

Tetrahedron 54 (1998) 13185-13202

TETRAHEDRON

An Efficient Protocol for the Stereoselective Dihydroxylation of Ene-Ester Systems

Stephen A. Hermitage, Alison Murphy, Poul Nielsen and Stanley M. Roberts

Department of Chemistry, Robert Robinson Laboratories, University of Liverpool, Liverpool, England, L69 7ZD.

Received 11 May 1998; revised 18 August 1998; accepted 19 August 1998

Abstract : Dihydroxylation of ene ester systems was achieved in good yield and diastereoselectivity under classical catalytic OsO₄ and NMO conditions using the intrinsic diastereoselectivity in α -methyl β -OTBS systems. This intrinsic diastereoselection can be reversed using 'super' AD-mix to give the opposite diastereomer also in good selectivity. The regioselection of dihydroxylation in diene esters using a modified 'super' AD-mix was poor. This methodology can be applied towards the synthesis of part structures of the marine macrolide Altohyrtin A. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction:

Syn-dihydroxylation using osmium based reagents has been used extensively to convert alkenes to the corresponding diol systems.¹ The stereoselectivity of such reactions can be influenced 'intrinsically' by a chiral centre spatially proximate to the reacting double bond or *via* 'external' control using chiral reagents. Indeed, the influence of allylic alkoxy groups on the stereoselectivity of dihydroxylation reactions is well known.² We sought to investigate the influence of allylic methyl groups and homoallylic OTBS groups on the intrinsic molecular diastereoselection for OsO₄ mediated dihydroxylations. We were also interested in the ability of an external chiral influence (the Sharpless AD mixes) to overcome this intrinsic diastereoselectivity.

Preparation of Substrates:

The syntheses of ene ester 6 is shown in Scheme 1. Condensation of Meldrum's acid 1 with benzyloxyacetyl chloride 2 in refluxing *iso*-propanol gave the β -keto ester 3 in moderate yield. Stereospecific reduction gave the β -hydroxy ester³ 4 in quantitative yield and >95% enantioselectivity. Dianion methodology⁴ was employed to stereoselectively methylate the ester in a 9:1 ratio and the product was protected as the *tert*-butyldimethylsilyl (TBS) ether 5. Reduction of the ester 5 to the corresponding alcohol (which was freed from contaminating <u>syn</u>-diastereoisomer by chromatography over silica) followed by a Dess Martin oxidation⁵ and Wittig homologation gave the ene ester 6 which was freed from the contaminating <u>syn</u>-diastereoisomer by chromatography over silica).



Reagents and Conditions : i) pyridine, *i*-PrOH, heat, (49%); ii) H₂, *i*-PrOH, 1200 Psi, 90°C (S)-Tol-BINAP-RuCl₂, (100%); iii) LDA (2 equiv.), MeI, -78°C, THF, (80%); iv) TBSOTf, 2,6-lutidine, CH₂Cl₂, (100%); v) a) DIBALH, THF, (60%), b) Dess Martin oxidation, CH₂Cl₂, (95%); vi) Ph₃P=CHCO₂Me, CH₂Cl₂, (86%). Scheme 1

The unsaturated ester 11 was prepared using technology developed by Roush⁶ whereby the crotyl boronate 7 and aldehyde 8 were combined to form the alcohol 9, which was protected as its TBS ether 10. Ozonolysis of the alkene 10 followed by reductive work up and subsequent Wittig homologation gave the ene ester 11.



Reagents and Conditions : i) toluene, overnight (37%); ii) TBSCl, imidazole, DMF, (97%); iii) a) O₃, CH₂Cl₂, MeOH, b) Me₂S; iv) Ph₃P=CHCO₂Me, CH₂Cl₂, (80% over 2 steps). Scheme 2

The ene ester system 11 was reduced to the corresponding alcohol using DIBALH, oxidised to the related ene aldehyde with the Dess Martin periodinane⁵ and subjected to a Wittig homologation using $Ph_3P=CHCO_2Me$ to give the diene ester 16 in an impressive overall yield of 93% for the three steps.



Reagents and Conditions : i) DIBALH, CH₂Cl₂; ii) Dess Martin periodinane, CH₂Cl₂; iii) Ph₃P=CHCO₂Me, CH₂Cl₂, (93% over 3 steps). Scheme 3

Dihydroxylation Reactions:

The ene esters 6 and 11 were subjected to dihydroxylation conditions previously reported by Schreiber⁷ whereby each ene ester was dissolved in an 8:1 acetone : water mixture and the cooxidant *N*-methylmorpholine-*N*-oxide (NMO) was added followed by catalytic quantities of OsO_4 . As shown in Table 1 both substrates displayed good intrinsic diastereoselection, presumably due to the influence of the silyloxy substituent since an analogous compound,



Reagents and Conditions: i) OsO₄ (cat.), NMO, acetone:H₂O (8:1), ii) (MeO)₂CMe₂, acetone, TsOH.

* Determined by integration of the anisochronous MeCH signal for each diastereomer in the ¹H n.m.r. spectrum.

Table 1

devoid of a trialkylsilyloxy substituent at the homoallylic position, namely methyl (S) - 8 benzyloxy - 4 - methyloct - 2 -enoate, gave a 1 : 1 mixture of stereoisomers on dihydroxylation using OsO4 and NMO under similar conditions.⁸ In order to obtain an alternative diastereomer, the ene esters were subjected to the Sharpless asymmetric dihydroxylation conditions using AD mix- β .⁸ The reaction was frustratingly slow as is often the case for ene ester systems^{9,10} and hence a 'super' AD-mix formulation was prepared. This required some subtle changes to the AD-mix formulation in order to achieve an acceptable rate of reaction. The amount of (DHQD)₂PHAL ligand was increased to 10 mol % and the catalytic oxidant changed from K₂OsO₂(OH)₄ to OsO₄, at a concentration between 8 and 10 mol % and used as a 2.5% w/w solution in *t*-BuOH. The co-oxidant, K₃Fe(CN)₆, remained at a concentration of 3 mole equivalents and K₂CO₃ (3 mole equivalents) was added to the mixture. In addition 3 mole equivalents of MeSO₂NH₂ (known to enhance the rate of reaction by increasing the rate of hydrolysis of the osmium glycolate intermediate) were added. The use of this 'super' AD-mix β proved successful in both cases and the diastereoselectivity of reaction was reversed with a 6:1 ratio for dihydroxylation of 6 and an 8:1 ratio for 11 (Table 2).



Reagents and Conditions: i) 'Super' AD-mix β , ii) (MeO)₂CMe₂, acetone, TsOH.

* Determined by integration of the anisochronous MeCH signal for each diastereomer in the ¹H n.m.r. spectrum.

Table 2

Treatment of the dihydroxyester (14) with tetrabutylammonium fluoride in THF gave the lactone (17). The assignment of relative stereochemistry around the six membered ring was made on the basis of nOe measurements and some key interactions are shown in Figure 1 (numbers refer to the percentage enhancements for the signals).



The diene ester 16 was subjected to a modified 'super' AD-mix α and a modified 'super' AD-mix β mixture in order to study further the stereoselectivity of dihydroxylation. To our surprise we obtained a mixture of *regioisomers*. After 31 hours at room temperature the reaction involving AD-mix α gave 37% starting material, 33% of the diol 18 and 8% of the diol 19. This lack of regioselectivity is in contrast to examples cited by Sharpless⁹ and others.¹¹ It is known that electronic factors greatly influence the regioselectivity of dihydroxylation, with osmylation preferentially occurring at the more electron-rich double bond.⁹ In this case, steric factors appear to outweigh the electronic influences with preferential dihydroxylation occurring to give mainly the α , β -diol 18. Note that the stereochemical assignments for 18 and 19 were made using the Sharpless 'mnemonic device'.⁹



Reagents and Conditions: i) Modified 'super' AD-mix α (changes : 1 mol% OsO₄, 5 mol % (DHQ)₂PHAL). Scheme 4

Using modified 'super' AD-mix β the diene ester 16 furnished only 41% of the diol 20 and 29% starting material after stirring at room temperature for 21 hours.

In conclusion, we have demonstrated the ability of a 'super' AD-mix to reverse the intrinsic diastereoselection of chiral γ -methyl and δ -OTBS ene-ester systems. This 'super' AD-mix increases the rate of dihydroxylation compared to the commercially available AD-mixes.



Reagents and Conditions: i) Modified 'super' AD-mix β (changes : 1 mol% OsO₄, 5 mol % (DHQD)₂PHAL) Scheme 5

Unexpectedly AD-mix oxidations of the diene ester 16 afforded largely or exclusively diol derivatives by modification of the α , β -alkene unit. We are currently applying this methodology to the synthesis of Altohyrtin A¹² and will report our findings in a subsequent paper.

Experimental Section.

Reactions were monitored by thin layer chromatography performed on glass-backed silica plates, coated with Merck 60F-254 silica gel. Visualisation was achieved via ceric ammonium nitrate and/or UV light. Column chromatography was performed using Merck 60-silica gel (0.040-0.063 mm). ¹H-NMR and ¹³C-NMR spectra were recorded on a Varian 300 Gemini 2000 or a Bruker AMX 400 using standard pulse sequences. Infrared spectra were recorded on a Perkin-Elmer 883 infrared spectrophotometer. Mass spectra (CI and accurate mass determination) were recorded on a VG Analytical 7070E double focusing magnetic sector mass spectrometer.

Elemental analysis were performed on a CARLO ERBA Model 1106 Elemental Analyzer. Optical rotations were determined in a 1 cm cell at 589 nm on a AA-1000 Polarimeter.

iso-Propyl 4-benzyloxyacetoacetate (3):-

Pyridine (44 mL, 0.54 mol) was added to a solution of Meldrum's acid (39 g, 0.27 mol) in dry CH₂Cl₂ (100 mL) and stirred for 1 hour. Benzyloxyacetyl chloride (50 g, 0.27 mol) in dry CH₂Cl₂ (20 mL) was added dropwise over a period of 1.5 hours at 5 - 10 $^{\circ}$ C and stirred for 3 hours at room temperature. The solution was washed with 2M HCl (3 x 100 mL) and water (2 x 100 mL), dried with MgSO4 and the solvent evaporated *in vacuo*.

The residue was dissolved in *iso*-propanol (100 mL) and stirred at room temperature for 20 hours and refluxed for a further 2 hours. The solvent was concentrated *in vacuo* and filtered through silica (washed with petroleum ether : ethyl acetate (1:1)). Purification by wipe film distillation (0.01 Torr at 175 °C) afforded the β -ketone ester 3 (30 g, 0.12 mol) in 49 % yield as a yellow oil. R_f (Petroleum ether : ethyl acetate 1:1) 0.67; (Found: [M+H]⁺ 251.1286. C14H18O4 requires [M+H] 251.1283); υ_{max} (film) /cm⁻¹ 3088 m, 3064 s, 3031 s, 2981 s, 2933 s (CH₃, CH₂), 1718 s (C=O), 1654 s, 1496 s, 1466 s, 1454 s, 1315 s, 734 s, 698 s; δ_{H}

(200 MHz; CDCl₃) 1.23 (6H, d, J 6.4, (CH₃)₂CH), 3.51 (2H, s, BnOCH₂), 4.14 (2H, s, CH₂CO₂ⁱPr), 4.59 (2H, s, PhCH₂), 5.32 (1H, sept, J 6.4, (CH₃)₂CH), 7.30-7.39 (5H, m, Ph); $\delta_{\rm C}$ (50 MHz; CDCl₃) 21.47, 46.15, 68.78, 73.24, 74.63, 127.66, 127.87, 128.34, 136.92, 166.32, 201.45; *m*/z (CI) 268 (M + NH4, 100 %), 251 (M+H, 45%), 162 (96%), 145 (59%), 108 (PhCH₂OH, 70 %), 102 (CH₂=C(OH)OⁱPr, 28%), 91 (PhCH₂, 28%).

(3R) iso-Propyl 4-benzyloxy-3-hydroxy butyrate (4):-

iso-Propyl 4-benzyloxyacetoacetate 3 (30 g, 0.12 mol) in iso-propanol (150 mL) was degassed and placed in an autoclave. ((R)Tol-BINAP)RuCl₂ (solution in iso-propanol : CH₂Cl₂, 5:2 8 mL, 303 mg, 0.360 mmol) was added via cannula. The autoclave was charged with H₂ (1200 psi)(8 MR) and stirred for 24 hours at 90 °C. The solvent was removed in vacuo, the resulting residue was filtered through silica and the silica pad washed with petroleum ether : ethyl acetate (4:1) to afford the β -hydroxy ester 4 (30.3 g, 0.12 mol) in 100 % yield and 95% e.e. (Chirapak AD 19:1 Heptane : iso-propanol, 27.56 minutes (S), 30.78 minutes (R)) as a colourless oil that crystallised slowly at 0 °C. Rf (petroleum ether : ethyl acetate 4:1) 0.26; (Found: $[M]^+$ 252.1360. C₁₄H₂₀O₄ requires M 252.1362); $[\alpha]_D^{22}$ + 9.5 (c 10, CHCl3); umax (film) /cm⁻¹ 3452 br s (OH), 3063 s, 2979 s, 2924 s (CH3, CH2), 1727 s (C=O), 1374 s, 1178 s; 8H (400 MHz; CDCl3) 1.23 (6H, d, J 6.3, (CH3)2CH), 2.51 (2 H, d, J 6.3, CHCO2ⁱPr), 3.10 (1 H, d, J 4.4, OH), 3.50-3.47 (2 H, m, BnOCH2), 4.20-4.28 (1 H, m, CHOH), 4.56 (2 H, s, PhCH₂), 5.04 (1 H, sept, J 6.3, (CH₃)₂CH), 7.30-7.36 (5 H, m, Ph); δ_C (100 MHz; CHCl₃) 21.79 (2xCH₃), 38.50, 67.41, 68.21, 73.13, 73.41, 127.79, 127.99, 128.10, 137.89, 171.73; *m/z* (EI) 252 (M⁺, 0.1%), 131 (M - BnOCH₂O, 7%), 107 (PhCH2O, 14%), 91 (PhCH2, 100%), 89 (39%), 77 (Ph, 3%), 43 (ⁱPr, 56%).

(2S,3S) iso-Propyl 4-benzyloxy-3-hydroxy-2-methyl butyrate:-

n-BuLi (2.5 M solution in hexanes, 28.2 mL, 0.071 mol) was added slowly to a stirred solution of diiso-propylamine (9.90 mL, 0.071 mol) in dry THF (50 mL) at 0 °C under nitrogen and stirred for 15 minutes. The hydroxy ester 4 (7.12 g, 0.028 mol) in dry THF (15 mL) was added quickly at - 78 °C and stirred for 30 minutes. The reaction mixture was allowed to warm up to - 30 °C and stirred for a further 30 minutes. Methyl iodide (2.63 mL, 0.042 mol) was added slowly at - 78 °C and stirred for 1.5 hours. A saturated solution of NH4Cl (100 mL) was added at 0 °C. The aqueous layer was extracted with ether (3 x 100 mL) and the combined organic layers dried with anhydrous MgSO4. The solvent was removed *in vacuo*. Purification by flash chromatography (4:1) afforded the ester (6.65 g, 0.023 mol) in 83 % yield and 9:1 anti:syn ratio as a colourless oil. Rf (Petroleum ether : ethyl acetate 4 :1) 0.49; (Found: [M]⁺ 266.1517. C15H22O4 requires *M* 266.1518); [α]D²² +11

(c 10, CHCl₃); v_{max} (film) /cm⁻¹ 3478 br s, 2981, s, 2938 s, 2876 s, 1727 s, 1453 s, 1374 s 1183 s; for major diastereoisomer $\delta_{\rm H}$ (400 MHz; CDCl₃) 1.17 (3 H, d, J 6.4, CHCH₃), 1.22 (6 H, d, J 6.0, OCH(CH₃)₂), 2.68 (1 H, pent, J 6.4, CH₃CH), 3.06 (1 H, d, J 4, OH), 3.51 (1 H, dd, J 9.6 and 5.2, BnOCH_A), 3.56 (1 H, dd, J 9.6 and 4.0, BnOCH_B), 3.85 (1 H, m, CHOH), 4.53 (1 H, d, J 12, PhCH_A), 4.58 (1 H, d, J 12, PhCH_B), 5.4 (1 H, sept, J 6.0), CH(CH₃)₂), 7.26-7.35 (5 H, m, Ph); $\delta_{\rm C}$ (100 MHz; CDCl₃) 13.98, 21.69, 42.41, 67.95, 71.65, 72.38 (CH₂), 75.30 (CH₂) 127.71, 127.76, 128.42, 137.91, 175.01; *m/z* (EI) 266 (M⁺, 0.2%), 107 (BnOCH₂, 11%), 103 (50%), 91 (PhCH₂, 100%), 77 (Ph, 2%), 43 (ⁱPr).

(2S,3S) iso-Propyl 4-benzyloxy-3-(t -butyldimethylsilyloxy) -2- methyl butyrate (5):-

tert -Butyldimethylsilyl triflate (13.13 mL, 0.057 mol) was added to a stirred solution of 2,6lutidine (9.32 mL, 0.080 mol) and (2S,3S)-iso-propyl 4-benzyloxy-3-hydroxy-2methylbutyrate (10.0 g, 0.038 mol) in dry CH2Cl2 (50 mL) at 0 °C under nitrogen. The reaction was stirred for 3 hours at room temperature. Water (50 mL) was added, the aqueous layer was extracted with CH2Cl2 (3 x 50mL) and the combined organic layers dried with anhydrous MgSO4. The solvent was removed in vacuo. Purification by flash chromatography (petroleum ether : ethyl acetate 4:1) afforded the ester 5 (14.50 g, 0.038 mol) in 100 % yield as a colourless oil. Rf (Petroleum ether : ethyl acetate 4:1) 0.78; (Found: C, 66.40 %; H, 9.52 %. C₂₁H₃₇O₄Si requires C, 66.26 %; H, 9.55 %. Found: [M+H]⁺ 381.2459 C₂₁H₃₇O₄Si requires [M+H] 381.2461); $[\alpha]_D^{22}$ +20.4 (c 10, CHCl₃); υ_{max} (film) /cm⁻¹ 2955 s, 2932 s, 2858 s (CH3, CH2), 1733 s (C=O), 1651 m, 1373 m, 1254 s, 1109 s; for the major diastereoisomer δH (400 MHz; CDCl3) 0.059 (3 H, s, SiCH3), 0.068 (3 H, s, SiCH3), 0.87 (9 H, br s, C(CH3)3), 1.11 (3 H, d, J 7.2, CH3CHCO2ⁱPr), 1.20 (3 H, d, J 6.4, CO2CH(CH3)), 1.21 (3 H, d, J6.4, CO₂CH(CH 3)), 2.70-2.72 (1 H, m, CH₃CH CO¹Pr), 3.47 (1 H, dd, J 10.0 and 5.6, BnOCH₂), 3.53 (1 H, dd, J 10.0 and 4.8, BnOCH₂), 4.06 (1 H, q, J5, CHOTBS), 4.06 (1 H, d, J 12.0, PhCHA), 4.54 (1 H, d, J 12.0, PhCHB), 4.98 (1 H, sept, J 6, CH (CH3)2), 7.28-7.34 (5 H, m, Ph); S_C (100 MHz; CHCl3) -2.94, 12.70, 18.07, 21.81, 25.80, 43.97, 67.40, 72.83 (CH2), 73.35 (CH2), 127.51, 127.67, 128.28, 138.33, 173.64; m/z (CI) 381 (M+H, 100%), 321 (M-O¹Pr, 6%), 248 (9%), 108 (PhCH₂OH, 13%), 91 (PhCH₂, 6%).

(2R,3S) 4-Benzyloxy-3-(tert -butyldimethylsilyl)oxy-2 methyl butanol:-

Diso-butylaluminium hydride (1 M solution in cyclohexane, 60 mL, 0.06 mol) was added dropwise to a stirred solution of the ester 5 (7.5 g, 0.02 mol) in dry THF (50 mL) at - 78 $^{\circ}$ C under nitrogen and stirred for 4.5 hours. Acetone (5 mL) was added and the reaction mixture allowed to warm to room temperature over a period of 0.5 hour. 1M Tartaric acid (50 mL) was added and stirred until the white solid had dissolved. The aqueous layer was extracted with CH₂Cl₂ (4 x 50 mL) and the combined organic layers dried with anhydrous MgSO₄.

The solvent was removed *in vacuo*. Purification by flash chromatography (petroleum ether : ethyl acetate 6:1) afforded the alcohol (3.84 g, 0.012 mol) in 60 % yield as a colourless oil. Rf (petroleum ether : ethyl acetate 6:1) 0.39; (Found: C, 66.41 %; H, 10.07 %. C₁₈H₃₃O₃Si requires C, 66.61 %; H, 9.95 %; Found: $[M+H]^+$ 325.2200. C18H3₃O₃Si requires [*M*+*H*] 325.2199); [α]D²² + 3.33 (*c* 1.2, CHCl₃); ν_{max} (film) /cm⁻¹ 3500 br s (OH), 2956 s, 2930 s (CH₃, CH₂), 1471 s, 1462 s, 1252 s, 1098 s, 836 s; δ_{H} (400 MHz; CHCl₃) 0.06 (3 H, s, SiCH₃), 0.09 (3 H, s, SiCH₃), 0.87 (9 H, br s, Si(CH₃)₂), 1.02 (3 H, d, *J* 7.2, CH₃CH), 1.84-1.96 (1 H, m, CHCH₃) 3.49 (1 H, dd, *J* 15.6 and 5.2, CH_AOH), 3.55-3.57 (2 H, m, BnOCH₂), 3.73 (1 H, dd, *J* 11.6 and 3.6, CH_BOH) 3.85-3.89 (1 H, m, CHOTBS), 4.52 (2 H, s, PhCH₂), 7.31-7.35 (5 H, m, Ph); δ_{C} (100 MHz; CDCl₃) 14.34 (CH₃), 18.06 (CH₃), 26.00 (CH₃), 37.78 (CH), 64.85 (CH₂), 72.94 (CH₂), 73.47 (CH₂), 75.76 (CH), 127.65 (CH), 127.73 (CH), 128.40 (CH), 137.90 (C); *m*/z (CI) 342 (M+NH₄, 8%), 325 (M+H, 100%), 108 (PhCH₂OH, 27%), 91 (PhCH₂, 28%).

(2S,3S) 4-Benzyloxy-3-(tert -butyldimethylsilyloxy) -2- methyl butanal:-

A solution of alcohol (2.12 g, 6.5 mmol) in dry CH₂Cl₂ (5 mL) was added to a suspension of the Dess-Martin periodinane (4.17 g, 9.8 mmol) at 0 °C under argon and stirred for 4 hours. 1M Na₂S₂O₃ (5 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic layers dried with anhydrous MgSO₄. The solvent removed *in vacuo*. Purification by flash chromatogaphy (petroleum ether : ethyl acetate 6:1) afforded the aldehyde (2.01g, 6.19 mmol) in 95 % yield as a colourless oil. R_f (Petroleum ether : ethyl acetate 4:1) 0.71; $[\alpha]D^{22}$ + 34.19 (*c* 3.1, CHCl₃); υ_{max} (film) /cm⁻¹ 2955 s, 2931 s, 2858 s (CH₃, CH₂), 1726 s (C=O), 1461 m, 1254 s, 1107 s, 837 s; $\delta_{\rm H}$ (400 MHz; CDCl₃) 0.054 (3 H, s, SiCH₃), 0.070 (3 H, s, SiCH₃), 0.87 (9 H, br s, SiC(CH₃)₂), 1.10 (3 H, d, J 6.8, CH₃CHCHO), 2.41-2.60 (1 H, m, CH₃CH CHO), 3.49 (2 H, d, J 6.0, BnOCH₂), 4.10-4.13 (1 H, m, CHOTBS), 4.51 (2 H, s, PhCH₂), 7.29-7.34 (5 H, m, Ph), 9.75 (1 H, d, J 2, CHO); $\delta_{\rm C}$ (100 MHz; CDCl₃) -5.04, -4.38, 10.04, 18.06, 25.75, 49.99, 72.02, 72.69, 73.46, 127.70, 127.72, 128.40, 137.85, 203.92; *m*/z (CI) 115 (TBS, 7%), 107 (PhCH₂O, 2%), 91 (PhCH₂, 100%), 77 (Ph, 3%).

(2*E*,4*S*,5*S*) Methyl 6-benzyloxy-5-(*tert*-butyldimethylsilyl)oxy -4- methyl hex-2-enoate (6):-

Methyl (triphenylphosphranylidene) acetate (4.71 g, 14.01 mmol) was added to a stirred solution of aldehyde (3.03 g, 9.39 mmol) in dry CH₂Cl₂ (20 mL) and refluxed for 14 hours. The solvent was removed *in vacuo*. Purification by flash chromatography (petroleum ether : ethyl acetate 10:1) afforded the alkene **6** (3.06 g, 8.08 mmol) in 86 % yield as a colourless oil. Rf (Petroleum ether : ethyl acetate 4:1) 0.71; (Found: $[M+H]^+$ 379.2303. C₂₁H₃₅O₄Si

requires [*M*+*H*] 379.2305); $[\alpha]D^{22}$ + 36.5 (*c* 2.0, CHCl₃); υ_{max} (film) /cm⁻¹ 2955 s, 2930 s, 2858 s (CH₃, CH₂), 1725 s (C=O), 1655 m, 1470 s, 1252 s, 1105 s, 837 s; $\delta_{\rm H}$ (400 MHz; CDCl₃) 0.05 (3 H, s, SiCH₃), 0.07 (3 H, s, SiCH₃), 0.87 (9 H, br s, Si(CH₃)₃), 1.08 (3 H, d, *J* 8.8, CH₃CH), 2.60-2.65 (1 H, m, CH₃CH), 3.33-3.40 (2 H, m, BnOCH₂), 3.76 (3 H, s, OCH₃), 3.76-3.80 (1 H, m, CHOTBS), 4.46 (1 H, d, *J* 11.6, PhCH_A), 4.50 (1 H, d, *J* 12.0, PhCH_B), 5.82 (1 H, dd, *J* 15.6 and 1.0, CHCO₂CH₃), 6.98 (1 H, dd, *J* 15.6 and 8.4, CH CHCO₂CH₃), 7.30-7.35 (5 H, m, Ph); $\delta_{\rm C}$ (75 MHz; CDCl₃) -4.97 (CH₃), -4.32 (CH₃), 16.28 (CH₃), 23.07 (C), 25.82 (CH₃), 40.17 (CH), 51.30 (CH₃), 72.92 (CH₂), 73.36 (CH₂), 74.48 (CH), 121.27 (CH), 127.70 (CH), 128.37 (CH), 138.23 (C), 150.86 (CH), 167.08 (C); *m/z* (CI) 396 (M+NH4, 100%), 379 (M+H, 30%), 347 (M-OTBS, 25%), 247 (16%), 108 (PhCH₂OH), 91 (PhCH₂, 19%).

(3R,4R,5R) 4-Hydroxy-5,6-(iso-propylidenedioxy)-3-methyl-hex-1-ene (9):-

To a 500ml 3 neck round bottom flask at -78°C (fitted with internal thermometer) was condensed trans-but-2-ene (12.6ml, 126mmol). Dry THF (90ml) was added slowly (to avoid boiling off the but-2-ene) and potassium tert-butoxide (14.4g, 127.5mmol) added. n-BuLi (51ml, 127.5mmol as a 2.5 molar solution in hexanes) was added at a rate so as to maintain the internal temperature below -65°C. On complete addition the mixture was stirred at -50°C for exactly 15 minutes, then immediately cooled to -78°C. Triiso-propyl borate (29.46ml, 127.5mmol) was added dropwise at a rate so as to ensure the internal temperature did not rise above -65°C. The solution was stirred at -78°C for 10 minutes and then poured into a 1 litre separating funnel containing hydrochloric acid that had been previously saturated with sodium chloride (240ml, 1 molar hydrochloric acid). The pH of the solution was immediately adjusted to pH 1 by the addition of hydrochloric acid (1 molar) and a solution of (S,S)-diisopropyl tartrate (30g, 127.5mmol) in Et₂O (45ml) added. The mixture was shaken and the Et₂O layer separated. The aqueous layer was extracted with Et₂O (600ml), and the combined Et₂O layers dried over MgSO₄ for 2 hours with stirring, then filtered and concentrated in vacuo. The residue was dried whilst stirring on a vacuum line for 1 hour. Meanwhile, whilst the solution was drying over MgSO₄, a solution of 1,2:5,6 di-O-iso-propylidene-D-mannitol (22.0g, 84.0mmol) in THF (300ml) was added to a suspension of NaIO₄ (19.7g, 92.1mmol) in water (40ml) and THF (60ml). The slurry was stirred vigorously for 1 hour then Et₂O (200ml) added. The mixture was filtered at suction and concentrated in vacuo. The residue was redissolved in CH2Cl2 (200ml), dried over MgSO4, filtered and concentrated in vacuo ensuring the temperature of the water bath on the rotary evaporator was <35°C. The aldehyde was stored at -78° C until required. The crude (S,S)-diiso-propyl tartrate (E)-crotyl boronate was dissolved in dry toluene (450ml) and 4Å molecular sieves (10g) added. The mixture was stirred for 30 minutes under N2 at room temperature, then cooled to -78°C, whereupon the aldehyde (the whole amount of the crude product prepared according to the procedure described above) was added in toluene (30ml) via cannula dropwise over 5 minutes. The solution was allowed to gradually warm to room temperature overnight. Aqueous NaOH (300ml, 0.5 molar solution) was added at 10°C and the solution stirred for 30 minutes. The

toluene layer was separated and the aqueous phase extracted with Et₂O (800ml). The combined organic extracts were washed with NaHCO₃ (600ml, saturated), brine (600ml), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluting with 9:1 hexane:Et₂O) to give the homoallylic alcohol (9) (8.79g, 37%) as a colourless oil. R_f (3:1 hexane:Et₂O) 0.27, (Found: M⁺+H, 187.1335. C₁₀H₁₉O₃ requires M+H, 187.1334); [α]_D²² +12.6 (*c* 0.94, CH₂Cl₂); v_{max} (thin film)/cm⁻¹ 3494br (OH), 3076, 2985, 2935 and 2876 (sp³ CH₃), 1639m (C=C); $\delta_{\rm H}$ (300 MHz; CDCl₃) 1.11 (3H, d, *J* 6.9, *CH*₃CH), 1.37 (3H, s, 1 of (*CH*₃)₂CO(O)), 1.43 (3H, s, 1 of (*CH*₃)₂CO(O)), 2.21-2.30 (2H, m, CH₃CH and OH), 3.23-3.43 (1H, m, CH(OH)), 3.73 (1H, dd, *J* 6.9 and 7.8, 1 of *CH*₂O), 3.98-4.14 (2H, m, 1 of *CH*₂O and OCH₂CHO), 5.02-5.10 (2H, m, CH₂=CH), 5.89 (1H, ddd, *J* 8.1, 10.5 and 18.6, CH₂=CH); $\delta_{\rm C}$ (75 MHz; CDCl₃) 16.56 (*CH*₃CH), 25.34 and 26.47 ((*CH*₃)₂CO(O)), 41.25

(CH₃CH), 66.13 (OCH₂), 75.24 (OCH₂CHO), 77.03 (CH(OH)), 109.26 ((CH₃)₂CO(O)), 115.53 (CH=CH₂), 139.65 (CH=CH₂); m/z (CI) 204 (M⁺+NH₄, 30%), 187 (M⁺+H, 100%).

(3R,4R,5R)-4-[(tert-Butyldimethylsilyl)oxy]-5,6-(iso-propylidenedioxy)-3-methyl-hex-1ene (10):-

To alcohol (9) (5.28g, 28.39mmol) in dry DMF (65ml) was added imidazole (4.25g, 62.46mmol) and TBSCI (9.41g, 62.46mmol). The solution was stirred at room temperature overnight. Et₂O (400ml) was added to the mixture and the solution washed with water (200ml), then brine (200ml). The solution was dried over MgSO₄, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (9:1 hexane:Et₂O) gave the silyl ether (10) (8.14g, 96%) as a colourless oil. R_f (3:1 hexane:Et₂O) 0.64, (Found: M⁺+H, 301.2192. C₁₆H₃₃O₃Si requires M+H, 301.2199); $[\alpha]_D^{22}$ -7.8 (c 1.4, CHCl₃); ν_{max} (thin film)/cm⁻¹ 2985, 2958, 2932, 2899 and 2858 sp³ CH₃, 1641 (m) C=C; $\delta_{\rm H}$ (300 MHz; CDCl₃) 0.08 and 0.10 (6H, 2 x s, Si(CH₃)₂C(CH₃)₃), 0.91 (9H, s, Si(CH₃)₂C(CH₃)₃), 1.07 (3H, d, J 6.9, (CH₃)CH), 1.32 (3H, s, 1 of (CH₃)₂CO(O)), 1.38 (3H, s, 1 of (CH₃)₂CO(O)), 1.98-2.11 (1H, m, CH₃CH), 3.45-3.55 and 3.91-3.96 (4H, m, CH(OTBS) and CH(O)CH₂O), 4.92-5.00 (2H, m, CH_2 =CH) 5.88 (1H, ddd, J 8.7, 10.5 and 17.1, CH_2 =CH); δ_C (75 MHz; CDCl₃) -5.05 and -4.06 $(Si(CH_3)_2C(CH_3)_3)$, 18.45 $(Si(CH_3)_2C(CH_3)_3)$, 18.46 $((CH_3)CH)$, 25.50 and 26.57 ((CH₃)₂CO(O)), 25.94 (Si(CH₃)₂C(CH₃)₃), 41.85 (CH₃CH), 65.78 (OCH₂), 78.04 and 79.01 (OCH₂CHO and CH(OTBS)), 108.74 ((CH₃)₂CO(O)), 114.73 (CH=CH₂), 139.77 (CH=CH₂); m/z (CI) 301 (M⁺+H, 100%), 243 (M⁺-'Bu, 65%).

(2E,4R,5R,6R)-5-[(tert-Butyldimethylsilyl)oxy]-6,7-O-iso-propylidene-4-methyl-hept-2enoic acid methyl ester (11):-

To a solution of alkene (10) (5.0g, 16.7mmol) in dry MeOH (30ml) and dry CH_2Cl_2 (30ml) at -78°C was bubbled a stream of O₃ in O₂. The reaction was monitored by t.l.c. until no starting material could be detected, then N₂ was bubbled through the solution for a further 20 minutes at -78°C to remove any residual O₃. At the point where starting material could not be detected

by t.l.c. the solution maintained a pale blue colouration. Me₂S (7.4ml, 100.6mmol) was added at -78°C and the solution allowed to warm to room temperature over 1.5 hours. The solution was diluted with CH₂Cl₂ (200ml) and washed with brine (200ml). The aqueous layer was back extracted with a further portion of CH₂Cl₂ (100ml) and the combined CH₂Cl₂ layers dried over MgSO₄. After filtration and concentration in vacuo, the residue was redissolved in dry CH₂Cl₂ (150ml) and Ph₃P=CHCO₂Me (13.89g, 41.7mmol) added. The mixture was heated at reflux overnight. Sand (ca. 20g) was added and the mixture concentrated in vacuo. The crude residue was purified by flash column chromatography (80:20 hexane:Et₂O) to give the ene ester (11) (4.75g, 80% over 2 steps) as a colourless oil which solidified at temperatures <-10°C. R_f (3:1 hexane:Et₂O) 0.36; (Found: C, 60.09; H, 9.61. C₁₈H₃₄O₅Si requires C, 60.29; H, 9.56%); (Found: M⁺+H, 359.2250. C₁₈H₃₄O₅Si requires M+H, 359.2254); $[\alpha]_D^{22}$ +9.4 (c 1.06, CHCl₃); v_{max} (thin film)/cm⁻¹ 2986, 2956, 2933, 2895 and 2858 (sp³ CH₃), 1727s (C=O), 1657m (C=C); δ_H (400 MHz; CDCl₃) 0.09 and 0.11 (6H, 2 x s, Si(CH₃)₂C(CH₃)₃), 0.91 (9H, s, Si(CH₃)₂C(CH₃)₃), 1.13 (3H, d, J 6.8, CH₃CH), 1.32 (3H, s, 1 of (CH₃)₂CO(O)), 1.39 (3H, s, 1 of (CH₃)₂CO(O)), 2.23-2.31 (1H, m, CH₃CH), 3.48-3.63 and 3.88-3.94 (4H, m, CH(OTBS) and CH(O)CH₂O), 3.74 (3H, s, CO₂(CH₃)) 5.78 (1H, dd, J 0.8 and 16.0, CH₃O₂CCH=CH) 7.04 (1H, dd, J 9.2 and 16.0, (CH₃O₂CCH=CH); δ_{C} (100 MHz; CDCl₃) -4.85 and -3.92 (Si(CH₃)₂C(CH₃)₃), 17.96 (CH₃CH), 18.44 (Si(CH₃)₂C(CH₃)₃), 25.50 and 26.62 ((CH₃)₂CO(O)), 26.04 (Si(CH₃)₂C(CH₃)₃), 40.29 (CH₃CH), 51.46 (CH₃O₂C), 65.67 (OCH2), 77.52 and 78.66 (OCH2CHO and CH(OTBS)), 109.05 ((CH3)2CO(O)), 121.14 and 149.99 (CH=CH), 166.79 (C=O); m/z (CI) 376 (M⁺+NH₄, 100%), 359 (M⁺+H, 45%), 301 $(M^{+}-Bu, 22\%).$

(2R,3S,4R,5R) Methyl 6-benzyloxy-5-(*tert*-butyldimethylsilyl)oxy-4-methyl-2-3dihydroxyhexanoate (12):-

OsO4 (2.5 % wt solution in tert -butanol 0.17 mL, 0.01 mmol) was added to a stirred solution of N-methylmorpholine N-oxide (90 mg, 0.77 mmol) and alkene 6 (100 mg, 0.26 mmol) in acetone / water (8:1) (2 mL) and stirred for 4 hours. Aqueous NaHSO3 (2 mL) was added. The aqueous layer was extracted with ethyl acetate $(3 \times 5 \text{ mL})$ and the combined organic layers dried with anhydrous MgSO4. The solvent was removed in vacuo. Purification by dry flash chromatography (petroleum ether : ethyl acetate 1:1) afforded the diol 12 (110 mg, 0.27 mmol) in 83 % yield and 5:1 deratio as a colourless oil. Rf (petroleum ether : ethyl acetate 4:1) 0.17; (Found: $[M+H]^+$ 413.2365. C₂₁H₃₇SiO₆ requires [M+H] 413.2359); $[\alpha]_D^{22}$ + 0.83 (c 6.0, CHCl3); vmax (CHCl3) /cm⁻¹ 3546 br, m (OH), 2957 s, 2932 s, 2859 m (CH3, CH2), 1740 s (C=O), 1462 m, 1256 s, 1095 s, 908 s; 8H (400 MHz; CDCl3) 0.06 (3 H, s, SiCH3), 0.08 (3 H, s, SiCH3), 0.89 (9 H, br s, SiC(CH3)3), 0.96 (3 H, d, J 8, CH3CH), 2.04-2.11 (1 H, m, CH₃CH), 2.8-3.1 (2 H, br s, OH), 3.45 (1 H, dd, J 9.6 and 4.8, BnOCH_A), 3.57 (1 H, dd, J 10.0 and 6.0, BnOCHB), 3.81 (3 H, s, OCH3), 3.92 (1 H, dd, J 9.2 and 1.2, CH3CHCH OH), 4.02 (1 H, q, J 4.8, CHOTBS), 4.22 (1 H, d, J 1.2, CHCO2CH3), 4.52 (2 H, s, PhCH₂), 7.27-7.35 (5 H, m, Ph); δ_C (100 MHz; CDCl₃) -4.96, -4.43, 11.49, 13.17, 18.09, 25.81, 39.53, 52.56, 71.91, 73.05, 73.45, 74.16, 127.58, 127.76, 128.40, 137.72, 174.25; m/z (CI) 430 (M+NH4, 20%), 413 (M+H, 100%), 396 (20%), 324 (50%), 287 (25%), 232 (24%), 132 (TBSH, 11%), 107 (PHCH₂O, 17%), 91 (PhCH₂, 15%).

(2R,3S,4R,5R,6R)-Methyl 5-[(*tert*-butyldimethylsilyl)oxy]-2,3:6,7-bis-O-iso-propylidene-4-methyl-heptanoate (13):-

To ene ester (11) (146mg, 0.408mmol) in acetone/water (1ml, 8:1) was added N-methyl morpholine N-oxide (143mg, 1.22mmol) and OsO4 (251µl, 0.02mmol as a 2.5% wt / wt solution in tert-BuOH). The solution was stirred at room temperature for 4 hours, then aqueous NaHSO₃ (0.5ml, saturated) added. The solution was concentrated in vacuo. EtOAc (50ml) was added and the mixture washed with brine (20ml). The aqueous phase was extracted with EtOAc (50ml), and the combined EtOAc extracts dried over MgSO₄, filtered and concentrated in vacuo. The residue was redissolved in acetone (1ml) and 2,2dimethoxypropane (1ml) and TsOH (10mg, cat.) added. The solution was stirred at room temperature overnight, then concentrated in vacuo. The residue was purified by flash column chromatography (80:20 hexane:Et₂O) to give the ester (13) (141mg, 80%) as a colourless oil. R_f (1:1 hexane:Et₂O) 0.57; (Found: C, 58.60; H, 9.37. C₂₁H₄₁O₇Si requires C, 58.30; H, 9.32%); (Found: M⁺+H, 433.2626. C₂₁H₄₁O₇Si requires M+H, 433.2622); $[\alpha]_D^{22}$ +3.2 (c 0.94, CHCl₃); v_{max} (thin film)/cm⁻¹ 2988, 2955, 2935, 2888 and 2858 (sp³ CH₃), 1754s (C=O); δ_{H} (400 MHz; CDCl₃) 0.08 and 0.12 (6H, 2 x s, Si(CH₃)₂C(CH₃)₃), 0.89 (9H, s, Si(CH₃)₂C(CH₃)₃), 0.99 (3H, d, J 7.1, (CH₃)CH), 1.34, 1.39, 1.40 and 1.43 (12H, 4 x 3H s, 2 x (CH₃)₂CO(O)), 1.68-1.76 (1H, m, CH₃CH), 3.55 (1H, dd, J 7.9 and 8.1, 1 of CH₂O), 3.66 (1H, dd, J 2.0 and 7.6, CH(OTBS)), 3.76 (3H, s, CO₂CH₃), 4.03 (1H, dd, J 6.3 and 7.9, 1 of CH2O), 4.22 (1H, d, J 7.0, CH3O2CCH), 4.29 (1H, ddd, J 6.3, 7.3 and 8.1, OCH2CH(O)), 4.43 (1H, dd, J 7.0 and 8.5, CH₃O₂CCH(O)CH(O)); δ_{C} (100 MHz; CDCl₃) -4.96 and -3.92 $(Si(CH_3)_2C(CH_3)_3)$, 13.83 (CH_3CH) , 18.48 $(Si(CH_3)_2C(CH_3)_3)$, 25.50 and 25.74 ((CH₃)₂CO(O)), 26.05 (Si(CH₃)₂C(CH₃)₃), 26.73 and 26.96 ((CH₃)₂CO(O)), 40.89 (CH₃CH), 52.30 (CH₃O₂C), 66.20 (OCH₂), 77.74 (CH(OTBS)), 77.98 (CH₃O₂CCH(O)CH(O)), 78.39 (CH₃O₂CCH(O)CH(O)), 78.62 ((O)CHCH₂O) 108.80 and 110.50 (2 x (CH₃)₂CO(O)), 171.54 (C=O); m/z (CI) 433 (M⁺+H, 100%), 375 (M⁺-^tBu, 80%).

(2S,3R,4R,5R) Methyl 6-benzyloxy-5-(*tert*-butyldimethylsilyl)oxy-4-methyl-2,3dihydroxyhexanoate (14):-

(DHQD)₂PHAL (0.348 g, 0.45 mmol), K₃Fe(CN)₆ (4.42 g, 13.4 mmol), K₂CO₃ (1.85 g, 13.4 mmol) were dissolved in *tert* -butanol : water (1:1) (40 mL). OsO₄ (2.5 % wt solution in *tert* -butanol, 5.41 mL, 0.45 mmol) and MeSO₂NH₂ (1.28 g, 13.4 mmol) were added and the solution was stirred for 5 minutes. Alkene 6 (1.69 g, 4.5 mmol) was added and stirred for 4 hours. Aqueous 1M Na₂SO₃ (30 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers dried with anhydrous MgSO₄. The solvent was removed *in vacuo*. Purification by dry flash chromatography (petroleum ether : ethyl acetate 1:1) afforded the diol 14 (1.68g, 0.41 mmol) in 91 % yield and 6:1 *de*. ratio as a colourless oil. Rf (Petroleum ether : ethyl acetate 4:1) 0.12; (Found: [M+H]⁺ 413.2368.

C₂₁H₃₇SiO₆ requires [*M*+*H*] 413.2359); $[\alpha]D^{22} + 22.5$ (*c* 2.0, CHCl₃); υ_{max} (CHCl₃) /cm⁻¹ 3546 br m (OH), 2957 s, 2932 s, 2859 m, (CH₃, CH₂), 1740 s (C=O), 1462 m, 1256 s, 1095 s, 908 s; δ_{H} (400 MHz; CDCl₃) 0.06 (3 H, s, SiCH₃), 0.09 (3 H, s, SiCH₃), 0.88 (9 H, br s, SiC(CH₃)₃), 1.10 (3 H, d, *J* 8.0, CH ₃CH), 2.01-2.04 (1 H, m, CH₃CH), 3.24 (1 H, d, *J* 6.4, CHO*H*), 3.34 (1 H, d, *J* 3.4, CHO*H*), 3.46-3.58 (2 H, m, BnOCH₂), 3.77 (3 H, s, OCH₃), 3.90-3.93 (1 H, m, CHOTBS), 4.15-4.12 (1 H, m, CH₃CH*C*HOH), 4.20-4.22 (1 H, m, CHCO₂CH₃) 4.53 (2 H, s, PhCH₂), 7.26-7.35 (5 H, m, Ph); δ_{C} (100 MHz; CDCl₃) -5.06 (CH₃), -4.46 (CH₃), 11.50 (CH₃), 18.03 (C), 25.81 (CH₃), 39.28 (CH), 52.48 (CH₃), 72.14 (CH₂), 73.21 (CH), 72.14 (CH₂), 73.52 (CH₂), 75.42 (CH), 127.58 (CH), 127.76 (CH), 128.41 (CH), 137.80 (C), 173.68 (C); *m*/z (CI) 340 (M+NH₄, 4%), 413 (M+H, 35%), 396 (31%), 287 (49%), 232 (76%), 215 (71%), 132 (TBSH, 35%), 108 (PhCH₂OH, 100%), 91 PhCH₂, 95%).

(2S,3R,4R,5R,6R)-Methyl 5-[(*tert*-butyldimethylsilyl)oxy]-2,3:6,7-bis-O-iso-propylidene-4-methyl-heptanoate (15):-

Solid (DHQD)₂PHAL (120.2mg, 0.154mmol, 10mol%), K₃Fe(CN)₆ (1.52g, 4.63mmol), K₂CO₃ (639.3mg, 4.63mmol) were dissolved in tert-BuOH/water (15ml, 1:1) and OsO₄ (1.94ml, 0.154mmol, 10mol% as a 2.5% wt / wt solution in tert-BuOH) added. MeSO₂NH₂ (440.1mg, 4.63mmol) was added and the mixture stirred at room temperature for 5 minutes. The 'super' AD-mix solution was transferred via syringe to ene ester (11) (552mg, 1.54mmol) and the mixture stirred at room temperature overnight. Solid Na₂SO₃ (2.31g, 18.35mmol) was added and the mixture stirred for 30 minutes at room temperature. The black solution was extracted with CH₂Cl₂ (250ml) and washed with water (100ml). The aqueous phase was back extracted with CH₂Cl₂ (100ml) and the combined CH₂Cl₂ layers dried over MgSO₄, filtered and concentrated in vacuo. The residue was redissolved in acetone (6ml), 2,2dimethoxypropane (6ml) and TsOH (25mg, cat.) were added. The solution was stirred at room temperature overnight, then CH₂Cl₂ (250ml) added. The mixture was washed with NaHCO₃ (100ml, saturated), brine (100ml), dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (80:20 hexane:Et₂O) to give the ester (15) (439.6mg, 66%) as a colourless oil. R_f (1:1 hexane:Et₂O) 0.50; (Found: C, 58.50; H, 9.35. C₂₁H₄₁O₇Si requires C, 58.30; H 9.32); (Found: M⁺+H, 433.2626. C₂₁H₄₁O₇Si requires M+H, 433.2622); $[\alpha]_D^{22}$ +25.3 (c 1.03, CHCl₃); v_{max} (thin film)/cm⁻¹ 2989, 2956, 2934, 2892 and 2859 (sp³ CH₃), 1761s (C=O); δ_{H} (400 MHz; CDCl₃) 0.08 and 0.10 (6H, 2 x s, Si(CH3)2C(CH3)3), 0.89 (9H, s, Si(CH3)2C(CH3)3), 1.02 (3H, d, J 8, CH3CH), 1.34, 1.40, 1.41 and 1.45 (12H, 4 x 3H s, 2 x (CH₃)₂CO(O)), 1.95-2.02 (1H, m, CH₃CH), 3.65-3.69 (2H, m, 1 of CH₂O and CH(OTBS)), 3.76 (3H, s, CO₂CH₃), 4.98 (1H, dd, J 6.4 and 8.0, 1 of CH₂O), 4.16-4.21 and 4.35-4.41 (3H, m, OCH₂CH(O) and CH₃O₂CCH(O)CH(O)); δ_{C} (100 MHz; CDCl₃); -4.81 and -3.90 (Si(CH₃)₂C(CH₃)₃), 10.81 (CH₃CH), 18.32 (Si(CH₃)₂C(CH₃)₃), 25.33 and 25.54 ((CH_3)₂CO(O)), 25.91 (Si(CH₃)₂C(CH_3)₃), 26.47 and 26.68 ((CH_3)₂CO(O)), 38.20 ((CH₃)CH), 55.16 (CH₃O₂C), 66.04 (OCH₂), 75.53, 76.70, 77.95 and 78.45 (CH(OTBS), CH₃O₂CCH(O)CH(O) and (O)CHCH₂O), 108.63 and 111.59 (2 x (CH₃)₂CO(O)), 171.89

(C=O); m/z (CI) 450 (M⁺+NH₄, 10%), 433 (M⁺+H, 30%), 375 (M⁺-'Bu, 100%).

(6R,7R,8R)-Methyl-7-[*tert*-(butyldimethylsilyl)oxy]-8-9-*O-iso*-propylidene-6-methylnona-2,4-dienoate (16):-

The α , β -unsaturated ester 11 (910 mg; 2.54 mmol) was dissolved in dry dichloromethane (13 mL) and cooled to -78°C. A 1 M solution of DIBAL in dichloromethane (6.35 mL; 6.35 mmol) was added and the solution was stirred for 90 min. at -78°C and quenched with a mixture of a pH7 phosphate buffer (21.5 mL), an 0.5 M aqueous solution of tartaric acid (44 mL) and ethyl acetate (27 mL). After warming to room temperature the mixture was extracted with dichloromethane (2 x 150 mL) and the combined organic extracts were dried with MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane-diethyl ether; 3:1) to give (2E,4R,5R,6R)-5-[(tert-butyldimethylsilyl)oxy]-6,7-0iso-propylidene-4-methyl hept-2-en-1-ol as a clear oil (840 mg; 100%); Rf 0.24 (1:1; hexane-ether); Found: C, 61.79; H, 10.40. C₁₇H₃₄O₄Si requires C, 61.77; H, 10.37%; (Found MNH_4^+ , 348.2574. C₁₇H₃₄O₄Si requires MNH_4^+ , 348.2570); v_{max} (film)/cm⁻¹ 3396m,br (OH), 2957s and 2932s (CH); $[\alpha_D]^{25}$ +0.8 (c 1.22 in CHCl₃); $\delta_H(300 \text{ MHz}; \text{ CDCl}_3)$ 0.08 (3 H, s, SiCH₃), 0.10 (3 H, s, SiCH₃), 0.91 (9 H, s, C(CH₃)₃), 1.07 (3 H, d, J 6.9, CH₃-4), 1.32 (3 H, s, CH₃CCH₃), 1.39 (3 H, s, CH₃CCH₃), 2.10 (1 H, m, H-4), 3.48-3.56 (2 H, m, H-7, H-5), 3.90-3.96 (2 H, m, H-7, H-6), 4.10 (2 H, dd, J 1.1 and 5.8, 2xH-1), 5.60 (1 H, m, H-2), 5.74 (1 H, ddd, J 1.1, 8.7 and 15.5, H-3); $\delta_{\rm C}(75.5~{\rm MHz};~{\rm CDCl_3})$ -4.92 and -3.93 (SiCH₃), 18.45 (SiC(CH₃)₃), 18.82 (CH₃), 26.04 (SiC(CH₃)₃), 25.54 and 26.60 (CH₃), 40.28 (CH), 63.67 (CH₂), 65.78 (CH₂), 77.98 (CH), 78.89 (CH), 108.88 (C), 129.47 (CH) and 133.64 (CH); m/z 348 (MNH4⁺, 28%).

To a solution of the above compound (256 mg; 0.774 mmol) in dry dichloromethane (5.1 mL) under argon was added Dess-Martin periodinane (492 mg; 1.16 mmol) and the mixture was stirred at room temperature for 1h. The reaction was added a mixture of pentane (7 mL) and diethylether (7 mL) and filtered through a layer of Celite. The filter was rinsed with the same mixture of solvents (20 mL) and the filtrates were combined and anhydrous sodium carbonate was added. The mixture was stirred for 15 min, dried with MgSO₄ and filtered through a layer of Celite. The filter was rinsed with the same mixture of solvents (30 mL) and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in hexane (10 mL) and filtered though a layer of Celite. The filter was rinsed with the same solvent (30 mL) and the combined filtrates were concentrated *in vacuo*. The crude aldehyde (R_f 0.53 (1:1; hexane-ether)) was dissolved in dry dichloromethane (9 mL) and Ph₃PCHCO₂CH₃ (646 mg; 1.94 mmol) was added.

The reaction was stirred under reflux for 16 h, cooled to room temperature, added silica and evaporated. The residue was purified by column chromatography (14:1; hexane-ether) to give ester 16 as a clear oil (277 mg, 93%); R_f 0.62 (1:1; hexane-ether); Found: C, 62.40; H, 9.48. C₂₀H₃₆O₅Si requires C, 62.46; H, 9.43; (Found: M⁺H⁺, 385.2402. C₂₀H₃₆O₅Si requires M⁺H⁺, 385.2410); v_{max} (film)/cm⁻¹ 2985s, 2955s and 2932s (CH), 1720s (C=O), 1642m and 1615m (C=C); $[\alpha_D]^{25}$ +4.5 (c 1.12 in CHCl₃); δ_H (400 MHz; CDCl₃) 0.08 (3 H, s, SiCH₃), 0.10 (3 H, s,

SiCH₃), 0.91 (9 H, s, C(CH₃)₃), 1.11 (3 H, d, J 6.8, CHCH₃), 1.31 (3 H, s, CH₃CCH₃), 1.39 (3 H, s, CH₃CCH₃), 2.20 (1 H, m, H-6), 3.52 (1 H, m, H-9), 3.59 (1 H, m, H-7), 3.74 (3 H, s, OCH₃), 3.85-3.92 (2 H, m, H-9, H-8), 5.81 (1 H, d, J 15.2, H-2), 6.12 (1 H, dd, J 15.6, 10.4, H-4), 6.22 (1 H, dd, J 15.2, 8.8, H-5), 7.27 (1H, dd, 15.2, 10.4, H-3); δ_{C} (100.6 MHz; CDCl₃) - 4.85 and -3.89 (SiCH₃), 18.46 (SiC(CH₃)₃), 18.62 (CH₃), 26.05 (SiC(CH₃)₃), 25.52 and 26.65 (CH₃), 40.90 (CH), 51.47 (OCH₃), 65.73 (CH₂), 77.89 (CH), 78.88 (CH), 109.01 (C), 119.51 (CH), 128.31 (CH), 144.97 (CH), 145.02 (CH) and 167.54 (C=O); *m/z* 385 (MH⁺, 35%).

(3S,4R,5R,6S)-5-Benzyloxymethyl-3,4-dihydroxy-5-methyl tetrahydropyran-2-one (17):-

TBAF (1M solution in THF, 2.2 mL, 2.20 mmol) was added dropwise to a stirred solution of diol (14) (700 mg, 1.69 mmol) in dry THF (20 mL) and stirred for 1.5 hours. Water (10 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (6 x 20 mL) and the combined organic layers dried with anhydrous MgSO4. The solvent was removed in vacuo. Purification by flash column chromatography (ethyl acetate) afforded the lactone (17) (306 mg) in 68% yield as an oil which crystallised slowly at room temperature. m.p. 55-57°C; Rf (EtOAc) 0.35; (Found: $[M]^+$ 266.1150. $C_{14}H_{18}O_5$ requires M 266.1154); $[\alpha]_D^{22}$ - 14.09 (c 2.2 CHCl₃); v_{max} (CHCl₃) /cm⁻¹ 3014 m (OH), 3584 m, 2929 m, 2871 m (CH₃), 1739 s (C=O), 1453 m, 1206 s, 1111 s; δ_H (400 MHz; CDCl₃) 1.03 (3H, d, J 8, CH₃CH), 1.50-1.70 (2H, br s, OH), 2.25-2.36 (1H, m, CH₃CH), 3.60 (1H, t, J 10.4, CH₃CHCH(OH)), 3.65 (1H, dd, J 11.2 and 3.2, BnOCH_A), 3.74 (1H, dd, J 13.6 and 2.4, BnOCH_B), 4.03 (1H, d, J 10.0, C(O)CH(OH), 4.09 (1H, dd, J 10.4 and 2.4, CH₂CH), 4.52 (1H, d, J 12.0, PhCH_A), 4.63 (1H, d, J 12.0, PhCH₂), 7.26-7.36 (5H, m, Ph); δ_C (100 MHz; CDCl₃) 13.32 (CH₃), 35.31 (CH), 69.06 (CH₂), 73.21 (CH), 73.27 (CH), 73.61 (CH₂), 83.33 (CH), 127.71 (2 x CH), 127.91 (CH), 128.50 (2 x CH), 137.54 (C), 172.93 (C); m/z (CI) 284 (M+NH4, 50%), 266 (M+H, 100%), 250 (31%), 233 (15%), 160 (16%), 108 (PhCH₂OH, 44%), 91 (PhCH₂, 19%).

(2R,3S,6R,7R,8R)-Methyl 7-[(*tert*-butyldimethylsilyl)oxy]-2,3-dihydroxy-8,9-*O-iso*-propylidene-6-methylnon-4-enoate (18) and (4S,5S,6R,7R,8R)-Methyl 7-[(*tert*butyldimethylsilyl)oxy]-4,5-dihydroxy-8,9-*O-iso*-propylidene-6-methylnon-2-enoate (19):-

To a solution of $K_3Fe(CN)_6$ (138.1 mg; 0.420 mmol), K_2CO_3 (58.0 mg;0.420 mmol) and $(DHQ)_2PHAL$ (5.6 mg; 0.0070 mmol) in a 1:1 mixture of *t*-BuOH and water (1.42 mL) was added a 2.5 w/w-% solution of OsO₄ in *t*-BuOH (17.7 µL; 0.00140 mmol) and MeSO₂NH₂ (39.8 mg; 0.420 mmol).

After stirring at room temperature for 10 min. the solution was poured into a flask containing ester 16 (54 mg; 0.140 mmol). The mixture was stirred at room temperature for 21 h, quenched with Na₂SO₃ (209 mg; 1.66 mmol) and diluted with water (3 mL). The mixture was extracted with dichloromethane (3x15 mL) and the combined organic phases were dried with MgSO₄ and concentrated *in vacuo*. Further purification using column chromatography (hexane:ether 1:1) afforded 18 as a clear oil (19.6 mg, 33%), 19 as an oil (4.5 mg, 7.6%) and starting material 16 as a clear oil (20.2 mg, 37%). Data for 18: R_f 0.45 (ether); (Found:

 MNH_4^+ , 436.2728. $C_{20}H_{38}O_7Si$ requires MNH_4^+ , 436.2731); $[\alpha_D]^{25}$ -7.8 (c 1.28 in CHCl₃); δ_H(300 MHz; CDCl₃) 0.08 (3 H, s, SiCH₃), 0.10 (3 H, s, SiCH₃), 0.91 (9 H, s, C(CH₃)₃), 1.10 (3 H, d, J 6.9 CH₃-6), 1.31 (3 H, s, CH₃CCH₃), 1.40 (3 H, s, CH₃CCH₃), 2.20 (1 H, m, H-6), 3.56-3.61 (2 H, m, H-9, H-7), 3.83 (3 H, s, OCH₃), 3.88-3.99 (2 H, m, H-9, H-8), 4.15 (1 H, m, H-2), 4.38 (1 H, m, H-3), 5.58 (1 H, dd, J 15.7, 6.4, H-4), 5.88 (1 H, dd, J 15.7, 9.0, H-5); $\delta_{\rm C}(75.5 \text{ MHz}; \text{CDCl}_3)$ -4.88 and -3.97 (SiCH₃), 18.43 (SiC), 18.82 (CH₃), 26.04 (SiC(CH₃)₃), 25.24 and 26.47 (CH₃), 40.15 (CH), 52.72 (CH₃), 65.53 (CH₂), 73.40 (CH), 73.86 (CH), 77.63 (CH), 78.59 (CH), 109.03 (C), 128.53 (CH), 134.74 (CH) and 173.21 (C=O); m/z 418 (M⁺, 71%), 436 (MNH4⁺, 100%). Physical data for compound 19: Rf 0.57 (ether); (Found: M⁺H⁺, 419.2471. C₂₀H₃₈O₇Si requires M⁺H⁺, 419.2465); δ_H(300 MHz; CDCl₃) 0.13 (3 H, s, SiCH₃), 0.14 (3 H, s, SiCH₃), 0.92 (9 H, s, C(CH₃)₃), 1.05 (3 H, d, J 7.0 CH₃-6), 1.41 (3 H, s, CH₃CCH₃), 1.43 (3 H, s, CH₃CCH₃), 1.86 (1 H, m, H-6), 3.61-3.74 (3 H, m, H-9, H-7, H-5), 3.75 (3 H, s, OCH₃), 4.04 (1 H, dd, J 8.3, 6.7, H-9), 4.24-4.31 (2 H, m, H-8, H-4), 6.15 (1 H, dd, J 15.7, 1.6, H-2), 7.02 (1 H, dd, J 15.7, 4.1, H-3); $\delta_{\rm C}(75.5 \text{ MHz}; \text{CDCl}_3)$ -4.90 and -4.22 (SiCH₃), 17.06 (CH₃), 18.29 (SiC), 25.95 (SiC(CH₃)₃), 25.28 and 26.48 (CH₃), 38.02 (CH), 51.55 (CH₃), 66.22 (CH₂), 71.29 (CH), 74.70 (CH), 79.30 (CH), 79.39 (CH), 109.41 (C), 121.54 (CH) and 149.31 (CH); *m/z* 419 (MH⁺, 83%), 401 (100%).

(2*S*,3*R*,6*R*,7*R*,8*R*)-Methyl 7-[(*tert*-butyldimethylsilyl)oxy]-2,3-dihydroxy -8,9-*O-iso*-propylidene-6-methylnon-4-enoate (20):-

To a solution of K₃Fe(CN)₆ (104.8 mg; 0.319 mmol), K₂CO₃ (44.0 mg;0.319 mmol) and (DHQD)₂PHAL (4.2 mg; 0.0053 mmol) in a 1:1 mixture of t-BuOH and water (1.08 mL) was added a 2.5 w/w-% solution of OsO4 in t-BuOH (13.4 µL; 0.00106 mmol) and MeSO2NH2 (30.3 mg; 0.319 mmol). After stirring at room temperature for 10 min. the solution was poured into a flask containing 16 (41 mg; 0.106 mmol). The mixture was stirred at room temperature for 21 h, quenched with Na₂SO₃ (159 mg; 1.36 mmol) and diluted with water (3 mL). The mixture was extracted with dichloromethane (3x10 mL) and the combined organic phases were dried with MgSO4 and concentrated in vacuo. Further purification using column chromatography (hexane:ether 1:1) afforded 20 as a pure clear oil (18.0 mg, 41%) and starting material 16 as a clear oil (11.7 mg, 29%). Rf 0.43 (ether); (Found: M⁺NH₄⁺, 436.2744. C20H38O7Si requires M⁺NH4⁺, 436.2737); v_{max} (film)/cm⁻¹ 2935s (CH) and 1734s (C=O); Found: C, 57.63; H, 9.22 C₂₀H₃₈O₇Si requires C, 57.39; H, 9.15; $[\alpha_D]^{25}$ +10.5 (c 1.14 in CHCl₃); $\delta_{H}(300 \text{ MHz}; \text{ CDCl}_3) 0.08 (3 \text{ H, s, SiCH}_3), 0.10 (3 \text{ H, s, SiCH}_3), 0.91 (9 \text{ H, s, s}_3)$ C(CH₃)₃), 1.10 (3 H, d, J 7.0 CH₃-6), 1.32 (3 H, s, CH₃CCH₃), 1.40 (3 H, s, CH₃CCH₃), 2.17 (1 H, m, H-6), 3.07 (1H, d, OH), 3.51-3.58 (2 H, m, H-9, H-7), 3.84 (3 H, s, OCH₃), 3.90-3.95 (2 H, m, H-9, H-8), 4.16 (1 H, m, H-2), 4.38 (1 H, m, H-3), 5.56 (1 H, dd, J 15.7, 6.7, H-4), 6.05 (1 H, dd, J 15.4, 8.9, H-5); $\delta_{\rm C}(75.5 \text{ MHz}; {\rm CDCl}_3)$ -4.90 and -3.92 (SiCH₃), 18.45 (SiC), 18.84 (CH₃), 26.06 (SiC(CH₃)₃), 25.46 and 26.56 (CH₃), 40.26 (CH), 52.77 (CH₃), 65.69 (CH₂), 73.40 (CH), 73.91 (CH), 77.88 (CH), 78.80 (CH), 108.99 (C), 128.50 (CH), 135.30 436 $(MNH_4^+,$ 48%), 401 (100%). (CH) and 171.2 (C**=**0); m/z

References :

- 1. Sweeney, J.B., in 'Comprehensive Organic Functional Group Transformations', Ed., Katritzky, A.R., Meth-Cohn, O, Rees, C.W., Pergamon Press, 1995, 2, 44.
- 2. Cha, J.K., Kim, N-S.; Chem. Rev., 1995, 95, 1761.
- a) Heiser, B., Broger, E.A., Crameri, Y., *Tetrahedron: Asymm.*, 1991, 2, 51. b) For an analogous substrate see: Beck, G., Jendralla, H., Kesseler, K., *Synthesis*, 1995, 1014.
- 4. Frater, G., Helv. Chim. Acta., 1979, 62, 2825.
- a) Schreiber, S.L., Meyer, S.D., J. Org. Chem., 1994, 59, 7549. b) Ireland, R.E., Liu,
 L., J. Org. Chem., 1993, 58, 2899. c) Dess, D.B., Martin, J.C., J. Am. Chem. Soc.,
 1991, 113, 7277.
- a) Roush, W.R., Coe, J.W., J. Org. Chem., 1989, 54, 915. b) Roush, W.R., Ando, K., Powers, D.B., Palkowitz, A.D., Halterman, R.L., J. Am. Chem. Soc., 1990, 112, 6339.
- 7. Schreiber, S.L., Ikemoto, N., J. Am. Chem. Soc., 1992, 114, 2524.
- 8. Sasaki, S., Hamada, Y., Shiori, T., Tetrahedron Lett., 1997, 38, 3013.
- 9. Kolb, H.C., VanNieuwenhze, M.S., Sharpless, K.B., Chem. Rev., 1994, 94, 2483.
- a) Hale, K.J., Lennon, J.A., Manaviazar, S., Javaid, M.H., Hobbs, C.J., *Tetrahedron* Lett., 1995, 36, 1359. b) Hale, K.J., Manaviazar, S., Delisser, V.M., *Tetrahedron*, 1994, 50, 9181.
- Guzman-Perez, A., Corey, E.J., *Tetrahedron Lett.*, **1997**, *38*, 5941; Sunazuka, A., Hirose, T., Harigaya, Y., Takamatsu, S., Hayashi, M., Komiyama, K., Omura, S., Sprengler, P.A. and Smith, A.B.III, *J. Am. Chem. Soc.*, **1997**, *119*, 10247.
- a) Kobayashi, M., Aoki, S., Sakai, H., Kawazoe, K., Kihara, N., Sasaki, T., Kitagawa, I., *Tetrahedron Lett.*, 1993, 34, 2795. b) Kobayashi, M., Aoki, S., Kitagawa, I., *Tetrahedron Lett.*, 1994, 35, 1243. c) Kobayashi, M., Aoki, S., Gato, K., Kitagawa, I., *Chem. Pharm. Bull.*, 1996, 44, 2142.