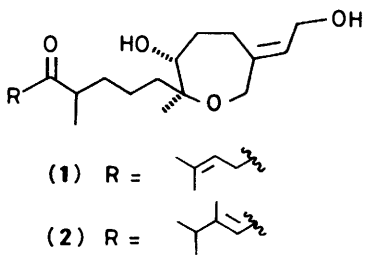
A Total Synthesis of Zoapatanol

Richard C. Cookson* and Nigel J. Liverton
Department of Chemistry, University of Southampton SO9 5NH

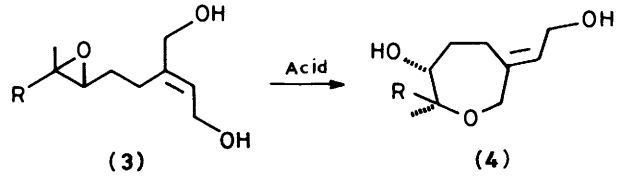
A key step in a new synthesis of zoapatanol involves stannic chloride catalysed isomerisation of the epoxy diol (**21**) to the oxepane (**22**) with inversion of configuration of the tertiary carbon atom. Differential protection of the hydroxy groups allows oxidation to the acid (**28**) followed by addition of the prenyl† group to complete the side-chain. An important step in construction of the intermediate epoxy diol (**21**) was the zirconium catalysed *cis*-addition of trimethylaluminium to the acetylene according to Negishi and reaction of the 'ate' complex with butyl-lithium with ethylene oxide to form the *E*-alcohol (**18**). The derived iodide (**13**) was used to alkylate the adduct of triphenylphosphine and diethyl maleate and the product reduced to the diol (**20**). Epoxidation of the diacetate occurred at the 6-double bond to give, after hydrolysis, the key epoxy diol (**21**).

Zoapatanol (**1**) and montanol (**2**), two structurally similar diterpenoids isolated from the zoapatle plant (*Montanoa tomentosa*)[1,2] have been shown to exhibit significant contragestational activity in several animal species.[3] This biological activity in conjunction with their novel structure prompted our interest in the synthesis of zoapatanol, the more active ot the two compounds.



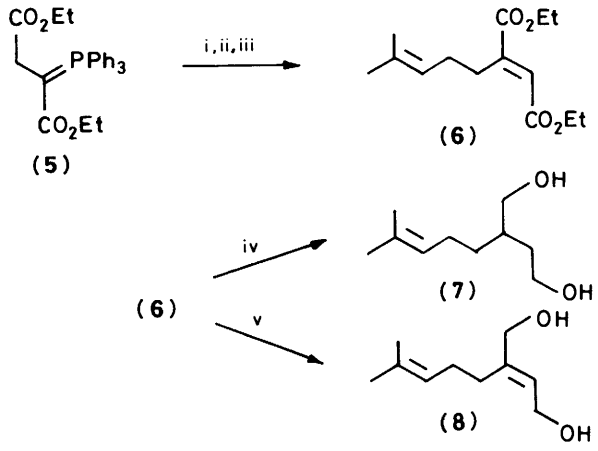
In particular, we desired a synthetic plan which would permit the preparation of reasonable quantities of both the natural product and analogues for biological evaluation. Since the outset of our work, other syntheses of zoapatanol have been reported.[4–6]

It was recognised at an early stage that the cornerstone of any successful synthesis would be the efficient construction of the oxepane ring with the desired substitution pattern. Our proposed method of ring formation centred on the acid catalysed cyclisation of an epoxy diol (**3**), although there were possible problems with the regiochemistry of the epoxide opening as well as competing rearrangement of the epoxide. With this in mind, we initially set out to synthesise a model compound (**4**; R=Me).



Towards this end, the anion of diethyl 2-triphenylphosphoranylidenebutanedioate (**5**) was alkylated with 5-iodo-2-methylpent-2-ene[7] to afford, after benzoic acid catalysed elimination of triphenylphosphine, the *E*-diester (**6**) in 54% yield along with *ca.* 20% of the *Z*-isomer.[8]

Reduction of the readily separable *E*-isomer with lithium aluminium hydride resulted in the formation of the saturated diol (**7**). Reduction of the conjugated double bond was suppressed completely by employing di-isobutylaluminium hydride (Dibal) which afforded the desired diol (**8**) in near quantitative yield (Scheme 1).



Scheme 1. *Reagents:* i, LDA/THF/−78 °C; ii, $Me_2C{:}CHCH_2CH_2I$; iii, $PhCO_2H$/PhMe/heat/3h; iv, $LiAlH_4$; v, Dibal/PhMe/−78 °C → −30 °C

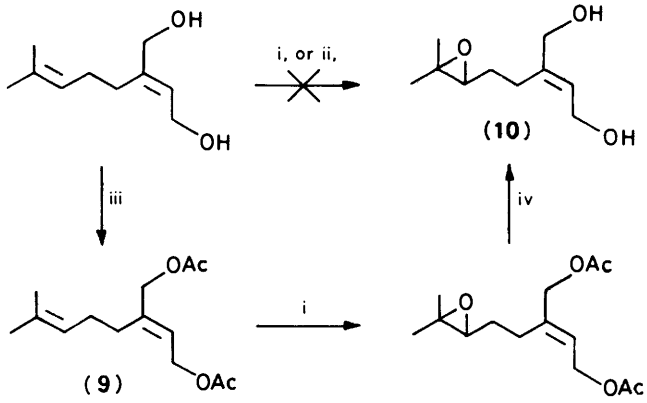
The resistance of the diol (**8**) to epoxidation was surprising; treatment with *m*-chloroperbenzoic acid in dichloromethane at room temperature led only to the recovery of starting material as did reaction with benzeneperoxyseleninic acid.[9] This problem was circumvented by protecting the hydroxy groups as the diacetate derivative (**9**) which was rapidly epoxidised to give, after removal of the acetate groups, the desired cyclisation precursor (**10**) (Scheme 2).

At this stage, Chen published[4] a synthesis of zoapatanol using a similar acid catalysed cyclisation to that envisaged by us. In our hands, however, treatment of the epoxide (**10**) with trifluoroacetic acid in dichloromethane afforded, after acylation, a 1:2 mixture of the oxepane (**11**) and tetrahydropyran (**12**). This somewhat disappointing result prompted us to examine the effect of using different acids and solvents. The results of these experiments are summarised in Table 1. Product

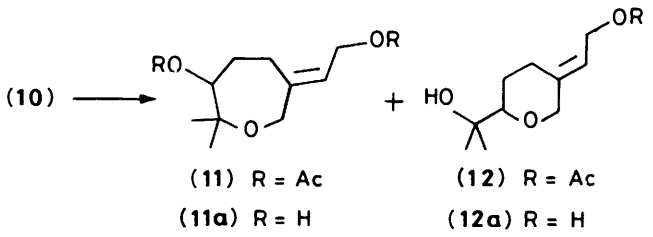
† Prenyl = $Me_2C{=}CHCH_2$

Table 1.

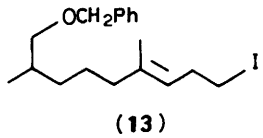
Acid	Solvent	Temp./Time	Ratio (**11a**):(**12a**)
CF_3CO_2H	CH_2Cl_2	20 °C/30 min	1:2
BF_3·Et_2O	CH_2Cl_2	20 °C/10 min	2:3
BF_3·Et_2O	CH_2Cl_2	−30 °C/10 min	2:3
BF_3·Et_2O	CH_2Cl_2	−60 °C/10 min	2:3
BF_3·Et_2O	THF	20 °C/10 min	2:1
$SnCl_4$	THF	20 °C/15 min	>20:1



Scheme 2. *Reagents:* i, *m*-CPBA, CH_2Cl_2; ii, $PhSeO_3H$, silica; iii, AcCl, NEt_3; iv, K_2CO_3, MeOH, room temp.

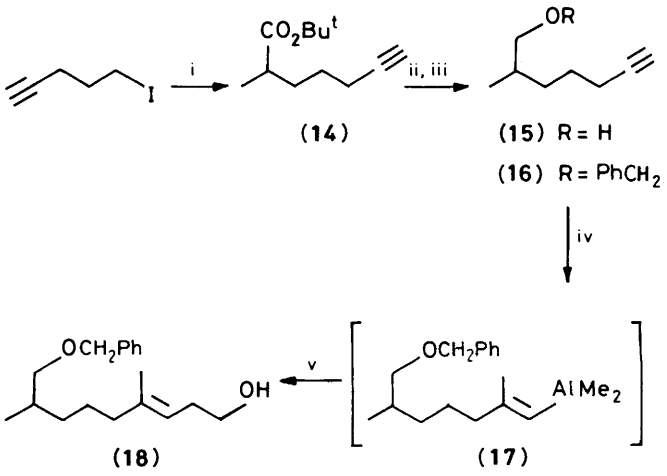


ratios were determined from the ^1H n.m.r. spectrum of the crude material, in which the *gem*-dimethyl groups of the starting epoxide and both products all have different chemical shifts. The success of the stannic chloride induced cyclisation augured well for the synthesis of zoapatanol, although a loss of stereochemistry in the cyclisation step could not be ruled out at this stage. To achieve a synthesis of zoapatanol, the homoallylic iodide (**13**) was a key intermediate.



(**13**)

Its preparation commenced with the alkylation in 85% yield of the enolate of t-butyl propionate with 5-iodopent-1-yne[10] in the presence of 0.5 equiv. of hexamethylphosphoramide (HMPA). Straightforward reduction of the acetylenic ester (**14**) with lithium aluminium hydride and subsequent benzylation of the resulting alcohol (**15**) gave the terminal acetylene (**16**) in 81% yield. Metallation of the acetylene with 'methylcopper'[11] proved unsuccessful, but alumination with trimethylaluminium in the presence of bis(cyclopentadienyl)zirconium dichloride proceeded smoothly.[12] Conversion of the intermediate vinyl alane (**17**) into the desired homoallylic alcohol (**18**) was achieved by formation of the more reactive aluminate with n-butyl-lithium, followed by quenching with ethylene oxide[13] in 62% overall yield (Scheme 3).



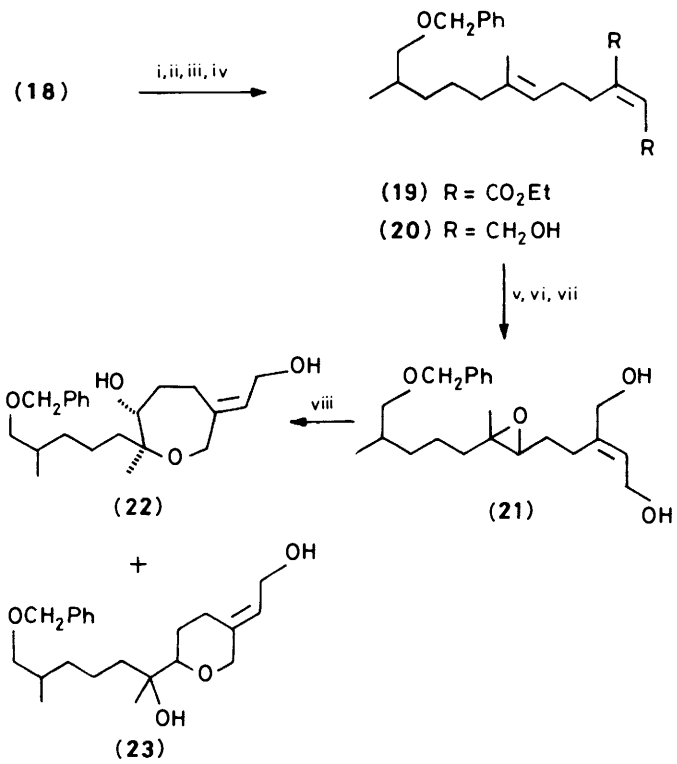
Scheme 3. *Reagents:* i, $CH_3\bar{C}HCO_2Bu^t$, THF, HMPA, −78 °C → room temp.; ii, $LiAlH_4$, Et_2O; iii, (a) NaH, DMF 0 °C (b) $PhCH_2Br$, 0 °C → room temp.; iv, Me_3Al, $[Zr(cp)_2]Cl_2$, $ClCH_2CH_2Cl$, room temp.; v, (a) Bu^nLi, −78 → −30 °C (b) ethylene oxide.

Conversion of the alcohol (**18**) into the iodide (**13**) was accomplished in near quantitative yield by formation of the mesylate and subsequent displacement with sodium iodide.

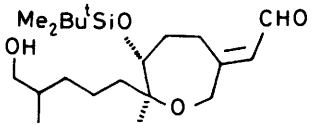
Application of the same strategy as that employed in the model compound synthesis proceeded uneventfully to give the epoxide (**21**). Cyclisation with stannic chloride was slightly less successful than in the case of the model compound, leading to an 8:1 mixture of the desired oxepane derivative (**22**) and the corresponding tetrahydropyran derivative (**23**). This was offset by the high yield of the conversion [65—70% overall from (**13**) to (**22**)] as well as the observation that the product contained only one methyl group singlet indicating that the epoxide opening had occurred stereospecifically, presumably with inversion.

To permit elaboration of the side-chain of zoapatanol, the hydroxy groups were protected as their dimethyl-t-butylsilyl ethers by treatment with dimethyl-t-butylsilyl trifluoromethanesulphonate and 2,6-dimethylpyridine. Selective deprotection of the benzyl ether of (**24**) in the presence of two allylic ether linkages proved problematic; Pd–H_2 resulted in concomitant reduction of the double bond and $PdCl_2$–H_2 gave a mixture of polar products. Some success was achieved on brief treatment with lithium in ammonia at −78 °C but the yields were only moderate (*ca.* 50%) and inconsistent. By modifying this procedure, consistent yields of 75—80% based on recovered starting material were attainable. Thus the benzyl ether was treated at −78 °C with small portions of a solution of lithium in ammonia. After decolourisation of the reaction mixture, t.l.c. of an aliquot was carried out. Quenching was then performed at *ca.* 60% conversion to avoid the formation of more polar products arising from allylic ether cleavage.

With the alcohol (**25**) in hand, oxidation was attempted using pyridinium dichromate;[14] however, the primary allylic silyl ether proved unstable, oxidising readily to the α,β-unsaturated aldehyde (**26**) isolated at a 1:1 *E*/*Z* mixture. As an alternative, the alcohol (**25**) was oxidised to the corresponding aldehyde (**27**) with pyridinium chlorochromate on alumina[15] and subsequent treatment with silver(I) oxide[16] afforded the carboxylic



Scheme 4. *Reagents:* i, MsCl, NEt_3, CH_2Cl_2; ii, NaI, Me_2CO, room temp.; iii, (a) (5), LDA, (b) $PhCO_2H$, PhMe heat, 3h; iv, Dibal, PhMe; v, AcCl/NEt_3; vi, *m*-CPBA, CH_2Cl_2; vii, K_2CO_3, MeOH; viii, $SnCl_4$, THF, room temp.



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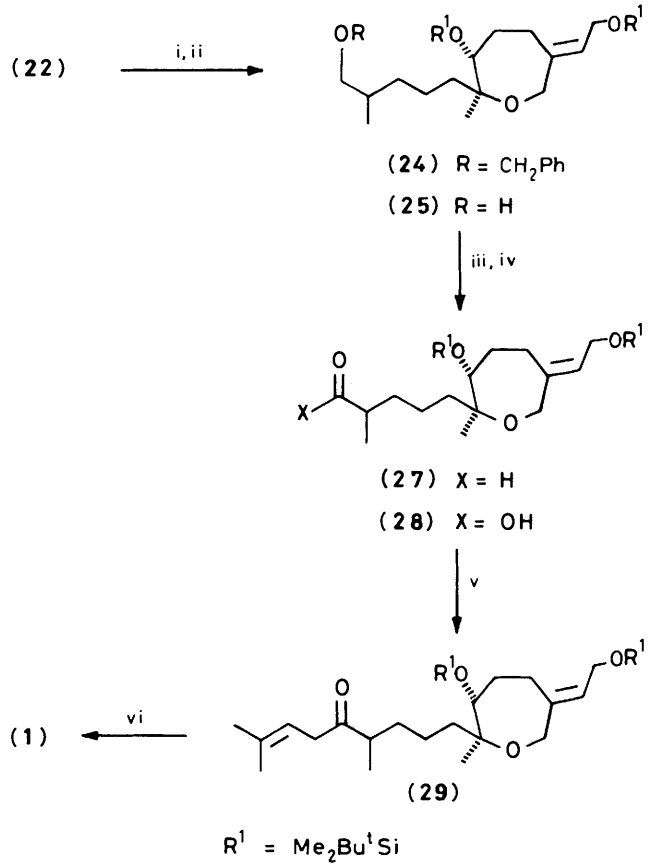

Scheme 5. *Reagents:* i, Dimethyl-t-butylsilyltrifluoromethanesulphonate, 2,6-dimethylpyridine, CH_2Cl_2; ii, Li, NH_3, THF, −75 °C; iii, PCC, Al_2O_3, CH_2Cl_2, room temp.; iv, $AgNO_3$, NaOH, MeOH, EtOH; v, dimethylallyl-lithium, THF, Et_2O, room temp.; vi, 25% HF, MeCN, room temp.

acid (**28**) in 75% overall yield. Addition of dimethylallyllithium[17] to the acid gave the desired β,γ-unsaturated ketone moiety (**29**) in 55% yield, providing that the lithium reagent was centrifuged under argon before use to remove insoluble lithium salts.

Completion of the synthesis now required only cleavage of the silyl ethers which occurred in 80% yield upon treatment with 25% hydrofluoric acid in acetonitrile[18] (Scheme 5).

The overall yield of the synthesis (4.9%) and the number of steps (17) compare favourably with the other published syntheses. The ready availability of the aldehyde (**27**) allows the introduction of a wide range of other groups in order to assess some structure activity relationships. The importance of this R group is shown by the relatively large difference in biological activity between zoapatanol and montanol.

Experimental

General.—^{1}H N.m.r. spectra were recorded in $CDCl_3$ at 60 MHz on a Perkin-Elmer R12 or R24B or at 100 MHz on a Varian Associates XL100/30 spectrometer with tetramethylsilane as internal standard. Chemical shifts are quoted as δ-values. I.r. spectra were recorded on a Perkin-Elmer 157G or 298 spectrometer either in $CHCl_3$ solution or as a liquid film. Mass spectra were recorded on a Kratos MS30 spectrometer with Digispec DS55 data system. E.i. spectra were run at 25 or 70 eV as indicated and c.i. spectra were run with ammonia as the carrier gas.

Tetrahydrofuran (THF) and diethyl ether (referred to as ether) were dried by distillation from sodium–benzophenone. Other reagents and solvents were purified by known procedures.[19] Petroleum refers to light petroleum, boiling range 40—60 °C. Analytical t.l.c. was carried out on precoated silica gel (Macherey-Nagel G25 UV_{254}) plates. Flash column chromatography[20] was performed using Macherey-Nagel Kieselgel 60 (230—400 mesh). All compounds were homogeneous by t.l.c.

(2E)-*Ethyl* 3-*Ethoxycarbonyl*-7-*methylocta*-2,6-*dienoate* (**6**).—Diethyl 2-triphenylphoranylidenebutanedioate (2.17 g, 5 mmol) in dry THF was added dropwise to a stirred solution of lithium di-isopropylamide (5.5 mmol) in dry THF (20 ml) at − 78 °C under nitrogen. After being stirred for 15 min, 5-iodo-2-methylpent-2-ene (1.05 g, 5.5 mmol) in dry THF was added. The reaction mixture was then allowed to warm to room temperature over 15 h, poured into saturated ammonium chloride solution, and extracted with ether (3 × 25 ml). The combined extracts were washed with brine (25 ml), dried, and the solvent evaporated. The residue was dissolved in toluene (40 ml) containing benzoic acid (0.67 g, 5.5 mmol) and heated under reflux for 3 h. After cooling to room temperature, the mixture was poured into saturated aqueous sodium bicarbonate (30 ml)

and extracted with dichloromethane (3 × 25 ml). The combined extracts were shaken with brine (25 ml), dried, and the solvent evaporated to give, after flash column chromatography (dichloromethane–petroleum, 1:1), the diester (**6**) (547 mg, 54%); $\nu_{max.}$ 1 720, 1 450, 1 370, 1 270, 1 210, and 1 170; δ 6.75 (1 H, s, =CH), 4.25, 4.27 (6 H, 2 × q, 2 × CH_2O), 2.8 (2 H, m, 4-H_2), 2.2 (2 H, br t, 5-H_2), 1.60, 1.66 (6 H, t, 2 × MeC), and 1.3 (6 H, t, 2 × $MeCH_2$); *m/z* (70 eV) 254 (3.2, M^+), 209 (5.6), 180 (14), 140 (24), 112 (28), 107 (21), and 69 (100) (Found: M^+, 254.16. Calc. for $C_{14}H_{22}O_4$: *M*, 254.15).

(2E)-3-*Hydroxymethyl*-7-*methylocta*-2,6-*dien*-1-*ol* (**8**).—Di-isobutylaluminium hydride in toluene (1.5M; 2.2 ml, 3.3 mmol) was added to a stirred solution of the diester (**6**) (196 mg, 0.77 mmol) in dry toluene (10 ml) at −78 °C under argon. The reaction mixture was stirred for 1 h and warmed to −30 °C over 3 h, before the addition of ether (10 ml), water (0.1 ml), 2M-aqueous sodium hydroxide (0.1 ml), and water (0.3 ml). The mixture was stirred for 15 min, filtered, and the precipitate washed with ether (6 × 10 ml). The filtrate was dried and the solvent evaporated to give the diol (**8**) (125 mg, 95%); $\nu_{max.}$ 3 375 (OH), 1 460s, 1 380m, 1 090m, and 1 020s; δ5.64 (1 H, t, *J* 7 Hz, 2-H), 5.12 (1 H, br t, 6-H), 4.4 (2 H, s, 2 × OH), 4.17 (2 H, d, *J* 7 Hz, 1-H_2), 4.02 (2 H, br s, 9-H_2), 2.1 (4 H, m, 4-H_2 and 6-H_2), and 1.60 and 1.66 (6 H, 2 × br s, 2 × Me); *m/z* (70 eV) 170 (0.5, M^+), 139 (5.0), 121 (6.5), 109 (13), 70 (11), 69 (100), 55 (15), and 41 (48) (Found: M^+, 170.15. Calc. for $C_{10}H_{18}O_2$: *M*, 170.13).

(2E)-3-*Hydroxymethyl*-7-*methyl*-6,7-*epoxyoct*-2-*en*-1-*ol* (**10**).—Acetyl chloride (1.4 ml, 20 mmol) was added dropwise to a stirred solution of the diol (**8**) (1.53 g, 9.0 mmol) and triethylamine (4.2 ml, 30 mmol) in dry THF (30 ml) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature over 1 h, poured into saturated aqueous sodium hydrogen carbonate (100 ml) and extracted with ether (3 × 25 ml). The combined extracts were washed with water (25 ml) and brine (25 ml), dried, and the solvent evaporated to give the diacetate (**9**) (2.22 g). This was dissolved in dichloromethane (20 ml) and *m*-chloroperbenzoic acid (1.85 g, 9.1 mmol) added. The mixture was stirred at room temperature for 2 h and then poured into saturated aqueous sodium hydrogen carbonate (40 ml) and the phases separated. The aqueous phase was extracted with dichloromethane (3 × 20 ml) and the combined extracts dried and the solvent evaporated to give the epoxy diacetate (2.44 g, 98%); this was dissolved in dry methanol (30 ml) at 0 °C containing anhydrous potassium carbonate (4.6 g, 33 mmol). The mixture was stirred for a further 20 min and then concentrated (to *ca.* 5 ml) and partitioned between ether (25 ml) and water (50 ml). The phases were separated and the aqueous phase extracted with ether (3 × 25 ml). The combined extracts were washed with brine (25 ml), dried, and the solvent evaporated, to give, after flash column chromatography (dichloromethane–methanol, 9:1), the epoxy diol (**10**) (1.39 g, 83%); $\nu_{max.}$ (liquid film) 3 400 (OH), 1 460m, 1 380m, 1 080m, and 1 000m; δ 5.7 (1 H, br t, *J* 7 Hz, 2-H), 4.15 (4 H, m, 1-H_2 and 9-H_2), 3.8 (2 H, br s, 2 × OH), 2.75 (1 H, t, *J* 7 Hz, 6-H), 2.25 (2 H, m, 4-H_2) 1.7 (2 H, m, 5-H_2), and 1.26 and 1.30 (6 H, 2 × s, 2 × Me); *m/z* (70 eV) 125 (25), 110 (23), 97 (50), 95 (44), 86 (45), 84 (100), 83 (52), 82 (62), 81 (62), 71 (56), 57 (68), and 55 (71).

(6E)-2,2-*Dimethyl*-6-(2-*hydroxyethylidene*)*oxepan*-3-*ol* (**11a**).—Stannic chloride (0.1 ml, 0.8 mmol) was added to a stirred solution of the epoxy diol (**10**) (150 mg, 0.8 mmol) in dry THF (10 ml) under nitrogen. After 15 min, triethylamine (1.0 ml) was added, the reaction mixture filtered through Celite and the solvent evaporated to give the diol (**11a**) (130 mg, 85%); $\nu_{max.}$ 3 400 (OH), 1 450m, 1 370m, 1 160m, and 1 040s; δ 5.42 (1 H, br t, *J* 7 Hz, =CH), 4.20 (4 H, m, 2 × CH_2-O), 3.55 (3 H, m, 2 × OH and 3-H), 2.3 (2 H, m, 5-H_2), 1.8 (2 H, m, 4-H_2), and 1.21 and 1.25 (6 H, 2 × s, 2 × Me); *m/z* (70 eV) 153 (3.2), 111 (12), 110 (74), 95 (36), 82 (61), 81 (51), 68 (100), and 59 (53).

t-Butyl 2-*Methylhept*-6-*ynoate* (**14**).—t-Butyl propionate (28.6 g, 220 mmol) was added dropwise to a stirred solution of LDA (240 mmol) in dry THF (300 ml) at −78 °C under nitrogen. Stirring was continued at this temperature for 45 min before the dropwise addition of 5-iodopent-1-yne (43.0 g, 220 mmol) in dry hexamethylphosphoramide (19.0 ml, 110 mmol) over 30 min. The mixture was stirred at −78 °C for 1 h and then allowed to warm slowly to room temperature over 15 h. Water (250 ml) and ether (150 ml) were added, the two phases separated, and the aqueous phase extracted with ether (3 × 150 ml). The combined extracts were washed with water (2 × 200 ml) and brine (100 ml) and dried. Evaporation of the solvent and distillation at reduced pressure gave the ester (36.3 g, 85%); $\nu_{max.}$ 3 300m, 2 110w, 1 730s, and 1 150s; δ 2.1—2.6 (3 H, m, 2-H, 5-H_2), 1.95 (1 H, t, *J* 2.5 Hz, 7-H), 1.4—1.6 (4 H, m, 2 × CH_2) and 1.45 (9 H, s, Bu^t) and 1.1 (3 H, t, *J* 7 Hz, Me); *m/z* (70 eV) 181 (0.2, M^+ − Me), 123 (11), 95 (17), 67 (7), 57 (100), 56 (6.2), and 55 (6.3).

2-*Methylhept*-6-*yn*-1-*ol* (**15**).—A solution of the ester (**14**) (32 g, 163 mmol) in dry ether (200 ml) was added dropwise over 30 min to a stirred suspension of lithium aluminium hydride (5.11 g, 134 mmol) in dry ether (300 ml) cooled to 0 °C under nitrogen. Stirring was continued for a further 1 h, before the careful consecutive addition of water (5.1 ml), 2M-aqueous sodium hydroxide (5.1 ml), and water (15.3 ml). The mixture was stirred vigorously for 15 min and then filtered and the precipitate washed with ether (8 × 50 ml). The filtrate was dried and the solvent evaporated to give the alcohol (19.2 g, 94%), b.p. 88—91 °C at 15 mmHg); $\nu_{max.}$ 3 350 (OH), 3 300s, 2 120w, 1 470m, and 1 030s; δ 3.47 (2 H, d, *J* 6 Hz, CH_2O), 2.45 (1 H, br s, OH), 2.2 (2 H, m, 5-H_2), 1.95 (1 H, t, *J* 2.5 Hz, 7-H), 1.2—1.8 (5 H, m) and 0.92 (3 H, d, *J* 6 Hz, Me); *m/z* 111 (3.2), 109 (0.8), 95 (54), 93 (29), 79 (29), 67 (65), and 55 (100).

7-*Benzyloxy*-6-*methylhept*-1-*yne* (**16**).—Sodium hydride (50% dispersion in oil; 1.90 g, 40 mmol) was washed with petroleum (3 × 10 ml), the last traces of solvent being removed with a stream of dry nitrogen. Dry dimethylformamide (50 ml) was then added and the stirred suspension cooled to 0 °C under nitrogen, before the dropwise addition of a solution of the alcohol (**15**) (4.5 g, 36 mmol) in dry dimethylformamide (5 ml). After 1 h, benzyl bromide (4.3 ml, 36 mmol) was added over 5 min, the reaction mixture allowed to warm to room temperature over 3 h and stirred for a further 12 h. Water (20 ml) was added carefully and the reaction mixture poured into water (500 ml) and extracted with ether (3 × 100 ml). The combined extracts were washed with water (2 × 100 ml) and brine (100 ml) and dried. Evaporation of the solvent gave, after flash column chromatography (petroleum–ether, 10:1), the benzyl ether (6.6 g, 85%), $\nu_{max.}$ (liquid film) 3 300m, 2 120w, 1 450m, 1 360m, 1 100s, 730s, and 630s; δ 7.33 (5 H, s, Ph), 4.48 (2 H, s, CH_2Ph), 3.27 (2 H, d, *J* 6 Hz, 1-H_2), 2.2 (2 H, m, 5-H_2), 1.95 (1 H, t, *J* 2.5 Hz, 7-H), 1.2—1.8 (5 H, m), and 0.95 (3 H, d, *J* 7 Hz); *m/z* (70 eV) 215 (0.1), 107 (5.2), 95 (8.6), 92 (21), 91 (100), and 55 (10).

(3E)-9-*Benzyloxy*-4,8-*dimethylnon*-3-*en*-1-*ol* (**18**).—Trimethylaluminium (25% in hexane; 17 ml, 44 mmol) was added to a stirred solution of zirconiumbis(cyclopentadienyl) dichloride (2.45 g, 8.4 mmol) in dry 1,2-dichloroethane (50 ml) under argon. The benzyl ether (**16**) (4.68 g, 22 mmol) in dry 1,2-dichloroethane (5 ml) was added to the yellow solution and the reaction mixture stirred at room temperature for 15 h. All the volatiles were removed under reduced pressure (0.1 mmHg, 0—

50 °C over 4 h) and the residue extracted with hexane (3 × 10 ml); the extracts were transferred by cannula to a second flask under argon and dry THF (30 ml) added. The solution was cooled to −78 °C, n-butyl-lithium (15.6 ml, 24 mmol) was added over 5 min, and the reaction mixture allowed to warm to −30 °C over 1 h. Ethylene oxide (3 ml) was distilled into the reaction mixture and after a further 4 h at −30 °C, ether (20 ml) and water (100 ml) were added carefully. The aqueous phase was acidified to pH 3 with 2M-HCl and extracted with ether (3 × 30 ml). The combined extracts were washed with brine (50 ml) and dried. Evaporation of the solvent gave, after flash column chromatography (1:2 petroleum–ether) the homoallylic alcohol (**18**) (3.75 g, 62%); $\nu_{max.}$ (liquid film) 3 400 (OH), 1 450m, 1 100s, 730s and 690s; δ 7.33 (5 H, s, Ph), 5.12 (1 H, br t, 3-H), 4.50 (2 H, s, CH_2Ph), 3.60 (2 H, t, CH_2OH), 3.27 (2 H, d, *J* 6 Hz, 9-H_2), 1.7 (1 H, br s, OH), 1.62 (3 H, br s, 4-Me), 1.2—2.5 (9 H, m), and 0.95 (3 H, d, *J* 7 Hz, 8-Me); *m/z* (70 eV) 276 (M^+, 0.8), 246 (5.0), 109 (8.1), 107 (10), 95 (14), 92 (11), 91 (100), and 85 (26) (Found: M^+, 276.23. Calc. for $C_{18}H_{28}O_2$: *M*, 276.21).

(3E)-9-*Benzyloxy*-1-*iodo*-4,8-*dimethylnon*-3-*ene* (**13**).—Methanesulphonyl chloride (3.4 ml, 44 mmol) was added dropwise to a stirred solution of the alcohol (**18**) (11.39 g, 41 mmol) and triethylamine (6.32 ml, 45 mmol) in dry dichloromethane (125 ml) at −5 °C under nitrogen. Stirring was continued for 1 h, and saturated aqueous sodium bicarbonate (100 ml) was added. The phases were separated and the aqueous phase extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with brine, dried, and the solvent evaporated. The resultant oil was dissolved in dry acetone (200 ml) containing dry sodium iodide (35 g, 230 mmol) and the mixture stirred at room temperature in the dark for 15 h. Most of the acetone was removed under reduced pressure and the residue poured into water and extracted with petroleum (3 × 100 ml). The combined extracts were washed with water (2 × 75 ml) and brine (75 ml), dried, and the solvent evaporated to give the iodide (**13**) (15.84 g, 99%); $\nu_{max.}$ (liquid film) 1 450m, 1 100s, 730s, and 690s; δ 7.35 (5 H, s, Ph), 5.10 (1 H, br t, 3-H), 4.52 (2 H, s, CH_2Ph), 3.27 (2 H, d, 9-H_2), 3.11 (2 H, t, *J* 7 Hz, CH_2I), 2.6 (2 H, m, 2-H_2), 1.8—2.2 (2 H, m, 5-H_2), 1.60 (3 H, s, 4-Me), 1.2—1.8 (5 H, m), and 0.95 (3 H, d, *J* 7 Hz, 8-Me); *m/z* (70 eV) 386 (M^+, 1.8), 295 (2.1), 277 (8.4), 95 (13), 92 (9.5), 91 (100), and 85 (23).

(2E,6E)-*Ethyl* 12-*Benzyloxy*-3-*ethoxycarbonyl*-7,11-*dimethyldodeca*-2,6-*dienoate* (**19**).—A solution of the phosphorane (**5**) (9.00 g, 20.7 mmol) in dry THF (30 ml) was added dropwise over 15 min to a stirred solution of LDA (23.2 mmol) in dry THF (100 ml) at −78 °C under nitrogen. After the blood red solution had been stirred for a further 15 min at this temperature, the iodide (**13**) (7.8 g, 20.2 mmol) was added. The reaction mixture was then allowed to warm to room temperature over 15 h. Saturated aqueous ammonium chloride solution (100 ml) and dichloromethane (75 ml) were added, the phases separated, and the aqueous phase extracted with dichloromethane (3 × 40 ml). The combined extracts were washed with brine (50 ml), dried, and the solvent evaporated. The resulting oil was dissolved in toluene (125 ml) containing benzoic acid (2.7 g, 22 mmol) and the mixture heated under reflux for 3 h. Saturated aqueous sodium hydrogen carbonate (100 ml) was added to the cooled solution, the phases separated, and the aqueous phase extracted with dichloromethane (2 × 30 ml). The combined extracts were washed with brine (50 ml), dried, and the solvent evaporated to give, after flash column chromatography (gradient elution 15:1 petroleum–ether to 4:1 petroleum–ether), the *E*-diester (**19**) (5.45 g, 64%); $\nu_{max.}$ (liquid film) 1 720s, 1 450m, and 1 250s; δ 7.35 (5 H, s, Ph), 6.75 (1 H, s, 2-H), 5.18 (1 H, br t, *J* 7 Hz, 6-H), 4.52 (2 H, s, CH_2Ph), 4.24, 4.28 (4 H, 2 × q, 2 × CH_2Me), 3.24, 3.32 (2H, AB of ABX, J_{AX}, J_{BX}, J_{AB}, 7,7, and 9 Hz, 12-H_2) 2.85 (2 H, br t, 4-H_2), 1.8—2.3 (4 H, m), 1.60 (3 H, s, 7-Me), 1.2—1.7 (11 H, m), and 0.95 (3 H, d, *J* 7 Hz, 11-Me); *m/z* (70 eV) 430 (M^+, 0.1), 385 (0.3), 339 (4.6), 247 (5.8), 105 (6.9), 95 (6.9), 92 (8.5), 91 (100), 85 (25), and 81 (13) (Found: M^+, 430.26. Calc. for $C_{26}H_{38}O_5$: *M*, 430.27).

(2E,6E)-12-*Benzyloxy*-3-*hydroxymethyl*-7,11-*dimethyldodeca*-2,6-*dien*-1-*ol* (**20**).—Di-isobutylaluminium hydride (1.5M in toluene; 29 ml, 43.5 mmol) was added dropwise to a stirred solution of the diester (**19**) (4.42 g, 10.3 mmol) in dry toluene (100 ml) at −78 °C under argon. The reaction was allowed to warm to −30 °C over 1 h, before the sequential addition of ether (75 ml), water (2 ml) 2M-aqueous sodium hydroxide (2 ml), and water (6 ml). The mixture was stirred vigorously for 15 min, and then filtered and the precipitate washed with ether (7 × 25 ml). The filtrate was washed with brine (50 ml), dried, and the solvent evaporated to give the diol (**20**) (3.74 g, 97%); $\nu_{max.}$ (liquid film) 3 350 (OH), 1 460m, 1 090s, 1 020s, 740m, and 700m; δ 7.35 (5 H, s, Ph), 5.65 (1 H, br t, *J* 7 Hz, 2-H), 5.15 (1 H, br t, 6-H), 4.50 (2 H, s, CH_2Ph), 4.19 (2 H, br d, 1-H_2), 4.07 (2 H, br s, CH_2OH), 3.27 (2 H, d, 12-H_2), 1.8—2.2 (8 H, m), 1.60 (3 H, br s, 7-Me), 1.2—1.7 (5 H, m), and 0.95 (3 H, d, *J* 7 Hz, 11-Me); *m/z* (c.i., NH_3) 364 (M^+ + 18, 1.5), 347 (0.3), 311 (17), 219 (13), 203 (10), 109 (12), 91 (100), and 81 (12) (Found: M^+ + NH_4), 364.28. Calc. for $C_{22}H_{38}NO_3$: *M*, 364.28).

(2E)-12-*Benzyloxy*-3-*hydroxymethyl*-7,11-*dimethyl*-6,7-*epoxydec*-2-*en*-1-*ol* (**21**).—Acetyl chloride (1.8 ml, 25 mmol) was added dropwise to a stirred solution of the diol (**20**) (3.74 g, 10 mmol) and triethylamine (4.9 ml, 35 mmol) in dry THF (40 ml) at −20 °C under nitrogen. The reaction mixture was allowed to warm to room temperature over 1 h, before the addition of ether (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The phases were separated and the aqueous phase extracted with ether (3 × 25 ml). The combined extracts were washed with brine (50 ml), dried, and the solvent evaporated to give the diacetate (4.07 g, 99%) which was dissolved in dichloromethane (35 ml) at 0 °C. To the stirred solution was added a solution of *m*-chloroperbenzoic acid (1.98 g, 9.5 mmol) in dichloromethane (15 ml). After 1 h, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution (50 ml) and extracted with dichloromethane (3 × 25 ml). The combined extracts were washed with brine (50 ml), dried, and the solvent evaporated to give the epoxy diacetate (4.20 g, 94%). This was dissolved in dry methanol (50 ml) at 0 °C and anhydrous potassium carbonate (3.5 g, 25 mmol) added. The mixture was stirred at 0 °C for 1 h and then filtered and the solid residues washed with methanol (2 × 20 ml). The filtrate was concentrated (to *ca.* 20 ml), poured into water, and extracted with ether (4 × 40 ml). The combined extracts were washed with brine (30 ml), dried, and the solvent evaporated to give the epoxy diol (**21**) (3.3 g, 97%); $\nu_{max.}$ (liquid film) 3 400 (OH), 1 450s, 1 100s, 1 080s, 1 020s, 740m, and 700m; δ 7.35 (5 H, s, Ph), 5.70 (1 H, br t, *J* 7 Hz, 2-H), 4.55 (2 H, s, CH_2Ph), 4.0—4.3 (4 H, m, 2 × CH_2OH), 3.6 (2 H, br s, 2 × OH), 3.3 (2 H, d, *J* 6 Hz, 12-H_2), 2.75 (1 H, t, *J* 7 Hz, 6-H), 2.0—2.3 (2 H, m, 4-H_2), 1.3—1.8 (9 H, m), 1.26 (3 H, s, 7-Me), and 0.95 (3 H, d, *J* 7 Hz, 11-Me); *m/z* (c.i. NH_3) 380 (M^+ + NH_4, 0.5), 345 (12), 109 (13), 108 (10), 92 (11), 91 (100), 84 (40), and 83 (51) (Found: M^+ + NH_4, 380.25. Calc. for $C_{22}H_{38}NO_4$: *M*, 380.28).

(6E)-2-(5-*Benzyloxy*-4-*methylpentyl*)-6-(2-*hydroxyethylidene*)-2-*methyl*-*oxepan*-3-*ol* (**22**) *and* (3E)-6-(6-*Benzyloxy*-1,5-*dimethyl*-1-*hydroxyhexyl*)-3-(2-*hydroxyethylidene*)*tetrahydropyran* (**23**).—Stannic chloride (1.1 ml, 9.4 mmol) was added dropwise to dry THF (110 ml) under nitrogen. After 5 min, a solution of the epoxide (**21**) (3.86 g, 9.3 mmol) in dry THF (10

ml) was added over 5 min. The reaction mixture was stirred at room temperature for 30 min, poured into saturated aqueous sodium hydrogen carbonate (150 ml) and extracted with ether (4 × 40 ml). The combined extracts were washed with brine (50 ml), dried, and the solvent evaporated to give after flash column chromatography (ethyl acetate–petroleum, 8:1), the oxepane (**22**) (2.65 g, 79%) and the pyran (**23**) (220 mg, 7%); (**22**) $\nu_{max.}$ (liquid film) 3 400 (OH), 1 100s, 1 070s, 1 030m, 740m, and 700m; δ 7.35 (5 H, s, Ph), 5.45 (1 H, br t, *J* 7 Hz, =CH), 4.50 (2 H, s, CH_2Ph), 4.1—4.3 (4 H, m, 2 × CH_2O), 3.44 (1 H, m, CHOH), 3.27 (2 H, d, CH_2O), 2.2—2.6 (2 H, m, 5-H_2), 1.25—2.0 (11 H, m), 1.17 (3 H, s, 2-Me), and 0.95 (3 H, d, *J* 7 Hz, CH*Me*); *m/z* (c.i. NH_3) 380 (M^+ + 18, 18), 346 (16), 345 (69), 144 (20), 127 (12), 108 (46), and 91 (100) (Found: M^+ + NH_4, 380.26. Calc. for $C_{22}H_{38}NO_4$: *M*, 380.28); (**23**) $\nu_{max.}$ (liquid film) 3 400 (OH), 1 450m, 1 370m, 1 100 (br s), 730m, and 690m; δ 7.35 (5 H, s, Ph), 5.44 (1 H, br t, *J* 7 Hz, =CH), 4.50 (2 H, s, CH_2Ph), 3.9—4.3 (4 H, m, 2 × CH_2O), 3.15—3.4 (3 H, m, CHO and CH_2O), 2.74 (1 H, br d, *J* 14 Hz, one of 4-H_2), 2.0—2.4 (3 H, m, one of 4-H_2 and 2 × OH), 1.25—2.0 (9 H, m), 1.14 (3 H, s, MeCO), and 0.95 (3 H, d, *J* 7 Hz, *Me*CH); *m/z* (CI, NH_3) 380 (M^+ + NH_4, 3.0), 363 (3.6), 345 (42), 327 (16), 235 (32), 108 (30), 91 (100), and 81 (17) (Found: M^+ + NH_4, 380.31. Calc. for $C_{22}H_{38}NO_4$: *M*, 380.28).

(6E)-2-(5-*Benzyloxy*-4-*methylpentyl*)-3-*dimethyl*-*t*-*butylsilyl*-*oxy*-6-2-*dimethyl*-*t*-*butylsilyloxyethylidene*-2-*methyloxepane* (**24**).—Dimethyl-t-butylsilyl trifluoromethanesulphonate (3.6 ml, 15.7 mmol) was added dropwise to a stirred solution of the diol (**22**) (2.38 g, 6.6 mmol) and 2,6-dimethylpyridine (2.4 ml, 20.6 mmol) in dry dichloromethane (60 ml) at −20 °C under nitrogen. After 20 min, the mixture was poured into saturated aqueous sodium hydrogen carbonate (150 ml). The two phases were separated and the aqueous phase extracted with dichloromethane (3 × 25 ml). The combined extracts were washed with cold 5% hydrochloric acid (100 ml) and brine (50 ml) and dried. Evaporation of the solvent and flash column chromatography (petroleum–ether 10:1) gave the protected diol (**24**) (3.64 g, 95%); $\nu_{max.}$ (liquid film) 1 470m, 1 260m, 1 100s, 840s, 740m, and 700m; δ 7.35 (5 H, s, Ph), 5.4 (1 H, br t, *J* 7 Hz, =CH), 4.55 (2 H, s, CH_2Ph), 4.25 (2 H, d, *J* 7 Hz, =CHCH_2O), 4.1 (2 H, br s, CH_2O), 3.6 (1 H, dd, *J* 8.4 Hz, CHOSi), 3.35 (2 H, d, *J* 6 Hz, CHCH_2O), 2.0—2.6 (2 H, m, 5-H_2), 1.3—2.0 (9 H, m), 1.15 (3 H, s, 2-Me), 1.1 (21 H, br s, *Me*CH and 2 × Bu^t, and 0.15 (12 H, s, 4 × MeSi); *m/z* (25 eV) 533 (0.5), 458 (0.9), 401 (1.6), 349 (2.9), 299 (7.6), 224 (10), 167 (23), 147 (38), 93 (100), 91 (81), 75 (45), and 73 (72).

(6E)-3-*Dimethyl*-*t*-*butylsilyloxy*-6-(2-*dimethyl*-*t*-*butylsilyl*-*oxyethylidene*)-2-(5-*hydroxy*-4-*methylpentyl*)-2-*methyloxepane* (**25**).—A solution of lithium (50 mg, 7 mmol) in ammonia (30 ml) was added in small portions (*ca.* 0.5 ml) to a stirred solution of the benzyl ether (**24**) (410 mg, 0.7 mmol) in dry THF (4 ml) and ammonia (30 ml) at −78 °C. After each addition, the reaction was examined by t.l.c. and when it was judged to be *ca.* 60% complete, aqueous ammonia (*d* 0.880; 10 ml) was added carefully. The mixture was warmed to room temperature, poured into water (20 ml), and extracted with ether (3 × 20 ml). The combined extracts were washed with water (20 ml) and brine (20 ml) and then dried and the solvent evaporated. Flash column chromatography afforded the alcohol (**25**) (189 mg, yield based on recovered starting material 85%); $\nu_{max.}$ (liquid film) 3 350 (OH), 1 460m, 1 250m, 1 090br s, and 840s; δ 5.40 (1 H, br t, *J* 7 Hz, =CH), 4.26 (2 H, br d, *J* 7 Hz, =CHCH_2O), 4.10 (2 H, br s, CH_2O), 3.4—3.6 (3 H, m, CHOSi and 2 × OH), 2.0—2.6 (2 H, m, =CCH_2), 1.2—1.9 (10 H, m), 1.14 (3 H, s, 2-Me), 0.92 (21 H, br s, *Me*CH and 2 × Bu^t) and 0.15 (12 H, s, 4 × MeSi); *m/z* (c.i., NH_3) 518 (M^+ + NH_4, 15), 501 (10), 370 (30), 369 (100), 311 (11), 237 (58), and 93 (62) (Found: M^+ + NH_4, 518.38. Calc. for $C_{27}H_{60}NO_4Si_2$: *M*, 518.41).

(6E)-3-*Dimethyl*-*t*-*butylsilyloxy*-6-(2-*dimethyl*-*t*-*butylsilyl*-*oxy*-*ethylidene*)-2-*methyl*-2-(4-*methyl*-5-*oxopentyl*)*oxepane* (**27**).—Pyridinium chlorochromate on alumina (7.8 g, 7.8 mmol) was added to a stirred solution of the alcohol (**25**) (1.25 g, 2.5 mmol) in dry dichloromethane (20 ml) under argon. Stirring was continued at room temperature for 4 h, after which the reaction mixture was filtered and the solid residues washed with dichloromethane (3 × 30 ml). The filtrate was concentrated (to *ca.* 10 ml), diluted with ether (25 ml), and refiltered through Celite; the precipitate was washed with ether (25 ml). Evaporation of the solvent gave the aldehyde (**27**) (1.11 g, 90%); $\nu_{max.}$ (liquid film) 2 720w, 1 730s, 1 450m, 1 240m, and 1 070br s; δ 9.7 (1 H, br s, CHO), 5.40 (1 H, br t, *J* 7 Hz, =CH), 4.19 (2 H, d, *J* 7 Hz, CH_2OSi), 4.10 (2 H, br s, CH_2O), 3.60 (1 H, dd, *J* 8.4 Hz, CHOSi), 2.0—2.6 (3 H, m), 1.3—2.0 (8 H, m), 1.15 (3 H, d, *J* 7 Hz, *Me*CH), 1.15 (3 H, s, 2-Me), 0.93 (18 H, s, 2 × Bu^t), and 0.15 (12 H, s, 4 × MeSi); *m/z* (c.i., NH_3) 516 (M^+ + NH_4, 13), 441 (13), 367 (59), 309 (14), 235 (19), 211 (14), 199 (15), 167 (25), 147 (15), 94 (14), 93 (100), 75 (33), 74 (34), and 73 (53) (Found: M^+ + NH_4, 516.43. Calc. for $C_{27}H_{58}NO_4Si_2$: *M*, 516.39).

(6E)-3-*Dimethyl*-*t*-*butylsilyloxy*-6-(2-*dimethyl*-*t*-*butylsilyl*-*oxy*-*ethylidene*)-2-(4-*carboxypentyl*)-2-*methyloxepane* (**28**).—To a stirred solution of silver nitrate (1.02 g, 6 mmol) and the aldehyde (**27**) (950 mg, 2 mmol) in methanol (19 ml) and ethanol (28 ml) was added 2M-aqueous sodium hydroxide solution (2.9 ml, 8.7 mmol) at room temperature under nitrogen. The mixture was stirred for a further 1 h after which it was filtered and the solid residue washed with methanol (10 ml). The filtrate was poured into water and extracted with ether (2 × 20 ml). The aqueous phase was then acidified to pH5 with dilute hydrochloric acid and re-extracted with ether (4 × 20 ml). The combined extracts were washed with brine, dried, and the solvent evaporated to give the carboxylic acid (**28**) (810 mg, 83%); $\nu_{max.}$($CHCl_3$) 2 500—3 500 (OH), 1 710m, 1 250m, 1 100s, and 830s; δ 9.7 (1 H, br s, CO_2H), 5.40 (1 H, br t, *J* 7 Hz, =CH), 4.23 (2 H, d, *J* 7 Hz, CH_2OSi), 4.10 (2 H, br s, CH_2O), 3.53 (1 H, dd, *J* 8.4 Hz, CHOSi), 2.0—2.6 (3 H, m), 1.3—1.9 (8 H, m), 1.20 (3 H, d, *J* 7 Hz, *Me*CH), 1.14 (3 H, s, 2-Me), 0.90 (18 H, s, 2 × Bu^t), and 0.12 (12 H, s, 4 × MeSi); *m/z* (c.i., NH_3) 532 (M^+ + NH_4, 0.2), 502 (4.6), 353 (10), 221 (6.2), 82 (4.0), and 35 (100) (Found: M^+ + NH_4, 532.41. Calc. for $C_{27}H_{58}NO_5Si_2$, *M*, 532.39).

(6E)-3-*Dimethyl*-*t*-*butylsilyloxy*-6-(2-*dimethyl*-*t*-*butylsilyl*-*oxyethylidene*)-2-(4,8-*dimethyl*-5-*oxonon*-7-*enyl*)-2-*methyl*-*oxepane* (**29**).—To a stirred solution of 3-methylbut-2-enyl phenyl ether (0.75 g, 4.6 mmol) in dry ether (3 ml) and dry THF (3 ml) under argon were added small pieces of lithium (1.0 g), followed by two drops of methanol. At the first appearance of a green colouration, the reaction mixture was cooled to 5 °C and stirred for a further 2 h. Centrifugation of the reagent thus obtained gave a clear orange solution. This was added to a stirred solution of the acid (**28**) (87 mg, 0.17 mmol) in dry ether (3 ml), until a yellow colour persisted. After a further 5 min, the reaction mixture was added dropwise to vigorously stirred aqueous methanol (15 ml). Ether (30 ml) and water (40 ml) were added, the phases separated, and the aqueous phase extracted with ether (3 × 10 ml). The combined extracts were washed with brine (20 ml), dried, and the solvent evaporated to give, after flash column chromatography (petroleum–ether, 6:1) the ketone (**29**) (51 mg, 54%); $\nu_{max.}$ (liquid film) 1 710s, 1 460m, 1 250s, 1 080s, 830s, 770s, and 730s; δ 5.4 (2 H, m, 2 × =CH), 4.24 (2 H, d, *J* 7 Hz, CH_2OSi), 4.12 (2 H, , br s, CH_2O), 3.54 (1 H, dd, *J* 8.4 Hz, CHOSi), 3.12 (2 H, br d, *J* 7 Hz, CH_2C=O), 2.0—

2.6 (3 H, m), 1.68, 1.81 (6 H, 2 × s, 2 × MeC=), 1.3—1.8 (8 H, m), 1.15 (3 H, s, 2-Me), 1.09 (3 H, d, *J* 7 Hz, MeCH), 0.92 (18 H, s, 2 × Bu^t), and 0.15 (12 H, s, 4 × MeSi); *m/z* (30 eV) 479 (0.2), 405 (0.4), 353 (1.5), 299 (3.4), 224 (4.7), 167 (18), 147 (29), 93 (100), 75 (45), 73 (63), and 69 (13).

Zoapatanol (**1**).—A solution of the ketone (**29**) (75 mg, 0.13 mol) and 40% hydrofluoric acid (1.0 ml) in acetonitrile (3 ml) was stirred at room temperature for 2 h. The mixture was poured into saturated aqueous sodium hydrogen carbonate (20 ml) and extracted with ether (4 × 15 ml). The combined extracts were washed with brine (10 ml), dried, and the solvent evaporated to give, after flash column chromatography (ethyl acetate), zoapatanol (35 mg, 80%); $\nu_{max.}$ (liquid film) 3 400 (OH), 1 710s, 1 440m, and 1 030s; δ 5.2—5.6 (2 H, m, 2 × =CH), 4.1—4.3 (4 H, m, 2 × CH_2O), 3.53 (1 H, m, C*H*OH), 3.14 (2 H, d, *J* 7 Hz, CH_2C=O), 2.0—2.7 (5 H, m), 1.65, 1.77 (6 H, 2 × s, 2 × MeC=), 1.2—1.8 (8 H, m), 1.16 (3 H, s, MeCO), and 1.09 (3 H, d, *J* 7 Hz, *Me*CH) (identical with a spectrum kindly provided by Professor K. C. Nicolaou); *m/z* (25 eV) 320 (0.8), 303 (0.6), 285 (1.0), 251 (5.5), 149 (17), 141 (41), 125 (23), 113 (58), 97 (44), 95 (34), 81 (30), 69 (57), 55 (43), and 43 (100).

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