Preparation of oxonanes and azonanes by oxidative ring expansion: synthesis of obtusan

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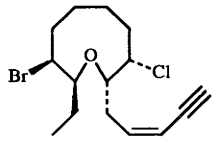
Oxonanes can be readily prepared from phthalans by a 3-step procedure involving Birch reduction, selective hydrogenation and oxidation. 2-Ethyl-9-pentyloxonane-3,8-dione has been deoxygenated to give obtusan. The method has been applied to the synthesis of an azonane.

A large number of marine natural products containing medium-ring ethers have been isolated in recent years.[1] The fascinating biological activity of these compounds, coupled with their novel structures, has prompted chemists to develop new methods for the preparation of such compounds.[2] Although 6- and 7-membered rings are most commonly found in such natural products, 8-membered and, to a lesser extent, 9-membered rings (*e.g.* obtusenyne)[3] are also known.



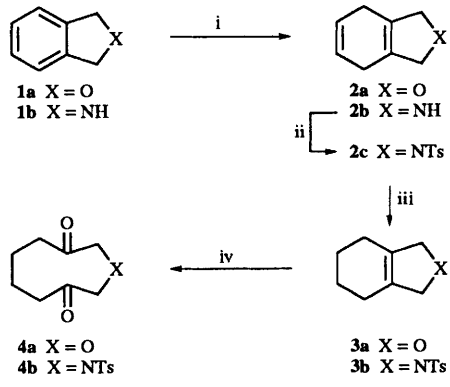
obtusenyne

Formation of 9-membered rings is known to be particularly troublesome[4] and consequently, far fewer methods are available for the formation of oxonanes compared to their smaller ring congeners. Recent research within our own group has centred on the use of rhodium carbenoid cyclisations for the preparation of functionalised oxepanes and oxocanes.[5] However, this method is unsatisfactory for larger rings, and therefore we sought an alternative methodology for the formation of these compounds. The synthesis of large rings by expansion/enlargement of smaller rings is a common tactic in organic synthesis, and the oxidative cleavage of the zero-ene-bridge in bicycles is an example of this.[6] However, with the exception of Quin's work on phosphonane 1-oxides and thionane 1,1-dioxides,[7] the method has not been used for monocyclic 9-membered rings.[8] Therefore, we investigated the preparation and oxidative cleavage of 1,3,4,5,6,7-hexahydrobenzo[*c*]furans (tetrahydrophthalans) as a route to the oxonane ring systems of the above mentioned natural products. This methodology seemed equally applicable to the preparation of azonanes, and therefore this was also investigated. We now report full details of these studies.[9]

Results and discussion

The required bicyclic precursors **3a**[10] and **3b** were prepared by Birch reduction of phthalan **1a** and 1,3-dihydro-2*H*-isoindole[11] **1b** followed by selective hydrogenation over Wilkinson's catalyst. In the case of the tetrahydrobenzo[*c*]pyrrole **2b**, Birch reduction was immediately followed by protection as a sulfonamide **2c**.

Ozonolysis of **3b** led to the azonane-3,8-dione **4b** in 50% yield. However, ozonolysis of **3a** was unreliable. In both cases the Sharpless modification[12] of the ruthenium-catalysed oxidation of alkenes was found to be more efficient, resulting



Scheme 1 *Reagents and conditions:* i, Na, NH_3; ii, TsCl, pyridine; iii, H_2, $[Rh(PPh_3)_3]Cl$, toluene; iv, $RuCl_3$, $NaIO_4$

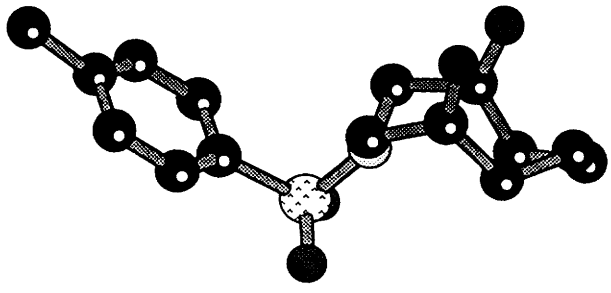
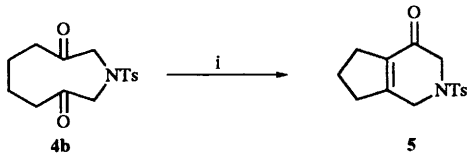


Fig. 1 X-ray crystal structure of **4b** (hydrogen atoms omitted for clarity); structure reproduced using the MolDraw program[13]

in the preparation of oxonane-3,8-dione **4a** (58%) and the azonane-3,8-dione **4b** (70%) (Scheme 1). The structure of **4b** was confirmed by X-ray crystallography (Fig. 1).[13] Treatment of **4b** with 4-methylbenzenesulfonic acid resulted in an intramolecular aldol reaction[14] giving **5** containing the ring system of the skytanthine alkaloids (Scheme 2).[15]

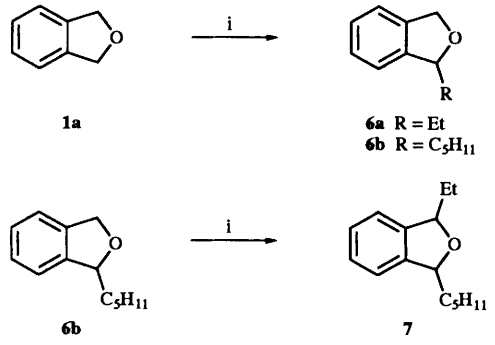


4b 5

Scheme 2 *Reagents and conditions:* i, 4-$MeC_6H_4SO_3H$, toluene, reflux

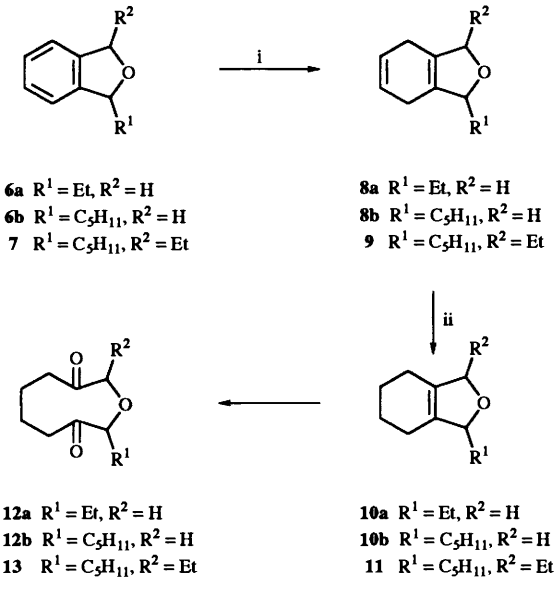
This methodology was next applied to alkyl substituted oxonanes. Phthalan **1a** was alkylated under the conditions reported by Davies and co-workers[16] to give the substituted phthalans **6a** and **6b**. A second alkylation of 1-pentylphthalan gave a diastereoisomeric mixture (1.4:1 by NMR) of 1-ethyl-3-pentylphthalans **7** (Scheme 3). The isomers were separated by

preparative HPLC to give the pure *cis*- and *trans*-dialkylphthalans. At this stage the stereochemistry of the isomers could not be assigned with certainty. However, since *trans*-obtusan, the saturated oxonane containing the carbon skeleton of the marine natural product obtusenyne,[3] has been prepared previously,[17] and ^{13}C NMR data recorded for a number of oxonanes suggesting that the 2- and 9-carbons of 2,9-disubstituted oxonanes resonate at lower field in the *cis* isomers than the *trans*,[17] we were confident that conversion of the two separated diastereoisomers of **7** into *cis*- and *trans*-obtusan would allow the assignment of their relative stereochemistry.



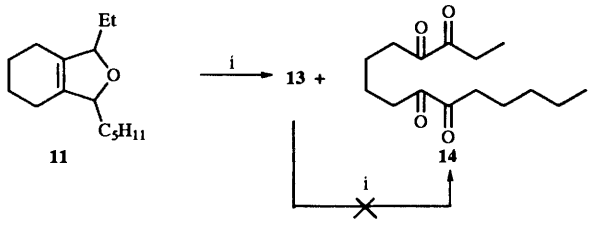
Scheme 3 *Reagents and conditions:* i, Bu^{t}Li then RI

These substituted phthalans were subjected to Birch reduction to give the tetrahydrophthalans **8a**, **8b** and **9** in good yields. For the monosubstituted phthalan derivatives, selective reduction over Wilkinson's catalyst was satisfactory. However, the dialkyl derivative could not be reduced by this method, and was instead reduced over palladium-on-carbon under a hydrogen pressure of 45 psi† to give the desired hexahydrobenzo[*c*]furan **11** in essentially quantitative yield. The monoalkyl hexahydroisobenzofurans and the mixture of diastereoisomers of the dialkyl compound were oxidised as before to give substituted oxonanes **12a**, **12b** and **13** in modest yields (Scheme 4).



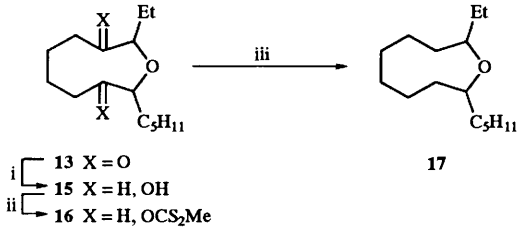
Scheme 4 *Reagents and conditions:* i, Na, NH_3; ii, H_2, $[Rh(PPh_3)_3]Cl$ (for **8a** and **8b**) or H_2, Pd–C (for **9**); iii, $RuCl_3$, $NaIO_4$

In addition to the desired product, oxidation of the dialkyl hexahydroisobenzofuran **11** gave the tetraketone **14**. When the oxonane **13** was treated with $RuCl_3$–$NaIO_4$ for 3 days, none of this compound was produced (Scheme 5), suggesting that the tetraketone is formed by initial cleavage of the cyclic ether in **11** followed by breaking of the double bond. The cleavage of cyclic ethers by ruthenium tetraoxide has been described previously.[18]



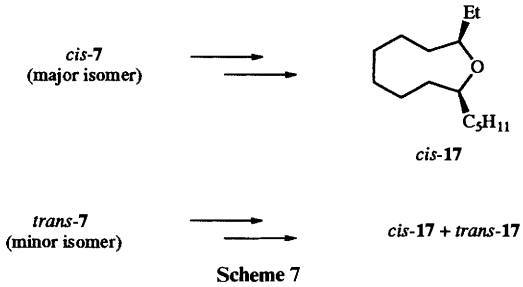
Scheme 5 *Reagents and conditions:* i, $RuCl_3$, $NaIO_4$

Deoxygenation of **13** to give obsutan was first performed on the diastereoisomeric mixture. Thus, reduction of **13** by lithium aluminium hydride gave the diol **15** (mixture of diastereoisomers) which was converted into its bis-xanthate **16**. Radical deoxygenation[19] gave obtusan **17** as a mixture of diastereoisomers (2.5:1 *cis*:*trans*) which were readily separated by flash column chromatography to give pure *cis*- and *trans*-obtusan (Scheme 6).



Scheme 6 *Reagents and conditions:* i, $LiAlH_4$; ii, NaH, CS_2, MeI, DMF; iii, Bu_3SnH, AIBN

The major isomer of the hexahydrobenzo[*c*]furan **11** (prepared from the major isomer of **7**) was converted into pure *cis*-obtusan under identical reaction conditions, thus establishing the stereochemistry of the original phthalan mixture. However, when the minor isomer of **11** was treated under the same conditions, obtusan **17** was obtained as a mixture of diastereoisomers (1.5:1 *trans*:*cis*) (Scheme 7). Since the oxonanedione *trans*-**13** (from the minor isomer of **11**) was a single stereoisomer, and since reduction and xanthate formation should not lead to any loss of stereochemical integrity, it seems likely that the epimerisation is occurring during the radical deoxygenation, possibly as a result of two intramolecular 1,5-hydrogen shifts.[20] The proposed mechanism for this isomerisation is shown in Scheme 8.



Scheme 7

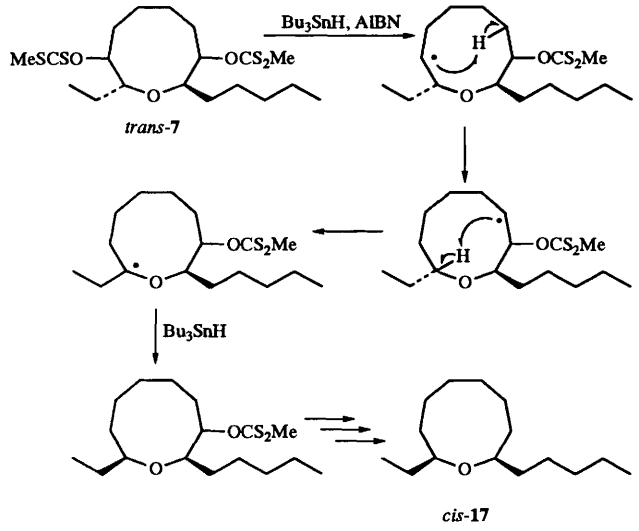
Experimental

For general experimental points see ref. 21.

1,3,4,7-Tetrahydrobenzo[*c*]furan 2a

Liquid ammonia (100 cm^3) was condensed into a round bottomed flask. Diethyl ether (19 cm^3), ethanol (18.3 cm^3) and phthalan (11.3 g, 94 mmol) were added sequentially to it

† 1 psi = 6.89 × 10^3 Pa.



Scheme 8

followed by the addition, over 45 min, of sodium (6.5 g, 283 mmol). When the addition was complete, the ammonia was allowed to evaporate and water (100 cm^3) and diethyl ether (100 cm^3) were added to the residue. The phases were separated and the aqueous phase extracted with diethyl ether (2 × 50 cm^3). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and purified by short path distillation to give the *title compound* (9.73 g, 85%) as a colourless liquid, bp 150 °C at 15 mmHg (Found: M^+, 121.065. $C_8H_{10}O$ −H requires *M*, 121.0653); ν_{max}(film)/cm^{-1} 3030, 2834, 1645, 1432, 1045, 1014, 957, 913, 893 and 815; δ_H(250 MHz; $CDCl_3$) 5.78 (2 H, s, 5-H and 6-H), 4.55 (4 H, s, 1-H_2 and 3-H_2) and 2.66 (4 H, s, 4-H_2 and 7-H_2); δ_C(62.9 MHz; $CDCl_3$) 128.5 (C), 123.9 (CH), 77.3 (CH_2O) and 23.6 (CH_2); *m*/*z* (EI) 121 (M^+ − H, 20%), 93 (65), 91 (100), 77 (60), 65 (30), 39 (35) and 29 (12).

2,3,4,7-Tetrahydro-1*H*-benzo[*c*]pyrrole 2b

Liquid ammonia (40 cm^3) was condensed into a 100 cm^3 3-necked round bottomed flask. Diethyl ether (2.5 cm^3), ethanol (2.44 cm^3) and isoindoline[11] (1.491 g, 12.5 mmol) were added to it in that order, followed by the addition, over 30 min, of sodium (0.86 g, 37.5 mmol). The ammonia was then allowed to evaporate, and water (20 cm^3) and diethyl ether (20 ml) were added to the residue. The phases were separated and the aqueous phase extracted with diethyl ether (2 × 20 cm^3). The combined organic phase was dried over potassium hydroxide pellets, filtered and concentrated under reduced pressure to give the title compound (1.143 g, 75%) as an orange oil which was used without further purification, δ_H(250 MHz; $CDCl_3$) 5.77 (2 H, br s, 5-H and 6-H), 3.68 (4 H, s, 1-H_2 and 3-H_2), 2.67 (4 H, s, 4-H_2 and 7-H_2) and 2.5 (1 H, br s, NH); δ_C(62.9 MHz; $CDCl_3$) 130.1 (C), 124.2 (alkene CH), 55.9 (CH_2N) and 25.2 (CH_2).

2,3,4,7-Tetrahydro-2-(*p*-tosyl)-1*H*-benzo[*c*]pyrrole 2c

To the crude 2,3,4,7-tetrahydro-1*H*-benzo[*c*]pyrrole **2b** (1.143 g, 9.45 mmol) were added *p*-tosyl chloride (1.8 g, 9.45 mmol) and pyridine (7 cm^3), and the resulting dark solution was heated under reflux for 30 min. The mixture was then poured into aqueous hydrochloric acid (2 mol dm^{-3}; 40 cm^3). The precipitate was filtered off and recrystallised from ethanol to give the *title compound* (2.211 g, 85%) as a buff coloured solid, mp 176–177 °C (Found: C, 65.3; H, 6.2; N, 5.1. $C_{15}H_{17}NO_2S$ requires C, 65.4; H, 6.2; N, 5.1%); ν_{max}($CHCl_3$)/cm^{-1} 3021, 1342, 1164, 1103 and 665; δ_H(250 MHz; $CDCl_3$) 7.74 (2 H, d, *J* 8.4, ArH), 7.31 (2 H, d, *J* 8.4, ArH), 5.70 (2 H, s, –CH=CH–), 4.01 (4 H, s, 1-H_2 and 3-H_2), 2.57 (4 H, s, 4-H_2 and 7-H_2) and 2.43 (3 H, s, CH_3); δ_C(62.9 MHz; $CDCl_3$) 143.4 (C), 134.0 (C), 129.8 (CH), 127.6 (CH), 123.5 (alkene CH), 122.6 (C), 56.9 (CH_2NCH_2), 24.6 (2 × CH_2) and 21.5 (CH_3); *m*/*z* (EI) 275 (M^+, 20%), 221 (20), 155 (100), 120 (95), 91 (80), 65 (30) and 35 (30).

1,3,4,5,6,7-Hexahydrobenzo[*c*]furan 3a

A solution of 1,3,4,7-tetrahydrobenzo[*c*]furan **2a** (1.22 g, 10 mmol) and tris(triphenylphosphine)rhodium(I) chloride (40 mg) in toluene (40 cm^3) was thoroughly degassed, then stirred under an atmosphere of hydrogen for 48 h. The solution was filtered through a pad of silica gel and the silica gel was washed with diethyl ether (100 cm^3). After removal of the solvent under reduced pressure the residue was purified by flash column chromatography (eluent light petroleum–diethyl ether, 3:1) to give the *title compound* (902 mg, 73%) as a colourless liquid, bp 150 °C at 15 mmHg (Found: M^+, 125.0972. $C_8H_{12}O + H^+$ requires *M*, 125.0966); ν_{max}(film)/cm^{-1} 2931, 2855, 1439, 1310, 1046, 908 and 806; δ_H(250 MHz; $CDCl_3$) 4.51 (4 H, s, 1-H_2 and 3-H_2), 2.1–1.9 (4 H, m, 2 × CH_2) and 1.7–1.6 (4 H, m, 2 × CH_2); δ_C(62.9 MHz; $CDCl_3$) 130.6 (C), 77.4 (CH_2O), 22.3 (CH_2) and 21.5 (CH_2); *m*/*z* (EI) 124 (M^+, 5%), 109 (6), 95 (10), 86 (34), 84 (55), 51 (40) and 49 (100).

2,3,4,5,6,7-Hexahydro-2-(*p*-tosyl)-1*H*-benzo[*c*]pyrrole 3b

A solution of 1,3,4,7-tetrahydro-2-(*p*-tosyl)-2*H*-benzo[*c*]pyrrole **2c** (275 mg, 1 mmol) and tris(triphenylphosphine)rhodium(I) chloride (30 mg) in degassed dry toluene (10 cm^3) was stirred under an atmosphere of hydrogen for 60 h. After removal of the catalyst by filtration through a pad of silica gel, the solvent was removed under reduced pressure and the solid residue purified by flash column chromatography (eluent light petroleum–diethyl ether 3:1) to give the *title compound* (225 mg, 81%) as a colourless solid, mp 133–134 °C (Found C, 64.7; H, 6.8; N, 5.0. $C_{15}H_{19}NO_2S$ requires C, 64.95; H, 6.9; N, 5.0%); ν_{max}(Nujol)/cm^{-1} 1340, 1162, 1099, 718 and 663; δ_H(250 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.4, ArH), 7.32 (2 H, d, *J* 8.4, ArH), 3.96 (4 H, s, 1-H_2 and 3-H_2), 2.43 (3 H, s, CH_3), 2.0–1.8 (4 H, m, 2 × CH_2) and 1.7–1.5 (4 H, m, 2 × CH_2); δ_C(62.9 MHz; $CDCl_3$) 143.2 (C), 134.5 (C), 129.7 (CH), 127.6 (CH), 122.6 (alkene C), 57.1 CH_2NCH_2), 22.8 (2 × CH_2), 22.1 (2 × CH_2) and 21.5 (CH_3); *m*/*z* (EI) 277 (M^+, 2%), 155 (100), 122 (76), 91 (40), 65 (21), 41 (20) and 35 (18).

Oxonane-3,8-dione 4a

Sodium metaperiodate (3.51 g, 16.4 mmol) was added to a solution of 1,3,4,5,6,7-hexahydrobenzo[*c*]furan **3a** (496 mg, 4 mmol) in tetrachloromethane (8 cm^3), acetonitrile (8 cm^3) and water (12 cm^3). Ruthenium(III) chloride hydrate (20 mg) was added to it and the reaction mixture stirred vigorously for 24 h when dichloromethane (50 cm^3) and water (50 cm^3) were added to it and the phases separated. The aqueous phase was extracted with dichloromethane (2 × 50 cm^3), and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a dark oil, which was purified by flash column chromatography (eluent light petroleum–ethyl acetate 3:1) to give the *title compound* (365 mg, 58%) as a colourless oil (Found: M^+, 156.0785. $C_8H_{12}O_3$ requires *M*, 156.0786); ν_{max}(film)/cm^{-1} 2937, 1714, 1447, 1256, 1161 and 1122; δ_H(250 MHz; $CDCl_3$) 4.15 (4 H, s, 2-H_2 and 9-H_2), 2.79–2.71 (4 H, m, 4-H_2 and 7-H_2) and 1.85–1.74 (4 H, m, 5-H_2 and 6-H_2); δ_C(62.9 MHz; $CDCl_3$) 212.9 (C=O), 79.9 (CH_2O), 36.5 (CH_2) and 23.7 (CH_2); *m*/*z* (EI) 156 (M^+, 2.3%), 126 (100), 98 (60), 83 (44), 70 (52), 55 (20) and 41 (19).

1-(*p*-Tosyl)azonane-3,8-dione 4b

By ozonolysis. A solution of 2,3,4,5,6,7-hexahydro-1-(*p*-tosyl)-2*H*-benzo[*c*]pyrrole **3b** (100 mg, 0.36 mmol) in CH_2Cl_2

($50\ cm^3$) containing Sudan III dye[22] (trace) was ozonised at −78 °C until the red colour was discharged. The solution was then purged with nitrogen for 15 min when dimethyl sulfide ($0.5\ cm^3$) was added to it. After the mixture had been stirred at room temperature for 30 min the volatiles were removed under reduced pressure to leave a brown solid which was recrystallised from absolute ethanol to give the *title compound* (56 mg, 50%) as a colourless solid, mp 126–127 °C (Found: M^+, 309.1026, $C_{15}H_{19}NO_4S$ requires *M*, 309.1035); $\nu_{max}(CHCl_3)/cm^{-1}$ 3010, 1716, 1353, 1165 and 1090; δ_H(250 MHz; $CDCl_3$) 7.68 (2 H, d, *J* 8.3, ArH), 7.37 (2 H, d, *J* 8.3, ArH), 3.70 (4 H, s, 2-H_2 and 9-H_2), 3.1–2.9 (4 H, m, 2 × CH_2), 2.46 (3 H, s, CH_3) and 1.9–1.7 (4 H, m, 2 × CH_2); δ_C(62.9 MHz; $CDCl_3$) 209.4 (C=O), 144.9 (C), 133.7 (C), 130.3 (CH), 127.4 (CH), 60.4 (2 × CH_2N), 35.5 (2 × CH_2), 23.5 (2 × CH_2) and 21.6 (CH_3); *m/z* (EI) 309 (M^+, 0.2%), 154 (25), 136 (7), 126 (22), 98 (55), 81 (45), 65 (10) and 42 (100).

By action of $RuCl_3$–$NaIO_4$. To 2,3,4,5,6,7-hexahydro-2-(*p*-tosyl)-1*H*-benzo[*c*]pyrrole **3b** (277 mg, 1 mmol) were added tetrachloromethane ($2\ cm^3$), acetonitrile ($2\ cm^3$) and water ($3\ cm^3$) followed by sodium metaperiodate (877 mg, 4.1 mmol) and ruthenium(III) chloride hydrate (5 mg). The reaction mixture was stirred vigorously for 24 h after which dichloromethane ($10\ cm^3$) and water ($10\ cm^3$) were added to it. The phases were separated and the aqueous phase was extracted with dichloromethane (2 × $10\ cm^3$). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a grey solid which was recrystallised from absolute ethanol to give the *title compound* (216 mg, 70%) as a colourless solid, mp 125–126 °C.

2-(*p*-Tosyl)-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*c*]pyridin-4-one 5

A solution of 1-(*p*-tosyl)azonane-3,8-dione **4b** (205 mg, 0.66 mmol) and 4-methylbenzenesulfonic acid (21 mg) in toluene ($30\ cm^3$) was heated under reflux with removal of water (Dean–Stark) for 5 h after which the solvent was removed under reduced pressure and the residue dissolved in dichloromethane ($30\ cm^3$). The solution was washed with water (3 × $10\ cm^3$), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a solid which was purified by flash column chromatography (eluent light petroleum–diethyl ether, 1:1) to give the *title compound* (171 mg, 89%) as a colourless solid, mp 122–123.5 °C (Found: C, 61.85; H, 5.85; N, 4.8. $C_{15}H_{17}NO_3S$ requires C, 61.9; H, 5.8; N, 4.8%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1679, 1354, 1271, 1168, 759 and 670; δ_H(250 MHz; $CDCl_3$) 7.65 (2 H, d, *J* 8.4, ArH), 7.33 (2 H, d, *J* 8.4, ArH), 4.0 (2 H, br s, 1-H_2), 3.77 (2 H, s, 3-H_2), 2.55 (2 H, m, 7-H_2), 2.45–2.35 (2 H, m, 5-H_2), 2.43 (3 H, s, CH_3) and 1.95–1.8 (2 H, m, 6-H_2); δ_C(62.9 MHz; $CDCl_3$) 189 (C=O), 160.2 (alkene C), 144.1 (aromatic C), 137.1 (aromatic C), 129.7 (aromatic CH), 128.1 (alkene C), 127.5 (aromatic CH), 52.5 (C-3), 45.7 (C-1), 35.5 (C-5), 28.4 (C-6), 21.6 (C-7) and 21.5 (CH_3) (assignments made with the aid of correlation spectra and NOE data; *m/z* (EI) 291 (M^+, 3%), 223 (12), 136 (91), 108 (100), 91 (22) and 79 (19).

1-Ethyl-1,3-dihydrobenzo[*c*]furan 6a

A solution of phthalan (5.4 g, 45 mmol) in THF ($150\ cm^3$) was cooled to −78 °C under an atmosphere of argon. A solution of *tert*-butyllithium in pentane ($29.1\ cm^3$, 49.5 mmol) was added dropwise to it and the resulting dark solution was stirred at −78 °C for 6 h. Iodoethane ($12\ cm^3$, 150 mmol) was added to it over 15 min, during which time the colour of the solution faded and a precipitate formed. After a further 90 min at −78 °C, methanol ($45\ cm^3$) was added to the solution after which it was allowed to warm to room temperature. After being stirred for 12 h the mixture was evaporated under reduced pressure and the residue was partitioned between water ($50\ cm^3$) and diethyl ether ($50\ cm^3$). The aqueous phase was separated and extracted with diethyl ether (2 × $50\ cm^3$), and the combined organic phases were washed with water ($25\ cm^3$) and brine (25 cm), dried ($MgSO_4$) filtered, concentrated under reduced pressure and distilled to give the *title compound* (5.135 g, 77%) as a clear oil, bp 100 °C at 5 mmHg (Found: M^+, 148.0885. $C_{10}H_{12}O$ requires *M*, 148.0888); ν_{max}(film)/cm^{-1} 2967, 2850, 1461, 1050, 1019 and 744; δ_H(250 MHz; $CDCl_3$) 7.28–7.15 (4 H, m, ArH), 5.20 (1 H, m, 1-H), 5.08 (2 H, m, 3-H_2), 1.93 and 1.76 (1 H each, m, CH_2CH_3) and 0.97 (3 H, t, *J* 7.4, CH_2CH_3); δ_C(62.9 MHz; $CDCl_3$) 141.8 (C), 139.5 (C), 127.2 (CH), 127.1 (CH), 121.1 (CH), 120.8 (CH), 84.9 (CH), 72.6 (CH_2O), 28.9 (CH_2) and 9.2 (CH_3); *m/z* (EI) 148 (M^+, 6%), 119 (100), 91 (40), 65 (10) and 39 (4).

1-Pentyl-1,3-dihydrobenzo[*c*]furan 6b

A solution of phthalan (18.6 g, 0.155 mol) in THF ($350\ cm^3$) was cooled to −78 °C under an atmosphere of nitrogen. A solution of *tert*-butyllithium in pentane ($100\ cm^3$, 0.17 mol) was added at such a rate as to keep the internal temperature below −70 °C. After the mixture had been stirred for 6 h at −78 °C, 1-iodopentane (100 g, 0.51 mol) was added dropwise to it and stirring continued for a further 90 min. The mixture was then diluted with methanol ($150\ cm^3$) and allowed to warm to room temperature overnight. The solvent was removed under reduced pressure and the residue partitioned between water ($200\ cm^3$) and diethyl ether ($200\ cm^3$). The aqueous phase was separated and extracted with diethyl ether (2 × $200\ cm^3$) and the combined organic phases were then washed with water ($200\ cm^3$) and saturated brine ($200\ cm^3$). The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure and distilled to give the *title compound* (25.37 g, 86%) as a colourless oil, bp 102 °C at 3 mmHg (Found: M^+, 190.1359. $C_{13}H_{18}O$ requires *M*, 190.1358); ν_{max}(film)/cm^{-1} 2955, 2857, 1461, 1037 and 746; δ_H(250 MHz; $CDCl_3$) 7.27–7.15 (4 H, m, ArH), 5.24 (1 H, m, 1-H), 5.06 (2 H, m, 3-H_2), 1.80 and 1.68 (1 H each, m, CH_2), 1.48–1.28 (6 H, m, $[CH_2]_3$) and 0.88 (3 H, m, CH_3); δ_C(62.9 MHz; $CDCl_3$) 142.2 (C), 139.4 (C), 127.2 (CH), 127.1 (CH), 121.0 (CH), 120.8 (CH), 83.9 (CH), 72.4 (CH_2O), 36.2 (CH_2), 31.9 (CH_2), 24.8 (CH_2), 22.6 (CH_2) and 14.0 (CH_3); *m/z* (EI) 190 (M^+, 2%), 119 (100), 91 (25), 65 (5) and 32 (4).

1-Ethyl-3-pentyl-1,3-dihydrobenzo[*c*]furan 7

A solution of 1-pentyl-1,3-dihydrobenzo[*c*]furan **6b** (25.37 g, 0.134 mol) in THF ($350\ cm^3$) was cooled to −78 °C under an atmosphere of argon and a 1.7 mol dm^{-3} solution of *tert*-butyllithium in pentane ($100\ cm^3$, 0.17 mol) was added dropwise to it at −78 °C. The mixture was stirred at −78 °C for 6 h after which iodoethane ($40\ cm^3$ 0.5 mol) was added dropwise to it and stirring was continued for a further 90 min. Methanol ($150\ cm^3$) was then added to the solution which was then allowed to warm to room temperature over 15 h. The solvent was removed under reduced pressure and the residue partitioned between water ($100\ cm^3$) and diethyl ether ($100\ cm^3$). The aqueous phase was extracted with diethyl ether (2 × $100\ cm^3$), and the combined organic phases were washed with water ($100\ cm^3$) and saturated brine ($100\ cm^3$), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Distillation of the residue gave the *title compound* (24.03 g, 82%) as a colourless oil (mixture of diastereoisomers), bp 100 °C at 1.4 mmHg (Found: M^+, 218.1667. $C_{15}H_{22}O$ requires *M*, 218.1671); ν_{max}(film)/cm^{-1} 2959, 2857, 1459, 1050 and 749; δ_H(250 MHz; $CDCl_3$) 7.27–7.12 (4 H, m, ArH), 5.27–5.10 (2 H, m, 1-H and 3-H), 1.91–1.66 (4 H, m, 2 × CH_2), 1.51–1.28 (6 H, m, $[CH_2]_3$) and 1.02–0.86 (6 H, m, 2 × CH_3); δ_C(62.9 MHz; $CDCl_3$) 143.0 (C), 142.9 (C), 142.4 (C), 142.3 (C), 127.2 (CH), 121.2 (CH), 121.1 (CH), 121.1 (CH), 121.0 (CH), 83.9 (CH-O), 83.8 (CH-O), 83.2 (CH-O), 82.8 (CH-O), 36.8 (CH_2), 32.0

(CH_2), 32.0 (CH_2), 29.3 (CH_2), 25.1 (CH_2), 24.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 9.5 (CH_3) and 9.1 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 218 (M^+, 0.7%), 189 (30), 147 (100), 129 (30), 119 (17), 91 (20) and 28 (16).

HPLC separation of the isomers of 7. The isomers of **7** were separated by preparative HPLC using a Lichrosorb Si60 7 micron column 25 cm in length with an internal diameter of 50 mm. Eluent was 2% methyl *tert*-butyl ether in hexane at a flow rate of 20 cm^3 min^{-1}. Detection was by UV at 254 nm. The minor isomer *trans*-**7** had a retention time of 18.5 min. The major isomer *cis*-**7** had a retention time of 22 min. In this way, 10 g of **7** was separated in 0.5 g portions to give 3.04 g of *trans*-**7** and 4.2 g of *cis*-**7**. (^1H NMR showed that this ratio does reflect that in the isomer mixture prepared by alkylation of **6b**.)

Data for *trans*-7. Colourless oil (Found: M^+, 218.1672. $C_{15}H_{22}O$ requires *M*, 218.1671); ν_{max}(film)/cm^{-1} 2931, 2850, 1465, 1050 and 744; δ_H(250 MHz; $CDCl_3$) 7.27–7.12 (4 H, m, ArH), 5.28–5.20 (2 H, m, 1-H and 3-H), 1.88–1.66 (4 H, m, 2 × CH_2), 1.44–1.28 (6 H, m, $[CH_2]_3$) and 0.96–0.85 (6 H, m, 2 × CH_3); δ_C(62.9 MHz; $CDCl_3$) 142.7 (C), 142.1 (C), 127.2 (CH), 127.1 (CH), 121.1 (CH), 121.0 (CH), 83.8 (CH-O), 83.1 (CH-O), 36.7 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 14.0 (CH_3) and 9.0 (CH_3); *m/z* (EI) 218 (M^+, 1.3%), 189 (32), 147 (100), 129 (20), 117 (8) and 91 (10).

Data for *cis*-7. Colourless oil (Found: M^+, 218.1676. $C_{15}H_{22}O$ requires *M*, 218.1671); ν_{max}(film)/cm^{-1} 2951, 2850, 1460, 1051, 1023 and 744; δ_H(250 MHz; $CDCl_3$) 7.27–7.11 (4 H, m, ArH), 5.17–5.11 (2 H, m, 1-H and 3-H), 2.09–1.64 (4 H, m, 2 × CH_2), 1.53–1.1.35 (6 H, m, $[CH_2]_3$) and 1.02–0.86 (6 H, m, 2 × CH_3); δ_C(62.9 MHz; $CDCl_3$) 142.9 (C), 142.3 (C), 127.1 (2 coincident CH), 121.0 (2 coincident CH), 83.7 (CH-O), 82.7 (CH-O), 36.7 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 25.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3) and 9.4 (CH_3); *m/z* (EI) 218 (M^+, 1%), 189 (35), 147 (100), 129 (18), 117 (7) and 91 (11).

Birch reduction of substituted 1,3-dihydrobenzo[*c*]furans: general procedure

Liquid ammonia (50 cm^3) was condensed into a round bottomed flask to which diethyl ether (6 cm^3), ethanol (5.3 cm^3, 90 mmol) and the appropriate 1,3-dihydrobenzo[*c*]furan (30 mmol) were added followed by sodium (2.07 g, 90 mmol), added over 30 min. The solvent was then allowed to evaporate after which the residue was partitioned between water (50 cm^3) and diethyl ether (50 cm^3). The aqueous phase was extracted with diethyl ether (2 × 50 cm^3), and the combined organic phases were washed with water (50 cm^3) and saturated brine (50 cm^3), dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified as described below.

1-Ethyl-1,3,4,7-tetrahydrobenzo[*c*]furan 8a. 1-Ethyl-1,3-dihydrobenzo[*c*]furan **6a** (4.144 g, 28 mmol) was reduced as described above to give, after distillation under reduced pressure, the *title compound* (3.64 g, 87%) as a colourless oil, bp 95 °C at 9 mmHg (Found: M^+, 150.1044. $C_{10}H_{14}O$ requires *M*, 150.1045); ν_{max}(film)/cm^{-1} 2964, 2825, 1046, 1019, 959 and 666; δ_H(250 MHz; $CDCl_3$) 5.79 (2 H, s, 5-H and 6-H), 4.67 (1 H, m, CH-O), 4.47 (2 H, m, 3-H_2), 2.58 (4 H, m, 4-H_2 and 7-H_2), 1.71 and 1.49 (1 H each, m, C$H_2$$CH_3$) and 0.91 (3 H, t, *J* 7.3, CH_3); δ_C(62.9 MHz; $CDCl_3$) 130.4 (C), 129.0 (C), 123.9 (alkene CH), 123.8 (alkene CH), 88.0 (CH-O), 76.4 (CH_2O), 26.8 (CH_2), 23.7 (CH_2), 23.5 (CH_2) and 8.6 (CH_3); *m/z* (EI) 150 (M^+, 5%), 121 (100), 103 (10), 91 (25), 77 (16) and 57 (6).

1-Pentyl-1,3,4,7-tetrahydrobenzo[*c*]furan 8b. Reduction of 1-pentyl-1,3-dihydrobenzo[*c*]furan **6b** (2.85 g, 15 mmol) according to the above general procedure followed by distillation under reduced pressure gave the *title compound* (2.408 g, 84%) as a colourless oil, bp 110 °C at 0.1 mmHg (Found: M^+, 192.1511. $C_{13}H_{20}O$ requires *M*, 192.1514); ν_{max}(film)/cm^{-1} 2929, 2857, 1036, 958 and 666; δ_H(250 MHz; $CDCl_3$) 5.78 (2 H, s, 5-H and 6-H), 4.69 (1 H, m, C*H*-O), 4.53 (2 H, m, 3-H_2), 2.7–2.5 (4 H, m, 4-H_2 and 7-H_2), 1.7–1.2 (8 H, m, $[CH_2]_4$) and 0.89 (3 H, t, *J* 6.5, CH_3); δ_C(62.9 MHz; $CDCl_3$) 131.0 (C), 128.7 (C), 124.0 (alkene CH), 123.9 (alkene CH), 87.3 (CH-O), 76.3 (CH_2O), 34.3 (CH_2), 32.1 (CH_2), 24.5 (CH_2), 23.8 (CH_2), 23.6 (CH_2), 22.7 (CH_2) and 14.1 (CH_3); *m/z* (EI) 192 (M^+, 2%), 121 (100), 119 (14), 91 (20), 77 (10), 65 (4) and 43 (3).

1-Ethyl-3-pentyl-1,3,4,7-tetrahydrobenzo[*c*]furan 9. 1-Ethyl-3-pentyl-1,3-dihydrobenzo[*c*]furan **7** was reduced by the general method described above and purification of the product by distillation gave the *title compound* (9.63 g, 95%) as a colourless oil, bp 200 °C at 3.5 mmHg (Found: M^+, 220.1830. $C_{15}H_{24}O$ requires *M*, 220.1827); ν_{max}(film)/cm^{-1} 3030, 2929, 2824, 1464, 957 and 666; δ_H(250 MHz; $CDCl_3$) 5.78 (2 H, br s, 5-H and 6-H), 4.7 (1 H, m, CH-O), 4.6 (1 H, m, CH-O), 2.6 (4 H, br s, 4-H_2 and 7-H_2), 1.8–1.25 (10 H, m, 5 × CH_2) and 0.96–0.86 (6 H, m, 2 × CH_3); δ_C(62.9 MHz; $CDCl_3$) 131.7 (C), 131.6 (C), 130.9 (C), 130.8 (C), 124.0 (alkene CH), 87.2 (CH-O), 87.1 (CH-O), 86.6 (CH-O), 86.2 (CH-O), 35.0 (CH_2), 34.5 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 27.4 (CH_2), 26.9 (CH_2), 24.9 (CH_2), 24.4 (CH_2), 23.8 (CH_2), 23.8 (CH_2) 22.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 14.1 (CH_3), 9.2 (CH_3) and 8.5 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 220 (M^+, 1%), 191 (58), 149 (100), 121 (18), 105 (22), 91 (30) and 79 (13).

1-Ethyl-1,3,4,5,6,7-hexahydrobenzo[*c*]furan 10a

A degassed solution of **8a** (600 mg, 4 mmol) in toluene (20 cm^3) containing tris(triphenylphosphine)rhodium(I) chloride (15 mg) was stirred under an atmosphere of hydrogen for 17 h. The solution was then filtered through a pad of silica gel, concentrated under reduced pressure and purified by flash column chromatography (eluent light petroleum) to give the *title compound* (544 mg, 90%) as a colourless oil (Found: M^+, 152.1202. $C_{10}H_{16}O$ requires *M*, 152.1201); ν_{max}(film)/cm^{-1} 2933, 2850, 1439, 1044 and 1019; δ_H(250 MHz; $CDCl_3$) 4.65 (1 H, m, 1-H), 4.47 (2 H, m, 3-H_2), 1.93 (4 H, m, 2 × CH_2), 1.60 (5 H, m, 2 × CH_2 and C*H*HCH$_3$), 1.44 (1 H, m, one of CH*H*CH$_3$) and 0.88 (3 H, t, *J* 7.3, CH_3); δ_C(62.9 MHz; $CDCl_3$) 132.8 (C), 131.4 (C), 88.4 (CH-O), 76.8 (CH_2O), 27.0 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 22.0 (CH_2), 21.8 (CH_2) and 8.6 (CH_3); *m/z* (EI) 152 (M^+, 9%), 135 (11), 123 (100), 95 (12), 79 (8), 67 (8) and 57 (8).

1-Pentyl-1,3,4,5,6,7-hexahydrobenzo[*c*]furan 10b

A degassed solution of 1-pentyl-1,3,4,7-tetrahydrobenzo[*c*]-furan **8b** (768 mg, 4 mmol) in toluene (20 cm^3) containing tris(triphenylphosphine)rhodium(I) chloride (15 mg) was stirred under an atmosphere of hydrogen for 48 h. After filtration through a pad of silica gel, the filtrate was evaporated under reduced pressure and the residue purified by flash column chromatography (eluent light petroleum) to give the *title compound* (482 mg, 62%) as a colourless oil (Found: M^+, 194.1677. $C_{13}H_{22}O$ requires *M*, 194.1671); ν_{max}(film)/cm^{-1} 2954, 2857, 1122, 1059 and 1036; δ_H(250 MHz; $CDCl_3$) 4.63 (1 H, m, 1-H), 4.47 (2 H, m, 3-H_2), 1.95–1.80 (4 H, m), 1.70–1.50 (5 H, m), 1.37–1.28 (7 H, m) and 0.88 (3 H, t, *J* 6.6, CH_3); δ_C(62.9 MHz; $CDCl_3$) 133.3 (C), 131.1 (C), 87.6 (CH-O), 76.6 (CH_2O), 34.5 (CH_2), 32.1 (CH_2), 24.5 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 21.8 (CH_2) and 14.1 (CH_3); *m/z* (EI) 194 (M^+, 4%), 135 (10), 123 (100), 119 (9) and 95 (8).

1-Ethyl-3-pentyl-1,3,4,5,6,7-hexahydrobenzo[*c*]furan 11

A suspension of 10% palladium-on-carbon (150 mg) in ethyl acetate (20 cm^3) was shaken for 15 min under an atmosphere of hydrogen (45 psi) after which a solution of 1-ethyl-3-pentyl-1,3,4,7-tetrahydrobenzo[*c*]furan **9** (6g, 27.3 mmol) in ethyl acetate (10 cm^3) was added to it. The reaction mixture was then shaken vigorously under the same pressure of hydrogen for 2 h. After the catalyst had been removed by filtration through a pad

of Celite the filtrate was concentrated under reduced pressure to give the *title compound* (5.88 g, 97%) as a colourless oil which was shown by NMR to contain *ca.* 10% of the corresponding 1,3-dihydrobenzo[*c*]furan **7** (Found: M^+, 222.1989. $C_{15}H_{26}O$ requires *M*, 222.1984); ν_{max}(film)/cm^{-1} 2958, 2930, 2858, 1129, 1064 and 1048; δ_H(300 MHz; $CDCl_3$) 4.65–4.45 (2 H, m, 1-H and 3-H), 1.95–1.20 (18 H, m, 9 × CH_2) and 0.95–0.80 (6 H, m, 2 × CH_3); δ_C(75.48 MHz; $CDCl_3$) 134.3 (C), 134.0 (C), 133.4 (C), 133.1 (C), 87.3 (CH-O), 86.9 (CH-O), 86.3 (CH-O), 35.2 (CH_2), 34.8 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 27.6 (CH_2), 27.1 (CH_2), 25.0 (CH_2), 24.4 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 21.9 (CH_2), 14.1 (CH_3), 9.2 (CH_3) and 8.4 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 222 (M^+, 3.5%), 193 (60), 151 (100), 135 (7), 123 (7), 91 (8) and 81 (9).

Oxidative ring expansion: general procedure

The substrate (0.66 mmol) was dissolved in tetrachloromethane (2 cm^3) and acetonitrile (2 cm^3) and water (3 cm^3), sodium metaperiodate (0.58 g, 2.7 mmol) and ruthenium(III) chloride hydrate (4 mg) were added to the solution. The resulting biphasic mixture was stirred rapidly for 24 h after which it was diluted with dichloromethane (20 cm^3) and washed with water (3 × 20 cm^3). The organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product which was purified as described below.

2-Ethyloxonane-3,8-dione 12a. Oxidation of **10a** (100 mg, 0.66 mmol) according to the general procedure described above was followed by flash column chromatography (eluent light petroleum–diethyl ether, 3:1) to give the *title compound* (59 mg, 49%) as a colourless oil (Found: M^+, 184.1098. $C_{10}H_{16}O_3$ requires *M*, 184.1099); ν_{max}(film)/cm^{-1} 2970, 2938, 1719 and 1113; δ_H(250 MHz; $CDCl_3$) 4.42 and 3.90 (2 H, AB, *J* 17.1, 9-H_2), 3.64 (1 H, t, *J* 6.6, 2-H), 3.20–3.06 (2 H, m, CH_2), 2.29–2.14 (2 H, m, CH_2), 1.89–1.66 (6 H, m; 3 × CH_2) and 0.96 (3 H, t, *J* 7.4, CH_3); δ_C(62.9 MHz; $CDCl_3$) 214.9 (C=O), 212.9 (C=O), 90.8 (CH-O), 78.6 (CH_2O), 36.6 (CH_2), 35.6 (CH_2), 26.0 (CH_2), 24.5 (CH_2), 23.1 (CH_2) and 9.6 (CH_3); *m/z* (EI) 184 (M^+, 0.8%), 155 (M − C_2H_5, 10), 127 (22), 110 (16), 97 (17), 81 (100), 55 (20) and 41 (14).

2-Pentyloxonane-3,8-dione 12b. Oxidation of **10b** (300 mg, 1.55 mmol) according to the general procedure described above, followed by flash column chromatography (eluent light petroleum–diethyl ether, 3:1) gave the *title compound* (124 mg, 35%) as a colourless oil (Found M^+, 226.1571. $C_{13}H_{22}O_3$ requires *M*, 226.1569); ν_{max}(film)/cm^{-1} 2954, 2871, 1713, 1461 and 1114; δ_H(250 MHz; $CDCl_3$) 4.41 and 3.90 (2 H, AB, *J* 17.1, CH_2O), 3.71 (1 H, dd, *J* 7.3 and 5.9, CH-O), 3.21–3.08 (2 H, m, CH_2CO), 2.40–2.15 (2 H, m, CH_2CO), 1.89–1.62 (6 H, m, 3 × CH_2), 1.40–1.27 (6 H, m, $[CH_2]_3CH_3$) and 0.89–0.85 (3 H, m, CH_3); δ_C(62.9 MHz; $CDCl_3$) 214.9 (C=O), 212.8 (C=O), 89.5 (CH-O), 78.3 (CH_2O), 36.5 (CH_2), 35.3 (CH_2), 32.6 (CH_2), 31.4 (CH_2), 24.7 (CH_2), 24.4 (CH_2), 22.9 (CH_2), 22.3 (CH_2) and 13.8 (CH_3); *m/z* (EI) 226 (M^+, 0.2%), 155 (M − C_5H_{11}, 10), 127 (14), 81 (100), 55 (19) and 41 (18).

2-Ethyl-9-pentyloxonane-3,8-dione 13. 1-Ethyl-3-pentyl-1,3,4,5,6,7-hexahydrobenzo[*c*]furan **11** (880 mg, 3.96 mmol) was oxidised as described above. Purification by flash column chromatography (eluent light petroleum–diethyl ether, 9:1) gave the impure *title compound* (493 mg, 49%) as a pale yellow oil (mixture of diastereoisomers) (Found M^+, 254.1876. $C_{15}H_{26}O_3$ requires *M*, 254.1882); ν_{max}(film)/cm^{-1} 2934, 2873, 1715, 1095 and 738; δ_H(250 MHz; $CDCl_3$) 4.02–3.63 (2 H, m, 2-H and 9-H), 3.06–2.10 (4 H, m, 2 × CH_2), 1.90–1.26 (14 H, m, 7 × CH_2) and 0.99–0.85 (6 H, m, 2 × CH_3); δ_C(62.9 MHz; $CDCl_3$) complex due to the presence of impurities, but including 88.4 (CH-O of major isomer), 87.4 (CH-O of major isomer), 80.9 (CH-O of minor isomer) and 79.7 (CH-O of minor isomer); ^1H–^{13}C correlation spectrum satisfactory; *m/z* (EI) 254 (M^+, 1%), 197 (8), 155 (18), 133 (21), 114 (26), 109 (100), 97 (26), 84 (23), 73 (22), 60 (37), 55 (41) and 41 (20).

Pentadecane-3,4,9,10-tetraone 14. Oxidation of **11** as described above yielded **14** (91 mg, 9%) as a yellow solid, mp 74–75 °C (from light petroleum) (Found: MH^+, 269.1743. $C_{15}H_{24}O_4$ + H^+ requires *M*, 269.1753); ν_{max}(CH_2Cl_2)/cm^{-1} 2974, 2939, 1710, 1454, 1395 and 727; δ_H(300 MHz; $CDCl_3$) 2.81–2.65 (8 H, m, 4 × CH_2), 1.65–1.53 (6 H, m, 3 × CH_3), 1.35–1.25 (4 H, m, 2 × CH_2), 1.07 (3 H, t, *J* 7.4, CH_2CH_3) and 0.88 (3 H, t, *J* 7.3, CH_2CH_3); δ_C(75.48 MHz; $CDCl_3$) 200.2 (C=O), 199.9 (C=O), 199.4 (C=O), 199.3 (C=O), 36.1 (CH_2), 35.8 (CH_2), 35.7 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 22.8 (CH_2), 22.4 (3 coincident CH_2), 13.9 (CH_3) and 7.0 (CH_3); *m/z* (methane CI) 269 (MH^+, 16%), 251 (100), 221 (16), 169 (36), 167 (58) and 125 (64).

2-Ethyl-9-pentyloxonane-3,8-diol 15

To a suspension of lithium aluminium hydride (615 mg, 15 mmol) in dry THF (7 cm^3) was added a solution of 2-ethyl-9-pentyloxonane-3,8-dione **13** (762 mg, 3 mmol) in dry THF (25 cm^3). The resulting solution was heated under reflux for 1 h and then allowed to cool to room temperature. After being quenched with hydrochloric acid (2 mol dm^{-3}; 50 cm^3), the mixture was extracted with diethyl ether (3 × 50 cm^3) and the combined organic phases were dried ($MgSO_4$) and evaporated to dryness. Purification by flash column chromatography (eluent light petroleum–diethyl ether, 1:1) afforded the *title compound* (523 mg, 68%) as a viscous clear oil (Found: M^+, 258.2186. $C_{15}H_{30}O_3$ requires *M*, 258.2195); ν_{max}(film)/cm^{-1} 3371br (OH), 2930, 2859, 1456 and 1045; δ_H (300 MHz; $CDCl_3$) 3.9–3.7 (2 H, m, 3-H and 8-H), 3.6–3.1 (2 H, m, 2-H and 9-H), 2.1–1.95 (2 H, br s, 2 × OH), 1.95–1.1 (18 H, m, 9 × CH_2) and 1.0–0.8 (6 H, m, 2 × CH_3); *m/z* (EI) 258 (M^+, 0.7%), 143 (42), 119 (42), 99 (42), 84 (69), 70 (73), 57 (76), 55 (68), 43 (71), 43 (100) and 29 (67).

Obtusan (mixture of diastereoisomers) 17

Sodium hydride (60% dispersion in mineral oil; 150 mg, 3.7 mmol) was washed with hexane, dried and suspended in DMF (5 cm^3). A solution of 2-ethyl-9-pentyloxonane-3,8-diol **15** (191 mg, 0.74 mmol) in DMF (2 cm^3) was added dropwise to it, followed, after 5 min, by carbon disulfide (2 cm^3, excess, freshly filtered through basic alumina). After the mixture had been stirred for 30 min, iodomethane (2 cm^3, excess) was added dropwise to it and stirring was continued for 90 min. The mixture was then diluted with water (20 cm^3) and extracted into diethyl ether (3 × 20 cm^3). The combined organic phases were washed with water (6 × 20 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oil which was purified by flash column chromatography (eluent light petroleum–diethyl ether, 9:1) to give the bis-xanthate **16** (293 mg, 90%) as a mobile yellow oil, which was used directly.

Thus, a solution of the above xanthate (267 mg, 0.61 mmol) in benzene (**CAUTION**) with AIBN (20 mg) was heated to reflux and tributyltin hydride (1.4 cm^3, 5.2 mmol) was added to it. The remelting mixture was heated under reflux for 45 min after which it was allowed to cool to room temperature and then concentrated under reduced pressure to give a clear oil. This was purified by flash column chromatography (eluent light petroleum–diethyl ether, 99:1) followed by short-path distillation (Kugelrohr apparatus) to afford the *title compound* (102 mg, 74%) as a clear liquid, bp 150 °C at 4 mmHg (Found: M^+, 226.2299. $C_{15}H_{30}O$ requires *M*, 226.2297); ν_{max}(film)/cm^{-1} 2957, 2927, 2859, 1465, 1158, 1141 and 1089; δ_H(250 MHz; $CDCl_3$) 3.65–3.25 (2 H, m, 2-H and 9-H), 1.8–1.2 (22 H, m, 11 × CH_2) and 1.0–0.8 (6 H, m, 2 × CH_3); δ_C(62.9 MHz; $CDCl_3$) 81.1 (CH-O, *cis*), 79.7 (CH-O, *cis*), 76.3 (CH-O, *trans*), 75.4 (CH-O, *trans*), 36.4 (CH_2), 32.4 (CH_2), 32.2 (CH_2), 32.1

(CH_2), 32.0 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.3, (CH_2) 25.2 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 10.8 (CH_3) and 10.7 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 226 (M^+, 4%), 155 (10), 137 (12), 95 (36), 83 (59), 69 (64), 55 (948) and 41 (100).

Elaboration of single isomers of the 1,3-dihydrobenzo[*c*]furan 7

Separated isomers of **7** were elaborated in a manner identical with that for the isomer mixture. Spectroscopic and related data for products are given below.

***cis*-1-Ethyl-3-pentyl-1,3,4,7-tetrahydrobenzo[*c*]furan *cis*-9**

Isolated as a colourless oil (3.60 g, 89%), bp 170 °C at 2 mmHg (Found: M^+, 220.1828. $C_{15}H_{24}O$ requires *M*, 220.1827); ν_{max}(film)/cm^{-1} 3029, 2958, 2929, 2857, 2823, 1465, 958 and 666; δ_H(300 MHz; $CDCl_3$) 5.8 (2 H, br s, 5-H and 6-H), 4.6 (2 H, br s, 1-H and 3-H), 2.6 (4 H, br s, 2 × CH_2), 1.75–1.53 (2 H, m, CH_2), 1.5–1.2 (8 H, m, 4 × CH_2), 0.91 (3 H, t, *J* 7.5, CH_3) and 0.87 (3 H, t, *J* 6.6, CH_3); δ_C(75.48 MHz; $CDCl_3$) 131.8 (C), 131.0 (C), 124.1 (2 × CH, alkene), 87.2 (CH-O), 86.3 (CH-O), 35.0 (CH_2), 32.1 (CH_2), 27.5 (CH_2), 25.0 (CH_2), 23.9 (2 × CH_2), 22.7 (CH_2), 14.1 (CH_3) and 9.2 (CH_3); *m/z* (EI) 220 (M^+, 0.7%), 191 (46), 149 (100), 91 (39), 79 (27), 57 (32), 43 (40) and 29 (38).

***cis*-1-Ethyl-3-pentyl-1,3,4,5,6,7-hexahydrobenzo[*c*]furan *cis*-11**

Isolated as a colourless oil (3.23 g, 100%) containing *ca.* 10% of the 1,3-dihydrobenzo[*c*]furan *cis*-**7** (NMR analysis) (Found: M^+, 222.1987. $C_{15}H_{26}O$ requires *M*, 222.1984); ν_{max}(film)/cm^{-1} 2931, 2858, 909 and 735; δ_H(300 MHz; $CDCl_3$) 4.60–4.45 (2 H, m, 1-H and 3-H), 1.95–1.20 (18 H, m, 9 × CH_2) and 0.95–0.80 (6 H, m, 2 × CH_3); δ_C(75.48 MHz; $CDCl_3$) 134.3 (C), 133.4 (C), 87.3 (CH-O), 86.4 (CH-O), 35.2 (CH_2), 32.1 (CH_2), 27.6 (CH_2), 25.0 (CH_2), 22.7 (CH_2), 22.6 (2 × CH_2), 21.9 (2 × CH_2), 14.1 (CH_3) and 9.2 (CH_3); *m/z* (EI) 222 (M^+, 4.1%), 193 (50), 151 (100), 147 (20), 81 (20), 57 (23), 41 (29) and 29 (32).

***cis*-2-Ethyl-9-pentyloxonane-3,8-dione *cis*-13**

Isolated (1.174 g, 34%) as a pale oil (Found: M^+, 254.1880. $C_{15}H_{26}O_3$ requires *M*, 254.1882); ν_{max}(film)/cm^{-1} 2957, 2934, 2873, 1713, 1464 and 1095; δ_H(300 MHz; $CDCl_3$) 3.75–3.65 (2 H, m, 2-H and 9-H), 2.4–1.2 (18 H, m, 9 × CH_2) and 1.0–0.8 (6 H, m, 2 × CH_3); δ_C(75.48 MHz; $CDCl_3$) complex due to the presence of impurities, but including 88.7 (CH-O) and 87.7 (CH-O); *m/z* (EI) 254 (M^+, 0.9%), 133 (61), 109 (80), 97 (39), 60 (60), 55 (100), 41 (99) and 29 (73).

2-Ethyl-9-pentyloxonane-3,8-diol *cis*-15

Isolated (517 mg, 64%) as a colourless oil (Found: M^+, 258.2193. $C_{15}H_{30}O_3$ requires *M*, 258.2195); ν_{max}(film)/cm^{-1} 3392 (br, OH), 2930, 2873, 1456, 1048 and 734; δ_H(300 MHz; $CDCl_3$) 3.9–3.8 and 3.5–3.1 (4 H, m, 2-H, 3-H, 8-H and 9-H), 2.6–2.4 (2 H, br, 2 × OH), 2.05–1.15 (18 H, m, 9 × CH_2) and 1.0–0.8 (6 H, m, 2 × CH_3); *m/z* (EI) 258 (M^+, 0.4%), 119 (41), 82 (82), 67 (100), 57 (58), 55 (69), 43 (52), 41 (95), 29 (60) and 27 (49).

***cis*-Obtusan *cis*-17**

Treatment of *cis*-**15** (400 mg, 1.55 mmol) as above led to the bis-xanthate *cis*-**16** (523 mg, 77%) as a mobile yellow oil which was used directly.

Thus, radical deoxygenation of the bis-xanthate *cis*-**16** (400 mg, 0.91 mmol) gave the *title compound* (165 mg, 80%) as a single distereoisomer (Found: M^+, 226.2299. $C_{15}H_{30}O$ requires *M*, 226.2297); ν_{max}(film)/cm^{-1} 2959, 2927, 2860, 1465 and 1089; δ_H(250 MHz; $CDCl_3$) 3.45–3.25 (2 H, m, 2-H and 9-H), 1.85–1.20 (22 H, m, 11 × CH_2), 0.90 (3 H, t, *J* 7.5, CH_3) and 0.88 (3 H, t, *J* 6.9, CH_3); δ_C(62.9 MHz; $CDCl_3$) 81.2 (CH-O), 79.8 (CH-O), 36.5 (CH_2), 32.5 (CH_2), 32.3 (CH_2), 32.2 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 22.9 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3) and 10.8 (CH_3); *m/z* (EI) 226 (M^+, 2.2%), 155 (5), 137 (6), 95 (22), 83 (41), 81 (29), 69 (43), 67 (29), 56 (41), 55 (88), 43 (59) and 41 (100).

***trans*-1-Ethyl-3-pentyl-1,3,4,7-tetrahydrobenzo[*c*]furan *trans*-9**

Birch reduction of *trans*-**7** (2.8 g, 12.8 mmol) by the above general method gave *trans*-**9** (2.58 g, 91%) as a colourless oil, bp 170 °C at 2 mmHg (Found: M^+, 220.1826. $C_{15}H_{24}O$ requires *M*, 220.1827); ν_{max}(film)/cm^{-1} 3029, 2958, 2928, 2856, 2824, 1462, 958 and 668; δ_H(300 MHz; $CDCl_3$) 5.8 (2 H, br s, 5-H and 6-H), 4.7 (2 H, br s, 1-H and 3-H), 2.6 (4 H, br s, 2 × CH_2), 1.8–1.2 (10 H, m, 5 × CH_2) and 0.86 (6 H, two coincident triplets, *J* 7.4, 2 × CH_3); δ_C(75.48 MHz; $CDCl_3$) 131.6 (C), 130.1 (C), 124.1 (2 × alkene CH), 87.1 (CH-O), 86.6 (CH-O), 34.5 (CH_2), 32.2 (CH_2), 27.0 (CH_2), 24.4 (CH_2), 23.8 (2 × CH_2), 22.7 (CH_2), 14.1 (CH_3) and 8.5 (CH_3); *m/z* (EI) 220(M^+, 0.8%), 191 (45), 149 (100), 91 (32), 79 (19), 57 (24), 43 (25) and 29 (24).

***trans*-1-Ethyl-3-pentyl-1,3,4,5,6,7-hexahydrobenzo[*c*]furan *trans*-11**

Hydrogenation of *trans*-**9** over palladium-on-carbon as described above gave *trans*-**11** (2.03 g, 100%) containing *ca.* 10% of the 1,3-dihydrobenzo[*c*]furan *trans*-**7** (NMR analysis) (Found: M^+, 222.1984. $C_{15}H_{26}O$ requires *M*, 222.1984); ν_{max}(film)/cm^{-1} 2929, 2857, 1458, 1053, 946 and 734; δ_H(300 MHz; $CDCl_3$) 4.65–4.55 (2 H, m, 1-H and 3-H), 1.95–1.8 (4 H, m, 2 × CH_2), 1.78–1.5 (6 H, m, 3 × CH_2), 1.5–1.2 (8 H, m, 4 × CH_2) and 0.8–0.95 (6 H, m, 2 × CH_3); δ_C(75.48 MHz; $CDCl_3$) 134.0 (C), 133.1 (C), 87.3 (CH-O), 86.9 (CH-O), 34.8 (CH_2), 32.3 (CH_2), 27.2 (CH_2), 24.4 (CH_2), 22.7 (3 × CH_2), 22.0 (2 × CH_2), 14.1 (CH_3) and 8.4 (CH_3); *m/z* (EI) 222 (M^+, 2.8%), 193 (47), 151 (100), 81 (22), 57 (28), 41 (34) and 29 (37).

***trans*-2-Ethyl-9-pentyloxonane-3,8-dione *trans*-13**

Oxidation of *trans*-**11** according to the above general procedure gave *trans*-**13** (1.214 g, 59%) as a pale oil (Found: M^+, 254.1889. $C_{15}H_{26}O_3$ requires *M*, 254.1882); ν_{max}(film)/cm^{-1} 2936, 2863, 1717, 1463, 1186 and 1094; δ_H(300 MHz; $CDCl_3$) 4.05–3.85 (2 H, m, 2-H and 9-H), 2.8–1.1 (18 H, m, 9 × CH_2) and 0.95–0.8 (6 H, m, 2 × CH_3); δ_C(74.48 MHz; $CDCl_3$) complex due to the presence of impurities, but including 81.3 (CH-O) and 80.1 (CH-O); *m/z* (EI) 254 (M^+, 0.5%), 133 (29), 109 (48), 99 (34), 84 (48), 67 (33), 60 (62), 57 (62), 55 (77), 41 (100), 29 (90) and 27 (70).

2-Ethyl-9-pentyloxonane-3,8-diol *trans*-15

Reduction of *trans*-**13** as described above gave *trans*-**15** (756 mg, 75%) as a slightly impure colourless oil (Found: M^+, 258.2194. $C_{15}H_{30}O_3$ requires *M*, 258.2195); ν_{max}(film)/cm^{-1} 3392 (br, OH), 2931, 2860, 1458, 1122 and 1042; δ_H(250 MHz; $CDCl_3$) 3.90–3.47 (4 H, m, 2-H, 3-H, 8-H and 9-H), 2.22 (2 H, br, 2 × OH), 1.93–1.31 (18 H, m, 9 × CH_2) and 1.00–0.87 (6 H, m, 2 × CH_3); *m/z* (EI) 258 (M^+, 0.6%), 119 (30), 99 (32), 81 (44), 67 (68), 57 (71), 55 (62), 43 (63), 41 (100) and 29 (69).

Deoxygenation of *trans*-15 to give a mixture of *trans*-17 and *cis*-17

Treatment of *trans*-**15** as described above gave the bis-xanthate *trans*-**16** (647 mg, 76%) as a mobile yellow oil which was used directly.

Thus, radical deoxygenation of the bis-xanthate *trans*-**16** (110 mg, 0.25 mmol) as described above gave a 1.5:1 mixture (by ^1H NMR) of *trans*-**17** and *cis*-**17** (31 mg, 55%) as a colourless oil (Found: M^+, 226.2302. $C_{15}H_{30}O$ requires *M*, 226.2297); ν_{max}(film)/cm^{-1} 2957, 2928, 2869, 1465, 1128, 1088, 1033 and 734; δ_H(250 MHz; $CDCl_3$) 3.63–3.46 (2 H of *trans*-**17** m, 2-H

and 9-H), 3.45–3.27 (2 H of *cis*-**17**, m, 2-H and 9-H), 1.85–1.25 (22 H, m, 11 × CH_2) and 1.0–0.85 (6 H, m, 2 × CH_3); δ_C(62.9 MHz; $CDCl_3$) 81.1 (CH-O, *cis*-**17**), 79.7 (CH-O, *cis*-**17**), 76.3 (CH-O, *trans*-**17**), 75.4 (CH-O, *trans*-**17**), 36.3 (CH_2), 32.4 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 10.8 (CH_3) and 10.7 (CH_3) (mixture of diastereoisomers, not fully resolved); *m/z* (EI) 226 (M^+, 3.8%), 155 (11), 137 (17), 95 (37), 83 (59), 69 (60), 55 (95) and 41 (100). Assignments of *cis*/*trans* isomers made on basis of ^{13}C NMR.[17]

Crystal structure of 4b

Crystals of **4b** were grown from ethanol. A crystal of dimensions 1.3 × 0.5 × 0.3 mm was chosen for data collection and mounted about the crystallographic *b* axis. Unit cell dimensions were obtained from oscillation and Weissenberg photographs and partially refined by least-squares refinement of 18 reflections in the *h*0*l* plane using a Stöe Stadi-2 Weissenberg diffractometer.

Crystal data. $C_{15}H_{19}NSO_4$, M_r 309.36. monoclinic: a = 11.263(11), b = 5.63(1), c = 23.915(19) Å. β = 95.38(7). V = 1509.79 Å^3, $F(000)$ = 656. Space group $P2_1/c$, Z = 4, ρc = 1.361 g cm^{-3}. Mo-Kα radiation, λ = 0.710 69 Å, μ = 1.84 cm^{-1}.

Data collection. Intensity data were collected on a Stöe Stadi-2 Weissenberg diffractometer using an ω scan, allowing the measurement of 2677 unique reflections of which 2110 had $F/\sigma(F) > 6$. max sin θ/λ = 0.6, h − 13 ⟶ 13, k 0 ⟶ 5, l − 28 ⟶ 28. Data were corrected for Lorentz and polarization effects but not absorption (t_{max} = 0.97, t_{min} = 0.85). R_{int} = 0.028.

Structure solution and refinement. The structure was solved by direct methods (SHELX76) and refined by full-matrix least-squares refinement. Non-hydrogen atoms were allowed anisotropic temperature factors. Hydrogen atoms were found from difference map and refined isotropically. The refinement converged with R = 0.064, R_W = 0.064 (unit weights). Maximum shift/error = 0.01; electron density residuals in the final difference map −0.4 ⟶ + 0.3 e Å^{-3}.‡

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‡ Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. For full details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1995, Issue 1.

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