Diels–Alder Routes to *Prosopis* Alkaloids

A thesis submitted to the University of Cambridge for the degree of

Doctor of Philosophy

by

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of

Clare College, Cambridge

July 1987

To My Wife

DECLARATION

Except where indicated to the contrary, either directly or by reference, everything described in this thesis is entirely the original work of the author. This thesis has not been submitted for any other degree or diploma at this or any other university, and does not exceed the prescribed word limit.

T. N. Birkinshaw

ACKNOWLEDGEMENTS

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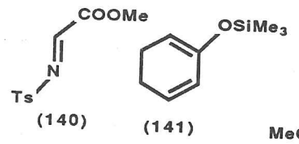
"A decent chemist is worth twenty poets."

Tugenev, *Fathers and Sons.*

Contents



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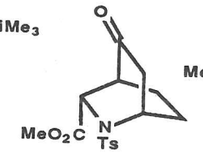

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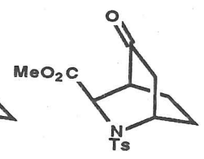

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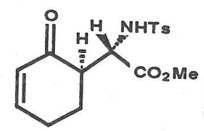

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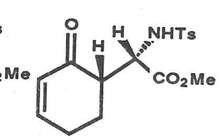

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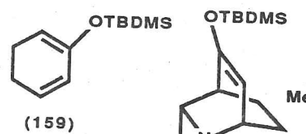

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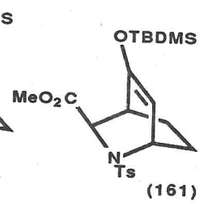

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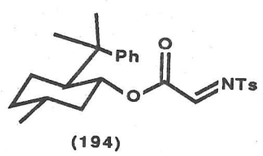

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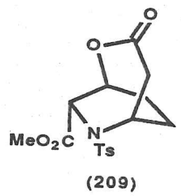

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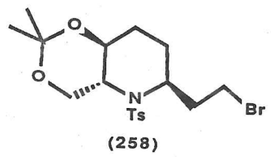

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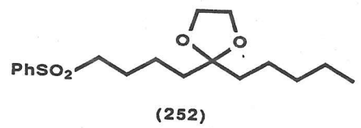

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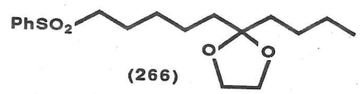

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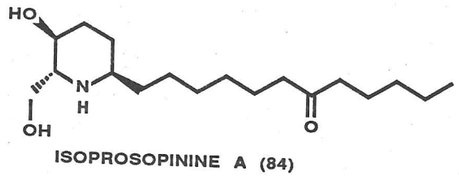

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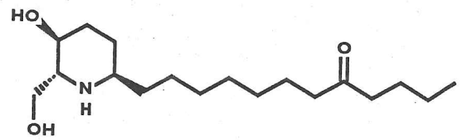

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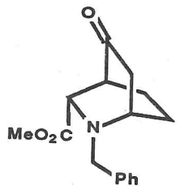
(274)



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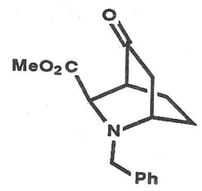

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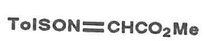

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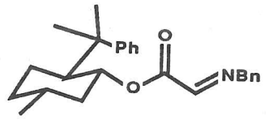

(288)

Summary

Diels–Alder Routes to Prosopis Alkaloids.

This thesis describes the investigation of the Diels–Alder reaction of the imine (140) with the diene (141) to give four products (142, 143, 156, 157). At low temperatures the enone (156) is the major product while at ambient temperature the bicyclic compounds (142) and (143) predominate. The reaction is highly solvent dependent, with the best results being obtained in benzene solution. Lewis acids appear to have little effect on the course of the reaction. The reaction of the imine (140) with the TBDMSO diene (159) gives the silyl enol ethers (160) and (161) as well as the above four products. Possible mechanisms are discussed.

In order to investigate asymmetric induction the 8–phenylmenthyl derived imine (194) was reacted with the diene (141) under a variety of conditions but no asymmetric induction was seen in the *exo* adducts, and only a small degree in the *endo* adducts.

The bromination and Baeyer–Villiger oxidation of the ketone (142) were investigated and the resultant lactone (209) was converted into the bromide (258).

Several methods to prepare a suitable side chain for isoprosopinine A were investigated. The *prosopis* alkaloids isoprosopinine A (84) and B (85) were prepared by alkylation of the sulphones (252) and (266) with the bromide (258) followed by reductive removal of the *N*-tosyl and sulphone moieties with sodium amalgam.

The imine (274) has been prepared and shown to undergo a Lewis acid catalysed imino–Diels–Alder reaction with the diene (141) to give the adducts (283) and (284).

Alternative imines for asymmetric synthesis, such as (299) and (288) have been investigated. Preparation of the sulphinamide imine (299) has proved difficult.

Attempts to carry out aqueous Diels–Alder reactions of the silyloxydiene (159) with iminium ions, generated *in situ* from amines, aldehydes and acids, have proved fruitless.

T. N. Birkinshaw
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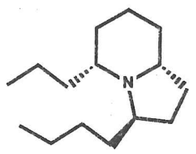
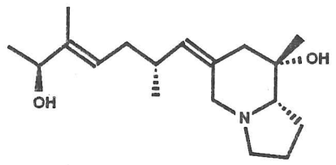


(-)-Gephyrotoxin 223AB (1)



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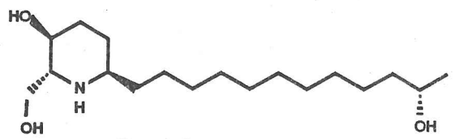
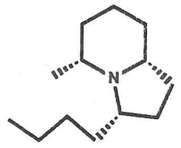
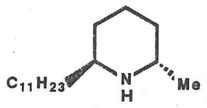


Prosopine (7)



(-)-Monomorine (3)



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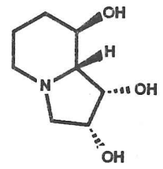

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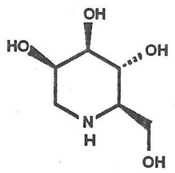
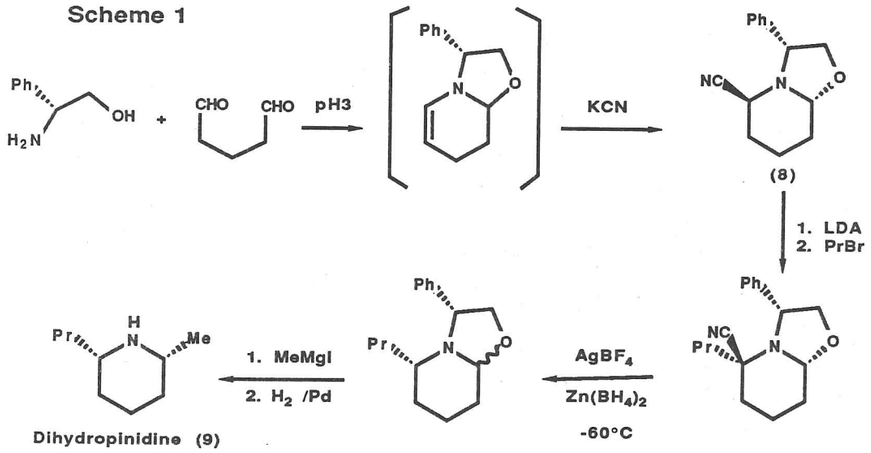


Deoxymannojirimycin (6)

Scheme 1



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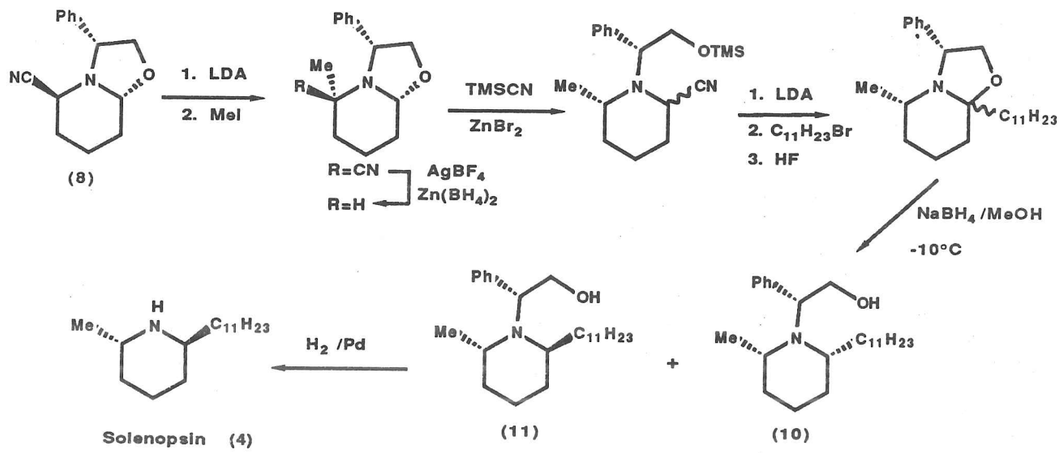

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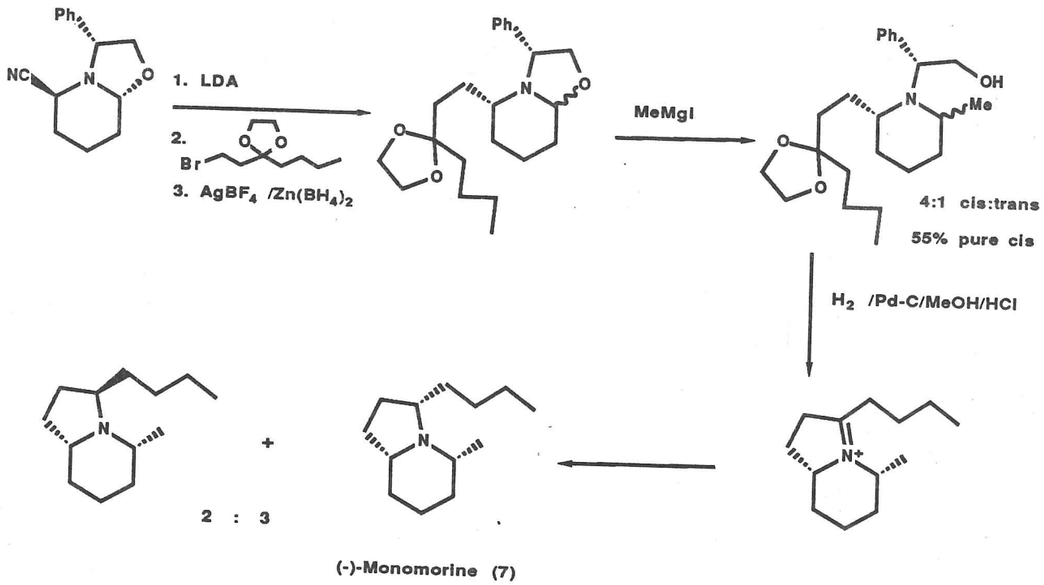

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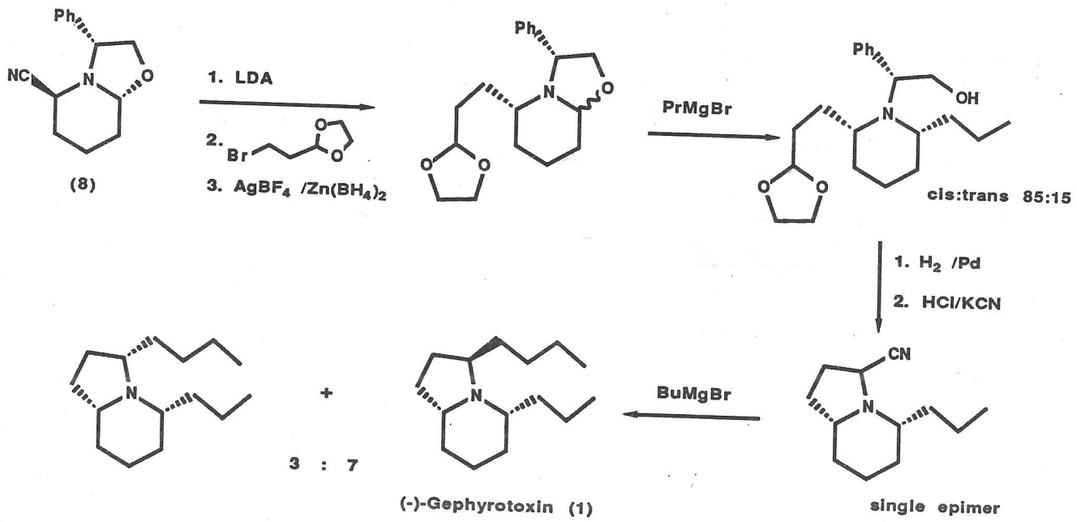
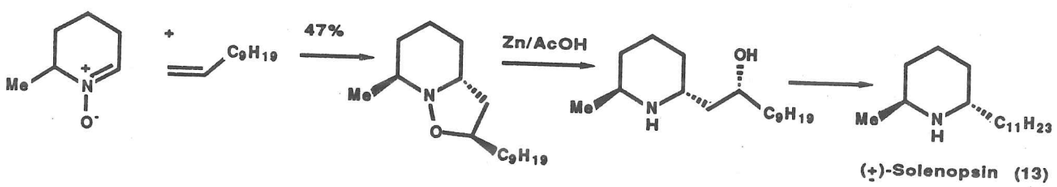


Scheme 5



1. Introduction

1.1 Syntheses of Piperidines and Piperidine Alkaloids.

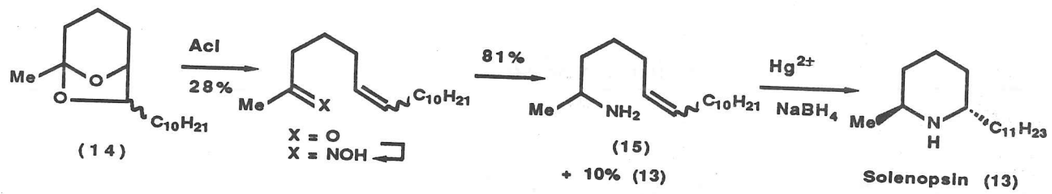
A wide variety of piperidine derivatives, often with interesting biological activities, have been isolated from natural sources, both animal and plant. These include gephyrotoxin 223AB (1)[1] and pumiliotoxin A (2)[2] from poison-dart frogs, the ant-trail pheremone monomorine (3),[3] the fire-ant venom solenopsin A (4),[4] the neurotoxin swainsonine (5),[5] deoxymannojirimycin (6), a plant-derived mannosidase inhibitor,[6] and prosopine (7),[7] also with a range of biological activities.

The isolation and synthesis of piperidine alkaloids up to June 1985 have been covered in a series of reviews by Pinder.[8] A number of new syntheses of piperidines and piperidine alkaloids, several of which give enantiomerically pure compounds, has been published recently. Husson has used the enantiomerically pure synthon (8) (prepared from phenylglycinol and glutaraldehyde) in a number of syntheses.[9-14] Dihydropinidine (9) was prepared by alkylation of the anion of the synthon (8) with propyl bromide in 98% yield, followed by reductive removal of the cyano group (Scheme 1). The silver salt complexes the cyano group and reduction is by axial attack (70-77%). Reaction with methyl magnesium iodide gives a separable mixture of *cis* and *trans* dialkyl piperidines (80:20, 70% yield of *cis*) which on hydrogenolysis gives optically pure dihydropinidine (9). The other enantiomer can be prepared by reversing the order of alkylation. The same synthon (8) has been used to generate the *trans* geometry of (+)-solenopsin (4) *via* the reactions shown in Scheme 2.[13] Opening of the oxazoline ring with TMSCN allows the piperidine ring to be alkylated on the other side. The key step is the reductive cleavage of the re–formed oxazoline. The given conditions lead to a 70:30 mixture (10):(11) while zinc borohydride in tetrahydrofuran (THF) or sodium borohydride in THF with TFA both give 5:95 mixtures of (10):(11).

The syntheses of (–)-monomorine (3)[10] and (–)-gephyrotoxin 223AB (1)[11] have also been completed, as shown in Schemes 3 and 4. The key step in the monomorine synthesis is the final hydrogenation where the intermediate iminium ion (12) is reduced with only 3:2 selectivity. The final step in the synthesis of gephyrotoxin (1), which involves displacement of an α-amino nitrile by a Grignard reagent is more selective. Despite some of the stereochemical problems these syntheses demonstrate the utility of the chiral synthon (8) as both *cis* and *trans* 2,6-dialkylpiperidines have been prepared.

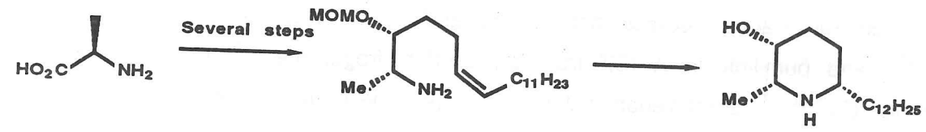
Two other syntheses of solenopsin, both racemic have been reported. Carruthers has used a nitrone cycloaddition, followed by reductive cleavage of the N-O bond and

Scheme 6



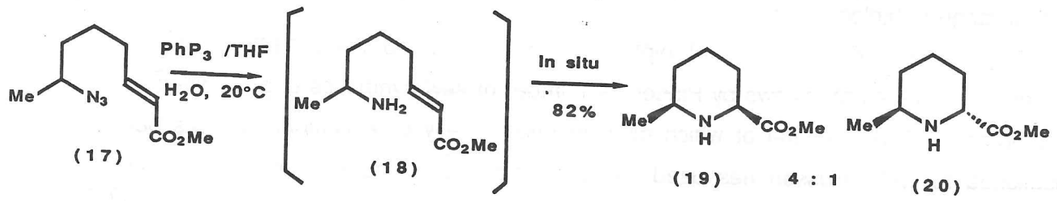
(14) (15) + 10% (13) Solenopsin (13)

Scheme 7



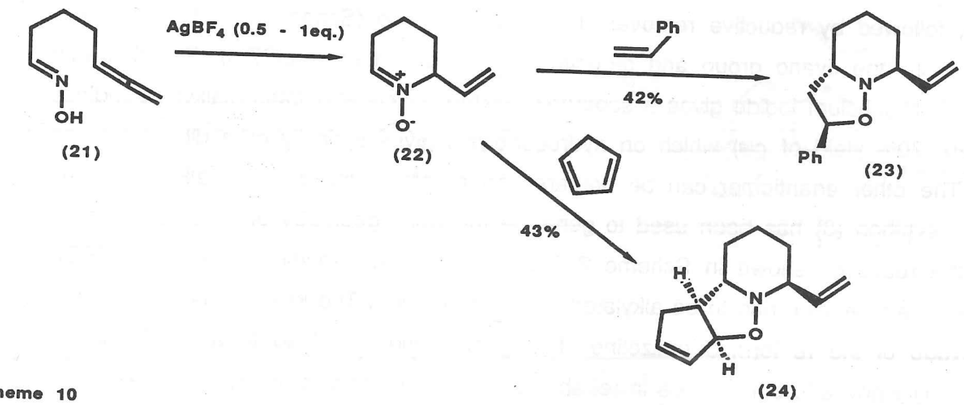
(-)-Deoxocassine (16)

Scheme 8



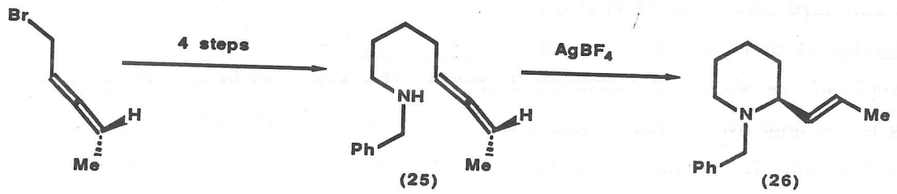
(17) (18) (19) 4 : 1 (20)

Scheme 9



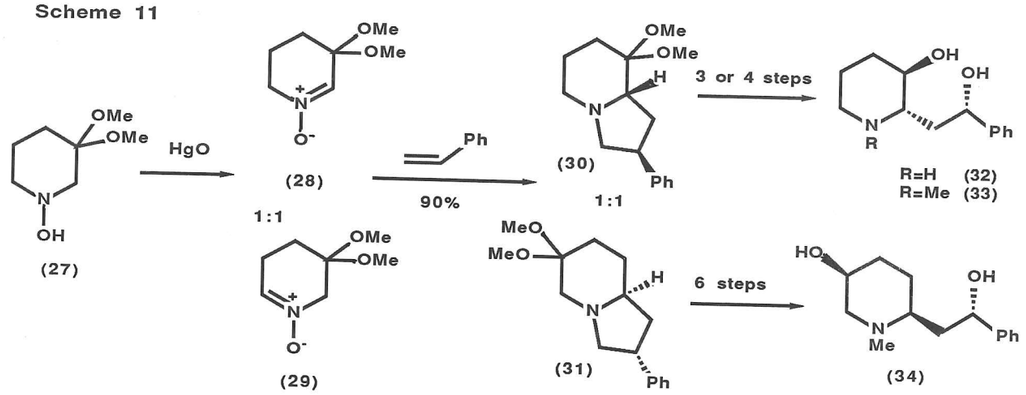
(21) (22) (23) (24)

Scheme 10



(25) (26)

Scheme 11



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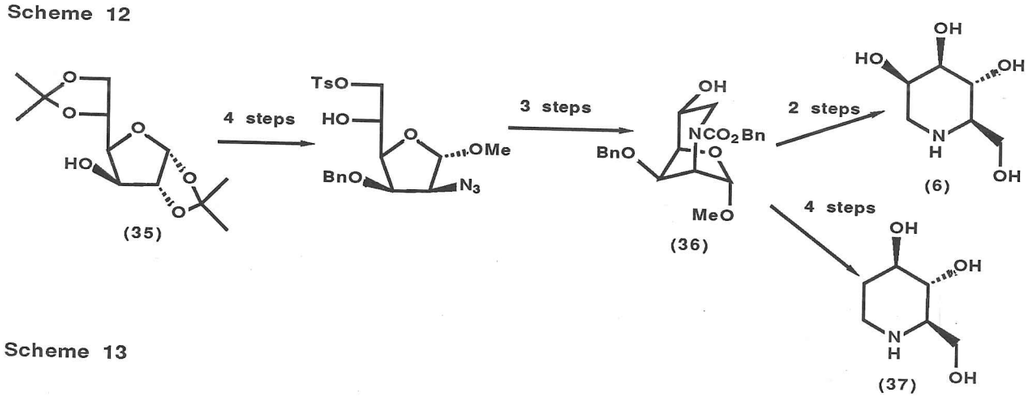

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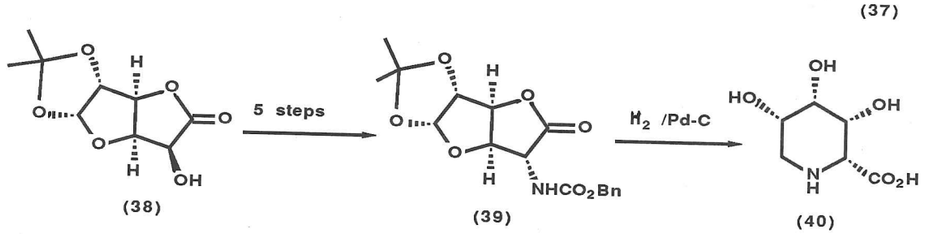

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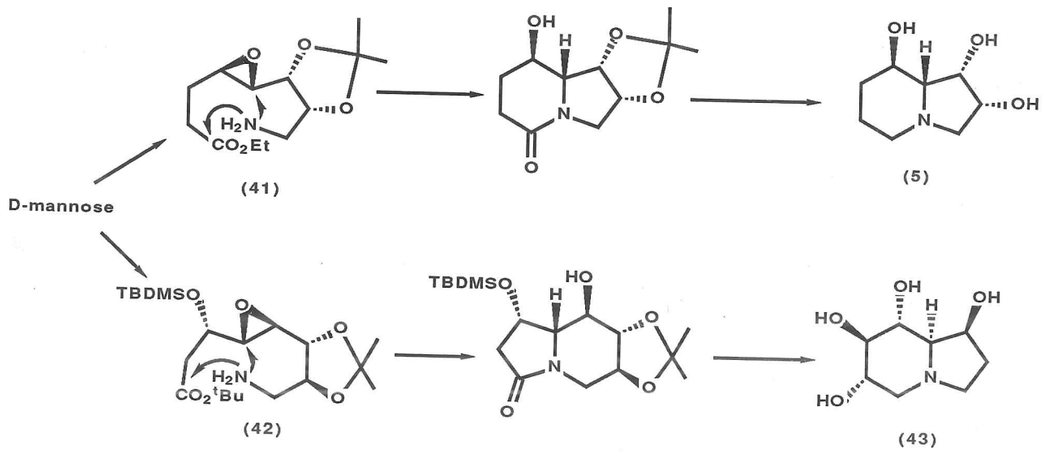


removal of the oxygen funtionality (Scheme 5).[14] The olefin attacks the nitrone from the opposite face to the methyl group to give the *trans* stereochemistry. Mundy uses a novel fragmentation reaction of the ketal (14) (Scheme 6) to give a ketone which is converted *via* its oxime into the amine (15) (some cyclistion to solenopsin occurs at this stage). [15] The amino-mercuration step is claimed to occur in quantitative yield to give racemic solenopsin (13). Khuong-Huu[16] carried out the same reaction (with starting amine (15) prepared by a different route) and obtained an 11% yield of the required *trans* compound along with 41% of the *cis* isomer and 31% recovered starting material.

Tsuyuki, Takahashi and Khuong–Huu have prepared (-)-deoxocassine (16) and two of its diastereomers from *D*-alanine *via* a similar amino–mercuration procedure (Scheme 7).[17]

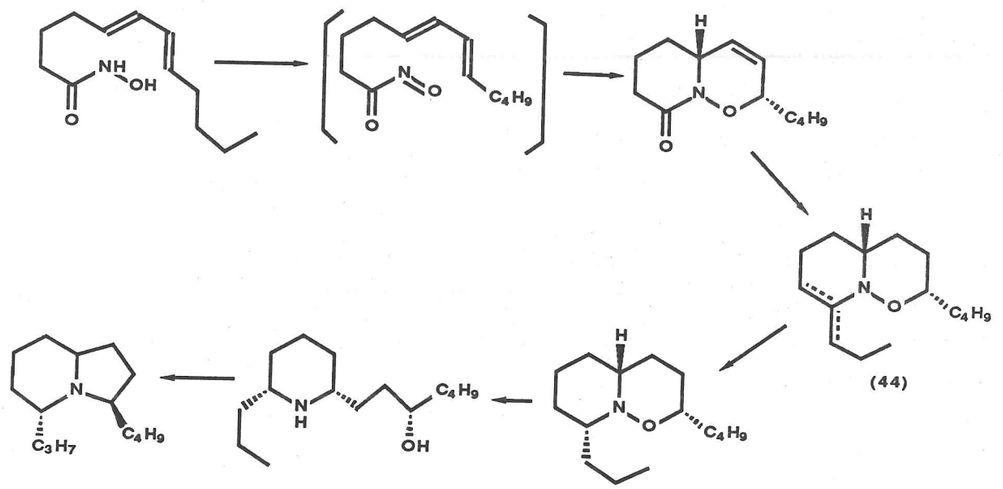
The intramolecular Michael addition of an amine to an electron–deficient olefin has been used by a French group to prepare pyrrolidines and piperidines (Scheme 8).[18] The problem in this type of reaction is generating the amine in the presence of the electron–deficient olefin, or *vice versa*. In this method the azide (17) is reduced to the amine (18) which then adds *in situ* to the α,β–unsaturated ester to give a 4:1 mixture of *cis* : *trans* isomers (19) and (20) in 82% yield. As the reaction is under kinetic control the stereoselectivity is a result of the conformation of the transition state (T.S.), not of the product stability.

Gallagher has used the silver–catalysed cyclisation of nitrogen onto allenes to prepare pyrrolidines[19] and piperidines (Scheme 9).[20,21] Silver tetrafluoroborate catalyses the cyclisation of the allenic oxime (21) to the nitrone (22) which then reacts with olefins in poor to moderate yields to give the *trans* substituted piperidines (23) and (24). The optically active allene–amine (25) (9:1 *R:S*) has been cyclised to give the optically piperidine (26) with less than 10% racemisation (8:1 *R:S*)(Scheme 10).[21] The availability of chiral allenes gives this type of reaction a great deal of potential in the non–racemic synthesis of piperidines.

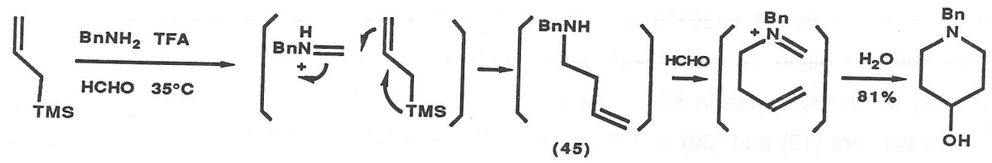
Hootelé has isolated the alkaloids (32), (33) and (34) from *Sedum acre* and synthesised them in racemic form from the hydroxylamine (27) (Scheme 11).[22] This was oxidised to the 1:1 mixture of nitrones (28) and (29) which were not separated but reacted with styrene in a regio- and stereo-selective reaction to give a 1:1 mixture of isoxazolidines (30) and (31). The former was elaborated to the piperidines (32) and (33) *via* Raney nickel and sodium borohydride reductions, while the latter isoxazolidine (31) requires a Mitsunobu inversion to obtain the correct side chain stereochemistry.

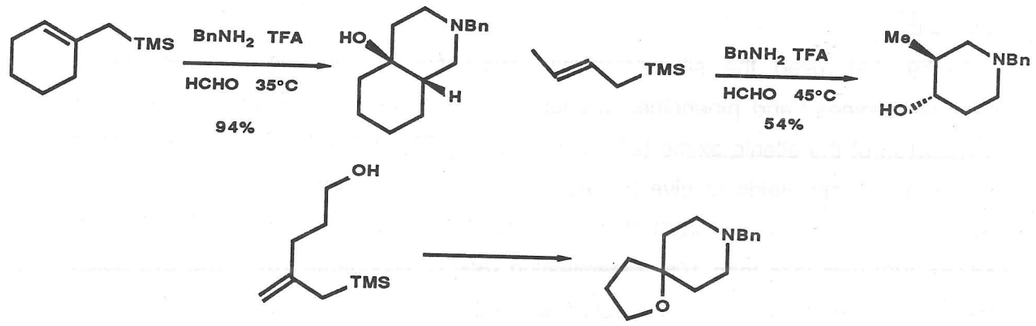
Fleet has prepared a number of polyhydroxylated piperidine alkaloids from sugars.[23-26] Deoxymannojirimycin (6) and fagomine (37) were prepared from diacetone glucose (35)

Scheme 15

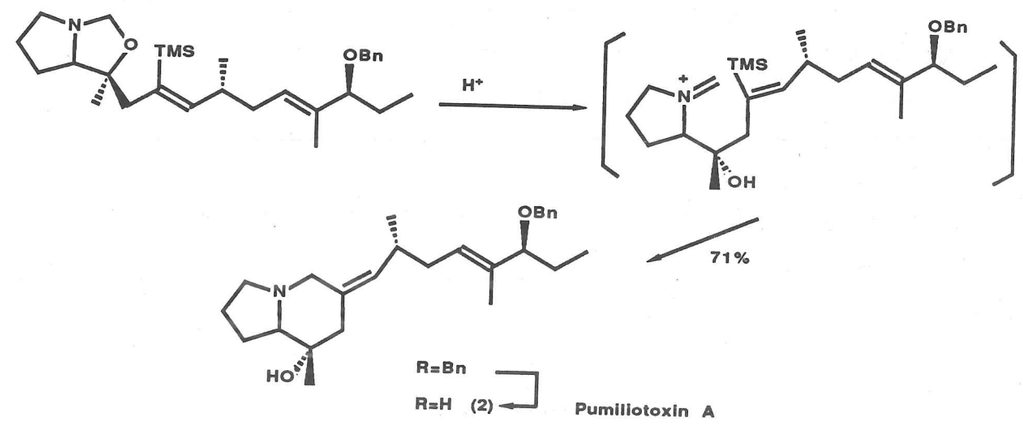


Scheme 16





Scheme 17



via the common intermediate (36) (Scheme 12).[23,24] All the chiral centres are derived from glucose; the piperidine ring being formed by alkylation of the nitrogen by the primary tosylate. The synthesis of the trihydroxypipecolic acid (40) starts from *D*-glucuronolactone acetonide (38), the key step being the intramolecular reductive amination of the lactol acetal (39) (Scheme 13).[27] Other similar compounds, which are potent glucosidase inhibitors, have been prepared.[25,26,28]

Hashimoto has prepared the indolizidine alkaloids swainsonine (5) and castanospermine (43) by double cyclisation of the intermediates (41) and (42) which are derived from *D*-mannose (Scheme 14).[29]

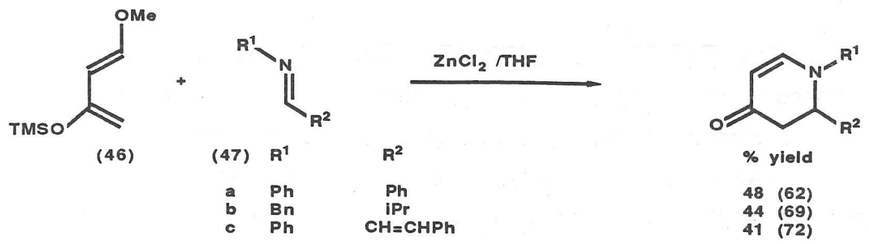
Kibayashi has used an intramolecular nitroso–Diels–Alder reaction in the synthesis of gephyrotoxin 223AB (1) (Scheme 15).[30] The 2,6 *trans* relationship is set up by axial attack of the sodium borohydride on the enamine (44). Reductive cleavage of the N-O bond followed by cyclisation of the mesylate of the side chain alcohol onto the nitrogen sets up the relative stereochemistry of the three chiral centres. Monomorine (3) has been prepared *via* a similar route.[31]

Simple piperidines can be prepared *via* the reaction of iminium ions, generated *in situ* in aqueous solution, with allyl silanes (Scheme 16).[32] The intermediate γ,δ–unsaturated amine (45) forms a second iminium ion which then cyclises and picks up water, chloride or even an internal nucleophile such as an hydroxyl.

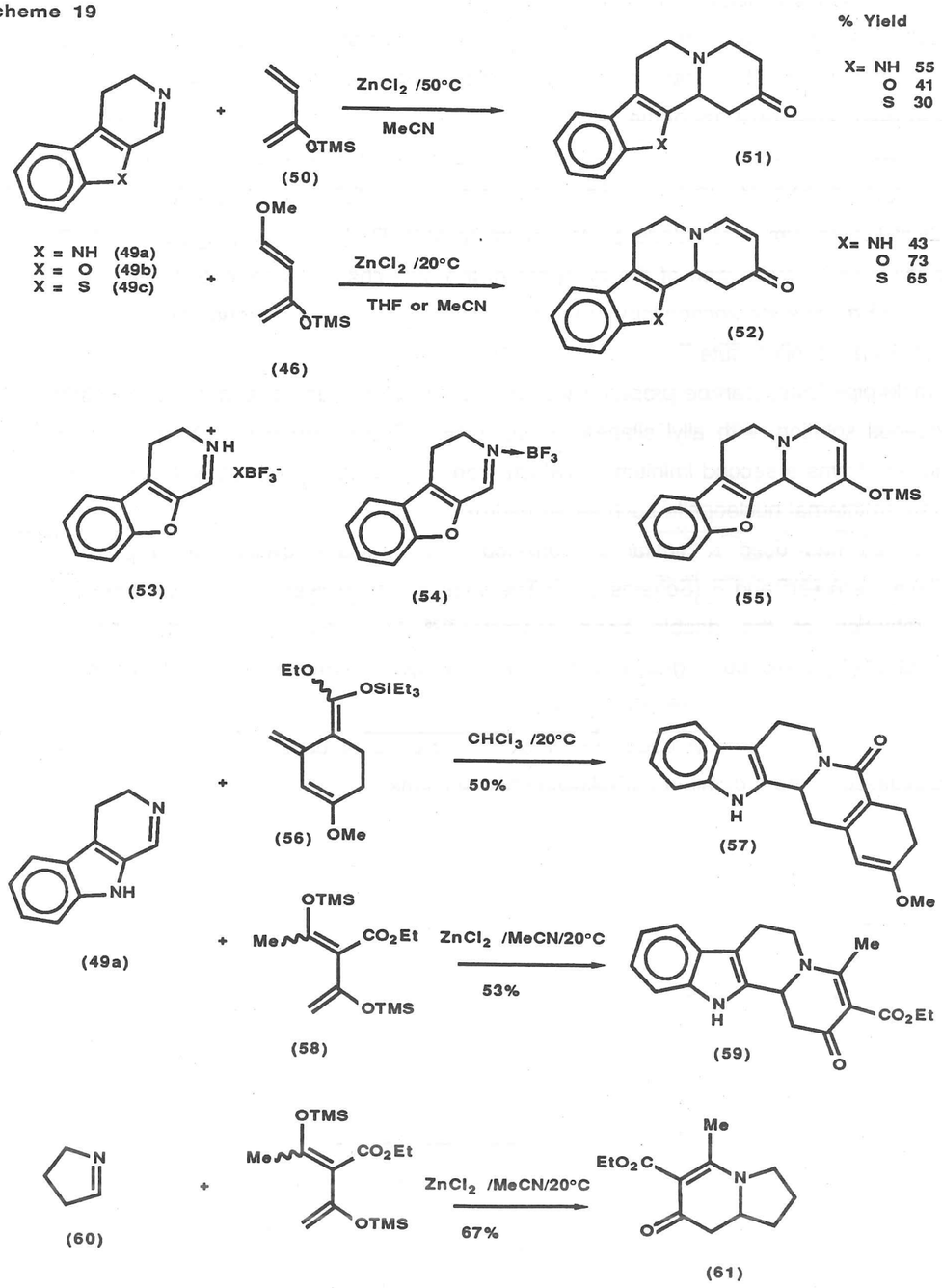
Overman has used a similar iminium ion – vinyl silane cyclisation to prepare pumiliotoxins A (2)[33] and B (Scheme 17).[34] The iminium ion cyclises onto the vinyl silane, with retention of the double bond geometry.[33,35] This step enables the difficult tri–substituted double bond geometry set up by a hydro–alumination epoxide opening sequence, to be introduced into the molecule.

Piperidines from [4+2] cycloaddition reactions and the syntheses of *Prosopis* alkaloids are discussed in more detail in the following two sections.

Scheme 18



Scheme 19



1.2 Recent Uses of Imines as Dienophiles

A wide variety of imines has been used in Diels–Alder reactions and the literature has been thoroughly reviewed up to 1982.[36] The reactions are mostly of doubly or triply activated imines, with Lewis acid and/or high temperature. Recently a number of publication has appeared where imino–Diels–Alder reactions have been carried out under milder conditions.

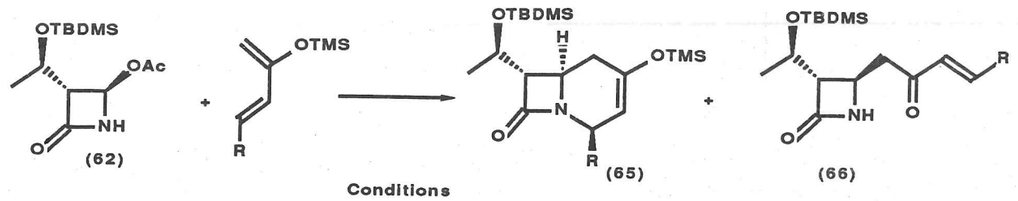
Kerwin and Danishefsky have prepared 4–piperidones (48) by the zinc chloride catalysed Diels–Alder reaction (Scheme 18).[37] The yields are for one equivalent of diene; the yields in parenthases are when 4eq. were used. This work set a precedent for future reactions under very mild conditions.

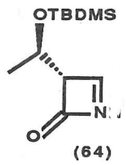
Vacca has found that the silyloxydienes (46) and (50) react with the tricyclic imines (49) in the presence of zinc chloride to give the piperidones (51) and (52)(Scheme 19).[38] An improved yield (65%) of compound (51b) was obtained with boron trifluoride etherate ($BF_3.Et_2O$) catalysis in chloroform – acetonitrile at 20°C with the intermediate silyl enol ether being isolated.

Another group at Merck, Sharp and Dohme has investigated the reaction of the imine (49b) and diene (50) in the presence of protic and Lewis acids.[39] They found that treatment of the imine (49b) with boron trifluoride etherate gave rise to two distinct species as observed by ^1H, ^{11}B and ^{19}F n.m.r.; namely the adducts (53) and (54). Only the protonated species (53) reacted with the diene (50) to give the silyl enol ether (55); the Lewis acid adduct (54) was inert. The latter compound could be prepared quantitatively and isolated as a solid if freshly distilled boron trifluoride etherate in anhydrous CH_2Cl_2 were used. ^{11}B and ^{19}F n.m.r. showed strong F–B coupling that indicated that a tetrahedral boron species was present. Treatment of the imine (49b) with trifluoroacetic acid and then 1eq. of $BF_3.Et_2O$ gave the species (53) (X = CF_3CO_2) which gave a quantitative yield of the enol ether when treated with the diene (50). When the $BF_3.Et_2O$ was omitted no cycloaddition occurred. Tetrafluoroboric acid was also effective as the catalyst for this reaction. The n.m.r. studies show that in the absence of BF_3 the counter ion ($CF_3CO_2^-$) is strongly associated with the iminium ion; the BF_3 is necessary to complex the counter ion and so make the iminium species more "naked". This result may explain the low yields achieved by Vacca and is likely to influence greatly future work in this area.

Danishefsky has extended the Vacca work to prepare a yohimbine precursor (57) in 50% yield using the diene (56) at 20°C without catalysis.[40] Catalysis is needed for the Diels–Alder reaction with the diene (58) which proceeds in 53% yield. This same diene also reacts with Δ^1-pyrroline (60) in moderate yield, again with catalysis.[41] Ueda and

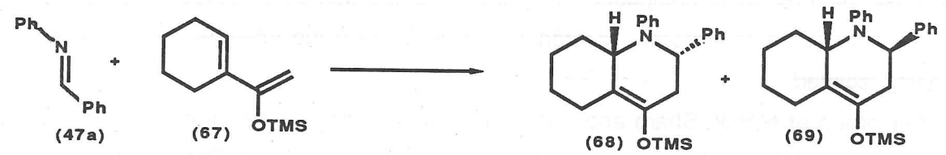
Scheme 20

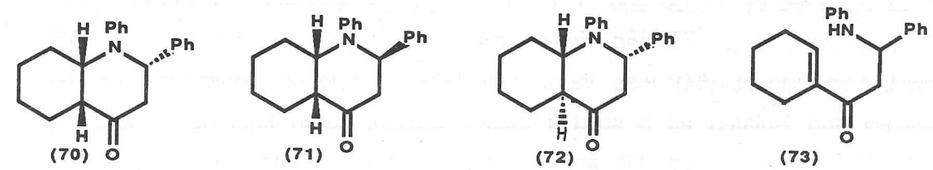


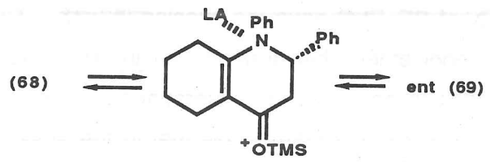


		%	%
R = H (50)	$ZnCl_2$/MeCN/80°C	18	75
R = H (50)	TMSOTf/CH_2Cl_2/20°C	0	18
R =Me (63)	$ZnCl_2$/MeCN/80°C	20	47

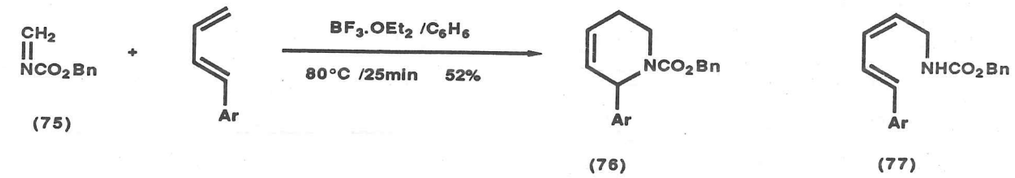
Scheme 21



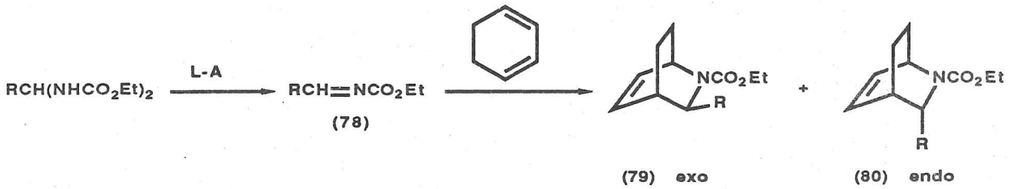




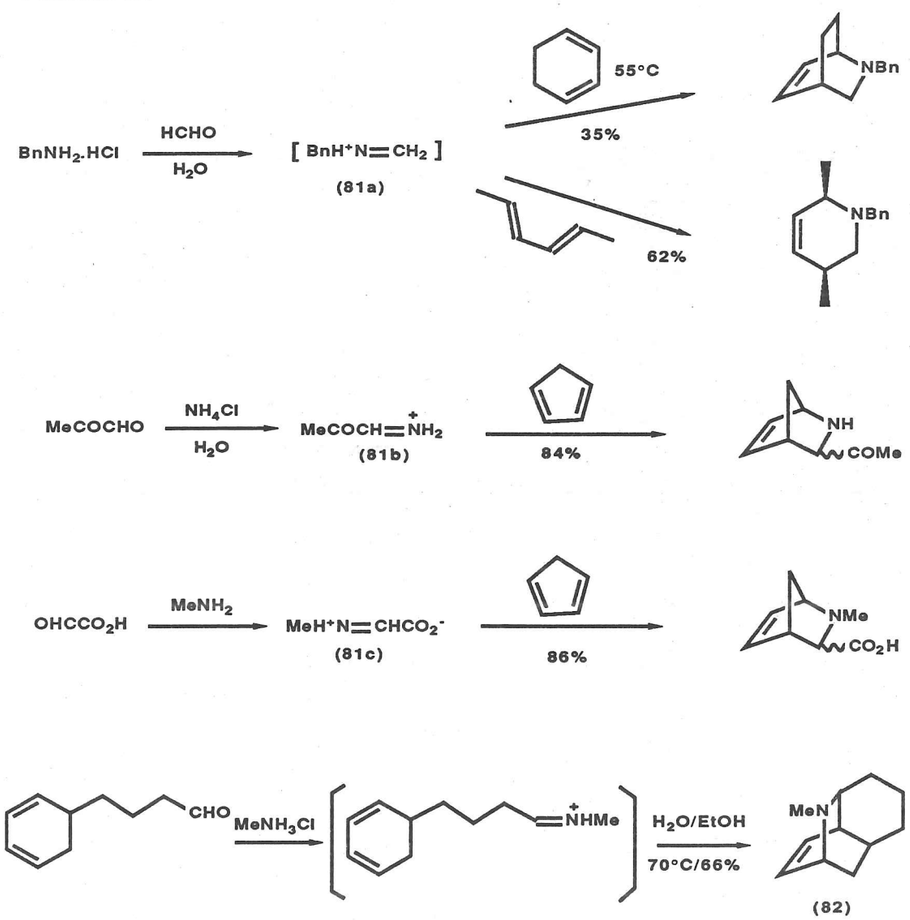
Scheme 22



Scheme 23



Scheme 24



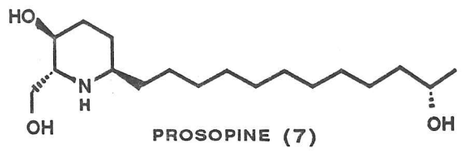
Maynard have reacted azetinone (64) (the probable reactive intermediate from the azetidinone (62)) with the silyloxydienes (50) and (63) to give low yields of carbacephems (65).[42] The major products (in some cases the only products) are the 4–substituted azetidinones (66)(Scheme 20). The [4+2] reaction appears to be in competition with a Mukaiyama–type aldol reaction.[43] The stereochemistry can be explained by either an *endo* transition state in a [4+2] reaction or a chair–like transition state in a step–wise mechanism.

Seydon-Penne has investigated the Lewis-acid catalysed Diels-Alder reaction of the imine (47a) with the silyloxydiene (67) (Scheme 21).[44] Products were isolated as the silyl enol ethers (68) and (69) or as the ketones (70-73). The kinetic ratio of products (short reaction times, milder Lewis acids, low temperatures) is 70:30 (68):(69) or (70):(71) which corresponds to *endo* : *exo* for the C-phenyl group. Longer reaction times and higher temperatures lead to greater proportions of (69) or (71) eg. $AlCl_3$ for 1.5h at 20°C gives 10:90 ratio and $TiCl_4$ 5 min, 20°C gives 2:98. Yields are 50-72%. This equilibration may occur *via* retro-Diels–Alder reaction or *via* an oxonium intermediate (74) from a retro-Michael reaction. The enone (73) was isolated in small amounts from several reactions and is the only product from a $BF_3.Et_2O$ reaction (70%) when treatment with water, then methanol was the work-up procedure. Treatment of enone (73) with $TiCl_4$ gave a mixture of compounds (70-72) after 1h and only (72) after 18h. Similarly long reaction times with excess $TiCl_4$ (for 1h) or $ZrCl_4$ (2.5h) gave only the ketone (72), possibly *via* titanium or zirconium enolate formation.

J.E. Baldwin has used an imino Diels-Alder reaction to prepare the piperidine (76) using the dienophile (75) (prepared *in situ* from a bisurethane (Scheme 22)).[45] Longer reaction times resulted in the formation of compound (77).

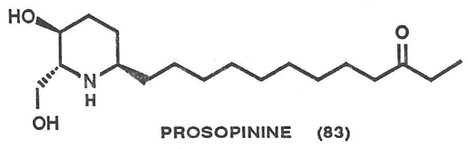
Krow, who has done much work on this type of system,[46] has investigated the stereoselectivity of the Lewis-acid catalysed reaction of imines (78) with cyclohexadiene (Scheme 23).[47] For most groups R (eg. Me, Ph, CO_2Me) the major product is where R is *exo* (79) (usually >80%), exceptions being where R=CCl_3 or iPr. Yields are generally low (6-42%).

Imino Diels Alder reactions can be carried out in high yield in aqueous solution (Scheme 24).[48] The reactive species are probably the iminium salts (81) generated *in situ*. Yields are generally good. The reaction of glyoxylic acid with methylamine and cyclopentadiene probably goes *via* a zwitterion (81c). An intramolecular version gives the tricyclic amine (82) in reasonable yield. It appears that more reactive dienes such as cyclopentadiene, are needed for the intermolecular reaction.

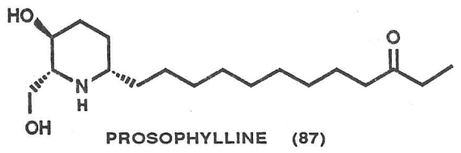


PROSOPINE (7)

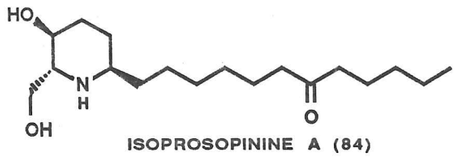
PROSOPINONE (86)



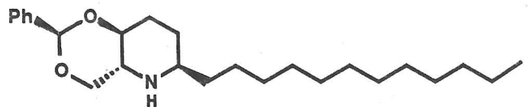
PROSOPININE (83)



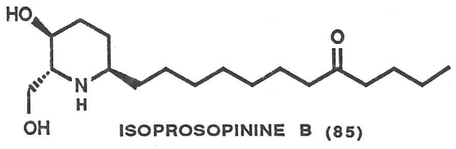
PROSOPHYLLINE (87)



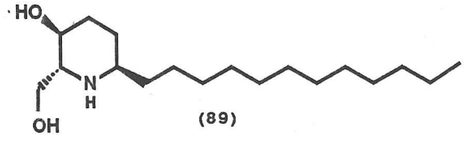
ISOPROSOPININE A (84)



(88)

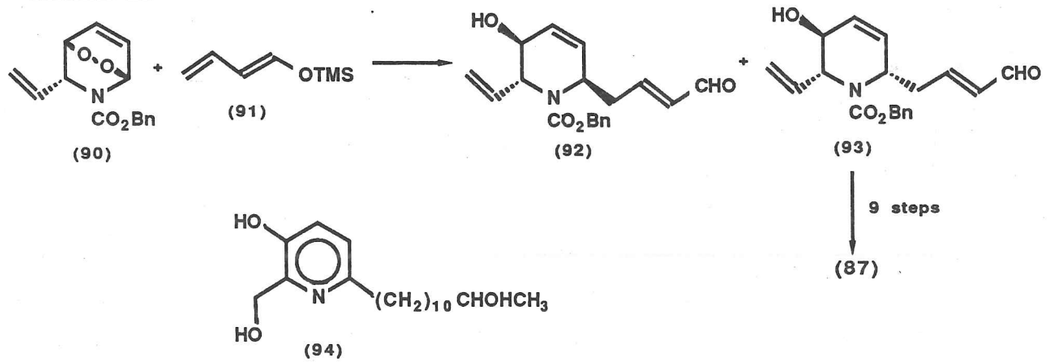


ISOPROSOPININE B (85)

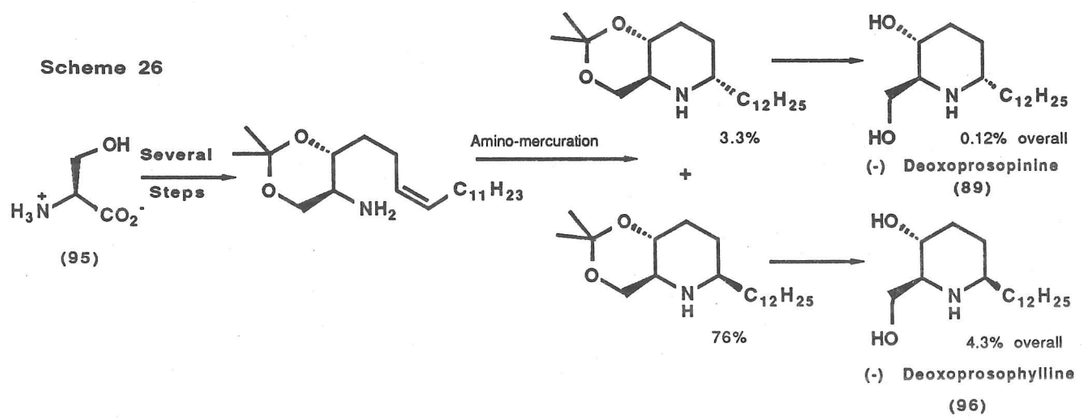


(89)

Scheme 25



Scheme 26



1.3 Prosopis Alkaloids.

1.3.1 Isolation.

Six members of the prosopis group of alkaloids (characterised by a 2-hydroxymethyl substituent) have been isolated; prosopine (7) and prosopinine (83) from *Prosopis africana* (Guill. & Perr.) Taub [7,49] isoprosopinine A (84) and isoprosopinine B (85) from the same species,[50] prosopinone (86) from *Cassia carnaval* ,[51] and (±)-prosophylline (87) from *Prosopis africana*.[50]

The structures of the alkaloids were determined by physical and chemical methods. Dehydrogenation of prosopinine (83) to a substituted pyridine showed the presence of a piperidine ring. Mass spectrometry of various derivatives gave the remaining structural information. High field ^{1}H n.m.r. studies[49] of the benzylidene acetal (88) of deoxoprosopinine (≡ deoxyprosopine (89)) were used to establish the relative stereochemistry, and the absolute stereochemistries were determined by Horeau's method. [52] Isoprospinines A (84) and B(85) were obtained as an inseparable mixture[50] which on Wolff-Kishner reduction gave a single product, identical with deoxyprosopine (89). Baeyer-Villiger oxidation of the isoprosopinine mixture gave pentanoic and hexanoic acids as the only volatile products, thus establishing the positions of the side-chain ketones.

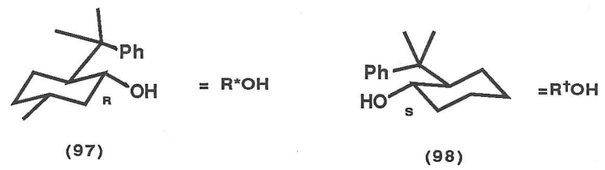
The ^{13}C n.m.r. spectra of prosopine (7), prosopinine (83) and the isoprosopinine A (84) and B (85) mixture have been assigned by comparison with model compounds.[53]

1.3.2 Synthesis.

(±)-Prosophylline (87) has been prepared from the endoperoxide (90) in ten steps, 3.2% overall yield.[54] The key step is the opening of the endoperoxide (90) with 1-silyloxybutadiene (91) (Scheme 25), to give the epimeric piperidines (92) and (93). The latter compound is used for the prosophylline synthesis. In principle the minor epimer (92) could be converted into *prosopis* alkaloids (e.g. prosopinone) *via* a similar sequence.

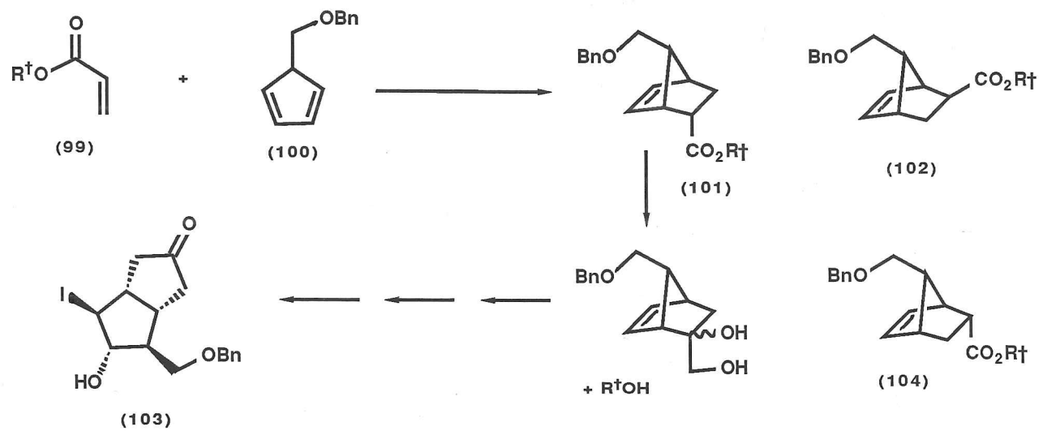
Fodor has reported the synthesis of prosopine (7) *via* hydrogenation of the pyridine (94) with subsequent epimerisation of the 2-hydroxymethyl group *via* an oxidation, epimerisation reduction sequence.[55] Few details are available.

(-)-Deoxyprosopine (89) (deoxoprosopinine) (i.e. the unatural configuration) and (-)-deoxoprosophylline (96) have been prepared *via* an amino–mercuration, from *L*-serine (95) (Scheme 26) in 0.12% and 4.3% overall yields respectively.[56] Although this is the only non-racemic synthesis of *prosopis*-related compounds the low yield in the amino–mercuration step (3.3%) and another low yield earlier in the synthesis (16.5%)

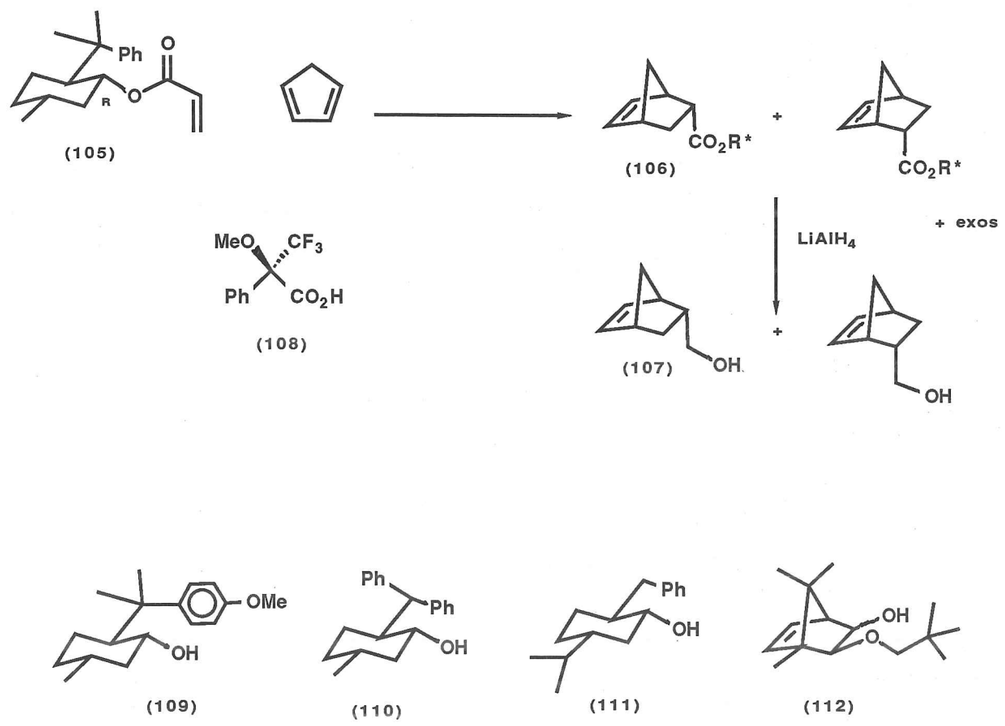


(97) (98)

Scheme 27



Scheme 28



make this an impractical route to prosopis alkaloids.

The synthesis of isoprosopinine B (85) by Holmes and Thompson will be discussed in more detail in Chapter 2.[57]

1.3.3 Pharmacology.

A wide range of pharmacological properties are claimed for the *prosopis* alkaloids[58-60] including local anasthesia (they are used as a folk remedy for toothache),[60] the treatment of angina, laryngitis, rhinitis and varicose veins. Anti–bacterial properties are also claimed,[61] but the irritant effect of *prosopis* alkaloids limits their usefulness.[62]

1.4 Some Uses of 8-Phenylmenthol as a Chiral Auxiliary.

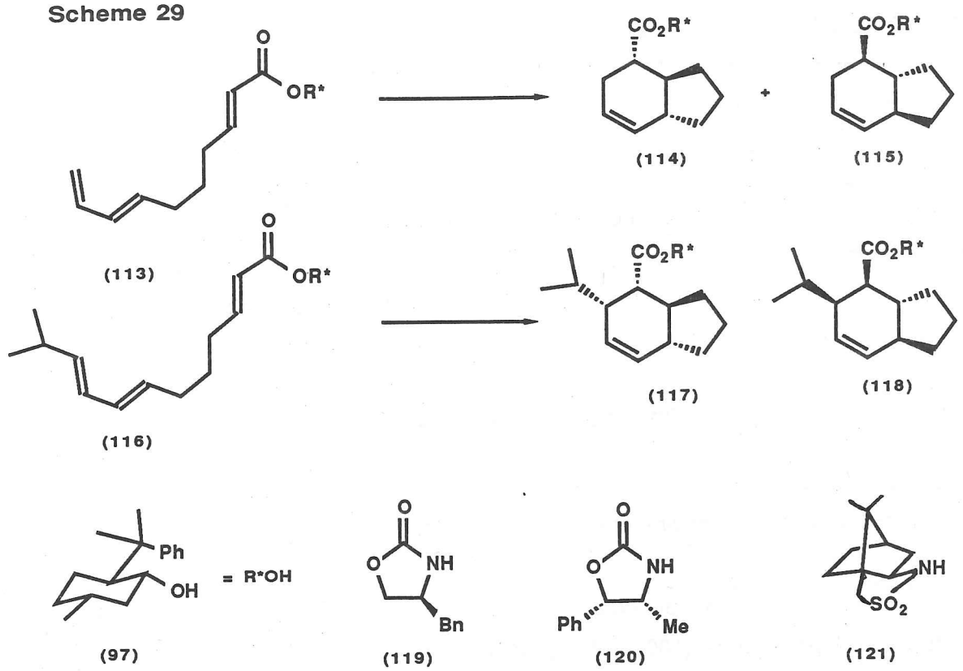
1.4.1 Diels–Alder Reactions.

The chiral auxiliary (*S*)-8-phenylmenthol (8-phenmenthol) (98) was first prepared and used by Corey and Ensley in a chiral Diels–Alder reaction in the synthesis of a prostaglandin intermediate (103) (Scheme 27).[63] Reaction of the chiral acrylate (99) with the substituted cyclopentadiene (100) in the presence of aluminium trichloride ($AlCl_3$) in CH_2Cl_2 at -55°C gave an 89% yield of the *endo* adduct (101) with 7% of an *exo* adduct (probably (102)). The auxiliary (98) was recovered in high yield and purity later in the synthesis. The other diasteriomer (104) was not observed. The analogous Diels–Alder reaction of the acrylate with cyclopentadiene gave, after $LiAlH_4$ reduction, the alcohol which was claimed to have an e.e. of 99% by optical rotation measurements. It is believed that the bulky $PhMe_2C$ group blocks one face of the enoate (which exists in the S-trans form). Most subsequent work with this auxiliary has been on the *R*-isomer (97) which is prepared from the more accesible (natural) *R*-pulegone.

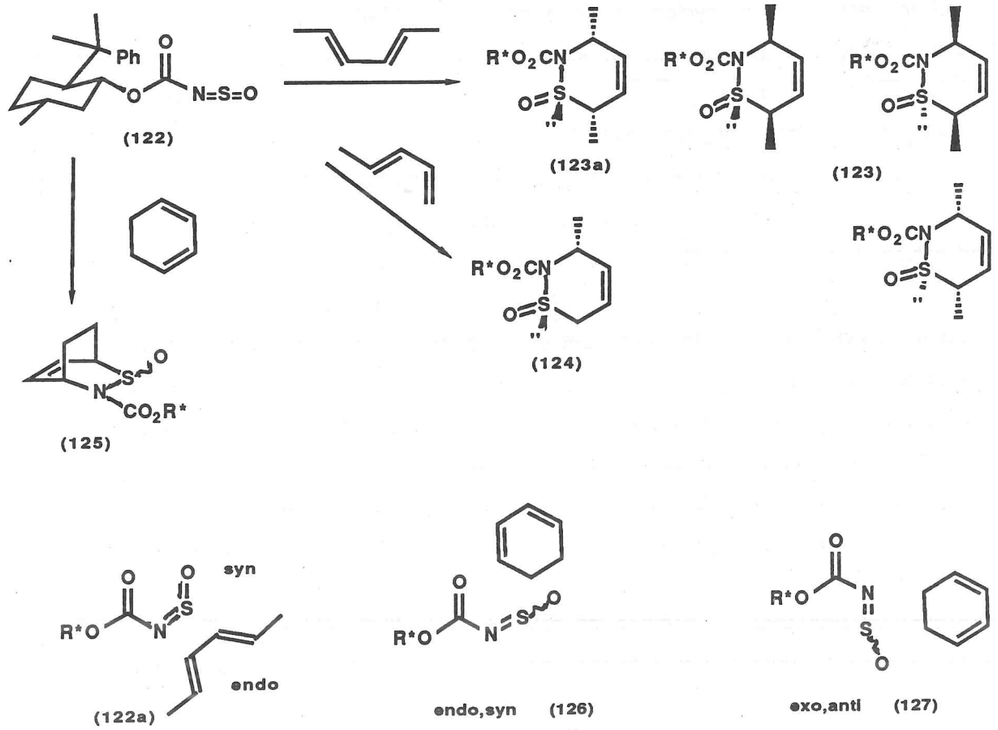
Oppolzer[64] has repeated this last reaction of Corey's varying the temperature, Lewis acid and solvent (Scheme 28). The % e.e. was determined by reduction of the reaction products and then derivatisation of the *endo* alcohol (107) with Mosher's acid (108).[65] Aluminium trichloride and dimethylaluminium chloride in CH_2Cl_2 or toluene gave lower e.e.s (47-70%) than did $SnCl_4$, $TiCl_4$ or $BF_3.Et_2O$ in the same solvents. When $BF_3.Et_2O$ was used as Lewis acid the reaction did not go to completion in the reaction time used (3.5h). E.e.s of 89-90%, with yields of 83-95% were obtained with 1.5eq. of $SnCl_4$ in toluene at 0°C or 1.5eq. of $TiCl_4$ in CH_2Cl_2 at -20°C. These results suggest that the degrees of chiral induction obtained by Corey and Ensley were not as high as were claimed.

Oppolzer has prepared a number of related and other chiral auxiliaries and investigated the Diels–Alder reaction of their acrylates with cyclopentadiene in order to

Scheme 29



Scheme 30

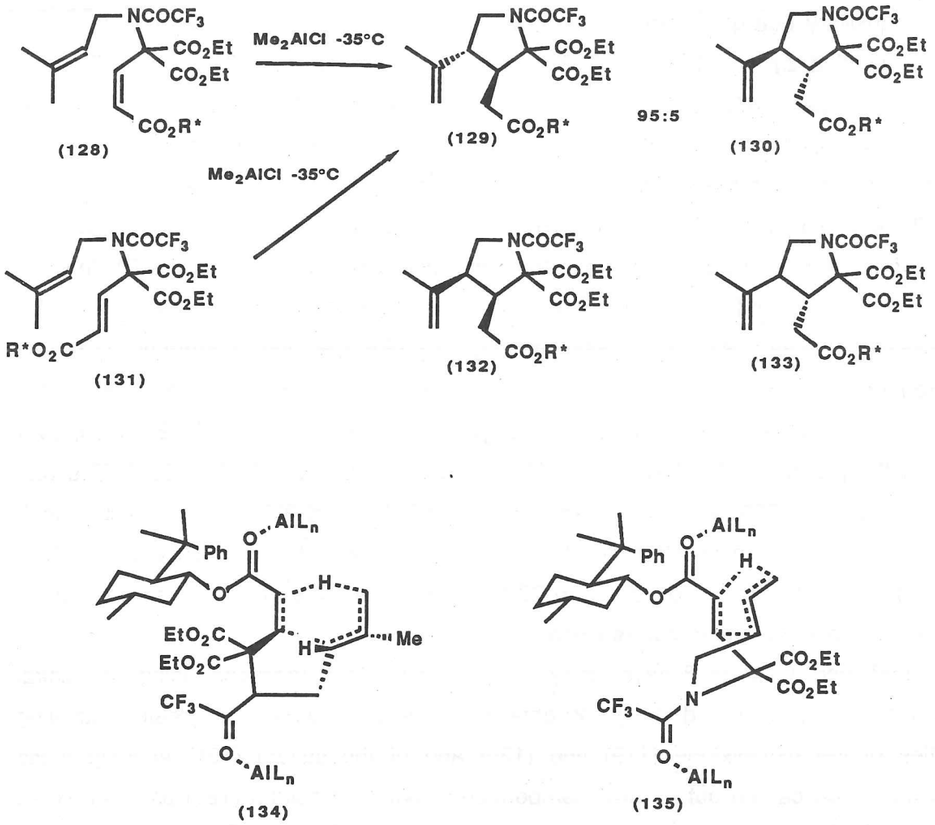


find an auxiliary that gives both high d.e.s and crystalline derivatives (so that products can be purified by crystallisation).[66] The two related auxiliaries (109) and (110) gave similar asymmetric inductions (87-88%) whilst the analogue (111) with a simple benzyl shield gave a poorer e.e.(63%). A number of camphor– and isoborneol–derived analogues have been prepared,[67] the highest d.e.s being obtained with the auxiliary (112) and its enantiomer (>99.2%; 96% yield). Thus there appears to be no relationship between the nature of the auxiliary and the steric bulk of the blocking group ($PhMe_2C$ for 8-phenylmenthol) and the amount of chiral induction obtained. An **intra**-molecular Diels–Alder reaction, using an 8–phenylmenthyl auxiliary, has been performed by Roush to prepare the *trans* fused perhydroindane ring system (Scheme 29).[68] The triene (113) cyclises to a mixture of the diasteriomeric bicycles (114) and (115) in 77-82% yield, 64% d.e., in the presence of a Lewis acid (*l*-bornyloxyaluminium chloride) at 23°C. The d.e. was increased to 72% when the reaction was carried out at 8°C but the reaction took two weeks. Under similar conditions the triene (116) gave, at best, a 36% d.e. $TiCl_4$ (1.1eq.) as Lewis acid improved this to 72%, but the yield was low (8%), polymerisation of the diene being a major side reaction.

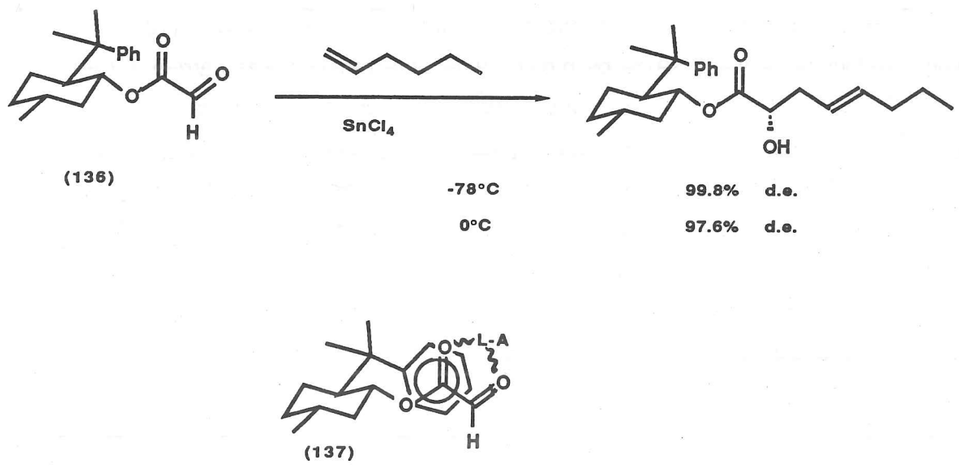
Evans[69] and Oppolzer[70] have done similar Diels–Alder reactions using the chiral auxiliaries (119), (120) and (121) and obtained d.e.s up to 95%. The greater activating abilities of the oxazolidone (119) and (120) and of the sultam (121) enabled these reactions to be carried out at lower temperatures. With the sultam (121) as auxiliary an 82% yield of material with d.e. of 95% was obtained. One crystallisation gave pure material in 75% yield.

Whitesell has prepared the cyclic thiazines (123) and (124) (Scheme 30) *via* a hetero-Diels Alder reaction.[71] The thermal reaction (20°C, toluene) of the *N*-sulphinyl carbamate (122) with hexadiene gave a 1:2:2.5:9 ratio of products (123). The thiazine (123a) was the major product (42% yield, >97% by h.p.l.c.) when the reaction was carried out with 1eq. of $SnCl_4$ in CH_2Cl_2 at 0°C. This product arises from an *endo -syn* transition state (122a). Weinreb reacted the same dienophile (122) with cyclohexadiene ($TiCl_4$, CH_2Cl_2, -50°C) and obtained a 9:1 mixture of compound (125) (epimeric at S) in 77% yield.[72] These must arise from reaction *via endo–syn* or *exo–anti* transition states (126) and (127), one face of the dienophile being blocked by the chiral auxiliary. (Whitesell and Weinreb differ in their definitions of *syn* and *anti* ; Whitesell does not consider the possibility of *trans* dienophile.) Reaction at 20°C in the absence of Lewis acid gave 2:4:1:3 mixture of isomers of (125) in 80% yield.

Scheme 31



Scheme 32



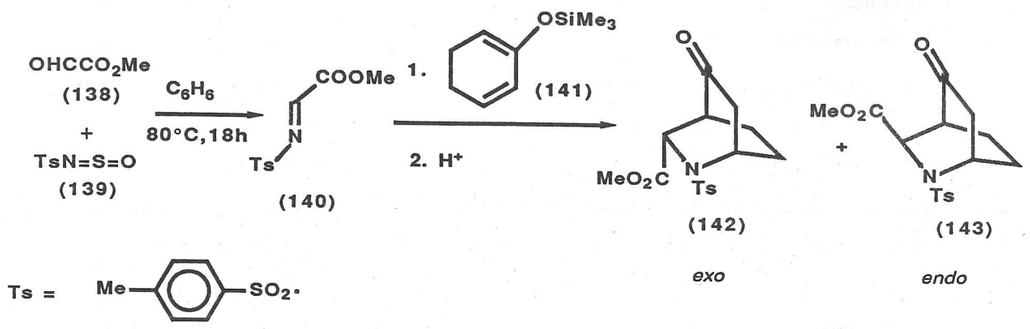
1.4.2 Ene Reactions

Oppolzer has used an 8–phenylmenthyl ester in an asymmetric "ene" reaction as the key step in the synthesis of (+)-α-allokainic acid (Scheme 31).[73] Lewis acid catalysed ene reaction of the 1,6 diene (128) gave a 95:5 mixure of the two pyrrolidines (129) and (130) (90% d.e.) in 60% yield. None of the two diastereomers (132) and (133) was seen. Similarly cyclisation of diene (131) gave an 11:89 mixture of (129) and (139) (78% d.e. in the opposite sense) in 81% yield with only a trace of the *cis* isomers (132) and (133). Thermal ene reaction (70°C, 80h, or 180°C, 15min) gave no chiral induction. The corresponding reactions with menthyl auxiliary gave in thermal or Lewis-acid catalysed reactions d.e.s. of less than 18%. The stereochemistries can be rationalised if the reactions proceed *via* the transition states (134) and (135) where one face of the enophile is blocked by the phenyl ring of the auxiliary as in the Diels-Alder reaction of 8-phenylmenthyl acrylate. Oppolzer notes that the ^{1}H n.m.r. signals of the C_α-H of the 8-phenylmenthyl esters (128) and (131) are shifted upfield by 1 p.p.m., in comparison to the ethyl and menthyl esters.

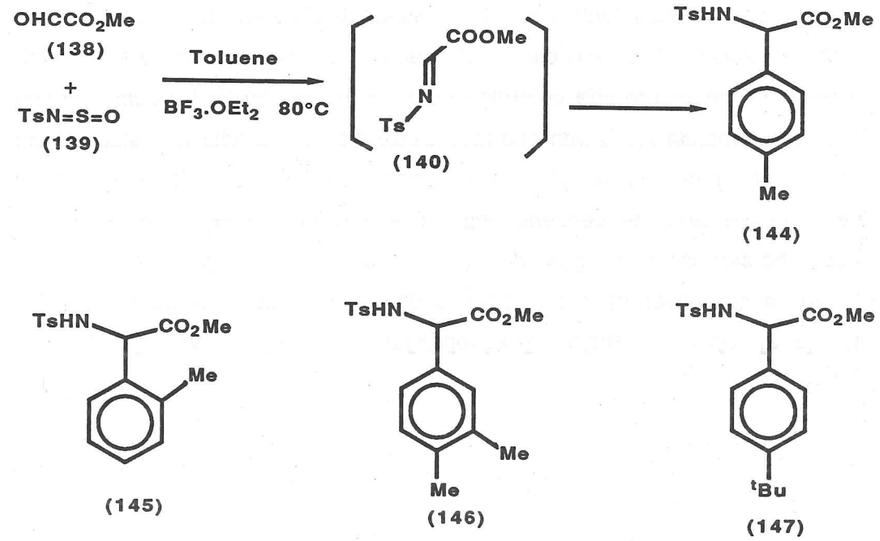
Whitesell has obtained very high d.e.s. in Lewis-acid-catalysed ene reactions with 8-phenylmenthyl glyoxylate (136) and olefins. (Scheme 32).[74] He suggests that the high d.e.s. are a result of the tin chloride co-ordinating to both the carbonyl groups, holding them in a fixed conformation (137) with one face blocked by the auxiliary. A study of the fluorescence quenching of this complex shows that there is a significant interaction between the carbonyls and the benzene ring.[75] The additions of Grignard reagents,[76] allylstannanes[77] and silanes[28] to the glyoxylate (136) also occur with high d.e.s.

8-Phenylmenthyl derivatives have also been used in asymmetric conjugate additions to enones,[79] [2+2] cycloadditions,[80] cyclopropanylations[81] and a variety of other reactions.[82]

Scheme 33



Scheme 34



2. Investigation of the Imino Diels–Alder Reaction

Thompson has reported that the (4+2) cycloaddition reaction of the imine (140)[83] and the silyloxydiene (141)[84] in benzene at 6°C gives the *exo* (142) and *endo* (143) azabicyclo[2.2.2]octanones in 57 and 24% yields respectively (Scheme 33).[57,85] The *exo* adduct has been used in the synthesis of isoprosopinine B (85).[57] (*Exo* and *endo* refer to the stereochemistry of the ester group with respect to the two senior bridges.)

The aim of this work is to investigate this imino Diels–Alder reaction under different conditions (e.g. low temperature with Lewis acid catalysis), to see if an enantioselective version, using a chiral auxiliary, could be developed.

2.1 Preparation of the Imine.

Thompson prepared the imine (140) from methyl glyoxylate (138) and *N*-sulphinyl-*p*-toluenesulphonamide (139)[87] in benzene, by heating under reflux for 18h by which time evolution of SO_2 had ceased.[85] ^{1}H n.m.r. (90MHz) showed the absence of the aldehyde methine signal (δ9.3) and the presence of the imine methine signal (δ8.1).

Considerable problems were experienced with this reaction. In most cases, using the above conditions, a white solid, insoluble in most organic solvents, was formed within the first half hour of reaction, which could be removed by filtration under nitrogen. In some cases the precipitate became gelatinous. N.m.r. and m.s. (FAB) evidence suggested that this precipitate is some sort of dimer. Purity of the imine was generally 30-50% as judged by the relative integrations of the imine methine signal and the aromatic hydrogen signals. Aluminium trichloride catalysis (the original Albrecht and Kresze conditions[83] as used by Weinreb[88] and Yamamoto[89]) reduced the reaction time to 4h but improved the quality of the imine only slightly (no greater than 65%). The use of boron trifluoride etherate as catalyst (0.1-0.2 eq.) was no better. N.m.r. analysis of the crude reaction mixtures (in $CDCl_3$ or C_6D_6) showed the presence of two or more sets of aromatic signals and (in deuteriobenzene) two MeAr signals. Dichloromethane and acetonitrile were considerably inferior as solvents for this reaction.

When the imine was formed in toluene by heating at 80°C for 16h with 0.2eq. of boron trifluoride etherate, the n.m.r. spectrum of the crude mixture showed two mysterious doublets at δ5.4 and 6.5, different aromatic signals and only a trace of the imine CH signal. T.l.c. analysis showed one major product, which on isolation (75% yield) was shown to be the *para*-substituted amino-ester (144) (Scheme 34). This arises from a Lewis acid catalysed Friedel-Craft acylation of the solvent. An alternative

mechanism, an "ene" reaction must be ruled out as this would give rise to the *ortho*-substituted compound (145). (Weinreb has used the ethyl ester analogue in both thermal and Lewis acid catalysed "ene" reactions.[88]) The analogues (146) and (147) were prepared by refluxing methyl glyoxylate, boron trifluoride etherate and a benzene solution of the *N*-sulphinyl-*p*-toluenesulphonamide with *ortho*-xylene or *t*-butylbenzene respectively. The high yield of compound (144) suggests that the imine was formed in good yield and then reacted before it could decompose, as is appears to have been doing in previous cases. When no Lewis acid was used the imine formed as usual.

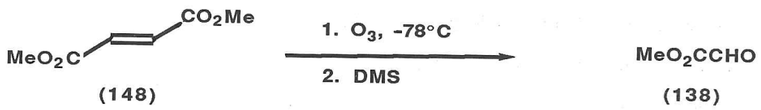
If tetrahydrofuran (THF) is used as the solvent with 0.1 -0.2eq. of boron trifluoride etherate the crude imine produced is then greater than 70% pure, and for the first time only one set of aromatic signals was seen in the n.m.r. spectrum. The reaction goes to completion in about half an hour at reflux and if a standard solution of the *N*-sulphinyl-*p*-toluenesulphonamide is used the purity of the imine (as judged by relative integrations of imine methine and aromatic signals in 90MHz n.m.r.) is usually better than 80%. About 5% of the imine with an *ortho*-toluenesulphonyl group is present (minor signals at δ8.2 and 2.4). This arises from *ortho*-isomer present in the commercial (Aldrich) toluenesulphonamide used to prepare the *N*-sulphinyl-*p*-toluenesulphonamide (139).

Aluminium trichloride (0.1eq.) is also an effective catalyst for this reaction; stannic chloride is slightly inferior (giving 60% pure imine) but titanium tetrachloride, zinc chloride and trimethylsilyl triflate give grossly impure imine. The boron trifluoride in THF procedure is now the method of choice as it gives good imine consistently. The original non-catalysed method in benzene[85,90] has been re-tried and this now gives imine 70-80% pure, although the crude imine solution is usually yellow, with a fine, white suspension present. The reaction is performed under a gentle stream of dry nitrogen.

The imine can be distilled (Kugelrohr, mercury diffusion pump) at 130°C, 10^{-3}mmHg to give imine of greater than 95% purity in up to 85% yield, as a pale yellow oil which turns to an off-white solid on scratching. It is essential to use reasonably pure crude imine as attempts to distil poorer quality imine have given imine of only 60-70% purity. Weinreb has distilled the imine derived from ethyl glyoxylate at 145-150°C (0.02mmHg) in 63% yield.

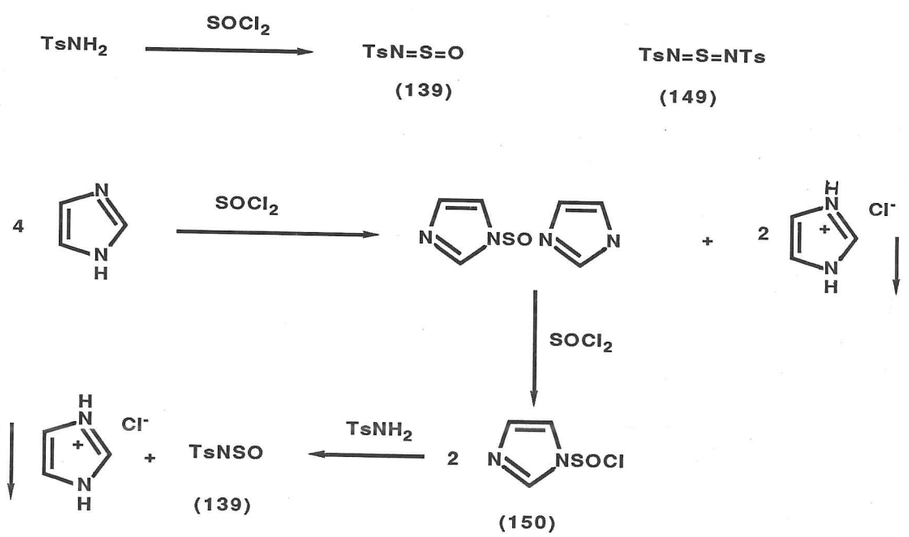
Methyl glyoxylate was prepared by Hook's method[91] which involves heating glyoxylic acid and methyl dimethoxyacetate together in the presence of *para*-toluenesulphonic acid (pTSA) and then with P_2O_5. Methyl glyoxylate (b.p. 37-8°C, 15mmHg) can then be distilled out of the "brew" as required. The material is 80-95% pure by n.m.r. (usually much nearer the latter figure). The major impurities give rise to signals at δ3.8 and sometimes at δ3.5. The crude glyoxylate "brew" must be heated to 80°C before material

Scheme 35



(148) (138)

Scheme 36



(139) (149) (139) (150)

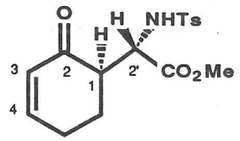
starts to distil over and there is an induction period of nearly ten minutes before boiling of the mixture occurs. The glyoxylate probably exists as a polymer which requires thermal "cracking". Care must be taken to exclude moisture as the glyoxylate is very hygroscopic and rapidly turns into a viscous gum when in contact with traces of acid or water. However solutions of methyl glyoxylate appear to decompose only slowly (of the order of 50% in 48h).

An alternative method of preparation of the glyoxylate, the ozonolysis of dimethylfumarate (148) in dichloromethane at -78°C with dimethylsulphide (DMS) work-up, has been tried (Scheme 35). In one case no glyoxylate could be distilled out of the crude reaction mixture, but on a second ozonolysis a low yield (17%) of methyl glyoxylate (essentially 100% pure) with only a trace of dimethylsulphoxide (DMSO) was obtained. Later fractions were heavily contaminated with DMSO. An alternative reducing agent may be a solution to this problem. This high purity glyoxylate gave a very similar result to "normal" glyoxylate when used to prepare the imine (140).

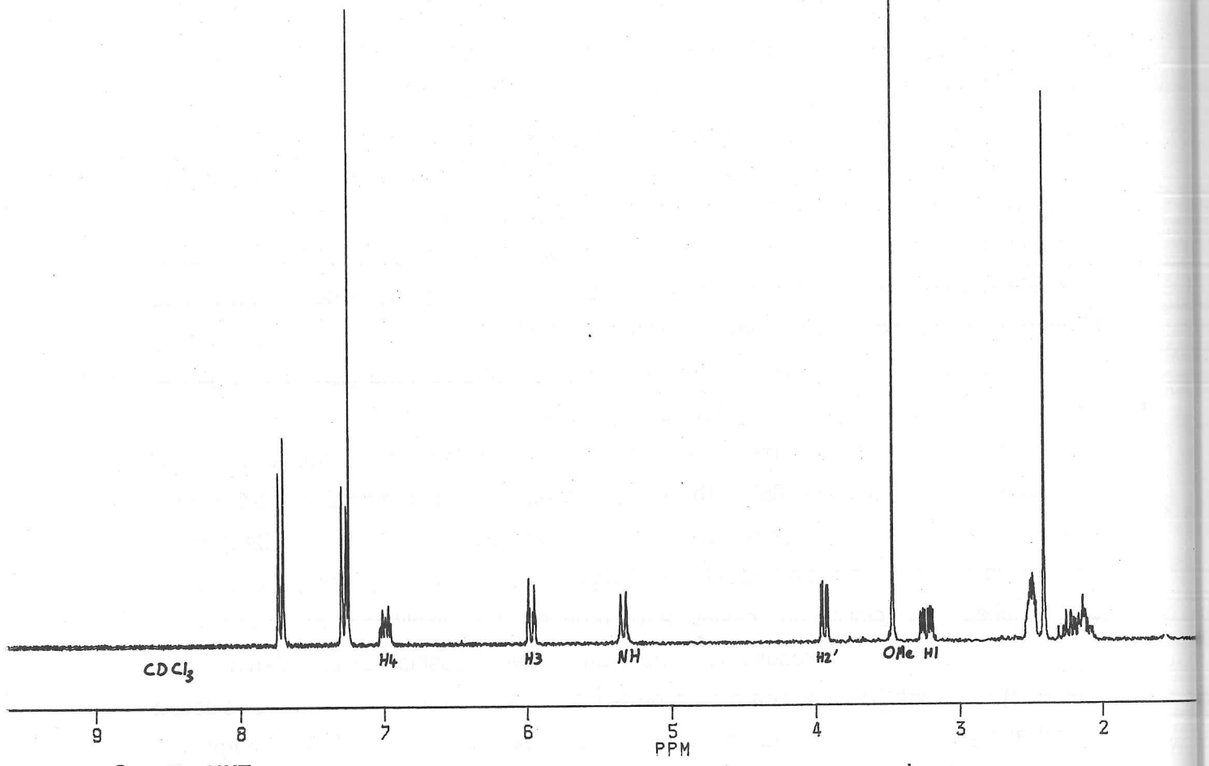
The *N*-sulphinyl-*p*-toluenesulphonamide (139) was prepared by the method of Kresze and Wucherpfennig (Scheme 36).[87] The crude material was distilled (120°C, 0.01mmHg or 102-6°C, 6 x 10^{-4}mmHg [mercury diffusion pump]) to give a yellow oil (37-62%) which solidified on cooling. The lower distillation temperature obtained by using the diffusion pump makes the distillation easier and reduces the likelihood of forming the sulphurdiimide (149) which results from the thermal decomposition of the *N*-sulphinyl-*p*-toluenesulphonamide (139).[87] The distillation is difficult as material seems to be reluctant to distil and yields are lower than those reported in the literature (75-80%). Sharpless's modified method (procedure A)[92] which involves refluxing thionyl chloride and sulphonamide in benzene for 6 days (instead of neat thionyl chloride for 16h) and then distilling gave a 50% yield, but has no advantages over the original method.

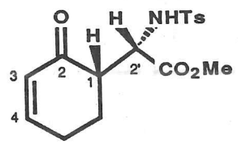
Kim and Shin have recently published a very mild method for preparing the *N*-sulphinyl derivatives of amines and amides.[93] An intermediate *N*-(chlorosulphinyl)imidazole reagent (150) is prepared in two stages and then reacted with amines and amides (Scheme 36). The product is then isolated by filtration and evaporation and can be distilled if necessary. With a certain amount of practice crude material of up to 95% purity could be obtained in 90-95% yield; the balance of the material appears to be toluenesulphonamide (by n.m.r). The pure *N*-sulphinyl-*p*-toluenesulphonamide can be used for the preparation of the imine. The reaction is difficult to scale up beyond about 10mmol as neither imidazole nor toluenesulphonamide are very soluble in the reaction solvent (CH_2Cl_2) and filtration of the large volumes of solvent becomes difficult.

Figure 3



(156)





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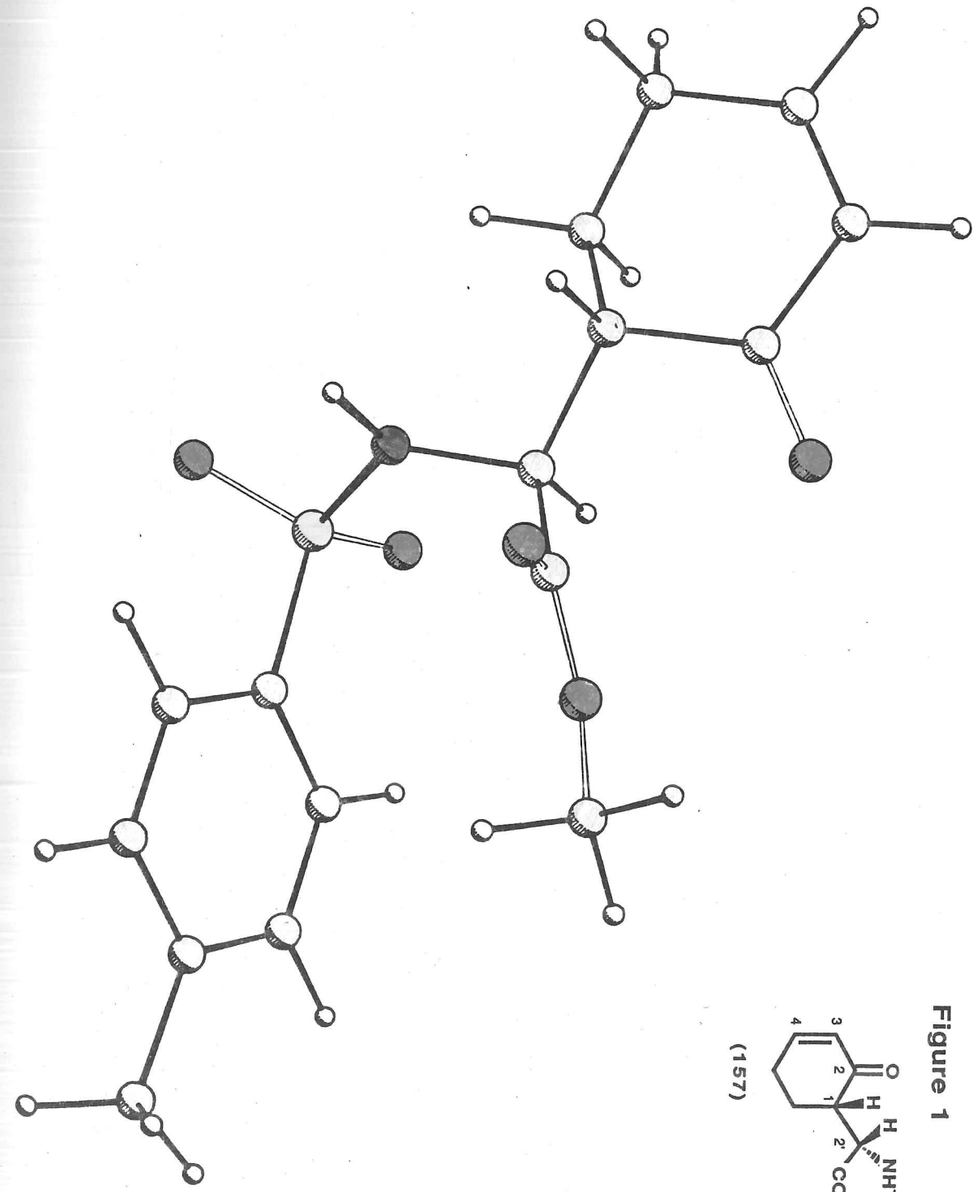


Figure 1

(157)

Scheme 37

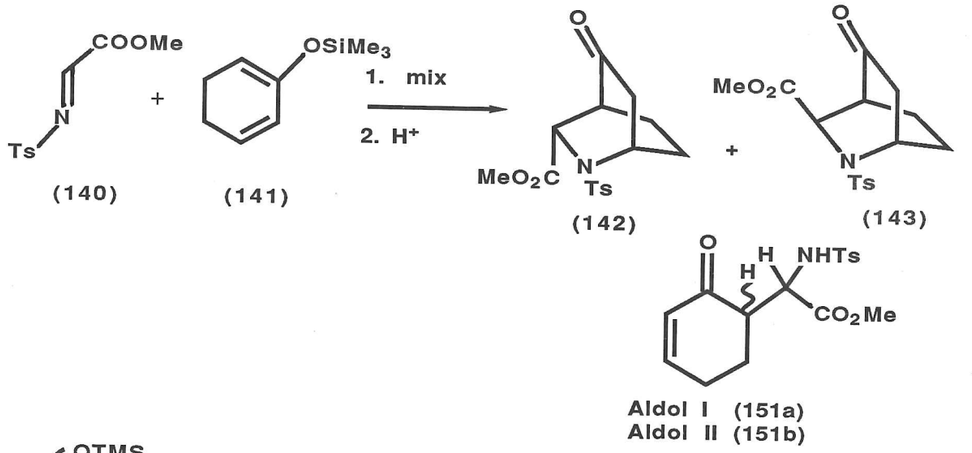
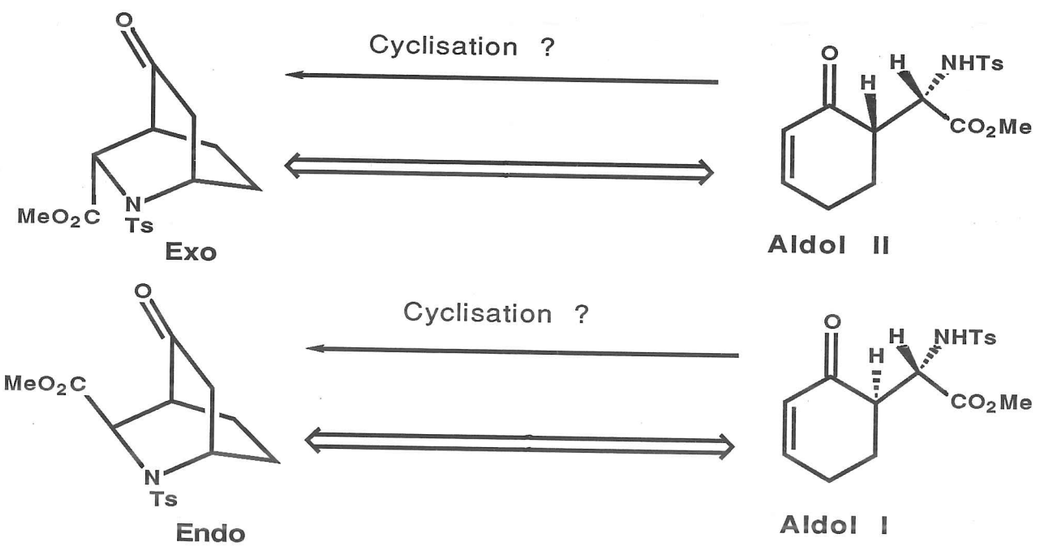


Figure 2



The *N*-sulphinyl-*p*-toluenesulphonamide (139) can be stored as a solution in either benzene or THF (2-3M) at 4°C for several months with no obvious sign of deterioration. The solution can then be syringed out as required. It is believed that this is one factor that has helped to improve the quality of imine prepared as contact of the readily-hydrolysed sulphinyl with air is greatly reduced. The solid is difficult to weigh out accurately as it is very hard, not easily broken into small pieces and must be handled under a stream of dry nitrogen.

2.2 Isolation of the "Aldol" Products.

A second source of problems proved to be the imino-Diels–Alder reaction itself. Before the problems associated with the preparation of the imine had been sorted out imine (140) of 40-50% purity was used in these reactions. Impurities made isolation of the products difficult, but the major product was one of the diastereomers of the enone (151a) (known as Aldol I). The other more polar diastereomer (Aldol II) (151b) was also isolated, as well as the two expected products (142) and (143) (Scheme 37). These "aldol" products could arise either by a retro–Michael reaction of the intermediate silyl enol ethers of *exo* (152) and *endo* (153) (or even from the *exo* and *endo* ketones during work-up) or an aldol-type reaction.[43]

An X-ray crystal structure of the minor aldol adduct was obtained (Figure 1)*. This allowed the structure (156) to be assigned to Aldol I and (157) to Aldol II. The stereochemical relationships of the four compounds are shown in Figure 2. *Exo* (142) is stereochemically related to Aldol I (156) and *endo* (143) is stereochemically related to Aldol II (157). The ^{1}H n.m.r. spectra of the aldol compounds are shown in Figure 3. The mechanism and stereochemistry of this aldol/retro-Michael reaction will be discussed later.

2.3 Studies on the Imino–Diels–Alder Reaction.

Once the problems with the preparation of the imine (140) had been resolved (Section 2.2) it then became possible to study the imino–Diels–Alder step in much more detail to see what the effects of Lewis acid, solvent and temperature were, and if the competing aldol/retro–Michael reaction could be suppressed.

Originally it was supposed that the "aldol" products were a result of the poor quality of imine used and so pure imine should give just the *exo* and *endo* compounds. However a reaction performed on pure imine (140) under similar conditions to those used by Thompson (benzene, 6°C; except that the reaction was stirred at 20°C for 33h

*My thanks to Dr. Perry Kaye for performing this crystal structure determination.

after the initial 3h at 6°C) gave, after mild acid work-up (THF–5x10^{-3}M HCl 4:1) a 47% yield of *exo* (142), 18.5% of *endo* (143), 14.5% of Aldol I (156) and 9% of Aldol II (157) (combined yield 88.5%). Aldol formation was thus an inherent quality of the reaction, not a result of impure imine or contamination with Lewis acid.

Closer examination of Thompson's practical details showed that he observed at least two other compounds (by t.l.c. analysis) in his crude Diels–Alder product that he did not isolate. These were more polar than *endo* (143) and probably correspond to the two Aldol products (156) and (157).

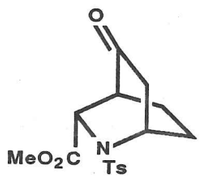
2.3.1 Protocol and Assay Procedure for Imino–Diels–Alder Reaction.

Although the four products from the Diels–Alder are separable by chromatography (order of elution *exo* , *endo* , Aldol I , Aldol II) the separations are not good and re–chromatography of the mixed fractions is necessary. Also the minor aldol isomer (157) co–runs with toluenesulphonamide which is the major by-product from these reactions. Loss of material through repeated chromatography, which would give inaccurate ratios could be a problem, especially for the two less abundant isomers (143) and (157). In order to overcome this the four products were isolated as one fraction (see Experimental) and the ratio of isomers obtained from the proton n.m.r. spectrum of the mixture. The signals due to the ester OMe group are fairly well resolved at 250MHz and were used for this purpose. Values are:–

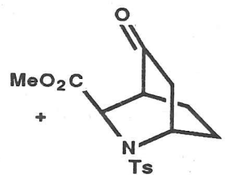
Exo	δ	3.80
Endo		3.71
Aldol I		3.46
Aldol II		3.44

All the compounds decompose on attempting g.c. analysis and so this is not a useful method in these circumstances. (Toluenesulphonamide occurs in the g.c. traces of even analytically pure samples.)

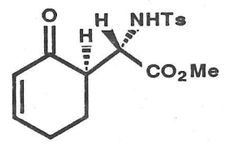
The general protocol is as follows. A batch of imine (4–6mmol) was prepared by the THF/BF_3.OEt_2 method and either distilled or used crude. If crude imine was used the solvent was removed under reduced pressure and the resultant off–white gum or solid dried at 0.1mmHg for 1h to remove any traces of the Lewis acid. Solvent was then added and the imine solution (ca. 0.5M) was divided into four portions. To each of these was added Lewis acid as required (usually 0.1eq.) and the mixtures were cooled or warmed as necessary under a nitrogen atmosphere. A solution of the silyloxydiene (1.1–1.3 eq.) was added, the reaction stirred for the required time and then quenched with dilute aqueous acidic THF for 1h,[94] or (for Lewis acid catalysed reactions) with water



(142)



(143)



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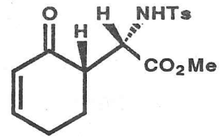


(157)

Table 1

Distilled imine reactions

Entry	Solvent	Temp C	Time h	Total Yield %	% Product Ratio exo	endo	AI	AII	Ratio exo:endo	AI:AII
1	C_6H_6	6→20	3	74.5	56	10	26	8	5.6	3.4
2	C_6H_6	6→20	36	89	53	21	17	10	2.5	1.7
3	C_6H_6	45	1	87	50	23	16	11	2.2	1.4
4	CH_2Cl_2	0	3	75	33	44	18	5	0.7	3.5
5a	CH_2Cl_2	0→20	16	73	44	33	-24-		1.3	-
5b	CH_2Cl_2	0→20	18	72	33	39	20	8	0.8	2.4
6	CH_2Cl_2	40	1	55	30	30	30	10	1.0	3.0
7	THF	0	3	72	47	6	36	11	7.8	3.2
8	THF	0→20	18	67.5	53	15	23	9	3.6	2.5
9	THF	40	0.8	87.5	60	11	23	7	5.5	3.0
10	MeCN	0	4.5	74	21	19	50	10	1.1	5.1
11	MeCN	0→20	18	81	19	30	44	7	0.7	6.5
12	MeCN	40	0.5	81.5	29	28	34	9	1.0	4.0
13	$C_6H_6/TiCl_4$(1eq)	6	1	29	3	2	57	37	1·5	1·5

Table 2

Crude imine r.t. reactions

Entry	Solvent/L-A (0.1eq)	Temp C	Time h	Total Yield %	% Product Ratio exo	endo	AI	AII	Ratio exo:endo	Ratio AI:AII
1	C_6H_6/Et_3N	20	18	55	52	8	29	11	6.5	2.6
2	C_6H_6	20	5	69	52	20	21	7	2.6	3.0
3	CH_2Cl_2	20	3	62	46	25	22	7	1.8	3.4
4	MeCN	0	2	50	15	9	67	10	1.7	6.8
5	$CH_2Cl_2/AlCl_3$	20	3	79	37	28	25	11	1.3	2.4
6	$CH_2Cl_2/AlCl_3$	20	18	51	42	34	18	5	1.2	3.6
7	$CH_2Cl_2/ZnCl_2$	20	2.5	62	8	0	71	22	-	3.3
8	$CH_2Cl_2/Ti(OiPr)_4$	20	2.5	49	40	23	31	7	1.8	4.6
9	THF/BF_3(0.3eq)	20	0.8	36	30	4	46	20	8.7	2.3
10	$THF/AlCl_3$(0.3eq)	20	0.8	49	27	6	45	22	4.6	2.0
11	THF/BF_3 (1eq)	20	0.8	0	-	-	-	-	-	-

Table 3

Low temperature reactions on crude imine

Entry	Solvent/L-A (0.1eq)	Temp C	Time h	Total Yield %	% Product Ratio exo	endo	AI	AII	Ratio exo:endo	Ratio AI:AII
1a	CH_2Cl_2/BF_3	-78	4	46	8	7	73	13	1.3	5.8
1b	CH_2Cl_2/BF_3	-78	3	34	5	14	72	8	0.4	8.7
2	$CH_2Cl_2/ZnCl_2$	-78	3	45	8	5	67	20	1.4	3.3
3	$CH_2Cl_2/TiCl_4$	-78	3	31	5	0	68	27	-	2.5
4	$CH_2Cl_2/Ti(OiPr)_2Cl_2$	-78	3	51	6	5	60	29	1.1	2.1
5	$CH_2Cl_2/Ti(OiPr)_4$	-78	3	47	14	14	65	7	0.9	9.6
6	CH_2Cl_2/Me_2AlCl	-78	2.5	45	8	11	67	14	0.7	4.5
7a	$CH_2Cl_2/AlCl_3$	-78	3	43	7	7	74	13	1.0	5.8
7b	$CH_2Cl_2/AlCl_3$	-78	3	41	8	6	79	7	1.3	10.6
8	$CH_2Cl_2/AlCl_3$	-50	2	40	6	6	75	13	1.1	5.8
9	$CH_2Cl_2/AlCl_3$	-78→20	36	73	16	25	53	6	0.7	9.3
10	CH_2Cl_2	-78	3.5	48	9	6	76	8	1.5	9.0
11	CH_2Cl_2	-78→20	3	47	13	11	70	6	1.2	11.2
12	$THF/AlCl_3$	-65	3	63	4	0	64	32	-	2.0
13	$THF/SnCl_4$	-65	3	48	9	0	60	32	-	1.9
14	THF/BF_3	-78	3	56	0	0	66	34	-	2.0
15	THF/BF_3	-78→20	40	76	17	4	48	31	4.1	2.4
16	$MeCN/AlCl_3$	-45→0	2.5	60	10	3	77	10	3.0	7.8
17	$Toluene/AlCl_3$	-75	4	20	12	3	62	24	3.5	2.6
18	CH_2Cl_2/THF/Li enolate	-78	1.5	30	0	0	62	38	-	1.6
19	CH_2Cl_2/THF/Me_2Al enolate	-78	3	17.5	0	0	88	12	-	7.6

for 15–30min. After work–up the products were isolated as one fraction by flash chromatography[95] and then analysed by 250MHz n.m.r. The percentage of each component in the mixture was calculated, along with the ratio *exo* : *endo* : Aldol I : Aldol II

2.3.2 Distilled Imine Reactions.

The results for reaction performed on distilled imine, at three temperatures in four solvents are presented in Table 1. There are some inconsistencies in the results (entries 5a and 5b which should be identical, entry 6 [especially the low yield] and possibly entry 11) but several trends are clear.

(a) THF gives a more favourable *exo* / *endo* ratio while acetonitrile gives a larger Aldol I : Aldol II ratio.

(b) Acetonitrile (MeCN) gives lower proportions of Diels–Alder products.

(c) With the exception of CH_2Cl_2 longer reaction times seem to give more *endo* and less Aldol I , suggesting that slow cyclisation may be taking place.

(d) Higher temperatures give greater proportions of Diels–Alder products.

Entry 2 is the best result, both in terms of total yield and of the yield of the desired *exo* adduct. The absolute yields of bicyclo compounds (142) and (143) are not much lower on those reported by Thompson (by 10% and 5% respectively).

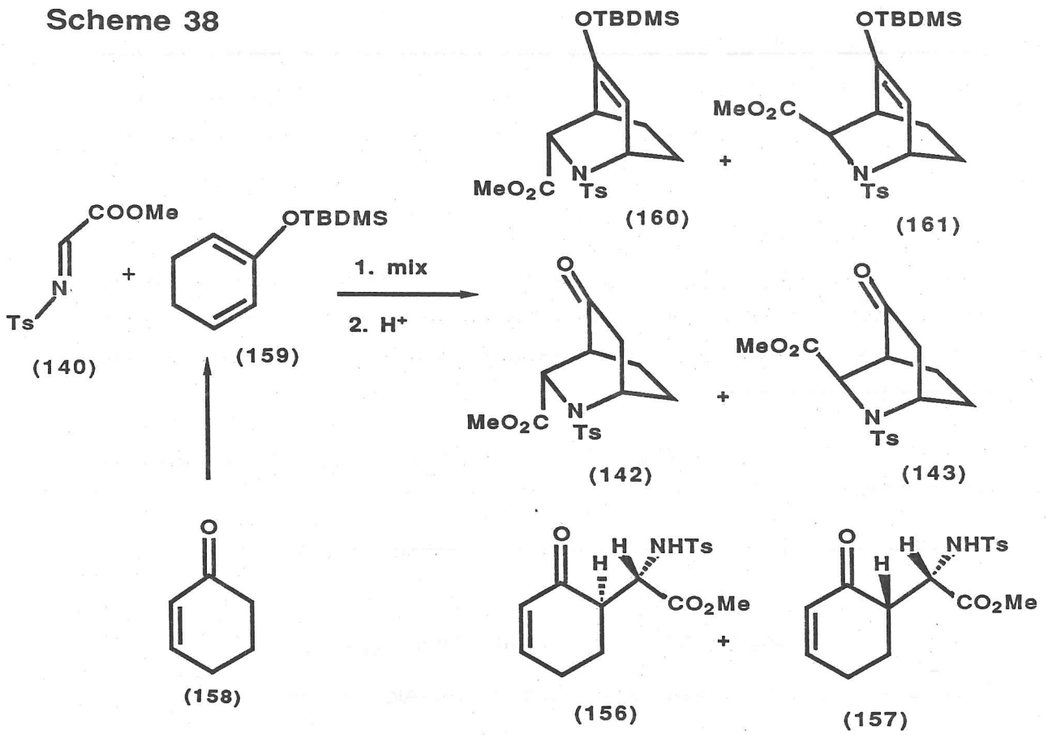
2.3.3 Non–Distilled Imine Reactions, With or Without Lewis Acid.

Table 2 details reactions on crude imine (140) at ambient temperature with and without Lewis acid present. Similar results to the distilled imine ones are obtained. The reaction in entry 1, with 1.5eq. of triethylamine was to determine whether a base would induce cyclisation *in situ*, which does not appear to be the case. With the exception of zinc chloride Lewis acid "catalysis" does not give very different results; possibly a little less selective. More than 0.1eq. tends to reduce yields slightly, while 1eq. gives much lower yields and proportions of Diels–Alder products.

2.3.4 Low Temperature Reactions.

A large number of reactions have been carried out at low temperature with a variety of Lewis acids to see if conditions could be found where the Diels–Alder reaction is favoured over the competing process (Table 3). At low temperature the aldol products predominate, CH_2Cl_2 and MeCN giving a higher aldol ratio than THF. The nature of the Lewis acid has little effect on the amounts; only titanium tetraisopropoxide gives a significantly different result. Several of the CH_2Cl_2 reactions give better–than–usual aldol

Scheme 38



Scheme 39

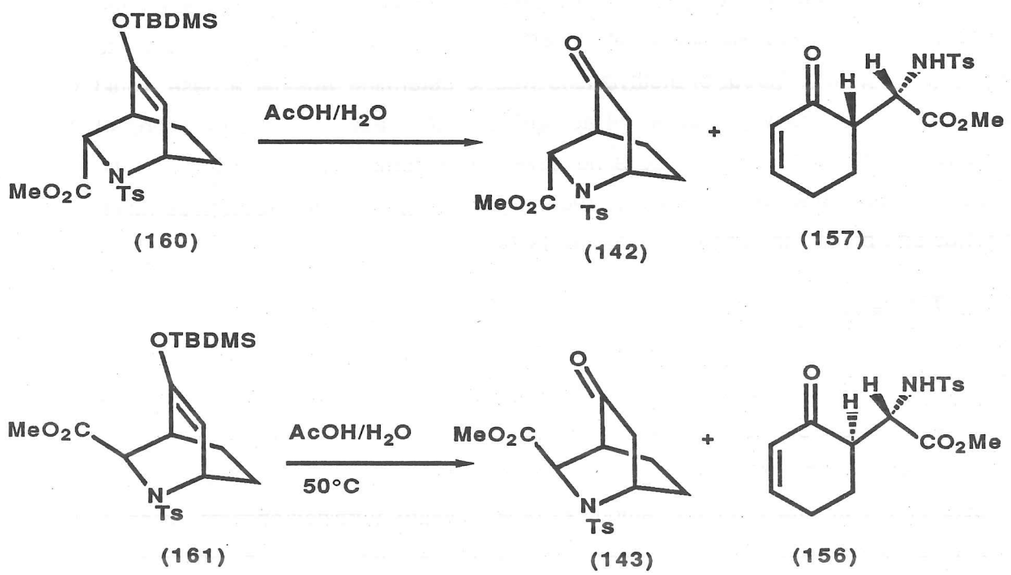
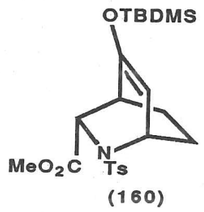


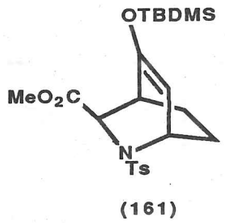
Table 4

TBDMSO Diene reactions

Entry	Solvent/L-A (0.1eq)	Temp C	Time h	Total Yield %	Enol ethers % Yield	% ratio	160:161	Other adducts % Yield	Ratio as % of total yield	Ratio I:II
1	C_6H_6	6	3	69	43	61 3	24	26	4 3 28 2	14.0
2	CH_2Cl_2	0	3	58	36	35 27	1.3	22	0 11 24 4	6.0
3	THF	0	3	87	43	47 3	19	44	14 10 24 3	8.0
4	MeCN	0	4.5	47	0	- -	-	47	13 7 66 14	4.7
5	THF/BF_3	-78	3	29	0	- -	-	29	0 0 91 9	10.0
6	$CH_2Cl_2/AlCl_3$	-78	3	45	4	7 3	2.4	41	1 4 68 19	4.0
7	C_6H_6/(141)	6→20	3	74	-	- -	-	74	56 10 26 8	3.4
8	CH_2Cl_2/(141)	0	3	75	-	- -	-	75	33 44 18 10	3.5
9	THF/(141)	0	3	72	-	- -	-	73	47 6 36 11	3.2
10	MeCN/(141)	0	4.5	74	-	- -	-	74	21 19 50 10	5.1



(160)



(161)

ratios, but this may reflect, in part, the fact that Aldol II is the most difficult isomer to isolate. The most notable feature (entries 9, 11 and 15) is that reactions that are allowed to warm up to ambient temperature, especially over a longer reaction time give considerably higher proportions of the bicyclic products; but not as much as reactions carried out wholly at r.t. Entries 10 and 11 show that reaction still occurs at -78°C even in the absence of a Lewis acid.

2.4 Diels–Alder Reaction With the TBDMSO Diene (159).

From the above reactions it was thought that increasing the size of either the silyl group or the ester should lead to a reaction that was more selective for *exo* and Aldol I. The TBDMSO diene (159) was prepared in slightly impure form from cyclohexenone (158) by a modified literature procedure[96] and was reacted with the distilled imine in several solvents (Scheme 38) (Table 4) and also with crude imine. (Several reactions of the imine with the TMSO diene are presented for the purposes of comparison.) In most cases the enol ethers (160) and (161) were isolated as well as the four usualproducts. The presence of the *exo* (142) and the *endo* (143) ketones is a little surprising as the very mild acid work–up should not be strong enough to hydrolyse the TBDMS enol ethers (*vide infra*). A white precipitate, insoluble in organic solvents, was formed in the MeCN reaction soon after the addition of the diene. This may possibly be a side reaction e.g. with the solvent and probably accounts for the low yield of this reaction. In contrast, of the two low temperature reactions (entries 5 and 6), one gives a higher aldol ratio than the corresponding TMS reaction (Table 3, entries 14 and 7), while the other gives a slightly poorer one. As before the proportion of bicyclic adducts formed at these temperatures is low.

The X–ray crystal structure of the major TBDMS enol ether (Figure 4) (assigned as the *exo* compound (160) by n.m.r. [the signal for H3 is a double doublet due to W–coupling with $H8_{anti}$]) was obtained and this confirmed the n.m.r.assignment*. The ^1H n.m.r. spectra of the enol ethers (160) and (161) are shown in Figure 5.

Treatment of the *exo* silyl enol ether (160) with aqueous acetic acid in THF at 20°C showed no sign of reaction after 2h but after 15h at 50°C t.l.c. analysis showed that no starting material was present. After work–up an essentially quantitative yield of an 8:1 mixture of *exo* (142) and Aldol II (157), with only a trace of *endo* (143) was obtained (Scheme 39). Similar treatment of the *endo* silyl enol ether (161) with the same conditions at 50°C for 48h gave, after work–up, a 100% yield of a 9.5:1 mixture of *endo* (143) and Aldol I (156) with only a trace of the *exo* compound (142). These reactions

*My thanks to Alethea Tabor for performing the X–ray structure determination.

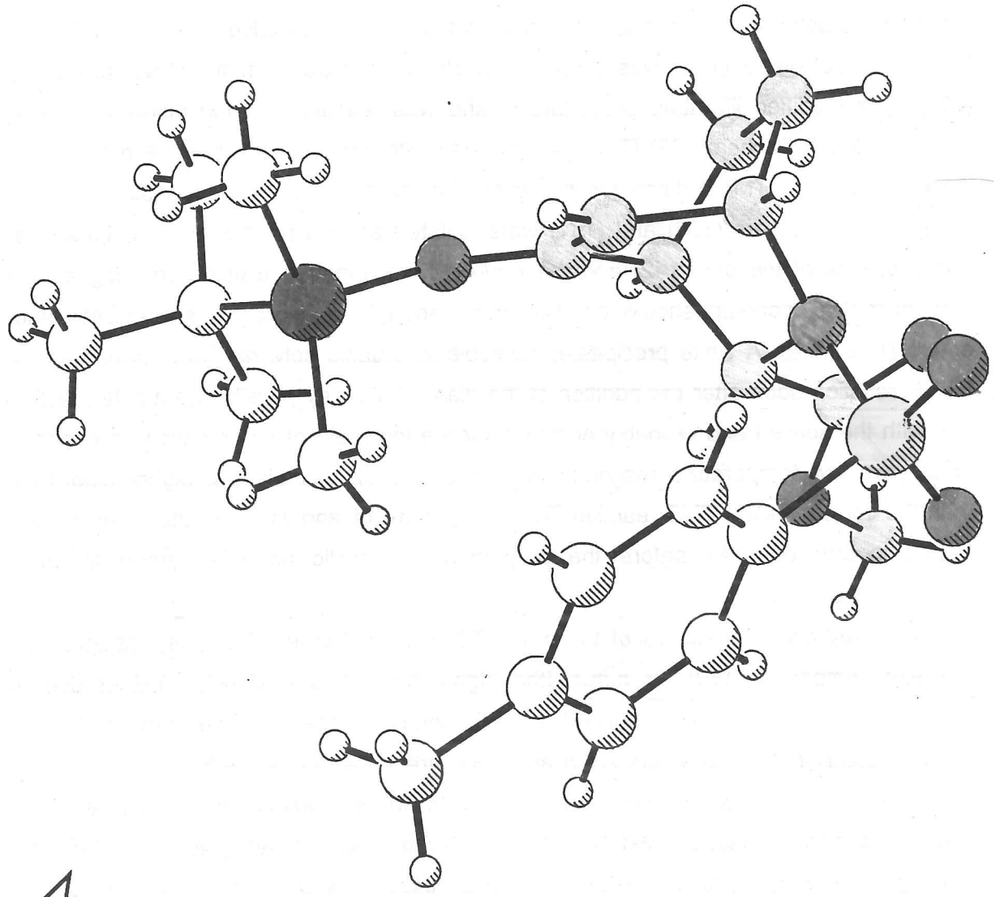
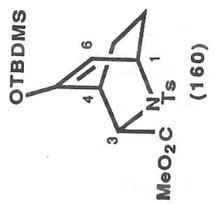
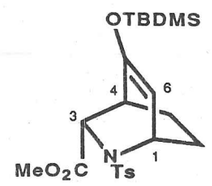


Figure 4

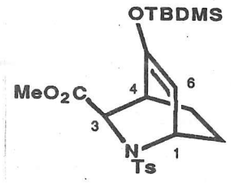


(160)

Figure 5



(160)



(161)

demonstrate the acid–stability of both the silyl enol ethers and the ketones. The aldol products in these hydrolyses probably arise from protonation of the silyl enol ethers (160) and (161) on nitrogen (rather than on the enol ether carbon) with a subsequent retro–Michael reaction. Other work (*vide infra*) suggests that both the *exo* (142) and *endo* (143) compounds are stable to dilute aqueous acid and do not readily undergo acid–catalysed retro–Michael reaction.

Treatment of the *exo* silyl enol ether (160) with tetrabutylammonium fluoride at 20°C for 50min gave predominantly the enone (157) with some *exo* (142) and traces of the other two isomers.

2.5 Discussion of the Results.

The large number of results obtained do not give a clear picture of the imino–Diels–Alder reaction. However a number of points and trends are apparent.

(a) The proportion of Diels–Alder products depends largely on the temperature, rather than on the presence or absence of a Lewis acid. Higher temperatures favour the Diels–Alder reaction.

(b) At ambient temperatures benzene and dichloromethane are the solvents that give the highest proportions of Diels–Alder products; THF is slightly inferior while acetonitrile is poorer still. This correlates with solvent polarity.

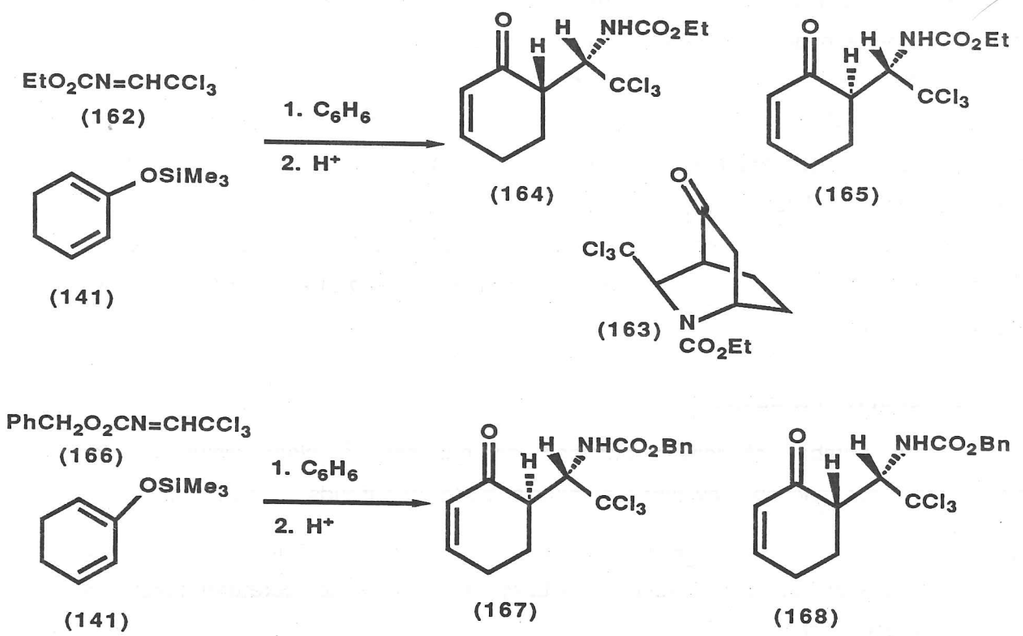
(c) THF gives a more favourable *exo* : *endo* ratio; while dichloromethane and acetonitrile give a more selective aldol reaction.

(d) When the bulkier TBDMSO–diene (159) is used in place of the TMSO–diene (141) greater *exo* : *endo* and Aldol I : Aldol II selectivities are seen, without much change in the proportions of bicyclic products in the reaction. The isolation of the ketones (142) and (143) as well as enol ethers (160) and (161) under conditions that should not cause significant hydrolysis suggests that cyclisation is occurring in solution or on work–up.

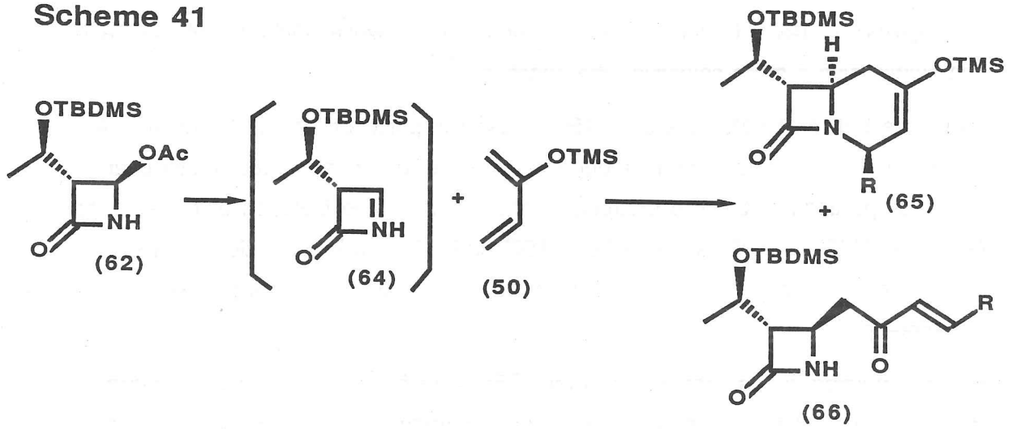
(e) Longer reaction times, especially when -78°C reactions are allowed to warm to 20°C , give significantly more of the *exo* and *endo* adducts. Cyclisation must be occurring, either by a direct cyclisation route of (152)→(154) and (153)→(155) (Scheme 37) or *via* some sort of retro–aldol Diels–Alder sequence.

(f) The rôle of any Lewis acid present is unclear. Reaction occurs when none is present even at -78°C, and the course of the reaction is not greatly affected. The proportion of Diels–Alder products is little changed but the *exo* : *endo* ratio is

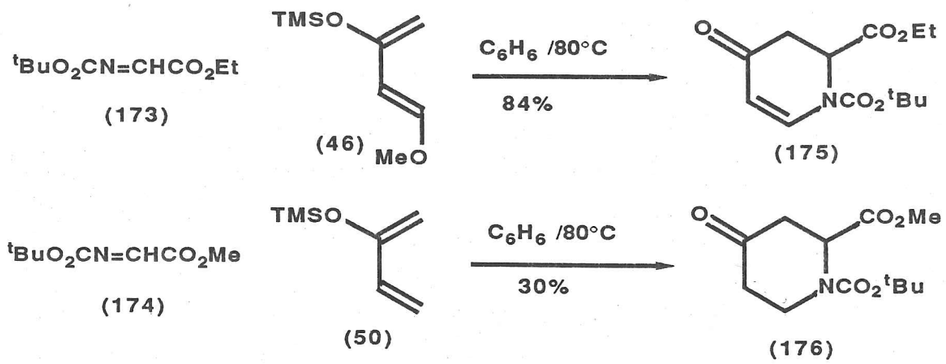
Scheme 40



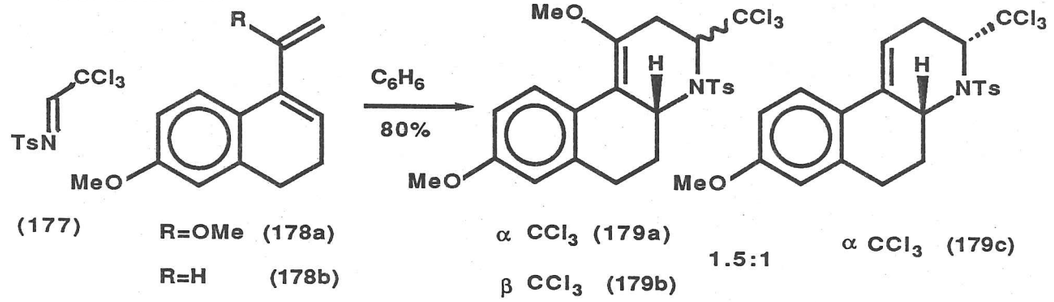
Scheme 41



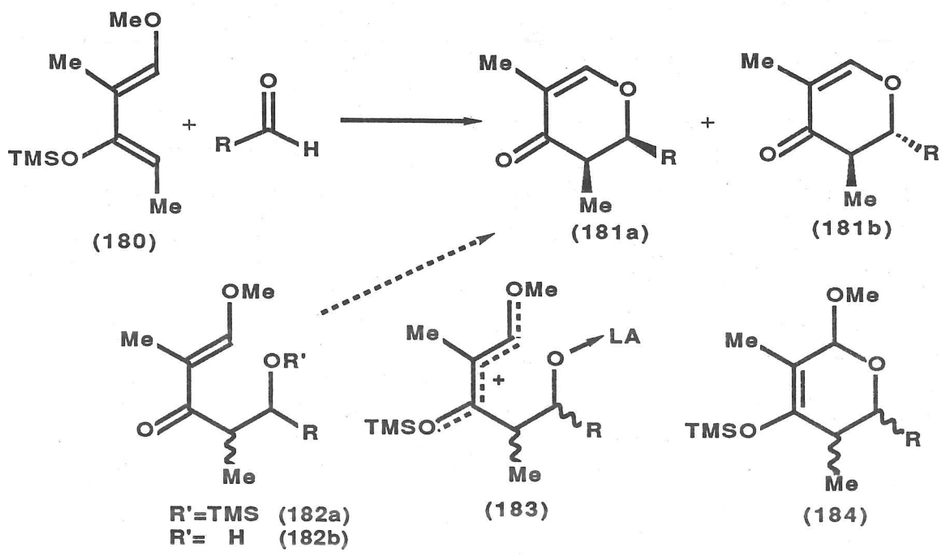
Scheme 42



Scheme 43



Scheme 44



poorer. This may be due to changes in the polarity of the reaction medium. The nature of the Lewis acid does not appear to be significant. Monodentate boron gives very similar results to bidentate aluminium, tin and titanium. Only zinc chloride at 20°C and titanium tetraisopropoxide at -78°C give anomalous results. The former gives less, and the latter more of the bicyclic products than similar reactions with other Lewis acids.

(g) Lithium and dimethyl aluminium enolates give low yields of aldol products only.

(h) The use of more than about 0.2eq. of Lewis acid generally gives much poorer results.

2.5.1 Mechanism.

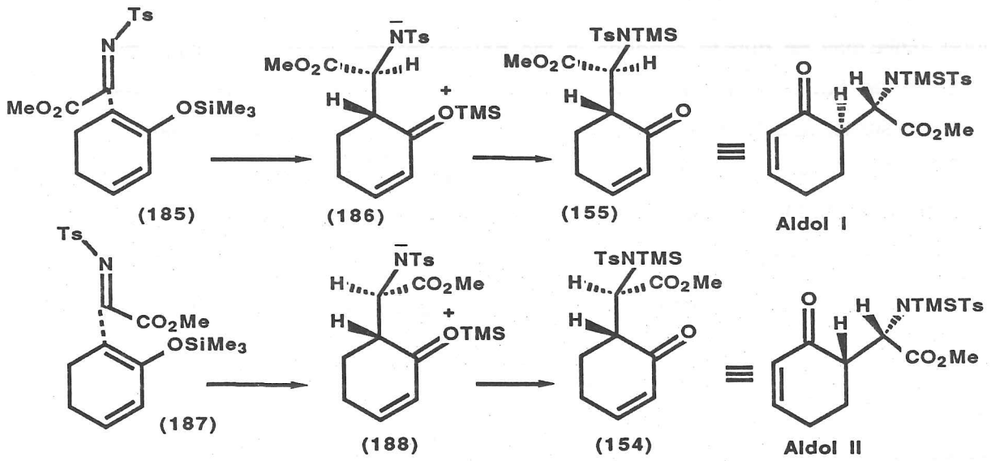
Thompson found that the imine (162) reacted with the silyloxydiene (141) in refluxing benzene to give the *endo* adduct (163)(38%) and the two "aldol" products (164)(29%) and (165)(15%).[85] Similarly the imine (166) gives the two enones (167) and (168) as a 1:1 mixture in 56% yield (Scheme 40). Some similarities between the n.m.r.spectra of these aldol products and the NTs aldol products (156) and (157) led to the wrong assignment of stereochemistries until the X–ray analysis of the minor adduct (157) determined the stereochemistry correctly.

Similarly Ueda and Maynard found that the imine (64) (generated *in situ* from the azetidinone (62)) reacts with the diene (50) to give, at best, an 18% yield of the cyclic product (65) and 75% of the "aldol" type product (66) (Scheme 41).[42]

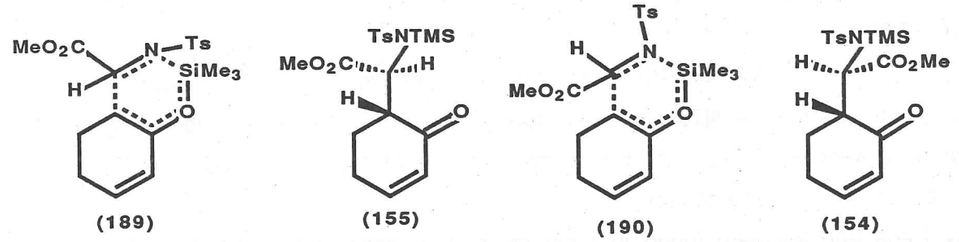
In contrast Jung has reacted the carboalkoxyimines (173) and (174) with the silyloxydienes (46) and (50) to give the piperidines (175) and (176), and has not observed any acyclic products (Scheme 42).[97] Speckamp[98] has used the toluenesulphonamide–derived imine (177)[99] in an imino–Diels–Alder reaction with the methoxydiene (178a) (Scheme 43).

Danishefsky has observed competing hetero–Diels–Alder/aldol reactions in a Lewis acid catalysed reaction of aldehydes with the diene (180)(Scheme 44).[100] When the reaction is run at -78°C for 1.5h only the pyrones (181a) and (181b) are observed. The nature of the Lewis acid is crucial. Zinc chloride in THF gives *cis* adduct (181a) almost exclusively, whereas boron trifluoride in CH_2Cl_2 gives mainly *trans* (181b). If the reaction is quenched after 5min both pyrones and aldol products (182) are observed. T.l.c. analysis of the reaction shows slow conversion of aldol (182) to pyrone (181). The rate of cyclisation of aldol is too slow to account for the significant amounts of pyrone formed initially. Danishefsky suggests that there ara two competing mechanisms, a [4+2] cycloaddition and a two–step, aldol–cyclisation; the latter step being the rate–determining

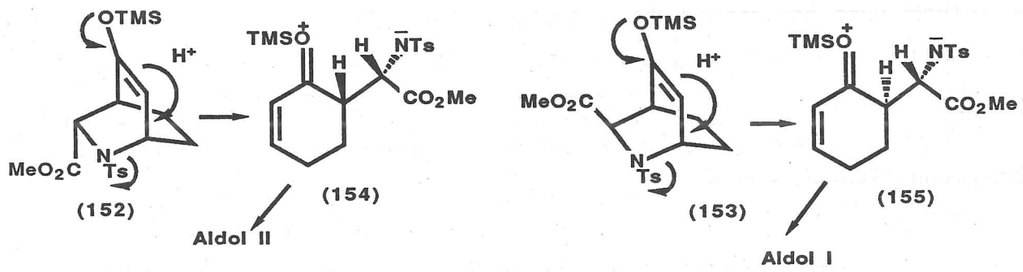
Scheme 45



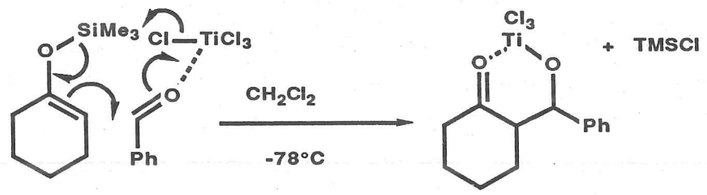
Scheme 46



Scheme 47



Scheme 48



one. Alternatively an intermediate betaine (183) could be formed which could undergo cyclisation to the enol ether (184) (precursor to the pyrones) or silyl transfer togive the aldol intermediate (182a). "Experimental differentiation ..... would be difficult by kinetic means."[100]

The geometry of the imine (140) is not known, but it is reasonable to assume that it is predominantly, if not exclusively *trans (E)* for steric reasons. Speckamp has rationalised the stereochemistry of his Diels–Alder adducts (179) on the basis of *E* imine (177).

2.5.2 Aldol Mechanism.

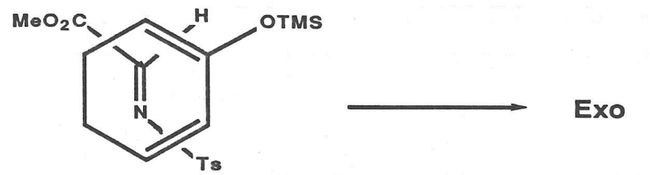
Similar mechanistic possibilities exist for the reaction of the imine (140) with the silyloxydienes (141) and (159). A straight–forward [4+2] cycloaddition appears to be taking place, leading to the *exo* (142) and *endo* (143) adducts. In competition with this is a route that leads to the aldol products. This must account for the observed selectivity of Aldol I over Aldol II Attack of silyl enol ether on the imine (140) would lead to the intermediate (186), which due to its zwitterionic structure is likely to undergo an intramolecular silyl transfer to give the Aldol I precursor (155) (Scheme 45). Similarly attack of the silyl enol ether on the imine from the other side would lead *via* the zwitterion (188) to the Aldol II precursor (154). These *N*-silylated compounds would be readily hydrolysed on work–up. A "sila–ene" reaction (Scheme 46) in which the silylated aldol products (154) and (155) arise directly *via* the transition states (189) and (190) is also a possibility. "Ene" reactions of this imine are known.[101,102]

A "retro–Michael" reaction (Scheme 47) of *exo* → Aldol II and *endo* → Aldol I , either during the reaction or on work–up is incompatible with the data. The proportion of Diels–Alder products would depend on work–up conditions not the reaction temperature if this were the case, and the hydrolysis conditions for the TBDMS enol ethers (160) and (161) show that under far more vigorous conditions only a small amount (10%) of retro–Michael reaction occurs.

The sila–ene mechanism seems to be unlikely as simple drawings and models show that the transition state (189) for the major product (155) has a very bad trimethylsilyl–toluenesulphonamide interaction which is not present in the other possible transition state (190). This latter one looks to be far better despite a possible ester–cyclohexene ring interaction.

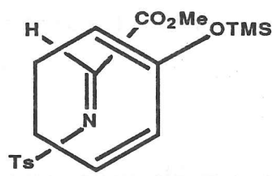
From the open transition states for aldol attack (185) and (186) it could be predicted that Aldol I (156) would be the major product and that increasing the size or either the ester or the silyl group would disfavour production of Aldol II (157), due to the ester – silyl steric interaction in the transition state (187). The low influence of any Lewis acid

Scheme 49



(191a)

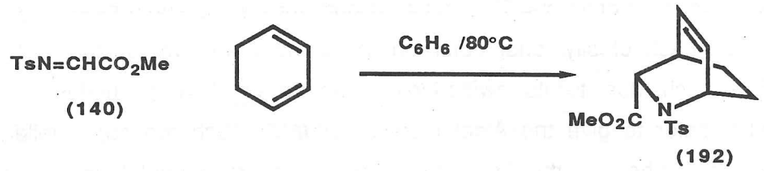
Exo



(191b)

Endo

Scheme 50



present on the outcome of the reactions suggests that Lewis acid co–ordination to either the imine or diene is not important. This is in contrast to the work of Danishefsky (Scheme 44)[100] and of Weinreb.[102] In the latter case the addition of Lewis acid to the ene reaction of the imine with olefins enabled the reaction temperature to be dropped from 170°C to 0°C. The Mukaiyama type aldol reaction of silyl enol ethers requires the Lewis acid ($TiCl_4$ preferred) (which is actually a reagent rather than a catalyst) for reaction at low temperatures (Scheme 48) and probably takes place *via* a cyclic transition state.[43]

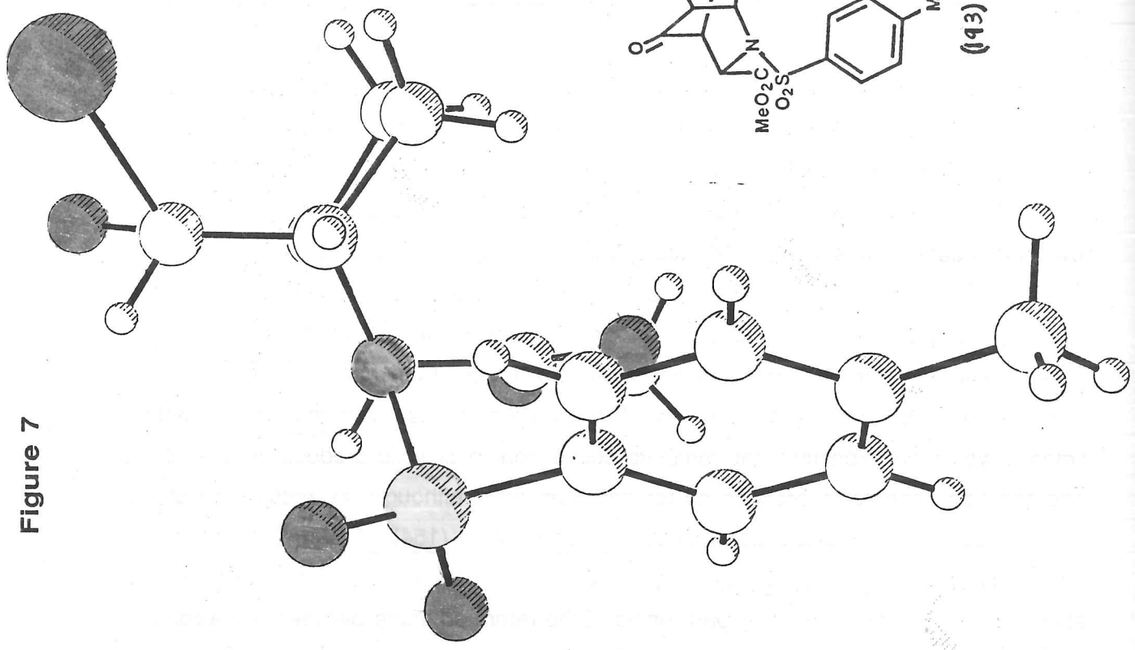
Although a "retro–Michael" mechanism for aldol formation has been ruled out, the reverse, Michael attack of the nitrogen on the enone seems to be taking place, especially with longer reaction times and when low temperature reactions are allowed to warm to 20°C However, if cyclisation were a favoured process, with the longer reaction times it would be expected that complete conversion to bicyclic products would occur. The reaction appears to proceed so far and then stop, although the results are by no means clear. An equilibrium between aldol intermediates (154) and (155) and the *exo* and *endo* enol ethers *via* Michael – retro–Michael is very unlikely for reasons stated above. A retro–aldol followed by partitioning of the reformed imine between the aldol and Diels–Alder pathways is possible, but again complete formation of Diels–Alder products should result, unless retro–Diels–Alder reaction was occurring. Again the stability of the TBDMS enol ethers (160) and (161) suggests that this is not the case. Although no firm conclusions can be drawn from all the results presented it is possible that aldol intermediates such as compounds (186) and (188) could be the initial products along the aldol pathway and these may then slowly react *via* cyclisation or silyl transfer (inter or intra molecularly) to give "Diels–Alder" and "aldol" products respectively. The *exo* (142) and *endo* (143) ketones in the TBDMS reaction may be formed by this route. Side by side with this would be a [4+2] cycloaddition leading directly to the silyl enol ethers (152) and (153) or (160) and (161).

There appear to be two competing mechanisms, as in Danishefsky's work[100]; an aldol reaction. which is favoured at low temperature and a [4+2] cycloaddition reaction which is favoured at higher temperatures. There also seems to be an unknown mechanism, much slower, whereby cyclisation of aldol to bicyclic products takes place when longer reaction times are used.

2.5.3 Diels–Alder Stereochemistry.

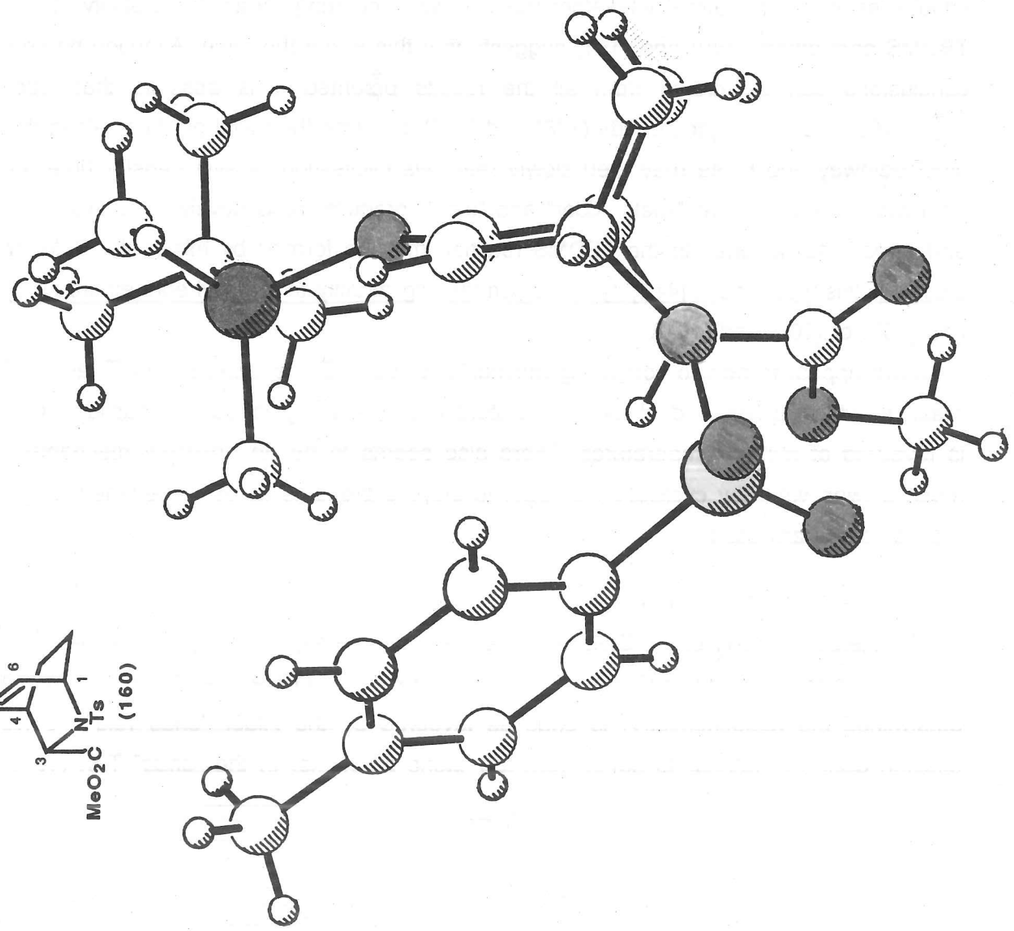
The stereochemistry of the Diels–Alder reaction can be explained by a combination of steric and electronic effects (Scheme 49). In the "*exo*" T.S. (191a) the NTs group (which determines the regiochemistry) is *endo* as favoured by the Alder "endo rule".[103] This position does not appear to suffer from any steric problems. In the "*endo*" T.S. (191b)

Figure 7



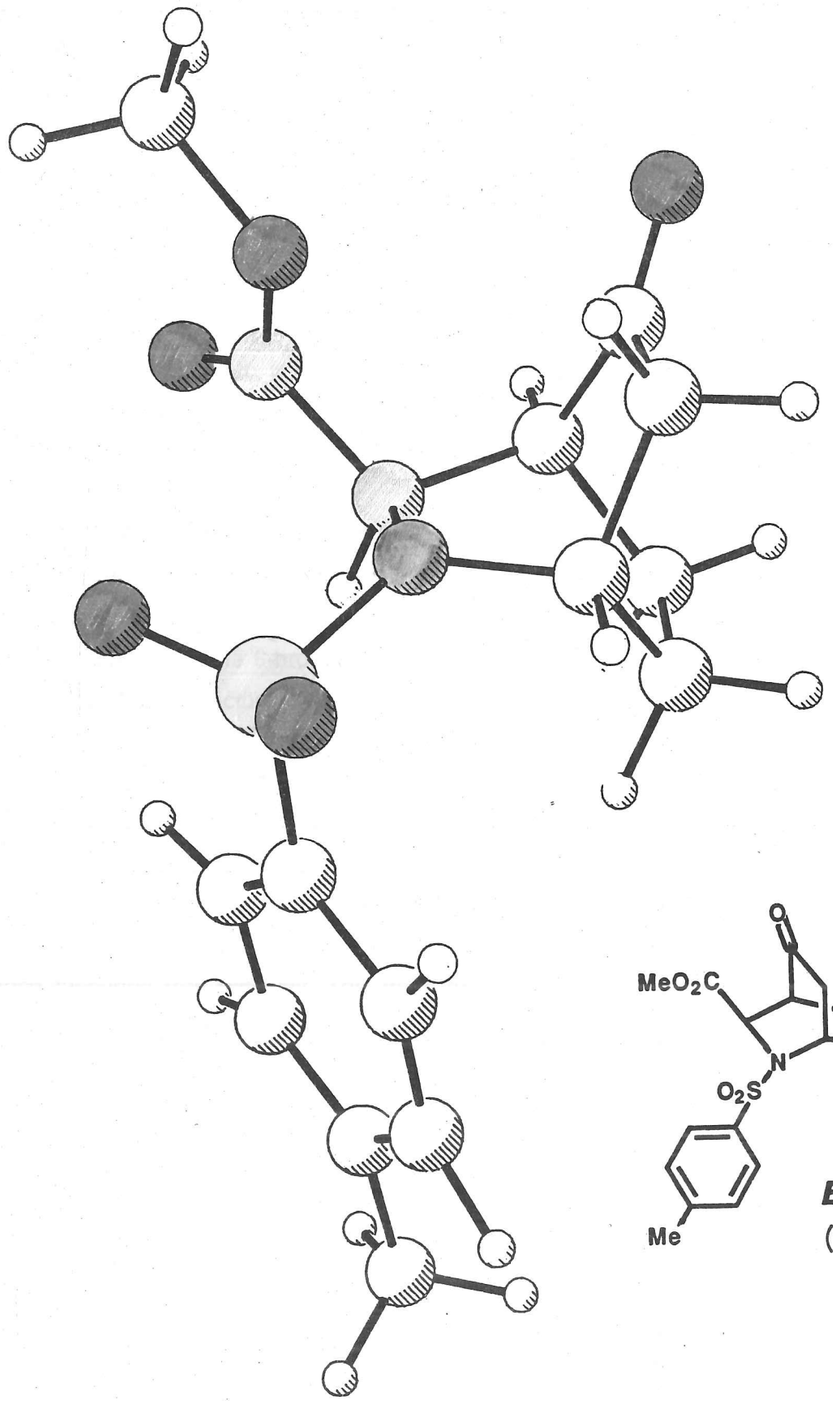
(143)

Figure 6



(160)

Figure 8



Endo
(143)

the ester group is now in the "endo rule" favoured position but the close proximity of this group to the bulky trimethylsilyl will cause some bad steric interactions. The tosyl group is now next to an sp^3 carbon and this will add to the crowding. When a bulkier silyl group (e.g. TBDMS) or a larger ester ester group (Chapter 3) is used less of the *endo* product is formed as predicted by the steric argument. The balance between the *endo* directing abilities of the NTs and ester groups may be quite fine. The Diels–Alder reaction of the imine (140) with cyclohexadiene gives only *exo* isomer (192) (the NTs being *endo* in the T.S.)(Scheme 50).[85] In contrast in the reaction of the imine (177) with the diene (178b) (Scheme 43) the trichloromethyl group takes up the *endo* position. to give the compound (179c).[99] The tosyl group is then *exo*. The related diene (178a) reacts with the imine (177) to give products derived from both *exo* and *endo* attack; the MeO – CCl_3 steric interaction being sufficient to favour an *exo* transition state.

2.6 Discussion of the X–Ray Structures.

The X–ray structures of several of the 2-azabicyclo[2.2.2]octanes have been obtained and these show a number of interesting features. Newman projections of the TBDMS enol ether (160) and the 6-bromo- *exo* -ketone (193) (Chapter 4) are shown in Figures 6 and 7. The X–ray structure of the *endo* ketone (143) is shown in Figure 8*. The feature common to them all is the considerable flattening of the nitrogen, almost completely in the case of the bromo–ketone (193). The greater flattening in this case may be a crystal packing effect or a long–range interaction with the bromine. This suggests that there must be considerable delocalisation of the nitrogen lone pair with the electron–withdrawing SO_2 group. This will make the nitrogen better able to stabilise any negative charge built up on it during the proposed mechanism for the aldol reaction, and hence favouring that pathway. The *trans* relationship of the tosyl and ester groups is what is expected on steric grounds.

*I would like to thank Alethea Tabor for the X–ray structure determination of compound (143)

Scheme 51

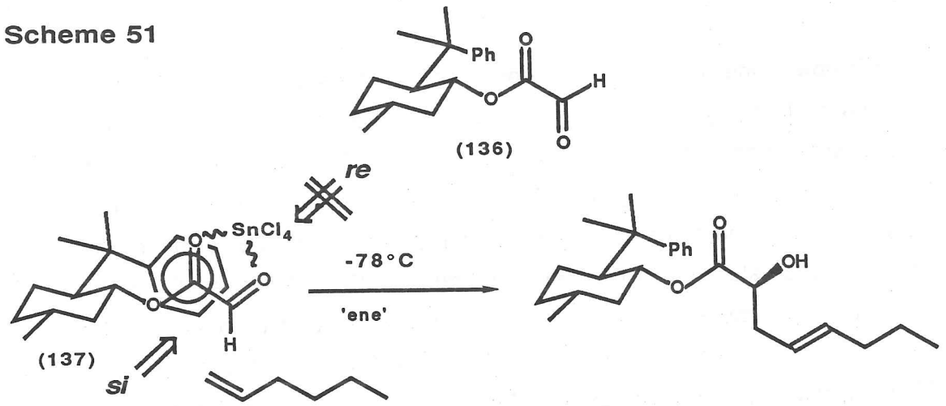
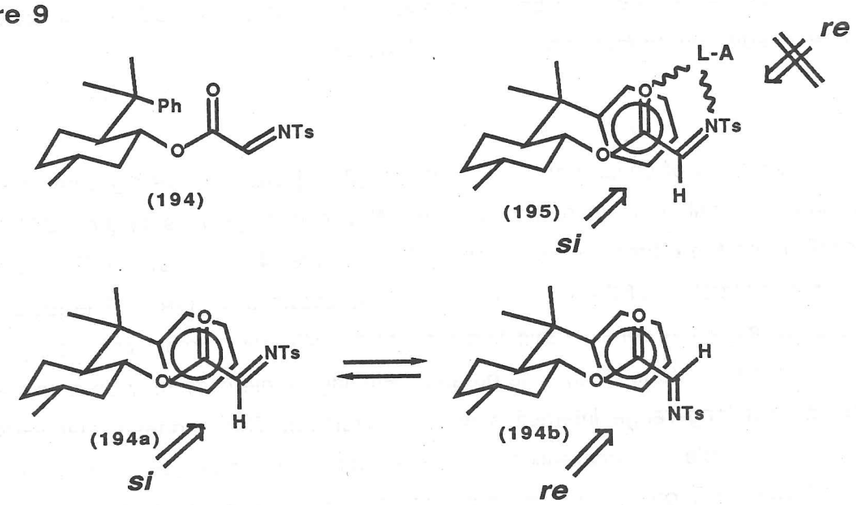
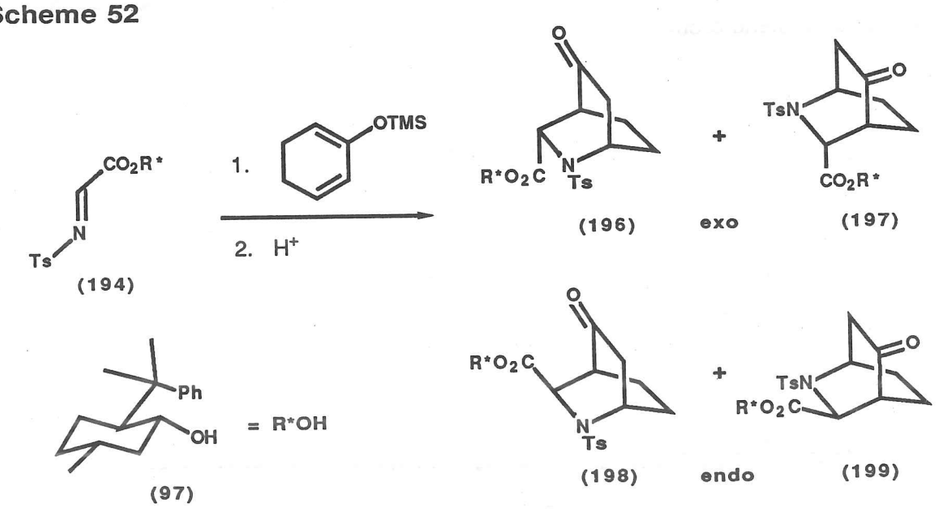


Figure 9



Scheme 52



3. Attempted Asymmetric Diels–Alder Reaction.

Whitesell has obtained very high chiral induction (>99%d.e.) in the Lewis acid catalysed ene reaction of 8–phenylmenthyl glyoxylate (136) with olefins (Scheme 51).[104] It is believed[75] that the Lewis acid co-ordinates to the two carbonyls, holding them in a *syn* conformation (137). The back (*re*) face of the enophile system is blocked by the bulky auxiliary so that the olefin can only approach from the *si* face.

It was hoped that the 8–phenylmenthyl -derived imine (194) would behave in a similar fashion, with a Lewis acid co-ordinating to the carbonyl and the nitrogen (195) and so exposing only the *si* face of the dieophile. Without this co-ordination it could be expected that the imine could exist in both conformations (194a) and (194b) (Figure 9) which would give little or no chiral induction. This is the rationale behind the use of the 8–phenylmenthyl auxiliary and the investigation of Lewis acid catalysis of the imino–Diels–Alder reaction.

3.1 Preliminary Result.

In a preliminary experiment Carling[105] prepared the chiral imine (194) and reacted it with the silyloxydiene (141) under Thompson's conditions (Scheme 52). After the mild acid work–up he isolated, by preparative t.l.c., three fractions: a 7:3 mixture of two *exo* adducts (196) and (197) (20% yield), a 3% yield of one *endo* adduct (Endo I) and a 7% yield of the other (Endo II) (198) and (199). Trituration of the mixture of *exo* compounds gave pure major isomer. An X–ray crystal structure determination (Figure 10) showed that this was the desired diastereomer (196), with the correct absolute stereochemistry of the ring for subsequent elaboration to prosopis alkaloids*.

3.2 Investigation of the Chiral Imino–Diels–Alder Reaction.

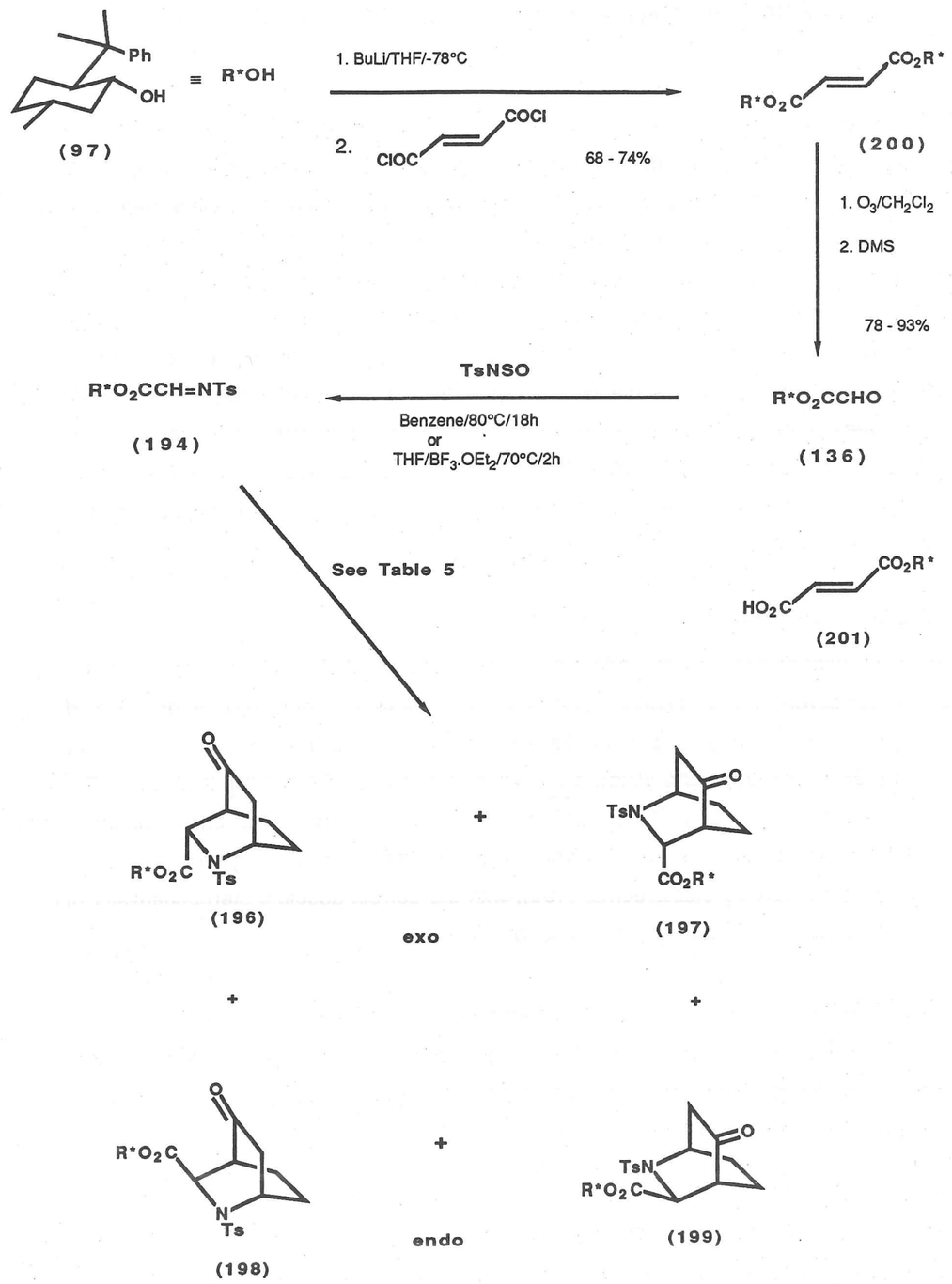
This promising initial result led to the investigation of this chiral reaction under a variety of conditions, similar to those used for the methyl ester imine (140) to see if this modest d.e. (40%) could be improved.

3.2.1 Preparation of the Chiral Imine.

At the time this work was started the published procedure for the preparation of 8–phenylmenthyl glyoxylate (136)[76] used the oxidation method of Kornblum[106], which is three steps and requires silver nitrate as a reagent. It was considered that ozonolysis of

*I would like to thank Dr. Paul Raithby for obtaining the X–ray crystal structure of compound (196).

Scheme 53



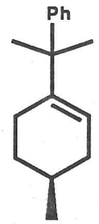
the bisfumarate (200) should be a facile and synthetically economical preparation of the required glyoxylate. Bis 8–phenylmenthyl fumarate[107,108] (200) was prepared in 69% yield by addition of excess fumaryl chloride to 8–phenylmenthol (97)[63] and dimethylaminopyridine (DMAP)(Scheme 53). Some of the mono–ester (201) (16%) was also formed. Polymerisation of fumaryl chloride is a problem and makes work up difficult. A better procedure is to add the lithium anion of 8–phenylmenthol at -78°C to fumaryl chloride. The product obtained contains an unidentified 8–phenylmenthyl derived impurity but recrystallisation gives pure fumarate (200)in 72% yield. Some mono–fumarate (201) and starting alcohol (97) were also isolated. Dicyclohexylcarbodiimide (DCC) has been tried as coupling reagent for fumaric acid and 8–phenylmenthol but even with very large excesses of DCC no reaction was observed.

Ozonolysis of bis–8–phenylmenthyl fumarate in CH_2Cl_2 at -78°C with dimethylsulphide work–up gives the crude glyoxylate which can be distilled (Kugelrohr) to give the glyoxylate (136) as a hygroscopic, viscous oil in up to 93% yield. A larger batch of fumarate can be ozonised and the crude glyoxylate distilled in portions as required*.

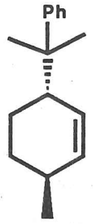
This two step process gives comparable yields (67%) to the three step Kornblum–oxidation method (71%) and is only slightly inferior to Whitesell's recently published procedure.[104] In this method 8–phenylmenthyl glyoxylate is prepared by ozonolysis of the corresponding acrylate, with an aqueous work–up and subsequent dehydration, giving a yield over two steps of 77%.

The imine was prepared in a similar fashion to the methyl ester imine; in THF with 0.1eq. boron trifluoride etherate (2h reflux) or in benzene with no Lewis acid present (18h reflux). It is difficult to estimate the purity of the imine from ^{1}H n.m.r. The influence of the aromatic ring of the chiral auxiliary shifts the glyoxylate and imine CH signals 0.8ppm upfield compared with the corresponding signals for the methyl ester compounds. Whitesell has observed the same effect in the derivatives (including glyoxylate) of 8–phenylmenthol and related chiral auxiliaries.[74b] In deuteroform solution the imine CH signal is buried underneath the aromatic signals, but in deuterobenzene the signals are reasonably well separated and it is possible to estimate the imine purity from the ratio of integrals. The imine was always used crude, with a similar procedure to that for the methyl analogue being used. (Removal of solvent and Lewis acid *in vacuo* and then dissolving the residue in the new solvent.) When an attempt to distil the imine (194) was made decomposition occurred and the only volatile fraction was a mixture of compounds which were probably (by n.m.r.) the olefins (202) and (203) and another compound. Some sort of thermal elimination, possibly an intramolecular "ene" reaction

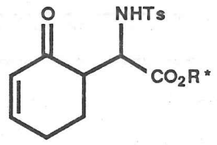
*Distillation from P_2O_5 is not necessary.



(202)



(203)



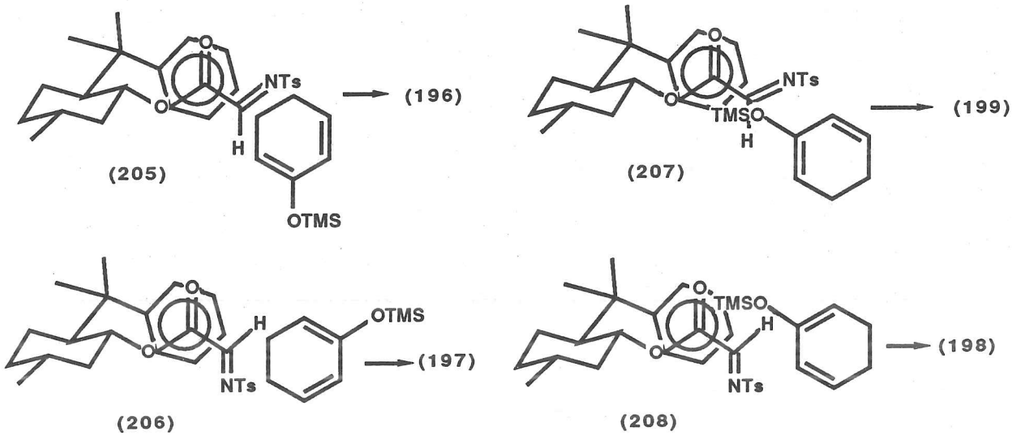
(204)

Table 5

Chiral imine reactions

Entry	Solvent/L-A (0.1eq)	Temp C	Time h	Total Yield %	% Yield exo (196)+(197)	%Yield endo (I) + (II)	% Yield Aldol
1	C_6H_6/Toluene (5:1)	-5-15	48	64	23 (1:1)	3.9 (3:7)	37
2	C_6H_6/CH_2Cl_2 (9:1)	4-12	40	70	20 "	5.2 (1:4)	45
3	C_6H_6/THF (2:1)	-15-0	4	67	17 "	traces	50
4	THF/BF_3	-78	2.5	60	3.5 (1:2)	0	56
5	MeCN/$AlCl_3$	-50	4	38	0	0	38
6	$C_6H_6/AlCl_3$	20	4	40	11 (1:1)	4.5 (1:3)	24.5
7	C_6H_6	20	4	67	21 "	1.6 (7:93)	45
8	C_6H_6	4-20	6	72	31.5 "	2 (45:55)	38.5
9	C_6H_6	35	0.5	78	33.5 "	12.5 (36:64)	32.5
10	$CH_2Cl_2/AlCl_3$	20	17	31	11 "	9.5 (38:62)	10.5
11	CH_2Cl_2	20	17	60	13 "	7 -	40
12	THF/$AlCl_3$	20	2.5	54	16.5 "	0	38
13	THF	20	2.5	58	24 "	0	34
14	MeCN	20	4	51	20 "	2 (1:3)	29

Figure 11



seems to have taken place.

3.2.2 The Diels–Alder Reaction.

The results of the chiral imino–Diels–Alder reactions carried out are presented in Table 5 and Scheme 52. The Lewis acid (0.1eq.) was added to the imine solution in the appropriate solvent, followed by a solution of the silyloxydiene (1.1 -1.2eq.). Work–up was the same as for the methyl ester reactions (Chapter 2). The crude products were purified by flash chromatography [95]and preparative thin layer chromatography. Yields and product ratios were calculated from n.m.r. spectra of the fractions. Complete separation of the products was not always achieved, but as the H3 signals are readily distinguishable calculation of ratios from the mixed fractions was possible. No separation of the two *exo* isomers was observed. In each reaction the aldol products (204) were isolated as a mixture of at least three of the four possible isomers. Isolation of the individual isomers was attempted but was not successful as the products streaked on chromatography. It is not known which *endo* isomer (I or II) corresponds to which structure (198) or (199).

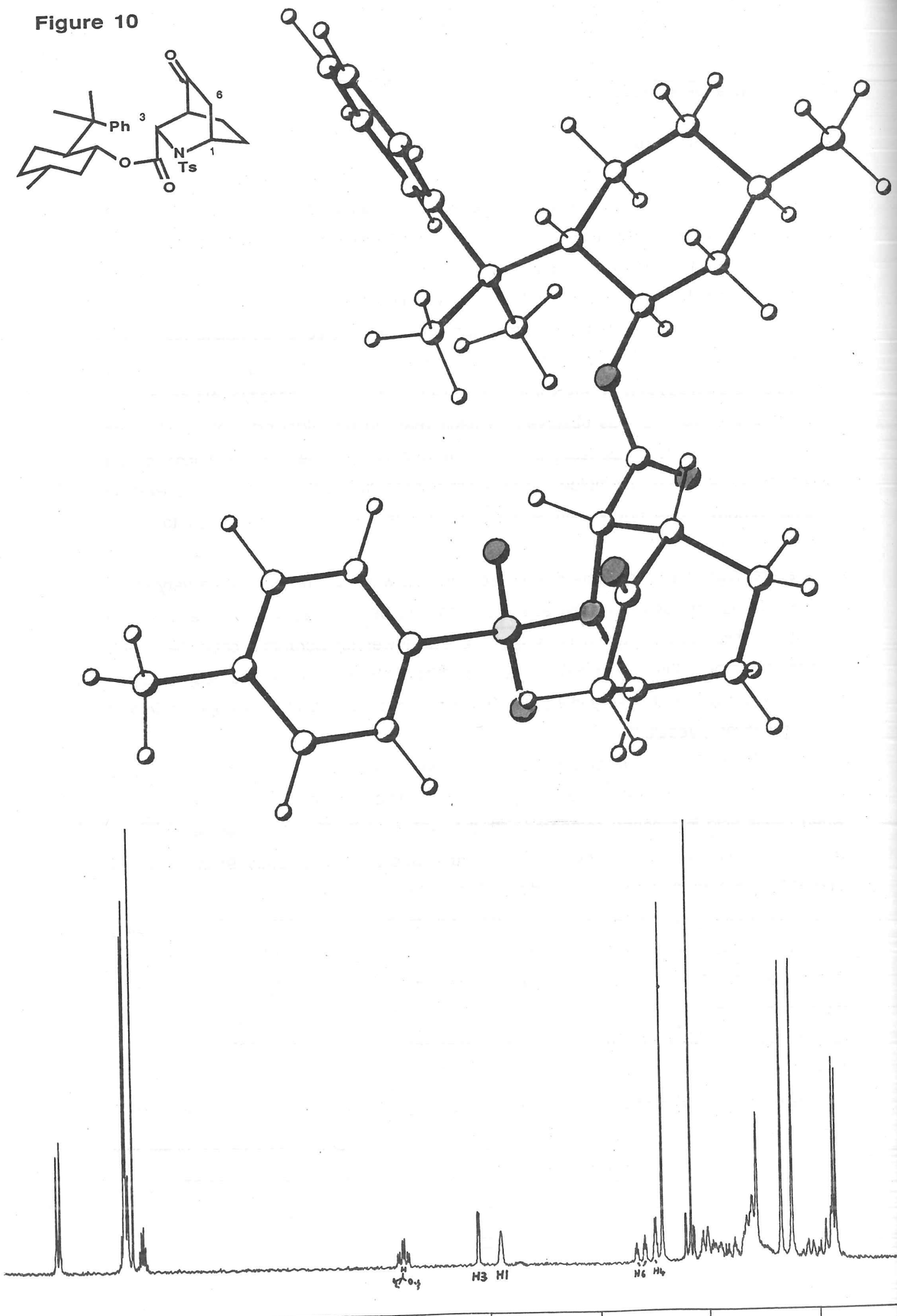
The first four entries in Table 5 are reactions that were carried out before very much of the investigation of the methyl ester reaction had been done, and were attempts to repeat the initial result (with a co–solvent so that lower temperatures could be used). The fourth entry is the only reaction where significant chiral induction has been obtained in the *exo* adducts, but in very low yield. The sense of chiral induction is opposite to that of the preliminary result.[105]

The yields of Diels–Alder products are lower than in the methyl ester case and overall yields are only slightly lower. The reactions show an improved *exo* : *endo* ratio (reduced when Lewis acid is present) compared with the corresponding methyl ester reactions, as discussed in Chapter 2. The best yield of *exo* adducts (33.5%) (Entry 9) is not much poorer than that obtained using non–distilled methyl ester imine.

The chiral induction observed in the *endo* adducts (198) and (199) is a little surprising in view of the almost complete lack of induction in the *exo* compounds (196) and (197). It is not obvious from the transition states for the *endo* products (207) and (208), or from models, that one should be favoured over the other (Figure 11). If, however, the ratio reflects the relative abundances of the two conformers of the imine (194a) and (194b) (*syn* and *anti*) it is not clear why a 1:1 ratio should then be obtained for the *exo* adducts.

The general degree of chiral induction in the *endo* isomers is between 2:1 and 4:1. It it probably not wise to read too much into the one much higher result (Entry 7) as this could very well have arisen from loss of only a small quantity of the minor isomer.

Figure 10



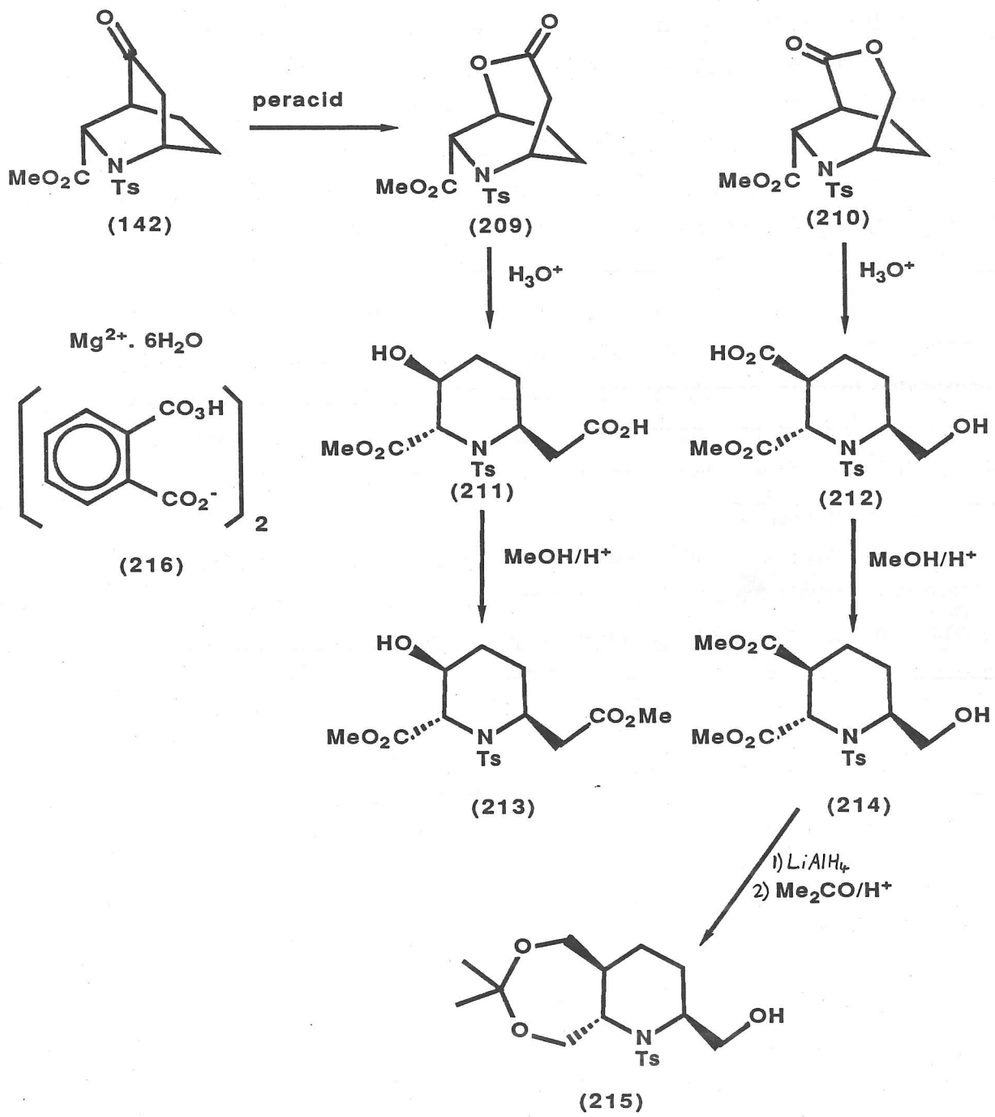
3.3 Discussion of the Results.

The reasons why this imine fails to give appreciable chiral induction can be understood from the results obtained with the methyl ester imine (140). The almost complete lack of influence of Lewis acids suggests that the reasoning behind the Lewis acid co–ordination (195) does not hold. No Lewis acid co–ordinates, so there is unlikely to be fixed conformation. Relatively free rotation about the C–C bond occurs. The nitrogen is probably a poor co–ordination site for Lewis acids as its lone pair is strongly delocalised with the electron–withdrawing SO_2 group, as suggested by the X–ray crystal structures.

The highest degrees of chiral induction are usually obtained at low temperature.[69,70,74,104] However an alternative reaction pathway is available in the imine–silyloxydiene reaction, namely the aldol reaction which is the dominant process at low temperatures, and is still significant at higher temperatures. Thus the lower temperatures where a more selective reaction would be expected to occur give very low yields of the required product.

The very reactive nature of the imine (194) is probably the downfall of this work. With a less reactive imine, where the aldol pathway is not so favourable, and where activation by Lewis acid is necessary there would be a far greater chance of achieving the goal: chiral induction.

Scheme 54



4. An Improved Route to a Piperidine Ring Synthon.

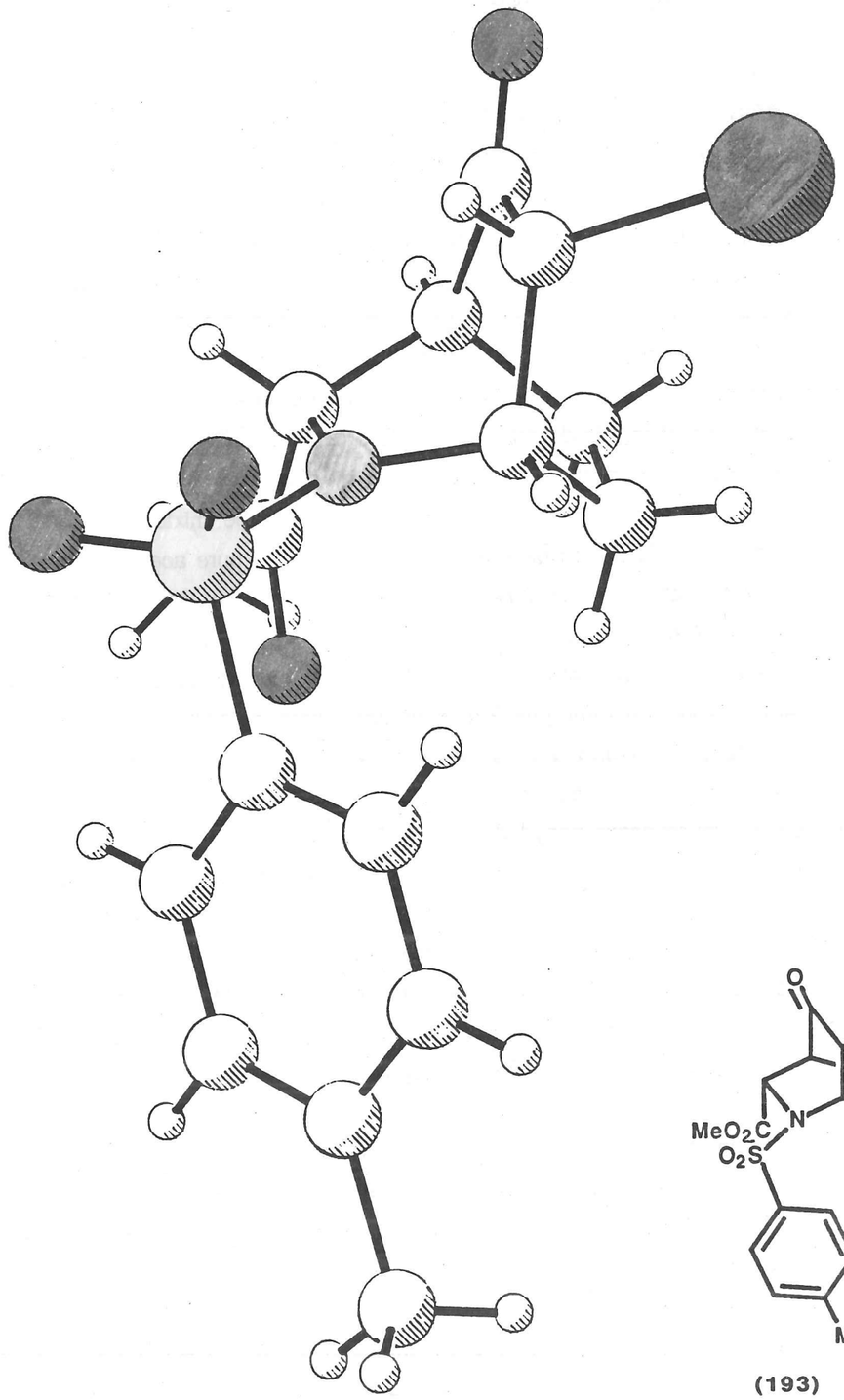
4.1 The Baeyer-Villiger Reaction of the Exo Ketone (142).

Thompson reported a yield of 47% for the required lactone (209) and only 4% of the methylene–migrated lactone (210), on Baeyer-Villiger oxidation of the *exo* ketone with sodium acetate buffered peracetic acid at 50°C for 2 days (Scheme 54).[85] Attempts to repeat this reaction have led to yields of the required lactone (209) of only about 10% and only 2% of the undesired lactone (210). Hydrolysis of the lactones to the hydroxy-acids (211) and (212) appears to be the problem. The aqueous layers from the work up of one of these reactions were acidified, extracted and esterified with acidic methanol to give a 59% yield of the crude mixture of esters (213) and (214), mainly the latter. The major component (214) could also be prepared by treatment of the methylene-migrated lactone (210) with acidic methanol. $LiAlH_4$ reduction of the mixture, followed by acid catalysed acetonide formation gave after crystallisation the pure acetonide-alcohol (215). The rate of formation of the 7-ring acetonide is not much slower than the rate of formation of the 6-ring (*vide infra*).

Treatment of the *exo* ketone (142) with buffered pertrifluoroacetic acid (PTFA) in CH_2Cl_2 at 0°C, and then stirring for 2 days at 20°C gave an 11% yield of the methylene-migrated lactone (210) and a 24% yield of the required bridgehead-migrated lactone (209). With a shorter reaction time, and better buffering (2eq. of Na_2HPO_4 for each equivalent of trifluoroacetic anhydride used in the preparation of the PTFA) the yields of lactones (209) and (210) were improved to 31% and 43.5% respectively, with 12.5% of mixed fractions, including some starting material. Without buffering the yields fell to 8% and 4% respectively with 48% of the hydroxy-acids (211) and (212). Mayne has shown that if the reaction proceeds to completion the maximum yield of lactone (209) that can be obtained is 40%,[109] the yield of the other lactone (210) varies from 8-30%. The "wrong" lactones of a number of related bicyclic systems are known to be hydrolysed at an appreciably faster rate than the "right" ones,[110,111] a fact that has been rationalised in terms of stereoelectronic effects.[112] The regioselectivities of the Baeyer-Villiger reactions of these azabicyclo[2.2.2]octan-5-ones and other bicyclic systems have been studied by several workers[110,113] and found to be heavily dependent on bridge substitution and stereochemistry, and on any hetero-atoms present.

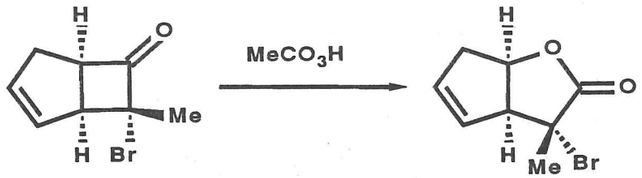
It is claimed that the per-acid MMPP (magnesium monoperoxyphthalate) (216) oxidizes a wide range of substrates under mild conditions.[114] It was hoped that using a milder per-acid such as MMPP would allow a more selective Baeyer-Villiger reaction to

Figure 12

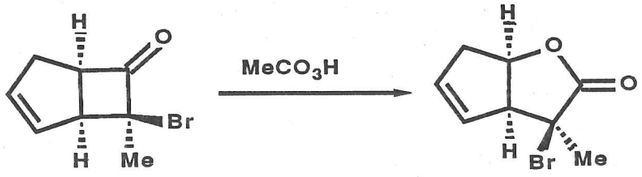


(193)

Scheme 55

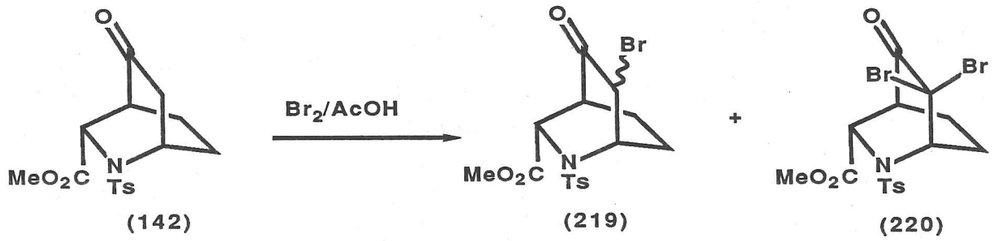


(217)

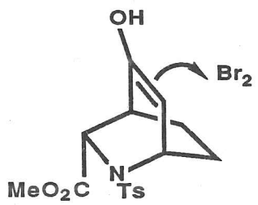


(218)

Scheme 56



(142) (219) (220)



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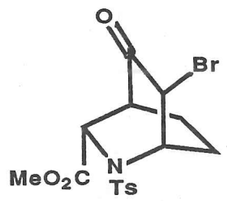

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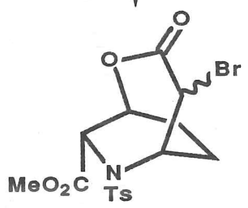
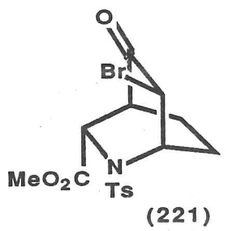


(223)



(221)

take place. MMPP is water-soluble and is suitable for use under phase-transfer catalysis conditions. This should enable a better control of the buffering of the reaction medium to be obtained, and so reduce the the likelihood of hydrolysis. Treatment of the *exo* ketone (142) with MMPP* (8eq.) under phase transfer conditions (chloroform-water, benzyltriethylammonium chloride) at 50°C for 22 days gave a 79% recovery of starting material, 2.7% yield of the required lactone (209) and 1% of the "wrong" lactone (210). MMPP is too mild to oxidise the ketone at a reasonable rate.

The method of choice for the Baeyer-Villiger oxidation is the buffered pertrifluoroacetic acid method as it gives moderate yields reproducibly.

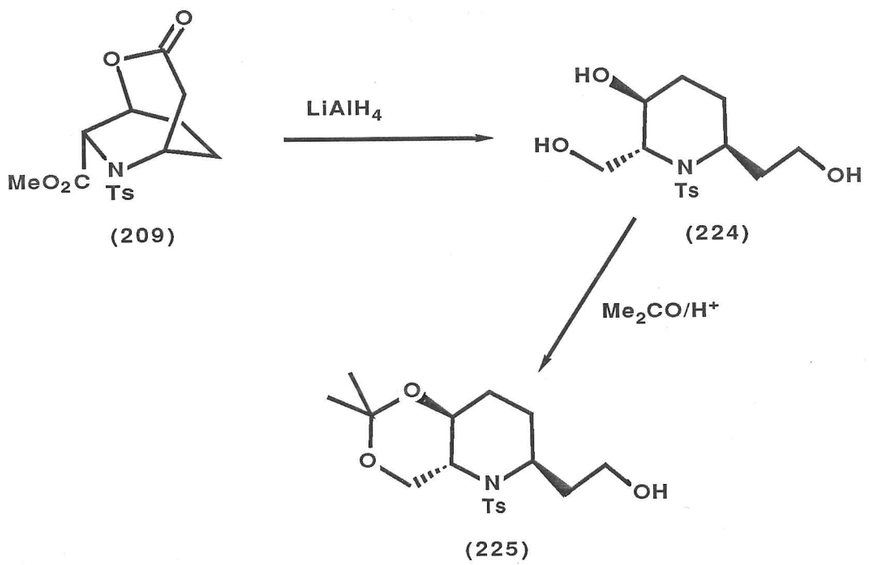
4.2 Bromination of the Exo Ketone.

If the methylene bridge (position 6) of the exo ketone (142) could be modified to reduce its migratory aptitude this should favour the migration of the bridgehead position. A suitable election withdrawing group on the α-carbon would disfavour migration as positive charge builds up the migrating group in the transition state.[115] Ali and Roberts have found that Baeyer–Villiger oxidation of ketones (e.g. (217) and (218) flanked by two secondary carbons, one with a bromine substituent gave, exclusively, migration of the non-brominated group (Scheme 55).[116] The rate of oxidation of the *exo* bromo ketone (217) was slower than that of the *endo* bromo ketone (218), because of the steric influence of the bromine on the approach of the peracid. Introducing an α-bromine in the ketone (142) should favour bridgehead migrated product by making the methylene group a poorer migrating group. It should then be possible to remove the bromine under mild conditions.

Bromination of the *exo* ketone (142) on a small scale with excess bromine in acetic acid at 50°C gave a 67% yield of a monobromo compound (219); the balance of the material was mixed fractions of this compound, starting material and another compound (Scheme 56). On a larger scale an 80% yield of bromoketone (219) was obtained, together with 10% of the other compound which was thought to be the 6-epimer. Another bromination reaction under seemingly identical conditions (1.1 eq of bromine) gave slightly lower yields with some recovered starting material. The second compound was shown to be the 6,6-dibromo compound (220) by m.s ($\underline{M}^+$ 493/ 495/497) and by halogen microanalysis. An X-Ray crystal structure determination of the bromoketone (219) (Figure 12) showed that the stereochemistry of the bromine is *exo* (i.e. compound (193))* . (See Chapter 2, Figure 7, for the Newman projection of this compound.) The

* I would like to thank Interox Chemicals Ltd. for a generous gift of MMPP.
* I would like to thank Alethea Tabor for determining the crystal structure of compound (193).

Scheme 57



notable feature of this structure is the almost planar nitrogen. None of the other bromoketone isomer (*endo*) (221) was observed. Presumably the intermediate enol ether (222) is attacked by bromine from the *exo* face as the *endo* is sterically hindered by the large tosyl group.

Treatment of the bromoketone (193) with buffered peracetic acid at 50°C, for 5 days gave, after work-up, a mixture of starting bromoketone (193), *exo* compound (142) and some dibromoketone (220) in 67% total yield! This does not appear to be possible, and may indicate impure starting material. Treatment of the ketone (193) with the pertrifluoroacetic acid conditions for 3h, gave a 40% recovery of starting material with 13% yield of a mixture that contained 4 compounds by n.m.r. With a longer reaction time less starting material (9%) and a similar mixture of 4 compounds (15%) were isolated. The dibromo starting material (220) did not react when treated with pertrifluoroacetic acid for 5 days and starting material (68%) was recovered. Presumably the bromine sterically hinders attack of peracid on the ketone.

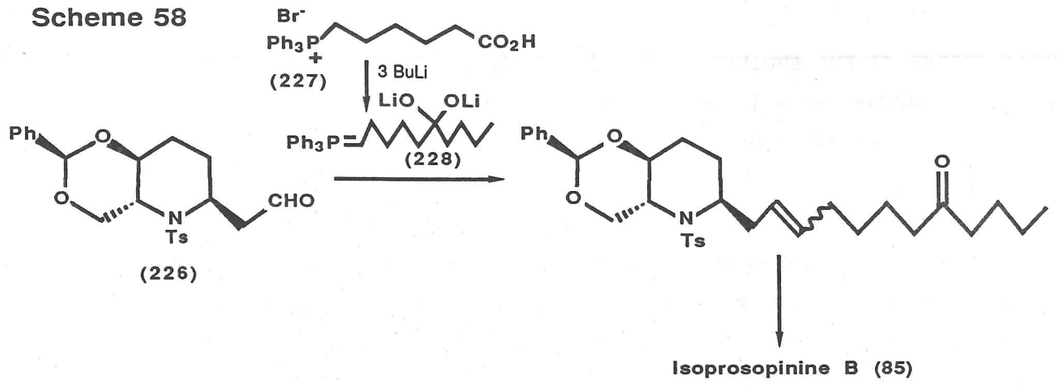
Treatment of the bromoketone (193) with zinc in methanol saturated with ammonium chloride for 15min[117] gave a quantitative yield of the de-brominated *exo* ketone (142).

4.3 Preparation of the Acetonide-Alcohol (225).

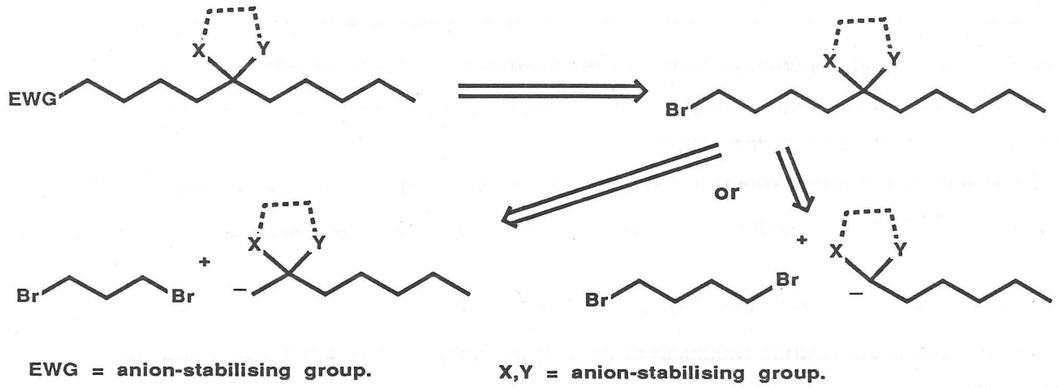
Lithium aluminium hydride reduction of the lactone (209) (Scheme 57) was carried out according to Thompson's procedure except that the work up conditions of Fleischer[118] (water and 5M sodium hydroxide) were used. The triol (224) is difficult to extract from the aluminium salts, or from aqueous solution. It is necessary to extract the aluminium residues with methanol, evaporate these fractions and then re-extract with ethyl acetate to ensure that all the aluminium salts are removed. The cyclic acetal (225) was prepared in 65-74% yield by treating the crude triol (224) with acetone and a catalytic amount of *para*-toluenesulphonic acid (pTSA) for 3-6h. Any starting material isolated was re-cycled. Pyridinium *para*-toluenesulphonate (PPTS) catalyses this reaction but after 40h it was still incomplete. On one occasion toluenesulphonamide (15%) was isolated from the reaction mixture. This may arise as a by-product in the lithium aluminium hydride reduction or from some acid-catalysed breakdown of the triol (224).

The acetonide alcohol (225) is a versatile synthon for *prosopis* alkaloid synthesis as it can be oxidised to the aldehyde for use in Wittig or sulphone couplings or the free alcohol can be converted to a suitable leaving group (Chapter 5) for alkylation reactions, e.g. with sulphones.

Scheme 58



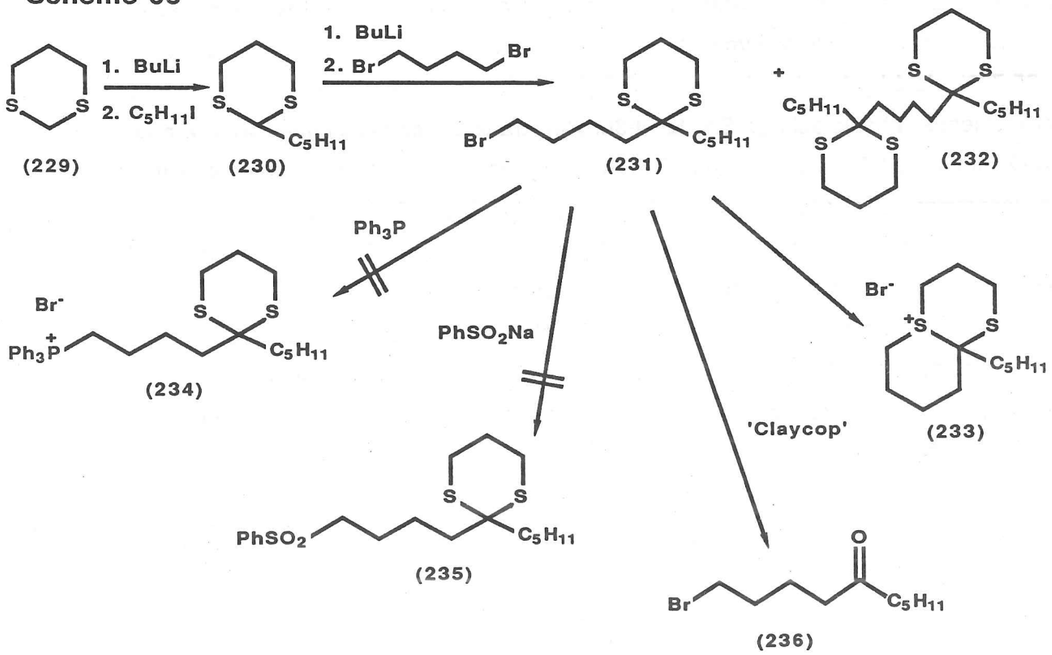
Scheme 59



EWG = anion-stabilising group.

X,Y = anion-stabilising group.

Scheme 60



5. The Syntheses of Isoprosopinines A and B.

In the Thompson synthesis of isoprosopinine B (85)[57,85] the side chain was prepared *in situ* from the phosphonium salt (227) by treatment with 3eq. of butyl lithium, which forms the ylid (228) (Scheme 58). It was then necessary to protect the ketone before effecting cleavage of the N-Ts group with "Redal"[119] [sodium bis-(2-methoxyethoxy)-aluminium hydride]. A more efficient and convergent route would be to introduce the side chain in one piece, ready protected. A different side chain synthon would need to be prepared for each *prosopis* alkaloid, but the "Thompson route" requires different phosphonium salts and alkyl lithiums for each alkaloid.

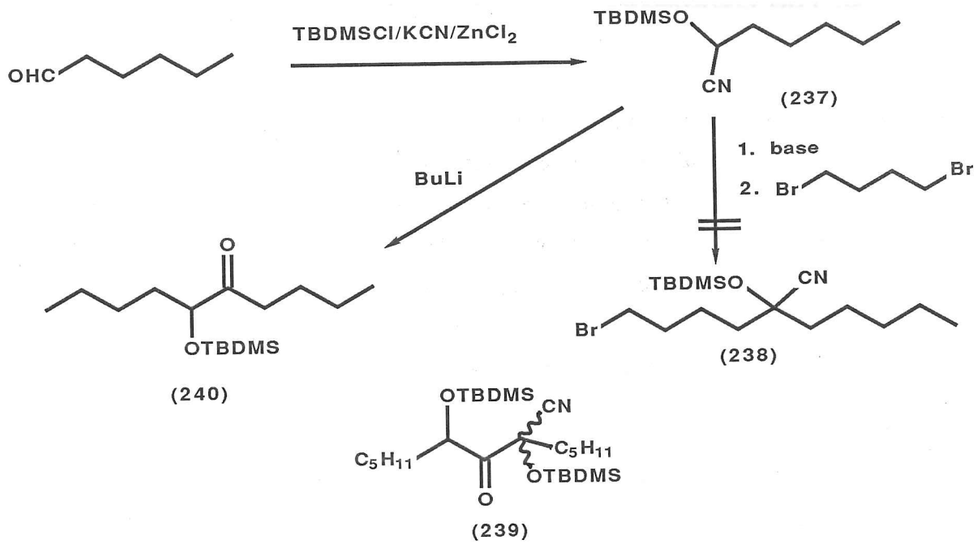
5.1 The Side Chain for Isoprosopinine A.

Isoprosopinine A (84) was used to exemplify this approach. It was hoped that the neccesary side chain, a 10 carbon, 1,5-difunctionalised compound, could be synthesised from a functional group which could then act as a protecting group for later steps in the synthesis, being unmasked at the end to give the required ketone. The retro–synthetic analysis is shown in Scheme 59. Several approaches to suitable compounds were tried before a satisfactory route was found.

5.1.1 Dithiane Route.

The 1,3-dithiane group has been used both as a protecting group for carbonyl compounds,[120] and as an acyl anion equivalent[121] and so seemed ideal for the purposes required. The bromo-dithiane (231) was prepared from pentyldithiane (230) in 45% yield as an unstable solid, which probably decomposes to the cyclised compound (233) (Scheme 60). The "bis" compound (232) was also isolated in 12% yield. Treatment of the bromide (231) with either triphenylphosphine in refluxing toluene or sodium benzenesulphinate in DMF[122] (standard conditions for the preparation of phosphonium salts and sulphones respectively) gave low mass recoveries of mixtures of compounds. In the former case triphenylphosphine was incorporated (as shown by a signal at 507 (M-Br) in the FAB m.s.) but the n.m.r. showed a gross mixture. In the latter case no benzenesulphinate was incorporated into the product. Removal of the dithiane moiety using Laszlo's "claycop" reagent[123] (copper nitrate on Montmorillonite K10) gave a multi-component mxture (by t.l.c. analysis). Evidence from mass spectrometry and t.l.c. comparison with an authentic sample of the bromide (236) showed that the desired product was one of the components of the mixture.

Scheme 61



Scheme 62

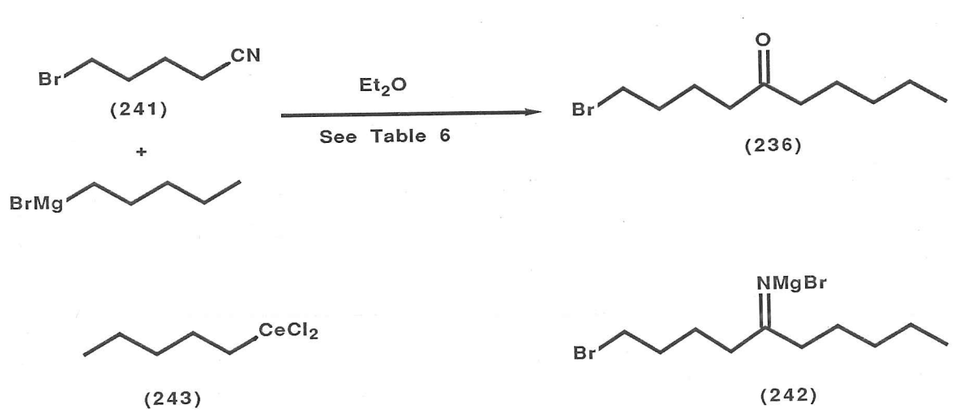


Table 6

Addition of pentyl magnesium iodide to bromovaleronitrile

Entry	Temp °C	Time	% Yield (236)	% Rec'd SM	% Other Prods.
1	-78 -40	3h	5	78	12
2	-15 -5	4h	6	52	15
3	20	2h	13	25	-
4	20	3.5h	17	21	18
5	35	40min	25	27	17
6*	10	4.5h	20.5	11.5	18
7*	40	40min	4.5	14.5	34

* Cerium reagent in THF/Et_2O

The modest yield in the alkylation step, the instability of the product and failure to prepare the two compounds (234) and (235) showed that an alternative approach was needed.

5.1.2 TBDMS Cyanohydrin.

TMS cyanohydrins of aldehydes have been used as acyl anion equivalents and alkylated to give ketones, after removal of the labile TMS group.[124] Chromatographically stable TBDMS cyanohydrins have been prepared[125] and an example of their use in an intramolecular alkylation has been reported.[126] The TBDMS cyanohydrin group can thus act both as an umpolung moiety and as a stable masked ketone.

The TBDMS cyanohydrin (237) was prepared from hexanal in 74% yield using Cava's procedure (TBDMSCl, KCN in acetonitrile) (Scheme 61).[127] Addition of this compound to lithium diisopropylamide (LDA) at -78°C in THF and then slow addition of this solution to 1,4-dibromobutane gave after work up an 8% recovery of starting material and a 14% yield of a compound that contained two TBDMS groups, possibly the adduct (239), arising from attack of the anion of (237) on another nitrile. None of the required material (238) was detected. A repeat of this reaction with more careful addition of the nitrile to the LDA gave a 46% yield of the adduct with two silyl groups (239) and a similar related compound.

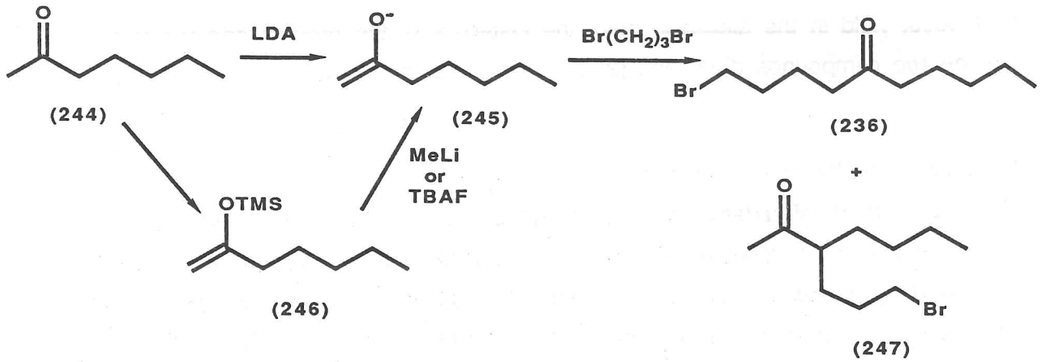
A number of deuterium-quench reactions were performed to determine whether the deprotonation step really was the problem. Slow addition of the cyanohydrin (237) to LDA solution at -78°C or -10°C and then quenching with monodeuterioacetic acid after 0.75h gave poor recoveries (<44%) of impure starting material in which very little, if any deuterium had been incorporated. No other material was recovered. In contrast, butyl lithium added to the nitrile at -78°C to give the ketone (240) in 45% yield.

From these few experiments it seems that de-protonation α to the nitrile is slow compared with the reactivity of the anion formed towards attack on another nitrile. The success of the intramolecular reaction mentioned[126] may lie in the ability of the molecule to quench the nitrile anion intramolecularly before any intermolecular reaction can take place.

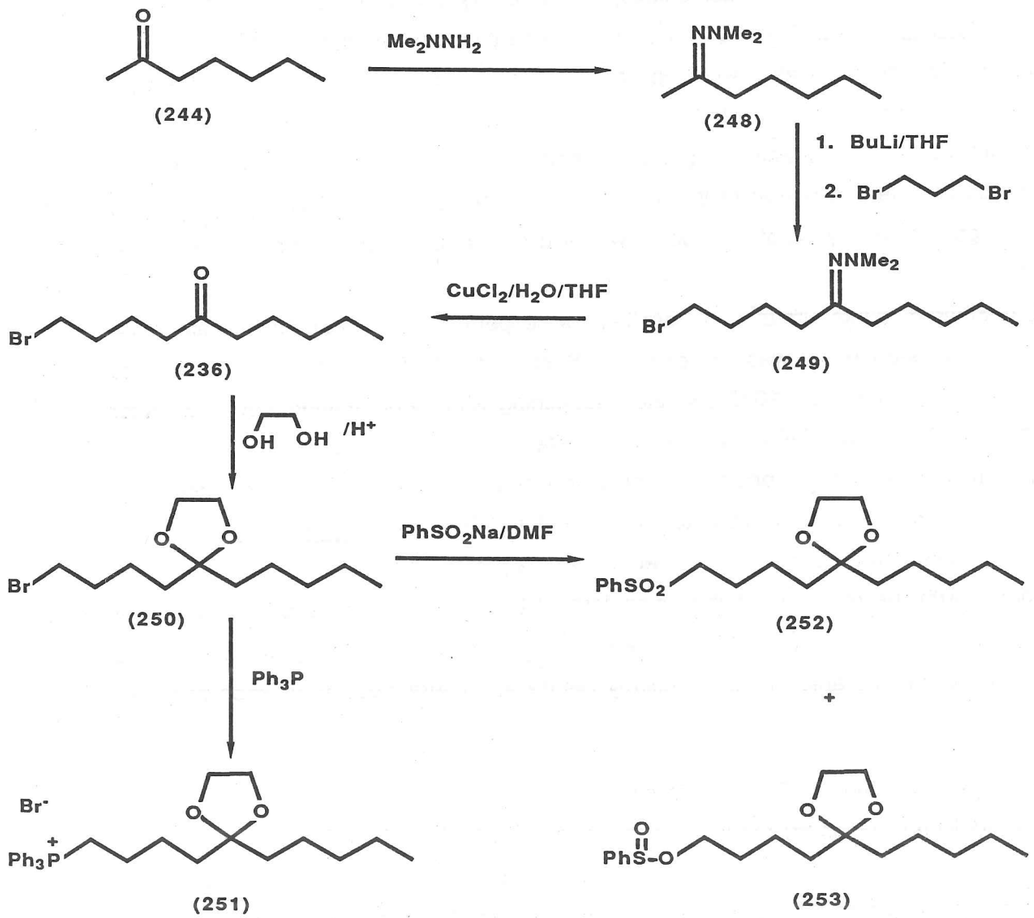
5.1.3 Grignard Addition to Bromovaleronitrile.

The addition of Grignard reagents to nitriles to give ketones is well known,[128] although yields are very variable. ω-Halo-nitriles also react with Grignard reagents.[129] An alternative approach to the ketone (236) is the addition of pentyl magnesium bromide to 5-bromovaleronitrile (241) (Scheme 62). The reaction is very slow at -40°C, with good recovery of starting materials, although some other products were isolated. At higher

Scheme 63



Scheme 64



temperatures the yield of the required bromoketone (236) increases (Table 6) but the recovery of starting materials drops markedly. At least three other products were formed, which could not be identified, and which contained both nitrile and carbonyl groups (by i.r.) (and in one case two nitriles and a carbonyl) and no terminyl methyl group (and therefore no pentyl chain) by n.m.r.

The Grignard reagent is probably acting as base and removing a proton α to the nitrile. This anion then goes on to attack another nitrile. A number of other side reactions are possible, including displacement of the bromine of the intermediate (242) by the nitrogen anion.

Cerium reagents,[130] prepared from the corresponding Grignard reagent and cerium chloride are claimed to be less basic than the Grignard reagents and have been used successfully where Grignard reagents have failed.[131] Addition of the cerium reagent (243) to bromovaleronitrile (241) gave only a slightly improved yield over the corresponding Grignard reaction under similar conditions, but was much inferior at higher temperatures (Entry 7).

It may be possible to optimise the yields of the bromoketone (236) from this reaction but the discovery of an improved route (Section 5.1.5) meant that this approach was discontinued.

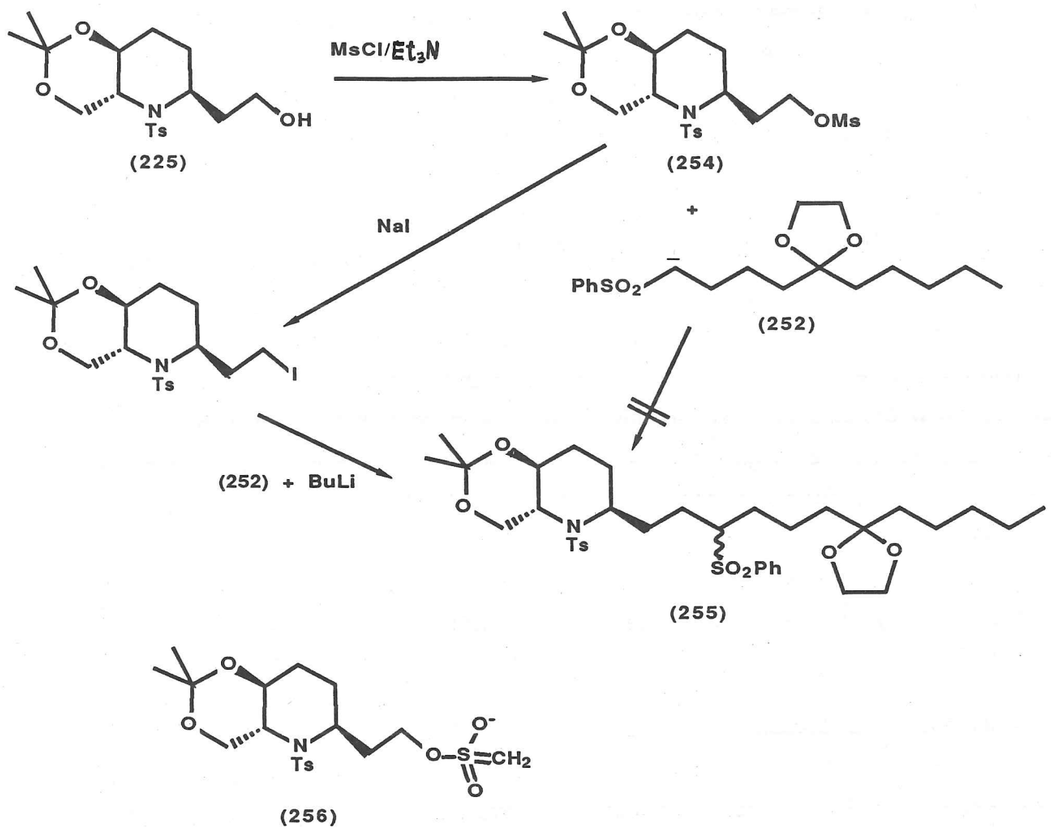
5.1.4 Alkylation of an Enolate.

Alkylation, with 1,3-dibromopropane, of the enolate of 2-heptanone (245) (generated from 2-heptanone (244) by treatment with LDA) gave no identifiable products (Scheme 63). The silyl enol ether (246) (prepared in 58% yield using Corey's procedure[132]) was treated with low–halide methyl lithium to generate the enolate[133], and then with dibromopropane, but none of the required product was formed. This may be because insufficient time was allowed for the enolate to form. Treatment of the silyl enol ether (246) with tetrabutylammonium fluoride (TBAF) over 4Åsieves and then with the dibromide gave a 16% yield of the required compound (236) and a 25% yield of its regioisomer (247). Further investigation was not carried out due to the success of the following method.

5.1.5 The Hydrazone Route to the Bromoketone (236).

At about the time that some of this work was being carried out, a paper was published in which the preparations of some ω-haloketones *via* hydrazone alkylation were described.[134] The hydrazone (248) was prepared in good yield from the corresponding ketone (244) (Scheme 64).[135] Treatment of this with butyl lithium, then addition of 2eq. of dibromopropane at -78°C and then warming to 20°C followed by

Scheme 65



hydrolysis of the hydrazone using Corey's conditions[136] gave a 40% yield of the required bromoketone (236). No other product was seen on t.l.c. The hydrazone (249) is unstable and decomposed during chromatography. Using a slightly larger excess of dibromide (2.7eq.) gave a 62% yield of the required compound. This is more than twice the previous best yield and demonstrates the utility of the hydrazone alkylation method.

5.1.6 The Side Chain Sulphone.

The ketone (236) was protected as the cyclic acetal (250) in high yield (Scheme 64). Treatment of this with triphenylphosphine under the standard conditions for phosphonium salt preparation (toluene, reflux) gave a viscous oil, which was only 70% pure by n.m.r. Attempts to crystallise this material, to give pure phosphonium salt (251), failed. No reaction occurred when the bromide (250) was stirred at 20°C for 17 days in THF and heating this solution under reflux gave another impure viscous gum.

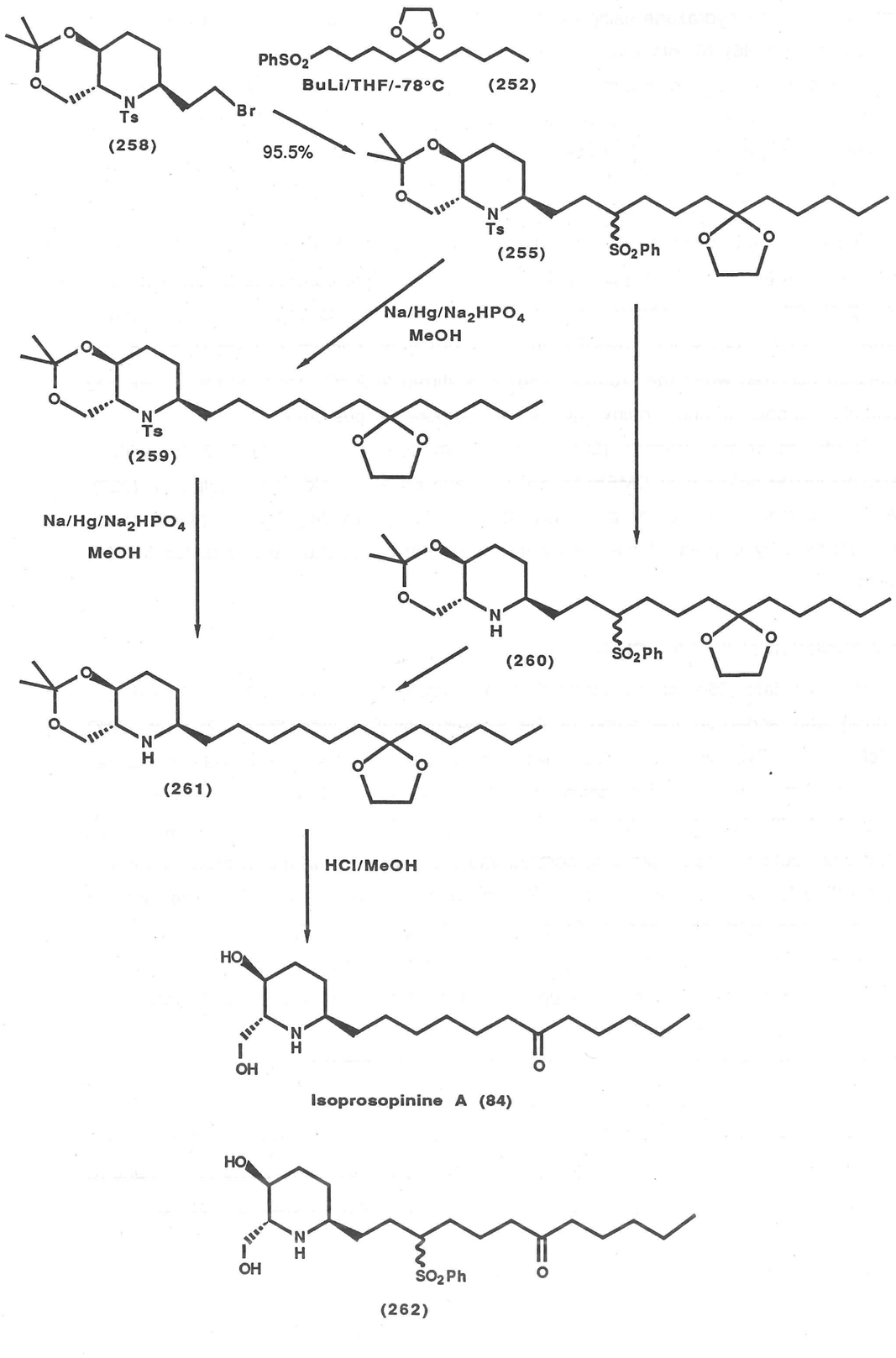
Treatment of the bromide (250) with sodium benzenesulphinate (with or without sodium iodide catalyst) in DMF[122] for 6 days gave 80-82% yield of the sulphone (252). Another compound, probably the sulphinite ester (253), resulting from displacement of the bromide by oxygen of the sulphinate instead of by sulphur, was isolated in 10% yield.

5.2 Alkylation of the Side Chain.

The mesylate (254) of the acetonide-alcohol (225) was prepared in good yield (80-100%) and added to the anion of the isoprosopinine A side chain (252) at -78°C (Scheme 65). Even when the mixture was stirred at 20°C for 40h no alkylation occurred and exellent recovery of side chain (95-100%) was achieved. When the reaction was quenched with deuterium oxide the n.m.r. spectrum of the recovered mesylate showed that one deuterium had been incorporated into the methyl of the mesyl group. (A triplet, integrating for two protons, J=4Hz, at δ3.1 replaced the singlet at δ3.07.) The anion of the sulphone must be acting as base and removing, completely, one of the mesylate protons, to give the stable anion (256). This is inert to further reaction and is then reprotonated or deuterated on work up. α-Metallation and alkylation of sulphonates has been reported when butyl lithium was used as base.[137]

The iodide (257) could be prepared from the mesylate (254) by treatment with sodium iodide (67-78%) and this iodide alkylated the side chain in 73% yield with 26% recovered starting material (Scheme 66). For subsequent work the bromide (258) was used. This was prepared from the alcohol (225) in 64-92% yield using Ph_3P/NBS.[138] Triphenyl phosphine-carbon tetrachloride in pyridine[139] gave only recovered starting material.

Scheme 66



Alkylation of a three-fold excess of the side chain (252) anion gave the required protected isoprosopinine A (255) as a 1:1 mixture of diastereomers, in exellent yield. The product was a foam from which it was difficult to remove the last traces of solvent. The excess of side chain could be recovered but only in impure form; some decomposition appears to have taken place.

5.3 Deprotection Steps.

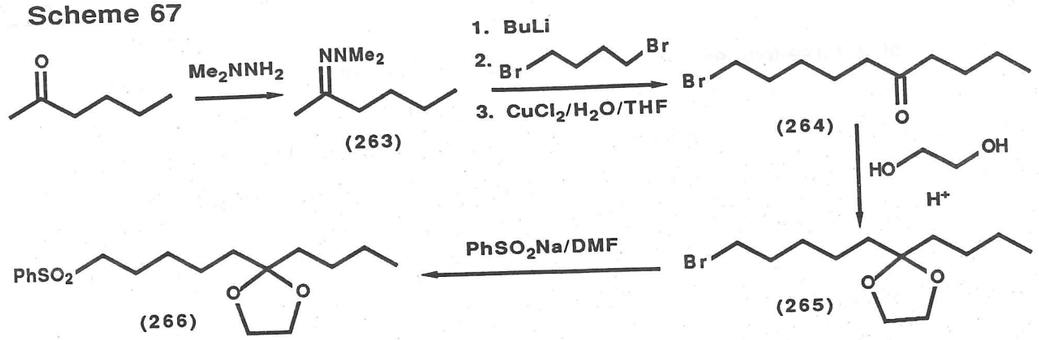
There are a number of methods for the removal of the *N*-tosyl group[140] and the sulphone moiety.[141] Thompson[85] used Redal to cleave the *N*-tosyl [119] in his synthesis, but this reagent is likely to reduce the sulphone to a sulphide, without cleavage. Dissolving metal reduction conditions are known to remove both sulphones and sulphonamides. Treatment of the sulphone (255) with sodium in liquid ammonia[142] at -78°C for 10min gave only a low mass recovery of a mixture of compounds which probably included the de-sulphonated compounds (259) and (261) by n.m.r. and t.l.c. analysis. Treatment of the same sulphone (255) with sodium naphthalenide[143] in dimethoxyethane (DME), 1h at 20°C again gave a mixture of at least five compounds in low yield. The main fraction corresponded to the major one from the sodium in liquid ammonia reaction.

It was thought that competing removal of suphone and *N*-tosyl groups may be causing complications, and removal of one group first would facilitate the removal of the second. Treatment of the *N*-tosyl sulphone (255) with Trost's mild conditions for removal of sulphone groups[144] (6% excess sodium amalgam in methanol buffered with disodium hydrogen phosphate for 24h) gave a 34% yield of the desulphonated compound (259), 12% starting material and 50% yield of the two amines (260) and (261) (Scheme 66). Not only was the amalgam removing the sulphone but it is also removing at a comparable rate, the *N*-tosyl group. Using a large excess (*ca* 20eq) of freshly prepared sodium amalgam, with recycling of the intermediates gave an 85% yield of the required amine (261) containing an extra 11% of the sulphone-amine (260) which was difficult to separate on chromatography.

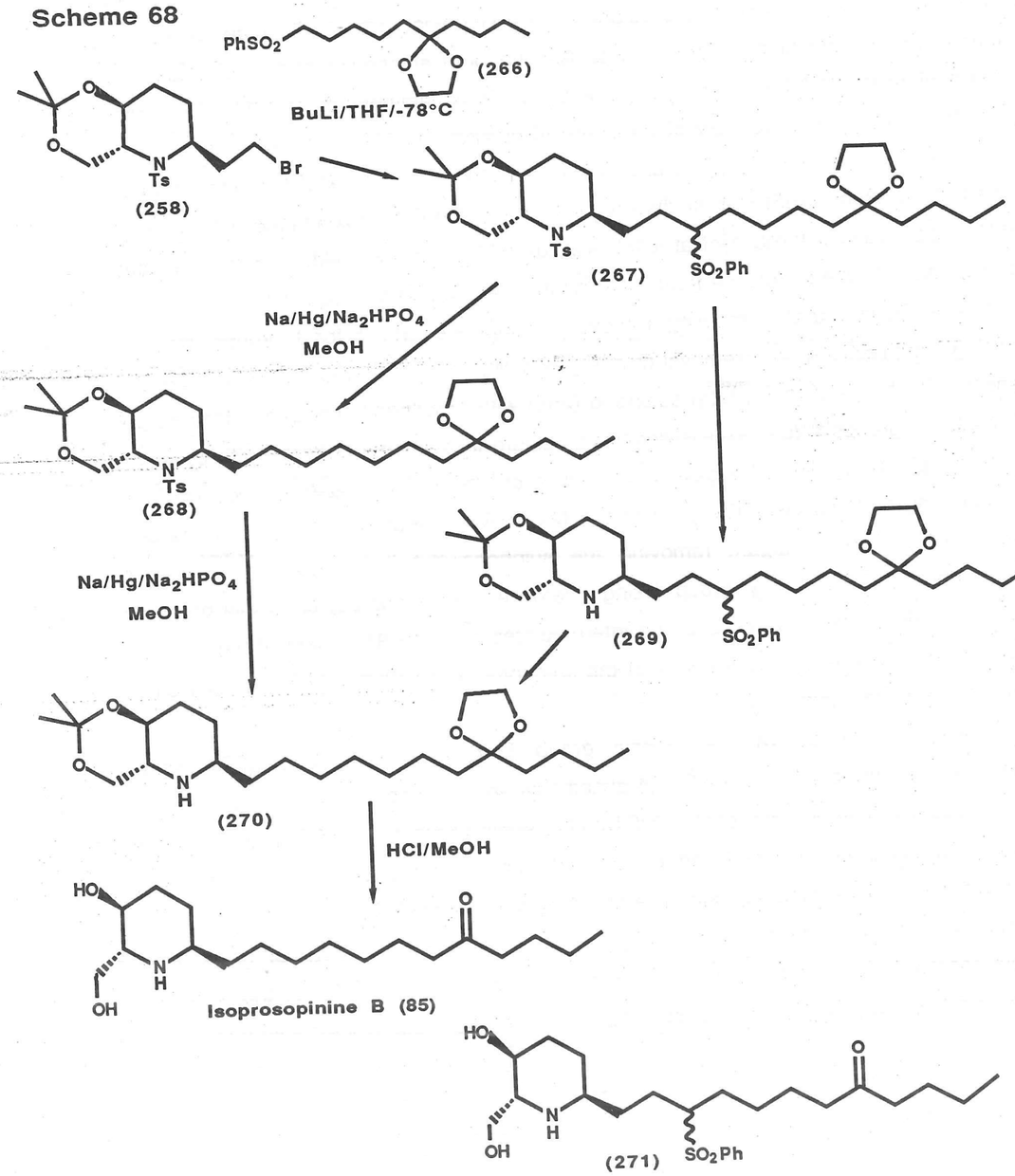
An attempt to remove the *N*-tosyl group from the intermediate (259) using Yonemitsu's photolytic conditions[145] (1,4-dimethoxybenzene, sodium borohydride) gave a gross mixture of compounds, containing, by t.l.c. some of the required amine (261). The success of the amalgam reduction meant that this method and the dissolving metal reduction methods of removing sulphone and tosyl were not pursued any further.

Removal of the remaining protecting groups with methanol-conc.HCl gave, after chromatography, (±)-isoprosopinine A (84) in 79% yield (89% allowing for the sulphone in the starting material (261); 76% over the two steps from the *N*-tosyl sulphone (255).

Scheme 67



Scheme 68



The isoprospinine A sulphone (262) was also isolated in 10% yield. Treatment of the latter compound with further sodium amalgam gave, by t.l.c. analysis, mainly isoprosopinine A. Crystallisation of the isoprospinine A from ethyl acetate gave pure material as a fine, white powder m.p. 86-7°C.

5.4 Isoprosopinine B

The success of the route to isoprosopinine A (84) led to the re-preparation of isoprosopinine B (85) using a similar route. Thompson had prepared insufficient material to fully characterise his racemic isoprosopinine B,[57,85] especially for a ^{13}C n.m.r. spectrum. ^{13}C n.m.r. is the only method where significant differences between isoprosopinines A and B can be seen.[53]

The side chain sulphone (266) was prepared from 2-hexanone (263) *via* a similar route to the isoprosopinine A side chain (Scheme 67). Alkylation of the hydrazone (264), followed by hydrolysis gave a 72% yield of the required bromoketone (265). Protection and dislacement of the bromine with sodium benzenesulphinate gave the necessary side chain (266). Treatment of an excess of the anion of this with the piperidine-bromide (258) gave the tosyl-sulphone (267) in excellent (96%) yield (Scheme 68).

Removal of the *N*-tosyl and sulphone groups from this intermediate (267) was not as facile for the isoprosopinine B series as for the A series. The reaction was much slower, required much larger excesses of sodium amalgam (30-40eq.) and more recycling of intermediates. The yield was lower as a consequence; 46% of the amine (270) containing a further 15% of the sulphone-amine (269) (61% overall). The quality of the amalgam is believed to be the difference between the "A" and "B" series. The amalgam used in the "A" reactions was freshly prepared. The same batch was used for the "B" reactions, but it was by then 4 months old. It appears that freshly prepared sodium amalgam is critical for the success of these de-tosylation, de-sulphonation reactions.

Acid treatment of the acetal mixture (269) and (270) gave, after chromatography, (±)-isoprosopinine B (85) in 67% yield (96% allowing for the sulphone in the starting material; 41% over the two steps from compound (267)) and the isoprosopinine B sulphone (271) in 28% yield. Isoprosopinine B was crystallised fron ethyl acetate to give pure material as a fine, white powder m.p. 90-1°C.

5.5 Comparison of Synthetic and Authentic Samples.

The i.r. and n.m.r. spectra of synthetic isoprosopinines A and B are almost identical to each other and very similar to those of the natural A+B mixture,[50] although comparison is a little difficult as the published n.m.r. and i.r. spectra are not very well resolved. The ^{1}H

Figure 14

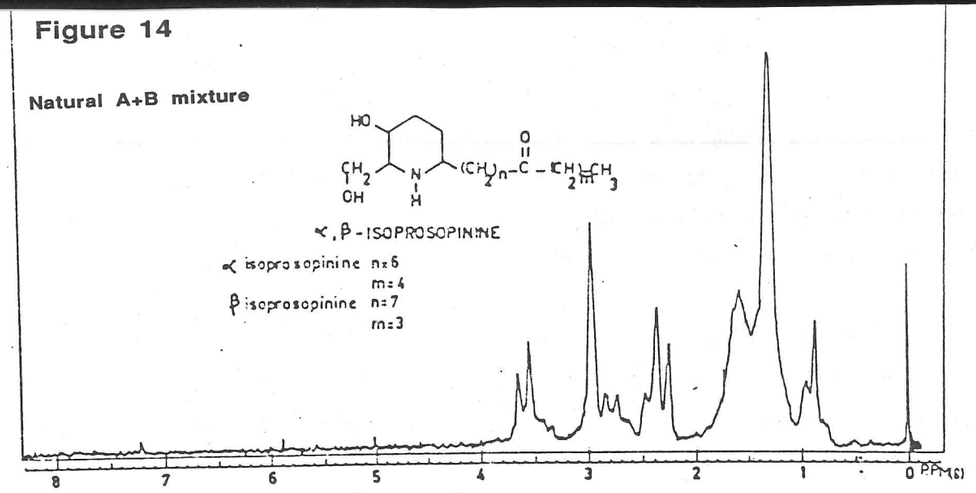
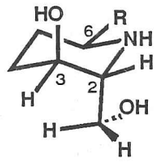
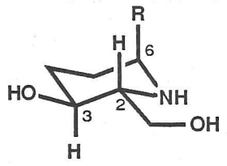


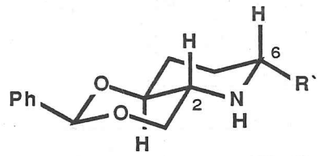
Figure 15



(272)



(273)



(88)

R=$(CH_2)_6COC_5H_{11}$
or
$(CH_2)_7COC_4H_9$

R`=$C_{12}H_{25}$

Table 7

Carbon no.	IPA (84) Lit.	IPA (84) Synth.	IPB (85) Lit.	IPB (85) Synth.
2	57.7	58.2	57.7	58.7
3	67.9	68.0	67.9	67.9
4	27.2	27.4	27.2	27.3
5	28.4	28.6	28.4	28.6
6	50.0	49.8	50.0	49.9
1"	62.3	62.3	62.3	62.9
1'	32.5	33.7	32.5	33.8
2'	26.2	26.1	26.2	26.1
3'	29.2	29.2	29.2	29.4
4'	29.2	29.4	29.2	29.3
5'	23.7	23.6	29.2	29.2
6'	42.5	42.7	23.7	23.8
7'		211.5	42.5	42.7
8'	42.5	42.8		211.4
9'	23.7	23.7	42.5	42.4
10'	31.3	31.4	26.2	26.2
11'	22.2	22.4	22.2	22.4
12'	13.7	13.8	13.7	13.8

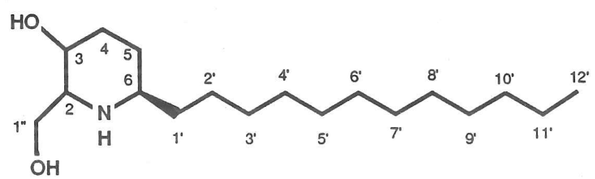
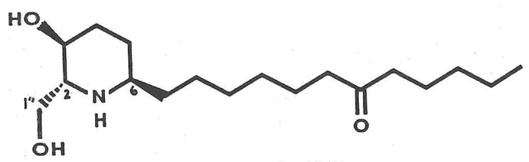


Figure 13



ISOPROSOPININE A (84)

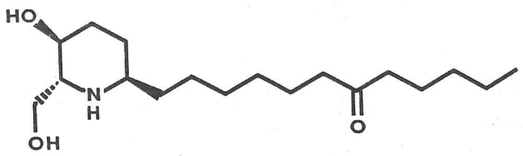
ISOPROSOPININE B (85)

n.m.r. spectra of isoprosopinines A and B are shown in Figure 13 and that of the natural AB mixture in Figure 14.

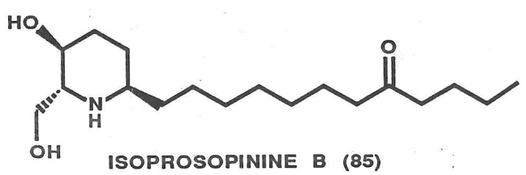
The n.m.r. spectra (Figure 13) of synthetic isoprosopinines A and B suggest that the conformation of the ring is as (272) (Figure 15), with two axial substituents (at C2 and C3) and not (273), with the ketone side chain at C6 axial. The H2-H3 coupling constant is 5.5Hz, consistent with an eq.-eq. coupling. In conformer (273) the expected value would be about 10Hz. This is the value obtained from the benzylidene acetal (88), used to confirm the *prosopis* alkaloid stereochemistry. In this compound all the ax.-eq. and eq.-eq. couplings are 5Hz. The coupling between H3 and the two protons at position 4 (4.2 and 6.5Hz) show that H3 must be equatorial. The smaller value (4.2Hz) is probably the $H3\text{-}H4_{ax}$ coupling, reduced due to the *trans* co-planar OH group. This preferred conformation (272) allows H-bonding between both oxygen atoms and the nitrogen. In the alternative (273) only one H-bond (O-O or O-N) is possible. The piperidine ring may be slightly puckered, or in dynamic equilibrium with small amounts of the other conformer (273).

The mass spectra of natural and synthetic isoprosopinines are very similar although the latter, run under slightly different conditions do not have an M^+. The ^{13}C n.m.r. spectra of the isoprosopinine A+B mixture has been obtained and assigned by comparison with the spectra of prosopione (83), deoxyprosopine (89) and several model hydroxy-piperidine compounds.[53] The data are presented in Table 7 with the data for the synthetic compounds. The fit is very good; most values being within 0.2ppm of the reported values. The only exceptions being the signals for C2 (and OCH_2 for "B"). These are carbons next to hetero-atoms capable of hydrogen bonding, which may affect the values. These very close correlation of spectra help confirm both the relative stereochemistries and the positions of the side chain ketones in the natural products. The spectra of the synthetic compounds are shown in Figure 16.

Figure 16

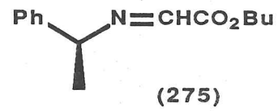


ISOPROSOPININE A (84)

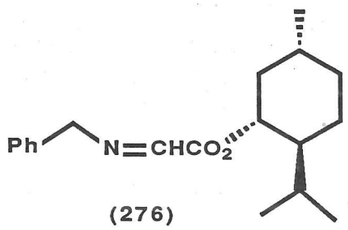


ISOPROSOPININE B (85)

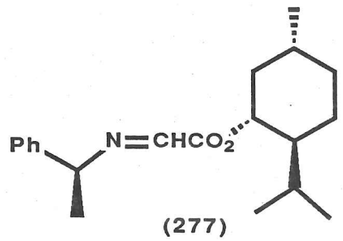
(274)



(275)

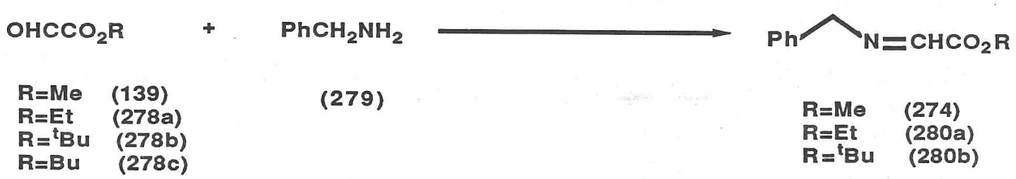


(276)



(277)

Scheme 69

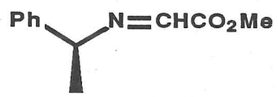


R=Me (139)
R=Et (278a)
R=^{t}Bu (278b)
R=Bu (278c)

(279)

R=Me (274)
R=Et (280a)
R=^{t}Bu (280b)

(281)



(282)

6. Diels-Alder Reaction of the N-Benzyl Imine

The problems associated with the NTs imine (140) led to the search for another imine that would be less likely to undergo an "aldol" type reaction; one that would be less reactive and so more amenable to Lewis acid catalysis and also adaptable to use in an asymmetric reaction. Removing the electron-withdrawing tosyl group from the nitrogen and replacing it with a simple alkyl or aryl group should fulfil all these criteria. The *N*-benzyl imine (274) should be a suitable compound as the nitrogen lone pair cannot be delocalised and so is available to co-ordinate to Lewis acids. The benzyl group can be readily removed and using either a chiral alcohol in the ester or a chiral amine opens up the possibility of asymmetric reactions. Similar imines (e.g. (275), (276) and (277)) have been used in asymmetric reactions,[146,147] the last one in a double asymmetric induction.[147]

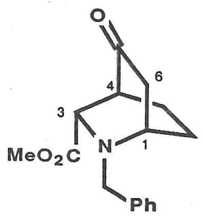
6.1 Imine Preparation.

Imines derived from simple amines can be prepared by mixing amine and aldehyde in the presence of a dehydrating agent such as $MgSO_4$ [148] or alumina.[149] Just has prepared, in quantitative yield, the imines (280a) and (280b) (Scheme 69) from ethyl (278a) or ^{t}butyl (278b) glyoxylates and benzylamine (279) in dry CH_2Cl_2 stirring for 17h over $MgSO_4$.[148] Yamamoto used a similar procedure to prepare the imine (275) from *S*-α-methylbenzylamine, this time with ether as solvent.[146] This imine is stable to racemisation for at least a week, but some racemisation does occur on distillation.

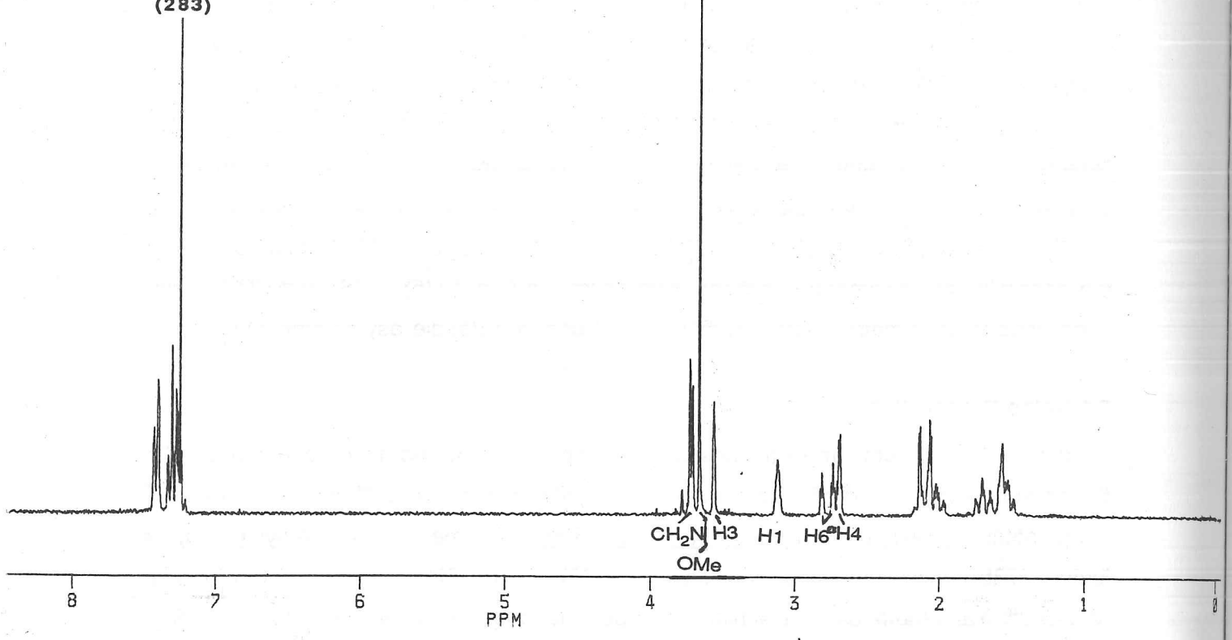
In contrast attempts to prepare imine (274) from methyl glyoxylate and benzylamine have not been very successful. Generally the purity of the imine was less than 30% when $MgSO_4$ was used as the drying agent. Sodium sulphate was no improvement. UG1 alumina was used as the drying agent[149] and this gave improved imine quality, but not reproducibly. The problem may lie in the mixing as this is very exothermic; but carrying out the mixing, or the entire reaction at 0°C or lower did not help. The order of addition of reagents and the reaction time (15 min to 2h) did not seem to make a great deal of difference. Several different batches of benzylamine have been used but none was any better than the rest.

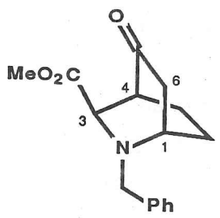
Methyl glyoxylate reacts with α-methylbenzylamine (281) under identical conditions ($MgSO_4$, 13h) to give imine (282) which is essentially 100% pure by n.m.r. The difference in reaction of methyl glyoxylate with α–methylbenzylamine (281) and benzylamine (279) is not readily explicable.

Figure 17



(283)





(284)

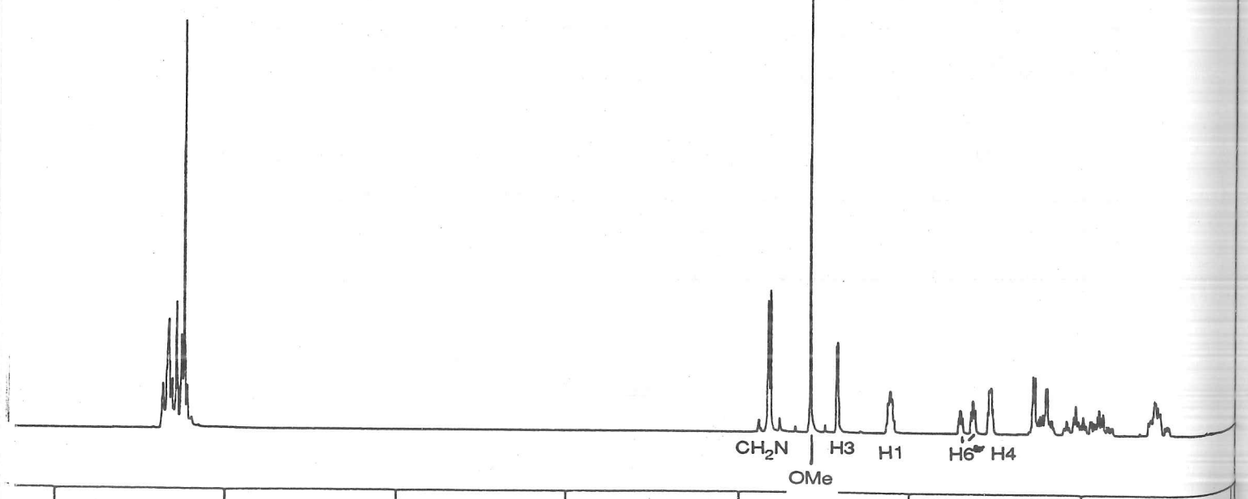
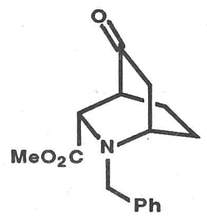


Figure 18



(283)

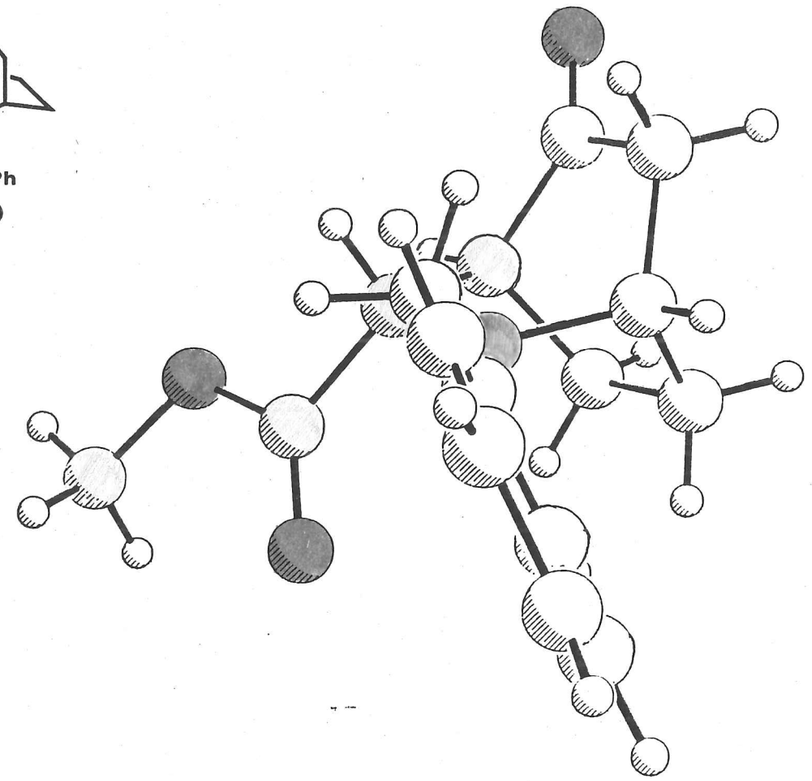
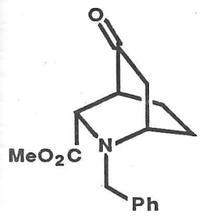
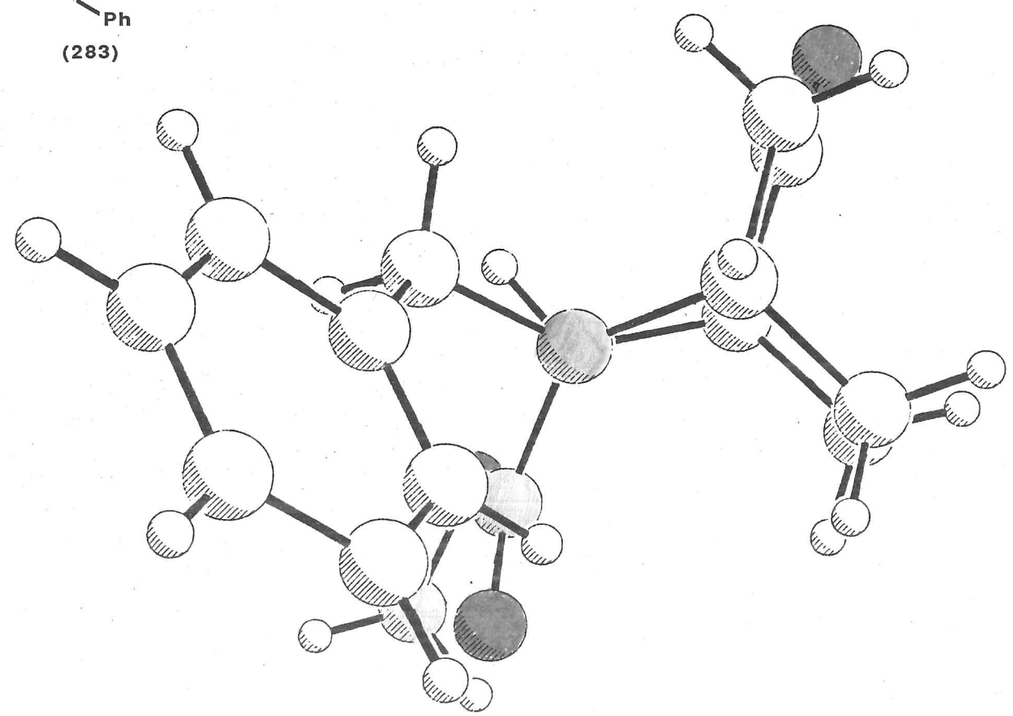


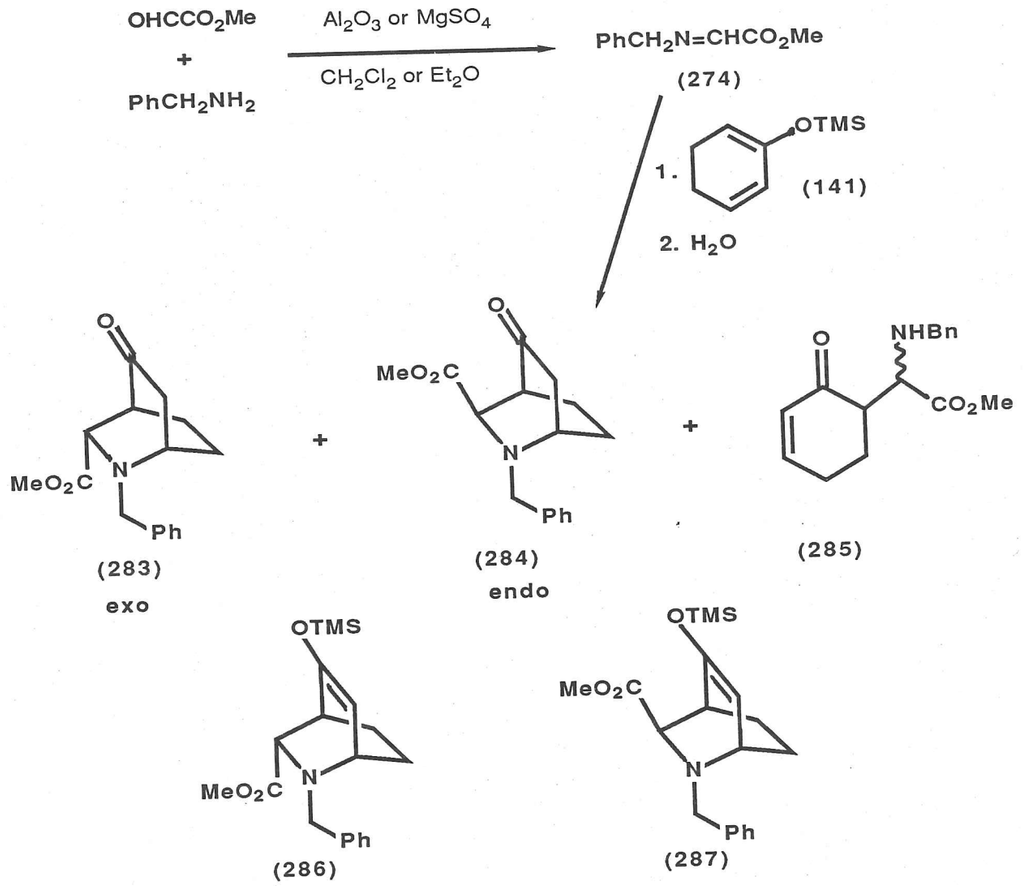
Figure 19



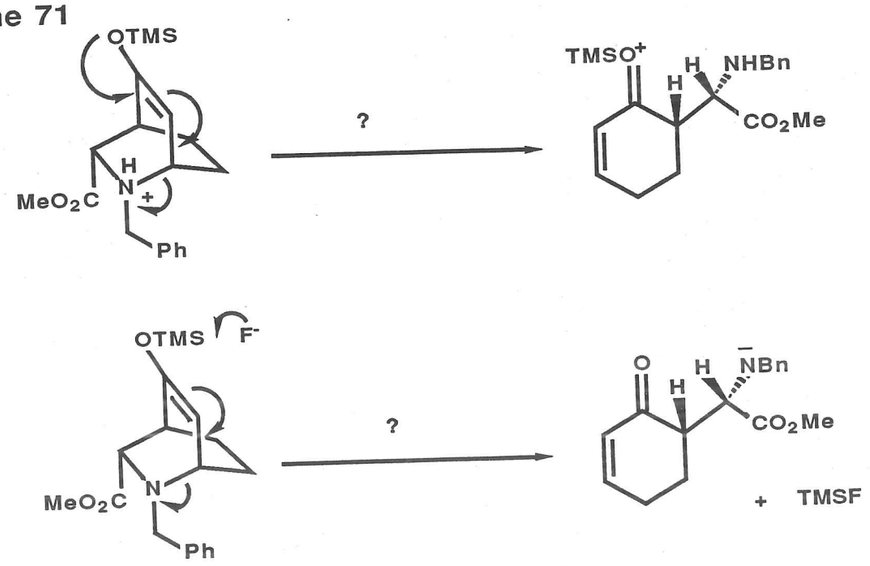
(283)



Scheme 70



Scheme 71



6.2 Diels-Alder Reaction.

The difficulty in obtaining pure imine (274) has hampered the investigation of the Diels–Alder reaction with the silyloxydiene (141). Reactions have been performed on imine of 50-70% purity. Treatment of the imine (274) (ca. 50% pure) in CH_2Cl_2 with aluminium trichloride (0.1eq.) and then the diene (141) for 2h gave, after aqueous work up, and extensive flash chromatography, two compounds in 9% and 10% yields (Scheme 70). These were assigned the structures (283) (*exo*) and (284) (*endo*) respectively on the basis of proton n.m.r. spectra (Figure 17). (*Exo* and *endo* refer to the stereochemistry of the ester group.) H-3 in the *endo* compound is a doublet due to coupling to H4. The same signal in the *exo* compound is an unresolved double doublet due to W-coupling to H8*anti*.

When $BF_3.OEt_2$ (0.3eq.) was used as the catalyst in CH_2Cl_2 yields of the *exo* (283) and *endo* (284) compounds were 6.5% and 11% respectively with a 3% yield of impure aldol material. Tin (IV) chloride (0.3eq.) with the same batch of imine gave yields of 8% and 11%. The best yield so far was obtained with 1eq. of zinc chloride in CH_2Cl_2 for 4h, which gave 13% and 21% of *exo* and *endo* compounds with 15% of a mixture that contained aldol products (285) and other material. Zinc chloride in THF gave slightly lower yields (12% and 17%), while $TiCl_2(OiPr)_2$ (1eq.) in CH_2Cl_2 gave none of the required bicyclic compounds. When no Lewis acid catalyst was used no identifiable products were isolated. These conditions have by no means been optimised.

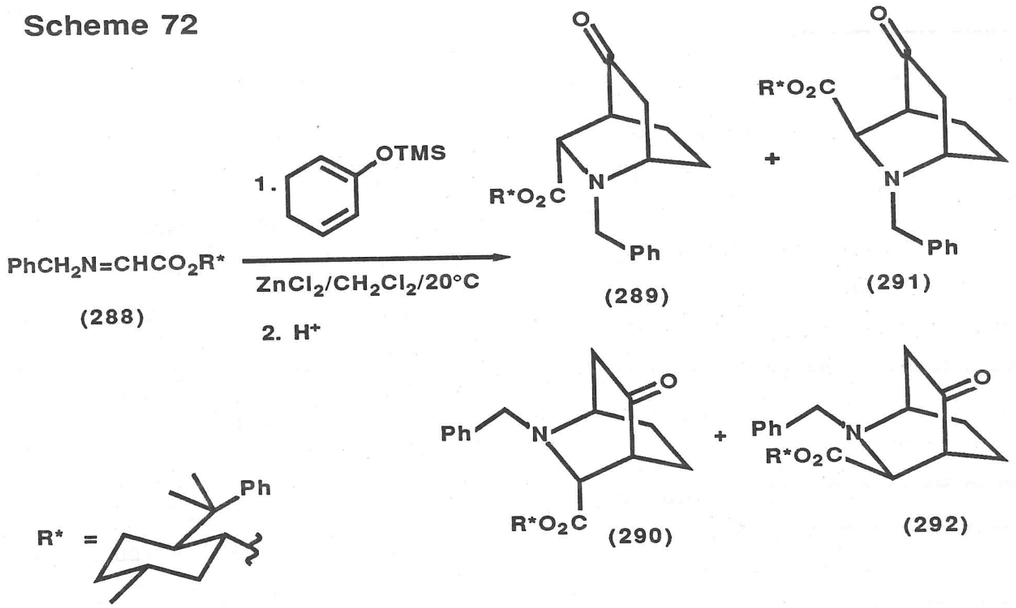
Work up conditions have not been optimised either. The intermediate silyl enol ethers (286) and (287) are much more likely to protonate on nitrogen than their *N*-tosyl counterparts, which would then facilitate an acid-catalysed retro-Michael reaction (Scheme 71). Conversely base (fluoride) catalysed work up ought to be less likely to cause elimination as the nitrogen is not attached to an electron-withdrawing group which could stabilise negative charge building up on it in an elimination.

Both the *exo* (283) and *endo* (284) products are crystalline and the X-ray crystal structure of the *exo* adduct has been obtained (Figure 18).* A Newman projection along the N-C3 bond of the same structure is shown in Figure 19. It can be seen that the benzyl group is *endo* (*trans* to the ester) as expected on steric grounds and that the nitrogen is tetrahedral (the lone pair occupying the fourth vertex).

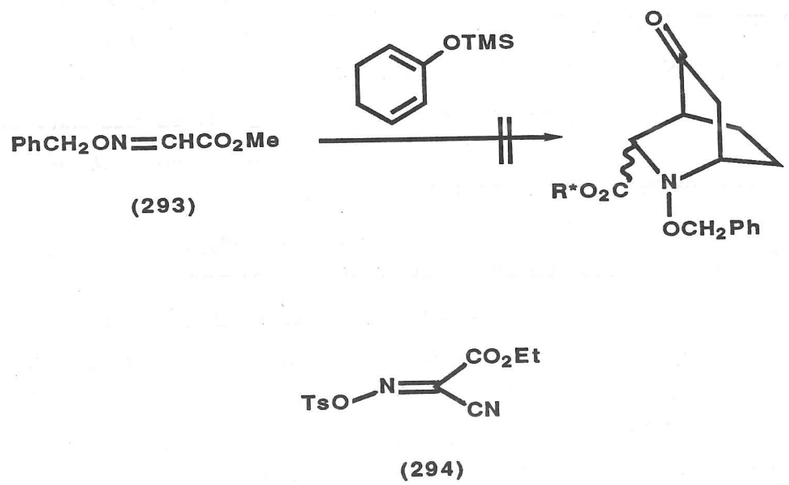
Further work needs to be done on this reaction in order to optimise the yields, determine the effect of Lewis acid, solvent and temperature and to see if aldol product formation is a problem.

*I would like to thany Alethea Tabor for performing the X-ray structure determination on compound (283).

Scheme 72



Scheme 73



6.3 Chiral Reaction.

The 8–phenylmenthyl derived imine (288) was prepared in a similar fashion to the methyl ester imine by stirring 8–phenylmenthyl glyoxylate (136) and benzylamine in CH_2Cl_2 over UG1 alumina for 50min. Estimation of the purity of the imine was difficult as the imine CH signal occurs at δ6.9 (upfield of the aromatic signals!) and is not fully resolve, but it was better than 50%. This imine was used in two imino–Diels–Alder reactions; one with BF_3OEt_2 catalysis which gave a 20% yield of four products and a second zinc chloride (1.0eq.) catalysed one (20°C, 24h) which after mild acid work up and extensive column and preparative plate chromatographies gave a 47% yield of a mixture of the same four isomeric compounds (Scheme 72). The NCH_2 signals of the four isomers are distinctive and it is on the basis of these ratios in the four mixed fractions isolated that the product ratios were calculated. The ratio is 8:63:19:10 in no particular order. The second isomer (X) is a crystalline solid, which appears to be an *exo* adduct by n.m.r. (the H3 signal is a multiplet with very small couplings) but a de-coupling experiment did not give an unambiguous answer. The third isomer (second most abundant) appears to be an *endo* compound as the H3 signal is a doublet (no W-coupling).

On the basis of this it appears that a considerable degree of chiral induction (of the order of 70% for the *exo* adducts) has been achieved, although further work needs to be done to ascertain the identities of the four isomers, and to see if different conditions can improve the extent of chiral induction; especially in the light of the *caveat* of Chapter 3.

6.4 An Oxime Dienophile.

The oxime (293), which is readily prepared from methyl glyoxylate (140) and *O*-benzylhydroxylamine hydrochloride,[150] was treated with the silyloxydiene (141) in an attempt to get it to undergo an imino–Diels–Alder reaction (Scheme 73). No reaction occurred under the following conditions:-

(1) CH_2Cl_2 20°C nocatalyst.

(2) CH_2Cl_2 20°C 0.1eq. $AlCl_3$, 2 days.

(3) MeCN, ZnI_2, 20°C 2 days then reflux for 16h.

Starting material was recovered in each case. The result is not too surprising as oximes are not normally reactive dienophiles,[36] although examples are known involving the use of *ortho*-quinone methides,[151] very high temperatures[152] or a triply-activated oxime (294).[153]

Scheme 74

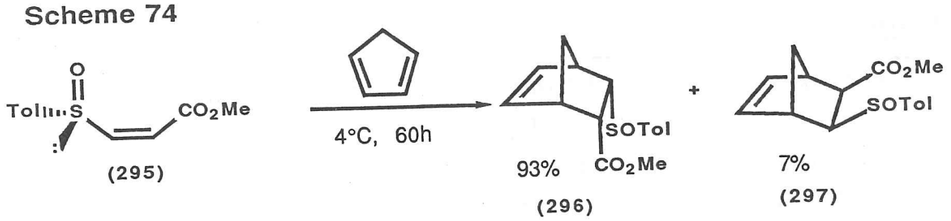
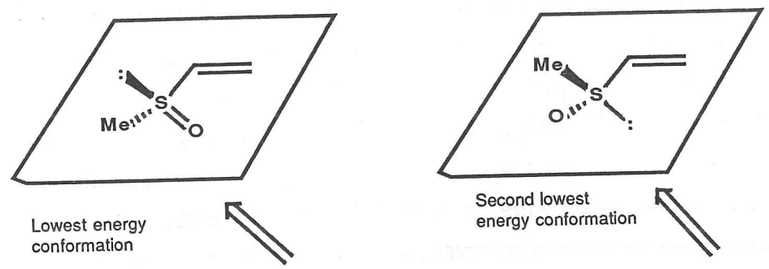
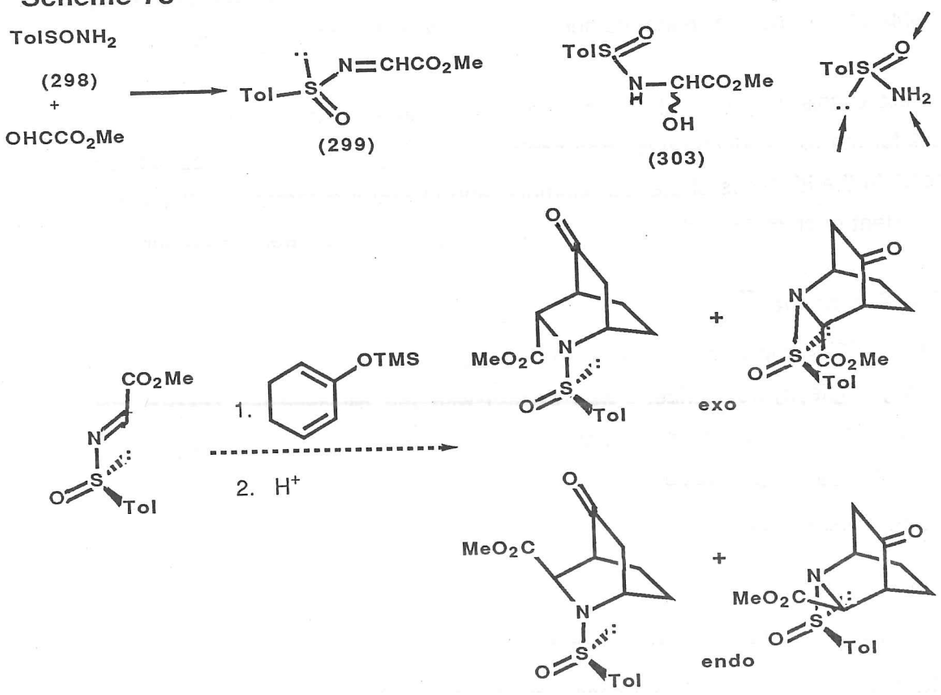


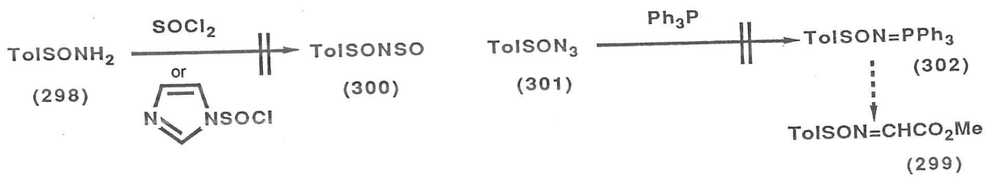
Figure 20



Scheme 75



Scheme 76



7. Toluenesulphinamide-Derived Imines.

Chiral sulphoxides have been shown to be powerful diastereofacial directing groups in Michael reactions,[154] [2+2] cycloadditions[155] and especially in Diels–Alder reactions.[156] Maignan has reacted the enantiomerically pure vinylic sulphoxide (295) with cyclopentadiene and obtained only one diasteriomer of the *endo* (296) and *exo* (297) adducts, as determined by n.m.r. and h.p.l.c. (Scheme 74). Calculations have been performed on this type of system which show that one face of the olefin is more reactive towards nucleophiles[157] and electron-rich dienes (Figure 20).[158]

Attaching a chiral sulphoxide to the nitrogen of the imine (i.e. the sulphinamide) should affect the C=N double bond in the same way as a C=C double bond, making one face more reactive than the other, hence using the chirality at sulphur to induce chirality in the newly formed bicyclic system.

The required imine is compound (299) formally derived from tolunesulphinamide and methylglyoxylate (Scheme 75). The poorer electron–withdrawing ability of sulphinyl compared to sulphonyl should make this a less reactive imine than (140) and also less likely to undergo an "aldol" reaction. For trial reactions to prove the method it is not necessary to use optically pure sulphinamide as it is the *relative* stereochemistry of sulphur and the ring that are of interest initially. When the sense of chiral induction from S to N=C is known then the correct enantiomer of the sulphinamide can be used. Optically active sulphinamides have been prepared; generally by reaction of a halomagnesium amide with an optically active sulphinate ester,[159] a reaction that occurs with inversion at sulphur.[160]

Toluenesulphinamide (298) was prepared from sodium toluenesulphinate by a modified literature procedure.[161] Attempts to prepare the *N*-sulphinyl compound (300) (Scheme 76) by the usual method failed. Treatment of the sulphinate with thionyl chloride gave the rapid evolution of a greenish-yellow gas. The brown residue could be distilled but was a mixture of compounds. The chlorosulphinyl imidazole reagent (150) gave a similar mixture of products when added to the sulphinamide. It is not possible to prepare the ylid (302), required for an aza-Wittig synthesis[162] of the imine (299), by the conventional method, as treatment of the azide (301) with triphenylphosphine gives a disulphide, and triphenylphosphine oxide.[163]

Direct condensation of methylgloxylate and toluenesulphinamide in the presence of alumina[149] was tried under a variety of conditions, with limited success (Scheme 75). Stirring a solution of the two reagents with alumina for 15-20h gave, by n.m.r. a mixture

containing 15-20% of an imine (signal at δ8.05). Addition of a Lewis acid ($BF_3.OEt_2$ or $AlCl_3$) or refluxing the solution for shorter or longer time gave very little improvement. Other conditions tried include:-

(a) Lewis acid alone.

(b) Montmorrilonite K10.

(c) 3A molecular sieves.

(d) Magnesium sulphate.

(e) Toluenesulphinamide pre-absorbed on alumina at 20°C, or 80°C.

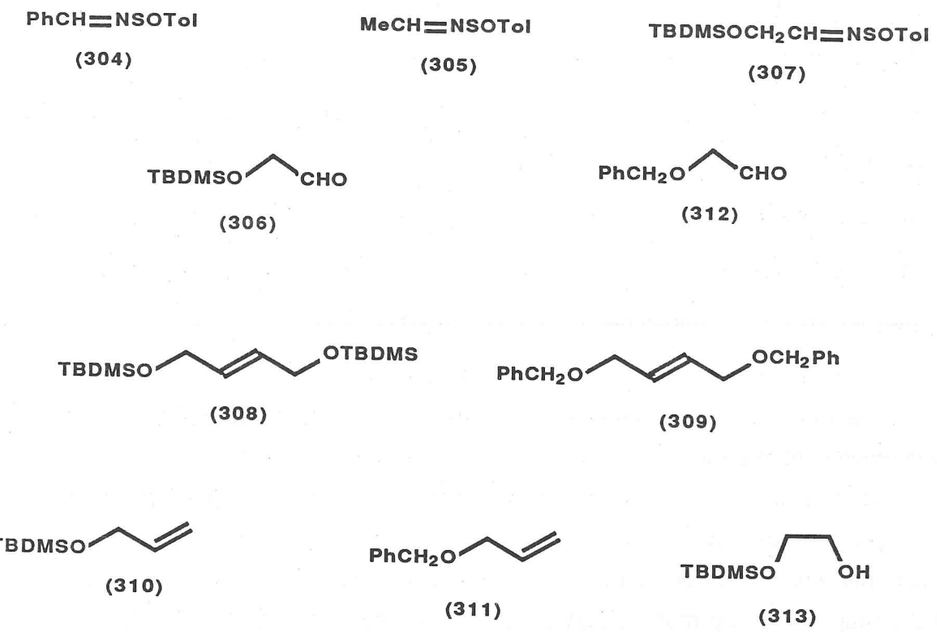
The purity of imine formed was 0-35%, the best conditions being sulphinamide on alumina, 0.5h reflux in benzene. Further stirring of this mixture for 2 days at 20°C did not give any improvement in purity.

It was noticed, that in the n.m.r. spectra of several crude imine preparations there were four equally spaced singlets at δ5.2 and four more broadened singlets at δ6.1. It was thought that these might be due to the two diastereomers of the hemi-aminol (303), with NH-CH coupling. Mixing methylglyoxylate and toluenesulphinamide in $CDCl_3$ for 0.5h gave, by n.m.r. a mixture containing 12% imine, more than ten OMe signals and the signals at δ5.2 and 6.1. A decoupling experiment showed that there was no coupling between the two sets of signals. Mixing the two reagents was carried out in the presence of acetic anhydride, to acylate any hydroxyl groups formed. Addition of a base (triethylamine or DBU) gave rapid decomposition of any imine formed. Disodium hydrogen phosphate could be added to remove acetate formed, but the purity of imine initially formed did not improve and the only change was slow hydrolysis of the acetic anhydride. The initial reaction (in the presence or absence of anhydride) is rapid; very little glyoxylate remains after 10min, and none after 30min, when the n.m.r. spectrum shows the presence of imine and the signals at δ5.2 and 6.1.

Those reactions suggest that, although imine formation is quite rapid and proceeds without a dehydrating agent it is in competition with other pathways. The sulphinamide (298) is potentially tridentate, i.e. it can attack an electrophile with N (as required), O, or S lone pair. The reactivity of glyoxylate makes it likely that the reaction is under kinetic control, i.e. it is not reversible.

Benzaldehyde reacts with the sulphinamide, in the presence of UGI alumina, to give the imine (304), cleanly by n.m.r. after 7 days. A suspension of sulphinamide and alumina in acetaldehyde gives imine (305) of 75% purity after just 24h. The imine (306) can be similarly prepared, in impure form from the impure aldehyde (307). When the

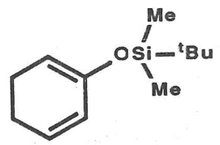
Scheme 77



benzaldehyde-derived imine (304) is heated with siloxyliene (141) in an n.m.r. tube for 18h at 20°C, no reaction occurs. No reaction occurrs when $BF_3.OEt_2$ (0.25eq) is added, with heating at 50°C for 24h. This is not surprising as the corresponding sulphonamide-derived imine is also inert and it is expected that the sulphinamide imine (304) will be less reactive. These reactions show that sulphinamide-derived imines can be prepared by direct condensation of the aldehyde and amide. It appears that the glyoxylate is the problem; its high reactivity may mean that the reaction may need to be carried out at low temperatures.

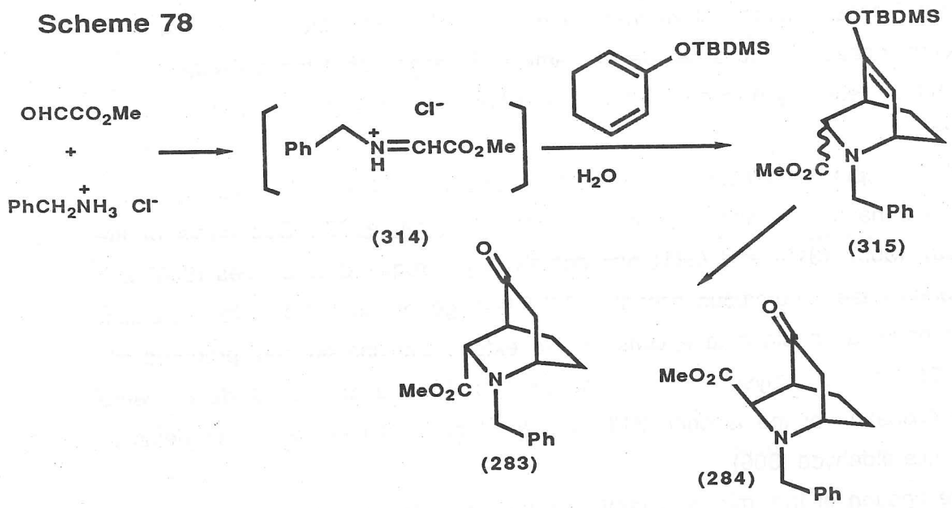
Several attempts to prepare a suitable α–alkoxy aldehyde, for use in these condensations, have met with only limited success (Scheme 77). Ozonolysis of the olefins (308), (309), (310) and (311) has not given the required aldehydes (306) and (312). In each case "anomalous ozonolysis"[164] (cleavage of the bond α to the olefin) appears to have taken place to a considerable extent. Danishefsky has prepared the aldehyde (312) by ozonolysis of the olefin (311) but no experimental details were reported.[165] Oxidation of the alcohol (313) with PCC or PDC gave only low yields of impure, volatile aldehyde (306).

The investigation of the imine's potential as a dienophile has been thwarted by the difficulty in preparing it. The possibility of chiral induction justify further investigation into the preparation of this imine (299), or another suitable imine, such as compound (307).



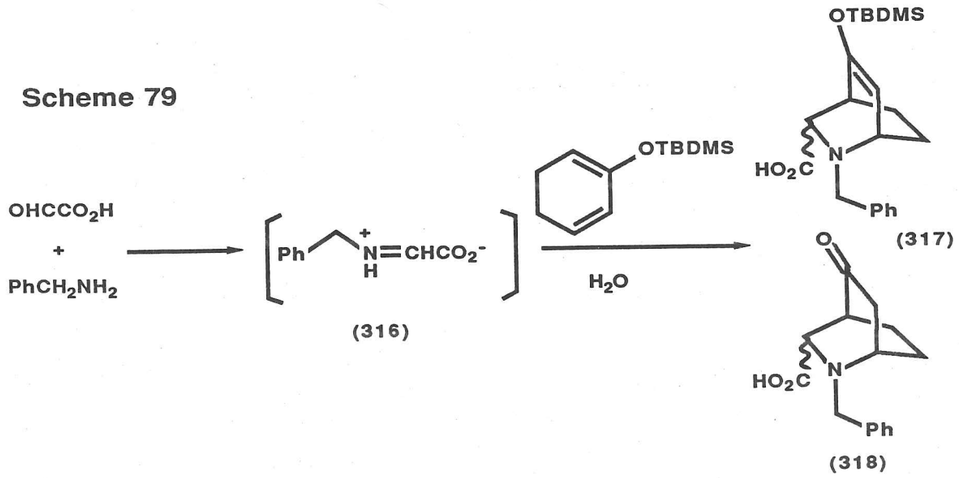
(159)

Scheme 78



(314) (315) (283) (284)

Scheme 79



(316) (317) (318)

8. Aqueous Diels-Alder Reactions.

Grieco has shown that iminium ions, generated *in situ* from aldehydes and amine salts undergo [4+2] cycloadditions with reactive dienes (see Chapter 1, Section 2; Scheme 24).[48] It was hoped that the silyloxydiene (159) would react with these iminium ions to give the required azabicyclo[2.2.2]octanes.

The TBDMS diene (159) in THF was added to a rapidly stirred solution of methyl glyoxylate and benzylamine hydrochloride in water (Scheme 78). The reaction was worked up after 24h by basification and extraction but t.l.c. analysis showed a multi-spot mixture. A repeat reaction under slightly different conditions gave a similar result. The materials isolated from these reactions were stored for several weeks. Comparison of these mixtures by t.l.c. with the *exo* (283) and *endo* (284) *N*-benzyl compounds (which had by then been synthesised by a different route, see Chapter 6) showed that these were present in the mixtures. Isolation of the two adducts from the combined mixtures gave a 1% yield of the *exo* (283) and 2.8% yield of the *endo* (284) compounds. It seems that the required aqueous imino–Diels–Alder reaction is taking place, but in competition with side reactions. The silyloxydiene (159) had only partly decomposed during the 24h reaction time so it is likely that the initially isolated product was the silyl enol ether (315) which was then slowly hydrolysed.

Grieco has used a zwitterionic iminium ion (316), prepared from glyoxylic acid and a free amine, in an aqueous Diels–Alder (Scheme 79). It was thought that better results might be obtained using this approach. Mixing benzylamine, glyoxylic acid and the diene (159) in water, with or without acetonitrile as co-solvent, gave, within an hour, a large quantity of a precipitate. The reaction was vigorously stirred for 24h. This precipitate was insoluble in acid, base and most organic solvents. T.l.c. analysis showed that it was a mixture of several very polar compounds, none of which could be identified by n.m.r. The extracts from the basified aqueous reaction mixture consisted mainly of silyl residues, but on chromatography one fraction was isolated (<5%) that was a mixture by n.m.r., but which probably contained the required acids (317) and (318). A rapid side reaction, giving the insoluble material, must be occurring. As Grieco experienced no problems using glyoxylic acid, the silyloxydiene is probably the cause.

9. Experimental

Proton n.m.r. spectra were recorded at ambient temperature using Varian EM390A (90MHz), Bruker WP80 (80MHz) or Bruker WH250 (250MHz) instruments. Carbon-13 spectra were recorded at 63MHz on the Bruker WH250 instrument. Chemical shift data are presented in units of δ relative to tetramethylsilane (TMS) where $\delta_{TMS}=0$, using either TMS or the solvent as internal reference.

Low resolution mass spectra were recorded on either MS902 or MS30 instruments. High resolution spectra were recorded on the MS30 in conjunction with a DS50S data system.

I.r. spectra were recorded on Perkin-Elmer 297, 983 or 1310 spectrophotometers, calibrated relative to polystyrene using either chloroform solution cell or neat oils between sodium chloride plates.

Melting points were determined on a Buchi 510 melting-point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589nm (Na).

Preparative t.l.c. was carried out on plates coated with Merck PF_{254} silica. Flash chromatography[95] was performed on Woelm 32-63 or Merck 9385 silica; column diameter and eluant as stated.

Microanalyses were performed in the University Chemical Laboratory by Mr. D. Flory and his staff.

Ether refers to diethylether.

Petrol refers to the petroleum ether fraction boiling between 40 and 60°C.

THF refers to tetrahydrofuran which was distilled from potassium in a recycling still.

Benzene was distilled from calcium chloride and stored over 4Å molecular sieves.

Dichloromethane was dried by passing it down a column of activated alumina and then storing it over 4Å molecular sieves.

DMF refers to dimethylformamide, dried over 4Å molecular sieves.

N-Sulphinyl-*p*-toluenesulphonamide (139)

p-Toluenesulphonamide (19.2g, 110mmol) and thionyl chloride (35ml) were heated under reflux for 8.5h. The excess of thionyl chloride was removed under reduced pressure (water-pump then oil-pump) and the residue was distilled under reduced pressure to give a pale yellow oil which solidified on cooling to give the title compound (139) as a pale yellow solid (15.1g, 62%) b.p. 102-6°C, $6x10^{-4}$mm Hg.

^1H δ ($CDCl_3$; 90MHz): 7.95 and 6.85 (4H,AB,aromatic) 2.58 and 2.03 (trace *ortho* isomer) 1.95 (3H,s,CH_3).

The compound was dissolved in either THF or benzene to give a solution of known concentration which was stored at 4°C and used as required.

2-Trimethylsilyloxycyclohexa-1,3-diene (141)

Butyl lithium (48ml, 1.6M in hexane, 71.4mmol) was added to a solution of diisopropylamine (10ml, 71.4mmol) in dry tetrahydrofuran (50ml) at -10°C under nitrogen and the pale yellow solution was stirred for 10 minutes and then cooled to -15°C. Cyclohexenone (6.3ml, 64.9mmol) was added over 20 min and the resultant solution was stirred at -15 to -20°C for a further 20 min. Trimethylsilyl chloride (13ml, 102mmol) was added rapidly and the mixture was allowed to warm to 20°C over 2h. Pentane (200ml) was added and the mixture was poured into ice-cold 8% sodium bicarbonate solution (60ml) and the organic layer separated. The aqueous was extracted with ether (50ml) and the combined organic layers were dried ($MgSO_4$) and evaporated to give a pale yellow oil (12.2g). Distillation at reduced pressure (oil pump and Cartesian manustat) gave the silyloxydiene (141) (7.82g, 71%), b.p. 44-5°C, 6mm Hg (lit. 56-8°C, 6mm Hg[84]).

^1H δ ($CDCl_3$; 90MHz): 5.70 (2H,m), 4.85 (1H,m), 2.10 (4H,m), 0.13 (9H,s).

$\nu_{max.}$($CHCl_3$): 2860(s), 2810(s), 1640(s), 1600(s) cm^{-1}.

Methyl 2-*p*-toluene-2-*p*-toluenesulphonamidoacetate(144)

N-Sulphinyl-*p*-toluenesulphonamide (139) (410mg, 1.88mmol) and boron trifluoride etherate (0.05ml, 0.2eq.) were added to a solution of methyl glyoxylate (166mg, 1.58mmol) in dry toluene (5ml) and the resultant pale yellow solution was heated at 80°C for 16h under a stream of dry nitrogen. Proton n.m.r. of the mixture showed the absence of both aldehyde and imine signals. 8% Sodium bicarbonate solution (5ml) was added and the mixture was extracted with dichloromethane (3x10ml). The organic extracts were washed with brine, combined, dried ($MgSO_4$), and evaporated to give a white solid

(750mg). Purification by flash chromatography (20mm column, petrol-ether (4:3) as eluant) gave a white solid (470mg, 75%) and impure fractions (179mg). Crystallisation from hexane-methyl acetate gave the title compound (144) as white crystals (283mg, 45%), m.p. 122-3°C.

^{1}H δ ($CDCl_3$; 90MHz): 7.4 (4H, AB, aromatic), 7.13 (4H, s, aromatic), 5.59 (1H, d; *J*=8.1Hz, NH), 5.00 (1H, d;*J*=8.1Hz, CH), 3.56 (3H, s, OCH_3), 2.38 (3H, s, Ar-CH_3), 2.29 (3H, s, Ar-CH_3).

$\nu_{max.}$($CHCl_3$): 3650, 3600 (NH stretch), 2950 (CH stretch), 1740 (C=O), 1600 (aromatic), 1330 (SO_2).

m/z 274 (100%, M-CO_2Me), 155 (32%, Me-Ar-SO_2).

Analysis. Found: C,61.5; H,5.7; N,4.1; S,9.5.

$C_{17}H_{19}NO_4S$ requires C,61.2; H,5.7; N,4.2; S,9.6%.

Methyl 2-(3,4-dimethylphenyl)-2-*p*-toluenesulphonamidoacetate (146)

N-Sulphinyl-*p*-toluenesulphonamide (139) (396mg, 1.82mmol) and boron trifluoride etherate (0.03ml, 0.1eq) were added to a solution of methyl glyoxylate (159mg, 1.80mmol) and *ortho*-xylene (0.4ml, 3.4mmol) in dry benzene (2ml) and the mixture was heated under reflux for 6h under a stream of nitrogen. 8% Sodium bicarbonate solution (5ml) was added and the mixture was extracted with dichloromethane (3x10ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography (silica, 20mm column, petrol-ether (1:1) as eluant) gave a white solid (390mg, 62%). Crystallisation from hexane-methyl acetate gave the title compound (146) as off-white crystals (230mg, 37%), m.p. 95-6°C.

^{1}H δ ($CDCl_3$; 250MHz): 7.60 and 7.18 (4H, AB, aromatic), 7.01 and 6.93 (2H, AB, aromatic), 6.91 (1H, s, aromatic), 5.56 (1H, d;*J*=8.0Hz, NH), 4.97 (1H, d; *J*=8.0Hz, CH), 3.55 (3H, s, OCH_3), 2.38 (3H, s, $ArCH_3$), 2.19 (3H, s, $ArCH_3$), 2.14 (3H, s, $ArCH_3$).

$\nu_{max.}$ ($CHCl_3$): 3360(NH stretch), 1745(C=O), 1600(aromatic), 1340(SO_2N).

m/z 288(100%, M-CO_2Me), 155(40%, $MeArSO_2$).

Analysis. Found: C,61.9; H,6.1; N,4.0; S,9.5;

$C_{18}H_{21}NO_4S$ requires C,62.2; H,6.1; N4.0; S,9.2%.

Methyl p-[2-(2-methylpropyl)]phenyl-2-p-toluenesulphonamidoacetate (147)

N-Sulphinyl-p-toluenesulphonamide (139) (381mg, 1.75mmol) and boron trifluoride etherate (0.03ml, 0.1eq.) were added to a solution of methyl glyoxylate (153mg, 1.74mmol) and *tert*-butylbenzene (0.4ml, 2.58mmol) in dry benzene (5ml) and the mixture was heated under reflux for 2 days. 8% Sodium bicarbonate solution (5ml) was added and the mixture was extracted with dichloromethane (3x10ml). The organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated to give an orange solid. Purification by flash chromatography (silica, 20mm column, petrol-ether (1:1) as eluant) gave a colourless oil (135mg, 21%) and impure fractions (97mg). Crystallisation from hexane-methyl acetate gave the title compound (147) as white crystals (58mg, 9%), m.p. 111-2°C.

^1H δ ($CDCl_3$; 250MHz): 7.58 and 7.15 (4H,AB, aromatic), 7.21 and 7.09 (4H,AB, aromatic), 5.63 (1H, d;*J*=7.9Hz, NH), 5.05 (1H, d;*J*=7.9Hz, CH), 3.57 (3H, s, OCH_3), 2.36 (3H, s, Ar-CH), 1.26 (9H, s, tBu).

$\nu_{max.}$($CHCl_3$): 3370(NH stretch), 2900(CH stretch), 1745(C=O), 1600(aromatic), 1340(SO_2N).

m/z 316(36%, M-CO_2Me), 155(19%, $MeArSO_2$), 91(100%, MeC_6H_4).

Analysis. Found: C,63.8; H,6.8; N3.8; S,8.4;

$C_{20}H_{25}NO_4S$ requires C,64.0; H,6.7; N,3.7; S,8.5%.

Methyl (*exo*)-5-oxo-2-*p*-toluenesulphonyl-2-azabicyclo[2.2.2]octanyl-3-carboxylate (142) *Exo*

Methyl (*endo*)-5-oxo-2-*p*-toluenesulphonyl-2-azabicyclo[2.2.2]octanyl-3-carboxylate (143)*Endo*

R*,S*-Methyl 2-(cyclohexa-3-en-2-one)-2-(*p*-toluenesulphonamido)ethanoate (156) (Aldol I)

R*,R*-Methyl 2-(cyclohexa-3-en-2-one)-2-(*p*-toluenesulphonamido)ethanoate (157) (Aldol II)

Non-Catalysed Imine Formation and Diels-Alder Reaction.

A solution of *N*-sulphinyl-*p*-toluenesulphonamide (139) in benzene (1.5ml, 2.1M, 3.2mmol) was added to methyl glyoxylate (140) (267mg, 3.0mmol) and the solution was heated under reflux for 14h. A small sample of this cloudy solution was evaporated for n.m.r. analysis which showed the absence of aldehydic protons and the presence of a new imine signal (δ8.1).

A solution of the silyloxydiene (141) (0.98g) in benzene (1ml) was added rapidly at 20°C (the reaction mixture got hot) and the resultant solution was stirred at 20°C for 5h. A 4:1 THF:0.005M HCl solution was added and the mixture was stirred for 1h. Aqueous sodium bicarbonate was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 15ml) and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography (30mm, dichloromethane-ethyl acetate) and then (20mm, hexane-ether (2:5)) gave four fractions:-

FR1 White solid 371mg (36.3%). *Exo.*

FR2 White solid 140mg (13.7%). *Endo.*

FR3 White solid 150mg (14.7%). $Aldol_I$.

FR4 White solid 50mg (4.9%). $Aldol_{II}$.

Exo Compound

^1H δ ($CDCl_3$; 250MHz): 7.85 and 7.30 (4H, AB, Ar), 4.64 (1H, d;*J*=2.0Hz, H3), 4.04 (1H, m, H1), 3.81 (3H, s, OMe), 2.81 (1H, m, H4), 2.50 (2H, m, H6), 2.43 (1H, s, MeAr), 2.2-1.5 (4H, m).

^{13}C δ ($CDCl_3$; 63MHz): 208.3, 170.0, 144.2, 136.5, 129.8, 127.8, 56.8, 52.7, 49.8, 46.2, 43.7, 25.8, 21.5, 17.4.

Endo Compound

^1H δ ($CDCl_3$; 250MHz): 7.84 and 7.31 (4H, AB, Ar), 4.48 (1H, d;*J*=2.3Hz, H3), 4.15 (1H, m, H1), 3.72 (3H, s, OMe), 2.81 (1H, m, H4), 2.71 (1H, m, H6), 2.44 (3H, s, MeAr), 2.27 (1H, dd;*J*=12.6, 2.5Hz, H6), 2.2-1.2 (4H, m).

^{13}C δ ($CDCl_3$; 63MHz): 208.3, 170.6, 144.1, 136.1, 129.7, 127.6, 59.8, 52.6, 49.5, 46.7, 45.9, 24.0, 21.5, 21.3.

FR3 was crystallised from hexane-dichloromethane to give pure cyclohexenone (156) (Aldol I) as white crystals (215mg), m.p. 132-3°C.

^1H δ ($CDCl_3$; 250MHz): 7.72 and 7.28 (4H, AB, Ar), 7.00 (1H, m, H4), 5.97 (1H, dt, *J*=10.1,2.0Hz, H3), 5.33 (1H, d, *J*=9.2Hz, NH), 3.94 (1H, dd, *J*=9.2,2.8Hz, H2'), 3.47 (3H, s, OCH_3), 3.23 (1H, ddd, *J*=13.5,5.2,2.8Hz, H1), 2.49 (2H, m, CH_2), 2.41 (3H, s, CH_3), 2.22 (2H, m, CH_2).

^{13}C δ ($CDCl_3$; 63MHz): 198.4, 170.4, 151.3, 143.4, 136.9, 129.4, 129.2, 127.2, 56.4, 52.5, 50.2, 26.1, 25.8, 21.4.

$\nu_{max.}$($CHCl_3$): 3350(NH stretch), 2940(m,CH stretch), 1740, 1735(s,ester C=O), 1675(s,enone C=O), 1590(m,Ar), 1350(s), 1170(s) cm^{-1}.

m/z No M^+. 278(62%, M-CO_2Me), 182(60%, M-Ts), 91(100%).

Analysis. Found: C,57.1; H,6.0; N,4.3; S,9.5;

$C_{16}H_{19}NO_5S$ requires C,57.0; H,5.7; N,4.2; S,9.5%.

FR4 was crystallised from hexane-dichloromethane to give pure cyclohexenone (157) (Aldol II) as fine white crystals m.p. 95-6°C.

^1H δ ($CDCl_3$; 250MHz): 7.73 and 7.28 (4H, AB, Ar), 6.98 (1H, m, H4), 5.98 (1H, dt;*J*=9.7, 1.9Hz, H3), 5.58 (1H, d;*J*=9.3Hz, NH), 4.17 (1H, dd;*J*=9.4, 4.4Hz, H2'), 3.45 (3H, s, OMe), 2.79 (1H, ddd;*J*=12.4, 5.0, 4.4Hz, H1), 2.45 (2H, m, CH_2), 2.41 (3H, s, MeAr), 2.17 (2H, m, CH_2).

^{13}C δ ($CDCl_3$; 63MHz): 197.4, 170.7, 150.6, 143.4, 137.1, 129.4, 129.2, 127.2, 55.7, 52.2, 50.7, 25.6, 25.5, 21.4.

$\nu_{max.}$ ($CHCl_3$): 3350 (NH stretch), 2900(CH stretch), 1735(s, ester C=O), 1675(s, enone C=O), 1595(w, Ar), 1330(s), 1150(s) cm^{-1}.

m/z No M^+. 278(70%, M-CO_2Me), 182(50%, M-Ts), 91(100%).

Analysis. Found: C,57.1; H,5.7; N,4.2; S,9.7;

$C_{16}H_{19}NO_5S$ requires C,57.0; H,5.7; N,4.2; S,9.5%.

Total yield = 69.5%.

Catalysed Imine Formation With Distillation of the Imine

A solution of *N*-sulphinyl-*p*-toluenesulphonamide (139) in THF (2.0ml, 2.75M, 5.5mmol) and then boron trifluoride etherate (0.08ml) were added to methyl glyoxylate (492mg, 5.58ml) and the solution was heated under reflux for 70min. The solvent was removed *in vacuo* and the pale yellow solid was distilled (kugelrohr and mercury diffusion pump) (125-135°C/10^{-3}mmHg) to give the imine (142) as a pale yellow gum (1.05g, 79%) which solidified on cooling to give an off-white amorphous solid.

^1H δ ($CDCl_3$; 90MHz): 8.1(1H, s, CH=N), 8.7 and 7.2(4H, AB, Ar), 3.7(3H, s, OMe), 2.3(3H, s, MeAr).

The imine was dissolved in dichloromethane (6ml) and divided into four portions each of 1.09mmol in 1.5ml.

One of these portions was cooled to 4°C under nitrogen and a solution of the silyloxydiene (141) (187mg, 1.1mmol) in dichloromethane (0.5ml) was added slowly. The solution was stirred at 4 - 15°C for 3h and then quenched with a 4:1 THF:0.005M HCl solution (2ml) for 1h. Sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3 x 15ml). The organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography (20mm, dichloromethane -ethyl acetate (19:1)) gave a colourless oil

(276mg,75%) which was shown by 250MHz n.m.r. (using the relative integrations of the OMe signals) to be a 33 : 44.4 : 17.5 : 5.1 mixture of *Exo:Endo*:Aldol I:Aldol II.

Lewis Acid-Catalysed Imine Formation and Diels-Alder Reaction

To a solution of methyl glyoxylate (521mg, 5.91mmol) in THF (5ml) was added *N*-sulphinyl-*p*-toluenesulphonamide (139) in THF (2.15ml, 2.75M, 5.91mmol) and then boron trifluoride etherate (0.08ml) and the solution was refluxed for 1h. A small sample was evaporated for n.m.r. analysis (90MHz) which showed the imine to be *ca.*80% pure (by integration). The sample was then divided into four portions:-

To one portion (1.31mmol in 1.6ml) at -78°C was added over 5min a solution of the silyloxydiene (141) (247mg, 1.5mmol) in THF(0.5ml). The solution was stirred at -78°C for 3h and then quenched with water (1ml). The mixture was stirred at 20°C for 30min, poured into aqueous sodium bicarbonate and extracted with dichloromethane (3 x 15ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow gum. Purification by flash chromatography (20mm, dichloromethane - ethyl acetate (24:1)) gave an off-white gum which was shown by 250MHz n.m.r. to be a 0:0:66.4:33.6 mixture of *Exo:Endo*:Aldol I:Aldol II containing 44 mol% toluenesulphonamide (28% by weight). Yield = 56%.

It was found that the toluenesulphonamide could be separated more readily if hexane – ether (2:5) was used as the chromatography eluant.

When this procedure was used for Diels-Alder reactions in other solvents with different Lewis acids the solution of the crude imine was evaporated and then pumped dry at 0.2mmHg for 1h to remove traces of boron trifluoride etherate.

(1,3-Cyclohexadien-2-yloxy)-(1,1-dimethylethyl)dimethylsilane (159)

Butyl lithium in hexane (10.8ml, 1.6M, 17.3mmol) was added to a solution of di-isopropylamine (2.5ml, 17.3mmol) in THF (10ml) at 0°C and the solution was stirred for 20min. A solution of cyclohexenone (1.5ml, 15.6mmol) in THF (5ml) was added over 20 min at -78°C. The solution was stirred for 30min and then a solution of TBDMS-Cl (3.01g, 1.2eq.) in THF (8ml) was added rapidly. The mixture was allowed to warm to 20°C and then heated under reflux for 1h. After cooling, water (20ml) was added and the mixture was extracted with pentane (20ml) and ether (2 x 50ml). The organic extracts were washed with brine, combined, dried (Na_2SO_4) and evaporated to give a yellow oil.

Distillation under reduced pressure gave two fractions:-

FR1 Colourless oil 230mg, b.p. 20-40°C/0.2mmHg.

Required Diene$_A$ (159) 70% pure by n.m.r.

FR2 Colourless oil 2.20g, 67%; b.p. 45-50°C/0.2mmHg.

Required diene (159), 88% pure by n.m.r. Remainder is $(TBDMS)_2O$.

^1H δ ($CDCl_3$; 80MHz): 5.7 (2H, m), 4.86 (1H, m), 2.1 (4H, m), 0.92 (9H, s, ^{t}Bu), 0.13 (6H, s, MeSi).

Methyl (*Exo*)-5-[(1,1-dimethylethyl)dimethylsilyloxy]-2-*p* -toluenesulphonamido-2-azabicyclo[2.2.2]oct-5-enyl-3-carboxylate (160)

Methyl (*Endo*)-5-[(1,1-dimethylethyl)dimethylsilyloxy]-2-*p* -toluenesulphonamido-2-azabicyclo[2.2.2]oct-5-enyl-3-carboxylate (161)

The TBDMSO-diene (159) (410mg of 60% pure material, 1.07eq.) in CH_2Cl_2(0.5ml) was added slowly to a solution of the distilled imine (142) (1.09mmol) in CH_2Cl_2(1.5ml) at -4°C and the solution was allowed to warm to 20°C over 3h. (4:1) THF-0.01M HCl (1ml) was added and the mixture was stirred for a further 1.25h. 1M Sodium hydrogen carbonate solution was added, the mixture was extracted with CH_2Cl_2(3 x 15ml) and the organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography [20mm, hexane-ether (3:1) then CH_2Cl_2-EtOAc (19:1)] gave three fractions:-

FR1 White solid (80mg, 16%).

FR2 White solid (96mg, 19.5%).

FR3 Colourless oil (82mg, 22%).

This was shown to be a 0:28.2:61.4:10.4 mixture of the *exo:endo*:A_I:$A_{II}$by n.m.r.

FR1 was crystallised from hexane-$CH_2Cl_2$to give the *endo* enol ether (161) as fine off-white needles, m.p.158-9°C.

^1H δ ($CDCl_3$; 250MHz): 7.7 and 7.3 (4H, AB, Ar), 5.22 (1H, dd, *J*=7.1, 2.5Hz, H6), 4.31 (1H, m, H1), 4.23 (1H, d, *J*=2.4Hz, H3), 3.64 (3H, S, OMe), 2.84 (1H, m, H4), 2.41 (3H, s, MeAr), 2.2-0.9 (4H, m), 0.87 (9H, s, ^{t}Bu), 0.13 (3H, s, MeSi), 0.12 (3H, s, MeSi).

$\nu_{max.}$ ($CHCl_3$): 2960(s), 2860(m), 1755(s), 1730(m), 1640(s), 1600(m) cm^{-1}.

m/z 451(M^+), 436(M-Me), 394(M-^{t}Bu).

Analysis. Found: C,58.6; H,7.2; N,2.9; S,7.4;

$C_{22}H_{33}NO_5SSi$ requires C,58.5; H,7.4; N,3.1; S,7.1%.

FR2 was crystallised from hexane-CH_2Cl_2 to give the *exo* adduct (160) as white cubes, m.p. 98-9°C.

^1H δ ($CDCl_3$; 250MHz): 7.7 and 7.3 (4H, AB, Ar), 4.79 (1H, dd, *J*=6.2, 2.1Hz, H6), 4.35 (1H, m, H1), 3.93 (1H, dd, *J*=2.6, 1.1Hz, H3), 3.80 (3H, s, OMe), 2.70 (1H, m, H4), 2.41 (3H, s, MeAr), 2.2-1.0 (4H, m), 0.82 (9H, s, ^{t}Bu), -0.03 (3H, s, MeSi), -0.13 (3H, s, MeSi).

$\nu_{max.}$ ($CHCl_3$): 2940(s), 2860(m), 1755(s), 1725(m), 1640(s), 1600(m) cm^{-1}.

m/z 451(65%, M^+), 394(100%, M-^{t}Bu).

Analysis. Found: C,58.8; H,7.2; N,3.3; S,7.4;

$C_{22}H_{33}NO_5SSi$ requires C,58.5; H,7.4; N,3.1; S,7.1%.

Bis(8-phenylmenthyl)fumarate(200)

Butyl lithium (10.6ml of 1.6M solution in hexane, 17.0mmol) was added to a solution of 8-phenylmenthol (97) (3.75g, 16.1mmol) in dry tetrahydrofuran (THF) (30ml) under nitrogen at -78°C and the resultant mixture was stirred at this temperature for 30min. This solution was then added over 1h *via* a cannula to a solution of fumaryl chloride (1.236g, 8.07mmol) in (THF) (20ml) at -78°C. The purple solution was stirred at -78°C for 30min, saturated ammonium chloride solution (10ml) was added, the mixture was allowed to warm to 20°C and extracted with ether (2x50ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a brown oil (4.0g). Purification by flash chromatography (silica, 60mm column, 40-60 petrol-ether (9:1) as eluant) gave the title compound as an impure pale yellow oil (3.48g, 79%) (with 10-15% impurity by n.m.r.), recovered starting material (240mg, 6%) and recovered starting material containing the mono fumaric ester (201) (245mg) as yellow oils.

The impure product (one spot by t.l.c. analysis) was crystallised from hexane-ether (small quantity) to give bis-ester (200) as opaque crystals (3.19g,72%), m.p. 129.5-130°C.*

^1H δ ($CDCl_3$; 250MHz): 7.23 and 7.18 (10H,m, aromatic H), 5.74 (2H,s, alkene), 4.84 (2H,ddd, *J*=10.69,6.30,4.44, -CHO-), 2.11 (16H,m, CH and CH_2), 1.27 (6H,s, CH_3), 1.20 (6H,s, CH_3), 0.89 (6H,d, *J*=6.5Hz, CH_3).

^{13}C δ ($CDCl_3$; 63MHz): 164.1, 151.4, 133.0, 128.0, 125.3, 125.1, (C=O and aromatic), 75.1, 50.6, 41.6, 39.6, 34.6, 31.3, 28.2, 26.5, 24.7, 21.8 (aliphatic C).

$\nu_{max.}$($CHCl_3$): 2980(s), 2950(s), 2930(m), 1720(s), 1640(m), 1600(m), 1320(s), 1270(m) cm^{-1}.

*The m.p. and optical rotation for the enantiomer are reported to be 165°C and $[\alpha]_D$ -15.3° c=0.485 ($CHCl_3$)[108]

$[\alpha]_D$= +10.7°(c=1.3, $CHCl_3$).

Analysis. Found: C,79.1; H,8.6;

$C_{36}H_{48}O_4$requires C,79.4; H,8.9%.

The mother liquors were evaporated to give a pale yellow, viscous oil (274mg) which is a 3:1 mixture (by n.m.r.) of an unidentified compound with the bis(phenylmenthyl)fumarate.

Alternative Preparation

A solution of fumaryl chloride (548mg, 3.6mmol) in dry dichloromethane (5ml) was added over 20min to a solution of 8-phenylmenthol (97) (1.674g, 7.2mmol) and dimethylaminopyridine (820mg, 6.7mmol) in dichloromethane (20ml) at 0°C and the mixture was stirred at 20°C for 16h. Triethylamine (0.2ml) was added followed by further fumaryl chloride (1.0ml), portionwise over 24h until no alcohol could be seen by t.l.c. analysis. Water (3ml) was added and the black liquid was filtered through 'Celite' and evaporated to give an amorphous solid.

Purification by flash chromatography [30mm, petrol–ether (4:1)] gave two fractions:-

FR1 Pale orange solid 1.24g, 63%.

This is the bis-ester (200), identical (n.m.r., t.l.c.) to that prepared by the first method.

FR2 Brown solid 366mg, 16%.

Mono ester.

(*R*)-8-Phenylmenthyl (*exo*)-5-oxo-2-*p* -toluenesulphonamido-2-azabicyclo[2.2.2]-octanyl-3-carboxylate [(196) and (197) 1:1]

(*R*)-8-Phenylmenthyl [1*S*-(*exo*)]-5-oxo-2-*p* -toluenesulphonamido-2-azabicyclo[2.2.2]-octanyl-3-carboxylate (196).

(*R*)-8-Phenylmenthyl (*endo*)-5-oxo-2-*p* -toluenesulphonamido-2-azabicyclo[2.2.2]-octanyl-3-carboxylate (2 isomers, *Endo* I and *Endo* II) (198) and (199).

A solution of bis(8-phenylmenthyl) fumarate (200) (360g, 0.66mmol) in CH_2Cl_2 (30ml) was cooled to -78°C and a stream of dry ozone was bubbled through for 30min until a blue colouration persisted. The excess of ozone was removed with a stream of dry oxygen and then dimethyl sulphide (0.06ml) was added. The mixture was allowed to warm to 20°c over 1h and then the solvent was removed *in vacuo*. The pale yellow gum was distilled (kugelrohr, 120-130°C, 0.2mm Hg) to give 8-phenylmenthyl glyoxylate (136)[104]as a colourless gum (355mg, 93%).

^1H δ ($CDCl_3$; 90MHz): 8.55 (1H, s, CHO), 7.4-7.2 (5H, m, Ph), 5.1 (1H, ddd, >CHO-), 2.1-0.7 (17H, m).

This was dissolved in benzene (3ml), a solution of the sulphinylsulphonamide in benzene (0.6ml, 2.1M, 1.22mmol) was added and the mixture was heated under reflux for 17h. N.m.r. analysis (90MHz, C_6D_6) showed the absence of the glyoxylate aldehyde signal and the presence of a new signal at δ7.6 (partially obscured by aromatic signals).

^1H δ(C_6D_6; 90MHz): 8.0 (2H, m, Ar), 7.6 (1H, s, CH=N), 7.5-6.9 (7H, m, Ar), 5.0 (1H, ddd, >CHO-), 2.7-0.9 (20H, m).

The imine may also be prepared in THF solution with borontrifluoride etherate catalysis, and heating under reflux for 2h.

A solution of the silyloxydiene (141) (229mg, 1.1eq.) in benzene (0.5ml) was added to the crude imine (194) solution at 35°C and the resultant solution was stirred at 35°C for 30min and at 20°C for 5.5h. The reaction was quenched with 4:1 THF:0.005M HCl (2ml) and two drops of acetic acid for 50min and then poured into sodium bicarbonate solution. This was extracted with dichloromethane (3 x 15ml) and the organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography (20mm, dichloromethane-ethyl acetate (49:1)) and extensive preparative plate chromatography [hexane - ether (1:2) and dichloromethane - ethyl acetate (99:1)] gave four fractions:-

FR1 White solid 221mg (33.5%). 1:1 Mixture of *exo* compounds.
FR2 Pale yellow oil 30mg (4.5%). *Endo* I.
FR3 Pale yellow oil 54mg (8%). *Endo* II.
FR4 Colourless oil 215mg (32%). Probably a mixture of 'aldol' compounds.

FR1 was triturated with ether to give pure 1:1 mixture of *exo* adducts (196 and 197) as a fine white powder, m.p. 162-3°C.

^1H δ ($CDCl_3$; 250MHz): 7.92 (2H, d;*J*=6.6Hz, Ar), 7.8 (2H, d;*J*=7.8Hz, Ar), 7.4 (12H, m, Ar), 7.1 (2H, m, Ar), 4.8 (2H, m, >CHCO-), 4.22 (1H, d;*J*=2.2Hz, H3), 4.1 (1H, d;*J*=2.6Hz, H3), 3.5-0.7 (26H, m), 2.46 (6H, s, MeAr), 1.35, 1.31, 1.24, 1.20 (12H, 4 x s, Me), 0.85 (6H, 2 x d, Me).

^1H δ (C_6D_6; 250MHz): 8.18 (2H, d;*J*=8.3Hz, Ar), 7.90 (2H, d;*J*=8.3Hz, Ar), 7.4 (10H, m, Ph), 6.83 (2H, d;*J*=8.3Hz, Ar), 6.74 (2H, d;*J*=8.3Hz, Ar), 5.05 (1H, td;*J*=10.7,4.4Hz, >CHO-), 4.84 (1H, td;*J*=10.7,4.4Hz, >CHO-), 4.45 (1H, dd;*J*=2.4,1.0Hz, (W-plan), H3), 4.40 (1H, dd;*J*=2.8,1.2Hz, (W-plan), H3), 3.68 (1H, m, H1), 3.58 (1H, m, H1), 2.8-0.7 (54H, m).

$\nu_{max.}$ ($CHCl_3$): 2950(m), 1735(s), 1600(m) cm^{-1}.

m/z NoM^+, 418(9%, M-$PhCMe_2$), 278(100%, M-$CO_2$8PM), 236(70%, M-$CO_2$8PM -CH_2CO), 119(100%, $PhCMe_2$).

$[\alpha]_D$ +2.6°, c= 13.6($CHCl_3$).

Analysis. Found: C,69.0; H,7.3; N,2.9; S,6.2;

$C_{31}H_{39}NO_5S$ requires C,69.2; H,7.31; N,2.6; S,6.0%.

This white powder was crystallised from hexane - dichloromethane (three times) to give the pure 1S-*(exo)*compound (196) as opaque cubes m.p. 183-4°C.

^1H δ ($CDCl_3$; 250MHz): 7.93 (2H, d;*J*=6.6Hz, Ar), 7.3 (6H, m, Ar), 7.16 (1H, m, Ar), 4.78 (1H, td;*J*=10.7,4.1Hz, >CHO-), 4.1 (1H, d;*J*=2.6Hz, H3), 3.9 (1H, m, H1), 2.55 (2H, m, CH_2CO), 2.43 (3H, s, MeAr), 2.2-0.8 (13H, m), 1.34 (3H, s, Me), 1.24 (3H, s, Me), 0.85 (3H, d;*J*=6.5Hz, Me).

^1H δ (C_6D_6; 250MHz): 8.18 (2H, d;*J*=8.3Hz, Ar), 7.4 (5H, m, Ph), 6.83 (2H, d;*J*=8.3Hz, Ar), 4.84 (1H, td;*J*=10.7,4.4Hz, >CHO-), 4.45 (1H, dd;*J*=2.4,1.0Hz, (W-plan), H3), 3.59 (1H, m, H1), 2.67 (1H, ddd;*J*=18.6,2.8,0.7Hz, H6-*endo*), 2.53 (1H, dd;*J*=5.2,2.4Hz, H4), 2.0-0.7 (13H, m), 1.85 (3H, s, MeAr), 1.35 (3H, s, Me), 1.16 (3H, s, Me), 0.74 (3H, d;*J*=6.4Hz, Me).

$\nu_{max.}$ ($CHCl_3$): 2950(m), 1737(s), 1600(w) cm^{-1}.

m/z No M^+, 418(5%, M-$PhCMe_2$), 278(15%, M-$CO_2$8PM), 119(100%, $PhCMe_2$).

$[\alpha]_D$-30.7°, c= 2.5 ($CHCl_3$).

Analysis. Found: C,69.5; H,7.4; N,2.5; S,6.1;

$C_{31}H_{39}NO_5S$ requires C,69.2; H,7.31; N,2.6; S,6.0%.

FR2 was crystallised from hexane - dichloromethane to give pure *Endo* I (198 or 199) as fine white needles m.p. 160.5-161.5°C.

^1H δ ($CDCl_3$; 250MHz): 7.94 (2H, d;*J*=8.3Hz, Ar), 7.3 (7H, m, Ar), 4.67 (1H, td;*J*=10.7,4.1Hz, >CHO-), 4.03 (1H, d;*J*=2.8Hz, H3), 3.92 (1H, m, H1), 2.57 (1H, dt;*J*=18.7,2.9Hz, H6endo), 2.43 (1H, s, MeAr), 2.4-0.8(14H, m), 1.33 (3H, s, Me), 1.22 (3H, s, Me), 0.85 (3H, d;*J*=6.5Hz, Me).

$\nu_{max.}$ ($CHCl_3$): 2950(m), 1735(s), 1600(m) cm^{-1}.

m/z No M^+ 418(4%, M-$PhCMe_2$), 278(60%, M-$CO_2$8PM), 236(60%, M-$CO_2$8PM-CH_2CO), 119(95%, $PhCMe_2$), 91(100%, C_7H_7).

$[\alpha]_D$, -21.1° c= 4.0 ($CHCl_3$).

Analysis. Found: C,69.1; H,7.4; N,2.9; S,6.3;

$C_{31}H_{39}NO_5S$ requires C,69.2; H,7.31; N,2.6; S,6.0%.

FR3 was crystallised from hexane - dichloromethane to give *Endo* II (198 or 199) as fine white needles m.p. 148-9°.

^{1}H δ ($CDCl_3$; 250MHz): 7.72 (2H, d;*J*=8.3Hz, Ar), 7.3 (7H, m, Ar), 4.69 (1H, td;*J*=10.7,4.1Hz, >CHO-), 4.10 (1H, m, H1), 3.69 (1H, d;*J*=2.3Hz, H3), 2.82 (1H, dt;*J*=18.4,3.0Hz, H6endo), 2.44 (1H, s, MeAr), 2.3-0.8(14H, m), 1.30 (3H, s, Me), 1.19 (3H, s, Me), 0.85 (3H, d;*J*=6.5Hz, Me).

$\nu_{max.}$ ($CHCl_3$): 2950(m), 1735(s), 1600(m) cm^{-1}.

m/z No M^+418(5%, M-$PhCMe_2$), 278(100%, M-$CO_2$8PM), 236(75%, M-$CO_2$8PM-CH_2CO).

$[\alpha]_D$ +36.8°c=10.8 ($CHCl_3$).

Analysis. Found: C,69.0; H,7.4; N,2.8; S,6.1;

$C_{31}H_{39}NO_5S$ requires C,69.2; H,7.31; N,2.6; S,6.0%.

2-[(5aα, 7α, 9aβ)-3,3-dimethyl-hexahydro-6-(4- methylphenylsulphonyl)-4*H*-[2,4]dioxepino[5,6-*b*]-7- pyridinyl]ethanol (215)

The mixture of the methylene-migrated lactone (210) and the hydroxyacid (212) (461mg) in methanol (10ml) and conc.-H_2SO_4 was stirred for 3 days. the solvent was removed *in vacuo*,sodium bicarbonate solution was added and the mixture was extracted with CH_2Cl_2 (3 x 15ml) The combined organic layers were dried ($MgSO_4$) and evaporated to give a yellow oil which was reduced to the triol with excess $LiAlH_4$. treatment of the product with pTSA in dry acetone (2ml) for 2 days followed by evaporation of the solvent and purification by flash chromatography (silica, 20mm, petrol-ether-ethyl acetate (1:1:1) as eluant) gave a white solid (189mg, 30%). Crystallisation of this from hexane-CH_2Cl_2gave the title compound (215) as white crystals, m.p. 149-50°C.

^{1}H δ ($CDCl_3$; 250MHz): 7.8-7.2 (4H, AB, Ar), 4.37 (1H, dd; J=10.0,12.0Hz, H-1^7), 4.20 (1H, m, H-2), 3.87 (2H, m, H-1' + H-1'''), 3.51 (1H, m, H-1'''), 3.00 (1H, dt; J=3.2,10.5Hz, H-6), 2.41 (3H, s, Ar), 1.8-0.8 (5H, m, CH and CH_2), 1.37 and 1.28 (6H, 2x s, Me).

$\nu_{max.}$($CHCl_3$) 3550(broad,s), 2850(s), 1720(w), 1600(m), 1330(s). m/z no M^+, 338(38%, M-CH_2OH), 280(40%).

Analysis. Found: C,58.5; H,7.6; N,3.6; S,9.0;

$C_{18}H_{27}NO_5S$ requires C,58.5; H,7.4; N,3.8; S,8.7%.

Methyl (*exo,exo*)-6-Bromo-5-oxo-2-*p*-toluenesulphonamido-2-azabicyclo-[2.2.2]octanyl-3-carboxylate (193)

Methyl (*exo*)-6,6-Dibromo-5-oxo-2-*p*-toluenesulphonamido-2-azabicyclo-[2.2.2]octanyl-3-carboxylate (220)

Bromine (0.09ml, 1.74mmol) was added to a solution of the *exo* compound (142) (536mg, 1.59mmol) in acetic acid (5ml) and heated at 50°C for 1.25h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (40mm, CH_2Cl_2) to give three fractions:-

FR1 Colourless oil 30mg, (4%).

Mixed fractions 44mg, (6%).

FR2 White solid 486mg, (72%).

FR3 White solid 72mg, (13%). Recovered starting material.

FR1 Was triturated with ether to give the dibromo compound (220) as a white solid, m.p.152-4°C.

^1H δ ($CDCl_3$; 250MHz): 7.7 and 7.3 (4H, AB, Ar), 4.67 (2H, m, H1 and H3), 3.71 (3H, s, OMe), 2.94 (1H, m, H4), 2.42 (3H, s, MeAr), 2.6-1.2 (4H, m).

$\nu_{max.}$ ($CHCl_3$): 1760(s), 1750(s), 1600(w) cm^{-1}.

m/z 493/495/497(5, 11, 7%,M^+), 434/436/438(12, 24, 12%, M-CO_2Me).

Analysis. Found: C,38.5; H,3.4; N,2.9; Br,32.0;

$C_{16}H_{17}Br_2NO_5S$ requires C,38.8; H,3.5; N,2.8; Br,32.4%.

FR2 was crystallised from hexane-$CH_2Cl_2$to give the 6-bromo compound (193) as fine, white needles, m.p. 151-2°C.

^1H δ ($CDCl_3$; 250MHz): 7.9 and 7.3 (4H, AB, Ar), 4.75 (1H, d; *J*=3.0Hz, H3), 4.43 (1H, dd; *J*=3.7, 1.6Hz, H6), 4.03 (1H, m, H1), 3.80 (3H, s, OMe), 3.02 (1H, td; *J*=5.9, 3.0Hz, H4), 2.44 (3H, s, MeAr), 2.4-1.2 (4H, m).

$\nu_{max.}$ ($CHCl_3$): 1760(s), 1750(s), 1600(w) cm^{-1}.

m/z 415/417(5%, M^+), 356/358(90%, M-CO_2Me).

Found: M^+, 415.0103. $C_{16}H_{18}{}^{79}BrNO_5S$ requires 415.0089.

2-[(4aα, 6α, 8aβ)-2,2-Dimethyl-hexahydro-5-(4-methylphenylsulphonyl)-4*H*-1,3-dioxino[5,4-*b*]-6-pyridinyl]ethanol (225)

Modified Procedure

A solution of the triol (224) (248mg, 0.75mmol) and pTSA (10mg) in dry acetone (5ml) with 4Å molecular sieves was stirred for 7h. Solid sodium bicarbonate (50mg)

was added and the solvent was removed *in vacuo* Purification by flash chromatography (silica, 20mm column, ether as eluant) gave the title compound (225) as a pale yellow gum (207mg, 74.5%), shown to be identical to an authentic sample.

2-(4-Bromobutyl)-2-pentyl-1,3-dithiane (231)

Butyl lithium (5.0ml, 1.6M in hexane, 8.0mmol) was added to a solution of the dithiane (230) (1.49g, 7.8mmol) in THF(15ml) at -40°C and the resultant colourless solution was stirred at -10°C for 1h. This was added over 1.5h to a solution of 1,4-dibromobutane (1.69g, 7.8mmol) in THF(5ml) at -78°C. The mixture was allowed to warm to 20°C and stirred for 16h. 8% Sodium bicarbonate solution (10ml) was added and the mixture was extracted with ether (3x10ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil (2.63g). Purification by flash chromatography (silica, 60mm column, petrol-ether (19:1) as eluant) gave two fractions:-

FR1 Colourless oil (726mg, 28%), slowly turning solid.

FR2 Colourless oil (245mg, 14%).

FR1 is the title compound (231).

^1H δ ($CDCl_3$; 80MHz): 3.42(2H, d; J 6.5Hz, CH_2Br), 2.80(4H, m, CH_2S), 2.07-1.1(16H, m, CH_2), 0.90(3H, t, CH_3).

$\nu_{max.}$ ($CHCl_3$) 2820, 1440.

m/z 324/326(15%, M^+), 253/255(70/75%, $M-C_5H_{11}$).

Found M^+ 324.0589.

$C_{13}H_{25}BrS_2$ requires M^+ 324.0581.

FR2 is 1,4-bis[2-(2-pentyl-1,3-dithianyl)]butane (232)

^1H δ ($CDCl_3$; 250MHz): 2.80(8H, m, CH_2S), 2.0-1.8(12H, m, CH_2), 1.49-1.25(16H, m, CH_2), 0.89(6H, t, CH_3).

$\nu_{max.}$ ($CHCl_3$) 2830, 1450.

m/z 434(34%, M^+), 189(100%).

Analysis. Found: C,60.5; H,9.6; S,29.3;

$C_{22}H_{42}S_4$ requires C,60.8; H,9.7; S,29.5%.

2-(1,1-Dimethylethyl,dimethylsilyloxy)heptanenitrile (237)

Tert-butyldimethylsilyl chloride (5.8g, 38.5mmol) and freshly distilled hexanal (3.1g, 31mmol) were added to potassium cyanide (8.2g, 126mmol) and the mixture was suspended in dry acetonitrile (150ml) under argon. Zinc iodide (150mg) was added and the mixture was stirred at 20°C for 4 days. The suspension was filtered through 'celite' and evaporated, taken up in ether, re-filtered and evaporated to give a colourless oil. Purification by flash chromatography (silica, 60mm column, petrol-ether (19:1) as eluant) gave the required compound (237) as a colourless oil (5.75g, 77%).

^1H δ ($CDCl_3$; 80MHz): 4.41 (1H, t;J 6.2Hz, CH), 1.8-1.2 (8H, M, CH_2), 0.91 (12H, s, Me), 0.18 and 0.13 (6H, 2xs, $SiMe_2$).

ν_{max}($CHCl_3$) 2950(s), 1500(m), 1390(m).

M/z no M^+184(17%, M-^{t}Bu), 157(100%).

Analysis. Found: C,64.9; H,11.3; N,5.6;

$C_{13}H_3NOSi$ requires C,64.7; H,11.27; N,5.8%.

1-Bromo-5-decanone (236)

A solution of pentylmagnesium bromide in ether (5ml) was formed from pentyl bromide (1.24g, 8.31mmol) and magnesium (200mg, 8.23mmol). A solution of 5-bromovaleronitrile (241) (1.27g, 7.84mmol) in ether (3ml) was added to the refluxing solution and the mixture was heated under reflux for 40min. Saturated ammonium chloride solution was added and the mixture was stirred for 1.5h. 0.5M HCl (7ml) was added and the mixture was extracted with ether (3 x 30ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography (20mm, petrol - ether (14:1) as eluant) gave the ketone (236) as a colourless oil (469mg, 25%).

^1H δ ($CDCl_3$; 80MHz): 3.39 (2H, t;J 6.3Hz, CH_2Br), 2.40 (4H, m, CH_2CO), 2.0-1.1 (10H,m, CH_2), 0.9 (3H, m, Me).

ν_{max} ($CHCl_3$) 2950, 1710(C=O), 1450(m), 1360(m).

m/z 234/236(4%, M^+), 155(48%, M-Br), 99(100%, $C_5H_{11}CO$).

Analysis. Found: C,51.4; H,8.1;

$C_{10}H_{19}BrO$ requires C,51.1; H,8.1%.

Alternative Preparation

Butyl lithium (2.2ml, 1.55M solution in hexane, 3.44mmol) was added to a solution of the hydrazone (248)[135] (538mg, 3.44mmol) in THF (8ml) at -78°C and the resultant white

suspension was stirred at -78°C for 30min. Dibromopropane (1.0ml, 2.7equiv.) was added and the solution was allowed to warm to 20°C over 2.5h. This was added to a solution of copper (II) chloride (650mg) in water (15ml) buffered with 0.05M pH7 phosphate (10ml) and the brown mixture was stirred for 3h. The THF was removed under reduced pressure and the residue was extracted with ether (3x30ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography (20mm, petrol-ether as eluant) gave ketone (236) as a pale yellow oil (501mg, 62%) which was shown to be identical (n.m.r., t.l.c.) to material prepared by the first route.

2-(4-Bromobutyl)-2-pentyl-1,3-dioxolane (250)

A solution of the ketone (236) (342mg, 1.45mmol), ethylene glycol (220mg, 3.6mmol) and pTSA (15mg) in toluene (7ml) was heated under Dean-Stark conditions for 16h. 8% Sodium bicarbonate solution (5ml) was added and the mixture was extracted with ether (3x20ml). The organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil (0.43g). Purification by flash chromatography (silica, 20mm column, petrol - ether (14:1) as eluant) gave the title compound (250) as a pale yellow oil (395mg, 97%).

^1H δ ($CDCl_3$; 80MHz): 3.92 (4H, s, ketal), 3.40 (2H, t;J 6.5Hz, CH_2Br), 2.0-1.1 (14H, m, CH_2), 0.9 (3H, m, Me).

$\nu_{max.}$($CHCl_3$) 3500(broad, w), 2900(s), 1710(w), 1440(m).

m/z no M^+, 207/209(73%, $M-C_5H_{11}$), 143(100%).

Analysis. Found: C,51.9; H,8.0;

$C_{12}H_{23}BrO_2$ requires C,51.6; H,8.3%.

[4-(2-Pentyl-1,3-dioxolan-2-yl)butyl]phenylsulphone (252)

A suspension of sodium benzenesulphinate (611mg, 3.72mmol), the bromide (250) (958mg, 3.43mmol) and sodium iodide (20mg) in dry DMF (6ml) was stirred under nitrogen at 15°C for 5 days. Water (10ml) was added and the mixture was extracted with ether (3x20ml). The organic layers were washed with water (twice) and brine, combined, dried ($MgSO_4$) and evaporated to give a colourless oil (1.24g). Purification by flash chromatography (silica, 30mm column, hexane-ether (1:1) as eluant) gave three fractions:-

FR1 Colourless oil 76mg, 8%.

Recovered SM by t.l.c.

FR2 Pale yellow oil 110mg, 9.5%.

Probably the sulphinite ester (253) by n.m.r.

FR3 Colourless oil 940mg, 80.5%, which turned to an off-white solid on standing. This is the required sulphone (252).

^{1}H δ ($CDCl_3$; 80MHz): 8.0-7.4 (5H, m, Ph), 3.87 (4H, s, ketal), 3.10 (2H, m, CH_2SO_2), 2.0-1.0 (14H, m, CH_2), 0.9 (3H, m, Me).

$\nu_{max.}$($CHCl_3$): 3540(w), 2900(shoulder), 2860(m), 1710(w), 1585(w), 1440(m), 1305(s).

m/z no M^+, 269(95%, M-C_5H_{11}), 143(100%).

Analysis. Found: C,63.4; H,8.3; S,9.7;

$C_{18}H_{28}O_4S$ requires C,63.5; H,8.3; S,9.4%.

(4aα, 6α, 8aβ)-2,2-dimethyl-hexahydro-5- (4-methylphenylsulphonyl)-6-(2-methylsulphonyloxyethyl)- 4*H*-1,3-dioxino[5,4-*b*]-6-pyridine (254)

Triethylamine (0.15ml, 1.1mmol) was added to a solution of methanesulphonyl chloride (0.05ml, 0.65mmol) and the acetonide-alcohol (225) (41mg, 0.11mmol) in CH_2Cl_2(1ml) at O°C, and the solution was stirred for 1h. The solvent was removed and the residue purified by flash chromatography (silica, 10mm, hexane-ether (1:4) as eluant) to give a colourless oil which was re-purified (silica, 10mm, CH_2Cl_2-EtOAc (9:1) as eluant) to give the mesylate (254) as a colourless oil (49mg, 98%).

^{1}H δ ($CDCl_3$; 250MHz): 7.8-7.2 (4H, AB, Ar), 4.46 (1H, m, H-6), 4.2 (4H, m, H-1'+ H-2"), 3.45 (1H, dt;J 4.5,10.4Hz, H-3), 3.18 (1H, dt;J 4.8,10.4Hz, H-2), 3.06 (3H, s, $MeSO_3$), 2.44 (2.44, s, MeAr), 2.4-1.2 (6H, m, CH_2), 1.34 and 1.33 (6H, 2x s, Me).

$\nu_{max.}$($CHCl_3$) 3500(broad,m), 2900(w), 2850(m), 1580(m), 1340(s).

Analysis. Found: C,51.4; H,6.5 ; N,3.4;

$C_{19}H_{29}NO_7S_2$ requires C,51.0; H,6.5; N,3.1%.

(4aα, 6α, 8aβ)-2,2-dimethyl-hexahydro-6-(2-iodoethyl)-5- (4-methylphenylsulphonyl)-4*H*-1,3-dioxino[5,4-*b*]-6-pyridine (257)

A solution of the mesylate (254) (47mg, 0.1mmol) and sodium iodide (91mg) in dry acetone (1ml) was stirred for 2.5days. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, 10mm, hexane-ether (2:1) as eluant) to give the iodide (257) as a white solid (39mg, 78%).

A small sample was crystallised from hexane-dichloromethane to give a fine white powder m.p. 142-3°C.

^1H δ ($CDCl_3$; 250MHz): 7.8-7.2 (4H, AB, Ar), 4.3 (2H, m, H-6 + H-1'), 4.03 (1H, dd;J 4.8,11.6Hz, H-1'), 3.58 (1H, dt;J 4.5,10.3Hz, H-3), 3.1 (3H, m, CH_2I + H-2), 2.43 (3H, s, MeAr), 2.4-1.2 (6H, m, CH_2), 1.38 and 1.34 (6H, 2x s, Me).

$\nu_{max.}$($CHCl_3$) 3550 (w), 2900(shoulder), 2850(m), 1595(m), 1440(m), 1340(s).

m/z 479(1%, M^+), 462(15%, M-Me), 324(48%, M-C_2H_4I).

Found: M^+, 479.0608. $C_{18}H_{26}INO_4S$ requires 479.0627.

Analysis. Found: C,44.7; H,5.2; N,2.9; S,6.8;

$C_{18}H_{26}INO_4S$ requires C,45.1; H,5.4; N,2.9; S,6.7%.

(4aα, 6α, 8aβ)-6-(2-bromoethyl)-2,2-dimethyl-hexahydro-5-(4-methylphenylsulphonyl)-4*H*-1,3-dioxino[5,4-*b*]-6-pyridine (258)

Triphenylphosphine (473mg, 1.8mmol) was added to a solution of N-bromosuccinimide (323mg, 1.81mmol) and the alcohol (225) (285mg, 0.77mmol) in dry CH_2Cl_2 (4ml) at 0°C, and the yellow solution was stirred for 4h. Methanol (3 drops) was added and the solvent was evaporated. Purification by flash chromatography [silica, 20mm column, petrol-ether (2:1) as eluant] gave the bromide (258) as a white crystalline solid (308mg, 92.5%).

A Portion of this was recrystallised from CH_2Cl_2-petrol to give white crystals, m.p. 93.5-94.5°C.

^1H δ ($CDCl_3$; 250MHz): 7.8-7.2 (4H, AB, Ar), 4.43 (1H, m, H-6), 4.31 (1H, dd; J=11.6, 10.8Hz, H-1'), 3.99 (1H, dd; J=11.6, 4.7Hz, H-1'), 3.61 (1H,ddd; J=10.6, 10.4, 4.4Hz, H-3), 3.38 (2H, t; J=7.1Hz, CH_2Br), 3.17 (1H, ddd; J=10.8, 10.4, 4.7Hz, H-2), 2.43 (3H, s, MeAr), 2.4-1.4 (6H, m, CH_2), 1.39 and 1.34 (6H, 2x s, Me).

$\nu_{max.}$($CHCl_3$) 3500(w), 2850(w), 1590(w), 1315(s). m/z noM^+, 416/418(5%, M-Me), 91(100%, C_7H_7).

Analysis. Found: C,49.9; H,6.0; N,3.1; S,7.5;

$C_{18}H_{26}BrNO_4S$ requires C,50.0; H,6.1; N,3.2; S,7.4.

(4aα, 6α, 8aβ)-2,2-dimethyl-hexahydro-5- (4-methylphenylsulphonyl)-6-[6-(2-pentyl-1,3-dioxolan-2-yl)-3- phenylsulphonylhexyl]-4*H*-1,3-dioxino[5,4-*b*]-6-pyridine (255)

Butyl lithium in hexane (0.88 ml, 1.6M, 1.41mmol) was added to a solution of the sulphone (252) (480mg, 1.41mmol) in THF (5ml) at -78°C, and the yellow solution was stirred for 20 min. A solution of the bromide (258) (275mg, 0.64mmol) in THF (2ml) was

added and the mixture was allowed to warm to 20°C over 1.5h. Sat. ammonium chloride solution (1ml) and water were added and the mixture was extracted with ether (3 x 10ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a yellow oil. Purification by flash chromatography [30mm, hexane-ether (2:3)] gave the sulphone (255) as a pale yellow foam (425mg; containing 1.1%wt CH_2Cl_2, 95.5%).

^1H δ ($CDCl_3$; 250MHz): 7.88, 7.6 and 7.3 (9H, m, Ar), 4.2 (2H, m, H6 and H1'), 4.0 (1H, m, H1'), 3.9 (4H, s, ketal), 3.46 (1H, m, H3), 3.0 (2H, m, $CHSO_2$and H2), 2.43 and 2.42 (3H, 2 x s, MeAr), 1.9 - 1.3 (28H, m), 0.9 (3H, m, Me).

$\nu_{max.}$ ($CHCl_3$): 2850(m), 1600(w), 1490(m) cm^{-1}.

m/z No M^+, 607(20%), 536(28%), 324(100%).

Analysis. Found: C,62.4; H,7.5; N,2.0; S,9.1;

$C_{36}H_{53}NO_8S_2$ requires C,62.5; H,7.7; N,2.0; S,9.3%.

(4aα, 6α, 8aβ)-2,2-dimethyl-hexahydro-6- [6-(2-pentyl-1,3-dioxolan-2-yl)hexyl]-4*H*-1,3-dioxino[5,4-*b*]-6- pyridine (261)

6% Sodium amalgam (1.04g) and disodium hydrogen phosphate (430mg) were added to a solution of the sulphone (255) (278mg, 0.4mmol) in dry methanol (5ml) and the mixture was stirred at 20°C for 4h. Further sodium amalgam (460mg) and phosphate (180mg) were added and stirring was continued for 2h. Portions of amalgam (100mg) were added at hourly intervals for 8h. The reaction was quenched with sat. potassium carbonate solution and extracted with CH_2Cl_2 (4 x 15ml). The combined organic layers were dried (Na_2SO_4) and evaporated to give a pale yellow oil. Purification by flash chromatography [20mm, dichloromethane-ethanol-ammonia (200:8:1)] gave two fractions:-

FR1 yellow oil 74mg; a mixture of starting material and de-sulphonated compound.

FR2 Yellow oil 119mg (75.5%). This is the amine (261) which contains 11% of the sulphone-amine (260).

FR1 Was recycled by treatment with sodium amalgam (900mg) and phosphate (350mg) in methanol (2ml) over 22h and then worked up and purified as above to give amine (261) as a pale yellow oil (33mg, 21%).

^1H δ ($CDCl_3$; 250MHz): 3.92 (4H, s, ketal), 3.6 (3H, m), 2.9 (1H, m), 2.8 (1H, m), 1.8-1.1 (30H, m), 0.9 (3H, m, Me).

$\nu_{max.}$ ($CHCl_3$): 3300(broad, m), 2840(s), 1715(w), 1480(broad, w) cm^{-1}.

m/z 397(6%, M$^+$), 382(10%, M-Me), 326(32%, M-C_5H_{11}).

Analysis. Found: C,69.2; H,10.6; N,3.4;

$C_{30}H_{35}NO_3$ requires C,69.5; H,10.9; N,3.5%.

(+)-Isoprosopinine A (84)

A solution of the ketal-amine (261) (116.2mg, 0.29mmol) in 85:15 methanol-conc.HCl (2ml) was stirred at 20°C for 2.5h. Saturated potassium carbonate solution (3ml) and 5M sodium hydroxide (2ml) were added and the mixture was extracted with CH_2Cl_2 (3 x 20ml). The organic extracts were washed with basic brine, combined, dried ($MgSO_4$) and evaporated to give a yellow oil. Purification by flash chromatography [20mm, dichloromethane-ethanol-ammonia (75:8:1)] gave two fractions:-

FR1 Colourless oil 12.7mg (10%). This is the sulphone (262).

FR2 Pale pink solid 69.7mg, 76%. Isoprosopinine A.

FR2 was crystallised from ethyl acetate to give (+)-Isoprosopinine A (84) (61.5mg) as a fine white powder, m.p. 86-7°C.

^{1}H δ ($CDCl_3$; 250MHz): 3.65 (1H, dd;*J*=10.6, 7.7Hz, H1'), 3.63 (1H, dd;*J*=10.6, 5.5Hz, H1'), 3.56 (1H, ddd;*J*=6.5, 5.5, 4.2Hz, H3), 2.90 (1H, dt;*J*=7.7, 5.5Hz, H2), 2.76 (1H,m, H6), 2.36 (4H, t;*J*=7.5Hz, CH_2CO), 2.11 (3H, broad), 1.7-1.1 (20H, m), 0.87 (3H, t;*J*=6.8Hz, Me).

^{13}C δ ($CDCl_3$; 63MHz): 211.5, 68.0, 62.3, 58.2, 49.8, 42.8, 42.7, 33.7, 31.4, 29.4, 29.2, 28.6, 27.4, 26.1, 23.7, 23.6, 22.4, 13.8.

$\nu_{max.}$ ($CHCl_3$): 3610(m), 3420(m, broad), 2935(m), 2860(m), 1710(s) cm^{-1}.

m/z No M$^+$, 312(5%, M-H), 282(85%, M-CH_2OH), 130(100%, M-$C_5H_{11}COC_6H_{12}$-).

Analysis. Found: C,68.9; H,11.3; N,4.4;

$C_{18}H_{35}NO_3$ requires C,69.0; H,11.3; N,4.5%.

2-Hexanone,dimethylhydrazone (263)

2-Hexanone (4.21g, 42.0mmol) and *N,N*-dimethylhydrazine (25.3g, 42.1mmol) were stirred at 70°C for 4.75h. The mixture was cooled, sodium hydroxide pellets were added and the aqueous layer was removed. The mixture was stood over solid sodium hydroxide for 4h and then distilled under reduced pressure to give the hydrazone (263) (5.02g, 84%) b.p. 54-6°C/17mm Hg.

^{1}H δ ($CDCl_3$; 80MHz): 2.41 (6H, s, NMe), 2.2 (2H, m, CH_2C=N), 1.92 (3H, s, MeC=N), 1.8-1.0, (4H, m, CH_2), 0.85 (3H, m, Me).

$\nu_{max.}$ (Thin film): 2930(s), 2860(s), 2820(s), 2780(m), 2470(m), 1630(s), 1450(s).

m/z 142(24%, M^+).

Found: M^+142.1480. $C_8H_{18}N_2$requires 142.1470.

Analysis. Found: C,67.2; H,12.5; N,19.6;

$C_8H_{18}N_2$requires C,67.6; H,12.8; N,19.7%.

10-Bromo-5-decanone (264)

Butyl lithium in hexane (8.5ml, 1.6M, 13.6mmol) was added to a solution of the hydrazone (263) (1.94g, 13.6mmol) in THF (10ml) at -78°C and the resultant white suspension was stirred for 30min. A solution of 1,4-dibromobutane (5ml, 42mmol) in THF (10ml) was added rapidly and the cloudy mixture was allowed to warm to 20°C over 3h. This was poured into a solution of copper(II)chloride (2.57g) in water (20ml) and 0.05M phosphate buffer (10ml), and the resultant brown suspension was stirred for 3h. The THF was removed *in vacuo* and the residue was extracted with ether (3 x 40ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography [40mm, hexane-ether (14:1)] gave the ketone (264) as a pale yellow oil (2.32g, 72%).

^1H δ ($CDCl_3$; 80MHz): 3.39 (2H, t; *J*=6.6Hz, CH_2Br), 2.4 (4H, m, CH_2CO), 2.0-1.0 (10H, m, CH_2), 0.9 (3H, m, Me).

$\nu_{max.}$ ($CHCl_3$): 2950(s), 2870(m), 1710(s).

m/z No M^+, 177/179(7%, M-C_4H_9), 155(6%, M-Br).

Analysis. Found: C,51.4; H,8.0;

$C_{10}H_{19}BrO$ requires C,51.1; H,8.1%.

2-(4-Bromopentyl)-2-butyl-1,3-dioxolane (265)

A mixture of the ketone (264) (2.03g, 8.6mmol), ethylene glycol (2ml) and pTSA (150mg) in toluene (20ml) were heated under Dean-stark conditions for 20h. 1M Sodium hydrogen carbonate solution was added and the mixture was extracted with ether (3 x 20ml). The organic extracts were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a colourless oil. Purification by flash chromatography [30mm, hexane-ether (14:1)] gave the ketal (265) as a colourless oil (2.15g, 89%).

^1H δ ($CDCl_3$; 80MHz): 3.92 (4H, s, ketal), 3.40 (2H, t;*J*=6.6Hz, CH_2Br), 2.1-0.8 (17H, m).

$\nu_{max.}$ (Thin film): 2940(m), 2860(m), 1450(m) cm^{-1}.

m/z No M^+, 221/223 (80%, M-C_4H_9).

Analysis. Found: C,51.9; H,8.1;

$C_{12}H_{23}BrO_2$ requires C,51.6; H,8.3%.

[5-(2-Butyl-1,3-dioxolan-2-yl)pentyl]phenylsulphone (266)

A suspension of sodium benzene sulphinate (1.44g, 8.77mmol), sodium iodide (30mg) and the bromide (265) (2.04g, 7.31mmol) in dry DMF (10ml) was stirred at 20°C for 6 days. Water (25ml) was added and the mixture was extracted with ether (3 x 25ml). The organic extracts were washed with water (twice) and brine, combined, dried ($MgSO_4$) and evaporated to give a colourless oil. Purification by flash chromatography [40mm, hexane-ether(1:1)] gave two fractions:-

FR1 Colourless oil 208mg, 8%.

Probably the sulphinite ester.

FR2 Colourless oil 1.84g, 74%.

This is the required sulphone (266).

^1H δ ($CDCl_3$; 80MHz): 7.7 (5H, m, Ar), 3.89 (4H, s, ketal), 3.1 (2H, m, CH_2SO_2), 2.1-0.8 (17H, m).

$\nu_{max.}$ (Thin film): 3600(w), 2970(s), 2880(s), 1600(w), 1460(m) cm^{-1}.

m/z No M^+, 283(40%, $M-C_4H_9$).

Analysis. Found: C,63.8; H,8.3; S,9.5;

$C_{18}H_{28}O_4S$ requires C,63.5; H,8.3; S,9.4%.

(4aα, 6α, 8aβ)-2,2-dimethyl-hexahydro-5- (4-methylphenylsulphonyl)-6-[6-(2-butyl-1,3-dioxolan-2-yl)-3- phenylsulphonylheptyl]-4*H*-1,3-dioxino[5,4-*b*]-6-pyridine (267)

Butyl lithium (0.85 ml, 1.6M, 1.36mmol) was added to a solution of the sulphone (266) (466mg, 1.37mmol) in THF (5ml) at -78°C and the yellow solution was stirred for 20 min. A solution of the bromide (258) (175mg, 0.40mmol) in THF (4ml) was added and the mixture was allowed to warm to 20°C over 1.5h. Sat. ammonium chloride solution (1ml) and water were added and the mixture was extracted with ether (3 x 10ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a yellow oil. Purification by flash chromatography [20mm, hexane-ether (2:3)] then [20mm, hexane-ether (1:2)] gave the sulphone (267) as a pale yellow viscous gum (261mg; containing 0.8%wt CH_2Cl_2, 96%).

^1H δ ($CDCl_3$; 250MHz): 7.88, 7.6 and 7.3 (9H, m, Ar), 4.2 (2H, m, H6 and H1'), 4.0 (1H, m, H1'), 3.9 (4H, s, ketal), 3.46 (1H, m, H3), 3.0 (2H, m, $CHSO_2$and H2), 2.43 and 2.42 (3H, 2 x s, MeAr), 1.9 - 1.3 (28H, m), 0.9 (3H, m, Me).

$\nu_{max.}$ ($CHCl_3$): 2950(s), 2870(s), 1600(m), 1490(m) cm^{-1}.

m/z No M^+, 578(8%), 536(22%, M-Ts), 478(68%).

Found: 536.3057. $C_{29}H_{46}NO_6S$ (M-Ts) requires 536.3046.

(4aα, 6α, 8aβ)-2,2-dimethyl-hexahydro-6- [6-(2-butyl-1,3-dioxolan-2-yl)heptyl]-4*H*-1,3-dioxino[5,4-*b*]-6- pyridine (270)

6% Sodium amalgam (828mg) and disodium hydrogen phosphate (310mg) were added to a solution of the sulphone (267) (249mg, 0.36mmol) in dry methanol (5ml) and the mixture was stirred at 20°C for 1h. Further sodium amalgam (880mg) and phosphate (350mg) were added and stirring was continued for 2h. Portions of amalgam (50mg) were added at hourly intervals for 8h; it was stirred for a further 16h, portions added hourly for 10h and then stirred for 14h. The reaction was quenched with sat. potassium carbonate solution and extracted with CH_2Cl_2 (4 x 15ml). The combined organic layers were dried (Na_2SO_2) and evaporated to give a pale yellow oil. Purification by flash chromatography [15mm, dichloromethane-ethanol-ammonia (200:8:1)] gave two fractions:-

FR1 yellow oil 168mg; a mixture of starting material and de-sulphonated compound.

FR2 Yellow oil 46mg.

FR1 Was recycled by treatment with sodium amalgam (1.8g) and phosphate (450mg) in methanol (2ml) over 90h and then worked up and purified as above to give a pale yellow oil (40.5mg). Total yield of the amine (270) is 86.5mg, 61%, containing 25 mol% of sulphone-amine (269) (by n.m.r. integration).

^1H δ ($CDCl_3$; 250MHz): 3.9 (4H, s, ketal), 3.6 (3H, m), 2.8 (2H, m), 2.0-1.1 (30H, m), 0.9 (3H, m, Me). Also 7.6 (m, Ar), sulphone-amine impurity.

$\nu_{max.}$ ($CHCl_3$): 3300(broad, w), 2960(s), 2870(s), 1715(w), 1600(w), 1490(m).

m/z 397(1%, M^+), 382(15%, M-Me), 340(30%, M-C_4H_9); also 522(sulphone M^+-C_4H_9).

M^+ Found: 397.3190. $C_{23}H_{43}NO_3$requires 397.3192.

(+)-Isoprosopinine B (85)

A solution of the ketal-amine (270) (85.5mg, 0.22mmol) in 85:15 methanol-conc. HCl (1.5ml) was stirred at 20°C for 3h. Saturated potassium carbonate solution (2ml) and 5M sodium hydroxide (2ml) were added and the mixture was extracted with CH_2Cl_2 (3 x 10ml). The organic extracts were washed with basic brine, combined, dried ($MgSO_4$) and

evaporated to give a yellow oil. Purification by flash chromatography [10mm, dichloromethane-ethanol-ammonia (50:8:1)] gave two fractions:-

FR1 Colourless oil 18.9mg (28%). This is the sulphone (271).

FR2 White solid 45.3mg, 67%. Isoprosopinine B (85).

FR2 was crystallised from ethyl acetate to give (+)-Isoprosopinine B (29.2mg) as a fine white powder, m.p. 90-1°C.

^{1}H δ ($CDCl_3$; 250MHz): 3.65 (1H, dd;*J*=10.8, 7.6Hz, H1'), 3.62 (1H, dd;*J*=10.8, 5.5Hz, H1'), 3.55 (1H, ddd;*J*=6.5, 5.5, 4.2Hz, H3), 2.88 (1H, dt;*J*=7.7, 5.5Hz, H2), 2.75 (1H, m, H6), 2.38 (4H, t;*J*=7.5Hz, CH_2CO), 2.05 (3H, broad), 1.8-1.1 (20H, m), 0.90 (3H, t;*J*=6.8Hz, Me).

^{13}C δ ($CDCl_3$; 63MHz): 211.4, 67.9, 62.9, 58.4, 49.9, 42.7, 42.5, 33.8, 29.4, 29.3, 29.2, 28.6, 27.3, 26.2, 26.1, 23.8, 22.4, 13.8.

$\nu_{max.}$ ($CHCl_3$): 3620(m), 3460(broad), 2930(s), 2860(s), 1710(s) cm^{-1}.

m/z 314(3%, MH^+), 312(5%, M-H), 282(100%, M-CH_2OH), 130(65%, M-$C_4H_9COC_7H_{14}$-).

Analysis. Found: C,68.7; H,11.0; N,4.3;

$C_{18}H_{35}NO_3$ requires C,69.0; H,11.3; N,4.5%.

Methyl (*exo*)-5-oxo-2-phenylmethyl-2-azabicyclo[2.2.2]octanyl-3-carboxylate (283)
Methyl (*endo*)-5-oxo-2-phenylmethyl-2-azabicyclo[2.2.2]octanyl-3-carboxylate (284)

Benzylamine (210mg, 1.96mmol) and UG1 alumina (0.45g) were added to a solution of methyl glyoxylate (173mg, 1.96mmol) in dichloromethane (2ml) and the mixture was stirred for 20min and then filtered under nitrogen. Zinc chloride (360mg, 2.6mmol) was added to this solution (now in 4ml CH_2Cl_2) and a solution of the silyloxydiene (141) (400mg, 1.2eq.) in dichloromethane (0.5ml) was added. The mixture was stirred for 4h at 20°C. Sodium bicarbonate solution (10ml, 1M) was added and the mixture was extracted with dichloromethane (3 x 15ml). The organic extracts were washed with brine, combined, dried (Na_2SO_4) and evaporated to give a brown gum. Purification by flash chromatography (20mm, dichloromethane - ethyl acetate (19:1)) then (20mm, hexane - ether (2:3)) gave four fractions:-

FR1 Pale yellow solid 69mg (13%). *Exo.*

FR2 Brown oil 112mg (21%). *Endo.*

FR3 Orange oil 48mg (9%).

FR4 Orange oil 34mg (6%).

FRs 3 and 4 were shown by n.m.r. to be mixtures containing some 'aldol' products but further chromatography did not give any purer material.

FR1 was crystallised from hexane – CH_2Cl_2 to give the *exo* adduct (283) as opaque plates m.p. 80-1°C.

^1H δ ($CDCl_3$; 250MHz): 7.45 (5H, m, Ar), 3.76 (1H, d;*J*=13.3Hz, CH_2N), 3.67 (1H, d;*J*=13.3Hz, CH_2N), 3.66 (3H, s, OMe), 3.56 (1H, m, H3), 3.12 (1H, m, H1), 2.77 (1H, dt;*J*=19.0,2.8Hz, H6endo), 2.69 (1H, m, H4), 2.1 (1H, dd;*J*=19.0,2.3Hz, H6exo), 2.05 (2H, m), 1.6 (2H, m).

$\nu_{max.}$ ($CHCl_3$): 2960(shoulder), 2820(m), 1730(s), 1440(m) cm^{-1}.

m/z 273(7%, M^+), 214(100%, M-CO_2Me), 172(85%, M-CO_2Me -CH_2CO), 91(100%).

Analysis. Found: C,70.4; H,6.9; N,5.1;

$C_{16}H_{19}NO_3S$ requires C,70.3; H,7.0; N,5.1%.

FR2 was crystallised from ether to give the *endo* adduct (284) as colourless plates, m.p. 68-9°C.

^1H δ ($CDCl_3$; 250MHz): 7.4-7.2 (5H, m, Ar), 3.85 (1H, d;*J*=13.2Hz, CH_2N), 3.77 (1H, d;*J*=13.2Hz, CH_2N), 3.57 (3H, s, OMe), 3.41 (1H, d;*J*=0.9Hz, H3), 3.10 (1H, m, H1), 2.65 (1H, dt;*J*=18.3,3.1Hz, H6endo), 2.52 (1H, m, H4), 2.3-1.4 (5H, m).

$\nu_{max.}$ ($CHCl_3$): 2820(m), 1730(s), 1440(w) cm^{-1}.

m/z No M^+; 214(85%, M-CO_2Me), 172(80%, M-CO_2Me -CH_2CO), 91(100%).

Analysis. Found: C,70.4; H,6.8; N,5.0;

$C_{16}H_{19}NO_3S$ requires C,70.3; H,7.0; N,5.1%.

Methyl Phenylmethoxyiminoacetate (293)

O-Benzylhydroxylamine hydrochloride (1.01g, 6.3mmol), sodium sulphate (200mg) and sodium acetate (549mg, 6.6mmol) were added to a solution of distilled methyl glyoxylate (555mg, 6.3mmol) in methanol (8ml) and the suspension was stirred for 3h. 1M sodium hydrogen carbonate was added and the mixture was extracted with CH_2Cl_2(3 x 20ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a cloudy oil. Purification by flash chromatography (20mm, 100mm column length, CH_2Cl_2) gave the required oxime (293) as a slightly cloudy oil (1.13g, 93%).

^1H δ ($CDCl_3$; 90MHz): 7.65 (1H, s, CH), 7.5 (5H, s, Ph), 5.32 (2H, s, CH_2O), 3.90 (3H, s, OMe).

$\nu_{max.}$ ($CHCl_3$): 2960(m), 1740(s), 1600(m), 1440(m) cm^{-1}.

m/z 193 (100%,M^+).

Analysis. Found: C,62.5; H,5.8; N,7.4;
$C_{10}H_{11}NO_3$ requires C,62.2; H,5.7; N,7.3%.

p-Toluenesulphinamide (298)

Sodium toluenesulphinate (14.81g, 69.1mmol) was added over 10min to thionyl chloride (37ml) under a stream of nitrogen and then stirred for 2h. The yellow oil was allowed to stand for 2h and then the oil was removed from the solid precipitate by pipette. This was evaporated, diluted with ether and re-evaporated. Distillation under reduced pressure gave a yellow oil (8.43g, 70%) b.p. 58-60°C/0.1mmHg.

This oil was dissolved in ether (15ml) and added to a mixture of ether (170ml) and liquid ammonia (40ml) over 15min at -50°C and then allowed to warm to ambient temperature. Water was added, the organic layer was separated and the aqueous was extracted with dichloromethane (2 x 30ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give an off-white powder. Crystallisation from methyl acetate (after a hot filtration) gave the title compound (298) as fine white flakes (4.73g, 63%) m.p 119-120°C. (lit.[160]120°C).

A second crop from the mother liquors yielded a further 1.38g (18.5%).

^1H δ ($CDCl_3$; 80MHz): 7.6 and 7.25 (4H, AB, Ar), 4.28 (<2H, broad, NH_2), 2.41 (3H, s, MeAr), 1.61 (,0.5H, broad, H-bonding to water in solvent ?).

$\nu_{max.}$ ($CHCl_3$): 3400 and 3300 (s, NH_2), 3220(shoulder), 1600(m), 1550(m, broad) cm^{-1}.

m/z 155(45%, M^+), 139(100%, M-NH_2or M-O), 107(80%).

Analysis. Found: C,54.1; H,5.7; N,8.9; S,20.9;
C_7H_9NOS requires C,54,2; H,5.8; N,9.0; S,20.7%.

1,4-Bis[(1,1-dimethylethyl-dimethyl)silyloxy]but-2-ene (308)

Buten-1,4-diol (0.81ml, 9.96m$_{\text{mol}}$) was added to a solution of TBDMS chloride (3.69g, 24.5mmol) and imidazole (3.65g, 53mmol) in DMF (15ml) and the mixture was stirred for 3h. Water (50ml) was added and the mixture was extracted with ether (3 x 40ml). The organic layers were washed with water and then brine, combined, dried ($MgSO_4$) and evaporated to give a colourless oil. Purification by flash chromatography (30mm, hexane - ether (3:1)) gave the title compound (308) as a colourless oil (2.83g, 90%).

^1H δ ($CDCl_3$; 80MHz): 5.5 (2H, m), 4.2 (4H, m), 0.89 (18H, s, ^{t}Bu), 0.06 (12H, s, SiMe).

$\nu_{max.}$ ($CHCl_3$): 3200(m), 2940(s), 2860(s), 2710(w), 1470(s), 1460(s), 1400(m) cm^{-1}.

m/z No M^+, 259(15%, M-^{t}Bu), 189(20%), 147(100%).

Analysis. Found: C,60.9; H,11.7;
$C_{16}H_{36}O_2Si_2$ requires C,60.7; H,11.5%.

2-(1,1-Dimethylethyldimethylsilyloxy)ethan-1-ol (313)

A solution of TBDMS chloride (1.76g, 11.68mmol) and imidazole (1.60g, 23.5mmol) in DMF (10ml) was added over 4min to a solution of ethylene glycol (2.5ml) in DMF (3ml) and stirred for 2h. Water (80ml) was added and the mixture was extracted with ether (4 x 30ml). The organic layers were washed with water and then brine, combined, dried ($MgSO_4$) and evaporated to give a pale brown oil. Purification by flash chromatography (30mm, hexane - ether (2:1)) gave the title compound (313) as a colourless oil (1.02g, 51%).

^1H δ ($CDCl_3$; 80MHz): 3.7 (4H, m), 1.9 (1H, broad, OH), 0.9 (9H, s, ^tBu), 0.07 (6H, s, SiMe).

$\nu_{max.}$ ($CHCl_3$): 3400(m,broad), 2960(s), 2940(s), 2860(s), 1470(m), 1460(m) cm_{+1}.

m/z 177(3%, MH^+), 161(5%, M-Me), 119(35%, M-^tBu), 75(100%).

Analysis. Found: C,54.3; H,11.2;
$C_8H_{20}O_2Si$ requires C,54.5; H,11.4%.

Attempted Diels–Alder Reaction of the Imine (140) with Lithium and Dimethylaluminium Enolates.

The lithium enolate of cyclohexenone was prepared by adding cyclohexenone (158) (0.3ml, 3.1mmol) in THF (3ml) to a solution of LDA (3.2mmol) in THF–Hexane (4ml, 1:1) over 15min at -78°C and then stirring for a further 15min. The solution was then split into two equal portions.

Lithium Enolate

One of the portions of lithium enolate (1.6mmol) was added over 2min to a solution of crude imine (140) (1.3mmol) in CH_2Cl_2 (2ml) at -78°C and the resultant solution was stirred for 1.5h. Sat. ammonium chloride was added, the mixture allowed to warm to 20°C basified with sodium bicarbonate solution and extracted with CH_2Cl_2 (3 x 15ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a yellow oil. Purification by flash chromatography [20mm, hexane – ether (1:3)] gave an off–white solid (218mg), which was shown by 250MHz n.m.r. to be a 62:38 mixture of Aldol I : Aldol II containing 54mol% (38% by weight) of toluenesulphonamide. Yield = 30%.

Dimethylaluminium Enolate

A solution of dimethylaluminium chloride in toluene (3ml, 1.6M, 4.8mmol) was added to the other half of the lithium enolate solution (1.6mmol) at -78°C and the resultant solution was stirred for 15min. This solution was then added to a solution of the crude imine (1.3mmol) in CH_2Cl_2 (2ml) at -78°C and stirred at -78°C for 3h. Saturated ammonium chloride solution was added, the mixture allowed to warm to 20°C basified with sodium bicarbonate solution and extracted with CH_2Cl_2 (3 x 15ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a yellow oil. Purification by flash chromatography [20mm, hexane – ether (1:3)] gave a white gum (134mg), which was shown by 250MHz n.m.r. to be an 88:12 mixture of Aldol I : Aldol II containing 42% by weight of toluenesulphonamide. (Yield = 17%).

TBAF Treatment of the TBDMS Enol Ether (160)

Tetrabutylammonium fluoride (TBAF) (0.12ml, 1.0M in THF, 0.12mmol) was added to a solution of the silylenol ether (160) (38mg, 0.1mmol) in THF (0.5ml) at 20°C and the solution was stirred for 50min. Water (1ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 5ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a brown oil (30mg, >100%). T.l.c. analysis indicated

that no starting material was present and that Aldol II was the predominant product with some *exo* (142) and traces of the *endo* (143) and Aldol I (156) isomers.

Hydrolysis of Silyl Enol Ether (160)

A solution of the silyl enol ether (160) (26mg, 0.06mmol) in acetic acid – water – THF (2ml, 1:1:3) was heated at 50°C for 15h. This was poured into aqueous sodium bicarbonate and extracted with CH_2Cl_2 (3 x 7ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a colourless oil (19.5mg, 100%). 250MHz n.m.r. showed this to be an 8:1 mixture of *exo* : Aldol II with a trace of *endo* isomer.

Hydrolysis of Silyl Enol Ether (161)

A solution of the silyl enol ether (161) (43mg, 0.10mmol) in acetic acid – water – THF (2ml, 1:1:3) was heated at 50°C for 48h and at 20°C for 16h. This was poured into aqueous sodium bicarbonate and extracted with CH_2Cl_2 (3 x 7ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a colourless oil. Purification by flash chromatography [10mm, CH_2Cl_2 – ethyl acetate (19:1)] gave a colourless oil (36.3mg, 100%). 250MHz n.m.r. showed this to be a 9.5:1 mixture of *endo* : Aldol I with a trace of *exo* isomer.

Methyl (*exo*)-3-oxo-6-*p*-toluenesulphonyl-2-oxa-6- azabicyclo[3.2.2]nonanyl-7-carboxylate (209)

Methyl (*exo*)-2-oxo-6-*p*-toluenesulphonyl-3-oxa-6- azabicyclo[3.2.2]nonanyl-7-carboxylate (210)

To a solution of the *exo* ketone (142) (988mg, 2.93mmol) in CH_2Cl_2 (10ml) at 0°C was added disodium hydrogen phosphate (5.01g, 35.3mmol) and then a solution of trifluoroperacetic acid (17.6ml) in CH_2Cl_2 (5ml) (containing 17.6mmol of trifluoroacetic acid) and the mixture was stirred at 20°C for 18h. The mixture was poured into aqueous sodium sulphite solution, basified with sodium bicarbonate solution and extracted with CH_2Cl_2 (3 x 40ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a colourless oil. Purification by flash chromatography [40mm, CH_2Cl_2 - ethyl acetate (19:1) then (14:1)] gave three fractions:-

FR1 Colourless oil 234mg (23%). Mixed fraction of starting material and lactone (210).

FR2 White solid 290mg (28%). Methylene–migrated lactone (210).

FR3 White solid 381mg (37%). Bridgehead–migrated lactone (209).

Both lactones were identical by spectroscopic methods (n.m.r.) to those prepared by Thompson.[85]

Attempted Baeyer-Villiger Oxidation using Magnesium Monoperoxyphthalate (MMPP)

A solution of magnesium monoperoxyphthalate hexahydrate (MMPP) (315mg, 0.64mmol) in water (3ml) was added to a solution of *exo* (142) (55mg, 0.16mmol) and benzyltriethylammonium chloride (12mg) in ethanol-free chloroform (2.5ml) and the mixture was stirred at 50°C for 22 days. The mixture was poured into saturated sodium sulphite solution and extracted with dichloromethane (3 x 10ml). The organic extracts were washed with brine, combined, dried and evaporated to give a pale yellow oil. Purification by flash chromatography [10mm, dichloromethane- ethyl acetate (19:1)] gave three fractions:-

FR1 White solid 44mg (79%). Recovered starting material.

FR2 Colourless oil 0.5mg (1%). This is the methylene-migrated lactone (210) by t.l.c. comparison with an authentic sample.

FR3 White solid 1.5mg (2.7%). This is the bridgehead migrated lactone (209) by t.l.c. comparison with an authentic sample.

Attempted Baeyer-Villager Oxidation of the 6-Bromo-ketone (192)

Trifluoroperacetic Acid

Trifluoroperacetic acid (1ml of a 1M solution in CH_2Cl_2 1mmol containing 1mmol of trifluoroacetic acid) was added at 0°C to a stirred mixture of the bromo-ketone (193) (67mg, 0.19mmol) and disodium hydrogen phosphate (307mg, 2.16mmol, 2.1eq w.r.t peracid) in CH_2Cl_2 (1ml) and the mixture was stirred at 20°C for 9h. T.l.c. analysis showed the presence of starting material and a new lower Rf compound. Further disodium hydrogen phosphate (593mg, 4.1mmol), CH_2Cl_2 (2ml) and 1M peracid solution (2ml, 2mmol) were added and the mixture was stirred for 27h at 20°C A further batch of peracid (3mmol in 4ml CH_2Cl_2) was added with more phosphate (895mg), and stirring continued for 24h. More peracid (2mmol in 2ml CH_2Cl_2) and phosphate (590mg) were added and stirring continued for 5 days. (A total of 42eq of trifluoroperacetic acid had been added). The mixture was poured into sodium sulphite solution, basified with sodium bicarbonate solution. The aqueous phase was extracted with dichloromethane (2 x 15ml)

and the organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography (10mm, CH_2Cl_2) gave two fractions:-

FR1 White solid 6.1mg (9%). Recovered starting material

FR2 White solid 10.8mg (15.5%).
N.m.r. spectrum (250MHz) suggests that this is a mixture of 4 compounds (4 OMe signals at δ3.7). Three sets of aromatic signals are visible but there is only a very small signal around δ3 corresponding to H4 (α to C=O) in the starting material.

Peracetic Acid

25% Peracetic acid in acetic acid (0.2ml, 0.8mmol) was added to a suspension of sodium acetate (156mg, 1.9mmol) in a solution of the bromo-ketone (193) (54.9mg, 0.13mmol) in acetic acid (1ml) and the mixture was stirred at 50°C for 3 days. Further peracid (0.2ml) was added and the mixture was stirred at 50°C for 2 days. The mixture was poured into aqueous sodium sulphite solution, basified with aqueous sodium bicarbonate and then extracted with CH_2Cl_2 (3 x 20ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give a pale yellow oil. Purification by flash chromatography [10mm, hexane-ether (1:2)] gave two fractions:-

FR1 White solid 33.9mg - mixture re-purified as below.

FR2 Colourless oil 4.1mg (9%).
Shown to be *exo* (142) by t.l.c. comparison with an authentic sample.

FR1 was re-columned [19mm, hexane-ether (1:1)] to give two fractions and a mixed fraction.

FR3 White solid 1.1mg (13%). Mono-bromoketone (193) by n.m.r.

FR4 Pale yellow oil 21mg (38%). Mixture of fractions 3 and 5.

FR5 White solid 6.5mg (10%). Dibromo compound (220) by n.m.r.

Attempted De-protonation and Deuterium Quench of the TBDMS Cyanohydrin (237)

A solution of the silyl cyanohydrin (237) (86mg, 0.36mmol) in THF (1.5ml) was added dropwise over 30min to a solution of LDA (0.54mmol) in THF (4ml) at -10°C and the resultant solution was stirred at -10°C for 5min. Monodeuterioacetic acid (0.3ml) was added to quench the reaction which was then basified with aqueous sodium bicarbonate. The aqueous layer was extracted with ether (3 x 10ml) and the combined organic layers

were washed with brine, dried ($MgSO_4$) and evaporated to give a yellow oil (85mg). N.m.r. (90MHz) shows that the mixture contains some protonated starting material (triplet at δ4.5, ca.40%) but there are multiplets visible at δ2.7-2 which are not present in the starting material. At least two sets of Me_2Si signals are present. T.l.c. indicated that starting material was present together with considerable amounts of base–line material.

In other deuterium–quench reactions the isolated material was purified by flash chromatography.

A solution of the cyanohydrin (85mg, 0.35mmol) in THF (1ml) was added over 5min to a solution of butyl lithium (0.25ml, 1.55mmol in hexane, 0.39mmol) in THF (1ml) at -78°C and the solution was stirred for 15min and then quenched by the addition of D_2O (0.3ml). Water was added and the mixture was extracted with ether (3 x 10ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give a yellow oil (100g). Purification by flash chromatography [10mm, hexane - CH_2Cl_2 (3:1)] gave two fractions:-

FR1 Oil 6mg Recovered starting material with very little deuterium incorporation by n.m.r.

FR2 Colourless oil 49mg.

^1H δ ($CDCl_3$; 90MHz): 4.4 (t;J=13.8Hz, trace impurity [12%]), 3.99 (1H, t;J=13Hz, O-CHC=O ?), 2.51 (2H, t;J=16Hz, CH_2CO ?), 1.8-1.1 (>13H [15H], m), 1.0-0.7 (>6H, m, Me), 0.91 (9H, s, ^{t}BuSi), 0.17 and 0.12 (2 x s, MeSi, trace impurity [14%]), 0.03 (6H, s, SiMe).

$\nu_{max.}$ (Thin film): 3400(w), 2960(s), 2930(s), 2850(s), 1710(m), 1460(m)cm^{-1}.

This is probably the α-silyloxy ketone (239) containing 12-14% of a silyl–containing impurity.

1-Bromo-5-decanone (236)

Cerium Reagent Method

A solution of pentyl magnesium bromide in ether (5ml) was prepared from magnesium (198mg, 8.15mmol) and pentyl bromide (1.13g, 7.5mmol). This was added to a suspension of cerium III chloride (dried at 150°C for 2h) (1.85g, 7.48mmol) in dry THF (5ml) at 0°C and the mixture was stirred at 0°C for 1.5h. A solution of bromovaleronitrile (241) (1.10g, 6.8mmol) in THF (4ml) was added and the mixture was stirred at 0 – 10°C for 4.5h. Saturated ammonium chloride (3ml) was added and the mixture was extracted with ether (3 x 10ml). The organic layers were washed with sodium bicarbonate solution

and then with brine, combined, dried ($MgSO_4$) and evaporated to give a pale brown oil (1.01g). Purification by flash chromatography [30mm, petrol – ether (14:1 then 9:1)] gave two fractions:-

FR1 Colourless oil 328mg (20.5%).
Ketone (236) identical with material prepared previously.

FR2 Colourless oil 126mg (11.5%).
Recovered starting material.

N.m.r. Data for FR2 From the Preparation of the Sulphone (252)

^1H δ ($CDCl_3$; 80MHz): 7.8-7.4 (5H, m, Ar), 4.3-3.95 (1H, m), 3.90 (4H, s, ketal), 3.8-3.4 (1H, m), 2.35 (0.3H, m, impurity ?), 1.8-1.1 (>14H [integrates for 18H], m, CH_2), 0.9 (3H, m, Me).
Probably the impure sulphinite ester (253).

N.m.r. Data for First Fraction Isolated from the Preparation of the Sulphone (266)

^1H δ ($CDCl_3$; 80MHz): 7.8-7.4 (5H, m, Ar), 4.3-3.95 (1H, m), 3.92 and 3.90 (4H, 2 x s, ketal), 3.8-3.4 (>1H, m), 2.35 (0.6H, m, impurity ?), 1.8-1.1 (>14H [integrates for 19H], m, CH_2), 0.9 (3H, m, Me).
Probably impure sulphinite ester.

Preparation of the Chiral Imine (288) and its Diels–Alder Reaction with the Silyloxydiene (141)

To a solution of freshly prepared 8–phenylmenthyl glyoxylate (137) (see preparation of (196)) (490mg, 1.6mmol; containing 4% DMSO) in dry CH_2Cl_2 (3ml) at 0°C under nitrogen was added UG1 alumina (1.2g) then a solution of benzylamine (180mg, 1.68mmol) in CH_2Cl_2 (1ml). The mixture was stirred at 20°C for 50min, and then filtered under nitrogen. A one third portion of the filtrate was removed and evaporated for n.m.r. analysis.

^1H δ ($CDCl_3$; 90MHz): 7.3 (10H, m, Ar), 6.9 (<1H, t;J=1.5Hz, CH=N), 4.9 (1H, m, >CH-O-), 4.7 (<2H, t;J=1.5Hz, CH_2N), 4.0-3.3 (impurities), 2.5 (s, DMSO), 2.3-0.5 (17H, m).
The imine is >50% pure by n.m.r.

Zinc chloride (137mg, 1.02mmol) was added to the remaining solution in CH_2Cl_2 (1mmol in 3ml) under nitrogen. A solution of the silylyoxydiene (190mg, 1.1mmol) in dry

CH_2Cl_2 (1ml) was added to the cloudy suspension and the mixture was stirred at 20°C for 24h. Water (1ml) and THF – 0.005M HCl (4:1, 0.2ml) were added and the mixture was stirred for 1h. Sodium bicarbonate solution was added and the mixture was extracted with CH_2Cl_2 (3 x 15ml). The organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give an orange–yellow oil. Purification by flash chromatography [20mm, CH_2Cl_2 – ethyl acetate (49:1)] gave three fractions, none of which was pure by t.l.c.:-

FR1 Pale yellow oil 34mg.

FR2 Pale yellow oil 177mg.

FR3 Pale yellow oil 74mg.

Extensive preparative plate chromatography (CH_2Cl_2 – ethyl acetate (99:1) as eluant, 3 elutions per plate) of each of the above fractions, with re-chromatography of some of the more impure fractions isolated from the plates gave four fractions:-

FR4 Colourless oil 16mg.

FR5 Colourless oil 24mg.

FR6 White solid 146mg.

FR7 Yellow oil 37mg.

Close inspection of the n.m.r. spectra of the four fractions (250MHz, $CDCl_3$ and C_6D_6 solution) showed that four compounds, probably the isomeric esters (289 - 292) were present in unequal amounts. The isomers were labelled W, X, Y and Z.

The constitutions of the four fractions are:-

	W	X	Y	Z
FR4	0	14	76	10
FR5	75	0	25	0
FR6	0	90	0	10
FR7	0	19	67	14

The calculated ratios and yield of the four isomers are:-

	Ratio	% Yield	Centre of CH_2N signal ($CDCl_3$)
W	8.1	3.8	3.62
X	63.1	29.7	3.58
Y	19.2	9.0	3.72
Z	9.6	4.5	3.46

FR6 was crystallised from CH_2Cl_2 – hexane to give the major isomer (X) as fine white needles (101mg) m.p. 144-5°C.

^1H δ (C_6D_6; 250MHz): 7.58 (1H, d;J=6.8Hz, Ar), 7.2 (8H, m, Ar), 4.91 (1H, td;J=10.4,4.2Hz, >CHO-), 3.63 (1H, d;J=13.7Hz, CH_2N), 3.34 (1H, d;J=13.7Hz, CH_2N), 2.79 (1H, broad d;J=1.6Hz, H3), 2.67 (1H, m, H1), 2.55 (1H, m, H4), 2.42 (1H, dm;J=18Hz, H6), 2.0-0.6 (23H, m).

$\nu_{max.}$ ($CHCl_3$): 2980(s), 2880(s), 2720(m), 1730(s), 1600(w)cm^{-1}.

$[\alpha]_D^{20}$ -1.9° c=2.7 ($CHCl_3$).

Analysis. Found: C,78.0; H,8.3; N,2.9;

$C_{31}H_{39}NO_3$ requires C,78.6; H,8.3; N,3.0%.

Methyl (*S*)-*N*-1-phenylethyliminoacetate (282)

A solution of *S*-α-methylbenzylamine (291mg, 2.4mmol) in ether (1ml) and $MgSO_4$ (0.9g) were added to a solution of methyl glyoxylate (210mg, 2.38mmol) in ether (1ml) at 15°C and the mixture was stirred for 13h, filtered through "Celite" and evaporated to give a pale yellow oil (460mg, 100%).

^1H δ ($CDCl_3$; 90MHz): 7.7 (1H, s, CH=N), 7.3 (5H, m, Ph), 4.5 (1H, q;J=7Hz, CH-N), 3.7 (3H, s, OMe), 1.5 (3H, d;J=7Hz, Me-C).

_N_-Benzylidene-_p_-toluenesulphinimide (304)

Toluenesulphinamide (298) (174mg, 1.12mmol) and UG1 alumina (0.6g) were added to a solution of benzaldehyde (119mg, 1.12mmol) in CH_2Cl_2 (2ml) and the mixture was stirred for 7 days. Filtration and evaporation gave a colourles gum.

^1H δ ($CDCl_3$; 90MHz): 8.8 (1H, s, CH=N), 8.0-7.1 (9H, m, Ar), 4.4 (<0.5H, broad, trace impurity), 2.3 (3H, s, MeAr).

_N_-Ethylidene-_p_-toluenesulphinimide (305)

A suspension of toluenesulphinamide (298) (112mg, 0.72mmol) and UG1 alumina (0.4g) in acetaldehyde (3ml) was heated under reflux for 5h and stirred at 16°C for 17h. Filtration and evaporation gave an oil containing some solid.

^1H δ ($CDCl_3$; 90MHz): 9.7 (0.25H, q;J=2.5Hz, residual MeCHO), 8.1 (1H, q;J=5Hz, CH=N), 7.5 and 7.2 (>4H, m, Ar), 6.2 (broad, NH_2 in residual sulphonamide), 2.3 (>3H, s, MeAr), 2.0 (3H, s, Me-C), 1.8 (d, residual MeCHO), 1.5-0.9 (m, polymerised MeCHO ?).

The material is *ca.* 75% pure imine (305).

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