Synthesis of Medium Ring Ethers. Part 2.† Synthesis of the Fully Saturated Carbon Skeleton of *Laurencia* Non-terpenoid Ether Metabolites Containing Seven-, Eight- and Nine-membered Rings

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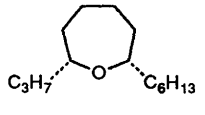
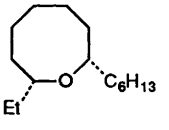
A general method for the construction of medium ring ethers is described in which a 2-substituted cycloalkanone was subjected to a Baeyer–Villiger ring expansion to the lactone, Tebbe methylenation of which afforded the enol ether which was subjected to a hydroboration–oxidation sequence to afford the 2,*n*-disubstituted oxacycle (*n* = ring size). Application of this procedure has led to efficient syntheses of the fully saturated skeletons corresponding to the naturally occurring *Laurencia* metabolites containing 2,*n*-dialkyl substituted seven- (isolaurepan), eight- (lauthisan and laurenan) and nine-membered (obtusan) ethers.

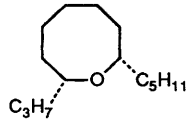
Medium ring ethers occur in a wide range of marine species, particularly in the alga *Laurencia* and as constituents of various toxins such as brevetoxin.[1,2] A number of years ago we embarked on a programme designed to provide a general strategy for the synthesis of the saturated medium ring ether skeleton present in many *Laurencia* non-terpenoid metabolites.[3] At about the same time there was an enormous increase in interest from the synthetic community resulting in some notable advances in methodology in the field. Recent achievements have been elegantly compiled in a review article,[4] but contributions from the groups of Masamune,[5] Kocienski,[6] Overman,[7] Nicolaou,[8] Schreiber,[9] Moody,[10] Kotsuki[11] and Paquette[12] deserve special mention.



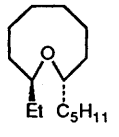
Isolaurepan 1



Lauthisan 2



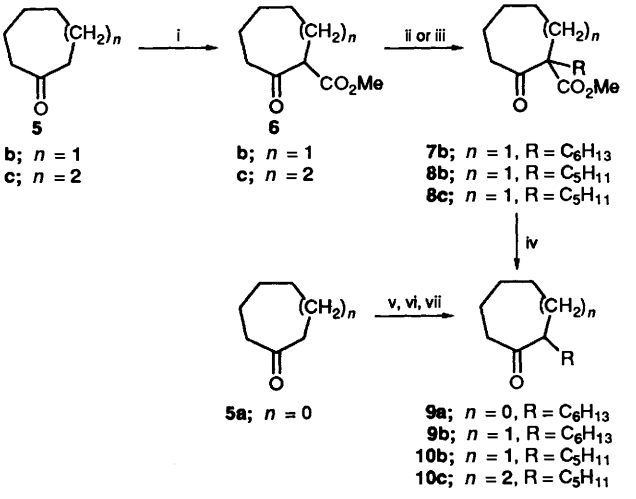
Laurenan 3



Obtusan 4

As initial targets we chose the four saturated ethers isolaurepan **1**, lauthisan **2**,[13] laurenan **3** and obtusan **4**, whose structures represent the basic skeletons present in naturally occurring non-terpenoid seven- (isolaurepinnacin), eight- (laurencin and laurenyne) and nine-membered ether (obtusenyne) metabolites of the red alga *Laurencia*. Our strategy was to prepare the racemic lactones **11–12** by Baeyer–Villiger ring expansion of the corresponding cyclic ketones **9–10** which in turn were expected to be available by alkylation of the unsubstituted precursors **5**. The lactones were to be elaborated to the required ethers by a one-carbon homologation (methylenation), and then functionalised by hydroboration/oxidation.

The synthesis of the required 2-substituted cycloalkanones **9–10** is summarised in Scheme 1. Methoxycarbonylation of the unsubstituted precursor ketones **5b, c** gave the β-ketoesters **6b, c** which were alkylated in the standard way to give the products **7, 8**. These were then hydrolysed and decarboxylated by the Krapcho procedure[14] to the alkylated ketones **9–10**. The alkylation of the cyclohexanone **5a** was carried out directly *via* the Corey–Enders[15] dimethylhydrazone procedure.



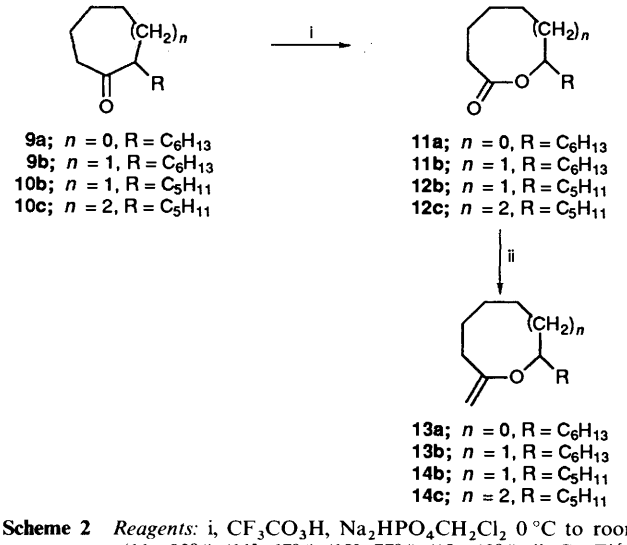
Scheme 1 *Reagents:* i, $(MeO)_2CO$, NaH, ether (**6b** 62%) (**6c** 56%); ii, NaH, $C_6H_{13}Br$, dimethylformamide (DMF) (**7b** 85%); iii, NaH, $C_5H_{11}Br$, DMF (**8b** 93%) (**8c** 61%); iv, LiCl, dimethyl sulfoxide (DMSO), water, 180 °C (**9b** 81%) (**10b** 64%) (**10c** 78%); v, Me_2NNH_2, 80 °C; vi, BuLi, THF, −78 °C then $C_6H_{13}Br$, −78 °C; vii, $CuCl_2$, THF, water (41% overall from **5a** to **9a**)

Ring expansion of the ketones **9–10** was achieved by Baeyer–Villiger oxidation with trifluoroperacetic acid (Scheme 2).[16] For optimum yields it was essential to use 85% hydrogen peroxide of good quality and to use a large excess of oxidant, while paying careful attention to the amount of phosphate buffer present. The more concentrated conditions reported by Still and Galynker were occasionally found to be advantageous.[17]

In order to convert the lactones into 2,*n*-disubstituted oxacycles we chose to employ the recently (at the outset of this work) reported methylenation of lactones using the Tebbe[18] reagent as described by Grubbs and Evans.[19] Subsequently this has emerged as an important 'neutral' methylenating agent[20] which has been applied widely in synthesis.[12,21] The very recent report by Petasis[22] of the thermal generation of the active species $[Cp_2Ti{=}CH_2]$ from dimethyltitanocene is an attractive alternative to the original procedure. Methylenation of the lactones **11–12** under Schlenk conditions followed by rapid chromatographic purification on neutral alumina gave the highly unstable enol ether intermediates **13–14** (δ_H 4.0, 4.2

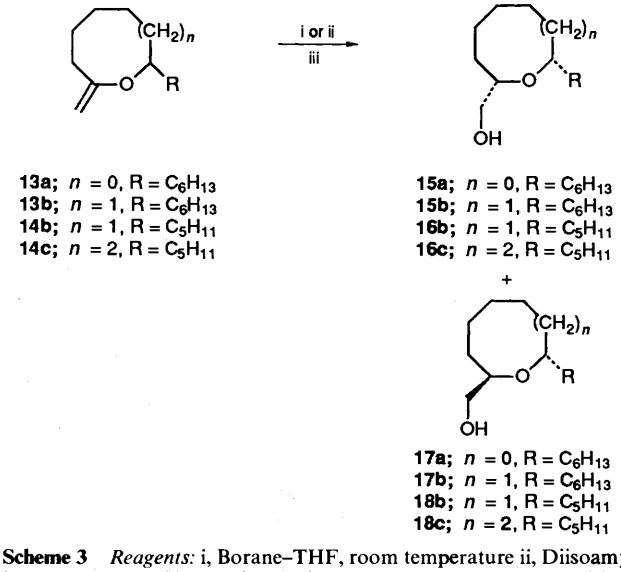
† Part 1. N. R. Curtis, A. B. Holmes and M. G. Looney, *Tetrahedron*, 1991, **47**, 7171.

terminal alkene). These compounds could not be fully characterised owing to their sensitivity to hydrolytic cleavage and so were immediately functionalised as shown in Scheme 3.

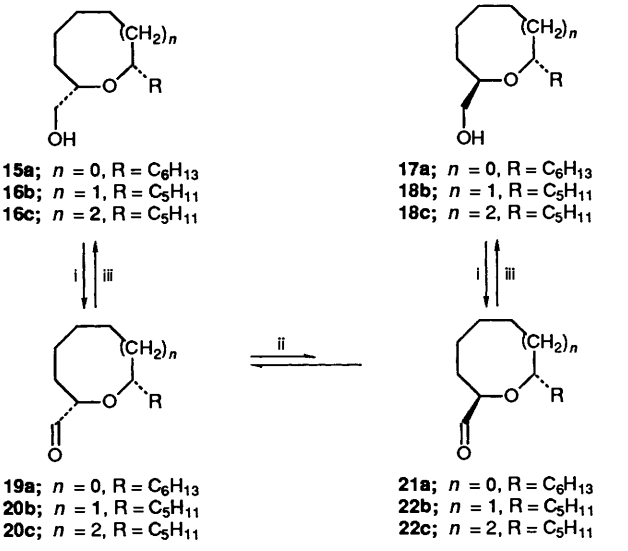


Scheme 2 *Reagents:* i, CF_3CO_3H, $Na_2HPO_4CH_2Cl_2$ 0 °C to room temperature (**11a** 82%) (**11b** 67%) (**12b** 77%) (**12c** 42%); ii, $Cp_2Ti\{\mu\text{-}(CH)_2\text{-}\mu\text{-}Cl\}AlMe_2$ (Tebbe reagent), tetrahydrofuran (THF), toluene, pyridine (cat.), −40 °C to room temperature

The hydroboration–oxidation sequence seemed ideally suited to functionalisation of the terminal carbon of the enol ethers **13**–**14**. (Scheme 3). Hydroboration with borane–THF reagent, followed by oxidative work-up with alkaline hydrogen peroxide at 0 °C afforded mixtures of *cis*- (**15**, **16**) and *trans*- (**17**, **18**) 2,*n*-disubstituted oxacycles. The hydroboration of enol ethers is known to be extremely susceptible to the presence of Lewis acids which can catalyse competitive hydride transfer or *trans* elimination of the intermediate organoborane.[23] The reaction temperature can also be of critical importance to these side reactions.[24] Optimum yields in the Tebbe methylenation–hydroboration sequence depended on good purification of the enol ether from the Lewis acid residues. Although pyridine was initially used as the ligand to decompose the Tebbe reagent and generate the active species in this work, it was later found that



Scheme 3 *Reagents:* i, Borane–THF, room temperature ii, Diisoamylborane, THF, 0 °C iii, H_2O_2, NaOH, 0 °C [**15a**:**17a** = 5:1 (50% from **11a**)] [**15b**:**17b** = 8:1 (43% from **11b**)] [**16b**:**18b** = 14:1 (52% from **12b** using i)] [**16b**:**18b** = 120:1 (59% from **12b** using ii)] [**16c**:**18c** = 1:9 (44% from **12c**)]



Scheme 4 *Reagents:* i, Pyridinium chlorochromate (PCC), molecular sieves (3 Å), ii, K_2CO_3, MeOH (**19a**:**21a** = 4:1; **20b**:**22b** = 6:1; **20c**:**22c** = 6:1), iii. NaBH4

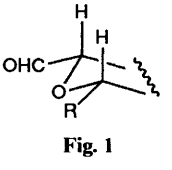


Fig. 1

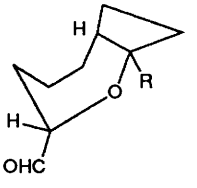


Fig. 2

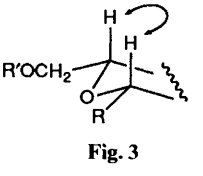


Fig. 3

dimethylaminopyridine was particularly effective at complexing and removing unwanted titanium salts.[20]

The assignment of the relative stereochemistry of the hydroboration products was made difficult by the lack of crystallinity of any derivatives (carboxylic acid, 3,5-dinitrobenzoate, benzeneamine carbamate) including *N*,*N*-diphenyldiazaphospholanes which had been reported to be uniformly crystalline compounds.[25] Two key experiments were therefore carried out on each pair of *cis*–*trans* alcohols. Oxidation of the less polar alcohol [by thin layer chromatography (TLC)] to the corresponding aldehyde, followed by base-catalysed equilibration and re-isolation of the product alcohols obtained by sodium borohydride reduction, gave a mixture of alcohols in which the less polar alcohol always predominated (Scheme 4). This isomer is assigned the *cis* configuration on the reasonable assumption that the preferred local conformation will always be pseudo-equatorial (Fig. 1). In particular Macromodel (v 2.5)[17] minimisation (using an MM2 force field) of the conformation of the aldehyde **20b** (Fig. 2) predicts it to be more stable by an energy consistent with the observed equilibrium constant for equilibration with **22b**.

Secondly, NOE experiments in the ^1H NMR of the following compounds confirmed the *cis* nature of the protons flanking oxygen (Fig. 3): **15a**-3,5-dinitrobenzoate; **16b**-toluene-*p*-sulfonate; **16c**-3,5-dinitrobenzoate. No such NOE could be detected between the corresponding methine protons flanking oxygen in the ester derivatives of **17a**, **18b** and **18c**, supporting the assignment of *trans* stereochemistry to these compounds.

Lastly, the successful total synthesis from **15b** of (±)-lauthisan **2**, identical in all respects (except rotation) with an authentic sample (see below), supports the *cis* stereochemistry for **15b**. In addition to the observation that the *cis*-hydroxymethyl isomers are less polar than the *trans*-compounds on TLC, some general trends in the NMR chemical shifts are evident in Table 1. Thus in the ^1H NMR spectra the chemical shifts of the methine protons flanking oxygen in the *cis*-isomers

Table 1 Comparison of the ^1H and ^{13}C NMR shifts of positions flanking oxygen in the ethers **15–18**

Compound	Ring Size (n)	δ_H C_2,C_n	δ_C C_2,C_n
15a (*cis*)	7	3.46, 3.60	82.0, 82.1
15b (*cis*)	8	3.47, 3.60	80.1, 80.7
16b (*cis*	8	3.47, 3.56	80.1, 80.7
16c (*cis*)	9	3.48, 3.48	82.4, 82.6
17a (*trans*)	7	3.67, 3.67	76.0, 76.9
17b (*trans*)	8	3.66, 3.72	73.2, 75.8
18b (*trans*)	8	3.66, 3.72	73.3, 75.75
18c (*trans*)	9	3.68, 3.68	75.4, 78.85

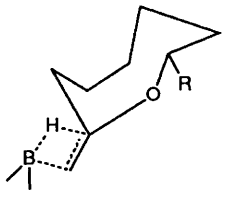


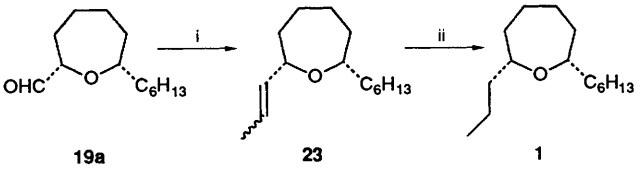
Fig. 4

all lie in the range (δ 3.47–3.60 whereas the corresponding protons in the *trans*-isomers are all significantly downfield (δ 3.66–3.72). In the ^{13}C NMR spectra the trend is reversed, with the carbon resonances flanking oxygen in the *trans*-isomers now occurring upfield (δ 73.2–78.85) of those in the *cis*-series (δ 80.1–82.6). These general trends should prove useful diagnostic tools in the field of medium ring saturated oxacycles.

There is a general trend in favour of the *cis*-2,*n*-disubstituted oxacycle in the hydroboration of exocyclic enol ethers in the seven- and eight-membered series. This is entirely consistent with the expectation that the borane reagent approaches the enol ether from the less hindered trajectory. Macromodel[17] minimisation of the conformation of the methyl-analogue of the eight-membered enol ethers **13/14b** predicts a minimum energy conformation as depicted in Fig. 4. It can be seen that one face of the double bond is completely shielded from attacking electrophiles by the ring carbon atoms, and assuming that the reaction with borane is under steric approach control, it is to be expected that the *cis*-2,8-disubstituted oxocane should be obtained as the major product by addition to the less hindered face of the enol ether. Experimentally, the observed ratio is 14:1. The use of a more hindered borane would be expected increase this ratio, and this is indeed born out by experiment with diisoamylborane, in which the *cis*:*trans* ratio increases to 120:1. Thus, it would appear quite general that reduction[8,9] at an sp^2 centre alpha to oxygen in a 2-substituted oxocane, or C–C bond formation to create an oxocane in a ring closure involving nucleophilic attack on an (*E*)-oxacarbenium ion,[7] favours formation of the *cis*-2,8-disubstitution product, unless very special metal ion chelation effects are invoked.[11]

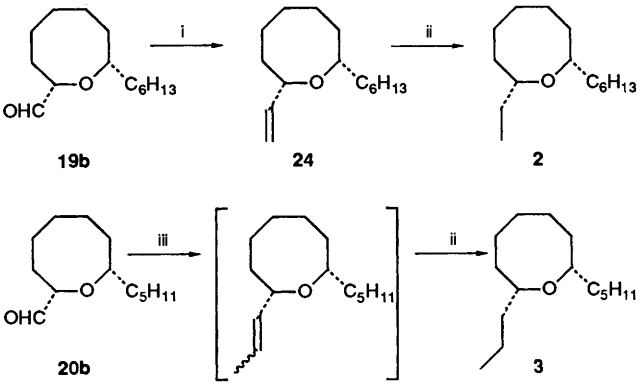
Surprisingly, hydroboration of the nine-membered enol ether **14c** gave predominantly the *trans*-disubstitution product **18c**; this unusual result demanded the unambiguous synthesis of the enantiomerically pure *trans*-2*R*,9*R*-dimethyloxonane from the corresponding 2*R*,9-methyleneoxonane in order to confirm the preference for *trans*-hydroboration in the nine-membered series.[3d] Molecular modelling of the enol ether precursor in this series provided no clear insight into the preference for *trans*-products. Indeed, the prediction was that **16c** and **18c** should be produced in roughly equal amounts. A possible explanation is that the disastereoisomer arising from *syn* attack of organoborane on the enol ether **14c** undergoes Lewis acid-catalysed elimination[23,24,26] faster than the corresponding diastereoisomer which would lead to the *trans*-product. There was some evidence for the competing elimination pathway in the by-products observed during the study on the asymmetric synthesis of 2*R*,9*R*-dimethyloxonane.[3d]

Conversion of the *cis*-aldehyde **19a** into isolaurepan **1**, the fully saturated skeleton corresponding to isolaurepinnacin,[27] was achieved by Wittig homologation and catalytic reduction of the resulting alkene **23** (Scheme 5). Since the completion of this work compound **1** has been prepared by two other groups,[10c,11] and a related compound has also been prepared by Overman.[7c]



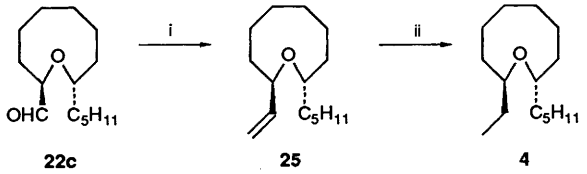
Scheme 5 *Reagents:* i, Ph_3P=CHMe, THF (55%), ii, H_2, 5% Pd–C, EtOAc (99%)

The synthesis of lauthisan **2** followed from the Wittig homologation of **19b** and subsequent catalytic reduction of the alkene **23** (Scheme 6). Racemic **2** was compared with an authentic sample derived by exhaustive reduction of (+)-laurencin[28] produced in the laboratory of Dr. A. Fukuzawa (Hokkaido) and was identical in all respects except optical rotation. Subsequently lauthisan has been synthesised by three other research groups.[8,12,29] In a similar manner the aldehyde **20b** was converted into laurenan **3**, containing the carbon skeleton of laurenyne[30] (Scheme 6).



Scheme 6 *Reagents:* i, Ph_3P=CH_2, THF (90%); ii, H_2, 5% Pd–C, EtOAc (**2** 85%) (**3** 72% from **20b**); iii, Ph_3P=CHMe, THF

Finally the nine-membered aldehyde **22c** was homologated by similar methodology to that described above into the fully reduced carbon skeleton obtusan **4**, corresponding to obtusenyne[31] (Scheme 7).



Scheme 7 *Reagents:* i, Ph_3P=CH_2, THF (40%), ii, H_2, 5% Pd–C, EtOAc (93%)

In summary a completely general method for the stereoselective synthesis of *cis*-disubstituted oxepanes and oxocanes and *trans*-disubstituted oxonanes has been presented, and appropriate epimerisation strategies provide access to the alternative diastereoisomers; this methodology has been applied to the preparation of fully reduced carbon skeletons corresponding to representative medium ring ether natural products derived from *Laurencia*. The regular appearance of contributions to the

literature in this field attests to the growing importance of the subject.[32]

Experimental

IR spectra were recorded on a Perkin Elmer 297 spectrometer, with the sample prepared as a neat film or in chloroform solution. The assignable absorptions are reported and the spectra were calibrated relative to polystyrene. ^{1}H NMR spectra were recorded on the following instruments: Varian EM 360A (60 MHz), EM 390 (90 MHz), CFT-20 (80 MHz), and Bruker WM 250 (250 MHz) and WH 400 (400 MHz). Chemical shifts are measured relative to tetramethylsilane (δ TMS = 0), using either tetramethylsilane or the solvent as internal reference. ^{13}C NMR spectra were recorded on Bruker WM 250 (63 MHz) and WH 400 (100 MHz) instruments, with proton decoupling. Chemical shifts are measured relative to δTMS = O, using the solvent as internal reference. All J values are given in Hz. Mass spectra were recorded on either an AEI MS 902 or MS 30 instrument, the latter being equipped with a DS 50 data system. High resolution spectra were recorded on the MS 30 instrument. Preparative thin layer chromatography was carried out on plates coated with Merck Kieselgel 60 F254 silica to a depth of 1 mm. Flash chromatography was performed using Merck Kieselgel 60, 230–400 mesh. Neutral grade II alumina was prepared by addition of water (6% w/w) to Fluka type 507C alumina. Gas chromatography was carried out using a Carlo Erba 4130 instrument, column (S.G.E. **B**P5, 5% phenylmethylsiloxane as stationary phase) length 25 m, diameter 0.33 mm, carrier gas flow rate 2.0 cm^3 min^{-1}. Elemental analyses were carried out by Mr. D. Flory and the staff of the University Chemical Laboratory microanalysis department. Brine refers to a saturated solution of sodium chloride in water. Dry THF was distilled from potassium in a recycling still and where appropriate, other reagents and solvents were purified by standard techniques.[33] All methylenations using the Tebbe reagent were carried out in Schlenk equipment using degassed (freeze–thaw technique) solutions under an atmosphere of dry oxygen-free nitrogen.

Cyclohexanone-N,N-*dimethylhydrazone*.—Cyclohexanone (20 g, 0.204 mol) and *N,N*-dimethylhydrazine (13.5 g, 0.22 mmol) were heated together at 80 °C for 14 h, then the mixture was cooled to room temperature, and solid sodium hydroxide (5 g) was added. The reaction mixture was stirred for 30 min, then the bottom layer was pipetted off. The remaining solution was distilled to give the pure *hydrazone* (27.8 g, 97%) as a colourless oil, b.p. 63–66 °C/18 mmHg; ν_{max}(neat)/cm^{-1} 2920 (CH), 2840 (N-CH$_3$) and 1640 (C=N); δ_H(CDCl$_3$; 250 MHz) 2.43 (2 H, m, CH$_2$), 2.35 (6 H, s, NMe$_2$), 2.16 (2 H, m, CH$_2$) and 1.64–1.54 (6 H, m, 3 × CH$_2$); *m/z* 140 (M$^+$, 100%), 125 (23, M − Me), 110 (2, M − 2 × Me) and 96 (38, M − NMe$_2$). (Found: M$^+$, 140.1315. $C_8H_{16}N_2$ requires *M*, 140.1313).

2-*Hexylcyclohexanone* **9a**.—Cyclohexanone-*N,N*-dimethylhydrazone (14 g, 0.1 mol) was dissolved in dry THF (300 cm^3), cooled to −78 °C, and butyllithium (62.5 cm^3 of a 1.6 mol dm^{-3} solution in hexane, 1 molar equivalent) was added slowly.[15] After the reaction was maintained at −78 °C for 30 min, hexyl bromide (14.04 cm^3, 0.1 mol) was added, and the reaction was stirred at −78 °C for 1 h, then it was allowed to warm to room temperature. The solution was stirred for 14 h, then partitioned between ether (3 × 250 cm^3) and water (100 cm^3). The organic layers were combined and dried (MgSO4) and concentrated under reduced pressure. The residue was dissolved in THF (1 dm^3) and added over 1 h to a solution of cuprous chloride (14.7 g, 0.11 mol), disodium hydrogen phosphate (10.65 g) and potassium dihydrogen phosphate (1.02 g) in water (700 cm^3). After being stirred for 4 h, the organic layer was separated, and the aqueous layer was extracted with ether (2 × 500 cm^3). The organic layers were combined, dried (MgSO$_4$) and evaporated under reduced pressure to leave a residue which was purified by distillation to give the *ketone* **9a** (7.6 g, 42%) as a colourless oil, b.p. 68–74 °C/0.3 mmHg (Found: C, 79.0; H, 12.3. $C_{12}H_{22}O$ requires C, 79.06; H, 12.17%); ν_{max}(neat)/cm^{-1} 2970 (CH), 2950 (CH), 2830 (CH), 1700 (ketone C=O) and 1110 (C–O); δ_H(CDCl$_3$; 250 MHz) 2.38–1.96 (3H, m, CHCOCH$_2$), 1.85–1.14 (16 H, m, 8 × CH$_2$) and 0.84 (3 H, t, J 6.5, CH$_3$); δ_C(CDCl$_3$; 63 MHz) 213.19 (ketone C=O), 50.75 and 41.85 (CHCOCH$_2$), 33.79, 31.71, 29.42, 27.96, 27.13, 24.75, 22.61, 22.56, (8 × CH$_2$) and 13.97 (CH$_3$); *m/z* 182 (M$^+$, 2.53%), 98 (100, M − C_6H_{12}) and 97 (10, M − C_6H_{13}) (Found: M$^+$, 182.1669. $C_{12}H_{22}O$ requires *M*, 182.1671).

7-(R,S)-*Hexyloxepan*-2-*one* **11a**.—The ketone **9a** (4 g, 0.022 mol) was dissolved in dichloromethane (80 cm^3) and disodium hydrogen phosphate (28 g) was added. Peroxytrifluoracetic acid [prepared from 22.4 cm^3 of trifluoroacetic anhydride and 5.44 cm^3 of 85% hydrogen peroxide in ice cold dichloromethane (50 cm^3)] was added dropwise at 0 °C and stirred at this temperature for 3 h. The solution was then filtered through a Celite plug and the filtrate was washed with 5% aqueous sodium thiosulfate (2 × 50 cm^3), saturated sodium hydrogen carbonate solution (2 × 100 cm^3), brine (100 cm^3), dried (MgSO$_4$) and evaporated under reduced pressure to leave residue which was purified by flash column chromatography on silica gel, firstly with 50% dichloromethane in hexane then neat dichloromethane as eluent, to give the *lactone* **11a** (3.58 g, 82%) as a colourless oil (Found: C, 72.6; H, 11.2. $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.19%); ν_{max}(neat)/cm^{-1} 2930 (CH), 2860 (CH) and 1750 (lactone C=O); δ_H(CDCl$_3$; 250 MHz) 4.21 (1 H, m, CHOC=O), 2.61 (2 H, m, CH$_2$C=O), 1.94–1.25 (16 H, m, 8 × CH$_2$) and 0.86 (3 H, t, J 6.5, CH$_3$); δ_C(CDCl$_3$; 250 MHz) 175.41 (lactone C=O), 80.43 (CH-O), 36.41, 34.91, 34.59, 31.64, 28.99, 28.25, 25.32, 23.07, 22.46 (9 × CH$_2$) and 13.88 (CH$_3$); *m z* 198 (M$^+$, 0.28%), 113 (60, M − C_6H_{13}), 85 (100, C_6H_{13}) (Found: M$^+$, 198.1610. $C_{12}H_{22}O_2$ requires *M*, 198.1620).

(μ-*Chloro*-μ-*methylene*)-*bis*(*cyclopentadieny*)*titaniumdimethyl-aluminium* (Tebbe Reagent).[18–20]—Titanocene dichloride (50 g, 0.2 mol) was purified by Soxhlet extraction with dry degassed dichloromethane (3 × freeze–thaw, 300 cm^3) and the solvent was evaporated under reduced pressure at 0 °C. Nitrogen was introduced into the vacuum and the crystalline residue was dissolved in dry degassed toluene (3 × freeze–thaw, 125 cm^3). Trimethylaluminium (140 cm^3 of a 3.5 mol dm^{-3} solution in hexane) was added by syringe and the reaction mixture was stirred at room temperature for 48 h under a positive pressure of nitrogen. The solvents were removed under high vacuum at 0 °C, then room temperature, and the residue was pumped dry under high vacuum for a further 12 h. Dry degassed toluene (3 × freeze–thaw, 200 cm^3) was added by syringe followed by dry degassed hexane (3 × freeze–thaw, 180 cm^3). The solution was cooled to −40 °C and maintained at this temperature for 4 h, then the mother liquors were removed by cannula. The crystalline mass was washed once with dry degassed pentane (3 × freeze–thaw, 80 cm^3) at −20 °C, and then the solvent was removed by cannula. The remaining solid was dried under high vacuum for 4 h, then redissolved in dry degassed toluene (3 × freeze–thaw, 250 cm^3). The concentration of this solution was calculated from the integral of a 90 MHz ^{1}H NMR spectrum and found to be 0.34 mol dm^{-3} (43% yield); an equally good method of assay was a standard methylenation of a reference lactone; δ_H(toluene; 90 MHz) 8.49 (2 H, s, CH$_2$), 5.84 (10 H, s, 2 × Cp) and −0.06 (6 H, s, 2 × CH$_3$).

(2S*,7S*)-2-*Hexyl*-7-*hydroxymethyloxepane* **15a** *and* (2S*,7R*)-*Hexyl*-7-*hydroxymethyloxepane* **17a**.—The lactone **11a** (99 mg, 0.0005 mol) and 4-dimethylaminopyridine (DMAP) (67.2 mg, 0.000 55 mol) were dissolved in dry THF (2 cm^3) and the whole solution was degassed (3 × freeze-thaw). The reaction mixture was then cooled to −40 °C and the Tebbe reagent (1.5 cm^3 of a 0.335 mol dm^{-3} solution, 1 molar equivalent) was added dropwise. It was then stirred at −40 °C for 30 min then allowed to warm to room temperature over 2.5 h. After the mixture was cooled to −15 °C, aqueous sodium hydroxide (15%; 0.3 cm^3) was added dropwise. After being warmed to room temperature, the reaction mixture was poured into dry ether (50 cm^3) (over anhydrous Na_2SO_4) and filtered through a Celite plug. The filtrate was concentrated under reduced pressure below 30 °C, and the residue was purified by passage down a column of neutral alumina (grade III) with hexane. After evaporation the residue was dissolved in dry THF (10 cm^3) and borane–THF complex (2 cm^3 of a 1 mol dm^{-3} solution, 2 molar equivalents) was added in one portion at 0 °C. After 20 min at 0 °C aqueous sodium hydroxide (1.2 cm^3; 3 mol dm^{-3}) and hydrogen peroxide (0.36 cm^3 of 30% v/v concentration) were added dropwise and the reaction mixture was stirred at 0 °C for 90 min. The whole solution was poured into ether (50 cm^3), washed with water (2 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, with dichloromethane as eluent, to give the *oxepane* **15a** (45 mg, 42%), (the less polar isomer) and the *oxepane* **17a** (9 mg, 8%), (the more polar isomer) as colourless oils. Data for **15a** (Found: C, 73.15; H, 11.9. $C_{13}H_{26}O_2$ requires C, 72.90; H, 12.15%): ν_{max}(neat)/cm^{-1} 3420 (OH), 2960 (CH), 2830 (CH) and 1110(CO); δ_H($CDCl_3$; 250 MHz) 3.60 (1 H, m, $HOCH_2CHOCH$), 3.46 (3 H, m, $HOCH_2CHOCH$), 2.18 (1 H, br, s, OH), 1.79–1.16 (18 H, m, 9 × CH_2) and 0.89 (3 H, t, *J* 6.3, CH_3); δ_C(CD_3OD; 63 MHz) 82.08 and 82.02 (*C*HOCH, 66.83 (CH_2OH), 38.30, 37.75, 33.48, 33.04, 30.48, 27.20, 26.67, 26.04, 23.67 (9 × CH_2) and 14.38 (CH_3); *m*/*z* 214 (M^+, 0.58%), 183 (6, M − CH_2OH), 129 (20, M − C_6H_{13}) and 55 (100) (Found: M^+, 214.1930. $C_{13}H_{26}O_2$ requires *M*, 214.1933).

Data for **17a** (Found: C, 72.7; H, 12.3. $C_{13}H_{26}O_2$ requires C, 72.90; H, 12.15%): ν_{max}(neat)/cm^{-1} 3320 (OH), 2930 (CH), 2860 (CH) and 1120 (CO); δ_H($CDCl_3$; 250 MHz) 3.67 (2 H, m, $HOCH_2CHOCH$), 3.42 (2 H, d, *J* 6.1, $HOCH_2$) 2.07 (1 H, br, s, OH), 1.84–1.20 (18 H, 9 × CH_2) and 0.87 (3 H, t, *J* 6.6, CH_3); δ_C(CD_3OD; 63 MHz) 76.92 and 76.02 (*C*HOCH), 66.44 (CH_2OH), 37.20 (2 carbons), 33.28, 33.01. 30.51, 28.61, 27.98, 27.33, 23.68 (9 × CH_2) and 14.38 (CH_3); *m*/*z* 214 (M^+, 0.28%), 183 (6, M − CH_2OH), 129 (65, M − C_6H_{13}) and 55 (100) (Found: M^+, 214.1925. $C_{13}H_{26}O_2$ requires *M*, 214.1933).

Equilibration of Alcohols **15a** *and* **17a** via *the Corresponding Aldehydes*.—The alcohol **15a** was oxidised with PCC to the corresponding aldehyde **19a** which was equilibrated in the presence of potassium carbonate in methanol as described in detail below for the aldehyde **20b**. The resulting mixture of aldehydes **19a** and **21a** was reduced with sodium borohydride to the mixture of alcohols **15a** and **17a** (ratio 4:1) which were separated as described above.

(2S*7S*)-2-(3,5-*Dinitrobenzoyl*)*oxymethyl*-7-*hexyloxepane*.—The *cis*-alcohol **15a** (6 mg, 0.028 mmol) was dissolved in dry dichloromethane (2 cm^3) with DMAP (3.45 mg, 0.028 mmol) and 3,5-dinitrobenzoyl chloride (6.5 mg, 0.028 mmol) and stirred at room temperature for 16 h. After being concentrated under reduced pressure the residue was purified by preparative thin layer chromatography, with 50% dichloromethane in hexane as eluent, to give (2S*,7S*)-2-(3,5-*dinitrobenzoyl*)-*oxymethyl*-7-*hexyloxepane* (10.6 mg, 93%) as a green oil. ν_{max}-($CHCl_3$)/cm^{-1} 2960 (CH), 2930 (CH), 1730 (conjugated ester C=O), 1630 (aromatic), 1550 (CNO_2) and 1350 (CNO_2); δ_C($CDCl_3$; 250 MHz) 9.22 (1 H, t, *J* 2.1, $O_2NC{=}CHCNO_2$), 9.17 (2 H, d, *J* 2.1, 2 × *ortho* aromatic H's), 4.42 (1 H, dd, *J* 11.4, 8.4, $CH_AH_BOC{=}O$), 4.32 (1 H, dd, *J* 11.4, 3.7, $CH_AH_BOC{=}O$), 3.91 (1 H, m, OCH_2CHOCH), 3.43 (1 H, m, OCH_2CHOCH), 1.82–0.96 (18 H, m, 9 × CH_2) and 0.75 (3 H, t, *J* 6.3, CH_3); *m*/*z* 378 (M^+ − NO, 0.31%,) 323 (4, M − C_6H_{13}), 195 (100, M − ArCOO) and 183 (66, M − $ArCOOCH_2$).

(2R*,7S*)-2-(3,5-*Dinitrobenzoyl*)*oxymethyl*-7-*hexyloxepane*.—The *trans*-alcohol **17a** (12 mg, 0.0568 mmol), DMAP (6.9 mg, 0.0568 mmol) and 3,5-dinitrobenzoyl chloride (13 mg, 0.0568 mmol) were dissolved in dry dichloromethane (3 cm^3) and stirred at room temperature for 14 h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC, with 50% dichloromethane in hexane as eluent, to give the *title compound* (20.2 mg, 88%) as a green oil; ν_{max}($CHCl_3$)/cm^{-1} 3100 (aromatic CH), 2930 (CH), 2860 (CH), 1725 (conjugated ester), 1630 (aromatics), 1550 (C-NO_2) and 1350 (CNO_2); δ_C ($CDCl_3$; 250 MHz) 9.23 (1 H, t, *J* 2.1, $O_2NC{=}CHCNO_2$), 9.17 (2 H, d, *J* 2.1, 2 × *ortho* aromatic H's), 4.39 (1 H, dd, *J* 11.4, 3.3, $CH_AH_BOC{=}O$), 4.27 (1 H, dd *J* 11.4, 3.7, $CH_AH_BOC{=}O$), 1.91–1.00 (18 H, m, 9 × CH_2) and 0.77 (3 H, t, *J* 6.4, CH_3); *m*/*z* 323 (100%, M − C_6H_{13}), 195 (76, M − ArCOO) and 183 (65, M − $ArCOOCH_2$).

(2S*,7S*)-2-(*Prop*-1-*enyl*)-7-*hexyloxepane* **23**.—The alcohol **19a** (150 mg, 0.71 mmol) was dissolved in dry dichloromethane (10 cm^3) and crushed 3Å molecular sieves (600 mg) and PCC (0.302 g, 2 molar equivalents) were added. The suspension was stirred at room temperature for 2 h then diluted with ether (30 cm^3) and filtered through a column of Florisil, with ether as eluent. The solvent was evaporated under reduced pressure to leave a residue which was dissolved in dry THF (5 cm^3) and added to a solution of ethylene triphenylphosphorane [formed from ethyltriphenyphosphonium bromide (0.87 g, 0.0023 mol) and butyllithium (1.3 cm^3 of a 1.6 mol dm^{-3} solution in hexane) in THF (15 cm^3)]. After the reaction mixture had been stirred at room temperature for 14 h, saturated ammonium chloride solution (5 cm^3) was added and the product was extracted with ether (3 × 15 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure to leave a residue which was purified by flash column chromatography on silica, with 80% dichloromethane in hexane as eluent, to give the *alkene* **23** (88 mg, 55%) as a colourless oil; ν_{max}(neat)/cm^{-1} 3010 (C=CH), 2960 (CH), 2860 (CH), 1100 (CO) and 710 [CH=CH (*cis*)]; δ_H ($CDCl_3$; 250 MHz) 5.47 (2 H, m, *CH*=*CH*), 4.25 (1 H, m, C=C*H*OCH), 3.45 (1 H, m, CH=CHCHOC*H*), 1.65 (3 H, d, *J* 5.1, $CH_3CH{=}CH$), 1.80–1.25 (18 H, m, 9 × CH_2) and 0.86 (3 H, t, *J* 6.6, CH_3); *m*/*z* 224 (M^+, 10%), 211 (1, M − CH_3), 139 (10, M − C_6H_{13}) and 71 (100) (Found: M^+, 224.2124. $C_{15}H_{28}O$ requires *M*, 224.2140).

(2S*,7R*)-2-*Hexyl*-7-*propyloxepane* (*Isolaurepan*) **1**.—The alkene **23** (60 mg, 0.2678 mmol) was dissolved in ethyl acetate (10 cm^3), 5% palladium on charcoal catalyst (6 mg) was added and the reaction mixture was stirred under an atmosphere of hydrogen for 2 h. The suspension was filtered through a Celite plug and the solvent was concentrated under reduced pressure to leave a residue which was purified by flash silica gel column chromatography, with dichloromethane as eluent, to give *isolaurepan* **1** (59.7 mg, 99%) as a colourless oil (Found: C, 79.45; H, 13.3. $C_{15}H_{30}O$ requires C, 79.58; H, 13.36%); ν_{max}(neat)/cm^{-1} 2960 (CH), 2850 (CH) and 1100 (CO); δ_H($CDCl_3$; 250 MHz) 3.37 (2 H, m, *CHOCH*), 1.75–1.26 (22 H, m, 11 × CH_2) and 0.91–0.84 (6 H, m, 2 × CH_3); δ_C (CD_3OD; 63 MHz) 81.86 and 81.58 (*C*HOCH), 40.68, 38.43, 37.97 (2 C), 33.03, 30.39, 27.33,

26.39, 26.36, 23.65, 20.46 (11 × CH_2) and 14.37 (2 C, 2 × CH_3); *m/z* 226 (M^+, 6.5%), 183 (52, M − C_3H_7), 141 (100, M − C_6H_{13}) (Found: M^+, 226.2313. $C_{15}H_{30}O$ requires *M*, 226.2296).

Methyl (1R,S)-2-*Oxocycloheptanecarboxylate* **6b**.—To a mechanically stirred solution of dimethyl carbonate (40.12 g, 37.53 cm^3, 0.45 mol) and sodium hydride (17.8 g of a 60% dispersion in oil, 0.45 mol) in dry ether (60 cm^3) was added cycloheptanone (25 g, 0.223 mol) dropwise over 1 h. After 6 h the reaction mixture was cooled to 0 °C and glacial acetic acid (26.76 g, 25.5 cm^3, 0.45 mol) was added dropwise. When the addition was complete, ice water (100 cm^3) was added slowly and the organic layer was separated, washed with brine (1 × 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by high vacuum distillation to give the *ester* **6b** (23.45 g, 62%) as a colourless oil.,b.p. 74–78 °C/0.25 mmHg (Found: C, 63.7; H, 8.5. $C_9H_{14}O_3$ requires C, 63.53; H, 8.24%); ν_{max}(neat)/cm^{-1} 2960 (CH), 2940 (CH), 2860 (CH), 1740 (ester C=O), 1700 (ketone C=O) and 1160 (CO); δ_H ($CDCl_3$; 60 MHz) 3.75 (3 H, s, CH_3O), 3.45 (1 H, m, COCHCOO), 2.80–2.30 (2 H, m, CH_2C=O) and 2.30–1.12 (8 H, m, 4 × CH_2); *m/z* 170 (M^+, 23%), 113 (34, M − CO_2Me) and 55 (100) (Found M^+, 170.0940. $C_9H_{14}O_3$ requires *M*, 170.0943).

Methyl (1R,S)-1-*Hexyl*-2-*oxocycloheptanecarboxylate* **7b**.—The ketoester **6b** (21.02 g, 0.1236 mol) was dissolved in dry DMF (250 cm^3), and sodium hydride (5.5 g of a 60% dispersion in oil, 0.14 mol) was added in portions. When the addition was complete 1-bromohexane (20.4 g, 17.35 cm^3, 0.1236 mol) was added in one portion. The reaction mixture was heated at 40 °C for 48 h, cooled to 0 °C, and excess sodium hydride was quenched with glacial acetic acid. The solvent was removed in high vacuum and the residue was partitioned between water (300 cm^3) and ether (3 × 300 cm^3). The combined organic layers were washed with brine (1 × 15 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue which was purified by high vacuum distillation to give a mixture of the C-*alkylation product* **7b** and methyl 2-hexyloxycyclohept-1-enecarboxylate (the *O*-alkylation product) (26.6 g, 85%) in a ratio of 29 : 1 respectively as a colourless oil (Found: C, 70.6; H, 10.0. $C_{15}H_{26}O_3$ requires C, 70.83; H, 10.30%); b.p. 110–115 °C/0.13–0.15 mmHg; ν_{max}(neat)/cm^{-1} 2960 (CH), 2940 (CH), 1745 (ester C=O), 1715 (ketone C=O) and 1125 (C-O); δ_H ($CDCl_3$; 250 MHz) 3.71 (3 H, s, CH_3OCO, *O*-alkylation product), 3.70 (3 H, s, CH_3OCO, *C*-alkylation product), 2.56 (1 H, m, CH_AH_BC=O), 2.47 (1 H, m, CH_AH_BC=O), 2.14–1.24 (18 H, m, 9 × CH_2) and 0.85 (3 H, t, *J* 6.8, CH_3); *m/z* 223 (2%, M^+ − CH_3O), 195 (5, M − CO_2CH_3) and 170 (100, M − C_6H_{12}).

2-(R,S)-*Hexylcycloheptanone* **9b**.—The ketoester **7b** (22.54 g, 0.089 mol) (containing 1/30 *O*-alkylation product) was dissolved in DMSO (100 cm^3) with lithium chloride (11.31 g, 0.27 mol) and water (2.4 cm^3, 0.13 mol). The reaction mixture was heated at 180 °C for 90 min then cooled, and extracted into light petroleum (b.p. 60–80 °C) (3 × 250 cm^3); the combined organic extracts were washed with brine (2 × 150 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by high vacuum distillation to give the *ketone* **9b** (14.15 g, 81%) as a colourless oil, b.p. 73–74 °C/0.03 mmHg (Found: C, 79.6; H, 12.05. $C_{13}H_{24}O$ requires C, 79.50; H, 12.24%); ν_{max}(neat)/cm^{-1} 2940 (CH), 2860 (CH) and 1705 (ketone C=O); δ_H($CDCl_3$; 250 MHz) 2.48–2.37 (3 H, m, CH_2COCH), 1.90–1.04 (18 H, m, 9 × CH_2) and 0.86 (3 H, t, *J* 6.5, CH_3); δ_C($CDCl_3$; 63 MHz) 216.14 (C=O), 52.38 and 42.60 (*C*HCO*C*H2), 32.24, 31.66, 31.24, 29.57, 29.30, 28.38, 27.17, 24.62, 22.52, (9 × CH_2) and 13.94 (CH_3); *m/z* 196 (M^+, 2.71%) and 112 (100, M − C_6H_{10}) (Found: M^+, 196.1831. $C_{13}H_{24}O$ requires *M*, 196.1827).

8-(R,S)-*Hexyloxocan*-2-*one* **11b**.—The ketone **9b** (1 g, 0.0051 mol) was dissolved in dry dichloromethane (20 cm^3), disodium hydrogen phosphate (8 g) was added and the suspension was cooled to 0 °C. To a solution of 85% hydrogen peroxide (5.44 cm^3, 0.136 mol) in dichloromethane (100 cm^3) at 0 °C was added dropwise trifluoroacetic anhydride (22.4 cm^3, 0.158 mol). The reaction was stirred at 0 °C for 5 min then 15 min at room temperature. The peroxytrifluoracetic acid was added dropwise to the reaction mixture which was stirred for 3 h at 0 °C, then 14 h at room temperature. The solution was filtered through Celite, and the filtrate was washed with saturated aqueous sodium metabisulfite (2 × 30 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 30 cm^3) and brine (1 × 30 cm^3); the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to leave a residue, which was purified by flash column chromatography on silica gel with 5% ether in light petroleum (b.p. 40–60 °C) as eluent, to give the *lactone* **11b** (0.69 g, 68%) as a colourless oil (Found: C, 73.4; H, 11.15. $C_{13}H_{24}O_2$ requires C, 73.58; H, 11.32%; ν_{max}(neat)/cm^{-1} 2960 (CH), 2940 (CH), 1735 lactone (C=O) and 1125 (C–O); δ_H($CDCl_3$; 250 MHz) 4.52 (1 H, m, CHOCO), 2.59–2.40 (2 H, m, CH_2C=O), 1.97–1.26 (18 H, m, 9 × CH_2) and 0.86 (3 H, t, *J* 6.9, CH_3); δ_C($CDCl_3$; 63 MHz) 176.78 (C=O), 78.82 (CHO), 37.33, 35.58, 32.58, 31.66, 29.03, 28.92, 26.52, 25.65, 24.04, 22.49, (10 × CH_2) and 13.93 (CH_3); *m/z* 127 (1%, M − C_6H_{11}), 99 (100, M − C_6H_{11} and CO).

(2S*,8S*)-2-*Hexyl*-8-*hydroxymethyloxocane* **15b** *and* (2S*,8R*)-2-*Hexyl*-8-*hydroxymethyloxocane* **17b**.—The Tebbe reagent (1.65 cm^3 of a 0.34 mol dm^{-3} solution in toluene, 0.55 mmol) was added dropwise to a solution of the lactone **11b** (106 mg, 0.5 mmol) and pyridine (25 cm^3) in dry, degassed THF (2 cm^3) (3 × freeze–thaw) at −40 °C. The reaction mixture was stirred at this temperature for 30 min, then allowed to warm to room temperature over 3 h. After this the reaction mixture was cooled to −15 °C, and 15% aqueous sodium hydroxide (0.15 cm^3) added dropwise; the mixture was allowed to warm to room temperature over 1 h. It was poured into dry ether (50 cm^3) over anhydrous sodium sulfate, filtered through a Celite plug, and evaporated under reduced pressure at below 30 °C to leave a residue which was dried under high vacuum. This was then passed down a column of neutral alumina (grade III), with hexane as eluent and the eluate was evaporated under reduced pressure to leave a residue which was dissolved in dry THF (10 cm^3) after which borane–tetrahydrofuran complex (2 cm^3 of a 1 mol dm^{-3} solution, 2 mmol) was added. After 30 min the solution was cooled to 0 °C and water (1 cm^3) was added dropwise. Aqueous sodium hydroxide (1.2 cm^3; 3 mol dm^{-3}) and hydrogen peroxide (0.36 cm^3; 30% v/v) were added dropwise and the reaction mixture was stirred at 0 °C for 90 min. The solution was poured into ether (50 cm^3) and the ether layer was washed with water (2 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue obtained was purified by column chromatography on flash silica gel, with 3% ethyl acetate in dichloromethane as eluent, to give the cis-*isomer* **15b** (43.2 mg, 38%) (the less polar isomer) and the trans-*isomer* **17b** (5.3 mg, 5%) (the more polar isomer) as colourless oils.

Data for **15b** (Found: C, 73.55; H, 12.0. $C_{14}H_{28}O_2$ requires C, 73.68; H, 12.28%); ν_{max}(neat)/cm^{-1} 3400 (OH), 2940 (CH), 2850 (CH) and 1090 (CO); δ_H($CDCl_3$; 250 MHz) 3.60 (1 H, m, CH_2CHOCH), 3.56–3.39 (3 H, m, CH_2CHOCH), 2.02 (1 H, br s, OH), 1.81–1.18 (20 H, m, 10 × CH_2) and 0.87 (3 H, t, *J* 6.5, CH_3); δ_C($CDCl_3$; 63 MHz) 80.71, 80.14 (*C*HOCH), 66.60 ($HOCH_2$), 36.92, 33.48, 31.82, 30.47, 29.43, 27.40, 26.33, 23.92 (2 carbons), 22.61 (10 × CH_2) and 14.03 (CH_3); *m/z* 197 (15%,

$M^+ - CH_2OH$), 55 (100). Data for **17b** (Found: C, 73.4; H, 12.3. $C_{14}H_{28}O_2$ requires C, 73.68; H, 12.28%); ν_{max}(neat)/cm^{-1} 3400 (OH), 2930 (CH), 2850 (CH) and 1090 (CO); δ_H($CDCl_3$; 250 MHz) 3.72 (1 H, m, $HOCH_2CHOCH$), 3.66 (1 H, m, $HOCH_2CHOCH$), 3.44 (2 H, d, *J* 5.7 $HOCH_2$), 1.97 (1 H, br s, OH), 1.74–1.19 (20 H, m, 10 × CH_2) and 0.87 (3 H, t, *J* 6.1, CH_3); δ_C($CDCl_3$; 63 MHz) 75.78, 73.19 (*C*HOCH), 66.13 ($HOCH_2$), 36.36, 31.86, 31.77, 29.84, 29.38, 26.56, 26.25 (2 C), 25.10, 22.56 (10 × CH_2) and 13.97 (CH_3); *m/z* 197 (23%, $M^+ - CH_2OH$), 143 (2, $M - C_6H_{13}$) and 55 (100).

(2S*,8S*)-2-*Toluene*-p-*sulphonyloxymethyl*-8-*hexyloxocane*.—The alcohol **15b** (44 mg, 0.193 mmol) was dissolved in dry dichloromethane (4 cm^3) with DMAP (64 mg, 0.386 mmol) and toluene-*p*-sulfonyl chloride (162 mg, 0.386 mmol). The reaction mixture was stirred at room temperature for 48 h then the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, with 75% hexane in dichloromethane as eluent, to give the *tosylate* (62 mg, 84%) as a colourless oil; ν_{max}(neat)/cm^{-1} 2940 (CH), 2860 (CH), 1600 (aromatics), 1370 (SO_2O), 1190 (SO_2O) and 1110 (CO); δ_H($CDCl_3$; 250 MHz) 7.78 (2 H, d, *J* 8.2, aromatic H's *ortho* to OSO_2), 7.32 (2 H, d, *J* 8.2, aromatic H's *meta* to OSO_2), 3.86 (2 H, m, CH_2OSO_2), 3.75 (1 H, m, SO_2OCH_2-CHOCH), 3.41 (1 H, m, SO_2OCH_2CHOCH), 2.43 (3 H, s, $ArCH_3$), 1.81–1.17 (20 H, m, 10 × CH_2) and 0.88 (3 H, t, *J* 6.5, CH_3).

(2S*,8S*)-2-*Hexyl*-8-*vinyloxocane* **24**.—To a stirred solution of the alcohol **15b** (111 mg, 0.487 mmol) in dry dichloromethane (8 cm^3) were added crushed 3Å molecular sieves (1 g) and PCC (0.22 g, 0.001 mol). After 1 h the reaction mixture was diluted with ether (30 cm^3), filtered through a Celite plug, and the filtrate was passed down a Florisil column with ether as eluent. The solvent was removed under reduced pressure to give the *aldehyde* **19b** as a colourless oil (101 mg, 92%) which was used without further purification in the Wittig reaction. A solution containing the aldehyde **19b** was added to a solution of methylenetriphenylphosphorane [formed from methyltriphenylphosphonium bromide (0.57 g, 0.0015 mol) and butyllithium (0.91 cm^3 of a 1.6 mol dm^{-3} solution in hexane)] in dry THF (20 cm^3). The reaction mixture was stirred at room temperature for 16 h then quenched by the dropwise addition of water (20 cm^3) and poured into ether (30 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (2 × 20 cm^3). The organic components were combined, dried ($MgSO_4$), and evaporated under reduced pressure to leave a residue which was purified by flash column chromatography on silica gel, with 40% dichloromethane in hexane as eluent, to give the *alkene* **24** (89 mg, 82%) as a colourless oil (Found: C, 80.0; H, 12.5. $C_{15}H_{28}O$ requires C, 80.29; H, 12.57%); ν_{max}(neat)/cm^{-1} 3075 (C=CH_2), 2960 (CH), 2850 (CH), 1640 (C=C), 1100 (CO), 1000 (C=CH_2) and 930 (C=CH_2); δ_H($CDCl_3$; 250 MHz) 5.86 (1 H, ddd, *J* 17.0, 10.6, 4.2, CH_AH_B=CH), 5.22 (1 H, dd, *J* 17.0 & fine coupling, CH_AH_B=CH), 5.03 (1 H, dd, *J* 10.6 & fine coupling, CH_AH_B=CH), 3.95 (1 H, m, CH_2=CH-CHO), 3.44 (1 H, m, CH_2=CHCHOCH), 1.86–1.14 (20 H, m, 10 × CH_2) and 0.87 (3 H, t, *J* 5.1, CH_3); *m/z* 139 (3%, $M^+ - C_6H_{13}$), 55 (100).

(2R*8S*)-2-*Ethyl*-8-*hexyloxocane* (*Lauthisan*) **2**.—The alkene **24** (70 mg, 0.31 mmol) was dissolved in ethyl acetate (30 cm^3) and 5% palladium on carbon catalyst (10 mg) was added. The reaction mixture was stirred under an atmosphere of hydrogen for 16 h then filtered through a Celite plug and concentrated under reduced pressure to give *lauthisan* **2** (59.4 mg, 85%) as a colourless oil (Found: C, 79.9; H, 13.4. $C_{15}H_{30}O$ requires C, 79.58; H, 13.36%); ν_{max}(neat)/cm^{-1} 2960 (CH), 2850 (CH) and 1100 (CO); δ_H($CDCl_3$; 250 MHz) 3.43 (1 H, m, CH_AOCH_B), 3.34 (1 H, m, CH_AOCH_B), 1.87–1.16 (22 H, m, 11 × CH_2), 0.98–0.82 (6 H, m, 2 × CH_3); δ_C(CD_3OD; 63 MHz) 82.71 and 81.17 (*C*HOCH), 38.07, 34.77, 34.45, 33.03, 30.77, 30.55, 28.22, 27.32, 25.16 (2 C), 23.66 (11 × CH2), 14.38 and 11.12 (2 × CH_3); *m/z* 226 (M^+, 1%), 197 (3, $M - C_2H_5$), 141 (3, $M - C_6H_{13}$) and 55 (100) (Found: M^+, 226.2302. $C_{15}H_{30}O$ requires *M*, 226.2296). A sample of synthetic racemic compound **2** was compared with an authentic sample derived by exhaustive degradation of (+)-laurencin in Hokkaido,[28] and was found to be identical in all respects except optical rotation.[34]

Methyl (1RS)-2-*Oxo*-1-*pentylcycloheptane carboxylate* **8b**.—Sodium hydride (0.48 g of a 60% dispersion in oil, 12 mmol) was added in portions to a solution of the keto ester **6b** (1.7 g, 0.01 mol) in dry dimethylformamide (DMF) (20 cm^3) at room temperature. When the addition was complete the reaction mixture was stirred at room temperature for 5 min then pentyl bromide (1.26 cm^3, 0.01 mol) was added in one portion. The solution was heated at 80 °C for 14 h then the solvent was removed under high vacuum. The residue was purified by flash column chromatography on silica gel, with 50% dichloromethane in light petroleum (b.p. 40–60 °C) as eluent, to give as a colourless oil the *alkylation product* **8b** (2.23 g, 93%) in a ratio of 13:1 (C *versus* O-alkylation product) respectively. (A ten fold increase in the scale of this reaction gave a yield of 89% with the same ratio of inseparable products) (Found: C, 70.2; H, 9.8. $C_{14}H_{24}O_3$ requires C, 70.00; H, 10.00%); ν_{max}(neat)/cm^{-1} 2960 (CH), 2940 (CH), 2870 (CH), 1740 (ester C=O) and 1705 (ketone C=O); δ_H($CDCl_3$; 250 MHz) 3.71 (3 H, s, OC=CCOOCH$_3$ of *O*-alkylation product), 3.70 (3 H, s, O=CCCOOCH$_3$ of *C*-alkylation product), 3.64 (2 H, t, *J* 7.0, OCH_2, *O*-alkyl.), 2.59 (1 H, m, CH_AH_BC=O), 2.46 (1 H, m CH_AH_BC=O), 2.18–1.12 (16 H, m, 8 × CH_2), 0.85 (3 H, t, *J* 6.6, CH_3); *m/z* 209 (3, $M^+ - CH_3O$), 181 (5, $M - CO_2CH_3$) and 170 (100).

2-(R,S)-*Pentylcycloheptanone* **10b**.—The β-keto ester **8b** (containing some *O*-alkylation product) (19.4 g, 80.8 mmol, 13:1 ratio) was dissolved in dimethyl sulfoxide DMSO (100 cm^3) with lithium chloride (9.67 g, 0.23 mol) and water (2.05 cm^3, 0.23 mol) and heated at 180 °C for 2 h. The reaction mixture was allowed to cool, extracted with light petroleum (b.p. 60–80 °C) (3 × 100 cm^3) and the organic layers were then washed with brine (2 × 50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, with 50% dichloromethane in hexane as eluent to give the *ketone* **10b** (9.5 g, 64%) as a colourless oil (Found: C, 79.4; H, 11.8. $C_{12}H_{22}O$ requires C, 79.12; H, 12.09%); ν_{max}(neat)/cm^{-1} 2960 (CH), 2940 (CH), 2860 (CH) and 1700 (ketone C=O); δ_H($CDCl_3$; 250 MHz) 2.51–2.34 (3 H, m, $CHCOCH_2$), 1.84–1.21 (16 H, m, 8 × CH_2) and 0.83 (3 H, t, *J* 6.4, CH_3); δ_H($CDCl_3$; 63 MHz) 216.18 (C=O), 52.37 and 42.59 ($CHCOCH_2$), 32.29, 31.85, 31.24, 29.57, 28.38, 26.87, 24.61 and 22.45 (8 × CH_2) and 13.91 (CH_3); *m/z* 182 (M^+, 4%), 112 (100, $M - C_5H_{10}$), 111 (3, $M - C_5H_{11}$) (Found: M^+, 182.1680. $C_{12}H_{22}O$ requires *M*, 182.1670)

8-(R,S)-*Pentyloxocan*-2-*one* **12b**.—To a solution of 85% hydrogen peroxide (5.44 cm^3, 0.136 mol) in dichloromethane (100 cm^3) at 0 °C was added dropwise trifluoroacetic anhydride (22.4 cm^3, 0.158 mol). The reaction was stirred at 0 °C for 5 min then 15 min at room temperature. The homogeneous solution was added dropwise to a suspension of the ketone **10b** (8 g, 0.044 mol) and disodium hydrogen phosphate (56 g) in dry dichloromethane (80 cm^3) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h then at room temperature for 14 h. After this time the whole mixture was filtered through a Celite plug and the filtrate was washed with saturated aqueous sodium

metabisulfite (2 × 100 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 100 cm^3) and brine (1 × 100 cm^3) then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, firstly with 50% dichloromethane in hexane then neat dichloromethane as eluent, to give the *lactone* **12b** (6.7 g, 77%) as a colourless oil (Found: C, 72.7; H, 11.0. $C_{12}H_{22}O_2$ requires C, 72.85; H, 10.93%); ν_{max}(neat)/cm^{-1} 2960 (CH), 2940 (CH), 2860 (CH), 1735 (lactone C=O) and 1120 (C–O); δ_H($CDCl_3$; 250 MHz) 4.52 (1 H, m, OC*H*C=O), 2.55–2.42 (2 H, m, CH_2C=O), 1.90–1.20 (16 H, m, 8 × CH_2) and 0.90 (3 H, t, *J* 6.7, CH_3); δ_C($CDCl_3$; 63 MHz) 176.82 (C=O), 78.79 (OCH), 37.29, 35.53, 32.46, 31.57, 28.85, 26.40, 25.37, 23.93, 22.48 (9 × CH_2) and 13.92 (CH_3); *m/z* 127 (36%, $M^+ - C_5H_{11}$) and 55 (100).

(2S*,8S*)-2-*Hydroxymethyl*-8-*pentyloxocane* **16b** *and* (2R*,8S*)-2-*hydroxymethyl*-8-*pentyloxocane* **18b**.—The lactone **12b** (99 mg, 0.0005 mol) was dissolved in dry THF (2 cm^3) with dry pyridine (25 cm^3) and the solution was degassed (3 × freeze–thaw) under nitrogen, cooled to −40 °C then the Tebbe reagent (1.7 cm^3 of a 0.312 mol dm^{-3} solution, 0.5 mmol) was added dropwise. The reaction mixture was stirred at −40 °C for 30 min then allowed to warm to room temperature over 3 h. The solution was then cooled to −15 °C and 15% aqueous sodium hydroxide solution (0.3 cm^3) was added dropwise. The reaction mixture was allowed to warm to room temperature over a period of 1 h, poured into dry ether (50 cm^3) over anhydrous sodium sulfate and filtered through a Celite plug. The solution was concentrated under reduced pressure at below 30 °C, then the residue was dried under high vacuum and passed down a column of neutral alumina (grade III) which was eluted with hexane.

(*a*) *Hydroboration with borane–THF complex.* The solvent was evaporated under reduced pressure, and the residue was dissolved in dry THF (10 cm^3), and borane-tetrahydrofuran complex (2 cm^3 of a 1 mol dm^{-3} solution, 2 molar equivalents) was added. After 30 min at room temperature the solution was cooled to 0 °C and water (1 cm^3) added dropwise. Aqueous sodium hydroxide (1.2 cm^3; 3 mol dm^{-3}) and hydrogen peroxide (0.36 cm^3; 30% v/v) were added dropwise, and the reaction mixture was stirred at 0 °C for 90 min. The whole solution was poured into ether (50 cm^3) and washed with water (2 × 20 cm^3). The organic solution was dried ($MgSO_4$) and evaporated under reduced pressure to leave a residue which was purified by flash silica column chromatography with 5% ethyl acetate in dichloromethane as eluent to give the *title compounds* **16b** (49 mg, 49%) (the less polar isomer) and **18b** (3.4 mg, 3%) (the more polar isomer) as colourless oils. Data for **16b** (Found: C, 73.1; H, 12.1. $C_{13}H_{26}O_2$ requires C, 72.90; H, 12.15%: ν_{max}(neat)/cm^{-1} 3420 (OH), 2930 (CH), 2860 (CH) and 1100 (CO); δ_H($CDCl_3$; 250 MHz) 3.56 (1 H, m, $HOCH_2CHOCH$), 3.56–3.38 (3 H, m, $HOCH_2CHOCH$), 1.89 (1 H, br s, OH), 1.91–1.28 (18 H, m, 9 × CH_2) and 0.88 (3 H, t, *J* 6.7, CH_3); δ_C ($CDCl_3$; 63 MHz) 80.68 and 80.12 (*C*HOCH), 66.56 ($HOCH_2$), 36.85, 33.44, 31.96, 30.43, 27.38, 26.00, 23.89 (2 C), 22.58, (9 × CH_2) and 13.10 (CH_3); *m/z* 214 (M^+, 8%), 184 (74), 165 (49), 143 (0.1, $M - C_5H_{11}$), 109 (50) and 55 (100) (Found: M^+, 214.1937. $C_{13}H_{26}O_2$ requires *M*, 214.1933).

Data for **18b** (Found: C, 73.1; H, 11.95. $C_{13}H_{26}O_2$ requires C, 72.90; H, 12.15%); ν_{max}(neat)/cm^{-1} 3400 (OH), 2930 (CH), 2860 (CH) and 1100 (CO); δ_H($CDCl_3$; 250 MHz) 3.72 (1 H, m, $HOCH_2CHOCH$), 3.66 (1 H, m, $HOCH_2CHOCH$), 3.44 (2 H, d, *J* 7.0, $HOCH_2CHOCH$), 1.92 (1 H, br s, OH), 1.75–1.15 (18 H, m, 9 × CH_2) and 0.89 (3 H, t, *J* 7.4, CH_3); δ_C ($CDCl_3$; 63 MHz) 75.75 and 73.28 (*C*HOCH), 66.21 ($HOCH_2$), 36.39, 31.95 (2 C), 29.85, 26.61, 26.29, 25.95, 25.17, 22.59 (9 × CH_2) and 13.96 (CH_3); *m/z* 183 (16%, $M - HOCH_2$), 143 (10, $M - C_5H_{11}$) and 55 (100).

(*b*) *Hydroboration with diisoamylborane.*—The lactone **14b** (100.70 mg, 0.508 mmol) and DMAP (67.83 mg, 0.559 mmol) were dissolved in dry THF (2 cm^3). The solution was degassed by freeze–thaw (three times) with nitrogen and cooled to −40 °C. Tebbe reagent (2.03 cm^3 of a 0.25 mol dm^{-3} solution in toluene, 0.5 mmol) was added dropwise by syringe to the solution at −40 °C and the reaction stirred for 30 min at this temperature, then allowed to come to room temperature over 2 h. The reaction was then cooled to −20 °C and 15% aqueous sodium hydroxide (0.15 cm^3, 0.56 mmol) was added dropwise. The reaction mixture was allowed to come to room temperature over 1 h and then poured into ether (50 cm^3) over anhydrous sodium sulfate. The solution was then filtered through Celite, the Celite being washed with more ether (150 cm^3) and the solvent was concentrated under reduced pressure at below 25 °C. The residue was passed through a column of neutral alumina (grade III), using hexane as the eluent, and the resulting solution was concentrated under reduced pressure at below 25 °C. The residue was dissolved in dry THF (5 cm^3), and the solution was cooled to 0° C. Diisoamylborane (1.41 cm^3 of a 0.36 mol dm^{-3} solution in THF, 0.51 mmol) was then added and the reaction was stirred at 0 °C for 5 h. With the reaction still at 0 °C, aqueous sodium hydroxide (3 mol dm^{-3}; 1.19 cm^3) was added, followed by hydrogen peroxide solution (30% v/v; 0.30 cm^3). The reaction was stirred for 1–2 h at 0 °C, then allowed to warm to room temperature. The reaction mixture was then poured into ether (50 cm^3) and washed with water (2 × 20 cm^3). The aqueous washings were extracted with ether (2 × 50 cm^3) and the combined organic extracts were dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (dichloromethane–ethyl acetate, 50:1) to afford the alcohol **16b** (64.70 mg, 59%) as a liquid. Only the *cis* isomer was isolated. Capillary GC analysis of the crude reaction mixture indicated a ratio of *cis* to *trans* isomers in excess of 120:1 (temperature program 150 °C for 5 mins., then 10 °C/min. to 250 °C, *cis*-isomer R_t 9.52 min., *trans*-isomer R_t 10.26 min.).

(2S*,8S*)-8-*Pentyl*-2-*toluene*-p-*sulfonyloxymethyloxocane.*—The alcohol **16b** (90 mg, 0.42 mmol) was dissolved in dry dichloromethane (10 cm^3) with DMAP (124 mg, 1.1 mmol) and toluene-*p*-sulfonyl chloride (352 mg, 0.92 mmol) and the mixture was stirred at room temperature for 14 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel with 50% dichloromethane in light petroleum (b.p. 40–60 °C) as eluent, to give the *title compound* (149 mg, 97%) as a colourless oil (Found: C, 65.6; H, 8.8. $C_{20}H_{32}O_4S$ requires C, 65.22; H, 8.7%); ν_{max}(neat)/cm^{-1} 2940 (CH), 2850 (CH), 1600 (aromatics), 1360 (SO_2O), 1180 (SO_2O) and 1110 (CO); δ_H($CDCl_3$; 250 MHz) 7.78 (2 H, d, *J* 8.2 aromatic H's *ortho* to OSO_2), 7.32 (2 H, d, *J* 8.2, aromatic H's *meta* to OSO_2), 3.86 (2 H, m, CH_2OSO_2), 3.72 (1 H, m, SO_2OCH_2CHOCH), 3.39 (1 H, m, SO_2OCH_2-$CHOCH$), 2.43 (3 H, s, $ArCH_3$), 1.76–1.24 (18 H, m, 9 × CH_2) and 0.87 (3 H, t, *J* 8.7, CH_3); δ_C($CDCl_3$; 63 MHz) 144.58, 133.34, 129.74 (2 C) and 127.95 (2 C) (aromatics), 81.32, 76.67 and 72.91 (SO_2OCH_2CHOCH), 36.32, 33.07, 31.94, 30.79, 27.08, 25.78, 24.34, 23.99, 22.60 and 21.57 (9 × CH_2 and Ar-CH_3) and 14.04 (CH_3); *m/z* 297 (1%, $M - C_5H_{11}$) 183 (21, $M - TsOCH_2$) and 91 (100).

(2R*,8S*)-8-*Pentyl*-2-*toluene*-p-*sulfonyloxymethyloxocane.* —The alcohol **18b** (17 mg, 0.0794 mmol) was esterified in dry dichloromethane (2 cm^3) with DMAP (21.3 mg, 0.174 mmol) and tosyl chloride (30 mg, 0.16 mmol) at room temperature for 4 h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC

(Kieselgel 1 mm), with dichloromethane as eluent, to give the *title compound* (29 mg, 99%) as a colourless oil; ν_{max}(neat)/cm^{-1} 2940 (CH), 2850 (CH), 1600 (aromatics), 1360 (SO_2O), 1190 (SO_2O) and 1110 (CO); δ_H($CDCl_3$; 250 MHz) 7.81 (2 H, d, *J* 8.2, aromatic H's *ortho* to OSO_2), 7.35 (2 H, d, *J* 8.3, aromatic H's *meta* to OSO_2) 3.94–3.82 (3 H, m, SO_2OCH_2CHO), 3.62 (1 H, m, SO_2OCH_2CHOCH), 2.46 (3 H, s, $ArCH_3$), 1.78–1.17 (18 H, m, 9 × CH_2) and 0.91 (3 H, t, *J* 6.7, CH_3); δ_C($CDCl_3$; 63 MHz) 144.67, 133.19, 129.77 (2 C) and 127.96 (2 C), (aromatics), 77.26, 72.81 and 69.60 (SO_2OCH_2CHOCH), 35.75, 31.84, 31.18, 30.55, 26.50, 26.16, 25.90, 24.59, 22.60 and 21.58 (9 × CH_2 and $ArCH_3$) and 14.01 (CH_3); *m/z* 368 (M^+, 0.27), 297 (1, M − C_5H_{11}), 183 (70, M − $TsOCH_2$) and 155 (100) (Found: M^+, 368.2008. $C_{20}H_{32}O_4S$ requires *M*, 368.2023).

(2R*,8R*)-2-*Pentyl*-8-*propyloxocane* (*Laurenan*) **3**.—The alcohol **16b** (212 mg, 0.99 mmol) was dissolved in dry dichloromethane (5 cm^3), and crushed 3Å molecular sieves (2 g) were added. PCC (0.43 g, 2 mmol) was added, and the reaction was stirred at room temperature for 1 h. Ether (20 cm^3) was added and the reaction mixture was filtered through a Celite plug and the filtrate was passed down a column of Florisil, with ether as eluent. The solvent was evaporated under reduced pressure to give the aldehyde **20b** (190 mg, 91%) as a colourless oil. To a stirred solution of ethylidenetriphenylphosphorane [formed from ethyltriphenylphosphonium bromide (0.87 g, 0.0023 mol) and butyllithium (1.3 cm^3 of a 1.6 mol dm^{-3} solution in hexane)] in THF (20 cm^3) was added aldehyde **30b** (170 mg, 0.8 mmol dm^{-3}) in dry THF (5 cm^3). The reaction mixture was stirred at room temperature for 16 h then quenched by the dropwise addition of water (20 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 cm^3). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to leave a residue which was purified by flash column chromatography on silica gel, with 40% dichloromethane in hexane as eluent, to give the alkene as a colourless oil (147 mg, 82%). A portion of this oil (102 mg, 0.4553 mmol) was dissolved in ethyl acetate (30 cm^3), in the presence of 10% palladium on charcoal catalyst (15 mg), and the reaction mixture was stirred under an atmosphere of hydrogen for 16h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give *laurenan* **3** (91 mg, 88%) as a colourless oil (Found: C, 79.7; H, 13.4. $C_{15}H_{30}O$ requires C, 79.58; H, 13.36%); ν_{max}(neat)/cm^{-1} 2940 (CH), 2850 (CH) and 1100 (CO); δ_H($CDCl_3$; 250 MHz) 3.43 (2 H, m, $CHOCH$), 1.83–1.00 (22 H, m, 11 × CH_2) and 0.92–0.85 (6 H, m, 2 × CH_3); *m/z* 226 (M^+, 0.71%), 183 (2, M − C_3H_7), 155 (3, M − C_5H_{11}) and 55 (100) (Found: M^+, 226.2302. $C_{15}H_{30}O$ requires *M*, 226.2296).

Equilibration of the Aldehyde **20b** *with its Epimer* **22b**.—The alcohol **16b** (474.61 mg, 2.214 mmol) was dissolved in dry dichloromethane (20 cm^3). Molecular sieves (3 Å, 4 g) and pyridinium chlorochromate (955 mg, 4.43 mmol) were then added to the solution. The reaction was stirred at room temperature for 1 h then poured into ether (200 cm^3). The reation mixture was filtered through Celite, and the solvent was removed under reduced pressure. The residue was then passed down a column of Florisil, eluting with ether. The solvent was removed under reduced pressure and the residue containing the aldehyde **20b** was dissolved in a methanolic solution of potassium carbonate (0.01 mol dm^{-3}). The reaction was then stirred for 3 d at room temperature to generate an equilibrium mixture of the aldehydes **20b** and **22b**. Sodium borohydride (166 mg, 4.4 mmol) was added and the mixture was stirred for 1 h at room temperature. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with 2% ethyl acetate in dichloromethane, to afford the *cis*-isomer **16b** (302.73 mg, 1.587 mmol) and the *trans*-isomer **18b** (48.53 mg, 0.226 mmol) in a combined yield of 74% (ratio 6:1).

Methyl (1R,S)-2-*Oxocyclooctanecarboxylate* **6c**.—To a stirred suspension of sodium hydride (17.8 g, 0.446 mol of a 60% dispersion in oil) and dimethyl carbonate (40.12 g, 0.446 mol) in dry ether (60 cm^3) at 0 °C was added cyclooctanone (28.14 g, 0.223 mol) dropwise over 1 h. The reaction mixture was stirred at room temperature for 8 h then cooled to 0 °C and quenched by the dropwise addition of acetic acid (25.54 cm^3, 0.446 mol). Ice–water (100 cm^3) was added cautiously, the organic layer was separated, and the aqueous layer was extracted with ether (2 × 300 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which was purified by high vacuum distillation to give the *keto ester* **6c** as a mixture of keto and enol forms (23 g, 56%) as a colourless oil, b.p. 159 °C/0.3 mmHg (Found: C, 65.4; H, 8.75. $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.76%); ν_{max}(neat oil)/cm^{-1} 2930 (CH), 2860 (CH), 1750 (ester C=O), 1710 (ketone C=O), 1645 (enol ether), 1610 (enol ether) and 1100 (C–O); δ_H($CDCl_3$; 250 MHz) 12.48 (s) and 3.59 (1 H, dd, *J* 7.5, 5.8, *H*OC=C and $COCHCO_2CH_3$), 3.71 and 3,64 (3 H, 2 × s, CO_2CH_3), 2.66–1.36 (12 H, m, 6 × CH_2); δ_C($CDCl_3$; 63 MHz) 211.98 (ketone C=O), 176.09 (ester C=O), 173.24 (ester C=O), 170.49 ($HOCH$=C), 99.02 (HOCH=*C*), 56.74, 52.15, 51.30, 41.71, 32.16, 29.86, 28.97, 28.61, 26.99, 26.45, 26.00, 25.35, 25.15, 24.49 and 23.83 (14 × CH_2 and 1 × CH); *m/z* 184 (M^+, 16.8%), 153 (8, M − CH_3O), 152 (16, M − CH_3OH) 124 (20, M − CH_3CO_2H) and 55 (100) (Found: M^+, 184.1106. $C_{10}H_{16}O_3$ requires *M*, 184.1100).

Methyl (1R,S)-2-*Oxo*-1-*pentylcyclooctanecarboxylate* **8c**.—The keto ester **6c** (19.7 g, 0.1072 mol) was dissolved in dry DMF (250 cm^3) and sodium hydride (3.96 g of a 60% dispersion in oil, 0.11 mol) was added in portions. Pentyl bromide (13.3 cm^3, 0.1072 mol) was added in one portion, stirred at room temperature for 48 h, then the solvent was evaporated under reduced pressure. The resultant residue was partitioned between water (250 cm^3) and dichloromethane (3 × 250 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by high vacuum distillation to give the *alkylation product* **8c** (16.5 g, 61%) as a colourless oil, b.p. 118–121 °C/0.1 mmHg; ν_{max}(neat)/cm^{-1} 2930 (CH), 2860 (CH), 1735 (ester C=O), 1705 (ketone C=O) and 1110 (C–O); δ_H($CDCl_3$; 250 MHz) 3.67 (3 H, s, $OCOCH_3$), 267 (1 H, ddd, *J* 12.6, 12.6, 4.2, $COCH_AH_B$), 2.45 (1 H, ddd, *J* 16.0, 12.6, 5.0, $COCH_AH_B$), 2.26–1.04 (18 H, m, 9 × CH_2) and 0.85 (3 H, t, *J* 6.7, CH_3); *m/z* 254 (M^+, 0.4%), 195 (3, M − CH_3OCO), 184 (40, M − C_5H_{10}) and 152 (100) (Found: M^+, 254.1886. $C_{15}H_{26}O_3$ requires *M*, 254.1882).

2-(R,S)-*Pentylcyclooctanone* **10c**.—The ketoester **8c** (16 g, 0.063 mol) was dissolved in DMSO (100 cm^3) with water (1.13 cm^3, 0.126 mol) and lithium chloride (5.35 g, 0.126 mol) and heated at 190 °C for 2 h. After cooling, the reaction mixture was extracted with light petroleum (b.p. 60–80 °C, 3 × 150 cm^3), washed with brine (2 × 100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue which was purified by high vacuum distillation to give the *ketone* **10c** (9.6 g, 78%) as a colourless oil (Found: C, 79.6; H, 12.1. $C_{13}H_{24}O$ requires C, 79.52: H, 12.32%), b.p. 74–76 °C/0.1 mmHg; ν_{max}(neat)/cm^{-1} 2930 (CH), 2860 (CH) and 1700 (ketone C=O); δ_H($CDCl_3$; 250 MHz) 2.54 (1 H, m, CHC=O), 2.44 (1 H, ddd, *J* 13.4, 5.5, 3.7, CH_AH_BC=O), 2.28 (1 H, ddd, *J* 13.4, 6.5, 5.5, CH_AH_BC=O), 2.05–1.11 (18 H, m, 9 × CH_2) and 0.85 (3 H, t,

J 6.8, CH_3); δ_C($CDCl_3$; 63 MHz) 220.31 (C=O), 50.78 and 41.95 (*C*HCOCH$_2$), 32.74, 32.65, 31.85, 27.34, 27.14, 25.91, 25.57, 24.82, 22.46 (9 × CH_2) and 13.97 (CH_3).

9-(R,S)-*Pentyloxonan*-2-*one* **12c**.—The ketone **10c** (4.312 g, 0.022 mol) was dissolved in dry dichloromethane (80 cm^3) and disodium hydrogen phosphate (56 g) was added. The reaction mixture was cooled to 0 °C and peroxytrifluoracetic acid [formed from 85% hydrogen peroxide (5.44 cm^3, 0.136 mol) and trifluoroacetic anhydride (14.2 cm^3, 0.1 mol) at 0 °C] was added dropwise. The reaction mixture was stirred at 0 °C for 3 h then at room temperature for 14 h. The suspension was filtered through a Celite plug and the filtrate was diluted with more dichloromethane (150 cm^3). The combined organic components were washed with 10% aqueous sodium thiosulfate (2 × 200 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 200 cm^3) and brine (1 × 200 cm^3), then evaporated under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel, with 30% dichloromethane in hexane as eluent, to give the *lactone* **12c** (1.8 g, 42%) as a colourless oil (Found C, 73.2; H, 11.1. $C_{13}H_{24}O_2$ requires C, 73.54; H, 11.39%); ν_{max}(neat)/cm^{-1} 2930 (CH), 2860 (CH), 1730 (lactone C=O) and 1130 (C–O); δ_H($CDCl_3$; 250 MHz) 4.91 (1 H, m, CHOC=O), 2.27 (2 H, m, CH_2COO), 2.02–1.09 (18 H, m, 9 × CH_2) and 0.88 (3 H, t, *J* 6.7, CH_3); δ_C($CDCl_3$; 63 MHz) 175.79 (C=O), 75.74 (*C*HOC=O), 35.78, 34.96, 33.55, 31.68, 29.53, 25.27, 24.99, 23.96, 22.53, 21.84 (10 × CH_2) and 13.96 (CH_3); *m*/*z* 212 (M^+, 1.26%), 141 (1, M − C_5H_{11}) and 113 (100) (Found: M^+ 212.1778. $C_{13}H_{24}O_2$ requires *M* 212.1764).

(2S*,9S*)-2-*Hydroxymethyl*-9-*pentyloxonane* **16c** *and* (2R*,9S*)-2-*Hydroxymethyl*-9-*pentyloxonane* **18c**.—The lactone **12c** (106 mg, 0.5 mmol) and DMAP (67.2 mg, 0.55 mmol) were dissolved in dry THF (2 cm^3) and the solution was degassed (3 × freeze-thaw) and cooled to −50 °C. The Tebbe reagent (1.5 cm^3 of a 0.335 mol dm^{-3} solution, 0.5 mmol) was added dropwise, and the reaction mixture was stirred at −40 °C for 30 min then allowed to warm to room temperature over 2.5 h. The reaction mixture was then cooled to −15 °C and aqueous sodium hydroxide (15% w/v; 0.3 cm^3) was added dropwise, and the resulting mixture was allowed to warm to room temperature. It was then poured into dry ether (over anhydrous Na_2SO_4) and filtered through a Celite plug. The filtrate was concentrated under reduced pressure below 30 °C and the residue was purified by passage down a neutral alumina column (grade III) with hexane. After evaporation of solvent the residue was dissolved in dry THF (10 cm^3) and borane-THF complex (2 cm^3; 1 mol dm^{-3}; 2 mmol) was added in one portion at 0 °C. After 20 min at 0 °C aqueous sodium hydroxide (1.2 cm^3; 3 mol dm^{-3}) and hydrogen peroxide (0.36 cm^3; 30% v/v) were added dropwise, and the reaction mixture was stirred at 0 °C for 90 min. The whole solution was poured into ether (50 cm^3) and washed with water (2 × 20 cm^3). The organic solution was dried ($MgSO_4$) and evaporated under reduced pressure to leave a residue which was purified by flash column chromatography on silica gel with 1% ethyl acetate in dichloromethane as eluent to give the cis-*alcohol* **16c** (4.9 mg, 4.3%) (the less polar isomer) and the trans-*alcohol* **18c** (45 mg, 39.5%) (the more polar isomer) as colourless oils.

Data for **16c** (Found: C, 73.5; H, 12.5. $C_{14}H_{28}O_2$ requires C, 73.63; H, 12.36%); ν_{max}(neat)/cm^{-1} 3420 (OH), 2940 (CH), 2860 (CH) and 1110 (CO); δ_H($CDCl_3$; 250 MHz) 3.53–3.46 (4 H, m, HOCH_2C*H*OC*H*), 2.10–1.24 (21 H, m, 10 × CH_2 and O*H*) and 0.87 (3 H, t, *J* 6.9, CH_3); δ_C(CD_3OD; 63 MHz) 82.59 and 82.37 (*C*HOCH), 66.51 (CH_2OH), 37.30, 33.42, 33.24, 31.35, 27.99, 27.66, 26.84, 24.18, 23.66, 23.61 (10 × CH_2) and 14.36 (CH_3); *m*/*z* 228 (M^+, 1.76%), 197 (70, M − CH_2OH), 157 (10, M − C_5H_{11}) and 95 (100) (Found: M^+, 228.2094. $C_{14}H_{28}O_2$ requires *M*, 228.2089).

Data for **18c** (Found: C, 73.9; H, 12.2. $C_{14}H_{28}O_2$ requires C, 73.63; H, 12.36%); ν_{max}(neat)/cm^{-1} 3420 (OH), 2940 (CH), 2860 (CH) and 1100 (CO); δ_H($CDCl_3$; 250 MHz) 3.68 (2 H, m, C*H*OC*H*CH_2OH), 3.48 (2 H, m, HOCH_2), 1.82–1.20 (21 H, m, 10 × CH_2 and O*H*) and 0.87 (3 H, t, *J* 6.5, CH_3); δ_C(CD_3OD; 63 MHz) 78.85 and 75.43 (*C*HOCH), 66.73 (HOCH_2), 36.71, 33.18, 32.49, 30.92, 28.20, 27.31 (2 C) 26.51, 25.90, 23.69, (10 × CH2) and 14.40 (CH_3); *m*/*z* 228 (M^+, 2.23%), 197 (100, M − CH_2OH) and 157 (18, M − C_5H_{11}) (Found: M^+ 228.2096. $C_{14}H_{28}O_2$ requires *M* 228.2089).

Equilibration of Alcohols **16c** *and* **18c** via *the Corresponding Aldehydes*.—The alcohol **18c** was oxidised with PCC to the corresponding aldehyde **22c** which was equilibrated in the presence of potassium carbonate in methanol as described in detail above for the aldehyde **20b**. The resulting mixture of aldehydes **20c** and **22c** was reduced with sodium borohydride to the mixture of alcohols **16c** and **18c** (ratio 4:1) which were separated as described above.

(2S*,9S*)-2-(3,5-*Dinitrobenzoyloxymethyl*)-9-*pentyloxonane*.—The *cis*-alcohol **16c** (6.2 mg, 0.0272 mmol) was dissolved in dry dichloromethane (2 cm^3) with DMAP (4 mg, 0.033 mmol) and 3,5-dinitrobenzoyl chloride (6.9 mg, 0.03 mmol) and the solution was stirred at room temperature for 14h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (Kieselgel, 1 mm), with 50% dichloromethane in hexane as eluent, to give the *title compound* (6.51 mg, 57%) as a green oil; ν_{max}(neat)/cm^{-1} 3100 (aromatic CH), 2930 (CH), 2860 (CH), 1735 (conjugated ester C=O), 1630 (aromatic), 1540 (CNO_2), 1340 (CNO_2) and 1080 (CO); δ_H($CDCl_3$; 250 MHz) 9.24 (1 H, t, *J* 2.1, NO_2CCH=CNO_2), 9.17 (2 H, d, *J* 2.1 remaining aromatic H's), 4.38 (2 H, m, COOCH_2CHOCH), 3.85 (1 H, m, COOCH_2C*H*OCH), 3.51 (1 H, m, CO_2CH_2CHOC*H*) 1.85–1.15 (20 H, m, 10 × CH_2) and 0.80 (3 H, t, *J* 6.6, CH_3); *m*/*z* 351 (9%, M − C_5H_{11}) and 55 (100).

(2S*,9R*)-2-(3,5-*Dinitrobenzoyloxymethyl*)-9-*pentyloxonane*.—The *trans*-alcohol **18c** (8.9 mg, 0.039 mmol), DMAP (5.7 mg, 0.047 mmol) and 3,5-dinitrobenzoyl chloride (9.9 mg, 0.042 mmol) were dissolved in dry dichloromethane (2 cm^3) and stirred at room temperature for 36 h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (Kieselgel, 1 mm), with 60% dichloromethane in hexane as eluent, to give the *title compound* (14.65 mg, 89%) as a green solid, m.p. 77–78 °C; ν_{max}($CHCl_3$)/cm^{-1} 3100 (aromatic CH), 2960 (CH), 2930 (CH), 2860 (CH), 1735 (conjugated ester C=O), 1630 (aromatic), 1550 (CNO_2), 1340 (CNO_2) and 1080; δ_H($CDCl_3$; 250 MHz) 9.23 (1 H, t, *J* 2.1, NO_2CCH=CNO_2), 9.16 (2 H, d, *J* 2.1, remaining aromatic H's), 4.42 (1 H, dd, *J* 11.3, 6.3, COOCH_AH_B), 4.29 (1 H, dd, *J* 11.3, 5.3, COOCH_AH_B), 4.0 (1 H, m, COOCH_AH_BC*H*OCH), 3.71 (1 H, m, COOCH_AH_B-CHOC*H*), 1.87–1.17 (20 H, m, 10 × CH_2) and 0.81 (3 H, t, *J* 6.6, CH_3); *m*/*z* 351 (6.8%, M − C_5H_{11}) and 55 (100).

(2R*,9S*)-2-*Pentyl*-9-*vinyloxonane* **25**.—The *trans*-alcohol **18c** (40 mg, 0.117 mmol) was dissolved in dry dichloromethane (2 cm^3) and dry 3Å molecular sieves (200 mg) and PCC (0.0567 g, 0.35 mmol) were added. The reaction mixture was stirred at room temperature for 1 h then ether (10 cm^3) added and the reaction mixture was filtered through a short column of Florisil with ether (3 column volumes). The solvent was removed under reduced pressure to leave a colourless oil which was added to a solution of methylenetriphenylphosphorane [prepared from methyltriphenylphosphonium bromide (0.285 g, 0.0008 mol) and butyllithium (0.46 cm^3 of a 1.6 mol dm^{-3} solution in

hexane)] in dry THF (10 cm^3) at room temperature and the resulting solution was stirred for 8 h. The reaction was quenched by the dropwise addition of water (10 cm^3), then the product was extracted into ether (3 × 30 cm^3), which was dried ($MgSO_4$); the solvent was evaporated under reduced pressure to leave a residue which was purified using flash column chromatography on silica gel, with 30% dichloromethane in hexane as eluent, to give the *alkene* **25** (15 mg, 40%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3070 (C=CH_2), 2930 (CH), 2860 (CH), 1630 (C=O) and 1130 (CO); $\delta_H(CDCl_3$; 250 MHz) 5.91 (1 H, ddd, *J* 17.2, 10.5, 6.5, C*H*=CH_2), 5.10 (1 H, d, *J* 17.4, CH=C*H*H), 5.05 (1 H, d, *J* 10.4, CH=CH*H*), 4.07 (1 H, m, CH_2=CHC*H*OCH), 3.59 (1 H, m, CH_2=CHCHOC*H*), 1.71–1.22 (20 H, m, 10 × CH_2) and 0.86 (3 H, t, *J* 6.7, CH_3); *m/z* 224 (M^+, 0.006%), 153 (12 , M − C_5H_{11}) and 84 (100). (Found: M^+, 224.2158. $C_{15}H_{28}O$ requires *M*, 244.2140).

(2S*,9S*)-2-*Ethyl*-9-*pentyloxonane* (*Obtusan*) **4**.—The alkene **25** (10 mg, 0.0446 mmol) was dissolved in ethyl acetate (5 cm^3), and 10% palladium on carbon catalyst (4 mg) was added. The reaction mixture was stirred under an atmosphere of hydrogen for 24 h then filtered through a Celite plug and concentrated under reduced pressure to give *obtusan* **4** (9.4 mg, 93%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2930 (CH), 2860 (CH) and 1100 (CO); $\delta_H(CDCl_3$; 250 MHz) 3.60–3.48 (2 H, m, C*H*OC*H*), 1.69–1.24 (22 H, m, 11 × CH_2), 0.89 (3 H, t, *J* 7.4, CH_3) and 0.87 (3 H, t, *J* 6.8, CH_3); $\delta_C(CDCl_3$; 63 MHz) 76.35 and 75.41 (*C*HOC*H*), 36.36, 32.17, 32.14, 31.78, 29.21, 26.44, 26.35, 26.03, 25.49, 25.35, 22.68 (11 × CH_2) 13.97 and 10.63 (2 × CH_3); *m/z* 226 (M^+, 4.51%), 197 (4, M − C_2H_5), 155 (9, M − C_5H_{11}) and 55 (100). (Found: M^+, 226.2308. $C_{15}H_{30}O$ requires *M*, 226.2296).

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