Regioselective Reactions of 2,3-*endo*-Epoxybicyclo[3.2.0]heptanone Ethylene Acetal involving Organometallic Reagents

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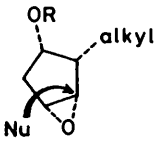
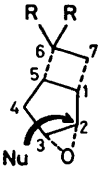
The preparation of (1'α,2'α,4'α,6'α)-spiro{[1,3]dioxolan-2,7'-[3']oxatricyclo[4.2.0.0$^{2',4'}$]octane} (3) and its reaction with various organometallic reagents is described. Attack occurred at C-2 preferentially (selectivity 67—83%) due to the influence of the neighbouring cyclobutane ring on the relative energies of the transition states leading to epoxy-ring opening. The conformation of the bicyclo[3.2.0]heptane system in the products is discussed.

EPOXY-RING opening in compounds of type (1) provides a facile entry into the prostaglandin (PG) system if the nucleophile is an entity which can be converted into the β-side chain of the natural products. The major concern in such a strategy is the control of the regioselectivity of the attack by the nucleophile, since the



(1)



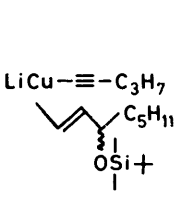
(2) RR = O

Nu = nucleophile (3) RR = OCH_2CH_2O

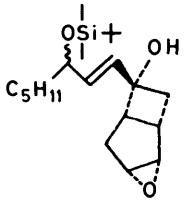
alternative mode of epoxy-ring opening leads to the formation of undesired isomeric products.[1-3] One elegant solution to this problem was provided by incorporating a hydroxy-function into the α-alkyl group and allowing this moiety to lead an alane to the requisite carbon atom.[4]

In complementary fashion the cyanobutane ring in compound (2) dictates the preferred mode of acid-catalysed epoxy-ring opening, with the nucleophile attacking C-2 predominantly.[5] Obviously if carbanion attack to form a new C–C bond also occurred preferentially at C-2, then a novel route to prostanoids would be feasible. We now report that attack on the epoxyacetal (3) by various organometallic reagents occurs with high regioselectivity in the desired sense. A future article will describe the prostaglandin synthesis based on this key step.[6]

Lithium organocuprates usually show low reactivity towards carbonyl groups.[7] However we found it was necessary to protect the ketone function, since treatment of the epoxyketone (2) with the mixed cuprate (4) at

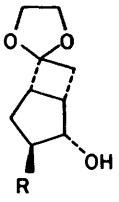


(4)



(5)

−78 °C gave the tertiary alcohol (5) as the major product. The bromohydrin (6) was converted into the cyclic acetal (7) (93% yield) which was dehydrobrominated using methanolic sodium hydroxide to give the key



(7) R = Br

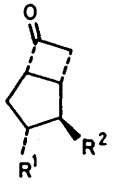
(8) R = $CH{=}CHCHC_5H_{11}$ (9)
$OSi+$

(11) R = C_4H_9-n (12)

(13) R = $\overline{CHS[CH_2]_3S}$ (14)

(15) R = CH(SMe)CH=CHSMe (16)

(22) R = $-C{\equiv}CCHC_5H_{11}$ (23)
OH



(6) R^1 = OH, R^2 = Br

(17) R^1 = OH, R^2 = CH(SMe)CH=CHSMe

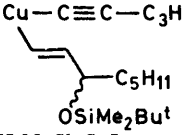
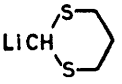
(19) R^1 = OH, R^2 = CH=CHCHO

(20) R^1 = CH=CHCHO, R^2 = OH

intermediate, the epoxide (3), in 88% yield. The cuprate (4) reacted over 16 h at −78 to −30 °C with this protected epoxide (3) to give, after chromatography, the required hydroxyacetal (8) and the isomer (9) (ratio 4 : 1 by g.l.c. analysis). It is interesting to note that the epoxyacetal (10) showed no sign of reacting with excess of cuprate (4) under the above conditions; this

TABLE 1

Reaction of the epoxyacetal (3) with organometallic reagents

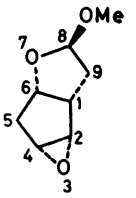
Organometallic reagent	Reaction temperature (°C)	Yield (%)	Products formed (ratio)
LiCu—C≡C—C_3H_7 	−78→30	86 [a]	(8), (9) (80 : 20)
C_4H_9MgCl–CuI	−30	98	(11), (12) (80 : 20)
	−20	91 [a]	(13), (14) (73 : 27)
LiCH(SMe)CH=CHSMe	−78	72 [a]	(15), (16) (83 : 17) [b]
$Me_2AlC{\equiv}C{-}CH(OSiMe_3){-}C_5H_{11}$	80	97 [c]	(22), (23) (67 : 33)

[a] After chromatography. [b] Ratio ascertained after conversion of (15),(16) into (19),(20) respectively. [c] After desilylation and chromatography.

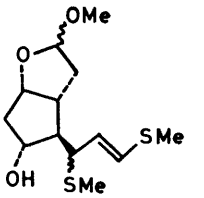
and a previous report [8] suggest that the epoxide (3) is more reactive towards a heterocuprate than would be expected normally. This fact might be ascribed to ring strain transmitted from the cyclobutane system and/or to assistance from the oxygen atom in the *endo*-position at C-6.

The versatility of the epoxide (3) as an intermediate for prostaglandin synthesis was demonstrated by reaction with a variety of organometallic reagents (Table 1). Thus, treatment with butylmagnesium chloride under copper(I) iodide catalysis afforded a 98% crude yield of the isomers (11) and (12) in the ratio 4 : 1 (ascertained by g.l.c.). Chromatography provided pure samples of (11) and (12).

On treatment with dithianyl-lithium at −20 °C the epoxyacetal (3) gave the acetals (13) and (14) cleanly (91% yield) in the ratio 73 : 27. Similarly, reaction of (3) with [1,3-bis(methylthio)prop-2-enyl]-lithium [9] at −78 °C gave a mixture of products (15) and (16). After removal of the cyclic acetal group a pure sample of the major component (17) was crystallised from the mixture, and this compound was converted into the known acetal (18) [2] on photolysis in methanol.[6] In a separate experiment the crude reaction mixture was treated with aqueous acid followed by $HgCl_2$–$CaCO_3$ in aqueous acetonitrile to afford a mixture of the aldehydes (19) and (20) in the ratio 83 : 17 (g.l.c.).



(10)



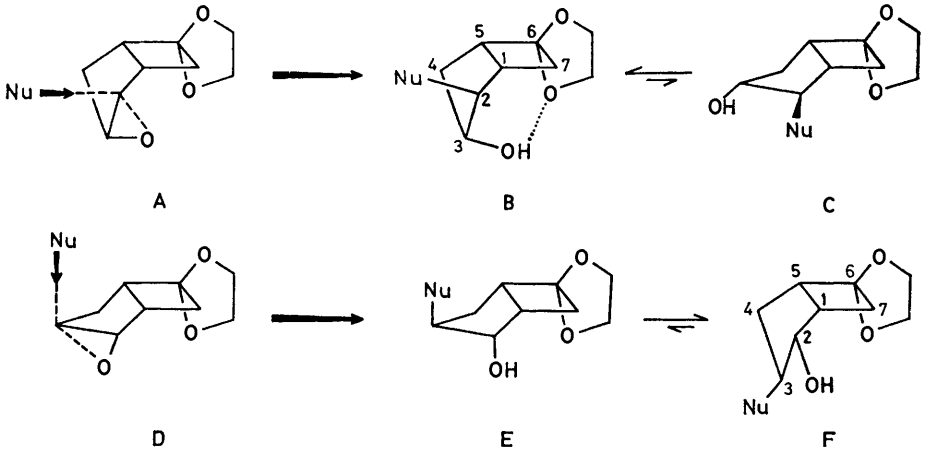
(18)

$Me_2AlC{\equiv}C{-}CH(OSiMe_3){-}C_5H_{11}$

(21)

The alane (21) [3,4] did not react with (3) at ambient temperature, but in toluene at 80 °C the reaction proceeded smoothly to give the alkynols (22) (64%) and (23) (32%) after desilylation and chromatography.

Stereochemistry and Conformation.—Conversion into known prostaglandin intermediates confirmed the structure and configuration of compounds (8), (15), and (22). For these and the other major products (11) and (13), infra-red spectra of dilute solutions show the hydroxy-group at C-3 to be intramolecularly hydrogen bonded ($\nu_{max.}$ 3 500 ± 30 cm^{-1}; independent of concentration). This supports a conformation close to the limiting *endo*-envelope (B); [10] the substituents are pseudo-axial, and hydrogen-bonding to the *endo*-oxygen atom of the cyclic acetal moiety is possible (O • • • O distance is *ca.* 2.7 Å as estimated from a Dreiding model). In the alternative *exo*-envelope (C) intramolecular hydrogen-bonding is rendered geometrically impossible. In contrast, for the 2-*endo*-hydroxy-3-*exo*-substituted compounds (9), (12), and (23) infra-red spectra indicate an absence of intramolecular hydrogen-bonding (free O–H; $\nu_{max.}$ 3 590—3 620 cm^{-1}). This also favours an *endo*-



SCHEME

TABLE 2

Interproton torsion angles and calculated coupling constants for alternative conformations of 2-*endo*-3-*exo*-bicyclo-[3.2.0]heptanes

	Torsion angles [a] (%)		Calculated coupling [b] constants (Hz)	
Conformation	$\omega_{1,2}$	$\omega_{2,3}$	$J_{1,2}$	$J_{2,3}$
Exo-envelope (E)	5	100	9	0
Endo-envelope (F)	30	150	7	9

[a] Measured from Dreiding models. [b] From Karplus equation [11] assuming J^0 9 Hz and J^{180} 12 Hz.

envelope conformation (F) for these molecules but with the substituents *pseudo*-equatorial. In an *exo*-envelope (E) the substituents would be *pseudo*-axial and intramolecular hydrogen-bonding possible (O · · · O distance *ca.* 3.4 Å). Additional evidence is provided by the n.m.r. spectra of compounds (9), (12), and (23). The methine proton adjacent to oxygen at C-2 (τ 6—6.5) may be identified as a doublet of doublets with splittings of 6—7 and 9 Hz. This is in accord with prediction for the *endo*-envelope conformation (F) but not for the alternative conformation (E) where the coupling with H-3-*endo* is expected to be very small (see Table 2).

Regioselectivity of the Epoxy-ring Opening Reactions.—We believe that the regioselectivity of the epoxy-ring opening reactions is due primarily to the presence of the four-membered ring, in that the transition state (A) leading to the bicycloheptan-3-ols is favoured over that (D) leading to the bicycloheptan-2-ols (Scheme). However, it is conceivable that the 6-*endo*-oxygen atom also exerts an influence on the regioselectivity of the reaction and we are presently engaged in work aimed at clarifying this point.

EXPERIMENTAL

Mass spectra were determined after ionisation by electron impact at 70 eV (e.i.m.s.) or chemical ionisation using ammonia (c.i.m.s.). T.l.c. was carried out with Camlab 'Polygram' precoated silica-gel plates. Short column chromatography [12] used Merck Kieselgel H or G. Light petroleum refers to the fraction of b.p. 60—80° and all solvents for chromatography were distilled before use.

(1α,2α,3β,5α)-2-*Bromospiro*{*bicyclo*[3.2.0]*heptane*-6,2'-[1,3]*dioxolan*}-3-*ol* (7).—2-*exo*-3-*endo*-2-Bromo-3-hydroxybicyclo[3.2.0]heptan-6-one (6) [10] (17.5 g, 85 mmol), ethylene glycol (8.0 g, 129 mmol), and toluene-*p*-sulphonic acid monohydrate (0.17 g, 0.9 mmol) were heated under reflux in benzene (175 ml) under nitrogen. Water was removed using a Dean–Stark trap, and after 6 h the solution was cooled and washed with 8% w/v sodium hydrogencarbonate–water, and water. The dried solution was stirred with charcoal, filtered, and evaporated to give the *cyclic acetal* (7) (19.7 g, 93%) as a pale yellow oil, homogeneous to t.l.c., $\nu_{max.}$ (film) 3 460, 2 950, 2 890, 1 420, 1 320, 1 300, 1 180, 1 120, 1 022, 948, 915, 840, 820, 779, and 700 cm^{-1}, τ($CDCl_3$) 5.5br (1 H, t, H-3), 5.75 (1 H, s, H-2), 5.9—6.1 (5 H, complex, $-OCH_2CH_2O-$ and −OH), 6.5—7.75 (5 H, complex), and 7.95br (1 H, d, H-4α). A sample for analysis was obtained by Kugelrohr distillation at 103—104° and 0.05 mmHg (Found: C, 42.49; H, 5.35. $C_9H_{13}BrO_3$ requires C, 42.39; H, 5.25%).

The Epoxyacetal (3).—The bromohydrinacetal (7) (10.6 g, 42.6 mmol) in methanol (25 ml) was added to a stirred solution of sodium hydroxide (4.0 g, 100 mmol) in methanol (75 ml). After 20 h at 20 °C, water (200 ml) was added and the mixture extracted with dichloromethane (4 × 30 ml). The combined extracts were washed with water, dried, and evaporated to give an oil (7.65 g). Distillation gave (1'α,-2'α,4'α,6'α)-*spiro*{[1,3]*dioxolan*-2,7'-[3]*oxatricyclo*[4.2.0.$0^{2,4}$]-*octane*} (3) (6.13 g, 88%) as a colourless oil, b.p. 70—84° at 0.5—0.8 mmHg. The distilled product slowly crystallised on standing to give colourless chunky crystals, m.p. 29—30.5°, $\nu_{max.}$ (film) 3 000, 2 945, 2 880, 1 318, 1 288, 1 188, and 845 cm^{-1}, τ($CDCl_3$) 6.0—6.5 (6 H, complex, $-OCH_2CH_2O-$ and H-2' and H-4'), 6.8br (1 H, m, H-6'), 7.2—7.7 (3 H, complex), 7.7 (1 H, q, H-5'β), and 8.2 (1 H, octet, H-5'α) (Found: C, 64.1; H, 7.1. $C_9H_{12}O_3$ requires C, 64.3; H, 7.2%).

Lithium 3-[*t-Butyl*(*dimethyl*)*silyloxy*]*oct*-1-*enyl* (*Pent*-1-*ynyl*) *Cuprate* (4).—Ethereal solutions of the mixed cuprate reagent (4) were prepared as follows. n-Butyl-lithium in hexane (1.6M; 1 equiv.) was added to a stirred solution of 3-[t-butyl(dimethyl)silyloxy]-1-iodo-oct-1-ene (1 equiv.) in anhydrous diethyl ether at −78 °C under nitrogen. After 1 h a solution of pent-1-ynylcopper(I) (1 equiv.) and hexamethylphosphoric triamide (2 equiv.) in ether was added. After stirring for a further 1 h at −78 °C the solution of the cuprate (4) was ready for use.

Reaction of the Epoxyketone (2) *with the Cuprate* (4).—3-Oxatricyclo[4.2.0.$0^{2,4}$]octan-7-one (2) (1.68 g, 13.5 mmol) in dichloromethane (30 ml) was added dropwise to a solution of the mixed cuprate (4) (27 mmol) in ether (60 ml) at −78 °C under nitrogen. The solution was maintained at −78 °C for 20 h by storage of the reaction vessel in a Dewar flask packed with solid carbon dioxide. Saturated aqueous ammonium chloride was added and the layers were separated. The organic layer was stirred with ice-cold 1N-sulphuric acid and the resultant yellow precipitate filtered off. The filtrate was separated into two layers and the organic layer washed with 8% w/v sodium hydrogencarbonate–water, dried, and evaporated. T.l.c. (SiO_2; 20% v/v ethyl acetate–light petroleum as eluant) of the residue revealed the presence of a substantial amount of starting epoxide (2) (R_F 0.3), together with a major new product (5) (R_F 0.7) and a number of other minor products. Short-column chromatography on silica gel (350 g) and elution with 10 v/v ethyl acetate–light petroleum gave (1α,2α,4α,6α,7β)-7-{3-[*t-butyl*(*dimethyl*)*silyloxy*]*oct*-1-*enyl*}-3-*oxatricyclo*[4.2.0.$0^{2,4}$]*octan*-7-*ol* (5) (1.63 g, 33%) as a colourless oil, $\nu_{max.}$ (1.0, 0.1, and 0.025% w/v solutions in CCl_4) 3 470 cm^{-1} (OH, intramolecularly hydrogen-bonded), τ($CDCl_3$) 4.38 (2 H, m, CH=CH), 5.70br (1 H, s, OH), 5.95 (1 H, m, CH−O−), 6.30 and 6.40 (2 H, 2 m, H-2 and -4), 7.05 (1 H, m, H-6), 7.2—7.8 (3 H, H-1, -8α, and -8β), 7.8—8.5 (2 H, m, H-5α and -5β), 8.4—9.0 (8 H, complex, $-CH_2-CH_2CH_2CH_2-$), 9.10 (12 H, s + t, Bu^t and CH_2CH_3), and 10.0 (6 H, s, $-SiMe_2$) (Found: C, 69.1; H, 10.9. $C_{21}H_{38}O_3Si$ requires C, 68.8; H, 10.5%).

Treatment of the Epoxyacetal (10) *with the Cuprate* (4).—(1α,2α,4α,6α)-4α-Methoxy-3,7-dioxatricyclo[4.3.0.$0^{2,4}$]nonane (10) [13] (468 mg, 3 mmol) in diethyl ether (15 ml) was added to a stirred solution of the mixed cuprate (4) (4.5 mmol) in ether (50 ml) at −70 °C under nitrogen. After 2 h at this temperature the solution was allowed to warm to −20 °C and stood at this temperature for 2 days (freezer). The reaction was quenched by addition of saturated aqueous

ammonium chloride and, after stirring for 24 h, the layers were separated and the aqueous layer was extracted with ether. The dried ($MgSO_4$) organic extracts were evaporated and the residue examined by t.l.c. (SiO_2, eluting with 25% v/v ethyl acetate–light petroleum). Treatment with 2,4-dinitrophenylhydrazine reagent showed the starting material (10) as the only coloured spot. Short-column chromatography on silica gel (150 g) and elution with 10% v/v ethyl acetate–light petroleum returned the unchanged starting epoxide (10) (410 mg, 88%) (i.r., n.m.r., t.l.c.).

Reactions of Organometallic Reagents with the Epoxyacetal (3).—1. *Reaction with lithium* 3-[*t-butyl(dimethyl)silyloxy*]-*oct*-1-*enyl*(*pent*-1-*ynyl*)*cuprate* (4). A solution of the epoxyacetal (3) (1 equiv.; 1—3 mmol ml^{-1}) in dry ether was added dropwise to a stirred solution of the mixed cuprate (4) (1.1 equiv.; *ca.* 0.5 mmol ml^{-1}) in ether at −78 °C under nitrogen. After *ca.* 1 h at this temperature the solution was allowed to warm to −30 °C and stirred at this temperature for 16—20 h. The reaction was quenched by addition of saturated aqueous ammonium chloride and the layers were separated. The organic layer was stirred with ice-cold 2N-sulphuric acid and after the yellow precipitate had been filtered off the layers were separated and the aqueous layer was extracted with ether. The combined extracts were washed with 8% w/v sodium hydrogencarbonate–water and water, dried ($MgSO_4$), and evaporated to give an oil. This contained a mixture of the isomers (8) and (9) in the ratio 4 : 1 (g.l.c.; trimethylsilyl ether derivative; 2% OV-17; 220 °C). Short-column chromatography on silica gel, eluting with 20% v/v ethyl acetate–light petroleum afforded a mixture of the pure isomers (8) and (9) in 65—86% yield. These were separated by short-column chromatography on silica gel, eluting with dichloromethane. The major isomer (higher R_F) was (E)-(1α,2α,-3β,5α)-2-{3-[*t-butyl(dimethyl)silyloxy*]*oct*-1-*enyl*}*spiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-3-*ol* (8) isolated as a colourless oil, $\nu_{max.}$ (0.1, 1.0, and 10% w/v solutions in CCl_4) 3 530 cm^{-1} (O–H, intramolecularly hydrogen-bonded), τ($CDCl_3$) 4.5—4.9 (2 H, m, CH=CH), 5.9—6.3 (6 H, complex, $-OCH_2CH_2O-$ and 2 × >CH–O–), 6.9—7.9 (6 H, complex, H-1, -2, -5, -7α, and -7β, and OH), 8.06 (2 H, t, H-4α and -4β), 8.4—9.0 (8 H, complex, $-CH_2CH_2CH_2CH_2-$), 9.06 (12 H, singlet overlapped by multiplet, Bu^t and $-CH_2CH_3$), and 10.03 and 10.05 (6 H, 2 × s, >$SiMe_2$) (Found: C, 66.9; H, 10.4. $C_{23}H_{42}O_4Si$ requires C, 67.2; H, 10.1%).

The minor isomer (lower R_F) was (E)-(1α,2β,3α,5α)-3-{3-[*t-butyl(dimethyl)silyloxy*]*oct*-1-*enyl*}*spiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-2-*ol* (9) as a colourless oil, $\nu_{max.}$ (0.5% w/v solution in $CHBr_3$) 3 600 cm^{-1} (free O–H), τ($CDCl_3$) 4.2—4.7 (2 H, m, CH=CH; irradiation at this frequency caused collapse of the quartet at τ 5.90 to a triplet), 5.90 [1 H, q, $-CH(OSiMe_2Bu^t)CH=CH$; irradiation at this frequency caused decoupling of the olefinic protons at τ 4.2—4.7], 6.0—6.3 [5 H, complex, H-2α and $-OCH_2CH_2-O-$; the signals due to H-2α may be resolved by addition of Eu(fod)$_3$; because this compound is a 1 : 1 mixture of epimers due to the centre of asymmetry in the side chain, two multiplets are seen, each a doublet of doublets *J* 9 and 6 Hz], 7.1—7.8 (5 H, complex, H-1, -3, -5, -7α, and -7β), 8.07 (1 H, dd, *J* 13 and 6 Hz, H-4β), 8.22br (1 H, s, OH), 8.3—8.9 (9 H, complex, H-4α and $-CH_2CH_2CH_2CH_2-$), 9.09 (12 H, s overlapped by m, Bu^t and CH_2CH_3), and 9.98 (6 H, s, >$SiMe_2$) [Found: $(M + NH_4)^+$ (NH_3 ionisation), 428.316 6. $C_{23}H_{42}O_4Si$ requires ($M + NH_4$), 428.319 6].

2. *Reaction with a copper-catalysed Grignard reagent.* Purified anhydrous copper(I) iodide [14] (840 mg, 4.4 mmol) was added to 2M-n-butylmagnesium chloride in ether (45 ml, 0.09 mol) at −30 °C under nitrogen. After stirring for 45 min a dark purple suspension had formed and a solution of the epoxyacetal (3) (8.4 g, 0.05 mol) in ether was added dropwise over 20 min. The reaction was exothermic and a cooling bath at −50 °C was used to hold the internal temperature at −30 °C during addition. When addition was complete the temperature was maintained at −30 °C for a further 2 h. After standing at 0 °C for 18 h the mixture was poured into a mixture of saturated aqueous ammonium chloride (300 ml) and 2N-hydrochloric acid (45 ml) and shaken until a colourless organic layer was obtained. The aqueous layer was further extracted with ether and the combined organic layers dried (Na_2SO_4). Evaporation gave a pale yellow oil (11.2 g, 98%) which contained a mixture of the isomers (11) and (12) in the ratio 4 : 1 [^{13}C n.m.r., g.l.c. analysis (trimethylsilyl ether derivative) 3% OV-275, 120 °C]. G.l.c. also showed a small amount of an unidentified impurity (6% by peak area).

The individual isomers were isolated by subjecting a portion (560 mg) of the mixture to preparative t.l.c. on silica gel (5% v/v methanol–dichloromethane). (1α,2α,3β,-5α)-2-*Butylspiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-3-*ol* (11) (R_F 0.4) was obtained as an oil (339 mg), $\nu_{max.}$ (0.1% and 1% w/v solution in CCl_4) 3 525 cm^{-1} (O–H, intramolecularly hydrogen-bonded; for a 10% solution an additional broad, less intense band was visible at 3 100—3 500 cm^{-1} due to intermolecularly hydrogen-bonded O–H), τ(C_6D_6) 6.04 (1 H, q, H-3α), 6.3—6.8 (4 H, complex, $-OCH_2-CH_2O-$), 6.9br (1 H, s, OH), 6.8—8.4 (7 H, complex), 8.5—9.0 (6 H, complex, $-CH_2CH_2CH_2-$), and 9.0—9.3 (3 H, m, CH_2CH_3) (Found: C, 69.1; H, 10.2. $C_{13}H_{22}O_3$ requires C, 69.0; H, 9.8%).

The minor isomer (R_F 0.3) was 3-*butylspiro*{*bicyclo*[3.2.0]-*heptane*-6,2′-[1,3]*dioxolan*}-2-*ol* (12), isolated as an oil (70 mg) which solidified in the refrigerator, $\nu_{max.}$ (0.1% solution in CCl_4) 3 620 cm^{-1} (free O–H) (for a 10% solution the main O–H band is broadened by intermolecular hydrogen-bonding and has $\nu_{max.}$ 3 460 cm^{-1}), τ(CCl_4) 6.1—6.35 (4 H, m, $-OCH_2CH_2O-$), 6.42 (1 H, dd, *J* 6.75 and 9.0 Hz, H-2α), 7.2—8.4 (8 H, complex), 8.5—9.0 (6 H, complex, $-CH_2-CH_2CH_2-$), and 9.08 (3 H, m, CH_2CH_3) (Found: C, 68.6; H, 10.0. $C_{13}H_{22}O_3$ requires C, 69.0; H, 9.8%).

3. *Reaction with* 1,3-*dithian*-2-*yl-lithium.* n-Butyllithium (1.6M solution in hexane; 6.3 ml, 10 mmol) was added dropwise to 1,3-dithian (1.213 g, 10 mmol) in dry tetrahydrofuran (30 ml) at −60 °C under nitrogen. After stirring for 3 h a solution of the epoxyacetal (3) (841 mg, 5 mmol) in tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to warm to −20 °C and kept at this temperature for 16 h. The reaction was quenched by addition of water (10 ml) and the layers separated. The organic layer was washed with 2N-sodium hydrogencarbonate, and brine, dried ($MgSO_4$), and evaporated to give an oil (2.04 g). Short-column chromatography on silica gel (120 g) eluting with 5% v/v ethyl acetate–light petroleum afforded the product (1.305 g, 91%) as a mixture of the isomers (13) and (14) (homogeneous by t.l.c.) in the ratio 73 : 27 [g.l.c. (trimethylsilyl ether derivative) 3% OV-210, 180 °C]. Spectroscopic data showed the major isomer to be (1α,2α,3β,5α)-2-(1,3-*dithian*-2-*yl*)*spiro*{*bicyclo*-[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-3-*ol* (13), $\nu_{max.}$ (0.1% solution in CCl_4) 3 520 cm^{-1} (O–H, intramolecularly hydrogen-

bonded), τ($CDCl_3$) 5.78 (1 H, q, H-3α), 6.05 (1 H, d, -S-CHS-), 6.1—6.3 (4 H, complex, $-OCH_2CH_2O-$), and 7.0—8.5 (14 H, complex) (Found: C, 54.2; H, 7.2. $C_{13}H_{20}O_3S_2$ requires C, 54.15; H, 6.95%).

4. *Reaction with* [1,3-*bis*(*methylthio*)*prop*-2-*enyl*]-*lithium*. A 1.55M solution of n-butyl-lithium in hexane (84.5 ml) was added to a stirred solution of 1,3-bis(methylthio)-2-methoxypropane [9] (10.9 g, 65.5 mmol) and di-isopropylamine (18.6 ml) in dry tetrahydrofuran (200 ml) at −78 °C under nitrogen. After being stored at 0—5 °C for 2 h the deep purple solution was cooled to −78 °C, treated with the epoxyacetal (3) (10.0 g, 59.5 mmol) over 20 min, and maintained at −78 °C for 2 h. The mixture was then allowed to warm slowly to −5 °C over 15 h and finally shaken with saturated aqueous ammonium chloride (250 ml). The aqueous layer was separated and extracted with ether (2 × 100 ml). The combined organic layers were then dried ($MgSO_4$) and concentrated under reduced pressure to give an orange oil (19.0 g). Chromatography on silica gel (25% v/v ethyl acetate–light petroleum as eluant) removed non-polar impurities. Further elution with 50% v/v ethyl acetate–light petroleum gave (1α,2α,3β,5α)-2-[1,3-*bis*-(*methylthio*)*prop*-2-*enyl*]*spiro*{*bicyclo*[3.2.0]*heptan*-6,2′-[1,3]-*dioxolan*}-3-*ol* (15), contaminated with a small proportion of its regioisomer (16), as a viscous orange oil (13.0 g, 72%), $\nu_{max.}$ (0.1% solution in CCl_4) 3 620 weak (free O–H) and 3 520 strong cm^{-1} (intramolecularly hydrogen-bonded O–H), τ($CDCl_3$) 3.65—4.15 (1 H, complex, -CH=C*H*-SMe), 4.25—5.30 (1 H, complex, -*CH*=CH-SMe), 5.60—6.35 (5 H, complex, $-OCH_2CH_2O-$ and H-3α), and 5.35—8.40 (15 H, complex) [Found: C, 56.7; H, 7.4%; M^+ (electron inpact), 302.099. $C_{14}H_{22}O_3S_2$ requires C, 55.6; H, 7.3%; *M*, 302.101]. This material is a complex mixture of isomers due to the presence in the side chain of both a centre of asymmetry and a disubstituted double bond. To determine the ratio of regioisomers (15) : (16) a sample was hydrolysed by sequential treatment first with 0.3M-hydrochloric acid in aqueous acetone and then with a mixture of calcium carbonate and mercuric chloride in aqueous acetonitrile [9] to give a mixture of the αβ-unsaturated aldehydes (19) and (20) (100%). The isomer ratio was 83 : 17 [^{1}H n.m.r. and g.l.c. (3% OV-225, 160 °C)].

5. *Reaction with dimethyl*-[3-(*trimethylsilyloxy*)*oct*-1-*ynyl*]-*aluminium*. 1.6M-n-Butyl-lithium in hexane (31.25 ml, 50 mmol) was added over 10 min to a stirred solution of 3-trimethylsilyloxyoct-1-yne [3] (9.9 g, 50 mmol) in toluene (30 ml) at 0 °C under nitrogen. After 15 min a 25% w/v solution of dimethylchloroalane in hexane (14.8 ml) was added over 10 min followed, after stirring for a further 1 h, by the epoxyacetal (3) (3.36 g, 20 mmol) in toluene (10 ml). The mixture was heated to 80 °C with stirring for 8 h, then cooled to 0 °C and quenched by the addition of saturated aqueous sodium sulphate (100 ml). The mixture was clarified by filtration and the layers were separated. The aqueous layer was extracted with ether and the combined organic layers washed with water, dried ($MgSO_4$), and evaporated to give an oil (15.15 g). This was dissolved in methanol (135 ml) and a solution of potassium carbonate (7.5 g) in water (30 ml) added. After 3 h at 20 °C the methanol was removed by evaporation and the residue extracted with ether. The dried ($MgSO_4$) extracts were evaporated to give an oil (9.5 g) containing two regioisomers (22) and (23) in the ratio 13 : 7 (g.l.c.; trimethylsilyl ether derivative, 2% OV-17, 200 °C). Short-column chromatography on silica gel eluting with 3% v/v ethanol–chloroform gave (in order of elution) oct-1-yn-3-ol (2.8 g, 22 mmol), identical (i.r. and t.l.c.) with authentic material; (1α,2α,3β,5α)-2-(3-*hydroxyoct*-1-*ynyl*)*spiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-3-*ol* (22) (3.7 g, 63%) as a colourless oil, $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 590 (free O–H on the side chain), 3 470 (intramolecularly hydrogen-bonded O–H on the ring), and 2 230w cm^{-1} (C≡C), τ($CDCl_3$) 5.5—5.85 (2 H, complex, 2 × -CH-O-), 6.1 (4 H, s, $-OCH_2CH_2O-$), 6.25 (1 H, d, ring OH), 6.90 (1 H, m, H-5α), 7.81br (1 H, s, H-2β), 7.3—8.2 (5 H, complex, H-1, -4α, -4β, -7α, and -7β), 7.8br (1 H, s, side-chain OH), 8.2—8.9 (8 H, complex, $-CH_2CH_2CH_2CH_2-$), and 9.10 (3 H, m, CH_2CH_3) (Found: C, 69.2; H, 8.85. $C_{17}H_{26}O_4$ requires C, 69.4; H, 8.85%); (1α,2β,3α,5α)-3-(3-*Hydroxyoct*-1-*ynyl*)*spiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]*dioxolan*}-2-*ol* (23) (1.85 g, 34%) as a colourless oil, $\nu_{max.}$ (0.5% solution in $CHBr_3$) 3 590 (free O–H) and 2 225w cm^{-1} (C≡C), τ($CDCl_3$) 5.70 (1 H, m, -CH-O in side-chain), 5.97 (1 H, dd, *J* 6 and 9 Hz, H-2α), 6.1—6.3 (4 H, m, $-OCH_2CH_2O-$), 6.8—9.0 (16 H, complex), and 9.10 (3 H, m, CH_2CH_3) (Found: C, 69.3; H, 8.85. $C_{17}H_{26}O_4$ requires C, 69.4; H, 8.95%).

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