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

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Abstract : Dihydroxylation of ene ester systems was achieved in good yield and diastereoselectivity under classical catalytic OsO_4 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 OsO_4 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 ester[3] **4** in quantitative yield and >95% enantioselectivity. Dianion methodology[4] 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 syn-diastereoisomer by chromatography over silica) followed by a Dess Martin oxidation[5] and Wittig homologation gave the ene ester **6** which was freed from the contaminating *syn*-diastereoisomer by chromatography over silica).

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The ene ester system **11** was reduced to the corresponding alcohol using DIBALH, oxidised to the related ene aldehyde with the Dess Martin periodinane[5] 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.

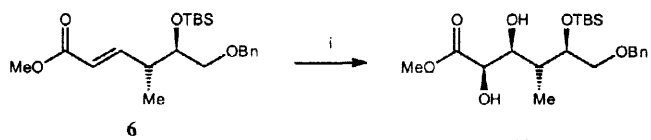
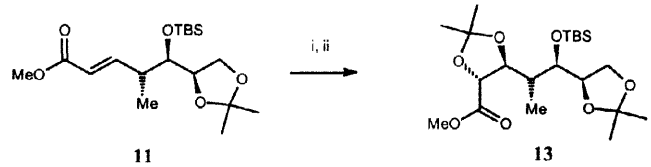
11 **16**

Reagents and Conditions : i) DIBALH, CH_2Cl_2; ii) Dess Martin periodinane, CH_2Cl_2; iii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, (93% over 3 steps).

Scheme 3

Dihydroxylation Reactions:

The ene esters **6** and **11** were subjected to dihydroxylation conditions previously reported by Schreiber[7] whereby each ene ester was dissolved in an 8:1 acetone : water mixture and the co-oxidant *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,

Reaction	*Ratio**	Yield
 **6** → **12**	5:1	83%
 **11** → **13**	12:1	80%

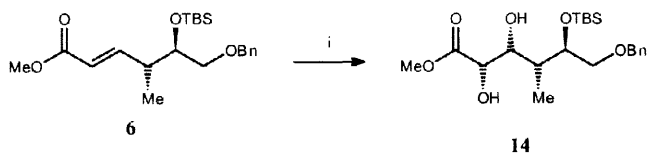
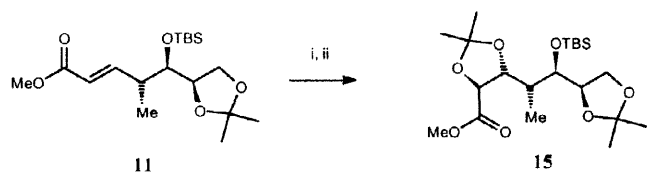
Reagents and Conditions: i) OsO_4 (*cat.*), NMO, acetone:H_2O (8:1), ii) $(MeO)_2CMe_2$, acetone, TsOH.

* Determined by integration of the anisochronous Me*CH* 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 OsO_4 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 $K_2OsO_2(OH)_4$ to OsO_4, at a concentration between 8 and 10 mol % and used as a 2.5% w/w solution in *t*-BuOH. The co-oxidant, $K_3Fe(CN)_6$, remained at a concentration of 3 mole equivalents and K_2CO_3 (3 mole equivalents) was added to the mixture. In addition 3 mole equivalents of $MeSO_2NH_2$ (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).

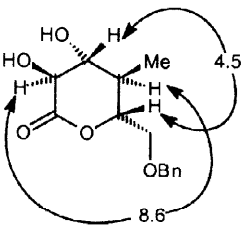
Reaction	*Ratio**	Yield
 **6** → **14**	6:1	91%
 **11** → **15**	8:1	66%

Reagents and Conditions: i) 'Super' AD-mix β, ii) $(MeO)_2CMe_2$, acetone, TsOH.

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

Table 2

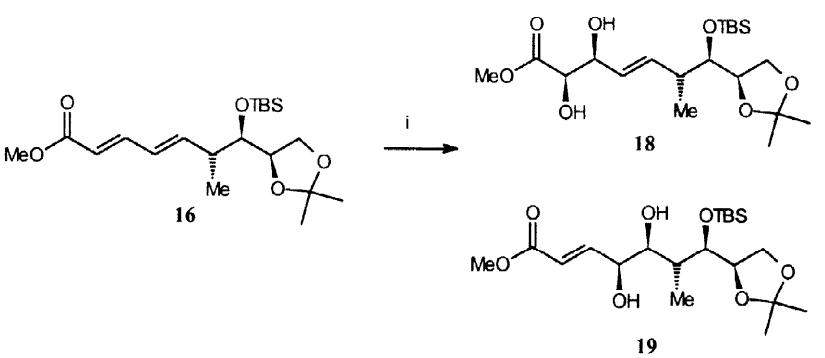
Treatment of the dihydroxyester (**14**) with tetrabutylammonium fluoride in THF gave the lactone (**17**). The assignment of relative stereochemistry around the six membered ring was made on the basis of nOe measurements and some key interactions are shown in Figure 1 (numbers refer to the percentage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



17

Figure 1

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 Sharpless[9] 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% OsO_4, 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.

(200 MHz; $CDCl_3$) 1.23 (6H, d, *J* 6.4, $(CH_3)_2CH$), 3.51 (2H, s, $BnOCH_2$), 4.14 (2H, s, $CH_2CO_2{}^iPr$), 4.59 (2H, s, $PhCH_2$), 5.32 (1H, sept, *J* 6.4, $(CH_3)_2CH$), 7.30-7.39 (5H, m, Ph); δ_C (50 MHz; $CDCl_3$) 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 + NH_4, 100 %), 251 (M+H, 45%), 162 (96%), 145 (59%), 108 ($PhCH_2OH$, 70 %), 102 (CH_2=C(OH)O^{i}Pr, 28%), 91 ($PhCH_2$, 28%).

(3*R*) *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)$RuCl_2$ (solution in *iso*-propanol : CH_2Cl_2, 5:2 8 mL, 303 mg, 0.360 mmol) was added *via* cannula. The autoclave was charged with H_2 (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. R_f (petroleum ether : ethyl acetate 4:1) 0.26 ; (Found: $[M]^+$ 252.1360. $C_{14}H_{20}O_4$ requires *M* 252.1362); $[\alpha]_D^{22}$ + 9.5 (*c* 10, $CHCl_3$); υ_{max} (film) /cm^{-1} 3452 br s (OH), 3063 s, 2979 s, 2924 s (CH_3, CH_2), 1727 s (C=O), 1374 s, 1178 s; δ_H (400 MHz; $CDCl_3$) 1.23 (6H, d, *J* 6.3, $(CH_3)_2CH$), 2.51 (2 H, d, *J* 6.3, $CHCO_2{}^iPr$), 3.10 (1 H, d, *J* 4.4, OH), 3.50-3.47 (2 H, m, $BnOCH_2$), 4.20-4.28 (1 H, m, CHOH), 4.56 (2 H, s, $PhCH_2$), 5.04 (1 H, sept, *J* 6.3, $(CH_3)_2CH$), 7.30-7.36 (5 H, m, Ph); δ_C (100 MHz; $CHCl_3$) 21.79 (2xCH_3), 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 - $BnOCH_2O$, 7%), 107 ($PhCH_2O$, 14%), 91 ($PhCH_2$, 100%), 89 (39%), 77 (Ph, 3%), 43 (^iPr, 56%).

(2*S*,3*S*) *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 di*iso*-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 NH_4Cl (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 $MgSO_4$. 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. R_f (Petroleum ether : ethyl acetate 4 :1) 0.49; (Found: $[M]^+$ 266.1517. $C_{15}H_{22}O_4$ requires *M* 266.1518); $[\alpha]_D^{22}$ +11

(*c* 10, $CHCl_3$); υ_{max} (film) /cm^{-1} 3478 br s, 2981, s, 2938 s, 2876 s, 1727 s, 1453 s, 1374 s 1183 s; for major diastereoisomer δ_H (400 MHz; $CDCl_3$) 1.17 (3 H, d, *J* 6.4, $CHCH_3$), 1.22 (6 H, d, *J 6.0*, $OCH(CH_3)_2$), 2.68 (1 H, pent, *J* 6.4, CH_3CH), 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, *CH*OH), 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), $CH(CH_3)_2$), 7.26-7.35 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$) 13.98, 21.69, 42.41, 67.95, 71.65, 72.38 (CH_2), 75.30 (CH_2) 127.71, 127.76, 128.42, 137.91, 175.01; *m/z* (EI) 266 (M^+, 0.2%), 107 ($BnOCH_2$, 11%), 103 (50%), 91 ($PhCH_2$, 100%), 77 (Ph, 2%), 43 (^iPr).

(2*S*,3*S*) *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 2,6-lutidine (9.32 mL, 0.080 mol) and (2*S*,3*S*)-*iso*-propyl 4-benzyloxy-3-hydroxy-2-methylbutyrate (10.0 g, 0.038 mol) in dry CH_2Cl_2 (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 CH_2Cl_2 (3 x 50mL) and the combined organic layers dried with anhydrous $MgSO_4$. 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. R_f (Petroleum ether : ethyl acetate 4:1) 0.78; (Found: C, 66.40 %; H, 9.52 %. $C_{21}H_{37}O_4Si$ requires C, 66.26 %; H, 9.55 %. Found: $[M+H]^+$ 381.2459 $C_{21}H_{37}O_4Si$ requires */M+H/* 381.2461); $[\alpha]_D^{22}$ +20.4 (*c* 10, $CHCl_3$); υ_{max} (film) /cm^{-1} 2955 s, 2932 s, 2858 s (CH_3, CH_2), 1733 s (C=O), 1651 m, 1373 m, 1254 s, 1109 s; for the major diastereoisomer δ_H (400 MHz; $CDCl_3$) 0.059 (3 H, s, $SiCH_3$), 0.068 (3 H, s, $SiCH_3$), 0.87 (9 H, br s, $C(CH_3)_3$), 1.11 (3 H, d, *J* 7.2, $CH_3CHCO_2{}^iPr$), 1.20 (3 H, d, *J* 6.4, $CO_2CH(CH_3)$), 1.21 (3 H, d, *J*6.4, $CO_2CH(CH_3)$), 2.70-2.72 (1 H, m, $CH_3CH\,CO^iPr$), 3.47 (1 H, dd, *J* 10.0 and 5.6, $BnOCH_2$), 3.53 (1 H, dd, *J* 10.0 and 4.8, $BnOCH_2$), 4.06 (1 H, q, *J*5, CHOTBS), 4.06 (1 H, d, *J* 12.0, $PhCH_A$), 4.54 (1 H, d, *J* 12.0, $PhCH_B$), 4.98 (1 H, sept, *J* 6, *CH* $(CH_3)_2$), 7.28-7.34 (5 H, m, Ph); δ_C (100 MHz; $CHCl_3$) -2.94, 12.70, 18.07, 21.81, 25.80, 43.97, 67.40, 72.83 (CH_2), 73.35 (CH_2), 127.51, 127.67, 128.28, 138.33, 173.64; *m/z* (CI) 381 (M+H, 100%), 321 (M-O^iPr, 6%), 248 (9%), 108 ($PhCH_2OH$, 13%), 91 ($PhCH_2$, 6%).

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

Di*iso*-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 °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 CH_2Cl_2 (4 x 50 mL) and the combined organic layers dried with anhydrous $MgSO_4$.

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. R_f (petroleum ether : ethyl acetate 6:1) 0.39; (Found: C, 66.41 %; H, 10.07 %. $C_{18}H_{33}O_3Si$ requires C, 66.61 %; H, 9.95 %; Found: $[M+H]^+$ 325.2200. $C_{18}H_{33}O_3Si$ requires *[M+H]* 325.2199); $[\alpha]_D^{22}$ + 3.33 (*c* 1.2, $CHCl_3$); υ_{max} (film) /cm^{-1} 3500 br s (OH), 2956 s, 2930 s (CH_3, CH_2), 1471 s, 1462 s, 1252 s, 1098 s, 836 s; δ_H (400 MHz; $CHCl_3$) 0.06 (3 H, s, $SiCH_3$), 0.09 (3 H, s, $SiCH_3$), 0.87 (9 H, br s, $Si(CH_3)_2$), 1.02 (3 H, d, *J* 7.2, CH_3CH), 1.84-1.96 (1 H, m, $CHCH_3$) 3.49 (1 H, dd, *J* 15.6 and 5.2, CH_AOH), 3.55-3.57 (2 H, m, $BnOCH_2$), 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, $PhCH_2$), 7.31-7.35 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$) 14.34 (CH_3), 18.06 (CH_3), 26.00 (CH_3), 37.78 (CH), 64.85 (CH_2), 72.94 (CH_2), 73.47 (CH_2), 75.76 (CH), 127.65 (CH), 127.73 (CH), 128.40 (CH), 137.90 (C); *m/z* (CI) 342 ($M+NH_4$, 8%), 325 (M+H, 100%), 108 ($PhCH_2OH$, 27%), 91 ($PhCH_2$, 28%).

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

A solution of alcohol (2.12 g, 6.5 mmol) in dry CH_2Cl_2 (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 $Na_2S_2O_3$ (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers dried with anhydrous $MgSO_4$. 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, $CHCl_3$); υ_{max} (film) /cm^{-1} 2955 s, 2931 s, 2858 s (CH_3, CH_2), 1726 s (C=O), 1461 m, 1254 s, 1107 s, 837 s; δ_H (400 MHz; $CDCl_3$) 0.054 (3 H, s, $SiCH_3$), 0.070 (3 H, s, $SiCH_3$), 0.87 (9 H, br s, $SiC(CH_3)_2$), 1.10 (3 H, d, *J* 6.8, CH_3CHCHO), 2.41-2.60 (1 H, m, CH_3CH CHO), 3.49 (2 H, d, *J* 6.0, $BnOCH_2$), 4.10-4.13 (1 H, m, CHOTBS), 4.51 (2 H, s, $PhCH_2$), 7.29-7.34 (5 H, m, Ph), 9.75 (1 H, d, *J* 2 , CHO); δ_C (100 MHz; $CDCl_3$) -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 ($PhCH_2O$, 2%), 91 ($PhCH_2$, 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 CH_2Cl_2 (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. R_f (Petroleum ether : ethyl acetate 4:1) 0.71; (Found: $[M+H]^+$ 379.2303. $C_{21}H_{35}O_4Si$

requires *[M+H]* 379.2305); $[\alpha]_D^{22}$ + 36.5 (*c* 2.0, $CHCl_3$); υ_{max} (film) /cm^{-1} 2955 s, 2930 s, 2858 s (CH_3, CH_2), 1725 s (C=O), 1655 m, 1470 s, 1252 s, 1105 s, 837 s; δ_H (400 MHz; $CDCl_3$) 0.05 (3 H, s, $SiCH_3$), 0.07 (3 H, s, $SiCH_3$), 0.87 (9 H, br s, $Si(CH_3)_3$), 1.08 (3 H, d, *J* 8.8, CH_3CH), 2.60-2.65 (1 H, m, CH_3CH), 3.33-3.40 (2 H, m, $BnOCH_2$), 3.76 (3 H, s, OCH_3), 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, $CHCO_2CH_3$), 6.98 (1 H, dd, *J* 15.6 and 8.4, CH $CHCO_2CH_3$), 7.30-7.35 (5 H, m, Ph); δ_C (75 MHz; $CDCl_3$) -4.97 (CH_3), -4.32 (CH_3), 16.28 (CH_3), 23.07 (C), 25.82 (CH_3), 40.17 (CH), 51.30 (CH_3), 72.92 (CH_2), 73.36 (CH_2), 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 ($M+NH_4$, 100%), 379 (M+H, 30%), 347 (M-OTBS, 25%), 247 (16%), 108 ($PhCH_2OH$), 91 ($PhCH_2$, 19%).

(3*R*,4*R*,5*R*) 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. Tri*iso*-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*)-di*iso*-propyl tartrate (30g, 127.5mmol) in Et_2O (45ml) added. The mixture was shaken and the Et_2O layer separated. The aqueous layer was extracted with Et_2O (600ml), and the combined Et_2O layers dried over $MgSO_4$ 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 $MgSO_4$, 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 $NaIO_4$ (19.7g, 92.1mmol) in water (40ml) and THF (60ml). The slurry was stirred vigorously for 1 hour then Et_2O (200ml) added. The mixture was filtered at suction and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (200ml), dried over $MgSO_4$, 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*)-di*iso*-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 N_2 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 Et_2O (800ml). The combined organic extracts were washed with $NaHCO_3$ (600ml, saturated), brine (600ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluting with 9:1 hexane:Et_2O) to give the homoallylic alcohol (**9**) (8.79g, 37%) as a colourless oil. R_f (3:1 hexane:Et_2O) 0.27, (Found: M^++H, 187.1335. $C_{10}H_{19}O_3$ requires *M+H*, 187.1334); $[\alpha]_D^{22}$ +12.6 (*c* 0.94, CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 3494br (OH), 3076, 2985, 2935 and 2876 (sp^3 CH_3), 1639m (C=C); δ_H (300 MHz; $CDCl_3$) 1.11 (3H, d, *J* 6.9, *CH*$_3$CH), 1.37 (3H, s, 1 of *(CH*$_3$*)*$_2$CO(O)), 1.43 (3H, s, 1 of *(CH*$_3$*)*$_2$CO(O)), 2.21-2.30 (2H, m, CH_3CH 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 OCH_2CHO), 5.02-5.10 (2H, m, CH_2=CH), 5.89 (1H, ddd, *J* 8.1, 10.5 and 18.6, CH_2=*CH*); δ_C (75 MHz; $CDCl_3$) 16.56 (*CH*$_3$CH), 25.34 and 26.47 (*(CH*$_3$*)*$_2$CO(O)), 41.25

(CH_3CH), 66.13 (OCH_2), 75.24 (OCH_2CHO), 77.03 (*C*H(OH)), 109.26 ((CH_3)$_2$*C*O(O)), 115.53 (CH=*C*H_2), 139.65 (*C*H=CH_2); *m/z* (CI) 204 (M^++NH_4, 30%), 187 (M^++H, 100%).

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

To alcohol (**9**) (5.28g, 28.39mmol) in dry DMF (65ml) was added imidazole (4.25g, 62.46mmol) and TBSCl (9.41g, 62.46mmol). The solution was stirred at room temperature overnight. Et_2O (400ml) was added to the mixture and the solution washed with water (200ml), then brine (200ml). The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography (9:1 hexane:Et_2O) gave the silyl ether (**10**) (8.14g, 96%) as a colourless oil. R_f (3:1 hexane:Et_2O) 0.64, (Found: M^++H, 301.2192. $C_{16}H_{33}O_3Si$ requires *M+H*, 301.2199); $[\alpha]_D^{22}$ -7.8 (*c* 1.4, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2985, 2958, 2932, 2899 and 2858 sp^3 CH_3, 1641 (m) C=C; δ_H (300 MHz; $CDCl_3$) 0.08 and 0.10 (6H, 2 x s, Si*(CH*$_3$*)*$_2$C(CH_3)$_3$), 0.91 (9H, s, Si(CH_3)$_2$C*(CH*$_3$*)*$_3$), 1.07 (3H, d, *J* 6.9, *(CH*$_3$*)*CH), 1.32 (3H, s, 1 of *(CH*$_3$*)*$_2$CO(O)), 1.38 (3H, s, 1 of *(CH*$_3$*)*$_2$CO(O)), 1.98-2.11 (1H, m, CH_3CH), 3.45-3.55 and 3.91-3.96 (4H, m, *CH*(OTBS) and *CH*(O)CH_2O), 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; $CDCl_3$) -5.05 and -4.06 (Si*(CH*$_3$*)*$_2$C(CH_3)$_3$), 18.45 (Si(CH_3)$_2$*C*(CH_3)$_3$), 18.46 (*(CH*$_3$*)*CH), 25.50 and 26.57 (*(CH*$_3$*)*$_2$CO(O)), 25.94 (Si(CH_3)$_2$C*(CH*$_3$*)*$_3$), 41.85 (CH_3CH), 65.78 (OCH_2), 78.04 and 79.01 (OCH_2CHO and *C*H(OTBS)), 108.74 ((CH_3)$_2$*C*O(O)), 114.73 (CH=*C*H_2), 139.77 (*C*H=CH_2); *m/z* (CI) 301 (M^++H, 100%), 243 (M^+-^{t}Bu, 65%).

(2*E*,4*R*,5*R*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6,7-*O*-*iso*-propylidene-4-methyl-hept-2-enoic 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 O_3 in O_2. The reaction was monitored by t.l.c. until no starting material could be detected, then N_2 was bubbled through the solution for a further 20 minutes at -78°C to remove any residual O_3. At the point where starting material could not be detected

by t.l.c. the solution maintained a pale blue colouration. Me_2S (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 CH_2Cl_2 (200ml) and washed with brine (200ml). The aqueous layer was back extracted with a further portion of CH_2Cl_2 (100ml) and the combined CH_2Cl_2 layers dried over $MgSO_4$. After filtration and concentration *in vacuo*, the residue was redissolved in dry CH_2Cl_2 (150ml) and $Ph_3P{=}CHCO_2Me$ (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:Et_2O) 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:Et_2O) 0.36; (Found: C, 60.09; H, 9.61. $C_{18}H_{34}O_5Si$ requires C, 60.29; H, 9.56%); (Found: M^++H, 359.2250. $C_{18}H_{34}O_5Si$ requires *M+H*, 359.2254); $[\alpha]_D^{22}$ +9.4 (*c* 1.06, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2986, 2956, 2933, 2895 and 2858 (sp^3 CH_3), 1727s (C=O), 1657m (C=C); δ_H (400 MHz; $CDCl_3$) 0.09 and 0.11 (6H, 2 x s, $Si(CH_3)_2C(CH_3)_3$), 0.91 (9H, s, $Si(CH_3)_2C(CH_3)_3$), 1.13 (3H, d, *J* 6.8, CH_3CH), 1.32 (3H, s, 1 of $(CH_3)_2CO(O)$), 1.39 (3H, s, 1 of $(CH_3)_2CO(O)$), 2.23-2.31 (1H, m, CH_3CH), 3.48-3.63 and 3.88-3.94 (4H, m, CH(OTBS) and $CH(O)CH_2O$), 3.74 (3H, s, $CO_2(CH_3)$) 5.78 (1H, dd, *J* 0.8 and 16.0, $CH_3O_2CCH{=}CH$) 7.04 (1H, dd, *J* 9.2 and 16.0, ($CH_3O_2CCH{=}CH$); δ_C (100 MHz; $CDCl_3$) -4.85 and -3.92 ($Si(CH_3)_2C(CH_3)_3$), 17.96 (CH_3CH), 18.44 ($Si(CH_3)_2C(CH_3)_3$), 25.50 and 26.62 ($(CH_3)_2CO(O)$), 26.04 ($Si(CH_3)_2C(CH_3)_3$), 40.29 (CH_3CH), 51.46 (CH_3O_2C), 65.67 (OCH_2), 77.52 and 78.66 (OCH_2CHO and CH(OTBS)), 109.05 ($(CH_3)_2CO(O)$), 121.14 and 149.99 (CH=CH), 166.79 (C=O); *m/z* (CI) 376 (M^++NH_4, 100%), 359 (M^++H, 45%), 301 (M^+-^{t}Bu, 22%).

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

OsO_4 (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 $NaHSO_3$ (2 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers dried with anhydrous $MgSO_4$. 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. R_f (petroleum ether : ethyl acetate 4:1) 0.17; (Found: $[M+H]^+$ 413.2365. $C_{21}H_{37}SiO_6$ requires *[M+H]* 413.2359); $[\alpha]_D^{22}$ + 0.83 (*c* 6.0, $CHCl_3$); υ_{max} ($CHCl_3$) /cm^{-1} 3546 br, m (OH), 2957 s, 2932 s, 2859 m (CH_3, CH_2), 1740 s (C=O), 1462 m, 1256 s, 1095 s, 908 s; δ_H (400 MHz; $CDCl_3$) 0.06 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$), 0.89 (9 H, br s, $SiC(CH_3)_3$), 0.96 (3 H, d, *J* 8, CH_3CH), 2.04-2.11 (1 H, m, CH_3CH), 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, $BnOCH_B$), 3.81 (3 H, s, OCH_3), 3.92 (1 H, dd, *J* 9.2 and 1.2, CH_3CHCH OH), 4.02 (1 H, q, *J* 4.8, CHOTBS), 4.22 (1 H, d, *J* 1.2, $CHCO_2CH_3$), 4.52 (2 H, s, $PhCH_2$), 7.27-7.35 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$) -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+NH_4, 20%), 413 (M+H, 100%), 396 (20%), 324 (50%), 287 (25%), 232 (24%), 132 (TBSH, 11%), 107 ($PHCH_2O$, 17%), 91 ($PhCH_2$, 15%).

(2*R*,3*S*,4*R*,5*R*,6*R*)-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 OsO_4 (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 $NaHSO_3$ (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 $MgSO_4$, filtered and concentrated *in vacuo*. The residue was redissolved in acetone (1ml) and 2,2-dimethoxypropane (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:Et_2O) to give the ester (**13**) (141mg, 80%) as a colourless oil. R_f (1:1 hexane:Et_2O) 0.57; (Found: C, 58.60; H, 9.37. $C_{21}H_{41}O_7Si$ requires C, 58.30; H, 9.32%); (Found: M^++H, 433.2626. $C_{21}H_{41}O_7Si$ requires *M+H*, 433.2622); $[\alpha]_D^{22}$ +3.2 (*c* 0.94, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2988, 2955, 2935, 2888 and 2858 (sp^3 CH_3), 1754s (C=O); δ_H (400 MHz; $CDCl_3$) 0.08 and 0.12 (6H, 2 x s, Si*(CH$_3$)*$_2$C(CH$_3$)$_3$), 0.89 (9H, s, Si(CH$_3$)$_2$C*(CH$_3$)*$_3$), 0.99 (3H, d, *J* 7.1, *(CH$_3$)*CH), 1.34, 1.39, 1.40 and 1.43 (12H, 4 x 3H s, 2 x *(CH$_3$)*$_2$CO(O)), 1.68-1.76 (1H, m, CH_3CH), 3.55 (1H, dd, *J* 7.9 and 8.1, 1 of CH_2O), 3.66 (1H, dd, *J* 2.0 and 7.6, *C*H(OTBS)), 3.76 (3H, s, CO_2CH_3), 4.03 (1H, dd, *J* 6.3 and 7.9, 1 of CH_2O), 4.22 (1H, d, *J* 7.0, CH_3O_2CCH), 4.29 (1H, ddd, *J* 6.3, 7.3 and 8.1, $OCH_2CH(O)$), 4.43 (1H, dd, *J* 7.0 and 8.5, $CH_3O_2CCH(O)CH(O)$); δ_C (100 MHz; $CDCl_3$) -4.96 and -3.92 (Si*(CH$_3$)*$_2$C(CH$_3$)$_3$), 13.83 (*CH$_3$*CH), 18.48 (Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 25.50 and 25.74 (*(CH$_3$)*$_2$CO(O)), 26.05 (Si(CH$_3$)$_2$C*(CH$_3$)*$_3$), 26.73 and 26.96 (*(CH$_3$)*$_2$CO(O)), 40.89 (CH_3CH), 52.30 (*CH$_3$*O$_2$C), 66.20 (O*C*H$_2$), 77.74 (*CH*(OTBS)), 77.98 ($CH_3O_2CCH(O)CH(O)$), 78.39 ($CH_3O_2CCH(O)CH(O)$), 78.62 ((O)*C*HCH$_2$O) 108.80 and 110.50 (2 x (CH$_3$)$_2$*C*O(O)), 171.54 (*C*=O); *m/z* (CI) 433 (M^++H, 100%), 375 (M^+-^{t}Bu, 80%).

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

$(DHQD)_2PHAL$ (0.348 g, 0.45 mmol), $K_3Fe(CN)_6$ (4.42 g, 13.4 mmol), K_2CO_3 (1.85 g, 13.4 mmol) were dissolved in *tert* -butanol : water (1:1) (40 mL). OsO_4 (2.5 % wt solution in *tert* -butanol, 5.41 mL, 0.45 mmol) and $MeSO_2NH_2$ (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 Na_2SO_3 (30 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers dried with anhydrous $MgSO_4$. 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. R_f (Petroleum ether : ethyl acetate 4:1) 0.12; (Found: $[M+H]^+$ 413.2368.

$C_{21}H_{37}SiO_6$ requires *[M+H]* 413.2359); $[\alpha]_D^{22}$ + 22.5 (*c* 2.0, $CHCl_3$); υ_{max} ($CHCl_3$) /cm^{-1} 3546 br m (OH), 2957 s, 2932 s, 2859 m, (CH_3, CH_2), 1740 s (C=O), 1462 m, 1256 s, 1095 s, 908 s; δ_H (400 MHz; $CDCl_3$) 0.06 (3 H, s, $SiCH_3$), 0.09 (3 H, s, $SiCH_3$), 0.88 (9 H, br s, $SiC(CH_3)_3$), 1.10 (3 H, d, *J* 8.0, C*H* $_3$CH), 2.01-2.04 (1 H, m, CH_3CH), 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, $BnOCH_2$), 3.77 (3 H, s, OCH_3), 3.90-3.93 (1 H, m, CHOTBS), 4.15-4.12 (1 H, m, $CH_3CHCHOH$), 4.20-4.22 (1 H, m, $CHCO_2CH_3$) 4.53 (2 H, s, $PhCH_2$), 7.26-7.35 (5 H, m, Ph); δ_C (100 MHz; $CDCl_3$) -5.06 (CH_3), -4.46 (CH_3), 11.50 (CH_3), 18.03 (C), 25.81 (CH_3), 39.28 (CH), 52.48 (CH_3), 72.14 (CH_2), 73.21 (CH), 72.14 (CH_2), 73.52 (CH_2), 75.42 (CH), 127.58 (CH), 127.76 (CH), 128.41 (CH), 137.80 (C), 173.68 (C); *m/z* (CI) 340 ($M+NH_4$, 4%), 413 (M+H, 35%), 396 (31%), 287 (49%), 232 (76%), 215 (71%), 132 (TBSH, 35%), 108 ($PhCH_2OH$, 100%), 91 $PhCH_2$, 95%).

(2*S*,3*R*,4*R*,5*R*,6*R*)-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%), $K_3Fe(CN)_6$ (1.52g, 4.63mmol), K_2CO_3 (639.3mg, 4.63mmol) were dissolved in *tert*-BuOH/water (15ml, 1:1) and OsO_4 (1.94ml, 0.154mmol, 10mol% as a 2.5% wt / wt solution in *tert*-BuOH) added. $MeSO_2NH_2$ (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 Na_2SO_3 (2.31g, 18.35mmol) was added and the mixture stirred for 30 minutes at room temperature. The black solution was extracted with CH_2Cl_2 (250ml) and washed with water (100ml). The aqueous phase was back extracted with CH_2Cl_2 (100ml) and the combined CH_2Cl_2 layers dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was redissolved in acetone (6ml), 2,2-dimethoxypropane (6ml) and TsOH (25mg, cat.) were added. The solution was stirred at room temperature overnight, then CH_2Cl_2 (250ml) added. The mixture was washed with $NaHCO_3$ (100ml, saturated), brine (100ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (80:20 hexane:Et_2O) to give the ester (**15**) (439.6mg, 66%) as a colourless oil. R_f (1:1 hexane:Et_2O) 0.50; (Found: C, 58.50; H, 9.35. $C_{21}H_{41}O_7Si$ requires C, 58.30; H 9.32); (Found: M^++H, 433.2626. $C_{21}H_{41}O_7Si$ requires *M+H*, 433.2622); $[\alpha]_D^{22}$ +25.3 (*c* 1.03, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2989, 2956, 2934, 2892 and 2859 (sp^3 CH_3), 1761s (C=O); δ_H (400 MHz; $CDCl_3$) 0.08 and 0.10 (6H, 2 x s, $Si(CH_3)_2C(CH_3)_3$), 0.89 (9H, s, $Si(CH_3)_2C(CH_3)_3$), 1.02 (3H, d, *J* 8, CH_3CH), 1.34, 1.40, 1.41 and 1.45 (12H, 4 x 3H s, 2 x $(CH_3)_2CO(O)$), 1.95-2.02 (1H, m, CH_3CH), 3.65-3.69 (2H, m, 1 of CH_2O and CH(OTBS)), 3.76 (3H, s, CO_2CH_3), 4.98 (1H, dd, *J* 6.4 and 8.0, 1 of CH_2O), 4.16-4.21 and 4.35-4.41 (3H, m, $OCH_2CH(O)$ and $CH_3O_2CCH(O)CH(O)$); δ_C (100 MHz; $CDCl_3$); -4.81 and -3.90 ($Si(CH_3)_2C(CH_3)_3$), 10.81 (CH_3CH), 18.32 ($Si(CH_3)_2C(CH_3)_3$), 25.33 and 25.54 ($(CH_3)_2CO(O)$), 25.91 ($Si(CH_3)_2C(CH_3)_3$), 26.47 and 26.68 ($(CH_3)_2CO(O)$), 38.20 ($(CH_3)CH$), 55.16 (CH_3O_2C), 66.04 (OCH_2), 75.53, 76.70, 77.95 and 78.45 (CH(OTBS), $CH_3O_2CCH(O)CH(O)$ and $(O)CHCH_2O$), 108.63 and 111.59 (2 x $(CH_3)_2CO(O)$), 171.89

(*C*=O); ***m/z*** (CI) 450 (M^++NH_4, 10%), 433 (M^++H, 30%), 375 (M^+-^{t}Bu, 100%).

(6*R*,7*R*,8*R*)-Methyl-7-[*tert*-(butyldimethylsilyl)oxy]-8-9-*O*-*iso*-propylidene-6-methyl-nona-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 $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane-diethyl ether; 3:1) to give **(2*E*,4*R*,5*R*,6*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-6,7-*O*-*iso*-propylidene-4-methyl hept-2-en-1-ol** as a clear oil (840 mg; 100%); R_f 0.24 (1:1; hexane-ether); Found: C, 61.79; H, 10.40. $C_{17}H_{34}O_4Si$ requires C, 61.77; H, 10.37%; (Found MNH_4^+, 348.2574. $C_{17}H_{34}O_4Si$ requires MNH_4^+, 348.2570); ν_{max} (film)/cm^{-1} 3396m,br (OH), 2957s and 2932s (CH); $[\alpha_D]^{25}$ +0.8 (*c* 1.22 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 0.08 (3 H, s, SiCH_3), 0.10 (3 H, s, SiCH_3), 0.91 (9 H, s, C(CH_3)$_3$), 1.07 (3 H, d, *J* 6.9, CH_3-4), 1.32 (3 H, s, CH_3CCH$_3$), 1.39 (3 H, s, CH$_3$CCH_3), 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); δ_C(75.5 MHz; $CDCl_3$) -4.92 and -3.93 (SiCH$_3$), 18.45 (SiC(CH$_3$)$_3$), 18.82 (CH$_3$), 26.04 (SiC(CH$_3$)$_3$), 25.54 and 26.60 (CH$_3$), 40.28 (CH), 63.67 (CH$_2$), 65.78 (CH$_2$), 77.98 (CH), 78.89 (CH), 108.88 (C), 129.47 (CH) and 133.64 (CH); *m/z* 348 (MNH_4^+, 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 $MgSO_4$ 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 $Ph_3PCHCO_2CH_3$ (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. $C_{20}H_{36}O_5Si$ requires C, 62.46; H, 9.43; (Found: M^+H^+, 385.2402. $C_{20}H_{36}O_5Si$ requires M^+H^+, 385.2410); ν_{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 $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 0.08 (3 H, s, SiCH_3), 0.10 (3 H, s,

SiCH_3), 0.91 (9 H, s, C(CH_3)$_3$), 1.11 (3 H, d, *J* 6.8, CHCH_3), 1.31 (3 H, s, CH_3CCH$_3$), 1.39 (3 H, s, CH$_3$CCH_3), 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, OCH$_3$), 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; $CDCl_3$) -4.85 and -3.89 (SiCH_3), 18.46 (SiC(CH$_3$)$_3$), 18.62 (CH$_3$), 26.05 (SiC(CH_3)$_3$), 25.52 and 26.65 (CH$_3$), 40.90 (CH), 51.47 (OCH$_3$), 65.73 (CH$_2$), 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%).

(3*S*,4*R*,5*R*,6*S*)-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 CH_2Cl_2 (6 x 20 mL) and the combined organic layers dried with anhydrous $MgSO_4$. 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; R_f (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 $CHCl_3$); ν_{max} ($CHCl_3$) /cm^{-1} 3014 m (OH), 3584 m, 2929 m, 2871 m (CH$_3$), 1739 s (C=O), 1453 m, 1206 s, 1111 s; δ_H (400 MHz; $CDCl_3$) 1.03 (3H, d, *J* 8, CH_3CH), 1.50-1.70 (2H, br s, OH), 2.25-2.36 (1H, m, CH$_3$C*H*), 3.60 (1H, t, *J* 10.4, CH$_3$CHC*H*(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)C*H*(OH), 4.09 (1H, dd, *J* 10.4 and 2.4, CH$_2$C*H*), 4.52 (1H, d, *J* 12.0, PhCH$_A$), 4.63 (1H, d, *J* 12.0, PhCH$_2$), 7.26-7.36 (5H, m, Ph); δ_C (100 MHz; $CDCl_3$) 13.32 (CH$_3$), 35.31 (CH), 69.06 (CH$_2$), 73.21 (CH), 73.27 (CH), 73.61 (CH$_2$), 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+NH$_4$, 50%), 266 (M+H, 100%), 250 (31%), 233 (15%), 160 (16%), 108 (PhCH$_2$OH, 44%), 91 (PhCH$_2$, 19%).

(2*R*,3*S*,6*R*,7*R*,8*R*)-Methyl 7-[(*tert*-butyldimethylsilyl)oxy]-2,3-dihydroxy-8,9-*O*-*iso*-propylidene-6-methylnon-4-enoate (18) and (4*S*,5*S*,6*R*,7*R*,8*R*)-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 OsO_4 in *t*-BuOH (17.7 μL; 0.00140 mmol) and $MeSO_2NH_2$ (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 Na_2SO_3 (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 $MgSO_4$ 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 $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 0.08 (3 H, s, SiC*H*$_3$), 0.10 (3 H, s, SiC*H*$_3$), 0.91 (9 H, s, C(C*H*$_3$)$_3$), 1.10 (3 H, d, *J* 6.9 C*H*$_3$-6), 1.31 (3 H, s, C*H*$_3$CCH$_3$), 1.40 (3 H, s, CH$_3$CC*H*$_3$), 2.20 (1 H, m, H-6), 3.56-3.61 (2 H, m, H-9, H-7), 3.83 (3 H, s, OCH$_3$), 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); δ_C(75.5 MHz; $CDCl_3$) -4.88 and -3.97 (SiCH$_3$), 18.43 (SiC), 18.82 (CH$_3$), 26.04 (SiC(*C*H$_3$)$_3$), 25.24 and 26.47 (CH$_3$), 40.15 (CH), 52.72 (CH$_3$), 65.53 (CH$_2$), 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 (MNH_4^+, 100%). Physical data for compound **19**: R_f 0.57 (ether); (Found: M^+H^+, 419.2471. $C_{20}H_{38}O_7Si$ requires M^+H^+, 419.2465); δ_H(300 MHz; $CDCl_3$) 0.13 (3 H, s, SiC*H*$_3$), 0.14 (3 H, s, SiC*H*$_3$), 0.92 (9 H, s, C(C*H*$_3$)$_3$), 1.05 (3 H, d, *J* 7.0 C*H*$_3$-6), 1.41 (3 H, s, C*H*$_3$CCH$_3$), 1.43 (3 H, s, CH$_3$CC*H*$_3$), 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, OCH$_3$), 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); δ_C(75.5 MHz; $CDCl_3$) -4.90 and -4.22 (SiCH$_3$), 17.06 (CH$_3$), 18.29 (SiC), 25.95 (SiC(*C*H$_3$)$_3$), 25.28 and 26.48 (CH$_3$), 38.02 (CH), 51.55 (CH$_3$), 66.22 (CH$_2$), 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 $K_3Fe(CN)_6$ (104.8 mg; 0.319 mmol), K_2CO_3 (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 OsO_4 in *t*-BuOH (13.4 μL; 0.00106 mmol) and $MeSO_2NH_2$ (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 Na_2SO_3 (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 $MgSO_4$ 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%). R_f 0.43 (ether); (Found: $M^+NH_4^+$, 436.2744. $C_{20}H_{38}O_7Si$ requires $M^+NH_4^+$, 436.2737); ν_{max} (film)/cm^{-1} 2935s (CH) and 1734s (C=O); Found: C, 57.63; H, 9.22 $C_{20}H_{38}O_7Si$ requires C, 57.39; H, 9.15; $[\alpha_D]^{25}$ +10.5 (*c* 1.14 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 0.08 (3 H, s, SiC*H*$_3$), 0.10 (3 H, s, SiC*H*$_3$), 0.91 (9 H, s, C(C*H*$_3$)$_3$), 1.10 (3 H, d, *J* 7.0 C*H*$_3$-6), 1.32 (3 H, s, C*H*$_3$CCH$_3$), 1.40 (3 H, s, CH$_3$CC*H*$_3$), 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, OCH$_3$), 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); δ_C(75.5 MHz; $CDCl_3$) -4.90 and -3.92 (SiCH$_3$), 18.45 (SiC), 18.84 (CH$_3$), 26.06 (SiC(*C*H$_3$)$_3$), 25.46 and 26.56 (CH$_3$), 40.26 (CH), 52.77 (CH$_3$), 65.69 (CH$_2$), 73.40 (CH), 73.91 (CH), 77.88 (CH), 78.80 (CH), 108.99 (C), 128.50 (CH), 135.30 (CH) and 171.2 (C=O); *m/z* 436 (MNH_4^+, 48%), 401 (100%).

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