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INSECT ANTIFEEDANTS FROM AZADIRACHTA INDICA (PART 5)[1]: CHEMICAL MODIFICATION AND STRUCTURE-ACTIVITY RELATIONSHIPS OF AZADIRACHTIN AND SOME RELATED LIMONOIDS

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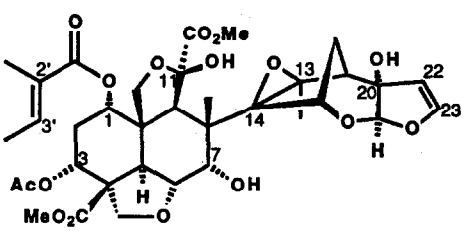
Abstract: *Chemical modification of the potent insect antifeedant and growth-disruption agent azadirachtin (1) and the related limonoids 3-tigloyl azadirachtol (6) and salannin (27) have permitted an exploration of the biological activity of these compounds. General comments are made regarding the structural dependency of the antifeedant effect.*

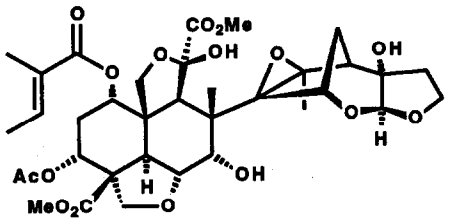
The need to protect our food supply from predatory insect attack using ecologically acceptable methods has led to a growing interest in behaviour modifying chemicals from natural sources. In particular the Indian neem tree, *Azadirachta Indica* A. Juss (Meliaceae), has provided a rich source of materials of which one component, the limonoid azadirachtin (**1**), has been the focus of most attention.



(**1**)

Since its first isolation in pure form in 1968[2] the activity of azadirachtin as an antifeedant and growth disruption agent has provided the stimulus for a considerable research effort.[3,4] The difficulties associated with the structure determination of (**1**)[5] prompted us to embark upon a detailed synthesis[1,6] and structure modification programme,[7,8] which has permitted the unambiguous determination of (**1**) by X-ray crystallographic methods[5a] and also provided many derivatives valuable to our investigation of the structure-activity relationships of these molecules. Preparation of the dihydro (**2**)[5a,9] and tetrahydro (**3**)[3] azadirachtin derivatives, the pyruvyl analogue (**4**)[9] and the detigloyl compound (**5**)[5a,9] has been reported previously. Here we report in full, further examples of skeletal and functional group conversions of azadirachtin and

the related natural product 3-tigloyl azadirachtol (**6**),[10] together with data describing the resulting changes in antifeedant activity against a variety of insects.[11]



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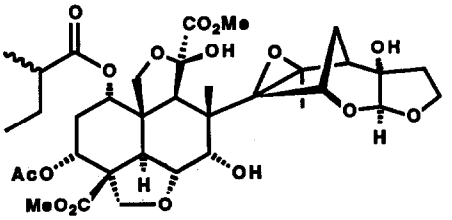

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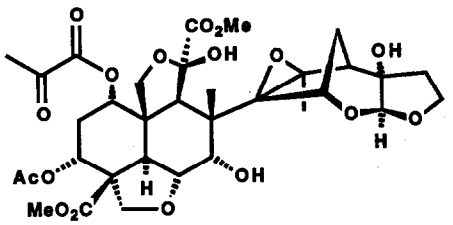

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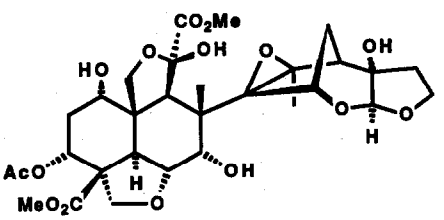

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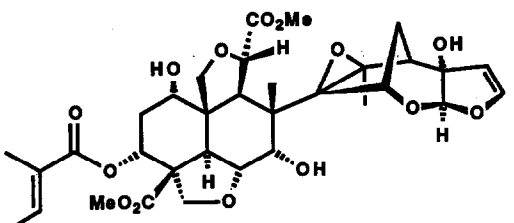
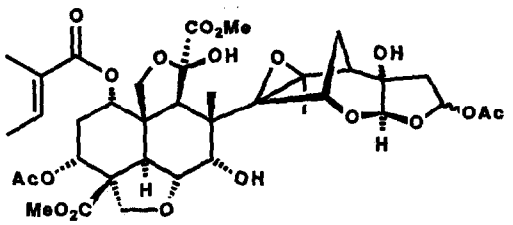


(**6**)

Reactions involving the C-22,23 enol-ether double bond of azadirachtin (**1**) have been extensively investigated.[8] It was found that (**1**) reacted with acetic acid over 72hr to give addition product (**7**) as a 2:1 (α:β) mixture in excellent yield. Disappointingly, we were unable to isolate similar addition products with other carboxylic acids (formic, propionic, etc). Significantly however, on pyrolysis at 170°C under high vacuum (1.7 $X10^{-3}$mm/Hg) (**7**) was quantitatively converted back to azadirachtin.[8] This reaction could well be of importance to our proposed total synthesis of these molecules since it may be regarded as a method of protection of this labile double bond.

Treatment of (**1**) with bromine in methanol also afforded addition products (**8**) in a 1:3 (α:β) mixture at the C-23 centre.[8] After separation by careful chromatography the major 23-β isomer may be reduced with tri-n-butyl tin hydride to give the corresponding ether (**9**) which is identical to the natural product 22,23-dihydro-β-methoxyazadirachtin previously isolated by Kraus.[12] The mixture (**8**) could be reduced similarly to give 22,23-dihydro-α,β-methoxyazadirachtin. Addition reactions using bromine in ethanol or isopropanol afforded the

adducts (10) or (11) respectively. Reductive removal of the bromine substituents as before produced the corresponding ethers (12) and (13).



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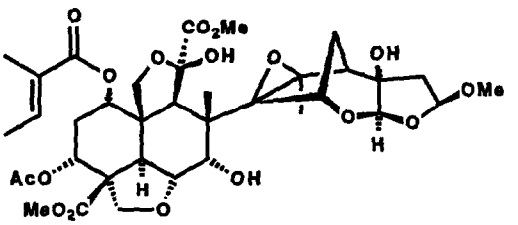

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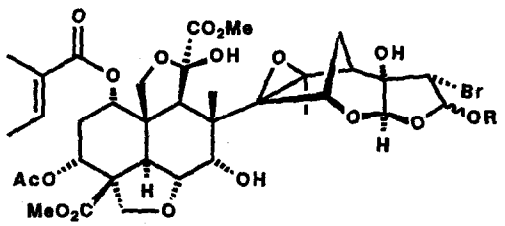
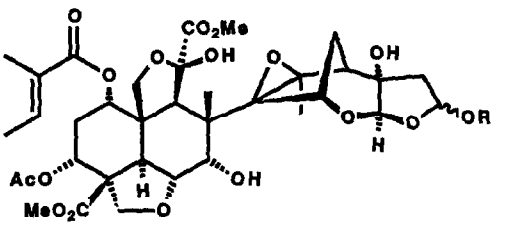
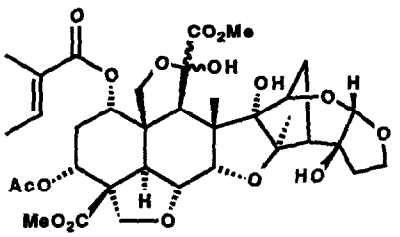


(8) R = Me
(10) R = Et
(11) R = ^{i}Pr



(12) R = Et
(13) R = ^{i}Pr



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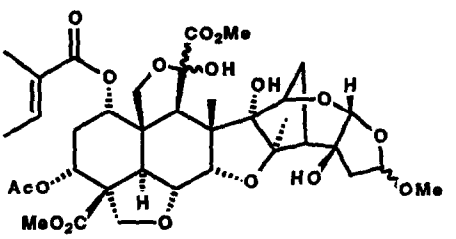
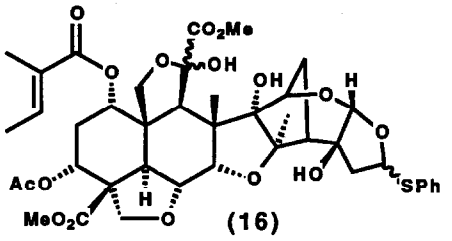


(15)

Under strongly acidic conditions the azadirachtin skeleton will undergo a rearrangement reaction involving the C13-C14 epoxide and the C7 hydroxyl group to give the azadirachtinin series of compounds. For example, treatment of the dihydro derivative (2) in acetonitrile with amberlyst-15 resin and 4Å molecular sieves affords the compound (14) in 51% yield.[7] This compound consists of a rapidly equilibrating mixture of C-11 isomers in which the natural C-11 hydroxy isomer predominates (7:2) over the epimeric C-11 structure. The rapid equilibration of these hemiacetals is in contrast to the starting compound (2) and is presumably due to the loss of the hydrogen bond stabilisation from the C-11 OH to the neighbouring epoxide oxygen atom. When azadirachtin (1) itself was similarly treated with acid catalysts a complex mixture of reaction products was obtained; however 22,23-dihydro-23-α,β-methoxyazadirachtin did

undergo rearrangment (41%) to the corresponding azadirachtinin **(15)**, again as a mixture of C-11 isomers (3:2). This is a useful compound since it can be used to restore the C-22,23 double bond. This was achieved *via* anomeric exchange with thiophenol, amberlyst-15 resin, and 4Å molecular sieves in acetonitrile to give the sulphides **(16)**, followed by oxidation and syn-elimination of the resulting sulphoxides to give azadirachtinin **(17)** as a (2:1) mixture at C-11.



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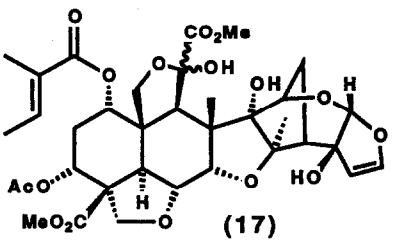
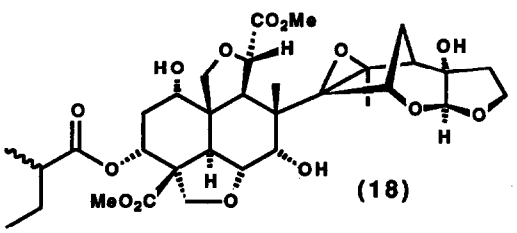


(17)

The natural product 3-tigloylazadirachtol **(6)**[10] and its derivatives are more amenable to chemical modification than azadirachtin **(1)** being significantly more stable and less base sensitive. Not surprisingly, however, acid catalysed rearrangement involving the C-7 hydroxyl group similar to that found with the azadirachtins (*vide supra*) was also observed with the azadirachtols. Tetrahydro-3-tigloylazadirachtol **(18)** was prepared by hydrogenation over palladium on charcoal. Dihydroazadirachtol **(19)** was obtained by initial hydrolysis of 3-tigloylazadirachtol **(6)** (Et_3N:MeOH:H_2O, 1:5:1, 65 °C 15 h) to give azadirachtol **(20)** followed by hydrogenation.



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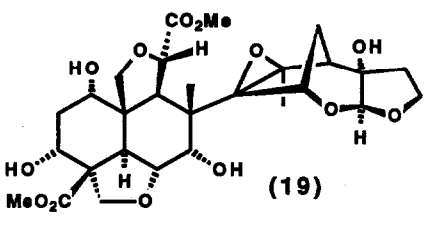

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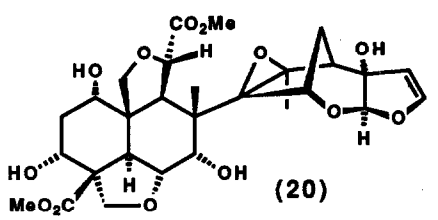

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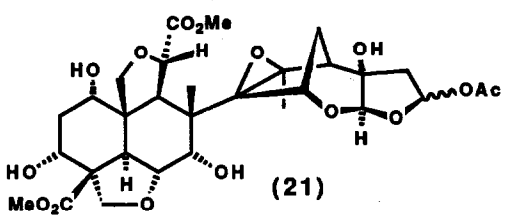
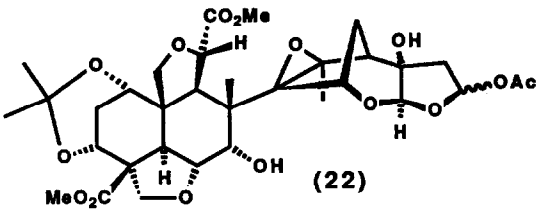


(21)

Reaction of **(20)** with acetic acid, as before, afforded 23-acetoxy-22,23-dihydroazadirachtol as an inseparable 2:1 (α:β) mixture at the C-23 centre **(21)** This mixture was protected as the acetonides **(22)** by treatment with 2-methoxy propene in dichloromethane under acid catalysis. Acetonides **(23)** and **(24)** were formed similarly. Conversion of **(22)** into **(24)** by heating at 160 °C and $5x10^{-4}$ mm Hg for 15 minutes once again exemplifies the use of the acetate group as protection for the sensitive 22,23-enol ether double bond.



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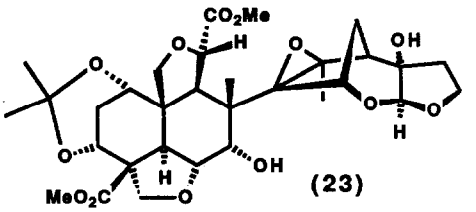

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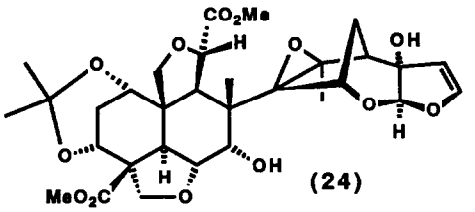
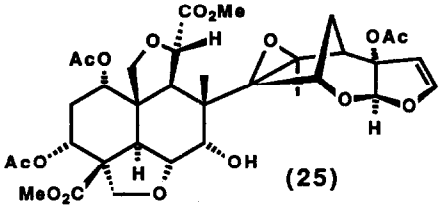


(24)

The reactivity order of hydroxyl functionality in azadirachtin has been previously investigated.[3,9,5a] We were interested to explore this reactivity in the less highly oxidised azadirachtol series. Exhaustive acetylation of **(20)** using excess acetic anhydride with triethylamine and catalytic 4-dimethylamino pyridine in dichloromethane yielded the triacetate **(25)** with no functionalisation of the C-7 hydroxyl group even after heating at 67 °C for 1 day. Treatment of **(6)** with excess trimethylsilyl trifluoromethanesulphonate and triethylamine yielded tris-silylated 3-tigloylazadirachtol **(26)** in 53% yield. This is the only intermolecular functionalisation of the highly hindered C-7 hydroxyl group of **(6)** which we have observed to date. Successful methylation of the corresponding hydroxyl group in azadirachtin **(1)** has been reported by Nakanishi[5a] and we have repeated this procedure in order to obtain material for our own biological screen; Morgan has prepared 1,7,20-tris-*O*-(trimethylsilyl)azadirachtin.[9]

We are currently investigated methods for the selective esterification of the C-1 and C-3 hydroxyl groups of azadirachtol in order to synthesise the potentially very interesting 11-deoxy azadirachtin.



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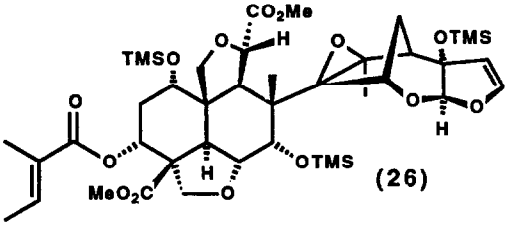


(26)

The antifeedant potential of the compounds was assessed by presenting them in combination with a phagostimulant, sucrose, on glass fibre discs (Whatman GF/A 2.1cm diam.) to larvae of *Spodoptera littoralis* (Boisduval) and *S. frugiperda* (J.E. Smith). These larvae were 24-36 hours into the final stadium and had been deprived of food for 4 hours before being placed individually into Petri dishes with two glass fibre discs (GFD). Both discs had been treated additionally with 100μl of a 50mM sucrose solution and allowed to dry. One disc acted as the control and the other disc, the treatment disc, was treated additionally with 100μl of a solution containing a test compound. The dried discs were weighed and presented to the larvae. The

bioassay terminated after the larvae had eaten approximately 50% of one of the discs, which took between 8-24 hours. The discs were reweighed and the Antifeedant Index [(C-T)/(C+T)]% calculated where C and T are the weight eaten of the control and treated disc, respectively. A potent antifeedant would be represented by a value greater than 75%.

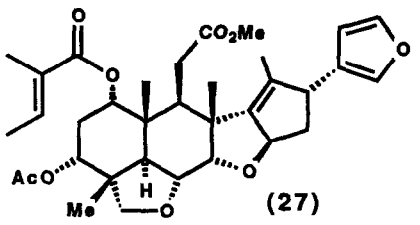
Table : Antifeedant index [(C-T)/(C+T)]% of test compounds [mean ±(SEM)] in dual choice test with glass fibre discs [control (C) versus treatment (T) (N=20)]

	S. littoralis		*S. frugiperda*	
Concentration applied (ppm)	10	1	10	1
Compound				
1	100 (0.0)	99 (1.1)	100 (0.0)	90 (9.4)
2	-	100 (0.0)	-	-
3	100 (0.0)	79 (10.6)	100 (0.0)	97 (3.2)
4	92 (3.2)	55 (12.7)	-	-
5	97 (2.0)	75 (8.1)	-	-
6	-	97 (3.9)	99 (0.8)	60 (12.3)
7	47 (15.0)	49 (9.6)	99 (2.1)	77 (12.9)
8	44 (21.4)	50 (13.2)	32 (21.4)	-10.1 (12.1)
9	98 (1.4)	81 (3.4)	-	-
10	21 (14.2)	28 (19.2)	-	-
11	25 (7.7)	16.6 (19.2)	-	-
12	52 (13.3)	66 (8.3)	-	-
13	44 (16.8)	16 (12.1)	-	-
14	-	96 (0.1)	-	-
15	15 (28.4)	30 (25.6)	-	-
16	24 (22.6)	37 (32.7)	-	-
17	100 (0.0)	100 (0.0)	-	-
19	-	-	57 (10.2)	60 (12.2)
20	-	-	80 (12.9)	86 (1.8)
22	-	-	54 (12.1)	28 (12.8)
24	-	-	83 (10.1)	56 (8.4)
25	-	-	90 (5.8)	16 (12.8)
27	54 (15.1)	72 (12.7)	-	-
28	35 (10.5)	0 (1.0)	-	-
29	-	44 (8.7)	-	-
30	-	9 (11.3)	-	-
31	-	41 (8.7)	18.1 (12.4)	24.8 (11.1)

From the antifeedant data obtained (Table) it is possible to draw some general conclusions concerning the structure-activity relationships in these molecules. Firstly, it is clear that hydrogenation of the C-22,23 enol ether double bond does not significantly diminish activity of either the azadirachtin or 11-deoxy series, while addition products arising from treatment with acetic acid or bromoalkoxidation all lead to reduced activity. Indeed it is apparent that bulky substituents at C-22, such as bromine, or increasingly larger groups (OMe→OEt→O^{i}Pr) at C-23 cause a considerable drop in antifeedancy. Compounds resulting from C-7 hydroxyl mediated intramolecular rearrangement of azadirachtins appear to retain some potency.

No conclusive picture emerges concerning the effect of acylation or substitution of the C-11 or C-20 hydroxyl groups although there is some evidence to suggest that it reduces activity,[3] particularly silylation or alkylation at C-20. The effect of changes in the ring A substituents at C-1 and C-3 produces only small variations in the biological screening data.

Salannin (27)[13] and related compounds (28) to (31) are apparently poor antifeedants. We believe this is due to the requirement for certain structural features contained within the hydroxy tricyclic hydrofuran acetal fragment inherent in all the above active examples. This is in accord with our previous observations, that for some species, antifeedancy can be demonstrated using simple hydroxytricyclic hydrofuran derivatives.[6]



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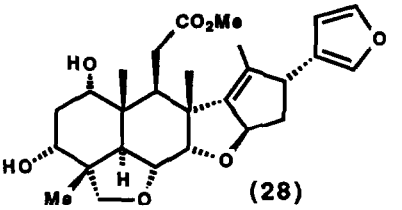

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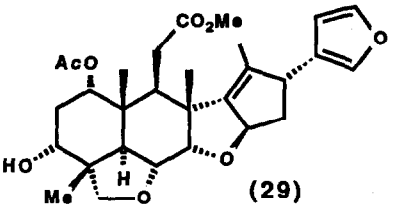

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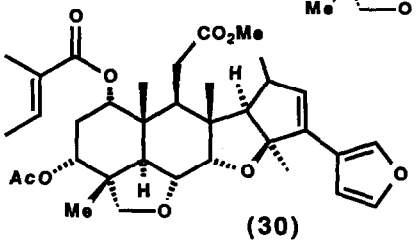

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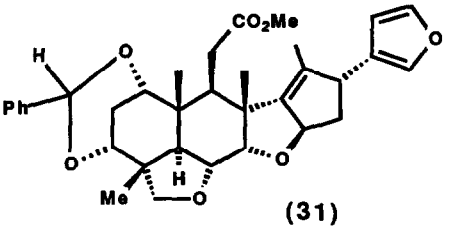

(31)

The above studies constitute a detailed examination of the substitutent changes affecting antifeedant activity in the azadirachtin area. Work is currently underway to further delineate all of the functional parameters essential to the biological activity of these molecules and will be reported at a later date.

Acknowledgements: We thank the SERC, Rohm and Haas Co., Spring House, Pennsylvania USA, and ICI plc. for financial support. Dr. J. A. Ballantine of the SERC Mass Spectroscopy Centre, University College, Swansea, is gratefully acknowledged for mass spectral data. The insect work was carried out under MAFF licence No. PHF 1020/10 issued under the Import and Export (Plant Health Great Britain) Order 1980 and Plant Pests (Great Britain) Order 1980.

Experimental

^{1}H nmr spectra were recorded in $CDCl_3$ using a Bruker AM-500 nmr spectrometer. Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer. Mass spectra were obtained using VG-7070B, VG 12-253 and VG ZAB-E instruments; microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations were measured using an AA-1000 polarimeter. Chromatography refers to column chromatography on Merck Kieselgel 60 (230-400 mesh) unless otherwise stated; petrol refers to petroleum ether b.p. 40-60 °C.

Preparation of 2',3',22,23-tetrahydroazadirachtin (3). Azadirachtin **(1)** (19.2 mg, 26.6 μmol) and 10% palladium on charcoal (Aldrich, 5 mg) was stirred in degassed redistilled methanol (1 ml) under hydrogen for 3 hours. The reaction mixture was then degassed, filtered over celite and evaporated to dryness to give a glassy solid that was purified by flash chromatography (silica, 10% petrol - ethyl acetate) to yield the tetrahydro derivative **(3)** as an inseparable 4:3 C-2' epimeric mixture (12.0 mg, 62%) as a glass (R_f 0.30, ethyl acetate); ν_{max} (film) 3437, 2958, 1732, 1434, 1377, 1244, 1221, 1187, 1152, 1042, 980 and 925 cm^{-1}; δ(500 MHz) for the major isomer,0.93 (3H, t, J 7.5 Hz, C4'-Me), 1.15 (3H, d, J 6.8 Hz, C5'-Me), 1.42 (1H, m, H-3'), 1.58 (1H, d, J 12.9 Hz, H-16), 1.70 (1H, ddd, J 13.1, 5.2, 4.0 Hz, H-16), 1.75-1.85 (2H, m, H-2' and H-3'), 2.07 (3H, s, C3-OAc), 2.16 (1H, m, H-2), 2.22 (3H, s, H-18), 2.24 (1H, m, H-2), 2.28 (1H, m, H-22), 2.29-2.38(1H, m, H-2), 2.52(1H, d, J 5.1 Hz, H-17), 2.58(1H, s, C7-OH), 3.07 (1H, d, J 12.5, H-5), 3.25 (1H, s, C20-OH), 3.35 (1H, s, H-9), 3.61 (1H, d, J 9.0 Hz, H-28), 3.62 (1H, d, J 9.7 Hz, H-19), 3.69 (3H, s, CO_2Me), 3.80 (3H, s, CO_2Me), 3.90 (1H, dd, J 16.3, 8.1 Hz, H-23), 4.02 (1H, dt, J 8.5, 4.4 Hz, H-23), 4.08 (1H, d, J 9.7 Hz, H-19), 4.09 (1H, d, J 8.9 Hz, H-28), 4.55 (1H, dd, J 12.6, 1.1 Hz, H-6), 4.59 (1H, t, J 2.9 Hz, H-1), 4.68 (1H, d, J 3.5 Hz, H-15), 4.74 (1H, br.s, H-7), 5.01 (1H, s, C11-OH), 5.24 (1H, s, H-21) and 5.50 (1H, t, J 3.0 Hz, H-3); and for the minor isomer, 0.95 (3H, t, J 7.5 Hz, C4'-Me), 1.17 (3H, d, J 6.8 Hz, C5'-Me), 1.42 (1H, m, H-3'), 1.58 (1H, d, J 12.9 Hz, H-16), 1.70 (1H, ddd, J 13.1, 5.2, 4.0 Hz, H-16), 1.75-1.85 (2H, m, H-2' and H-3'), 2.06 (3H, s, C3-OAc), 2.16 (1H, m, H-2), 2.22 (3H, s, H-18), 2.24 (1H, m, H-2), 2.28 (1H, m, H-22), 2.29-2.38(1H, m, H-2), 2.52(1H, d, J 5.1 Hz, H-17), 2.58(1H, s, C7-OH), 3.09 (1H, d, J 12.5, H-5), 3.25 (1H, s, C20-OH), 3.36 (1H, s, H-9), 3.61 (1H, d, J 9.0 Hz, H-28), 3.62 (1H, d, J 9.7 Hz, H-19), 3.70 (3H, s, H-12), 3.80 (3H, s, H-29), 3.90 (1H, dd, J 16.3, 8.1 Hz, H-23), 4.02 (1H, dt, J 8.5, 4.4 Hz, H-23), 4.08 (1H, d, J 9.7 Hz, H-19), 4.09 (1H, d, J 8.9 Hz, H-28), 4.55 (1H, dd, J 12.6, 1.1 Hz, H-6), 4.56 (1H, t, J 2.9 Hz, H-1), 4.68 (1H, d, J 3.5 Hz, H-15), 4.74 (1H, br.s, H-7), 5.01 (1H, s, C11-OH), 5.24 (1H, s, H-21) and 5.50 (1H, t, J 3.0 Hz, H-3), *m/z* (FAB thiodiethanol) 725 (MH^+), 707 (MH^+-H_2O), 690, 605, 291 and 167. (Found: (MH^+) 725.3120. $C_{35}H_{49}O_{16}$ requires 725.3219).

Preparation of 23-α,β-acetoxy-22,23-dihydroazadirachtin (7). Azadirachtin **(1)** (200 mg, 0.278 mmol) was stirred in dry acetic acid (5 ml) at room temperature under argon for three days. After this time the mixture was evaporated to dryness and then purified by flash chromatography (25% petrol - ethyl acetate) to give, in order of elution, the pure α-acetate (67.1 mg, 31%) as a white glassy solid (R_f 0.37, 10% petrol - ethyl acetate); ν_{max} (film) 3451, 2954, 1738, 1435, 1374, 1266, 1141, 1047, 977 and 923 cm^{-1}; δ(500 MHz) 1.53 (1H, d, J 13.2 Hz, H-16b), 1.69 (1H, ddd, J 13.3, 5.1, 4.0 Hz, H-16a), 1.75 (3H, s, H-30), 1.79 (3H, dq, J 7.1, 1.0 Hz, H-4'), 1.85 (3H, t, J 1.1 Hz, H-5'), 1.94 (3H, s, C3-OAc), 2.03 (3H, s, C23-OAc), 2.04 (3H, s, H-18), 2.22 (1H, dt, J 16.9, 3.3 Hz, H-2), 2.27 (1H, d, J 14.9 Hz, H-22α), 2.32 (1H, dt, J 16.9, 2.6 Hz, H-2), 2.44 (1H, d, J 5.4 Hz, H-17), 2.45 (1H, dd, J 15.0, 5.7 Hz, H-22β), 2.73 (1H, s, C7-OH), 3.23 (1H, d, J 12.5 Hz, H-5), 3.30 (1H, s, H-9), 3.62 (1H, d, J 9.7 Hz, H-19), 3.69 (3H, s, H-29), 3.73 (1H, br s, C20-OH), 3.75 (1H, d, J 9.0 Hz, H-28), 3.80 (3H, s, H-12), 4.08 (1H, d, J 9.0 Hz, H-28), 4.15 (1H, d, J 9.9 Hz, H-19), 4.60 (1H, dd, J 12.5, 2.8 Hz, H-6), 4.70 (1H, d, J 3.5 Hz, H-15), 4.76 (2H, m, H-1

and H-7), 4.93(1H, s, C11-OH), 5.50 (1H, t, J 2.8 Hz, H-3), 5.54 (1H, s, H-21), 6.37 (1H, d, J 5.4 Hz, H-23) and 6.86 (1H, qq, J 7.1, 1.4 Hz, H-3'); *m/z* (FAB, thiodiethanol) 721 (M^+-AcO), 703 (M^+-AcO-H_2O), 685 (M^+-AcO$^-$-2H_2O), 391, 187 and 95 (C_6H_7O); (Found: C, 56.73; H, 6.09. $C_{37}H_{48}O_{18}$ requires C, 56.92; H, 6.20%) and the α,β-acetoxy mixture (138.7 mg, 64%, and therefore a total yield of 95%) as a white glassy solid (Rf 0.29-0.37, 10% petrol - ethyl acetate); δ(500 MHz) for β-acetate, 1.74 (1H, m, H-16), 1.75 (3H, s, H-30), 1.78 (3H, dq, J 7.1, 0.9 Hz, H-4'), 1.85 (3H, s, H-5'), 1.92 (1H, m, H-16), 1.94 (3H, s, H-18), 2.01 (3H, s, C23-OAc), 2.04 (3H, s, C3-OAc), 2.21 (1H, dt, J 16.7,3.2 Hz, H-2), 2.32 (1H, dt, J 2.5 Hz, H-2), 2.35 (1H, dd, J 14.9, 2.8 Hz, H-22), 2.52 (1H, m, H-17), 2.53 (1H, dd, J 15.1, 6.8 Hz, H-22), 2.63 (1H, s, OH), 2.82 (1H, s, OH), 3.26 (1H, d, J 12.4 Hz, H-5), 3.29 (1H, s, H-9), 3.61 (1H, d, J 9.7 Hz, H-19), 3.68 (3H, s, CO_2Me), 3.74 (1H, d, J 9.1 Hz, H-28), 3.79 (3H, s, CO_2Me), 4.06 (1H, d, J 9.0 Hz, H-28), 4.15 (1H, d, J 9.8 Hz, H-19), 4.57 (1H, dd, J 12.5, 2.6 Hz, H-6), 4.61 (1H, d, J 2.5 Hz, H-15), 4.71 (1H, br.s, H-7), 4.75 (1H, t, J 2.7 Hz, H-1), 5.00 (1H, s, C11-OH), 5.49 (1H, t, J 2.9 Hz, H-3), 5.64(1H, s, H-21), 6.42 (1H, dd, J 6.8, 2.8 Hz, H-23) and 6.89 (1H, qq, J 7.1, 1.4 Hz, H-3').

Preparation of 22-α-bromo-22,23-dihydro-23-α,β-methoxy azadirachtin (8). A weak methanolic solution of bromine was added dropwise to a stirred solution of azadirachtin (19.6 mg, 27.2 μmol.) in methanol (1 ml.) at room temperature in air until a faint yellow colour persisted. Subsequent addition of 20% aq. sodium sulfite (2 drops) and evaporation to dryness was followed by flash chromatography (gradient elution: 45% to 35% petrol - ethyl acetate) to give, in order of elution, the 22-α-bromo-22,23-dihydro-23-α,β-methoxyazadirachtin epimeric mixture **(8)** (7.8 mg, 35%) as a white glassy solid (Rf 0.55, 20% petrol - ethyl acetate) and the pure22-α-bromo-22,23-dihydro-23-β-methoxyazadirachtin (13.5 mg, 61%, and therefore 86% total yield) as a white glassy solid (Rf 0.48, 20% petrol - ethyl acetate); ν_{max} (film) 3462, 2922, 1735, 1648, 1435, 1375, 1260, 1144 and 1039 cm^{-1}; δ(500 MHz) 1.73 (1H, ddd, J 10.8, 5.3, 2.1 Hz, H-16a), 1.74 (3H, s, H-30), 1.78 (3H, dq, J 7.1, 1.1 Hz, H-4'), 1.85 (3H, dq, J 1.1, 1.5 Hz, H-5'), 1.92 (3H, s, C3-OAc), 1.96 (3H, s, H-18), 2.01 (1H, d, J 10.8 Hz, H-16b), 2.20 (1H, ddd, J 16.9, 2.8, 2.5 Hz, H-2), 2.34 (1H, br.d, J 5.3 Hz, H-17), 2.35 (1H, ddd, J 16.4, 2.9, 2.8 Hz, H-2), 2.54 (1H, s, C7-OH), 2.74 (1H, s, C20-OH), 3.32 (1H, s, H-9), 3.37 (1H, d, J 12.5 Hz, H-5), 3.53 (3H, s, C23-OMe), 3.60 (1H, d, J 9.8 Hz, H-19), 3.65 (3H, s, C12-OMe), 3.77 (1H, d, J 7.1 Hz, H-28), 3.79 (3H, s, C29-OMe), 4.12 (1H, d, J 7.1 Hz, H-28), 4.15 (1H, d, J 9.9 Hz, H-19), 4.38 (1H, d, J 5.5 Hz, H-22), 4.56 (1H, d, J 2.1 Hz, H-15), 4.58 (1H, dd, J 12.5, 2.6 Hz, H-6), 4.77 (1H, dd, J 2.8, 2.9 Hz, H-1), 4.77 (1H, d, J 2.6 Hz, H-7), 4.97 (1H, s, C11-OH), 5.14 (1H, d, J 5.9 Hz, H-23), 5.51 (1H, dd, J 2.9, 2.8 Hz, H-3), 5.76 (1H, s, H-21) and 6.94 (1H, qq, J 7.1, 1.5 Hz, H-3'); *m/z* (FAB, thiodiethanol) 830 and 832 (M^+), 815, 795, 783, 700, 669, 603, 468, 391, 291 and 199.

The corresponding bromo ethoxy **(10)** and bromo isopropoxy **(11)** derivatives were prepared in an analogous fashion.

Data for 22-α-bromo-22,23-dihydro-23-α,β-ethoxyazadirachtin (10) (97%) as a white glassy solid (Rf 0.38, 30% petrol - ethyl acetate); ν_{max} (film) 3462, 2953, 2252, 1737, 1647, 1436, 1375, 1268, 1221, 1143, 1081, 1041 and 980 cm^{-1}; δ(500 MHz) for 23-β-ethoxy, 1.26 (3H, t, J 7.1 Hz, H-2"), 1.57 (1H, d, H-16), 1.72 (1H, m, H-16), 1,74 (3H, s, H-30), 1.79 (3H, dq, J 7.0, 1.1 Hz, H-4'), 1.85 (3H, d, J 1.1 Hz, H-5'), 1.93 (3H, s, C3-OAc), 1.97 (3H, s, H-18), 2.20 (1H, dt, J 17.0, 3.2 Hz, H-2), 2.34 (1H, d, J 5.2 Hz, H-17), 2.35 (1H, dt, J 16.8, 2.6 Hz, H-2), 2.50 (1H, s, OH), 2.74 (1H, s, OH), 3.31 (1H, s, H-9). 3.36 (1H, d, J 12.8 Hz, H-5), 3.60 (1H, d, J 9.7 Hz, H-19), 3.62 (1H, dq, J 9.6, 7.1 Hz, H-1"), 3.68 (3H, s, CO_2Me), 3.73 (1H, d, J 9.0 Hz, H-28), 3.78 (3H, s, CO_2Me), 3.90 (1H, dq, J 9.6, 7.1 Hz, H-1"), 4.05 (1H, d, J 9.0 Hz, H-28), 4.14 (1H, d, J 9.7 Hz, H-19), 4.36 (1H, d, J 6.2 Hz, H-22), 4.55-4.61 (2H, dd, J 2.5 Hz, H-6, and m, H-7), 4.73-4.79 (2H, m, H-1 and

H15), 4.97 (1H, s, C11-OH), 5.21 (1H, d, J 6.2 Hz, H-23), 5.50 (1H, t, J 2.3 Hz, H-3), 5.71 (1H, s, H-21) and 6.94 (1H, qq, J 7.1, 1.5 Hz, H-3'); *m/z* (FAB, thiodiethanol) 845 and 847 (MH^+), 827 (M^+-H_2O), 811, 801 and 799 (MH^+-OEt), 781 and 783 (MH^+-OEt-H_2O), 771, 765 (M^+-Br), 765, 683, 619, 578, 563, 549, 391, 167 and 149; (Found: C, 52.44; H, 5.96. $C_{37}H_{49}BrO_{17}$ requires C, 52.55; H, 5.84%).

Data for 22-α-bromo-22,23-dihydro-23-α,β-isopropoxyazadirachtin (11) (96%) as a white glassy solid (Rf 0.32, 40% petrol - ethyl acetate); ν_{max} (film) 3442, 2969, 1735, 1435, 1375, 1266, 1218, 1142, 1043 and 979 cm^{-1}; δ(500 MHz) for 23-β-isopropoxy, 1.21 (3H, d, J 6.1 Hz, H-3"), 1.26 (3H, d, J 6.2 Hz, H-2"), 1.59 (1H, d, H-16), 1.69 (1H, m, H-16), 1.73 (3H, s, H-30), 1.79 (3H, dq, J 7.0, 1.0 Hz, H-4'), 1.86 (3H, s, H-5'), 1.93 (3H, s, C3-OAc), 1.97 (3H, s, H-18), 2.20 (1H, dt, J 17.0, 3.3 Hz, H-2), 2.34 (1H, d, J 5.2 Hz, H-17), 2.34 (1H, dt, J 16.7, 2.6 Hz, H-2), 2.51 (1H, s, OH), 2.77 (1H, s, OH), 3.31 (1H, s, H-9), 3.35 (1H, d, J 12.2 Hz, H-5), 3.60 (1H, d, J 9.7 Hz, H-19), 3.68 (3H, s, CO_2Me), 3.73 (1H, d, J 9.0 Hz, H-28), 3.78 (3H, s, CO_2Me), 3.94 (1H, septet, J 6.2 Hz, H-1"), 4.05 (1H, d, J 9.0 Hz, H-28), 4.14 (1H, d, J 9.7 Hz, H-19), 4.29 (1H, d, J 6.5 Hz, H-22), 4.56 (1H, dd, J 12.3, 2.5 Hz, H-6), 4.58 (1H, br.d, J 3.8 Hz, H-7), 4.73-4.79 (2H, m, H-1 and H-15), 4.97 (1H, s, C11-OH), 5.23 (1H, d, J 6.5 Hz, H-23), 5.50 (1H, t, J 2.8 Hz, H-3), 5.63 (1H, s, H-21) and 6.94 (1H, qq, J 7.1, 1.4 Hz, H-3'); *m/z* (FAB, thiodiethanol) 861 and 859 (MH^+), 843 and 841 (MH^+-H_2O), 825 and 823 (MH^+-$2H_2O$), 801 and 799 (MH^+-^iPrO), 783 and 781 (MH^+-^iPrO-H_2O), 763, 741, 683, 619, 603 and 167; (Found: C, 52.94; H, 6.15. $C_{38}H_{51}BrO_{17}$ requires C, 53.09; H, 5.98%).

Preparation of 22-23-dihydro-23-β-methoxy azadirachtin (9). Tri-n-butyl tin hydride (10 μl, 3 eq.) was added dropwise to a magnetically stirred solution of 22-α-bromo-22,23-dihydro-23-β-methoxyazadirachtin (10.4 mg, 12.5 μmol) and a trace of azo-bis-isobutyronitrile in anhydrous benzene (1 ml) at 80°C under argon. After ten minutes carbon tetrachloride (1 ml) was added and the mixture allowed to cool to room temperature. Saturated potassium fluoride solution (0.5 ml) was added with vigorous stirring before filtering the white precipitate. The filtrate was partitioned between water (1 ml) and dichloromethane (10 ml), separated and the aqueous fraction further extracted with dichloromethane (3x5 ml). The combined organic layers were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a clear oil that was purified by flash chromatography (10% petrol - ethyl acetate) to yield the 23-β-methoxy derivative (7.7 mg, 82%) as a glass with physical data identical in all respects to the literature.[12]

The corresponding α,β-ethoxy **(12)** and α,β isopropoxy **(13)** derivatives were prepared in an analogous fashion.

Data for 22,23-dihydro-23-α,β-ethoxyazadirachtin (12) (69%) as a white glassy solid (Rf 0.31, 20% petrol - ethyl acetate); ν_{max} (film) 3452, 3054, 2954, 2923, 2854, 1739, 1706, 1647, 1436, 1375, 1267, 1222, 1143, 1080, 1042, 973 and 936 cm^{-1}; δ(500 MHz) for 23-β-ethoxy, 1.20 (3H, t, J 7.1 Hz, H-2"), 1.64 (1H, ddd, J 13.0, 5.4, 3.9 Hz, H-16), 1.75 (3H, s, H-30), 1.78 (3H, dq, J 7.1, 1.1 Hz, H-4'), 1.85 (3H, d, J 1.1 Hz, H-5'), 1.95 (3H, s, C3-OAc), 2.00 (1H, m, H-16), 2.01 (3H, s, H-18), 2.19-2.24 (2H, m, H-2 and H-22), 2.32 (1H, dt, J 16.9, 2.6 Hz, H-2), 2.38 (1H, dd, J 14.5, 6.3 Hz, H-22), 2.47 (1H, d, J 5.3 Hz, H-17), 2.55 (1H, s, OH), 2.91 (1H, s, OH), 3.24 (1H, d, J 12.5 Hz, H-5), 3.30 (1H, s, H-9), 3.49 (1H, dq, J 9.4, 7.1 Hz, H-1"), 3.62 (1H, d, J 9.7 Hz, H-19), 3.68 (3H, s, CO_2Me), 3.74 (1H, d, J 9.0 Hz, H-28), 3.79 (3H, s, CO_2Me), 3.85 (1H, dq, J 9.6, 7.1 Hz, H-1"), 4.07 (1H, d, J 9.0 Hz, H-28), 4.16 (1H, d, J 9.7 Hz, H-19), 4.58 (1H, dd, J 12.5, 2.7 Hz, H-6), 4.68 (1H, d, J 3.6 Hz, H-15), 4.70 (1H, d, J 2.6 Hz, H-7), 4.74 (1H, t, J 2.8 Hz, H-1), 5.03 (1H,

s, C11-OH), 5.26 (1H, dd, J 6.3, 3.4 Hz, H-23), 5.42 (1H, s, H-21), 5.50 (1H, t, J 2.8 Hz, H-3) and 6.87 (1H, qq, J 7.1, 1.5 Hz, H-3'); *m/z* (FAB, thiodiethanol) 722 (MH^+-EtO), 704 (MH^+-EtO-H_2O), 686 (MH^+-EtO-2H_2O), 620, 392, 291, 221, 179, 165, 149; (Found: C, 58.29; H, 6.73. $C_{37}H_{50}O_{17}$ requires C, 57.96; H, 6.57%).

Data for 22,23-dihydro-23-α,β-isopropoxyazadirachtin (13) (68%) as a white glassy solid (Rf 0.40, 20% petrol - ethyl acetate); ν_{max} (film) 3447, 2955, 2923, 2854, 1739, 1647, 1436, 1377, 1268, 1221, 1139, 1082, 1045, 978 and 933 cm^{-1}; δ(500 MHz) for 23-β-isopropoxy 1.14 (3H, d, J 6.1 Hz, H-2"), 1.21 (3H, d, J 6.2 Hz, H-2"), 1.60-1.69 (1H, m, H-16), 1.75 (3H, s, H-30), 1.78 (3H, dd, J 7.1, 1.1 Hz, H-4'), 1.85 (3H, d, J 1.1 Hz, H-5'), 1.95 (3H, s, C3-OAc), 2.01 (3H, s, H-18), 2.07 (1H, d, J 12.9 Hz, H-16), 2.16 (1H, dd, J 14.4, 3.6 Hz, H-22), 2.21 (1H, dt, J 16.9, 3.3 Hz, H-2), 2.32 (1H, dt, J 17.4, 2.4 Hz, H-2), 2.36 (1H, dd, J 14.4, 6.3 Hz, H-22), 2.46 (1H, d, J 5.3 Hz, H-17), 2.57 (1H, s, OH), 2.97 (1H, br.s, OH), 3.23 (1H, d, J 12.5 Hz, H-5), 3.30 (1H, s, H-9), 3.62 (1H, d, J 9.7 Hz, H-19), 3.68 (3H, s, CO_2Me), 3.74 (1H, d, J 9.0 Hz, H-28), 3.79 (3H, s, CO_2Me), 3.96 (1H, septet, J 6.2 Hz, H-1"), 4.07 (1H, d, J 9.0 Hz, H-28), 4.15 (1H, d, J 9.7 Hz, H-19), 4.58 (1H, dd, J 12.5, 2.7 Hz, H-6), 4.67 (1H, d, J 3.5 Hz, H-15), 4.71 (1H, d, J 2.4 Hz, H-7), 4.74 (1H, t, J 2.8 Hz, H-1), 5.04 (1H, s, C11-OH), 5.35 (1H, dd, J 6.2, 3.6 Hz, H-23), 5.37 (1H, s, H-21), 5.49 (1H, t, J 2.9 Hz, H-3) and 6.87 (1H, qq, J 7.1, 1.4 Hz, H-3'); *m/z* (FAB, thiodiethanol) 803 ($M+Na^+$), 743, 721 ((M^+-^{i}PrO), 703 (M^+-^{i}PrO-H_2O), 685 (M^+-^{i}PrO-2H_2O), 555, 320, 300, 291, 235, 194, 177, 167, 149, 133; (Found: C, 58.59; H, 6.67. $C_{38}H_{52}O_{17}$ requires C, 58.45; H, 6.71%).

Preparation of R,S-11-(22,23-dihydro)azadirachtinin (14). Dihydroazadirachtin **(2)** (55 mg, 76.1 μmol), activated 4Å molecular sieves (10 beads) and amberlyst-15 ion exchange resin(10 beads) were stirred in anhydrous acetonitrile (2 ml) for three days under argon at room temperature. After filtration and evaporation *in vacuo* the residue was purified by flash chromatography (gradient elution 25% to 50% ethyl acetate - dichloromethane) to yield the titled compound **(14)** (28.0 mg, 51%) as a white glassy solid (Rf 0.38, ethyl acetate) consisting of a 7:2 C-11 epimeric mixture; ν_{max} (film) 3408, 2954, 1741, 1648, 1435, 1379, 1268, 1218, 1130, 1103, 1084, 1046 and 979 cm-1; δ(500 MHz) for the major natural C-11 epimer 1.55 (3H, s, H-18), 1.68 (3H, s, H-30), 1.82 (3H, dq, J 7.5, 1.0 Hz, H-4'), 1.86 (3H, dq, J 1.4, 1.0 Hz, H-5'), 2.00 (3H, s, C3-OAc), 2.13 (1H, m, H-2), 2.10-2.20 (2H, m, 2xH-22), 2.20-2.28 (2H, m, H-16 and H-17), 2.25 (1H, s, C20-OH), 2.26 (1H, dt, J 16.7, 2.8 Hz, H-2), 3.17 (1H, d, J 12.8 Hz, H-5), 3.49 (1H, s, H-9), 3.66 (1H, d, J 9.8 Hz, H-19), 3.67 (1H, d, J 8.8 Hz, H-28), 3.72 (1H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 3.82 (1H, m, H-23), 4.01 (1H, m, H-23), 4.04 (1H, d, J 8.8 Hz, H-28), 4.07 (1H, s, C11-OH), 4.20 (1H, br.s, H-15), 4.28 (1H, d, J 9.8 Hz, H-19), 4.40 (1H, dd, J 12.8, 2.9 Hz, H-6), 4.56 (1H, d, J 2.9, H-7), 4.75 (1H, t, J 2.6 Hz, H-1), 5.11(1H, s, H-21), 5.50 (1H, dt, J 2.9 Hz, H-3), 6.03 (1H, s, C14-OH) and 6.88 (1H, qq, J 7.5, 1.4 Hz, H-3'), for the unnatural C-11 epimer 1.27 (3H, s, H-30), 1.36 (3H, m, H-18), 1.80 (3H, dq, J 7.0, 1.0 Hz, H-4'), 1.85 (3H, dq, J 1.0, 1.0 Hz, H-5'), 2.07 (3H, s, C3-OAc), 2.10 (1H, m, H-16), 2.10-2.20 (2H, m, 2xH-22), 2.24 (1H, m, H-17), 2.25 (1H, m, H-2), 2.44 (1H, dt, J 16.8, 3.0 Hz, H-2), 3.22 (1H, d, J 12.6 Hz, H-5), 3.36 (1H, s, H-9), 3.61 (1H, d, J 8.6 Hz, H-28), 3.77 (3H, s, CO_2Me), 3.82 (1H, d, J 9.9 Hz, H-19), 3.83 (1H, m, H-23), 3.85 (3H, s, CO_2Me), 3.96 (1H, d, J 9.9 Hz, H-19), 4.01 (1H, d, J 8.6 Hz, H-28), 4.02 (1H, m, H-23), 4.10 (1H, br.s, H-15), 4.27 (1H, dd, J 12.6, 3.0 Hz, H-6), 4.48 (1H, d, J 3.0 Hz, H-7), 5.07 (1H, s, H-21), 5.54 (1H, t, J 2.9 Hz, H-3), 5.57 (1H, t, J 2.9 Hz, H-1), 5.95 (1H, s, OH), 6.05 (1H, s, OH) and 6.99 (1H, qq, J 7.0, 1.0 Hz, H-3'); *m/z* (FAB thiodiethanol) 723 (MH^+), 705 (MH^+-H_2O), 687 (MH^+-2H_2O), 663, 605, 587, 563, 545, 405 and167; (Found: (MH^+) 723.2971. $C_{35}H_{45}O_{16}$ requires 723.3078).

Preparation of R,S-11-22,23-dihydro-23-α,β-methoxyazadirachtinin (15). 22,23-Dihydro-23-α,β-methoxyazadirachtin (10.5 mg, 13.9 μmol), amberlyst-15 ion exchange resin (20 grains) and activated 4Å molecular sieves (20 beads) were stirred together in anhydrous acetonitrile (1 ml) at room temperature under argon. After five minutes the reaction mixture was filtered through glass wool, evaporated and purified by flash chromatography (ethyl acetate) to give the azadirachtinin analogue **(15)** as an inseparable complex mixture of diastereoisomers at the C-11 and C-23 centres (4.3 mg, 41%) as a white glassy solid (R_f 0.42, ethyl acetate); ν_{max} (film) 3403, 1741, 1435, 1378, 1267, 1216, 1127, 1102, 1038 and 981 cm^{-1}; δ(500MHz) of the major diastereoisomer: 1.57 (3H, s, H-18), 1.67 (3H, s, H-30), 1.77 (1H, m, H-16), 1.81 (3H, dq, J 7.1, 0.9 Hz, H-4'), 1.86 (3H, d, J 4.0 Hz, H-5'), 1.95 (1H, m, H-16), 1.99 (3H, s, C3-OAc), 2.07-2.18 (2H, m, H-2 and H-22), 2.23 (1H, m, H-17), 2.26 (1H, dt, J 16.8, 2.7 Hz, H-2), 2.31 (1H, dd, J 14.4, 5.5 Hz, H-22), 3.15 (1H, d, J 12.8 Hz, H-5), 3.40 (3H, s, C23-OMe), 3.48 (1H, s, H-9), 3.65 (1H, d, J 8.8 Hz, H-28), 3.65 (1H, d, J 9.7 Hz, H-19), 3.72 (3H, s, CO_2Me), 3.76 (3H, s, CO_2Me), 4.01 (1H, d, J 8.8 Hz, H-28), 4.22 (1H, br.d, J 1.4 Hz, H-15), 4.29 (1H, d, J 9.7 Hz, H-19), 4.39 (1H, dd, J 12.8, 3.0 Hz, H-6), 4.43 (1H, s, C14-OH), 4.56 (1H, d, J 3.0 Hz, H-7), 4.74 (1H, t, J 2.7 Hz, H-1), 5.03 (1H, d, J 4.9 Hz, H-23), 5.41 (1H, s, H-21), 5.49 (1H, t, J 2.9 Hz, H-3), 5.99 (1H, s C20-OH) and 6.88 (1H, qq, J 7.1, 1.4 Hz, H-3'); *m/z* 775 ($M+Na^+$), 736 (MH^+-H_2O), 721 (M^+-MeO), 703 (M^+-MeO-H_2O), 677, 563, 543, 391, 281, 207, 167; (Found: (MH^+), 753.2966. $C_{36}H_{49}O_{17}$ requires 753.2962).

Preparation of 11 RS-22,23-dihydro-23-α,β-phenylthioazadirachtinin (16). Thiophenol (33 μl, 5eq.) was added, via syringe, to a magnetically stirred solution of 22,23-dihydro-23-α,β-methoxyazadirachtin (48.4 mg, 64.3 μmol), amberlyst-15 ion exchange resin (50 beads) and activated 4Å molecular sieves (50 beads) in anhydrous acetonitrile (3 ml) at room temperature under argon. After ten minutes the mixture was filtered, evaporated to dryness and then purified by flash chromatography (Fluorosil, gradient elution 50% to 30% petrol - ethyl acetate) to give, in order of elution, a complex diastereoisomeric mixture of the above sulphides (15.3 mg, 29%) as a white glassy solid (R_f 0.69, 30% petrol - ethyl acetate) and a diastereoisomerically pure sulphide **(16)** (16.9 mg, 31%, and therefore a total yield of 60%) as a white glassy solid (R_f 0.39, 30% petrol - ethyl acetate); ν_{max} (film) 3398, 2954, 1741, 1583, 1436, 1378, 1267, 1218, 1127, 1098, 1042 and 978 cm^{-1}; δ(500MHz) 1.55 (3H, s, H-18), 1.67 (3H, s, H-30), 1.82 (3H, dq, J 7.1, 1.0 Hz, H-4'), 1.86 (3H, s, H-5'), 1.90 (1H, m, H-16), 2.00 (3H, s, C3-OAc), 2.09-2.15 (2H, m, H-2 and H-16), 2.25 (1H, d, J 3.5 Hz, H-17), 2.26 (1H, m, H-2), 2.34 (1H, dd, J 14.7, 2.5 Hz, H-22), 2.69 (1H, dd, J 14.8, 8.3 Hz, H-22), 3.16 (1H, d, J 12.8 Hz, H-5), 3.49 (1H, s, H-9), 3.65 (1H, d, J 9.8 Hz, H-19), 3.67 (1H, d, J 8.8 Hz, H-28), 3.71 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 4.03 (1H, d, J 8.9 Hz, H-28), 4.21 (1H, br.s, H-15), 4.28 (1H, d, J 9.8 Hz, H-19), 4.40 (1H, dd, J 12.9, 3.0 Hz, H-6), 4.53 (1H, br.s, C14-OH), 4.58 (1H, d, J 3.0 Hz, H-7), 4.73 (1H, t, J 2.7 Hz, H-1), 5.49 (1H, t, J 2.9 Hz, H-3), 5.67 (1H, s, H-21), 5.73 (1H, dd, J 8.2, 2.3 Hz, H-23), 6.09 (1H, s, C20-OH), 6.89 (1H, qq, J 7.1, 1.4 Hz, H-3'), 7.22-7.27 (1H, m, Ar$_p$H), 7.29 (2H, tm, J 7.3 Hz, Ar$_m$H) and 7.51 (2H, dd, J 8.3, 1.2 Hz, Ar$_o$H); *m/z* (FAB, thiodiethanol) 831 (MH^+), 813 (MH^+-H_2O), 721 (M^+-SAr), 703 (M^+-SAr-H_2O), 685 (M^+-SAr-$2H_2O$), 677, 661, 563, 391, 291, 279, 213, 167; (Found: C, 59.29; H, 6.20. $C_{41}H_{50}O_{16}S$ requires C, 59.27; H, 6.07%).

Preparation of 11 RS-azadirachtinin (17). A solution of *meta*-chloroperbenzoic acid (80 μl of 22.5 mg in 500 μl, 1.2 eq.) in anhydrous dichloromethane was added dropwise, via syringe, to a magnetically stirred solution of the sulphide **(16)** (11.5 mg, 13.8 μmol) in anhydrous dichloromethane (1 ml) at 0°C under argon. 20% aq. Sodium sulphite (2 drops) was added after 5 minutes with stirring for 10 minutes before the addition of saturated aq. sodium bicarbonate (0.5 ml) with stirring for 5 minutes. The heterogeneous mixture was partitioned between water (1 ml)

and dichloromethane(10 ml), separated and the aqueous phase further extracted with dichloromethane (3x5 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a white amorphous solid (Rf 0.36, ethyl acetate) that was used without further purification. The mixture of sulphoxides with anhydrous triethylamine (6 µl, 3.5 eq.) was dissolved in anhydrous toluene(1.5 ml) and heated to 90°C under argon for 5 minutes. The cooled reaction mixture was then evaporated to dryness and purified by flash chromatography (Fluorosil, gradient elution 30 to 0% petrol - ethyl acetate) to yield the title compound **(17)** (4.7 mg, 47%) as a slightly yellow glassy solid (Rf 0.45, 5% methanol - ethyl acetate); ν_{max} (film) 3406, 2956, 1742, 1626, 1437, 1380, 1269, 1218, 1162, 1129, 1099, 1039 and 981 cm^{-1}; δ(500 MHz) 1.55 (3H, s, H-18), 1.69 (3H, s, H-30), 1.80 (1H, m, H-16), 1.83 (3H, dq, J 7.1, 1.0 Hz, H-4'), 1.86 (3H, d, J 1.0 Hz, H-5'), 1.89 (1H, dd, J 14.1, 1.1 Hz, H-16), 2.00 (3H, s, C3-OAc), 2.14 (1H, m, H-2), 2.16 (1H, s, H-17), 2.27 (1H, dt, J 16.8, 2.6 Hz, H-2), 3.17 (1H, d, J 12.8 Hz, H-5), 3.50 (1H, s, H-9), 3.66 (1H, d, J 9.7 Hz, H-19), 3.69 (1H, d, J 8.8 Hz, H-28), 3.72 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 4.04 (1H, d, J 8.8 Hz, H-28), 4.18 (1H, s, H-15), 4.28 (1H, d, J 9.8 Hz, H-19), 4.41 (1H, dd, J 12.9, 3.0 Hz, H-6), 4.45 (1H, br.s, C14-OH), 4.52 (1H, d, J 3.0 Hz, H-7), 4.75 (1H, t, J 2.8 Hz, H-1), 4.88 (1H, d, J 2.9 Hz, H-22), 5.50 (1H, t, J 2.9 Hz, H-3), 5.65 (1H, s, H-21), 5.99 (1H, s, C20-OH), 6.39 (1H, d, J 3.0 Hz, H-23) and 6.89 (1H, qq, J 7.1, 1.4 Hz, H-3'); *m/z* (FAB, thiodiethanol) 721 (MH^+), 703 (MH^+-H_2O), 685 (MH^+-$2H_2O$), 563, 391, 279, 199, 167; (Found: (MH^+) 721.2750. $C_{35}H_{45}O_{16}$ requires 721.2792).

Preparation of 2',3',22,23-tetrahydro-3-tigloylazadirachtol (18). 3-Tigloylazadirachtol **(6)** (9.3 mg, 13.2 µmol) and 10% palladium on charcoal (Aldrich, 2 mg) was stirred in degassed redistilled methanol (0.5 ml) under hydrogen for 10 minutes. The mixture was then degassed, filtered through celite and evaporated to dryness to give a glassy solid that was purified by flash chromatography (20% petrol - ethyl acetate) to yield the tetrahydro derivative **(18)** as an inseperable 4:3 C-2' epimeric mixture (8.5 mg, 91%) as a glass (Rf 0.42, ethyl acetate); ν_{max} (film) 3447, 2958, 1727, 1435, 1381, 1230, 1156, 1120, 1082, 1042, 971 and 929 cm^{-1}; δ(500 MHz) for the major diastereomer: 0.92 (3H, d, J 7.4 Hz, C5'-Me), 1.15 (3H, dd, J 11.9, 7.1 Hz, H-4'), 1.43 (3H, s, H-30), 1.46-1.52 (1H, m, H-3'), 1.56 (1H, d, J 12.8 Hz, H-16b), 1.63 (1H, ddd, J 12.9, 5.1, 3.9 Hz, H-16a), 1.69-1.75 (1H, m, H-3'), 2.02 (1H, m, H-2'), 2.03 (3H, s, H-18), 2.04 (1H, m, H-22), 2.09-2.17 (1H, m, H-22), 2.32 (1H, ddd, J 13.4, 5.8, 3.0 Hz, H-2), 2.42 (1H, ddd, J 13.9, 6.9, 2.0 Hz, H-2), 2.43 (1H, d, J 4.8 Hz, H-17), 2.63 (1H, br.s, OH), 3.14 (1H, s, H-9), 3.22 (1H, d, J 12.6 Hz, H-5), 3.34 (2H, m, H-1 and OH), 3.46 (1H, d, J 9.4 Hz, H-19), 3.47 (1H, m, OH), 3.75 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 3.88 (1H, d, J 8.9 Hz, H-28), 3.89 (1H, dd, J 15.4, 6.6 Hz, H-23), 3.92 (1H, d, J 9.4 Hz, H-19), 4.01 (1H, ddd, J 13.2, 9.2, 4.0 Hz, H-23), 4.03 (1H, d, J 8.9 Hz, H-28), 4.45 (1H, d, J 0.8 Hz, H-11), 4.53 (1H, dd, J 12.6, 2.9 Hz, H-6), 4.57 (1H, d, J 3.4 Hz, H-15), 4.72 (1H, d, J 2.8 Hz, H-7), 5.23 (1H, s, H-21) and 5.43 (1H, dd, J 4.9, 2.7 Hz, H-3); and for the minor diastereomer exactly the same as above except: 0.93 (3H, d, J 7.4 Hz, C5'-Me); *m/z* (FAB thiodiethanol) 667 (MH+), 649 (MH^+-H_2O), 631 (MH^+-$2H_2O$), 605, 563, 521, 451, 391, 281 and 287; (Found: (MH^+) 667.2966. $C_{33}H_{47}O_{14}$ requires 667.2966).

Preparation of 22,23-dihydroazadirachtol (19). To a solution of azadirachtol **(20)** (20 mg, 34.0 µmol) in dry methanol (1 ml) under argon was added 10% palladium on charcoal (Aldrich, 3 mg). The atmosphere of argon was replaced with hydrogen and the solution stirred for 2.5 h. at r.t.. Exhaustive evacuation of the reaction vessel to remove the hydrogen was followed by dilution of the reaction mixture with dichloromethane. The solution was filtered through celite, rinsing the pad with ethyl acetate. Evaporation of the solvents *in vacuo* followed by column chromatography of the residue (ethyl acetate) gave 22, 23-dihydroazadirachtol **(19)** (20 mg, 100%) as a colourless oil, (Rf 0.09, ethyl acetate); ν_{max} (film) 3436, 1721 and 1043 cm^{-1}; δ(500 MHz) 1.43 (3H, s, H-30), 1.52 (1H, d, J 13 Hz, H-16b), 1.59 (1H, ddd, J 12.5, 5.0, 4.5 Hz, H-16a),

1.83 (1H, br d, J 15.5 Hz, H-2ax), 2.01 (3H, s, H-18), 2.0-2.13 (2H, m, 2xH-22), 2.24 (1H, dt, J 15.5, 3.5 Hz, H-2eq), 2.42 (1H, d, J 5 Hz, H-17), 2.90 (1H, br s, OH), 2.98 (1H, br s, H-9), 3.08 (1H, d, J 13 Hz, H-5), 3.39 (1H, br s, OH), 3.43 (1H, d, J 10 Hz, H-19), 3.59-3.63 (1H, m, H-1), 3.72 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 3.87 (1H, ddd, J 16, 8, 2 Hz, H-23), 3.97-4.03 (1H, m, H-23), 4.02 (1H, br d, J 10 Hz, C1-OH), 4.06 (1H, d, J 9 Hz, H-28), 4.07 (1H, d, J 10 Hz, H-19), 4.21 (1H, d, J 9 Hz, H-28), 4.33 (1H, br s, H-3), 4.42 (1H, d, J 1 Hz, H-11), 4.47 (1H, dd, J 13, 3 Hz, H-6), 4.56 (1H, d, J 4.5 Hz, H-15), 4.68 (1H, d, J 3 Hz, H-7) and 5.23 (1H, s, H-21); *m/z* 582 (M^+); (found: (M^+) 582.2309 . $C_{28}H_{38}O_{13}$ requires 582.2312).

Preparation of azadirachtol (20). A solution of 3-tigloylazadirachtol **(6)** (100 mg, 0.155 mmol) in triethylamine : methanol : water (1 : 5 : 1 , 7 ml) was heated at 65 °C for 20 h. After allowing to cool, the mixture was concentrated *in vacuo* then partitioned between dichloromethane and saturated aqueous sodium hydrogen bicarbonate solution. The aqueous layer was extracted with further dichloromethane and the combined organic layers washed twice with brine then dried ($MgSO_4$). Removal of the drying agent followed by evaporation of solvents and column chromatography (80% ethyl acetate-petrol) gave azadirachtol **(20)** (84 mg, 96%) as a white amorphous solid, (R_f 0.24, ethyl acetate); $[\alpha]_D^{20}$ = -47° ((c=1.38 ($CHCl_3$)); ν_{max} (film) 3442, 2951, 1724, 1210 and 1062 cm^{-1}; δ(500 MHz) 1.31 (1H, d, J 3.1 Hz, H-16b), 1.46 (3H, s, H-30), 1.63 (1H, ddd, J 13.1, 5.3, 4.0 Hz, H-16a), 1.83 (1H, d, J 15.3 Hz, H-2ax), 2.01 (3H, s, H-18), 2.25 (1H, dt, J 15.6, 2.9 Hz, H-2eq), 2.34 (1H, d, J 5.2 Hz, H-17), 2.75 (1H, s, OH), 3.02 (1H, br s, H-9), 3.10 (1H, d, J 12.5 Hz, H-5), 3.29 (1H, s, OH), 3.45 (1H, d, J 9.8 Hz, H-19), 3.62 (1H, m, H-1), 3.72 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 3.92 (1H, d, J 8.6 Hz, C3-OH), 4.00 (1H, d, J 5.0 Hz, C1-OH), 4.08 (1H, d, J 8.6 Hz, H-28), 4.09 (1H, d, J 9.6 Hz, H-19), 4.23 (1H, d, J 8.6 Hz, H-28), 4.33 (1H, dt, J 8.5, 2.8 Hz, H-3), 4.42 (1H, d, J 1.3 Hz, H-11), 4.49 (1H, dd, J 12.4, 2.9 Hz, H-6), 4.54 (1H, d, J 3.7 Hz, H-15), 4.71 (1H, d, J 2.9 Hz, H-7), 5.03 (1H, d, J 2.9 Hz, H-22), 5.68 (1H, s, H-21) and 5.42 (1H, d, J 2.9 Hz, H-23); *m/z* 580 (M^+), 562 (M^+-H_2O), 544 (M^+-$2H_2O$), 479, 367, 151, 124, 95; (found: (M^+), 580.21304. $C_{28}H_{36}O_{13}$ requires 580.2156).

Preparation of 23-α,βacetoxy-22,23-dihydroazadirachtol (21). A solution of azadirachtol **(20)** (10 mg, 15 μmol) in acetic acid (7 ml)was allowed to stand at r.t. for seven days. The excess acetic acid was removed *in vacuo* and the residue chromatographed (ethyl acetate) to give **(21)** as an inseparable mixture of diastereomers (2:1 α:β) (6.5 mg, 59%), as a colourless oil, (R_f maj. 0.38, min. 0.32, ethyl acetate); ν_{max} 3452, 2952, 1724, 1435, 1234 and 1053; δ(500 MHz) major diastereoisomer: 1.42 (3H, s, H-30), 1.53 (1H, d, J 13 Hz, H-16), 1.50-1.73 (1H, m, H-16), 1.83 (1H, br d, J 17 Hz, H-2), 1.99 (3H, s, H-18), 2.06 (3H, s, C23-OAc), 2.20-2.28 (1H, m, H-2), 2.28-2.58 (3H, m, H-17, 2xH-22), 2.98 (1H, s, H-9), 3.05 (1H, d, J 12.4 Hz, H-5), 3.09 (1H, s, OH), 3.43 (1H, d, J 11.2 Hz, H-19), 3.61 (1H, m, H-1), 3.71 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 3.94 (1H, d, J 9.4 Hz, H-28), 3.98-4.08 (2H, m, H-19 and H-15), 4.19 (1H, d, J 9.4 Hz, H-28), 4.31 (1H, m, OH), 4.39 (1H, s, H-11), 4.46 (1H, dd, J 12.4, 2.4 Hz, H-6), 4.57 (1H, m, H-3), 4.68 (1H, d, J 3.5 Hz, H-7), 5.50 (1H, s, H-21) and 6.33 (1H, d, J 6.5 Hz, H-23); δ(500 MHz) minor diastereoisomer: 1.41 (1H, d, J 16 Hz, H-16), 1.50-1.73 (1H, m, H-16) 1.82 (1H, s, H-30), 1.83 (1H, br d, J 17 Hz, H-2), 1.99 (3H, s, H-18), 2.03 (3H, s, C23-OAc), 2.20-2.28 (1H, m, H-2), 2.28-2.58 (3H, m, H-17 and 2xH-22), 2.99 (1H, s, H-9), 3.09 (1H, s, OH), 3.10 (1H, d, J 11.8 Hz, H-5), 3.23 (1H, s, OH), 3.42 (1H, d, J 11.2 Hz, H-19), 3.61 (1H, m, H-1), 3.70 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 3.91 (1H, d, J 9.4 Hz, H-28), 3.98-4.08 (2H, m, H-19, H-15), 4.18 (1H, d, J 9.4 Hz, H-28), 4.31 (1H, m, OH), 4.41 (1H, s, H-11), 4.44 (1H, dd, J 11.2, 2.4 Hz, H-6), 4.57 (2H, m, H-3 and H-7), 5.68 (1H, s, H-21) and 6.39 (1H, dd, J 6.5, 1.8 Hz, H-23); m/z FAB, (thioglycerol) 641 (MH^+).

Preparation of 23-α,β-acetoxy-22,23-dihydroazadirachtol-1,3-acetonide (22). To a solution of 23-α,β-acetoxyazadirachtol **(21)** (24 mg, 38.3 μmol) and a catalytic amount of pyridinium *para* -toluenesulphonate in dry dichloromethane (2 ml) at r.t. under argon was added excess 2-methoxypropene (100 μl, 1.04 mmol), with stirring. After 3 h. at r.t. shielded from light, solvent and excess reagent were removed *in vacuo* . The residue contained 23-acetoxyazadirachtol 1,3-acetonide as a 2:1 mixture at C-23 which could be separated by careful column chromatography (60% ethyl acetate-petrol) to give 23-α-acetoxy-22,23-dihydroazadirachtol 1,3-acetonide (16 mg, 62%) as a colourless glass, (R_f 0.29, ethyl acetate); $[\alpha]_D^{20}$ = +4° (c=0.37 ($CHCl_3$)); ν_{max} (film) 3200, 1735, 1193 and 1093 cm^{-1}; δ(500 MHz) 1.38 (3H, s, acetonide Me), 1.41 (1H, d, J 4 Hz, H-2), 1.43 (3H, s, acetonide Me), 1.54 (1H, d, J 13 Hz, H-16), 1.61 (3H, s, H-30), 1.67 (1H, dt, J 13, 5 Hz, H-16), 2.06 (3H, s, H-18), 2.07 (3H, s, C3-OAc), 2.31 (1H, d, J 15 Hz, H-22), 2.40 (1H, d, J 5 Hz, H-17), 2.41 (1H, dd, J 13, 6 Hz, H-22), 2.76 (1H, dt, J 16, 5 Hz, H-2), 2.81 (1H, s, OH), 3.23 (1H, d, J 13 Hz, H-5), 3.26 (1H, s, H-9), 3.48 (1H, d, J 11 Hz, H-19), 3.73 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 3.87 (1H, d, J 5 Hz, H-15), 3.98 (1H, d, J 9 Hz, H-28), 4.02 (1H, d, J 9 Hz, H-28), 4.10 (1H, s, OH), 4.21 (1H, d, J 11 Hz, H-19), 4.45 (1H, dd, J 13, 3 Hz, H-6), 4.46 (1H, s, H-11), 4.55 (1H, d, J 5 Hz, H-1), 4.62 (1H, d, J 4 Hz, H-3), 4.72 (1H, d, J 3 Hz, H-7), 5.53 (1H, s, H-21) and 6.35 (1H, d, J 5 Hz, H-23); *m/z* 698 (M^++NH_3); and 23β-acetoxy-22,23-dihydroazadirachtol 1,3-acetonide (8 mg, 31%) as a colourless glass, (R_f 0.25, ethyl acetate); $[\alpha]_D^{20}$ = -15° (c=0.36 ($CHCl_3$)); ν_{max} (film) 3442, 2951, 1732, 1195, and 1093 cm^{-1}; 1.39 (3H, s, acetonide Me), 1.40 (1H, d, J 14 Hz, H-16), 1.44 (3H, s, acetonide Me), 1.60 (3H, s, H-30), 1.55-1.62 (1H, m, H-16), 1.72-1.80 (1H, m, H-2), 2.07 (3H, s, H-18), 2.08 (3H, s, OAc), 2.31 (1H, dd, J 15, 2 Hz, H-22), 2.51 (1H, d, J 5 Hz, H-17), 2.56 (1H, dd, J 15, 7 Hz, H-22), 2.63 (1H, s, OH), 2.75 (1H, dt, J 16, 5 Hz, H-2), 2.95 (1H, s, OH), 3.24 (1H, s, H-9), 3.25 (1H, d, J 13 Hz, H-5), 3.56 (1H, d, J 10 Hz, H-19), 3.73 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 3.84 (1H, d, J 5 Hz, H-15), 3.97 (1H, d, J 9 Hz, H-28), 4.01 (1H, d, J 9 Hz, H-28), 4.21 (1H, d, J 10 Hz, H-19), 4.43 (1H, dd, J 13, 3 Hz, H-6), 4.48 (1H, s, H-11), 4.55 (1H, d, J 5 Hz, H-1), 4.60 (1H, d, J 3 Hz, H-7), 4.63 (1H, d, J 3 Hz, H-3), 5.65 (1H, s, H-21) and 6.41 (1H, dd, J 7, 3 Hz, H-23); *m/z* 698 (M^++NH3); (found: (M^++NH_3) 698.3039. $C_{33}H_{48}O_{15}N$ requires 698.3054).

Preparation of 22,23-dihydroazadirachtol 1,3-acetonide (23). A solution of 22,23-dihydroazadirachtol **(19)** (17 mg, 29.2 μmol) and (*dl*)-camphorsulphonic acid (three crystals) in 2,2-dimethoxy propane (2 ml) was heated under reflux for 2 h. After allowing to cool and concentrating *in vacuo* the mixture was filtered through celite, rinsing the pad with dichloromethane. Evaporation of the solvent followed by chromatography of the residue (80% to 100% ethyl acetate-petrol) gave **(23)** (3 mg, 18%) as a colourless oil, (R_f 0.35, ethyl acetate); $[\alpha]_D^{20}$ = -10° (c= 0.22 ($CHCl_3$)); ν_{max} (film) 3441, 2949, 1733, 1193, 1140, 1123, 1093 and 1037 cm^{-1}; δ(500 MHz) 1.39 (3H, s, acetonide Me), 1.41 (1H, d, J 10 Hz, H-16b), 1.44 (3H, s, acetonide Me), 1.57 (1H, d, J 16.2 Hz, H-2), 1.59 (3H, s, H-30), 1.63-1.70 (1H, m, H-16a), 2.07 (3H, s, H-18), 1.99-2.18 (2H, m, H-22), 2.44 (1H, d, J 4.6 Hz, H-17), 2.73 (1H, s, OH), 2.75 (1H, dt, J 16.2, 4.6 Hz, H-2), 3.25 (1H, d, J 12.5 Hz, H-5), 3.27 (1H, s, H-9), 3.44 (1H, s, OH), 3.57 (1H, d, J 11.2 Hz, H-19), 3.73 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 3.81-3.89 (2H, m, H-23 and H-1), 3.98 (1H, d, J 8.3 Hz, H-28), 3.98-4.03 (1H, m, H-23), 4.01 (1H, d, J 8.3 Hz, H-28), 4.21 (1H, d, J 11.2 Hz, H-19), 4.46 (1H, dd, J 12.5, 3.7 Hz, H-6), 4.48 (1H, s, H-11), 4.56 (1H, d, J 4.2 Hz, H-15), 4.60 (1H, d, J 3.8 Hz, H-3), 4.71 (1H, d, J 3.7 Hz, H-7) and 5.22 (1H, s, H-21); m/z 623 (M^+), 604, 586, 561, 519, 503; (found:(M^+), 622.2630. $C_{31}H_{42}O_{13}$ requires 622.2626).

Preparation of azadirachtol 1,3-acetonide (24). Azadirachtol **(20)** (86 mg, 0.148 mmol) and pyridinium *para* -toluene sulphonate (2 mg, 7.4 μmol, 0.05 eq.) were dissolved in

dichloromethane under argon at r.t. and 2-methoxy propene (35 µl, 0.37 mmol, 2.5 equiv.) added dropwise. The mixture was stirred for 3 h. at r.t. in a flask shielded from light. Evaporation of the solvent and excess reagent followed by column chromatography of the residue (60% ethyl acetate-petrol) gave **(24)** (47 mg, 51%) as a white foam, (R_f 0.45, ethyl acetate); ν_{max} (film) 3437, 2950, 1733, 1194, 1141, 969, 921 and 737 cm^{-1}; δ(500 MHz) 1.31 (1H, d, J 13 Hz, H-16b), 1.40 (3H, s, acetonide Me), 1.43 (3H, s, acetonide Me), 1.66-1.71 (1H, m, H-16a), 2.06 (3H, s, H-18), 2.35 (1H, d, J 5 Hz, H-17), 2.74 (1H, dt, J 15.6, 4.9 Hz, H-2), 2.99 (1H, s, OH), 3.27 (1H, s, H-9), 3.30 (1H, d, J 12.7 Hz, H-5), 3.47 (1H, s, OH), 3.57 (1H, d, J 10.2 Hz, H-19), 3.73 (3H, s, CO_2Me), 3.75 (3H, s, CO_2Me), 3.85 (1H, d, J 7.0 Hz, H-1), 3.96 (1H, d, J 8.4 Hz, H-28), 4.00 (1H, d, J 8.4 Hz, H-28), 4.20 (1H, d, J 10.2 Hz, H-19), 4.45 (1H, dd, J 12.7, 3.1 Hz, H-6), 4.47 (1H, s, H-11), 4.55 (1H, d, J 4.6 Hz, H-15), 4.58 (1H, d, J 3.6 Hz, H-3), 4.70 (1H, d, J 3.1 Hz, H-7), 5.02 (1H, d, J 2.9 Hz, H-22), 5.68 (1H, s, H-21) and 6.41 (1H, d, J 2.9 Hz, H-23); *m/z* 621 (M^+), 603 (M^+-H_2O), 585, 563, 545; (found: (M^+), 621.2547. $C_{31}H_{40}O_{13}$ requires 621.2547).

Preparation of 1,3,20-tri-*O*-acetylazadirachtol (25). To a solution of azadirachtol **(20)** (10.8 mg, 18.7 µmol) and a catalytic amount of 4-dimethylaminopyridine in dry dichloromethane (0.5 ml) at r.t. under argon, was added triethylamine (39 µl, 0.28 mmol, 15 eq.) followed by acetic anhydride (17.6 µl, 0.187 mmol, 10 eq.) with stirring. After stirring for 2 days at r.t. saturated aqueous sodium hydrogen carbonate solution was added. The aqueous layer was extracted twice with dichloromethane and the combined organic layers dried ($MgSO_4$). Removal of the drying agent followed by evaporation of solvent and column chromatography (75% ethyl acetate-petrol) gave 1, 3, 20-tri-O-acetylazadirachtol **(25)** (12.5 mg, 95%) as a white foam, (R_f 0.47, ethyl acetate); $[\alpha]_D^{20}$ = -75° (c=0.57 ($CHCl_3$)); ν_{max} (film) 3436, 2954, 1738, 1369, 1252, 1164 and 1043 cm^{-1}; δ(500 MHz) 1.23 (1H, d, J 13 Hz, H-16b), 1.39 (3H, s, H-30), 1.73 (1H, ddd, J 13.1, 6.0, 3.5 Hz, H-16a), 1.98 (3H, s, H-18), 2.02 (3H, s, OAc), 2.04 (3H, s, OAc), 2.08 (3H, s, OAc), 2.23 (1H, dt, J 16.9, 3.3 Hz, H-2), 2.38 (1H, dt, J 16.9, 2.5 Hz, H-2), 3.23 (1H, d, J 6 Hz, H-17), 3.28 (1H, s, H-9), 3.32 (1H, d, J 12.4 Hz, H-5), 3.62 (1H, d, J 9.6 Hz, H-19), 3.68 (3H, s, CO_2Me), 3.73 (1H, d, J 8.8 Hz, H-28), 3.78 (3H, s, CO_2Me), 3.86 (1H, d, J 9.6 Hz, H-19), 4.08 (1H, d, J 8.8 Hz, H-28), 4.48 (1H, dd, J 12.5, 2.6 Hz, H-6), 4.51 (1H, t, J 2.8 Hz, H-1), 4.58 (2H, br s, H-11 and H-15), 4.73 (1H, br d, J 1.7 Hz, H-7), 5.49 (1H, t, J 2.8 Hz, H-3), 5.63 (1H, d, J 2.8 Hz, H-22), 5.98 (1H, s, H-21) and 6.50 (1H, d, J 2.8 Hz, H-23); *m/z* 646 (M^+-AcOH), 629 (M^+-AcOH-H_2O), 587, 557; (found: (M^+-AcOH-H_2O), 628.2148. $C_{32}H_{36}O_{13}$ requires 628.2156).

Preparation of 3-tigloyl-1,7,20-tris-*O*-(trimethylsilyl)azadirachtol (26). To a solution of 3-tigloylazadirachtol **(6)** (40 mg, 61.8 µmol) in dry dichloromethane (1 ml) at r.t. under argon was added triethylamine (186 µl, 1.3 mmol, 15 eq.) followed by trimethylsilyltriflate (120 µl, 0.63 mmol, 7 eq.) dropwise with stirring. The reaction occurred immediately. Evaporation of solvent and reagents followed by chromatography (gradient elution 10% to 30% ethyl acetate-petrol) gave **(26)** (29 mg, 53%) as a colourless oil, (R_f 0.28, 30% ethyl acetate); $[\alpha]_D^{20}$ = -44° (c=0.13 ($CHCl_3$)); ν_{max} (film) 2953, 1760, 1725, 1710, 1655, 1613, 1434, 1250, 1139, 1097, 882, and 841 cm^{-1}; δ(500 MHz) 0.09 (9H, s, Me_3Si), 0.11 (9H, s, Me_3Si), 0.12 (9H, s, Me_3Si), 0.99 (3H, s, H-30), 1.19 (1H, d, J 13 Hz, H-16b), 1.70-1.80 (1H, m, H-16a), 1.76 (3H, s, H-18), 1.77 (3H, dd, J 7, 1 Hz, H-4'), 1.83 (3H, d, J 1 Hz, H-5'), 2.04 (1H, dt, J 17, 1 Hz, H-2), 2.18 (1H, d, J 7 Hz, H-17), 2.41 (1H, dt, J 17, 3 Hz, H-2), 3.58 (1H, d, J 13 Hz, H-5), 3.62 (1H, d, J 9 Hz, H-28), 3.70 (1H, d, J 10 Hz, H-19), 3.73 (3H, s, CO_2Me), 3.75 (1H, d, J 10 Hz, H-19), 3.76 (3H, s, CO_2Me), 3.92 (1H, d, J 9 Hz, H-28), 4.20 (1H, br s, H-15), 4.26 (1H, br s, H-1), 4.28 (1H, dd, J 13, 2 Hz, H-6), 4.40 (1H, br s, H-7), 4.72 (1H, br s, H-11), 4.96 (1H, d, J 4 Hz, H-22), 5.44 (1H, s, H-21), 5.53 (1H, m, H-3),

6.38 (1H, d, J 4 Hz, H-23) and 6.98 (1H, br q, J 7 Hz, H-3'); *m/z* 878 (M^+), 863 (M^+-Me), 705, 623, 223, 213, 196, 157, 95; (found: (M^+), 878.3745. $C_{42}H_{66}O_{14}Si_3$ requires 878.3745).

Preparation of deacetyldetigloylsalannin (28). A stirred solution of salannin **(27)** (360 mg, 0.60 mmol) in methanol (18 ml) was treated with Triton B (2.16 ml of a 40% solution in methanol) and stirred at r.t. for three days. The methanol was removed *in vacuo* and the residue added to saturated ammonium chloride solution (20 ml) and extracted with ethyl acetate (4x20 ml). The combined organic extracts were washed with brine (2x10 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil which was purified by column chromatography (50% ethyl acetate-dichloromethane followed by 75% ethyl acetate-dichloromethane) to give deacetyldetigloylsalannin (161.9 mg, 57%) as a white solid, m.p. 195-197 °C (lit.[13] 201-205 °C); $[\alpha]_D^{20}$= + 150°, (c=0.5, (dichloromethane)) (lit.[13] $[\alpha]_D^{20}$= +135 ° (c=1.13)); ν_{max} (film) 3394, 2930 and 1734 cm^{-1}; δ(500 MHz) 0.90 (3H, s, H-19), 1.11 (3H, s, H-29), 1.27 (3H, s, H-30), 1.73 (3H, d, J 1.7 Hz, H-18), 2.11 (2H, br s, 2xH-2), 2.15 (1H, dd, J 12.0, 8.4 Hz, H-16), 2.24 (1H, dd, J 12.0, 6.5 Hz, H-16), 2.34 (1H, dd, J 16.8, 3.9 Hz, H-11), 2.46 (1H, dd, J 16.8, 6.8 Hz, H-11), 2.53 (1H, dd, J 6.7, 3.9 Hz, H-9), 2.71 (1H, d, J 12.6 Hz, H-5), 3.55 (1H, dd, J 5.7, 2.9 Hz, H-3), 3.59 (4H, m, CO_2Me and H-28), 3.66 (1H, d, J 8.7 Hz, H-17), 3.83 (1H, dt, J 8.9, 2.8 Hz, H-1), 3.98-4.01 (2H, m, H-6 and C1-OH), 4.11 (1H, d, J 7.2 Hz, H-28), 4.26 (1H, d, J 3.4 Hz, H-7), 4.54 (1H, d, J 3.5 Hz, C3-OH), 5.46 (1H, m, H-15), 6.14 (1H, s, H-22), 7.14 (1H, s, H-21) and 7.32 (1H, t, J 1.7 Hz, H-23); *m/z* 472 (M^+); (found: C, 68.46; H, 7.69. $C_{27}H_{36}O_7$ requires C, 68.62; H, 7.68%).

Preparation of 1-*O*-acetyldeacetyldetigloylsalannin (29). A stirred solution of deacetyldetigloylsalannin **(28)** (20 mg, 42.33 μmol) and 4-N, N-dimethylaminopyridine (1 mg) in dichloromethane (1 ml) and pyridine (0.5 ml) was treated with acetyl chloride (3.4 μl, 47.82 μmol, 1.1 eq.). The reaction mixture was partitioned between 1N hydrochloric acid (5 ml) and dichloromethane (20 ml), the organic layer was removed and washed with saturated aqueous sodium bicarbonate solution (5 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil which was purified by column chromatography (25% ethyl acetate-dichloromethane) to give **(29)** (18.1 mg, 83%) as a white solid, m.p. 141-144 °C; $[\alpha]_D^{20}$= +126.7 ° (c=0.52 (dichloromethane)); ν_{max} (film) 3482, 2927, 1733 and 1587 cm^{-1}; δ(500 MHz) 0.92 (3H, s, H-19), 1.19 (3H, s, H-29), 1.27 (3H, s, H-30), 1.71 (3H, s, H-18), 2.09 (3H, s, OAc), 2.02-2.26 (4H, m, 2xH-16 and 2xH-2), 2.32 (1H, dd, J 15.2, 5.7 Hz, H-11), 2.41 (1H, dd, J 15.0, 6.1 Hz, H-11), 2.58 (1H, d, J 12.5 Hz, H-5), 2.73 (1H, t, J 5.9 Hz, H-9), 2.93 (1H, d, J 7.5 Hz, OH), 3.51 (3H, s, CO_2Me), 3.54-3.60 (3H, m, 2xH-28 and H-3), 3.66 (1H, d, J 8.4 Hz, H-17), 3.98 (1H, dd, J 3.4 Hz, H-6), 4.20 (1H, d, J 3.3 Hz and H-7), 5.03 (1H, t, J 2.8 Hz, H-1), 5.54 (1H, br t, J 7.0 Hz, H-15), 6.32 (1H, s, H-22), 7.25 (1H, s, H-21) and 7.32 (1H, s, H-23); *m/z* 514 (M^+); (found: (M^+), 514.2565. $C_{29}H_{38}O_8$ requires (M^+), 514.2567).

Preparation of (30). A stirred solution of salannin **(27)** (200 mg, 0.34 mmol) and sodium iodide (100 mg, 0.67 mmol) in acetonitrile (10 ml) was treated with chlorotrimethyl silane (85 μl, 0.67 mmol) and stirred at r.t. for 5 min. Saturated aqueous sodium thiosulphate solution (1 ml) was added and the mixture stirred for 10 min. Following removal of the organic solvent *in vacuo* the aqueous residue was extracted with diethyl ether (3x10 ml). The combined ethereal extracts were washed with brine (5 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil which was purified by column chromatography (50% diethyl ether-petrol) to give **(30)** (78.6 mg, 39%) as white needles, m.p. 168-170 °C (dichloromethane-petrol); ν_{max} (film) 2950, 1734, 1703 and 1648 cm^{-1}; δ(500 MHz) 0.93 (3H, s, H-19), 1.03 (3H, s, H-30), 1.20 (3H, s, H-29), 1.60 (3H, s, H-18), 1.83 (3H, d, J 7.1 Hz, $C\underline{H}_3CH{=}CCH_3CO_2R$), 1.94 (3H, s, $CH_3CH{=}CC\underline{H}_3CO_2R$), 1.98 (3H, s, OAc), 2.14 (1H, dd, J 14.8, 5.6 Hz, H-11), 2.19-2.21 (2H, m, 2xH-2), 2.28 (1H, dd, J 14.8, 6.3 Hz,

H-11), 2.32-2.35 (1H, m, H-14), 2.37-2.39 (2H, m, 2xH-13), 2.57 (1H, t, J 5.9 Hz, H-9), 2.91 (1H, d, J 12.7 Hz, H-5), 3.55 (4H, m, CO_2Me and H-28), 3.63 (1H, t, J 7.4 Hz, H-28), 3.71 (1H, d, J 3.4 Hz, H-7), 3.95 (1H, dd, J 12.6, 3.5 Hz, H-6), 4.68 (1H, t, J 2.8 Hz, H-3), 4.96 (1H, t, J 2.9 Hz, H-1), 5.82 (1H, t, J 2.4 Hz, H-17), 6.51 (1H, t, J 1.7 Hz, H-22), 7.02 (1H, qd, J 7.1, 1.3 Hz, $CH_3C\underline{H}$=CCH_3CO_2R), 7.35 (1H, t, J 1.6 Hz, H-21) and 7.77 (1H, s, H-23); *m/z* 596 (M^+); (found: C, 68.46; H, 7.49. $C_{34}H_{44}O_9$ requires C, 68.43; H, 7.43%).

Preparation of (31). A stirred solution of the diol **(28)** (45 mg, 95.24 μmol) in benzene (7 ml) was treated with benzaldehyde (1 ml) and pyridinium *para*-toluenesulphonate (5 mg) and heated under reflux under Dean and Stark conditions for 0.5 h. The reaction mixture was allowed to cool to r.t. and partitioned between saturated aqueous sodium bicarbonate solution (10 ml) and diethyl ether (50 ml). The ethereal solution was removed and the aqueous layer extracted with diethyl ether (3x10 ml). The combined ethereal extracts were washed with brine (2x20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil which was purified by column chromatography (74% diethyl ether-petrol) to give **(31)** (33.1 mg, 62%) as a white solid, m.p. 88-89 °C; $[\alpha]_D^{20}$= +244.1 ° (c=0.49 (dichloromethane)); ν max (film) 2924, 2884 and 1724 cm^{-1}; δ(500 MHz) 1.00 (3H, s, H-19), 1.15 (3H, s, H-29), 1.27 (3H, s, H-30), 1.71 (3H, d, J 1.6 Hz, H-18), 2.04 (1H, d, J 15.6 Hz, H-2), 2.16-2.26 (3H, m, 2xH-16 and H-11), 2.36 (1H, dd, J 13.8, 8.1 Hz, H-11), 2.70 (1H, dt, J 15.7, 4.7 Hz, H-2), 2.89 (1H, dd, J 8.0, 4.0 Hz, H-9), 3.13 (3H, s, CO_2Me), 3.25 (1H, d, J 12.9 Hz, H-5), 3.54 (1H, d, J 7.0 Hz, H-28), 3.67 (1H, d, J 8.1 Hz, H-17), 3.99 (2H, m, H-6 and H-28), 4.05 (1H, d, J 4.4 Hz, H-3), 4.28 (1H, d, J 3.4 Hz, H-7), 4.32 (1H, d, J 4.6 Hz, H-1), 5.50 (1H, dd, J 8.1, 6.5 Hz, H-15), 6.15 (1H, s, PhCH), 6.22 (1H, d, J 1.0 Hz, H-22), 7.21 (1H, s, H-21), 7.28 (1H, t, J 1.6 Hz, H-23), 7.32 (3H, t, J 3.1 Hz, m and p arom.) and 7.59-7.61 (2H, m, o arom.); *m/z* 560 (M^+); (found: C, 72.61; H, 7.34. $C_{34}H_{40}O_7$ requires C, 72.83; H, 7.19%).

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