Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5115–5121

TETRAHEDRON

A concise enantioselective synthesis of a fully oxygen substituted ring A taxol precursor

Olivier Roy, Gerald Pattenden,* David C. Pryde and Claire Wilson

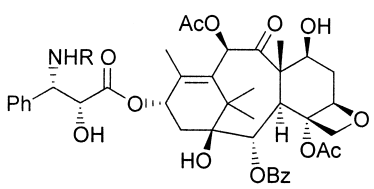
School of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK

Received 27 February 2003; revised 3 April 2003; accepted 28 April 2003

Abstract—A concise synthesis of the oxygen substituted ring A compound **2** found in Taxol® **1a** and Taxotere® **1b** starting from 2,2-dimethylcyclohexane-1,3-dione and proceeding via the key intermediates **8** and **11**, is described. The absolute configuration of **2** was established from an X-ray crystal structure determination of a 4-bromophenylbenzoate derivative, viz. **15**. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Taxol® (paclitaxel) **1a** and Taxotere® (docetaxel) **1b** are amongst the most effective chemotherapeutic agents for the treatment of cancer, particularly ovarian and breast cancers, in the clinic today.[1] However, after six published total syntheses[2] and a plethora of ingenious synthetic designs to the unique ring system in the natural product,[3] Taxol **1a** remains one of the most revered and sought-after targets to challenge the synthetic chemist. During our own synthetic endeavours we have examined the scope for a range of cascade radical-mediated cyclizations to elaborate the 6, 8, 6-tricyclic ABC-ring system in the taxoids.[4] To complement these studies, and as a prelude to extending them to more advanced oxygenated precursors, we required a robust synthesis of the fully oxygen substituted ring A system in **1**. In this paper a concise enantioselective synthesis of the protected ring A tetrol **2** starting from the readily available 2,2-dimethylcyclohexane-1,3-dione, and proceeding via the allylic alcohol **8** and the cyclic carbonate **11** as key intermediates, is described.[5]



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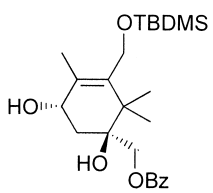


2

a, R = Bz; Taxol®

b, R= CO_2But; Taxotere®

2. Results and discussion

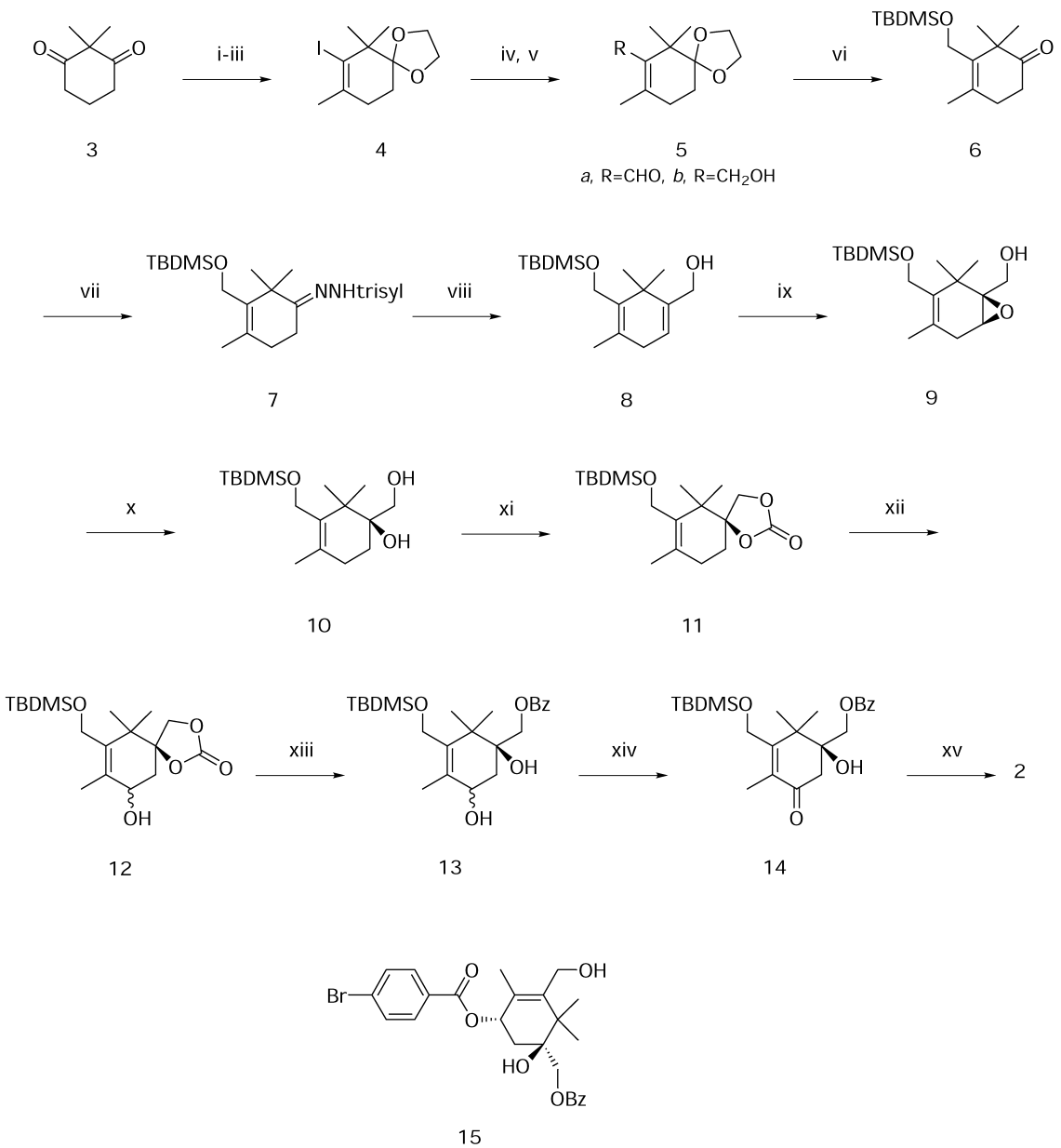
Thus, 2,2-dimethylcyclohexane-1,3-dione **3** was first converted into the known vinyl iodide **4** using a modified literature procedure.[6] Metallation of **4**, using butyllithium, followed by quenching the resulting vinyllithium species with dimethylformamide next gave the unsatured aldehyde **5a** which was then reduced to the corresponding alcohol **5b** using Luche conditions.[7] After deprotection of the dioxolan group in **5b**, the resulting hydroxymethyl substituted cyclohexenone was protected as its TBDMS ether **6**[8] and then converted into the known trisylhydrazone **7**.[6,8] Under Shapiro conditions,[9] the hydrazone **7** was next converted into the corresponding vinyllithium species, which on quenching with dimethylformamide followed by Luche[7] reduction of the resulting α,β-unsatured aldehyde produced the key allylic alcohol intermediate **8**. The epoxidation of **8** under standard Sharpless conditions[10] gave the β-epoxide **9** with 86% ee, which underwent regioselective reduction using lithium aluminium hydride leading to the crystalline diol **10** in 96% yield (Scheme 1).

After protection of the diol **10** as the corresponding cyclic carbonate **11**, treatment with selenium dioxide gave a 1:1 mixture of diasteroisomers of the corresponding allylic alcohol **12**. Treatment of **12** with phenyllithium resulted in regioselective ring-opening of the carbonate and led to the 1,3-diol **13** which was then oxidized using PCC at 0°C leading to the conjugated enone **14** in excellent overall

Keywords: taxol; ring A; synthesis.

* Corresponding author. Tel.: +44-115-951-3530; fax: +44-115-951-3535; e-mail: gp@nottingham.ac.uk

0040–4020/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4020(03)00699-9



Scheme 1. *Reagents, conditions and yields*: (i) Ethylene glycol, (±)-CSA, benzene, reflux 88%; (ii) LiHMDS, MeI, THF, −78°C, 89%; (iii) (a) NH_2NH_2, Et_3N, ethanol, reflux; (b) DBN, I_2, ether, 61%; (iv) *t*BuLi, DMF, THF, −78°C; (v) $NaBH_4$, $CeCl_3$, MeOH, 0°C, 55% (3 steps); (vi) HCl_2M; then, TBDMS-CI, imidazole. DCM, 92%; (vii) trisylhydrazine, DCM, 87%; (viii) (a) *n*BuLi, DMF, THF, −78°C; (b) $NaBH_4$, $CeCl_3$, MeOH, 0°C, 62% (2 steps); (ix) (+)-L-DET, $Ti(OiPr)_4$, TBHP, MS 3 Å, DCM, −23°C, 81%, ee 86%; (x) $LiAlH_4$, ether, 0°C, 96%; (xi) phosgene, pyridine, DCM, −78°, 98%; (xii) SeO_2, 1,4-dioxane, 100°C, 44%; (xiii) PhLi, THF, −78°C, 86%; (xiv) PCC, NaOAc, DCM, 0°C, 95%; (xv) $Na(OAc)_3BH$, AcOH, MeCN, 0°C, 62%.

yield. Finally, reduction of **14** using sodium triacetoxyborohydride in acetic acid and acetonitrile at 0°C gave the target taxol ring A tetrol derivative **2** (84% ee) as a colorless oil. The absolute configuration of **2** was confirmed by conversion into the crystalline 4-bromophenylbenzoate derivative **15** followed by an X-ray crystal structure determination.

3. Experimental

3.1. General

All melting points were determined on a Kŏfler hot stage apparatus and are uncorrected. Optical rotations were measured on a JASCO DIPA-370 polarimeter; $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were obtained using a Perkin–Elmer 1600 series FT-IR instrument as either nujol, liquid films or as dilute solutions in spectroscopic grade chloroform. Proton NMR spectra were recorded on either a Bruker WM250 (250 MHz), a Bruker AM400 (400 MHz), a Bruker DRX360 (360 MHz), a Bruker DRX (500 MHz) spectrometer as dilute solutions in deuterochloroform. Chemical shifts are recorded relative to a solvent standard and the multiplicity of a signal is designated by one of the following abbreviations: s=singlet; d=doublet; t=triplet; q=quartet; br=broad; m=multiplet. All coupling constants, *J*, are reported in Hertz. Carbon-13

NMR spectra were recorded on either a Bruker AM400 (100.6 MHz), a Bruker DRX360 (90.5 MHz) instrument. The spectra were recorded as dilute solutions in deuterochloroform with chemical shifts reported relative to a solvent standard on a broad band decoupled mode and the multiplicities obtained using a DEPT sequence. The following symbolisms are used for the multiplicities in carbon-13 spectra: q=primary methyl; t=secondary methylene; d=tertiary methine; s=quarternary. Mass spectra were recorded on a AE1 MS-902, MM-70E or VG Autospec spectrometer using electron ionization (EI) techniques. Microanalytical data were obtained on a Perkin–Elmer 240B elemental analyser.

Flash chromatography was performed on Merck silica gel 60 as the stationary phase and the solvents employed were either of analytical grade or were distilled before use. All reactions were monitored by TLC using Merck silica gel 60 F_{254} precoated plastic backed plates, which were visualized with ultraviolet light and then with either vanillin solution, basic potassium permanganate solution, or phosphomolybdic acid solution. Commonly used organic solvents were dried by distillation from the following: THF (sodium benzophenone ketyl), dichloromethane (calcium hydride) and methanol (magnesium methoxide). Other organic solvents and reagents were purified by accepted literature procedures. Solvents were removed on a Büchi rotary evaporator using water aspirator pressure. Petrol refers to light petroleum with distillation range 40–60°C. Where necessary, reactions requiring anhydrous conditions were performed in a flame dried apparatus under a nitrogen atmosphere.

3.1.1. Ethylenedioxa-2-iodo-1,3,-trimethyl-cyclohex-1-ene 4.[6] A mixture of 2,2-dimethylcyclohexane-1,3-dione **3** (5 g, 30 mmol), ethylene glycol (9.2 ml, 180 mmol) and (±)-camphor-10-sulfonic acid (1.7 g, 7.1 mmol) in benzene was heated under reflux for 30 min and then allowed to cool to room temperature. The mixture was diluted with water (15 ml) and diethyl ether (25 ml) and the separated organic layer was dried over $MgSO_4$ and concentrated in vacuo to leave a colorless oil. Purification by chromatography on silica, eluting with 20% ether in light petroleum gave the corresponding mono-ketal (3.8 g, 88%)[6] as an oil, ν_{max} (film)/cm^{-1} 1711; δ_H (250 MHz; $CDCl_3$) 1.17 (s, 6H, 2×Me), 1.73–1.84 (m, 2H), 1.88–1.96 (m, 2H), 2.44 (t, J=6.7 Hz, 2H, CH_2CO), 3.97 (s, 4H, 2×OCH_2); δ_C (67.8 MHz; $CDCl_3$) 19.2 (t), 20.0 (2×q), 29.8 (t), 36.5 (t), 53.7 (s), 65.4 (2×t), 112.1 (s), 212.4 (s).

A solution of *n*-butyl-lithium (32.7 ml, 50 mmol) in hexanes (1.6 M) was added dropwise over 30 min to a stirred solution of hexamethyldisilazane (11.1 ml, 50 mmol) in dry THF (35 ml) at −78°C under nitrogen. The mixture was stirred at −78°C for 1 h and then a solution of the mono-ketal (8 g, 50 mmol) in dry THF (20 ml) was added dropwise over 10 min. The mixture was stirred at −78°C for a further 1 h and then methyl iodide (6.5 ml, 0.1 mol) in dry THF (10 ml) was added dropwise over 20 min. After 30 min at −78°C, the mixture was allowed to warm to room temperature over 3 h and then quenched with water (20 ml) and diluted with ether (20 ml). The organic layer was separated and the aqueous layer was extracted with ether (2×25 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (20 ml), then dried over $MgSO_4$ and concentrated in vacuo to leave the corresponding α-methyl ketone (7.7 g, 89%)[6] as a colorless oil. ν_{max} (film)/cm^{-1} 1709; δ_H (250 MHz; $CDCl_3$) 1.06 (d, J=6.6 Hz, 3H, Me), 1.08 (s, 3H, Me), 1.30 (s, 3H, Me), 1.42 (m, 1H, CH), 1.79 (ddd, J=13.9, 4.2, 4.2 Hz, 1H, CH), 1.86–1.96 (m, 1H), 2.16 (ddd, J=13.9, 13.9, 4.6 Hz, 1H, CH), 2.62–2.76 (m, 1H, CHCO), 3.91–4.01 (m, 4H, 2×OCH_2); δ_C (67.8 MHz; $CDCl_3$) 14.7 (q), 16.5 (q), 24.0 (q), 28.2 (t), 30.1 (t), 39.1 (d), 54.8 (s), 65.3 (2×t), 113.6 (s), 213.7 (s); *m/z* (EI) 198.1252 (M^+. $C_{11}H_{18}O_3$ requires 198.1256), which was used immediately without further purification.

A mixture of the ketone (9.7 g, 48.9 mmol) and hydrazine hydrate (11.85 ml, 0.22 mol) in triethylamine (13 ml, 78.2 mmol) and ethanol (40 ml) was heated under reflux for 13 days. The mixture was allowed to cool to room temperature and the volatile materials were then removed in vacuo. The residue was purified by chromatography on silica, eluting with ether, to give the corresponding hydrazone (8.7 g) as a colorless solid. DBN (35.5 ml, 0.288 mol) was added to a solution of the hydrazone in ether (80 ml) and then the mixture was stirred at 25°C for 10 min. A solution of iodine (28.2 g, 0.11 mol) in ether (280 ml) was added dropwise over 15 min and the mixture was stirred at room temperature for 30 min and then quenched with saturated aqueous sodium hydrogen carbonate (50 ml). The organic layer was separated and the aqueous layer was extracted with ether (3×50 ml). The combined organic layers were dried over $MgSO_4$ and then concentrated in vacuo. Purification by chromatography on silica, eluting with 30% ether in light petroleum, gave the vinyl iodide (9.2 g, 61%) as a colorless oil.[6] ν_{max} (film)/cm^{-1} 1703, 1631; δ_H (250 MHz; $CDCl_3$) 1.25 (s, 6H, 2×Me), 1.89 (t, J=6.6 Hz, 2H, CH_2) 2.01 (s, 3H, Me), 2.41 (t, J=6.6 Hz, 2H, C:CCH_2), 4.10 (s, 4H, 2×OCH_2); δ_C (67.8 MHz; $CDCl_3$) 26.2 (2×q), 26.8 (t), 30.4 (q), 31.4 (t), 47.5 (s), 64.9 (2×t), 109.9 (s), 113.9 (s), 136.6 (s); *m/z* (EI) 181.1236 (M^+−I. $C_{11}H_{17}O_2$ requires 181.1228).

3.1.2. 3-(*tert*-Butyldimethylsiloxymethyl)-2,2,4-trimethyl-cyclohex-3-ene-1-one 6.[8] A solution of *tert*-butyl-lithium (40 ml, 60 mmol) in pentane (1.5 M) was added dropwise over 10 min to a solution of the iodide **4** (9.2 g, 30 mmol) in dry THF (30 ml) at −78°C. After 30 min at −78°C, DMF (8.8 ml, 120 mmol) was added in one portion and the mixture was stirred at −78°C for 40 min and then allowed to warm to room temperature over 1 h. The reaction was quenched with water (10 ml) and the separated aqueous layer was then extracted with ether (2×25 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (20 ml) then dried over $MgSO_4$ and concentrated in vacuo to leave the aldehyde **5a** (5 g) as a yellow oil.

Cerium trichloride heptahydrate (25.7 g, 68.8 mmol) was added in one portion to a solution of the aldehyde **5a** (5 g) in methanol (100 ml) at 0°C and then sodium borohydride (4 g, 105 mmol) was added portionwise over 20 min. The mixture was stirred at 0°C for 30 min, then water (15 ml) and 2 M HCl (30 ml) were added and the mixture was stirred at room temperature for a further 20 min. The organic layer was separated and the aqueous layer was

extracted with ethyl acetate (2×25 ml). The combined organic extracts were dried over $MgSO_4$ then concentrated in vacuo to leave a residue which was purified by chromatography on silica, eluting with 50% ether in light petroleum to give the ketone corresponding to deprotected **5b** (2.75 g, 55%) as a clear oil,[8] ν_{max} (film)/cm^{-1} 1708; δ_H (250 MHz; $CDCl_3$) 1.16 (s, 6H, 2×Me), 1.81 (s, 3H, Me), 2.35 (t, J=6.8 Hz, 2H, C:CCH_2) 2.49 (t, J=6.8 Hz, 2H, CH_2CO), 4.13 (s, 2H, CH_2OH); δ_C (67.8 MHz; $CDCl_3$) 19.9 (q), 24.5 (2×q), 31.6 (t), 35.6 (t), 47.0 (s), 58.7 (t), 133.3 (s), 136.4 (s), 214.9 (s); m/z (EI) 168.1161 (M^+. $C_{10}H_{16}O_2$ requires 168.1150).

tert-Butyldimethylsilyl chloride (2.7 g, 17.7 mmol) was added to a solution of imidazole (2.7 g, 40 mmol) in dichloromethane (60 ml) at room temperature. After 30 min, a solution of the aforementioned ketone (2.7 g, 16.1 mmol) in dichloromethane (8 ml) was added dropwise over 10 min. The mixture was stirred at room temperature for 14 h and then quenched with water (20 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×25 ml). The combined organic layers were dried over $MgSO_4$, then concentrated in vacuo to leave a residue which was purified by chromatography on silica, eluting with 20% ether in light petroleum to give the silyl ether (4.18 g, 92%) as colorless oil.[8] ν_{max} (film)/cm^{-1} 1716; δ_H (250 MHz; $CDCl_3$) 0.01 (s, 6H, Me_2Si), 0.81 (s, 9H, *tBu*), 1.12 (s, 6H, 2×Me), 1.70 (s, 3H, Me), 2.29 (t, J=6.9 Hz, 2H, C:CCH_2) 2.44 (t, J=6.9 Hz, 2H, CH_2CO), 4.06 (s, 2H, CH_2OSi); δ_C (67.8 MHz; $CDCl_3$) −5.4 (2×q), 18.6 (s), 19.4 (q), 24.7 (2×q), 25.9 (3×q), 31.8 (t), 35.8 (t), 47.3 (s), 59.2 (t), 131.8 (s), 135.7 (s), 215.3 (s); m/z (EI) 226.1322 (M^+−tBu. $C_{12}H_{22}O_2Si$ requires 226.1389).

3.1.3. 2-(*tert*-Butyldimethylsiloxymethyl)-4,4-(2,4,6-triisopropyl-benzenesulfonyl-hydrazono)-1,3,3-trimethyl-cyclohex-1-ene 7.[6,8] Freshly made 2,4,6-triisopropylbenzenesulfonyl-hydrazide[11] (5.3 g, 17.7 mmol) was added in one portion to a solution of the ketone **6** (5 g, 17.7 mmol) in dichloromethane (50 ml) at room temperature and the mixture was then stirred at 25°C for 16 h. The solvent was removed in vacuo and the residue was crystallized from pentane to give the hydrazone (8.7 g, 87%) as a colorless powder,[6,8] mp 128–130°C (lit.[6] mp 118–120°C or lit.[8] mp 135–137°C), (Found: C, 65.7; H, 9.9; N, 4.8. Calcd for $C_{31}H_{51}N_2O_3SSi$: C, 66.1; H, 9.7; N, 5.0%); ν_{max} (nujol mull)/cm^{-1} 1599; δ_H (400 MHz; $CDCl_3$) 0.03 (s, 6H, Me_2Si), 0.87 (s, 9H, *tBu*), 1.08 (s, 6H, 2×Me), 1.25 (d, J=6.9 Hz, 6H, 2×Me), 1.26 (d, J=6.8 Hz, 6H, 4×Me), 1.71 (s, 3H, Me), 2.18 (t, J=6.9 Hz, 2H, C:CCH_2) 2.34 (t, J=6.9 Hz, 2H, CH_2CN), 2.90 (septet, J=6.9 Hz, 1H, CHMe$_2$), 4.09 (s, 2H, CH_2OSi), 4.18 (septet, J=6.8 Hz, 1H, 2×CHMe$_2$), 7.15 (s, 2H, Ar); δ_C (100 MHz; $CDCl_3$) −4.9 (2×q), 18.3 (s), 19.9 (q), 21.8 (t), 24.0 (2×q), 25.3 (3×q), 26.3 (2×q), 26.4 (4×q), 30.3 (d), 31.0 (t), 34.6 (2×d), 42.7 (s), 59.4 (t), 123.9 (2×d), 130.8 (s), 131.9 (s), 136.6 (2×s), 151.6 (s), 152.9 (s), 164.7 (s).

3.1.4. 2-(*tert*-Butyldimethylsiloxymethyl)-4-hydroxymethyl-1,3,3-trimethyl-cyclohexa-1,4-diene 8. A solution of *n*-butyl-lithium (6.3 ml, 15.7 mmol) in hexanes (2.5 M) was added dropwise over 10 min to a solution of the hydrazone **7** (2.2 g, 3.9 mmol) in dry THF (30 ml) at −78°C. After 1 h at −78°C, DMF (2.4 ml, 31.3 mmol) was added in one portion and the mixture was stirred at −78°C for 40 min and then allowed to warm to room temperature over 1 h. The reaction was quenched with water (10 ml) and the separated aqueous layer was extracted with ether (2×25 ml). The combined organic extracts were dried over $MgSO_4$ and then concentrated in vacuo to leave the corresponding aldehyde (976 mg). Cerium trichloride heptahydrate (1.36 g, 3.65 mmol) was added in one portion to a solution of the aldehyde in methanol (20 ml) at 0°C and then sodium borohydride (252 mg, 6.64 mmol) was added portionwise over 20 min. The mixture was stirred at 0°C for 30 min and then water (15 ml) and 2 M HCl (15 ml) were added. The organic layer was separated and the aqueous layer was extracted with ether (2×20 ml). The combined organic extracts were dried over $MgSO_4$ and then concentrated in vacuo to leave a colorless residue. The residue was purified by chromatography on silica, eluting with 20% ether in light petroleum to give the carbinol (718 mg, 62%) as a colorless oil. ν_{max} (film)/cm^{-1} 1472; δ_H (400 MHz; $CDCl_3$) 0.01 (s, 6H, Me_2Si), 0.91 (s, 9H, *tBu*), 1.18 (s, 6H, 2×Me), 1.76 (s, 3H, Me), 2.67 (br. m, 2H), 4.16 (br. s, 2H, CH_2OH), 4.19 (br. s, 2H, CH_2OSi), 5.75 (br. m, 1H, C:CH); δ_C (100 MHz; $CDCl_3$) −4.9 (2×q), 18.8 (s), 19.6 (q), 26.1 (3×q), 26.4 (q), 27.1 (q), 33.8 (t), 38.3 (s), 59.1 (t), 63.1 (t), 120.6 (d), 129.6 (s), 135.8 (s), 144.3 (s); m/z (EI) 151.1117 (M^+−TBDMS−H_2O. $C_{10}H_{15}O$ requires 151.1123).

3.1.5. (4*S*,5*S*)-2-(*tert*-Butyldimethylsiloxymethyl)-4,5-epoxy-4-(hydroxymethyl)-1,3,3-trimethyl-cyclohex-1-ene 9. A solution of *tert*-butylhydroperoxide (1.4 ml, 7.6 mmol) in decane (5.5 M) was added to a solution of (+)-L-diethyl tartrate (56 μl, 0.2 mmol), titanium tetraisopropoxide (39 μl, 0.23 mmol) and 3 Å molecular sieves (3 g) in dry dichloromethane (20 ml) at −23°C. The mixture was stirred at −23°C for 30 min and then a solution of the alcohol **8** (1.12 g, 3.8 mmol) in dichloromethane (5 ml) was added dropwise over 20 min. The flask was placed in a freezer at −23°C for 24 h and then the mixture was poured in a solution of citric acid (420 mg) and ferrous sulphate (1.25 g) in water (4 ml) at 0°C. The organic layer was separated and the aqueous layer was extracted with ether (2×10 ml). The combined organic extracts were stirred with a solution (1 ml) of 30% (w/v) sodium hydroxide saturated with sodium chloride at 0°C for 1 h. Water (5 ml) was added, the organic layer was separated, and the aqueous layer was extracted with ether (2×10 ml). The combined organic layers were dried over $MgSO_4$ and then concentrated in vacuo. The residue was purified by chromatography on silica, eluting with 40% ether in light petroleum to give the epoxide (956 mg, 81%. ee[12]=86%) as a colorless oil. $[\alpha]_D^{29}$=−46.7 (c 0.18 in $CHCl_3$); (Found: C, 65.3; H, 10.4. $C_{18}H_{32}O_5Si$ requires C, 65.3; H, 10.3%); ν_{max} ($CHCl_3$ sol.)/cm^{-1} 1421; δ_H (360 MHz; $CDCl_3$) 0.08 (s, 6H, Me_2Si), 0.89 (s, 9H, *tBu*), 1.12 (s, 3H, Me), 1.25 (s, 3H, Me), 1.71 (s, 3H, Me), 2.51 (br s, 2H), 3.44 (br app. t, J=2.0 Hz, 1H, CHOC), 3.79 (dd, J=11.9, 2.1 Hz, 1H, CHOH), 3.90 (dd, J=11.9, 10.1 Hz, 1H, CHOH), 4.11 (d, J=11.3 Hz, 1H, CHOSi), 4.17 (d, J=11.3 Hz, 1H, CHOSi); δ_C (67.8 MHz; $CDCl_3$) −5.4 (2×q), 18.3 (s), 19.6 (q), 21.0 (q), 24.3 (q), 25.9 (3×q), 31.9 (t), 37.3 (s), 55.1 (d), 58.6 (t), 58.8 (t), 64.5 (s), 125.5 (s), 133.2 (s); m/z (EI) 237.1311 (M^+−*t*Bu−H_2O. $C_{13}H_{21}O_2Si$ requires 237.1311).

3.1.6. (4*S*)-2-(*tert*-Butyldimethylsiloxymethyl)-4-hydroxy-4-(hydroxymethyl)-1,3,3-trimethyl-cyclohex-1-ene 10. Lithium aluminium hydride (99 mg, 2.6 mmol) was added portionwise over 10 min to a solution of the epoxide **9** (270 mg, 0.86 mmol) in ether (20 ml) at 0°C. The mixture was stirred at 0°C for 30 min, then carefully quenched with water (15 ml) and diluted with ether (10 ml). The organic layer was separated and the aqueous layer was extracted with ether (2×10 ml). The combined organic extracts were washed with brine (10 ml), then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica, eluting with 40% ethyl acetate in light petroleum to give the diol (260 mg, 96%) which crystallized from ethyl acetate–light petroleum as colorless crystals, mp 72–74°C. $[\alpha]_D^{23}=+14.2$ (*c* 0.11 in $CHCl_3$); (Found: C, 65.3; H, 11.3. $C_{18}H_{32}O_4Si$ requires C, 64.9; H, 10.9%); ν_{max} ($CHCl_3$ sol.)/cm^{-1} 1462; δ_H (360 MHz; $CDCl_3$) 0.08 (s, 6H, Me_2Si), 0.90 (s, 9H, *tBu*), 1.02 (s, 3H, Me), 1.12 (s, 3H, Me), 1.72 (s, 3H, Me), 1.75–1.85 (m, 2H), 2.03–2.10 (m, 2H), 3.49 (d, *J*=11.0 Hz, 1H, C*H*OH), 3.73 (d, *J*=11.0 Hz, 1H, C*H*OH), 4.11 (s, 2H, CH_2OSi); δ_C (67.8 MHz; $CDCl_3$) −5.4 (2×q), 18.3 (s), 19.4 (q), 21.7 (q), 22.6 (q), 25.9 (3×q), 26.4 (t), 29.4 (t), 40.7 (s), 58.9 (t), 65.0 (t), 75.0 (s), 131.4 (s), 135.0 (s); *m/z* (EI) 225.1313 (M^+-tBu–MeOH. $C_{13}H_{21}O_2Si$ requires 225.1311).

3.1.7. (5*S*)-7-(*tert*-Butyldimethylsiloxymethyl)-1,3-dioxa-2-oxo-6,6,8-trimethyl-spiro-[4,5]-dec-7-ene 11. A solution of phosgene (8.3 mmol) in toluene (4.4 ml, 10%) was added dropwise over 10 min to a stirred solution of the diol **10** (523 mg, 1.7 mmol) and pyridine (2.2 ml, 26.6 mmol) in dichloromethane (20 ml) at −78°C. The mixture was stirred at −78°C for 15 min and then allowed to warm to room temperature over 2 h, when it was quenched with water (20 ml) and diluted with dichloromethane (10 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×30 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml), then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica, eluting with 30% ethyl acetate in light petroleum to give the carbonate (552 mg, 98%) which crystallized from ethyl acetate–light petroleum as colorless crystals, mp 49–51°C. $[\alpha]_D^{24}=-20.4$ (*c* 0.225 in $CHCl_3$); (Found: C, 63.9; H, 9.8. $C_{18}H_{32}O_4Si$ requires C, 63.5; H, 9.5%); ν_{max} ($CHCl_3$ sol.)/cm^{-1} 1471; δ_H (360 MHz; $CDCl_3$) 0.08 (s, 6H, Me_2Si), 0.90 (s, 9H, *tBu*), 1.13 (s, 3H, Me), 1.19 (s, 3H, Me), 1.70 (s, 3H, Me), 1.86–1.95 (m, 1H), 2.03–2.13 (m, 1H), 2.14–2.23 (m, 1H), 2.27–2.37 (m, 1H), 4.03 (d, *J*=8.7 Hz, 1H), 4.09 (d, *J*=11.4 Hz, 1H), 4.18 (d, *J*=11.4 Hz, 1H), 4.39 (d, *J*=8.7 Hz, 1H); δ_C (67.8 MHz; $CDCl_3$) −5.6 (2×q), 17.9 (s), 18.9 (q), 21.3 (q), 22.5 (q), 25.7 (3×q), 28.3 (t), 28.6 (t) 40.1 (s), 58.7 (t), 71.2 (t), 86.7 (s), 130.7 (s), 133.5 (s) 154.7 (s); *m/z* (EI) 283.1343 (M^+-tBu. $C_{14}H_{23}O_4Si$ requires *M*, 283.1366).

3.1.8. (5*S*)-7-(*tert*-Butyldimethylsiloxymethyl)-1,3-dioxa-2-oxo-9-hydroxy-6,6,8-trimethyl-spiro-[4,5]-dec-7-ene 12. Selenium dioxide (150 mg, 1.35 mmol) was added in one portion to a stirred solution of the carbonate **11** (460 mg, 1.35 mmol) in 1,4-dioxane (10 ml) and the mixture was then heated at 100°C for 2 h. The mixture was allowed to cool to room temperature and then ether (15 ml) was added. The separated organic layer was washed with brine (3×10 ml), then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica, eluting with 30% ethyl acetate in light petroleum to give recovered starting material (61 mg) and a mixture of diastereoisomers of the alcohol (212 mg, 44%) as a colorless oil. (Found: C, 60.7; H, 9.4. $C_{18}H_{32}O_5Si$ requires C, 60.6; H, 9.1%); ν_{max} ($CHCl_3$ sol.)/cm^{-1} 1803, 1668, 1471; ($_H$ (360 MHz; $CDCl_3$) 0.09 (s, 3H, Me_2Si), 0.10 (s, 3H, Me_3Si), 0.91 (s, 9H, *tBu*), 1.08 (s, 1.5H, Me), 1.79 (s, 3H, Me), 1.27 (s, 1.5H, Me), 1.83 (s, 1.5H, Me), 1.83 (s, 1.5H, Me), 2.07 (dd, *J*=13.9, 4.9 Hz, 0.5H), 2.32 (d, *J*=4.5 Hz, 1H), 2.51 (dd, *J*=13.9, 6.1 Hz, 0.5H), 3.97 (t, *J*=4.5 Hz, 0.5H), 4.04 (d, *J*=8.8 Hz, 0.5H), 4.12 (d, *J*=11.4 Hz, 0.5H), 4.16 (s, 1H), 4.26 (d, *J*=11.4 Hz, 0.5H), 4.32 (t, *J*=5.5 Hz, 0.5H), 4.39 (s, 1H), 4.46 (d, *J*=8.8 Hz, 0.5H); δ_C (67.8 MHz; $CDCl_3$) −5.5 (2×q), 16.6 (q), 18.1 (s), 20.6 (q), 22.7 (q), 25.8 (3×q), 37.8 (t), 40.6 (s), 59.1 (t), 68.2 (d), 71.1 (t), 86.9 (s), 132.5 (s), 135.9 (s) 153.2 (s); *m/z* (EI) 338.1984 (M^+-H_2O. $C_{14}H_{23}O_4Si$ requires *M*, 338.1913).

3.1.9. (4*S*)-2-(*tert*-Butyldimethylsiloxymethyl)-4,6-dihydroxy-4-benzoyloxymethyl-1,3,3-trimethyl-cyclohex-1-ene 13. A solution of phenyllithium (150 μl, 0.27 mmol) in hexanes–ether (1.8 M) was added dropwise over 10 min to a stirred solution of the alcohol **12** (98 mg, 0.27 mmol) in THF (10 ml) at −78°C. The mixture was stirred at −78°C for 20 min, then quenched with water (2 ml) and allowed to warm to room temperature over 1 h. The organic layer was separated and the aqueous layer was extracted with ether (2×10 ml). The combined organic extracts were dried over $MgSO_4$ and then concentrated in vacuo. The residue was purified by chromatography on silica, eluting with 30% ethyl acetate in light petroleum to give a mixture of diastereoisomeric diols (101 mg, 86%) as a colorless oil. (Found: C, 66.0; H, 8.81. $C_{18}H_{32}O_5Si$ requires C, 66.3; H, 8.8%); ν_{max} (film)/cm^{-1} 1803, 1668, 1471; δ_H (360 MHz; $CDCl_3$) 0.10 (s, 6H, Me_2Si), 0.91 (s, 9H, *tBu*), 1.10 (s, 1.5H, Me), 1.18 (s, 3H, Me), 1.27 (s, 1.5H, Me), 1.86 (s, 1.5H, Me), 1.90 (s, 1.5H, Me), 1.98 (dd, *J*=13.9, 5.6 Hz, 0.5H), 2.11 (dd, *J*=14.3, 5.3 Hz, 0.5H), 2.20 (dd, *J*=14.3, 3.2 Hz, 0.5H), 2.30 (dd, *J*=13.9, 5.4 Hz, 0.5H), 4.00 (m, 0.5H), 4.12–4.32 (m, 3H), 4.44 (d, *J*=9.6 Hz, 0.5H), 4.58 (app. t, *J*=11.5 Hz, 1H), 7.43–7.51 (m, 2H), 7.56–7.63 (m, 1H), 8.06–8.10 (m, 2H); δ_C (67.8 MHz; $CDCl_3$) −5.4 (2×q), 15.2/15.5 (q), 18.2 (s), 21.2/22.1 (q), 22.7/23.5 (q), 26.5 (3×q), 34.9/36.6 (s), 41.6/41.8 (s), 59.0/59.2 (t), 68.4/68.6 (t), 68.8/69.0 (t), 74.4/75.3 (s), 128.1/128.4 (d), 129.5/129.6 (d), 129.8/129.9 (s), 132.4/132.7 (s), 133.1/133.2 (d), 136.7/137.5 (s), 166.9/167.0 (s); *m/z* (EI) 338.1984 (M^+-H_2-O. $C_{18}H_{30}O_4Si$ requires *M*, 338.1913).

3.1.10. (5*S*)-3-(*tert*-Butyldimethylsiloxymethyl)-5-hydroxy-5-benzoyloxymethyl-2,4,4-trimethyl-cyclohex-2-en-1-one 14. A solution of the diol **13** (50 mg, 0.12 mmol) in dichloromethane (2 ml) was added to a suspension of pyridinium chlorochromate (37 mg, 0.17 mmol) and sodium acetate (14 mg, 0.17 mmol) in dichloromethane (5 ml) at 0°C. The mixture was stirred at 0°C for 3 h, and then evaporated to small volume (ca. 1 ml) and purified by chromatography on silica, eluting with 25% ethyl acetate in light petroleum to give the ketone (47 mg, 95%) as a

colorless oil. $[\alpha]_D^{26}=-19.7$ (*c* 0.20 in $CHCl_3$); (Found: C, 66.4; H, 8.6. $C_{24}H_{36}O_5Si$ requires C, 66.6; H, 8.4%); ν_{max} (film)/cm^{-1} 1723, 1668, 1603, 1463; δ_H (360 MHz; $CDCl_3$) 0.08 (s, 6H, Me_2Si), 0.92 (s, 9H, *tBu*), 1.35 (s, 3H, Me), 1.37 (s, 3H, Me), 1.88 (s, 3H, Me), 2.84 (d, *J*=17.1 Hz, 1H), 2.87 (d, *J*=17.1 Hz, 1H), 4.30–4.41 (m, 3H), 4.60 (d, *J*=11.6 Hz, 1H), 7.46 (br t, *J*=7.7 Hz, 2H), 7.60 (br t, *J*=7.7 Hz, 1H), 8.04 (brt, *J*=7.7 Hz, 2H); δ_C (67.8 MHz; $CDCl_3$) −5.5 (2×q), 11.1 (q), 18.2 (s), 21.7 (q), 22.1 (q), 25.8 (3×q), 43.2 (s), 43.9 (t), 59.8 (t), 67.9 (t), 76.0 (s), 128.5 (d), 129.4 (s), 129.7 (d), 132.5 (s), 133.4 (d), 157.8 (s), 167.0 (s), 197.4 (s); *m*/*z* (EI) 432.2315 (M^+. $C_{24}H_{36}O_5Si$ requires *M*, 432.2332).

3.1.11. (4*S*,5*R*)-2-(*tert*-Butyldimethylsiloxymethyl)-4,6-dihydroxy-4-benzoyloxymethyl-1,3,3-trimethyl-cyclohex-1-ene 2. A solution of sodium triacetoxyborohydride (231 mg, 1.1 mmol) in acetic acid (1.1 ml) was stirred at room temperature for 1 h, then cooled to 0°C and treated dropwise over 5 min with a solution of the ketone **14** (47 mg, 0.109 mmol) in acetonitrile (2 ml). The mixture was stirred at 0°C for 6 h, and then at room temperature for 16 h. Water (1 ml) and methanol (4 ml) were added and the volatiles were then removed in vacuo; this procedure was repeated twice, and then water (3 ml) and dichloromethane (10 ml) were added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×10 ml). The combined organic extracts were dried over $MgSO_4$ and then concentrated in vacuo. The residue was purified by chromatography on silica, eluting with 30% ethyl acetate in light petroleum to give the diol (29 mg, 62%) as a colorless oil. $[\alpha]_D^{29}=-19.2$ (*c* 0.25 in $CHCl_3$); (Found: C, 65.9; H, 8.9. $C_{24}H_{38}O_5Si$ requires C, 66.3; H, 8.8%); ν_{max} (film)/cm^{-1} 1710, 1451; δ_H (360 MHz; $CDCl_3$) 0.11 (s, 6H, Me_2Si), 0.95 (s, 9H, *tBu*), 1.20 (s, 6H, Me), 1.86 (s, 3H, Me), 1.99 (dd, *J*=13.9, 5.4 Hz, 1H), 2.30 (dd, *J*=13.9, 6.4 Hz, 1H), 4.17 (d, *J*=2.8 Hz, 2H), 4.23 (t, *J*=6.4 Hz, 1H), 4.42 (d, *J*=11.6 Hz, 1H), 4.55 (d, *J*=11.6 Hz, 1H), 7.51 (t, *J*=7.3 Hz, 2H), 7.59 (t, *J*=7.3 Hz, 1H), 8.07 (t, *J*=7.3 Hz, 2H); δ_C (67.8 MHz; $CDCl_3$) −5.4 (2×q), 15.6 (q), 18.3 (s), 22.2 (q), 22.6 (q), 25.9 (3×q), 36.6 (s), 41.7 (s), 59.2 (t), 68.7 (t), 69.0 (t), 74.4 (s), 128.5 (d), 129.7 (d), 129.9 (s), 132.6 (s), 133.3 (d), 137.6 (s), 167.0 (s); *m*/*z* (EI) 432.2315 (M^+. $C_{24}H_{36}O_5Si$ requires *M*, 432.2332).

3.1.12. (4*S*,5*R*)-4-(4-Bromobenzoyloxy)-5-hydroxy-3-hydroxymethyl-2,4,4-trimethyl-5- benzoyloxymethyl-cyclohex-2-ene 15. Pyridine (40 μl, 0.27 mmol), 4-dimethylaminopyridine (8.1 mg, 0.07 mmol) and 4-bromobenzoyl chloride (15 mg, 0.13 mmol) were added to a solution of the 1,3-diol **2** (29 mg, 0.07 mmol) in dichloromethane (20 ml). The mixture was stirred at room temperature for 4 h and then quenched with brine. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×10 ml). The combined organic extracts were dried over $MgSO_4$ and then concentrated in vacuo. The residue was purified by chromatography on silica, eluting with 30% ethyl acetate in light petroleum to give the *sec*-alcohol benzoate (30 mg, 73%) which crystallized from dichloromethane–diethyl ether–light petroleum as colorless crystals. Mp 53–55°C. $[\alpha]_D^{24}=-16.2$ (*c* 0.27 in $CHCl_3$); ν_{max} ($CHCl_3$ sol.)/cm^{-1} 1714, 1590, 1452; δ_H (360 MHz; $CDCl_3$), 1.25 (s, 3H, Me), 1.29 (s, 3H, Me), 1.89 (s, 3H, Me), 2.36 (dd, *J*=14.8, 5.5 Hz, 1H), 2.42 (dd, *J*=14.8, 3.6 Hz, 1H), 4.29 (d, *J*=11.7 Hz, 1H), 4.34 (4, *J*=11.7 Hz, 1H), 4.49 (s, 2H), 5.47 (dd, *J*=5.5, 3.6 Hz, 1H), 7.29 (t, *J*=8.0 Hz, 2H), 7.37 (t, *J*=8.0 Hz, 2H), 7.48 (t, *J*=8.0 Hz, 1H), 7.67 (t, *J*=8.0 Hz, 4H); δ_C (90.5 MHz; $CDCl_3$) 16.3 (q), 20.8 (q), 23.1 (q), 32.8 (t), 41.5 (s), 58.9 (t), 68.6 (t), 72.6 (d), 76.6 (s), 128.1 (d), 128.6 (s), 129.2 (s), 129.7 (d), 130.8 (d), 131.4 (d), 131.6 (s), 132.0 (d), 142.0 (s), 165.5 (s), 166.7 (s); *m*/*z* (EI) 525.0927 (M^++Na. $C_{25}H_{27}BrO_3Na$ requires *M*, 525.0889).

3.2. X-Ray crystal structure determination of the benzoate 15

A colorless plate-like crystal of dimensions 0.30×0.22×0.05 mm^3 was selected for the study and found to crystallize in the monoclinic space group $P2_1$ with *a*=8.2582(10) Å, *b*=11.5071(13) Å, *c*=24.438(3) Å, β=95.737(2)°, *V*=2310.7(5) $Å^3$, *Z*=4, *T*=150 K. 13001 reflections were collected on a Bruker SMART CCD area detector diffractometer equipped with an Oxford Cryosystem open-flow nitrogen cryostat using Mo Kα X-radiation, and were corrected for absorption using an integration method ($T_{min/max}$=0.674 and 0.908), μ (Mo Kα)=1.818 mm^{-1}. Data were averaged to give 9634 unique data (R_{int}=0.035), 9622 of which were used in all calculations. The structure was solved by direct methods (SHELXS-97) and refined using full-matrix least squares refinement against F^2, all non-H atoms were refined with anisotropic atomic displacement parameters (adps) and H atoms placed in geometrically calculated positions and refined as part of a riding model, except the OH hydrogen which was located from difference Fourier syntheses and refined as a rigid rotor. The final $wR(F^2)$ was 0.075 for all data, $R_1(F)$ was 0.045 for 5709 observed data where $I>2\sigma(I)$. The Flack parameter refined to −0.009(6), indicating the correct assignment of the absolute configuration. The structure contains two independent molecules with essentially the same conformation and exactly the same absolute configuration.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC205720. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ (fax: +44-1223-336033 or email: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank GlaxoSmithKline (formerly SmithKline Beecham) for support of this work via an EPSRC CASE studentship (to D. C. P.).

References

1. Taxol is the registered trademark of Bristol–Myers Squibb for the generic name paclitaxel. Likewise, Taxotere is the

registered trademark of Rhône-Poulenc Rorer for the generic name docetaxel.

2. (a) Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653. (b) Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599. (c) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723. (d) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757. (e) Morihara, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980. (f) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121.
3. For review (a) Kingston, D. G. I. *Chem. Commun.* **2001**, 867. (b) Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47. (c) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.
4. Hitchcock, S. A.; Houldsworth, S. J.; Pattenden, G.; Pryde, D. C.; Thomson, N. M.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3181.
5. Pryde, D. C. Ph.D. Thesis, University of Nottingham, 1994.
6. Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989.
7. Luche, J.-L. J. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
8. Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634.
9. (a) Shapiro, R. H. *Org. React.* **1976**, *23*, 405. (b) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734.
10. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B.; J, *J. Am. Chem. Soc.* **1987**, *109*, 5765.
11. Csack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157–2162.
12. Enantiomeric excess determined by ^{19}F NMR of Mosher's acid derivatives Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.