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Enantioselective sulfoxide-directed preparation of 1,2-diols from oxalic compounds: formal synthesis of the 10-membered lactone core of ascidiatrienolides and didemnilactones

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Abstract—The synthesis of diene **17**, which is available in both possible absolute configurations is described. This diene constitutes the key intermediate of a previous synthesis of the 10-membered lactone core of the marine natural products ascidiatrienolides and didemnilactones. This intermediate is available via two successive highly diastereoselective sulfoxide-directed reductions of oxalic diamide **18**.
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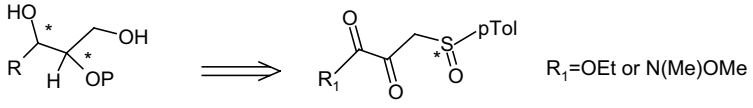
1. Introduction

A few years ago, we described a straightforward access to enantiomerically pure monoprotected 1,2-diols by two successive diastereoselective sulfoxide-directed reductions of oxalate derivatives (Scheme 1).[1] As a synthetic application, we planned to prepare the common 10-membered lactone core of ascidiatrienolide A **1**[2] and didemnilactones **2**–**4** (Fig. 1).[3] As we were able to prepare both *anti*- or *syn*-configured diols, our strategy should also be efficient for the synthesis of the epimers at C-8 (ascidiatrienolide numbering), ascidiatrienolides B **5** and C **6**.[2c]

The ascidiatrienolides were originally assigned as nine-membered lactone structures until Holmes and co-workers[2a] established unambiguously that ascidiatrienolide A possessed a 10-membered lactone structure, and presumably the other members of the ascidiatrienolide family are also 10-membered lactones. Ascidiatrienolides and didemnilactones are fatty acid metabolites extracted from the marine ascidian *Didemnum candidum* or isolated from the colonial tunicate *Didemnum moseleyi* and exhibit strong in vitro inhibitory activity towards the enzyme phospholipase A_2[2] and weak binding affinities to leukotriene B_4 receptors, respectively.[3] Metabolites **1**–**4** have already been subject of total synthesis[2,3] or formal total synthesis in the past, starting from natural sources.[4]

Herein, we report our synthetic investigations to obtain the common lactone core segment of **1**–**4** and of the epimers at the 9 position of **5** and **6** starting from oxalic derivatives.

We first embarked upon synthetic studies to prepare the (9*R*,10*S*) lactone **7** from diethyl oxalate **8** and (*S*)-methyl-*p*-tolylsulfoxide **9** (Scheme 2).[1c] Protection and



Scheme 1.

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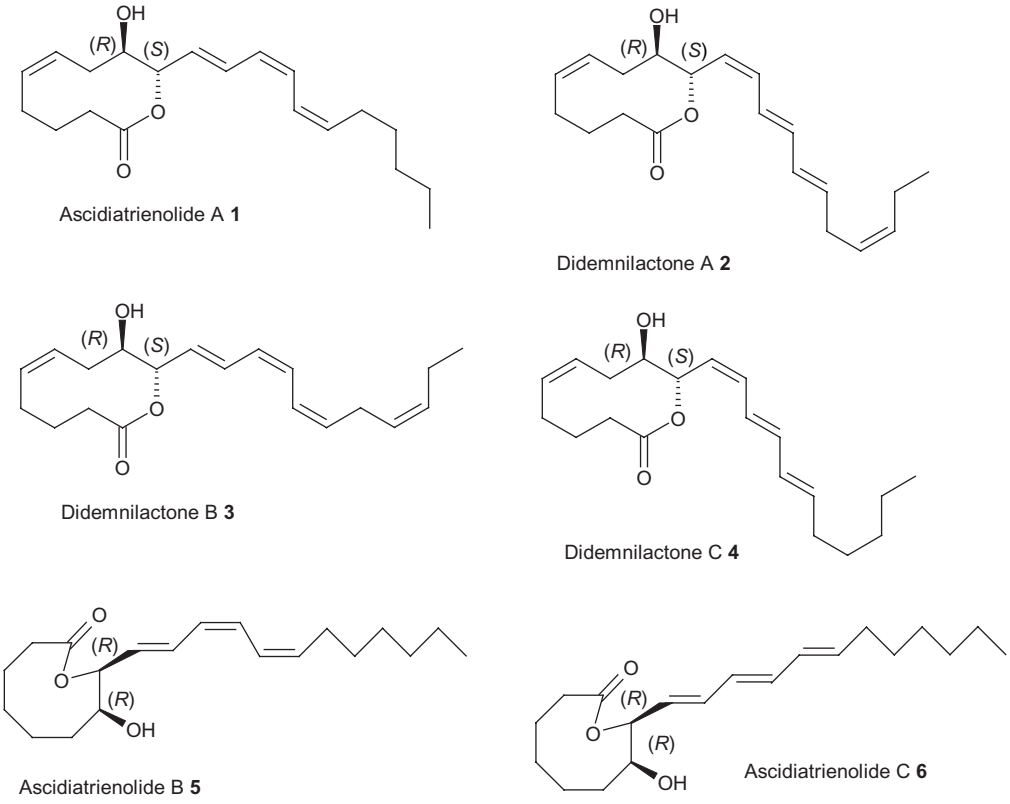
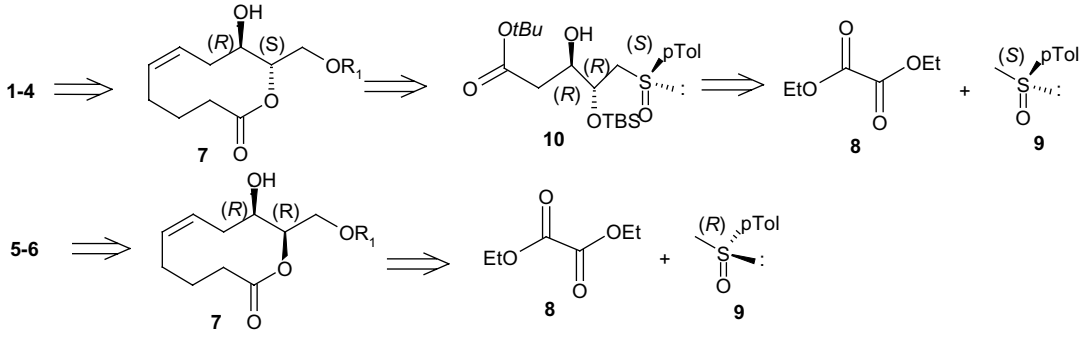


Figure 1.



Scheme 2.

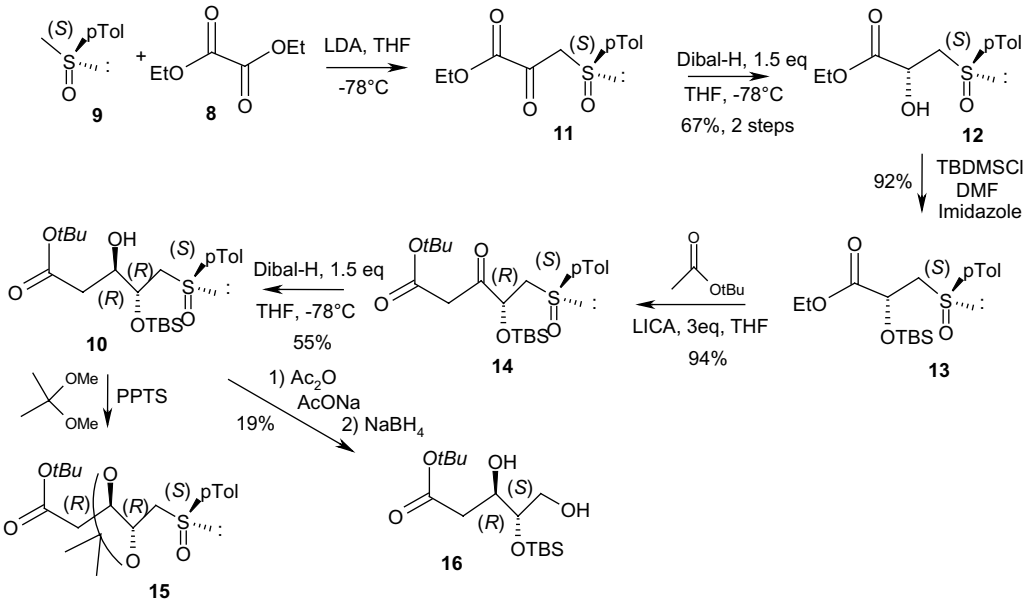
reduction of the key intermediate **10** into the corresponding aldehyde, followed by Wittig reaction with the ylide of (4-carboxybutyl)triphenyl phosphonium bromide[5] provided an excellent precursor of the (*R*,*S*)-lactone **7**.

2. Results and discussion

Diethyl oxalate **8** was transformed into the corresponding β-ketosulfoxide **11**. This condensation occurred with excellent conversion using 0.5 equiv of methyl-*p*-tolylsulfoxide in the presence of 0.75 equiv of LDA[6] but needed attention during purification.[7]

β-Ketosulfoxide **11** was then stereoselectively reduced to β-hydroxysulfoxide **12** using Dibal-H (Scheme 3). After protection of the hydroxyl group, β-silyloxysulfoxide **13** was transformed into the β-silyloxy-γ-ketosulfoxide **14** by condensation of the lithium *tert*-butylacetate enolate. Dibal-H reduction of the latter gave a high de (>95%) in favour of the desired *anti*-diol[8] **10** but a low yield (55%). The use of $Yb(OTf)_3$ in order to increase the yield[1] provided no conversion in this case.

The next step was the protection of the γ-hydroxy group, which proved very difficult. No protection was observed under mild basic conditions ($BnBr/Ag_2O$; TBDPSCl/imidazole or MEMCl/Hünig's base) while stronger conditions (NaH; DBU) resulted in decomposition of the starting material. We therefore attempted to prepare triol **16** using a Pummerer/LAH or $NaBH_4$ reduction sequence. Unfortunately, this resulted in only 19% yield of the required triol **16**.

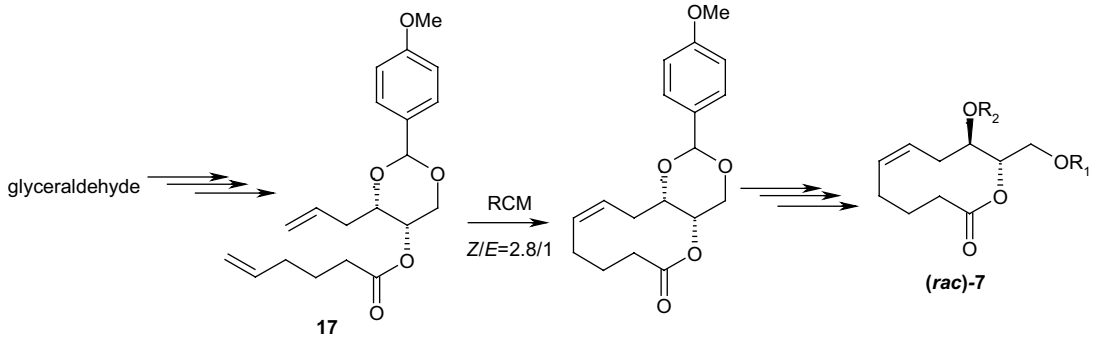


Scheme 3.

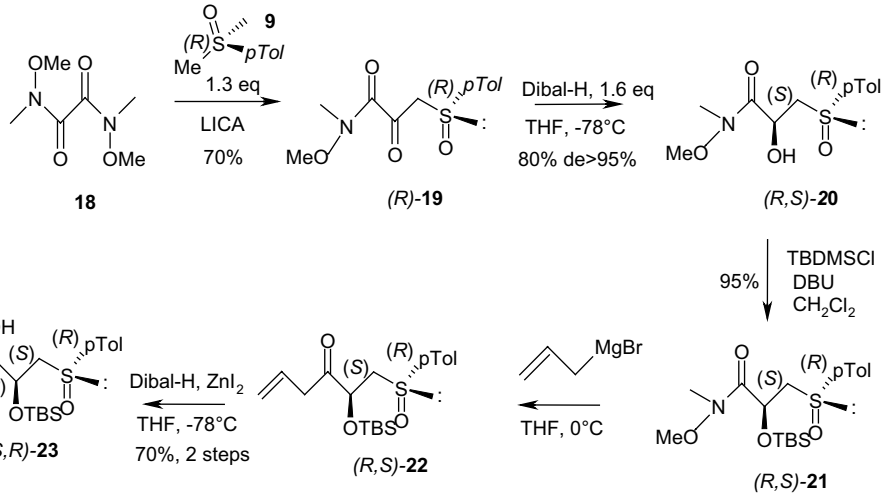
During this time, Fürstner and Schlede[4] described a concise racemic synthesis of lactone **7** (R_1 = H, R_2 = TBDPS) starting from glyceraldehyde and using a metathesis olefination as the key step. He showed that a better *Z*/*E* ratio was obtained from the *syn*-configured-diene **17**, using the 'second generation' Grubbs type catalyst bearing an *N*-heterocyclic carbene ligand. Subsequent epimerization at C-9 using Mitsunobu conditions[9] installed the required *anti*-configuration of lactone **7** (Scheme 4).

As our methodology depicted a straightforward access to 1,2-diols in all possible absolute configurations, we decided to prepare the *syn*-configured (9*R*,10*R*)-diene **17** starting from oxalic diamide[10] **18** and (*R*)-methylsulfoxide **9** (Scheme 5).

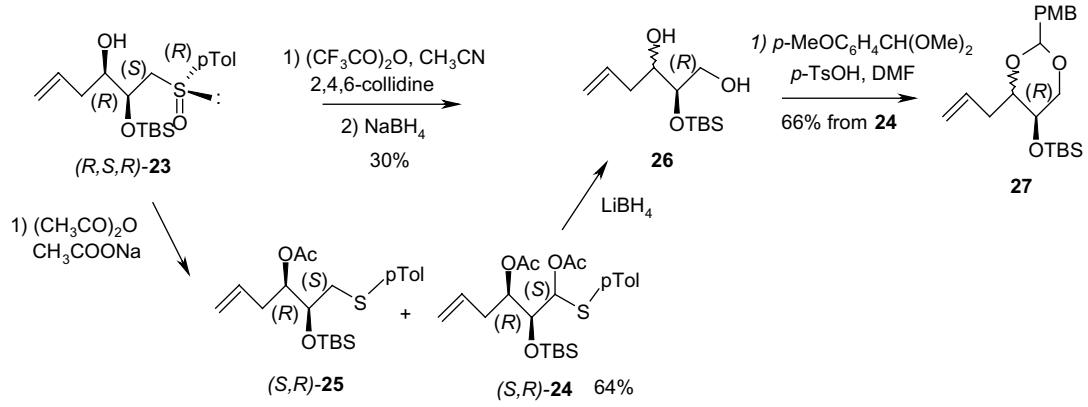
The lithium anion of (*R*)-methyl-*p*-tolylsulfoxide **9** was added to diamide **18**. Quenching of the reaction needed a strong acid and carefully demetalled silica gel[11] for purification to obtain good yields. The resulting β-ketosulfoxide **19** was subjected to Dibal-H reduction to give the corresponding β-hydroxysulfoxide **20** in high de (>95%). The (*S*)-absolute configuration of the secondary carbinol has previously been established by the solid-state molecular structure of a structurally close derivative.[1b] Protection of the resulting secondary alcohol in **21** as a TBDMS ether followed by addition of the allyl-magnesium bromide afforded β-silyloxy-γ-ketosulfoxide **22** in good overall yields. As chromatography of the latter gave a mixture of the desired product with the corresponding α,β-unsaturated ketone, even when treated silica gel (NEt_3 5%) was used, the crude product was used in the next step without purification. Highly diastereoselective Dibal-H/ZnI_2 reduction of the crude product afforded, after purification, the required *syn*[12] γ-hydroxy-β-silyloxysulfoxide **23** in 70% yield for two steps. We next turned our attention to the removal of the chiral auxiliary. We first tried to perform a Pummerer reaction on free alcohol **23**. We selected two different procedures. The first one used trifluoroacetic anhydride, 2,4,6-collidine in acetonitrile, followed by $NaBH_4$ reduction.[13] Unfortunately, the best result was only 30% yield of expected product **26** (Scheme 6).



Scheme 4.



Scheme 5.



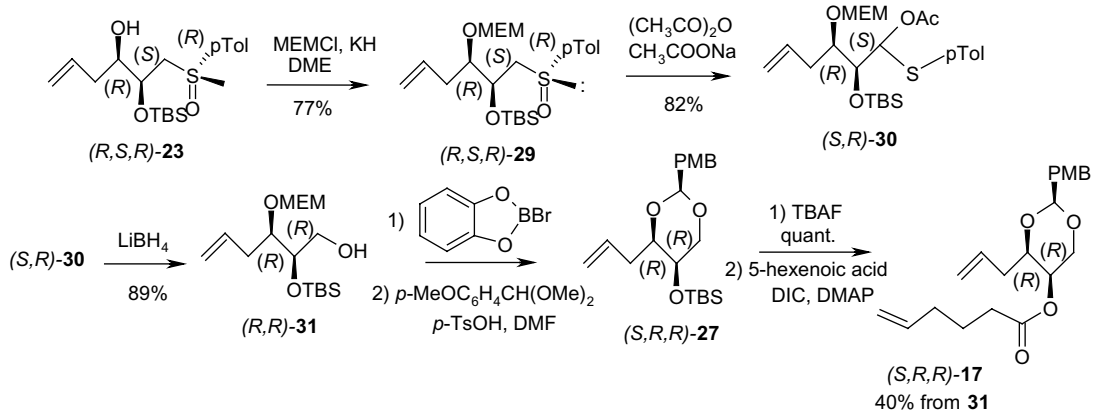
Scheme 6.

The second method used classical conditions (Ac_2O, AcONa, 135 °C, 30 h) and gave a mixture of two acetates, namely the desired **24** (64% yield) and the corresponding sulfide **25** (in variable proportions). Reduction of the acetate **24** was successful using $LiBH_4$[14] in ether as hydride transfer reagent. These conditions of reduction gave the most reproducible results as $NaBH_4$ or $LiAlH_4$ gave lower yields or resulted in the cleavage or migration of the TBS group. Crude diol **26** was protected without previous purification using *p*-anisaldehyde dimethyl acetal to afford the acetal **27**.[15] Unfortunately, we detected partial epimerization at the homoallylic hydroxylic centre, which had probably occurred during the precedent reductive step (Scheme 6) in variable amounts from one attempt to another (0–25%).

As we were unable to control this epimerization, we tried to repeat this sequence starting from the protected sulfoxide **23**. Not surprisingly, we encountered difficulties associated with the protection step, as already observed with the *anti*-diol **10**. Finally we found that the use of KH/MEMCl[16] in THF at −78 °C to room temperature gave the most reproducible and acceptable result (77%). Pummerer reaction of the resulting MEM–ether **29** gave the thioacetal **30** in 82% yield while the subsequent reduction using $LiBH_4$ resulted in the primary alcohol **31** in 89% isolated yield (Scheme 7). Selective cleavage of the MEM–ether using catechol boron bromide[17] in dichloromethane followed by acetalization of the crude diol[15] afforded acetal **27** in 62% yield. Finally, treatment with TBAF and esterification of the alcohol **28** with 5-hexenoic acid delivered the diene **17** (24% overall yield from **23**), which was identical ($[\alpha]_D$) = −37 (*c* 0.2, $CHCl_3$) to the racemic key intermediate prepared by Fürstner.

3. Conclusion

In summary, this study witnesses the efficiency of sequential Dibal-H sulfoxide-directed reduction of oxalic derivatives to prepare enantiomerically pure 1,2-monosilylated diols. Contrary to the use of natural sources, this methodology opens the door to the preparation of the 10-membered lactone core in both absolute configurations. The total syntheses of acsidiatrienolides B and C are currently under investigation in our laboratory.



Scheme 7.

4. Experimental

4.1. General remarks

All reactions were carried out under dry argon. Standard syringe and cannula techniques were employed for transfer of dry solvents and air- or moisture-sensitive reagents. Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone, dichloromethane from phosphorus pentoxide, diisopropylamine from KOH. *n*-Butyllithium was purchased as a 1.6 M solution in hexane. Starting materials not mentioned below were commercially available. Enantiopure menthyl-*p*-tolylsulfinates **3** and methyl-*p*-tolylsulfoxides **4** in both configurations were prepared according to the previously described methods.[18] Di-*N*-methoxy-*N*-methylamide of oxalic acid was prepared from oxalyl chloride according to the literature.[10] Reactions were monitored by thin layer chromatography on silica gel plates (Merck $60F_{254}$) and stained by the use of *p*-anisaldehyde. Merck silica gel 60H was used for column chromatography and demetallated following a known procedure[11] when required. NMR spectra were obtained at 200 MHz (^{1}H) or 50 MHz (^{13}C) and 300 MHz (^{1}H) or 75 MHz (^{13}C) on Bruker AC 200 and AC 300 instruments, with deuterochloroform as solvent. Chemical shifts (δ) are given in ppm relative to tetramethylsilane ($\delta = 0$ ppm) or to residual protons in the solvent as internal standard. IR spectra were recorded with a Perkin–Elmer Spectrum One, and absorption bands are given in cm^{-1}. The Microanalyses Service of the Strasbourg Faculty of Chemistry performed microanalyses.

4.2. Ethyl (S_S)-2-oxo-3-(*p*-tolylsulfinyl)propionate 11

n-Butyllithium (28 mL of a 1.45 M solution in hexane, 40 mmol, 1.5 equiv) was added dropwise to a stirred solution of diisopropylamine (5.4 mL, 39 mmol, 1.45 equiv) in THF (150 mL) at −78 °C. After 15 min, (*S*)-methyl-*p*-tolylsulfoxide **9** (4.2 g, 27 mmol, 1 equiv) in THF (20 mL) was added dropwise and the solution stirred over 1.5 h. Diethyl oxalate **8** (8.3 g, 55.3 mmol, 2 equiv) in THF (10 mL) was then added as a single aliquot and the reaction mixture stirred for a further 2 h, then quenched with saturated ammonium chloride solution (50 mL). The pH was adjusted to 3–4 (universal indicator paper) with 5% H_2SO_4, and the product extracted into ether (4 × 100 mL). The organic layers were washed with brine, dried over magnesium sulfate and the solvent removed. Unreacted diethyl oxalate was removed by chromatography on a short column composed of two layers; the lower, deactivated silica gel, and the upper, Celite, in equal volume. The column was eluted rapidly, first with hexane, then 50% hexane in ether and finally with ether. The product thus obtained was a yellow oil (5.5 g), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 ($(AB)_2$ system, 4H, $J_{AB} = 8$ Hz, $\Delta\nu = 40$ Hz), 4.15 (q, 2H $J = 7$ Hz), 4.1 (2H, AB system, $J_{AB} = 12$ Hz), 2.46 (s, 3H), 1.32 (t, 3H, $J = 7$ Hz).

4.3. Ethyl (2*R*,S_S)-2-hydroxy-3-(*p*-tolylsulfinyl)propionate 12

Crude sulfinyl ketone **11** (5.4 g, 22 mmol) was dissolved in THF (200 mL) and cooled to −78 °C with stirring. Dibal-H (23.3 mL, 1 M in toluene, 1.1 equiv) was then added dropwise over 2.5 h. After a further 15 min, the reaction was quenched by the addition of methanol (10 mL) and then a saturated ammonium chloride solution (100 mL), and allowed to warm to 0 °C. The pH was then cautiously adjusted to 3–4 with 5% H_2SO_4. The THF was removed under vacuum at room temperature and the residue extracted with ether (8 × 100 mL). The aqueous layer was tested before each extraction, and 5% H_2SO_4 added cautiously as required to keep the pH between 3 and 4.[19] The organic extracts were then washed with brine (50 mL), dried over $MgSO_4$ and concentrated to afford a yellow oil, which was purified by flash chromatography on demetallated silica gel to give 4.6 g, 67% from **8**. A sample was recrystallized from ether to afford white prisms. $[\alpha]_D = -170$ (*c* 0.2, EtOH). Mp = 86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 ($(AB)_2$ system, 4H, $J_{AB} = 8$ Hz, $\Delta\nu = 40$ Hz), 4.73 (dd, X of an ABX system, 1H), 4.22 (q, 2H $J = 7$ Hz), 3.9 (br s, 1H), 3.08 (AB fragment of an ABX system, 2H, $J_{AX} = 3$ Hz, $J_{BX} = 9.8$ Hz, $J_{AB} = 13.1$ Hz, $\Delta\nu = 55$ Hz), 2.43 (s, 3H), 1.28 (t, 3H, $J = 7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 141.9, 139.8, 130.1, 124, 85.9, 62.2, 61.1, 21.4, 14.1. Anal. Calcd for $C_{11}H_{16}O_4S$ (244): C, 54.08; H, 6.60. Found: C, 53.97; H, 6.38.

4.4. Ethyl (2*R*,S_S)-2-*tert*-butyl-dimethylsilyloxy-3-(*p*-tolylsulfinyl)propionate 13

Alcohol **12** (2.2 g, 9 mmol) was dissolved in DMF (100 mL). Imidazole (1.3 g, 18 mmol, 2 equiv) was then added and the stirred mixture cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (2.1 g, 13.5 mmol, 1.5 equiv) was added and the mixture allowed to stir overnight at room temperature. Saturated ammonium chloride solution (100 mL) and ether (100 mL) were added at 0 °C and the biphasic mixture stirred for 30 min. The organic layer was removed and the aqueous phase further extracted with ether (2 × 100 mL). The organic extracts were washed with saturated ammonium chloride solution (2 × 100 mL), then with brine and dried over $MgSO_4$ and the solvent removed. Chromatography on silica gel (40% ether/60% hexane) gave the product as a colourless oil (3 g, 92%). $[\alpha]_D = -152$ (*c* 0.3, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 ($(AB)_2$ system, 4H, $J_{AB} = 8$ Hz, $\Delta\nu = 40$ Hz), 4.76 (dd, X of an ABX system, 1H), 4.15 (q, 2H, $J = 7.5$ Hz), 2.94 (AB of an ABX system, 2H, $J_{AX} = 2$ Hz, $J_{BX} = 10$ Hz, $J_{AB} = 14$ Hz, $\Delta\nu = 45$ Hz), 2.41 (s, 3H), 1.24 (t, 3H, $J = 7.5$ Hz), 0.92 (s, 9H), 0.1 and 0.2 (2s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 141.5, 140.8, 130, 123.7, 67, 63.9, 61.5, 25.7, 21.4, 18.4, 4.1. Anal. Calcd for $C_{17}H_{30}O_4SSi$ (358.6): C, 56.94; H, 8.43. Found: C, 57.07; H, 8.58.

4.5. *tert*-Butyl (4*R*,S_S)-3-oxo-4-*tert*-butyl-dimethylsilyloxy-5-(*p*-tolylsulfinyl)pentanoate 14

n-Butyllithium (14 mL of a 1.45 M solution in hexane, 20 mmol, 3 equiv) was added dropwise to a stirred solution of dicyclohexylamine (4 mL, 20 mmol, 3 equiv) in THF (50 mL) at −78 °C. After 15 min, *tert*-butylacetate (2.3 g, 20 mmol, 3 equiv) in THF (20 mL) was added dropwise and the solution stirred 1.5 h. Silyloxy-sulfoxide **13** (2.4 g, 6.5 mmol) in THF (10 mL) was then added via cannula and the reaction mixture stirred until it reached room temperature, at which point it was quenched with saturated ammonium chloride solution (50 mL). The THF was removed under vacuum at room temperature and the residue extracted with ethyl acetate (3 × 100 mL). The organic extracts were then washed with brine (50 mL), dried over $MgSO_4$ and concentrated to afford a pale-yellow oil, which was purified by flash chromatography on silica gel to give 3 g, 94% of pure **14**. $[\alpha]_D = -158$ (*c* 0.1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 ($(AB)_2$ system, 4H, $J_{AB} = 8$ Hz, $\Delta\nu = 40$ Hz), 4.71 (dd, X of an ABX system, 1H), 3.5 (2H, AB system, $J_{AB} = 14$ Hz), 2.9 (AB of an ABX system, 2H, $J_{AX} = 2$ Hz, $J_{BX} = 9$ Hz, $J_{AB} = 13$ Hz, $\Delta\nu = 40$ Hz), 2.41 (s, 3H), 1.45 (s, 9H), 1.06 (s, 9H), 0.19 and 0.26 (2s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 175.7, 166, 141.7, 130.1, 123.8, 82.2, 73.2, 45.8, 27.9, 25.7, 18.1, −4.7, −5.

4.6. *tert*-Butyl (3*R*,4*R*,S_S)-3-hydroxy-4-*tert*-butyl-dimethylsilyloxy-5-(*p*-tolylsulfinyl)pentanoate 10

β-Silyloxy-sulfoxide **14** (1.5 g, 3.5 mmol) in solution in THF (50 mL) was cooled to −78 °C and stirred under argon. Dibal-H (5.3 mL, 1 M in toluene, 1.5 equiv) was then added dropwise over 2 h. After a further 30 min, the reaction was quenched by the addition of methanol (10 mL) and THF removed under vacuum. The residue was dissolved in ethyl acetate (50 mL) and stirred with a saturated solution of disodium tartrate until a good separation of phases occurred. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated to afford a pale-yellow solid, which was purified by flash chromatography on silica gel to give 0.85 g, 55% of pure **10** as white solid. $[\alpha]_D = -142$ (*c* 0.1, EtOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39 ($(AB)_2$ system, 4H, $J_{AB} = 8$ Hz, $\Delta\nu = 40$ Hz), 4.18 (m, 1H), 4.09 (m, 1H), 2.88 (2H, non-interpretable AB part of ABX system), 2.8 (br, 1H), 2.41 (s, 3H), 2.32 (d, 2H, $J = 6.4$ Hz), 1.44 (s, 9H), 0.96 (s, 9H), 0.18 and 0.25 (2s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171, 141.5, 131, 123.8, 81.5, 71.4, 69.6, 62.5, 37.9, 28.1, 26, 18.3, −4.1, −4.6. Anal. Calcd for $C_{22}H_{40}O_5SSi$ (444): C, 59.42; H, 9.07. Found: C, 59.37; H, 9.01.

4.7. *tert*-Butyl (3*R*,4*R*,S_S)-3,4-(diisopropylidene ketal)-5-(*p*-tolylsulfinyl)pentanoate 15

Monosilylated diol **10** (0.5 g, 1.2 mmol) was dissolved at −40 °C in THF (20 mL) with TBAF (1.5 mL, 1 M in THF, 1.1 equiv) and the mixture stirred until disappearance of the starting material (TLC). The crude mixture was concentrated under vacuum and the residue dissolved in acetone (5 mL). Dimethoxypropane (2 mL) and PPTS (10 mg) were added and the mixture stirred overnight. Acetone was removed on vacuum and the residue poured into dichloromethane (20 mL). The mixture was washed with a 5% sodium bicarbonate solution (20 mL), then, dried over $MgSO_4$ and concentrated to afford a pale-yellow solid, which was purified by flash chromatography on silica gel to give 0.35 g, 70% of pure **15** as a white crystals. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44 ($(AB)_2$ system, 4H, $J_{AB} = 8$ Hz, $\Delta\nu = 40$ Hz), 4.74 (m, 1H), 4.61 (m, 1H), 2.43 (s, 3H), from 2.25 to 2.87 (2 AB parts of 2 ABX systems, 4H), 1.51 (s, 3H), 1.42 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.3, 141.5, 130.2, 123.9, 109.3, 81.5, 74, 71.6, 60.3, 36.7, 28.3, 28.07, 25.7, 21.5.

4.8. (R_S)-*N*-Methyl-*N*-methoxy-2-oxo-3-(*p*-tolylsulfinyl)-propionamide 19

To a solution of cyclohexyl-isopropylamine (2.2 mL, 13.6 mmol) in dry THF (20 mL), cooled to −78 °C, a solution of *n*-BuLi (9.1 mL, 1.6 M in hexane) was added. The solution was stirred for 30 min at −78 °C and (*R*)-methyl-*p*-tolylsulfoxide (1.7 g, 11.0 mmol), dissolved in dry THF (20 mL) added. The solution was stirred for 1 h at −78 °C then warmed to −40 °C and Weinreb amide **18** (1.5 g, 8.52 mmol), dissolved in THF (20 mL, the dissolution is slow), was added. The solution was stirred overnight. A solution of H_2SO_4 (∼30 mL, 10%) was added until pH 3–4 and the mixture extracted three times with ethyl acetate (10 mL × 3) and one time with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced

pressure. The crude product was purified by flash chromatography (the product has to be purified immediately) on silica gel affording a yellow oil (1.6 g, 70%). Column: $d = 4$ cm, $h = 14$ cm silica gel demetalled, 1 cm silica gel normal; solvent: Et_2O (~500 mL), Et_2O–AcOEt (~400 mL, 4:1), Et_2O–AcOEt (~200 mL, 1:1). R_f: (hexane–ethyl acetate 3:2) 0.37. ^1H NMR (200 MHz, $CDCl_3$): δ 7.44 ($(AB)_2$ system, 4H, $J_{AB} = 8.2$ Hz, $\Delta\nu = 40$ Hz), 4.12 (2H, AB system, $J = 14$ Hz), 3.70 (s, 3H), 3.20 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.2, 165.1, 142.1, 139.5, 129.8, 123.9, 65.7, 62.2, 31.8, 21.2.

4.9. (2*S*,R_S)-*N*-Methyl-*N*-methoxy-2-hydroxy-3-(*p*-tolylsulfinyl)-propionamide 20

To a solution of **19** (1.22 g, 4.53 mmol) in dry THF (25 mL), cooled to −78 °C under argon, Dibal-H (7.2 mL, 1 M in toluene, 7.2 mmol, 1.6 equiv) was added dropwise for 10 min. The solution was stirred for 20 min at the same temperature and MeOH (4 mL) added. The solution was concentrated in vacuum, dissolved in ethyl acetate (30 mL) and a saturated solution of sodium and potassium tartrate (15 mL) added. The mixture was stirred vigorously until two phases were visible (~3 h). Then the mixture was extracted two times with ethyl acetate (10 mL × 3) and one time with CH_2Cl_2 (10 mL). The combined organic layers, were dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash chromatography (ether–methanol: 1–5% gradient) and the resulting white solid recrystallized in ether/hexane/ethyl acetate. R_f: (ethyl acetate–methanol 96:4) 0.21. Mp = 126 °C. $[\alpha]_D = +232$ (c 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 ($(AB)_2$ system, 4H, $J_{AB} = 8.2$ Hz, $\Delta\nu = 41$ Hz), 4.97 (dd, X of an ABX system, 1H), 3.78 (d, 1H, $J = 7$ Hz), 3.70 (s, 3H), 3.20 (s, 3H), 2.95 (AB fragment of an ABX system, 2H, $J_{AX} = 1.4$ Hz, $J_{BX} = 10.4$ Hz, $J_{AB} = 13$ Hz, $\Delta\nu = 50$ Hz), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174, 141.7, 140.9, 130.1, 124, 64.1, 62.6, 61.8, 32.7, 21.5. Anal. Calcd for $C_{12}H_{17}NO_4S$ (271): C, 53.12; H, 6.32. Found: C, 53.07; H, 6.38.

4.10. (2*S*,R_S)-*N*-Methyl-*N*-methoxy-2-*tert*-butyl-dimethylsilyloxy-3-(*p*-tolylsulfinyl)-propionamide 21

To a solution of **20** (1.00 g, 3.69 mmol) in dry CH_2Cl_2 (25 mL), DBU (0.82 mL, 5.5 mmol) and TBDMSCl (0.945 g, 6.27 mmol) were added. The mixture was stirred for 2 h then CH_2Cl_2 (15 mL) and a saturated aqueous solution of NH_4Cl (15 mL) added. The resulting mixture was extracted three times with CH_2Cl_2 (30 mL × 3). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude was purified by flash chromatography (hexane–ether 1:1 to ether) affording a colourless oil (1.20, 84%).

R_f: (hexane–ethyl acetate 3:2) 0.25. $[\alpha]_D = +201$ (c 0.5, acetone). ^1H NMR (300 MHz, $CDCl_3$): δ 7.4 ($(AB)_2$ system, 4H, $J_{AB} = 8$ Hz, $\Delta\nu = 42$ Hz), 5.15 (dd, X of an ABX system, 1H), 3.70 (s, 3H), 3.14 (s, 3H) 2.94 (m, 2H), 2.39 (s, 3H), 0.98 (s, 9H), 0.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 141.6, 141.1, 130, 123.7, 65.5, 61.9, 61.2, 32.9, 25.8, 21.3, 19.1, 14. Anal. Calcd for $C_{18}H_{31}NO_4SSi$ (386): C, 56.07; H, 8.1. Found: C, 55.97; H, 8.18.

4.11. (2*S*,R_S)-1-(*p*-Tolylsulfinyl)-2-*tert*-butyl-dimethylsilyloxy-5-ene-3-hexanone 22

To a solution of **21** (1.20 g, 3.12 mmol) in dry THF (25 mL), cooled to −20 °C, allyl-magnesium bromide (6.2 mL, 1 M ether, 2 equiv) was added and the mixture stirred for 1 h. Saturated aqueous solution of NH_4Cl (15 mL) was added and the mixture extracted three times with CH_2Cl_2 (30 mL × 3). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude residue (1.3 g) was filtered on silica gel (1 cm) and used in the next step without further purification. Chromatography should be avoided. R_f: (hexane–ethyl acetate 3:2) 0.6. ^1H NMR (200 MHz, $CDCl_3$): δ 7.42 ($(AB)_2$ system, 4H, $J_{AB} = 8.2$ Hz, $\Delta\nu = 40$ Hz), 5.6 (m, 1H), 4.95 (m, 2H), 4.76 (dd, 2H), 2.72–3.01(2 AB fragment of 2 ABX systems, 4H), 2.42 (s, 3H), 0.97 (s, 9H), 0.23 and 0.34 (2s, 6H).

4.12. (3*R*,2*S*,R_S)-1-(*p*-Tolylsulfinyl)-2-*tert*-butyl-dimethylsilyloxy-3-hydroxy-5-hexene 23

ZnI_2 (1.09 g, 3.4 mol) was warmed under reduced pressure. Then a solution of the α,β unsaturated ketone **22** (1.24 g, 3.09 mmol) in dry THF (25 mL) was added and the mixture stirred for 1 h at room temperature. The solution was cooled to −78 °C and Dibal-H (4.6 mL, 1 M in hexane, 4.6 mmol) added dropwise. After 20 min, MeOH (4 mL) was added. The solution was concentrated in vacuum, dissolved in ethyl acetate (30 mL) and a saturated solution of sodium and potassium tartrate (15 mL) added. The mixture was stirred vigorously until two phases were visible (~2 h). Then the mixture was extracted with ethyl acetate (10 mL × 3) and one time with CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel (hexane–ethyl acetate 4:1 to hexane–ethyl acetate 3:2) affording a colourless oil (0.802 g, 70%, two steps).

$[\alpha]_D = +181$ (c 0.1, acetone). ^1H NMR ($CDCl_3$): δ 7.52 ($(AB)_2$ system, 4H, $J_{AB} = 8.2$ Hz, $\Delta\nu = 40$ Hz), 5.75 (m, 1H), 5.14 (m, 2H), 4.25 (dt, 1H, $J = 10.6$, 1.7 Hz), 3.55 (m, 1H), 2.9 (AB fragment of an ABX system, 2H, $J_{AX} = 1.7$ Hz, $J_{BX} = 10.6$ Hz, $J_{AB} = 13.1$ Hz, $\Delta\nu = 40$ Hz), 2.41 (s, 3H), 2.30 (m, 1H), 2.20 (m, 1H), 0.96 (s, 9H), 0.26 (s, 3H), 0.16 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 141.5, 141.1, 134.8, 130.1, 129.9, 117.8, 73.6, 69.2, 63.1, 37.3, 26.0, 21.5, 18.3, −4.2.

4.13. (3*R*,2*S*)-1-(*p*-Tolylsulfenyl)-1-(acetoxy)-2-*tert*-butyl-dimethylsilyloxy-3-acetoxy-5-hexene 24

To a solution of **23** (200 mg, 0.56 mmol) in glacial Ac_2O (10 mL) was added AcONa (700 mg, 8 mmol) under argon. The mixture was refluxed for 36 h at 125–135 °C. Toluene was added many times and evaporated to

eliminate Ac_2O. The crude was dissolved in diethyl ether and filtered on a short plug of Celite. The Et_2O was evaporated in vacuum and the crude purified by flash chromatography on silica gel (hexane–ether 8:2–65:35) to afford a colourless oil **24** (143 mg, 64%). Sulfide **25** (10–30%) was isolated as the secondary product during the various attempts. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36 (d, 2H, J = 8.0 Hz, C_6H_4, I dia), 7.32 (d, 2H, J = 8.0 Hz, C_6H_4, II dia), 7.11 (d, 4H, J = 8.0 Hz, C_6H_4, I and II dia), 6.4 (d, 1H, J = 3 Hz, I dia), 6.12 (d, 1H, J = 7 Hz, II dia), 5.80 (m, 2H, I and II dia), 5.3 (m, 2H, I and II dia), 5.02 (m, 4H, I and II dia), 4.88 (dd, 1H, J = 7 and 3 Hz, I dia), 3.86 (dd, 1H, J = 7 and 1 Hz, II dia), 2.31 (s, 6H), 2.05 (s, 3H), 2.01 (s, 6H), 1.99 (s, 3H, II dia), 2.43–1.99 (m, 4H), 0.87 (s, 9H, s, I dia), 0.85 (s, 9H, II dia), 0.07, 0.06, 0.05 (s, 12H, I and II dia). ^{13}C NMR ($CDCl_3$): δ 169.7, 169.5, 168.5, 138.4, 137.8, 134.5, 134.2, 132.6, 129.5, 129, 127.7, 117.7, 117.4, 97.1, 96.3, 82.3, 81.0, 72.8, 72.3, 38.2, 37.6, 25.8, 21.1, 18.2, −4.1, −4.5. ^{1}H NMR (200 MHz, $CDCl_3$) of sulfide **25**: δ 7.29 (d, 2H, J = 7 Hz), 7.12 (d, 2H, J = 7 Hz), 5.72 (m, 1H), 5.05 (m, 3H), 3.85 (m, 1H), 3.02 (AB of an ABX system, 2H, J_{AX} = 3 Hz, J_{BX} = 7 Hz, J_{AB} = 13 Hz, $\Delta\nu$ = 45 Hz), 2.2–3 (m, 2H), 2.02 (s, 3H), 0.88 (s, 9H), 0.1 (2s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) of sulfide **25**: δ 168.5, 136.2, 127.4, 129.9, 124.6, 117.6, 75.2, 72.5, 36.8, 33.3, 25.7, 20.9, 18.6, −0.4, −0.43.

4.14. (3*R*,2*S*,R_S)-1-(*p*-Tolylsulfinyl)-2-*tert*-butyl-dimethylsilyloxy-3-methoxyethoxymethyloxy-5-hexene 29

To a suspension of KH (9.5 mg, 0.316 mmol) in dry THF (1 mL) cooled to −78 °C was added dropwise a solution of alcohol **23** (58 mg, 0.158 mmol) in dry THF (1.5 mL). The suspension was stirred for 30 min at −78 °C and MEMCl (36 μL, 0.316 mmol) added. The solution was stirred at −78 °C for 15 min and at rt for 1 h 30 min. Saturated aqueous NH_4Cl (5 mL) was added and the mixture extracted twice times with AcOEt (10 mL × 2) and once with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel (hexane–ether 1:1 to ether) to afford a colourless oil (53 mg, 77%). R_f: (hexane–ethyl acetate 3:2) 0.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 ($(AB)_2$ system, 4H, J_{AB} = 8.2 Hz, $\Delta\nu$ = 40 Hz), 5.75 (m, 1H), 4.99 (m, 2H), 4.91 (d, 1H, J = 7.0 Hz), 4.89 (d, 1H, J = 7.0 Hz), 4.13 (m, 1H), 3.97 (m, 1H), 3.78 (m, 2H), 3.58 (m, 2H), 3.39 (s, 3H), 2.87 (AB fragment of an ABX system, 2H, J_{AX} = 1.7 Hz, J_{BX} = 10.6 Hz, J_{AB} = 13.1 Hz, $\Delta\nu$ = 45 Hz), 2.40 (s, 3H), 1.98 (m, 2H), 0.85 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 142.0, 141.4, 135.6, 130.0, 123.9, 117.1, 96.4, 75.2, 72.2, 71.8, 67.6, 59.3, 59.1, 36.1, 25.9, 21.4, 18.0, −4.33, −4.51. $[\alpha]_D$ = +140 (c 2.0 $CHCl_3$).

4.15. (3*R*,2*S*)-1-(*p*-Tolylsulfenyl)-1-(acetoxy)-2-*tert*-butyl-dimethylsilyloxy-3-methoxyethoxymethyl-5-hexene 30

To a solution of **29** (84 mg, 0.18 mmol) in Ac_2O (4 mL) was added AcONa (177 mg, 2.16 mmol). The mixture was refluxed overnight at 120–130 °C. Toluene was added many times and evaporated to eliminate Ac_2O. The crude was dissolved in diethyl ether and filtered on a short plug of Celite. Et_2O was evaporated in vacuum and the crude purified by flash chromatography on silica gel (hexane–ether 8:2–65:35) affording a colorless oil (74 mg, 82%).

R_f (two diastereoisomers, half point): 0.52. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, 2H, J = 8.0 Hz, C_6H_4, I dia), 7.33 (d, 2H, J = 8.0 Hz, C_6H_4, II dia), 7.09 (d, 4H, J = 8.0 Hz, I and II dia), 6.34 (d, 1H, J = 4.2 Hz, I dia), 6.32 (d, 1H, J = 2.7 Hz, II dia), 5.80 (m, 2H, I and II dia), 5.02 (m, 4H, I and II dia), 4.85 (d, 4H, J = 7.0 Hz superimposed of I and II dia), 3.98–3.52 (m, 12H, I and II dia), 3.37 (s, 3H, I dia), 3.36 (s, 3H, II dia), 2.31 (s, 9H), 2.01 (s, 3H, I dia), 1.99 (s, 3H, II dia), 2.43–1.99 (m, 4H), 0.88 (s, 9H, I dia), 0.86 (s, 9H, II dia), 0.07, 0.06, 0.05 (s, 12H, I and II dia). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 169.1, 138.6, 138.0, 134.7, 134.4, 132.8, 129.7, 129.2, 127.9, 117.7, 117.4, 97.1, 96.5, 82.3, 81.0, 80.5, 80.1, 72.8, 72.3, 71.6, 67.8, 67.4, 58.9, 38.2, 37.6, 25.8, 21.1, 17.9, −4.4, −4.7.

4.16. (3*R*,2*R*)-1-Hydroxy-2-*tert*-butyl-dimethylsilyloxy-3-methoxyethoxymethyloxy-5-hexene 31

To a solution of **30** (0.248 g, 0.496 mmol) in dry Et_2O (12 mL), $LiBH_4$ (43 mg, 1.99 mmol) was added. The solution was stirred at room temperature for 3 h. The solution was cooled to 0 °C, diluted with Et_2O (10 mL) and HCl (1 M, 10 mL) added slowly. The aqueous phase was extracted twice with CH_2Cl_2 (20 mL) and once with AcOEt (20 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuum. The crude was purified by flash chromatography (hexane–ethyl acetate 4:1–3:2) affording a white amorphous crystals (118 mg, 71%). R_f: (hexane–ethyl acetate 3:2) 0.4; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.77 (m, 1H), 5.02 (br d, 1H), 5.01 (br d, 1H), 4.81 (d, 1H, J = 7.0 Hz), 4.71 (d, 1H, J = 7.0 Hz,), 3.86–3.46 (m, 6H), 3.35 (s, 3H), 2.34 (m, 1H), 2.10 (m, 1H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.0, 117.0, 96.5, 84.0, 72.6, 71.5, 67.3, 62.2, 58.8, 37.2, 25.7, 17.9, −4.6, −4.7. $[\alpha]_D$ = +36 (c 2.2, $CHCl_3$).

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6. Optimum yields of β-ketosulfoxides from ester displacement by the lithium anion of methyl-*p*-tolylsulfoxide have previously been found to occur with 2 equiv of sulfinyl anion (better conversions were generally observed under these conditions rather than using 1 equiv of methyl-*p*-tolylsulfoxide and 2 equiv of lithium amide). Such an excess was necessary because of the acidity of the methylene protons of the β-ketosulfoxide. Initial experiments in this work carried out under these conditions led to a mixture of products, with the α-diketo-β-disulfoxide being formed in highest yield.
7. Silica gel chromatography of the β-ketosulfoxide **11** resulted in decomposition, even when the silica gel was deactivated. Separation from the excess of the starting diethyloxalate was achieved using a two layer column; the lower layer being deactivated silica gel, the upper, Celite. The crude product was dissolved in dichloromethane and loaded onto the column, which had been prepared with hexane. β-Ketosulfoxide **11** precipitated in the Celite layer in the non-polar solvent, whilst the diethyloxalate could be washed through. Some other impurities were then removed by changing to a 50% ether–hexane mixture, then the product was isolated by rapid flushing with ether.
8. The relative configuration of the monoprotected diol **10** was determined by ^{13}C NMR analysis of the corresponding acetonide **15**.
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19. A common work-up procedure for Dibal-H reduction of β-ketosulfoxides is the precipitation of aluminium salts as their tartrate. For this substrate, this led to poor recovery and it was found that a pH of 3–4 was best to obtain the highest yields of alcohol **12**. This was achieved by initially quenching the reaction with saturated ammonium chloride solution, followed by the careful addition of dilute sulfuric acid to the mixture so as to avoid lowering the pH too dramatically, since it was found that the alcohol readily epimerized at lower pH.