The design, synthesis and biological evaluation of stable ozonides with antimalarial activity

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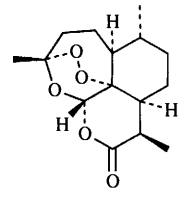
The synthesis of variously substituted 8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}]undecan-4-ones by ozonolysis of various 8-oxabicyclo[3.2.1]oct-6-en-3-ones is described. Several of these stable ozonides exhibited activity (IC_{50}s of 2–20 microgram cm^{-3}) against a chloroquine-resistant strain of the malaria parasite *Plasmodium falciparum*.

Despite the current preoccupation with AIDS, malaria remains a much greater problem. The WHO estimates that there are around 280 million cases of malaria each year and about two million deaths can be attributed to the disease. About half of these fatalities are children under the age of five years.[1] Although there are numerous drugs on the market for both treatment and prevention, parasites with multiple drug resistance are now prevalent in all parts of the world where malaria is endemic.[2] There is thus an urgent need for new antimalarial drugs, especially those with novel modes of action. The sesquiterpene artemisinin **1** from Chinese *Artemisia annua* is such a drug.

Although crude extracts of the plant have been used for at least 2000 years for the treatment of all types of fever including that due to malaria, the major active constituent, artemisinin or *qinghaosu* was not isolated and characterised until 1971.[3] Clinical trials in 1979 established high potency (at the nanogram level) for the pure drug, and there has been enormous synthetic and pharmacological interest ever since.[4] At the present time analogues such as **2** and **3** are proving to be particularly interesting.[5]

Our interest was aroused following the serendipitous isolation of the ozonide **4a**. We were attempting an ozonolytic cleavage of the cycloaddition product of oxyallyl cation **5** and furan, 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **6a**, when this unexpected product was obtained. The ozonide had a melting point in excess of 100 °C and was stable enough to be the object of an X-ray crystallographic study.[6] It was submitted for speculative evaluation as an antimalarial agent and proved to have an IC_{50} of around 20 μg cm^{-3} against a chloroquine-resistant strain of *Plasmodium falciparum* from Thailand. In order to rationalise the synthesis of other potential antimalarial agents, we used molecular modelling and energy minimisation including considerations of charge, van der Waals forces, bond, angle and torsion energies, together with a unique space-hunting algorithm to avoid local minima.[7] Energy minima were of the order of 400 kJ mol^{-1}, and the RMS fits, based on key oxygen atoms, were close to 0.2 Å for the comparison (Fig. 1) between **1** and **4a** (and also for most of the other ozonides which are described in this paper). This encouraged us to prepare a range of similar structures and this work forms the basis of this paper.[8]

The substrates **6** for the ozonolyses were prepared using our standard methods for the generation of the oxyallyl cation **5**[9] and its entrapment with various 2-substituted furans. The simplest cycloadduct **6a** was reduced to the axial alcohol **7** ($NaBH_4$, EtOH) and converted into the methyl ether **8**, the dithiocarbonate **9** and thence into the alkene **10** (Bu_3SnH). Ozonolyses were then carried out in dichloromethane at −5 to



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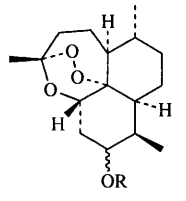

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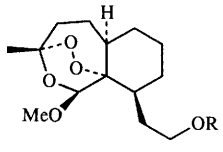

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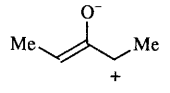

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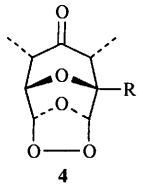

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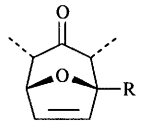
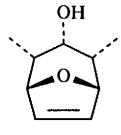


6

a R = H
b R = Et
c R = CH_2OAc
d R = heptyl
e R = $CH_2CH_2CH_2OAc$

f R = $CH_2CH_2CH_2OH$
g R = $CH_2CH_2CH_2OC(O)Ph$
h R = $CH_2CH_2CH_2OCH_2Ph$
i R = $CH_2CH_2CH_2OMe$
j R = $CH_2CH_2CH_2Cl$



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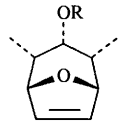
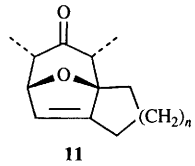


8 R = Me
9 R = C(S)SMe

10



11

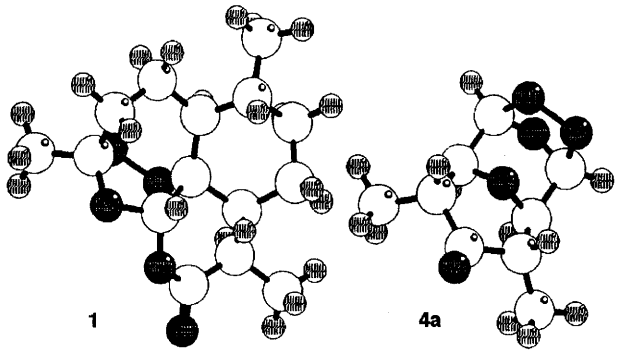


Fig. 1 Energy minimised structures of **1** and **4a**

Table 1 Anti-malarial activities of ozonides[a]

Compound	IC_{50}/μg cm^{-3}
4a	18
4b	12
4c	> 500
4d	26
4e	3
4g	11
4h	6
4i	2
4j	7

[a] For comparison: artemisinin **1** has an IC_{50} of 10^{-3} μg cm^{-3} and quinine has an IC_{50} of 0.18 μg cm^{-3}. Each result is the mean of two determinations with errors ≤ 10%.

0 °C, and the ozonides **4a–j** from substrates **6a–j** usually crystallised directly from the reaction mixture or could be obtained following evaporation of the solvent. Only polymeric material was obtained when compounds **8** and **10** were ozonised. This interesting difference in reactivity between the bicyclic ketone **6a** and these reduced counterparts is possibly due to the overlap between the lone pair orbital of the bridgehead oxygen and the carbonyl π-system of **6**. This interaction, which is absent in the other compounds, would be expected to reduce the nucleophilicity of the bridgehead oxygen, thus stabilizing the adjacent ozonide against destruction by this centre.

All of the ozonides were submitted for biological evaluation [10] *in vitro* against a multi-resistant strain of *Plasmodium falciparum* from Thailand, and the results of these investigations are shown in Table 1. While it is impossible to establish whether some of the compounds were metabolised or deactivated prior to interacting with the parasites, it is clear from these results that the antimalarial activity first observed with compound **4a** was not an isolated 'fluke'. Further computer modelling has suggested that ozonides from 1,7-disubstituted oxabicycles such as **11** would have even closer structural similarity to artemisinin, and these compounds are the target of our present investigations.

Experimental

IR spectra were recorded using a Perkin-Elmer 881 series double-beam spectrophotometer, and samples were run as thin films or in solution using NaCl plates. Low resolution and accurate mass data were recorded on a VG Analytical ZAB-IF mass spectrometer by the SERC mass spectrometry service at the University of Swansea. ^{1}H NMR spectra were recorded on a Bruker WH250 spectrometer or on a JEOL FX400 instrument; *J* values are given in Hz. ^{13}C NMR spectra were recorded on the JEOL instrument. Flash chromatography was carried out using Sorbsil™ C60 silica gel (40–60 μm). Solvents were distilled from calcium hydride when required anhydrous. Light petroleum (petrol) refers to the fraction with distillation range 40–60 °C, and ether refers to diethyl ether.

3-(2-Furyl)propan-1-ol

To a stirred suspension of $LiAlH_4$ (1.14 g, 30 mmol) in dry ether (80 cm^3), kept under a nitrogen atmosphere, a solution of 3-(2-furyl)propenal (2.85 g, 23.36 mmol) in THF (15 cm^3), was added over a period of 15 min. After 5 h stirring at room temperature the reaction was worked up by careful addition of ethyl acetate (30 cm^3) followed by water (1 cm^3). The resultant mixture was stirred for 40 min and the solid formed removed by filtration. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product as a colourless oil. This oil was purified by flash chromatography over silica gel (1:2 petrol–ether) to give the required product (1.56 g, 53%) as a colourless oil; R_f 0.23 (1:1, petrol–ether); ν_{max}(thin film)/cm^{-1} 3344, 3100, 1598 and 1509; δ_H(400 MHz, $CDCl_3$) 1.88 (br quintet, 2 H, *J* 6.5, CH_2), 2.37 (s, 1 H, O*H*), 2.71 (t, 2 H, *J* 7.5, CH_2), 3.65 (t, 2 H, *J* 6.4, CH_2OH), 5.99 (dd, 1 H, *J* 3.3 and 0.8, H-3′), 6.27 (dd, 1 H, *J* 3.3 and 1.9, H-4′) and 7.29 (dd, 1 H, *J* 1.9 and 0.8, H-5′); *m/z* 126.0679 (M^+, $C_7H_{10}O_2$ requires 126.0681).

3-(2-Furyl)propyl acetate

A solution of 3-(2-furyl)propan-1-ol (2.61 g, 20.69 mmol) in dry pyridine (5 cm^3) and Ac_2O (2 cm^3) was stirred at room temperature for 24 h. After that time dichloromethane (180 cm^3) was added to the reaction mixture. The resultant solution was washed with brine (5 × 50 cm^3), HCl (2 mol dm^{-3}; 3 × 30 cm^3) and saturated aq. $NaHCO_3$ (50 cm^3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford a yellow oil. This oil was purified by flash chromatography over silica gel (3:2, petrol–ether) to give the required product as a colourless oil (3.08 g, 81%); R_f 0.48 (3:2, petrol–ether); ν_{max}(thin film)/cm $^{-1}$ 1736 and 1598; δ_H(400 MHz, $CDCl_3$) 1.91 (br quintet, 2 H, *J* 6.5, CH_2), 1.97 (s, 3 H, CH_3), 2.65 (t, 2 H, *J* 7.5, CH_2), 4.04 (t, 2 H, *J* 6.4, CH_2), 5.95 (dd, 1 H, *J* 1.85 and 0.85, H-3′), 6.21 (dd, 1 H, *J* 1.85 and 2.93, H-4′) and 7.24 (dd, 1 H, *J* 1.85 and 0.85, H-5′); *m/z* 168.0784 (M^+, $C_9H_{12}O_3$ requires 168.0786, 3%).

1-Ethyl-2-*endo*,4-*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one 6b

A 250 cm^3, two-necked round bottom flask was fitted with a 50 cm^3 dropping funnel and charged with dry acetonitrile (40 cm^3). Dry NaI (11.25 g, 75 mmol) was added with vigorous stirring under a slow stream of nitrogen. Powdered copper (2.5 g, 37.5 mmol) was added, followed by 2-ethylfuran (6.5 g, 67.7 mmol). A solution of 2,4-dibromopentan-3-one (4.5 g, 17.3 mmol) in dry acetonitrile (5 cm^3) was added over 50 min at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 18 h. After that time the flask was cooled to 0 °C and dichloromethane (100 cm^3) was added. The resultant mixture was then poured into a 1 dm^3 conical flask containing water (100 cm^3) and crushed ice (100 cm^3), and it was thoroughly stirred to allow the precipitation of copper salts. After filtration through a Celite pad, the mother liquor was washed with aqueous NH_3 (35% v/v, 3 × 50 cm^3), brine (60 cm^3), dried over $MgSO_4$ and concentrated to afford a pale yellow oil. Further purification by flash chromatography (3:1, petrol–ether) gave the required product **6b** (2.27 g, 73%) as a colourless oil; R_f 0.36 (3:1, petrol–ether); ν_{max}(thin film)/cm^{-1} 1712 and 1595; δ_H(250 MHz, $CDCl_3$) 1.95–2.05 (3 d, 9 H, *J* 7, 3 × CH_3), 2.84 (multiplet with seven lines, *J* 7.5, CH_2), 2.62 (q, 1 H, *J* 7, H-2), 2.78 (dq, 1 H, *J* 7 and 5, H-4), 4.88 (dd, 1 H, *J* 5 and 1, H-5), 6.10 (d, 1 H, *J* 6, H-7) and 6.27 (dd, 1 H, *J* 6 and 1, H-6); *m/z* 181.1228 ([M + 1]$^+$, $C_{11}H_{17}O_2$ requires 181.1229).

1-Acetoxymethyl-2-*endo*,4-*endo*-dimethyl-8-oxabicyclo[3.2.1]-oct-6-en-3-one 6c

Using the methodology described for **6b**, compound **6c** was prepared as a pale yellow solid (49%), mp 53.5–54.0 °C; R_f 0.23 (3:1, petrol–ether); ν_{max}($CHCl_3$)/cm^{-1} 1725, 1712 and 1595;

δ_H(250 MHz, $CDCl_3$) 1.01 (2 d, 6 H, *J* 8.02, 2 × CH_3), 2.15 (s, 3 H, CH_3), 2.82 (m, 2 H, H-2 and H-4), 4.37 (d, 1 H, *J* 12.32, 1 of CH_2OAc), 4.43 (d, 1 H, *J* 12.32, 1 of CH_2OAc), 4.93 (dd, 1 H, *J* 4.71 and 1.67, H-5), 6.12 (d, 1 H, *J* 6.06, H-7) and 6.37 (dd, 1 H, *J* 6.06 and 1.70, H-6); (Found: C, 64.0; H, 7.2. $C_{11}H_{16}O_4$ requires C, 64.27; H, 7.17%).

1-Heptyl-2-*endo*,4-*endo*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one 6d

Using the methodology described for **6b**, compound **6d** was prepared as a colourless oil (71%); R_f 0.27 (9:1, petrol–ether); ν_{max}(thin film)/cm^{-1} 1711 and 1594; δ_H(250 MHz, $CDCl_3$) 1.80–2.00 (2d + t, 9 H, *J* 7, 3 × CH_3), 1.20–1.50 (m, 10 H, 5 × CH_2), 1.75–1.85 (m, 2 H, O–C–CH_2), 2.62 (q, 1 H, *J* 6.8, H-2), 2.77 (dq, 1 H, *J* 6.8 and 4.5, H-4), 4.85 (dd, 1 H, *J* 4.5 and 1.5, H-5), 6.10 (d, 1 H, *J* 6.5, H-7) and 6.23 (dd, 1 H, *J* 6.5 and 1.5, H-6); *m/z* (CI, NH_3) 251.2011 ([M + 1]$^+$, $C_{16}H_{27}O_2$ requires 251.2011, 2%).

1-(3-Acetoxypropyl)-2-*endo*,4-*endo*-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one 6e

Using the methodology described for **6b**, compound **6e** was prepared (52%); R_f 0.48 (3:2, petrol–ether); ν_{max}(thin film)/cm^{-1} 1739, 1712 and 1595; δ_H(400 MHz, $CDCl_3$) 0.96 and 0.99 (2d, 6 H, *J* 7.0, 2 × CH_3), 1.65–1.95 (m, 4 H, CH_2CH_2), 2.06 (s, 3 H, CH_3), 2.59 (q, 1 H, *J* 7.3, H-2), 2.76 (dq, 1 H, *J* 7.96 and 4.77, H-4), 4.12 (br t, 2 H, *J* 8.0, CH_2O), 4.84 (dd, 1 H, *J* 4.77 and 1.83, H-5), 6.08 (d, 1 H, *J* 5.86, H-7) and 6.26 (dd, 1 H, *J* 5.86 and 1.83, H-6); δ_C(100 MHz, $CDCl_3$) 9.55 (CH_3), 10.21 (CH_3), 20.82 (CH_3CO), 22.85 (CH_2), 30.30 (CH_2), 49.53 (C-2), 53.98 (C-4), 64.31 (CH_2O), 82.40 (C-5), 89.82 (C-1), 133.55 (C-6), 135.30 (C-7), 170.95 (*C*OO) and 208.99 (*C*O); *m/z* 252.1362 (M$^+$, $C_{14}H_{20}O_4$ requires 252.1362, 15%).

1-(3-Hydroxypropyl)-2-*endo*,4-*endo*-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one 6f

To a stirred solution of the acetate **6e** (600 mg, 2.38 mmol) in methanol (5 cm^3), was added aq. K_2CO_3 (10%; 5 cm^3). After 8 h stirring at room temperature, water (30 cm^3) was added and the methanol was removed under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 50 cm^3) and the combined organic extract was washed with brine (30 cm^3), dried over $MgSO_4$ and concentrated under reduced pressure to leave a colourless oil. This oil was purified by flash chromatography over silica gel (1:3, petrol–ether) to afford the required product as a pale yellow oil (0.46 g, 92%); R_f 0.15 (1:3, petrol–ether); ν_{max}(thin film)/cm^{-1} 3411, 1710 and 1596; δ_H(400 MHz, $CDCl_3$) 0.96 and 0.99 (2d, 6 H, *J* 6.96, 2 × CH_3), 1.60–2.01 (m, 4 H, CH_2CH_2), 2.55 (s, 1 H, O*H*), 2.63 (q, 1 H, *J* 6.96, H-2), 2.76 (dq, 1 H, *J* 6.96 and 4.76, H-4), 3.68 (br t, 2 H, *J* 6.00, CH_2O), 4.86 (dd, 1 H, *J* 4.76 and 1.83, H-5), 6.09 (d, 1 H, *J* 5.86, H-7) and 6.25 (dd, 1 H, *J* 5.86 and 1.83, H-6); δ_C(100 MHz, $CDCl_3$) 9.63, 10.23, 26.65, 30.59, 49.57, 53.90, 62.61, 82.45, 90.20, 133.25, 135.65 and 209.22; *m/z* 210.1258 (M$^+$, $C_{12}H_{18}O_3$ requires 210.1252, 26%).

1-(3-Benzoyloxypropyl)-2-*endo*,4-*endo*-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one 6g

To an ice-cooled solution of the alcohol **6f** (420 mg, 2 mmol) in dry dichloromethane (12 cm^3) was added pyridine (0.4 cm^3) and benzoyl chloride (0.60 cm^3, 5 mmol). The resultant mixture was allowed to warm up to room temperature and stirred overnight (14 h). After that time dichloromethane (150 cm^3) and water (50 cm^3) were added and the two layers separated. The organic phase was washed with HCl (2 mol dm^{-3}, 30 cm^3), saturated aq. $NaHCO_3$ (30 cm^3) and brine (30 cm^3), and then dried over $MgSO_4$. After filtration the solution was concentrated under reduced pressure to leave a yellow oil. This oil was purified by column chromatography (2:1, petrol–ether) to afford the required product as a colourless viscous oil (570 mg, 91%); R_f 0.27 (1:2, petrol–ether); ν_{max}(thin film)/cm^{-1} 1713 (CO and COO), 1603 and 1586; δ_H(400 MHz, $CDCl_3$) 0.96 and 1.00 (2d, 6 H, *J* 6.96, 2 × CH_3), 1.80–2.00 (m, 4 H, CH_2CH_2), 2.61 (q, 1 H, *J* 6.96, H-2), 2.76 (dq, 1 H, *J* 6.96 and 4.76, H-4), 4.37 (br t, 2 H, *J* 6.60, CH_2O), 4.85 (dd, 1 H, *J* 4.76 and 1.83, H-5), 6.10 (d, 1 H, *J* 6.23, H-7), 6.26 (dd, 1 H, *J* 6.23 and 1.83, H-6), 7.44 (t, 2 H, *J* 8.06, 2 × H_m), 7.55 (dt, 1 H, *J* 8.06 and 1.46, H_p) and 8.04 (dd, 2 H, *J* 8.06 and 1.46, 2 × H_o); *m/z* 314.1517 (M$^+$, $C_{19}H_{22}O_4$ requires 314.1518, 30%).

1-(3-Benzyloxypropyl)-2-*endo*,4-*endo*-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one 6h

To a solution of the alcohol **6f** (315 mg, 1.5 mmol) in dry DMF (5 cm^3), kept at room temperature and under a nitrogen atmosphere, was added NaH (66.7 mg, ~1.66 mmol; 60% in mineral oil). The resultant suspension was then stirred at room temperature for 15 min before addition of benzyl bromide (308 mg, 1.8 mmol). The reaction mixture was then stirred at 45–50 °C for 18 h before addition of ether (150 cm^3) and water (40 cm^3). The two layers were separated and the aqueous phase was extracted with ether (3 × 30 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to leave a yellow oil. This oil was subjected to flash chromatography (2:1, petrol–ether) to afford the required ether as a pale yellow oil (87 mg, 19%); R_f 0.32 (2:1, petrol–ether); ν_{max}(thin film)/cm^{-1} 1711, 1600 and 1497; δ_H(400 MHz, $CDCl_3$) 0.95 and 0.98 (2d, 6 H, *J* 6.96, 2 × CH_3), 1.78–1.98 (m, 4 H, CH_2CH_2), 2.58 (q, 1 H, *J* 6.96, H-2), 2.75 (dq, 1 H, *J* 6.96 and 4.76, H-4), 3.45–3.54 (m, 2 H, CH_2O), 4.51 (s, 2 H, CH_2), 4.82 (dd, 1 H, *J* 4.76 and 1.83, H-5), 6.06 (d, 1 H, *J* 5.86, H-7), 6.22 (dd, 1 H, *J* 5.86 and 1.83, H-6) and 7.31–7.34 (m, 5 H, phenyl); *m/z* 300.1722 (M$^+$, $C_{19}H_{24}O_3$ requires 300.1725, 2%). Starting material (35%) was also recovered.

1-(3-Methoxypropyl)-2-*endo*,4-*endo*-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one 6i

The same procedure described for **6h** was used to prepare compound **6i** as a pale yellow oil (70%; 93% if recovered starting material is taken into account); R_f 0.20 (2:1, petrol–ether); ν_{max}(thin film)/cm^{-1} 1712 and 1596; δ_H(400 MHz, $CDCl_3$) 0.96 and 0.99 (2d, 6 H, *J* 6.96, 2 × CH_3), 1.55–1.99 (m, 4 H, CH_2CH_2), 2.59 (q, 1 H, *J* 6.96, H-2), 2.75 (dq, 1 H, *J* 6.96 and 4.77, H-4), 3.34 (s, 3 H, OCH_3), 3.40–3.45 (m, 2 H, CH_2O), 4.83 (dd, 1 H, *J* 4.77 and 1.84, H-5), 6.08 (d, 1 H, *J* 5.86, H-7) and 6.23 (dd, 1 H, *J* 5.86 and 1.84, H-6); δ_C(100 MHz, $CDCl_3$) 9.57, 10.23, 23.62, 30.55, 49.57, 55.56, 58.38, 72.52, 82.40, 90.08, 133.24, 135.63 and 209.28; *m/z* 224.1406 (M$^+$, $C_{13}H_{20}O_3$ requires 224.1412, 40%).

1-(3-Chloropropyl)-2-*endo*,4-*endo*-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one 6j

To a stirred solution of the alcohol **6f** (315 mg, 1.5 mmol) in dry acetonitrile (10 cm^3) and CCl_4 (3 cm^3), kept at room temperature and under a nitrogen atmosphere, was added triphenylphosphine (524.6 mg, 2 mmol in 4 cm^3 of CCl_4). The reaction mixture was stirred for 15 h, before removal of the solvent under reduced pressure to leave the crude product as a yellow oil. This oil was subjected to flash chromatography (2:1, petrol–ether) to afford the required chloro-compound as a pale yellow oil (310 mg, 91%); R_f 0.26 (2:1, petrol–ether); ν_{max}(thin film)/cm^{-1} 1712 and 1596; δ_H(400 MHz, $CDCl_3$) 0.96 and 1.00 (2d, 6 H, *J* 6.96, 2 × CH_3), 1.79–2.04 (m, 4 H, CH_2CH_2), 2.58 (q, 1 H, *J* 6.96, H-2), 2.76 (dq, 1 H, *J* 6.96 and 4.77, H-4), 3.60 (br t, 1 H, *J* 6.00, CH_2Cl), 4.84 (dd, 1 H, *J* 4.77 and 1.83, H-5), 6.09 (d, 1 H, *J* 5.86, H-7) and 6.26 (dd, 1 H, *J* 5.86 and 1.83, H-6); δ_C(100 MHz, $CDCl_3$) 9.54, 10.19, 26.80, 31.17, 45.16, 49.51, 54.05, 82.40, 89.78, 133.58, 135.27 and 208.86; *m/z* 228.0911/230.0882 (M$^+$, $C_{12}H_{17}ClO_2$ requires 228.0917/230.0887, 36%).

Typical procedure for ozonisation

Ozone was passed through a solution of the alkene (2 mmol) in dichloromethane–petrol (3:50 cm^3) held at −70 °C. After 10–15 min the reaction was judged to be completed when ozone was issuing from the exit tube connected to the flask. The solvent was removed to afford the required product in quantitative yield as a yellow oil or white solid. The oily ozonides were not subjected to further purification, and the solids were recrystallised from dichloromethane–ether.

2-Ethyl-3-*exo*,5-*exo*-dimethyl-8,9,10,11-tetraoxatricyclo-[5.2.1.1^{2,6}]undecan-4-one 4b. A white solid; mp 90–100 °C (decomp.); ν_{max}($CHCl_3$)/cm^{-1} 1717; δ_H(250 MHz, $CDCl_3$) 1.10 (t, 3 H, *J* 7, CH_3), 1.17 (2d, 6 H, *J* 7, 2 × CH_3) 1.50 and 1.72 (2 multiplets with six lines each, 2 H, *J* 7.2, CH_2), 2.70 (dq, 1 H, *J* 7 and 1.5, H-3), 2.90 (br quintet, 1 H, *J* 6.8, H-5), 4.08 (d, 1 H, *J* 6.0, 1.0 and 1.0, H-6), 5.47 (m, 1 H, H-1) and 5.75 (m, 1 H, H-7); δ_C(62 MHz, $CDCl_3$) 5.77 (CH_3), 8.49 and 9.46 (3-Me and 5-Me), 25.22 (CH_2), 44.88 and 46.69 (C-3 and C-5), 76.06 (C-6), 80.94 (C-2), 99.14 and 102.14 (C-1 and C-7) and 207.40 (C-4) (Found: C, 57.9; H, 7.1. $C_{10}H_{16}O_5$ requires C, 57.89; H, 7.07%).

2-Acetoxymethyl-3-*exo*,5-*exo*-dimethyl-8,9,10,11-tetra-oxatricyclo[5.2.1.1^{2,6}]undecan-4-one 4c. ν_{max}(thin film)/cm^{-1} 1721 (COO and CO); δ_H(400 MHz, $CDCl_3$) 1.15 (d, 3 H, *J* 7.0, CH_3), 1.16 (d, 3 H, *J* 7.0, CH_3), 2.12 (s, 3 H, CH_3CO), 2.65 (q, 1 H, *J* 7.0, H-3), 2.87 (br quintet, 1 H, *J* 7.0, H-5), 4.04–4.18 (m, 3 H, CH_2O and H-6), 5.59 (s, 1 H, H-1) and 5.73 (s, 1 H, H-7); *m*/*z* 290.1240 ([M + NH_4]$^+$, $C_{12}H_{20}O_7$ requires 290.1239, 16%).

2-Heptyl-3-*exo*,5-*exo*-dimethyl-8,9,10,11-tetraoxatricyclo-[5.2.1.1^{2,6}]undecan-4-one 4d. A white solid, mp 75–76 °C; ν_{max}($CHCl_3$)/cm^{-1} 1716; δ_H(250 MHz, $CDCl_3$) 0.88 (br t, 3 H, *J* 7, CH_3), 1.17 (d, 6 H, *J* 7, 3-CH_3 and 5-CH_3), 1.20–1.80 (m, 12 H, 6 × CH_2, side chain), 2.70 (br q, 1 H, *J* 7, H-3), 2.88 (br quintet, 1 H, *J* 7, H-5), 4.07 (br d, 1 H, *J* 6.5, H-6), 5.44 (s, 1 H, H-1) and 5.72 (s, 1 H, H-7); δ_C(62 MHz, $CDCl_3$) 8.82 (C-7′), 9.68 and 14.06 (3-Me and 5-Me), 21.67, 22.62, 29.19, 29.73, 31.76 and 32.73 (carbons 1′ to 6′ from side chain), 45.10 and 47.30 (C-3 and C-5), 76.55 (C-6), 81.21 (C-2), 99.33 and 102.34 (C-1 and C-7) and 207.45 (C-4) (Found: C, 64.4; H, 8.9. $C_{16}H_{26}O_5$ requires C, 64.41; H, 8.78%).

2-(3-Acetoxypropyl)-3-*exo*,5-*exo*-dimethyl-8,9,10,11-tetra-oxatricyclo[5.2.1.1^{2,6}]undecan-4-one 4e. ν_{max}(thin film)/cm^{-1} 1721 (COO and CO); δ_H(400 MHz, $CDCl_3$) 1.15 (d, 3 H, *J* 6.96, CH_3), 1.16 (d, 3 H, *J* 7.33, CH_3), 1.80–1.98 (m, 4 H, CH_2CH_2), 2.07 (s, 3 H, CH_3), 2.65 (q, 1 H, *J* 6.96, H-3), 2.87 (quintet, 1 H, *J* 7.33, H-5), 4.04–4.18 (m, 3 H, CH_2O and H-6), 4.45 (s, 1 H, H-1) and 5.72 (s, 1 H, H-7); δ_C(100 MHz, $CDCl_3$) 8.83 (CH_3), 9.67 (CH_3), 20.98 (CH_3), 21.32 (CH_2), 29.36 (CH_2), 45.09 (C-5), 47.66 (C-3), 64.30 (CH_2O), 76.22 (C-6), 80.74 (C-2), 99.29 (C-7), 102.05 (C-1), 171.34 (COO) and 207.20 (CO); *m*/*z* 300.1209 (M$^+$, $C_{14}H_{20}O_7$ requires 300.1209, 5%).

2-(3-Benzoyloxypropyl)-3-*exo*,5-*exo*-dimethyl-8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}]undecan-4-one 4g. ν_{max}(thin film)/cm^{-1} 1715 (COO and CO), 1603, 1586 and 1493; δ_H(400 MHz, $CDCl_3$) 1.14 and 1.16 (2d, 6 H, *J* 6.96, 2 × CH_3), 1.80–2.13 (m, 4 H, CH_2CH_2), 2.69 (q, 1 H, *J* 6.96, H-3), 2.87 (br quintet, 1 H, *J* 6.00, H-5), 4.08 (d, 1 H, *J* 5.90, H-6), 5.48 (s, 1 H, H-1), 5.73 (s, 1 H, H-7), 7.44 (t, 2 H, *J* 8.06, 2 × H_m), 7.57 (br t, 1 H, *J* 8.06, H_p) and 8.02 (br d, 2 H, *J* 8.06, 2 × H_o); δ_C(100 MHz, $CDCl_3$) 8.42 (CH_3), 9.39 (CH_3), 21.26 (CH_2), 29.05 (CH_2), 44.87 (C-5), 47.43 (C-3), 64.66 (CH_2O), 75.99 (C-6), 80.58 (C-2), 99.06 (C-7), 101.76 (C-1), 122.23 (2 × C_m), 129.30 (2 × C_o), 129.80 (C-1′ aromatic), 132.91 (C_p), 166.52 (COO) and 207.45 (CO); *m*/*z* 362.1374 (M$^+$, $C_{19}H_{22}O_7$ requires 362.1366, 3%).

2-(3-Benzyloxypropyl)-3-*exo*,5-*exo*-dimethyl-8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}]undecan-4-one 4h. ν_{max}(thin film)/cm^{-1} 1716, 1604 and 1498; δ_H(400 MHz, $CDCl_3$) 1.13 and 1.14 (2d, 6 H, *J* 7.33, 2 × CH_3), 1.58–1.91 (m, 4 H, CH_2CH_2), 2.65 (q, 1 H, *J* 7.33, H-3), 2.46 (br quintet, 1 H, *J* 7.00, H-5), 3.43–3.58 (m, 2 H, OCH_2), 4.05 (d, 1 H, *J* 5.86, H-6), 4.51 (s, 2 H, OCH_2Ph), 5.42 (s, 1 H, H-1), 5.68 (s, 1 H, H-7) and 7.25–7.36 (m, 5 H, phenyl); δ_C(100 MHz, $CDCl_3$) 8.69, 9.66, 22.18, 29.70, 45.06, 47.66, 70.01, 72.97, 76.21, 80.96, 99.27, 102.18, 127.67, 128.42, 138.22 and 207.59; *m*/*z* 348.1582 (M$^+$, $C_{19}H_{24}O_6$ requires 348.1573, 3%).

2-(3-Methoxypropyl)-3-*exo*,5-*exo*-dimethyl-8,9,10,11-tetraoxatricyclo[5.2.1.1^{2,6}]undecan-4-one 4i. ν_{max}(thin film)/cm^{-1} 1714; δ_H(400 MHz, $CDCl_3$) 1.14 and 1.16 (2d, 6 H, *J* 6.96, 2 × CH_3), 1.57–1.87 (m, 4 H, CH_2CH_2), 2.66 (q, 1 H, *J* 6.96, H-3), 2.88 (br quintet, 1 H, *J* 6.50, H-5), 3.38 (s, 3 H, OCH_3), 3.39–3.55 (m, 2 H, CH_2O), 4.08 (d, 1 H, *J* 5.86, H-6), 5.46 (s, 1 H, H-1) and 5.73 (s, 1 H, H-7); δ_C(100 MHz, $CDCl_3$) 8.74 (CH_3), 9.64 (CH_3), 21.82 (CH_2), 29.37 (CH_2), 45.09 (C-5), 47.69 (C-3), 58.54 (CH_3O), 72.60 (OCH_2), 76.24 (C-6), 80.92 (C-2), 99.29 (C-7), 102.14 (C-1) and 207.85 (C-4); *m*/*z* 272.1258 (M$^+$, $C_{13}H_{20}O_6$ requires 272.1259, 6%).

2-(3-Chloropropyl)-3-*exo*-,5-*exo*-dimethyl-8,9,10,11-tetraoxa-tricyclo[5.2.1.1^{2,6}]undecan-4-one 4j. Mp 102–110 °C (decomp.); ν_{max}($CHCl_3$)/cm^{-1} 1718; δ_H(400 MHz, $CDCl_3$) 1.14 and 1.16 (2d, 6 H, *J* 6.96, 2 × CH_3), 1.65–2.15 (m, 4 H, CH_2CH_2), 2.64 (q, 1 H, *J* 6.96, H-3), 2.89 (br quintet, 1 H, *J* 6.50, H-5), 3.51–3.57 and 3.61–3.70 (m, 2 H, CH_2Cl), 4.08 (d, 1 H, *J* 5.86, H-6), 5.50 (s, 1 H, H-1) and 5.75 (s, 1 H, H-7); δ_C(100 MHz, $CDCl_3$) 8.72 (CH_3), 9.60 (CH_3), 25.24 (CH_2), 30.24 (CH_2), 45.08 (C-5 and CH_2Cl), 47.75 (C-3), 76.20 (C-6), 86.78 (C-2), 99.27 (C-7), 101.98 (C-1) and 207.66 (C-4); *m*/*z* 276.0768/278.0740 (M$^+$, $C_{12}H_{17}ClO_5$ requires 276.0764/ 278.0735).

S-Methyl *O*-(2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-dithiocarbonate 9

To a stirred solution of the oxabicycle **6a** (1.52 g, 10 mmol) in toluene (30 cm^3), held at −24 °C and under a nitrogen atmosphere, was added DIBAL-H (1.5 mol dm^{-3} in toluene; 7 cm^3, 10.5 mmol). The reaction mixture was stirred for 2 h before addition of 10% aqueous tartaric acid (30 cm^3), and extraction with CH_2Cl_2 (4 × 60 cm^3). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (30 cm^3) and water (50 cm^3), dried over $MgSO_4$ and concentrated under reduced pressure to leave the required alcohol **7** as a white residue (1.5 g, 9.7 mmol).

A solution of this crude alcohol in dry THF (7 cm^3), was added to a suspension of NaH (60% dispersion in mineral oil, washed with petrol twice; 1.1 g, *ca.* 23 mmol) and imidazole (80 mg) in THF (15 cm^3), under nitrogen atmosphere. The reaction mixture was refluxed for 3 h (oil bath was kept at 70–80 °C) and after that time it had turned into a pale tan colour. On addition of CS_2 (2.85 cm^3, 47 mmol) and refluxing for 20 min, the reaction mixture became dark brown. MeI (3 cm^3, 47 mmol) was then added and the mixture turned dark yellow. After stirring at 70–80 °C for 30 min and at room temperature overnight, the reaction was worked up by slow addition of cold saturated aq. NH_4Cl (30 cm^3) and CH_2Cl_2 (50 cm^3). The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 cm^3). The combined extracts were washed with $Na_2S_2O_3$ (10%, 20 cm^3) and brine (50 cm^3), dried over $MgSO_4$ and concentrated under reduced pressure to afford a dark brown oil. This oil was purified by flash chromatography (3:1 petrol–ether) to afford the required product as a pale yellow oil (1.71 g, 69.5%); R_f 0.35 (3:1, petrol–ether); ν_{max}(thin film)/cm^{-1} 3076, 1593, 1223 and 1049; δ_H(250 MHz, $CDCl_3$) 0.82 (d, 6 H, *J* 7, 2 × CH_3), 2.40–2.55 (m, 2 H, H-2 and H-4), 2.56 (s, 3 H, SCH_3), 4.50 (d, 2 H, *J* 4, H-1 and H-5), 6.29 (t, 1 H, *J* 5, H-3) and 6.42 (s, 2 H, H-6 and H-7); *m*/*z* 244.0589 (M$^+$, $C_{11}H_{16}O_2S_2$ requires 244.0592, 5%).

2-*endo*,4-*endo*-Dimethyl-8-oxabicyclo[3.2.1]oct-6-ene 10

To a stirred solution of the dithiocarbonate **9** (1.1 g, 4.51 mmol) and AIBN (60 mg) in dry benzene (20 cm^3), under a nitrogen atmosphere, was added Bu_3SnH (1.58 cm^3, 5.86 mmol). The

reaction flask was transferred to an oil bath at 80–90 °C, and stirred for 25 h. After that time the solvent was removed with a stream of nitrogen and the oil obtained was purified by flash chromatography (5:1, petrol–ether) to afford the required product as a pale yellow oil (460 mg, 73.9%). The product was distilled at 10 mmHg (40 °C) to afford a colourless oil; R_f 0.27 (5:1, petrol–ether); ν_{max}(thin film)/cm^{-1} 3075 and 1594; δ_H(250 MHz, $CDCl_3$) 0.70 (d, 6 H, *J* 8, 2 × CH_3), 0.90 (dt, 1 H, J 13.5 and 11, H-3$_{endo}$), 1.58 (dt, 1 H, *J* 13.5 and 5, H-3$_{exo}$), 1.78–1.95 (m, 2 H, H-2 and H-4), 4.48 (d, 2 H, *J* 2, H-1 and H-5) and 6.18 (s, 2 H, H-6 and H-7); *m/z* 138.1045 (M^+, $C_9H_{14}O$ requires 138.1041, 18%) (Found: C, 77.4; H, 10.2. $C_9H_{14}O$ requires C, 77.65; H, 10.14%).

2,4-Dimethyl-3-methoxy-8-oxabicyclo[3.2.1]oct-6-ene 8

The alcohol **7** was transformed using the same procedure described for the preparation of compound **6h**, to give ether **8** as a pale yellow oil (57%); R_f 0.38 (1.5:1, petrol–ether); ν_{max}($CHCl_3$)/cm^{-1} 2884, 1206 and 1136; δ_H(250 MHz, $CDCl_3$) 1.07 (d, *J* 5, 2 × CH_3), 2.40 (m, H-2 and H-4), 3.37 (t, *J* 4.4, H-3), 3.45 (s, OCH_3), 5.52 (d, *J* 4.4, H-1 and H-5) and 6.48 (s, H-6 and H-7); *m/z* 168.1150 (M^+, $C_{10}H_{16}O_2$ requires 168.1150, 8%).

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