Use of Diazophosphonates in the Synthesis of Cyclic Ethers. Part 2.[1] Synthesis of the Pyranooxepane and Oxepanooxepane Subunits of Marine Polyether Toxins

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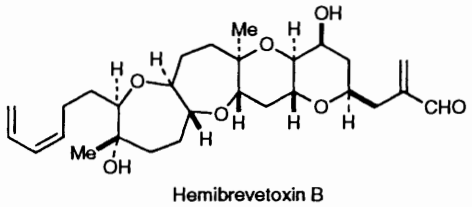
3-Oxooxepan-2-ylphosphonates **3**, prepared by rhodium carbenoid cyclisation of the diazophosphonates **1**, are readily elaborated into the keto alcohols **6**, by Wadsworth–Emmons reaction, hydrogenation and epimerisation. Cyclisation of **6** using trimethylsilyl triflate–triethylsilane results in formation of 7-6- and 7-7-bicyclic ethers **10**, with *trans* selectivity.

In recent years a number of biologically active polyether toxins, such as the brevetoxins,[2] ciguatoxins,[3,4] gambiertoxins[5–7] and maitotoxin,[8] have been isolated from marine organisms. The structural complexity of these molecules has attracted the attention of synthetic chemists, and many new methods for the synthesis of cyclic ethers have been developed over the last few years.[9] With the polycyclic structure of the marine toxins in mind, several new synthetic methods, most notably those arising from the Nicolaou group,[10] have been aimed at bi-, tri- and tetra-cyclic systems containing 6-, 7-, 8- and 9-membered cyclic ethers,[11–22] and recently this has culminated in Nicolaou's total synthesis of hemibrevetoxin **B**.[23–25]



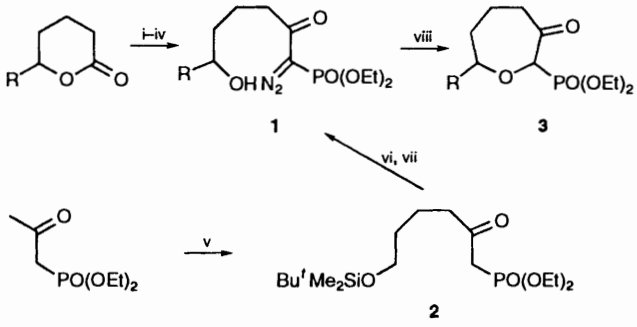
Hemibrevetoxin B

Our own interest in cyclic ether synthesis has centred on the use of rhodium carbenoid cyclisations as a route to 7- and 8-membered rings,[26–32] and on the use of diazophosphonates and the intramolecular Wadsworth–Emmons reaction.[1,33] We now report an extension of this methodology which allows the synthesis of the 7-6- and 7-7-bicyclic subunits (pyranooxepane and oxepanooxepane) of marine polyether toxins.

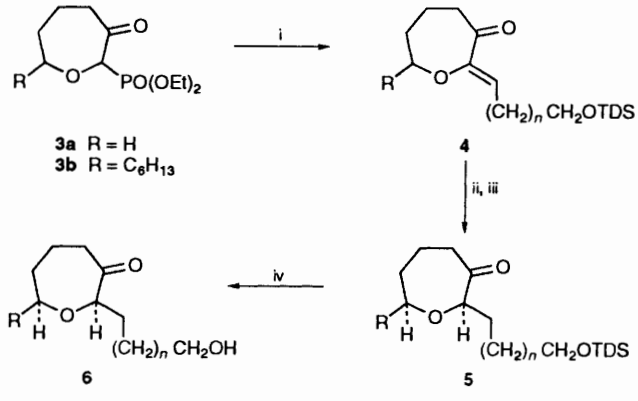
Results and Discussion

The starting materials were the diazophosphonates **1**, prepared on a 5 g-scale from δ-valerolactone or undecanoic acid δ-lactone as previously described.[29,31] The diazophosphonate **1a** was also prepared by alkylation of the dianion of diethyl 2-oxopropylphosphonate with the *tert*-butyldimethylsilyl ether of 3-iodopropanol, followed by diazo-transfer and deprotection (Scheme 1). The diazophosphonates **1** cyclised smoothly to the 3-oxooxepan-2-ylphosphonates **3** on treatment with rhodium(II) acetate in refluxing benzene.[29,31]

The oxepane-2-ylphosphonates **3** were readily converted into the precursors for the second cyclisation—the keto alcohols **6**—using standard chemistry as shown in Scheme 2. Thus, Wadsworth–Emmons reaction with the thexyldimethylsilyl (TDS) ethers of 3-hydroxypropanal, 4-hydroxybutanal or 5-hydroxypentanal gave the oxepanes **4** in satisfactory yield (51–76%). Hydrogenation, followed, in the case of **4b–d**, by



Scheme 1 [**a**, R = H; **b**, R = C_6H_{13}] *Reagents and conditions:* i, $LiCH_2PO(OEt)_2$; THF, −78 °C; LDA (1 equiv.), Me_3SiCl (2 equiv.); ii, aq. NH_4Cl; iii, MsN_3, Et_3N, CH_2Cl_2; iv, H_3O^+; v, NaH, BuLi, THF, 0 °C; then $Bu^tMe_2SiOCH_2CH_2CH_2I$; vi, NaH, TsN_3, THF; vii, aq. AcOH, THF; viii, $Rh_2(OAc)_4$, benzene, heat.

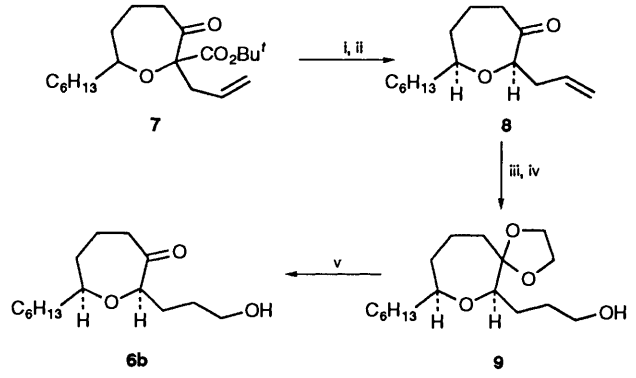


Scheme 2 [for **4–6**; **a** R = H, *n* = 2; **b** R = C_6H_{13}, *n* = 1; **c** R = C_6H_{13}, *n* = 2; **d** R = C_6H_{13}, *n* = 3] *Reagents and conditions:* i, NaH, THF, $OHC(CH_2)_nCH_2OTDS$; ii, Pd-C, EtOAc; iii, cat. NaOMe, MeOH; iv, 5% aq. HCl, EtOH

epimerisation of the isomer mixture with a catalytic amount of sodium methoxide gave the oxepanes **5** (66–98% over the 2 steps). Presumably, the initial isomer mixture (*ca.* 2:1 *cis*:*trans*) obtained in the hydrogenation is readily epimerised to the thermodynamically favoured *cis*-2,7-disubstituted oxepanes **5b–d** in which both groups are pseudo-equatorial. Finally, removal of the TDS group using dilute hydrochloric acid in ethanol gave the desired oxepane keto alcohols **6** (58–78%).

The oxepane **6b** was also prepared in a different manner starting from the *tert*-butyl 3-oxooxepane-2-carboxylate **7**, obtained by palladium-catalysed allylation of *tert*-butyl 7-

hexyl-3-oxooxepane-2-carboxylate as previously described.[32] Removal of the *tert*-butyl ester by heating at 150 °C in the presence of a catalytic amount of toluene-*p*-sulfonic acid (PTSA),[34] followed by base-mediated epimerisation gave *cis*-2-allyl-7-hexyloxepanone **8**, the *cis*-stereochemistry being confirmed by NOE difference spectroscopy. Protection of the ketone (63%), followed by hydroboration–oxidation of the allyl group (61%), and subsequent hydrolysis of the ketal (74%) gave the oxepane **6b** (Scheme 3).

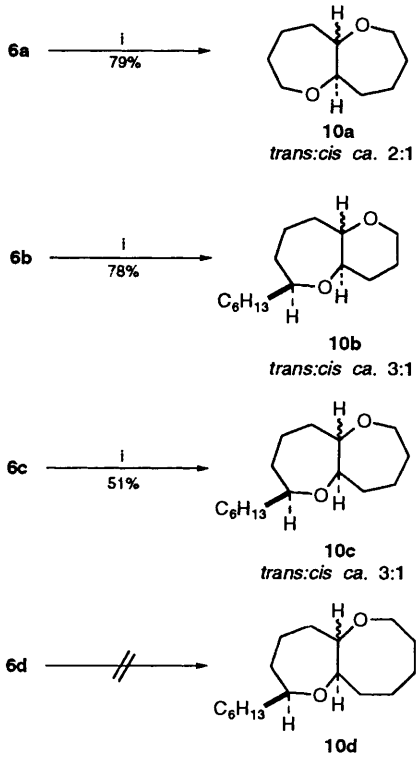


Scheme 3 *Reagents and conditions:* i, PTSA, heat; ii, cat. NaOMe, MeOH; iii, ethane-1,2-diol, PTSA, toluene, heat; iv, BH_3–THF then NaOH, H_2O_2; v, H_2O^+

On treatment with trimethylsilyl triflate and triethylsilane in dichloromethane at 0 °C, conditions developed by Olah [35] and used to great effect by Nicolaou,[36] the oxepane keto alcohols **6a–c** readily cyclised to bicyclic ethers. Thus, the oxepanes **6a** and **6c** gave the 7-7-bicyclic oxepanooxepanes **10a** and **10c** (79 and 51% respectively) and the oxepane **6b** gave the 7-6-bicyclic pyrano-oxepane **10b** (78%) (Scheme 4). Attempts to prepare the 7-8 bicyclic system **10d** from oxepane **6d** were unsuccesful.

The bicyclic ethers **10** are formed as mixtures of *cis*/*trans*-isomers, with the *trans*-isomer predominating in every case. The isomeric ratio was determined by NMR spectroscopy, and, in the case of **10c**, the isomers were separated by careful chromatography. The major (less polar) isomer was shown to have *trans*-ring fusion by NOE difference experiments (Fig. 1a). Thus pre-irradiation of the multiplet at δ 3.31–3.36 (10a-H) resulted only in enhancement of the signal at δ 3.62–3.76 (2-Hb), whilst pre-irradiation at δ 3.22–3.28 (5a-H) enhanced only the signal at δ 3.41–3.46 (7-H). The observed *trans*-selectivity in the triethylsilane trimethylsilyl triflate cyclisations, which has also been noted by Nicolaou in related cyclisations, presumably originates from the selective reduction of the oxonium intermediate (in its bicyclic chair-chair form) by the silane [Fig. 1(*b*)].

The relationship between *trans*-**10c** (Fig. 1(*a*)) and hemibrevetoxin **B** is clear, and studies towards the synthesis of analogues of **10c** containing additional functionality for further transformations are in progress.



Scheme 4 *Reagents and conditions:* i, Me_3SiOTf, Et_3SiH, CH_2Cl_2, 0 °C

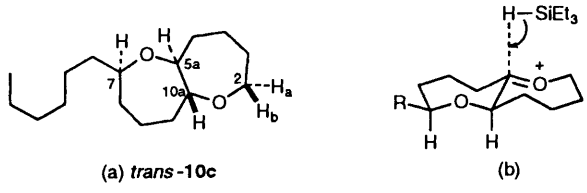


Fig. 1

Experimental

For general experimental points, see ref. 1. Compounds characterised by high resolution mass spectrometry were chromatographically homogeneous.

Preparation of Diazophosphonates.—Diethyl (1-diazo-6-hydroxy-2-oxohexyl)phosphonate **1a**

(a) This was prepared as previously described,[31] or, alternatively, as follows.

(b) A solution of diethyl 2-oxopropylphosphonate (1.50 g, 7.73 mmol) in THF (10 cm^3) was added dropwise to a suspension of sodium hydride (80%; 0.28 g, 9.28 mmol) in THF (60 cm^3) at 0 °C. After being stirred for 1.5 h at room temperature, the reaction mixture was cooled to −10 °C and a solution of butyllithium in hexanes (1.6 mol dm^{-3}; 5.8 cm^3, 9.28 mmol) was added dropwise to it. The reaction mixture was stirred for 20 min at 0 °C, after which 3-*tert*-butyldimethylsiloxy-1-iodopropane (7.73 mmol) was added to it and stirring continued for 1 h at 0 °C. The reaction was then quenched by the careful addition of water (60 cm^3) to the mixture. This was followed by the addition of ether (60 cm^3) after which the aqueous phase was extracted with ether (3 × 40 cm^3). The combined ethereal extracts were washed with brine (80 cm^3), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica to yield *diethyl (6-tert-butyldimethylsiloxy-2-oxohexyl)phosphonate* **2** (63%) (Found: M + H^+, 367.2070. $C_{16}H_{35}O_5PSi$ + H requires 367.2070); ν_{max}(film)/cm^{-1} 2952, 2928, 2856, 1714, 1256, 1096, 1028, 970, 838 and 778; δ_H(360 MHz; $CDCl_3$) 0.04 (6 H, s, $SiMe_2$), 0.89 (9 H, s, Bu^{t}Si), 1.34 (6 H, t, *J* 7.0, OCH_2Me), 1.47–1.55 (2 H, m, $COCH_2CH_2$), 1.60–1.66 (2 H, m, CH_2CH_2O), 2.65 (2 H, t, *J* 7.0, $COCH_2$), 3.07 (2 H, d, *J* 22.7, PCH_2CO), 3.61 (2 H, t, *J* 6.3, CH_2OSi) and 4.08–4.19 (4 H, m, OCH_2Me); *m*/*z* (Cl^+) 384 (M + NH_4^+, 100%), 367 (MH^+, 80), 325 (8) and (M^+–Bu^t, 11).

A solution of the above phosphonate (6.58 mmol) in THF (10 cm^3) was added dropwise to a suspension of sodium hydride (80%; 0.22 g, 7.24 mmol) in THF (50 cm^3) at 0 °C. After the mixture had been stirred for 45 min, tosyl azide (1.43 g, 7.24 mmol) was added dropwise to it. The reaction mixture was then

stirred at 0 °C for 2 h after which ether (60 cm^3) and water (60 cm^3) were added to it. The aqueous phase was extracted with ether (3 × 40 cm^3) and the combined organic extracts were washed with brine (60 cm^3), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (ether–hexane) to yield *diethyl* (6-tert-*butyldimethylsiloxy*-1-*diazo*-2-*oxohexyl*)-*phosphonate* (69%) (Found: M + H^+, 393.1980. $C_{16}H_{33}N_2O_5PSi$ + H requires 393.1975); ν_{max}(film)/cm^{-1} 2931, 2121, 1659, 1257, 1164, 1101, 1048, 1019, 975, 837 and 777; δ_H(360 MHz; $CDCl_3$) 0.04 (6 H, s, $SiMe_2$), 0.89 (9 H, s, Bu^t), 1.38 (6 H, t, *J* 7.0, OCH_2Me), 1.50–1.58 (2 H, m, $COCH_2CH_2$), 1.66–1.74 (2 H, m, CH_2CH_2O), 2.58 (2 H, t, *J* 7.2, $COCH_2$), 3.61 (2 H, t, *J* 6.3, CH_2OSi) and 4.12–4.26 (4 H, m, OCH_2Me); δ_C(62.9 MHz; $CDCl_3$) −5.31 ($SiMe_2$), 16.13 (OCH_2Me), 16.23 (OCH_2Me), 18.33 (C-Si), 20.79 ($COCH_2CH_2$), 25.95 (Bu^t), 32.24 (CH_2CH_2OSi), 39.20 ($COCH_2$), 62.74 (CH_2OSi), 63.42 (OCH_2Me), 63.51 (OCH_2Me) and 192.82 (1 C, d, *J* 13.0, C=O); *m*/*z* (CI^+) 393 (MH^+, 25%), 365 ($MH^+ - N_2$, 100), 337 (6), 307 ($MH^+ - N_2$ – Bu^t, 31), 279 (12), 233 (13), 189 (29) and 108 (6).

Deprotection of the above silyl ether using aqueous acetic acid in THF under standard conditions gave the title compound **1a** (68%), with spectroscopic properties identical with those of the sample prepared by the alternative route.

Diethyl(1-*diazo*-6-*hydroxy*-3-*oxodocecyl*)*phosphonate* **1b**. This was prepared as previously described.[31]

Preparation of Oxepan-2-ylphosphonates.—*Diethyl* 3-*oxooxepan*-2-*ylphosphonate* **3a**. This was prepared as previously described.[31]

Diethyl 7-*hexyl*-3-*oxooxepan*-2-*ylphosphonate* **3b**. This was prepared as previously described.[31]

Preparation of 2-*Alkylidene oxepanones* **4**: *General Procedure.*—Sodium hydride (80%; 0.23 g, 7.78 mmol) was added to a solution of the oxepanylphosphonate **3** (5.99 mmol) in THF (80 cm^3) at 0 °C, after which the mixture was stirred for 30 min. The appropriate dimethylthexylsiloxyalkanal (0.01 mol) was then added to it and the solution allowed to warm to room temperature overnight. Ether (80 cm^3) and water (80 cm^3) were then added to the mixture and the aqueous phase extracted with ether (3 × 50 cm^3). The combined ethereal extracts were washed with brine (80 cm^3), dried ($MgSO_4$) and evaporated and the residue chromatographed on silica (light petroleum–ether) to yield the respective 2-alkylidene-3-oxooxepane as a colourless oil.

2-(4-*Dimethylthexylsiloxybutylidene*)*oxepan*-3-*one* **4a** (51%) (Found: M + H^+, 327.2355. $C_{18}H_{34}O_3Si$ + H requires 327.2355); ν_{max}(film)/cm^{-1} 2952, 2864, 1694, 1628, 1324, 1250, 1150, 1056, 830 and 776; δ_H(250 MHz; $CDCl_3$) 0.08 (6 H, m, $SiMe_2$), 0.84–0.97 (13 H, m, Si-thex), 1.56–1.92 (6 H, m, 5-CH_2, 6-CH_2 and $CHCH_2CH_2$), 2.20–2.29 (2 H, m, $CHCH_2$), 2.64–2.69 (2 H, m, 4-CH_2), 3.60 (2 H, t, *J* 6.3, CH_2OSi), 4.11–4.14 (2 H, m, 7-CH_2) and 6.08 (1 H, t, *J* 7.7, C=$CHCH_2$); *m*/*z* (CI^+) 327 (MH^+, 66%), 243 (100), 167 (25), 151 (25), 91 (18), 74 (21) and 55 (13).

2-(3-*Dimethylthexylsiloxypropylidene*)-7-*hexyloxepan*-3-*one* **4b**. (63%) (Found: M + H^+, 397.3138. $C_{23}H_{44}O_3Si$ + H requires 397.3138); ν_{max}(film)/cm^{-1} 2952, 2860, 1694, 1630, 1326, 1252, 1098, 1058, 832 and 778; δ_H(250 MHz; $CDCl_3$) 0.08 (6 H, s, $SiMe_2$), 0.82–0.89 (16 H, m, Si-thex and Me), 1.26 [8 H, br s, $Me(CH_2)_4$], 1.26–1.84 [6 H, m, 5-CH_2, 6-CH_2 and $(CH_2)_4CH_2$], 2.39–2.48 (3 H, m, $CHCH_2$ and 4-CHH), 2.78 (1 H, dt, *J* 2.9, 12.2, 4-CHH), 3.40–3.55 (1 H, m, 7-CH), 3.65 (2 H, dt, *J* 1.7, 6.7, CH_2OSi) and 6.01 (1 H, t, *J* 7.5, C=$CHCH_2$); *m*/*z* (CI^+) 413 (M + NH_4^+, 29%), 397 (MH^+, 100), 311 (9), 273 (9), 261 (19), 241 (24), 202 (26), 185 (18) and 92 (19).

2-(4-*Dimethylthexylsiloxybutylidene*)-7-*hexyloxepan*-3-*one* **4c** (76%) (Found: M + H^+, 411.3294. $C_{24}H_{46}O_3Si$ + H requires 411.3294); ν_{max}(film)/cm^{-1} 2952, 1694, 1626, 1464, 1326, 1250, 1098, 828, 776 and 656; δ_H(250 MHz; $CDCl_3$) 0.08 (6 H, s, $SiMe_2$), 0.84–0.91 (16 H, m, Me and Si-thex), 1.29 [8 H, br s, $Me(CH_2)_4$], 1.29–1.64 [8 H, m, $CHCH_2CH_2$, $(CH_2)_4CH_2$, 5-CH_2 and 6-CH_2], 2.20–2.39 (2 H, m, $CHCH_2$), 2.42–2.58 (1 H, m, 4-CHH), 2.78 (1 H, dt, *J* 2.6, 12.6, 4-CHH), 3.36–3.47 (1 H, m, 7-CH), 3.61 (2 H, t, *J* 6.3, CH_2OSi) and 6.00 (1 H, t, *J* 7.6, C=$CHCH_2$); *m*/*z* (CI^+) 411 (MH^+, 5%), 327 (3), 247 (41), 233 (100), 185 (34), 88 (26) and 71 (31).

2-(5-*Dimethylthexylsiloxypentylidene*)-7-*hexyloxepan*-3-*one* **4d** (47%) (Found: M + H^+, 425.3451. $C_{25}H_{48}O_3Si$ + H requires 425.3451); ν_{max}(film)/cm^{-1} 2932, 2860, 1694, 1626, 1464, 1326, 1250, 1174, 1098, 830 and 776; δ_H(250 MHz; $CDCl_3$) 0.08 (6 H, s, $SiMe_2$), 0.84–0.91 (16 H, m, Me and Si-thex), 1.29 [8 H, br s, $Me(CH_2)_4$], 1.29–1.64 [10 H, m, $CHCH_2CH_2CH_2$, $(CH_2)_4CH_2$, 5-CH_2 and 6-CH_2], 2.20–2.39 (2 H, m, $CHCH_2$), 2.42–2.58 (1 H, m, 4-CHH), 2.78 (1 H, dt, *J* 2.6, 12.6, 4-CHH), 3.36–3.47 (1 H, m, 7-CH), 3.61 (2 H, t, *J* 6.3, CH_2OSi) and 6.00 (1 H, t, *J* 7.6, C=$CHCH_2$); *m*/*z* (CI^+) 425 (MH^+, 25%), 407 (21), 341 (100), 265 (50), 241 (33), 169 (25), 145 (21) and 92 (19).

Hydrogenation of Enol Ethers **4**: *General Procedure.*—A mixture of the enol ether **4** (2.44 mmol) and palladium on charcoal (10%; 0.1 g) was hydrogenated at atmospheric pressure for 1 h in ethyl acetate (20 cm^3). After the catalyst had been filtered off, the filtrate was evaporated and the residue chromatographed on silica (light petroleum–ether) to yield the oxepanone as a mixture of diastereoisomers. Epimerisation of the diastereoisomeric mixture (if necessary) was carried out by dissolving it in dry methanol (10 cm^3), adding a small amount of sodium (*ca.* 10 mg) to the solution and stirring the mixture for 48 h. Ether (30 cm^3) and water (30 cm^3) were then added to the mixture and the aqueous phase was extracted with ether (3 × 30 cm^3). The combined ethereal extracts were washed with brine (60 cm^3), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (light petroleum–ether) to yield the oxepanone **5** as the single *cis*-diastereoisomer.

2-(4-*Dimethylthexylsiloxybutyl*)*oxepan*-3-*one* **5a** (98%) (Found: M^+, 328.2434. $C_{18}H_{36}O_3Si$ requires 328.2434); ν_{max}(film)/cm^{-1} 2952, 2860, 1710, 1462, 1252, 1100, 832 and 776; δ_H(250 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.83–0.89 (13 H, m, Me and Si-thex), 1.42–1.91 (10 H, m, 5-CH_2, 6-CH_2 and $CH_2CH_2CH_2CH_2OSi$), 2.37–2.40 (1 H, m, 4-CHH), 2.84 (1 H, ~dt, *J* 2.8, 11.5, 4-CHH), 3.27 (1 H, ~dt, 7-CHH), 3.57 (2 H, t, *J* 5.9, CH_2OSi), 3.70 (1 H, m, 7-CHH) and 4.19–4.25 (1 H, m, 2-CH); *m*/*z* (EI^+): 243 (23%), 151 (17), 105 (13), 81 (28), 75 (100), 55 (28), 41 (42) and 27 (14).

2-(3-*Dimethylthexylsiloxypropyl*)-7-*hexyloxepan*-3-*one* **5b** (66%) (Found: M + H^+, 399.3294. $C_{23}H_{46}O_3Si$ + H requires 399.3294); ν_{max}(film)/cm^{-1} 2952, 2928, 2860, 1712, 1250, 1098 and 830; δ_H(250 MHz; $CDCl_3$) 0.08 (6 H, s, $SiMe_2$), 0.83–0.93 (16 H, m, Me and Si-thex), 1.28 [8 H, br s, $Me(CH_2)_4$], 1.28–1.75 [9 H, m, 5-CH_2, 6-CHH, $(CH_2)_4CH_2$ and $(CH_2)_2CH_2O$], 1.93–1.98 (1 H, m, 6-CHH), 2.28–2.35 (1 H, m, 4-CHH), 2.91 (1 H, ~dt, *J* 2.5, 11.6, 4-CHH) and 3.15 (1 H, m, 7-CH) and 3.58–3.71 (3 H, m, 2-CH and CH_2OSi); *m*/*z* (CI^+) 399 (MH^+, 100%), 313 (12), 258 (19), 239 (22), 221 (10), 145 (6), 127 (7) and 92 (6).

2-(4-*Dimethylthexylsiloxybutyl*)-7-*hexyloxepan*-3-*one* **5c** (76%) (Found: M + H^+, 413.3451. $C_{24}H_{48}O_3Si$ + H, requires 413.3451); ν_{max}(film)/cm^{-1} 2940, 2856, 1712, 1462, 1378, 1250, 1114, 1108, 876, 830 and 776; δ_H(250 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.84–0.89 (16 H, m, Me and Si-thex), 1.28 [8 H, br s, $Me(CH_2)_4$], 1.28–1.80 [12 H, m, 5-CH_2, 6-CH_2, $(CH_2)_4CH_2$ and $(CH_2)_3CH_2O$], 2.28–2.35 (1 H, m, 4-CHH), 2.91 (1 H, dt, *J* 3.0, 14.0, 4-CHH), 3.07–3.16 (1 H, m, 7-CH) and 3.58–3.75 (3 H,

m, 2-CH and CH_2OSi); *m/z* (CI^+) 413 (MH^+, 100%), 327 (25), 235 (12), 159 (12), 92 (10) and 74 (10).

2-(5-*Dimethylthexylsiloxypentyl*)-7-*hexyloxepan*-3-*one* **5d** (75%) (Found: M + H^+, 427.3607. $C_{25}H_{50}O_3Si$ + H, requires 427.3607); ν_{max}(film)/cm^{-1} 2930, 2860, 1710, 1465, 1250, 1100, 830 and 775; δ_H(250 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.82–0.89 (16 H, m, Me and Si-thex), 1.21 [8 H, br s, $Me(CH_2)_4$], 1.21–1.75 [13 H, m, 5-CH_2, 6-C*H*H, $(CH_2)_4CH_2$ and $(CH_2)_4CH_2OSi$], 1.80–2.00 (1 H, m, 6-C*H*H), 2.28–2.33 (1 H, m, 4-C*H*H), 2.90 (1 H, ~dt, 4-C*H*H), 3.07–3.16 (1 H, m, 7-CH), 3.57 (2 H, t, *J* 6.3, CH_2OSi) and 3.66–3.71 (1 H, m, 2-CH); *m/z* (CI^+) 427 (MH^+, 100%), 275 (54), 247 (39), 201 (25), 185 (51), 115 (25), 102 (39) and 85 (55).

Preparation of Hydroxyalkyloxepanones **6**: *General Procedure*.—The dimethylthexylsiloxyalkyloxepanone **5** (0.63 mmol) was stirred in a 5% hydrochloric acid–ethanol mixture (10 cm^3) until all of the starting material had been consumed (TLC) (*ca.* 1 h). Ether (20 cm^3) and water (20 cm^3) were then added to the mixture and the aqueous layer was extracted with ether (3 × 20 cm^3). The combined ethereal extracts were washed successively with saturated aqueous sodium hydrogencarbonate (40 cm^3) and brine (40 cm^3), dried ($MgSO_4$) and evaporated and the residue chromatographed on silica (ether) to yield the respective hydroxyalkyloxepanone **6** as a colourless oil.

2-(4-*Hydroxybutyloxepan*-3-*one* **6a** (72%) (Found: M^+, 186.1256. $C_{10}H_{18}O_3$ requires 186.1256); ν_{max}(film)/cm^{-1} 3420, 3404, 2936, 2860, 1708, 1320, 1140, 1120, 1086 and 1074; δ_H(250 MHz; $CDCl_3$) 1.34–1.95 [10 H, m, 5-CH_2, 6-CH_2 and $(CH_2)_3$], 2.39–2.41 (1 H, m, 4-C*H*H), 2.90 (1 H, dt, *J* 2.8, 12.8, 4-C*H*H), 3.28 (1 H, dt, *J* 2.3, 10.6, 7-C*H*H), 3.64 (2 H, t, *J* 6.3, CH_2OH), 3.70–3.75 (1 H, m, 7-C*H*H) and 4.20–4.26 (1 H, m, 2-CH) (OH not observed); *m/z* (EI^+) 186 (M^+, 9%), 111 (3), 85 (100), 67 (9), 56 (30), 41 (55) and 31 (22).

7-*Hexyl*-2-(3-*hydroxypropyl*)*oxepan*-3-*one* **6b** (58%) (Found: M^+, 256.2038. $C_{15}H_{28}O_3$ requires 256.2038); ν_{max}(film)/cm^{-1} 3436, 2924, 2856, 1708, 1452, 1320 and 1120; δ_H(250 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.8, Me), 1.28 [8 H, br s, $Me(CH_2)_4$], 1.28–2.39 [10 H, m, 5-CH_2, 6-CH_2, $(CH_2)_4CH_2$ and CH_2CH_2], 2.31–2.39 (1 H, m, 4-C*H*H), 2.87–2.93 (1 H, m, 4-C*H*H), 3.20–3.90 (4 H, m, 2-CH, 7-CH and CH_2OH) (OH not observed); *m/z* (CI^+) 274 (M + NH_4^+, 16%), 257 (MH^+, 67), 239 (M^+ − OH, 100), 221 (7), 171 (3), 143 (6), 71 (7) and 58 (3).

7-*Hexyl*-2-(4-*hydroxybutyl*)*oxepan*-3-*one* **6c** (71%) (Found: M^+, 270.2182. $C_{16}H_{30}O_3$ requires 270.2195); ν_{max}(film)/cm^{-1} 3420, 2932, 2856, 1710, 1454, 1434, 1376, 1322, 1120 and 870; δ_H(250 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.2, Me), 1.28 [8 H, br s, $Me(CH_2)_4$], 1.28–1.82 [11 H, m, 5-CH_2, 6-C*H*H, $(CH_2)_4CH_2$ and $(CH_2)_3$], 1.92–2.00 (1 H, m, 6-C*H*H), 2.30–2.37 (1 H, m, 4-C*H*H), 2.90 (1 H, dt, *J* 2.6, 12.6, 4-C*H*H), 3.16 (1 H, ~t, *J* 7.1, 7-CH), 3.63–3.73 (3 H, m, 2-CH and CH_2OH) (OH not observed) *m/z* (CI^+) 288 (M + NH_4^+, 44%), 271 (M + H^+, 77), 253 (100), 235 (12), 157 (25), 139 (12), 116 (8) and 85 (25).

7-*Hexyl*-2-(5-*hydroxypentyl*)*oxepan*-3-*one* **6d** (70%) (Found: M^+, 284.2350. $C_{17}H_{32}O_3$ requires 284.2351); ν_{max}(film)/cm^{-1} 3420, 2930, 2860, 1710, 1455, 1320, 1120 and 1055; δ_H(250 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.4, Me), 1.24 [8 H, br s, $Me(CH_2)_4$], 1.24–1.85 [13 H, m, 5-CH_2, 6-C*H*H, $(CH_2)_4CH_2$ and $(CH_2)_4$], 1.89–2.04 (1 H, m, 6-C*H*H), 2.27–2.38 (1 H, m, 4-C*H*H), 2.91 (1 H, dt, *J* 2.6, 12.6, 4-C*H*H), 3.15 (1 H, ~t, 7-CH), 3.61 (2 H, t, *J* 6.6, CH_2OH) and 3.64–3.71 (1 H, m, 2-CH) (OH not observed); *m/z* (EI^+) 284 (M^+, 30%), 256 (1), 213 (1), 198 (9), 187 (4) and 169 (100).

7-*Hexyl*-2-(3-*hydroxypropyl*)*oxepan*-3-*one* **6b**: *Alternative Preparation*.—A stirred mixture of the allyl oxepanone **7**[48] (0.47 g, 1.39 mmol) and a few crystals of toluene-*p*-sulfonic acid was heated slowly to 150–160 °C and maintained at this temperature for 10 min. The mixture was allowed to cool after which ether (20 cm^3) and water (20 cm^3) were added to it and the aqueous phase was extracted with ether (3 × 20 cm^3). The combined ethereal extracts were washed with brine (40 cm^3), dried ($MgSO_4$) and evaporated and the residue was chromatographed on silica (light petroleum–ether) to yield a mixture of diastereoisomers. Epimerisation was carried out by adding a small amount of sodium (*ca.* 5 mg) to the mixture in dry methanol (3 cm^3) and stirring it for 48 h. A further portion of sodium was then added to the mixture and stirring continued for a further 48 h. The mixture was then treated with aqueous hydrochloric acid (0.5 mol dm^{-3}; 5 cm^3) and the methanol removed by evaporaton. The aqueous mixture was extracted with ether (3 × 10 cm^3) and the combined ethereal extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated and the residue chromatographed on silica (light petroleum–ether) to yield 7-*hexyl*-2-(*prop*-1-*enyl*)*oxepan*-3-*one* **8** as a single *cis*-diastereoisomer (by NOE studies) (0.19 g, 59%) (Found: C, 75.1; H, 11.2. $C_{15}H_{26}O_2$ requires C, 75.58; H, 11.20%) (Found: M + H^+, 239.2011. $C_{15}H_{26}O_2$ + H requires 239.2011); ν_{max}(film)/cm^{-1} 2928, 2856, 1710, 1638, 1432, 1378, 1316, 1260, 1142, 1106, 996 and 914; δ_H(400 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 7.0, Me), 1.26 [8 H, br s, $Me(CH_2)_4$], 1.26–1.61 (4 H, m, CH_2 and 5-CH_2), 1.76–1.79 (1 H, m, 6-C*H*H), 1.93–1.97 (1 H, m, 6-C*H*H), 2.31–2.42 (3 H, m, $CH_2CH{=}CH_2$ and 4-C*H*H), 2.86 (1 H, dt, *J* 2.4, 12.2, 4-C*H*H), 3.16–3.17 (1 H, m, 7-C*H*H), 3.74–3.77 (1 H, m, 2-CH), 5.06 (1 H, dd, J_{gem} 1.5, J_{cis} 9.2, CH=C*H*H), 5.10 (1 H, dd, J_{gem} 1.5, J_{trans} 15.8, CH=C*H*H) and 5.80–5.90 (1 H, m, C*H*=CH_2); δ_C(125 MHz; $CDCl_3$) 14.11 (Me), 22.61 (CH_2), 23.78 (CH_2), 25.64 (CH_2), 29.16 (CH_2), 31.82 (CH_2), 36.29(CH_2), 37.17 (CH_2), 37.55 (CH_2), 41.51 (CH_2), 83.71 (7-CH), 86.49 (2-CH), 117.50 (CH=*C*H_2), 133.94 (*C*H=CH_2) and 216.690 (C=O); *m/z* (CI^+) 239 (MH^+, 100%), 221 (18), 198 (32), 169 (21), 151 (18), 125 (9), 95 (8) and 84 (8).

A mixture of the allyloxepanone **8** (0.50 g, 2.1 mmol), ethane-1,2-diol (0.13 cm^3, 0.14 g, 2.31 mmol) and toluene-*p*-sulfonic acid (4.0 mg, 0.021 mmol) in toluene (30 cm^3) was refluxed for 45 min in a flask fitted with a Dean-Stark trap. After the mixture had been allowed to cool, it was diluted with water (30 cm^3) and the aqueous phase extracted with ether (3 × 20 cm^3). The combined ethereal extracts were washed with brine (40 cm^3), dried ($MgSO_4$) and evaporated and the residue chromatographed on silica (light petroleum–ether) to yield the 7-*hexyl*-2-(*prop*-1-*enyl*)*oxepan*-3-*one ethylene ketal* as a colourless oil (0.26 g, 63%) (Found M^+, 282.2195. $C_{17}H_{30}O_3$ requires 282.2195); ν_{max}(film)/cm^{-1} 2924, 1452, 1438, 1178, 1158, 1140, 1104, 1064, 1040, 948 and 912; δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 7.0, Me), 1.26 [8 H, br s, $Me(CH_2)_4$], 1.26–1.83 (8 H, m, 4-CH_2, 5-CH_2, 6-CH_2 and CH_2), 2.19–2.32 (2 H, m, $CH_2CH{=}CH_2$), 3.33–3.39 (1 H, m, 7-CH), 3.48–3.51 (1 H, dd, *J* 3.0, 10.0, 2-CH), 3.80–4.02 (4 H, m, OCH_2CH_2O), 5.01 (1 H, ~dd, J_{cis} 10.0, CH=C*H*H), 5.09 (1 H, dd, J_{gem} 1.8, J_{trans} 17.2, CH=C*H*H) and 5.85–5.96 (1 H, m, C*H*=CH_2); δ_C(125 MHz; $CDCl_3$) 14.00 (Me), 20.49 (CH_2), 22.53 (CH_2), 26.06 (CH_2), 29.16 (CH_2), 31.75 (CH_2), 34.06 (CH_2), 37.12 (CH_2), 37.17 (CH_2), 37.41 (CH_2), 63.71 (OCH_2), 65.51 (OCH_2), 83.81 (7-CH), 84.66 (2-CH), 112.92 (3-C), 116.07 (CH=*C*H_2) and 136.363 (*C*H=CH_2); *m/z* (CI^+) 283 (M + H^+, 43%), 265 (7), 227 (28), 141 (11), 99 (100), 86 (9) and 73 (8).

A solution of the above allyloxepane (0.16 g, 0.57 mmol) in THF (2 cm^3) was added dropwise to a solution of borane–tetrahydrofuran complex (1 mol dm^{-3}; 0.62 cm^3, 0.62 mmol) at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was recooled to 0 °C and aqueous sodium hydroxide (3 mol dm^{-3}, 0.19 cm^3, 0.57 mmol) added to it dropwise. This was followed by the dropwise addition of

hydrogen peroxide solution (30%; 0.23 cm^3, 1.99 mmol). After the mixture had been stirred for 1.5 h at room temperature, it was diluted with ether (20 cm^3) and the organic phase was separated. This was washed successively with water (4 × 10 cm^3) and brine (10 cm^3), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (ether) to yield the 7-*hexyl*-2-(3-*hydroxypropyl*)*oxepan*-3-*one ethylene ketal* **9** as a colourless oil (0.10 g, 61%) (Found: M + H^+, 301.2379. $C_{17}H_{32}O_4$ + H requires 301.2379); ν_{max}(film)/cm^{-1} 3428, 2928, 2856, 1452, 1176, 1156, 1106, 1020, 950 and 926; δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 7.0, Me), 1.28 [8 H, br s, Me(CH_2)$_4$], 1.28–1.89 [12 H, m, (CH_2)$_2$$CH_2$OH, 4-$CH_2$, 5-$CH_2$, 6-$CH_2$ and (CH_2)$_4$$CH_2$], 3.37–3.41 (1 H, m, 7-CH), 3.43–3.46 (1 H, m, 2-CH), 3.63–3.66 (2 H, m, CH_2OH), 3.82–3.91 (2 H, m, O$CH_2$$CH_2$O) and 3.93–3.99 (2 H, m, O$CH_2$$CH_2$O) (OH not observed); δ_C(125 MHz; $CDCl_3$) 13.98 (Me), 20.38 (CH_2), 22.53 (CH_2), 25.63 (CH_2), 26.05 (CH_2), 29.23 (CH_2), 29.36 (CH_2), 31.71 (CH_2), 36.88 (CH_2), 37.05 (CH_2), 37.13 (CH_2), 63.05 (CH_2OH), 63.78 (OCH_2), 65.45 (OCH_2), 83.67 (7-CH), 84.63 (2-CH) and 112.91 (3-C); *m*/*z* (CI^+) 301 (M + H^+, 13%), 239 (100), 210 (19), 141 (9), 113 (16), 99 (96), 86 (15) and 71 (11).

The hydroxyalkyloxepane **9** (0.07 g, 0.23 mmol) was stirred in 5% HCl–THF (5 cm^3) for 4 h at room temperature after which the mixture was diluted with ether (20 cm^3) and water (10 cm^3). The aqueous phase was separated and extracted with ether (3 × 10 cm^3) and combined ethereal extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated and the residue chromatographed on silica (light petroleum–ether) to yield the *title compound* **6b** as a colourless oil (0.044 g, 74%). This displayed spectral properties identical with those of the same compound prepared previously.

Cyclisation of Hydroxyalkyloxepanones **6**: *General Procedure*.—A mixture of the hydroxyalkyloxepanone **6** (0.30 mmol) and triethylsilane (0.47 cm^3, 0.34 g, 2.96 mmol) in dichloromethane (5 cm^3) at 0 °C was treated dropwise with trimethylsilyl triflate (0.057 cm^3, 66 mg, 0.30 mmol) and then stirred for 1 h at 0 °C. After the mixture had been allowed to come to room temperature it was diluted with dichloromethane (20 cm^3) and water (20 cm^3). The aqueous layer was separated and extracted with dichloromethane (3 × 10 cm^3) and the combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica (light petroleum–ether) to yield the respective bicyclic ether **10**.

Decahydrooxepino[3,2-b]*oxepine* **10a** (79%) (Found: M^+, 170.1307. $C_{10}H_{18}O_2$ requires 170.1307); ν_{max}(film)/cm^{-1} 2928, 2856, 1450, 1124, 1104, 1084, 1032, 1014, 998 and 978; (mixture of *cis*/*trans*-isomers) δ_H(400 MHz; $CDCl_3$) 1.24–2.16 (12 H, m, 3-CH_2, 4-CH_2, 5-CH_2, 8-CH_2, 9-CH_2 and 10-CH_2), 3.28–3.34 (2 H, m, 10a-CH and 7-C*H*H), 3.56–3.67 (2 H, m, 5a-CH and 2-C*H*H), 3.84–3.90 (1 H, m, 2-C*H*H) and 4.02–4.07 (1 H, m, 7-C*H*H); δ_C(125 MHz; $CDCl_3$) 20.99 (CH_2), 22.40 (CH_2), 29.77 (CH_2), 32.06 (CH_2), 32.78 (CH_2), 34.88 (CH_2), 70.31 (CH_2), 72.45 (CH_2), 83.43 (CH) and 84.85 (CH); *m*/*z* (EI^+) 170 (M^+, 28%), 85 (100), 69 (53), 57 (75), 41 (86) and 29 (55).

6-*Hexyloctahydropyrano*[3,2-b]*oxepine* **10b** (78%) (Found: M + H^+, 241.2168. $C_{15}H_{28}O_2$ + H requries 241.2168); ν_{max}(film)/cm^{-1} 2924, 2852, 1454, 1144, 1094 and 1036; (mixture of *cis*/*trans*-isomers) δ_H(250 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 6.8, Me), 1.27 [8 H, br s, Me(CH_2)$_4$], 1.27–2.03 [12 H, m, 3-CH_2, 4-CH_2, 7-CH_2, 8-CH_2, 9-CH_2 and (CH_2)$_4$$CH_2$], 3.00–3.04 (1 H, m, 4a-CH), 3.30–3.56 (3 H, m, 2-C*H*H, 6-CH and 9a-CH) and 3.84–3.90 (1 H, m, 2-C*H*H); δ_C(62.9 MHz; $CDCl_3$) 14.03, 19.60, 20.33, 21.25, 22.56, 25.81, 26.16, 26.29, 29.18, 29.67, 31.34, 31.80, 32.70, 33.88, 34.46, 36.75, 37.03, 37.87, 67.62, 76.19, 77.49, 78.25, 79.85, 79.90, 82.28 and 83.22; *m*/*z* (CI^+) 258 (M + NH_4^+, 71%), 241 (M + H^+, 100), 223 (12), 155 (65), 98 (15) and 71 (29).

7-*Hexyldecahydrooxepino*[3,2-b]*oxepine* **10c** (51%) (Found: C, 75.7; H, 12.0. $C_{16}H_{30}O_2$ requires C, 75.54; H, 11.89%) (Found: M + H^+, 255.2324. $C_{16}H_{30}O_2$ + H requires 255.2324); ν_{max}(film)/cm^{-1} 2928, 2856, 1452, 1378, 1118, 1098, 1022 and 882; (*trans* isomer) δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 7.0, Me), 1.26 [8 H, br s, Me(CH_2)$_4$], 1.26–1.77 [12 H, m, 3-CH_2, 4-CH_2, 5-C*H*H, 8-CH_2, 9-CH_2, 10-C*H*H and (CH_2)$_4$$CH_2$], 1.89–1.96 (1 H, m, 10-C*H*H), 2.00–2.06 (1 H, m, 5-C*H*H), 3.22–3.28 (1 H, m, 5a-CH), 3.31–3.36 (1 H, m, 10a-CH), 3.41–3.46 (1 H, m, 7-CH), 3.62–3.76 (1 H, m, 2-C*H*H) and 3.77–3.82 (1 H, m, 2-C*H*H); δ_C(125 MHz; $CDCl_3$) 13.99, 19.86, 20.90, 22.52, 26.15, 29.02, 29.13, 31.78, 34.39, 35.14, 35.87, 36.94, 69.22, 81.87, 82.29 and 84.60; *m*/*z* (EI^+) 255 (MH^+, 3%), 237 (2), 169 (15), 97 (10), 85 (100), 67 (23), 57 (16) and 41 (12).

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