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Chemistry of Insect Antifeedants from Azadirachta Indica (Part 4):[1] Synthesis Towards the Limonoid Azadirachtin; Preparation of a Functionalised Decalin Fragment

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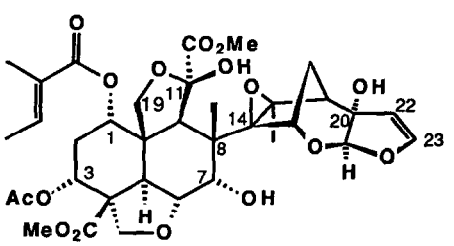
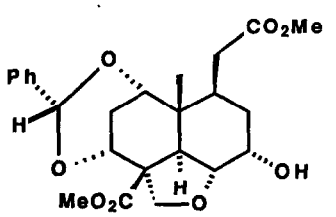
Abstract: Synthetic studies are described towards the functionalised decalin **(2)**. This represents an advanced intermediate in a proposed total synthesis of the naturally occurring insect antifeedant azadirachtin **(1)** involving a late coupling reaction to form the C-8 – C-14 bond. The final route to **(2)** involved an intramolecular Diels-Alder reaction of **(13)** and subsequent internal Michael addition to construct the *trans* -decalin **(26)**. A series of stereoselective functional group interconversions were used to transform this compound into **(2)** in good overall yield.

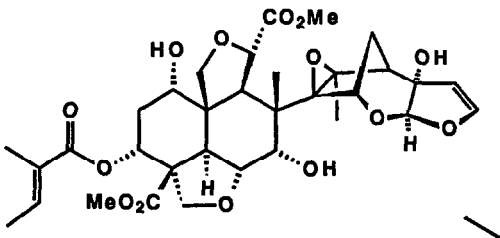
The potent antifeedant and growth regulatory properties of the limonoid azadirachtin **(1)** have stimulated interest in its synthesis and in the preparation of simpler structural fragments which may display similar activity.[1-5] Our unambiguous structural assignment of **(1)** by X-ray crystallographic analysis has set the stage to begin these investigations.[5a] Since azadirachtin contains 16 chiral centres, a plethora of oxygen functionality and is both acid and base labile, its synthesis presents a formidable challenge. Inspection of the structure of **(1)** reveals the presence of a multifunctional decalin and a polycyclic hydroxydihydrofuran fragment joined at C-8 – C-14 , and suggests a convergent approach in which these two units are connected at some late stage in the synthetic scheme. Here we report in full the preparation of the functionalised decalin **(2)** which has considerable homology with the natural product **(1)** and related limonoids such as 3-tigloylazadirachtol **(3)**[6] and salannin **(4)**.[7]



(1)



(2)



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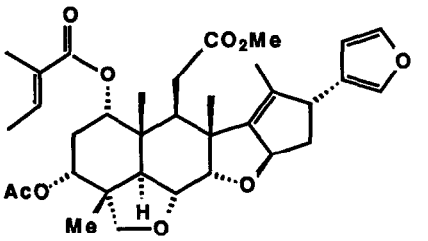
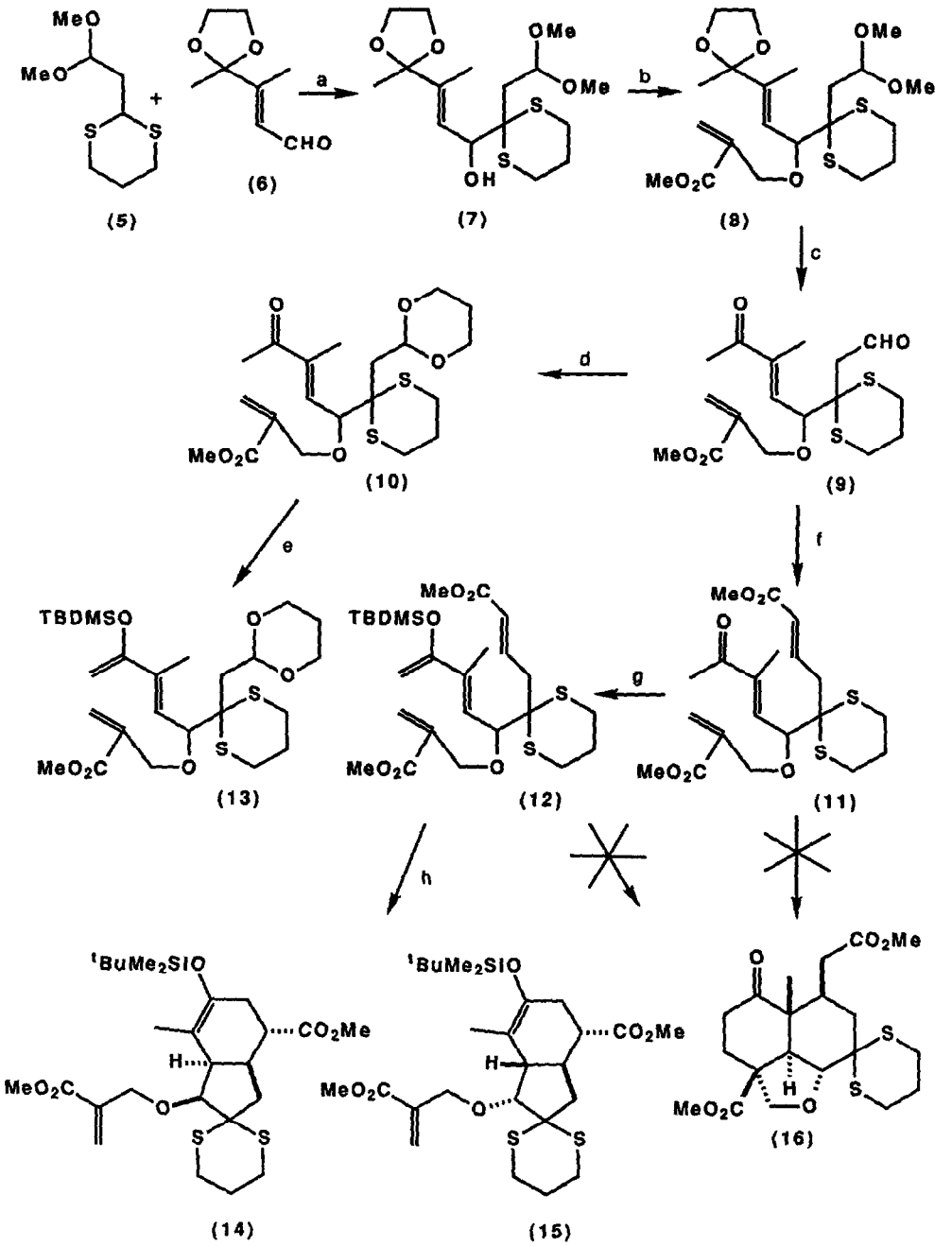


(4)

The synthesis began with dithiane anion coupling of **(5)** with the unsaturated aldehyde **(6)** to give **(7)** (93%) followed by alkylation with methyl bromomethacrylate[8] using potassium hydride and tetramethylethylene diamine (TMEDA) to afford the mixed acetal **(8)** (80%). This was heated under reflux in aqueous acetone containing a catalytic amount of pyridinium p-toluenesulphonate to afford **(9)** (94%) which was then reacted with methyl triphenylphosphoranylidene acetate to give **(11)** (88%). Disappointingly, under a variety of conditions designed to promote an intramolecular triple Michael reaction **(11)** failed to yield any of **(16)**. As an alternative, **(11)** was converted to the t-butyldimethylsilyl enol ether **(12)** and heated to 130 °C in the hope of achieving a selective intramolecular Diels-Alder reaction. However, under these conditions a mixture of cycloaddition products was obtained including **(14)** and **(15)** resulting from preferential reaction of the least hindered dienophilic double bond (Scheme 1).

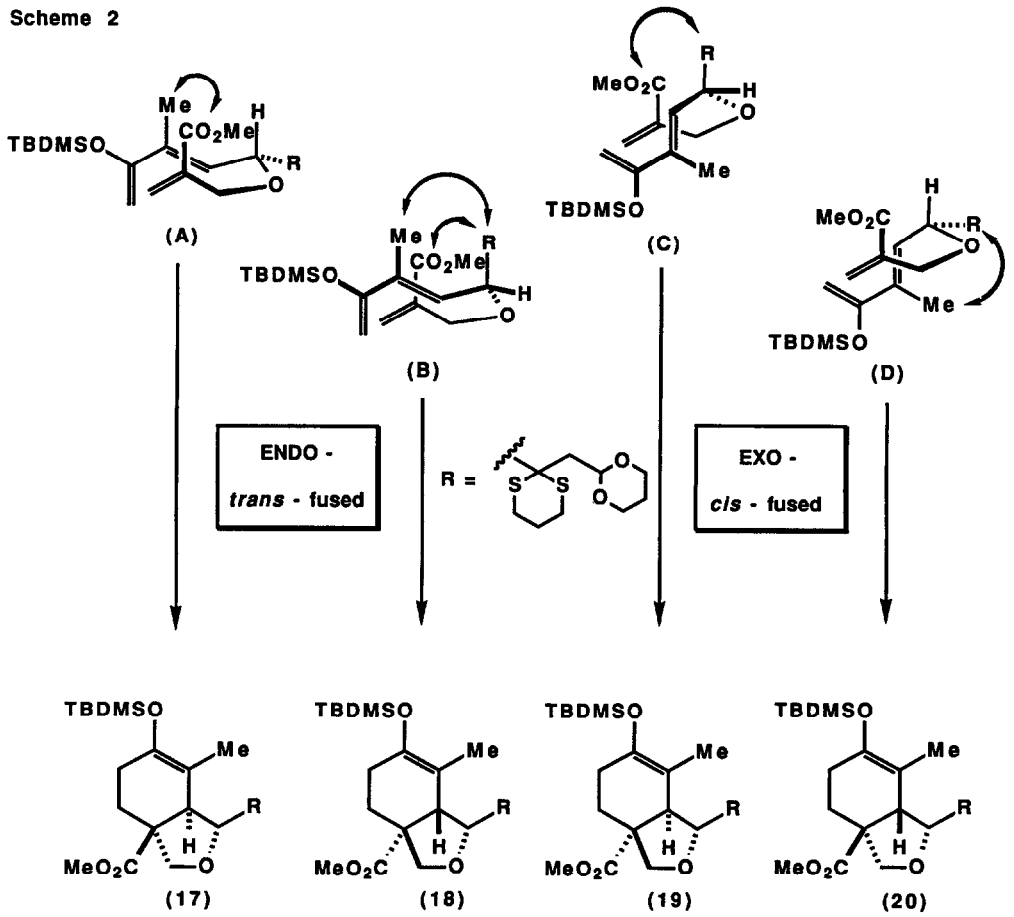
Owing to these results we chose to progress the synthesis from **(9)** *via* **(10)** prepared by selective acetal formation using propane-1,3-diol and pyridinium tosylate (79%). The expectation was that an intramolecular Diels-Alder reaction of the derived t-butyldimethylsilyl dienol ether **(13)** (t-butyldimethylsilyl triflate and triethylamine) should provide, stereoselectively, a compound containing two of the three rings required for our synthesis. It might initially have been anticipated, in view of literature precedents,[9] that the reaction would exhibit an *exo* -product stereochemical bias following asynchronous peripheral bond formation in the transition state.[10, 11] However a more detailed analysis of the reaction pathway and the four possible transition states **(A)**, **(B)**, **(C)** and **(D)** leading to the products **(17)**, **(18)**, **(19)** and **(20)** revealed that use of the especially bulky dithiane side chain might introduce an interesting and significant perturbation (Scheme 2).



Scheme 1

a)BuLi, TMEDA 93%. b)KH, TMEDA 80%. c)PPTS, Actone-H_2O.94%. d)Propane-1,3-diol, PPTS 79%. e)TBDMSOTf, Et_3N 87%. f)$Ph_3P{=}CHCO_2Me$, DCM. g)TBDMSOTf, Et_3N. 86%. h)Toluene, 110 °C

Scheme 2

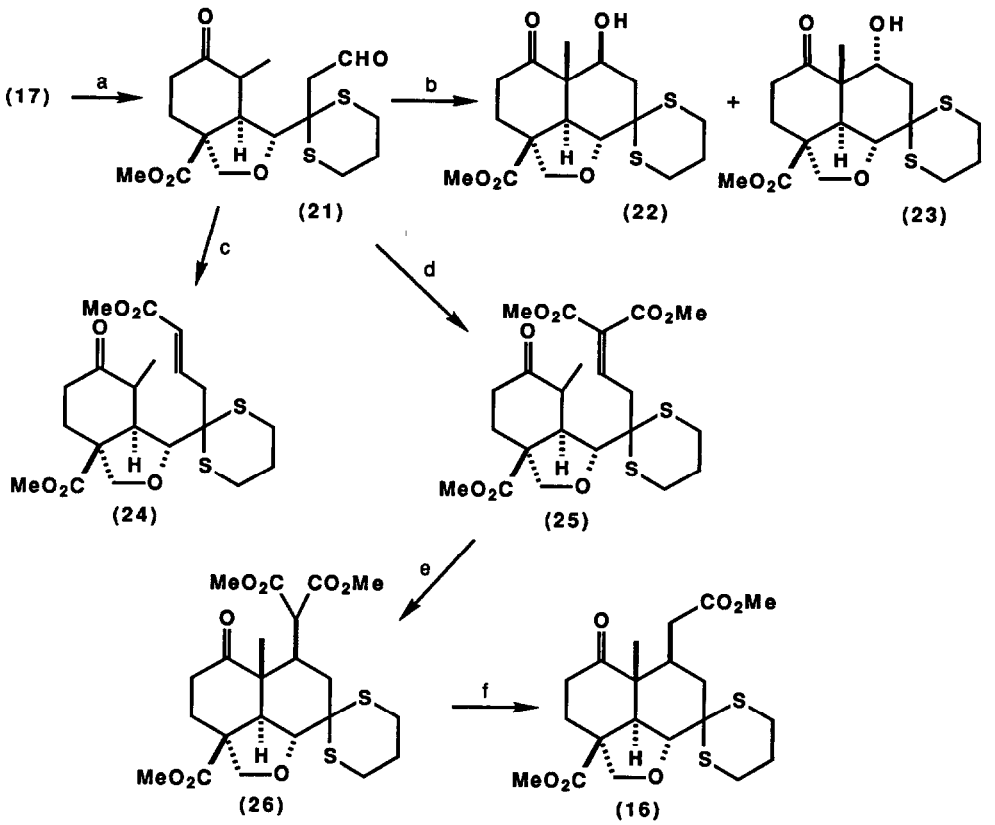


Examination of the steric factors operating suggested that in the *endo* - mode **(B)** substantial interactions would exist between the ester, the diene methyl and side chain substituents thus clearly disfavouring this process. Furthermore in *exo* - arrangement **(C)** large interactions between the diene methyl and the *syn* - pseudo equatorially orientated dithiane chain would inhibit the formation of **(19)**. Since peripheral bond formation should be preferred in the transition states of these diene and dienophile combinations *trans* -annular effects were expected to be reduced. Nevertheless examination of the required *endo* - **(A)** versus the unwanted *exo* - **(C)** modes indicated a likely selectivity for **(A)** where the largest substituent in the linking chain adopts a pseudoequatorial position. This crude analysis therefore predicted production of the desired *endo trans* - fused product **(17)**. Indeed in the actual experiment we found that only two products were obtained. On heating **(13)** at 135 °C for 45 mins in DMSO **(17)** and **(19)** were formed in the very pleasing separable ratio of 5:2 respectively. Structural assignment of these compounds

was made based on ^1H nmr and infra-red spectroscopy in comparison with literature precedents and our own model studies.[9] Carbon-carbon double bond stretching frequencies of 1648 and 1681 cm^{-1} for **(17)** and **(19)** respectively indicate the greater strain present in the *trans* -fused bicyclo[4.3.0] arrangement of the former. Furthermore the 7a-H nmr signals for **(17)** and **(19)** occurred at 3.47 and 3.74 ppm, suggesting the *cis* vicinal relationship of the ester group and 7a-H in the latter.

Having devised a route to a compound **(17)** containing three of the required relative chiral centres we next sought methods for effecting the final ring closure. Firstly it was found that **(17)** could be deprotected (73%) with AcOH/THF/H_2O to **(21)**. Under basic aldol conditions **(21)** gave a 3:1 mixture of the crystalline alcohols **(22)** and **(23)**. Single crystal X-ray diffraction analysis of alcohol **(24)** enabled us to confirm our structural assignment of this compound and by inference also confirmed our assignment of compound **(17)** (fig. 1a). Treatment of **(21)** with methyl triphenylphosphoranylideneacetate produced the unsaturated ester **(24)** (90%) but under a large range of reaction conditions we were unable to effect its cyclisation. Failure in this last reaction was not especially surprising since we were attempting to form a *trans*- fused decalin by ring closure involving equatorial bond formation: normally *cis* - decalins result from this type of bond construction. However in this special case the constraining effect of the fused five membered cyclic ether would probably preclude the formation of a *cis* - ring junction. Therefore in order to maximise the chances of success for cyclisation we decided to enhance the electrophilicity of the sidechain. To this end **(21)** was reacted with dimethyl malonate, piperidine and acetic acid to give a 90% yield of the triester **(25)** in which the additional ester group was expected to confer the desired increase in reactivity of the cyclisation substrate. Indeed, when **(25)** was treated with sodium methoxide in methanol at room temperature a single product **(26)** was obtained in 60% yield. Since the full structure assignment of **(26)** was crucial to the synthesis and difficult to obtain from spectroscopic data we resorted to X-ray crystallographic methods (fig.1b) which clearly showed the equatorial placement of the malonyl group and the *trans* - fused decalin arrangement.

Decarboxylation of **(26)** using sodium chloride in DMSO at 160 °C followed by remethylation with diazomethane gave **(16)** in 81% yield (scheme 3). For the remaining steps of the synthesis the correct introduction and orientation of hydroxyl groups at C-1, C-3 and C-7 needed to be established and this was achieved using the following sequence of reactions. Dehydrogenation of **(16)** was accomplished by selenenylation, using N-phenylselenophthalimide[12] and *syn* -elimination of the corresponding selenoxide obtained by selective selenium oxidation with 3-(p-nitrophenyl)-2-phenylsulphonyl-oxaziridine,[13] to give **(27)** in 62% overall yield. Since the planned introduction of the C-3 hydroxyl group involved an oxidation it was necessary to firstly remove the dithiane group in **(27)** using MeI in H_2O to give the dione **(28)** (70%), which was subsequently reduced with sodium borohydride and $CeCl_3.7H_2O$ to the diols **(29)** (78%).[14] This reaction demonstrates that stereoselective reduction at C-7, to give

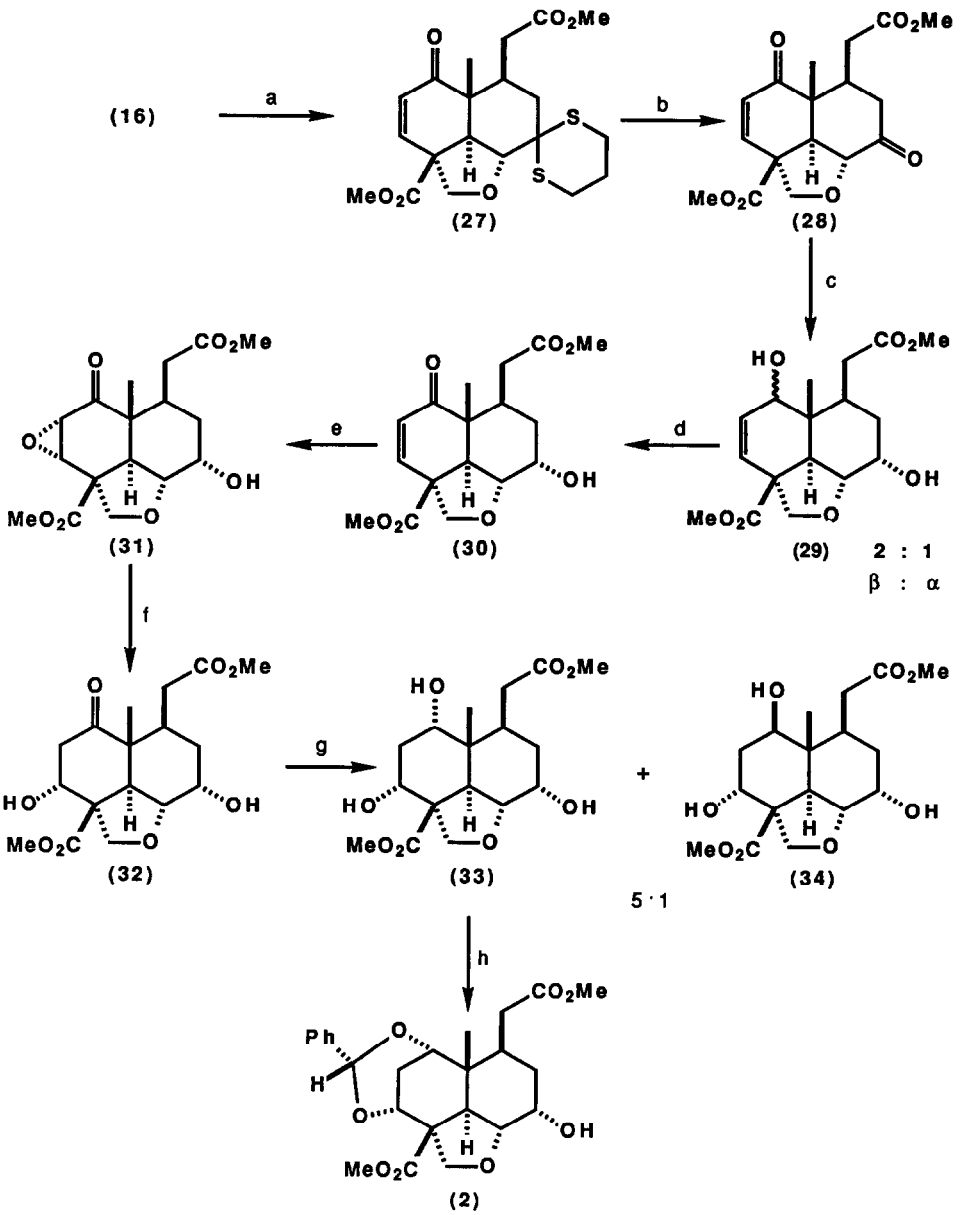


Scheme 3

a) AcOH-THF-H_2O, 65 °C. 73% b) NaOMe, MeOH, O °C. 75%. c) $Ph_3P{=}CHCO_2Me$, DCM 90%.
d) Dimethyl malonate, piperidine, AcOH, 80 °C. 90% e) NaOMe, MeOH, r.t 60%.
f) i. DMSO, NaCl, H_2O, 160 °C ii. CH_2N_2 80%

the natural axial hydroxyl configuration can be effected. Oxidation of **(29)** to **(30)** with manganese dioxide re-established the enone arrangement in ring A.

Treatment of this enone **(30)** with hydrogen peroxide and potassium carbonate quantitatively produced the α-epoxide **(31)**, which underwent reductive ring opening with aluminium amalgam to afford the ketodiol **(32)** in excellent yield. Stereoselective reduction of the carbonyl group in **(32)** to produce the required triol **(33)** appeared unlikely using standard methodology and therefore necessitated some experimentation. It was discovered that the use of sodium borohydride in THF containing sodium bicarbonate and magnesium bromide caused reduction to occur selectively to afford **(33)** together with a small amount of the undesired isomer



Scheme 4

a) i LDA, NPSP ii 3-(p-nitrophenyl)-2-(phenylsulphonyl)oxaziridine, $NaHCO_3$-DCM 62%. b)MeI, CH_3CN-H_2O. 70%. c)$NaBH_4$, $CeCl_3.7H_2O$. 78% d)MnO_2, DCM. 60% e)H_2O_2, K_2CO_3, MeOH 95%. f)Al/Hg, $NaHCO_3$, EtOH. 95% g)$NaBH_4$, $MgBr_2$, $NaHCO_3$, THF. 80%. h)PhCHO, PPTS, benzene, 80 °C. 95%

(34) in a ratio of 5:1 in 80% yield. The role of $MgBr_2$ in this reaction was crucial; we believe initial α-face complexation of magnesium to the axial hydroxyl group directed reduction from the top face as required. Final protection of the 1,3-*cis* -diaxial diol in **(33)** as the benzylidine acetal gave the target decalin molecule **(2)**‡‡ (95%) (Scheme 4). This molecule contains 8 of the chiral centres of azadirachtin with correct relative configuration and represents a key substrate for the investigation of our coupling strategy towards a total synthesis of azadirachtin.

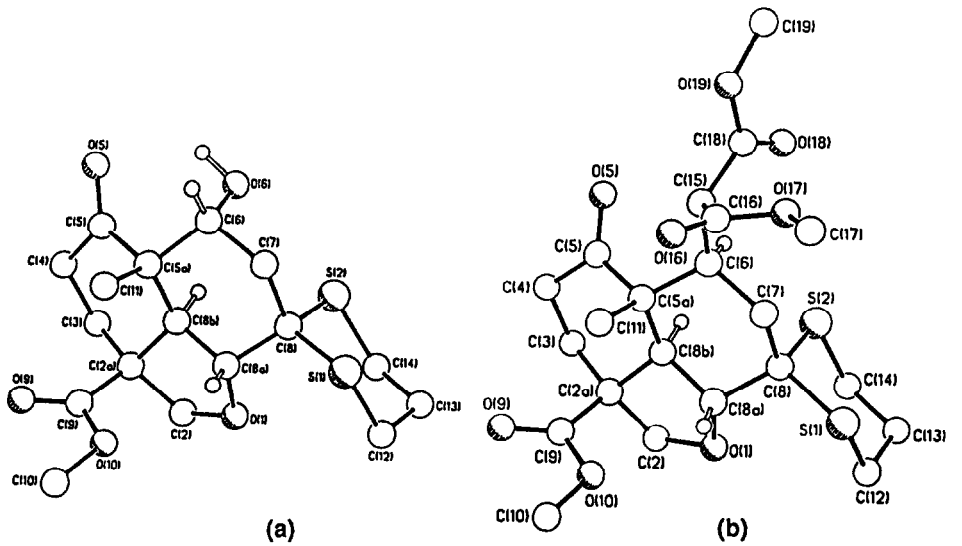


Figure 1. Perspective views of **a) (23)** and **b) (26)** with crystallographic numbering. The geometries of the principal ring systems, O(1) to C(14) in both molecules are virtually identical, with a maximum deviation from the least squares fit of 0.22Å for C(5). In **(23)** there are both *intra-* and *inter-* molecular hydrogen bonds between the hydroxy oxygen O(6) and the carbonyl oxygen O(5), 2.88 and 2.99Å respectively.

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Experimental

^{1}H nmr spectra were recorded in $CDCl_3$ using a Bruker AM-500, Bruker WM-250 or a JEOL FX-90Q spectrometer Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer. Mass spectra were recorded on a VG-7070B instrument and microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Chromatography refers to column chromatography on Merck Kieselgel 60 (230-400 mesh), petrol refers to petroleum ether b.p. 40-60 °C Compound numbering for nmr purposes follows systematic names until decalin closure at which point we revert to azadirachtin numbering. All compounds are racemic.

Crystal Data· All data for crystal structures was measured on a Nicolet R3m diffractometer with Cu-$K\alpha$ radiation (graphite monochromator) using ω-scans. Compound **(23)**; 1846 independent reflections were measured ($2\theta \leq 100$ °), of which 1761 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed; $C_{17}H_{24}O_5S_2$, M =372.5, triclinic, a =7.941(3), b =10.028(5), c =12.691(7) Å, α=108 74(4), β=92 29(4), γ=108.05(3) °, U =899 Å^3, space group $P\bar{1}$, Z =2, Dc=1.38 gcm^{-3}, Cu radiation, λ=1.54178 Å, μ (Cu-$K\alpha$) =28 cm^{-1}, F(000)=396 Compound **(26)**; 2679 independent reflections were measured ($2\theta \leq 100$ °) of which 2383 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed; $C_{22}H_{30}O_8S_2 \cdot (C_6H_6)_{0.25}$, M=506.1, monoclinic, a =23.420(5), b =12.497(4), c =19.848(5) Å, β=115.70(2) °, U =5234 Å^3, space group $I2/a$, Z =8, Dc=1 28 gcm^{-3}, Cu radiation, λ=1.54178 Å μ(Cu-$K\alpha$)=22 cm^{-1}, F(000)=2148.

Structure analysis and refinement: Both structures were solved by direct methods The non-hydrogen atoms were refined anisotropically The hydroxy proton on O(6) in **(23)** was located from a ΔF map and refined isotropically The positions of the remaining hydrogen atoms were idealised, C-H=0.96 Å, assigned isotropic thermal parameters, U(H)=1.2U_{eq}(C), and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies Refinement was by block-cascade, full-matrix least-squares to R =0.045, R_w=0.054 [$w^{-1}=\sigma^2(F)+0.00112F^2$] for **(23)** and R =0 067, R_w=0.078 [$w^{-1}=\sigma^2(F)+0\ 00759F^2$] for **(26)**. Computations were carried out on the Eclipse S140 using the SHELXTL[15] program system. Fractional atomic coordinates, tables of bond lengths and angles and isotropic thermal parameters have been deposited with the Cambridge Crystallographic Data Centre

(E)-Ethyl 3-methyl-oxopent-2-enoate. To a stirred solution of ethyl 2-triphenylphosphoranylideneacetate (104.90 g, 301 mmol) in dichloromethane (1200 ml) at r.t. was added 2,3-butanedione (26.5 ml, 302 mmol) in dichloromethane (30 ml) After 48 h the solvent was removed under reduced pressure and the residue passed through a short column of silica gel (25% ether-petrol) to remove triphenylphosphine oxide. The remaining solution consisted of a mixture (ca. 3:1) of E and Z isomers which were separated by medium pressure liquid chromatography on silica gel (gradient elution· 5% to 60% ether-petrol) to give **(E)-Ethyl 3-methyl-oxopent-2-enoate** (30 20 g, 64%) as a colourless oil, λ_{max} 228nm, ν_{max} (film) 2984, 1721, 1684, 1639 and 1445 cm^{-1}; δ(90 MHz) 1 32 (3H, t, J 7Hz, $OCH_2\underline{CH_3}$-H_3, 2 21 (3H, d, J 1 5 Hz, C3-Me), 2.39 (3H, s, C5-H_3), 4.23 (2H, q, J 7 Hz, $O\underline{CH_2}CH_3$-H_2), 6 55 (1H, q, J 1.5 Hz, 2-H_1), m/z 156 (M+) and 43

(E)-3-(2-methyl-1,3-dioxolan-2-yl)-but-2-enoate. A mixture of **(E)-Ethyl 3-methyl-oxopent-2-enoate** (30.20 g, 193 mmol), ethylene glycol (53.9 ml, 999 mmol) and pyridinium *para* -toluenesulphonate (4.86 g, 19.3 mmol) in dry benzene (500 ml) was heated under reflux with azeotropic removal of water for 60 h. The mixture was allowed to cool then washed with water (3x300 ml), brine (300 ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave **(E)-3-(2-methyl-1,3-dioxolan-2-yl)-but-2-enoate** (38.7 g, 100%) as a colourless oil b.p. 110 °C (3 mm Hg) which was used without further purification; ν_{max} (film) 2986, 2891, 1717, 1652, 1445 and 1373 cm^{-1};δ(90 MHz) 1.20 (3H, t, J 7 Hz, $OCH_2\underline{CH_3}$-H_3), 1.39 (3H, s, 2'-H_3), 2.05 (3H, d, J 1.5 Hz, 4-H_3), 3.79 (4H, m, 4'-H_2 and 5'-H_2), 4.08 (2H, q, J 7 Hz, $O\underline{CH_2}CH_3$-H_2), and 6.00 (1H, q, J 1.5 Hz, 2-H_1); *m/z* 185(M+), 155, 127 and 113; found: C, 60.29; H, 8.03%. $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05%.

(E)-3-(2-Methyl-1,3-dioxolan-2-yl)but-2-en-1-ol. To a stirred solution of **(E)-3-(2-methyl-1,3-dioxolan-2-yl)-but-2-enoate** (37.30 g, 186 mmol) in dry ether (1200 ml) at -50 °C under argon was added lithium aluminium hydride (27.50 g, 725 mmol) portionwise during 10 min. After 20 min. the mixture was allowed to warm to 0 °C and quenched by cautious addition of water (27.5 ml), 15% aqueous sodium hydroxide solution (27.5 ml), and water (82.5 ml). The mixture was stirred for a further 30 min. then filtered. The residue was washed with ether and the combined washings and filtrate concentrated under reduced pressure to give **(E)-3-(2-Methyl-1,3-dioxolan-2-yl)but-2-en-1-ol** (28.80 g, 98%) as a colourless oil; ν_{max} (film) 3418, 2988, 2888 and 1668 cm^{-1}; δ(90 MHz) 1.45 (3H, s, 2'-H_3), 1.67 (3H, d, J 1.5 Hz, 4-H_3), 1.84 (1H, br s, OH), 3 88 (4H, 1.84 m, 4'-H_2 and 5'-H_2), 4.20 (2H, br d, J 6.5 Hz, 1-H_2), and 5.85 (1H, tq, J 6.5 and 1.5 Hz, 2-H_1); *m/z* 158 (M+) and 143; found: C, 60.64; H, 8.73%. $C_8H_{14}O_3$ requires C, 60.74; H, 8.92%.

2-(2,2-Dimethoxyethyl)-1,3-dithiane (5). To a stirred solution of 1,3-dithiane (7.60 g, 63.2 mmol) in dry tetrahydrofuran (100 ml) at -30 °C under argon was added dropwise n-butyl lithium (6.50 ml of a 10.0 M solution in hexanes, 65.0 mmol). After 80 min. the pale yellow solution was cooled to -78 °C and hexamethylphosphoramide (20 ml, 115 mmol) added followed by 1-bromo-2,2-dimethoxyethane (10.24 g, 60.6 mmol). The reaction mixture was allowed to warm to r.t. over 1 h and quenched by addition of water (4 ml). Following the addition of more water (100 ml) the mixture was extracted with ether (4x75 ml). The combined organic layers were washed with water (3x100 ml), brine (2x100 ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and distillation of the residue gave (5) (7.85, 60%) as a colourless liquid, b.p. 84-92 °C (0.03 mm Hg); ν_{max} (film) 2933, 2898, 2828, 1421, 1381, 1363, 1276, 1243 and 1124 cm^{-1}; δ(250 MHz) 1.78-1.95 (1H, m, 5-H_1), 2.00 (2H, dd, J 7 5 and 5.5 Hz, 1'-H_2), 2 03-2.16 (1H, m, 5-H_1), 2.75-2.94 (4H, m, 4-H_2 and 6-H_2), 3.33 (6H, s, 2 OMe), 4.08 (1H, t, J 7.5 Hz, 2'-H_1), and 4.64 (1H, t, J 5.5 Hz, 2'-H_1); m/z 208 (M+), 176, 119 and 75.

(E)-3-(2-Methyl-1,3-dioxolan-2-yl)but-2-enal (6). A solution of **(E)-3-(2-Methyl-1,3-dioxolan-2-yl)but-2-en-1-ol** (5.00 g, 31 6 mmol) in chloroform (300 ml) was stirred with manganese (IV) oxide (22.0 g, 253 mmol) at r.t

After 24 h. a further portion of MnO_2 was added. After another 48 h the reaction mixture was filtered through a pad of silica gel. The pad was rinsed with dichloromethane. The combined filtrate and washings were concentrated under reduced pressure and the residue distilled to give **(6)** (4.41 g, 89%) as a colourless liquid b.p. 135 °C (16 mm Hg) and 70 °C (0.03 mm Hg); ν_{max} (film) 2991, 2890, 2759 and 1675 cm^{-1}; δ(250MHz) 1.49 (3H, s, 2'-H_3), 2.16 (3H, d, J 1.5 Hz, 4-H_3), 3.88 (4H, m, 4'-H_2 and 5'-H_2), 6.22 (1H, dq, J 8 and 1.5 Hz, 2-H_1), and 10.03 (1H, d, J 8Hz, CHO), *m/z* 141 (M+-CH_3); found:C, 61.38, H, 7.79%. $C_8H_{12}O_3$ requires C, 61.52; H, 7.74%.

(E)-1-[2-(2,2-Dimethoxyethyl)-1,3-dithian-2-yl]-3-(2-methyl-1,3-dioxolan-2-yl)but-2-en-1-ol (7). To a stirred solution of dithiane **(5)** (4 59 g, 22.03 mmol) in dry tetrahydrofuran at -30 °C under argon was added, dropwise via syringe, n-butyl lithium (8.41 ml of a 2.62 M solution in hexanes, 22.03 mmol). After 90 min. the reaction mixture was cooled to -92 °C and enal **(6)** (1 72 g, 11.02 mmol) in dry tetrahydrofuran (5 ml) added rapidly via syringe After 10 min the reaction was quenched by the addition of 10% v/v acetic acid in tetrahydrofuran (13.4 ml, 22.03 mmol of acetic acid). The mixture was allowed to warm to r.t. during 1 h. and diluted with ether (100 ml) and water (100 ml) The aqueous layer was extracted with ether (3x50 ml) and the combined organic layers washed with water (100 ml) and brine (100 ml), and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure followed by chromatography of the residue (gradient elution: 10% to 70% ether-petrol) gave **(7)** as a solid, m p. 64-65 °C (hexane); ν_{max} (KBr disc) 3446, 2985, 2934, 2829, 1439, 1422, 1374, 1273 and 1119 cm^{-1}; δ(250MHz) 1.48 (3H, s, CH_3), 1.77 (3H, d, J 1.5 Hz, CH_3), 1.96 (2H, m, $SCH_2\underline{CH_2}$), 2 17 (1H, dd, J 15 and 3.5 Hz, CH_2-H_1), 2.36 1H, dd, J 15 and 6.5 Hz, CH_2-H_1), 2.67-2.90 (4H, m, 2 SCH_2-H_2), 3,34 (3H, s, OMe), 3 38 (3H, s, OMe), 3.41 (1H, d, J 5 Hz, OH), 3.74-3.97 (4H, m, 2 OCH_2-H_2), 4 58 (1H, dd, J 9.5 and 5 Hz, C<u>H</u>OH), 4.81 (1H, dd, J 6.5 and 3.5 Hz, C<u>H</u>OMe), and 5.84 (1H, br dd, J 9.5 and 1.5 Hz, HC=C); *m/z* 332 M+ - CH_2OH), 207, 118 and 75; found: M+ - CH_3OH, 332.1128. $C_{16}H_{28}O_5S_2$ requires M+ -CH_3OH, 332 1116, found: C, 52.74; H, 7.90. $C_{16}H_{28}O_5S_2$ requires C, 52.72; H, 7 74%.

(E)-Methyl 2-{1-[2-(2,2-dimethoxyethyl)-1,3-dithian-2-yl]-3-(2-methyl-1,3-dioxolan-2-yl)but-2-enyloxymethyl}prop-2-enoate (8). To a stirred slurry of prewashed potassium hydride (535 mg, 13.41 mmol) in dry benzene (75 ml) at 20 °C under argon was added, dropwise via syringe, alcohol **(7)** (3.26 g, 8 94 mmol) in dry benzene (40 ml). After 1 5 h methyl 2-bromomethylprop-2-enoate (7 5 ml, 65.8 mmol) was added rapidly with vigorous stirring. Heat was evolved and a dense white precipitate appeared. After 2.5 h the reaction was quenched by cautious addition of saturated aqueous ammonium chloride solution (5 drops) and saturated aqueous sodium hydrogencarbonate solution (25 ml) Water (100 ml) was added and the aqueous layer extracted with ether (4x60 ml). The combined organic layers were washed with water (2x100 ml) and brine (150 ml), and dried (Na_2SO_4). Removal of solvent under reduced pressure followed by chromatography of the residue (gradient elution: 5% to 50% ether-petrol) gave excess methyl 2-bromomethylprop-2-enoate (5.0 g, 49% recovery) and **(8)** (3 30 g, 80%) as a viscous, colourless oil. ν_{max} (film) 2950, 2829, 1718, 1634, 1437, 1373, 1304, 1275, 1198 and 1159 cm^{-1};δ(250MHz) 1.51 (3H, s, CH_3), 1 75 (3H, d, J 1 5 Hz, CH_3) 1.88-2.00 (2H, m, $SCH_2\underline{CH_2}$), 2.17 (1H, dd, J 15 and 3.5 Hz, CH_2-H_1), 2 38 (1H, dd, J 15 and 5 Hz, CH_2-H_1), 2.70-2.98 (4H, m, 2 SCH_2-H_2), 3.34 (3H, s, OMe), 3.35 (3H, s, OMe), 3.75 (3H, s, COOMe), 3.76-

4.00 (4H, m, 2 OCH_2-H_2), 4.04 (1H, dt, J 14 and 1.5 Hz, CH_2C=C), 4.17 (1H, dt, J 14 and 1.5 Hz, CH_2C=C), 4.44 (1H, d, J 8.5 Hz, C<u>H</u>OCH_2), 4.77 (1H, dd, J 5 and 3.5 Hz, C<u>H</u>OMe), 5.88 (1H, br dd, J 8.5 and 1.5 Hz, HC=C), 5.96 (1H, br q, J 1.5 Hz, <u>H</u>C=CCOOMe *anti*), and 6.29 (1H, br q, J 1.5 Hz, <u>H</u>C=CCOOMe *syn*); *m/z* 431 (M+ - OMe), 225, 207, 87 and 75; found: M+ - OMe, 431.1556. $C_{21}H_{34}O_7S_2$ requires M+ -OMe, 431.1562; found: C, 54.82; H, 7.60. $C_{21}H_{34}O_7S_2$ requires C, 54.52; H, 7.41%. Some aldehyde resulting from de-acetalisation of **(8)** was also obtained (0.37 g, 10%).

(E)-Methyl 2-{3-methyl-4-oxo-1-[2-(2-oxoethyl)-1,3-dithian-2-yl]pent-2-enyloxymethyl}prop-2-enoate (9) A solution of acetal **(8)** and the corresponding aldehyde (3.41 g, of a 10:1 mixture, ca. 8 mmol) in 2% aqueous acetone (100 ml) containing pyridinium *para* -toluenesulphonate (620 mg, 2.47 mmol) was heated under reflux for 5 h. The reaction mixture was allowed to cool and diluted with water (50 ml) and ether (50 ml). The aqueous layer was extracted with ether (3x70 ml) and the combined organic layers washed with saturated aqueous sodium hydrogencarbonate solution (100 ml), water (100 ml) and brine (100 ml), and dried (Na_2SO_4). Removal of the solvent under reduced pressure and chromatography of the residue (gradient elution: 50% to 60% ether-petrol) gave **(E)-methyl 2-{3-methyl-4-oxo-1-[2-(2-oxoethyl)-1,3-dithian-2-yl]pent-2-enyloxymethyl}prop-2-enoate (9)** (2.79 g, 94%) as a yellow oil; ν_{max} (film) 2950, 1715, 1672, 1633, 1433, 1371, 1350, 1306, 1278, 1245, 1198 and 1161 cm^{-1}; δ(250 MHz) 1.89 (3H, d, J 1.5 Hz, C=CMe), 2.00 (2H, m, SCH_2<u>CH_2</u>-H_2), 2.39 (3H, s, Me), 2 73-3.05 (6H, m, 2 SCH_2-H_2 and <u>CH_2</u>CHO-H_2), 3.76 (3H, s, COOMe), 4.08 (1H, dt, J 13 and 1.5 Hz, CH_2O, 4.55 (1H, d, J 9 Hz, C=CCH), 5.87 (1H, br q, J 1.5 Hz, <u>H</u>C=CCOOMe *anti*), 6.31 (1H, br q, J 1.5 Hz, <u>H</u>C=CCOOMe *syn*), 6.57 (1H, br dd, J 9 and 1.5 Hz, HC=C), and 9.86 (1H, t, J 2.5 Hz, CHO); *m/z* 372 (M+), 341, 257 and 161; found: M+ - OMe, 341.0875. $C_{17}H_{24}O_5S_2$ requires M+ - OMe, 341.0881, found C, 54.66; H, 6.37; S, 17.12%; $C_{17}H_{24}O_5S_2$ requires C, 54.82; H, 6.49, S, 17.22%.

(E)-Methyl 2-{1-[2-(1,3-dioxan-2-ylmethyl)-1,3-dithian-2-yl]-3-methyl-4-oxopent-2-enyloxymethyl}prop-2-enoate (10). A solution of the ketoaldehyde **(9)** (710 mg, 1.91 mmol) in dry benzene (50 ml) containing propane-1,3-diol (138 µl, 1-91 mmol) and pyridinium *para* -toluenesulphonate (48 mg, 0.191 mmol) was heated under reflux with azeotropic removal of water. After 12 h the mixture was allowed to cool then poured into saturated aqueous sodium hydrogencarbonate solution (50 ml). The aqueous layer was extracted with ether (4x20 ml) and the combined organic layers washed with further saturated aqueous sodium hydrogencarbonate solution (100 ml), brine (100 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by chromatography of the residue (55% ether-petrol) gave **(10)** (650 mg, 79%) as a colourless oil. ν_{max} (film) 2952, 2923, 2854, 2733, 1718, 1671, 1634, 1436, 1398, 1374, 1349, 1305, 1276, 1245 and 1196 cm-1; δ(250 MHz) 1 32 (1H, br d, J 13 Hz, OCH_2<u>CH_2</u>-H_1), 1.86 (3H, d, J 1 5 Hz, CH_3), 1.90-2.15 (3H, m, SCH_2<u>CH_2</u> -H_2 and OCH_2<u>CH_2</u> -H1), 2 20 (1H, dd, J 15 and 3 Hz, CH_2 -H_1), 2.37 (1H, dd, J15 and 4.5 Hz, CH_2-H_1), 2.39 (3H, s, CH_3), 2.72-3.01 (4H, m, 2 SCH_2-H_2), 3.76 (3H, s, COOMe), 3.77-3.86 (2H, m, 2 OCH_2-H_1), 4.03-4 22 (4H, m, CH_2C=C and 2 OCH_2-H_1), 4.63 (1H, d, J 9.5 Hz, C=CC<u>H</u>OCH_2), 4.91 (1H, dd, J 4.5 and 3 Hz, CH_2<u>C</u>HO), 5.95 (1H, br d, J 1 5 Hz, <u>H</u>C=CCOOMe *anti*), 6.31 (1H, br d, J 1.5 Hz, <u>H</u>C=CCOOMe *syn*), and 6.73 (1H, br dd, J 9 5 and 1.5 Hz, HC=C) ; *m/z* 430 (M+), 315, 219, and 87, found M+,

430.1478. $C_{20}H_{30}O_6S_2$ requires M+, 430.1484; found: C, 55.51; H, 7.03. $C_{20}H_{30}O_6S_2$ requires C, 55.79; H, 7.02%

(E, E)-Methyl 2-{1-[2-(3-carbomethoxyprop-2-enyl)-1,3-dithian-2-yl]-3-methyl-4-oxopent-2-enyloxymethyl}prop-2-enoate (11). A solution of ketoaldehyde **(9)** (104 mg, 0.297) in dichloromethane (5 ml) containing methyl 2-triphenylphosphoranylideneacetate (140 mg, 0.49 mmol) was stirred at r.t. for 24 h. The solvent was removed under reduced pressure and the residue chromatographed (55% ether-petrol) to give **(11)** (105 mg, 88%) as a colourless oil; ν_{max} (film) 2949, 1720, 1672, 1433, 1369, 1332, 1305, 1274, 1240, 1194 and 1167 cm^{-1}; δ(250 MHz) 1.88 (3H, d, J 1.5 Hz, C=CCH$_3$), 1.98 (2H, m, SCH$_2$CH$_2$-H$_2$), 2.39 (3H, s, COCH$_3$), 2.70-3 05 (6H, m, 2 SCH$_2$-H$_2$ and C=CCH$_2$-H$_2$), 3.74 (3H, s, COOMe), 3.76 (3H, s, COOMe), 4.00 (1H, br d, J 13 5 Hz, OCH$_2$-H$_1$), 4 20 (1H, br d, J 13.5 Hz, OCH$_2$-H1), 4.46 (1H, d, J 10 Hz, OCHC=C), 5 89 (1H, br d, J 15 Hz, HCCOOMe), 5.94 (1H, m, C=CH$_2$-H$_1$ *anti*), 6.32 (1H, br d, J 1.5 Hz, C=CH$_2$-H$_1$ *syn*), 6.65 (1H, br dd, J 10 and 1.5 Hz, MeC=CH), and 7 13 (1H, dt, J 15 and 7.5 Hz, HC=CHCOOMe); *m/z* 428 (M+), 397, 313 and 217, found: M+, 428.1338. $C_{20}H_{28}O_6S_2$ requires M+, 428.1327 .

(E,E)-Methyl-2-{4-t-butyldimethylsilyloxy-1-[2-(3-carbomethoxyprop-2-enyl)-1,3-dithian-2-yl]-3-methylpenta-2,4-dienyloxymethyl}prop-2-enoate (12). To a stirred solution of enone **(11)** (44 mg, 0.103 mmol) in dry dichloromethane (2 ml) at -20 °C under argon was added, dropwise, triethylamine (43 µl, 0.308 mmol) followed by t-butyldimethylsilyl triflate (48 µl, 0.206 mmol). After 10 min. the reaction mixture was allowed to warm to 0 °C during 5 min. then quenched by the addition of saturated aqueous sodium hydrogencarbonate solution (5 ml) The aqueous layer was extracted with dichloromethane (3x10 ml) and the combined organic layers dried (Na_2SO_4) Removal of the solvent followed by chromatography of the residue (25% ether-petrol) gave **(12)** (52 mg, 98%) as a colourless oil, ν max (film) 2950, 2856, 1722, 1652, 1596, 1433, 1309, 1269, 1193 and 1166 cm^{-1}; δ(250 MHz) 0.18 (3H, s, SiMe), 0.98 (9H, s, t-BuSi), 1.87 (3H, d, J 1.5 Hz, C=CMe), 1.95 (2H, m, SCH$_2$CH$_2$-H$_2$), 2.65-3.07 (6H, SCH$_2$-H$_2$ and C=CHCH$_2$-H$_2$), 3.73 (3H, s, COOMe), 3.75 (3H, s, COOMe), 4.04 (1H, br d, J 14 Hz, OCH$_2$-H$_1$), 4.18 (1H, br d, J 14 Hz, OCH$_2$-H$_1$), 4.40 (1H, br d, J 1.5 Hz, SiOC=CH$_2$-H$_1$), 4.41 (1H, d, J 10 Hz, OCHC=C), 4.58 (1H, br d, J 1 5 Hz, SiOC=CH-H$_1$), 5.84 (1H, d, J 15 5 Hz, CHCOOMe), 5.93 (1H, m, C=CH$_2$-H$_1$ *anti* to ester), 6.16 (1H, br d, J 10 Hz, MeC=CH), 6.29 (1H, br d, J 1.5 Hz, C=CH$_2$-H$_1$ *syn* to ester), and 7.16 (1H, dt, J 15.5 and 7 Hz, CH=CHCOOMe); *m/z* 542 (M+), 427 and 217; found: M+, 242 2200. $C_{26}H_{42}O_6S_2Si$ requires M+, 542.2192 .

(E)-Methyl 2-{4-t-butyldimethylsilyloxy-1-[2-(1,3-dioxan-2-ylmethyl)-1,3-dithian-2-yl]-3-methylpenta-2,4-dienyloxymethyl}prop-2-enoate (13). To a stirred solution of enone **(10)** (688 mg, 1.60 mmol) in dry dichloromethane (15 ml) at -20 °C under argon was added dropwise, triethylamine (667 µl, 4.79 mmol) followed by t-butyldimethylsilyl triflate (618 µl, 2.69 mmol). After 30 min saturated aqueous sodium hydrogencarbonate solution (10 ml) was added. The aqueous layer was extracted with dichloromethane (3x10 ml) and the combined organic

layers dried (Na_2SO_4). Removal of the solvent under reduced pressure gave **(13)** (761 mg, 87%) as a colourless oil. ν_{max} (film) 2953, 2928, 2854, 1716, 1634, 1459, 1436, 1398, 1375, 1359, 1313, 1256 and 1196 cm^{-1}; δ(250 MHz) 0.14 (3H, s, SiMe), 0.18 (3H, s, SiMe), 0.96 (9H, s, t-BuSi), 1.29 (1H, br d, J 14 Hz, $OCH_2\underline{CH_2}$-H_1), 1.78-2.10 (6H, m, including 1.83 (3H, br s, CH_3), remainder $SCH_2\underline{CH_2}$-H_2 and OCH_2CH_2-H_1), 2.17 (1H, dd, J 15 and 3.5 Hz, CH_2-H_1), 2.32 (1H, dd, J 15 and 4 Hz, CH_2-H_1), 2.68-3.00 (4H, m, 2 SCH_2-H_2), 3.70-3.82 (5H, m, including3.73 (3H, s, COOMe), remainder 2 OCH_2-H_1), 4.00-4.19 (4H, m, C=CCH_2 and 2 OCH_2-H_1), 4.36 (1H, br s, C=CH_2-H_1), 4.50 (1H, d, J 8 Hz, C=CCHO), 4.52 (1H, br s, C=CH_2-H_1), 4.89 (1H, m, $CH_2\underline{C}HO$), 5.94 (1H, br d, J 1.5 Hz, $\underline{H}C$=CCOOMe *anti*), 6.19 (1H, br d, J 9 Hz, $\underline{H}C$=CHO), and (1H, br d, J 1,5 Hz, $\underline{H}C$=CCOOMe *syn*); *m/z* 544 (M^+), 513, 429, 325, 219 and 87; found: C, 57.47; H, 8.23% $C_{26}H_{44}O_6S_2Si$ requires C, 57.32; H, 8.14%.

Intramolecular Diels-Alder reaction of (13). A solution of triene **(13)** (14.3 g, 26.3 mmol) in dry dimethyl sulphoxide (400 ml) under argon was heated at 135 °C for 1 h. The reaction mixture was allowed to cool. Saturated aqueous sodium hydrogen carbonate solution (300 ml) and ether (300 ml) were added. The aqueous layer was extracted with ether (4x200 ml) and the combined extracts washed with water (4x200 ml) and brine (2x200 ml), and dried (Na_2SO_4). Concentration under reduced pressure and chromatography of the residue (gradient elution: 45% to 55% ether-petrol) gave, in order of elution, **methyl 1α, 3aβ, 7aα,1, 4, 5, 7a-tetrahydro-6-t-butyldimethylsilyloxy-1-[2-(1,3-dioxan-2-ylmethyl)-1,3-dithian-2-yl]-isobenzofuran-3a-carboxylate (17)** (3.35 g, 23%) as a white waxy solid; ν_{max} ($CHCl_3$) 2928, 2855, 1728, 1671, 1431, 1376, 1353, 1256, 1212 and 1173 cm^{-1}; δ(250 MHz) 0.10 (6H, s, $Si(Me)_2$), 0.92 (9H, s, t-BuSi), 1.31 (1H, br d, J 14 Hz, $OCH_2\underline{CH_2}$-H_1), 1.79 (3H, br s, C-7 Me), 1 81-2.18 (7H, m, 4-H_2, 5-H_2, $SCH_2\underline{CH_2}$-H_2 and $OCH_2\underline{CH_2}$-H_1), 2.23 (1H, dd, J 15 and 3Hz, 2'-H_1), 2.36 (1H, dd, J 15 and 4.5 Hz, 2'-H_1), 2.69-3.01(4H, m, 2 SCH_2-H_2), 3 47 (1H, br d, J 4.5 Hz 7a-H_1), 3.68 (3H, s, COOMe), 3.68 (1H, d, J 9 Hz, 3-H_1), 3.71-3 88 (2H, m, 2 SCH_2-H_2), 4.08 (3H, m, 1-H_1, 2 OCH_2-H_1), 4 44 (1H, d, J 9 Hz, 3-H_1), and 4.92 (1H, dd, J 4.5 and 3Hz, 3'-H_1); *m/z* 544 (M^+), 325, 219 and 87; found: M^+, 544.2348. $C_{26}H_{44}O_6S_2Si$ requires M^+, 544 2349; and **Methyl-1α, 3aα, 7aα, 1, 4, 5, 7α-tetrahydro-6-t-butyldimethylsilyloxy-1-[2-(1,3,-dioxan-2-ylmethyl)-1,3-dithian-2-yl]-isobenzofuran-3a-carboxylate (19)** (8.69 g, 61%) as a colourless foam; ν_{max} (film) 2953, 2929, 2854, 1724, 1648, 1458, 1430, 1376, 1359, 1345, 1304, 1252 and 1197 cm^{-1}; δ(250 MHz) 0.08 (3H, s, SiMe), 0 11 (3H, s, SiMe), 0.91 (9H, s, tBuSi), 1.31 (1H, br d, J 13 Hz, $OCH_2C\underline{H_2}$-H_1), 1 62-2.48 (12H, m, including 1.79 (3H, br s, C-7 Me), remainder 4-H_2 5-H_2, $SCH_2C\underline{H_2}$-H_2, 2'-H_2 and $OCH_2C\underline{H_2}$-H_1), 2.65-2.95 (4H, m, 2 SCH_2-H_1), 3.74 (1H, br d, J 9 Hz, 7a-H), 3 82 (2H, m, 2 OCH_2-H_1), 4.01 (1H, d, J 9 Hz, 3-H_1), 4.11 (2H, m, 2 OCH_2-H_1), 4.83 (1H, d, J 9Hz, 1-H_1), and 4 93 (1H, t, J 4.5 Hz, 3'-H_1); m/z 544 (M+), 325, 219 and 87; found: M+, 544 2348. $C_{26}H_{44}O_6S_2Si$ requires M+, 544.2349.

Hydrolysis of (17). A solution of the enol-ether **(17)** (6.5 g, 11.9 mmol) in acetic acid:water:tetrahydrofuran 3:1:1 was heated under reflux for 18 h. The reaction mixture was allowed to cool to r.t. and diluted with saturated aqueous sodium hydrogencarbonate solution (200 ml) and ether (200 ml). The aqueous layer was extracted with ether (3x200 ml) and the combined organic layers washed with brine (2x100 ml) and dried (Na_2SO_4) Evaporation of the solvent

under reduced pressure and chromatography of the residue (gradient elution: 75%-85% ether-petrol) gave **Methyl 1α, 3aβ, 7αβ, 7aβ, 1, 4, 5, 6, 7, 7a-hexahydro-1-[2-(formylmethyl)-1,3-dithian-2-yl]-7-methyl-6-oxoisobenzofuran-3a-carboxylate (21)** (3.24 g, 73%) as a solid, m.p. 84-86 °C; ν_{max} ($CHCl_3$) 2946, 1707, 1423, 1376, 1341, 1276, 1216 and 1162 cm^{-1}; δ(250 MHz) 1.09 (3H, d, J 7.5 Hz, 7-Me), 1.70 (1H, ddd, J 14, 10 and 7.5 Hz, 4-H_1), 1.88-2.17 (2H, m, $SCH_2\underline{CH_2}$-H_2), 2.42-2.57 (2H, m, 4-H_1 and 5-H_1), 2.74-3.10 (8H, m, 5-H_1, 7a-H_1, $\underline{CH_2}CHO$-H_2 and 2 SCH_2-H_2), 3.18 (1H, quintet, J 7.5 Hz, 7 H_1), 3.43 (1H, d, J 9 Hz, 3-H_1), 3.78 (3H, s, COOMe), 4.04 (1H, d, J 9 Hz, 3-H_1), 4.68 (1H, d, J 10 Hz, 1-H_1), and 9.82 (1H, dd J 4 and 2 Hz, CHO); *m/z* 372 (M^+), 343, 329, 211 and 161; found· C, 54.81; H, 6.52%. $C_{17}H_{24}O_5S_2$ requires C, 54.82; H, 6.52%

Intramolecular aldol reaction of ketoaldehyde (21). To a stirred solution of ketoaldehyde **(21)** (93 mg, 0.25 mmol) in dry methanol (1.5 ml) at 0 °C was added aqueous sodium hydroxide solution (410 µl, 1.03 mmol). After 1 h. the reaction mixture was neutralised by the addition of dilute hydrochloric acid. Ether (3 ml) was added, and the aqueous layer extracted with dichloromethane (3x5 ml). The combined organic layers were dried (Na_2SO_4), the solvent removed under reduced pressure and the residue chromatographed (gradient elution: 30% to 40% ethyl acetate-petrol) to give, in order of elution, **Methyl 2aα, 5aα, 6α, 8aβ, 8bβ, 3, 4, 5, 7, 8-decahydro-6-hydroxy-5a-methyl-5-oxo-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-8-spiro-2-(1,3-dithiane) (22)**; (70 mg, 75%) as a solid, m.p. 208.5-209.5 (methanol-benzene); *ν* max (KBr disc) 3526, 2941, 2893, 1716, 1683, 1233, 1221, 1156 and 1076 cm^{-1}; δ(300 MHz) 1.01 (3H, s, 19-H_3), 1.68-1.80 (2H, m, 3-H_1 and 8-H_1), 1.87-2.20 (3H, m, 8-H_1 and $SCH_2\underline{CH_2}$-H_1), 2.36 (1H, ddd, J 17, 5.5 and 1.5 Hz, 2-H_1), 2.52-2.78 (4H, m, 3-H, 5-H_1 and SCH_2-H_2), 3.00 (1H, d, J 2.5 Hz, OH), 3 02 (1H, ddd, J 17, 13 and 6.5 Hz, 2-H_1), 3.38 (2H, m, SCH_2-H_1), 3.71 (1H, d, J 8.5 Hz,28-H_1), 3.84 (3H, s, COOMe), 4.17 (1H, ddd, J 12, 4 and 2.5 Hz, 9-H1), 4.18 (1H, d, J 8.5 Hz, 28-H_1), and 4.64 (1H, d, J 11.5 Hz, 6-H_1), *m/z* 372 (M^+); found· C, 54.64; H, 6.44%. $C_{17}H_{24}O_5S_2$ requires C, 54.82; H, 6.49% . and **Methyl 2aα, 5aα, 6β, 8aβ, 8bβ, 3, 4, 5, 7, 8-decahydro-6-hydroxy-5a-methyl-5-oxo-2H-naphtho[4, 4a, 5, bc]furan-2a-carboxylate-8-spiro-2-(1,3-dithiane) (23)** (15 mg, 16%) as a solid, m.p. 198-200 °C (benzene-petrol); *ν* max (KBr disc) 3498, 2957, 2913, 2879, 1718, 1698, 1251, 1426, 1397, 1382, 1229, 1208, 1283, 1263, 1251, 1221, and 1182 cm^{-1}; δ(250 MHz) 0,96 (3H, s, 19-H_3), 1.70-2 01(3H, m, 3-H1, 8-H_1 and $SCH_2\underline{CH_2}$-H_1), 2 06-2.20 (1H, m, $SCH_2\underline{CH_2}$-H_1), 2.33 (1H, dd, J 14.5 and 3 Hz, 8-H_1), 2.38-2.79 (4H, m, 3-H_1, 2-H_1 and SCH_2-H_2), 2.91-3 06 (2H, m, 2-H_1 and OH), 3.24 (1H, d, J 11.5 Hz, 5-H_1), 3.39-3.54 (2H, m, SCH_2-H_2), 3.77 (1H, d, J 8.5 Hz, 28-H_1), 3 82 (3H, s, COOMe), 4.02 (1H, d, J 11 5 Hz, 9-H_1), 4.18 (1H, d, J 8.5 Hz, 28-H_1), and 4 68 (1H, d, J 11.5 Hz, 6-H_1); *m/z* 372 (M^+); found. C, 55.01; H, 6.51% . $C_{17}H_{24}O_5S_2$ requires C, 54.82; H, 6.49% .

Wittig reaction of ketoaldehyde (21). A solution of ketoaldehyde **(21)** (100 mg, 0.295 mmol) in dichloromethane (3 ml) containing methyl 2-triphenylphosphoranylideneacetate (120 mg, 0.359 mmol) was stirred at r.t for 48 h. The solvent was evaporated under reduced pressure and the residue chromatographed (75% ether-petrol) to give **Methyl (E) 1α, 3aβ, 7β, 7aα, 1, 4, 5, 6, 7, 7a-hexahydro-1-[2-(3-carbomethoxyprop-2-enyl)-1,3-dithian-2-yl]-7-methyl-6-oxoisobenzofuran-3a-carboxylate (24)** (120 mg, 90%) as a colourless

foam; ν max (film) 2922, 1716, 1648, 1432, 1375, 1335, 1273, 1222, and 1170 cm^{-1}; δ(250 MHz) 1.04 (3H, d, J 7 5 Hz, 7-CH_3), 1.62-1.75 (1H, m, 4-H_1), 1.80-2.10 (2H, m, $SCH_2\underline{CH}_2$-H_2), 2.41-2.58 (2H, m, 4-H_1 and 5-H_1), 2.70-3.25 (9H, m, 5-H_1, 7-H_1, 7a-H_1 HC=CHC$\underline{H}_2$-H_2 and 2 SCH_2-H_2), 3.55 (1H, d, J 8.5 Hz, 3-H_1), 3 75 (6H, s, 2 COOMe), 4.07 (1H, d, J 8.5 Hz, 3-H_1), 4.48 (1H, d, J 10 Hz, 1-H_1), 5.96 (1H, br d, J 16 Hz, HC=C$\underline{H}$COOMe-H_1), and 7.13 (1H, m, $\underline{H}$C=CHCH_2-H_1); *m/z* 428(M+), 397, 329, and 217; found: M+-CH_2CH=CHCOOMe 329 0883. $C_{20}H_{28}O_6S_2$ requires M+-CH_2CH=CHCOOMe, 329.00881.

Knoevenagel condensation of (21) with dimethyl malonate. A solution of ketoaldehyde **(21)** (181 mg, 0.486 mmol) in dry benzene (2 ml) containing dimethyl malonate (90 µl, 0.787 mmol), piperidine (9 µl, 0.09 mmol) and acetic acid (37 µl, 0.646 mmol) was heated under reflux for 15 h. Further dimethyl malonate (90 µl, 0 787 mmol) was added and heating continued for 3 h. The cooled reaction mixture was diluted with ether (5 ml) and washed with water (5 ml), brine (5 ml) saturated aqueous sodium hydrogencarbonate solution (10 ml), and brine (5 ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure followed by chromatography of the residue (33% ethyl acetate-petrol) gave, as a mixture (ca. 3:2) with the deconjugated isomers, **Methyl 1α, 3aβ, 7αβ, 7aα, 1, 4, 5, 6, 7, 7a-hexahydro-1-{2-[3,3-bis(carbomethoxy)-prop-2-enyl]-1,3-dithian-2-yl}-6-oxoisobenzofuran-3a-carboxylate (25)** (212 mg total yield, 90%) as a colourless foam; ν_{max} (film) 2952, 2874, 1718, 1637, 1435, 1369, 1221, 1162, 1121 and 1063 cm^{-1}; δ(250 MHz) 1.06 (3H, d, J 7 5 Hz, C7-Me), 1.64-! 80 (1H, m, 4-H_1), 1.81-2.11 (2H, m, SCH_2CH_2-H_2), 2.40-2.55 (2H, m, 4-H_1 and 5-H_1), 2.70-3.25 (7H, m, 5-H_1, 7-H_1, 7a-H_1 and 2 SCH_2-H_1), 3 48 (1H, d, J 8.5 Hz, 3-H_1), 3.75 (3H, s, COOMe), 3.78 (3H, s, COOMe), 3 82 (3H, s, COOMe), 4.01 (1H, d, J 8.5 Hz, 3-H_1), and 4.56 (1H, d, J 11 Hz, 1-H_1); *m/z* 486 (M+), 329; found· C, 54.29, H, 6 25% $C_{22}H_{30}O_8S_2$ requires C, 54 30; H, 6 21%.

Cyclisation of triester (25). To a stirred solution of triester **(25)** (179 mg, 0 386 mmol), in dry methanol (3 5 ml) at r t. under argon was added sodium methoxide (0.386 mmol) in dry methanol (1.5 ml). The mixture was stirred at r.t. for 8 3 h , then cooled to 0 °C and quenched by dropwise addition of dilute aqeuous hydrochloric acid (1 M, 8 drops) Water (5 ml) was added and the aqueous layer extracted with ether (3x5 ml) The combined extracts were washed with brine (20 ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and chromatography of the residue (33% ethyl acetate-petrol) gave **Dimethyl 2aα, 5aα, 6α, 8aα, 8bβ, 3, 4, 5, 7, 8-decahydro-5a-methyl-5-oxo-2H-naphtho[4.4a.5.bc]furan-2a carboxylate-8-spiro-2-(1,3-dithian-2-yl)-6-malonate (26)** (108 mg, 60%) as a solid m.p. 194-196 °C (benzene-petrol), ν_{max} (KBr disc) 1734, 1436, 1303, 1197, 1086 and 1014 cm^{-1}; δ(250 MHz) 1 03 (3H, s, 19-H_3), 1 67 (1H, dt, 13 5 and 5Hz, 3-H_1), 1.88 (1H, m, 8-H_1), 1-90-2.16 (2, m, $SCH_2\underline{CH}_2$-H_2), 2 22-2.36 (2H, m, 2-H_1 and 8-H_1), 2.60-2.90 (4H, m, 3-H_1, 5b-H_1, 2 CH_2-H_1), 2.94-3.08 (2H, m, 2-H_1 and 9-H_1), 3 23 (2H, m, 2 SCH_2-H_1), 3 65 (1H, d, J 8.5 Hz, 28-H_1), 3.68 (3H, s, COOMe), 3.77 (3H, s, COOMe), 3.82 (3H, s, COOMe), 4 10 (1H, d, J 8 5 Hz, 28-H_1), 4 30 (1H, d, J 3 Hz, CH$(COOMe)_2$), 4.55 (1H, d, J 11 Hz, 6-H_1), m/z 486 (M+); compound crystallises with 0 25 molecules of benzene, found: C, 56 19; H, 6.25% $C_{23\ 5}H_{31.5}O_8S_2$ requires C, 55 77; H, 6 27%.

Decarboxylation of (26). A mixture of triester **(26)** (31 mg, 0.062 mmol) and sodium chloride (10 mg, 0.17 mmol) in dimethyl suphoxide (3 ml) containing water (ca. 4 mg, 0.22 mmol) was heated at 160 °C under argon for 4 h. The reaction mixture was allowed to cool then poured into water (20 ml) The resulting mixture was extracted with ether (3x5 ml) and the combined ethereal layers treated with ethereal diazomethane. Removal of the solvent under reduced pressure and chromatography of the residue (50% ether-petrol) gave **Methyl {methyl-2aα, 5aα, 6α, 8aα, 8bβ, 3, 4, 5, 7, 8, decahydro-5a-methyl-5-oxo-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-8-spiro-2-(1,3,-dithiane)-6-}acetate (16)** (22 mg, 91%) as a solid m.p. 139-141 °C (benzene-petrol), ν_{max} (KBr disc) 2953, 1721, 1437, 1379, 1290, 1224, 1179, 1086 and 1013 cm^{-1}, δ(500 MHz) 0.93 (3H, s, 19-H_3), 1 42 (1H, dd, J 13 and 15 Hz, 8-H_1), 1.68 (1H, ddd, J 5, 13, and 13 Hz, 3-H_1), 1.9 (1H, dd, J 11 and 16 Hz, 16-H_1), 1.94 (1H, m, $SCH_2\underline{CH_2}$-H_1), 2.0 (1H, m, $SCH_2\underline{CH_2}$-H_1), 2.16 (1H, dd, 8-H_1), 2.3 (1H, ddd, J 2, 5 and 16 Hz, 2-H_1), 2.6-2 7 (3H, m, 9-H_1, 2-H_1 and SCH_2-H_1), 2 74-2.80 (1H, m, SCH_2-H_1), 2 79 (1H, d, J 12 Hz, 5-H_1). 2.98 (1H, ddd, J 6, 13 and 16 Hz, 3-H_1), 3.1 (1H, dd, J 3 and 16 Hz, 11-H_1), 3.26 (1H, ddd, 3, 10 and 13 Hz, SCH_2-H_1), 3.31(1H, ddd, J 3, 10 and 13 Hz, SCH_2-H_1), 3.64 (1H, d, J 9 Hz, 28-H_1), 3 68 (3H, s, COOMe), 3 82 (1H, s, COOMe), 4.1 (1H, d, J 9 Hz, 28-H1), 4.57 (1H, d, J 12 Hz, 6-H_1); *m/z* 428 (M+); found. M+, 428.1309. $C_{20}H_{28}O_6S_2$ requires M+, 428 1327

α-Selenylation of (16). Diisopropylamine (144 µl, 1 027 mmol) was added dropwise to a stirred solution of n-butyl lithium (428 µl of a 2.4 M solution in hexanes, 1 027 mmol) in dry tetrahydrofuran (3 ml) at 0 °C under argon. After 20 min. the solution was cooled to -78 °C and **(16)** (200 mg, 0.467 mmol) in dry tetrahydrofuran (3 ml) added via canula The bright yellow solution was stirred at -78 °C for 30 min. then N-(phenylseleno)phthalimide added portionwise Stirring was continued for 45 min. then saturated aqueous ammonium chloride solution (6 ml) added and the mixture allowed to warm to r.t. Water (5 ml) was added and the aqueous layer extracted with dicloromethane (3x20 ml) The combined organic layers were washed with brine (20 ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and chromatography of the residue (33% ethyl acetate-petrol) gave **Methyl {methyl 2aα, 4β, 5aα, 6α, 8aα, 3, 4, 5, 7, 8-decahydro-5a-methyl-5-oxo-4-phenylselenylyl-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-8-spiro-2-(1,3-dithiane)-6-}acetate** (245 mg, 90%) as a white solid; ν_{max} ($CHCl_3$) 1725, 1434, 1224, 1012 and 909 cm-1; δ(500 MHz) 1.0 (3H, s, 19-H_3), 1 43 (1H, dd, J 15 and 13 Hz, 8-H_1), 1.84-1.95 (3H, m, 3-H_1, 11-H_1, and SCH_2CH_2-H_1), 2.1 (1H, m, SCH_2CH_2-H_1), 2.2 (1H, dd, J 15 and 4 Hz, 8-H_1), 2 6-2 8 (3H, m, 9-H_1 and 2 SCH_2-H_1), 2.82 (1H, dd, J 14 and 6 Hz, 3-H_1), 2.87 (1H, d, J 12 Hz, 5-H_1), 3 02 (1H, dd,J 16 and 2 Hz, 11-H_1), 3 20-3 30 (2H, m, 2 SCH_2-H_1), 3.57 (1H, d, J 8 Hz, 28-H_1), 3 68 (3H, s, COOMe), 3 76 (3H, s, COOMe), 4 02 (1H, d, J 8 Hz, 28-H_1), 4.57 (1H, d, J 12 Hz, 6-H_1), 4.96 (1H, dd, J 14 and 8 Hz, 2-H_1), 7.28 (3H, m, arom), and 7 59 (2H, m, arom); *m/z* 584 (M+), and 428; found: 584.0801 $C_{26}H_{32}O_6S_2Se$ requires 584 0806

Elimination of selenoxide. To a solution of **Methyl {methyl 2aα, 4β, 5aα, 6α, 8aα, 3, 4, 5, 7, 8-decahydro-5a-methyl-5-oxo-4-phenylselenylyl-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-8-**

spiro-2-(1,3-dithiane)-6-}acetate (240 mg, 0.41 mmol) in dry dichloromethane (10 ml) at r.t. was added 2-(phenylsulphonyl)-3-p-nitrophenyloxaziridine (125 mg, 0 41 mmol) followed by saturated aqueous sodium hydrogencarbonate solution (5 ml). The mixture was stirred vigorously for 90 min The aqueous layer was then extracted with dichloromethane (3x25 ml) and the combined organic layers washed with brine (20 ml) and dried (Na_2SO_4) Evaporation of the solvent under reduced pressure and chromatography of the residue (33% ethyl acetate-petrol) gave **Methyl {methyl 2aα, 5aα, 6α, 8aα, 5a-methyl 5, 7, 8-octahydro-5-oxo-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-8-spiro-2-(1,3-dithiane-6-}acetate (27)** (119 mg, 68%) as a solid, ν_{max} ($CHCl_3$) 1727, 1673, 1340, 1200, 1165 cm^{-1}; δ(500 MHz) 0.92 (3H, s, 19-H_3), 1.53 (1H, dd, J 16 and 12 Hz, 8-H_1), 1.95 (1H, m, $SCH_2C\underline{H}_2$-H_1), 2.04 (1H, dd, J 16 and 10 Hz, 11-H_1), 2.12 (1H, m, $SCH_2C\underline{H}_2$-H_1), 2.18 (1H, dd, J 16 and 4 Hz, 8-H_1), 2 57-2.68 (2H, m, 9-H_1 and SCH_2-H_1), 2.79 (1H, m, SCH_2-H_1), 3.19 (1H, d, J 13 Hz, 5-H_1), 3.25-3 33 (2H, m, 2 SCH_2-H_1), 3 47 (1H, dd, J 16 and 2 Hz, 11-H_1), 3.68 (3H, s, COOMe), 3.77 (3H, s, COOMe), 3 84 (1H, d, J 8 Hz, 28-H_1), 4.24 (1H, d, J Hz, 28-H_1), 4.71 (1H, d, J 13 Hz, 6-H_1), 6.02 (1H, d, J 9 Hz, 2-H_1), and 7 08 (1H, d, J 9 Hz, 3-H_1); *m/z* 426 (M+), 395, 367; found. 426.1172 . $C_{20}H_{26}O_6S_2$ requires 426.1171 .

Dithiane removal. Methyl iodide (146 µl, 2.35 mmol) was added to a suspension of the enone **(27)** (100 mg, 0.235 mmol) in CH_3CN H_2O (1.1) (15 ml) containing calcium carbonate (47 mg, 0.47 mmol) under reflux. After 3 h. the reaction mixture was allowed to cool to r.t., diluted with water (10 ml) and the aqueous layer extracted with dichloromethane (3x15ml) The combined organic laters were washed with brine (20 ml) and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue (70% ethyl acetate-petrol) gave **Methyl {methyl 2aα, 5aα, 6α, 8aα, 5a-methyl-5,7,8-octahydro-5,8-dioxo-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-8-spiro-2-(1,3-dithiane)-6-}acetate (28)** (55 mg, 70%) as a colourless oil; ν_{max} (film) 1726, 1674 and 1203 cm^{-1}; δ(500 MHz) 1.09 (3H, s, 19-H_3), 2.19 (1H, dd, J 16 and 5 Hz, 11-H_1), 2.26 (1H, dd, J 16 and14 Hz, 8-H_1), 2 45 (1H, dd, J 14 and 4 Hz, 8-H_1), 2.55 (1H, d, J 14 Hz, 5-H_1), 2.53-2 63 (1H, m, 9-H_1), 3.47 (1H, dd, J 16 and 2 Hz, 11-H_1), 3.64 (3H, s, COCMe), 3.75 (3H, s, COOMe), 3 81 (1H, d, J 8 Hz, 28-H_1), 4.28 (1H, d, J 8 Hz, 28-H_1), 5.0 (1H, d, J 14 Hz, 6-H_1), 6.03 (1H, d, J 10 Hz, 2-H_1), 7.04 (1H, d, J 10 Hz, 3-H_1), *m/z* 336 (M+), 305, 277, and 149; found: 336.1210; $C_{17}H_{20}O_7$ requires 336.1209

Reduction of the diketone (28). To a solution of the diketone **(28)** (50 mg, 0.148 mmol) in dry methanol (3 ml) at r.t was added cerium trichloride heptahydrate (66.2 mg, 0.177 mmol) followed by sodium borohydride (6 7 mg, 0.177 mmol). After 5 min the reaction mixture was diluted with water, neutralised with 10% aqueous hydrochloric acid (3 drops) and extracted with dichloromethane (3x10 ml). The combined extracts were washed with brine (10 ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and chromatography of the residue (90% ethyl acetate-petrol) gave **Methyl {methyl 2aα, 5αβ, 5aα, 6α, 8β, 8aα, 5, 8-dihydroxy-5a-methyl-5, 7, 8-octahydro-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-6-}acetate (29)** (78%) as a 2 1 mixture at C-5; ν_{max} ($CHCl_3$) 3422, 2925, 1721, 1436, 1378, 1206, 1171 and 1149 cm^{-1}, δ(500 MHz) 0 77 (3H, s, 19-H_3), 1 39 (1H, m, 8-H_1), 1 82 (1H, d, O$\underline{H}$), 1 88 (1H, m, 8-H_1), 2.07 (1H, s, O$\underline{H}$), 2.08 (1H, dd, J 16 and 11 Hz, 11-H_1), 2 29 (1H, m, 9-H_1),

2.37 (1H, d, J 14 Hz, 5-H_1), 2.86 (1H, dd, J 16 and 5 Hz, 11-H_1), 3.59 (1H, d, J 8 Hz, 28-H_1), 3.68 (3H, s, COOMe), 3.71 (3H, s, COOMe), 4.13 (1H, d, J 8 Hz, 28-H_1), 4.28 (2H, m, 1-H_1, 7-H_1), 4.37 (1H, dd, J 14 and 4 Hz, 6-H_1), 5.68 (1H, dd, J 10 and 2 Hz, 3-H_1), 6 03 (1H, dd, J 10 and 2 Hz, 2-H_1); *m/z* 340 (M+), 338; found:340.1526 ; $C_{17}H_{24}O_7$ requires 340 1526 .

Allylic oxidation of (29). To a solution of the diol **(29)** (23 mg, 0.067 mmol) in dichloromethane (6 ml) was added MnO_2 (59 mg, 0.67 mmol), with stirring at r t After 7 h. further MnO_2 (23 mg, 0 27 mmol) was added. The mixture was stirred for another 3 h then filtered through celite rinsing with ethyl acetate. Evaporation of solvents under reduced pressure followed by silica gel chromatography (5% MeOH-DCM) of the residue gave **Methyl {methyl-2aα, 5α, 5aα, 6α, 8β, 8aα-5,8-dihydroxy-5a-methyl-5,7,8-octahydro-5-oxo-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-6-}acetate (30)** (13 5 mg, 60%) as a glass; ν_{max} 3720, 2926, 1672, 1434, 1379, 1286, 1259, 1205 and 1171 cm-1; δ(500 MHz) 0.90 (3H, s, 19-H_3), 1 39 (1H, m, 8-H_1), 1.99 (1H, ddd, J 15, 4 and 4 Hz, 8-H_1), 2.07 (1H, dd, J 15 and 11 Hz, 11-H_1), 2.08 (1H, d, J 1 Hz, OH), 2.55 (1H, m, 9-H_1), 2 97 (1H, d, J 12 Hz, 5-H_1), 3.46 (1H, dd, J 15 and 3 Hz, 11-H_1), 3.67 (3H, s, COOMe), 3.74 (3H, s, COOMe), 3 76 (1H, d, J 8 Hz, 28-H_1), 4.23 (1H, m, 7-H_1), 4.27 (1H, d, J 8 Hz, 28-H_1), 4 37 (1H, dd, J 12 and 3 Hz, 6-H_1), 6 01 (1H, d, J 10 Hz, 3-H_1), 7 04 (1H, d, J 10 Hz, 2-H_1; *m/z* 338 (M+), 320; found: 338.1373 ; $C_{17}H_{22}O_7$ requires 338.1366

Epoxidation of enone (30). To a solution of the enone **(30)** (6 mg, 0 0178 mmol) in MeOH (1 4 ml) at 0 °C was added H_2O_2 (25 µl of a 30% solution in water, 0.222 mmol) dropwise with stirring. Saturated aqueous potassium carbonate (78 µl) was added over 20 min The mixture was stirred for 105 min. Brine (2 ml) was added and the solution extracted with dichloromethane (4x 2 ml). After drying (Na_2SO_4) the solvent was evaporated to give **Methyl {methyl-2aα, 3β, 4β, 5aα, 6α, 8β, 8aα-3,4-epoxy-8-hydroxy-5a-methyl-3, 4, 5, 7, 8-decahydro-5-oxo-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-6-}acetate (31)** as a glass (6 mg, 95%); ν_{max} 3459, 2926, 1721 and 1214 cm^{-1}; δ(500 MHz) 0.78 (3H, s, 19-H_3), 1 32 (1H, br t, J 15 Hz, 8-H_1), 1.97 (1H, ddd, J 15, 4 and 4 Hz, 8-H_1), 2 41 (1H, dd, J 15 and 11 Hz, 11-H_1), 2 16 (1H, br s, 7-OH), 2 55 (3H, m, 9-H_1), 3 19 (1H, dd, J 15 and 4 Hz,11-H_1), 3 34 (1H, d, J 12 Hz, 5-H_1), 3 41 (1H, d, J 4 Hz, 3-H_1), 3 68 (3H, s, COOMe), 3 79 (3H, s, COOMe), 3 81 (1H, d, J 4 Hz, 2-H_1), 3 95 (1H, d, J 8 Hz, 28-H_1), 4.11 (1H, dd, J 12 and 4 Hz, 6-H_1), 4 18 (1H, m, 7-H_1), 4 30 (1H, d, J 8 Hz, 28-H_1); *m/z* 354 (M+), 336; found· 354 1307 ; $C_{17}H_{22}O_8$ requires 354 1315 .

Reduction of epoxide (31). To a solution of the epoxide **(31)** (7 mg, 0 02 mmol) in EtOH (1 ml) was added 10% aqueous sodium hydrgencarbonate solution (16 µl) followed by aluminium amalgam (from aluminium foil 12 mg, 0 44 mmol) in three pieces. After stirring at r t for 100 min. dichloromethane was added and the mixture filtered through celite rinsing the pad with dichloromethane Evaporation of the solvents followed by silica gel chromatography (6% MeOH-DCM) gave **Methyl {methyl-2aα, 3β, 5aα, 6α, 8β, 8aα-3, 4, 5, 7, 8-decahydro-3, 8-dihydroxy-5a-methyl-5-oxo-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-6-}acetate (32)** (7 mg, 95%)

as a glass; ν_{max} 3403, 1710, 1218 and 1078 cm^{-1}; δ(500MHz) 0.93 (3H, s, 19-H_3), 1.33 (1H, td, J 15 and 3 Hz, 8-H_1), 1.94 (1H, dd, J 16 and 12 Hz, 11-H_1), 1.98 (1H, dt, J 14 and 4 Hz, 8-H_1), 2.28 (1H, br s, OH), 2.36 (1H, br s, OH), 2 46 (1H, dd, J 16 and 4 Hz, 2-H_1), 2.65 (1H, m, 9-H_1), 3.07 (1H, d, J 12 Hz, 5-H_1), 3.07 (1H, dd, J 16 and 4 Hz, 11-H_1), 3.33 (1H, dd, J 16 and 5 Hz, 2-H_1), 3.69 (3H, s, COOMe), 3.84 (3H, s, COOMe), 3.98 (1H, d, J 8 Hz, 28-H_1), 4.12 (1H, d, J 8 Hz, 28-H_1), 4.19 (1H, m, 7-H_1), 4.32 (1H, dd, J 12 and 4 Hz, 6-H_1), 4.70 (1H, m, 3-H_1); *m/z* 356 (M+), 338, 320, and 139; found: 356.1471 ; $C_{17}H_{24}O_8$ requires 356.1471 .

Reduction of (32) to the triol. To a solution of diol **(32)** (4 mg, 0.011 mmol) in dry tetrahydrofuran (1 ml) was added solid sodium hydrogencarbonate (3 mg, 0.035 mmol) and 3Å sieves. The suspension was cooled to -78 °C under argon and magnesium dibromide mono-etherate (4.5 mg, 0.018 mmol) added with stirring. After 15 min. $NaBH_4$ (1.3 mg, 0.034 mmol) was added as a solid. The mixture was stirred at -78 °C for 3 h. then allowed to warm to r t. The mixture was partitioned between dichloromethane (3 ml) and brine (3 ml) and the aqueous layer re-extracted with dichloromethane (5x3 ml). The combined organic layers were dried (Na_2SO_4). Evaporation of the solvent follwed by silica gel chromatography (6% MeOH-DCM gave less polar **Methyl {methyl-2aα, 3β, 5β, 5aα, 6α, 8β, 8aα-3, 4, 5, 7, 8-decahydro-5a-methyl-3, 5, 8-trihydroxy-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-6-}acetate (33)** (27 mg, 68%) as a white foam; ν_{max} 3394, 2923, 1721, 1674, 1433, 1200 and 1054 cm^{-1}, δ(500 MHz) 0 66 (3H, s, 19-H_3), 1.56 (1H, br t, J 14 Hz, 8-H_1), 1.83 (1H, dt, J 15 and 4 Hz, 8-H_1), 2.10 (1H, dd, J 17 and 4 Hz, 11-H_1), 2.16 (1H, m, OH), 2 18 (1H, dd, J 3 and 3 Hz, 2-H_1), 2.22 (1H, br s, OH), 2.37 (1H, dd, J 17 and 9 Hz, 11-H_1), 2.74 (1H, m, 9-H_1), 2.81 (1H, d, J 12 Hz, 5-H_1), 3.47 (1H, dd, J 6 and 3 Hz, 2-H_1), 3 70 (3H, s, COOMe), 3.73 (3H, s, COOMe), 3.90 (1H, d, J 8 Hz, 28-H_1), 4.14 (1H, d, J 8 Hz, 28-H_1), 4.18 (1H, d, J 9 Hz, OH), 4.23 (1H, br dd, J 6 and 3 Hz, 7-H_1), 4.27 (1H, dd, J 12 Hz and 3 Hz 6-H_1), 4.40 (1H, dt, J 9 and 3 Hz, 1-H_1), 4.47 (1H, br d, J 2 Hz, 3-H_1); *m/z* 358 (M+), 340 322, 284, and 252; found: 358.1634 ; $C_{17}H_{26}O_8$ requires 358.1628 ; and more polar **Methyl {methyl-2aα, 3β, 5α, 5aα, 6α, 8β, 8aα-3, 4, 5, 7, 8-decahydro-5a-methyl-3, 5, 8-trihydroxy-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-6-}acetate (34)** (0.5 mg, 12%) as a colourless oil; ν_{max} 3394, 1718, 1434, 1209, 1073, 1048 and 1026 cm^{-1}; δ(500MHz) 0.71 (3H, s, 19-H_3), 1.39 (1H, br t, J 15 Hz, 8-H_1), 1.85 (1H, dt, J 15 and 4 Hz, 8-H_1), 1.99 (1H, dd, J 16 and 8 Hz, 11-H_1), 2 17 (1H, dt, J 10 and 2 Hz, 2-H_1), 2.20 (1H, br s, OH), 2.30 (2H, m, 9-H_1 and 2-H_1), 2.58 (1H, d, J 16 Hz, 5-H_1), 3.12 (1H, dd, J 16 and 4 Hz, 11-H_1), 3.68 (3H, s, COOMe), 3.77 (3H, s, COOMe), 3.87 (1H, d, J 8 Hz, 28-H_1), 4.02 (1H, d, J 8 Hz, 28-H_1), 4.02 (1H, m, 1-H_1), 4.20 (1H, m, 7-H_1), 4 28 (1H, dd, J 16 and 4 Hz,6-H_1), 4.50 (1H, m, 3-H_1); *m/z* 358 (M+), 340 (M+-H_2O), 322, 308, 284, and 252; found: 340.1526 for M+-H_2O; $C_{17}H_{24}O_7$ requires 340.1522 .

Methyl {methyl-2aα, 3β, 5β, 5aα, 6α, 8β, 8aα-3, 4, 5, 7, 8-decahydro-5a-methyl-3, 5, 8-trihydroxy-2H-naphtho[4.4a.5.bc]furan-2a-carboxylate-6-}acetate-3,5-benzylidene acetal (2). To a solution of the triol **(33)** (4 mg, 0.0111 mmol) in dry benzene (1 ml) was added pyridinium p-toluene sulphonate (1 crystal) and benzaldehyde (14 µl, 1.27 mmol). The mixture was heated under reflux with azeotropic removal of water, for 1.5 h. After allowing to cool saturated aqueous sodium hydrogencarbonate (2 ml) was added and the mixture extracted

with dichloromethane (4x2 ml). The combined extracts were dried ($MgSO_4$). Removal of the solvents under reduced pressure followed by chromatography (65% ethyl acetate-petrol) gave (2) (4.7 mg, 95 %) as a colourless oil; δ(500 MHz) 0.73 (3H, s, 19-H_3), 1.48 (1H, br t, J 4 Hz, 8-H_1), 1.95 (1H, dd, J 10 and 15 Hz, 11-H_1), 1.97 (1H, d, J 16 Hz, 2-H_1), 2.05 (1H, dt, J 15 and 4 Hz, 8-H_1), 2.20 (1H, s, OH), 2 36 (1H, dd, J 15 and 4 Hz, 11-H_1), 2.86 (1H, dt, J 16 and 5 Hz, 2-H_1), 3 06 (1H, m, 9-H_1), 3 40 (1H, d, J 13 Hz, 5-H_1), 3.59 (3H, s, COOMe), 3.77 (3H, s, COOMe), 3.84 (1H, d, J 8 Hz, 28-H_1), 3.93 (1H, d, J 8 Hz, 28-H_1), 4.09 (1H, br d, J 5 Hz, 1-H_1), 4.28 (1H, br d, J 2 Hz, 7-H_1), 4.33 (1H, dd, J 13 and 3 Hz, 6-H_1), 4 86 (1H, d, J 5 Hz, 3-H_1), 6.20 (1H, s, PhCH), 7.34-7.61 (5H, m, arom.).

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Footnotes

‡ On study leave from Departamento Quimica Organica, Facultad de Quimicas, Valencia.

‡‡ Compound (2) was obtained as a single diastereomer as indicated by 500 MHz nmr spectroscopy. Molecular mechanics calculations performed using Clark Still's MACROMODEL^{TM} package implied that (2) was approximately 30 KJ mol^{-1} more stable than its diastereomer epimeric at the benzylic position.