

SYNTHETIC APPROACHES TO TRICYCLIC AZA[10]ANNULENES

A Thesis presented by

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Finally and most importantly, my thanks are extended to my husband Howard, whose enthusiasm, advice and support has made the production of this thesis possible.

To my husband, Howard

ABSTRACT

The synthesis of a variety of azaannulenes is reviewed, and their properties are compared and contrasted with those of pyridine and the corresponding carbocyclic compounds.

Approaches to aza analogues of the novel 10π aromatic system, 7b-methyl-7bH-cyclopent[cd]indene, are discussed. The first of these employs the [8+2] cycloaddition reaction of 3-methoxy-3a-methyl-3aH-indene with various nitrogenous dienophiles. The use of either dimethyl azodicarboxylate or *bis*-trichloroethyl azodicarboxylate allows the formation of the corresponding tricyclic [8+2] adducts. However, further elaboration of these adducts to give the desired 1,2-diaza [10]-annulene was unsuccessful.

Isocyanates also prove to be effective dienophiles and both toluene-4-sulphonyl and chlorosulphonyl isocyanate give [8+2] cycloaddition products. The reaction of chlorosulphonyl isocyanate with 3-methoxy-3a-methyl-3aH-indene gives a mixture of regioisomeric [8+2] adducts in variable proportions. Both cycloadducts are readily hydrolysed to the corresponding lactams which may be further elaborated to the respective imidates. Although the lactams and imidates are formally direct precursors of the 1-aza and 2-aza [10]annulenes, these compounds have proved elusive. An ionic form of a substituted 2-aza-[10]annulene is postulated as an intermediate.

The second approach involves the formation of the final five-membered ring of the tricyclic system *via* a stepwise procedure. This is accomplished by reacting 5,7a-dihydro-7a-methyl-1H-inden-1-one with trimethylsilyl cyanide to give the corresponding trimethylsilyl cyano-hydrin. Subsequent reduction and cyclisation allows the isolation of

a high yield of the required tricyclic system, 2a-hydroxy-7b-methyl-2a,6,7,7b-tetrahydro-2H-cyclopent[cd]indole. While this compound could be dehydrogenated the final elimination to give the 1-aza[10]-annulene has yet to be achieved.

Approaches to the 1,2-diaza[10]annulene based on the cyclisation of hydrazines and hydrazones are also described.

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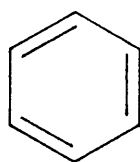
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1. INTRODUCTION

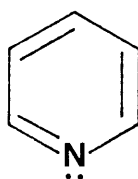
1.1 INTRODUCTION

The discovery of benzene (1) in 1825 and the subsequent investigation of its unusual properties generated interest in the subject of aromatic chemistry. In the 1930's the results of Hückel Molecular Orbital Theory led to the prediction that fully conjugated cyclic systems with $(4n + 2)\pi$ -electrons would be aromatic providing they adopted an approximately planar geometry¹. Those systems containing $(4n)\pi$ -electrons will be either antiaromatic or non aromatic. The subsequent years have seen the synthesis of many compounds which substantiate the validity of this rule.

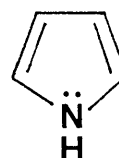
There are two types of heterocyclic compound which may exhibit aromatic character. Firstly, those in which a CH unit has been replaced by a heteroatom donating one electron to the π -system (*e.g.* pyridine (2)). This type of compound is known as π -deficient due to the lower electron density associated with each carbon atom compared to the corresponding carbocyclic system. This is a direct result of the electronegativity of the heteroatom. Secondly, where a CH = CH unit has been replaced by a heteroatom donating two electrons to the π -system (*e.g.* pyrrole (3)). These compounds are known as π -excessive due to the greater associated electron density at the carbon atoms.



(1)



(2)



(3)

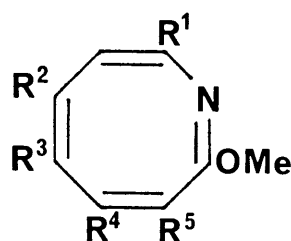
This review will be concerned with the higher homologues of pyridine and pyrrole which would be predicted by Hückel's Rule to possess aromatic character. Of the many criteria used to determine aromaticity, ring diamagnetism is the least equivocal. Other spectral characteristics as well as thermal stability and reactivity may be used as a guide to the presence or absence of aromatic character.

1.2 COMPOUNDS CONTAINING 10π - ELECTRONS

1.2.1 Eight Membered Rings

1.2.1.1 Containing one nitrogen atom

The dianion of cyclooctatetraene was shown to possess aromatic character by Katz² and this prompted the study of the related azocine system. The 2-alkoxyazocines (4a-e) have been prepared by Paquette and are thought to exist in a tub-shaped conformation³.



(4)

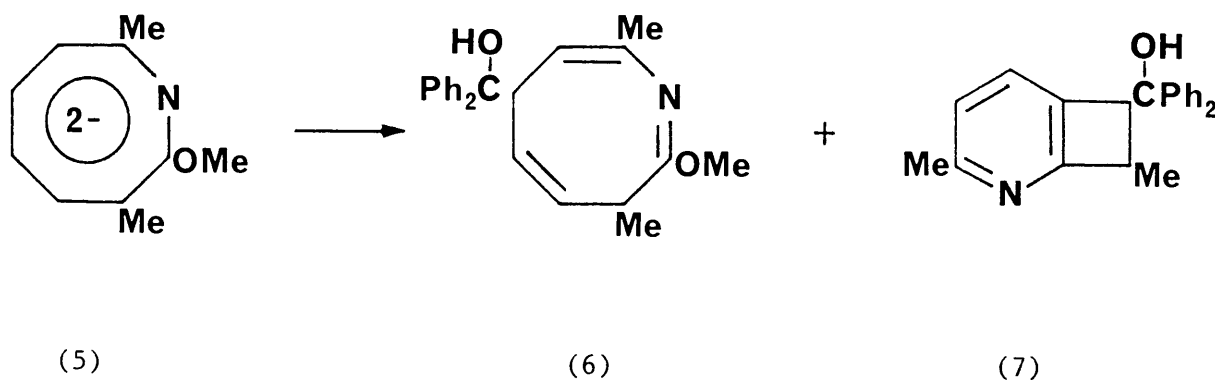
	R ¹	R ²	R ³	R ⁴	R ⁵
a	H	H	H	H	H
b	CH ₃	H	H	H	H
c	CH ₃	H	H	H	CH ₃
d	CH ₃	CH ₃	H	CH ₃	H
e	CH ₃	CH ₃	CH ₃	H	CH ₃

These compounds undergo ready electrochemical⁴ and chemical reduction⁵. Interestingly, in contrast to the behaviour of cyclooctatetraene, which undergoes two one-electron reductions, the azocines (4a-e)

are reduced *via* a two electron process to form the dianion directly. It is thought that the addition of the first electron gives a near planar radical anion which is more easily reduced than the parent heterocycle.

The aromatic nature of these dianions was ascertained from a comparison of the ^1H n.m.r. spectra of the dipotassium salts of (4e) and 1,3,5,7-tetramethylcyclooctatetraene. Protonation of the dianions gives rise to mainly 3,4- and 3,6-dihydroazocines. The lack of skeletal rearrangement products is seen as evidence for the stability of these anions and hence their aromaticity.

The dianions of (4a-e) have been reacted with benzophenone to give C_6 -monoalkylated products together with the 2,3-pyridocyclobutene derivatives in varying yields (Scheme 1)⁶.

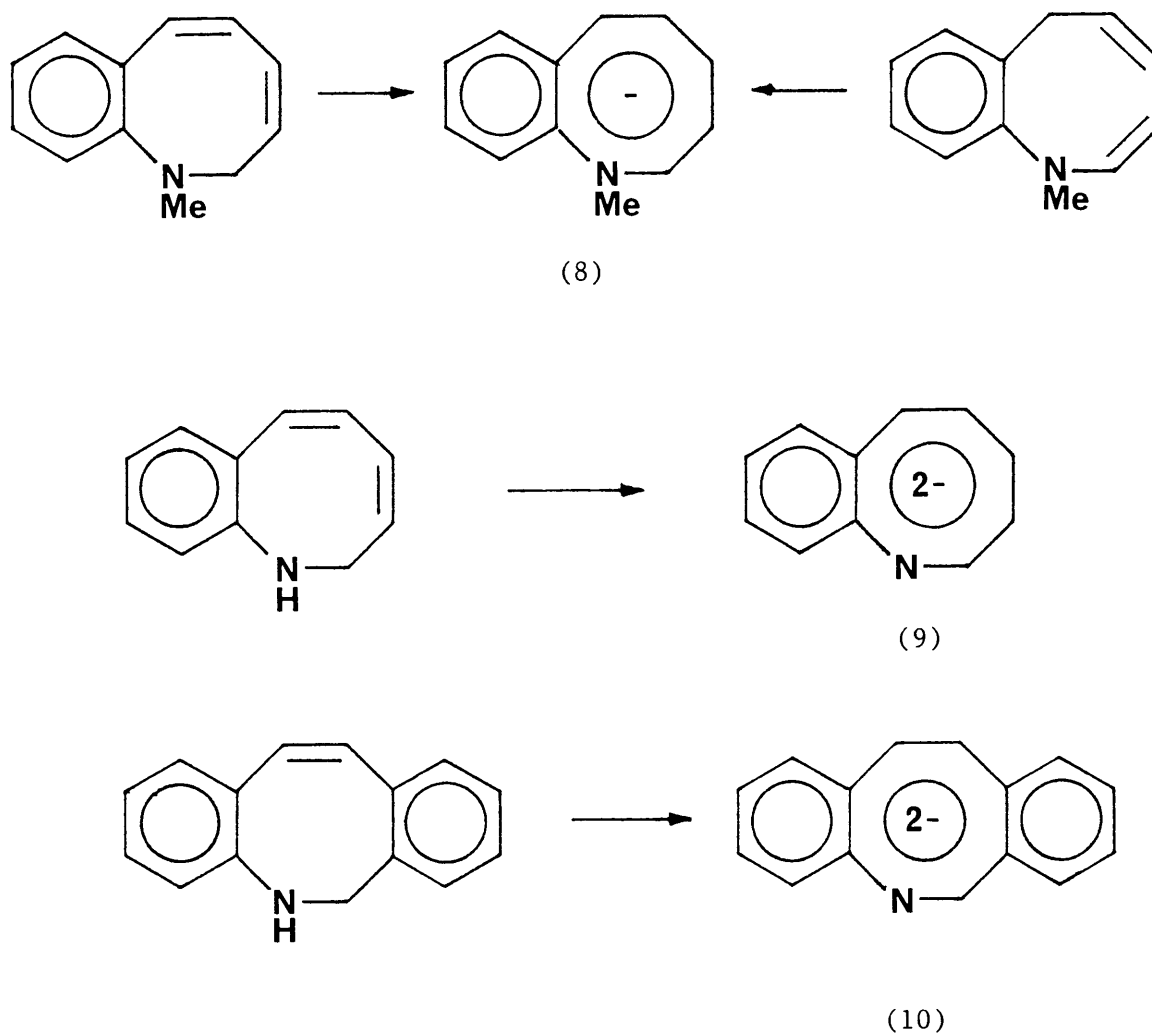


Scheme 1.

The reduction of several benzo fused derivatives of azocine have also been investigated⁷. It was found that the tendency to delocalise was dependent on the extent of benzo fusion as this is usually accompanied by bond fixation⁸.

Anastassiou has studied the behaviour of the isoelectronic anions

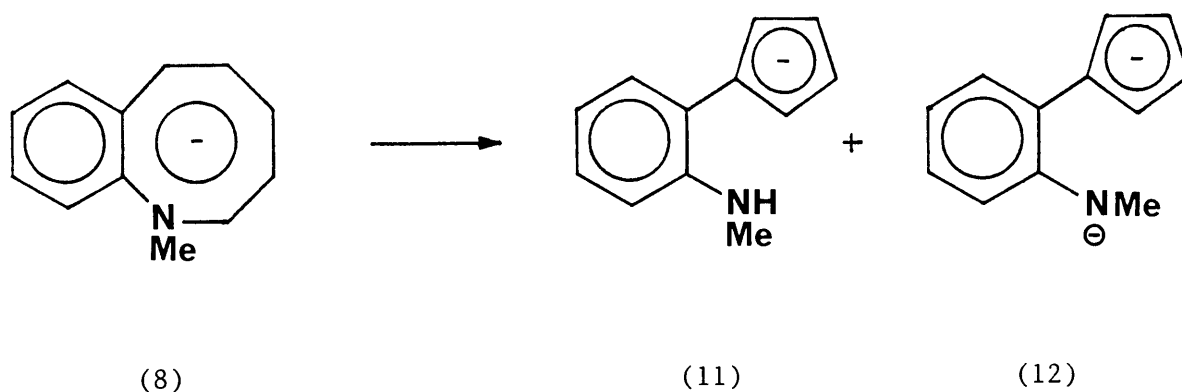
(8), (9) and (10) which were generated from the appropriate precursors on treatment with potassamide in liquid ammonia (Scheme 2)⁹.



Scheme 2.

The anion (8) was observed, from a comparison of the ^1H n.m.r. spectrum with that of a model compound, to have some degree of aromatic character. It was found, however, to be thermally labile and on warming rearranged to a mixture of anions (11) and (12).

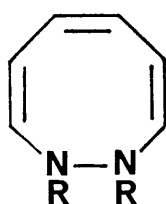
The anions (9) and (10) showed a substantial degree of diatropic π -mobility. The ^{13}C n.m.r. C-H coupling constants being significantly



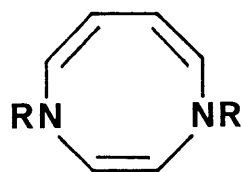
smaller than those found in the neutral molecule and this is normally indicative of molecular flattening¹⁰.

1.2.1.2 Containing two nitrogen atoms

There are two isomeric dihydrodiazocine systems which are iso- π -electronic with the dianion of cyclooctatetraene.

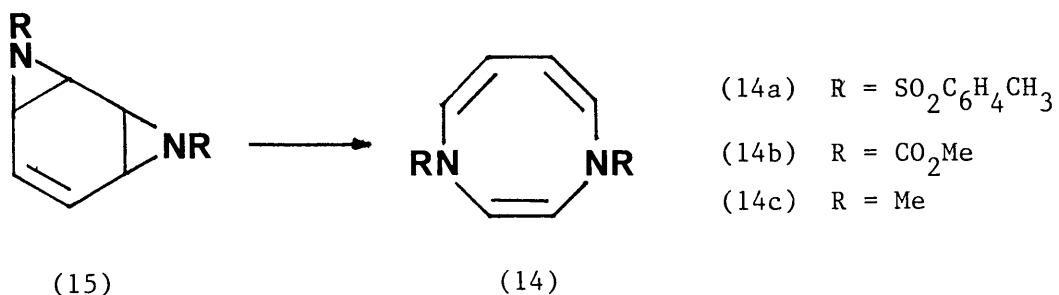


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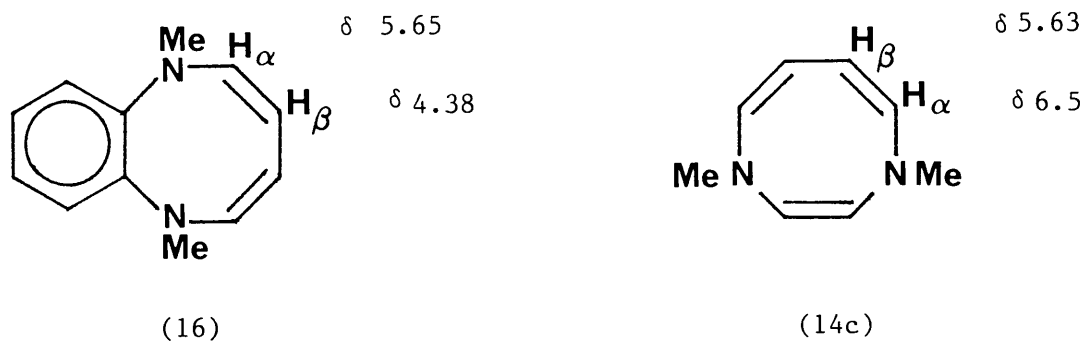


(14)

Of the two dihydrodiazocines (13) and (14) the 1,4-isomer has been more widely studied being first reported in 1975 by Prinzbach¹¹. The ring system was synthesised *via* the ready $2\sigma \rightarrow 2\pi$ isomerisation of *cis*-diazabis- σ -homobenzene derivatives (15).

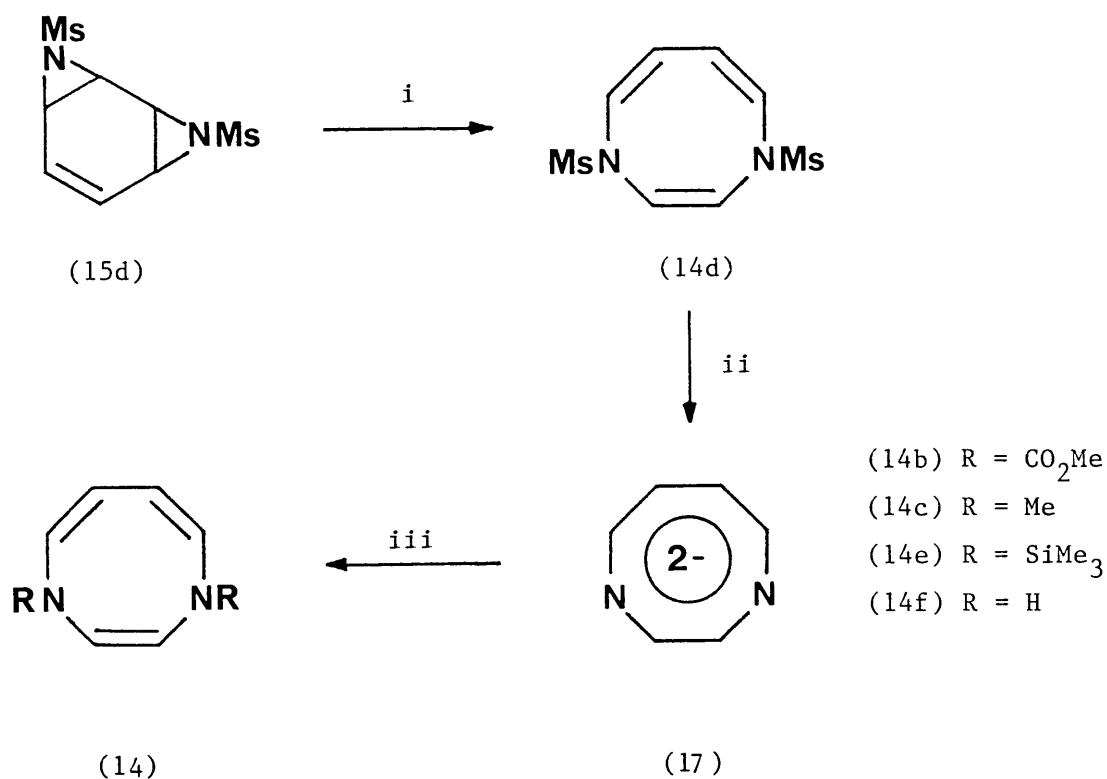


A comparison of the ^1H n.m.r. data of compound (14c) with 1,4,7-trimethyl-1*H*-4,7-dihydro-1,4,7-triazonines and the dihydro-dimethylbenzodiazocine (16)¹² shows a considerable downfield shift of the proton resonances, indicative of the presence of a significant diamagnetic ring current.



Several derivatives of the diheterocin system (14) have now been reported utilising the dianion (17) as a common intermediate¹³. This provides a good convergent synthesis of substituted 1,4-dihydro-1,4-diazocines (Scheme 4). The parent compound (14f) has been synthesised

independently by Prinzbach *via* alcoholysis of the urethane (14b)¹⁴. The stability of (14f) towards acid and base catalysed prototropic shift coupled with spectroscopic evidence indicates the aromatic nature of this compound. Compounds (14c) and (14e) were also considered to possess aromatic character while (14a), (14b) and (14d) were decidedly olefinic.



Scheme 3.

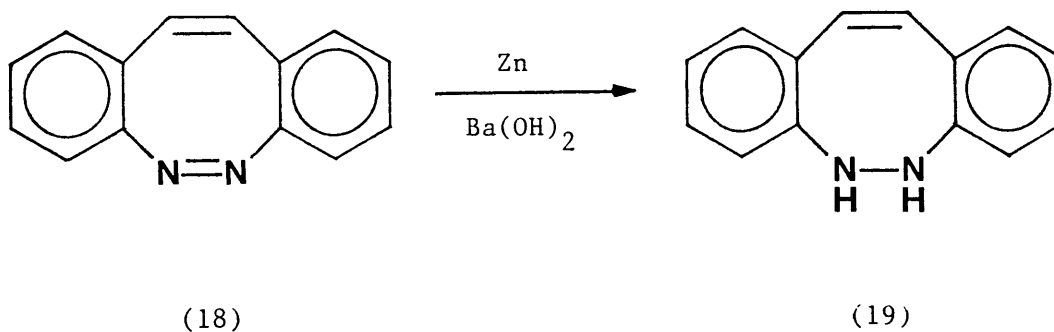
Reagents: *i*, Δ ; *ii*, K, NH₃; *iii*, RX or ROH.

This was corroborated by the X-ray crystal structures of compounds (14c), (14f) and (14d). 1,4-Dihydro-1,4-diazocine (14f) and (14c) were found to be planar and they showed considerable equalisation of bond lengths. The X-ray structure of (14d), however, indicated that this compound adopts a twisted conformation with definite bond alternation.

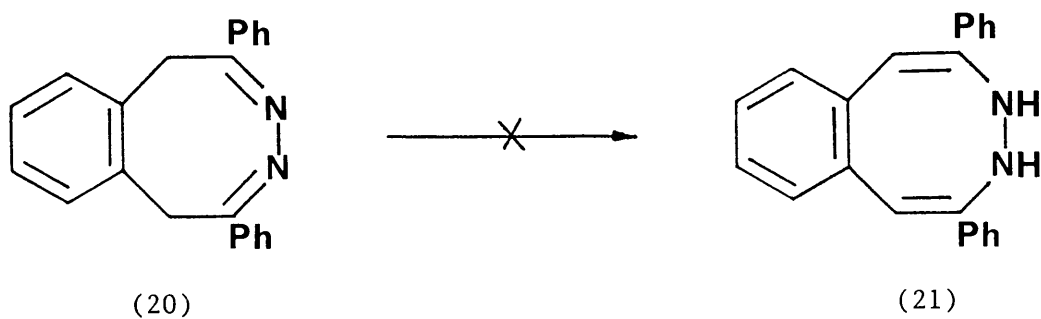
That (14b) and (14d) do not show aromatic stabilisation may be

explained by the participation of the nitrogen lone pair in amide resonance. It is therefore, less available for delocalisation in the ring. A similar relationship between the electronegativity of the substituent on nitrogen and the extent of aromatic character has been found in the azonine system¹⁵.

In contrast to the 1,4-dihydro-1,4-diazocine system the 1,2-isomer has not been extensively studied. This may be a result of the prediction that the 1,2-isomer would not have a delocalised frame¹⁶. The dihydro-dibenzodiazocine (19) was synthesised by Paudler and a comparison of the u.v. spectral data of (18) and (19) showed (19) to have enhanced conjugation¹⁷. On this basis compound (19) was judged to be at least partially planar and highly conjugated.

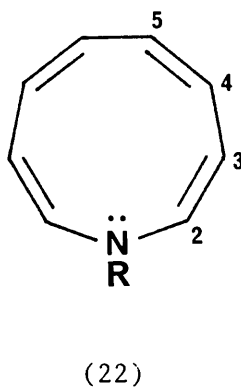


The only other report of this system was the attempted synthesis of the monobenzo derivative (21)¹⁸. The isomerisation of (20) to (21) could not be effected and this seems to indicate that there is little, if any, aromatic stabilisation associated with (21).

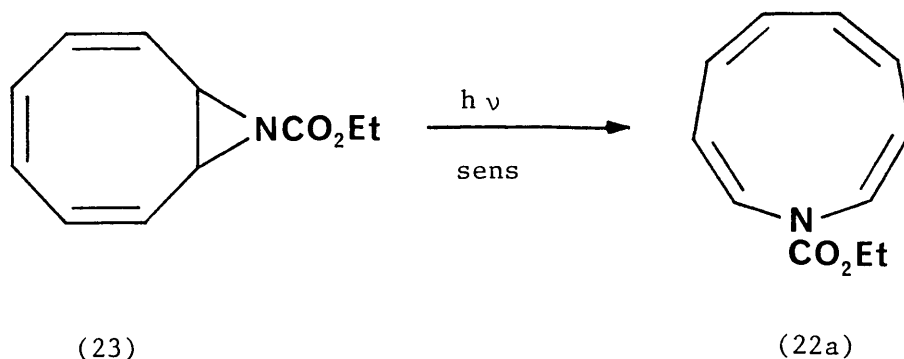


1.2.2 Nine Membered Rings

1.2.2.1 Containing one nitrogen atom



The $1H$ -azonine system (22) is isoelectronic with cyclononatetraenyl anion and it would therefore be expected to exhibit aromatic character if a planar geometry was adopted. The first derivative of this system (22a) was synthesised by Anastassiou *via* the photolysis of the bicyclic urethane (23)¹⁹.



N-Ethoxycarbonyl-1-azacyclonona-2,4,6,8-tetraene (22a) was observed from ^1H n.m.r. data (Table 1) to be typically olefinic and was found to be unstable at ambient temperature rearranging to *N*-ethoxycarbonyl-3a, 7a-dihydroindole. Although the lack of observed aromaticity was disappointing, several other derivatives were synthesised *via* base induced exchange of the substituent (Scheme 5)²⁰. The relevant spectral data for some of these derivatives is shown in Table 1.

Compounds (22c-h) were found to be polyenic in nature having none of the characteristics associated with a delocalised π -system. This is presumably due to the electron-withdrawing effect of these substituents. The parent system (22b), obtained by the exposure of the anion (24) to water, showed significant downfield shifts of the protons, indicating the presence of a diamagnetic ring current^{21,22}. In contrast to compound (22a), 1*H*-azonine (22b) was found to be thermally stable in an inert atmosphere and this is further evidence for the aromaticity of this compound. The alkyl derivatives (22i-k) were found to have some indication of aromatic character but this was insufficient to allow unambiguous classification.

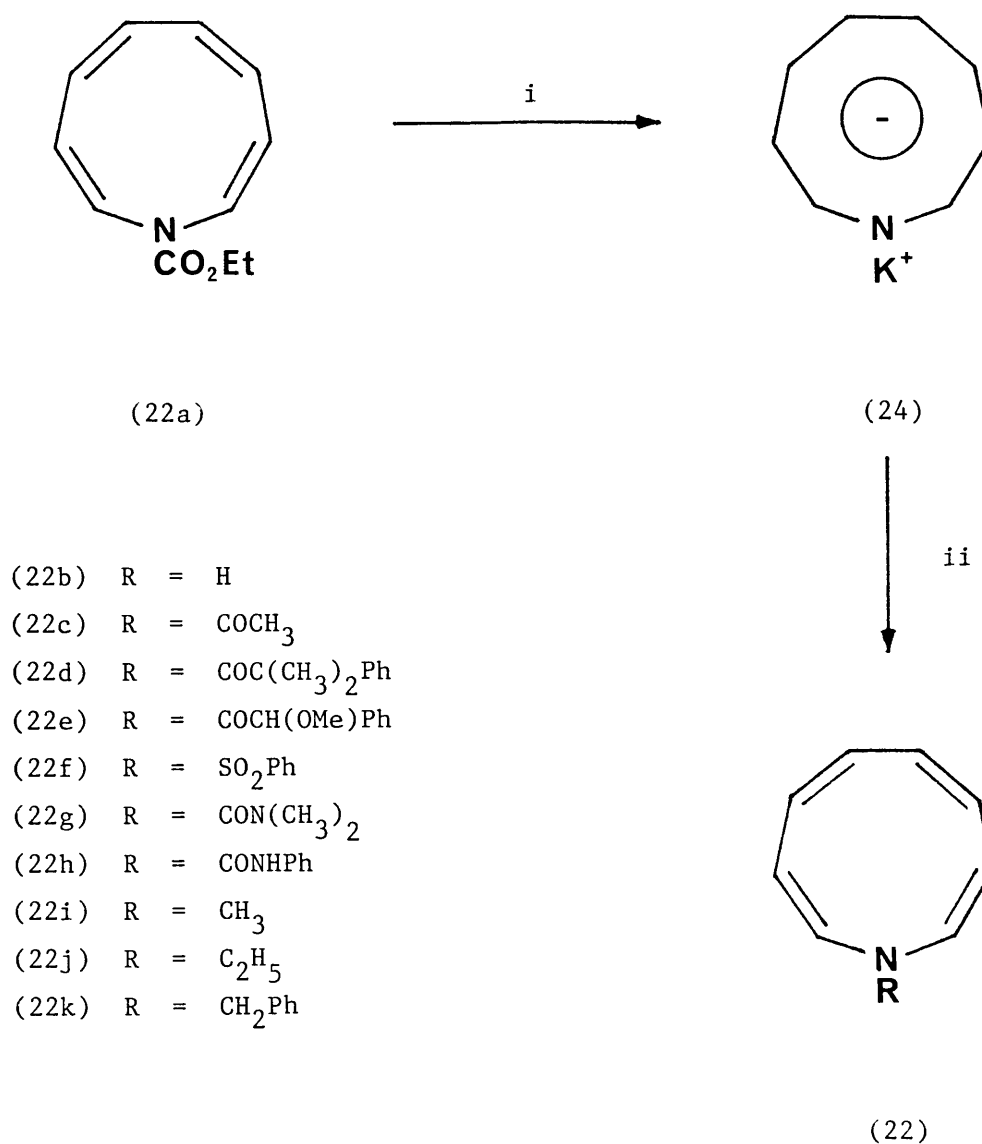
TABLE 1

Spectroscopic Properties of 1*H*-Azonines and
Related Models

PROPERTY	COMPOUND					
	CNT ^a	22a	22i	22b	24	CNT- ^b
¹ H n.m.r. (δ)						
H ₂	-	6.37	5.85	7.07	8.64	-
H ₃	-	5.32	4.88	6.00	~6.63	-
H ₄ , H ₅	-	5.87	6.0-6.1	6.7-7.0	~6.65	-
J _{HH} (Hz)						
H ₂ - H ₃	-	9.6	10.5	11.0	-	-
¹³ C n.m.r. (p.p.m.)						
(C ₄ + C ₅)/2	128.54	-	121.75	117.61	113.20	109.5
J _{CH} (Hz)						
(C ₄ -H+C ₅ -H)/2	157	-	153	152	140	137
Low Energy u. v. (nm)	248	265	303	335	339	320

a. 1,3,5,7-Cyclononatetraene

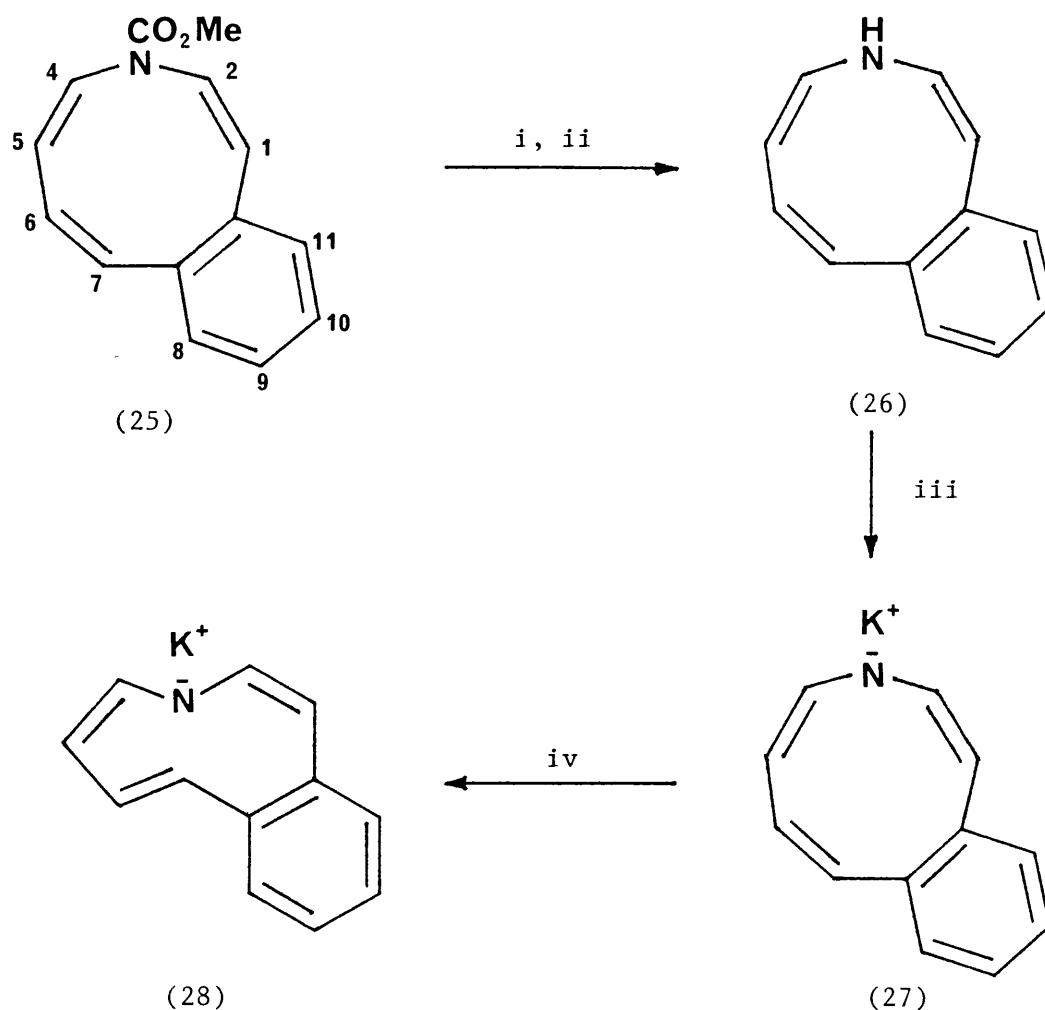
b. Cyclononatetraenyl anion

Scheme 5.Reagents: i, $t\text{-BuO}^-\text{K}^+$, THF; ii, RX or H₂O

Various metal azonides (Li^+ , Na^+ , K^+ , Rb^+ , Cs^+) have been isolated²³. The ^1H n.m.r. spectra of these species in d_6 -dimethylsulphoxide showed the α protons at $\delta 8.5 - 8.7$ while the β , γ and δ protons resonated at $\delta 6.49 - 6.66$. The strong deshielding effect observed on the α protons is attributed to the ring diamagnetism and the proximity of the positive counterion. Thus it may be seen that the development of aromaticity

in the 1*H*-azonine system is dependent on the electronegativity of the nitrogen substituent.

The effect of benzannulation of the 1*H*-azonine system was investigated by Anastassiou²⁴. Surprisingly, the 1*H*-benzazonine (26) and the corresponding anion (27) were observed from their spectral properties to be olefinic. On warming (27) from -35 to 0°C, however, it was found



Scheme 6.

Reagents: i, MeLi, -78°C; ii, H₂O;
iii, KNH₂, NH₃, -78 → -35°C; iv, Δ, -35° → 0°C

to undergo a *cis* → *trans* isomerisation to give anion (28)²⁵. The ¹H n.m.r. data of the anions (27) and (28) indicate that a consequence of the

isomerisation process is the restoration of aromaticity in the azonine unit (Table 2).

TABLE 2

^1H n.m.r. Data of 26, 27 and 28 (δ)

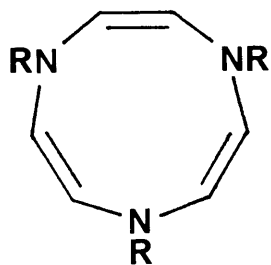
COMPOUND	H-1	H-2	H-4	H-5	H-6	H-7
26	5.28	6.08	5.63	4.29	6.10	6.45
27	4.90	6.62	6.27	3.37	6.4-5.9	6.4-5.9
28	6.7-7.3	6.7-7.3	7.76	5.65	6.7-7.3	-0.95

The observed isomerisation was unexpected since the parent system (22) shows no tendency towards such a transformation. Benzannellation is thought to disturb the aromaticity of (26) and (27) by setting up unfavourable peri-interactions in the system. These prevent the azonine unit from adopting a planar conformation and thus result in the observed loss of aromaticity. The *cis* $\rightarrow$ *trans* isomerisation of (27) to (28) relieves the 7,8-peri-interaction. This allows the azonine unit to adopt a planar geometry with the restoration of aromatic character.

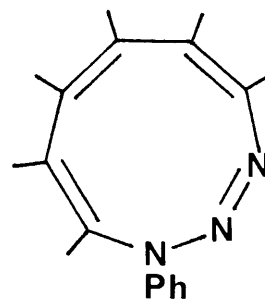
1.2.2.2 Containing three nitrogen atoms

There are several possible polyazonine systems of which only two examples have been reported.

The triazonin (29) has been extensively studied and found to have a highly puckered conformation²⁶. The triazonin (30) formed on

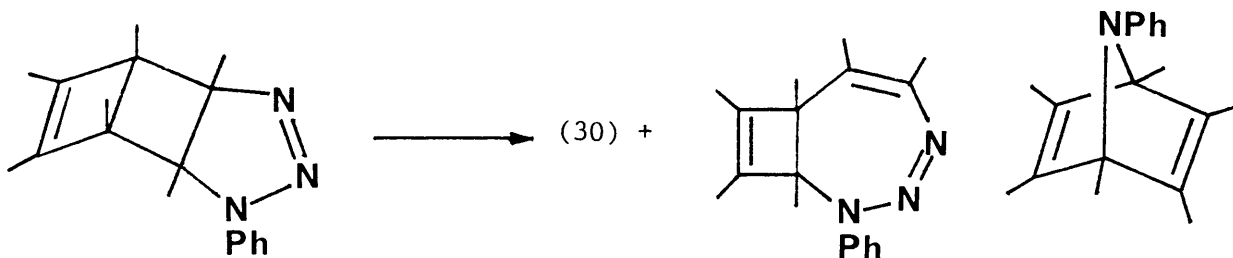


(29)



(30)

thermolysis of the corresponding triazoline (31), has 10π -electrons and is potentially able to sustain a diamagnetic ring current²⁷.



(31)

The aromaticity or otherwise of (30) is a matter of debate. The spectral characteristics and the high stability of this compound towards oxygen, dienophiles, catalytic hydrogenation and photolysis led Paquette to the belief that this ring system did indeed have aromatic character. The steric crowding of the methyl substituents in a planar geometry, however, would be expected to exert a destabilising influence on this compound. A less substituted derivative of this ring system is required for unequivocal categorisation.

1.2.3 Ten Membered Periphery

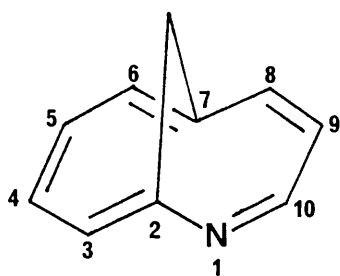
1.2.3.1 Containing one nitrogen atom

In 1964 Vogel synthesised 1,6-methano[10]annulene, the spectral properties of which were consistent with this compound being aromatic²⁸.

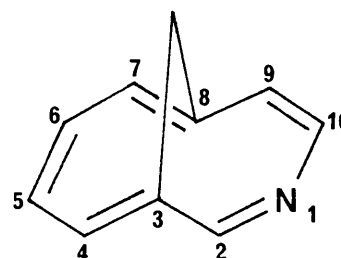
There are two possible monoaza derivatives of this system, namely

2,7-methanoaza[10]annulene (32) and 3,8-methanoaza[10]annulene (33).

These compounds are of considerable theoretical and practical interest as they constitute the first 10π -analogues of pyridine.



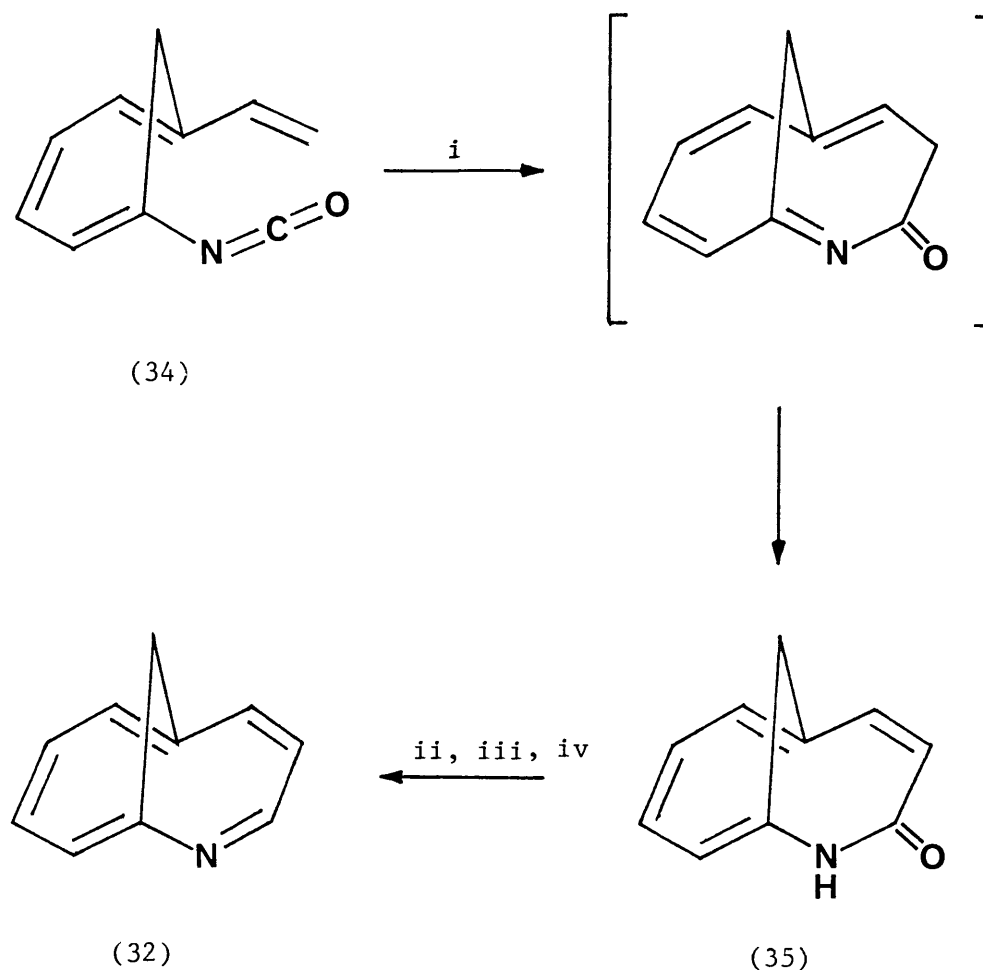
(32)



(33)

The synthesis of compound (32) was reported by Vogel in 1978, the key step in the sequence being the thermal isomerisation of the isocyanate (34) in a 10π -electrocyclic process²⁹.

The most convincing evidence for the aromatic nature of (32) is provided by the ^1H n.m.r. spectrum. This shows the methylene protons resonating at δ -0.4 and δ 0.65 and the peripheral protons appearing in the aromatic region. The u.v. spectrum of (32) was found to be very similar to that of 1,6-methano[10]annulene, with the slight differences observed corresponding to those seen between naphthalene and quinoline.

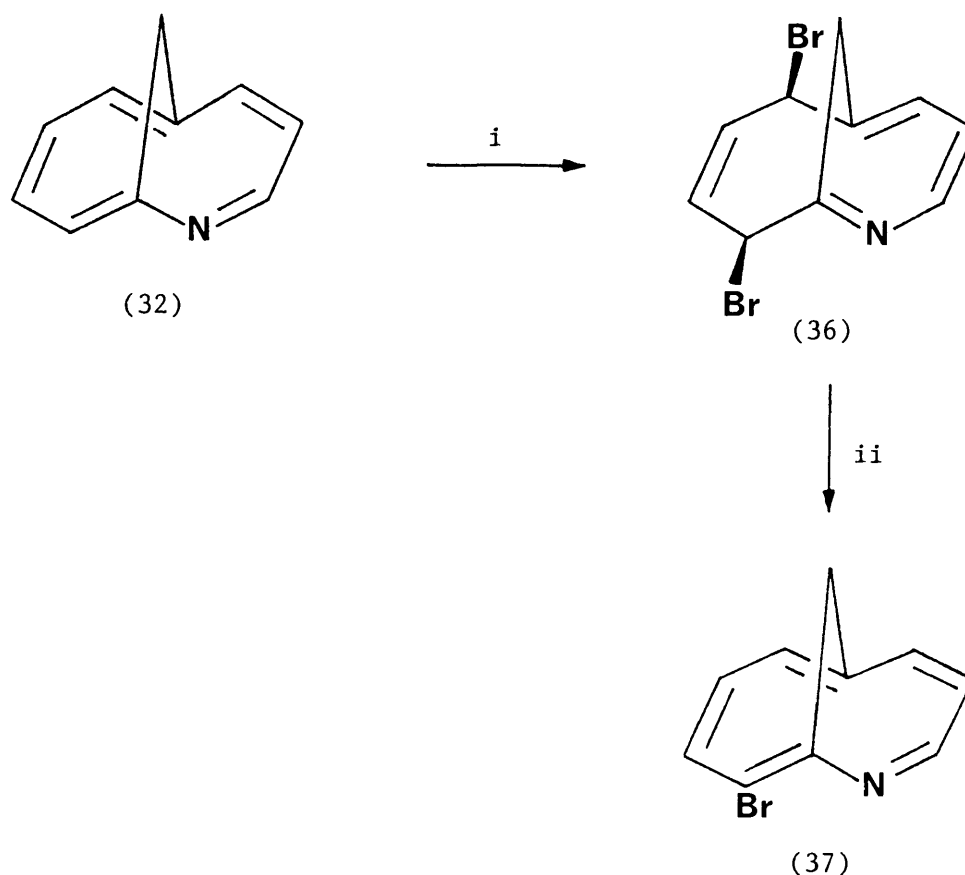


Scheme 7.

Reagents: *i*, 110°C, toluene; *ii*, *p*-TsCl, THF; *iii*, LiAlH₄, Et₂O; *iv*, DDQ.

Although the aza[10]annulene (32) has a lower pK_a than pyridine or quinoline it nevertheless forms a stable hydrochloride salt and reacts with various alkylating agents giving the corresponding quaternary salts. Bromination of the aza[10]annulene (32) by an addition elimination procedure gives only 3-bromo-2,7-methanoaza[10]annulene (37) (Scheme 8)³⁰.

The intermediate dibromide (36) has been isolated and an X-ray analysis shows that attack of bromine occurs in a stereoselective fashion giving the *syn*-adduct.

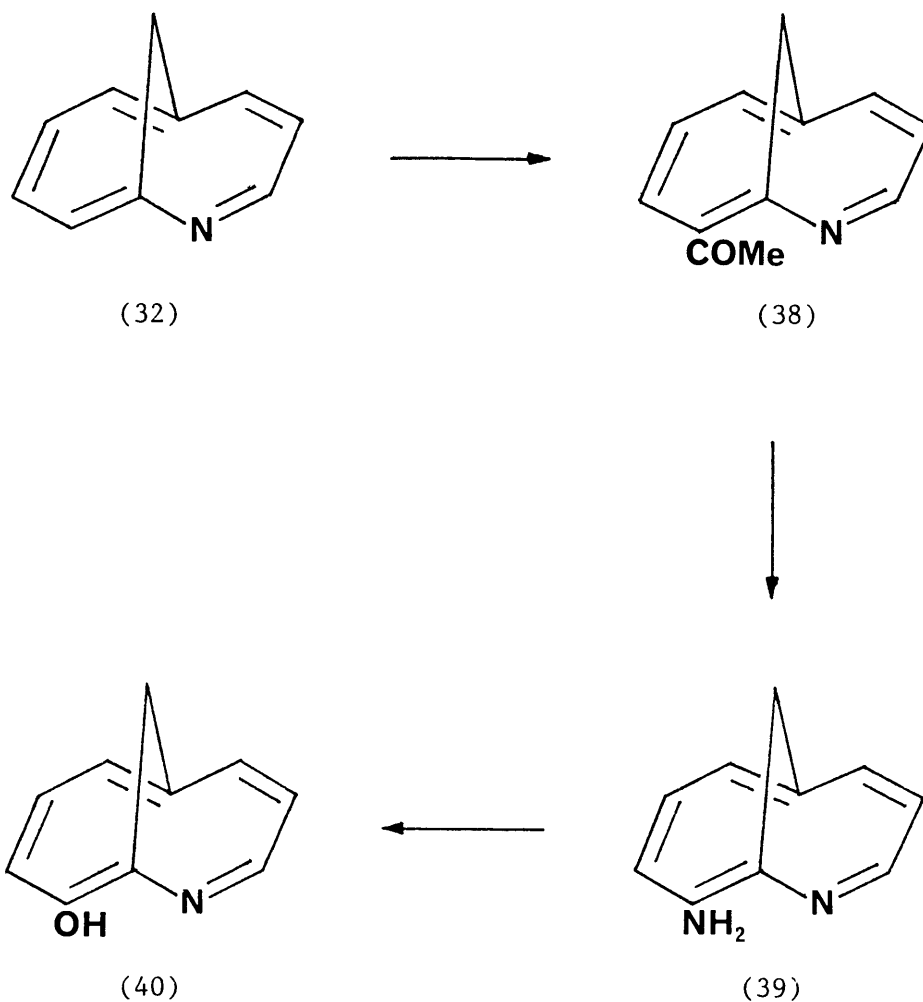


Scheme 8.

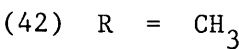
Reagents: i, Br₂; ii, DBN.

Strong evidence for a delocalised system was obtained from the X-ray analysis of the bromide (37) which showed the C-N bond lengths to be almost equal³¹. The transannular distance (C₂-C₇) was found to be slightly smaller than the corresponding distance (C₁-C₆) in 1,6-methano-[10]annulene-2-carboxylic acid. This suggests that there is a stronger homoaromatic interaction in compound (37).

Acetylation of (32) gave predominantly 3-acetyl-2,7-methanoaza[10]-annulene (38) with only a small amount of the 6-acetyl isomer being observed³². This compound has recently been reported to give access to the interesting hydroxy-derivative (40) of this system.

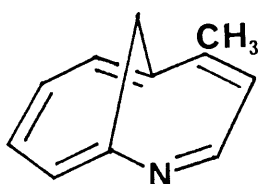


The spectral characteristics of this compound have yet to be published and they will afford an interesting comparison to the labile 2-hydroxy-1,6-methano[10]annulene³³. Photolysis of the *N*-oxide (41) yielded 9-hydroxy-2,7-methanoaza[10]annulene (44) and this is believed to proceed *via* the intermediate (43)³². Some support for this mechanism was obtained from the irradiation of the *N*-oxide (42) which affords the 1,3-oxazepine (45).

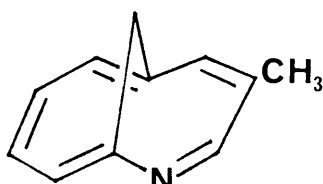


Chemical reaction scheme showing the photochemical conversion of a 10-substituted phenoxazine derivative (46) to a 10-substituted phenoxazinone derivative (47). Structure 46 is a phenoxazine with a positive charge on the nitrogen atom and a negative charge on an oxygen atom. Structure 47 is a phenoxazinone with a carbonyl group at the 10-position. The reaction is initiated by light ($h\nu$).

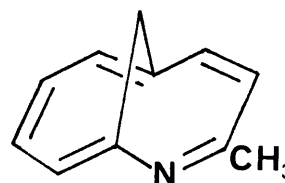
The reactivity of 2,7-methanoaza [10]annulene (32) shows certain similarities to that of pyridine. The synthesis of the 8-, 9- and 10-monomethyl derivatives was undertaken in order to afford a comparison with the corresponding methyl pyridines.



(48)



(49)



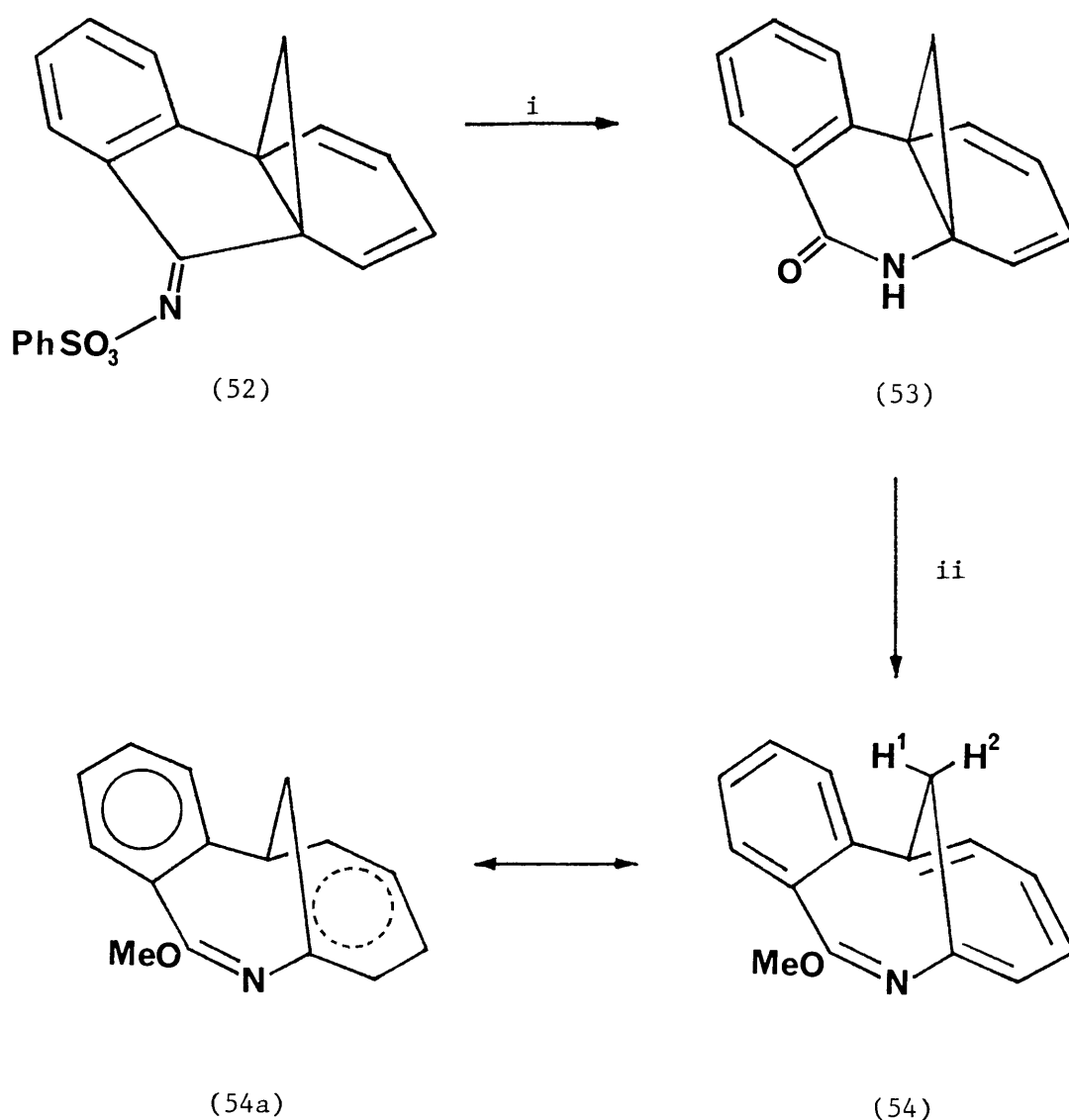
(50)

On sequential treatment with selenium dioxide and silver oxide, compounds (48) and (50) were oxidised to the corresponding acids whereas compound (49) was recovered unchanged from these reaction conditions³². This parallels the reactivity observed in the oxidation of the 2-, 3- and 4- methyl pyridines.

The reaction of (32) with triamminetricarbonylchromium occurs with the formation of a π -complex (51) rather than a σ -complex with the metal bound to nitrogen³⁶. This is in direct contrast to the behaviour of pyridine and quinoline which form σ -complexes. The ¹H n.m.r. spectrum and X-ray analysis show that the delocalisation of the 10 π -system is maintained on complexation. The tendency for (32) to prefer π - rather than σ -bonding may be accounted for by the lower basicity of the aza[10]annulene (32).



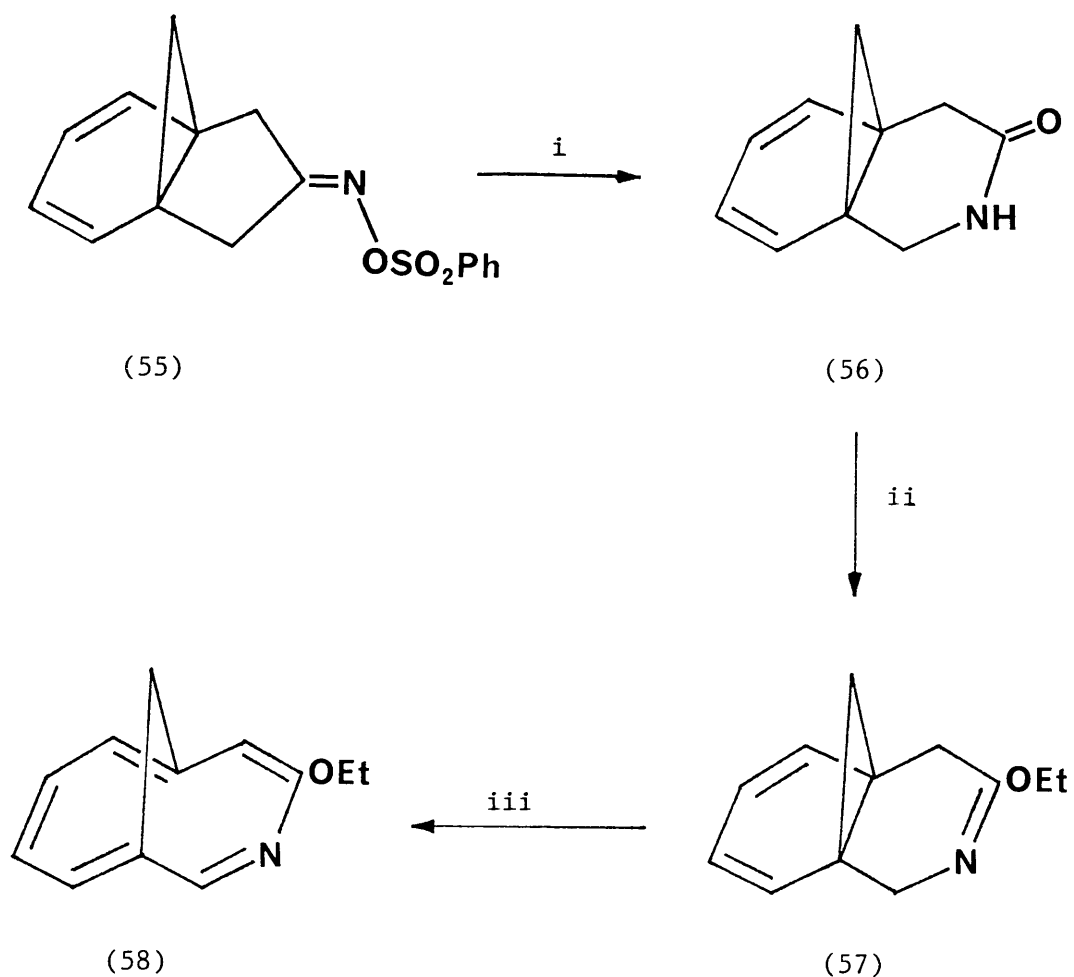
A monobenzo derivative (54) of the 2,7-methanoaza[10]annulene system has been synthesised by Helmkamp³⁷. The methylene protons of compound (54) were found to resonate at δ 1.65 and δ 0.32 for H-1 and H-2 respectively. The corresponding protons in 10-methoxy-2,7-methanoaza[10]-annulene are observed at δ 0.22 and δ 0.4. A comparison of these values shows that the extent of π -delocalisation is lowered on benzannelation. The same effect was observed by Vogel when comparing 1,6-methano[10]-annulene to 2,3-benzo-1,6-methano [10]annulene³⁸. Although H-1 in compound (54) is not apparently affected by a ring current, H-2 is strongly shielded and this suggests that there is a considerable contribution from the resonance form (54a) to the overall electronic configuration.



Scheme 9.

Reagents: *i*, NaOH; *ii*, $(\text{Me}_3\text{O})^+ \text{BF}_4^-$

Although 3,8-methanoaza [10] annulene (33) has not yet been synthesised, 10-alkoxy derivatives of this system have been prepared independently by three groups^{29, 39, 40}. The route used by Maddox *et al* is illustrated (Scheme 10). The spectral characteristics of compound (58) are consistent with the presence of a diamagnetic ring current. Further study of these interesting compounds, however, has been hampered due to the low overall yields of these syntheses.

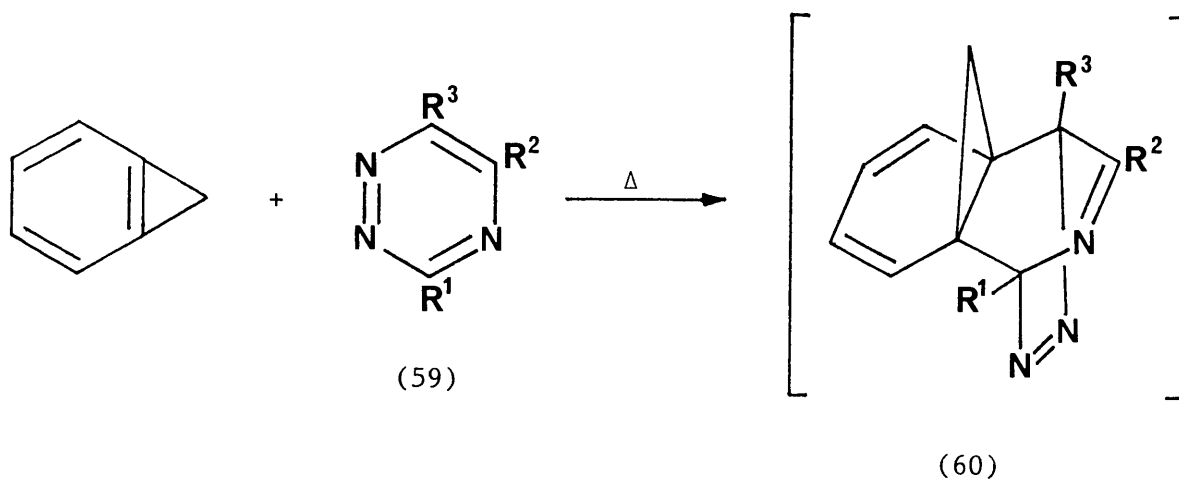


Scheme 10.

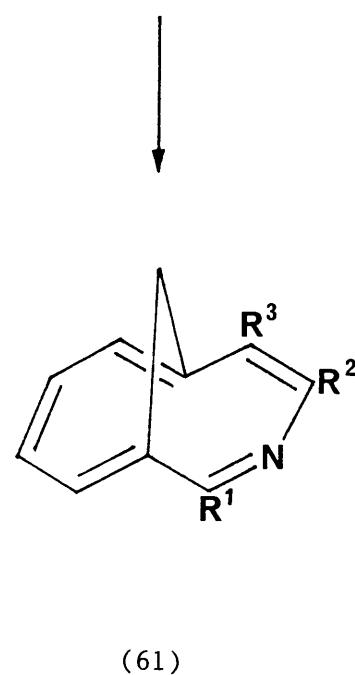
Reagents: i, dioxane (aq.), 2,6-dimethylpyridine; ii, $\text{Et}_3\text{O}^+ \text{BF}_4^-$, CH_2Cl_2 ; iii, DDQ.

A one step synthesis of substituted 3,8-methanoaza[10]annulene derivatives has recently been developed by Maddox using the cycloaddition of benzocyclopropene with appropriately substituted 1,2,4-triazines (59)⁴¹.

The cycloadditions to give compounds (61c) and (61d) were carried out at very high pressure due to the decreased reactivity of the triazines. Unfortunately the reaction between 1,2,4-triazine and benzocyclopropene to give the parent 3,8-methanoaza[10]annulene (33) has not yet been successful. The spectral characteristics of compounds (61a-d) are consistent with these molecules having a fully delocalised π -system.

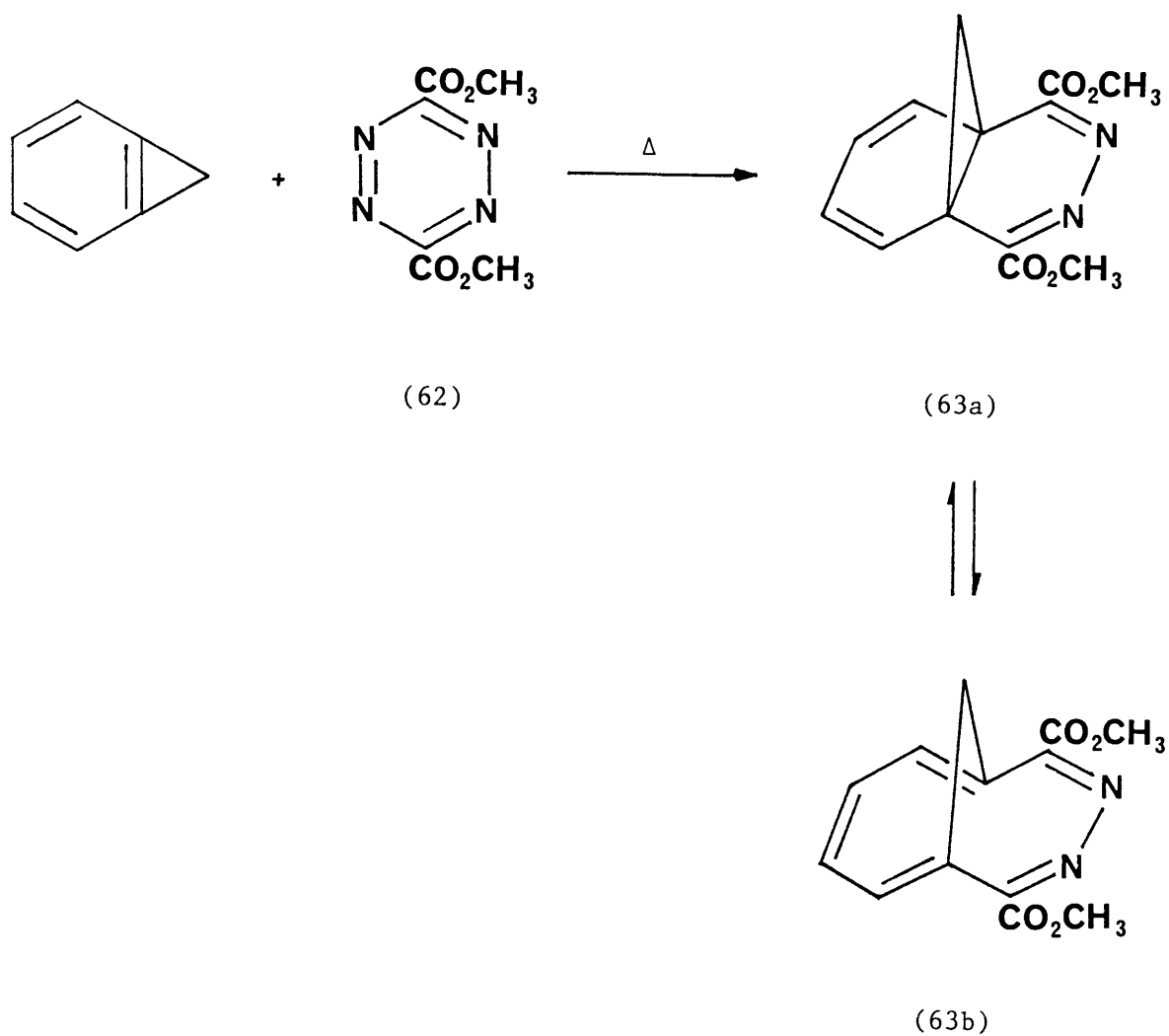


	R^1	R^2	R^3
(61a)	CO_2Et	CO_2Et	CO_2Et
(61b)	CN	CO_2Et	CO_2Et
(61c)	H	CO_2Et	CO_2Et
(61d)	CO_2Et	H	H



1.2.3.2 Containing two nitrogen atoms

The synthesis of a diaza analogue (63b) of 1,6-methano[10]-annulene was attempted *via* the cycloaddition of benzocyclopropene and 1,2,4,5-tetrazine (62)⁴². The ^1H n.m.r. spectrum of the product of this reaction was not consistent with either the norcaradiene form (63a) or the aromatic compound (63b) and it was suggested that an equilibrium between the two structures would account for the spectral



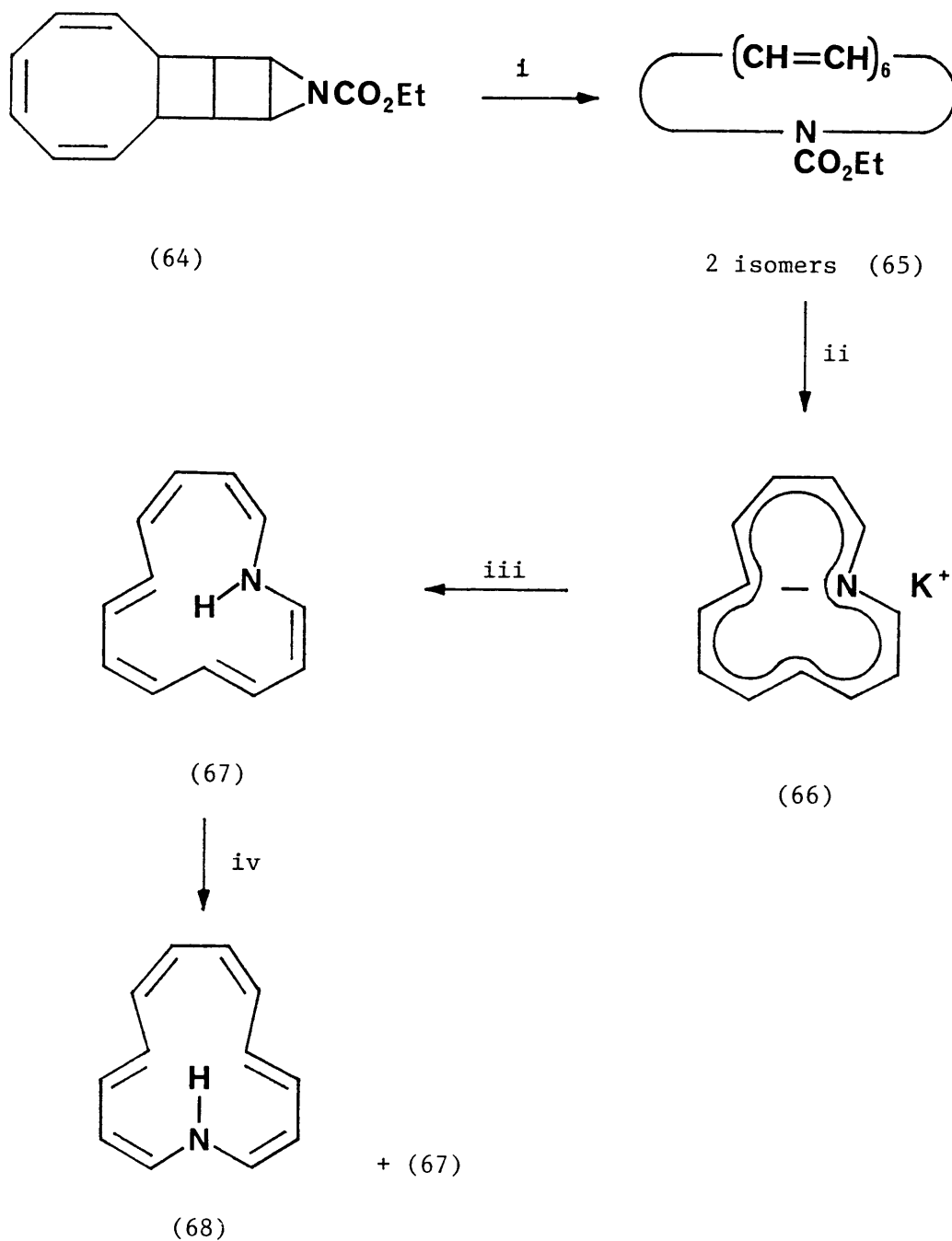
properties. This was confirmed by a simulated proton spectrum and variable temperature measurements.

1.3 COMPOUNDS CONTAINING 14π -ELECTRONS

1.3.1 Thirteen Membered Rings

In 1973 Schröder *et al* reported the synthesis of an aza[13]-annulene (65) which was found from its spectral characteristics to be atropic⁴³. The presence of a strong electron-withdrawing substituent

on nitrogen is known to prevent the development of aromaticity in related systems. The unsubstituted aza[13]annulene (67) and the anion (66) would be expected to show aromatic characteristics if a planar geometry was assumed.



Scheme 11.

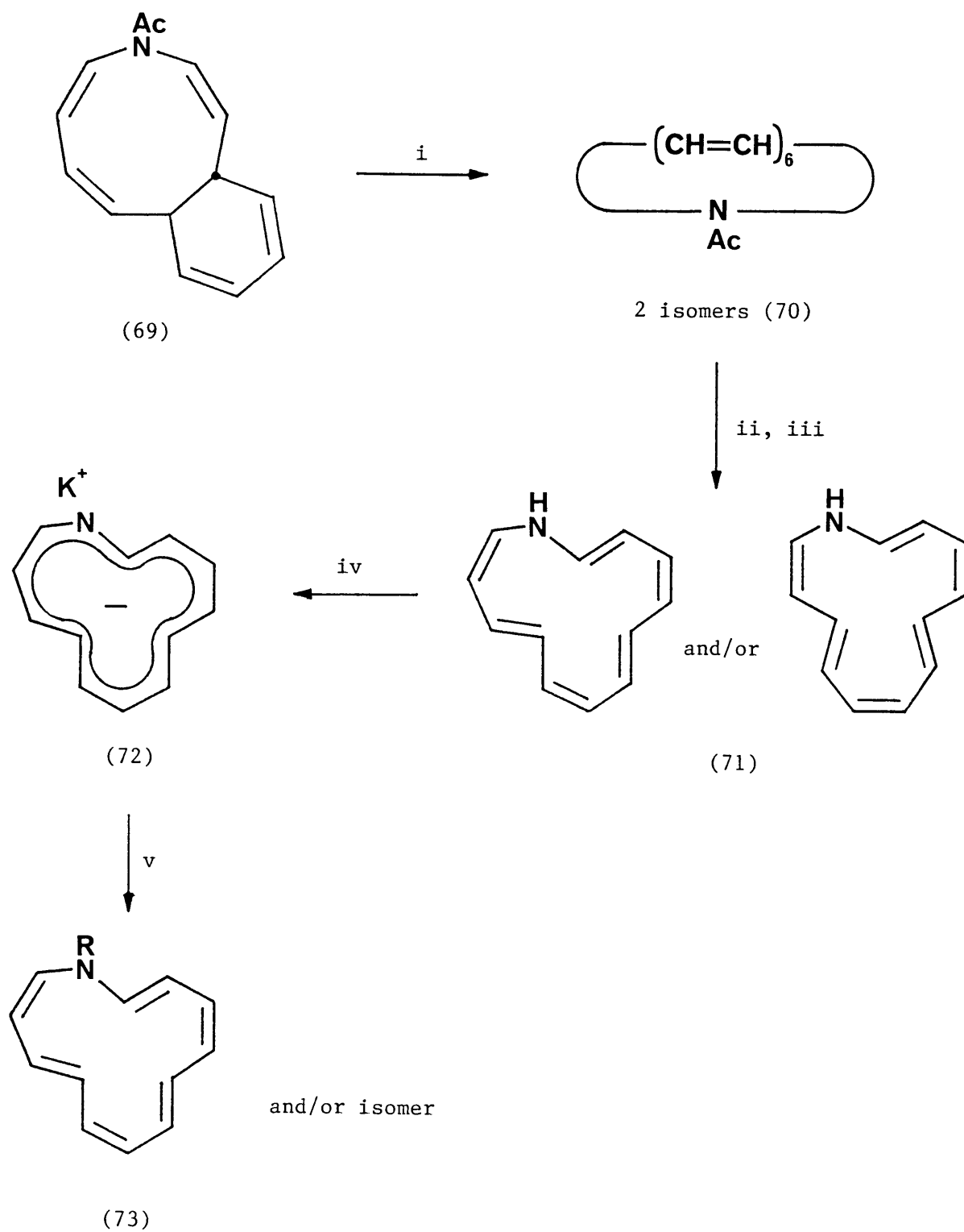
Reagents: i, $h\nu$; ii, $K^+ t\text{-BuO}^-$, 0°C ;
 iii, $\text{CH}_3\text{CO}_2\text{H}$; iv, Δ , $25\text{--}50^\circ\text{C}$

This supposition was borne out by the synthesis of the aza[13]annulenyl anion (66), the configuration of which was deduced from ^1H n.m.r. studies⁴⁴. The most striking feature of the proton spectrum is the difference of 10 p.p.m. between the resonances of the inner (shielded) and outer (deshielded) protons. This is convincing evidence of the diatropic nature of this anion.

The fact that the two isomeric aza[13]annulenes give only one anion indicates that the anions must be configurationally labile with the most thermodynamically stable species being formed. Protonation of the anion (66) was found to occur from the inside of the ring at the nitrogen atom to give compound (67) which rearranged on warming to (68). These compounds were shown to possess a diamagnetic ring current although it was appreciably smaller than that present in the anion (66).

Anastassiou *et al* also prepared isomeric aza[13]annulenes (70) from the precursor (69)⁴⁵. The anion generated by the exposure of (71) to potassium mirror at -78°C was found to possess a different configuration to that obtained by Schröder. On warming (72), however, it was observed to interconvert to anion (66) which is thought to be thermodynamically more stable due to the lowering of the steric repulsion between the inner protons.

Several derivatives of this system have been synthesised and the ^1H n.m.r. shifts of the inner protons as well as u.v. data are given (Table 3)⁴⁶.



Scheme 12.

Reagents: i, $h\nu$; ii, MeLi, -78°C ; iii, H_2O ; iv, K° , THF; v, RX.

TABLE 3

Spectral Characteristics of Aza[13]annulenes

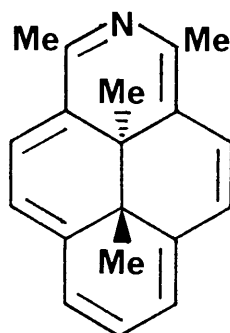
COMPOUND No.	R	¹ H n.m.r. (δ)	u.v. (nm)	
		Inner Protons	Weak Band	Strong Band
73a	CO ₂ Me	>5.8	335	263
73b	COMe	>5.8	350	260
73c	CONMe ₂	5.5	350	280
73d	CFCF ₂	4.7	334	278
71	H	2.78	360	297
73e	Me	2.63	360	300
72	K	-2.5		

The development of aromaticity in this system is deduced by the evidence of molecular flattening from the u.v. spectral data and the distinct rise in diatropicity shown by the chemical shifts of the inner protons. Thus it may be observed from Table 3 that compounds (73e), (71) and (72) are clearly aromatic while those compounds incorporating electron-withdrawing groups on nitrogen are not. The aromaticity of this system shows the same dependence on the heteroatom electronegativity as seen for the azonine system discussed earlier.

1.3.2 Fourteen Membered Periphery

The first aza[14]annulene to be synthesised, *trans*-1,3,10b,10c-tetramethyl-10b,10c-dihydro-2-azapyrene (74), was reported by Boekelheide in 1969⁴⁷. This compound was found to be highly diatropic as indicated

by the proton resonances of the internal methyl groups at δ -3.75 and δ -3.8. The physical properties of (74) were analagous to those of the carbocyclic 10b,10c-dihydropyrenes previously reported⁴⁸.



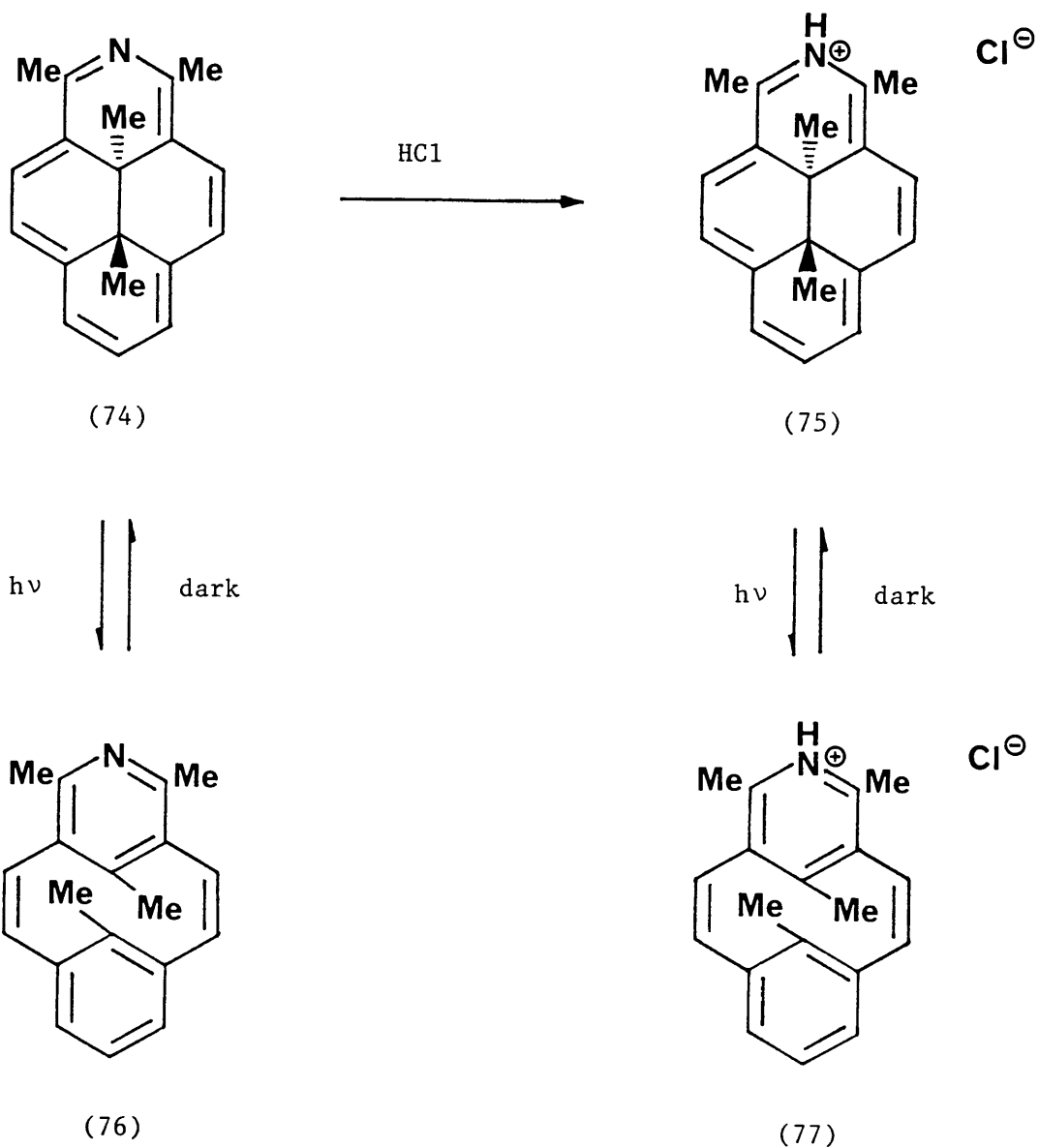
(74)

Compound (74) is readily protonated with dilute hydrochloric acid and the resonances of the internal methyl groups in the resulting hydrochloride (75) are at δ -3.8 and δ -3.82. The small upfield shift of these signals, rather than the expected downfield shift, indicates the presence of a stronger diamagnetic ring current.

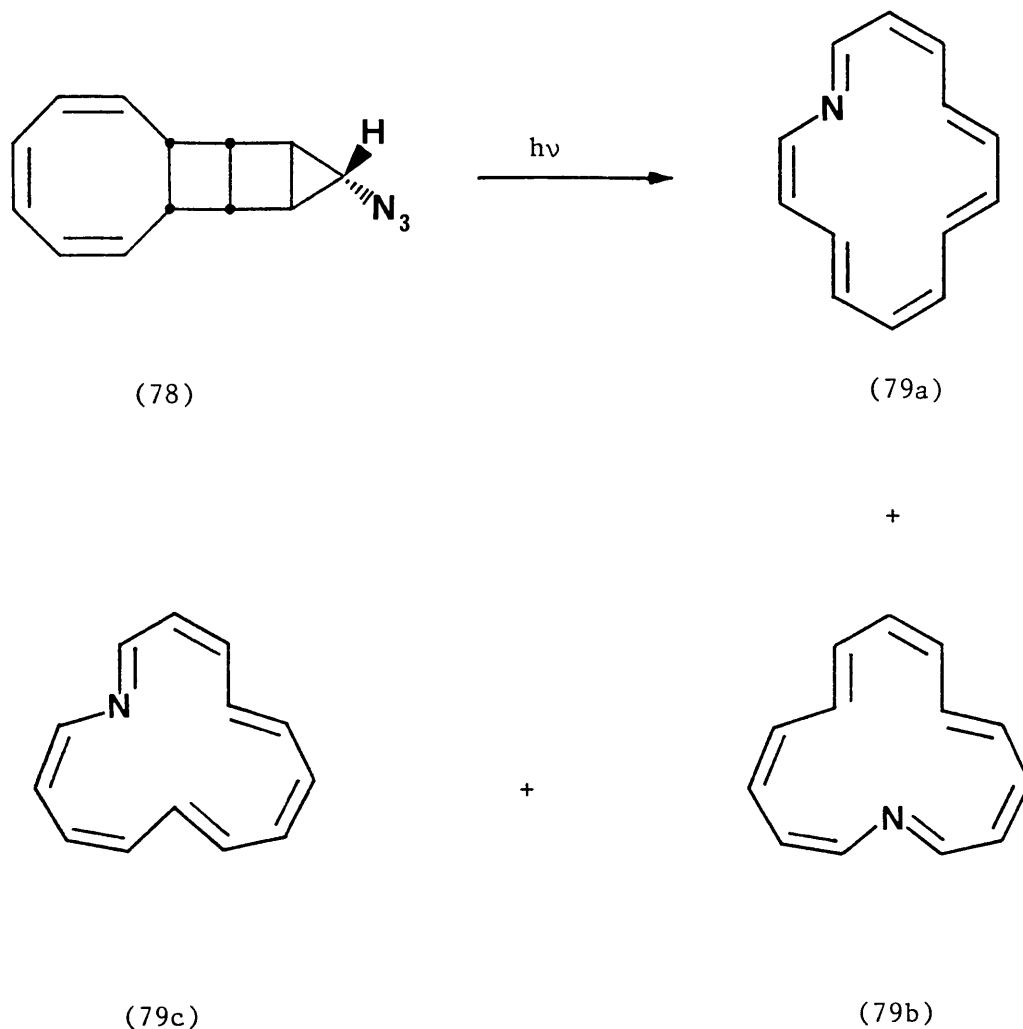
An interesting reaction of these 10b,10c-dihydropyrene systems is their facility to undergo a photo-isomerisation to the corresponding metacyclophane-1,9-diene valence tautomers.

Compounds (74) and (75) readily undergo this isomerisation to give (76) and (77) respectively.

The dark thermal reaction for (76) and (77) back to the corresponding dihydropyrenes has been observed. The rate of isomerisation of (77) to (75) is the fastest yet recorded for the dihydropyrene series and it is in accord with the concept that the development of charge in one aromatic ring promotes interaction and bond formation with the opposite ring.



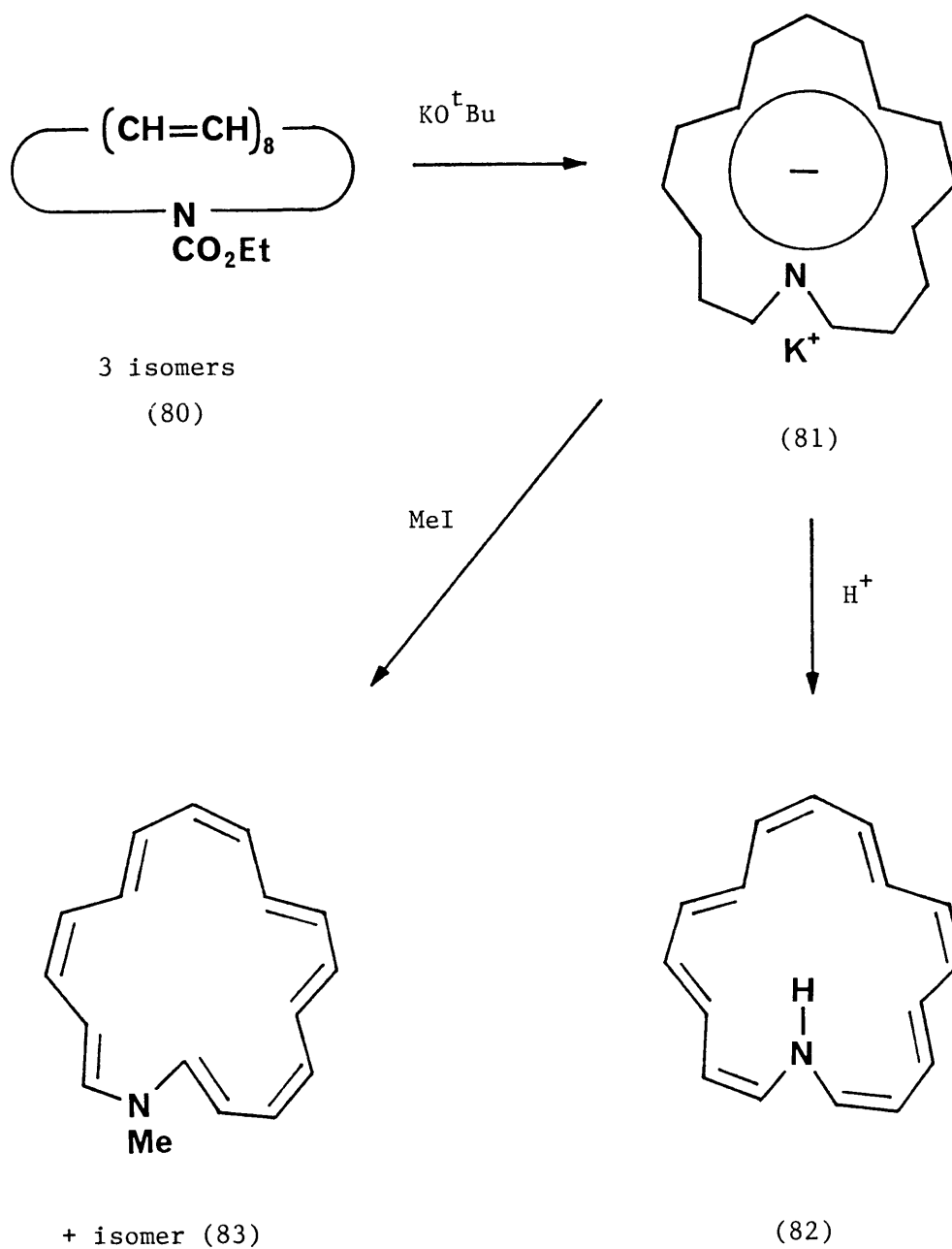
A synthesis of the monocyclic aza [14]annulenes (79a-c) has recently been reported by Schröder *via* the low temperature photolysis of the azide (78)⁴⁹. The three annulenes (79a), (79b) and (79c) are formed in a ratio of 83:8.5:8.5. The ¹H n.m.r. resonances of the inner protons of these molecules attest to their aromaticity and show that (79b) and (79c) are more diatropic than (79a). This may be due in part to a reduction in internal steric crowding in (79b) and (79c).



1.4 COMPOUNDS CONTAINING 18 OR MORE π -ELECTRONS

The synthesis of aza[17]annulene (80) was reported by Schröder⁵⁰ and is closely related to that described earlier for the aza[13]annulene. The isomeric annulenes (80) were shown to be olefinic by a consideration of the ^1H n.m.r. data. However the anion (81) was found to be aromatic⁵¹.

Protonation of the anion (81) occurs on nitrogen from the inside of the ring to give (82). In contrast, methylation of (81) gives (83)

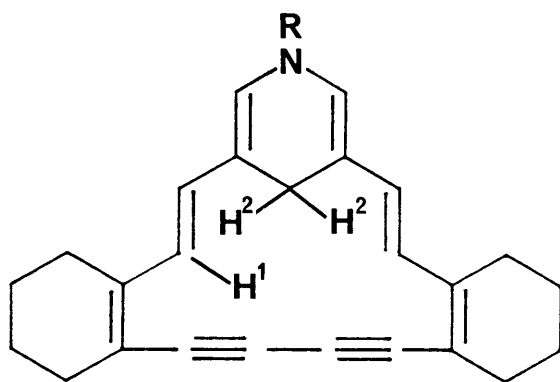


indicating that the molecular cavity is not sufficiently large to accommodate the bulk of a methyl group.

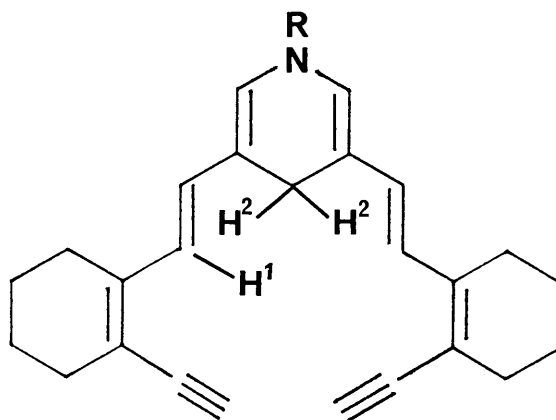
Compounds (82) and (83) are quite clearly aromatic as shown by the proton resonances of the inner hydrogens at $\delta 1.5 - 2.4$ and $\delta 0.5 - 2.5$ respectively. The ring current present in these systems is appreciably less than that found in the anion (81) in which the inner protons

resonate at δ -4.9. The behaviour of this system closely parallels that of the aza[13]annulene described previously.

In 1972 Sondheimer reported the synthesis of the highly restricted didehydroaza[17]annulene (84)⁵². The effect of the bridging unit, annelation and the presence of the *trans* double bonds combined to produce a rigidly flat periphery in this molecule. The proton spectra of (84) were compared with those of the model compounds (85) and all the aza[17]annulenes (84a-d) were found to be aromatic (Table 4).



(84)



(85)

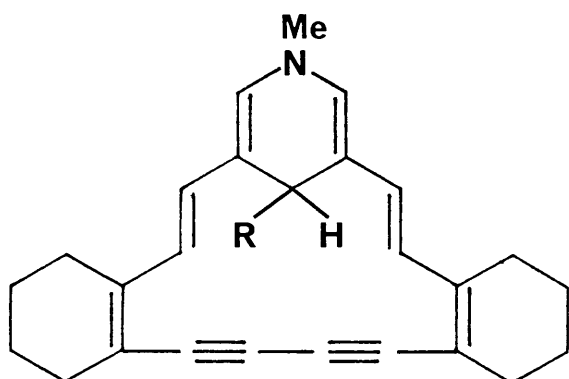
TABLE 4

¹H n.m.r. data of (84) and (85) (δ)

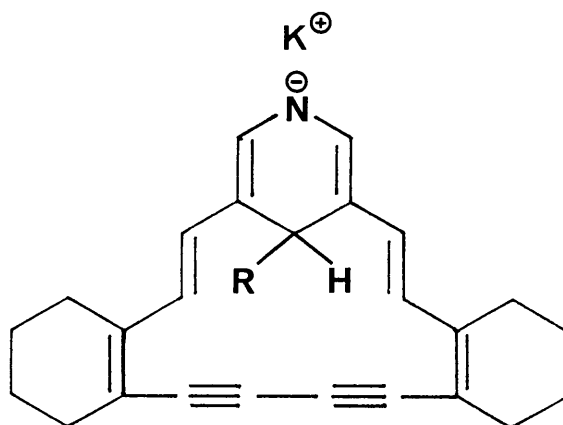
	R	84		85	
		H-1	H-2	H-1	H-2
a	H	3.01	-0.55	6.74	3.15
b	Me	2.67	-0.83	6.75	3.15
c	CO ₂ Me	5.22	1.23	6.94	3.09
d	COMe	5.49	1.46	7.03	3.14

It may be seen from Table 4 that the magnitude of the ring current is inversely related to the electronegativity of the nitrogen substituent. The observation that compound (84c) is aromatic, in contrast to the monocyclic aza[17]annulene (80), is presumably due to the increased planarity of the system.

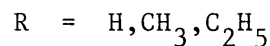
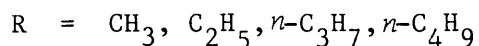
The synthesis of several bridged *N*-methyldidehydroaza[17]annulenes (86) bearing alkyl substituents within the cavity of the π -electron cloud was undertaken⁵³. It was found that while all the compounds were diatropic, the ring current was appreciably less than observed for (84b). This is attributed to the greater deviation from planarity caused by the presence of the alkyl groups.



(86)

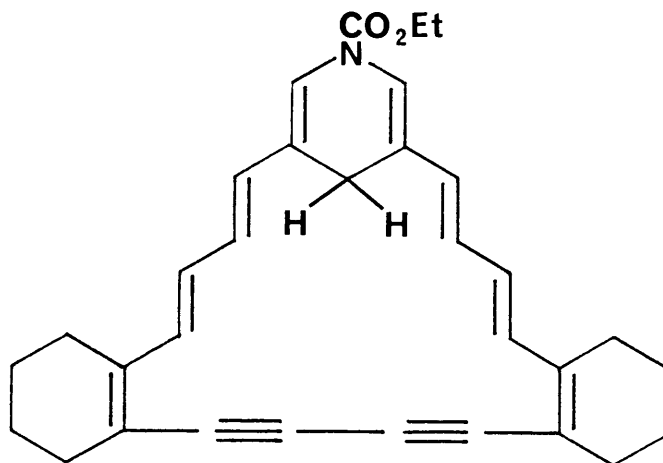


(87)



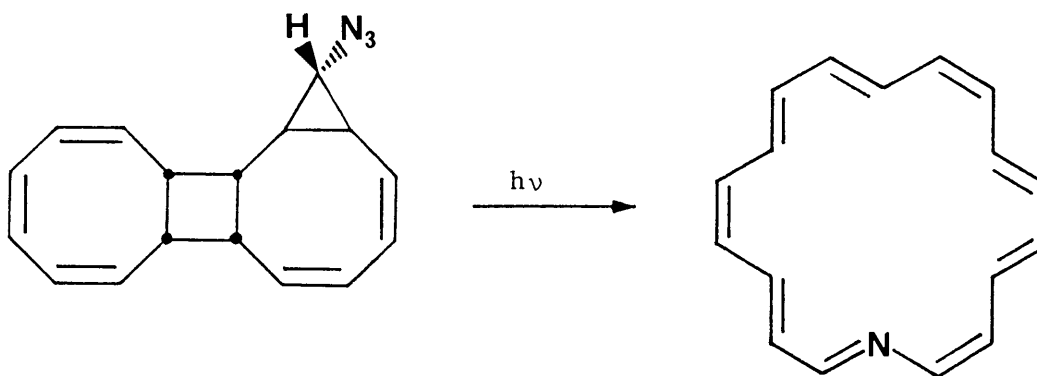
The anions (87) were found to be more diatropic than the corresponding *N*-methyl derivatives, all the outer protons being moved to lower field and the inner proton signals to higher field⁵⁴. A homologue of this system, the bridged didehydroaza[21]annulene (88) was found to

have properties consistent with the presence of a diatropic ring current⁵⁵. A comparison of the ^1H n.m.r. spectra of (84c) and (88) shows that the larger macrocycle has a smaller ring current possibly due to the increased flexibility of the periphery.



(88)

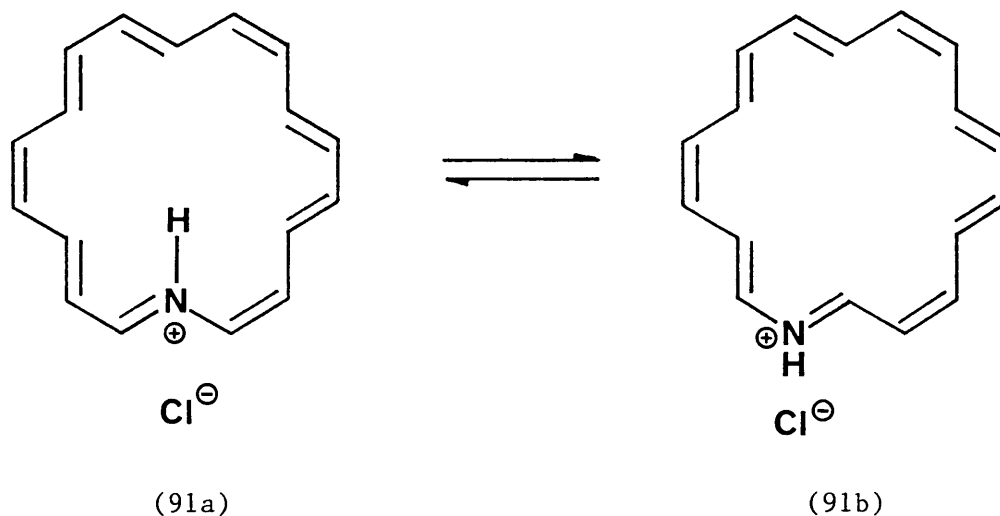
The final compound to be discussed is the aza[18]annulene (90) reported by Schröder in 1969⁵⁶. The synthesis of this molecule *via* the photolysis of the azide (89), is similar to the strategy employed for the aza [14]annulene (79).



(89)

(90)

The structure of (90) was deduced from ^1H n.m.r. data with the inner position occupied by the nitrogen atom being inferred from the *cis*-arrangement of H_α and H_β . The compound has a high thermal stability and is found to be extensively delocalised. Protonation occurs readily to give the hydrochloride salt as a black crystalline solid which, from ^1H n.m.r. evidence, was shown to exist in two rapidly interconverting forms.



This may be explained by considering the extra destabilising internal proton-proton repulsion which results on going from (90) to (91). The diatropicity of this system is indicated by the striking ^1H n.m.r. shift difference of almost 20 p.p.m. between the inner N-H proton of (91a) at $\delta -0.81$ and its outer counterpart in (91b) at $\delta 19$.

1.5 CONCLUSION

A number of azaannulenes have been investigated and some comparison may be drawn between these heterocycles and their corresponding

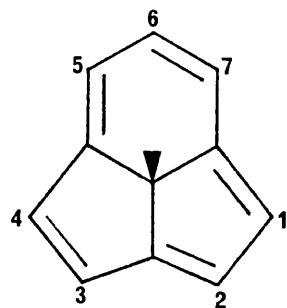
carbocyclic counterparts e.g. between H -azonine and cyclononatetraenyl anion. Very little chemistry of these systems has been reported although the reactivity of 2,7-methanoaza[10]annulene was observed to parallel that of pyridine.

The development of aromaticity in the π -excessive heterocycles was found to be dependent on the electronegativity of the nitrogen atom (*i.e.* $N^- > NH \sim N\text{-alkyl} > N\text{-acyl}$). In most cases compounds with an N -acyl unit were found to be atropic except where the conformation of the periphery was held rigidly planar.

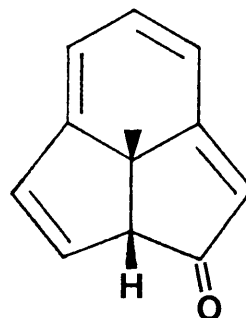
2. RESULTS AND DISCUSSION

2.1 INTRODUCTION

The novel tricyclic[10]annulene 7b-methyl-7b*H*-cyclopent[*cd*]indene (92) has recently been reported^{57,58}. This compound was found to sustain a considerable diamagnetic ring current as evidenced by the proton resonance of the central methyl group at δ -1.67. An investigation of the chemical properties of (92) by McCague showed that it could be classified as an aromatic compound^{59,60}. It was, however, found to be reactive due to the inherent ring strain of the system, which is greatest at the 2a-position. This is shown by the preference of 2-hydroxy-7b-methyl-7b*H*-cyclopent[*cd*]indene to exist exclusively as the ketone tautomer (93)⁶¹.



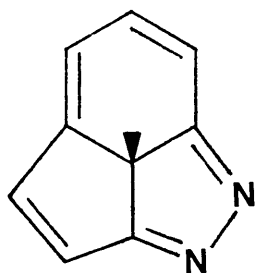
(92)



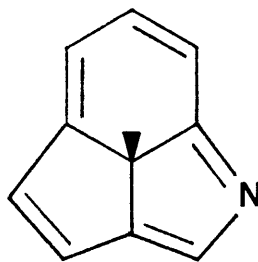
(93)

The aim of this project was the synthesis and study of aza analogues of the tricyclic[10]annulene (92). Of the many possibilities (94), (95) and (96) were chosen as synthetic targets.

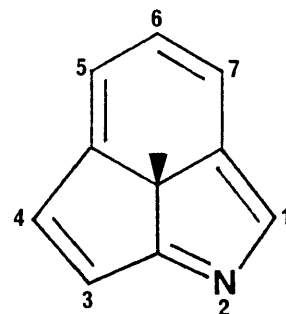
Compound (94) was a particularly attractive target since it is a potential precursor of the didehydro-3a*H*-indene (97). Preliminary calculations by Rzepa showed that the bis carbene (97b) would be preferred over the ionic form (97c)⁶². The reactive intermediate (97) is of considerable theoretical and practical interest since its reactivity



(94)

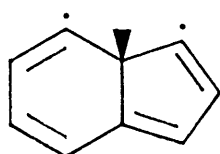


(95)

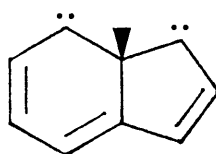


(96)

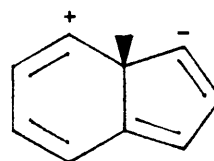
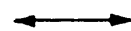
could be compared and contrasted with that of benzyne (98) and of
1,8-didehydronaphthalene (99)⁶³.



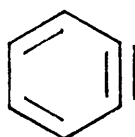
(97a)



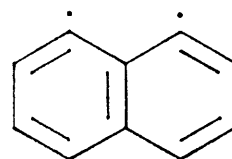
(97b)



(97c)

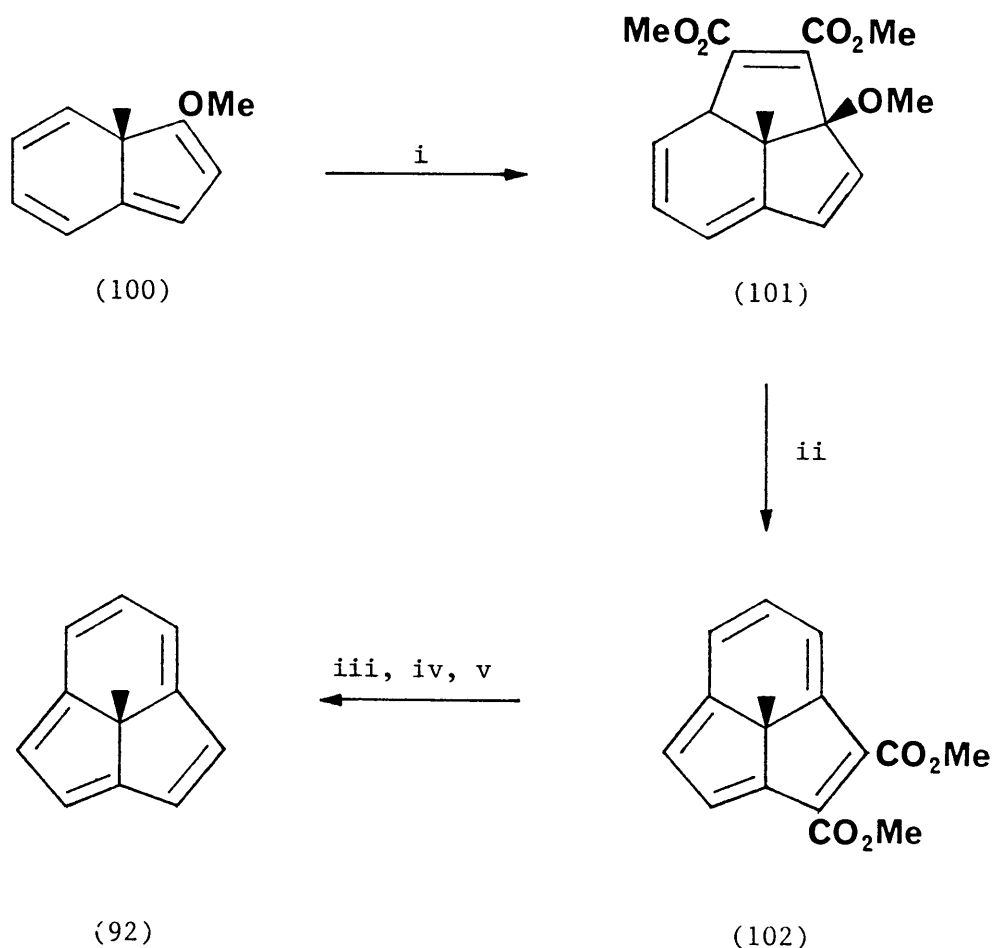


(98)



(99)

The aza[10]annulenes (95) and (96) were chosen as they are higher analogues of pyridine and it was thought that they would afford an interesting comparison to 2,7-methanoaza[10]annulene²⁹. At the outset of this work the only synthesis of the tricyclic annulene (92) involved the [8+2] cycloaddition of 3-methoxy-3a-methyl-3a*H*-indene (100) with dimethyl acetylenedicarboxylate (DMAD) as the key step (Scheme 13)⁵⁷. It was envisaged that similar cycloaddition reactions with nitrogenous dienophiles would allow access to the aza[10]annulenes (94), (95) and (96).



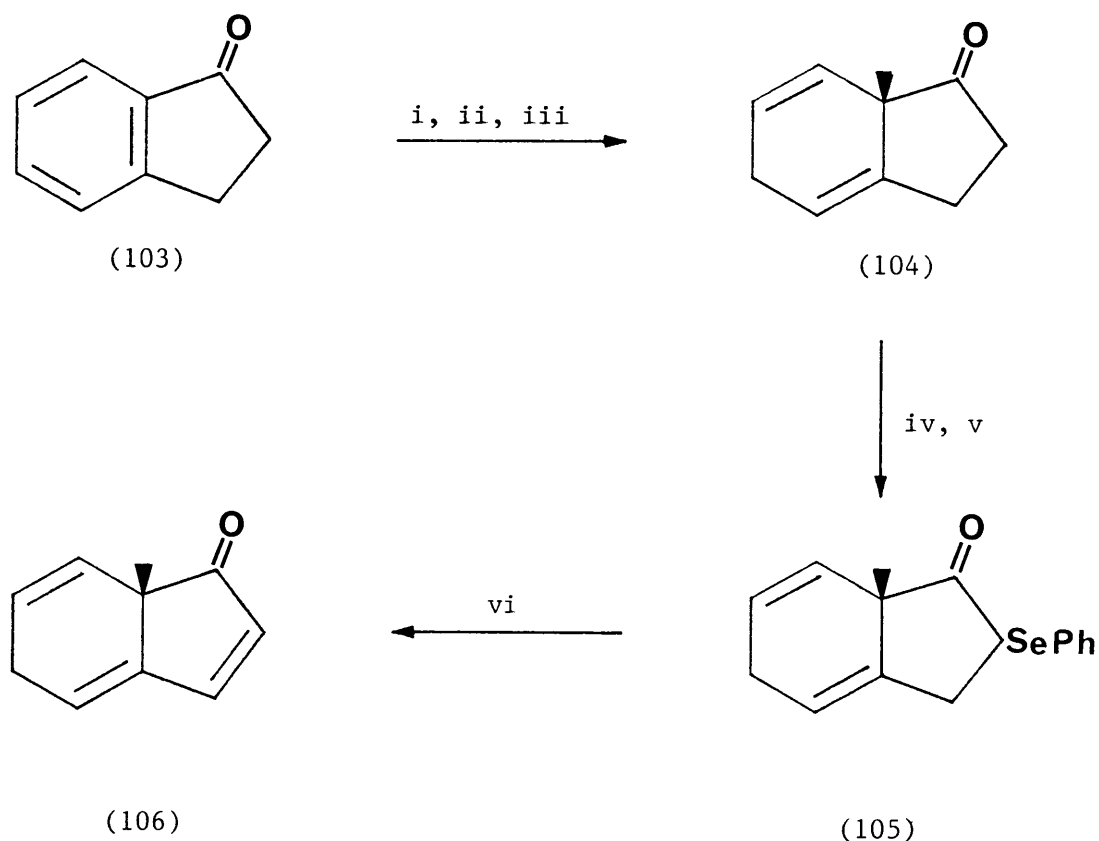
Scheme 13.

Reagents: i, DMAD; ii, H₂SO₄, MeOH, 0°C or *p*-TsOH, C₆H₆, 80°C; iii, LiAlH₄, Et₂O, 25°C; iv, BaMnO₄, CH₂Cl₂; v, Rh (PPh₃)₃Cl, C₆H₆, 80°C.

2.2 CYCLOADDITION ROUTES TO TRICYCLIC AZA[10]ANNULENES

2.2.1 The Synthesis of 3-Methoxy-3a-methyl-3aH-indene (100)

The Birch reduction and methylation of 1-indanone was first investigated by Narisada and Watanabe⁶⁴ and subsequently by Tuddenham⁶⁵ and McCague⁶⁰. A similar procedure was used in this investigation to give a reasonable yield (50%) of 7a-methyl-2,3,5,7a-tetrahydro-1H-inden-1-one (104). The reaction was carried out on a large scale and because of this, column chromatography was not a viable purification technique. Fractional distillation of the crude reaction mixture gave material of sufficient purity for use in the next step.

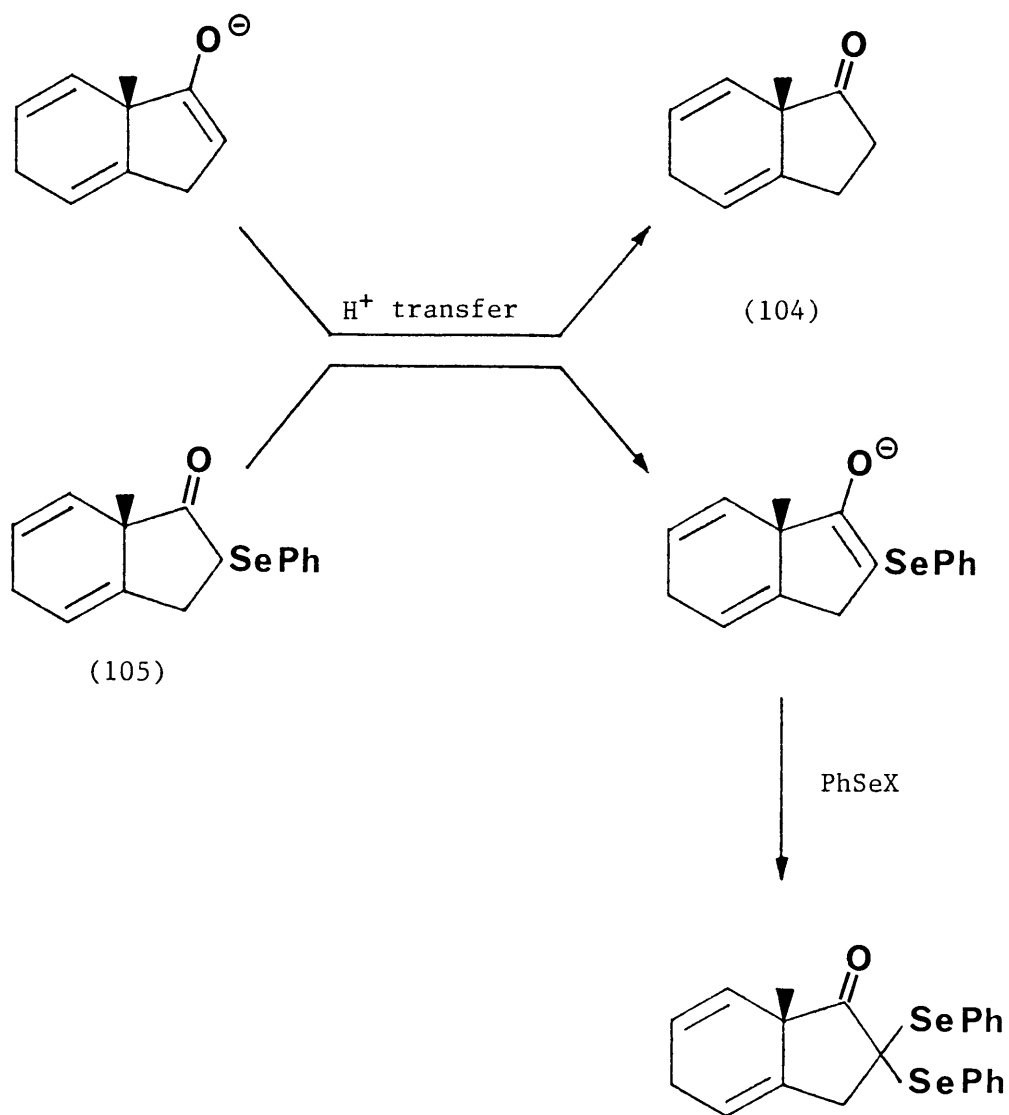


Scheme 14.

Reagents: i, K, *t*-BuOH, THF, NH₃, -78°C;
 ii, LiBr, THF; iii, MeI, H₂O, THF; iv, Me₃SiCl,
 NaI, Et₃N, CH₃CN, 40°C; v, PhSeBr, THF, -78°C;
 vi, H₂O₂, H₂O, pyridine, THF, 5°C.

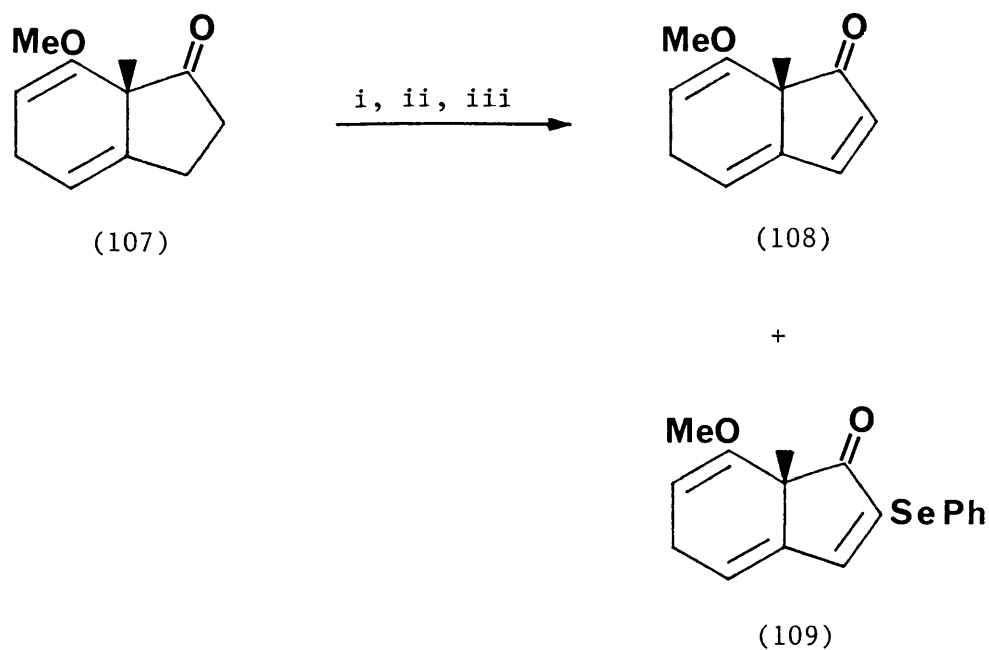
The introduction of a further unit of unsaturation into the five-membered ring to give compound (106) proved troublesome and despite various attempts to improve the yield of this transformation it remained only moderate (35-50%)⁶⁰. The best yields were obtained by converting the dienone (104) into its trimethylsilyl enol ether followed by treatment with phenylselenenyl bromide in tetrahydrofuran (THF) at -78°C ⁶⁰. The resulting selenide (105) was then oxidised to the corresponding selenoxide which underwent a *syn* elimination to give 5,7a-dihydro-7a-methyl-1*H*-inden-1-one (106).

An alternative route used by Tuddenham was found to result in lower yields⁶⁵. This involved the formation of the enolate anion of (104) using lithium di-isopropylamide (LDA) in THF followed by quenching with phenylselenenyl bromide. A similar oxidation and *syn* elimination procedure was then used. The low overall yield of this transformation was at first attributed to the oxidation step⁶⁵. However, the stability of the trienone (106) towards hydrogen peroxide and the observation that other oxidising agents gave similar yields, showed this assumption to be false⁶⁰. The problem was found to be an acid-base reaction which occurred during the selenation (Scheme 15). This unwanted side reaction has also been observed using different substrates. When 7-methoxydienone (107) is selenated under basic conditions and *m*-chloroperoxybenzoic acid (*m*-CPBA) is used as the oxidising agent the trienones (108) and (109) are isolated. This observation will be discussed more fully in Section 2.3.2 (p.119).



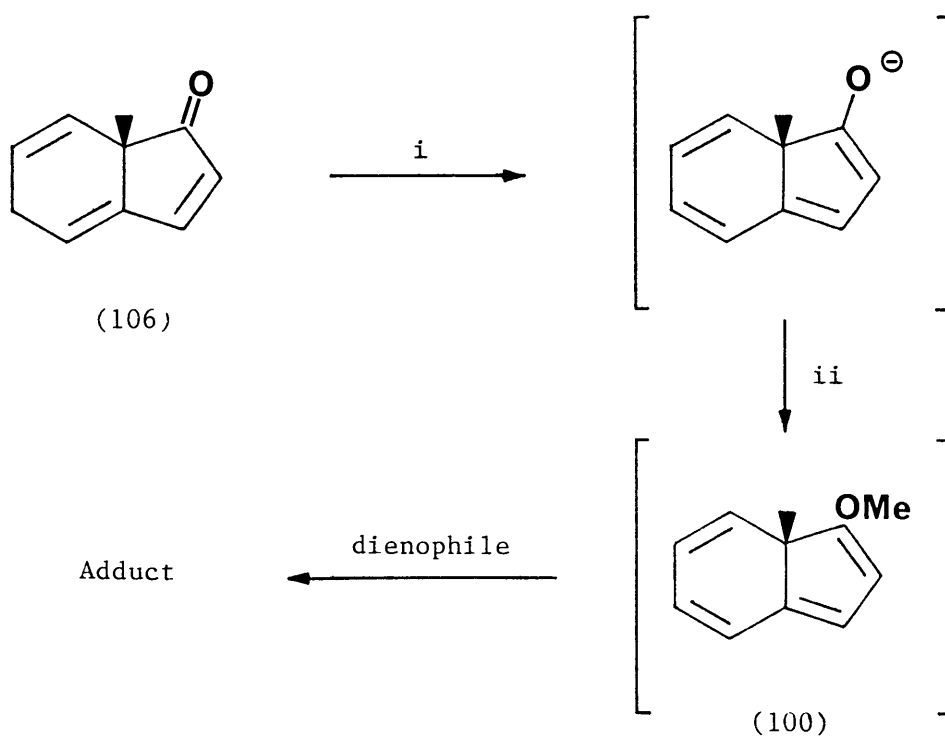
Scheme 15.

3-Methoxy-3a-methyl-3a*H*-indene (100) was generated using the method developed by Tuddenham⁶⁶. This involved the enolisation of the trienone (106) using potassium hydride and 18-crown-6 in 1,2-dimethoxyethane (DME), followed by the trapping of the enolate anion with methyl fluorosulphonate (Scheme 17). The use of this highly toxic material was required to ensure that alkylation occurred on oxygen. The resulting 3a*H*-indene (100) is not usually isolated but reacted *in situ* with a suitable dienophile.



Scheme 16.

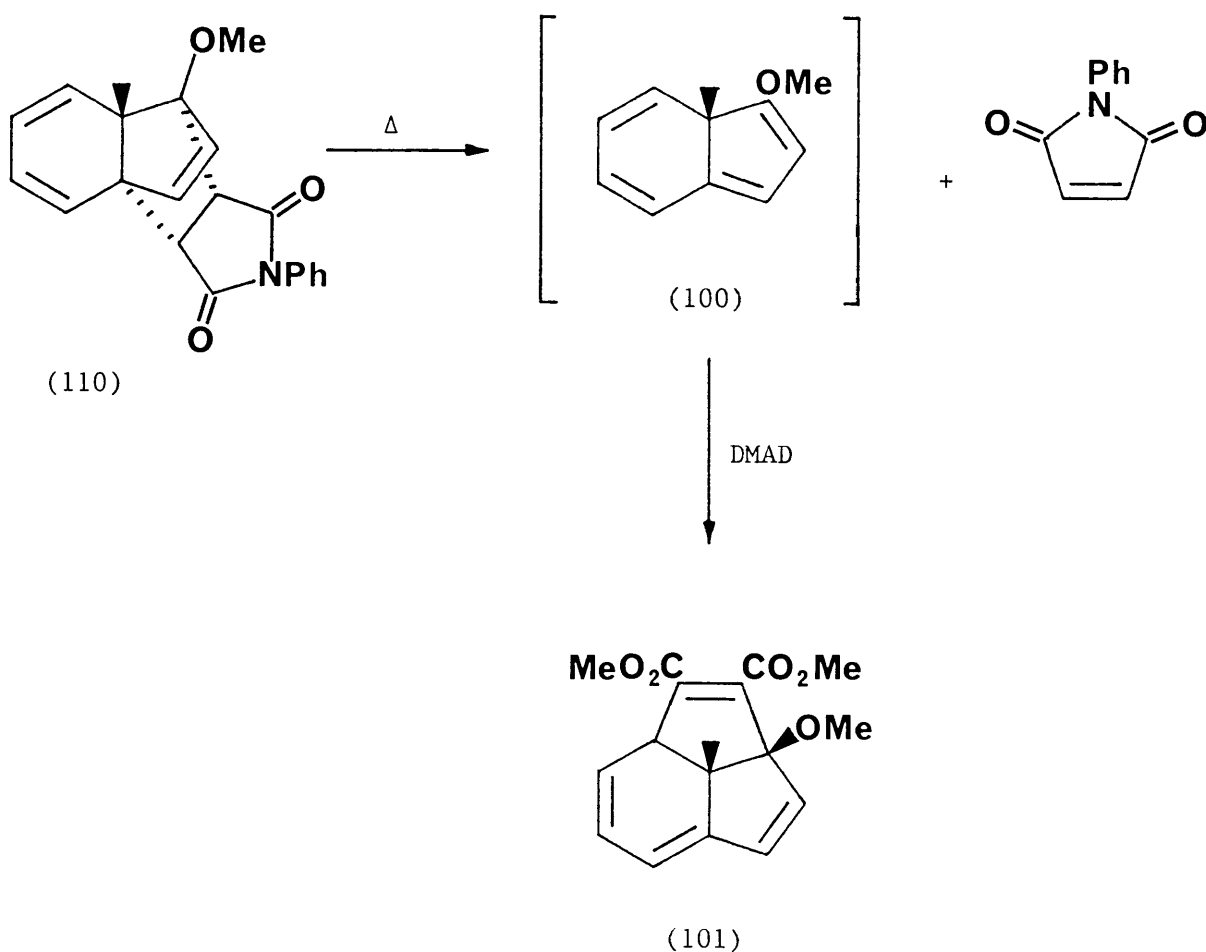
Reagents: i, LDA, THF, -78°C ; ii, PhSeCl, THF, -78°C ; iii, *m*-CPBA, Et_2NH , -10°C .



Scheme 17.

Reagents: i, KH, 18-crown-6, DME, -23°C ; ii, MeOSO_2F .

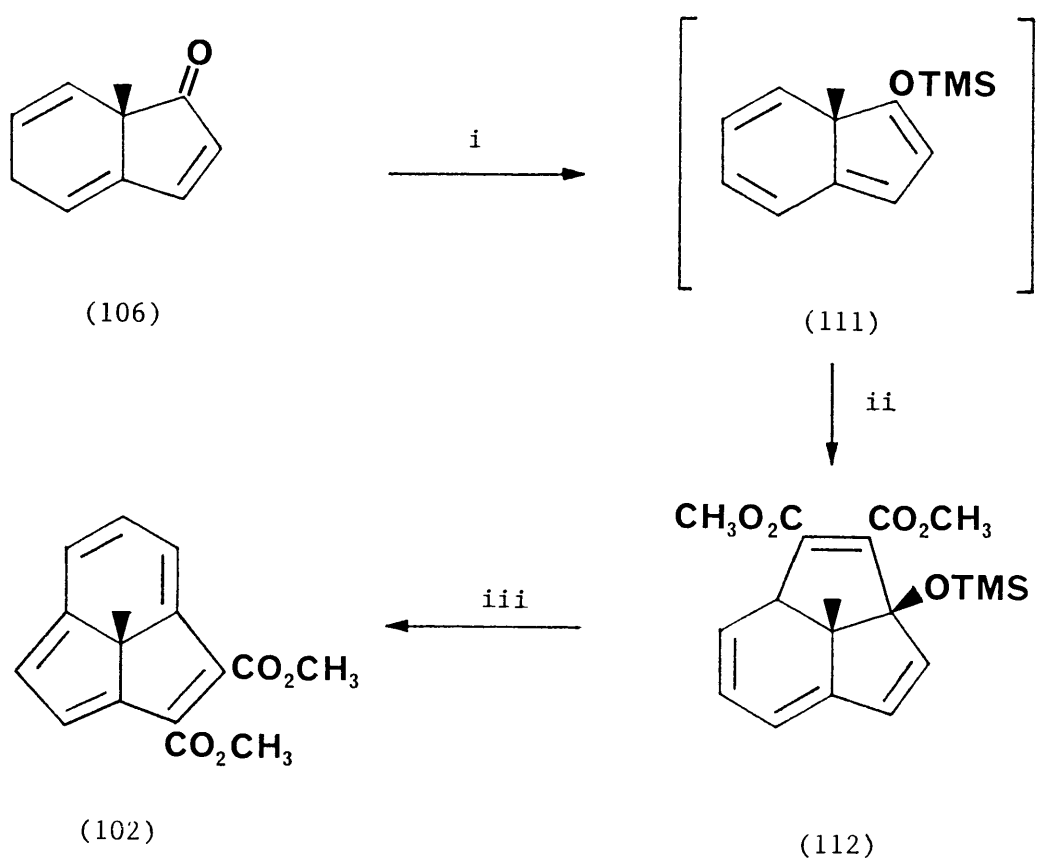
An alternative method of generating the 3a*H*-indene (100) *via* the retro-[4+2] cycloaddition of the *N*-phenylmaleimide adduct (110) was also investigated. Tuddenham showed that the reaction of 3-methoxy-3a-methyl-3a*H*-indene and *N*-phenylmaleimide gave the [4+2] cycloadduct (110) which rearranged to a mixture of *exo*- and *endo*-[8+2] cycloadducts on heating^{66b}. It was later shown by McCague, using trapping experiments, that the 3a*H*-indene (100) was an intermediate in the process and this was seen as evidence for a dissociation-recombination mechanism for the thermal rearrangement⁶⁰.



The *N*-phenylmaleimide adduct (110) was synthesised in 46% yield using the method developed by Tuddenham. It was envisaged that the

regeneration of the 3a*H*-indene (100), *via* the thermolysis of the adduct (110), would provide a useful method of assessing the suitability of different dienophiles. An excess of the dienophile was used in order to inhibit the [8+2] cycloaddition of the 3-methoxy-3a-methyl-3a*H*-indene (100) with the liberated *N*-phenylmaleimide. These reactions will be discussed later in this section (p. 75).

The use of a related tetraene, 3a-methyl-3-trimethylsiloxy-3a*H*-indene (111), was pioneered by McCague⁶⁰. Treatment of the trienone (106) with trimethylsilyl trifluoromethanesulphonate and triethylamine gave a solution of the 3a*H*-indene (111), which was reacted *in situ* with various dienophiles. The reaction with DMAD gave the cycloadduct (112) which was then converted into the annulene (102) on treatment with *p*-toluenesulphonic acid (Scheme 18)⁶⁰.



Scheme 18.

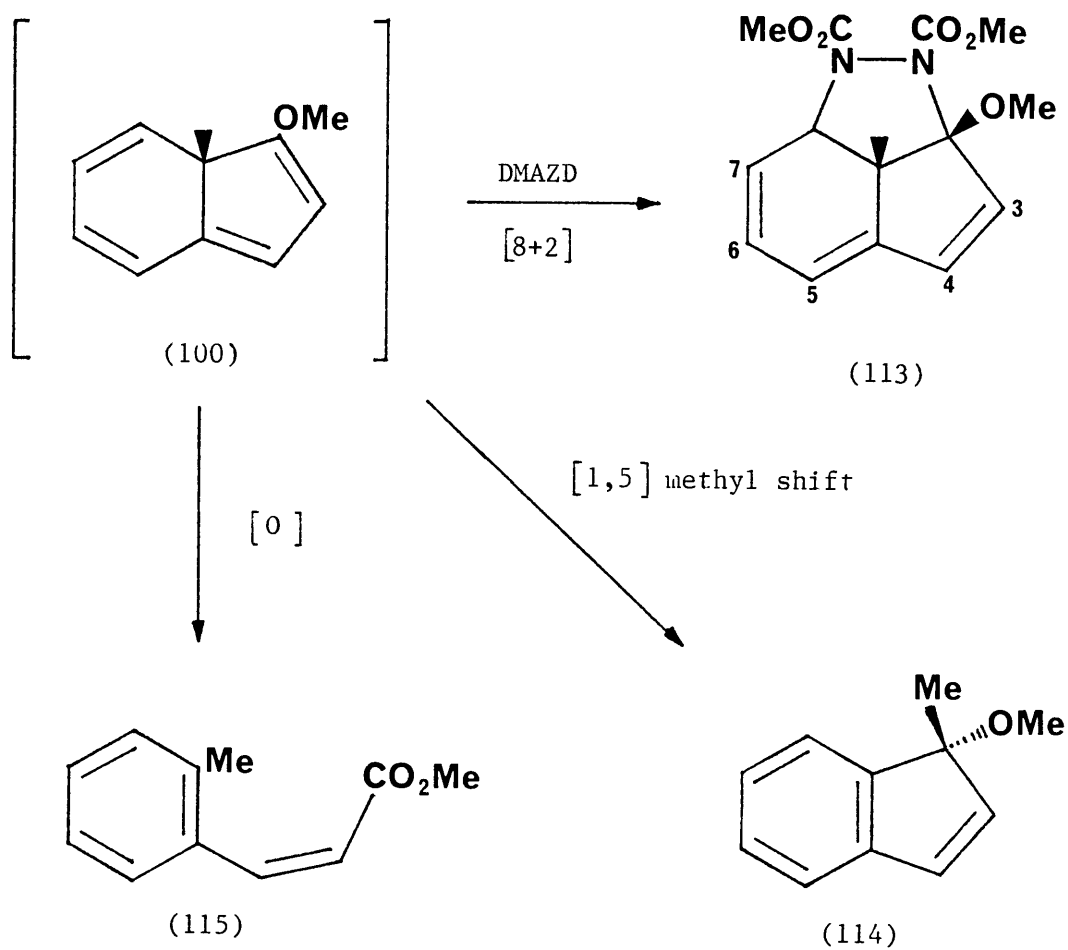
Reagents: i, $\text{Me}_3\text{SiOSO}_2\text{CF}_3, \text{Et}_3\text{N}, \text{Et}_2\text{O}$;
 ii, DMAD; iii, *p*-TsoH, C_6H_6 .

2.2.2 Cycloaddition Reactions of 3-Methoxy-3a-methyl-3aH-indene with Azo Compounds

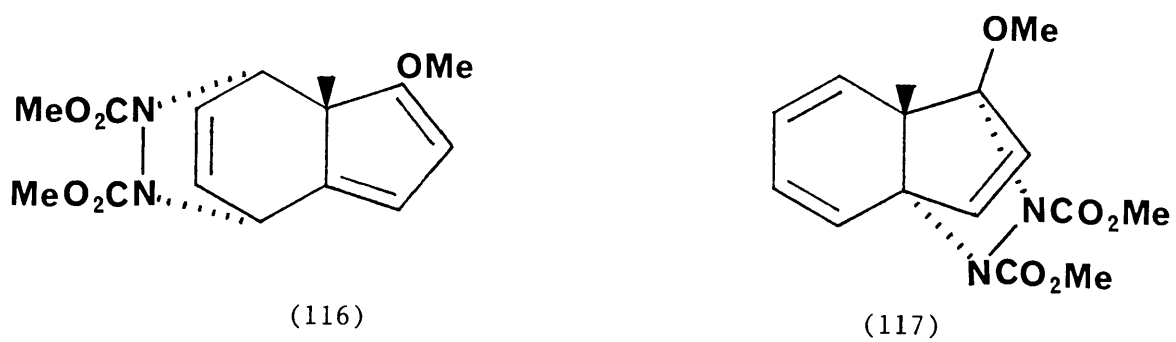
The [8+2] cycloaddition of the 3aH-indene (100) with diethyl azodicarboxylate (DEAZD) was briefly studied by Tuddenham^{66b}. The yield of this reaction was found to be low (~24%) and the product could not be isolated in a pure state. It was decided to reinvestigate this reaction with a view to the synthesis of the 1,2-diaza [10]annulene (94).

Dimethyl azodicarboxylate (DMAZD) was chosen as the dienophile since kinetic studies on the reaction of azodicarboxylates with cyclopentadiene showed that DMAZD reacts 5-6 times faster than the diethyl azoester (DEAZD)⁶⁷. 3-Methoxy-3a-methyl-3aH-indene (100) was formed as described previously and reacted with DMAZD. It was observed that the azo compound was consumed faster than the 3aH-indene and more dienophile was added at intervals until no 3aH-indene remained as indicated by t.l.c.. This gave a 50% yield of the required [8+2] cycloadduct (113) together with small amounts of 1-methoxy-1-methyl-1H-indene (114) and 2-methyl-*cis*-cinnamate (115) (Scheme 19). The former by-product arises from the 3aH-indene (100) *via* a [1,5] sigmatropic migration of the methyl group and the later by oxidative decomposition of (100)⁶⁶.

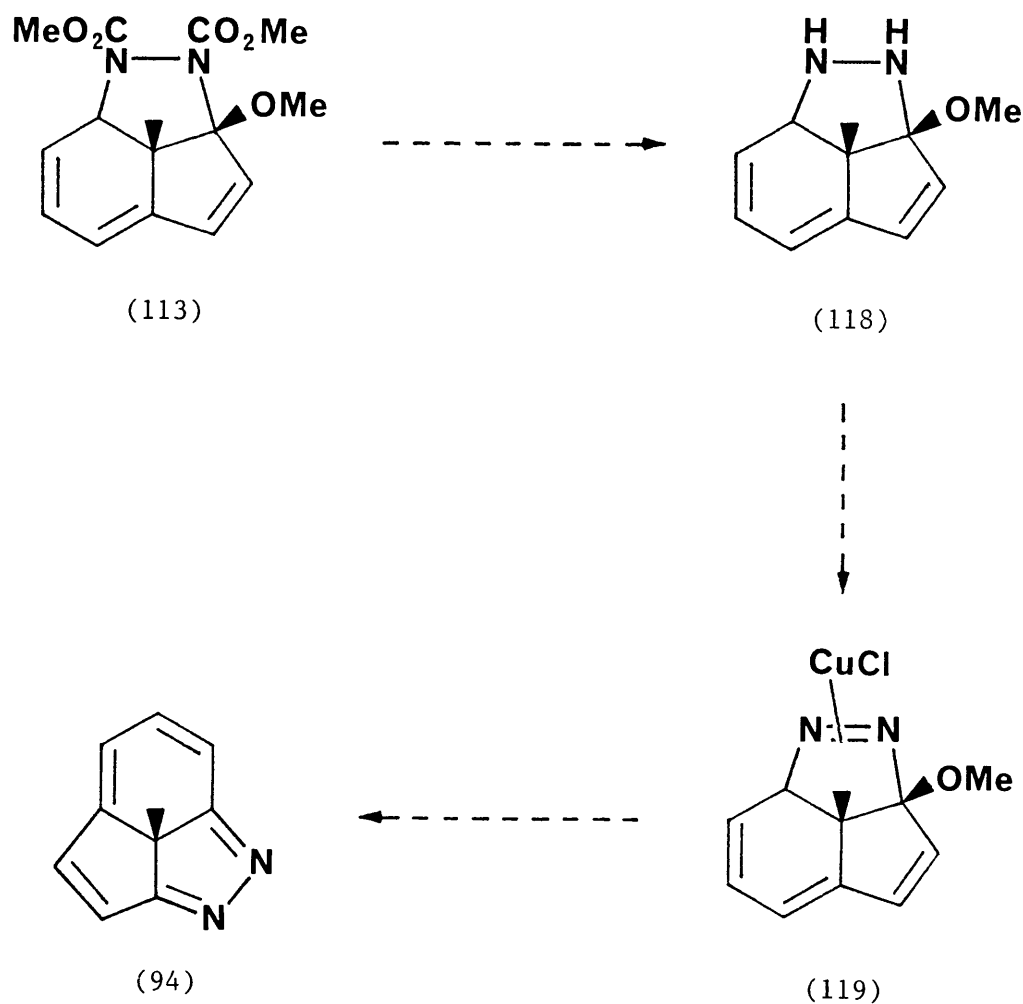
The assignment of structure (113) was based on spectroscopic evidence. The ¹H n.m.r. spectrum contains a one proton doublet at δ4.34 which is assigned to the hydrogen α to nitrogen (H-7a). There are two possible [4+2] cycloadducts (116) and (117). One of these, (116), would require two protons α to nitrogen whilst the other would not require any protons in this region of the ¹H n.m.r. spectrum. Other spectroscopic evidence and the elemental analysis were also in accord with structure (113).



Scheme 19.



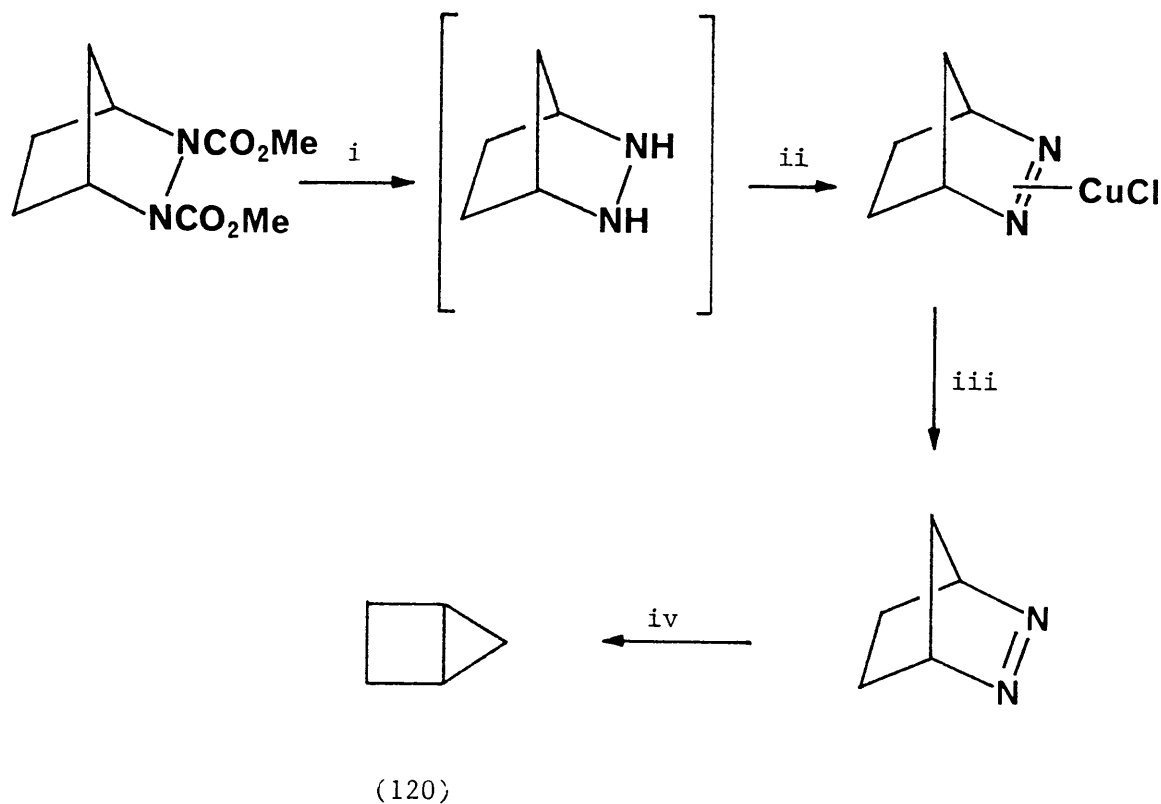
It was hoped that the [8+2] cycloadduct (113) could be converted into the 1,2-diaza[10]annulene (94). The proposed route involved hydrolysis of the urethane functionality followed by oxidation to the azo compound (119). Subsequent elimination of the elements of methanol and decomplexation would give the desired compound (94) (Scheme 20).



Scheme 20.

It was decided to use copper (II) chloride to oxidise the hydrazine (118) since this would allow the isolation of the copper (I) complex (119), which was expected to be more stable than the free azo

compound. A similar sequence of reactions has been used in the preparation of other azo compounds and this is exemplified by Gassman's synthesis of bicyclo[2.1.0]pentane (120) (Scheme 21)⁶⁸.



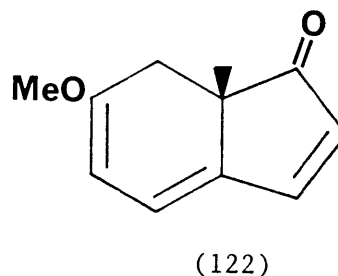
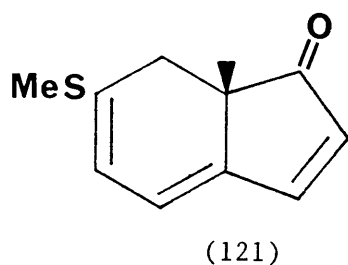
Scheme 21.

Reagents: i, KOH, HOCH₂CH₂OH;
ii, CuCl₂; iii, NaOH; iv, Δ.

The hydrolysis of the adduct (113) was attempted using potassium hydroxide in aqueous methanol, followed by *in situ* oxidation using cupric chloride⁶⁸. This did not give the expected product (119) but led to a multi-component mixture from which no identifiable product could be obtained. Although the reaction of trimethylsilyl iodide in chloroform⁶⁹ with (113) caused the disappearance of the signals in the ¹H n.m.r. spectrum associated with the urethane groupings, subsequent work up of the reaction failed to give any recognisable

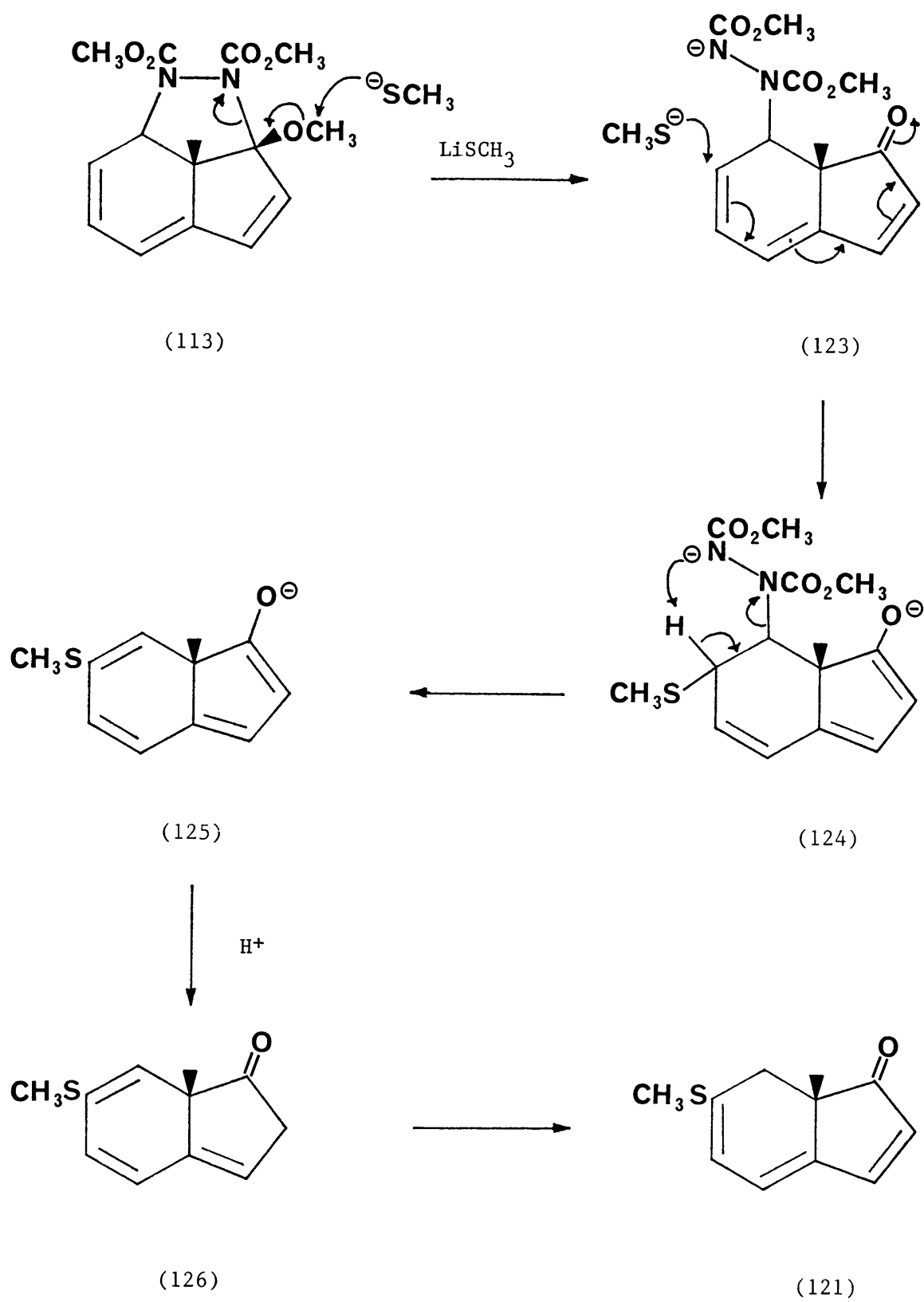
product. Attempted hydrolysis of the adduct (113) using either potassium *tert*-butoxide in dimethyl sulphoxide (DMSO)^{70a} or methyl-lithium in THF^{70b} also resulted in complex mixtures.

A related transformation has been effected by using lithium thiomethoxide in hexamethylphosphoramide (HMPA)⁷¹. The use of this reagent with the cycloadduct (113) gave a multi-component mixture from which only one compound was isolated. This was assigned structure (121) on the basis of its spectral properties; in particular the striking resemblance of the ¹H n.m.r. spectrum with that of 7,7a-dihydro-6-methoxy-7a-methyl-1*H*-inden-1-one (122)⁷².



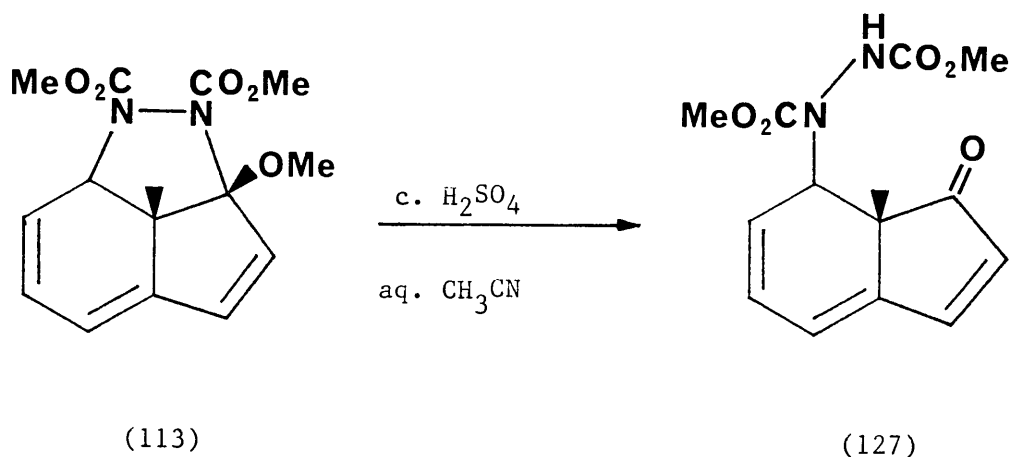
One possible mechanism for the formation of (121) is shown (Scheme 22). The final isomerisation of (126) into (121) presumably results from the greater thermodynamic stability of (121) in which the electron withdrawing and releasing groups are conjugated. The low yield of this product (9.5%) is not unexpected when one considers the intermediacy of the reactive anion (125).

The failure to hydrolyse adduct (113) under alkaline conditions prompted an investigation into the use of acidic hydrolysis. Treatment of the cycloadduct (113) with a drop of concentrated sulphuric acid in aqueous acetonitrile gave the ketone (127) *via* cleavage of the



Scheme 22.

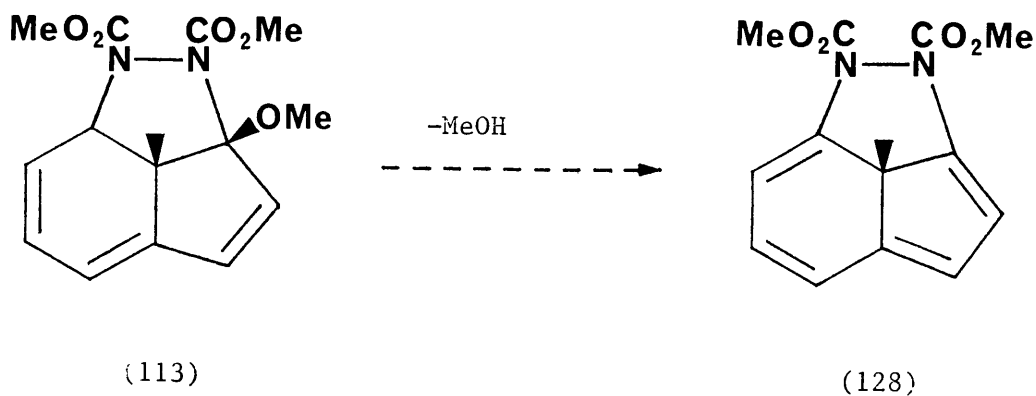
aminal linkage. The ^1H n.m.r. spectrum of this compound was found to be temperature dependent and this was attributed to hindered



rotation about the N-C bond of the urethane group. The signals assigned to H-5, H-6 and H-7 and one of the urethane groups were observed to sharpen considerably on warming. Attempts to utilize this compound in the synthesis of the 1,2-diaza[10]annulene (94) will be discussed in Section 2.3.1 (page 104).

An investigation into the possibility of eliminating the elements of methanol from adduct (113) to give compound (128) was prompted by the failure of the hydrolysis reactions. It was thought that the removal of the aminal linkage, which has been shown to be susceptible towards hydrolysis, would facilitate the cleavage of the urethane groups. However, it must be remembered that compound (128) incorporates a 3aH-indene skeleton which is known to be very reactive.

This elimination reaction was attempted using *p*-toluenesulphonic acid in refluxing benzene, and *n*-butyl lithium in THF. Unfortunately both sets of conditions gave rise to complex reaction mixtures from which no identifiable products were isolated.

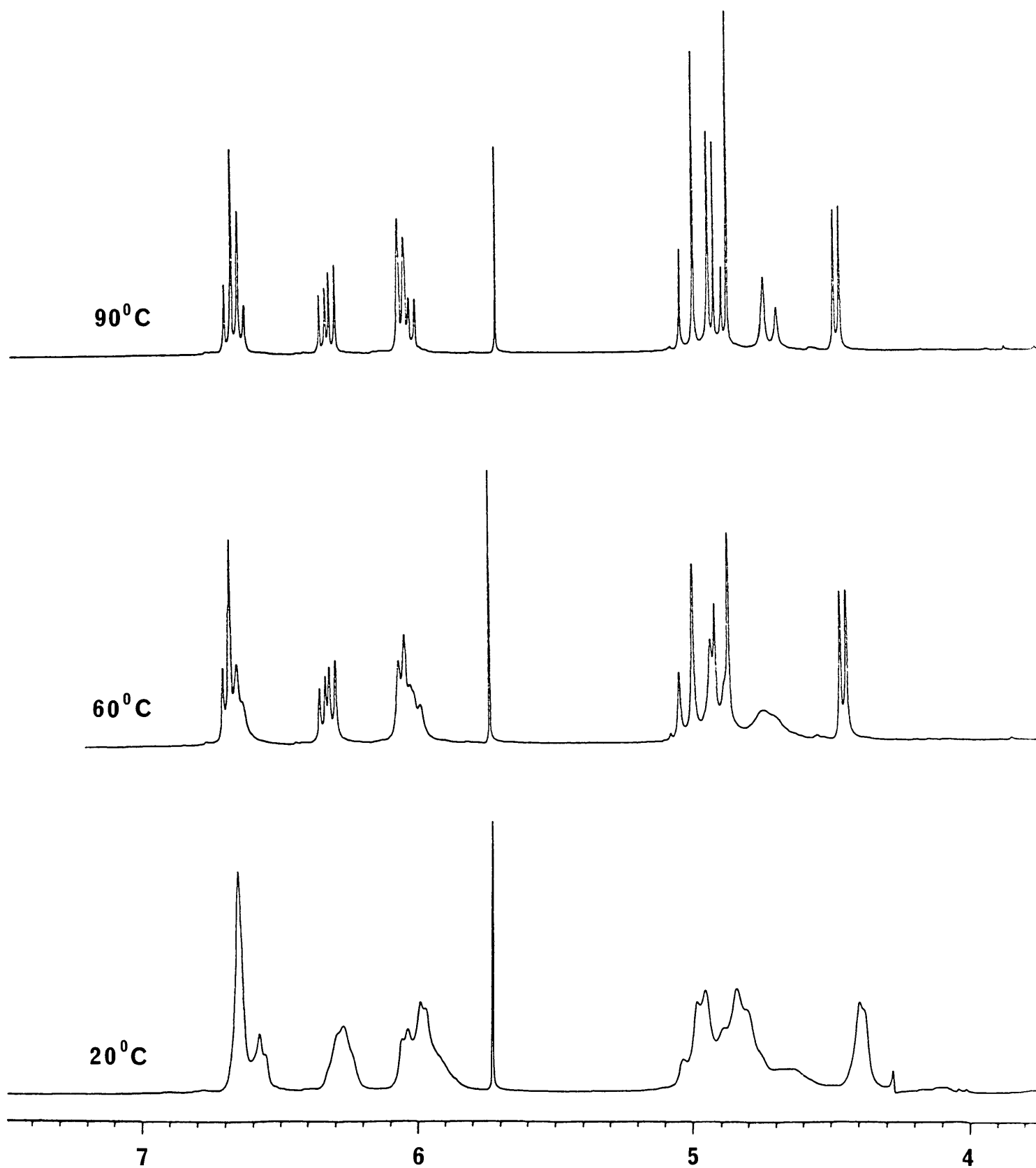
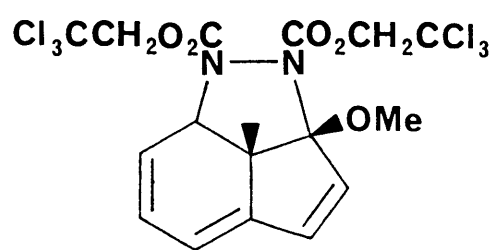


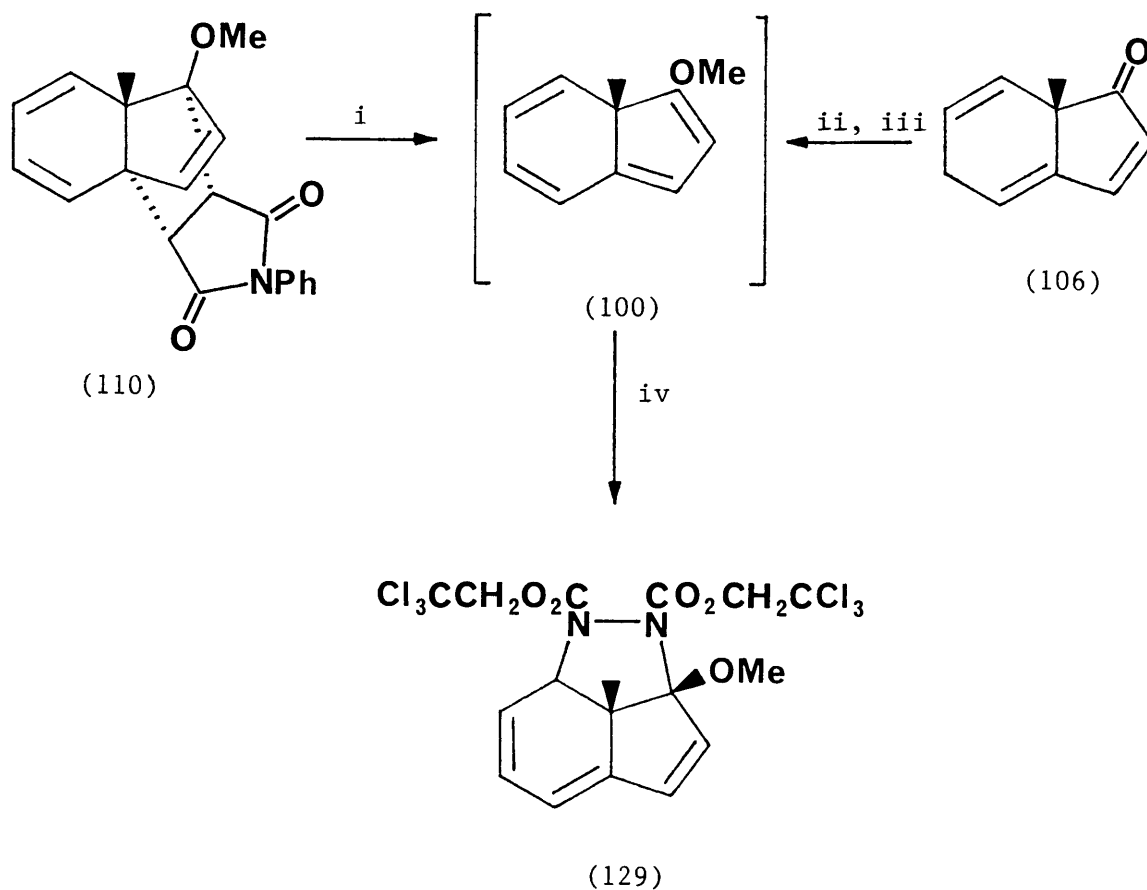
At this juncture a study of the use of an alternative azo compound was instigated. The compound chosen was *bis*-trichloroethyl azodicarboxylate since this is known to participate in cycloaddition reactions, and the conditions required to cleave the urethane groups in the cycloadducts are relatively mild⁷³.

The reaction of *bis*-trichloroethyl azodicarboxylate and the 3a*H*-indene (100) was performed in toluene at 100°C, using the thermal decomposition of the *N*-phenylmaleimide adduct (110) as the source of 3a*H*-indene (100). This gave a 63% yield of the required [8+2] cycloadduct (129). The cycloaddition was also carried out generating the 3a*H*-indene (100) from the trienone (106) as described previously. In this case only a low yield of the product (129), which could not be separated from an impurity, was obtained.

The ¹H n.m.r. spectrum of (129) showed considerable temperature dependence with all the signals being considerably broadened at ambient temperature. The resonances attributed to the methylene protons of the two urethane groups were observed to resolve into two AB quartets on warming (Figure 1). This is because the methylene groups are prochiral.

FIGURE 1

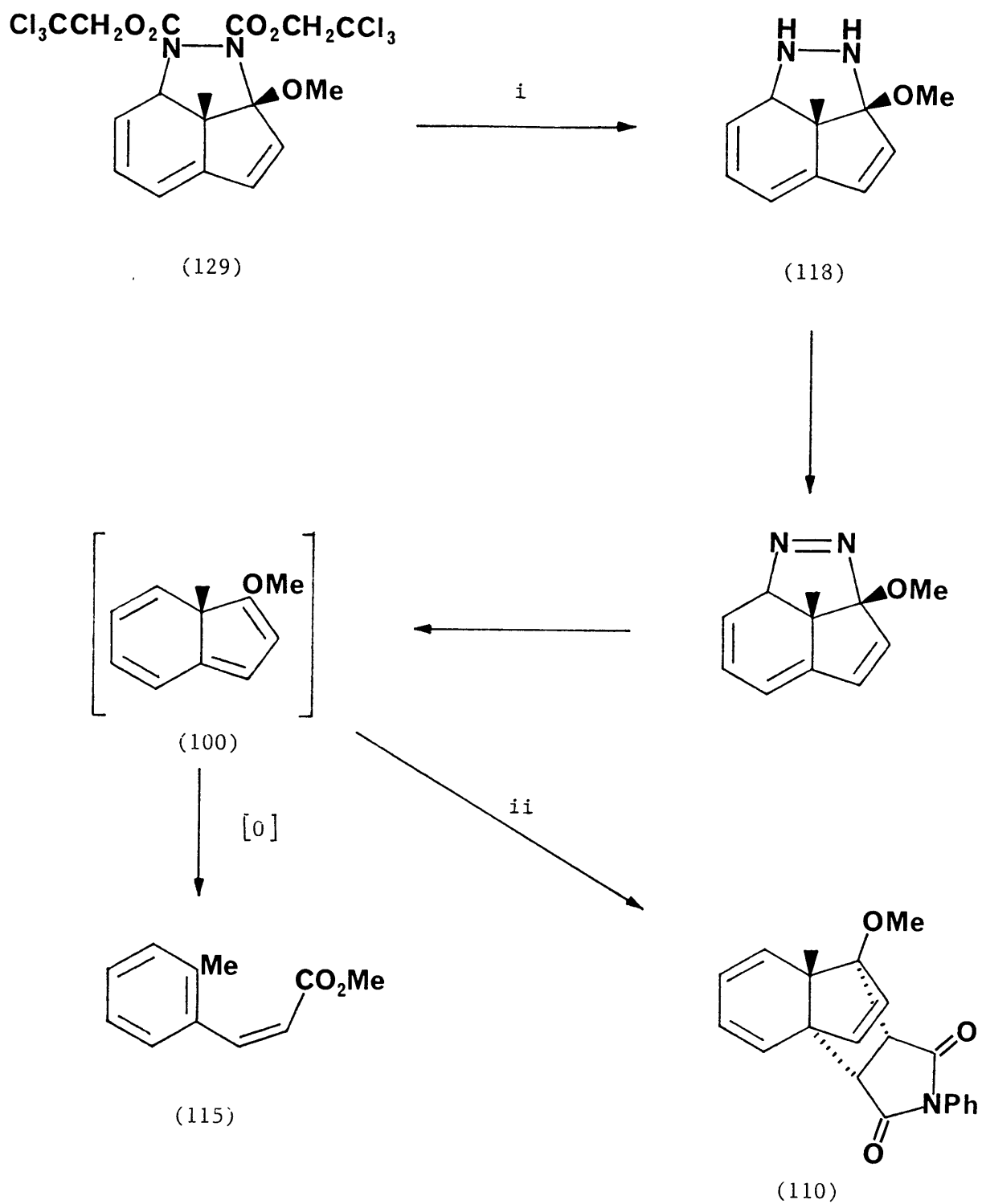




Scheme 23.

Reagents: **i**, toluene, 100°C ; **ii**, KH, DME
 18-crown-6; **iii**, MeOSO_2F , -23°C ;
iv, $\text{Cl}_3\text{CCH}_2\text{O}_2\text{CN}=\text{NCO}_2\text{CH}_2\text{CCl}_3$.

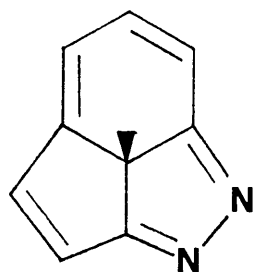
The conversion of (129) into the hydrazine (118) was undertaken using activated zinc in a mixture of acetic acid and THF⁷⁴. This was followed by *in situ* oxidation using cupric chloride. However, the only product isolated from this reaction was the *cis*-cinnamate (115), and a possible mechanism for its formation is shown (Scheme 24).



Scheme 24.

Reagents: i, $\text{Zn}, \text{AcOH}, \text{THF}, 0^\circ\text{C}$;
 ii, *N*-phenylmaleimide.

Evidence for the intermediacy of the tetraene (100) was obtained by repeating the reaction in the presence of *N*-phenylmaleimide to intercept any 3a*H*-indene (100) formed; 26% of the *N*-phenylmaleimide adduct (110) was isolated. The observed sensitivity of the hydrazine (118) was disappointing and further investigation of the route outlined in Scheme 20 was curtailed.

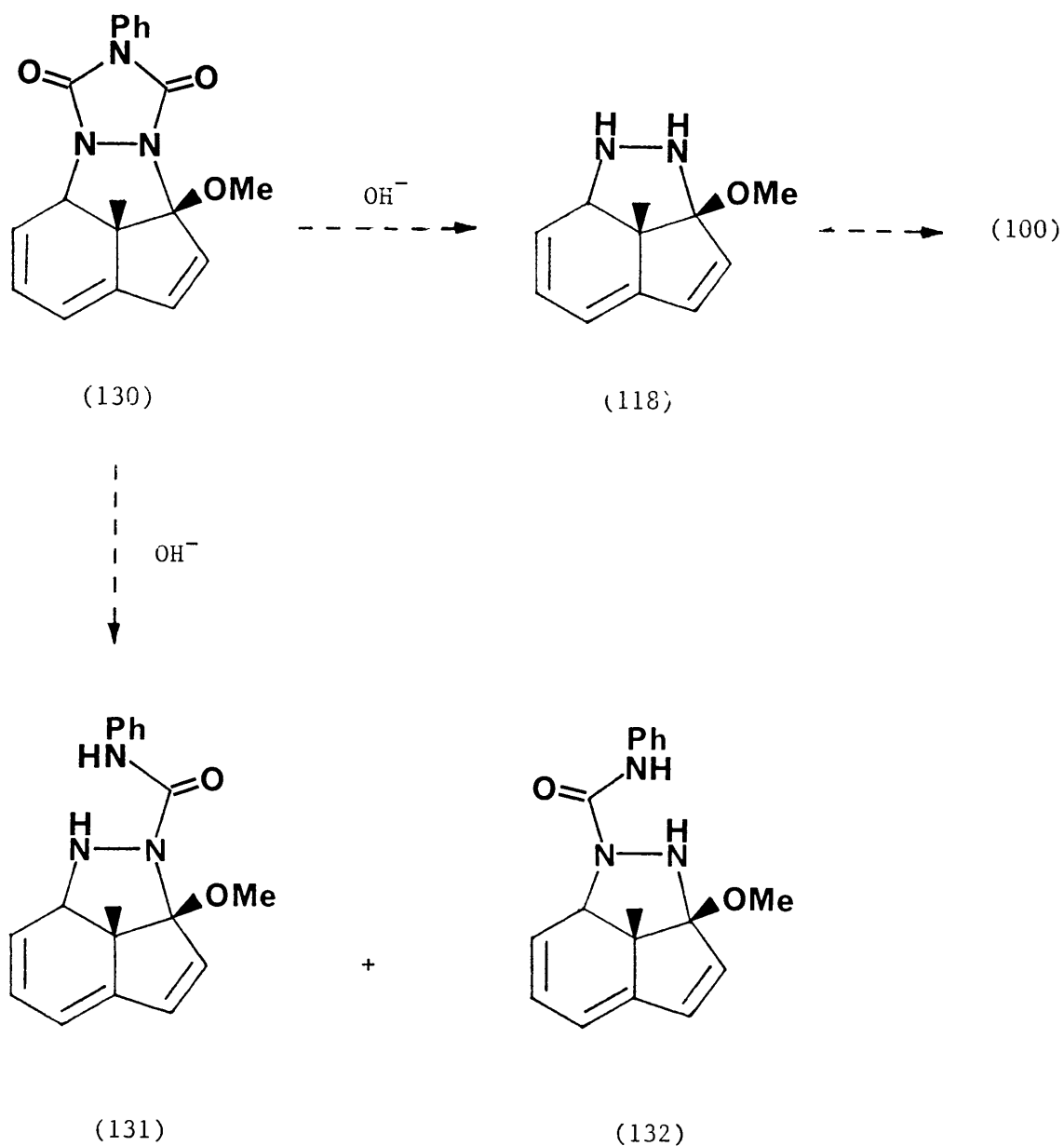


(94)

The [8+2] cycloadduct (130), obtained from the reaction of 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) with 3-methoxy-3a-methyl-3a*H*-indene (100), was investigated as a possible precursor to the 1,2-diaza[10]annulene (94). The alkaline hydrolysis of compound (130) would be expected to lead to the unstable hydrazine (118). Alternatively, partial hydrolysis products (131) and (132) might be isolated and these may provide a route to the required annulene (94) (Scheme 25).

Treatment of the cycloadduct (130) with methanolic potassium hydroxide⁷⁵ gave a 49% yield of a product which was identified from a consideration of its spectroscopic properties as structure (133).

The mass spectrum exhibited a molecular ion peak at 309 m.u. [M^+ of (130) 335 m.u.] which indicated that partial hydrolysis had occurred.

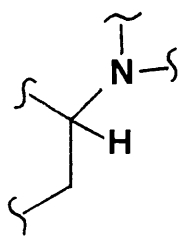


Scheme 25.

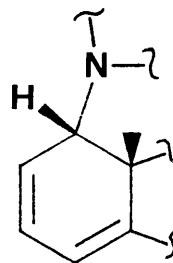
An examination of the ^1H n.m.r. spectrum showed the presence of only three olefinic protons and thus structures (131) and (132) were discounted since they require five protons in this region. The observation that the product contained four aliphatic protons, two of which

were α to nitrogen, implied that some rearrangement process had occurred.

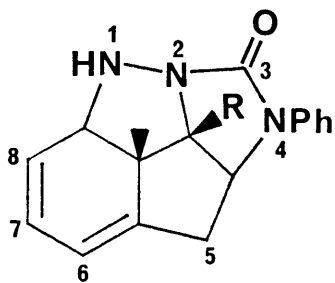
From a consideration of ^1H n.m.r. decoupling experiments the partial structures (A) and (B) were deduced. The products (133) and (134) have structures which are compatible with these fragments.



(A)

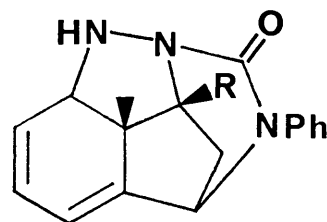


(B)



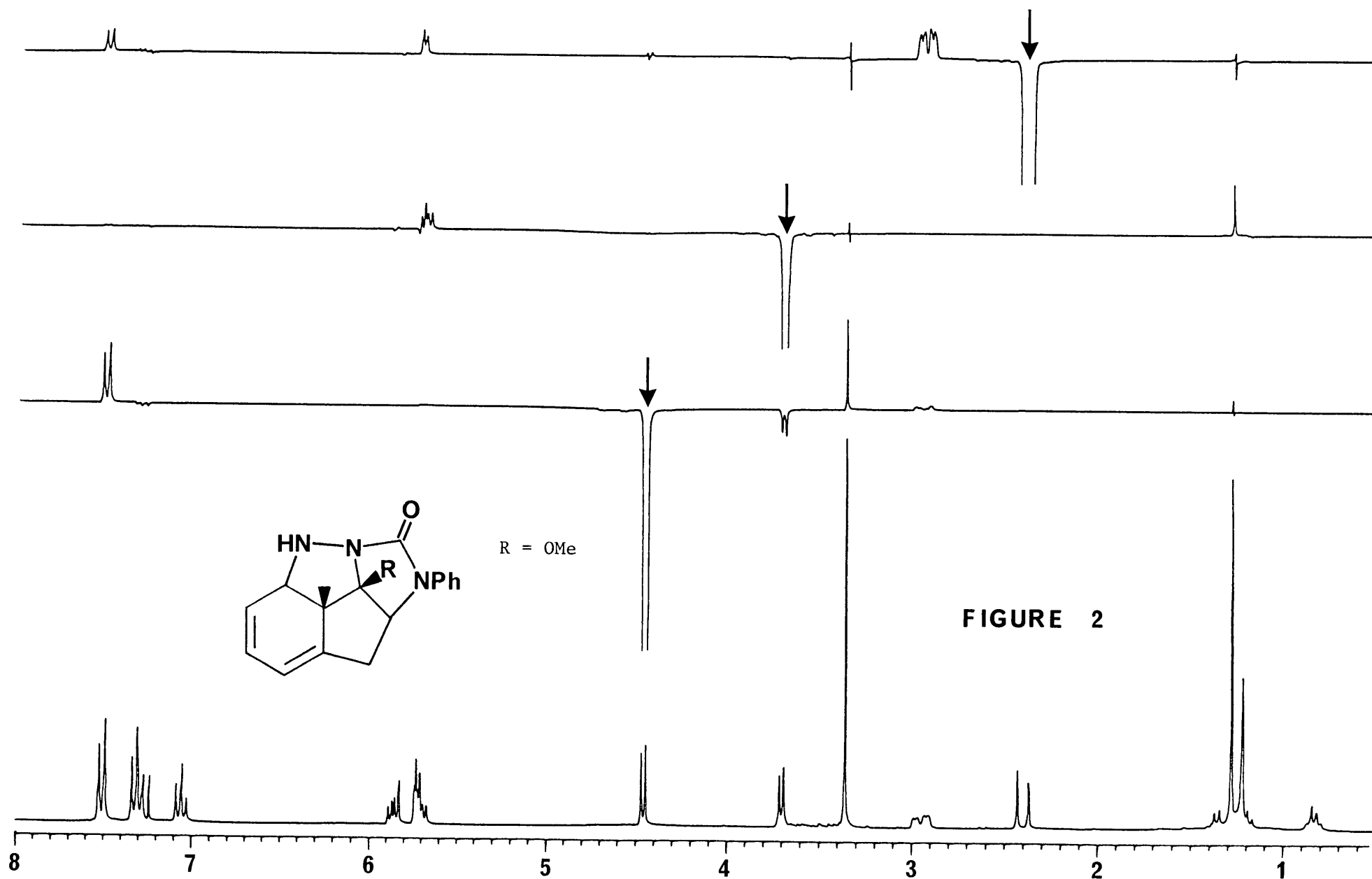
(133)

R = OMe

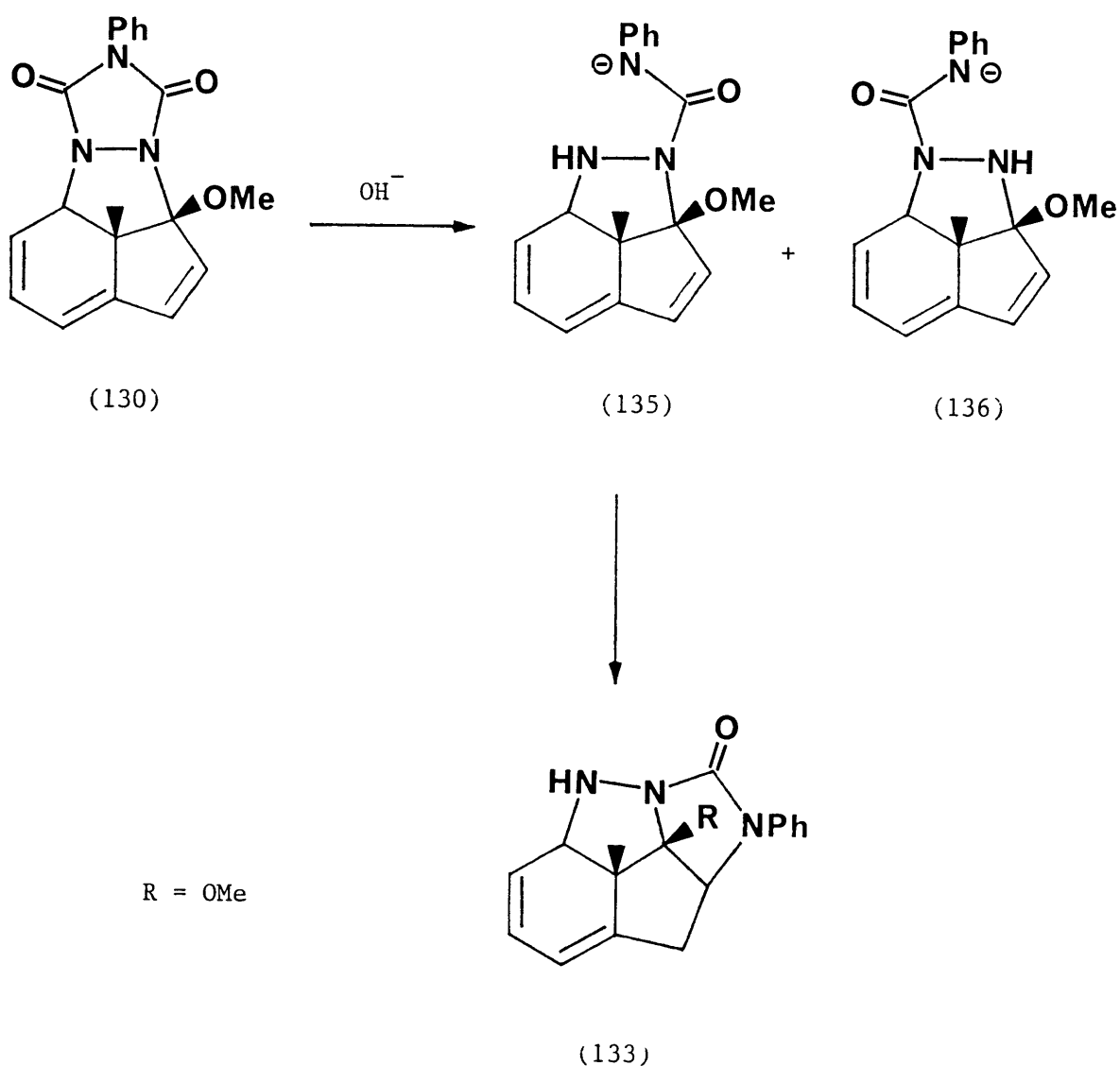


(134)

An n.O.e. difference experiment allowed the assignment of the reaction product as compound (133). Irradiation of H-4a caused an enhancement of the methoxy signal thus establishing their close proximity (Figure 2). A small enhancement of the olefinic resonance assigned to H-6 was also observed on irradiation of H-5 β .



The mechanism proposed for the formation of compound (133) is shown in Scheme 26. The hydrolysis reaction should give both (135)



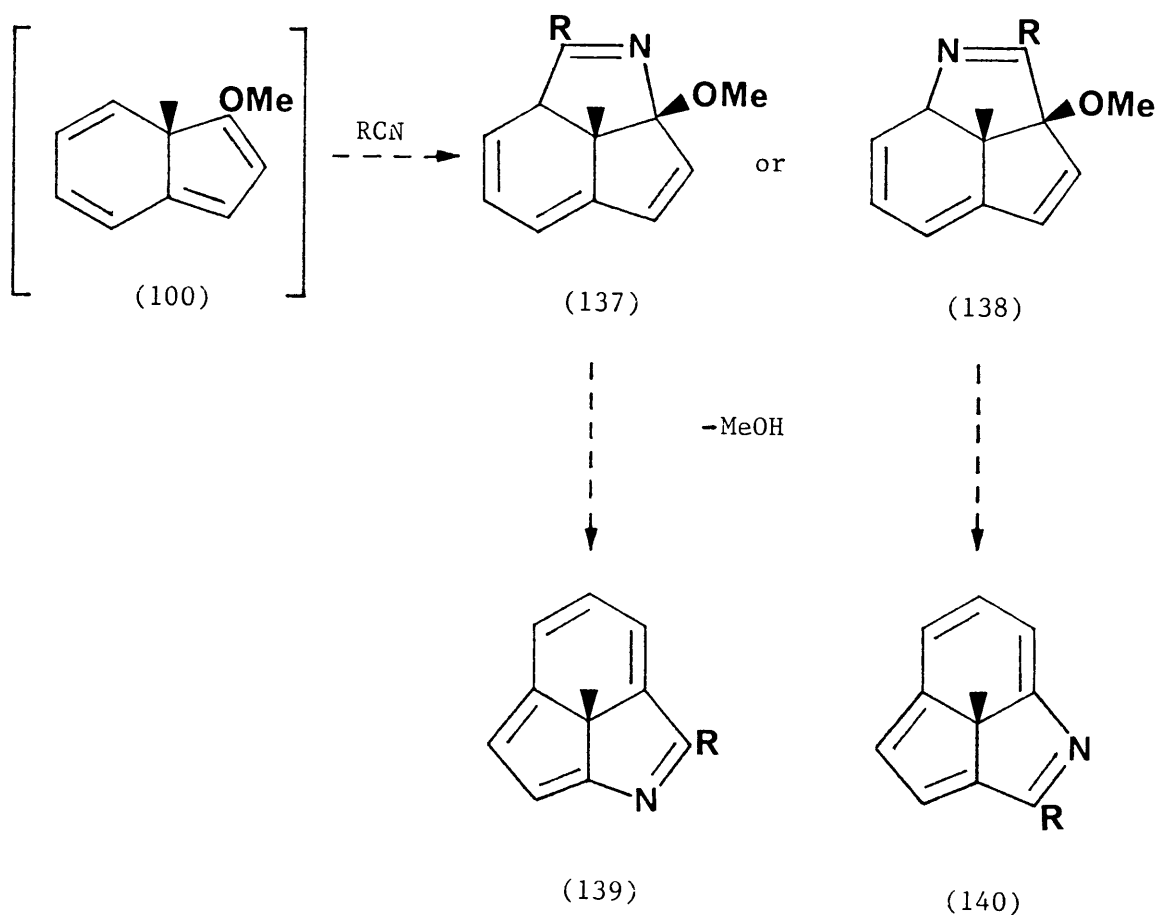
Scheme 26.

and (136) and the fact that no product derived from (136) is obtained may be because subsequent reaction leads to the unstable 3aH-indene (100). The driving force for the cyclisation is unclear although one factor may be the relief of strain in the five membered ring.

The hydrolysis of the cycloadduct (130) does not lead to a precursor of the required 1,2-diaza[10]annulene (94) and further investigation of this synthetic strategy was abandoned.

2.2.3 Cycloaddition Reactions of 3a-Methyl-3-substituted-3aH-indenes (100) and (111) with Nitriles

The synthesis of 7b-methyl-7bH-cyclopent[*cd*]indene (92) *via* the [8+2] cycloaddition reaction of DMAD with the 3aH-indene (100) prompted the investigation of the corresponding reaction using an activated nitrile. It was envisaged that the elimination of the elements of methanol from the resulting [8+2] cycloadduct would allow the synthesis of an aza[10]annulene (Scheme 27).



Scheme 27.

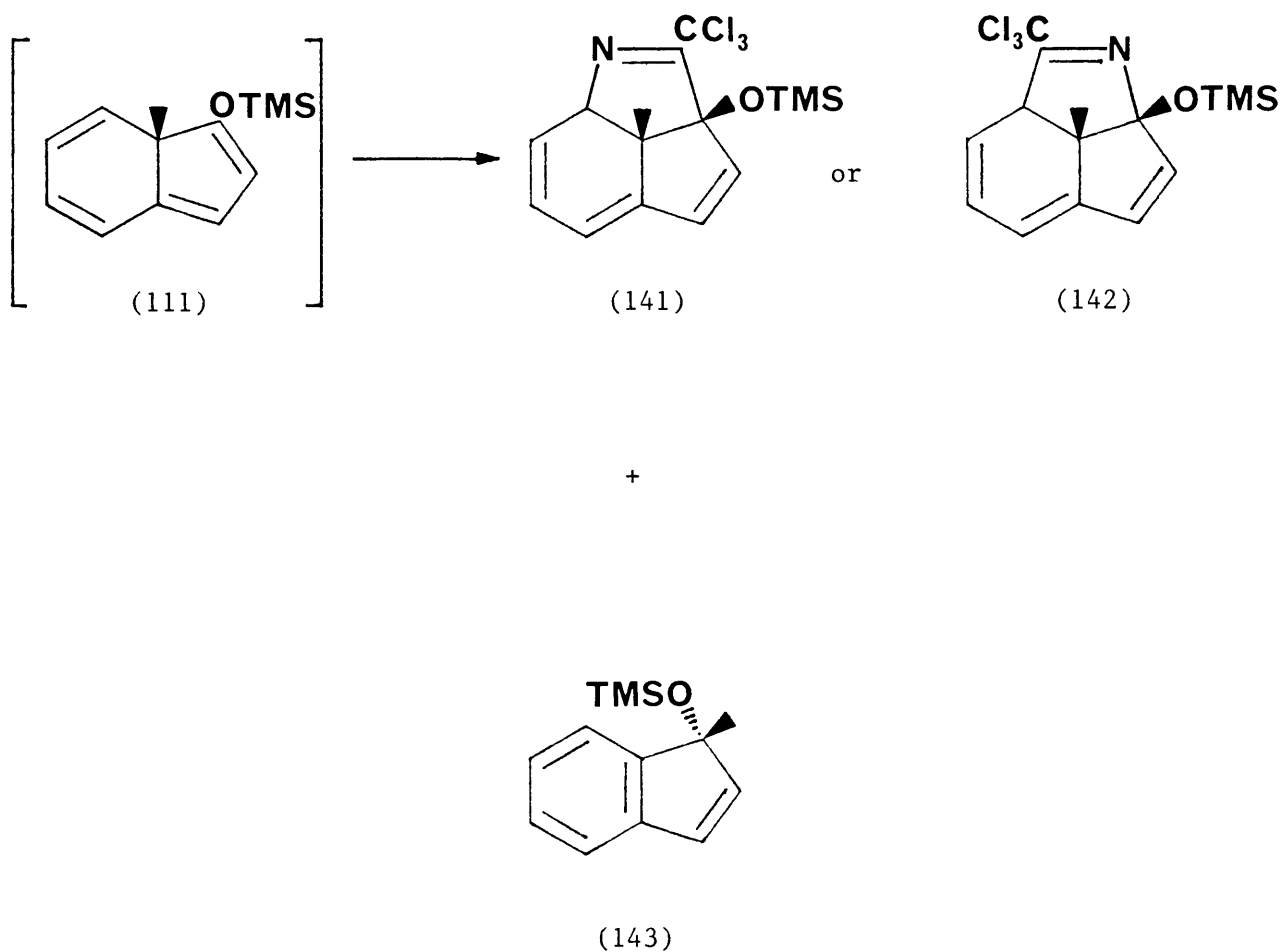
Cycloaddition reactions of simple nitriles are known to require high temperatures but this may be circumvented by using an activated nitrile⁷⁶. Cyanides with a strong electron withdrawing group in the α -position are known to participate more readily in cycloaddition reactions.

The generation of the 3a*H*-indene (100), *via* the decomposition of the *N*-phenylmaleimide adduct (110), in the presence of methyl cyanoformate at 110°C gave only the *exo*- and *endo*-[8+2] *N*-phenylmaleimide adducts. This indicated that methyl cyanoformate was not sufficiently reactive to compete with the liberated *N*-phenylmaleimide, despite the use of a vast excess of the nitrile.

Repetition of the reaction, using trichloroacetonitrile as the dienophile, resulted in a complex mixture. Despite the failure of this reaction the cycloaddition of trichloroacetonitrile and 3a-methyl-3-trimethylsiloxy-3a*H*-indene (111) was attempted. Column chromatography of the reaction mixture gave a low yield of an inseparable mixture of a single [8+2] cycloadduct and 1-methyl-1-trimethylsiloxy-1*H*-indene (143) (Scheme 28). Attempts made to optimise the yield of this cycloaddition reaction met with limited success (Table 5).

The product was identified as being an [8+2] adduct from the typical olefinic pattern and the presence of one aliphatic proton in the ¹H n.m.r. spectrum. The position of H-7a at δ 3.65 indicated that of the two possible products, (142) was perhaps more likely. A consideration of the electronic and steric factors also indicated that (142) was the expected product.

Removal of the trimethylsilyl group was undertaken in order to establish the regiochemistry of the cycloadduct. Treatment with



Scheme 28.

potassium fluoride in aqueous THF gave only 1-methyl-1*H*-inden-1-ol and no product derived from the [8+2] cycloadduct was detected. The use of *p*-toluenesulphonic acid in refluxing benzene, however, afforded the ketone (144) in 47% yield. This arose *via* removal of the trimethylsilyl group followed by subsequent hydrolysis of the resulting imine.

TABLE 5

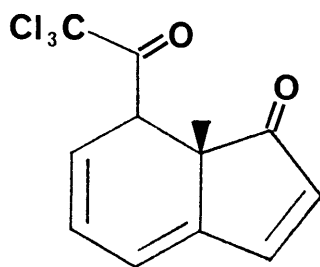
THE CYCLOADDITION REACTION OF THE 3aH-INDENE (111) WITH $\text{Cl}_3\text{CC}\equiv\text{N}$

Solvent	No. of equivalents of $\text{Cl}_3\text{CC}\equiv\text{N}$	Reaction Conditions	Yield of (142) %
Et_2O	4	22°C (16 h)	13
Et_2O	2	22°C (12 h) reflux (4 h)	18
DME	5	22°C (2 h) 45°C (2 h)	-
$\text{ClCH}_2\text{CH}_2\text{Cl}$	2	83°C (1 h)	-

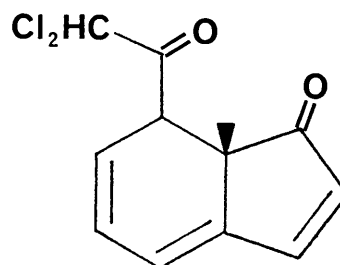
The ketone (144) was identified from a comparison of its ^1H n.m.r. spectrum with that of compound (145)⁶⁰. This reaction established the [8+2] cycloaddition product as (142).

The elimination of the elements of trimethylsilanol from (142) was attempted using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)⁶⁰. This, however, led to decomposition of the starting material with no identifiable product being isolated. As a result of the low yield of this cycloaddition reaction and the inability to separate

(142) from the by-product (143) this route was abandoned and alternative dienophiles were investigated.



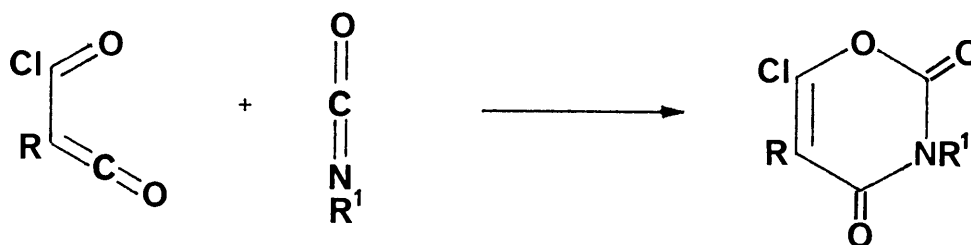
(144)



(145)

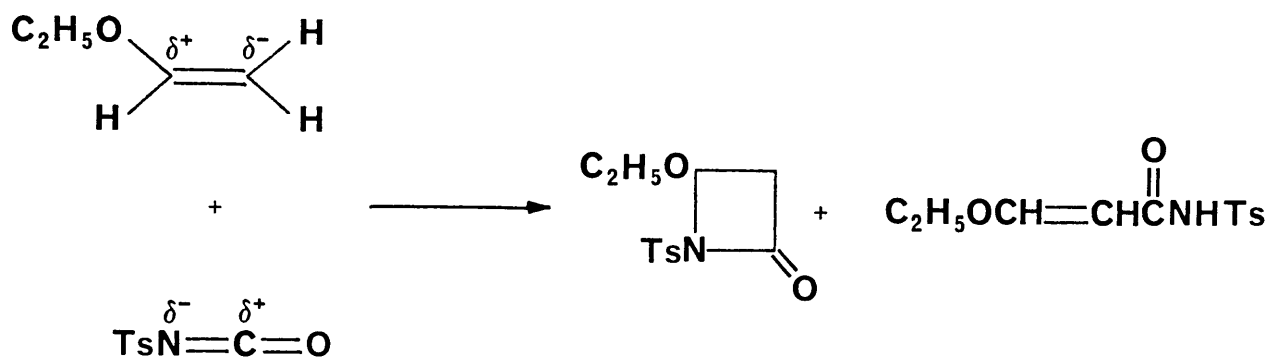
2.2.4 The Cycloaddition Reaction of 3-Methoxy-3a-methyl-3aH-indene (100) with Isocyanates

Isocyanates are known to participate in $[\pi 2_s + \pi 2_a]$ cycloaddition reactions with olefins and 1,3-dienes⁷⁷. The thermally allowed $[\pi 2_s + \pi 4_s]$ reaction does not occur with simple systems such as butadiene, although highly functionalised, reactive dienes may react with isocyanates to give $[4+2]$ products (Scheme 29)⁷⁸.



Scheme 29.

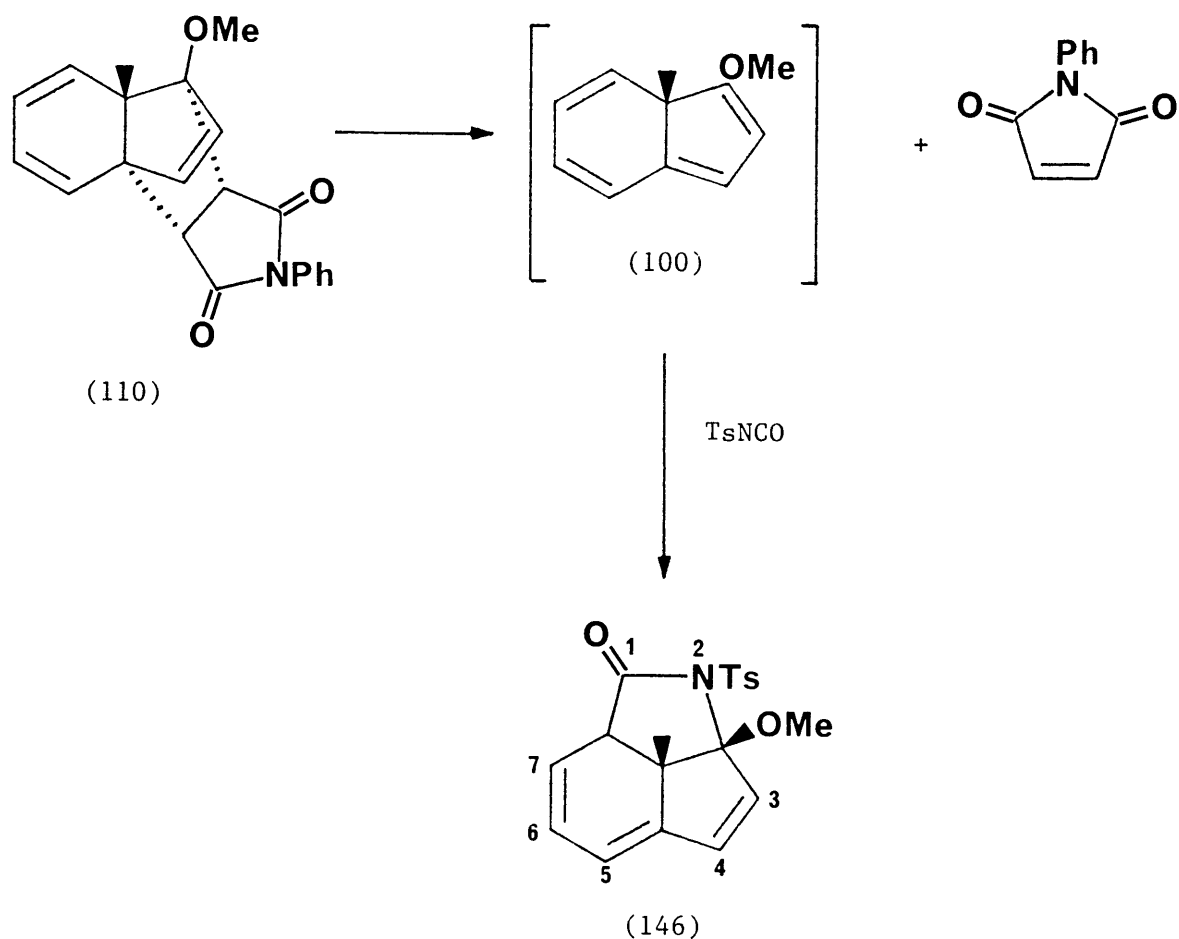
The reaction of vinyl ethers with arylsulphonyl isocyanates was observed by Effenberger and Gleiter to give 1:1 cyclic and linear products⁷⁹. The course of the [2+2] cycloaddition reaction was found to be in good agreement with the polarity of the bonds involved.



The reaction of sulphonyl isocyanates with 3-methoxy-3a-methyl-3a*H*-indene (100) was investigated. The 3a*H*-indene (100) was generated, *via* the decomposition of the *N*-phenylmaleimide adduct (110), in the presence of toluenesulphonyl isocyanate at 100°C. Column chromatography of the reaction mixture gave a 43% yield of a 1:1 adduct.

The carbonyl absorption in the i.r. spectrum at 1727 cm⁻¹, coupled with the appearance of one aliphatic resonance in the ¹H n.m.r. spectrum, suggested (146) as a possible product. The regiochemistry of the addition was assigned from the position of H-7a at δ3.04 and mechanistic considerations.

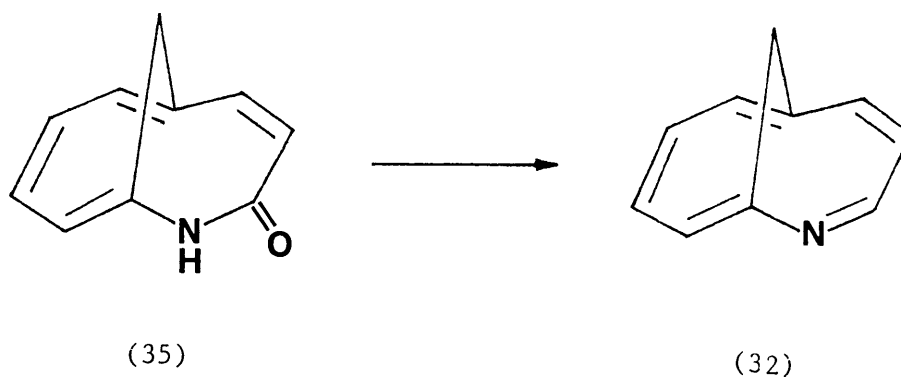
The same reaction was attempted generating the 3a*H*-indene (100) from the trienone (106) as previously described. This reaction



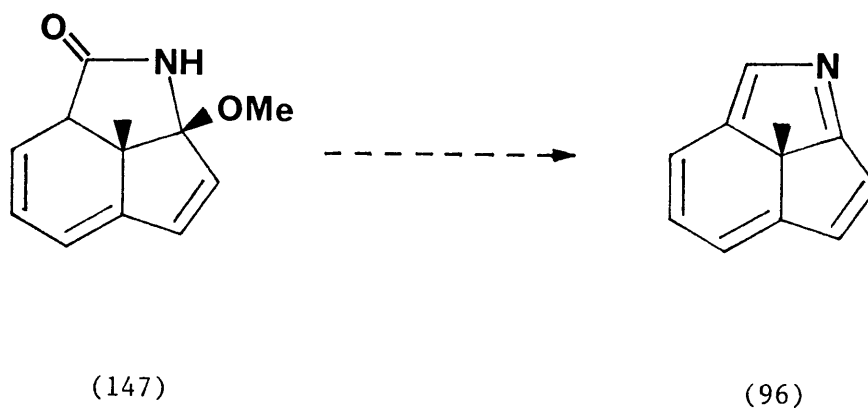
Scheme 30.

gave only a trace of the required product and the failure is probably linked to the lower reaction temperature.

Vogel showed that the lactam (35) could be converted into 2,7-methanoaza[10]annulene (32) in a number of steps²⁹. It therefore



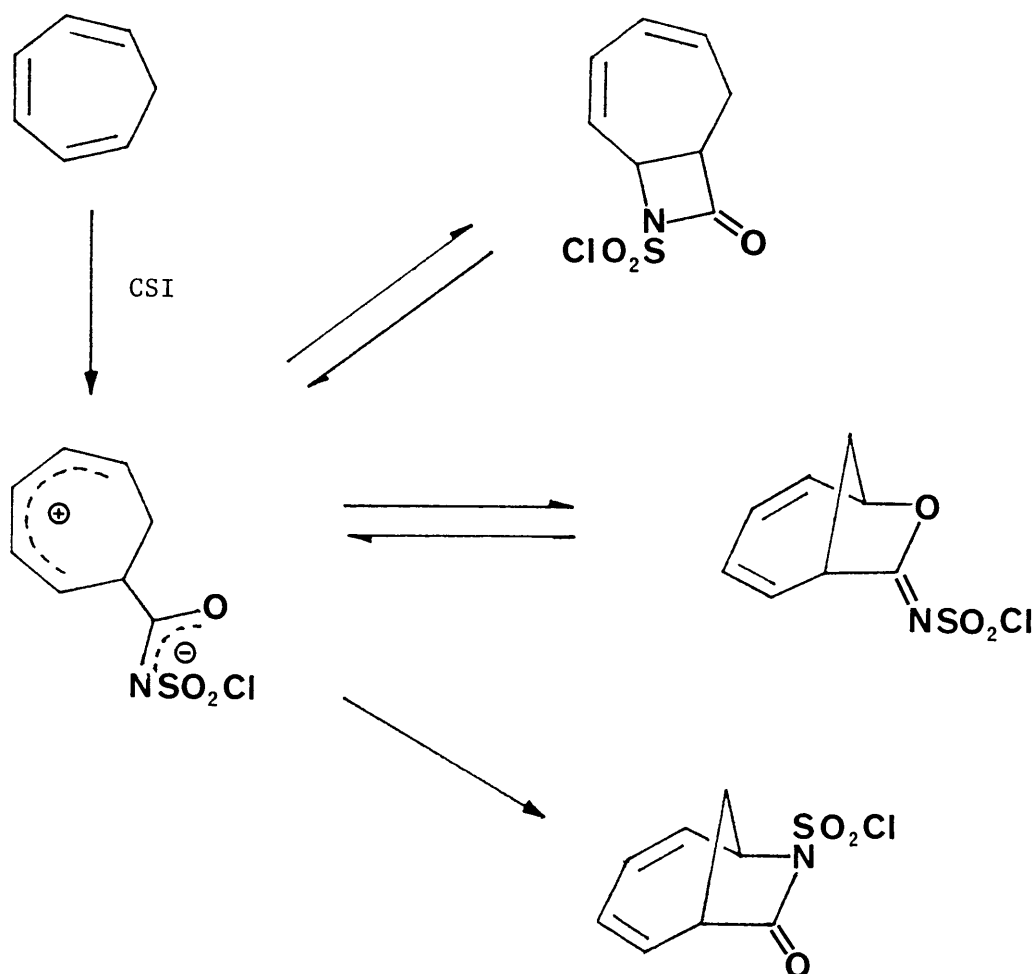
seemed desirable to obtain the lactam (147) since this should provide access to the aza[10]annulene (96).



The reaction conditions used in the hydrolysis of *N*-toluenesulphonyl groups were not expected to be compatible with this ring system. In contrast the *N*-chlorosulphonyl group was known to be cleaved under relatively mild conditions^{80,81} and for this reason the reaction of chlorosulphonyl isocyanate (CSI) with the 3a*H*-indene was investigated.

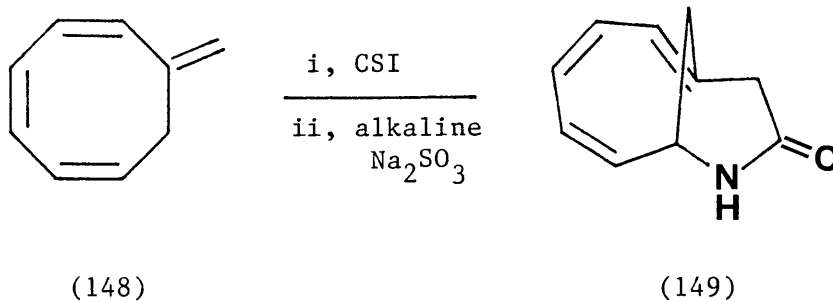
Chlorosulphonyl isocyanate, one of the most reactive isocyanates known, reacts readily with olefins to give biologically important β -lactams⁸¹. The mechanism of this reaction may be a thermally allowed $[\pi 2_s + \pi 2_a]$ cycloaddition or it may involve a 1,4-dipolar intermediate. Evidence supporting the concerted cycloaddition reaction includes (1) the stereospecific addition to *cis* and *trans* olefins and (2) the initial formation of $[2+2]$ cycloadducts with conjugated dienes which then rearrange to the more stable $[4+2]$ adducts⁸¹. The observations which indicate the operation of a 1,4-dipolar mechanism are (1) the increase in rate produced on using polar as compared to non-polar solvents and (2) the influence of olefin nucleophilicity on the

rate of reaction⁸². The addition of chlorosulphonyl isocyanate to cycloheptatriene, which was originally rationalised as a near concerted process leading to 1,2 and 1,6-cycloaddition products⁸³, was reinvestigated by Malpass. A 1,4-dipolar mechanism (Scheme 31) was proposed on spectroscopic evidence and was supported by the fact that the reaction did not occur in non polar solvents⁸⁴.

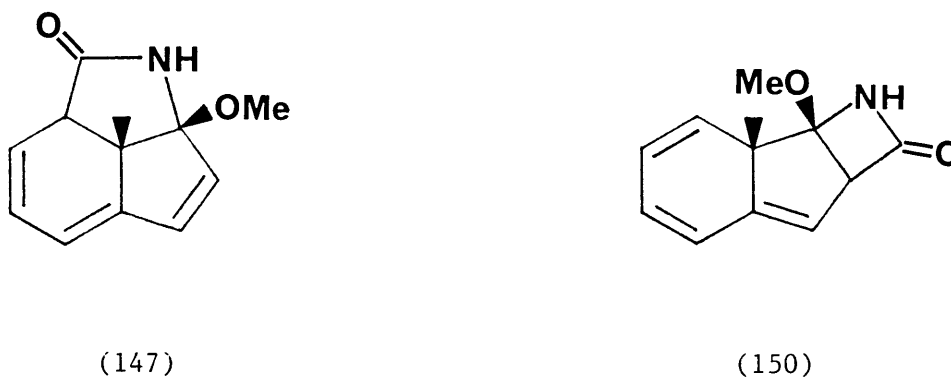


Scheme 31.

It has recently been reported that the reaction of chlorosulphonyl isocyanate with 7-methylenecycloocta-1,3,5-triene (148) gives an [8+2] adduct (149), presumably *via* a 1,4-dipolar intermediate⁸⁵.

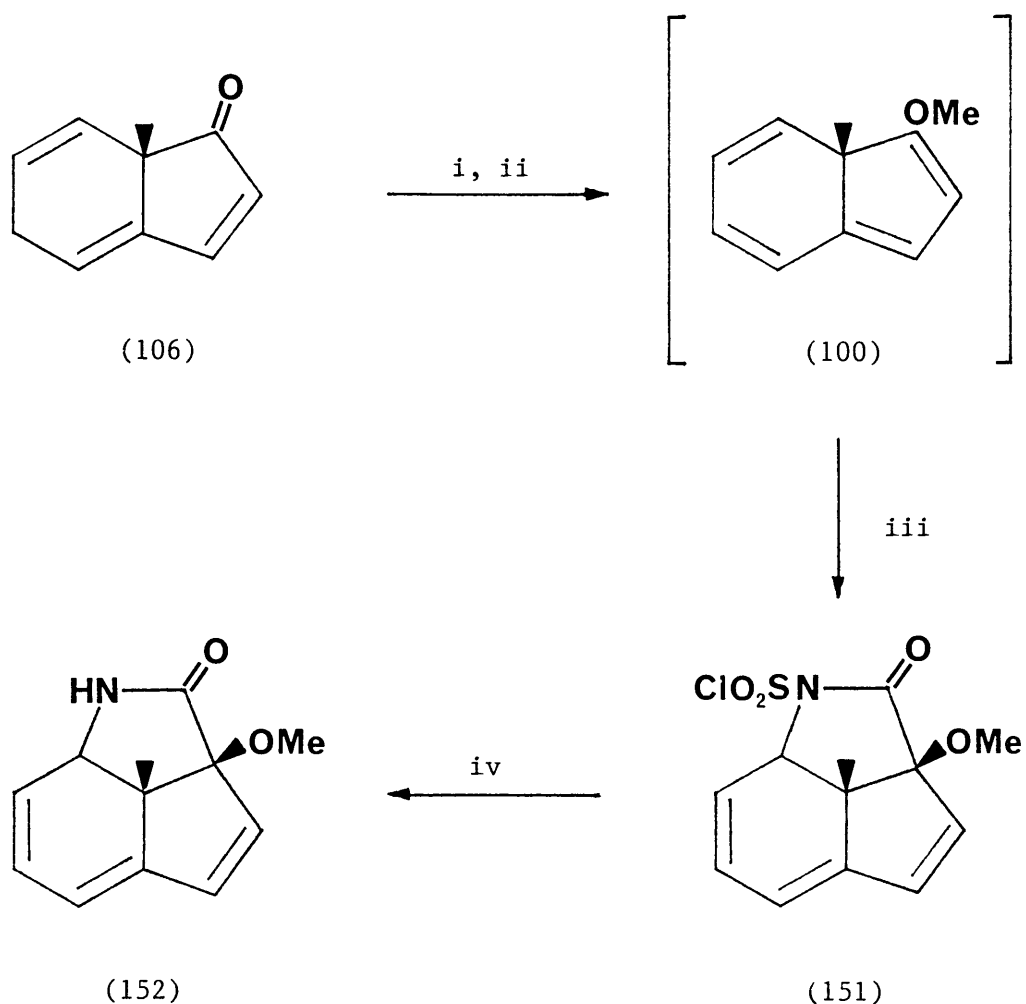


The reaction of chlorosulphonyl isocyanate with the 3a*H*-indene (100) might be expected to give the [8+2] cycloadduct (147) in an analogous fashion to the formation of (149). The other possible product would be the [2+2] cycloadduct (150) but formation of this was thought to be less likely because of the associated ring strain.



3-Methoxy-3a-methyl-3a*H*-indene (100) was generated from the trienone (106) as described previously and reacted with chlorosulphonyl isocyanate. The chlorosulphonyl group was then hydrolysed *in situ* using aqueous sodium sulphite-sodium bicarbonate solution⁸⁰ to give

a 1:1 adduct which was eventually identified as the [8+2] cycloadduct (152) (Scheme 32).



Scheme 32.

Reagents: **i**, KH, 18-crown-6, DME, -18°C ; **ii**, MeOSO_2F ; **iii**, $\text{ClSO}_2\text{N}=\text{C}=\text{O}$; **iv**, 10% sodium sulphite, 10% sodium bicarbonate solution.

The ^1H n.m.r. spectrum indicated that the product was an [8+2] cycloadduct and the position of H-7a at $\delta 4.12$ [*c.f.* H-7a of compound (146) at $\delta 3.04$] suggested that structure (152) was more likely than (147). However, the regiochemistry of the cycloaddition reaction of

the 3a^H-indene (100) with chlorosulphonyl isocyanate was expected to parallel that observed with tosyl isocyanate. This dilemma was resolved when the reaction using chlorosulphonyl isocyanate was repeated and found to give an inseparable mixture of both regioisomers (152) and (147) in a ratio of 2.5:1. An n.O.e. difference experiment on the mixture showed that the product obtained initially was (152). The results of the n.O.e. experiment are shown in Figure 3.

Irradiation of the N-H signal (δ 7.25) of the major isomer caused an enhancement of the resonance attributed to H-7a at δ 4.12 and *vice versa*. This established the close proximity of the N-H group to H-7a and this is satisfied by structure (152). Irradiation of the other N-H signal at δ 7.84 resulted in an enhancement of the corresponding methoxy resonance at δ 3.39. Thus, this established the minor isomer as compound (147).

The formation of the minor component (147) may occur *via* a dipolar intermediate (153) which can collapse to give the observed product (Scheme 33). An alternative mechanism involving a concerted [8+2] cycloaddition was thought to be less likely.

No such rationale is available to explain the formation of the regioisomer (152). Chlorosulphonyl isocyanate is known to give [2+2] adducts when reacted with conjugated polyenes and these frequently undergo rearrangement to more stable products (i.e. [4+2] adducts⁸⁶).

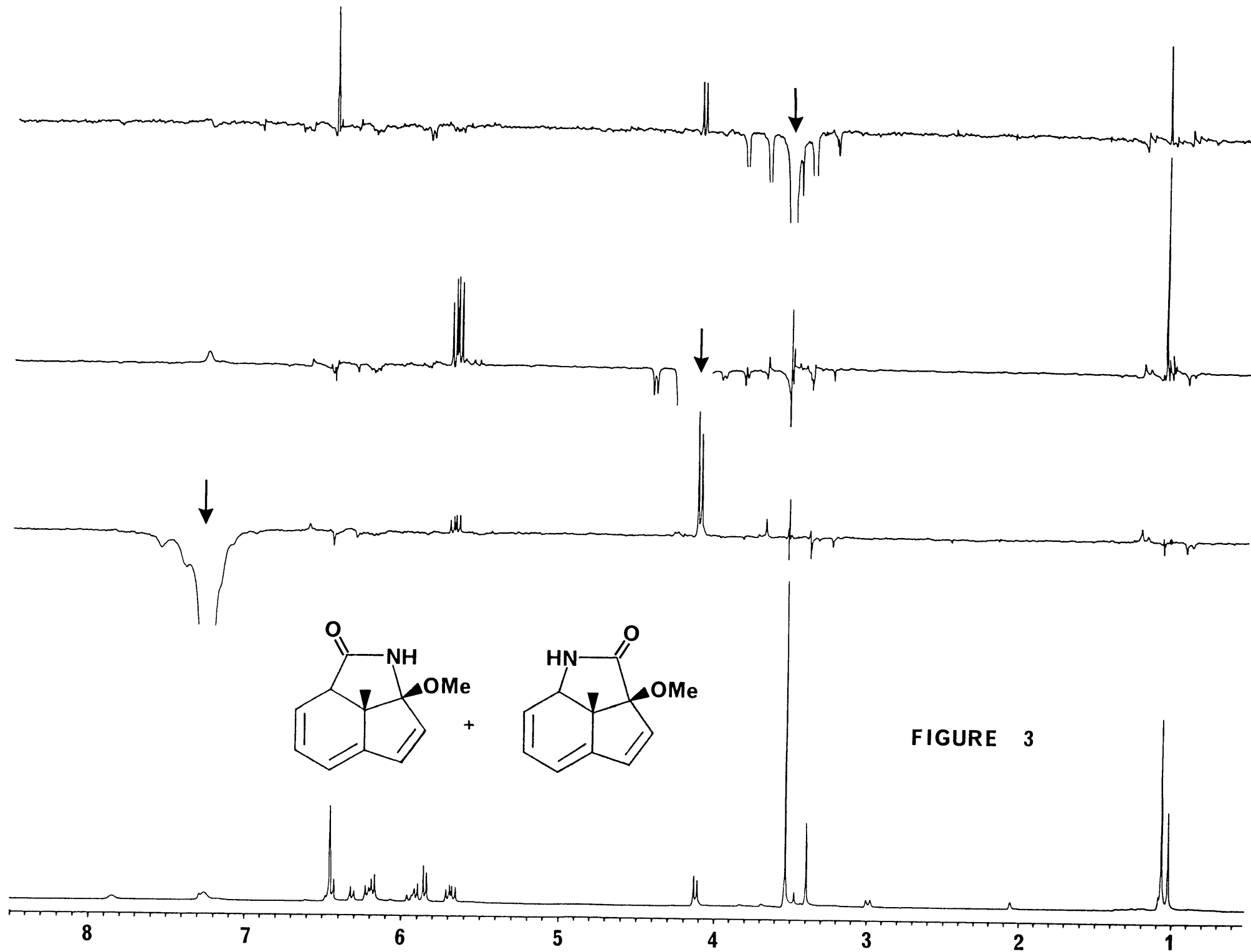
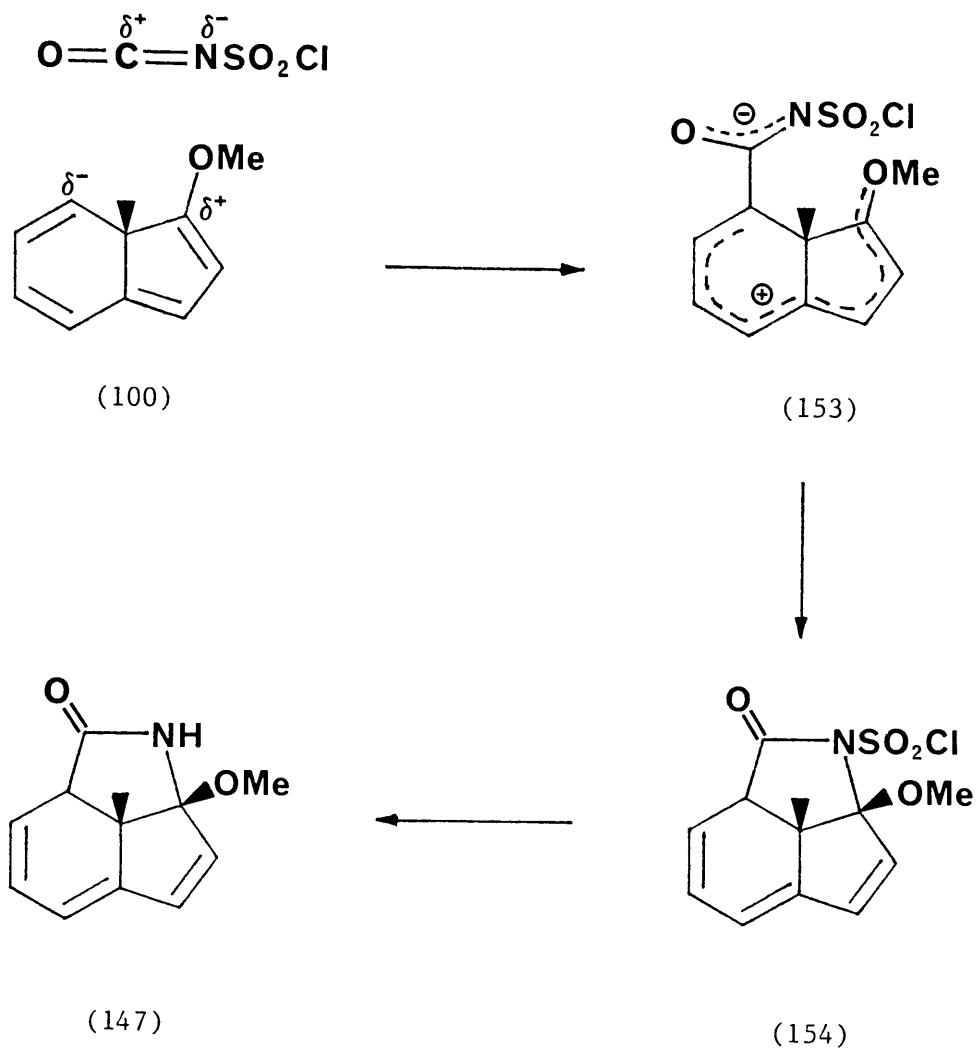
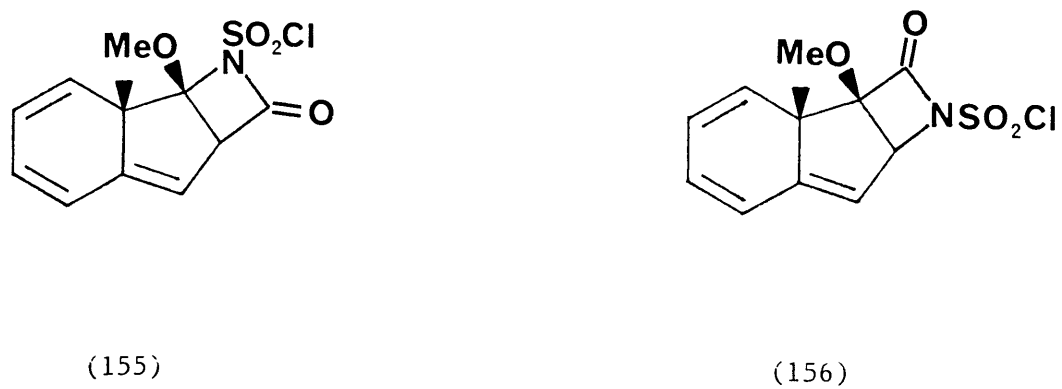


FIGURE 3



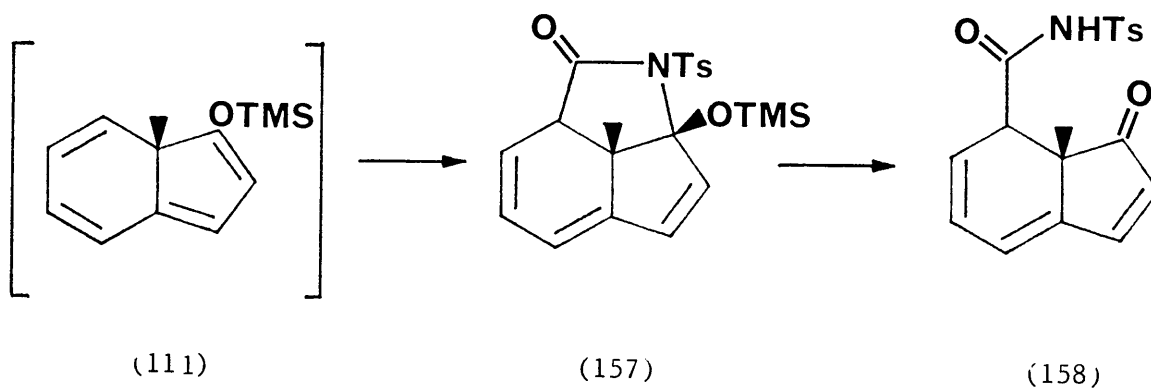
Scheme 33.

However, no simple mechanism can be envisaged which would allow the rearrangement of the expected $[2+2]$ adduct (155) to compound (152).



If, however, the [2+2] cycloaddition reaction gave compound (156), this could rearrange to the observed product (152). Alternatively a concerted thermally allowed [8+2] cycloaddition reaction may account for the formation of isomer (152). The variation in selectivity observed for the cycloaddition reaction of the 3a*H*-indene (100) with chlorosulphonyl isocyanate could not be accounted for. Distillation of the isocyanate before use was found to have no effect on the course of the reaction.

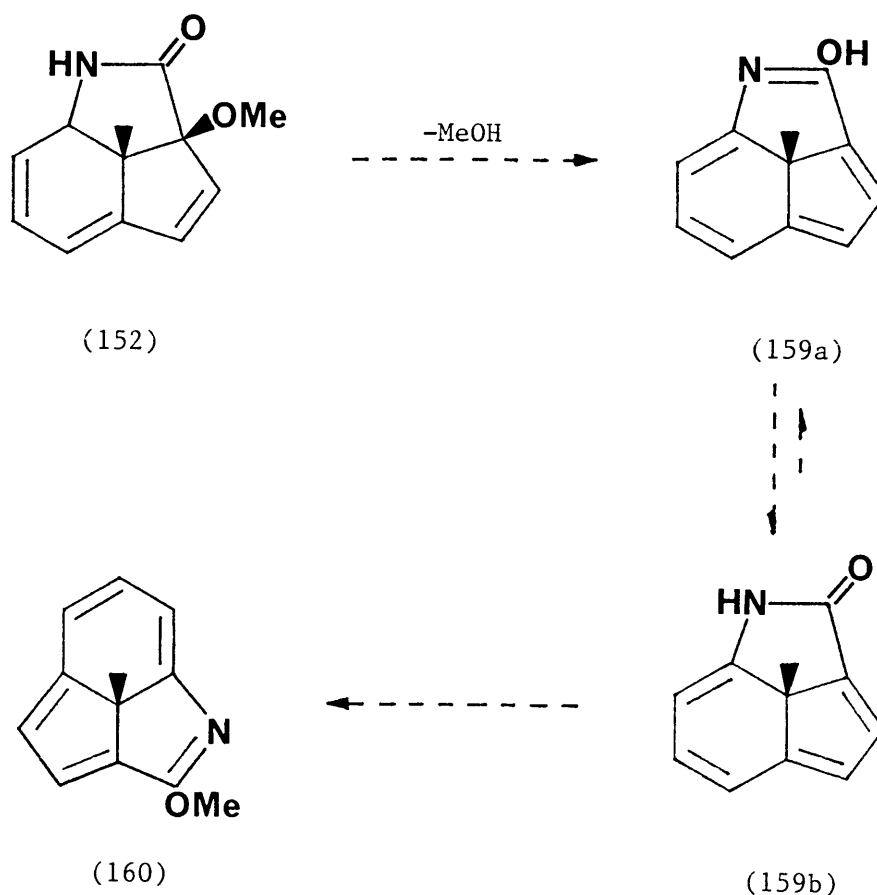
The cycloaddition reaction of 3a-methyl-3-trimethylsiloxy-3a*H*-indene (111) with chlorosulphonyl isocyanate was attempted but no identifiable product was obtained. This was surprising since the corresponding reaction using tosyl isocyanate was shown to give the expected product (158) (Scheme 34)⁷².



Scheme 34.

The successful elimination of the elements of methanol from the cycloadduct (152) would give compound (159) which may exist either as the hydroxy aza[10]annulene (159a) or the lactam (159b) (Scheme 35). From the work of Vogel²⁹ and the preference of 2-hydroxypyridine to

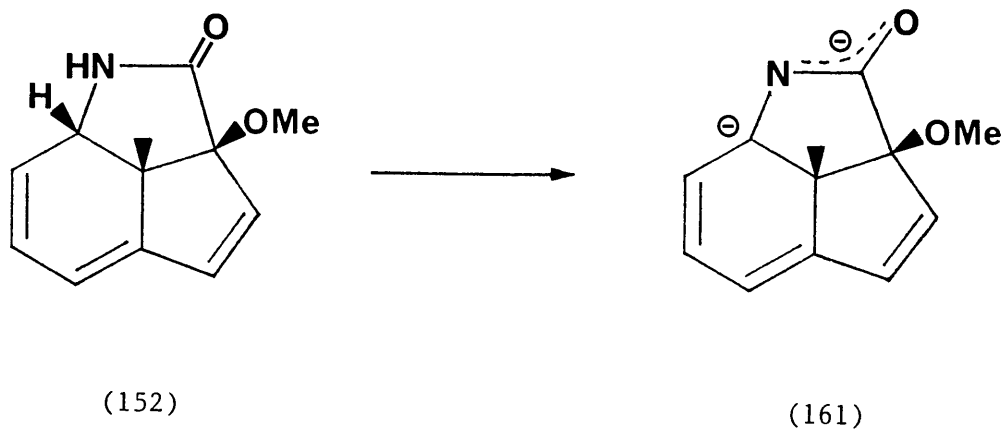
exist as the 2-pyridone⁸⁷ the lactam (159b) was expected.



Scheme 35.

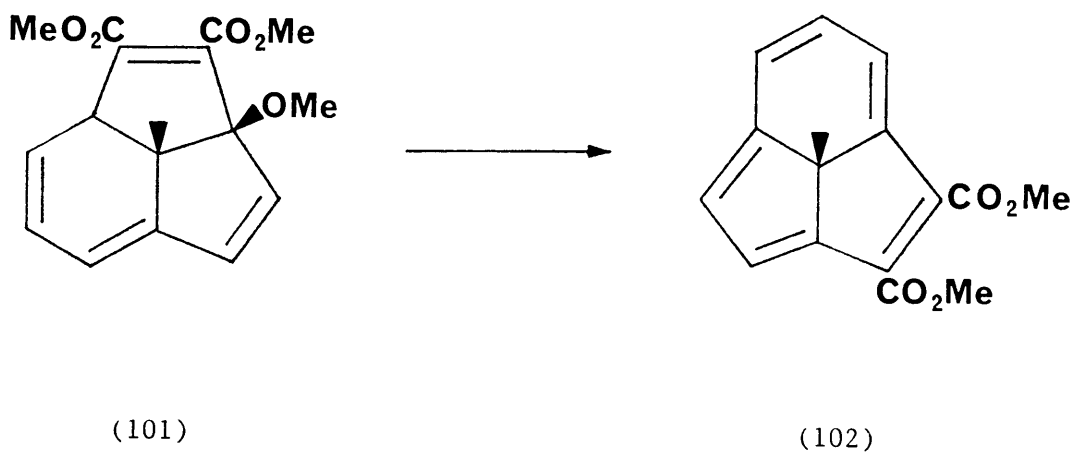
This elimination reaction was attempted, using two equivalents of sodium hydride in DME, but led only to decomposition of the starting material. Treatment of the amide (152) with two equivalents of *n*-butyl lithium followed by methyl fluorosulphonate, in an attempt to form the annulene (160), gave no identifiable product. The use of DBU at 100°C to effect the desired elimination resulted only in a high yield of recovered starting material. This elimination reaction requires the formation of the dianion (161) and the unactivated nature

of H-7a in compound (152) may account for the failure of these reactions.



An investigation into the use of acidic conditions to effect the desired transformation was prompted by the failure of base induced elimination.

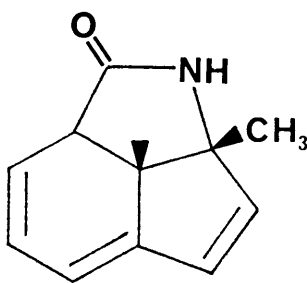
Treatment of the amide (152) with either concentrated sulphuric acid in a mixture of methanol and chloroform, or *p*-toluenesulphonic acid in refluxing benzene, gave only returned starting material. These conditions are known to convert the adduct (101) into the corresponding tricyclic[10]annulene (102)⁶⁰.



The failure of the acidic elimination conditions may be indicative of the preference of compound (159) to exist as the lactam (159b) rather than the hydroxyaza[10]annulene (159a). If (159a) was favoured then this would be expected to facilitate the elimination reaction.

Although the cycloadduct (152) could not be transformed into either (159a) or (159b) it was hoped that the other regioisomer (147) might show different reactivity. When both regioisomers were formed in the reaction of the 3aH-indene (100) with chlorosulphonyl isocyanate, they were found to be inseparable and the elimination reaction was therefore attempted on the mixture of isomers.

It had been shown that an excess of methyl-lithium would effect a related transformation in analogous systems⁶⁰. The mixture of adducts (147) and (152) was treated with five equivalents of methyl-lithium in THF at room temperature. Subsequent work-up of the reaction mixture gave a 25% yield of a product derived from the minor isomer, (147). This was deduced from the position of H-7a at δ 2.86. A consideration of the ¹H n.m.r. spectrum showed that the methoxy group had been eliminated and the product contained two methyl groups. Structure (162) was assigned and this was supported by the mass spectrum which showed a molecular ion at 187 m.u.

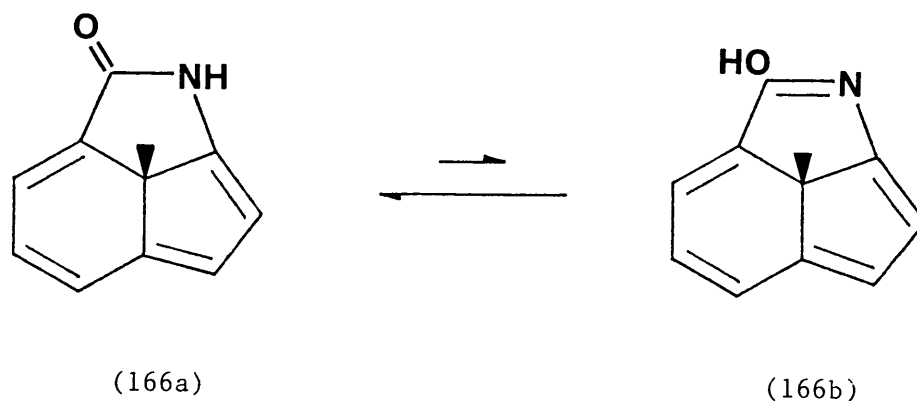


(162)

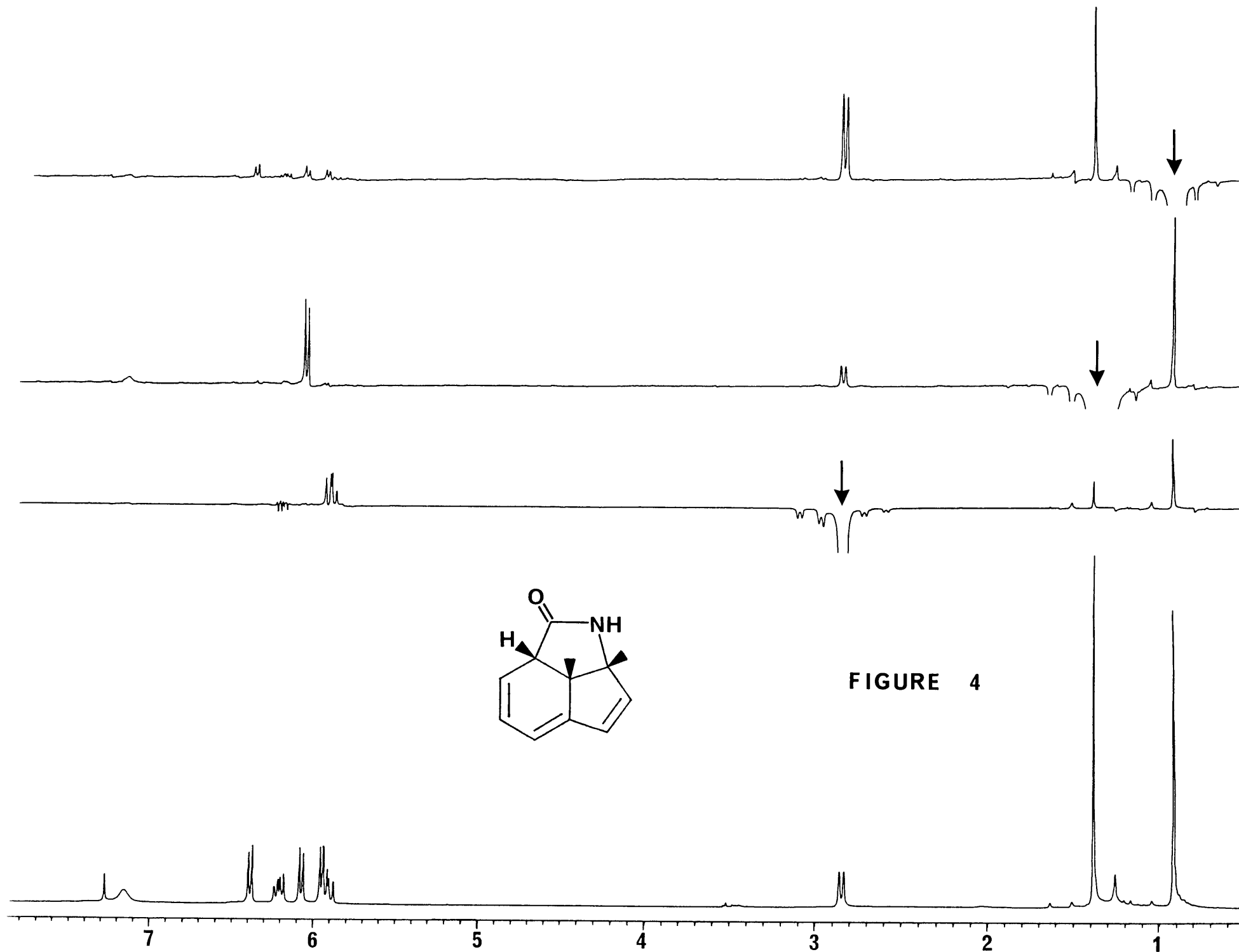
An n.O.e. difference experiment established the stereochemistry at C-2a and the results are shown in Figure 4. Irradiation at $\delta 0.91$ (7b-Me) caused an enhancement of the signals attributed to H-7a and the methyl group at C-2a. This indicated that the two methyl groups were on the same face. A *trans* arrangement of these two groups would not be expected because of the resulting increase in ring strain.

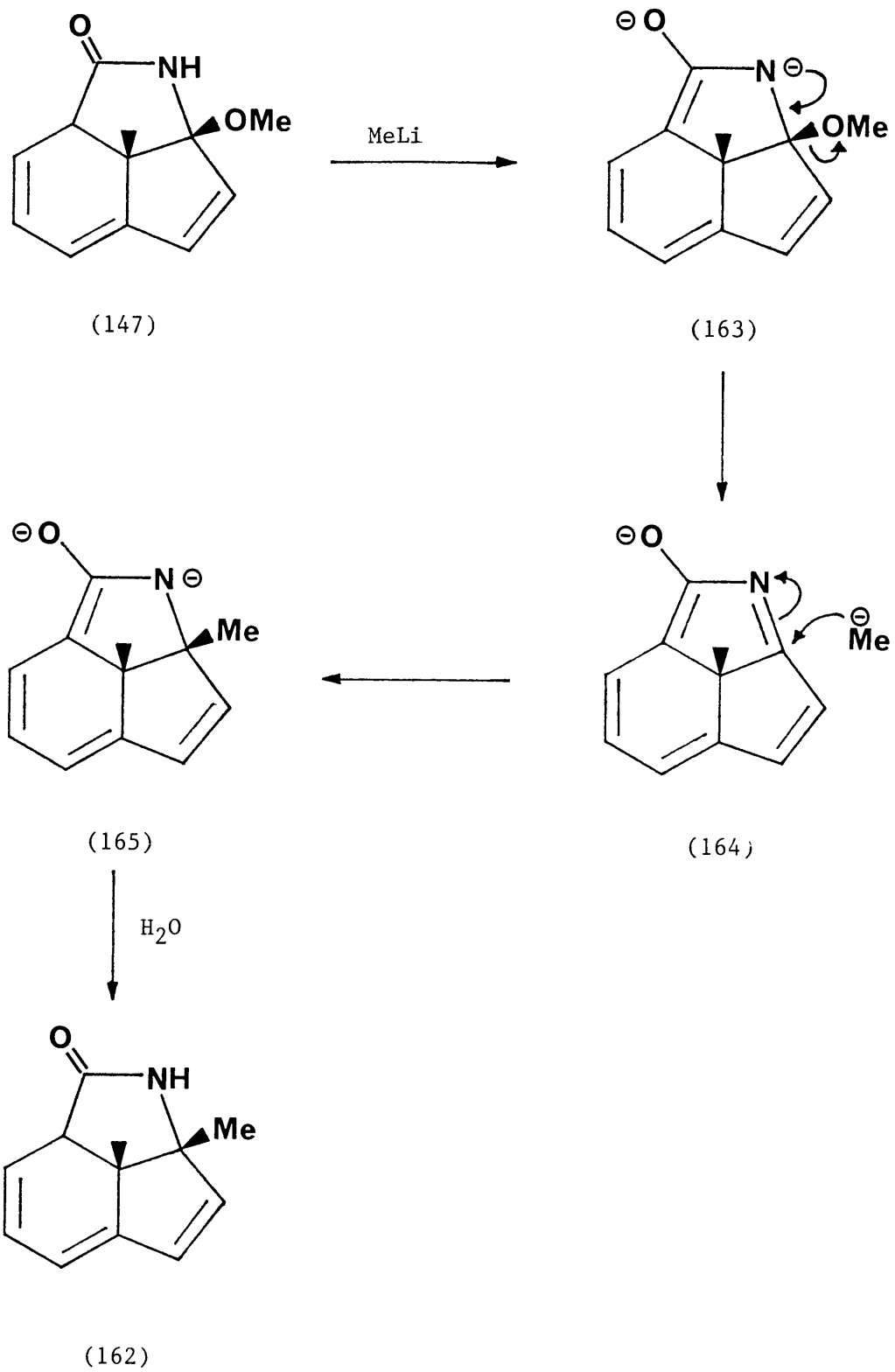
A possible mechanism for the formation of compound (162) is shown in Scheme 36. The driving force for the elimination of methoxide from (163) is believed to be the favourable gain in energy on formation of the aromatic anion (164). The increase in ring strain being offset by the delocalisation energy and the relief of electrostatic repulsion. Unfortunately the excess methyl-lithium attacked the resulting imine (164) to give, after protonation, compound (162).

It was envisaged that by using two equivalents of a non-nucleophilic base, such as lithium di-isopropylamide (LDA), the lactam (166a) might be isolated. The mixture of adducts (147) and (152) was treated



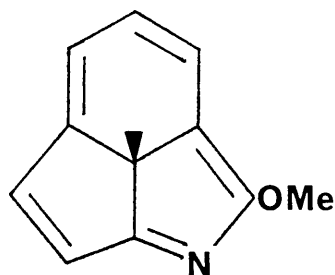
with two equivalents of LDA at room temperature. This, however, gave only 16% of isomer (152) with no product derived from (147) being isolated.



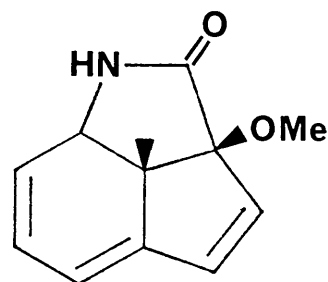


Scheme 36.

The reaction was also attempted using two equivalents of methyl-lithium followed by one equivalent of dimethyl sulphate in an attempt to obtain the annulene (167). The only products isolated from this

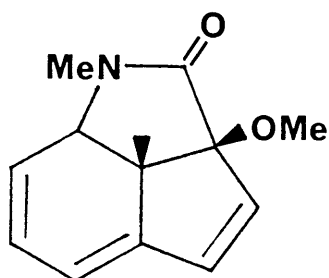


(167)



(152)

reaction were a small amount of an *N*-methylated compound (7%), assigned the structure (168) from spectroscopic evidence, and a 21% yield of the adduct (152). Again no product derived from compound (147) was observed.



(168)

Acidic conditions were also used in an attempt to effect the desired elimination. Treatment of the mixture of amides (147) and (152) with *p*-toluenesulphonic acid in refluxing benzene gave only a 24% yield of (152).

The conditions used in attempting to eliminate the elements of methanol from the amides (147) and (152) are summarised in Table 6.

TABLE 6 THE ATTEMPTED ELIMINATION OF MeOH FROM AMIDES (147) and (152)

Amide(s)	Reagent	Products (%)
(152)	NaH (2eq)	-
	i, <i>n</i> -BuLi (2eq); ii, MeOSO ₂ F	-
	DBU (excess)	80% (152)
	c.H ₂ SO ₄	66% (152)
	<i>p</i> -TsOH	56% (152)
(147) + (152)	MeLi (5eq)	25% (162)
	LDA (2eq)	16% (152)
	i, MeLi (2eq), ii, (MeO) ₂ SO ₂	21% (152) + 7% (168)
	<i>p</i> -TsOH	24% (152)

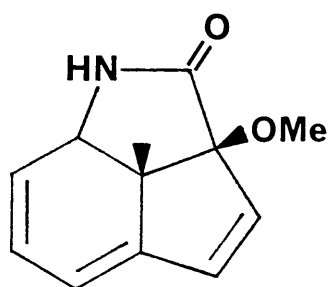
It was envisaged that the conversion of the amides (152) and (147) into the corresponding imidates (169) and (170) would facilitate the synthesis of the required aza [10]annulenes (160) and (167). This assumed that there was a greater driving force for the elimination of the elements of methanol as a result of the resonance energy gained on attaining an aromatic system.

The amide (152) was treated with methyl fluorosulphonate in DME to give the desired imidate (169). The elimination was attempted using neat DBU but this resulted only in decomposition. Acidic conditions led to hydrolysis of the imidate (169) with a mixture of starting material and the amide (152) being recovered.

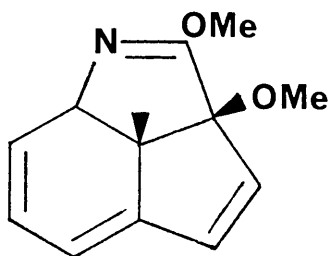
The mixture of amides (152) and (147) was converted into the imidates (169) and (170) (a 2:1 mixture) which were found to be inseparable. Elimination of the elements of methanol from the mixture of imidates was attempted using basic conditions. However, the use of one equivalent of either LDA or methyl-lithium gave only high yields (95%) of starting materials. Treatment with two equivalents of *tert*-butyl lithium or ten equivalents of LDA gave a 55% recovery of imidate (169). No product derived from (170) could be detected.

It is probable that the activated proton in imidate (170) will be readily removed by base. However, since no product derived from this isomer could be isolated the anion was presumed to be unstable under the reaction conditions. The high recovery of imidate (169) is attributed to the lower acidity of H-7a which will suppress deprotonation and hence the subsequent reactions.

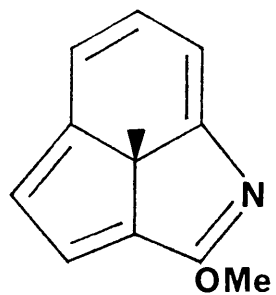
The attempted elimination of the elements of methanol from either the lactams (147) and (152) or the imidates (169) and (170) has so far been unsuccessful. Although treatment of the lactam (147)



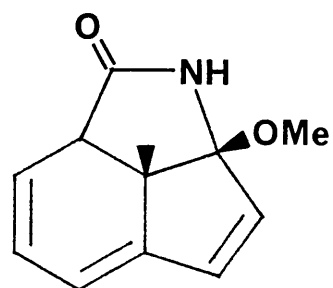
(152)



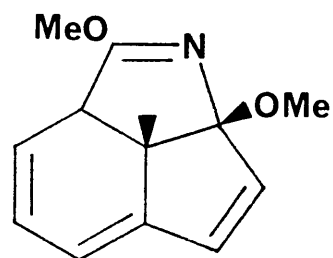
(169)



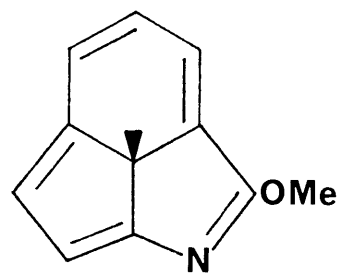
(160)



(147)



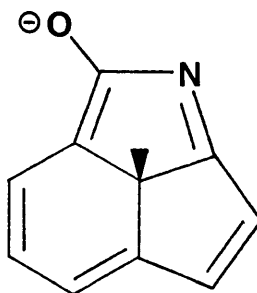
(170)



(167)

Scheme 37.

with methyl-lithium is believed to generate the aromatic anion (164) this intermediate could not be intercepted to give the desired aza[10]-annulene.



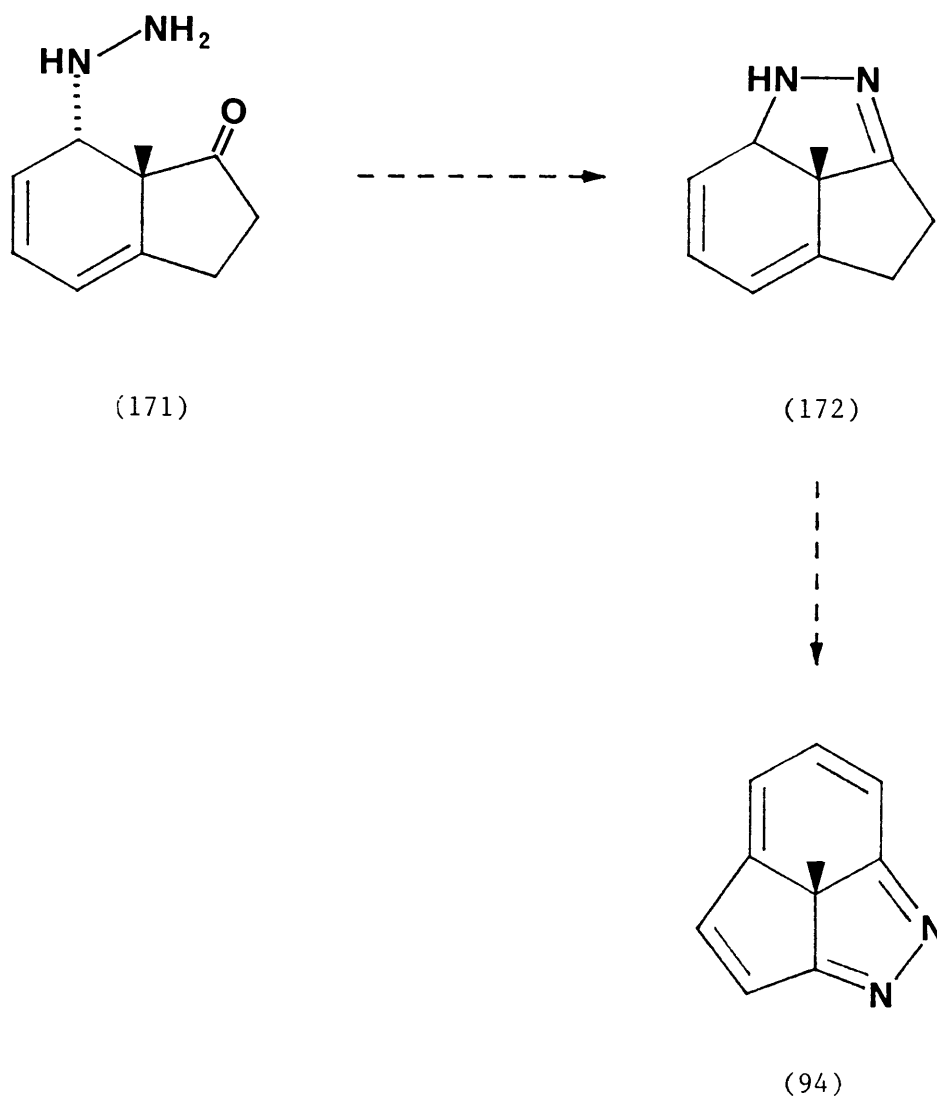
(164)

On the basis of these results an investigation of alternative routes to the aza[10]annulenes (95) and (96) was instigated. The formation of the tricyclic skeleton, using a ring closure approach to construct the final five-membered ring, will be discussed in Sections 2.3.2 and 2.3.3.

2.3 CYCLISATION APPROACHES TO TRICYCLIC AZA[10]ANNULENES

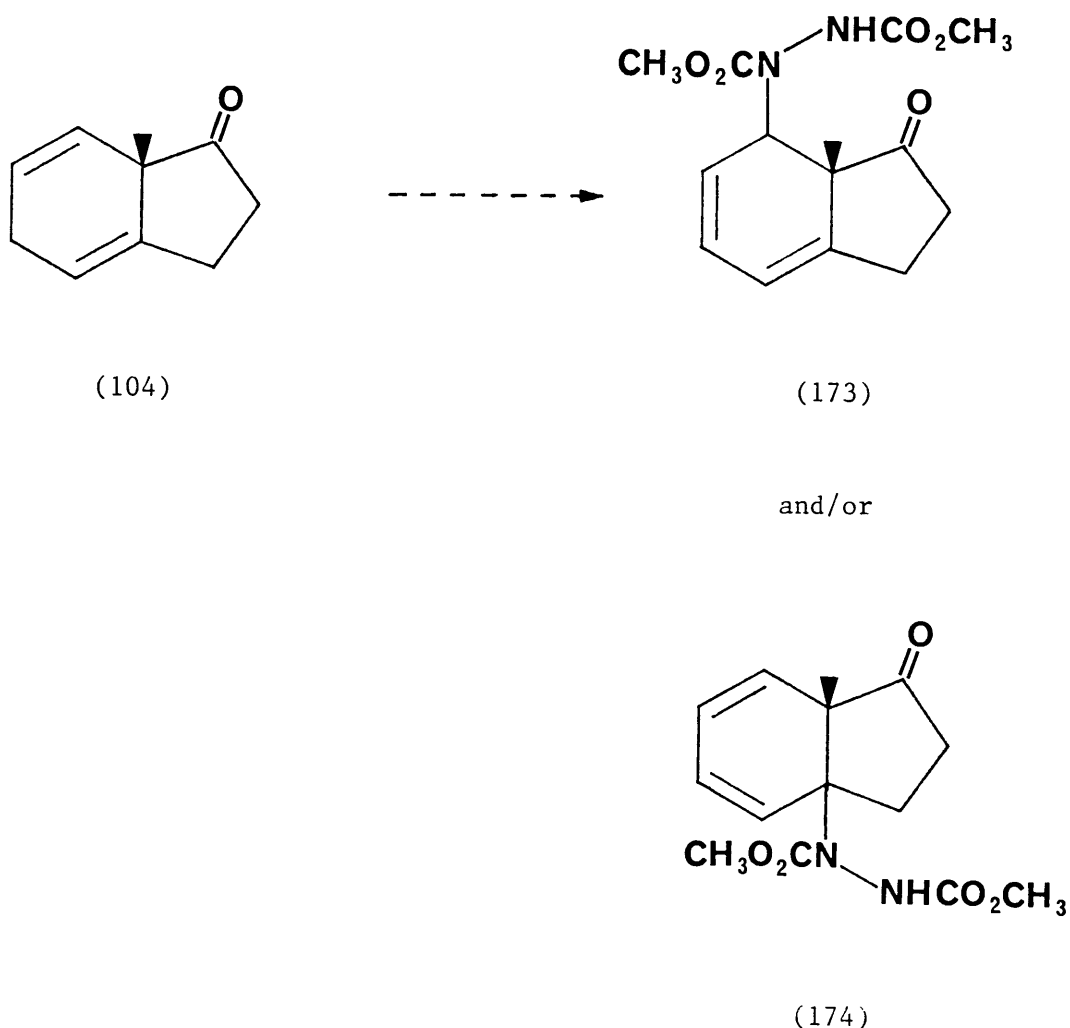
2.3.1 Ring Closure Routes to the 1,2-Diaza[10]annulene (94)

The failure of the cycloaddition route to the 1,2-diaza[10]annulene (94) described in Section 2.2.2 prompted the investigation of alternative methods of constructing the required tricyclic skeleton. It was envisaged that the cyclisation of the hydrazine (171) would provide a useful annulene precursor (172) (Scheme 38).



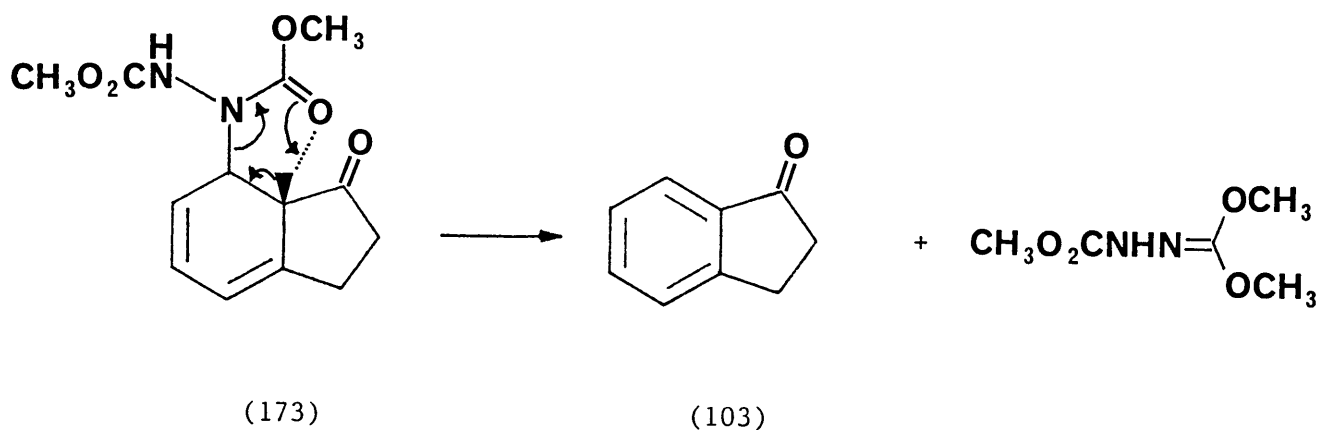
Scheme 38.

A possible route to the hydrazine (171) *via* the modification of the dienone (104) was investigated. The electron deficient N=N bond of azodicarbonyl compounds is known to participate readily in the ene reaction⁸⁹. It was hoped that compound (173), one of the possible products of the ene reaction between dienone (104) and dimethyl azodicarboxylate (DMAZD), would give the hydrazine (171) after hydrolysis of the urethane groups.



Dienone (104) was dissolved in toluene and refluxed in the presence of DMAZD. This reaction gave a complex mixture of products from which only one component could be isolated and identified.

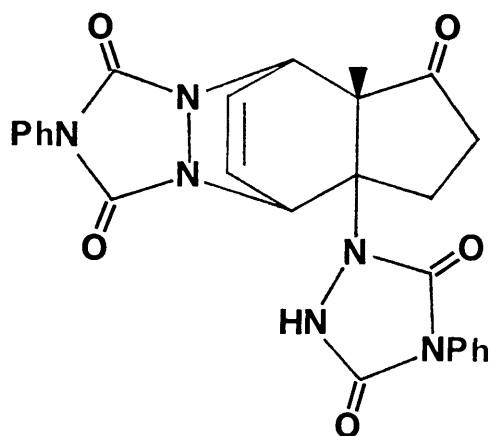
1-Indanone was obtained in 30% yield and although an electrocyclic fragmentation of the initial ene product (173) may be written, this mechanism is somewhat speculative.



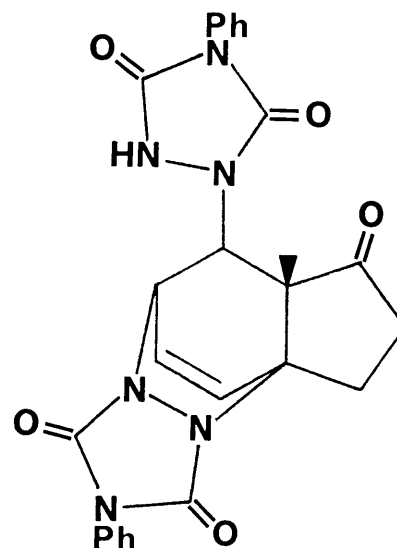
The corresponding reaction using trienone (106) as the substrate was also attempted but in this case no identifiable products could be isolated. It is speculated that if a similar electrocyclic process occurred then this would lead to the formation of the corresponding 1-indenone, which may not be stable under the reaction conditions.

4-Phenyl-1,2,4-triazole-3,5-dione (PTAD) was also used as the enophile and in an attempt to avoid any subsequent electrocyclic fragmentation, the reaction was carried out at room temperature. The product isolated was identified as a 2:1 adduct (M^+ 498 m.u.) for which two structures (175) and (176) were considered. They arise *via* an initial ene reaction followed by a $[4+2]$ cycloaddition of the resulting diene with the PTAD.

A consideration of the ^1H n.m.r. spectrum and the relevant decoupling experiments indicated that the two resonances attributed



(175)

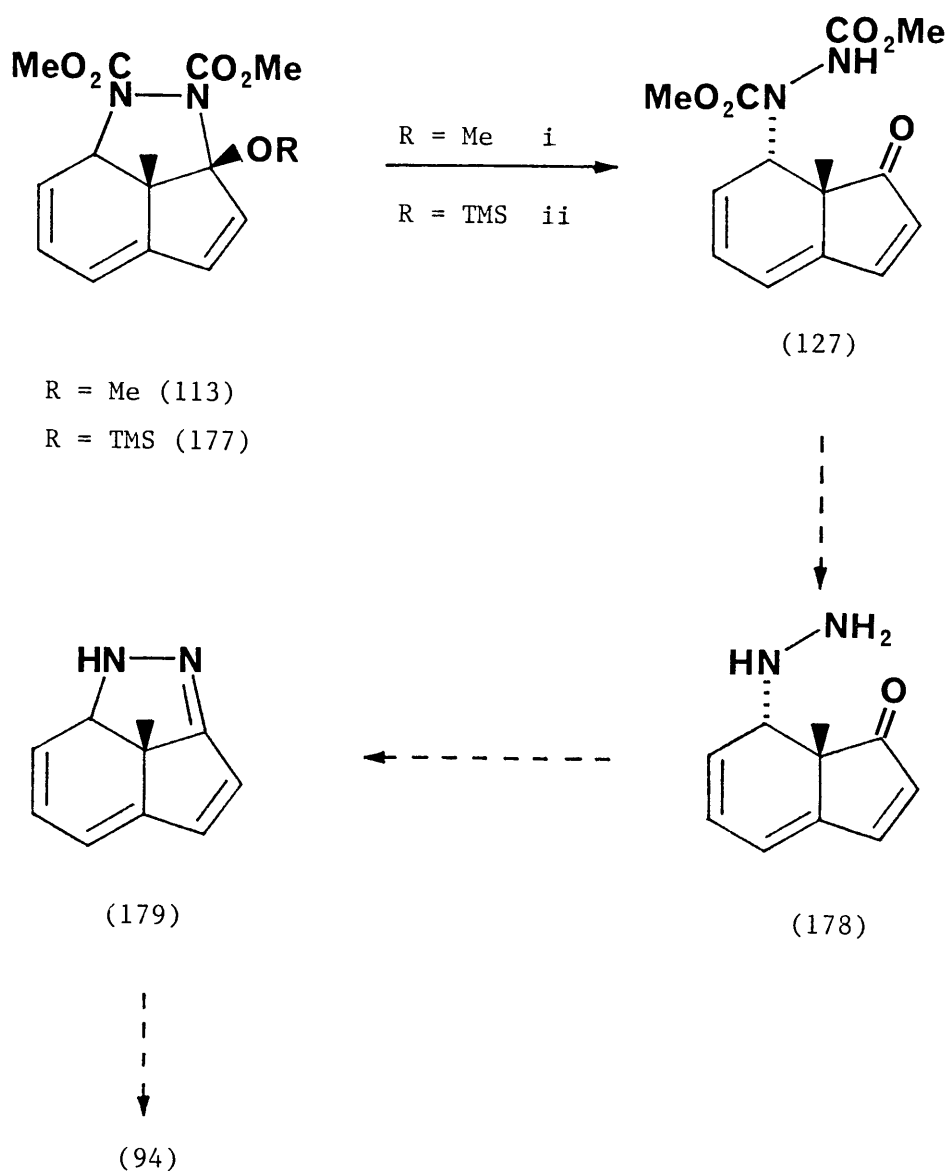


(176)

to the protons α to nitrogen were not coupled to each other. This identified the product as (175) thus showing that the initial ene reaction resulted in functionalisation at C-3a under these conditions. The selectivity shown here is thought to result from the higher electron density associated with the trisubstituted double bond.

The disappointing results obtained from these preliminary experiments led to the curtailment of this particular investigation. However, the strategy was still considered viable and a similar route utilising the related hydrazine (178) was explored. Previous work had shown that the cycloadduct (113) could be ring opened to give the functionalised trienone (127) (p. 64). It was hoped that subsequent hydrolysis of the urethane groups would result in the formation of the

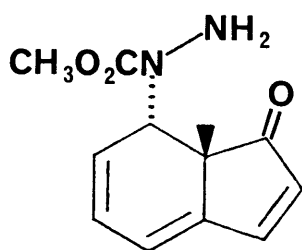
hydrazine (178). This could then be condensed to give the required tricyclic system (179), a possible precursor to the 1,2-diaza[10]-annulene (94) (Scheme 39). This route has the advantage that the nitrogen functionality is introduced unambiguously at the correct position. However, the lower reactivity of the carbonyl group in compound (178) means that the intramolecular cyclisation reaction may be less facile.



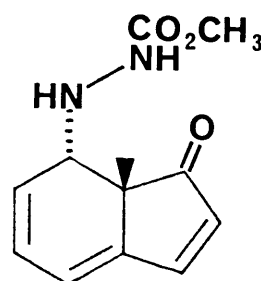
Scheme 39.

Reagents: i, $\text{c.H}_2\text{SO}_4, \text{CH}_3\text{CN}, \text{H}_2\text{O}$;
ii, $\text{KF}, \text{THF}, \text{H}_2\text{O}$.

The required trienone (127) was prepared from either cycloadduct (113) or (177) using the reagents shown (Scheme 39). Compound (127) was then treated with methanolic potassium hydroxide in an attempt to form the hydrazine (178). This resulted in the isolation of a low yield of a mono urethane which could not be rigorously identified owing to the lack of material. Of the two possible structures, (181) was believed to be the more likely since a comparison of the ^1H n.m.r. spectra of the starting material and the product, indicated that the resonances assigned to H-7 differed by about 1 p.p.m. An attempt to effect the desired transformation using trimethylsilyl iodide in



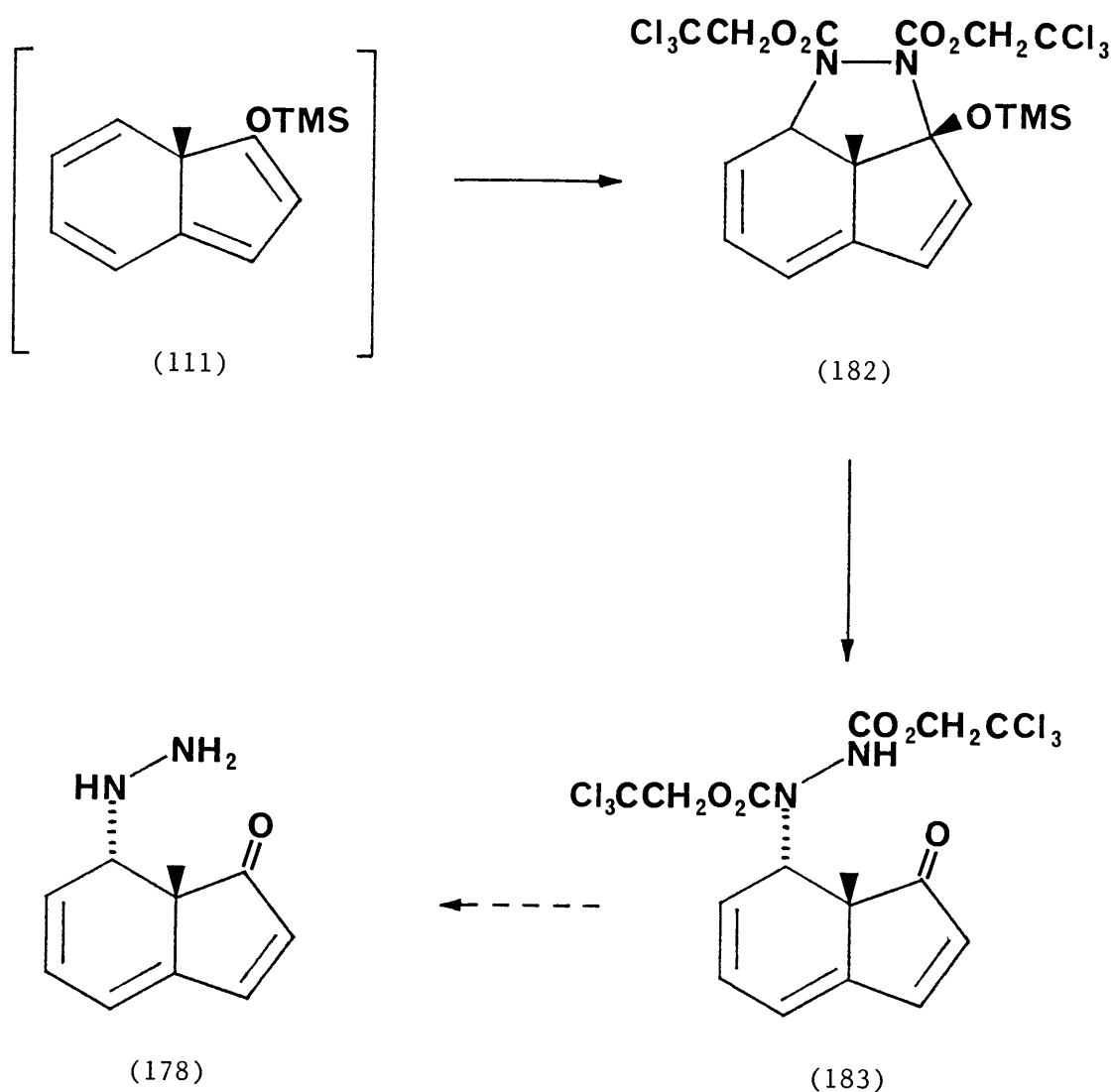
(180)



(181)

chloroform resulted in no identifiable product being isolated⁶⁹.

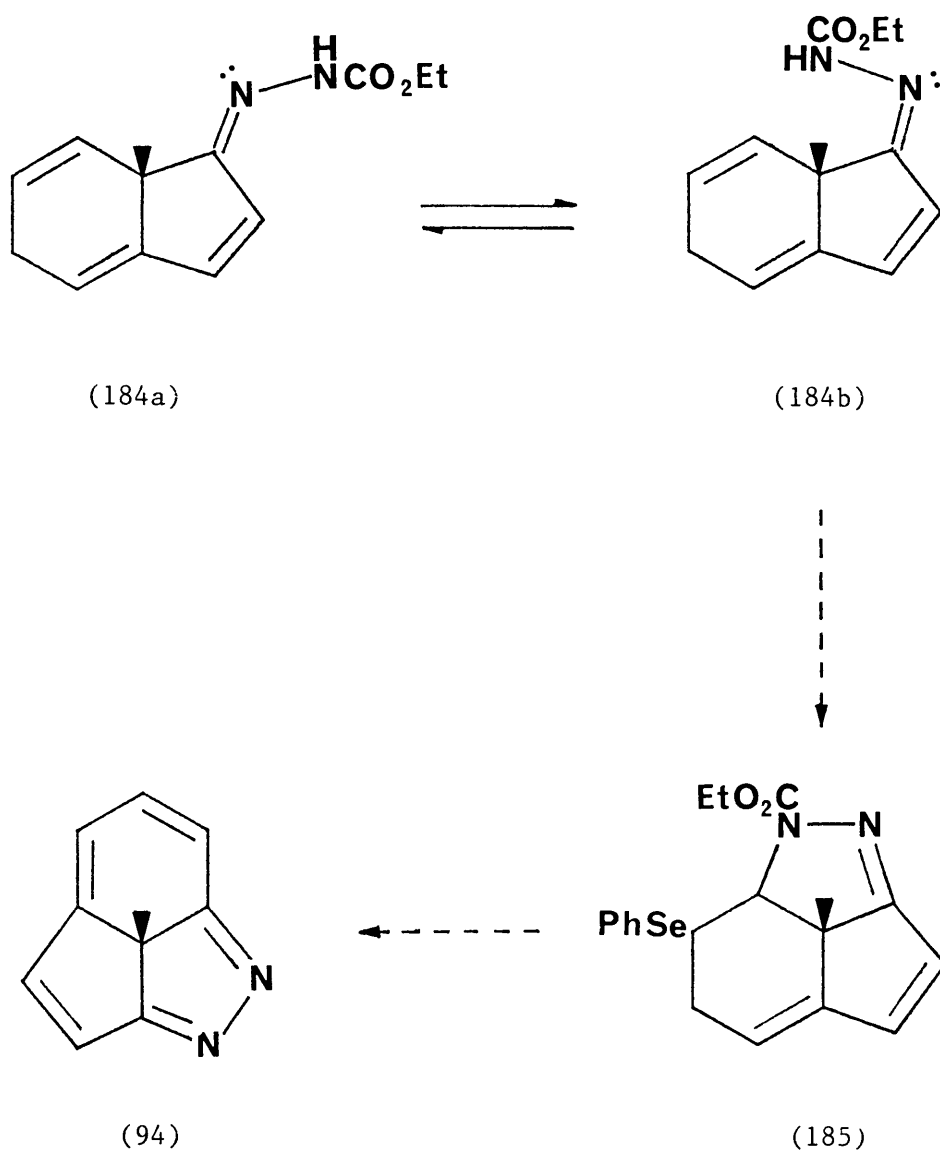
At this juncture the related ketone (183) was prepared since cleavage to give the desired hydrazine should occur under milder conditions⁷⁴. The 3aH-indene (111) was treated with *bis*-trichloroethyl azodicarboxylate⁹⁰ to give the ketone (183) (41%) which was presumably formed *via* cleavage of the [8+2] adduct (182) on work up (Scheme 40). The cleavage of the urethane (183) was attempted using activated zinc in a mixture of THF and glacial acetic acid⁷⁴. These conditions, however, resulted in no identifiable product being isolated and this may be a consequence of the instability of the expected hydrazine (178).



Scheme 40.

It was envisaged that an alternative approach to the 1,2-diaza[10]annulene (94) might involve the hydrazone (184). The selenium mediated cyclisation of isomer (184b) would be expected to lead to a possible diaza[10]annulene precursor (185) and the proposed route is outlined in Scheme 41.

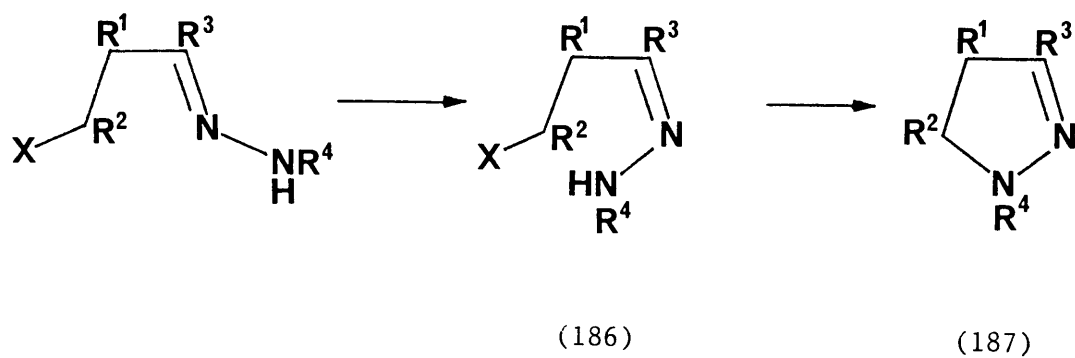
Although the preparation of hydrazones usually leads to the formation of the more stable, less hindered isomer, they are known



Scheme 41.

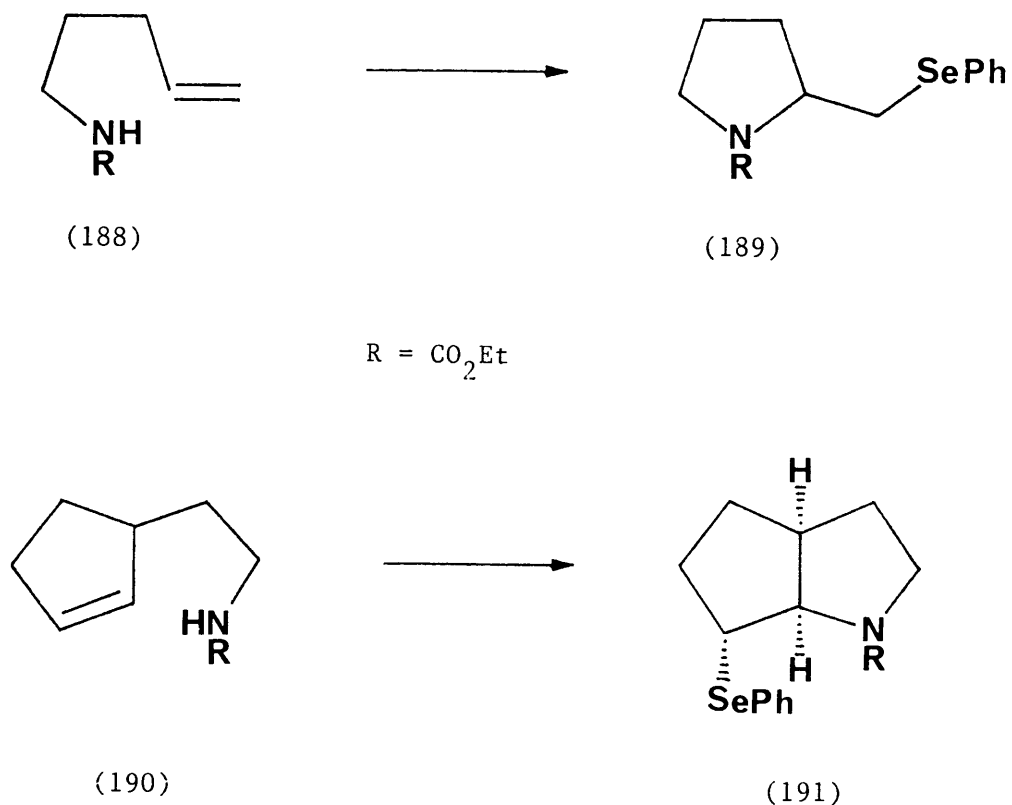
to equilibrate in solution⁹¹. An example of this isomerisation has been observed in the formation of Δ^2 -pyrazolines (187) from the corresponding hydrazones (186) (Scheme 42)⁹².

The use of selenium mediated ring closure reactions in the synthesis of heterocyclic systems has found many applications⁹³. Clive *et al* found that the urethanes (188) and (190) gave the cyclised products (189) and (191) respectively, on treatment with phenylselenenyl



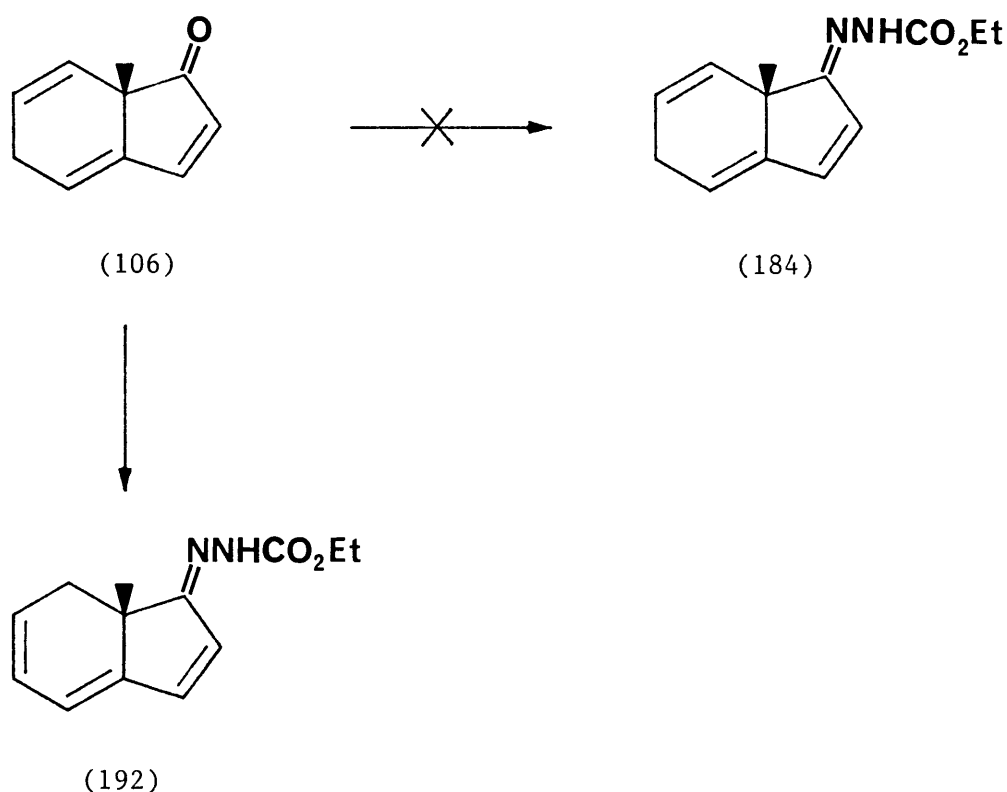
Scheme 42.

chloride (Scheme 43)⁹⁴. However, the corresponding free amines were found to be unsuitable substrates. The application of this cyclisation procedure to the hydrazone (184) was attempted, with a view to the preparation of the tricyclic system (185).



Scheme 43.

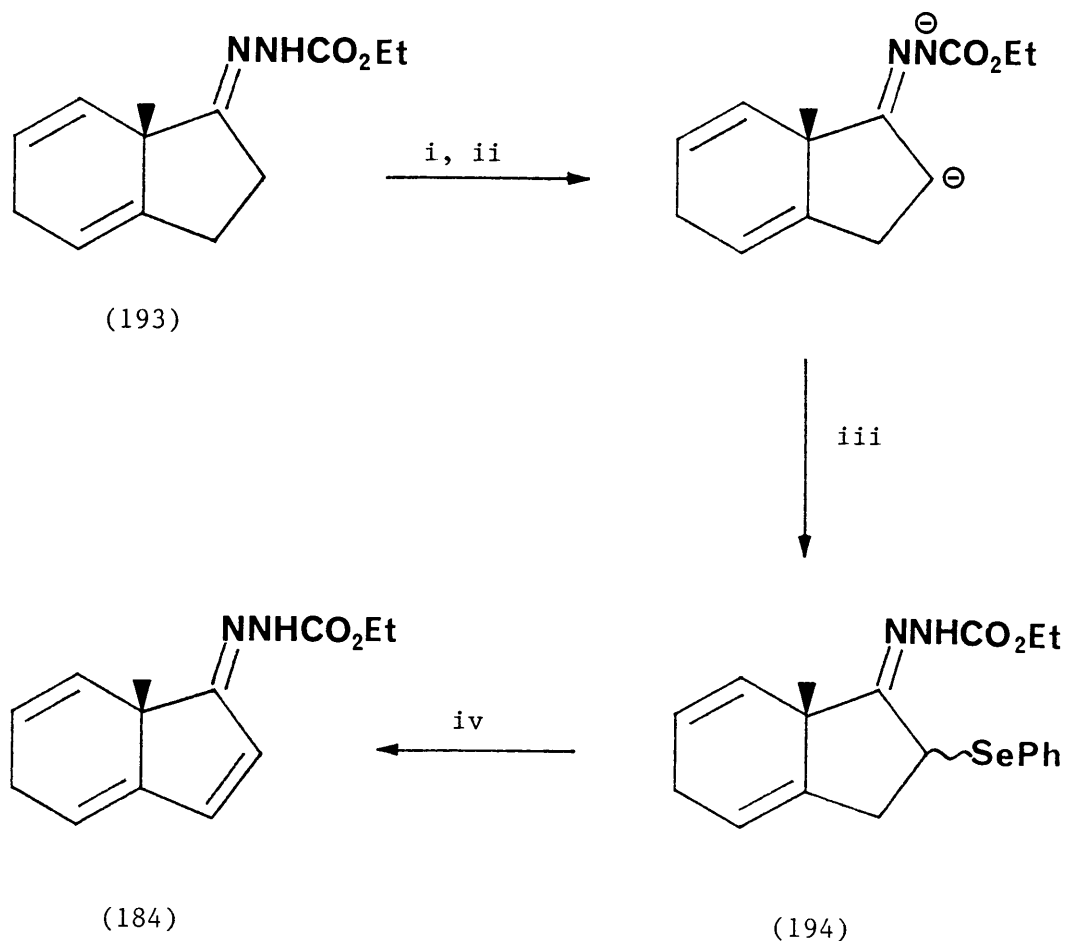
Initial attempts to prepare the hydrazone involved treating the trienone (106) with ethyl carbazate. However, when the condensation was carried out in the presence of concentrated sulphuric acid no sign of the desired hydrazone was observed. Repetition of the reaction in refluxing benzene containing a trace of *p*-toluenesulphonic acid gave a small amount of a new product. This was identified as the triene hydrazone (192) by the observation of extended conjugation as indicated by the u.v. and ^1H n.m.r. spectral data.



Scheme 44.

The preparation of the required hydrazone (184) was accomplished using the route outlined in Scheme 45. Compound (193) was readily prepared from the dienone (104). However, treatment of the hydrazone

(193) with two equivalents of LDA at -78°C , followed by phenylselenenyl chloride, gave only a low yield of the required selenides (194). The inefficiency of this reaction was attributed to incomplete dianion formation as evidenced by the disappearance of the characteristic deep green colour after the addition of approximately 20% of the selenating agent. Repetition of the reaction using one equivalent of LDA followed by one equivalent of *n*-butyl lithium led to the isolation of the selenides (194) in 45% yield. Subsequent oxidation using *m*-chloroperoxybenzoic acid gave the required trienehydrazone (184) in 73% yield (Scheme 45).

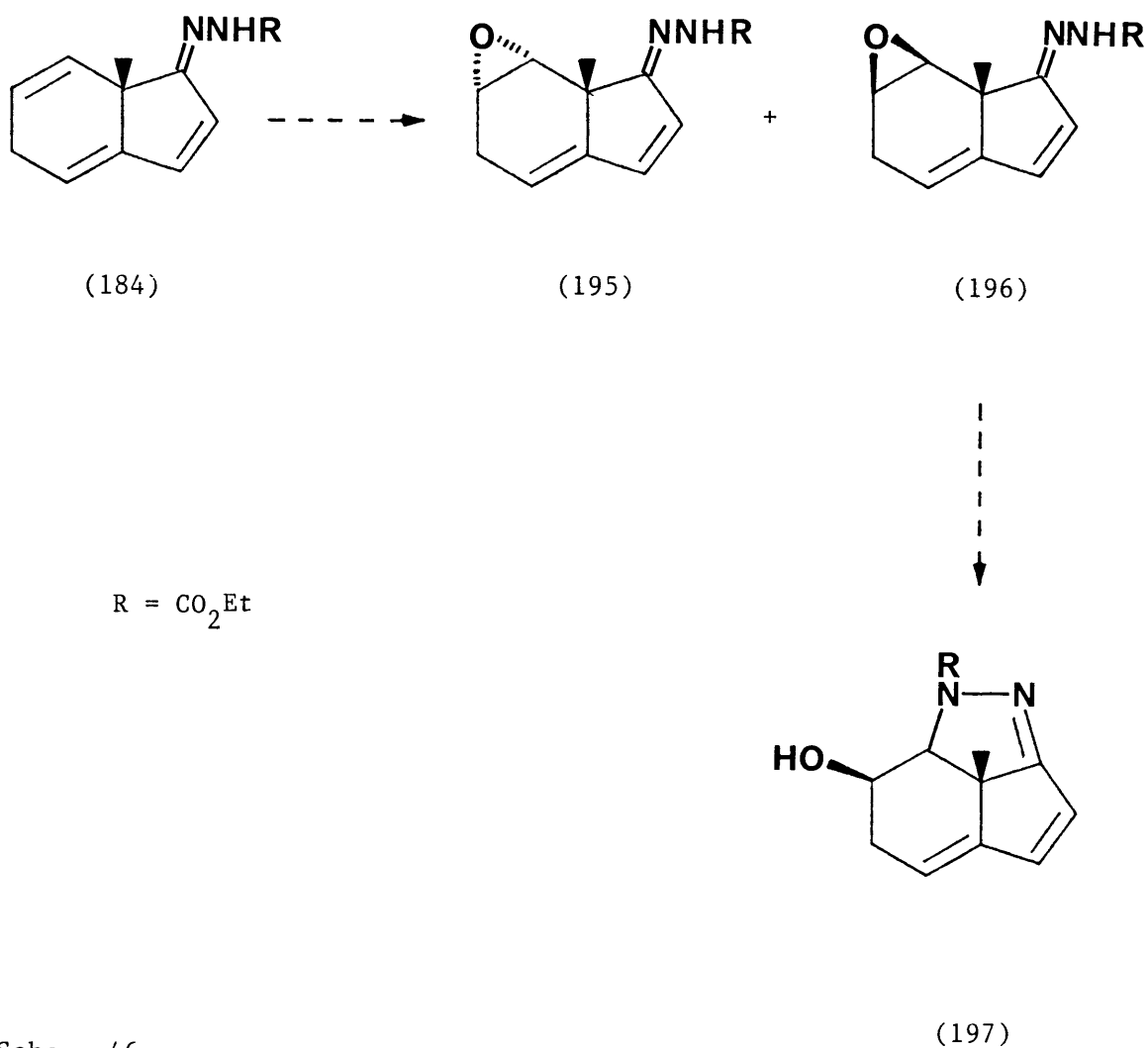


Scheme 45.

Reagents: *i*, LDA, THF, -78°C ;
ii, *n*-BuLi, -78°C ; *iii*, PhSeCl, -78°C ;
iv, *m*-CPBA, NH_4Et_2 , THF, -10°C .

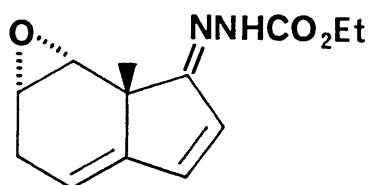
The trienehydrazone (184) was reacted with phenylselenenyl chloride at -78°C and then allowed to warm to room temperature⁹⁴. This, however, gave only a 55% yield of recovered starting material and no sign of the desired product.

An alternative strategy to form the tricyclic system involved selective epoxidation of the isolated double bond of the trienehydrazone (184). Subsequent intramolecular ring opening of the epoxide would result in the formation of the desired product (197).

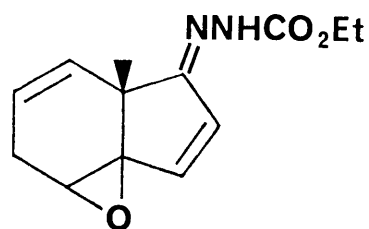


Scheme 46.

Treatment of (184) with *m*-chloroperoxybenzoic acid gave a mixture of epoxides (195) and (198), the expected regioselectivity not being observed. The stereochemistry of the epoxide (195) was determined by an n.O.e. difference experiment. Irradiation at H-7 gave an enhancement of the central methyl group (7a-Me) and *vice versa*. The stereochemistry of the epoxidation reaction made the required ring closure reaction unlikely and although a stepwise procedure might have been employed the low yield of this step prompted the abandonment of this route.

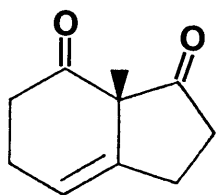


(195)

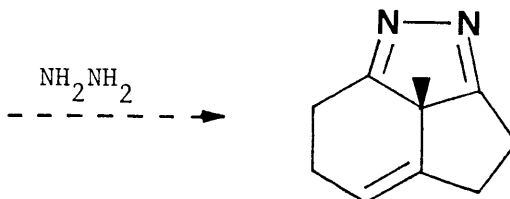


(198)

An attempt was made to form the tricyclic system in one step *via* the condensation of the diketone (199) with hydrazine⁹⁵. This reaction, however, gave a complex mixture of products and was not pursued.



(199)

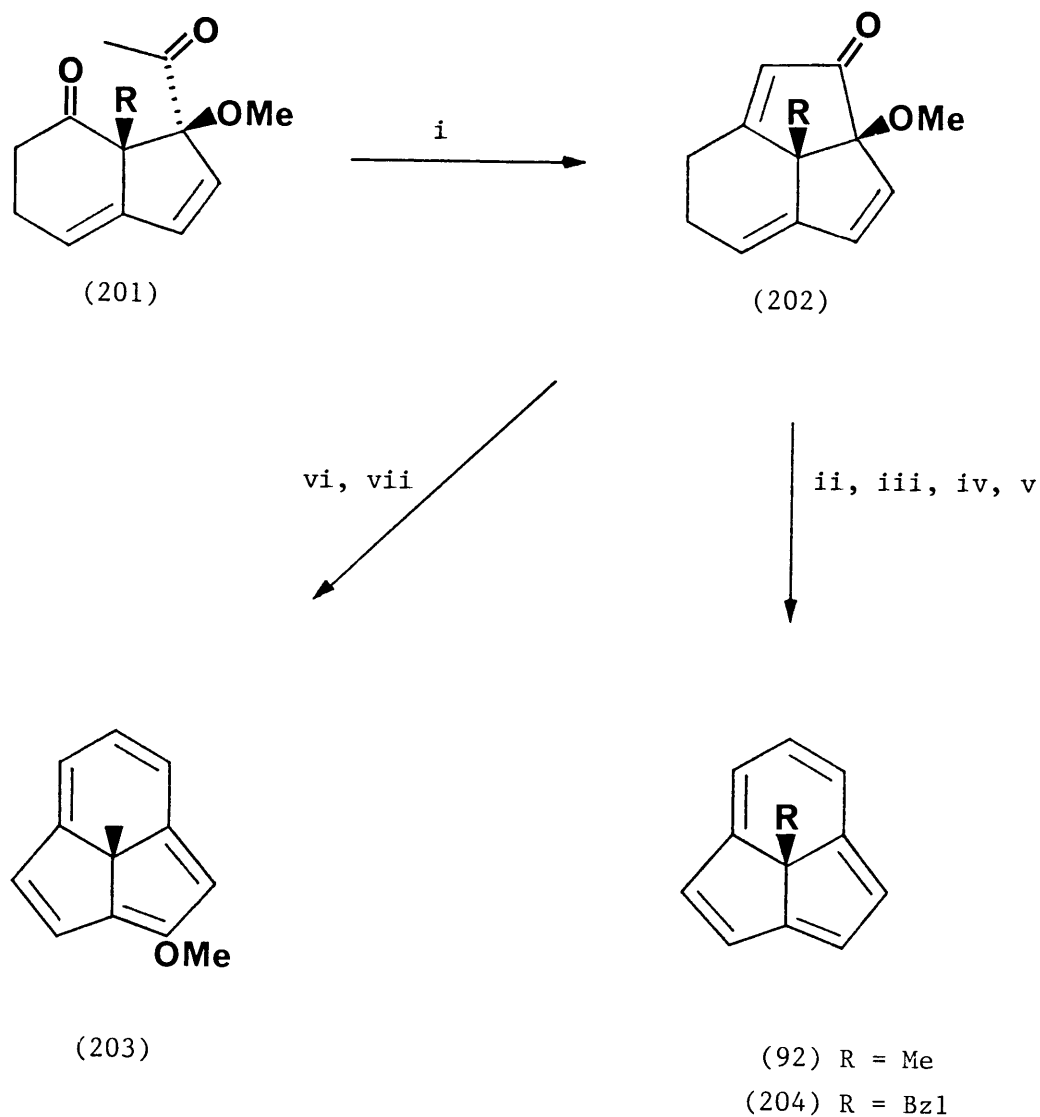


(200)

This Section describes several ring closure strategies which have been explored in an attempt to synthesise the 1,2-diaza[10]-annulene (94). Although there is still scope for further investigation of these routes, the difficulty encountered in obtaining the requisite precursors led to the formulation of synthetic approaches to the 1-aza and 2-aza derivatives (95) and (96).

2.3.2 Ring Closure Route to the 1-Aza[10]annulene (95)

An investigation into alternative methods for the preparation of 7b-methyl-7b*H*-cyclopent[*cd*]indene (92) led to the development of a ring closure route (Scheme 47)⁵⁸. The key step in this synthesis involved

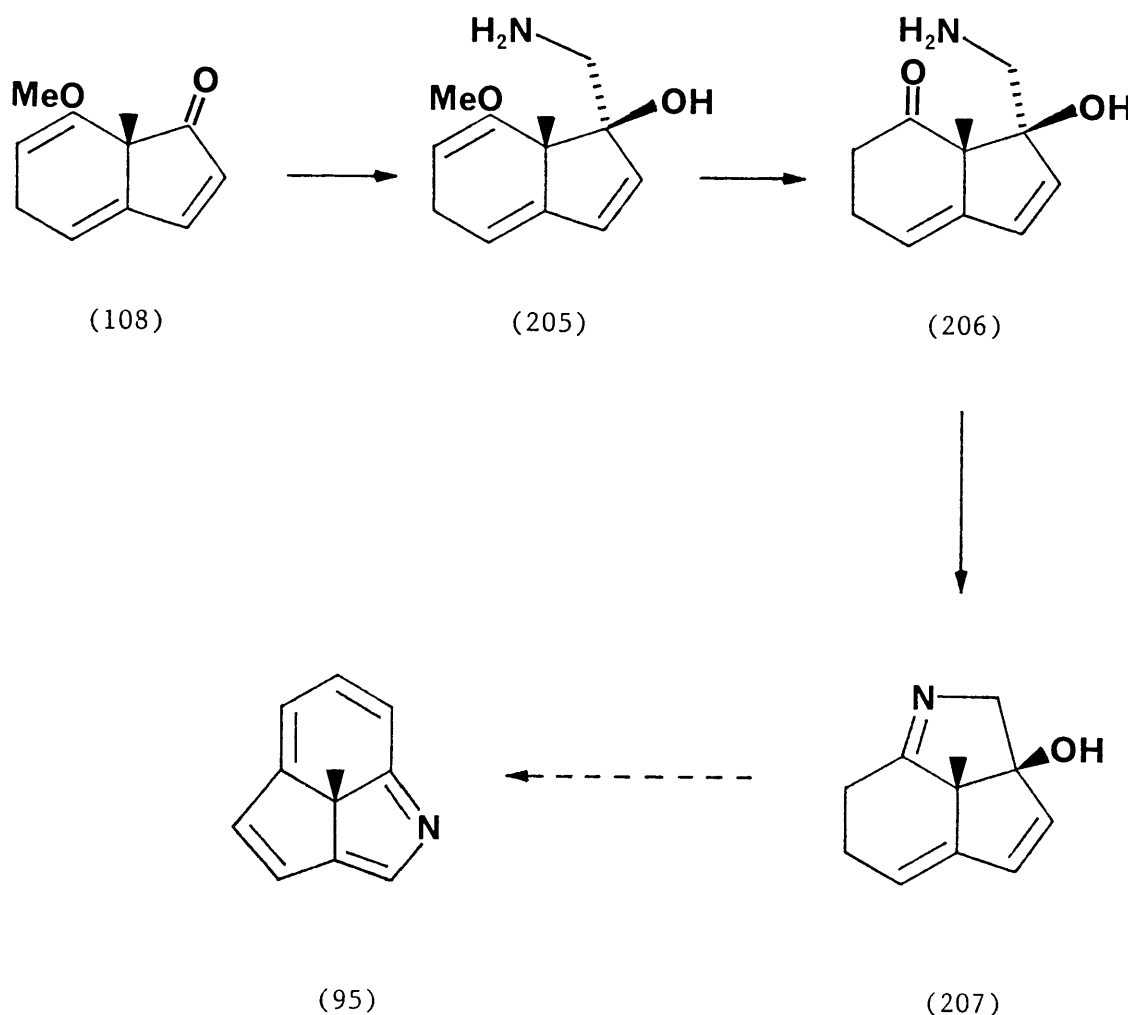


Scheme 47.

Reagents: i, 5% KOH, H₂O, MeOH; ii, di-isobutylaluminium hydride, hexane; iii, MTPI, HMPA; iv, 10% NaOH, H₂O; v, *p*-MeC₆H₄SO₃H (catalytic), CH₂Cl₂; vi, KH, 18-crown-6, DME, -20°C; vii, MeOSO₂F, -20°C to reflux (DME).

the formation of the tricyclic system *via* an intramolecular aldol condensation. The ketone (202) was then readily transformed to the required annulene (92). This approach avoided the intermediacy of the labile 3a*H*-indene (100) and in principle should allow different 7b-substituted derivatives of the tricyclic[10]annulene (92) to be synthesised. 7b-Benzyl-7b*H*-cyclopent[*cd*]indene was recently prepared using the methodology shown in Scheme 47. A study of the properties of this compound has also been undertaken and a comparison with 7b-methyl-7b*H*-cyclopent[*cd*]indene (92) has been made⁹⁶.

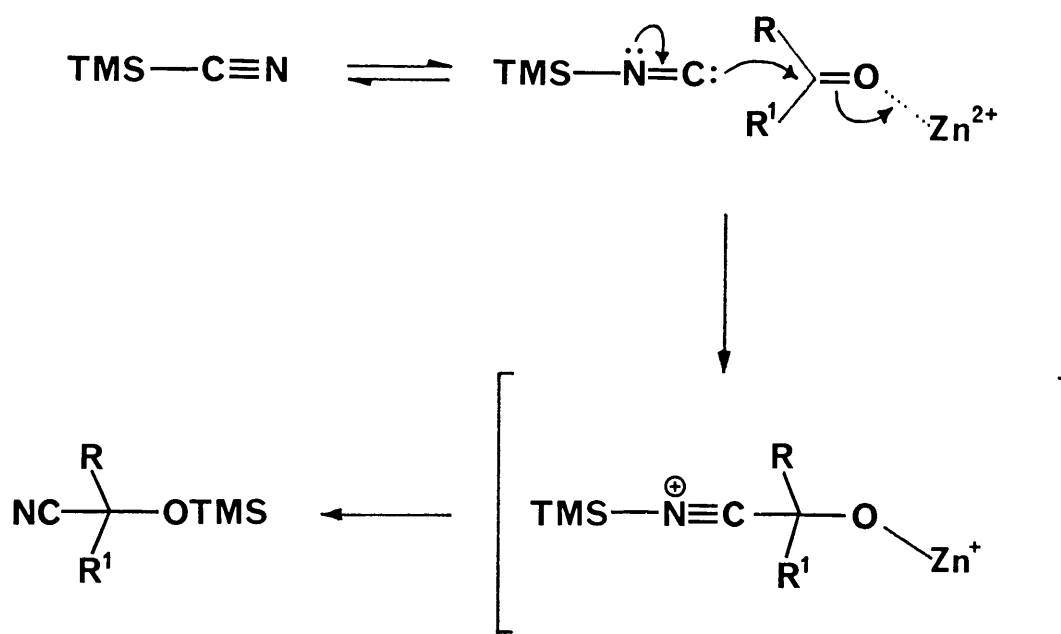
An investigation of a related cyclisation reaction of the amino alcohol (206) was instigated in the belief that the resulting tricyclic imine (207) might provide access to the 1-aza[10]annulene (95) (Scheme 48).



Scheme 48.

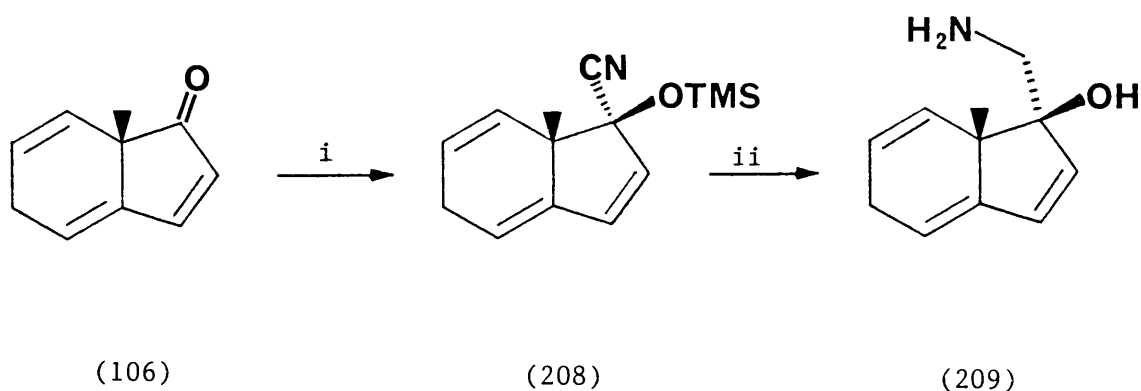
The synthesis of the amine (205) required the 1,2-addition of an aminomethyl anion equivalent to the unsaturated ketone (108). One method of achieving this is *via* the introduction of a cyano group. The base catalysed addition of hydrogen cyanide to α,β -unsaturated ketones generally gives 1,4-addition products, often in low yields⁹⁷. In contrast, treatment of unsaturated ketones and aldehydes with trimethylsilyl cyanide, in the presence of a catalytic amount of zinc iodide, has been observed to give exclusive 1,2-addition⁹⁸.

Trimethylsilyl cyanide has been shown to exist as an equilibrium mixture of the cyanide and isocyanide forms⁹⁹. The addition of this reagent to carbonyl compounds, using zinc iodide as a catalyst, is thought to involve the coordination of the zinc cation with the oxygen of the carbonyl group. This facilitates nucleophilic attack by the isonitrile form of trimethylsilyl cyanide by increasing the electrophilic nature of the carbonyl group. The transfer of the trimethylsilyl group onto oxygen then completes the reaction sequence (Scheme 49).



Scheme 49.

From a consideration of this mechanistic rationale the reaction between trimethylsilyl cyanide and the methoxy trienone (108) would be expected to proceed *via* attack of the isocyanide form from the least hindered face. In order to test this hypothesis a model study was initiated using the trienone (106) as the substrate (Scheme 50).



Scheme 50.

Reagents: i, $\text{Me}_3\text{SiCN}, \text{ZnI}_2$; ii, $\text{LiAlH}_4, \text{Et}_2\text{O}$.

Trienone (106) was treated with trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide. Kugelrohr distillation of the reaction mixture gave a high yield (95%) of the desired trimethylsilyl cyanohydrin derivative (208), identified from a consideration of its spectroscopic properties. The amino alcohol (209) was obtained on reduction of the cyanohydrin derivative (208) with lithium aluminium hydride¹⁰⁰.

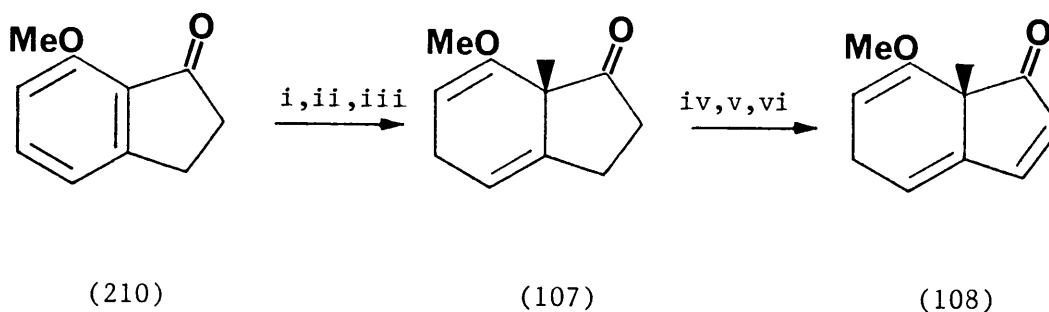
The stereochemical outcome of these reactions was determined from the results of a n.o.e. difference experiment carried out on the amino alcohol (209). Irradiation of the central methyl group showed no enhancement of the amino methyl signal, indicating that these groups must be present in a *trans* arrangement. This result suggested that

the synthesis of the amino alcohol (205) could be achieved from the methoxy trienone (108) *via* a similar sequence of reactions.

The methoxy trienone (108) was synthesised by an analogous route to that described for the trienone (106) (Section 2.2.1, page 52).

7-Hydroxy-1*H*-indan-1-one was prepared using the method of Barnes *et al*¹⁰¹ and subsequently converted into 7-methoxy-1*H*-indan-1-one (210)¹⁰².

Birch reduction of this compound followed by *in situ* methylation gave the required dienone (107) (50%) (Scheme 51).

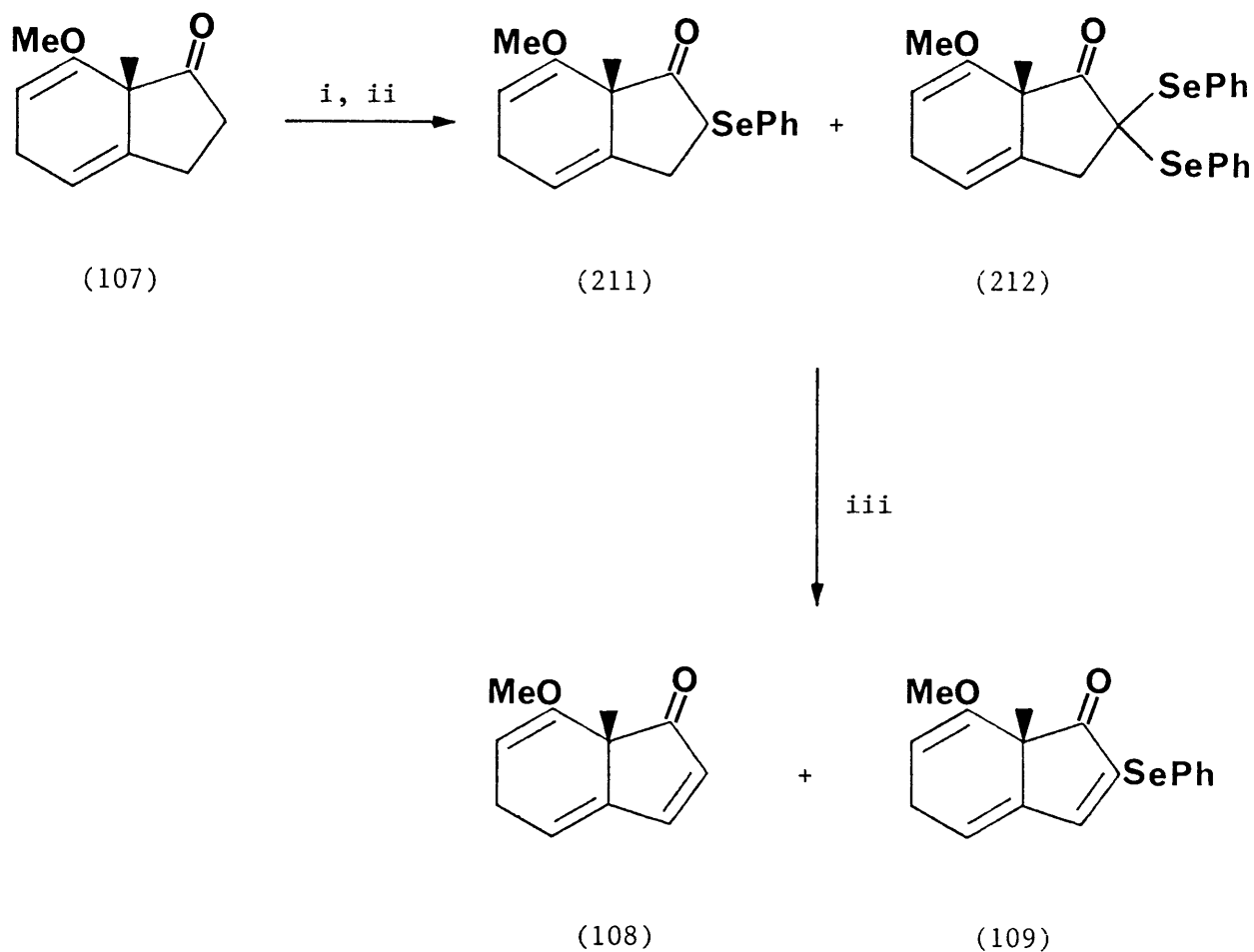


Scheme 51.

Reagents: i, K,*t*-BuOH, THF, NH₃, -78°C;
 ii, LiBr, THF, -78°C; iii, MeI, THF, -78°C;
 iv, LDA, THF, -78°C; v, PhSeCl, THF, -90°C;
 vi, *m*-CPBA, THF, NHEt₂, -10°C.

The introduction of further unsaturation into the five-membered ring was again found to be problematical. Attempts to improve the yield of trienone (108) by varying the reaction conditions are outlined in Table 6. The low yield of this transformation was attributed to an acid-base reaction which may occur during the selenation procedure (*c.f.* Scheme 15, page 54). This was confirmed by the isolation of the selenated trienone (109) (Scheme 52). The addition of phenylselenenyl chloride at lower temperatures (-90°C or below) was found to

suppress this unwanted side reaction. There is, however, considerable scope for improvement in this transformation.



Scheme 52.

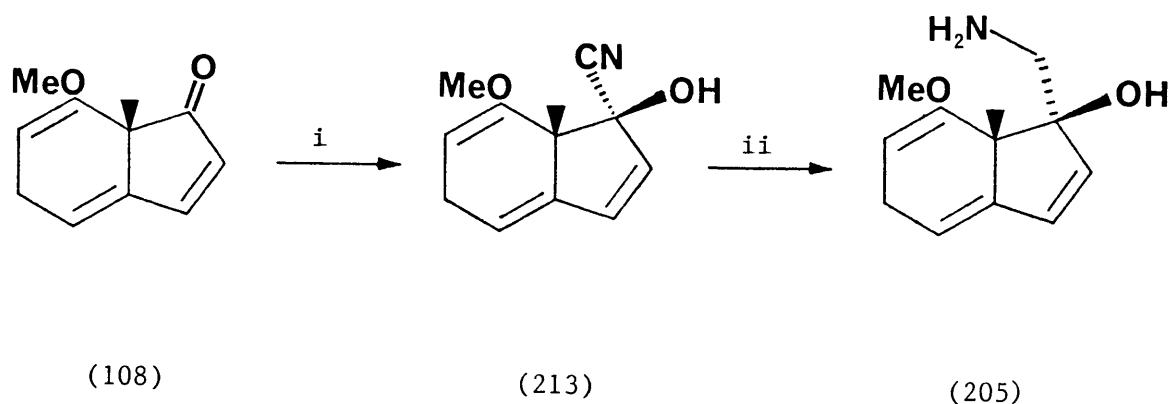
Reagents: *i*, LDA, THF, -78°C ; *ii*, PhSeCl, -78°C ; *iii*, *m*-CPBA, THF, -10°C .

The methoxy trienone (108) was reacted with trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide. This gave, after distillation, the required trimethylsilyl cyanohydrin derivative (213) (82-86%) which was reduced using lithium aluminium hydride, to the

TABLE 7 CONVERSION OF DIENONE (107) TO THE
 TRIENONE (108)

Reaction Conditions			Yield (%)	
			(108)	(109)
A.	i, 1.2eq LDA, THF, -78°C ; ii, PhSeCl, THF, -78°C ; iii, <i>m</i> -CPBA, THF, NHet_2 , -10°C		24	22
B.	i, 1.1eq LDA, THF, -78°C ; ii, PhSeCl, THF, -78°C ; iii, <i>m</i> -CPBA, THF, NHet_2 , -10°C .		10	10.5
C.	i, 1.1eq LDA, THF, -78°C ; ii, PhSeCl, THF, $<-90^{\circ}\text{C}$; iii, <i>m</i> -CPBA, THF, NHet_2 , -10°C .		35	-
D.	i, TMSCl , Et_3N , NaI , CH_3CN , 45°C ; ii, PhSeBr, THF, -78°C ; iii, <i>m</i> -CPBA, THF, NHet_2 , -10°C .		11	-

corresponding amino alcohol (205) (87%). The ^1H n.m.r. spectrum of the alcohol (205), obtained by evaporation of the crude reaction mixture, showed no apparent impurity. Attempted distillation, however, led to extensive decomposition and it seemed advisable to avoid the isolation of this compound. As a result deprotection of the enol ether function was carried out using the crude product.



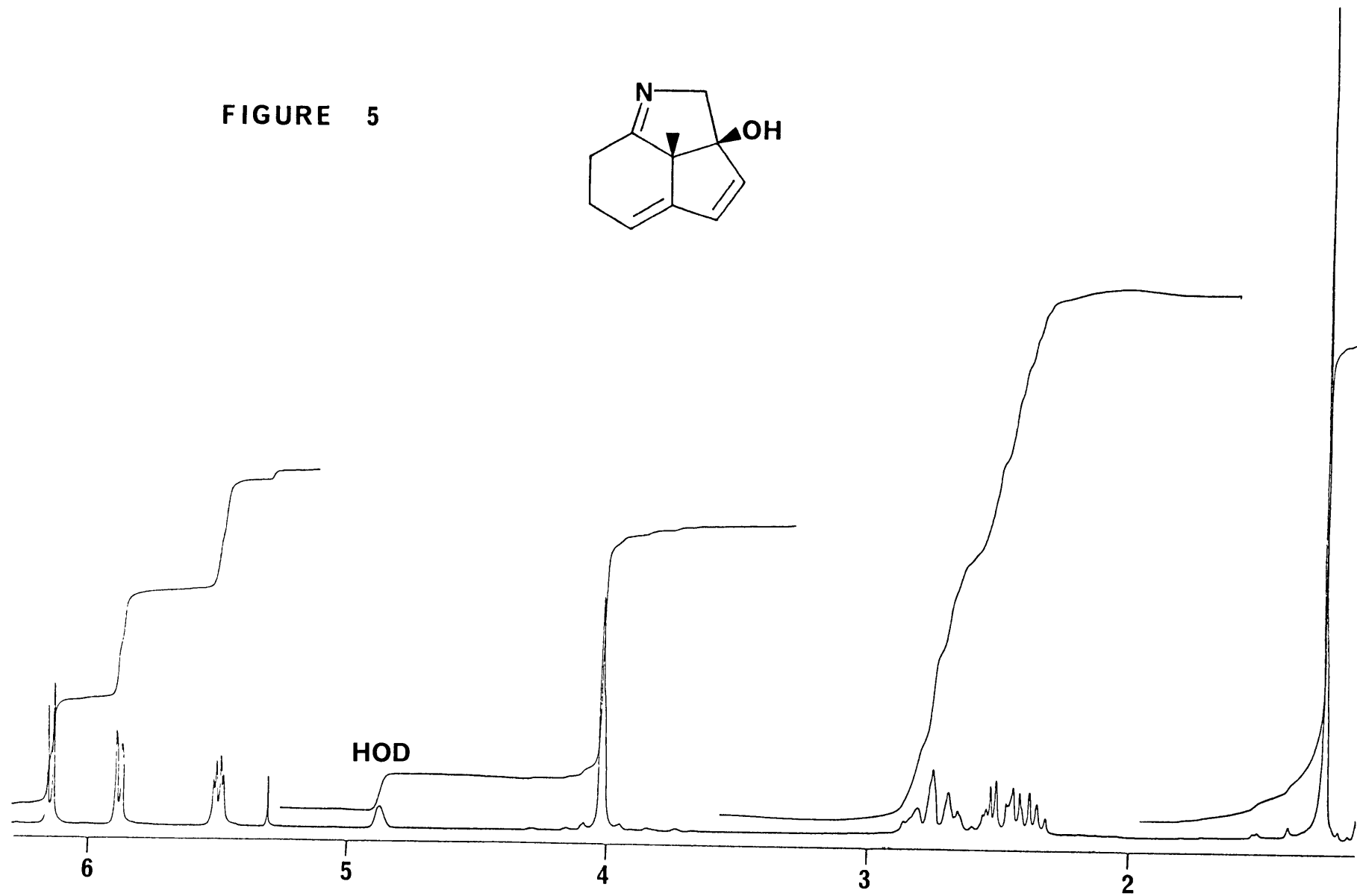
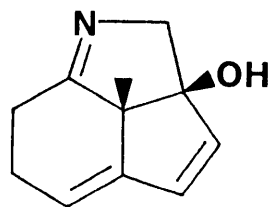
Scheme 53.

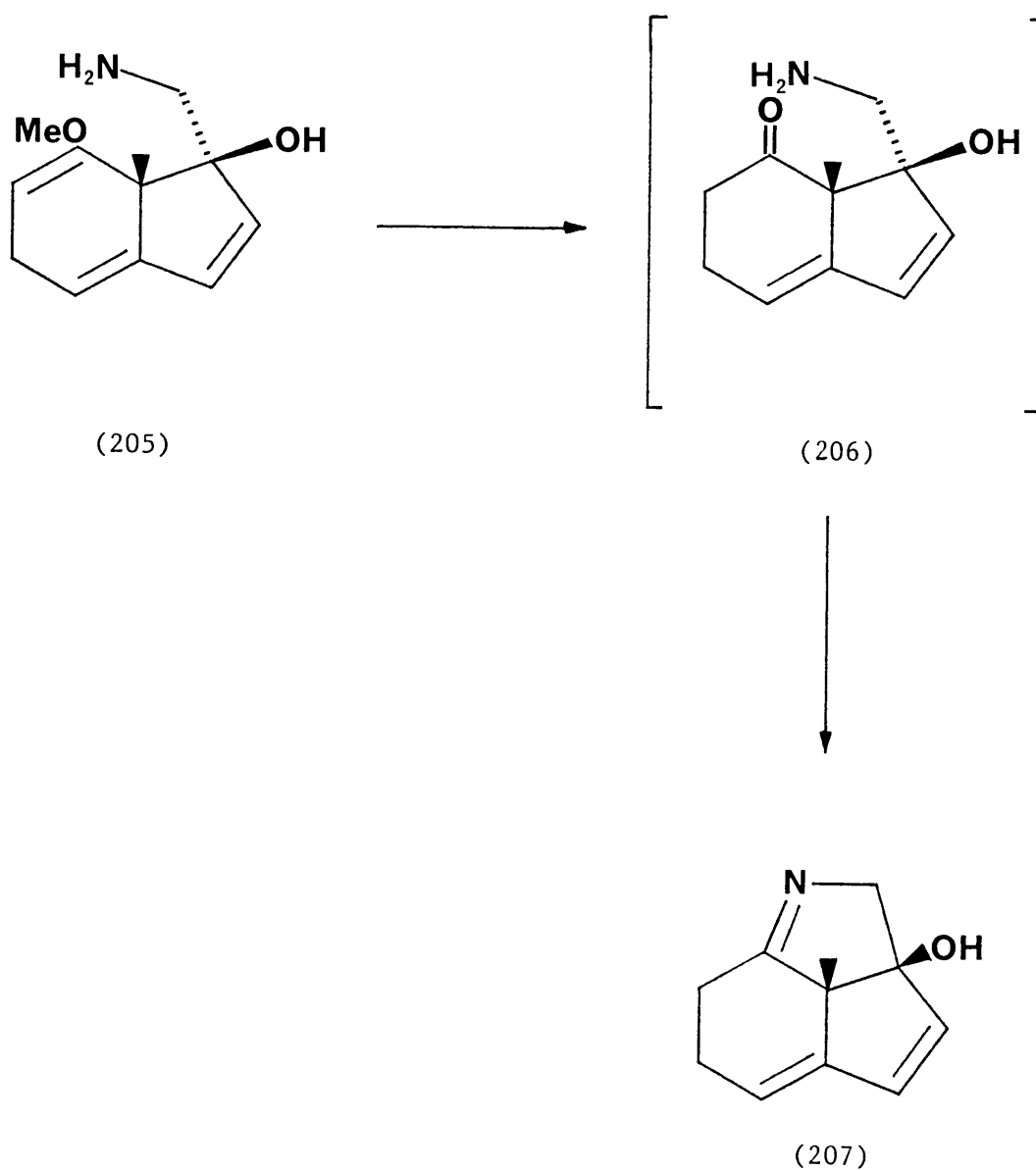
Reagents: i, $\text{Me}_3\text{SiCN}, \text{ZnI}_2$; ii, $\text{LiAlH}_4, \text{Et}_2\text{O}$.

Treatment of (205) with *p*-toluenesulphonic acid in refluxing benzene led only to extensive decomposition. The use of 0.1M hydrochloric acid in ether¹⁰³, however, gave a high yield of the tricyclic imine (207) (89%) which is presumable formed *via* ring closure of the resulting ketone (206) (Scheme 54). The product was identified from a consideration of its spectroscopic properties.

The presence in the i.r. spectrum of a strong imine stretch at 1645 cm^{-1} coupled with the absence of a methoxy resonance in the ^1H n.m.r. spectrum (Figure 5) allowed structure (207) to be assigned. The overall yield of (207) from the trienone (108) was improved to 71% by *in situ* deprotection of the enol ether.

FIGURE 5

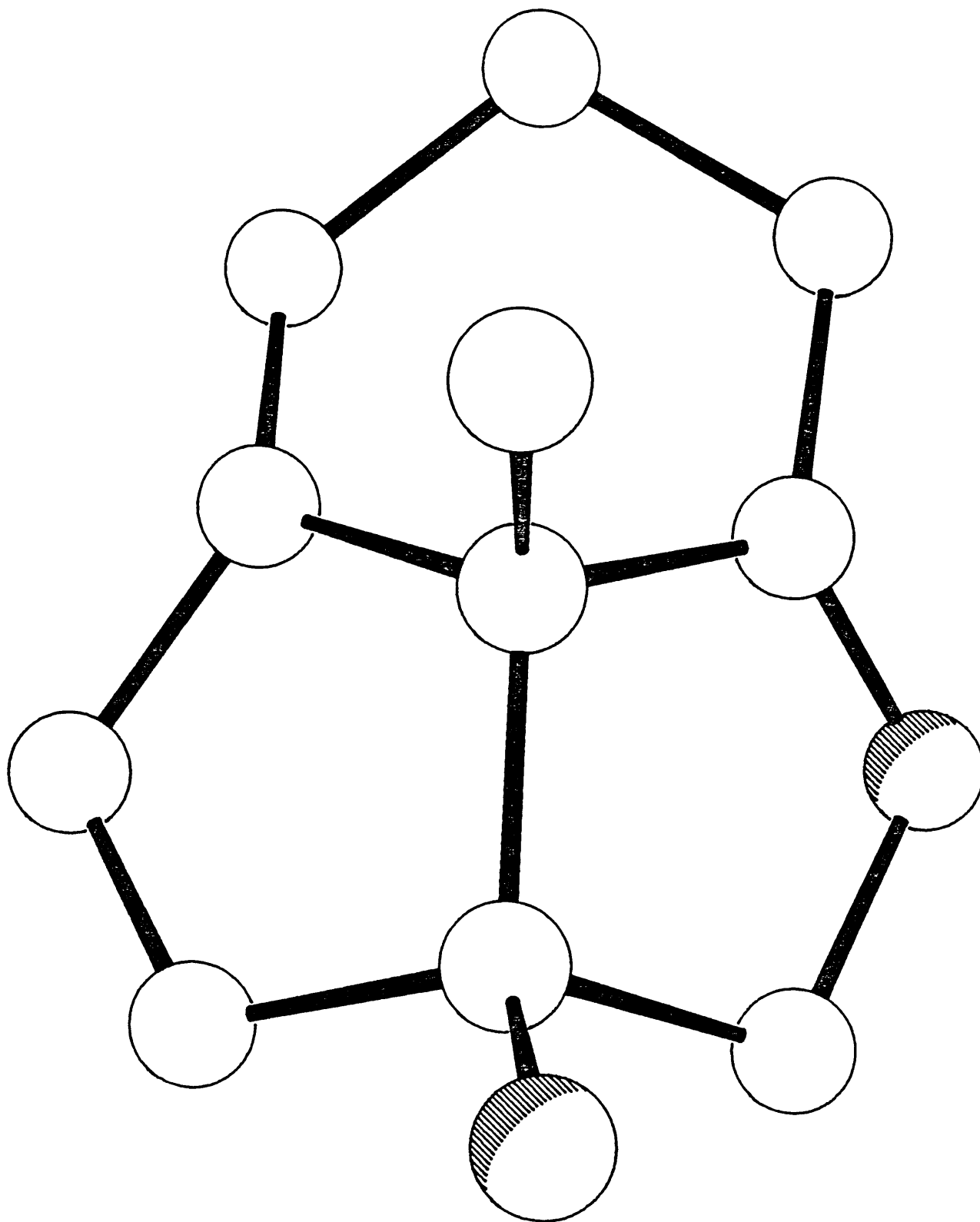




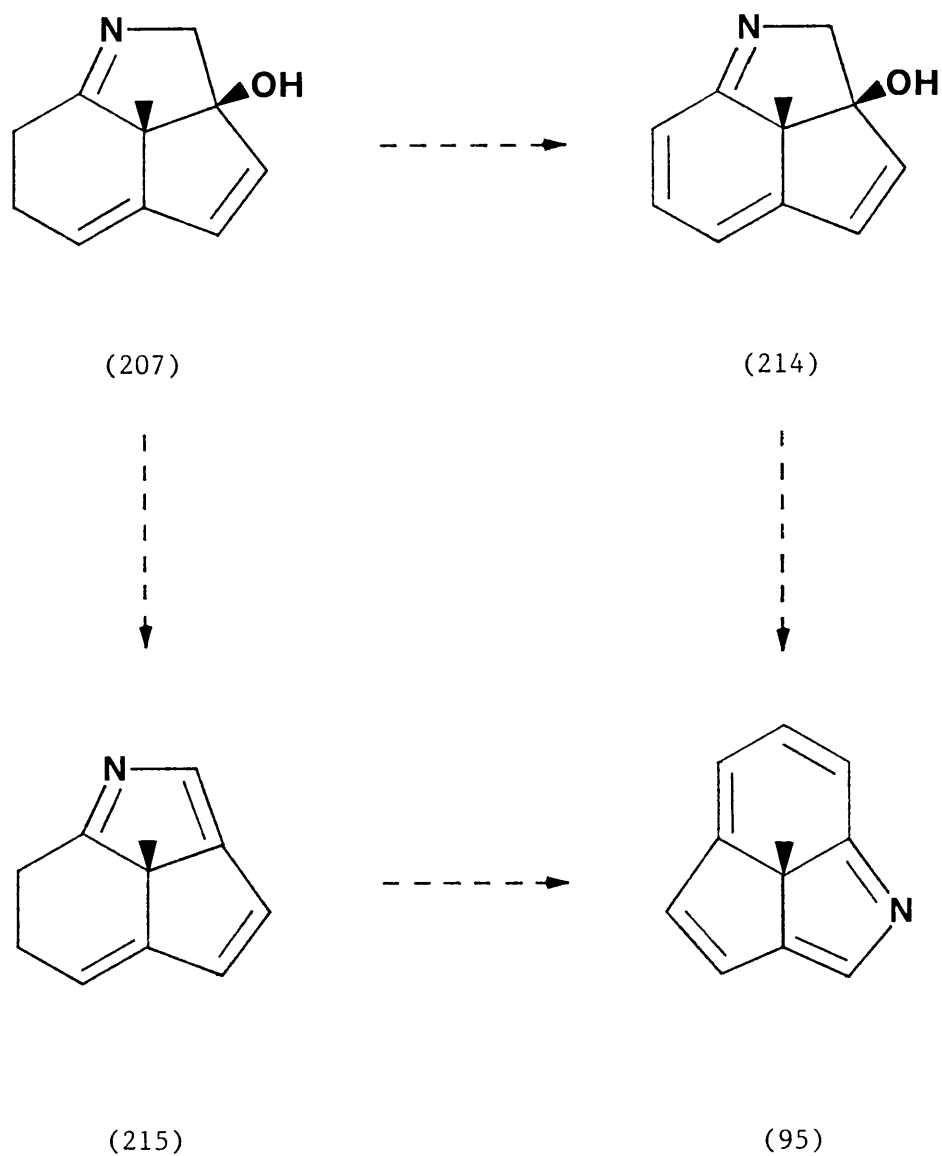
Scheme 54.

The importance of this compound led to definitive proof of its structure being sought by X-ray analysis¹⁰⁴ (Figure 6). This confirmed the assigned structure (207) and the bond lengths were found to be as expected. There was evidence of a strong intermolecular hydrogen bond which presumably contributes to the crystallinity of compound (207).

FIGURE 6: X-Ray Structure of 2a-Hydroxy-7b-methyl-2a,6,7,7b-tetrahydro-2*H*-cyclopent[*cd*]indole (207)



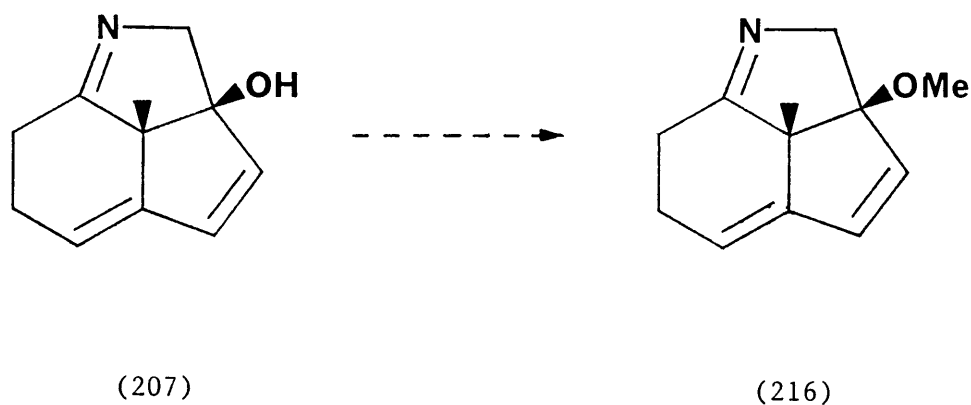
It was hoped that this compound would provide access to the tricyclic aza[10]annulene (95), *via* an oxidation-dehydration sequence (Scheme 55). In principle these operations may be carried out in either order but it seemed preferable to avoid oxidation as the final step. The observation that 7b-methyl-7b*H*-cyclopent[*cd*]indene (92) decomposed on prolonged exposure to air suggested that the desired aza[10]annulene (95) might be sensitive towards oxidising conditions.



Scheme 55.

The introduction of further unsaturation into the six-membered ring was attempted using direct oxidation. However, treatment of the tricyclic imine (207) with either benzeneseleninic anhydride in chlorobenzene¹⁰⁵ or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene¹⁰⁶ gave no identifiable products. This led to a consideration of a selenation-oxidation sequence analogous to that used in the preparation of the methoxy trienone (108) (p. 118).

Treatment of the imine (207) with two equivalents of *n*-butyl lithium followed by phenylselenenyl chloride resulted only in substantial decomposition. For this reason protection of the hydroxyl function was undertaken and initial efforts were concentrated on the formation of the methyl ether (216). The reaction was attempted using sodium

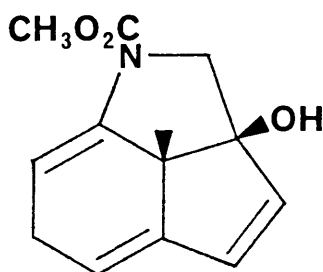


hydride in THF followed by treatment with methyl iodide, however, this gave only returned starting material. When dimethyl-sodium was used as the base substantial decomposition resulted¹⁰⁷. A final attempt to effect this transformation involved treatment of (207) with methyl fluorosulphonate in DME. This, however, gave no identifiable product.

The failure of these reactions led to an investigation into the formation of the corresponding ester derivative. Acetylation using

acetic anhydride and trimethylsilyl chloride¹⁰⁸ gave a 50% yield of a mono-acetylated product. However, the spectral characteristics of this product, were not consistent with the expected structure. This result will be discussed later in this Section (p. 134). The use of acetic anhydride and 4-dimethylaminopyridine in pyridine¹⁰⁹ gave a complex mixture of products and because of the small quantities of material isolated none of these could be characterised.

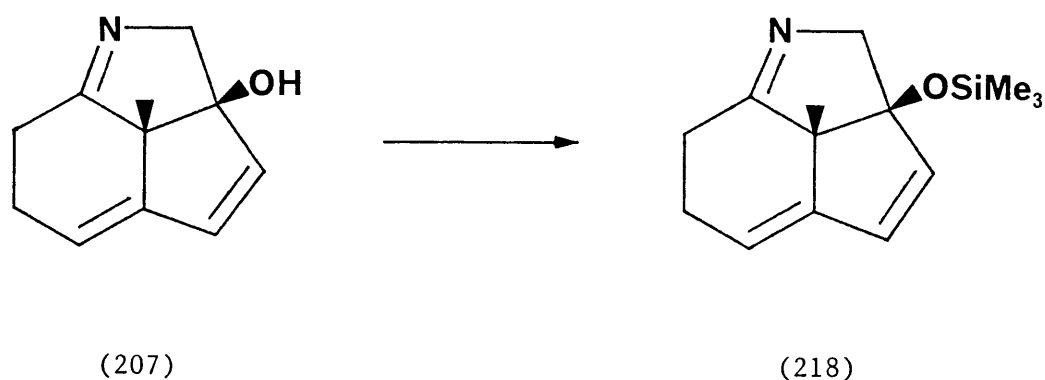
Attempts to form the mesylate and phosphate derivatives of the alcohol (207) were also unsuccessful. In each case these reactions gave mixtures of products which proved to be inseparable by column chromatography. The reaction of the alcohol (207) with methyl chloroformate in THF, using triethylamine as the base, gave a mixture of products, one of which has been tentatively assigned as the enamine (217).



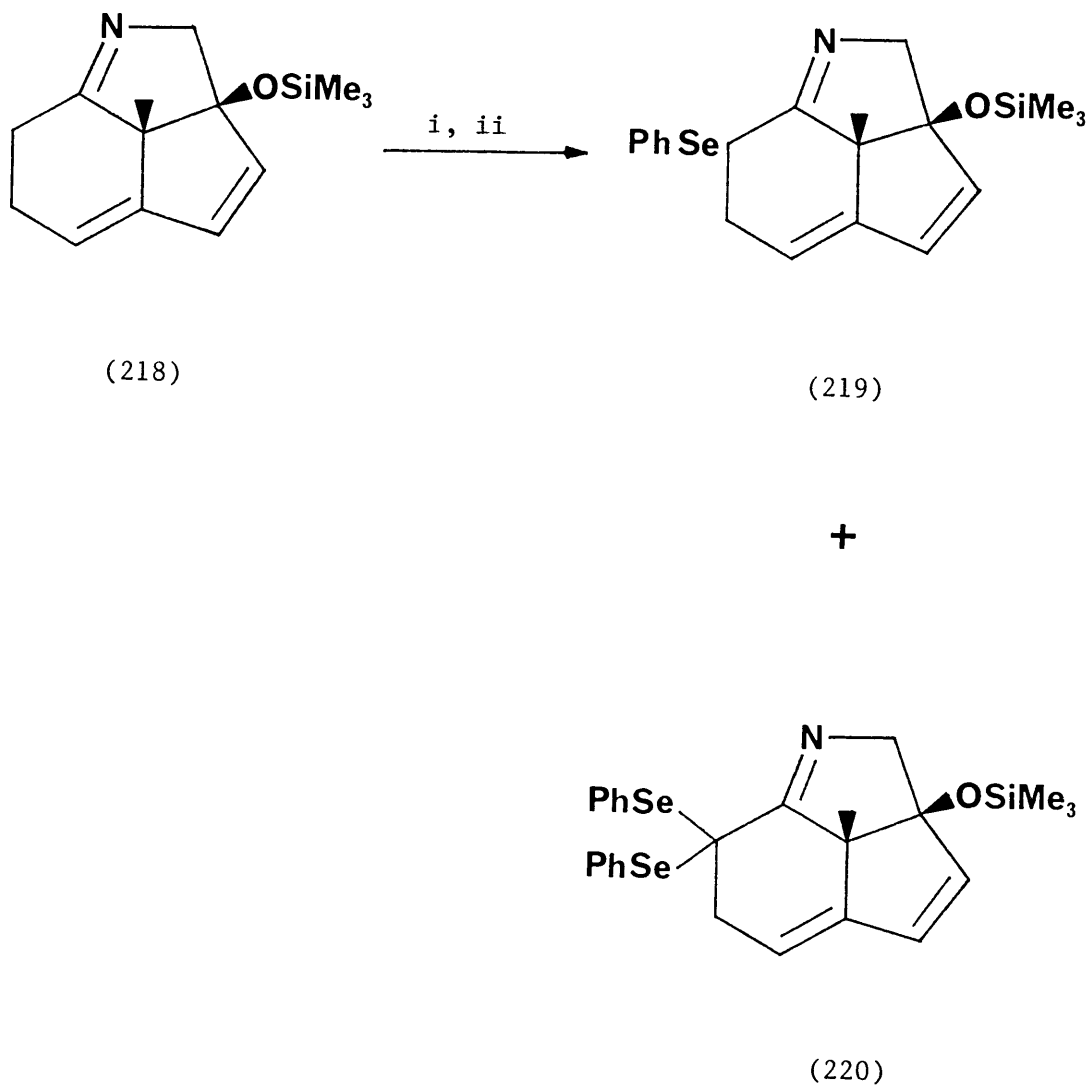
(217)

The structural assignment of (217) was based on the ¹H n.m.r. spectrum which exhibited four olefinic resonances. The i.r. spectrum also indicated the presence of both amide and hydroxyl functionality. Unfortunately due to the instability of this compound it could not be fully characterised. This result showed the nitrogen atom of compound (207) to be more nucleophilic than the oxygen atom.

The synthesis of the trimethylsilyl ether (218) was then attempted since it was argued that the strong affinity of silicon for oxygen would result in the formation of the trimethylsilyl ether (218). Indeed, treatment of the alcohol (207) with trimethylsilyl chloride and triethylamine in THF¹¹⁰ gave the required ether (218) in 85% yield.



A further unit of unsaturation was introduced into the six-membered ring *via* a selenation-oxidation procedure. The trimethylsilyl ether (218) was treated with *n*-butyl lithium at -78°C and after 30 min. phenylselenenyl chloride was added. This gave both the required selenide (219) (25%) and the *bis*-selenide (220) (20%) (Scheme 56). The *bis*-selenide (220) presumably arises *via* a similar acid-base reaction to that described earlier (p. 54). The yields of this reaction were found to be variable with starting material frequently being recovered. It was observed that higher yields of the required selenide (219) were obtained if the anion was allowed to stir at -55°C for 25 min., and the phenylselenenyl chloride was then added at -100°C . These conditions ensured complete anion formation and yields of up to 56% of selenide (219) were obtained. This compound was readily oxidised using *m*-CPBA in THF to give the required tricyclic imine (221). The extended conjugation of this compound was evidenced by both u.v. and ^1H n.m.r. spectral data (Figure 7).



Scheme 56.

Reagents: i, LDA, THF, -78°C , ii, PhSeCl, THF, -78°C .

It was believed that deprotection of the trimethylsilyl ether (221) and subsequent elimination of the elements of water (Scheme 57) would be straightforward. Unfortunately this did not prove to be the case. Treatment of the trimethylsilyl ether (221) with potassium fluoride in aqueous THF gave only partial decomposition of the starting material.

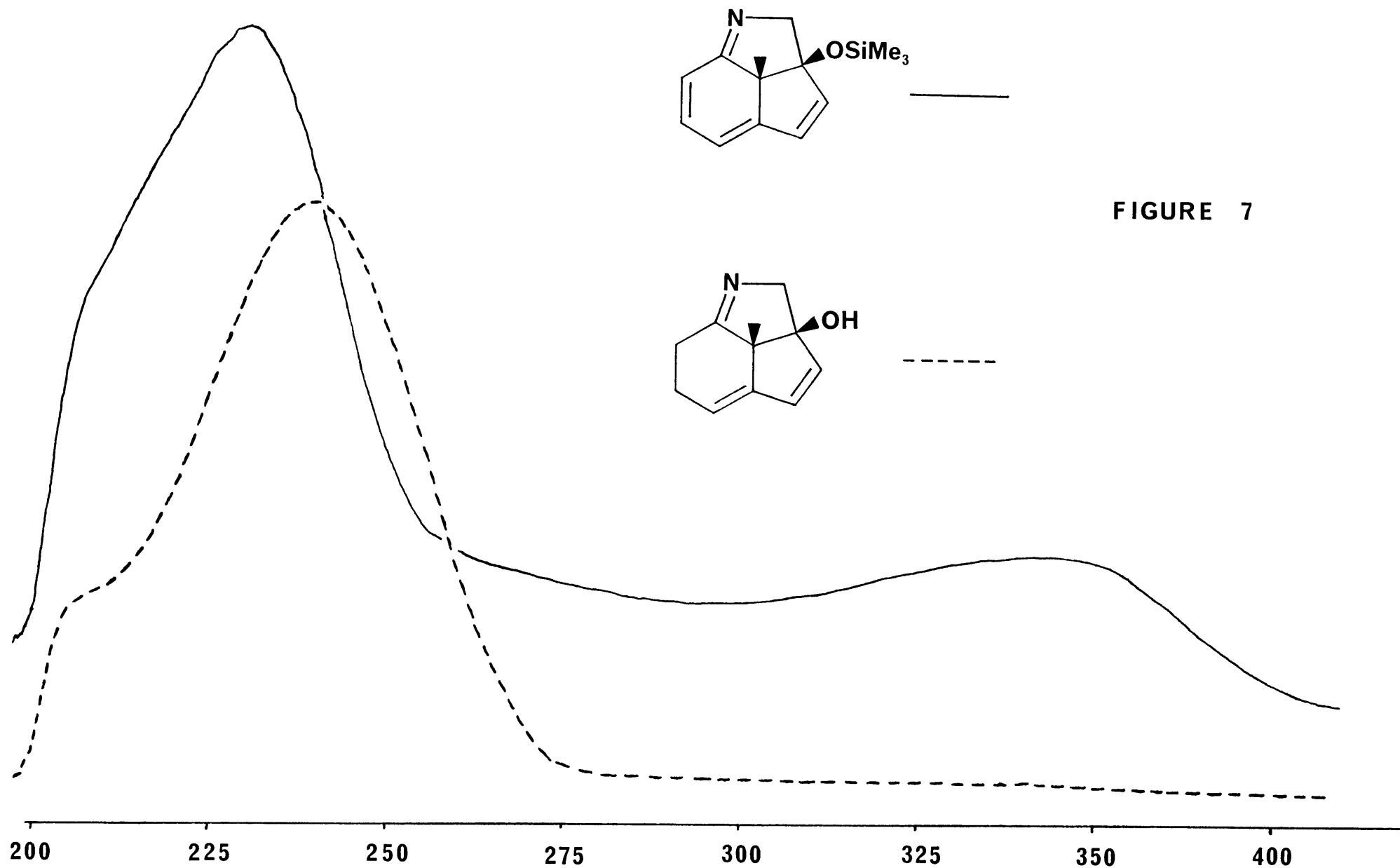
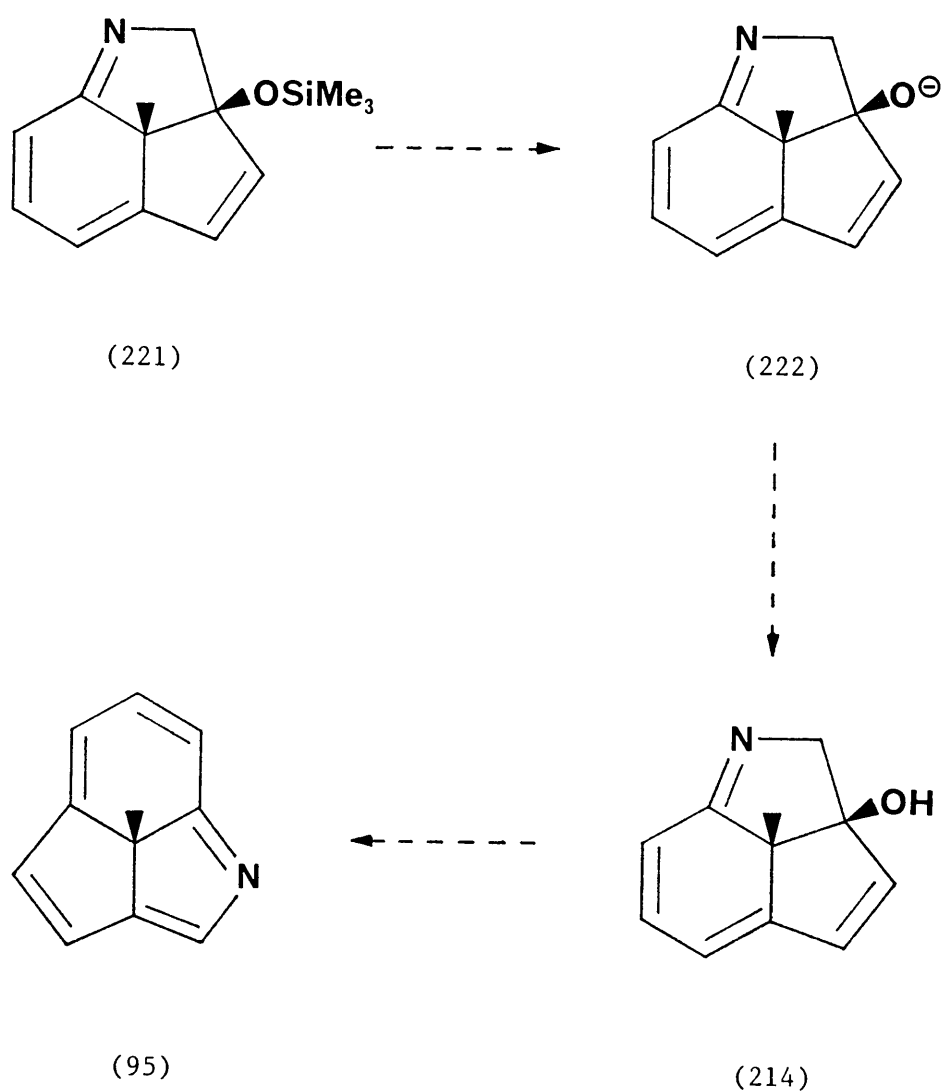


FIGURE 7

Use of the more reactive tetrabutylammonium fluoride¹¹⁰ in THF at either -78°C or 0°C also resulted in decomposition of the starting material. These results suggested that the intermediate anion (222)

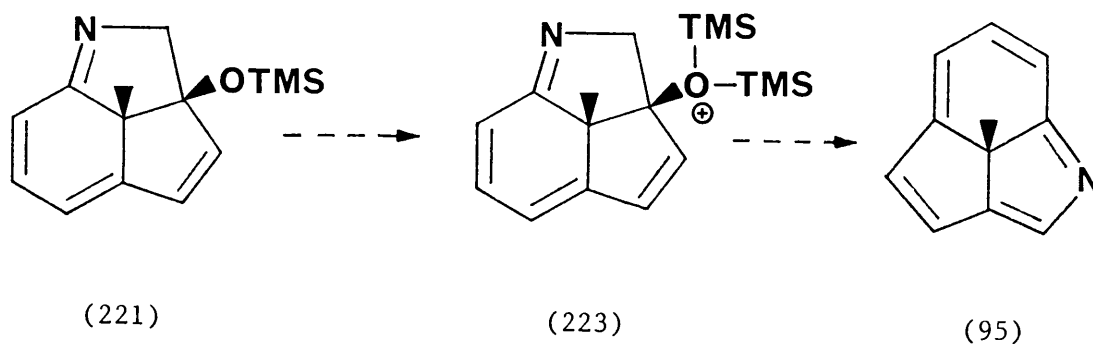


Scheme 57.

was unstable under the reaction conditions and an investigation into the use of acidic deprotection conditions was instigated. This was not favoured initially owing to the presence of the relatively delicate imine functionality in compound (221). Treatment of the unsaturated imine (221) with either 0.1M hydrochloric acid in THF or toluene-4-sulphonic

acid in refluxing benzene¹¹¹ gave an intractable black tar from which no identifiable product could be isolated.

The sensitivity of the tricyclic imine (221) towards these deprotection conditions prompted a consideration of the direct elimination of the elements of trimethylsilanol to afford the desired aza[10]-annulene (95). An attempt to carry out this transformation was made using trimethylsilyl trifluoromethanesulphonate and triethylamine in DME. It was hoped that this would lead to the formation of the intermediate (223) and subsequent elimination of the trimethylsilyl ether would yield the desired [10]annulene (Scheme 58). However, no recognisable product was obtained from this reaction.

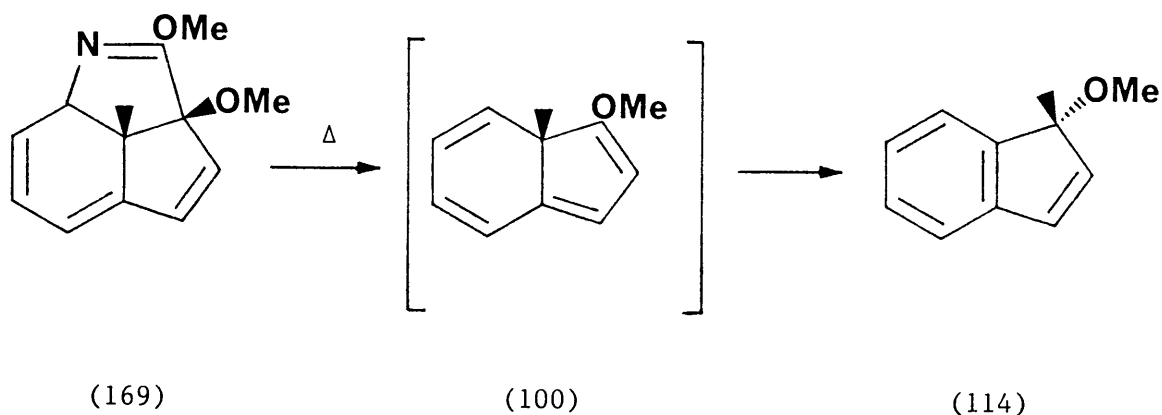


Scheme 58.

Similarly, attempts to effect the elimination of the elements of trimethylsilanol using either *t*-butyl lithium in THF or neat DBU led to complete decomposition of the starting material. The failure of these reactions was disappointing and led to the consideration of flash vacuum pyrolysis (FVP) conditions to effect the desired transformation.

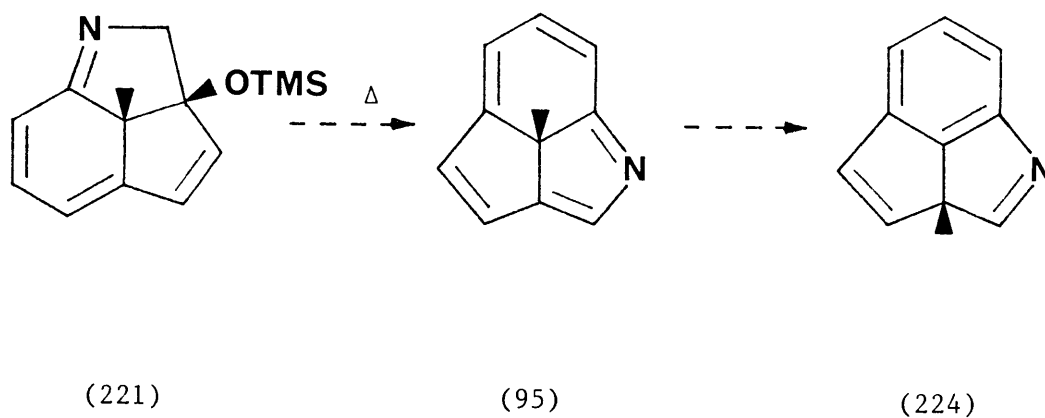
The imidate (169) had previously been subjected to FVP conditions at 580°C and 8×10^{-1} mmHg resulting in the formation of 1-methyl-1-

methoxy-1*H*-indene (114). This product is presumably formed *via* a retro [8+2] cycloaddition followed by a [1,5]methyl sigmatropic rearrangement (Scheme 59). The tricyclic imine (221) cannot undergo a similar



Scheme 59.

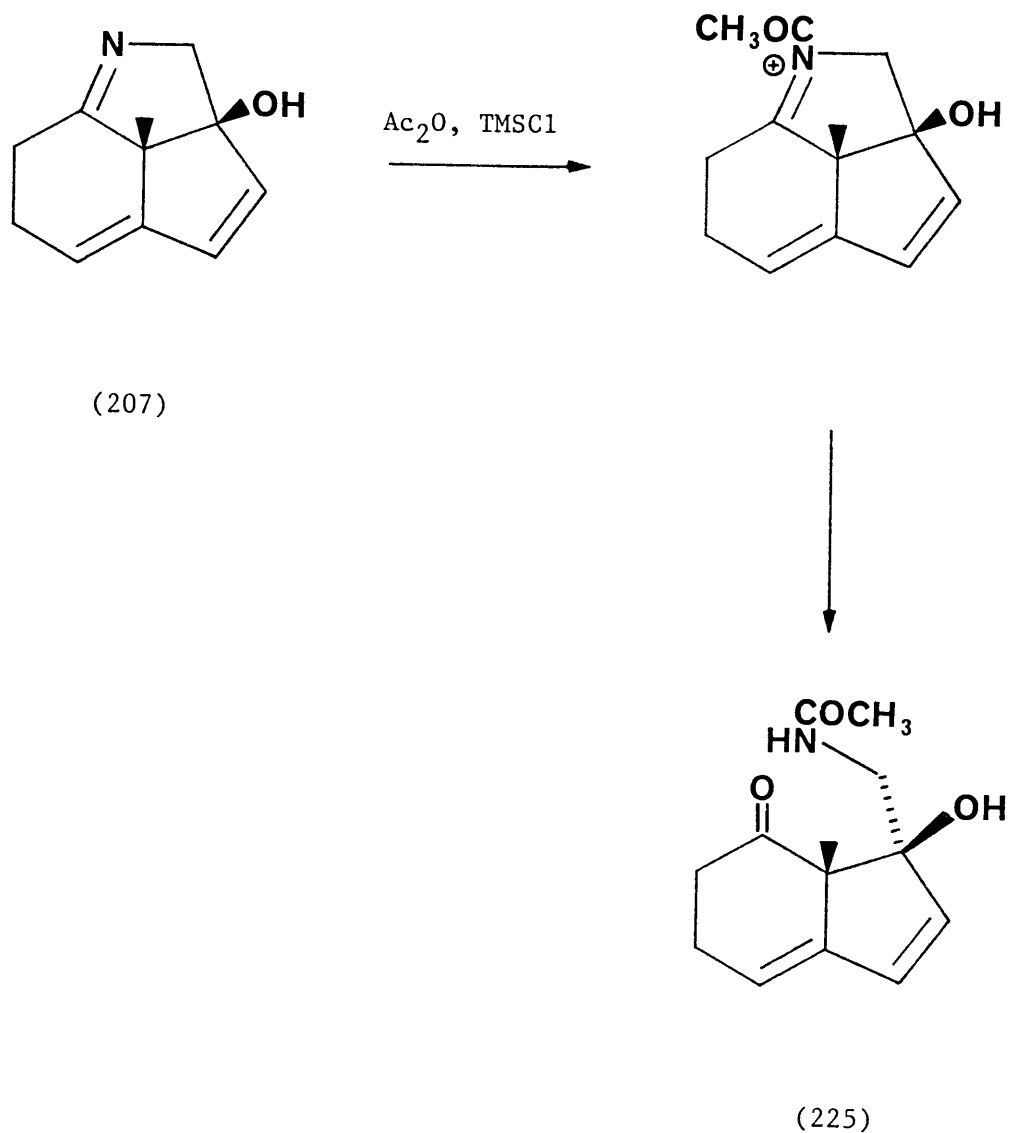
reaction and it was hoped that the elements of trimethylsilanol would be eliminated. The aza[10]annulene formed in this way would be expected to undergo a [1,5] methyl sigmatropic migration to give the isomer (224) (Scheme 60).



Scheme 60.

The tricyclic imine (221) was subjected to FVP conditions, 425°C and 4×10^{-1} mmHg. The pyrolysate, collected on the cold finger, was analysed using ^1H n.m.r. spectroscopy which indicated that a complex mixture of products had been formed. The mass spectrum of this mixture contained a peak at 155 m.u. which is the molecular weight of the desired aza[10]annulene (95) or an isomer. The presence of aromatic peaks in the ^1H n.m.r. spectrum of the mixture may indicate that the reactions shown in Scheme 60 had indeed taken place. However, the individual components could not be isolated satisfactorily by p.l.c..

The acetylation of the tricyclic imine (207) using acetic anhydride and trimethylsilyl chloride gave an unexpected product which was identified as having structure (225). The observation that there were two carbonyl carbons in the ^{13}C n.m.r. spectrum coupled with the fact that the methylene α to nitrogen appeared as two double doublets in the ^1H n.m.r. spectrum allowed the assignment to be made. All other spectral data and the elemental analysis were in accord with structure (225). This appeared to confirm the previous observation that the most nucleophilic site of the compound (207) was the nitrogen atom. Treatment of this compound (225) with toluene-4-sulphonic acid in refluxing benzene gave 65% of the ester (226). The observation of peaks in the i.r. spectrum at 1740 cm^{-1} and 1650 cm^{-1} indicated the presence of both an ester and an imine functionality which supported the assignment of structure (226). An examination of the ^1H n.m.r. spectrum, however, showed the methylene α to nitrogen as two double doublets, although one of the couplings was small (1.8 Hz). This was later shown to arise from a five bond coupling from H-7 by a two dimensional n.m.r. technique (Figure 8).



Scheme 61.

In an attempt to introduce further unsaturation into the six membered ring of compound (226), it was treated with DDQ in refluxing benzene¹⁰⁶. This unfortunately gave an intractable tar from which no identifiable product could be obtained. A shortage of both time and material resulted in no further progress being made. Provided the extra unit of unsaturation can be introduced into the six membered ring

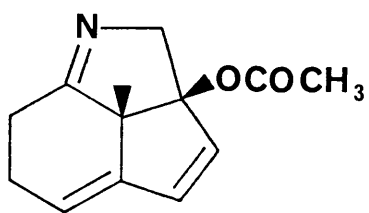
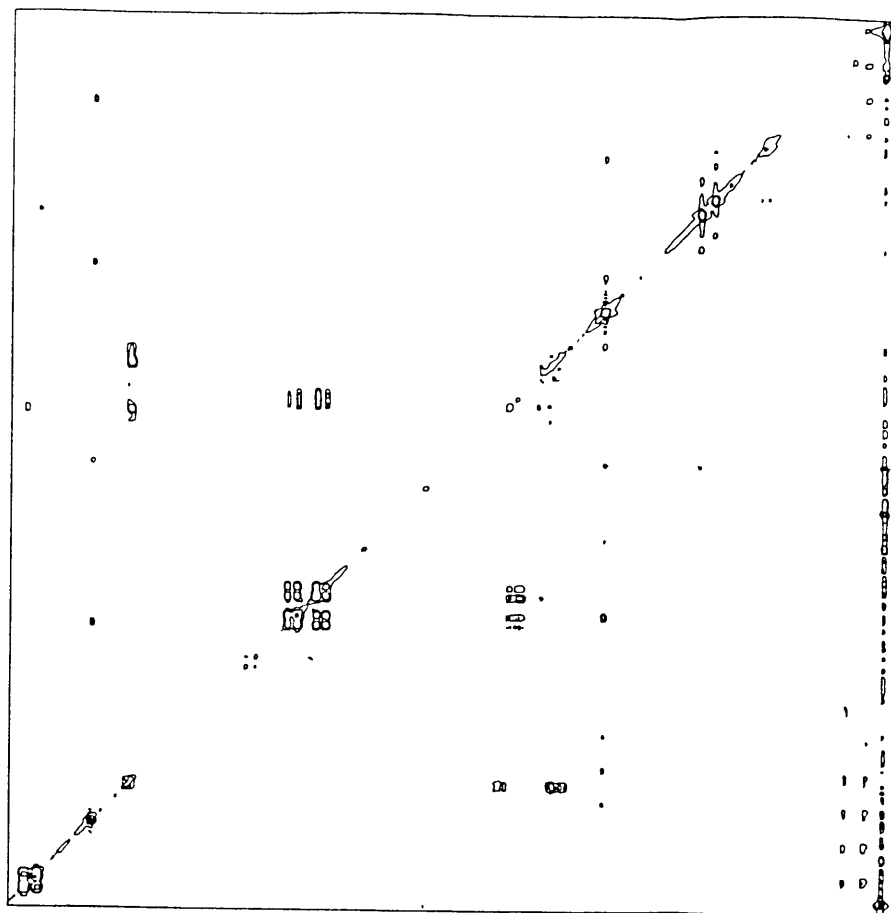
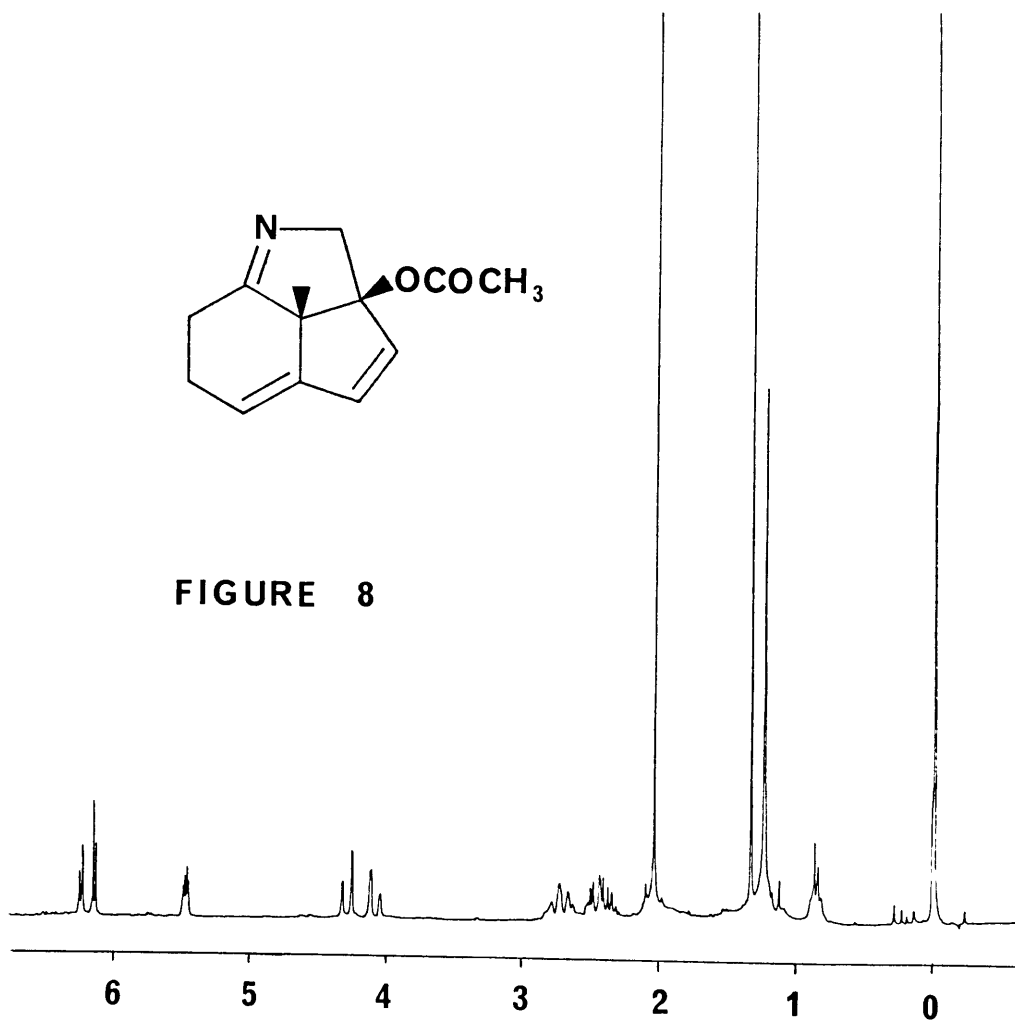
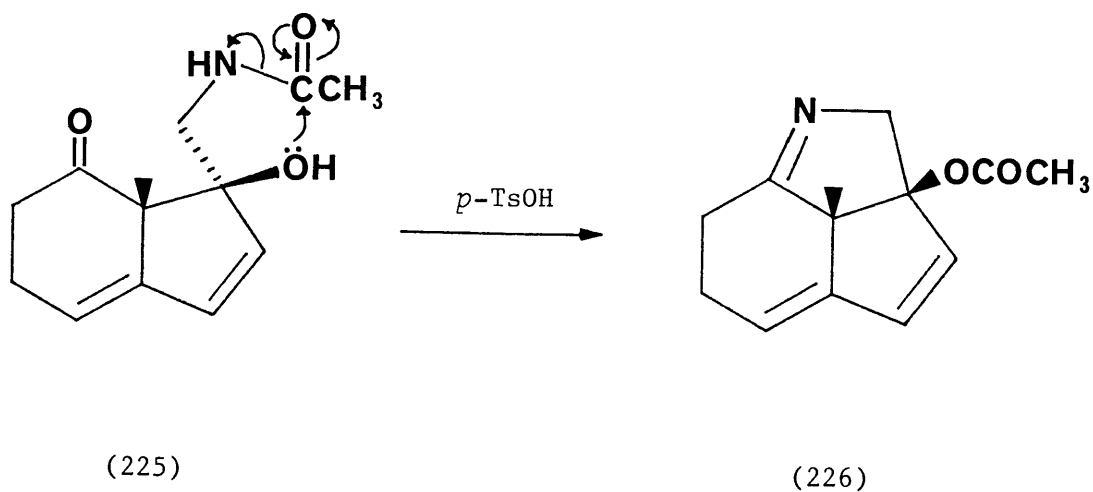
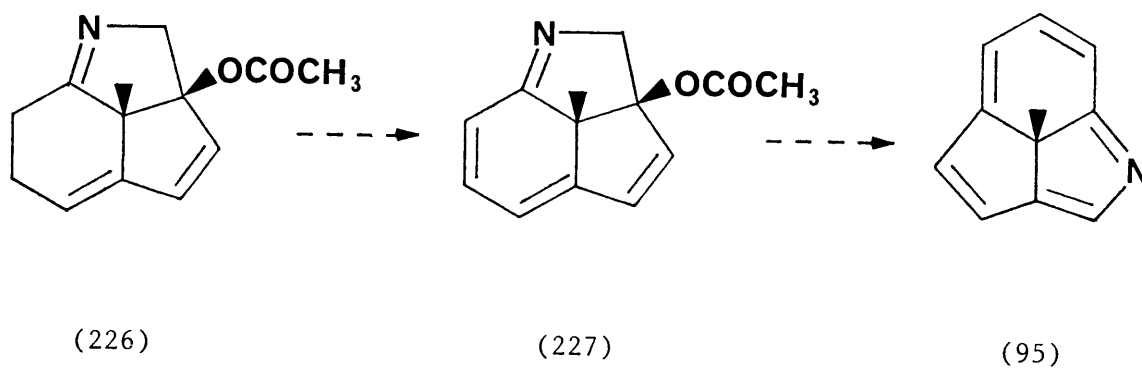


FIGURE 8





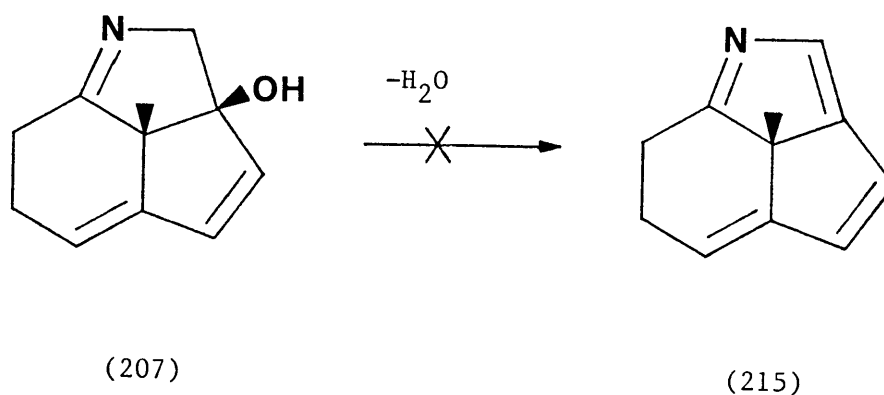
then it is believed that the resulting conjugated imine (227) would, *via* the loss of the elements of acetic acid, yield the desired aza[10]annulene (95). Although it has been seen that such elimination reactions are by no means straightforward, it was thought that acetate would prove to be a better leaving group than the trimethylsiloxy moiety.



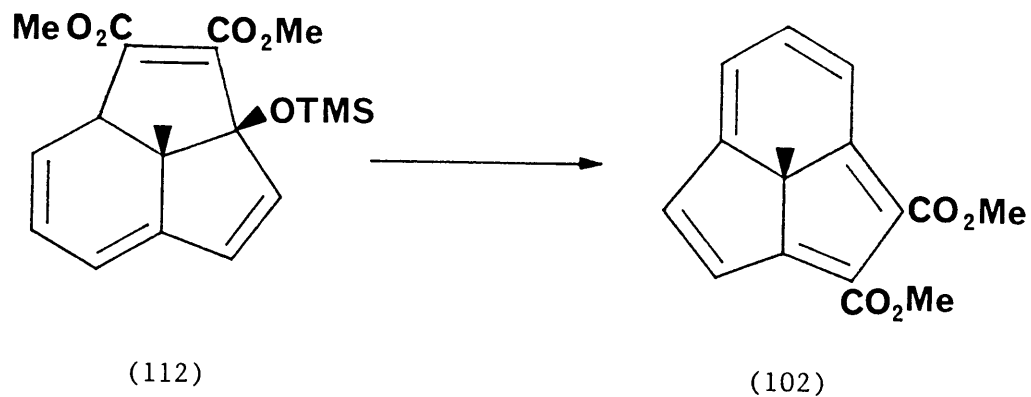
Although it was originally considered advantageous to have the elimination reaction as the final step in the synthesis some attempts

were made to remove the elements of water from the alcohol (207).

Treatment of this compound with toluene-4-sulphonic acid in benzene¹¹², under Dean and Stark conditions for 7 days, gave only returned starting material. Similarly, the use of triphenylphosphine and carbon tetrachloride in dry acetonitrile¹¹³ gave recovered starting material (53%) and no other product could be detected. Reaction with thionyl chloride in pyridine resulted in complete decomposition of the alcohol (207).



The ring closure approach, based on the reaction of the trienone (108) with trimethylsilyl cyanide, outlined in this Section has proved to be an efficient method for the preparation of the tricyclic system (207). Although this compound could be converted into the tricyclic imine (221), the final elimination of the elements of trimethylsilanol has so far proved to be unsuccessful. It was expected that such a transformation could be accomplished since McCague had shown that the [8+2] cycloadduct (112) was readily converted to the [10] annulene (102) on treatment with acid. The reluctance of the trienimine (221) to undergo a similar transformation was both surprising and disappointing.

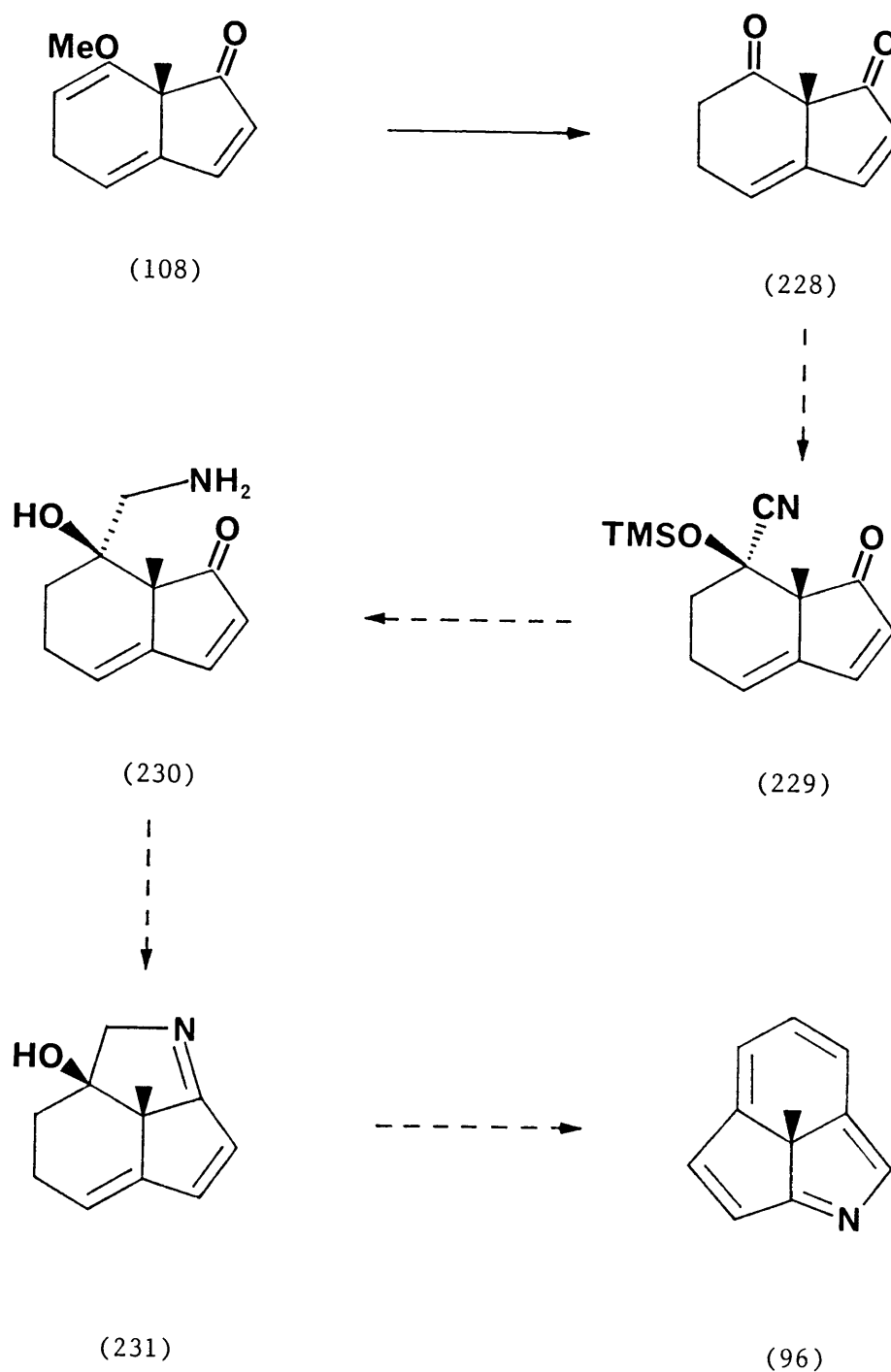


The failure to isolate any identifiable products from these reactions made it difficult to ascertain whether the problem lies in the lack of stability of the aza[10]annulene (95) or with some other aspect of the reaction.

Despite considerable effort the aza[10]annulene remained tantalisingly elusive. However, it is believed that this type of strategy has the best chance of success when considering possible avenues for future work.

2.3.3 Ring Closure Approach to the 2-Aza[10]annulene (96)

In principle a similar strategy to that described in Section 2.3.2 could be applied to the synthesis of the 2-aza[10]annulene (96). The proposed reaction sequence is outlined in Scheme 62. The reaction



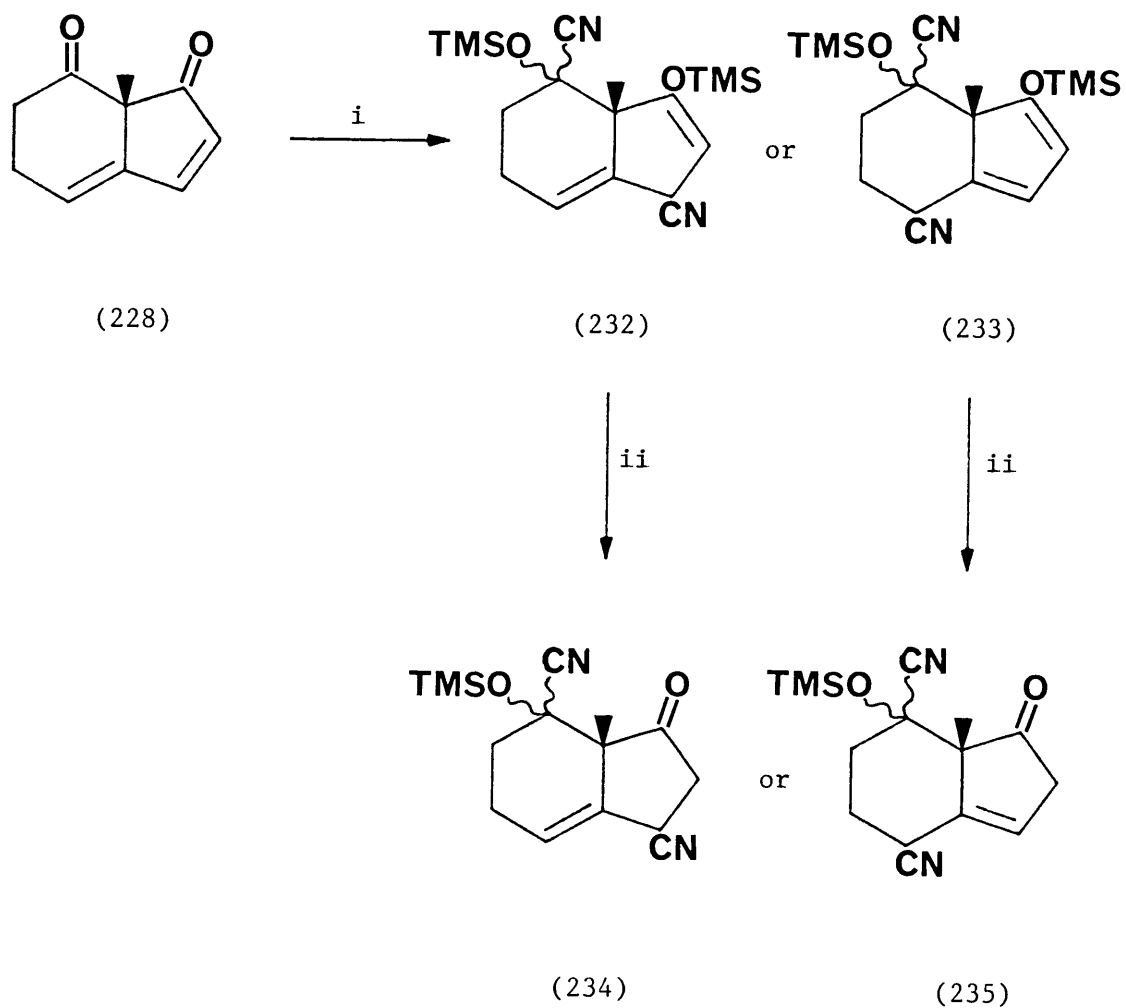
Scheme 62.

of trimethylsilyl cyanide with the dienedione (228) was expected to occur preferentially at the saturated ketone. This should result in the formation of the β -cyanide (229) assuming that the attack takes place from the least hindered face of the molecule. The intramolecular condensation between the amine and the conjugated ketone of compound (230), although not necessarily as facile as the corresponding reaction described in Section 2.3.2 (p. 121), should yield the desired annulene precursor (231).

The dienedione (228) was prepared from 7-methoxy trienone (108) by treatment with 1.2M hydrochloric acid, in 69% yield. Reaction of the diketone (228) with 1.1 equivalents of trimethylsilyl cyanide in the presence of zinc iodide, gave after distillation, an impure product. The ^1H n.m.r. spectrum of the distillate was complex but it did show the presence of two resonances between $\delta 4$ and $\delta 5$. Subsequent chromatography of the distillate led to the isolation of a product (29%) which had only one resonance in this region. A consideration of the spectroscopic properties of the initial product suggested that a 2:1 adduct, either (232) or (233), had been formed. This was subsequently hydrolysed to the corresponding ketone, either (234) or (235) on silica gel chromatography (Scheme 63).

The i.r. spectrum of the distillate prior to column chromatography showed a strong absorbance at 1630 cm^{-1} which was attributed to the presence of enol ether functionality. In contrast, the i.r. spectrum of the chromatographed product contained a strong ketone absorption at 1750 cm^{-1} . The observation, in the ^1H n.m.r. spectrum, that the resonances assigned to H-2 and H-2' were coupled to the proton α to the cyanide established the reaction product as (234).

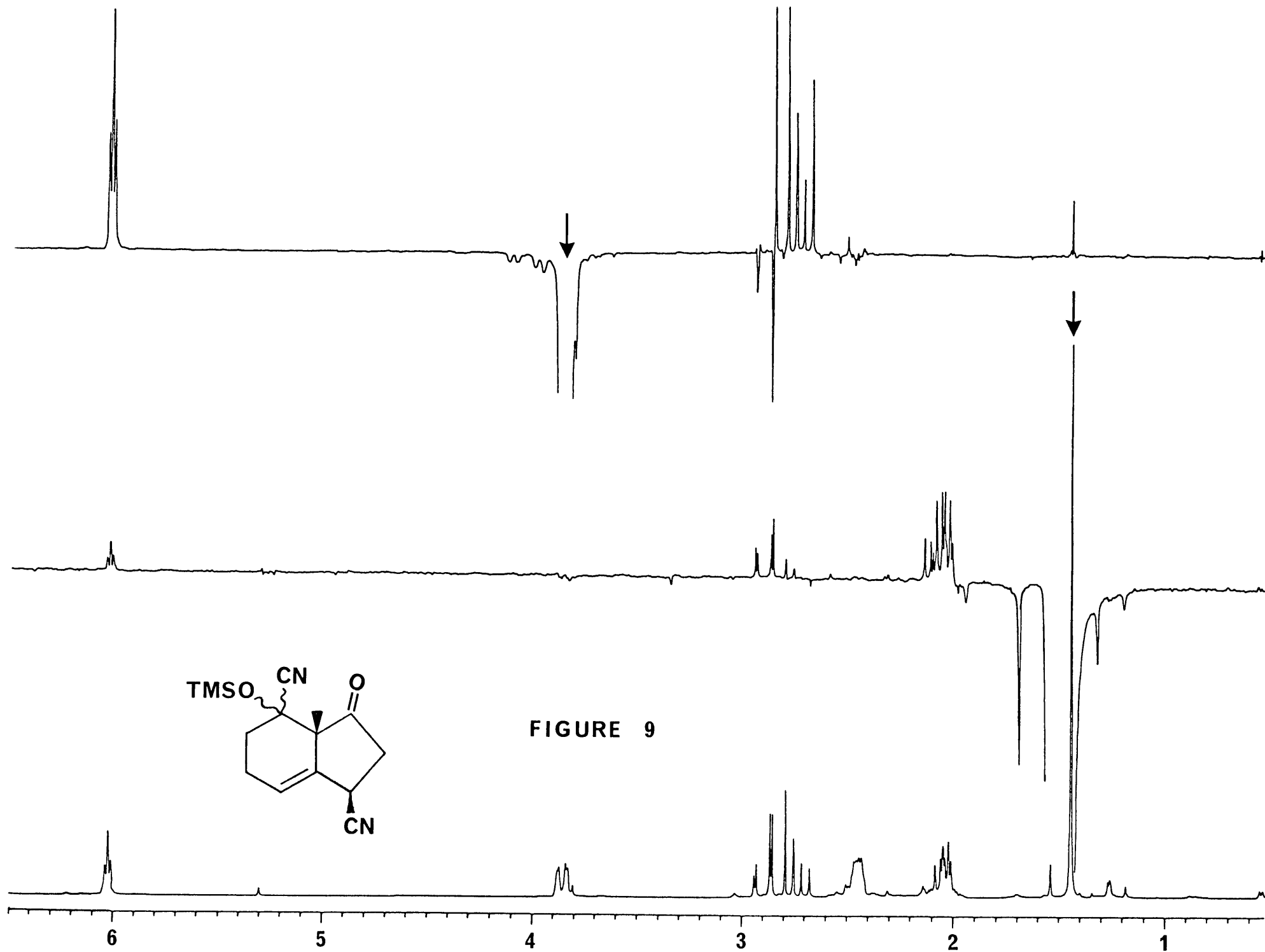
The stereochemistry at C-3 was determined from the results of an n.O.e. difference experiment (Figure 9). Irradiation of the

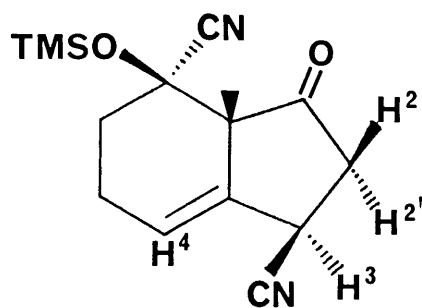


Scheme 63.

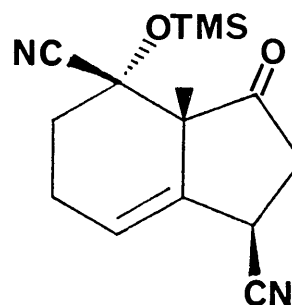
Reagents: i, $\text{Me}_3\text{SiCN}, \text{ZnI}_2$; ii, SiO_2 .

central methyl group gave an enhancement of the signals assigned to H-2 and H-4. There is, however, no enhancement of H-3. This indicated that the cyanide was *syn* to the methyl group. Irradiation of H-3 gave an enhancement of H-2' and what appeared to be an enhancement of the methyl signal. This is believed to be an artifact of the experiment since the line is unusually sharp and the opposite enhancement is not observed. The size of the coupling constant between





(234a)

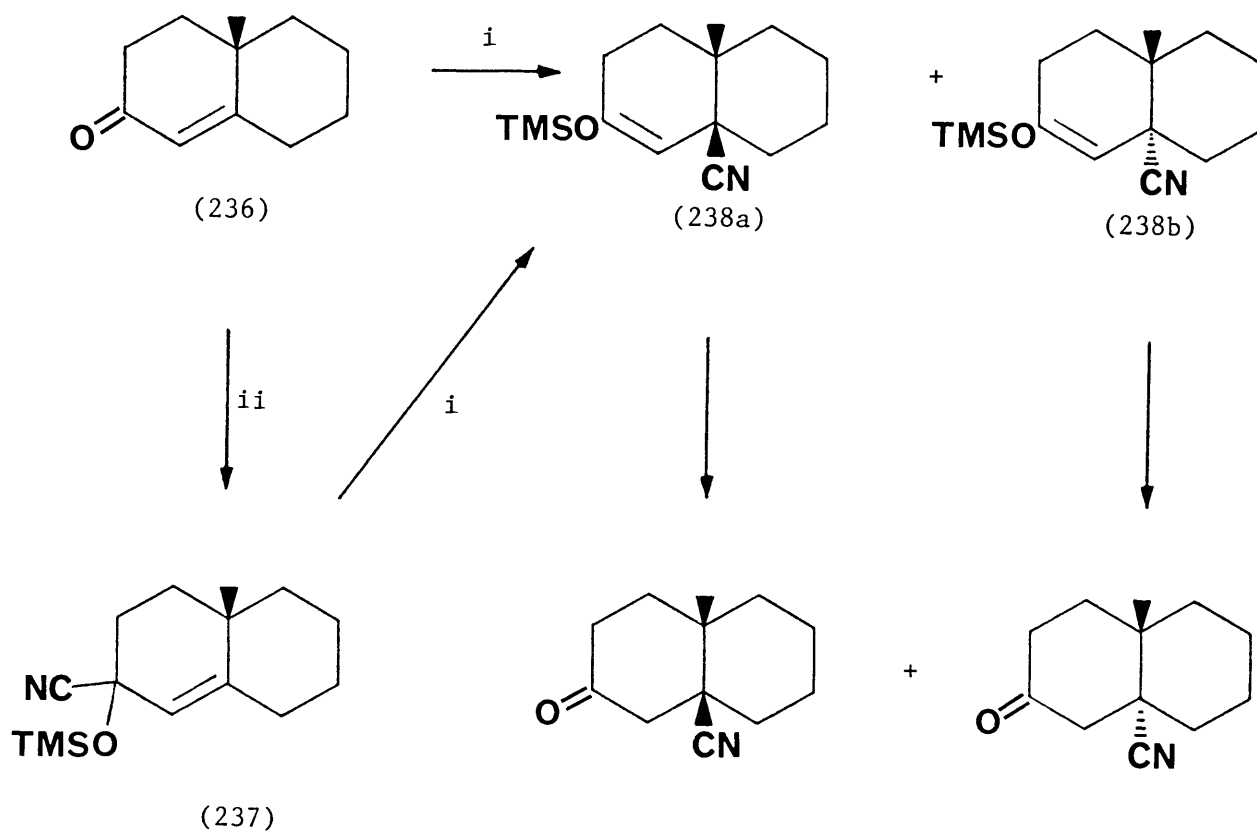


(234b)

H-2 and H-3 (2.5Hz) also suggests a *trans* arrangement, since an examination of a model shows the dihedral angle to be $\sim 110^\circ$. The addition of trimethylsilyl cyanide would be expected to occur from the least hindered face and hence the most likely structure for the product is (234a). However (234b) cannot be ruled out on the spectral data available.

This product was unexpected since 1,4-addition of trimethylsilyl cyanide to unsaturated ketones, under these conditions, has not previously been reported. Utimoto *et al* report the 1,4-addition of trimethylsilyl cyanide when it is reacted with the ketone (236) in the presence of two equivalents of triethylaluminium. When only 0.2 equivalents of triethylaluminium are used then the expected 1,2-product is formed (Scheme 64)¹¹⁴.

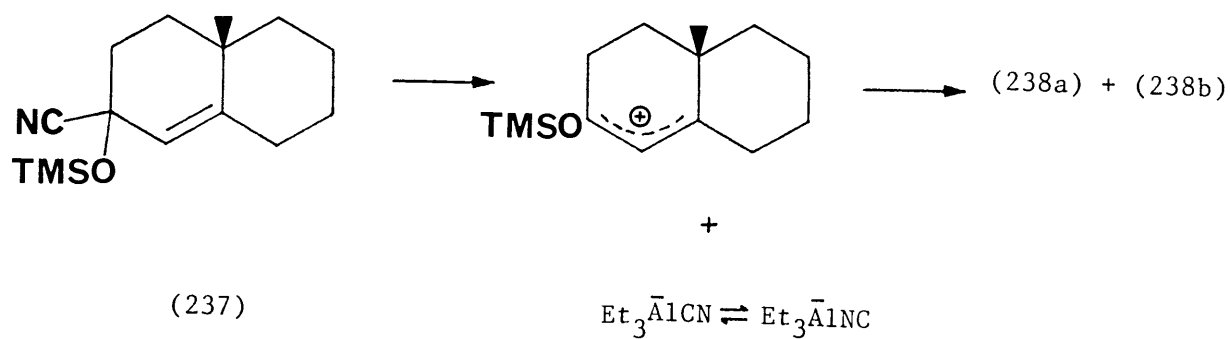
It was observed that the 1,2-adduct (237) could be isomerised to the 1,4 adducts (238) on treatment with one equivalent of trimethylsilyl cyanide and two equivalents of triethylaluminium. The role of the trimethylsilyl cyanide is not clear but it does seem to be required for the reaction. The proposed mechanism for the isomerisation is shown¹¹⁴. This, however, does not account for the requirement of the trimethylsilyl cyanide and it is possible that



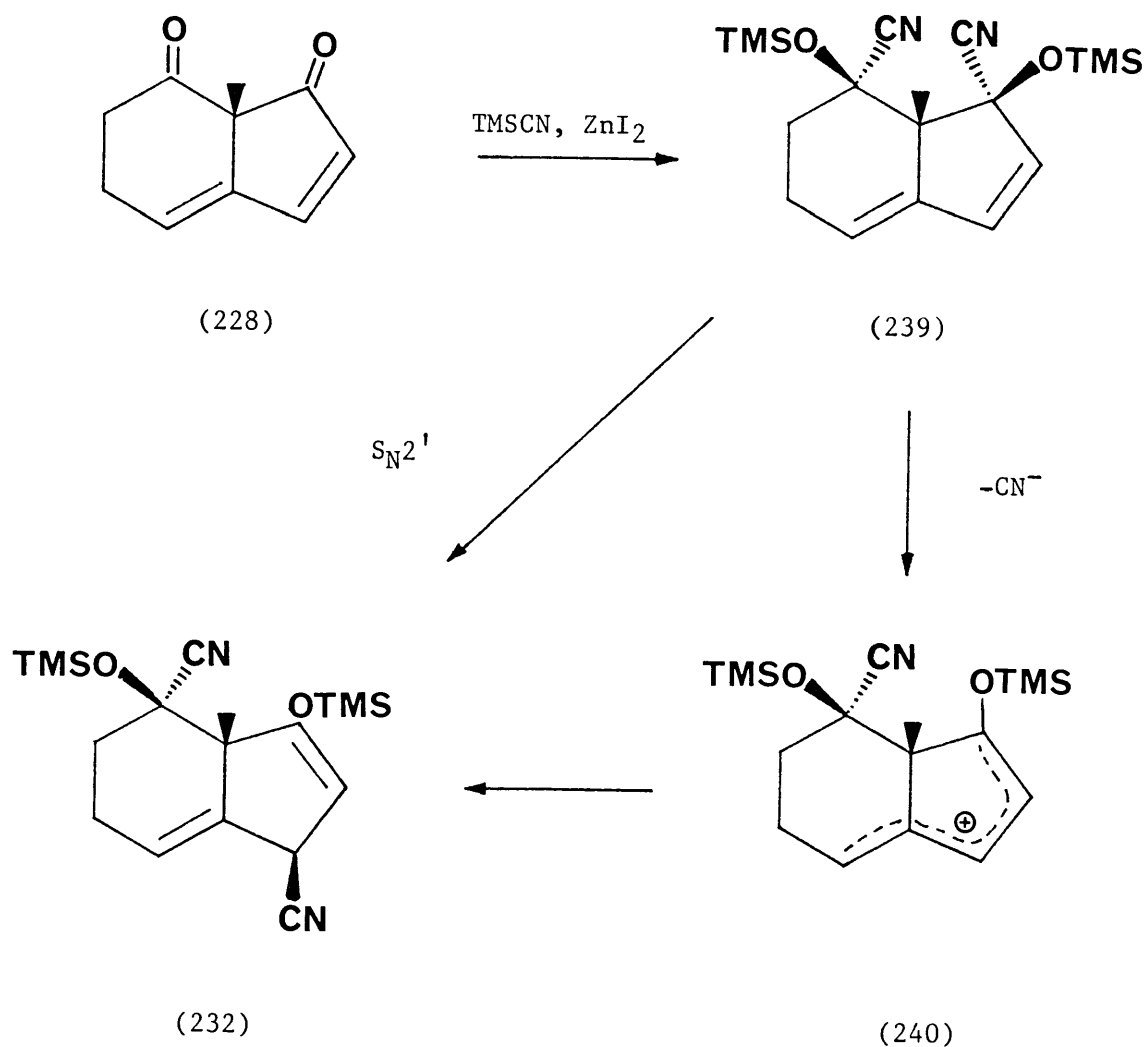
Scheme 64.

Reagents: *i*, Me_3SiCN , Et_3Al (2 eq.);
ii, Me_3SiCN , Et_3Al (0.2 eq.).

this delivers the cyanide to the bridgehead rather than the triethylaluminium species.



The conditions described by Utimoto *et al* are rather different to those used in the reaction of the dienedione (228). A possible mechanism to account for the formation of the enol ether (232) is outlined in Scheme 65. The *bis* adduct (239) is sterically congested

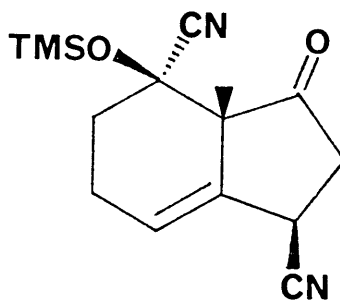


Scheme 65.

and some relief of strain would be afforded by the formation of the stabilised cation (240). Quenching of this cation by the liberated cyanide would give the enol ether (232). The observed selectivity, however, cannot be explained. An alternative mechanism might involve an S_N2' mode of attack of either trimethylsilyl cyanide or cyanide

ion on the *bis*-adduct (239). This mechanism is thought to be less likely since apofacial attack would be required and synfacial is the more usual mode¹¹⁵.

Attempts to eliminate the elements of hydrogen cyanide from compound (234a) using either triethylamine in benzene or neat DBU gave returned starting material and decomposition respectively. The unexpected formation of the adduct (234a) from the reaction of trimethylsilyl cyanide and the dienedione (228) precluded further investigation of this synthetic strategy.



(234a)

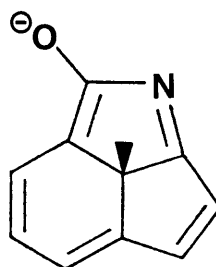
2.4 CONCLUSION

The cycloaddition reactions of 3-methoxy-3a-methyl-3a*H*-indene with various nitrogenous dienophiles allowed the synthesis of several potential precursors of tricyclic aza[10]annulenes. The reactions of the 3a*H*-indene with each of dimethyl azodicarboxylate, *bis*-trichloroethyl azodicarboxylate and 4-phenyl-1,2,4-triazole-3,5-dione gave the corresponding [8+2] cycloadducts in moderate yields. Attempts to elaborate these compounds to the desired 1,2-diaza[10]annulene have not been successful. This is believed to be a consequence of the instability of the intermediate hydrazine which was observed to undergo subsequent fragmentation to regenerate the 3a*H*-indene. The hydrolysis of the PTAD adduct gave a completely unexpected tetracyclic product which, although interesting, was not synthetically useful.

The cycloaddition reaction of 3a-methyl-3-trimethylsiloxy-3a*H*-indene with trichloroacetonitrile gave an [8+2] cycloadduct in low yield. Although the elimination of the elements of trimethylsilanol was attempted this did not lead to the desired aromatic product.

Chlorosulphonyl isocyanate proved to be an effective dienophile in the reaction with 3-methoxy-3a-methyl-3a*H*-indene giving a mixture of regioisomeric [8+2] adducts in variable proportions. These were readily hydrolysed to the corresponding lactams which are potential precursors of the respective aza[10]annulenes. Attempted elimination of the elements of methanol from either of the lactams failed to furnish the required aromatic systems. However, the use of methyl lithium to effect this transformation resulted in the loss of the elements of methanol from 2a-methoxy-7b-methyl-2,2a,7a,7b-tetrahydro-1*H*-cyclopent-[cd]-isoindol-1-one, to give a derivative of the desired system. This,

however, subsequently reacted with the excess of reagent present and

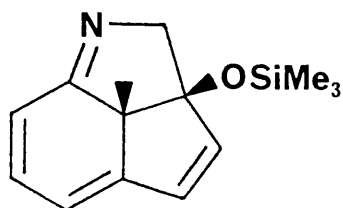


gave 2a,7b-dimethyl-2,2a,7a,7b-tetrahydro-1*H*-cyclopent[*cd*]isoindol-1-one.

The mixture of lactams was readily transformed to the corresponding imidates which although subjected to a variety of reaction conditions did not yield the methoxy aza[10]annulenes. The failure to eliminate the elements of methanol from either the lactams or the imidates was both surprising and disappointing in view of the ease with which this transformation occurs in the related carbocyclic system. There may be either a high barrier towards the elimination or the aza-annulenes once formed may be unstable to the reaction conditions.

An alternative approach to the synthesis of aza analogues of 7b-methyl-7*H*-cyclopent[*cd*]indene involves the construction of the final five-membered ring *via* a stepwise procedure. The tricyclic skeleton was formed by reacting 5,7a-dihydro-7-methoxy-7a-methyl-1*H*-inden-1-one with trimethylsilyl cyanide followed by reduction and subsequent ring closure. This proved to be an efficient method of synthesising the tricyclic compound 2a-hydroxy-2a,6,7,7b-tetrahydro-2*H*-cyclopent[*cd*]indole. The formation of the corresponding

trimethylsilyl ether facilitated the introduction of further unsaturation into the six-membered ring to give 2a,7b-dihydro-7b-methyl-2a-trimethylsiloxy-2*H*-cyclopent[*cd*]indole. The final elaboration to



the desired 1-aza[10]annulene has yet to be achieved. The failure of the final elimination of the elements of trimethylsilanol was disappointing. However, the introduction of a more labile oxygenated substituent at the 2a-position should facilitate the synthesis of the target molecule. One possible improvement would be to proceed *via* 2a-acetoxy-2a,6,7,7b-tetrahydro-2*H*-cyclopent[*cd*]indole which was formed in a two-step procedure from the corresponding alcohol.

It was envisaged that a similar ring closure strategy could be employed in the synthesis of the 2-aza[10]annulene by the selective reaction between trimethylsilyl cyanide and 7a-methyl-5,6,7,7a-tetrahydro-1*H*-inden-1,7-dione. However, this reaction resulted in the formation of a 2:1 adduct which, after hydrolysis, gave 3,7-dicyano-2,3,5,6,7,7a-hexahydro-7a-methyl-7-trimethylsiloxy-1*H*-inden-1-one. The formation of this product involves the formal 1,4-addition of trimethylsilyl cyanide to the unsaturated carbonyl which is unprecedented under the conditions used.

Although several synthetic strategies have been employed in

the attempted syntheses of tricyclic aza [10] annulenes, these compounds remain elusive. However, a modification of the ring closure approach may allow the synthesis of 7b-methyl-7b*H*-cyclopent[*cd*]indole in the future.

3. EXPERIMENTAL

GENERAL INFORMATION

a. Reagents

Commercially available reagents were used without purification unless otherwise stated. Other reagents and starting materials were prepared according to the literature procedures quoted.

b. Solvents

Tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane were dried by refluxing over potassium metal in the presence of benzophenone and distilled as required. Chlorinated solvents were dried over phosphorus pentoxide. Acetonitrile, triethylamine, di-isopropylamine, DMSO and chlorotrimethylsilane were dried by refluxing over powdered calcium hydride and distilled immediately prior to use.

c. Chromatography

The organic extracts were invariably dried over magnesium sulphate prior to column chromatography. Chromatography was carried out using Merck silica gel H (type 60), eluting with petrol containing an increasing proportion of ether, unless otherwise stated. Petrol refers to light petroleum spirit, b.p. 40-60°C and ether refers to diethyl ether. Thin layer chromatography of column fractions was carried out on commercial plates of silica gel 60F₂₅₄ coated on aluminium foil. Analysis of plates was effected by u.v. irradiation and/or treatment with iodine vapour.

d. Spectra

Proton n.m.r. spectra were recorded on a Bruker WM250, a Perkin-

Elmer R32 and a Varian EM360. All data quoted are from 250MHz spectra unless otherwise stated. The chemical shifts (δ_H) are given in p.p.m. relative to tetramethylsilane as the internal reference. The abbreviations used in the quotation of spectral data include: singlet (s), doublet (d), triplet (t), multiplet (m) and broad (br.). Coupling constants (J) are quoted to one decimal place and are accurate to $\pm 0.5\text{Hz}$.

Carbon-13 spectra were recorded on a Bruker WM250 spectrometer operating at 62.9MHz and chemical shifts (δ_C) are quoted with respect to tetramethylsilane.

Infra red (i.r.) spectra were recorded in the range $600\text{--}4,000\text{cm}^{-1}$ using a Perkin-Elmer 298 spectrometer and are calibrated against a polystyrene reference. Spectra of solids were recorded as Nujol mulls or in solution cells in either carbon tetrachloride or chloroform. Spectra of oils were recorded as thin films between sodium chloride plates.

Ultraviolet and visible spectra (u.v.) were recorded using a Pye Unicam SP 800 spectrophotometer. Extinction coefficients ($\log \epsilon$) are quoted in parenthesis and the abbreviation (sh) refers to a shoulder.

Low and high resolution mass spectra were recorded on a VG Micromass 707B instrument operating at 70eV and using a direct insertion probe.

e. Melting Points

Melting points were measured using a Kofler Hot Stage apparatus and are uncorrected.

f. Analyses

Micro-analyses were carried out in the organic analytical laboratory at Imperial College, under the supervision of Mr. K.I. Jones.

3.1 CYCLOADDITION ROUTES TO TRICYCLIC AZA[10] ANNULENES

3.1.1 The Synthesis of 3-Methoxy-3a-methyl-3aH-indene (100)

1. The Birch reduction and methylation of 1-indanone

A solution of 1-indanone (103) (118g, 0.89mol) and dry *tert*-butanol (150g, 2.03mol) in dry THF (400ml) was added dropwise over 1h to a solution of potassium (100g, 2.55gatom) in liquid ammonia (51) at -78°C under nitrogen. Anhydrous lithium bromide (206g, 2.34mol) in dry THF (600ml) was then added followed after 0.5h by the simultaneous addition of 50% aqueous THF (900ml) and methyl iodide (134g, 0.94mol). The external cooling was removed and the ammonia allowed to evaporate. Water (21) was added to the residual solution which was then extracted with ether (3x800ml). The combined extracts were dried and evaporated. The resulting oil was distilled and the fraction boiling between 86 and 94°C at 7mmHg collected (74g).

A sample of this oil (2.0g) was subjected to column chromatography to give 7a-methyl-2,3,5,7a-tetrahydro-1H-inden-1-one (104) (1.75g). The amount of this compound in the oil is 87.5% and hence the yield was 64.4g (49%). The spectral characteristics of this compound were identical to those previously reported^{66b}. The distilled material was sufficiently pure for use in the preparation of 5,7a-dihydro-7a-methyl-1H-inden-1-one.

2. The preparation of 5,7a-dihydro-7a-methyl-1H-inden-1-one (106)

a. *Via* the lithium enolate of 7a-methyl-2,3,5,7a-tetrahydro-1H-inden-1-one (104)

A solution of LDA was prepared by the addition of *n*-butyl

lithium (216ml of a 1.5M solution in hexane, 0.324mol) to freshly distilled di-isopropylamine (35.28g, 0.349mol) in dry THF (120ml) at 0°C under nitrogen. The LDA solution was then added dropwise over 0.5h to a stirred solution of dienone (104) (87.5% pure; 40g, 0.236mol) in dry THF (140ml) at -78°C under nitrogen. After stirring for 20 min a solution of phenylselenenyl bromide [prepared by the addition of bromine (26.4g, 0.165mol) to diphenyl diselenide¹¹⁶ (52g, 0.167mol) in dry THF (60ml) at 0°C] was added. The mixture was allowed to warm to room temperature and poured into hydrochloric acid (0.5M; 700ml). The product was extracted with ether, dried and evaporated.

The crude selenide was dissolved in THF (600ml) and pyridine (40ml) was added. The solution was cooled to 0°C and hydrogen peroxide (30%; 450ml) was added in aliquots such that the temperature was maintained between 0 and 5°C. The mixture was then poured into water (700ml) and extracted with ether (3x300ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography (petrol/ether) to give (i) starting material (104) (10g, 29%) and (ii) 5,7a-dihydro-7a-methyl-1*H*-inden-1-one (106)^{66b} (8.45g, 25%).

b. *Via* 3a,6-dihydro-3a-methyl-3-trimethylsiloxy-1*H*-indene

Chlorotrimethylsilane (27ml, 0.213mol) was added to a stirred solution of sodium iodide (31.95g, 0.213mol) in dry acetonitrile (200ml) at room temperature under nitrogen. A mixture of 7a-methyl-2,3,5,7a-tetrahydro-1*H*-inden-1-one (104) (25.55g, 87.5% pure; 0.151mol) and dry triethylamine (27.6ml, 0.213mol) was then added and the resulting solution warmed to 45°C. After stirring for 2h the solution was extracted with petrol (3x250ml) and the combined extracts evaporated.

Distillation of the residue gave 3a,6-dihydro-3a-methyl-3-trimethylsiloxy-1*H*-indene (26.5g, 80%) as a mobile oil, b.p. 82-85°C/3mmHg.

To a stirred solution of the trimethylsilyl enol ether (26.5g, 0.120mol) in dry THF (150ml) at -78°C under an atmosphere of nitrogen was added phenylselenenyl bromide [prepared at 0°C from diphenyl diselenide (20.6g, 0.066mol) and bromine (10.56g, 0.066mol) in dry THF (30ml)]. The external cooling was removed and the solution allowed to warm to room temperature. The reaction mixture was poured into aqueous saturated sodium bicarbonate solution (100ml) and extracted with ether (3x150ml). The combined extracts were washed with water (300ml), dried and evaporated to give the crude selenide. This was oxidised in the manner described previously to give (i) recovered dienone (104) (4.12g, 18%) and (ii) 5,7a-dihydro-7a-methyl-1*H*-inden-1-one (106) (7.9g, 36%).

3. Preparation of a solution of 3-methoxy-3a-methyl-3a*H*-indene (100) and subsequent cycloaddition with *N*-phenylmaleimide

A solution of 18-crown-6 (4.0g, 15mmol) in dry 1,2-dimethoxyethane (DME) (20ml) was added to a stirred suspension of potassium hydride (5.75g of a 25% suspension in oil, 36mmol) in dry DME (50ml) at -23°C under an atmosphere of nitrogen. Subsequent addition of 5,7a-dihydro-7a-methyl-1*H*-inden-1-one (106) (2g, 14mmol) in dry DME (10ml) followed by stirring for 0.5h allowed the generation of the anion. Methyl fluorosulphonate (1.46ml, 18mmol) was added and this gave the characteristic yellow colour of the 3-methoxy-3a-methyl-3a*H*-indene (100).

N-Phenylmaleimide (2.61g, 15mmol) in dry DME (5ml) was added

and the reaction mixture allowed to warm to room temperature. The solution was then filtered before removal of the solvent *in vacuo*. The residue was subjected to column chromatography (petrol/dichloromethane) to give the *endo*-[4+2] adduct (110) (2.64g, 57%), m.p. 91-93.5°C (petrol, b.p. 60-80°C), (Lit.^{66b} m.p. 91-93°C).

3.1.2 Cycloaddition Reactions of 3-Methoxy-3a-methyl-3aH-indene (100) with Azo Compounds

1. The cycloaddition of 3-methoxy-3a-methyl-3aH-indene (100) with dimethyl azodicarboxylate

A solution of dimethyl azodicarboxylate¹¹⁷ (DMAZD) (1.2g, 8.2 mmol) in dry DME (6ml) was added to a solution of the 3aH-indene (100) in dry DME prepared as described in Section 3.1.1.3 from the trienone (106) (1.1g, 7.5mmol). The reaction mixture was filtered under nitrogen through Celite and the filtrate stirred overnight. DMAZD (0.3g, 2.05mmol) was added and the reaction monitored until t.l.c. analysis indicated the absence of the 3aH-indene (100). The solvent was then removed and the residue subjected to column chromatography (petrol/ether) to give (i) a 1.8:1 mixture of 2-methyl-*cis*-cinnamate (115) and 1-methoxy-1-methyl-1H-indene (114)^{66b} (90mg), and (ii) *dimethyl 2a-methoxy-7b-methyl-2,2a,7a,7b-tetrahydro-1H-cyclopent[cd]-indazole 1,2-dicarboxylate* (113) (1.13g, 49%), as a crystalline solid m.p. 77-78°C (dichloromethane/petrol), (Found: C, 58.82; H, 5.90; N, 9.08. C₁₅H₁₈N₂O₅ requires C, 58.82; H, 5.92; N, 9.15%); $\nu_{\max.}$ (CCl₄) 2960, 1710, 1445, 1355, 1297 and 1198 cm⁻¹; $\lambda_{\max.}$ (EtOH) 296nm (log ϵ 3.81); δ_{H} (CDCl₃) 1.06(3H, s, 7b-Me), 3.52(3H, s, CO₂Me), 3.65(3H, s, CO₂Me), 3.80(3H, s, OMe), 4.33(1H, d, $J_{7a,7}$ 6.0Hz, H-7a), 5.91(1H, d, $J_{5,6}$ 5.6Hz,

H-5), 5.99(1H, m, decoupled at δ 4.33 gives a broad doublet, $J_{6,7}$ 9.5Hz, H-7), 6.20(1H, dd, $J_{6,7}$ 9.5Hz, $J_{5,6}$ 5.6Hz, H-6), 6.41(1H, d, $J_{3,4}$ 5.6Hz, H-4) and 6.62(1H, m, H-3); δ_C (CDCl₃) 17.7(7b-CH₃), 53.0(2xCO₂CH₃), 53.4(OCH₃), 55.9(C-7b), 60.7(C-7a), 105.2(C-2a), 114.4, 122.1, 126.2, 131.9, 132.9, 145.2(CO₂Me), 154.9 and 158.0(CO₂Me); m/z 306(M^+), 291, 275, 263, 247, 231, 215, 160 and 145.

2. Attempted hydrolysis of adduct (113) followed by *in situ* oxidation

The [8+2]-adduct (113) (0.1g, 0.33mmol) was dissolved in methanol (2ml) and potassium hydroxide (0.064g, 1.14mmol) was added. The reaction mixture was refluxed for 1.5h before being poured onto ice and neutralised with aqueous hydrochloric acid (1.5M). Copper (II) chloride (0.103g, 0.8mmol) in methanol (1ml) was added and the resulting solution stirred for 2h at room temperature. The reaction mixture was then diluted with water (15ml) and extracted with chloroform (3x30ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography. This, however, gave no identifiable product.

3. Attempted hydrolysis of the [8+2]cycloadduct (113)

a. Using potassium *t*-butoxide in DMSO

The cycloadduct (113) (0.10g, 0.33mmol) was dissolved in DMSO (5ml) containing water (1 drop) and potassium *t*-butoxide (0.143g, 1.3mmol) were added. The resulting black solution was stirred under nitrogen for 1h after which time water was added and the solution extracted with chloroform. T.l.c. analysis of the residue showed it to be a very complex mixture comprising mostly of baseline material.

b. Using trimethylsilyl iodide⁶⁹

The adduct (113) (0.08g, 0.26mmol) was dissolved in *d*-chloroform (5ml) and stirred under nitrogen at room temperature. Trimethylsilyl iodide (0.11ml, 0.77mmol) was added and the solution stirred at room temperature for 1h. Analysis of the reaction mixture by ¹H n.m.r. spectroscopy showed the disappearance of the three methoxy signals. The solution was poured into water and extracted with chloroform (3x30ml). The combined extracts were washed with sodium thiosulphate, dried and the solvent evaporated. A ¹H n.m.r. analysis of the resulting oil showed no recognisable peaks and the reaction was not pursued.

c. Using lithium thiomethoxide⁷¹

The adduct (113) (0.135g, 0.44mmol) was dissolved in hexamethylphosphoramide (HMPA) (3ml) and the mixture was deoxygenated by the passage of nitrogen through the solution for 1h. Lithium thiomethoxide (0.06g, 1.1mmol) in HMPA (2ml) was then added and the reaction mixture stirred between 0-6°C for 4h. The solution was poured into hydrochloric acid (1M, 15ml) and extracted with chloroform. The combined extracts were washed with sodium bicarbonate, dried, and the solvent evaporated. The resulting oil was found to be a multi-component mixture and was subjected to preparative plate chromatography (p.l.c.). This gave *7,7a-dihydro-7a-methyl-6-methylthio-1H-inden-1-one* (121) (8mg, 9.5%); (Found: *M*^t 192.0604. C₁₁H₁₂OS requires *M* 192.0609); *v*_{max}. (CCl₄) 2930, 1703, 1510, 1450, 1422, 1370 and 1350 cm⁻¹; *λ*_{max}. (MeOH) 218(log *ε* 3.73), 275(log *ε* 3.77) and 400nm (log *ε* 3.87); *δ*_H (CDCl₃) 1.09(3H, s, 7a-CH₃), 2.27(2H, br.s, 2xH-7), 2.37(3H, s, SMe), 5.80(1H, dd, *J*_{5,7} 1.6Hz, *J*_{4,5} 5.6Hz, decoupled at

δ 2.27 gives a doublet, H-5), 6.17(1H, d, $J_{4,5}$ 5.6Hz, decoupling at H-5 gives a singlet, H-4), 6.9(1H, d, $J_{2,3}$ 5.3Hz, becomes a singlet on decoupling H-3, H-2) and 7.73(1H, d, $J_{2,3}$ 5.3Hz, H-3); m/z 192(M^+), 177, 145, 117 and 115. The aqueous layer was neutralised and extracted with chloroform (3x25ml). The combined extracts were dried and evaporated. The resulting oil was shown by t.l.c. to be a complex mixture and although p.l.c. was attempted no recognisable product was obtained.

d. Using sulphuric acid

The adduct (113) (92mg, 0.3mmol) was dissolved in acetonitrile (5ml) to which had been added water (5ml) containing concentrated sulphuric acid (2 drops). The reaction mixture was stirred under nitrogen for 18h before being poured into water and extracted with chloroform (3x30ml). The combined extracts were dried and evaporated to give *Dimethyl 1-(7,7a-dihydro-7a-methyl-1H-inden-1-on-7-yl)hydrazine 1,2-dicarboxylate* (127) (85mg, 97%) b.p. 100-105°C/0.2mmHg (Kugelrohr); (Found: C, 57.20; H, 5.62; N, 9.29. $C_{14}H_{16}N_2O_5$ requires C, 57.53; H, 5.52; N, 9.58%); $\nu_{\max.}$ (CCl₄) 3495, 2960, 1767, 1730, 1710, 1485 and 1445 cm⁻¹; $\lambda_{\max.}$ (EtOH) 233(log ϵ 3.64), 322 sh., 333(log ϵ 3.74) and 345 nm sh.; δ_H (CDCl₃) 1.23 (3H, s, 7a-CH₃), 2.35(1H, br.s, N-H), 3.64(3H, s, CO₂CH₃), 3.73(3H, br.s, CO₂CH₃), 4.84(1H, br.signal, H-7), 6.09(1H, br.signal, some change observed on decoupling at H-7, H-6), 6.16(1H, d, $J_{4,5}$ 5.2Hz, H-4), 6.25(1H, d, $J_{2,3}$ 5.7Hz, becomes a singlet on irradiation at δ 7.74, H-2), 6.39(1H, dd, $J_{5,6}$ 9.3Hz, $J_{4,5}$ 5.2Hz, H-5) and 7.74(1H, d, $J_{2,3}$ 5.7Hz, H-3) the spectrum was observed to be temperature-dependent; m/z 292(M^+), 275, 217 and 145.

4. Cycloaddition of the 3aH-indene (100) with bis-trichloroethyl azodicarboxylate

- a. Via the retro [4+2] cycloaddition of the *N*-phenylmaleimide adduct (110)

The [4+2] *N*-phenylmaleimide adduct (110) (0.10g, 0.29mmol) was dissolved in toluene and bis-trichloroethyl azodicarboxylate⁹⁰ (0.223g, 0.59mmol) was added. The reaction mixture was refluxed under nitrogen for 0.5h before the solvent was removed and the residue subjected to column chromatography (petrol/ether) to give bis-trichloroethyl 2a-methoxy-7b-methyl-2,2a-7a,7b-tetrahydro-1H-cyclopent[cd]-indazole 1,2-dicarboxylate (129) (0.10g, 63%) as a viscous oil, (Found: M^+ 537.9195. $C_{17}H_{16}Cl_6N_2O_5$ requires M 537.9190); $\nu_{\max.}$ (neat) 2935, 1755, 1725, 1453 and 1390cm^{-1} ; δ_H (d_6 -DMSO, 90°C) 1.04(3H, s, 7b-CH₃), 3.52(3H, s, OMe), 4.42(1H, d, $J_{7a,7}$ 5.5Hz, H-7a), 4.67(1H, d, J 12.2Hz, CH_AH_B), 4.85(1H, d, J 12.2Hz, irradiation at δ 4.67 removes this coupling, CH_AH_B), 4.87(1H, d, J 12.2Hz, CH_AH_B'), 4.97(1H, d, J 12.2Hz, CH_AH_B'), 5.98(1H, dd, $J_{6,7}$ 9.3Hz, $J_{7,7a}$ 5.5Hz, irradiation at δ 4.42 removes the smaller coupling, H-7), 6.01(1H, d, $J_{5,6}$ 5.5Hz, H-5), 6.27(1H, dd, $J_{6,7}$ 9.3Hz, $J_{5,6}$ 5.5Hz, H-6), 6.58(1H, d, $J_{2,3}$ 5.8Hz, H-2 or H-3), and 6.63(1H, d, $J_{2,3}$ 5.8Hz, H-2 or H-3), the spectrum was poorly resolved at normal operating temperature; δ_C (CDCl₃) 17.7(7b-CH₃), 53.4(OCH₃), 55.8(C-7b), 60.4(C-7a), 60.9, 75.0, 76.5, 95.1(C-2a), 115.1, 121.4, 121.7, 126.4, 131.8, 132.2, 132.8, 144.4(C=O) and 152.5(C=O); m/z The molecular ion pattern was 546(5), 544(19), 542(44), 540(53), 538(28); calculated ratio is 5:20:45:54:27.

5. Alternative preparation of adduct (129)

To a solution of 3-methoxy-3a-methyl-3aH-indene (100) in DME

[prepared as described in Section 3.1.1.3 from trienone (106) (0.25g, 1.7mmol)] was added *bis*-trichloroethyl azodicarboxylate (0.72g, 1.89mmol). The resulting solution was allowed to stir at room temperature overnight before being filtered through celite. The solvent was removed and the residue subjected to column chromatography. This gave the desired adduct (129) (0.15g, 16%).

6. Attempted hydrolysis of the [8+2]-cycloadduct (129)

a. Followed by *in situ* oxidation

The adduct (129) (0.10g, 0.19mmol) was dissolved in glacial acetic acid (5ml) and the reaction solution purged with nitrogen. After cooling to 0°C dry THF (5ml) and activated zinc (0.75g, 11.5mmol) were added to the reaction mixture which was stirred for 2h. It was then cooled to -30 to -40°C for 0.5h before being filtered under nitrogen. This gave a yellow filtrate which went orange on standing. The volume of the filtrate was reduced and it was then added to the aqueous filtrate obtained from washing the zinc with water. The combined extracts were acidified to pH 3 using hydrochloric acid (1.0M). Copper (II) chloride (2N soln; 0.5ml, 1mmol) was added and the solution was stirred for 0.5h. Ammonium hydroxide was then added until the pH of the solution was 5. It was then extracted with chloroform (3x30ml) and the combined extracts washed with sodium bicarbonate, dried and evaporated. The residue was subjected to column chromatography to give 2-methyl-*cis*-cinnamate (115) (5mg, 15%).

b. Followed by reaction with *N*-phenylmaleimide

The adduct (129) (0.114g, 0.21mmol) was dissolved in glacial

acetic acid (5ml) and the reaction flask purged with nitrogen. The solution was cooled to 0°C and THF (5ml) was added. Activated zinc (0.83g, 12.7mmol) was then transferred to the reaction vessel and the solution was observed to turn yellow. After stirring at 0°C for 2h the solution was filtered under nitrogen. *N*-phenylmaleimide (0.039g, 0.22mmol) was added to the filtrate and the reaction mixture stirred for 0.5h at room temperature. The pH of the solution was adjusted to 2 and copper (II) chloride (2N; 0.5ml, 1mmol) was added and stirring continued for 0.5h. The reaction mixture was neutralised using ammonium hydroxide and extracted with chloroform. The combined extracts were dried and evaporated and the residue subjected to column chromatography. This gave the [4+2] *N*-phenylmaleimide adduct (110) (18mg, 26%).

7. Cycloaddition reaction of 3-methoxy-3a-methyl-3a*H*-indene (100) with 4-phenyl-1,2,4-triazole-3,5-dione

To a solution of the 3a*H*-indene (100) in DME [prepared as described in Section 3.1.1.3 from trienone (106) (0.55g, 3.77mmol)] was added 4-phenyl-1,2,4-triazole-3,5-dione (PTAD)¹¹⁸ (0.724g, 4.14mmol). The resulting solution was allowed to stir for 2h after which time it was filtered through Celite and the solvent removed. The residue was subjected to column chromatography (petrol, ether) to give the [8+2] cycloadduct (130) (0.27g, 21%). The spectral properties of this compound were identical to those previously recorded^{66b}.

8. Attempted hydrolysis of cycloadduct (130) using methanolic potassium hydroxide

The adduct (130) (100mg, 0.3mmol) was added to a solution of

potassium hydroxide in 95% ethanol (2.1N; 14ml) and the solution refluxed under nitrogen for 1.5h. The reaction mixture was then neutralised using dilute hydrochloric acid and extracted with chloroform (3x40ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography (petrol, ether, methanol) to give *the hydrolysis product* (133) (45mg, 49%) as an oil (Found: M^+ 309.1470. $C_{18}H_{19}N_3O_2$ requires M 309.1477); $\nu_{\max.}(\text{CCl}_4)$ 3270, 2940, 1730, 1380, 1275 and 913cm^{-1} ; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.32(3H, s, 8b- CH_3), 2.43(1H, d, $J_{5\alpha,5\beta}$ 14.8Hz, coupling removed by irradiation at δ 2.98, H-5 β), 2.98(1H, m, $J_{5\alpha,5\beta}$ 14.8Hz, $J_{4a,5\alpha}$ 5.8Hz, large coupling removed by irradiation at δ 2.43, smaller coupling removed by irradiation at δ 4.49, H-5 α), 3.40(3H, s, OCH_3), 3.73(1H, d, $J_{8a,8}$ 5.2Hz, collapses to a singlet on irradiation at δ 5.75, H-8a), 4.49(1H, d, $J_{4a,5\alpha}$ 5.8Hz, H-4a), 5.73(1H, dd, $J_{7,8}$ 9.2Hz, $J_{8,8a}$ 5.2Hz, H-8), 5.76(1H, d, $J_{6,7}$ 5.2Hz, H-6), 5.89(1H, dd, $J_{7,8}$ 9.2Hz, $J_{6,7}$ 5.2Hz, H-7), 7.08(1H, tt, J 7.1Hz, J 1Hz, $p\text{-Ar-H}$), 7.32(2H, m, $m\text{-ArH}$) and 7.53(2H, m, $o\text{-ArH}$); $\delta_{\text{C}}(\text{CDCl}_3)$, 17.0(8b- CH_3), 36.9(C-5), 51.3(OCH_3), 55.9(C-8b), 59.7(C-4a or C-8a), 62.8(C-4a or C-8a), 104.6(C-8c), 119.4, 119.5(Ar-CH), 122.8, 123.6, 129.0(Ar-CH), 138.4(C-5a or Ar-C), 140.1(C-5a or Ar-C) and 158.8(C-3); m/z 309(M^+), 294, 278, 277, 262, 236 and 205. The stereochemistry was assigned from the results of an n.o.e. difference experiment (see Figure 2, page 72).

3.1.3 Cycloaddition Reactions of 3a-Methyl-3-substituted-3a^H-indenenes (100) and (111) with Nitriles

1. Cycloaddition reactions of 3-methoxy-3a-methyl-3a^H-indene (100) with nitriles
 - a. With methyl cyanoformate

The [4+2] *N*-phenylmaleimide adduct (110) (100mg, 0.3mmol) was added to methyl cyanoformate (0.5ml) and the mixture refluxed under nitrogen for 2h. The excess methyl cyanoformate was then removed by evaporation and the residue was subjected to column chromatography. Elution with petrol containing an increasing amount of 3:1 dichloromethane-ether gave (i) the *exo*-[8+2]-*N*-phenylmaleimide adduct (29mg, 29%) and (ii) the *endo*-[8+2]-*N*-phenylmaleimide adduct (36mg, 36%). The ^1H n.m.r. spectra and t.l.c. characteristics of these compounds were identical to those already reported⁶⁰.

b. With trichloroacetonitrile

The [4+2] *N*-phenylmaleimide adduct (110) (100mg, 0.3mmol) was added to trichloroacetonitrile (2ml) and the mixture refluxed under nitrogen for 1h. After this time the excess trichloroacetonitrile was removed *in vacuo*. Analysis of the residue using ^1H n.m.r. spectroscopy showed no recognisable signals and this reaction was not pursued.

2. Reaction of 3a-methyl-3-trimethylsiloxy-3a*H*-indene (111) with trichloroacetonitrile

A solution of 3a-methyl-3-trimethylsiloxy-3a*H*-indene (111) was formed by the addition of triethylamine (0.1ml, 0.75mmol) and trimethylsilyl trifluoromethanesulphonate (0.14ml, 0.75mmol) to a stirred solution of trienone (106) (100mg, 0.68mmol) in dry ether (15ml) under nitrogen at 0°C. The reaction mixture was stirred at this temperature for 1h, trichloroacetonitrile (0.1ml, 1mmol) was added, and the solution refluxed for 4h. T.l.c. analysis of

the reaction indicated the presence of the 3aH-indene (111) necessitating the further addition of trichloroacetonitrile (0.1ml, 1mmol). After stirring at room temperature overnight the reaction mixture was poured into water (50ml) and extracted with ether (3x40ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography (petrol 95%, ether 5%) to give a 1:2.5 mixture (70mg) of (i) 1-methyl-1-trimethylsiloxy-1H-indene (143), $\delta_{\text{H}}(\text{CDCl}_3)$ -0.12(9H, s, SiMe₃), 1.53(3H, s, Me), 6.31(1H, d, $J_{5,7}$ 5.7Hz), 6.57(1H, d, $J_{5,7}$ 5.7Hz), 7.12-7.23(3H, m, Ar-H) and 7.37(1H, m, Ar-H); and (ii) 7a,7b-dihydro-7b-methyl-1-trichloromethyl-2a-trimethylsiloxy-2aH-cyclopent[cd]isoindole (142), $\nu_{\text{max.}}(\text{CCl}_4)$ 1620cm⁻¹(C=N); $\delta_{\text{H}}(\text{CDCl}_3)$ 0.22(9H, s, SiMe₃), 0.91(3H, s, Me), 3.63(1H, dd, $J_{7,7a}$ 6.3Hz, $J_{6,7a}$ 1Hz, H-7a), 5.97(1H, d, $J_{5,6}$ 4.7Hz, H-5), 6.03(1H, dd, $J_{6,7}$ 8.9Hz, $J_{7,7a}$ 6.3Hz, collapses to a doublet on irradiation at δ 3.63, H-7), 6.21(1H, ddd, $J_{5,6}$ 4.7Hz, $J_{6,7}$ 8.9Hz, $J_{6,7a}$ 1Hz, irradiation at δ 3.63 removes the 1Hz coupling, H-6), 6.37(1H, d, $J_{3,4}$ 5.2Hz, H-3 or H-4) and 6.54(1H, d, $J_{3,4}$ 5.2Hz, H-3 or H-4); m/z 362(M^+).

3. The formation of 7,7a-dihydro-7a-methyl-7-trichloroacetyl-1H-inden-1-one (144)

The mixture of [8+2] cycloadduct (142) and the 1H-indene (143) (15mg) was dissolved in benzene and toluene-4-sulphonic acid (8mg, 0.04mmol) was added. The mixture was refluxed under an atmosphere of nitrogen for 4h before being poured into water and extracted with chloroform (3x20ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give *the title compound* (4mg, 45%) as an oil, (Found: M^+ 289.9667. C₁₂H₉Cl₃O₂ requires M 289.9668); $\nu_{\text{max.}}(\text{CCl}_4)$ 2930, 1748, 1715, 1452, 1370, 1350 and

1309 cm^{-1} ; δ_{H} (CDCl_3) 1.15(3H, s, Me), 4.25(1H, d, $J_{6,7}$ 6.7Hz, H-7), 6.17(1H, d, $J_{4,5}$ 5Hz, H-4), 6.28(1H, dd, $J_{5,6}$ 9.2Hz, $J_{6,7}$ 6.7Hz, H-6), 6.43(1H, ddd, $J_{5,6}$ 9.2Hz, $J_{4,5}$ 5Hz, $J_{5,7}$ 1.2Hz, H-5), 6.49(1H, d, $J_{2,3}$ 5.4Hz, H-2) and 7.83(1H, d, $J_{2,3}$ 5.4Hz, H-3); m/z 294(M^+), 292, 290, 217 and 145.

4. Attempted elimination of the elements of trimethylsilanol from the [8+2] cycloadduct (142)

The mixture of [8+2] cycloadduct (142) and the 1H-indene (143) (10mg) was dissolved in benzene (2ml) and DBU (0.02g, 0.13mmol) was added. The reaction mixture was refluxed under an atmosphere of nitrogen for 3h after which time the solvent was removed *in vacuo*. The residue was subjected to ^1H n.m.r. analysis which failed to indicate the presence of any signals upfield of tetramethylsilane and the reaction was not pursued.

3.1.4 Cycloaddition Reactions of 3-Methoxy-3a-methyl-3aH-indene (100) with Isocyanates

1. Cycloaddition reaction of 3-methoxy-3a-methyl-3aH-indene (100) with toluenesulphonyl isocyanate

a. Generated from the [4+2] -N-phenylmaleimide adduct (110)

A solution of the [4+2] -N-phenylmaleimide adduct (110) (223mg, 0.67mmol) in 4-toluenesulphonyl isocyanate (7ml) was heated at 100 $^{\circ}\text{C}$ for 0.5h under an atmosphere of nitrogen. After pouring the reaction mixture into water (50ml) and extracting with ether (3x50ml), the combined extracts were washed with aqueous potassium hydroxide

(2.5%; 50ml), dried and evaporated. The residue was subjected to column chromatography (petrol/ether) to give 2a-methoxy-7b-methyl 2,2a,7a,7b-tetrahydro-2-toluenesulphonyl-1H-cyclopent[cd]isoindol-1-one (146) (103mg, 43%) as a solid m.p. 192-194°C (dichloromethane) (Found: C, 64.12; H, 5.28; N, 3.99. $C_{19}H_{19}NO_4S$ requires C, 63.85; H, 5.36; N, 3.92%); $\nu_{\max}$. (Nujol) 2925, 1727, 1590, 1250, 1220, 1187 and 1170cm^{-1} ; $\lambda_{\max}$. (EtOH) 229(log ϵ 4.14) and 302nm(log ϵ 3.74); δ_H (CDCl₃) 1.0(3H, s, 7b-Me), 2.39(3H, s, Ar-Me), 3.04(1H, dd, $J_{7,7a}$ 6.8Hz, $J_{6,7a}$ 0.8Hz, H-7a), 5.86(1H, dd, $J_{6,7}$ 9.1Hz, $J_{7,7a}$ 6.8Hz, H-7), 5.91(1H, d, $J_{5,6}$ 5.2Hz, H-5), 6.15(1H, ddd, $J_{6,7}$ 9.1Hz, $J_{5,6}$ 5.2Hz, $J_{6,7a}$ 0.8Hz, H-6), 6.61(1H, d, $J_{3,4}$ 5.7Hz, H-3 or H-4), 6.85(1H, d, $J_{3,4}$ 5.7Hz, H-3 or H-4), 7.24(2H, d, J 8.3Hz, Ar-H) and 7.81(2H, d, J 8.3Hz, Ar-H); m/z 357(M^+), 333, 160 and 145.

b. Generated from the trienone (106)

Toluenesulphonyl isocyanate (0.818g, 4.2mmol) in dry THF (5ml) was added to a solution of the 3aH-indene (100) prepared from the trienone (106) (0.55g, 3.8mmol) as described in Section 3.1.1.3 (p. 158). The reaction mixture was allowed to stir for 1h at room temperature under nitrogen before being filtered through Celite to remove the excess potassium hydride. After stirring the solution overnight, the solvent was removed and the residue subjected to column chromatography. This, however, failed to furnish the desired product and the reaction was not pursued.

2. Cycloaddition reaction of 3-methoxy-3a-methyl-3aH-indene (100) with chlorosulphonyl isocyanate

To a solution of the 3aH-indene (100) [prepared from the trienone

(106) (1.6g, 11mmol) as described in Section 3.1.1.3] was added chlorosulphonyl isocyanate (1.2ml, 12mmol). The reaction mixture was stirred for 2h under an atmosphere of nitrogen before being filtered through Celite to remove the excess potassium hydride. The solution was then poured into a mixture of aqueous sodium sulphite (10%; 100ml), aqueous sodium bicarbonate (10%; 100ml) and ether (100ml). After stirring vigorously for 2h, the resulting solution was extracted with ether (3x75ml) and chloroform (50ml). The combined extracts were dried, evaporated and subjected to column chromatography (ether, ethyl acetate) to give 2a-methoxy-7b-methyl-1,2a,7a,7b-tetrahydro-2H-cyclopent[cd]indol-2-one (152) (1.0g, 45%) (Found: C, 70.42; H, 6.64; N, 6.63. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%); $\nu_{\max.}$ (CHCl₃) 3430, 2930, 1700 and 1452cm⁻¹; $\lambda_{\max.}$ (EtOH) 245.5(log ϵ 3.40) and 312nm(log ϵ 3.73); δ_H (CDCl₃) 1.07(3H, s, 7b-CH₃), 3.54(3H, s, OMe), 4.12(1H, d, $J_{7,7a}$ 5.7Hz, H-7a), 5.68(1H, dd, $J_{6,7}$ 8.9Hz, $J_{7,7a}$ 5.7Hz, irradiation at δ 4.12 removes the smaller coupling, H-7), 5.85(1H, d, $J_{5,6}$ 5.2Hz, H-5), 6.21(1H, dd, $J_{6,7}$ 8.9Hz, $J_{5,6}$ 5.2Hz, H-6), 6.46(2H, s, H-3 and H-4) and 6.99(1H, br. signal, D₂Oexch., N-H); m/z 203(M^+), 160 and 145.

Repetition of this reaction using trienone (2g, 13.7 mmol) in the procedure described above gave an inseparable mixture of the [8+2] adduct (152) and 2a-methoxy-7b-methyl-2,2a,7a,7b-tetrahydro-1H-cyclopent[cd]isoindol-1-one (147) in a ratio of 2.5:1 (1.6g, 57%), δ_H (CDCl₃) minor component, 1.02(3H, s, 7b-CH₃), 2.99(1H, d, $J_{7,7a}$ 6.8Hz, H-7a), 5.90(1H, d, $J_{5,6}$ 5.7Hz, H-5), 5.92(1H, dd, $J_{6,7}$ 9.1Hz, $J_{7,7a}$ 6.8Hz, H-7), 6.31(1H, d, $J_{3,4}$ 5.7Hz, H-3 or H-4), 6.43(1H, d, $J_{3,4}$ 5.7Hz, H-3 or H-4) and 7.84(1H, br. signal, D₂O exch., N-H) other signal obscured; the regiochemistry of the cycloaddition products was assigned from a consideration of the n.o.e. difference experiment shown in Figure 3, (p. 86).

3. Attempted cycloaddition of 3a-methyl-3-trimethylsiloxy-3aH-indene (111) with chlorosulphonyl isocyanate

Chlorotrimethylsilane (0.06ml, 0.47mmol) was added to a stirred solution of sodium iodide (0.07g, 0.47mmol) in dry acetonitrile (15ml) at room temperature under an atmosphere of nitrogen. A mixture of trienone (106) (0.05g, 0.34mmol), and triethylamine (0.06ml, 0.43mmol) was added and the resulting solution heated at 35°C for 1h. The trimethylsiloxy-3aH-indene (111) was then extracted using petrol and transferred to another flask. Chlorosulphonyl isocyanate (0.033ml, 0.033mmol) was added to the solution which was then stirred at room temperature for 0.75h before the solvent was removed *in vacuo*. T.l.c. analysis showed the residue to be a complex mixture and this reaction was not pursued.

4. Attempted elimination of the elements of methanol from the [8+2] cycloadduct (152)

a. Using sodium hydride

Sodium hydride (8mg, of a 50% oil suspension; 0.17mmol) was added to a stirred solution of the cycloadduct (152) (15mg, 0.07mmol) in dry DME (3ml), under an atmosphere of nitrogen. The reaction mixture was stirred for 16h at room temperature. T.l.c. analysis (ethyl acetate) indicated only the presence of baseline material and the reaction was not pursued.

b. Using *n*-butyl lithium

n-Butyl lithium (0.35ml of a 1.54M solution, 0.54mmol) was

added to a solution of the cycloadduct (152) (50mg, 0.25mmol) in dry THF (25ml) at -78°C under an atmosphere of nitrogen. After stirring for 1h the resulting solution was warmed to -20°C before the addition of methyl fluorosulphonate (0.02ml, 0.26mmol). Stirring was continued for 0.5h before water (20ml) was added and the solution extracted with ether (3x25ml). The combined extracts were dried, evaporated and the residue analysed using ^1H n.m.r. spectroscopy. The absence of olefinic signals in the spectrum led to this reaction being abandoned.

c. Using DBU⁶⁰

The cycloadduct (152) (50mg, 0.25mmol) was dissolved in DBU (3ml) and the solution heated under nitrogen for 8h at 100°C (oil bath temperature). Column chromatography of the resulting solution gave the [8+2] cycloadduct (152) (40mg, 80%).

d. Using concentrated sulphuric acid

The [8+2] cycloadduct (152) (15mg, 0.07mmol) was dissolved in a mixture of methanol and chloroform (1:5; 6ml) and cooled to 0°C under nitrogen. Concentrated sulphuric acid (1ml) was then added and the solution stirred at 0°C for 15min. The reaction mixture was poured into water (15ml), neutralised using sodium bicarbonate and extracted with chloroform (3x10ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give returned starting material (152) (10mg, 66%).

e. Using toluene-4-sulphonic acid

Toluene-4-sulphonic acid (275mg, 1.45mmol) was added to a

solution of the [8+2] cycloadduct (152) (133mg, 0.66mmol) in dry benzene (10ml) under an atmosphere of nitrogen. The reaction mixture was refluxed for 2h, after which time it was poured into 20% aqueous sodium bicarbonate solution (25ml) and extracted with chloroform (3x25ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give returned starting material (152) (74mg, 56%).

5. Attempted elimination of the elements of methanol from the mixture of [8+2] cycloadducts (152) and (147)

a. Using excess methyl lithium⁵⁹

The mixture of cycloadducts (152) and (147) (141mg, 0.7mmol) obtained in Section 3.1.4.2 was dissolved in dry THF (10ml) and cooled to -78°C under an atmosphere of nitrogen. Methyl lithium (2.89ml of a 1.2M solution, 3.5mmol) was added and the reaction mixture stirred for 0.5h at -78°C . After allowing the solution to warm to room temperature over a period of 0.5h, it was then poured into water (15ml) and extracted with ether (3x25ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography (ethyl acetate 70%, ether 30%) to give 2a,7b-dimethyl-2a-methoxy-2,2a,7a,7b-tetrahydro-1H-cyclopent[cd]isoindol-1-one (162) (32mg, 25%) as a solid m.p. $163-166^{\circ}\text{C}$ (dichloromethane/petrol), (Found: C, 76.66; H, 6.99; N, 7.45. $\text{C}_{12}\text{H}_{13}\text{NO}$ requires C, 76.98; H, 7.00; N, 7.48%); $\nu_{\text{max.}}(\text{CCl}_4)$ 3180, 3060, 2975, 1690, 1382, 1152 and 863cm^{-1} ; $\lambda_{\text{max.}}(\text{EtOH})$ 305nm(log ϵ 3.69); $\delta_{\text{H}}(\text{CDCl}_3)$ 0.92(3H, s, 7b- CH_3), 1.38(3H, s, 2a- CH_3), 2.85(1H, dd, $J_{7,7a}$ 6.7Hz, $J_{6,7a}$ 1Hz, H-7a), 5.92(1H, dd, $J_{6,7}$ 9.2Hz, $J_{7,7a}$ 6.7Hz, irradiation at δ 2.85 removes the

smaller coupling, H-7), 5.96(1H, d, $J_{5,6}$ 5.2Hz, H-5), 6.06(1H, d, $J_{3,4}$ 5.4Hz, H-3), 6.21(1H, ddd, $J_{6,7}$ 9.2Hz, $J_{5,6}$ 5.2Hz, $J_{6,7a}$ 1Hz, irradiation at δ 2.85 removes the smallest coupling, H-6), 6.40(1H, d, J 5.4Hz, H-4) and 6.52(1H, br. signal, D₂O exch., N-H); δ_C (CDCl₃) 16.8(CH₃), 19.9(CH₃), 45.9(C-7a), 46.2, 70.4, 116.6 (olefinic C-H), 120.5 (olefinic C-H), 126.0 (olefinic C), 133.8 (olefinic C), 141.1 (olefinic C), 149.3 (C-4a) and 175.6(C-1); m/z 187(M^+), 144 and 129.

b. Using lithium di-isopropylamide

To a solution of the [8+2] cycloadducts (152) and (147) (158mg, 0.78mmol) in dry THF (5ml), at -78°C under nitrogen, was added LDA [prepared from di-isopropylamine (0.17g, 1.7mmol) in dry THF (5ml) and *n*-butyl lithium (1.13ml of a 1.5M solution, 1.7mmol)]. The reaction mixture was allowed to warm to room temperature over a period of 0.5h and stirring continued for a further 0.5h at this temperature. Water (15ml) was then added and the solution extracted with chloroform (3x25ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give the [8+2] cycloadduct (152) (26mg, 16.5%). No other products could be isolated.

c. Using 2 equivalents of methyl lithium

To a solution of the [8+2] cycloadducts (152) and (147) (115mg, 0.57mmol) in dry THF (5ml), at -78°C under an atmosphere of nitrogen, was added methyl lithium (0.84ml of a 1.34M solution, 1.13mmol). The solution was allowed to warm to room temperature over a period of 0.5h and stirring was continued at this temperature for a further 4h. Dimethyl sulphate (0.054ml, 0.57mmol) was added followed after

15min by water (20ml). The reaction mixture was extracted using chloroform (3x25ml) and the combined extracts dried and evaporated. The residue was subjected to column chromatography to give (i) 1,7b-dimethyl-2a-methoxy-1,2a,7a,7b-tetrahydro-2H-cyclopent[cd]indol-2-one (168) (8.4mg, 7%) as an oil, $\nu_{\text{max.}}$ (CCl₄) 2940, 1690, 1450, 1418, 1395, 1295, 1205, 1122 and 1058cm⁻¹; δ_{H} (90MHz, CDCl₃), 1.02(3H, s, 7b-CH₃), 2.75(3H, s, N-CH₃), 3.56(3H, s, O-CH₃), 3.98(1H, d, $J_{7,7a}$ 6.4Hz, H-7a), 5.73(1H, dd, $J_{6,7}$ 10.1Hz, $J_{7,7a}$ 6.4Hz, H-7), 5.89(1H, d, $J_{5,6}$ 5.8Hz, H-5), 6.37(1H, dd, $J_{6,7}$ 10.1Hz, $J_{5,6}$ 5.8Hz, H-6), 6.50(1H, d, $J_{3,4}$ 5.8Hz, H-3 or H-4) and 6.59(1H, d, $J_{3,4}$ 5.8Hz, H-3 or H-4); m/z 217(M^+) 160, and 145; and (ii) the [8+2] cycloadduct (152) (25mg, 22%). No product derived from the cycloadduct (147) could be detected.

d. Using toluene-4-sulphonic acid

The mixture of [8+2] cycloadducts (152) and (147) (166mg, 0.82mmol) was dissolved in dry benzene (25ml) and toluene-4-sulphonic acid (170mg, 0.89mmol) was added. After refluxing the solution for 4h under an atmosphere of nitrogen, water (25ml) was added and the reaction mixture extracted with chloroform (3x25ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give the [8+2] cycloadduct (152) (40mg, 24%). No product derived from the cycloadduct (147) could be isolated.

6. Formation of 7a,7b-dihydro-2,2a-dimethoxy-7b-methyl-2aH-cyclopent[cd]indole

Methyl fluorosulphonate (0.06ml, 0.75mmol) was added to a solution of the [8+2] cycloadduct (152) (114mg, 0.56mmol) in dry

DME (15ml) and the reaction mixture stirred at room temperature under an atmosphere of nitrogen for 12h. Triethylamine (1ml) was then added before the solvent was removed and the residue subjected to column chromatography on alumina. This gave *the title compound* (169) (85mg, 70%) as an oil, (Found: M^+ 217.1108. $C_{13}H_{15}NO_2$ requires M 217.1103); $\nu_{\max.}(\text{CHCl}_3)$ 2925, 1623, 1338, 1292 and 1158cm^{-1} ; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.02(3H, s, 7b- CH_3), 3.40(3H, s, OCH_3), 3.83(3H, s, OCH_3) 4.23(1H, d, $J_{7,7a} 5.9\text{Hz}$, H-7a), 5.86(1H, d, $J_{5,6} 5\text{Hz}$, H-5), 6.06(1H, dd, $J_{6,7} 9.3\text{Hz}$, $J_{7,7a} 5.9\text{Hz}$, collapses to a doublet on irradiation at δ 4.23, H-7), 6.20(1H, d, $J_{3,4} 5.9\text{Hz}$, H-3 or H-4), 6.22(1H, dd, $J_{6,7} 9.3\text{Hz}$, $J_{5,6} 5\text{Hz}$, H-6) and 6.43(1H, d, $J_{3,4} 5.9\text{Hz}$, H-3 or H-4); m/z 217(M^+), 160 and 145.

7. Attempted elimination of the elements of methanol from the imidate (169)

a. Using toluene-4-sulphonic acid

Toluene-4-sulphonic acid (15mg, 0.08mmol) was added to a solution of the imidate (169) (10mg, 0.04mmol) in deuteriochloroform and the reaction mixture refluxed under an atmosphere of nitrogen for 1h. T.l.c. analysis indicated the formation of a complex mixture which included the amide (152). The absence of any resonance upfield of tetramethylsilane caused the abandonment of this reaction.

b. Using DBU

The imidate (169) (9mg, 0.04mmol) was dissolved in DBU (3ml) and heated for 8h at 100°C (oil bath temperature), under nitrogen. After this time, water (10ml) was added and the solution extracted

using ether (3x10ml). The combined extracts were dried, evaporated and the residue analysed by ^1H n.m.r. spectroscopy. The absence of any olefinic or aromatic resonances resulted in this reaction not being pursued.

8. Formation of the mixture of imidates (169) and (170)

The mixture of [8+2] cycloadducts (152) and (147) (159mg, 0.78mmol) was dissolved in dry DME (10ml) and stirred at room temperature under an atmosphere of nitrogen. Methyl fluorosulphonate (0.08ml, 0.99mmol) was added and the reaction mixture stirred for 6h before triethylamine (0.3ml) was added. The solution was then poured into water (15ml) and extracted with ether (3x15ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give an inseparable mixture of the imidates (169) and (170) (113mg, 66%) in a ratio of 2:1, δ_{H} (CDCl_3 , 90MHz) minor component. 1.93(3H, s, CH_3), 3.22(1H, d, J 6.5Hz, H-7a), 3.45(3H, s, OCH_3), 3.68(3H, s, OCH_3) and 5.7-6.65(olefinic protons obscured by peaks from major isomer).

9. Attempted elimination of the elements of methanol from the mixture of imidates (169) and (170)

a. Using 1 equivalent of LDA

The mixture of imidates (169) and (170) (20mg, 0.09mmol) obtained previously, was dissolved in dry THF (2ml) and cooled to -78°C under an atmosphere of nitrogen. LDA [1ml of a solution formed from di-isopropylamine (0.16ml, 1.1mmol) in dry THF (10ml) and *n*-butyl lithium (0.825ml of a 1.1M solution, 0.9mmol)] was added and the

resulting solution allowed to warm to room temperature over 0.5h. After heating the reaction mixture at 50–60°C for 5h, water (5ml) was added and the solution extracted with chloroform (3x5ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give the starting materials (169) and (170) (19mg, 95%).

b. Using 1 equivalent of methyl lithium

The procedure described above was repeated except that methyl lithium (0.07ml of a 1.34M solution, 0.09mmol) was used instead of LDA. This resulted in the isolation of recovered starting materials (169) and (170) (18mg, 90%).

c. Using *t*-butyl lithium

The mixture of imidates (169) and (170) (20mg, 0.09mmol) was reacted as described previously except that *t*-butyl lithium (0.1ml of a 1.6M solution, 0.16mmol) was used instead of LDA. This resulted in the isolation of the imidate (169) (11mg, 55%). No product derived from the other isomer (170) could be isolated.

d. Using excess LDA

The mixture of imidates (169) and (170) (20mg, 0.09mmol) was dissolved in dry THF (3ml) and stirred at -78°C under an atmosphere of nitrogen. LDA [formed by the addition of *n*-butyl lithium (0.825ml of a 1.1M solution, 0.9mmol) to a solution of di-isopropylamine (0.16ml, 1.1mmol) in dry THF (1ml)] was added and the reaction mixture allowed to warm to room temperature. After stirring for 0.5h the

solution was then cooled to -78°C and methyl iodide (1ml) was added. The external cooling was removed and stirring continued for a further 1.5h. Water (10ml) was then added, followed by extraction of the solution using chloroform (3x10ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give the imidate (169 (10mg, 50%). No product derived from the imidate (170) could be observed.

3.2 CYCLISATION APPROACHES TO TRICYCLIC AZA[10]ANNULENES

3.2.1 Ring Closure Routes to the 1,2-Diaza[10]annulene (94)

1. Ene reactions using dimethyl azodicarboxylate

- a. Dimethyl azodicarboxylate (600mg, 4.1mmol) was added to a solution of the dienone (104) (500mg, 3.4mmol) in toluene (20ml) and the reaction mixture refluxed under an atmosphere of nitrogen for 24 h. The solvent was removed and the residue subjected to column chromatography to give 1-indanone (103) (140mg, 31%). No other identifiable products could be isolated.
- b. Dimethyl azodicarboxylate (150mg, 1.03mmol) was added to a solution of the trienone (106) (100mg, 0.7mmol) in xylene (3ml) and the reaction mixture refluxed for 24h under a nitrogen atmosphere. The solvent was removed and the residue analysed by ^1H n.m.r. spectroscopy. The lack of olefinic resonances in the spectrum caused the abandonment of this reaction.

2. Ene reaction using PTAD

PTAD (0.65g, 3.71mmol) was added in portions to a solution of the dienone (104) (0.5g, 3.4mmol) in toluene (10ml). The solution was stirred under an atmosphere of nitrogen until the colour of the PTAD was discharged. After this time the white precipitate which had formed during the reaction was filtered. The filtrate was triturated with petrol and then re-filtered to give the crude product (420mg). This solid was recrystallised (dichloromethane/petrol) to give *the 2:1 adduct* (175) (320mg, 19%) m.p. 220–230°C dec., (Found: M^+ 498.1662. $\text{C}_{26}\text{H}_{22}\text{N}_6\text{O}_5$ requires M 498.1652); ν_{max} . (Nujol) 1770, 1705, 1505, 1245,

1140, 1067 and 782cm^{-1} ; λ_{max} 222 ($\log \epsilon$ 4.34), and 253nm (sh. $\log \epsilon$ 3.74); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.64 (3H, s, 7a-Me), 1.97(1H, dt, $J_{3',3}$ 13.8Hz, $J_{2,3}$ 9.4Hz, H-3) 2.23(1H, ddd, $J_{2,2'}$ 18.8Hz, $J_{2,3}$ 9.4Hz $J_{2,3'}$ 3.1Hz, H-2) 2.55 (1H, m, H-3'), 3.01(1H, ddd, $J_{2,2'}$ 18.8Hz, $J_{2',3'}$ 11.9Hz, $J_{2',3}$ 9.4Hz, H-2'), 4.83 (1H, dd, J 5.0Hz, J 1.9Hz, H-4 or H-7), 5.72(1H, dd, J 5.6Hz, J 1.3Hz, H-4 or H-7) 6.54(2H, m, H-5 and H-6), 7.3-7.6(10H, m, Ar-H) and 8.65(1H, br. signal, D_2O exch., N-H); $\delta_{\text{C}}(\text{CDCl}_3)$ 18.9(7a- CH_3), 31.1(C-3), 37.4 (C-2), 56.5(C-7a), 57.3(C-4 or C-7), 58.3(C-4 or C-7), 70.1(C-3a), 125.3, 125.5, 128.1, 128.6, 128.7, 129.3, 131.0, 132.2, 154.0 (2x $\text{C}=\text{O}$), 156.5 (C=O), 156.6(C=O) and 216.3(C-1); m/z 498(M^+), 323, 271, 226 and 177.

3. Cycloaddition reaction of 3a-methyl-3-trimethylsiloxy-3aH-indene (111) with dimethyl azodicarboxylate

Triethylamine (0.4ml, 3mmol) and trimethylsilyl trifluoromethanesulphonate (0.56ml, 3mmol) were added to a solution of the trienone (106) (0.4g, 2.7mmol) in dry ether (20ml) and the reaction mixture stirred at 0°C under an atmosphere of nitrogen for 1h. Dimethyl azodicarboxylate (0.88g, 6mmol) was added and the solution warmed to room temperature. Stirring was continued for 3h before pouring the solution into water and extracting with ether (3x40ml). The combined extracts were evaporated and dissolved in aqueous THF (THF: H_2O , 3:1) (25ml) containing potassium fluoride (200mg, 3.4mmol). The resulting solution was stirred for 3h at room temperature before being poured into water (25ml) and extracted with ether (3x30ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give (i) *dimethyl 7b-methyl-2,2a,7a,7b-tetrahydro-2a-trimethylsiloxy-1H-cyclopent[cd]indazole-1,2-dicarboxylate*

(177) (100mg, 10%) as an oil, b.p. 95–98°C/0.15mmHg (Kugelrohr), (Found: C, 55.69; H, 6.56; N, 7.50. $C_{17}H_{24}N_2O_5Si$ requires C, 56.02; H, 6.64; N, 7.69%), $\nu_{\max.}$ (CCl₄) 2965, 1743, 1710, 1445, 1355, 1200 and 1165cm⁻¹; $\lambda_{\max.}$ (EtOH) 214 and 294nm; δ_H (CDCl₃) 0.18(9H, s, SiMe₃), 0.97(3H, s, 7b-Me), 3.58(3H, br. signal, CO₂Me), 3.72(3H, s, CO₂Me) 4.28(1H, d, $J_{7a,7}$ 5.3Hz, H-7a), 5.86(1H, d, $J_{5,6}$ 5.3Hz, H-5), 5.98 (1H, m, H-7), 6.15(1H, dd, $J_{6,7}$ 9.4Hz, $J_{5,6}$ 5.3Hz, H-6), 6.31(1H, d, $J_{2,3}$ 5.3Hz, H-3) and 6.38(1H, br. signal, H-2), m/z 364(M^+), 349, 273, 218, 202, and 145, and (ii) the functionalised ketone (127) (250mg, 31%).

4. Attempted hydrolysis of dimethyl 1-(7,7a-dihydro-7a-methyl-1H-inden-1-on-7-yl) hydrazine-1,2-dicarboxylate (127)

a. Using methanolic potassium hydroxide

The functionalised ketone (127) (43mg, 0.15mmol) was treated with a solution of potassium hydroxide (100mg, 2mmol) in methanol (15ml). The reaction mixture was refluxed under a nitrogen atmosphere for 4h before being neutralised using dilute hydrochloric acid and extracted with ether (3x20ml). The combined extracts were dried, evaporated and the residue subjected to column chromatography to give *methyl 2-(7,7a-dihydro-7a-methyl-1H-inden-1-on-7-yl) hydrazine-1-carboxylate* (181), (8mg, 23%) as an oil (Found: M^+ 234.1001. $C_{12}H_{14}N_2O_3$ requires M 234.1004); $\nu_{\max.}$ (CCl₄) 3440, 2930, 1730, 1705, 1450 and 1250cm⁻¹; δ_H (CDCl₃) 1.08 (3H, s, 7a-CH₃), 3.60(1H, d, J 5.8Hz, H-7), 3.72(3H, s, CO₂Me), 6.15–6.38(4H, m, olefinic C-H) and 7.83(1H, d, J 5.0Hz, H-3); m/z 234, 160, 159, 146 and 145.

b. Using trimethylsilyl iodide⁶⁹

Trimethylsilyl iodide (0.05ml, 0.35mmol) was added to a stirred solution of the functionalised ketone (127) (46mg, 0.16mmol) in deuterio-chloroform (3ml) under an atmosphere of nitrogen. After stirring for 1h. the reaction mixture was poured into dilute hydrochloric acid (10ml) and extracted with chloroform. The chloroform extracts were washed with aqueous sodium thiosulphate (10% solution; 20ml), dried and evaporated. The residue was analysed using ¹H n.m.r. spectroscopy which showed the absence of any olefinic resonances. The acid layer was neutralised using sodium bicarbonate and then extracted with chloroform (3x15ml). The combined extracts were dried, evaporated and the residue examined by ¹H n.m.r. spectroscopy. The lack of any olefinic resonances caused the abandonment of this reaction.

5. Cylcoaddition reaction of 3a-methyl-3-trimethylsiloxy-3aH-indene (111) with bis-trichloroethyl azodicarboxylate

Triethylamine (0.52ml, 3.9mmol) and trimethylsilyl trifluoromethanesulphonate (0.7ml, 3.8mmol) were added to a solution of the trienone (106) (0.5g, 3.4mmol) in dry ether (25ml) and the reaction mixture stirred at 0°C under an atmosphere of nitrogen for 1h. *bis*-Trichloroethyl azodicarboxylate⁹⁰ (2.87g, 7.5mmol) was added and the solution warmed to room temperature. After stirring overnight the reaction solution was poured into water (25ml) and extracted with ether (3x30ml). The combined extracts were dried, evaporated and subjected to column chromatography to give *bis-trichloroethyl 1-(7,7a-dihydro-7a-methyl-1H-inden-1-on-7-yl) hydrazine-1,2-dicarboxylate* (183) (745mg, 41%) as an oil, (Found: M^+ 523.9042. $C_{16}H_{14}N_2O_5Cl_6$ requires M 523.9034);

$\nu_{\text{max.}}$ (CCl_4) 3400, 2960, 1785, 1742, 1710, 1403 and 1195cm^{-1} ; $\lambda_{\text{max.}}$ (EtOH) 231 ($\log \epsilon$ 3.58) and 332nm ($\log \epsilon$ 3.70); δ_{H} (90MHz, CDCl_3) 1.28 (3H, s, 7a-Me), 4.4-5.1 (5H, m, H-7 and $2 \times \text{Cl}_3\text{CCH}_2$), 6.0-6.6 (4H, m, olefinic C-H), 6.74 (1H, br. signal, N-H) and 7.72 (1H, d, J 5.5Hz, H-3); m/z the molecular ion pattern was 531 (5), 529 (21), 527 (45), 525 (53) and 523 (28); the calculated ratio is 5:20:45:54:27.

6. Attempted cleavage of the substituted ketone (183)

The substituted ketone (183) (150mg, 0.29mmol) was dissolved in glacial acetic acid (7ml) and the reaction flask purged with nitrogen. The solution was cooled to 0°C before dry THF (7ml) and activated zinc (1.125g, 17.2mmol) were added. After stirring for 1h at 0°C the reaction mixture was filtered under nitrogen and the residue washed with water and ether. The combined filtrate was neutralised using sodium bicarbonate and extracted with dichloromethane (3x30ml). The combined extracts were dried, evaporated and the residue analysed using ^1H n.m.r. spectroscopy. The absence of any recognisable olefinic resonances meant that this reaction was abandoned.

7. Condensation of ethyl carbazate with the trienone (106)

Ethyl carbazate (88mg, 0.85mmol) and toluene-4-sulphonic acid (20mg) were added to a solution of the trienone (106) (124mg, 0.85mmol) in dry benzene (15ml) under a nitrogen atmosphere. The reaction mixture was refluxed with a Dean and Stark trap for 58h after which time the solvent was removed. The residue was subjected to column chromatography to give (i) the trienone (106) (33mg, 27%) and (ii)

the ethoxycarbonylhydrazone of 7,7a-dihydro-7a-methyl-1H-inden-1-one (192) (38mg, 19%) as an oil, $\nu_{\max.}(\text{CCl}_4)$ 3240, 3130, 2930, 1757, 1695, 1380, 1340 and 1207cm^{-1} ; $\lambda_{\max.}(\text{EtOH})$ 249 and 348nm; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.06(3H, s, 7a-CH₃), 1.30(3H, t, J 7.4Hz, CO₂CH₂CH₃), 2.23(1H, br.d., J 18.2Hz, H-7), 2.57(1H, dd, J 18.2Hz, J 6.2Hz, H-7'), 4.27(2H, qt, J 7.4Hz, CO₂CH₂CH₃), 6.0(1H, ddd, $J_{5,6}$ 8.5Hz, $J_{6,7'}$ 6.2Hz, $J_{6,7}$ 2.3Hz, H-6), 6.07(1H, d, $J_{4,5}$ 5.1Hz, H-4), 6.14(1H, ddd, $J_{5,6}$ 8.5Hz, $J_{4,5}$ 5.1Hz, $J_{5,7}$ 2.8Hz, H-5), 6.71(1H, d, $J_{2,3}$ 5.1Hz, H-2) and 6.97(1H, d, $J_{2,3}$ 5.1Hz, H-3); m/z 232(M^+) and 217.

8. Condensation of ethyl carbazate and the dienone (104)

Ethyl carbazate (2.09g, 20mmol) was added to a solution of the dienone (104) (2.7g, 18.2mmol) in ethanol (25ml). Dilute hydrochloric acid (0.25ml) was added and the reaction mixture was refluxed for 4h under nitrogen. The solvent was then removed *in vacuo* and the residue subjected to column chromatography to give *the ethoxycarbonylhydrazone of 7a-methyl-2,3,5,7a-tetrahydro-1H-inden-1-one* (194) (3.8g, 89%) as a solid m.p. 130-131.5°C (dichloromethane/petrol) (Found: C, 66.44; H, 7.86, N, 11.91. C₁₃H₁₈N₂O₂ requires C, 66.64; H, 7.74; N, 11.96%), $\nu_{\max.}(\text{Nujol})$ 3230, 1727, 1702, 1547 and 1250cm^{-1} ; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.21(3H, s, 7a-CH₃), 1.31(3H, t, J 7.1Hz, CO₂CH₂CH₃), 2.15-2.75(6H, m, 3xCH₂), 4.26(2H, qt, J 7.1Hz, CO₂CH₂CH₃) 5.61(1H, m, olefinic-H), 5.76(1H, m, olefinic-H) 6.23(1H, d, $J_{6,7}$ 10Hz, H-7) and 7.4(1H, br. signal, D₂O exch., N-H); m/z 234, 233, 229 and 146.

9. The ethoxycarbonylhydrazone of 5,7a-dihydro-7a-methyl-1H-inden-1-one (184)

LDA [prepared from di-isopropylamine (0.36ml, 2.54mmol) and

n-butyl lithium (1.7ml of a 1.5M solution, 2.55mmol) in dry THF (10ml)] was added to a solution of the hydrazone (194) (540mg, 2.31mmol) in dry THF (5ml) at -78°C under an atmosphere of nitrogen. After allowing the solution to stir for 0.5h *n*-butyl lithium (1.7ml of a 1.5M solution, 2.55mmol) was added and stirring continued for a further 0.75h. Phenylselenenyl chloride (0.619g, 3.2mmol) in dry THF (2ml) was then added to the solution followed after 15 min by water (2ml). The resulting solution was warmed to room temperature, poured into water and extracted with dichloromethane (3x50ml). The combined extracts were dried, evaporated and subjected to column chromatography to give (i) *the ethoxycarbonylhydrazone of 7a-methyl-2-phenylseleno-2,3,5,7a-tetrahydro-1H-inden-1-one* (193) (408mg, 45%) as a mixture of isomers; major component $\nu_{\text{max.}}$ (CCl_4) 3300, 2965, 1760 and 1505cm^{-1} ; δ_{H} (90MHz, CDCl_3) 0.78(3H, s, 7a- CH_3), 1.31(3H, t, J 7.5Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.4-3.1(4H, m, $2\times\text{CH}_2$), 3.84(1H, t, $J_{2,3}$ 9Hz, H-2), 4.29(2H, qt, J 7.5Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.5-5.85(2H, m, H-4 and H-6), 6.28(1H, m, H-7), 7.25-7.5(3H, m, Ar-H), 7.55-7.75(2H, m, *o*-Ar-H) and 9.02(1H, broad signal, N-H); m/z 390(M^+), 388, 314, 312 and 157; minor isomer as a crystalline solid m.p. $155-158^{\circ}\text{C}$ (dichloromethane, petrol), (Found: C, 58.58; H, 5.81; N, 7.15. $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2\text{Se}$ requires C, 58.61; H, 5.70; N, 7.19%); $\nu_{\text{max.}}$ (Nujol) 3260, 1705 and 1340cm^{-1} ; δ_{H} (CDCl_3 , 90MHz) 1.18(3H, s, 7a- CH_3), 1.30(3H, t, J 7.5Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.4-2.85(3H, m), 3.2(1H, m), 4.23(3H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$ and H-2), 5.45-5.8(2H, m, H-4 and H-6), 6.05(1H, m, H-7), 7.2-7.45(3H, m, Ar-H), 7.45-7.7(2H, m, *o*-Ar-H) and 8.20(1H, br. signal, N-H); m/z 390(M^+), 388, 234, 157 and 144; and (ii) recovered starting material (194) (120mg, 22%).

The mixture of selenides (193) (408mg, 1.0mmol) was oxidised

in the manner described in Section 3.3.2.4, to give *the title compound* (184) (177mg, 73%) as a solid m.p. 136-138°C (dichloromethane), (Found: M^+ 232.1209. $C_{13}H_{16}N_2O_2$ requires M 232.1212), $\nu_{\max.}$ (CCl₄) 3240, 2980, 1760, 1695 and 1340cm⁻¹; $\lambda_{\max.}$ (EtOH) 312nm (log ϵ 4.04); δ_H (90MHz, CDCl₃), 1.24(3H, s, 7a-CH₃), 1.30(3H, t, J 7.5Hz, CO₂CH₂CH₃), 2.82(2H, m, 2xH-5), 4.26(2H, qt, J 7.5Hz, CO₂CH₂CH₃), 5.65-6.01(2H, m, H-4 and H-6), 6.35(1H, m, H-7), 6.68(1H, d, J 5.5Hz, H-2), 6.88(1H, d, J 5.5Hz, H-3) and 8.81(1H, br. signal, N-H); m/z 232(M^+), 217, 144, and 115.

10. Attempted cyclisation of the conjugated hydrazone (184)

The hydrazone (184) (65mg, 0.28mmol) was dissolved in dry dichloromethane (4ml) and dry silica gel (100mg) was added. After cooling the solution to -78°C, phenylselenenyl chloride (60mg, 0.31mmol) in dichloromethane (4ml) was added and the reaction mixture stirred under an atmosphere of nitrogen for 20min. The external cooling was then removed and the solution stirred for a further 3h before being filtered, evaporated and subjected to column chromatography to give (i) diphenyl diselenide (33mg, 67%) and (ii), returned starting material (184) (35mg, 54%).

11. Epoxidation of the conjugated hydrazone (184)

m-CPBA (0.104g of 80% pure material, 0.55mmol) and disodium hydrogen orthophosphate (347mg, 1.0mmol) were added to a solution of the unsaturated hydrazone (184) (102mg, 0.44mmol) in dichloromethane (15ml) at 0°C under an atmosphere of nitrogen. After stirring the reaction mixture for 8h the reaction mixture was poured

into aqueous sodium sulphite (10% solution; 25ml) and extracted with dichloromethane (3x25ml). The combined extracts were washed with sodium bicarbonate, dried and evaporated. Column chromatography of the residue gave (i), starting material (184) (25mg, 25%); (ii), *the ethoxycarbonylhydrazone of 3a,4-epoxy-7a-methyl-3a,4,5,7a-tetrahydro-1H-inden-1-one* (198) (24mg, 22%) as a solid m.p. 165-167°C (carbon tetrachloride), (Found: M^+ 248.1165. $C_{13}H_{16}N_2O_3$ requires M 248.1161); $\nu_{\max.}$ (CHCl₃) 3395, 2935, 1735, 1493 and 1340cm⁻¹; δ_H (90MHz, CDCl₃) 1.31(3H, s, 7a-CH₃), 1.33(3H, t, J 7Hz, CO₂CH₂CH₃), 2.55(2H, m, 2xH-5), 3.45(1H, m, H-4), 4.48(2H, qt, J 7Hz, CO₂CH₂CH₃), 5.5(1H, m, H-6), 5.97(1H, m, H-7), 6.37(1H, d, $J_{2,3}$ 6.0Hz, H-2), 6.74(1H, d, $J_{2,3}$ 6.0Hz, H-3) and 8.18(1H, br. signal, N-H); m/z 248(M^+), 233, 219, 202, 175, 160 and 144; and (iii), *the ethoxycarbonylhydrazone of 6,7-epoxy-7a-methyl-5,6,7,7a-tetrahydro-1H-inden-1-one* (195) (19mg, 17%) as a solid m.p. 177-180°C (carbon tetrachloride), (Found: M^+ 248.1158. $C_{13}H_{16}N_2O_3$ requires M 248.1161.) $\nu_{\max.}$ (CHCl₃) 3390, 1737, 1492 and 1340cm⁻¹; δ_H (CDCl₃) 1.30(3H, s, 7a-CH₃), 1.32(3H, t, J 6.8Hz, CO₂CH₂CH₃), 2.55-2.85(2H, m, 2xH-5), 3.30(1H, m, H-6), 3.70(1H, d, J 4.2Hz, H-7), 4.27(2H, qt, J 6.8Hz, CO₂CH₂CH₃), 5.52(1H, d, J 5.4Hz, H-4), 6.42(1H, d, $J_{2,3}$ 5.4Hz, H-2), 6.83(1H, d, $J_{2,3}$ 5.4Hz, H-3) and 8.19(1H, br. signal, N-H); m/z 248(M^+), 233, 219, 202, 175, 160 and 144.

12. Attempted condensation of the diketone (199) with hydrazine hydrate

Hydrazine hydrate (0.03ml, 0.6mmol) and toluene-4-sulphonic acid (20mg) was added to a solution of the diketone (199) (91mg,

0.55mmol) in dry benzene (12ml), under a nitrogen atmosphere.

The reaction mixture was refluxed with a Dean and Stark trap for 8h. Hydrazine hydrate (0.01ml, 0.2mmol) was again added and refluxing continued for a further 2h before the solvent was removed. Column chromatography of the residue yielded no identifiable product.

3.2.2 Ring Closure Route to the 1-Aza[10]annulene (95)

1. Reaction of 5,7a-dihydro-7a-methyl-1H-inden-1-one (106) with trimethylsilyl cyanide¹⁰⁰

Trimethylsilyl cyanide (0.224g, 2.5mmol) was added to the trienone (106) (0.30g, 2.05mmol) containing a catalytic amount of dry zinc iodide. The reaction mixture was stirred at room temperature under nitrogen for 8h after which time the excess trimethylsilyl cyanide was removed. Distillation of the residue at 125–130°C/0.6mbar (Kugelrohr) gave (7a α)-5,7a-dihydro-1 β -cyano-7a-methyl-1 α -trimethylsiloxy-1H-indene (208) (0.48g, 95%), $\nu_{\text{max.}}$ (neat) 2980, 2235, 1455, 1347, 1260, 1165, 1117 and 1055cm⁻¹; δ_{H} (CDCl₃) 0.26(9H, s, Si(CH₃)₃), 1.04(3H, s, 7a-CH₃), 2.75(2H, m, CH₂), 5.74(1H, m, becomes a singlet on irradiation at δ 2.75, H-4), 5.75(1H, d, $J_{2,3}$ 5.8Hz, irradiation at δ 6.41 removes coupling, H-2 or H-3), 5.87(1H, m, becomes a doublet on irradiation at δ 2.75, $J_{6,7}$ 10Hz, H-6) 6.06(1H, dt, $J_{6,7}$ 10Hz, $J_{5,7}$ 1.7Hz, smaller coupling removed on irradiation at δ 2.75, H-7) and 6.41(1H, d, $J_{2,3}$ 5.8Hz, H-2 or H-3); m/z 245(M^+) 230, 215, 146 and 131.

2. Reduction of the trimethylsilyl cyanohydrin derivative (208)¹⁰⁰

The cyanohydrin derivative (208) (0.20g, 0.82mmol) in dry ether (5ml) was added to a suspension of lithium aluminium hydride (50mg, 1.3mmol) in dry ether (5ml). The reaction mixture was stirred at room temperature under nitrogen until t.l.c. analysis indicated the absence of starting material. At this point sufficient water, to destroy the excess lithium aluminium hydride, was added dropwise. The solution was filtered and evaporated to give (7 α)-1 β -aminomethyl-5,7a-dihydro-1 α -hydroxy-7a-methyl-1H-indene (209) (0.11g, 76%) as an oil, (Found: M^+ 174.0915. $C_{11}H_{12}NO$ requires M 174.0919), $\nu_{\max}$. (Nujol) 3355, 3295, 1600, 1210, 1142 and 965cm^{-1} ; δ_{H} (CDCl_3) 1.14(3H, s, 7a- CH_3), 2.35-2.9(6H, m), 5.5(1H, m, H-4), 5.76(1H, d, $J_{2,3}$ 6.5Hz, H-2 or H-3), 5.77(1H, m, H-6), 5.94(1H, d, $J_{6,7}$ 9.8Hz, H-7) and 6.26(1H, d, $J_{2,3}$ 6.5Hz, H-3 or H-2); m/z 174(M^+), 160, 147 and 129. The stereochemistry was assigned on the basis of an n.O.e. difference experiment. Irradiation at δ 1.14 showed no enhancement of the methylene signals.

3. 7-Methoxy-7a-methyl-2,3,5,7a-tetrahydro-1H-inden-1-one (107)

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A solution of 7-methoxy-1-indanone (5g, 0.03mol) and *t*-butanol (4.13g, 0.066mol) in dry THF (40ml) was added dropwise to a solution of potassium (3.54g, 0.09 gatom) in liquid ammonia (300ml) at -78°C under nitrogen. After stirring for 0.5h, lithium bromide (7.91g, 0.09mol) in THF (40ml) was added and stirring was continued for 0.5h. This was followed by the simultaneous addition of 50% aqueous THF (50ml) and iodomethane (4.73g, 0.033mol). The ammonia was allowed to evaporate overnight and water (250ml) was added. The mixture

was extracted with ether (3x300ml), and the combined extracts dried and evaporated. The residue was subjected to column chromatography (petrol/ether) to give the title compound (107) (2.6g, 48%) as a colourless oil, δ_{H} (90MHz, CDCl_3) 1.35(3H, s, 7a- CH_3), 2.1-2.95 (6H, m), 3.65(3H, s, OCH_3), 4.73(1H, m, H-6) and 5.78(1H, m, H-4). T.l.c. analysis was identical to an authentic sample⁵⁸.

4. 5,7a-Dihydro-7-methoxy-7a-methyl-1H-inden-1-one (108)

Method A

The dienone (107) (275mg, 1.54mmol) in dry THF (5ml) was added to a solution of lithium di-isopropylamide [prepared from di-isopropylamine (0.25ml, 1.79 mmol) in dry THF (25ml) and *n*-butyl lithium (1.3ml, 1.4M solution; 1.82mmol)] at -78°C under nitrogen. The solution was allowed to stir for 0.5h, after which time phenylselenyl chloride (0.35g, 1.82mmol) in dry THF (5ml) was added. The reaction mixture was allowed to warm to room temperature and quenched with water (5ml). The solution was then poured into water (25ml) and extracted with ether (3x30ml). The combined extracts were dried and evaporated to give the crude product mixture.

The crude product was dissolved in THF (20ml) and the solution cooled to -10°C . *m*-Chloroperoxybenzoic acid (0.393g, 80% pure material; 1.82mmol) was added in portions such that the temperature of the solution remained at -10°C . The reaction mixture was then stirred for 0.5h after which time diethylamine was added and the cooling bath removed. The solution was poured into water (20ml) and extracted with ether (3x25ml). The combined extracts were washed with aqueous sodium bicarbonate (10% solution; 20ml), dried

and evaporated. The residue was subjected to column chromatography (petrol/ether) to give (i), 5,7a-dihydro-7-methoxy-7a-methyl-2-phenyl-seleno-1H-inden-1-one (109) (110mg, 22%) as an oil, $\nu_{\max.}$ (neat) 2920, 1705, 1660, 1630, 1435, 1225 and 1118cm^{-1} ; δ_{H} (90MHz, CDCl_3) 1.39(3H, s, 7a- CH_3), 2.72-2.94(2H, m, 2xH-5), 3.57(3H, s, OCH_3), 4.60 (1H, m, H-6), 5.76(1H, m, H-4), 6.98(1H, s, H-3), 7.2-7.42(3H, m, Ph-H) and 7.57(2H, m, o-Ph-H); m/z 332 (M^+), 330, 178 and 135; and (ii), the title compound (108) (65mg, 24%) as an oily solid, $\nu_{\max.}$ (CCl_4) 2930, 1718, 1670, 1635, 1450, 1344, 1230 and 1125cm^{-1} ; δ_{H} (90MHz, CDCl_3) 1.36(3H, s, 7a- CH_3), 2.84-3.02(2H, m, 2xH-5), 3.60(3H, s, OCH_3), 4.63(1H, dd, $J_{4,5} 4.5\text{Hz}$, $J_{3,4} 3\text{Hz}$, H-6), 5.98(1H, d, $J_{2,3} 5.5\text{Hz}$, H-2), 6.05 (1H, m, H-4) and 7.63(1H, d, $J_{2,3} 5.5\text{Hz}$, H-3); m/z 176 (M^+), 161 and 83. Hydrolysis (1.2M hydrochloric acid) gave the dienedione (228) (see Section 3.2.3, p. 211).

Method B

Dienone (107) (2.15g, 0.012mol) was reacted in the manner described in Method A except that only 1.1 equivalents of both LDA and phenylselenenyl chloride were used. Column chromatography gave (i) the selenated trienone (109) (0.4g, 10%) and (ii), the title compound (108) (0.22g, 10.5%).

Method C

The dienone (107) (4.0g, 22.5mmol) in dry THF (20ml) was added to a solution of lithium di-isopropylamide [prepared from di-isopropylamine (2.49g, 24.7mmol) in dry THF (230ml) and *n*-butyl lithium 16ml, 1.55M solution; 24.7mmol)] at -78°C under an atmosphere of nitrogen. The solution was allowed to stir for 0.5h after which

time it was cooled to -90°C and phenylselenenyl chloride (4.76g, 24.75 mmol) in THF (20ml) was added. The reaction mixture was allowed to warm to -35°C at which temperature water (5ml) was added. The solution was then poured into water (100ml) and extracted with ether (3x150ml). The combined extracts were dried and evaporated to give the crude selenide. This was oxidised using the procedure described in Method A. Column chromatography of the resulting mixture gave the methoxy trienone (108) (1.37g, 35%).

Method D

To a solution of dry sodium iodide (1.05g, 7mmol) in dry acetonitrile (50ml) was added trimethylsilyl chloride (0.89ml, 7mmol) under an atmosphere of nitrogen. This was followed by the addition of triethylamine (0.98ml, 7mmol) and dienone (107) (1.0g, 5.6mmol). The reaction mixture was heated to 40°C and kept at this temperature for 1h. After this time the product was extracted with petrol (3x 50ml) and the combined extracts evaporated. The residue was distilled (Kugelrohr) to give 3a,6-dihydro-4-methoxy-3a-methyl-3-trimethylsiloxy-1*H*-indene (960mg, 68%).

The trimethylsilyl ether was dissolved in dry THF (20ml) and the solution cooled to -78°C under nitrogen. Phenylselenenyl bromide [from diphenyl diselenide (0.66g, 2.11mmol) and bromine (0.338g, 2.11 mmol)] in dry THF (10ml) was added in a dropwise fashion and the reaction mixture then allowed to stir at -78°C for 10min. The solution was allowed to warm to room temperature over a period of 0.5h. The reaction mixture was extracted and the crude product oxidised in the manner described in Method A. Column chromatography of the resulting mixture gave the methoxy trienone (108) (115mg, 11.5% from dienone (107)).

5. (7 α)-1 β -Cyano-5,7 α -dihydro-7-methoxy-7 α -methyl-1 α -trimethyl-siloxy-1H-indene (213)

Trimethylsilyl cyanide (0.713g, 0.96ml, 7.18mmol) was added with stirring to the trienone (108) (1.15g, 6.53mmol) containing a catalytic amount of zinc iodide. The reaction mixture was allowed to stir under nitrogen for 12h and this was followed by the removal of the excess trimethylsilyl cyanide *in vacuo*. Distillation of the reaction mixture at 130°C/0.25mmHg (Kugelrohr) gave *the title compound* (213) (1.51g, 84%), (Found: C, 64.85; H, 7.59; N, 4.63. C₁₅H₂₁NO₂Si requires C, 65.35; H, 7.69, N, 5.09%), $\nu_{\max}$. (neat) 2970, 2240, 1685, 1653, 1455, 1375, 1258 and 1230cm⁻¹; δ_{H} (CDCl₃) 0.28(9H, s, Si(CH₃)₃), 1.21(3H, s, 7 α -CH₃), 2.89(2H, m, CH₂), 3.62(3H, s, OCH₃), 4.7(1H, t, $J_{5,6}$ 3.6Hz, H-6), 5.65(2H, m, decoupling at δ 6.37 simplifies signal, H-4 and H-3) and 6.37(1H, d, $J_{2,3}$ 6.2Hz, H-2); m/z 275 (M^+), 274, 190, 162, 147 and 103.

6. (7 α)-1 β -Aminomethyl-5,7 α -dihydro-1 α -hydroxy-7-methoxy-7 α -methyl-1H-indene (205)

The trimethylsilyl cyanohydrin derivative (213) (0.313g, 1.14mmol) in ether (5ml) was added to a suspension of lithium aluminium hydride (0.10g, 2.6mmol) in ether (15ml) under nitrogen. The reaction mixture was stirred for 1h and water was then added dropwise to destroy the excess lithium aluminium hydride. The solution was then filtered, dried and evaporated to give *the title compound* (205) (0.2g, 87%), $\nu_{\max}$. (neat) 3370, 2940, 1682, 1647, 1450 and 1225cm⁻¹; δ_{H} (90MHz, CDCl₃) 1.29(3H, s, 7 α -CH₃), 2.2-3.3(6H, m), 3.55(3H, s, OMe), 4.12(1H, t, $J_{5,6}$ 3.7Hz, H-6), 5.45(1H, t, $J_{4,5}$ 3.7Hz,

H-4), 5.76(1H, d, $J_{2,3}$ 6Hz, H-3) and 6.22(1H, d, $J_{2,3}$ 6Hz, H-2);
 m/z 177(M^+ -30), 159 and 147.

7. Attempted hydrolysis of the enol ether (205)

a. Using *p*-toluene sulphonic acid

The amino alcohol (205) (0.04g, 0.19mmol) was dissolved in benzene (3ml) and *p*-toluenesulphonic acid (0.054g, 0.29mmol) and water (1 drop) was added. The reaction mixture was refluxed under nitrogen for 0.5h before a Dean and Stark trap was fitted. Refluxing was continued for a further 0.5h and the solvent then removed. The ^1H n.m.r. spectrum of the residue indicated the presence of starting material and none of the desired product could be observed.

b. Using dilute hydrochloric acid

Hydrochloric acid (0.1M; 20ml) was added to a solution of the amino alcohol (205) (205mg, 1mmol) in ether (40ml). The reaction mixture was stirred vigorously for 2h. The layers were then separated and the aqueous layer neutralised using sodium bicarbonate. The solution was then extracted with dichloromethane (3x50ml). The ether and dichloromethane extracts were combined, dried and evaporated to give 2a-*hydroxy*-7b-*methyl*-2a,6,7,7b-*tetrahydro*-2H-*cyclopent* [cd] *indole* (207) (0.154g, 89%) as a crystalline solid m.p. 148-151°C (from dichloromethane), (Found: C, 75.62; H, 7.50; N, 8.01. $\text{C}_{11}\text{H}_{13}\text{NO}$ requires C, 75.40; H, 7.48; N, 7.99%), ν_{max} . (Nujol) 3110, 1645, 1294, 1240, 1140, 1060 and 1035 cm^{-1} ; λ_{max} . (EtOH) 239.5nm (log ϵ 4.02); δ_{H} (CDCl_3) 1.24(3H, s, 7b-Me), 2.29-2.88(4H, m), 3.0(1H, br. signal, D_2O exch., O-H), 4.02(2H, m, irradiation at δ 2.75 gives an AB qt.,

$J_{2,2}$ 16.5Hz, 2xH-2), 5.51(1H, dd, $J_{5,6}$ 6.8Hz, $J_{5,6}$ 2.3Hz, H-5), 5.88 (1H, d, $J_{3,4}$ 5.7Hz, H-3 or H-4) and 6.16(1H, d, $J_{3,4}$ 5.7Hz, H-3 or H-4); δ_C (CDCl₃) 12.7(7b-CH₃), 23.3(C-6), 25.8(C-7), 64.4(C-7b), 76.5(C-2), 90.7(C-2a), 116.9 (olefinic C-H), 130.9 (olefinic C-H), 138.0 (olefinic C-H), 153.2 (C-4a) and 181.6(C-7a); m/z 175(M^+), 160 and 146.

8. Attempted dehydrogenation of the tricyclic imine (207)

a. Using DDQ¹⁰⁶

The tricyclic imine (207) (9mg, 0.05mmol) was dissolved in benzene (3ml) and DDQ (12mg, 0.05mmol) was added. The reaction mixture was refluxed under nitrogen for 2.5h and the solvent then removed. This resulted in an insoluble brown residue which could not be identified.

b. Using benzeneseleninic anhydride (BSA)¹⁰⁵

The tricyclic imine (207) (21mg, 0.12mmol) was dissolved in chlorobenzene (3ml) and heated under an atmosphere of nitrogen to 100°C. The BSA (48mg, 0.13mmol) was added and the reaction mixture stirred for 5 mins. The solution was cooled and chloroform was added. After washing with 5% aqueous potassium hydroxide solution (15ml) the chloroform extract was dried and evaporated. The residue was subjected to ¹H n.m.r. analysis and this showed no recognisable peaks.

c. via a selenation-oxidation procedure

n-Butyl lithium (0.21ml of a 1.5M solution, 0.31mmol) was added to a solution of the tricyclic imine (207) (25mg, 0.14mmol)

in dry THF (5ml) at -78°C under an atmosphere of nitrogen. The solution was allowed to warm to -10°C and kept at this temperature for 0.5h. The reaction mixture was then cooled to -80°C and phenylselenenyl chloride (33mg, 0.17mmol) in dry THF (0.5ml) was added. After stirring for 10 mins water (0.5ml) was added and the solution allowed to warm to room temperature. After pouring into water (10ml) and extracting with chloroform (3x15ml) the combined extracts were dried and evaporated. The residue was subjected to column chromatography on alumina to give starting material (13mg, 52%).

9. Attempted O-methylation of the tricyclic imine (207)

a. Using sodium hydride followed by methyl iodide

The tricyclic imine (207) (21mg, 0.12mmol) was added to a suspension of sodium hydride (8mg, 0.33mmol) in dry THF (5ml) and stirred at room temperature under nitrogen for 0.75h. Methyl iodide (45mg, 0.32mmol) was added and stirring continued for 0.5h. The reaction mixture was poured into water (10ml) and extracted with ether (3x15ml). The combined extracts were dried and evaporated. The residue was subjected to ^1H n.m.r. analysis which only indicated the presence of starting material.

b. Using Dimsyl-sodium followed by methyl iodide

Sodium hydride (12mg, 0.5mmol) was added to DMSO (5ml) and heated at $60-65^{\circ}\text{C}$ (oil bath temperature) under an atmosphere of nitrogen for 1h. The solution was cooled to room temperature and the tricyclic imine (207) (30mg, 0.17mmol) was added. The reaction mixture was stirred for 0.5h before methyl iodide (45mg, 0.32mmol) was added and stirring continued for a further 0.5h. The reaction

mixture was poured into water and extracted with ether (3x20ml). The combined extracts were dried and evaporated. The absence of any significant olefinic resonances in the ^1H n.m.r. spectrum of the residue caused the reaction to be abandoned.

c. Using methyl fluorosulphonate

The tricyclic imine (207) (62mg, 0.35mmol) was dissolved in dry DME (5ml) and stirred at room temperature under nitrogen. Methyl fluorosulphonate (48mg, 0.42mmol) was added and the reaction mixture allowed to stir for 24h. Triethylamine (0.1ml) was added and the reaction mixture poured into water before being extracted with dichloromethane (3x20ml). The combined extracts were dried and evaporated. T.l.c. analysis of the residue indicated a complex mixture of products and the reaction was not pursued.

10. Attempted acetylation of the tricyclic imine (207)

a. Using acetic anhydride and trimethylsilyl chloride¹⁰⁸

The tricyclic imine (207) (0.144g, 0.82mmol) was dissolved in acetic anhydride (6ml) and trimethylsilyl chloride (0.358g, 3.3mmol) was added under nitrogen. The reaction mixture was stirred at room temperature for 2h after which time the excess acetic anhydride was removed *in vacuo*. The residue was subjected to column chromatography (methanol/ether) to give (7a α)-N-acetyl-1 β -aminomethyl-1 α -hydroxy-7a-methyl-7-oxo-5,6,7,7a-tetrahydro-1H-indene (225) (0.101g, 52%) as a crystalline solid m.p. 138-140 $^{\circ}\text{C}$ (ether), (Found: C, 66.73; H, 7.35; N, 5.97. $\text{C}_{13}\text{H}_{17}\text{NO}_3$ requires C, 66.36; H, 7.28; N, 5.95%); ν_{max} . (Nujol) 3405, 3220, 1704, 1654, 1558, 1300,

1210 and 1170 cm^{-1} ; $\lambda_{\text{max.}}$ (EtOH) 238.5nm ($\log \epsilon$ 4.14); δ_{H} (CDCl_3) 1.28 (3H, s, 7a- CH_3), 2.0 (3H, s, COCH_3) 2.2–2.7 (4H, m), 3.25 (1H, dd, $J_{1',1'}$ 13.9Hz, $J_{1',2'}$ 3.7Hz, irradiation at δ 6.20 removes the smaller coupling, H-1'), 3.36 (1H, br.s., D_2O exch., O-H), 3.42 (1H, dd, $J_{1',1'}$ 13.9Hz, $J_{1',2'}$ 7.4Hz, irradiation at δ 6.20 removes the smaller coupling, H-1'), 5.80 (2H, m, H-4, H-2 or H-3), 6.20 (1H, br. signal, N-H) and 6.23 (1H, d, $J_{2,3}$ 6.2Hz, H-2 or H-3); δ_{C} (CDCl_3) 21.1 (7a- CH_3), 22.8 (C-5 or C-6), 23.2 (C-5 or C-6), 39.3 (COCH_3), 46.2 (C-1'), 59.7 (C-7a), 85.4 (C-1), 117.0 (olefinic C-H), 130.4 (olefinic C-H), 138.2 (olefinic C-H), 147.8 (C-3a), 171.1 (COCH_3) and 214.7 (C-7); m/z 235 (M^+), 217, 176, 163 and 121.

b. Using acetic anhydride in pyridine

The tricyclic imine (207) (42mg, 0.24mmol) was dissolved in pyridine (2ml) and a few crystals of 4-dimethylaminopyridine were added. The solution was stirred at room temperature under nitrogen and acetic anhydride (37mg, 0.36mmol) was added. After stirring for 2.5h, the solution was poured into water and extracted using dichloromethane (3x20ml). The combined extracts were washed with dilute hydrochloric acid (0.1M; 10ml) and sodium bicarbonate. The solvent was then removed *in vacuo* to give an oily residue which was indicated by t.l.c. to be a complex mixture of products. Although p.l.c. was attempted, none of the components could be isolated in sufficient amount to allow identification.

11. Attempted mesylation of the tricyclic imine (207)

The tricyclic imine (207) (50mg, 0.29mmol) was dissolved in

pyridine (1ml) and methanesulphonyl chloride (0.33g, 2.9mmol) was added. The reaction mixture was stirred under nitrogen for 1h at room temperature after which time water was added. The solution was extracted using dichloromethane (3x10ml) and the combined extracts dried and evaporated. The residue was subjected to column chromatography (ether/methanol) and gave a fraction (10mg) which from a consideration of its ^1H n.m.r. spectrum was a mixture of two compounds. The low yield and inseparable nature of the products led to this experiment being abandoned.

12. Reaction of the tricyclic imine (207) with methyl chloroformate

The tricyclic imine (207) (50mg, 0.29mmol) was dissolved in dry THF (10ml) and triethylamine (35mg, 0.35mmol) and methyl chloroformate (33mg, 0.35mmol) were added. The reaction mixture was stirred for 0.25h and the solvent then removed. The residue was subjected to column chromatography (ether/methanol) to give (i) *methyl 2a-hydroxy-7b-methyl-2,2a,6,7b-tetrahydro-1H-cyclopent[cd]indole-1-carboxylate* (217) (19mg, 28%), $\nu_{\text{max.}}(\text{CHCl}_3)$ 3555, 2935, 1700, 1445, 1383, 1370, 1330 and 1138cm^{-1} ; $\delta_{\text{H}}(90\text{MHz}, \text{CDCl}_3)$ 1.15 (3H, s, 7b-CH₃), 2.02(1H, br.s., O-H), 2.8-3.1(2H, m, 2xH-6) 3.56 (1H, d, $J_{2,2}$ 12Hz, H-2), 3.74(3H, s, CO₂CH₃), 4.07(1H, d, $J_{2,2}$ 12Hz, H-2), 5.63-5.81(2H, m, H-5 and H-7), 5.88(1H, d, $J_{3,4}$ 6Hz, H-3 or H-4) and 6.30(1H, d, $J_{3,4}$ 6Hz, H-3 or H-4); m/z 233(M^+), 173, 146, and 121; and (ii) a fraction (16mg) which from ^1H n.m.r. analysis was observed to be a mixture of products.

13. 7b-Methyl-2a,6,7,7b-tetrahydro-2a-trimethylsiloxy-2H-cyclopent-[cd]indole (218)

Trimethylsilyl chloride (0.214ml, 1.3mmol) and triethylamine

(0.24ml, 1.7mmol), were added to a solution of the tricyclic imine (207) (227mg, 1.3mmol) in dry THF (25ml) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature overnight after which time it was filtered through a celite pack and the solvent was removed. The residue was subjected to column chromatography to give *the title compound* (256mg, 80%), $\nu_{\text{max.}}$ (neat) 2960, 2940, 1650, 1455, 1350, 1255, 1147, 1112 and 1077 cm^{-1} ; δ_{H} (CDCl_3) 0.08(9H, s, OSiMe_3), 1.15(3H, s, 7b-Me), 2.2–2.82(4H, m, 2xH-6 and 2xH-7), 3.97(2H, d, 2xH-2), 5.41(1H, dd, $J_{5,6}$ 7.1Hz, $J_{5,6}$ 2.9Hz, H-5), 5.88(1H, d, $J_{3,4}$ 5.6Hz, H-4) and 6.06(1H, d, $J_{3,4}$ 5.6Hz, H-3); m/z 247(M^+), 232 and 219.

14. Selenation of the tricyclic imine (218)

Method A

The tricyclic imine (218) (50mg, 0.2mmol) was dissolved in dry THF(10ml) and cooled to -78°C under nitrogen. *n*-Butyl lithium (0.15ml of a 1.45M solution, 0.22mmol) was added and the solution stirred for 15min. The reaction was quenched using phenylselenenyl chloride (43mg, 0.22mmol) in dry THF(2ml) and the resulting solution was allowed to warm to room temperature. Water was then added and the products extracted using dichloromethane (3x20ml). The combined extracts were dried and evaporated and the resulting residue subjected to column chromatography to give (i) 7,7-bis-phenylseleno-7b-methyl-2a,6,7,7b-tetrahydro-2a-trimethylsiloxy-2H-cyclopent [cd] indole (220) (23mg, 20%), $\nu_{\text{max.}}$ (CCl_4) 2960, 1625, 1475, 1452, 1437, 1250 and 1147 cm^{-1} ; δ_{H} (60MHz, CDCl_3) 0.09(9H, s, OSiMe_3), 1.22(3H, s, 7b-Me), 2.62–3.04(2H, m, 2xH-6), 4.0(2H, m, 2xH-2), 5.25(1H, dd,

$J_{5,6}$ 8Hz, $J_{5,6}$ 3Hz, H-5), 5.88(1H, d, $J_{3,4}$ 6Hz, H-3 or H-4), 6.04 (1H, d, $J_{3,4}$ 6Hz, H-3 or H-4), 7.3(6H, m, Ph-H) and 7.65(4H, m, *ortho* Ph-H); m/z 559(M^+) 557, 402, 400 and 245; and (ii) 7b-methyl-7-phenyl-seleno-2a,6,7,7b-tetrahydro-2a-trimethylsiloxy-2H-cyclopent[cd]indole (219) (20mg, 25%) as a 2:1 mixture of isomers; $\nu_{\max.}$ (neat) 2960, 1635, 1582, 1480, 1438, 1350, 1255, 1152, 1115 and 1083 cm^{-1} ; δ_{H} (CDCl_3) major component, 0.15 (9H, s, OSiMe_3), 1.34(3H, s, CH_3) 2.72–2.88 (2H, m, 2xH-6), 4.06(2H, s, 2xH-2), 4.11(1H, m, H-7), 5.51(1H, dd, $J_{5,6}$ 7.1Hz, $J_{5,6}$ 3.7Hz, H-5), 5.97 (1H, d, $J_{3,4}$ 5.4Hz, H-3 or H-4), 6.14(1H, d, $J_{3,4}$ 5.4Hz, H-3 or H-4), 7.2–7.4(3H, m, Ar-H) and 7.64–7.73(2H, m, o-Ar-H); δ_{H} (CDCl_3) minor component 0.15(9H, s, OSiMe_3), 1.22(3H, s, 7b-Me), 2.63(1H, ddd, $J_{6,6'}$ 18.3Hz, $J_{5,6}$ 7.1Hz, $J_{6,7}$ 1.7Hz, H-6) 5.47(1H, dd, $J_{5,6}$ 7.1Hz, $J_{5,6'}$ 2.5Hz, H-5), 7.2–7.4(3H, m, Ar-H) and 7.55–7.62(2H, m, o-Ar-H); m/z for the mixture 403(M^+), 401, 313 and 312.

Method B

The tricyclic imine (218) (327mg, 1.32mmol) was dissolved in dry THF (45ml) and cooled to -78°C under nitrogen. Tetramethylethylenediamine (0.22ml, 1.5mmol) was added followed by *n*-butyllithium (0.97ml of a 1.5M solution, 1.46mmol). The reaction mixture was allowed to warm slowly to -45°C over a period of 30min and the temperature maintained between -45°C and -60°C for a further 30 min. After this period the solution was cooled to below -90°C before the addition of phenylselenenyl chloride (281mg, 1.45mmol) in dry THF (3ml). The resulting solution was allowed to warm to -35°C , water (1ml) was then added and the reaction mixture extracted using dichloromethane (3x50ml). The combined extracts were dried, evaporated and subjected

to column chromatography (petrol/ether) to give 7b-methyl-7-phenyl-seleno-2a,6,7,7b-tetrahydro-2a-trimethylsiloxy-2H-cyclopent[cd] indole (219) (315mg, 59%).

15. 2a, 7b-Dihydro-7b-methyl-7-phenylseleno-2a-trimethylsiloxy-2H-cyclopent[cd]indole

The *bis*-selenide (220) (79mg, 0.14mmol) was dissolved in dry THF (25ml) and the solution cooled to -10°C under nitrogen. *m*-CPBA (34mg, of 80% pure material; 0.16mmol) was added and the reaction mixture allowed to stir at this temperature for 0.5h. After this time diethylamine was added and the external cooling removed. The resulting solution was poured into water (40ml) and extracted with dichloromethane (3x30ml). The combined extracts were washed with aqueous sodium bicarbonate solution (30ml) before being dried and evaporated. Column chromatography of the residue gave *the title compound* as an oil (24mg, 42%), $\nu_{\text{max.}}$ (neat) 2960, 1660, 1615, 1478, 1440 and 1255cm^{-1} ; δ_{H} (CDCl₃) 0.14(9H, s, OSiMe₃), 1.02(3H, s, 7b-Me), 3.83(1H, d, $J_{2',2}$ 18.3Hz, H-2), 4.28(1H, d, $J_{2',2}$ 18.3Hz, H-2'), 5.68(1H, d, $J_{5,6}$ 5.2Hz, H-5), 6.32(1H, d, $J_{3,4}$ 5.2Hz, H-3 or H-4), 6.37(1H, d, $J_{3,4}$ 5.2Hz, H-3 or H-4), 6.40(1H, d, $J_{5,6}$ 5.2Hz, H-6), 7.30(3H, m, Ar-H) and 7.62(2H, m, *o*-Ar-H); m/z 401(M^+), 399 and 244.

16. 2a,7b-Dihydro-7b-methyl-2a-trimethylsiloxy-2H-cyclopent[cd]-indole (221)

The selenide (219) (315mg, 0.78mmol) was oxidised using the procedure described previously. Column chromatography of the residue gave *the title compound* (221) (79mg, 41%) as an oil; (Found: M^+ 245.1261. C₁₄H₁₉NOSi requires M 245.1259), $\nu_{\text{max.}}$ (neat)

2960, 1665, 1625, 1253, 1110 and 1073cm^{-1} ; $\lambda_{\text{max.}}(\text{EtOH})$ 343nm
 (log ϵ 3.46); $\delta_{\text{H}}(\text{CDCl}_3)$ 0.17(9H, s, OSiMe₃), 1.05(3H, s, 7b-Me),
 3.79(1H, d, J 17.9Hz, H-2), 4.25(1H, d, J 17.9Hz, H-2'), 5.77(1H, m, H-5),
 6.37(2H, m, H-6 and H-7) and 6.45(2H, m, H-3 and H-4); $\delta_{\text{C}}^{2.0}(\text{Si}(\text{CH}_3)_3)$,
 15.4(7b-CH₃), 61.4(C-7b), 69.9(C-2), 89.5(C-2a), 113.3 (olefinic-C)
 122.9 (olefinic-C), 130.9 (olefinic-C) 133.4 (olefinic-C), 141.5
 (olefinic-C), 159.2(C-4a) and 183.0(C-7a); m/z 245 (M^+), 230 and 157.

17. Attempted removal of the trimethylsilyl protecting group

a. Using potassium fluoride

The tricyclic imine (221) (29mg, 0.12mmol) was dissolved in aqueous THF (9ml; 1:2, H₂O:THF) and potassium fluoride (60mg) was added. The reaction mixture was stirred for 1h under nitrogen. Water (10ml) was then added and the mixture extracted using dichloromethane (3x15ml). The combined extracts were dried, evaporated and the resulting residue subjected to column chromatography. This resulted in the isolation of recovered starting material (8mg, 28%).

b. Using tetrabutylammonium fluoride at 0°C

The tricyclic imine (221) (8.8mg, 0.04mmol) was dissolved in dry THF (1ml) and cooled to 0°C under nitrogen. Tetrabutylammonium fluoride (0.01g, 0.04mmol) was added and caused an immediate darkening of the reaction mixture. After stirring for 20 min at 0°C the reaction was quenched using 10% aqueous ammonium chloride solution (0.5ml) and water (10ml) was then added. The solution was extracted with dichloromethane (3x10ml) and the combined extracts dried and

evaporated. ^1H n.m.r. analysis of the residue showed no sign of any olefinic or aromatic resonances and hence this reaction was not pursued.

c. Using tetrabutylammonium fluoride at -78°C

The tricyclic imine (221) (10mg, 0.041mmol) was dissolved in dry THF (3ml) and cooled to -78°C under nitrogen. Tetrabutylammonium fluoride (0.012g, 0.046mmol) was added and the reaction mixture stirred at -78°C for 1h. The solution was then quenched with 10% aqueous ammonium chloride and allowed to warm to room temperature. Water (20ml) was added and the solution extracted using dichloromethane (3x10 ml). The combined extracts were dried, evaporated and the residue analysed by ^1H n.m.r. spectroscopy which indicated only the presence of starting material. No other products could be observed and the reaction was not pursued.

d. Using 0.1M hydrochloric acid

The tricyclic imine (221) (6mg) was dissolved in THF (4.5ml) and aqueous hydrochloric acid (0.1M; 0.5ml) was added. The mixture was stirred at room temperature for 6h, after which time aqueous sodium bicarbonate (10% solution; 3ml) was added. The mixture was extracted with dichloromethane (3x10ml) and the combined extracts dried and evaporated. ^1H n.m.r. analysis of the residue did not show any recognisable signals and the reaction was abandoned.

e. Using toluene-4-sulphonic acid

The tricyclic imine (221) (9mg) was dissolved in benzene (3ml)

and a few crystals of toluene-4-sulphonic acid were added. The reaction mixture was refluxed for 3h. During the reaction a black oily deposit formed in the flask. The solvent was removed and the residue subjected to ^1H n.m.r. analysis. The absence of any olefinic or aromatic resonances in the spectrum led to this reaction being abandoned.

18. Attempted elimination of the elements of trimethylsilanol from the tricyclic imine (221)

a. Using trimethylsilyl trifluoromethanesulphonate

Trimethylsilyl trifluoromethanesulphonate (0.015ml, 0.08mmol) and triethylamine (0.011ml, 0.08mmol) were added to a solution of the tricyclic imine (221) (10mg, 0.041mmol) in dry DME (3ml). The reaction mixture was refluxed for 18h under nitrogen before being quenched with water (10ml). The mixture was extracted using dichloromethane (3x10ml) and the combined extracts dried and evaporated. Analysis of the residue using ^1H n.m.r. spectroscopy indicated the absence of any aromatic or olefinic protons hence the reaction was abandoned.

b. Using *t*-butyl lithium

t-Butyl lithium (0.078ml of a 2.6M solution, 0.2mmol) was added to a solution of the tricyclic imine (221) (10mg, 0.041mmol) in dry THF (3ml) at -78°C under nitrogen. The reaction mixture was allowed to warm to room temperature and then stirred for 2h. At the end of this period deuterium oxide (0.1ml) was added and the solution then poured into water (5ml). The mixture was extracted

with dichloromethane (3x5ml) and the combined extracts dried and evaporated. However, t.l.c. and ^1H n.m.r. analysis failed to indicate the presence of any identifiable products.

The reaction was repeated and the mixture allowed to stir for only 10min at -78°C after the addition of the *t*-butyl lithium before being quenched with deuterium oxide. The reaction was then worked up in the manner described previously. The residue was subjected to column chromatography but no identifiable product was eluted.

c. Using DBU

The tricyclic imine (221) (10mg, 0.041mmol) was dissolved in DBU (0.5ml) and heated under nitrogen at an oil bath temperature of 100°C . The mixture was stirred for 4h at this temperature before being subjected to t.l.c. and ^1H n.m.r. analysis. The absence of any resonance in the region upfield of tetramethylsilane, coupled with the lack of peaks in the olefinic and aromatic regions of the spectrum led to this reaction being abandoned.

d. Using F.V.P. conditions

The tricyclic imine (221) (21mg) was distilled at 0.4mmHg through a tube heated to 425°C containing a rod coated with alumina. ^1H n.m.r. analysis of the pyrolysate indicated the presence of aromatic and olefinic protons. The mass spectrum of the crude pyrolysate gave m/z 155, 154 and 127. Although p.l.c. was attempted, no identifiable product could be isolated.

19. Formation of 2a-acetoxy-7b-methyl-2a,6,7,7b-tetrahydro-2H-cyclopent[cd]indole (226)

The bicyclic ketone (225) (25mg, 0.1mmol) was added to a solution of toluene-4-sulphonic acid (22mg, 0.12mmol) in benzene (10ml) which had been refluxed under Dean and Stark conditions for 2h. After the addition of the ketone (225) the reaction mixture was refluxed for a further 6h. The solvent was then removed, the residue subjected to column chromatography on alumina to give *the title compound* (226) (15mg, 65%) as an oil; (Found M^+ 217.1103. $C_{13}H_{15}NO_2$ requires M 217.1103); $\nu_{\max.}$ (CCl₄) 2935, 1737, 1650, 1450, 1368, 1238, 1205 and 1045 cm^{-1} ; $\lambda_{\max.}$ (EtOH) 237nm; δ_H (CDCl₃) 1.35 (3H, s, 7b-Me), 2.07 (3H, s, -OC(O)CH₃), 2.33-2.60 (2H, m, 2xH-6), 2.65-2.90 (2H, m, 2xH-7), 4.14 (1H, dd, $J_{2,2'}$ 17.2Hz, $J_{2,7}$ 2.6Hz, H-2), 4.34 (1H, dd, $J_{2',2}$ 17.2Hz, $J_{2',7}$ 1.8Hz, H-2'), 5.54 (1H, dd, $J_{5,6}$ 7.0Hz, $J_{5,6'}$ 2.9Hz, H-5), 6.22 (1H, d, $J_{3,4}$ 5.7Hz, H-3 or H-4) and 6.31 (1H, d, $J_{3,4}$ 5.7Hz, H-3 or H-4); m/z 217 (M^+), 191, 174 and 160.

20. Attempted dehydrogenation of the imine (226)

The tricyclic imine (226) (15mg, 0.07mmol) was dissolved in dry benzene (2ml) and DDQ (18mg, 0.08mmol) was added. The reaction mixture was refluxed for 3h and the solvent then removed. This gave an intractable residue from which no product could be isolated.

21. Attempted dehydration of the tricyclic alcohol (207)

a. Using triphenylphosphine and carbon tetrachloride¹¹³

A solution of the tricyclic alcohol (207) (30mg, 0.17mmol) was treated with triphenylphosphine (54mg, 0.2mmol) and carbon

tetrachloride (33 μ l, 0.34mmol). The resulting mixture was refluxed under nitrogen for 29h after which time the solvent was removed. The residue was subjected to column chromatography on alumina to give starting material (16mg, 53%).

b. Using thionyl chloride in pyridine

The tricyclic alcohol (207) (58mg, 0.33mmol) was dissolved in pyridine and cooled to 0°C. Thionyl chloride (0.6ml, 8mmol) was added and the reaction stirred for 4h. The mixture was poured into water and extracted with ether. The aqueous layer was then neutralised and then re-extracted with ether. The combined extracts were dried, evaporated and the residue subjected to ^1H n.m.r. analysis. The absence of any recognisable olefinic peaks led to this reaction being abandoned.

c. Using toluene-4-sulphonic acid

A solution of the tricyclic alcohol (207) (33mg, 0.2mmol) in toluene (10ml) was treated with toluene-4-sulphonic acid (23mg, 0.12mmol) and the resulting solution refluxed for 7 days under Dean and Stark conditions. The reaction was monitored by t.l.c. which showed only the slow decomposition of starting material. ^1H n.m.r. analysis indicated the presence of starting material and no other significant peaks were observed.

3.2.3 Ring Closure Approach to the 2-Aza[10] annulene (96)

1. Hydrolysis of 5,7a-dihydro-7-methoxy-7a-methyl-1H-inden -1-one (108) using dilute hydrochloric acid

The trienone (108) (0.215g, 1.22mmol) was dissolved in THF (10ml) and hydrochloric acid (1.2M; 15ml) was added. The reaction mixture was stirred at room temperature for 0.5h after which time the solution was poured into water, neutralised using sodium bicarbonate, and extracted with ether. This gave 7a-methyl-5,6,7,7a-tetrahydro-1H-indene-1,7-dione (228) (0.137g, 69%) as a crystalline solid m.p. 81.5-82.5°C (from dichloromethane/petrol), (Found: C, 74.33; H, 6.25. $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21%); $\nu_{\max.}(CCl_4)$ 2940, 1738, 1705, 1453, 1340 and 1185 cm^{-1} ; $\lambda_{\max.}(EtOH)$ 285nm (log ϵ 3.90); $\delta_H(CDCl_3, 90MHz)$ 1.48(3H, s, 7a-Me), 2.15-2.95(4H, m), 6.09(1H, d, $J_{2,3}$ 5.8Hz, H-2), 6.34(1H, dd, $J_{4,5}$ 3.7, 6.4Hz, H-4) and 7.72(1H, d, $J_{2,3}$ 5.8Hz, H-3); m/z 162(M^+), 134, 120, and 91.

2. Reaction of dienedione (228) with trimethylsilyl cyanide

To the dienedione (228) (0.137g, 0.85mmol) and dry zinc iodide (catalytic) was added trimethylsilyl cyanide (0.12ml, 0.90mmol) and the reaction mixture was stirred at room temperature under nitrogen for 1h. The excess trimethylsilyl cyanide was removed *in vacuo* and the residue distilled. The distillate was then subjected to column chromatography (petrol, ether) to give (7a α)-3 α ,7-dicyano-2,3,5,6,7,7a-hexahydro-7a-methyl-7-trimethylsiloxy-1H-inden -1-one (234) (70mg, 29%) as a crystalline solid m.p. 148-149°C (from ether) (Found: C, 62.51; H, 6.94; N, 9.72. $C_{15}H_{20}N_2O_2Si$ requires C, 62.43; H, 6.95; N, 9.71%), $\nu_{\max.}(Nujol)$ 2225, 1750, 1360, 1153 and 850 cm^{-1} ;

δ_{H} 0.30(9H, s, OSiMe₃), 1.44(3H, s, 7a-Me), 2.05(2H, m, 2xH-6), 2.46(2H, m, decoupling at δ 6.04 simplifies multiplet, 2xH-5), 2.73 (1H, dd, $J_{2\alpha,2\beta}$ 18.8, $J_{2\beta,3}$ 9.4Hz, decoupled at δ 3.86 removes smaller coupling, H-2 β) 2.90(1H, dd, $J_{2\alpha,2\beta}$ 18.8, $J_{2\alpha,3}$ 2.3Hz, decoupled at δ 3.86 removes smaller coupling, H-2 α), 3.86(1H, dd, $J_{2\alpha,3}$ 2.3 $J_{2\beta,3}$ 9.4Hz, H-3) and 6.04(1H, t, $J_{4,5}$ 3.1Hz, H-4); δ_{C} 1.2(t, SiMe₃), 18.8(qt, 7a-CH₃), 23.9(t, CH₂), 28.4(d, C-3), 31.6(t, CH₂), 41.0(t, C-2), 54.6(s, C-7b), 70.2(s, C-7), 119.3(s, CN), 120.2(s, CN), 127.1(d, C-4), 133.8(C-3a) and 209.0(s, C-1); m/z 288(M^+), 273, 260, 246, 232, 220 and 204.

3. Attempted elimination of the elements of hydrogen cyanide from the ketone (234)

a. Using triethylamine

The ketone (234) (20mg, 0.07mmol) was dissolved in benzene (1ml) and triethylamine (1ml) was added. After stirring the reaction mixture for 24h at room temperature under nitrogen, the solvent was removed to give the starting ketone (20mg, 100%).

b. Using DBU

The ketone (234) (20mg, 0.07mmol) was dissolved in DBU (1ml) and stirred at room temperature for 4h under nitrogen. This was followed by warming to 60°C for 3h. The reaction mixture was then subjected to column chromatography (petrol, ether) but no identifiable product was eluted.

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