Triterpenoid Total Synthesis. Part 2.[1] Synthesis of Glycinoeclepin A, a Potent Hatching Stimulus for the Soybean Cyst Nematode†

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Glycinoeclepin A, a natural hatching stimulus for the soybean cyst nematode, was enantioselectively synthesized starting from two chiral building blocks, both of which were obtained by reduction of prochiral 1,3-diketones with baker's yeast. The key reactions are aldol condensation to introduce asymmetry at C-12 and -13 and reductive lactone cleavage followed by aldol-type condensation for C-ring formation.

Cyst nematodes are well known as serious pests of many crops, and their extermination is an important agricultural problem. They generally have a limited host range and the specificity is thought to be based on a response to a chemical hatching stimulus secreted by the host plants. In 1985, Masamune *et al.* isolated a degraded triterpenoid, glycinoeclepin A, as a potent hatching stimulus for the soybean cyst nematode (*Heteropdera glycines* Ichinohe) from the dried root of the kidney bean (*Phaseolus vulgaris*) and determined its structure as **1**.[2] In addition to its strong hatch-stimulating activity for the soybean cyst nematode (10^{-12}–10^{-13} g cm^{-3}), its unusual structure (especially, the four contiguous asymmetric centres at C-12, -13, -17 and -20, and cross-conjugated diene carboxylic acid system) made it an attractive target for synthetic chemists. Up to now, three groups, including ours, have reported its synthesis,[3–5] and syntheses of simple model compounds were also reported.[6,7] Herein we describe our total synthesis of compound **1** in detail.

Results and Discussion

Synthetic Plan.—Our planned synthetic route to glycinoeclepin A **1** is convergent as shown in Scheme 1. There are three key steps as follows: (i) asymmetric reduction of prochiral 1,3-diketones **A** and **C** with baker's yeast to give (*S*)-hydroxy ketones **B** and **D**, (ii) stereoselective aldol condensation to introduce the C-12 and -13 asymmetry (**E** + **F** → **G**), and (iii) reductive lactone cleavage and subsequent aldol condensation to construct the C,D-ring system (**H** → **1**).

Asymmetric reduction (**A** → **B**) with baker's yeast was developed by our group some years ago,[8] and the hydroxy ketone **B** was utilized as a chiral starting material for several natural product syntheses.[8–10] It can be converted into a species **E** by bridged-ether formation and four-carbon elongation. Another (*S*)-hydroxy ketone, **D**, can also be obtained by reduction of the corresponding 1,3-diketone **C** with baker's yeast. In parallel with this work, we studied the asymmetric reduction of 1,3-diketones of the bicyclo[2.2.2]octane system, and showed the usefulness of baker's yeast as an asymmetric reducing agent.[11,12] By taking advantage of the bicyclic system **D**, chirality at the hydroxy and the three methyl groups of the target molecule are thought to be introduced stereoselectively. Intermediate **D** can be converted into the bicyclooctanone **F** after stereoselective methylation and ring expansion. Aldol condensation of compounds **E** and **F** gives **G** which possesses all of the asymmetric carbons in their desired configuration. Introduction of a two-carbon unit to ketone **G** gives lactone **H**. The precursor **H** is thought to be convertible into the target molecule **1** by reductive fission of the lactone carbon–oxygen bond followed by the nucleophilic addition of the resulting ester carbanion to the carbonyl group to generate the six-membered C-ring.

Preparation of the Aldehyde **E**.—One of the key intermediates, aldehyde **E** was prepared as shown in Scheme 2. Protected ketone **3**,[13] obtained from hydroxy ketone **2** (≡ **B**) of 97% ee, was treated with lithium diisopropylamide (LDA) and acetaldehyde to give an alcohol **4a**, contaminated with a small amount of dehydration product **5**. The hydroxy group of the alcohol **4a** was methanesulphonylated and the ester **4b** was then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the enone **5** in 94% yield from ketone **3**. Reduction of enone **5** with sodium borohydride gave an alcohol **6a** (88%), whose ^{1}H NMR data showed it to be a single isomer. Though we have no evidence for the configuration of the newly introduced hydroxy group nor any for the geometry of the olefin, we presumed that it was *syn* to the *t*-butyldimethylsiloxy group on the basis of analogy with Masamune's intermediate.[3] Protection of the hydroxy group of compound **6a** as the 1-ethoxyethyl (EE) ether gave compound **6b** (98%), and its *t*-butyldimethylsilyl (TBDMS) group was then removed by using tetrabutylammonium fluoride in tetrahydrofuran (THF) to give the alcohol **6c** in 96% yield. Iodotheration was accomplished in 70% yield by reaction of compound **6c** with *N*-iodosuccinimide (NIS) in acetonitrile to give the iodide **7**. Heating of compound **7** with DBU in toluene afforded an olefin **8** (95%), which was treated with 9-borabicyclo[3.3.1] nonane (9-BBN) and then with H_2O_2–NaOH to give the alcohol **9** in quantitative yield. Swern oxidation[14] of alcohol **9** to the corresponding aldehyde **10** was followed by three-carbon elongation using allylmagnesium chloride in THF to give the secondary alcohol **11a** (92% in two steps). The hydroxy group of compound **11a** was protected as its TBDMS ether **11b** (90%), which was submitted to Lemieux–Johnson oxidation to give the aldehyde **12** (≡ **E**) in 75% yield.

Preparation of the Ketone **F**.—The other substrate of the yeast reduction, compound **19** (≡ **C**) was synthesized in 40% yield through 6 steps as follows (see Scheme 3). Conjugate addition of vinylmagnesium bromide to 3-methylcyclopent-2-enone in the presence of tributylphosphine–copper(I) iodide[15,16] afforded the cyclopentanone **14** in 78% yield. Although we first planned to prepare hydroxy ketone **18** from substrate **13** by Sakurai reaction[17] followed by ozonolysis and acid treatment,[11,12] the 1,4-adduct could not be obtained by the Sakurai reaction. The carbonyl group of compound **14** was protected as the ethylene acetal in 88% yield to give compound **15**, hydroboration–oxidation of which gave the alcohol **16** in

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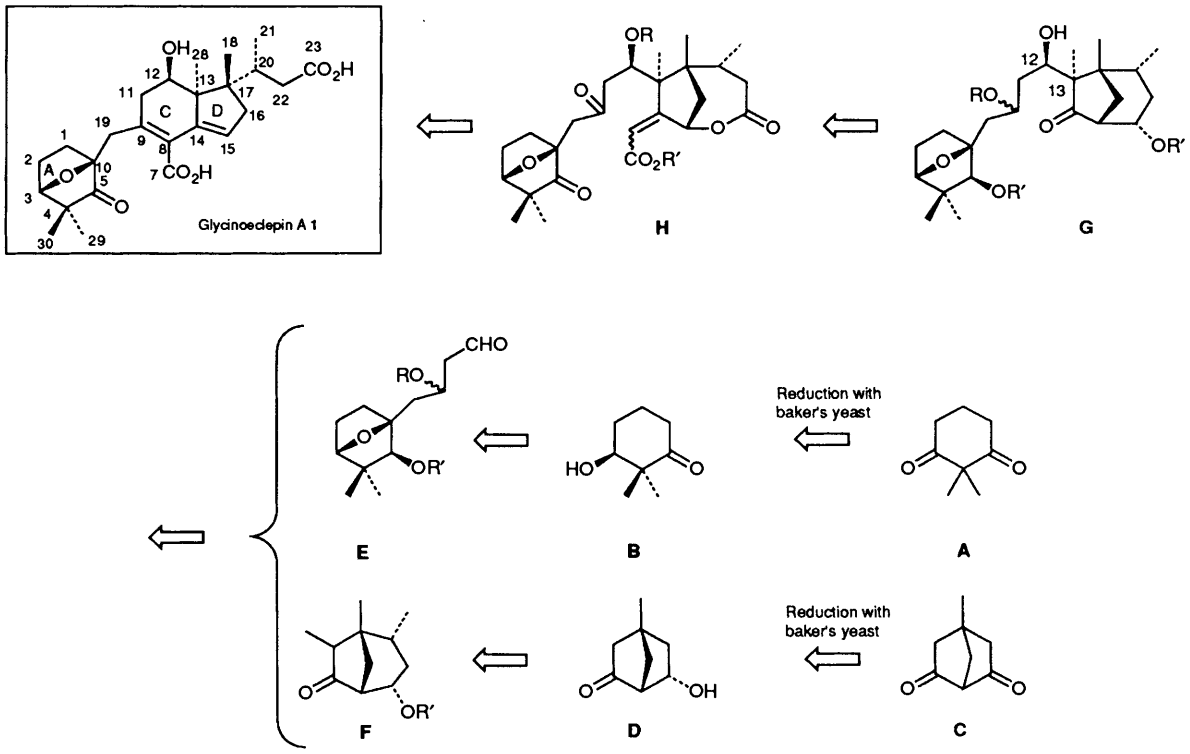
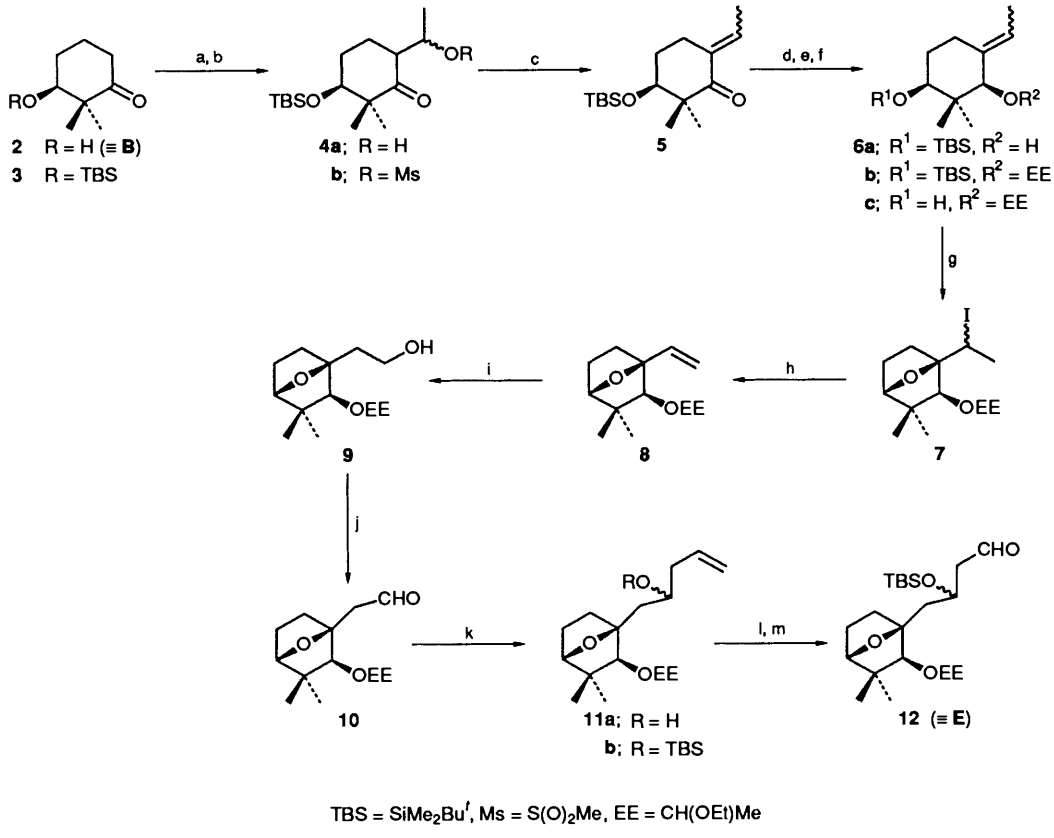
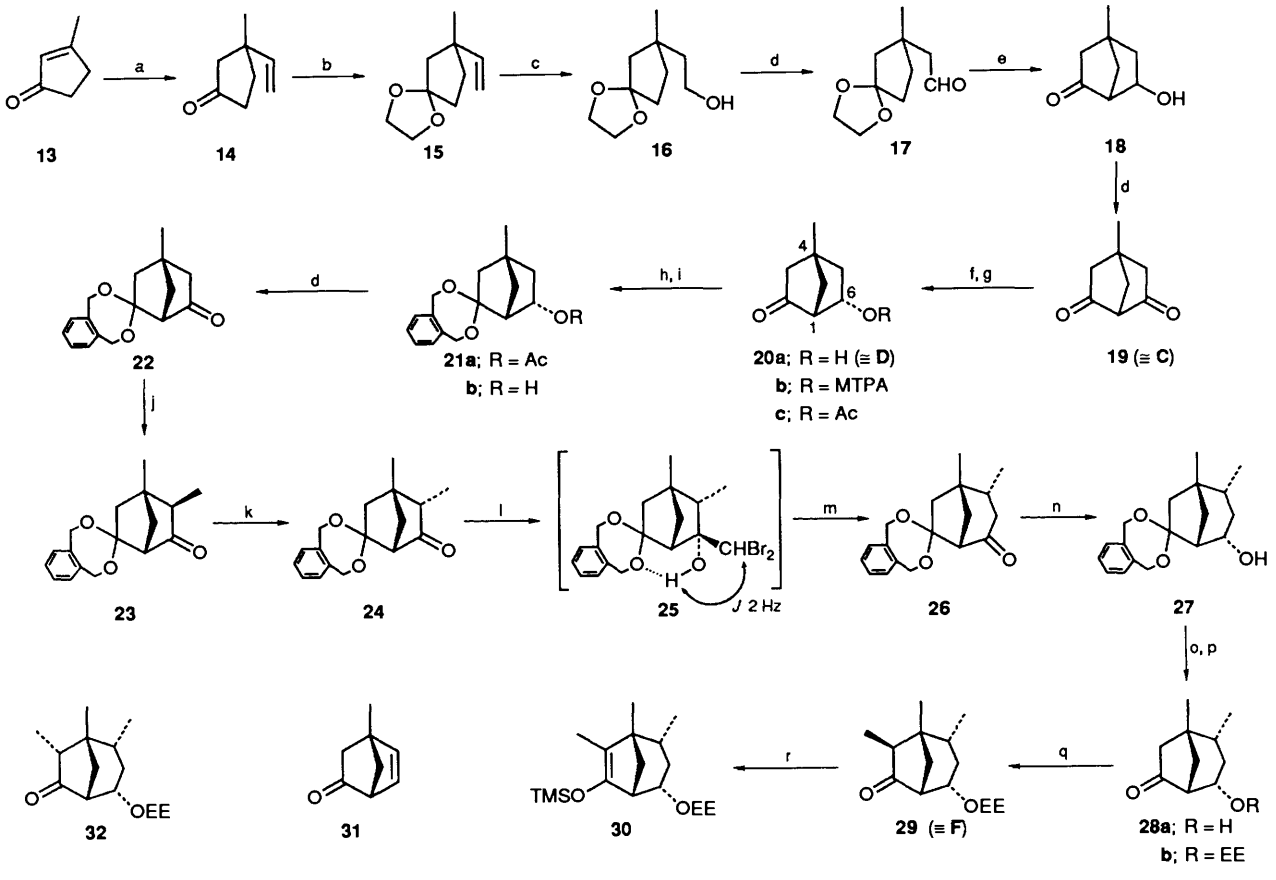


Scheme 1 Synthetic plan



Scheme 2 Synthesis of the Aldehyde **E**. *Reagents, conditions and yields:* (a) LDA, MeCHO–THF (quant.); (b) MsCl, Et_3N–CH_2Cl_2; (c) DBU, THF (2 steps, 94%); (d) $NaBH_4$, THF–EtOH (88%); (e) CH_2=CHOEt, *p*-TsOH (98%); (f) Bu_4NF, THF (96%); (g) NIS, MeCN, room temp. (70%); (h) DBU, PhMe, reflux (95%); (i, 9-BBN, THF; then H_2O_2, NaOH (quant.); (j) $(COCl)_2$, DMSO–CH_2Cl_2, Et_3N; (k) CH_2=$CHCH_2MgBr$, THF (2 steps 92%); (l) TBSCl, imidazole, DMF (90%); (m) OsO_4, $NaIO_4$, Et_2O–water (75%)

quantitative yield. The alcohol **16** was oxidized to the aldehyde **17** by using pyridinium chlorochromate (PCC) and molecular sieves 3 Å[18] in dichloromethane (87%). Heating of compound **17** with hydrochloric acid in acetone afforded the deprotected aldol condensation product **18** as an *exo* and *endo* mixture in 82% yield. Oxidation of compound **18** with PCC gave the



Scheme 3 Synthesis of the ketone **F**. *Reagents, conditions and yields:* (a) CH_2=CHMgBr, Bu_3P•CuI, THF (78%); (b) HO[CH_2]$_2$OH, *p*-TsOH, C_6H_6, reflux (−H_2O) (88%); (c) BH_3•THF, then H_2O_2, NaOH (quant.); (d) PCC, mol sieves 3 Å CH_2Cl_2 [87% (**16** → **17**); 81% (**18** → **19**); 97% (**21b** → **22**)]; (e) HCl–aq. acetone (82%); (f) baker's yeast, sucrose, pH 7 phosphate buffer (55%); (g) Ac_2O, DMAP, C_5H_5N (93%); (h) *o*-xylene-α,α′-diol, *p*-TsOH, PhMe, reflux (70–75 °C; −H_2O) (87%); (i) NaOMe–MeOH; then recryst'n (80%); (j) LDA, MeI, THF–HMPA (97%); (k) LiHMDS, THF–HMPA; then aq. NH_4Cl (98%); (l) $LiCHBr_2$, THF; (m) MeLi (1 mol equiv.) BuLi (1 mol equiv.), THF (2 steps, 50%); (n) $NaBH_4$, THF–EtOH (96%); (o) H_2, Pd–C, EtOAc (99%); (p) CH_2=CHOEt, *p*-TsOH (quant.): (q) NaH, MeI, THF (94%); (r) NaH, TMSCl, Et_3N, THF (99%).

substrate of the yeast reduction, the dione **19** (≡ **C**) in 81% yield.

Unfortunately, dione **19** was unstable in water even at pH 7 and competitive hydrolysis to give the corresponding keto carboxylic acid diminished the yield of the alcohol **20a** to 34% under the conditions reported for the reduction of compound **A**[8] or other bridged bicyclic compounds.[11,12] To increase the ratio of the desired reduction product, a larger amount of baker's yeast (130 g of dry yeast/1 dm^3 of water) was used for the reduction of a small amount of the substrate (4 g). Furthermore, addition of the substrate to the medium was divided into four portions (see Experimental section). By these improvements compound **20a** was obtained in acceptable yield (58%).

Though the *exo*-isomer could not be detected on TLC during the reaction, a small amount appeared after working up. We believe it was formed by isomerization of compound **20a** by retroaldol–aldol condensation.

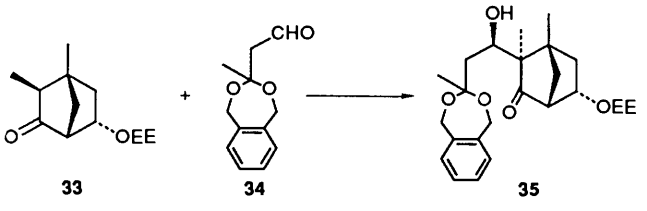
The absolute configuration of compound **20a** was determined to be 1*R*,4*S*,6*S* by the fact that the CD spectrum of compound **31**, which was derived from the intermediate **21b** by dehydration followed by deprotection, showed a positive Cotton effect [Δε (308 nm) +17.3].[19]

The enantiomeric purity of compound **20a** was estimated to be 80–87% ee by HPLC analysis of the corresponding (*R*)- and (*S*)-α-methoxy-α-trifluoromethyl(phenyl)acetate (MTPA ester) **20b**,[20] and it could be enhanced to 100% ee by recrystallization [m.p. 56.5–57.5 °C (from hexane–diethyl ether)]. In our synthetic route, however, optical enrichment by recrystallization could be achieved more effectively at a later stage, and we therefore employed the alcohol **20a** of 82.5% ee directly. After conversion of the alcohol **20a** into its acetate **20c** in the usual manner [acetic anhydride, 4-(dimethylamino)pyridine (DMAP)–pyridine, 93% yield], the carbonyl group of the acetate **20c** was protected as its *o*-xylylene-α,α′-dioxy acetal to give compound **21a** in 87% yield. This protective group has the merit of being removable by neutral catalytic hydrogenolysis[21–23] and is thought to be suitable for avoiding undesired isomerization of compound **28a** by retroaldol–aldol condensation during the deprotection process (**27** → **28a**). The acetyl group was removed by treatment of compound **21a** with sodium methoxide in methanol to give the free alcohol **21b**, which was readily purified to 100% ee by recrystallization [80% yield after recrystallization, m.p. 102–102.5 °C (from hexane–ethyl acetate)]. Oxidation of the alcohol **21b** with PCC and molecular sieves 3 Å[18] in dichloromethane gave the ketone **22** in 97% yield. When the latter compound was treated with LDA and iodomethane in THF–hexamethylphosphoric triamide (HMPA) at −10 to 0 °C, methylation took place from the *exo*-face and compound **23** was obtained as the sole product (97%). In order to ensure that the newly introduced methyl group was in the correct configuration corresponding to the methyl group on the side-chain of **1**, our target compound, compound **23** was enolized by treatment with lithium hexamethyldisilazide (LiHMDS) in THF (40 °C; 10 h) and then the resulting enolate was protonated with aq. NH_4Cl at −15 to 0 °C to give an

epimer **24** (98%). This alkylation–epimerization process was quite stereoselective, and in both reactions the C-3 epimer of the products was not detected. In addition to that, it should be noted that the second enolization step was quite slow and LDA instead of LiHMDS gave poor results. Ring expansion of compound **24** to give the bicyclooctanone **26** was achieved by Nozaki's method[24] with a small modification because the yield was only 26% when his original procedure was employed. In Nozaki's report, an intermediate dibromo alcohol was treated with butyllithium (2 mol equiv.), while we used one mol equiv. each of methyllithium and butyllithium (see Experimental section). ^{1}H NMR study of the intermediate **25** showed its hydroxy group to be highly sterically hindered and stabilized by strong hydrogen bonding with the acetal oxygen. Indeed, its proton exchange with D_2O was very slow ($T_{\frac{1}{2}}$ *ca.* 1.5 h) and it shows long-range coupling with $CH Br_2$ (J 2 Hz); because of that, when only butyllithium was used, metal–halogen exchange was thought to take place prior to alkoxide formation,[24] which decreased the yield. On the other hand, methyllithium is sterically more compact, and its ability to cause metal–halogen exchange is lower than that of butyllithium. So we first added one mol equiv. of methyllithium for alkoxide formation prior to the addition of another mol equiv. of butyllithium. By these modifications, the yield was raised to 50%. The structure of compound **26** was confirmed by 400 MHz ^{1}H NMR measurement, and a regioisomer in which the methylene group was inserted at an undesired position was not isolated.

Reduction of the ketone **26** with sodium borohydride in THF–ethanol gave the equatorial alcohol **27** (96%). As we expected at this stage of the synthetic plan, deprotection of *o*-xylylene-α,α′-dioxy acetal **27** proceeded quite cleanly to afford hydroxy ketone **28a** by hydrogenolysis (H_2/Pd–C in ethyl acetate) in almost quantitative yield. In addition, it should be noted that all the intermediates **21b**–**27** were crystalline by virtue of the nature of the *o*-xylylene-α,α′-dioxy acetal group. Protection of the hydroxy group of compound **28a** as its EE ether gave compound **28b** in quantitative yield, which was subsequently methylated by treatment with sodium hydride and iodomethane in THF to give compound **29** (≡ **F**) in 97% yield. This methylation was also stereoselective and the isomer **32** could not be detected.

Completion of the Synthesis of Glycinoeclepin A.—With both intermediates (compounds **12** and **29**) in hand, we tried the key aldol condensation. In a model study, shown in Scheme 4., the

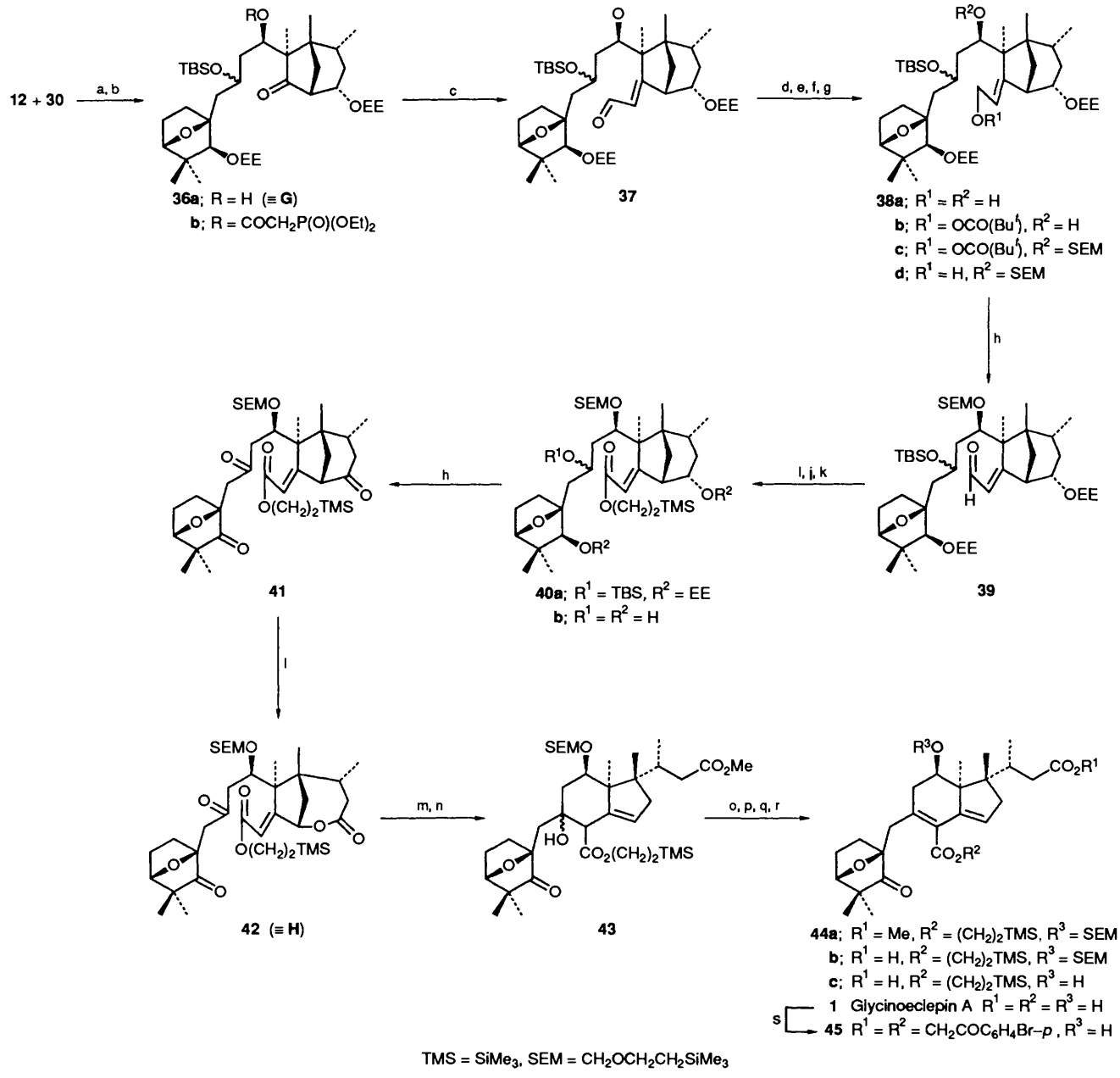


33 **34** **35**

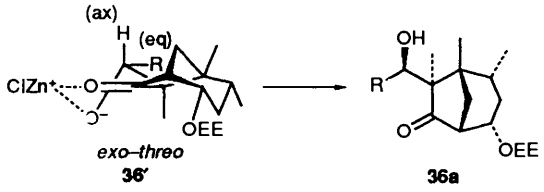
Scheme 4 Model study on aldol condensation. *Reagents, conditions and yield:* LDA, THF, −78 °C, (94%).

lithium enolate of ketone **33** reacted smoothly with aldehyde **34** and the secondary alcohol **35** was obtained with high stereoselectivity in 94% yield. Under the same conditions, however, reaction of substrates **12** and **29** did not give the desired hydroxy ketone **36a**. At the same time, we observed that enolate formation from compound **29** was slower than that from ketone **33** and gave unknown by-products. These results suggest that the *endo*-face of compound **29** was so sterically crowded that the newly generated *endo*-methyl group made the product **36a** unstable. We then employed the zinc enolate to stabilize the aldol product according to House's method.[25] Compound **29** was enolized by being refluxed with sodium hydride in THF for 15 h and was then trapped with chlorotrimethylsilane (TMSCl) to give the bis-ether **30** in 99% yield. The zinc enolate was generated by treatment of compound **30** with methyllithium and zinc chloride in diethyl ether, which reacted successfully with the aldehyde **12** at −78 °C to give 3:2:2 mixture of products **36a** (≡ **G**), **12** and **32**. As this compound was too unstable to be isolated by silica gel or neutral alumina column chromatography, the crude product obtained by careful work-up (see Experimental section) was immediately converted into the corresponding diethyl phosphonoacetate **36b**, which was purified by silica gel column chromatography (Scheme 5). Considering the amounts of the recovered substrate **12** and **32** (42% each), the yield of compound **36b** was 99.6%. By utilizing the recovered compounds for the same reaction again, compound **36b** was obtained in 82% total yield. Stereoselectivity of the aldol condensation is illustrated in Scheme 6. Electrophilic attack of the aldehyde took place from the less hindered *exo*-face and the *threo*-isomer was favoured due to the stability of the intermediate **36′**. Treatment of the phosphonoacetate **36b** with sodium hydride in THF gave a lactone **37** in 84% yield by the intramolecular olefination reaction. To obtain the precursor of C-ring formation, the lactone should be cleaved. However, attempted direct opening of the lactone by sodium hydroxide in aq. methanol or sodium methoxide in methanol failed. We therefore carried out the following conversions. First, the lactone **37** was reduced with calcium borohydride[26,27] to give the diol **38a** in high yield. This reagent was very effective in this case, but when lithium aluminium hydride, diisobutylaluminium hydride or lithium borohydride was used instead, compound **38a** was obtained only in poor yield. Selective acylation of the primary hydroxy group gave mono ester **38b** (95% in 2 steps), whose secondary hydroxy group was protected as its [2-(trimethylsilyl)ethoxy]methyl (SEM) ether[28] to give compound **38c** (94%). Then the pivaloyl group was removed (methyllithium–diethyl ether, 93% yield) and the deprotected hydroxy group was oxidized to an aldehyde by Swern's method[14] to give compound **39** *via* the allyl alcohol **38d** in 96% yield. Further oxidation into the carboxylic acid by using $NaClO_2$ in *t*-butylalcohol and phosphate buffer[29] was followed by Mitsunobu reaction[30] to give 2-(trimethylsilyl)ethyl ester **40a** (82% in 2 steps). For this esterification, *N*,*N*′-dicyclohexylcarbodiimide (DCC) did not work even in the presence of a catalytic amount of DMAP. Two EE groups and a TBDMS group were removed by treatment of compound **40a** with pyridinium toluene-*p*-sulphonate (PPTS) in aq. methanol to give triol **40b** in 83% yield. Swern oxidation[14] of triol **40b** gave triketone **41** (86%) as crystals, m.p. 100–100.5 °C. Quite fortunately, the Baeyer–Villiger oxidation of compound **41** proceeded with excellent selectivity to give compound **42** (≡ **H**) in 99% yield.

Prior to the next key C-ring formation, we studied the reaction using a model compound **46** (see Scheme 7). Reduction of ester lactone **46** using 2 mol equiv. of lithium naphthalenide[31] in THF at −78 °C gave bicyclic diester **47** in 50% yield after treatment of the product with diazomethane for isolation. Treatment of compound **47** with methanesulphonyl chloride and triethylamine in dichloromethane afforded dehydration product **48** (61%), which has the same C,D-ring system as that of glycinoeclepin A. However, compound **42** (Scheme 5) gave a complex mixture under the same conditions. We supposed that a bridged ether adjacent to the carbonyl group on the A-ring was also reactive and competitive side-reactions took place. We then chose lithium dimethylcuprate as an electron source with a smaller redox potential $-E_{\frac{1}{2}} = 0.159$ V, *cf.* $-E_{\frac{1}{2}}$ of naphthalenide, 1.98 V. It is known that cuprate reduces γ-acetoxy-α,β-unsaturated ketones,[32] and more recently, Takano *et al.* reported the same type of reaction as ours when using this

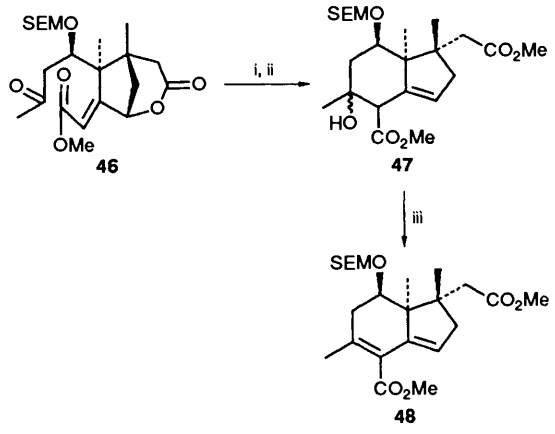


Scheme 5 Completion of the glycinoeclepin A synthesis. *Reagents, conditons and yields:* (a) MeLi, $ZnCl_2$, Et_2O; (b) $(EtO)_2P(O)CH_2CO_2H$, DCC, CH_2Cl_2 (2 steps, 82%); (c) NaH, THF (84%); (d) $Ca(BH_4)_2$, EtOH; (e) Bu^tCOCl, Et_3N, CH_2Cl_2 (2 steps, 95%); (f) SEMCl, Pr^i_2NEt, Bu_4NBr, CH_2Cl_2 (94%); (g) MeLi, EtOH(93%); (h) $(COCl)_2$, DMSO–CH_2Cl_2, Et_3N [96% (**38d** → **39**); 86% (**40b** → **41**)]; (i) $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, Bu^tOH–water; (j) $TMS[CH_2]_2OH$, DEAD, Ph_3P, THF (2 steps, 82%); (k) PPTS, aq. MeOH (83%); (l) MCPBA, $NaHCO_3$, CH_2Cl_2 (99%); (m) Me_2CuLi, THF; (n) CH_2N_2, Et_2O (2 steps, 73%); (o) $SOCl_2$, C_5H_5N (82%); (p) LiOH, Bu_4NOH, aq. TFH (92%); (q) $LiBF_4$, MeCN; (r) $(Me_2N)_3S^+$ $Me_3SiF_2^-$, MeCN (2 steps, 97%); (s) *p*-bromophenacyl bromide, Pr^i_2NEt, Me_2CN (95%).



Scheme 6 Stereoselectivity of aldol condensation

reagent.[33] When compound **42** was treated with lithium dimethylcuprate in THF at −78 °C, the reaction proceeded smoothly to give the indene diester **43** in 72% isolated yield after methylation. Our mechanistic interpretation of this reaction is shown in Scheme 8. The first step of this reaction is one-electron transfer followed by the fission of the lactone C–O bond to form a radical carboxylate **49**, which then reacts with another electron to form an enolate **50**. Finally, an intramolecular aldol condensation of dianion **50** afforded the indene **51**. Dehydration of a tertiary alcohol was accomplished by treatment of the indene **43** with thionyl dichloride in pyridine in 82% yield. The final task for our synthesis was the removal of the three protective groups of the product **44a**. To obtain the final product in an easily purifiable state, we adopted a stepwise process; first, by a mild saponification of the methyl ester to give monoacid **44b** (lithium hydroxide, tetrabutylammonium hydroxide, aq. THF; secondly, removal of the SEM ether by lithium tetrafluoroborate to give compound **44c**,[34] and finally removal of the trimethylsilylethyl ester by tris(dimethylamino)-sulphonium diflurotrimethylsiliconate.[35] The crude product, obtained by the process described above, could be directly



Scheme 7 Model study on reductive cyclization. *Reagents and yields*: i, $Li^+C_{10}H_8^-$, THF; ii, CH_2N_2 (together 50%); iii, MsCl, Et_3N, CH_2Cl_2 (61%).

purified by recrystallization from ethyl acetate to afford pure glycinoeclepin A **1** in 89% total yield; m.p. 120–121.5 °C (needles); $[\alpha]_D^{20}$ −10.2° (*c* 0.63, MeOH). The total amount of synthetic glycinoeclepin A was 220 mg, and this was the first time that it had been obtained crystalline. Attempts to elucidate its conformation by X-ray analysis, however, ended in failure. Our synthetic glycinoeclepin A **1** showed almost the same (slightly stronger) hatch-stimulating activity as the natural product. For identification, synthetic glycinoeclepin A **1** was converted into its bis-(*p*-bromophenacyl) diester **45** by the reported procedure[2,3] in 95% yield; m.p. 133.5–134.5 °C, $[\alpha]_D^{22}$ −19.1° (*c* 0.57, $CHCl_3$). The IR, ^1H and ^{13}C NMR data were identical with those of natural glycinoeclepin A's derivative.[2]

In summary, glycinoeclepin A **1** was stereoselectively synthesized starting from the (*S*)-hydroxy ketones **3** and **20a**, obtained by microbial methods. The overall yield of compound **1** was 5.2% from **3** and 4.4% from **20a** (2.6% from **16**).

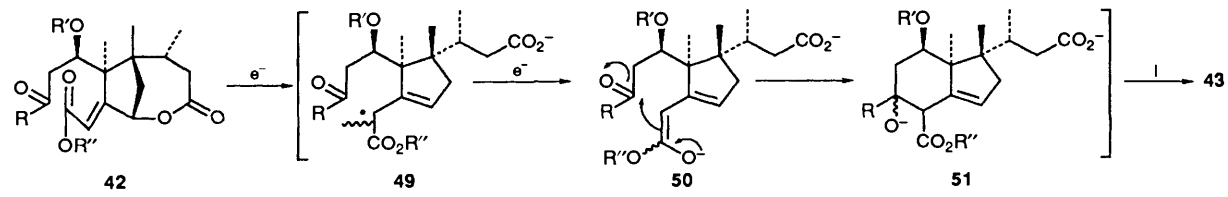
Experimental

All b.p.s and m.p.s are uncorrected; m.p.s were measured on a Yanaco micro melting point apparatus. IR spectra were measured for samples as films for oils or as Nujol mulls for solids on a JASCO IRA-102 spectrometer. NMR spectra were recorded with $SiMe_4$ as internal standard at 60 MHz on a Hitachi R-24A spectrometer, at 90 MHz on a JEOL JNM-EX 90, at 100 MHz on a JEOL JNM-FX 100, at 300 MHz on a Bruker AC 300, or at 400 MHz on a JEOL JNM-FX 400 spectrometer. *J* Values are in Hz. Optical rotations were measured on a JASCO DIP 140 polarimeter. Mass spectra were recorded on a JEOL SX-102 instrument at 10 eV. Refractive indexes were measured on a ERMA new Abbe refractometer.

(3S)-3-(t-*Butyldimethylsiloxy*)-6-(1-*hydroxyethyl*)-2,2-*dimethylcyclohexanone* **4a**.—To a stirred and cooled solution of diisopropylamine (32.3 cm^3, 231 mmol) in dry THF (150 cm^3) at −78 to −25 °C was added dropwise butyllithium (1.62 mol dm^{-3} in hexane; 143 cm^3, 232 mmol) under Ar. After being stirred for 15 min at −45 to −25 °C the mixture was treated with a solution of compound **3** (53.9 g, 210 mmol) in dry THF (100 cm^3) dropwise at −78 to −45 °C, and the mixture was stirred at −78 °C for 30 min. A solution of acetaldehyde (29 cm^3, 519 mmol) in dry THF (50 cm^3) was then added to this mixture at −78 to −55 °C. After being stirred at −78 °C for 1 h, the reaction mixture was poured into saturated aq. NH_4Cl and extracted three times with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give crude compound **4a** (72.2 g, quant.) as a diastereomeric mixture contaminated with ~25% of dehydration product **5**, ν_{max}(film)/cm^{-1} 3450 and 1695; δ_H(100 MHz; $CDCl_3$) 0.04 (6 H, s, Me_2Si), 0.87, 0.90, 0.92 and 0.96 (total 9 H, 4 × s, Me_3CSi), 1.05–1.30 [9 H, m, 2-Me_2 and *Me*CH(OH)], 1.30–2.70 (6 H, m, 4- and 5-H_2, 6-H and OH), 3.35–4.05 [2 H, m, 3-H and MeC*H*(OH)] and 5.31 (small peak for **5**, ~0.3 H, q *J* 6, C=CH). As the product contained compound **5**, which was desired for the next reaction, this was employed for the next step without further purification.

(3S)-3-(t-*Butyldimethylsiloxy*)-6-*ethylidene*-2,2-*dimethylcyclohexanone* **5**.—To a cooled and stirred solution of crude compound **4a** (72.0 g, 240 mmol) and Et_3N (70 cm^3, 502 mmol) in dry THF (700 cm^3) at 0–15 °C was added dropwise methanesulphonyl chloride (28 cm^3, 362 mmol). After the mixture had been stirred at 0–5 °C for 2 h, further Et_3N (20 cm^3) and methanesulphonyl chloride (10 cm^3) were added to the reaction mixture, and the mixture was stirred at room temperature for 1 h, before being ice-cooled again and DBU (108 cm^3, 722 mmol) was added. After the addition, the mixture was stirred for 1 h at 50 °C before being poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to give compound **5** (56.0 g, 94.3%) (Found: C, 67.7; H, 10.6. $C_{16}H_{30}O_2Si$ requires C, 68.03; H, 10.70%); n_D^{21} 1.4749; $[\alpha]_D^{23}$ +0.27° (*c* 1.09, $CHCl_3$); ν_{max}(film)/cm^{-1} 1683, 1615, 1250, 1080 and 835; δ_H(300 MHz; $CDCl_3$) 0.04 (3 H, s, MeSi), 0.05 (3 H, s, MeSi), 0.88 (9 H, s, Me_2CSi), 1.07 (3 H, s, 2-Me), 1.10 (3 H, s, 2-Me), 1.72 (3 H, d, *J* 9.6, *Me*CH=C), 1.79 (1 H, m, 4-H), 1.95 (1 H, m, 4-H), 2.44 (1 H, br dt, *J* 21 and 7.6, 5-H), 2.60 (1 H, br m, 5-H), 3.76 (1 H, dd, *J* 3.3 and 8.7, 3-H) and 6.55 (1 H, tq, *J* 2.8 and 9.6, C=CH).

(1R,3S)-3-(t-*Butyldimethylsiloxy*)-6-*ethylidene*-2,2-*dimethylcyclohexanol* **6a**.—To a stirred and cooled solution of ketone **5** (55.5 g, 196 mmol) in THF (250 cm^3) was added dropwise a solution of $NaBH_4$ (8.2 g, 217 mmol) in EtOH (250 cm^3) during 10 min. After being stirred at 0–5 °C for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Crude product was recrystallized from hexane to give compound **6a** (40.8 g). The mother liquor was evaporated and the residue was purified by SiO_2 chromatography to give a further crop (8.5 g; total 49.3 g, 88%) of *compound* **6a**, m.p. 42.5–43.5 °C (rods) (Found: C, 67.6; H, 11.3.



Scheme 8 Mechanism of reductive C-ring formation. *Reagent*: i, H_3O^+, then CH_2N_2.

$C_{16}H_{32}O_2Si$ requires C, 67.55; H, 11.34%); $[\alpha]_D^{23}$ +61.8° (*c* 1.05, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3550, 1155, 1105, 1060, 870 and 830; δ_H(100 MHz; $CDCl_3$) 0.10 (6 H, s, Me_2Si), 0.81 (3 H, s, 2-Me), 0.91 (9 H, s, Me_3CSi), 1.13 (3 H, s, 2-Me), 1.67 (3 H, dd, *J* 1 and 7, *Me*CH=C), 1.50–1.80 (3 H, m, 4-H_2 and OH), 2.15–2.55 (2 H, m, 5-H_2), 3.51 (1 H, br s, 1-H), 3.64 (1 H, br t, 3-H) and 5.49 (1 H, br q, *J* 7, C=CH).

(1S,3R)-1-(t-*Butyldimethylsiloxy*)-3-(1-*ethoxyethoxy*)-4-*ethylidene*-2,2-*dimethylcyclohexane* **6b**.—To an ice-cooled and stirred solution of the alcohol **6a** (38.7 g, 136 mmol) in ethyl vinyl ether (300 cm^3) was added toluene-*p*-sulphonic acid monohydrate (TsOH·H_2O, 100 mg). After the mixture had been stirred at room temperature for 10 min, further TsOH·H_2O (30 mg) was added and the mixture was stirred for 5 min. The addition was repeated four times until the starting material disappeared on TLC monitoring. The reaction mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Distillation of the residue gave the *title compound* **6b** (47.6 g, 98.1%), b.p. 120–125 °C/0.6 mmHg (Found: C, 67.1; H, 11.2. $C_{20}H_{40}O_3Si$ requires C, 67.36; H, 11.31%); n_D^{20} 1.4602; $[\alpha]_D^{23}$ −49.1° (*c* 1.04, $CHCl_3$); ν_{max}(film)/cm^{-1} 1270, 1015, 1060 and 900; δ_H(90 MHz; $CDCl_3$) 0.02 (6 H, s, Me_2Si), 0.65–1.25 (12 H, m, Me × 4), 0.87 (9 H, s, Me_2CSi), 1.29 ($\frac{3}{2}$ H, d, *J* 6, *Me*CH=C), 1.30 ($\frac{3}{2}$ H, d, *J* 6, *Me*CH=C), 1.35–1.85 (3 H, m, 5-H, 6-H_2), 2.50 (1 H, m, 5-H), 3.25–3.85 (4 H, m, 1- and 3-H, OCH_2Me), 4.60 ($\frac{1}{2}$ H, q, *J* 5.5, OC*H*MeO), 3.67 ($\frac{1}{2}$ H, q, OC*H*MeO), 5.27 ($\frac{1}{2}$ H, br q, *J* 6, C=C*H*Me) and 5.56 ($\frac{1}{2}$ H, br q, *J* 6, C=C*H*Me).

(1S,3R)-3-(1-*Ethoxyethoxy*)-4-*ethylidene*-2,2-*dimethylcyclohexanol* **6c**.—To a stirred solution of compound **6b** (45.0 g, 126 mmol) in dry THF (450 cm^3) was added a solution of tetrabutylammonium fluoride (1 mol dm^{-3} in THF; 150 cm^3, 150 mmol). The reaction mixture was heated under reflux for 4 h. After the mixture had cooled, water was added and the mixture was extracted with diethyl ether. The extract was washed successively with water (× 2), saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography to give *compound* **6c** (29.3 g, 96%) (Found: C, 68.9; H, 11.0. $C_{14}H_{26}O_3$ requires C, 69.38; H, 10.81%); n_D^{21} 1.4657; $[\alpha]_D^{23}$ +18.3° (*c* 1.16, $CHCl_3$); ν_{max}(film)/cm^{-1} 3530, 1130, 1080, 1020, 990 and 950; δ_H(90 MHz; $CDCl_3$) 0.81 and 0.91 (total 6 H, 2 × s, 2-Me_2), 1.00–1.35 (6 H, m, *Me*CH_2O and OCH*Me*O), 1.67 (3 H, d, *J* 6, *Me*CH=C), 1.70–2.45 (5 H, m, 5- and 6-H_2 and OH), 3.25–3.85 (4 H, m, 1- and 3-H and MeCH_2O), 4.54 ($\frac{1}{2}$ H, q, *J* 5.2, OC*H*MeO), 4.63 ($\frac{1}{2}$ H, q, *J* 5.2, OC*H*MeO) and 5.32–5.55 (1 H, m, CC*H*Me).

(1R,2S,4S)-2-(1-*Ethoxyethoxy*)-1-(1-*iodoethyl*)-3,3-*dimethyl*-7-*oxabicyclo*[2.2.1]*heptane* **7**.—A solution of compound **6c** (27.5 g, 113 mmol) and NIS (38.3 g, 170 mmol) in dry acetonitrile (500 cm^3) was stirred at room temperature in the dark for 12 h. The resulting mixture was poured into water and extracted with diethyl ether. The extract was washed successively with 10% aq. $Na_2S_2O_3$, water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compound* **7** (29.4 g, 70%) (Found: C, 46.0; H, 6.9. $C_{14}H_{25}IO_3$ requires C, 45.66; H, 6.84%); n_D^{20} 1.4982; $[\alpha]_D^{20}$ +11.4° (*c* 1.18, $CHCl_3$); ν_{max}(film)/cm^{-1} 1200, 900, 860 and 815; δ_H(60 MHz; $CDCl_3$) 0.90–1.30 (15 H, m, 5 × Me), 1.30–2.60 (4 H, m, 5- and 6-H_2), 3.10–3.75 [5 H, m, 2-, 4- and 1-(1-H) and MeCH_2O] and 4.25–4.65 (1 H, m, OC*H*MeO).

(1S,2S,4S)-2-(1-*Ethoxyethoxy*)-3,3-*dimethyl*-1-*vinyl*-7-*oxabicyclo*[2.2.1]*heptane* **8**.—A solution of the iodide **7** (22.5 g, 61.1 mmol) and DBU (14.0 g, 92.1 mmol) in toluene (200 cm^3) was heated under reflux. After 12 h DBU (4.7 g, 31 mmol) was added to the mixture and the mixture was heated for a further 12 h. After cooling, the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by short SiO_2 column chromatography and vacuum distillation to give *compound* **8** (13.9 g, 95%), b.p. 78–81 °C/0.35 mmHg (Found: C, 69.5; H, 9.9. $C_{14}H_{24}O_3$ requires C, 69.96; H, 10.06%); n_D^{20} 1.4565; $[\alpha]_D^{23}$ +18.6° (*c* 1.18, $CHCl_3$); ν_{max}(film)/cm^{-1} 3100, 1650, 1100, 1013, 970, 945, 910 and 700; δ_H(100 MHz; $CDCl_3$) 1.05–1.35 (12 H, m, 4 × Me), 1.04–2.00 (4 H, m, 5- and 6-H_2), 3.38 ($\frac{2}{3}$ H, s, major 2-H), 3.46 ($\frac{1}{3}$ H, s, minor 2-H), 3.39–3.66 (2 H, m, MeCH_2), 3.88 (1 H, d, *J* 4, 4-H), 4.63 ($\frac{1}{3}$ H, q, *J* 6, minor OC*H*MeO), 4.67 ($\frac{2}{3}$ H, q, *J* 6, major OC*H*MeO), 5.15–5.43 (2 H, m, C=CH_2), 6.19 ($\frac{2}{3}$ H, dd, *J* 11 and 18, major CH_2=C*H*) and 6.27 ($\frac{1}{3}$ H, dd, *J* 11 and 18, minor CH_2=C*H*).

2-{(1S,2S,4S)-2-(1-*Ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*-[2.2.1]*heptan*-1-*yl*}*ethanol* **9**.—To a stirred and cooled solution of compound **8** (12.5 g, 52.0 mmol) in dry THF (50 cm^3) was added 9-BBN (0.5 mol dm^{-3} solution in THF; 125 cm^3, 62.5 mmol) at 0–5 °C under Ar. After the addition the mixture was stirred at room temperature for 2 h and was then ice-cooled and excess of 9-BBN was destroyed by the addition of water (10 cm^3) at 0–5 °C. To the reaction mixture at 50–60 °C were added 3 mol dm^{-3} aq. NaOH (21 cm^3, 63 mmol) and 35% aq. H_2O_2 (19 cm^3, 196 mmol), and the mixture was stirred at 30–60 °C for 1 h, poured into water, and extracted with diethyl ether (× 3). The extract was washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was distilled under reduced pressure to give *compound* **9** (13.4 g, quant.), b.p. 117–118 °C/0.45 mmHg (Found: C, 64.8; H, 9.9. $C_{14}H_{26}O_4$ requires C, 65.09; H, 10.14%); n_D^{20} 1.4621; $[\alpha]_D^{23}$ +8.94° (*c* 1.28, $CHCl_3$); ν_{max}(film)/cm^{-1} 3460, 1135, 1060 and 998; δ_H(100 MHz; $CDCl_3$) 1.07 [3 H, s, 2-(3-Me)], 1.09 [3 H, s, 2-(3-Me)], 1.26 (3 H, t, *J* 7, *Me*CH_2), 1.34 (2 H, d, *J* 6, MeCH_2O), 1.35–2.60 (7 H, m, 5- and 6-H_2, CH_2CH_2OH and OH), 3.35–4.30 (6 H, m, 2- and 4-H, CH_2CH_2OH and MeCH_2O) and 4.63 (1 H, q, *J* 7, OC*H*MeO).

{(1S,2S,4S)-2-(1-*Ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*-[2.2.1]*heptan*-1-*yl*}*acetaldehyde* **10**.—To an ice-cooled and stirred solution of oxalyl dichloride (6.57 cm^3, 76.6 mmol) in dry CH_2Cl_2 (130 cm^3) was added dropwise dimethyl sulphoxide (DMSO) (10.9 cm^3, 153 mmol) at −60 to −45 °C under Ar. After the mixture had been stirred at −50 °C for 15 min, a solution of the alcohol **9** (13.2 g, 51.1 mmol) in dry CH_2Cl_2 (60 cm^3) was added dropwise to the reaction mixture at −60 to −50 °C, and the mixture was stirred at the same temperature. After 1 h, triethylamine (23.5 cm^3, 168 mmol) was added to the reaction mixture at −60 to −40 °C and the temperature was allowed to rise gradually to −10 °C during 1 h 10 min. The resulting suspension was poured into water and extracted with diethyl ether (× 2). The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give crude aldehyde **10** (14.1 g), ν_{max}(film)/cm^{-1} 2730 and 1722; δ_H(100 MHz; $CDCl_3$) 1.00–1.30 (12 H, m, Me × 4), 1.30–1.95 (4 H, m, 5- and 6-H_2), 2.74–2.86 (2 H, m, CH_2CHO), 3.33 ($\frac{2}{3}$ H, s, major 2-H) 3.51 (2 H, q, *J* 6, MeCH_2), 3.52 ($\frac{1}{3}$ H, s, minor 2-H), 3.85–3.93 (1 H, br m, 4-H), 4.45 ($\frac{2}{3}$ H, q, *J* 6, major OC*H*MeO), 4.58 ($\frac{1}{3}$ H, q, *J* 6, minor OC*H*MeO), 9.81 ($\frac{2}{3}$ H, t, *J* 2, CHO) and 9.83 ($\frac{1}{3}$

H, t, *J* 2, CHO). This was employed for the next step without further purification.

1-{(1S,2S,4S)-2-(1-*Ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*-[2.2.1]*heptan*-1-*yl*}*pent*-4-*en*-2-*ol* **11a**.—A mixture of Mg (6.1 g, 251 mg-atom), a trace amount of I_2, 1,2-dibromoethane (0.5 g) and dry THF (20 cm^3) was heated under Ar until a reaction started and a reddish brown colour disappeared. The mixture was then diluted with dry THF (80 cm^3). To this was added dropwise a solution of allyl chloride (3-chloroprop-1-ene) (10.4 g, 136 mmol) and 1,2-dibromomethane (0.5 g) in dry THF (200 cm^3) at −10 to −5 °C during 3 h. After the addition, the mixture was stirred for 1 h at the same temperature. The resulting Grignard reagent solution was cooled to −78 °C, and to this was added dropwise a solution of crude aldehyde **10** (14.0 g, 51 mmol) in dry THF (40 cm^3) at −78 to −65 °C. The reaction mixture was stirred at −78 °C for 1 h, and then was quenched by being poured into saturated aq. ammonium chloride and was extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a crude product (15.4 g). This was purified by SiO_2 column chromatography to give *compound* **11a** (13.9 g, 92% from **9**) (Found: C, 68.3; H, 10.1. $C_{17}H_{30}O_4$ requires C, 68.42; H, 10.13%); n_D^{21} 1.4725; $[\alpha]_D^{22}$ +6.2° (*c* 0.92, $CHCl_3$); ν_{max}(film)/cm^{-1} 3490, 3080 and 1640; δ_H(100 MHz; $CDCl_3$) 1.00–1.40 (12 H, m, Me × 4), 1.40–2.55 [9 H, m, 1-(5-H_2) and 1-(6-H_2), CH_2CH-(OH)CH_2 and OH], 3.29–4.15 (5 H, m, 1-(2-H) and 1-(4-H), C*H*OH and MeCH_2), 4.40–4.73 (1 H, m, OC*H*MeO), 4.95–5.25 (2 H, m, CH_2=CH) and 5.60–6.10 (1 H, m, C*H*=CH_2).

(1S,2S,4S)-1-[2-(t-*Butyldimethylsiloxy*)*pent*-4-*enyl*]-2-(1-*ethoxyethyl*)-3,3-*dimethyl*-7-*oxabicyclo*[2.2.1]*heptane* **11b**.—A solution of compound **11a** (13.0 g, 43.6 mmol), inidazole (8.90 g, 131 mmol), *t*-butyl(chloro)dimethylsilane (9.85 g, 65.4 mmol) and DMAP (0.1 g) in dry dimethylformamide (130 cm^3) was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography to give the *bis-ether* **11b** (16.1 g, 90%) (Found: C, 67.0; H, 10.6). $C_{23}H_{44}O_4Si$ requires C, 66.94; H, 10.75%); $[\alpha]_D^{23}$ +4.1° (*c* 1.05, $CHCl_3$); ν_{max}(film)/cm^{-1} 3080, 1640, 1250, 835 and 770; n_D^{21} 1.4629; δ_H(100 MHz; $CDCl_3$) 0.10 (6 H, s, Me_2Si), 0.91 (9 H, s, Me_3C), 1.06 (6 H, s, 3-Me_2), 0.95–1.35 (6 H, m, *Me*CH_2 and OCHMeO), 1.40–2.36 [8 H, m, 5- and 6-H_2 and CH_2CH(OTBS)CH_2], 3.14, 3.20 and 3.21 (total 1 H, 3 × s, 2-H), 3.40–3.63 (2 H, m, MeCH_2), 3.70–3.83 (1 H, br, 4-H), 3.83–4.25 (1 H, m, C*H*OTBS), 4.50, 4.51 and 4.65 (total 1 H, q, *J* 6, OC*H*MeO), 4.90–5.17 (2 H, m, CH_2=CH) and 5.63–6.20 (1 H, m, C*H*=CH_2).

3-(t-*Butyldimethylsiloxy*)-4-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}*butyraldehyde* **12**.—A mixture of compound **11b** (13.0 g, 31.5 mmol), OsO_4 (1.00 g, 3.93 mmol), $NaIO_4$ (20.2 g, 94.4 mmol), diethyl ether (200 cm^3) and water (200 cm^3) was heated under reflux and vigorously stirred under Ar. After 9 h, $NaIO_4$ (10.0 g, 46.7 mmol) was added and the mixture was vigorously stirred for a further 4 h. After cooling, the ethereal layer was separated and the aq. solution was extracted with diethyl ether (× 2). The combined extracts were washed successively with water, 10% aq. $Na_2S_2O_3$, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the aldehyde **12** (9.80 g, 75%), n_D^{18} 1.4580; ν_{max}(film)/cm^{-1} 2720, 1728, 838 and 778; δ_H(100 MHz; $CDCl_3$) 0.03–0.12 (6 H, m, Me_2Si), 0.88 (9 H, s, Me_3CSi), 0.89–1.36 (12 H, m, Me × 4), 1.38–2.34 [7 H, m, 4-(5-H_2), 4-(6-H_2), 4-H_2 and 2-H], 2.67 (1 H, m, 2-H), 3.15–3.65 (3 H, m, 2-H and MeCH_2O) and 3.78 [1 H, br m, 4-(4-H)], 4.38–5.04 (2 H, m, 3-H and OC*H*MeO) and 9.80 (1 H, m, CHO). This was employed for the next step without further purification.

3-*Methyl*-3-*vinylcyclopentanone* **14**.—To a cooled and stirred solution of 3-methylcyclopent-2-enone (168 g, 1.75 mol) and $(Bu_3P{\cdot}CuI)_4$ (103 g, 65.6 mmol) in dry THF (1.5 dm^3) was added dropwise a solution of vinylmagnesium bromide (1.0 mol dm^{-3} in THF; 2.2 dm^3, 2.2 mol) during 2 h at −45 to 40 °C under Ar. After the addition the mixture was stirred for 1 h at −45 to −35 °C, then was poured into saturated aq. NH_4Cl, and the resulting suspension was stirred overnight at room temperature. The organic phase was separated and the aq. phase was extracted three times with diethyl ether. The combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was distilled under reduced pressure to give crude compound **14** (178 g), b.p. 60–80 °C/30 mmHg. The crude product **14** was distilled again to give almost pure *compound* **14** (169.5 g, 78%), b.p. 68.5–73.0 °C/19 mmHg (Found: C, 77.6; H, 9.9. $C_8H_{12}O$ requires C, 77.38; H, 9.74%); n_D^{21} 1.4721; ν_{max}(film)/cm^{-1} 3090, 1736, 1638, 1400 and 915; δ_H(300 MHz; $CDCl_3$) 1.96 (3 H, s, 3-Me), 1.82 (1 H, dt, *J* 17 and 10, 4-H), 1.97 (1 H, dt, *J* 17 and 10, 4-H), 2.07 (1 H, d, *J* 23, 2-H), 2.28 (2 H, t, *J* 10, 5-H_2), 2.32 (1 H, d, *J* 23, 2-H), 4.96–5.02 (2 H, m, C=CH_2) and 5.88 (1 H, dd, *J* 15 and 23, C*H*=CH_2).

7-*Methyl*-7-*vinyl*-1,4-*dioxaspiro*[4.4]*nonane* **15**.—The solution of the ketone **14** (156 g, 1.26 mol), ethylene glycol (313 g, 5.04 mol) and TsOH·H_2O (7.2 g, 37.9 mmol) in benzene (470 cm^3) was heated under reflux with azeotropic removal of water using a Dean–Stark trap. When generation of water ceased (after 6 h), the reaction mixture was cooled, poured into saturated aq. $NaHCO_3$, and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was distilled under reduced pressure to give *spirane* **15** (185 g, 88%), b.p. 112–115 °C/55 mmHg (Found: C, 71.0; H, 9.5. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%); n_D^{21} 1.4589; ν_{max}(film)/cm^{-1} 3090, 1638, 1330, 1105, 1030 and 953; δ_H(60 MHz; $CDCl_3$) 1.12 (3 H, s, 7-Me), 1.30–2.55 (6 H, m, 6-, 8-and 9-H_2), 3.77 (4 H, s, 2- and 3-H_2), 4.70–5.10 (2 H, m, C=CH_2) and 6.85 (1 H, dd, *J* 11 and 18, C*H*=CH_2).

2-(7-*Methyl*-1,4-*dioxaspiro*[4.4]*nonan*-7-*yl*)*ethanol* **16**.—To a solution of olefin **15** (180 g, 1.07 mol) in dry THF (350 cm^3) at 5 °C was added borane–THF complex (2.4 mol dm^{-3} in THF; 220 cm^3, 0.53 mol) during 1 h under Ar. After being stirred for 30 min at room temperature the reaction mixture was ice cooled and water (55 cm^3) was added to destroy the excess of borane. After the completion of hydrogen generation, 3 mol dm^{-3} aq. NaOH (180 cm^3, 0.54 mol) was added dropwise to the ice-cooled reaction mixture, and 35% aq. H_2O_2 (104 cm^3, 1.07 mol) was then added dropwise at <40 °C. The resulting mixture was stirred at 50 °C for 1 h and then poured into brine. The THF solution was separated, dried ($MgSO_4$), and filtered. The aq. solution was extracted with $CHCl_3$ (× 3), and the extract was dried ($MgSO_4$) and filtered. The combined filtrate was concentrated under reduced pressure to give crude compound **16** (202 g, quant.). A small amount of the product **16** was chromatographed to give an *analytical sample* (Found: C, 64.3; H, 9.6. $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74%); n_D^{21} 1.4719; ν_{max}(film)/cm^{-1} 3400, 1165, 1080, 1040 and 980; δ_H(100 MHz; $CDCl_3$) 1.04 (3 H, s, 7-Me), 1.30–2.45 (9 H, m, 6-, 8- and 9-H_2, CH_2CH_2OH and OH) and 3.55–4.05 (6 H, m, 2- and 3-H_2 and CH_2OH).

(*7-Methyl-1,4-dioxaspiro*[4.4]*nonan-7-yl*)*acetaldehyde* **17**.—To an ice-cooled, mechanically stirred suspension of the crude alcohol **16** (200 g, 1.07 mol) and powdered mol. sieves 3 Å (300 g) in dry CH_2Cl_2 (3.5 dm^3) was added portionwise PCC (400 g, 1.85 mol). The mixture was stirred at 20–35 °C for 4.5 h. Florisil (200 g) and diethyl ether (4 dm^3) were then added to the reaction mixture and the resulting slurry was filtered through Florisil (500 g). The filter-cake was washed with diethyl ether. The combined filtrate and washings were concentrated under reduced pressure to give crude aldehyde **17** (173 g, 87%), ν_{max}(film)/cm^{-1} 3470, 2760, 1735 and 1400; δ_H(300 MHz; $CDCl_3$) and δ_H (90 MHz; $CDCl_3$) 1.20 (3 H, s, 7-Me), 1.40–2.10 (6 H, m, 6-, 8- and 9-H_2), 2.47 (2 H, d, *J* 3, CH_2CHO), 3.89 [4 H, s, $O(CH_2)_2O$] and 9.81 (1 H, t, *J* 3, CHO). This was immediately used for the next reaction without further purification.

6-Hydroxy-4-methylbicyclo[2.2.1]*heptan-2-one* **18**.—A mixture of crude aldehyde **17** (169 g, 917 mmol) and conc. HCl (75 cm^3) in acetone–water (8:2; 1.5 dm^3) was heated under reflux under Ar for 2 h. Then the reaction mixture was ice-cooled and 8 mol dm^{-3} aq. NaOH (100 cm^3, 800 mmol) was added. Solid $NaHCO_3$ was added portionwise to the mixture until it became slightly alkaline (pH ~8, universal indicator). Acetone was evaporated off and the resulting aq. solution was saturated with NaCl and extracted with $CHCl_3$ (× 5). The combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compound* **18** (93.7 g, 73%) as a 2:3 mixture of the *exo*- and *endo*-isomer. Less polar fractions which were eluted earlier than compound **18** were evaporated and the resulting oil (22.2 g, mainly consisting of non-cyclized keto aldehyde) was heated again with conc. HCl (10 cm^3) in acetone–water (8:2; 200 cm^3) for 2 h. The same work-up and purification as above gave a further crop (11.5 g) of compound **18** (total 105.2 g, 82%) (Found: C, 68.3; H, 8.6. $C_8H_{12}O_2$ requires C, 68.55; H, 8.63%); ν_{max}(film)/cm^{-1} 3440, 1730, 1120 and 1035; δ_H(100 MHz; $CDCl_3$) 1.27 ($\frac{9}{5}$ H, s, 4-Me), 1.35 ($\frac{6}{5}$ H, s, 4-Me), 1.85–2.50 (7 H, m, 3-, 5- and 7-H_2 and OH), 2.64 ($\frac{2}{5}$ H, br s, 1-H), 2.76 ($\frac{3}{5}$ H, dt, *J* 1 and 5, 1-H), 4.16 ($\frac{2}{5}$ H, br d, *J* 7, 6-H) and 4.55 ($\frac{3}{5}$ H, ddd, *J* 3, 5 and 8, 6-H).

4-Methylbicyclo[2.2.1]*heptane-2,6-dione* **19**.—To an ice-cooled mechanically stirred mixture of compound **18** (93 g, 663 mmol) and powdered mol. sieves 3 Å (150 g) in dry CH_2Cl_2 (2.5 dm^3) was added portionwise PCC (286 g, 1.33 mol). After being stirred at 25–35 °C for 4 h the mixture was treated with Florisil (140 g) and diethyl ether (2 dm^3) and the resulting slurry was filtered through Florisil (200 g). The filter-cake was washed with diethyl ether. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by short SiO_2 column chromatography to give dione **19** as an unstable, wet solid (74 g, 81%), ν_{max}(film)/cm^{-1} 1760, 1320, 1035, 984, 965, 918, 900 and 760; δ_H(60 MHz; $CDCl_3$) 1.47 (3 H, s, 4-Me), 2.10 (6 H, br s, 3-, 5- and 7-H_2) and 3.10 (1 H, br s, 6-H). Owing to the instability of this compound it was employed for the next step without further purification.

(1R,4S,6S)-*6-Hydroxy-4-methylbicyclo*[2.2.1]*heptan-2-one* **20a**.—A suspension of dry baker's yeast (100 g), sucrose (100 g), KH_2PO_4 (5.5 g) and $Na_2HPO_4 \cdot 12H_2O$ (21.5 g) in water (1 dm^3) was incubated at 30 °C on a rotary platform shaker for 10 min. A solution of dione **18** (1.0 g, 7.2 mmol) in EtOH (3 cm^3) was then added to the mixture and the incubation was continued at 30 °C. After 10 min, further sucrose (10 g) and dry baker's yeast (10 g) were added to the mixture, and after a further 2 min of incubation further dione **18** (1.0 g, 7.2 mmol) was added to the mixture. These additions of sucrose, baker's yeast and dione **18** were repeated twice more. After the completion of the additions, the incubation was continued for 30 min. The reaction mixture was then filtered through Celite, and filter-cake was washed with acetone. The filtrate was made slightly alkaline (pH ~8, universal indicator) by addition of $NaHCO_3$, and was then saturated with NaCl and extracted six times with EtOAc. On the other hand, the washings (acetone solution) were evaporated, and the residue was diluted with EtOAc and washed with saturated aq. $NaHCO_3$. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography to give compound **20a** as crystals (2.04 g, 55%). A portion of the product was recrystallized from hexane–diethyl ether (3:1) to give pure *compound* **20a** in 42% yield, m.p. 56.5–57.5 °C (prisms) (Found: C, 68.5; H, 8.7. $C_8H_{12}O_2$ requires C, 68.55; H, 8.63%); $[\alpha]_D^{23}$ −16.6° (*c* 1.06, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3450, 1745, 1250, 1175, 1135, 1080 and 1040; δ_H(60 MHz; $CDCl_3$) 1.21 (3 H, s, 4-Me), 1.30–2.30 (6 H, m, 3-, 5- and 7-H_2), 2.72 (1 H, br d, *J* 5, 1-H), 3.28 (1 H, br s, OH, exchangeable with D_2O) and 4.50 (1 H, br m, 6-H, after D_2O addition; ddd, *J* 3, 5 and 8). For determination of the enantiomeric purity, compound **20a** was converted into the corresponding (*R*)-and (*S*)-MTPA ester **20b**.[20] HPLC analysis revealed the ester to be 82.5% ee [column, NUCLEOSIL® 50-5, 25 cm × 4.6 mm diam; solvent, hexane–THF (20:1), 1.0 cm^3 min^{-1}; detected at 254 nm] (*S*)-MTPA ester **20b**, t_R 20.0 min (91.3%) and 28.5 min (8.7%).

(1R,4S,6S)-*6-Acetoxy-4-methylbicyclo*[2.2.1]*heptan-2-one* (*4-Methyl-6-oxobicyclo*[2.2.1]*heptan-2-yl Acetate*) **20c**.—To an ice-cooled, stirred solution of the alcohol **20a** (23.0 g, 164 mmol) and acetic anhydride (60 cm^3) in pyridine (60 cm^3) was added DMAP (0.40 g, 3.3 mmol, 0.02 mol equiv.). After being stirred for 10 min at 5 °C and for 1.5 h at room temperature, the reaction mixture was poured into water and extracted with diethyl ether (× 3). The extract was washed successively with 1 mol dm^{-3} hydrochloric acid, water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was distilled under reduced pressure to give *acetate* **20c** (27.9 g, 93%), b.p. 83–88 °C/0.95 mmHg (Found: C, 65.9; H, 7.6. $C_{10}H_{14}O_3$ requires C, 65.92; H, 7.74%); n_D^{21} 1.4648; $[\alpha]_D^{23}$ −47.6° (*c* 1.37, $CHCl_3$); ν_{max}(film)/cm^{-1} 1740, 1370 and 1245; δ_H(60 MHz; $CDCl_3$) 1.24 (3 H, s, 4-Me), 1.35–1.70 (2 H, m, 5-H_2), 1.93 (3 H, s, AcO), 1.75–2.15 (4 H, m, 3- and 7-H_2), 2.76 (1 H, br d, *J* 5, 1-H) and 5.21 (1 H, m, 6-H).

(1′R,4′S,6′S)-*Spiro*-{*1,5-dihydro-2,4-benzodioxepine*-3,2′-(*4′-methylbicyclo*[2.2.1]*heptane*)}-*6′-yl Acetate* **21a**.—A mixture of compound **20c** (5.3 g, 29.1 mmol), *o*-xylene-α,α′-diol (10 g, 72.4 mmol) and *p*-TsOH·H_2O (0.40 g) in toluene (50 cm^3) was heated and refluxed through a column of mol. sieves 4 Å (30 g) under slightly reduced pressure for 3 h. (The reflux temperature was kept at 70–75 °C by controlling the pressure.) After cooling, the solution was poured into saturated aq. $NaHCO_3$ and was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography to give *compound* **21a** (7.62 g, 87%) as a viscous oil (Found: C, 71.2; H, 7.2. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%); $[\alpha]_D^{23}$ +58.5° (*c* 0.47, $CHCl_3$); ν_{max}(film)/cm^{-1} 3060, 3030, 1495, 1295, 1210, 1155, 1005, 1040, 955, 870 and 750; δ_H(60 MHz; $CDCl_3$) 1.10 (3 H, s, 4′-Me), 1.00–2.30 (6 H, m, 3′-, 5′- and 7′-H_2), 2.00 (3 H, s, AcO), 2.70 (1 H, br d, *J* 4, 1′-H), 4.50 (1 H, d, *J* 14, ArCH*H*O), 4.67 (2 H, s, ArCH_2O), 4.71 (1 H, d, *J* 14, ArC*H*HO), 4.90 (1 H, br m, 6′-H) and 7.00 (4 H, br m, ArH).

(1′R,4′S,6′S)-*Spiro*-{*1,5-dihydro-2,4-benzodioxepine*-3,2′-(*4′-methylbicyclo*[2.2.1]*heptan-6′-ol*)} **21b**.—A solution of compound **21a** (18.1 g, 59.9 mmol) and sodium methoxide (28% in

MeOH, 3 cm^3) in MeOH (150 cm^3) was stirred under Ar at 30 °C. After 4 h, the reaction mixture was neutralized (universal indicator) by addition of acetic acid and the resulting solution was concentrated under reduced pressure. The residue was diluted with water and extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue (17.8 g) was recrystallized three times from hexane–EtOAc (5:1) to give the *pure alcohol* **21b** (12.5 g, 80%), m.p. 102–102.5 ° (leaflets) (Found: C, 73.6; H, 7.7. $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.74%); $[\alpha]_D^{23.5}$ −44.4° (*c* 1.59, $CHCl_3$); ν_{max}(film)/cm^{-1} 3500, 1320, 1165, 1145, 1110, 1050, 1025 and 955; δ_H(300 MHz; $CDCl_3$) 1.12 (3 H, s, 4′-Me), 1.18 (1 H, dt, *J* 13 and 4, 5′-H), 1.24 (1 H, br d, *J* 10.8, 3′-H), 1.54–1.63 (2 H, m, 3′-H and OH), 1.81 (2 H, br s, 7′-H_2), 2.00 (1 H, tm, *J* 12, 5′-H), 2.58 (1 H, br d, *J* 4.3, 1′-H), 4.10 (1 H, d, *J* 11, ArC*H*HO), 4.26 (1 H, tt, *J* 4.3, 10.8, 6′-H), 4.77 (1 H, d, *J* 14.7, ArC*H*HO), 4.93 (2 H, br d, *J* 16, ArCH*H*O × 2) and 7.05–7.25 (4 H, m, ArH). For the determination of its enantiomeric purity, compound **21b** was converted into the corresponding (*R*)- and (*S*)-MTPA esters in the usual manner.[20] HPLC analysis revealed the product to be 100% ee [column, NUCLEOSIL® 50-5, 25 cm × 4.6 mm diam.; solvent, hexane–THF (20:1), 1.0 cm^3 min^{-1}; detected at 254 nm] (*S*)-MTPA ester, t_R 20.6 min (single peak) and (*R*)-MTPA ester, t_R 25.6 min (single peak).

(1′R,4′S)-*Spiro*-{1,5-*dihydro*-2,4-*benzodioxepine*-3,2′-(4′-*methylbicyclo*[2.2.1]*heptan*-6′-*one*)} **22**.—To an ice-cooled, stirred mixture of the alcohol **21b** (8.3 g, 31.9 mmol), sodium acetate (3.92 g, 47.8 mmol), and powdered mol. sieves 3Å (10.3 g) in dry CH_2Cl_2 (220 cm^3) was added portionwise PCC (10.3 g, 47.8 mmol). After the addition, the ice-bath was removed and the resulting slurry was stirred overnight at room temperature. To the reaction mixture were added Florisil (20 g) and diethyl ether (250 cm^3) and the mixture was filtered through a Florisil column. The filter-cake was washed with diethyl ether and the combined filtrate and washings were concentrated under reduced pressure. The residue was recrystallized to give the ketone **22** (7.45 g). The mother liquor was concentrated under reduced pressure and the residue was purified by SiO_2 column chromatography followed by recrystallization to give *ketone* **22** (0.52 g) (total 7.97 g, 97%), m.p. 125–125.5 °C [from hexane–EtOAc (5:1), as rods] (Found: C, 74.25; H, 7.0. $C_{16}H_{18}O_3$ requires C, 74.40; H, 7.02%); $[\alpha]_D^{24}$ +52.8° (*c* 1.33, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 1750, 1085 and 1020; δ_H(100 MHz; $CDCl_3$) 1.31 (3 H, s, 4′-Me), 1.55–2.15 (6 H, m, 3′-, 5′- and 7′-H_2), 2.98 (1 H, br s, 1′-H), 4.82 (4 H, br s, ArCH_2O × 2) and 6.95–7.25 (4 H, m, ArH).

(1′R,4′R,5′R)-*Spiro*-{1,5-*dihydro*-2,4-*benzodioxepine*-3,2′-(4′,5′-*dimethylbicyclo*[2.2.1]*heptan*-6′-*one*)} **23**.—To a solution of diisopropylamine (6.0 cm^3, 42.9 mmol) in dry THF (40 cm^3) at −30 to −20 °C was added dropwise BuLi (1.53 mol dm^{-3} in hexane; 26.8 cm^3, 41.0 mmol) under Ar. Then HMPA (14.3 cm^3, 82.2 mmol) was added to the LDA solution and the mixture was stirred for 30 min at −30 °C. To the solution at −78 °C was added dropwise a solution of ketone **22** (10.0 g, 38.7 mmol) in dry THF (50 cm^3). The temperature was gradually raised from −78 to −5 °C during 2 h. To this solution at −30 to −20 °C was added iodomethane (93% purity; 3.24 cm^3, 48.4 mmol) and the mixture was stirred for 2 h at −10 to 0 °C before being poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 column chromatography followed by recrystallization to give *compound* **23** (8.44 g, 80%). The starting material (1.72 g) was recovered by chromatography followed by recrystallization from hexane–EtOAc (5:1). The yield of title compound **23**, considering the recovery of starting material **22**, was 97%, m.p. 95.0–96.0 °C (plates) (Found: C, 74.8; H, 7.4. $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40%); $[\alpha]_D^{21.5}$ +41.9° (*c* 1.98, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 1745, 1374, 1265, 1130, 1100 and 1035; δ_H(100 MHz; $CDCl_3$) 1.05 (3 H, d, *J* 7.6, 5′-Me), 1.20 (3 H, s, 4′-Me), 1.65–2.20 (5 H, m, 3′- and 7′-H_2 and 5′-H), 2.93 (1 H, br s, 1′-H), 4.83 (4 H, br s, ArCH_2O × 2) and 6.95–7.25 (4 H, m, ArH).

(1′R,4′R,5′S)-*Spiro*-{1,5-*dihydro*-2,4-*benzodioxepine*-3,2′-(3′,4′-*dimethylbicyclo*[2.2.1]*heptan*-6′-*one*)} **24**.—To a stirred solution of $HN(TMS)_2$ (4.03 cm^3, 19.1 mmol) in dry THF (15 cm^3) at −15 to 0 °C was added BuLi (1.53 mol dm^{-3} in hexane; 11.7 cm^3, 17.9 mmol) under Ar. After the mixture had been stirred at 0 °C for 30 min, HMPA (3.1 cm^3, 17.8 mmol) and a solution of compound **23** (3.25 g, 11.9 mmol) in dry THF (14 cm^3) were added successively to the solution at room temperature, and the mixture was stirred at 40 °C. After 10 h, the starting material had disappeared on TLC. The reaction was quenched by dropwise addition of saturated aq. ammonium chloride to the mixture cooled at −15 to 0 °C. The reaction mixture was diluted with water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography and recrystallization to give *compound* **24** (3.20 g, 98%), m.p. 122.0–123.0 °C (from hexane, as needles) (Found: C, 74.6; H, 7.3%); $[\alpha]_D^{22}$ +50.7° (*c* 1.29, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 1741, 1140, 1099, 1035 and 755; δ_H(100 MHz; $CDCl_3$) 1.06 (3 H, d, *J* 7, 5′-Me), 1.21 (3 H, s, 4′-Me), 1.20–2.20 (5 H, m, 3′- and 7′-H_2 and 5′-H), 2.98 (1 H, br s, 1′-H), 4.82 (4 H, br s, $ArCH_2O$ × 2) and 6.95–7.25 (4 H, m, ArH).

(1′R,2′R,5′R)-*Spiro*{1,5-*dihydro*-2,4-*benzodioxepine*-3,6′-(1′,2′-*dimethylbicyclo*[3.2.1]*octan*-4′-*one*)} **26**.—A solution of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was prepared by dropwise addition of BuLi (1.59 mol dm^{-3} in hexane; 60.7 cm^3, 96.5 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (16.3 cm^3, 96.6 mmol) in dry THF (80 cm^3) at −10 to 0 °C under Ar. The LiTMP solution was added dropwise to a stirred solution of compound **24** (8.20 g, 30.1 mmol) and CH_2Br_2 (6.34 cm^3, 90.3 mmol) in dry THF (300 cm^3) at −100 to −85 °C under Ar during 20 min. After being stirred at −100 to −95 °C for 1.5 h the reaction mixture was quenched at −100 to −90 °C by dropwise addition of a solution of acetic acid (9.05 g, 151 mmol) in THF (50 cm^3) during 20 min. The resulting mixture was poured into water and extracted with $CHCl_3$. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give compound **25** (10.5 g, 78%) and the starting material (1.21 g recovery). The recovered starting material **24** was resubmitted to the same reaction to give a further crop of product **25** (1.7 g; total 12.2 g, 90%), δ_H(100 MHz; $CDCl_3$) 1.02 (3 H, d, *J* 7, 5′-Me), 1.11 (3 H, s, 4′-Me), 1.28 (1 H, dm *J* 11, 7′-H), 1.56 (1 H, dm, *J* 13, 3′-H), 1.62 (1 H, m, 5′-H), 1.75 (1 H, dd, *J* 2 and 11, 7′-H), 2.02 (1 H, dd, *J* 3 and 13, 3′-H), 2.79 (1 H, br s, 1′-H), 4.80 (1 H, d, *J* 15, ArC*H*HO), 4.91 (1 H, d, *J* 15, ArCH*H*O), 4.96 (2 H, s, ArCH_2O), 5.50 (1 H, d, *J* 2, OH, exchangeable with D_2O, $t_{\frac{1}{2}}$ *ca.* 1.5 h), 5.70 (1 H, d, *J* 2, $CHBr_2$, changed into a singlet at δ 5.69 by the D_2O addition) and 7.03–7.30 (4 H, m, ArH).

To a stirred solution of intermediate **25** (12.0 g, 26.9 mmol) in dry THF (360 cm^3) at −95 to −90 °C was added dropwise MeLi (1.0 mol dm^{-3} in diethyl ether; 26.9 cm^3, 26.9 mmol) under Ar during 10 min. After the mixture had been stirred at −95 °C for 15 min, BuLi (1.59 mol dm^{-3} in hexane; 18.6 cm^3,

29.6 mmol) was added to the reaction mixture at −95 to −90 °C during 15 min, and the mixture was stirred for 1 h at −95 °C. Then the cooling bath was removed and the temperature was allowed to rise to ambient during 30 min. The reaction was quenched by dropwise addition of a solution of acetic acid (1.68 g, 28.0 mmol) in THF (10 cm^3). The resulting mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 and recrystallized from hexane–EtOAc (10:1) to give compound **26** (3.30 g, 42.8%). The mother liquor was evaporated and the residue was chromatographed (SiO_2) again to give a further crop (0.94 g, 12.2%; total 4.24 g (55%)] *of compound* **26**, m.p. 139.5–141.0 °C (Found: C, 75.5; H, 7.8. $C_{18}H_{22}O_3$ requires C, 75.50; H, 7.74%); $[\alpha]_D^{15}$ −51.0° (*c* 1.44, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 1719, 1122, 1040 and 754; δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6.5, 2′-Me), 1.14 (3 H, s, 1′-Me), 1.72 (1 H, dd, *J* 2.2 and 12.3, 8′-H), 1.80 (1 H, d, *J* 14.3, 7′-H), 1.84 (1 H, ddq, *J* 7.1, 11.2 and 6.5, 2′-H), 2.15 (1 H, dd, *J* 4.8 and 12.3, 8′-H), 2.28 (1 H. dd, *J* 2.2 and 14.3, 7′-H), 2.33 (1 H, dd, *J* 11.2 and 16.7, 3′-H), 2.37 (1 H, dd, *J* 7.1 and 16.7, 3′-H), 3.09 (1 H, d, *J* 4.8, 5′-H), 4.73 (1 H, d, *J* 14.9, ArC*H*HO), 4.81 (2 H, s, ArCH_2O), 4.84 (1 H, d, *J* 14.9, ArCH*H*O), 7.03 (1 H, m, ArH), 7.08 (1 H. m, ArH) and 7.14–7.20 (2 H, m, ArH).

(1′R,2′R,4′S,5′R)-*Spiro*-{1,5-*dihydro*-2,4-*benzodioxepine*-3,6′-(1′,2′-*dimethylbicyclo*[3.2.1]*octan*-4′-*ol*)} **27**.—To an ice-cooled solution of compound **26** (3.10 g, 10.8 mmol) in THF (31 cm^3) was added dropwise a solution of $NaBH_4$ (0.82 g, 21.7 mmol) in ethanol (16 cm^3). After being stirred at 0 °C for 3 h the reaction mixture was evaporated, diluted with water, and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 and recrystallized to give the *alcohol* **27** (2.78 g, 89%). The mother liquor was evaporated and the residue was chromatographed (SiO_2) again to give a further crop (0.23 g, 7.4%) of compound **27** (total 3.01 g, 96%), m.p. 127–127.5 °C [from hexane–EtOAc (4:1), as rods] (Found: C, 74.8; H, 8.4. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%); $[\alpha]_D^{18.5}$ −119° (*c* 2.25, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3570, 1076, 1028 and 834; δ_H(100 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6, 2′-Me), 1.11 (3 H, s, 1′-Me), 1.15–2.25 (7 H, m, 2′-H, 3′-, 7′- and 8′-H_2), 2.59 (1 H, br t, *J* 8, 5′-H), 3.34 (1 H, d, *J* 11, OH), 3.75 (1 H, m, 4′-H), 4.72 (1 H, d, *J* 15, ArC*H*HO), 4.90 (1 H, d, *J* 15, ArC*H*HO), 5.15 (2 H, d, *J* 15, ArCH*H*O × 2) and 7.05–7.38 (4 H, m, ArH).

(1R,2R,4S,5R)-4-*Hydroxy*-1,2-*dimethylbicyclo*[3.2.1]*octan*-6-*one* **28a**.—A mixture of compound **27** (2.92 g, 10.1 mmol) and 10% Pd–C (150 mg) in EtOAc (40 cm^3) was stirred vigorously under Ar at room temperature. After 40 min, the starting material had disappeared on TLC. The catalyst was removed by filtration through Celite–SiO_2 and the filter-cake was washed with EtOAc. Combined filtrate and washings were concentrated under reduced pressure and the residue was recrystallized from hexane–EtOAc (4:1) to give *compound* **28a** (1.69 g, 99%), m.p. 110–110.5 °C (rods) (Found: C, 71.4: H, 9.5. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%); $[\alpha]_D^{17.5}$ −80.9° (*c* 1.09, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3470, 1728, 1235, 1076 and 1039; δ_H(100 MHz; $CDCl_3$) 0.87 (3 H, d, *J* 7, 2-Me), 1.13 (3 H, s, 1-Me), 1.58 (1 H, dd, *J* 3 and 12, 8-H), 1.55–2.20 (6 H, m, 2-H, 3-H_2, 7-H, 8-H and OH), 1.69 (1 H, dd, *J* 3 and 19, 7-H), 2.51 (1 H, br t, *J* 3.6, 5-H) and 3.84 (1 H, ddd, *J* 3.5, 6 and 11.5, 4-H).

(1R,2R,4S,5R)-4-(1-*Ethoxyethoxy*)-1,2-*dimethylbicyclo*[3.2.1]-*octan*-6-*one* **28b**.—To an ice-cooled, stirred solution of the alcohol **28a** (5.72 g, 34.0 mmol) in ethyl vinyl ether (60 cm^3) was added $TsOH{\cdot}H_2O$ (5 mg) and the mixture was stirred at 0 °C for 40 min. To the reaction mixture was then added saturated aq. $NaHCO_3$, and ethyl vinyl ether was evaporated off. The resulting mixture was extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography and vacuum distillation to give the *ether ketone* **28b** (8.17 g, quant.), b.p. 103–110 °C/0.6 mmHg (Found: C, 69.7; H, 9.9. $C_{14}H_{24}O_3$ requires C, 69.96; H, 10.06%); n_D^{18} 1.4662; $[\alpha]_D^{18}$ −143° (*c* 2.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 1748, 1170, 1136, 1084 and 1070; δ_H(100 MHz; $CDCl_3$) 0.86 (3 H, d, *J* 6.5, 2-Me), 1.10 (3 H, s, 1-Me), 1.19 (3 H, t, *J* 7.1, *Me*CH_2), 1.31 ($\frac{3}{2}$ H, d, *J* 5.4, OCH*Me*O), 1.34 ($\frac{3}{2}$ H, d *J* 5.4, OCH*Me*O), 1.40–2.05 (6 H, m, 2-H, 3-H_2, 7-H and 8-H_2), 2.19 (1 H, dd, *J* 3 and 15, 7-H), 2.57 (1 H, br t, *J* 3.5, 5-H), 3.30–3.96 (3 H, m, 4-H and MeCH_2), 4.82 ($\frac{1}{2}$ H, q, *J* 5.4, OC*H*MeO) and 4.89 ($\frac{1}{2}$ H, q, *J* 5.4, OC*H*MeO).

(1S,2R,4S,5R,7S)-4-(1-*Ethoxyethoxy*)-1,2,7-*trimethylbicyclo*-[3.2.1]*octan*-6-*one* **29**.—A stirred suspension of NaH (60% oil dispersion; 2.00 g, 50 mmol) in a solution of compound **28b** (8.02 g, 33.4 mmol) in dry THF (120 cm^3) was heated under reflux under Ar. After 4 h, generation of H_2 gas ceased. To the cooled reaction mixture at −5 to 0 °C was added dropwise MeI (93% purity; 3.35 cm^3, 50 mmol), and the mixture was stirred at −5 to 0 °C for 30 min before being poured into ice–water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography and vacuum distillation to give *compound* **29** (8.01 g, 94%), b.p. 101–103 °C/0.75 mmHg (Found: C, 70.5; H, 10.1. $C_{15}H_{16}O_3$ requires C, 70.83; H, 10.30%); n_D^{20} 1.4661; $[\alpha]_D^{20}$ −139° (*c* 1.35, $CHCl_3$); ν_{max}(film)/cm^{-1} 2990, 1744, 1135, 1075 and 1035; δ_H(100 MHz; $CDCl_3$) 0.83 (3 H, d, *J* 6.4, 2- or 7-Me) 0.98 (3 H, s, 1-Me), 0.98 (3 H, d, *J* 7.7, 7- or 2-Me), 1.18 ($\frac{3}{2}$ H, t, *J* 7.0, *Me*CH_2), 1.19 ($\frac{3}{2}$ H, t, *J* 7.0, *Me*CH_2), 1.31 ($\frac{3}{2}$ H, d, *J* 5.4, OCH*Me*O), 1.34 ($\frac{3}{2}$ H, d, *J* 5.4, OCH*Me*O), 1.40–2.10 (6 H, m, 2-H, 3-H_2, 7-H and 8-H_2), 2.53 (1 H, br t, *J* 3, 5-H), 3.30–4.00 (3 H, m, 4-H and MeCH_2), 4.81 ($\frac{1}{2}$ H, q, *J* 5.4, OC*H*MeO) and 4.89 ($\frac{1}{2}$ H, q, *J* 5.4, OC*H*MeO).

(1S,2R,4S,5R)-4-(1-*Ethoxyethoxy*)-1,2,7-*trimethyl*-6-(*trimethylsiloxy*)*bicyclo*[3.2.1]*oct*-6-*ene* **30**.—A stirred suspension of NaH (60% oil dispersion; 2.47 g, 61.8 mmol) in a solution of compound **29** (7.85 g, 30.9 mmol) in dry THF (140 cm^3) was heated under reflux under Ar. After 15 h, generation of H_2 gas ceased. To the cooled reaction mixture at −40 to −30 °C was added dropwise a mixture of TMSCl (5.13 cm^3, 37.0 mmol) and Et_3N (2.15 cm^3, 15.5 mmol) in dry THF (20 cm^3). After being stirred for 30 min at −5 to 0 °C the reaction mixture was carefully poured into a vigorously stirred mixture of ice, water, and pentane and was extracted with pentane. The extract was washed successively with water and saturated aq. $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was distilled to give *bis-ether* **30** (9.94 g, 99%), b.p. 95–101 °C/0.65 mmHg (Found: C, 67.2; H, 9.8. $C_{18}H_{34}O_3Si$ requires C, 67.19; H, 9.89%); n_D^{18} 1.4584; $[\alpha]_D^{18}$ −75.2° (*c* 0.54, pentane); ν_{max}(film)/cm^{-1} 1669, 1253, 1105, 860 and 845; δ_H(100 MHz; C_6D_6) 0.26 ($\frac{9}{2}$ H, s, Me_3Si), 0.29 ($\frac{9}{2}$ H, s, Me_3Si), 0.82 (3 H, d, *J* 6.5, 2-Me), 1.01 (3 H, s, 1-Me), 1.20 (3 H, t, *J* 7.1, *Me*CH_2), 1.34 ($\frac{3}{2}$ H, d, *J* 5.4, OCH*Me*O), 1.39 ($\frac{3}{2}$ H, d, *J* 5.4, OCHMeO), 1.70 (3 H, d, *J* 2.7, 7-Me), 1.00–2.15 (5 H, m, 2-H and 3- and 8-H_2), 2.51 (1 H, m, 5-H), 3.25–3.85 (2 H, m, MeCH_2), 3.73 (1 H, m, 4-H), 4.73 ($\frac{1}{2}$ H, q, *J* 5.4, OC*H*MeO) and 4.85 ($\frac{1}{2}$ H, q, *J* 5.4, OC*H*MeO).

Determination of the Absolute Configuration by the Measurement of the CD Spectrum of (1R,4R)-4-*Methylbicyclo*[2.2.1]*hept-5-en-2-one* **31**.—To an ice-cooled, stirred solution of compound **21b** (42 mg, 0.16 mmol), DMAP (trace amount, ~3 mg), and triethylamine (0.1 cm^3) in dry CH_2Cl_2 (1 cm^3) was added MsCl (37 mm^3, 0.48 mmol). After being stirred for 1 h at 0 °C the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude mesyl derivative of compound **21b** (57 mg), ν_{max}(film)/cm^{-1} 1355 and 1175.

The crude mesyl ester (56 mg) and DBU (80 mg) were dissolved in toluene (1.5 cm^3) and the solution was heated under reflux for 2 days. After cooling, the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a crude crystalline product (31 mg), ν_{max}(KBr)/cm^{-1} 1620, 1420, 735 and 715, which was used for the next deprotection reaction without further purification.

The crude crystalline compound (27 mg) was dissolved in acetone–water (10:1; 1 cm^3), and PPTS (10 mg) was added to the solution. After being stirred for 8 h at room temperature the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure at low temperature (0 °C). The residue was purified by SiO_2 column chromatography to give *compound* **31** (11 mg, 66% from **21b**) (Found: M^+, 122.0766. $C_8H_{10}O$ requires *M*, 122.0731); ν_{max}(film)/cm^{-1} 1740 and 1620; δ_H(100 MHz; $CDCl_3$) 1.42 (3 H, s, 4-Me), 1.65–2.15 (4 H, m, 3- and 7-H_2), 3.02 (1 H, br m, 1-H), 6.09 (1 H, dd, *J* 3.5 and 5.5, 6-H) and 6.26 (1 H, d, *J* 5.5, 5-H); $\Delta\varepsilon(\lambda)$ [2.15 × 10^{-3} mol dm^{-3} in 'isooctane' (2,2,4-trimethylpentane)] +9.12 (287 nm), +14.2 (297), +17.3 (308) and +11.9 (319). Comparison of the CD spectral data of compound **31** with the reported data of (1*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-one[19] revealed the stereochemistry of compound **31** to be 1*R*,4*R*.

(1S,2R,4S,5R,7R)-7-[(1R,3RS)-3-(t-*Butyldimethylsiloxy*)-4-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}-1-*hydroxybutyl*]-4-(1-*ethoxyethoxy*)-1,2,7-*trimethylbicyclo*[3.2.1]*octan*-6-*one* **36a**.—To a stirred solution of compound **30** (6.70 g, 20.5 mmol) in dry diethyl ether (25 cm^3) at 5–10 °C was added dropwise a solution of MeLi (1.00 mol dm^{-3} in diethyl ether; 21.5 cm^3, 21.5 mmol) under Ar. After the mixture had been stirred at 0–5 °C for 35 min a solution of $ZnCl_2$ in dry diethyl ether (prepared according to House's procedure;[25] 0.652 mol dm^{-3}; 33.0 cm^3, 21.5 mmol) was added dropwise to the reaction mixture at −5 to 0 °C. After the mixture had been stirred at −10 to −5 °C for 30 min, a solution of the aldehyde **12** (8.10 g, 19.5 mmol) in dry diethyl ether (25 cm^3) was added dropwise to the reaction mixture at −20 to −15 °C. After the addition, the reaction mixture was stirred at −20 °C for 1 h and at −50 °C for 2 h, and then was quenched at −65 to −60 °C by dropwise addition of a solution of acetic acid (1.29 g) in diethyl ether (5 cm^3). The resulting mixture was poured into a stirred mixture of ice–water (100 cm^3) and 29% aq. NH_4OH (20 cm^3, ~340 mmol) and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ (×2) and brine, dried ($MgSO_4$), filtered quickly through a small column of a little SiO_2 (Merck Kieselgel 60 reinst, Art. 7754; *ca.* 15 g), and concentrated under reduced pressure to give a crude mixture of compounds **12**, **32** and **36a** (14.2 g), ν_{max}(film)/cm^{-1} 3470 and 1736. This was immediately employed for the next step without further purification to avoid the retro-aldol reaction to give compounds **12** and **32**.

(1S,2R,4S,5R,7R)-7-[(1R,3RS)-3-(t-*Butyldimethylsiloxy*)-1-(*diethoxyphosphonylacetoxy*)-4-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*[2.2.1.]*heptan*-1-*yl*}*butyl*]-4-(1-*ethoxyethoxy*)-1,2,7-*trimethylbicyclo*[3.2.1]*octan*-6-*one* * **36b**.—To an ice-cooled, stirred mixture of the crude mixture of compound **36a** (and **12** + **32**) (13.9 g, ≤20.8 mmol) and DCC (4.29 g, 20.8 mmol) in dry CH_2Cl_2 (150 cm^3) was added a solution of diethylphosphonoacetic acid (diethoxy phosphonylacetic acid) (4.08 g) in dry CH_2Cl_2 (30 cm^3). After the mixture had been stirred for 1 h at room temperature, diethyl ether (150 cm^3) was added to the reaction mixture, which was then stirred at 0 °C for 10 min. The resulting slurry was filtered, and the filter-cake was washed with diethyl ether. The combined filtrate and washings were evaporated, diluted with hexane–diethyl ether (1:1; 200 cm^3) and stirred at 0 °C for 10 min. Precipitates were filtered off and the filtrate was evaporated under reduced pressure. The residue was chromatographed over SiO_2. Compound **12** (3.35 g, 42% recovery) was recovered, and compounds **32** (2.15 g, 42% from **30**) and **36b** (10.02 g, 62%) were obtained. Compound **32** could be converted into the bis-ether **30** in 83% yield in the same manner as described for the conversion of compound **29** into compound **30** (35% recovery). Aldol reaction, followed by diethyl phosphonoacetylation of the recovered substrates **12** (3.28 g) and **30** (3.87 g), gave a further crop (3.28 g, total 13.3 g, 82% in two steps) of compound **36b**, ν_{max}(film)/cm^{-1} 1735, 1265, 1215 and 1028; δ_H(100 MHz; $CDCl_3$) 0.05 (2 H, s, minor Me_2Si), 0.09 (4 H, s, major Me_2Si), 0.89 (9 H, s, Me_3C), 0.95–1.45 (33 H, m, Me × 11), 1.45–2.35 {13 H, m, 2-H, 3-H_2, 8-H_2, 7-(2-H_2), 7-(4-H_2), 7-[4-(5-H_2)] and 7-[4-(6-H_2)]}, 2.60 (1 H, br m, 5-H), 2.86, 2.88, 2.92 and 2.97 (total 2 H, 4 × d, *J* 20, PCH_2), 3.15 {$\frac{2}{3}$ H, s, major 7-[4-(2-H)]}, 3.32 {$\frac{1}{3}$ H, s, minor 7-[4-(2-H)]}, 3.35–4.30 {11 H, m, 4-H, 7-(3-H), 7-[4-(4-H)] and MeCH_2O × 4}, 4.45–4.69 (1 H, m, OC*H*MeO), 4.81 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 4.86 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO) and 5.10–5.35 [1 H, br m, 7-(1-H)]. This was employed for the next step without further purification.

(1S,6R,7S,8S,9R,11S)-6-[2(RS)-(t-*Butyldimethylsiloxy*)-3-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}*propyl*]-11-(1-*ethoxyethoxy*)-7,8,9-*trimethyl*-5-*oxatricyclo*[6.3.1.$0^{2,7}$]*dodec*-2-*en*-4-*one* **37**.—To an ice-cooled, stirred solution of the phosphonate **36b** (9.95 g, 11.7 mmol) in dry THF (150 cm^3) was added NaH (60% oil dispersion; 0.59 g, 14.8 mmol) under Ar. After the addition, the ice-bath was replaced with a water-bath at room temperature, and the mixture was stirred for 15 h at room temperature. The reaction mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography to give *tricyclo* **37** (6.82 g, 84%) (Found: C, 66.6; H, 10.5. $C_{39}H_{68}O_8Si$ requires C, 66.21; H, 10.49%); $[\alpha]_D^{18}$ −5.71° (*c* 1.07, $CHCl_3$); ν_{max}(film)/cm^{-1} 1730, 1655, 1256 and 1234; δ_H(100 MHz; $CDCl_3$) 0.01 (3 H, s, Me_2Si), 0.06 (3 H, s, Me_2Si), 0.86 (9 H, s, Me_3C), 0.90–1.40 (27 H, m, 9 × Me), 1.40–2.30 {13 H, m, 9-H, 10- and 12-H_2, 6-(1-H_2), 6-(3-H_2), 6-[3-(5-H_2)] and 6-[3-(6-H_2)]}, 2.94 (1 H, br m, 1-H), 3.17 {$\frac{2}{3}$ H, s, major 6-[3-(2-H)]}, 3.20–4.45 {$\frac{25}{3}$ H, m, 6- and 11-H, 6-(2-H), 6-[3-(4-H)], minor 6-[3-(2-H)] and CH_2Me × 2}, 4.63 (1 H, q, *J* 6, OC*H*MeO), 4.80 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 4.86 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 5.73 ($\frac{1}{2}$ H, s, 3-H) and 5.78 ($\frac{1}{2}$ H, s, 3-H).

* Non-systematic name.

(1R,3RS)-3-(t-*Butyldimethylsiloxy*)-4-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}-1-{(1S,2S,4R,5S,6S)-2-(1-*ethoxyethoxy*)-7-[(Z)-2-*hydroxyethylidene*]-4,5,6-*trimethylbicyclo*[3.2.1]*octan*-6-*yl*}*butan*-1-*ol* **38a**.—To a stirred suspension of $CaCl_2$ (6.51 g, 58.7 mmol) in dry EtOH (120 cm^3) was added portionwise $NaBH_4$ (4.44 g, 117 mmol) at room temperature. The resulting slurry was stirred at 30–40 °C for 15 min, and a solution of lactone **37** (8.13 g, 11.7 mmol) in dry EtOH (30 cm^3) was added dropwise to the mixture at room temperature. After being stirred at room temperature for 2.5 h the reaction mixture was poured into ice–water and extracted four times with diethyl ether. The extract was washed successively with water and saturated aq. $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compound* **38a** as an amorphous solid (8.37 g) (Found: C, 67.0; H, 10.3. $C_{39}H_{72}O_8Si$ requires C, 67.20; H, 10.32%); $[\alpha]_D^{18}$ −18.1° (*c* 1.04, $CHCl_3$); ν_{max}(film)/cm^{-1} 3480 and 838; δ_H*(100 MHz; $CDCl_3$) 0.09, 0.12 and 0.16 (total 6 H, 3 s, Me_2Si), 0.92 (9 H, s, Me_3C), 0.95–1.40 (27 H, m, Me × 9), 1.40–2.50 {15 H, m, 4-H, 3- and 8-H_2, 6-(2-H_2), 6-(4-H_2), 6-[4-(5-H_2)], 6-[4-(6-H_2)] and OH × 2}, 2.55–2.75 (1 H, br m, 1-H), 3.14, 3.19 and 3.36 {total 1 H, 3 s, 6-[4-(2-H)]}, 3.53 (4 H, q, *J* 6, CH_2Me × 2), 3.79 {1 H, br d, *J* 4, 6-[4-(4-H)]}, 3.20–4.50 [5 H, m, 2-H, 6-(1-H), 6-(3-H) and =CHCH_2OH], 4.56 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 4.61 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 4.78 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 4.89 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 5.72 ($\frac{1}{2}$ H, br t, *J* 8, C=CH) and 5.92 ($\frac{1}{2}$ H, br t, *J* 8, C=CH).

2-{(1S,2R,4S,5S,7S)-7-[(1R,3RS)-3-(t-*Butyldimethylsiloxy*)-4-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*-[2.2.1]*heptan*-1-*yl*}-1-*hydroxybutyl*]-4-(1-*ethoxyethoxy*)-1,2,7-*trimethylbicyclo*[3.2.1]*octan*-6(Z)-*ylidene*}*ethyl Pivalate* **38b**.—To an ice-cooled solution of diol **38a** (8.14 g, 11.7 mmol) in triethylamine (7 cm^3)–dry CH_2Cl_2 (50 cm^3) was added pivaloyl chloride (1.80 cm^3, 14.6 mmol) and the mixture was stirred at room temperature for 3.5 h. Excess of acid chloride was destroyed by dropwise addition of MeOH (0.2 cm^3) to the mixture at 0 °C, and the solution was stirred for 10 min, poured into water, and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$ (× 2), and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *monoester* **38b** (8.50 g, 95% from **37**) as an amorphous solid (Found: C, 67.7; H, 10.4. $C_{44}H_{80}O_9Si$ requires C, 67.65; H, 10.32%): $[\alpha]_D^{21}$ +13.0° (*c* 0.945, $CHCl_3$); ν_{max}(film)/cm^{-1} 3500, 1728, 1280 and 1150; δ_H(100 MHz; $CDCl_3$) 0.08, 0.09, 0.11 and 0.14 (total 6 H, 4 s, Me_2Si), 0.88 (6 H, s, major Me_3CSi), 0.91 (3 H, s, minor Me_3CSi), 1.20 (9 H, s, Me_3CO), 0.92–1.40 (27 H, m, Me × 9), 1.40–2.35 {14 H, m, 2-H, 3- and 8-H_2, 7-(2-H_2), 7-(4-H_2), 7-[4-(5-H_2)], 7-[4-(6-H_2)] and OH}, 2.55–2.75 (1 H, br m, 5-H), 3.13, 3.17 and 3.34 {total 1 H, 3 s, 7-[4-(2-H)]}, 3.35–3.85 {7 H, m, 4-H, 7-(1-H), 7-[4-(4-H)] and CH_2Me × 2}, 4.00–4.40 [1 H, br m, 7-(3-H)], 4.50–4.95 (4 H, m, =CHCH_2O and OC*H*MeO × 2), 5.54 ($\frac{2}{3}$ H, t, *J* 7, minor C=CH) and 5.75 ($\frac{1}{3}$ H, t, *J* 7, minor C=CH).

2-{(1S,2R,4S,5S,7S)-7-{(1R,3RS)-3-(t-*Butyldimethylsiloxy*)-4-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*-[2.2.1]*heptan*-1-*yl*}-1-[2-(*trimethylsilyl*)*ethoxymethoxy*]*butyl*}-4-(1-*ethoxyethoxy*)-1,2,7-*trimethylbicyclo*[3.2.1]*octan*-6(Z)-*ylidene*}*ethyl Pivalate* **38c**.—A mixture of hydroxy ester **38b** (8.32 g, 10.7 mmol), chloro(trimethylsilylethoxy)methane (SEMCl) (5.33 g, 32.0 mmol), Bu_4NBr (687 mg, 2.13 mmol) and diisopropylethylamine (6.88 g, 53.2 mmol) in dry CH_2Cl_2 (50 cm^3) was stirred and heated under reflux under Ar. After 13 h, further diisopropylethylamine (3.0 g) was added to the reaction mixture. After 3.5 days, further SEMCl (1.0 g) was added. The mixture was stirred and refluxed for 5 days in all before being ice-cooled, and saturated aq. $NaHCO_3$ was added dropwise. After being stirred for 5 min, the mixture was poured into water and extracted twice with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give compound **38c** (8.61 g, 89%) and recovered substrate **38b** (530 mg, 6.4% recovery). The recovered substrate **38b** was employed for the same reaction again, and a further crop (0.46 g, 4.7%) of *product* **38c** was obtained (total 9.17 g, 94%) as an amorphous solid (Found: C, 66.0; H, 10.4. $C_{50}H_{94}O_{10}Si_2$ requires C, 65.89; H, 10.39%); $[\alpha]_D^{16.5}$ +57.2° (*c* 0.78, $CHCl_3$); ν_{max}(film)/cm^{-1} 1730, 1252, 1090, 1028 and 860; δ_H(100 MHz; $CDCl_3$) 0.01 (6 H, s, major Me_3Si), 0.02 (3 H, s, minor Me_3Si), 0.08, 0.09, 0.11 (total 6 H, 3 s, Me_2Si), 0.87 (6 H, s, major Me_3CSi), 0.90 (3 H, s, minor Me_3CSi), 0.95–1.35 (29 H, m, 9 × Me and CH_2Si), 1.27 (9 H, s, Me_3CCO), 1.35–2.35 {13 H, 2-H, 3- and 8-H_2, 7-(2-H_2), 7-(4-H_2), 7-[4-(5-H_2)] and 7-[4-(6-H_2)]}, 2.55–2.70 (1 H, br m, 5-H), 3.17 {$\frac{2}{3}$ H, s, major 7-[4-(2-H)]}, 3.25–3.87 {$\frac{28}{3}$ H, m, 4-H, 7-(1-H), minor 7-[4-(2-H)], 7-[4-(4-H)], $SiCH_2CH_2$ and CH_2Me × 2}, 4.05–4.25 [1 H, br m, 7-(3-H)], 4.33 (1 H, d, *J* 8, OCHHO), 4.53 (1 H, d, *J* 8, OCH*H*O), 4.45–4.90 (2 H, m, OCH*H*MeO × 2), 4.86 (2 H, d, *J* 7, =CHCH_2O), 5.40 ($\frac{1}{2}$ H, t, *J* 7, C=CH) and 5.61 ($\frac{1}{2}$ H, t, *J* 7, C=CH).

2-{(1S,2R,4S,5S,7S)-7-{(1R,3RS)-3-(t-*Butyldimethylsiloxy*)-4-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*-[2.2.1]*heptan*-1-*yl*}-1-[2-(*trimethylsilyl*)*ethoxymethoxy*]*butyl*}-4-(1-*ethoxyethoxy*)-1,2,7-*trimethylbicyclo*[3.2.1]*octan*-6(Z)-*ylidene*}*ethanol* **38d**.—To a stirred solution of compound **38c** (9.05 g, 9.93 mmol) in dry diethyl ether (50 cm^3) at −20 °C was added dropwise MeLi (1.0 mol dm^{-3} in ether; 23.8 cm^3, 23.8 mmol) under Ar. After the addition the mixture was stirred at −20 °C for 30 min, poured into a stirred mixture of ice and saturated aq. NH_4Cl, and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compound* **38d** (7.64 g, 93%) as an amorphous solid (Found: C, 65.0; H, 10.4. $C_{45}H_{86}O_9Si_2$ requires C, 65.33; H, 10.48%); $[\alpha]_D^{14}$ +11.2° (*c* 0.99, $CHCl_3$); ν_{max}(film)/cm^{-1} 3480 and 1125; δ_H(100 MHz; $CDCl_3$) 0.01 (9 H, s, Me_3Si), 0.09 (3 H, s, Me_2Si), 0.10 (3 H, s, Me_2Si), 0.88 (6 H, s, major Me_3CSi), 0.90 (3 H, s, minor Me_3CSi), 0.95–1.40 (29 H, m, Me × 9 and CH_2Si), 1.40–2.30 {14 H, 2-H, 3- and 8-H_2, 7-(2-H_2), 7-(4-H_2), 7-[4-(5-H_2)], 7-[4-(6-H_2)] and OH}, 2.55–2.70 (1 H, br m, 5-H), 3.18 {$\frac{2}{3}$ H, s, major 7-[4-(2-H)]}, 3.33 {$\frac{1}{3}$ H, s, minor 7-[4-(2-H)]}, 3.10–4.30 {12 H, m, 4-H, 7-(1-H), 7-(3-H), 7-[4-(4-H)], =CHCH_2O, $SiCH_2CH_2$ and CH_2Me × 2}, 4.35–4.73 (3 H, m, OC*H*MeO and OCH_2O), 4.79 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 4.88 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO) and 5.50–5.85 (1 H m, C=CH).

2-{(1S,2R,4S,5S,7S)-7-{(1R,3RS)-3-(t-*Butyldimethylsiloxy*)-4-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*-[2.2.1]*heptan*-1-*yl*}-1-[2-(*trimethylsilyl*)*ethoxymethoxy*]*butyl*}-4-(1-*ethoxyethoxy*)-1,2,7-*trimethylbicyclo*[3.2.1]*octan*-6(Z)-*ylidene*}*acetaldehyde* **39**. To a stirred solution of oxalyl dichloride (1.16 cm^3, 13.5 mmol) in dry CH_2Cl_2 (20 cm^3) at −78 °C was added dropwise a solution of DMSO (1.92 cm^3, 27.0 mmol) in dry CH_2Cl_2 (6 cm^3) under Ar. After 15 min at −78 °C, the mixture was treated with a solution of compound **38d** (5.60 g, 6.77 mmol) in dry CH_2Cl_2 (20 cm^3) and the mixture

* NMR locants are presented throughout with the bicyclooctane ring system as the base component.

was stirred at the same temperature for 30 min. To the resulting mixture at −78 °C was added dropwise Et_2N (4.15 cm^3, 29.8 mmol) and the mixture was stirred for 30 min at −78 °C and for 30 min at −10 to −5 °C before being poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *aldehyde* **39** (5.35 g, 96%) as an amorphous solid (Found: C, 65.5; H, 10.2. $C_{45}H_{84}O_9Si_2$ requires C, 65.49; H, 10.26%); $[\alpha]_D^{26}$ +51.5° (*c* 0.795, $CHCl_3$); ν_{max}(film)/cm^{-1} 1670 and 1620; δ_H(100 MHz; $CDCl_3$) 0.00 ($\frac{9}{2}$ H, s, Me_3Si), 0.01 ($\frac{9}{2}$ H, s, Me_3Si), 0.08 (3 H, s, Me_2Si), 0.10 (3 H, s, Me_2Si), 0.88 ($\frac{9}{2}$ H, s, Me_3C), 0.90 ($\frac{9}{2}$ H, s, Me_3C), 0.92–1.45 (29 H, m, Me × 9 and CH_2Si), 1.45–2.40 {13 H, 2-H, 3- and 8-H_2, 7-(2-H_2), 7-(4-H_2), 7-[4-(5-H_2)] and 7-[4-(6-H_2)]}, 2.70–2.85 (1 H, br m, 5-H), 3.18 {$\frac{2}{3}$ H, s, major 7-[4-(2-H)]}, 3.23–3.85 {$\frac{28}{3}$ H, m, 4-H, 7-(1-H), minor 7-[4-(2-H)], 7-[4-(4-H)], $SiCH_2CH_2$ and CH_2Me × 2}, 4.05–4.48 [3 H, m, 7-(3-H) and OCH_2O], 4.50–4.73 (1 H, m, OC*H*MeO), 4.79 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 4.87 ($\frac{1}{2}$ H, q, *J* 6, OC*H*MeO), 5.94 ($\frac{2}{3}$ H, d, *J* 9, C=CH), 6.13 ($\frac{1}{3}$ H, br, d, *J* 9, C=CH) and 10.01 (1 H, 3 d, *J* 9, CHO).

2-(*Trimethylsilyl*)*ethyl* 2-{(1S,2R,4S,5S,7S)-7-{(1R,3RS)-3-(t-*Butyldimethylsiloxy*)-4-{(1S,2S,4S)-2-(1-*ethoxyethoxy*)-3,3-*dimethyl*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}-1-[2-(*trimethylsilyl*)-*ethoxymethoxy*]*butyl*}-4-(1-*ethoxyethoxy*)-1,2,7-*trimethylbicyclo*[3.2.1]*octan*-6(Z)-*ylidene*}*acetate* **40a**.—A mixture of aldehyde **39** (3.46 g, 4.19 mmol), NaH_2PO_4 (10.5 g, 67.3 mmol), $NaClO_2$ (12.1 g, 134 mmol), 2-methylbut-2-ene (42 cm^3), *t*-butyl alcohol (9.5 cm^3) and water (30 cm^3) was stirred vigorously at room temperature for 1 h. The reaction mixture was diluted with water and extracted with diethyl ether. The extract was washed successively with 10% aq. $Na_2S_2O_3$, water, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude carboxylic acid (3.92 g) as an amorphous solid, ν_{max}(film)/cm^{-1} 3500–2500, 1730 and 1635.

To an ice-cooled, stirred solution of the crude carboxylic acid (3.92 g), 2-(trimethylsilyl)ethanol (606 mg, 5.12 mmol) and triphenylphosphine (1.41 g, 5.38 mmol) in dry THF (36 cm^3) was added dropwise diethyl azodicarboxylate (DEAD) (844 mm^3, 5.36 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure. The residue was diluted with diethyl ether (50 cm^3) and hexane (40 cm^3), and a small crystal of triphenylphosphine oxide was added as a seed to the stirred solution. When precipitates appeared, the mixture was left overnight in a refrigerator. Crystalline triphenylphosphine oxide was filtered off and the filter-cake was washed with hexane–diethyl ether (1:1). The combined filtrate and washings were concentrated under reduced pressure and the residue was chromatographed over SiO_2 to give *ester* **40a** (3.24 g, 82% in 2 steps) (Found: C, 63.4; H, 10.1. $C_{50}H_{96}O_{10}Si_3$ requires C, 63.78; H, 10.28%); $[\alpha]_D^{26.5}$ +23.3° (*c* 1.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 1718, 1635, 1250, and 1160; δ_H(100 MHz; $CDCl_3$) 0.00–0.10 (24 H, m, Me_3Si × 2 and Me_2Si), 0.83 (9 H, s, Me_3C), 0.90–1.40 (31 H, m, Me × 9 and CH_2Si × 2), 1.40–2.40 {13 H, 2-H, 3- and 8-H_2, 7-(2-H_2), 7-(4-H_2), 7-[4-(5-H_2)] and 7-[4-(6-H_2)]}, 2.60–2.75 (1 H, br m, 5-H), 3.13 {$\frac{2}{3}$ H, s, major 7-[4-(2-H)]}, 3.30 {$\frac{1}{3}$ H, s, minor 7-[4-(2-H)]}, 3.35–3.85 {8 H, m, 4-H, 7-[4-(4-H)], $SiCH_2CH_2$ and CH_2Me × 2}, 3.95–4.25 (4 H, m, 7-(1-H), 7-(3-H) and CO_2CH_2), 4.50–4.95 (4 H, m, OC*H*MeO × 2 and OCH_2O), 6.73 ($\frac{2}{3}$ H, s, major C=CH) and 6.93 ($\frac{1}{3}$ H, s, minor C=CH).

2-(*Trimethylsilyl*)*ethyl* 2-{(1S,2R,4S,5S,7S)-4-*Hydroxy*-7-{(1R,3RS)-3-*hydroxy*-4-{(1S,2S,4S)-2-*hydroxy*-3,3-*dimethyl*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}-1-[2-(*trimethylsilyl*)*ethoxymethoxy*]*butyl*}-1,2,7-*trimethylbicyclo*[3.2.1]*octan*-6-(Z)-*ylidene*}*acetate* **40b**.—A solution of protected ester **40a** (2.68 g, 2.85 mmol) and PPTS (210 mg, 0.84 mmol) in methanol (80 cm^3) containing water (4 cm^3) was stirred at room temperature. After 2, 5, 7, 10, 16, 21 and 30 h, water (4 cm^3 each time) was added to the reaction mixture, which was stirred for 48 h in all before being poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compound* **40b** (1.61 g, 83%) (Found: C, 63.1; H, 9.6. $C_{36}H_{66}O_8Si_2$ requires C, 63.30; H, 9.74%); $[\alpha]_D^{24}$ +65.1° (*c* 1.09, $CHCl_3$); ν_{max}(film)/cm^{-1} 3450, 1710, 1632, 1250, 1170, 1160 and 1025. A small amount of compound **40b** was further purified by preparative SiO_2 TLC to give two isomers, whose NMR data are as follows: less polar isomer—δ_H(100 MHz; $CDCl_3$) 0.01 (9 H, s, Me_3Si), 0.03 (9 H, s, Me_3Si), 0.85–1.10 (19 H, m, Me × 5 and $SiCH_2$ × 2), 1.10–2.45 {16 H, m, 2-H, 3- and 8-H_2, 7-(2-H_2), 7-(4-H_2), 7-[4-(5-H_2)], 7-[4-(6-H_2)] and OH × 3}, 2.62 (1 H, br, 5-H), 3.40 {1 H, br s, 7-[4-(2-H)]}, 3.45–4.00 {4 H, m, 4-H, 7-[4-(4-H)] and $SiCH_2CH_2$}, 4.05–4.25 [4 H, m, 7-(1-H), 7-(3-H) and CO_2CH_2], 4.67 (2 H, s, OCH_2O) and 5.92 (1 H, s, C=CH); more polar isomer—δ_H(100 MHz; $CDCl_3$) 0.01 (9 H, s, Me_3Si), 0.05 (9 H, s, Me_3Si), 0.80–1.10 (19 H, m, Me × 5 and $SiCH_2$ × 2), 1.10–2.35 {16 H, m, 2-H, 3- and 8-H_2, 7-(2-H_2), 7-(4-H_2), 7-[4-(5-H_2)], 7-[4-(6-H_2)] and OH × 3}, 2.62 (1 H, br, 5-H), 3.28 {1 H, br s, 7-[4-(2-H)]}, 3.35–3.75 (3 H, m, 4-H and $SiCH_2CH_2$), 3.80 {1 H, br, 7-[4-(4-H)]}, 4.05–4.40 [4 H, m, 7-(1-H), 7-(3-H) and CO_2CH_2], 4.75 (1 H, d, *J* 7} OC*H*HO), 4.85 (1 H, d, *J* 7, OCH*H*O) and 5.89 (1 H, s, C=CH).

2-(*Trimethylsilyl*)*ethyl* 2-{(1S,2R,4S,7S)-7-{(R)-4-{(1S,4S)-3,3-*Dimethyl*-2-*oxo*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}-3-*oxo*-1-[2-(*trimethylsilyl*)*ethoxymethoxy*]*butyl*}-1,2,7-*trimethyl*-4-*oxobicyclo*[3.2.1]*octan*-6(Z)-*ylidene*}*acetate* **41**.—To a stirred solution of oxalyl chloride (1.43 cm^3, 16.7 mmol) in dry CH_2Cl_2 (23 cm^3) at −78 °C was added dropwise a solution of DMSO (2.36 cm^3, 33.2 mmol) in dry CH_2Cl_2 under Ar. After the mixture had been stirred for 15 min at −78 °C, a solution of compound **40b** (2.27 g, 3.32 mmol) in dry CH_2Cl_2 (18 cm^3) was added dropwise to the reaction mixture, and the mixture was stirred for 2 h at −78 °C. Et_3N (5.10 cm^3, 36.6 mmol) was added dropwise to the resulting suspension at −78 °C, and the temperature was allowed to rise to −5 °C during 10 min. After being stirred at −5 to 0 °C for 30 min the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed successively with water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give compound **41** (2.15 g, 96%). The product was recrystallized twice from hexane to give pure *compound* **41** (1.93 g, 90% recovery, 86% yield), m.p. 100–100.5 °C (needles) (Found: C, 64.0; H, 8.9. $C_{36}H_{62}O_8Si_2$ requires C, 63.87; H, 8.93%); $[\alpha]_D^{24}$ −2.37° (*c* 1.01, $CHCl_3$); ν_{max}(film)/cm^{-1} 1750, 1728, 1714 and 1634; δ_H(100 MHz; $CDCl_3$) 0.00 (9 H, s, Me_3Si), 0.02 (9 H, s, Me_3Si), 0.80–1.10 (4 H, m, $SiCH_2$), 1.01 (3 H, s, Me), 1.10 (3 H, d, *J* 7, 2-Me), 1.21 (3 H, s, Me), 1.24 (3 H, s, Me), 1.61 (3 H, s, Me), 1.30–2.00 {7 H, m, 2-H, 8-H_2, 7-[4-(5-H_2)] and 7-[4-(6-H_2)]}, 2.10–2.90 [4 H, m, 3-H_2 and 7-(2-H_2)], 2.98 [2 H, s, 7-(4-H_2)], 3.23 (1 H, d, *J* 6, 5-H), 3.54 (2 H, m, $SiCH_2CH_2$), 4.15 (2 H, m, CO_2CH_2), 4.27 {1 H, br s, 7-[4-(4-H)]}, 4.61 (1 H, d, *J* 7, OC*H*HO), 4.63 (1 H, d, *J* 7, OCH*H*O), 4.71 [1 H, m, 7-(1-H)] and 5.90 (1 H, d, *J* 1, C=CH).

2-(*Trimethylsilyl*)*ethyl* 2-{(1S,2R,5S,8S)-8-{(R)-4-{(1S,4S)-3,3-*Dimethyl*-2-*oxo*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}-3-*oxo*-1-[2-(*trimethylsilyl*)*ethoxymethoxy*]*butyl*}-1,2,8-*trimethyl*-4-*oxo*-5-*oxabicyclo*[4.2.1]*nonan*-7(E)-*ylidene*}*acetate* **42**.—A mixture of compound **41** (1.89 g, 2.79 mmol), *m*-chloroperbenzoic acid

(MCPBA) (80% purity; 722 mg, 3.35 mmol) and $NaHCO_3$ (352 mmol, 4.19 mmol) in CH_2Cl_2 (100 cm^3) was stirred at room temperature for 14 h. The reaction mixture was poured into 10% aq. $Na_2S_2O_3$ and extracted twice with diethyl ether. The extract was washed successively with saturated aq. $NaHCO_3$ (× 3) and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compound* **42** (1.91 g, 99%) (Found: C, 62.4; H, 8.7. $C_{36}H_{60}O_9Si_2$ requires C, 62.39; H, 8.73%); $[\alpha]_D^{23.5}$ +128° (*c* 2.27, $CHCl_3$); ν_{max}(film)/cm^{-1} 1765, 1740, 1728, 1645 and 1180; δ_H(400 MHz; $CDCl_3$) 0.01 (9 H, s, Me_3Si), 0.03 (9 H, s, Me_3Si), 0.88 (2 H, m, $SiCH_2$), 1.01 (2 H, m, $SiCH_2$), 1.02 (3 H, s, Me), 1.07 (3 H, d, *J* 7.1, 2-Me), 1.14 (3 H, s, Me), 1.26 (3 H, s, Me), 1.27 (3 H, s, Me), 1.52 (1 H, d, *J* 15.2, 9-H), 1.62 {1 H, m, 8-[4-(5-H)] or 8-[4-(6-H)]}, 1.73–1.95 {4 H, m, 2-H, 8-[4-(6-H)] or 8-[4-(5-H)] and 8-[4-(6-H_2)] or 8-[4-(5-H_2)]}, 2.57 (1 H, dd, *J* 2.8 and 15.3, 3-H), 2.67 [1 H, dd, *J* 5.6 and 18.4, 8-(2-H)], 2.83 (1 H, dd, *J* 8.4 and 15.2, 9-H), 2.88 (1 H, dd, *J* 13.4 and 15.3, 3-H), 2.98 [1 H, d, *J* 16.8, 8-(4-H)], 3.03 [1 H, d, *J* 16.8, 8-(4-H)], 3.37 [1 H, dd, *J* 4.0 and 18.4, 8-(2-H)], 3.47 (1 H, dt, *J* 10.3 and 8.6, $SiCH_2CHH$), 3.52 (1 H, dt, *J* 10.3 and 8.6, $SiCH_2CHH$), 4.20 (2 H, m, CO_2CH_2), 4.26 [1 H, dd, *J* 4.0 and 5.6, 8-(1-H)], 4.28 {1 H, d, *J* 4.8, 8-[4-(4-H)]}, 4.49 (1 H, d, *J* 6.8, $OCHHO$), 4.56 (1 H, d, *J* 6.8, $OCHHO$), 4.92 (1 H, dd, *J* 1.5 and 8.4, 6-H) and 6.32 (1 H. d, *J* 1.5, C=CH).

2-(*Trimethylsilyl*)*ethyl* (1S,4RS,5RS,7R,7aS)-5-[{(1S,4S)-3,3-*Dimethyl*-2-*oxo*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}*methyl*]-2,4,5,-6,7,7a-*hexahydro*-5-*hydroxy*-1-[(R)-2-*methoxycarbonyl*-1-*methylethyl*]-1,7a-*dimethyl*-7-[2-(*trimethylsilyl*)*ethoxymethoxy*]-1H-*indene*-4-*carboxylate* **43**.—To a stirred suspension of copper(I) iodide (2.57 g, 13.5 mmol) in dry THF (42 cm^3) at −30 °C was added MeLi (1.12 mol dm^{-3} in Et_2O; 24.1 cm^3, 27.0 mmol) under Ar, and the mixture was stirred for 20 min at −30 to −20 °C. To the Me_2CuLi solution at −78 °C was added dropwise a solution of compound **42** (1.87 g, 2.70 mmol) in dry THF (15 cm^3). The colour immediately changed to yellow and a precipitate appeared. The yellow suspension was stirred at −78 °C for 8 h. The reaction was quenched at −78 °C by dropwise addition of a solution of acetic acid (2.43 g, 40.5 mmol) in THF (6 cm^3). The mixture was poured into saturated aq. NH_4Cl and extracted three times with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue (1.99 g) was diluted with diethyl ether (30 cm^3) and to the solution at 0 °C was added dropwise a solution of diazomethane in diethyl ether until a yellow colour persisted. The mixture was then stirred at 0 °C for 2 h. Excess of diazomethane was destroyed by addition of acetic acid to the mixture at 0 °C, the resulting ethereal solution was washed with saturated aq. $NaHCO_3$, and the aq. solution was extracted twice with diethyl ether. The combined ethereal solutions were washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give compound **43** as a diastereoisomeric mixture (1.39 g, 73%), ν_{max}(film)/cm^{-1} 3500, 1760, 1740, 1720, 1185, 1170 and 1020; δ_H(100 MHz; $CDCl_3$) 0.01 (9 H, s, Me_3Si), 0.05 (9 H, s, Me_3Si), 0.85–1.25 (19 H, Me × 5 and $SiCH_2$ × 2), 1.30–2.60 [12 H, 6-H_2, 1-(1-H), 1-(2-H_2), 5-CH_2, 5-(5-H_2), 5-(6-H_2) and OH], 2.80, 2.95 and 3.04 (total 2 H, br m, 2-H_2), 3.30 (1 H, br m, 4-H), 3.66 ($\frac{3}{2}$ H, s, CO_2Me), 3.67 ($\frac{3}{2}$ H, s, CO_2Me), 3.40–3.70 (2 H, m, $SiCH_2CH_2$), 3.86 ($\frac{1}{2}$ H, br m, 7-H), 3.90 ($\frac{1}{2}$ H, br m, 7-H), 4.10–4.40 [3 H, m, 5-(4-H) and CO_2CH_2], 4.50–4.80 (2 H, m, OCH_2O), 5.58 ($\frac{1}{2}$ H, br m, 3-H) and 5.70 ($\frac{1}{2}$ H, br m, 3-H). This was employed in the next step without further purification.

2-(*Trimethylsilyl*)*ethyl* (1S,7R,7aS)-5-[{(1S,4S)-3,3-*Dimethyl*-2-*oxo*-7-*oxabicyclo*[2.2.1]*heptan*-1-*yl*}*methyl*]-2,6,7,7a-*tetrahydro*-1-[(R)-2-*methoxycarbonyl*-1-*methylethyl*]-1,7a-*dimethyl*-7-[2-(*trimethylsilyl*)*ethoxymethoxy*]-1H-*indene*-4-*carboxylate* **44a**.—To a cooled, stirred solution of compound **43** (1.24 g, 1.75 mmol) in dry pyridine (16 cm^3) at −25 °C was added dropwise $SOCl_2$ (1.91 cm^3, 26.2 mmol). After the addition, the resulting mixture was stirred for 1.5 h at −20 °C, poured into stirred ice–water, and extracted with diethyl ether. The extract was washed successively with saturated aq. $CuSO_4$, water, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *compound* **44a** as an amorphous solid (990 mg, 82%) (Found: C, 64.2; H, 8.9. $C_{37}H_{62}O_8Si_2$ requires C, 64.31; H, 9.04%); $[\alpha]_D^{21}$ −17.0° (*c* 1.43, $CHCl_3$); ν_{max}(film)/cm^{-1} 1760, 1735, 1720 and 1050; δ_H(400 MHz; $CDCl_3$) 0.00 (9 H, s, Me_3Si), 0.04 (9 H, s, Me_3Si), 0.91 [3 H, d, *J* 7, 1-(1-Me)], 0.93 (3 H, s, 1- or 7a-Me), 0.93 (2 H, m, $SiCH_2$), 1.01 [3 H, s, 5-(3-Me)], 1.02 (3 H, s, 7a- or 1-Me), 1.17 (2 H, m, $SiCH_2$), 1.16 [3 H, s, 5-(3-Me)], 1.42 [1 H, ddd, *J* 5, 9 and 13, 5-(6-H)], 1.69 [1 H, dt, *J* 3, 10 and 13, 5-(6-H)], 1.78 [1 H, tt, *J* 5 and 10, 5-(5-H)], 1.88 [1 H, ddd, *J* 3, 9 and 10, 5-(5-H)], 1.98 (1 H, dd, *J* 3 and 17, 2-H), 2.14 [1 H, dd, *J* 12 and 15, 1-(2-H)], 2.34–2.51 [5 H, m, 2- and 6-H, 1-(1-H), 1-(2-H) and 5-C*H*H], 2.67 (1 H, br d, *J* 19, 6-H), 3.09 (1 H, d, *J* 15, 5-CH*H*), 3.45 (1 H, dt, *J* 9 and 8, $SiCH_2CHH$), 3.62 (1 H, dt, *J* 9 and 8, $SiCH_2CHH$), 3.67 (3 H, s, CO_2Me), 3.82 (1 H, br t, *J* 1.5, 7-H), 4.22 [1 H, d, *J* 5, 5-(4-H)], 4.29 (2 H, m, CO_2CH_2), 4.60 (1 H, d, *J* 7, OCHHO), 4.67 (1 H, d, *J* 7, $OCHHO$) and 5.59 (1 H, br t, *J* 3, 3-H).

2-(*Trimethylsilyl*)*ethyl* (1S,7R,7aS)-1-[(R)-2-*Carboxy*-1-*methylethyl*]-5-[{(1S,4S)-3,3-*dimethyl*-2-*oxo*-7-*oxabicyclo*-[2.2.1]*heptan*-1-*yl*}*methyl*]-2,6,7,7a-*tetrahydro*-1,7a-*dimethyl*-7-[2-(*trimethylsilyl*)*ethoxymethoxy*]-1H-*indene*-4-*carboxylate* **44b**.—A mixture of diester **44a** (438 mg, 634 μmol), tetrabutylammonium hydroxide (10% in water; 0.5 cm^3, 193 μmol), THF (10 cm^3) and 1 mol dm^{-3} aq. LiOH (5 cm^3) was stirred vigorously at room temperature for 30 h. The reaction mixture was acidified to pH 5 (universal indicator) by addition of 1 mol dm^{-3} hydrochloric acid and extracted three times with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give acid ester **44b** (395 mg, 92%), $[\alpha]_D^{23}$ −22.4° (*c* 0.52, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3150, 1760, 1705 and 1245; δ_H(300 MHz; $CDCl_3$) 0.90–1.00 [8 H, m, 1-(1-Me), 1- or 7a-Me and $SiCH_2$], 1.02 [3 H, s, 5-(3-Me)], 1.05 (3 H, s, 7a- or 1-Me), 1.09 (2 H, m, $SiCH_2$), 1.19 [3 H, s, 5-(3-Me)], 1.38–1.95 [4 H, m, 5-(6-H_2) and 5-(5-H_2)], 2.01 [1 H, dd, *J* 3 and 17, 2-H), 2.19 (1 H, dd, *J* 12 and 15, 1-(2-H)], 2.34–2.55 (5 H, m, 2- and 6-H, 1-(1-H), 1-(2-H) and 5-C*H*H), 2.69 (1 H, br d, *J* 19, 6-H), 3.08 (1 H, d, *J* 15, 5-CH*H*), 3.48 (1 H, dt, *J* 9 and 8, $SiCH_2CHH$), 3.63 (1 H, dt, *J* 9 and 8, $SiCH_2CHH$), 3.84 (1 H, br t, *J* 1.5, 7-H), 4.23 [1 H, d, *J* 5, 5-(4-H)], 4.31 (2 H, m, CO_2CH_2), 4.62 (1 H, d, *J* 7, $OCHHO$), 4.69 (1 H, d, *J* 7, $OCHHO$) and 5.61 (1 H, br t, *J* 3, 3-H). This was employed for the next step without further purification.

Glycinoeclepin A **1**.—To a stirred solution of the acid ester **44b** (142 mg, 0.21 mmol) in dry MeCN (1.5 cm^3) was added dropwise $LiBF_4$ (1 mol dm^{-3} in MeCN; 0.6 cm^3, 0.6 mmol) under Ar. After the addition, the mixture was stirred at 50 °C for 24 h, poured into saturated aq. $(NH_4)_2SO_4$, and extracted with EtOAc. The extract was washed with saturated aq. $(NH_4)_2SO_4$ and concentrated under reduced pressure. The residue was diluted with EtOAc, filtered through Celite, and concentrated under reduced pressure to give crude hydroxy acid ester **44c** (128 mg), whose TLC analysis showed contamination with a small amount of glycinoeclepin A generated by deprotection of the trimethylsilylethyl ester.

Crude compound **44c** (124 mg) was dissolved in dry MeCN (0.4 cm^3), and a solution of tris(dimethylamino)sulphonium difluorotrimethylsiliconate (2 mol dm^{-3} in MeCN, 0.42 cm^3, 0.84 mmol) was added to the solution at room temperature under Ar. After being stirred at room temperature for 4 h the reaction mixture was poured into water and extracted with $CHCl_3$–THF (4:1). The extract was washed with saturated aq. $(NH_4)_2SO_4$ and concentrated under reduced pressure. The residue was diluted in EtOAc–$CHCl_3$ (1:1), filtered through Celite, and concentrated under reduced pressure to give crude glycinoeclepin A **1**, which was recrystallized from EtOAc to give pure glycinoeclepin A (88 mg, 97% from **44b**), m.p. 120–121.5 °C (needles) (Found: C, 67.3; H, 7.65. $C_{25}H_{34}O_7$ requires C, 67.24; H, 7.67%); $[\alpha]_D^{20}$ −10.2° (*c* 0.63, MeOH); ν_{max}(Nujol)/cm^{-1} 3340, 2650, 1748, 1680, 1410, 1323, 1300, 1055, 1020, 948, 928 and 847; δ_H*(300 MHz; CD_3OD) 0.99 (3 H, s, 18- or 28-H_3), 1.00 (3 H, d, *J* 6, 21-H_3), 1.05 (3 H, s, 29- or 30-H_3), 1.16 (3 H, s, 28- or 18-H_3), 1.20 (3 H, s, 30- or 29-H_3), 1.47 (1 H, m, 1-H), 1.77 (1 H, dt, *J* 3 and 12, 1-H), 1.84 (1 H, tt, *J* 5 and 12, 2-H), 1.94–2.09 and 2.45–2.60 (6 H, m, 2-, 11-, 16-, 19-, 20- and 22-H), 2.16 (1 H, dd, *J* 12 and 15, 22-H), 2.20 (1 H, br d, *J* 17, 16-H), 2.90 (1 H, br d, *J* 19, 11-H), 3.04 (1 H, d, *J* 14.5, 19-H), 4.08 (1 H, br t, *J* 2, 12-H), 4.31 (1 H, d, *J* 4.8, 3-H) and 5.66 (1 H, br s, 15-H).

Glycinoeclepin A Bis-(p-*bromophenacyl*) *Ester* **45**.—To a stirred solution of glycinoeclepin A **1** (8.0 mg, 17.9 μmol) and diisopropylethylamine (10 mm^3) in dry MeCN (0.2 cm^3) was added *p*-bromophenacyl bromide (20 mg, 72 μmol). After 1 h, the reaction mixture was diluted with water and extracted with EtOAc. The extract was directly purified by preparative TLC to give crude diester **45**. Recrystallization of the crude product gave pure *diester* **45** (14.3 mg, 95%), m.p. 133.5–134.5 °C [from hexane–EtOAc (2:1), as plates] [Found: (FAB-MS) M + 1 843.1386. $C_{41}H_{45}Br_2O_9$ requires *m/z*, 843.1389]; $[\alpha]_D^{22}$ −19.1° (*c* 0.57 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3400, 1762, 1738, 1702, 1692, 1585, 1460, 1430, 1377, 1225, 1205, 1188, 1180, 1113, 1063, 978 and 821; δ_H(400 MHz; $CDCl_3$–D_2O) 0.99 (3 H, s, 28-H_3), 1.02 (3 H, s, 29-H_3), 1.04 (3 H, d, *J* 6.5, 21-H_3), 1.15 (3 H, s, 18-H_3), 1.17 (3 H, s, 30-H_3), 1.55 (1 H, m, 1-H), 1.67–1.95 (3 H, m, 1-H and 2-H_2), 2.08 (1 H, dd, *J* 3.5 and 17, 16-H), 2.37 (1 H, dd, *J* 11.5 and 14.5, 22-H), 2.39 (1 H, br d, *J* 18, 11-H), 2.47 (1 H, br d, *J* 17, 16-H), 2.58 (1 H, m, 20-H), 2.64 (1 H, br d, *J* 14.5, 22-H), 2.85 (1 H, d, *J* 14.5, 19-H), 2.88 (1 H, br d, *J* 18, 11-H), 3.00 (1 H, d, *J* 14.5, 19-H), 4.07 (1 H, br t, *J* 2, 12-H), 4.26 (1 H, d, *J* 5, 3-H), 5.28 (1 H, d, *J* 16.5, C*H*HCOAr), 5.32 (1 H, d, *J* 16.5, CH*H*COAr), 5.36 (1 H, d, *J* 16.5, C*H*HCOAr), 5.51 (1 H, d, *J* 16.5, CH*H*COAr), 6.08 (1 H, br, 15-H), 7.645 (2 H, d, *J* 8.5, ArH), 7.655 (2 H, d, *J* 8.5, ArH), 7.79 (2 H, d, *J* 8.5, ArH) and 7.83 (2 H, d, *J* 8.5, ArH); δ_C(75 MHz; $CDCl_3$) 16.4, 18.6, 19.3, 20.0, 22.9, 25.2, 29.7, 33.6, 35.3, 38.2, 41.1, 46.2, 48.9, 51.4, 53.5, 65.7, 66.1, 71.5, 83.7, 88.6, 126.7, 127.4, 129.1, 129.27, 129.33, 132.2, 133.0, 133.8, 139.1, 167.1, 172.9, 191.2, 191.4 and 217.1.

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* NMR locants given in structure **1**, Scheme 1.

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