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Chemistry of Insect Antifeedants from *Azadirachta Indica* (Part 15):[1] Degradation Studies of Azadirachtin leading to C8-C14 Bond Cleavage.

Steven V. Ley*, Peter J. Lovell, Alexandra M. Z. Slawin, Stephen C. Smith, David J. Williams and Anthony Wood.

Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, UK

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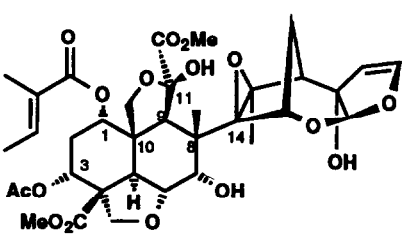
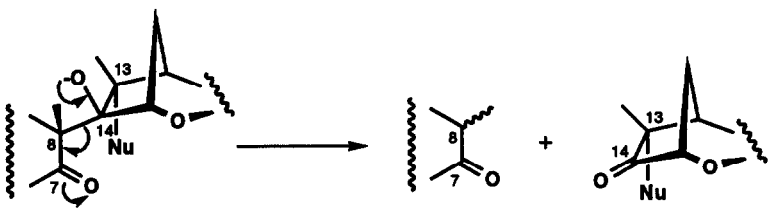
Abstract: The synthesis of a novel macrocyclic carbonate (5) is described which undergoes a base mediated retro-Aldol reaction to cleave the C8-C14 bond giving the highly functionalised decalin unit (7). This key reaction has allowed the preparation of further derivatives for synthetic studies and biological evaluation.

For some years we have been studying the structure,[1,2] synthesis[3] and biological activity[4] of the potent insect antifeedant and growth disrupting agent azadirachtin (1). This work has led to a detailed understanding of the functional groups required for biological activity. Furthermore, we have devised synthetic strategies which have facilitated the construction of key fragments of the natural product.[5,6]



(1)

Our ultimate aim is to provide a better understanding of insect feeding mechanisms and host plant recognition processes in the hope that this will stimulate the commercial development of new, environmentally acceptable materials for integrated pest management programmes. Azadirachtin, with its complex array of oxygen functionality, stereogenic and quaternary centres and chemical sensitivity, provides a challenging compound for further study. In this work we have investigated degradation reactions of (1) leading to cleavage of the central C8-C14 bond with the intention of providing useful compounds for total synthesis studies and further derivatives to complement our structure activity relationship programme.[7] In order to achieve cleavage of this highly hindered bond we conceived the retro-Aldol degradation sequence shown in Scheme 1. This transformation requires prior C(7) oxidation and C(13)-C(14) oxirane ring opening.



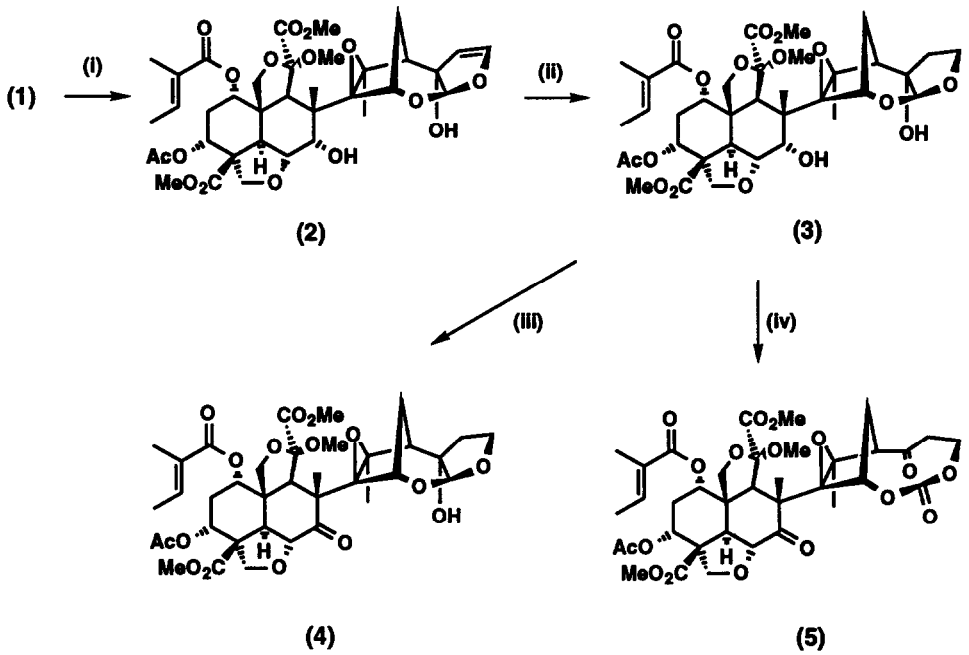
Scheme 1

Although this process appeared reasonable, other labile functional groups in (1) required modification prior to its examination. The three major problems were the sensitivity of the tigloyl and acetate groups to base, the reversibility of the hemiacetal unit at C11 and the sensitivity of the C22-C23 enol ether. For these reasons we chose to investigate reactions on more stable derivatives. In the first experiments we made use of substrates previously reported during our studies on the rearrangements of azadirachtin and its derivatives.[8] Hence azadirachtin was selectively methylated at the C11 hydroxyl group using methyl iodide and silver (I) oxide to give (2) which was partially hydrogenated to (3) and then oxidised at C7 to give (4) with the Dess-Martin periodinane reagent (Scheme 2).[9]

All attempts to selectively open the hindered epoxide of (4) at C13 with either acidic or basic reagents were unsuccessful and gave complex mixtures and/or rearrangement products.

We therefore had to revise our approach and it occurred to us that if we were able to achieve oxidative cleavage of the C20-21 bond leaving a carbonyl function at C20, thermodynamic enolate formation and β elimination would lead to epoxide ring opening. We argued that this C20-21 bond would be unstable towards oxidative cleavage owing to the effect of the C21 acetal unit. Indeed we found that by treating (3) with an excess

of pyridinium chlorochromate (PCC)[10] and 4Å sieves, oxidation of the C7 hydroxyl group and concomitant C20-C21 bond cleavage occur giving the novel diketo-carbonate (**5**) in excellent yield. The structure of (**5**) was proved by single crystal X-ray determination.[8] This very pleasing result now gave us access to a possible fragmentation reaction.

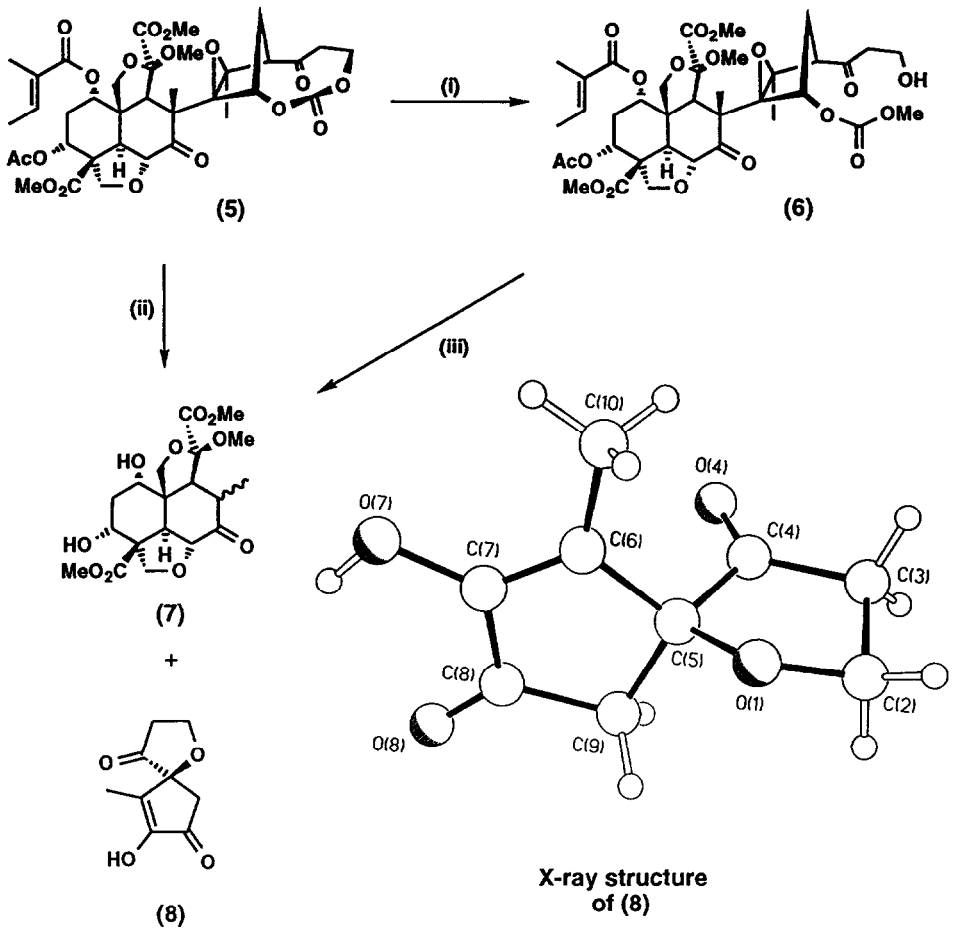


Reagents: (i) Ag_2O, MeI, 37 C, 86%; (ii) H_2, Pd/C, MeOH, 82%; (iii) Periodinane, CH_2Cl_2, 86%; (iv) PCC, 4Å sieves, CH_2Cl_2, 52%.

Scheme 2

In fact when (**5**) was reacted with sodium methoxide in methanol at room temperature the desired fragmentation process occured to give the decalin unit (**7**) as a 2:1 mixture of C8 epimers in 92% yield (Scheme 3). It is therefore apparent that methoxide anion effects ring opening of the carbonate and that after base catalysed enolisation and ß elimination, the retro-aldol reaction occurs as predicted along with hydrolysis of the ester units at C1 and C3.

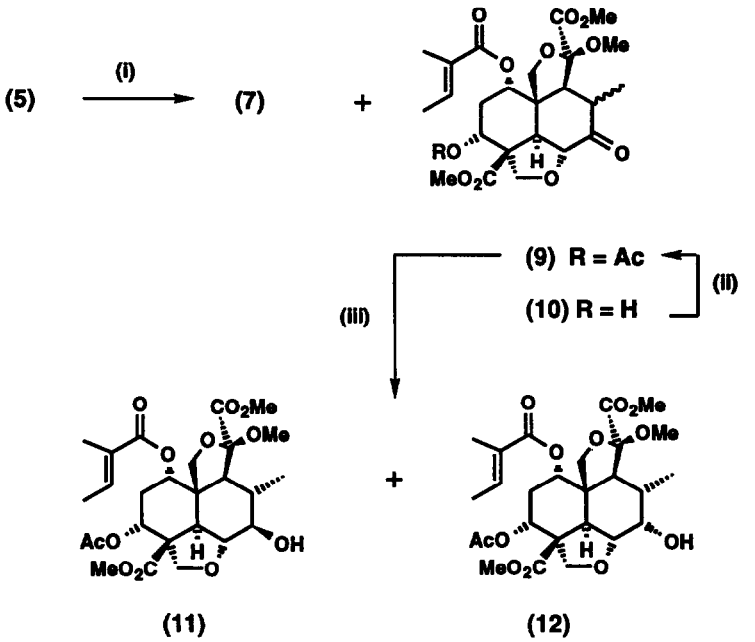
In order to shed more light on this reaction pathway we found that (5) also reacts with methanol alone to give an unstable intermediate (6) which may be converted to (7) (82%) on treatment with sodium methoxide. The fate of the right hand side fragment in these degradations is complicated by further reactions but a product was isolated and has been characterised by high field nmr experiments and later X-ray and assigned the structure (8). In other reactions designed to effect cleavage of the C8-C14 bond in (5) under milder conditions we find that (5) will react with Et_3N / H_2O / THF 1:5:1 to give (7) together with the compounds (9) and (10) in a 2:3:3 ratio.



Reagents: (i) MeOH, 85%; (ii) MeONa, MeOH, 0°C, 92%; (iii) MeONa, MeOH, 0°C, 82%.

Scheme 3

Compound **(10)** may be reacetylated with acetic anhydride, triethylamine and 4-N,N-dimethylaminopyridine (DMAP) in dichloromethane to give **(9)** (Scheme 4).



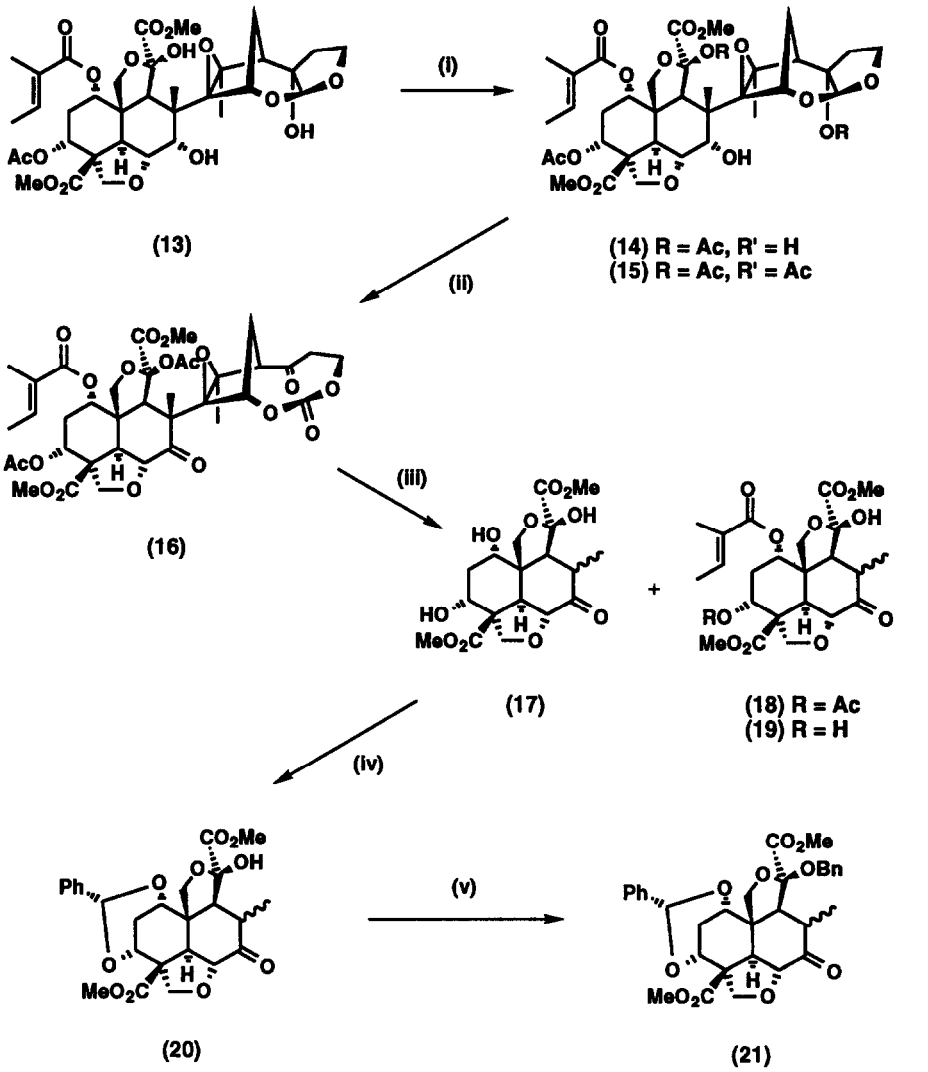
Reagents: (i) Et_3N / H_2O / THF (1:5:1) **(7)** 30%, **(9)** 19%, **(10)** 33%; (ii) Et_3N, DMAP, Ac_2O, 81%; (iii) $NaBH_4$, $CeCl_3.7H_2O$, **(11)** : **(12)** 1:1, 62%.

Scheme 4

These studies have relevance for biological evaluation of the various cleaved fragments in that we wished to screen materials with similar substituents at C1 and C3 to the natural product. We also elected to study the reduction of the C7 carbonyl group to give closer analogues for biological testing. Accordingly the fragment **(9)** was reduced under the Luche conditions[11] to afford the alcohols **(11)** and **(12)** in 62% yield and in a ratio of 1:1 (Scheme 4). The assignment of structure of **(11)** and **(12)** followed after careful HPLC separation. The stereochemistry was derived by detailed nmr and n.O.e. experiments and appropriate correlation with predicted values obtained from MM2 energy minimised geometries using Macromodel (Batchmin) program.[12]

As the methoxy substituent at C11 in these structures is relatively inert towards exchange or demethylation to give the free C11 hydroxyl derivatives, we have also studied a series of reactions to give unsubstituted compounds necessary for biological screening and total synthesis studies.

Here dihydroazadirachtin (**13**) was treated with acetic anhydride, triethylamine and DMAP to give the C11 acetate (**14**) in 65% yield with less than 5% of the C11, C20 diacetate (**15**). Compound (**14**) was then subjected to the oxidation reaction with pyridinium dichromate (PDC)[13] or PCC as reported earlier to give the corresponding diketocarbonate (**16**) in 50% yield.



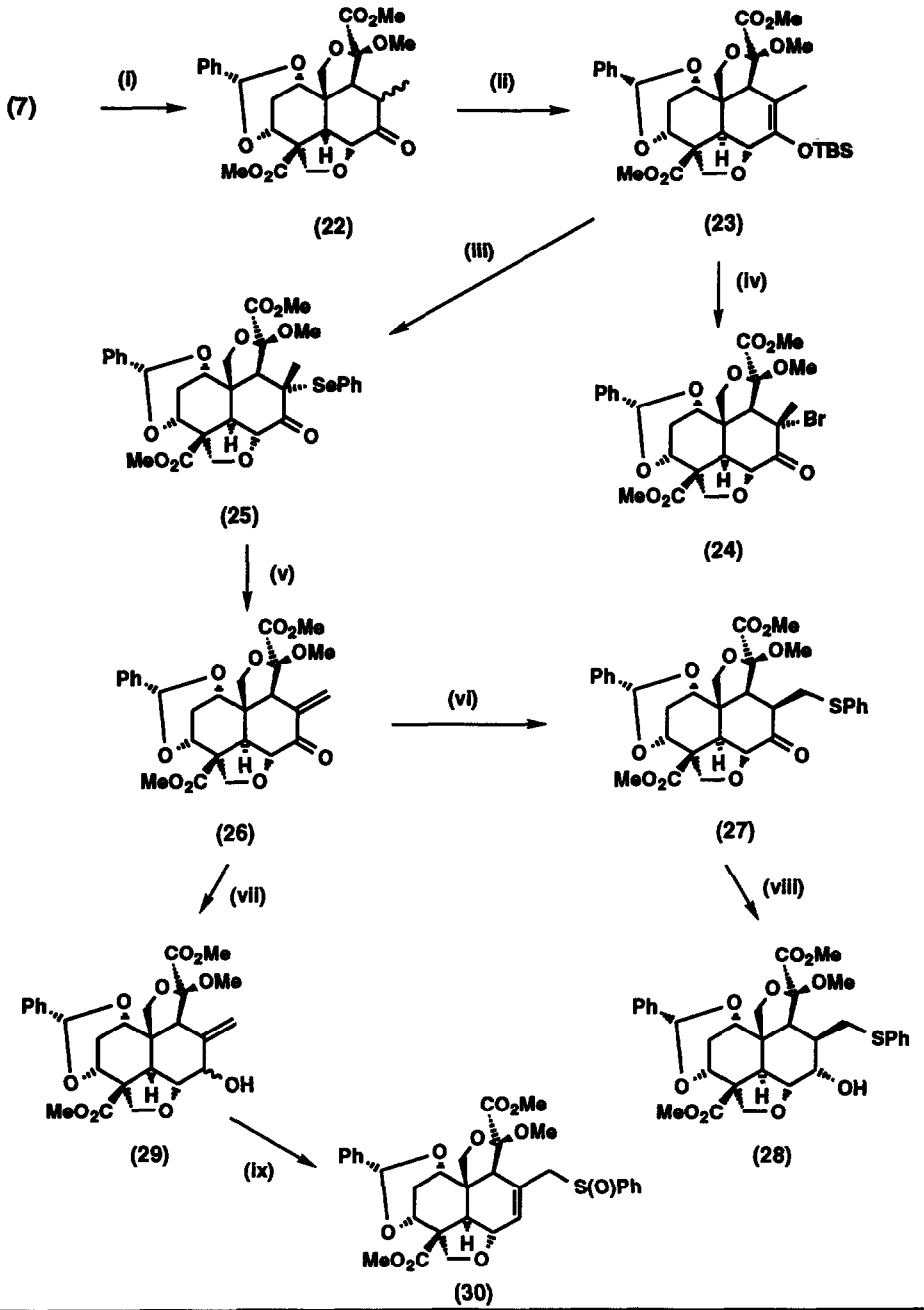
Reagents: (i) Ac_2O, Et_3N, DMAP, (**14**) 65%, (**15**) 5%; (ii) PCC, CH_2Cl_2, 4Å sieves, 50%; (iii) Et_3N, H_2O, THF, (**17**) 32%, (**18**) 15%, (**19**) 38%; (iv) PhCHO, ppts, benzene, reflux, 72%; (v) Ag_2O, BnBr, DMF, 71%.

Scheme 5

Degradation reactions of **(16)** similar to those described earlier with Et_3N in methanol gave the decalin fragments **(17)**, **(18)** and **(19)** in 85% yield in the ratio 1:2:2 respectively. Compound **(17)** was elaborated for use in total synthesis and analogue studies by protecting the diaxial 1,3-diol as its benzylidene acetal **(20)** using benzaldehyde and pyridinium *para*-toluenesulphonate (ppts) as catalyst. Finally the C11 hydroxyl group was benzylated using benzyl bromide and silver oxide in DMF to give the fully protected decalin **(21)** (Scheme 5).

These degradation studies involving the cleavage of the C8-C14 bond in azadirachtin derivatives now provide quantities of substituted decalins suitable for other reactions centered on the C7 and C8 atoms since it is these positions which will be used in coupling reactions for the total synthesis of **(1)** and for the preparation of novel analogues. The remainder of this paper is concerned only with reactions of the benzylidene protected 11-OMe derivative **(22)** since this represents the best model system being easily prepared from the initial diol **(7)** using benzaldehyde dimethyl acetal and catalytic ppts.

Deprotonation of **(22)** with potassium hydride at 0°C in THF followed by reaction with t-butyldimethylsilylchloride gave the corresponding silyl enol ether **(23)** (67%). This enol derivative readily reacts with electrophiles allowing substitution at C8. For example with N-bromosuccinimide we can obtain a single bromide **(24)** in which attack has occured from the least hindered α face. In a similar fashion **(23)** reacts at -78°C with phenylselenenyl chloride in CH_2Cl_2 to give the selenide **(25)** (57%) (scheme 6). This selenide is also a useful precursor for further elaboration since upon oxidation with Davis oxaziridine[14] reagent *syn* elimination of the intermediate selenoxide exclusively affords the *exo*-alkene **(26)** (81%). The enone **(26)** in the presence of thiophenol and sodium hydride rapidly produces the addition product **(27)**. The assignment of the stereochemistry of this adduct follows from the coupling constant in the ^1H nmr of the C8 proton of 6.4Hz. Reduction of **(27)** is also stereoselective and affords **(28)** upon reaction with zinc borohydride in THF. Lastly we studied the reaction of the enone with sodium borohydride and ceric trichloride which gives the alcohols **(29)** in a 4:1 ratio of β:α isomers. Treatment of the β isomer with phenylsulphenyl chloride and triethylamine at room temperature in dichloromethane gave a single sulphoxide **(30)** after [2,3] sigmatropic rearrangement of the intermediate sulphenate derivative (Scheme 6).



Reagents: (i) $PhCH(OMe)_2$, ppts, benzene, 96%; (ii) KH, THF, 0°C, TBDMSCl, 67%; (iii) PhSeCl, CH_2Cl_2, -78°C, 57%; (iv) NBS, THF, -20°C, 96%; (v) Davis oxaziridine, $CHCl_3$, 81%; (vi) PhSH, NaH, THF, 0°C, 96%; (vii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 87%; (viii) $Zn(BH_4)_2$, THF, 0°C, 92%; (ix) Et_3N, PhSCl, CH_2Cl_2, -78°C, 94%.

Scheme 6

Although we have investigated many other reactions of these decalin derivatives, the above serve as representative examples of some of the substitutions that can be achieved at the C7 and C8 positions of these molecules. These reactions set the scene for further carbon-carbon bond coupling reactions, details of which will be reported at a later date.

Experimental:

^{1}H and ^{13}C nmr spectra were recorded in $CDCl_3$ unless otherwise stated, on a Bruker AM-500 nmr spectrometer, using residual protic solvent $CHCl_3$ (δ_H=7.26 ppm) or $CDCl_3$ (δ_C=77.0 ppm, t) as internal reference. Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer. Mass spectra were recorded using VG-7070B, VG 12-253 and VG ZAB-E instruments in the Imperial College Chemistry Department Mass Spectroscopy laboratory and the SERC Mass Spectrometry Service in Swansea. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Melting points were determined on a Reichert hot stage apparatus. Optical rotations were measured using an Optical Activity AA-1000 polarimeter. Molecular modelling was performed using the MACROMODEL package,[19] on an Evans and Sutherland PS-390 graphics terminal. Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh). Florisil refers to 230-300 U.S. mesh Florisil as supplied by BDH Ltd. Dichloromethane (DCM) was distilled from phosphorous pentoxide and methanol from magnesium. Petrol refers to petroleum ether b.p. 40-60°C which was distilled prior to use as was ethyl acetate. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised by acidic ammonium molybdate (IV). Numbering for ^{1}H nmr assignments follows the natural product numbering system. Coupling constants are measured in hertz. The nmr assignments follow the azadirachtin carbon skeleton numbering system.

Crystal data for compound (8)

Single crystals of compound (8) were grown at room temperature from petrol/ether. $C_9H_{10}O_4$, triclinic, a=7.267(5), b=7.731(6), c=8.148(6)Å, α=68.93(2), β=78.46(2), γ=87.06(2), V=418.4(5)Å^3, space group $P1$,Z=2, D_C=1.45gm cm^{-3}, Cu radiation, λ=1.54178Å, μ(Cu-K_α)=9.7cm^{-1}, F(000)=192. Data were measured on a Siemens P3/Pc diffractometer with Cu-$K\alpha$ radiation (graphite monochromator) using ω scans. A crystal of dimensions 0.03 x 0.43 x 0.50mm was used. 1111 Independant reflections ($2\theta \leq 116$) were measured, of which 1005 had $|F_0| > 4\sigma(|F_0|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods and the non-hydrogen

atoms refined anisotropically. All the hydrogen atoms were located from a ΔF map. The hydroxy hydrogen atom was refined isotropically subject to an O-H distance constraint. The positions of the remaining hydrogen atoms were idealised, C-H=0.96Å, assigned isotropic thermal parameters, $U(H)=1.2U_{eq}(C)$ and allowed to ride on their parent carbon atoms. The methyl group was refined as a rigid body. Refinement was by full matrix least squares to R=0.057, R_w = 0.060 [$w^{-1}=\sigma^2(F)+0.0005F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.28 and -0.30eA^{-3}. The mean and maximum shift error in the final refinement were 0.000 and 0.001, respectively. Computations were carried out on an IBM 70 386 PC using the SHELXTL program system. Atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre.

Preparation of 11-methoxyazadirachtin (2).

Freshly prepared silver (I) oxide (1.61g, 6.94mmol, 5 equiv) was added to a stirred solution of azadirachtin (1) (1.00g, 1.39mmol) in iodomethane (65ml) in the dark. The mixture was heated to 37°C for 3hr, cooled, filtered through a pad of Celite and the solvent removed *in vacuo* (caution, iodomethane carcinogen). The residue was purified by flash chromatography (80% ethyl acetate/petrol) to give 11-methoxyazadirachtin (880mg, 86%) as a colourless foam; $[\alpha]_D^{20}$=-26.5 (c=1.49, chloroform); υ_{max} (film) 3448, 2952, 1738, 1647, 1617, 1435, 1375, 1265, 1054 and 735 cm^{-1}; ^{1}H δ ($CDCl_3$) 1.24 (1H, d, J 8.9, H-16), 1.58 (3H, s, 3xH-30), 1.77 (3H, dd, J 7.0, 1.4, 3xH-4'), 1.79-1.82 (1H, m, H-16), 1.85 (3H, d, J 1.2, 3xH-5'), 1.89 (3H, s, C3-OAc), 1.94 (3H, s, 3xH-18), 2.26 (1H, dt, J 16.9, 3.2, H-2), 2.27 (1H, d, J 5.3, H-17), 2.32 (1H, dt, J 16.7, 2.7, H-2), 2.86 (1H, br s, C20-OH), 3.33 (3H, s, OMe), 3.34 (1H, d, J 14.0, H-5), 3.47 (1H, br s, H-9), 3.66 (3H, s, CO_2Me), 3.65 (1H, d, J 9.5, H-19), 3.72 (1H, d, J 8.8, H-28), 3.79 (3H, s, CO_2Me), 4.06 (1H, d, J 8.8, H-28), 4.07 (1H, d, J 9.6, H-19), 4.56 (1H, br s, H-7), 4.59 (1H, dd, J 12.5, 2.8, H-6), 4.73-4.74 (2H, m, H-1 and H-15), 5.01 (1H, d, J 2.9, H-22), 5.48 (1H, t, J 2.9, H-3), 5.58 (1H, s, H-21), 6.44 (1H, d, J 2.9, H-23) and 6.90 (1H, dq, J 1.4, 7.1, H-3'); m/z (FAB, thiodiethanol), 734 (MH^+), 717 (MH^+-H_2O), 703, 685, 678, 291, 167, 95, 83 and 70; Found (MH^+) 735.2864. $C_{36}H_{46}O_{16}$ requires 735.2864; Found: C, 57.31; H, 6.20. $C_{36}H_{46}O_{16}.H_2O$ requires C, 57.44; H, 6.43%.

Preparation of 22,23 dihydro-11-methoxy azadirachtin (3)

A degassed solution of 11-methoxyazadirachtin (2) (287mg, 0.392mmol) in methanol (20ml) containing 10% Pd/C (20mg) was hydrogenated at 1 atm for 20min. The mixture was degassed, filtered through a small pad of Celite and evaporated *in vacuo*. The residue was purified by flash chromatography (gradient elution, 60-100%

ethyl acetate/petrol) to give 22,23-dihydro-11-methoxyazadirachtin (236mg, 82%) as a colourless foam; $[\alpha]_D^{20}$=-8.8 (c=1.28, chloroform); υ_{max} (film) 3473, 2952, 1735, 1646, 1266, 1221, 1160, 1044 and 734 cm^{-1}; ^1H δ ($CDCl_3$) 1.46 (1H, d, J 12.7, H-16), 1.62 (3H, s, 3xH-30), 1.76 (3H, dd, J 7.0, 0.7, 3xH-4'), 1.83 (3H, s, 3xH-5'), 1.88 (3H, s, C3-OAc), 1.93 (3H, s, 3xH-18), 1.96-2.04 (2H, m, H-16 and H-22), 2.10-2.16 (1H, m, H-22), 2.25-2.27 (2H, m, 2xH-2), 2.34 (1H, d, J 5.3, H-17), 2.76 (1H, s, OH), 3.23 (1H, d, J 12.9, H-5), 3.31 (3H, s, C11-OMe), 3.35 (1H, s, H-9), 3.63 (1H, d, J 9.6, H-19), 3.64 (3H, s, CO_2Me), 3.69 (1H, d, J 8.9, H-28), 3.78 (3H, s, CO_2Me), 3.87 (1H, q, J 8.4, H-23), 3.99 (1H, m, H-23), 4.04 (1H, d, J 9.6, H-19), 4.05 (1H, d, J 8.9, H-28), 4.56 (2H, m, H-6 and H-7), 4.64 (1H, d, J 3.3, H-15), 4.72 (1H, t, J 2.8, H-1), 5.18 (1H, s, H-21), 5.46 (1H, t, J 2.9, H-3) and 6.84 (1H, q, J 7.1, H-3'); m/z (EI) 718 (M^+-H_2O), 677 (M^+-CO_2Me), 659 (M^+-H_2O-CO_2Me), 643, 633, 420, 384, 291, 253, 187, 151 and 144; found (M^+-CO_2Me) 677.2792. $C_{34}H_{45}O_{14}$ requires 677.2809.

Preparation of 22,23-dihydro-11-methoxy-7-ketoazadirachtin (4)

To a solution of 22,23-dihydro-11-methoxyazadirachtin (3) (17.0mg. 23.1μmol) in dichloromethane (1ml) was added Dess Martin periodinane (98mg, 0.231mmol, 10 equiv). After stirring for 72hr the mixture was warmed to 35°C and further periodinane (49mg, 5 equiv) was added. After 48hr (120hr total) the mixture was diluted with ethyl acetate (10ml) and poured into sat. $NaHCO_3$ (aq) (10ml) containing $Na_2S_2O_3$ (50mg). After stirring for 20min, the layers were separated. The aqueous layer was re-extracted with ethyl acetate (10ml) and the combined extracts were washed with sat. $NaHCO_3$ (aq) (10ml), dried (Na_2SO_4) and evaporated *in vacuo*. Purification of the residue by flash chromatography (gradient elution, 70-100% ethyl acetate/petrol) gave the ketone (4) (14.6mg, 86%) as a colourless foam; $[\alpha]_D^{20}$=+22.8 (c=1.0, chloroform); υ_{max} (film) 3498, 2955, 1739, 1433, 1263, 1219, 1129, 1040, 988 and 731 cm^{-1}; ^1H δ ($CDCl_3$) 1.56 (3H, s, 3xH-30), 1.62 (1H, d, J 8.4, H-16), 1.73 (4H, dd, J 7.1, 1.0, 3xH-4' and obscured H-16), 1.80 (3H, d, J 1.0, 3xH-5'), 1.90 (3H, s, C3-OAc), 2.01 (3H, s, 3xH-18), 2.03-2.12 (2H, m, 2xH-22), 2.19 (1H, dt, J 16.9, 3.2, H-2), 2.31 (1H, dt, 16.9, 2.6, H-2), 2.43 (1H, d, J 5.2, H-17), 2.76 (1H, d, J 14.3, H-5), 3.33 (3H, s, OMe), 3.64 (1H, s, H-9), 3.69 (3H, s, CO_2Me), 3.77 (2H, d, J 10.0, H-19 and obscured OH), 3.81 (1H, d, J 9.1, H-28), 3.83 (3H, s, CO_2Me), 3.84-3.87 (1H, m, H-23), 3.99 (1H, dt, J 3.4, 8.8, H-2), 4.10 (1H, d, J 9.0, H-28), 4.42 (1H, d, J 3.3, H-15), 4.46 (1H, d, J 9.9, H-19), 4.76 (1H, t, J 2.8, H-1), 5.09 (1H, s, H-21), 5.41 (1H, d, J 14.3, H-6), 5.49 (1H, t, J 2.8, H-3) and 6.65-6.66 (1H, m, H-3'); ^{13}C δ ($CDCl_3$) 12.1 (C5'), 14.1 (C4'), 18.0 (C18), 20.8, 21.4 (C30 and C3-OCOMe), 24.5 (C22), 29.7 (C2), 41.4 (C16), 45.9 (C5), 48.4 (C10), 48.6 (C-9), 52.4 (C17), 53.0, 53.1, 53.1, 53.2, 53.2 (C4, C8, OMe, 2xCO_2Me), 64.4 (C23), 65.1 (C13), 66.2 (C3), 66.6 (C14), 69.4 (C28), 70.1

(C1), 73.1 (C19), 76.0, 76.1 (C6 and C15), 81.0 (C20), 107.2, 108.0 (C11 and C21), 128.6 (C2'), 137.4 (C3'), 166.0, 168.9, 169.5, 172.2 (C1', C12, C19, C3-OCOMe) and 205.8 (C7); m/z (EI) 734 (M^+), 716 (M^+-H_2O), 702 (M^+-MeOH), 684, 675 (M^+-CO_2Me), 631, 506, 405, 320, 251, 178, 136, 95 and 83; found (M^+) 734.2787. $C_{36}H_{46}O_{16}$ requires 734.2786.

Preparation of [2aR, 4R (4S, 5R, 6S, 7R), 4aR, 5S, 7aS, 8S (E), 10R, 10aR, 10bR] Dimethyl 10-acetoxy-4-methyl-4-(6-methyl-2,8-dioxo-5,6-epoxy-4,7-methano-1,3dioxecan-5-yl)-5-methoxy-8-(2-methylbut-2-enoyloxy)-3-oxodecahydronaphtho[1,8-bc;4,4a,4ac']difuran-5,10a-dicarboxylate (5).

To a solution of 22,23-dihydro-11-methoxyazadirachtin (4) (54.4mg 73.9μmol) in dichloromethane (2ml) was added PCC (159mg, 0.739mmol, 10 equiv) and powdered activated 4Å molecular sieves (200mg). The mixture was stirred at room temperature for 48hr, after which time ethyl acetate (5ml) was added and stirring continued for 10min. The mixture was filtered through a pad of Florisil and the filtrate evaporated *in vacuo*. Purification by flash chromatography (gradient elution, 70-100% ethyl acetate/petrol) gave the rearranged compound (5) (28.5mg 52%) as a colourless solid; m.pt. 152°C (dec.); $[\alpha]_D^{20}$=+16.6 (c=6.10, chloroform); υ_{max} (film) 2954, 1750, 1740, 1700, 1434, 1390, 1268, 1128, 1042 and 734 cm^{-1}; ^1H δ ($CDCl_3$, natural prod. numbering) 1.64 (3H, s, 3xH-18 or 3xH-30), 1.75 (3H, dd, J 7.1, 1.0, 3xH-4'), 1.81 (3H, d, J 1.1, 3xH-5'), 1.85 (3H, s, 3xH-18 or 3xH-30), 1.90 (3H, s, C3-OAc), 1.94 (1H, d, J 14.7, H-16), 2.00-2.05 (1H, m, H-16), 2.20 (1H, dt, J 16.9, 3.2, H-2), 2.26 (1H, dt, J 16.9, 2.6, H-2), 2.64 (1H, ddd, J 14.5, 9.4, 1.3, H-22), 2.76 (1H, d, J 14.3, H-5), 2.89 (1H, d, J 6.8, H-17) 2.94 (1H, dd, J 14.7, 6.4, H-22), 3.33 (3H, s, OMe), 3.62 (1H, s, H-9), 3.69 (3H, s, CO_2Me), 3.75 (1H, d, J 9.0, H-28), 3.76 (1H, d, J 10.0, H-19), 3.80 (3H, s, CO_2Me), 4.06 (1H, d, J 9.0, H-28), 4.27 (1H, dd, J 11.4, 9.4, H-23), 4.39 (1H, d, J 10.0, H-19), 4.61 (1H, ddd, J 11.8, 6.5, 1.4, H-23), 4.80 (1H, t, J 2.8, H-1), 5.20 (1H, d, J 14.3, H-6), 5.35 (1H, d, J 2.7, H-15), 5.48 (1H, t, J 3.0, H-3) and 6.66 (1H, dq, J 1.4, 7.1, H-3'); ^{13}C δ ($CDCl_3$) 12.5 (C5'), 14.6 (C4'), 17.2 (C18), 21.0 and 21.4 (C30 and C3-OCOMe), 30.2 (C2), 31.4 (C22), 42.5 (C16), 45.5 (C5), 48.7 (C10), 52.5, 52.9, 53.2, 53.4, 53.4, 53.5 (C4, C8, C9, OMe, 2xCO_2Me), 55.1 (C17), 66.5 (C3), 67.3 (C13 and C14), 68.0 (C23), 69.8 (C19), 70.8 (C1), 73.5 (C28), 75.6 (C6), 82.6 (C15), 107.5 (C11), 129.3 (C2'), 132.0 (C3'), 152.7 (C21), 166.2, 169.0, 169.6, 172.5 (C1', C12, C29, C3-OCOMe), 201.9 (C20) and 208.2 (C7); m/z (EI) 689 (M^+-CO_2Me), 672 (MH^+-CO_2Me-H_2O), 654 (MH^+-CO_2Me-$2H_2O$), 645, 506, 479, 319, 291, 259, 231, 199 and 83; found (M^+-CO_2Me) 689.243. $C_{34}H_{41}O_{15}$ requires 689.245; Found C, 57.40; H, 5.79. $C_{36}H_{44}O_{17}$ requires C, 57.75; H, 5.92%.

Preparation of [2aR, 4R (1S, 2S, 3S, 4S), 4aR, 5S, 7aS, 8S (E), 10R, 10aR, 10bR] Dimethyl 10-acetoxy-4-[2,3-epoxy-1-(3-hydroxypropanyl)-4-methoxycarbonyloxy-2-methylcyclopent-3-yl]-5-methoxy-8-(2-methylbut-2-enoyloxy)-3-oxodecahydronaphtho[1,8-bc;4,4a,4a-c']difuran-5,10a-dicarboxylate (6).

A solution of the carbonate (5) (33.0mg, 44.1μmol) in anhydrous methanol (4ml) was stirred at room temperature for 45min and the solvent evaporated *in vacuo*. Purification of the residue by flash chromatography (gradient elution 80-100% ethyl acetate/petrol) gave the ring-opened compound (6) (29.4mg, 85%) as a colourless glass; υ_{max} (film) 3518, 2955, 1745, 1713, 1439, 1372, 1264, 1113, 1044, 918, 817, 790 and 732 cm^{-1}; ^1H δ (310K, $CDCl_3$, natural prod. numbering) (rotamers broaden spectrum more at room temperature) 1.37 (3H, s, 3xH-30), 1.72-1.75 (1H, m, obscured H-16), 1.74 (3H, dd, J 7.0, 1.0, 3xH-4'), 1.76 (3H, s, 3xH-18), 1.84 (3H, br s, 3xH-5'), 1.94 (3H, s, OAc), 2.11 (1H, ddd, J 15.9, 9.4, 3.5, H-16), 2.23 (1H, dt, J 16.9, 2.6, H-2), 2.30 (1H, dt, J 16.9, 3.3, H-2), 2.38 (1H, br t, J 6.3, OH), 2.90 (1H, ddd, J 18.5, 7.4, 3.8, H-22), 2.95-2.98 (1H, m, H-22), 3.03 (1H, d, J 8.8, H-17), 3.23 (1H, br d, J 14.8, H-5), 3.35 (3H, s, OMe), 3.54 (1H, s, H-9), 3.70 (3H, s, OCO_2Me), 3.73 (1H, d, J 8.9, H-28), 3.74 (1H, d, J 9.7, H-19), 3.77 (3H, s, CO_2Me), 3.81 (3H, s, CO_2Me), 3.82-3.87 (1H, m, H-23), 3.89-3.96 (1H, m, H-23), 4.07 (1H, d, J 8.9, H-28), 4.23 (1H, d, J 9.6, H-19), 4.94 (1H, br s, H-1), 5.03 (1H, br d, J 13.5, H-6), 5.40 (1H, d, J 6.1, H-15), 5.50 (1H, t, J 3.1, H-3) and 6.68 (1H, q, J 7.0, H-3').

Preparation of (2aR, 4RS, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) Dimethyl 8,10-dihydroxy-5-methoxy-4-methyl-3-oxodecahydronaphtho[1,8-bc;4,4a-c']difuran-5,10a-dicarboxylate(7) and (5*R*) 8-hydroxy-9-methyl-1-oxa-spiro[4,4]non-8-en-4,7-dione (8).

A solution of the carbonate (5) (34.0mg, 45.5μmol) in anhydrous methanol (5ml) was stirred at room temperature for 40min, by which time tlc showed disappearance of starting material. The solution was cooled to 0°C and sodium methoxide (125μl of a freshly prepared 1.82M solution in methanol, 0.22mmol, 5 equiv) was added *via* syringe. The solution turned pale yellow and was allowed to warm to room temperature and stirred for 24hr. To the now orange/yellow solution was added acetic acid (100μl) causing some of the colour to discharge. The mixture was stirred for 5min, poured into sat. $NaHCO_3$ (aq) (30ml), extracted with dichloromethane (3x20ml) and the combined extracts were dried (Na_2SO_4). Evaporation of the solvent *in vacuo* and purification of the residue by flash chromatography (gradient elution, 70-100% ethyl acetate/petrol) gave (8) (380mg, 92%) as a crystalline solid ; mp. 128-130°C; $[\alpha]_D^{20}$=-16.0 (c=0.1, chloroform); υ_{max} (film) 2240, 2923, 2880, 1722, 1675, 1402, 1356, 1283, 1212, 1149, 1062cm^{-1}; ^1H δ 5.69 (1H, brs, OH), 4.45 (1H, ddd, J 9.4, 7.7, 5.2, H-2),

4.17 (1H, m, H-2), 2.69 (2H, m, 2H-3), 2.58 (1H, d, J 18.1, H-6), 2.40 (1H, d, J 18.1, H-6), 1.86 (3H, s, Me); *m/z* (EI+) 200 (MNH_4^+), 183 (MH^+), 170, 155, 143, 124, 112, 98, 83; found (MNH_4^+) 200.0923. $C_9H_4NO_4$ requires 200.0923; and (7) (17.3mg, 92%) (an inseparable 2:1 α:β mixture at C8) as a colourless glass; υ_{max} (film) 3438, 2953, 1722, 1435, 1288, 1240, 1089, 912 and 733cm^{-1}; ^{1}H δ ($CDCl_3$, natural prod. numbering) for α isomer: 1.25 (3H, d, J 6.7, 3xH-30), 1.95 (1H, dt, J 15.8, 2.7, H-2), 2.28 (1H, dt, J 15.8, 3.1, H-2), 2.71 (1H, d, J 14.2, H-5), 2.85 (1H, d, J 8.1, H-9), 3.06-3.08 (1H, m, H-8), 3.35 (3H, s, C11-OMe), 3.43 (1H, d, J 6.5, OH), 3.57 (1H, d, J 9.8, H-19), 3.74 (1H, d, J 7.4, OH), 3.76 (3H, s, CO_2Me), 3.82 (3H, s, CO_2Me), 4.11-4.17 (4H, m, H-1, H-19 and 2xH-28), 4.49-4.52 (1H, m, H-3) and 4.77 (1H, dd, J 14.2, 1.2, H-6); and for β isomer 1.15 (3H, s, 3xH-30), 2.25-2.33 (2H, m, 2xH-2), 2.75 (1H, quint, J 6.5, H-8), 3.06-3.11 (3H, m, OH, H-5 and H-9), 3.29 (3H, s, C11-OMe), 3.61 (1H, d, J 9.5, H-19), 3.66 (1H, br. s, OH), 3.69 (1H, d, J 9.8, H-19), 3.77 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 4.02 (1H, m, H-1), 4.07 (1H, d, J 8.4, H-28), 4.13 (1H, d, J 8.4, H-28), 4.42 (1H, d, J 14.0, H-6) and 4.50 (1H, m, H-3); m/z (CI, NH_3) 432 ($M+NH_4^+$), 414 (M^+), 400 ($M+NH_4^+$-MeOH), 383 (M^+-OMe), 355 (M^+-CO_2Me), 291, 274, 195 and 178; Found (M^+) 414.1526. $C_{19}H_{26}O_{10}$ requires 414.1526.

Preparation of (2a*R*, 4*RS*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 10-acetoxy-5-hydroxy-4-methyl-8-(2-methylbut-2-enoyloxy)-3-oxodecahydronaphtho-[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate (9), (2a*R*, 4*RS*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 5,10-dihydroxy-4-methyl-8-(2-methylbut-2-enoyloxy)-3-oxodecahydronaphtho-[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate (10) and (2aR, 4RS, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) Dimethyl 8,10-dihydroxy-5-methoxy-4-methyl-3-oxodecahydronaphtho-[1,8-bc;4,4a-c'] difuran-5,10a-dicarboxylate (7).

A solution of the cyclic carbonate (36mg, 48.1μmol) in triethylamine (285ul), methanol (714μl) and water (285μl) was stirred at room temperature for 26hrs and then concentrated. The residue was partitioned between dichloromethane (3x10ml) and saturated sodium bicarbonate. The combined organic extracts were dried over anhydrous sodium sulphate and evaporated in vacuo. The residue was purified by flash chromatography (40% ethylacetate/petrol, then 50% ethylacetate/petrol, then 80% ethyl acetate/petrol) to give in order of elution; fragment (9) (4.0mg, 17%) (an impure inseparable 3:1 α:β mixture at C8) as a colourless glass; υ_{max} (film) 3450, 2958, 1734, 1681, 1656, 1625, 1508, 1437, 1375, 1258, 1135, 1043 and 734 cm^{-1}; ^{1}H δ ($CDCl_3$, natural prod. numbering) for major α isomer only: 1.11 (3H, d, J 6.5, 3xH-30), 1.80-1.84 (6H, m, 3xH-4' and 3xH-5'), 1.92 (3H, s, OAc), 2.15 (1H, dt, J 16.8, 3.3, H-2), 2.48 (1H, dt, J 16.8, 2.5, H-2), 2.87 (1H, d, J 14.1,

H-5), 2.89 (1H, d, J 9.6, H-9), 3.10-3.13 (1H, m, H-8), 3.61 (1H, d, J 9.8, H-19), 3.71 (3H, s, CO_2Me), 3.82 (3H, s, CO_2Me), 3.84 (1H, d, J 9.1, H-28), 4.06 (1H, d, J 9.0, H-28), 4.25 (1H, d, J 9.8, H-19), 4.95 (1H, dd, J 14.1, 1.4, H-6), 5.17 (1H, t, J 2.8, H-1), 5.57 (1H, t, J 2.9, H-3), 6.82 (1H, dq, J 1.3, 7.0, H-3'); m/z (CI, NH_3) 542 ($M+NH_4^+$), 507 (M^+-OH) and 83; Found ($M+NH_4^+$) 542.2236. $C_{25}H_{36}NO_{12}$ requires 542.2238; and fragment (10) (4.7mg, 24%) (an inseparable 4:1 α:β mixture at C8) as a colourless glass; υ_{max} (film) 3468, 2922, 1723, 1648, 1439, 1271, 1144, 1046 and 732 cm^{-1}; ^1H δ ($CDCl_3$, natural prod. numbering) for major α isomer only: 1.10 (3H, d, J 6.5, 3xH-30), 1.81-1.83 (6H, m, 3xH-4' and 3xH-5'), 1.99 (1H, d, J 7.0, OH), 2.13 (1H, dt, J 16.6, 3.1, H-2), 2.37 (1H, dt, J 16.6, 2.7, H-2), 2.82 (1H, d, J 14.0, H-5), 2.84 (1H, br d, J 9.5, H-9), 3.10-3.13 (1H, m, H-8), 3.60 [1H, dd, J 9.8, 0.7 (W coupling to H-9), H-19], 3.71 (3H, s, CO_2Me), 3.79 (3H, s, CO_2Me), 4.07 (1H, d, J 8.7, H-28), 4.25 (1H, d, J 8.6, H-28), 4.27 (1H, d, J 9.8, H-19), 4.29 (1H, s, OH), 4.49 (1H, dt, J 7.0, 2.9, H-3), 4.93 (1H, dd, J 14.0, 1.5, H-6), 5.25 (1H, t, J 2.9, H-1) and 6.80 (1H, dq, J 1.1, 6.7, H-3'); m/z (CI, NH_3) 500 ($M+NH_4^+$), 482 ($M+NH_4^+-H_2O$), 468 ($M+NH_4^+$-MeOH) and 83; Found ($M+NH_4^+$) 500.2132. $C_{23}H_{34}NO_{11}$ requires 500.2132; and fragment (7) identical in all respects to material prepared earlier.

Preparation of (2a*R*, 3*R*, 4*RS*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 10-acetoxy-3,5-dihydroxy-4-methyl-8-(2-methylbut-2-enoyloxy)-decahydronaphtho-[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate (11) and (2a*R*, 3*S*, 4*RS*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 10-acetoxy-3,5-dihydroxy-4-methyl-8-(2-methylbut-2-enoyloxy)-decahydronaphtho-[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate (12).

Sodium borohydride (2mg, 54μmol) was added to a solution of the ketone (14.6mg, 27.1μmol) and cerium trichloride heptahydrate (20mg, 54μmol) in methanol (2ml) under argon at -15°C. Stirring was continued at -15°C for 45 minutes, then acetone (0.5ml) was added and the solution allowed to warm to room temperature. 1M HCl (4 drops) were added and the homogeneous solution stirred at ambient temperature for 15mins before being concentrated and partitioned between ethylacetate (4x10ml) and water (4ml). The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*.The residue was purified by HPLC (Semiprep Dynamax 10cm^3 min^{-1} 30% IPA/petrol) to give in order of elution the alcohol (11) $[\alpha]_D^{20}$=-36.8 (c=0.4, chloroform); υ_{max} (film) cm^{-1} 3498, 2919, 2850, 1740, 1645, 1432, 1372, 1262, 1223, 1143, 1043 1H δ ($CDCl_3$) 6.95 (1H, dq, J7.1, 1.5, =CH), 5.54 (1H, t, J 2.9, H-3), 5.14 (1H, t, J 2.8, H-1), 4.22 (1H, dd, J 12.3, 2.5, H-6), 4.05 (1H, dd, J 2.5, 2.5, H-7), 3.99 (1H, d, J 8.8, H-28), 3.80 (1H, d, J 9.5, H-19), 3.77

(3H, s, CO_2Me), 3.73 (1H, d, J 8.8, H-28), 3.66 (3H, s, CO_2Me), 3.54 (1H, dd, J 9.5, 0.9, H-19), 3.38 (1H, d, J 12.5, H-5), 3.29 (3H, s, OMe), 2.44 (2H, m, incl (1H, d, 11.6H, H-2 and H-9), 2.24 (1H, m, H-8), 2.19 (1H, dt, J 16.8, 0.7, H-2), 1.85 (3H, s, Me), 1.80 (1H, dd, 7.1, 0.9Hz, Me), 1.21 (3H, d, 6.5Hz, 30-Me) ; *m/z* (FAB) 563 (MNa^+), 509, 481, 413, 349, 37, 289, 271, 259, 227, 213; found (MNa^+) 563.2104 $C_{26}H_{36}O_{12}Na$ requires 563.2104; and the alcohol (12) $[\alpha]_D^{20}$=-51.0 (c=0.5, chloroform); υ_{max} (film) 3483, 2919, 2849, 1741, 1646, 1433, 1373, 1262, 1224, 1142, 1105, 1064, 1040, 966, 930, 848, 812, 733, 703cm^{-1}; 1H δ ($CDCl_3$) 6.85 (1H, dq, J 6.9, 0.6, =CH), 5.53 (1H, t, J 2.8, H-3), 5.15 (1H, t, J 2.8, H-1), 4.12 (1H, dd, J 12.2, 8.5, H-6), 4.00 (1H, d, J 9.0, H-28), 3.86 (1H, d, J 9.6, H-19), 3.78 (3H, s, CO_2Me), 3.72 (1H, d, J 9.0, H-28), 3.67 (3H, s, CO_2Me), 3.53 (1H, dd, J 9.6, 1.0, H-19), 3.29 (4H, m, incl (3H, s, OMe), H-7), 2.54 (1H, d, J 12.2, H-5), 2.43 (1H, dd, J 10.5, 0.9, H-9), 2.38 (1H, m, H-2), 2.20 (2H, m, H-2 and H-8), 1.84 (3H, s, Me), 1.82 (3H, dd, J 7.0, 1.0, Me), 1.21 (3H, d, J 6.2, 30-Me);*m/z* (FAB) 563 (MNa^+), 509, 481, 413, 349, 37, 289, 271, 259, 227, 213; found (MNa^+) 563.2104 $C_{26}H_{36}O_{12}Na$ requires 563.2104.

Preparation of 11-Acetoxy-22,23-dihydroazadirachtin (14)

To a stirred solution of 22,23-dihydroazadirachtin (13) (273mg, 0.378mmol) in anhydrous dichloromethane (15ml) was added triethylamine (1.05ml, 7.56mmol, 20 equiv) and a trace of DMAP (20mg) followed by acetic anhydride (0.357ml, 3.78mmol, 10 equiv). After 95min, the reaction mixture was diluted with dichloromethane (30ml) and washed with sat. $NaHCO_3$ (aq). The aqueous layer was re-extracted with dichloromethane (2x20ml), the combined organic layers dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (gradient elution, 80% ethyl acetate/petrol to 5% methanol/ethyl acetate) to give the 11-acetate (14) (174mg, 60%) as a colourless glass; $[\alpha]_D^{20}$=-19.9 (c=1.3, chloroform); υ_{max} (film) 3462, 2953, 1743, 1707, 1647, 1435, 1373, 1269, 1141, 1087, 1063, 1042, 983, 924, 849, 823, 795 and 733 cm^{-1}; 1H δ ($CDCl_3$) 1.53 (1H, d, J 12.8, H-16), 1.71-1.72 (1H, m, H-16), 1.74 (3H, s, 3xH-30), 1.76 (3H, dd, J 7.3, 1.0, 3xH-4'), 1.81 (3H, d, J 2.2, 3xH-5'), 1.87 (3H, s, C3-OAc), 1.94 (3H, s, 3xH-18), 2.04 (3H, s, C11-OAc), 2.12-2.22 (3H, m, H-2, H-17 and H-22), 2.35 (1H, dt, J 17.0, 2.5, H-2), 2.41 (1H, d, J 5.2, H-22), 2.72 (1H, br s, OH), 3.175 (1H, s, H-9), 3.18 (1H, br s, OH), 3.25 (1H, d, J 12.5, H-5), 3.67 (3H, s, CO_2Me), 3.72 (1H, d, J 9.0, H-28), 3.78 (1H, d, J 9.7, H-19), 3.785 (3H, s, CO_2Me), 3.90 (1H, q, J 8.3, H-23), 4.02 (1H, dt, J 8.3, 4.4, H-23), 4.06 (1H, d, J 9.0, H-28), 4.25 (1H, d, J 9.7, H-19), 4.59 (1H, dd, J 12.5, 2.8, H-6), 4.65 (1H, d, J 3.5, H-15), 4.66 (1H, d, J 2.7, H-7), 5.16 (1H, t, J 2.8, H-1), 5.20 (1H, s, H-21), 5.48 (1H, t, J 2.9, H-3) and 6.81 (1H, dq, J 1.5, 7.1, H-3'); m/z (FAB, thioglycerol) 765 (MH^+), 705

(M^+-CO_2Me), 687 (M^+-CO_2Me-H_2O), 601, 291 and 215; Found (MH^+) 765.2950. $C_{37}H_{49}O_{17}$ requires 765.2948; Found: C, 58.07; H, 6.03. $C_{37}H_{48}O_{17}$ requires C, 58.11; H 6.33%.

Preparation of [2aR, 4R (4S, 5R, 6S, 7R), 4aR, 5S, 7aS, 8S (E), 10R, 10aR, 10bR] Dimethyl 5,10-diacetoxy-4-methyl-4-(6-methyl-2,8-dioxo-5,6-epoxy-4,7-methano-1,3-dioxecan-5-yl)-8-(2-methylbut-2-enoyloxy)-3-oxodecahydronaphtho [1,8-bc;4,4a,4a-c']difuran-5,10a-dicarboxylate (16).

To a solution of 11-acetoxy-22,23-dihydroazadirachtin (14) (684mg, 0.895mmol) in anhydrous dichloromethane (5ml) was added PCC (1.93g, 8.95mmol, 10 equiv) and powdered activated 4Å molecular sieves (2.0g). The mixture was stirred at room temperature. Further PCC (0.97g, 5 equiv) was added after 24hr and again after 48hr. After warming to 35°C for 24hr (72hr total) ethyl acetate (15ml) was added and stirring continued for a further 10min. The reaction mixture was filtered through a pad of Florisil (It was necessary to grind some residual solid in a pestle and mortar with ethyl acetate to extract all of the products). Evaporation of the solvent *in vacuo* and purification by flash chromatography (gradient elution, 60-100% ethyl acetate/petrol) gave the rearranged compound (16) (334mg, 49%) as a colourless foam which could be recrystallised from ethyl acetate/petrol to give colourless microcrystals; m.pt. 175-177°C; $[\alpha]_D^{20}$=+17.8 (c=3.4, chloroform); υ_{max} (film) 2960, 1763, 1748, 1735, 1370, 1220 and 1045 cm^{-1}; ^1H δ ($CDCl_3$, natural prod. numbering) 1.67 (3H, s, 3xH-18 or 3xH-30), 1.75 (3H, dd, J 7.0, 1.0, 3xH-4'), 1.79 (3H, t, J 1.1, 3xH-5') 1.90-1.96 (1H, m, H-16), 1.91 (3H, s, 3xH-18 or 3xH-30), 1.95 (3H, s, OAc), 2.02-2.08 (1H, m, H-16), 2.11 (3H, s, OAc), 2.14 (1H, dt, J 16.9, 3.3, H-2), 2.37 (1H, dt, J 17.0, 2.6, H-2), 2.67 (1H, br dd, J 13.6, 9.7, H-22), 2.72 (1H, d, J 14.4, H-5), 2.97 (2H, m, H-17 and H-22), 3.47 (1H, s, H-9), 3.73 (3H, s, CO_2Me), 3.78 (1H, d, J 9.0, H-28), 3.82 (3H, s, CO_2Me), 3.95 (1H, d, J 10.1, H-19), 4.09 (1H, d, J 9.1, H-28), 4.29 (1H, dd, J 11.5, 9.5, H-23), 4.63 (1H, d, J 10.2, H-19), 4.65 (1H, ddd, J 11.9, 5.3, 1.5, H-23), 5.29 (1H, t, J 2.9, H-1), 5.295 (1H, d, J 14.4, H-6), 5.43 (1H, br s, H-15), 5.50 (1H, t, J 2.9, H-3) and 6.64 (1H, dq, J 1.4, 7.1, H-3'); ^{13}C δ ($CDCl_3$) 12.1 (C5'), 14.2 (C4'), 16.7 (C18), 20.8, 21.3, 21.8 (C30 and 2xOCO<u>Me</u>), 29.7 (C2), 30.9 (C22), 42.4 (C16), 45.3 (C5), 48.3 (C10), 53.1, 53.2, 53.6, 53.6, 54.3, 54.5 (C4, C8, C9, C17 and 2xCO_2<u>Me</u>), 66.0 (C3), 66.6, 66.9 (C13 and C14), 67.9 (C23), 70.2 (C19), 71.4 (C1), 73.1 (C28), 75.7 (C6), 82.0 (C15), 104.2 (C11), 128.5 (C2'), 137.7 (C3'), 152.4 (C21), 165.9, 167.9, 169.0, 169.4, 172.2 (C-1', C12, C29 and 2xO<u>C</u>OMe), 200.5 (C20) and 207.6 (C7); m/z (CI, NH_3) 717 (M^+-CO_2Me) (only one peak observed) ; Found (M^+-CO_2Me) 717.2395. $C_{35}H_{41}O_{16}$ requires 717.2395; Found C, 56.71; H, 6.06. $C_{37}H_{44}O_{18}.1/2H_2O$ requires C, 56.56; H, 5.77%.

Preparation of (2a*R*, 4*RS*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 10-acetoxy-5-hydroxy-4-methyl-8-(2-methylbut-2-enoyloxy)-3-oxodecahydronaphtho-[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate (18) and (2a*R*, 4*RS*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 5,10-dihydroxy-4-methyl-8-(2-methylbut-2-enoyloxy)-3-oxodecahydronaphtho-[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate (19) and (2a*R*, 4*RS*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 4-methyl-3-oxo-5,8,10-trihydroxydecahydronaphtho[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate (17) .

Triethylamine was added to a solution of the carbonate (16) (273mg, 43.3μmol) in methanol and the solution was heated to reflux under argon overnight. Most of the solvent was evaporated *in vacuo* and the residue was partitioned between 1N HCl (aq) (10ml) and dichloromethane (20ml). The aqueous layer was re-extracted with dichloromethane (3x10ml) and the combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was taken up in dichloromethane and treated with diazomethane under a continuous flow for 15min. Evaporation of the solvent and purification of the residue by flash chromatography (gradient elution, 50-80% ethyl acetate/petrol) gave, in order of elution, fragment (18) (28mg, 15% (an impure inseparable 3:1 α:β mixture at C8) as a colourless glass; υ_{max} (film) 3450, 2958, 1734, 1681, 1656, 1625, 1508, 1437, 1375, 1258, 1135, 1043 and 734 cm^{-1}; ^1H δ ($CDCl_3$, natural prod. numbering) for major α isomer only: 1.11 (3H, d, J 6.5, 3xH-30), 1.80-1.84 (6H, m, 3xH-4' and 3xH-5'), 1.92 (3H, s, OAc), 2.15 (1H, dt, J 16.8, 3.3, H-2), 2.48 (1H, dt, J 16.8, 2.5, H-2), 2.87 (1H, d, J 14.1, H-5), 2.89 (1H, d, J 9.6, H-9), 3.10-3.13 (1H, m, H-8), 3.61 (1H, d, J 9.8, H-19), 3.71 (3H, s, CO_2Me), 3.82 (3H, s, CO_2Me), 3.84 (1H, d, J 9.1, H-28), 4.06 (1H, d, J 9.0, H-28), 4.25 (1H, d, J 9.8, H-19), 4.95 (1H, dd, J 14.1, 1.4, H-6), 5.17 (1H, t, J 2.8, H-1), 5.57 (1H, t, J 2.9, H-3), 6.82 (1H, dq, J 1.3, 7.0, H-3'); m/z (CI, NH_3) 542 ($M+NH_4^+$), 507 (M^+-OH) and 83; Found ($M+NH_4^+$) 542.2236. $C_{25}H_{36}NO_{12}$ requires 542.2238; and fragment (19) (64mg, 38%) (an inseparable 4:1 α:β mixture at C8) as a colourless glass; υ_{max} (film) 3468, 2922, 1723, 1648, 1439, 1271, 1144, 1046 and 732 cm^{-1}; ^1H δ ($CDCl_3$, natural prod. numbering) for major α isomer only: 1.10 (3H, d, J 6.5, 3xH-30), 1.81-1.83 (6H, m, 3xH-4' and 3xH-5'), 1.99 (1H, d, J 7.0, OH), 2.13 (1H, dt, J 16.6, 3.1, H-2), 2.37 (1H, dt, J 16.6, 2.7, H-2), 2.82 (1H, d, J 14.0, H-5), 2.84 (1H, br d, J 9.5, H-9), 3.10-3.13 (1H, m, H-8), 3.60 [1H, dd, J 9.8, 0.7 (W coupling to H-9), H-19], 3.71 (3H, s, CO_2Me), 3.79 (3H, s, CO_2Me), 4.07 (1H, d, J 8.7, H-28), 4.25 (1H, d, J 8.6, H-28), 4.27 (1H, d, J 9.8, H-19), 4.29 (1H, s, OH), 4.49 (1H, dt, J 7.0, 2.9, H-3), 4.93 (1H, dd, J 14.0, 1.5, H-6), 5.25 (1H, t, J 2.9, H-1) and 6.80 (1H, dq, J 1.1, 6.7, H-3'); m/z (CI, NH_3) 500 ($M+NH_4^+$), 482 ($M+NH_4^+-H_2O$), 468 ($M+NH_4^+$-MeOH) and 83; Found ($M+NH_4^+$) 500.2132. $C_{23}H_{34}NO_{11}$ requires 500.2132; and pure C8 β-methyl fragment (17) (11.0mg, 17%) as a pale yellow oil; ^1H δ ($CDCl_3$, natural prod.

numbering) 1.08 (3H, d, J 6.8, 3xH-30), 2.31 (2H, br m, 2xH-2), 2.76 (1H, quint, J 6.5, H-8), 3.13 (1H, d, J 14.1, H-5), 3.27 (1H, dd, J 6.0, 1.7, H-9), 3.42 (1H, v br d, J 5.0, OH), 3.51 (1H, v br d, J 6.0, OH), 3.58 (1H, d, J 9.5, H-19), 3.77 (3H, s, CO_2Me), 3.85 (3H, s, CO_2Me), 3.95 (1H, d, J 9.4, H-9), 3.99 (1H, br m, H-1), 4.05 (1H, d, J 1.9, OH), 4.08 (1H, d, J 8.4, H-28), 4.13 (1H, d, J 8.4, H-28), 4.52 (1H, br s, H-3) and 4.61 (1H, d, J 14.1, H-6); and a mixture of C8 α-methyl and β-methyl fragments (17) (27.4mg, 43%) (as a 1:1 mixture) as a pale yellow oil; υ_{max} (film) (for mixture) 3428, 2952, 1720, 1244, 1058 and 731 cm^{-1}; ^1H δ ($CDCl_3$, natural prod. numbering) for α isomer 1.18 (3H, d, J 5.9, 3xH-30), 1.81 (1H, dt, J 15.7, 2.7, H-2), 2.29 (1H, dt, J 15.7, 3.1, H-2), 2.68 (1H, d, J 14.1, H-5), 2.98-3.02 (2H, m, H-8 and H-9), 3.52 (1H, d, J 9.9, H-19), 3.65 (1H, v br d, J 5.9, OH), 3.76 (3H, s, CO_2Me), 3.79 (1H, v br d, J 8.2, OH), 3.84 (3H, s, CO_2Me), 4.03 (2H, m, H-1 and OH), 4.06 (1H, d, J 8.3, H-28), 4.12 (1H, d, J 8.4, H-28), 4.38 (1H, d, J 9.9, H-19), 4.51 (1H, br m, H-3) and 4.84 [1H, dd, J 14.1, 1.0 (W coupling to H-8), H-6]; m/z (CI, NH_3) 418 ($M+NH_4^+$), 400 ($M+NH_4^+-H_2O$), 383, 279, 262, 174; Found ($M+NH_4^+$) 418.1713. $C_{18}H_{28}NO_{10}$ requires 418.1713.

Preparation of (2a*R*, 4*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 4-methyl-3-oxo-5,8,10-trihydroxydecahydronaphtho[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate-8,10-benzylidene and (2a*R*, 4*S*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 4-methyl-3-oxo-5,8,10-trihydroxydecahydronaphtho[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate-8,10-benzylidene (20)

PPTS (15mg) and freshly distilled benzaldehyde (0.5ml) were added to a solution of the triols (17) (~1:1 mixture) (21.3mg, 53.2μmol) in benzene (10ml). The mixture was heated to reflux with azeotropic removal of water (Dean Stark) for 6hr. The solution was cooled, poured into sat. $NaHCO_3$ (aq) (20ml) and extracted with ether (2x20ml). The combined organic phases were dried ($MgSO_4$), evaporated *in vacuo* and the residue was purified by repeated flash chromatography (gradient elution, 40-90% ethyl acetate/petrol then twice with gradient elution, 60-90% ethyl acetate/petrol) to give, in order of elution, the C8 β-methyl benzylidene (20) (10.1mg, 39%) as a colourless oil; $[\alpha]_D^{20}$=-14.7 (c=0.79, chloroform); υ_{max} (film) 3443, 2950, 1724, 1448, 1245, 1178, 1106, 1050, 984, 731 and 698 cm^{-1}; ^1H δ ($CDCl_3$, natural prod. numbering) 1.04 (3H, d, J 6.8, 3xH-30), 1.87 (1H, d, J 15.9, H-2), 2.74 (1H, quint, J 6.6, H-8), 3.03 (1H, dt, J 15.9, 4.8, H-2), 3.26 (1H, d, J 6.0, H-9), 3.66 (1H, d, J 14.3, H-5), 3.67 (1H, d, J 9.8, H-19), 3.80 (3H, s, CO_2Me), 3.82 (3H, s, CO_2Me), 3.98 (1H, d, J 1.5, OH), 4.07 (1H, d, J 8.5, H-28), 4.13 (1H, d, J 8.5, H-28), 4.36 (1H, d, J 9.7, H-19), 4.45 (1H, d, J 4.7, H-1), 4.62 (1H, d, J 14.5, H-6), 4.91 (1H, d, J 4.8, H-3), 6.27 (1H, s, PhC<u>H</u>) and 7.37-7.41 (5H, m, Ph); m/z (CI, NH_3)

506 ($M+NH_4^+$), 488 (M^+), 471 (M^+-OH) and 105; Found (M^+) 488.1682. $C_{25}H_{28}O_{10}$ requires 488.1682; and the C8 α-methyl benzylidene (20) (8.6mg, 33%) (contaminated with ~15% of an unknown impurity, possibly C11 epimer) as a colourless oil; υ_{max} (film) 3442, 2953, 1727, 1450, 1388, 1291, 1200, 1116, 1062, 989, 731 and 698 cm^{-1}; ^1H δ ($CDCl_3$, natural prod. numbering) 1.13 (3H, d, J 6.2, 3xH-30), 1.64 (1H, d, J 15.9, H-2), 3.93 (1H, dt, J 15.9, 4.8, H-2), 3.05 (1H, d, J 9.5, H-9), 3.09-3.12 (1H, m, H-8), 3.22 (1H, d, J 14.6, H-5), 3.69 (1H, d, J 10.6, H-19), 3.78 (3H, s, CO_2Me), 3.81 (3H, s, CO_2Me), 4.05 (1H, d, J 8.6, H-28), 4.09 (1H, d, J 8.6, H-28), 4.13 (1H, s, OH), 4.45 (1H, d, J 10.4, H-19), 4.61 (1H, d, J 4.8, H-1), 4.79 [1H, dd, J 14.6, 0.7 (W coupling to H-8), H-6], 4.82 (1H, d, J 4.7, H-3), 6.16 (1H, s, PhC<u>H</u>) and 7.32-7.37 (5H, m, Ph); m/z (CI, NH_3) 488 (M^+), 471 (M^+-OH), 382, 105, 91 and 77; Found (M^+) 488.1682. $C_{25}H_{28}O_{10}$ requires 488.1682.

Preparation of (2a*R*, 4*R*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 5-benzyloxy-8,10-dihydroxy-4-methyl-3-oxodecahydronaphtho[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate-8,10-benzylidene and (2a*R*, 4*S*, 4a*S*, 5*S*, 7a*S*, 8*S*, 10*R*, 10a*R*, 10b*R*) Dimethyl 5-benzyloxy-8,10-dihydroxy-4-methyl-3-oxodecahydronaphtho[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate-8,10-benzylidene (21)

DMF (3ml) was added to a mixture of the lactol (20) (a 3:1 α:β mixture at C8, 36mg, 73.7μmol) and silver (I) oxide (160mg, 0.69mmol, 30 equiv) followed by benzyl bromide (200μl) *via* syringe. After 2.5hr the reaction mixture was diluted with ether (10ml), filtered through a pad of cotton wool and washed with water (2x5ml). The organic layer was dried ($MgSO_4$), evaporated *in vacuo* and the residue purified by flash chromatography (gradient elution, 40% ethyl acetate/petrol) to give the benzyl ether (21) (30mg, 71%) as a 3:1 α:β mixture at C8; υ_{max} (film) 2952, 1731, 1451, 1298, 1234, 1198, 1072, 998, 732 and 698 cm^{-1}; ^1H δ ($CDCl_3$, natural prod. numbering) for β isomer: 1.18 (3H, d, J 6.8, 3xH-30), 1.83 (1H, d, J 15.8, H-2), 2.74 (1H, quint, J 6.6, H-8), 3.01 (1H, dt, J 15.9, 4.9, H-2), 3.16 (1H, d, J 6.6, H-9), 3.56 (1H, d, J 14.4, H-5), 3.59 (3H, s, CO_2Me), 3.71 (1H, d, J 9.9, H-19), 3.78 (3H, s, CO_2Me), 3.96 (1H, d, J 8.5, H-28), 4.01 (1H, d, J 9.9, H-19), 4.04 (1H, d, J 8.6, H-28), 4.12 (1H, d, J 14.4, H-6), 4.48 (2H, m, including d, J 11.4, C<u>H</u>$_2$Ph and d, J 4.8, obscured H-1), 4.83 (1H, obscured d, J 11.0, C<u>H</u>$_2$Ph), 4.85 (1H, d, J 3.0, H-3), 6.25 (1H, s, PhC<u>H</u>$(OR)_2$) and 7.28-7.37 (10H, m, Ph); ^1H δ ($CDCl_3$, natural prod. numbering) for α isomer: 1.26 (3H, d, J 6.5, 3xH-30), 1.64 (1H, d, J 15.9, H-2), 2.86 (1H, d, J 8.8, H-9), 2.94 (1H, dt, J 15.9, 4.8, H-2), 3.19 (1H, d, J 14.6, H-5), 3.19-3.23 (1H, m, H-8), 3.75 (3H, s, CO_2Me), 3.76 (3H, s, CO_2Me), 3.79 (1H, d, J 10.6, H-19), 4.04 (1H, d, J 8.6, H-28), 4.07 (1H, d, J 8.6, H-28), 4.37 (1H, d, J 10.4, H-19), 4.45 (1H, d, J 11.4, C<u>H</u>$_2$Ph),

4.58 (1H, d, J 4.7, H-1), 4.70 [1H, dd, J 14.6, 1.2 (W coupling to H-8), H-6], 4.71 (1H, d, J 11.4, $C\underline{H}_2Ph$), 4.81 (1H, d, J 4.8, H-3), 6.13 (1H, s, $PhC\underline{H}(OR)_2$) and 7.28-7.47 (10H, m, Ph); ^{13}C δ ($CDCl_3$) 15.3 (C30), 23.4 (C2), 41.2, 43.1 (C5 and C9), 52.4 ($CO_2\underline{Me}$), 52.5 (C4 or C10), 53.0 ($CO_2\underline{Me}$), 56.2 (C4 or C10), 58.7 (C8), 66.6, 67.7 (C28 and $\underline{C}H_2Ph$), 68.3 (C3), 70.7 (C1), 72.8 (C19), 77.2 (C6), 93.5 ($Ph\underline{C}H(OR)_2$), 104.1 (C11), 126.4, 127.5, 127.8, 128.4, 128.5, 129.4 (10x aromatic $\underline{C}H$), 137.3, 137.4 (2 aromatic quaternary C), 170.2, 172.7 (C12 and C29) and 206.7 (C7); m/z (CI, NH_3) 596 ($M+NH_4^+$), 513, 488, 471, 108 and 91; Found ($M+NH_4^+$) 596.2496. $C_{32}H_{38}O_{10}$ requires 596.2496; Found C, 66.17; H, 5.93. $C_{32}H_{34}O_{10}$ requires C, 66.43; H, 5.92%.

Preparation of (2aR, 4RS, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 5 - methoxy -4-methyl-3-oxo-8,10-phenylmethylenedioxyper- hydronaphtho [1,8-bc:4,4a,4a-c'] difuran 5,10a dicarboxylate (22).

A solution of the diol (7) (95mg, 0.23 mmol), benzaldehyde dimethyl acetal (500μl, large excess) and catalytic ppts in benzene were heated to reflux under Dean-Stark conditions for 1hr. The solution was concentrated before being partitioned between saturated aqueous sodium bicarbonate (20ml) and dichloromethane (3 x 30ml). The organic extracts were dried over magnesium sulphate, concentrated and purified by flash chromatography (50% ethyl acetate/petrol to give the benzylidene acetal (22) (111mg, 96%); υ_{max} (film) 2950, 1724, 1449, 1379, 1290, 1245, 1199, 1181cm^{-1}; 1H δ ($CDCl_3$) 7.35-7.39 (5H, m, Ar-H) , 6.25 (1H, s, Ar-CH) , 4.90 (1H, d, J 4.9, H-1 or H-3), 4.48 (1H, d, J 4.7, H-1 or H-3), 4.43 (1H, d, J 14.3, H-6), 4.12 (2H, m, H-19 and H-28), 4.07 (1H, d, J 8.5, H-28), 3.79 (3H, s, MeO_2C), 3.75 (3H, s, MeO_2C), 3.71 (1H, d, J 10.0, H-19), 3.61 (1H, d, J 14.3, H-5), 3.32 (3H, s, OMe), 3.12 (1H, d, J 6.15, H-9), 3.03 (1H, dt, J 15.9, 4.9, H-2ax), 2.73 (1H, m, H-8), 1.78 (1H, d, J 15.9, H-2eq), 1.11 (3H, d, J 6.8, C8-Me); m/z (EI+) 502 (M+), 471 (M^+-OMe), 459, 443, 415, 396, 364, 346, 309, 277, 259, 231, 199, 171, 149, 140, 105, 91, 77; found(M+) 502.1839, $C_{26}H_{30}O_{10}$ requires.502.1839.

Preparation of (2aR, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 5 - methoxy -4-methyl-8,10-phenylmethylenedioxy-3-silyloxy 1, 4, 4a, 5, 6, 7, 8, 8a octahydronaphtho [1,8-bc:4,4a,4a-c'] difuran 5,10a dicarboxylate (23).

A solution of the benzylidene acetal (22) (99mg, 0.197mmol) was added to a suspension of potassium hydride (35% dispersion in mineral oil, 1.20g, 10.47mmol) in THF(40ml) under argon at 0°C.Stirring was continued for 2hrs before TBDMSCl (750mg, 4.98mmol) was added dropwise as a solution in THF (10ml). After stirring for

an additional 1hr at 0°C, saturated aqueous sodium bicarbonate (5ml) was added dropwise. The solution was then partitioned between saturated aqueous sodium bicarbonate(30ml) and dichloromethane (5 x 50ml). The combined organic extracts were dried over magnesium sulphate, concentrated and purified by flash chromatography (25% ethyl acetate/petrol) to give the silyl enol ether (23) (80mg, 67%); υ_{max} (film) 2949, 2854, 1751, 1722, 1434, 1241, 1179, 1125, 1091, 1064, 1035, 991, 907, 841, 779, 738, 690 cm^{-1}; 1H δ ($CDCl_3$) 0.19 (3H,s, MeSi), 0.22 (3H,s, MeSi), 0.99 (9H, s, ^tBuSi), 1.62 (1H, d, 15.6Hz, H-2), 1.70 (3H, s, 3 x H-30), 2.91 (1H, dt, 15.6, 4.7Hz, H-2), 3.15 (1H, d, 11.8Hz, H-5), 3.24 (3H, s, OMe), 3.47 (1H, s, H-9), 3.64 (1H, d, 10.4Hz, H-19), 3.76 (3H, s, CO2Me), 3.78 (3H, s, CO2Me), 4.02 (1H, d, 10.4Hz, H-19), 4.03 (1H, d, 8.5Hz, H-28), 4.08 (1H, d, H-28), 4.41 (1H, d, 4.7Hz, H-1), 4.43 (1H, d, 11.8Hz, H-6), 4.77 (1H, d, 4.7Hz, H-3), 6.15 (1H, s, ArCH), 7.33-7.40 (5H, m, Ar-H); m/z (CI) 617 (MH^+), 585 (MH^+-MeOH), 559, 477, 453, 421, 393, 367, 190, 105, 90, 73; found (MH^+) 617.2780. $C_{32}H_{43}O_{10}Si$ requires 617.2782.

Preparation of (2aR, 4S, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 4-bromo-5 -methoxy -4-methyl-3-oxo-8,10-phenylmethylenedioxyper-hydronaphtho[1,8-bc:4,4a,4a-c']difuran 5,10a dicarboxylate (24).

A solution of N-bromo succinimide (6mg, 33.7μmol) in THF (1ml) was added to the silyl enol ether (23) (10mg, 16.2umol) in THF (1ml) under argon at -25°C. Stirring was continued for 15mins. before saturated aqueous sodium bicarbonate (5ml) was added. The aqueous extracts were extracted with dichloromethane (3 x 10ml), dried over sodium sulphate, concentrated and purified by flash chromatography (40% ethyl acetate/petrol) to give the bromo ketone (24) (9mg, 96%); υ_{max} (film) 3527, 2954, 1726, 1602, 1437, 1373, 1317, 1274, 1243, 1176, 1124, 1095, 1072, 1025, 996, 927, 886, 832, 795, 782, 714cm^{-1}; 1H δ ($CDCl_3$) 1.72 (1H, d, 15.8Hz, H-2), 1.92 (1H, s, 3 x H-30), 3.10 (1H, dt, 15.8Hz, 4.7Hz, H-2) 3.32 (3H, s, OMe), 3.64 (1H, s, H-9), 3.67 (1H, d, 10.0Hz, H-19), 3.83 (3H, s, CO_2Me), 3.84 (3H, s, CO_2Me), 4.15 (1H, d, 8.4Hz, H-28), 4.20 (1H, d, 10.0Hz, H-19), 4.29 (1H, d, 8.4Hz, H-28), 4.43 (1H, 14.5Hz, H-5), 4.48 (1H, d, 4.7Hz, H-1), 4.51 (1H, d, 14.5Hz, H-6), 4.96 (1H, d, 4.7Hz, H-3), 6.37 (1H, s, ArCH), 7.27-7.48 (5H, m, Ar-H) ; m/z (EI^+) ^{81}Br, 585 (M^+-Me), 539, 518, 485 (M^+-Br-Me), 459, 433, 414, 380, 307, 247, 217, 187, 161, 149,, 105.

Preparation of (2aR, 4S, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 5-methoxy -4-methyl-3-oxo-8,10-phenylmethylene-4-phenylselenenodioxyper-hydronaphtho[1,8-bc:4,4a,4a-c'] difuran 5,10a dicarboxylate (25)

A solution of phenylselenenyl chloride (80mg, 0.418mmol) in dichloromethane (1ml) was added dropwise to a solution of the silyl enol ether (23) (80mg, 0.130mmol) in dichloromethane (1ml) under argon at -78°C. Stirring was continued for 1hr before saturated aqueous sodium bicarbonate (5ml) was added. The organic layer was separated and the aqueous extracts were further extracted with dichloromethane. The combined organic extracts were dried over magnesium sulphate, concentrated and purified by flash chromatography (gradient elution, 25% to 60% ethyl acetate / petrol) to give the selenide (25) υ_{max} (film) cm^{-1}; 1H δ ($CDCl_3$) 1.30 (3H, s, 3 x H-30), 1.79 (1H, d, 15.8Hz, H-2), 3.09 (1H, dt, 15.8, 4.9, H-2), 3.31 (3H, s, OMe), 3.45 (1H, s, H-9), 3.68 (1H, d, 9.9Hz, H-19), 3.78 (3H, s, CO_2Me), 3.80 (3H, s, CO_2Me), 4.18 (1H, d, 9.9Hz, H-19), 4.19 (1H, d, 8.3Hz, H-28), 4.39 (1H, d, 8.3Hz, H-28), 4.39 (1H, d, 14.1Hz, H-5), 4.53 (1H, d, 4.8Hz, H-1), 4.83 (1H, d, 14.1Hz, H-6), 4.98 (1H, d, 4.8Hz, H-3), 6.43 (1H, s, ArCH), 7.12 - 7.57 (5H, m, Ar-H)7; m/z (FAB) ; found 659.1395 $C_{32}H_{35}O_{10}Se$ requires 659.1395.

Preparation of (2aR, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 5 - methoxy -3-oxo-8,10-phenylmethylenedioxyper-4-ylidene- hydronaphtho [1,8-bc:4,4a,4a-c'] difuran 5,10a dicarboxylate.(26)

Davis oxaziridine (23mg, 75.1μmol) and pyridine (5 drops) were added to a solution of the selenide (25mg, 37.9μmol) in chloroform at room temperature. The solution was stirred for 1hr before being concentrated and purified by flash chromatography (gradient elution 40% to 70% ethyl acetate petrol) to give the exo enone (26) (15mg, 81%);υ_{max} (film) cm^{-1} 2951, 1740, 1721, 1615, 1450, 1396, 1292, 1225, 1199, 1127, 1095, 1054; 1H δ ($CDCl_3$) 1.68 (1H, d, 15.7Hz, H-2), 3.00 (1H, dt, 15.7, 4.8Hz, H-2), 3.24 (3H, s, OMe), 3.42 (1H, d, 14.7Hz, H-5), 3.64 (1H, s, H-9), 3.71 (1H, d, 10.3Hz, H-19), 3.78 (3H, s, CO_2Me), 3.79 (3H, s, CO_2Me), 3.97 (1H, d, 8.5Hz, H-28), 4.05 (1H, d, 8.5Hz, H-28), 4.36 (1H, d, 10.2Hz, H-19), 4.46 (1H, d,4.7 Hz, H-1), 4.64 (1H, d, 14.7Hz, H-6), 4.87 (1H, d, 4.8Hz, H-3), 5.44 (1H, brs, H-18), 6.16 (1H, ArCH), 6.39 (1H, d, 1.5Hz, H-18), 7.29-7.34 (5H, m, Ar-H); m/z (CI) 518 (MNH_4^+), 501 (MH^+), 486, 469, 365, 278, 207, 136, 105; found ($MNH4^+$) 518.2026 $C_{26}H_{32}O_{10}N$ requires 518.2026.

Preparation of (2aR, 4R, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 5 - methoxy -3-oxo-8,10-phenylmethylenedioxy-4-thiophenoxymethylper- hydronaphtho [1,8-bc:4,4a,4a-c'] difuran 5,10a dicarboxylate (27)

Sodium phenylthiolate (29μl of a 1M solution in THF, 29μmol) was added to a solution of the enone (12mg, 24.0 μmol) in THF (1ml) under argon at 0°C. The resulting yellow solution was stirred at 0°C for 15mins before

saturated aqueous ammonium chloride was added.The solution was partitioned between water (5ml) and dichloromethane (5 x 10ml). The combined organic extracts were dried over magnesium sulphate, concentrated and purified by flash chromatography (50% ethyl acetate / petrol) to give the b thiophenoxy ketone (27) (14mg 96%); υ_{max} (film) cm^{-1} 2951, 1731, 1581, 1435, 1387, 1292, 1199, 1120, 1101, 1056, 1034, 986, 912, 878, 801, 734, 698 1H δ ($CDCl_3$) 1.67 (1H, d, 15.8Hz, H-2), 2.97 (1H, dt, 15.8, 4.8Hz, H-2), 3.13 (1H, dd, 13.3, 5.2Hz, H-18), 3.16 (3H, s, OMe), 3.23 (1H, dd, 13.3, 6.3Hz, H-18), 3.24 (1H, d, 14.8Hz, H-5), 3.28 (1H, d, 6.4 Hz, H-9), 3.33 (3H, s, CO_2Me), 3.36 (1H, m, H-8), 3.74 (1H, d, 10.4Hz, H-19), 3.78 (3H, s, CO_2Me), 4.08 (1H, d, 10.9Hz, H-28), 4.09 (1H, d, H-28), 4.28 (1H, d, 4.7Hz, H-1), 4.69 (1H, dd, 14.8, 0.9, H-6), 4.87 (1H, d, 4.75Hz, H-3), 6.19 (1H, s, ArCH), 7.07-7.44 (10H, m, Ar-H) ; m/z (CI) 611 (MH+), 610 (M+), 579, 551, 522, 501, 469, 451, 363, 275, 110; found 610.1870. $C_{32}H_{34}O_{10}S$ requires 610.1873.

Preparation of (2aR, 3S, 4R, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 3-hydroxy-5 - methoxy -3-oxo-8,10-phenylmethylenedioxy-4-thiophenoxymethylper-hydronaphtho [1,8-bc:4,4a,4a-c'] difuran 5,10a dicarboxylate (28)

Zinc borohydride (100µl of a 0.24M solution in THF, 24.0 µmol) was added to a solution of the ketone (27) (12mg, 19.7µmol) in THF under argon at 0°C. The solution was stirred at 0°C for 1hr before water (1ml) was added and extracted with dichloromethane (5 x 5ml). The combined organic extracts were dried over magnesium sulphate, concentrated and purified by flash chromatography (30% ethyl acetate / petrol) to give the alcohol (28) (11mg, 92%);υ_{max} (film) cm^{-1} 3490, 2926, 1735, 1436, 1290, 1199, 1135, 1109, 1052, 983, 739; 1H δ ($CDCl_3$) 1.58 (1H, d, 15.7Hz, H-2), 1.99 (1H, brs, OH), 2.43 (1H, m, H-8), 2.74 (1H, d, 10.7 Hz, H-9), 2.87 (1H, dt, 15.8, 4.8Hz, H-2). 3.11 (1H, dd, 13.3, 11.1Hz, H-18), 3.20 (3H, s, OMe), 3.61 (1H, d, 10.4Hz, H-19), 3.70 (1H, dd, 13.3, 4.1 Hz, H-18), 3.73 (3H, s, CO_2Me) , 3.76 (3H, s, CO_2Me), 3.81 (1H, d, 12.6Hz, H-5), 3.95 (1H, d, 8.5Hz, H-28), 3.97 (1H, d, 10.4Hz, H-19), 3.98 (1H, d, 8.5Hz, H-28), 4.11 (1H, dd, 12.6, 2.7Hz, H-6), 4.47 (1H, d, 4.8Hz, H-1), 4.72 (1H, brs, H-7), 4.75 (1H, d, 4.8Hz, H-3), 6.11 (1H, s, ArCH), 7.04-7.59 (10H, m, Ar-H); m/z (CI) 612, 581, 553, 471, 416, 309, 169, 142, 123, 105, 91, 77; found (M^+) 612.2030. $C_{32}H_{36}O_{10}S$ requires 612.2029.

Preparation of (2aR, 3R, 4R, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 3-hydroxy-5 - methoxy -8,10-phenylmethylenedioxy-4-ylideneper- hydronaphtho [1,8-bc:4,4a,4a-c'] difuran 5,10a dicarboxylate and (2aR, 3S, 4R, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 3-

hydroxy-5 - methoxy -8,10-phenylmethylenedioxy-4-ylidene per- hydronaphtho [1,8-bc:4,4a,4a-c'] difuran 5,10a dicarboxylate (29)

Sodium borohydride (4mg, 0.106mmol) and cerium (III) chloride heptahydrate (40mg. 0.107mmol) were added to a solution of the enone (26) (23mg, 45.9μmol) in methanol (2ml) at -20°C. Stirring was continued for 1hr before acetone (1ml) was added and the solution allowed to warm to room temperature. The solution was concentrated and the residue was purified by flash chromatography (gradient elution, 40% to 60% ethyl acetate / petrol) to give in order of elution the β allylic alcohol (29) (16mg, 70%);υ_{max} (film) cm^{-1} 3493, 2950, 1744, 1450, 1289, 1254, 1199, 1133, 1108, 1053, 985, 879, 765, 737, 699; 1H δ ($CDCl_3$) 1.63 (1H, d, 15.7Hz, H-2), 2.94 (1H, dt, 15.7, 4.8Hz, H-2), 3.02 (1H, d, 2.9Hz, OH), 3.20 (1H, d, 12.7Hz, H-5), 3.26 (3H, s, OMe), 3.46 (1H, s, H-9), 3.63 (1H, d, 10.2 Hz, H-19), 3.77 (6H, s, 2 x CO_2Me), 3.97 (1H, d, 8.3Hz, H-28), 4.08 (1H, d, 8.3Hz, H-28), 4.25 (1H, d, 10.2Hz, H-19), 4.36 (1H, d, 4.6Hz, H-1), 4.51 (1H, dd, 12.6, 6.6Hz, H-6), 4.81 (2H, m, H-3 + H-7), 5.17 (1H, d, 1.5Hz, H-18), 5.74 (1H, d, 1.8Hz, H-18), 6.12 (1H, s, ArCH), 7.35 (3H, m, Ar-H), 7.46 (2H, m, Ar-H); m/z (CI) 503 (MH^+), 471, 443, 379, 365, 347, 261, 245, 231, 201, 185, 163, 136, 105; found (MH^+) 503.1917. $C_{26}H_{31}O_{10}$ requires 503.1917; and the α allylic alcohol (4mg, 17%); υ_{max} (film) cm^{-1} 3510, 2924, 2853, 1728, 1458, 1378, 1285, 1121, 1074, 1054, 742, 701; 1H δ ($CDCl_3$) 1.63 (1H, d, 15.7Hz, H-2), 2.80 (1H, d, 10.4Hz, H-5), 2.94 (1H, dt, 15.7, 4.8Hz, H-2), 3.35 (3H, s, OMe), 3.49 (1H, s, H-9), 3.68 (1H, d, 10.5Hz, H-19), 3.76 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 3.91 (1H, d, 8.4Hz, H-28), 3.99 (1H, d, 8.4 Hz, H-28), 4.29 (1H, d, 10.5Hz, H-19), 4.39 (1H, dd, 10.4, 3.5 Hz, H-6), 4.80 (2H, m, H-3 + H-7), 5.26 (1H, brs, H-18), 5.56 (1H, brs, H-18), 6.13 (1H, s, ArCH), 7.32 - 7.40 (5H, m, Ar-H)

Preparation of (2aR, 4aS, 5S, 7aS, 8S, 10R, 10aR, 10bR) dimethyl 5 - methoxy -8,10-phenylmethylenedioxy-4-phenylsulphinylmethyl-1, 4, 4a, 5, 6, 7, 8, 8a octahydronaphtho [1,8-bc:4,4a,4a-c'] difuran 5,10a dicarboxylate (30).

Triethylamine (20μl, 0.143mmol) and phenylsulphenyl chloride (15mg, 0.104mmol) were added to a solution of the allylic alcohol (7mg, 13.9μmol) in dichloromethane (2ml) under argon at -78°C. The solution was allowed to slowly warm to room temperature and stirred for a further 6hrs. Saturated aqueous sodium bicarbonate was added and extracted with dichloromethane (5 x 10ml). The combined organic extracts were dried over sodium sulphate, concentrated and purified by flash chromatography (gradient elution, 50% to 60% ethyl acetate / petrol) to give the allylic sulphoxide (30) (8mg, 94%); υ_{max} (film) 2952, 1735, 1443, 1298, 1245, 1200, 1120, 1102, 1049, 986, 909, 732cm^{-1}; 1H δ ($CDCl_3$) 7.67-7.64 (2H, m) and 7.56-7.54 (2H, m) and 7.48-7.43 (5H, m) and 7.36-7.33

(1H, m) PhS(O) and PhCH, 6.46 (1H, s) H2a, 6.17 (1H, s) ArCH, 4.80 (1H, d, 4.7Hz) H-8 or H-10, 4.56 (1H, dd, 11.9, 1.0Hz) H-2a, 4.45 (1H, d, 4.5Hz) H-8 or H-10, 3.82 (3H, s) MeO_2C, 3.76 (3H, s) MeO_2C, 3.35 (1H, d, 13.0Hz), 3.21 (3H, s) OMe, 3.17 (1H, d, 12.0Hz), 2.96 (1H, dt, 15.7, 4.8Hz) H-9, 1.69 (1H, d, 15.7Hz) H-9; m/z (FAB) 611, 579, 485, 453, 413, 391, 347, 329, 289, 261, 243, 213; found (M^+) 611.1951 $C_{32}H_{34}O_{10}S$ requires 611.1951.

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