Synthesis of 2,5- and 2,6-Norbornane† Derivatives with Prostaglandin-like Side Chains

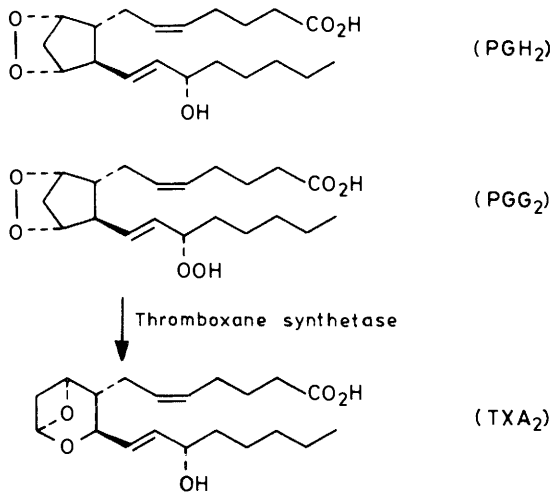
David I. Davies* and Peter M. Gomez
Department of Chemistry, King's College, Strand, London WC2R 2LS
Peter Hallett*
Chemistry Research Department, Glaxo Group Research Ltd., Priory Street, Ware, Herts SG12 0DJ

Norborn-5-en-2-*endo*-ylmethyl toluene-4-sulphonate, readily prepared from the Diels–Alder adduct of cyclopentadiene and acrylic acid, has been converted, in six and seven stages respectively, into the prostaglandin-like compounds 2-*endo*-(6-carboxyhex-2-enyl)norbornan-5- and -6-*exo*-yl 2-hydroxyheptyl ethers. The synthesis of the former compounds involves a novel hydroxyethoxy mercuriation of a norbornene double bond.

Since the identification of the potent biological activity of the prostaglandin endoperoxides (PGH_2 and PGG_2) in the early 1970's[1] a number of syntheses of analogues have been described, in which the unstable endoperoxy linkage of the bicyclo[2.2.1] ring system has been replaced.[2] Most of the analogues mimic the biological activity found in the natural compounds although some inhibit the enzyme thromboxane (TX) synthetase and/or have thromboxane A_2 (TXA_2)/(PGH_2) receptor antagonist activity.[2,3] TXA_2 is implicated in various types of occlusive vascular disease where vasospasm and platelet aggregation are thought to play a major role. Thus a selective inhibitor of TXA_2 biosynthesis or a TXA_2 receptor antagonist could provide an effective treatment for thrombosis and related disorders.[4] In the search for suitable compounds, and to extend studies[5] on norbornane derivatives as analogues of the endoperoxides, the synthesis has been undertaken of the novel compounds (**1**) and (**2**). These contain side chains having, respectively, a 2,5 and 2,6 disposition, which contrasts with the endoperoxide analogues reported to date, all of which have the side chains attached to the adjacent carbon atoms of the bicyclic system. The choice of target compounds (**1**) and (**2**) was made following an examination of the molecular models; this suggested that, because of the rigidity of the norbornane system, the α- and β-side chains, particularly when at the respective 2- and 6-positions, will have a spatial disposition similar to that of the side chains in PGG_2 and PGH_2. As an additional variation in compounds (**1**) and (**2**), the β-side chains have the conventional *trans* double bond replaced by $-OCH_2-$, since changes of this type are thought to reduce the susceptibility of the side chain hydroxy group to enzymic oxidation.[3,6]

The syntheses of compounds (**1**) and (**2**) are outlined in the Scheme. Starting with cyclopentadiene and acrylic acid, an epimeric mixture of the norborn-5-en-2-ylcarboxylic acids (**3**) is readily obtained[7] from which, *via* the iodolactone (**4**),[8] the pure *endo*-acid (**5**) was separated.[9] Reduction of compound (**5**) with lithium aluminium hydride afforded the alcohol (**6**), which was efficiently derivatised as the toluene-4-sulphonate (**7**),[10] the key intermediate in the separate synthetic pathways to (**1**) and (**2**). The toluene-4-sulphonate (**7**) has a 2-*endo* substituent that can be elaborated into the α-side chain. It also has a double bond from which a β-side chain can be constructed *via* initial addition which, according to precedent,[11] will take place from an *exo* direction.

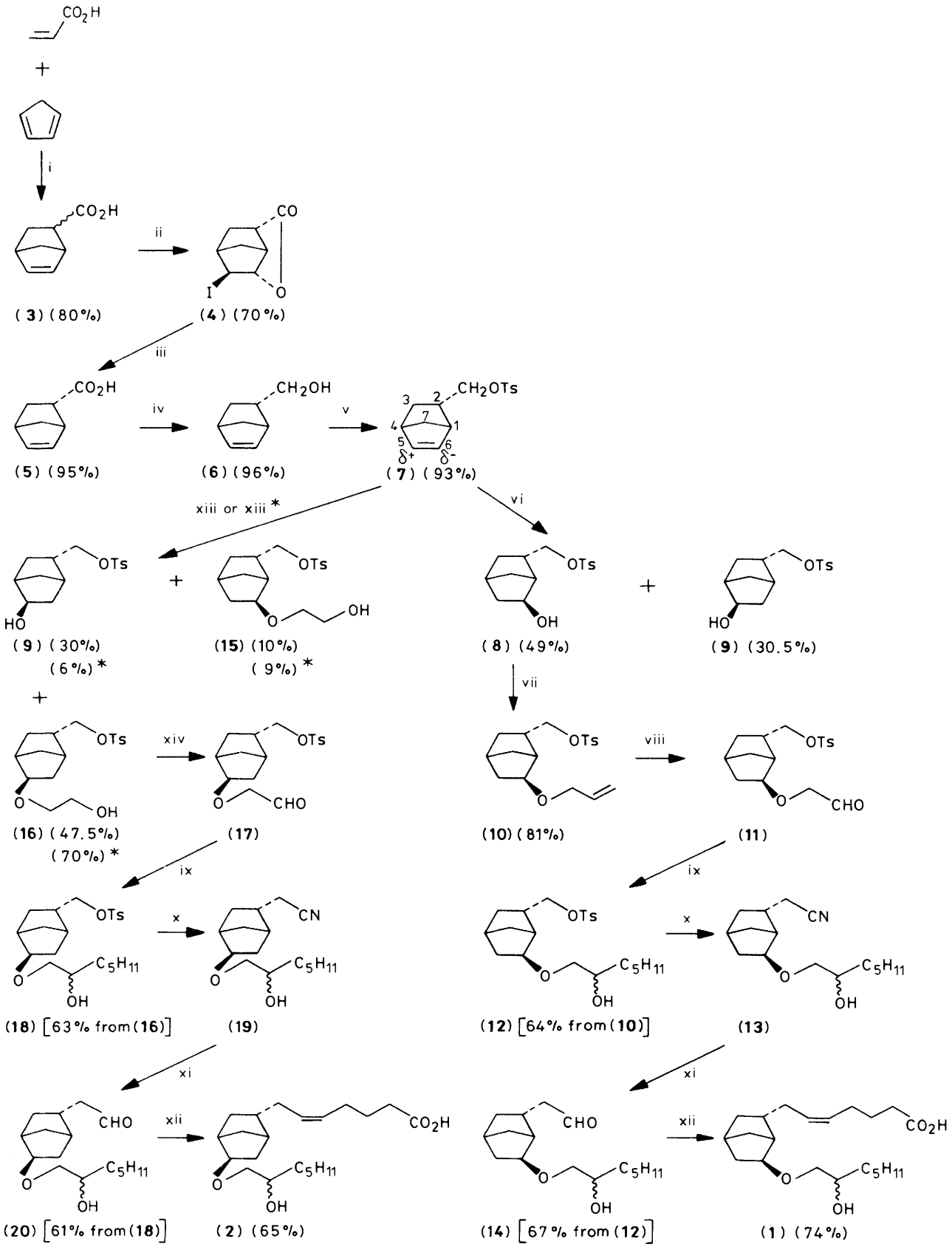
In the first synthetic approach, hydroboration/oxidation of compound (**7**) gave a 5:3 mixture of the alcohols (**8**) and (**9**)



which could be separated by chromatography on silica. The orientation favouring reaction at C-6 rather than C-5 implies, as shown in (**7**), polarisation to some extent of the 5,6 double bond due to electron withdrawal by the CH_2OTs group. After separation, the alcohol (**8**) was readily alkylated with allyl bromide and sodium hydride giving the allyl ether (**10**), the double bond of which could be cleaved on ozonolysis to afford the aldehyde (**11**). This aldehyde (**11**), without purification, was treated with n-pentylmagnesium bromide to give the secondary alcohol (**12**), which was readily purified by chromatography on silica. The toluene-4-sulphonate function in (**12**) was displaced on treatment with potassium cyanide to give the nitrile (**13**) which, without purification, was reduced with di-isobutylaluminium hydride to the hydroxyaldehyde (**14**). In the final step, the Wittig reaction of (**14**) with 4-carboxybutyltriphenylphosphonium bromide proceeded to give the target molecule (**1**).

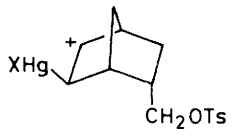
Since the alcohol (**9**) was the minor component of the product from hydroboration/oxidation of (**7**), an alternative route to that for the conversion of (**8**) into (**1**) was sought to give the product (**2**). Alkoxymercuriation/demercuriation[12] of an olefin usually results in products with the opposite orientation to those resulting from hydroboration/oxidation.[13] The formal addition of water to a double bond *via* oxymercuriation/demercuriation or the addition of an alcohol *via* alkoxymercuriation/demercuriation are well known[12] reactions, but there appears to be no literature precedent for the use of ethylene glycol, or indeed any other diol, as a nucleophile in such reactions. However, when the alkene (**7**) was treated with

† The use of norbornane is not recommended by I.U.P.A.C. but is retained for ease of comparison with the literature. The systematic name for the parent compound is 8,9,10-trinorbornane.

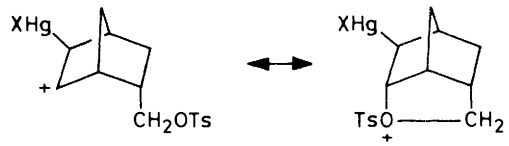


Scheme. *Reagents:* i, 50 °C; ii, $NaHCO_3$–I_2; iii, Zn–AcOH; iv, $LiAlH_4$; v, *p*-$CH_3C_6H_4SO_2Cl$–pyridine; vi, B_2H_6, $NaOH$–H_2O_2; vii, $CH_2{=}CHCH_2Br$–NaH; viii, O_3, Zn–HOAc; ix, n-$C_5H_{11}MgBr$; x, KCN; xi, $HAl(CHMe_2)_2$; xii, $Ph_3\overset{+}{P}CH(CH_2)_3CO_2^-$; xiii, $Hg(OCOCF_3)_2$–$HOCH_2CH_2OH$, $NaBH_4$; xiii * $Hg(NO_3)_2$–$HOCH_2CH_2OH$, $NaBH_4$; xiv, Me_2SO–$(COCl)_2$

ethylene glycol and mercuric trifluoroacetate, and the product reduced with sodium borohydride, a mixture was obtained in which the alcohol (**9**) and the 6- and 5-hydroxyethoxy ethers (**15**) and (**16**) were present in the proportions 30:10:47.5. When mercuric nitrate was used in place of mercuric trifluoroacetate, the proportion of the desired product (**16**) was substantially increased, the ratio of products (**9**), (**15**), and (**16**) being 6:9:70. Assuming polarisation of the double bond as shown in structure (**7**), attack by a species $(HgOCOCF_3)^+$ will occur preferentially



(**21**)

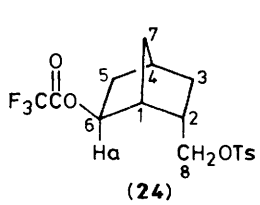


(**22**) (**23**)

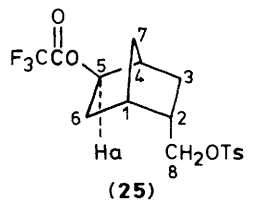
a; X = $F_3CCO_2^-$
b; X = NO_3^-

at C-6 to afford (**21a**) in which the positive charge is at C-5 and competes for reaction with the available nucleophiles. (Water is probably not among these available nucleophiles since both commercial ethylene glycol and extensively dried ethylene glycol lead to the same ratio of products.) Attack on (**21a**) by ethylene glycol followed by borohydride reduction leads to the ether (**16**) while attack by trifluoroacetate anion followed by borohydride reduction leads to the alcohol (**9**) assuming that the trifluoroacetate group is reduced or hydrolysed to a hydroxy group in the alkaline reaction medium. The intermediate (**22a**) formed by attack of $(HgOCOCF_3)^+$ at C-5 appears to react only with ethylene glycol and, following borohydride reduction, gives (**15**). The intermediate (**22a**) is more stable than (**21a**) as a result of a contributing structure (**23a**). This may result in (**22a**) being less reactive and consequently more selective so that it reacts only with ethylene glycol; intermediate (**21a**), however, is less stable, more reactive and hence less selective so that it reacts with both of the competing nucleophiles ethylene glycol and trifluoroacetate anion. When $(HgNO_3)^+$ reacts with compound (**7**) the intermediates, (**21b**) and (**22b**), compete for reaction with nitrate ion and ethylene glycol. Since nitrate ion is a weaker nucleophile than the trifluoroacetate ion, (**21b**) reacts preferentially with ethylene glycol so that the final product, after borohydride reduction, contains a greater proportion of (**16**) relative to (**9**) than that obtained from mercuric trifluoroacetate. Chromatography of the mixture of products (**9**), (**15**), and (**16**) on silica allowed the isolation of (**16**), with (**9**) and (**15**) being obtained as an inseparable mixture. For the oxidation of (**16**) to the aldehyde (**17**), the most effective reagent was $(COCl)_2$–dimethyl sulphoxide, due to Swern.[14] Without purification, the aldehyde (**17**) was readily converted into the secondary alcohol (**18**) on reaction with n-pentylmagnesium bromide. The conversion of (**19**) into the target compound (**2**) was achieved *via* (**20**) in a similar manner to the conversion of (**13**) into (**1**).

The isomeric alcohols (**8**) and (**9**), and by inference those compounds derived from them, were distinguished by use of the nuclear Overhauser effect (n.O.e.). Their corresponding trifluoroacetate derivatives (**24**) and (**25**) were prepared; the C-8 protons were well separated in the n.m.r. spectra from the 6-*endo*-H [in (**24**)] the 5-*endo*-H [in (**25**)]. The n.O.e. difference spectra on saturation of H_a in the major isomer (δ 4.87) gave a



(**24**)



(**25**)

positive signal (η = 0.026 and 0.063) for the C-8 protons (δ 3.89, 4.13) and also for the C-1 proton (δ 2.53, η 0.046). No signal was observed for the 3-*endo*-H (δ 0.070). Conversely, saturation of H_a in the minor isomer (δ 4.68) produced a positive n.O.e. for the C-4 proton (δ 2.4, η 0.053) and for the 3-*endo*-H (octet, δ 0.6, η 0.043). No signal was observed for the C-8 protons (δ 3.94, 4.02). Thus the trifluoroacetates (**24**) and (**25**), and hence the major isomer (**8**) and the minor isomer (**9**) from the hydroboration/oxidation of (**7**), were identified.

The endoperoxide analogues (**1**) and (**2**) were examined in a variety of test procedures[15] but failed to show any significant prostaglandin-like activity.

Experimental

An epimeric mixture of norborn-5-en-2-ylcarboxylic acids (**3**),[7] 6-*endo*-hydroxy-5-*exo*-iodonorbornan-2-*endo*-ylcarboxylic acid δ-lactone (**4**),[8] norborn-5-en-2-*endo*-ylcarboxylic acid (**5**),[9] norborn-5-en-2-*endo*-ylmethanol (**6**),[10] and norborn-5-en-2-*endo*-ylmethyl toluene-4-sulphonate (**7**)[10] were prepared by literature procedures. For column chromatography, the silica used was Merck Kieselgel 60 (Art 7729) and for thin layer chromatography (t.l.c.) Merck Kieselgel 60F 254 (Art 5735). The light petroleum used had b.p. 60—80 °C. Ether refers to diethyl ether.

6-exo-*Hydroxynorbornan*-2-endo-*ylmethyl Toluene*-4-*sulphonate* (**8**) *and* 5-exo-*Hydroxynorbornan*-2-endo-*ylmethyl Toluene*-4-*sulphonate* (**9**).—The toluene-4-sulphonate (**7**) (23.4 g, 84.17 mmol) was dissolved in dry tetrahydrofuran (50 ml) and the solution cooled to 0 °C in an ice–water bath. A solution of borane in tetrahydrofuran (65 ml of 0.6M, 40 mmol) prepared by the method of Brown[16] was then added *via* a syringe to the stirred solution of (**7**) under nitrogen. Stirring was continued for 1 h when water (3 ml) was added to quench the excess of borane. This was followed by the successive additions of sodium hydroxide solution (30 ml of 3M) and hydrogen peroxide solution (30 ml of 100 vol), and stirring was continued for a further 30 min. A saturated solution of sodium chloride (40 ml) was then added and the layers separated. The aqueous layer was extracted with ether (2 × 30 ml) and the extracts combined with the organic layer, washed with water (2 × 30 ml), and dried ($MgSO_4$). Evaporation of the solvent left a viscous oil (26 g) which was separated by column chromatography (silica, 200 g; 30—40% ethyl acetate in light petroleum as eluant) to afford the following compounds. (i) 6-exo-*Hydroxynorbornan*-2-endo-*ylmethyl toluene*-4-*sulphonate* (**8**) (12.3 g, 39 mmol) as a clear oil which crystallised on standing at 0 °C as a white solid, m.p. 49—50 °C (Found: C, 60.5; H, 6.8. $C_{15}H_{20}O_4S$ requires C, 60.79; H, 6.8%). T.l.c. R_F 0.52 with ethyl acetate–light petroleum, 1:1, as eluant; $\nu_{max.}(CHBr_3)$ 3 590 (OH), 1 358 and 948 cm^{-1} (OSO_2); δ (250 MHz; $CDCl_3$) 0.53 (ddd, 3-*endo*-H), 1.20 (m, 7-H *anti* to OH), 1.37 (m, 5-*exo*-H), 1.56 (m, 5-*endo*-H), 1.6—1.75 (m, 7-H *syn* to OH, 3-*exo*-H), 2.1—2.3 (m, 2-*exo*-H, 1-H, 4-H), 2.5 (s, CH_3), 3.87 (m, 8-H, 6-*endo*-H), and 3.98 (m, H-8); *J* (2-*exo*, 3-*endo*) 5.0, (3-*endo*, 3-*exo*) 12.5, (3-*endo*, 7-*syn*) 2.5, (5-*endo*, 5-*exo*) 13.5, (5-*endo*, 6-*endo*) 7, and (5-*endo*, 7-*syn*) 2.5 Hz; *m/z* 314 $(M + NH_4)^+$, 124 $(M - HOSO_2C_6H_4CH_3\text{-}p)^+$ For the trifluoroacetate derivative (**24**), δ (250 MHz; $CDCl_3$) 0.70 (octet, 3-

endo-H), 1.38 (m, 7-H *anti* to $OCOCF_3$), 1.57 (m, 5-*exo*-H), 1.68 (m, 7-H *syn* to $OCOCF_3$), 1.7—1.85 (m, 3-*exo*-H, 5-*endo*-H), 2.3—2.4 (m, 2-*exo*-H, 4-H), 2.53 (m, 1-H), 3.89, 4.13 (m, 8-H), and 4.87 (m, 6-*endo*-H). (ii) 5-exo-*Hydroxynorbornan*-2-endo-*ylmethyl toluene*-4-*sulphonate* (**9**) (7.6 g, 25.6 mmol) as a viscous oil which crystallised on standing, m.p. 58—59 °C (Found: C, 60.4; H, 6.8. $C_{15}H_{20}O_4S$ requires C, 60.79; H, 6.80%). T.l.c. R_F 0.37 with ethyl acetate–light petroleum, 1:1 as eluant; $\nu_{max.}$ ($CHBr_3$) 3 600 (OH), 1 360 and 950 cm^{-1} (OSO_2); δ (250 MHz; $CDCl_3$) 0.42 (ddd, 3-*endo*-H), 1.12 (m, 6-*exo*-H), 1.25 (m, 7-H *anti* to OH), 1.5 (s, OH), 1.6—1.8 (m, 3-*exo*-H, 7-H *syn* to OH), 1.73 (m, 3-*endo*-H), 2.1 (m, 2-*exo*-H, 4-H), 2.26 (m, 1-H), 2.45 (s, Me), 3.58 (m, 5-*endo*-H), and 3.78 and 3.95 (2 × q, 8-H); *J* (2-*exo*, 3-*endo*) 5.0, (3-*endo*, 3-*exo*) 12.0, (3-*endo*, 7-*syn*) 2.0, (5-*endo*, 6-*endo*) 7, (5-*endo*, 6-*exo*) 3.5, (5-*endo*, 7-*syn*) 3.5, (6-*endo*, 6-*exo*) 14, and (6-*endo*, 7-*syn*) 2.5 Hz; *m/z* 314 $(M + NH_4)^+$, 142 $(M + NH_4 - HOSO_2C_6H_4CH_3\text{-}p)^+$, and 124 $(M - HOSO_2C_6H_4CH_3\text{-}p)^+$. For the trifluoroacetate derivative (**25**), δ (250 MHz; $CDCl_3$) 0.58 (octet, 3-*endo*-H), 1.4 (m, 7-H *anti* to $OCOCF_3$, 6-*exo*-H), 1.67 (m, 7-H *syn* to $OCOCF_3$), 1.82 (octet, 3-*exo*-H), 1.91 (octet, 6-*endo*-H), 2.22 (m, 2-*exo*-H), 2.4 (m, 1-H, 4-H), 3.94 and 4.02 (m, 8-H), and 4.68 (m, 5-*endo*-H).

2-endo-(4-*Tolylsulphonyloxymethyl*)*norbornan*-6-exo-*yl Prop*-2-*enyl Ether* (**10**).—The alcohol (**8**) (3 g, 10.1 mmol) was dissolved in dimethoxyethane (10 ml) and the solution added dropwise to a stirred slurry of allyl bromide (5.32 g, 40.4 mmol) and sodium hydride (0.7 g of an 80% suspension in oil, 20.2 mmol) under nitrogen at room temperature.

After completion of the addition the resultant slurry was stirred for a further 2.5 h, cooled in an ice–water bath and water (10 ml) carefully added dropwise to decompose the excess of sodium hydride. Most of the dimethoxyethane and excess of allyl bromide was evaporated under reduced pressure to afford a residue which was extracted with ether (3 × 75 ml). The combined ether layers were washed with water (2 × 50 ml), dried ($MgSO_4$), and the solvent evaporated to afford an oil which was purified by column chromatography (silica, 80 g; 15—20% ethyl acetate in light petroleum as eluant) to afford the *allyl ether* (**10**) (2.75 g, 8.2 mmol) as a clear oil (Found: C, 64.2; H, 7.4. $C_{18}H_{24}O_4S$ requires C, 64.26; H, 7.19%). T.l.c. R_F 0.47 with 20% ethyl acetate in light petroleum as eluant; $\nu_{max.}$($CHBr_3$) 1 360, 1 175 (OSO_2), and 810 cm^{-1} (*p*-C_6H_4); δ (250 MHz; $CDCl_3$) 0.52 (ddd, 3-*endo*-H), 1.16 (d, 7-H *syn* to OTs), 1.4 (m, 5-*endo*-H, 5-*endo*-H), 1.65 (m, 3-*exo*-H, 7-H *anti* to OTs), 2.2 (m, 2-H, 4-H), 2.45 (m, 1-H, $OSO_2C_6H_4Me\text{-}p$), 3.5 (m, 6-*endo*-H), 3.85 (m, $OCH_2CH{=}CH_2$), 3.98, 3.85 (m, 8-H), 5.1—5.3 (m, $OCH_2CH{=}CH_2$), and 5.88 (m, $OCH_2CH{=}CH_2$); *J* (2-*exo*, 3-*endo*) 5, (3-*endo*, 3-*exo*) 12.0, (3-*endo*, 7-*anti*) 2.5, and (7-*syn*, 7-*anti*) 10 Hz; *m/z* 336 (M^+), 295 ($M^+ - C_3H_5$), 279 ($M^+ - OC_3H_5$), and 181 ($M^+ - OSO_2C_6H_4Me\text{-}p$).

2-*Hydroxyheptyl* 2-endo-(4-*Tolylsulphonyloxymethyl*)*norbornan*-6-exo-*yl Ether* (**12**).—The allyl ether (**10**) (1.37 g, 4 mmol) was dissolved in methylene dichloride (30 ml) and the solution cooled to −78 °C in a dry ice–acetone bath. A stream of 2% ozone in oxygen was passed through this stirred solution for 20 min, after which time a blue colouration persisted indicating the presence of an excess of ozone. Zinc dust (1.5 g, 23 mmol) and glacial acetic acid (5 ml) was then added to this cold solution with stirring, and the cooling bath removed. Stirring was continued for 1.5 h at room temperature when the solution was filtered and the solvent evaporated from the filtrate. The resultant residue was dissolved in ether (150 ml) and the ether solution washed successively with sodium hydroxide solution (2 × 40 ml of 1M) and water (2 × 40 ml) before being dried ($MgSO_4$). Evaporation of the solvent afforded crude formylmethyl 2-*endo*-(4-tolylsulphonyloxymethyl)norbornan-6-*exo*-yl ether (**11**) as a clear oil (1.23 g, 3.6 mmol), t.l.c. R_F 0.18 using 30% ethyl acetate in light petroleum as eluant; $\nu_{max.}$ ($CHBr_3$) 1 730 cm^{-1} (C=O); δ (250 MHz; $CDCl_3$) 0.57 (ddd, 3-*endo*-H), 1.1—1.8 (m, 3-*exo*-H, 5-H, 7-H), 2.26 (m, 2-*exo*-H, 4-H), 2.45 (br s, 1-H, CH_3), 3.58 (m, 6-*endo*-H), and 3.8—4.1 (m, 8-H, OCH_2CHO); *J* (2-*exo*, 3-*endo*) 6, (3-*endo*, 3-*exo*) 12.5, and (3-*endo*, 7-*anti*) 2.5 Hz; *m/z* 338 (M^+), 295 ($M^+ - CH_2CHO$), and 279 ($M^+ - OCH_2CHO$).

The crude aldehyde (**11**) (1.2 g, 3.5 mmol) was dissolved in dry tetrahydrofuran (10 ml) and the solution cooled to 0 °C under nitrogen. n-Pentylmagnesium bromide (5 ml of 2M solution in ether) was added slowly during 15 min to the stirred solution. After completion of the addition the solution was allowed to warm up to room temperature during 30 min, stirring was continued for a further 30 min, and the solution was then acidified with dilute hydrochloric acid and partitioned between water (30 ml) and ether (75 ml). The ether layers were then separated and the aqueous layer extracted with ether (2 × 30 ml) and these extracts were combined with the original ether layer, washed with water (2 × 30 ml), dried ($MgSO_4$), and the solvent evaporated to leave a colourless oil (1.8 g). Purification by column chromatography (silica, 45 g; 25% ethyl acetate in light petroleum as eluant) gave the *secondary alcohol* (**12**) as a colourless oil (1.05 g, 2.5 mmol) (Found: C, 64.5; H, 8.5. $C_{22}H_{34}O_5S$ requires C, 64.37; H, 8.35%). T.l.c. R_F 0.3 using 30% ethyl acetate in light petroleum as eluant; $\nu_{max.}$($CHBr_3$) 3 580 (OH), 1 360 and 949 cm^{-1} (OSO_2); δ (250 MHz; $CDCl_3$) 0.52 (m, 3-*endo*-H), 1.88 (t, CH_3), 1.17 (d, 7-H *syn* to OTs), 2.1—2.3 (m, 2-*exo*-H, 4-H, OH), 2.35—2.55 (m, 1-H, CH_3), 3.0—3.3 [m, $OCH_2CH(OH)C_5H_{11}$], 3.47 (br m, 6-*endo*-H), 3.67 [br m, $OCH_2CH(OH)C_5H_{11}$], and 3.38 and 3.97 (m, 8-H); *J* (2-*exo*, 3-*endo*) 5.5, (3-*endo*, 3-*exo*) 12.0, and (3-*endo*, 7-*anti*) 2.5 Hz; *m/z* 410 (M^+), 295 ($M^+ - C_7H_{15}O$), and 279 ($M^+ - C_7H_{15}O_2$).

2-*Hydroxyheptyl* 2-endo-*Formylmethylnorbornan*-6-exo-*yl Ether* (**14**).—Potassium cyanide (0.36 g, 5.5 mmol) was added to a stirred solution of the secondary alcohol (**12**) (1.8 g, 4.4 mmol) in dry dimethyl sulphoxide (30 ml) at room temperature. The solution was heated in an oil-bath at 110 °C and stirring continued for 6 h. The cooled mixture was poured into brine (200 ml) and extracted with ether (3 × 75 ml). The combined ether extracts were washed with brine (2 × 50 ml), dried ($MgSO_4$), and the solvent evaporated to afford crude 2-*endo*-cyanomethylnorbornan-6-*exo*-yl 2-hydroxyheptyl ether (**13**) as a light brown oil (1.15 g, 4.3 mmol), t.l.c. R_F 0.23 using 30% ethyl acetate in light petroleum as eluant; $\nu_{max.}$(film) 3 450 (OH) and 2 240 cm^{-1} (CN).

The crude nitrile (**13**) (1.1 g, 4.1 mmol) was dissolved in dry toluene (30 ml) and the solution cooled to −70 °C. To this stirred solution di-isobutylaluminium hydride (11 ml of 1M solution in toluene) was added dropwise *via* a syringe during 5 min, and stirring was continued for a further 30 min at −70 °C. The reaction mixture was then allowed to warm up to room temperature and stirring continued for 4.5 h; the reduction was then stopped by the addition of methanol (10 ml) to destroy the unchanged di-isobutylaluminium hydride. A saturated solution of ammonium chloride (150 ml) was added and the stirring was continued for 30 min prior to acidification with 2M-H_2SO_4 and extraction with ether (3 × 100 ml). The combined ether extracts were washed with water (2 × 50 ml), dried ($MgSO_4$), and the solvent evaporated to yield a yellow oily residue which was purified by column chromatography (silica, 30 g; 20% ethyl acetate in light petroleum as eluant) to afford the *aldehyde* (**14**) as a colourless oil (760 mg, 2.8 mmol) (Found: C, 71.8; H, 10.4. $C_{16}H_{28}O_3$ requires C, 71.60; H, 10.52%); T.l.c. R_F 0.40 using 30% ethyl acetate in light petroleum as eluant; $\nu_{max.}$(film) 3 400 (OH) and 1 715 cm^{-1} (CHO); δ (250 MHz; $CDCl_3$) 0.60 (m, 3-*endo*-H), 0.90 (m, CH_3), 1.2—2.0 (m, aliphatic-H), 2.2—2.6

(m, 1-H, 2-H, 4-H, 8-H), 3.16, 3.38 [m, $OCH_2CH(OH)C_5H_{11}$], 3.6 (m, 6-*endo*-H), 3.7 [m, $OCH_2CH(OH)C_5H_{11}$], and 9.76 (t, CHO); *J* (2-*exo*, 3-*endo*) 4.5, (3-*endo*, 3-*exo*) 13.0, (3-*endo*, 7-*anti*) 1.5, (5-*endo*, 6-*endo*) 6.5, (5-*exo*, 6-*endo*) 3, and (6-*endo*, 7-*syn*) 1.5 Hz; *m/z* 268 (M^+), 1.53 ($M^+ - C_7H_{15}O$), and 137 ($M^+ - C_7H_{15}O_2$).

2-endo-(6-*Carboxyhex*-2-*enyl*)*norbornan*-6-exo-*yl* 2-*Hydroxyheptyl Ether* (**1**).—4-Carboxybutyltriphenylphosphonium bromide (2.3 g, 5.2 mmol) was added to a stirred solution of potassium t-butoxide (1.16 g, 10.4 mmol) in dry tetrahydrofuran (1.16 g, 10.4 mmol) under nitrogen. The resultant red ylide solution was stirred at room temperature for 10 min and a solution of the aldehyde (**14**) (350 mg, 1.3 mmol) in tetrahydrofuran (10 ml) then added. The reaction mixture was stirred for a further 20 min before being poured into saturated ammonium chloride solution (40 ml), which was acidified to pH 3.5 with dilute hydrochloric acid and then extracted with ether (4 × 30 ml). The combined ether extracts were washed with water (2 × 30 ml), dried ($MgSO_4$), and the solvent evaporated to leave a yellow oily residue (1 g) which was purified by column chromatography (silica, 25 g; 30% ethyl acetate in light petroleum as eluant) to afford the *unsaturated acid* (**1**) (340 mg, 0.96 mmol) as a clear viscous oil (Found: C, 71.1; H, 10.3. $C_{21}H_{36}O_4$ requires C, 71.55; H, 10.29%). T.l.c. R_F 0.18 using 30% ethyl acetate in light petroleum as eluant; $\nu_{max.}$(film) 3 400 (OH) and 1 705 cm^{-1} (CO_2H); δ (250 MHz; $CDCl_3$) 0.58 (ddd, 3-*endo*-H), 0.90 (t, CH_3), 1.1—2.5 (m, aliphatic-H), 3.18 and 3.42 [2 × m, $OCH_2CH(OH)C_5H_{11}$], 3.7 [m, 6-*endo*-H, $OCH_2CH(OH)C_5H_{11}$], and 5.38 (m, $CH{=}CH_2$); *J* (2-*exo*, 3-*endo*) 4, (3-*endo*, 3-*exo*) 11, [3-*endo*, 7-*anti* to $CH_2CH{=}CH(CH_2)_3CO_2H$] 2.5, and (5-*endo*, 6-*endo*) 6 Hz; *m/z* 352 (M^+) and 221 ($M^+ - C_7H_{15}O_2$).

2-*Hydroxyethyl* 2-endo-(4-*Tolylsulphonyloxymethyl*)*norbornan*-5-exo-*yl Ether* (**16**).—The toluene-4-sulphonate (**7**) (9.5 g, 35 mmol) was dissolved in tetrahydrofuran (30 ml) and the solution added to a stirred slurry of mercuric trifluoroacetate (18.4 g, 40 mmol) in ethylene glycol (10 g) and tetrahydrofuran (15 ml). The resulting stirred mixture became homogeneous and after 1 h at room temperature it was cooled in an ice–water bath and sodium hydroxide solution (40 ml of 3M) and then sodium borohydride solution (40 ml of 0.5M in 3M-NaOH) were added. Stirring of the mixture was continued for 1 h after the addition and then left to stand for 30 min and the elemental mercury coagulated. The organic layer was separated and the residue extracted with ether (4 × 150 ml). The combined extracts were added to the ether layer, washed with water (3 × 150 ml), and dried ($MgSO_4$), and the solvents evaporated to leave an oil (11.5 g) which was purified by column chromatography (silica, 200 g; 35% ethyl acetate in light petroleum as eluant) to afford the following compounds: (i) the *hydroxy ether* (**16**) (5.70 g, 16.7 mmol) as a white solid, m.p. 61—62 °C (Found: C, 59.8; H, 7.1. $C_{17}H_{24}O_5S$ requires C, 59.98; H, 7.11%). T.l.c. R_F 0.19 using 45% ethyl acetate in light petroleum as eluant; $\nu_{max.}$($CHBr_3$) 3 590 (OH), 1 360 (OSO_2), and 955 and 812 cm^{-1} (*p*-C_6H_4); δ (250 MHz; $CDCl_3$) 0.4 (ddd, 3-*endo*-H), 1,22 (m, 7-H *syn* to OTs, 6-*endo*-H), 1.7 (m, 3-*exo*-H, 6-*exo*-H), 1.58 (m, 7-H *anti* to OTs), 2.1 (m, 2-*exo*-H, OH), 2.25 (m, 1-H, 4-H), 2.45 (s, $CH_3C_6H_4$), 3.22 (m, 5-*endo*-H), 3.4—3.5 (m, OCH_2CH_2OH), 3.7 (m, OCH_2CH_2OH), and 3.95, 3.77 (2 × q, 8-H); *J* (2-*exo*, 3-*endo*) 5.5, (3-*endo*, 3-*exo*) 13, (3-*endo*, 7-*anti*) 2.0, (5-*endo*, 6-*endo*) 7, (5-*endo*, 6-*exo*) 3, (5-*endo*, 7-*syn*) 1.5, and (7-*syn*, 7-*anti*) 10 Hz; *m/z* 358 $(M + NH_4)^+$, 296 $(M + NH_4 - HOCH_2CH_2OH)^+$, 204 $(M + NH_4 - C_7H_6SO_2)^+$, and 186 $(M + NH_4 - HOSO_2C_6H_4CH_3\text{-}p)^+$. (ii) An inseparable 3:1 mixture (4.3 g) of the alcohol (**9**) and the hydroxy ether (**15**). The product proportions were deduced from the relative integrals of the 3-*endo*-H protons of (**9**) and (**15**) in the 250 MHz n.m.r. spectrum of the mixture. The following resonances for protons in the ether (**15**) could also be distinguished: δ 0.43 (ddd, 3-*endo*-H), 3.42 (m, OCH_2CH_2OH), 3.52 (m, 6-*endo*-H), 3.68 (m, OCH_2CH_2OH), and 3.75—4.05 (m, 8-H).

When the reaction was repeated using mercuric nitrate in place of mercuric trifluoroacetate, the hydroxy ether (**16**) (70%) and an inseparable mixture of the alcohol (**9**) (6%) and the hydroxy ether (**15**) (9%) were obtained.

2-*Hydroxyheptyl* 2-*endo*-(4-*Tolylsulphonyloxymethyl*)-*norbornan*-5-exo-*yl Ether* (**18**).—Oxalyl chloride (2.5 ml, 26.25 mmol) was dissolved in dry methylene dichloride (20 ml) and the solution added *via* a syringe to a three-necked flask equipped with stirrer and injection port under nitrogen. The contents of the flask were cooled to −72 °C in a solid CO_2–acetone bath and dry dimethyl sulphoxide (2.4 g, 30 mmol) dissolved in methylene dichloride (12 ml) was added dropwise during *ca.* 10 min *via* a syringe. After a further 10 min, the hydroxy ether (**16**) (2.63 g, 7.7 mmol) dissolved in methylene dichloride (15 ml) was added during 10 min. Stirring was continued for 1 h, and triethylamine (20 ml) was then added during 5 min, the cooling bath removed, and water (30 ml) added with stirring during a further 30 min. The organic layer was separated and the aqueous layer extracted with methylene dichloride (2 × 50 ml). The organic layer and extracts were combined and then washed successively with dilute hydrochloric acid (30 ml), water, dilute sodium carbonate solution (30 ml), and water (30 ml) before being dried ($MgSO_4$); the solvent was evaporated to afford the crude aldehyde (**17**) (2.3 g, 6.8 mmol) as a yellow oil; $\nu_{max.}$(film) 1 740 cm^{-1} (CHO); δ (250 MHz; $CDCl_3$) 0.40 (ddd, 3-*endo*-H), 1.1—1.8 (m, aliphatic-H), 2.14 (m, 2-*exo*-H), 2.28 (m, 1-H, 4-H), 2.45 (s, CH_3), 3.28 (m, 5-*endo*-H), 3.7—4.0 (m, 8-H, OCH_2CHO), and 9.7 (s, CHO); *J* (2-*exo*, 3-*endo*) 6.5, (3-*endo*, 3-*exo*) 13.0, and (3-*endo*, 7-*anti*) 2.5 Hz; *m/z* 338 (M^+) and 279 $(M - OCH_2CHO)^+$.

The crude aldehyde (**17**) (1.8 g) was dissolved in dry tetrahydrofuran (40 ml) and the solution stirred under nitrogen and cooled in an ice-bath at 0 °C. A solution of n-pentylmagnesium bromide (6 ml of 2M) was added dropwise *via* a syringe and when addition was complete (15 min) the ice-bath was removed and the mixture allowed to warm up to room temperature during 20 min. Water (50 ml) was carefully added, the mixture acidified with dilute hydrochloric acid, the layers separated, and the aqueous layer extracted with ether (2 × 50 ml). The organic layer and ether extracts were combined, washed with water (50 ml), dried ($MgSO_4$), and the solvent evaporated. The resulting oil was purified by column chromatography (silica, 60 g; 30% ethyl acetate–light petroleum as eluant) to afford the *secondary alcohol* (**18**) (2.0 g, 4.9 mmol) as a colourless oil (Found: *m/z* 428.2478. $C_{22}H_{34}O_5S{\cdot}NH_4$ requires *m/z* 428.2471); $\nu_{max.}$(film) 3 560, 3 460 (OH), 1 358, and 950 cm^{-1} (OSO_2); δ (250 MHz; $CDCl_3$) 0.40 (ddd, 3-*endo*-H), 0.90 (t, CH_3), 1.15—1.80 (aliphatic-H), 2.13 (m, 2-*exo*-H), 2.3 (m, 1-H, 4-H, OH), 2.47 (s, $C_6H_4CH_3$-*p*), 3.1—3.5 [m, $OCH_2CH(OH)C_5H_{11}$, 5-*endo*-H], and 3.6—4.0 [m, 8-H, $OCH_2CH(OH)C_5H_{11}$]; *J* (2-*exo*, 3-*endo*) 5.5, (3-*endo*, 3-*exo*) 13.0, and (3-*endo*, 7-*anti*) 2.0 Hz; *m/z* 428 $(M + NH_4)^+$, 296 $[M - HOCH_2CH(OH)C_5H_{11} + NH_4]^+$, and 274 $(M + NH_4 - C_7H_6SO_2)^+$.

2-endo-*Formylmethylnorbornan*-5-exo-*yl* 2-*Hydroxyheptyl Ether* (**20**).—Using procedures identical with those for the conversions (**12**) ⟶ (**13**) ⟶ (**14**), the secondary alcohol (**18**) (1.6 g, 3.9 mmol) afforded the crude nitrile (**19**) (0.9 g, 3.4 mmol) as a clear oil. T.l.c. R_F 0.24 using 30% ethyl acetate in light petroleum as eluant; $\nu_{max.}$(film) 2 250 cm^{-1} (CN). The

crude nitrile (**19**) was converted into the *aldehyde* (**20**) (0.65 g, 2.4 mmol) as a clear oil (Found: *m/z* 286.2357. $C_{16}H_{28}O_3NH_4$ requires *m/z* 286.2382). T.l.c. R_F 0.5 using 35% ethyl acetate in light petroleum as eluant; $\nu_{max.}$($CHBr_3$) 3 580 (OH), and 2 720, 1 720 cm^{-1} (CHO); δ (250 MHz; $CDCl_3$) 0.45 (ddd, 3-*endo*-H), 0.87 (t, CH_3), 1.2—1.7 (aliphatic-H), 1.8—2.0 (m, 3-*exo*-H, 6-*endo*-H), 2.1—2.4 (m, 1-H, 2-H, CH_2CHO), 3.2, 3.4 [m, $OCH_2CH(OH)C_5H_{11}$], 3.29 (m, 5-*endo*-H), 3.70 [br m, $OCH_2CH(OH)C_5H_{11}$], and 9.73 (t, CHO); *J* (2-*exo*, 3-*endo*) 5.0, (3-*endo*, 3-*exo*) 12.0, and (3-*endo*, 7-*anti*) 2.0 Hz; *m/z* 286 $(M + NH_4)^+$ and 137 $(M + H - HOCH_2CH(OH)C_5H_{11})^+$.

2-endo-(6-*Carboxyhex*-2-*enyl*)*norbornan*-5-exo-*yl* 2-*Hydroxyheptyl Ether* (**2**).—Using identical procedures with those for the conversion (**14**) ⟶ (**1**), the aldehyde (**20**) (0.2 g, 0.74 mmol) afforded the *unsaturated acid* (**2**) (0.225 g, 0.64 mmol) as a clear viscous oil (Found: C, 71.3; H, 10.35. $C_{21}H_{36}O_4$ requires C, 71.35; H, 10.29%). T.l.c. R_F 0.22 using 25% ethyl acetate in light petroleum as eluant; $\nu_{max.}$($CHBr_3$) 3 500 (OH), 3 500, 1 740, and 1 705 cm^{-1} (CO_2H); δ (250 MHz; $CDCl_3$) 0.42 (m, 3-*endo*-H), 0.9 (t, CH_3), 1.2—2.13 (m, aliphatic-H), 2.15 (m, 1-H), 2.27 (m, 4-H), 2.38 (t, CH_2CO_2H), 3.22, 3.45 [m, OCH_2-$CH(OH)C_5H_{11}$], 3.30 (m, 5-*endo*-H), 3.73 [m, OCH_2-$CH(OH)C_5H_{11}$], and 5.36 (m, CH=CH); *m/z* 370 $(M + NH_4)^+$, 238 $[M + NH_4 - HOCH_2CH(OH)C_5H_{11}]^+$, 221 $[M + H - HOCH_2CH(OH)C_5H_{11}]^+$, and 150 $[NH_4 + HOCH_2$-$CH(OH)C_5H_{11}]^+$.

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