Novel Route to Some Biologically Important Compounds Starting with a Common Chiral, Bicyclic, Fused Lactone: Enantioselective Synthesis of (−)-Boschnialactone and Two Antithrombotics

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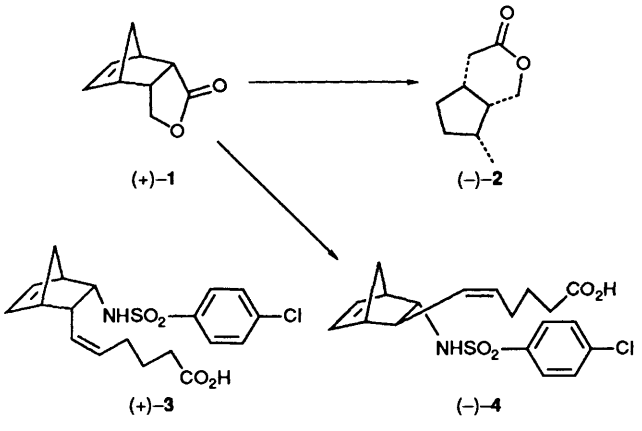
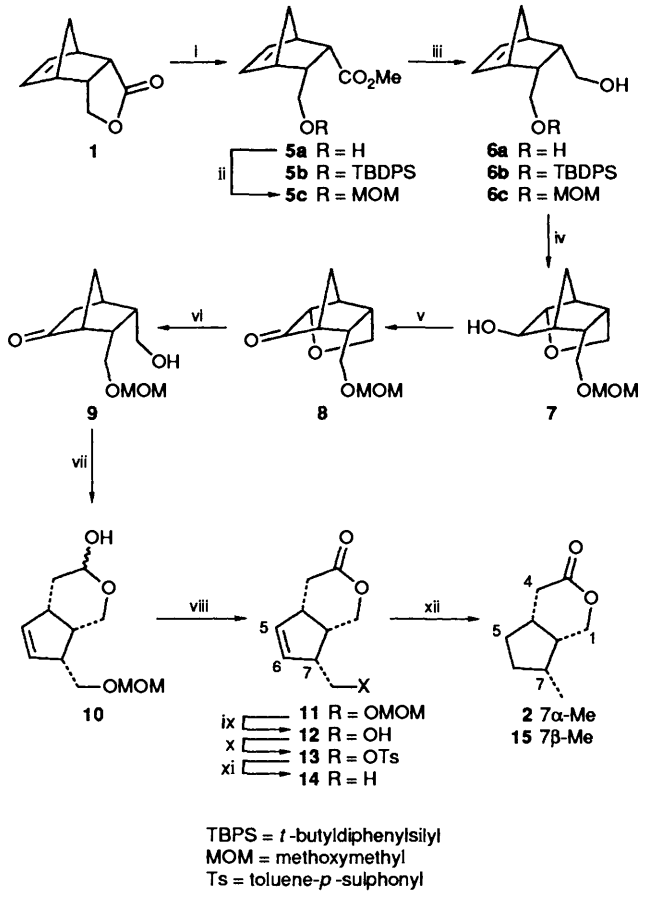
Three biologically important compounds, (−)-boschnialactone and the antithrombotics (+)- and (−)-(5*Z*)-6-{(1*S*,4*R*)-3-*endo*-(4-chlorophenylsulphonylamino)bicyclo[2.2.1]hept-5-en-2-*endo*- and *exo*-yl}hex-5-enoic acid have been synthesized starting from a common chiral lactone which is easily available *via* an asymmetric Diels–Alder reaction.

Chirally functionalised bicyclo[2.2.1]heptane derivatives have attracted a great deal of attention as starting materials in the synthesis of natural products[1] as well as of pharmacological agents.[2] For the construction of these systems in optically active form, (i) asymmetric Diels–Alder reactions with cyclopentadiene and congeners and (ii) enzymatic resolution of racemic derivatives of bicyclo[2.2.1]heptane have appeared to date. In particular, chiral tricyclic lactone **1** seemed to be a useful starting material whose utility has been demonstrated by its conversion to prostanoids[3] and a prostaglandin precursor.[4] Enantioselective preparation of (+)-**1** by the action of pig liver esterase was first described in 1985.[5] The resolution method using a chiral alkaloid as a catalyst has also been reported.[6] In view of this synthetic interest, we[7] reported an enantiodivergent route to lactone **1** based upon the asymmetric Diels–Alder reaction strategy. As an application of this methodology to the synthesis of biologically important compounds, we were intrigued by the synthesis of (−)-boschnialactone **2**[8] and the thromboxane/prostaglandin receptor antagonists[9] (+)-**3** and (−)-**4**, starting with the chiral lactone **1**, and we now describe our observations in full detail.



Synthesis of (−)-*Boschnialactone*.—Boschnialactone **2** was isolated from *Boschniakia rossica* Hult. by Sakan *et al.*[10] The absolute configuration was determined by chemical correlation.[10] Its interesting biological properties such as its cat-attracting and insecticidal activities led to it receiving much attention from synthetic chemists. There are now several reported syntheses of (±)-**2**;[11] however, no chiral synthesis has appeared to date. We undertook the enantioselective synthesis of (−)-**2**, the isomer with the natural configuration.

The methodology for the enantioselective synthesis of compound **2** is illustrated in Scheme 1. The construction of the framework was based upon photolytic cleavage of a bicyclo[2.2.1]heptan-5-one system.[12] Following the literature method,[13] the lactone **1** was transformed into the ester alcohol **5a** by saponification followed by esterification. Owing to the instability of compound **5a**, which tends to cyclise readily back to lactone **1** even upon evaporation of its solutions, the hydroxy group in compound **5a** was protected as the *t*-butyldiphenylsilyl



Scheme 1 *Reagents, conditions and yields:* i, KOH, MeOH–water; CH_2N_2, Et_2O (92%); ii, MOMCl, Pr^i_2NEt, CH_2Cl_2 (89%); iii, $LiAlH_4$, THF (89%); iv, MCPBA, CH_2Cl_2 (59%); v, PCC, molecular sieves 4 Å, CH_2Cl_2 (72% from **5c**); vi, Al–Hg, THF, EtOH (91%); vii, *hν* (200 W, low-pressure Hg lamp, quartz filter), MeCN; HCl (cat.); viii, Jones' reagent, acetone (64% from **9**); ix, PPTS, Bu^tOH (86%); x, toluene-*p*-sulphonyl chloride, pyridine (93%); xi, NaI, Zn, 1,2-dimethoxyethane (100%); xii, H_2, 5% Pt on alumina, Bu^tOH (85%)

Table 1 Epimerisation of compound **20**

Entry	Substrate ratio	Reagent, mol equiv.	Solvent	Temp. (T/°C)	Time (t/h)	Yield (%)	Product proportions[a] **20**:**21**
1	1.8:1	NaOH, 2	MeOH–water	20	1		Decomposed
2	1.8:1	K_2CO_3, 1.6	THF–water	0	0.5		Unchanged
3	6:1	K_2CO_3, 2	THF–water	20	20	71	1:1.4
4	6:1	Et_3N, 2	CH_2Cl_2	20	20		Decomposed
5	6:1	Silica gel	Hexane–AcOEt	20	18	97	1:12

[a] Proportions were determined by integration of the two aldehydic signals in the ^1H NMR spectrum.

(TBDPS) ether **5b**. However, reduction of compound **5b** with $LiAlH_4$ produced not the corresponding alcohol **6b** but a *meso* diol **6a**. In turn, the reduction of the methoxymethyl (MOM) ether **5c**, $[\alpha]_D^{25}$ −3.8° (*c* 1.02), obtained from lactone **1** by the usual method, produced the protected alcohol **6c**, $[\alpha]_D^{25}$ −0.93° (*c* 0.51), $[\alpha]_D^{25}$ −23.6° (*c* 1.11, acetone), in 89% yield. Exposure of compound **6c** to 3-chloroperbenzoic acid (MCPBA) gave the tricyclic ether **7**, m.p. 82–84 °C; $[\alpha]_D^{26}$ −30.2° (*c* 1.69), in moderate yield. Further transformations were based on those developed by Vandewalle and co-workers[11c] for their racemic synthesis of compound **2**. Pyridinium chlorochromate (PCC) oxidation[14] and subsequent reductive cleavage of the ether group of the product **8** with aluminium amalgam gave hydroxy ketone **9**, $[\alpha]_D^{25}$ −5.0° (*c* 1.9), in 72% yield. A Norrish Type-I cleavage by photolysis of ketone **9**, followed by treatment of the resulting hemiacetal **10** with PCC, afforded the bicyclic lactone **11**, m.p. 42–44 °C; $[\alpha]_D^{25}$ −17.3° (*c* 2.1). Attempted deprotection of the MOM group in compound **11** with acid[15] was unsatisfactory; however, treatment with pyridinium toluene-*p*-sulphonate (PPTS) and *t*-butyl alcohol under Monti conditions[16] produced the alcohol **12**, m.p. 78–80 °C; $[\alpha]_D^{25}$ −3.0° (*c* 1.22), in good yield. The use of BF_3·Et_2O/alkanethiol was also effective for the deprotection.[17] Tosylation of the alcohol **12** (to give ester **13**) and subsequent treatment with Zn–NaI[18] led to didehydroboschnialactone **14**, m.p. 90–91 °C; $[\alpha]_D^{25}$ −19.8° (*c* 0.77). Hydrogenation of compound **14** over Pd–C gave compound **2**, accompanied by a substantial amount of the stereoisomer, which could be assigned to be C-7 epimer **15**[11e] as judged by NMR analysis of the crude product. The formation of epimer **15** can be explained by the isomerisation of the C(5)–C(6) double bond to the C(6)–C(7) position during the reduction. Similar results were observed in the reduction of bicyclic olefins.[19] Ir-catalysed hydrogenation[20] afforded the target compound **2** but in capricious yield. Finally, the use of 5% Pt on alumina as the catalyst[19] effected selective reduction to give (−)-boschnialactone **2** as an oil, $[\alpha]_D^{25}$ −21.3° (*c* 0.34) {lit.,[10] $[\alpha]_D^{21}$ −18.2° (*c* 2.10)}, without contamination by any isomer. The spectroscopic data were in good agreement with those of an authentic sample by direct comparison.

Synthesis of Prostaglandin H_2 Receptor Antagonists.—Thromboxane A_2 (TXA_2) and prostaglandin H_2 (PGH_2) exhibit highly potent inhibition of blood platelet aggregation and of smooth muscle contraction. Since the discovery of TXA_2 and its biosynthetic precursor PGH_2, numerous studies on the synthesis of its stable analogues as medicinally useful agents have been reported. A number of them possess 7-oxabicyclo[2.2.1]- and bicyclo[2.2.1]-heptane systems. Both compounds **3** and **4** were reported to be effective receptor antagonists by the Bayer groups.[9] These syntheses, however, did not deal with any enantiomeric control. Hence, we were interested in the chiral synthesis of antithrombotics **3** and **4**.

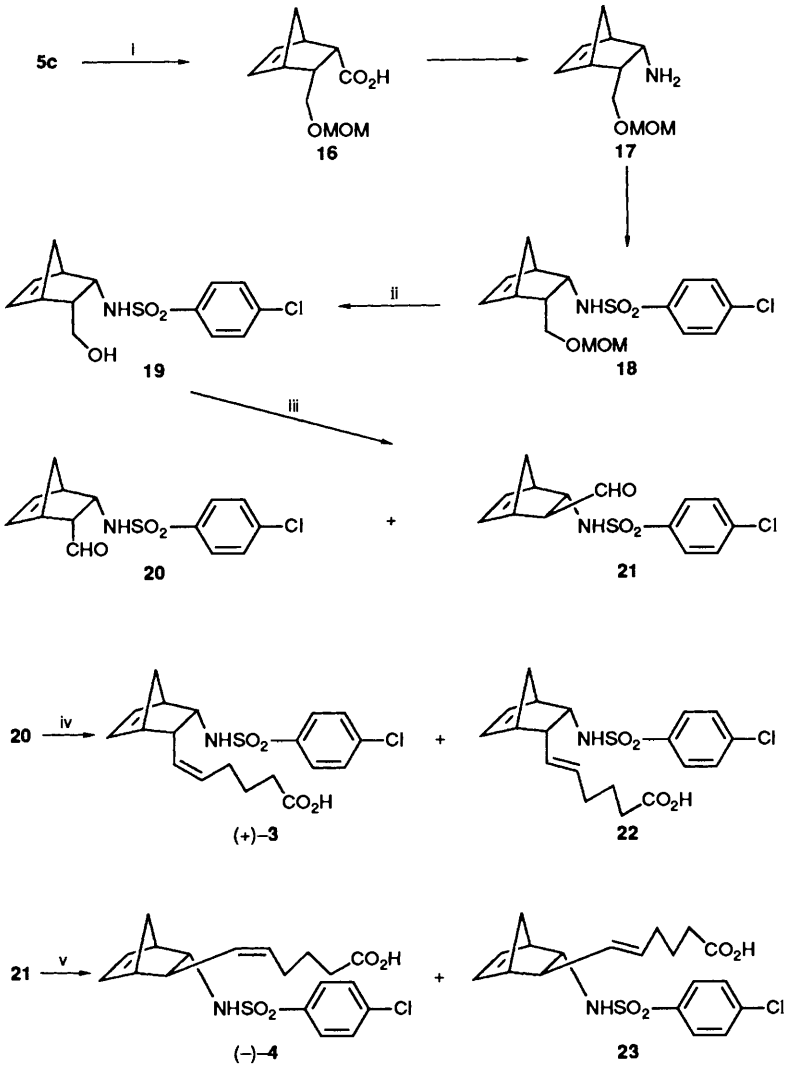
Ester **5c** is also a starting material for this synthesis (Scheme 2). Careful saponification of compound **5c** with NaOH afforded the carboxylic acid **16**. Transformation of the carboxy group in the acid **16** into the amino group was carried out by the usual mixed-anhydride reaction sequence. Accordingly, treatment of compound **16** with ethyl chloroformate followed by successive addition of sodium azide produced the azido compound, which upon being heated in aq. HOAc gave the amino ether **17**. Sulphonylation of the amine **17** with 4-chlorobenzenesulphonyl chloride and Et_3N gave the sulphonamide **18**, m.p. 121–123 °C; $[\alpha]_D^{24}$ +17.8° (*c* 1). Ester **5c** was thus converted into compound **18**, without the need to purify any of the intermediates such as **17**, in 64% yield. Deprotection of the MOM group in compound **18** led to the alcohol **19**, m.p. 122–123 °C; $[\alpha]_D^{25}$ +55.2° (*c* 1.43), whose racemate has been reported as the intermediate in the synthesis of compounds (±)-**3** and (±)-**4**. It was reported[9] that alcohol (±)-**19** was oxidised under Swern conditions to give an isomeric mixture of compounds (±)-**20** and (±)-**21** in the ratio 2:5, and the final mixtures obtained from the aldehydes contained nearly equal amounts of compounds (+)-**3** and (±)-**4**. The lack of the stereocontrol in this synthesis prompted us to seek a procedure to prepare either aldehyde **20** or **21** in a highly stereoselective manner. It was found that PCC oxidation produced the aldehydes **20** and **21** in the ratio 6:1 in good yield. Pure aldehyde **20**, m.p. 141–143 °C; $[\alpha]_D^{24}$ +24.2° (*c* 1.07), could be obtained by one recrystallisation of the crude oxidation product. On the other hand, exposure of a 6:1 mixture of aldehydes **20** and **21** to silica gel resulted in the predominant formation of the aldehyde **21** (**20**:**21** 1:12). Pure aldehyde **21**, m.p. 116 °C; $[\alpha]_D^{24}$ +39.9° (*c* 0.93), was also obtained by recrystallisation from the mixture. Attempts at epimerisation of compound **20** by the use of base were unfruitful (Table 1). Following the method reported,[9] *cis-endo*-aldehyde **20** was transformed into compound (+)-**3**, $[\alpha]_D^{24}$ +100.8° (*c* 1.73), as an oil, by a Wittig reaction with (4-carboxybutyl)triphenylphosphonium bromide and dimsyl sodium; the *Z*-isomer **3** was contaminated by the *E*-isomer **22** (*Z*:*E* 5.5:1). The ratio was determined by the ^1H NMR spectrum of the mixture of the corresponding methyl esters. The desired *Z*-isomer **3** was separable from *E*-isomer **22** in an almost pure form (isomeric purity 93%) by recrystallisation of a mixture of the corresponding cyclohexylamine salts followed by acidic treatment of the resulting almost pure salt (m.p. 134–135 °C). The use of other bases such as KOBu^t for the condensation of compound **20** resulted in predominant formation of the *E*-isomer **22**, as shown in Table 2. On the other hand, aldehyde **21** was treated with the phosphonium salt and KOBu^t as base to give predominantly the *Z*-isomer **4**, accompanied by the *E*-isomer **23**, in 86% yield. The ratio of *Z* and *E* isomers could be estimated as 14:1 respectively, judged by the ^1H NMR spectrum of the mixture of its methyl esters. The acid **4**, $[\alpha]_D^{25}$ −40.5° (*c* 0.98), was obtained in an almost pure form (isomeric purity 96%) by acidic treatment of the cyclohexyl amine salt (m.p. 113–115 °C), in a similar manner to the procedure of the preparation of compound **3**.

In summary, we have succeeded the chiral synthesis of (−)-boschnialactone **2** and two antithrombotics starting with a common chiral, bicyclic, fused lactone.

Table 2 Results of the Wittig condensation of compound **20**

Entry	Base[a]	Solvent	Temp. (T/°C)	Time (t/h)	Yield (%)	Product proportions[b] **3**:**22**
1	Bu'OK	THF	0	1	*c*	1:13
2	Bu'OK	THF	−78 → 25	1.7	~100	1:5.9
3	Bu'OK	Benzene	25	4	*c*	1:11
4	Dimsyl sodium	DMSO	50	5	90	5.5:1

[a] 5 Mol equiv. of the phosphonium salt and 10 mol equiv. of the base were used. [b] The ratio was determined by ^{1}H NMR spectroscopy. [c] Yields were not determined. No starting material **20** was detected in the ^{1}H NMR spectrum of the crude product.



Scheme 2 *Reagents:* i, NaOH–water, THF; Et_3N, $ClCO_2Et$; NaN_3, water; HOAC–water; Et_3N, 4-chlorobenzenesulphonyl chloride; ii, BF_3·Et_2O, PhSH; iii, PCC, NaOAc, molecular sieves 4 Å, CH_2Cl_2; iv, NaH, DMSO, (4-carboxybutyl)triphenylphosphonium bromide; cyclohexylamine; H^+; v, Bu'OK, (4-carboxybutyl)triphenylphosphonium bromide, THF; cyclohexylamine; H^+

Experimental

M.p.s were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. B.p.s for bulb-to-bulb distillation indicate bath temperature. IR spectra were recorded on a JASCO A-102 or a Perkin-Elmer 1600 spectrometer. NMR spectra were measured in $CDCl_3$ with tetramethylsilane as internal standard on a JEOL PMX SI (60 MHz ^{1}H) or a JEOL GX-270 (270 MHz ^{1}H) and a Varian XL-200 (50.1 MHz ^{13}C) spectrometer. *J*-Values are in Hz. Mass spectra were recorded on a JEOL JMS-300 spectrometer. Optical rotations were recorded on a JASCO DIP-140 digital polarimeter and were taken in chloroform solution unless otherwise indicated. TLC analyses were performed using Merck pre-coated silica 60F254 plates (0.2 mm). Column chromatography was carried out on Merck silica (70–230 mesh) or Nakarai Chemicals silica (70–230 mesh). Flash chromatography was carried out on Merck silica (230–400 mesh) or Nakarai Chemicals silica (230–400 mesh). Dry tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. Dry methylene dichloride was distilled from phosphorus pentaoxide and stored with molecular sieves 4 Å. Organic extracts were dried over anhydrous magnesium sulphate.

(−)-*Methyl* (1R,4S)-3-endo-[(*Methoxymethoxy*)*methyl*]*bi*-

cyclo[2.2.1]*hept*-5-*ene*-2-endo-*carboxylate* **5c**.—To a solution of compound **5a** [5] (1.00 g, 5.49 mmol) in dry CH_2Cl_2 (3 cm^3) at 0 °C was added diisopropylethylamine (2.87 cm^3, 16.5 mmol) followed by chloromethyl methyl ether (1.24 cm^3, 16.5 mmol). The solution was stirred at room temperature overnight before being poured onto cold, 1 mol dm^{-3} hydrochloric acid (15 cm^3), and the aq. layer was extracted with chloroform (4 × 10 cm^3). The extracts were washed with brine (10 cm^3), dried, and concentrated. The residue was purified by column chromatography on silica with hexane–AcOEt (4:1) as eluent to afford *compound* **5c** as an oil (1.11 g, 89%) (Found: M^+, 226.1196. $C_{12}H_{18}O_4$ requires M, 226.1204); b.p. 131–139 °C/10 mmHg; $[\alpha]_D^{25}$ −3.8° (*c* 1.02); ν_{max}(neat)/cm^{-1} 2950, 1740, 1150, 1045 and 920; δ_H(270 MHz) 1.33 (1 H, d, *J* 8.5, 7-H^a), 1.49 (1 H, dt, *J* 8.5, 2, 7-H^b), 2.73 (1 H, m, 2-H), 2.99 (1 H, br s, 1- or 4-H), 3.08 (1 H, br s, 4- or 1-H), 3.08 (1 H, dt, *J* 8, 3, 3-H), 3.21 (1 H, t, *J* 9, 8-H^a), 3.35 (3 H, s, Me), 3.44 (1 H, dd, *J* 9, 7, 8-H^b), 3.59 (3 H, s, Me), 4.55 (2 H, ABq, *J* 7, OCH_2O), 6.13 (1 H, dd, *J* 6, 3, 5- or 6-H) and 6.29 (1 H, dd, *J* 6, 3, 6- or 5-H); *m*/*z* (EI) 226 (M^+), 211, 195, 129 and 99.

(−)-(1R,4S)-3-endo-[(*Methoxymethoxy*)*methyl*]*bicyclo*-[2.2.1]*hept*-5-*ene*-2-endo-*methanol* **6c**.—To a solution of ester **5c** (1.17 g, 5.18 mmol) in dry THF (10 cm^3) at 0 °C was added $LiAlH_4$ (197 mg, 5.18 mmol) portionwise. The mixture was stirred for 15 min, after which ice–water (15 cm^3) was carefully added. Most of the solvent was evaporated off and the aq. layer was extracted with diethyl ether (3 × 15 cm^3). The extracts were washed with brine (15 cm^3), dried, and concentrated. The residue was purified by column chromatography [hexane–AcOEt (2:1)] on silica to give *compound* **6c** as an oil (0.908 g, 89%) (Found: M^+, 198.1228. $C_{11}H_{18}O_3$ requires M, 198.1255); $[\alpha]_D^{25}$ −0.93° (*c* 0.51); $[\alpha]_D^{25}$ −23.6° (*c* 1.11, acetone); b.p. 162–170 °C/25 mmHg; ν_{max}(neat)/cm^{-1} 3400, 2950, 1150, 1100 and 1040; δ_H(270 MHz) 1.38 (1 H, d, *J* 8, 7-H^a), 1.45 (1 H, dt, *J* 8, 1.7, 7-H^b), 2.45–2.63 (2 H, m, 2- and 3-H), 2.86 (2 H, br s, 1- and 4-H), 3.11 (1 H, br s, OH, disappeared with D_2O), 3.31–3.51 (4 H, m, 8- and 11-H_2), 3.37 (3 H, s, Me), 4.61 (2 H, s, OCH_2O) and 6.04–6.11 (2 H, m, 5- and 6-H); *m*/*z* (EI) 199 (M^+ + 1), 167, 101, 91 and 79.

(−)-(3R,6R)-9-endo-[(*Methoxymethoxy*)*methyl*]-4-*oxatricyclo*[4.2.1.$0^{3,7}$]*nonan*-2-exo-*ol* **7**.—To a solution of compound **6c** (126 mg, 0.64 mmol) in dry CH_2Cl_2 (10 cm^3) at 0 °C was added MCPBA (80% purity; 276 mg, 1.28 mmol) portionwise. The mixture was stirred at room temperature for 2.5 h, washed successively with 5% aq. sodium thiosulphate (10 cm^3) and saturated aq. sodium hydrogen carbonate (10 cm^3), dried, and concentrated. The residue was purified by flash chromatography [hexane–AcOEt (1:1)] on silica to afford *compound* **7** (80 mg, 59%) as needles (Found: C, 61.5; H, 8.3. $C_{11}H_{18}O_6$ requires C, 61.66, H, 8.47%), m.p. 82–84 °C (from hexane); $[\alpha]_D^{26}$ −30.2° (*c* 1.69); ν_{max}(KBr)/cm^{-1} 3375, 2900 and 1340; δ_H(270 MHz) 1.50 (1 H, br s, OH), 1.53 (1 H, d, *J* 10, 8-H^a), 1.99 (1 H, d, *J* 10, 8-H^b), 2.19 (1 H, br s, 1-H), 2.26 (1 H, dddd, *J* 10, 8, 3.5, 1, 9-H), 2.41 (1 H, ddd, *J* 10, 5, 4, 6-H), 2.74 (1 H, t, *J* 5, 7-H), 3.37 (3 H, s, Me), 3.56 (2 H, d, *J* 8, CH_2O), 3.67 (1 H, dd, *J* 6, 4, 5-H^a), 3.7 (1 H, br s, 2-H), 3.74 (1 H, d, *J* 6, 5-H^b), 4.00 (1 H, dd, *J* 5, 1, 3-H) and 4.63 (2 H, s, OCH_2O); *m*/*z* (EI) 214 (M^+), 169, 152, 95 and 93.

(−)-(3R,6R)-9-endo-[(*Methoxymethoxy*)*methyl*]-4-*oxatricyclo*[4.2.1.$0^{3,7}$]*nonan*-2-*one* **8**.—To a suspension of PCC (239 mg, 1.1 mmol) and molecular sieves 4 Å (powder, 100 mg) in dry CH_2Cl_2 (10 cm^3) was added a solution of alcohol **7** (74 mg, 0.35 mmol) in dry CH_2Cl_2 (10 cm^3) in one portion and the mixture was stirred overnight. After being diluted with diethyl ether (30 cm^3), the reaction mixture was filtered with the aid of a short plug of Florisil. The filtrate was concentrated and the residue was purified by column chromatography [hexane–AcOEt (2:1)] on silica to give *compound* **8** (53 mg, 72%) (Found: M^+, 212.1091. $C_{11}H_{16}O_4$ requires M, 212.1048) as an oil, b.p. 102–104 °C/0.15 mmHg; $[\alpha]_D^{25}$ −112.3° (*c* 1.30); ν_{max}-($CHCl_3$)/cm^{-1} 2950, 2900, 1760, 1150 and 1040; δ_H(270 MHz) 1.78 (1 H, dt, *J* 11.5, 1.5, 8-H^a), 1.87 (1 H, dt, *J* 11.5, 1.5, 8-H^b), 2.41 (1 H, ddt, *J* 10, 8, 5, 6-H), 2.56 (1 H, m, 1-H), 2.77 (1 H, ddt, *J* 10, 2.5, 2, 9-H), 3.09 (1 H, dt, *J* 5, 1.5, 7-H), 3.36 (3 H, s, Me), 3.45 (1 H, dd, *J* 10, 8, 5-H^a), 3.48 (1 H, dd, *J* 10, 8, 5-H^b), 3.88 (2 H, d, *J* 2.5, CH_2O), 3.90 (1 H, d, *J* 5, 3-H) and 4.60 (2 H, s, OCH_2O); *m*/*z* (EI) 212 (M^+), 194, 181, 167, 93 and 69.

(−)-(1R,4R)-5-endo-*Hydroxymethyl*-6-endo-[(*methoxymethoxy*)*methyl*]*bicyclo*[2.2.1]*heptan*-2-*one* **9**.—To a solution of the tricyclic ketone **8** (260 mg, 1.23 mmol) in dry THF (9 cm^3)–dry EtOH (3.5 cm^3) at 0 °C was added aluminium amalgam [prepared from aluminium foil (153 mg) and 5% mercury(II) chloride in THF]. The mixture was stirred vigorously at that temperature for 3 h, and was then filtered through a short pad of Celite and the solid residue was washed with AcOEt (3 × 10 cm^3). The filtrate and washings were concentrated and the residue was purified by column chromatography with chloroform and then AcOEt as eluent to give *compound* **9** (240 mg, 91%) (Found: M^+, 214.1218. $C_{11}H_{18}O_4$ requires M, 214.1204) as an oil, b.p. 121–125 °C/0.15 mmHg; $[\alpha]_D^{25}$ −5.0° (*c* 1.90); ν_{max}(neat)/cm^{-1} 3450, 2950, 1740, 1110 and 1040; δ_H-(270 MHz) 1.77 (2 H, br s, 7-H_2), 1.98 (1 H, dd, *J* 18, 4, 3-H^a), 2.08 (1 H, dd, *J* 18, 3, 3-H^b), 2.52–2.67 (3 H, m, 4-, 5- and 6-H), 2.73 (1 H, br s, 1-H), 3.02 (1 H, br, OH), 3.37 (3 H, s, Me), 3.52 (2 H, d, *J* 7, HOC*H*$_2$), 3.6 (1 H, m, C*H*HO), 3.85 (1 H, m, CH*H*O) and 4.60 (2 H, s, OCH_2O); *m*/*z* (EI) 214 (M^+), 169, 93, 79 and 69.

(3R/3S,4aS,7R,7aS)-7-[(*Methoxymethoxy*)*methyl*]-1,3,4,4a,7,7a-*hexahydrocyclopenta*[c]*pyran*-3-*ol* **10**.—A solution of compound **9** (270 mg, 1.26 mmol) in dry, degassed MeCN (500 cm^3) at 0 °C was irradiated with a 200 W low-pressure Hg lamp through a quartz filter for 4 h. To the mixture at ambient temperature was added conc. HCl (1 drop) and the mixture was stirred overnight. After concentration at reduced pressure, the residue was passed through a short plug of silica [hexane–AcOEt (2:1)] to afford the crude oily product **10** (~0.3 g) as a 3:2 anomeric mixture, judged by ^1H NMR spectroscopy; δ_H(270 MHz) 1.43 (0.4 H, ddd, *J* 14, 10, 7, 4-H), 1.77 (0.6 H, ddd, *J* 14, 8, 7, 4-H), 1.90 (0.6 H, ddd, *J* 14, 4, 3.5, 4-H), 2.08 (0.4 H, ddd, *J* 14, 6, 4, 4-H), 2.48–2.56 (1.6 H, m, 7a- and 4a- or 7-H), 2.78 (0.4 H, m, 4a- or 7-H), 2.94 (0.4 H, d, *J* 5, OH), 2.99–3.10 (1 H, m, 7- or 4a-H), 3.04 (0.6 H, d, *J* 5, OH), 3.37 (1.2 H, s, Me), 3.38 (1.8 H, s, Me), 3.50–3.64 (2 H, m, OCH_2), 3.68 (0.4 H, dd, *J* 12, 8, 1-H), 3.72 (0.6 H, dd, *J* 12, 6, 1-H), 3.93 (0.6 H, dd, *J* 12, 5, 1-H), 4.10 (0.4 H, dd, *J* 12, 8, 1-H), 4.63 (2 H, s, OCH_2O), 5.02 (0.4 H, dt, *J* 7, 5, 3-H), 5.67–5.75 (1.6 H, m, CH=) and 5.84 (0.4 H, dt, *J* 5.5, 2, CH=). The crude hemiacetal was used for the next step without further purification.

(−)-(4aS,7R,7aS)-7-[(*Methoxymethoxy*)*methyl*]-4,4a,7,7a-*tetrahydrocyclopenta*[c]*pyran*-3(1H)-*one* **11**.—To a solution of the acetal **10** in acetone (20 cm^3) at 0 °C was added dropwise Jones' reagent (10 drops). After the mixture had been stirred for 1 h, propan-2-ol was added to the mixture until the orange colour changed to green. After being diluted with water (20 cm^3) the mixture was evaporated and the aq. layer was extracted with diethyl ether (4 × 20 cm^3). The extracts were washed successively with dil. aq. Na_2CO_3 (30 cm^3) and brine (30 cm^3), dried, and concentrated. The residue was purified by flash chromatography [hexane–AcOEt (1:1)] to give *compound* **11** (170 mg, 64%) as needles, m.p. 42–44 °C (from hexane) (Found: C, 62.3;

H, 7.6. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60%); $[\alpha]_D^{25}$ −17.3° (*c* 2.10); ν_{max}(KBr)/cm^{-1} 2895, 1730, 1230, 1100 and 1040; δ_H(270 MHz) 2.42 (1 H, dd, *J* 15, 7, 4-H), 2.75 (1 H, dd, *J* 15, 7, 4-H), 2.85 (1 H, ddt, *J* 9, 7, 5, 7a-H), 3.3 (1 H, m, 4a- or 7-H), 3.38 (3 H, s, Me), 3.4 (1 H, m, 7- or 4a-H), 3.60 (1 H, dd, *J* 10, 5.5, OC*H*H), 3.66 (1 H, dd, *J* 10, 6, OCH*H*), 4.29 (1 H, dd, *J* 12, 5, 1-H), 4.38 (1 H, dd, *J* 12, 7, 1-H), 4.63 (2 H, s, OCH_2O), 5.63 (1 H, dt, *J* 5.5, 2, CH=) and 5.68 (1 H, dt, *J* 5.5, 2, CH=); *m*/*z* (EI) 213 (M^+ + 1), 150, 91, 79, 77 and 74.

(−)-(4a*S*,7*R*,7a*S*)-7-*Hydroxymethyl*-4,4a,7,7a-*tetrahydrocyclopenta*[c]*pyran*-3(1H)-*one* **12**.—A mixture of compound **11** (85 mg, 0.4 mmol) and PPTS (200 mg, 8 mmol) in Bu^{t}OH (4 cm^3) was heated under reflux for 8 h. The mixture was concentrated and the residue was purified on silica [hexane–AcOEt (1:2)] to give *compound* **12** (58 mg, 86%) as needles, m.p. 78–80 °C (from diethyl ether–hexane) (Found: C, 64.3; H, 7.2. $C_9H_{12}O_3$ requires C, 64.27; H, 7.19%); $[\alpha]_D^{25}$ −3.0° (*c* 1.22); ν_{max}(KBr)/cm^{-1} 3520, 2920, 1730, 1290 and 1250; δ_H(270 MHz) 1.65 (1 H, br, OH), 2.45 (1 H, dd, *J* 15, 6.5, 4-H), 2.74 (1 H, dd, *J* 15, 6.8, 4-H), 2.88 (1 H, ddt, *J* 9.5, 6.5, 5, 7a-H), 3.26 (1 H, m, 4a- or 7-H), 3.40 (1 H, m, 7- or 4a-H), 3.70–3.88 (2 H, br, CH_2OH), 4.33 (1 H, dd, *J* 12, 5, 1-H), 4.48 (1 H, dd, *J* 12, 6.5, 1-H) and 5.64–5.72 (2 H, m, CH=).

(+)-{(4a*S*,7*R*,7a*S*)-3-*Oxo*-1,3,4,4a,7,7a-*hexahydrocyclopenta*[c]*pyran*-7-*yl*}*methyl Toluene*-p-*sulphonate* **13**.—To a solution of compound **12** (33 mg, 0.2 mmol) in pyridine (0.5 cm^3) was added toluene-*p*-sulphonyl chloride (121 mg, 0.6 mmol) and a pinch of 4-(dimethylamino)pyridine and the mixture was stirred overnight before being poured into 1 mol dm^{-3} hydrochloric acid (10 cm^3), and the aq. layer was extracted with diethyl ether (3 × 10 cm^3). The extracts were washed with brine (10 cm^3), dried, and concentrated. The residue was purified by column chromatography on silica [hexane–AcOEt (1:1)] to give *compound* **13** (60 mg, 93%) as needles, m.p. 127 °C (from hexane–$CHCl_3$) (Found: C, 59.3; H, 5.7. $C_{16}H_{18}O_5S$ requires C, 59.62; H, 5.63%); $[\alpha]_D^{25}$ +19.9° (*c* 2.73); ν_{max}(KBr)/cm^{-1} 1730, 1175, 1105 and 970; δ_H(270 MHz) 2.43 (1 H, dd, *J* 15, 5, 4-H), 2.47 (3 H, s, Me), 2.71 (1 H, dd, *J* 15, 7, 4-H), 2.86 (1 H, apparent sep., *J* 5, 7a-H), 3.31–3.49 (2 H, m, 4a- and 7-H), 4.08 (1 H, dd, *J* 9, 9, C*H*HO$_3$S), 4.16 (1 H, dd, *J* 9, 5.5, CH*H*SO$_3$), 4.17 (1 H, dd, *J* 12, 5.5, 1-H), 4.19 (1 H, dd, *J* 12, 5, 1-H), 5.57 (1 H, dt, *J* 5.5, 2, CH=), 5.65 (1 H, dt, *J* 5.5, 2, CH=), 7.37 (2 H, d, *J* 8, ArH) and 7.80 (2 H, d, *J* 8, ArH); *m*/*z* (EI) 322 (M^+), 155, 150 and 91.

(−)-5,6-*Didehydroboschnialactone* **14**.—A mixture of compound **13** (100 mg, 0.3 mmol), zinc (605 mg), and sodium iodide (233 mg, 1.55 mmol) in 1,2-dimethoxyethane (5 cm^3) was heated at 80 °C for 2 h. The mixture was diluted with diethyl ether (10 cm^3) and filtered through a short pad of Celite, and the solid filter was washed with diethyl ether (4 × 10 cm^3). The filtrate and washings were washed with brine (10 cm^3), dried, and concentrated at reduced pressure (~30 mmHg) below 10 °C. The residue was purified by column chromatography [hexane–AcOEt (1:1)] on silica to give compound **14** (47 mg, quantitative) as needles, m.p. 90–91 °C (from diethyl ether–pentane) (Found: C, 71.3; H, 7.9. Calc. for $C_9H_{12}O_2$: C, 71.02; H, 7.95%), identified by direct comparison with an authentic sample[11c] provided by Professor Vandewalle; $[\alpha]_D^{25}$ −19.8° (*c* 0.77).

Boschnialactone **2**.—A mixture of compound **14** (20 mg, 0.13 mmol) and 5% Pt on alumina (0.2 g) in Bu^{t}OH (2.5 cm^3) was degassed and covered with hydrogen. The mixture was stirred vigorously at ambient temperature for 5 h, then was filtered through a short pad of Celite, and the solid filter was washed with AcOEt (10 cm^3). The combined filtrate and washings were concentrated and the residue was purified by column chromatography [hexane–AcOEt (1:1)] on silica to afford compound **2** (17 mg, 85%) as an oil, identified by comparison with an authentic sample by its IR and ^{1}H NMR spectra. B.p. 109–115 °C/13 mmHg; $[\alpha]_D^{25}$ −21.3° (*c* 0.34) {lit.,[10] $[\alpha]_D^{21}$ −18.2° (*c* 2.70, $CHCl_3$)}.

(+)-(1*S*,4*R*)-5-endo-(4-*Chlorobenzenesulphonylamino*)-6-endo-[(*methoxymethoxy*)*methyl*]*bicyclo*[2.2.1]*hept*-2-*ene* **18**.—To a solution of compound **5c** (262 mg, 1.16 mmol) in dry THF (10 cm^3) was added 0.25 mol dm^{-3} aq. NaOH (9.3 cm^3, 2.32 mmol) and the mixture was stirred overnight before being acidified with 1 mol dm^{-3} HCl to pH 4 and the aq. layer was extracted with $CHCl_3$ (3 × 10 cm^3). The combined extracts were washed with brine (10 cm^3), dried, and concentrated.

The crude acid **16** (246 mg) was dissolved in acetone (10 cm^3), and the solution was cooled to 0 °C and treated with Et_3N (0.242 cm^3) and then with ethyl chloroformate (0.167 cm^3). After the mixture had been stirred for 40 min, aq. NaN_3 (151 mg, 2.32 mmol in 4 cm^3) was added and the mixture was stirred at 0 °C for 1 h. After dilution with water (15 cm^3), the aq. layer was separated and extracted with $CHCl_3$ (3 × 10 cm^3). The extracts were washed with brine (10 cm^3), dried, and concentrated.

The crude azido ether was dissolved in AcOH–water (4 cm^3; 3:1) and the mixture was heated under reflux for 1 h. The aq. solution was partitioned between diethyl ether (10 cm^3) and 1 mol dm^{-3} HCl (10 cm^3), and the layers were separated. The organic layer was extracted with 1 mol dm^{-3} HCl (2 × 10 cm^3). The pH of the combined aq. layers was adjusted to 10 by the addition of 10% aq. NaOH. The alkaline solution was extracted with $CHCl_3$ (4 × 5 cm^3), and the extracts were dried and concentrated.

The crude amino ether **17** (170 mg) was dissolved in CH_2Cl_2 (4 cm^3), and the solution was treated with Et_3N (0.4 cm^3) and cooled to 0 °C. To the solution was added 4-chlorobenzenesulphonyl chloride (245 mg, 1.16 mmol) and the mixture was stirred at room temperature overnight, washed with brine (10 cm^3), dried, and concentrated. The residue was purified by chromatography [hexane–AcOEt (6:1)] on silica to give *compound* **18** (266 mg, 64%) as needles, m.p. 121–123 °C (from hexane–AcOEt) (Found: C, 54.0; H, 5.6; N, 3.6. $C_{16}H_{20}ClNO_4S$ requires C, 53.70; H, 5.63; N, 3.91%); $[\alpha]_D^{24}$ +17.8° (*c* 1.0); ν_{max}(KBr)/cm^{-1} 3212, 2973, 1352, 1159, 1110, 1040, 822 and 754; δ_H(270 MHz) 1.26 (1 H, d, *J* 9, 7-H^a), 1.47 (1 H, dt, *J* 9, 2, 7-H^b), 2.46 (1 H, ddt, *J* 9, 7.5, 3, 6-H), 2.83–2.86 (2 H, br, 1- and 4-H), 3.21 (1 H, A of ABX, *J* 10, 7.5, OC*H*H), 3.30 (1 H, B of ABX, *J* 10, 7.5, OCH*H*), 3.34 (3 H, s, OMe), 3.89 (1 H, ddd, *J* 9, 8, 3.5, 5-H), 4.52 (1 H, d, *J* 6, OC*H*HO), 4.55 (1 H, d, *J* 6, OCH*H*), 4.71 (1 H, br d, *J* 8, NH), 6.00 (1 H, dd, *J* 6, 3, CH=), 6.26 (1 H, dd, *J* 6, 3, CH=), 7.51 (2 H, dt, *J* 8.5, 2, ArH) and 7.82 (2 H, dt, *J* 8.5, 2, ArH); *m*/*z* (EI) 357 (M^+).

(+)-{(1*S*,4*R*)-3-endo-(4-*Chlorobenzenesulphonylamino*)*bicyclo*[2.2.1]*hept*-5-*en*-2-*yl*}*methanol* **19**.—To a suspension of compound **18** (367 mg, 1.03 mmol) in benzenethiol (2.5 cm^3) was added dropwise boron trifluoride–diethyl ether complex (0.5 cm^3) *via* syringe. The mixture was stirred at room temperature for 4 h. After dissolution of the precipitate with a minimal amount of $CHCl_3$ the solution was directly charged onto a silica column. The eluents with hexane–AcOEt (1:1) were collected and concentrated to give *compound* **19** (322 mg, quant.) as needles, m.p. 122–123 °C (from hexane–AcOEt) (Found: C, 53.7; H, 5.2; N, 4.5. $C_{14}H_{16}ClNO_3S$ requires C, 53.59; H, 5.14; N, 4.46%); $[\alpha]_D^{25}$ +55.2° (*c* 1.43); ν_{max}(KBr)/cm^{-1} 3123, 2891, 1321, 1156, 1091 and 756; δ_H(270 MHz) 1.27 (1 H, d, *J* 9, 7-H^a), 1.45 (1 H, dt, *J* 9, 2, 7-H^b), 1.95 (1 H, br, OH), 2.43 (1 H, ddt, *J* 8.8, 7, 3, 3-H), 2.73 (1 H, br s, 1- or 4-H), 2.83 (1 H, br s, 4- or 1-H), 3.43–3.45 (2 H, br, HOCH_2), 3.90 (1 H, dt, *J* 8.8, 4, 2-H), 4.91 (1 H, d, *J* 8.8,

NH), 6.01 (1 H, dd, *J* 6, 3, CH=), 6.29 (1 H, dd, *J* 6, 3, CH=), 7.52 (2 H, dt, *J* 9, 2, ArH) and 7.84 (2 H, dt, *J* 9, 2, ArH); *m/z* (EI) 314 ($M^+ + 1$), 313 (M^+), 249, 177, 175 and 111.

(+)-(1S,4R)-3-endo-(4-*Chlorobenzenesulphonylamino*)*bicyclo*[2.2.1]*hept*-5-*ene*-2-endo- *and* -2-exo-*carbaldehyde* **20** *and* **21**.—To a suspension of PCC (400 mg, 1.85 mmol), molecular sieves 4 Å (powder, 310 mg), and NaOAc (30 mg) in dry CH_2Cl_2 (25 cm^3) at 0 °C was added a solution of the alcohol **19** (193 mg, 0.62 mmol) in dry CH_2Cl_2 (10 cm^3) in one portion. After being stirred at that temp. for 1 h, the mixture was treated with diethyl ether (55 cm^3), stirred for 5 min, and filtered through a short plug of Florisil. The solid filter was washed with diethyl ether (2 × 50 cm^3) and the combined filtrate and washings were concentrated. The residue was filtered with hexane–AcOEt (1:1) with the aid of a short pad of Celite. The filtrate was concentrated to give a mixture of compounds **20** and **21** (163 mg, 85%), as a solid, in the ratio 6:1. The isomer ratio (**20**:**21** 6:1) was determined by the integration of the aldehydic protons (δ 9.46 and 9.67) in the ^1H NMR spectrum.

Compound **20** as needles, m.p. 141–143 °C (from hexane) (Found: C, 54.2; H, 4.3; N, 4.5. $C_{14}H_{14}ClNO_3S$ requires C, 53.93; H, 4.53; N, 4.49%); $[\alpha]_D^{24}$ +24.2° (*c* 1.07); ν_{max}(KBr)/cm^{-1} 3245, 2984, 1711, 1478, 1349, 1165, 1085 and 755; δ_H(270 MHz) 1.32 (1 H, d, *J* 9, 7-H^a), 1.50 (1 H, dt, *J* 9, 2, 7-H^b), 2.97 (1 H, br s, 1- or 4-H), 3.11 (1 H, ddd, *J* 9, 3.5, 2, 2-H), 3.18 (1 H, br s, 4- or 1-H), 4.22 (1 H, dt, *J* 9, 3.5, 3-H), 5.35 (1 H, br d, *J* 9, NH), 6.12 (1 H, dd, *J* 5.5, 3, CH=), 6.31 (1 H, dd, *J* 5.5, 3, CH=), 7.50 (2 H, dt, *J* 9, 2, ArH), 7.79 (2 H, dt, *J* 9, 2, ArH) and 9.46 (1 H, d, *J* 2, CHO); *m/z* (EI) 312 ($M^+ + 1$), 311 (M^+), 248, 246, 218, 177, 175, 113 and 111.

Compound **21** as prisms, m.p. 116 °C (from hexane) (Found: C, 53.9, H, 4.6; N, 4.1%); $[\alpha]_D^{24}$ +39.9° (*c* 0.93); ν_{max}(KBr)/cm^{-1} 3239, 2979, 1703, 1444, 1332, 1165, 1086, 1013 and 754; δ_H(270 MHz) 1.34 (1 H, d, *J* 9.5, 7-H^a), 1.44 (1 H, dq, *J* 9.5, 2, 7-H^b), 2.13 (1 H, br, 2-H), 2.91 (1 H, br s, 1- or 4-H), 3.05 (1 H, br, 4- or 1-H), 4.21 (1 H, dt, *J* 9.5, 3.5, 3-H), 4.55 (1 H, br, NH), 6.14 (1 H, dd, *J* 5.5, 3, CH=), 6.45 (1 H, dd, *J* 5.5, 3, CH=), 7.50 (2 H, dt, *J* 9, 2, ArH), 7.80 (2 H, dt, *J* 9, 2, ArH) and 9.67 (1 H, d, *J* 1, CHO); *m/z* 312 ($M^+ + 1$), 311 (M^+), 282, 248, 246, 177, 175 and 111.

Epimerisation of Compound **20**.—To a silica column (diameter 1.5 cm; Merck # 9385; 5 g) packed with hexane–AcOEt (4:1) was charged and adsorbed a solution of a mixture of aldehydes **20** and **21** (38 mg; 6:1) in $CHCl_3$ (0.5 cm^3). Next day the column was eluted with that solvent and the eluents were concentrated to give compounds **20** and **21** (37 mg, 97%) in the ratio 1:12. Recrystallisation from hexane afforded the pure 2-*exo*-aldehyde **21** (28 mg, 74%).

(+)-(5Z)-6-{(1S,4R)-3-endo-(4-*Chlorophenylsulphonylamino*)*bicyclo*[2.2.1]*hept*-5-*en*-2-endo-*yl*}*hex*-5-*enoic Acid* (+)-**3**.—A suspension of NaH (48 mg, 2.0 mmol, prewashed with dry diethyl ether) and dimethyl sulphoxide (DMSO) (1.5 cm^3) was heated at 60 °C for 45 min. To the solution cooled to room temp. was added (4-carboxybutyl)triphenylphosphonium bromide (443 mg, 1 mmol) and the mixture was stirred for 0.5 h. To the orange coloured solution was added a solution of compound **20** (40 mg, 0.13 mmol) in DMSO (0.5 cm^3) *via* syringe. After being stirred at 50 °C for 5 h the mixture was partitioned between AcOEt (5 cm^3) and 1 mol dm^{-3} HCl. The aq. layer (pH 4) was extracted with $CHCl_3$ (3 × 10 cm^3) and the combined organic extracts were dried and concentrated. The crude product was dissolved in MeOH (10 cm^3) and the solution was treated with excess of ethereal CH_2N_2. After usual work-up, the residue was purified by chromatography [hexane–AcOEt (6:1)] on silica to give the methyl ester derivatives of acids **3** and **22** (48 mg, 90%) in the ratio 5.5:1. The ratio was determined by integration of olefinic (5-H) signals in the ^1H NMR spectrum [δ 5.42 (dt, *J* 10.8, 6.8) and 5.30 (dt, *J* 15, 7.2)].

The methyl esters were treated with LiOH (6 mg, 0.26 mmol) in THF–water (4 cm^3; 3:1) and the mixture was stirred at room temp. for 48 h. After acidification with dil. HCl usual work-up gave the acids **3** and **22**. A solution of the crude acids **3** and **22** was treated with cyclohexylamine (35 mg, 0.35 mmol) in acetone (5 cm^3) at room temp. for 3 h. The precipitate was collected, and crystallised from acetone to give the cyclohexylamine salt of acid **3** which was then acidified with conc. HCl to give the free acid **3** (26 mg, 51%) (isomeric purity 93%) as an oil, $[\alpha]_D^{24}$ +100.8° (*c* 1.73). The spectroscopic data were in good agreement with those reported previously.[9]

Wittig–Horner Condensation of Compound **20** *by the Use of* Bu^{t}OK *as Base*.—To a suspension of (4-carboxybutyl)triphenylphosphonium bromide (214 mg, 0.48 mmol) in dry THF (20 cm^3) was added Bu^{t}OK (108 mg, 0.96 mmol) and the mixture was stirred at room temp. for 0.5 h. To the orange coloured solution was added a solution of compound **20** (30 mg, 0.096 mmol) in dry THF (20 cm^3) during 5 min. The mixture was then stirred for 4.5 h and treated with 1 mol dm^{-3} HCl to pH 2. Most of the THF was removed under reduced pressure, and the aq. layer was extracted with $CHCl_3$ (3 × 20 cm^3). The combined extracts were washed with brine, dried, and concentrated. The residue was dissolved in MeOH (10 cm^3) and treated with CH_2N_2. After usual work-up, the residue was purified by chromatography [hexane–AcOEt (6:1)] to give the methyl esters (48 mg, 100%) in the ratio 1:5.9.

(−)-(5Z)-6-{(1S,4R)-3′-endo-(4-*Chlorophenylsulphonylamino*)*bicyclo*[2.2.1]*hept*-5′-*en*-2′-exo-*yl*}*hex*-5-*enoic Acid* **4**.—By using the same method as in the preparation described above, treatment of compound **21** (54 mg, 0.17 mmol) with Bu^{t}OK (216 mg, 1.93 mmol) and (4-carboxybutyl)triphenylphosphonium bromide (428 mg, 0.97 mmol) in dry THF (10 cm^3) gave compounds (−)-**4** and **23** (58 mg, 86%) as a mixture of geometrical isomers, in the ratio 14:1, which was determined by the integration of the 5- and 6-H (acid chain) protons of its methyl ester derivatives in the ^1H NMR spectrum [δ 6.08 (2 H, t) and 5.82, 6.39 (each 1 H, each dd)]. The mixture was treated with cyclohexylamine, followed by recrystallisation from acetone, to give the almost pure amine salt of acid (−)-**4**, m.p. 113–115 °C. Treatment of the salt with conc. HCl afforded free acid (−)-**4** (29 mg, 43%) as an oil, $[\alpha]_D^{24}$ −40.5° (*c* 0.98). The spectroscopic data were in good agreement with those reported previously.[9]

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