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A New Approach to the Skeletons of Both the Aphidicolin and Stemodin Diterpenoids

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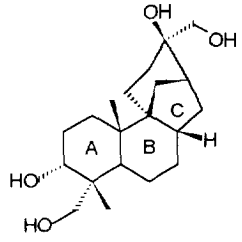
Abstract: We describe a concise synthesis of 4,4,10,16 tetra-desmethyl-1,2,3,4-tetra-dehydro-16α-hydroxystemodan-13-one[1] which has the skeleton of the diterpene stemodin using a trimethylsilyl ketyl radical / nitrile cyclisation of 1,1-bis-cyanoethyl-2-tetralone as the key step. This compound could be transformed to 4,4,10,16 tetra-desmethyl-1,2,3,4-tetra dehydro-16α-hydroxyaphidicolane, which has the skeleton of aphidicolin, via hydrogenation of the alkene derived from aprotic Bamford Stevens elimination of an arylsulphonylhydrazone derivative.



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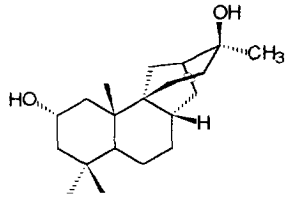


(2)

Aphidicolin[2] (1), from the fungus *Cephalosporium aphidicola* Petch has attracted considerable interest ever since its isolation in 1973 and the demonstration that it inhibited the mitotic rate of mouse "L" cells growing in tissue culture and also inhibited the growth of Herpes simplex type 1 virus both *in vitro* and in the rabbit eye[3]. It was shown that this biological activity was due to inhibition of the enzyme DNA polymerase α[4]. An inhibitor of DNA polymerase α is likely to have a broad spectrum of biological activity but most attention has been centred on aphidicolin's potential as both an anti-cancer[5] and anti-herpes agent[6]. The closely related diterpene stemodin[7] (2) was isolated from the above ground portion of *Stemodia maritima* L. a plant used on the Caribbean island of Curacao for the treatment of venereal disease. Much less attention has been paid to the biological activity of stemodin derivatives but a recent formal total synthesis of stemodin involved synthetic intermediates possessing potent biological activity[8].

Whilst the stuctures of these diterpenes are relatively simple by today's standards of synthetic bravura, their numerous chiral centres and novel tetracyclic skeleta have provided enough challenge to attract the interests of several leading research groups[9]. The main structural difference between the two skeleta lies in the fusion of the

B and C rings - aphidicolin having a *trans* fused B/C ring system while stemodin has a *cis* fused B/C ring system. We were intrigued by the possibility of devising a synthetic route that would provide a key intermediate for elaboration into both skeleta, especially if the intermediate would allow access to a wide variety of analogues in gramme quantities. The approach described in this paper allows for access to both ring systems from the same intermediate and opens up the way for the synthesis of numerous aromatic A ring analogues of the diterpenes for biological evaluation.

Most synthetic approaches have involved construction of a functionalised A/B ring system and then construction of the C/D rings. Our approach envisaged assembly of the entire carbocycle (with an aromatic A ring) early in the synthesis and then further elaboration to provide the correct level of functionality on both the A and D rings. Our approach is depicted in (FIG 1) and involved disconnection of the diterpenoid skeleton to the simple dinitrile (4) which is easily made by *bis* cyanoethylation of β tetralone (3). The key step in this approach envisaged a ketyl nitrile cyclisation of the dinitrile (4) which sets up the B/C ring system with a 3-carbon appendage already in place for either an intramolecular Dieckman type cyclisation or an aldol condensation to give the required bicyclo [3.2.1] octane moiety.

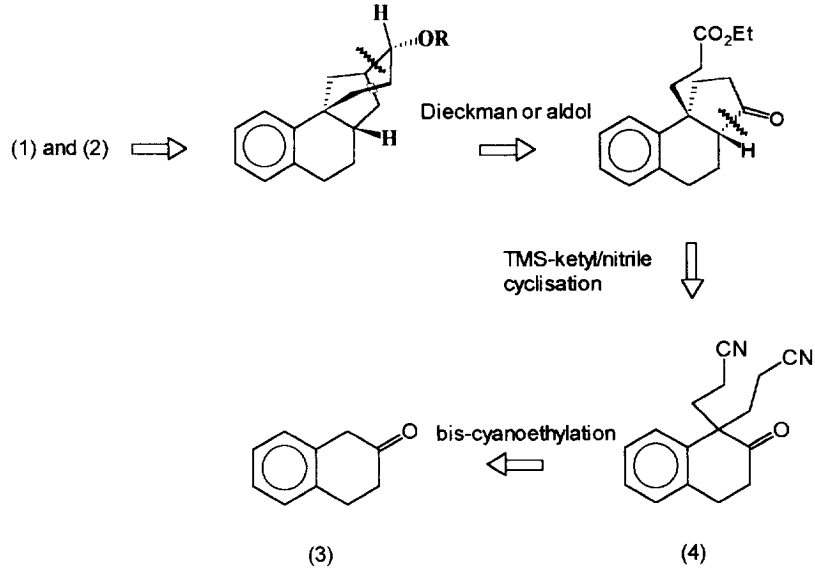
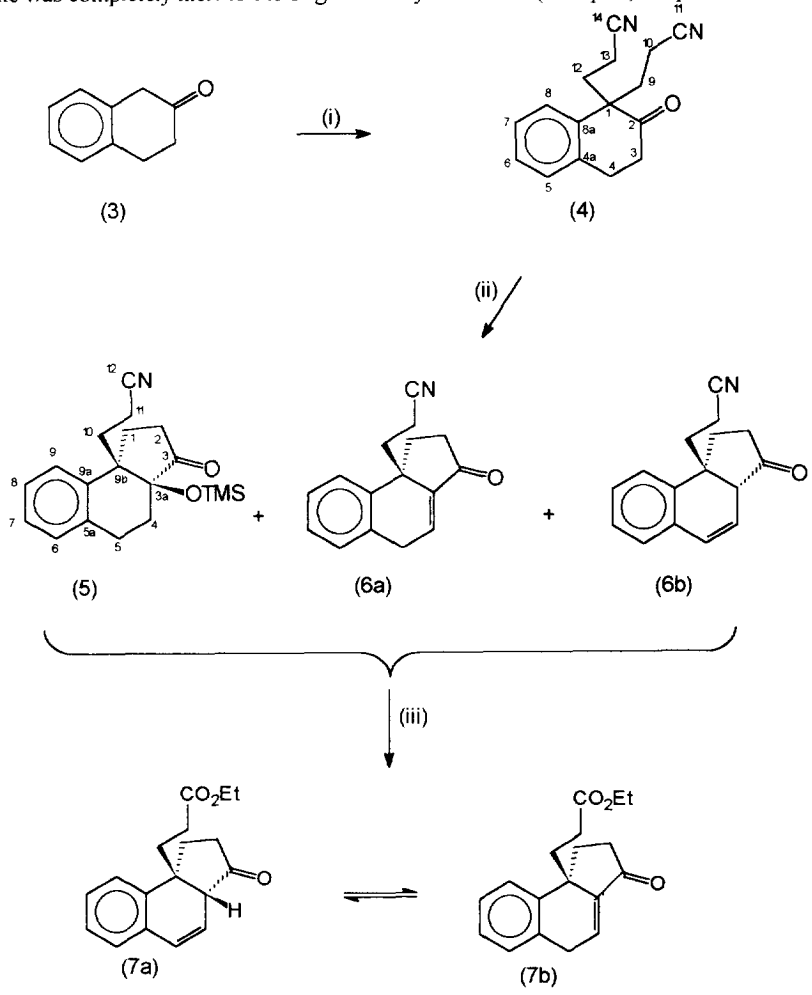


Fig 1

Ketyl radicals have played a significant role in natural product synthesis ever since they were first used by Stork in his synthesis of gibberellic acid[10]. The powerful reducing conditions used by Stork were later superseded by conditions which could be used with systems containing sensitive functionality[11]. While the generation of ketyl radicals and their interception by alkenes and alkynes is a relatively common process (see ref. 11), the corresponding process where the ketyl radical is trapped by a nitrile is much less common and is only reported under conditions where the ketyl radical is first trapped with trimethylsilyl chloride to give the trimethylsilyl ketyl radical. This is then trapped by the nitrile (Corey/Pine) or electrochemically, where electron transfer and cyclisation occurs on the surface of a tin cathode (Shono/Kise-see ref. 11).

Selective *bis*-cyanoethylation of β tetralone (3) (cat. Triton B, 2 eq acrylonitrile, tBuOH) gave the dinitrile (4) in 80% isolated yield (scheme 1). After this first reaction all of the carbons which are needed for both skeleta are present, together with the crucial spiro centre. This initial success was followed by a long period of frustration during which numerous attempts were made to effect TMS-ketyl radical formation and cyclisation.

The *bis*-nitrile was completely inert to the original Corey conditions (20 eq Zn, 6 eq TMSCl, 2-6 lutidine) and

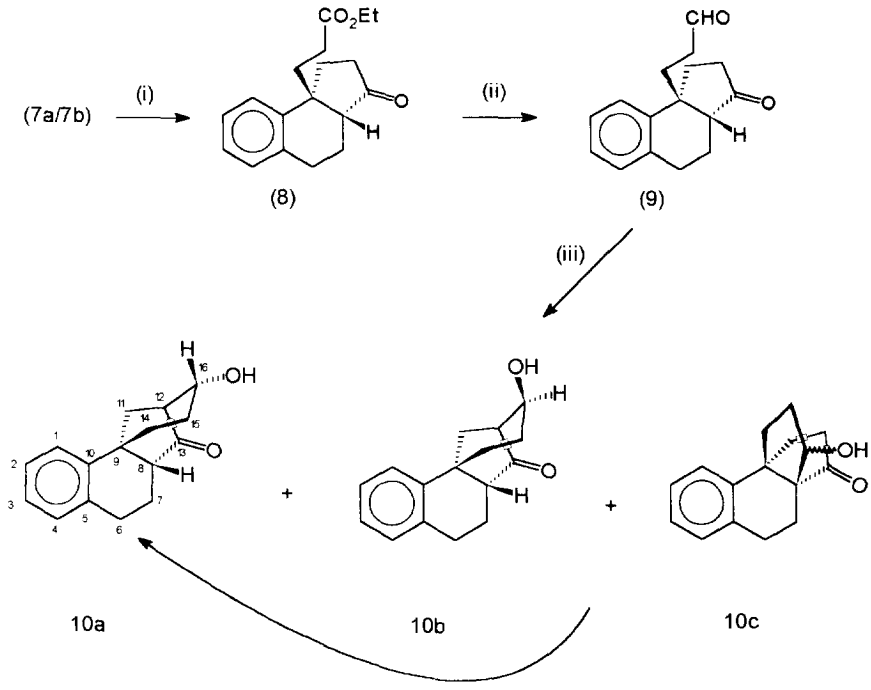


Reagents: (i) Cat. Triton B, 2 eq. acrylonitrile, tBuOH. (ii) 7-10 eq. Zn, 7-10 eq Mg, 6 eq. TMSCl, THF, reflux. (iii) H_2SO_4, EtOH, heat.

(Scheme 1)

after exhausting the different methods of Zn activation[12] it was surmised that our system required a slightly more potent electron donor - magnesium. Adding magnesium turnings (2 equivalents) to the reaction mixture (20 eq Zn, 6 eq TMSCl, THF reflux) gave modest yields of cyclised product (23%). By then varying the ratios of Mg : Zn we found that having Mg and Zn together in equal quantities (10 eq. of each) it was possible to obtain good yields of cyclised product - 40% yield of the TMS ether (5) together with 20 % yield of a mixture of unsaturated ketones (6a, 6b) formed by Lewis acid catalysed elimination of -OTMS from (5). The TMS ether was surprisingly stable to acid workup with 2M HCl and it is thus likely that (6a) and (6b) are derived from Lewis acid catalysed elimination from *trans*-fused cyclised product which we expect to be less stable[13].

Heating the crude mixture (5+6a+6b) from the cyclisation with sulphuric acid in ethanol followed by aqueous workup yielded the tricyclic unsaturated keto-ester as a mixture of isomeric alkenes (7a+7b) in an overall yield of 50% from the dinitrile. This intermediate has considerable potential since it is not only a key compound *en route* to the diterpenoid skeletons but also provides possible access to B-ring analogues.



(i) H_2, Pd/C, EtOH (ii) $LiAlH_4$ THF then PCC/NaOAc, DCM (iii) PTSA, Toluene, 60°C.

(Scheme 2)

For the present work it was hydrogenated at atmospheric pressure over Pd/C in ethanol to yield the keto ester (8) (Scheme 2). Attempts to effect a base-catalysed Dieckmann type cyclisation (NaOEt/EtOH) of this compound to produce the diketone were frustrated by the compound's inability to form a stable enolate as formation of the enolate in this case (this step being the driving force for this type of condensation) would require deprotonation and enolate formation at a bridgehead position. TLC analysis of the reaction mixture gave the impression that no reaction was taking place, but on work-up, ^{13}C NMR analysis of the crude material showed the presence of a second keto ester i.e. 220ppm (cyclopentanone of 8), 201ppm (cyclohexanone of 8b), 179ppm (ester of 8) and 178ppm (ester of 8b). The series of equilibria shown in (Fig 2) seem reasonable.

In consequence, the ester (8) was reduced to the diol using $LiAlH_4$ (scheme 2) and this was oxidised (PCC/NaOAc buffer) to the keto aldehyde (9) (overall yield of 43% from (8)). A variety of base-catalysed aldol reactions (KOH/EtOH, LiOH/MeOH, MeOLi/MeOH, Na_2CO_3/wet THF, tBuOK/toluene) only ever yielded small amounts of all possible aldol products (10a+10b+10c) (10-15% of each). In contrast reaction of (9) with catalytic pTSA in toluene at 60°C resulted in complete consumption of starting material and production of the three aldol products in the approximate ratio of 2:1:2. The ketol could easily be separated by chromatography from the other two products, and these could then be resubjected to the aldol conditions to re-establish the

equilibrium and provide a further quantity of (10a)[14]. In this way the overall yield of (10a) could be raised to 55%. The ketol was then protected as the methyl ether (scheme 3) (MeI, Ag_2O, CH_3CN) and converted to its thioketal derivative (12). Raney nickel desulphurisation then provided the desired stemodin skeleton (13) (*cis* B/C ring fusion).

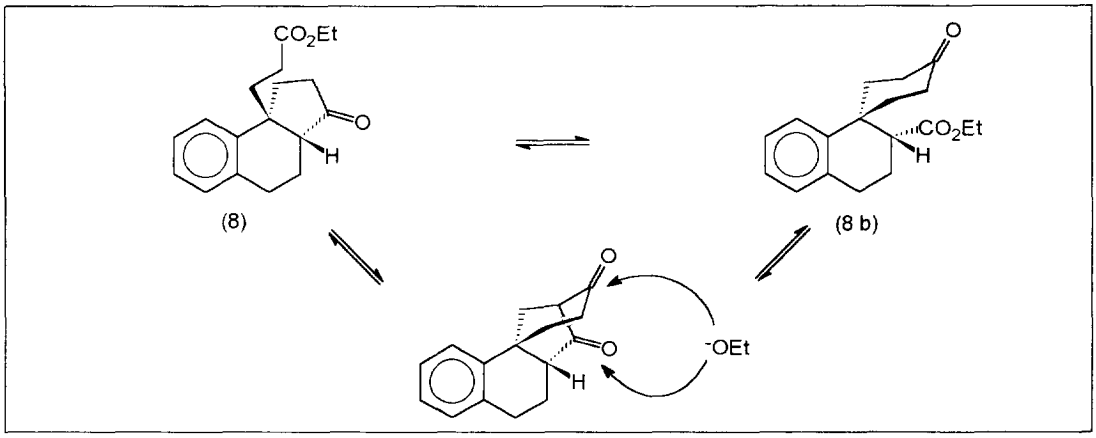
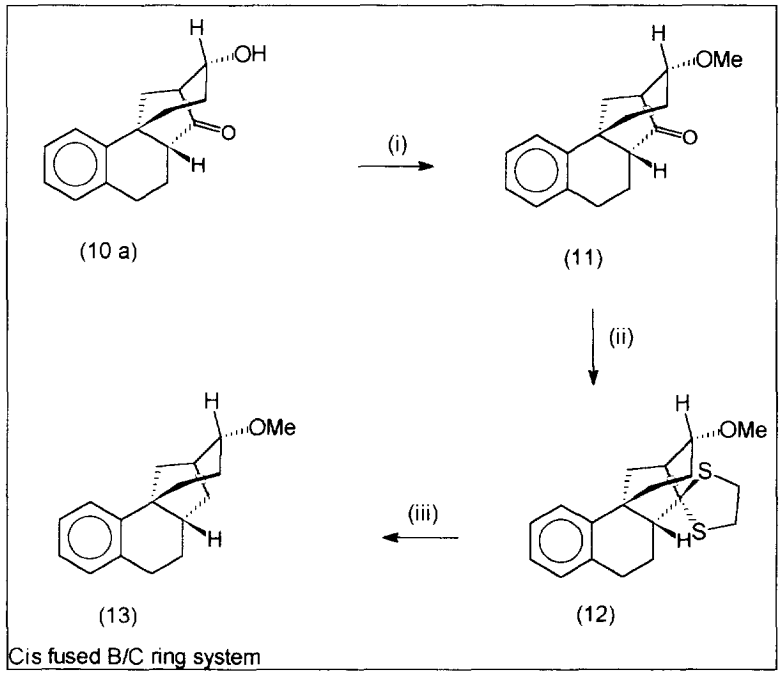


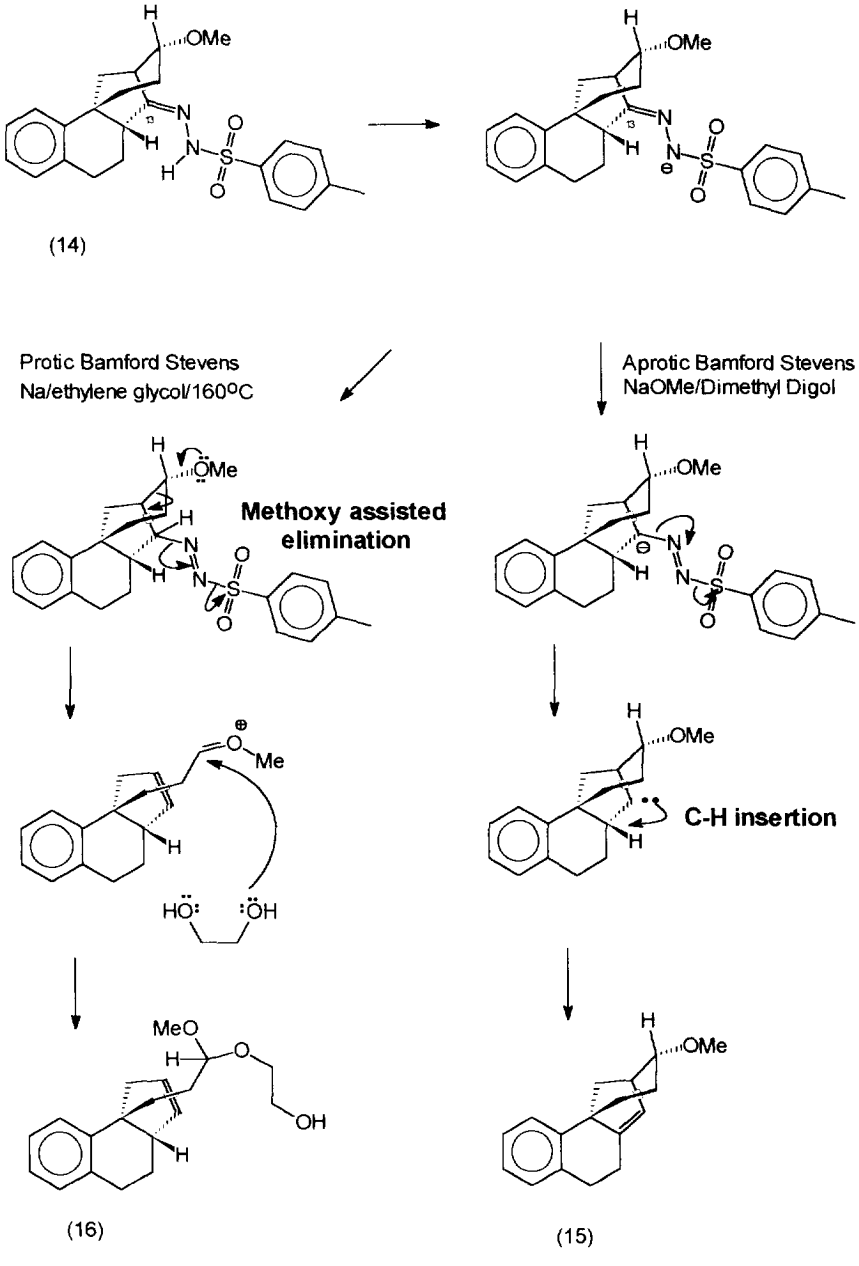
Fig 2



Reagents: (i) MeI, Ag_2O, CH_3CN (ii) Ethanedithiol, BF_3 etherate, $CHCl_3$ (iii) Raney nickel

(Scheme 3)

To access the aphidicolin ring system (*trans* fused ring system - thermodynamically less stable in this case) we originally intended to make the enol triflate or enol phosphate derivative and hydrogenate as both of these



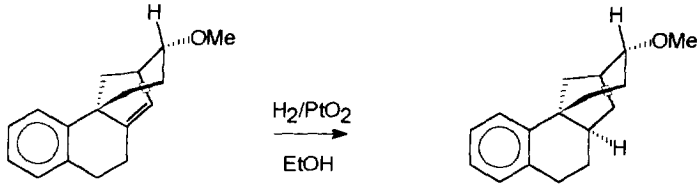
(Fig 3)

are known to hydrogenate directly to the corresponding alkane. It was expected that the hydrogen would be delivered to the face of the molecule opposite the three carbon bridge thus giving the required *trans* fused ring

system. Unfortunately all attempts to make the enol ether derivitives (2,6 di-tert-butyl-4-methyl-pyridine/ trifluoromethane sulphonic anhdride, LDA /diethylchlorophosphate) failed. The ketone in question was also inert to lithium aluminium hydride reduction (THF, reflux, 3 days!). The rigidity of the skeleton makes it difficult to form the ring junction enolate and also makes it difficult for the carbonyl to accomodate an incoming nucleophile (the angle of approach of a nucleophile to the carbonyl is blocked by the three carbon bridge on one face and by the one carbon methylene "lip" on the other).

We were able to overcome these difficulties, however, by making the arylsulphonyl hydrazone derivative of the ketone (14) (Fig 3) and converting it via aprotic Bamford Stevens elimination to the alkene (15). Only aprotic Bamford Stevens conditions gave the required alkene however, protic Bamford Stevens conditions gave the unusual mixed acetal (16). This compound was stable to chromatography and the structure evident from both ^{1}H and ^{13}C NMR analysis. These two results provide a graphic illustration of the two different mechanisms in operation depending on whether a protic or aprotic solvent is used. Under protic conditions carbon-13 in the base catalysed decomposition of the sulphonylhydrazone appears to be cationic in nature, while carbon-13 under aprotic conditions has the properties of a carbene.

Gratifyingly, hydrogenation of the alkene (15) over platinum gave the required *trans* fused B/C ring system (17) as present in aphidicolin. Platinum was chosen in preference to palladium as double bond isomerisation (into conjugation with the aromatic ring for example) before hydrogenation is less likely to occur and consequently stereoselectivity is expected to be much higher. In the event their was no evidence for formation of the unwanted *cis* fused isomer .

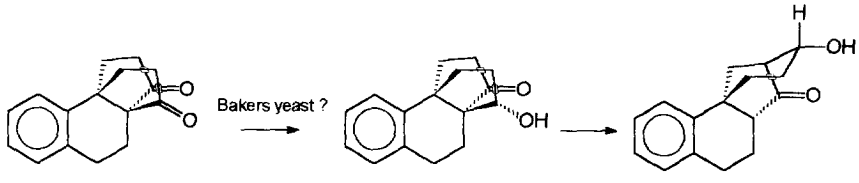


(15) (17)

Trans fused B/C ring system

(Scheme 4)

In conclusion, we have shown that both the skeletons of aphidicolin and stemodin (with an aromatic A ring) can be produced from the key intermediate (11). Future work will be directed towards elaboration of the A ring and to the production of chiral intermediates through stereospecific reduction of the symmetrical di-ketone (18).



(18)

(Scheme 5)

EXPERIMENTAL

IR spectra were recorded using a Perkin-Elmer 881 series double-beam spectrophotometer, and samples were run as thin films or in solution using NaCl plates. Low-resolution and accurate mass data were recorded on a VG Analytical ZAB-1F mass spectrometer by the SERC mass spectrometry serevice at the University of Swansea. ^{1}H NMR spectra were recorded on a Bruker WH250 spectrometer or on a Jeol FX400 instrument and J-values are given in Hz. ^{13}C NMR spectra were recorded on the Jeol spectrometer. Flash chromatography was carried out using SorbsilTM C60 silica gel (40-60 microns). TLC was carried out using 0.25 mm layers of silica gel on plastic sheets. Solvents were distilled from calcium hydride when required anhydrous.

1,1 bis-Cyanoethyl-2-tetralone(4):

To a well stirred mixture of ß-tetralone (3) (20 ml) and Triton-B (2 ml of 40% dispersion in MeOH) in 150 ml. of tBuOH was added (while keeping the temperature at or below room temp) 18 ml of acrylonitrile in 30 ml of THF over a period of 15 minutes. Towards the end of this addition period the product began to precipitate out of solution as a white solid. The reaction mixture was then allowed to stand for one hour by which time the reaction had gone to completion and the product had fully precipitated from solution. The product was then filtered using a Buchner funnel and successive washings with ethanol and subsequent drying gave a white powder in 80% yield. An analytically pure sample was obtained by recrystalisation from a 1:1 ether/ethyl acetate solution (m.p. 105.5-106.5). (Found: M+, 252.1263. $C_{16}H_{16}N_2O$ requires M, 252.1263); υ_{max}(mull)/cm^{-1} 1709 (C=O) and 2244 (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) 1.97-2.1 (6H, m, H-9 H-10 H-12), 2.71 (2H, t, J=6.8 Hz, H-3), 3.10 (2H, t, J=6.8 Hz, H-4), 7.21-7.36 (4H, m, H-5 H6 H7 H8). ^{13}C NMR ($CDCl_3$) 211.36 (C-2), 136.55 (C-8a), 135.87 (C-4a), 129.08 (C-8), 128.02 (C-6), 127.86 (C-7), 126.03 (C-5), 118.53 (CN), 53.61 (C-4), 39.00 (C-3), 34.92 (C-12 and C-9), 27.99 (C-1), 12.94 (C-10 C-13).

The TMS-ketyl nitrile cyclisation followed by hydrolysis and hydrogenation to give 9b(2'Carboethoxy-ethyl)2,3,9b,3a,4,5 hexahydro-1H-benz[e]indene-3-one (8):

Zinc dust (27 g, 7 eq) and magnesium (10 g, 7 eq) in 200 ml of anhydrous THF was ultrasonically irradiated for two hours (i.e. 8 x 15 min. periods with 2 min. intervals). The dinitrile (4) (15 g, .06 mol) in 100 ml of anhydrous THF was then added followed by 45 ml of freshly distilled TMSCl (6 eq). The reaction mixture was then refluxed (bath temp 70 °C) for 16 hours, then allowed to cool to room temp and was filtered through celite to remove the excess metal. HCl (200 ml 2N) was then added and the mixture was allowed to stand for two hours. The mixture was then divided into two portions and each portion was extracted with 5 x 100 ml portions of ethyl acetate. The organic layer was then washed with sodium bicarbonate, brine and finally distilled water. It was dried over magnesium sulphate and concentrated to give 14 g of a dark red oil.[15] This material was heated for five hours (bath temp. 80 °C) in 280 ml of ethanol containing 28 ml of conc. sulphuric acid. The reaction mixture was allowed to cool and was then poured into iced water (300 ml). After extraction with ether, the organic layer was washed with saturated sodium bicarbonate, brine and distilled water and dried over magnesium sulphate. After concentration under reduced pressure, purification by flash chromatography (silica, 50/50 ether/petrol Rf. 0.3) yielded 8.5 g of a mixture of isomeric alkenes (7a+7b)[16] (50% yield from (3) as an orange sweet smelling oil. This material was then hydrogenated over 10% Pd/C catalyst (0.33 gram) EtOH (50 ml) using a balloon of hydrogen. The solution was then filtered and concentrated under reduced pressure. Flash chromatography (petrol/ether 1:1 Rf:0.36) on silica gave (8) as a colourless oil in 80% yield. Found M+, 286.1581 ($C_{18}H_{22}O_3$ requires M, 286.1569). ν_{max}(film)/cm^{-1} 1720-1760 (C=O and CO_2Et). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.33 (1H, d, J=8.1 Hz, H-9), 7.21 (1H, m) and 7.12 (1H, m) H7 and H8, 7.05 (1H, d, J=7.7 Hz, H-6), 4.05 (2H, q, J=7Hz, $CH_3\underline{CH_2}$), 2.68 (2H, m, H-5), 1.9-2.4 (11H, m, H-4 H3a H1 H2 H10 H11), 1.2 (3H, t, J=7Hz, $\underline{CH_3}CH_2$). ^{13}C ($CDCl_3$) 220.23 (C-3), 173.27 (C-12), 139.62 137.15 (C-5a) (C-9a), 129.05 (C-9), 126.78 126.56 126.27 (C-6) (C-7) (C-8), 60.45 ($\underline{CH_2}CH_3$), 53.34 (C-5), 45.23 (C-9b), 37.28 (C-3a), 36.33 (C-2), 36.18 (C-11), 30.33 (C-1), 27.44 (C-10), 21.33 (C-4), 14.13 ($\underline{CH_3}CH_2$).

Reduction/oxidation of (8) to give 9b(2' Formyl-ethyl) 2,3,9b,3a,4,5 hexahydro-1H-benz[e]indene-3-one(9):

To lithium aluminium hydride (0.25 g, 1.4 eq) in anhydrous THF (10 ml) was added, dropwise,a solution of the keto-ester (8) (1 g in 10 ml of THF) over a period of 10 minutes. The reaction mixture was then stirred at

room temp. for 30 minutes followed by gentle heating (bath temp 40°C) for a further 15 minutes by which time the reaction had gone to completion. Ethyl acetate (30 ml) was then added (very slowly at first) to destroy the excess lithium aluminium hydride and water was then added dropwise until a white granular precipitate formed . This was then filtered, 50 ml of water was added, and the crude product extracted with 3x30ml portions of ethyl acetate. It was then washed with brine, distilled water, and, dried over magnesium sulphate. After concentration under reduced pressure, the crude material was oxidised with pyridinium chloro-chromate as follows. The diol (0.7 g of crude) in 5 ml of DCM. was added dropwise to a suspension of PCC (1.6 g, 3eq) and NaOAc (0.12 g, 0.6 eq) in 15 ml of DCM. The reaction mixture was stirred at room temp. for 30 minutes followed by gentle reflux for a further 30 minutes by which time the reaction had gone to completion. It was then allowed to cool and was added to 50 mls of ether. The residual material was washed many times, first with DCM, and then with ether. Vacuum filtration through "florisil" followed by concentration under reduced pressure gave the crude aldehyde which was then purified by flash chromatography to give the aldehyde (9) as a colourless oil in 55% yield (from the ester). (Found M^+, 242.1307. ($C_{16}H_{18}O_2$ requires M, 242.1307); ν_{max}(film)/cm^{-1} 1710-1760 CHO and C=O; ^1H NMR ($CDCl_3$ 400 MHz) 9.65 (1H, t, J 1.3 Hz, H-12), 7.32 (1H, m, H-9), 7.1-7.25 (2H, m, H-7 H-8), 7.07 (1H, m, H-6), 2.65-2.75 (2H, m, H-5), 1.9-2.45 (11H, m, H-4 H-3a H-1 H-2 H-10 H-11). ^{13}C NMR ($CDCl_3$) 220.13 (C3), 201.42 (C12), 139.59 (C9a), 137.22 (C5a), 129.17, 126.88, 126.48, 126.43 (C6 C7 C8 C9), 53.44 (C3a), 45.06 (C9b), 40.14 (C2), 36.38 (C5), 34.33 (C11), 27.49 (C10), 21.40 (C4).

The (acid catalysed) aldol condensation of (9)

The keto-aldehyde (9) (0.75 g, 3.1 x 10^{-3} mole) and pTSA (1/18 equivalents, 0.033 g, 1.7 x 10^{-4} mole) in 15 ml. of toluene was heated at 60° C for 3 hours. The solution was then cooled, 15 ml. of ether was added and the mixture washed with brine and distilled water. Drying over magnesium sulphate and concentration gave an orange oil (three components by TLC) which on purification by flash chromatography (Rf, neat ether, of 14(b)=0.53, 14(c)=0.43, 14(a)=0.27) yielded 0.28 g of 14(a) (37%) (m.p.158.2-158.6), 0.14 g of 14(b) (18%) and 0.28 g of 14(c) (which was an inseparable mixture of epimers contaminated by a small amount of starting material). Submitting a mixture of (10b) and (10c) to the above conditions re-established the equilibrium and raised the yield of (10a) to 55% . (Found for **10(a):** C, 78.72; H 7.59%; M+, 242.131. $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.43% M, 242.13068). ν_{max}(mull)/cm^{-1} 1720 C=O, 3440 (OH). ^1H NMR ($CDCl_3$, 400 MHz) 7.3 (1H, d, J 7.7 H-1), 7.18-7.22 (1H, m) and 7.1-7.15 (2H, m) H-4 H-3 H-2, 4.00 (1H, m H-16), 2.79 (1H, d, J 3.4) and 2.77-2.75 (1H, m) H-11, 2.61-2.59 (1H, m H-12), 2.13-2.28, (5H, m H-14ax H-15eq H-8 H-15ax H-11eq), 1.96 (1H, d, J 7,OH), 1.89-1.86 (1H, dd, J 12.5 and J 2.2, H-11ax, 1.65-1.7 (1H, m, H-14eq), 1.38-1.57 (2H, m, H-7). ^{13}C NMR ($CDCl_3$) 220.15 (C-13), 141.26 (C-10), 135.97 (C-5), 128.97 (C-1), 126.64, 126.08, 125.95 (C-4 C-3 C-2), 71.56 (C-16), 54.88 (C-8), 53.27 (C-12), 42.56 C-9, 40.56 (C-6), 37.42 (C-7), 30.12 (C-14), 29.94 (C-11), 22.82 (C-15). Found for **10(b)** M+, 242.1307 ($C_{16}H_{18}O_2$ requires M, 242.1307); ν_{max}(film)/cm^{-1} 1730 (C=O), 3420 (O-H). ^1H NMR ($CDCl_3$, 400 MHz) 7.41 (1H, m, H-1), 7.23 (1H, m, H-3), 7.13 (2H, m, H-4 H-2), 4.14 (1H, bs, H-16), 2.78 (2H, m, H6), 2.68 (1H, m, H-12), 2.55 (1H, m, H-11ax), 2.5 (1H, m, H-14ax), 2.35 (1H, m, H-8), 2.15 (1H, m, H-7α), 1.88 (1H, m, H-11eq), 1.82 (1H, m, H-15eq), 1.79 (1H, m, H-15ax), 1.5 (2H, m, H-7β H-14eq). ^{13}C NMR ($CDCl_3$) 128.67 (C-1), 126.51 126.408 125.81 (C-4 C-3 C-2), 141.90 (C-5), 135.55 (C-10), 34.77 (C-6), 29.85 (C-7), 51.48 (C-8), 42.92 (C-9) 27.89 (C-11), 54.64 (C-12), 218.93 (C-13), 22.89 C-14, 34.50 (C-15), 66.30 (C-16). Found for **10(c):** (mixture of epimers) ν_{max} (film)/cm^{-1} 1700-1760 (C=O), 3440 (OH). ^1H NMR ($CDCl_3$, 400 MHz) 7.33 (1H, m, H-1), 7.25 (1H, m, H-2), 7.10 (1H, m, H-3), 7.05 (1H, m, H-4), 4.18 (1H, t, J 6.2, H-16), (there is a similiar triplet at 4.3 for the β epimer which from integration trace makes up about 15% of the mixture) 2.7 (1H, m, H-6α), 2.59 (1H, m, H-6β), 2.2-2.5 (4H, m, H-12 H-11α H-14β, 1.95-2.19 (3H, m, H-11β H-15α H-7α, 1.72 (2H, m, H-15β H-7β. ^{13}C NMR ($CDCl_3$) 128.23 (C-1), 127.09 (C-2), 126.90 (C-3), 125.59 (C-4), 144.08 (C-5), 134.69 (C-10), 35.84 (C-6), 33.78 (C-7), 62.13 (C-8), 52.85 (C-9), 26.49 (C-11), 39.38 (C-12), 223.94 (C-13), 26.41 (C-14), 38.68 (C-15), 80.05 (C-16).

Protection of 4,4,10,16 tetra des-methyl 1,2,3,4 tetra dehydro-16α-hydroxy stemodan-13-one (10a) as its methyl ether derivative (11):

The ketol (10a) (0.566 g, 2.3 mmol) and Ag_2O (0.70 g, 3 mmol) were stirred in 7 ml of methyl iodide and 4 ml of acetonitrile for 48 hrs at room temperature in a round bottomed flask wrapped in tin foil (to protect from light). The mixture was then diluted with 20 ml of ether and filtered to remove the insoluble salts. Rotary

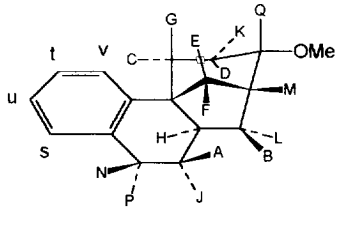
evaporation and column chromatography on silica yielded 0.456 g (78% yield) of the methyl ether (11) as a white solid. An analytically pure sample was obtained by recrystalisation from diethyl ether. (m.p. 120.5-121.0). Found: C, 79.58; H, 7.88%; M+, 256.146. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.86%; M, 256.146). ν_{max}(mull)/cm^{-1} 1736 (C=O), 1105 (C-O). ^{1}H NMR ($CDCl_3$,400 MHz) 7.31 (1H, d, J 7.3, H-1), 7.19-7.24 (1H, m) and 7.09-7.16 (2H, m) (H4 H3 H2), 3.53-3.59 (1H, m, H-16), 3.44 (3H, s, OCH3), 2.79-2.83 (1H, m, H12), 2.73-2.79 (2H, m, H6), 2.10-2.28 (5H, m, H-14ax H-15eq H-8 H-15ax H11eq), 1.82-1.87 (1H, dd, J 12.5 and J 2.2, H-11ax), 1.65-1.73 (1H, m, H-14eq), 1.41-1.58 (2H, m, H-7). 13C NMR 218.47 (C-13), 141.57 (C_10), 136.19 (C-5), 128.93 (C-1), 126.59 126.08 126.00 (C4 C3 C2), 80.32 (C16), 56.31 (O-CH3), 52.89 (C8), 50.40 (C12), 42.63 (C9), 40.27 (C6), 37.56 (C7), 29.99 (C14), 27.19 (C11), 23.08 (C15).

Formation of the thioketal derivative of (11):

To a stirred solution of the ketone (11) (200 mg, 0.78 mmol) and ethanedithiol (0.1 ml, 2.3 mmol) in 1 ml of chloroform was added 0.1 ml of borontrifluoride etherate. After 20 minutes the mixture was diluted with 5 ml of DCM, and quenched with 7 ml of saturated sodium bicarbonate solution. After seperation of the layers the aqueous layer was extracted with 3 x 5 ml portions of DCM. The combined organic extracts were then washed successively with 5 ml portions of 1N sodium hydroxide, brine and distilled water. After drying over magnesium sulphate and evaporation of the solvent the crude material was purified by flash column chromatography on silica (60 petrol/40 ether Rf = 0.52) to yield 171 mg (66% yield) of thioketal (12). Found: M+NH4$^+$, 350.1612 ($C_{19}H_{24}S_2O$ requires M+NH4$^+$, 350.1614). ν_{max}(film)/cm^{-1} 1107 (C-O). ^{1}H NMR ($CDCl_3$ 400 MHz) 7.15-7.20 (2H, m) and 7.07-7.10 (2H, m) H1 H2 H3 H4, 3.47-3.5 (1H, m, H-16), 3.42 (3H, s, OCH_3), 3.37-3.25 (4H, m, SCH_2CH_2S), 2.80-2.84 (1H, m, H12), 2.58-2.76 (2H, m, H6), 2.45-2.50 (1H, m, H8), 1.7-1.82 (2H, m, H7), 2.10-2.16 (1H, m) and 1.98-2.08 (3H, m) and 1.82-1.88 (1H, m) and 1.42-1.55 (1H,m) H11 H14 H15. ^{13}C NMR 143.52 (C10), 137.75 (C5), 128.03 (C1), 126.66 126.41 125.44 (C2 C3 C4), 82.69 (C16), 77.63 (C13), 56.78 (C12), 56.24 (OMe), 51.88 (C8), 46.10 (C9), 43.47 (C6), 41.44 (C7), 38.30 and 38.24 (CH2CH2), 30.78 (C14), 28.97 (C15), 26.94 (C11).

Raney nickel desulphurisation of (12) to give 4,4,10,16 tetra des-methyl 1,2,3,4 tetra dehydro-16α-methoxy stemodane (13):

The thioketal (12) (100 mg, 0.3 mmol) and Raney nickel (1g of a 50% slurry in water) in ethanol (2 ml) was heated to 60 °C for 3 hours. The reaction mixture was then diluted with 5 ml of ethanol and filtered. Evaporation of the solvent and column chromatography (petrol/ether 7:3) yielded 45 mg (72% yield) of as a colourless oil which crystalised on standing (m.p. 57-57.5). (Found: C, 83.78; H, 9.42%; M+NH4$^+$, 260.2014. $C_{17}H_{22}O$ requires C, 84.25; H, 9.15%; MNH4$^+$ 260.2016). ν_{max}(film)/cm^{-1} 1099 (C-O).



^{1}HNMR (600 MHz, $CDCl_3$): 7.25 (1H, m, Hv), 7.12-7.16 (2H, m, Hu Ht), 7.06 (1H, m, Hs), 3.34 (3H, s, -OMe), 3.30 (1H, m, HQ), 2.67 (1H, ddd, J=15.7, 4.3 and 3.3, HP), 2.64 (1H, ddd, J=15.7, 12.3 and 3.4, HN), 2.41 (1H, m, HM), 2.17-2.22 (1H, ddd, J=1.92, 8.55 and 13.46, HL), 1.95-2.01 (1H, m, HK), 1.87-1.93 (1H, m, HJ), 1.82-1.87 (2H, m, HG HH), 1.79-1.81 (1H, dd, J=2.99 and 5.77, HF), 1.60 (1H, d, J=11.57, HE), 1.40-1.49 (2H, m, HC HD), 1.24-1.34 (2H, m, HA HB). ^{13}C NMR: 143.72 and 137.31 C10 and C5, 128.39 127.41 125.92 and 125.05 C1 C2 C3 and C4, 80.83 C16, 55.61 O-CH3, 45.49 C9, 42.55 C11, 42.00 C8, 39.46 C14, 38.44 C12, 32.95 C13, 31.26 C6, 31.16 C7, 26.25 C15.

Formation of the tosyl hydrazone derivative of (11):

The ketone (11) (300 mg, 1.18 mmol) and p-toluene sulphonyl hydrazine (0.22 g, 1.18 mmol) in 1 ml of 0.118 molar solution of HCl in ethanol was heated to 100 °C for 10 minutes. The reaction mixture was then allowed to cool and left stand at room temperature for 3 hrs during which time the tosyl hydrazone crystalised from solution. Vacuum filtration and recrystalisation from ethanol (m.p. 155.5-155.8) yielded 375 mgs (75% yield) of tosyl hydrazone (14). (Found: C, 67.50; H, 6.63; N, 6.60%; MH$^+$, 425.1899. $C_{24}H_{30}N_2SO_3$ requires C, 67.58; H, 7.09; N, 6.57%; MH$^+$, 425.1899). ν_{max}(mull) / cm^{-1} 1596 (C=N), 1091 (C-O). ^{1}H NMR (CDCl3, 400 MHz) 7.81 (2H, d, J=8.4, H18 and H22), 7.30 (2H, d, J=8.1, H19 and H21), 7.05-7.26 (4H, m, H1 H2 H3

H4), 3.54-3.59 (1H, m, H16), 3.31 (3H, s, OMe), 3.2 (1H, m, N-H), 2.69-2.72 (2H, m, H6), 2.43 (3H, s, Ar-CH_3), 2.22-2.24 (1H, m) and 2.19-2.21 (1H,m) H8 and H12, 2.11-1.0 (8H, m, H7 H11 H14 H15). ^{13}C NMR 168.07 (C13), 143.35 (C10), 141.01 (C17), 136.60 (C5), 136.03 (C20), 129.25, 129.94, 127.84, 126.43, 126.29, 125.94 C1 C2 C3 C4 {C18/C22} {C19/C21} 82.25 (C16), 55.86 (OMe), 48.76 (C12), 44.32 (C8), 43.72 (C9), 41.06 (C6), 37.22 (C7), 30.02 (C14), 26.27 (C11), 25.43 (C15), 21.57 (Ar-CH3).

Protic Bamford Stevens elimination of (14) to give (16):

The tosyl hydrazone (14) (100 mg, 0.24 mmol) in 1 ml of 1N $NaOCH_2CH_2OH$ (formed by adding sodium metal to the solvent) in ethyleneglycol was heated to 160°C for 3 hrs by which time all starting material was consumed. After quenching with saturated ammonium chloride solution and extracting with ether the organic extracts were washed with brine distilled water and dried over magnesium sulphate. Column chromatography yielded 33 mg (60% yield) of the alkene(16) as a colourless oil. ^{1}H NMR ($CDCl_3$ 400 MHz) 7.04-7.10 (2H, m, H6 H9), 7.15-7.23 (2H, m, H7 H8), 5.65-5.71 (2H, m, H2 H3), 4.28 (1H,t, J=5.5, H12), 3.64-3.68 (2H, m, H14), 3.45-3.49 (2H, m, H13), 3.24 (3H, s, OMe), 2.57-2.68 (5H, m, H5 H1, H3a), 2.19 (1H, m, OH), 1.1-2.0 (6H, m, H4 H10 H11). ^{13}C NMR ($CDCl_3$) 144.20 (C9a), 138.11 (C5a), 133.96 (C2), {128.44, 128.00, 127.67, 126.52, 125.02 C6 C7 C8 C9 C3}, 104.48 C12, 66.715 C13, 62.106 C14, 52.94 (OMe), 49.73 (C3a), 49.05 (C1), 46.91 (C9b), 39.06 (C5), 30.05, 28.57, 28.22, C4 C10 C11.

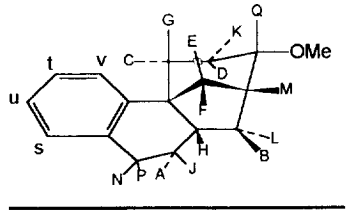
Aprotic Bamford Stevens of (14) to give (15):

The tosyl hydrazone (14) (100 mg, 0.24 mmol) in 1 ml of 1N sodium methoxide in dimethyl diethylene glycol was heated at 180 °C for 4 hours by which time all starting material was consumed. Column chromatography (ether/petrol 70:30) gave 25 mg (45% yield) of the required alkene (15) (permanganate active on TLC). (Found: M+, 240.1514. $C_{17}H_{20}O$ requires M+ 240.1514). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.15-7.20 (2H, m) and 7.08-7.13 (2H, m) H1 H2 H3 H4, 5.59 (1H, m, H13), 3.37 (3H, s, OCH3), 3.30-3.36 (1H, m, H16), 2.85-2.95 (2H, m, H6), 2.73-2.81 (1H, m, H12), 2.54-2.61 (1H, m) and 2.36-2.45 (1H, m) H7, 1.96-2.06 (2H, m, H15), 1.73-1.77 (1H, m) and 1.61-1.69 (1H, m) H11, 1.96-2.06 (2H, m, H15). ^{13}C NMR 146.22 (C8), 143.42 (C10), 136.25 (C5), 128.66 (C1), 126.29 125.87 125.56 (C2 C3 C4), 120.22 (C13), 76.87 (C16), 55.90 (OCH3), 48.43 (C9), 47.83 (C6), 42.58 (C12), 31.28 (C7), 30.38 (C11), 36.51 (C15), 23.89 (C14).

Hydrogenation of (15) over platinum to give 4,4,10,16 tetra des-methyl 1,2,3,4 tetra dehydro-16α-hydroxy aphidicolane (17):

A three necked round bottomed flask containing 10 mg of PtO_2 in 1 ml of ethanol was flushed with nitrogen and then exposed to an atmosphere of hydrogen (balloon). After stirring this mixture for 1 hour the alkene (15) in 0.3 mls of ethanol was added and stirring was continued for 48 hours. The reaction mixture was then purged with nitrogen and diluted with 2 ml of ethanol. Gravity filtration and evaporation of the solvent yielded 20 mg of saturated compound (17).

^{1}H NMR ($CDCl_3$, 400 MHz) 7.06-7.09 (4H, m, Hu Ht Hv Hs), 3.37-3.34 (1H, m, Hq), 3.33 (3H, s, -OMe), 3.08-3.0 (1H, ddd, J=18, 8.5 and 1.5, Hp), 2.90-2.98 (1H, ddd, J=18, 9 and 9, Hn), 2.64-2.60 (1H, m, Hm), 1.92-2.04 (2H, m, Hl and Hk), 1.90-1.78 (4H, m, Hj Hg Hf Hh), 1.78-1.70 (1H, m, He), 1.58-1.36 (4H, m, Ha Hb Hc Hd). ^{13}CNMR 146.90 and 136.35 C10 C5, 128.96 125.57 125.02 124.06 C1 C2 C3 C4, 81.18 C16, 55.53 -OCH_3, 45.20 C9, 44.25 C11, 40.31 C8, 38.23, C14, 35.10 C12, 28.90 C13, 27.26 C6, 25.57 C7, 21.31 C15.



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[13] Molecular modelling minimisation of both possible cyclised products (i.e. cis fused B/C and trans fused B/C rings) show that the compound with the cis fused ring system is considerably more stable. This preference of the B/C ring system to adopt a cis ring fusion is indicated by molecular modelling minimisation for all subsequent compounds mentioned in this paper
[14] Structure supported by X ray crystallographic determination.
[15] The material could be separated into (5) (40% yield) and a mixture of (6a) and (6b) (20% yield) at this stage by flash chromatography. Analysis for (5): Found MH^+ = 328.1733 ($C_{19}H_{25}O_2SiN$ requires M+H 328.17326). ν_{max} (mull)/cm^{-1} 2241 (CN), 1746 (C=O). ^1H NMR (400 MHz, $CDCl_3$) 7.25 (2H, m, H-6 H-7), 7.15 (1H, m, H-8), 7.05 (1H, m, H-9), 2.9 (1H, m, H-4β), 2.64 (1H, m, H-4α), 2.39 (1H, m, H-10α), 2.33 (1H, m, H -2β), 2.12-2.28 (4H, m, H-1 H-11), 1.93-2.10 (3H, m, H-2α H-4β H-10β), 1.75 (1H, m, H-4α). ^{13}C NMR ($CDCl_3$) 129.03 (C9), 126.88 126.66 126.50 (C8 C7 C6), 137.69 (C5a), 136.02 (C9a), 34.29 (C5), 33.19 (C4), 82.50 (C3a), 48.86 (C9b), 216.37 (C3), 33.38 (C2), 25.480 (C1), 27.67 (C10), 13.87 (C11), 120.07 (C12), 1.80 (TMS-O).
[16] Analysis for the mixture (7a+7b). (Found: M+, 284.1407. $C_{18}H_{20}O_3$ requires 284.1412). υ_{max}(neat)/cm^{-1} 1700-1745 (br) C=O, CO_2Et; 1660 C=C. The ratio of 11a:11b is 60: 40 from the ^1H NMR.

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