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Chemistry of Insect Antifeedants from *Azadirachta Indica* (Part 19):[1]A Potential Relay Route for the Synthesis of Azadirachtin.

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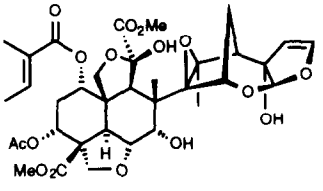
Abstract: A potential relay route for the synthesis of azadirachtin (**1**) has been established. An advanced intermediate **4** has been prepared and methods to convert this back to the natural product have been developed, in particular, the reintroduction of the enol double bond using an acetal exchange process.

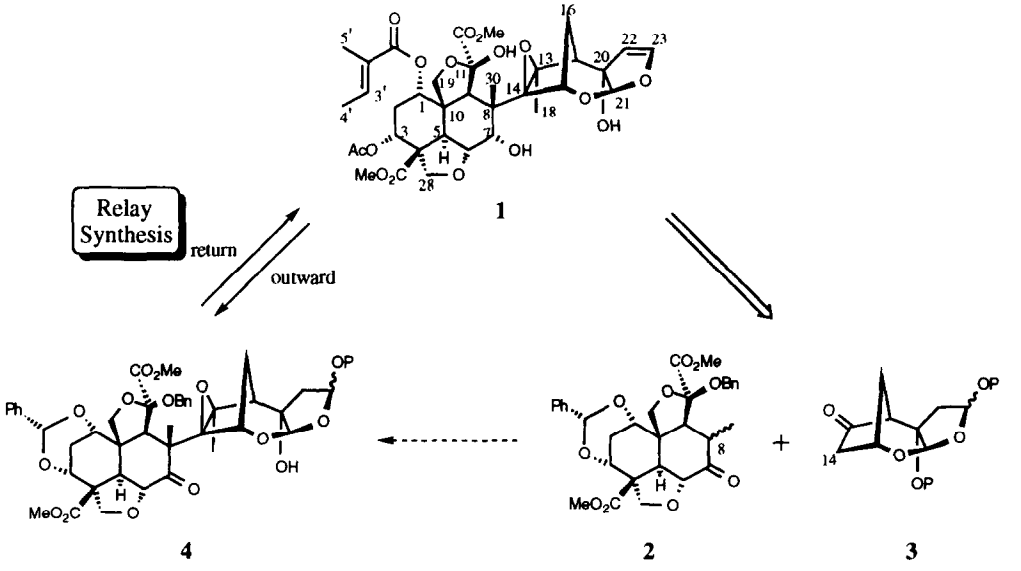
Introduction

Azadirachtin (**1**)[2] is one of a range of natural products isolated from the Indian neem tree *Azadirachta Indica* A. Juss (*Meliacae*). It is a potent insect antifeedant and displays a variety of other biological properties, such as insect growth disruption and anti-malarial activity.[3] Together with its biodegradability, species selectivity and low mammalian toxicity, these factors have resulted in the application of azadirachtin in integrated pest-management programmes[2] and commercial development.[4]



(**1**) Azadirachtin

Azadirachtin is a complex molecule, having sixteen stereogenic centres, seven of which are quaternary. It is photosensitive and both acid and base labile, which often leads to skeletal rearrangement.[2] This, together with the high density of oxygen atoms, makes the synthesis of azadirachtin a formidable challenge, requiring careful manipulation of functionality. We have been interested in the synthesis of azadirachtin for a number of years. Our strategy involves the disconnection of the compound at the central C8-C14 bond (**Scheme 1**), resulting in two fragments, a decalin unit **2** and a protected hydroxytetrahydrofuran acetal **3**. We have previously reported the syntheses of these molecules in enantiopure form.[1,5] The late coupling of the fragments **2** and **3** should produce a compound closely resembling **4**, which can be considered as an advanced intermediate in the projected total synthesis of azadirachtin.

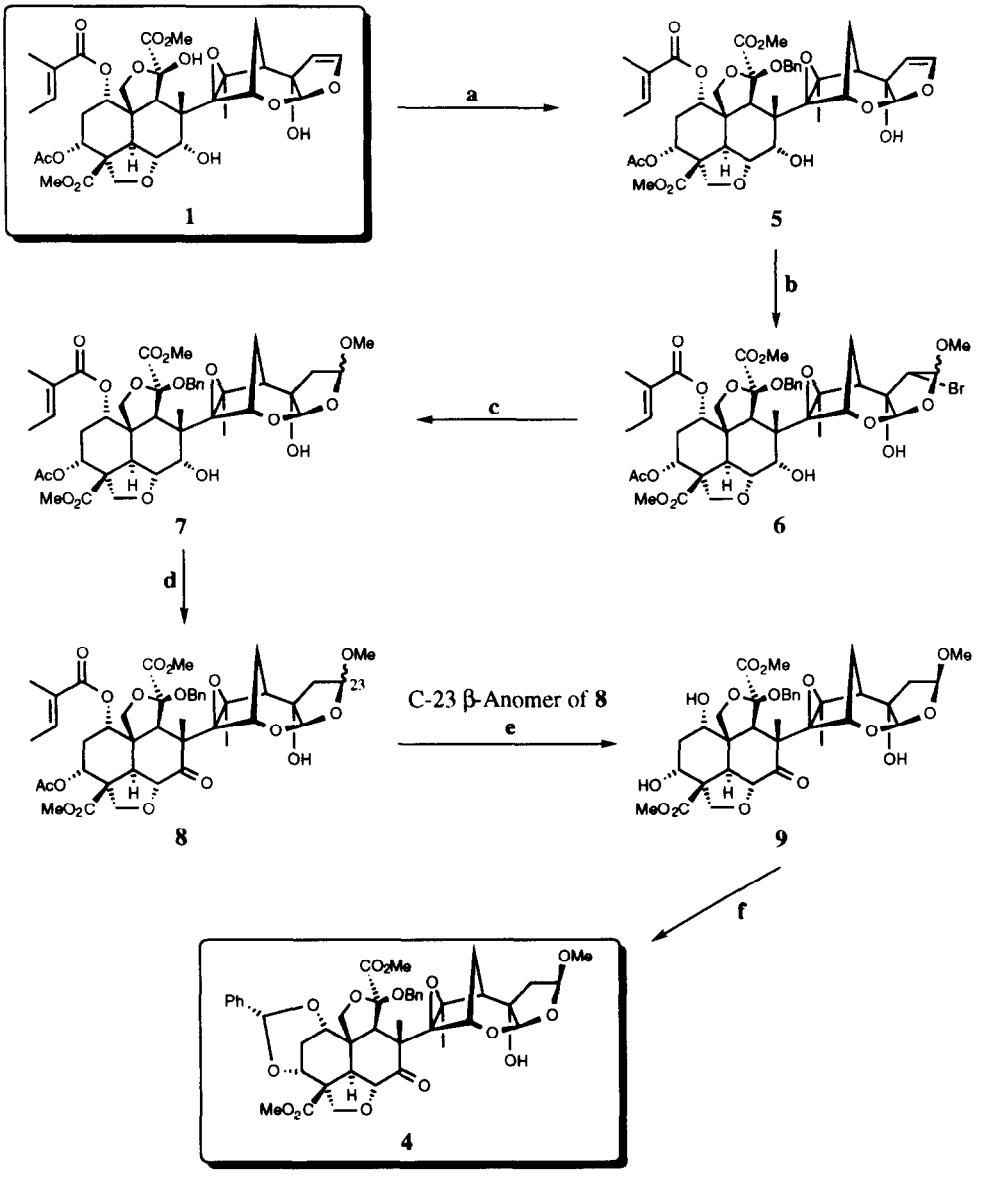


Scheme 1

A potential relay synthesis of azadirachtin involves functionalisation of the natural product **1** by various protection steps, culminating in the formation of the advanced intermediate **4**, thereby meeting the projected total synthesis pathway. The return of compound **4** to the natural product would therefore complete the relay route (**Scheme 1**). A relay synthesis of azadirachtin, such as this, allows us to investigate end-game strategies and enrich supplies of materials for the total synthesis of **1**. It also provides access to a range of azadirachtin analogues, for biological testing and to study the structure-activity relationships of **1** and its derivatives.[6] Herein, we describe the chemistry involved in one of these relay routes developed for azadirachtin synthesis.

Results and Discussion

A complex system of hydrogen bonding exists in azadirachtin that allows the molecule to adopt a relatively rigid framework.[7] For example, there is a strong C-11 hydroxyl-epoxide hydrogen bond and a weaker one between the C-20 and the C-7 hydroxyl groups, with the former group acting as the hydrogen bond donor. Most selective functionalisation of azadirachtin can only be performed after this hydrogen bonding has been disrupted to some extent, for example by alkylation of the C-11 hydroxyl group of **1**. Thus, azadirachtin (**1**) was treated with silver (I) oxide and benzyl bromide in dimethylformamide (DMF),[8] to provide the selectively protected compound, 11-benzyloxyazadirachtin (**5**) in good yield (**Scheme 2**). Prolonged reaction times led to the formation of the C-11, C-20 dibenzylated compound as a by-product. The use of reagents such as benzyl 2,2,2-trichloroacetimidate[9] or sodium hydride as base, led to the decomposition of **1**.



Reagents

a) BnBr, Ag_2O, DMF, 71%; **b)** Br_2, MeOH, 0 °C, 83% (α:β, 1:10); **c)** *n*-Bu_3SnH, AIBN, PhH, reflux, 95%; **d)** PCC on Alumina, CH_2Cl_2, 88%; **e)** NEt_3/MeOH /H_2O (1:5:1), 62%; **f)** $PhCH(OMe)_2$, PPTS, PhH, 65%.

Scheme 2

One of the most chemically sensitive functionalities in azadirachtin is the C-22/C-23 enol ether double bond, which requires masking early on in the relay route. A number of acetals at the C-23 position were investigated, although the methyl acetal was eventually found to be most stable to the subsequent reaction sequences, yet relatively easy to remove in the final stages. This methyl acetal was introduced by bromomethoxylation of the enol ether of **5**, giving bromide **6** as a mixture of anomers at C-23.[10] This compound was debrominated using tri-*n*-butyltin hydride under radical reduction conditions, to give acetal **7** in excellent yield.

Oxidation of the C-7 hydroxyl group further reduces the hydrogen bonding in these molecules and makes them more accessible for manipulation. A variety of reagents will oxidise the 7-position, although freshly prepared pyridinium chlorochromate (PCC) supported on alumina[11] gave the best results, oxidising alcohol **7** to the ketone **8** in high yield. The quality of the reagents was vital to the success of this capricious reaction and yields in the range 40-50 % were obtained if commercially available PCC was used.

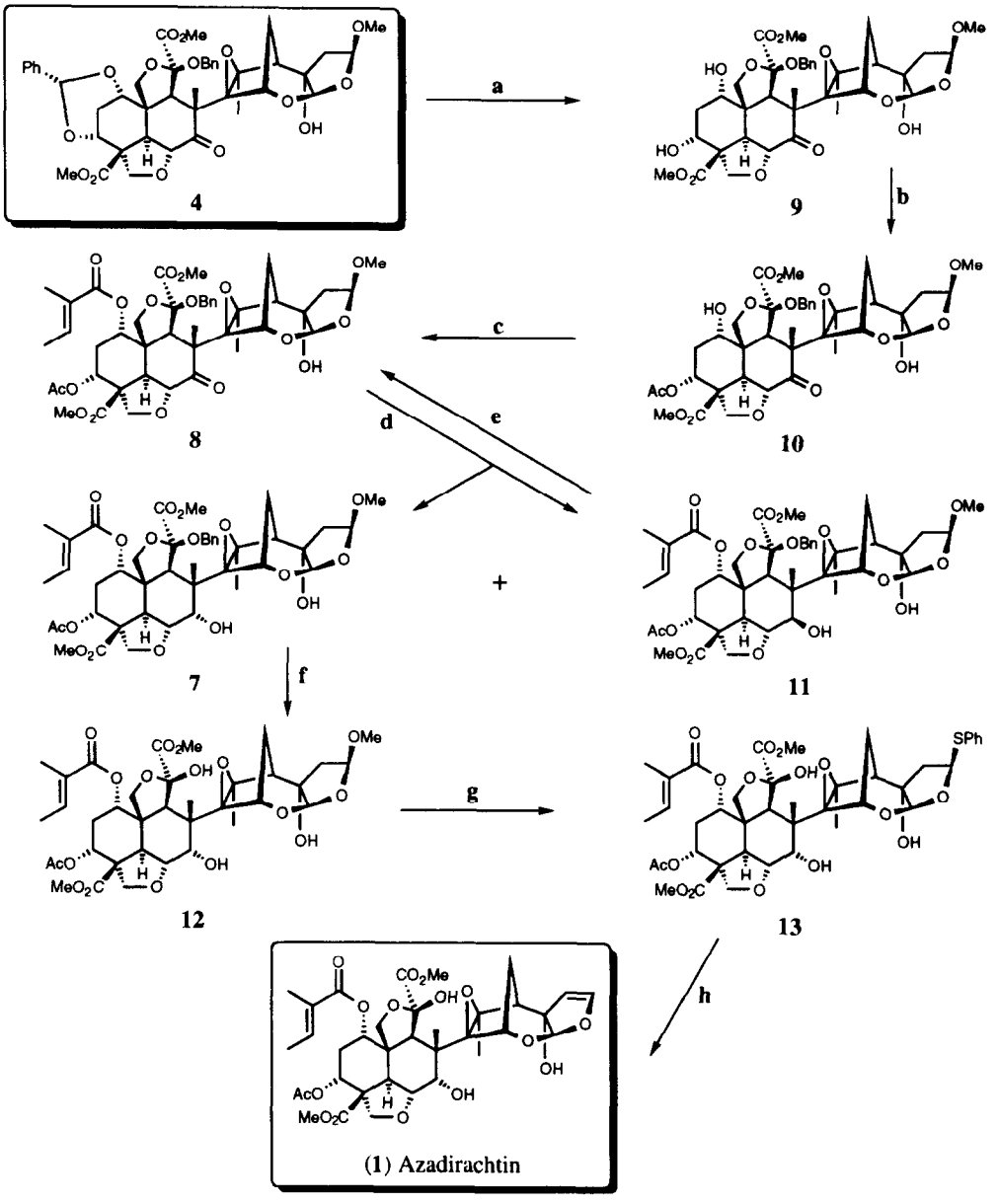
Hydrolysis of the C-1 and C-3 esters of **8** was accomplished with triethylamine in methanol, producing the 1,3-diol **9**. During this reaction, the hindered tiglate ester at C-1 was hydrolysed more slowly and the C-3 acetate could be selectively removed if desired. Apparently, the oxidation level at C-7 affects the ester hydrolysis at C-3, since this was slow for the alcohol **7**, but rapid when the ketone **8** was similarly treated.

Finally, the 1,3-diol function of compound **9** was protected as a benzylidene acetal using benzaldehyde dimethyl acetal and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). The product of this reaction **4**, was the advanced intermediate required for the outward relay route for the total synthesis of azadirachtin (**Scheme 1**).

The 'return' relay route involves conversion of this compound **4** to the natural product, azadirachtin (**1**). Removal of the benzylidene acetal from **4** was achieved in excellent yield by the use of PPTS in slightly wet acetonitrile, regenerating the 1,3-diol **9** (**Scheme 3**). Selective acetylation at the C3-position of **9** was achieved with acetic anhydride, triethylamine and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP), producing acetate **10** in reasonable yield. Some acetylation of the C-1 hydroxyl group of **10** was also observed if the reaction was not carefully monitored.

The esterification of the hindered C-1 hydroxyl group with the tiglate ester, as in azadirachtin, proved to be much more problematic than the previous acetylation reaction. A variety of literature methods for this type of conversion were attempted, but all these reaction conditions proved fruitless. For example, tigloyl chloride[12] (*trans*-$CH_3C{=}C(CH_3)COCl$) was unreactive with the C-1 hydroxyl group of **10**, using triethylamine and a catalytic amount of DMAP, even at 110 °C. The mixed anhydride of tiglic acid, prepared from 2,4,6-trichlorobenzoyl chloride[13] and the activated ester from dicyclohexylcarbodiimide (DCC)[14] were similarly unsuccessful for the tigloylation of **10**.

Owing to the poor reactivity, we decided to investigate the use of the carboxylic acid fluoride to perform this transformation. Acid fluorides have been reported to be superior to the standard acid activation reagents used for difficult esterifications.[15] Their reactivity, *e.g.* towards anionic nucleophiles and amines, has been discussed in terms of the nature of the C-F bond.[16] Tigloyl fluoride was prepared from tiglic acid and cyanuric fluoride[17] and on a small scale it was easier to use as a mixture with triethylamine, as repeated distillation led to some hydrolysis of the acid fluoride. Treatment of **10** with an excess of the tigloyl fluoride/triethylamine mixture and DMAP in dichloromethane produced the esterified product, **8** albeit in low yield.



Reagents

a) PPTS, aq. MeCN, 96%; **b)** Ac_2O, NEt_3, DMAP, CH_2Cl_2, 64%; **c)** NEt_3, DMAP, *trans*-$CH_3CH{=}C(CH_3)COF$, CH_2Cl_2, 21%; **d)** $CeCl_3.7H_2O$, $NaBH_4$, MeOH, 0 °C, 49% of **7** and 43% of **11**; **e)** PCC on Alumina, CH_2Cl_2, 65%; **f)** H_2, Pd/C, MeOH, 81%; **g)** PhSH, PPTS, $Cl(CH_2)_2Cl$, reflux, 70%; **h)** 1) Dimethyldioxirane in Me_2CO, CH_2Cl_2, 2) 90 °C, $PhCH_3$, 61% over two steps.

Scheme 3

Our next problem was the stereoselective reduction of the C-7 ketone of **8**. The steric hindrance of this position made it impossible for bulky substrates, such as the Selectride® reagents to react with the ketone. We were also concerned that this hindrance may favour hydride attack from the lower face of the molecule, thus resulting in the opposite diastereomer of the alcohol to that required, *i.e.* with the hydroxyl group in the equatorial position. A further complication was provided by the presence of the tiglate ester, which could be susceptible to both 1,2- and 1,4-reduction. A number of reagents were however successful for this reduction, with varying degrees of selectivity. Zinc borohydride at -20 °C gave a 30% yield of the desired diastereomer **7**, but loss of the C-3 acetate was also noticed. Sodium borohydride also gave disappointing results, producing a 40% yield of **7**, with the mass balance being unidentified material, apparently obtained from rearrangement of the right-hand side of the molecule.

The use of lanthanoid chlorides with sodium borohydride is reported to give regioselective 1,2-reduction of α,β-unsaturated enones.[18] The mechanistic interpretation of this process is that the lanthanoid cation aids the decomposition of borohydride by the hydroxylic solvent, to generate alkoxyborohydrides, which perform the reduction. Luche reports the best conditions for these regioselective reductions to be sodium borohydride and cerium trichloride in a methanolic solution.[18] The use of these reduction conditions with the C-11 methoxy analogue of **8** had given encouraging results at -78 °C,[19] producing an approximately 1:1 ratio of the two diastereomers at C-7, in 83% yield. However, these same conditions provided exclusively the opposite epimer at C-7, alcohol **11**, when used to reduce the ketone **8**. In this case, the larger protecting group on the C-11 hydroxyl group was apparently responsible for the preferred attack of hydride from the lower face. By raising the temperature of the reaction, the ratio could be improved in favour of the required axial alcohol **7**, so that at 0 °C it was produced in 49% yield, accompanied by the diastereomer **11** in 43% (**Scheme 3**). (The stereochemistry was confirmed by NOESY and COSY NMR experiments). We were pleased to find there was no evidence of either tiglate or acetate reduction with this protocol.

The production of the alcohol **11**, was to some extent overcome, when it was found that it could be oxidised by PCC, back to ketone **8** in yields of around 65%. Thus, we were able to improve the overall yield of alcohol **7** by using this 'recycling' process of oxidation and reduction. The benzyl ether of **7** was rapidly cleaved using standard hydrogenolysis conditions (H_2, Pd/C, MeOH), producing the C-11 alcohol **12** in good yield, with no accompanying reduction of the tiglate ester.

The final unmasking of the C-22/C-23 enol ether was performed at the conclusion of the relay synthesis, where the C-23 methyl acetal proved to be the substituent of choice. The initial studies to determine the appropriate protecting group for this enol ether bond showed that an anomeric C-23 acetate could be removed by pyrolytic elimination of acetic acid, thereby reintroducing the enol double bond. However, the acetate proved to be too labile to be carried through the reaction sequence of the relay route.[20] The pentenyl acetal was prepared and shown to be inert to the sequence of reactions, but required a number of steps involving conversions to the lactol, sulfide, then elimination, to complete the relay route.[21] The methyl acetal **12** on the other hand, could be directly converted to the anomeric sulfide **13** by treatment with thiophenol and a catalytic amount of PPTS in hot 1,2-dichloroethane. Oxidation of **13** to the corresponding sulfoxide, using dimethyldioxirane, followed by pyrolytic elimination of phenylsulfenic acid by heating in hot toluene, led to the reintroduction of the enol double bond and formation of azadirachtin (**1**) and thus, the completion of the return relay sequence.

In conclusion, we have described a potential relay route for the synthesis of azadirachtin (**1**). The natural product was converted to an advanced intermediate **4**, in a sequence of six reactions and returned to (**1**) using seven steps. In addition, this relay route has afforded many new compounds for biological testing.[6] The chemistry described in this potential relay route however, represents only a fraction of that investigated to establish the pathway from **4** to **1**.[19,20,21]

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Experimental Procedures

All solvents were distilled prior to use; methanol from magnesium methoxide; dichloromethane, toluene, dimethylformamide, acetonitrile, benzene and triethylamine from calcium hydride. Petrol refers to the 40-60 °C fraction of petroleum ether and ether refers to diethyl ether. Proton NMR spectra were recorded on a Bruker AM400 (400 MHz) or DRX500 (500 MHz) spectrometer as indicated. NOESY and COSY spectra, where required to confirm NMR assignments, were recorded on a DRX500 (500 MHz) spectrometer. Residual protic solvent, $CHCl_3$ (δ_H 7.26 ppm) was used as internal reference. Coupling constants (*J*) are measured in Hz. Natural product numbering of azadirachtin is used in the assignment of NMR data. An obscured signal is abbreviated as obs. Infra-red spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer, as thin films, or nujol mulls. Optical rotations were measured with an Optical Activity AA-1000 polarimeter using acid- and ethanol-free solvent. Mass spectra were recorded as positive FAB spectra, using NOBA, on a Kratos MS 890 spectrometer. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Flash column chromatography was performed on Merck 9385 Kieselgel 60 silica (230-400 mesh) unless otherwise stated. Crude azadirachtin, 30 %, was chromatographed (70 % ethyl acetate/petrol) before use; crude azadirachtin, 12 %, required two such chromatographic purifications prior to use. The experimental procedures are described in the order the compounds appear in Schemes **2** and **3**.

11-Benzyloxyazadirachtin (5). Freshly prepared silver (I) oxide (5.28 g, 22.8 mmol) was added to a solution of azadirachtin (**1**) (2.74 g, 3.8 mmol) and benzyl bromide (2.26 mL, 19.0 mmol) in DMF (100 mL). After stirring at ambient temperature in the dark for 5 h, the reaction mixture was filtered through Celite®, washing through with ether (200 mL). Further ether (200 mL) was added and the solution was washed with water (3x200 ml). The organics were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (80 % ethyl acetate/petrol) afforded **5** (2.18 g, 71 %) as a white crystalline solid, m.p. 120-123 °C; $[\alpha]_D^{25}$ = -5.3 (*c* = 0.90, chloroform); υ_{max} (film) 3440, 2922, 2360, 1738, 1433, 1375, 1260, 1048 and 736 cm^{-1}; δ_H (400 MHz) 7.34 (2H, d, *J* 6.6, 2xAr-H), 7.25-7.21 (3H, m, 3xAr-H), 6.88 (1H, dq, *J* 1.3, 7.1, H-3'), 6.43 (1H, d, *J* 2.9, H-23), 5.55 (1H, s, H-21), 5.50 (1H, t, *J* 2.7, H-3), 5.01 (1H, d, *J* 2.9, H-22), 4.74-4.71 (2H, obs t, H-1 and obs d, PhC*H*H), 4.60 (1H, dd, *J* 12.4, 2.8, H-6), 4.55 (1H, br s, H-7), 4.48 (1H, d, *J* 11.3,

PhCH*H*), 4.37 (1H, d, *J* 3.4, H-15), 4.14 (1H, d, *J* 9.6, H-19), 4.06 (1H, d, *J* 8.9, H-28), 3.79 (3H, s, CO_2Me), 3.73 (1H, d, *J* 8.9, H-28), 3.69 (1H, d, *J* 9.7, H-19), 3.66 (3H, s, CO_2Me), 3.42 (1H, s, H-9), 3.31 (1H, d, *J* 12.5, H-5), 3.08 (1H, br s, OH), 3.03 (1H, s, OH), 2.30 (2H, m, H-17 and H-22), 2.11 (1H, m, H-2), 2.05 (1H, m, H-2), 2.03 (1H, d, *J* 1.3, H-16), 1.97 (3H, s, 3-OAc), 1.93 (3H, s, 18-Me), 1.84 (3H, s, 5'-Me), 1.76 (3H, d, *J* 7.9, 4'-Me), 1.72-1.69 (1H, m, H-16) and 1.58 (3H, s, 30-Me); *m/z* 811[M+H]$^+$, 711, 685, 559, 351, 291 and 231 (Found [M+H]$^+$: 811.31768. $C_{42}H_{51}O_{16}$ requires *M*, 811.31570).

11-Benzyloxy-22-α-bromo-22,23-dihydro-23-α,β-methoxyazadirachtin (6). A 10 % by volume solution of bromine in methanol (~6 mL) was added to a solution of 11-benzyloxyazadirachtin **5** (2.37 g, 2.9 mmol) at 0 °C until a faint yellow colour persisted. The colour was discharged by the addition of 10 % aq. sodium thiosulfate solution (1.5 mL) and the flask contents were concentrated *in vacuo*. The residue was partitioned between dichloromethane (100 mL) and water (150 mL), the organic phase was separated and the aqueous layer was further extracted with dichloromethane (2×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (80 % ethyl acetate/petrol) gave **6** (2.22 g, 83 %) as an off-white solid, as an inseparable (1:10 α:β) mixture of C-23 anomers; υ_{max} (film) 3472, 2952, 1742, 1707, 1437, 1376, 1263, 1220, 1138, 1081, 1040, 997, 935 and 735 cm^{-1}; δ_H (400 MHz, major β anomer) 7.32 (2H, dd, *J* 3.2, 1.7, 2×Ar-H), 7.27-7.20 (3H, m, 3×Ar-H), 6.88 (1H, dq, *J* 1.5, 7.1, H-3'), 5.58 (1H, s, H-21), 5.48 (1H, t, *J* 3.0, H-3), 5.12 (1H, d, *J* 5.9, H-23), 4.73-4.70 (2H, m, H-1 and PhC*H*H), 4.55 (1H, dd, *J* 12.4, 2.6, H-6), 4.48-4.45 (2H, m, H-15 and PhCH*H*), 4.37 (1H, d, *J* 2.7, H-7), 4.34 (1H, d, *J* 5.9, H-22), 4.13 (1H, d, *J* 9.6, H-19), 4.04 (1H, d, *J* 8.9, H-28), 3.78 (3H, s, CO_2Me), 3.68-3.66 (2H, m, H-19 and H-28), 3.66 (3H, s, CO_2Me), 3.50 (3H, s, 23-OMe), 3.44 (1H, s, H-9), 3.43 (1H, br s, OH), 3.30 (1H, d, *J* 12.5, H-5), 2.79 (1H, s, OH), 2.57 (1H, s, H-17), 2.30 (1H, dt, *J* 16.9, 2.6, H-2), 2.24 (1H, dt, *J* 16.6, 3.2, H-2), 1.93 (3H, s, 3-OAc), 1.86 (3H, s, 18-Me), 1.84 (3H, d, *J* 1.0, 5'-Me), 1.77 (3H, dd, *J* 7.1, 1.0, 4'-Me), 1.72-1.66 (1H, m, H-16), 1.55 (3H, s, 30-Me) and 1.44 (1H, d, *J* 13.1, H-16); *m/z* 921 [M+H]$^+$, 892, 864, 816, 788, 782, 732, 710, 684, 654, 624, 598, and 560 (Found [M+H]$^+$: 921.25446. $C_{43}H_{54}O_{17}{}^{79}Br$ requires *M*, 921.25610).

11-Benzyloxy-22,23-dihydro-23-α,β-methoxyazadirachtin (7). Tributyltin hydride (165 μL, 613 μmol) was added to a solution of 11-benzyloxy-22-α-bromo-22,23-dihydro-23-α,β-methoxyazadirachtin **6** (513 mg, 557 μmol) and catalytic AIBN in benzene (50 mL) and the resultant solution was placed in an oil bath at 80 °C and heated for 40 min. On cooling, the reaction was quenched by the addition of carbon tetrachloride (1 mL) and the flask contents were concentrated *in vacuo*. The residue was taken up in ethyl acetate (50 mL), saturated aq. potassium fluoride solution (10 mL) was added and the mixture was stirred vigorously for 30 min. The flask contents were filtered through Celite®, the aqueous layer was separated and further extracted with ethyl acetate (2×50 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (70 % ethyl acetate/petrol) afforded **7** (446 mg, 95 %) as a white crystalline solid (an inseparable mixture of C-23 anomers) ; υ_{max} (film) 3470, 2954, 2922, 1741, 1706, 1436, 1376, 1268, 1220, 1161, 1135, 1080, 1042, and 736 cm^{-1}; δ_H (400 MHz, major β anomer) 7.35-7.33

(2H, m, 2×Ar-H), 7.28-7.22 (3H, m, 3×Ar-H), 6.84 (1H, dq, *J* 1.4, 7.1, H-3'), 5.49 (1H, t, *J* 2.9, H-3), 5.37 (1H, s, H-21), 5.15 (1H, dd, *J* 6.4, 3.3, H-23), 4.74-4.70 (2H, m, H-1 and PhC*H*H), 4.58 (1H, dd, *J* 12.5, 2.8, H-6), 4.48-4.46 (2H, m, H-7 and PhCH*H*), 4.43 (1H, m, H-15), 4.14 (1H, d, *J* 9.6, H-19), 4.06 (1H, d, *J* 8.9, H-28), 3.79 (3H, s, CO_2Me), 3.70-3.66 (2H, m, H-19 and H-28), 3.67 (3H, s, CO_2Me), 3.46 (1H, s, H-9), 3.40 (3H, s, 23-OMe), 3.36 (1H, s, OH), 3.22 (1H, d, *J* 12.5, H-5), 2.91 (1H, br s, OH), 2.38 (1H, d, *J* 5.1, H-17), 2.34-2.23 (3H, m, 2×H-2 and H-22), 2.19 (1H, d, *J* 3.0, H-22), 1.95 (3H, s, 3-OAc), 1.87 (3H, s, 5'-Me), 1.84 (3H, s, 18-Me), 1.76 (3H, d, *J* 3.9, 4'-Me), 1.71-1.65 (1H, m, H-16), 1.58 (3H, s, 30-Me) and 1.38-1.29 (1H, m, H-16); *m/z* 843 $[M+H]^+$, 812, 788, 732, 664, 648, 623, and 597 (Found $[M+H]^+$: 843.34389. $C_{43}H_{55}O_{17}$ requires *M*, 843.33990).

11-Benzyloxy-22,23-dihydro-23-α,β-methoxy-7-oxoazadirachtin (8). PCC on alumina[11] (0.80 g, 1 mmol of PCC/g, 0.80 mmol) was added to a solution of 11-benzyloxy-22,23-dihydro-23-α,β-methoxyazadirachtin **7** (135 mg, 0.16 mmol) in dichloromethane (13 mL) and the heterogeneous mixture was stirred in the dark for 22 h at ambient temperature. The mixture was allowed to settle and the organic phase decanted. The residue was stirred with ethyl acetate (10 mL) for 30 min, the solvent was decanted and the process was repeated twice further. The combined organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and the residue was purified by flash chromatography (70 % ethyl acetate/petrol) to give, in order of elution, **8**, a mixture of 23-α,β anomers (52 mg, 1:4 α:β), as a white foam and **8**, the 23-β anomer (66 mg) as a white crystalline solid and therefore a total yield of 88 %. Data for the major β anomer: m.p. 135-138 °C; $[\alpha]_D^{22}$ = +40.9 (*c* = 1.00, chloroform); υ_{max} (film) 3421, 2955, 2919, 1743, 1456, 1437, 1375, 1265, 1219, 1130, 1076, 1040, 986, and 734 cm^{-1}; δ_H (400 MHz) 7.27 (5H, m, Ar-H), 6.61 (1H, dq, *J* 1.4, 7.1, H-3'), 5.50 (1H, t, *J* 2.8, H-3), 5.44 (1H, d, *J* 11.8, H-6), 5.22 (1H, s, H-21), 5.07 (1H, dd, *J* 6.1, 1.8, H-23), 4.80 (1H, t, *J* 2.7, H-1), 4.68 (1H, d, *J* 10.7, H-19), 4.54 (1H, d, *J* 9.9, H-28), 4.40 (1H, d, *J* 10.7, H-19), 4.10 (1H, d, *J* 9.1, PhC*H*H), 3.86 (1H, d, *J* 3.3, H-15), 3.84 (3H, s, CO_2Me), 3.78 (2H, m, H-28 and PhCH*H*), 3.70 (1H, s, H-9), 3.68 (3H, s, CO_2Me), 3.59 (1H, s, OH), 3.38 (3H, s, 23-OMe), 2.76 (1H, d, *J* 14.4, H-5), 2.42 (2H, m, H-17 and H-22), 2.33 (1H, dt, *J* 16.9, 2.5, H-2), 2.21 (1H, dt, *J* 16.9, 3.2, H-2), 2.06 (1H, dd *J* 14.3, 4.5, H-22), 1.94 (3H, s, 18-Me), 1.90 (3H, s, 3-OAc), 1.80 (3H, s, 5'-Me), 1.76 (1H, d, *J* 12.7, H-16), 1.17 (3H, dd, *J* 7.1, 0.9, 4'-Me), 1.58 (3H, s, 30-Me) and 1.52 (1H, m, H-16); *m/z* 841 $[M+H]^+$, 734, 708, 664, 601, 531, 460, 391, 351, and 307 (Found $[M+H]^+$: 841.32824. $C_{43}H_{53}O_{17}$ requires *M*, 841.33130).

11-Benzyloxy-3-desacetyl-1-destigloyl-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin (9). A solution of 11-benzyloxy-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin **8** (87 mg, 104 μmol) in triethylamine: methanol: water (1: 5: 1) (10 mL) was heated at 65 °C for 34 h. The solution was allowed to cool to room temperature and then concentrated *in vacuo*. The residue was partitioned between dichloromethane (10 mL) and dilute hydrochloric acid (10 mL), the layers were separated, and the aqueous phase was further extracted with dichloromethane (2×10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (70 % ethyl acetate/petrol) gave **9** (46 mg, 62 %) as a colourless, glassy solid, m.p. 157-160 °C; $[\alpha]_D^{26}$ = +33.5 (*c* = 0.89, chloroform); υ_{max}

(film) 3430, 2955, 1726, 1438, 1242, 1117, 1092, 1081, 985, 931, and 753 cm^{-1}; δ_H (400 MHz) 7.34-7.30 (2H, m, 2×Ar-H), 7.28-7.26 (3H, m, 3×Ar-H), 5.22 (1H, s, H-21), 5.14 (1H, dd, *J* 3.8, 2.4, H-23), 4.95 (1H, d, *J* 11.6, H-19), 4.76 (1H, d, *J* 14.4, H-6), 4.64 (1H, d, *J* 11.6, H-19), 4.46 (1H, m, H-1), 4.41 (1H, t, *J* 3.6, H-3), 4.25 (1H, d, *J* 9.9, PhC*H*H), 4.14 (1H, d, *J* 8.5, H-28), 4.11 (1H, d, *J* 8.5, H-28), 3.79 (3H, s, CO_2Me), 3.77 (1H, m, H-15), 3.74 (1H, s, H-9), 3.70 (1H, br s, OH), 3.64 (3H, s, CO_2Me), 3.61 (1H, d, *J* 9.9, PhCH*H*), 3.38 (3H, s, 23-OMe), 3.33 (1H, d, *J* 7.3, OH), 3.20 (1H, d, *J* 14.4, H-5), 2.91 (1H, s, OH), 2.42 (1H, d, *J* 5.4, H-17), 2.32 (1H, dd, *J* 14.6, 6.3, H-22), 2.25 (1H, dt, *J* 15.8, 2.9, H-2), 2.17 (1H, dd, *J* 14.6, 3.8, H-22), 2.01 (1H, dt, *J* 17.5, t not resolved, H-2), 1.85 (3H, s, 30-Me), 1.72 (1H, d, *J* 12.8, H-16), 1.62 (3H, s, 18-Me) and 1.49-1.54 (1H, m, H-16); *m/z* 717 $[M+H]^+$, 686, 667, 641, 609, 583, 560, 531, 514, 459, and 363 (Found $[M+H]^+$: 717.27582. $C_{36}H_{45}O_{15}$ requires *M*, 717.27940).

11-Benzyloxy-3-desacetyl-1-destigloyl-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin-1,3-benzylidene (4). Benzaldehyde dimethyl acetal (0.1 mL, 0.67 mmol), PPTS (~2 crystals), 11-benzyloxy-3-desacetyl-1-destigloyl-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin **9** (1.8 mg, 2.5 μmol) and 4Å molecular sieves (~5) were heated in benzene (3 mL) under reflux for 30 min. The cooled reaction mixture was partitioned between 10 % aq. sodium bicarbonate solution (2 mL) and dichloromethane (5 mL) and the separated aqueous layer was extracted with dichloromethane (2×5 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (60 % ethyl acetate/petrol) afforded **4** (1.3 mg, 65 %) as a colourless glass, m.p. 140-143 °C; $[\alpha]_D^{25}$ = -60.0 (*c* = 0.11, chloroform); υ_{max} (nujol) 3470, 2954, 1744, 1730, 1121, 1072, 1028, 926 and 735 cm^{-1}; δ_H (500 MHz) 7.31-7.22 (10H, m, Ar-H), 6.14 (1H, s, PhC*H*), 5.20 (1H, d, *J* 14.9, H-6), 5.19 (1H, s, H-21), 5.03 (1H, dd, *J* 6.2, 1.6, H-23), 4.85 (1H, d, *J* 10.4, PhC*H*H), 4.82 (1H, d, *J* 4.7, H-3), 4.71 (1H, d, *J* 11.0, H-19), 4.44 (1H, d, *J* 11.0, H-19), 4.23 (1H, d, *J* 4.9, H-1), 4.15 (1H, d, *J* 8.7, H-28), 4.12 (1H, d, *J* 8.7, H-28), 3.90 (1H, d, *J* 3.3, H-15), 3.82-3.78 (7H, m, 2xCO_2Me and PhCH*H*), 3.68 (1H, s, H-9), 3.57 (1H, br s, OH), 3.38 (3H, s, 23-OMe), 2.93 (1H, d, *J* 14.9, H-5), 2.87 (1H dt, *J* 15.8, 4.8, H-2), 2.39 (1H, dd, *J* 14.4, 6.2, H-22), 2.32 (1H, d, *J* 5.3, H-17), 2.00 (1H, dd, *J* 14.3, 4.4, H-22), 1.92 (3H, s, 18-Me), 1.73 (1H, d, *J* 13.0, H-16), 1.58 (1H, d, *J* 15.9, H-2), 1.56 (3H, s, 30-Me) and 1.52-1.47 (1H, m, H-16); m/z 805 $[M+H]^+$, 717, 665, 583, 514 and 463 (Found $[M+H]^+$: 805.30400. $C_{43}H_{49}O_{15}$ requires *M*, 805.30712).

11-Benzyloxy-3-desacetyl-1-destigloyl-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin (9). PPTS (~2 crystals) and 11-benzyloxy-3-desacetyl-1-destigloyl-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin-1,3-benzylidene **4** (11.1 mg, 13.8 μmol) were stirred in 2 % aq. acetonitrile (10 mL) at ambient temperature for 15 h. The solvent was removed *in vacuo* and purification by flash chromatography (60 % ethyl acetate/petrol) gave **9** (9.5 mg, 96 %) as a colourless glass, whose data matched that of the compound previously prepared by the saponification of **8**.

11-Benzyloxy-1-destigloyl-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin (10). Acetic anhydride (0.27 mL, 0.3 mmol), triethylamine (0.66 mL, 0.5 mmol), DMAP (~10 mg) and 11-benzyloxy-3-desacetyl-1-destigloyl-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin **9** (0.34 g, 0.5 mmol) were stirred in dichloromethane (70 mL) for 4 h at ambient temperature. The reaction mixture was washed with water (50 mL), the organic layer separated and further extracted with dichloromethane (3×50 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (90 % ethyl acetate/petrol) gave **10** (0.23 g, 64 %) as a colourless, glassy solid, m.p. 89-91 °C; $[\alpha]_D^{26}$ = +12.9 (*c* = 0.90, chloroform); υ_{max} (film) 3438, 2996, 1750, 1730, 1599, 1433, 1242, 1217, 1087, 1072, 1037, 926 and 735 cm^{-1}; δ_H (400 MHz) 7.36-7.26 (2H, m, 2×Ar-H), 7.25-7.23 (3H, m, 3×Ar-H), 5.53 (1H, t, *J* 2.8, H-3), 5.27-5.24 (2H, m, H-21 and H-23), 5.01 (1H, d, *J* 2.1, H-1), 4.97 (1H, d, *J* 11.5, H-19), 4.48 (1H, d, *J* 11.5, H-19), 4.23 (1H, d, *J* 13.9, PhC*H*H), 3.95 (1H, d, *J* 8.6, H-28), 3.89-3.83 (5H, m, H-6, CO_2Me and, PhCH*H*), 3.72 (1H, m, H-15), 3.70 (1H, br s, OH), 3.55 (1H, dd, *J* 8.7, 2.8, H-28), 3.51 (3H, s, CO_2Me), 3.40 (5H, m, H-9, 23-OMe and OH), 3.03 (1H, d, *J* 10.8, H-5), 2.43 (1H, d, *J* 5.7, H-17), 2.38 (1H, dt, *J* 16.3, 3.1, H-2), 2.32 (1H, dd, *J* 14.9, 3.1, H-22), 2.28-2.20 (2H, m, H-2 and H-22), 2.07 (3H, s, 18-Me), 1.82 (3H, s, 3-OAc), 1.69 (1H, m, H-16), 1.44 (1H, dd, *J* 12.8, 3.2, H-16) and 1.58 (3H, s, 30-Me); *m/z* 781[M+Na]$^+$, 727, 651, 463, 329 and 289 (Found [M+Na]$^+$: 781.26860. $C_{38}H_{46}O_{16}Na$ requires *M*, 781.26840).

11-Benzyloxy-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin (8). Tigloyl fluoride[17] (280 mg, 2.7 mmol) mixed with triethylamine (0.38 mL, 2.7 mmol) were added to a stirred solution of, DMAP (3 mg, 0.2 mmol) and 11-benzyloxy-1-destigloyl-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin **10** (17 mg, 123 μmol) in 1,2-dichloroethane (1 mL). The mixture was heated under reflux conditions and inert atmosphere for 48 h, then cooled and concentrated *in vacuo*. Purification by flash chromatography (80 % ethyl acetate/petrol) gave **8** (4 mg, 21 %) as a colourless, glassy solid, whose data matched that of the compound previously prepared by oxidation of **7**.

11-Benzyloxy-22,23-dihydro-23-β-methoxyazadirachtin (7) and its C-7 epimer **[7*R*] 11-benzyloxy-22,23-dihydro-23-β-methoxyazadirachtin (11).** Cerium trichloride heptahydrate (50 mg, 0.13 mmol) was added to a stirred solution of 11-benzyloxy-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin **8** (96 mg, 0.12 mmol) in distilled methanol (4 mL). The solution was cooled to approximately -5 to 0 °C, sodium borohydride (5.5 mg, 0.15 mmol) was added and the mixture stirred for 4 h at this temperature. The mixture was brought to pH 7 with dilute hydrochloric acid (3 mL) and water (5 mL) was added. The mixture was extracted with dichloromethane (4×20 mL), the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (90 % ethyl acetate/petrol) gave, in order of elution **7** (48 mg, 49 %) as a colourless glass, m.p. 139-142 °C; $[\alpha]_D^{25}$ = -0.65 (*c* = 0.96, chloroform), whose other data matched that of the compound previously prepared, followed by **11** (41 mg, 43 %) as a colourless solid, m.p. 97-100 °C; $[\alpha]_D^{26}$ = +7.54 (*c* = 0.65, chloroform); υ_{max} (nujol) 3430, 2725, 1745, 1705, 1308, 1268, 1157, 1037, 936 and 725 cm^{-1}; δ_H (500 MHz) 7.28-7.25 (5H, m, Ar-H), 6.84 (1H, dq, not resolved H-3'), 5.47 (1H, t, *J* ~3, H-3), 5.43 (1H, s, H-21), 5.07 (1H, m, H-23), 4.70-4.68

(2H, m, H-1 and H-19), 4.49 (1H, d, *J* 6.6, H-19), 4.42 (1H, dd, *J* 9.1, 11.8, H-6), 4.24 (1H, d, *J* 9.1, PhC*H*H), 4.04 (1H, d, *J* 9.1, H-28), 3.81-3.79 (7H, m, H-7 and 2×CO_2Me), 3.77 (1H, d, *J* 9.1, H-28), 3.70-3.68 (2H, m, H-15 and PhCH*H*), 3.63 (1H, s, H-9), 3.37 (3H, s, 23-OMe), 3.03 (1H, br s, OH), 2.79 (1H, br s, OH), 2.53 (1H, d, *J* ~10, H-5), 2.39-2.35 (2H, m, H-2 and H-22), 2.30 (1H, d, *J* 5.3, H-17), 2.19 (1H, dt, not resolved, H-2), 2.10 (1H, dd, not resolved, H-22), 1.93 (6H, s, 3-OAc and 18-Me), 1.87 (3H, s, 5'-Me), 1.78 (3H, d, *J* 7.0, 4'-Me), 1.70 (3H, s, 30-Me), 1.63 (1H, d, *J* 12.8, H-16), 1.45 (1H, m, H-16); *m/z* 843 $[M+H]^+$, 812, 788, 732, 624 and 597 (Found $[M+H]^+$: 843.34420. $C_{43}H_{55}O_{17}$ requires *M*, 843.34390).

11-Benzyloxy-22,23-dihydro-23-β-methoxy-7-oxoazadirachtin (8). PCC on alumina[11] (4.5 mg, 1 mmol of PCC/g, 45 μmol) was added to a solution of [7*R*] 11-benzyloxy-22,23-dihydro-23-β-methoxyazadirachtin **11** (7.5 mg, 8.9 μmol) in dichloromethane (2 mL) and the heterogeneous mixture was stirred in the dark for 20 h. Work-up as described previously, followed by purification by flash chromatography (ethyl acetate) gave **8** (5 mg, 65 %) as a white crystalline solid, whose data matched that of the compound previously prepared by the oxidation of **7**.

22,23-Dihydro-23-β-methoxyazadirachtin (12). 10 % Palladium on carbon (2 mg) was added to a degassed solution of 11-benzyloxy-22,23-dihydro-23-β-methoxyazadirachtin **7** (8 mg, 9.5 μmol) in methanol (1 mL). The flask was evacuated and then stirred under an atmosphere of hydrogen for 14 h. The solution was degassed and the catalyst was filtered off over a plug of Celite®, washing with ethyl acetate (10 mL). The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography (80 % ethyl acetate/petrol) to afford **12** (5.8 mg, 81 %) as a white crystalline solid, m.p. 159-162 °C; $[\alpha]_D^{26}$ = -17.3 (*c* = 0.41, chloroform); υ_{max} (film) 3442, 2921, 1735, 1437, 1376, 1266, 1220, 1040, and 734 cm^{-1}; δ_H (400 MHz) 6.86 (1H, dq, *J* 1.4, 7.1, H-3'), 5.49 (1H, t, *J* 3.0, H-3), 5.48 (1H, s, H-21), 5.17 (1H, dd, *J* 6.3, 5.2, H-23), 5.03 (1H, s, 11-OH), 4.73 (1H, t, *J* 2.7, H-1), 4.67 (2H, m, H-7 and H-15), 4.58 (1H, dd, *J* 12.5, 2.7, H-6), 4.15 (1H, d, *J* 9.7, H-19), 4.06 (1H, d, *J* 9.0, H-28), 3.78 (3H, s, CO_2Me), 3.73 (1H, d, *J* 9.0, H-19), 3.68 (3H, s, CO_2Me), 3.61 (1H, d, *J* 9.8, H-28), 3.42 (3H, s, 23-OMe), 3.29 (1H, s, H-9), 3.24 (1H, d, *J* 12.5, H-5), 2.81 (1H, s, OH), 2.55 (1H, s, OH), 2.47 (1H, d, *J* 5.3, H-17), 2.38 (1H, dd, *J* 14.7, 6.4, H-22), 2.32 (1H, dt, *J* 17.0, 2.4, H-2), 2.24-2.18 (2H, m, H-2 and H-22), 2.00 (3H, s, 18-Me), 1.94 (3H, s, 3-OAc), 1.91 (1H, d, *J* 8.2, H-16), 1.84 (3H, s, 5'-Me), 1.77 (3H, dd, *J* 7.1, 0.9, 4'-Me), 1.74 (3H, s, 30-Me) and 1.65-1.61 (1H, m, H-16) ; *m/z* 753 $[M+H]^+$, 736, 722, 704, 686, 661, 619, 603, 564, 543, 460, 409, 391, 351, 331, and 321 (Found $[M+H]^+$: 753.30310. $C_{36}H_{49}O_{17}$ requires *M*, 753.29695).

22,23-Dihydro-23-β-thiophenoxyazadirachtin (13). Thiophenol (24 μL, 233 μmol) was added to a solution of 22,23-dihydro-23-β-methoxyazadirachtin **12** (35 mg, 46.5 μmol) and PPTS (~ 5 crystals) in 1,2-dichloroethane (4 mL). The flask was placed in an oil bath at 80 °C and heated for 3 h. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Flash chromatography (50 % ethyl acetate/petrol) gave **13** (27 mg, 70 %) as a colourless glass-like solid, m.p. 91-93 °C (decomp.); $[\alpha]_D^{23}$

= -115.6 (*c* = 1.00, chloroform); υ_{max} (film) 3431, 2954, 1739, 1438, 1378, 1265, 1220, 1138, 1042, 979, 917, and 735 cm^{-1}; δ_H (400 MHz) 7.51-7.49 (2H, m, 2×Ar-H), 7.32-7.26 (3H, m, 3×Ar-H), 6.87 (1H, dq, *J* 1.3. 7.1, H-3'), 5.73 (1H, dd, *J* 7.9, 2.6, H-23), 5.67 (1H, s, H-21), 5.49 (1H, t, *J* 2.7, H-3), 4.97 (1H, s, 11-OH), 4.77 (1H, d, *J* 2.5, H-7), 4.75 (1H, t, *J* 2.6, H-1), 4.69 (1H, d, *J* 3.2, H-15), 4.58 (1H, dd, *J* 12.6, 2.7, H-6), 4.14 (1H, d, *J* 9.7, H-19), 4.07 (1H, d, *J* 9.0, H-28), 3.78 (3H, s, CO_2Me), 3.74 (1H, d, *J* 9.0, H-28), 3.68 (3H, s, CO_2Me), 3.61 (1H, d, *J* 9.7, H-19), 3.30 (1H, s, H-9), 3.25 (1H, d, *J* 12.5, H-5), 2.85 (1H, s, OH), 2.76 (1H, s, OH), 2.67 (1H, dd, *J* 14.7, 8.0, H-22), 2.44 (1H, d, *J* 4.8, H-17), 2.31 (1H, dt, *J* 14.9, 2.5, H-2), 2.26 (1H, d, *J* 2.7, H-22), 2.21 (1H, dt, *J* 17.0, 3.1, H-2), 2.02 (3H, s, 18-Me), 1.93 (3H, s, 3-OAc), 1.84 (3H, s, 5'-Me), 1.78 (3H, d, *J* 7.1, 4'-Me), 1.74 (3H, s, 30-Me), 1.70-1.65 (1H, m, H-16) and 1.56 (1H, d, *J* 4.6, H-16); *m/z* 831 $[M+H]^+$, 813, 722, 661, 606, 519, 460, 409, and 355 (Found $[M+H]^+$: 831.29100. $C_{41}H_{51}O_{16}S$ requires *M*, 831.28975).

Azadirachtin (1). Freshly prepared dimethyl dioxirane (171 µL of a 0.1 M solution in acetone, 17.1 µmol) was added to a solution of 22,23-dihydro-23-β-thiophenoxyazadirachtin **13** (13 mg, 15.5 µmol) in dichloromethane (1 mL) at -78 °C. After 15 min, the flask was allowed to warm to ambient temperature and the solvent removed *in vacuo*. The residue was taken up in toluene (1.5 mL), triethylamine (2 drops) was added and the flask was placed in an oil bath at 90 °C. After heating for 30 min, the flask contents were concentrated *in vacuo*. Flash chromatography on Florisil® (60 % ethyl acetate/petrol) gave azadirachtin (**1**) (7 mg, 61 %) as a white crystalline solid, m.p. 155-157 °C (lit.[22] 155-157 °C); $[\alpha]_D^{26}$ = -55.6 (*c* = 0.68, chloroform); υ_{max} (film) 3441, 2923, 2852, 1740, 1438, 1376, 1268, 1144, 1044, and 736 cm^{-1} ; δ_H (500 MHz) 6.92 (1H, dq, *J* 1.4, 7.1, H-3'), 6.46 (1H, d, *J* 2.9, H-23), 5.64 (1H, s, H-21), 5.50 (1H, t, *J* 2.8, H-3), 5.05 (1H, d, *J* 2.9, H-22), 5.02 (1H, s, 11-OH), 4.76 (1H, t, *J* 2.8, H-1), 4.74 (1H, br s, H-7), 4.67 (1H, d, *J* 3.5, H-15), 4.61 (1H, dd, *J* 12.5, 2.7, H-6), 4.15 (1H, d, *J* 9.7, H-19), 4.07 (1H, d, *J* 9.0, H-28), 3.79 (3H, s, CO_2Me), 3.77 (1H, d, *J* 9.0, H-28), 3.69 (3H, s, CO_2Me), 3.63 (1H, s, *J* 9.7, H-19), 3.35 (1H, d, *J* 12.4, H-5), 3.34 (1H, s, H-9), 2.84 (1H, br s, 20-OH), 2.79 (1H, br s, 7-OH), 2.38 (1H, d, *J* 5.3, H-17), 2.34 (1H, dt, *J* 16.9, t not resolved, H-2), 2.23 (1H, dt, *J* 16.9, 3.3, H-2), 2.00 (3H, s, 18-Me), 1.95 (3H, s, 3-OAc), 1.85 (3H, s, 5'-Me), 1.78 (3H, d, *J* 7.1, 4'-Me), 1.75 (3H, s, 30-Me), 1.76 (1H, ddd, *J* 13.2, 5.4, 3.4, H-16), 1.31 (1H, ddd, *J* 13.2, 0.4, 0.3, H-16); *m/z* 743 $[M+Na]^+$, 703, 685, 620, 585, 407, 291, 229 and 183 (Found $[M-OH]^+$: 703.25680. $C_{35}H_{43}O_{15}$ requires *M*, 703.26017).

References and Footnotes

1. Chemistry of Insect Antifeedants from *Azadirachta Indica*, Part 18: Koot, W.-J.; Ley, S. V. *Tetrahedron* **1995**, *51*, 2077-2090.
2. For a recent and complete review on the chemistry of azadirachtin, see: Ley, S. V.; Denholm, A. A.; Wood, A. *Nat. Prod. Reports* **1993**, 109-157.
3. Mordue (Luntz), A. J.; Blackwell, A. *J. Insect Phys.* **1993**, *39*, 903-924.
4. (a) Lidert, Z. *USP* **1990**, 4943434.
   (b) Ellenberger, W. P.; Ellenberger, S. R. *USP* **1993**, 5229007.
5. (a) Kolb, H. C.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**,

2735-2762.
(b) Anderson, J. C.; Ley, S. V. *Tetrahedron Lett.* **1990**, *31*, 3437-3440.
(c) Anderson, J. C.; Ley, S. V.; Santafianos, D.; Sheppard, R. N. *Tetrahedron* **1991**, *47*, 6813-6850.
6. Blaney, W. M.; Simmonds, M. S. J.; Ley, S. V.; Anderson, J. C.; Bänteli, R.; Denholm, A. A.; Green, P.; Grossman, R. B.; Gutteridge, C. E.; Jennens, L.; Smith, S. C.; Toogood, P. L. *Entomol. Exp. Appl.* in press.
7. Broughton, H. B.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1985**, 46-47.
8. Kuhn, R.; Löw, I.; Trischmann, H. *Chem. Ber.* **1957**, *90*, 203-218.
9. Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240-1241.
10. Compounds **6** and **7** are approximately a 1:10, α:β mixture of C-23 anomers. The small quantities of α-anomer present made it impossible to determine separate NMR data for these compounds.
11. Cheng, Y.-S.; Liu, W.-L.; Chen, S.-H. *Synthesis* **1980**, 223-224.
12. Tigloyl chloride was prepared from commercially available tiglic acid (*trans*-2-methyl-2-butenoic acid) by standard treatment with oxalyl chloride.
13. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Japan* **1979**, *52*, 1989-1993.
14. Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067-1068.
15. (a) Mayer, S. C.; Joullie, M. M. *Synth. Commun.* **1994**, *24*, 2367-2377.
(b) Carpino, L. A.; Mansour, E.-S. M. E.; El-Faham, A. *J. Org. Chem.* **1993**, *58*, 4162-4164.
16. Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 246-248.
17. Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 487-488.
18. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.
19. Ley, S. V.; Wood, A. unpublished observations.
20. Anderson, J. C. PhD Thesis, Imperial College, London, 1990.
21. Denholm, A. A.; Ley, S. V. unpublished observations.
22. Butterworth, J. H.; Morgan, E. D.; *J. Chem. Soc., Chem. Commun.* **1968**, 23-24.

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