 0.96 (s, 9H), 1.57 (dd, J = 4.8, 14.6 Hz, 1H), 2.45 (dd, J = 6.8, 14.6 Hz, 1H), 3.90 (t, J = 5.8 Hz, 1H), 7.21 (m, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.68 (m, 1H), 8.44 (d, J = 4.6 Hz, 1H);

^{13}C NMR δ 29.3, 31.2, 43.3, 43.9, 121.1, 123.8, 138.0, 147.9, 158.3, 173.2;

EIMS *m/z* 239 (M^+, 6), 195 (67), 182 (93), 138 (100), 111 (90);

HRMS (EI) calcd for $C_{12}H_{17}NO_2S$ 239.09800, found 239.09696.

3-Cyclohexyl-2-(2-pyridinylthio)propionamide (37)



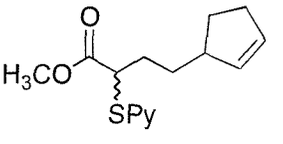
^{1}H NMR δ 0.83-1.00 (m, 2H), 1.14-1.25 (m, 3H), 1.55-1.80 (m, 7H), 2.03 (m 1H), 4.00 (t, J = 7.4 Hz, 1H), 7.21 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.68 (m, 1H), 8.42 (d, J = 4.4 Hz, 1H);

^{13}C NMR δ 26.0, 26.1, 26.4, 32.7, 33.2, 34.9, 37.3, 45.3, 121.1, 124.1, 138.0, 147.8, 158.4, 172.9.

Cascade Radical Cyclization of Barton Ester (38) on Solid Phase (40-42)

The acrylate bound Wang resin (0.43 mmol) was agitated in dichloromethane with (**38**) (1.01 g, 4.3 mmol) at 0 °C. Photolysis was initiated with two commercial 100 W tungsten lamps. After 5 h, the resin was filtered, washed with DMF (3 × 5 mL), CH_3OH (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), CH_3OH (5 mL) and CH_2Cl_2 (5 mL), and dried *in vacuo*. The products were then cleaved from the resin by treatment with 75% TFA in CH_2Cl_2 (8 mL) for 90 min. The resin was washed successively with 30% CH_3OH/CH_2Cl_2 (4 × 5 mL), and the combined filtrates evaporated and dried *in vacuo*. The crude products were then dissolved in anhydrous methanol (3 mL) at –15 °C followed by addition of thionyl chloride (58 μL, 0.8 mmol). After 30 min, the reaction mixture was warmed to room temperature and stirred overnight. Evaporation of solvent and purification of the residue by preparative TLC with 20% ethyl acetate/hexanes as the developing solvent gave the products (**40**) (16 mg, 13%), (**41**) (29 mg, 24%) and (**42**) (28 mg, 36%).

Methyl 4-(2-cyclopentene)-2-(2-pyridinylthio)butanoate (40)



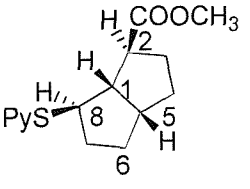
IR ν2859, 1732, 1578, 1455 cm^{-1};

^{1}H NMR δ 1.30-2.10 (m, 6H), 2.24-2.38 (m, 2H), 2.68 (m, 1H), 3.73 (s, 3H), 4.58 (t, J = 7.3 Hz, 1H), 5.60-5.75 (m, 2H), 6.99 (m, 1H), 7.19 (m, 1H), 7.48 (m, 1H), 8.40 (m, 1H);

^{13}C NMR δ 29.6, 30.3, 32.0, 33.5, 45.2, 46.6, 52.5, 119.9, 122.3, 130.8, 134.5, 136.1, 149.5, 157.4, 173.3;

EIMS *m/z* 277 (M^+, 44), 244 (55), 164 (72), 112 (100), 80 (95).

Methyl (1α,3aα,6α,6aα)-Octahydro-6-(2-pyridinylthio)-1-pentalenecarboxylate (41a)



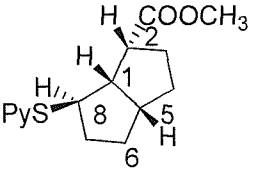
IR ν 2871, 1731, 1570, 1447 cm^{-1};

^{1}H NMR δ 1.30-1.42 (m, 2H), 1.62-1.82 (m, 2H), 1.90-2.08 (m, 3H), 2.22 (m, 1H), 2.60-2.65 (m, 1H, C^2H), 2.65-2.75 (m, 2H, $C^1H + C^5H$), 3.66 (s, 3H), 3.90 (m, 1H, C^8H), 6.95 (m, 1H), 7.15 (m, 1H), 7.45 (m, 1H), 8.39 (m, 1H);

^{13}C NMR δ 31.3, 31.9, 33.1, 33.2, 42.9 (*C*H), 49.3 (C^8H), 50.8 (C^2H), 51.7 (OCH_3), 54.6 (*C*H), 119.3 (*C*H), 122.5 (*C*H), 135.7 (*C*H), 149.4 (*C*H), 159.7 (*C*), 176.0 (*C*=O);

EIMS *m/z* 277 (M^+, 86), 244 (97), 184 (40), 111 (100).

Methyl (1α,3aα,6α,6aα)-Octahydro-6-(2-pyridinylthio)-1-pentalenecarboxylate (41b)



IR ν 2871, 1731, 1570, 1447 cm^{-1};

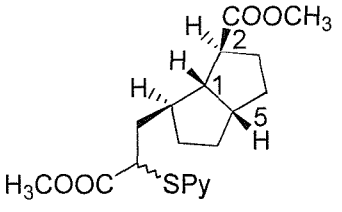
^{1}H NMR δ 1.28 (m, 1H), 1.48-1.68 (m, 3H), 1.73-1.79 (m, 1H), 1.87-2.10 (m, 2H), 2.32-2.40 (m, 1H), 2.62-2.70 (m, 2H, $C^1H + C^5H$), 2.70-2.80 (m, 1H, C^2H), 3.57

(s, 3H), 3.73 (m, 1H, C^{8}*H*), 6.94 (m, 1H), 7.14 (m, 1H), 7.45 (m, 1H), 8.40 (m, 1H);

^{13}C NMR δ 27.4, 31.7, 33.2, 36.2, 42.8 (*C*H), 45.3 (*C*^{8}H), 47.6 (*C*^{2}H), 50.8 (*C*H), 51.4 (*OC*H$_3$), 119.2 (*C*H), 122.0 (*C*H), 135.8 (*C*H), 149.5 (*C*H), 160.0 (*C*), 174.2 (*C*=O);

EIMS *m/z* 277 (M^{+}, 70), 244 (86), 184 (37), 111 (100).

Methyl (1α,3aα,6α,6aα)-Octahydro-6-(methoxycarbonyl)-2-(2-pyridinylthio)-1-pentalenepropanoate (42a)



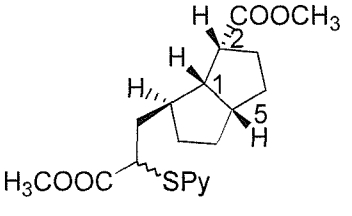
IR ν 2865, 2359, 1729, 1586, 1457 cm^{-1};

^{1}H NMR δ 1.10-1.16 (m, 2H), 1.40-1.95 (m, 7H), 2.05-2.12 (m, 2H), 2.29 (m, 1H, C^{1}*H*), 2.55 (m, 1H, C^{5}*H*), 2.70 (m, 1H, C^{2}*H*), 3.68 (s, 3H), 3.75 (s, 3H), 4.48 (dd, *J* = 3.7, 10.9 Hz, 1H, C*H*SPy), 6.98 (m, 1H), 7.17 (m, 1H), 7.47 (m, 1H), 8.39 (m, 1H);

^{13}C NMR δ 26.9, 31.3, 33.5, 33.6, 38.7, 41.2, 43.6 (*C*^{5}H), 45.5 (*C*HSPy), 47.9 (*C*^{2}H), 51.3 (*OC*H$_3$), 51.8 (*C*^{1}H), 52.4 (*OC*H$_3$), 119.8 (*C*H), 122.1 (*C*H), 136.1 (*C*H), 149.5 (*C*H), 157.4 (*C*), 172.8 (*C*=O), 174.3 (*C*=O);

EIMS *m/z* 363 (M^{+}, 24), 332 (25), 196 (100), 111 (95), 79 (69).

Methyl (1α,3aα,6α,6aα)-Octahydro-6-(methoxycarbonyl)-2-(2-pyridinylthio)-1-pentalenepropanoate (42b)



IR ν2861, 2373, 1729, 1588, 1464 cm^{-1};

^{1}H NMR δ 1.00-1.14 (m, 2H), 1.38-1.60 (m, 2H), 1.65-1.98 (m, 7H), 2.31 (m, 1H, C^1*H*), 2.54 (m, 1H, C^5*H*), 2.70 (m, 1H, C^2*H*), 3.68 (s, 3H), 3.70 (s, 3H), 4.51 (dd, *J* = 4.3, 10.1 Hz, 1H, C*H*SPy), 6.98 (m, 1H), 7.19 (m, 1H), 7.47 (m, 1H), 8.38 (m, 1H);

^{13}C NMR δ 27.0, 31.3, 33.5, 33.5, 37.4, 40.9, 43.7 (*C*^{5}H), 45.8 (*C*HSPy), 48.0 (*C*^{2}H), 51.3 (O*C*H$_3$), 51.7 (*C*^{1}H), 52.5 (O*C*H$_3$), 119.8 (*C*H), 122.3 (*C*H), 136.0 (*C*H), 149.3 (*C*H), 157.5 (*C*), 173.6 (*C*=O), 174.4 (*C*=O);

EIMS *m/z* 363 (M$^+$, 13), 196 (100), 111 (82), 79 (39).

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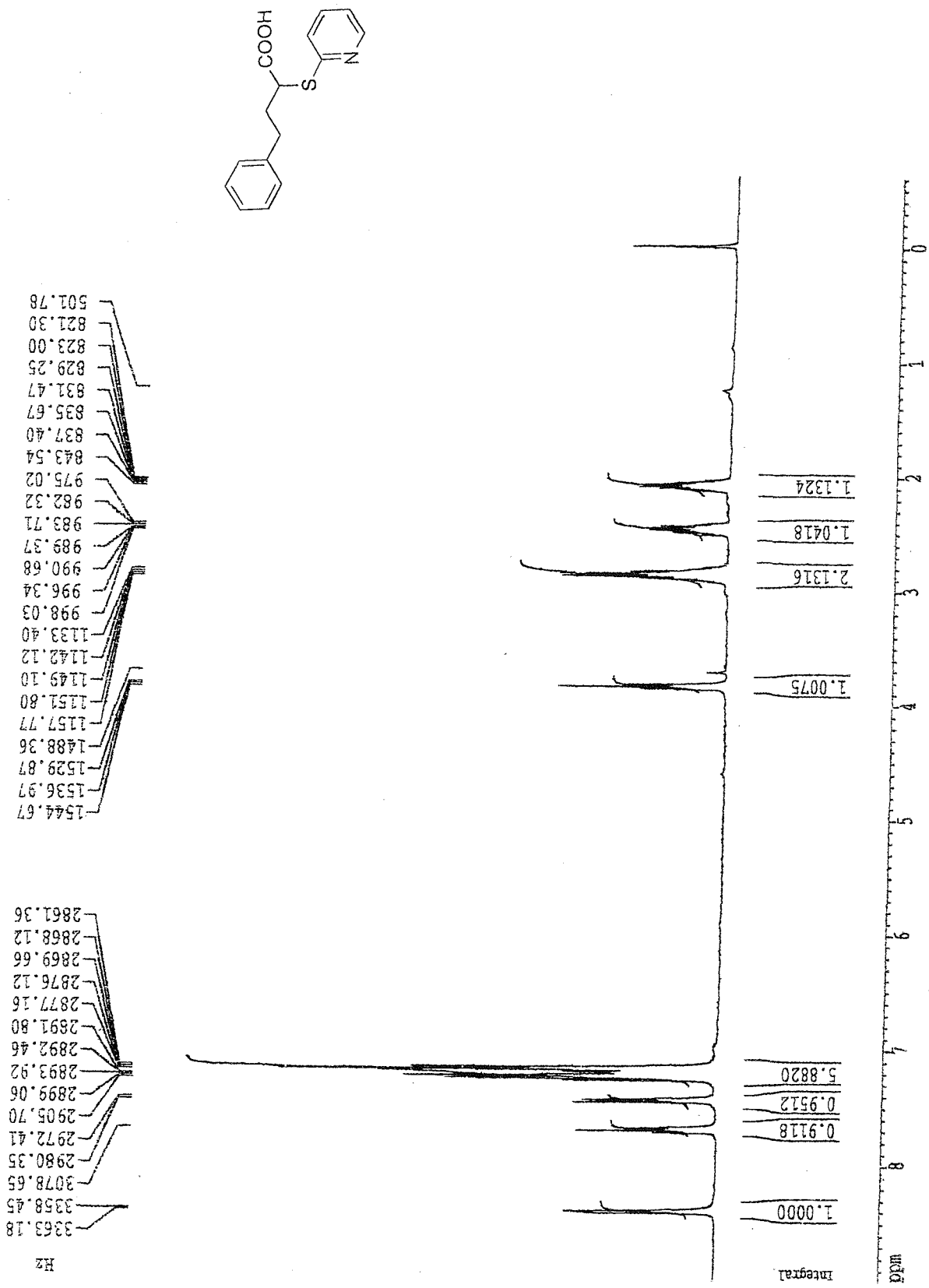
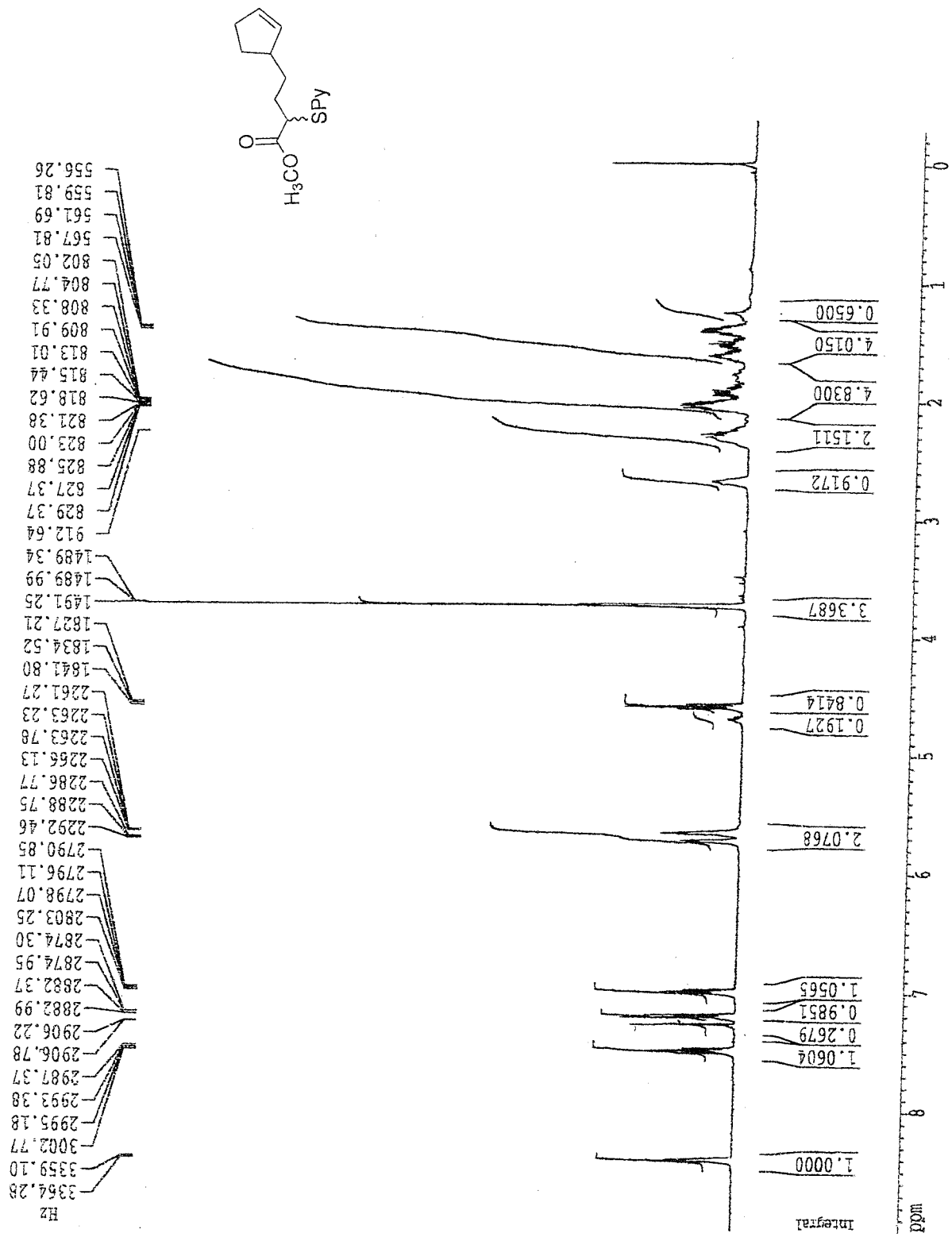
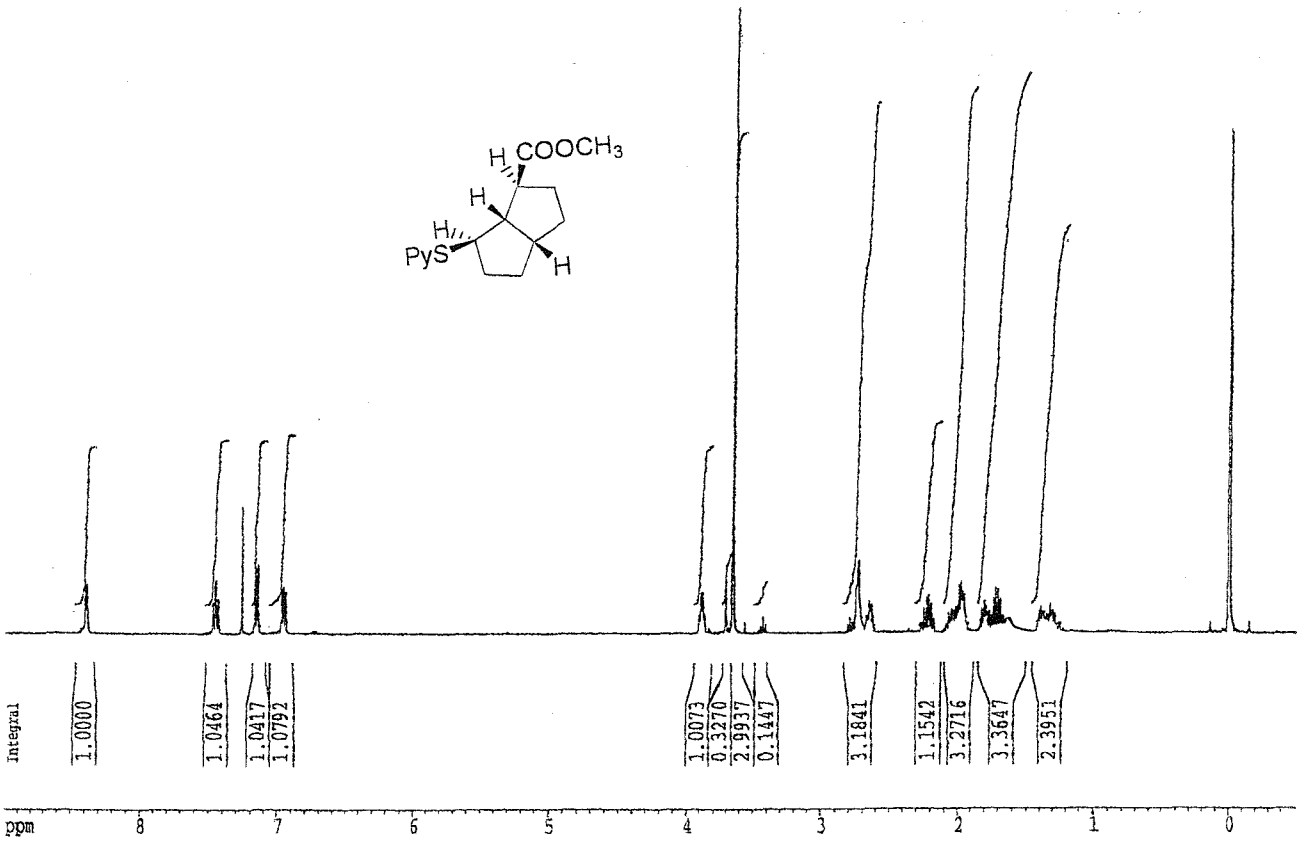
Appendix 1: ^{1}H NMR spectrum of compound (**36a**) in $CDCl_3$

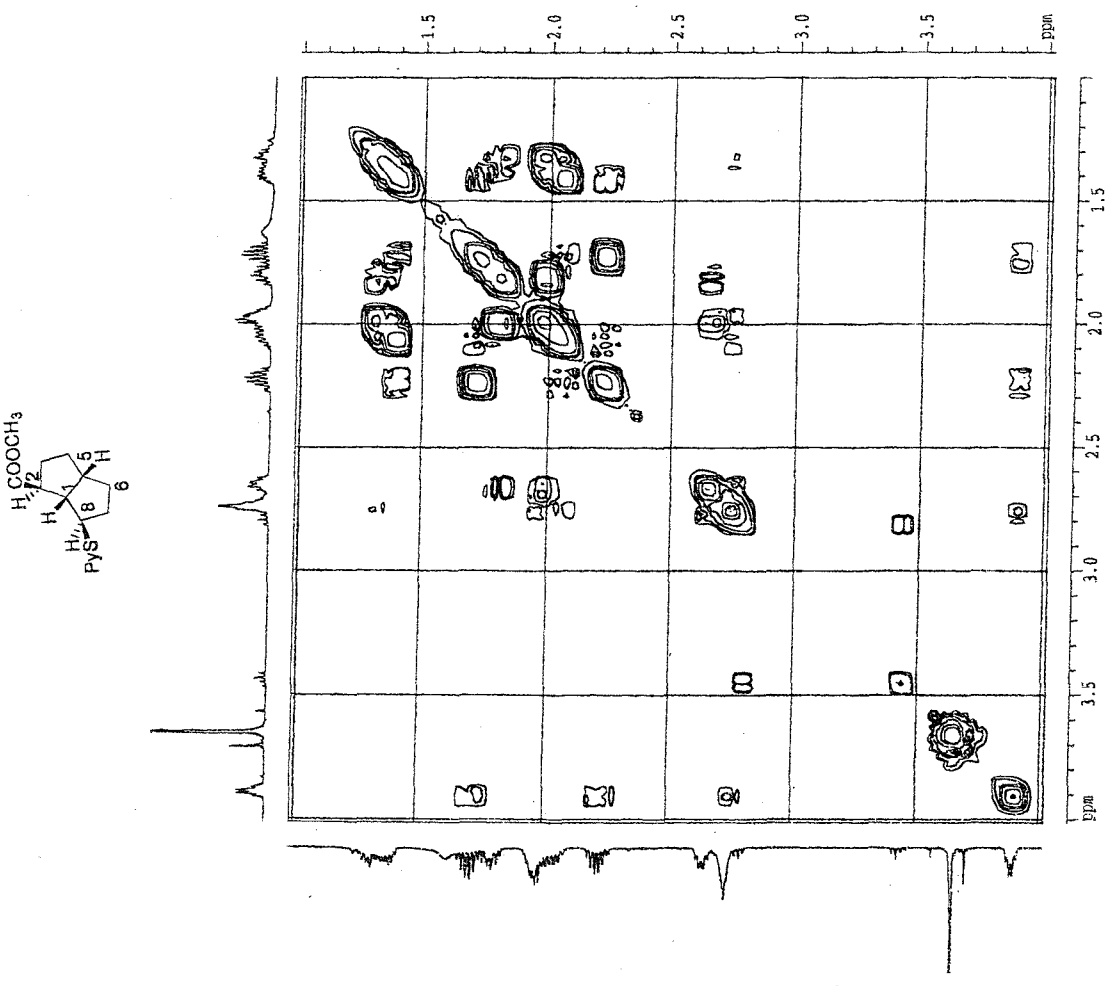


Appendix 2: ^{1}H NMR spectrum of compound (**40**) in $CDCl_3$

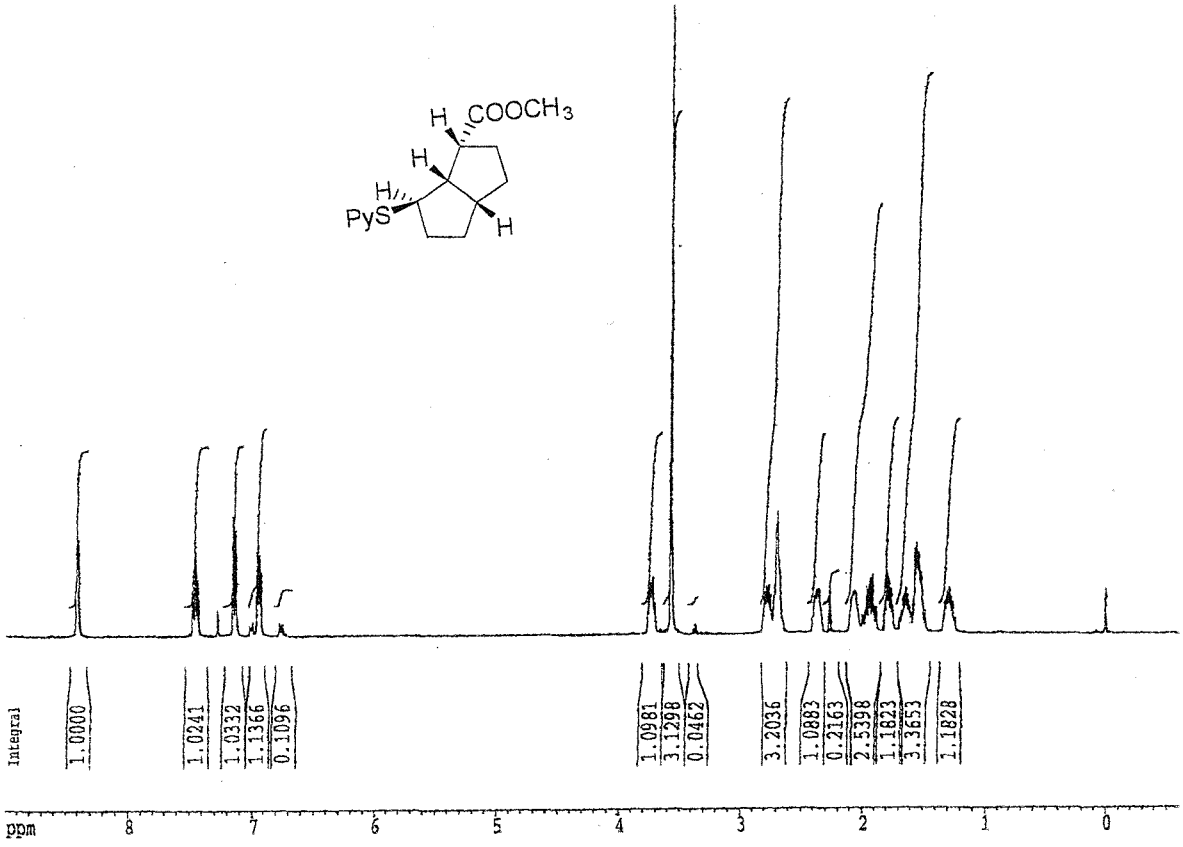


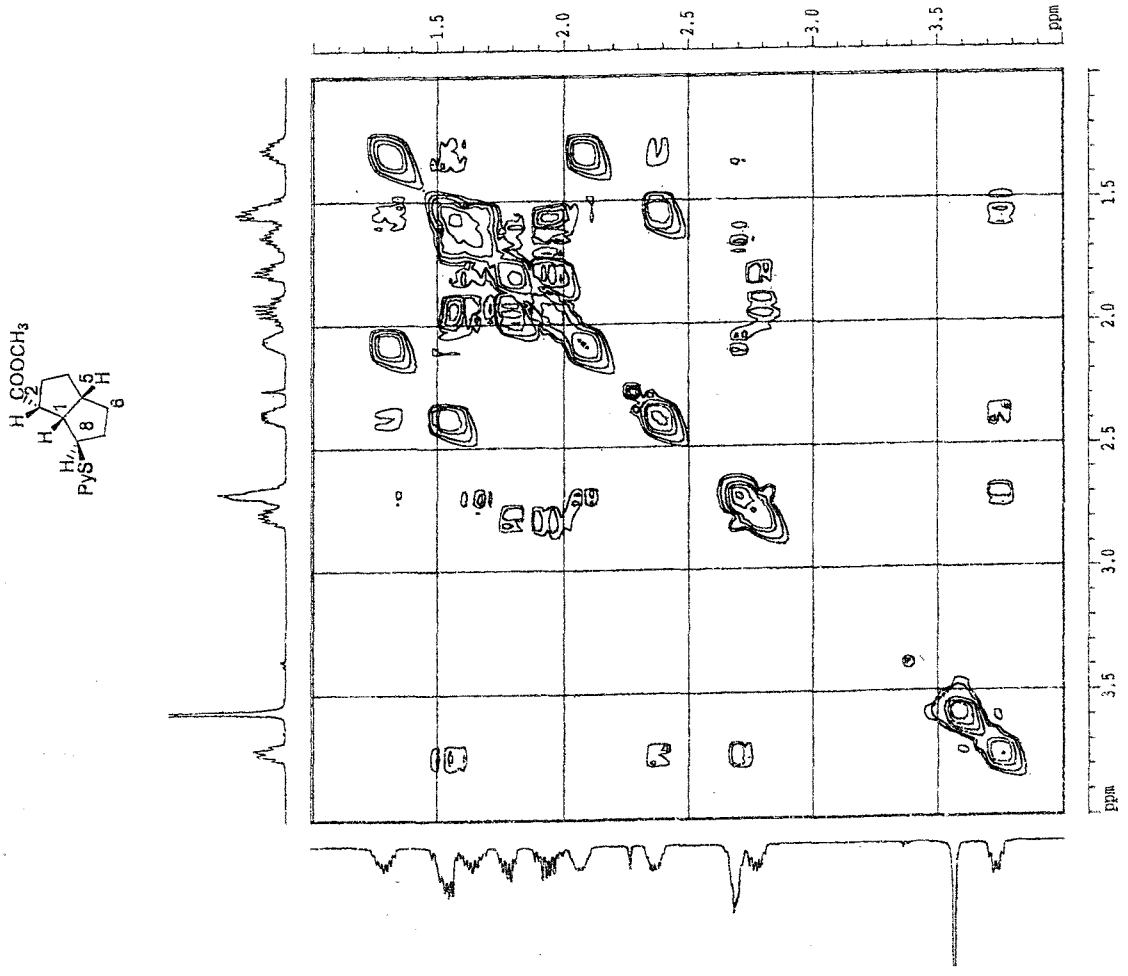
Appendix 3: ^{1}H NMR and 2D NMR (COSY) spectra of compound (**41a**) in $CDCl_3$



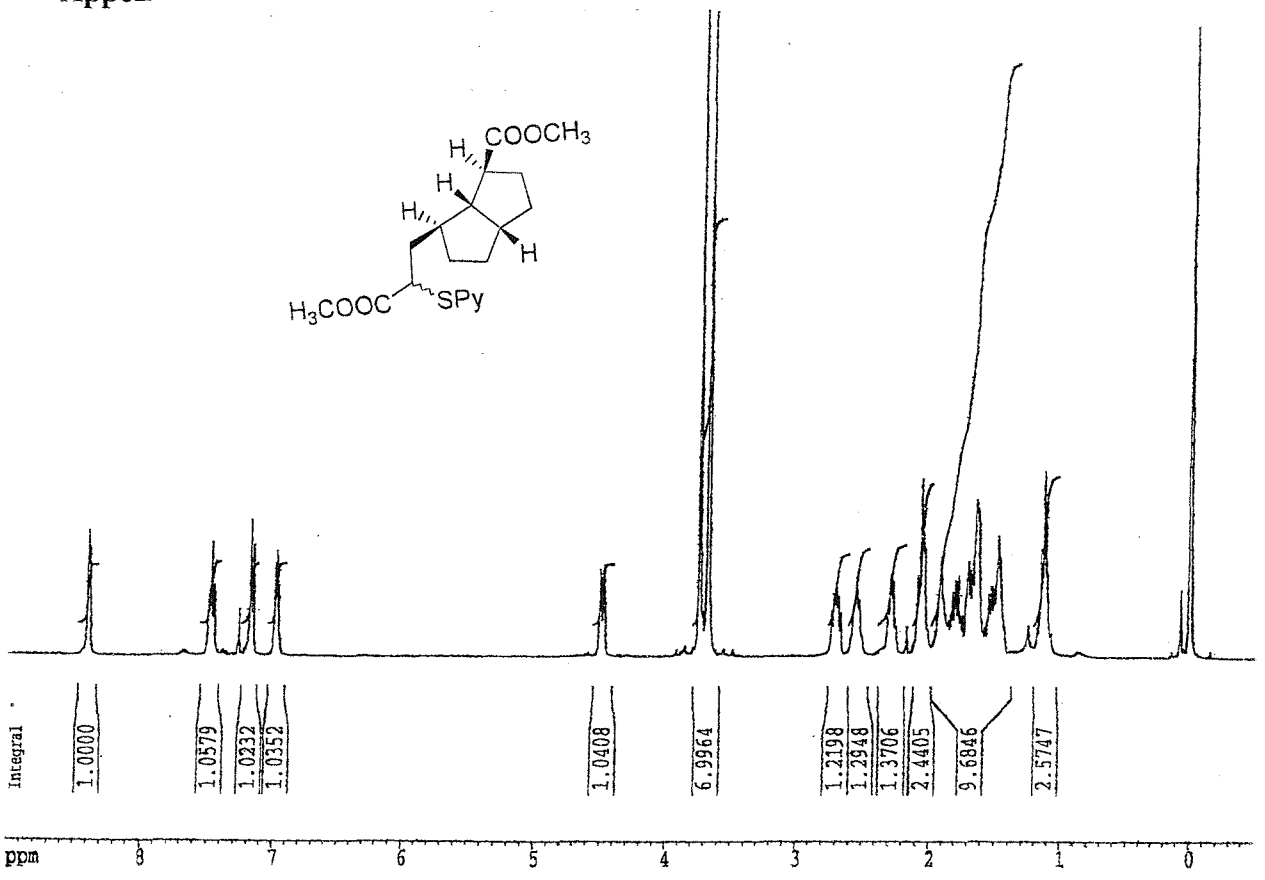


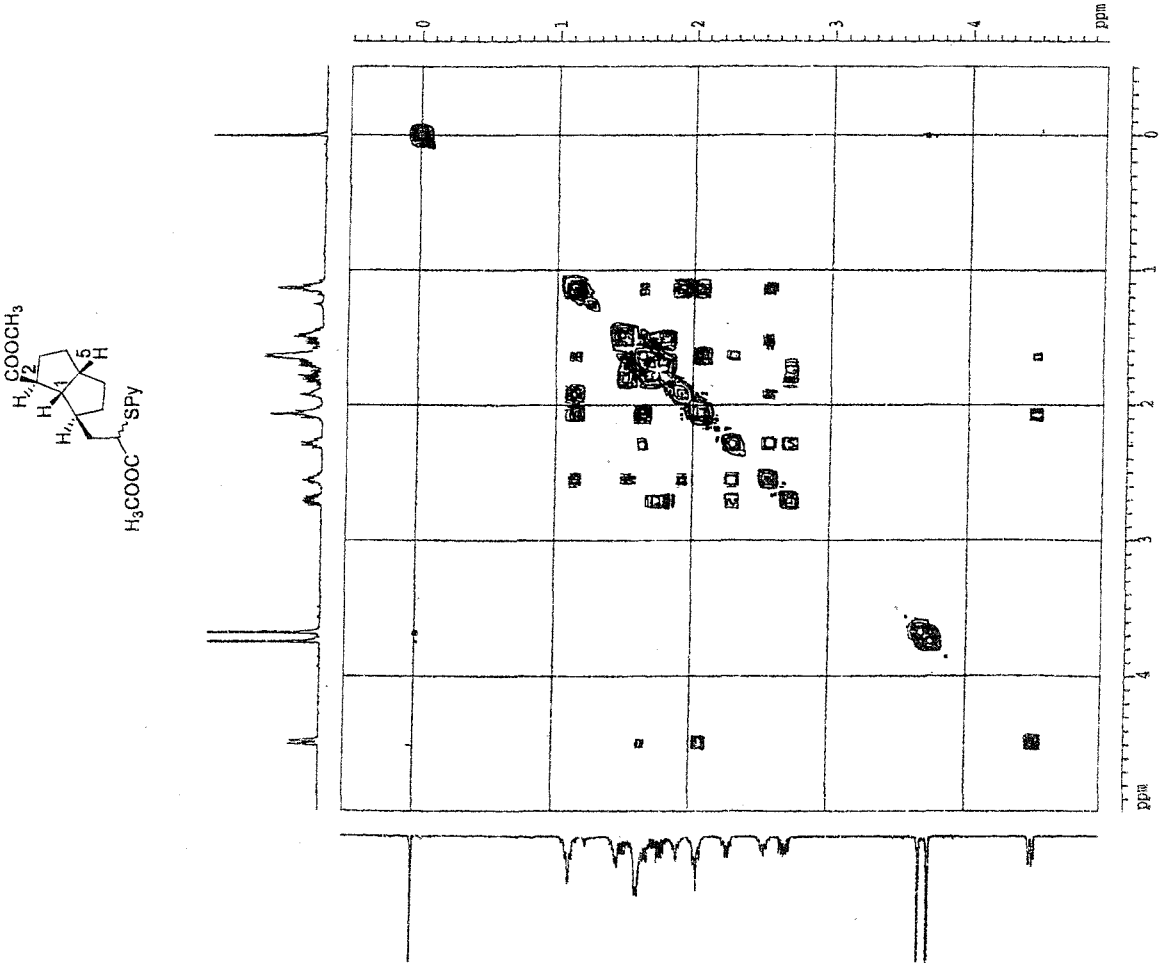
Appendix 4: ^{1}H NMR and 2D NMR (COSY) spectra of compound (**41b**) in $CDCl_3$



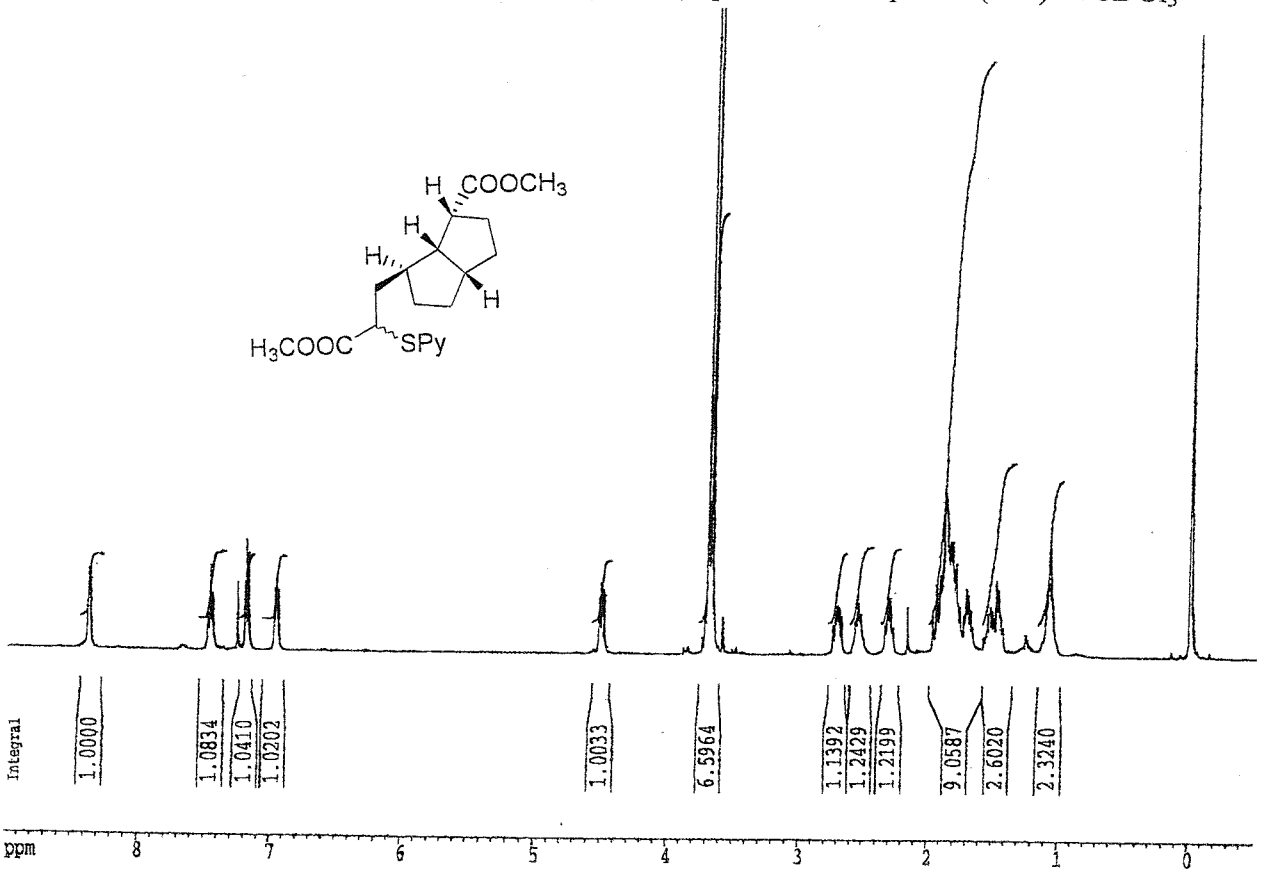


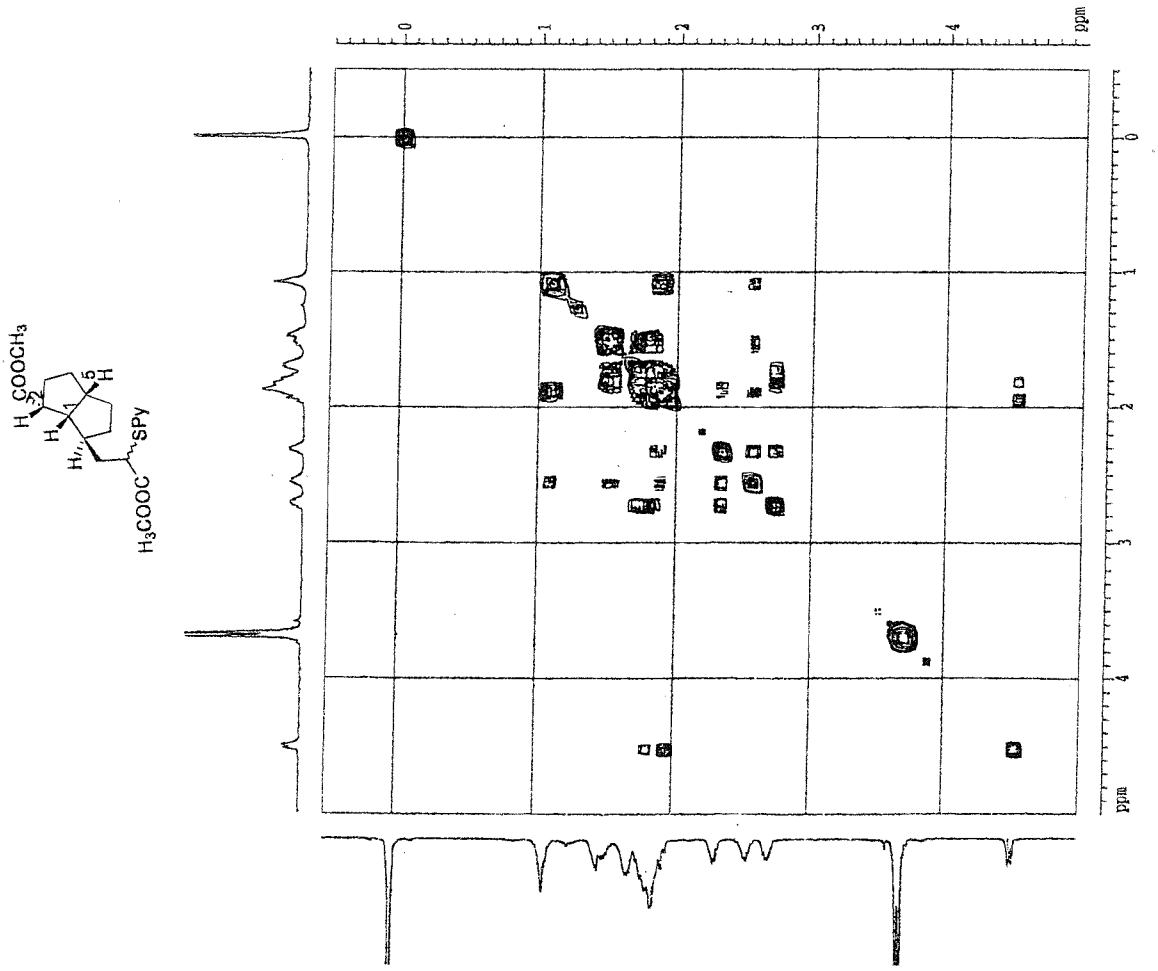
Appendix 5: ^{1}H NMR and 2D NMR (COSY) spectra of compound (**42a**) in $CDCl_3$





Appendix 6: ^{1}H NMR and 2D NMR (COSY) spectra of compound (**42b**) in $CDCl_3$





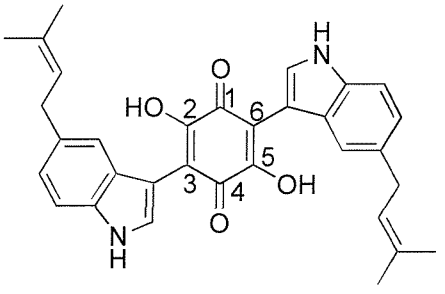
Chapter 2: Synthetic Strategies Towards Asterriquinones

1. The Asterriquinone Natural Products

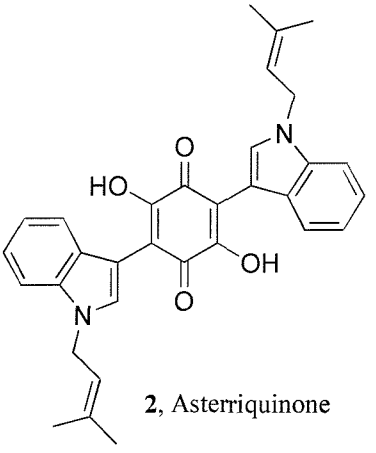
1.1. The Asterriquinone Family

The asterriquinones are a family of naturally occurring bis(indolyl)dihydroxybenzoquinones found in fungi. The purple antibiotic, cochliodinol (**1**) (Figure 1), isolated in 1968 from *Chaetomium* species was the first asterriquinone structure reported.[1] The antitumor agent, asterriquinone itself (*N*-1,1-dimethylallyl indolyl benzoquinone) (**2**) (Figure 1) is a metabolite produced by *Aspergillus terreus* IFO 6123.[2] Many other asterriquinones with either 1,1-dimethylallyl (prenyl) and/or 3,3-dimethylallyl (reverse prenyl) side chain(s) at different positions of the indole moiety have been identified.[3,4,5,6]

Figure 1



1, Cochliodinol

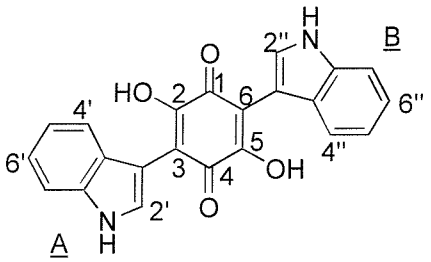


2, Asterriquinone

The asterriquinones exhibit a wide range of biological activities (Figure 2), including antitumour properties,[2b,7] inhibition of serine proteases in the blood coagulation pathway[4] and the inhibition of HIV reverse transcriptase.[5] Some asterriquinone analogues have been discovered to directly inhibit the binding of Grb2 adaptor protein to tyrosine-phosphorylated EGF receptor, an interaction implicated in many classes of cancerous tumours.[6] A group at Merck also disclosed that demethylasterriquinone B1 functions as the first small molecule insulin receptor activator which mimics the function of insulin. Therefore this result may lead to new therapies for the treatment of diabetes.[8] All of these properties

apparently stem from the ability of asterriquinones to either promote or prevent protein-protein interactions.

Figure 2



	Substituent on indole A	Substituent on indole B	Biological Activities (μM)
asterriquinone E (neoasterriquinone)	C-2'	C-2"	Grb-2-EGF RTK binding IC_{50}, 2.5
demethylasterriquinone	C-7'	C-2"	insulin receptor agonist 3
isocochliodinol	C-6'	C-6"	HIV-1 protease IC_{50}, 0.18
semicochliodinol A	C-5'		cathepsin D IC_{50}, 2.5

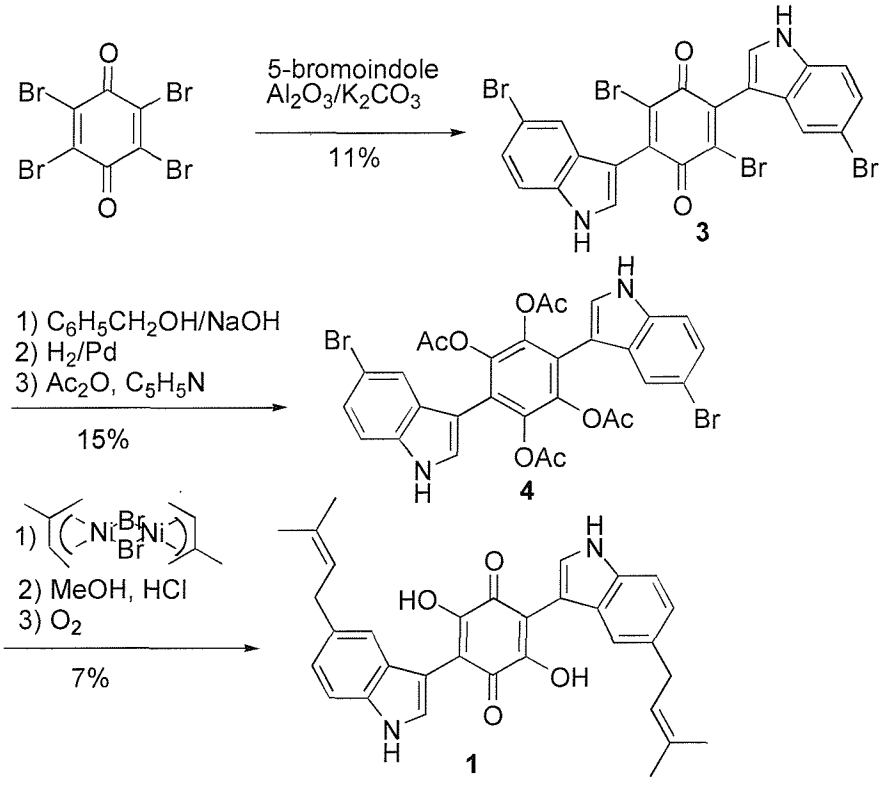
To gain insight into the structure-activity relationships of asterriquinones, a series of chemically modified derivatives of asterriquinones and 2,5-dihydroxyl benzoquinone analogues were prepared, and the cytotoxic activity against mouse leukemia P388 cells investigated. Asterriquinone analogues having a 2,5-dimethoxybenzoquinone moiety and the 2,5-diamino-benzoquinone moiety did not show any cytotoxicity.[7] Further study shows that at least one hydroxy group or acetoxy group in the benzoquinone moiety is important to exhibit cytocoxicity, and a single methoxy group and/or one acetoxy group substitution is more potent than when two hydroxy groups are substituted.[9] The prenyl and reverse prenyl groups at different positions of the indole ring have similar activity.[10] Synthetic tetrahydroasterriquinone E having a saturated prenyl groups at 2-position of both indole moieties, was found to show more potent inhibition of the Grb2 adapter protein to tyrosine-phosphorylated EGF receptor (IC_{50}, 1.2 μM) than the natural asterriquinone E with prenyl groups, [11] indicating that the olefin functionality

present in the indole moiety is also not necessary for Grb2 inhibition. Both the 2,5-dihydroxybenzoquinone core and the indole ring are essential for biological activity.[9,10,12]

1.2. Syntheses of Asterriquinones

The wide array of interesting biological activities and their challenging structures have intrigued organic chemists to target the syntheses of this group of compounds. The first route was described by Hörcher *et al.*, who prepared cochliodinol in six steps from *p*-bromanil and 5-bromoindole (Scheme 1).[13]

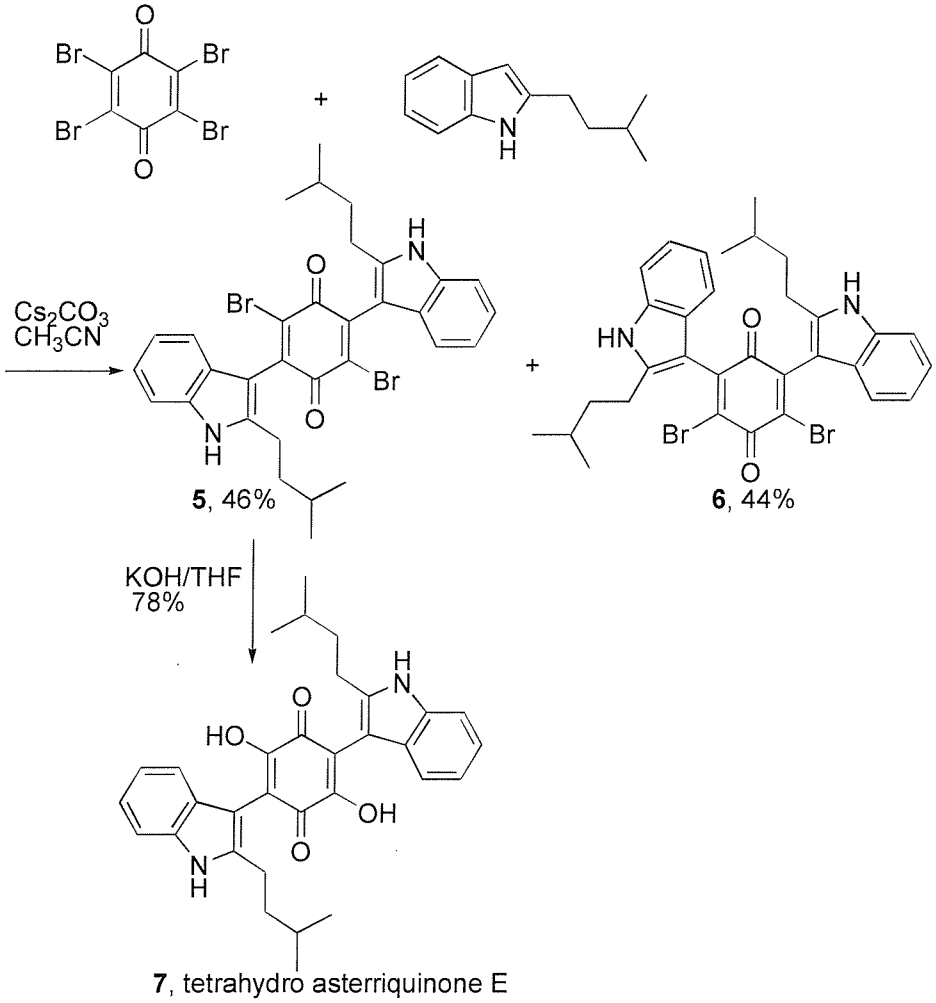
Scheme 1 Synthesis of cochliodinol



Tetrahydro asterriquinone E (**7**) was synthesized by a one-pot, two step route (Scheme 2).[11] The short synthesis was accomplished by treating *p*-bromanil with 2 equivalents of 2-(3-methylbutyl)indole in the presence of cesium carbonate in acetonitrile at ambient temperature to provide a 1:1 mixture of the dibromo regioisomers (**5**) and (**6**). Compound (**5**) was then hydrolysed to afford (**7**). Alternatively, these two reactions could be carried out in one pot, without the

isolation of (**5**). Hydrolysis of the crude mixture of regioisomers provided (**7**) in a total of 31% yield from bromanil.

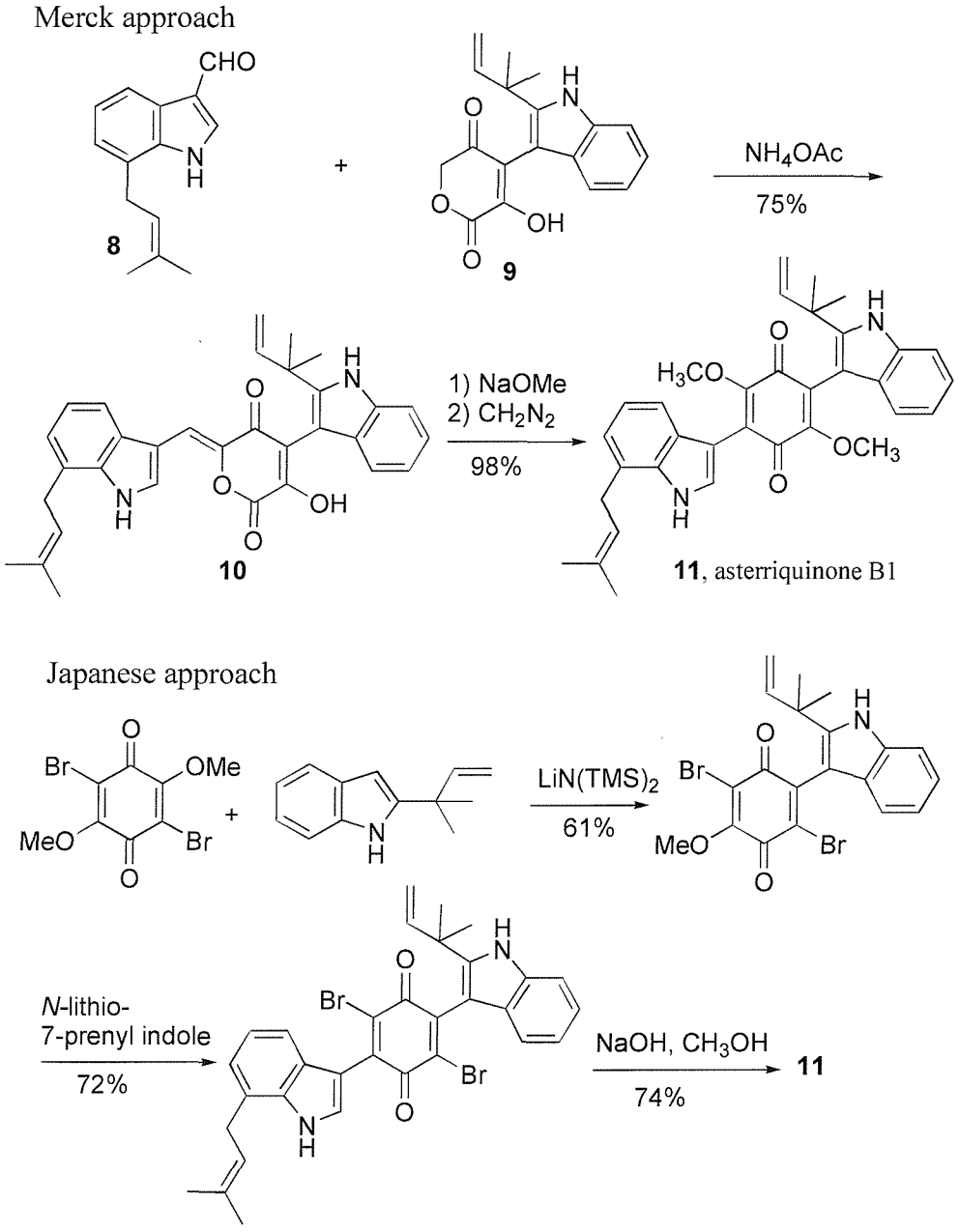
Scheme 2 Synthesis of tetrahydro asterriquinone E



Introduction of two indolyl moieties to the benzoquinone core structure in a single step, as seen in these two examples, inevitably results in low yield due to the formation of regioisomers. Such routes are only suitable for symmetrical compounds. Liu and co-workers at Merck reported a convergent approach, as demonstrated by the first total synthesis of asterriquinone B1 (Scheme 3).[14] Condensation of prenyl indole carboxaldehyde (**8**) with pyrandione (**9**) gave an intermediate (**10**), which underwent rearrangement under basic conditions to give asterriquinone B1 (**11**). This approach is applicable for both symmetrical and unsymmetrical compounds. A series of 3,6-diaryl-2,5-dihydroxybenzoquinones

were prepared for biological study using this approach.[15] Another convergent synthesis of asterriquinone B1 (Scheme 3) was recently reported[16] by a Japanese group. Selective introduction of two substituted indoles onto the dibromobenzoquinone core was followed by treatment with sodium hydroxide in methanol, affording the purple product (**11**) in an overall yield of 33%.

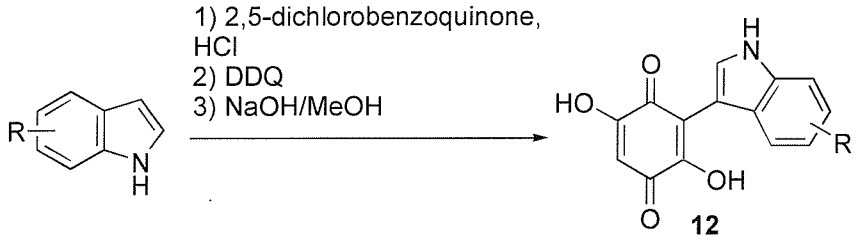
Scheme 3 Synthesis of asterriquinone B1



The 3-indolylquinone substructure is reported to be efficiently prepared by the acid-catalyzed condensation of indoles with 2 equivalents of 2,5-

dichlorobenzoquinone, followed by DDQ oxidation.[17] The resulting dichloroquinones were then hydrolyzed to the 3-indolylquinones (**12**) (Scheme 4). The first condensation step is affected by electronic and steric factors. Electron rich indoles are good reactants, while indoles with bulky alkyl substitution fail completely in the reaction.

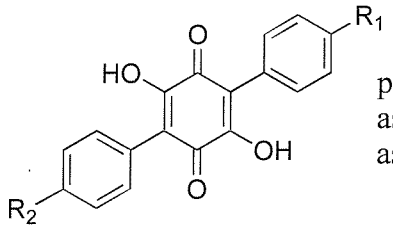
Scheme 4 Synthesis of 3-indolylquinone



2. The Terphenylquinone Natural Products

2.1. The Terphenylquinones and Related Fungal Pigments

Figure 3 Simple terphenylquinones

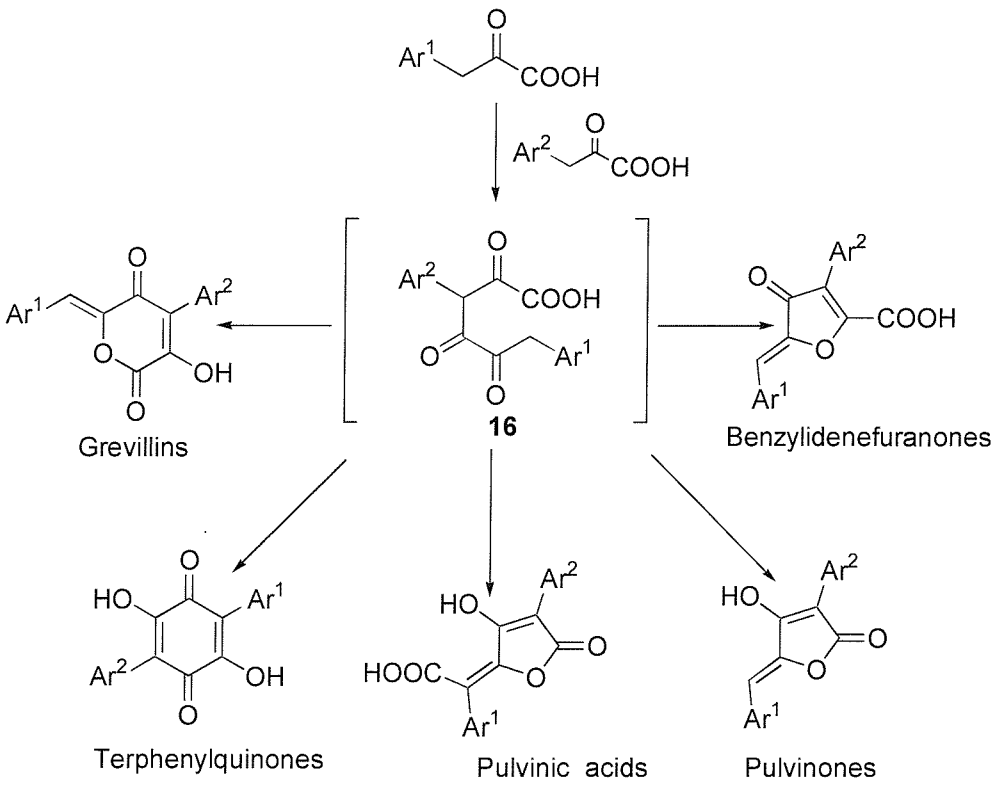


	R_1	R_2
polyporic acid (**13**)	H	H
ascocorynin (**14**)	OH	H
astromentin (**15**)	OH	OH

The asterriquinone scaffold is similar to that of the terphenylquinones, magenta-coloured fungal pigments having bisphenylbenzoquinone skeleton, simple terphenylquinones being shown in Figure 3. Terphenylquinones, together with other metabolites such as the orange grevillins, the yellow and red pulvinic acids, the red xylerythrins, the orange furanones, and yellow-green fluorescent pulvinones have attracted the attention of organic chemists for over a century as they generate a variety of colours and colour changes in organisms.[18] It is thought that all these natural colouring matters have a similar biosynthetic origin and could

arise from a common ketocarboxylic acid of the type (**16**), a dimer derived by enzymatic condensation of arylpyruvic acids (Scheme 5). The biogenetic interrelationships between grevillins and terphenylquinones, xylerythrins and pulvinic acids are also exemplified with the *in vitro* conversion of terphenylquinones to these fungal pigments. The grevillins can be transformed to terphenylquinones by treatment with NaOEt/EtOH, while Perkin-type condensation of terphenylquinones with arylacetic acid gives xylerythrins, and rearrangement of terphenylquinones in the presence of dimethyl sulphoxide leads to pulvinic acid derivatives.[19,20]

Scheme 5

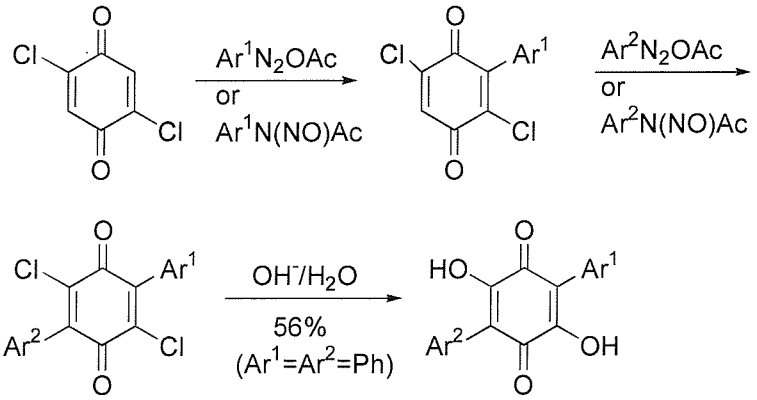


2.2. Syntheses of the Terphenylquinones

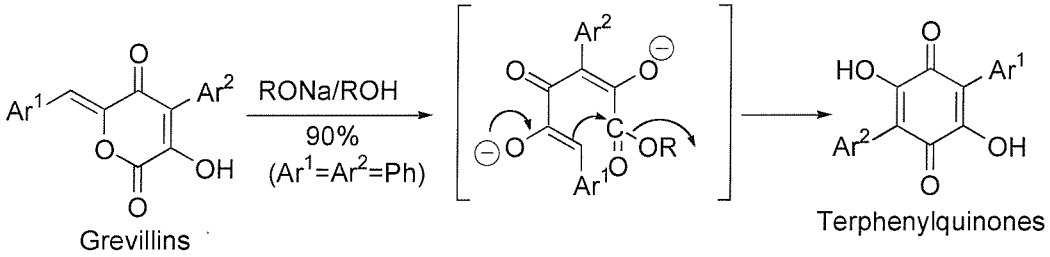
Polyporic acid (2,5-dihydroxy-3,6-diphenyl-p-benzoquinone, **13**), isolated in 1877, was reported to be active against the leukemia L-1210 cell line.[21] Astromentin (**15**) shows significant smooth muscle stimulant activity and proves to be an effective anticoagulant.[22] These interesting biological activities have induced the development of synthetic routes to these fungal pigments. Early syntheses were based on elaboration of the core benzoquinone by arylation with *N*-

nitrosoacetanilides or diazotised aromatic amines twice to introduce two aryl groups, followed by alkaline hydrolysis.[23] This approach in general gives only moderate overall yields, especially in the case of unsymmetrically substituted terphenylquinones.

Scheme 6



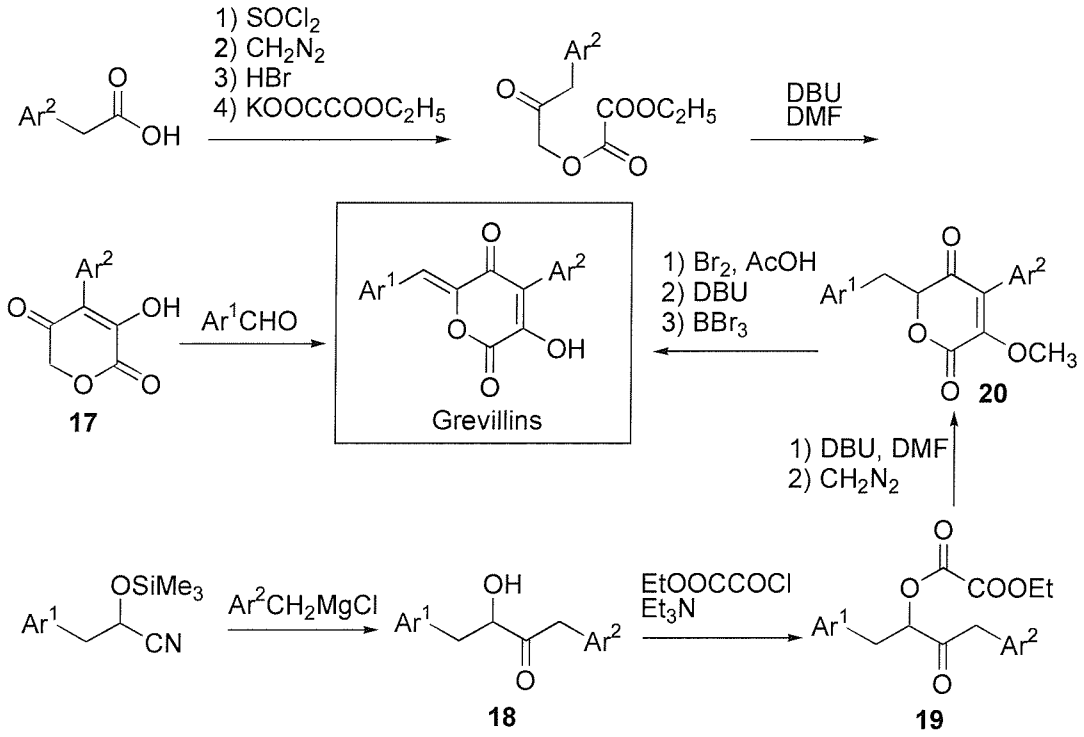
Scheme 7



An efficient and versatile route to unsymmetrically substituted terphenylquinones was developed which makes use of the base catalysed rearrangement of grevilllins, affording terphenylquinones in high yield (Scheme 7).[20,24] The enolate involved in this transformation is similar to the putative intermediate (**16**) in the biosynthesis of grevillins, terphenylquinones and other fungal pigments. The flexibility of this approach is demonstrated by the syntheses of polyporic acid, ascocorynin, and leucomelone as well as of terphenylquinones which contain 2,4,5-trihydroxyphenyl, 4-nitrophenyl, 2,4-dichlorophenyl, naphthyl, indolyl, and styryl residues. The grevillins can be prepared by either condensation of pyrandione intermediate (**17**) with an aldehyde[24] or using bis-benzylacyloins (**18**) and their corresponding oxalate derivatives (**19**) as key intermediates (Scheme 8).[20,25]

Merck's approach to the asterriquinones relies on these well-established syntheses of grevillins and terphenylquinones.

Scheme 8 Syntheses of grevillins

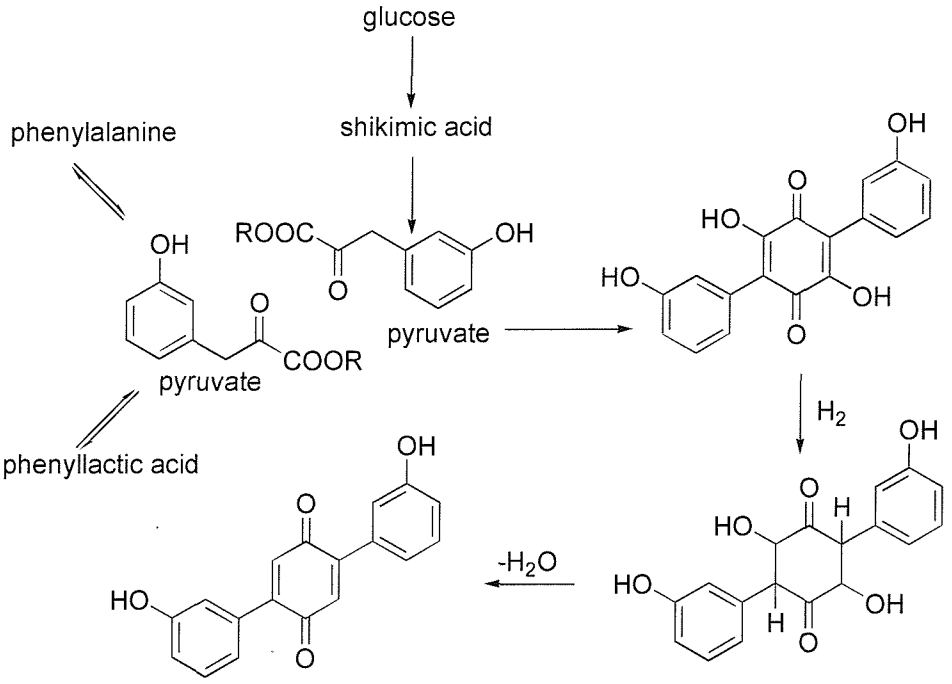


3. Biosyntheses of Terphenylquinones and Asterriquinones

In the late 1950s, Read and Vining[26] suggested that the naturally occurring terphenylquinones are assembled biosynthetically by co-condensation between two activated phenyl pyruvate units at the 1- and 3-positions. This was later demonstrated by efficient incorporation of ^{14}C-labelled shikimic acid, L-phenylalanine, DL-phenyllactic acid and DL-*meta*-tyrosine into the unique terphenylquinone pigment volucrisporin (**21**), as illustrated in Scheme 9.[27] Condensation of two molecules of pyruvate provided a dihydroxybenzoquinone, which was reduced and dehydrated to give (**21**). It is also suggested that phenylpyruvic acid is likely to be the most direct precursor of volucrisporin. Polyporic acid (**13**), which can be produced in artificial culture, similarly arises

from phenylalanine by "dimerization" of phenylpyruvate.[28] In the biogenesis of terphenylquinones with hydroxy groups in the aromatic rings, hydroxy phenylpyruvic acids are involved in the condensation steps.[27]

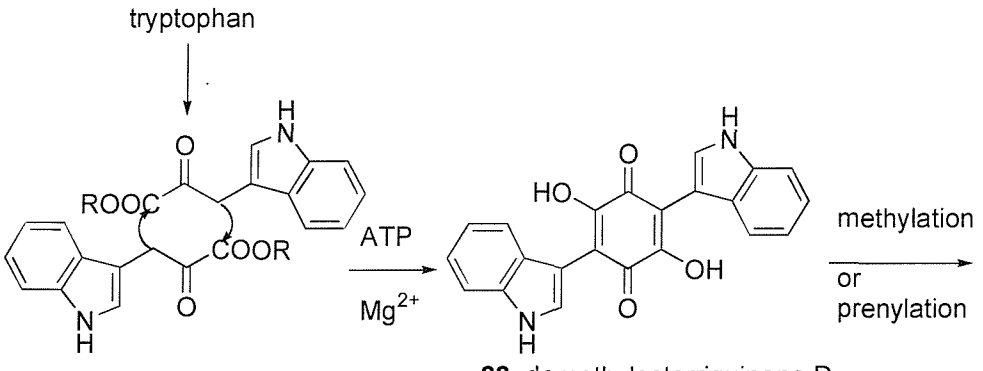
Scheme 9 Biogenesis of volucrisporin



21, volucrisporin

Enzymatic activities for the formation of asterriquinones were detected in a crude extraction of fungal mycelium.[29] Demethylasterriquinone (**22**) is initially built from condensation of two molecules of indolepyruvic acid (Scheme 10), and then methylation of the hydroxyl group of the quinone moiety occurs. Prenylation proceeds simultaneously at the different positions of the indole ring.

Scheme 10 Biogenesis of asterriquinones



22, demethylasterriquinone D

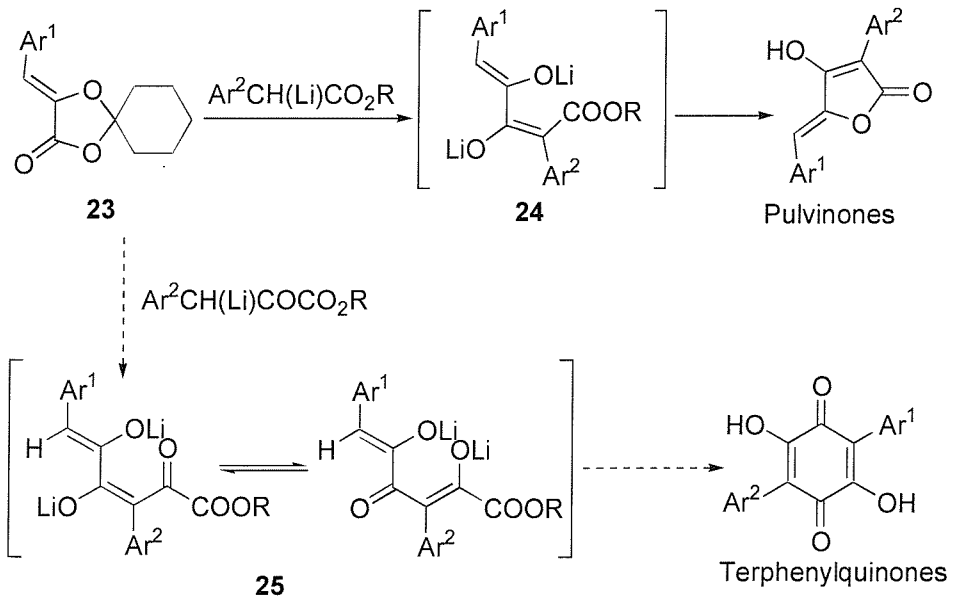
4. Our Synthetic Strategies Towards 2,5-Dihydroxybenzoquinone

Asterriquinones and terphenylquinones have the same dihydroxybenzoquinone skeleton. Biogenetically, both of these compounds may result from a condensation of two molecules of aryl pyruvate. This biosynthetic pathway brings up a question: can a similar condensation be accomplished under laboratory conditions? To investigate this possibility, polyporic acid (**13**), the simplest terphenylquinone, was chosen as our synthetic target. If successful, our biomimetic approach would also be applicable to symmetrical and unsymmetrical asterriquinones.

4.1. An Attempt Towards Polyporic Acid Using Ramage's Approach

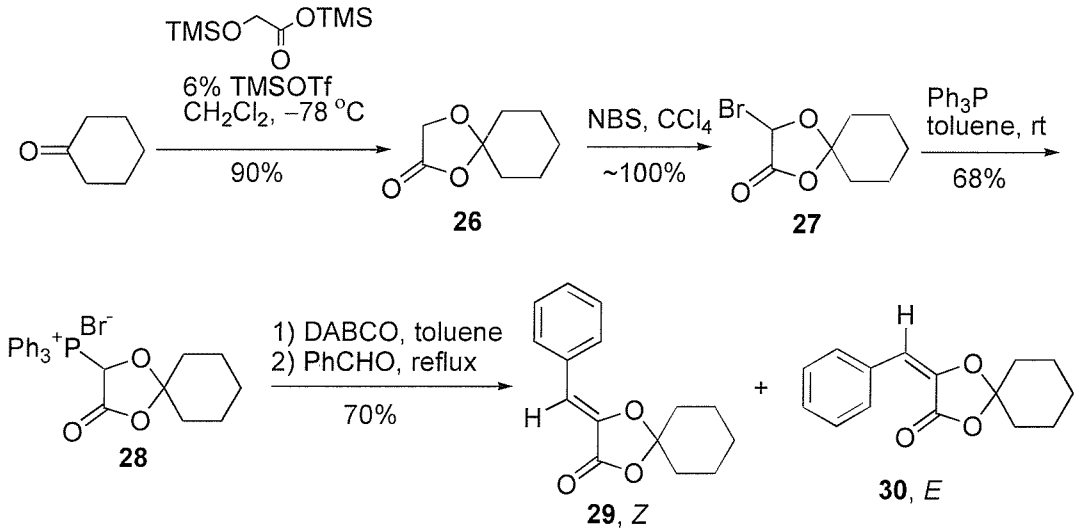
During the survey of the literature, a paper regarding the biomimetic synthesis of pulvinones by Ramage and co-workers was found.[30] The Ramage approach to pulvinones was achieved by nucleophilic attack at the lactone carbonyl group of dioxolanes of type (**23**) by appropriately substituted arylacetic ester anion, presumably *via* the intermediate (**24**) and with the extrusion of cyclohexanone (Scheme 11). In a similar fashion, 2,5-dihydroxybenzoquinones could be from the condensation of compound (**23**) and the anion of aryl pyruvate, *via* the intermediate (**25**) (Scheme 11).

Scheme 11



Our attempt at repeating the Ramage procedure[31] for condensation of cyclohexanone with glycolic acid to make (**26**) under acid (*p*-toluenesulfonic acid) catalysis was unsuccessful. Under these conditions (catalytic boron trifluoride or p-toluenesulfonic acid), reaction of several ketones and aldehydes with glycolic acid either failed to afford the desired dioxolanones or proceeded in poor yield.[32] However, using Pearson's method[33] of reacting cyclohexanone and trimethylsilyl (trimethylsilyloxy)acetate with a catalytic amount of trimethylsilyl triflate provided the desired product (**26**) in excellent yield.

Scheme 12

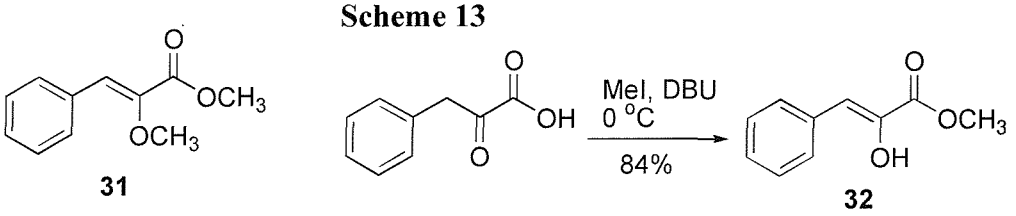


Bromination of (**26**) using *N*-bromosuccinimide (NBS) in carbon tetrachloride gave an almost quantitative yield of the bromide (**27**). Without further purification, (**27**) was treated with triphenylphosphine in toluene to give the phosphonium salt (**28**), isolated as a pale yellow solid. Finally, the yellow phosphonium ylide was generated *in situ* from the salt using 1,4-diazabicyclo[2.2.2]octane (DABCO) in toluene at room temperature under an inert atmosphere. Condensation with benzaldehyde afforded two geometrical isomers (**29**) and (**30**) after purification in a combined yield of 70% (*Z*:*E* = 8:1). The *Z*- and *E*-alkenes were separable, although Ramage reported that only one single isomer assigned as *Z* was present after chromatography.[31]

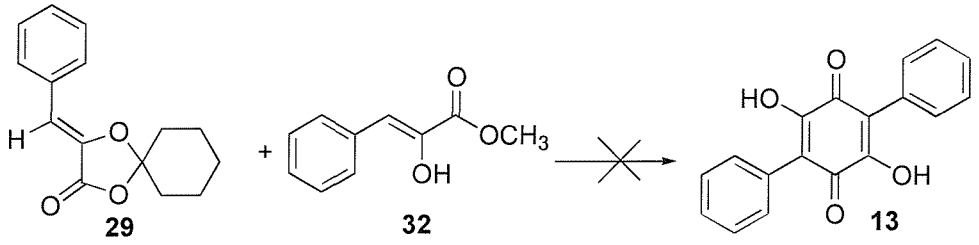
Under normal esterification conditions, phenylpyruvic acid and methanol with acid or even without acid catalysis inevitably led to the formation of some pyruvate

methyl enol ether (**31**), which makes it difficult to recrystallise the product from the reaction mixture. Instead, nucleophilic ester formation using methyl iodide in the presence of 1,5-diazabicyclo[5.4.0]undecane (DBU) afforded the desired methyl phenylpyruvate (**32**), existing completely in the enolic form, in 84% yield (Scheme 13).[34]

Scheme 13

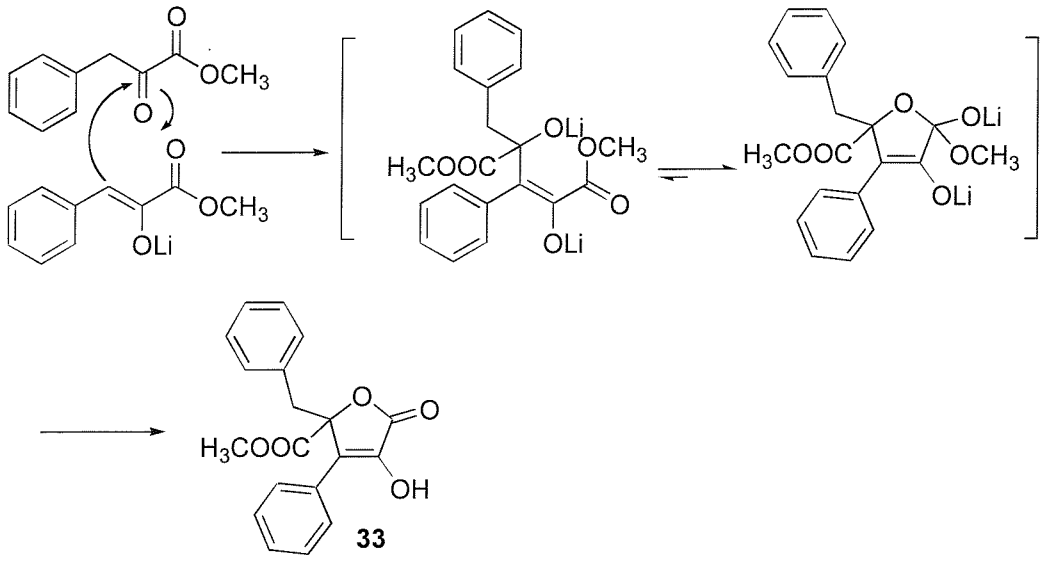


Scheme 14



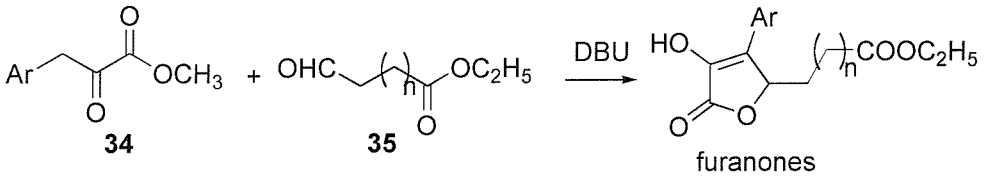
I tried the key step with the compounds (**29**) and (**32**) (Scheme 14). The lithium enolate of phenyl pyruvate (3 equivalents) was generated *in situ* using lithium diisopropylamide (LDA) (3 equivalents) in THF at –78 °C. After 20 minutes, the compound (**29**) (1 equivalent) in THF was added. The reaction mixture was warmed to room temperature and stirred overnight. After purification by column chromatography, the compound (**29**) was recovered, together with a white solid. Both ^{1}H and ^{13}C NMR show that the white solid was the same compound as the by-product isolated from the acid-catalysed esterification of phenylpyruvic acid, which suggests that it was derived from methyl phenyl pyruvate itself. Its structure was assigned as (**33**), based on comparison with the literature.[35] This dimer is formed by the self-condensation of (**32**) (Scheme 15). Further attempts using different bases (LDA, NaHMDS) or changing the ratio of (**29**) to (**32**) were also not successful. It was thought that the dioxolanone compound was not reactive enough toward nucleophilic attack. Attention was turned to more reactive electrophiles.

Scheme 15



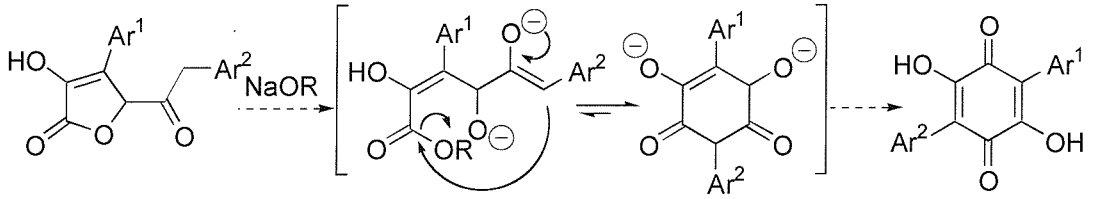
4.2. Second Approach by Ring Opening and Rearrangment of Furanones

Scheme 16

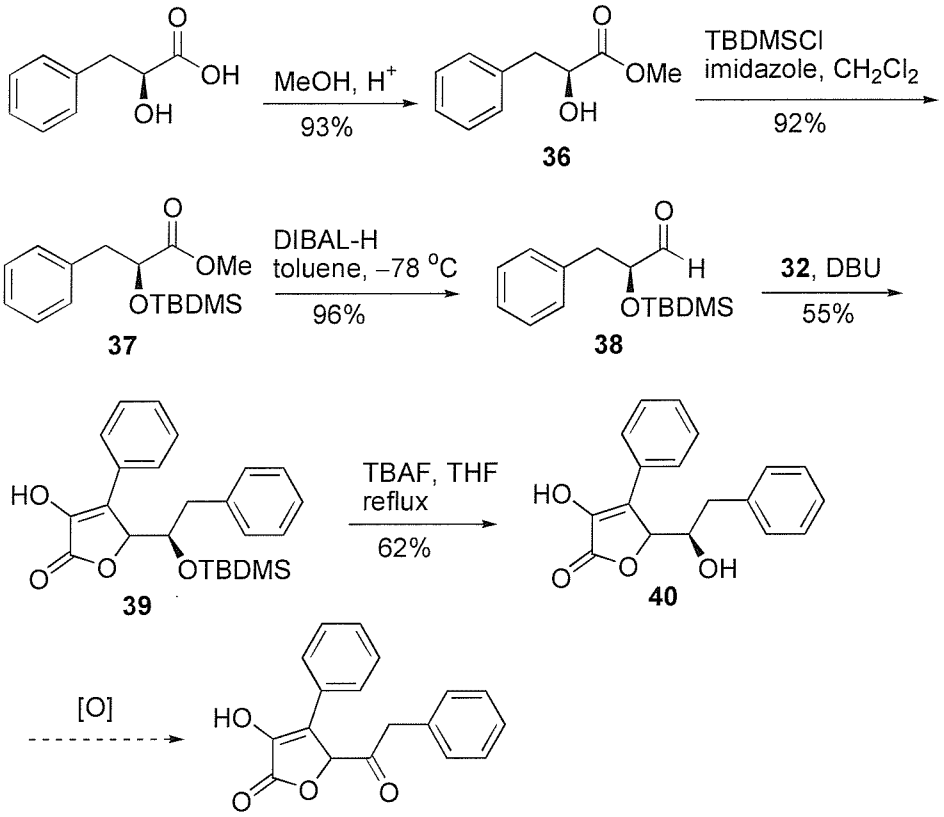


Hashimoto *et al.*[34] have synthesized a series of furanone compounds by aldol condensation of aryl pyruvate (**34**) and ω-formylalkanoates (**35**) (Scheme 16). Polyporic acid might be achieved by ring opening and rearragement of such furanones (Scheme 17).

Scheme 17



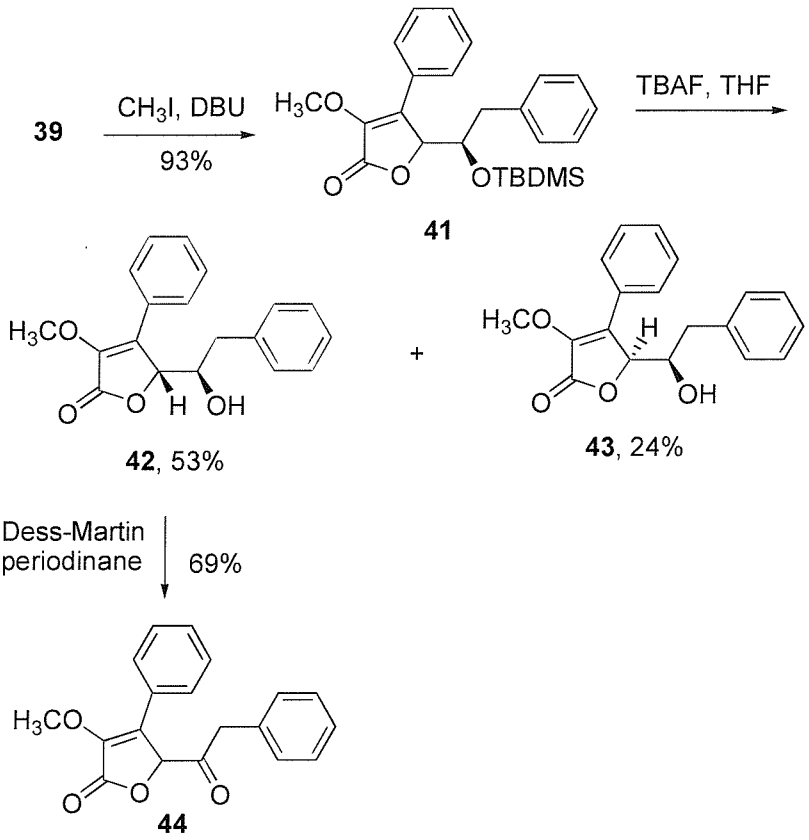
Scheme 18



As outlined in Scheme 18, *L*-phenyllactic acid was converted to its methyl ester (**36**),[36] followed by silylation and then reduction with DIBAL-H to give aldehyde (**38**),[37] which was reacted with compound (**32**) in the presence of DBU in DMF to give furanone (**39**). A small amount (10%) of (**33**) was also isolated. Removal of the TBDMS protective group did not occur upon treatment with fluoride at room temperature, but was accomplished under refluxing conditions in THF. Oxidation of (**40**) was not successful with chromium (VI) reagents (PDC or PCC, 2 equivalents, room temperature, overnight) or Parikh-Doering conditions (SO_3•Py in DMSO, 3-7 equivalents, room temperature, 24 h). NMR of the crude material from these reactions showed unreacted starting material. This was possibly due to the presence of the enolic keto group. The enol might also lead to other side reactions in our projected ring opening-rearrangement. So, the enol group of (**39**) was protected as its methyl ether by reaction with methyl iodide and DBU in DMF, providing (**41**) (Scheme 19). With the enol ether, removal of the TBDMS protective group with TBAF was complete in 30 minutes at 0 °C, two compounds being isolated. One was obtained as an oil in 53% yield and easily assigned

spectroscopically as the desired product (**42**). The other was obtained as a crystalline solid in 24% yield and identified as its diastereoisomer (**43**) by X-ray analysis (C*H*OH was overlapped by CH_3O in ^{1}H NMR spectra).

Scheme 19

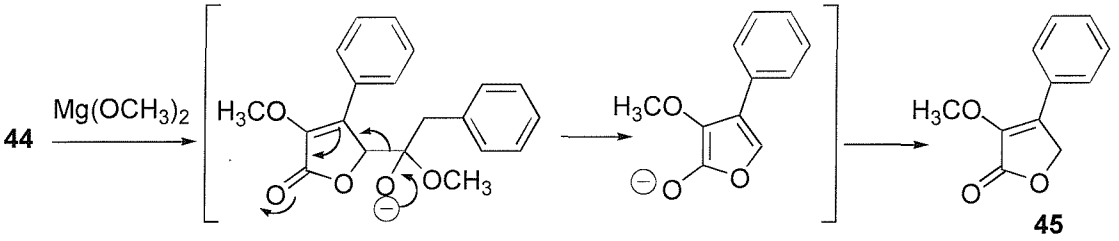


Oxidation of the hydroxy group in (**42**) was still problematic with Cr (VI) or SO_3•Py, as no reaction was observed by ^{1}H NMR. However, the Dess-Martin periodinane[38] successfully afforded ketone compound (**44**) in good yield (Scheme 19).

The rearrangement step with compound (**44**) under different basic conditions ($NaOCH_3$ in dry methanol, NaHMDS in anhydrous THF, $Mg(OCH_3)_2$ in dry methanol and DBU in DMF) was investigated. Unfortunately, all these reactions gave messy product mixtures by HPLC analysis. By TLC, the starting material was consumed by using 2 equivalents of base at room temperature, and a number of unidentified products were formed. In the case of $Mg(OCH_3)_2$, a retro-Claisen condensation pathway occurred, giving compound (**45**) (Scheme 20). Under basic

conditions, the more acidic C-5 proton may also be deprotonated. Several reactive sites are present in compound (**44**), leading to many potential equilibrations.

Scheme 20



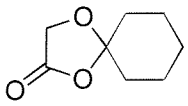
5. Conclusion

Preliminary attempts to synthesize polyporic acid (**13**) by condensation of two molecules of pyruvate in a biomimetic manner were not successful. In the first method, dioxolanone compound (**29**) can be viewed as a potential pyruvate in which two hydroxy groups were protected in a ketal form. Condensation of (**29**) with phenyl pyruvate failed due to its poorly electrophilic character. The second approach was a condensation of phenyl pyruvate with phenyllactic acid, which is also a precursor of phenyl pyruvate. Unfortunately, the anticipated ring opening-rearrangement step of furanone (**44**) resulted in a complicated mixture of unidentified products. While the biomimetic synthetic strategies are attractive, further work needs to be done to optimise the reaction conditions.

Experimental Section

General. All chemicals obtained commercially were used without further purification unless specifically stated. The following solvents were dried using reagents given in parentheses and distilled immediately before use: dichloromethane (calcium hydride), tetrahydrofuran (sodium wire/benzophenone), toluene (sodium). *N*,*N*-dimethylformamide was dried over molecular sieves. Light petroleum ether refers to the fraction boiling in the range 40-60 °C. Analytical TLC was performed on precoated aluminium backed plates (60 F-254, MERCK). Flash column chromatography was performed with silica gel (70-230 mesh, APOLLO). Melting points were taken on an electrothermal melting point apparatus and are uncorrected. IR spectra were obtained neat on a Mattson Satellite FT-IR spectrometer. ^{1}H, ^{13}C NMR and $DEPT_{135}$ spectra were recorded at 300 and 75 MHz respectively with a Bruker AC300 instrument in $CDCl_3$ unless otherwise stated. 2D NMR spectra were recorded with a Bruker DPX400 instrument. Chemical shifts (δ) were measured in ppm relative to tetramethylsilane as an internal standard (0.00 ppm) and coupling constants (J) are reported in Hz. Mass spectra were obtained on Thermoquest Trace MS and Micromass Platform II instruments, or a VG70-250SE spectrometer (HRMS), and relative intensities of ions are indicated in parentheses.

Cyclohexanespiro-2'-(1',3'-dioxolan)-4'-one (26)



A solution of freshly distilled cyclohexanone (1.97 g, 20 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of trimethylsilyl (trimethylsiloxy)acetate (6.35 mL, 26 mmol) and trimethylsilyl triflate (0.22 mL, 6 mol%) in CH_2Cl_2 (15 mL) at –78 °C. The solution was stirred at this temperature for 4 h, followed by the addition of pyridine (1.62 mL, 26 mmol). After warming to room temperature, the solution was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with ether (2 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to afford the title compound

as a colourless oil (2.80 g, 90%), bp 48-50 °C at 0.3 mbar. ^{1}H NMR was identical to that reported.[31]

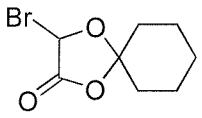
IR ν2938, 1790, 1704, 1217 cm^{-1};

^{1}H NMR δ1.38-1.55 (m, 2H), 1.60-1.90 (m, 8H), 4.34 (s, 2H);

^{13}C NMR δ23.0, 24.4, 35.4, 63.3, 113.6, 171.6;

CIMS *m/z* 157 (M^+ + 1, 100), 123 (13), 98 (22), 55 (25).

5'-Bromocyclohexanespiro-2'-(1',3'-dioxolan)-4'-one (27)



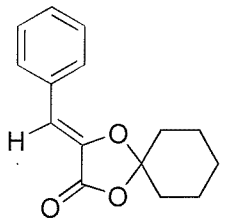
A mixture of *N*-bromosuccinimide (1.89 g, 10.6 mmol), (**26**) (1.56 g, 10 mmol) and azobis(cyclohexanecarbonitrile) (7.5 mg, 0.03 mmol) in CCl_4 (20 mL) was heated to reflux for 5 h. The pale yellow suspension was cooled to 5 °C, the solid filtered off, and washed with CCl_4 (2 × 5 mL). The combined organics were evaporated *in vacuo* and the yellow oil (**27**) obtained (2.35 g, 100%) was used without further purification. ^{1}H NMR was identical to that reported.[31]

^{1}H NMR δ1.40-1.60 (m, 2H), 1.65-1.85 (m, 6H), 2.05-2.25 (m, 2H), 6.53 (s, 1H);

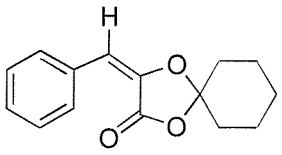
^{13}C NMR δ22.8, 22.9, 24.1, 34.0, 36.6, 72.0, 116.1, 166.4 (*C*=O);

EIMS *m/z* 236 (M^+ + 1, 37), 201 (84), 192 (58), 153 (70), 112 (100).

3-(Phenylmethylene)-1,4-dioxaspiro[4,5]decan-2-one
(5'-Benzylidenecyclohexanespiro-2'-(1',3'-dioxolan)-4'-one) (29 and 30)



29, *Z*



30, *E*

Triphenylphosphine (2.06 g, 7.87 mmol) in toluene (10 mL) was added dropwise to a stirred solution of (**27**) (1.85 g, 7.87 mmol) in toluene (20 mL). The reaction mixture was stirred overnight at room temperature under nitrogen atmosphere. The

precipitate was filtered off, washed and purified by dissolution in ethanol followed by reprecipitation with ether to afford (**28**) as a white solid (2.67 g, 68%).

^{1}H NMR ($CD_3COCD_3 + D_2O$) δ 1.25-2.30 (m, 10H), 7.80-8.42 (m, 16H).

To a suspension of (**28**) (2.67 g, 5.41 mmol) in anhydrous toluene (16 mL) was added DABCO (0.61 g, 5.44 mmol) in anhydrous toluene (10 mL) under nitrogen. The mixture was stirred for 10 min at 60 °C to give the yellow phosphorane, followed by addition of benzaldehyde (0.53 mL, 5.2 mmol) in toluene (2 mL). The mixture was refluxed for another 2 h, filtered to remove DABCO•HBr and concentrated *in vacuo* to give an oily solid, which was triturated with petroleum ether (30 mL) to remove triphenylphosphine oxide. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography with 20% petroleum ether in ether as eluent to afford both *Z*- and *E*-isomers (890 mg, 70%).

Z-isomer (**29**): a white solid, mp 68-69 °C (Lit.[31] 71-72 °C);

IR ν 2938, 1774, 1648, 1448, 1192 cm^{-1};

^{1}H NMR δ 1.45-1.60 (m, 2H), 1.70-1.95 (m, 8H), 6.46 (s, 1H), 7.25-7.45 (m, 3H), 7.63-7.70 (m, 2H);

^{13}C NMR δ 23.0 (2 × CH_2), 24.2 (CH_2), 36.3 (2 × CH_2), 108.1 (*C*H), 112.7 (*C*), 128.5 (*C*H), 128.7 (2 × *C*H), 129.5 (2 × *C*H), 133.0 (*C*), 137.0 (*C*), 163.9 (*C*=O);

EIMS *m/z* 244 (M^+, 8), 211 (24), 189 (10), 112 (100), 101 (69).

E-isomer (**30**): an oil;

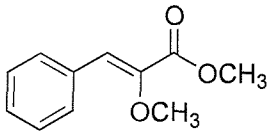
IR ν 2938, 1774, 1648, 1448, 1188 cm^{-1};

^{1}H NMR δ 1.40-1.60 (m, 2H), 1.70-1.95 (m, 8H), 6.51 (s, 1H), 7.23-7.40 (m, 3H), 7.65-7.75 (m, 2H);

^{13}C NMR δ 22.8 (2 × CH_2), 24.1 (CH_2), 36.2 (2 × CH_2), 111.1 (*C*), 114.8 (*C*H), 128.2 (3 × *C*H), 129.8 (2 × *C*H), 132.0 (*C*), 137.9 (*C*), 161.5 (*C*=O);

EIMS *m/z* 244 (M^+, 8), 211 (40), 189 (20), 112 (61), 100 (100).

2-Methoxy-3-phenyl-2-propenoic acid methyl ester (31)



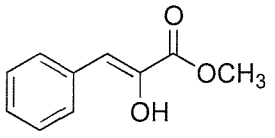
Isolated from the attempted esterification of phenylpyruvic acid with methanol under acid catalysis. ^{1}H and ^{13}C NMR were identical to those reported.[39]

^{1}H NMR δ 3.77 (s, 3H), 3.85 (s, 3H), 7.02 (s, 1H), 7.30-7.45 (m, 3H), 7.70-7.80 (m, 2H);

^{13}C NMR δ 52.2, 59.2, 124.2, 128.6, 129.0, 130.2, 133.3, 145.5, 165.0;

EIMS *m/z* 192 (M^{+}, 29), 160, 118 (100).

2-Hydroxy-3-phenyl-2-propenoic acid methyl ester (32)



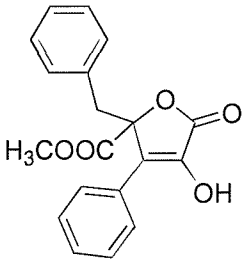
Methyl iodide (0.62 mL, 10 mmol) and DBU (0.3 mL, 2 mmol) were added to a solution of phenylpyruvic acid (330 mg, 2 mmol) in DMF (8 mL). The mixture was stirred at 0 °C for 2.5 h and poured into a mixture of ether (10 mL) and 1 N HCl (5 mL). The organic layer was separated and washed with water (2 × 15 mL), saturated NaCl (10 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo*, and the crystalline light yellow solid (**32**) (300 mg, 84%) obtained was used without further purification. ^{1}H NMR was identical to that reported.[40]

^{1}H NMR δ 3.92 (s, 3H), 6.42 (s, 1H, O*H*), 6.53 (s, 1H, =C*H*), 7.25-7.40 (m, 3H), 7.70-7.80 (m, 2H);

^{13}C NMR δ 53.3, 111.2, 128.0, 128.5, 129.8, 134.0, 139.0, 166.7;

EIMS *m/z* 179 (M^{+} + 1, 9), 163 (63), 127 (100), 103 (20).

2,5-Dihydro-4-hydroxy-5-oxo-3-phenyl-2-benzyl-2-furancarboxylic acid methyl ester (33)



A white solid, isolated from the reaction of compound (**29**) and (**32**). ^{13}C NMR was identical to that reported.[35]

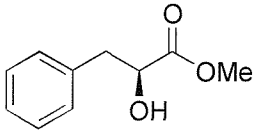
IR ν3282, 1737, 1669, 1391, 1176 cm^{-1};

^{1}H NMR δ 3.59, 3.67 (AB system, 2H, J = 14 Hz), 3.80 (s, 3H), 6.78-6.85 (m, 2H), 7.10-7.18 (m, 3H), 7.45-7.52 (m, 3H), 7.68-7.75 (m, 2H);

^{13}C NMR δ 39.1 (CH_2), 53.6 (CH_3), 86.1 (*C*), 127.3 (*C*H), 127.6 (2 × *C*H), 127.7 (*C*), 128.0 (2 × *C*H), 129.1 (2 × *C*H), 129.3 (*C*H), 129.5 (*C*), 130.4 (2 × *C*H), 132.6 (*C*), 138.7 (*C*), 169.2 (*C*), 169.4 (*C*);

CIMS *m/z* 324 (M$^+$, very weak), 281 (85), 251 (60), 189 (65), 91 (100).

Methyl 2-hydroxy-3-phenylpropionate (36)



L-(-)-phenyllactic acid (500 mg, 3 mmol) and several drops of concentrated sulphuric acid in distilled methanol (15 mL) were refluxed for three hours. The solvent was removed and the residue was dissolved in dichloromethane (15 mL), washed with water (2 × 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded the methyl ester as a white solid (500 mg, 93%), mp 48-49 °C (Lit.[36] mp 46-47 °C).

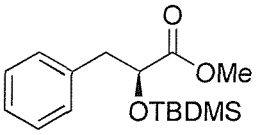
IR ν3272, 1749, 1732, 1101 cm^{-1};

^{1}H NMR δ2.70 (br s, 1H, O*H*), 2.96 (dd, J = 6.5, 14.0 Hz, 1H, PhC*H*H), 3.13 (dd, J = 4.4, 14.0 Hz, 1H, PhCH*H*), 3.78 (s, 3H, OCH_3), 4.46 (dd, J = 4.4, 6.5 Hz, 1H, HOC*H*), 7.20-7.40 (m, 5H);

^{13}C NMR δ 40.5 (Ph*C*H_2), 52.5 (O*C*H_3), 71.2 (HO*C*H), 126.9 (*C*H), 128.4 (2 × *C*H), 129.5 (2 × *C*H), 136.3 (*C*), 174.6 (*C*=O);

EIMS *m/z* 178 (M^+ - 2, 3), 121 (10), 91 (100), 77 (11), 65 (19).

Methyl 2-*tert*-butyldimethylsilyloxy-3-phenylpropionate (37)



To a solution of (**36**) (500 mg, 2.77 mmol) and imidazole (377 mg, 5.54 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise *tert*-butyldimethylchlorosilane (543 mg, 3.60 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight, poured into water and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by column chromatography with 20% ethyl acetate in petroleum ether as eluent to give the title compound as an oil (750 mg, 92%).

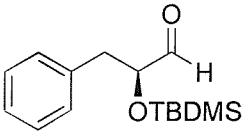
IR ν 1757, 1129 cm^{-1};

^{1}H NMR δ -0.22 (s, 3H, SiCH_3), -0.14 (s, 3H, SiCH_3), 0.78 (s, 9H, 3 × CH_3), 2.87 (dd, J = 8.8, 13.2 Hz, 1H, PhC*H*H), 3.07 (dd, J = 3.7, 13.2 Hz, 1H, PhCH*H*), 3.73 (s, 3H, OCH_3), 4.33 (dd, J = 3.7, 8.8 Hz, 1H, TBDMSOC*H*), 7.18-7.35 (m, 5H);

^{13}C NMR δ -5.7 (SiCH_3), -5.6 (SiCH_3), 18.2 (*C*(CH_3)$_3$), 25.5 (3 × *C*H_3), 41.6 (Ph*C*H_2), 51.8 (O*C*H_3), 73.8 (TBDMSiO*C*H), 126.6 (*C*H), 128.2 (2 × *C*H), 129.8 (2 × *C*H), 137.4 (*C*), 173.6 (*C*=O);

ESMS *m/z* 312 (M + NH_4^+, 32), 102 (100).

2-*tert*-Butyldimethylsilyloxy-3-phenylpropanal (38)



To a solution of (**37**) (710 mg, 2.41 mmol) in dry toluene (25 mL) was added DIBAL-H (2.89 mL of a 1.0 M solution in toluene, 2.89 mmol) dropwise over 5 min at −78 °C under nitrogen. After being stirred for 3 h, the reaction mixture was

quenched by addition of 2 N HCl (10 mL), and extracted with ether (3 × 15 mL). The extract was washed with saturated sodium hydrogen carbonate (2 × 20 mL) and water (3 × 25 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography with 10% diethyl ether in petroleum ether as eluent to give the title compound as a colourless oil (610 mg, 96%). ^{1}H NMR was similar to that reported.[37]

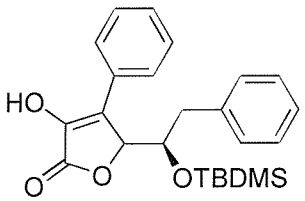
IR ν1724, 1254 cm^{-1};

^{1}H NMR δ -0.25 (s, 3H, SiCH_3), -0.12 (s, 3H, SiCH_3), 0.83 (s, 9H, 3 × CH_3), 2.77 (dd, J = 8.8, 14.0 Hz, 1H, PhC*H*H), 3.00 (dd, J = 3.7, 14.0 Hz, 1H, PhCH*H*), 4.13 (ddd, J = 1.5, 3.7, 8.8 Hz, 1H, TBDMSOC*H*), 7.15-7.50 (m, 5H), 9.65 (d, J = 1.5 Hz, 1H, O=C*H*);

^{13}C NMR δ -5.5 (Si*C*H$_3$), -5.2 (Si*C*H$_3$), 18.1 (*C*(CH$_3$)$_3$), 25.8 (3 × *C*H$_3$), 39.1 (PhCH$_2$), 79.0 (TBDMSO*C*H), 126.7 (*C*H), 128.3 (2 × *C*H), 129.9 (2 × *C*H), 136.8 (*C*), 203.6 (*C*=O);

EIMS *m/z* 265 (M^+ + 1, 0.3), 207 (91), 177 (59), 161 (24), 115 (27), 91 (100).

3-Hydroxy-5-(1-*tert*-butyldimethylsilyloxy-2-phenylethyl)-4-phenyl-2(5*H*)-furanone (39)



DBU (0.45 mL, 3.00 mmol) was added to a mixture of (**38**) (600 mg, 2.27 mmol) and compound (**32**) (526 mg, 2.95 mmol) in dry DMF (20 mL) at 0 °C. The reaction mixture was stirred for 8 h at the same temperature, then poured into a mixture of ether and dilute HCl. The organic layer was separated, the aqueous layer extracted with ether (3 × 20 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 20% ethyl acetate in petroleum ether as eluent afforded the title compound as a colourless oil (510 mg, 55%).

IR ν3305, 1735, 1106 cm^{-1};

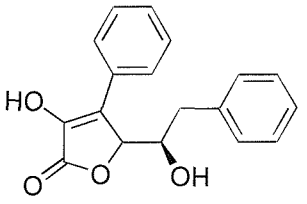
^{1}H NMR δ -0.40 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3), 0.88 (s, 9H, 3 × CH_3), 2.50-2.65 (m, 2H, PhCH_2), 4.28-4.33 (m, 1H, TBDMSOC*H*), 5.51 (d, J = 2.2 Hz, 1H, OC*H*), 6.87-6.96 (m, 2H), 7.12-7.20 (m, 3H), 7.40-7.55 (m, 3H), 7.60-7.68 (m, 2H);

^{13}C NMR δ -5.4 (SiCH_3), -4.8 (SiCH_3), 17.9 (C(CH_3)$_3$), 25.7 (3 × CH_3), 36.7 (PhCH_2), 74.3 (TBDMSOC*H*), 83.1 (OC*H*), 126.3 (*C*H), 127.5 (2 × *C*H), 127.9 (*C*), 128.2 (2 × *C*H), 128.9 (2 × *C*H), 129.3 (*C*H), 129.6 (2 × *C*H), 130.0 (*C*), 137.65 (*C*), 137.77 (*C*), 170.5 (*C*=O);

CIMS *m/z* 428 (M + NH_4^+, 100), 411 (M^+ + 1, 30), 235 (86), 221 (28), 132 (47), 91 (82);

HRMS (CI) calcd for $C_{24}H_{34}NO_4Si$ ($C_{24}H_{30}O_4Si$ + NH_4^+) 428.22571, found 428.22673.

3-Hydroxy-5-(1-hydroxy-2-phenylethyl)-4-phenyl-2(5*H*)-furanone (40)



Tetra-*n*-butylammonium fluoride (0.78 mL of a 1.0 M solution in THF, 0.78 mmol) was added to a solution of the compound (**39**) (160 mg, 0.38 mmol) in THF (3 mL). The reaction mixture was refluxed for 4 h, cooled down, poured into water, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with water and brine, and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 40% ethyl acetate in petroleum ether as eluent gave the title compound as a white solid (70 mg, 62%), mp 165-167 °C.

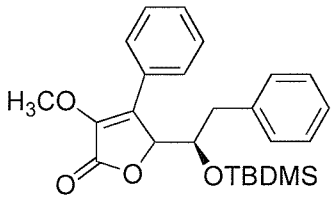
IR ν 3516, 1753, 1738, 1012 cm^{-1};

^{1}H NMR (CD_3COCD_3) δ 2.51-2.62 (m, 2H), 4.20-4.30 (m, 1H), 5.72 (d, J = 2.2 Hz, 1H), 6.95-7.05 (m, 2H), 7.05-7.20 (m, 3H), 7.35-7.54 (m, 3H), 7.70-7.80 (m, 2H);

^{13}C NMR δ 36.6 (Ph*C*H$_2$), 73.8 (HO*C*H), 83.2 (O*C*H), 126.6 (*C*H), 127.9 (*C*), 128.3 (2 × *C*H), 128.7 (2 × *C*H), 129.25 (2 × *C*H), 129.31 (*C*H), 129.8 (2 × *C*H), 131.5 (*C*), 139.3 (*C*), 139.5 (*C*), 169.8 (*C*=O);

EIMS *m/z* 234 (M^+ - 62, 100), 205 (38), 191 (18), 128 (40), 115 (20), 91 (33).

3-Methoxy-5-(1-*tert*-butyldimethylsilyloxy-2-phenylethyl)-4-phenyl-2(5*H*)-furanone (41)



Methyl iodide (0.03 mL, 0.48 mmol) was added to a stirred mixture of DBU (0.04 mL, 0.28 mmol) and compound (**39**) (100 mg, 0.24 mmol) in DMF (2.5 mL). The reaction mixture was stirred at room temperature for 3 h, then poured into water (15 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a pale yellow oil (95 mg, 93%).

IR ν 2927, 1753, 1651, 1358, 1090 cm^{-1};

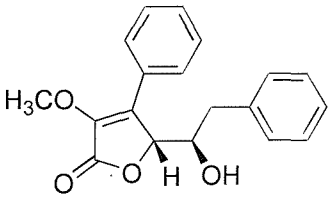
^{1}H NMR δ -0.42 (s, 3H, SiC*H*$_3$), -0.02 (s, 3H, SiC*H*$_3$), 0.84 (s, 9H, 3 × C*H*$_3$), 2.47 (dd, J = 4.4, 14.0 Hz, 1H, PhC*H*H), 2.57 (dd, J = 8.1, 14.0 Hz, 2H, PhCH*H*), 4.03 (s, 3H, OC*H*$_3$), 4.15-4.22 (m, 1H, TBDMSOC*H*), 5.38 (d, J = 2.2 Hz, 1H, OC*H*), 6.85-6.90 (m, 2H), 7.10-7.25 (m, 3H), 7.42-7.50 (m, 5H);

^{13}C NMR δ -5.4 (SiCH$_3$), -4.9 (SiCH$_3$), 17.9 (*C*(CH$_3$)$_3$), 25.7 (3 × *C*H$_3$), 37.0 (Ph*C*H$_2$), 58.6 (OCH$_3$), 74.2 (TBDMSO*C*H), 81.8 (O*C*H), 126.3 (*C*H), 127.8 (2× *C*H), 128.2 (2 × *C*H), 128.7 (2 × *C*H), 129.45 (*C*H), 129.51 (2 × *C*H), 130.2 (*C*), 135.0 (*C*), 137.7 (*C*), 141.2 (*C*), 168.2 (*C*=O);

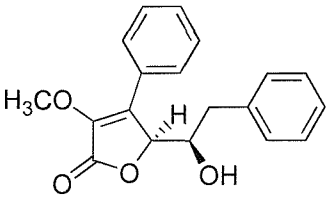
CIMS *m/z* 425 (M^+ + 1, 44), 367 (30), 310 (60), 293 (100), 235 (44), 91 (50);

HRMS (CI) calcd for $C_{25}H_{36}NO_4Si$ ($C_{25}H_{32}O_4Si$ + NH_4^+) 442.24136, found 442.24109.

3-Methoxy-5-(1-hydroxy-2-phenylethyl)-4-phenyl-2(5*H*)-furanone (42 and 43)



42



43

Tetra-*n*-butylammonium fluoride (0.71 mL of a 1.0 M solution in THF, 0.71 mmol) was added to a solution of compound (**41**) (200 mg, 0.47 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (12 mL), washed with water (2 × 5 mL) and brine (8 mL), dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by column chromatography with 40% ethyl acetate in petroleum ether as eluent to afford compound (**42**) as a colourless oil (78 mg, 53%), and (**43**) as a white solid (35 mg, 24%) which was recrystallised from ether and petroleum ether to give needles, mp 99-101 °C.

Compound (**42**):

IR ν3423, 1743, 1358, 1073 cm^{-1};

^{1}H NMR δ 2.60-2.65 (m, 2H, PhCH_2), 2.93 (br s, 1H, O*H*), 4.06 (s, 3H, OCH_3), 4.15-4.21 (m, 1H, HOC*H*), 5.60 (d, J = 2.9 Hz, 1H, OC*H*), 6.94-7.00 (m, 2H), 7.10-7.25 (m, 3H), 7.40-7.50 (m, 3H), 7.53-7.60 (m, 2H);

^{13}C NMR δ 36.1 (PhCH_2), 58.5 (OCH_3), 73.0 (HOCH), 81.2 (OCH), 126.3 (*C*H), 127.6 (2 × *C*H), 128.2 (2 × *C*H), 128.6 (2 × *C*H), 129.0 (2 × *C*H), 129.4 (*C*), 129.6 (*C*H), 135.4 (*C*), 137.1 (*C*), 140.6 (*C*), 168.2 (*C*=O);

CIMS *m/z* 311 (M^+ + 1, 4), 208 (100), 191 (78), 175 (16), 138 (10), 91 (29);

HRMS (CI) calcd for $C_{19}H_{22}NO_4$ ($C_{19}H_{18}O_4$ + NH_4^+) 328.15488, found 328.15470.

Compound (**43**):

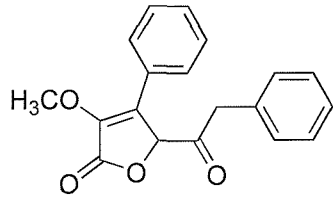
IR ν3409, 1750, 1655, 1361, 1092 cm^{-1};

^{1}H NMR δ 1.78 (br s, 1H, O*H*), 3.00-3.18 (m, 2H, PhCH_2), 4.06 (s, 3H, OCH_3), 4.06 (m, overlapped, 1H, HOC*H*), 5.20 (d, J = 1.5 Hz, 1H, OC*H*), 7.20-7.45 (m, 10H);

^{13}C NMR δ 40.5 ($PhCH_2$), 58.7 (OCH_3), 71.1 (HO*C*H), 78.3 (O*C*H), 126.9 (*C*H), 127.5 (2 × *C*H), 128.80 (2 × *C*H), 128.82 (2 × *C*H), 129.38 (2 × *C*H), 129.48 (*C*), 129.54 (*C*H), 135.0 (*C*), 137.1 (*C*), 140.9 (*C*), 168.4 (*C*=O);

CIMS *m/z* 311 (M^+ + 1, 3), 208 (82), 191 (100), 161 (10), 91 (50).

3-Methoxy-5-(1-oxo-2-phenylethyl)-4-phenyl-2(5*H*)-furanone (44)



Compound (**42**) (220 mg, 0.71 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of Dess-Martin periodinane (362 mg, 0.85 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 18 h. The solution was diluted with ether (10 mL) and poured into saturated aqueous $NaHCO_3$ (10 mL) containing $Na_2S_2O_3$ (1 g) and stirred for 5 min, then extracted with ether (3 × 8 mL). The combined organics were washed with saturated $NaHCO_3$ (10 mL), H_2O (10 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent and purification of the residue by column chromatography with 20% ethyl acetate in petroleum ether as eluent provided the title compound as a white solid (150 mg, 69%), mp 75-77 °C.

IR ν 1752, 1724, 1637, 1359 cm^{-1};

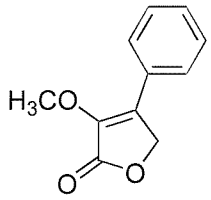
^{1}H NMR δ 3.75 (d, J = 4.4 Hz, 2H, $PhCH_2$), 4.09 (s, 3H, OCH_3), 5.65 (s, 1H, O*CH*), 6.98-7.02 (m, 2H), 7.20-7.25 (m, 3H), 7.35-7.45 (m, 3H), 7.57-7.62 (m, 2H);

^{13}C NMR δ 43.3 (CH_2), 58.6 (OCH_3), 82.0 (O*C*H), 127.2 (*C*H), 127.9 (*C*H), 128.4 (*C*), 128.6 (*C*H), 129.5 (*C*H), 130.0 (*C*H), 132.1 (*C*), 133.2 (*C*), 140.7 (*C*), 167.4 (*C*=O), 201.2 (*C*=O);

CIMS *m/z* 309 (M^+ + 1, 12), 264 (5), 190 (48), 118 (15), 91 (100);

HRMS (CI) calcd for $C_{19}H_{20}NO_4$ ($C_{19}H_{16}O_4$ + NH_4^+) 326.13923, found 326.13929.

3-Methoxy-4-phenyl-2(5*H*)-furanone (45)



To a solution of compound (**44**) (60 mg, 0.19 mmol) in methanol (2 mL) was added magnesium methoxide (0.4 mL of a 10% solution in methanol, 0.4 mmol). The reaction mixture was refluxed for 18 h under nitrogen, cooled down, poured into ice-water, extracted with ethyl acetate (3 × 8 mL). The combined organics were dried over anhydrous $MgSO_4$. Evaporation of solvent and purification of the residue by column chromatography gave the title compound as a solid (7 mg, 20%).

^{1}H NMR δ 4.15 (s, 3H), 5.09 (s, 2H), 7.35-7.50 (m, 3H), 7.63-7.73 (m, 2H);

^{13}C NMR δ 58.5 (OCH_3), 67.3 (CH_2), 126.6 (2 × *C*H), 128.9 (2 × *C*H), 129.90 (*C*H), 129.92 (*C*), 133.8 (*C*), 140.1 (*C*), 168.9 (*C*=O);

CIMS *m/z* 208 ($M + NH_4^+$, 100), 191 ($M^+ + 1$, 71).

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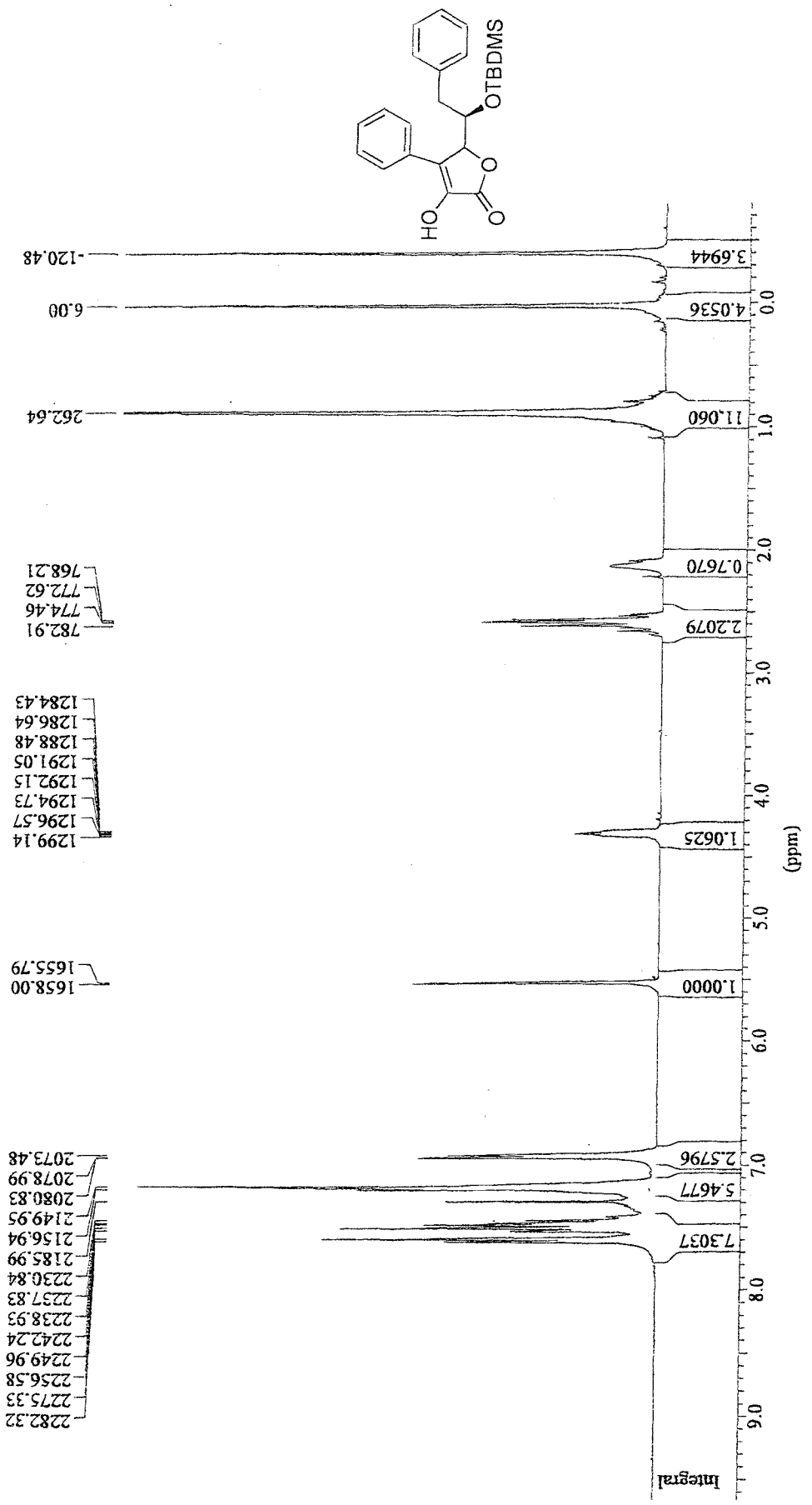
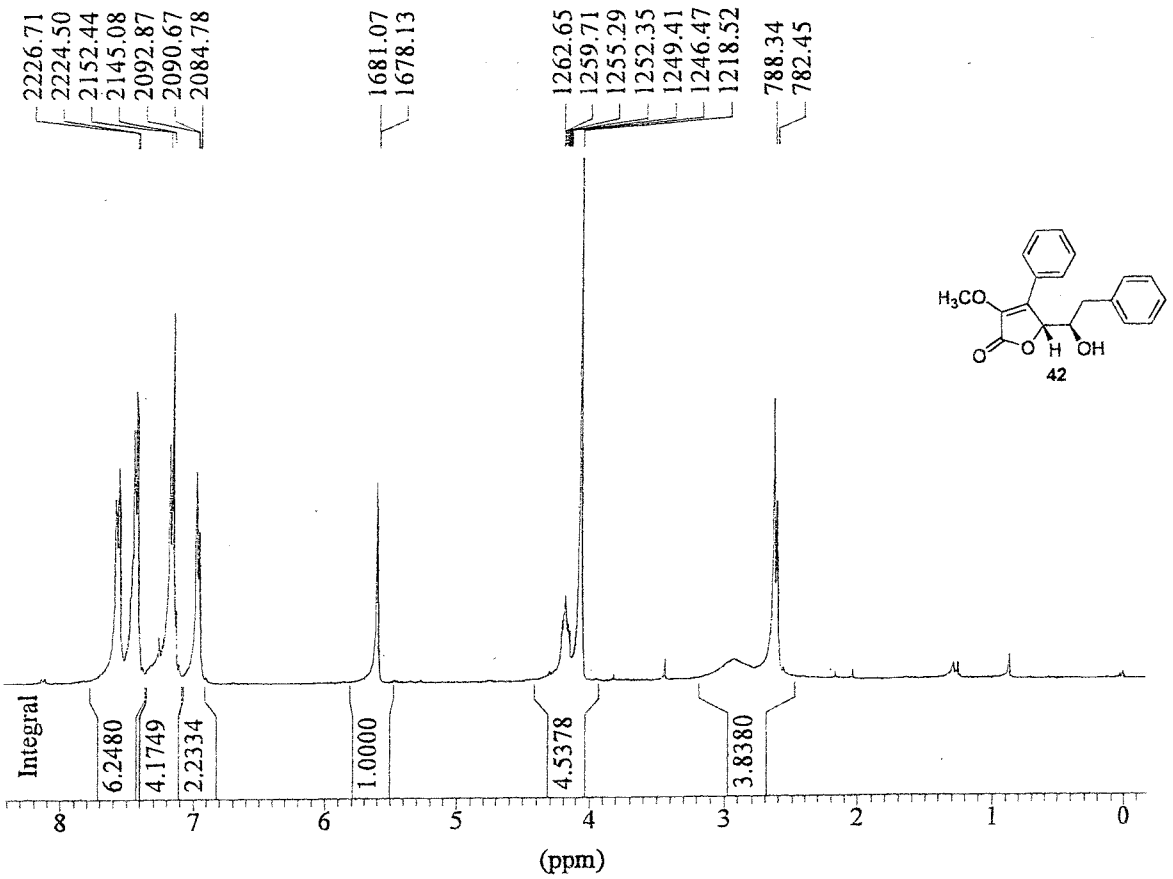
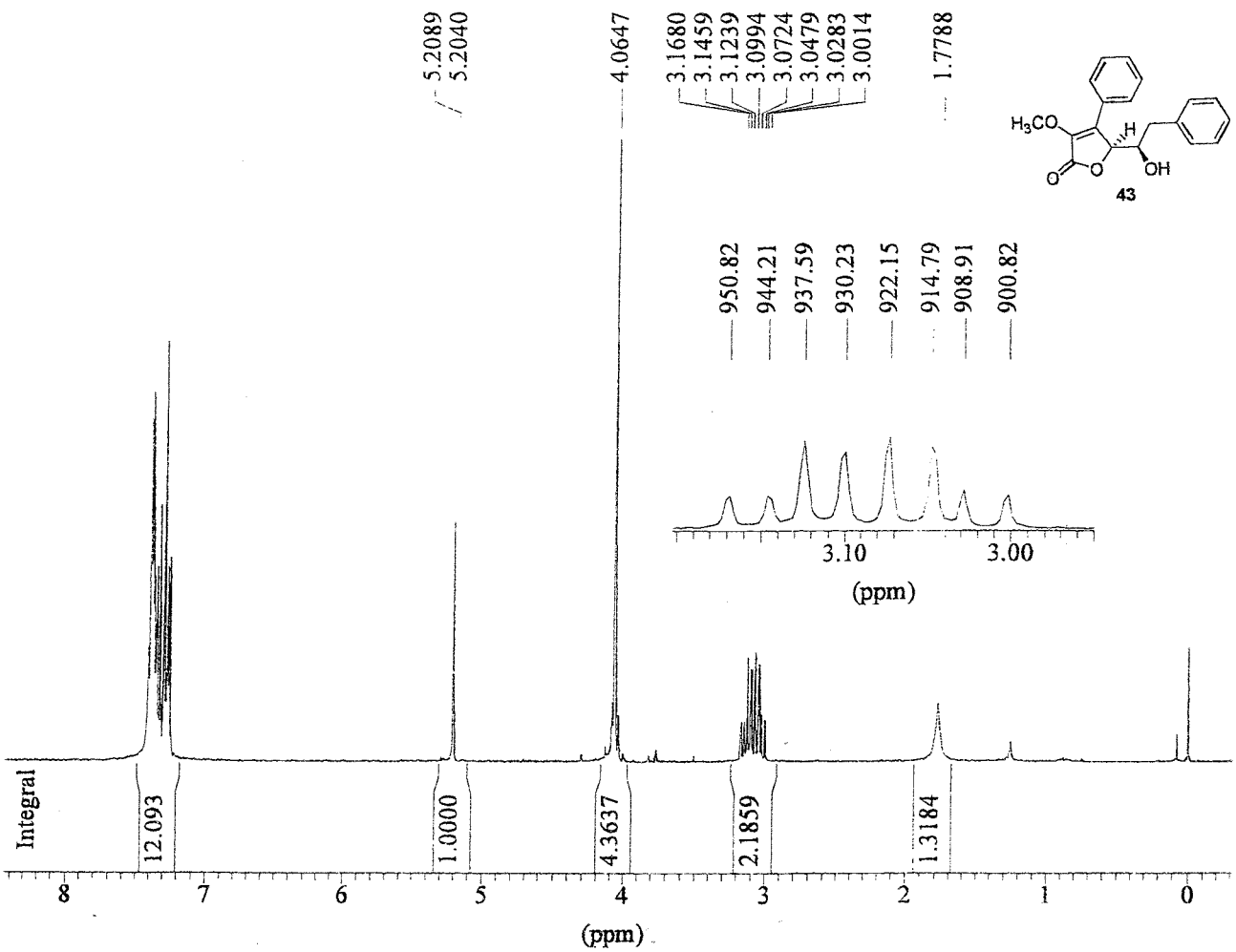
Appendix 1: ^{1}H NMR spectrum of compound (**39**) in $CDCl_3$



Appendix 2: ^{1}H NMR spectra of compound (**42**) and (**43**) in $CDCl_3$





Appendix 3: X-ray crystallographic data of compound (**43**)

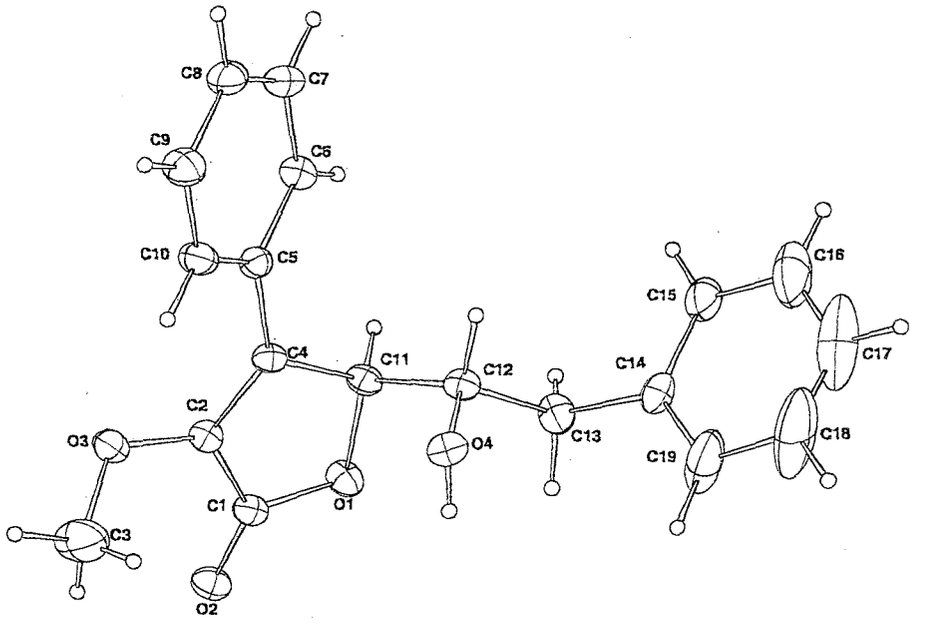


Table 1. Crystal data and structure refinement.

Identification code	**00sot133**	
Empirical formula	$C_{19}H_{18}O_4$	
Formula weight	310.33	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C*2	
Unit cell dimensions	$a = 22.512(5)$ Å	$\alpha = 90°$
	$b = 5.3797(11)$ Å	$\beta = 92.35(3)°$
	$c = 13.511(3)$ Å	$\gamma = 90°$
Volume	1634.9(6) Å^3	
Z	4	
Density (calculated)	1.261 Mg / m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	656	
Crystal	Needle; colourless	
Crystal size	0.50 × 0.10 × 0.10 mm^3	
θ range for data collection	3.02 – 27.50°	
Index ranges	$-28 \le h \le 28$, $-6 \le k \le 6$, $-15 \le l \le 17$	
Reflections collected	6002	
Independent reflections	3500 [$R_{int} = 0.0353$]	
Completeness to $\theta = 27.50°$	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9913 and 0.9573	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3500 / 19 / 212	
Goodness-of-fit on F^2	1.051	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0560, *wR2* = 0.1447	
R indices (all data)	*R1* = 0.0717, *wR2* = 0.1553	
Absolute structure parameter	1.4(13)	
Extinction coefficient	0.029(4)	
Largest diff. peak and hole	0.539 and –0.271 e Å^{-3}	

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1870(1)	556(4)	10577(2)	32(1)	1
C2	1581(1)	−88(5)	11504(2)	34(1)	1
C3	866(2)	−3036(10)	10923(3)	93(2)	1
C4	1926(1)	615(4)	12271(2)	30(1)	1
C5	1809(1)	636(5)	13330(2)	31(1)	1
C6	2042(1)	2513(5)	13940(2)	37(1)	1
C7	1923(1)	2559(6)	14936(2)	43(1)	1
C8	1574(1)	777(6)	15333(2)	45(1)	1
C9	1339(1)	−1094(6)	14741(2)	45(1)	1
C10	1454(1)	−1164(5)	13740(2)	39(1)	1
C11	2500(1)	1570(4)	11883(2)	31(1)	1
C12	3045(1)	76(4)	12237(2)	30(1)	1
C13	3607(1)	1007(5)	11765(2)	40(1)	1
C14	4172(1)	95(5)	12276(2)	38(1)	1
C15	4422(1)	1423(9)	13065(2)	68(1)	1
C16	4930(2)	676(15)	13572(3)	104(2)	1
C17	5197(2)	−1442(14)	13321(6)	124(3)	1
C18	4969(2)	−2815(10)	12596(7)	132(3)	1
C19	4450(2)	−2069(8)	12044(4)	90(2)	1
O1	2421(1)	1380(3)	10811(1)	35(1)	1
O2	1669(1)	521(4)	9732(1)	39(1)	1
O3	1023(1)	−993(4)	11529(1)	47(1)	1
O4	2958(1)	−2517(3)	12094(1)	34(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O2	1.210(3)
C1–O1	1.343(3)
C1–C2	1.477(3)
C2–C4	1.325(3)
C2–O3	1.348(3)
C3–O3	1.407(4)
C4–C5	1.465(3)
C4–C11	1.505(3)
C5–C10	1.385(4)
C5–C6	1.393(3)
C6–C7	1.383(4)
C7–C8	1.363(4)
C8–C9	1.378(4)
C9–C10	1.387(4)
C11–O1	1.456(3)
C11–C12	1.527(3)
C12–O4	1.421(3)
C12–C13	1.524(3)
C13–C14	1.504(4)
C14–C19	1.364(5)
C14–C15	1.384(5)
C15–C16	1.371(5)
C16–C17	1.338(10)
C17–C18	1.314(9)
C18–C19	1.419(7)
O2–C1–O1	122.2(2)
O2–C1–C2	129.5(2)
O1–C1–C2	108.22(19)
C4–C2–O3	126.9(2)
C4–C2–C1	109.4(2)
O3–C2–C1	123.3(2)
C2–C4–C5	129.9(2)
C2–C4–C11	108.0(2)
C5–C4–C11	122.0(2)
C10–C5–C6	118.6(2)
C10–C5–C4	121.1(2)
C6–C5–C4	120.3(2)
C7–C6–C5	120.3(2)
C8–C7–C6	120.6(3)
C7–C8–C9	119.9(2)
C8–C9–C10	120.2(3)
C5–C10–C9	120.3(3)
O1–C11–C4	104.54(18)
O1–C11–C12	109.84(19)
C4–C11–C12	113.65(19)
O4–C12–C13	112.2(2)
O4–C12–C11	111.62(19)
C13–C12–C11	111.42(19)
C14–C13–C12	113.6(2)
C19–C14–C15	116.2(3)
C19–C14–C13	124.1(3)
C15–C14–C13	119.7(3)
C16–C15–C14	122.6(5)
C17–C16–C15	119.8(6)
C18–C17–C16	120.2(5)
C17–C18–C19	121.4(5)
C14–C19–C18	119.8(4)
C1–O1–C11	109.40(18)
C2–O3–C3	118.6(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	38(1)	29(1)	29(1)	−3(1)	−2(1)	2(1)
C2	32(1)	36(1)	35(1)	−6(1)	1(1)	−2(1)
C3	82(3)	109(3)	90(3)	−49(3)	31(2)	−54(3)
C4	35(1)	27(1)	28(1)	−2(1)	1(1)	2(1)
C5	32(1)	33(1)	27(1)	−1(1)	−2(1)	5(1)
C6	41(1)	36(1)	35(1)	−3(1)	−1(1)	−1(1)
C7	49(2)	46(1)	34(1)	−12(1)	3(1)	−1(1)
C8	49(2)	59(2)	27(1)	−4(1)	2(1)	7(1)
C9	50(2)	50(2)	35(1)	4(1)	2(1)	−4(1)
C10	43(2)	40(1)	34(1)	−7(1)	1(1)	−5(1)
C11	39(1)	28(1)	25(1)	2(1)	−3(1)	−5(1)
C12	37(1)	28(1)	26(1)	2(1)	2(1)	−4(1)
C13	37(1)	49(2)	33(1)	10(1)	2(1)	−7(1)
C14	32(1)	42(2)	42(1)	9(1)	11(1)	4(1)
C15	43(2)	121(3)	41(2)	−6(2)	0(1)	15(2)
C16	46(2)	199(6)	66(2)	28(3)	−7(2)	15(3)
C17	44(3)	129(5)	199(7)	96(5)	6(3)	6(3)
C18	52(3)	63(3)	282(9)	6(4)	13(4)	23(2)
C19	44(2)	59(2)	169(5)	−30(2)	22(2)	3(2)
O1	40(1)	38(1)	25(1)	8(1)	−2(1)	−5(1)
O2	45(1)	44(1)	27(1)	1(1)	−4(1)	0(1)
O3	36(1)	72(1)	35(1)	−15(1)	3(1)	−13(1)
O4	44(1)	27(1)	33(1)	2(1)	7(1)	−1(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

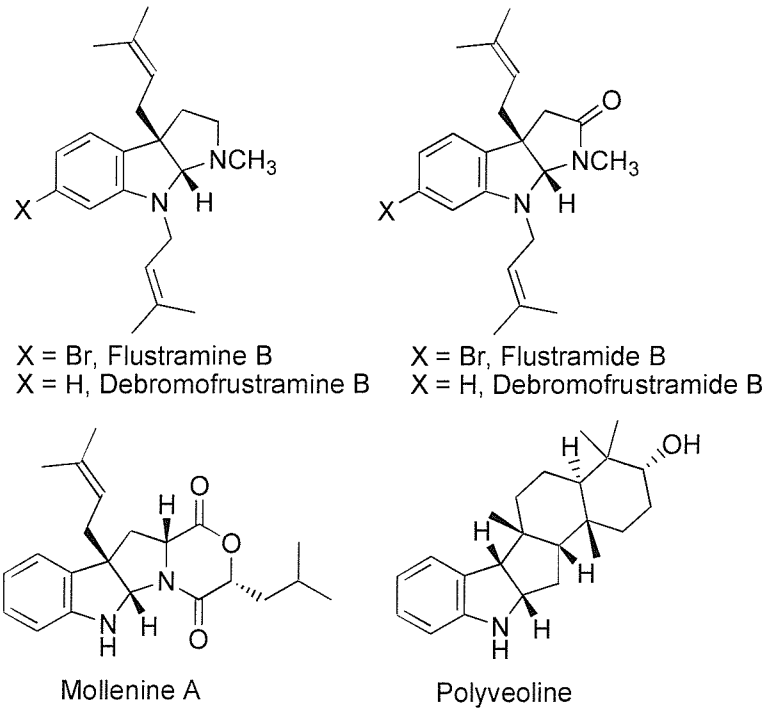
Atom	x	y	z	U_{eq}	*S.o.f.*
H3A	865	−2529	10226	139	1
H3B	469	−3624	11082	139	1
H3C	1156	−4377	11038	139	1
H6	2285	3767	13671	45	1
H7	2085	3844	15346	52	1
H8	1493	825	16017	54	1
H9	1098	−2340	15019	54	1
H10	1289	−2453	13335	47	1
H11	2555	3353	12075	37	1
H12	3099	357	12967	36	1
H13A	3600	466	11064	47	1
H13B	3607	2848	11772	47	1
H15	4233	2912	13263	82	1
H16	5093	1660	14100	124	1
H17	5551	−1955	13668	149	1
H18	5157	−4339	12438	159	1
H19	4296	−3072	11514	108	1
H4	2986	−2862	11491	51	1

Chapter 3: New Methods for Indole Alkylation

1. Introduction

Many alkaloids such as flustramine B,[1] debromoflustramine B,[2] flustramide B,[3] mollenine A,[4] and polyveoline[5] (Figure 1) can be formally derived by the addition of isoprenoid units to the β-position (C-3) of an indole. Consequently, the synthesis of 3-alkylindoles has been the subject of considerable interest in connection with the biomimetic synthesis of such natural products. Two major synthetic methods have been employed to prepare 3-alkylindoles: the direct alkylation of indolylmagnesium species[6] and the alkylation of *N*-protected indoles, followed by deprotection.[6,7,8]

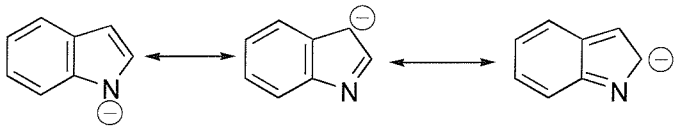
Figure 1



Direct C-3 alkylation is generally straightforward, but tends to give low yields in many cases. This is mainly attributed to the competitive formation of *N*-alkylated product due to the ambident character of the indole system. Indole has a relatively low pKa (*ca.*17), and the indolyl anion is mesomeric with the negative charge delocalised, mainly concentrated on the nitrogen and the β-carbon, as expressed in

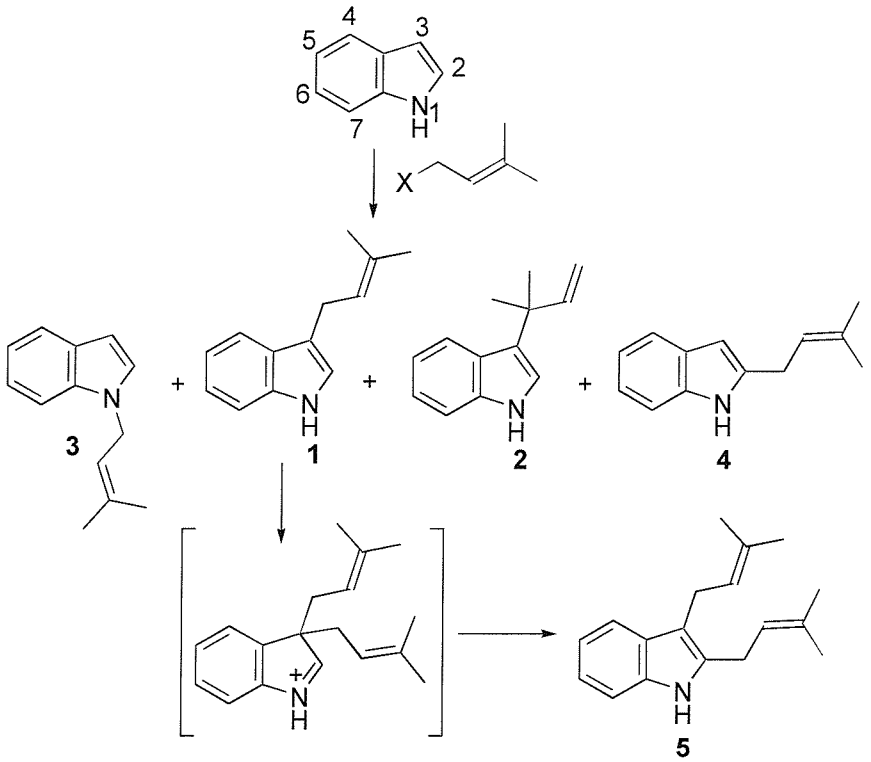
the following canonical forms (Figure 2).

Figure 2



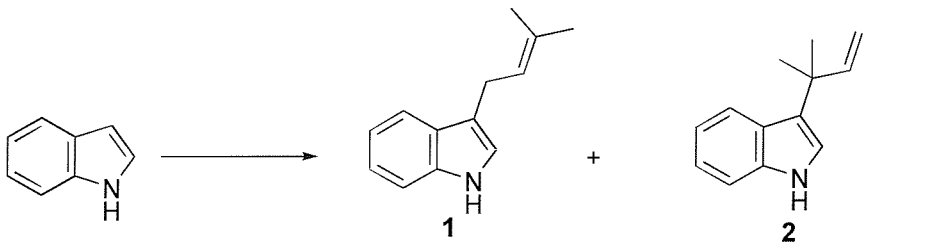
Therefore, C-3 versus N nucleophilic reaction of the indole ring is always a major issue when functionalizing indole. The C-2 alkylated product is also observed although it is less favoured as it involves disruption of benzenoid aromaticity in the molecule. The C-3 prenyl (γ,γ-dimethylallyl) group is a common structural feature of indole natural products as seen in the structures of mollenine A and flustra-alkaloids (Figure 1). However, alkylation of indoles with prenyl halides is plagued by problems of regioselectivity and overalkylation (Scheme 1). The prototypical example[6] of direct prenylation of indole by using indolylmagnesium species with prenyl bromide affords a mixture of prenyl and its reverse prenyl (α,α-dimethylallyl) isomer (**1** and **2**) in only 34% yield (17:1 ratio) (Scheme 2, Entry 1), together with smaller amounts of N-1, C-2, as well as diprenyl byproducts (**3**, **4**, **5**, respectively).

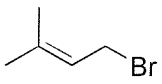
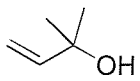
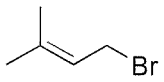
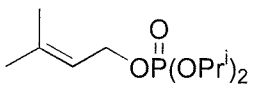
Scheme 1



Other reported methods for the direct prenylation (Scheme 2) by treatment with a Grignard reagent reacting with allyl alcohol in the presence of bis(triphenylphosphine)nickel dichloride[6] (Entry 2), prenylation of indole with prenyl bromide in acetate buffer conditions[9] (Entry 3) or with prenyl diisopropyl phosphate catalysed by a Lewis acid (BF_3)[10] (Entry 4) are also unsatisfactory. Comparatively, indirect methods (Scheme 3), which involve *N*-protection (protected by benzenesulfonyl,[6] *tert*-butyldimethylsilyl[7] or triisopropylsilyl,[8] *etc*), alkylation and deprotection, usually produce higher overall yield, but suffer from the disadvantage of multistep reaction sequences involving air sensitive organometallic reagents.

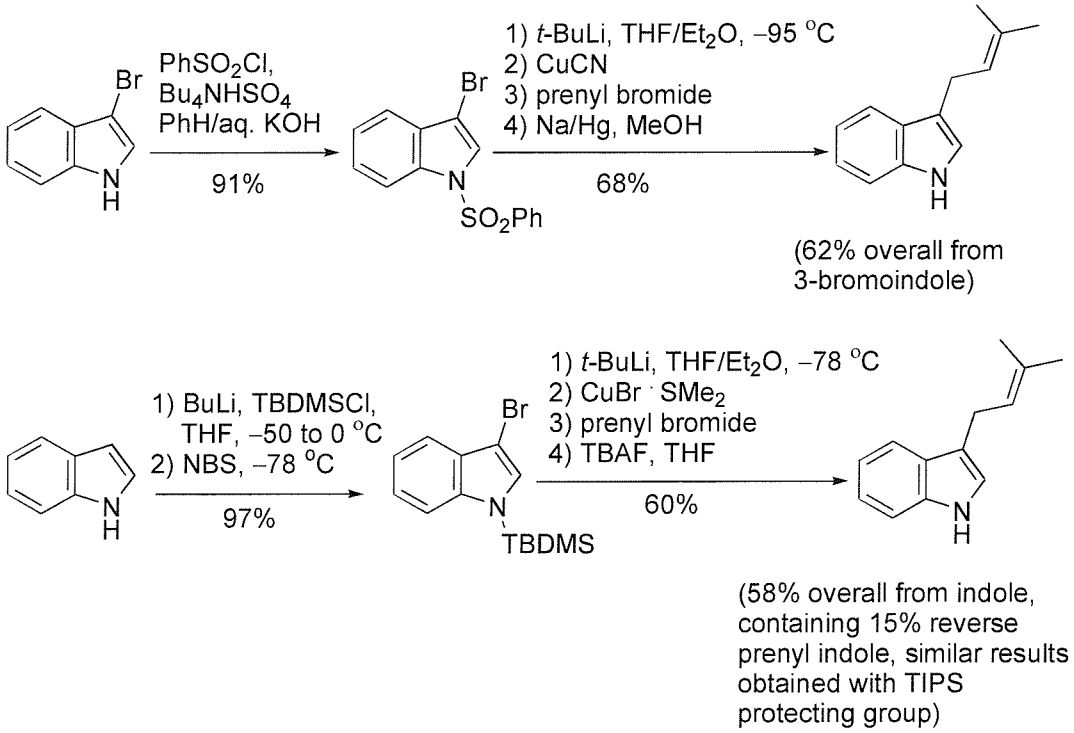
Scheme 2 Present methods for direct prenylation of indole



Entry	Conditions	Yield (%)	Ratio of **1**:**2**
1	CH_3MgBr, 	34	17:1
2	MeMgI, cat. $(Ph_3P)_2NiCl_2$, 	29	1:3
3	 aq. AcOH/NaOAc, pH 3	30 (GLC)	
4	 $BF_3{\cdot}Et_2O$	26	4:1

In order to lay the groundwork for our future natural product syntheses, combinatorially screening new reaction conditions for direct indole prenylation was carried out.

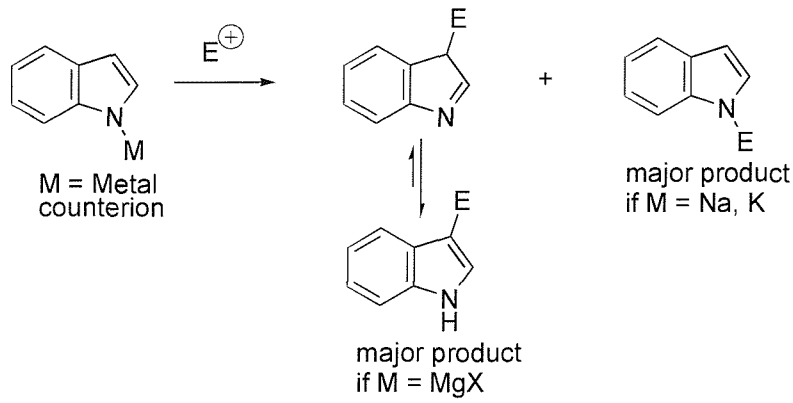
Scheme 3 Present methods for indirect prenylation of indole



2. Screening of Metal Triflates for Indole Prenylation

The alkylation of indolyl anions has been extensively studied.[11] The tightness of the ion pair (metal cation/indole anion) affects strongly the reactivity of the indole and the selectivity of the alkylation (Scheme 4). The more ionic sodium and potassium salts tend to react preferentially at nitrogen, particularly with 'hard' electrophiles. Substitution at nitrogen is also favoured by the use of dipolar solvents, like THF or DMF. However, with magnesium as the counterion,[12] the *N*-metallated indole intermediate has an essentially covalent rather than ionic structure, and reactions tends to occur at the C-3 position. Generally, β-alkylation is favoured by more covalently coordinated metals, soft leaving groups, and nonpolar solvent. A mild and efficient method for β-prenylation of indole by using a metal salt was developed, which avoid the use of strongly basic and air sensitive reagents.

Scheme 4 *C* versus *N* reactivity of indolylmetal species



Lanthanide metals play a prominent role in the synthesis and functionalization of indoles. Recently, ytterbium triflate[13] and scandium triflate[14] were successfully employed to catalyse 3-substitution of indoles. These and other metal triflates were screened for their ability to affect the prenylation of indole (Scheme 5). Screening reactions were carried out at room temperature under inert gas by addition of prenyl bromide to a stirred reaction mixture of indole, metal salt, and triethylamine in anhydrous toluene. Two equivalents of indole were used in these reactions to minimize the further reaction of prenyl indole (**1**) to form the diprenyl compound (**5**) and the yields were calculated based on the prenyl bromide. Although prenylation was observed in all cases (Table 1), the nature of the metal cation has a significant effect on both the yield and the ratio of prenyl to reverse prenyl isomers. Zinc triflate was found to give the best yield in this initial screen. The success with zinc is not wholly unexpected: zinc species, as soft reagents, have previously been used to promote indole alkylation and acylation (Scheme 6). Zinc triflate was found to be the best Lewis acid for effecting enantiospecific alkylation of indole by 1-(Cbz)aziridine-2-carboxylate esters (Entry 1).[15] Bergman and Venemalm reported that the indolylmagnesium salt can be transmetallated with anhydrous $ZnCl_2$, followed by acylation with a number of acid chlorides to give 3-acylindoles in yields superior to those obtained directly with the indolylmagnesium salt (Entry 2).[16] Russian chemists[17] also found that zinc chloride effected Friedel-Crafts alkylation at the β position of indole (Entry 3).

Scheme 5

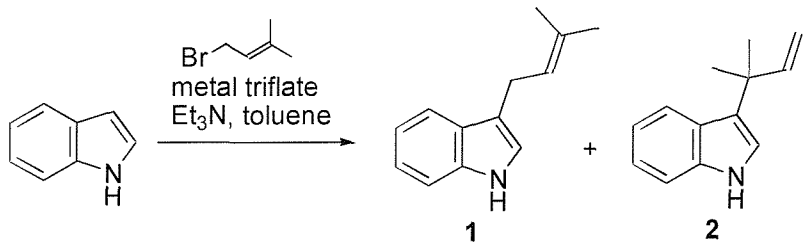


Table 1. Screening of metal triflates for indole prenylation.

Metal triflate	Zn (II)	Yb (III)	In (III)	Ag (I)	Hg (II)	Cu (I)	Cu (II)	La (III)	Sn (II)	Sc (III)
Yield (%)[a]	55	13	30	29	36	18	5	4[c]	1.6[c]	2[c]
Ratio of **1**:**2**[b]	10:1	37:1	13:1	32:1	>80	2:1	1:1	-	-	-

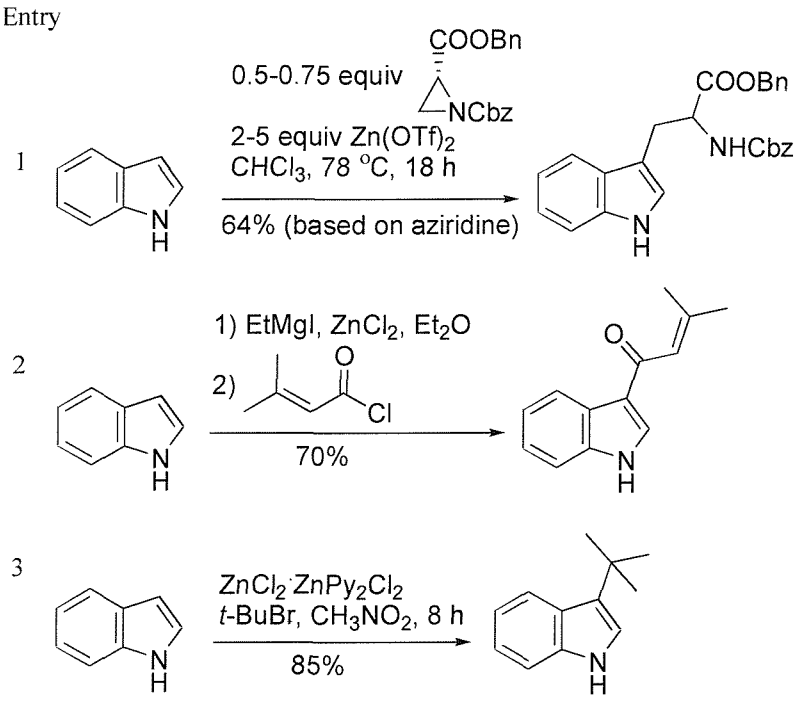
Screening conditions: 0.43 mmol prenyl bromide, 2 equiv indole, 1.2 equiv metal triflate, 2.2 equiv triethylamine in 2.5 mL anhydrous toluene, room temperature, overnight

[a]Here and in all subsequent tables, yield is based on bromide and refers to the isolated pure material obtained after preparative TLC.

[b]Here and in all subsequent tables, the ratio of prenyl to reverse prenyl product was determined by ^{1}H NMR peak integration.

[c]In these cases, yield was estimated by HPLC analysis of the reaction mixture.

Scheme 6 Examples of zinc species promoting indole alkylation and acylation



3. Optimisation of the Zinc Triflate Mediated Prenylation

In our preliminary investigations, 3-prenyl indole was formed in good yield in the presence of zinc triflate and an amine base. A systematic optimisation study was undertaken in order to determine the ideal reaction conditions for this process.

3.1. Solvent

The reaction was carried out in the following different solvents in the presence of zinc triflate: toluene, CH_2Cl_2, THF and DMF. By HPLC analysis, the best result was obtained with toluene, which is consistent with non-polar solvents lowering the degree of dissociation of the nitrogen-metal bond and favouring attack at C-3.

3.2. Amine Base

A survey of amine bases [triethylamine, *N,N'*-diisopropylethylamine (DIEA), 1,2,2,6,6-pentamethylpiperidine (pempidine), pyridine and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)] (Table 2) revealed that the optimal yield of β-prenyl indole was obtained with DIEA. In subsequent investigation, two molar equivalents of base was observed providing higher yield, while one equivalent leads to product in 10% lower yield.

Table 2 A survey of amine bases

Base	Et_3N	DIEA	pempidine	pyridine	DBU
Yield (%)	55	59	36	35	45
Ratio of **1**:**2**	10:1	20:1	23:1	12:1	18:1

Conditions: 0.43 mmol prenyl bromide, 2 equiv indole, 1.2 equiv zinc triflate, 2.2 equiv base, in 2.5 mL anhydrous toluene, room temperature, overnight

3.3. Zinc Salt

The effect of varying the zinc activator was also investigated. Both zinc bromide (44% yield, 37:1 ratio of **1**:**2**) and zinc acetate (33% yield, 45:1 ratio of **1**:**2**) gave inferior yields under the conditions using DIEA as a base, but with increased regioselectivity.

3.4. Reaction Time

HPLC analysis shows that the reaction (0.43 mmol prenyl bromide, 2 equivalents of indole, 1.2 equivalents of zinc triflate, 2.2 equivalents of base in 2.5 mL anhydrous toluene) was complete within 1.5 hours.

3.5. Temperature

Reaction carried out at 0 °C using the same amount of reagents for 4 hours resulted in 3-prenyl indole in 49% yield with 28:1 ratio of **1**:**2**. Thus, lowering temperature gives a better ratio, but in a slightly lower yield.

3.6. Reagent Stoichiometry

As seen from table 3, the yield was dramatically increased by 17% by using 2 equivalents (Entry 2) instead of 1 equivalent of indole (Entry 1). Increasing the amount of zinc triflate gave rise to lower yield and a poorer ratio of prenyl to reverse prenyl indole (Entry 3 and 5, 6 comparing with Entry 1 and 4, respectively), whereas substoichiometric quantities of zinc triflate gave a better ratio, but at the expense of lower yield and longer reaction time (Entry 7, 8).

Table 3 Amounts of reagents

Entry	Indole (molar equiv)	Zinc triflate (molar equiv)	DIEA (molar equiv)	Yield (%)	Ratio of **1**:**2**
1	**1**	**1**	**1.2**	**35**	**17:1**
2	2	1	1.2	52	18:1
3	1	2	2.2	23	13:1
4	**2**	**1.2**	**2.2**	**59**	**20:1**
5	2	2	2.2	45	16:1
6	2	2	3	44	15:1
7	2	0.5	2.2	45	30:1
8	2	0.25	2.2	48	36:1

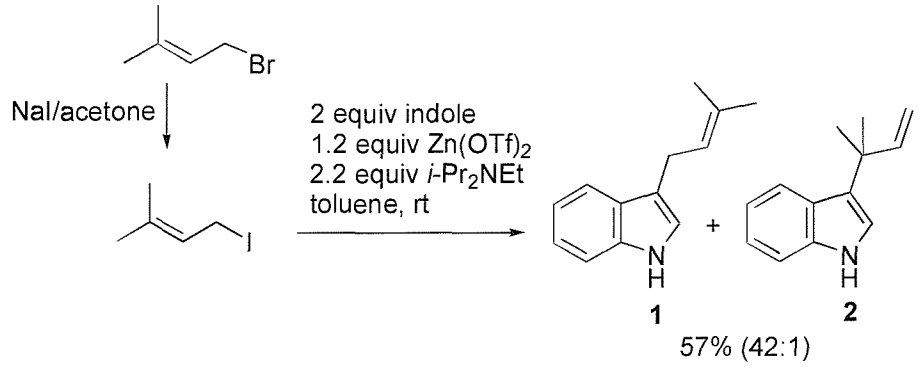
Conditions: 0.43 mmol prenyl bromide in 2.5 mL anhydrous toluene, room temperature.

3.7. Alkylating Reagent

Changing the electrophile from prenyl bromide to the iodide, either preformed by Finkelstein exchange (Scheme 7) or more simply by *in situ* generation with tetrabutylammonium iodide (Scheme 8) dramatically improved the regioselectivity of 3-prenylation, the ratio of **1**:**2** now being >70:1. Iodide is more polarized, better leaving group for S_N1. Further investigation (Table 4) shows that stoichiometric ammonium iodide gave almost exclusively the prenyl product; catalytic amounts led to higher yield but a less satisfactory ratio of **1**:**2**. Our attempt to synthesize

even more active alkylating agents (prenyl triflate or tosylate) failed due to difficulty in handling these relatively unstable compounds.[18]

Scheme 7



Scheme 8

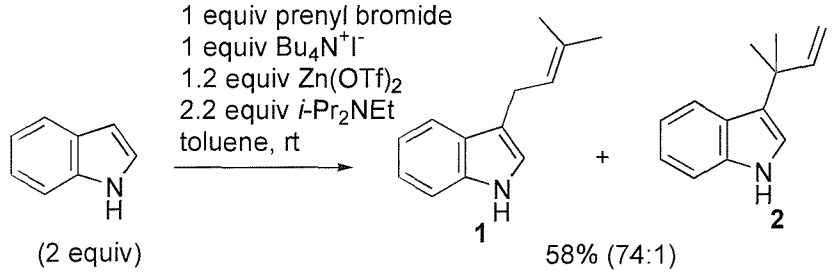


Table 4

$Bu_4N^+I^-$ (molar equiv)	1	0.5	0.25
Yield (%)	58	63	65
Ratio of **1**:**2**	74:1	30:1	25:1

Conditions: 0.43 mmol prenyl bromide, 2 equiv of indole, 1.2 equiv of zinc triflate, 2.2 equiv of DIEA in 2.5 mL anhydrous toluene, room temperature, 2 h.

3.8. Large Scale Preparation

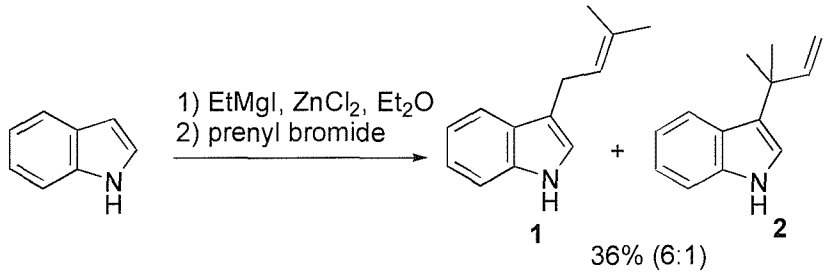
A large-scale reaction carried out under the established conditions (2 mmol indole, 1 mmol prenyl bromide, 1.2 mmol zinc triflate, 2.2 mmol DIEA, 1 mmol $Bu_4N^+I^-$ in 5.8 mL anhydrous toluene, room temperature, 2 hours) provided 3-prenyl indole in 59% yield, 2-prenyl indole in 11% yield and small amounts of *N*-prenyl and diprenyl indole being isolated, 58% of the total indole used being recovered. Thus our method is also reliable for large scale preparation.

4. Prenylation of Indole Using Other Methods

Wenkert *et al.*[6] reported that 3-prenyl indole was obtained in 34% yield (17:1 ratio of **1**:**2**) using 1 equivalent of indolylmagnesium reagent and 1 equivalent of prenyl bromide (Scheme 2, Entry 1). In our hands, 3-prenyl indole (17:1 ratio) was isolated in 41% yield. But when the reaction was conducted with 2 equivalents of indolylmagnesium reagent, surprisingly, the yield (38%) was not improved and the ratio of **1**:**2** (9:1) was dramatically decreased.

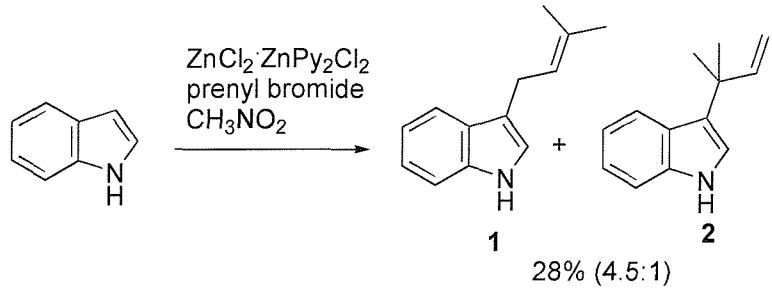
Bergman *et al.* reported acylation of indole with the zinc indolyl salt generated by transmetallation of the Grignard reagent (Scheme 6, Entry 2).[16] The prenylation reaction under their transmetallation conditions (Scheme 9) was tested. The indolymagnesium species was treated with 1 equivalent of zinc triflate, and prenyl bromide was then added after 20 minutes. After work-up, purification provided an unsatisfactory yield (36%) and ratio of **1**:**2** (6:1), also *N*-prenyl (**3**) and 2-prenyl indole (**4**) being isolated in 25% and 9% yield respectively.

Scheme 9

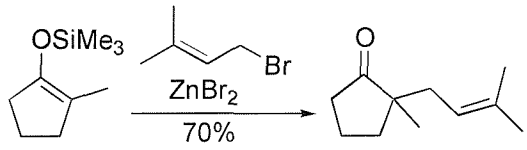


Prenylation was also conducted with the Russian alkylation method[17] (Scheme 6, Entry 3) using a complex formed from zinc chloride and pyridine (Scheme 10). The complex was prepared by dissolving zinc chloride in a mixture of water, concentrated hydrochloric acid and absolute alcohol, followed by addition of 2 equivalents of pyridine. The precipitate obtained was then recrystallized from absolute alcohol.[19] Prenyl bromide was added to a reaction mixture of indole, zinc chloride pyridine complex (0.75 equivalents) and zinc chloride (0.75 equivalents) in nitromethane at room temperature. After 2 hours, the reaction was worked up and purified to afford (**1**) and (**2**) in 28% yield. (4.5:1 ratio of **1**:**2**).

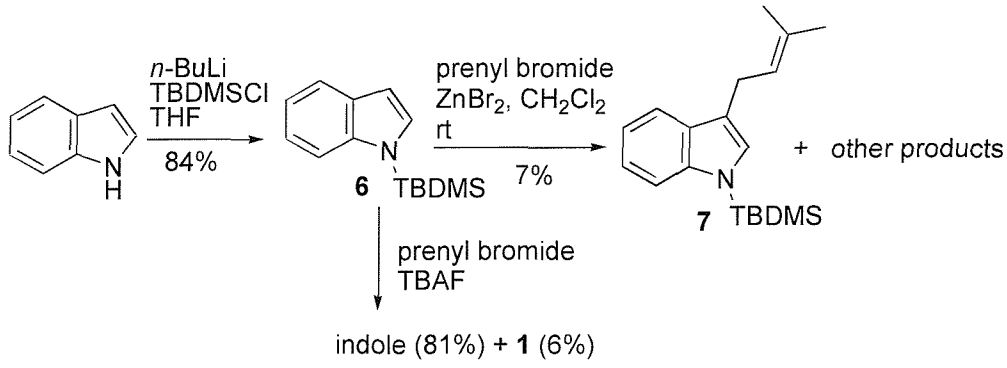
Scheme 10



Scheme11



Scheme 12



O-Silylated ketone enolates of ketones, esters and lactones can be alkylated regiospecifically with certain types of halides using a catalytic amount of zinc bromide to give the monoalkylated carbonyl compounds in good yield, an example being shown in Scheme 11.[20] It was thought that *N*-silylated indole probably would follow the same reaction route to provide 3-prenyl indole. *N*-TBDMS indole (1 equivalent) (**6**), prepared from indole by treatment with *n*-BuLi and TBDMSCl, was reacted with prenyl bromide (1.2 equivalents) in the presence of zinc bromide (2 mol%) at room temperature, giving a complex mixture of (**7**), indole, 3-prenyl and diprenyl indole by GC-EIMS analysis. Product (**7**) was isolated in only 7% yield (Scheme 12). It was wondered if the indolyl anion generated by deprotection of the silyl group in (**6**) would undergo nucleophilic attack towards prenyl bromide. A mixture of (**6**) and prenyl bromide was treated with tetrabutylammonium fluoride, but gave only 81% indole and 6% 3-prenyl indole

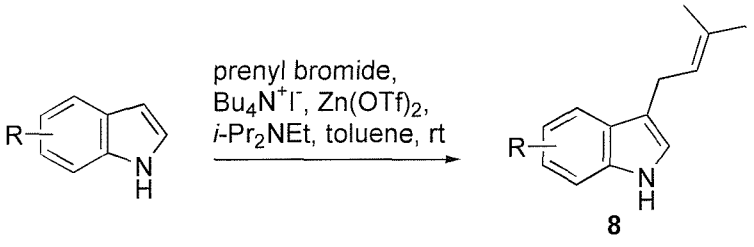
by HPLC analysis, suggesting the indolyl anion itself is not active towards electrophilic attack.

In summary, the literature methods for the prenylation of indole were not satisfactory. Our zinc triflate mediated procedure provides the 3-prenyl product in high yield and regioselectivity under very mild conditions.

5. Scope of the Zinc Triflate Mediated Alkylation

The optimized prenylation conditions were then tested with a series of other indole substrates. Prenylations were successful with 4-nitro, 5-benzyloxy, 6-chloro or 7-chloro indoles (Scheme 13), the yields not being strongly affected by the nature or position of these substituents. In the case of 5-nitroindole, a mixed solvent (dichloromethane:toluene = 1:3) was used due to poor solubility of the indole.

Scheme 13 C-3 Prenylation with substituted indoles



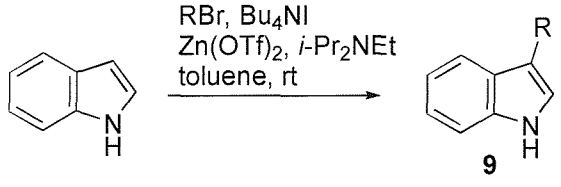
8

R	Product	Yield (%)
4-NO_2	**8a**	69
5-BzO	**8b**	51
6-Cl	**8c**	56
7-Cl	**8d**	59

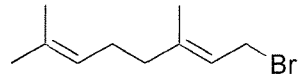
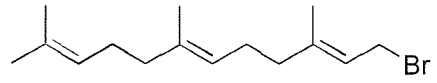
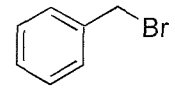
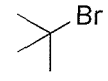
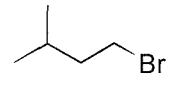
The zinc triflate mediated prenylation can also be extended to more complex allyl halides (Scheme 14). 3-Geranyl indole was obtained in 60% yield (Entry 1) when indole was treated with geranyl bromide. The byproduct 2-geranyl isomer

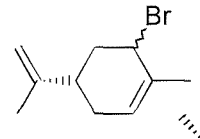
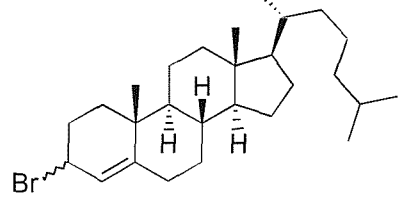
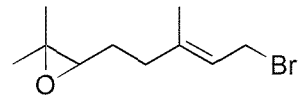
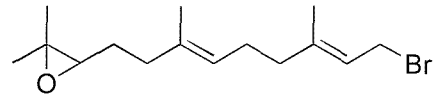
was isolated in 9% yield. In the literature, 3-farnesyl indole was prepared in 35% yield by using 8 equivalents of the indolylmagnesium species with farnesyl bromide.[21] Under our alkylation conditions, 3-farnesyl indole was obtained in 49% yield with only 2 equivalents of indole (Entry 2). Our method is also suitable for tertiary and benzylic halides. Alkylation with benzyl bromide led to 3-benzyl indole (**9c**), which was inseparable from indole. The yield given in the table was estimated by ^{1}H NMR peak integration of a purified mixture of (**9c**) and indole. Alkylation with *t*-butyl bromide afforded (**9d**) in 54% yield, together with 7% of the *N*-*t*-butyl isomer. No reaction was observed with isopentyl bromide by TLC or GC-EIMS analysis. Entries 6 and 7 highlight the application of our alkylation to the conjugation of indoles with natural products ((-)-carveol and cholest-4-en-3-ol, respectively). Compound (**9f**) was obtained as a mixture of separable equatorial and axial isomers in a ratio of 3.2:1. The axial isomer was identified by X-ray crystallography. Compound (**9g**) was obtained as a 1:1 mixture of equatorial and axial isomers, and a further 22% of the *N*-alkylated byproduct was also isolated. The mildness of the alkylation conditions can be discerned in Entries 8 and 9, in which the epoxide group is unaffected.

Scheme 14



9

Entry	RBr	Products	Yield (%)
1		**9a**	60
2		**9b**	49
3		**9c**	53
4		**9d**	54
5		**9e**	0

Entry	RBr	Products	Yield (%)
6		**9f**	71 (3.2:1)[a]
7		**9g**	66 (1:1)[a]
8		**9h**	69[b]
9		**9i**	53[b]

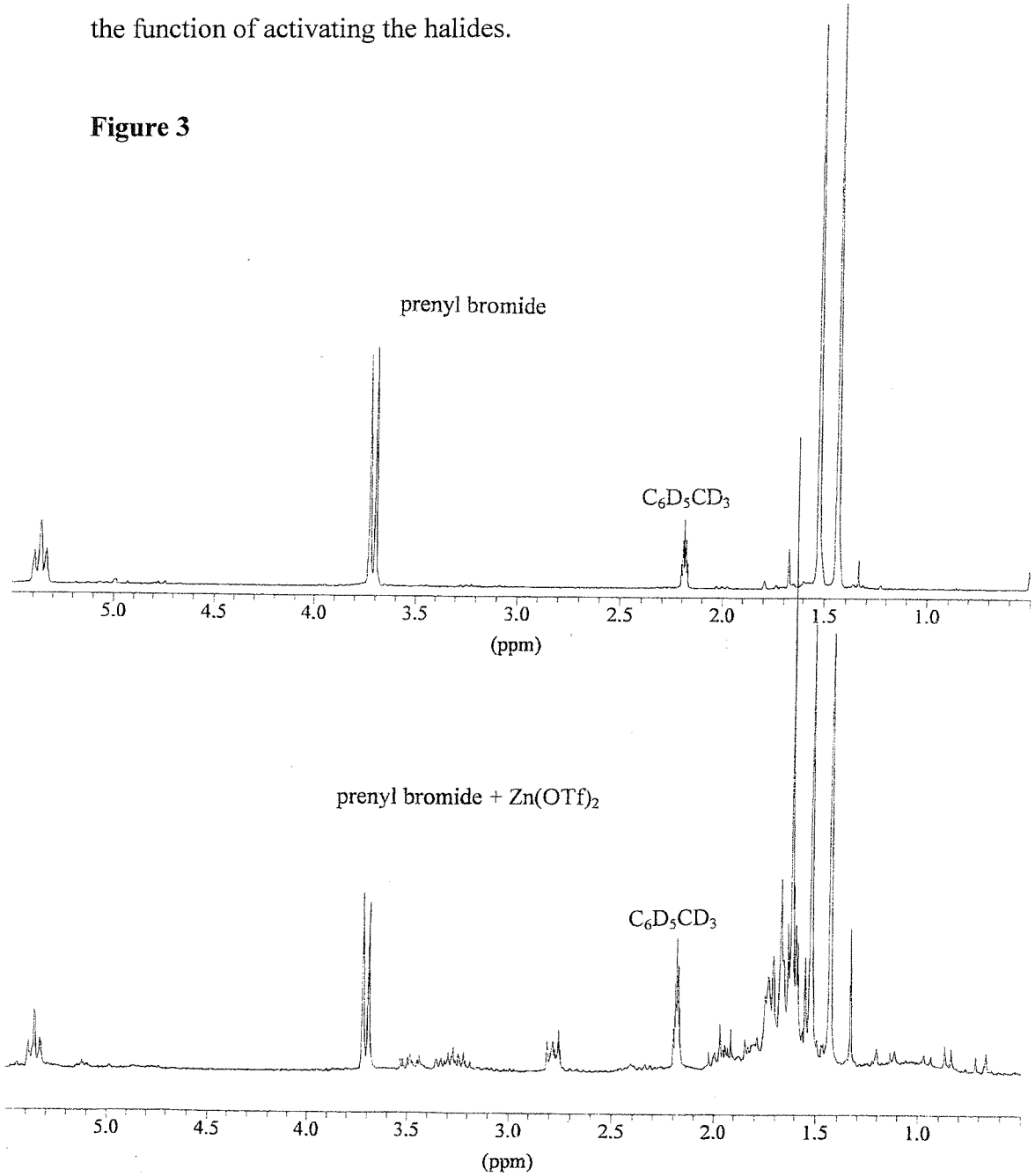
[a] Ratio of equatorial to axial isomer.
[b] Details of preparation are given in the next chapter.

6. Mechanistic Studies on the Zinc Triflate Mediated Alkylation of Indole

The zinc triflate mediated alkylation appears to be general for halides with an S_N1-like reactivity (Scheme 14), while unsuitable for saturated primary halides. This suggests activation of the halide by the zinc species, as supported by ^1H NMR experiments (Figure 3) in deuterated toluene. Upon addition of zinc triflate (1 equivalent) the proton spectrum of prenyl bromide shows additional multiplets between δ 2.5 and 3.5 ppm, as well as new signals for the gem-dimethyl group at ~ δ 1.5 ppm. Although we are unable to unambiguously interpret these new signals, the changes appear consistent with formation of a π-allyl-like complex[22] with the zinc. However, a similar change is not observed with saturated halides such as isopentyl bromide. Activation with zinc acetate instead of zinc triflate was not immediately observed after the addition of zinc acetate to prenyl bromide. Only

after 2 hours did the proton spectrum start to show some changes. Since zinc acetate is less Lewis acidic, this implies it is not sufficiently reactive to activate the halide. The ability of zinc triflate is in contrast to the classical indole alkylation using indolylmagnesium species. When used in excess, the indolylmagnesium species does not improve the yield of alkylation partially because it does not have the function of activating the halides.

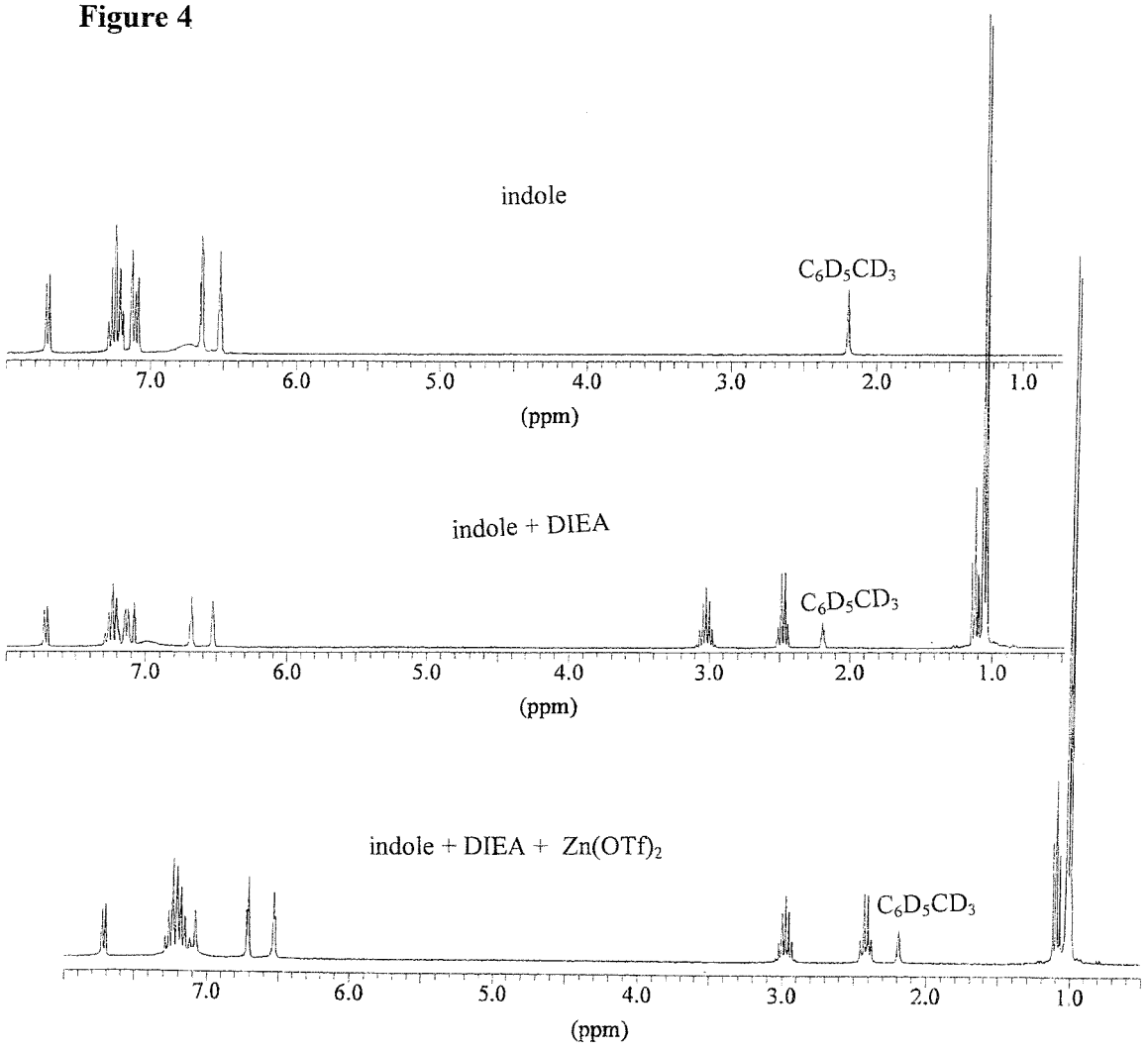
Figure 3



Although halide activation is important, some of the metals in table 1 with higher Lewis acidic character than zinc gave poorer yields. Zinc triflate is believed to serve an equally important function in activating the indole. Upon addition of zinc triflate, the proton spectrum of indole is the same as that of indole alone. There are some changes in the spectrum after the addition of diisopropylethylamine to the

mixture, but these are also observed with a mixture of indole and the amine by itself. Thus the activation of indole by zinc triflate is not directly supported by the ^{1}H NMR spectrum (Figure 4). In order to investigate the potential zinc-nitrogen coordination, the prenylation reaction was conducted with *N*-methylindole. The resulting yield of *N*-methyl-3-prenyl indole was significant lowered (36%). This result suggests metal coordination of the zinc cation to the electronegative nitrogen atom, which then influences the relative reactivity of the ambident anion. It greatly reduces the nucleophilic reactivity of the nitrogen, and partially weakens the reactivity of the less electronegative C-3 position, so that alkylation is possible only with reagents with a more marked S_N1 character. In the next section, the potential application of our alkylation method to a natural product synthesis was described.

Figure 4

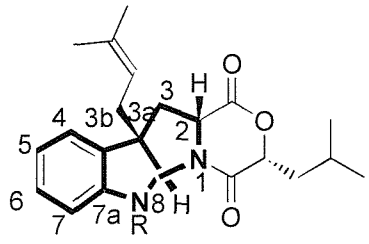


7. Model Study Towards Mollenines

7.1. Background

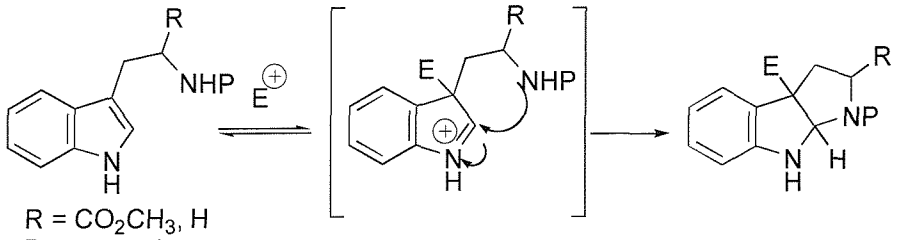
Mollenine A and B (Figure 5) were isolated from the sclerotid ascostromata of *Eupenicillium molle*. Mollenine A exhibited moderate cytotoxicity and antibacterial activity. An uncommon dioxomorpholine structure in these compounds apparently results from condensation of a tryptophan subunit with an α-hydroxy acid moiety, rather than the more usual fungal metabolites containing dioxopiperazine structures.

Figure 5



R = H, Mollenine A
R = CHO, Mollenine B

Scheme 15



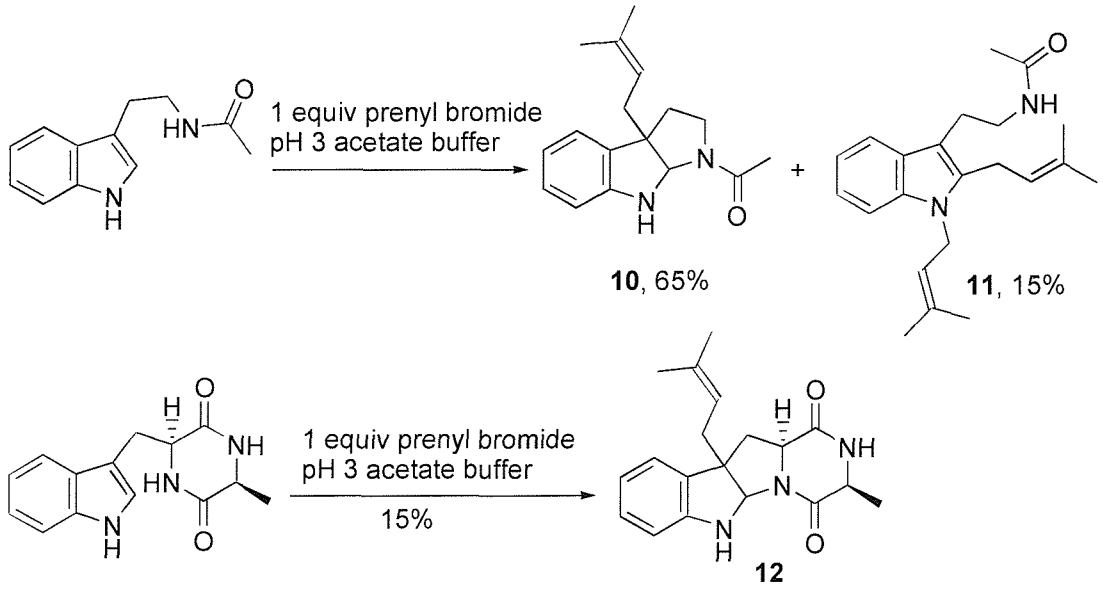
R = CO_2CH_3, H
P = protective group

The core structure of 1,2,3,3a,8,8a-hexahydropyrrol[2,3-*b*] indole (highlighted in the structure of mollenines in Figure 5) with various substituents is an attractive intermediate in the synthesis and biosynthesis of many natural indole derivatives. One route is electrophilic attack at the C-3 position of indole moiety in tryptophan and tryptamine derivatives, generating an electrophilic centre at the C-2 position, which is then intramolecularly trapped by the nucleophilic nitrogen of the side chain to form the cyclic skeleton (Scheme 15). A variety of electrophiles including carbon electrophiles,[9(b),23,24,25,26] protons,[27,28] positive halogen donors,[29,30,31] positive oxygen donors,[32] and selenium donors[33] have been well documented for

triggering this type of ring closure.

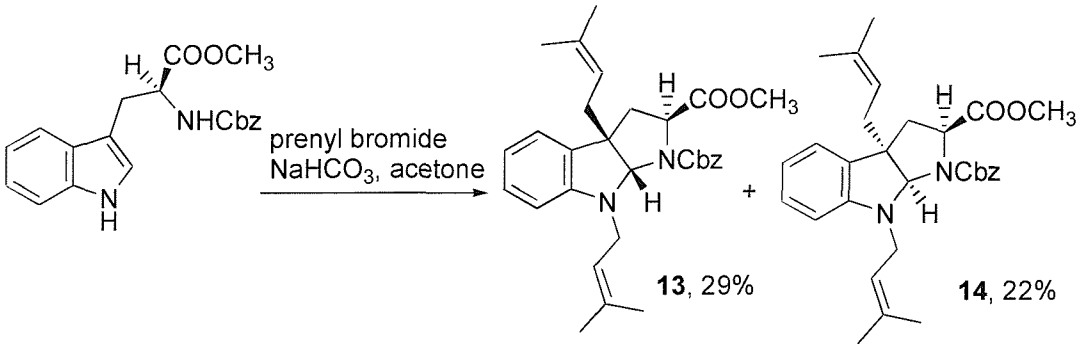
The earliest example of introducing a prenyl group as a carbon electrophile onto the C-3 position of indole ring with simultaneous ring closure to form the tricyclic system was reported by Casnati in 1969 (Scheme 16).[9] *N*-Acetyltryptamine was reacted with prenyl bromide at pH 3 in an acetate buffer to simulate biological conditions, affording the tricyclic product (**10**) in 65% yield, along with 1,2-dialkylated byproduct (**11**). However, the corresponding reaction with tryptophan was unsuccessful.[9(a)] A more complex example with a tryptophan derivative having a diketopiperazine moiety was shown to undergo cyclization in low yield (15%).[9(b)] The acetic acid buffer conditions were used to synthesize the marine alkaloids (±)-debromoflustramide B and E, (±)-debromoflustramine B and E, and related compounds.[23]

Scheme 16

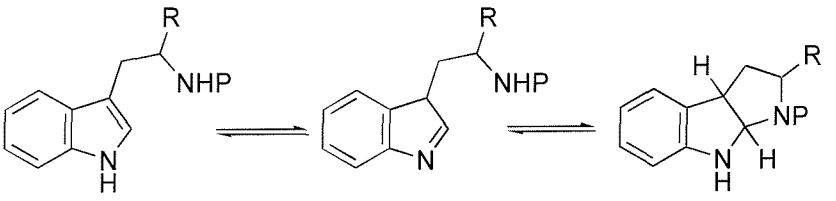


Another method for the direct prenylation of C-3 of indole in tryptophans was reported in which *N*-Cbz-L-tryptophan methyl ester was treated with prenyl bromide in the presence of $NaHCO_3$ in acetone, producing diprenyl cyclic tautomers (**13**) and (**14**) in a ratio of *ca.* 1:1 (Scheme 17).[26]

Scheme 17

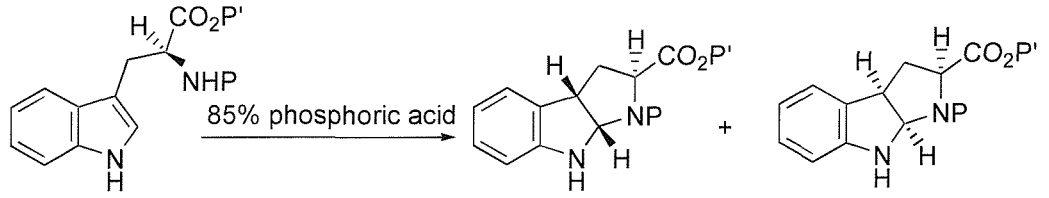


Scheme 18



Efficient asymmetric synthesis is more problematic owing to difficulties in controlling the absolute stereochemistry at the quaternary carbon C-3a. Hino and his co-workers have extensively studied the chemistry of cyclic tautomers of tryptophans.[27] They held the opinion that there are three possible tautomers: indole, indolenine and cyclic tautomer, in tryptophans and tryptamines, although the indole form is strongly favoured in neutral solvents (Scheme 18). Acidic pH and a suitable protective group for the nitrogen on the side chain are crucial for obtaining the tricyclic tautomer, as the nitrogen needs to retain enough nucleophilicity to attack at the 2-position of the protonated indolenine form. They found that *N*-methoxycarbonyltryptophan methyl ester in 85% phosphoric acid underwent clean tautomerization to a mixture of two diastereomeric tautomers, and the *endo* isomer predominated to the extent of *ca.* 9:1 over the *exo* isomer (Scheme 19). They also observed that the cyclic tautomers are somewhat unstable with respect to reversion to the indole form in the absence of strong acid. *N*-Acetyl tryptophan ethyl ester in 85% phosphoric acid was cyclized to the corresponding tautomer in 29% yield, 56% lower than the cyclization with tryptophan ethyl ester having methoxycarbonyl protective group due to the less nucleophilic character of the *N*-acetyl group.

Scheme 19



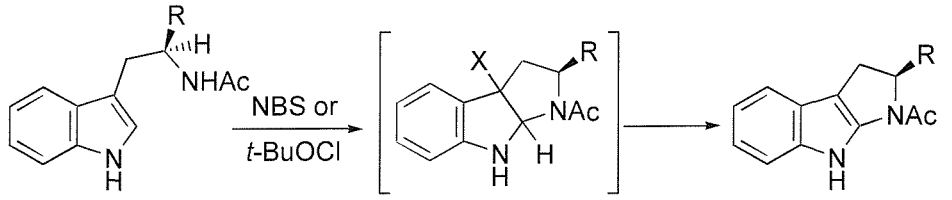
P, P' = protective group

exo isomer

endo isomer (major)

Witkop reported that acid-labile tricyclic compounds were achieved by treatment of *N*-acetyl L-tryptophan and tryptamine derivatives in phosphate buffer at pH 9 with NBS or in methylene chloride containing triethylamine with *t*-butyl hypochlorite (Scheme 20),[29] suggesting the presumed intermediate C-3a halogen derivative could not be isolated and underwent rapid elimination to give (**15**). The tetracyclic compound (**16**) was also synthetically approached by *t*-BuOCl oxidation of *N*-methyl-L-alanyl-L-tryptophan diketopiperazine. Recently Danishefisky reported the synthesis of pyrroloindoline using the tryptophan derivative (**17**) in their total synthesis of a structure proposed for himastatin (Scheme 21).[31] The carboxyl function in the tryptophan protected as a *tert*-butyl ester gave a much higher *anti* to *syn* stereoselectivity in subsequent oxidation step than the corresponding methyl ester, and the anthracene sulfonyl protective group at N_b nitrogen is also crucial.

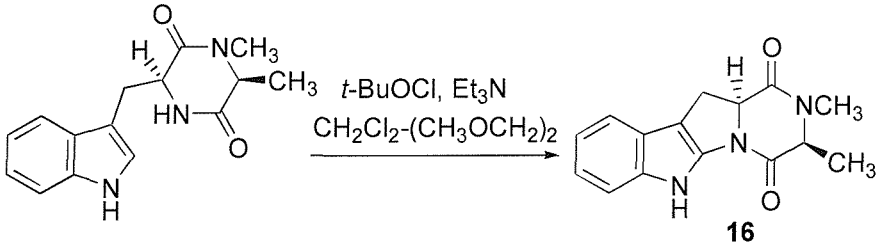
Scheme 20



R = $CO_2C_2H_5$, CO_2CH_3, $CONH_2$, H

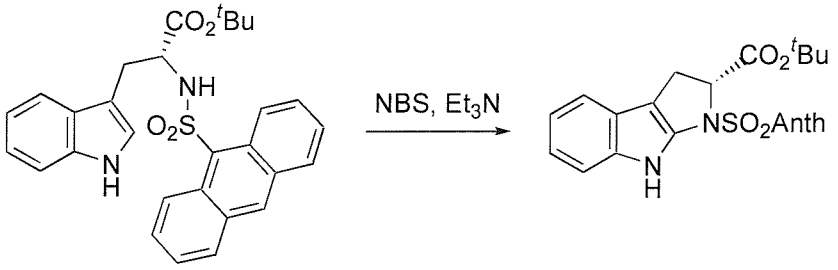
X = Br, Cl

15



16

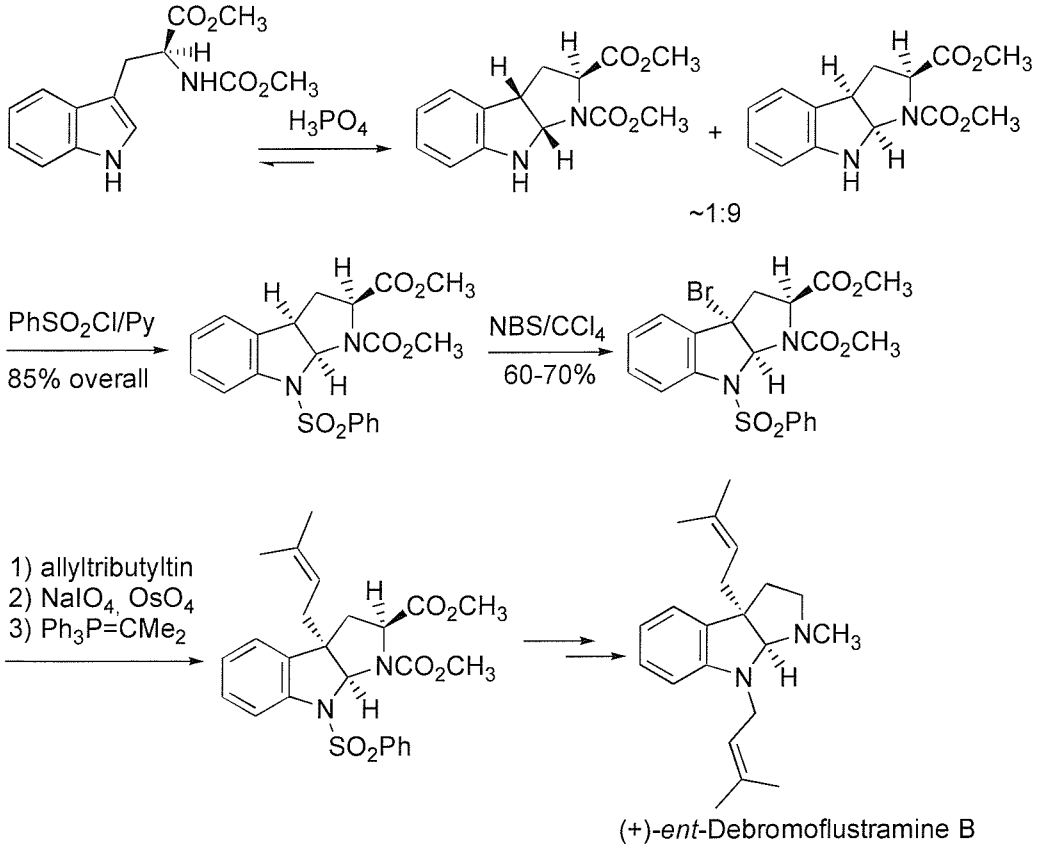
Scheme 21



17

Based on Hino and Witkop's syntheses, Crich *et al.*[34] introduced the phenylsulfonyl protecting group at *N*-8 which greatly enhances the stability of the tricyclic compound and allows isolation of the crystalline *endo* sulfonamide derivative in excellent yield. Radical bromination, followed by allylation and conversion to the prenyl derivative led to a diastereoselective synthesis of the marine alkaloid (+)-*ent*-debromoflustramine B (Scheme 22).[35]

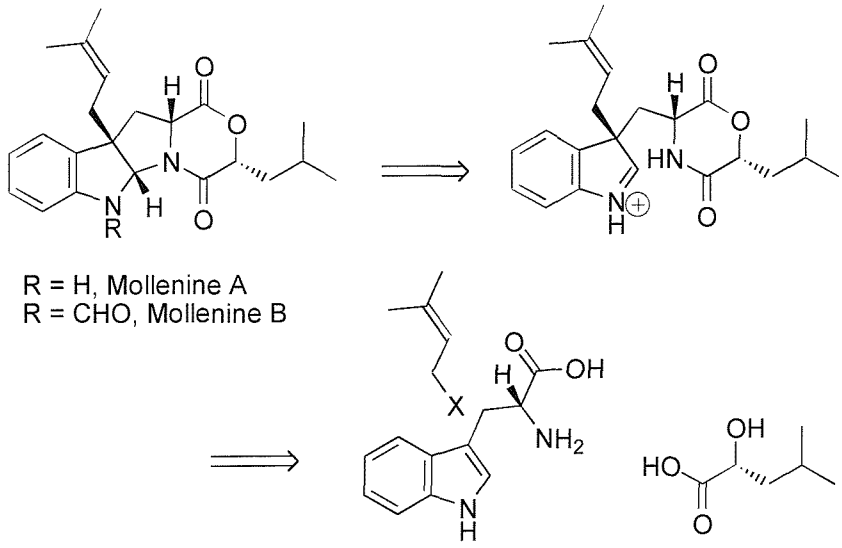
Scheme 22



7.2. Model Study Towards Mollenines

Mollenines are interesting synthetic targets due to their uncommon diketomorpholine moiety and their potential as a lead for drug discovery. The biogenesis of these metabolites may originate from prenylation of tryptophan at C-3 position of indole with concomitant intramolecular nucleophilic attack at the C-2 position of the protonated indole by nitrogen of the side chain, forming the tricyclic hexahydropyrrolo[2,3-*b*]indole system (Scheme 23). It was interesting to see if the prenylation could be accomplished by our zinc triflate conditions.

Scheme 23 Retrosynthesis of mollenines

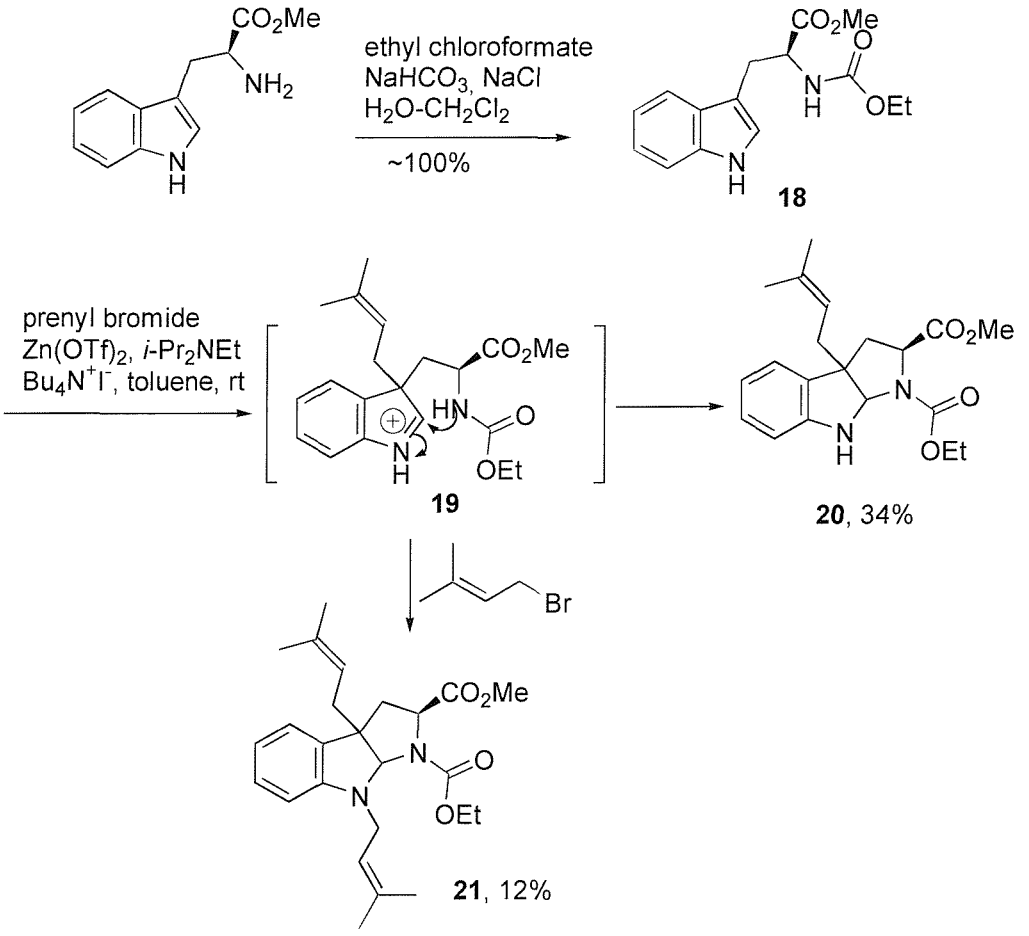


As a model study towards mollenines, the nitrogen in L-tryptophan methyl ester was protected as an ethyl carbamate (**18**) to maintain its nucleophilicity. This compound was subjected to our prenylation conditions (Scheme 24). In this case, 1 equivalent of (**18**) was used because the intermediate (**19**) would not undergo further C-3 alkylation. Although the reaction conditions were not optimized, this initial trial afforded monoprenylated cyclization product (**20**) as two diastereoisomers, isolated in 34% yield (major:minor = 1.7:1). Another compound was isolated in 12% yield, identified on the basis of NMR and MS as the diprenylation byproduct (**21**).

This promising result already represents the highest yield reported for an intramolecular cyclization of a tryptophan derivative to form the

hexahydropyrrolo[2,3-*b*] indole system. In future work, the reaction condition will be optimized further with respect to both yield and diastereoselectivity. This will lay the groundwork for a short asymmetric synthesis of mollenine A, and also be applicable to other natural product targets.

Scheme 24



8. Conclusion

In conclusion, a one-step procedure was developed, which provides the prenylation products of indole in high yield under very mild and straightforward reaction conditions. This method is also suitable for substituted indoles and the alkylation of indole with other allylic, benzylic and tertiary halides. A model study with tryptophan shows the procedure is also adaptable to the core skeleton of mollenines and other alkaloid natural products.

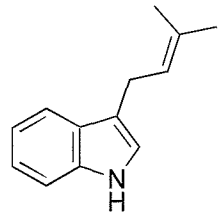
Experimental Section

For **General** methods, refer to Chapter 2.

Prenylation of Indole

To a mixture of indole (234 mg, 2 mmol), zinc triflate (436 mg, 1.2 mmol), and tetrabutylammonium iodide (369 mg, 1 mmol) in toluene (5.8 mL) was added DIEA (0.38 mL, 2.2 mmol) at room temperature under nitrogen. After stirring for 15 min, prenyl bromide (0.12 mL, 1 mmol) was then added. The reaction mixture was stirred for 2 h, quenched with saturated aqueous NH_4Cl, diluted with water and extracted with ether (3 × 20 mL). The combined organic layers were washed with water (30 mL) and dried over $MgSO_4$. Evaporation of solvent and purification of the residue by column chromatography with 15% ether in petroleum ether as eluent gave 3-prenyl indole (110 mg, 59%) and 2-prenyl indole (20 mg, 11%). Small amounts of *N*-prenyl and diprenyl product were also isolated.

3-(3-Methyl-but-2-enyl) indole (1)



^{1}H NMR was identical to that reported.[6]

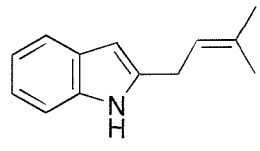
IR ν 3398, 2903, 1454, 1358, 1220 cm^{-1};

^{1}H NMR δ 1.75 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 3.45 (d, J = 6.6 Hz, 2H, ArCH_2), 5.41-5.46 (m, 1H, =C*H*), 6.91 (s, 1H), 7.05-7.25 (m, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.81 (br s, 1H, N*H*);

^{13}C NMR δ 17.8, 24.1, 25.7, 111.0, 116.0, 119.0, 119.1, 121.1, 121.9, 123.0, 127.4, 131.9, 136.4;

EIMS *m/z* 185 (M^+, 95), 170 (100), 154 (26), 130 (56), 117 (64).

2-(3-Methyl-but-2-enyl) indole (4)

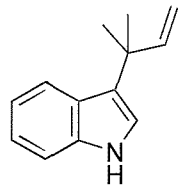


^{1}H NMR was identical to that reported.[6]

^{1}H NMR δ 1.73 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 3.45-3.55 (m, 2H, ArCH_2), 5.35-5.46 (m, 1H, =C*H*), 6.24 (s, 1H), 7.03-7.75 (m, 4H), 7.83 (br s, 1H, N*H*);

EIMS *m/z* 185 (M^+, 100), 170 (61), 154 (21), 131 (65), 117 (69).

3-(1,1-Dimethylallyl) indole (2)



Isolated from the copper triflate mediated prenylation of indole. ^{1}H NMR was identical to that reported.[6]

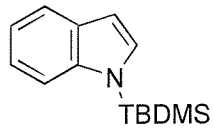
IR ν3410, 2910, 1630, 1450 cm^{-1};

^{1}H NMR δ 1.52 (s, 6H, 2 × CH_3), 5.02-5.10 (m, 2H, =CH_2), 6.15 (dd, J = 11.2, 17.7 Hz, 1H, =C*H*), 6.97 (d, J = 2.2 Hz, 1H), 7.04-7.25 (m, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.4 Hz, 1H), 7.90 (br s, 1H, N*H*);

^{13}C NMR δ 28.0, 37.5, 110.6, 111.2, 118.8, 120.1, 121.4, 121.6, 123.9, 126.0, 137.0, 147.7;

EIMS *m/z* 185 (M^+, 50), 170 (100), 154 (28), 143 (26), 128 (18), 115 (23).

1-*tert*-butyldimethylsilyl indole (6)



n-Butyllithium (1.28 mL of a 2.5 M solution in hexane, 3.2 mmol) was added to a solution of indole (0.35 g, 3 mmol) in THF (6 mL) at −10 °C. The reaction mixture was allowed to warm to room temperature and stirred for 15 min, then re-cooled to −10 °C followed by dropwise addition of *tert*-butyldimethylsilyl chloride (0.54 g, 3.6 mmol) in THF (4 mL). The reaction mixture was stirred overnight at room temperature, poured into water and extracted with ether (3 × 15 mL). The combined organics were washed with water and dried over $MgSO_4$. Evaporation of solvent and purification of the residue by column chromatography with 10% ether

in petroleum ether as eluent afforded the title compound as a white solid (0.58 g, 84%). ^{1}H NMR was identical to that reported.[36]

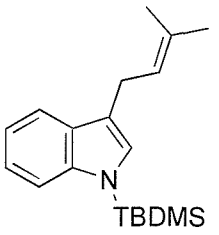
IR ν2949, 2928, 1510, 1448, 1254, 1138 cm^{-1};

^{1}H NMR δ 0.57 (s, 6H, Si(CH_3)$_2$), 0.91 (s, 9H, 3 × CH_3), 6.59 (d, J = 3.7 Hz, 1H), 7.07-7.16 (m, 3H), 7.50 (d, J = 8.1 Hz, 1H), 7.61-7.63 (m, 1H);

^{13}C NMR δ -4.0, 19.5, 26.3, 104.8, 113.8, 119.7, 120.6, 121.3, 130.9, 131.3, 141.0;

EIMS *m/z* 231 (M^+, 49), 174 (100), 117 (11).

1-*tert*-Butyldimethylsilyl 3-(3-Methyl-but-2-enyl) indole (7)



Zinc bromide (2 mg, 2 mol %), was added to a solution of *N*-TBDMS indole (**6**) (100 mg, 0.43 mmol) and prenyl bromide (50 μL, 0.43 mmol) in CH_2Cl_2 (1.5 mL). After stirring for 40 min at room temperature, CH_2Cl_2 (10 mL) was added and the organic layer separated and washed with water successively (3 × 10 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent and purification of the residue by preparative TLC with ether/petroleum ether (1/10) as the developing solvent afforded the title compound as an oil (16 mg, 7%).

IR ν2926, 1694, 1450, 1255, 1135 cm^{-1};

^{1}H NMR δ 0.57 (s, 6H), 0.92 (s, 9H), 1.75 (s, 3H), 1.77 (s, 3H), 3.43 (d, J = 7.4 Hz, 2H), 5.39-5.44 (m, 1H), 6.89 (s, 1H), 7.07-7.17 (m, 2H), 7.45-7.48 (m, 1H), 7.54-7.57 (m, 1H);

^{13}C NMR δ -3.9, 17.8, 19.5, 24.2, 25.7, 26.3, 113.9, 117.8, 118.9, 119.1, 121.3, 123.2, 127.8, 130.9, 131.7, 141.6;

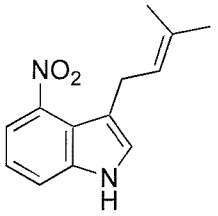
EIMS *m/z* 299 (M^+, 100), 284 (53), 242 (80), 199 (32), 174 (62).

General Procedure for 3-Prenylation of Substituted Indoles (8a-8d)

To a mixture of substituted indole (2 equivalents), zinc triflate (1.2 equivalents) and tetrabutylammonium iodide (1 equivalent) in anhydrous toluene was added DIEA (2.2 equivalents) at room temperature under argon. The reaction mixture

was stirred for 15 min at room temperature followed by addition of prenyl bromide (1 equivalent). The reaction mixture was stirred for 2 h, quenched with saturated aqueous NH_4Cl, diluted with water and extracted with ether. The combined organics were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated and the residue purified by column chromatography. Isolated yields of compounds (**8a-8d**) are given in Scheme 13.

4-Nitro-3-(3-methyl-but-2-enyl)-1*H*-indole (8a)



Chromatography eluent 50% ether in hexane. Orange red solid, mp 107-108 °C.

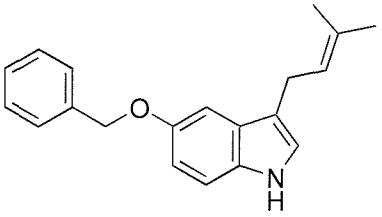
IR ν 3369, 2908, 1536, 1500, 1290, 1109 cm^{-1};

^{1}H NMR δ 1.69 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 3.52 (d, J = 7.0 Hz, 2H, $ArCH_2$), 5.30 (br t, J = 7.0 Hz, 1H, =C*H*), 7.17-7.22 (m, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 8.43 (br s, 1H, N*H*);

^{13}C NMR δ 17.8 (*C*H_3), 25.7 (*C*H_3), 26.1 (*C*H_2), 116.0 (*C*), 116.8 (*C*H), 117.2 (*C*H), 119.2 (*C*), 120.6 (*C*H), 122.8 (*C*H), 126.3 (*C*H), 132.9 (*C*), 139.2 (*C*), 143.5 (*C*);

ESMS *m/z* 229 (M^+ - 1, 5), 146 (100).

5-Benzyloxy-3-(3-methyl-but-2-enyl)-1*H*-indole (8b)



Chromatography eluent 20% ether in hexane. Pale yellow oil which solidified upon standing, mp 60-62 °C.

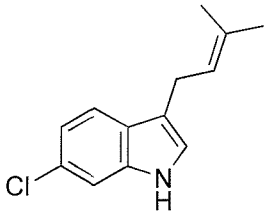
IR ν 3400, 2911, 1619, 1582, 1479, 1449, 1190 cm^{-1};

^{1}H NMR δ 1.74 (s, 6H, 2 × CH_3), 3.38 (d, J = 6.6 Hz, 2H, ArCH_2), 5.10 (s, 2H, PhCH_2), 5.40 (br t, J = 6.6 Hz, 1H, =CH), 6.85 (d, J = 2.2 Hz, 1H), 6.91 (dd, J = 2.2, 8.8 Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H), 7.16 (m, 1H), 7.25-7.50 (m, 5H), 7.72 (br s, 1H, NH);

^{13}C NMR δ 17.8 (*C*H_3), 24.1 (*C*H_2), 25.7 (*C*H_3), 71.0 (*C*H_2), 102.6 (*C*H), 111.7 (*C*H), 112.7 (*C*H), 115.7 (*C*), 122.1 (*C*H), 123.0 (*C*H), 127.6 (2 × *C*H), 127.70 (*C*), 127.73 (*C*H), 128.5 (2 × *C*H), 131.78 (*C*), 131.87 (*C*), 137.7 (*C*), 152.9 (*C*);

ESMS *m/z* 290 (M^+ - 1, 100), 143 (92).

6-Chloro-3-(3-methyl-but-2-enyl)-1*H*-indole (8c)



Chromatography eluent 20% ether in petroleum ether. Pale yellow solid, mp 84-85 °C.

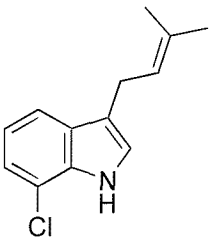
IR ν3400, 2906, 1610, 1445, 1220, 1089 cm^{-1};

^{1}H NMR δ 1.75 (s, 6H, 2 × CH_3), 3.41 (d, J = 7.3 Hz, 2H, ArCH_2), 5.40 (br t, J = 7.3 Hz, 1H, =CH), 6.90 (d, J = 1.5 Hz, 1H), 7.06 (dd, J = 1.5, 8.1 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.82 (br s, 1H, NH);

^{13}C NMR δ 17.8 (*C*H_3), 23.9 (*C*H_2), 25.7 (*C*H_3), 110.9 (*C*H), 116.3 (*C*), 119.84 (*C*H), 119.88 (*C*H), 121.8 (*C*H), 122.6 (*C*H), 126.1 (*C*), 127.8 (*C*), 132.3 (*C*), 136.7 (*C*);

ESMS *m/z* 218 (M^+ - 1, 22), 143 (100).

7-Chloro-3-(3-methyl-but-2-enyl)-1*H*-indole (8d)



Chromatography eluent 20% ether in hexane. Pale yellow oil.

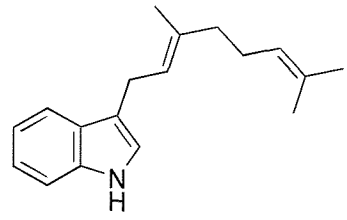
IR ν3421, 2910, 1620, 1433, 1200, 1047 cm^{-1};

^{1}H NMR δ 1.76 (s, 6H, 2 × CH_3), 3.43 (d, J = 6.6 Hz, 2H, ArCH_2), 5.40 (br t, J = 6.6 Hz, 1H, =C*H*), 6.95-7.05 (m, 2H), 7.18 (d, J = 7.4 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 8.09 (br s, 1H, N*H*);

^{13}C NMR δ 17.8 (*C*H_3), 24.2 (*C*H_2), 25.7 (*C*H_3), 116.5 (*C*), 117.3 (*C*), 117.7 (*C*H), 119.9 (*C*H), 121.3 (*C*H), 121.8 (*C*H), 122.6 (*C*H), 128.9 (*C*), 132.3 (*C*), 133.7 (*C*);

ESMS *m/z* 218 (M^+ - 1, 12), 143 (24).

3-(3,7-Dimethyl-oeta-2,6-dienyl)-1*H*-indole (3-Geranyl indole) (9a)



DIEA (0.16 mL, 0.95 mmol) was added to a mixture of indole (100 mg, 0.86 mmol), zinc triflate (188 mg, 0.52 mmol) and tetrabutylammonium iodide (158 mg, 0.43 mmol) in toluene (2.5 mL) under nitrogen. The reaction mixture was stirred for 15 min at room temperature, and then geranyl bromide (86 μL, 0.43 mmol) was added. The reaction mixture was stirred for 6 h, quenched with saturated aqueous NH_4Cl (5 mL), diluted with water (10 mL) and extracted with ether (3 × 15 mL). The combined organics were washed with water and dried over $MgSO_4$. Evaporation of solvent and purification of the residue by preparative TLC with ether/petroleum ether (1/4) as the developing solvent provided the title compound as a pale yellow oil (66 mg, 60%) and 2-geranyl indole as a yellow oil (10 mg, 9%).

IR ν3410, 2910, 1453, 1221, 1087 cm^{-1};

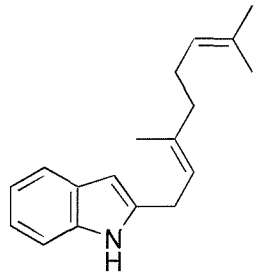
^{1}H NMR δ 1.60 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.05-2.15 (m, 4H), 3.45 (d, J = 6.7 Hz, 2H, ArCH_2), 5.15 (m, 1H, =C*H*), 5.45 (dt, J = 1.5, 6.6 Hz, 1H, =C*H*), 6.87 (d, J = 1.5 Hz, 1H), 7.05-7.18 (m, 2H), 7.28 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.73 (br s, 1H, N*H*);

^{13}C NMR δ 16.0 (CH_3), 17.7 (CH_3), 24.0 (CH_2), 25.7 (CH_3), 26.6 (CH_2), 39.7 (CH_2), 111.0 (*C*H), 116.0 (*C*), 119.0 (*C*H), 119.1 (*C*H), 121.2 (*C*H), 121.9 (*C*H), 122.9 (*C*H), 124.4 (*C*H), 127.4 (*C*), 131.4 (*C*), 135.6 (*C*), 136.4 (*C*);

EIMS *m/z* 253 (M^+, 74), 184 (100), 168 (65), 130 (88), 117 (44);

HREIMS calcd for $C_{18}H_{23}N$ 253.18305, found 253.18403.

2-(3,7-Dimethyl-octa-2,6-dienyl)-1*H*-indole (2-Geranyl indole)

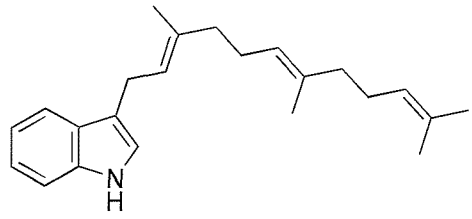


^{1}H NMR δ 1.63 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.05-2.16 (m, 4H), 3.50 (d, J = 7.3 Hz, 2H, ArCH_2), 5.12 (br t, J = 6.6 Hz, 1H, =C*H*), 5.40 (dt, J = 1.5, 7.3 Hz, 1H, =C*H*), 6.23 (s, 1H), 7.00-7.15 (m, 2H), 7.28 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.86 (br s, 1H, N*H*);

^{13}C NMR δ 16.1 (CH_3), 17.8 (CH_3), 25.8 (CH_3), 26.5 (CH_2), 27.0 (CH_2), 39.6 (CH_2), 99.5 (*C*H), 110.3 (*C*H), 119.6 (*C*H), 119.8 (*C*H), 120.1 (*C*H), 120.9 (*C*H), 124.1 (*C*H), 129.0 (*C*), 131.8 (*C*), 135.9 (*C*), 138.2 (*C*), 138.6 (*C*);

EIMS *m/z* 253 (M^+, 85), 185 (100), 168 (68), 130 (99), 117 (58).

3-(3,7,11-Trimethyl-dodeca-2,6,10-trienyl)-1*H*-indole (3-Farnesyl indole) (9b)



DIEA (0.27 mL, 1.54 mmol) was added to a mixture of indole (164 mg, 1.4 mmol) and zinc triflate (305 mg, 0.84 mmol) and tetrabutylammonium iodide (258 mg, 0.7 mmol) in toluene (4 mL) at room temperature under nitrogen. The reaction mixture was stirred for 15 min at room temperature, and then farnesyl bromide (190 μL, 0.7 mmol) was added. The reaction mixture was stirred for 6 h, quenched with saturated aqueous NH_4Cl (8 mL), diluted with water (10 mL) and extracted

with ether (3 × 15 mL). The combined organics were washed with water and dried over Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ether in hexane provided the title compound as a pale yellow oil (110 mg, 49%).

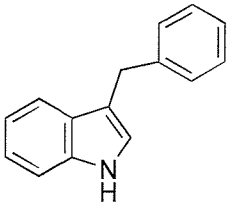
IR ν3412, 2910, 1453, 1377, 1087 cm^{-1};

^{1}H NMR δ 1.60 (s, 6H, 2 × CH_3), 1.67 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.90-2.20 (m, 8H), 3.46 (d, J = 6.6 Hz, 2H, ArCH_2), 5.10 (m, 2H, 2 × =C*H*), 5.45 (br t, J = 7.3 Hz, 1H, =C*H*), 6.90 (d, J = 1.5 Hz, 1H), 7.00-7.25 (m, 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.83 (br s, 1H, N*H*);

^{13}C NMR δ 16.0 (*C*H_3), 16.1 (*C*H_3), 17.7 (*C*H_3), 24.0 (*C*H_2), 25.7 (*C*H_3), 26.6 (*C*H_2), 26.7 (*C*H_2), 39.70 (*C*H_2), 39.74 (*C*H_2), 111.0 (*C*H), 116.1 (*C*), 119.03 (*C*H), 119.09 (*C*H), 121.2 (*C*H), 121.9 (*C*H), 122.9 (*C*H), 124.2 (*C*H), 124.4 (*C*H), 127.4 (*C*), 131.3 (*C*), 135.0 (*C*), 135.6 (*C*), 136.4 (*C*);

EIMS *m/z* 321 (M^+, 10), 184 (84), 168 (41), 130 (100).

3-Benzyl-1*H*-indole (9c)



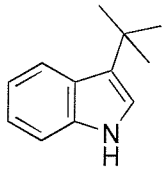
To a mixture of indole (234 mg, 2 mmol), zinc triflate (436 mg, 1.2 mmol) and tetrabutylammonium iodide (369 mg, 1 mmol) in toluene (5.8 mL) was added DIEA (383 μL, 2.2 mmol) at room temperature under argon. The reaction mixture was stirred for 15 min at room temperature, benzyl bromide (215 mg, 1 mmol) was then added. The reaction mixture was stirred for 3 h, quenched with saturated aqueous NH_4Cl (10 mL), diluted with water (15 mL) and extracted with ether (3 × 20 mL). The combined organics were washed with water and dried over Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent gave a solid (273 mg, a mixture with indole). The title compound was 109 mg (53%) by ^{1}H NMR peak integration. ^{1}H NMR was identical to that reported.[37]

^{1}H NMR δ 4.09 (s, 2H, PhCH_2), 6.80 (d, J = 2.2 Hz, 1H), 7.05-7.30 (m, 8H), 7.50 (d, J = 8.1 Hz, 1H), 7.93 (br s, 1H, N*H*);

^{13}C NMR δ 31.5 (Ph*C*H_2);

GCEIMS t_R 14.85 min, *m/z* 207 (M^+, 84), 178 (20), 130 (100), 103 (20); t_R 9.89 min indole, *m/z* 117 (M^+).

3-*tert*-Butyl-1*H*-indole (9d)



To a mixture of indole (100 mg, 0.85 mmol), zinc triflate (188 mg, 0.56 mmol) and tetrabutylammonium iodide (32 mg, 0.086 mmol) in toluene (2.5 mL) was added DIEA (0.16 mL, 0.95 mmol) at room temperature under nitrogen. The reaction mixture was stirred for 15 min at room temperature, then *t*-butyl bromide (50 μL, 0.43 mmol) was added. The reaction mixture was stirred for 4 h, quenched with saturated aqueous NH_4Cl (5 mL), diluted with water (10 mL) and extracted with ether (3 × 10 mL). The combined organics were washed with water and dried over $MgSO_4$. Evaporation of solvent and purification of the residue by preparative TLC with ether/petroleum ether (1/4) as the developing solvent provided the title compound as a light yellow oil (40 mg, 54%) and 1-*tert*-butyl indole as an oil (12 mg, 7%).

IR ν3391, 2960, 1615, 1458, 1359, 1332, 1100 cm^{-1};

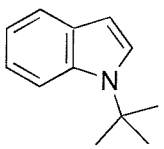
^{1}H NMR δ 1.45 (s, 9H, 3 × CH_3), 6.87 (d, J = 3.0 Hz, 1H), 7.06-7.19 (m, 2H), 7.30 (d, J = 7.4 Hz, 1H), 7.73 (br s, 1H, N*H*), 7.82 (d, J = 8.0 Hz, 1H);

^{13}C NMR δ 30.7 (3 × CH_3), 31.6 (*C*), 111.3 (*C*H), 118.7 (*C*H), 119.2 (*C*H), 121.2 (*C*H), 121.4 (*C*H), 125.8 (*C*), 126.7 (*C*), 137.1 (*C*);

EIMS *m/z* 173 (M^+, 59), 158 (100), 143 (29), 130 (28), 117 (21).

HREIMS calcd for $C_{12}H_{15}N$ 173.12045, found 173.12047.

1-*tert*-Butyl-1*H*-indole

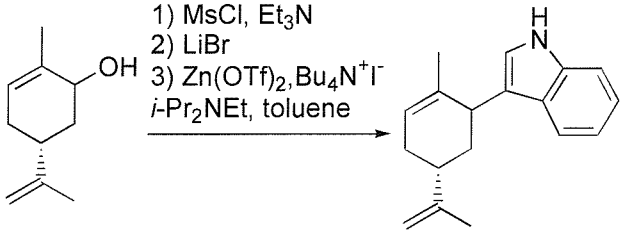


^{1}H NMR δ 1.73 (s, 9H, 3 × CH_3), 6.44 (d, J = 3.0 Hz, 1H), 7.05-7.20 (m, 2H), 7.28 (d, J = 3.0 Hz, 1H), 7.62-7.67 (m, 2H);

^{13}C NMR δ 29.8 (3 × CH_3), 55.8 (*C*), 100.1 (*C*H), 113.3 (*C*H), 118.8 (*C*H), 120.6 (*C*H), 121.1 (*C*H), 125.2 (*C*H), 130.3 (*C*), 134.9 (*C*);

EIMS *m/z* 173 (M^+, 25), 117 (100), 89 (24).

3-(5-Isopropenyl-2-methyl-cyclohex-2-enyl)-1*H*-indole (9f)



To a solution of carveol (0.24 mL, 1.5 mmol) and MsCl (0.17 mL, 2.25 mmol) in dry THF (10 mL) was added Et_3N (0.42 mL, 3 mmol) dropwise at –40 °C. The reaction mixture was stirred at that temperature for 45 min. LiBr (521 mg, 6 mmol) was then added, and the reaction mixture stirred for another 3 h at 0 °C, followed by partitioning between hexanes and cold water. The organic layer was separated and the aqueous layer was extracted with hexane (3 × 15 mL). The combined organics were washed with brine and dried over Na_2SO_4. Evaporation of solvent afforded the crude bromide (287 mg, 89%), which was used without further purification.

To a mixture of indole (234 mg, 2 mmol), zinc triflate (436 mg, 1.2 mmol) and tetrabutylammonium iodide (369 mg, 1 mmol) in toluene (5.8 mL) was added DIEA (383 μL, 2.2 mmol) at room temperature under argon. The reaction mixture was stirred for 15 min at room temperature, carveyl bromide (215 mg, 1 mmol) was then added. The reaction mixture was stirred for 4 h, quenched with saturated NH_4Cl (8 mL), diluted with water (10 mL) and extracted with ether (3 × 15 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent gave the equatorial isomer as a colourless oil (136 mg, 54%), and the axial isomer (43 mg, 17%) as a white solid, which was recrystallized from hexane to give colourless crystals.

Equatorial isomer:

IR ν3412, 2911, 1738, 1642, 1453, 1217 cm^{-1};

^{1}H NMR δ 1.48 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.82-2.45 (m, 5H), 3.63 (m, 1H, ArC*H*), 4.70 (m, 2H, =CH_2), 5.65 (m, 1H, =C*H*), 7.00 (d, J = 2.2 Hz, 1H), 7.05-7.22 (m, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.87 (br s, 1H, N*H*);

^{13}C NMR δ 20.8 (*C*H_3), 21.8 (*C*H_3), 31.4 (*C*H_2), 37.6 (*C*H_2), 39.4 (*C*H), 42.1 (*C*H), 108.5 (*C*H_2), 111.1 (*C*H), 119.1 (*C*H), 119.56 (*C*), 119.64 (*C*H), 121.74 (*C*H), 121.80 (*C*H), 122.5 (*C*H), 126.6 (*C*), 136.2 (*C*), 136.5 (*C*), 150.0 (*C*);

EIMS *m/z* 251 (M^+, 100), 236 (45), 182 (91), 167 (89), 143 (61), 117 (87).

Axial isomer, mp 67-69 °C:

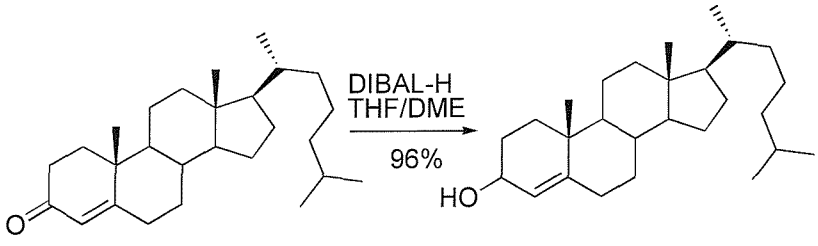
IR ν3400, 2911, 1738, 1643, 1453, 1221 cm^{-1};

^{1}H NMR δ 1.61 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.70-2.00 (m, 3H), 2.15-2.30 (m, 2H), 3.68 (m, 1H, ArC*H*), 4.61 (m, 2H, =CH_2), 5.65 (m, 1H, =C*H*), 6.85 (d, J = 2.2 Hz, 1H), 7.10-7.25 (m, 2H), 7.34 (d, J = 7.4 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.89 (br s, 1H, N*H*);

^{13}C NMR δ 21.0 (*C*H_3), 22.6 (*C*H_3), 31.1 (*C*H_2), 34.2 (*C*H_2), 35.8 (*C*H), 36.7 (*C*H), 108.4 (*C*H_2), 111.1 (*C*H), 118.8 (*C*H), 119.1 (*C*H), 119.3 (*C*), 121.8 (*C*H), 122.5 (*C*H), 122.8 (*C*H), 127.2 (*C*), 134.8 (*C*), 136.5 (*C*), 150.0 (*C*);

EIMS *m/z* 251 (M^+, 95), 236 (37), 182 (95), 167 (86), 143 (40), 117(100).

Cholest-4-en-3-ol



To a solution of 4-cholesten-3-one (577 mg, 1.5 mmol) in THF (15 mL) and dimethoxyethane (15 mL) was added DIBAL-H (2 mL of a 1.5 M solution in toluene, 3 mmol) over 30 min. After stirring for another 15 min, the reaction mixture was quenched with methanol (0.3 mL), followed by addition of 1 N HCl (10 mL) and extraction with ether (3 × 15 mL). The combined organics were washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification

(10 mL) and extraction with ether (3 × 15 mL). The combined organics were washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 20% ethyl acetate in hexane as eluent afforded the title compound as a white solid (555 mg, 96%), mp 133-134 °C (Lit.[38] 133.5-134.5 °C)

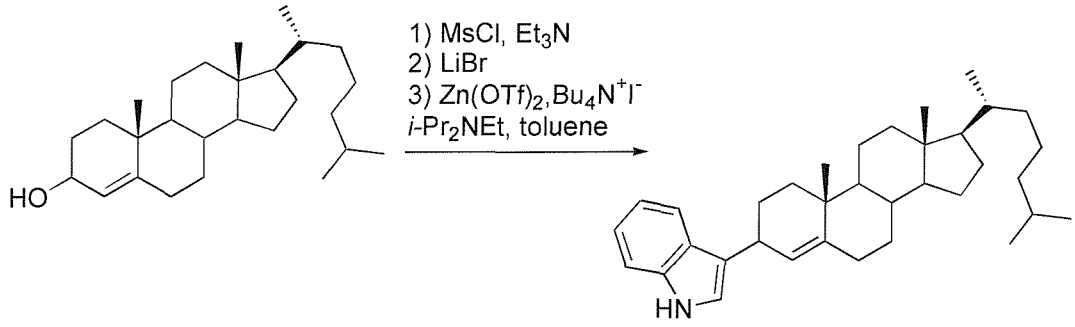
IR ν3328, 2925, 1442, 1373, 1030 cm^{-1};

^{1}H NMR δ 0.67 (s, 3H, CH_3), 0.85 (d, J = 1.5 Hz, 3H, CHCH_3), 0.87 (d, J = 1.5 Hz, 3H, CHCH_3), 0.89 (d, J = 6.6 Hz, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.70-2.05 (m, 27H), 2.10-2.25 (m, 1H), 4.10-4.20 (m, 1H, C*H*OH), 5.27 (d, J = 1.5 Hz, 1H, =C*H*);

^{13}C NMR δ 12.0, 18.6, 18.9, 21.0, 22.6, 22.8, 23.8, 24.2, 28.0, 28.2, 29.5, 32.2, 33.1, 35.4, 35.8, 35.9, 36.1, 37.3, 39.5, 39.8, 42.4, 54.4, 56.13, 56.15, 68.0 (*C*HOH), 123.2 (=*C*H), 147.8 (=*C*);

CIMS *m/z* 387 (M^+ + 1, 1), 370 (100), 81 (40).

3-(4-Cholestenyl)-1*H*-indole (9g)



To a solution of alcohol (387 mg, 1 mmol) and MsCl (0.1 mL, 1.3 mmol) in dry THF (10 mL) was added Et_3N (0.28 mL, 2 mmol) dropwise at –40 °C. The reaction mixture was stirred at that temperature for 45 min, LiBr (347 mg, 4 mmol) was then added, and the reaction mixture stirred for another 3 h at 0 °C followed by partitioning between hexanes and cold water. The organic layer was separated and the aqueous layer extracted with hexanes (3 × 15 mL). The combined organics were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent afforded the crude bromide (426 mg, 95%), which was used without further purification.

was stirred for 15 min at room temperature, cholesteryl bromide (300 mg, 0.67 mmol) was then added. The reaction mixture was stirred for 4 h, quenched with saturated NH_4Cl (8 mL), diluted with water (10 mL) and extracted with ether (3 × 15 mL). The combined organics were washed with water and dried over Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent gave two diastereomers in *ca.* 1:1 ratio (215 mg, 66%) and *N*-substituted indole (70 mg, 22%).

Diastereomer 1:

IR ν3400, 2911, 1738, 1643, 1453, 1221 cm^{-1};

^{1}H NMR δ 0.69 (s, 3H, CH_3), 0.85 (d, J = 1.5 Hz, 3H, CHCH_3), 0.87 (d, J = 1.5 Hz, 3H, CHCH_3), 0.90 (d, J = 6.6 Hz, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.70-2.15 (m, 27H), 2.22-2.38 (m, 1H), 3.69 (m, 1H, ArC*H*), 5.49 (d, J = 5.2 Hz, 1H, =C*H*), 6.85 (d, J = 2.2 Hz, 1H), 7.08-7.34 (m, 2H), 7.32 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.85 (br s, 1H, N*H*);

^{13}C NMR δ 12.0, 18.7, 19.3, 21.6 (*C*H_2), 22.6, 22.8, 23.8 (*C*H_2), 24.3 (*C*H_2), 25.3 (*C*H_2), 28.0, 28.3 (*C*H_2), 31.8, 32.7 (*C*H_2), 33.2 (*C*H_2), 33.9 (*C*H_2), 35.8, 36.1, 36.2 (*C*H_2), 37.3 (*C*), 39.5 (*C*H_2), 40.0 (*C*H_2), 42.6 (*C*), 54.9, 56.28, 56.33, 111.1 (*C*H), 118.98 (*C*H), 119.08 (*C*H), 120.5 (*C*), 120.9 (*C*H), 121.8 (*C*H), 122.7 (*C*H), 126.7 (*C*), 136.7 (*C*), 146.1 (*C*).

Diastereomer 2:

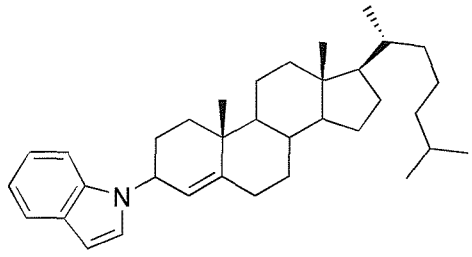
IR ν3413, 2928, 1454, 1373, 1093 cm^{-1};

^{1}H NMR δ 0.72 (s, 3H, CH_3), 0.86 (d, J = 1.5 Hz, 3H, CHCH_3), 0.88 (d, J = 1.5 Hz, 3H, CHCH_3), 0.91 (d, J = 6.6 Hz, 3H, CH_3), 1.12 (s, 3H, CH_3), 0.85-2.10 (m, 27H), 2.20-2.35 (m, 1H), 3.56-3.60 (m, 1H, ArC*H*), 5.47 (s, 1H, =C*H*), 6.95 (d, J = 2.2 Hz, 1H), 7.06-7.20 (m, 2H), 7.33 (d, J = 7.4 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.86 (br s, 1H, N*H*);

^{13}C NMR δ 12.0, 18.7, 19.5, 21.4 (*C*H_2), 22.6, 22.9, 23.9 (*C*H_2), 24.3 (*C*H_2), 27.6 (*C*H_2), 28.0, 28.3 (*C*H_2), 32.6 (*C*H_2), 33.4 (*C*H_2), 34.4, 35.8, 36.1, 36.2 (*C*H_2), 37.2 (*C*), 37.9 (*C*H_2), 39.5 (*C*H_2), 40.0 (*C*H_2), 42.5 (*C*), 54.6, 56.2, 56.3, 111.1 (*C*H), 119.0 (*C*H), 119.5 (*C*H), 120.3 (*C*H), 121.7 (*C*), 121.8 (*C*H), 123.2 (*C*H), 126.7 (*C*), 136.6 (*C*), 145.0 (*C*);

ESMS *m/z* 485 (M^+, 14), 468 (100), 438 (57), 200 (59).

1-(4-Cholestenyl)-1*H*-indole



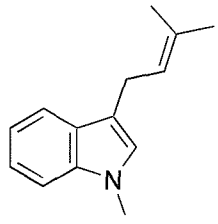
IR *v*2926, 1737, 1457, 1363, 1209 cm^{-1};

^{1}H NMR δ 0.70 (s, 3H, CH_3), 0.86 (d, J = 1.5 Hz, 3H, $CHCH_3$), 0.88 (d, J = 1.5 Hz, 3H, $CHCH_3$), 0.91 (d, J = 6.6 Hz, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.70-2.40 (m, 28H), 4.92 (m, 1H, ArC*H*), 5.48 (d, J = 4.4 Hz, 1H, =C*H*), 6.44 (d, J = 2.9 Hz, 1H), 7.00-7.30 (m, 3H), 7.39 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H);

^{13}C NMR δ 12.0, 18.63, 18.66, 21.5 (CH_2), 22.6, 22.8, 23.8 (CH_2), 24.3 (CH_2), 25.7 (CH_2), 28.0, 28.2 (CH_2), 32.61 (CH_2), 32.69 (CH_2), 33.3 (CH_2), 35.8, 35.9, 36.1 (CH_2), 37.5 (*C*), 39.5 (CH_2), 39.8 (CH_2), 42.5 (*C*), 50.0, 54.4, 56.05, 56.18, 99.6 (*C*H), 109.5 (*C*H), 116.5 (*C*H), 119.3 (*C*H), 120.9 (*C*H), 121.0 (*C*H), 127.0 (*C*H), 129.2 (*C*), 135.3 (*C*), 152.2 (*C*);

EIMS *m/z* 368 (M^+ - 117, 29), 147 (64), 105 (70), 43 (100).

1-Methyl-3-(3-methyl-but-2-enyl)-1*H*-indole



To a mixture of 1-methyl indole (256 μL, 2 mmol), zinc triflate (436 mg, 1.2 mmol) and tetrabutylammonium iodide (369 mg, 1 mmol) in toluene (5.8 mL) was added DIEA (383 μL, 2.2 mmol) at room temperature under argon. The reaction mixture was stirred for 15 min at room temperature, prenyl bromide (115 μL, 1 mmol) was then added. The reaction mixture was stirred for 4 h, quenched with saturated aqueous NH_4Cl (8 mL), diluted with water (15 mL) and extracted with ether (3 × 10 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by

column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (72 mg, 36%).

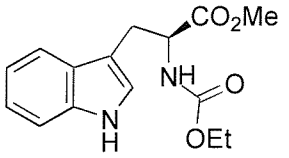
IR ν 2910, 1613, 1470, 1371, 1324 cm^{-1};

^{1}H NMR δ 1.75 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 3.43 (d, J = 6.6 Hz, 2H, $ArCH_2$), 3.70 (s, 3H, NCH_3), 5.42 (m, 1H, =CH), 6.78 (s, 1H), 7.05-7.28 (m, 3H), 7.58 (d, J = 8.1 Hz, 1H);

^{13}C NMR δ 17.8 (CH_3), 24.0 ($ArCH_2$), 25.7 (CH_3), 32.5 (CH_3), 109.1 (CH), 114.5 (C), 118.5 (CH), 119.1 (CH), 121.4 (CH), 123.3 (CH), 126.0 (CH), 127.7 (C), 131.7 (C), 137.1 (C);

EIMS *m/z* 199 (M^+, 100), 184 (98), 168 (77), 144 (86), 131 (87), 115 (59).

N^{α}-Ethoxycarbonyl-L-tryptophan methyl ester (18)



To a stirred reaction mixture of H-Trp-OMe·HCl (764 mg, 3 mmol) in a solution of water (7.5 mL) and dichloromethane (7.5 mL) containing NaCl (750 mg)-$NaHCO_3$ (633 mg, 7.5 mmol) was added ethyl chloroformate (0.43 mL, 4.5 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organics were washed with water, dried and concentrated. Flash chromatography with 50% ethyl acetate in hexane afforded the title compound as a white solid (870 mg, 100%), mp 88-90 °C.

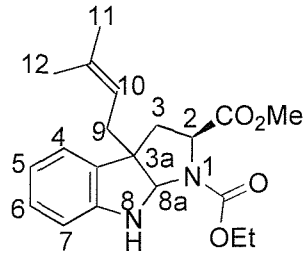
IR ν 3368, 3338, 2926, 1728, 1694, 1440, 1222, 1024 cm^{-1};

^{1}H NMR δ 1.21 (t, J = 7.0 Hz, 3H, CH_2CH_3), 3.29 (d, J = 5.5 Hz, 2H, $ArCH_2$), 3.67 (s, 3H, OCH_3), 4.12 (q, J = 7.0 Hz, 2H, CH_2CH_3), 4.71 (m, 1H, $CHCO_2Me$), 5.24 (d, J = 8.1 Hz, 1H, NHCO), 6.96 (d, J = 1.5 Hz, 1H), 7.08-7.25 (m, 2H), 7.32 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 8.29 (br s, 1H, NH);

^{13}C NMR δ 14.5 (CH_3), 27.9 (CH_2), 52.3 (CH_3), 54.3 (CH), 61.1 (CH_2), 109.8 (C), 111.2 (CH), 118.5 (CH), 119.6 (CH), 122.1 (CH), 122.8 (CH), 127.5 (C), 136.1 (C), 156.1 (C=O), 172.6 (C=O);

ESMS *m/z* 291 (M^+ + 1, 35), 242 (100).

3-(3-Methyl-but-2-enyl)-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1,2-dicarboxylic acid 1-ethyl ester 2-methyl ester (20)



To a mixture of (**18**) (515 mg, 1.77 mmol), zinc triflate (772 mg, 2.12 mmol), tetrabutylammonium iodide (702 mg, 1.90 mmol) in toluene (8 mL) was added DIEA (0.37 mL, 2.12 mmol) at room temperature under argon. The reaction mixture was stirred for 15 min at room temperature, then prenyl bromide (0.22 mL, 1.90 mmol) was added. The reaction mixture was stirred for 5 h, quenched with saturated aqueous NH_4Cl (10 mL), diluted with water (15 mL) and extracted with ether (3 × 15 mL). The combined organics were washed with water and dried over Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a pale oil (214 mg, 34%).

IR ν 3393, 2974, 2930, 1746, 1694, 1608, 1414, 1327, 1172 cm^{-1};

^{1}H NMR δ 1.15/1.34 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.50/1.51 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.22 (dd, J = 8.6, 12.5 Hz, 1H, C^3HH), 2.29-2.42 (m, 2H, C^9H_2), 2.58/2.53 (dd, J = 7.6, 12.5 / 7.0, 12.5 Hz, 1H, C^3HH), 3.72/3.75 (s, 3H, OCH_3), 3.95 (q, J = 7.0 Hz, 1H, $CHHCH_3$) and 4.15 (q, J = 7.5 Hz, 1H, $CHHCH_3$) / 4.20 (m, 2H, CH_2CH_3), 4.05 (dd, J = 7.6, 8.6 Hz, 1H, C^2H), 5.08-5.15 (m, 1H, $=C^{10}H$), 5.26/5.24 (s, 1H, $C^{8a}H$), 5.38 (br s, 1H, NH), 6.58-6.79 (m, 2H), 7.02-7.10 (m, 2H);

^{13}C NMR δ 14.4/14.8 (CH_2CH_3), 17.9 (CH_3), 25.9 (CH_3), 35.3/35.5 (C^9H_2), 39.2/39.3 (C^3H_2), 52.2/52.3 (OCH_3), 56.2/57.2 (C^{3a}), 59.2/59.6 (C^2H), 61.3/61.8 (CH_2CH_3), 81.4/80.6 ($C^{8a}H$), 109.8/109.4 (CH), 118.7/118.8 (CH), 118.9/119.2 (CH), 123.2 (CH), 128.46/128.50 (CH), 132.1/131.9 (C), 135.4/135.3 (C), 148.5/148.1 (C), 154.6/154.3 (C=O), 173.3/172.9 (C=O);

EIMS *m/z* 358 (M^+, 26), 289 (53), 157 (45), 130 (100).

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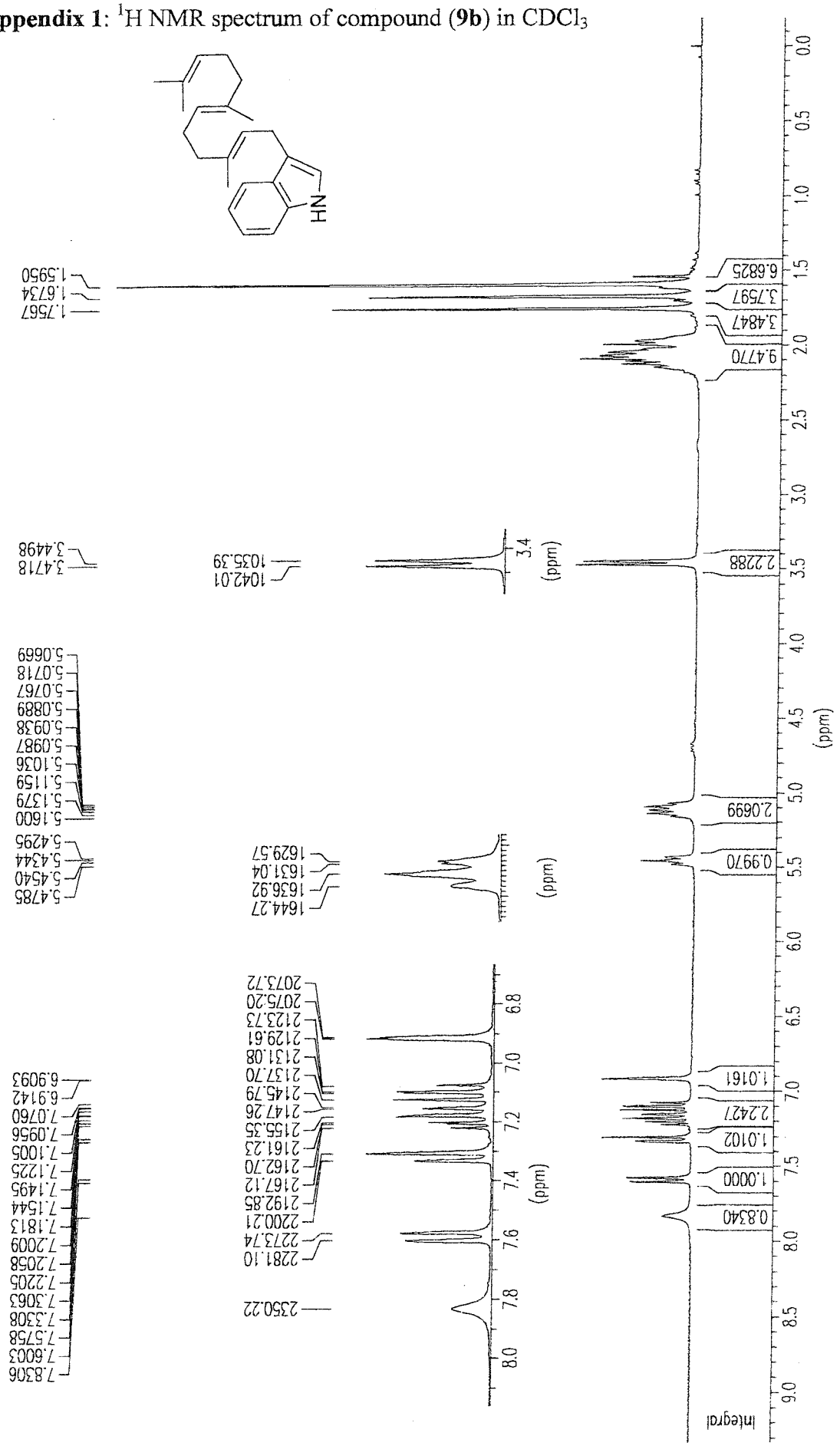
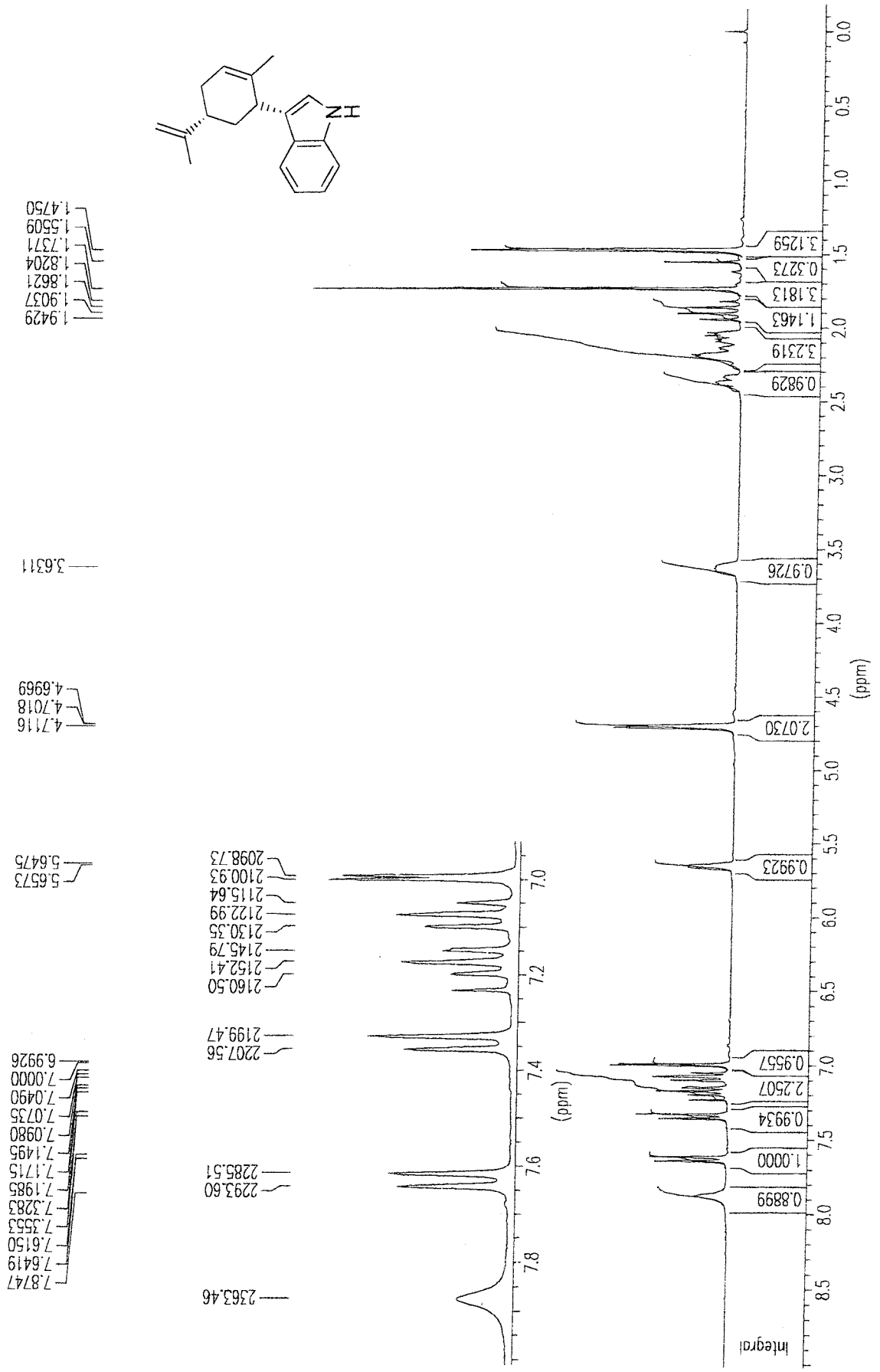
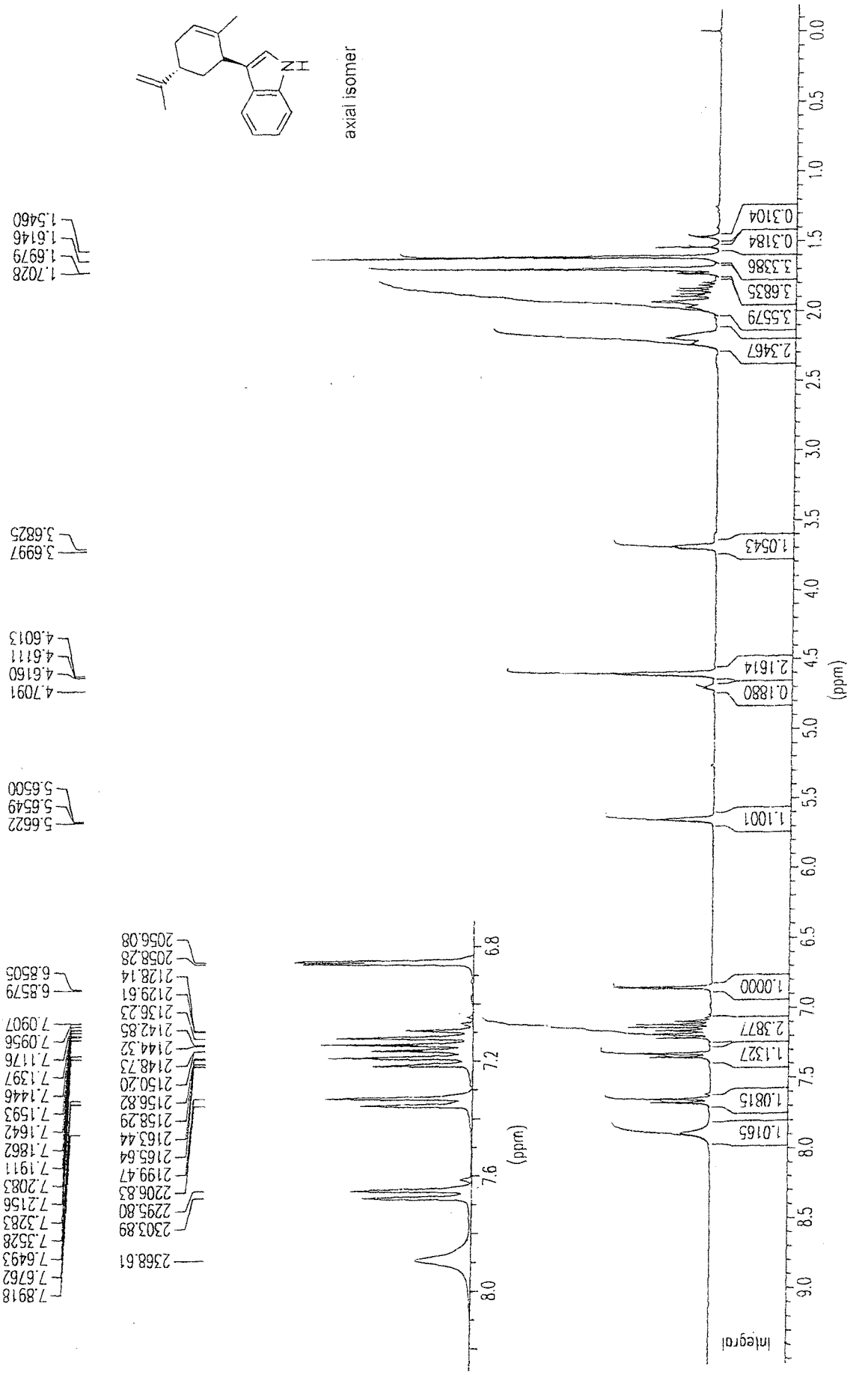
Appendix 1: ^{1}H NMR spectrum of compound (**9b**) in $CDCl_3$



Appendix 2: ^{1}H NMR spectrum of equatorial isomer of compound (**9f**) in $CDCl_3$



Appendix 3: ^{1}H NMR spectrum of axial isomer of compound (**9f**) in $CDCl_3$



Appendix 4: X-ray crystallographic data of axial isomer of compound (**9f**)

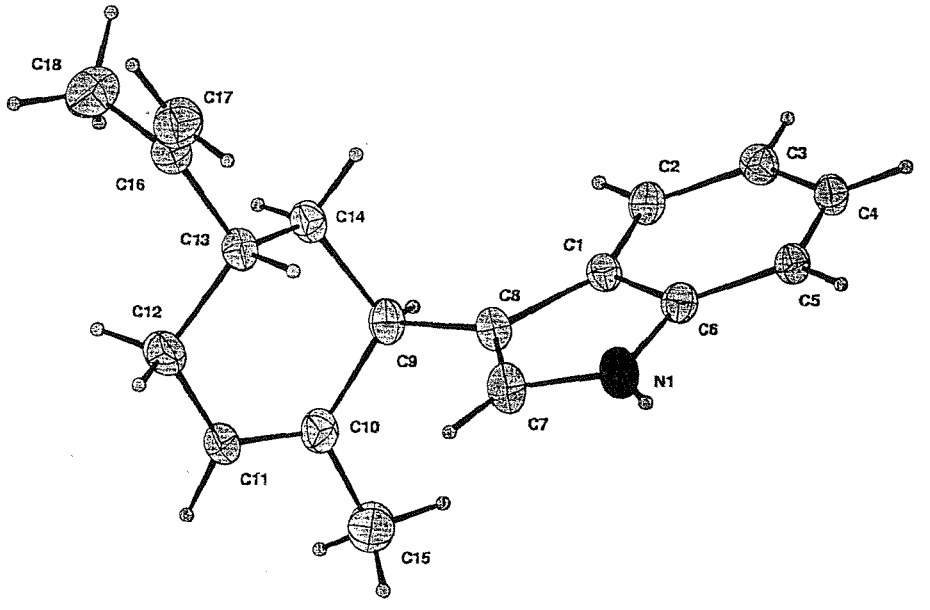


Table 1. Crystal data and structure refinement.

Identification code	**s92**	
Empirical formula	$C_{18}H_{21}N$	
Formula weight	251.36	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	$a = 7.30670(10)$ Å	$\alpha = 90°$
	$b = 6.95810(10)$ Å	$\beta = 97.683(3)°$
	$c = 15.0593(3)$ Å	$\gamma = 90°$
Volume	758.75(2) Å^3	
Z	2	
Density (calculated)	1.100 Mg / m^3	
Absorption coefficient	0.063 mm^{-1}	
F(000)	272	
Crystal	Colourless Plates	
Crystal size	0.2 x 0.15 x 0.02 mm^3	
θ range for data collection	2.96 – 23.25°	
Index ranges	$-8 \le h \le 8, -7 \le k \le 7, -16 \le l \le 16$	
Reflections collected	5544	
Independent reflections	2144 [$R_{int} = 0.0772$]	
Completeness to $\theta = 23.25°$	99.6 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2144 / 1 / 173	
Goodness-of-fit on F^2	1.004	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0516$, $wR2 = 0.1309$	
R indices (all data)	$R1 = 0.0728$, $wR2 = 0.1445$	
Absolute structure parameter	1(6)	
Extinction coefficient	0.084(17)	
Largest diff. peak and hole	0.167 and –0.168 e Å^{-3}	

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1973(4)	3942(4)	4345(2)	44(1)	1
C2	977(4)	4909(4)	4918(2)	51(1)	1
C3	1337(4)	4595(4)	5829(2)	55(1)	1
C4	2704(4)	3286(5)	6178(2)	56(1)	1
C5	3727(4)	2318(5)	5629(2)	56(1)	1
C6	3361(4)	2651(5)	4712(2)	50(1)	1
C7	3331(4)	2684(5)	3223(2)	65(1)	1
C8	1988(4)	3937(5)	3384(2)	51(1)	1
C9	739(4)	5098(4)	2706(2)	54(1)	1
C10	1707(4)	5762(5)	1947(2)	61(1)	1
C11	1349(5)	5033(6)	1135(2)	69(1)	1
C12	–42(6)	3497(6)	865(2)	77(1)	1
C13	–760(4)	2523(5)	1655(2)	55(1)	1
C14	–1067(4)	4034(5)	2351(2)	55(1)	1
C15	3119(6)	7325(7)	2153(3)	96(1)	1
C16	–2417(5)	1294(6)	1341(2)	67(1)	1
C17	–2273(6)	–637(6)	1338(2)	87(1)	1
C18	–4183(5)	2219(8)	997(3)	99(1)	1
N1	4174(4)	1894(4)	4021(2)	67(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.377(4)	C9–C10	1.496(4)
C1–C6	1.411(4)	C9–C14	1.545(4)
C1–C8	1.448(4)	C10–C11	1.317(4)
C2–C3	1.379(4)	C10–C15	1.503(5)
C3–C4	1.401(4)	C11–C12	1.493(5)
C4–C5	1.364(4)	C12–C13	1.522(5)
C5–C6	1.390(4)	C13–C16	1.506(5)
C6–N1	1.371(4)	C13–C14	1.521(4)
C7–C8	1.359(4)	C16–C17	1.348(5)
C7–N1	1.388(4)	C16–C18	1.472(5)
C8–C9	1.510(4)		

C2–C1–C6	118.6(2)	C10–C9–C14	110.6(2)
C2–C1–C8	134.7(3)	C8–C9–C14	112.9(2)
C6–C1–C8	106.8(2)	C11–C10–C9	122.3(3)
C1–C2–C3	120.0(3)	C11–C10–C15	121.1(3)
C2–C3–C4	120.5(3)	C9–C10–C15	116.6(3)
C5–C4–C3	121.0(3)	C10–C11–C12	124.9(3)
C4–C5–C6	118.1(3)	C11–C12–C13	113.5(3)
N1–C6–C5	130.1(3)	C16–C13–C14	115.0(3)
N1–C6–C1	108.0(2)	C16–C13–C12	110.7(2)
C5–C6–C1	121.8(3)	C14–C13–C12	109.2(3)
C8–C7–N1	110.3(3)	C13–C14–C9	111.9(2)
C7–C8–C1	106.4(3)	C17–C16–C18	120.0(4)
C7–C8–C9	127.5(3)	C17–C16–C13	120.5(4)
C1–C8–C9	126.1(3)	C18–C16–C13	119.5(4)
C10–C9–C8	112.2(3)	C6–N1–C7	108.5(3)

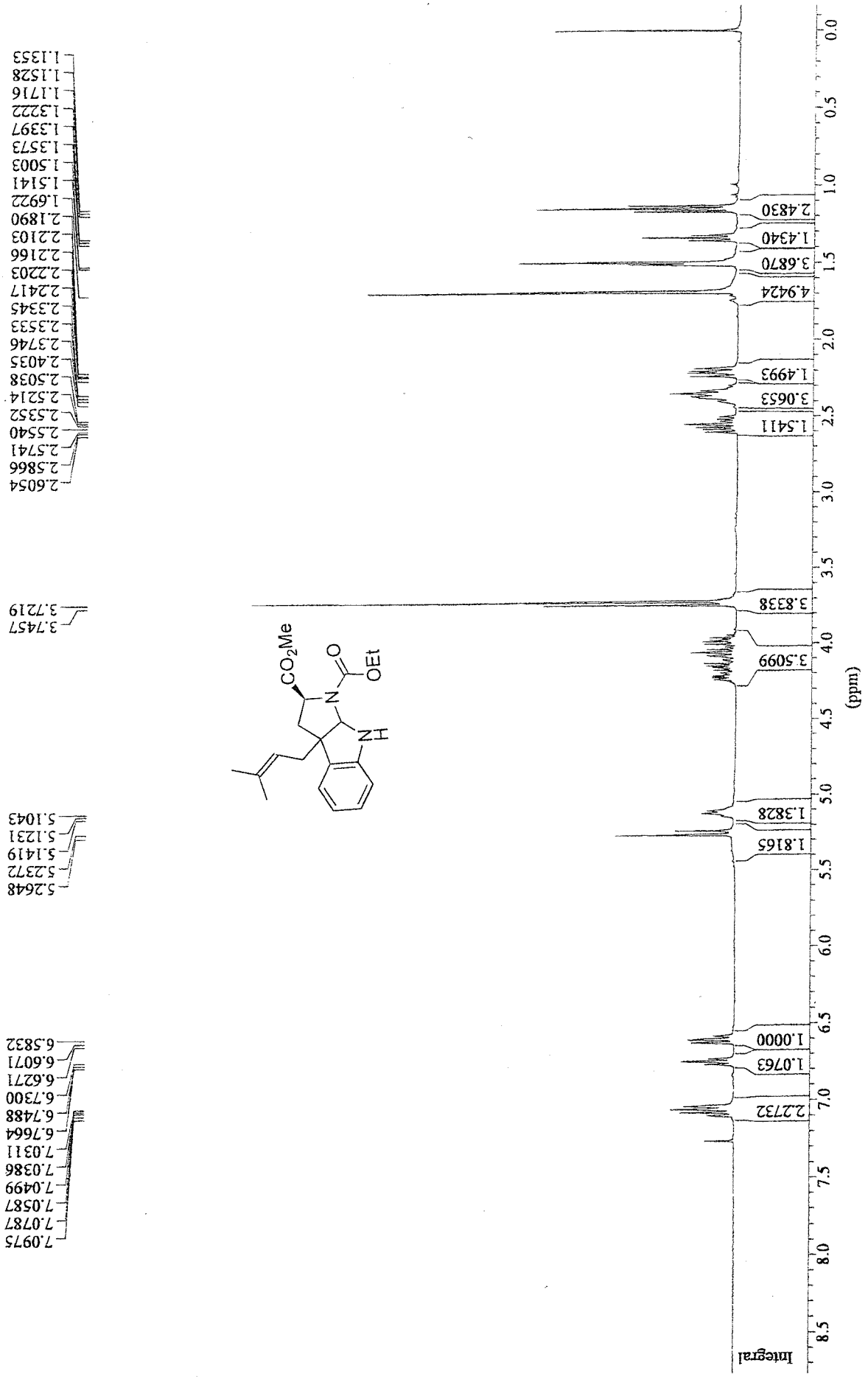
Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	51(2)	41(2)	41(2)	3(1)	4(1)	1(2)
C2	55(2)	47(2)	49(2)	1(2)	−1(1)	9(1)
C3	64(2)	54(2)	48(2)	−8(2)	9(1)	−3(2)
C4	62(2)	63(2)	41(2)	6(2)	−1(2)	−9(2)
C5	56(2)	61(2)	49(2)	15(2)	−3(2)	−1(2)
C6	53(2)	46(2)	49(2)	1(2)	1(1)	3(1)
C7	78(2)	70(2)	47(2)	−2(2)	2(2)	22(2)
C8	64(2)	51(2)	38(2)	0(1)	1(1)	5(2)
C9	64(2)	48(2)	46(2)	−2(2)	−2(1)	12(2)
C10	67(2)	58(2)	54(2)	16(2)	−5(2)	−1(2)
C11	72(2)	87(3)	47(2)	15(2)	4(2)	−14(2)
C12	90(3)	92(3)	50(2)	−9(2)	16(2)	−22(2)
C13	65(2)	54(2)	47(2)	−1(2)	4(1)	0(2)
C14	59(2)	63(2)	44(2)	9(2)	5(1)	11(2)
C15	103(3)	100(3)	81(3)	17(3)	−5(2)	−33(3)
C16	72(2)	73(3)	54(2)	3(2)	6(2)	−6(2)
C17	96(3)	77(3)	86(3)	3(2)	1(2)	−20(2)
C18	77(3)	109(3)	108(3)	−1(3)	3(2)	−3(3)
N1	74(2)	72(2)	54(2)	2(1)	3(1)	31(2)

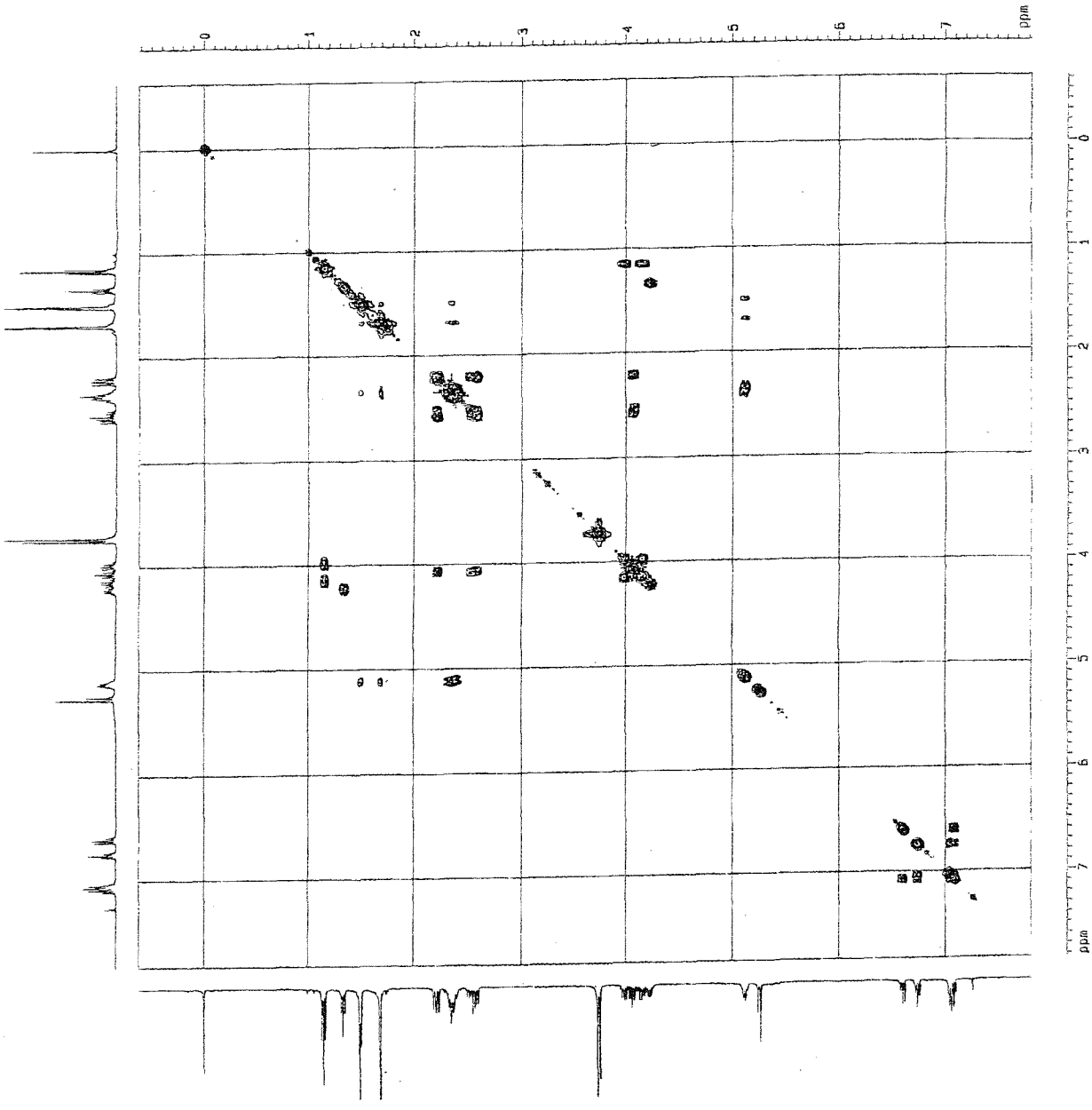
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	x	y	z	U_{eq}	*S.o.f.*
H2	62	5774	4691	61	1
H3	667	5257	6215	66	1
H4	2918	3075	6793	67	1
H5	4643	1459	5861	67	1
H7	3642	2397	2659	78	1
H9	386	6253	3015	64	1
H11	2012	5510	698	83	1
H12A	512	2533	520	92	1
H12B	−1076	4056	480	92	1
H13	217	1663	1931	66	1
H14A	−1556	3419	2847	66	1
H14B	−1974	4957	2085	66	1
H15A	3202	7667	2775	144	1
H15B	2757	8431	1791	144	1
H15C	4299	6877	2026	144	1
H17A	−3288	−1385	1118	105	1
H17B	−1158	−1221	1555	105	1
H18A	−4059	3588	1056	148	1
H18B	−5128	1779	1333	148	1
H18C	−4513	1892	376	148	1
H1	5058	1068	4073	81	1

Appendix 5: ^{1}H NMR spectrum of compound (**20**) in $CDCl_3$



Appendix 6: 2D NMR spectrum (COSY) of compound (**20**)



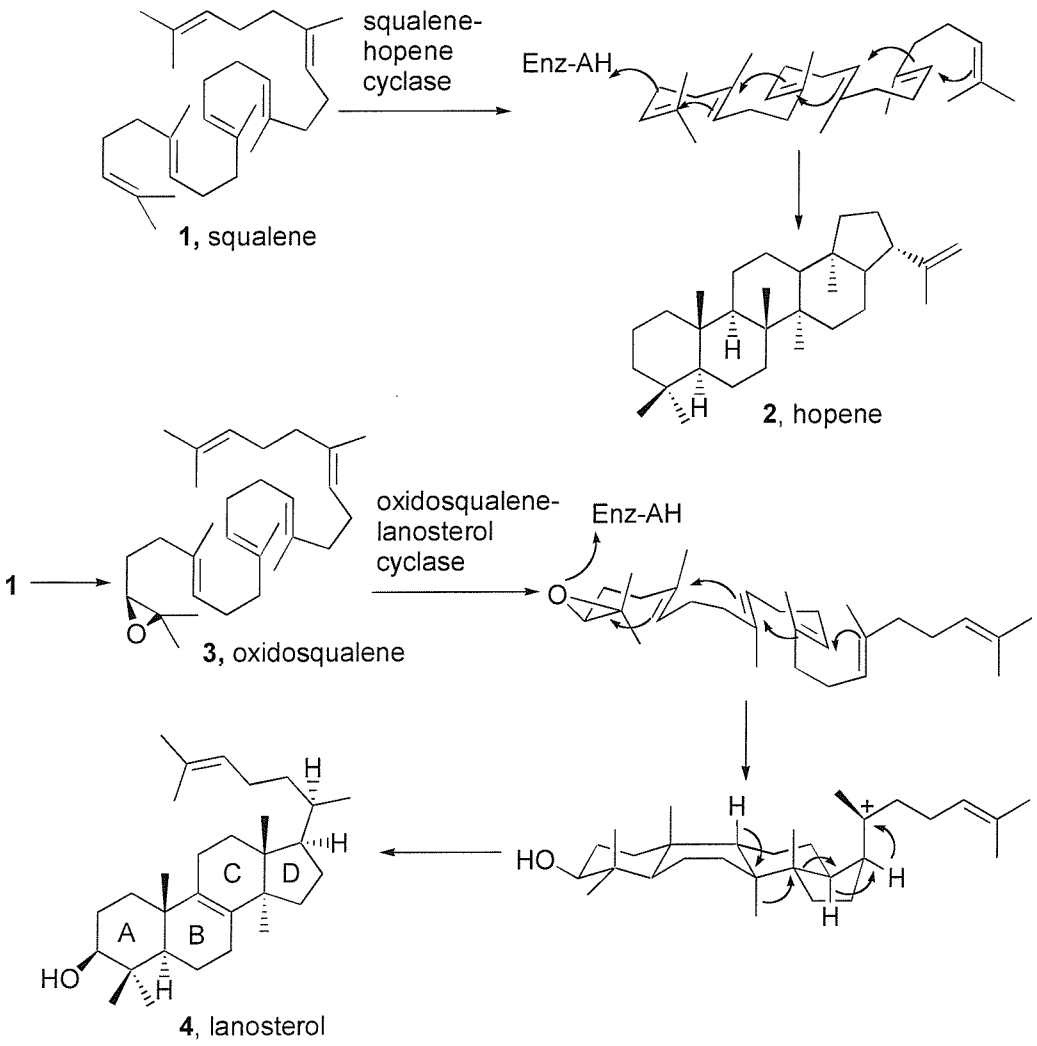
Chapter 4: Biomimetic Polyene Cyclizations Terminated by Indole

1. Introduction

1.1. Polyene Cyclizations

The enzymatic cyclizations of squalene (**1**) and oxidosqualene (**3**) are the most remarkable steps in the biosyntheses of steroids and triterpenoids.[1] It is now accepted that tight enzymatic control of substrate conformation is a prerequisite for the highly selective formation of products such as hopene (**2**) and lanosterol (**4**), as seen in Scheme 1. Squalene-hopene cyclase allows the formation of hopene (**2**) proceeding in all chair conformation without migration of atoms. However, the formation of lanosterol (**4**) proceeds *via* the "chair-boat-chair" conformation, and

Scheme 1



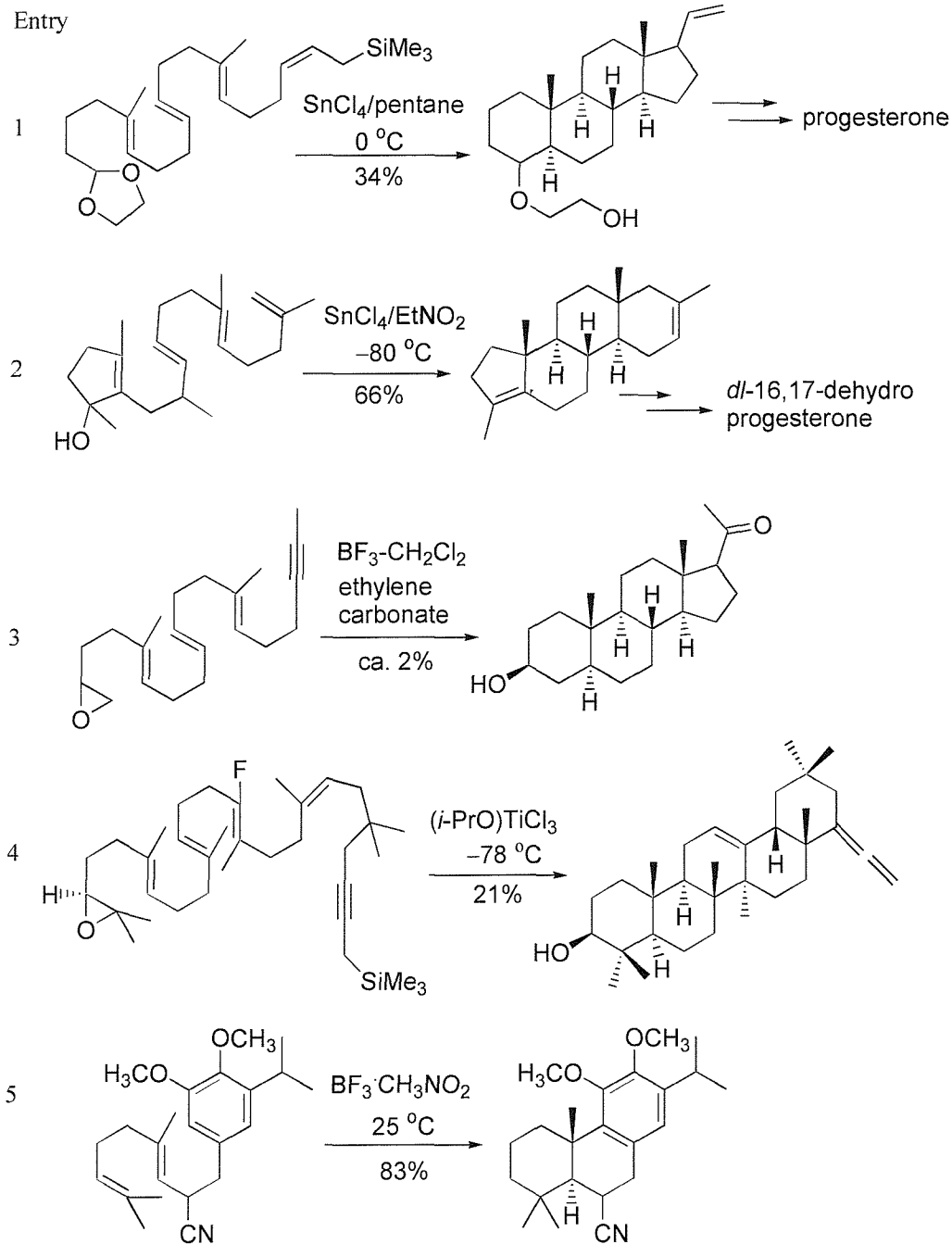
the cyclization is initiated by oxirane ring opening with participation by a neighbouring π-bond.

Woodward and Bloch first proposed the open chain polyalkene squalene as the key biogenetic precursor of lanosterol in 1953.[2] Shortly after, Stork *et al.* at Columbia University and Eschenmoser *et al.* at the ETH, Zurich, independently proposed a rationalization for the course of these biochemical cyclizations.[3] The major elements of this hypothesis are that cyclization occurs *via* chairlike conformations of the nascent rings, and that addition to each double bond takes place in an antiparallel fashion. It explains in an elegant way that the all *trans* double bond geometry of squalene is transformed into the *trans*-anti-*trans* stereochemistry of polycyclic terpenes. Inspired by the pioneering work of Woodward and Bloch and the theoretical Stork-Eschenmoser postulate, and also attracted by the fascination and challenge of this synthetic strategy, chemists have started investigations into the non-enzymatic cyclization of polyenes since the early 1960s. The attraction of this synthetic construction is the high degree of molecular complexity as well as stereoselectivity and regioselectivity furnished in a single step. For nearly half a century, biomimetic non-enzymatic polyene cyclizations have been employed in the syntheses of a wide variety of steroids and terpenes.[4] Johnson and his group in particular have made great contributions to the development of polyene cyclizations.

1.2. Initiation, Propagation and Termination of Polyene Cyclization

A successful polyene cyclization relies on a complex interplay between the methods of initiation, propagation and the mechanism of termination although it is perhaps artificial to define each stage involved in the cyclization.[4b] Cyclization efficiency is strongly dependent on the initiating group. Early cyclization experiments carried out in Johnson's group were unsuccessful until they discovered certain acetal functions serving as excellent initiators in polyene cyclizations (an example[5] shown in Scheme 2, Entry 1). At about the same time, they found allylic cations to be good initiators, and these were successfully adapted in syntheses of natural products such as *dl*-16,17-dehydroprogesterone (Scheme 2, Entry 2).[6]

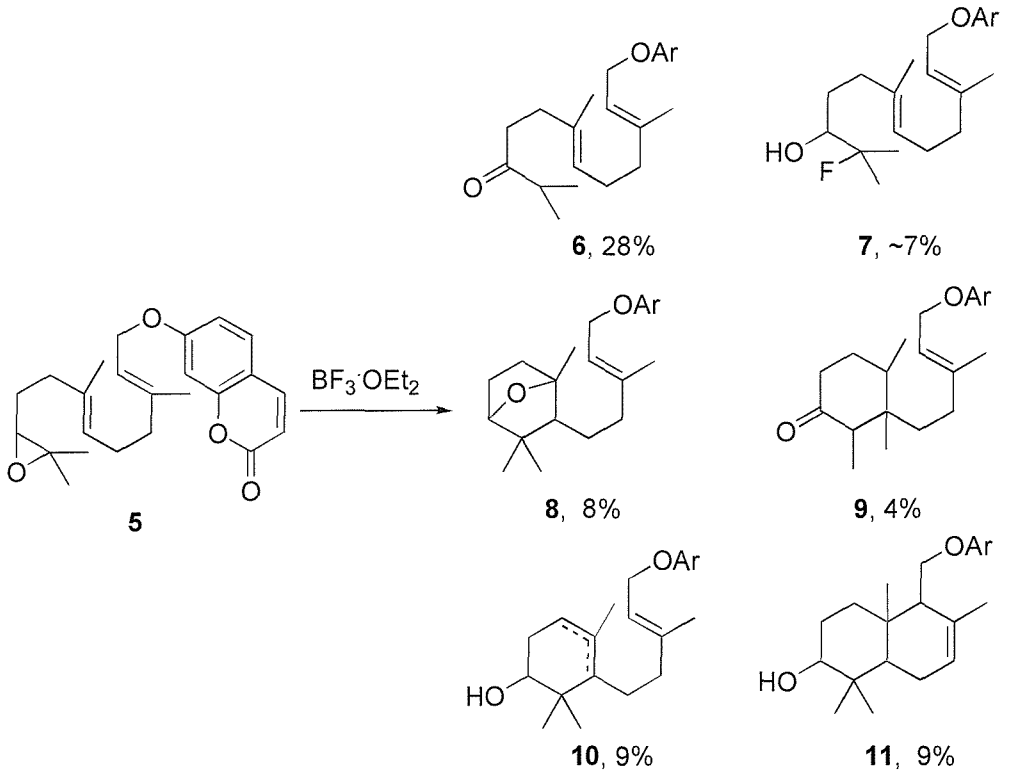
Scheme 2



Cyclizations triggered by epoxide ring opening,[7,8] particularly investigated by van Tamelen and co-workers, generally proceed in poor yield, on the average of 20%. The use of the epoxide function as a initiator has met with problems: facile pinacol rearrangement to a carbonyl compound, formation of 1,2-diol or halohydrin derivatives, partial cyclization as well as incompatible acid promoters, resulting in low yields as seen in an example[9] given in Scheme 3. The epoxide initiated tetracyclization furnished (±)-alloprenanolone in about 2% yield (Scheme

2, Entry 3).[10] The pentacyclization reported by Johnson was achieved in 21% yield by using a suitably functionalized epoxide substrate in which fluorine atom functions as a cation-stabilizing auxiliary (Scheme 2, Entry 4).[8] Cyclization can also be initiated with a double bond, an example [11] being shown in Scheme 2, Entry 5.

Scheme 3

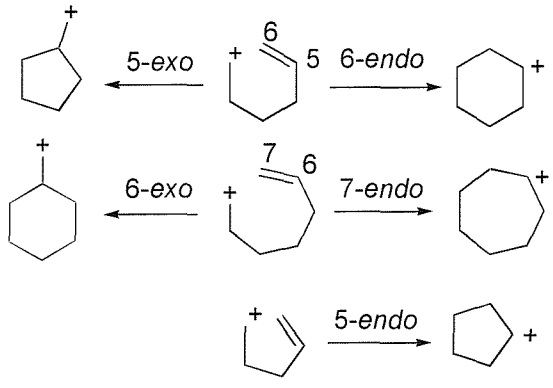


The Stork-Eschenmoser postulate has been tested by a host of examples of monocyclization, many bicyclizations, a substantial number of tricyclizations and a few tetracyclizations. Nearly all of these cyclizations involve *E*-alkenes cyclizing to *trans*-fused rings *via* a chair-like transition state. It has been a useful guiding principle in designing a synthetic plan for polyene cyclizations. The enzymatic cyclization of oxidosqualene (**1**) to lanosterol (**4**), however, as seen in Scheme 1 does not proceed *via* all chair process: the B ring is generated as a boat. Van Tamelen studied the acid-catalyzed cyclizations of a number of partially cyclized analogues of oxidosqualene.[12] Without enzymatic control, products with the 9,10-*cis* stereochemistry could also be isolated, but the yields were extremely low, indicating that non-enzymatic polyene cyclizations exhibit a very strong bias against boat-like ring closure. A corollary of the Stork-Eschenmoser postulate is that the generation of *cis*-fused rings could be traced back to the *cis* double bond

geometry of their olefinic precursors, which has also been demonstrated by some examples. Cyclization of the *cis* olefins is in general somewhat less efficient than for the corresponding *trans* isomers. This may be accounted for by steric hindrance from the *cis* substituents in the transition state for cyclization and the intervention of side reactions when the initiation event is irreversible.[4c]

In cyclization of 1,5-dienes, the nucleophilic double bond can be endocyclic or exocyclic to the ring. If the double bond is electronically unbiased or substituted at C-5 position, six-membered ring closure *via* the endocyclic process is greatly predominant (Scheme 4). In cyclization of 1,6-dienes, 6-*exo* cyclization is favoured (Scheme 4), and with 1,4-dienes, 5-*endo* cyclization which is contrary to Baldwin's rules, is seldom observed.[4b]

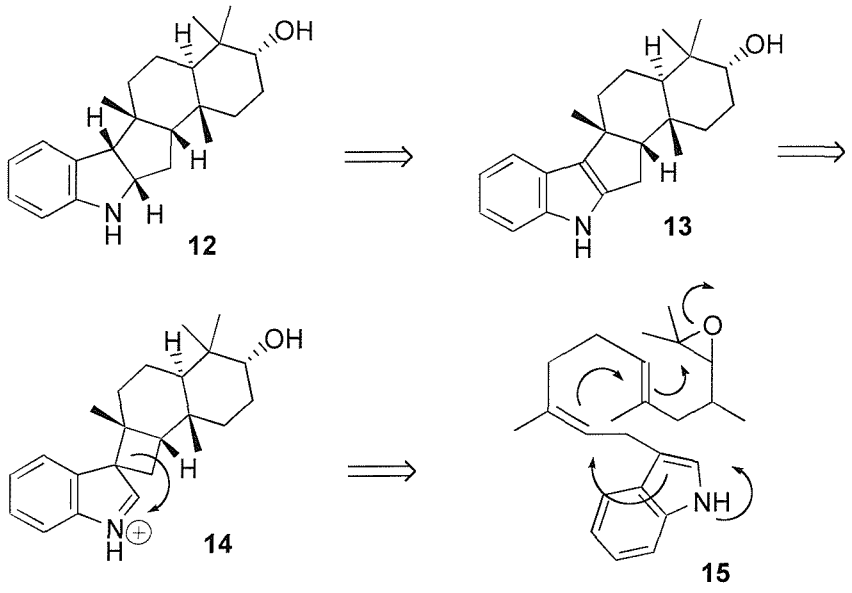
Scheme 4



Termination of cyclization can be achieved by elimination and/or attack by an internal or external nucleophile. Proton elimination is the most common elimination mode for tertiary cations and also for secondary cations especially in the presence of a Lewis acid. Allyl and propargyl silanes are excellent terminators, which can control the double bond position in the way that it reacts at the far end of the double bond with concomitant loss of the silyl residue (Scheme 2, Entry 1 and 4). Other terminating groups include alkynes, allenes, enols and enol derivatives. Aryl and heteroaryl rings, particularly when electron rich, are good terminators (Scheme 2, Entry 5).

1.3. Epoxide Initiated Polyene Cyclization Using Indole as A Terminator

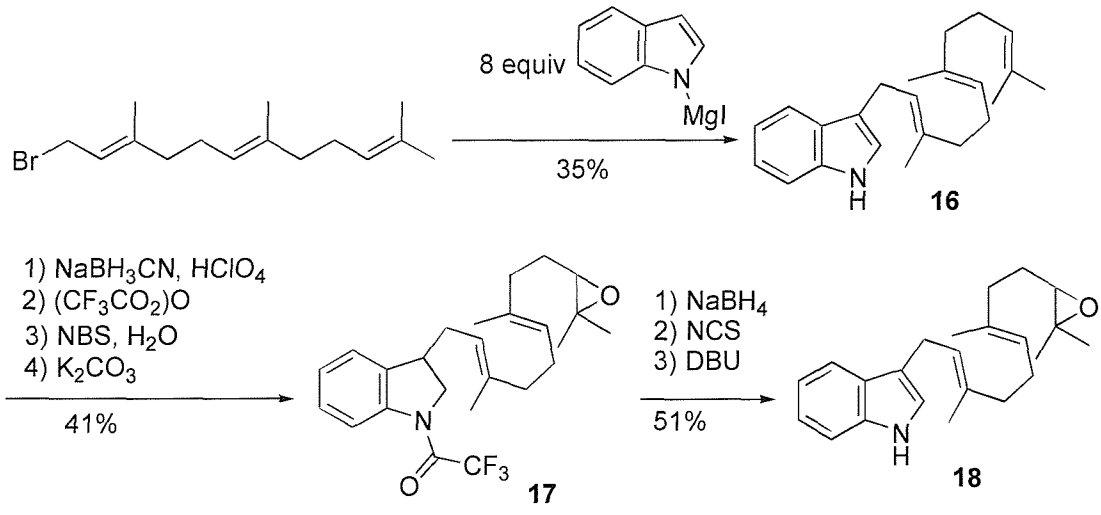
Scheme 5



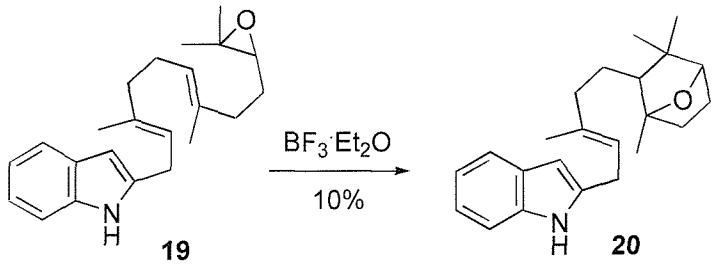
Polyveoline (**12**),[13] a representative of a series of indolosesquiterpene natural products, might result from a polyenic cyclization of a 3-ω-epoxyfarnesyl indole (**15**) (Scheme 5). This hypothesis suggests indole as a terminator in a polyene cyclization. In accordance with the Stork-Eschenmoser postulate, the required *cis-trans* ring junctions in polyveoline may come from the *Z,E*-farnesyl indole derivative instead of the *E,E*-isomer. Epoxide initiated polyene cyclization of (**15**) would lead to a spiro-intermediate (**14**) followed by rearrangement *via* bond migration. It appears that the initial bond at the C-3 position of indole has priority towards migration. A French group attempted to achieve this polyene cylization in the laboratory. 3-ω-Epoxyfarnesyl bromide could not be directly attached to indole by the prototypical method for C-3 alkylation using the indolylmagnesium species, as the harsh reaction conditions would destroy the epoxide function. So, 3-*E,E*-farnesyl indole (**16**) was prepared in 35% yield by using 8 equivalents of indolylmagnesium iodide with farnesyl bromide (Scheme 6). Compound (**16**) was then reduced to the indoline followed by protection of nitrogen and formation of the terminal epoxide to give (**17**). Deprotection and oxidation afforded 3-ω-epoxyfarnesyl indole (**18**). Compound (**18**) was subjected to Lewis acidic conditions ($BF_3{\cdot}Et_2O$, 1.2 equivalents), resulting in a complex mixture containing at least 13 isomers.[14] They then switched to cyclization with the isomeric 2-ω-

epoxyfarnesyl indole (**19**) prepared from 2-farnesyl indole.[15] Cyclization of (**19**) using borontrifluoride etherate in dichloromethane still gave a complex mixture, and only the tricyclic oxide (**20**) isolated in 10% yield could be characterized with confidence (Scheme 7). Polyene cyclization with sulphonamide protected indole derivative (**21**) again met with the same fate. But besides compound (**22**), a crystalline compound was also isolated and identified as (**23**) (Scheme 8). Removal of sulphonamide (**23**) and further reduction to indoline afforded a diastereoisomer of polyveoline due to the employment of *E,E* substrate in the polyene cyclization.

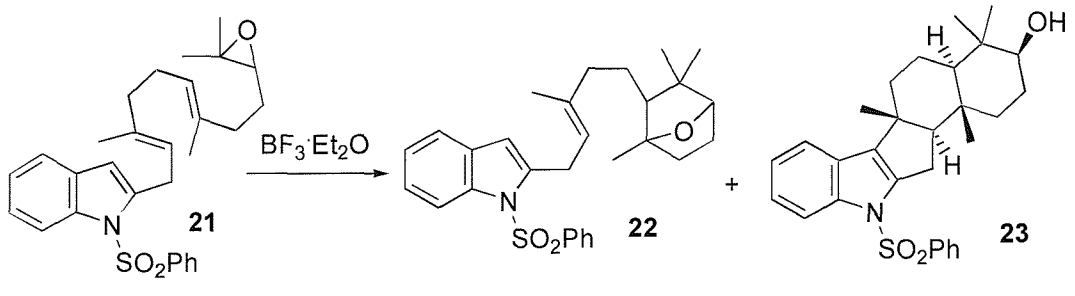
Scheme 6



Scheme 7



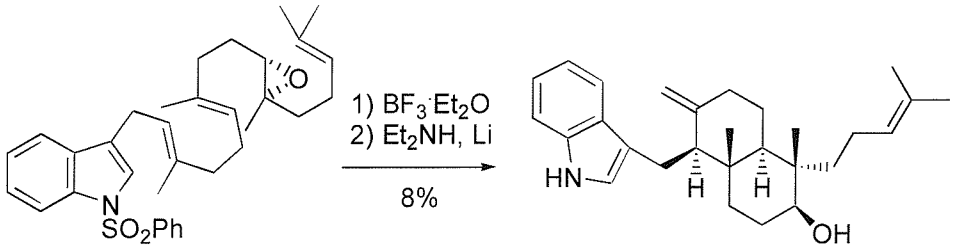
Scheme 8



13% each + other isomers

Recently, Rainier and Smith III reported the first biomimetic synthesis of (+)-emindole SA (**24**) using polyene cyclization as a key step (Scheme 9).[16] Boron trifluoride etherate was used to trigger the cyclization, giving moderate yield (20%). Other regimes of Lewis acids, temperatures and solvents led to lower yields and often produced significant quantities of monocyclic materials.

Scheme 9

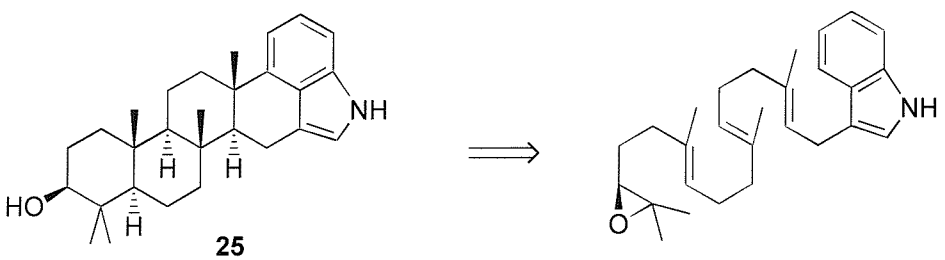


24

1.4. Retrosynthesis of Petromindole

Petromindole (**25**),[17] isolated in 1997, is the first example of an indoloditerpene in which the diterpene is connected to the C-3 and C-4 positions of the indole moiety. From the retrosynthetic perspective (Scheme 10), a straightforward epoxide initiated polyene cyclization of a geranylgeranyl indole derivative *via* all chair conformation, would provide the requisite skeleton of the natural product. Such a synthesis would proceed in a biomimetic manner, using indole as a terminator. The epoxy polyene precursor could be prepared in a straightforward manner by our zinc triflate promoted indole alkylations discussed in the previous chapter.

Scheme 10



25

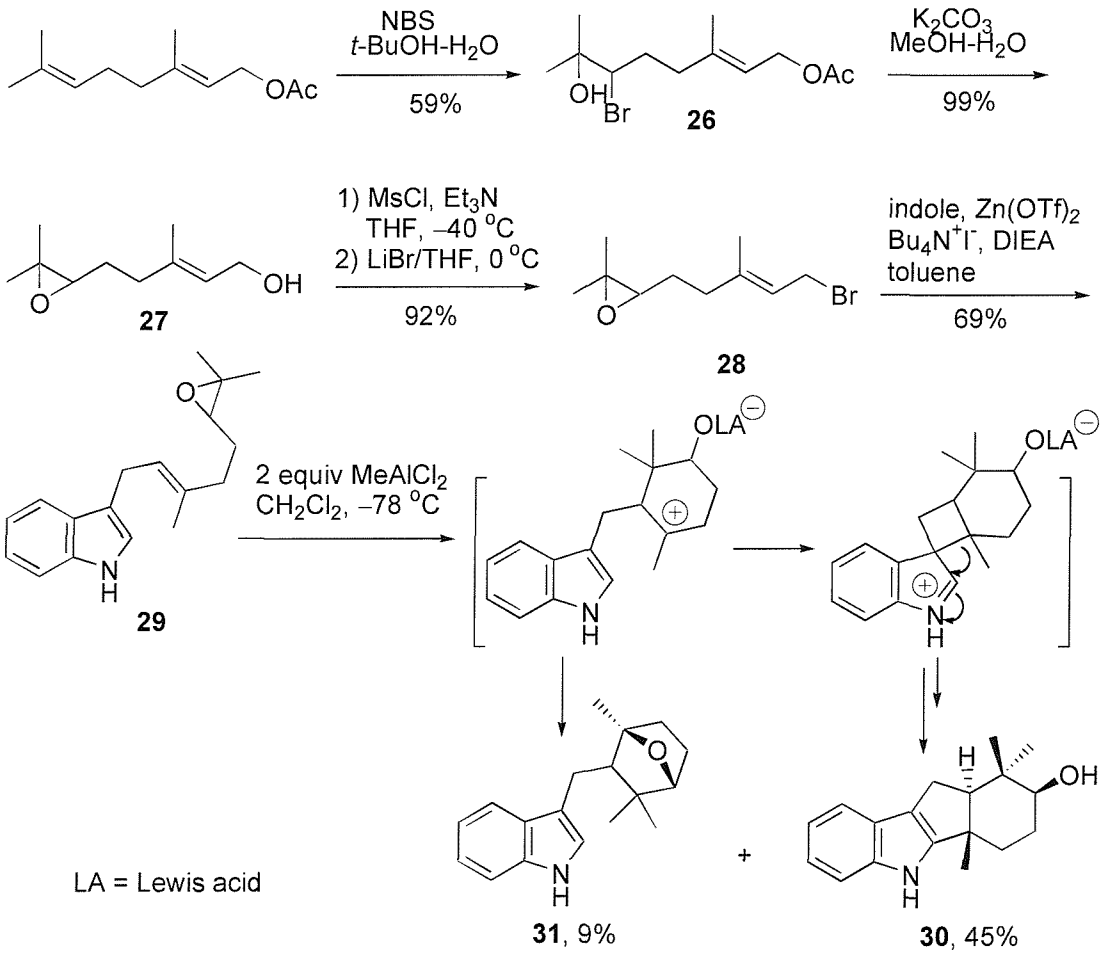
2. Studies In Indole-terminated Polyene Cyclizations

2.1. Model Studies with 3-ω-Epoxygeranyl Indoles

As a model study, the cyclization of epoxygeranyl indole, which was prepared by our established alkylation conditions, was investigated. Encouraging results were obtained.

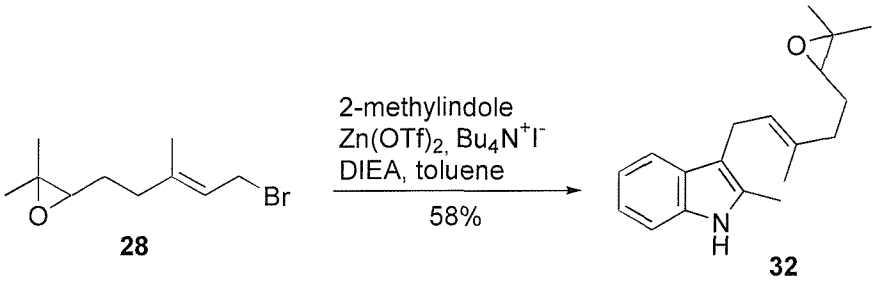
Starting with geranyl acetate (Scheme 11), highly regioselective attack of the terminal double bond was achieved by using NBS in *tert*-BuOH and H_2O following the procedure developed by van Tamelen.[18] Treatment of the bromohydrin (**26**) with K_2CO_3 in methanol and simultaneous hydrolysis of the acetate function afforded oxidogeraniol (**27**), which was then converted to the bromide (**28**) by activation of the hydroxy group (MsCl and Et_3N) followed by displacement with lithium bromide. After aqueous work-up, the unstable bromide was immediately employed in the subsequent alkylation step. Under our established indole C-3 alkylation conditions, compound (**28**) was attached to the indole C-3 position in good yield, the epoxide function being unaffected. Many Lewis acids have been employed for epoxide initiated polyene cyclizations, and such cyclizations tend to give low yields and are also strongly affected by parameters such as the nature of the Lewis acid, amount of reagent, and temperature. Early work mainly concentrated on Lewis acids like tin and boron trifluoride. Corey recently reported methylaluminuim dichloride to be a good Lewis acid in promoting epoxide initiated cation-olefin cyclizations,[7] as evident in the successful synthesis of β-amyrin.[19] So this type of Lewis acid was first focused on. Methylaluminium dichloride opened the epoxide in compound (**29**) regioselectively generating a tertiary carbocation, which initiated a stereoselective cyclization cascade. The major tricycle (**30**) features cyclization at C-2 and C-3 of indole. A minor product (**31**) is tetrahydrofuran being formed by the alkoxide capturing the intermediate carbocation. Both structures were confirmed by X-ray crystallography.

Scheme 11



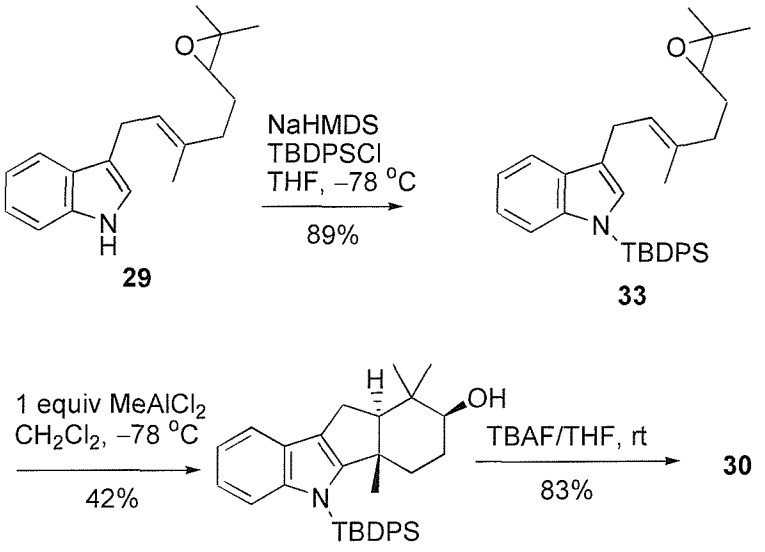
Would cyclization to the C3-C4 positions (as in the natural product petromindole) be favoured with 2-methylindole derivative (**32**) since C-2 is already occupied? Compound (**32**) was prepared from bromide (**28**) and 2-methylindole (Scheme 12). Unfortunately, (**32**) did not give a clean reaction under aluminium Lewis acidic conditions and none of the products could be identified. An alternative strategy for leading to the C3-C4 cyclization product would be to choose a larger protective group on the nitrogen of the indole, which might block the C-2 position of indole. Epoxide (**29**) was thus protected as the TBDPS derivative (**30**). However, treatment of (**30**) with $MeAlCl_2$ followed by removal of TBDPS still gave the same C3-C2 cyclization product (Scheme 13). These results suggest that although the TBDPS group is sterically bulky, it does not deactivate the indole ring. A group which is both bulky and electron withdrawing would be preferable.

Scheme 12



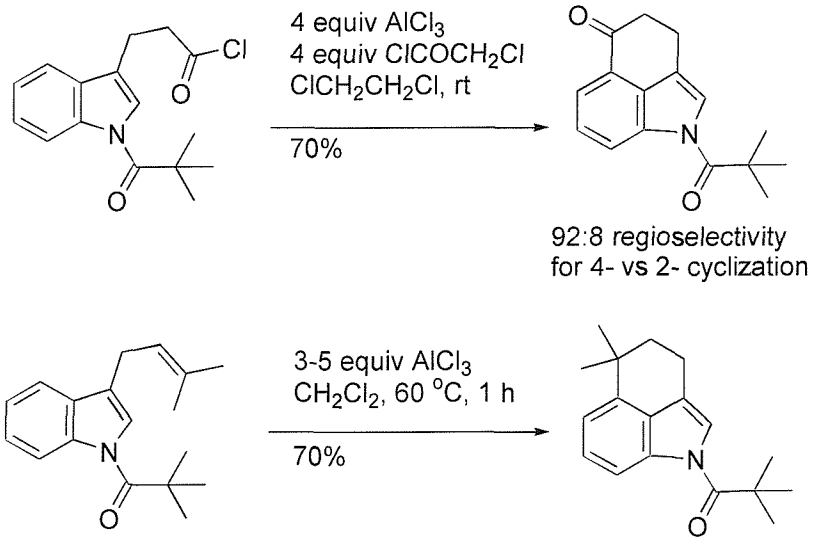
28 32

Scheme 13



29 33

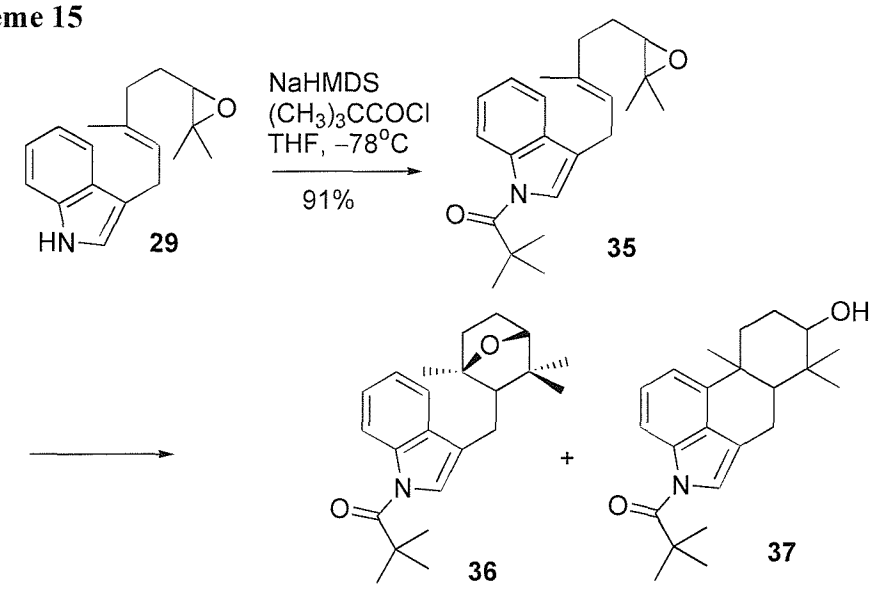
Scheme 14



One possibility would be to use the *N*-pivaloyl indole, as this should decrease the electron-density of the pyrrole ring. Nakatsuka reported Friedel-Crafts cyclization

onto the C-4 position of indole with *N*-pivaloyl indole derivative using aluminium chloride (Scheme 14).[20] In the structure of *N*-pivaloyl indole, it is also known that the methyl proton of the pivaloyl has a strong NOE with C-2 proton,[21] indicating a close relationship in space and providing steric hindrance at C-2. So the nitrogen of the indole derivative (**29**) was protected to afford (**35**) (Scheme 15). Compound (**35**) was treated with $MeAlCl_2$, giving furan compound (**36**) as the major product. C3-C4 cyclization product was not observed with 1 or 2 equivalents of this Lewis acid. However, besides (**36**), C3-C4 cyclization product (**37**) was obtained in 18% yield with $AlCl_3$ as the cyclization promoter. Boron trifluoride is a common Lewis acid for promoting polyene cyclization.[22] Cyclization with this boron reagent appeared more efficient at lower temperature, as significant decomposition occurred at higher temperature. Ferric chloride was also reported to be highly effective in polyene cyclization.[23] In our case, ferric chloride caused decomposition of (**35**). Under these Lewis acidic conditions, C3-C2 cyclization product was not observed. Our initial premise of deactivating the pyrrole ring and inhibition of C3-C2 cyclization was hence successful by using pivaloyl protective group. However, cyclization at the nonactivated C-4 position of the aromatic ring appears to be slower than competing cyclization by the alkoxide to give (**36**).

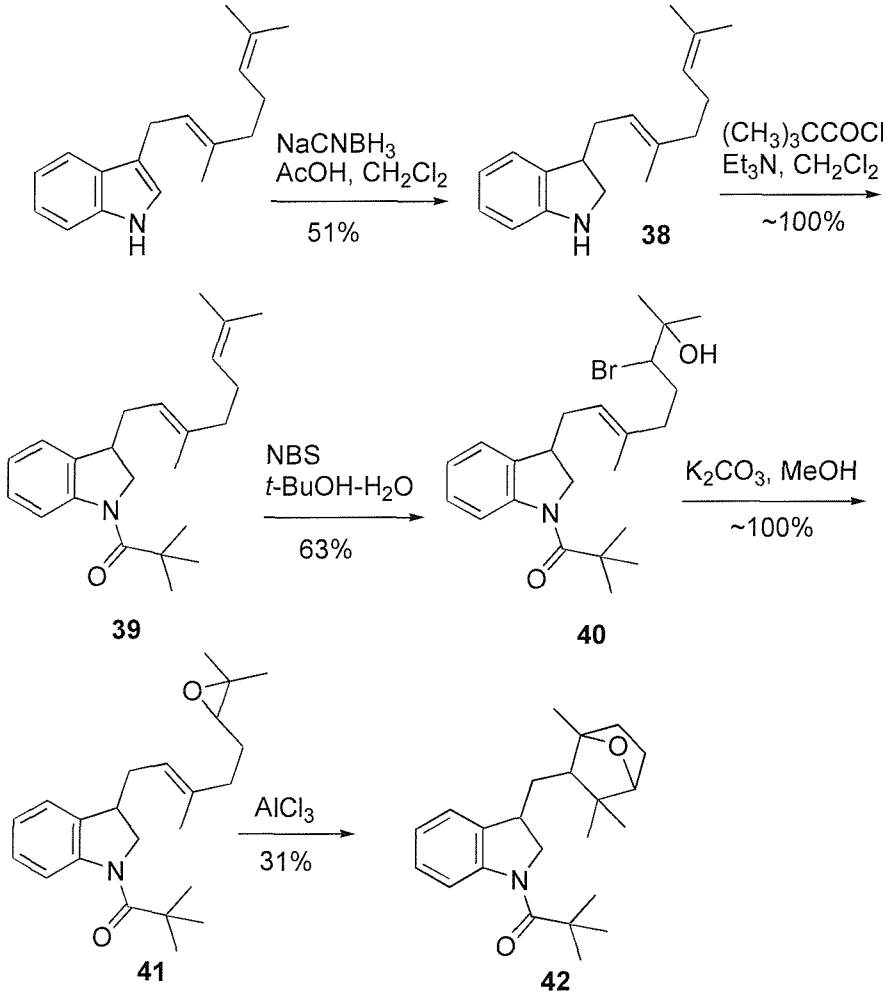
Scheme 15



Conditions	Yield (%) of **36**	Yield (%) of **37**
1 equiv $MeAlCl_2$,CH_2Cl_2, –78 °C	31	-
2.5 equiv $MeAlCl_2$,CH_2Cl_2, –78 °C	39	-
4 equiv $AlCl_3$, CH_2Cl_2, rt	26	18
4 equiv $BF_3{\cdot}Et_2O$, CH_3NO_2, –20 °C	38	-
4 equiv $BF_3{\cdot}Et_2O$, CH_3NO_2, 0 °C	36	trace
4 equiv $BF_3{\cdot}Et_2O$,CH_3NO_2, 50 °C	16	trace

The *N*-pivaloyl protective group did serve the function of preventing C3-C2 cyclization. At the same time, this strongly electron withdrawing group partially weakens the electron density of the benzene ring. So if the indole compound (**35**) could be converted to the corresponding indoline derivative, the electron density of the benzene ring would not be strongly affected by the nature of a protective group on the nitrogen. This might increase the chances of cyclization at C-4 position. The reduction of indoles to indolines is most commonly effected under acidic conditions *via* initial protonation at the C-3 position followed by reduction of the resultant indolenium species with borohydride.[24] Direct reduction of (**35**) to indoline was not successful as the expoxy function was sensitive to the reducing agent. So the epoxide function had to be formed after reduction of indole to the indoline.

Scheme 16



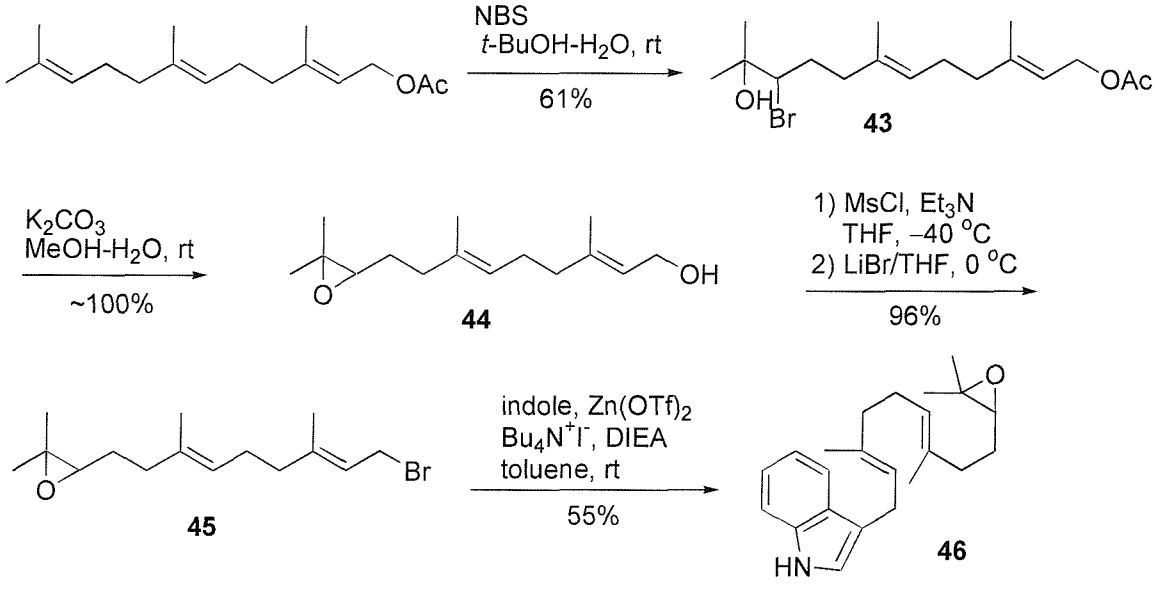
No reaction was found in the reduction of 3-geranyl indole[25] with sodium triacetoxyborohydride in acetic acid at room temperature, while the reduction was

effective with sodium cynoborohydride (Scheme 16). The reaction needed to be maintained at 15 °C as it was vigorously exothermic. Otherwise, *N*-acetyl and/or *N*-ethyl byproducts were formed. Indoline compound (**38**) was protected as pivalamide followed by formation of bromohydrin. Compound (**40**) was obtained as two diastereomers in a ratio of 1:1. Treatment of the mixture (**40**) with K_2CO_3 in methanol afforded epoxygeranyl indoline (**41**), which was then exposed to $AlCl_3$ in dichloromethane. Unfortunately, the bicyclic furan compound (**42**) was still the major product.

In summary, these model studies with the geranyl indole indicate that both the C3-C2 cyclization (as present in natural products like polyveoline) and the C3-C4 cyclization (as in the natural product petromindole) could be attained. Our attention was then turned to the epoxyfarnesyl indole, which would contain an additional double bond.

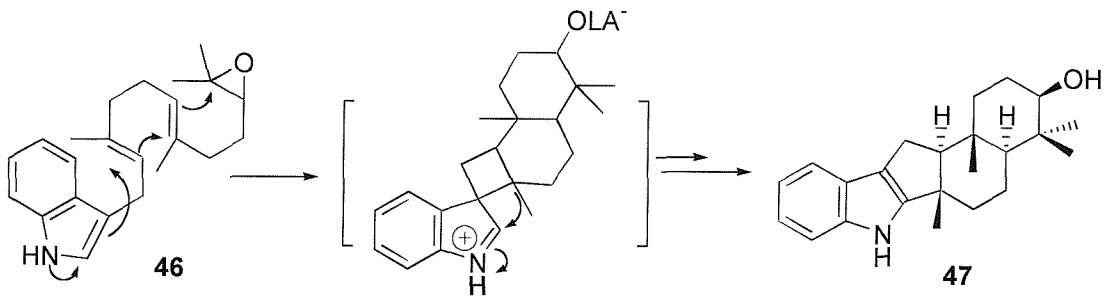
2.2. Model Studies with 3-ω-Epoxyfarnesyl Indoles

Scheme 17



Similar methods to the epoxygeranyl indole synthesis were used to prepare compound (**46**) (Scheme 17) starting from farnesyl acetate. Alkylation of indole with epoxyfarnesyl bromide (**45**) was also successful, compound (**46**) being obtained in good yield.

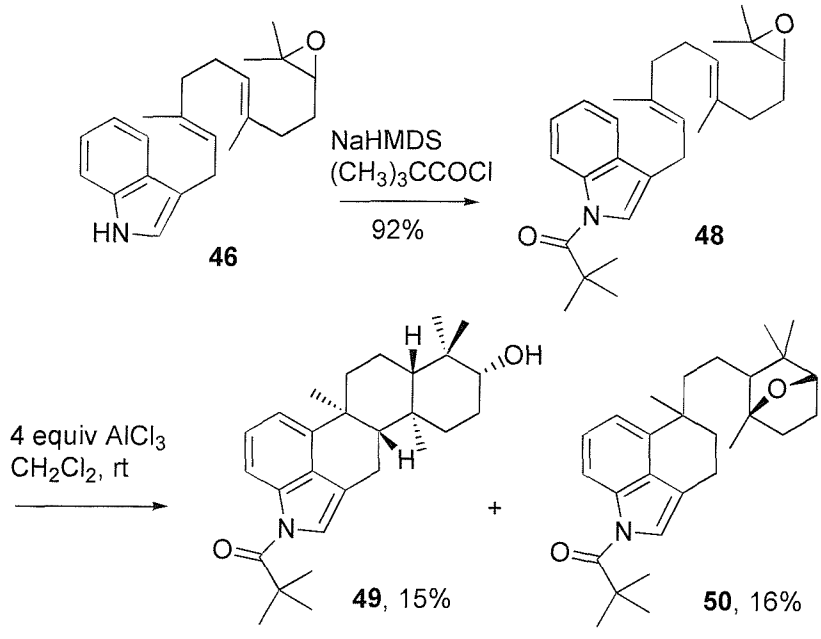
Scheme 18



Conditions	Yield (%)
4 equiv $AlCl_3$, CH_2Cl_2, rt	14
2 equiv $MeAlCl_2$,CH_2Cl_2, –78 °C	12

The polyene cyclization reaction is now more complex, as an increased number of rings is being formed. With the nitrogen in compound (**46**) unprotected, treatment of (**46**) with aluminium Lewis acids gave a messy reaction by TLC. One major compound was isolated and assigned as C3-C2 cyclization product (**47**), and its structure confirmed by X-ray crystallography (Scheme 18).

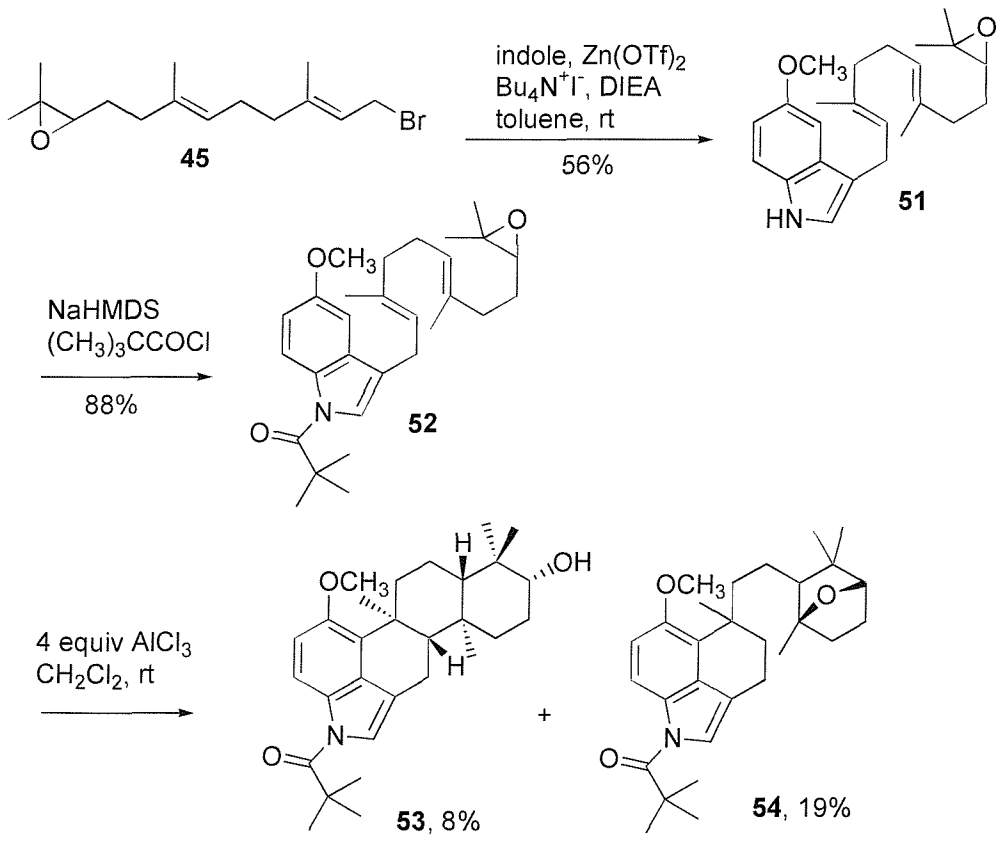
Scheme 19



Compound (**46**) was treated with pivaloyl chloride, affording (**48**) in high yield, which was then subjected to several different Lewis acidic conditions (Scheme 19). Ferric chloride led largely to decomposition of (**48**) and unidentifiable products.

$BF_3{\cdot}Et_2O$ (in CH_3NO_2 at room temperature for 30 minutes), $Ti(O^iPr)Cl_3$ (in CH_2Cl_2 at 0 °C for 20 minutes and room temperature for 15 minutes)[8] and $Sc(OTf)_2$ (in CH_2Cl_2 at −78 °C to 0 °C over 2 hours)[26] only gave partial cyclization products. The C3-C4 cyclization product (**49**) was only successfully obtained with $AlCl_3$ as Lewis acid. Compound (**50**) was also isolated, suggesting sequential polyene cyclization competing with Friedel-Crafts alkylation. The cyclization using $AlCl_3$ (in $ClCH_2CH_2Cl$) carried out at 60 °C did not improve the result.

Scheme 20

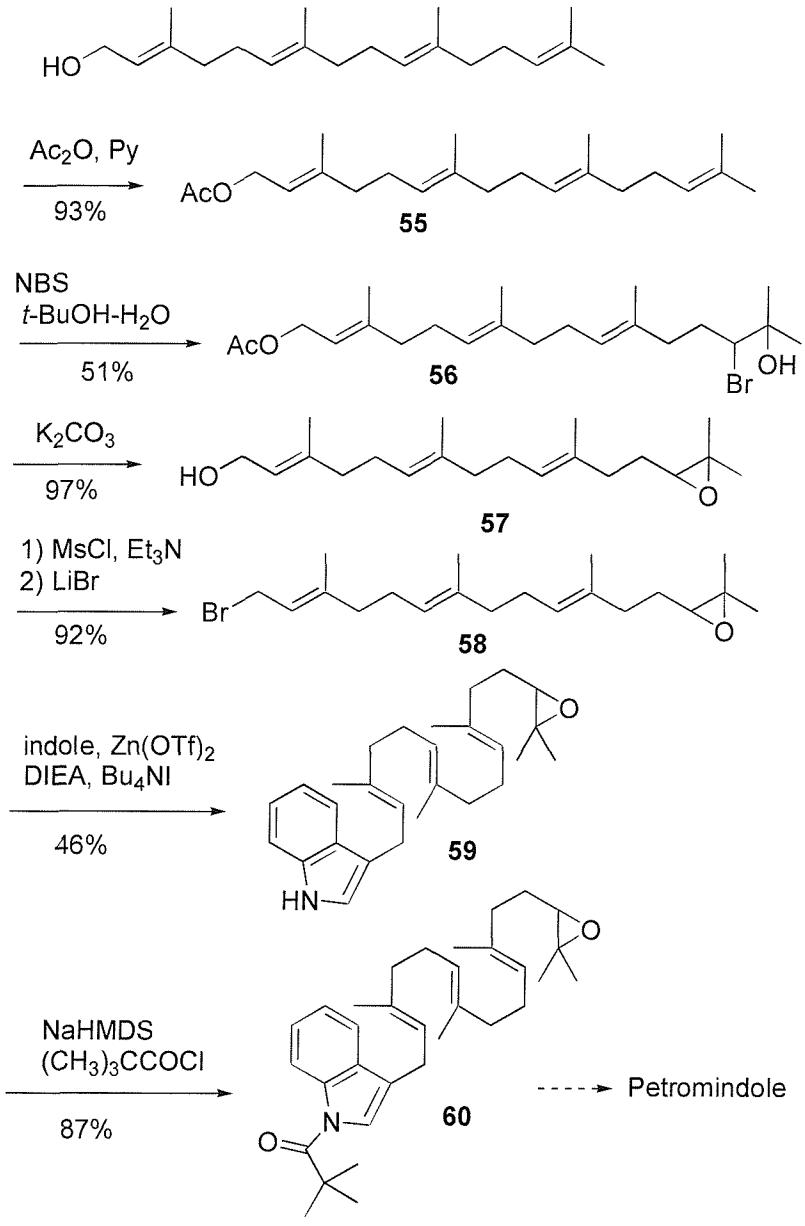


Electron rich arenes are thought to be good terminators. So the polyene cyclization with the 5-methoxyindole derivative was investigated as the electron donating methoxy group would increase the electron density of the benzene ring. Coupling of bromide (**45**) with 5-methoxyindole gave compound (**51**) in 56% yield, which was then protected as pivalamide (**52**) (Scheme 20). Treatment of compound (**52**) with $AlCl_3$ gave C3-C4 cyclization product (**53**) in a low yield,

compound (**54**) now being the major product. The competitive Friedel-Crafts alkylation became predominant in this case.

2.3. Polyene Cyclization with 3-ω-Epoxygeranylgeranyl Indole

Scheme 21



3-Epoxygeranylgeranyl indole (**59**) was prepared in overall 19% yield from geranylgeraniol, after which the nitrogen was then protected with pivaloyl chloride to give (**60**). Treatment of (**60**) with $AlCl_3$ gave a complex reaction by TLC. Fractions collected from column chromatography contain several products from which it has been difficult to identify individual compounds so far.

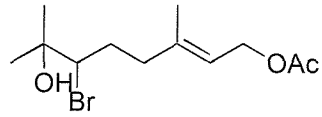
3. Conclusion

Epoxide initiated polyene cyclizations using indole as a terminator were extensively studied. Bicyclization with 3-epoxygeranyl indoles and tricyclization with 3-epoxyfarnesyl indoles proceeded in reasonable yields at the C2-C3 position of indoles. The regiochemistry of cyclization was successfully altered to C3-C4 position by using the *N*-pivaloyl indoles. In polyene tricylization of the farnesyl indole derivative (**48**), a Friedel-Crafts alkylation was competing. This might account for the low efficiency of the tetracyclization as sequential polyene cyclization was not faster than alkylation. In the future, asymmetric generation of the epoxide can be used to give enantio pure products. Further investigation of optimal reaction conditions will be undertaken to provide increased yield and also inhibit the competitive Friedel-Crafts alkylation during polyene cyclization.

Experimental Section

For **General** methods, refer to Chapter 2.

1-Acetate, 6-bromo-3,7-dimethyl-2-octene-1,7-diol (26)



To a solution of geranyl acetate (20 g, 0.10 mol) in *tert*-BuOH (400 mL)-H_2O (300 mL) was added NBS (21.76 g, 0.12 mol) in one portion (the reaction flask was covered with aluminium foil). The reaction mixture was stirred at room temperature for 6 h, then diluted with water and extracted with ether (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (17.25 g, 59%). ^1H and ^{13}C NMR were identical to those reported.[27]

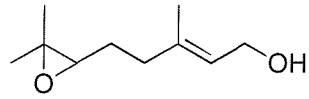
IR ν 3463, 2976, 1715, 1365, 1228 cm^{-1};

^1H NMR δ 1.35 (s, 6H, 2 × CH_3), 1.72 (s, 3H, CH_3), 1.73-1.92 (m, 1H), 2.06 (s, 3H, COCH_3), 2.00-2.25 (m, 2H), 2.35-2.46 (m, 2H), 3.94 (dd, J = 2.2, 11.0 Hz, 1H, BrC*H*), 4.59 (d, J = 7.4 Hz, 2H, OCH_2), 5.41 (dt, J = 1.5, 7.4 Hz, 1H, =C*H*);

^{13}C NMR δ 16.3 (*C*H_3), 20.9 (*C*H_3), 26.1 (*C*H_3), 26.3 (*C*H_3), 31.6 (*C*H_2), 38.0 (*C*H_2), 61.1 (*C*H_2), 69.8 (*C*H), 72.3 (*C*), 119.5 (=*C*H), 140.3 (=*C*), 171.0 (*C*=O);

CIMS *m/z* 310 (M + NH_4^+, 5), 214 (3), 172 (10), 153 (68), 137 (100).

5-(3,3-Dimethyloxiranyl)-3-methyl-2*E*-penten-1-ol (27)
(6,7-Epoxygeraniol, 6,7-Oxidogeraniol)



To a solution of geranyl bromohydrin (**26**) (14.65 g, 0.05 mol) in MeOH (250 mL) and H_2O (40 mL) was added K_2CO_3 (34.55 g, 0.25 mol) The reaction mixture was stirred for 4 h at room temperature. Solvent was evaporated and the residue was

taken up in water and extracted with dichloromethane (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by fast column chromatography with 40% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (8.38 g, 99%). ^1H and ^{13}C NMR were identical to those reported.[28]

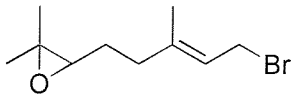
IR ν 3398, 2959, 2923, 1446, 1378, 1115 cm^{-1};

^1H NMR δ 1.27 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.62-1.70 (m, 2H), 2.05-2.28 (m, 2H), 2.35 (s, 1H, O*H*), 2.73 (t, J = 6.3 Hz, 1H, OC*H*), 4.14 (d, J = 6.6 Hz, 2H, CH_2OH), 5.45 (dt, J = 1.4, 6.6 Hz, 1H, =C*H*);

^{13}C NMR δ 16.1 (CH_3), 18.6 (CH_3), 24.7 (CH_3), 27.0 (CH_2), 36.1 (CH_2), 58.4 (*C*), 58.9 (CH_2), 64.0 (*C*H), 124.1 (=*C*H), 137.9 (=*C*);

ESMS *m/z* 188 ($M + NH_4^+$, 8), 146 (20), 105 (99), 100 (27), 59 (100).

3-(5-Bromo-3-methyl-3*E*-pentenyl)-2,2-dimethyl-oxirane (28)
(6,7-Epoxygeranyl bromide)



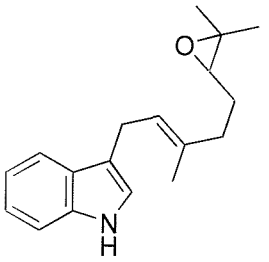
To a stirred solution of (**27**) (1.10 g, 6.47 mmol) and MsCl (0.65 mL, 8.41 mmol) in anhydrous THF (35 mL) was added Et_3N (1.80 mL, 12.94 mmol) at –40 °C. After 45 min, LiBr (2.25 g, 25.88 mmol) in THF (35 mL) was then added to the reaction mixture. The whole reaction mixture was stirred for 1.5 h at 0 °C, then partitioned between hexane (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with hexane (3 × 20 mL). The combined extracts were dried over anhydrous Na_2SO_4. Evaporation of solvent afforded the title compound as a light yellow oil (1.38 g, 92%), which was used without further purification.

^1H NMR δ 1.27 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.63-1.70 (m, 2H), 1.75 (s, 3H, CH_3), 2.10-2.34 (m, 2H), 2.70 (t, J = 6.2 Hz, 1H, OC*H*), 4.02 (d, J = 8.5 Hz, 2H, BrCH_2), 5.58 (dt, J = 1.4, 8.5 Hz, 1H, =C*H*);

^{13}C NMR δ 15.8 (CH_3), 18.6 (CH_3), 24.7 (CH_3), 26.9 (CH_2), 29.1 (CH_2), 36.1 (CH_2), 58.3 (*C*), 63.7 (O*C*H), 121.0 (=*C*H), 142.4 (=*C*);

ESMS *m/z* 255 ($M + Na^+$, 16), 254 (100).

3-[5-(3,3-Dimethyl-oxiranyl)-3-methyl-pent-2-enyl]-1*H*-indole (29)



To a mixture of indole (1.25 g, 10.60 mmol), zinc triflate (2.32 g, 6.36 mmol) and tetrabutylammonium iodide (1.96 g, 5.30 mmol) in anhydrous toluene (40 mL) was added DIEA (2.03 mL, 11.66 mmol) at room temperature under argon. After 15 min, bromide (**28**) (1.24 g, 5.30 mmol) in toluene (15 mL) was added dropwise. The reaction mixture was stirred for 5 h, quenched with saturated NH_4Cl (30 mL), diluted with water and extracted with ether (3 × 40 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a pale yellow oil (982 mg, 69%).

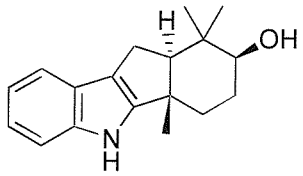
IR ν3410, 3333, 2958, 2912, 1454, 1377, 1222 cm^{-1};

^{1}H NMR δ 1.25 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.63-1.72 (m, 2H), 1.78 (s, 3H, CH_3), 2.09-2.27 (m, 2H), 2.73 (t, J = 6.3 Hz, 1 H, OC*H*), 3.46 (d, J = 7.3 Hz, 2H, ArCH_2), 5.49 (dt, J = 1.5, 7.1 Hz, 1H, =C*H*), 6.90 (d, J = 2.2 Hz, 1H), 7.06-7.22 (m, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.96 (br s, 1H, N*H*);

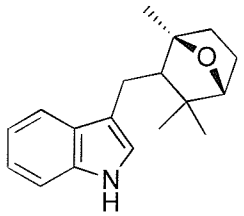
^{13}C NMR δ 16.1 (*C*H_3), 18.7 (*C*H_3), 24.0 (*C*H_2), 24.8 (*C*H_3), 27.4 (*C*H_2), 36.3 (*C*H_2), 58.4 (*C*), 64.2 (O*C*H), 111.0 (*C*H), 115.7 (*C*), 118.9 (*C*H), 119.0 (*C*H), 121.2 (*C*H), 121.8 (*C*H), 123.6 (*C*H), 127.3 (*C*), 134.5 (*C*), 136.4 (*C*);

EIMS *m/z* 269 (M^+, 19), 170 (67), 143 (18), 130 (100), 117 (47).

1,1,4a-Trimethyl-1,2,3,4,4a,5,10,10a-octahedro-indeno[1,2-*b*]indol-2-ol (30) and 3-(1,3,3,-trimethyl-7-oxa-bicyclo[2,2,1]hept-2-ylmethyl)-1*H*-indole (31)



30



31

$MeAlCl_2$ (2.74 mL of a 1 M solution in hexanes, 2.74 mmol) was added to a solution of compound (**29**) (369 mg, 1.37 mmol) in dry CH_2Cl_2 (10 mL) at –78 °C under argon. The solution was stirred for 1 h, then quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography with 40% ethyl acetate in hexane as eluent afforded compound (**30**) (165 mg, 45%) and compound (**31**) (35 mg, 9%).

Compound (**30**) was recrystallized as colourless blades from ethyl acetate/hexane, mp 225-227 °C (decomposed).

IR ν3536, 3250, 1737, 1446, 1000 cm^{-1};

^{1}H NMR (CD_3OD) δ 1.05 (s, 3H, C*H*$_3$), 1.09 (s, 3H, C*H*$_3$), 1.12 (s, 3H, C*H*$_3$), 1.71 (dt, J = 4.1, 13.0 Hz, 1H), 1.71-1.90 (m, 2H), 2.00-2.10 (m, 2H), 2.52 (dd, J = 11.1, 13.1 Hz, 1H, ArCH*H*), 2.62 (dd, J = 6.0, 13.1 Hz, 1H, ArC*H*H), 3.36 (dd, J = 5.0, 11.1 Hz, HOC*H*), 6.86-6.95 (m, 2H), 7.20-7.35 (m, 2H);

^{13}C NMR δ 16.7 (*C*H$_3$), 20.7 (*C*H$_3$), 23.4 (*C*H$_2$), 29.3 (*C*H$_3$), 29.5 (*C*H$_2$), 34.9 (*C*H$_2$), 39.9 (*C*), 43.9 (*C*), 64.0 (*C*H), 80.4 (HO*C*H), 112.6 (*C*H), 116.3 (*C*), 118.9 (*C*H), 119.7 (*C*H), 120.6 (*C*H), 126.5 (*C*), 141.1 (*C*), 153.5 (*C*);

EIMS *m/z* 269 (M^+, 75), 254 (100), 236 (87), 194 (33), 167 (48), 130 (32).

Compound (**31**) was recrystallized as colourless needles from ethyl acetate/hexane, mp 160-162 °C.

IR ν3242, 2953, 1438, 1382, 1102 cm^{-1};

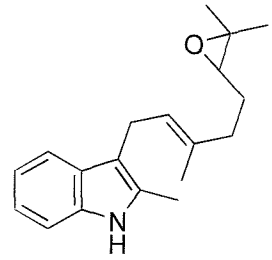
^{1}H NMR δ 1.02 (s, 3H, C*H*$_3$), 1.05 (s, 3H, C*H*$_3$), 1.36 (s, 3H, C*H*$_3$), 1.48-1.80 (m, 3H), 1.90-2.00 (m, 2H), 2.77 (d, J = 7.4 Hz, 2H, ArC*H*$_2$), 3.78 (d, J = 5.2 Hz, 1H,

OC*H*), 6.92 (d, *J* = 2.2 Hz, 1H), 7.08-7.20 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.95 (br s, 1H, N*H*);

^{13}C NMR δ 19.0 (*C*H$_3$), 22.9 (*C*H$_2$), 23.5 (*C*H$_3$), 26.0 (*C*H$_2$), 26.1 (*C*H$_3$), 38.9 (*C*H$_2$), 45.5 (*C*), 54.8 (*C*H), 86.1 (OCH), 86.9 (O*C*), 111.0 (*C*H), 116.4 (*C*), 118.9 (*C*H), 119.1 (*C*H), 121.4 (*C*H), 121.9 (*C*H), 127.5 (*C*), 136.3 (*C*);

CIMS *m/z* 269 (M$^+$, 12), 158 (14), 130 (100).

3-[5-(3,3-Dimethyl-oxiranyl)-3-methyl-pent-2-enyl]-2-methyl-1*H*-indole (32)



To a mixture of 2-methylindole (525 mg, 4 mmol), zinc triflate (872 mg, 2.4 mmol) and tetrabutylammonium iodide (739 mg, 2 mmol) in anhydrous toluene (8 mL) was added DIEA (0.77 mL, 4.4 mmol) at room temperature under argon. After 15 min, bromide (**28**) (466 mg, 2 mmol) in toluene (2 mL) was added to the mixture dropwise. The reaction mixture was stirred for 6 h, quenched with saturated NH_4Cl (15 mL), diluted with water (15 mL) and extracted with ether (3 × 20 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography with 20% ethyl acetate in hexane as eluent afforded the title compound as a yellow oil (330 mg, 58%).

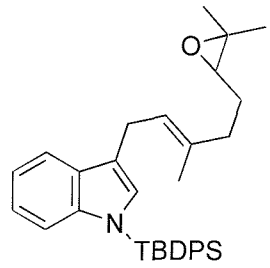
IR ν 3321, 2959, 2923, 1694, 1582, 1448, 1297 cm^{-1};

^{1}H NMR δ 1.22 (s, 6H, 2 × C*H*$_3$), 1.55-1.70 (m, 2H), 1.83 (s, 3H, C*H*$_3$), 2.03-2.18 (m, 2H), 2.34 (s, 3H, C*H*$_3$), 2.68 (t, *J* = 6.3 Hz, 1H, OC*H*), 3.39 (d, *J* = 6.6 Hz, 2H, ArC*H*$_2$), 5.33 (dt, *J* = 1.5, 6.6 Hz, 1H, =C*H*), 7.00-7.15 (m, 2H), 7.22 (d, *J* = 6.6 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.76 (br s, 1H, N*H*);

^{13}C NMR δ 11.7 (*C*H$_3$), 16.2 (*C*H$_3$), 18.7 (*C*H$_3$), 23.1 (*C*H$_2$), 24.8 (*C*H$_3$), 27.3 (*C*H$_2$), 36.2 (*C*H$_2$), 58.4 (*C*), 64.2 (OCH), 110.1 (*C*H), 111.0 (*C*), 118.2 (*C*H), 119.0 (*C*H), 120.8 (*C*H), 124.5 (*C*H), 128.6 (*C*), 130.5 (*C*), 133.3 (*C*), 135.2 (*C*);

EIMS *m/z* 283 (M$^+$, 19), 184 (33), 168 (16), 144 (100), 131 (45).

1-(*tert*-Butyl-diphenyl-silanyl)-3-(5-dimethyloxiranyl-3-methyl-pent-2-enyl)-1*H*-indole (33)



NaHMDS (1.1 mL of a 2 M solution in THF, 2.2 mmol) was added to a solution of compound (**29**) (538 mg, 2.0 mmol) in dry THF (20 mL) at –78 °C under argon. The reaction mixture was stirred for 30 min followed by addition of *tert*-butyl diphenylsilyl chloride (0.62 mL, 2.4 mmol) dropwise. The reaction mixture was warmed slowly to 0 °C over 2 h, poured into water and extracted with ether (3 × 15 mL). The combined organics were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a pale oil (979 mg, 89%).

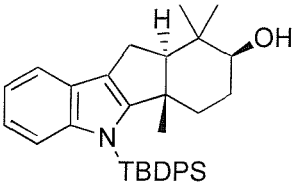
IR ν 2957, 2856, 1448, 1426, 1107 cm^{-1};

^{1}H NMR δ 1.22 (s, 9H), 1.25 (s, 6H), 1.55-1.75 (m, 2H), 1.79 (s, 3H), 2.05-2.25 (m, 2H), 2.72 (t, J = 6.3 Hz, 1H), 3.49 (d, J = 6.6 Hz, 2H), 5.50 (dt, J = 1.4, 6.6 Hz, 1H), 6.65-7.05 (m, 3H), 7.16 (s, 1H), 7.30-7.75 (m, 11H);

^{13}C NMR δ 16.2 (CH_3), 18.7 (CH_3), 19.9 (*C*), 24.2 (CH_2), 24.8 (CH_3), 27.6 (CH_2), 28.3 (3 × CH_3), 36.3 (CH_2), 58.3 (O*C*), 64.2 (O*C*H), 115.5 (*C*H), 118.2 (*C*), 118.6 (*C*H), 119.4 (*C*H), 121.1 (*C*H), 123.6 (*C*H), 128.1 (4 × *C*H), 128.6 (*C*H), 130.1 (2 × *C*H), 131.0 (*C*), 132.5 (*C*), 134.7 (*C*), 135.8 (4 × *C*H), 141.6 (*C*);

ESMS *m/z* 507 (M^+, 3), 275 (15), 156 (49), 143(100), 130 (38).

5-(*tert*-Butyl-diphenyl-silanyl)-1,1,4a-trimethyl-1,2,3,4,4a,5,10,10a-oetahedro-indeno[1,2-*b*]indol-2-ol (34)



$MeAlCl_2$ (0.8 mL of a 1 M solution in hexanes, 0.8 mmol) was added to a solution of compound (**33**) (715 mg, 1.41 mmol) in dry CH_2Cl_2 (8 mL) at –78 °C under argon. The reaction mixture was stirred for 15 min, after which another portion of $MeAlCl_2$ (0.6 mL, 0.6 mmol) was added. The reaction mixture was stirred for 10 min, quenched with saturated NH_4Cl (10 mL) and extracted with ether (3 × 20 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 40% ethyl acetate in hexane as eluent afforded the title compound as an oil (300 mg, 42%).

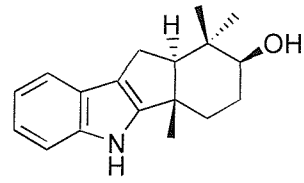
IR ν 3411, 2930, 2859, 1442, 1426, 1101 cm^{-1};

^{1}H NMR δ 0.81 (s, 3H), 0.91 (s, 3H), 1.03 (s, 3H), 1.29 (s, 9H), 1.00-1.30 (m, 4H), 2.00 (dd, J = 6.6, 11.8 Hz, 1H), 2.46 (dd, J = 11.8, 14.0 Hz, 1H), 2.62 (dd, J = 6.6, 14.0 Hz, 1H), 3.18 (dd, J = 5.1, 11.0 Hz, 1H), 6.77-7.15 (m, 3H), 7.27-7.80 (m, 11H);

^{13}C NMR δ 15.8 (CH_3), 19.1 (CH_3), 21.4 (CH_2), 21.8 (C), 28.5 (CH_3), 28.7 (CH_2), 30.2 (3 × CH_3), 33.7 (CH_2), 38.7 (C), 46.1 (C), 62.0 (CH), 78.9 (CH), 117.7 (CH), 118.6 (CH), 119.3 (CH), 119.9 (CH), 123.6 (C), 127.7 (2 × CH), 128.0 (2 × CH), 128.3 (C), 129.9 (CH), 130.1 (CH), 134.2 (C), 135.4 (C), 136.1 (2 × CH), 137.2 (2 × CH), 145.5 (C), 158.6 (C);

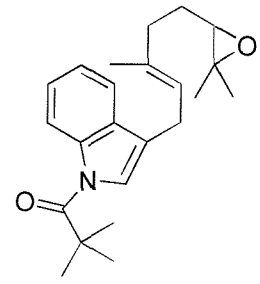
ESMS *m/z* 507 (M^+, 100), 146 (24), 130 (80).

1,1,4a-Trimethyl-1,2,3,4,4a,5,10,10a-octahedro-indeno[1,2-*b*]indol-2-ol (30)



TBAF (0.54 mL of a 1 M solution in THF, 0.54 mmol) was added to a solution of compound (**34**) (228 mg, 0.45 mmol) in THF (5 mL). The reaction mixture was stirred for 2 h at room temperature and partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 15 mL). The combined organics were washed with saturated $NaHCO_3$ (10 mL), water (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 50% ethyl acetate in hexane as eluent afforded the title compound as a white solid (100 mg, 83%). NMR was identical to that of (**30**) obtained by polyene cyclization of (**29**).

1-3-[5-(3,3-Dimethyl-oxiranyl)3-methyl-pent-2-enyl]-indol-1-yl)-2,2-dimethyl-propan-1-one (35)



NaHMDS (1.8 mL of a 2 M solution in THF, 3.6 mmol) was added to a solution of compound (**29**) (940 mg, 3.49 mmol) in THF (20 mL) at –78 °C under argon. The reaction mixture was stirred for 15 min followed by addition of pivaloyl chloride (0.52 mL, 4.19 mmol). The reaction mixture was stirred for another 1 h at that temperature, quenched with saturated aqueous NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 20% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (1.12 g, 91%).

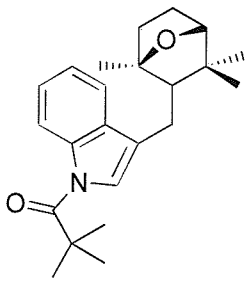
IR ν2958, 2926, 1685, 1447, 1344, 1319, 1177 cm^{-1};

^{1}H NMR δ 1.26 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.50 (s, 9H, 3 × CH_3), 1.60-1.73 (m, 2H), 1.79 (s, 3H, CH_3), 2.26 (m, 2H), 2.73 (t, J = 5.9 Hz, 1H, OC*H*), 3.42 (d, J = 6.6 Hz, 2H, ArCH_2), 5.48 (dt, J = 1.5, 6.6 Hz, 1H, =C*H*), 7.20-7.55 (m, 4H), 8.51 (d, J = 8.8 Hz, 1H);

^{13}C NMR δ 16.2 (*C*H_3), 18.7 (*C*H_3), 23.8 (*C*H_2), 24.8 (*C*H_3), 27.5 (*C*H_2), 28.6 (3 × *C*H_3), 36.3 (*C*H_2), 41.1 (*C*), 58.2 (O*C*), 64.0 (O*C*H), 117.5 (*C*H), 118.6 (*C*H), 121.2 (*C*), 121.7 (*C*H), 122.2 (*C*H), 123.2 (*C*H), 125.2 (*C*H), 129.5 (*C*), 136.3 (*C*), 137.4 (*C*), 176.7 (*C*=O);

CIMS *m/z* 354 (M^+ + 1, 8), 338 (100), 270 (25), 254 (82), 214 (94), 130 (62).

2,2-Dimethyl-1-[3-(1,3,3,-trimethyl-7-oxa-bicyclo[2,2,1]hept-2-ylmethyl)-indol-1-yl]-propan-1-one (36)



$MeAlCl_2$ (1.88 mL of a 1 M solution in hexanes, 1.88 mmol) was added to a solution of compound (**35**) (265 mg, 0.75 mmol) in dry CH_2Cl_2 (10 mL) at –78 °C under argon. The reaction mixture was stirred for 1 h, then quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 20-35% ethyl acetate in hexane as eluent afforded the title compound as a white solid (103 mg, 39%), mp 138-139 °C.

IR ν2939, 1680, 1446, 1319, 1188 cm^{-1};

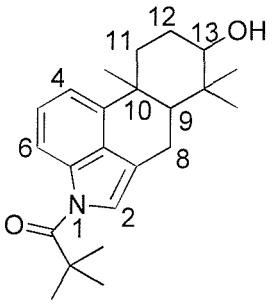
^{1}H NMR δ 1.05 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.51 (s, 9H, 3 × CH_3), 1.50-1.80 (m, 3H), 1.90-2.00 (m, 2H), 2.72 (d, J = 7.4 Hz, 2H, ArCH_2), 3.79 (d, J = 5.2 Hz, 1H, OC*H*), 7.25-7.55 (m, 4H), 8.52 (d, J = 8.1 Hz, 1H);

^{13}C NMR δ 19.0 (*C*H_3), 22.8 (*C*H_2), 23.6 (*C*H_3), 25.9 (*C*H_2), 26.2 (*C*H_3), 28.7 (3 × *C*H_3), 38.8 (*C*H_2), 41.0 (*C*), 45.5 (*C*), 54.3 (*C*H), 86.0 (O*C*H), 86.7 (O*C*), 117.4

(*C*H), 118.4 (*C*H), 121.6 (*C*), 122.4 (*C*H), 123.3 (*C*H), 125.3 (*C*H), 129.5 (*C*), 137.1 (*C*), 176.6 (*C*=O);

CIMS *m/z* 354 (M^+ + 1, 100), 270 (14), 214 (88), 130 (85).

1-(8-Hydroxy-7,7,10a-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-4-aza-acephenanthrylen-4-yl)-2,2-dimethyl-propan-1-one (37)



To a stirred mixture of $AlCl_3$ (395 mg, 2.96 mmol) in CH_2Cl_2 (3 mL) was added compound (**35**) (260 mg, 0.74 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 45 min, then poured into ice-water. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 30% ethyl acetate in hexane as eluent afforded (**36**) as a white solid (67 mg, 26%) and (**37**) as a white solid (48 mg, 18%).

Compound (**37**): mp 195-196 °C;

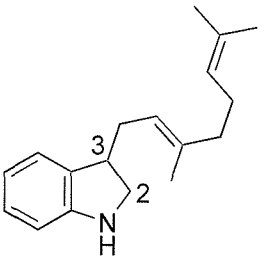
IR ν3342, 2929, 1738, 1673, 1322 cm^{-1};

^{1}H NMR δ 1.03 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.51 (s, 9H, 3 × CH_3), 1.64 (dd, J = 3.5, 12.5 Hz, 1H, C^9H), 1.70-1.80 (m, 1H, C^{11}HH), 1.80-1.92 (m, 2H, C$^{12}H_2$), 2.41 (td, J = 3.0, 12.5 Hz, 1H, C^{11}HH), 2.70-3.00 (m, 2H, ArC$^8H_2$), 3.32 (m, 1H, HOC^{13}H), 7.03 (d, J = 7.5 Hz, 1H), 7.28 (m, 1H), 7.39 (d, J = 2.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H);

^{13}C NMR δ 15.5 (*C*H_3), 19.1 (*C*H_2), 23.7 (*C*H_3), 27.6 (*C*H_2), 28.3 (*C*H_3), 28.6 (3 × *C*H_3), 34.8 (*C*H_2), 37.2 (*C*), 39.4 (*C*), 40.9 (*C*), 51.3 (*C*^{9}H), 78.6 (HO*C*H), 115.0 (*C*H), 116.2 (*C*H), 118.5 (*C*H), 119.3 (*C*), 126.1 (*C*H), 126.4 (*C*), 135.1 (*C*), 143.7 (*C*), 177.0 (*C*=O);

ESMS *m/z* 354 (M^+ + 1, 12), 146 (100).

3-(3,7-Dimethyl-octa-2,6-dienyl)-2,3-dihydro-1*H*-indole (38)



To a stirred solution of 3-geranyl indole (520 mg, 2.05 mmol) in acetic acid (3 mL) and dichloromethane (3 mL) was added $NaCNBH_3$ (386 mg, 6.15 mmol) in one portion at 15 °C under argon (exothermic reaction, temperature maintained using ice-water bath). The reaction mixture was stirred for 1.5 h, poured into ice-water adjusted to pH 8 using NaOH pellet, and extracted with dichloromethane (3 × 15 mL). The combined organics were washed with water, brine and dried. Evaporation of solvent and purification of the residue by column chromatography with 15% ether in petroleum ether as eluent afforded the title compound as a colourless oil (267 mg, 51%).

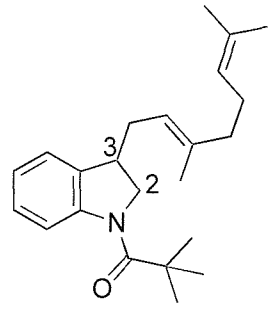
IR ν 3380, 2912, 1606, 1485, 1461, 1245 cm^{-1};

^{1}H NMR δ 1.59 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.95-2.15 (m, 4H), 2.20-2.50 (m, 2H, C^3HCH_2CH=), 3.19 (m, 1H, C^2HH), 3.30 (m, 1H, C^3H), 3.62 (m, 1H, C^2HH), 5.08 (br t, J = 7.0 Hz, 1H, =C*H*), 5.22 (br t, J = 7.0 Hz, 1H, =C*H*), 6.62 (d, J = 7.5 Hz, 1H), 6.70 (t, J = 7.5 Hz, 1H), 7.01 (m, 1H), 7.10 (d, J = 7.0 Hz, 1H);

^{13}C NMR δ 16.2 (*C*H_3), 17.7 (*C*H_3), 25.7 (*C*H_3), 26.6 (*C*H_2), 32.5 (C^3HCH_2CH=), 39.8 (*C*H_2), 42.4 (C^3H), 53.0 (C^2H_2), 109.5 (*C*H), 118.6 (*C*H), 122.1 (=*C*H), 123.9 (*C*H), 124.3 (=CH), 127.4 (*C*H), 131.4 (*C*), 133.0 (*C*), 136.7 (*C*), 151.4 (*C*);

EIMS *m/z* 255 (M^+, 45), 118 (100), 91 (40).

1-[3-(3,7-Dimethyl-octa-2,6-dienyl)-2,3-dihydro-indol-1-yl]-2,2-dimethyl-propan-1-one (39)



To a stirred solution of (**38**) (400 mg, 1.57 mmol) and Et_3N (0.33 mL, 2.35 mmol) in dichloromethane (8 mL) was added pivaloyl chloride (0.29 mL, 2.35 mmol) dropwise at 0 °C. The reaction mixture was stirred for 4 h at room temperature, poured into water and extracted with dichloromethane (3 × 15 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 20% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (533 mg, 100%).

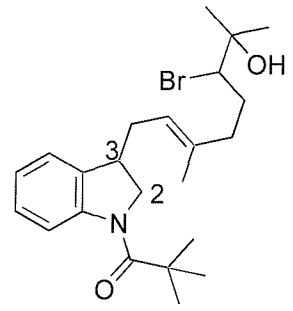
IR ν 2967, 1700, 1645, 1476, 1358, 1186 cm^{-1};

^{1}H NMR δ 1.36 (s, 9H, 3 × CH_3), 1.57 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.95-2.15 (m, 4H), 2.20-2.45 (m, 2H, C^{3}HCH_2CH=), 3.25-3.40 (m, 1H, C^3H), 3.93 (dd, J = 5.1, 10.3 Hz, C^2HH), 4.20 (dd, J = 8.8, 10.3 Hz, C^{2}HH), 5.09 (br t, J = 6.0 Hz, =CH), 5.17 (t, J = 6.6 Hz, =CH), 7.00-7.26 (m, 3H), 8.22 (d, J = 8.0 Hz, 1H);

^{13}C NMR δ 16.3 (*C*H$_3$), 17.7 (*C*H$_3$), 25.7 (*C*H$_3$), 26.5 (*C*H$_2$), 27.6 (3 × *C*H$_3$), 33.1 (*C*H$_2$), 39.8 (*C*H$_2$), 40.1 (*C*), 41.4 (*C*^{3}H), 54.9 (*C*^{2}H$_2$), 118.3 (*C*H), 120.9 (=*C*H), 123.58 (*C*H), 123.59 (*C*H), 124.0 (=CH), 127.6 (*C*H), 131.6 (*C*), 134.6 (*C*), 138.0 (*C*), 144.5 (*C*), 176.5 (*C*=O);

EIMS *m/z* 339 (M$^+$, 7), 202 (52), 118 (100), 85 (84).

1-[3-(6-Bromo-7-hydroxy-3,7-dimethyl-oct-2-enyl)-2,3-dihydro-indol-1-yl]-2,2-dimethyl-propan-1-one (40)



To a stirred solution of (**39**) (500 mg, 1.47 mmol) in *tert*-BuOH (8 mL) and H_2O (6 mL) was added NBS (263 mg, 1.47 mmol) in one portion at room temperature. The reaction mixture was stirred for 6 h, diluted with water (20 mL) and extracted with ether (3 × 15 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 20% ethyl acetate in hexane afforded two isomers in a ratio of 1:1 (405 mg, 63%).

Isomer 1:

IR ν 3450, 2969, 1627, 1475, 1359, 1188 cm^{-1};

^{1}H NMR δ 1.33 (s, 6H, 2 × C*H*$_3$), 1.36 (s, 9H, 3 × C*H*$_3$), 1.51 (s, 3H, C*H*$_3$), 1.65-2.50 (m, 6H), 3.30-3.48 (m, 1H, C^3*H*), 3.86 (m, 1H, BrC*H*), 3.94 (dd, J = 5.1, 10.3 Hz, 1H, C^2*H*H), 4.21 (dd, J = 8.8, 10.3 Hz, 1H, C^{2}H*H*), 5.22 (t, J = 6.7 Hz, 1H, =C*H*), 7.00-7.23 (m, 3H), 8.21 (d, J = 8.0 Hz, 1H);

^{13}C NMR δ 16.1 (*C*H$_3$), 26.17 (*C*H$_3$), 26.26 (*C*H$_3$), 27.6 (3 × *C*H$_3$), 31.8 (*C*H$_2$), 33.1 (*C*H$_2$), 38.2 (*C*H$_2$), 40.1 (*C*), 41.2 (*C*H), 54.8 (*C*H$_2$), 69.9 (*C*H), 72.5 (HO*C*), 118.3 (*C*H), 121.9 (*C*H), 123.7 (2 × *C*H), 127.7 (*C*H), 134.3 (*C*), 136.3 (*C*), 144.5 (*C*), 176.6 (*C*=O);

CIMS *m/z* 356 (M^+ - 79, 32), 202 (100), 272 (18), 118 (80).

Isomer 2:

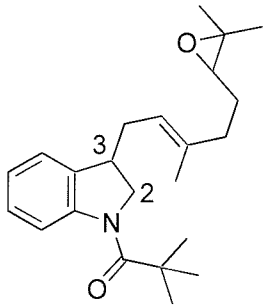
IR ν 3436, 2969, 1626, 1475, 1359 cm^{-1};

^{1}H NMR δ 1.34 (s, 6H, 2 × C*H*$_3$), 1.37 (s, 9H, 3 × C*H*$_3$), 1.55 (s, 3H, C*H*$_3$), 1.65-2.50 (m, 6H), 3.25-3.45 (m, 1H, C^3*H*), 3.92-3.97 (m, 2H, BrC*H* + C^2*H*H), 4.22 (dd, J = 8.8, 10.3 Hz, 1H, C^{2}H*H*), 5.26 (t, J = 6.6 Hz, 1H, =C*H*), 7.00-7.23 (m, 3H), 8.21 (d, J = 8.0 Hz, 1H);

^{13}C NMR δ 16.1 (CH_3), 26.0 (CH_3), 26.6 (CH_3), 27.6 (3 × CH_3), 31.8 (CH_2), 33.1 (CH_2), 38.2 (CH_2), 40.2 (*C*), 41.3 (*C*H), 55.0 (CH_2), 70.4 (*C*H), 72.4 (HO*C*), 118.4 (*C*H), 122.4 (*C*H), 123.59 (*C*H), 123.64 (*C*H), 127.7 (*C*H), 134.4 (*C*), 136.2 (*C*), 144.4 (*C*), 176.6 (*C*=O);

CIMS *m/z* 356 (M^+ - 79, 94), 272 (50), 202 (100), 118 (94).

1-{3-[5[(3,3-Dimethyl-oxiranyl)-3-methyl-pent-2-enyl]-2,3-dihydro-indol-1-yl}-2,2-dimethyl-propan-1-one (41)



To a stirred solution of (**40**) (340 mg, 0.78 mmol) in MeOH (5 mL) and H_2O (1 mL) was added K_2CO_3 (640 mg, 4.64 mmol). The reaction mixture was stirred for 4 h at room temperature. Solvent was evaporated, the residue taken up in water (20 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried with anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 30% ethyl acetate in hexane as eluent afforded the title compound as a yellow oil (276 mg, 100%).

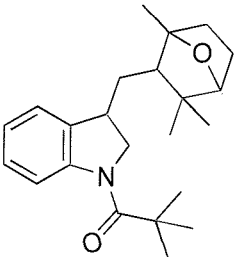
IR ν 2957, 1642, 1475, 1358, 1185 cm^{-1};

^{1}H NMR δ 1.27 (s, 3H), 1.31 (s, 3H), 1.36 (s, 9H), 1.60 (s, 3H), 1.50-1.70 (m, 2H), 2.10-2.50 (m, 4H), 2.70 (t, J = 6.3 Hz, 1H, OC*H*), 3.25-3.45 (m, 1H, C^3H), 3.92 (dd, J = 5.2, 10.3 Hz, 1H, C^2HH), 4.21 (dd, J = 8.8, 10.3 Hz, 1H, C^2HH), 5.23 (br t, J = 7.0 Hz, 1H, =C*H*), 6.95-7.25 (m, 3H), 8.22 (d, J = 8.1 Hz, 1H);

^{13}C NMR δ 16.25/16.31 (CH_3), 18.7 (CH_3), 24.9 (CH_3), 27.4 (CH_2), 27.6 (3 × CH_3), 33.00/33.08 (CH_2), 36.46/36.56 (CH_2), 40.1 (*C*), 41.27/41.32 (*C*H), 54.88/54.91 (CH_2), 58.19/58.28 (*C*), 63.97/63.99 (*C*H), 118.3 (*C*H), 121.4/121.5 (*C*H), 123.52/123.54 (*C*H), 123.57 (*C*H), 127.7 (*C*H), 134.41/134.45 (*C*), 137.11/137.16 (*C*), 144.5 (*C*), 176.49/176.53 (*C*=O);

CIMS *m/z* 356 (M^+ + 1, 100), 202 (29).

2,2-Dimethyl-1-[3-(1,3,3-trimethyl-7-oxa-bicyclo[2.2.1]hept-2-ylmethyl)-2,3-dihydro-indol-1-yl]-propan-one (42)



To a stirred suspension of $AlCl_3$ (389 mg, 2.92 mmol) in dichloromethane (6 mL) was added compound (**41**) (260 mg, 0.73 mmol) in dichloromethane (2 mL) at room temperature under argon. The reaction mixture was stirred for 20 min, poured into ice-water, extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a pale yellow oil (80 mg, 31%).

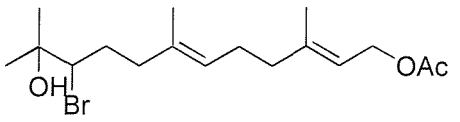
IR ν2960, 1640, 1475, 1358, 1185 cm^{-1};

^{1}H NMR δ 1.00/1.13 (s, 3H), 1.16/1.17 (s, 3H), 1.37/1.40 (s, 3H), 1.39 (s, 9H), 1.14-2.10 (m, 7H), 3.20 (m, 1H), 3.78 (dd, J = 2.2, 5.1 Hz, 1H), 3.80-4.35 (m, 2H), 6.95-7.20 (m, 3H), 8.20 (m, 1H);

^{13}C NMR δ 18.9 (CH_3), 23.5/24.1 (CH_3), 25.7/25.8 (CH_2), 26.0/26.5 (CH_3), 27.9 (3 × CH_3), 32.8/33.3 (CH_2), 38.9/39.0 (CH_2), 40.04/40.06 (*C*), 40.3 (*C*H), 45.2/45.6 (*C*), 53.1/53.3 (*C*H), 55.4/56.0 (CH_2), 85.9/86.2 (O*C*H), 86.5/86.6 (O*C*), 118.5/118.6 (*C*H), 123.2/123.68 (*C*H), 123.72/123.81 (*C*H), 127.8 (*C*H), 135.04/123.06 (*C*), 144.0/144.1 (*C*), 176.3/176.5 (*C*=O);

GC-EIMS t_R 16.85 min, *m/z* 355 (M^+, 7), 118 (53), 57 (100); t_R 16.90 min, *m/z* 355 (M^+, 8), 118 (54), 57 (100).

1-Acetate, 10-bromo-3,7,11-trimethyl-2*E*,6*E*-dodecadiene-1,11-diol (43)



To a solution of farnesyl acetate (1 g, 3.78 mmol) in *tert*-BuOH (20 mL)-H_2O (15 mL) was added NBS (0.74 g, 4.16 mmol) in one portion. The reaction mixture was

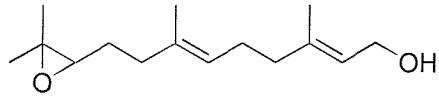
stirred at room temperature for 6 h, diluted with water and extracted with ether. The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexanes as eluent afforded the title compound as a pale yellow oil (832 mg, 61%).

IR ν3430, 2973, 2931, 1735, 1365, 1228, 1020 cm^{-1};

^{1}H NMR δ 1.34 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.70-2.40 (m, 8H), 2.06 (s, 3H, COCH_3), 3.96 (m, 1H, BrC*H*), 4.59 (d, J = 6.6 Hz, 2H, OCH_2), 5.19 (t, J = 6.7 Hz, 1H, =C*H*), 5.34 (dt, J = 1.5, 6.9 Hz, 1H, =C*H*);

^{13}C NMR δ 15.8 (*C*H_3), 16.4 (*C*H_3), 21.1 (*C*H_3), 25.9 (*C*H_3), 26.1 (*C*H_2), 26.5 (*C*H_3), 32.0 (*C*H_2), 38.1 (*C*H_2), 39.3 (*C*H_2), 61.4 (O*C*H_2), 70.7 (Br*C*H), 72.4 (*C*), 118.4 (=*C*H), 125.3 (=*C*H), 133.5 (=*C*), 142.0 (=*C*), 171.2 (*C*=O).

9-(3,3-Dimethyloxiranyl)-3,7-dimethyl-2*E*,6*E*-nonadien-1-ol (44)
(10,11-Epoxyfarnesol)



To a solution of farnesyl bromohydrin (**43**) (560 mg, 1.55 mmol) in MeOH (10 mL) and H_2O (1 mL) was added K_2CO_3 (1.30 g, 9.3 mmol). The reaction mixture was stirred for 4 h at room temperature. Solvent was evaporated, the residue taken up in water, and extracted with dichloromethane (3 × 20 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 50% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (370 mg, 100%). ^{1}H and ^{13}C NMR were identical to those reported.[29]

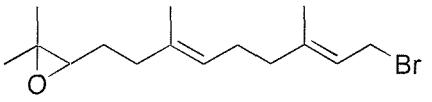
IR ν3380, 2959, 2920, 1444, 1377, 1000 cm^{-1};

^{1}H NMR δ 1.26 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.60-1.65 (m, 2H), 1.67 (s, 3H, CH_3), 2.00-2.20 (m, 6H), 2.68 (t, J = 6.2 Hz, 1H, OC*H*), 4.13 (d, J = 6.6 Hz, 2H, OCH_2), 5.14 (t, J = 6.7 Hz, 1H, =C*H*), 5.38 (dt, J = 1.4, 6.6 Hz, 1H, =C*H*);

^{13}C NMR δ 15.9 (CH_3), 16.1 (CH_3), 18.7 (CH_3), 24.8 (CH_3), 26.1 (CH_2), 27.2 (CH_2), 36.2 (CH_2), 39.3 (CH_2), 58.4 (C), 59.2 (CH_2), 64.1 (OCH), 123.6 (=CH), 124.5 (=CH), 134.2 (=C), 139.0 (=C);

CIMS *m/z* 239 (M^+ + 1, 11), 222 (100), 203 (72), 135 (20).

3-(9-Bromo-3*E*,7*E*-dimethyl-3,7-nonadienyl)-2,2-dimethyl oxirane (45)

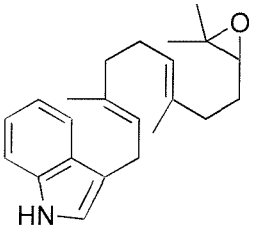


To a stirred solution of compound (**44**) (375 mg, 1.57 mmol) and MsCl (0.16 mL, 2.05 mmol) in anhydrous THF (6 mL) was added Et_3N (0.44 mL, 3.14 mmol) at –40 °C. After 45 min, LiBr (545 mg, 6.28 mmol) in THF (4 mL) was then added. The reaction mixture was stirred for 2 h at 0 °C, and partitioned between hexane (20 mL) and water (25 mL). The organic layer was separated, and the aqueous layer extracted with hexane (3 × 15 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent afforded the title compound as a light yellow oil (452 mg, 96%), which was used without further purification.

^{1}H NMR δ 1.26 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.60-1.70 (m, 2H), 1.73 (s, 3H, CH_3), 2.06-2.16 (m, 6H), 2.70 (t, J = 6.2 Hz, 1H, OCH), 4.02 (d, J = 8.1 Hz, 2H, BrCH_2), 5.13 (br t, J = 6.6 Hz, 1H, =CH), 5.53 (br t, J = 7.6 Hz, 1H, =CH);

^{13}C NMR δ 15.9 (CH_3), 16.0 (CH_3), 18.7 (CH_3), 24.9 (CH_3), 26.0 (CH_2), 27.4 (CH_2), 29.6 (CH_2), 36.2 (CH_2), 39.4 (CH_2), 58.3 (C), 64.1 (OCH), 120.6 (=CH), 123.9 (=CH), 134.7 (=C), 143.4 (=C).

3-[9-(3,3-Dimethyl-oxiranyl)-3,7-dimethyl-nona-2*E*,6*E*-dienyl]-1*H*-indole (46)



To a mixture of indole (2.78 g, 23.78 mmol), zinc triflate (5.19 g, 14.27 mmol) and tetrabutylammonium iodide (4.39 g, 11.89 mmol) in anhydrous toluene (60 mL) was added DIEA (4.56 mL, 26.16 mmol) at room temperature under argon. After 15 min, bromide (**45**) (3.58 g, 11.89 mmol) in toluene (10 mL) was added dropwise. The reaction mixture was stirred for 6 h, quenched with saturated NH_4Cl (30 mL), diluted with water and extracted with ether (3 × 40 mL). The combined organics were washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 20% ether in hexane as eluent afforded the title compound as a colourless oil (2.22 g, 55%).

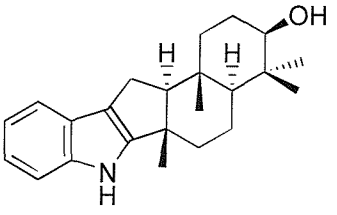
IR ν3413, 2915, 1454, 1377, 1090 cm^{-1};

^{1}H NMR δ 1.24 (s, 3H), 1.30 (s, 3H), 1.61 (s, 3H), 1.55-1.65 (m, 2H), 1.75 (s, 3H), 1.90-2.20 (m, 6H), 2.71 (t, J = 5.8 Hz, 1H), 3.45 (d, J = 6.6 Hz, 2H), 5.18 (t, J = 6.6 Hz, 1H), 5.45 (br t, J = 7.1 Hz, 1H), 6.90 (d, J = 1.5 Hz, 1H), 7.00-7.20 (m, 2H), 7.32 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 7.4 Hz, 1H), 8.09 (br s, 1H, N*H*);

^{13}C NMR δ 15.9 (*C*H_3), 16.0 (*C*H_3), 18.7 (*C*H_3), 23.9 (*C*H_2), 24.9 (*C*H_3), 26.4 (*C*H_2), 27.4 (*C*H_2), 36.3 (*C*H_2), 39.5 (*C*H_2), 58.5 (O*C*), 64.3 (O*C*H), 111.0 (*C*H), 115.9 (*C*), 118.9 (*C*H), 119.0 (*C*H), 121.3 (*C*H), 121.8 (*C*H), 123.2 (*C*H), 124.8 (*C*H), 127.4 (*C*), 134.0 (*C*), 135.3 (*C*), 136.5 (*C*);

ESMS *m/z* 337 (M^+, 7), 249 (96), 192 (100), 130 (75).

4,4,6a,12a,12b-Tetramethyl-1,2,3,4,4a,5,6,6a,7,12,12a,12b-dodecahydro-7-aza-benzo[4,5]pentaleno[2,1-*a*]naphthalene-3-ol (47)



To a stirred suspension of $AlCl_3$ (494 mg, 3.70 mmol) in dichloromethane (4 mL) was added compound (**46**) (250 mg, 0.74 mmol) in dichloromethane (2 mL) at room temperature under argon. The reaction mixture was stirred for 20 min, poured into ice-water (20 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4.

Evaporation of solvent and purification of the residue by column chromatography with 20% ethyl acetate in hexane as eluent afforded the title compound as a white solid (35 mg, 14%), which was recrystallized from ethyl acetate/hexane to give colourless crystals, mp 249-251 °C (decomposed).

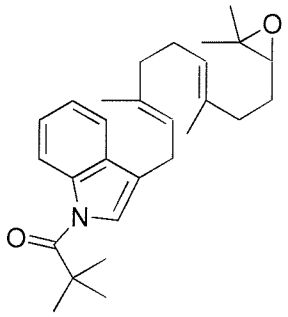
IR ν3490, 2920, 1440, 1090 cm^{-1};

^{1}H NMR (CD_3OD) δ0.90 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.05-1.10 (m, 1H), 1.17 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.25-1.45 (m, 1H), 1.65-1.85 (m, 6H), 2.15-2.28 (m, 2H), 2.51 (dd, J = 11.0, 13.0 Hz, 1H, ArCH*H*), 2.61 (dd, J = 6.0, 13.0 Hz, 1H, ArC*H*H), 3.25 (dd, J = 4.5, 11.6 Hz, 1H, HOC*H*), 6.94-7.00 (m, 2H), 7.25-7.38 (m, 2H);

^{13}C NMR δ 15.8 (*C*H_3), 17.4 (*C*H_3), 20.2 (*C*H_2), 21.9 (*C*H_3), 22.9 (*C*H_2), 27.9 (*C*H_2), 28.7 (*C*H_3), 37.7 (*C*H_2), 38.4 (*C*), 39.7 (*C*H_2), 40.1 (*C*), 44.4 (*C*), 57.9 (*C*H), 69.6 (*C*H), 79.9 (HO*C*H), 112.6 (*C*H), 115.9 (*C*), 118.8 (*C*H), 119.6 (*C*H), 120.5 (*C*H), 126.5 (*C*), 141.0 (*C*), 153.9 (*C*);

ESMS *m/z* 337 (M^+, 10), 146 (100).

1-{3-[9-(3,3-Dimethyl-oxiranyl)-3,7-dimethyl-nona-2*E*,6*E*-dienyl]-indol-1-yl}-2,2-dimethyl-propan-1-one (48)



NaHMDS (1.8 mL of a 2 M solution in THF, 3.60 mmol) was added to a solution of compound (**46**) (1.20 g, 3.56 mmol) in THF (20 mL) at −78 °C under argon. After 15 min, pivaloyl chloride (0.53 mL, 4.27 mmol) was added. The reaction mixture was stirred for 1 h at that temperature, quenched with saturated aqueous NH_4Cl (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (1.38 g, 92%).

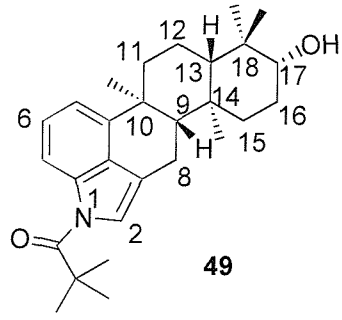
IR ν2958, 1686, 1447, 1319, 1177 cm^{-1};

^{1}H NMR δ 1.25 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.50 (s, 9H, 3 × CH_3), 1.50-1.70 (m, 2H), 1.62 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.03-2.20 (m, 6H), 2.69 (t, J = 6.2 Hz, 1H, OC*H*), 3.40 (d, J = 6.6 Hz, 2H, ArCH_2), 5.17 (t, J = 6.6 Hz, 1H, =C*H*), 5.42 (t, J = 6.6 Hz, 1H, =C*H*), 7.24 -7.38 (m, 2H), 7.44 (s, 1H), 7.49 (d, J = 7.4 Hz, 1H), 8.51 (d, J = 8.1 Hz, 1H);

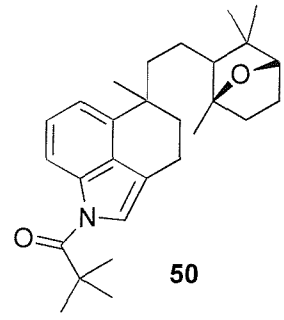
^{13}C NMR δ 16.0 (*C*H_3), 16.2 (*C*H_3), 18.7 (*C*H_3), 23.8 (*C*H_2), 24.9 (*C*H_3), 26.8 (*C*H_2), 27.4 (*C*H_2), 28.6 (3 × *C*H_3), 36.3 (*C*H_2), 39.6 (*C*H_2), 41.0 (*C*), 58.3 (*C*), 64.1 (O*C*H), 117.4 (*C*H), 118.6 (*C*H), 121.2 (*C*H), 121.4 (*C*), 122.2 (*C*H), 123.2 (*C*H), 124.5 (*C*H), 125.2 (*C*H), 129.5 (*C*), 134.3 (*C*), 137.1 (*C*), 137.4 (*C*), 176.7 (*C*=O);

ESMS *m/z* 444 (M + Na^+, 38), 420 (7), 212 (30), 192 (100).

1-(9-Hydroxy-6b,10,10,12a-tetramethyl-6a,6b,7,8,9,10,10a,11,12,12a-decahydro-6*H*-4-aza-cyclopenta[*hi*]chrysten-4-yl)-2,2-dimethyl-propan-1-one (49) and 2,2-dimethyl-1-{5-methyl-5-[2-(1,3,3-trimethyl-7-oxa-bicyclo[2.2.1]hept-2-yl)-ethyl]-4,5-dihydro-3*H*-benzo[*cd*]indol-1-yl}-propan-1-one (50)



49



50

To a stirred suspension of $AlCl_3$ (316 mg, 2.37 mmol) in dry CH_2Cl_2 (6 mL) was added compound (**48**) (250 mg, 0.59 mmol) in CH_2Cl_2 (2 mL) dropwise under argon. The reaction mixture was stirred for 35 min, poured into ice-water (20 mL), and extracted with dichloromethane (3 × 15 mL). The combined organics were washed with water and brine, dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15-35% ethyl acetate in hexane as eluent gave compound (**49**) as a white solid (38 mg, 15%) and compound (**50**) as a pale yellow oil (40 mg, 16%). Compound (**49**) was

recrystallised from ethyl acetate/hexane to give colourless crystals, mp 248-250 °C.

Compound (**49**):

IR ν 3500, 2930, 1686, 1434, 1167 cm^{-1};

^{1}H NMR δ 0.86 (s, 3H, CH_3), 0.90 (m, 1H, C^{13}H), 1.01 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.10 (m, 1H), 1.18 (s, 3H, CH_3), 1.50 (s, 9H, 3 × CH_3), 1.55 (dd, J = 3.5, 13.0 Hz, 1H, C^9H), 1.60-1.82 (m, 5H), 1.90 (td, J = 3.5, 13.0 Hz, 1H), 2.51 (m, 1H), 2.60-2.93 (m, 2H, ArC$^8H_2$), 3.20 (m, 1H, HOC^{17}H), 7.03 (d, J = 7.5 Hz, 1H), 7.26 (m, 1H), 7.35 (d, J = 1.5 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H);

^{13}C NMR δ 15.5 (*C*H_3), 16.3 (*C*H_3), 18.2 (*C*H_2), 18.5 (*C*H_2), 24.8 (*C*H_3), 27.3 (*C*H_2), 28.1 (*C*H_3), 28.7 (3 × *C*H_3), 37.4 (*C*), 37.8 (*C*), 38.62 (*C*H_2), 38.69 (*C*H_2), 38.9 (*C*), 40.9 (*C*), 55.5 (*C*^{13}H), 56.4 (*C*^{9}H), 78.7 (HO*C*H), 114.8 (*C*H), 116.3 (*C*H), 118.4 (*C*H), 119.5 (*C*), 126.1 (*C*H), 126.3 (*C*), 135.1 (*C*), 144.5 (*C*), 176.9 (*C*=O);

ESMS *m/z* 421 (M^+, 3), 146 (100).

Compound (**50**):

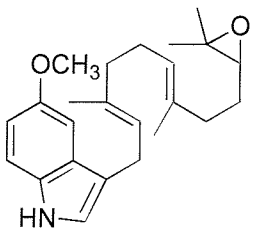
IR ν 2926, 1680, 1460, 1252 cm^{-1};

^{1}H NMR δ 0.91/0.99 (s, 3H), 1.00 (s, 3H), 1.24/1.29 (s, 3H), 1.33/1.34 (s, 3H), 1.51 (s, 9H), 1.00-2.00 (m, 11H), 2.82 (t, J = 5.9 Hz, 2H), 3.69 (dd, J = 2.9, 5.1 Hz, 1H, OC*H*), 7.11 (d, J = 8.1 Hz, 1H), 7.25-7.33 (m, 1H), 7.38 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H);

^{13}C NMR δ 18.3 (*C*H_2), 18.8/19.0 (*C*H_3), 22.06/22.11 (*C*H_2), 23.2/23.4 (*C*H_3), 25.66/25.71 (*C*H_2), 25.8/26.1 (*C*H_3), 26.16/26.22 (*C*H_3), 28.6 (3 × *C*H_3), 35.6/36.2 (*C*H_2), 36.90/36.93 (*C*), 38.9 (*C*H_2), 40.79/40.82 (*C*H_2), 40.85 (*C*), 45.21/45.25 (*C*), 56.49/56.52 (*C*H), 86.01/86.02 (O*C*H), 86.70/86.75 (O*C*), 114.87/114.90 (*C*H), 118.26/118.41 (*C*H), 118.43/118.55 (*C*H), 118.73/118.75 (*C*), 125.57/125.65 (*C*H), 127.19/127.21 (*C*), 135.4 (*C*), 139.4/139.5 (*C*), 176.9 (*C*=O);

ESMS *m/z* 422 (M^+ + 1, 5), 146 (100).

3-[9-(3,3-Dimethyl-oxiranyl)-3,7-dimethyl-nona-2*E*,6*E*-dienyl]-5-methoxy-1*H*-indole (51)



To a mixture of 5-methoxyindole (555 mg, 3.77 mmol), zinc triflate (824 mg, 2.27 mmol) and tetrabutylammonium iodide (698 mg, 1.89 mmol) in anhydrous toluene (8 mL) was added DIEA (0.72 mL, 4.16 mmol) at room temperature under argon. After 15 min, bromide (**45**) (568 mg, 1.89 mmol) in toluene (2 mL) was added dropwise. The reaction mixture was stirred for 6 h, quenched with saturated NH_4Cl (10 mL), diluted with water (10 mL) and extracted with ether (3 × 15 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 30% ether in hexane as eluent afforded the title compound as pale yellow oil (390 mg, 56%).

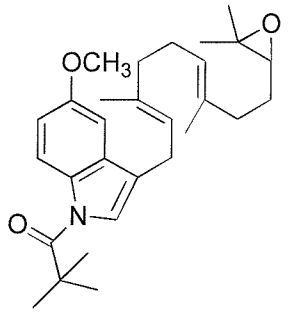
IR ν 3340, 2918, 1738, 1483, 1210 cm^{-1};

^{1}H NMR δ 1.24 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.58-1.65 (m, 2H), 1.76 (s, 3H, CH_3), 2.00-2.20 (m, 6H), 2.71 (t, J = 6.3 Hz, 1H, OC*H*), 3.41 (d, J = 7.3 Hz, 2H, ArCH_2), 3.85 (s, 3H, OCH_3), 5.18 (br t, J = 6.3 Hz, 1H, =C*H*), 5.45 (br t, J = 6.6 Hz, 1H, =C*H*), 6.84 (dd, J = 2.2, 8.8 Hz, 1H), 6.90 (d, J = 2.2 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 8.03 (br s, 1H, N*H*);

^{13}C NMR δ 15.96 (*C*H_3), 16.05 (*C*H_3), 18.7 (*C*H_3), 24.0 (*C*H_2), 24.9 (*C*H_3), 26.4 (*C*H_2), 27.4 (*C*H_2), 36.3 (*C*H_2), 39.6 (*C*H_2), 55.9 (O*C*H_3), 58.5 (*C*), 64.3 (O*C*H), 100.8 (*C*H), 111.8 (*C*H), 111.9 (*C*H), 115.5 (*C*), 122.2 (*C*H), 123.0 (*C*H), 124.7 (*C*H), 127.8 (*C*), 131.6 (*C*), 134.1 (*C*), 135.3 (*C*), 153.7 (*C*);

ESMS *m/z* 368 (M^+ + 1, 70), 242 (100).

1-{3-[9-(3,3-Dimethyl-oxiranyl)-3,7-dimethyl-nona-2*E*,6*E*-dienyl]-5-methoxy-indol-yl}-2,2-dimethyl-1-propan-1-one (52)



NaHMDS (1.0 mL of a 2 M solution in THF, 2.0 mmol) was added to a solution of compound (**51**) (730 mg, 1.99 mmol) in THF (10 mL) at –78 °C under argon. After 15 min, pivaloyl chloride (0.29 mL, 2.38 mmol) was added. The reaction mixture was stirred for 1 h at that temperature, quenched with saturated aqueous NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (780 mg, 88%).

IR ν2964, 1678, 1474, 1361, 1214, 1172 cm^{-1};

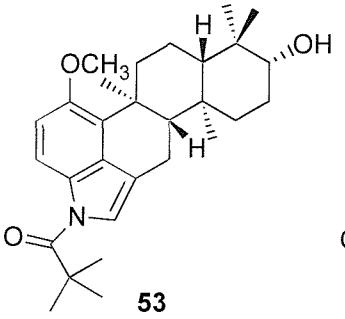
^{1}H NMR δ 1.25 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.49 (s, 9H, 3 × CH_3), 1.62 (s, 3H, CH_3), 1.55-1.65 (m, 2H), 1.78 (s, 3H, CH_3), 2.00-2.40 (m, 6H), 2.69 (t, J = 6.3 Hz, 1H, OC*H*), 3.36 (d, J = 7.4 Hz, 2H, ArCH_2), 3.86 (s, 3H, OCH_3), 5.18 (br t, J = 6.6 Hz, 1H, =C*H*), 5.41 (br t, J = 6.9 Hz, 1H, =C*H*), 6.92 (m, 2H), 7.42 (s, 1H), 8.39 (d, J = 9.5 Hz, 1H);

^{13}C NMR δ 16.0 (*C*H_3), 16.2 (*C*H_3), 18.7 (*C*H_3), 23.9 (*C*H_2), 24.9 (*C*H_3), 26.9 (*C*H_2), 27.4 (*C*H_2), 28.7 (3 × *C*H_3), 36.3 (*C*H_2), 40.0 (*C*H_2), 40.9 (*C*), 55.7 (O*C*H_3), 58.3 (*C*), 64.2 (O*C*H), 101.9 (*C*H), 113.0 (*C*H), 118.3 (*C*H), 121.10 (*C*H), 121.13 (*C*), 122.9 (*C*H), 124.5 (*C*H), 130.6 (*C*), 132.1 (*C*), 134.4 (*C*), 137.2 (*C*), 156.2 (*C*), 176.4 (*C*=O);

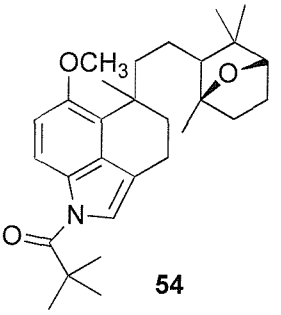
ESMS *m/z* 474 (M + Na^+, 30), 295 (88), 130 (100).

1-(9-Hydroxy-1-methoxy-6b,10,10,12a-tetramethyl-6a,6b,7,8,9,10,10a,11,12,12a-decahydro-6*H*-4-aza-cyclopenta[*hi*]chrysten-4-yl)-2,2-dimethyl-propan-1-one (53) and 1-{6-methoxy-5-methyl-5-[2-(1,3,3-

trimethyl-7-oxa-bicyclo[2.2.1]hept-2-yl)-ethyl]-4,5-dihydro-3*H*-benzo[*cd*]indol-1-yl}-2,2-dimethyl-propan-1-one (54)



53



54

To a stirred suspension of $AlCl_3$ (473 mg, 3.55 mmol) in dry CH_2Cl_2 (8 mL) was added compound (**52**) (400 mg, 0.89 mmol) in CH_2Cl_2 (2 mL) dropwise under argon. The reaction mixture was stirred for 40 min, poured into ice-water, and extracted with dichloromethane (3 × 20 mL). The combined organics were washed with water and brine, dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15-35% ethyl acetate in hexane as eluent gave compound (**53**) as a white solid (32 mg, 8%) and compound (**54**) as a pale yellow oil (76 mg, 19%).

Compound (**53**), mp 314-315 °C (decomposed):

IR ν3574, 2926, 1667, 1428, 1185, 1059 cm^{-1};

^{1}H NMR δ 0.85 (s, 3H, C*H*$_3$), 0.90 (m, 1H), 0.99 (s, 3H, C*H*$_3$), 1.04 (s, 3H, C*H*$_3$), 1.10 (m, 1H), 1.25 (s, 3H, C*H*$_3$), 1.49 (s, 9H, 3 × C*H*$_3$), 1.50-1.75 (m, 6H), 1.90 (td, J = 3.5, 13.0 Hz, 1H), 2.55 (m, 1H, ArC*H*H), 2.85 (m, 1H, ArCH*H*), 3.20 (m, 2H), 3.83 (s, 3H, OC*H*$_3$), 6.90 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H);

^{13}C NMR δ 15.4 (*C*H$_3$), 16.4 (*C*H$_3$), 17.9 (*C*H$_2$), 18.7 (*C*H$_2$), 21.7 (*C*H$_3$), 27.3 (*C*H$_2$), 28.0 (*C*H$_3$), 28.7 (3 × *C*H$_3$), 38.1 (*C*), 38.85 (*C*H$_2$), 38.89 (*C*H$_2$), 38.90 (*C*), 39.4 (*C*), 40.7 (*C*), 55.2 (*C*H), 56.6 (O*C*H$_3$), 57.1 (*C*H), 78.7 (HO*C*H), 112.2 (*C*H), 115.7 (*C*H), 118.7 (*C*H), 120.1 (*C*), 128.2 (*C*), 129.7 (*C*), 130.4 (*C*), 152.5 (*C*), 176.4 (*C*=O);

ESMS *m/z* 451 (M^+, 3), 146 (100).

Compound (**54**):

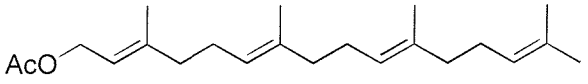
IR ν2950, 1678, 1460, 1431, 1257 cm^{-1};

^{1}H NMR δ 0.95/0.98 (s, 3H), 0.98/1.03 (s, 3H), 1.22/1.28 (s, 3H), 1.39/1.41 (s, 3H), 1.49 (s, 9H), 1.00-2.00 (m, 11H), 2.75 (t, J = 6.6 Hz, 2H), 3.69 (dd, J = 2.0, 5.0 Hz, 1H, OC*H*), 3.84/3.85 (s, 3H, OCH_3), 6.90 (d, J = 8.5 Hz, 1H), 7.34 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H);

^{13}C NMR δ 18.39/18.43 (*C*H_2), 18.92/18.95 (*C*H_3), 22.42/22.48 (*C*H_2), 23.3/23.4 (*C*H_3), 25.72/25.76 (*C*H_2), 25.99/26.07 (*C*H_3), 26.1/26.3 (*C*H_3), 28.7 (3 × *C*H_3), 36.8/37.2 (*C*H_2), 37.55/37.60 (*C*), 39.07/39.09 (*C*H_2), 40.2/40.4 (*C*H_2), 40.8 (*C*), 45.29/45.36 (*C*), 56.0/56.1 (O*C*H_3), 56.87/56.97 (*C*H), 86.0/86.1 (O*C*H), 86.79/86.85 (O*C*), 110.7/110.9 (*C*H), 115.8 (*C*H), 118.96 (*C*H), 118.97/119.23 (*C*), 125.0/125.1 (*C*), 129.34/129.35 (*C*), 130.50/130.54 (*C*), 153.15/153.23 (*C*), 176.46/176.48 (*C*=O);

ESMS *m/z* 452 (M^+ + 1, 14), 146 (100).

1-acetate, 3,7,11,15-Tetramethylhexadeca-2*E*,6*E*,10*E*,14*E*-tetraen-1-ol (Geranylgeranyl acetate) (55)



To a stirred and ice-cooled solution of geranylgeraniol (14 g, 48.2 mmol) in pyridine (15 mL) was added acetic anhydride (5.90 mL, 62.7 mmol). The reaction mixture was stirred for 4 h at room temperature and another 1 h after addition of water (40 mL), diluted with water and extracted with ether (3 × 50 mL). The combined organics were washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 10% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (14.9 g, 93%). ^{1}H and ^{13}C NMR were identical to those reported.[30]

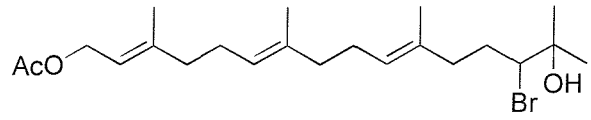
IR ν 2917, 1737, 1365, 1228, 1021 cm^{-1};

^{1}H NMR δ 1.60 (s, 9H, 3 × CH_3), 1.68 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.06 (s, 3H, COCH_3), 1.90-2.15 (m, 12H), 4.58 (d, J = 7.3 Hz, 2H, OCH_2), 5.05-5.15 (m, 3H, 3 × =C*H*), 5.34 (br t, J = 6.8 Hz, 1H, =C*H*);

^{13}C NMR δ 15.99 (*C*H_3), 16.02 (*C*H_3), 16.5 (*C*H_3), 17.7 (*C*H_3), 21.0 (*C*H_3), 25.7 (*C*H_3), 26.2 (*C*H_2), 26.6 (*C*H_2), 26.8 (*C*H_2), 39.5 (*C*H_2), 39.68 (*C*H_2), 39.71 (*C*H_2),

61.4 (CH_2), 118.2 (*C*H), 123.6 (*C*H), 124.2 (*C*H), 124.4 (*C*H), 131.3 (*C*), 135.0 (*C*), 135.5 (*C*), 142.3 (*C*), 171.1 (*C*=O).

1-Acetate, 14-bromo-3,7,11,15-tetramethyl-2*E*,6*E*,10*E*-hexadecatriene-1,15-diol (56)



To a solution of geranylgeranyl acetate (**55**) (14 g, 42.1 mmol) in *tert*-BuOH (280 mL) and H_2O (250 mL) was added NBS (9 g, 50.5 mmol) in one portion. The reaction mixture was stirred at room temperature for 4 h, diluted with water (200 mL) and extracted with ether (3 × 80 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (9.20 g, 51%).

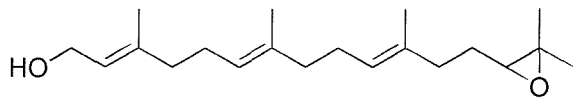
IR ν3462, 2923, 1736, 1365, 1229, 1021 cm^{-1};

^{1}H NMR δ 1.33 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.60 (s, 6H, 2 × CH_3), 1.71 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.70-2.40 (m, 12H), 3.98 (m, 1H, BrC*H*), 4.58 (d, J = 7.4 Hz, 2H, OCH_2), 5.10 (br t, J = 6.3 Hz, 1H, =C*H*), 5.20 (br t, J = 6.6 Hz, 1H, =C*H*), 5.35 (br t, J = 6.8 Hz, 1H, =C*H*);

^{13}C NMR δ 15.8 (*C*H_3), 15.9 (*C*H_3), 16.4 (*C*H_3), 21.0 (*C*H_3), 25.9 (*C*H_3), 26.1 (*C*H_2), 26.47 (*C*H_3), 26.50 (*C*H_2), 32.0 (*C*H_2), 38.1 (*C*H_2), 39.46 (*C*H_2), 39.52 (*C*H_2), 61.3 (*C*H_2), 70.7 (Br*C*H), 72.4 (*C*), 118.2 (=*C*H), 123.7 (=*C*H), 125.9 (=*C*H), 133.0 (=*C*), 135.2 (=*C*), 142.2 (=*C*), 171.1 (*C*=O);

CIMS *m/z* 429 (M^+ + 1, 3), 307 (18), 290 (100), 203 (48), 153 (84), 127 (90).

13-(3,3-Dimethyl-oxiranyl)-3,7,11-trimethyl-2*E*,6*E*,10*E*-tridecatrien-1-ol (14,15-Epoxygeranylgeraniol) (57)



To a stirred solution of bromohydrin (**56**) (8.20 g, 19.1 mmol) in MeOH (200 mL) and H_2O (10 mL) was added K_2CO_3 (13.20 g, 95.5 mmol). The reaction mixture

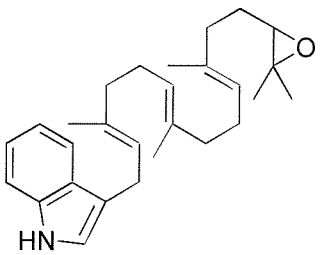
was stirred for 4 h at room temperature. Solvent was evaporated, the residue taken up in water (60 mL) and extracted with dichloromethane (3 × 50 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 50% ethyl acetate in hexane as eluent afforded the title compound as a colorless oil (5.687 g, 97%). ^1H and ^{13}C NMR were identical to those reported.[30]

IR ν 3430, 2917, 1444, 1377 cm^{-1};

^1H NMR δ 1.26 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.55-1.65 (m, 2H), 1.62 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.95-2.20 (m, 10H), 2.71 (t, J = 6.2 Hz, 1H, OC*H*), 4.13 (d, J = 6.6 Hz, 2H, HOCH_2), 5.11 (br t, J = 6.7 Hz, 1H, =C*H*), 5.16 (br t, J = 6.6 Hz, 1H, =C*H*), 5.41 (br t, J = 6.8 Hz, 1H, =C*H*);

^{13}C NMR δ 15.9 (2 × *C*H_3), 16.1 (*C*H_3), 18.6 (*C*H_3), 24.8 (*C*H_3), 26.2 (*C*H_2), 26.4 (*C*H_2), 27.3 (*C*H_2), 36.2 (*C*H_2), 39.4 (*C*H_2), 39.5 (*C*H_2), 58.3 (*C*), 59.1 (*C*H_2), 64.1 (O*C*H), 123.5 (=*C*H), 123.8 (=*C*H), 124.7 (=*C*H), 133.9 (=*C*), 135.0 (=*C*), 139.0 (=*C*).

3-[13-(3,3-Dimethyl-oxiranyl)-3,7,11-trimethyl-trideca-2*E*,6*E*,10*E*-trienyl]-1*H*-indole (59)



To a stirred solution of epoxide (**57**) (5.30 g, 17.28 mmol) and MsCl (1.74 mL, 22.46 mmol) in anhydrous THF (60 mL) was added Et_3N (4.82 mL, 34.56 mmol) at –40 °C. The reaction mixture was stirred for 45 min at that temperature followed by addition of LiBr (6 g, 69.12 mmol) in THF (40 mL). The reaction mixture was stirred for another 2 h at 0 °C, then partitioned between hexane and water. The organic layer was separated, and the aqueous layer extracted with hexane (3 × 80 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent afforded the bromide (**58**) as a light yellow oil (5.89 g, 92%), which was used without further purification.

To a mixture of indole (3.71 g, 31.7 mmol), zinc triflate (6.92 g, 19.03 mmol) and tetrabutylammonium iodide (5.85 g, 15.85 mmol) in anhydrous toluene (80 mL) was added DIEA (6.08 mL, 34.89 mmol) at room temperature under argon. After 15 min, the bromide (**58**) (5.85 g, 15.85 mmol) in toluene (10 mL) was added dropwise. The reaction mixture was stirred for 8 h, quenched with saturated NH_4Cl (30 mL), diluted into water (20 mL) and extracted with ether (3 × 45 mL). The combined organics were washed with water and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 15% ether in hexane as eluent afforded the title compound as a pale yellow oil (2.96 g, 46%).

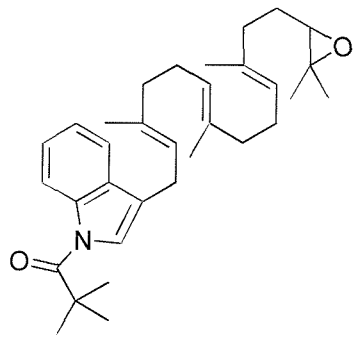
IR ν 3413, 2914, 1454, 1378, 1090 cm^{-1};

^{1}H NMR δ 1.25 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.59 (s, 6H, 2 × CH_3), 1.55-1.70 (m, 2H), 1.75 (s, 3H, CH_3), 1.95-2.20 (m, 10H), 2.71 (t, J = 6.2 Hz, 1H, OC*H*), 3.45 (d, J = 7.4 Hz, 2H, ArCH_2), 5.14 (m, 2H, 2 × =C*H*), 5.44 (br t, J = 6.6 Hz, 1H, =C*H*), 6.85 (s, 1H), 7.05-7.20 (m, 2H), 7.26 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 8.06 (br s, 1H, N*H*);

^{13}C NMR δ 15.90 (*C*H_3), 15.95 (*C*H_3), 16.00 (*C*H_3), 18.7 (*C*H_3), 23.9 (*C*H_2), 24.8 (*C*H_3), 26.45 (*C*H_2), 26.52 (*C*H_2), 27.3 (*C*H_2), 36.2 (*C*H_2), 39.54 (*C*H_2), 39.61 (*C*H_2), 58.4 (O*C*), 64.2 (O*C*H), 111.0 (*C*H), 115.7 (*C*), 118.9 (2 × *C*H), 121.2 (*C*H), 121.6 (*C*H), 123.0 (*C*H), 124.2 (*C*H), 124.9 (*C*H), 127.3 (*C*), 133.8 (*C*), 134.7 (*C*), 135.3 (*C*), 136.4 (*C*);

ESMS *m/z* 405 (M^+, 8), 317 (47), 249 (45), 143 (55), 130 (100).

1-{3-[13-(3,3-Dimethyl-oxiranyl)-3,7,11-trimethyl-trideca-2*E*,6*E*,10*E*-trienyl]-indol-1-yl}-2,2-dimethyl-propan-1-one (60)



NaHMDS (2.4 mL of a 2 M solution in THF, 4.8 mmol) was added to a solution of compound (**59**) (1.90 g, 4.68 mmol) in THF (30 mL) at –78 °C under argon. The reaction mixture was stirred for 15 min followed by addition of pivaloyl chloride (0.69 mL, 5.62 mmol). The reaction mixture was stirred for 1 h at that temperature, then quenched with saturated aqueous NH_4Cl (40 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organics were dried over anhydrous Na_2SO_4. Evaporation of solvent and purification of the residue by column chromatography with 20% ethyl acetate in hexane as eluent afforded the title compound as a colourless oil (2 g, 87%).

IR ν2917, 1687, 1447, 1319, 1177 cm^{-1};

^{1}H NMR δ 1.25 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.50 (s, 9H, 3 × CH_3), 1.60 (s, 6H, 2 × CH_3), 1.50-1.70 (m, 2H), 1.77 (s, 3H, CH_3), 1.95-2.20 (m, 10H), 2.70 (t, J = 6.2 Hz, 1H, OC*H*), 3.40 (d, J = 6.6 Hz, 2H, ArCH_2), 5.10-5.15 (m, 2H, 2 × =C*H*), 5.43 (br t, J = 7.0 Hz, 1H, =C*H*), 7.24-7.38 (m, 2H), 7.44 (s, 1H), 7.49 (d, J = 6.6 Hz, 1H), 8.51 (d, J = 8.1 Hz, 1H);

^{13}C NMR δ 15.9 (*C*H_3), 16.18 (*C*H_3), 16.19 (*C*H_3), 18.7 (*C*H_3), 23.7 (*C*H_2), 24.8 (*C*H_3), 26.5 (*C*H_2), 26.8 (*C*H_2), 27.4 (*C*H_2), 28.6 (3 × *C*H_3), 36.2 (*C*H_2), 39.56 (*C*H_2), 39.62 (*C*H_2), 41.0 (*C*), 58.2 (*C*), 64.1 (O*C*H), 117.4 (*C*H), 118.6 (*C*H), 121.0 (*C*H), 121.3 (*C*), 122.2 (*C*H), 123.1 (*C*H), 124.0 (*C*H), 124.7 (*C*H), 125.1 (*C*H), 129.5 (*C*), 133.9 (*C*), 135.0 (*C*), 137.22 (*C*), 137.36 (*C*), 176.6 (*C*=O);

ESMS *m/z* 512 (M + Na^+, 100).

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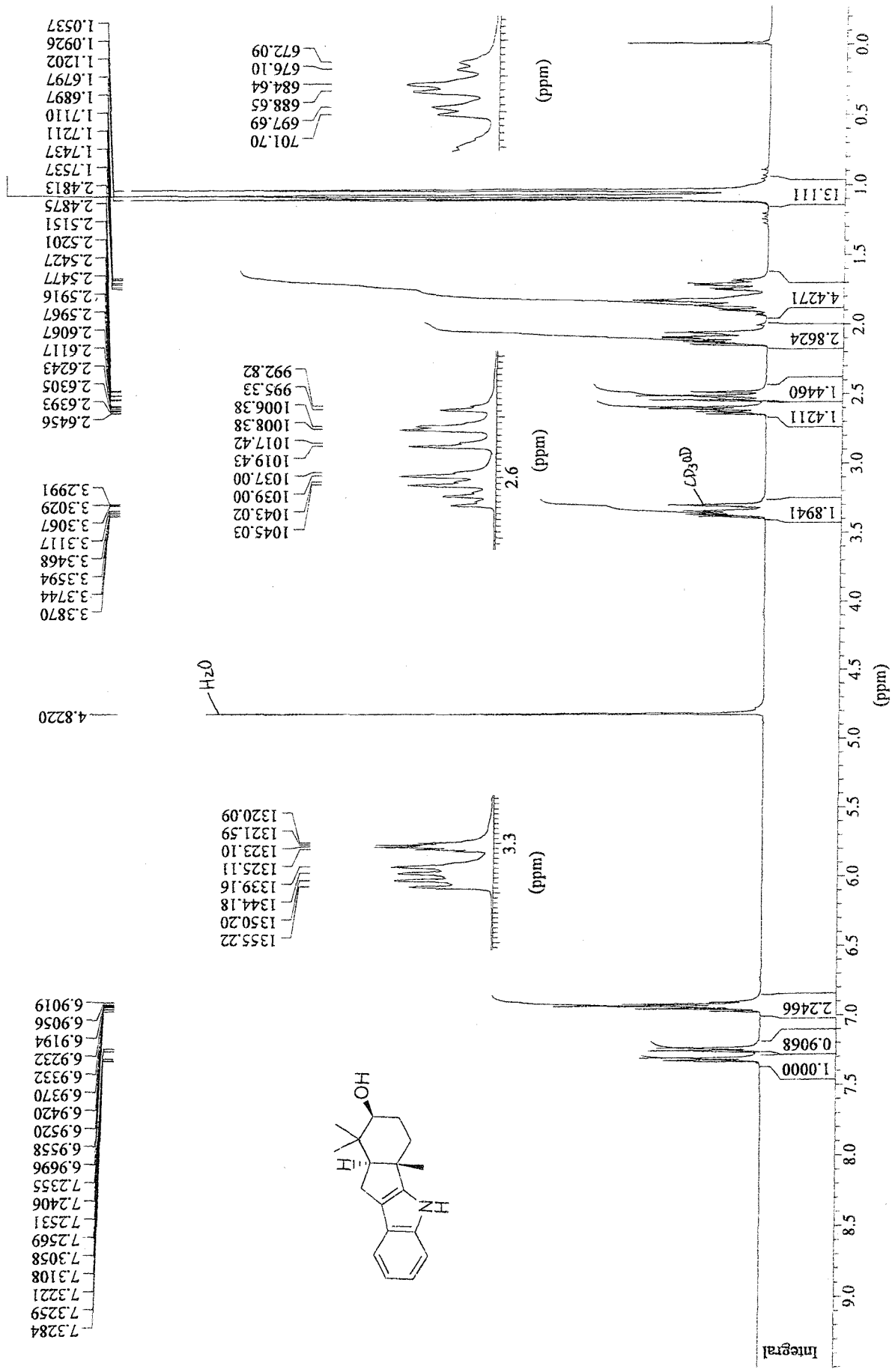
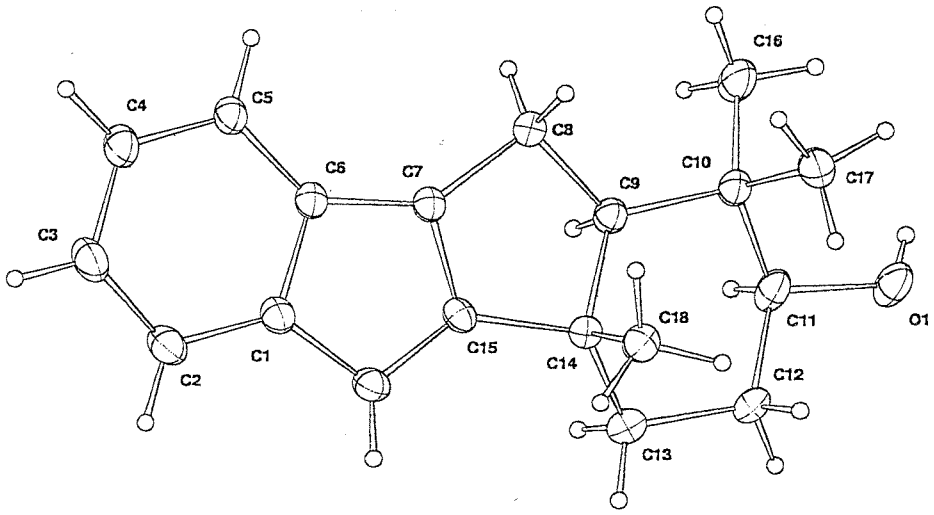
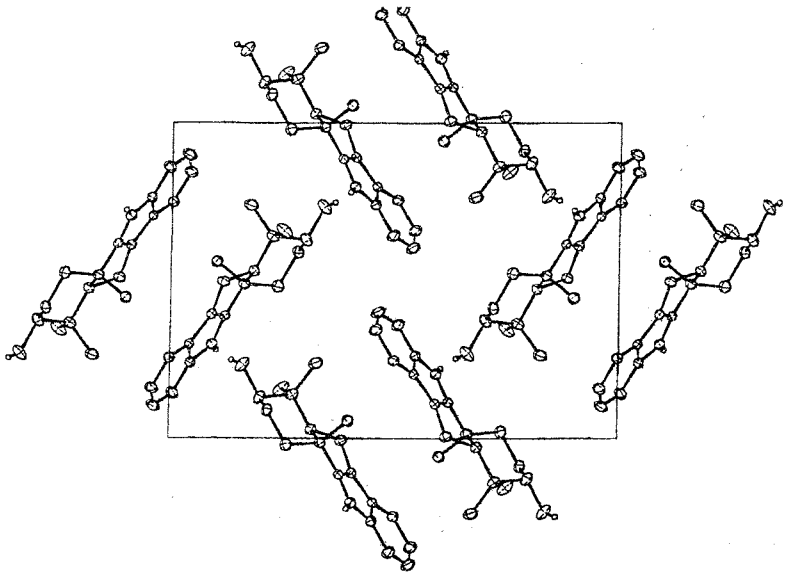
Appendix 1: ^{1}H NMR spectrum of compound (**30**) in CD_3OD



Appendix 2: X-ray crystallographic data of compound (**30**)



Molecular structure with thermal ellipsoids drawn at the 30 % probablity level.



Packing diagram viewed down the *a* axis.

Table 1. Crystal data and structure refinement.

Identification code	**01SOT02**
Empirical formula	$C_{18}H_{23}NO$
Formula weight	269.37
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 7.1595(5) Å
	b = 12.2585(8) Å β = 100.866(3)°
	c = 17.4219(16) Å
Volume	1501.6(2) Å^3
Z	4
Density (calculated)	1.192 Mg / m^3
Absorption coefficient	0.073 mm^{-1}
F(000)	584
Crystal	Colourless blade
Crystal size	0.40 × 0.1 × 0.05 mm^3
θ range for data collection	2.92 – 23.25°
Index ranges	$-7 \le h \le 7, -13 \le k \le 13, -19 \le l \le 19$
Reflections collected	10001
Independent reflections	2146 [R_{int} = 0.0970]
Completeness to θ = 23.25°	99.7 %
Max. and min. transmission	0.9978 and 0.9928
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2146 / 0 / 186
Goodness-of-fit on F^2	1.025
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0570, $wR2$ = 0.1453
R indices (all data)	$R1$ = 0.1000, $wR2$ = 0.1680
Extinction coefficient	0.010(4)
Largest diff. peak and hole	0.239 and –0.153 e Å^{-3}

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	–929(4)	12609(3)	5461(2)	45(1)	1
C2	–858(5)	13585(3)	5063(2)	62(1)	1
C3	–2523(6)	13981(3)	4629(2)	73(1)	1
C4	–4241(5)	13426(3)	4585(2)	64(1)	1
C5	–4321(5)	12460(3)	4980(2)	49(1)	1
C6	–2659(4)	12032(2)	5431(2)	40(1)	1
C7	–2174(4)	11094(2)	5919(2)	39(1)	1
C8	–3000(4)	10060(2)	6172(2)	45(1)	1
C9	–1401(4)	9719(2)	6851(2)	42(1)	1
C10	–1360(4)	8617(3)	7263(2)	47(1)	1
C11	235(4)	8719(3)	7988(2)	55(1)	1
C12	2124(4)	9115(3)	7817(2)	48(1)	1
C13	1973(4)	10208(3)	7386(2)	48(1)	1
C14	505(4)	10136(2)	6636(2)	40(1)	1
C15	–282(4)	11144(2)	6211(2)	38(1)	1
C16	–3265(5)	8442(3)	7513(2)	71(1)	1
C17	–1013(5)	7627(3)	6757(2)	62(1)	1
C18	1280(4)	9430(3)	6022(2)	49(1)	1
N1	528(4)	12036(2)	5931(1)	46(1)	1
O1	626(3)	7678(2)	8381(1)	66(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–N1	1.389(4)	C9–C14	1.567(4)
C1–C2	1.389(5)	C10–C16	1.524(4)
C1–C6	1.418(4)	C10–C11	1.541(5)
C2–C3	1.374(5)	C10–C17	1.547(5)
C3–C4	1.395(5)	C11–O1	1.451(4)
C4–C5	1.377(5)	C11–C12	1.518(5)
C5–C6	1.398(4)	C12–C13	1.531(4)
C6–C7	1.433(4)	C13–C14	1.516(4)
C7–C15	1.356(4)	C14–C15	1.495(4)
C7–C8	1.499(4)	C14–C18	1.557(4)
C8–C9	1.540(4)	C15–N1	1.370(4)
C9–C10	1.528(4)		

N1–C1–C2	129.5(3)	C9–C10–C11	105.0(3)
N1–C1–C6	108.9(3)	C16–C10–C17	107.6(3)
C2–C1–C6	121.6(3)	C9–C10–C17	114.7(3)
C3–C2–C1	118.0(3)	C11–C10–C17	110.9(3)
C2–C3–C4	121.5(3)	O1–C11–C12	105.9(2)
C5–C4–C3	120.7(3)	O1–C11–C10	111.3(3)
C4–C5–C6	119.5(3)	C12–C11–C10	114.5(3)
C5–C6–C1	118.6(3)	C11–C12–C13	113.2(2)
C5–C6–C7	136.0(3)	C14–C13–C12	110.2(3)
C1–C6–C7	105.4(2)	C15–C14–C13	120.9(2)
C15–C7–C6	107.4(3)	C15–C14–C18	105.5(2)
C15–C7–C8	110.5(3)	C13–C14–C18	110.2(2)
C6–C7–C8	142.0(3)	C15–C14–C9	97.1(2)
C7–C8–C9	100.3(2)	C13–C14–C9	107.9(2)
C10–C9–C8	123.1(2)	C18–C14–C9	114.9(2)
C10–C9–C14	117.4(2)	C7–C15–N1	111.2(3)
C8–C9–C14	106.4(2)	C7–C15–C14	113.9(3)
C16–C10–C9	108.6(3)	N1–C15–C14	133.7(3)
C16–C10–C11	110.0(3)	C15–N1–C1	107.0(2)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	54(2)	39(2)	38(2)	1(2)	−1(1)	−6(2)
C2	72(3)	51(2)	55(2)	11(2)	−11(2)	−21(2)
C3	90(3)	47(2)	69(3)	20(2)	−18(2)	−20(2)
C4	75(3)	46(2)	58(2)	10(2)	−16(2)	−5(2)
C5	57(2)	37(2)	45(2)	0(2)	−5(2)	−2(2)
C6	51(2)	33(2)	32(2)	−5(1)	0(1)	0(1)
C7	45(2)	36(2)	34(2)	−3(1)	5(1)	−1(1)
C8	42(2)	40(2)	52(2)	5(2)	6(1)	1(1)
C9	42(2)	42(2)	41(2)	5(2)	7(1)	2(1)
C10	43(2)	44(2)	54(2)	11(2)	10(1)	4(1)
C11	52(2)	62(2)	52(2)	18(2)	10(2)	16(2)
C12	40(2)	58(2)	43(2)	5(2)	0(1)	8(1)
C13	42(2)	55(2)	46(2)	−1(2)	5(1)	2(2)
C14	38(2)	39(2)	43(2)	1(1)	5(1)	−1(1)
C15	47(2)	34(2)	33(2)	−5(1)	7(1)	−6(1)
C16	52(2)	75(3)	87(3)	42(2)	16(2)	8(2)
C17	64(2)	46(2)	70(3)	10(2)	−2(2)	−5(2)
C18	50(2)	49(2)	47(2)	−3(2)	7(1)	3(2)
N1	46(2)	43(2)	46(2)	−1(1)	3(1)	−8(1)
O1	53(2)	79(2)	68(2)	37(1)	15(1)	16(1)

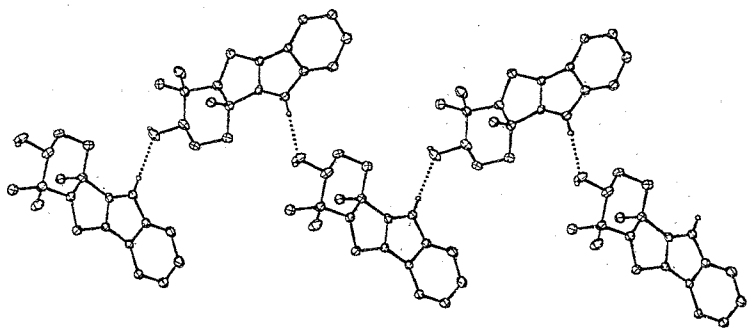
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	306	13968	5090	75	1
H3	−2504	14647	4352	88	1
H4	−5369	13717	4278	76	1
H5	−5496	12087	4948	58	1
H8A	−3205	9509	5749	54	1
H8B	−4211	10195	6352	54	1
H9	−1586	10238	7273	50	1
H11	−191	9243	8360	66	1
H12A	2629	8560	7497	58	1
H12B	3041	9189	8316	58	1
H13A	1604	10787	7725	58	1
H13B	3225	10404	7262	58	1
H16A	−3545	9070	7821	107	1
H16B	−3207	7779	7831	107	1
H16C	−4269	8366	7049	107	1
H17A	−1362	6954	7000	93	1
H17B	334	7598	6718	93	1
H17C	−1792	7701	6233	93	1
H18A	218	9189	5618	74	1
H18B	1946	8793	6281	74	1
H18C	2164	9866	5782	74	1
H1	1741	12213	6030	55	1
H1A	−246	7531	8626	99	1

Table 6. Hydrogen bonds [Å and °].

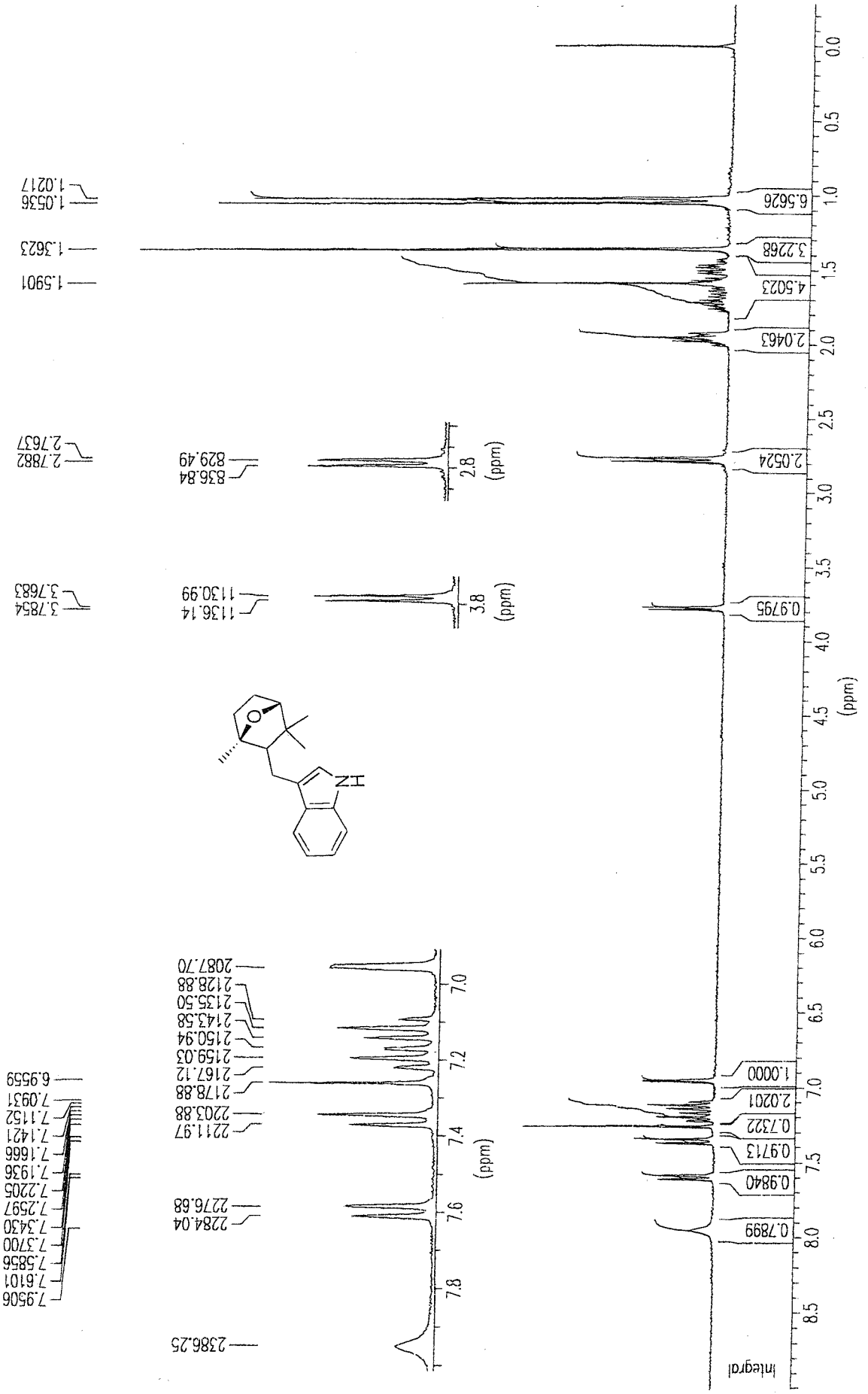
D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N1–H1···O1^{i}	0.88	2.05	2.897(3)	161.3

Symmetry transformations used to generate equivalent atoms:
(i) −x+1/2,y+1/2,−z+3/2

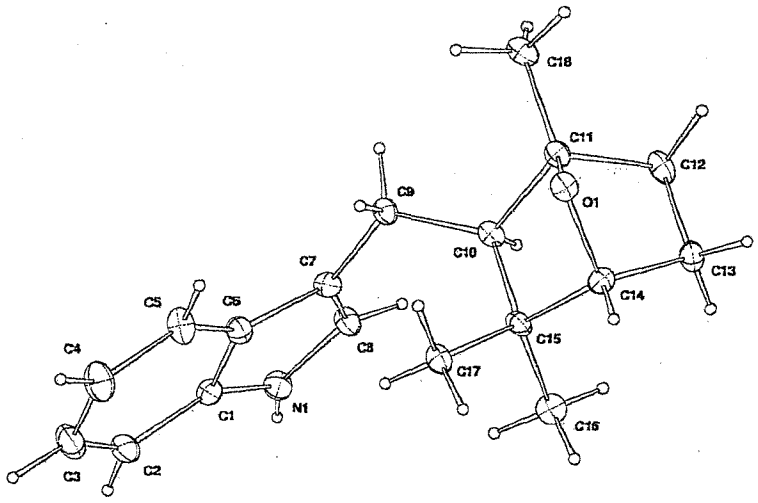


Part of the hydrogen bonded chains that extend along the *c* axis.

Appendix 3: ^{1}H NMR spectrum of compound (**31**) in $CDCl_3$



Appendix 4: X-ray crystallographic data of compound (**31**)



Molecular structure of one of the two chemically identical molecules in the symmetric unit – thermal ellipsoids drawn at the 35 % probablity level.

Table 1. Crystal data and structure refinement.

Identification code	**01SOT043**	
Empirical formula	$C_{18}H_{23}NO$	
Formula weight	269.37	
Temperature	180(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 8.0157(4) Å	α = 87.671(3)°
	b = 11.9997(7) Å	β = 83.952(3)°
	c = 16.3287(10) Å	γ = 71.779(4)°
Volume	1483.49(15) Å^3	
Z	4	
Density (calculated)	1.206 Mg / m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	584	
Crystal	Colourless rod	
Crystal size	0.15 × 0.06 × 0.03 mm^3	
θ range for data collection	3.07 – 25.03°	
Index ranges	$-9 \le h \le 9$, $-13 \le k \le 14$, $-18 \le l \le 19$	
Reflections collected	9842	
Independent reflections	4973 [R_{int} = 0.0858]	
Completeness to θ = 25.03°	94.6 %	
Max. and min. transmission	0.9978 and 0.9890	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4973 / 0 / 361	
Goodness-of-fit on F^2	0.951	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0644, *wR2* = 0.1370	
R indices (all data)	*R1* = 0.1396, *wR2* = 0.1655	
Largest diff. peak and hole	0.512 and –0.305 e Å^{-3}	

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
N1	10095(3)	1156(2)	3558(2)	25(1)	1
O1	4602(3)	3172(2)	704(1)	22(1)	1
C1	10029(4)	2301(3)	3661(2)	22(1)	1
C2	11178(4)	2746(3)	4036(2)	28(1)	1
C3	10804(5)	3943(3)	4045(2)	35(1)	1
C4	9351(5)	4684(3)	3671(2)	36(1)	1
C5	8223(5)	4247(3)	3302(2)	31(1)	1
C6	8550(4)	3027(3)	3294(2)	22(1)	1
C7	7691(4)	2274(3)	2969(2)	22(1)	1
C8	8688(4)	1153(3)	3145(2)	23(1)	1
C9	6037(4)	2639(3)	2536(2)	21(1)	1
C10	6218(4)	1996(3)	1721(2)	19(1)	1
C11	4469(4)	2257(3)	1303(2)	19(1)	1
C12	4647(4)	1238(3)	726(2)	26(1)	1
C13	5934(4)	1438(3)	5(2)	28(1)	1
C14	6308(4)	2524(3)	288(2)	22(1)	1
C15	7494(4)	2279(3)	999(2)	20(1)	1
C16	9214(4)	1278(3)	832(2)	29(1)	1
C17	7974(4)	3401(3)	1122(2)	26(1)	1
C18	2727(4)	2670(3)	1827(2)	25(1)	1
N2	3183(4)	5484(2)	1394(2)	24(1)	1
O2	2937(3)	9326(2)	4204(1)	30(1)	1
C19	1467(4)	6121(3)	1326(2)	22(1)	1
C20	152(5)	5817(3)	969(2)	26(1)	1
C21	−1482(5)	6653(3)	962(2)	33(1)	1
C22	−1813(4)	7759(3)	1309(2)	31(1)	1
C23	−529(4)	8047(3)	1670(2)	27(1)	1
C24	1154(4)	7226(3)	1683(2)	20(1)	1
C25	2762(4)	7222(3)	1995(2)	21(1)	1
C26	3952(4)	6160(3)	1801(2)	23(1)	1
C27	3106(4)	8206(3)	2427(2)	22(1)	1
C28	3976(4)	7827(3)	3230(2)	19(1)	1
C29	4519(4)	8801(3)	3635(2)	23(1)	1
C30	5895(5)	8250(3)	4230(2)	34(1)	1
C31	4758(5)	7898(3)	4976(2)	34(1)	1
C32	2954(5)	8261(3)	4652(2)	31(1)	1
C33	2809(4)	7465(3)	3967(2)	24(1)	1
C34	3537(6)	6148(3)	4185(2)	42(1)	1
C35	867(5)	7728(3)	3840(2)	33(1)	1
C36	4881(5)	9754(3)	3080(2)	28(1)	1

Table 3. Bond lengths [Å] and angles [°].

N1–C8	1.374(4)	N2–C19	1.362(4)
N1–C1	1.376(4)	N2–C26	1.387(4)
O1–C14	1.456(4)	O2–C32	1.444(4)
O1–C11	1.462(4)	O2–C29	1.473(4)
C1–C2	1.400(5)	C19–C20	1.404(5)
C1–C6	1.409(4)	C19–C24	1.409(5)
C2–C3	1.373(5)	C20–C21	1.379(5)
C3–C4	1.406(5)	C21–C22	1.401(5)
C4–C5	1.375(5)	C22–C23	1.376(5)
C5–C6	1.404(5)	C23–C24	1.402(5)
C6–C7	1.443(4)	C24–C25	1.433(4)
C7–C8	1.369(4)	C25–C26	1.357(5)
C7–C9	1.502(4)	C25–C27	1.510(4)
C9–C10	1.535(4)	C27–C28	1.536(4)
C10–C11	1.562(4)	C28–C29	1.560(4)
C10–C15	1.576(4)	C28–C33	1.577(4)
C11–C18	1.509(5)	C29–C36	1.509(4)
C11–C12	1.536(4)	C29–C30	1.522(5)
C12–C13	1.544(5)	C30–C31	1.567(5)
C13–C14	1.524(5)	C31–C32	1.520(5)
C14–C15	1.539(4)	C32–C33	1.536(5)
C15–C16	1.527(4)	C33–C35	1.524(5)
C15–C17	1.537(4)	C33–C34	1.544(5)

C8–N1–C1	108.4(3)	O1–C11–C18	109.4(3)
C14–O1–C11	96.8(2)	O1–C11–C12	100.7(2)
N1–C1–C2	129.5(3)	C18–C11–C12	114.6(3)
N1–C1–C6	107.7(3)	O1–C11–C10	102.3(2)
C2–C1–C6	122.7(3)	C18–C11–C10	119.1(3)
C3–C2–C1	117.3(3)	C12–C11–C10	108.5(3)
C2–C3–C4	121.0(3)	C11–C12–C13	102.4(2)
C5–C4–C3	121.7(3)	C14–C13–C12	101.7(3)
C4–C5–C6	118.8(3)	O1–C14–C13	101.4(2)
C5–C6–C1	118.5(3)	O1–C14–C15	101.7(2)
C5–C6–C7	134.1(3)	C13–C14–C15	113.5(3)
C1–C6–C7	107.4(3)	C16–C15–C17	107.7(3)
C8–C7–C6	105.5(3)	C16–C15–C14	113.9(3)
C8–C7–C9	127.1(3)	C17–C15–C14	107.1(3)
C6–C7–C9	127.4(3)	C16–C15–C10	113.0(3)
C7–C8–N1	110.9(3)	C17–C15–C10	114.3(3)
C7–C9–C10	113.6(3)	C14–C15–C10	100.8(2)
C9–C10–C11	114.8(2)	C19–N2–C26	108.2(3)
C9–C10–C15	116.6(2)	C32–O2–C29	96.5(2)
C11–C10–C15	101.6(2)	N2–C19–C20	129.7(3)
N2–C19–C24	108.0(3)	O2–C29–C36	108.8(3)
C20–C19–C24	122.3(3)	O2–C29–C30	101.7(3)
C21–C20–C19	117.6(3)	C36–C29–C30	115.5(3)
C20–C21–C22	120.8(3)	O2–C29–C28	100.9(2)
C23–C22–C21	121.4(3)	C36–C29–C28	117.6(3)
C22–C23–C24	119.6(3)	C30–C29–C28	110.0(3)
C23–C24–C19	118.3(3)	C29–C30–C31	102.1(3)
C23–C24–C25	134.6(3)	C32–C31–C30	100.9(3)
C19–C24–C25	107.1(3)	O2–C32–C31	102.0(3)
C26–C25–C24	106.2(3)	O2–C32–C33	102.1(2)
C26–C25–C27	126.3(3)	C31–C32–C33	113.7(3)
C24–C25–C27	127.5(3)	C35–C33–C32	108.5(3)
C25–C26–N2	110.5(3)	C35–C33–C34	107.5(3)
C25–C27–C28	113.8(3)	C32–C33–C34	112.6(3)
C27–C28–C29	114.4(3)	C35–C33–C28	115.4(3)
C27–C28–C33	116.4(3)	C32–C33–C28	100.9(2)
C29–C28–C33	101.4(2)	C34–C33–C28	111.9(3)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N1	22(2)	25(2)	26(2)	1(1)	−8(1)	−2(1)
O1	25(1)	22(1)	21(1)	4(1)	−5(1)	−9(1)
C1	22(2)	28(2)	18(2)	−2(1)	0(1)	−8(2)
C2	23(2)	40(2)	24(2)	−1(2)	−7(2)	−11(2)
C3	38(2)	44(3)	33(2)	−3(2)	−8(2)	−25(2)
C4	49(2)	25(2)	41(2)	−1(2)	−10(2)	−18(2)
C5	39(2)	28(2)	28(2)	0(2)	−10(2)	−12(2)
C6	23(2)	22(2)	21(2)	−1(1)	−3(1)	−9(2)
C7	19(2)	24(2)	22(2)	−1(1)	−2(1)	−7(2)
C8	22(2)	23(2)	24(2)	−1(1)	−8(2)	−7(2)
C9	20(2)	23(2)	21(2)	1(1)	−6(1)	−6(2)
C10	18(2)	17(2)	23(2)	3(1)	−6(1)	−7(1)
C11	20(2)	17(2)	22(2)	2(1)	−5(1)	−7(1)
C12	29(2)	22(2)	32(2)	1(2)	−11(2)	−13(2)
C13	26(2)	29(2)	29(2)	−10(2)	−6(2)	−8(2)
C14	22(2)	24(2)	21(2)	−3(1)	1(1)	−7(2)
C15	18(2)	20(2)	24(2)	−2(1)	−4(1)	−9(1)
C16	28(2)	32(2)	29(2)	−2(2)	−3(2)	−10(2)
C17	27(2)	27(2)	28(2)	−4(2)	−4(2)	−13(2)
C18	21(2)	25(2)	32(2)	2(2)	−8(2)	−8(2)
N2	27(2)	16(2)	28(2)	−4(1)	−9(1)	−3(1)
O2	29(1)	30(2)	28(1)	−4(1)	−3(1)	−7(1)
C19	26(2)	20(2)	24(2)	0(2)	−3(2)	−9(2)
C20	35(2)	24(2)	27(2)	−3(2)	−5(2)	−18(2)
C21	27(2)	44(3)	33(2)	−5(2)	−8(2)	−16(2)
C22	19(2)	40(2)	33(2)	−6(2)	−8(2)	−4(2)
C23	27(2)	25(2)	28(2)	−8(2)	−6(2)	−3(2)
C24	24(2)	23(2)	15(2)	−1(1)	−3(1)	−9(2)
C25	26(2)	20(2)	18(2)	0(1)	−4(1)	−9(2)
C26	24(2)	20(2)	26(2)	2(2)	−8(2)	−8(2)
C27	25(2)	20(2)	23(2)	−2(1)	−5(1)	−8(2)
C28	19(2)	17(2)	21(2)	−1(1)	−6(1)	−5(1)
C29	27(2)	24(2)	22(2)	−4(2)	−4(2)	−14(2)
C30	30(2)	36(2)	39(2)	−1(2)	−13(2)	−13(2)
C31	40(2)	38(2)	26(2)	2(2)	−14(2)	−12(2)
C32	33(2)	35(2)	26(2)	3(2)	−5(2)	−13(2)
C33	28(2)	28(2)	22(2)	−2(2)	−4(2)	−15(2)
C34	47(2)	38(2)	42(2)	9(2)	−9(2)	−15(2)
C35	30(2)	46(2)	30(2)	5(2)	−3(2)	−22(2)
C36	36(2)	21(2)	34(2)	−4(2)	−6(2)	−16(2)

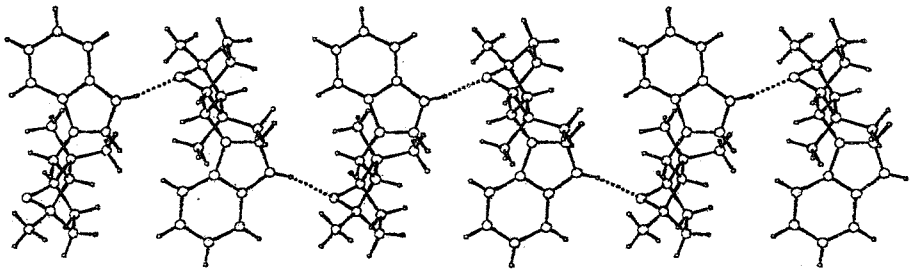
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	10901	531	3728	30	1
H2	12176	2240	4274	34	1
H3	11537	4276	4307	42	1
H4	9143	5508	3672	43	1
H5	7240	4760	3058	37	1
H8	8440	466	3002	27	1
H9A	5707	3493	2424	25	1
H9B	5068	2489	2906	25	1
H10	6653	1134	1837	23	1
H12A	3495	1281	538	31	1
H12B	5143	470	999	31	1
H13A	7024	760	−63	33	1
H13B	5377	1586	−518	33	1
H14	6714	2974	−177	27	1
H16A	8948	548	752	44	1
H16B	9915	1185	1301	44	1
H16C	9885	1457	335	44	1
H17A	6891	4061	1230	39	1
H17B	8656	3565	624	39	1
H17C	8679	3292	1591	39	1
H18A	2723	3316	2177	38	1
H18B	2561	2020	2174	38	1
H18C	1766	2943	1470	38	1
H2A	3712	4767	1211	29	1
H20	381	5063	740	32	1
H21	−2395	6475	720	40	1
H22	−2947	8322	1294	38	1
H23	−781	8798	1909	32	1
H26	5145	5914	1927	28	1
H27A	1972	8834	2551	27	1
H27B	3877	8541	2048	27	1
H28	5063	7146	3106	23	1
H30A	6458	8821	4396	40	1
H30B	6818	7554	3988	40	1
H31A	5185	7045	5092	41	1
H31B	4747	8335	5479	41	1
H32	1967	8387	5102	37	1
H34A	4787	5951	4273	62	1
H34B	3410	5679	3732	62	1
H34C	2875	5979	4689	62	1
H35A	755	7231	3401	50	1
H35B	373	8555	3686	50	1
H35C	224	7567	4353	50	1
H36A	3929	10053	2722	43	1
H36B	6005	9433	2743	43	1
H36C	4943	10395	3417	43	1

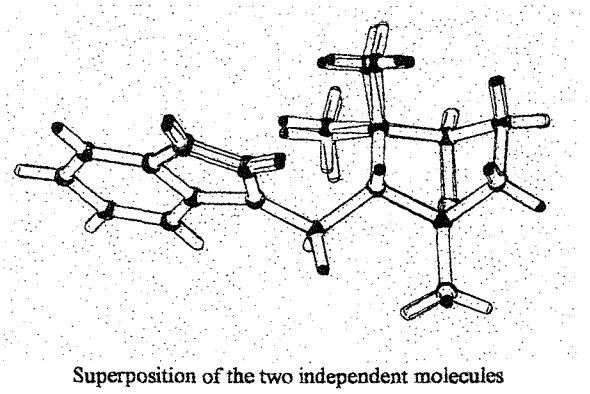
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N1–H1···O2^{i}	0.88	2.01	2.883(3)	168.9
N2–H2A···O1	0.88	2.00	2.876(3)	171.5

Symmetry transformations used to generate equivalent atoms:
(i) x+1,y–1,z

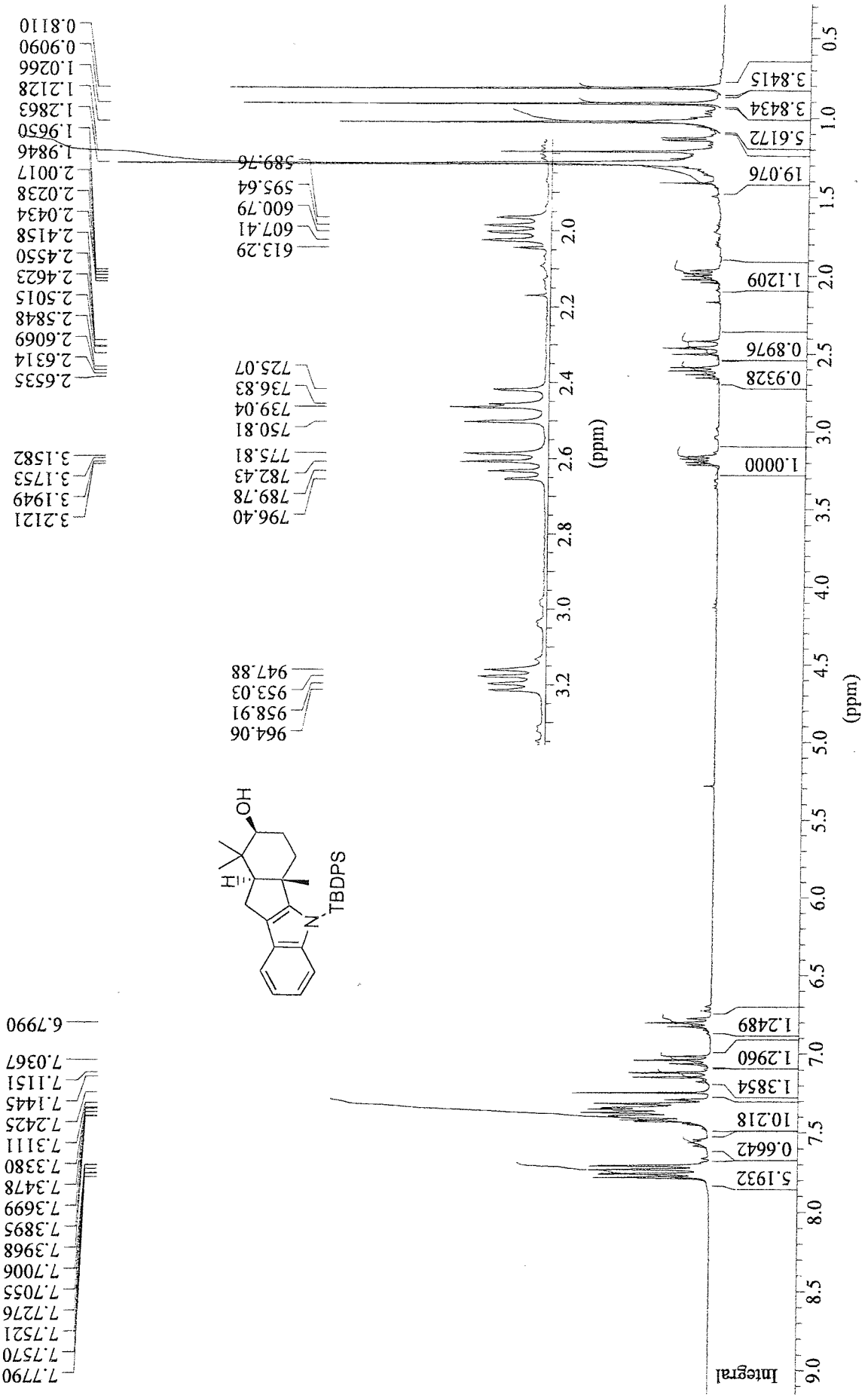


Hydrogen bonded chains

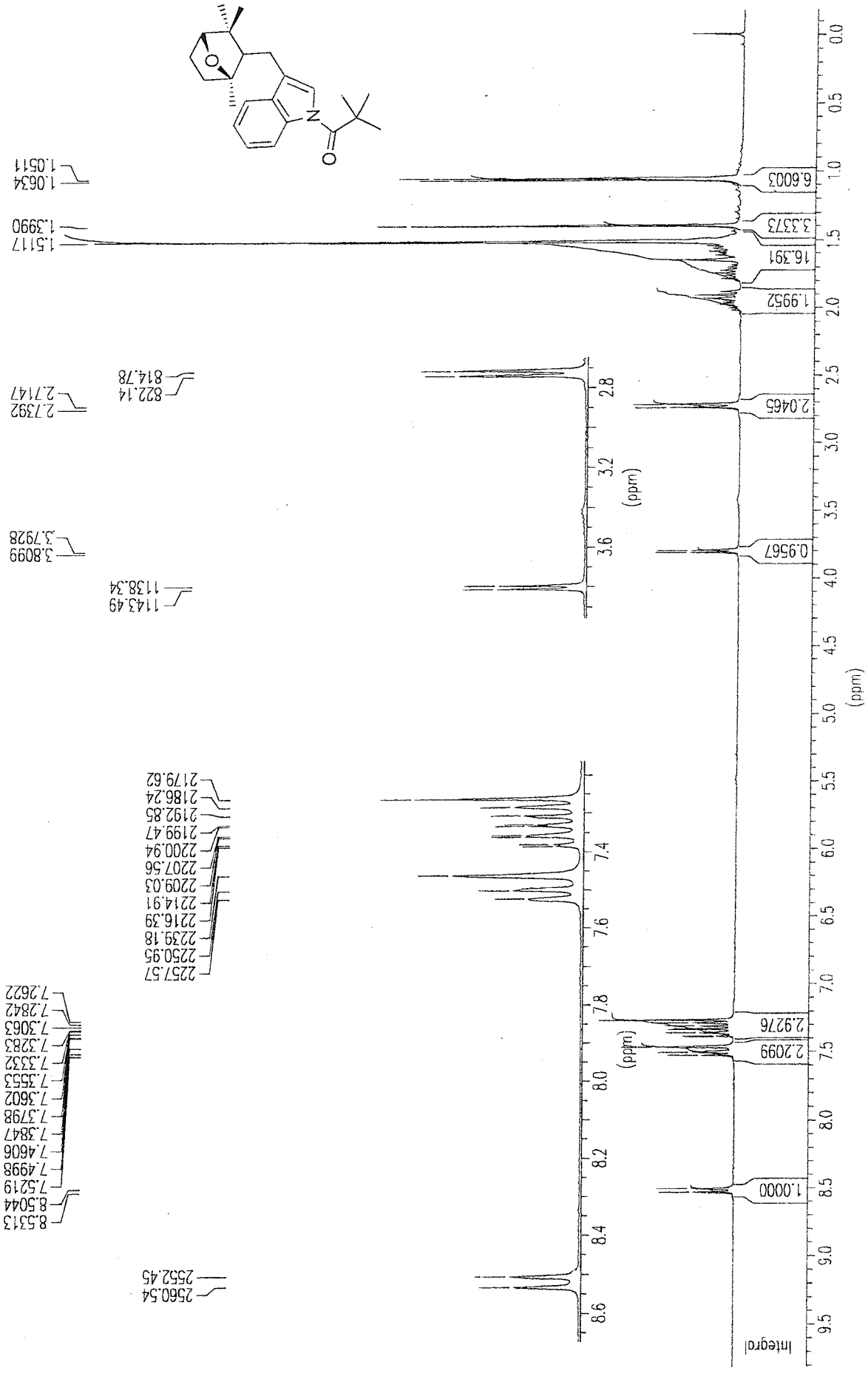


Superposition of the two independent molecules

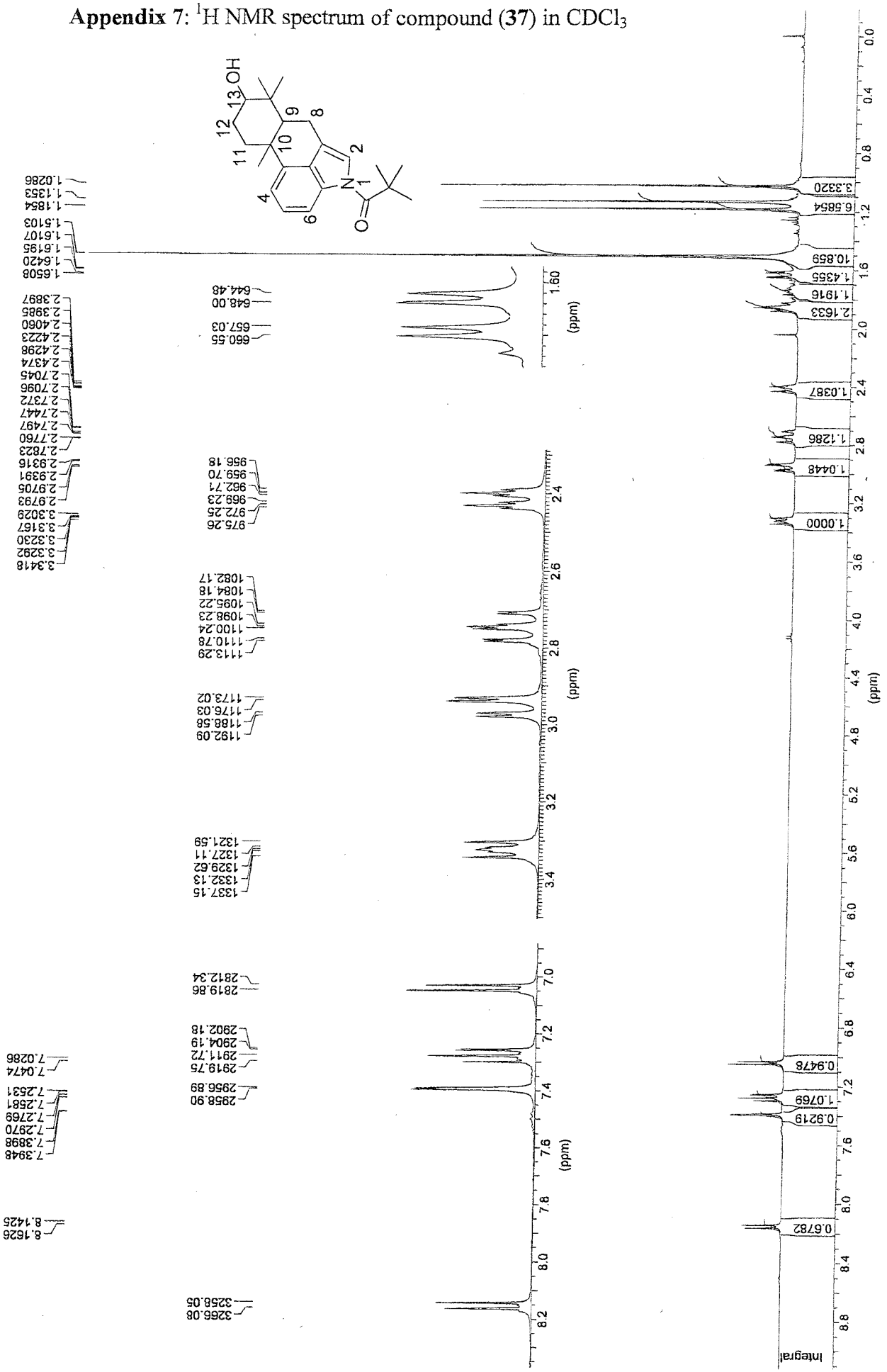
Appendix 5: ^{1}H NMR spectrum of compound (**34**) in $CDCl_3$



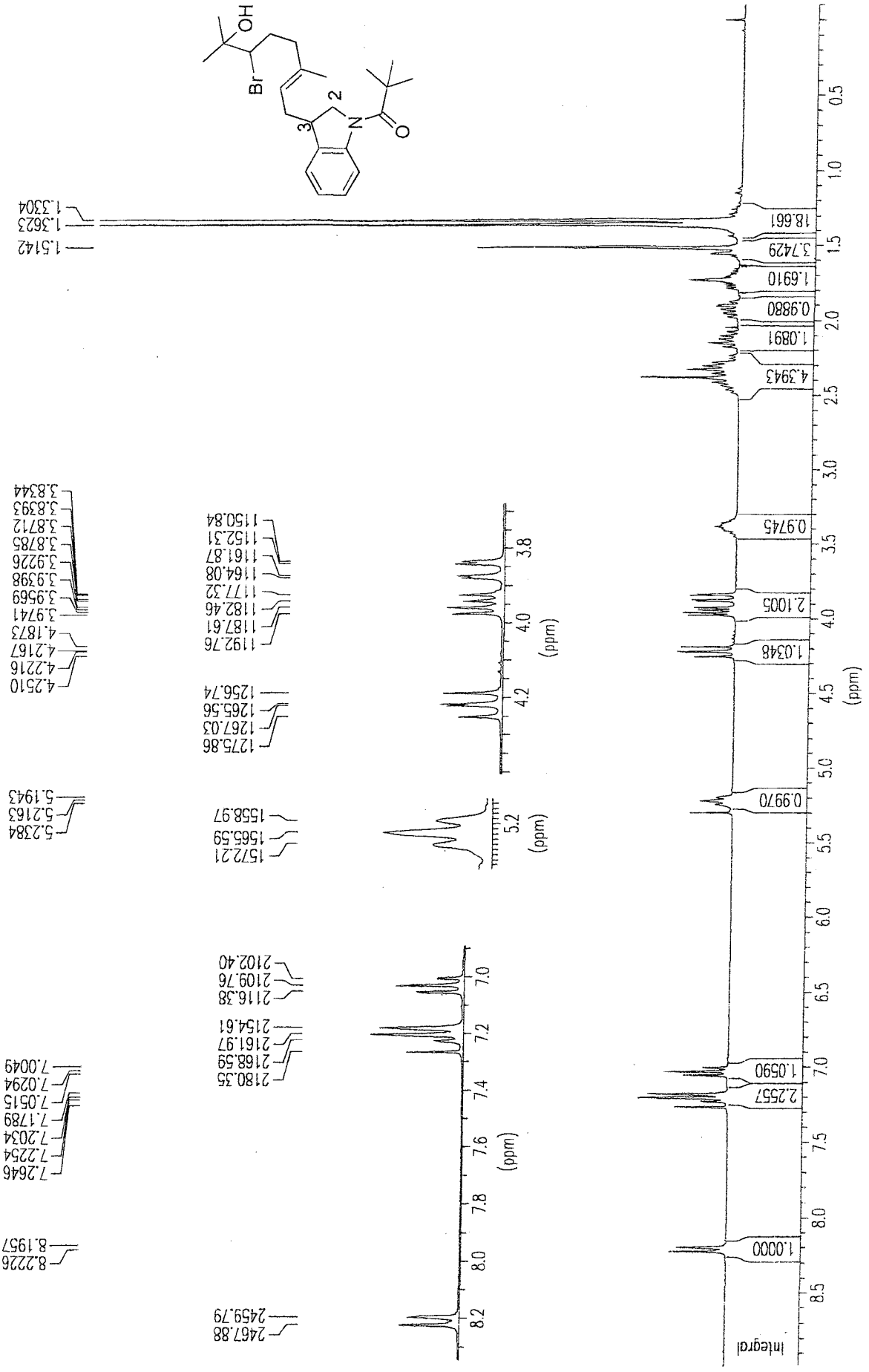
Appendix 6: ^{1}H NMR spectrum of compound (**36**) in $CDCl_3$



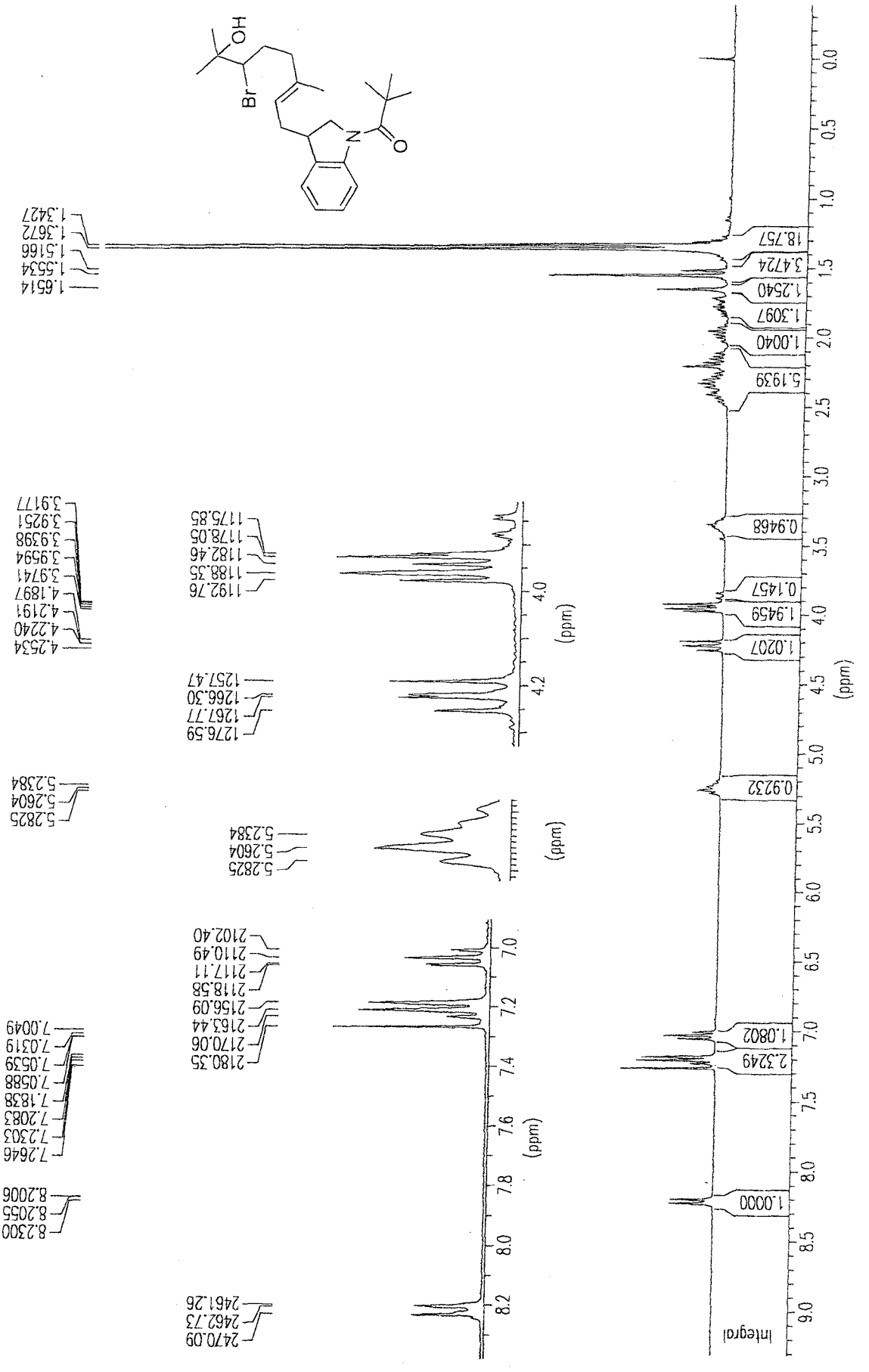
Appendix 7: ^{1}H NMR spectrum of compound (**37**) in $CDCl_3$



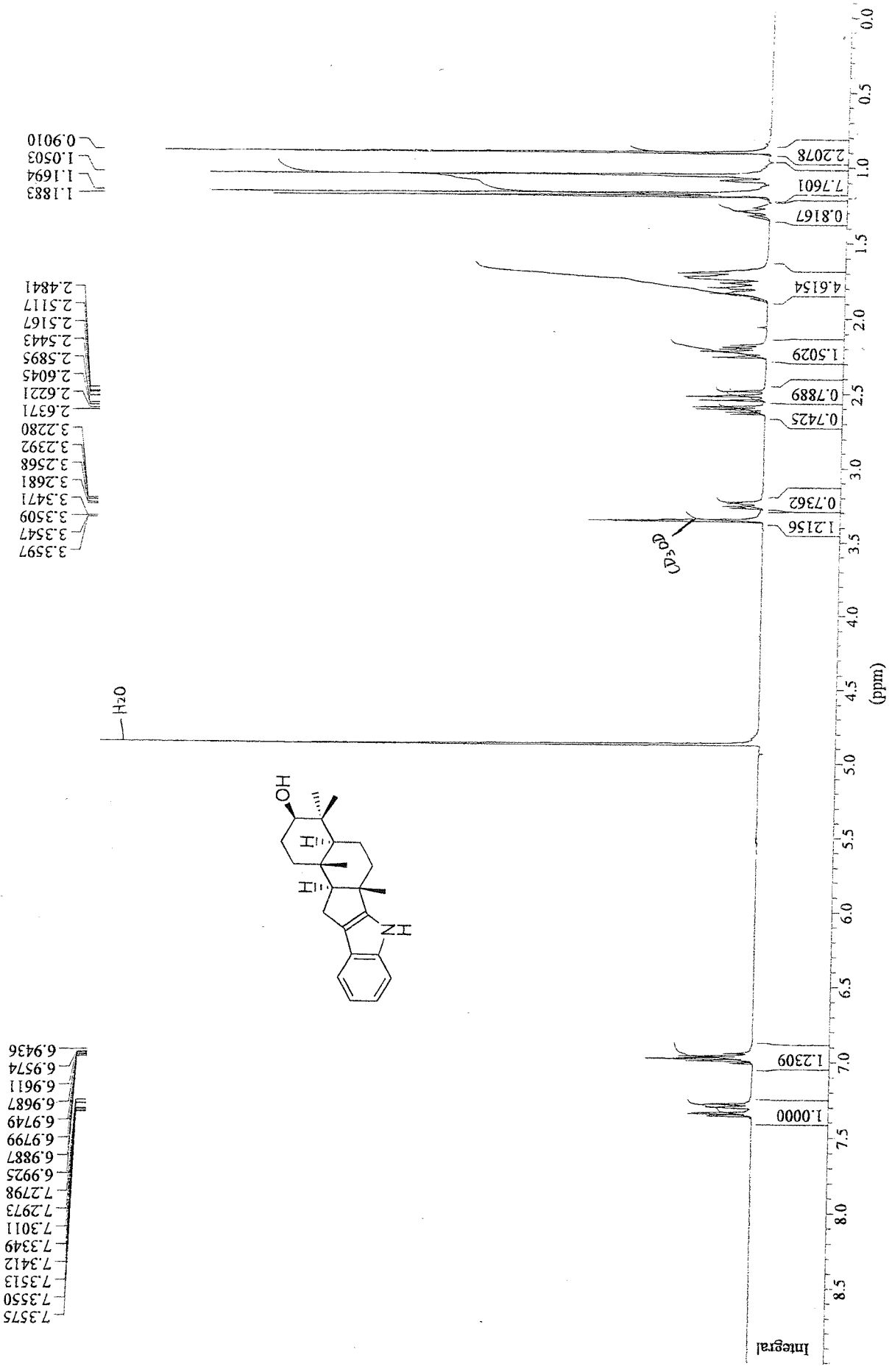
Appendix 8: ^{1}H NMR spectrum of isomer 1 of compound (**40**) in $CDCl_3$



Appendix 9: ^{1}H NMR spectrum of isomer 2 of compound (**40**) in $CDCl_3$



Appendix 10: ^{1}H NMR spectrum of compound (**47**) in CD_3OD



Appendix 11: X-ray crystallographic data of compound (**47**)

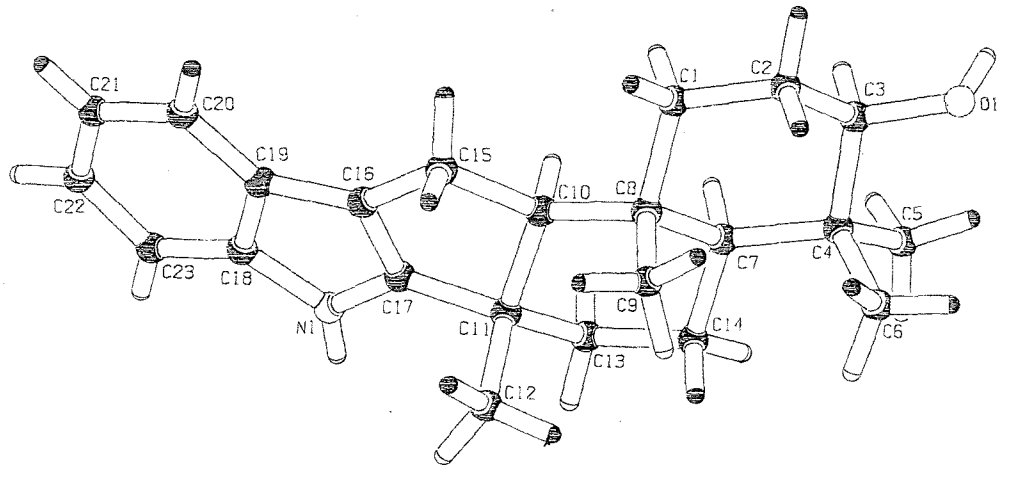


Table 1. Crystal data and structure refinement.

Identification code	**01sot087**	
Empirical formula	$C_{23}H_{31}NO$	
Formula weight	337.49	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.370(2) Å	α = 90°
	b = 16.919(3) Å	β = 115.72(3)°
	c = 11.228(2) Å	γ = 90°
Volume	1945.9(7) Å^3	
Z	4	
Density (calculated)	1.152 Mg / m^3	
Absorption coefficient	0.069 mm^{-1}	
F(000)	736	
Crystal	Block; colourless	
Crystal size	0.30 × 0.20 × 0.10 mm^3	
θ range for data collection	3.12 – 27.48°	
Index ranges	$-14 \le h \le 14$, $-21 \le k \le 21$, $-14 \le l \le 14$	
Reflections collected	21421	
Independent reflections	4407 [R_{int} = 0.1288]	
Completeness to θ = 27.48°	98.7 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9931 and 0.9796	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4407 / 0 / 232	
Goodness-of-fit on F^2	1.007	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0509, $wR2$ = 0.1146	
R indices (all data)	$R1$ = 0.0947, $wR2$ = 0.1337	
Extinction coefficient	0.0083(17)	
Largest diff. peak and hole	0.275 and –0.237 e Å^{-3}	

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	5767(2)	1338(1)	4492(2)	25(1)	1
C2	4677(2)	1921(1)	3715(2)	27(1)	1
C3	3460(2)	1504(1)	2750(2)	25(1)	1
C4	3682(2)	967(1)	1753(2)	24(1)	1
C5	2426(2)	491(1)	993(2)	33(1)	1
C6	3930(2)	1466(1)	734(2)	31(1)	1
C7	4816(1)	399(1)	2588(1)	21(1)	1
C8	6116(2)	794(1)	3590(2)	22(1)	1
C9	6855(2)	1286(1)	2971(2)	28(1)	1
C10	6941(2)	103(1)	4428(2)	21(1)	1
C11	7236(2)	−583(1)	3658(2)	22(1)	1
C12	8093(2)	−373(1)	2949(2)	29(1)	1
C13	5936(2)	−926(1)	2675(2)	24(1)	1
C14	5061(2)	−270(1)	1788(2)	26(1)	1
C15	8224(2)	229(1)	5701(2)	24(1)	1
C16	8690(2)	−616(1)	5962(2)	23(1)	1
C17	8089(2)	−1058(1)	4852(2)	23(1)	1
C18	9392(2)	−1895(1)	6384(2)	26(1)	1
C19	9544(2)	−1134(1)	6984(2)	24(1)	1
C20	10383(2)	−1064(1)	8339(2)	30(1)	1
C21	11010(2)	−1730(1)	9045(2)	37(1)	1
C22	10825(2)	−2469(1)	8432(2)	40(1)	1
C23	10025(2)	−2563(1)	7102(2)	34(1)	1
N1	8508(1)	−1827(1)	5068(1)	25(1)	1
O1	2467(1)	2087(1)	2058(1)	31(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.527(2)	C2–C1–C8	112.77(13)
C1–C8	1.542(2)	C3–C2–C1	111.81(13)
C2–C3	1.511(2)	O1–C3–C2	109.00(13)
C3–O1	1.4455(18)	O1–C3–C4	110.28(12)
C3–C4	1.545(2)	C2–C3–C4	114.07(13)
C4–C5	1.535(2)	C5–C4–C6	107.49(13)
C4–C6	1.543(2)	C5–C4–C3	107.87(13)
C4–C7	1.554(2)	C6–C4–C3	110.81(13)
C7–C14	1.544(2)	C5–C4–C7	109.80(13)
C7–C8	1.566(2)	C6–C4–C7	114.48(13)
C8–C10	1.538(2)	C3–C4–C7	106.24(12)
C8–C9	1.546(2)	C14–C7–C4	114.48(12)
C10–C15	1.551(2)	C14–C7–C8	112.28(12)
C10–C11	1.568(2)	C4–C7–C8	116.55(12)
C11–C17	1.502(2)	C10–C8–C1	108.36(12)
C11–C13	1.524(2)	C10–C8–C9	112.18(12)
C11–C12	1.543(2)	C1–C8–C9	108.61(12)
C13–C14	1.534(2)	C10–C8–C7	104.50(11)
C15–C16	1.509(2)	C1–C8–C7	107.18(12)
C16–C17	1.356(2)	C9–C8–C7	115.68(12)
C16–C19	1.435(2)	C8–C10–C15	122.64(12)
C17–N1	1.3704(19)	C8–C10–C11	116.43(12)
C18–N1	1.385(2)	C15–C10–C11	105.63(12)
C18–C23	1.392(2)	C17–C11–C13	119.35(13)
C18–C19	1.429(2)	C17–C11–C12	106.04(12)
C19–C20	1.407(2)	C13–C11–C12	110.18(12)
C20–C21	1.383(2)	C17–C11–C10	96.50(12)
C21–C22	1.398(3)	C13–C11–C10	108.02(12)
C22–C23	1.380(3)	C12–C11–C10	116.58(12)

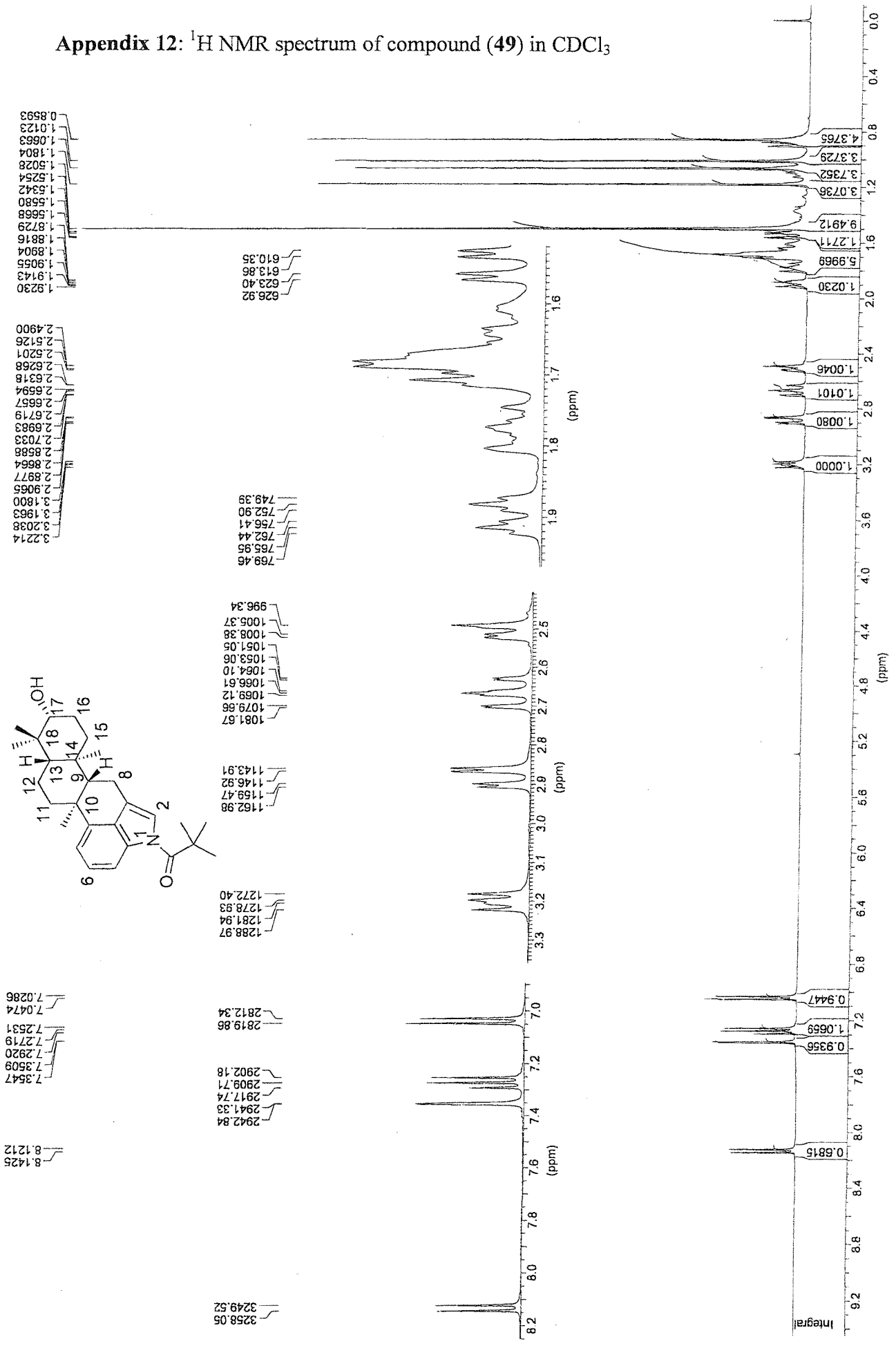
C11–C13–C14	110.29(13)
C13–C14–C7	112.52(13)
C16–C15–C10	99.19(12)
C17–C16–C19	107.14(14)
C17–C16–C15	110.44(13)
C19–C16–C15	142.42(14)
C16–C17–N1	111.28(14)
C16–C17–C11	113.46(14)
N1–C17–C11	134.91(14)
N1–C18–C23	129.69(15)
N1–C18–C19	108.13(13)
C23–C18–C19	122.12(16)
C20–C19–C18	118.13(14)
C20–C19–C16	136.05(15)
C18–C19–C16	105.77(14)
C21–C20–C19	119.40(16)
C20–C21–C22	121.04(18)
C23–C22–C21	121.56(17)
C22–C23–C18	117.74(16)
C17–N1–C18	107.65(12)

Symmetry transformations used to generate equivalent atoms:

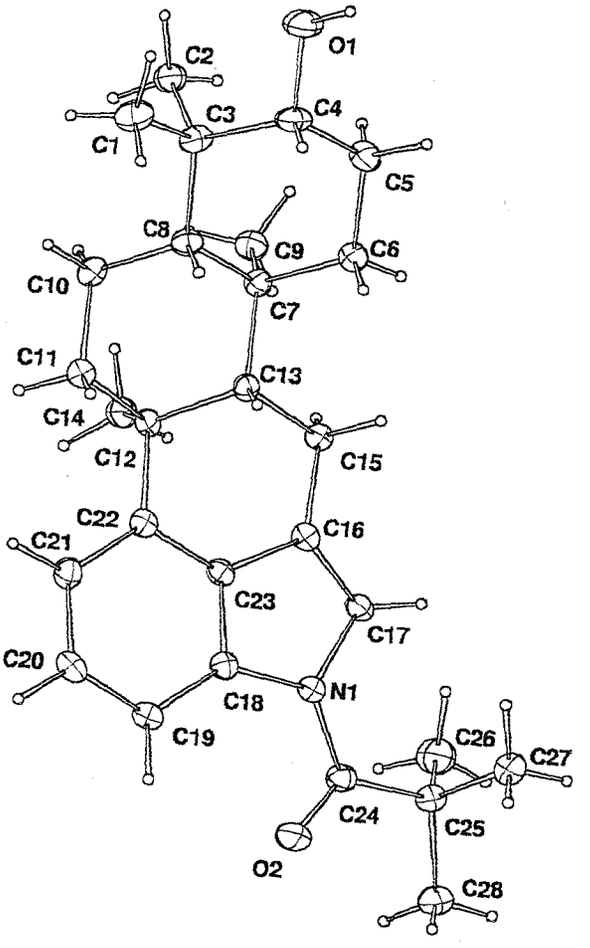
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	25(1)	22(1)	25(1)	−2(1)	8(1)	−1(1)
C2	31(1)	24(1)	27(1)	−2(1)	14(1)	3(1)
C3	25(1)	24(1)	28(1)	6(1)	13(1)	5(1)
C4	23(1)	27(1)	22(1)	3(1)	8(1)	2(1)
C5	26(1)	37(1)	30(1)	1(1)	6(1)	3(1)
C6	34(1)	35(1)	26(1)	8(1)	14(1)	9(1)
C7	22(1)	23(1)	19(1)	2(1)	9(1)	−1(1)
C8	22(1)	21(1)	22(1)	0(1)	9(1)	−2(1)
C9	26(1)	25(1)	35(1)	5(1)	14(1)	−1(1)
C10	22(1)	21(1)	20(1)	0(1)	9(1)	−3(1)
C11	22(1)	21(1)	22(1)	1(1)	9(1)	0(1)
C12	28(1)	30(1)	33(1)	4(1)	17(1)	3(1)
C13	26(1)	23(1)	23(1)	−2(1)	10(1)	0(1)
C14	28(1)	25(1)	22(1)	−1(1)	9(1)	−1(1)
C15	23(1)	22(1)	25(1)	−2(1)	7(1)	−3(1)
C16	19(1)	22(1)	26(1)	1(1)	8(1)	−3(1)
C17	21(1)	21(1)	28(1)	1(1)	11(1)	−1(1)
C18	20(1)	28(1)	29(1)	4(1)	10(1)	0(1)
C19	17(1)	27(1)	27(1)	4(1)	7(1)	−2(1)
C20	22(1)	34(1)	31(1)	3(1)	8(1)	−2(1)
C21	23(1)	47(1)	32(1)	9(1)	3(1)	0(1)
C22	29(1)	38(1)	45(1)	17(1)	9(1)	8(1)
C23	29(1)	27(1)	45(1)	7(1)	14(1)	5(1)
N1	27(1)	19(1)	29(1)	−1(1)	11(1)	1(1)
O1	26(1)	35(1)	36(1)	9(1)	15(1)	10(1)

Appendix 12: ^{1}H NMR spectrum of compound (**49**) in $CDCl_3$



Appendix 13: X-ray crystallographic data of compound (**49**)



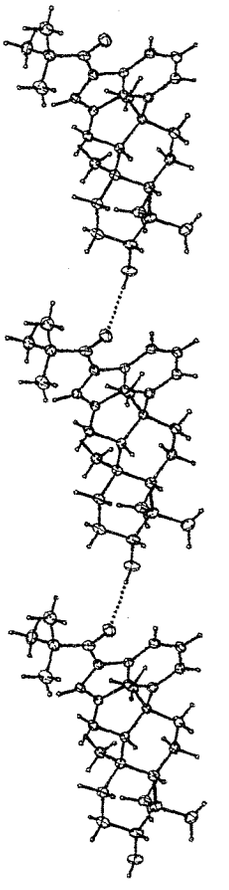


Table 1. Crystal data and structure refinement.

Identification code	**01SOT055**
Empirical formula	$C_{28}H_{39}NO_2$
Formula weight	421.60
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 14.3644(2) Å
	b = 11.0634(2) Å β = 100.966(3)°
	c = 14.6545(2) Å
Volume	2286.35(6) Å^3
Z	4
Density (calculated)	1.225 Mg / m^3
Absorption coefficient	0.075 mm^{-1}
F(000)	920
Crystal	Colourless Block
Crystal size	0.20 × 0.10 × 0.10 mm^3
θ range for data collection	3.42 – 25.03°
Index ranges	$-17 \le h \le 16$, $-13 \le k \le 13$, $-17 \le l \le 17$
Reflections collected	12643
Independent reflections	4001 [R_{int} = 0.0507]
Completeness to θ = 25.03°	99.0 %
Max. and min. transmission	0.9925 and 0.9851
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4001 / 0 / 289
Goodness-of-fit on F^2	1.039
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0412, $wR2$ = 0.1020
R indices (all data)	$R1$ = 0.0609, $wR2$ = 0.1118
Extinction coefficient	0.010(2)
Largest diff. peak and hole	0.230 and –0.206 e Å^{-3}

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	6599(1)	1344(1)	831(1)	32(1)	1
O2	15182(1)	−141(1)	1430(1)	29(1)	1
C23	12556(1)	1453(1)	1001(1)	17(1)	1
C10	9372(1)	3170(1)	−228(1)	22(1)	1
N1	13807(1)	452(1)	1810(1)	19(1)	1
C7	9617(1)	1985(1)	1288(1)	19(1)	1
C22	12004(1)	2156(1)	316(1)	18(1)	1
C15	11340(1)	1365(1)	2043(1)	21(1)	1
C8	8978(1)	2169(1)	311(1)	19(1)	1
C18	13469(1)	1058(1)	961(1)	18(1)	1
C3	7887(1)	2271(1)	271(1)	22(1)	1
C20	13317(1)	2007(1)	−504(1)	23(1)	1
C4	7576(1)	1171(1)	786(1)	24(1)	1
C13	10644(1)	1690(1)	1131(1)	17(1)	1
C2	7578(1)	3457(1)	670(1)	25(1)	1
C16	12310(1)	1075(1)	1857(1)	18(1)	1
C11	10364(1)	2868(1)	−379(1)	22(1)	1
C21	12406(1)	2422(1)	−453(1)	23(1)	1
C12	11076(1)	2646(1)	530(1)	18(1)	1
C9	9608(1)	3078(1)	1950(1)	23(1)	1
C5	8167(1)	973(2)	1747(1)	26(1)	1
C1	7370(1)	2190(2)	−750(1)	30(1)	1
C6	9227(1)	874(1)	1737(1)	23(1)	1
C19	13873(1)	1333(1)	193(1)	21(1)	1
C17	13069(1)	477(1)	2334(1)	20(1)	1
C14	11344(1)	3847(1)	1045(1)	24(1)	1
C26	15019(1)	457(2)	3753(1)	34(1)	1
C24	14714(1)	−73(1)	2038(1)	21(1)	1
C25	15092(1)	−518(2)	3023(1)	25(1)	1
C28	16147(1)	−818(2)	3092(1)	36(1)	1
C27	14579(1)	−1688(2)	3197(1)	35(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C4	1.4299(17)	C8–C3	1.561(2)
O2–C24	1.2157(17)	C18–C19	1.395(2)
C23–C22	1.392(2)	C3–C2	1.537(2)
C23–C18	1.395(2)	C3–C1	1.542(2)
C23–C16	1.430(2)	C3–C4	1.542(2)
C10–C11	1.520(2)	C20–C19	1.388(2)
C10–C8	1.531(2)	C20–C21	1.403(2)
N1–C24	1.4085(19)	C4–C5	1.516(2)
N1–C18	1.4146(19)	C13–C12	1.577(2)
N1–C17	1.4223(18)	C16–C17	1.351(2)
C7–C6	1.549(2)	C11–C12	1.536(2)
C7–C9	1.552(2)	C12–C14	1.541(2)
C7–C8	1.560(2)	C5–C6	1.529(2)
C7–C13	1.570(2)	C26–C25	1.535(2)
C22–C21	1.391(2)	C24–C25	1.525(2)
C22–C12	1.526(2)	C25–C27	1.535(2)
C15–C16	1.503(2)	C25–C28	1.535(2)
C15–C13	1.551(2)		

C22–C23–C18	123.80(13)	C1–C3–C4	107.27(13)
C22–C23–C16	126.50(13)	C2–C3–C8	114.12(12)
C18–C23–C16	109.65(13)	C1–C3–C8	109.14(12)
C11–C10–C8	111.37(12)	C4–C3–C8	107.85(12)
C24–N1–C18	123.44(12)	C19–C20–C21	123.28(13)
C24–N1–C17	129.12(13)	O1–C4–C5	110.92(12)
C18–N1–C17	107.44(11)	O1–C4–C3	107.20(12)
C6–C7–C9	107.87(12)	C5–C4–C3	113.86(12)
C6–C7–C8	107.16(12)	C15–C13–C7	113.00(11)
C9–C7–C8	113.49(12)	C15–C13–C12	112.31(11)
C6–C7–C13	108.90(11)	C7–C13–C12	115.04(12)
C9–C7–C13	111.98(12)	C17–C16–C23	106.69(13)
C8–C7–C13	107.28(11)	C17–C16–C15	134.07(13)
C21–C22–C23	115.80(13)	C23–C16–C15	119.23(13)
C21–C22–C12	127.17(13)	C10–C11–C12	113.42(12)
C23–C22–C12	116.75(12)	C22–C21–C20	120.60(14)
C16–C15–C13	111.16(12)	C22–C12–C11	110.02(11)
C10–C8–C7	110.96(11)	C22–C12–C14	105.11(11)
C10–C8–C3	113.24(12)	C11–C12–C14	110.48(12)
C7–C8–C3	117.08(12)	C22–C12–C13	109.18(12)
C23–C18–C19	120.28(14)	C11–C12–C13	108.90(11)
C23–C18–N1	106.25(12)	C14–C12–C13	113.09(12)
C19–C18–N1	133.42(13)	C4–C5–C6	112.61(12)
C2–C3–C1	107.37(13)	C5–C6–C7	112.87(12)
C2–C3–C4	110.87(12)	C20–C19–C18	116.20(13)

C16–C17–N1	109.96(13)	C24–C25–C28	107.52(12)
O2–C24–N1	117.83(14)	C27–C25–C28	107.81(14)
O2–C24–C25	121.86(13)	C24–C25–C26	111.94(13)
N1–C24–C25	120.30(12)	C27–C25–C26	112.24(13)
C24–C25–C27	109.48(13)	C28–C25–C26	107.64(13)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	17(1)	28(1)	51(1)	3(1)	10(1)	−1(1)
O2	23(1)	39(1)	28(1)	4(1)	11(1)	7(1)
C23	17(1)	17(1)	19(1)	−1(1)	5(1)	−2(1)
C10	20(1)	25(1)	20(1)	4(1)	1(1)	2(1)
N1	16(1)	22(1)	20(1)	2(1)	5(1)	1(1)
C7	18(1)	18(1)	21(1)	1(1)	5(1)	0(1)
C22	18(1)	17(1)	20(1)	−2(1)	4(1)	−2(1)
C15	19(1)	25(1)	20(1)	4(1)	6(1)	3(1)
C8	18(1)	19(1)	22(1)	−3(1)	4(1)	1(1)
C18	17(1)	17(1)	20(1)	−1(1)	3(1)	−2(1)
C3	17(1)	20(1)	27(1)	−2(1)	2(1)	1(1)
C20	24(1)	26(1)	20(1)	0(1)	9(1)	−4(1)
C4	15(1)	22(1)	37(1)	−2(1)	7(1)	1(1)
C13	19(1)	16(1)	18(1)	0(1)	4(1)	1(1)
C2	21(1)	22(1)	35(1)	2(1)	8(1)	2(1)
C16	19(1)	18(1)	18(1)	0(1)	5(1)	−1(1)
C11	20(1)	23(1)	22(1)	4(1)	6(1)	1(1)
C21	23(1)	25(1)	19(1)	4(1)	3(1)	0(1)
C12	18(1)	19(1)	19(1)	2(1)	4(1)	−1(1)
C9	22(1)	25(1)	23(1)	−2(1)	5(1)	0(1)
C5	24(1)	23(1)	32(1)	5(1)	11(1)	−1(1)
C1	21(1)	35(1)	32(1)	−1(1)	0(1)	1(1)
C6	20(1)	21(1)	27(1)	4(1)	7(1)	0(1)
C19	18(1)	23(1)	23(1)	−3(1)	6(1)	−2(1)
C17	18(1)	24(1)	18(1)	2(1)	6(1)	0(1)
C14	22(1)	20(1)	30(1)	2(1)	7(1)	0(1)
C26	29(1)	48(1)	24(1)	0(1)	2(1)	3(1)
C24	18(1)	18(1)	28(1)	−1(1)	6(1)	−1(1)
C25	18(1)	31(1)	26(1)	7(1)	5(1)	5(1)
C28	21(1)	51(1)	37(1)	14(1)	7(1)	9(1)
C27	29(1)	33(1)	45(1)	17(1)	13(1)	8(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

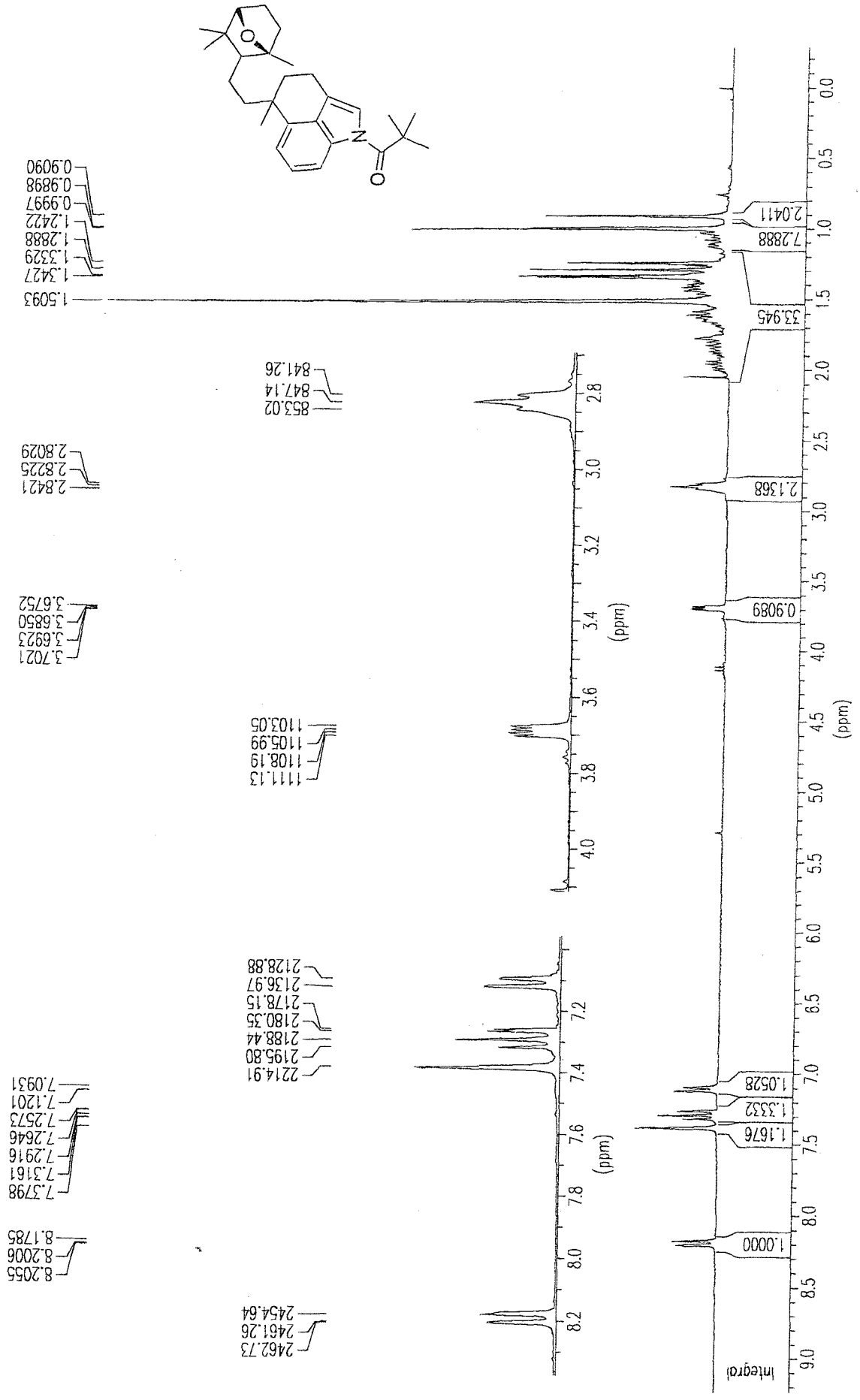
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	6367	686	968	48	1
H10A	8947	3281	−839	26	1
H10B	9389	3939	119	26	1
H15A	11386	2053	2481	25	1
H15B	11093	659	2337	25	1
H8	9059	1410	−37	23	1
H20	13566	2196	−1043	27	1
H4	7627	432	405	29	1
H13	10577	931	753	21	1
H2A	6887	3537	503	38	1
H2B	7878	4141	415	38	1
H2C	7771	3451	1349	38	1
H11A	10597	3542	−719	26	1
H11B	10333	2136	−773	26	1
H21	12059	2890	−947	27	1
H9A	9092	2979	2296	34	1
H9B	9511	3825	1585	34	1
H9C	10215	3121	2388	34	1
H5A	7954	224	2013	31	1
H5B	8062	1655	2153	31	1
H1A	7640	1528	−1060	45	1
H1B	7445	2953	−1067	45	1
H1C	6694	2035	−771	45	1
H6A	9340	138	1389	27	1
H6B	9578	783	2383	27	1
H19	14494	1075	149	25	1
H17	13105	125	2931	23	1
H14A	11731	3681	1659	35	1
H14B	10765	4275	1120	35	1
H14C	11705	4349	686	35	1
H26A	15259	1226	3558	51	1
H26B	15398	214	4353	51	1
H26C	14355	552	3811	51	1
H28A	16216	−1433	2628	54	1
H28B	16407	−1126	3715	54	1
H28C	16491	−86	2977	54	1
H27A	13895	−1537	3104	52	1
H27B	14809	−1962	3836	52	1
H27C	14704	−2313	2762	52	1

Table 6. Hydrogen bonds [Å and °].

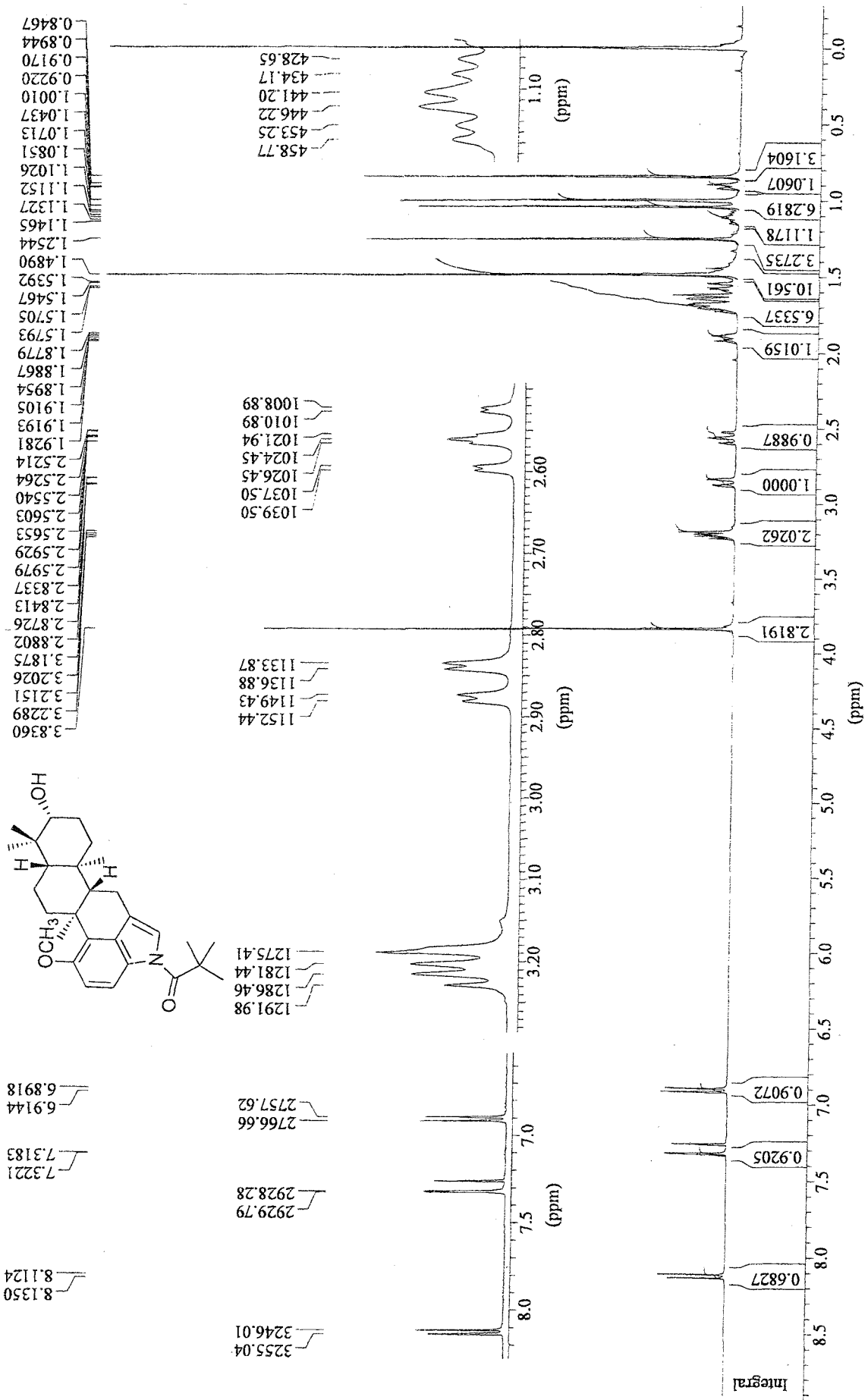
D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1···O2^{i}	0.84	2.15	2.8796(15)	144.8

Symmetry transformations used to generate equivalent atoms:
(i) x−1,y,z

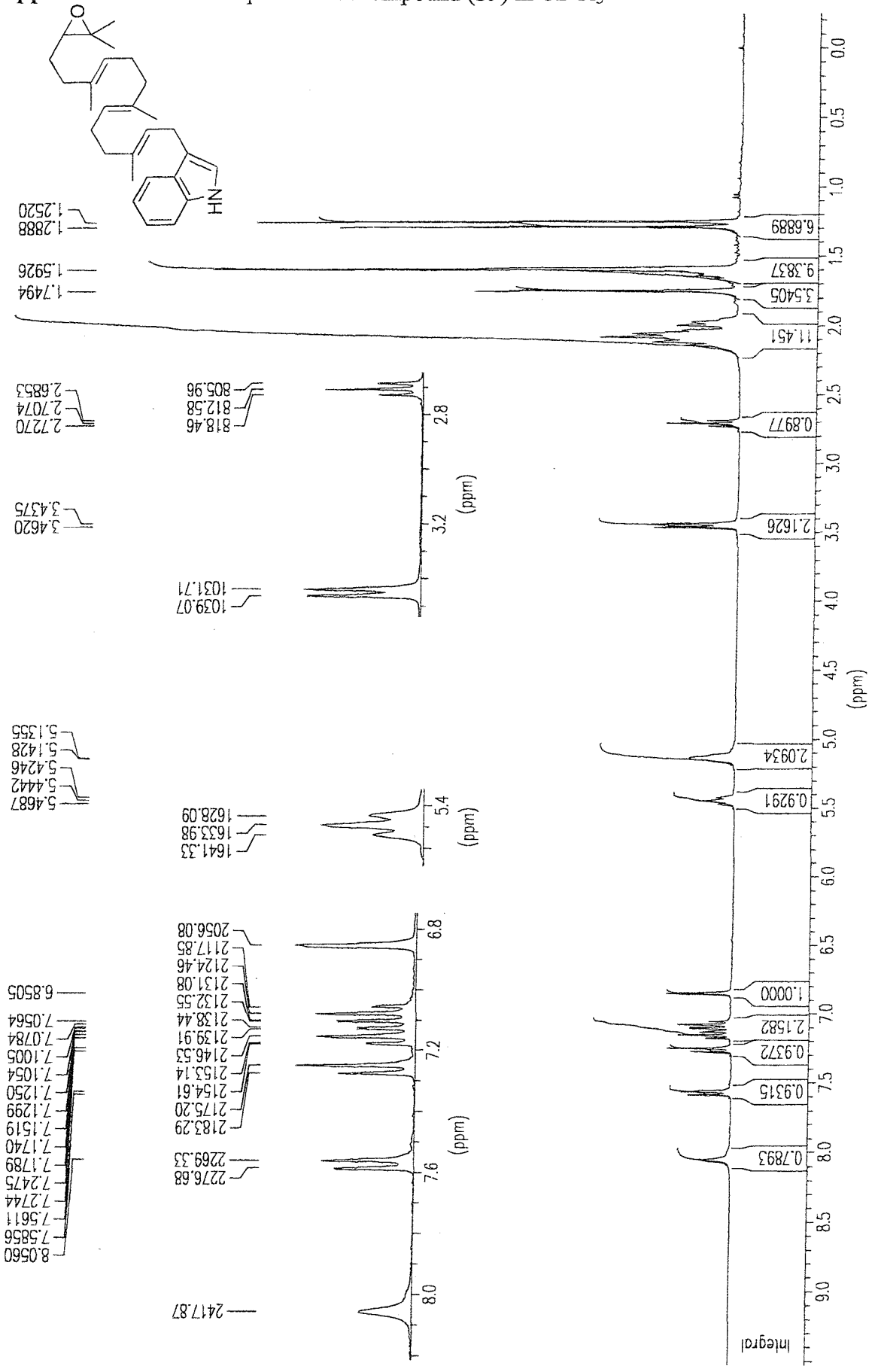
Appendix 14: ^{1}H NMR spectrum of compound (**50**) in $CDCl_3$



Appendix 15: ^{1}H NMR spectrum of compound (**53**) in $CDCl_3$



Appendix 16: ^{1}H NMR spectrum of compound (**59**) in $CDCl_3$



Appendix 17: ^{1}H NMR spectrum of compound (**60**) in $CDCl_3$