ORGANOLITHIUM-INDUCED SYNTHESIS OF UNSATURATED DIOLS FROM EPOXIDES OF DIHYDROFURANS AND DIHYDROPYRANS

David M. Hodgson,* a Matthew A. H. Stent, a Francis X. Wilson b

a Dyson Perrins Laboratory, Department of Chemistry, University of Oxford, South Parks Road, Oxford OX1 3QY, UK
Fax: +44(1865)275674; E-mail: david.hodgson@chem.ox.ac.uk
b Roche Discovery (Welwyn), 40 Broadwater Road, Welwyn Garden City, Herts AL7 3AY, UK

Received 2 February 2002

Abstract: Dihydrofuran and dihydropyran epoxides undergo a stereospecific alkylative double ring-opening with organolithiums to provide a new route to substituted alkenediols.

Key words: epoxides, organolithiums, alkenes, diols, eliminations

Epoxides are versatile synthetic intermediates. Their reactions are dominated by cleavage of the strained three-membered ring by nucleophilic opening and acid- or base-induced isomerization reactions. The alkylative deoxygenation of epoxides using organolithiums to give substituted alkenes (Scheme 1) was originally discovered by Crandall and Lin, and a number of research groups have subsequently made contributions to this area.5

Scheme 1

In one development of this methodology, Mioskowski and co-workers in 1996 reported that the reaction of organolithiums with cyclopentene- and cyclohexene-derived epoxides possessing a $\alpha$-methoxy substituent results in the elimination of methoxide and formation of substituted cyclic allylic alcohols (e.g. Scheme 2).5

Scheme 2

We chose readily available 3,4-epoxytetrahydrofuran 5 as a substrate to test our hypothesis.5 Reaction of 5 with BuLi (2.5 equiv.) in THF at $\sim$78 °C cleanly gave 3-methyleneheptane-1,2-diol 7 in excellent yield (90%, Scheme 4).7 As in Mioskowski’s work (Scheme 2), the current reaction proceeds via ether cleavage rather than loss of Li2O; this is despite $\beta$-elimination from the presumed lithiated intermediate 6 (Scheme 4) being the reverse of a stereoelectronically disfavoured 5-endo-trig cyclization.9

Scheme 4

The reaction is tolerant of a range of organolithiums (Scheme 5). Primary, secondary, and tertiary alkylolithiums, as well as phenyllithium, 2-furanyllithium, (trimethylsilylmethyl)lithium, and [1-(trimethylsilyl)hexy]lithium all underwent successful reaction with 3,4-epoxytetrahydrofuran 5 under the above conditions. Given the utility of allylsilanes in synthesis, the straightforward synthesis of 3,4-epoxytetrahydrofuran 5 is noteworthy.

The process can also be extended to organolithiums generated by Li–I exchange. However, removal of LiI, prior to reaction with the epoxide, is necessary for satisfactory yields (Scheme 6).

We next chose to study a trisubstituted epoxide. Pentylsubstituted epoxide 17 was prepared from known allylic alcohol 16 by allylation, ring-closing metathesis and epoxidation (Scheme 7). On treatment with BuLi 17 gave tertiary allylic alcohol 18 in 90% yield, comparable to the parent system 5 (Scheme 7). The Prins-pinacol...
rearrangement\textsuperscript{18} of 18 to the 3-acyl-substituted tetrahydrofuran 19 (Scheme 7) demonstrates one application of such a tertiary allylic alcohol formed in this reaction. A study of 2,5-disubstituted 3,4-epoxytetrahydrofurans was undertaken to further examine the effect of substituents on the reaction, and as a probe of the stereospecificity\textsuperscript{4b} of the process. Protection of diol 20 as the bis(tert-butyldimethylsilyl)ether (TBSCl, imidazole, DMF, 25 °C, 16 h, 91% yield) followed by epoxidation (\(m\)CPBA, CH\(_2\)Cl\(_2\), 25 °C, 16 h, 70% yield) gave only an inseparable 1:1 mixture of both diastereomeric epoxides 21 and 22 (Scheme 8, Me = TBS). However, methylation and epoxidation\textsuperscript{17} of 20\textsuperscript{19} gave a mixture of epoxides 21 and 22 which proved to be chromatographically separa-
The relative stereochemistry of 21 and 22 were determined by $^1$H NOE studies (Scheme 8).

On treatment with BuLi each diastereomeric epoxide gave a geometric isomer of the same trisubstituted olefin. These reactions are stereospecific; cis,trans-21 exclusively gave the E-olefin 23 in 90% yield, and cis,cis-22 exclusively gave the Z-olefin 24 in 65% yield (Scheme 9) (olefin geometries were determined by $^1$H NOESY studies on both isomers: diol 23 showed strong correlations between the olefinic proton and the protons α-OH, whilst 24 showed correlations between the olefinic proton and the butyl chain only).

The above results are consistent with a reaction mechanism, which proceeds from the lithiated epoxide (e.g. 25 from 21, Scheme 10) via a 1,2-metallate shift (with concomitant epoxide opening), followed by anti-$\beta$-elimination of Li and furanyl O from alkoxide 26. Assuming an early transition state for the elimination, then the required anti alignment of bonds is easily achieved. Syn elimination is not possible.

The process failed with cyclic and acyclic derivatives of cis-but-2-ene-1,4-diol (Figure), which all underwent decomposition. The failure of non-cyclic substrates to react via oxiranyl anion chemistry has been previously observed.5,23

However, the reaction was successfully extended to dihydropyran epoxides (Scheme 11). Dihydropyran epoxides 27 and 29 were synthesised from tetrahydropyran-4-one (Scheme 11),24,25 and subsequent treatment with BuLi gave the corresponding substituted pentene-1,3-diols 28 (60% yield) and 30 (70% yield). Formation of pentenediol 28 suggests that the ‘cyclic’ alkoxy substituent $\beta$ to the epoxide directs the epoxide lithiation vicinal to itself.23

In conclusion, we have demonstrated that treatment of dihydrofuran and dihydropyran epoxides with a diverse range of organolithiums provides a new route to substituted alkenediols. Extensions of the process to other epoxides, organolithiums, asymmetric transformations and manipulation of the adducts towards targets of biological interest, are under investigation.
and allowed to cool in a desiccator over P₂O₅ before use. Ethers were distilled from sodium benzenophene ketyl under argon; CH₂Cl₂, pentane and Et₂N from CaH₂ under Argon. External reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC using commercially available glass-backed plates, pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator (Merck). Organic layers were dried over MgSO₄ unless stated otherwise. Column chromatography was carried out on Kieselgel (60–43 μm). Petroleum ether refers to the fraction with bp 40–60 °C. ¹H and ¹³C NMR spectra were recorded in CDCl₃ unless stated otherwise with Varian Gemini 200, Bruker AC200, Bruker WM250, Bruker WH300, JEOL EX400, Bruker AM500 or Bruker AMX500 spectrometers. Chemical shifts are reported relative to CHCl₃ (δ₀ = 7.26 δ, central line of δ 77.0).

Alkaline Double Ring-Opening Reaction; General Procedure
To a solution of the epoxide in THF (5 mL) at –78 °C was added dropwise the organolithium compound. Following complete addition, the mixture was stirred at 0 °C for 2 h, recooled to –78 °C and treated dropwise with a solution of MgSO₄ (3,4-epoxytetrahydrofuran) 5 in hexanes, 1.1 mL, 2.4 mmol). Column chromatography (SiO₂, 90% Et₂O in petroleum ether) gave a colourless oil (0.13 g, 29%; Rf 0.20 (90% Et₂O in petroleum ether).

IR (film): 3368, 2957, 2930, 1458, 1074, 1029, 903 cm⁻¹.

1H NMR (400 MHz): δ = 5.05 (s, 1 H, C=CH₂), 4.87 (s, 1 H, C=CH₂), 4.12 [dd, 1 H, J = 6.8 Hz, C(2)-H], 3.97 (br s, 1 H, OH), 3.89 (br s, 1 H, OH), 3.62 [dd, 1 H, J = 11.2 Hz, C(1)-H], 3.44 [dd, 1 H, J = 11.2, 8.0 Hz, C(1)-H], 2.05–1.88 [m, 2 H, C(4)-H], 1.43–1.36 [m, 2 H, C(5)-H], 1.33–1.24 [m, 2 H, C(6)-H], 0.87 (t, 3 H, J = 7.2 Hz, CH₃).

¹³C NMR (100 MHz): δ = 148.5 [C(3)], 110.2 [C(=CH₂)], 75.1 [C(2)], 66.2 [C(1)], 32.3 [C(4)], 30.5 [C(5)], 22.5 [C(6)], 13.9 [C(7)].

MS-CI (NH₃): m/z (%) = 162 (100, [M + NH₄⁺]), 128 (50).

HRMS: m/z calc for C₈H₂₀NO₂, 162.1494; found, 162.1492.

4,4-Dimethyl-3-methylenepentane-1,2-diol (10)³⁹
From 3,4-epoxytetrahydrofuran 5 (80 mg, 930 μmol) and t-BuLi (1.1 M in pentane, 2.1 mL, 2.3 mmol). Column chromatography (SiO₂, 90% Et₂O in petroleum ether) gave a colourless oil (0.13 g, 93%); Rf 0.20 (90% Et₂O in petroleum ether).

IR (film): 3369, 2962, 2872, 1464, 1074, 911, 735 cm⁻¹.

1H NMR (400 MHz): δ = 5.10 (s, 1 H, C=CH₂), 5.06 (s, 1 H, C=CH₂), 4.30 [dd, 1 H, J = 8.8, 2.5 Hz, C(2)-H], 4.01 (br s, 1 H, OH), 3.70 (br s, 1 H, OH), 3.53 [dd, 1 H, J = 11.7, 2.5 Hz, C(1)-H], 1.63 [s, 9 H, 3 × CH₃].

¹³C NMR (100 MHz): δ = 157.6 [C(3)], 109.4 [C(=CH₂)], 70.9 [C(2)], 67.9 [C(1)], 35.4 [C(4)], 28.5 [C(5)], 20.9 (C(6)).

MS-CI (NH₃): m/z (%) = 162 (100, [M + NH₄⁺])

HRMS: m/z calc for C₉H₁₅NO₂, 164.1494; found, 164.1492.

4-Methyl-3-methylenepentane-1,2-diol (11)³⁹
From 3,4-epoxytetrahydrofuran 5 (80 mg, 930 μmol) and t-BuLi (1.1 M in pentane, 2.1 mL, 2.3 mmol). Column chromatography (SiO₂, 90% Et₂O in petroleum ether) gave a colourless oil (0.13 g, 93%); Rf 0.20 (90% Et₂O in petroleum ether).

IR (film): 3369, 2966, 2872, 1464, 1364, 1074, 911, 735 cm⁻¹.

1H NMR (400 MHz): δ = 5.10 (s, 1 H, C=CH₂), 5.06 (s, 1 H, C=CH₂), 4.30 [dd, 1 H, J = 8.8, 2.5 Hz, C(2)-H], 4.01 (br s, 1 H, OH), 3.70 (br s, 1 H, OH), 3.53 [dd, 1 H, J = 11.7, 2.5 Hz, C(1)-H], 1.63 [s, 9 H, 3 × CH₃].

¹³C NMR (100 MHz): δ = 157.6 [C(3)], 109.4 [C(=CH₂)], 70.9 [C(2)], 67.9 [C(1)], 35.4 [C(4)], 28.5 (C(3)).

3-Methylbut-3-ene-1,2-diol (11)³⁹
From 3,4-epoxytetrahydrofuran 5 (80 mg, 930 μmol) and MeLi (1.0 M in Et₂O, 2.3 mL, 2.3 mmol). Column chromatography (SiO₂, 90% Et₂O in petroleum ether) gave a colourless oil (51 mg, 54%); Rf 0.20 (90% Et₂O in petroleum ether).

IR (film): 3368, 2922, 2879, 1653, 1448, 1069, 900 cm⁻¹.

1H NMR (400 MHz): δ = 5.02 [s, 1 H, C(4)-H], 4.91 [s, 1 H, C(4)-H], 4.14 [dd, 1 H, J = 6.6 Hz, C(2)-H], 3.76–3.63 [m, 3 H, C(3, C(1)-H, 2 × OH)], 3.50 [dd, 1 H, J = 11.0, 7.8 Hz, C(1)-H], 1.72 (s, 3 H, CH₃).

¹³C NMR (100 MHz): δ = 144.0 [C(3)], 111.8 [C(4)], 75.7 [C(2)], 65.3 [C(1)], 18.9 (CH₃).

3-Furan-2-ylbut-3-ene-1,2-diol (12)
To a solution of furan (0.34 mL, 4.7 mmol) in THF (5 mL) at –78 °C was added dropwise BuLi (2.0 M in hexanes, 2.3 mL, 4.7 mmol). Following complete addition, the mixture was stirred at 0 °C for 2 h, recooled to –78 °C and treated dropwise with a solution of 3,4-epoxytetrahydrofuran 5 (80 mg, 930 μmol) in THF (3 mL). After stirring at –78 °C for 1 h, and then at r.t., for 1 h phosphate buffer (pH 7, 5 mL) was added. The mixture was extracted with

Scheme 11
EtOAc (2 × 10 mL), the combined organic layers dried, filtered, and concentrated under reduced pressure. Column chromatography (SiO₂, 80% Et₂O in petroleum ether) gave a pale yellow gum (70 mg, 49%); Rf 0.20 (80% Et₂O in petroleum ether).

IR (CHCl₃): 3369, 2935, 1215 cm⁻¹.

1H NMR (400 MHz): δ = 7.35 (s, 1 H, ArH), 6.37–6.35 (m, 2 H, 2 × ArH), 5.66 (s, 1 H, C=CH₂), 5.34 (s, 1 H, CH₂CH₂), 4.66 [d, 1 H, J = 7.2 Hz, C(3)-H], 3.84–3.75 [m, 2 H, C(1)-H, OH], 3.62–3.57 (m, 2 H, C(2)-H), 0.11–0.09 (s, 9 H, TMS).

13C NMR (100 MHz): δ = 151.0 [C(3)], 106.3 (C₆H₅), 75.9 [C(2)], 65.7 [C(1)], 32.6 (CH₃), 31.6 (CH₂), 29.1 (CH₂), 28.7 (CH₂), 22.5 [C(4)], 14.7 [C(9)], –2.3 (3 × CH₃).

MS-CI (NH₃): m/z (%) = 262 (60, [M + NH₄⁺]), 245 (70, [M + H⁺]), 227 (85), 221 (100).

HRMS: m/z calcd for C₈H₁₅NO₂Si, 262.2202; found, 262.2202.

4-(Trimethylsilyl)-3-methylenebutane-1,2-diol (15)
From 3,4-epoxytetrahydrofuran 5 (80 mg, 930 μmol) and TMSCH₂Li (1.0 M in pentane, 2.3 mL, 2.3 mmol). Column chromatography (SiO₂, 75% Et₂O in petroleum ether) gave a colourless oil (0.12 g, 73%); Rf 0.25 (75% Et₂O in petroleum ether).

IR (film): 2956, 2928, 2857, 1648, 1460, 1087, 901 cm⁻¹.

1H NMR (500 MHz): δ = 4.83 (s, 1 H, C=CH₂), 4.59 (s, 1 H, CH₂CH₂), 3.91–3.86 [m, 1 H, C(1)-H], 3.57–3.50 [m, 1 H, C(2)-H], 3.34–3.20 [m, 3 H, C(1)-H, 2 × OH], 1.46 [d, 1 H, J = 14.0 Hz, C(4)-H], 1.51 [d, 1 H, J = 14.0 Hz, C(4)-H], –0.12 (s, 9 H, TMS).

13C NMR (100 MHz): δ = 146.0 [C(3)], 108.2 (C₆H₅), 75.6 [C(2)], 65.5 [C(1)], 23.3 [C(4)], –1.5 (CH₃).

MS-CI (NH₃); m/z (%) = 192 (100, [M + NH₄⁺]), 90 (100), 52 (20).

HRMS: m/z calcd for C₈H₁₈NO₂, 192.1420; found, 192.1426.

3-Methylenehept-6-ene-1,2-diol
To a solution of 3,4-epoxytetrahydrofuran 5 (80 mg, 930 μmol) in THF (10 mL) at –78 °C was added dropwise tBuLi (1.6 M in pentane, 60 mL, 98 mmol). The resulting solution was stirred at –78 °C for 1 h and then at r.t. 1 h, and concentrated under a stream of argon. Addition of pentane (5 mL) to the residue precipitated LiI; the mixture was collected in a syringe and added over 10 min through a syringe filter to a solution of 3,4-epoxytetrahydrofuran 5 (80 mg, 930 μmol) in THF (5 mL) at –78 °C.

The reaction mixture was stirred at –78 °C for 1 h and then at r.t. for 1 h. Phosphate buffer (pH 7.5, 5 mL) was added and the mixture extracted with EtOAc (2 × 10 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO₂, 90% Et₂O in petrol) gave a colourless oil (0.11 g, 80%); Rf 0.25 (90% Et₂O in petroleum ether).

IR (film): 3369, 2928, 1641, 1439, 1074 cm⁻¹.

1H NMR (500 MHz): δ = 5.81 [dd, 1 H, J = 17.5, 10.3, 6.5 Hz, C(6)-H], 5.14 (s, 1 H, C=CH₂), 5.06–4.96 [m, 2 H, C(7)-H], 4.96 (s, 1 H, C=CH₂), 4.18 [dd, 1 H, J = 7.3, 5.2 Hz, C(2)-H], 3.67 [dd, 1 H, J = 11.5, 8.0 Hz, C(1)-H], 3.51 [dd, 1 H, J = 11.5, 6.4 Hz, C(1)-H], 3.28 [br s, 1 H, OH], 3.14 [br s, 1 H, OH], 2.27–2.13 [m, 3 H, C(4)-H], 2.10–2.03 (m, 1 H, C(4)-H).

13C NMR (125 MHz): δ = 147.5 [C(3)], 137.8 [C(6)], 114.9 [C(7)], 110.9 (CH₂), 75.0 [C(2)], 65.5 [C(1)], 31.9 [C(5)], 31.6 [C(4)].

MS-CI (NH₃); m/z (%) = 160 (100, [M + NH₄⁺]), 90 (100), 52 (20).

HRMS: m/z calcd for C₈H₁₄NO₂, 160.1348; found, 160.1340.

Allyl 2-pentyl allyl ether
To a solution of 2-methyleneheptanol 16 (3.5 g, 27 mmol) and allyl bromide (12 mL, 140 mmol) in THF (54 mL) at 0 °C was added NaN₄ (60% dispersion on oil, 2.7 g, 68 mmol) in portions over 15 min. The reaction mixture was allowed to attain r.t. over 2 h, poured into sat. aq NaHCO₃ (200 mL) and extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by bulb-to-bulb distillation (70 °C, 0.5 mbar) gave a colourless oil (4.4 g, 96%).

IR (film): 2956, 2928, 2857, 1648, 1460, 1087, 901 cm⁻¹.
1H NMR (400 MHz): δ = 5.96–5.86 (m, 1 H, CH=CH2), 5.30–5.24 (m, 1 H, CH=CH2), 5.18–5.15 (m, 1 H, CH=CH2), 4.99 (s, 1 H, C=CH2), 4.88 (s, 1 H, C=CH2), 3.96–3.94 (m, 2 H, OCH2CH3), 3.90 (s, 2 H, OCH2C), 2.04 (br t, 2 H, J = 7.5 Hz, CH2CH2CH3), 1.48–1.40 (m, 2 H, CH2CH2CH3), 1.34–1.24 (m, 4 H, CH2CH2CH3), 0.91–0.86 (m, 3 H, CH3).
13C NMR (100 MHz): δ = 146.3 (C=CH2), 134.8 (CH=CH2), 111.1 (C=CH2), 73.0 (OCH2C), 70.6 (OCH2CH3), 33.1 [(CH2)4CH3], 27.3 [(CH2)3CH2], 22.5 (CH2CH3), 14.0 (CH3).

MS-CI (NH4): m/z (%) = 186 (50, [M + NH4]+), 197 (85), 183 (70).

IR (film): 2957, 2933, 2872, 1457, 1379, 1368, 1212, 1059 cm⁻¹.

HRMS: m/z calcd for C18H19NO, 287.1453; found, 287.1450.

HRM: H, 249.2526.

1H NMR (400 MHz): δ = 5.13 (s, 1 H, C=CH2), 5.01 (s, 1 H, C=CH2), 3.62 (d, 1 H, J = 11.0 Hz, CH2OH), 3.44 (d, 1 H, J = 11.0 Hz, CH2OH), 2.25–1.70 (brs, 2 H, 2 x OH), 1.96–1.91 (m, 2 H, CH2CH2C=CH2), 1.51–1.49 (m, 2 H, CH2COH), 1.46–1.17 (m, 10 H, 5 x CH3), 0.91 (t, 3 H, J = 7.2 Hz, CH3), 0.85 (t, 3 H, J = 7.0 Hz, CH3).

13C NMR (100 MHz): δ = 150.6 (C=CH2), 110.4 (C=CH2), 78.4 (COH), 68.2 (CH2OH), 35.5 (CH2COH), 32.2 (CH3), 31.0 (CH3-C=CH2), 30.4 (CH2), 22.7 (CH2), 22.6 (CH2), 22.5 (CH3), 14.0 (2 x CH3).

MS-CI (NH4): m/z (%) = 232 (100, [M + NH4]+), 215 (40, [M + H]+), 198 (50), 181 (85).

HRMS: m/z calcd for C18H19NO, 232.2277; found, 232.2274.

1H NMR (400 MHz): δ = 5.11 (s, 1 H, C=CH2), 4.89 (s, 1 H, C=CH2), 3.85 (dd, 1 H, J = 21.0, 10.5 Hz, OCH2), 1.97–1.83 (m, 2 H, CH2CH2CH3), 1.63–1.58 (m, 2 H, CH2CO), 1.47–1.43 (m, 2 H, CH2CH2CH2C=CH3), 1.43 (s, 3 H, CCH3), 1.36–1.23 (m, 8 H, 4 x & C=OCH2C), 1.33 (s, 3 H, CCH3), 0.91 (t, 3 H, J = 7.2 Hz, CH3), 0.86 (t, 3 H, J = 7.2 Hz, CH3).

13C NMR (100 MHz): δ = 150.7 (C=CH2), 109.3 ([C=CH2]), 108.5 (C=CH2), 86.5 (CH2CO), 73.2 (CH2C), 38.1 (CH2CO), 32.1 (CH2), 31.6 (CH2=CH2), 30.1 (CH2=CH2CH2=CH2), 27.4 ([C=CH2]), 26.0 ([C=CH2]), 23.5 (CH3), 22.7 (CH2), 22.5 (CH3), 14.1 (2 x CH3).

MS-CI (NH4): m/z (%) = 255 (100, [M + H]+), 239 (20), 225 (10), 197 (85), 183 (70).

HRMS: m/z calcd for C18H31N2O2, 255.2146; found, 255.2145.

1-(Tetrahydro-3-butyl-5,5-dimethyl-3-furanyl)hexane (18)
To a solution of 2,2-dimethyl-4-(1-methylenepentyl)-4-pentyl-1,3-dioxolane (90 mg, 350 μmol) in CH2Cl2 (0.7 mL) at −78 °C was added SnCl4 (46 mL, 390 μmol). The resulting mixture was allowed to attain r.t. over 1 h, then recooled to −78 °C and quenched with Et3N (0.3 mL). The aqueous layer was extracted with CH2Cl2 (3 x 25 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO2, 5% EtO in petroleum ether) gave a colourless oil (0.12 g, 86%); Rf 0.20 (25% CH2Cl2 in petroleum ether).

IR (film): 2923, 2862, 1707, 1458, 1367, 1214, 1059 cm⁻¹.

1H NMR (400 MHz): δ = 4.17 (d, 1 H, J = 9.2 Hz, OCH3), 3.63 (d, 1 H, J = 9.2 Hz, OCH3), 2.44 (t, 2 H, J = 7.6 Hz, C=OCH2C), 3.35 (d, 1 H, J = 13.2 Hz, C(CH3)2CH2), 1.71–1.66 (m, 2 H, CH2CH2CH2CH2CH2), 1.60–1.53 (m, 3 H, C=CH2CH2CH3), 1.34–1.21 (m, 9 H, C(CH3)2), CCH2CH2CH2CH3, C=OCH2CH2CH3), 1.16 (s, 3 H, C(CH3)2), CCH2CH2CH2CH3), 0.90–0.84 (m, 6 H, 2 x CH2CH3).

13C NMR (100 MHz): δ = 212.1 (C=O), 80.9 [OCH2(CCH2)], 72.3 (OCH2), 61.8 (CC=C), 46.2 (2 x CH2), 37.9 (CH2CO), 37.2 (CCH2CH2CH2CH3), 31.4 (C(CH3)2CH2CH2=CH3), 28.7 [C(CH3)2], 28.1 (C(CH3)2CH2CH2=CH3), 27.8 [C(CH3)], 23.6 (C=OCH2C), 23.1 (C=OCH2C), 22.5 (C=OCH2C), 13.8 (2 x CH2CH3).


HRMS: m/z calcd for C18H31NO2, 255.2324; found, 255.2320.
cis-2,5-Bis(methoxymethyl)-2,5-dihydrofuran  
To a solution of cis-2,5-bis(methoxymethyl)-2,5-dihydrofuran 210 (1.3 g, 10 mmol) and Mel (6.4 mL, 0.1 mol) in THF (100 mL) was added NaH (60% suspension in mineral oil, 2.0 g, 50 mmol) portionwise over 20 min. After stirring at r.t. for 16 h the reaction mixture was poured into sat. aq NH4Cl (200 mL) and extracted with CH2Cl2 (2 × 100 mL), the combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO2, 75% Et2O in petroleum ether) gave a colourless oil (1.2 g, 75%); Rf 0.30 (75% EtOAc in petroleum ether).

IR (film): 2897, 1461, 1194, 1097, 949, 922, 761 cm⁻¹.

1H NMR (400 MHz): δ = 5.69 [t, 1 H, C=C(2)-H], 4.85 [br d, 1 H, J = 6.4 Hz, C(3)-H], 4.05–3.95 [m, 2 H, C(1)-H, C(5)-H].

13C NMR (100 MHz): δ = 77.5 [C(2), C(5)], 72.8 [2 × CH2], 59.2 [C(3), C(4)], 58.9 [2 × CH2].

HRMS: m/z calcd for C12H28NO4, 250.2021; found, 250.2011.

(2R,3RS)-1-Methoxy-4-(2-methoxyethylene)-octane-2,3-diol (23)
From cis-2,5-bis(methoxymethyl)-3,4-epoxytetrahydrofuran 21 (80 mg, 460 μmol) and BuLi (2.3 M in hexanes, 0.50 mL, 1.2 mmol). Column chromatography (SiO2, 75% EtOAc in petroleum ether) gave a pale yellow oil (96 mg, 90%); Rf 0.25 (75% EtOAc in petroleum ether).

HR (film): 3436, 2929, 2821, 1456, 1379, 1193, 1092, 958 cm⁻¹.

1H NMR (400 MHz): δ = 5.69 [t, 1 H, J = 6.4 Hz, CH=C(4)], 4.19 [br d, 1 H, J = 5.6 Hz, C(3)-H(3)], 4.05–3.95 [m, 2 H, CH2=CH2(2)], 3.82–3.78 [m, 1 H, C(2)-H], 3.54–3.50 [m, 2 H, C(1)-H], 3.36 [2 × CH3, O], 2.98 [br s, 1 H, OH], 2.91 [br s, 1 H, OH], 2.19–2.11 [m, 1 H, C(5)-H], 1.97–1.90 [m, 1 H, C(5)-H].

13C NMR (100 MHz): δ = 142.5 [C(4)], 123.5 [C(3)], 76.4 [C(3)], 73.3 [C(1)], 70.7 [C(2)], 68.5 [CH2=CH2C(CH3)], 59.2 [CH2=CH2O], 58.1 [CH2O], 31.8 [C(6)], 28.2 [C(5)], 23.0 [C(7)], 13.8 [C(8)].

HRMS: m/z calcd for C10H18O5Na, 250.1820; found, 250.201.

(2Z,3RS)-1-Methoxy-4-(2-methoxyethylene)-octane-2,3-diol (24)
From cis,cis-2,5-bis(methoxymethyl)-3,4-epoxytetrahydrofuran 22 (80 mg, 460 μmol) and BuLi (2.3 M in hexanes, 0.50 mL, 1.2 mmol). Column chromatography (SiO2, 75% EtOAc in petroleum ether) gave the product as a pale yellow oil (66 mg, 65%); Rf 0.20 (75% EtOAc in petroleum ether).

HR (film): 3401, 2929, 1658, 1457, 1194, 1092 cm⁻¹.

1H NMR (400 MHz): δ = 5.54 [t, 1 H, J = 6.2 Hz, CH=C(4)], 4.42 [br d, 1 H, J = 7.2 Hz, C(3)-H], 4.07 [dd, 1 H, J = 12.0, 7.2 Hz, CH2=CH=C(2)], 3.95 [dd, 1 H, J = 12.0, 6.2 Hz, CH2=CH=C(2)], 3.78–3.74 [m, 1 H, C(2)-H], 3.45–3.29 [m, 2 H, C(1)-H], 3.36 [2 × CH3, O], 3.35–3.29 [m, 2 × CH3, O], 3.05 [br s, 2 H, 2 × OH], 2.19–2.12 [m, 1 H, C(5)-H], 2.01–1.93 [m, 1 H, C(5)-H], 1.49–1.41 [m, 2 H, C(6)-H], 1.38–1.29 [m, 2 H, C(7)-H], 0.90 [3 × H, J = 7.2 Hz, C(8)-H].

13C NMR (100 MHz): δ = 142.7 [C(4)], 128.6 (CH=CH2), 73.2 [C(1)], 72.1 [C(2)], 71.6 [C(3)], 68.2 (CH2=CH2C(CH3)], 59.1 [CH2O], 58.1 (CH2O), 31.6 [C(5)], 30.8 [C(6)], 22.6 [C(7)], 14.0 [C(6)].

HRMS: m/z calcd for C10H18O5Na, 250.1820; found, 253.1753.

4-Methylenecoctane-1,3-diol (28)
From 3,4-epoxytetrahydropryan 27 (80 mg, 460 μmol) and BuLi (2.3 M in hexanes, 0.87 mL, 2.0 mmol). Column chromatography (SiO2, 90% EtO in petroleum ether) gave a colourless oil (75 mg, 60%); Rf 0.20 (90% EtO in petroleum ether).

HR (film): 3350, 2929, 2872, 1456, 1052 cm⁻¹.

1H NMR (400 MHz): δ = 5.60 [s, 1 H, C=C(4)], 4.85 [s, 1 H, C=C(4)], 4.28 [dd, 1 H, J = 8.2, 3.2 Hz, C(3)-H], 3.84–3.73 [m, 2 H, C(1)-H], 3.30 [br s, 2 H, 2 × OH], 2.07–1.93 [m, 2 H, C(5)-H], 1.84–1.70 [m, 2 H, C(2)-H], 1.47–1.40 [m, 4 H, C(6)-H, C(7)-H], 0.90 [3 × H, J = 7.2 Hz, C(8)-H].

13C NMR (100 MHz): δ = 151.7 [C(4)], 108.9 (CH=CH2), 74.6 [C(3)], 61.1 [C(1)], 36.8 [C(2)], 31.5 [C(5)], 30.1 [C(6)], 22.6 [C(7)], 14.0 [C(6)].

HRMS: m/z calcd for C10H18O5Na, 250.1820; found, 253.1753.
3,4-Epoxy-4-methyltetrahydropyran (29)
To a solution of 4-methyl-3,6-diohydro-2H-pyran and 4-methylene tetrahydropyran$^2$ (~1: 1 mixture) in CH$_2$Cl$_2$ (90 mL) at –10 °C was added mCPBA (55% in H$_2$O, 7.7 g, 25 mmol) and the mixture was allowed to attain t.r. over 16 h. Sat. aq Na$_2$SO$_4$ (80 mL) was added and the mixture stirred vigorously for 5 min. The organic phase was separated, washed with brine (50 mL), dried, filtered and concentrated under reduced pressure.

Purification of the residue by column chromatography (SiO$_2$, 50% Et$_2$O in petroleum ether) gave two products, first to elute was the desired product 29 arising from the endocyclic alkene, a colourless oil (0.67 g, 26%); R$_f$ 0.25 (50% Et$_2$O in petroleum ether).

IR (film): 3369, 2930, 2822, 1456, 1372, 1124, 1085, 1053, 906 cm$^{-1}$.

3,4-Epoxy-4-methyltetrahydropyran (29)
Anal. Found: C, 65.2; H, 6.1; N, 2.0%. Calcd for C$_{16}$H$_{20}$NO$_2$: C, 65.4; H, 6.4; N, 2.0%.

From 3,4-epoxy-4-methyltetrahydropyran (29) and BuLi (2.3 M in hexanes, 0.76 mL, 1.8 mmol) in CH$_2$Cl$_2$ (90 mL) at –10 °C was added Epoxidation (CPBA, CH$_2$Cl$_2$, 25 °C, 101 h) of the corresponding alkenes: (a) Mischitz, M.; Kranich, I.; Wengen, J.; Kirch, M.; Luitpold, K.; Linscheid, G. Helv. Chim. Acta. 1990, 73, 1396. (b) Hodgson, D. M.; Robinson, L. A.; Wilson, F. X. Org. Lett. 2001, 3, 3401.

3-Methyl-4-methyleneoctane-1,3-diol (30)
HRMS: m/z (%): 190 (40, [M + NH$_4^+$]$^+$), 155 (100).

Acknowledgement
We thank the EPSRC and Roche for a CASE award (to M.A.H.S.), the EPSRC National Mass Spectrometry Service Centre for mass spectra, and Dr Barbara Odell for NOE NMR experiments.

References
(1) New address: Xenova Limited, 957 Buckingham Avenue, Slough, Berks SL1 4NL, UK.


(8) 3,4-Epoxytetrahydrofuran 5 can be prepared by epoxidation of widely available 2,5-dihydrofuran: Barill, P. L.; Berti, G.; Mastorrelli, E. Tetrahedron 1993, 49, 6263.


Epoxidation with mCPBA (1.1 equiv, CH$_2$Cl$_2$, 25 °C, 16 h) gave epoxides 21 and 22 (21: 22; 1: 2) in 75% yield.


