Chemistry of insect antifeedants from *Azadirachta indica* (part 21):[1] synthesis of model compounds of azadirachtin using a decalin framework as a functional group scaffolding

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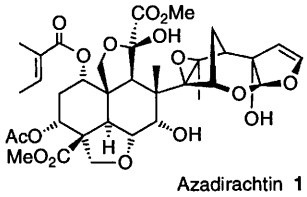
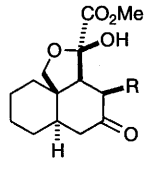
An investigation has been carried out of the synthesis of structural models for the left hand portion of the natural product azadirachtin 1. This work has culminated in a concise and high-yielding route to decalin derivative 2. The significant antifeedant activity shown by this mimic 2 (AI_{50} at 9.4 ppm) is greater than that of the other analogues synthesised during this study and has led to the synthesis of further mimics 3 and 4.

In previous papers [1,2] we have investigated the total synthesis of the insect antifeedant azadirachtin **1** [3] and also the preparation of various model compounds, in order to find simple analogues displaying comparable biological activity.[4] A fairly extensive body of work has now been completed on the preparation of models for the left hand portion of the natural product and has led to the design of an effective route to a decalin fragment **2**, containing some of the functionality required for antifeedant activity. This present paper details the chemical synthesis of, and biological aspects related to, the compounds **2**, **3** and **4**.



Azadirachtin **1**



R= H **2**
R= Me **3**
R= $(CH_2)_3$-CH_2OH **4**

These studies also give ready access to suitable models for possible coupling studies with appropriate hydroxy acetal right hand fragments of the natural product.

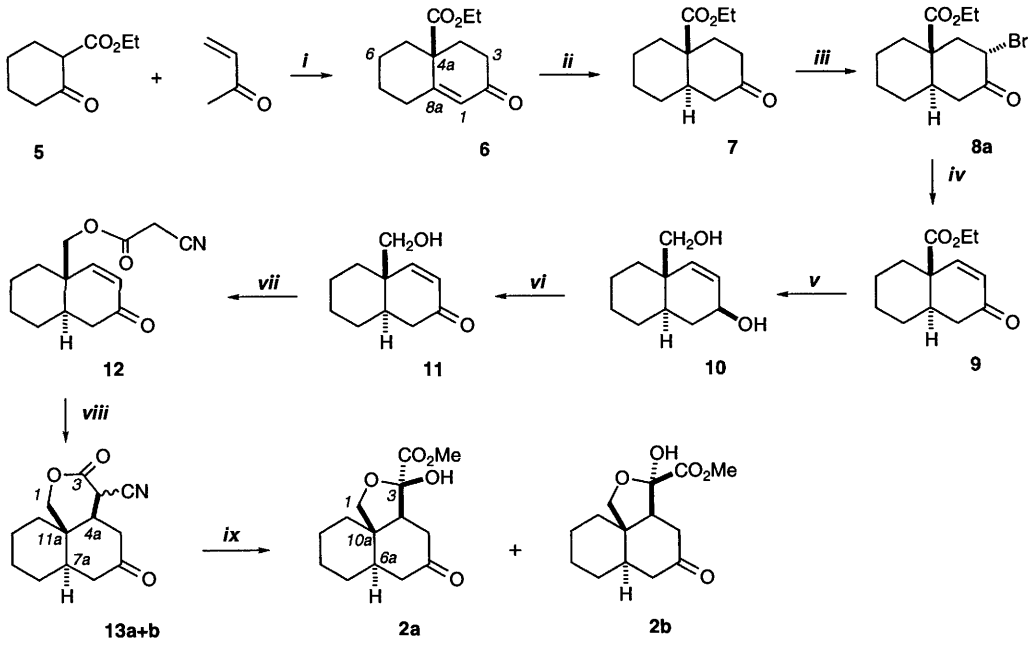
The synthetic approach to the decalin **2** involves nine steps and allows for the preparation of multigram quantities necessary for further coupling studies.[3] The successful strategy for the preparation of **2** is outlined in Scheme 1. In the biological evaluation of the analogues the results show that all three compounds **2**, **3** and **4** do have a significant antifeedant effect, with the model compound **2** being a potent antifeedant (AI = 73%, at 100 ppm). The ready availability of these active compounds means that the biological properties of azadirachtin may be better understood at a molecular level. We are hopeful that other simple analogues can be designed which may show even higher activity based upon these initial encouraging results.

Results and discussion

The synthesis of the decalin model **2** has been achieved in nine steps (Scheme 1) starting from commercially available ethyl 2-oxocyclohexane-1-carboxylate **5**. The functionalised intermediate decalin **11** was synthesised by a modification of a known procedure.[5] Condensation of **5** with methyl vinyl ketone, by heating in the presence of potassium *tert*-butoxide, gave the naphthalenone **6**. Subsequent reduction with hydrogen, using a platinum(IV) oxide catalyst, gave the required *trans* fused decalone **7** in an excellent overall yield. This keto ester intermediate **7** was then brominated by the slow addition of 0.9 mol equivalents of bromine in a chilled solution in diethyl ether, to afford an inseparable mixture of the 3-bromo (**8a**) and 1-bromo (**8b**) derivatives, in an 82% yield and a 3:1 ratio. Attempts directed to improve the yield of this step by using stoichiometric quantities of bromine, or by prolonging the time of the reaction, generated dibromo derivatives. Nevertheless, under the conditions described above a high selectivity for monobromide compounds was observed, although approximately 10% of the starting material **7** often remained unreacted. After investigation of a number of elimination conditions, we found that dehydrobromination carried out by heating the mixture **8a** + **b** in collidine at reflux, gave the unsaturated ketone **9** in a good yield. A trace amount of enone **6** was also formed under these conditions, but the components were readily separable by flash column chromatography on silica gel. With the necessary double bond in place, lithium aluminium hydride reduction of **9** was achieved with high axial selectivity to furnish the β-alcohol **10**. Subsequent selective oxidation of the allylic secondary alcohol was accomplished under phase-transfer catalysis conditions, by using a solid mixture of barium manganate on basic alumina and copper(II) sulfate pentahydrate, to give **11** (Scheme 1).[6]

Preparation of the cyclic nitrile intermediates **13a** + **b** was achieved in a two step sequence. Thus esterification of the hydroxy enone **11** with cyanoacetic acid, in the presence of toluene-*p*-sulfonyl chloride, in pyridine furnished the cyanoacetate **12** which on subsequent treatment with base underwent an intramolecular Michael addition to give **13a** + **b** as a 1:1 inseparable mixture of cyano epimers.

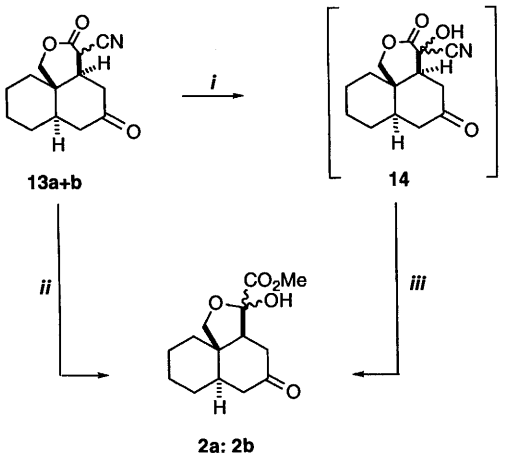
With the α-cyanolactones **13a** + **b** available, the stage was set for a study of the final ring contraction step. This involved an oxidative rearrangement in methanol to afford **2a**, a procedure discovered previously in our laboratories.[2,7] Indeed, the hydroxytetrahydrofurancarboxylate hemiketal moiety could be introduced by treatment of **13a** + **b** with Davis' oxaziridine [2,8]



Scheme 1 *Reagents and conditions:* i, KOBu^t, EtOH, reflux, 4 h, 95%; ii, H_2, PtO_2, EtOAc, 4 h, RT, 98%; iii, Br_2, ether, dark, 0 °C, 7 min, 82% (62% for **8a**); iv, collidine, reflux, 2 h, 68%; v, $LiAlH_4$, diethyl ether, 2 h, 0 °C to RT, 83%; vi, $BaMnO_4$–basic Al_2O_3, $CuSO_4$•$5H_2O$, benzene, 5 h, RT, 80%; vii, HO_2CCH_2CN, toluene-*p*-sulfonyl chloride, py, RT, 35 min, 84%; viii, KOBu^t, Bu^{t}OH, RT, 5 h, 87%; ix, 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)oxaziridine, KOBu^t, methanol, −78 °C to RT, 1 h, then silica gel, CH_2Cl_2, RT, overnight, 80% (1 : 1 mixture at C_3, 40% for **2a**)

in a methanolic solution containing potassium *tert*-butoxide. In this way, **2a** and **2b** were obtained as a mixture of readily separable hemiacetal isomers.

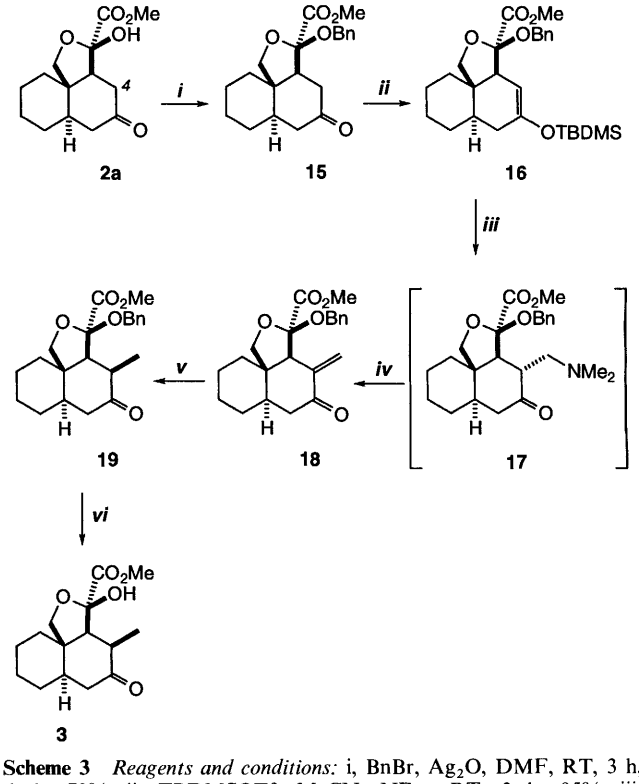
Alternatively, a number of conditions such as direct α-hydroxylation of the α-cyanolactones **13a** + **b** with dimethyldioxirane, followed by methanolysis under mildly acidic conditions,[7] were investigated for this reaction. However, all generated a mixture of both diastereoisomers **2a** and **2b** (Scheme 2). Numerous repetitions of the reaction failed to give



Scheme 2 *Reagents and conditions:* i, dimethyldioxirane, 0 °C, 45 min, 85%; ii, 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)oxaziridine, KOBu^t, methanol, −78 °C to RT, 1 h, then silica gel, CH_2Cl_2, RT, overnight, 80% (1 : 1 mixture at C_3); iii, pyridinium toluene-*p*-sulfonyl chloride (cat), methanol, RT, overnight, then silica gel, CH_2Cl_2, RT, overnight, 72% (1 : 1 mixture at C_3)

a consistent ratio of isomers. It seems that the equilibrium is complex and influenced in an unpredictable fashion. Pleasingly, we found that equilibration of both diastereoisomers was most effectively and simply achieved by stirring the mixture of **13a** + **b** in a slurry of silica gel in dichloromethane at room temperature, to furnish the hydroxytetrahydrofuran-carboxylate hemiketal moiety in quantitative yield, and in a consistent 1 : 1 ratio for the two compounds (Scheme 2).

A suitably protected decalin **15** was synthesised by the reaction of **2a** with benzyl bromide and silver oxide to give the benzyl ether **15** (Scheme 3). The proton and carbon NMR



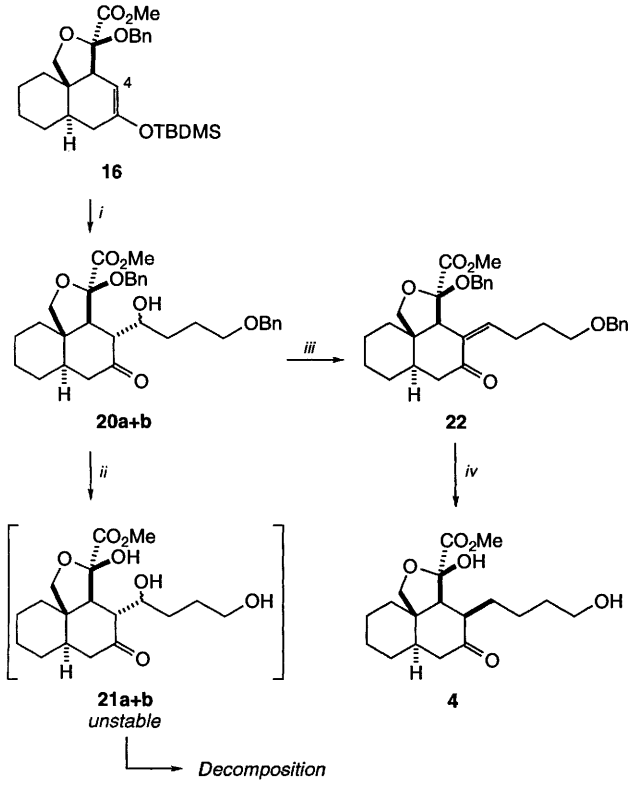
Scheme 3 *Reagents and conditions:* i, BnBr, Ag_2O, DMF, RT, 3 h, dark, 73%; ii; TBDMSOTf, MeCN, NEt_3, RT, 3 h, 95%; iii, $H_2C{=}N(CH_3)_2I$, CH_2Cl_2, RT, 4 h; iv, silica, CH_2Cl_2, RT, overnight, 84% (over two steps); v, H_2, Pd/C, EtOH, RT, 2 h, 98%; vi, H_2, Pd/C, EtOH, RT, 3 h, 98%

spectra were assigned with the aid of a ^1H–^{13}C correlation experiment and they were found to be in complete agreement with the proposed structure and stereochemistry. This compound is suitable for further analogue synthesis and also serves as a useful model in potential coupling studies, needed in the total synthesis of azadirachtin.

Next, we investigated preparation of the (β-)C_4 methyl

compound **3**, as a possible mimic of azadirachtin. This was achieved by allowing compound **15** to react with *tert*-butyldimethylsilyl triflate and triethylamine in acetonitrile to give **16**. Subsequent reaction of this silyl enol ether **16** with Eschenmoser's salt [9] in dichloromethane, afforded the dimethylamino ketone **17**, which was not purified but dissolved in a slurry of silica and dichloromethane and stirred overnight, to give the desired enone **18** in 84% yield over the two steps. Hydrogenation of this intermediate in the presence of Pd/C yielded **19** in quantitative yield as a single (β-)C_4 epimer. Deprotection of the benzyl ether in **19** was effected under standard conditions, by hydrogenation on Pd/C, to give the analogue **3** in an excellent overall yield.

We also wished to have compounds with more complex side chains at C_4, *i.e.* substituents that might emulate the right hand side of azadirachtin. We therefore undertook the preparation of the mimic **4** (Scheme 4). To our surprise, neither Lewis acid-promoted alkylation of silyl enol ethers, nor transmetallation reactions were effective for the alkylation of the ketone **15**, and all methods investigated resulted in recovery of starting material. Although it is well known that carbonyl compounds undergo α-alkylation *via* the corresponding silyl enol ethers, using active alkyl halides in the presence of Lewis acids,[10] our hindered silyl enol ether **16**, even with the strong Lewis acid $TiCl_4$, failed to promote C–C bond formation with a variety of halides. It has also been reported that alkyl groups may be introduced by Lewis acid-promoted phenylthioalkylation of O-silylated enolates using α-chloroalkylphenyl sulfides, followed by Raney nickel desulfurisation, this method being particularly effective for alkylation at the more substituted position of unsymmetrical ketones and hindered enolates.[11] Once again, the silyl enol ether **16** did not undergo addition under a variety of conditions. For these reasons we therefore chose to use the aldol reaction as a means of introducing side chains into the silyl enol ether **16**. In our case, the desired aldehyde was prepared from the commercially available *cis*-4-benzyloxybut-2-en-1-ol, by hydrogenation of the double bond with platinum(IV) oxide and subsequent pyridinium dichromate promoted oxidation, giving 4-benzyloxybutanal, whose spectroscopic data are in agreement with those previously reported (Scheme 4).[12]



Scheme 4 *Reagents and conditions:* i, 4-benzyloxybutan-1-al, BF_3·OEt_2, CH_2Cl_2–Et_2O 9:1, −78 °C, 2 h, 63%; ii, H_2, Pd/C, RT, overnight; iii, BF_3·OEt_2, CH_2Cl_2, 0 °C to RT, 1 h, 46%; iv, H_2, Pd/C, EtOH, RT, overnight, 89%

Reaction of the silyl enol ether **16** with the 4-benzyloxybutanal was best achieved using boron trifluoride–diethyl ether as a mono-coordinating Lewis acid in dichloromethane–diethyl ether at −78 °C.[13] Under these conditions, a 4:1 ratio of epimeric alcohols **20a** + **b** was obtained in 63% yield. The secondary hydroxy group in **20a** + **b** was then efficiently removed by dehydration to afford enone **22**. It has been reported that the Lewis acid, boron trifluoride–diethyl ether, when used in dichloromethane at room temperature, is effective for the easy and mild conversion of secondary and tertiary alcohols into the corresponding thermodynamically more stable alkenes.[14] The optimal reaction time, 45 minutes, was determined by TLC analysis of small aliquots of the reaction mixtures; prolonged reaction times caused deterioration of the alkene products probably *via* carbocation intermediates. Finally, cleavage of the benzyl ethers in **22** and hydrogenation of the double bond was simultaneously carried out by hydrogenation on Pd/C to give the desired analogue **4** in a good overall yield (Scheme 4). Unfortunately it was not possible to deprotect **20a** + **b** effectively and hydrogenolysis on palladium resulted in eventual decomposition.

The syntheses delineated above exemplifies the flexibility of our strategy, which should allow the preparation of many other simple decalin fragments for mimicking the biological action of azadirachtin.

Biological results

The aim of this work has been to devise routes to analogues of azadirachtin, since their biological evaluation may yield insight into fundamental feeding and growth development processes by insects. Apart from our own studies, we are not aware of any other publications in this area.

Against the African leafworm, *Spodoptera littoralis*, it can be seen that the hydroxyfuranacetal moiety is clearly important for the expression of potent antifeedant activity.[15] We have shown that the stereochemistry at C_3 in the decalin model (C_{11} in azadirachtin) is crucial for the biological properties of analogues of azadirachtin **1**, since the *S* epimer at C_3, analogue **2a** is associated with potent antifeedant activity, whereas the *R* epimer at C_3, compound **2b**, results in loss of activity (Table 1). The differences in the activity of analogues **2a**, **3** and **4** indicate the importance of the substitution at C_4. Analogues **2a** and **3** show potent antifeedant activity at 100 ppm, whereas analogue **4** stimulates feeding at this concentration.

Although none of these analogues match the potency of azadirachtin, the antifeedant activity of analogue **2a** is greater

Table 1 Effects of compounds **2a**, **2b**, **3**, **4**, **18** and azadirachtin **1** on the feeding behaviour of larvae of *Spodoptera littoralis*

Compound	Antifeedant index[a] at 100 ppm	AI_{50}[b]/ppm
2a (*S* epimer at C_3)	73*	9.4
2b (*R* epimer at C_3)	24	820
3	44*	154
4	−11	640
18	39*	> 1000
Azadirachtin, **1**	100*	0.06

[a] Antifeedant index = $[(C - T)/(C + T)]\%$, * = significant activity $p < 0.05$ (Wilcoxon matched pairs test, $n = 10$). [b] AI_{50} = concentration (ppm) required to elicit an antifeedant index of 50% (probit analysis).

than that recorded from any of the other dihydrofuran or decalin fragments of azadirachtin **1**.[1,2] This makes it worthy of further biological and chemical studies.

Experimental

Biological studies and general details[1]

4a-Ethoxycarbonyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one 6

Potassium *tert*-butoxide (580.0 mg, 5.3 mmol) was slowly added *via* cannula to a stirred solution of ethyl 2-oxocyclohexane-1-carboxylate **5** (16.0 cm^3, 100.0 mmol) and methyl vinyl ketone (8.3 cm^3, 100.0 mmol) in anhydrous ethanol (50 cm^3). The mixture was heated to reflux for 4 h. The solution was then allowed to cool, poured into 1 M HCl (6 cm^3) and the solvent was evaporated. The residue was diluted with diethyl ether (300 cm^3) and water (25 cm^3) and the layers were separated. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* affording *compound* **6** as a viscous oil (19.6 g, 88.0 mmol, 88%) (Found: C, 70.4; H, 8.3. $C_{13}H_{18}O_3$ requires C, 70.3; H, 8.2%); ν_{max}/cm^{-1} 2862, 1723, 1680, 1625, 1451, 1367, 1297, 1233, 1146, 1053, 1018; δ_H(400 MHz) 5.90 (1 H, s, 1-H), 4.20 (1 H, q, *J* 7.0, CO_2CH_2Me), 4.19 (1 H, q, *J* 7.0, CO_2CH_2Me), 2.61–1.29 (12 H, m, 3-H, 4-H, 5-H, 6-H, 7-H, 8-H), 1.25 (3 H, t, *J* 7.1, CO_2CH_2Me); δ_C(100 MHz) 198.9 (C-2), 173.4 (CO_2Et), 163.2 (C-8a), 126.5 (C-1), 61.4 (CO_2CH_2Me), 48.9 (C-4a), 38.5 (C-3), 34.9, 34.7 and 34.2 (C-5, C-7 and C-8), 26.6 (C-6), 23.2 (C-4), 14.3 (CO_2CH_2Me); *m*/*z* (EI) 222, 149, 138, 121, 107.

(4a*S,8a*R**)-4a-Ethoxycarbonylperhydronaphthalen-2-one 7[5]**

Platinum(IV) oxide (567.8 mg, 2.5 mmol) was added to a solution of **6** (16.0 g, 72.0 mmol) in ethyl acetate (900 cm^3). After purging with hydrogen, the reaction mixture was stirred vigorously under a hydrogen atmosphere at room temperature for 4 h. The suspension was filtered through a pad of Celite®, washed with ethyl acetate (3 × 200 cm^3) and the filtrate was concentrated. Purification of the residue by flash column chromatography (eluent petrol–ethyl acetate 4:1) gave *compound* **7** as a colourless oil (15.8 g, 70.6 mmol, 98%) (Found: C, 69.7; H, 9.1. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%); ν_{max}/cm^{-1} 2859, 1718, 1450, 1372, 1299, 1237, 1136, 1034, 1022; δ_H(400 MHz) 4.19 (1 H, q, *J* 7.0, CO_2CH_2Me), 4.18 (1 H, q, *J* 7.1, CO_2CH_2Me), 2.96 (2 H, t, *J* 14.5, 1-H or 3-H), 1.27 (3 H, t, *J* 7.0, CO_2CH_2Me), 2.31–1.43 (13 H, m, 1-H or 3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 8a-H); δ_C(100 MHz) 210.9 (C-2), 174.6 (CO_2Et), 60.3 (CO_2CH_2Me), 47.2 (C-4a), 45.4 (C-1), 44.6 (C-8a), 39.1 (C-3), 37.4, 37.2 (C7 and C8), 29.2 (C-5), 25.7 (C-6), 23.3 (C-4), 14.3 (CO_2CH_2Me); *m*/*z* (EI) 224, 196, 178, 168, 150, 139, 122.

(4a*S,8a*R**)-3-Bromo-4a-ethoxycarbonylperhydronaphthalen-2-one 8a[5]**

Bromine (1.7 g, 5.0 mmol, 258.0 μl) was added, in the dark and with stirring, to a solution of **7** (2.2 g, 10.0 mmol) in ether (75 cm^3) cooled in ice. The mixture was chilled at 0 °C for 7 min and then was washed at 0 °C, sequentially with sodium sulfite (20 cm^3) and saturated sodium hydrogen carbonate (30 cm^3). After extraction with ethyl acetate (2 × 150 cm^3), the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, to afford an inseparable 3:1 mixture of 3-bromo and 1-bromo ketones **8a** + **b** as a white solid, which was recrystallised from ether to give the *bromoketones* **8a** + **b** as white crystals (2.5 g, 8.2 mmol, 82%) (Found: C, 51.4; H, 6.4. $C_{13}H_{19}O_3Br$ requires C, 51.5; H, 6.3%); ν_{max}/cm^{-1} 2854, 1719, 1456, 1377, 1292, 1239, 1198, 1158, 1136, 1120, 1066, 1036; data for **8a**: δ_H(500 MHz) 4.54 (1 H, ddd, *J* 14.0, 6.0, 1.0, 3-H), 4.23 (2 H, m, CO_2CH_2Me), 3.13 (1 H, dd, *J* 15.0, 1.0, 1-H), 2.86 (1 H, dd, *J* 13.5, 6.0, 4-H), 2.48 (1 H, dd, *J* 15.0, 14.0, 1-H), 1.99 (1 H, dd, *J* 13.5, 13.5, 4-H), 1.83 (1 H, m, 7-H), 1.75 (1 H, m, 8-H), 1.65 (1 H, m, 8a-H), 1.46 (1 H, m, 8-H), 1.35 (3 H, t, *J* 7.0, CO_2CH_2Me), 2.24–1.15 (5 H, m, 5-H, 6-H, 1 × 7-H); δ_C(100 MHz) 200.5 (C-2), 173.8 (CO_2Et), 60.9 (CO_2CH_2Me), 53.2 (C-3), 49.5 (C-4a), 48.9 (C-1), 45.2 (C-8a), 44.7 (C-4), 36.9 (C-8), 28.7 (C-5), 25.4 (C-6), 22.7 (C-7), 14.3 (CO_2CH_2Me); *m*/*z* (EI) 302 (M^+), 276, 259, 231, 223, 196, 168, 139, 122.

(4a*S,8a*R**)-4a-Ethoxycarbonyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one 9[5]**

Bromoketones **8a** + **b** (9.0 g, 29.7 mmol) and 2,4,6-trimethylpyridine (collidine; 16.0 cm^3, 14.7 g) were heated to reflux (170–180 °C) for 45 min. The mixture was then cooled, quenched with ice-cold 1 M HCl (until acidic pH) and extracted with ethyl acetate (3 × 250 cm^3). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, giving a pale yellow oil. Purification of the residue by flash column chromatography (eluent petrol–ethyl acetate 7:3) afforded *compound* **9** as a viscous colourless oil (4.5 g, 20.2 mmol, 68%); ν_{max}/cm^{-1} 2860, 1728, 1686, 1450, 1322, 1266, 1094, 1022; δ_H(400 MHz) 6.65 (1 H, d, *J* 10.0, 4-H), 5.93 (1 H, d, *J* 10.0, 3-H), 4.14 (2 H, m, CO_2CH_2Me), 3.04 (1 H, dd, *J* 18.0, 4.3, 1-H), 2.25 (1 H, dd, *J* 18.0, 14.0, 1-H), 1.23 (3 H, t, *J* 7.0, CO_2CH_2Me), 2.05–1.26 (9 H, m, 5-H, 6-H, 7-H, 8-H, 8a-H); δ_C(100 MHz) 200.0 (C-2), 171.5 (CO_2Et), 152.2 (C-4), 129.5 (C-3), 60.8 (CO_2CH_2Me), 48.8 (C-4a), 43.3 (C-8a), 41.6 (C-1), 35.9 (C-8), 28.2 (C-5), 25.6 (C-6), 23.4 (C-7), 14.1 (CO_2CH_2Me); *m*/*z* (EI) 222 (M^+), 194, 149, 121, 107 [Found: (EI) M^+, 222.1255. $C_{13}H_{18}O_3$ requires *M*, 222.1256].

(4a*S,8a*R**)-4a-Hydroxymethyl-1,2,4a,5,6,7,8,8a-octahydro-2-naphthol 10[5]**

Lithium aluminium hydride (1.17 g, 30.7 mmol) was added portionwise to a solution of **9** (4.5 g, 20.2 mmol) in diethyl ether (300 cm^3) cooled to 0 °C. The reaction was allowed to warm to room temperature and was stirred for 24 h. The mixture was recooled to 0 °C and poured into aqueous sodium sulfate. After extraction with ethyl acetate (400 cm^3) the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* affording a solid residue which was purified by crystallisation from petrol–acetone to give *diol* **10** as white crystals (3.2 g, 17.5 mmol, 83%); mp 126 °C (lit.,[6] 126 °C) (Found: C, 72.5; H, 10.1. $C_{11}H_{18}O_2$ requires C, 72.5; H, 10.0%); ν_{max}/cm^{-1} 3320, 2359, 1454, 1027; δ_H(500 MHz) 5.78 (1 H, ddd, *J* 10.0, 2.5, 1.0, 3-H), 5.57 (1 H, dd, *J* 10.0, 1.5, 4-H), 4.35 (1 H, m, 2-H), 3.88 (1 H, br d, *J* 10.7, CH_2OH), 3.61 (1 H, br d, *J* 10.5, CH_2OH), 2.23 (1 H, br s, 1-H), 2.01–1.09 (11 H, m, 5-H, 6-H, 7-H, 8-H, 8a-H, 2 × OH), 1.83 (1 H, br s, 1-H); δ_C(100 MHz) 136.7 (C-3), 132.5 (C-4), 68.5 (C-2), 64.1 (CH_2OH), 42.1 (C-8a), 40.0 (C-4a), 35.7 (C-1), 34.5 (C-8), 27.9 (C-5), 26.5 (C-6), 21.4 (C-7); *m*/*z* (EI) 182 (M^+), 178, 164, 151, 134, 107.

(4a*S,8a*R**)-4a-Hydroxymethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one 11[5]**

The oxidation of **10** was performed on a solid support ($BaMnO_4$–Al_2O_3, 1:1.2) by stirring the benzene solution (200 cm^3) of the alcohol **10** (3.0 g, 16.5 mmol) with the solid mixture of $BaMnO_4$ (21.3 g, 96.6 mmol) and $CuSO_4 \cdot 5H_2O$ (1.8 g, 7.2 mmol) at room temperature. After 5 h, the supported reagent was removed by filtration, washing with ethyl acetate (350 cm^3). Concentration *in vacuo* of the filtrate gave a viscous colourless oil. Purification by silica gel chromatography (eluent petrol–ethyl acetate 1:1) afforded the desired *compound* **11** as white crystals (2.4 g, 13.2 mmol, 80%); mp 167–168 °C; ν_{max}/cm^{-1} 3418, 2855, 1666, 1453, 1386, 1280, 1116, 1082; δ_H(400 MHz) 6.77 (1 H, d, *J* 10.0, 3-H), 6.02 (1 H, d, *J* 10.0, 4-H), 4.01 (1 H, dd, *J* 11.0, 4.5, CH_2OH), 3.81 (1 H, br d, *J* 11.0, CH_2OH), 2.55 (1 H, dd, *J* 8.0, 14.5, 1-H), 2.20 (1 H, dd, *J* 14.5, 4.5, 1-H), 2.03–1.23 (10 H, m, 5-H, 6-H, 7-H, 8-H, 8a-H, OH); δ_C(100 MHz) 200.5 (C-2), 158.4 (C-4), 129.7 (C-3), 63.3 (CH_2OH), 42.8 (C-8a), 41.3 and 41.0 (C-1 and C-4a), 32.9 (C-8), 27.5 (C-5), 25.8 (C-6), 21.4 (C-7); *m*/*z* (EI) 180, 150, 138, 121, 108 [Found: (EI) M^+, 180.1148. $C_{11}H_{16}O_2$ requires *M*, 180.1150].

(4a*S,8a*R**)-4a-(2-Cyanoacetoxy)methyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one 12**

Toluene-*p*-sulfonyl chloride (5.1 g, 26.7 mmol) was added slowly to a stirred solution of the ketol **11** (2.4 g, 13.2 mmol), cyanoacetic acid (3.4 g, 40.0 mmol) and pyridine (7.5 cm^3, 93.9 mmol) in dichloromethane (200 cm^3). After 20 min, the reaction mixture was poured into 1 M HCl (250 cm^3) and extracted with dichloromethane (450 cm^3). The combined organic fractions were washed with saturated sodium hydrogen carbonate (200 cm^3), then dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the crude product by flash column chromatography (eluent petrol–ethyl acetate 1:1) afforded *cyanoacetate* **12** as a very viscous colourless oil which quickly solidified on standing at low temperature (4 °C) (2.7 g, 11.1 mmol, 84%); mp 95 °C (Found: C, 67.8; H, 6.9; N, 5.5. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.7%); ν_{max}/cm^{-1} 2862, 1747, 1682, 1454, 1381, 1250, 1124, 1013; δ_H(400 MHz) 6.71 (1 H, d, *J* 10.0, 3-H), 6.02 (1 H, d, *J* 10.0, 4-H), 4.62 (1 H, d, *J* 11.0, CH_2CN), 4.32 (1 H, d, *J* 11.0, CH_2CN), 3.42 (2 H, s, $CH_2O_2CCH_2CN$), 2.42–1.18 (11 H, m, 1-H, 5-H, 6-H, 7-H, 8-H, 8a-H); δ_C(100 MHz) 198.9 (C-2), 162.8 ($CH_2O_2CCH_2CN$), 155.9 (C-4), 130.0 (C-3), 112.6 (CN), 67.1 ($CH_2O_2CCH_2CN$), 42.7 (C-8a), 41.0 (C-1), 39.2 (C-4a), 33.0 (C-8), 27.5 (C-5), 25.4 (C-6), 24.7 (CH_2CN), 21.3 (C-7); *m*/*z* (EI) 247 (M^+), 162, 149, 121, 107.

(4*RS,4a*R**,7a*R**,11a*S**)-4-Cyanoperhydronaphtho[8a,1-*c*]-pyran-3,6-dione 13a + b**

A stirred solution of **12** (462.0 mg, 1.9 mmol) in dry *tert*-butyl alcohol (80 cm^3) was treated with potassium *tert*-butoxide (231.0 mg, 2.1 mmol). After continued stirring for 5 h, the reaction was quenched with 1 M HCl (10 cm^3) and the solvent evaporated. Dichloromethane (225 cm^3) was then added and the layers separated. The aqueous phase was extracted with ethyl acetate (3 × 50 cm^3). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*, affording a white solid which was slowly crystallised from ethanol to give *cyanolactones* **13a** + **b** as an inseparable mixture of two isomers in a ratio 1:1, epimeric at C_4 (401.0 mg, 1.7 mmol, 87%). Data for mixture (Found: C, 67.9; H, 7.0; N, 5.6. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.7%); ν_{max}/cm^{-1} 2928, 1742, 1708, 1452, 1353, 1276, 1202, 1180, 1164, 1040, 1016; δ_H(500 MHz) (distinguishable signals only) 4.69 (1 H, dd, *J* 12.5, 1.5, 1-H), 4.59 (1 H, d, *J* 12.5, 1-H), 4.57 (1 H, d, *J* 12.5, 1-H), 4.08 (1 H, d, *J* 5.0, 4-H), 4.04 (1 H, dd, *J* 12.5, 1.0, 1-H), 3.38 (1 H, d, *J* 9.5, 4-H), 3.01 (1 H, m, 4a-H), 2.96 (1 H, m, 4a-H), 2.45–2.05 (8 H, m, 5-H, 5-H, 6-H and 6-H); δ_C(100 MHz) 208.2, 204.6 (C-6), 163.9, 162.3 (C-2), 115.0, 114.0 (CN), 68.5, 66.2 (C-1), 43.7, 43.2 (C-4a), 43.6, 42.9 (C-11a), 42.4, 39.8 (C-4), 42.1, 41.1 (C-7), 37.9, 36.6 (C-7a), 37.1, 35.2 (C-5), 34.6, 33.3 (C-8), 28.6, 27.8 (C-11), 25.4, 25.1 (C-10), 21.3, 21.0 (C-9); *m*/*z* (EI) 247 (M^+), 192, 163, 109.

Methyl (3*SR,3a*R**,6a*R**,10a*R**)-3-hydroxy-5-oxoperhydronaphtho[1,8a-*c*]furan-3-carboxylate 2a and 2b**

Potassium *tert*-butoxide (123.4 mg, 1.1 mmol) was added to a stirred solution of **13a** + **b** (247.0 mg, 1.0 mmol) in dry methanol (20 cm^3). The suspension was cooled to −78 °C and 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)oxaziridine (740.0 mg, 2.0 mmol) was added. The mixture was allowed to warm to room temperature and stirred. After 1 h the solvent was removed *in vacuo* and azeotroped with dichloromethane to remove any remaining methanol. Repeated purification by flash column chromatography (eluent petrol–ethyl acetate 6:4 then dichloromethane–diethyl ether 9:1) afforded a mixture of the two *hemiacetal isomers* **2a** and **2b**, which were dissolved in a slurry of silica and dichloromethane and stirred overnight to give a 1:1 readily separable mixture of the two epimers at C_3, **2a** and **2b** (214.4 mg, 0.8 mmol, 80%); ν_{max}/cm^{-1} 3415, 2857, 1747, 1714, 1449, 1265, 1192, 1010; δ_H(500 MHz) 4.05 (1 H, d, *J* 9.5, 1-H), 3.96 (1 H, dd, *J* 9.5, 2.0, 1-H), 3.83 (3 H, s, CO_2Me), 3.73 (1 H, br s, OH), 2.65 (1 H, dd, *J* 7.0, 1.5, 3a-H), 2.43 (1 H, dd, *J* 18.5, 14.5, 6-H), 2.38 (1 H, dd, *J* 16.5, 7.0, 4-H), 2.31 (1 H, dd, *J* 16.5, 1.5, 4-H), 2.14 (1 H, dd, *J* 18.5, 3.5, 6-H), 1.96–1.24 (9 H, m, 6a-H, 7-H, 8-H, 9-H, 10-H); δ_C(100 MHz) 211.1 (C-5), 170.2 (CO_2Me), 103.2 (C-3), 70.1 (C-1), 53.5 (CO_2Me), 50.8 (C-3a), 44.7 (C-10a), 41.6 (C-6), 38.9 (C-6a), 38.7 (C-4), 37.0 (C-7), 29.1 (C-10), 25.5 (C-9), 23.8 (C-8); *m*/*z* (EI) 268 (M^+), 250, 236, 222, 209, 163, 121, 109 [Found: (EI) M^+, 268.1309. $C_{14}H_{20}O_5$ requires *M*, 268.1311]. Differential data for **2b**; δ_H(500 MHz) 4.03 (1 H, d, *J* 9.5, 1-H), 3.94 (1 H, dd, *J* 9.5, 2.0, 1-H), 3.81 (3 H, s, CO_2Me), 2.62 (1 H, dd, *J* 7.0, 2.0, 3a-H), 2.41 (1 H, dd, *J* 18.5, 14.5, 6-H), 2.37 (1 H, dd, *J* 17.0, 7.0, 4-H), 2.30 (1 H, dd, *J* 17.0, 2.0, 4-H), 2.11 (1 H, dd, *J* 18.5, 3.5, 6-H), 1.96–1.24 (10 H, m, 6a-H, 7-H, 8-H, 9-H, 10-H).

Methyl (3*S,3a*S**,6a*R**,10a*R**)-3-benzyloxy-5-oxoperhydronaphtho[1,8a-*c*]furan-3-carboxylate 15**

Freshly prepared silver(I) oxide (1.4 g, 6.0 mmol, 6.0 equiv.) and benzyl bromide (1.2 cm^3, 10.0 mmol) were added to a stirred solution of the hemiketal **2a** (268.0 mg, 1.0 mmol) in dry DMF (34 cm^3) in the dark. After the mixture had been stirred at room temperature for 3 h, it was filtered through a pad of Celite® which was washed with ether (125 cm^3). The solvent was removed *in vacuo* and the resultant cloudy solution was then filtered through a pad of silica gel and washed with ethyl acetate (2 × 75 cm^3). The fractions were evaporated *in vacuo* to give a DMF solution which was washed with a mixture of ether–water 8:1. The ether phase was washed a second time with water (50 cm^3), dried ($MgSO_4$) and evaporated giving a viscous pale yellow oil. Purification by flash column chromatography (eluent petrol–ethyl acetate 4:1 with 1% NEt_3) afforded a solid, which was recrystallised from ether to give *ketone* **15** as white crystals (261.3 mg, 7.3 mmol, 73%); mp 98–99 °C (Found: C, 70.4; H, 7.4. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%); ν_{max}/cm^{-1} 2866, 2360, 1748, 1714, 1608, 1453, 1386, 1235, 1180, 1053; δ_H(500 MHz) 7.30 (5 H, m, *H*Ph), 4.56 (1 H, d, *J* 12.0, OCH_2Ph), 4.42 (1 H, d, *J* 12.0, OCH_2Ph), 4.04 (1 H, d, *J* 9.5, 1-H), 3.70 (3 H, s, CO_2Me), 3.63 (1 H, d, *J* 9.5, 1-H), 2.68 (1 H, d, *J* 16.5, 4-H), 2.38 (1 H, dd, *J* 16.5, 7.5, 4-H), 2.28 (1 H, d, *J* 7.5, 3a-H), 2.15 (1 H, dd, *J* 18.5, 14.5, 6-H), 2.01 (1 H, dd, *J* 18.5, 3.5, 6-H), 1.73 (1 H, m, 6a-H), 1.78–1.47 (8 H, m, 7-H, 8-H, 9-H, 10-H); δ_C(100 MHz) 210.3 (C-5), 168.9 (CO_2Me), 137.0 (*C*Ph), 128.3, 127.6 (×2), 127.4 (×2) (5 × *C*HPh), 106.1 (C-3), 69.3 (C-1), 65.7 (OCH_2Ph), 53.1 (CO_2Me), 52.6 (C-3a), 44.3 (C-10a), 41.6 (C-6), 38.9 (C-6a), 38.8 (C-4), 36.7 (C-7), 29.0 (C-10), 25.5 (C-9), 23.7 (C-8); *m*/*z* (EI) 358 (M^+), 299, 252, 220, 150, 121, 109.

Methyl (3*S,3a*S**,6a*R**,10a*R**)-3-benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3,3a,6,6a,7,8,9,10-octahydro-1*H*-naphtho-[1,8a-*c*]furan-3-carboxylate 16**

tert-Butyldimethylsilyl triflate (781.9 μl, 3.4 mmol, 4 equiv.) was added to a solution of the ketone **15** (300.0 mg, 0.8 mmol) and NEt_3 (1.9 cm^3) in acetonitrile (5.1 cm^3). The mixture was stirred for 4 h at room temperature and then poured into saturated aqueous sodium hydrogen carbonate (50 cm^3) and extracted with diethyl ether (2 × 125 cm^3). The organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid which was purified by flash column chromatography (eluent petrol–ethyl acetate 95:5 with 1% NEt_3) and recrystallised from petrol–dichloromethane, affording *silyl enol ether* **16** as white needles (358.7 mg, 0.76 mmol, 95%); mp 65–66 °C (Found: C, 68.7; H, 8.7. $C_{27}H_{40}O_5Si$ requires C, 68.6; H, 8.6%); ν_{max}/cm^{-1} 2953, 2858, 2232, 1750, 1672, 1498, 1391, 1336, 1254, 1135, 1109, 1008; δ_H(400 MHz) 7.28 (5 H, m, *H*Ph), 4.86 (1 H, d, *J* 3.5, 4-H), 4.65 (1 H, d, *J* 11.5, OCH_2Ph), 4.34 (1 H, d, *J* 11.5, OCH_2Ph), 3.99 (1 H, d, *J* 8.5, 1-H), 3.81 (1 H, d, *J* 8.5, 1-H), 3.75 (3 H, s, CO_2Me), 2.86 (1 H, br s, 3a-H), 2.28–0.87 (11 H, m, 6-H, 6a-H, 7-H, 8-H, 9-H, 10-H),

0.84 [9 H, s, $SiC(Me)_3$], −0.02 (3 H, s, SiMe), −0.07 (3 H, s, SiMe); δ_C(100 MHz) 171.5 (CO_2Me), 149.4 (C-5), 137.9 (*C*Ph), 128.1 (×4), 127.4 (5 × *C*HPh), 106.4 (C-3), 101.4 (C-4), 68.1 (C-1), 66.5 (OCH_2Ph), 55.0 (C-3a), 52.5 (CO_2Me), 45.4 (C-10a), 39.5 (C-6a), 35.6 (C-7), 33.5 (C-6), 30.6 (C-10), 26.1 [3 × $SiC(Me)_3$], 25.6 (2 × SiMe), 25.9 (C-9), 23.0 (C-8), 17.9 [$SiC(Me)_3$], −4.4 (SiMe), −5.0 (SiMe); *m*/*z* (EI) 413 (M^+ − CO_2Me), 381, 366, 278, 199, 162, 136, 113, 105.

Methyl (3*S,3a*S**,6a*R**,10a*R**)-3-benzyloxy-4-methylidene-5-oxoperhydronaphtho[1,8a-*c*]furan-3-carboxylate 18**

A solution of **16** (236.1 mg, 0.5 mmol) and *N*,*N*-dimethylmethylideneammonium iodide (925.9 mg, 5.0 mmol) in dichloromethane (13 cm^3) was stirred at room temperature for 20 h. The resulting mixture was poured into saturated aqueous sodium hydrogen carbonate, extracted with dichloromethane (3 × 50 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then redissolved in dichloromethane (50 cm^3) and silica gel was added (5 g). The resulting slurry was stirred for 24 h before being filtered. The residue was washed with ethyl acetate (100 cm^3) and the combined organic fractions were concentrated *in vacuo*. Purification by flash column chromatography (eluent petrol–ethyl acetate 3:2 with 1% NEt_3) afforded a white solid, which was crystallised from petrol–dichloromethane to give *compound* **18** as white crystals (148.2 mg, 0.4 mmol, 84%); mp 87–88 °C (Found: C, 71.3; H, 7.1. $C_{22}H_{26}O_5$ requires C, 71.4; H, 7.1%); ν_{max}/cm^{-1} 2926, 2854, 1750, 1705, 1616, 1451, 1320, 1253, 1233, 1072, 1021; δ_H(400 MHz) 7.26 (5 H, m, *H*Ph), 6.01 (1 H, d, *J* 1.5, C=CH_2), 5.23 (1 H, d, *J* 1.5, C=CH_2), 4.58 (1 H, d, *J* 12.0, OCH_2Ph), 4.46 (1 H, d, *J* 12.0, OCH_2Ph), 4.08 (1 H, d, *J* 9.5, 1-H), 3.74 (3 H, s, CO_2Me), 3.72 (1 H, d, *J* 9.5, 1-H), 2.87 (1 H, s, 3a-H), 2.34 (1 H, dd, *J* 17.5, 15.0, 6-H), 1.98 (1 H, dd, *J* 17.5, 2.5, 6-H), 1.95–1.20 (9 H, m, 6a-H, 7-H, 8-H, 9-H, 10-H); δ_C(100 MHz) 200.9 (C-5), 171.5 (CO_2Me), 141.0 (C=*C*H_2), 137.1 (*C*Ph), 128.3 (×2), 127.6, 127.4 (×2) (5 × *C*HPh), 124.6 (C-4), 106.5 (C-3), 69.7 (OCH_2Ph), 65.6 (C-1), 61.3 (C-3a), 52.6 (CO_2Me), 46.4 (C-10a), 41.4 (C-6), 39.1 (C-6a), 38.6 (C-7), 28.8 (C-10), 25.4 (C-9), 23.5 (C-8); *m*/*z* (EI) 370 (M^+), 352, 264, 162, 105.

Methyl (3*S,3a*S**,4*R**,6a*R**,10a*R**)-3-benzyloxy-4-methyl-5-oxoperhydronaphtho[1,8a-*c*]furan-3-carboxylate 19**

Pd/C (10%) (31.9 mg) was added to a stirred solution of **18** (111.1 mg, 0.3 mmol) in ethanol (20 cm^3). After purging with hydrogen, the mixture was stirred vigorously under a hydrogen atmosphere for 2 h, and then filtered through a pad of Celite®, washed with ethyl acetate (75 cm^3) and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent petrol–ethyl acetate 3:2) to give *compound* **19** as a viscous colourless oil (109.0 mg, 0.3 mmol, 98%) (Found: C, 70.7; H, 7.3. $C_{22}H_{28}O_5$ requires C, 70.9; H, 7.5%); ν_{max}/cm^{-1} 2858, 1749, 1715, 1452, 1330, 1252, 1221, 1154, 1020; δ_H(400 MHz) 7.28 (5 H, m, *H*Ph), 4.67 (1 H, d, *J* 12.0, OCH_2Ph), 4.50 (1 H, d, *J* 12.0, OCH_2Ph), 4.02 (1 H, d, *J* 9.5, 1-H), 3.77 (3 H, s, CO_2Me), 3.52 (1 H, d, *J* 9.5, 1-H), 2.49 (1 H, apparent quintet, *J* 6.5, 4-H), 2.45 (1 H, d, *J* 6.5, 3a-H), 2.03 (1 H, dd, *J* 14.0, 5.0, 6-H), 1.16 (3 H, d, *J* 6.5, Me), 1.99–1.22 (10 H, m, 1 × 6-H, 6a-H, 7-H, 8-H, 9-H, 10-H); δ_C(100 MHz) 200.1 (C-5), 169.6 (CO_2Me), 137.4 (*C*Ph), 128.3, 127.7 (×2), 127.5 (×2) (5 × *C*H-Ph), 106.6 (C-3), 70.1 (C-1), 65.8 (OCH_2Ph), 59.5 (C-3a), 52.6 (CO_2Me), 46.1 (C-6), 41.3 (C-10a), 40.9 (C-6a), 39.0 (C-4), 38.8 (C-7), 28.7 (C-10), 25.5 (C-9), 23.8 (C-8), 11.7 (Me); *m*/*z* (EI) 372 (M^+), 313, 266, 234, 207, 164, 122, 105.

Methyl (3*S,3a*R**,4*R**,6a*R**,10a*R**)-3-hydroxy-4-methyl-5-oxoperhydronaphtho[1,8a-*c*]furan-3-carboxylate 3**

Pd/C (10%) (85.3 mg) was added to a solution of **19** (109.0 mg, 0.3 mmol) in dry ethanol (20 cm^3). The mixture was hydrogenated for 3 h as above, then filtered through a pad of Celite® and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent petrol–ethyl acetate 1:1) to give *compound* **3** as white crystals (81.9 mg, 0.29 mmol, 98%); mp 111–112 °C (Found: C, 63.9; H, 8.0. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.9%); ν_{max}/cm^{-1} 3470, 2855, 1746, 1714, 1448, 1284, 1251, 1173, 1071, 1048; δ_H(400 MHz) 4.04 (1 H, d, *J* 9.0, 1-H), 3.93 (1 H, d, *J* 9.0, 1-H), 3.83 (3 H, s, CO_2Me), 3.80 (1 H, br s, OH), 2.67 (1 H, d, *J* 6.5, 3a-H), 2.51 (1 H, apparent quintet, *J* 6.5, 4-H), 2.50 (1 H, m, 6-H), 2.13 (1 H, dd, *J* 18.5, 3.5, 6-H), 1.90 (1 H, br d, *J* 11.5, 6a-H), 1.80–1.12 (8 H, m, 7-H, 8-H, 9-H, 10-H), 1.01 (3 H, d, *J* 6.5, Me); δ_C(100 MHz) 212.5 (C-5), 170.8 (CO_2Me), 102.4 (C-3), 70.4 (C-1), 56.5 (C-3a), 53.6 (CO_2Me), 45.6 (C-6), 40.6 (C-6a), 40.5 (C-10a), 39.2 (C-4), 38.8 (C-7), 28.7 (C-10), 25.6 (C-9), 23.9 (C-8), 11.5 (Me); *m*/*z* (EI) 282 (M^+), 264, 250, 223, 196, 168, 165, 144, 112, 103.

Methyl (3*S,3a*S**,4*R**,6a*R**,10a*R**,1′*RS**)-3-benzyloxy-4-(4-benzyloxy-1-hydroxybutyl)-5-oxoperhydronaphtho[1,8a-*c*]-furan-3-carboxylate 20a + b**

BF_3·OEt_2 (31.8 μl, 0.26 mmol) was carefully added to a solution of 4-benzyloxybutanal[11] (41.7 mg, 0.23 mmol) in dichloromethane–diethyl ether 9:1 (2 cm^3) cooled to −78 °C. After stirring for 15 min a solution of the silyl enol ether **16** (54.0 mg, 0.12 mmol) in dichloromethane–ether 9:1 (2 cm^3) was added. After further stirring at −78 °C for 2 h, the mixture was quenched by the addition of saturated aqueous sodium hydrogen carbonate (2 cm^3), and extracted with dichloromethane (2 × 25 cm^3) and ethyl acetate (2 × 20 cm^3). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*, to give a colourlesss oil which was purified by flash column chromatography (eluent petrol–ethyl acetate 1:1) affording a 4:1 inseparable mixture of the two *isomers* **20a** + **b** (40.6 mg, 0.08 mmol, 63%). Data for the major isomer: ν_{max}/cm^{-1} 3434, 3030, 2857, 1750, 1703, 1496, 1452, 1362, 1232, 1174, 1095, 1026; δ_H(500 MHz) 7.27 (10 H, m, *H*Ph), 4.58 (1 H, d, *J* 12.0, OCH_2Ph), 4.53 (1 H, d, *J* 12.0, OCH_2Ph′), 4.49 (1 H, d, *J* 12.0, OCH_2Ph′), 4.40 (1 H, d, *J* 12.0, OCH_2Ph), 4.07 (1 H, d, *J* 9.5, 1-H), 3.76 (1 H, m, 1′-H), 3.68 (3 H, s, CO_2Me), 3.67 (1 H, d, *J* 9.5, 1-H), 3.51 (2 H, m, 4′-H), 2.83 (1 H, d, *J* 8.0, 3a-H), 2.20 (1 H, m, 4-H), 2.02 (1 H, m, 6-H), 1.76 (2 H, m, 3′-H), 1.50 (2 H, m, 2′-H), 1.92–1.24 (11 H, m, 1 × 6-H, 6a-H, 7-H, 8-H, 9-H, 10-H, OH); δ_C(100 MHz) 212.0 (C-5), 168.9 (CO_2Me), 138.2, 136.9 (2 × *C*Ph), 128.4 (×2), 128.3 (×2), 127.9, 127.7 (×2), 127.6 (×2), 127.4 (10 × CHPh), 105.8 (C-3), 73.0 (OCH_2Ph′), 72.3 (C-1′), 70.2 (C-4′), 69.1 (C-1), 65.6 (OCH_2Ph), 56.0 (C-3a), 53.7 (C-4), 52.6 (CO_2Me), 44.4 (C-10a), 41.7 (C-6), 39.2 (C-7), 37.1 (C-6a), 33.6 (C-2′), 28.9 (C-10), 25.7 (C-3′), 25.4 (C-9), 23.6 (C-8) [Found: (FAB) M^+, 537.0000. $C_{32}H_{40}O_7$ requires *M*, 536.9774].

Methyl (3*S,3a*S**,6a*R**,10a*R**)-3-benzyloxy-4-(4-benzyloxybutylidene)-5-oxoperhydronaphtho[1,8a-*c*]furan-3-carboxylate 22**

A stirred solution of **20a** + **b** (40.6 mg, 0.08 mmol) in dichloromethane (380 μl) was cooled to 0 °C and BF_3·OEt_2 (11.2 μl, 0.09 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 1 h after which time it was recooled to 0 °C, poured into saturated aqueous sodium hydrogen carbonate (0.5 cm^3) and extracted with dichloromethane (2 × 10 cm^3) and ethyl acetate (2 × 10 cm^3). The resulting organic fractions were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a pale yellow oil. Purification of the residue by flash column chromatography (eluent petrol–ethyl acetate 3:2) afforded *compound* **22** as a colourless oil (19.1 mg, 0.04 mmol, 46%); ν_{max}/cm^{-1} 2853, 1749, 1697, 1631, 1496, 1452, 1364, 1270, 1233; δ_H(500 MHz) 7.28 (10 H, m, *H*Ph), 6.61 (2 H, dd, *J* 8.5, 6.5, 1′-H), 4.55 (1 H, d, *J* 12.0, OCH_2Ph), 4.49 (2 H, br s, OCH_2Ph′), 4.48 (1 H, d, *J* 12.0, OCH_2Ph), 4.08 (1 H, d, *J* 9.5, 1-H), 3.70 (1 H, d, *J* 9.5, 1-H), 3.65 (3 H, s, CO_2Me), 3.48 (1 H, apparent t, *J* 6.0, 4′-H), 3.17 (1 H, s, 3a-H), 2.31 (1 H, dd, *J* 17.5, 4.5, 6-H), 2.27 (1 H, m, 2′-H),

2.08 (1 H, m, 2′-H), 1.95 (1 H, dd, *J* 17.5, 2.5, 6-H), 1.82 (1 H, m, 3′-H), 1.66 (1 H, m, 3′-H), 1.57–1.19 (9 H, m, 6a-H, 7-H, 8-H, 9-H, 10-H); δ_C(100 MHz) 201.7 (C-5), 168.9 (CO_2Me), 140.7 (C-1′), 138.4, 137.2 (2 × *C*Ph), 133.5 (C-4), 128.4 (× 2), 128.3 (× 2), 127.6 (× 3), 127.5 (× 2), 127.4 (10 × *C*HPh), 106.2 (C-3), 72.9 (O*C*H_2Ph′), 69.7 (C-4′), 69.5 (C-1), 65.7 (O*C*H_2Ph), 55.5 (C-3a), 52.7 (CO_2*Me*), 46.4 (C-10a), 41.5 (C-6), 39.1 (C-6a), 38.9 (C-7), 29.1 (C-2′), 28.7 (C-10), 25.4 (C-9), 24.7 (C-3′), 23.6 (C-8); *m/z* (EI) 518 (M^+), 491, 427, 335, 321, 261, 202, 105 [Found: (EI) M^+, 518.2657. $C_{32}H_{38}O_6$ requires *M*, 518.2268].

Methyl (3*S,3a*R**,4*R**,6a*R**,10a*R**)-3-hydroxy-4-(4-hydroxybutyl)-5-oxoperhydronaphtho[1,8a-*c*]furan-3-carboxylate 4**

Pd/C (10%) (25.7 mg) was added to a stirred solution of **22** (10.0 mg, 0.019 mmol) in ethanol (2 cm^3). The mixture was hydrogenated for 12 h under the same conditions as above. After that time, the suspension was degassed, filtered over a pad of Celite®, washed with ethyl acetate (30 cm^3) and concentrated to dryness to give a colourless oil which was purified by flash column chromatography (eluent petrol–ethyl acetate 1:4) to yield *compound* **4** (6.1 mg, 0.018 mmol, 89%); ν_{max}/cm^{-1} 3410, 2360, 1746, 1708, 1448, 1150, 1070; δ_H(500 MHz) 4.05 (1 H, d, *J* 9.0, 1-H), 3.93 (1 H, d, *J* 9.0, 1-H), 3.85 (3 H, s, CO_2Me), 3.63 (2 H, apparent t, *J* 6.5, 4′-H), 2.74 (1 H, d, *J* 6.0, 3a-H), 2.63 (1 H, s, OH), 2.48 (1 H, dd, *J* 18.5, 14.5, 6-H), 2.32 (1 H, dd, *J* 12.5, 6.0, 4-H), 2.00 (1 H, m, 6-H), 1.82–1.26 (16 H, m, 6a-H, 7-H, 8-H, 9-H, 10-H, 1′-H, 2′-H, 3′-H, OH); δ_C(100 MHz) 212.1 (C-5), 171.1 (CO_2Me), 102.3 (C-3), 70.4 (C-1), 62.3 (C-4′), 54.5 (CO_2*Me*), 53.7 (C-3a), 45.6 (C-10a), 46.3 (C-4), 41.6 (C-6), 38.8 (C-6a), 38.7 (C-7), 32.6 (C-3′), 28.6 (C-10), 25.5 (C-2′), 25.3 (C-9), 23.8 (C-8), 23.7 (C-1′); *m/z* (EI) 340 (M^+), 322, 281, 263, 245, 221, 209, 164, 121, 109 [Found: (EI) M^+, 340.1891. $C_{18}H_{28}O_6$ requires *M*, 340.1886].

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References

1 For Part 20, see: M. L. de la Puente, S. V. Ley, R. B. Grossman, M. S. J. Simmonds and W. M. Blaney, *J. Chem. Soc., Perkin Trans. 1*, 1996, preceeding paper.
2 R. B. Grossman and S. V. Ley, *Tetrahedron*, 1994, **50**, 11 553.
3 For a recent and complete review article on the chemistry of azadirachtin see: S. V. Ley, A. A. Denholm and A. Wood, *Nat. Prod. Rep.*, 1993, 109.
4 (*a*) For a recent and complete review article on the biology of azadirachtin see: A. J. Mordue (Luntz) and A. Blackwell, *J. Insect Physiol.*, 1993, **39**, 903; (*b*) I. Jones, S. V. Ley, A. A. Denholm, H. Lovell, A. Wood and R. E. Sinden, *FEMS Microbiol. Lett.*, 1994, **120**, 267.
5 P. C. Mukharji and A. N. Ganguly, *Tetrahedron*, 1969, **25**, 5281.
6 K. S. Kim, S. Chung, I. H. Cho and C. S. Hahn, *Tetrahedron Lett.*, 1989, **30**, 2559.
7 H. C. Kolb, S. V. Ley, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2735.
8 F. A. Davis and O. D. Stringer, *J. Org. Chem.*, 1982, **47**, 1774.
9 W.-J. Koot and S. V. Ley, *Tetrahedron*, 1995, **51**, 2077.
10 M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 96.
11 I. Paterson and I. Fleming, *Tetrahedron Lett.*, 1979, **23**, 2179.
12 G. Solladié, I. Fernández and C. Maestro, *Tetrahedron: Asymmetry*, 1991, **2**, 801.
13 (*a*) I. Paterson and J. D. Smith, *J. Org. Chem.*, 1992, **57**, 3261; (*b*) I. Paterson and J. D. Smith, *Tetrahedron Lett.*, 1993, **34**, 5351.
14 G. H. Posner, E. M. Shulman-Roskes, C. H. Oh, J.-C. Carry, J. V. Green, A. B. Clark, H. Dai and T. E. N. Anjeh, *Tetrahedron Lett.*, 1991, **32**, 6489.
15 W. M. Blaney, M. S. J. Simmonds, S. V. Ley, J. C. Anderson, S. C. Smith and A. Wood, *Pestic. Sci.*, 1994, **40**, 169.

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