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CHEMISTRY OF INSECT ANTIFEEDANTS FROM *AZADIRACHTA INDICA* (PART 11)[1]: CHARACTERISATION AND STRUCTURE ACTIVITY RELATIONSHIPS OF SOME NOVEL REARRANGED AZADIRACHTINS.

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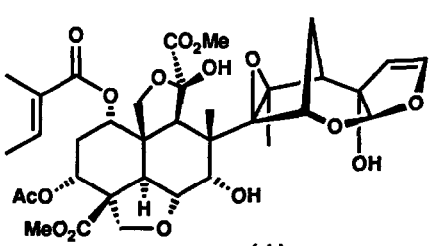
Summary Several novel rearrangement reactions of the natural product azadirachtin and related derivatives have been characterised using a combination of x-ray crystallographic and high field nmr techniques The insect antifeedant properties of these and a number of C7 modified compounds have been investigated

During a systematic programme designed to probe the structure-activity relationships of the potent insect antifeedant and growth disrupting agent azadirachtin (**1**), we[2,3] and others[4,5] have reported upon simple functional group changes and their resultant effects on biological activity In further studies, initiated by our desire to construct a concise relay sequence to enrich supplies of advanced synthetic intermediates, we have noted more extensive skeletal changes. We have also shown that simple structural fragments of the natural product can display antifeedant activity against some species of insect [6] Furthermore, during our synthetic studies, we have defined strategies for the preparation of key units of these interesting molecules [1,7,8]



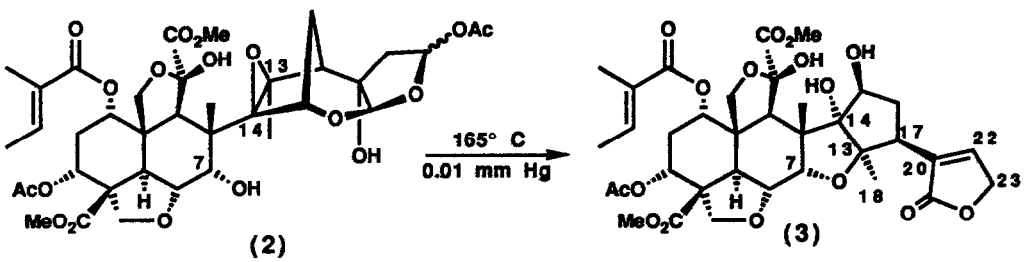
(1)

The aim of this work is to provide new environmentally safe, behaviour modifying compounds which may be used in integrated pest control programmes This will encompass compounds that will aid our understanding of host-plant selection and feeding mechanisms of insects. The complex structures presented are amongst the first examples of highly rearranged limonoids from the azadirachtin series to be evaluated as antifeedants. The biological characterisation of these molecules has provided us with new compounds (*vide infra*) which are more stable than the parent azadirachtin (**1**) and yet retain full biological activity This observation could be important in the future commercialisation of these materials Moreover, the reported rearranged compounds give new insight into the structure-activity relationships of these important molecules Eventually these studies will be directed towards the design and synthesis of smaller molecules capable of mimicking the activity of their more complex natural counterparts

Here we describe some novel rearrangement reactions of the azadirachtin skeleton which have provided a diverse array of new compounds for screening and also assisted in the formulation of synthetic pathways Additionally, we will discuss modifications centred on the C7 hydroxyl group, including the first examples of oxidation at this position.[9] It is our belief that the correct disposition of hydroxyl functionality at this site is essential for biological activity

We had previously shown that the azadirachtin-acetic acid adduct (**2**) could be thermolysed to recover near quantitative yields of (**1**) [2a] We now find that on a larger scale this reaction also affords a new compound (**3**), isolated in 17% yield, along with (**1**) as the major product (22%) (Scheme 1) The structure of (**3**), which follows from its spectral properties, requires an involved rearrangement of the right hand portion of the molecule

Scheme 1.



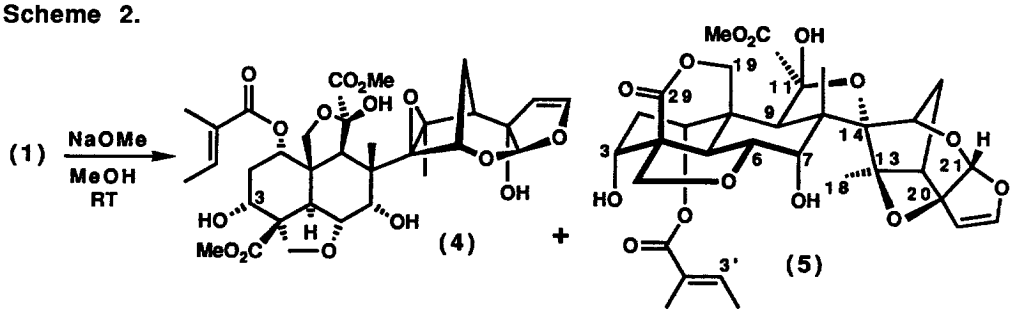
(**2**) (**3**) + (**1**)

This new compound (**3**) has some structural similarities to that which we obtained on Lewis acid catalysed rearrangement of salannin [2b] The C-ring tetrahydrofuran, formed *via* C7-OH ring opening of the C13-C14 epoxide, is identical to that found in the azadirachtinins.[9,10] In the ^{13}C nmr spectrum of (**3**) the original C13 and C14 quaternary epoxide carbons and the C18-methyl resonances were shifted upfield with respect to the starting material (see experimental section), indicating epoxide opening. The butenolide function could be identified by its characteristic double bond carbon resonances (δ148 5 and δ132 2) and by the presence of one olefinic resonance in the ^{1}H nmr spectrum (δ7 32) This olefinic proton was shown to be attached to the more upfield carbon (δ132 2) by a ^{13}C-^{1}H heteroatom correlation spectrum This, and the nOe enhancement of +2 4% observed between H-22 and H-23 indicates that the butenolide is attached to the D ring by a C17-C20 bond A small coupling exists between H-22 and H-17 In selective one dimensional decoupling experiments

irradiation of H-17 (δ3.21, 1H, br d, J 7 6 Hz) sharpened the broad resonance of H-22, confirming this coupling The assignment of the geminal H-16 resonances (δ2 31, 1H, dd, J 15 0, 3.2 Hz and δ2 07, 1H, dd, J 15 6, 8 0 Hz) also follows from the irradiation of H-17 due to the sharpening of the signal at δ2 31 and the collapse of the signal at δ2 07 to a doublet (J 15.6 Hz) Extensive nOe experiments, a high resolution accurate mass measurement and elemental analysis were all consistent with this assignment.

During the hydrolysis of azadirachtin (1) with sodium methoxide in methanol to give the expected product (4) (64%)[4,9a] we also noticed the formation of a second product, isolated in 10% yield, which was later characterised as (5) (Scheme 2) Once again extensive rearrangement had occurred in the right hand portion giving a novel oxetane *via* base-catalysed opening of the epoxide at C13 by the angular C20-hydroxyl group The resulting C14-oxygen then adds to the C11 position, while the liberated C19-hydroxyl group undergoes lactonisation at the C29-ester group. The C3-acetate is lost by the normal hydrolysis process

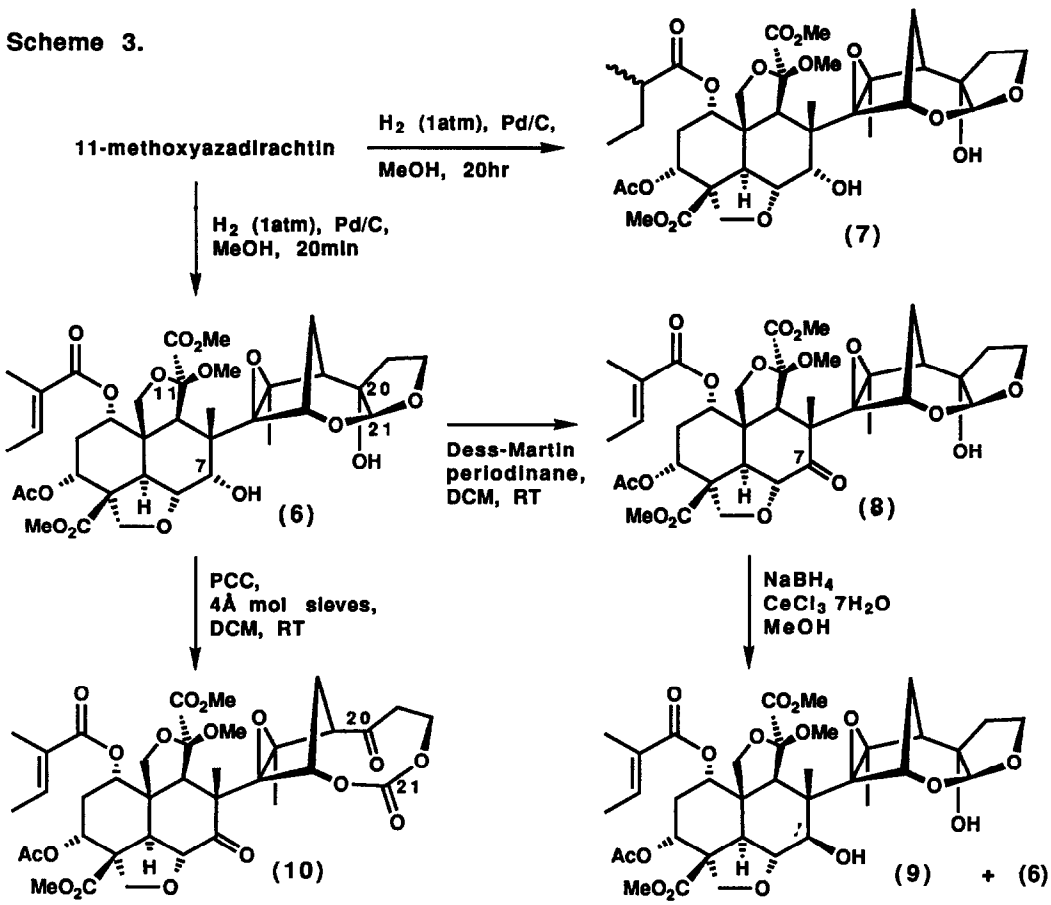
Scheme 2.



Unambiguous characterisation was difficult because of the reluctance of (5) and some of its derivatives[12] to produce suitable crystals for single crystal x-ray diffraction The structure follows from detailed spectroscopic analysis Fortunately, most of the resonances in the ^{1}H nmr spectrum of (5) were distinct They possessed slightly different chemical shifts, but comparable and characteristic coupling constants common to many other azadirachtins The most striking difference in the nmr spectrum of (5) compared to that of 3-desacetylazadirachtin (4) was the loss of a methyl ester resonance From extensive nOe experiments, irradiation of the single methyl ester resonance (δ3 65, 3H, s) gave an enhancement of the H-3' tigloyl proton (δ7 08, 1H, qq, J 7 1, 1 5 Hz, +1 3%) and the C18-methyl (δ1 65, 3H, s, +0 5%) Formation of the δ-lactone between C19 and C29 accounted for the loss of the C29-methyl ester signal and the observed n O e enhancements The ^{1}H nmr spectrum was complicated by fine couplings to some of the signals From a comparison with known data, H-9 normally appeared as a singlet instead of the observed doublet (δ3 54, 1H, J 1 7 Hz) and H-6 as a double doublet instead of the apparent double triplet (δ4 22, 1H, J 11 9, 1.3 Hz) that was recorded A deuterium oxide exchange experiment removed these extra fine couplings to give the expected multiplicities. Under the deuterium exchange conditions three signals, δ4 66 (1H, dd, J 4 0, 1 0 Hz), δ4 61 (1H, d, J 1 8 Hz) and δ2 14 (1H, d, J 8 8 Hz) disappeared from the spectrum indicating the presence of three hydroxyl groups Selected decoupling experiments showed that H-9 possessed a long range coupling to the hydroxyl group at δ4 61 assigned to C11 and H-6 also had a four-bond coupling to the hydroxyl group at δ4 66 assigned to C7 The latter hydroxyl resonance was also coupled to H-7 (J 3 9 Hz) The third and final hydroxyl resonance at δ2 14 was assigned to C3 from comparison with (4) From these experiments it was

evident that the hydroxyl group at C20 had disappeared The ^{13}C nmr revealed the disappearence of the characteristic epoxide resonances of C13 and C14 The opening of the epoxide was also apparent from the upfield shift of the C18-methyl [δ2 01 in (1) to δ1 65 in (5)], a characteristic of the azadirachtinin skeleton [10,11] The spectral data is consistent with the formation of an oxetane ring through the opening of the epoxide function at C13 by the C20-hydroxyl group. This is further supported by the observed nOe enhancement of H-7 (δ4 45, 1H, dd, J 3.9, 2 7 Hz, +5 0%) upon irradiation of H-21 (δ5 56, 1H, s) and by other chemical experiments on related derivatives [13] High resolution accurate mass measurement and elemental analysis were both consistent with this assignment.

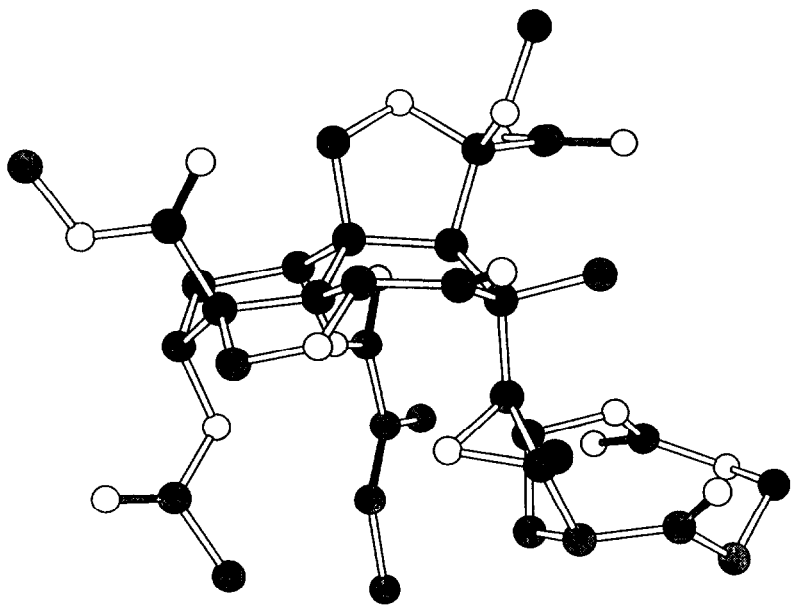
Scheme 3.



For other studies, we were interested in oxidation products of the hindered C7-hydroxyl group At first the oxidation of this secondary hydroxyl group appeared trivial Unfortunately, due to strong hydrogen bonds between the C7 and C20-hydroxyl groups and the C11-hydroxyl group and the C13-C14-epoxide, the right hand portion of azadirachtin effectively shields the C7 position After much experimentation it became clear that efficient oxidation was only possible following C11-OH protection This was selectively and efficiently achieved by reacting azadirachtin with methyl iodide in the presence of silver (I) oxide at 43°C for 4h to give

11-methoxyazadirachtin[4] in 86% yield,[7c] accompanied by some 11,20-dimethoxyazadirachtin. 11-Methoxyazadirachtin could be selectively hydrogenated in methanol over Pd/C to give (**6**) in 82% yield (Scheme 3).[14] Hydrogenation for longer periods gave a 93% yield of 11-methoxy-2',3',22,23-tetrahydroazadirachtin (**7**). Compound (**6**) can be oxidised to the C7-ketone derivative (**8**) in 86% yield using Dess-Martin periodinane[15] (Scheme 3) It was rationalised that methylation of the C11 hydroxyl group effectively removed one of the hydrogen bonds which resulted in an increased availability of a more reactive conformer where the right hand side lay away from C7. Reduction of (**8**) with the Luche reagent[16] regenerated (**6**) (44 %) and also provided the C7 epimeric alcohol (**9**) (34 %), an important compound for our structure-activity profile The ^{1}H nmr spectrum of (**9**) showed significant broadening of a number of resonances due to restricted rotation. This fluctional behaviour augments our ideas concerning the importance of specific hydrogen bonds in determining the conformation of azadirachtin.

Figure 1.



Prolonged treatment of (**6**) with pyridinium chlorochromate[17] (PCC) in the presence of 4Å molecular sieves in anhydrous dichloromethane gave the novel diketocarbonate (**10**) isolated in 72% yield (Scheme 3) This oxidatively cleaved product was also produced when pyridinium dichromate[18] (PDC) was used as oxidant The formation of (**10**) is probably due to chromate ester formation at the angular C20-hydroxyl group followed by C20-C21 cleavage assisted by the β-acetal moiety

The structure of (**10**) followed from ^{1}H and ^{13}C nmr experiments and unambiguously by single crystal x-ray diffraction analysis (Fig 1) The novel compound (**10**) can be further degraded by base mediated retro Aldol reaction to give key building blocks for our total synthesis studies [7c] The resultant decalin fragments from the cleavage reaction are suitable for additional modification to novel analogues to probe further the biological activity of these systems The diketocarbonate (**10**) therefore plays a pivotal role in our research programme

Owing to the problem of oxidative ring cleavage we also investigated oxidation reactions of 22,23-dihydro-11,20-dimethylazadirachtin (**11**) This compound was prepared in 72% yield from 11,20-dimethoxyazadirachtin by selective hydrogenation over Pd/C in methanol. Oxidation of (**11**) with PDC in dichloromethane smoothly afforded (**12**) in 91% yield Treatment of (**12**) with anhydrous methanol in the presence of an excess of Amberlyst 15 sulphonic acid ion exchange resin, at room temperature, for three days, led to the formation of a new rearranged product (**13**) in 59% yield (Scheme 4)

Scheme 4.

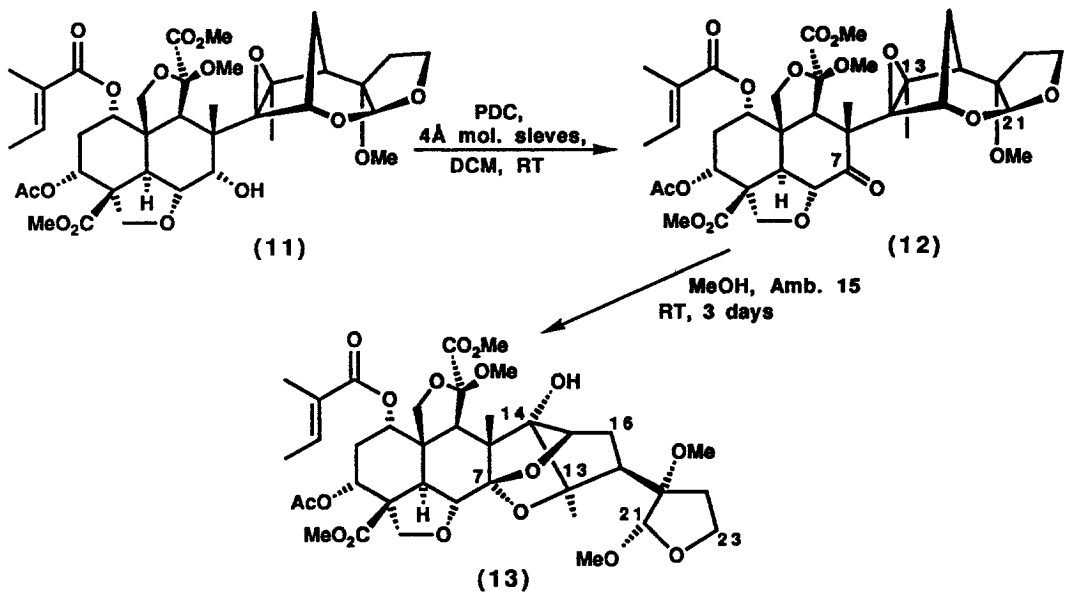
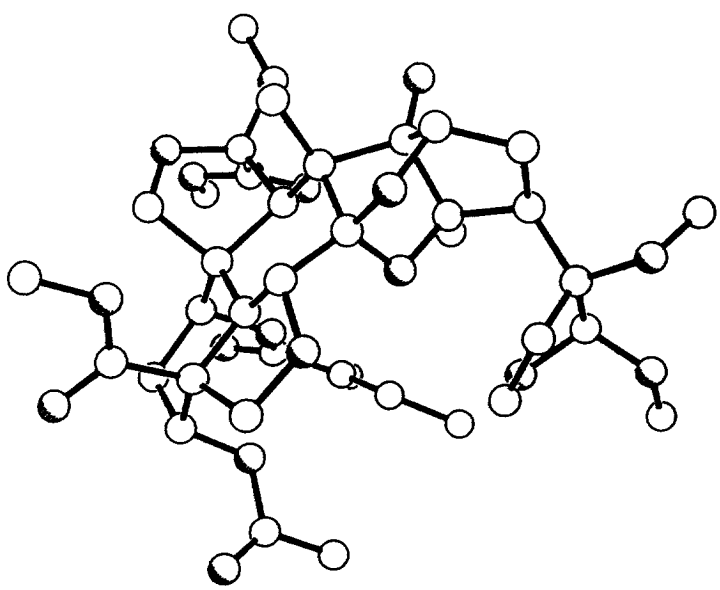


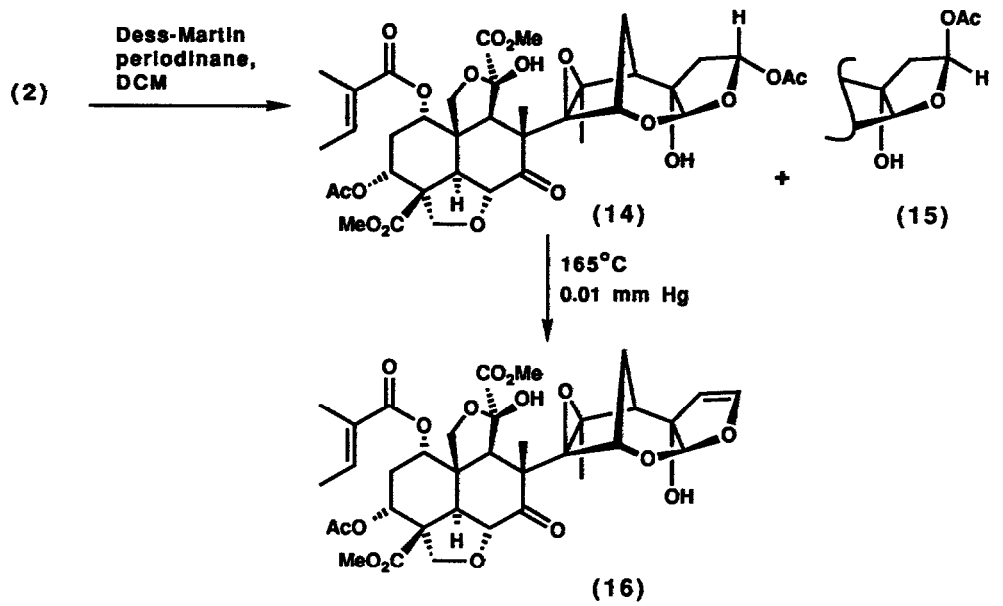
Figure 2.



Compound (13) arises by methanol opening of the C21-acetal followed by reacetalisation at the C7-carbonyl group, with the resultant C7-α-hemiacetal intermediate opening the epoxide ring at C13 The structure of (13) was again determined by single crystal x-ray diffraction analysis (Fig. 2)

Finally, encouraged by our earlier success in the use of Dess-Martin[15] periodinane as a mild and selective oxidant, we addressed the problem of obtaining 7-ketoazadirachtin, a vital compound for completion of our structure activity profile. Indeed, oxidation of the azadirachtin acetic acid adduct (2) with periodinane did provide the corresponding C7-ketones (14) and (15) Thermolysis of (15) then allowed isolation of 7-ketoazadirachtin (16) (Scheme 5) The initial oxidation step in this sequence has subsequently proved somewhat capricious, however (16) has been obtained in sufficient quantity to allow its characterisation and biological assesment.

Scheme 5.



With a collection of novel and highly rearranged azadirachtins in hand it was necessary to assess thier potential as insect antifeedants To date it is still unclear how much of the molecules activity is due to the left-hand decalin portion. These studies complement our analysis of the importance of the right-hand portion to azadirachtins potent biological activity [6]

Larvae of the African leafworm *Spodoptera littoralis* (Boisduval) were used to assess the antifeedant activity of the compounds in a choice bioassay. Larvae, 24-36hr into the final stadium, were placed individually in Petri dishes (8 5cm diam.) with two glass-fibre discs (Whatman GF/A, 2 1cm diam.) The discs were made palatable by the addition of a 100µl aliquot of 50mM sucrose and allowed to dry One disc acted as a control and the other was treated with 100µl of a solution containing the test compound at either 1ppm or 10ppm The dried discs were weighed before being presented to the larvae. The bioassay was terminated after the larvae had eaten approximately 50% of one of the discs, or after 24hr if larvae failed to eat 50% of either disc The discs

were reweighed and the Antifeedant Index calculated, where C and T represent the mass eaten of the control and treatment disc, respectively A potent antifeedant would be represented by a value greater than 75%

The table illustrates that compounds showing gross structural rearrangement of the hydroxydihydrofuran acetal portion of the molecule, for example, (**3**), (**5**), and (**13**), are less active than azadirachtin (**1**) Interestingly, the potency of compound (**3**) is comparable to that of a similar product isolated from the Lewis acid catalysed rearrangement of salannin. [2b] From the table one can see that methylation of the C11-hydroxy group and hydrogenation of the acid labile C22,23-enol ether moieties in (**6**) and (**7**) has no detrimental effect on activity The fact that methylation of the C11-hydroxy group is possible without reducing activity is important as the hemiacetal feature of the parent molecules causes them to be unstable However, further alkylation at C20, as in compound (**11**), results in a decrease in activity, especially at 1 ppm. This activity is further reduced when the C7-hydroxy group is oxidised as in compound (**12**) A comparison of the activity of (**6**) with (**8**) and (**1**) with (**16**) shows clearly that oxidation at C7 results in a decrease in activity Further support that the C7-hydroxy group may play a role in enhancing antifeedant activity can be obtained by comparing the potent activity of (**6**) with the significantly less active epimeric alcohol (**9**) However, the observation that the novel ring cleaved carbonate (**10**) has reasonable antifeedant activity shows that a hydroxy group at C7 is not essential for activity, nor apparently is the rigidity and specific substitution pattern associated with the hydroxyfuran acetal fragment essential for activity Overall, these results offer valuable insight into the complexities associated with the design of simpler alternative structures to the potent antifeedant azadirachtin

Table: Antifeedant Index [(C-T)/(C+T)]% of test compounds [mean ±(sem)]

	Concentration (ppm) applied to discs	
Compound[a]	10	1
1	100 (0 0)**	99 (1 1)**
3	64 (8 8)*	41 (15 2)*
5	16 (13 2)	22 (15 2)
6	100 (0 0)**	100 (0 0)**
7	100(0 0)**	98(1 6)**
8	100 (0 0)**	26 (14 0)
9	46(12 1)*	35(7 4)*
10	63 (12 8)*	61 (13 1)*
11	95 (2 3)**	66 (12 6)*
12	100 (0 0)**	29 (13 8)*
13	31 (10 8)*	33 (6 9) *
16	23(12 3)	21(6 0)

a = 15-20 replications

Significant activity, ** = P<0 01, * = P<0 05, Wilcoxon matched-pairs test, C versus T

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Experimental:

^1H 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 ^1H nmr assignments follows the natural product numbering system Coupling constants are measured in Hertz The nmr assignments follow the azadirachtin carbon skeleton numbering system

Preparation of (2a*R*, 3*R*, 5*S*, 5a*S*, 8*S*, 8a*R*, 8b*S*, 9*S*, 10*S*, 12*R*, 13*R*, 14a*R*, 14b*R*, 14c*R*) Dimethyl 3-acetoxy-12-(2,5-dihydro-2-oxo-3-furanyl)-5-(2-methylbut-2-enoyloxy)-8,9,10-trihydroxyhexadecahydro-9,13-methanodifuro[2",3",4":4,4a,5;3',4':1,8a]naphth[2,3-*b*]-oxocine-2a,8-dicarboxylate (3). A flask containing a thin, even film of 23-α,β-acetoxy-22,23-dihydroazadirachtin (2) (153mg, 0.196mmol) was heated rapidly to 165°C under vacuum (0 01mmHg pressure, mercury diffusion pump) for 50 min After cooling, the residue was purified by flash chromatography (gradient elution, 0-10% methanol/ethyl acetate) to give, in order of elution, azadirachtin (1) (31 4mg, 22%), and the rearranged compound (3) (23 8mg, 17%) as a colourless foam, $[\alpha]_D^{20}$=-45 5 (c=1 32, chloroform), υ_{max} (film) 3375, 2963, 1739, 1705, 1433, 1374, 1266, 1215, 1138, 1042, 978, 928 and 734 cm-1, ^1H δ ($CDCl_3$, natural prod numbering) 1 45 (3H, s, 18-CH_3), 1 60 (3H, s, 30-CH_3), 1 78 (3H, dd, J 7 1, 1 1, 4'-CH_3), 1 86 (3H, d, J 1 1, 5'-CH_3), 1 94 (3H, s, 3-OAc), 2 07 (1H, dd, J 15 6, 8 0, H-16), 2 13 (1H, dt, J 16 8, 3 3, H-2), 2 27-2 33 (2H, m, H-2 and H-16), 3 14 (1H, d, J 12 7, H-5), 3 21 (1H, d, J 7 6, H-17), 3 49 (1H, s, H-9), 3 67 (1H, d, J 9 9, H-19), 3 71 (3H, s, CO_2Me), 3 75 (3H, s, CO_2Me), 3 81 (1H, d, J 8 9, H-28), 3 95 (1H, d, J 3 4, H-7), 4 01 (1H, d, J 8 9, H-28), 4 17 (1H, d, J 3 8, H-15), 4 19 (1H, d, J 9 9, H-19), 4.38 (1H, dd, J 12 7, 3 4, H-6), 4 76 (1H, t, J 2 8, H-1), 4 84 (1H, dd, J 19 8, 1 3, H-23), 4 86 (1H, dt, J 19 8, 1 4, H-23), 4 90 (1H, s, OH), 5 47 (1H, t, J 3 0, H-3), 6 89 (1H, dq, J 1 5, 7 1, H-3') and 7 32 (1H, m, H-22), ^{13}C δ ($CDCl_3$) 12 1 (C5'), 14 1 (C4'), 18 0 (C30), 21 1 (C3-OCO*Me*), 24 3 (C18), 29 9 (C2), 31 3 (C16), 37 8 (C5), 48 5 (C9), 43 1, 49 6, 53 2 (C4, C8 and C10), 52 7, 52 8 (2xCO_2*Me*), 55 5 (C17), 60 0 (C3), 67 9 (C15), 69 7 (C1), 70 0 (C22), 70 4 (C19), 72 3 (C6), 72 5 (C-28), 83 1 (C7), 85 7, 86 8 (C13 and C14), 103 3 (C11), 128 9 (C2'), 132 2 (C20), 137 2 (C3'), 148 5 (C22), 166 3, 169 8, 171 2, 172 9, 173 3 (C1', C12, C21, C29, C3-O*C*OMe), m/z (FAB, thiodiethanol) 703 (MH^+-H_2O), 685 (MH^+-2H_2O), 643, 585, 551 and 523, Found (MH^+-H_2O) 703 2602 $C_{35}H_{43}O_{15}$ requires 703 2602, Found C, 58 55, H, 6 11 $C_{35}H_{44}O_{16}$ requires C, 58 33, H, 6 15%

Preparation of 3-Desacetylazadirachtin (4) and Methyl-(1*S*, 2*R*, 3*R*, 5*R*, 6*S*, 7*S*, 8*R*, 11*R*, 15*S*, 17*R*, 18*R*, 1'*S*, 5'*R*, 7'*S*, 9'*R*, 11'*S*)-3,7,17-trihydroxy-6,9'-dimethyl-15-[(2-methyl-1-oxo-2-butenyl)oxy]-12-oxospiro[[4,9,14]trioxapentacyclo[9.3.3.1^{1,8}.0^{2,4}.0^{11,15}] octadecane-5,8'[4,6,10]trioxatetracyclo[5.3.2.0^{1,5}.0^{9,11}]dodec-2'-ene]-3-carboxylate (5). A solution of sodium methoxide (67µl of a 3 26M solution in methanol, 0 218 mmol, 6.7 eq) in anhydrous methanol was added, *via* syringe, to a magnetically stirred solution of azadirachtin (1) (23 3 mg, 32 3 µmol) in anhydrous methanol (1 ml) at room temperature, under argon After 40 min the reaction was quenched by the addition of two small spatulas of solid ammonium chloride and then stirred until the evolution of ammonia had ceased (~2 hr) The mixture was then filtered over a small plug of celite, washed copiously with dichloromethane and evaporated The resultant white solid was then redissolved in dichloromethane and the heterogeneous mixture filtered through a small plug of glass wool Evaporation gave a yellow glass that was purified by flash chromatography (gradient elution 70-80% ethyl acetate/petrol) to give, in order of elution, the rearranged compound (5) (2 2 mg, 10%) as a clear glass; $[\alpha]_D^{20}$=-42.3 (c=1 10, chloroform), υ_{max} (film) 3437, 2926, 2855, 1733, 1650, 1585, 1440, 1377, 1265, 1197, 1152, 1120, 1080, 1045, 1018 and 945 cm^{-1}, ^{1}H δ 1 66 (1H, d, J 14 9, H-16b), 1.65 (3H, s, H-18), 1 80 (1H, m, H-16a), 1 84 (3H, dd, J 8 2, 1 1, H-4'), 1 91 (3H, t, J 1 2, H-5'), 1 92-1 94 (1H, m, H-2), 1 93 (3H, s, H-30), 2 14 (1H, d, J 8 8, C3-OH), 2 37 (1H, dt, J 16 6, 2 3, H-2), 2 90 (1H, br.d, J 4 9, H-17), 3 27 (1H, d, J 11 9, H-5), 3 54 (1H, d, J 1 7, H-9), 3 65 (3H, s, C12-OMe), 4 06 (1H, br d, J 7 7, H-3), 4 08 (1H, d, J 14 7, H-19a), 4 22 (1H, dt, J 11 9, 1 3, H-6), 4 36 (1H, d, J 9 1, H-28), 4 45 (1H, dd, J 3 9, 2 7, H-7), 4 51 (1H, d, J 9 1, H-28), 4 56 (1H, br d, J 3 1, H-15), 4 61 (1H, d, J 1 8, C11-OH), 4 66 (1H, dd, J 4 0, 1 0, C7-OH), 4 69 (1H, t, J 2 6, H-1), 5 24 (1H, d, J 3 2, H-22), 5 51 (1H, d, J 14 6, H-19b), 5 56 (1H, s, H-21), 6 41 (1H, d, J 3 1, H-23) and 7 08 (1H, qq, J 7 1, 1 5, H-3'), ^{13}C δ (d$_6$-DMSO) 173 2 (C=O), 170 2 (C=O), 165 9 (C1'), 148 7 (C23), 136 8 (C3'), 128 4 (C2'), 106 7 and 106 6 (C21 and C22), 99 3 (C11), 95.2 and 89 5 (C13 and C14), 87 6 (C20), 82 8 (C15), 77 1 (C1), 72 5 (C19 or C28), 72 3 (C6), 71 6 (C19 or C28), 69 7 (C7), 65 3 (C3), 56 4 (C10), 52 6 (OCH_3), 52 5 (C4), 52 2 (C17), 45 9 (C9), 35 8 (C8), 34 5 (C5), 31 7 (C2), 26 2 (C16), 22 0 (C18), 20 0 (C30), 14 1 (C4') and 11 9 (C5'), m/z (FAB, thiodiethanol) 647 (MH^+), 639 (MH^+-H_2O), 553, 529, 511, 279, 213, 167, 149, 137 and 95 ($C_6H_7O^+$), [Found (MH^+) 647 2309 $C_{32}H_{39}O_{14}$ requires 647 2278], (Found C, 59 52, H, 6 12 $C_{32}H_{38}O_{14}$ requires C, 59 44, H, 5 92%), and 3-desacetylazadirachtin (4)[4,11] (14 0 mg, 64%) as a white, glassy solid

A modified procedure for the preparation of (5) in higher yield, but at the expense of (4) was developed Treatment of azadirachtin (1) with sodium methoxide (3 eq prepared as above) in methanol, at room temperature for 2 hr after the consumption of starting material (30 min) gave, after work up and purification as above, (5) (23%) and an inseparable mixture of the 3-desacetyl compound (4) and its rearranged azadirachtinin diastereoisomers (~50%)

Preparation of 22,23-Dihydro-11-methoxyazadirachtin (6). A degassed solution of 11-methoxyazadirachtin (287mg, 392µmol) over 10% Pd/C (20mg) in methanol (20ml) was hydrogenated at 1 atm for 20 min The mixture was degassed, filtered through a small pad of celite and evaporated The residue was purified by flash chromatography (gradient elution 60-100% ethyl acetate/petrol) to give 22,23-dihydro-11-methoxyazadirachtin (6) (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}, ^{1}H δ ($CDCl_3$) 1 46 (1H, d, J 12 7, H-16), 1 62 (3H, s, H-30), 1 76 (3H, dd, J 7 0, 0 7, H-5'), 1 83 (3H, s, H-4'), 1 88 (3H, s, C3-OAc), 1 93 (3H, s, H-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, 2H-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 (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 11-Methoxy-2',3',22,23-tetrahydroazadirachtin (7) A degassed solution of 11-methoxyazadirachtin (711mg, 0 969mmol) in anhydrous methanol containing 10% Pd/C (70mg) was hydrogenated at 1atm for 20hr The mixture was then degassed thoroughly and filtered through a pad of celite The solvent was evaporated and the residue purified by flash chromatography (gradient elution 80-100% ethyl acetate/petrol) to give the tetrahydro product (7) (664mg, 93%) (3 2 mixture at C2') as a colourless foam, υ_{max} (film) 3464, 2964, 1736, 1248, 1220, 1042 and 732 cm^{-1}, ^1H δ ($CDCl_3$) (major isomer, although most signals overlap exactly) 0 91 (3H, t, J 7 5, 4'-CH_3), 1 15 (3H, d, J 6 9, 5'-CH_3), 1 36-1 42 (1H, m, H-3'), 1 49 (1H, d, J 12 8, H-16), 1 62 (3H, s, 30-CH_3), 1 73-1 79 (2H, m, H-3' and H-16), 1 97-2 03 (1H, m, H-22), 2 04 (3H, s, 18-CH_3 or 3-OAc), 2 05 (3H, s, 18-CH_3 or 3-OAc), 2 10-2 38 (4H, m, 2xH-2, H-2' and H-22 inclusive), 2 39 (1H, d, J 5 4, H-17), 2 62 (1H, br s, OH), 3 08 (1H, d, J 12 3, H-5), 3 31 (3H, s, OMe), 3 34 (1H, br m, OH), 3 42 (1H, s, H-9), 3 58 (1H, d, J 8 9, H-28), 3 62 (1H, d, J 9 5, H-19), 3 69 (3H, s, CO_2Me), 3 78 (3H, s, CO_2Me), 3 86-3 91 (1H, m, H-23), 3 98-4 02 (2H, m, H-23, including d, J 9 4, H-19), 4 07 (1H, d, J 8 9, H-28), 4 53-4 57 (2H, m, H-6 and H-7), 4 60 (1H, t, J 2 6, H-1), 4 67 (1H, d, J 3 3, H-15), 5 19 (1H, s, H-21) and 5 47 (1H, m, H-3), m/z (EI) 679 (M^+-CO_2Me), 661 (M^+-CO_2Me-H_2O), 645, 635, 577, 425, 351, 291, 253 and 151, Found (M^+-CO_2Me) 679 2953 $C_{34}H_{47}O_{14}$ requires 679 2966, Found C, 56 94, H, 6 69 $C_{36}H_{50}O_{16}$ H_2O requires C, 57 14, H, 6 93%

Preparation of 22,23-Dihydro-7-keto-11-methoxyazadirachtin (8). To a solution of 22,23-dihydro-11-methoxyazadirachtin (**6**) (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 Purification of the residue by flash chromatography (gradient elution, 70-100% ethyl acetate/petrol) gave the C7-ketone (**8**) (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, 30-CH_3), 1 62 (1H, d, J 8 4, H-16), 1 73 (4H, dd, J 7 1, 1 0, 4'-CH_3 and obscured H-16), 1 80 (3H, d, J 1 0, 5'-CH_3), 1 90 (3H, s, 3-OAc), 2 01 (3H, s, 18-CH_3), 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-*O*COMe) 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 22,23-Dihydro-7-*epi*-11-methoxyazadirachtin (9) A solution of 22,23-dihydro-7-keto-11-methoxyazadirachtin (23mg, 32μmol) in methanol (1 0 cm^3) was added dropwise to a stirred solution of sodium borohydride (2 5 mg, 66μmol) and cerium trichloride heptahydrate (24mg, 66μmol) in methanol (1 0 cm^3), admixed at -78°C The resulting solution was stirred under argon at -78°C for 1hr then quenched by the addition of analar acetone (0 5 cm^3) The flask contents were allowed to warm to ambient temperature,

then aqueous hydrochloric acid (1 drop, 1M) was added and the resulting solution concentrated under reduced pressure The residue was then partitioned between water (1 cm^3) and ethyl acetate (3x5 cm^3) The combined organic extracts were dried over anhydrous sodium sulphate and concentrated Flash chromatography (80 % ethyl acetate/petrol) gave in order of elution, 22,23-dihydro-11-methoxyazadirachtin (**6**) (11 mg, 14 μmol, 44%) and 22,23-dihydro-7-*epi*-11-methoxyazadirachtin (**9**) (8 mg, 11 μmol, 34 %),$[\alpha]_D^{20}$=-2 0 (c=0 2, chloroform), υ_{max} (film) 3442, 2919, 2850, 2251, 1740, 1645, and 1439 cm^{-1}, ^1H δ ($CDCl_3$, natural prod numbering) 1 5 (1H, br, H-16), 1.57 (3H, s, 30-CH_3), 1.8 (1H, br, H-16), 1 79 (3H, dd, J 7 1 and J'1 1, 4'-CH_3), 1 87 (3H, t, J 1 1, 5'-CH_3), 1.92 (6H, s, 18-CH_3 and 3-OAc), 1 9 (1H, br, H-22), 2 16 (1H, dt, J 17 1 and J'3 2, H-2), 2 2 (1H, br, H-22), 2.4 (3H, b, H-2, H-17, and OH), 2 5 (1H, br, OH), 3 30 (3H, s, 11-OCH_3), 3 31 (1H, d, J 12 5, H-5), 3 64 (1H, d, J 9 5, H-19), 3 67 (1H, d, J 9 1, H-28), 3.68 (3H, s, 29-OCH_3), 3 76 (1H, s, H-9), 3 78 (1H, d, J 9 0, H-7), 3 78 (3H, s, 12-OCH_3), 4 0 (2H, br, H-23), 4 04 (1H, d, J 9 1, H-28), 4 18 (1H, d, J 9 5, H-19), 4 43 (1H, dd, J 12 0 and J' 9 0, H-6), 4 6 (1H, br, H-15), 4 61 (1H, t, J 2 9 H-1), 5 43 (1H, s, H-21), 5 46 (1H, t, J 2 8, H-3), and 6 8 (1H, s, H-3'), m/z (FAB, MNBA) 759 (MNa^+), 737 (MH^+), 705 (MH^+-MeOH), 687 (MH^+-MeOH-H_2O), and 633, Found (MNa^+) 759 2840 $C_{36}H_{48}O_{16}Na$ requires 759 2840

Preparation of [2a*R*, 4*R* (4*S*, 5*R*, 6*S*, 7*R*), 4a*R*, 5*S*, 7a*S*, 8*S* (*E*), 10*R*, 10a*R*, 10b*R*] Dimethyl 10-acetoxy-4-methyl-4-(6-methyl-2,8-dioxo-5,6-epoxy-4,7-methano-1,3-dioxecan-5-yl)-5-methoxy-8-(2-methylbut-2-enoyloxy)-3-oxodecahydronaphtho[1,8-*bc*;4,4a-*c*']difuran-5,10a-dicarboxylate (10) To a solution of 22,23-dihydro-11-methoxyazadirachtin (**6**) (203mg 0 276mmol) in dichloromethane (5ml) was added PCC (292mg, 1 36mmol, 5 equiv) and powdered activated 4Å molecular sieves (200mg) The mixture was stirred at room temperature for 24hr, after which time further PCC (292mg, 1 36mmol, 5 equiv) and powdered activated 4Å molecular sieves (200mg) were added After stirring for a further 24hr, ethyl acetate (5ml) was added and stirred for 10min The mixture was filtered through a pad of Florisil and the filtrate evaporated Purification by flash chromatography (gradient elution, 70-100% ethyl acetate/petrol) gave the rearranged compound (**10**) (149mg, 72%) 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, 18-CH_3 or 30-CH_3), 1 75 (3H, dd, J 7 1, 1 0, 4'-CH_3), 1 81 (3H, d, J 1 1, 5'-CH_3), 1 85 (3H, s, 18-CH_3 or 30-CH_3), 1 90 (3H, s, 3-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-OCO*Me*), 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_2*Me*), 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-*O*COMe), 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 22,23-Dihydro-11,20-dimethoxyazadirachtin (11). A degassed solution of 11,20-dimethoxyazadirachtin (223mg, 0 298mmol) in methanol (15ml) was hydrogenated over 10% Pd/C for 60min at 1atm The mixture was degassed, filtered over celite, evaporated and the residue purified by flash chromatography (ethyl acetate) to give the 22,23-dihydro compound (**11**) (162mg, 72%) as a colourless foam, $[\alpha]_D^{20}$=+2 39 (c=2 72, chloroform), υ_{max} (film) 3478, 2951, 1739, 1439, 1372, 1265, 1221, 1160, 1044,

915 and 733 cm^{-1}; ^1H δ ($CDCl_3$) 1.16 (1H, d, J 13.0, H-16), 1.54 (3H, s, 3xH-30), 1.77 (3H, dd, J 6 9, 1 1, 3xH-4'), 1 81 (3H, s, 3xH-18), 1.83 (1H, obscured m, H-16), 1.85 (3H, t, J 1 2, 3xH-5'), 1 86-1 92 (1H, m, H-22), 1.92 (3H, s, C3-OAc), 2.16-2.20 (1H, m, H-22), 2.24 (1H, dt, J 16.9, 3.2, H-2), 2.34 (1H, dt, J 17.0, 2 6, H-2), 2.37 (1H, C7-OH), 2.62 (1H, d, J 6.0, H-17), 3 25 (3H, s, OMe), 3 31 (3H, s, OMe), 3 39 (1H, d, J 12 4, H-5), 3 55 (1H, s, H-9), 3.64 (3H, s, CO_2Me), 3 645 (1H, d, J 11 2, H-19), 3.68 (1H, d, J 8 8, H-28), 3 78 (3H, s, CO_2Me), 3 98-4.04 (1H, m, H-23), 4 03 (1H, d, J 8.7, H-28), 4 04 (1H, d, J 10.4, H-19), 4 07-4.13 (1H, m, H-23), 4 42 (1H, d, J 1.4, H-7), 4.54 (1H, dd, J 12.4, 2.6, H-6), 4 70 (1H, t, J 2.8, H-1), 4.79 (1H, d, J 2 4, H-15), 5 46 (1H, t, J 3.0, H-3), 5.57 (1H, s, H-21) and 6.94 (1H, dq, J 1.5, 7.1, H-3'); m/z (EI) 691 (M^+-CO_2Me), 675, 659 (M^+-CO_2Me-MeOH), 643, 633, 575, 543, 451, 423, 351, 291, 267, 151, 108 and 81, Found (M^+-CO_2Me) 691 2957 $C_{35}H_{47}O_{14}$ requires 691.2968

Preparation of 22,23-Dihydro-7-oxo-11,20-dimethoxyazadirachtin (12). To a solution of 22,23-dihydro-11,20-dimethoxyazadirachtin (**11**) (150mg, 0.20mmol) in dichloromethane (3ml), was added powdered activated 4Å molecular sieves (500mg) followed by PDC (348mg, 1.0mmol, 5 equiv). After stirring at room temperature for 48hr, ethyl acetate (3ml) was added. The mixture was stirred for 10min and then filtered through a pad of Florisil. Evaporation and purification by flash chromatography (90% ethyl acetate/petrol) gave the C7-ketone (**12**) (137mg, 91%) as a colourless foam, $[\alpha]_D^{20}$=+17 3 (c=1 36, chloroform), υ_{max} (film) 2954, 1740, 1646, 1436, 1373, 1263, 1219, 1129, 1105, 1042, 989, 916, 860 and 733 cm^{-1}, ^1H δ ($CDCl_3$) 1 16 (1H, d, J 12 5, H-16), 1.56 (3H, s, 30-CH_3), 1 72 (3H, dd, J 7 0, 1 1, 4'-CH_3), 1 79 (3H, s, 5'-CH_3), 1.87 (3H, s, 18-CH_3), 1.88-1 97 (2H, m, H-16 and H-22), 2 00 (3H, s, 3-OAc), 2.14 (1H, dt, J 16 9, 3.2, H-2), 2.18-2.23 (1H, m, H-22), 2.33 (1H, br m, J 16 8, H-2), 2 65 (1H, d, J 5 8, H-17), 2 81 (1H, d, J 14.3, H-5), 3.29 (4H, br s, H-9 and OMe), 3.30 (3H, s, OMe), 3 67 (3H, s, CO_2Me), 3 74 (1H, d, J 9 8, H-19), 3 78-3 79 (1H, obscured H-28), 3 79 (3H, s, CO_2Me), 3 94 (1H, q, J 8 8, H-23), 4 06 (1H, d, J 9.0, H-28), 4.12-4 16 (1H, m, H-23), 4 39-4 43 (2H, m, H-15 and H-19), 4 74 (1H, br t, H-1), 5 25 (1H, d, J 14 4, H-6), 5 45 (1H, t, J 2 5, H-3), 5.86 (1H, s, H-21) and 6 71 (1H, br q, J 7 0, H-3'); m/z (EI) 748 (M^+), 689 (M^+-CO_2Me), 661 (M^+-CO_2Me-CO), 641, 631, 613, 573, 541, 513, 479, 405, 231 and 167, Found (M^+-CO_2Me) 689.2809 $C_{35}H_{45}O_{14}$ requires 689 2809.

Preparation of [2a*R*, 3*R*, 5*S* (*E*), 5a*S*, 8*S*, 8a*R*, 8b*R*, 9*S*, 10*S*, 12*R* (2*S*, 3*S*), 13*R*, 14a*R*, 14b*R*, 14c*R*] Dimethyl 3-acetoxy-12-(2,3-dimethoxytetrahydro-3-furyl)-8b,13-dimethyl-9-hydroxy-8-methoxy-5-(2-methylbut-2-enoyloxy)-10,14a-epoxyhexadecahydro-9,13-methanodifuro[2",3",4":4,4a,5;3',4':1,8a]naphth[2,3-*b*]oxocine-2a,8-dicarboxylate (13). To a solution of 22,23-dihydro-11,20-dimethoxy-7-ketoazadirachtin (**12**) (110mg, 0 147mmol) in methanol (10ml) was added Amberlyst 15 ion exchange resin (3g). The mixture was stirred at room temperature for 72hr, filtered, evaporated and the residue purified by flash chromatography (gradient elution, 60-100% ethyl acetate/petrol) to give the rearranged compound (**13**) (68mg, 59%) as a colourless solid, m pt 224-227°C; $[\alpha]_D^{20}$=+8.8 (c=0 98, chloroform), υ_{max} (film) 3520, 2954, 1749, 1704, 1430, 1381, 1062 and 738 cm^{-1}, ^1H δ ($CDCl_3$, natural prod numbering) 1 42 (3H, s, 18-CH_3 or 30-CH_3), 1.60 (3H, s, 18-CH_3 or 30-CH_3), 1.82 (3H, d, J 1.0, 5'-CH_3), 1.82-1.85 (1H, m, H-22), 1.85 (3H, dd, J 7 0, 1 0, 4'-CH_3), 1 91 (3H, s, 3-OAc), 1 97 (1H, dd, J 15 4, 5 2, H-16), 2 03-2 06 (1H, m, H-16), 2 10 (1H, dt, J 16 9, 3 1, H-2), 2 25 (1H, dt, J 16 8, 2 8, H-2), 2.63-2 68 (1H, m, H-22), 2.75 (1H, dd, J 11 3, 5 2, H-17), 3 18 (1H, d, J 12 2, H-5), 3 26 (3H, s, OMe), 3.34 (3H, s, OMe), 3 42 (3H, s, OMe), 3.64 (1H, d, J 9 0, H-28), 3 69 (3H, s, CO_2Me), 3 72 (1H, d, J 9 8, H-19), 3 74 (3H, s, CO_2Me), 3 81 (1H, s, H-9), 3.87 (1H, s, OH), 3 92-3 98 (1H, m, H-23), 3.99 (1H, d, J 9 0, H-28), 4 04-4 19 (1H, m, H-23), 4 21 (1H, d, J, 3 3, H-15), 4 28 (1H, d, J 9 8, H-19), 4.40 (1H, d, J 12.2, H-6), 4.74 (1H, t, J 1.8, H-1), 4.88 (1H, s, H-21), 5 45 (1H, t, J 2.9, H-3) and 7.0 (1H, dq, J 1 4, 6 9, H-3'), ^{13}C δ ($CDCl_3$) 12 2 (C5'), 14.4 (C4'), 15.9 (C18), 22 1, 20 7 (C30, C3-OCO*Me*), 29 9, 30.0, 31.9 (C2, C16, C22), 42 2 (C5), 48 1 (C9), 50 6 (C10), 50 8 (C17), 52 1, 52 5, 52.6, 52.6, 53.0, 53.6, 54.2 (C4, C8, 3xOMe, 2xCO_2Me), 65.1 (C23), 66 6 (C3), 70 2 (C1), 71.7 (C19 or C28), 72 6 (C6), 72.9 (C19 or C28), 83 3 (C15), 87 9, 88 4 (C13 and C14), 95 5 (C20), 104 5

(C21), 104 7 (C11), 106 8 (C7), 127 8 (C2'), 139 7 (C3'), 166 1, 169 4, 169.6, 172 3 (C1', C12, C29 and C3-OCOMe), m/z (EI), 748 (M^+-MeOH), 733, 721 (M^+-CO_2Me), 721, 705, 689, 673, 641, 631, 575, 562, 506, 405, 211, 139, 130, 111, 100 and 83, Found (M^+-CO_2Me) 721 3059 $C_{36}H_{49}O_{15}$ requires 721.3071, Found C, 58 21, H, 6 73 $C_{38}H_{52}O_{17}$ requires C, 58 45, H, 6 71%

Preparation of 22,23-Dihydro-23-α-acetoxy-7-ketoazadirachtin (14) and 22,23-Dihydro-23-β-acetoxy-7-ketoazadirachtin (15). Dess-Martin periodinane (33 mg, 77 μmol) was added to a solution of azadirachtin acetic acid adduct (2) (20 mg, 26 μmol) in dry dichloromethane under argon After stirring at ambient temperature for 2hr, further periodinane (900 mg, 212 μmol) was added and stirring continued at 40°C for 16 hr The flask was then cooled to ambient temperature and saturated aqueous sodium bicarbonate (1 cm^3) and sodium thiosulphate (1 cm^3) added and the mixture stirred vigorously for 10 minutes The organic phase was then removed and the residue further extracted with dichloromethane (3x2 cm^3) The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure Flash chromatography (60-80 % ethyl acetate/petrol) gave, in order of elution, (**14**) (7 mg, 9 μmol, 35 %), $[\alpha]_D^{20}$=+12.9 (c=0.3, chloroform), υ_{max} (film) 3517, 2922, 1743, 1646, and 1433 cm^{-1}, ^1H δ ($CDCl_3$, natural prod numbering) 1 54 (3H, s, 30-CH_3), 1 61 (1H, d, J 13 2, H-16), 1 69 (1H, m, H-16), 1 75 (3H, dd, J 7 1, J' 1 0, 4'-CH_3), 1 80 (3H, d, J 1 1, 5'-CH_3), 1 95 (3H, s, 18-CH_3), 2 01 (3H, s, 23-OAc), 2 05 (3H, s, 3-OAc), 2 27 (1H, dt, J 17 1, J' 3 2, H-2), 2 32 (1H, d, J 14 9, H-22), 2 37 (1H, dt, J 17.1, J' 3 3, H-2), 2 39 (1H, dd, J 14 9, J' 5 5, H-22), 2 43 (1H, d, J 5 1, H-17), 2 80 (1H, d, J 14 5, H-5), 3 65 (1H, s, H-9), 3 78 (3H, s, 29-OCH_3), 3 79 (1H, d, J 9 0, H-28), 3 84 (3H, s, 12-OCH_3), 3 96 (1H, d, J 10 4, H-19), 4 03 (1H, s, 20-OH), 4 13 (1H, d, J 9.1, H-28), 4.28 (1H, d, J 3 1, H-15), 4 58 (1H, d, J 10 3, H-19), 5 33 (1H, d, J 14 6, H-6), 5 44 (1H, t, J 2 8, H-1), 5 47 (1H, s, H-21), 5 55 (1H, t, J 2 9, H-3), 6 35 (1H, d, J 5 1, H-23), and 6 71 (1H, dq, J 7 1, J' 1 4, H-3') and (**15**) (5 mg, 25 %), $[\alpha]_D^{20}$=+37 8 (c 0 2, chloroform), υ_{max} (film) 3414, 2916, 1745, 1646, and 1433 cm^{-1}, ^1H δ ($CDCl_3$, natural prod numbering) 1 52 (1H, d, J 12 1, H-16), 1 53 (3H, s, 30-CH_3), 1 71 (1H, m, H-16), 1 74 (3H, dd, J 7 1, J' 1 1, 4'-CH_3), 1 80 (3H, d, J 1.1, 5'-CH_3), 1 93 (3H, s, 18-CH_3), 2 01 (3H, s, 23-OAc), 2 07 (3H, s, 3-OAc), 2 28 (1H, dt, J 17 0, J' 3 2, H-2), 2 32 (1H, m, H-22), 2 38 (1H, dt, J 17 0, J' 2 5, H-2), 2 54 (1H, d, J 5 3, H-17), 2 66 (1H, dd, J 14.9 and J' 7 0, H-22), 2 82 (1H, d, J 14 6, H-5), 3 41 (1H, s, 20-OH), 3 71 (1H, s, H-9), 3 78 (1H, d, J 9.2, H-28), 3 80 (3H, s, 29-OCH_3), 3 84 (3H, s, 12-OCH_3), 3.96 (1H, d, J 10 3, H-19), 4 12 (1H, d, J 9 0, H-28), 4 30 (1H, d, J 3 2, H-15), 4 56 (1H, d, J 10 2, H-19), 5 32 (1H, d, J 14 6, H-6), 5 43 (1H, t, J 2 8, H-1), 5 50 (1H, s, H-21), 5.54 (1H, t, J 2 8, H-3), 6 39 (1H, dd, J 6 9, J' 2 8, H-23), and 6 73 (1H, dq, J 7 1 and J' 1 4, H-3'), m/z (EI), 604, 577, 551, 479, 449, 437, and 423

Preparation of 7-Ketoazadirachtin (16) 22,23-Dihydro-23-α-acetoxy-7-ketoazadirachtin (**14**) (3 mg, 4 μmol) was heated at 165 °C under high vacuum, $2x10^{-3}$ mm Hg, for 15 minutes The flask was then cooled and the residue flash chromatographed (80 % ethyl acetate/petrol) to give 7-ketoazadirachtin (**16**) (2 mg, 2 5 μmol, 63 %), $[\alpha]_D^{20}$=+1 6 (c=0 2, chloroform), υ_{max} (film) 3424, 2954, 2921, 1743, 1646, 1617, 1434, and 1371 cm^{-1}, ^1H δ ($CDCl_3$, natural prod numbering) 1 40 (1H, d, J 13 0, H-16), 1 55 (3H, s, 18-CH_3), 1 72 (1H, m, H-16), 1 75 (3H, dd, J 7 1, J' 1 2, 4'-CH_3), 1 80 (3H, d, J 1 2, 5'-CH_3), 1 94 (3H, s, 30-CH_3), 2 02 (3H, s, 3-OAc), 2.28 (1H, dt, J 17 0, J' 3 3, H-2), 2.39 (1H, dt, J 17 0, J' 3 3, H-2), 2 40 (1H, d, J 5 4, H-17), 2.83 (1H, d, J 14 6, H-5), 3 31 (1H, s, 20-OH), 3 70 (1H, s, H-9), 3 77 (3H, s, 29-OCH_3), 3.80 (1H, d, J 9 1, H-28), 3 84 (3H, s, 12-OCH_3), 3 97 (1H, d, J 10 3, H-19), 4 12 (1H, d, J 9 1, H-28), 4 23 (1H, d, J 3 2, H-15), 4 58 (1H, d, J 10 3, H-19), 5 04 (1H, d, J 3 0, H-22), 5 33 (1H, d, J 14 6, H-6), 5 44 (1H, t, J 2.9, H-1), 5.55 (1H, t, J 3 0, H-3), 5 72 (1H, s, H-21), 6.42 (1H, d, J 3 0, H-23), and 6 73 (1H, dq, J 7 1 and J' 1 4, H-3'), m/z (FAB, MNBA) 701 (MH^+-H_2O), 683 (MH^+-$2H_2O$), 659 (MH^+-HOAc) and 601, Found (MH^+-H_2O) 701 2445 $C_{35}H_{41}O_{15}$ requires 701 2445

Crystal data for (10): (Crystallised from ethyl acetate/petrol) $C_{36}H_{44}O_{17}$, M=748 7, orthorhombic, a = 13 039(2), b = 14 524(2), c = 19 244(4)Å, V = 3644Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1 36gcm^{-3}, Cu

radiation, λ = 1 54178Å, μ(Cu-K_α) = 9cm^{-1}, F(000) = 1584 Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω scans 2774 independent reflections ($2\theta \leq 116°$) were measured, of which 2509 had $|F_o| > 3\sigma(|F_o|)$, 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 . The non-hydrogen atoms were refined anisotropically The leading protons on the methyl groups on the sp^2 centres were located from a ΔF map The positions of the remaining hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1 2 U_{eq}(C), and allowed to ride on their parent carbon atoms The methyl groups were refined as rigid bodies The absolute configuration of the molecule could not be determined unambiguously Refinement was by block-cascade full-matrix least-squares to R = 0 046, R_w = 0 052 [$w^{-1} = \sigma^2(F) + 0\ 00103F^2$] The maximum and minimum residual electron densities in the final ΔF map were 0 30 and -0 20eÅ^{-3} respectively The mean and maximum shift/error in the final refinement were 0 023 and 0 124 respectively Computations were carried out on an Eclipse S140 computer using the SHELTXL program system [20]

Crystal data for (13): (Crystallised from ether/petrol) $C_{38}H_{52}O_{17}$, M=780 8, orthorhombic, a = 11 386(4), b = 11 669(3), c = 28 692(8)Å, V = 3812Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1 36gcm^{-3}, Cu radiation, λ = 1 54178Å, μ(Cu-K_α) = 9cm^{-1}, F(000) = 1664 Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω scans 2922 independent reflections ($2\theta \leq 116°$) were measured, of which 2633 had $|F_o| > 3\sigma(|F_o|)$, 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 The non-hydrogen atoms were refined anisotropically The leading protons on the methyl groups on the sp^2 centres were located from a ΔF map The hydroxy proton on O(14) was located from a ΔF map and refined isotropically The positions of the remaining hydrogen atoms were idealised, C-H = 0 96Å, assigned isotropic thermal parameters, U(H) = 1 2 U_{eq}(C), and allowed to ride on their parent carbon atoms The methyl groups were refined as rigid bodies The absolute configuration of the molecule could not be determined unambiguously Refinement was by block-cascade full-matrix least-squares to R = 0 040, R_w = 0 044 [$w^{-1} = \sigma^2(F) + 0\ 00134F^2$] The maximum and minimum residual electron densities in the final ΔF map were 0 18 and -0 19eÅ^{-3} respectively The mean and maximum shift/error in the final refinement were 0 071 and 0 570 respectively Computations were carried out on an Eclipse S140 computer using the SHELTXL program system [20]

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