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A Synthesis of (+)-Prelog-Djerassi Lactonic Acid

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†This paper is dedicated to Professor Madeleine Joullié in honour of her 70th birthday

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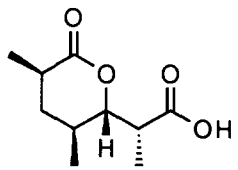
Abstract: A new approach to the synthesis of Prelog-Djerassi Lactonic acid (**1**) is reported. A key step in this synthesis involves an Ireland-Claisen rearrangement/silicon-mediated fragmentation sequence to provide the carbon framework in (**1**).

INTRODUCTION

The isolation of (+)-Prelog-Djerassi Lactonic acid (PDLA) (**1**) was reported in 1956 independently by Prelog and Djerassi.[1-3] Prelog *et al.* isolated the six-membered lactone (**1**) as a key oxidative degradation product of the macrolide antibiotics narbomycin and pikromycin.[1] Djerassi and Zderic initially reported the lactone as a degradation fragment of the macrolide antibiotic methymycin[2] and subsequently, as a degradation product of neomethymycin.[3] The fragment holds a prominent position in the field of macrolide antibiotic chemistry, not only having provided essential information for their structure elucidation,[4,5] but it has also served in their synthesis.[6] The structure of (+)-PDLA was determined in 1970 by Rickards and Smith[4] and shown to be (**1**).



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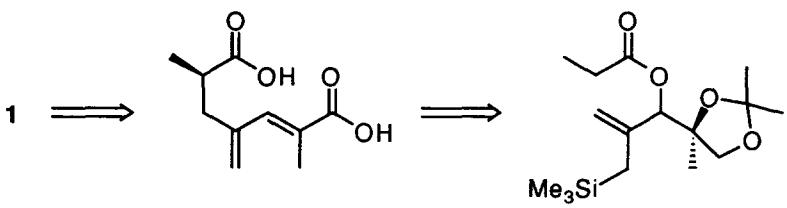
We now report our synthesis of (+)-PDLA based on the retrosynthetic analysis shown in Scheme 1.



Scheme 1

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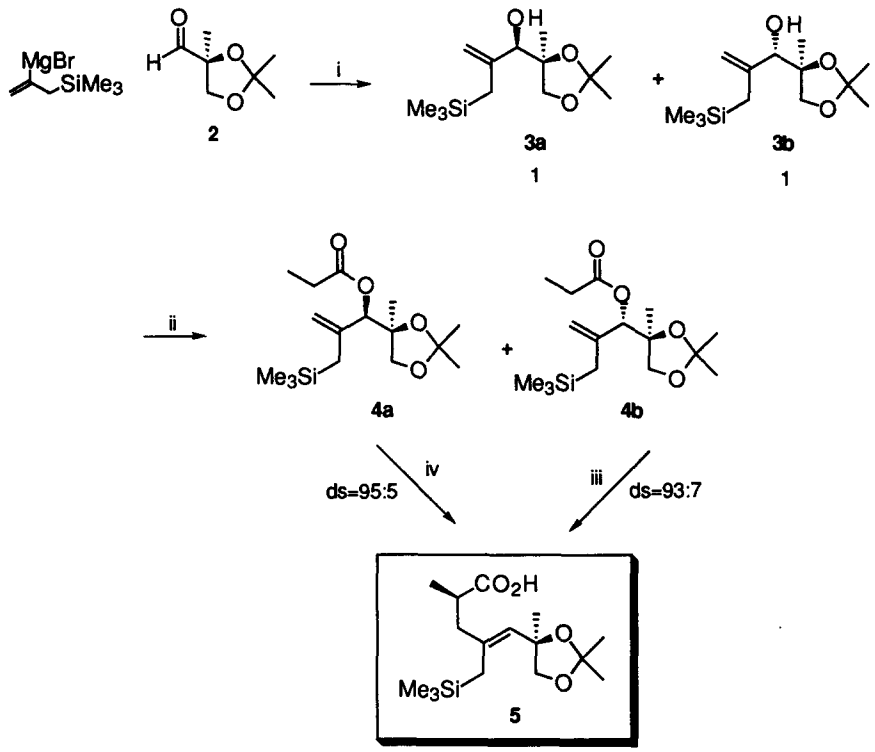
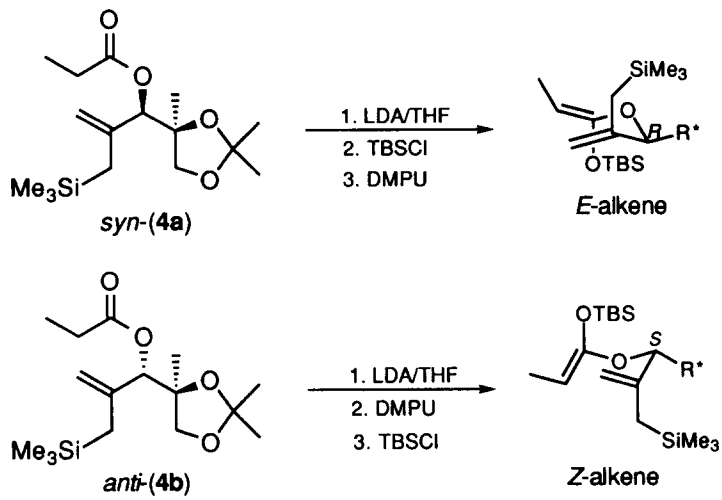
RESULTS & DISCUSSION

We have recently investigated the remote control of asymmetry by cascade rearrangement/silicon-mediated fragmentation of allylic epoxides,[7] and now report our work on the fragmentation of acetals. Our synthesis of (+)-PDLA relied on the construction of key acid (**5**), and our approach is shown in Scheme 2. Treatment of the homochiral aldehyde (**2**)[8] with 1-trimethylsilyl-2-propenyl-magnesium bromide[9] gave an easily separable mixture of allylic alcohols (**3a**) and (**3b**) in 80 % yield, with the stereochemical assignments determined *via* single crystal x-ray analysis of the corresponding *p*-nitrobenzoates. The *syn*- and *anti*-allylic alcohols were then each subjected to esterification in the presence of propionic anhydride, triethylamine and 4-(dimethylamino)pyridine,[10] to give the corresponding propionate esters (**4a**) and (**4b**) in excellent yield (98 %). Both the *syn*- and *anti*-propionate esters could be converted to a single diastereomeric acetonide-acid (**5**) in optically pure form by modifying the reaction conditions to obtain either the *E*- or the *Z*-silyl ketene acetal (Scheme 3) as intermediate for the key Ireland-Claisen rearrangement.[11]



Reagents: (i) 0°C/THF (82 %); (ii) $(EtCO)_2O/Et_3N$/DMAP/DCM (97 %); (iii) LDA/THF/TBDMSCl then DMPU (88 %); (iv) LDA/THF/DMPU then TBDMSCl (65 %)

Scheme 2



Scheme 3

Scheme 4 depicts the remainder of our total synthesis. The acid (**5**) was subjected to RedAl® reduction[12] to give the hydroxymethyl intermediate (**6**) in 99 % yield, which was then protected as the *tert*-butyldiphenylsilyl ether (**7**) under standard conditions (96 %).[13] Silicon-mediated fragmentation of the acetonide (**7**) was carried out under Lewis acid-mediated conditions (BF_3•OEt_2) to furnish allylic alcohol (**8**) in 96 % yield. Sharpless epoxidation provided (**9**),[14] followed by a diastereoselective diimide reduction of the remaining olefin,[15] to give the epoxyalcohol (**10**) in satisfactory yield, and as exclusively one diastereoisomer.

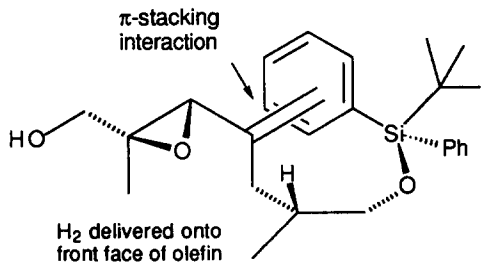
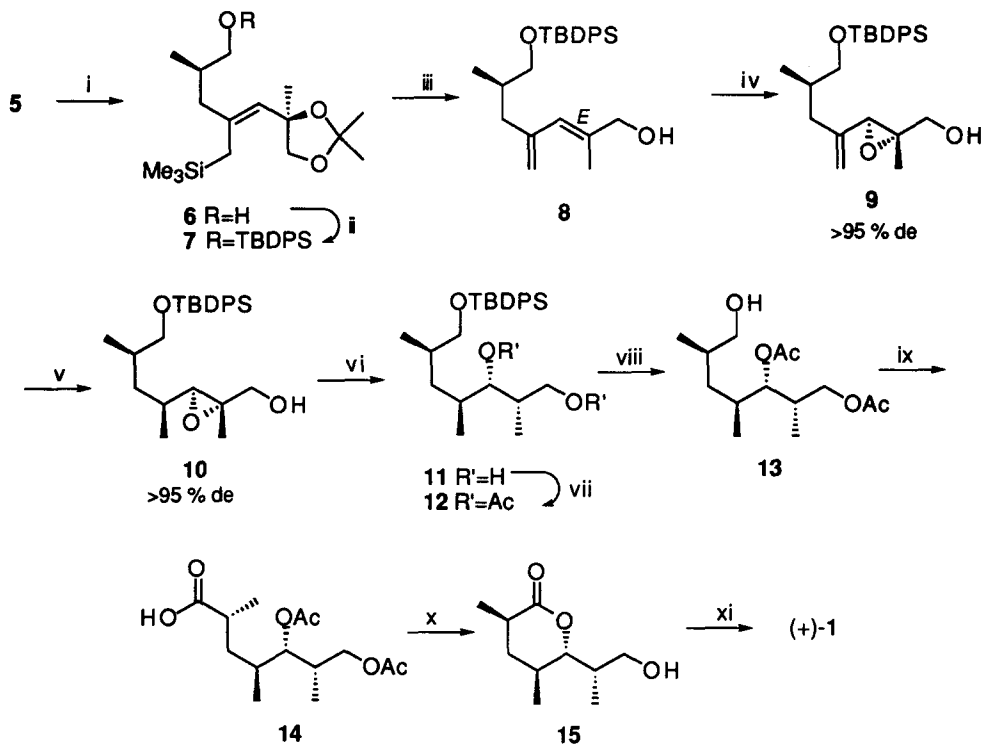


Figure 1

We invoke π-stacking of the alkene with a phenyl moiety on the silicon protecting group (since this high degree of selectivity was only observed for TBDPS and not with TBS), in the precursor to explain this remarkable selectivity (Figure 1).[16] Lewis acid induced reduction of the epoxide with sodium cyanoborohydride led regioselectively to the 1,3-diol (**11**); the hydride attacks the more substituted position *via* an S_N2 mechanism.[17]



Reagents: (i) RedAl/THF/0°C (80 %); (ii) TBDPSCl/DMAP/DMF/imidazole (95 %); (iii) BF_3•OEt_2/THF/–78°C to rt/48 h (95 %); (iv) $Ti(O^iPr)_4$/(+)-DET/–20°C (93 %); (v) $(NH_2)_2$/EtOH/$CuSO_4$/Δ (65 %); (vi) BF_3•OEt_2/$NaCNBH_3$/THF/Δ(90 %); (vii) $(CH_3CO)_2O$/Et_3N/DMAP (80 %); (viii) TBAF/THF (70 %); (ix) $RuCl_3$•$3H_2O$/$NaIO_4$/CCl_4/MeCN/H_2O; (x) LiOH/H_2O/THF (67 % from **13**); (xi) $RuCl_3$•$3H_2O$/$NaIO_4$/CCl_4/MeCN/H_2O (93 %)

Scheme 4

With the full complement of stereogenic centres required, the 1,3-diol (**11**) was then taken through a protection/ deprotection sequence to afford the corresponding diacetoxy alcohol (**13**), thereby completing the formal synthesis of (+)-PDLA. The remaining steps in the total synthesis followed the route employed by Yamaguchi and co-workers.[18] Diacetoxy alcohol (**13**) was oxidised with $RuCl_3/NaIO_4$ to provide acid (**14**), which underwent concomitant lactonisation to (**15**) under saponification conditions. The primary alcohol (**15**) was then oxidised to afford (+)-Prelog-Djerassi lactonic acid in an overall 9 % yield, with all spectroscopic data in accord with the literature values.

EXPERIMENTAL

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. Light petrol (b.p. 40-60°C) for chromatographic purposes was distilled before use. Dry diethyl ether and tetrahydrofuran were distilled from sodium / benzophenone under an atmosphere of nitrogen.

Dichloromethane, chloroform, acetonitrile, dimethyl sulfoxide and *N,N*-dimethylformamide were distilled from calcium hydride under an atmosphere of nitrogen. After distillation, triethylamine was dried and stored over potassium hydroxide and pyridine was dried and stored over 4Å molecular sieves.

Reactions requiring anhydrous conditions were conducted in flame dried or oven dried (175°C; overnight) apparatus under a dry atmosphere of nitrogen or argon, unless otherwise stated. All air and moisture sensitive liquids were measured and transferred by gas tight syringe.

Analytical thin layer chromatography (t.l.c.) was performed on Merck glass backed thin layer chromatography plates pre-coated with a 0.25 mm layer of 60 F_{254} silica gel containing a fluorescent indicator. Visualisation was achieved by ultra violet light (254 nm), iodine or by staining with alkaline potassium permanganate solution, phosphomolybdic acid solution (5% in ethanol) or acidic ceric ammonium sulfate solution, followed by heating. Evaporation under reduced pressure was achieved on a Büchi rotary evaporator, using water aspirator reduced pressure, followed by drying on a static oil pump (0.5 mmHg). Flash column chromatography was carried out using Merck Kieselgel 60 silica gel (Merck art. no. 9385, 230-400 mesh, 0.04-0.063 nm). Vacuum liquid chromatography was performed with Merck Kieselgel 60 silica gel (Merck art. no. 7729, particle size less than 0.063 mm).

Melting points (m.p.) were recorded on an electrothermal melting point apparatus and are uncorrected.

Optical rotations were recorded on a Perkin Elmer 241 Polarimeter using a cell with a 1 cm path length. Optical rotation data are given in 10^{-1} deg cm^2 g^{-1} and solution concentrations are given in g 100 cm^{-3}. Optical rotations of compounds obtained as mixtures of diastereomers are not quoted.

Infrared spectra were recorded on a Perkin-Elmer 881 dispersive spectrophotometer or on a Perkin-Elmer 1710 Fourier transform spectrophotometer as a thin film between NaCl plates. The following abbreviations are used in reference to the intensity of absorption: s = strong, m = medium, w = weak, br = broad.

^1H nuclear magnetic resonance spectra were recorded at 399.784 MHz on a Jeol Ex400 FT-NMR instrument or at 300.132 MHz on a Bruker Advance AC-300 instrument. Chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (δ 7.27 ppm) or tetramethylsilane as the internal reference (δ 0.00 ppm). The following abbreviations are used to describe the multiplicity of a given signal: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex. = sextet, m = multiplet, br = broad. Coupling constants, *J*, are given in Hertz.

^{13}C nuclear magnetic resonance spectra were recorded at 100.775 MHz on the Jeol Ex400 FTNMR instrument and at 75.432 MHz, on the Bruker Advance AC-300 instrument. Chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (central line of triplet δ 77.00 ppm).

Gas-chromatographic-mass spectra (GC-MS) were obtained on a Fisons Instruments MD 800. Fast atom bombardment mass spectra (FAB-MS) were obtained on a Kratos MS80RF instrument. High-resolution mass spectra (HRMS) and electron ionisation mass spectra (EI) were obtained on a Fisons Instruments VG Autospec under the conditions stated. High-resolution fast atom bombardment mass spectra were obtained from the E.P.S.R.C.'s Mass Spectrometry Service Centre on a Fisons Instruments VG Autospec.

Where references are quoted they refer to the previous use of the compound. They have been included because their spectroscopic data is incomplete in the literature or they were prepared by an alternative procedure.

(+)-(1R)-2-(Trimethylsilylmethyl)-1-[(4'S)-2',2',4'-trimethyl-1',3'-dioxolan-4'-yl]prop-2-en-1-ol ***(3a)***: To a stirred suspension of magnesium turnings (1.75 g, 72.0 mmol; pre-activated with iodine) in tetrahydrofuran

(33 ml), was added 2-bromo-3-(trimethylsilyl)propene (11.2 ml, 65.5 mmol) dropwise, maintaining a gentle reflux after initiation. After 30 minutes of heating under reflux, the dark green suspension was diluted with tetrahydrofuran (33 ml) and cooled to 0°C. A solution of *aldehyde* (**2**) (7.26 g, 50.4 mmol) in tetrahydrofuran (63 ml) was added dropwise over 1 hour, and the grey / black suspension was allowed to warm to room temperature. After 2 hours, and after cooling to 0°C, saturated ammonium chloride solution (100 ml) and water (100 ml) were added. The phases were separated and the aqueous layer was extracted into diethyl ether (3 x 100 ml). The combined organic extracts were washed with brine (150 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Vacuum liquid chromatography, eluting with a gradient of 4% diethyl ether / light petrol to 10% diethyl ether / light petrol, provided a diastereomeric pair of *alcohols* (**3a**) and (**3b**). *Alcohol* (**3a**) was a clear, colourless oil (5.06 g, 39%); t.l.c., (20% diethyl ether / light petrol) $R_f = 0.41$; $[\alpha]^{20}_D$ +43.9 (*c* 2.39 in chloroform); ν_{max} (thin film)/cm^{-1} 3487 (br s), 2984, 2954 and 2893 (s), 1687 (w), 1250 (s), 1062 (s), 856 (m); δ_H(300 MHz; $CDCl_3$) 4.93 (1 H, s); 4.75 (1 H, s); 4.16 (1 H, d, *J* 8.6 Hz); 3.94 (1 H, s); 3.65 (1 H, d, *J* 8.6 Hz); 2.16 (1 H, br s); 1.62 (1 H, d, *J* 13.7 Hz); 1.56 (1 H, d, *J* 13.7 Hz); 1.40, 1.37 and 1.22 (3 x (3 H, s)); 0.02 (9 H, s); δ_C(100 MHz; $CDCl_3$) 146.51, 109.59, 109.37, 83.79, 77.59, 70.86, 27.57, 26.62, 21.92, 25.26, –1.38; EIMS 258 (M^+, 1%), 243 (5), 200 (5), 185 (10), 115 (100), 73 (83); HRMS (EI) found 258.1660, (M^+, $C_{13}H_{26}O_3Si$ requires 258.1651).

*(-)-(1S)-2-(Trimethylsilylmethyl)-1-[(4'S)-2',2',4'-trimethyl-1',3'-dioxolan-4'-yl]prop-2-en-1-ol (**3b**):* *Alcohol* (**3b**) was a clear, colourless oil (5.32 g, 41%); t.l.c., (20% diethyl ether / light petrol) $R_f = 0.52$; $[\alpha]^{19}_D$ -7.98 (*c* 2.38 in chloroform); ν_{max} (thin film)/cm^{-1} 3490 (br m), 2985, 2953 and 2892 (s), 1669 (w), 1250 (s), 1061 (s), 857 (m); δ_H (300 MHz; $CDCl_3$) 4.89 (1 H, s); 4.73 (1 H, s); 4.04 (1 H, d, *J* 8.6 Hz); 3.87 (1 H, d, *J* 3.8 Hz); 3.65 (1 H, d, *J* 8.6 Hz); 2.38 (1 H, d, *J* 3.8 Hz); 1.65 (1 H, d, *J* 13.8 Hz); 1.37 (1 H, d, *J* 13.8 Hz); 1.38, 1.37, 1.20 (3 x (3 H, s)), 0.03 (9 H, s); δ_C (100 MHz; $CDCl_3$) 146.02, 110.76, 109.68, 83.68, 78.46, 72.03 (CH_2-5'), 27.17, 26.89, 21.39, 23.65, –1.18; EIMS 258 (M^+, 1%), 243 (3), 200 (3), 185 (8), 115 (100), 73 (73); HRMS (EI) found 258.1659, (M^+, $C_{13}H_{26}O_3Si$ requires 258.1651).

*(+)-(1R)-1-[(Propanoyl)oxy]-1-[(4'S)-2',2',4'-trimethyl-1',3'-dioxolan-4'-yl]-2-(trimethylsilylmethyl) prop-2-ene (**4a**):* To a stirred solution of *syn-alcohol* (**3a**) (835 mg, 3.23 mmol), 4-(dimethylamino)pyridine (39 mg, 0.323 mmol) and triethylamine (676 µl, 4.85 mmol) in dichloromethane (8.0 ml) at 0°C, was added propionic anhydride (621 µl, 4.85 mmol) dropwise over 10 minutes. The white suspension was allowed to attain room temperature and was stirred for 20 hours. The reaction mixture was diluted with dichloromethane (8 ml) and saturated sodium bicarbonate solution (4 ml) was added. The phases were separated and the aqueous layer was extracted into dichloromethane (3 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Flash column chromatography, eluting with 7% diethyl ether / light petrol, provided *propionate ester* (**4a**) as a clear, colourless oil (996 mg, 98%). t.l.c., (20% diethyl ether / light petrol) $R_f = 0.53$; $[\alpha]^{19}_D$ +50.7 (*c* 2.94 in chloroform); ν_{max} (thin film)/cm^{-1} 2985, 2952 and 2894 (s), 1749 (s), 1634 (m), 1371 (s), 1214 (s), 1064 (s), 857 (s); δ_H (300 MHz; $CDCl_3$) 5.11 (1 H, s); 4.80 (1 H, s); 4.75 (1 H, s); 3.93 (1 H, d, *J* 8.7 Hz); 3.75 (1 H, d, *J* 8.7 Hz); 2.37 (2 H,

q, *J* 7.6 Hz); 1.88 (1 H, d, *J* 14.0 Hz); 1.60 (1 H, d, *J* 14.0 Hz); 1.42, 1.40, 1.26 (3 x (3 H, s)); 1.12 (3 H, t, *J* 7.6 Hz); 0.06 (9 H, s); δ_C (75.5 MHz; $CDCl_3$) 172.61, 143.41, 110.13, 109.77, 83.03, 78.50, 72.93, 27.77, 27.37, 26.50, 21.41, 24.73, 9.09, 1.28; EIMS 314 (M^+, 3%), 299 (25), 241 (2), 183 (13), 115 (100), 73 (54), 57 (63); HRMS (EI) found 314.1902, (M^+, $C_{16}H_{30}O_4Si$ requires 314.1913).

*(-)-(1S)-1-[(Propanoyl)oxy]-1-[(4'S)-2',2',4'-trimethyl-1',3'-dioxolan-4'-yl]-2-(trimethylsilylmethyl) prop-2-ene (**4b**):* To a stirred solution of *anti-alcohol* (**3b**) (1.00 g, 3.87 mmol), 4-(dimethylamino)pyridine (47 mg, 0.387 mmol) and triethylamine (810 µl, 5.81 mmol) in dichloromethane (10 ml) at 0°C, was added propionic anhydride (744 µl, 5.81 mmol) dropwise over 10 minutes. The white suspension was allowed to attain room temperature and was stirred for 20 hours. The reaction mixture was diluted with dichloromethane (10 ml) and saturated sodium bicarbonate solution (5 ml) was added. The phases were separated and the aqueous layer was extracted into dichloromethane (3 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Flash column chromatography, eluting with 9% diethyl ether / light petrol, provided *propionate ester* (**4b**) as a clear, colourless oil (1.23 g, 99%). t.l.c., (20% diethyl ether / light petrol) R_f = 0.59; $[\alpha]^{19}_D$ -25.6 (*c* 2.42 in chloroform); ν_{max} (thin film)/cm^{-1} 2985, 2953 and 2894 (s), 1745 (s), 1634 (m), 1371 (s), 1249 (s), 1178 (s), 1023 (s), 846 (s); δ_H (300 MHz; $CDCl_3$) 5.15 (1 H, s); 4.88 (1 H, s); 4.79 (1 H, s); 4.05 (1 H, d, *J* 8.8 Hz); 3.63 (1 H, d, *J* 8.8 Hz); 2.43-2.23 (2 H, m); 1.67 (1 H, d, *J* 14.2 Hz); 1.58 (1 H, d, *J* 14.2 Hz); 1.43, 1.36 and 1.26 (3 x (3 H, s)); 1.11 (3 H, t, *J* 7.6 Hz); 0.01 (9 H, s); δ_C (75.5 MHz; $CDCl_3$) 173.13, 143.44, 112.02, 110.00, 82.13, 79.01, 71.37, 27.85, 27.24, 26.16, 23.60, 25.57, 9.09, –1.23; EIMS 314 (M^+, 2%), 299 (4), 241 (1), 183 (5), 115 (100), 73 (63), 57 (72); HRMS (EI) found 314.1923, (M^+, $C_{16}H_{30}O_4Si$ requires 314.1913).

*(-)-(4E)-(2R)-2-Methyl-5-[(4'R)2',2',4'-trimethyl-1',3'-dioxolan-4'-yl]-4-(trimethylsilylmethyl)pent-4-enoic acid (**5**). From syn-ester (**4a**):* To a stirred solution of di-*iso*-propylamine (1.84 ml; 14.0 mmol) in tetrahydrofuran (42 ml) at 0°C, was added *n*-butyllithium (5.30 ml, 12.7 mmol; 2.45M in hexanes) dropwise. After 15 minutes, the yellow solution was cooled to -78°C and a solution of *syn-ester* (**4a**) (2.00 g, 6.36 mmol) in tetrahydrofuran (32 ml) was added dropwise. The vibrant yellow solution was stirred at -78°C for 30 minutes before a solution of *tert*-butyldimethylsilyl chloride (4.82 g, 31.8 mmol) in tetrahydrofuran (10 ml) was added dropwise, followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (40 ml; 45% by volume). The solution was allowed to attain room temperature slowly (the vibrant yellow colour faded to pale yellow at -20 to -10°C) and was heated under reflux for 6 hours. After cooling to 0°C, 2M sodium hydroxide solution (32 ml) was added and the reaction mixture was allowed to attain room temperature. After 30 minutes, diethyl ether (100 ml) was added, the phases separated and the organic phase was extracted into 2M sodium hydroxide solution (4 x 50 ml). The combined basic extracts were washed with diethyl ether (2 x 150 ml) and at 0°C, the yellow basic solution was acidified with concentrated hydrochloric acid providing a white milky emulsion which was extracted into diethyl ether (4 x 100 ml). The combined organic extracts were washed with brine (2 x 100 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. The residue was passed through a silica plug, eluting with 60% diethyl ether / light petrol, providing *acid* (**5**) as a colourless, viscous oil (1.77 g, 88%).

From anti-ester (4b): To a stirred solution of di-*iso*-propylamine (2.22 ml; 16.9 mmol) in tetrahydrofuran (47 ml) at 0°C, was added *n*-butyllithium (5.77 ml, 14.1 mmol; 2.45M in hexanes) dropwise. After 15 minutes, the yellow solution was cooled to -78°C and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (40 ml; 45% by volume) was added dropwise, followed by a solution of *anti-ester* (**4b**) (2.02 g, 6.42 mmol) in tetrahydrofuran (38 ml). The vibrant yellow solution was stirred at -78°C for 30 minutes before a solution of *tert*-butyldimethylsilyl chloride (4.84 g, 32.1 mmol) in tetrahydrofuran (9.0 ml) was added dropwise. The solution was allowed to attain room temperature slowly (the vibrant yellow colour faded to pale yellow at -20 to -10°C) and was heated under reflux for 7 hours. After cooling to 0°C, 2M sodium hydroxide solution (32 ml) was added and the reaction mixture was allowed to attain room temperature. After 30 minutes, diethyl ether (100 ml) was added, the phases separated and the organic phase was extracted into 2M sodium hydroxide solution (4 x 50 ml). The combined basic extracts were washed with diethyl ether (2 x 150 ml) and at 0°C, the yellow basic solution was acidified with concentrated hydrochloric acid providing a white milky emulsion which was extracted into diethyl ether (4 x 100 ml). The combined organic extracts were washed with brine (2 x 100 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. The residue was passed through a silica plug, eluting with 60% diethyl ether / light petrol, providing *acid* (**5**) as a colourless, viscous oil (1.46 g, 73%). t.l.c., (60% diethyl ether / light petrol) R_f = 0.34; $[\alpha]^{24}_D$ -7.51 (*c* 3.19 in chloroform); ν_{max} (thin film)/cm^{-1} 3660-2400 (br s), 2983, 2963 and 2881 (s), 1709 (s), 1250 (s), 854 (s); δ_H (300 MHz; $CDCl_3$) 5.34 (1 H, s); 3.88 (1 H, d, *J* 8.1 Hz); 3.85 (1 H, d, *J* 8.1 Hz); 2.66-2.50 (1 H, m); 2.39 (1 H, dd, *J* 13.8 and 7.1 Hz); 1.99 (1 H, dd, *J* 13.8 and 8.1 Hz); 1.58 (2 H, s); 1.44, 1.37, 1.33 (3 x (3 H, s)); 1.14 (3 H, d, *J* 6.9 Hz); 0.09 (9 H, s); δ_C (75.5 MHz; $CDCl_3$) 182.43, 135.65, 129.31, 108.91, 80.52, 75.33, 43.07, 37.73, 27.67, 27.18, 26.05, 21.36, 16.26, 0.39; EIMS 314 (M^+, 2%), 299 (29), 256 (19), 241 (14), 183 (35), 73 (100); HRMS (EI) found 314.1919, (M^+, $C_{16}H_{30}O_4Si$ requires 314.1913).

(+)-(4E)-(2R)-2-Methyl-5-[(4'R)-2',2',4'-trimethyl-1',3'-dioxolan-4'-yl]-4-(trimethylsilylmethyl)pent-4-en-1-ol (6): To a stirred solution of *acid* (**5**) (750 mg, 2.38 mmol) in tetrahydrofuran (15 ml) at 0°C, was added a solution of sodium *bis*(2-methoxyethoxy)aluminium hydride (1.50 ml, 4.77 mmol; 3.2M in toluene, diluted with 10 ml of tetrahydrofuran) dropwise. The reaction mixture was stirred at 0°C for 1.5 hours before a saturated solution of potassium sodium tartrate (15 ml), water (10 ml) and diethyl ether (25 ml) were added and the mixture was allowed to attain room temperature. The phases were separated and the aqueous layer was extracted into diethyl ether (3 x 20 ml). The combined organic extracts were washed with brine (2 x 50 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Vacuum liquid chromatography, eluting with 1.5% methanol / dichloromethane, provided *alcohol* (**6**) as a viscous pale orange oil (710 mg, 99%); t.l.c., (1.5% methanol / dichloromethane) R_f = 0.15; $[\alpha]^{23}_D$ +4.55 (*c* 4.18 in chloroform); ν_{max} (thin film)/cm^{-1} 3437 (br s), 2954, 2927 and 2871 (s), 1650 (w), 1370 (s), 1250 (s), 1060 (s), 853 (s); δ_H (300 MHz; $CDCl_3$) 5.32 (1 H, s); 3.88 (1 H, d, *J* 8.7 Hz); 3.85 (1 H, d, *J* 8.7 Hz); 3.49 (1 H, dd, *J* 10.6 and 5.6 Hz); 3.41 (1 H, dd, *J* 10.6 and 5.9 Hz); 2.04 (1 H, dd, *J* 12.7 and 6.4 Hz); 1.95-1.73 (2 H, m); 1.70 (1 H, d, *J* 13.8 Hz); 1.63 (1 H, d, *J* 13.8 Hz); 1.43, 1.37 and 1.33 (3 x (3 H, s)); 0.87 (3 H, d, *J* 6.5 Hz); 0.07 (9 H, s); δ_C (75.5 MHz; $CDCl_3$) 137.53, 128.42, 108.73, 80.91, 75.29, 67.96, 43.68, 33.63, 27.64, 27.17, 26.11, 21.37, 16.53, –0.40; EIMS 300

(M^+, 2%), 285 ([M-CH_3]$^+$, 35), 242 ([M-acetone]$^+$, 11), 184 (19), 169 (27), 115 (41), 73 (100); HRMS (EI) found 285.1881, ([M-CH_3]$^+$, $C_{15}H_{29}O_3Si$ requires 285.1886).

(+)-(4E)-(2R)-1-[(tert-Butyldiphenylsilyl)oxy]-2-methyl-5-[(4'R)-2',2',4'-trimethyl-1',3'-dioxolan-4'-yl]-4-(trimethylsilylmethyl)pent-4-ene (7): To a stirred solution of *alcohol* (**6**) (850 mg, 2.83 mmol), 4-(dimethylamino)pyridine (35 mg, 0.283 mmol) and imidazole (482 mg, 7.08 mmol) in dimethylformamide (2.8 ml) at room temperature, was added *tert*-butyldiphenylsilyl chloride (1.10 ml, 4.25 mmol) dropwise. The reaction mixture was stirred at room temperature for 20 hours before water (15 ml) and diethyl ether (20 ml) were added. The phases were separated and the aqueous layer was extracted into diethyl ether (3 x 20 ml). The combined organic extracts were washed with brine (2 x 50 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Vacuum liquid chromatography eluting with 5% diethyl ether / light petrol provided *silyl ether* (**7**) as a colourless, viscous oil (1.46 g, 96%); t.l.c., (20% diethyl ether / light petrol) R_f = 0.57; $[\alpha]^{23}_D$ +0.48 (*c* 4.16 in chloroform); ν_{max} (thin film)/cm^{-1} 3072 and 3050 (m), 2955, 2929 and 2859 (s), 1653 (w), 1428 (s), 1214 (s), 1113 (s), 701 (s); δ_H (300 MHz; $CDCl_3$) 7.67 (4 H, d, *J* 7.5 Hz); 7.47-7.30 (6 H, m); 5.25 (1 H, s); 3.85 (1 H, d, *J* 7.9 Hz); 3.81 (1 H, d, *J* 7.9 Hz); 3.50 (1 H, dd, *J* 9.7 and 5.5 Hz); 3.42 (1 H, dd, *J* 9.7 and 6.7 Hz); 2.12 (1 H, dd, *J* 13.3 and 6.1 Hz); 1.98-1.76 (1 H, m); 1.68 (1 H, dd, *J* 13.3 and 8.5 Hz); 1.55 (2 H, s); 1.44, 1.32 and 1.29 (3 x (3 H, s)); 1.06 (9 H, s); 0.90 (3 H, d, *J* 6.5 Hz); δ_C (75.5 MHz; $CDCl_3$) 137.15, 135.61, 135.59, 133.93, 133.90, 129.49, 128.35, 127.56, 108.67, 80.98, 75.39, 68.75, 43.35, 33.66, 27.78, 25.29, 26.13, 26.87, 21.30, 19.28, 16.58, 0.31; EIMS 538 (M^+, 1%), 523 (9), 481 (2), 480 (2), 423 (29), 296 (84), 239 (84), 199 (80), 115 (43), 73 (100); HRMS (EI) found 523.3069, ([M-CH_3]$^+$, $C_{31}H_{47}O_3Si_2$ requires 523.3064).

(-)-(2E)-(6R)-7-[(tert-Butyldiphenylsilyl)oxy]-2,6-dimethyl-4-methylenehept-2-en-1-ol (8): To a stirred solution of *allyl silane* (**7**) (1.15 g, 2.13 mmol) in tetrahydrofuran (21 ml) at -78°C, was added boron trifluoride diethyl etherate (1.12 ml, 10.7 mmol) dropwise. The reaction mixture was allowed to attain room temperature and was stirred for 24 hours before water (5 ml), brine (25 ml) and diethyl ether (60 ml) were added. The phases were separated and the organic layer was washed with brine (2 x 40 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Vacuum liquid chromatography, eluting with a gradient of 20% diethyl ether / light petrol to 25% diethyl ether / light petrol, provided *1,3-diene* (**8**) as a colourless, viscous oil (1.46 g, 96%); t.l.c., (20% diethyl ether / light petrol) R_f = 0.57; $[\alpha]^{24}_D$ -9.91 (*c* 2.72 in chloroform); ν_{max} (thin film)/cm^{-1} 3343 (br s), 3071 and 3050 (m), 2958, 2929 and 2857 (s), 1627 (w), 1428 (s), 1113 (s), 701 (s); δ_H (300 MHz; $CDCl_3$) 7.59 (4 H, d, *J* 7.4 Hz); 7.40-7.25 (6 H, m); 5.72 (1 H, s); 4.92 (1 H, s); 4.78 (1 H, s); 3.96 (2 H, s); 3.46-3.29 (2 H, m); 2.27 (1 H, dd, *J* 12.9 and 5.3 Hz); 1.84-1.61 (2 H, m); 1.69 (3 H, s); 0.98 (9 H, s); 0.81 (3 H, d, *J* 6.5 Hz); δ_C (75.5 MHz; $CDCl_3$) 143.86 and 137.22, 135.63, 133.98, 129.51, 127.57, 126.03, 115.20, 68.98, 68.46, 41.53, 34.45, 26.87, 19.33, 16.58, 15.41; EIMS 408 (M^+, 3%), 351 (41), 333 (6), 296 (23), 239 (55), 199 (74), 135 (100); HRMS (EI) found 408.2487, (M^+, $C_{26}H_{36}O_2Si$ requires 408.2485).

(+)-(2S,3R,6R)-7-[(tert-Butyldiphenylsilyl)oxy]-2,6-dimethyl-2,3-epoxy-4-methyleneheptan-1-ol ***(9)***: To a stirred suspension of powdered 3Å molecular sieves (330mg) and freshly distilled (+)-diethyl tartrate (163 mg, 0.79 mmol) in dichloromethane (44 ml) at -20°C, was added a solution of freshly distilled titanium tetra-*iso*-propoxide (196 µl, 0.658 mmol) in dichloromethane (5.0 ml) followed by a solution of *allylic alcohol* (**8**) (2.69 g, 6.58 mmol) in dichloromethane (16 ml) dropwise. After 30 minutes, and at -20°C, a pre-dried (with 4Å molecular sieves) solution of *tert*-butylhydroperoxide (2.44 ml, 13.2 mmol; 5.4M in dichloromethane) was added dropwise maintaining the reaction temperature. The reaction mixture was stirred at -20°C for 4 hours before a freshly prepared solution of tartaric acid (119 mg, 0.790 mmol) and iron (II) sulfate heptahydrate (2.20 g, 7.90 mmol) in water (30 ml) was added and the reaction mixture was allowed to attain room temperature. After 30 minutes, the biphasic mixture was filtered through Celite™, washing with chloroform (3 x 40 ml). The phases were separated and the aqueous layer was extracted into chloroform (3 x 20 ml). The combined organic extracts were washed with brine (200 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Vacuum liquid chromatography, eluting with a gradient of 20% diethyl ether / light petrol to 25% diethyl ether / light petrol, provided the *epoxy alcohol* (**9**) as a clear, colourless oil (2.61 g, 93%); t.l.c., (50% diethyl ether / light petrol) $R_f = 0.20$; $[\alpha]^{22}_D$ +16.3 (*c* 3.13 in chloroform); ν_{max} (thin film)/cm^{-1} 3438 (br m), 3071 and 3050 (m), 2960, 2930 and 2857 (s), 1650 (w), 1428 (s), 1113 (s), 702 (s); δ_H (300 MHz; $CDCl_3$) 7.57 (4 H, d, *J* 7.2 Hz); 7.40-7.23 (6 H, m); 4.89 (2 H, br s); 3.66 (1 H, d, *J* 12.4 Hz); 3.51 (1 H, d, *J* 12.4 Hz); 3.41 (1 H, d, *J* 10.4 Hz); 3.38 (1 H, d, *J* 10.4 Hz); 2.30-2.16 (1 H, m); 2.01 (1 H, br s); 1.87-1.66 (2 H, m); 1.03 (3 H, s); 0.98 (9 H, s); 0.86 (3 H, d, *J* 6.1 Hz); δ_C (75.5 MHz; $CDCl_3$) 141.07, 135.56, 133.75, 133.72, 129.55, 127.57, 112.77, 68.08, 64.88, 63.17, 60.73, 38.04, 34.15, 26.82, 19.26, 16.84, 12.95; EIMS 367 ([M-*t*-Bu]$^+$, 9%), 309 (73), 239 (28), 199 (100), 139 (68), 57 (13); (FAB-MS) 447 ([MNa]$^+$, 22%), 425 ([MH]$^+$, 14); HRMS (EI) found 367.1747, ([M-*t*-Bu]$^+$, $C_{22}H_{27}O_3Si$ requires 367.1729).

(-)-(2S,3R,4S,6R)-7-[(tert-Butyldiphenylsilyl)oxy]-2,3-epoxy-2,4,6-trimethylheptan-1-ol ***(10)***: To a stirred solution of *alkene* (**9**) (200 mg, 0.471 mmol) in ethanol (18 ml) was added 1M copper sulfate solution (24 µl) followed by hydrazine monohydrate (2.28 ml, 47.1 mmol). Air was passed through the translucent solution which was heated under reflux for 16 hours. The reaction mixture was concentrated under reduced pressure before water (30 ml) and diethyl ether (30 ml) were added. The phases separated and the aqueous layer was extracted into diethyl ether (3 x 20 ml). The combined organic extracts were washed with brine (2 x 50 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Vacuum liquid chromatography eluting with a gradient of 30% diethyl ether / light petrol to 35% diethyl ether / light petrol provided the *saturated epoxy alcohol* (**10**) as a clear, colourless oil (131 mg, 65%); t.l.c., (60% diethyl ether / light petrol) $R_f = 0.19$; $[\alpha]^{22}_D$ – 5.93 (*c* 4.05 in chloroform); ν_{max} (thin film)/cm^{-1} 3435 (br s), 3071 and 3049 (m), 2953, 2930 and 2849 (s), 1428 (s), 1113 (s), 701 (s); δ_H (300 MHz; $CDCl_3$) 7.70 (4 H, d, *J* 7.3 Hz); 7.50-7.32 (6 H, m); 3.68 (1 H, br d, *J* 12.0 Hz); 3.62-3.51 (2 H, m); 3.48 (1 H, dd, *J* 9.8 and 6.3 Hz); 2.72 (1 H, d, *J* 9.1 Hz); 2.10-1.81 (2 H, m); 1.68 (1 H, ddd, *J* 13.4, 7.4 and 7.4 Hz); 1.63-1.48 (1 H, m); 1.30 (3 H, s); 1.25-1.12 (1 H, m); 1.08 (9 H, s); 0.99 (3 H, d, *J* 6.6 Hz); 0.92 (3 H, d, *J* 6.7 Hz); δ_C (75.5 MHz; $CDCl_3$) 136.59, 133.96, 133.90, 129.45, 127.53, 69.06, 65.52, 65.32, 59.87, 40.95, 33.14, 30.12, 26.83, 19.25 17.43, 16.93, 14.25; EIMS 369 ([M-*t*-

Bu]$^+$, 6%), 351 (13), 311 (83), 199 (100), 139 (73), 57 (53); (FAB-MS) 449 ([MNa]$^+$, 23%), 429 ([MH]$^+$, 17); HRMS (EI) found 369.1900, ([M-*t*-Bu-H_2O]$^+$, $C_{22}H_{29}O_3Si$ requires 369.1886).

(-)-(2S,3S,4S,6R)-7-[(tert-Butyldiphenylsilyl)oxy]-2,4,6-trimethylheptan-1,3-diol (11): To a stirred solution of *epoxy alcohol* (**10**) (120 mg, 0.281 mmol) in tetrahydrofuran (9.4 ml) at 0°C, was added sodium cyanoborohydride (212 mg, 3.37 mmol) in a single portion. Boron trifluoride diethyl etherate (178 µl, 1.69 mmol) was added dropwise and the reaction mixture was allowed to attain room temperature before it was heated to 65°C. After 1.5 hours, the reaction mixture was cooled to room temperature and poured onto a mixture of ice and saturated sodium bicarbonate solution (10 ml). Dichloromethane (20 ml) was added, the phases separated and the aqueous layer extracted into dichloromethane (3 x 8 ml). The combined organic extracts were washed with brine (25 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Vacuum liquid chromatography, eluting with a gradient of 30% diethyl ether / light petrol to 38% diethyl ether / light petrol, provided *1,3-diol* (**11**) as a viscous pale yellow oil (102 mg, 85%); t.l.c., (60% diethyl ether light petrol) R_f = 0.29; $[\alpha]^{22}_D$ -6.61 (*c* 3.63 in chloroform); ν_{max} (thin film)/cm^{-1} 3381 (br s), 3071 and 3048 (m), 2964, 2929 and 2866 (s), 1462 (s), 1113 (s), 701 (s); δ_H (300 MHz; $CDCl_3$) 7.67 (4 H, d, *J* 7.5 Hz); 7.48-7.30 (6 H, m); 3.74 (1 H, dd, *J* 10.5 and 3.8 Hz); 3.66 (1 H, dd, *J* 10.5 and 5.3 Hz); 3.54 (1 H, dd, *J* 10.3 and 5.1 Hz); 3.51-3.39 (2 H, m); 2.54 (1 H, br s); 2.35 (1 H, br s); 1.92-1.68 (3 H, m); 1.63-1.45 (1 H, m); 1.08 (9 H, s); 1.14-0.82 (1 H, m); 0.99 (3 H, d, *J* 6.2 Hz); 0.91 (3 H, d, *J* 7.0 Hz); 0.79 (3 H, d, *J* 6.7 Hz); δ_C (75.5 MHz; $CDCl_3$) 135.63, 135.57, 133.73, 133.70, 129.55, 127.58, 79.51, 68.23, 68.04, 37.64, 35.92, 34.57, 33.43, 26.85, 19.22, 18.97, 16.45, 8.84; FAB-MS 451 ([MNa]$^+$, 3%), 429 ([MH]$^+$, 20), 353 (4), 239 (11), 199 (54), 137 (100), 57 (70); HRMS (EI) found 353.1930, ([M-*t*-Bu-H_2O]$^+$, $C_{22}H_{29}O_2Si$ requires 353.1937).

(+)-(2S,3S,4S,6R)-7-[(tert-Butyldiphenylsilyl)oxy]-1,3-diacetoxy-2,4,6-trimethylheptane (12): To a stirred solution of *diol* (**11**) (500 mg, 1.17 mmol), 4-(dimethylamino)pyridine (50 mg, 0.410 mmol) and triethylamine (571 µl, 4.10 mmol) in dichloromethane (2.9 ml) at 0°C, was added acetic anhydride (382 µl, 4.10 mmol) dropwise. The yellow solution was allowed to attain room temperature and was stirred for 6 hours. Saturated sodium bicarbonate solution (5 ml) and dichloromethane (5 ml) were added, the phases separated and the aqueous layer was extracted into dichloromethane (3 x 5 ml). The combined organic extracts were washed with brine (2 x 10 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Vacuum liquid chromatography, eluting with a gradient of 4% diethyl ether / light petrol to 10% diethyl ether / light petrol, provided *diacetate* (**12**) as a clear, colourless oil (496 mg, 83%); t.l.c., (10% diethyl ether / light petrol) R_f = 0.22; $[\alpha]^{22}_D$ +3.37 (*c* 4.16 in chloroform); ν_{max} (thin film)/cm^{-1} 3071 and 3050 (m), 2965, 2948 and 2899 (s), 1739 (s), 1242 (s), 1112 (s), 702 (s); δ_H (300 MHz; $CDCl_3$) 7.68 (4 H, d, *J* 7.1 Hz); 7.47-7.31 (6 H, m); 4.83 (1 H, dd, *J* 8.4 and 3.2 Hz); 3.92 (1 H, dd, *J* 10.8 and 7.6 Hz); 3.83 (1 H, dd, *J* 10.9 and 6.3 Hz); 3.51 (1 H, dd, *J* 10.9 and 6.3 Hz); 3.45 (1 H, dd, *J* 10.9 and 5.8 Hz); 2.24-2.10 (1 H, m); 2.07 (3 H, s); 2.05 (3 H, s); 1.70-1.66 (2 H, m); 1.49 (1 H, ddd, *J* 13.7, 10.0 and 3.8 Hz); 1.07 (9 H, s); 1.02-0.76 (1 H, m); 0.99 (3 H, d, *J* 6.7 Hz); 0.90 (3 H, d, *J* 6.9 Hz); 0.84 (3 H, d, *J* 6.7 Hz); δ_C (75.5 MHz; $CDCl_3$) 171.05, 170.84, 135.63, 135.57, 133.89, 133.79, 129.55, 127.60, 77.11, 67.70, 66.43, 36.35, 33.56, 32.96, 32.31, 26.84, 20.91, 20.88, 19.30, 18.86, 16.17, 10.57; EIMS 455 ([M-*t*-Bu]$^+$, 11%), 395 (40), 257 (10), 199 (98), 137 (100), 43

(73); (FAB-MS) 535 ([MNa]$^+$, 7%), 513 ([MH]$^+$, 4); HRMS (EI) found 455.2258, ([M-*t*-Bu]$^+$, $C_{26}H_{35}O_5Si$ requires 455.2254).

(-)-(2R,4S,5S,6S)-5,7-Diacetoxy-2,4,6-trimethylheptan-1-ol (13)[18] To a stirred solution of *silyl ether* (**12**) (447 mg, 0.872 mmol) in tetrahydrofuran (35 ml) at 0°C, was added tetrabutylammonium fluoride (1.74 ml, 1.74 mmol; 1M in tetrahydrofuran) dropwise. The solution immediately turned cyan, then faded to pale yellow over 5 minutes. The reaction mixture was allowed to attain room temperature and was stirred for 3.5 hours before it was concentrated under reduced pressure. The crude mixture was taken into chloroform (50 ml), washed with water (30 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. Vacuum liquid chromatography eluting with a gradient of 30% diethyl ether / light petrol to 50% diethyl ether / light petrol provided *alcohol* (**238**) as a clear, colourless oil (189 mg, 79%); t.l.c., (50% diethyl ether / light petrol) R_f = 0.29; $[\alpha]^{22}_D$ -9.80 (*c* 2.86 in chloroform); ν_{max} (thin film)/cm^{-1} 3456 (m), 2965, 2948 and 2899 (s), 1733 (s), 1373 (s), 1243 (s), 1039 (m), 734 (m); δ_H (300 MHz; $CDCl_3$) 4.82 (1 H, dd, *J* 7.2 and 4.3 Hz); 3.96 (1 H, dd, *J* 11.0 and 6.9 Hz); 3.81 (1 H, dd, *J* 11.0 and 6.4 Hz); 3.52 (1 H, dd, *J* 10.6 and 4.6 Hz); 3.31 (1 H, dd, *J* 10.5 and 6.3 Hz); 2.23-2.09 (1 H, m); 2.06 (3 H, s); 2.05 (3 H, s); 1.91-1.60 (3 H, m); 1.41 (1 H, ddd, *J* 13.2, 9.6 and 3.6 Hz); 1.00-0.80 (1 H, m); 0.95 (3 H, d, *J* 6.6 Hz); 0.91 (3 H, d, *J* 6.9 Hz); 0.90 (3 H, d, *J* 6.6 Hz); δ_C (75.5 MHz; $CDCl_3$) 171.17, 170.90, 77.31, 66.96, 66.40, 35.87, 33.59, 33.02, 32.35, 20.88, 18.32, 16.65, 11.17; FAB-MS 297 ([MNa]$^+$, 8%), 275 ([MH]$^+$, 12), 215 (16), 155 (58), 55 (100); HRMS (FAB-MS) found 275.1856, ([MH]$^+$, $C_{14}H_{27}O_5$ requires 275.1858).

(2R,4S,5S,6S)-5,7-Diacetoxy-2,4,6-trimethylheptanoic acid(14)[18] To a stirred, biphasic mixture of *alcohol* (**13**) (115 mg, 0.419 mmol) in acetonitrile (838 µl), carbon tetrachloride (838 µl) and water (1.3 ml) at room temperature, was added sodium periodate (367 mg, 1.72 mmol) in a single portion. Ruthenium trichloride trihydrate (2 mg, 9.2 µmol) was added and the dark brown reaction mixture was stirred for 2 hours before dichloromethane (5 ml) and water (3 ml) were added. The phases were separated and the aqueous layer was extracted into dichloromethane (3 x 4 ml). The combined organic extracts were washed with brine (10 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude product was taken into diethyl ether (2 ml), filtered through Celite™, washing with diethyl ether (3 x 4 ml) and concentrated under reduced pressure. The residue could not be purified at this stage and was taken through to the next reaction; t.l.c., (50% diethyl ether / light petrol) R_f = 0.31; ν_{max} (thin film)/cm^{-1} 3700-2600 (m), 2988, 2948 and 2875 (m), 1742 and 1718 (s), 1239 (s); δ_H (300 MHz; $CDCl_3$) 4.85 (1 H, dd, *J* 6.8 and 4.4 Hz); 3.95 (1 H, dd, *J* 10.9 and 7.1 Hz); 3.86 (1 H, dd, *J* 10.9 and 6.1 Hz); 2.18-2.50 (1 H, m); 2.24-2.10 (1 H, m); 2.09 (3 H, s); 2.06 (3 H, s); 1.88-1.70 (2 H, m); 1.36-1.07 (1 H, m); 1.22 (3 H, d, *J* 6.8 Hz); 0.93 (3 H, d, *J* 6.2 Hz); 0.92 (3 H, d, *J* 6.7 Hz); δ_C (75.5 MHz; $CDCl_3$) 171.17, 171.03, 170.98, 76.91, 66.19, 36.19, 33.66, 32.75, 30.28, 20.89, 20.85, 18.59, 16.06, 11.12; GC-MS 288 (M$^+$, 1%), 229 (26), 127 (70), 43 (100); HRMS (EI) found 229.1448, ([M-OAc]$^+$, $C_{12}H_{21}O_4$ requires 229.1440).

(+)-(2R)-2-[(2'S,3'S,5'R)-3',5'-Dimethyl-6'-oxo-tetrahydropyran-2'-yl]propan-1-ol (15)[18] To a stirred solution of *diacetate* (**14**) (122 mg, 0.423 mmol) in tetrahydrofuran (70 ml) at 0°C, was added 0.15M lithium

hydroxide solution (28 ml, 4.23 mmol) dropwise. The reaction mixture was allowed to attain room temperature and was stirred for 2 hours before, at 0°C, 1M hydrochloric acid solution was added dropwise to pH 3. Again, the reaction mixture was allowed to attain room temperature and was stirred for 1.5 hours. Diethyl ether (100 ml) was added, the phases separated and the aqueous phase extracted into diethyl ether (3 x 30 ml). The combined organic extracts were washed with saturated sodium bicarbonate solution (70 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. The residue was passed through a silica plug, eluting with diethyl ether, providing *alcoholic lactone* (**15**) as a white crystalline solid (82 mg, 67% for two steps). An analytical sample was obtained by re-crystallisation (diethyl ether / pentane); t.l.c., (80% diethyl ether / light petrol) R_f = 0.21; m.p. 67-68°C (from diethyl ether / pentane); $[\alpha]^{23}_D$ +51.8 (*c* 2.82 in chloroform); (Found: C, 64.5; H, 10.0. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.75%); ν_{max} (thin film)/cm^{-1} 3417 (br s), 2969, 2936 and 2880 (s), 1712 (s), 1461 (m), 1213 (s), 1043 (m); δ_H (300 MHz; $CDCl_3$) 4.23 (1 H, d, *J* 10.4 Hz); 3.73 (1 H, dd, *J* 10.4 and 8.7 Hz); 3.59 (1 H, dd, *J* 10.6 and 5.9 Hz); 2.49 (1 H, ddq, *J* 13.1, 6.6 and 6.6 Hz); 2.38 (1 H, br s); 2.06-1.73 (3 H, m); 1.38 (1 H, ddd, *J* 12.9, 12.9 and 12.9 Hz); 1.26 (3 H, d, *J* 7.1 Hz); 0.96 (3 H, d, *J* 6.4 Hz); 0.87 (3 H, d, *J* 6.9 Hz); δ_C (75.5 MHz; $CDCl_3$) 174.84, 86.22, 64.60, 37.68, 36.57, 36.33, 30.64, 17.26, 16.88, 8.91; FAB-MS 209 ([MNa]$^+$, 11%), 187 ([MH]$^+$, 57), 169 ([M-H_2O]$^+$, 77), 149 (68), 55 (100).

(+)-(2R)-2-[(2'S,3'S,5'R)-3',5'-Dimethyl-6'-oxo-tetrahydropyran-2'-yl]propanoic acid [(+)-Prelog-Djerassi lactonic acid] (1): To a stirred biphasic mixture of the alcohol (**15**) (30 mg, 0.160 mmol) in acetonitrile (320 µl), carbon tetrachloride (320 µl) and water (480 µl) at room temperature, was added sodium periodate (140 mg, 0.656 mmol) in a single portion. Ruthenium trichloride trihydrate (0.7 mg, 3.5 µmol) was added and the dark brown reaction mixture was stirred for 2 hours before dichloromethane (4 ml) and water (3 ml) were added. The phases were separated and the aqueous layer was extracted into dichloromethane (3 x 4 ml). The combined organic extracts were washed with brine (10 ml), dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude product was taken into diethyl ether (2 ml), filtered through Celite™ washing with diethyl ether (3 x 4 ml) and concentrated under reduced pressure providing (+)-Prelog-Djerassi lactonic acid (**1**) as a white crystalline solid (30 mg, 93%) with data consistent with literature: t.l.c. (diethyl ether) R_f = 0.15; m.p. 123-124°C (from diethyl ether / pentane) (lit., 122.5-123.5°C[19], 122-124°C[20] and 124-125°C[21]); $[\alpha]^{23}_D$ +41.1 (*c* 2.90 in chloroform) (lit., $[\alpha]_D$ +41.3 *c* 2.1 in chloroform[19], $[\alpha]_D$ +42.6; *c* 0.4 in chloroform[20] and $[\alpha]_D$ +39.8; *c* 0.71 in chloroform[20]); (Found: C, 59.8; H, 8.0. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.05%); ν_{max} (thin film)/cm^{-1} 3650-2920 (s), 2980, 2939 and 2882 (m), 1747 (s), 1727 (s), 1383 (m), 1181 (s), 1115 (m); δ_H (300 MHz; $CDCl_3$) 9.66 (1 H, br s); 4.59 (1 H, dd, *J* 10.5 and 1.9 Hz); 2.75 (1 H, dq, *J* 7.1 and 2.2 Hz); 2.52 (1 H, ddq, *J* 13.2, 6.6 and 6.6 Hz); 2.02-1.82 (2 H, m); 1.43 (1 H, ddd, *J* 12.8, 12.8 and 12.8 Hz); 1.28 (3 H, d, *J* 7.1 Hz); 1.20 (3 H, d, *J* 7.1 Hz); 1.01 (3 H, d, *J* 6.4 Hz); δ_C (75.5 MHz; $CDCl_3$) 177.76, 174.59, 86.28, 40.88, 37.07, 36.16, 30.73, 17.14, 16.80, 8.24; EI 200 (M$^+$, 38%), 127 (99), 99 (77), 74 (55), 56 (99), 45 (17), 41 (100).

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REFERENCES

1. Anliker, R.; Dvornik, D.; Gubler, K.; Heusser, H.; Prelog, V. *Helv. Chim. Acta* **1956**, *39*, 1785
2. Djerassi, C.; Zderic, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 6390; Djerassi, C.; Bowers, A.; Hodges, R.; Rinker, B. *J. Am. Chem. Soc.* **1956**, *78*, 1733; Djerassi, C.; Zderic, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 2907
3. Djerassi, C.; Halpern, O. *J. Am. Chem. Soc.* **1957**, *79*, 2023
4. Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1025; Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1029
5. For a review concerning the synthesis of Prelog-Djerassi lactonic acid, see: Martin, S. F.; Guinn, D. E. *Synthesis* **1991**, 245 and references cited therein
6. Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569
7. Eshelby, J. J.; Parsons, P. J.; Sillars, N. C.; Crowley, P. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1497
8. Dung, J. S.; Armstrong, R. W.; Anderson, O. P.; Williams, R. M. *J. Org. Chem.* **1983**, *48*, 3592
9. Eshelby, J. J.; Parsons, P. J.; Crowley, P. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 191
10. Steglich, W.; Hoefle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981
11. Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897; Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868
12. *Encyclopedia of Reagents for Organic Synthesis*, Ed. Paquette, L. A.; Wiley and Sons, **1995**, *2*, 4518
13. Greene, T. W.; Wuts, P. G. M., *Protective Groups in Organic Synthesis*, 2nd Edition, Wiley-Interscience, New York, **1991**, 39
14. Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974; Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765
15. *Encyclopedia of Reagents for Organic Synthesis*, Ed. Paquette, L. A., Wiley and Sons, **1995**, *3*, 1892
16. d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112; Smith, A. B.; Liverton, N. J.; Hriab, H. J.; Sivaramakrishnan, H.; Winzenberg, K. *J. Am. Chem. Soc.* **1986**, *108*, 3040; Kallmerton, J.; Gould, T. J. *J. Org. Chem.* **1986**, *51*, 1152
17. Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1981**, *46*, 5214; Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569
18. Yamaguchi, M.; Katsuki, T.; Honda, M. *Tetrahedron Lett.* **1984**, *25*, 3857
19. Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, *23*, 807
20. Miyashita, M.; Hoshino, M.; Yoshikoshi, A.; Kawamine, K.; Yoshihara, K.; Irie, H. *Chem. Lett.* **1992**, 1101
21. Oppolzer, W.; Walther, E.; Balado, C. P.; De Brabander, J. *Tetrahedron Lett.* **1997**, *38*, 809