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NEW METHODS FOR ALKALOID SYNTHESIS

GENERATION OF INDOLE-2, 3-DIQUINOMETHANES AS A ROUTE TO INDOLE ALKALOIDS.

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Abstract—The generation of an indole-2,3-quinodimethane intermediate and its use for the synthesis of indole alkaloids is described.

Many methods have been devised for the practical generation of so-called *ortho*-xylylene or quinodimethane intermediates (3), but they all suffer from not being readily, or indeed if at all, applicable to heteroaromatic systems (Scheme A). The benzocyclobutane method (1) when extended to heteroaromatic compounds such as pyridine, furan, thiophene, pyrrole and indole would necessitate the synthesis of a 4-membered ring fused to these heterocycles; a formidable task in itself, and when further combined with the regiochemical problems of either intermolecular or intramolecular cycloaddition reactions, it is hardly surprising that to date there are no examples where heterocyclic diquinomethane intermediates have been used for the synthesis of natural products.[1] The same considerations apply to construction and utilization of sulfone precursors (2) of diquinomethane intermediates (3) derived from heterocyclic systems.

We recently described a method of generating diquinomethane intermediates based upon the fluoride-ion induced fragmentation of a benzylsilane for the synthesis of 11α-hydroxyestrone 0-methylether (**4**→**5**→**6**).[2] Most importantly this reaction takes place at room tem-

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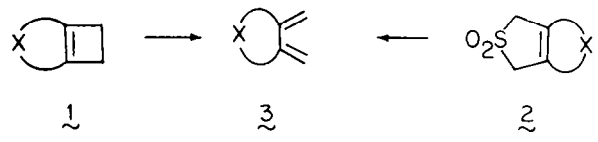
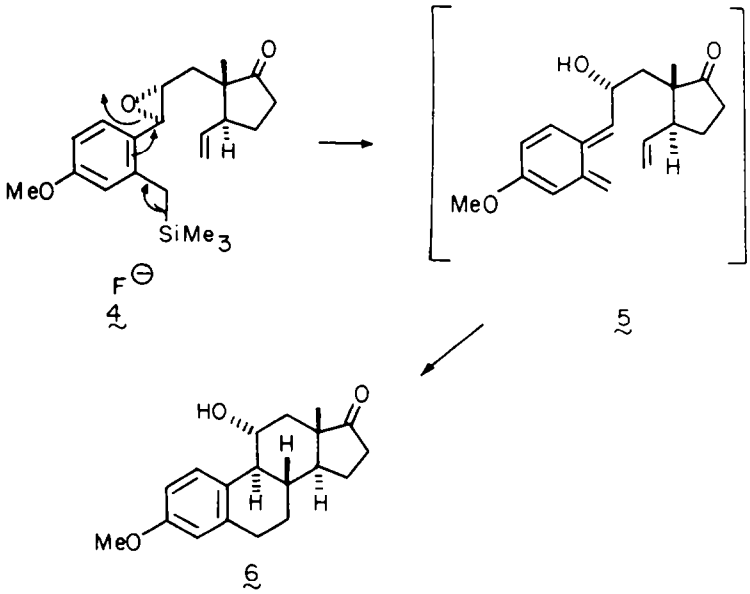


1 3 2

SCHEME A



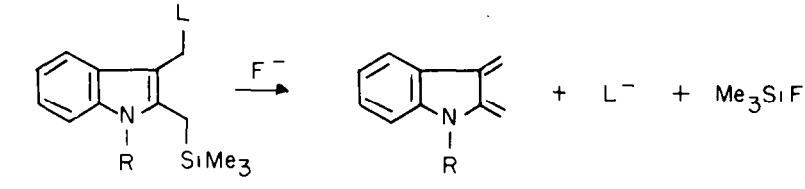
4 5 6

perature [contrast the thermal (200°) methods of generating quinodimethanes], and in keeping with many stereochemical observations, occurs predominately by an *exo*-intramolecular Diels–Alder reaction to give the *trans*-BC-ring fused steroid (**6**).

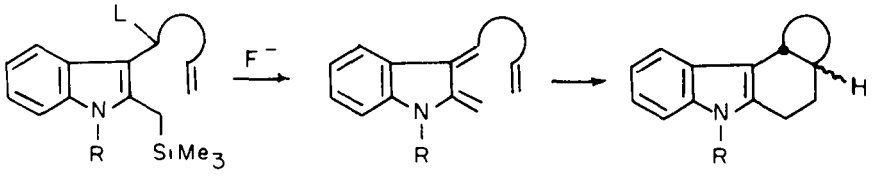
A particularly intriguing extension of this fluoride-ion induced benzylsilane fragmentation to generate quinodimethanes is the possibility of using this mild method to probe the synthesis of indole alkaloids via an indole-2, 3-quinodimethane intermediate. This previously unexplored strategy for indole alkaloid synthesis[3] is outlined in Scheme B and more specifically elaborated for an intramolecular system in Scheme C. To be of direct application to the synthesis of indole alkaloids, in particular those related to the Aspidosperma alkaloids, the carbon-side chain, containing the leaving group (L) and the C=C double bond, should also contain a N atom. The simplest way of doing this is to incorporate the leaving group, as a N atom, into the carbon-side chain attached to C-3 and to have the N atom present as an imine. In this way the plan reduces to Scheme D. Here we report the experimental implementation of this plan, that, while suggested by the organosilicon methodology alluded to above, does not in fact need the trimethylsilyl group to be successful.

It was decided to use the 4-methoxybenzenesulfonyl group to protect the indole N atom for two reasons. First, to remove any vinylogous amide character present in indole-3-carboxaldehyde derivatives, and secondly, to direct lithiation into the 2-position of the indole nucleus.[4] Indole-3-carboxaldehyde was treated with sodium hydride in glyme followed by 4-methoxybenzenesulfonyl chloride to give **7**. Conversion of **7** into the *t*-butylimine (**8**), and treatment with n-butyllithium in tetrahydrofuran at $-60°$ followed by quenching with methyl iodide gave, after chromatography, the 2-methylated indole (**9**) in 43% yield from **7**, m.p. 129–130°. The t-butylimine (**10**) on further treatment with n-butyllithium followed by trimethylsilylchloride, in an attempt to prepare the required 2-methyltrimethylsilyl system (**11**), gave, after chromatography, **12**, the product resulting from lithiation *ortho* to the aryl sulfonamide group and the formyl indole (**9**). In another effort to obtain **11** the 2-lithioindole derived from **8** was treated with HMPA and quenched with $CF_3SO_3CH_2SiMe_3$.[5] The ^1H NMR spectrum of the crude mixture suggested that the desired product was present (singlets at δ2.80 and 0.15) in approximately 25% yield, but even at this stage extensive desilylation had already occurred and the only product isolated, after chromatography, was **9** in 53% yield. Interestingly, when $CF_3SO_3CH_2SiMe_3$ was mixed with HMPA, the salt, $(Me_2N)_3\overset{+}{P}OCH_2SiMe_3\ CF_3SO_3^-$, precipitated. This salt is easily handled and provides a very convenient source of electrophilic–CH_2SiMe_3.

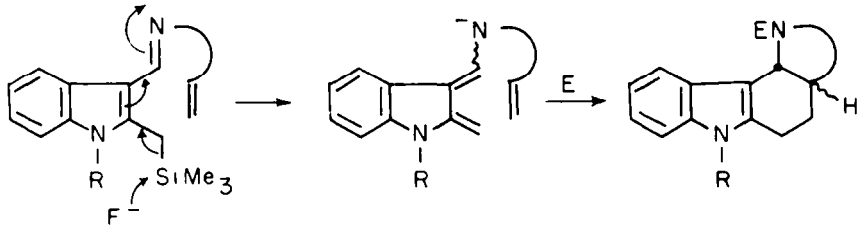
This extremely facile removal of the trimethylsilyl group suggested that the 2-methyltrimethylsilyl group is very acidic and that protodesilylation is proceeding via the desired 2, 3-quinodimethane intermediate, Scheme E. Before proceeding to the logical extension of this observation, namely the exclusion of the trimethylsilyl group, we conducted the following experiment. The aldehyde **7** was converted into the imine **13** by treatment with 4-pentenylamine.[6] Lithiation of **13** with *n*-butyllithium in tetrahydrofuran followed by addition of $CF_3SO_3CH_2SiMe_3$ gave the required compound **14** (δ2.87 and 0.11), in 75% yield, based upon the ^1H NMR spectrum of the crude mixture. The remainder of the mixture



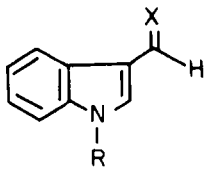
SCHEME B



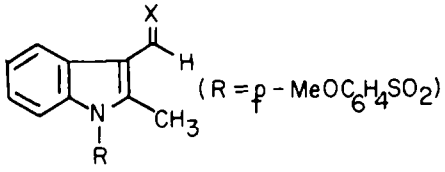
SCHEME C



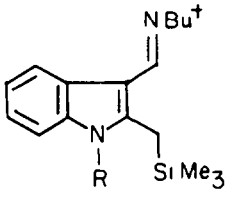
SCHEME D



7, X = O ; 8, X = NBu$^+$



9, X = O ; 10, X = NBu$^+$



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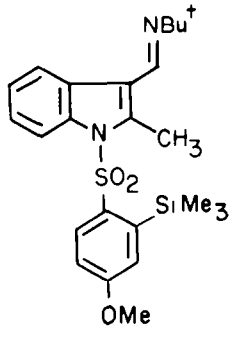

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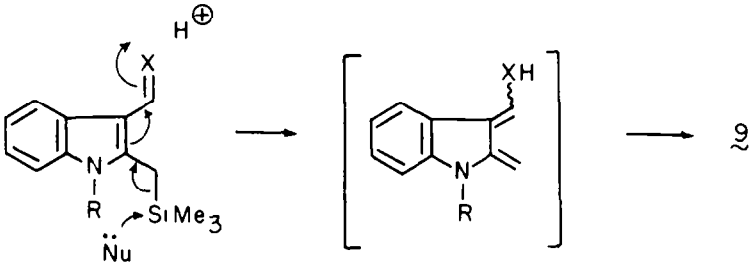
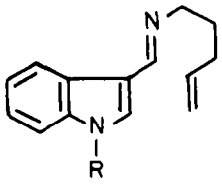


SCHEME E

appeared to be the 2-methylimine (**15**). No products resulting from competitive reactions *ortho* to the sulfonamide group were detected. Treatment of **14** with cesium fluoride at 70° in glyme merely resulted in removal of the trimethylsilyl group to give **15** as the sole product. Although presumably formed, the 2, 3-quinodimethane intermediate (Scheme D) failed to undergo Diels-Alder cyclization at this relatively low temperature. This conclusion, as will be seen, is based upon subsequent observations.

2-Methylindole was converted into the 3-formyl derivative (**9**; R=H)[7] and the indolic nitrogen protected, for the reasons outlined above, as the 4-methoxybenzenesulfonamide (**9**). Treatment of **9** with 4-pentenylamine, with provision for removal of water, gave the imine **15**. When **15** was heated in acetic anhydride at 140° for 4 hr a clean transformation took place to give a single compound in 64% yield. The ^{1}H NMR spectrum of this product exhibited two singlets attributable to the Me group of the acetamide. When the ^{1}H NMR was run at approximately 90° the above singlets coalesced into one signal which on cooling, again became two singlets. This phenomena can be attributed to amide resonance.

The gross structure of this product and its stereochemical features, namely that of the newly formed fused ring, were difficult to determine from NMR spectra. Mechanistic considerations provide several reasonable possibilities shown below which cannot be readily distinguished, although the *meta* mode **18** involving a 7-membered ring transition state appears most unlikely. The designations, *E* and *Z*, refer to the geometry of the dienamine with respect to the benzenoid ring. The relationship between the four most likely transition states [*exo-Z, exo-E, endo-Z and endo-E*] is such that *exo-Z/endo-E* and *exo-E/endo-Z* are diastereomeric pairs, since the product resulting from *exo-E* is the mirror image of the product from *endo-Z* and likewise for *exo-Z* and *endo-E*. On the basis of previous experience with quinodimethane intramolecular cyclisations[1,2] the *exo*-transition state would appear to be the most likely, *exo-E* or *exo-Z*, the geometry of the dienamine determining the ultimate stereochemical course. The *endo-Z* transition state has a number of severe non-bonded interactions between the methylene groups and the indole system and the *endo-E* transition state is badly strained. Consequently we are left with *exo-Z* or *exo-E*. It should be noted that the *trans*-fused product **16** *is not* the natural relative configuration present in the Aspidosperma alkoids **19**, although the C-3′ position is epimerizable *via* a retro-Mannich/Mannich reaction, first manifested in the Stork, and subsequently, Ban synthesis of aspidospermine.[3] Consequently, while the *trans*-



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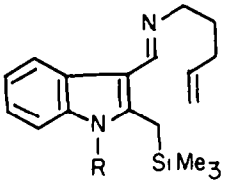

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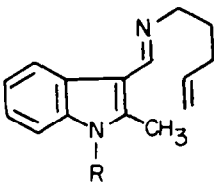

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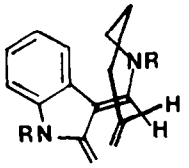
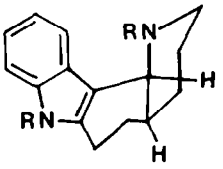
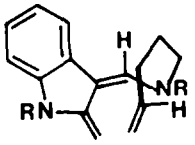


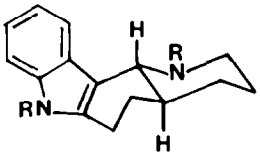
endo (Z)



17



endo (E)



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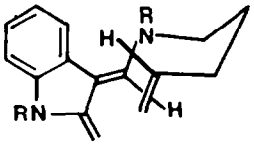
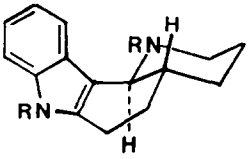
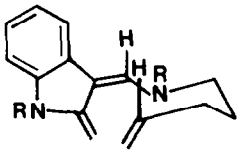


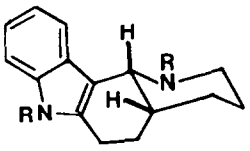
exo (Z)



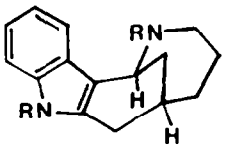
16



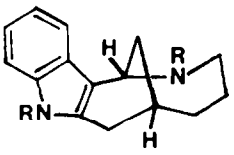
exo (E)



17

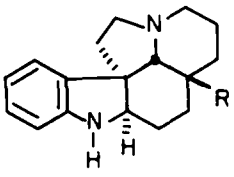


meta (Z)



meta (E)

18



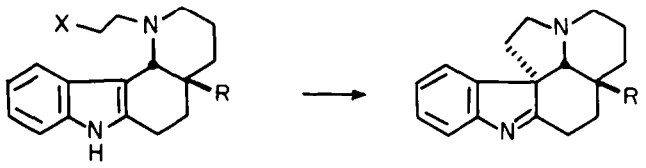
19 R = H or Et

product **16** is the most likely from literature precedent and is of use since the C-3′ stereochemistry is epimerizable, it would be considerably more satisfactory to have *cis*-stereochemistry. In particular, for the subsequent introduction of the two carbon bridge, essential for the Aspidosperma alkaloids, *cis*-stereochemistry is more appropriate for C–C bond formation between C-3 and a two carbon appendage attached to the non-indolic N atom through an intramolecular alkylation or acylation. This proposition has previously been expressed by Potier and Wenkert[8] and reflects the fact that orbital overlap between C-3 (π-system) and the pseudo-pentacoordinatetransition state(alkylation) or tetrahedral transition state (acylation) is less sterically strained when the ring fusion is *cis* (Scheme F).

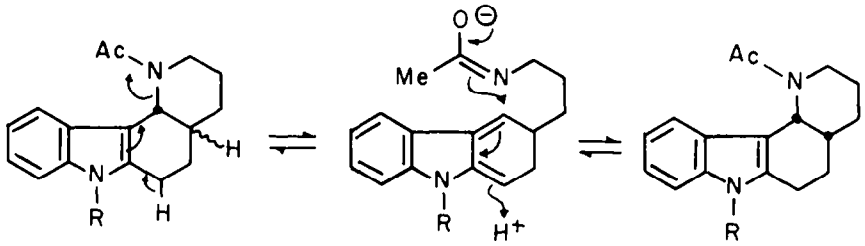
To set aside speculation, a single crystal *X*-ray crystallographic structure determination of the above adduct was carried out by Dr. John Huffman of Indiana University and the outcome is shown as the computer generated structure **17**.[9] Fortunately the newly formed ring-junction is *cis*-fused; indicating a preference for the *exo-E* transition state.

For the particular intramolecular Diels–Alder reaction, **15** to **17**, consideration of the various transition states is not adequate, since "molecular life" is not so simple, in this unusual case. The initial product(s), whether *trans*-**16** or *cis*-**17**, can undergo reversible fragmentation, as shown in Scheme G, leading to the *cis*-fused compound (**17**) through simple stereoelectronic control. Since we know that the C-2 Me group of **15** must be acidic to generate a dienamine intermediate, the resulting C-2′ methylene group in the product must also be acidic and therefore readily able to enter into the equilibration process suggested above. Carrying out the cyclisation in a medium that allows for H/D exchange, or merely exposing **17** to D_2O/base, with the intention of exchanging the C-2′ protons would not provide any evidence for the suggested mechanism of formation of the *cis*-product **17**. This is because H/D exchange can take place without rupture of the C-3′–N bond and, as a consequence, cannot provide even circumstantial evidence for the generation of the intermediate **20**.

All attempts to deprotect the non-indolic nitrogen of **17** were unsuccessful and as a result a number of other electrophilic additions to the imine **15** were conducted to find a high yield cyclisation procedure combined with an easily removed group attached to the non-indolic N atom. The Table below shows these results for a series of chloroformates. The best conditions were found to be treatment of **15** with methyl chloroformate in chlorobenzene at 130° for 3.5 hr in the presence of diisopropylethylamine. In this way the tetracyclic carbamate



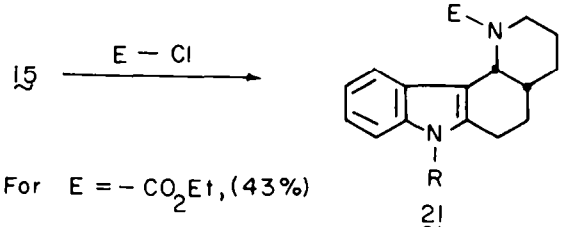
SCHEME F



20

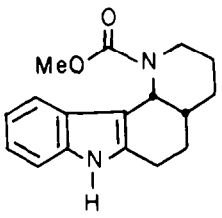
SCHEME G

TABLE

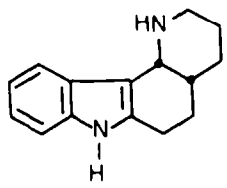


21

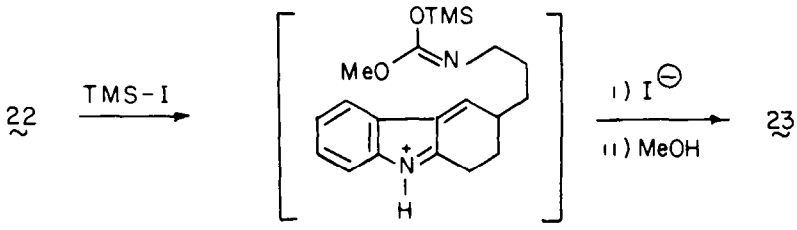
For E = $-CO_2Et$, (43%)
$-CO_2CH_2Ph$, (0%)
$-CO_2Ph$, (68%)
$-CO_2Me$ (88%)



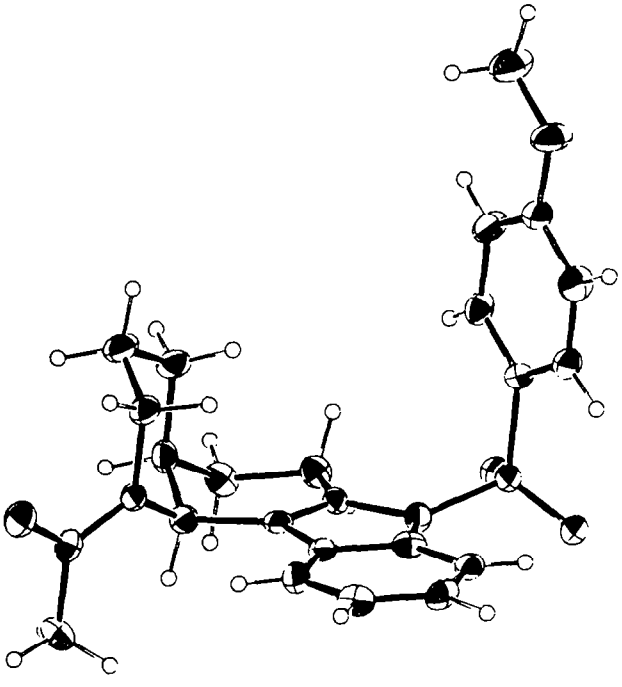
22



23



SCHEME H



21 ($R=CO_2Me$) was formed in 88% yield after purification by chromatography. Benzyl chloroformate was unstable at the temperatures required for cyclisation of the unsaturated imine **15**.

Treatment of **21**($R=CO_2Me$) with aqueous potassium hydroxide in methanol gave the deprotected indole in good yield. Exposure of **22** to trimethylsilyl iodide, generated *in situ* from trimethylsilyl chloride and sodium iodide in acetonitrile, for 2 hr at 80° gave the diamine **23** in 66% yield.[10] If the order of deprotection is reversed by attempting to remove the O-methylcarbamate with trimethylsilyl iodide prior to removal of the aryl-sulfonamide group, then even under forcing conditions the carbamate remained intact. This unusual observation can be explained by using the indolic nitrogen lone pair to open the piperidine ring, rendering the carbamate sterically unhindered and attached to a primary rather than a secondary amine. As a result the carbamate becomes labile towards trimethylsilyl iodide, whereas for the sulfonamide **21** the cleavage of the piperidine ring cannot take place nearly so readily since the nitrogen lone pair is restrained by the sulfone group (Scheme H).

In conclusion we have demonstrated a new method for constructing the basic carbon skeleton of the Aspidosperma alkaloids that provides, in a highly convergent manner, the correct *cis*-fused relative stereochemistry. This new strategy also illustrated, for the first time, the formation and utilization of an indole-2,3-quinodimethane in synthesis.

EXPERIMENTAL

N-(4-Methoxybenzenesulfonyl)indole-3-carboxaldehyde (**7**).

To a stirred slurry of NaH (2.5 g, 0.104 mol) in glyme (20 ml)

was added a soln of indole-3-carboxaldehyde (14.52 g, 0.1 mol) in glyme (200 ml). After stirring for 1 hr the soln was heated under reflux for 10 min to ensure complete anion formation. The mixture was then cooled to 0° and a soln of 4-methoxybenzenesulfonyl chloride (21.5 g, 0.104 mol) and imidazole (400 mg, 6 mmol) in glyme (40 ml) was added. After heating under reflux for 2 hr the mixture was cooled and poured onto ice/water. The product was collected by the filtration and recrystallization (EtOAc–hexane) gave **7** (22 g, 70%) as colourless leaves, m.p. 138–140°. (Found: C, 61.06; H, 4.11; N, 4.43; S, 10.11. $C_{16}H_{13}NO_4S$ requires: C, 60.94; H, 4.16; N, 4.44; S, 10.16%). ν max (Nujol) 1675, 1255 and 1158 cm^{-1}. NMR ($CDCl_3$) δ9.10(1H, s), 8.30–8.18 (2H, m), 8.00–7.80 (3H, m), 7.55–7.21 (2H, m), 7.00–6.82 (2H, d, J8Hz) and 3.76 (2H, s). MS. *m/e* 315.055 (calcd. for $C_{16}H_{13}NO_4S$: 315.056).

N-{[(4-*Methoxybenzenesulfonyl*)-1H-*indol*-3-*yl*]*methylene*}-2-*methyl*-2-*propanamine* (**8**).

Aldehyde 7 (1.60 g, 5 mmol) in CH_2Cl_2 (20 ml) containing anhyd$MgSO_4$ was treated with an excess of t-butylamine and heated under reflux for 1hr. The imine **8** was obtained as a colourless foam after filtration and concentration of the filtrate. ν max (Nujol) 1640, 1262 and 1168 cm^{-1}, NMR ($CDCl_3$) δ8.50–8.32 (2H, m), 8.00–7.68 (4H, m), 7.34–7.15 (2H, m), 6.85–6.68 (2H, d, J8Hz), 3.74 (3H, s) and 1.32 (9H, s). The crude imine was used directly in the next step.

N-(4-*Methoxybenzenesulfonyl*)-2-*methylindole*-3-*carboxaldehyde* (**9**)

(i) *By lithiation and subsequent methylation of t-butylimine* (**8**). A soln of **8** (3.70g, 10 mmol) in THF (70 ml) at −60° was treated over 10 min with a soln of n-BuLi in hexane (1.13 M, 9.7 ml, 11 mmol). The soln was warmed to −30°, stirred for 30 min and then cooled to −78° and treated with an excess of MeI. The mixture, after warming to room temp overnight, was poured into NH_4Claq and the product extracted with ether. The combined extracts were dried ($MgSO_4$), and chromatography of the residue over silica gel gave, on elution with $CHCl_3$-petrol (1:1), **9** (1.4g, 43%) as colourless crystals m.p. 129–130° ($CHCl_3$ hexane). (Found: C, 61.74; H, 4.73; N, 4.16; S, 10.08. $C_{17}H_{15}NO_4S$ requires: C, 61.99; H, 4.59; N, 4.25; S, 9.73%). ν max (Nujol) 1665, 1590 and 1165 cm^{-1}. NMR ($CDCl_3$) δ 10.27 (1H, s); 8.31–8.11 (2H, m), 7.78 (2H, d, J8Hz), 7.47–7.23 (2H, m), 6.86 (2H, d, J8Hz), 3.75 (3H, s) and 2.91 (3H, s). MS *m/e* 329.073 (calcd. for $C_{17}H_{15}NO_4S$: 329.072).

(ii) *From* 2-*methylindole*-3-*carboxaldehyde* (**9**; R=H). Following the procedure described above for **7**, treatment of **9** (R=H)[7] with NaH followed by 4-methoxybenzenesulfonyl chloride and imidazole gave **9** in 45% yield after purification by chromatography. Considerable decomposition occurred on workup and best results were obtained when the mixture was poured into 10% NaH_2PO_4 soln (pH = 4.5). The product **9** obtained in this manner was identical to that obtained by lithiation and methylation of **8**.

Attempts to prepare the 2-*methyltrimethylsilylindole derivative* (**11**)

(i) *Lithiation and alkylation of* **8**. A soln of **8** (740 mg, 2 mmol) in THF (20 ml) was cooled to −25° and a soln of n-BuLi in hexane (1.48 M, 1.5 ml, 2.2 mmol) was added over 3 min. After 30 min at −25° the soln was cooled to −78° and HMPA (453 mg, 2.5 mmol) followed by trimethylsilylmethyl trifluoromethanesulfonate (519 mg, 2.2 mmol)[5] in THF (1 ml) was added. After stirring at −78° for 4 hr the soln was allowed to warm to room temp overnight. The mixture was quenched with NH_4Claq and immediately extracted with EtOAc. The extracts were dried ($MgSO_4$) and the ^1H NMR spectrum of the crude mixture showed two singlets at δ 2.65 and 2.80, in a ratio of 3:1, assigned as the 2-Me protons of **10** and the 2-methylene protons of **11** respectively. Chromatography over silica gel gave **9** (360 mg, 53%) as the sole product.

(ii) *Lithiation and silylation of* N-{[(4-*methoxylbenzenesulfonyl*)-2-*methyl*-1H-*indol*-3-*yl*]*methylene*}-2-*methyl*-2-*propanamine* (**10**). To a soln of **8** (740 mg, 2.6 mmol) in THF (10 ml) at −15° was added n-BuLi in hexane (1.6 M, 1.5 ml, 2.4 mmol). After stirring for 30 min at −15° the mixture was cooled to −78° and MeI (372 mg, 2.6 mmol) was added. After warming to room temp the mixture was stirred for 3 hr, then poured into water and the product extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated to give **10** as a colourless foam ν max ($CHCl_3$) 1630, 1592 and 1085 cm^{-1}. NMR ($CDCl_3$) δ 8.60 (1H, s), 8.53 (1H, M), 8.20 (1H, m), 7.72 (2H, d, J8Hz), 7.30 (2H, m), 6.80 (2H, d, J8Hz), 3.70 (3H, s), 2.69 (3H, s) and 1.29 (9H, s).

Imine **10** was immediately redissolved in THF (10 ml), cooled to −78° and n-BuLi in hexane (1.6 M, 1.5 ml, 2.4 mmol) was added to give a deep red soln. After stirring for 15 min trimethylsilyl chloride (1 ml) was added and the soln allowed to warm to room temp. At −50° the red colour was discharged and the soln became pale yellow. Following the workup procedure described above, chromatography of the residue over silica gel gave, on elution with $CHCl_3$–petrol (1:3), N-(4-*methoxy*-2-*trimethylsilylbenzenesulfonyl*)-2-*methylindole*-3-*carboxaldehyde* **12** (120 mg, 15%) as colourless crystals m.p. 147–148° (ether-hexane). ν max ($CHCl_3$) 1660 cm^{-1}. NMR ($CDCl_3$) δ 10.36 (1H, s), 8.35 (1H, m), 8.03 (1H, m), 7.48–7.23 (3H, m), 6.70 (2H, m), 3.78 (3H, s), 2.78 (3H, s) and 0.60 (9H, s). MS. *m/e* 401.112 (calcd. for $C_{20}H_{23}NO_4SSi$: 401.112).

Continued elution with $CHCl_3$-petrol (1:1) gave **9** (320 mg, 51%).

In a similar experiment where the intermediate **10** was not first isolated considerable polymerization occurred on attempt relithiation.

N-{[(3-*Methoxybenzenesulfonyl*)-1H-*indol*-3-*yl*]*methylene*}-4-*pentenylamine* (**13**.

A soln of **7** (315 mg, 1 mmol) in benzene (10 ml) was treated with 4-pentenylamine[6] (100 mg, 1.2 mmol). After stirring for 1 hr, anhyd Na_2SO_4 was added and stirring continued for a further 2 hr. The mixture was then filtered and the filtrate allowed to stand over 4A molecular sieves overnight. Filtration and concentration of the soln gave **13** as a colourless oil. ν max ($CHCl_3$) 1641, 1261 and 1166 cm^{-1}. NMR ($CDCl_3$) δ8.50–8.30 (2H, m), 8.05–7.79 (3H, m), 7.43–7.28 (2H, m), 6.89 (2H, d, J8Hz), 5.82 (1H, m), 5.03 (2H, m) 3.83 (3H, s), 3.62 (2H, d, J7.5 Hz), 2.19 (2H, q, J7.5Hz) and 1.78 (2H, m). The product **13** was used directly in the next step.

Attempted synthesis and cyclization of silane (**14**).

To a soln of **13** (380 mg, 1 mmol) in THF (8 ml) at −55° was added n-BuLi in hexane (1.48 M, 0.8 ml, 1.2 mmol) over 10 min. After stirring for a further 20 min the soln was cooled to −78° and trimethylsilylmethyl trifluoromethanesulfonate (200 mg, 1.2 mmol)[5] in THF (1 ml) was added. After warming to room temp overnight the mixture was quenched by pouring into buffered sodium phosphate soln (pH7) and the product extracted with ether. The soln was dried ($MgSO_4$) and the ^1H NMR spectrum showed singlets at δ2.87 and 0.11 assigned as the 2-methylene and trimethlsilyl protons of **14**. A singlet at δ 2.70 was assigned to the 2-Me protons of **15**. The ratio of **14** to **15** in the crude reaction was 3:1. The product was then divided into two portions and used as described in (a) and (b) below.

(a) Concentration of the soln and chromatography of the residue over silica gel gave (9) (70 mg, 45%) as the only isolated product.

(b) The soln was concentrated and the residue taken up in glyme (5 ml) and treated with an excess of cesium fluoride at 70° for 2 hr. Following the workup procedure described above, the only product observed by NMR was **15** identical to an authentica sample prepared from **9**.

N-{[(4-*Methoxybenzenesulfonyl*)-2-*methyl*-1H-*indol*-3-*yl*]*methylene*}-4-*pentenylamine* (**15**).

Following the same procedure described for **13**, **15** was obtained as a colourless oil which crystallized on standing at 0°. ν max ($CHCl_3$) 1638 and 1174 cm^{-1}. NMR ($CDCl_3$) δ 8.58 (1H, s),

8.44–8.20 (2H, m), 7.73 (2H, d, J8Hz), 7.40–7.25 (2H, m), 3.85 (3H, s), 5.56 (2H, t, J6Hz), 2.71 (3H, s), 2.19 (2H, q, J6Hz) and 1.81 (2H, m). The imine **15** was used directly in the next step.

1-*Acetyl*-7-(4-*methoxybenzenesulfonyl*)-1, 2, 3, 4, 4aα, 5, 6, 11cα-*octahydro*-7H-*pyrido*[3, 2, c]*carbazole* (**17**)

A soln of **15** (400 mg, 1 mmol) in freshly distilled Ac_2O (10 ml) was heated under reflux for 4 hr. Concentration under reduced pressure followed by chromatography over silica gel gave, on elution with $CHCl_3$–petrol (1:1), **17** (280 mg, 64%) as colourless crystals, m.p. 194–195° ($CHCl_3$–hexane). (Found: C, 65.99; H, 6.13; N, 6.12; S, 7.14. $C_{24}H_{26}N_2O_4S$ requires: C, 65.73; H, 5.98; N, 6.39; S, 7.31%). ν max ($CHCl_3$) 1629 and 1170 cm^{-1}. NMR ($CDCl_3$) δ 8.00 (1H, m), 7.63–7.38 (2H, d, J8Hz), 7.16–6.92 (3H, m), 6.70 (2H, d, J8Hz) 5.87 and 4.90 (1H, m, ratio of peaks 2:1), 4.30 and 3.26 (1H, br. d, J14Hz), ratio of peaks 2:1), 3.60 (3H, s), 3.00–2.71 (2H, m), 2.10 and 2.08 (3H, s, ratio of peaks 1:2), 1.98–1.19 (8H, m). When the NMR spectrum was run at approx. 90° the Me signals at δ2.10 and 2.08 coalesced and signals at δ 5.87/4.90 and 4.30/3.26 broadened. MS. *m/e* 438.162 (calcd. for $C_{24}H_{26}N_2O_4S$: 438.161).

1-*Carboethoxy*-7-(4-*methoxybenzenesulfonyl*)-1, 2, 3, 4, 4aα, 5, 6, 11cα-*octahydro*-7H-*pyrido* [3,2,c] *carbazole* (**21**; E=CO_2Et).

A soln of **15** (200 mg, 0.5 mmol) and ethyl chloroformate (0.5 ml, 560 mg, 5.2 mmol) in xylene (10 ml) was heated under reflux for 3 hr. Concentration of the mixture followed by chromatography over silica gel gave, on elution with $CHCl_3$–petrol (1:4) **21**(R=CO_2Et) (100 mg, 43%) as pale yellow needles, m.p. 134–136° (ether-hexane). ν max ($CHCl_3$) 1678, 1596, 1268 and 1167 cm^{-1}. NMR ($CDCl_3$) δ 8.32–8.12 (1H, m), 7.75 (2H, d, J8Hz), 7.43–7.19 (3H, m), 6.89 (2H, d, J8Hz), 5.60 (1H, m), 4.30 (2H, q, J6Hz), 4.10 (1H, m), 3.28 (3H, s), 3.15–2.89 (2H, m), 2.22–1.81 (4H, m), 1.60–1.15 (7H, m). MS. *m/e* 468.173 (calcd. for $C_{25}H_{28}N_2O_5S$: 468.172).

1-*Carbophenoxy*-7-(4-*methoxylbenzenesulfonyl*)-1, 2, 3, 4, 4aα, 5, 6, 11cα-*octahydro*-7H-*pyrido* [3,2,c] *carbazole* (**21**; E=CO_2Ph)

The same procedure described for **21** (R=CO_2Et) gave, with phenyl chloroformate, **21** (R=CO_2Ph) in 68% yield from **15** as a pale yellow foam. ν max ($CHCl_3$) 1705, 1598 and 1169 cm^{-1}. NMR ($CDCl_3$) 8.10 (1H, m), 7.71 (2H, d, J8Hz), 7.45–7.05 (8H, m), 6.82 (2H, d, J8Hz) 5.65 (1H, m), 4.09 (1H, m), 3.76 (3H, s), 3.23–2.86 (2H, m), 2.55–1.79 (4H, m) and 1.65–1.32 (4H, m). MS. *m/e* 516.172 (calcd. for $C_{29}H_{28}N_2O_5S$: 516.172).

1-*Carbomethoxy*-7-(4-*methocybenzenesulfonyl*) 1, 2, 3, 4, 4aα, 5, 6, 11cα-*octahydro*-7H-*pyrido* [3,2,c] *carbazole* (**21**; R=CO_2Me).

To a solution of **15** (1.2 g, 3 mmol) and diisopropylethylamine (520 mg, 4 mmol) in chlorobenzene (30 ml) at 0° was added methyl chloroformate (474 mg, 5 mmol). The mixture was then heated to 130° for 3.5 hr. Concentration of the mixture and chromatography over silica gel gave, on elution with $CHCl_3$–petrol (1:2), **21** (R=CO_2Me) (1.2 g, 88%) as a pale yellow foam. ν max ($CHCl_3$) 1680, 1598, 1267 and 1169 cm^{-1}. NMR ($CDCl_3$) δ 8.20 (1H, m), 7.70 (2H, d, J8Hz), 7.33–7.13 (3H, m), 6.84 (2H, d, J8Hz), 5.52 (1H, m), 3.85 (3H, s), 3.76 (3H, s), 3.15–2.85 (2H, m), 2.32–1.80 (4H, m) and 1.60–1.22 (4H, m). MS. *m/e* 454.157 (calc. for $C_{24}H_{26}N_2O_5S$: 454.156).

1-*Carbomethoxy*-1, 2, 3, 4, 4aα, 5, 6, 11cα-*octahydro*-7H-*pyrido* [3,2,c]*carbazole* (**22**).

A soln of **21** (R=CO_2Me) (530 mg, 1.16 mmol) in MeOH (20 ml) and 20% KOHaq (3 ml) was heated under reflux for 14 hr. Water was then added and the product extracted with EtOAc. The combined extracts were dried ($MgSO_4$), concentrated and chromatography over silica gel gave, on elution with $CHCl_3$–petrol (1:2), **22** (230 mg, 68%) as a colourless foam. ν max ($CHCl_3$) 3462 and 1680 cm^{-1}. NMR ($CDCl_3$) δ 8.36 (1H, s), 7.37–6.93 (4H, m), 5.73 (1H, m), 4.04 (1H, m), 3.86 (3H, s), 2.78–2.33 (3H, m), 2.20–1.71 (3H, m) and 1.56–1.34 (4H, m). MS. *m/e* 284.153 (calcd. for $C_{17}H_{20}N_2O_2$: 284.152).

1, 2, 3, 4, 4aα, 5, 6, 11cα-*Octahydro*-7H-*pyrido*[3,2,c]*carbazole* (**23**)

A soln of **22** (195 mg, 1.15 mmol), NaI (515 mg, 2.06 mmol) and trimethylsilyl chloride (150 mg, 1.37 mmol) in acetonitrile (8 ml) was heated at reflux for 2 hr. MeOH (0.5 ml) was added and after stirring for 10 min the soln was evaporated to dryness. 2N NaOH was added and the slurry extracted thoroughly with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and removal of solvent gave **23** (100 mg, 66%) as a pale yellow oil. ν max ($CHCl_3$) 3465, 3400–2700 (br. NH), 1590, and 1468 cm^{-1}. NMR ($CDCl_3$) δ 8.51 (1H, s), 7.15 (1H, m), 7.13–6.90 (3H, m), 4.05 (1H, d, J2Hz) and 3.15–1.30 (12H, m). MS. *m/e* 226. 146 (calcd. for $C_{15}H_{18}N_2$: 226.147).

Trimethylsilymethoxytris(dimethylamino) phosphonium trifluoromethanesulfonate

To a soln of trimethylsilylmethyl trifluoromethanesulfonate (519 mg, 2.2 mmol) in THF (5 ml) was added HMPA (447 mg, 2.5 mmol). Heat was rapidly evolved and a colourless ppt formed which was filtered off and dried to give the triflate (660 mg, 69%) m.p. 150–152°. NMR (d_6DMSO) δ 3.88 (1H, s), 3.82 (1H, s), 2.68 (9H, s), 2.54 (9H, s) and 0.09 (9H, s).

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