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Taxane Diterpenes 5: Synthesis of the A- and C-Rings: An Unusual Rearrangement of an *N*-Hydroxyimino Lactone

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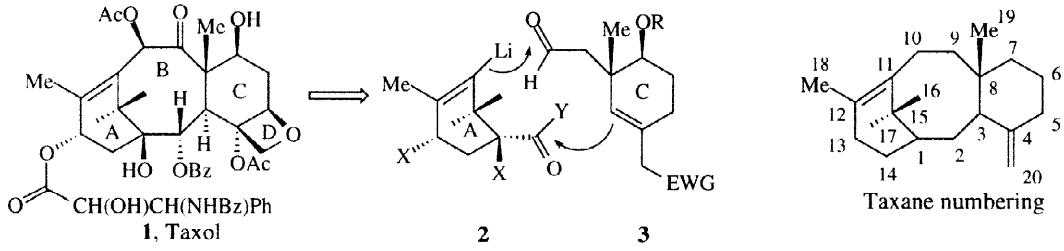
Abstract: Ring A of taxol was synthesized from the bromodiene **5** and acryloyl chloride to give **6**, which was resolved by separation of diastereomers **7**. Allylic oxidation of **7** gave **8**, which on deprotection, esterification and reduction gave **11**. Heating **11** followed by reduction and protection gave **13**. The C-ring component was made using asymmetric Birch reduction methodology combined with standard functional group manipulations to give **28**. Combining **13** and **28** gave **29**, which was converted into **33**. Thermolysis of **33** did not generate a nitrile oxide but rather ionized to an oxydienyl cation, eventually leading to **34**.
Keywords: taxol, antitumor, asymmetric Birch reduction, oxydienyl cation.

Introduction

Research on the synthesis of the antitumor diterpene taxol® **1**[1] has produced an wide variety of strategies for the construction of the core structure,[2] and to-date six total syntheses have been reported.[3a-f] Our recent studies in this area have focused on the strategy depicted in **Scheme 1** involving the synthesis of the A- and C-rings, **2** and **3** respectively, and their subsequent connection to form the central B-ring.[4]

Scheme 1



1, Taxol **2** **3** Taxane numbering

Synthesis of Ring A

Tetramethylethylene was converted into the *gem*-dibromocyclopropane **4**, which on treatment with $PhNMe_2$ at 140-190 °C gave the bromodiene **5**, **Scheme 2**.[5] This modification of the literature procedure more than doubles the yield of **5**, and is amenable to large scale preparations (100 g). The diene **5** reacted cleanly with acryloyl chloride in a thermal (110 °C) Diels-Alder process to give **6** (90%), with no more than traces of the other regioisomer (<5%). All attempts to make this reaction enantioselective by using chiral Lewis acids, or chiral derivatives of acryloyl chloride were unsuccessful.[6] Consequently, **6** was treated with *S*-(-)-$PhCHMeNH_2$ to give a 1:1 mixture of **7** (*R,S*) and **7** (*S,S*) which were readily separable, and the absolute stereochemistry of the *S,S* diastereomer was determined by X-ray crystallography.[7]

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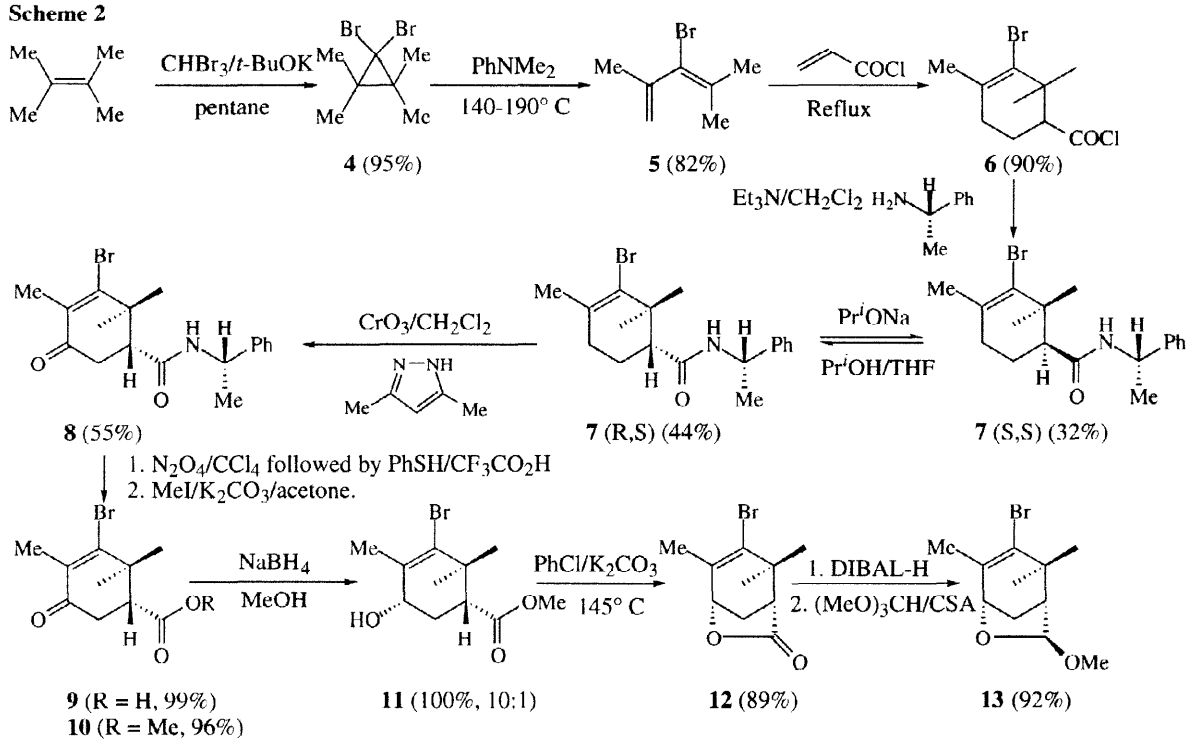
The diastereomer **7** (*R,S*) corresponds to the correct absolute configuration needed for the synthesis of taxol. The undesired stereoisomer **7** (*S,S*) was equilibrated to a mixture of **7** (*R,S*) (45%) and starting material by treatment with $Pr^iONa/Pr^iOH/THF$.

While it is possible to introduce the C-13 oxygen functionality into very advanced taxol intermediates[8] we were intrigued with the possibility of subjecting **7** to allylic oxidation reactions. A priori, an electron-deficient vinyl bromide might be rather resistant towards this type of transformation, and indeed perusal of the literature did not reveal any pertinent examples other than the oxidation of a vinyl iodide to a β-iodoenone during the course of Kishi's approach to taxol.[9] In the event, treatment of **7** with CrO_3.3,5-dimethylpyrazole[10] gave the required β-bromoenone **8** (55% on a 58 g scale). *N*-Nitrosation of **8**,[11] followed by treatment with $CF_3CO_2H/PhSH$ gave the acid **9**, which was converted into the methyl ester **10**. Reduction of **10** using $NaBH_4/MeOH$ proceeded with good stereoselectivity to give **11** and its C13 epimer (taxol numbering) in a 10:1 ratio. Heating **11** in chlorobenzene in the presense of K_2CO_3 gave the known lactone **12**.[12] The lactone was reduced with DIBAL-H and the crude lactol treated with $CH(OMe)_3/MeOH/H^+$ to give **13**.

Scheme 2

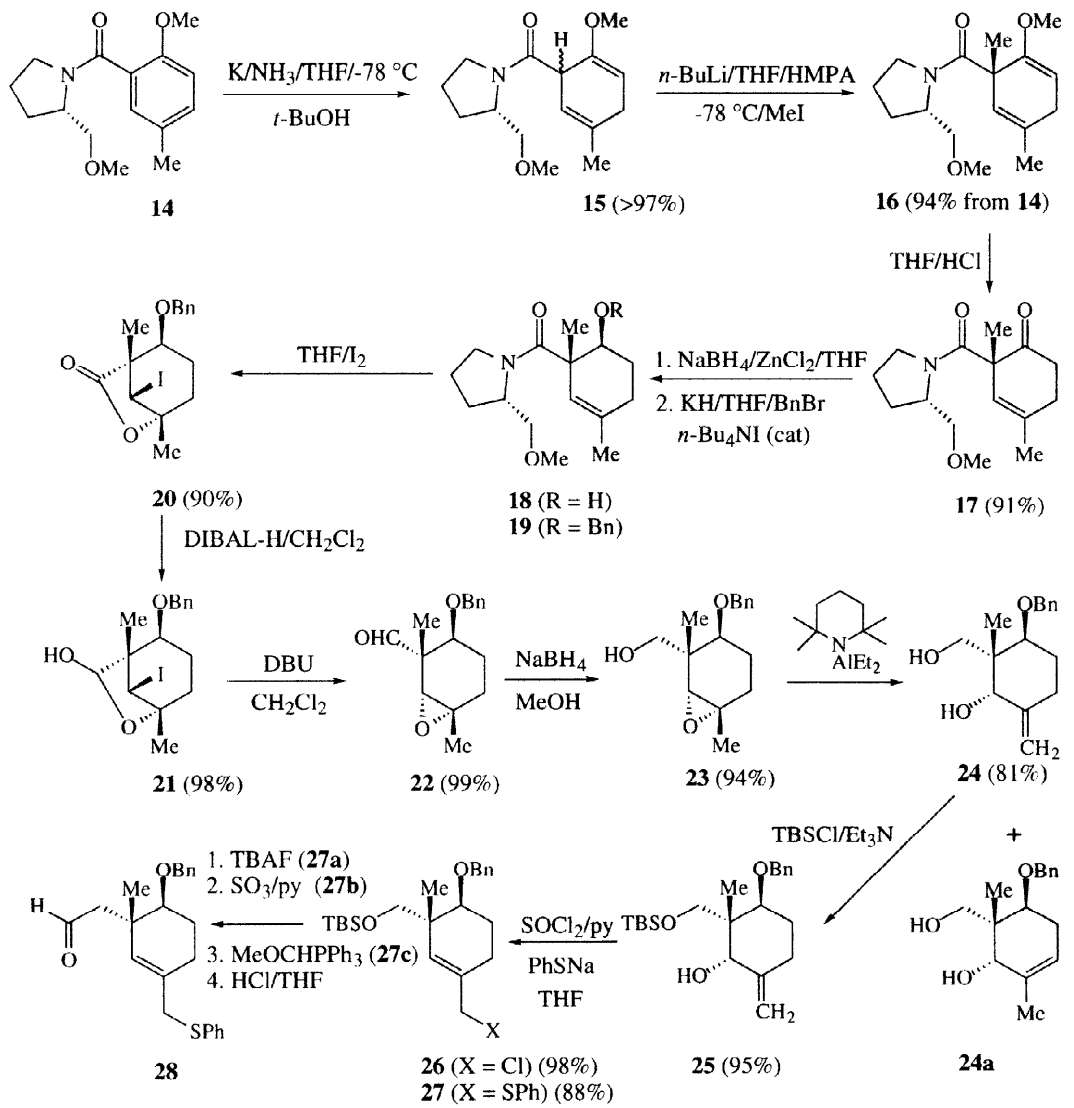


Synthesis of Ring C

While there have been a number of strategies reported for the synthesis of the C-ring portion of the taxane diterpenes,[13] none have taken advantage of the Schultz asymmetric Birch reduction methodology which would appear to be ideally suited for the synthesis of **3**, **Scheme 1**.[14] Reduction of the known amide **14**[15] with $K/NH_3/THF/t$-BuOH gave **15**, which on treatment with *n*-BuLi at -78 °C, warming to 25°C and cooling to 0 °C, followed by addition of HMPA, and recooling to -78 °C followed by addition of MeI gave the desired diastereomer **16** (>99:1).[16] If the amide enolate is not brought to 25°C, then the undesired diastereomer is the major product. After acid hydrolysis the ketone **17** was reduced with $Zn(BH_4)_2/Et_2O$, and

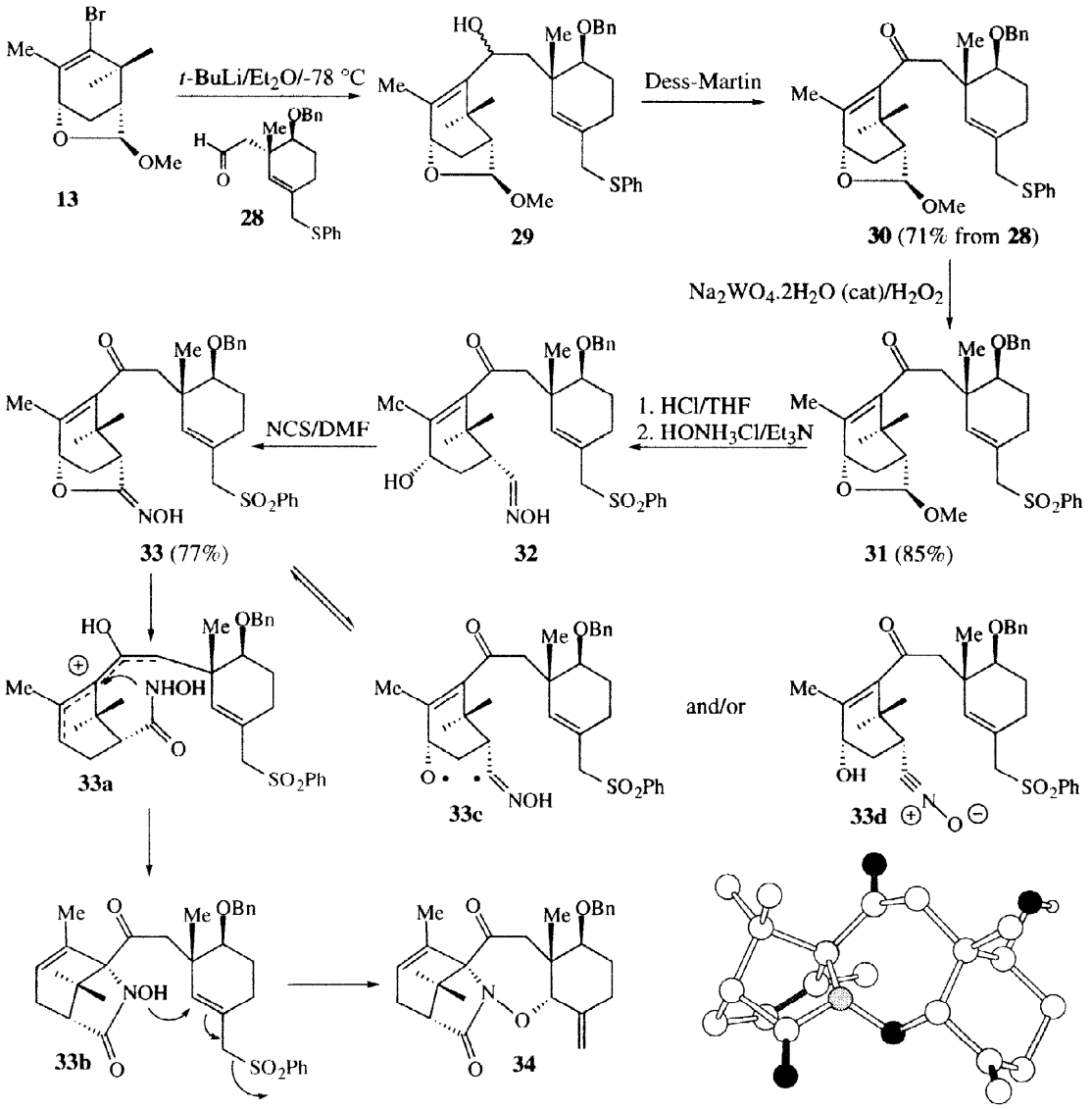
the resulting alcohol **18** (R = H) protected as the benzyl ether **19** (R = Bn). Reduction of **17** with $NaBH_4$/MeOH gave **18** and its epimer (1:1). Attempts to hydrolyze the hindered *tert*-amide **19** were unsuccessful, whereas iodolactonization of **19** proceeded cleanly to give **20**, **Scheme 3**. Reduction of the lactone using DIBAL-H gave the lactol **21**, which was converted into the epoxyaldehyde **22** when treated with DBU. Reduction of **22** using $NaBH_4$/MeOH gave **23**. Exposure of **23** to the classical Crandall[17] epoxide elimination conditions ($LiNEt_2/Et_2O$) proceeded slowly, even at reflux, to give a mixture of allylic alcohols, **24** and **24a** (3:1)[18], whereas, treatment of **23** with Olofson's "Harpoon" base[19] at 25 °C cleanly produced **24** and **24a** (6:1) in 84% yield. A further improvement was found by treating **23** with diethylaluminum 2,2,6,6-tetramethylpiperidide[20] to give **24** in excellent yield without any observable formation of **24a**. It is necessary to conduct the above epoxide rearrangement on the unprotected primary alcohol **23** since the corresponding TBS derivative does not undergo any conversion into **25**. This suggests that aluminum coordination to the adjacent hydroxyl group greatly facilitates the exocyclic elimination process.

Scheme 3



The TBS protected exocyclic allylic alcohol **25** was surprisingly reluctant to participate in [2.3]-sigmatropic rearrangement chemistry. This problem was readily solved by making use of standard S_N2' chemistry. Treatment of **25** with thionyl chloride/pyridine cleanly gave the rearranged allylic chloride **26**, which was converted directly into the sulfide **27**. Deprotection of **27** gave **27a** (98%) which was oxidized to **27b** (94%), and standard Wittig homologation[21] of **27b** gave **27c**, which was hydrolyzed to the required C-ring component **28** (86% from **27b**).

Scheme 4



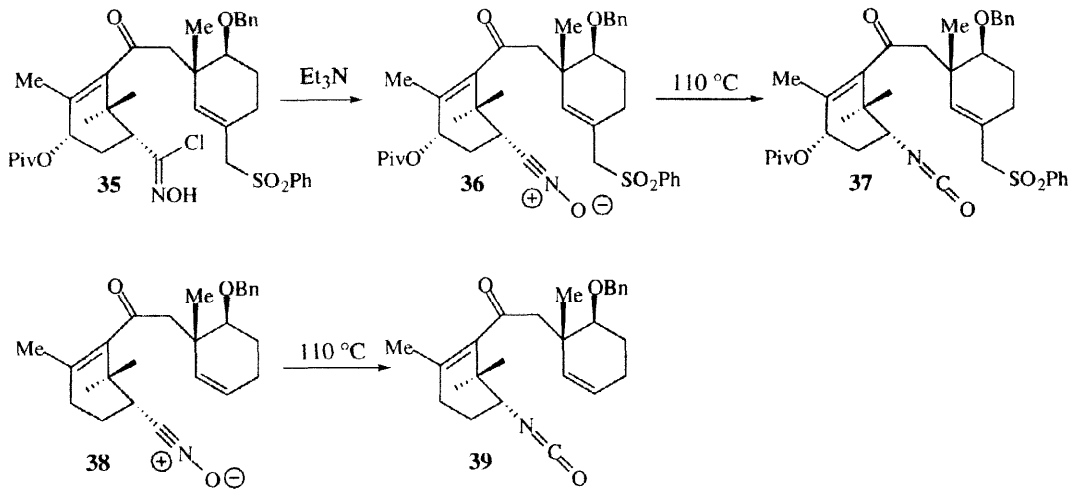
Chem 3D representation of **34** from the X-ray coordinates (-Bn)

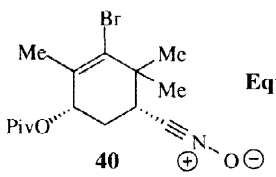
Ring A + Ring C

The formation of the C_{10}-C_{11} bond to unite the ring A and ring C components was accomplished by treating **13** with *t*-BuLi (bromine-lithium exchange), followed by the aldehyde **28** to give **29** as a 1:1 mixture of diastereomers, **Scheme 4**. Oxidation of **29** using the Dess-Martin periodinane reagent[22] gave **30** as a single

compound. The derived lactolsulfone **31** was hydrolyzed and treated with hydroxylamine to give **32**. It was expected that treatment of **32** with *N*-chlorosuccinimide would generate the hydroxyimoyl chloride which would cyclize to give **33**,[23] and indeed this was the case. We had hoped that thermolysis of **33** would give rise to intermediates such as **33c** and/or **33d** which could respectively undergo radical addition and 1,3-dipolar cycloaddition to the allylic sulfone functionality. In the event, heating **33** in *o*-dichlorobenzene/EtNPr$^i_2$ at 160 °C gave **34** (24%) as the only isolable pure compound from a complex mixture. The structure of **34** was confirmed by x-ray crystallography, and appears to have been formed by ionization of **33** to the oxydienyl cation **33a**[24] which leads to **33b**, and S_N2'-type displacement of the allylic sulfone to give **34**.

Scheme 5

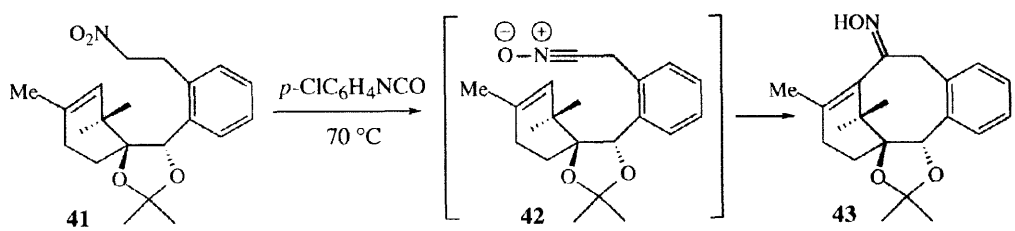




Eqn 1

In a related investigation the α-chlorooxime **35** was treated with Et_3N to give the nitrile oxide **36** (IR 2296 cm^{-1}), **Scheme 5**. While **36** under went intermolecular 1,3-dipolar cycloaddition reaction with 1-hexene, heating **36** at 110 °C caused rearrangement to the isocyanate **37** (IR 2261 cm^{-1}).[25] The nitrile oxide **38** also did not undergo intramolecular 1,3-dipolar cycloaddition, but rather rearranged to the isocyanate **39**. Finally, we have observed that the simple ring A nitrile oxide **40** is a stable monomeric species and shows no inclination to dimerize to a furoxan, Eqn 1.[23]

Scheme 6



While this strategy to close the eight-membered at C_2-C_3 using a nitrile oxide 1,3-dipolar cycloaddition was unsuccessful, it is noteworthy that Nagaoka reported that dehydration of the nitroalkene **41** gave **43** (94%) *via* the intermediate nitrile oxide **42** and fragmentation of the isoxazoline, **Scheme 6**.[26]

Experimental

3-Bromo-2,4-dimethylpenta-2,4-diene 5. To a 1L, 2-neck round bottom flask, equipped with a thermometer and a wide-bore Liebig condenser (with a large cold finger, filled with dry-ice/acetone, stacked on top), was added a solution of **4** (157 g, 0.61 mol) in *N,N*-dimethylaniline (200 mL). The mixture was heated cautiously with stirring to 140 °C and a vigorous exotherm took place (internal temperature rose rapidly to 190 °C), and the heating bath was removed immediately (caution). The mixture was allowed to cool to room temperature and quenched with a slurry of crushed ice and concentrated HCl (1L, 1:1 mixture). The mixture was extracted with Et_2O (3 x 800 mL). The combined extracts were washed with 2N HCl (1 L) and water (1L), dried ($MgSO_4$), and evaporated *in vacuo* to give **5** (88.34 g, 82%) as a pale brown liquid. B.p. 149-150 °C (Lit.[5] 157-158 °C). IR (film) 2974, 2915, 2856, 1626 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.80 (3H, s), 1.88-2.00 (3H, m), 2.01 (3H, s), 4.89-4.92 (1H, m), 5.02-5.05 (1H, m). HRMS (FAB) calcd for $C_7H_{11}Br$ ($M^+ + 1$) 175.0122. Found 175.0118.

3-Bromo-2,2,4-trimethylcyclohex-3-ene carbonyl chloride 6. A solution of **5** (25 g, 0.143 mol) in freshly distilled acryloyl chloride (58.1 mL, 0.715 mol) was heated at reflux, under nitrogen, for 48 h. Excess acryloyl chloride was removed by distillation at atmospheric pressure. The residue was fractionally distilled under reduced pressure to give **6** (31.8 g, 90%). B.p. 117-123 °C/8 mmHg. IR (film) 2957, 2864, 1807 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.32 (3H, s), 1.80 (3H, s), 1.95-2.23 (4H, m), 3.09 (1H, m). Used directly in the next stage.

(+)-*N*-(α-Methylbenzyl)-3-bromo-2,2,4-trimethylcyclohex-3-ene carboxamide 7 (*R,S*) and (-)-*N*-(α-Methylbenzyl)-3-bromo-2,2,4-trimethylcyclohex-3-ene carboxamide 7 (*S,S*). To a mixture of (*S*)-(-)-α-methylbenzylamine (50 mL, 47 g, 0.386 mol) and Et_3N (107.6 mL, 78.12 g, 0.772 mol) in dry CH_2Cl_2 (2.5 L), at 0 °C under nitrogen, was added a solution of **6** (102.5 g, 0.385 mol) in dry CH_2Cl_2 (100 mL) dropwise over *ca.* 30 min. The mixture was allowed to warm to room temperature for 1 h, and quenched with 2N HCl (400 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (200 mL). The combined extracts were washed with water (1 L), brine (1 L), dried ($MgSO_4$), and concentrated *in vacuo* to give **7** (*R,S*) and **7** (*S,S*) as a colorless solid (135 g). The diastereomers were separated by pre-adsorption onto flash silica (*ca.* 200 g) and eluted from a column of flash silica (10 cm x 55 cm) using sequentially 2:1 hexanes/Et_2O, 1:1 Et_2O/hexanes, Et_2O followed by EtOAc as eluents (fraction size 500 mL). **7** (*R,S*), (59.1 g, 44%): M.p. 141-143 °C (Et_2O/pentane). $[\alpha]_D^{23}$ +1.71 (c = 1, $CHCl_3$). IR (Nujol mull) 3284, 1637 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, s), 1.30 (3H, s), 1.51 (3H, d, *J* = 7.0 Hz), 1.66-1.76 (1H, m), 1.81 (3H, s), 1.86-1.98 (1H, m), 2.10-2.18 (2H, m), 2.33 (1H, dd, *J* = 11.5, 3.0 Hz), 5.16 (1H, quintet, *J* = 7.0 Hz), 5.64 (1H, br. d, *J* = 7 Hz), 7.27-7.49 (5H, m). HRMS (FAB) calcd for $C_{18}H_{24}BrNO$ ($M^+ + 1$) 350.1120. Found 350.1122. **7** (*S,S*), (43.31 g, 32%): M.p. 167-168 °C (Et_2O/pentane). $[\alpha]_D^{23}$ -10.33 (c = 1, $CHCl_3$). IR (Nujol mull) 3336, 1638 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, s), 1.23 (3H, s), 1.45 (3H, d, *J* = 7.0 Hz), 1.58-1.70 (1H, m), 1.72 (3H, s), 1.78-1.92 (1H, m), 2.02-2.11 (2H, m), 2.17 (1H, dd, *J* = 11.5, 2.5 Hz), 5.08 (1H, quintet, *J* = 7.0 Hz), 5.68 (1H, br. d, *J* = 7.0 Hz), 7.15-7.33 (5H, m). HRMS (FAB) calcd for $C_{18}H_{24}BrNO$ ($M^+ + 1$) 350.1120. Found 350.1111.

Equilibration of 7 (*S,S*) and 7 (*R,S*). To stirred 2-propanol (1 L), at 60 °C under dry nitrogen, was added hexane washed sodium pellets (30.2 g, 1.31 mol) portion wise over *ca.* 20 min. The mixture was heated under reflux for 90 min (no sodium visible), and allowed to cool to 60 °C. A solution of **7** (*S,S*) (46 g, 0.131 mol) in dry THF (300 mL) was added and the mixture was heated at 80 °C for 7 days. The mixture was cooled to room temperature and neutralized by the addition of 6N HCl (160 mL). The mixture was concentrated *in vacuo* at 50 °C to a residual volume of *ca.* 100 mL and partitioned between water (800 mL) and Et_2O (800 mL). The aqueous phase was further extracted with Et_2O (2 x 500 mL), and the combined extracts were washed with water (x1), brine (x1), and dried ($MgSO_4$). Concentration *in vacuo* onto flash silica (100 g) followed by chromatography over a column of flash silica gel (36 cm x 10 cm), eluting with Et_2O/pentane (1:1) (fraction size ca, 500 mL), achieved separation of **7** (*R,S*) (20.7 g, 45%) and **7** (*S,S*) (19 g, 41%), (plus 4.5 g of mixed fractions).

(-)-*N*-(α-Methylbenzyl)-3-bromo-2,2,4-trimethylcyclohex-3-ene-4-one carboxamide 8. A mechanically stirred suspension of chromium trioxide (281.5 g, 2.815 mol) in dry CH_2Cl_2 (2.3 L), in a 4 L vessel, was cooled to -20 °C under dry nitrogen. 3,5-Dimethylpyrazole (270.6 g, 2.815 mol) was added in one portion and the dark purple mixture allowed to warm to -15 °C with stirring over 20 min. A solution of **7** (*R,S*) (58 g, 0.165 mol) in dry CH_2Cl_2 (250 mL) was added dropwise *via* a pressure-equalizing dropping funnel over *ca.* 15 min, and a further portion of CH_2Cl_2 (100 mL) was added to the mixture. The mixture was stirred at -15 °C under nitrogen for 18 h, cooled to -20 °C, and treated with 5N NaOH solution (1.2 L) portion wise over *ca.* 5 min (the internal temperature rose to 10 °C). External cooling was continued (cooling bath at -25 °C) such that the temperature of the mixture was maintained between 0 °C and 10 °C for 1 h. The mixture was transferred under suction to a 5 L separating funnel and the organic layer isolated. The aqueous phase was extracted with CH_2Cl_2 (5 x 2 L, and the extracts were washed with 2M HCl (x 3), brine (x 3), dried ($MgSO_4$), and evaporated *in vacuo* to give a dark brown oily residue. Elution through a column of Florisil® using a gradient elution (2:1 to 1:1 pentane/Et_2O, Et_2O, followed by EtOAc) gave **8** (33.06 g, 55%) as a colorless crystalline solid. M.p. 137-138 °C (Et_2O). $[\alpha]_D^{25}$ -1.14 (c = 1, $CHCl_3$). IR (Nujol mull) 3290, 1679, 1636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, s), 1.42 (3H, s), 1.51 (3H, d, *J* = 7.0 Hz), 1.97 (3H, s), 2.48-2.64 (2H, m), 2.83 (1H, dd, *J* = 16.5, 10.5 Hz), 5.13 (1H, quintet, *J* = 7.0 Hz), 5.69 (1H, d, *J* = 7.0 Hz), 7.27-7.49 (5H, m). HRMS (FAB) calcd for $C_{18}H_{22}BrNO_2$ ($M^+ + 1$) 364.0912. Found 364.0892. The yield of **8** is typically 74-76% when conducted on a 1-3 g scale using 20 equivalents of oxidant.

3-Bromo-2,2,4-trimethylcyclohex-3-ene-4-one carboxylic acid 9. To a stirred suspension of NaOAc (15.93 g, 0.194 mol) and 1,2-dichloroethane (160 mL), at 0 °C under nitrogen, was added a dark brown solution of dinitrogen tetroxide in carbon tetrachloride (*ca.* 2.2 M, 44.1 mL, 0.097 mol). The resulting bright green reaction mixture was cooled to -10 °C and stirred at -10 °C for 15 min. A solution of **8** (17.68 g, 0.0485 mol) in 1,2-dichloroethane (100 mL) was added dropwise over *ca.* 3 min. The mixture was allowed to warm to 0 °C, and stirred at 0 °C for 16 h. The bright yellow mixture was filtered cold through a small pad of Celite® (10 mm), and the pad was washed thoroughly with 1,2-dichloroethane (2 x 50 mL). The filtrate was heated under reflux with vigorous stirring for 2 h then cooled to room temperature. Thiophenol (5.48 mL, 0.053 mol) and trifluoroacetic acid (37.4 mL, 0.485 mol) were added and the mixture stirred at room temperature for *ca.*

18 h. The mixture was concentrated *in vacuo* to give a brown oil. Residual trifluoroacetic acid was removed by addition of toluene (500 mL) and the mixture evaporated *in vacuo*. The residue was dissolved in Et_2O (500 mL) and extracted with cold (*ca.* 5 °C) 2M NaOH solution (2 x 250 mL). The combined aqueous extracts were washed with Et_2O (300 mL) and acidified, with cooling, to pH 2 by slow addition of concentrated HCl (100 mL). The resulting brown, opaque mixture was extracted with Et_2O (4 x 300 mL). The combined extracts were washed with water (800 mL), saturated brine (800 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **9** (12.54 g, 99%) as a brown oil which was used directly in the next stage. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.47 (3H, s), 1.97 (3H, s), 2.68 and 2.78 (2H, ABX, J = 17.0, 10, 5 Hz), 3.01 (1H, X part of ABX, J = 10.0, 5.0 Hz). HRMS (CI^+) calcd for $C_{10}H_{13}BrO_3$ ($M^+ + 1$) 261.0126. Found 261.0121. To establish the optical purity of the above ketoacid **9** a portion was recoupled with (*S*)-(-)-α-methylbenzylamine. To a solution of **9** (20 mg, 0.0766 mmol) in CH_2Cl_2 (0.5 mL) was added EDC (29 mg, 0.153 mmol), DMAP (*ca.* 1 mg) and (*S*)-(-)-α-methylbenzylamine (0.02 mL, *ca.* 0.153 mmol). The mixture was stirred at room temperature for 24 h, evaporated *in vacuo*, and analyzed by ^1H NMR. Only one diastereomeric amide could be detected whose ^1H NMR spectrum was identical to **8**.

(+)-Methyl 3-bromo-2,2,4-trimethylcyclohex-3-ene-5-one carboxylate 10. To a solution of **9** (12.54 g, 0.048 mol) in acetone (120 mL) was added K_2CO_3 (33.12 g, 0.24 mol) and methyl iodide (30 mL, *ca.* 0.48 mol). The mixture was stirred at room temperature for 4 h and diluted with Et_2O (200 mL). The resulting fine suspension was filtered through a pad of Celite® (5 mm) and the pad washed thoroughly with Et_2O (2 x 100 mL). The filtrate was concentrated *in vacuo* to afford **10** (12.68 g, 96%) as a brown oil, which was sufficiently pure to be used directly in the next stage. $[\alpha]_D^{23}$ +6.54 (c = 1, $CHCl_3$). IR (thin film) 2975, 2951, 1738, 1683, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, s), 1.41 (3H, s), 1.96 (3H, s), 2.62 and 2.76 (2H, ABX, J = 17.0, 10.0, 4.5 Hz), 2.99 (1H, X part of ABX, J = 10.0, 4.5 Hz), 3.70 (3H, s). HRMS (CI^+) calcd for $C_{11}H_{15}BrO_3$ ($M^+ + 1$) 275.0283. Found 275.0273.

(+)-Methyl 3-bromo-5α-hydroxy-2,2,4-trimethylcyclohex-3-ene carboxylate 11. To a stirred solution of **10** (12.06 g, 43.9 mmol) in MeOH (200 mL) at -15 °C was added $NaBH_4$ (1.66 g, 43.9 mmol), portion wise over *ca.* 2 min. The mixture was stirred at -15 °C for 40 min, quenched with saturated aqueous NH_4Cl (30 mL), and stirred at -15 °C for 5 min. The mixture was warmed to room temperature and diluted with water (100 mL). Most of the methanol was removed by evaporation *in vacuo* to a residual volume of *ca.* 100 mL, and the mixture was extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine (300 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a pale yellow oil. Purification of the oil by flash chromatography, using 2:1 pentane/Et_2O as eluent, gave a mixture of **11** and the corresponding epimeric alcohol (*ca.* 10:1 ratio) (12.16 g, 100%) which was taken through to the next stage as a mixture. $[\alpha]_D^{23}$ +2.53 (c = 1, $CHCl_3$). IR (thin film) 3418, 2976, 2951, 2874, 1733, 1636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, s), 1.24 (3H, s), 1.94 (3H, s), 1.95-2.03 (1H, m), 2.15-2.23 (1H, m), 2.68 (1H, dd, J = 7.5, 4.0 Hz), 3.69 (3H, s), 4.00 (1H, t, J = 6.0 Hz). HRMS (FAB) calcd for $C_{11}H_{16}BrO_3$ ($M^+ + 1$) 275.0283. Found 275.0276.

(+)-3-Bromo-2,2,4-trimethyl-6-oxabicyclo[3.2.1]oct-3-en-7-one 12. A mixture of crude **11** (6.95 g, 0.025 mol) (contaminated with *ca.* 9% of the epimeric alcohol), K_2CO_3 (17.30 g, 0.125 mol) and chlorobenzene (90 mL) was heated at reflux, under nitrogen, for 18 h. The mixture was cooled to room temperature, diluted with EtOAc (200 mL), and filtered through a pad of Celite® (5 mm). The pad was washed thoroughly with EtOAc (2 x 100 mL), and the filtrate was evaporated *in vacuo* to give a brown oil. Purification of the oil by flash chromatography over silica gel eluting with pentane/Et_2O (2:1) gave **12** (5.45 g, 89% from **10**) as a straw colored oil which solidified on standing to give a waxy beige solid. $[\alpha]_D^{23}$ +1.68 (c = 1, $CHCl_3$). IR (thin film) 2976, 2935, 1779, 1639 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.83 (3H, s), 1.26 (3H, s), 1.28 (1H, d, *J* = 12.0 Hz), 1.43 (1H, dt, *J* = 12.0, 5.0 Hz), 1.55 (3H, s), 2.03 (1H, dd, *J* = 5.0, 1.5 Hz), 3.77 (1H, dd, *J* = 5.0, 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.20, 26.68, 28.52, 32.97, 41.62, 49.89, 78.89, 134.45, 134.74, 176.46. HRMS (FAB) calcd for $C_{10}H_{13}BrO_2$ (M^+) 244.0099. Found 244.0092.

(+)-3-Bromo-2,2,4-trimethyl-6-oxa-7-methoxybicyclo[3.2.1]oct-3-ene 13. A solution of **12** (2.0 g, 8.16 mmol) in dry CH_2Cl_2 (40 mL) at -78 °C under nitrogen was treated with a 1.0 M solution of DIBAL-H in hexanes (8.16 mL, 8.16 mol), dropwise *via* syringe, over *ca.* 4 min (added down the inside walls of the flask so as to pre-cool the DIBAL-H solution). After stirring the mixture at -78 °C for 2 h another portion of DIBAL-H solution (4.1 mL, 4.1 mmol) was added as before. After a further 30 min the mixture was quenched at -78 °C with MeOH (1.7 mL) and warmed to 0 °C. Saturated aqueous NH_4Cl (3.4 mL) was added, and the mixture allowed to warm to room temperature and stirred for 10 min to give a gel. The mixture was diluted with CH_2Cl_2 (*ca.* 80 mL) to give a fine suspension, and filtered through a bed of coarse sand (*ca* 3 mm with filter paper on top) in a sintered glass funnel. The bed was washed thoroughly with CH_2Cl_2 (*ca.* 150 mL), and the resulting clear colorless filtrate was washed with saturated brine (200 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a colorless oil (2.05g). The oil was dissolved in trimethyl orthoformate (50 mL) and treated with CSA (*ca.* 20 mg). The mixture was stirred at room temperature for 18 h, Et_3N (0.05 mL) was added, and the mixture concentrated *in vacuo* to give a colorless liquid. Purification by flash chromatography over silica gel (*ca.* 20 g; 3 cm x 7 cm) using pentane/Et_2O (6:1) as eluent gave **13** (1.97 g, 92%) as a colorless oil. $[\alpha]_D^{23}$ +5.01 (c = 1, C_6H_6). IR (thin film) 2952, 1643 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 1.00 (3H, s), 1.09 (3H, s), 1.56 (1H, d, *J* = 11.0 Hz), 1.75 (3H, s), 2.00 (1H, dt, *J* = 11.0, 5.0 Hz), 2.11 (1H, d, *J* = 5.0 Hz), 3.24 (3H, s), 3.97 (1H, dd, *J* = 5.0, 1.0 Hz), 4.98 (3H, s). HRMS (FAB) calcd for $C_{11}H_{17}BrO_2$ (M^+ + 1) 260.0412. Found 260.0407.

(2'*S*,2*S*)-2,4-Dimethyl-2-[[2'-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one 17. To a 4 L kettle vessel, equipped with mechanical stirrer and cold finger condenser, was added a solution of **14** (13.97 g, 0.053 mol) in dry THF (600 mL) under dry nitrogen. Dry *t*-butanol (5.08 mL) was added and the solution cooled to -78 °C (dry ice/acetone bath). To the cold finger was added dry ice/acetone, and ammonia (600 mL ± 50 mL) condensed into the mixture. Potassium metal (5.5 g, 0.141 mol; enough to give a permanent dark blue color) was added to the mixture portion wise over *ca.* 10 min. The mixture was stirred at -78 °C for 30 min and quenched (at -78 °C) by addition of solid NH_4Cl (50 g) in one portion (color changed from dark blue to dark green, to dark yellow to bright yellow, to pale yellow to colorless, all within *ca.* 7 sec). An exhaust tube was fitted to the reaction vessel and the cooling bath mixture was replaced with freshly mixed

methanol/ice (1:1). The mixture was stirred at -20 °C for 20 min and the cooling bath mixture replaced with warm water (*ca.* 35 °C). Nitrogen was flushed through the apparatus for 40 min to remove the residual ammonia (absence of ammonia shown by holding moist Litmus paper in the exhaust gas stream). The mixture was diluted with Et_2O (600 mL), and filtered through a sintered glass funnel (vessel rinsed with more Et_2O (200 mL). The clear, colorless filtrate was washed with saturated brine (800 mL) and dried ($MgSO_4$). Evaporation *in vacuo* gave crude **15** (14 g, >97%) as a colorless oil, which was sufficiently pure for use in the next stage.

To a solution of **15** (14 g, 0.0528 mol) in dry THF (250 mL), at -78 °C under dry nitrogen, was added a solution of *n*-BuLi (2.5 M in hexanes; 23.2 mL, 0.058 mol) dropwise over *ca.* 7 min (the *n*-BuLi solution was pre-cooled by addition down the inside walls of the reaction vessel). The mixture was stirred at -78 °C for 30 min then allowed to warm to room temperature over *ca.* 20 min and stirred for 60 min. The mixture was cooled to 0 °C over *ca.* 10 min and treated with dry HMPA (15.33 mL, 0.088 mol), cooled to -78° C, and treated with methyl iodide (13.15 mL, 0.2112 mol). The mixture was stirred at -78 °C for 90 min, and poured into a saturated aqueous NH_4Cl (800 mL) and extracted with Et_2O (4 x 800 mL). The combined extracts were washed with water (x 2), saturated brine (x 2), and dried ($MgSO_4$). Evaporation *in vacuo* afforded **16** (13.84 g, 94% over 2 steps from **29**) as a yellow oil, which was sufficiently pure for use in the next stage.

A solution of **16** (13.84 g, 0.0496 mol) in THF (60 mL), at room temperature, was treated with concentrated HCl (1 mL) and stirred for 2 h. The mixture was poured into a saturated aqueous Na_2CO_3 (600 mL), extracted with Et_2O (3 x 600 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a pale yellow oil which crystallized on standing. Recrystallization from hexane/Et_2O (250 mL; 4:1) gave **17** as colorless crystalline solid suitable for X-ray crystallographic analysis [9.96 g in the first 2 crops, and 1.95 g obtained by flash chromatography (using hexane/EtOAc 2:1) of the mother liquor to give a total yield of 11.91 g, 91%]. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.76 (3H, s), 1.68-1.88 (4H, m), 2.38-2.64 (4H, m), 2.97-3.04 (1H, m), 3.14-3.22 (1H, m), 3.26 (3H, s), 3.31 (1H, dd, J = 10.0, 3.0 Hz), 3.46 (1H, dd, J = 10.0, 3.0 Hz), 4.24 (1H, m), 5.30 (1H, br s). ^{13}C (75 MHz, $CDCl_3$) δ 22.9, 23.9, 24.4, 26.6, 30.7, 35.5, 46.6, 57.2, 57.5, 58.8, 71.8, 125.1, 134.6, 170.0, 203.7.

(1*S*,2'*S*,2*S*)-2,4-Dimethyl-2-[[2'-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-ol 18 (R = H). To a 4 L kettle vessel, equipped with mechanical stirrer, thermometer, reflux condenser and nitrogen inlet was added $NaBH_4$ (19.66 g, 0.52 mol) and dry THF (1.30 L). A solution of zinc chloride (0.5 M in THF, 520 mL, 0.26 mol) was added to the mixture with vigorous stirring, and the heterogeneous mixture heated at reflux under nitrogen for 2 h. The mixture was cooled to -60 °C (over 30 min), and treated with a solution of **17** (34.48 g, 0.13 mol) in dry THF (300 mL) dropwise over *ca.* 10 min. The mixture was allowed to warm slowly to -15 °C (over *ca.* 1 h) and quenched by cautious addition of saturated aqueous NH_4Cl (2.0 L). The mixture was extracted with Et_2O (4 x 2.5 L), and the extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated *in vacuo* to give an orange oil (40 g). The crude product was dissolved in 9:1 EtOAc/MeOH (100 mL) and passed through a column of flash silica (400 g) using 9:1 EtOAc/MeOH as eluent. The product fractions were evaporated *in vacuo* to give **18** (34.92 g, 100%) as a colorless foam, which was sufficiently pure for use in the next stage. IR (thin film) 3424, 1628 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.64 (3H, s), 1.64-2.05 (8H, m), 3.30 (3H, s), 3.30-3.63 (5H, m), 4.04 (1H, dd, J = 11.0, 4.0),

4.29 (1H, m), 5.41 (1H, m). ^{13}C (75 MHz, $CDCl_3$) δ 19.8, 23.3, 25.2, 25.7, 26.4, 28.8, 48.1, 49.4, 58.0, 58.9, 70.2, 72.3, 124.5, 133.4, 175.0. HRMS (CI^+) calcd for $C_{15}H_{26}NO_3$ 268.1909 ($M^+ + 1$). Found 268.1913.

(1*S*,2'*S*,2*S*)-2,4-Dimethyl-2-[[2'-(methoxymethyl)pyrrolidinyl]carbonyl]-1-benzyl(oxy)-3-cyclohexene 19 (R = Bn). To a dispersion of hexane washed potassium hydride (35% in mineral oil, 14.67 g, *ca.* 0.128 mol) in dry THF (400 mL) was added a solution of **18** (28.7 g, 0.107 mol) and benzyl bromide (21.96 g, 0.128 mol) in dry THF (200 mL). To this mixture was added tetra *n*-butylammonium iodide (1 g), and the mixture stirred at room temperature for 24 h. Further aliquots of potassium hydride (35% in mineral oil, 5 g) and benzyl bromide (10 g) were added, and the mixture heated at reflux for 3 days. The mixture was cooled to room temperature and quenched by cautious addition of saturated aqueous NH_4Cl (600 mL), evaporated *in vacuo* to a residual volume of *ca.* 600 mL, and extracted with EtOAc (4 x 500 mL). The combined extracts were washed with water (2.0 L), saturated brine (1.5 L), dried ($MgSO_4$), and evaporated *in vacuo* to give a brown oil (51 g). The crude product was purified by flash chromatography over silica gel using 2:1 hexane/EtOAc as eluent to give **19** (24.09 g, 63%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (3H, s), 1.69 (3H, s), 1.69-2.12 (8H, m), 3.20-3.39 (**4H**, m), 3.36 (3H, s), 3.58 (1H, m), 3.97 (1H, m), 4.24 (1H, m), 4.57 (2H, q, J = 7.5 Hz), 5.22 (1H, s). Used directly in the next stage.

(1*R*,2*S*,5*S*,8*R*)-1,5-Dimethyl-2-benzyl(oxy)-8-iodo-6-oxabicyclo[3.2.1]octan-7-one 20. A solution of **19** (10 g, 0.028 mol) in THF (100 mL) was treated with water (100 mL) and iodine (14.21 g, 0.056 mol). The dark red mixture was stirred vigorously at room temperature for *ca* 18 h, and quenched with a 1.0 M solution of sodium thiosulphate (150 mL). The colorless mixture was extracted with Et_2O (4 x 200 mL), and the combined extracts were washed with 2N HCl (500 mL), water (500 mL), saturated brine (500 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **20** (9.70 g, 90%) as a colorless solid. IR (thin film) 2933, 2875, 1775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, s), 1.51 (3H, s), 1.68-1.83 (2H, m), 1.97-2.04 (1H, m), 2.37-2.48 (1H, m), 3.49 (1H, d, J = 4.5 Hz), 4.02 (1H, s), 4.44 (1H, d, J = 12.0 Hz), 4.66 (1H, J = 12.0 Hz), 7.25-7.42 (5H, m). ^{13}C (75 MHz, $CDCl_3$) δ 17.3, 23.5, 23.7, 26.5, 30.5, 50.6, 72.2, 74.6, 85.5, 127.2, 127.4, 128.2, 137.9, 174.8. HRMS (CI^+) calcd for $C_{16}H_{19}O_3I$ ($M^+ + 1$) 387.0459. Found 387.0459.

(1*S*,2*R*,3*R*)-1-Benzyl(oxy)-2-methyl-2-hydroxymethyl-3-hydroxy-4-methylenecyclohexane 24. To a solution of **20** (10 g, 25.9 mmol) in dry CH_2Cl_2 (300 mL) at -10 °C under dry nitrogen, was added a 1.0 M solution of DIBAL-H in CH_2Cl_2 (38.8 mL, 38.8 mmol) dropwise over *ca.* 15 min. The mixture was allowed to warm to 0 °C, stirred for 15 min, and treated with MeOH (5.5 mL) dropwise (caution: copious effervescence), and stirred for a further 10 min at 0 °C. Saturated aqueous NH_4Cl (11 ml) was added dropwise, and the mixture allowed to warm to room temperature. The mixture was stirred vigorously for 10 min, and filtered through a bed of coarse sand (*ca.* 4 mm) in a sintered glass filter funnel. The bed was rinsed with CH_2Cl_2 (100 mL), and the filtrate dried ($MgSO_4$) and concentrated *in vacuo* to afford **21** (9.81 g, 98%) as a colorless oil.

To a solution of **21** (9.8 g, 0.025 mol) in CH_2Cl_2 (350 mL) was added 1,5-diazabicyclo[5.4.0]undecene-5 (4.2 g, 27.6 mmol). The mixture was stirred at room temperature for 1 h and quenched with 0.1 N HCl (200 mL). The organic layer was separated, washed with water (200 mL), saturated brine (200 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **22** (6.44 g, 99%) as a colorless oil.

To a solution of **22** (5.25 g, 20.2 mmol) in MeOH (100 mL) was added $NaBH_4$ (763 mg, 20.2 mmol). The mixture was stirred at room temperature for 30 min and quenched with saturated aqueous NH_4Cl (100 mL). The mixture was concentrated *in vacuo* to a residual volume of *ca.* 100 mL and extracted with EtOAc (4 x 100 mL). The combined extracts were washed with water (200 mL), saturated brine (200 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **23** (4.95 g, 94%) as a colorless oil.

To a solution of 2,2,6,6-tetramethylpiperidine (12.84 mL, 0.076 mol) in dry toluene (90 mL) at 0 °C under dry nitrogen, was added a 2.5 M solution of *n*-BuLi in hexanes (30.42 mL, 0.076 mol) dropwise *via* syringe over *ca.* 6 min (internal reaction temperature rose to a maximum of 5 °C during addition). The mixture was stirred at 0 °C for 30 min and treated with a 1.8 M solution of diethyl aluminum chloride in toluene (42.25 mL, 0.076 mol) dropwise over *ca.* 10 min. The mixture was stirred at 0 °C for 40 min, and a solution of **23** (4.95 g, 0.019 mol) in dry toluene (70 mL) was added portion wise over *ca.* 15 min (syringe rinsed with 20 mL of dry toluene into the reaction mixture). The mixture was stirred at 0 °C for 20 h, and treated with MeOH (3 mL) (reaction mixture temperature rose rapidly to 25 °C). The mixture was recooled to 0 °C and treated with saturated NH_4Cl (6 ml) portion wise. The mixture was allowed to warm to room temperature, diluted with Et_2O (150 mL), and stirred vigorously for 15 min. The mixture was filtered through a pad of Celite® (*ca.* 5 mm), and the pad washed with Et_2O (3 x 100 mL). The filtrate was washed with saturated brine (200 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **24** (4.0 g, 81%) as a straw colored oil. IR (thin film) 3334, 2938, 1652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (3H, s), 1.39-1.53 (1H, m), 1.82-1.93 (1H, m), 2.08-2.18 (1H, m), 2.78-2.90 (1H, m), 3.47 (1H, d, J = 11.0 Hz), 3.74 (1H, d, J = 11.0 Hz), 3.89 (1H, dd, J = 10.5, 4.5 Hz), 3.93 (1H, s), 4.42 (1H, d, J = 11.5 Hz), 4.57 (1H, d, J = 11.5 Hz), 4.75 (1H, br s), 7.16-7.27 (5H, m). ^{13}C (75 MHz, $CDCl_3$) δ 14.5, 26.5, 28.0, 43.6, 68.9, 71.3, 75.9, 81.7, 111.4, 127.3, 127.4, 128.2, 139.0, 146.7. HRMS (CI^+) calcd for $C_{16}H_{22}O_3$ (M^+ + 1) 263.1647. Found 263.1635.

(1*S*,2*R*,3*R*)-1-Benzyl(oxy)-2-methyl-2-*tert*-butyldimethylsilyl(oxy)methyl-3-hydroxy-4-methylenecyclohexane 25. To a solution of **24** (4 g, 15.2 mmol) in CH_2Cl_2 (120 mL) was added Et_3N (3.17 mL, 23.0 mmol), *t*-butyldimethylsilyl chloride (2.53 g, 16.8 mmol) and 4-dimethylaminopyridine (*ca.* 10 mg). The mixture was stirred at room temperature for 48 h, diluted with CH_2Cl_2 (200 mL), and washed with 0.1 N HCl (200 mL). The aqueous extract was extracted with CH_2Cl_2 (200 mL), and the combined extracts were washed with 0.05 N HCl (400 mL), saturated aqueous Na_2CO_3 (400 mL), brine (400 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **25** (5.43 g, 95%) as a straw colored oil, which was sufficiently pure for use in the next stage. IR (thin film) 3462, 2932, 2857, 1464 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.05 (3H, s), 0.76 (3H, s), 0.87 (9H, s), 1.48-1.57 (1H, m), 1.87-1.94 (1H, m), 2.14-2.19 (1H, m), 2.40-2.49 (1H, m); 3.43 (1H, d, J = 9.5 Hz), 3.92 (1H, dd = J = 10.0, 4.5 Hz), 3.97 (1H, d, J = 9.5 Hz), 4.04 (1H, s), 4.39 (1H, d, J = 11.5 Hz), 4.61 (1H, d, J = 11.5 Hz), 4.81-4.83 (2H, m), 7.19-7.31 (5H, m). ^{13}C (75 MHz, $CDCl_3$) δ -5.7, -5.8, 15.1, 18.0, 25.8, 26.5, 28.2, 43.9, 63.2, 71.1, 75.3, 81.8, 110.8, 127.1, 127.2, 128.1, 139.3, 147.0. HRMS (CI^+) calcd for $C_{22}H_{36}O_3Si$ (M^+ + 1) 377.2512. Found 377.2511.

(1*S*,2*R*)-1-Benzyl(oxy)-2-methyl-2-*tert*-butyldimethylsilyl(oxy)methyl-4-thiophenylmethyl-3-cyclohexene 27. To a solution of **25** (1.18 g, 3.14 mmol) in Et_2O (100 mL) containing pyridine (1.27 mL, 16.0 mmol), at 0 °C under dry nitrogen, was added freshly distilled thionyl chloride (0.688 mL, 9.43 mmol)

dropwise over *ca.* 3 min. The mixture was added to cold water (50 mL), partitioned, and the aqueous layer further extracted with Et_2O (3 x 75 mL). The combined extracts were washed with brine (1 x 75 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **26** (1.23 g) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ -0.10 (6H, s), 0.83 (9H, s), 0.94 (3H, s), 1.69-1.80 (1H, m), 1.90-1.96 (1H, m), 2.05-2.19 (2H, m), 3.33 (1H, d, *J* = 7.5 Hz), 3.43 (1H, d, *J* = 7.5 Hz), 3.60 (1H, dd, *J* = 9.0, 3.0 Hz), 3.95 (2H, s), 4.43 (1H, *J* = 12.0 Hz), 4.64 (1H, *J* = 12.0 Hz), 5.47 (1H, s), 7.22-7.30 (5H, m). HRMS (CI^+) calcd for $C_{22}H_{35}O_2ClSi$ ($M^+ + 1$) 395.2173. Found 395.2163.

To a solution of crude **26** (1.23 g) in dry THF (70 mL) at 0 °C was added by cannular a freshly prepared solution of sodium thiophenoxide [7.86 mmol, 2.5 eq, prepared by addition of thiophenol (0.807 mL, 7.86 mmol) to hexane washed sodium hydride suspended in dry THF (21 mL)]. The mixture was allowed to warm to room temperature and stirred for 1.5 h, saturated aqueous NH_4Cl (100 mL) was added carefully, and the mixture extracted with CH_2Cl_2 (4 x 150 mL). The combined extracts were dried ($MgSO_4$), and evaporated *in vacuo* to give a colorless oil which was purified by flash chromatography over silica gel eluting with 30% EtOAc/hexane to give **27** (1.37 g, 2.77 mmol, 88%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.91 (9H, s), 1.76-1.95 (2H, m), 2.08-2.19 (1H, m), 2.30-2.38 (1H, m), 3.30 (2H, s), 3.46 (2H, s), 3.60 (1H, dd, *J* = 10.0, 3.0 Hz), 4.46 (1H, d, *J* = 12.0 Hz), 4.68 (1H, d, *J* = 12.0 Hz), 5.19 (1H, s), 7.18-7.39 (10H, m). ^{13}C (75 MHz, $CDCl_3$) δ -5.5, 18.2, 18.4, 22.7, 25.8, 41.9, 68.8, 71.1, 76.6, 126.3, 127.2, 127.4, 128.1, 128.5, 131.0, 131.9, 132.1, 136.1, 139.3. HRMS (CI^+) calcd for $C_{28}H_{41}O_2SSi$ ($M^+ + 1$) 469.2596. Found 469.2586.

[(1*R*,2*S*)-1-Methyl-2-benzyl(oxy)-5-thiophenylmethyl-5-cyclohexenyl]acetaldehyde 28. To a solution of **27** (500 mg, 1.06 mmol) in dry THF (10 mL) was added a 1 M solution of TBAF in THF (1.6 mL, 1.6 mmol). The mixture was stirred at room temperature for 18 h and treated with water (30 mL). The mixture was extracted with Et_2O (5 x 30 mL), and the combined extracts were washed with brine (100 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a colorless oil. Purification by flash chromatography over silica gel eluting with 2:1 Et_2O/hexane gave **27a** (368 mg, 98%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, s), 1.62-1.72 (1H, m), 1.98-2.05 (1H, m), 2.13-2.32 (2H, m), 3.18 (1H, d, *J* = 10.5 Hz), 3.34 (1H, d, *J* = 10.5 Hz), 3.41 (2H, s), 3.56 (1H, dd, *J* = 11.0, 3.0 Hz), 4.44 (1H, d, *J* = 11.5 Hz), 4.64 (1H, d, *J* = 11.5 Hz), 4.95 (1H, s), 7.19-7.36 (10H, m). ^{13}C (75 MHz, $CDCl_3$) δ 17.8, 22.6, 26.2, 42.0, 42.2, 69.9, 70.7, 78.1, 126.8, 127.4, 128.2, 128.7, 130.9, 131.6, 134.1, 135.2, 138.7.

To a mixture of sulfur trioxide pyridine complex (5.57 g, 35.0 mmol), **27a** (3.1 g, 8.75 mmol) and Et_3N (8.52 mL, 61.25 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under dry nitrogen, was added dry DMSO (8.69 mL, 122.5 mmol). The mixture was stirred at 0 °C for 1 h and warmed to room temperature. After 4 h at room temperature the mixture was cooled to 0 °C and treated with 1 N HCl (200 mL). The mixture was extracted with CH_2Cl_2 (4 x 100 mL), and the combined extracts were washed with brine (400 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a colorless semi-solid (*ca.* 10 g) which was found to contain triethylammonium chloride. The crude product was dissolved in Et_2O (100 mL), washed with water (100 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **27b** (2.89 g, 94%) as a light orange oil, which was sufficiently pure for use in the next stage. IR (thin film) 2937, 1724 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, s), 1.76-1.95 (2H, m), 2.20-2.25 (1H, m), 2.31-2.39 (1H, m), 3.41 (2H, s), 3.77 (1H, dd, *J* = 9.5, 3.5 Hz), 4.43 (1H, d, *J* = 11.0 Hz),

4.61 (1H, d, J = 11.0 Hz), 4.93 (1H, s), 7.20-7.36 (10H, m), 9.15 (1H, s). ^{13}C (75 MHz, $CDCl_3$) δ 16.2, 22.8, 25.2, 42.1, 53.2, 70.8, 75.3, 124.5, 127.0, 127.46, 127.52, 128.3, 128.7, 132.0, 134.8, 136.5, 138.3, 202.5. HRMS (CI$^+$) calcd for $C_{22}H_{25}O_2S$ (M^+ + 1) 353.1575. Found 353.1571.

To a stirred suspension of $MeOCH_2PPh_3Cl$ (22.5 g, 0.066 mol) in dry toluene (80 mL), at 0 °C under dry nitrogen was added a 0.5 M solution of KHMDS in toluene (131.2 mL, 0.066 mol) dropwise over *ca.* 15 min. The mixture was stirred at 0° C for 2 h and a solution of **27b** (5.78 g, 0.0164 mol) in dry toluene (20 mL) was added dropwise over *ca.*15 min (syringe rinsed with 10 mL of extra toluene into the mixture). The mixture was stirred at 0 °C for 1 h and warmed to room temperature. After 2 h at room temperature the mixture was diluted with EtOAc (400 mL), washed with water (400 mL), and the aqueous phase was extracted with EtOAc (400 mL). The combined extracts were washed with saturated brine (600 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **27c** as an oil, which was taken through to the next stage without purification.

The enol ether **27c** was dissolved in THF (120 mL) and treated with 2 M HCl (40 mL). After 18 h the mixture was neutralized by cautious addition of solid $NaHCO_3$, and the mixture was evaporated *in vacuo* to a residual volume of *ca.* 40 mL and extracted with EtOAc (3 x 80 mL). The combined extracts were washed with saturated brine (200 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a semi-solid containing **28** and triphenyl phosphine oxide. The crude product was dissolved in THF (20 mL) and added dropwise to vigorously stirred hexane (150 mL). The resulting precipitate of triphenyl phosphine oxide was filtered off, and the filtrate was evaporated *in vacuo* to give an orange oil which was purified by flash chromatography over silica gel eluting with 10:1 hexane/EtOAc to give **28** (5.16 g, 86%) as a colorless oil. IR (thin film) 2938, 1715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, s), 1.60-1.72 (1H, m), 1.97-2.05 (1H, m), 2.14-2.35 (4H, m), 3.29 (1H, dd, J = 7.5, 2.0 Hz), 3.42 (2H, s), 4.35 (1H, d, J = 9.5 Hz), 4.61 (1H, d, J = 9.5 Hz), 5.17 (1H, m), 7.19-7.37 (10H, m), 9.46 (1H, t, J = 3.0 Hz). ^{13}C (75 MHz, $CDCl_3$) δ 21.3, 22.5, 26.4, 40.1, 41.8, 53.6, 70.7, 80.3, 126.8, 127.5, 127.6, 128.3, 128.7, 131.5, 132.2, 132.3, 135.2, 138.5, 202.6. HRMS (CI$^+$) calcd for $C_{23}H_{27}O_2S$ (M^+ + 1) 367.1721. Found 367.1732.

Ketosulfide 30. To a solution of **13** (105 mg, 0.402 mmol, 1.12 eq) in Et_2O (3.0 mL) at -78 °C under argon was added *t*-BuLi (1.68 M in pentane, 478 µl, 0.804 mmol, 1.24 eq). The yellow mixture was stirred at -78 °C for 30 min and added via cannular to a solution of **28** (132 mg, 0.360 mmol) in dry Et_2O (3.0 mL) at -78 °C. The mixture was allowed to warm to -20 °C over 1 h and the resulting colorless solution was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined fractions were dried ($MgSO_4$), and evaporated *in vacuo* to give a colorless oil (191 mg) which was purified by flash column chromatography eluting with 20% EtOAc/hexane containing Et_3N to give a diastereomeric mix of alcohols **29** (approximately 1:1) (151 mg, 0.275 mmol).

To a solution of the alcohols **29** (151 mg, 0.275 mmol) in dry CH_2Cl_2 (25 mL) was added solid sodium bicarbonate (100 mg) and Dess-Martin reagent (175 mg, 0.413 mmol, 1.5 eq). After stirring at room temperature for 2 h, the reaction was quenched with 1 M sodium thiosulphate solution (5 mL), saturated $NaHCO_3$ solution (5 mL), water (5 mL). CH_2Cl_2 (30 mL) was added and the reaction stirred vigorously for 10 min to give two clear layers. The reaction was partitioned and the aqueous layer further extracted with CH_2Cl_2 (2 x 75 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The resulting oil was purified by flash column chromatography eluting with 15% EtOAc/hexane containing Et_3N to give the desired

compound **30** as a colorless oil (140 mg, 0.256 mmol, 71% over two steps). IR (thin film) 2946, 1694 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.91 (3H, s), 0.98 (3H, s), 1.13 (3H, s), 1.38 (3H, s), 1.52-1.69 (3H, m), 1.86 (1H, d, *J* = 5.0 Hz), 1.94-2.11 (3H, m), 2.35 (1H, d, *J* = 19.5 Hz), 2.60 (1H, d, *J* = 19.5 Hz), 3.18 (2H, s), 3.20 (3H, s), 3.56 (1H, dd, *J* = 10.5, 3.5 Hz), 3.81 (1H, d, *J* = 4.5 Hz), 4.03 (1H, d, *J* = 12.0 Hz), 4.38 (1H, d, *J* = 12.0 Hz), 4.92 (1H, s), 5.58 (1H, s), 6.64-7.25 (10H, m). ^{13}C (75 MHz, C_6D_6) δ 19.0, 21.5, 22.6, 25.8, 26.2, 28.5, 29.7, 37.3, 39.7, 41.7, 53.5, 54.3, 54.5, 70.9, 78.1, 79.9, 105.2, 126.3, 127.5, 128.5, 128.9, 130.9, 131.4, 132.8, 134.1, 137.0, 139.7, 141.1, 207.1. HRMS (CI^+) calcd for $C_{34}H_{43}O_4S$ (M^+ + 1) 547.2882. Found 547.2887.

Ketosulfone 31. To a solution of **30** (399 mg, 0.730 mmol), in CH_2Cl_2 (1.5 mL), H_2O (1.5 mL), was added aliquat 366 (approx. 100 μl), $Na_2WO_4.2H_2O$ (catalytic) and 30% aq hydrogen peroxide solution (450 μl). The mixture was stirred vigorously at room temperature for 1 h and a further portion of 30% aq hydrogen peroxide solution (450 μl).was added. After 3 h the mixture was quenched with saturated aqueous $NaHSO_3$ (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and Et_2O (40 mL), and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. to give an oil which was purified by flash column chromatography eluting with 30% EtOAc/hexane containing Et_3N to give **31** (359 mg, 0.620 mmol, 85%) as a colorless oil. IR (thin film) 2946, 1693 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.89 (3H, s), 0.96 (3H, s), 0.99 (3H, s), 1.35 (3H, s), 1.44-1.61 (3H, m), 1.64 (1H, d, *J* = 5.0 Hz), 1.91-2.03 (2H, m), 2.13-2.15 (1H, m), 2.23 (1H, d, *J* = 19.5 Hz), 2.51 (1H, d, *J* = 19.5 Hz), 3.18 (3H, s), 3.35 (2H, s), 3.43 (1H, dd, *J* = 10.0, 3.0 Hz), 3.81 (1H, d, *J* = 5.0 Hz), 4.00 (1H, d, *J* = 12.0 Hz), 4.34 (1H, d, *J* = 12.0 Hz), 4.88 (1H, s), 5.33 (1H, s), 6.91-7.18 (8H, m), 7.68-7.70 (2H, m). ^{13}C (75 MHz, C_6D_6) δ 19.0, 21.0, 22.5, 25.8, 27.4, 28.4, 29.9, 37.3, 39.9, 53.1, 54.2, 54.5, 64.1, 70.1, 78.0, 79.0, 125.0, 128.5, 128.9, 133.2, 134.2, 139.0, 139.3, 139.5, 140.9, 207.1. HRMS (CI^+) calcd for $C_{34}H_{43}O_6S$ (M^+ + 1) 579.2780. Found 579.2771.

Oximino ether 33. A solution of **31** (R = Me) (359 mg, 0.62 mmol) in THF/ 4 N HCl solution (1:1, 36 mL) was stirred at room temperature for 1.5 h. Saturated aqueous $NaHCO_3$ (50 mL) was carefully added and the mixture extracted with CH_2Cl_2 (3 x 75 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give **31** (R = H) (355 mg) as a white foam.

To a solution of the crude **31** (R = H) in EtOH (27 mL) was added hydroxylamine hydrochloride (65 mg, 0.930 mmol, 1.5 eq.) and Et_3N (110 mg, 151 μl, 1.09 mmol, 1.75 eq). The mixture was stirred at room temperature for 1.5 h during which time it became homogeneous. The mixture was evaporated *in vacuo* and partitioned between Et_2O (150 mL) and saturated aqueous NH_4Cl (100 mL). The aqueous layer was further extracted with Et_2O (2 x 150 mL) and the combined organic extracts dried ($MgSO_4$), and evaporated *in vacuo* to give **32** as a white foam (314 mg, 0.542 mmol, 87%).

To a solution of **32** (179 mg, 0.309 mmol) in dry DMF (4 mL) was added *N*-chlorosuccinimide (41 mg, 0.309 mmol, 1.0 eq) and the mixture was stirred for 40 min at room temperature. A further portion of *N*-chlorosuccinimide (4 mg, 0.1 eq) was added, and after stirring for 30 min the mixture was treated with Et_3N (2 mL), and after 30 min, diluted with water (130 mL), and extracted with Et_2O (3 x 150 mL). The combined extracts were washed with water (2 x 50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a colorless oil which was purified by flash column chromatography over Florisil® eluting with 75% EtOAc/hexane to give

33 as a colorless oil (137 mg, 0.237 mmol, 77%). IR (thin film) 3280, 2952, 1693 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.99 (3H, s), 1.11 (3H, s), 1.17 (3H, s), 1.32 (3H, s), 1.49-1.61 (4H, m), 2.12-2.20 (4H, m), 2.47 (1H, d, J = 19.5 Hz), 33.36 (2H, s), 3.46 (1H, t, J = 7.0 Hz), 3.85 (1H, s), 4.09 (1H, d, J = 12.0 Hz), 4.41 (1H, d, J = 12.0 Hz), 5.32 (1H, s), 7.00 (2H, t, J =7.5 Hz), 7.11-7.27 (6H, m), 7.63 (1H, s), 7.78 (2H, d, J = 7.0 Hz). ^{13}C (75 MHz, C_6D_6) δ 18.9, 20.7, 22.5, 26.7, 26.9, 28.0, 33.0, 38.5, 39.8, 48.9, 53.1, 64.2, 71.1, 78.6, 80.5, 125.2, 127.9, 128.6, 129.0, 130.8, 133.4, 138.7, 139.3, 139.4, 143.5, 160.0, 206.5. HRMS (CI^+) calcd for $C_{33}H_{40}NO_6S$ (M^+ + 1) 578.2576. Found 578.2552.

Hydroxamic ether 34. To a solution of **33** (54 mg, 0.094 mmol) in *o*-dichlorobenzene (27 mL) was added $EtNPr^i_2$ (121 mg, 163 μl, 0.935 mmol, 10 eq) under argon at room temperature. The mixture was heated (in a sealed tube) at 160 °C for 22 h, cooled to room temperature, and evaporated *in vacuo*. Purification of the crude mixture by flash column chromatography over silica gel eluting with 40% EtOAc/hexane gave **34** (10 mg, 0.023 mmol, 24%) as a white solid. The white solid was recrystallised by slow evaporation from Et_2O under a hexane atmosphere to give crystals suitable for X-ray crystallographic analysis. M.p. 195-197 °C. IR (thin film) 2921, 1738, 1703 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) 0.73 (3H, s), 0.91 (3H, s), 0.95 (3H, s), 1.19-1.35 (1H, m), 1.64-1.74 (1H, m), 1.77-1.84 (1H, m), 1.90-1.93 (2H, m), 1.96 (3H, s), 2.02-2.08 (1H, m), 2.11-2.18 (1H, m), 2.68 (1H, d, J = 12.5 Hz), 3.16 (1H, d, J = 12.5 Hz), 3.73 (1H, dd, J = 11.5, 4.5 Hz), 4.18 (1H, s), 4.41 (2H, q, J = 10.5 Hz), 4.83 (1H, s), 4.96 (1H, s), 5.10 (1H, s), 7.12 (1H, t, J = 7.5 Hz), 7.24 (2H, t, J = 7.5 Hz), 7.56 (2H, d, J = 7.5 Hz). HRMS (CI^+) calcd for $C_{27}H_{34}NO_4$ (M^+ + 1) 436.2488. Found 436.2476.

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References and Footnotes

† Author for inquiries concerning the X-ray data.

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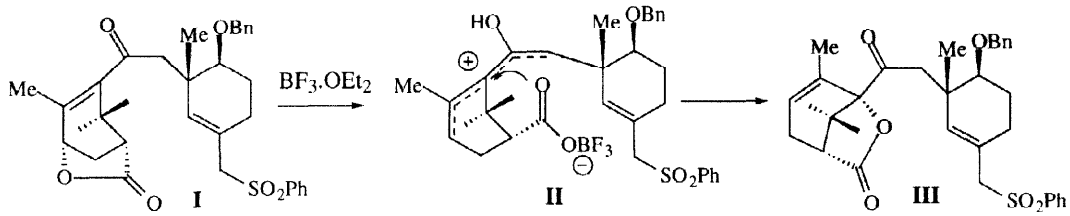
24. We have observed that exposure of the lactone **I** to $BF_3.OEt_2/CH_2Cl_2$ gave the rearranged lactone **III**, which presumably arises from the oxydienyl cation **II**.



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