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Bakers' Yeast Oxidation of Methyl *para*-Tolylsulfide : Synthesis of a Chiral Intermediate in the Preparation of the Mevinic Acid-type Hypocholestemic Agents

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Dedicated to honour Professor Hans Suschitzky on the occasion of his 80th birthday

Abstract : The use of (*R*)-methyl *para*-tolylsulfoxide as a chiral auxiliary in a novel synthesis of a key intermediate en route to mevinic acid-type hypocholestemic agents is described. The synthesis is short and simple consisting of eight steps to yield enantiomerically pure β-silyloxy-δ-lactone. The chiral sulfoxide used in the synthesis was obtained *via* a straightforward biooxidation of methyl *para*-tolylsulfide using bakers' yeast (*Saccharomyces cerevisiae* NCYC 73). The biotransformation involves the use of whole cells and affords the sulfoxide in good yield and with high stereoselectivity.

INTRODUCTION

The importance of chiral molecules in both medicine and agricultural chemistry has led to the continuing need to develop efficient methods for the synthesis of enantiomerically pure synthons. One area which has generated much interest is the use of sulfoxides as chiral auxiliaries in asymmetric synthesis.[1-6]

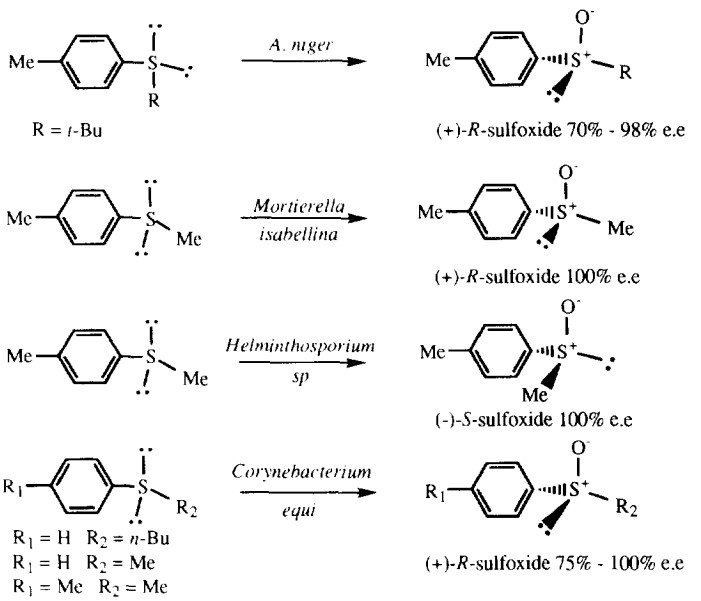
Classical methods for the preparation of chiral sulfoxides[7] include the Sharpless/Kagan asymmetric sulfoxidation,[8-15] in which tertiary butyl hydroperoxide is used in the presence of a titanium complex (Ti(O-*i*Pr)4), diethyl tartrate and water to afford sulfoxides with high degrees of enantiomeric purity. In addition, chiral oxaziridines have also been shown to perform asymmetric sulfoxidations with a high degree of stereoselection.[16-21] Alternatively, enzymatic systems can be employed for the preparation of chiral sulfoxides;[7, 22-24] such systems exhibit high degrees of regio- and stereoselectivity. These factors coupled with the increasing awareness of the need for "environmentally friendly" alternatives to some of the more hazardous chemicals have contributed to the increasing interest in the potential applications of enzymatic systems.

Previous reports on biosulfoxidations *via* whole cell systems have mainly been focused on fungi such as *Aspergillus niger* ,[22, 25] *Mortierella isabellina*,[26] *Helminthosporium sp*[27] and the bacterium *Corynebacterium equi* [28](Scheme 1). Despite the good to excellent stereoselection demonstrated by these

microorganisms, low abundance coupled with often complex and labour intensive protocols for the cultivation of the cells have limited the scope and the applications of such biotransformation systems.

Isolated enzymes such as rat liver cytochrome P450 monooxygenase,[29] pig liver FAD-dependent monooxygenase,[30] monooxygenases from *Pseudomonas* sp,[31] the cyclohexanone monooxygenase from *Acinetobacter calcoaceticus*[32] and the chloroperoxidase from *Caldaromyces fumago*[33] have all been reported to perform biosulfoxidations with good to excellent enantioselectivities. However, these biocatalysts are not readily available and need to be used in conjunction with expensive cofactors such as NADH, NADPH and FAD.

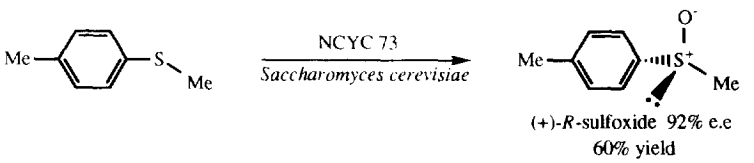
Scheme 1



In the past, the success of bakers' yeast to perform biosulfoxidations with good stereoselection has been limited to sulfides such as 9-thiostearate[34] and methylstyryl sulfide.[35] The attractions of using bakers' yeast as a biocatalyst are associated with its abundance and low cost and the ease of the protocol for the cultivation of the cells.

Here we report a novel and simple biooxidation of methyl *para*-tolylsulfide to the corresponding (*R*)-sulfoxide using bakers' yeast (*Saccharomyces cerevisiae* NCYC 73).[36] The biotransformation involves the use of whole cells and affords the sulfoxide in good yield (60%) and with high enantioselectivity (92% e.e) (Scheme 2).

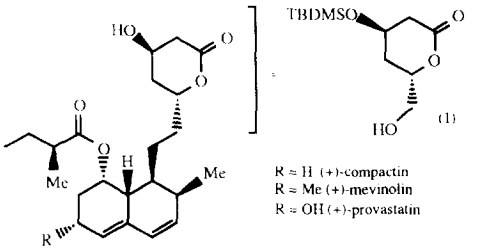
Scheme 2



The chiral sulfoxide ((*R*)-methyl *para*-tolylsulfoxide) obtained from this whole cell biotransformation was used as a chiral auxiliary in the synthesis of a key intermediate (1) in the preparation of the mevinic acid-type hypocholestemic agents.[36]

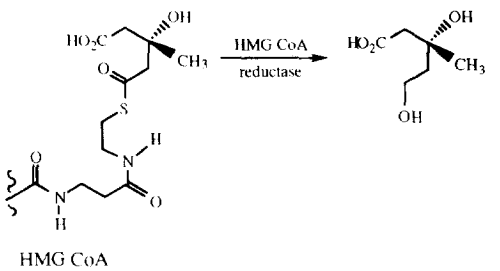
Mevinic acids such as compactin, mevinolin and provastatin (Figure 1) have been known to be inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase since the 1970's.[37-39]

Figure 1



The considerable interest in this class of compounds is associated with their ability to lower the level of cholesterol in blood plasma via the inhibition of the enzyme responsible for the rate determining step in the biosynthesis of cholesterol. During the rate determining step HMG-CoA is reduced to mevalonic acid (Eq 1).

Equation 1



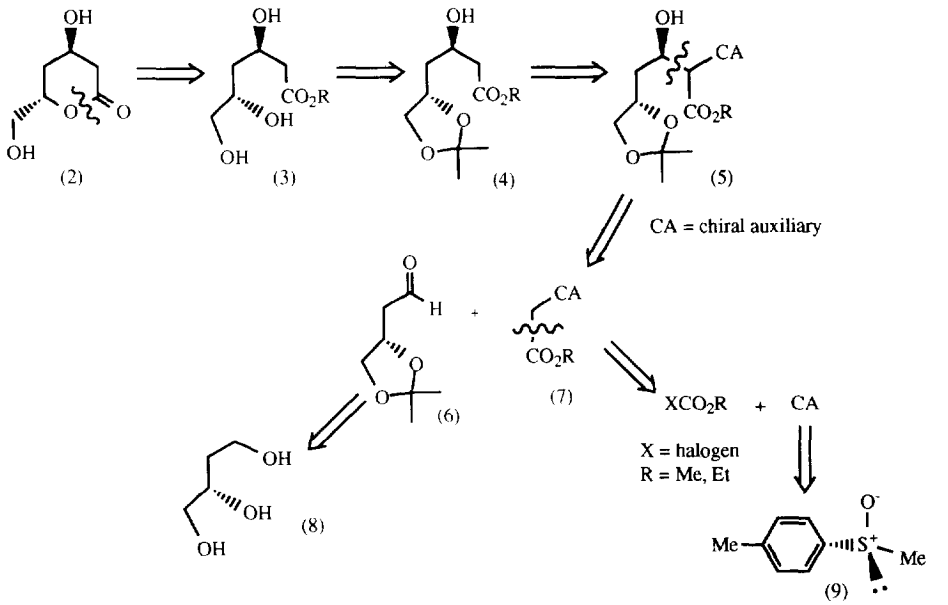
HMG CoA

The key structural feature common to all HMG-CoA reductase inhibitors is the β-hydroxy-δ-lactone moiety in the 4*R*, 6*R* configuration. The ability of mevinic acids to inhibit the reductase is thought to be associated with the similarity of the lactone functionality to the HMG unit. Hence, considerable effort has been directed towards the synthesis of the lactone moiety in enantiomerically pure form.[40-43]

RESULTS AND DISCUSSION

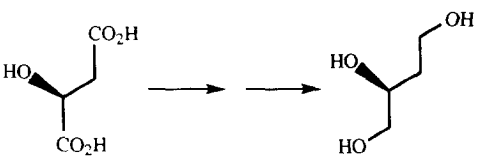
Our retrosynthetic analysis of lactone (2) is shown in Scheme (3). It was envisaged that lactone (2) could be formed from triol (3), which in turn could be masked in the form of acetonide (4). Acetonide (4) could be perceived to undergo a retro aldol to afford fragments (6) and (7). Aldehyde (6) could be obtained from a precusor, (*S*)-(-)-1, 2, 4-butanetriol (8) which possesses the correct configuration for the chirality required at the C-5 atom of (2).

Scheme 3



The triol (8) is commercially available or alternatively can be derived from L-malic acid (Scheme 4).[44]

Scheme 4



The chiral centre at C-3 of (2) could be created during the aldol condensation between aldehyde (6) and ester (7). Generally, the degree of control of the stereoselectivity of aldol condensations is low, resulting in the formation of mixtures of diastereoisomers and enantiomers. However, previous work by Solladié [2, 45] based on the incorporation of chiral α-sulfinylesters into aldol-type condensations was found to improve the

stereoselectivity of such reactions, with the newly formed C-C bond being governed by the chirality of the α-sulfinylester. Such a strategy could be used to establish the correct configuration at the C-3 centre of (2). The advantage of using an α-sulfinylester is that it could be easily removed at a later stage in the synthesis. The α-sulfinylester could be formed from the reaction of a chiral sulfoxide with a haloformate ester. The chiral sulfoxide employed in this synthesis of the lactone moiety was (*R*)-methyl *para*-tolylsulfoxide (9), obtained from a whole cell biotransformation using bakers' yeast.

Scheme 5 shows the total synthesis of the lactone moiety found in mevinic acids. The first step of the synthesis was the whole cell biotransformation of methyl *para*-tolylsulfide to the corresponding (*R*)-sulfoxide (9) using bakers' yeast.

The biotransformation proceeded in good yield and with a high degree of enantioselectivity, with no detectable formation of the corresponding sulfone. The whole cells used to perform the biotransformation were cultivated under semi-anaerobic conditions. Such conditions are essential in inducing the formation of the required monooxygenase.

Contrary to the conditions required for the cultivation of the cells, the biotransformation itself requires aeration and thus was performed on an orbital shaker. The biotransformation was monitored by gas chromatography and was shown to reach an equilibrium after 24-48 hours. A simple work up procedure yielded the pure sulfoxide. The enantiomeric excess of the sulfoxide was determined by ^{1}H NMR spectroscopy in the presence of [Eu(hfc)$_3$]. The absolute configuration of the major enantiomer was determined by comparison with the spectra of authentic *R* and *S* enantiomers.

The enolate ion of (9) was generated using lithium diisopropylamide and reacted with methyl or ethyl chloroformate to afford the α-sulfinylesters (10) and (11), respectively. Subsequent treatment of the α-sulfinylesters (10) and (11) with *t*-BuMgCl yielded the corresponding enolate ions.

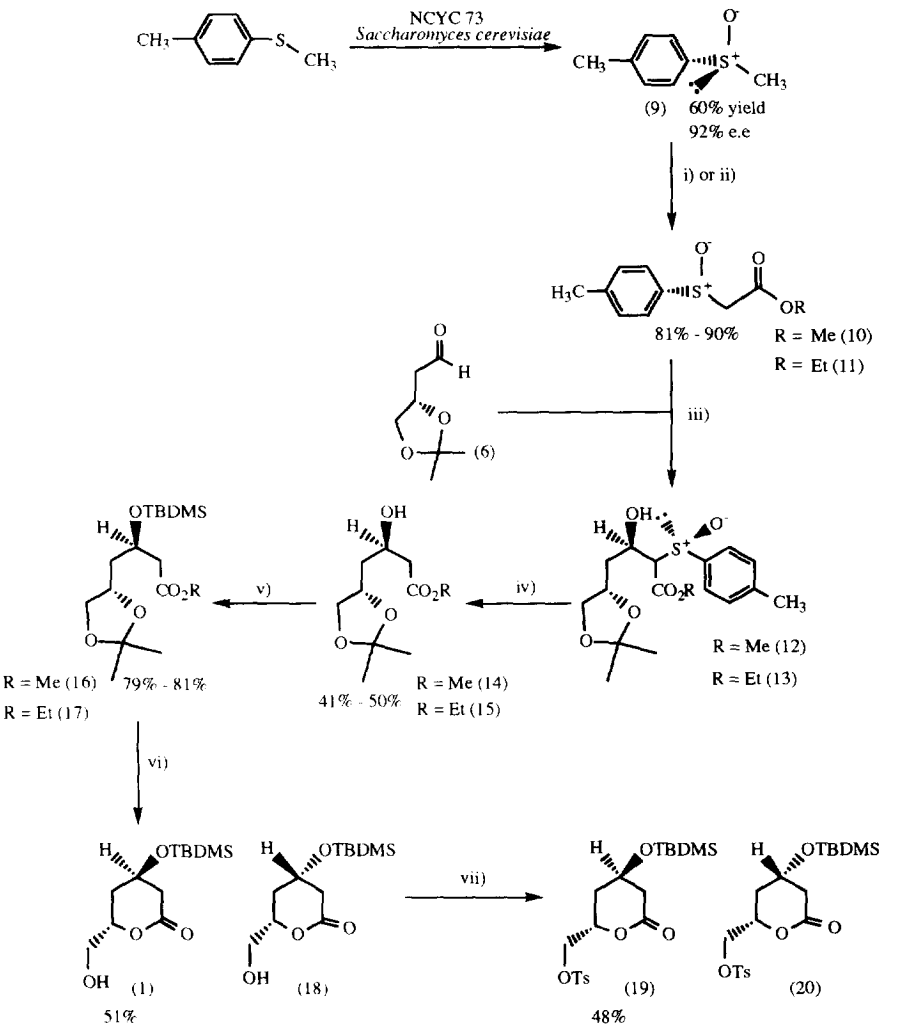
The key step in the synthesis involves the aldol condensation between the enolate ions of (10) and (11) and aldehyde (6) to yield the esters (12) and (13). During the aldol condensation two new chiral centres are generated at C-2 and C-3 in (12) and (13). The stereochemistry of these two new centres are governed by the chirality of the α-sulfinylester. Desulphurisation[46] of (12) and (13) yielded the C-3 epimers of (14) and (15) in a ratio of 4:1, as determined by ^{13}C NMR spectroscopy. The origin of the major and minor C-3 epimers, as formed during the condensation, can be explained by looking at the four possible transition states that may arise during the reaction (Figure 2).

Transition state A is the most favoured, largely because it exhibits minimium steric interactions. Thus, the bulky tolyl group of the sulfoxide is far removed from the acetonide group on the aldehyde and only the lone pair of electrons on the sulfur atom interacts with the hydrogen atom of the aldehyde. Hence, it is believed that the major C-3 epimer is formed *via* the low energy transition state A. In accord with previous work by Solladié,[45] the subsequent stereochemistry dictated by transition state A at the C-2 and the C-3 atoms of (12) and (13) is *R*, *R*, with the configuration being correct at C-3 for the stereochemistry required at the C-3 atom of the lactone moiety found in mevinic acids. The minor C-3 epimer was formed as a result of competitive reactions that proceed *via* transition states B and C.

The β-hydroxyesters (14) and (15) were protected using *tert*-butyldimethylsilyl chloride to afford the corresponding *tert*-butyldimethylsilylethers (16) and (17), in good yield. Lactonisation of (16) and (17), by heating to reflux in 80% acetic acid, afforded the desired lactone (1) and (18); successive recrystallisations from hexane gave (1) in pure form. Alternatively, tosylation of a mixture of (1) and (18) afforded the

corresponding tosyl derivatives (19) and (20); flash column chromatography of the mixture yielded the major tosyl derivative (19) in pure form. The configuration of the major C-3 epimer (1) and (19) was determined by n.O.e studies and was found to possess a 4*R*, 6*S* configuration (as expected), the correct configuration for the lactone moiety found in mevinic acids.

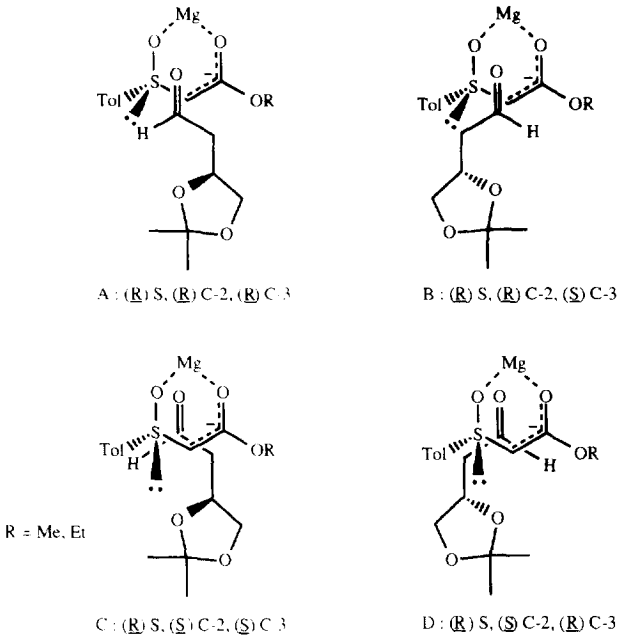
Scheme 5



Reagents and conditions :

i) LDA, $ClCO_2CH_3$, THF, N_2, -78°C
ii) LDA, $ClCO_2CH_2CH_3$, THF, N_2, -78°C
iii) *t*-BuMgCl, THF, N_2, -78°C
iv) Al/Hg, THF, H_2O (10:1), 0°C
v) TBDMSCl, imidazole, DMF, N_2, 50°C, 2hr
vi) 80% acetic acid, 100°C, 1hr
vii) $ClSO_2C_6H_4CH_3$, pyridine

Figure 2



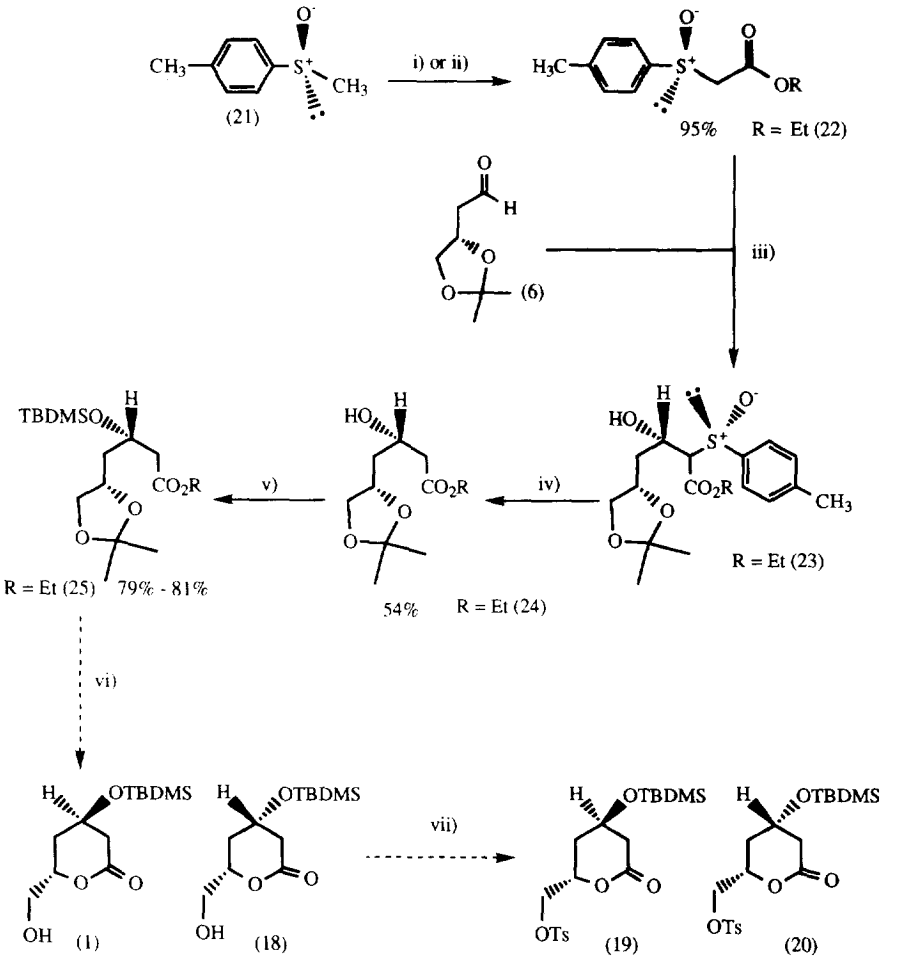
Use of (*S*)-methyl *para*-tolylsulfoxide as the chiral auxiliary and its effect on the diastereoselectivity.

The effect on the diastereoselectivity of the aldol condensation by substituting the chiral auxiliary, (*R*)-methyl *para*-tolylsulfoxide with the enantiomer, (*S*)-methyl *para*-tolylsulfoxide, was investigated. The synthesis was performed under identical conditions to those used previously (Scheme 6).

The transition states arising from the aldol condensation between (22) and (6) are shown in Figure 3. Transition state C exhibits the minimium degree of steric interactions and hence is the favoured transition state of the aldol condensation. The resulting stereochemistry dictated by transition state C is C-2 *S*, C-3 *S*, with the minor diastereoisomers of (23) (*R*, *R* and *S*, *R* at the C-2 and the C-3 atoms) occurring as a result of transition states A and D.

The ^{1}H NMR spectrum of (25) (obtained by the reduction of (23) and protection of the hydroxyl group of (24), in the usual manner) indicated a 4:1 ratio of the C-3 epimers. Comparison of the spectral data obtained for (25) with the spectral data of (17) showed that the intensity of the two sets of signals associated with the methylene protons α to the C-3 centre and the ester group were reversed, indicating that the C-3 centre of (25) is predominantly in the *S* configuration.

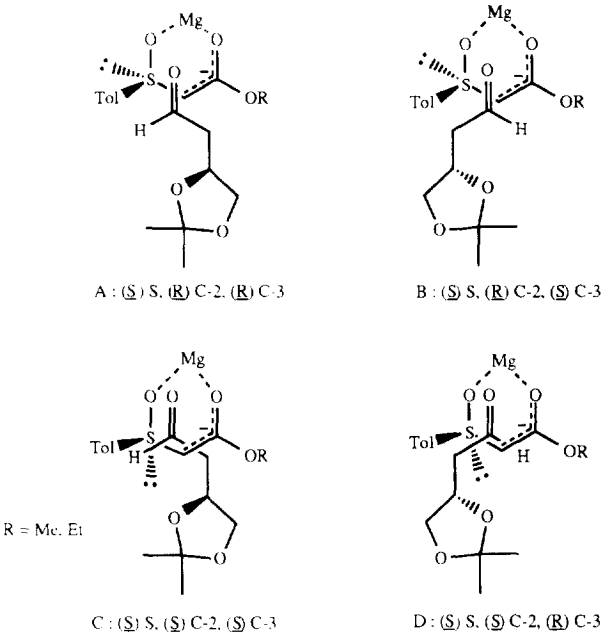
Scheme 6



Reagents and conditions :

i) LDA, $ClCO_2CH_3$, THF, N_2, -78°C
ii) LDA, $ClCO_2CH_2CH_3$, THF, N_2, -78°C
iii) *t*-BuMgCl, THF, N_2, -78°C
iv) Al/Hg, THF, H_2O (10:1), 0°C
v) TBDMSCl, imidazole, DMF, N_2, 50°C, 2hr
vi) 80% acetic acid, 100°C, 1hr
vii) $ClSO_2C_6H_4CH_3$, pyridine

Figure 3



It can be concluded that the degree of diastereoselectivity of the aldol condensation was maintained when (*S*)-methyl *para*-tolylsulfoxide was used as the chiral auxiliary.

These studies have generated a short and novel synthesis of the lactone moiety found in mevinic acids *via* modification of the Heathcock procedure.[43] The modification was based on the incorporation of a chiral auxiliary to control the stereochemistry at the C-3 centre of the lactone. The diastereoselectivity obtained from this synthesis was far superior to that obtained from the Heathcock procedure, resulting in a 4:1 ratio in favour of the lactone with the correct configuration for mevinic acids. The chiral auxiliary used in this synthesis was obtained from a whole cell biotransformation of methyl *para*-tolylsulfide using bakers' yeast. This novel biotransformation provided a simple method of producing the sulfoxide in good yield and with high enantioselectivity.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

General methods

Solvents were dried and distilled as follows: tetrahydrofuran with sodium metal and benzophenone, dichloromethane with calcium hydride, triethylamine with potassium hydroxide. (*S*)-methyl *para*-tolylsulfoxide was obtained from Aldrich Chemical Company, other reagents and solvents were used as obtained commercially and without further purification. Thin layer chromatography (TLC) was performed on pre-coated glass plates (Merck silica gel 60 F_{254}). The plates were visualised using U.V light (254 nm), *para*-anisaldehyde or cerium ammonium molybdate dip followed by heating. Flash chromatography was performed on silica gel (Merck silica gel 60, 40-63 μm). Gas chromatography (GC) was performed on a Shimadzu GC-14A gas chromatograph equipped with a capillary column, BP1 (25 m), using helium as the carrier gas, the detector and injector temperatures were 280 °C. ^{1}H NMR, ^{13}C NMR spectroscopy, ^{1}H NMR spectroscopy in the presence of [Eu(hfc)3] and n.O.e experiments were carried out on a Brüker AM 300 or DRX 400 spectrometer. Chemical shifts (δ) were quoted in ppm and coupling constants (*J*) in Hz. IR spectra were recorded on a Nicolet Magna-IR 550 spectrometer as liquid films between sodium chloride plates, in the solid state in potassium bromide discs or in solution using CHCl3 in sodium chloride cells. Mass spectra were recorded on a Kratos Profile HV 3000 spectrometer. Optical rotations were measured on an Optical Activity AA-1000 polarimeter at the University of Exeter or at Birkbeck College, University College of London. Rotations were recorded in units of 10^{-1} deg cm^2 g^{-1}. Melting points were determined using a Gallenkamp melting apparatus and are uncorrected. Chemicals for the medium, used in the cultivation of the yeast cells, were obtained from Oxoid Ltd. Methyl *para*-tolylsulfide for the biotransformation was obtained from Sigma Ltd. *Saccharomyces cerevisiae* NCYC 73 was obtained from The National Collection of Yeast Cultures, Norwich. Centrifugation was performed using a MSE Cool Spin Centrifuge.

Cultivation of *Saccharomyces cerevisiae* NCYC 73

Saccharomyces cerevisiae NCYC 73 was grown on a medium composed of glucose (10 g), yeast extract (3 g), malt extract (3 g) and neutralised bacterial peptone (3 g) per litre of distilled water adjusted to pH 6.2 with 2M HCl. An inoculum of *Saccharomyces cerevisiae* NCYC 73 was grown in 25 mL of medium for 24 hours, transferred aseptically to 1 L for 24 hours, and then grown in 10 L for 48 hours at 25 °C without aeration. The thick white mat of yeast cells at the base of the vessel was harvested by centrifugation (5000*G* for 30 minutes at 4 °C), washed once with 100 mM citrate/phosphate buffer pH 6.0 and finally re-suspended in 1% glucose in this buffer at 12.5 times the concentration of the growing cells (0.125 g wet mass per mL buffer).

Synthesis of (*R*)-(+)-methyl *para*-tolyl sulfoxide(9) by *Saccharomyces cerevisiae* NCYC 73

A solution of methyl *para*-tolylsulfide in ethanol (1.30 mmol, 200 mg/mL) was prepared and added to the described culture of *Saccharomyces cerevisiae* NCYC 73 to a final concentration of 7.2 mmol dm^{-3}. The mixture was shaken at ambient temperature in an orbital shaker (at 200 r.p.m). The formation of methyl-*para*-tolylsulfoxide was monitored by a BP1 non-polar GC column at 150 °C. After 24-48 hours the reaction mixture was centrifuged and the supernatant solution extracted with ethyl acetate (or chloroform). The organics were dried over magnesium sulfate and the solvent removed under reduced pressure. The residue was then purified by flash column chromatography on silica gel with ethyl acetate as the eluent (R_f = 0.4), to obtain (*R*)-methyl *para*-tolylsulfoxide (9) as a white crystalline derivative in 60% yield (0.12 g).
m.p 72-74 °C (*lit.*,[47] 73-75 °C); IR (KBr): ν_{max}/cm^{-1} 3055, 3004 (Ar-H) (w), 2910, 2876 (C-H) (w), 1498 (Ar-H) (m), 1063 (S=O) (s); ^1H NMR (300 MHz; $CDCl_3$): δ_H 2.41 (s, 3H, CH_3), 2.70 (s, 3H, CH_3SO), 7.34 (d, 2H, *J* = 4, *meta* - H), 7.54 (d, 2H, *J* = 4, *ortho* - H); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C 21.33 (*para* - CH_3), 43.96 (CH_3SO), 123.50 (2(CH), *meta* - CH), 129.98 (2(CH), *ortho* - CH), 141.44 ($\underline{C}CH_3$, *para* - C), 142.56 (C, *ipso* - C); $[\alpha]_D^{24}$ +129 (c = 1, CH_3CH_2OH) (*lit.*,[47] +141); m/z Found M^+ 154.04536 $C_8H_{10}OS$: Required 154.04524; GC retention time 5.13 minutes at a column temperature of 150 °C (BP1 non-polar column).

Synthesis of (*R*)-(+)-methyl-α-(*para*-tolylsulfinyl) acetate (10)

Lithium diisopropylamide (LDA) was prepared by the addition of *n*-butyllithium (13 mmol, 5.2 mL from a 2.5M solution in hexane) to a solution of diisopropylamine (8.4 mmol, 850 mg, 1.1 mL) in THF (30 mL) at -78 °C, under N_2. The solution was stirred for 40 minutes. To the solution, (*R*)-methyl*para*-tolylsulfoxide (6.48 mmol, 1 g) dissolved in THF (20 mL) was added dropwise over a period of 10 minutes. The reaction mixture was stirred at -78 °C for a further 40 minutes. Methyl chloroformate (13 mmol, 1.23 g, 1 mL) was then added dropwise to the reaction mixture and stirred for 1 hour. The reaction was monitored by TLC and on completion was quenched at -78 °C by the addition of saturated ammonium chloride solution (20 mL). The reaction mixture was warmed to room temperature and then diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed in brine (20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica gel with 1:1 ethyl acetate/hexane as the eluent (R_f = 0.32), to give (10) (1.12 g, 81% yield), as a yellow oil.
IR (neat): ν_{max}/cm^{-1} 2961, 2919 (C-H) (w), 1736 (C=O) (s), 1497, 1438 (Aryl-H) (m), 1089 (C-O) (m), 1055 (S=O) (s); ^1H NMR (300MHz; $CDCl_3$): δ_H 2.42 (s, 3H, *para* - CH_3), 3.64 (d, 1H, *J* = 13, HC), 3.71 (s, 3H, CH_3), 3.84 (d, 1H, *J* = 13, HC), 7.34 (d, 2H, *J* = 4, *meta* - H), 7.56 (d, 2H, *J* = 4, *ortho* - H); ^{13}C NMR (75MHz; $CDCl_3$): δ_C 21.45 (*para* - CH_3), 52.67 (CH_3), 61.64 (CH_2), 124.15 (2(CH), *meta* - CH), 130.10 (2(CH), *ortho* - CH), 139.91 ($\underline{C}CH_3$, *para* - C), 142.43 (C, *ipso* - C), 165.22 (CO_2); $[\alpha]_D^{20}$ +115 (c = 2, $CHCl_3$); m/z Found M^+ 212.05025 $C_{10}H_{12}O_3S$: Required 212.05072.

Synthesis of (*R*)-(+)-ethyl-α-(*para*-tolylsulfinyl) acetate (11)

Lithium diisopropylamide (LDA) was prepared by the addition of *n*-butyllithium (13 mmol, 5.2 mL from a 2.5M solution in hexane) to a solution of diisopropylamine (8.4 mmol, 850 mg, 1.1 mL) in THF (30 mL) at -78 °C, under N_2. The solution was stirred for 40 minutes. To the solution, (*R*)-methyl *para*-tolylsulfoxide (6.48 mmol, 1 g) dissolved in THF (20 mL) was added dropwise over a period of 10 minutes. The reaction mixture was stirred for a further 40 minutes. Ethyl chloroformate (7.1 mmol, 774 mg, 0.68 mL) was then added dropwise to the reaction mixture and stirred at -78 °C for 1 hour. The reaction was monitored by TLC and on completion was quenched at -78 °C by the addition of saturated ammonium chloride solution (20 mL). The reaction was worked up following the same procedure used previously in the synthesis of (10). The solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica gel with 1:1 ethyl acetate/hexane as the eluent (R_f = 0.35), to give (11) (1.32 g, 90% yield), as a yellow oil.

IR (neat): ν_{max}/cm^{-1} 2987, 2927 (C-H) (w), 1744 (C=O) (s), 1497, 1438 (Aryl-H) (m), 1089 (C-O) (m), 1055 (S=O) (s); ^1H NMR 400 MHz ($CDCl_3$): δ_H 1.21 (t, 3H, CH_3), 2.42 (s, 3H, *para* - CH_3), 3.63 (d, 1H, J = 12, HC), 3.84 (d, 1H, J = 12, HC), 4.13 (d, 1H, J = 6, CH_2), 4.17 (d, 1H, J = 6, CH_2), 7.34 (d, 2H, J = 4, 2(CH), *meta* - H), 7.58 (d, 2H, J = 4, 2(CH), *ortho* - H); ^{13}C NMR 106 MHz ($CDCl_3$): δ_C 14.01 (CH_3), 21.45 (*para* - CH_3), 61.82 (CH_2O), 61.96 (CH_2SO), 124.26 (2(CH), *meta* - CH), 130.06 (2(CH), *ortho* -CH) , 139.99 ($\underline{C}CH_3$, *para* - C), 142.39 (C, *ipso* - C), 164.76 (CO_2); $[\alpha]_D^{20}$ +110.6 (c = 1, $CHCl_3$); m/z Found M^+ 226.06719 $C_{11}H_{14}O_3S$: Required 226.06637.

Synthesis of (*S*)-(+)-3, 4-*O*-isopropylidene-3, 4-dihydroxybutanol

para-Toluenesulfonic acid (0.63 mmol, 120 mg) in acetone (250 mL) was added to (*S*)-(-)-1,2,4-butanetriol (8) (94 mmol, 10 g) and stirred at room temperature for 24 hours. The reaction was monitored by TLC and on completion an excess of solid sodium hydrogen carbonate was added and stirred for 30 minutes. After filtration, the solvent was removed under reduced pressure. The crude product was then purified by distillation under reduced pressure to give (*S*)-(+)-3, 4-*O*-isopropylidene-3, 4-dihydroxybutanol (11.79 g 86% yield), as a colourless oil. (R_f = 0.32 eluent 1:1 ethyl acetate/hexane)

b.p 98-104 °C (~15 mmHg) (*lit.*,[43] 87 °C (22 mmHg)); IR (neat): ν_{max}/cm^{-1} 3438 (OH) (s), 2987, 2936, 2885 (C-H) (w), 1072 (C-O) (m); ^1H NMR 400 MHz ($CDCl_3$): δ_H 1.35 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.82 (dd, 2H, J = 4, 9, 2-H), 2.25 (broad t, 1H, OH), 3.59 (t, 1H, J = 7.5, 4-H), 3.79 (m, 2H, 1-H), 4.08 (dd, 1H, J = 6, 8, 4-H), 4.26 (m, 1H, 3-H); ^{13}C NMR 106 MHz ($CDCl_3$): δ_C 25.66 (CH_3), 26.88 (CH_3), 35.66 (2-C), 60.53 (4-C), 69.45 (1-C), 75.06 (3-C), 109.07 (CO_2); $[\alpha]_D^{25\ °C}$ +1.0 (c = 2, $CHCl_3$); m/z Found $[M+H]^+$ 147.10260 $C_7H_{14}O_3S$: Required 146.09430.

Synthesis of (*S*)-(+)-3, 4-*O*-isopropylidene-3, 4-dihydroxybutanal (6)

To a solution of oxalyl chloride (45 mmol, 5.70 g, 3.9 mL) in CH_2Cl_2 (75 mL) at -78 °C, under N_2, DMSO (90 mmol, 7.03 g, 6.39 mL) in CH_2Cl_2 (15 mL) was added dropwise over a period of 10 minutes. The reaction mixture was stirred for a further 10 minutes, (*S*)-(+)-3,4-*O*-isopropylidene-3,4-dihydroxybutanol in CH_2Cl_2 (30 mL) was added dropwise over a period of 10 minutes and then left to stir at -78 °C for 15 minutes. Triethylamine (27 mL, excess) was added to the reaction mixture at -78 °C, left to stir for 10 minutes and then allowed to warm to room temperature. Water (150 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were washed with a 1% solution of HCl (60 mL), followed by a solution of saturated sodium hydrogen carbonate (60 mL), water (60 mL) and brine (60 mL). The organics were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude residue was then purified by distillation under reduced pressure to give (6) (4.2 g, 71% yield), as a colourless oil.
b.p 77-79 °C (~15 mmHg); IR (neat): ν_{max}/cm^{-1} 2982, 2939, 2887 (C-H) (w), 1725 (C=O) (s), 1075 (C-O) (m); ^1H NMR 400MHz ($CDCl_3$): δ_H 1.34 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.62 (ddd, 1H, J = 2.0, 6.0, 18, 2-H), 2.82 (ddd, 1H, J = 2.0, 7.5, 18, 2-H), 3.57 (dd, 1H, J = 6.0, 8.0, 4-H), 4.17 (dd, 1H, J = 6.0, 8.0, 4-H), 4.51 (m, 1H, 3-H), 9.78 (t, 1H, 1-H); ^{13}C NMR 106 MHz($CDCl_3$): δ_C 25.42 (CH_3), 26.77 (CH_3), 47.84 (2-C), 69.12 (4-C), 70.66 (3-C), 109.25 (CO_2), 199.89 (1-C); $[\alpha]_D^{26}$ +6.7 (c = 2, $CHCl_3$); m/z Found $[M+1]^+$ 145.07864 $C_7H_{12}O_3$: Required 144.07864.

Synthesis of intermediate (12) by the aldol condensation of (*R*)-(+)-methyl-α-(*para*-tolylsulfinyl) acetate (10) and (6)

(*R*)-(+)-Methyl-α-(*para*-tolylsulfinyl) acetate (10) (5.28 mmol, 1.12 g) was dissolved in THF (100 mL) and cooled to -78 °C under N_2. To the solution, *t*-BuMgCl (7.92 mmol, 7.92 mL from a 1M solution in THF) was added and stirred for 30 minutes. (*S*)-(+)-3,4-*O*-isopropylidene-3, 4-dihydroxybutanal (6) (7.92 mmol, 1.14 g) in THF (20 mL) was then added dropwise to the reaction mixture over a period of 10 minutes and then stirred for a further hour. The reaction was monitored by TLC and on completion was quenched by the addition of a saturated solution of ammonium chloride (50 mL), this was then followed by the addition of CH_2Cl_2 (50 mL) and 2M HCl (50 mL). The solution was allowed to warm up to room temperature, the layers were then separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give (12), as a yellow oil. Due to the instability of (12), it was taken through to the next step of the synthesis, without further purification. (R_f = 0.15 eluent 1:1 ethyl acetate/hexane)

Synthesis of intermediate (13) by the aldol condensation of (*R*)-(+)-ethyl-α-(*para*-tolylsulfinyl) acetate (11) and (6)

(*R*)-(+)-Ethyl-α-(*para*-tolylsulfinyl) acetate (11) (5.0 mmol, 1.13 g) was dissolved in THF (100 mL) and cooled to -78 °C under N_2. To the solution, *t*-BuMgCl (7.50 mmol, 7.50 mL from a 1M solution in THF) was added and stirred for 30 minutes. (*S*)-(+)-3,4-*O*-3,4-dihydroxybutanal (6) (7,50 mmol, 1.08 g) in THF (20 mL) was then added dropwise to the reaction mixture over a period of 10 minutes and then stirred for a further 60 minutes. The reaction was worked up following the same procedure used previously in the synthesis of (12). Due to the instability of (13), it was taken through to the next step of the synthesis, without further purification. (R_f = 0.16 eluent 1:1 ethyl acetate/hexane)

Synthesis of methyl (3*R*, 5*S*)- and (3*S*, 5*S*)-5, 6-*O*-isopropylidene-3,5,6-trihydroxyhexanoate (14)

The crude product (12) (11 mmol, 4.0 g) was added to a solution of THF/H_2O (10:1, 20 mL). The reaction was stirred and cooled to 0 °C. Aluminium strips (24 mmol, 6.5 g) were exposed sequentially to 1M KOH, H_2O, 2% $HgCl_2$, H_2O and THF and added to the reaction mixture over a period of 1 hour. The reaction mixture was kept at 0°C and stirred for 24 hours. The reaction mixture was then allowed to warm to room temperature and THF (20 mL) added, the reaction mixture was stirred for a further 30 minutes and then filtered through celite. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with 3:2 chloroform/ethyl acetate as the eluent (R_f = 0.29) to give (14), a colourless oil (0.48 g, 50% yield), as a mixture of epimers in a ratio of 4:1.
IR (neat): ν_{max}/cm^{-1} 3476 (OH) (m), 2987, 2952, 2879 (C-H) (m), 1737 (C=O) (s), 1071 (C-O) (m); ^1H NMR (300 MHz: $CDCl_3$): δ_H 1.32 (s, 3H, CH_3C), 1.38 (s, 3H, CH_3C), 1.72 (m, 2H, 4-H), 2.50 (dd, 2H, *J* = 5, 8, 2-H), 3.43 (d, 1H, *J* = 2.5, OH), 3.55, (m, 1H, 3-H), 3.67 (s, 3H, CH_3O), 4.05 (dd, 1H, *J* = 6, 8, 5-H), 4.25 (m, 2H, 6-H); ^{13}C NMR major C-3 epimer (75 MHz; $CDCl_3$): δ_C 25.68 ($\underline{C}H_3C$), 26.86 ($\underline{C}H_3C$), 39.71 (4-C), 41.34 (2-C), 51.69 (CH_3O), 66.94 (5-C), 69.51 (6-C), 74.57 (3-C), 109.32 (C), 172.53 (CO_2); ^{13}C NMR minor C-3 epimer (75 MHz; $CDCl_3$): δ_C 25.65 ($\underline{C}H_3C$), 26.91 ($\underline{C}H_3C$), 39.88 (4-C), 41.41(2-C), 51.69 (CH_3O), 65.56 (5-C), 69.59 (6-C), 73.28 (3-C), 108.82 (C), 172.56 (CO_2); m/z Found $[M+H]^+$ 219.12427 $C_{10}H_{18}O_5$: Required 218.11542; GC retention time 2.38 min, column temperature 200 °C (BP1 non-polar column).

Synthesis of ethyl (3*R*, 5*S*)- and (3*S*, 5*S*)-5, 6-*O*-isopropylidene-3,5,6-trihydroxyhexanoate (15)

The crude product (13) (6.04 mmol, 2.23 g) was added to a solution of THF/H_2O (10:1, 10 mL), whilst stirring at 0 °C. Aluminium strips (133 mmol, 3.59 g) were exposed sequentially to 1M KOH, H_2O, 2% $HgCl_2$, H_2O and THF and added to the reaction mixture over a period of 1 hour. The reaction mixture was kept at 0°C and stirred for 24 hours. The reaction was worked up following the same procedure used previously in the synthesis of (14). The residue was purified by flash column chromatography on silica gel

with 3:2 chloroform/ethyl acetate as the eluent (R_f= 0.42) to give (15), a colourless oil (0.54 g, 41% yield), as a mixture of epimers in a ratio of 4:1.
IR (neat): ν_{max}/cm^{-1} 3480 (OH) (m), 2987, 2936 (C-H) (m), 1736 (C=O) (s), 1081 (C-O) (m) ; ^1H NMR (400 MHz; $CDCl_3$): δ_H 1.26 (t, 3H, $C\underline{H}_3CH_2$), 1.35 (s, 3H, CH_3C), 1.40 (s, 3H, CH_3C), 1.75 (m, 2H, 4-H), 2.50 (dd, 2H, J = 5, 8, 2-H), 3.45 (d, 1H, J = 2, OH), 3.57, (m, 1H, 3-H), 4.05-4.25 (m, 5H, 6-H, 5-H, $CH_3C\underline{H}_2O$); ^{13}C NMR major C-3 epimer (106; MHz $CDCl_3$): δ_C 14.16 (CH_3), 25.70 ($\underline{C}H_3C$), 26.87 ($\underline{C}H_3C$), 39.73 (4-C), 41.53 (2-C), 60.64 (6-C), 66.89 (5-C), 69.52 ($\underline{C}H_2OCO$), 74.49 (3-C), 109.27 (C), 172.18 (CO_2); ^{13}C NMR minor C-3 epimer (106 MHz; $CDCl_3$): δ_C 14.16 (CH_3), 25.70 ($\underline{C}H_3C$), 26.93 ($\underline{C}H_3C$), 39.95 (4-C), 41.63 (2-C), 60.70 (6-C), 65.56 (5-C), 69.63 ($\underline{C}H_2OCO$), 73.31 (3-C), 108.79 (C), 172.56 (CO_2); m/z Found $[M+H]^+$ 233.13886 $C_{11}H_{20}O_5$: Required 232.13074; GC retention time 2.60 min at a column temperature of 200°C (BP1 non-polar GC column).

Synthesis of methyl (3*R*, 5*S*)- and (3*S*, 5*S*)-3-*O*-(*tert*-butyldimethylsilyl)-5, 6-*O*-isopropylidene-3, 5, 6-trihydroxyhexanoate (16)

To a 1M solution of (14) (2.23 mmol, 486 mg) in DMF (2.23 mL), under N_2 was added imidazole (4.46 mmol, 304 mg) and TBDMSCl (3.34 mmol, 504 mg). The solution was stirred and heated to 50 °C for 2 hours. The reaction mixture was monitored by TLC and on completion was cooled to room temperature. Water (5 mL) was added, the layers were separated and the aqueous layer extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with 4:1 petroleum ether (40-60)/diethyl ether as the eluent (R_f = 0.32), to give (16), a colourless oil (0.59 g, 79% yield), as a mixture of two epimers in a ratio of 4:1.
IR (neat): ν_{max}/cm^{-1} 2987, 2961, 2927 (C-H (m), 1745 (C=O) (s), 1080 (C-O) (m); ^1H NMR (300 MHz; $CDCl_3$): δ_H 0.04, 0.06 (2(s), 6H, $Si(CH_3)_2$), 0.86, 0.87, 0.94 (3(s), 9H, $C(CH_3)_3$), 1.33, 1.34 (2(s), 6H, $O_2C(CH_3)_2$), 1.80 (m, 2H, 4-H), 2.50 (d, 2H, J = 6, 2-H), 3.51 (m, 1H, 3-H), 3.66 (s, 3H, CH_3O), 4.10 (dd, 1H, J = 6, 14, 5-H), 4.25 (m, 2H, 6-H); ^{13}C NMR major C-3 epimer (75 MHz; $CDCl_3$): δ_C -4.95, -4.63 ($Si(CH_3)_2$), 17.89 ($\underline{C}(CH_3)_3$), 25.69 ($C(\underline{C}H_3)_3$), 26.94 ($O_2C(\underline{C}H_3)_2$), 41.98 (4-C), 43.38 (2-C), 51.43 (CH_3O), 66.95 (3-C), 69.79 (6-C), 72.64 (5-C), 108.68 (CO_2), 171.90 ($\underline{C}O_2(CH_3)_2$); ^{13}C NMR minor C-3 epimer (75 MHz; $CDCl_3$): δ_C -4.95, -4.63 ($Si(CH_3)_2$), 17.93 ($\underline{C}(CH_3)_3$), 25.69 ($3(C(\underline{C}H_3)$), 26.94 ($O_2C(\underline{C}H_3)_2$), 41.04 (4-C), 41.51 (2-C), 51.43 (CH_3O), 66.95 (3-C), 69.79 (6-C), 72.40 (5-C), 108.68 (C), 171.60 (CO_2); m/z Found $[M+H]^+$ 333.20996 $C_{16}H_{32}O_5Si$: Required 332.20190; GC retention time 4.17 min, column temperature of 200 °C (BP1 non-polar GC column).

Synthesis of ethyl (3*R*, 5*S*)- and (3*S*, 5*S*)-3-*O*-(*tert*-butyldimethylsilyl)-5, 6-*O*-isopropylidene-3, 5, 6-trihydroxyhexanoate (17)

To a 1M solution of (15) (2.67 mmol, 619 mg) in DMF (2.67 mL), under N_2 was added imidazole (5.47 mmol, 372 mg) and TBDMSCl (4.10 mmol, 618 mg). The solution was stirred and heated to 50 °C for 2 hours. The reaction was worked up following the same procedure used previously in the synthesis of (16). The crude residue was purified by flash column chromatography on silica gel with 4:1 petroleum ether (40-60)/diethyl ether as the eluent (R_f = 0.45), to give (17), a colourless oil (0.75 g 81% yield), as a mixture of epimers in a ratio of 4:1.
IR (neat): ν_{max}/cm^{-1} 2996, 2944, 2868 (C-H), 1745 (C=O), 1089 (C-O); ^1H NMR (400 MHz; $CDCl_3$): δ_H 0.05, 0.06 (2(s), 6H, $Si(CH_3)_2$), 0.86 (s, 9H, $C(CH_3)_3$), 1.26 (t, 3H, $C\underline{H}_3CH_2$), 1.34 (s, 3H, O_2CCH_3), 1.38 (s, 3H, O_2CCH_3), 1.80 (m, 2H, 4-H), 2.60 (d, 2H, *J* = 6.5, 2-H), 3.50 (m, 1H, 3-H), 4.00-4.32(m, 5H, 6-H, $CH_3C\underline{H}_2OCO$, 5-H); ^{13}C NMR major C-3 epimer (106 MHz; $CDCl_3$); δ_C -4.90, -4.62 ($Si(CH_3)_2$), 14.18 ($\underline{C}H_3CH_2$), 17.91 ($\underline{C}(CH_3)_3$), 25.77 ($C(\underline{C}H_3)_3$), 27.02 ($O_2C(\underline{C}H_3)_2$), 41.01 (4-C), 42.20 (2-C), 60.35 (6-C), 66.89 (3-C), 69.81 ($CO_2\underline{C}H_2CH_3$), 72.46 (5-C), 108.64 (C), 171.49 (CO_2); ^{13}C NMR minor C-3 epimer (106 MHz; $CDCl_3$): δ_C -4.75, -4.71($Si(CH_3)_2$), 14.18 ($\underline{C}H_3CH_2$), 17.96 ($\underline{C}(CH_3)_3$), 25.77 ($C(\underline{C}H_3)_3$), 27.02 ($O_2C(\underline{C}H_3)_2$), 41.47 (4-C), 43.61 (2-C), 60.33 (6-C), 66.89 (3-C), 69.82 ($CO_2\underline{C}H_2CH_3$), 72.66 (5-C), 108.71 (C), 171.20 (CO_2); m/z Found $[M]^+$ 346.20826 $C_{17}H_{34}O_5Si$: Required 346.217554; GC retention time 4.79, column temperature 200 °C (BP1 non-polar GC column).

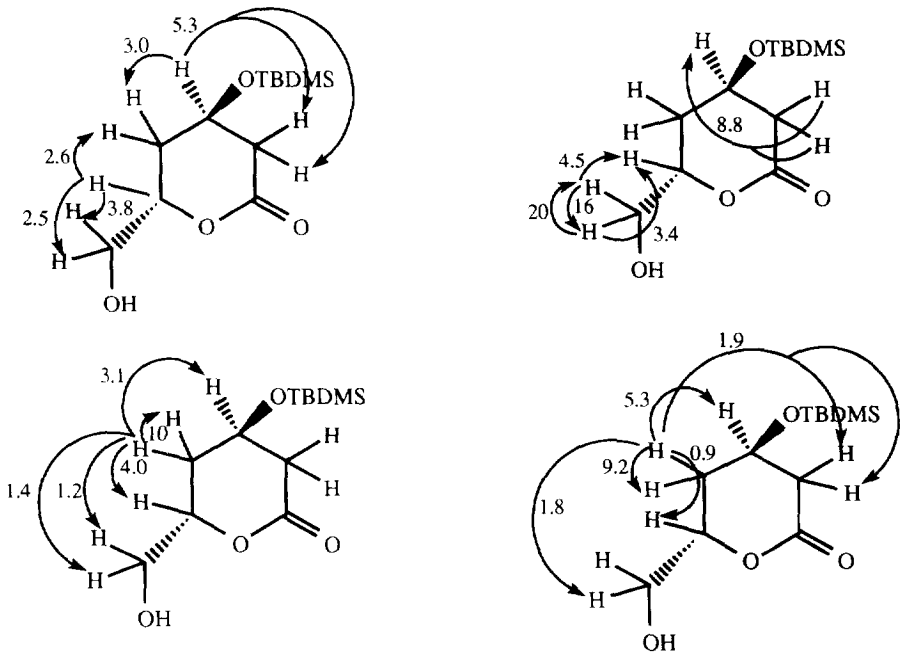
Synthesis of (3*R*, 5*S*)-3-*O*-(*tert*-butyldimethylsilyl)-3, 5, 6-trihydroxyhexanoic acid δ-lactone (1) by the reaction of methyl (3*R*, 5*S*)- and (3*S*, 5*S*)-3-*O*-(*tert*-butyldimethylsilyl)-5, 6-*O*-isopropylidene-3, 5, 6-trihydroxyhexanoate (16) with acetic acid

A 1M solution of (16) (0.3 mmol, 100 mg) in 80% acetic acid (0.3 mL) was heated at 100 °C for 1 hour. The reaction was monitored by TLC and on completion the reaction mixture was cooled to room temperature. Water was added and the aqueous layer extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with a saturated solution of sodium hydrogen carbonate and water. The organics were dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure, to give a colourless oil. The crude residue was then recrystallised from hexane to give a white crystalline product. Successive recrystallisations gave only (1) (11 mg, 11% yield). (R_f = 0.26, 1:1 ethyl acetate/hexane as the eluent).
m.p 74-76 °C (*lit.*,[43] 74-75 °C); IR ($CHCl_3$): ν_{max}/cm^{-1} 3475 (OH), 2989, 2945 (C-H), 1745 (C=O), 1085 (C-O); ^1H NMR (300 MHz; $CDCl_3$): δ_H 0.06, 0.07 (2(s), 6H, $(Si(CH_3)_2)$, 0.86, 0.87, 0.88 (3(s), 9H, $C(CH_3)_3$), 1.85 (m, 2H, 4-H), 2.20 (broad s, 1H, OH), 2.58 (d, 2H, *J* = 4 2-H), 3.65 (d, 1H, *J* = 12, 6-H), 3.89 (d, 1H, *J* = 12, 6-H), 4.36 (m, 1H, 3-H), 4.78 (m, 1H, 5-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ_C -4.90 ($Si(CH_3)_2$), 17.93 ($\underline{C}(CH_3)_3$), 25.65 ($C(\underline{C}H_3)_3$), 32.02 (4-C), 39.21 (2-C), 63.49 (3-C), 64.75 (6-C), 76.73 (5-C), 169.95 (CO_2); $[\alpha]_D^{20}$ -7.5 (c = 1, $CHCl_3$); m/z Found (100°C) $[M]^+$ 260.14528 $C_{12}H_{24}O_4Si$: Required 260.14438; GC retention time 4.82 min, column temperature 200 °C (BP1 non polar column).

Synthesis of (3*R*, 5*S*)-3-*O*-(*tert*-butyldimethylsilyl)-3, 5, 6-trihydroxyhexanoic acid δ-lactone (1) by the reaction of ethyl (3*R*, 5*S*)- and (3*S*, 5*S*)-3-*O*-(*tert*-butyldimethylsilyl)-5, 6-*O*-isopropylidene-3, 5, 6-trihydroxyhexanoate (17) with acetic acid

A 1M solution of (17) (0.2 mmol, 70 mg) in 80% acetic acid (0.2 mL) was heated at 100 °C for 1 hour. The reaction was monitored by TLC and on completion the reaction mixture was cooled to room temperature. The reaction was worked up following the same procedure used previously. Successive recrystallisations from hexane gave only (1) (27 mg, 51% yield). (R_f = 0.26 1:1 ethyl acetate/hexane as the eluent) m.p 72-74 °C (*lit.*,[43] 74-75 °C); IR ($CHCl_3$): ν_{max}/cm^{-1} 3475 (OH), 2989, 2945 (C-H), 1745 (C=O), 1085 (C-O); ^1H NMR (400 MHz; $CDCl_3$): δ_H 0.06, 0.07 (2(s), 6H, ($Si(CH_3)_2$), 0.86, 0.87, 0.88 (3(s), 9H, $C(CH_3)_3$), 1.85 (m, 2H, 4-H), 2.44 (broad s, 1H, OH), 2.58 (d, 2H, J = 4, 2-H), 3.65 (d, 1H, J = 12, 6-H), 3.89 (d, 1H, J = 12, 6-H), 4.36 (m, 1H, 3-H), 4.78 (m, 1H, 5-H); ^{13}C NMR (106MHz; $CDCl_3$): δ_C -4.90 ($Si(CH_3)_2$), 17.93 ($\underline{C}(CH_3)_3$), (25.65 ($C(\underline{C}H_3)_3$), 32.02 (4-C), 39.21 (2-C), 63.49 (3-C), 64.75 (6-C), 76.73 (5-C), 169.95 (CO_2); $[\alpha]_D^{20}$ -7.5 (c = 1, $CHCl_3$); m/z Found (100 °C) $[M]^+$ 260.14528 $C_{12}H_{24}O_4Si$: Required 260.144389; GC retention time 4.82 min, column temperature 200 °C (BP1 non-polar column).

n.O.e difference 400 MHz ($CDCl_3$):



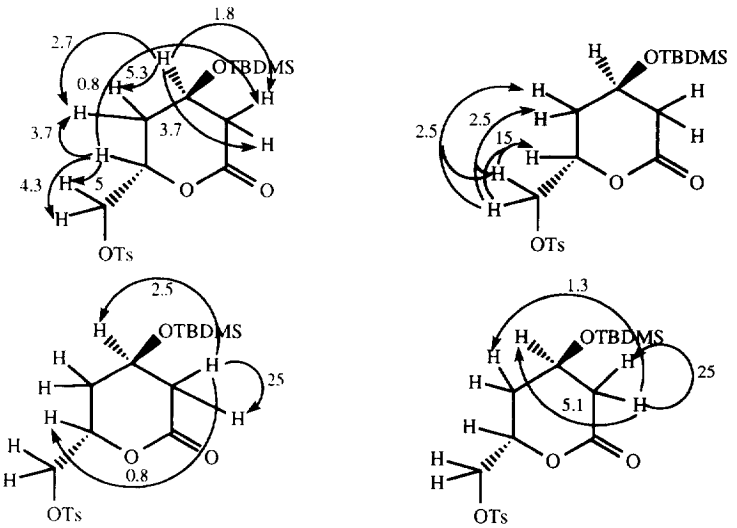
Values quoted as percentage enhancements

Synthesis of (3*R*, 5*S*)-and (3*S*, 5*S*)-3-*O*-(*tert*-butyldimethylsilyl)-6-(*para*-tolylsulfonyl)-3, 5, 6-trihydroxyhexanoic acid δ–lactone (19), (20)

To a solution of crude (1) and (18) (0.1 mmol, 26 mg) in pyridine (0.1 mL) at 0 °C, under N_2 was added *para*-toluenesulfonyl chloride (0.15 mmol, 29 mg). The reaction mixture was stirred for 48 hours and gradually allowed to warm to room temperature. The reaction was monitored by TLC and on completion was diluted with diethyl ether (0.5 mL). The reaction mixture was washed with a cold solution of 5% HCl, H_2O and a saturated solution of sodium hydrogen carbonate. The organics were dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure, to give a yellow oil. The crude residue was purified by flash column chromatography on silica gel with 1:1 hexane/diethyl ether as the eluent (R_f = 0.19 (19), 0.12 (20)), to obtain a white crystalline solid (19) (20 mg, 48% yield) and a colourless oil (19),(20) (5 mg, 12% yield, as a mixture of the two epimers in a ratio of 1:1).

(3*R*, 5*S*)-3-*O*-(*tert*-butyldimethylsilyl)-6-(*para*-tolylsulfonyl)-3, 5, 6-trihydroxyhexanoic acid δ–lactone (19): m.p 106-108 °C (*lit.*,[43] 108-109 °C); IR ($CHCl_3$): ν_{max}/cm^{-1} 2995, 2985 (C-H) (m), 1740 (C=O); ^1H NMR (400 MHz; $CDCl_3$); δ_H 0.06, 0.07 (2(s), 6H, $Si(CH_3)_2$), 0.86 (s, 9H, $C(CH_3)_3$), 1.88 (m, 2H, 4-H), 2.45 (s, 3H, $C\underline{H}_3Ph$, *para* - CH_3), 2.54 (d, 2H, *J* = 3, 2-H), 4.15 (m, 2H, 6-H), 4.35 (m, 1H, 3-H), 4.85 (m, 1H, 5-H), 7.35 (d, 2H, *J* = 8, 2(CH), *meta* - CH), 7.80 (d, 2H, *J* = 8, 2(CH), *ortho* - CH); ^{13}C NMR (106 MHz; $CDCl_3$): δ_C -4.96, -4.92, $(Si(CH_3)_2)$, 17.91 ($\underline{C}(CH_3)_3$), 21.65 (CH_3Ph, *para* - CH_3), 25.62 ($C(\underline{C}H_3)_3$), 32.16 (4-C), 39.05 (2-C), 63.21 (3-C), 70.46 (6-C), 72.98 (5-C), 128.01 (2(CH), *meta* -CH), 129.98 (2(CH), *ortho* - CH), 132.46 (C, *para* - C), 145.24 (C, *ipso* - C), 168.65 (CO_2).

n.O.e difference 400 MHz (C_6D_6):



Values quoted as percentage enhancements

$[\alpha]_D^{20}$ +5 (c = 0.82, $CHCl_3$); m/z Found $[M]^+$ 414.15219 $C_{19}H_{20}O_6SSi$: Required 414.15324

Synthesis of (*S*)-(-)-ethyl-α-(*para*-tolylsulfinyl) acetate (22)

Lithium diisopropylamide (LDA) was prepared by the addition of *n*-butyllithium (11 mmol, 4.4 mL from a 2.5M solution in hexane) to a solution of diisopropylamine (7.1 mmol, 1 mL, 725 mg) in THF (30 mL) at -78 °C, under N_2. The solution was stirred for 40 minutes. To the solution, (*S*)-methyl-*para*-tolylsulfoxide (5.5 mmol, 850 mg) dissolved in THF (20 mL) was added dropwise over a period of 10 minutes. The reaction mixture was stirred for a further 40 minutes. Ethyl chloroformate (6 mmol, 660 mg, 0.58 mL) was then added dropwise to the reaction mixture and stirred for 1 hour. The reaction was monitored by TLC and on completion was quenched at -78 °C by the addition of saturated ammonium chloride solution (20 mL). The reaction mixture was allowed to warm up to room temperature and then diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed in brine (20 mL) and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica gel with 1:1 ethyl acetate/hexane as the eluent (R_f = 0.35), to give (22) (1.18 g, 95% yield), as a yellow oil.
IR (neat): ν_{max}/cm^{-1} 2985, 2924 (C-H) (w), 1746 (C=O) (s), 1496, 1435 (Aryl-H) (m), 1087 (C-O) (m), 1053 (S=O) (s); ^1H NMR (400 MHz; $CDCl_3$): δ_H 1.22 (t, 3H, CH_3), 2.40 (s, 3H, *para* - CH_3), 3.64 (d, 1H, *J* = 13.5, HC), 3.81 (d, 1H, *J* = 13.5, HC), 4.13 (d, 1H, *J* = 7, CH_2), 4.17 (d, 1H, *J* = 7, CH_2), 7.35 (d, 2H, *J* = 4, *meta* - H), 7.60 (d, 2H, *J* = 4, *ortho* - H); ^{13}C NMR (106 MHz; $CDCl_3$): δ_C 14.01 ($\underline{C}H_3CH_2$), 21.45 (*para* - CH_3), 61.80 (CH_2O), 61.95 (CH_2SO), 124.26 (2(CH), *meta* - CH), 130.06 (2(CH), *ortho* - CH), 139.97 ($\underline{C}CH_3$, *para* - C), 142.39 (C, *ipso* - C), 164.76 (CO_2); $[\alpha]_D^{24}$ -126 (c = 1, $CHCl_3$); m/z Found M^+ 226.06619 $C_{11}H_{14}O_3S$: Required 226.06637.

Synthesis of intermediate (23) by the aldol condensation of (*S*)-(-)-ethyl-α-(*para*-tolylsulfinyl) acetate (22) and (6)

(*S*)-(-)-Ethyl-α-(*para*-tolylsulfinyl) acetate (22) (5.0 mmol, 1.13 g) was dissolved in THF (100 mL) and cooled to -78 °C under N_2. To the solution, *t*-BuMgCl (7.50 mmol, 7.50 mL from a 1M solution in THF) was added and stirred for 30 minutes. (*S*)-(+)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal (6) (7.50 mmol, 1.08 g) in THF (20 mL) was then added dropwise to the reaction mixture over a period of 10 minutes and then stirred for a further 1 hour. The reaction was monitored by TLC and on completion was quenched by the addition of a saturated solution of ammonium chloride (50 mL), this was then followed by the addition of CH_2Cl_2 (50 mL) and 2M HCl (50 mL). The solution was allowed to warm up to room temperature, the layers were then separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give (23), as a yellow oil. Due to the instability of (23), it was taken through to the next step of the synthesis, without further purification. (R_f = 0.16 eluent 1:1 ethyl acetate/hexane)

Synthesis of ethyl (3*S*, 5*S*)- and (3*R*, 5*S*)-5, 6-*O*-isopropylidene-3,5,6-trihydroxyhexanoate (24)

The crude product (23) (9.31 mmol, 3.44 g) was added to a solution THF/H_2O (10:1, 20 mL). The reaction was stirred and cooled to 0 °C. Aluminium strips (205 mmol, 5.50 g) were exposed sequentially to 1M KOH, H_2O, 2% $HgCl_2$, H_2O and THF and added to the reaction mixture over a period of 1 hour. The reaction mixture was kept at 0 °C and stirred for 24 hours. The reaction mixture was then allowed to warm to room temperature and THF (20 mL) added, the reaction mixture was stirred for a further 30 minutes and then filtered through celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel with 3:2 chloroform/ethyl acetate as the eluent (R_f= 0.42) to give (24) a colourless oil (0.63 g, 54% yield), as a mixture of epimers in a ratio of 4:1.
IR (neat): ν_{max}/cm^{-1} 3480 (OH) (m), 2989, 2938 (C-H) (m), 1740 (C=O) (s), 1087 (C-O) (m) ; ^1H NMR (400 MHz; $CDCl_3$): δ_H 1.26 (t, 3H, $C\underline{H}_3CH_2$), 1.35 (s, 3H, CH_3CO_2), 1.40 (s, 3H, CH_3CO_2), 1.75 (m, 2H, 4-H), 2.50 (dd, 2H, *J* = 5, 8, 2-H), 3.45 (d, 1H, *J* = 2, OH), 3.57, (m, 1H, 3-H), 4.10-4.30 (m, 5H, 6-H, 5-H, $CH_3C\underline{H}_2O$); ^{13}C NMR major C-3 epimer (106 MHz; $CDCl_3$): δ_C 14.16 (CH_3), 25.70 ($\underline{C}H_3CO_2$), 26.93 ($\underline{C}H_3CO_2$), 39.95 (4-C), 41.63 (2-C), 60.70 (6-C), 65.56 (5-C), 69.63 ($\underline{C}H_2OCO$), 73.31 (3-C), 108.79 (C), 172.56 (C=O); ^{13}C NMR minor C-3 epimer (106 MHz; $CDCl_3$): δ_C 14.16 (CH_3), 25.70 ($\underline{C}H_3CO_2$), 26.87 ($\underline{C}H_3CO_2$), 39.73 (4-C), 41.53 (2-C), 60.64 (6-C), 66.89 (5-C), 69.52 ($\underline{C}H_2OCO$), 74.49 (3-C), 109.27 (C), 172.18 (C=O); m/z Found $[M+H]^+$ 233.13756 $C_{11}H_{20}O_5$: Required 232.13074; GC retention time 2.60 min at a column temperature of 200 °C (BP1 non-polar GC column).

Synthesis of ethyl (3*R*, 5*S*)- and (3*S*, 5*S*)-3-*O*-(*tert*-butyldimethylsilyl)-5, 6-*O*-isopropylidene-3, 5, 6-trihydroxyhexanoate (25)

To a 1M solution of (24) (2.71 mmol, 628 mg) in DMF (2.71 mL), under N_2 was added imidazole (5.42 mmol, 369 mg) and TBDMSCl (4.06 mmol, 612 mg). The solution was stirred and heated to 50 °C for 2 hours. The reaction mixture was monitored by TLC and on completion was cooled to room temperature. Water (5 mL) was added, the layers were separated and the aqueous layer extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with 4:1 petroleum ether (40-60)/diethyl ether as the eluent (R_f = 0.45), to give (25) a colourless oil (0.88 g, 89% yield), as a mixture of epimers in a ratio of 4:1.
IR (neat): ν_{max}/cm^{-1} 2994, 2946, 2866 (C-H), 1746 (C=O), 1080 (C-O); ^1H NMR (400 MHz; $CDCl_3$): δ_H 0.07, 0.09 (2(s), 6H, $Si(CH_3)_2$), 0.86 (s, 3H, $C(CH_3)_3$), 0.87 (2(s), 6H, $C(CH_3)_3$), 1.25 (t, 3H, $C\underline{H}_3CH_2$), 1.33 (s, 3H, CH_3CO_2), 1.38 (s, 3H, CH_3CO_2), 1.70 (m, 2H, 4-H), 2.50 (d, 2H,*J* = 6.5, 2-H), 3.50 (m, 1H, 3-H), 4.00-4.30 (m, 4H, 6-H, $CH_3C\underline{H}_2OCO$), 4.20 (m, 1H, 5-H); ^{13}C NMR major C-3 epimer (106 MHz; $CDCl_3$): δ_C -4.74, -4.71 ($Si(CH_3)_2$), 14.18 ($\underline{C}H_3CH_2$), 17.96 ($\underline{C}(CH_3)_3$), 25.77 ($C(\underline{C}H_3)_3$), 27.02 ($O_2C(\underline{C}H_3)_2$), 41.47 (4-C), 43.61 (2-C), 60.32 (6-C), 66.89 (3-C), 69.81 ($CH_3\underline{C}H_2OCO$), 72.66 (5-C), 108.70 ($O_2\underline{C}(CH_3)_2$), 171.20 (CO_2); ^{13}C NMR minor C-3 epimer (106 MHz; $CDCl_3$): δ_C -4.90, -4.62 ($Si(CH_3)_2$), 14.18 ($\underline{C}H_3CH_2$), 17.91 ($\underline{C}(CH_3)_3$), 25.77 ($C(\underline{C}H_3)_3$), 27.02 ($O_2C(\underline{C}H_3)_2$), 41.01 (4-C),

42.20 (2-C), 60.32 (6-C), 66.89 (3-C), 69.81 ($CH_3\underline{C}H_2OCO$), 72.46 (5-C), 108.64 ($O_2\underline{C}(CH_3)_2$), 171.49 (CO_2); m/z Found $[M]^+$ Found 346.20788 $C_{17}H_{34}O_5Si$: Required 346. 217554.

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