Chemistry of insect antifeedants from *Azadirachta indica* (Part 20):[1] synthesis of biologically active, simple analogues of azadirachtin, containing the hydroxytetrahydrofurancarboxylate hemiketal moiety

María L. de la Puente,[a] Robert B. Grossman,[a] Steven V. Ley,*[,a] Monique S. J. Simmonds[b] and Wally M. Blaney[c]

[a] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK*

[b] *Behavioural Entomology Group, Biological Interactions Section, The Jodrell Laboratory, Royal Botanic Gardens, Kew, Richmond, Surrey TW9 3AB, UK*

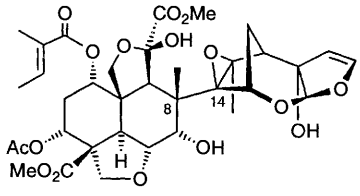
[c] *Behavioural Entomology Group, Birkbeck College, Malet Street, London, UK*

A synthetic route to mimics of the insect antifeedant azadirachtin 1 containing the hydroxytetrahydrofurancarboxylate hemiketal functional moiety has been developed. Two of these compounds, 2 and 11, show significant antifeedant activity against *Spodoptera littoralis*, although they are not as active as azadirachtin.

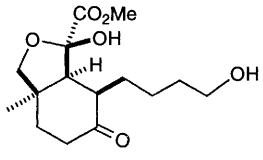
The Indian Neem tree, *Azadirachta indica* A. Juss (Meliaceae), provides a source of the tetranortriterpenoid natural product azadirachtin **1**,[2] which has been shown to be a potent antifeedant at low concentrations, an inhibitor of insect growth in around fifty insect species[3a] and has anti-malarial properties.[3b] Over the past few years an extensive study has been carried out in our laboratories towards the total synthesis of azadirachtin **1**[4] and the preparation of various model compounds in order to find simple analogues that display similar biological activity. Recent structure-activity relationship studies have shown that the decalin portion of the natural product itself has some antifeedant effect and changes to the functional groups present on this decalin fragment alters the antifeedant activity.[5,6]

We recently devised a short, highly-yielding route to the decalin portion of azadirachtin **1**, by degrading the natural product to cleave the linking C_8–C_{14} bond. This afforded compounds useful for our total synthesis studies and provided us with material useful for structure-activity relationship studies.[4]

In this work we have prepared a simple mimic, compound **2**, which contains some of the key features of the decalin fragment of the natural product. The approach used for its construction is based upon the previously described strategy developed in these laboratories for the synthesis of the first simple mimic **3**.[6]



Azadirachtin **1**



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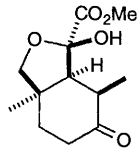

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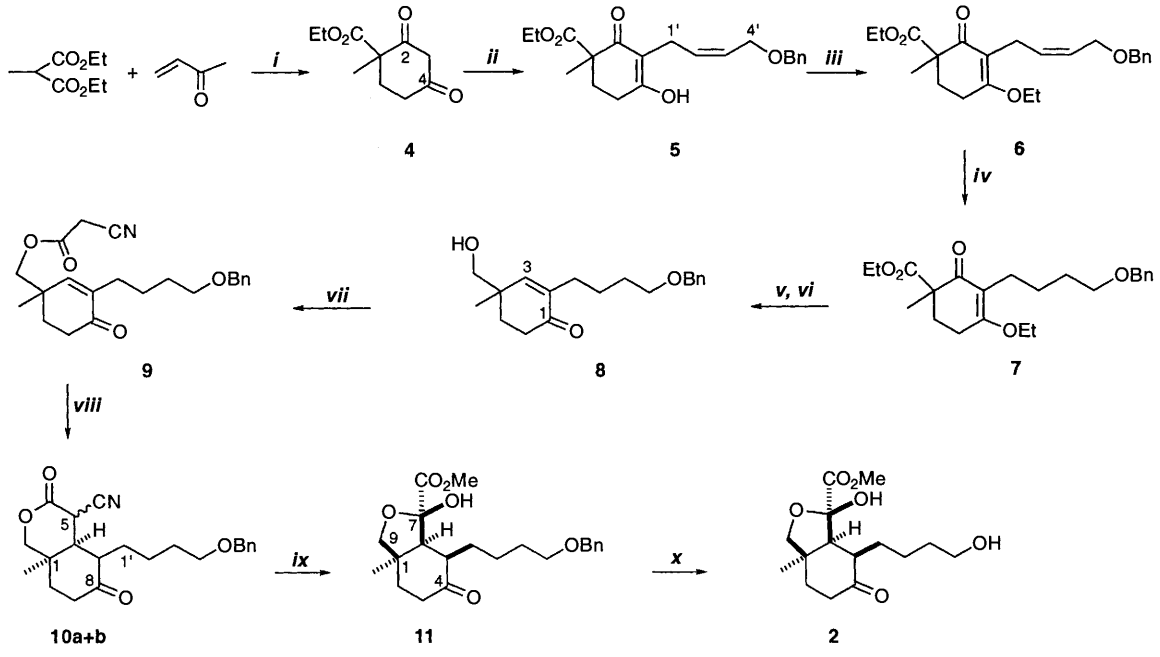
Results and discussion

Addition of diethyl methylmalonate to methyl vinyl ketone, followed by intramolecular acylation of the resulting ketone, gave the 2,4-diketone **4**[7] in 95% yield (Scheme 1) present in its enol form as determined from NMR spectra. In the ^{13}C spectrum, the ketone carbon signals are hardly visible, due to rapid keto–enol tautomerism of the 2,4-dicarbonyl moiety. The C-alkylation of this diketone proved to be extremely problematic. It is well known that there is concurrent formation of both C-alkylated and O-alkylated products during this type of reaction. For these cases, the literature provides numerous examples in which C-alkylation is favoured by the use of heterogeneous reaction conditions,[8] due to the fact that oxygen is shielded by the associated metal atom; allylic halides,[9] quaternary salts as phase-transfer catalysts[10] and aprotic solvents,[11] such as toluene or tetrahydrofuran, which do not solvate the enolate anion and consequently do not diminish its reactivity as a nucleophile. In our case, however, none of these procedures afforded the expected product and all the attempts carried out on the diketone **4** led to the exclusive formation of undesired O-alkylated and/or C-dialkylated derivatives.

Due to this extremely poor selectivity, we decided to investigate the use of a strong base, Triton® B (*N*-benzyltrimethylammonium hydroxide), in aqueous solution, as an alternative approach.[12] Treatment of the diketone **4** under these conditions followed by addition of (*Z*)-4-benzyloxybut-2-en-1-yl bromide,[13] furnished the desired C-monoalkylated product **5** in a moderate yield (30%), together with recovered starting material (45%) (Scheme 1). This product was also found to exist in its enol form. Many reasons were considered to explain the origin of this low yield, however further attempts at optimisation did not lead to any significant inprovement, affording considerable amounts of the O-alkylated derivative. Nevertheless, the Triton® B procedure was found to be practical and simple, allowing the recovery of 50% of the starting material which could be readily recycled.

Subsequent enol ether formation of **5** was effected in benzene, under reflux, in the presence of ethanol and a catalytic amount



Scheme 1 *Reagents and conditions:* i, EtONa–EtOH, reflux, overnight, 95%; ii, *N*-benzyltrimethylammonium hydroxide, (*Z*)-4-benzyloxybut-2-en-1-yl bromide, H_2O, 36 h, RT, 30%; iii, Pyridinium toluene-*p*-sulfonate, EtOH–benzene, reflux (Dean–Stark), overnight, 95%; iv, H_2, PtO_2, EtOAc, RT, 99%; v, $LiAlH_4$, ether, 2 h, 0 °C to RT; vi, 1 M HCl, THF, 2 h, RT, 60% (over last two steps); vii, HO_2CCH_2CN, toluene-*p*-sulfonyl chloride, pyridine, RT, 35 min, 96%; viii, KOBu^t, Bu^{t}OH, RT, 6 h 15 min, 60%; ix, KOBu^t, methanol, 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)oxaziridine, −78 °C to RT, 81%; x, H_2, Pd/C, EtOAc, 12 h, RT, 98%

of pyridinium toluene-*p*-sulfonate, to afford the β-alkoxyenone **6** in very good yield. Selective hydrogenation of the double bond in **6** proceeded cleanly on reaction with platinum(IV) oxide and hydrogen in ethyl acetate, to give the expected intermediate **7** in quantitative yield. Further reduction with lithium aluminium hydride and acidic hydrolysis yielded the corresponding hydroxy enone **8**. The preparation of the cyanoacetate intermediate **9** was achieved in excellent yield by esterification of the alcohol **8** with cyanoacetic acid in the presence of toluene-*p*-sulfonyl chloride and pyridine.[14] An intramolecular Michael addition of **9** was effected by addition of one equivalent of potassium *tert*-butoxide to obtain the cyclic nitriles **10a** + **b** as an inseparable 1:1 mixture of C_5 epimers in a very good overall yield. The complexity of the NMR spectra of **10a** + **b** prevented complete interpretation; nevertheless, from the absence of olefinic protons, and from evidence arising from later products, it followed that cyclisation had indeed taken place. The general synthetic strategy developed earlier by our group[6] for the formation of the tetrahydrofurancarboxylate portion of azadirachtin **1**, utilised oxidation with Davis' oxaziridine.[15] Pleasingly, treatment of the mixture of the α-cyanolactones **10a** + **b** with this oxidant in anhydrous methanol in the presence of one equivalent of potassium *tert*-butoxide, furnished the benzyl-protected compound **11** in diastereoisomerically pure form in an excellent, 81%, yield. The ring contraction was highly selective for the newly formed quaternary centre at C_7 (C_{11} in the natural product) affording the desired and natural *S* configuration with respect to the *S* (or *R*) configuration at C1. The complete assignment of both the ^1H and the ^{13}C NMR spectra was accomplished by the use of a COSY spectrum. These spectra were in complete accord with the proposed structure containing a hydroxytetrahydrofurancarboxylate hemiketal unit. Additionally, proton and carbon NMR data of centres belonging to the tetrahydrofuran part of the molecule were found to be very similar to those of the corresponding centres in azadirachtin **1**.[6,16] The question remained as to which of the C_5 diastereoisomers had been formed. The assignment of the stereochemistry at this centre was based on the coupling constant $J_{H5,H6}$,[6] which indicated that the substituent at C_5 was in the axial position. For the preparation of the model compound **2**, the cleavage of the benzyl ether was performed using palladium-catalysed hydrogenation with overall retention of configuration to give **2** in 98% yield.

Biological Results

Azadirachtin **1** is a classic example of a natural plant defence chemical affecting feeding, primarily through chemorcception, but also through a reduction in food intake, due to toxic effects if consumed.[10]

The need for environmentally acceptable methods of plant protection has stimulated the search for new classes of insecticides. With this aim, we have undertaken much of our work to design simple structural mimics of azadirachtin to investigate the resulting effects on biological activity. To give an indication of these data, larvae of the African leafworm *Spodoptera littoralis* were used to assess the antifeedant activity of our products. Compounds **2** and **11** showed significant antifeedant activity at 100 ppm, and gave estimated AI_{50} values of 93 and 95%, respectively. Although these compounds showed potent antifeedant activity, they do not match the *efficacy* of azadirachtin (Table 1).

During these studies we have developed a flexible synthetic

Table 1 Effects of compounds **11**, **2** and azadirachtin **1** on the feeding behaviour of larvae of *Spodoptera littoralis*

Compound	Antifeedant index[a] at 100 ppm	AI_{50}[b]/ppm
11	51*	93
2	42*	95
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).

programme, to allow access to a number of novel, simple analogues of azadirachtin **1**, and illustrated that partial structural units of this natural product might function as biologically active compounds. Our synthetic efforts are now directed towards the design of a new series of advanced prototype analogues, containing a decalin fragment as a scaffolding group, capable of improved mimicking of the activity of this potent antifeedant.

Experimental

Biological studies

A choice bioassay was used to assess the antifeedant activity of the compounds.[5] The compounds were applied to glass-fibre discs (Whatman GF/A 2.1 cm diam.) made palatable by the addition of 100 mm^3 of a 50 mM sucrose solution. Control discs carried just sucrose, whereas the treatment discs carried in addition to sucrose, 100 mm^3 of one of the test compounds at 10, 100 or 1000 ppm. The discs were left to dry, and then weighed. Larvae of *Spodoptera littoralis* were placed individually in Petri dishes (8.5 cm diam.), each with a control and treatment disc. The bioassay terminated after 50% of either disc was eaten or after 18 h if the insects had not eaten 50% of either disc. The larvae were removed, the discs dried and reweighed. The antifeedant index $[(C - T)/(C + T)] \times 100$ was calculated, where C and T represent the mass eaten of control and treatment discs, respectively. The Wilcoxon matched pairs test was used to assess the significance of the activity and probit analysis was used to establish the concentration required to obtain an antifeedant index of 50% (AI_{50}).

General

^1H NMR spectra were recorded in $CDCl_3$ at 400 and 500 MHz on Bruker AM-400 and Bruker DRX-500 spectrometers respectively. Residual protic solvent, *i.e.* $CDCl_3$ (δ_H 7.26) was used as internal reference, with J values measured in Hertz. ^{13}C NMR were recorded in $CDCl_3$ at 100.12 MHz on a Bruker AM-400 spectrometer using the resonance of $CDCl_3$ (δ_C 77.00) as internal reference. IR spectra were recorded on a Perkin-Elmer FTIR 1620 spectrometer. Mass spectra were recorded on a Kratos MS890MS spectrometer at the Department of Chemistry, University of Cambridge. Elemental analyses were performed in the Microanalytical Laboratory in the Department of Chemistry, Cambridge. Flash column chromatography was performed on Merck 9385 Kieselgel 60 (230–400 mesh). Diethyl ether and THF were distilled from the sodium–benzophenone ketyl radical, dichloromethane from calcium hydride, acetonitrile from calcium hydride and methanol from magnesium. Petrol refers to the fraction of light petroleum boiling in the range 40–60 °C, which was distilled prior to use. Other solvents and reagents were purified by standard procedures as necessary. All reactions were carried out under an argon atmosphere unless specified otherwise.

Ethyl 1-methyl-2,4-dioxocyclohexane-1-carboxylate 4[7]

A solution of sodium (2.5 g, 110.0 mmol) in anhydrous ethanol (100 cm^3) was slowly added *via* cannula to a stirred solution of diethyl methylmalonate (17.2 cm^3, 100.0 mmol) and methyl vinyl ketone (8.3 cm^3, 100.0 mmol) in anhydrous ethanol (200 cm^3). When the addition was complete, the mixture was heated to reflux for 12 h under a $CaCl_2$ drying tube. The solution was cooled and quenched with 3 M HCl (40 cm^3) and the solvent was evaporated. The residue was partitioned between diethyl ether (250 cm^3) and water (25 cm^3) and the organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*, affording compound **4** as a viscous oil (18.0 g, 90.0 mmol, 90%). The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra showed **4** to be a mixture of both tautomers of the expected diketone. The crude product was used in the next step without further purification.

Ethyl 3-[(*Z*)-4-benzyloxy-but-2-en-1-yl]-1-methyl-2,4-dioxocyclohexane-1-carboxylate 5

A 40% solution of *N*-benzyltrimethylammonium hydroxide in methanol (68.0 mg, 0.4 mmol, 0.5 cm^3) was added to a solution of the dione **4** (200.0 mg, 1.0 mmol) in water (0.5 cm^3). The resulting solution was allowed to stir for 10 min, then (*Z*)-4-benzyloxybut-2-en-1-yl bromide[12] (300.0 mg, 1.2 mmol) was added slowly and the reaction mixture was stirred for 36 h at room temperature. The aqueous solution was poured into aqueous NH_4Cl (pH = 7) and extracted with ethyl acetate (2 × 30 cm^3). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (petrol–ethyl acetate 7:3) affording *compound* **5** as a pale yellow oil (108.4 mg, 0.3 mmol, 30%); ν_{max}/cm^{-1} 2983, 2939, 1789, 1731, 1658, 1602, 1454, 1382, 1349, 1261, 1186, 1103, 699; δ_H(400 MHz) 7.30 (5 H, m, *H*Ph), 5.81 (1 H, m, 3′-H), 5.70 (1 H, m, 2′-H), 5.34 (1 H, s, OH), 4.50 (2 H, s, OCH_2Ph), 4.47 (2 H, d, J 6.0, 4′-H), 4.15 (1 H, q, J 7.0, CO_2CH_2Me), 4.14 (1 H, q, J 7.0, CO_2CH_2Me), 4.05 (2 H, d, J 6.0, 1′-H), 2.38 (3 H, m, 5-H and 6-H), 1.83 (1 H, m, 6-H), 1.44 (3 H, s, Me), 1.21 (3 H, t, J 7.0, CO_2CH_2Me); δ_C(100 MHz) 198.2 (C-2), 176.0 (C-4), 173.1 (CO_2Et), 137.8 (*C*Ph), 130.7 (C-3′), 128.4 (×2), 127.9, 127.8, 126.0 (5 × *C*HPh), 127.9 (C-3), 103.7 (C-2′), 72.6 (OCH_2Ph), 65.9 and 65.1 (C-4′ and CO_2CH_2Me), 61.5 (C-5), 47.7 (C-1), 33.8 and 33.2 (C-6 and C-1′), 21.4 (CO_2CH_2Me), 14.1 (Me); m/z (EI) 358, 338, 313, 288, 267, 250, 198, 177, 105 [Found: (EI) M^+, 358.1778. $C_{21}H_{26}O_5$ requires M, 358.1780].

Ethyl 3-[(*Z*)-4-benzyloxybut-2-en-1-yl]-4-ethoxy-1-methyl-2-oxocyclohex-3-ene-1-carboxylate 6

Pyridinium toluene-*p*-sulfonate (70.3 mg, 0.3 mmol) was added to a stirred solution of compound **5** (2.4 g, 6.7 mmol) in benzene (250 cm^3) and EtOH (925 cm^3). The reaction mixture was heated to reflux for 12 h under a Dean–Stark trap. After cooling, the resulting solution was poured into saturated aqueous sodium carbonate, diluted with diethyl ether (400 cm^3) and water (50 cm^3) and the layers were separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* giving a yellow oil which was purified by flash column chromatography (petrol–ethyl acetate 3:2) to yield compound **6** as an unstable oil (2.3 g, 6.5 mmol, 96%); ν_{max}/cm^{-1} 2981, 2936, 1728, 1654, 1609, 1496, 1453, 1376, 1254, 1195, 1108, 1023, 819; δ_H(400 MHz) 7.32 (5 H, m, *H*Ph), 5.50 (2 H, m, 2′-H and 3′-H), 4.51 (2 H, s, OCH_2Ph), 4.22 (2 H, d, J 4.0, 4′-H), 4.13 (2 H, q, J 7.0, CO_2CH_2Me), 4.02 (2 H, dq, J 7.0, 4.0, OCH_2CH_3), 3.10 (2 H, m, 1′-H), 2.53 (1 H, m, 5-H), 2.45 (1 H, m, 6-H), 2.42 (1 H, m, 5-H), 1.79 (1 H, m, 6-H), 1.35 (3 H, s, Me), 1.29 (3 H, t, J 7.0, OCH_2Me), 1.18 (3 H, t, J 7.0, CO_2CH_2Me); δ_C(100 MHz) 194.9 (C-2), 172.8 (CO_2CH_2Me), 170.2 (C-4), 138.7 (*C*Ph), 131.0 (C-3′), 128.4 (×2), 127.8, 127.4, 125.8 (5 × *C*HPh), 116.7 (C-3), 101.7 (C-2′), 72.1 (OCH_2Ph), 66.2 (C-4′), 63.5 (OCH_2Me), 61.2 (CO_2CH_2Me), 51.4 (C-1), 31.8 (C-1′), 31.0 (C-5), 23.1 (C-6), 20.7 (CO_2CH_2Me), 15.2 (OCH_2Me), 14.1 (Me).

Ethyl 3-(4-benzyloxybutyl)-4-ethoxy-1-methyl-2-oxocyclohex-3-ene-1-carboxylate 7

Platinum(IV) oxide (70.0 mg, 0.3 mmol) was added to a stirred solution of compound **6** (3.0 g, 7.8 mmol) in ethyl acetate (100 cm^3). After purging with hydrogen, the reaction mixture was vigorously stirred at room temperature for 7 h under a hydrogen atmosphere. The suspension was filtered through a pad of Celite® and the residue was washed with ethyl acetate (2 × 15 cm^3) and concentrated *in vacuo* giving a crude product which was purified by flash column chromatography (petrol–ethyl acetate 3:2) to yield *compound* **7** (3.0 g, 7.7 mmol, 99%); ν_{max}/cm^{-1} 2980, 2934, 1729, 1650, 1613, 1496, 1454, 1375, 1237, 1179, 1108, 1026; δ_H(400 MHz) 7.32 (5 H, m, *H*Ph), 4.47 (2 H, s, OCH_2Ph), 4.11 (2 H, q, J 7.0, CO_2CH_2Me), 4.01 (2 H, dq, J

7.0, 2.5, OCH_2CH_3), 3.45 (2 H, apparent t, *J* 7.0, 4′-H), 2.68 (1 H, m, 5-H), 2.45 (1 H, m, 5-H), 2.41 (1 H, m, 6-H), 2.33 (2 H, m, 1′-H), 1.80 (1 H, m, 6-H), 1.57 (2 H, m, 3′-H), 1.40 (2 H, m, 2′-H), 1.35 (3 H, s, Me), 1.30 (3 H, t, *J* 7.0, OCH_2Me), 1.18 (3 H, t, *J* 7.0, CO_2CH_2Me); δ_C(100 MHz) 195.5 (C-2), 173.0 (CO_2CH_2Me), 169.8 (C-4), 138.9 (*C*Ph), 128.3, 128.2, 127.6 (×2), 127.4, (5 × *C*HPh), 118.6 (C-3), 72.8 (OCH_2Ph), 70.7 (C-4′), 63.3 (OCH_2Me), 61.1 (CO_2CH_2Me), 51.4 (C-1), 31.0 (C-5), 29.5 (C-3′), 24.8 (C-2′), 22.3 (C-6), 22.2 (C-1′), 20.8 (CO_2CH_2Me), 15.2 (OCH_2Me), 14.1 (Me); *m*/*z* (EI) 388, 343, 316, 297, 237, 195, 165 [Found: (EI) M^+, 388.2246. $C_{23}H_{32}O_5$ requires *M*, 388.2249].

2-(4-Benzyloxybutyl)-4-hydroxymethyl-4-methylcyclohex-2-en-1-one 8

Compound **7** (3.0 g, 7.7 mmol) was slowly added to a stirred suspension of lithium aluminium hydride (438.0 mg, 11.5 mmol) in ether (25 cm^3) cooled to 0 °C. When the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred. After 2 h the suspension was cooled back to 0 °C and then water (0.44 cm^3), 15% aq. NaOH (0.44 cm^3) and water (1.32 cm^3) were slowly added. The suspension was then filtered, washed with ethyl acetate (2 × 300 cm^3) and the filtrate was evaporated, affording a residue which was redissolved in THF (10 cm^3). 1 M HCl (10 cm^3) was added and the reaction was stirred at room temperature for 30 min. The solution was washed with brine and extracted with ethyl acetate (3 × 200 cm^3). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a product which was subjected to flash column chromatography (petrol–ethyl acetate 1:1) affording *compound* **8** as a colourless oil (1.2 g, 4.0 mmol, 53%) (Found: C, 75.3; H, 8.9. $C_{19}H_{26}O_3$ requires C, 75.4; H, 8.7%); ν_{max}/cm^{-1} 3441, 2931, 2863, 1669, 1454, 1369, 1048; δ_H(500 MHz) 7.32 (5 H, m, *H*Ph), 6.39 (1 H, s, 3-H), 4.48 (2 H, s, OCH_2Ph), 3.49 (1 H, d, *J* 10.5, CH_2OH), 3.42 (1 H, d, *J* 10.5, CH_2OH), 3.45 (2 H, apparent t, *J* 6.5, 4′-H), 2.47 (2 H, m, 6-H), 2.30 (1 H, br s, OH), 2.18 (2 H, m, 1′-H), 2.03 (1 H, m, 5-H), 1.69 (1 H, m, 5-H), 1.59 (2 H, m, 3′-H), 1.47 (2 H, m, 2′-H), 1.10 (3 H, s, Me); δ_C(100 MHz) 198.1 (C-1), 147.8 (C-3), 139.7 (C-2), 138.6 (*C*Ph), 128.4 (×2), 127.8 (×2), 127.6 (5 × *C*HPh), 73.0 (OCH_2Ph), 72.5 (CH_2OH), 70.2 (C-4′), 36.7 (C-4), 34.0 and 31.2 (C-6 and C-1′), 29.4 and 29.3 (C-5 and C-3′), 25.0 (C-2′), 22.3 (Me); *m*/*z* (EI) 302, 272, 211, 196, 178, 165, 145, 135, 124, 109, 91, 79.

2-(4-Benzyloxybutyl)-4-(2-cyanoacetoxy)methyl-4-methylcyclohex-2-en-1-one 9

Toluene-*p*-sulfonyl chloride (5.5 g, 28.6 mmol) was added slowly to a stirred solution of compound **8** (4.2 g, 13.9 mmol), cyanoacetic acid (3.5 g, 41.5 mmol) and pyridine (8.0 cm^3, 98.9 mmol) in dichloromethane (200 cm^3). The reaction mixture was stirred for 20 min, then diluted with dichloromethane and poured into 1 M HCl (250 cm^3). The resulting organic layer was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 cm^3). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil which was purified by flash column chromatography (petrol–ethyl acetate 3:2) affording *compound* **9** as a viscous pale yellow oil (4.7 g, 12.7 mmol, 92%) (Found: C, 71.5; H, 7.4; N, 3.9. $C_{22}H_{27}NO_4$ requires C, 71.5; H, 7.4; N, 3.8%); ν_{max}/cm^{-1} 2933, 2262, 1754, 1673, 1496, 1371, 1335, 1261, 1182, 1101, 1007; δ_H(400 MHz) 7.29 (5 H, m, *H* Ph), 6.31 (1 H, s, 3-H), 4.47 (2 H, s, OCH_2Ph), 4.17 (1 H, d, *J* 11.0, CH_2CN), 3.99 (1 H, d, *J* 11.0, CH_2CN), 3.45 (2 H, apparent t, *J* 6.5, 4′-H), 3.45 (2 H, s, $CH_2O_2CCH_2CN$), 2.48 (2 H, m, 6-H), 2.23 (1 H, m, 5-H), 2.13 (1 H, m, 5-H), 2.08 (1 H, m, 1′-H), 1.79 (1 H, m, 1′-H), 1.57 (2 H, m, 3′-H), 1.47 (2 H, m, 2′-H), 0.99 (3 H, s, Me); δ_C(100 MHz) 198.1 (C-1), 162.8 ($OOCCH_2CN$), 147.8 (C-3), 139.7 (C-2), 138.6 (*C*Ph), 128.4 (×2), 127.7 (×2), 127.6 (5 × *C*HPh), 112.7 (CN), 73.0 (OCH_2Ph), 72.5 ($CH_2O_2CH_2CN$), 70.2 (C-4′), 36.7 (C-4), 34.0 (C-6), 31.2 (C-1′), 29.4 and 29.3 (C-5 and C-3′), 25.0 (C-2′), 24.6 (CH_2CN), 22.6 (Me); *m*/*z* (EI) 369, 278, 263, 178, 163, 147, 135, 124, 109.

[1*R,5*RS**,6*R**,7*R*(*S*)*]-7-(4-Benzyloxybutyl)-5-cyano-1-methyl-3-oxabicyclo[4.4.0]decane-4,8-dione 10a + b**

Potassium *tert*-butoxide (1.3 g, 11.8 mmol) was added to a stirred solution of compound **9** (4.0 g, 10.8 mmol) in dry *tert*-butyl alcohol (220 cm^3). After continued stirring for 6 h, the reaction was quenched with 1 M HCl (60 cm^3) and the solvent was evaporated. The residue was redissolved in dichloromethane (300 cm^3) and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 × 150 cm^3). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* affording an orange viscous oil which was purified by flash column chromatography (petrol–ethyl acetate 1:1) to give an inseparable 1:1 mixture of two *isomers* **10a** + **b** which were epimeric at C5 (2.9 g, 7.9 mmol, 73%) (Found: C, 71.5; H, 7.4; N, 3.9. $C_{22}H_{27}NO_4$ requires C, 71.5; H, 7.4; N, 3.8%); data for the mixture: ν_{max}/cm^{-1} 2934, 2254, 1760, 1714, 1496, 1363, 1208, 1156, 1102; δ_H(400 MHz) 7.28–7.32 (10 H, m, *H*Ph), 4.60 and 3.80 (2 H, d, *J* 12.5, 5-H), 4.48 and 4.47 (4 H, s, OCH_2Ph), 4.19–4.08 (4 H, m, 2-H), 3.47 (4 H, apparent t, *J* 6.0, 4′-H), 2.65 (2 H, m, 7-H), 1.89–1.51 (12 H, m, 2′-H, 3′-H, 10-H), 1.04 and 0.87 (6 H, s, Me); δ_C(100 MHz) 209.4–209.2 (C-8), 163.8 and 163.1 (C-4), 138.5 (*C*Ph), 128.4 (×4), 127.8 (×2), 127.7 (×2), 127.6 (×2) (10 × *C* Ph), 76.0 and 74.8 (C-2), 73.0 (OCH_2Ph), 70.0 and 69.9 (C-4′), 48.3 and 50.9 (C-7), 46.2 and 44.6 (C-6), 36.9 and 35.4 (C-5), 35.0 and 34.7 (C-9), 33.8 and 33.7 (C-1), 29.7 (C-3′), 29.4 (C-2′), 29.3 and 28.4 (C-10), 25.7 and 26.0 (Me), 24.2 and 24.0 (C-1′); *m*/*z* (EI) 369, 263, 207, 165, 147, 123, 107.

Methyl (1*R,5*R**,6*S**,7*S**)-5-(4-benzyloxybutyl)-7-hydroxy-1-methyl-4-oxo-8-oxabicyclo[4.3.0]nonane-7-carboxylate 11**

A suspension of the cyanolactones **10a** + **b** (369.0 mg, 1.0 mmol) in dry methanol (20 cm^3) was treated with potassium *tert*-butoxide (124 mg, 1.1 mmol). Once the solid was dissolved completely, the solution was cooled to −78 °C and 2-(4-methoxybenzenesulfonyl)-3-(4-nitrophenyl)oxaziridine (74.0 mg, 0.2 mmol) was added. The suspension was allowed to warm to room temperature and was 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 (petrol–ethyl acetate 3:2 and dichloromethane–diethyl ether 9:1 respectively) afforded *compound* **11** (312.0 mg, 0.8 mmol, 81%) as a yellow oil (Found: C, 67.9; H, 7.8. $C_{22}H_{30}O_6$ requires C, 67.7; H, 7.7%); ν_{max}/cm^{-1} 3410, 2868, 1747, 1713, 1496, 1454, 1277, 1100; δ_H(400 MHz) 7.30 (5 H, m, *H*Ph), 4.47 (2 H, s, OCH_2Ph), 4.20 (1 H, br s, OH), 3.89 (1 H, d, *J* 8.5, 9-H), 3.79 (3 H, s, CO_2Me), 3.77 (1 H, d, *J* 8.5, 9-H), 3.43 (2 H, apparent t, *J* 6.5, 4′-H), 2.52 (1 H, m, 3-H), 2.46 (1 H, br d, *J* 5.5, 6-H), 2.43–2.27 (2 H, m, 1 × 3-H and 5-H), 1.70 (1 H, m, 2-H), 1.59 (1 H, m, 1′-H), 1.55 (2 H, m, 3′-H), 1.35 (4 H, m, 1 × 2-H, 1 × 1′-H and 2′-H), 1.24 (3 H, s, Me); δ_C(100 MHz) 212.9 (C-4), 171.2 (CO_2Me), 138.6 (*C*Ph), 128.4 (×2), 127.7 (×2), 127.5 (5 × *C*HPh), 103.4 (C-7), 72.9 (OCH_2Ph), 70.2 (C-4′), 80.3 (C-9), 56.0 (C-5), 53.5 (CO_2Me), 47.1 (C-6), 39.7 (C-1), 35.0, 31.4 and 30.2 (C-2, C-3 and C-1′), 29.6 (C-2′), 25.6 (Me), 24.2 (C-3′); *m*/*z* (EI) 390, 372, 358, 338, 281, 266, 207, 177, 124, 109.

Methyl (1*R,5*R**,6*S**,7*S**)-5-(4-hydroxybutyl)-7-hydroxy-1-methyl-4-oxo-8-oxabicyclo[4.3.0]nonane-7-carboxylate 2**

A solution of compound **11** (39.0 mg, 0.1 mmol) and Pd/C (10.6 mg, 0.01 mmol) in ethyl acetate (5 cm^3) was stirred under a hydrogen atmosphere for 12 h. The resulting reaction mixture was filtered through a pad of Celite® and the residue was washed with ethyl acetate (2 × 10 cm^3). Purification by flash column chromatography (petrol–ethyl acetate 3:7) gave *compound* **2** as a colourless oil (30 mg, 0.1 mmol, 98%);

ν_{max}/cm^{-1} 3418, 2875, 1745, 1705, 1456, 1280, 1163, 1065; δ_H(400 MHz) 4.29 (1 H, s, OH), 3.89 (1 H, d, *J* 8.5, 9-H), 3.82 (3 H, s, CO_2Me), 3.78 (1 H, d, *J* 8.5, 9-H), 3.60 (2 H, apparent t, *J* 6.5, 4′-H), 2.56 (1 H, m, 3-H), 2.46 (1 H, d, *J* 6.0, 6-H), 2.36–2.26 (2 H, m, 1 × 3-H and 5-H), 1.68–1.61 (5 H, m, 2-H, 1 × 1′-H and 3′-H), 1.49 (2 H, m, 2′-H), 1.33 (1 H, dd, *J* 2.5 and 7.0, 1′-H), 1.23 (3 H, s, Me); δ_C(100 MHz) 213.4 (C-4), 171.3 (CO_2Me), 103.4 (C-7), 80.3 (C-9), 62.4 (C-4′), 56.2 (C-5), 53.6 (CO_2*Me*), 47.0 (C-6), 39.9 (C-1), 35.0 (C-3), 32.2 (C-3′), 31.2 (C-2), 29.5 (C-2′), 25.7 (Me), 23.5 (C-1′); *m*/*z* (EI) 300, 282, 268, 250, 228, 208, 196, 181, 163, 124, 109 [Found: (EI) M^+, 300.1584. $C_{15}H_{24}O_6$ requires *M*, 300.1573].

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