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Asymmetric synthesis induced by chiral sulfoxides : 2-deoxy-sugars from β-ketoesters *via* malic acid.

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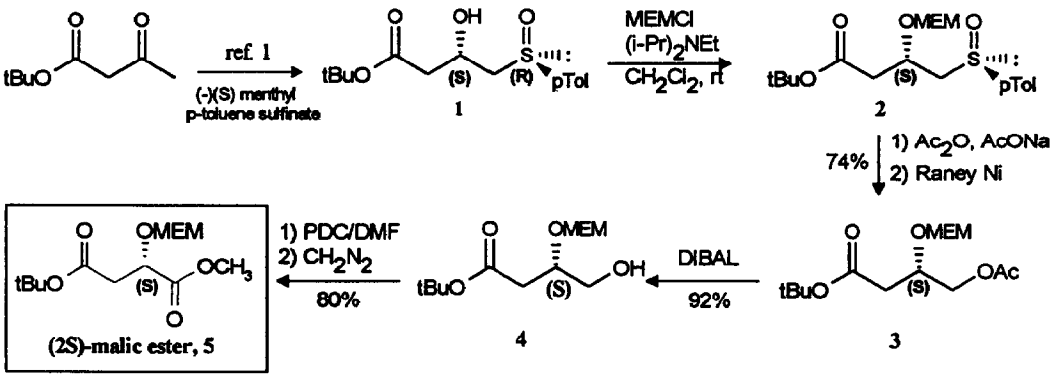
Abstract : the asymmetric synthesis of (S)-malic esters was carried out by reduction of β-ketosulfoxides derived from β-ketoesters as well as the transformation of (S)-malic esters into *syn* and *anti*-1,2-diols *via* the reduction of β-keto-γ–alkoxy-sulfoxides. An application to the preparation of 2-deoxy-D-ribose and 2-deoxy-L-xylose derivatives is described.

Functionalized optically active 1,2-diols are very important building blocks for the total synthesis of natural products. We recently described [1] a very efficient transformation of chiral α-hydroxyesters (lactic and mandelic esters) into enantiomerically pure *syn* and *anti*-1,2-diols *via* β-keto-γ-alkoxy sulfoxides. We report now the asymmetric synthesis of (S) and (R) t-butyl methyl malate by reduction of the β-ketosulfoxide derived from t-butyl acetoacetate and the transformation of (S) t-butyl methyl malate into 2-deoxy-D-ribose and 2-deoxy-L-xylose derivatives. One important feature of these enantioselective syntheses is the generation of 2-deoxysugar derivatives having different protecting groups on the reactive sites, making these molecules suitable for application in total synthesis.

We recently reported in a short communication [2] that the dianion of t-butyl acetoacetate reacted with (-)-(S)-menthyl p-toluenesulfinate to give the corresponding (+)-(R)-t-butyl-4-[p-tolylsulfinyl]-3-oxobutyrate in 92% yield, which was then reduced with DIBAL to give in 78% yield only the [3(S), S(R)] diastereomer of t-butyl 4-[p-tolylsulfinyl]-3-hydroxybutyrate 1.

The hydroxyl group of 1 was protected with a MEM group [3] and the crude adduct 2 submitted to a Pummerer rearrangement and desulfurized with Raney Ni to give the acetate 3 in 74% overall yield from 1. The selective DIBAL reduction of the acetate, followed by oxidation and esterification of the resulting carboxylic acid lead to the (S)-t-butyl methyl malate 5 with the hydroxyl group protected by a MEM group (scheme I).

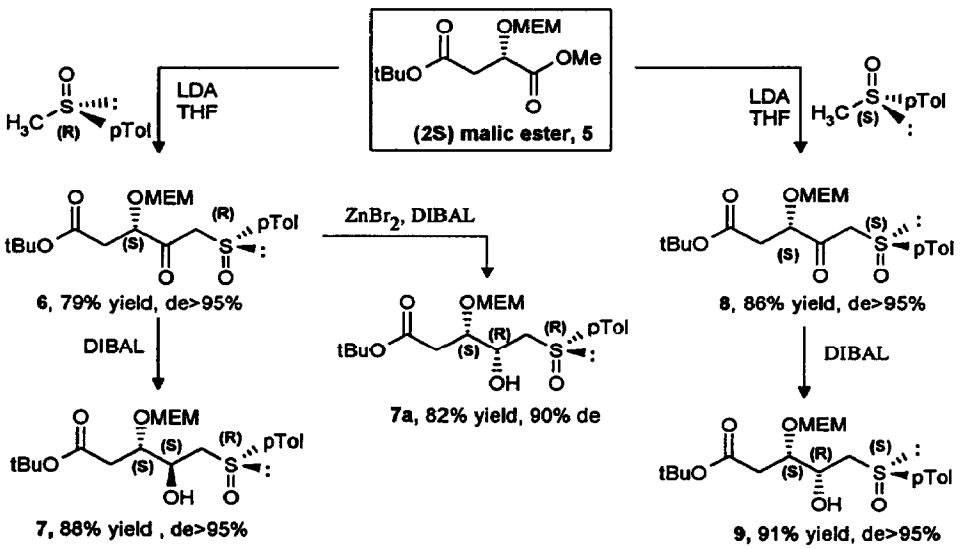
Scheme I



Reaction of the ester 5 with (+)-(R) or (-)-(S) methyl p-tolylsulfoxide gave in high yield the corresponding β-ketosulfoxides 6 and 7 respectively; at low temperature no reaction of the sulfinyl carbanion on the t-butyl ester has been observed.

The β-ketosulfoxide 6 was then reduced with DIBAL following our preliminary results of β-keto γ-hydroxysulfoxides [1] (scheme II). In this way, the corresponding hydroxysulfoxide 7 was formed in 88% yield as a single diastereomer (only one diastereomer could be detected in the ^{1}H and ^{13}C NMR spectra of the crude product). The absolute configuration (S) of the created hydroxylic center was deduced from our previous results [1] and will be confirmed by chemical correlation.

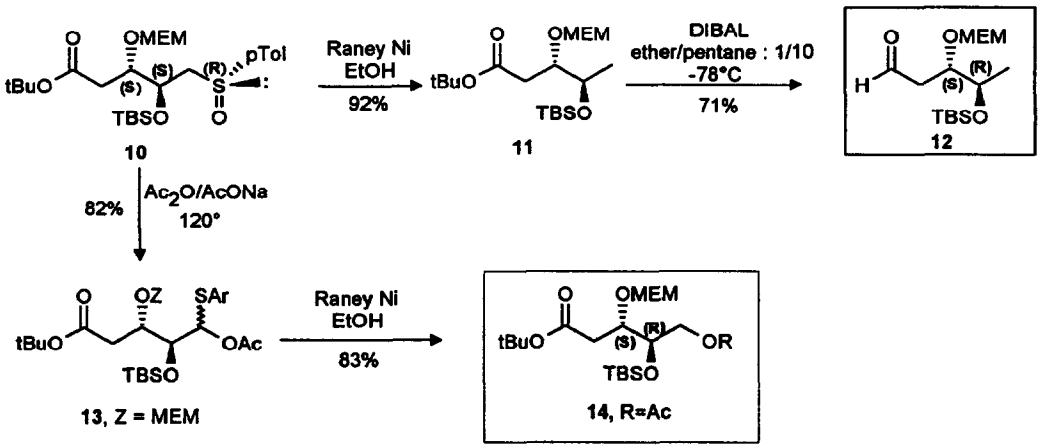
Scheme II



The $ZnBr_2$-DIBAL reduction of 6 gave the diastereomer 7a with a lower diastereoselectivity (95/5) , easily identified by ^{1}H and ^{13}C NMR spectra. This lower stereoselectivity was consistent

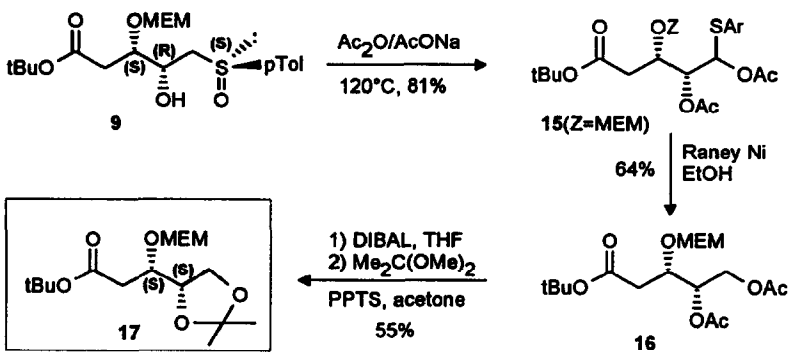
with our preceeding results [1] and is probably due to the fact that the substrate offers, besides the oxygens of the keto and sulfoxide groups, other chelating sites to zinc bromide. As an alternative route to the pure *syn*-1,2-diol, the DIBAL reduction of the β-ketosulfoxide **8**, featuring an (S)-configuration at sulfur, furnished the β-hydroxysulfoxide **9** with an excellent diastereomeric excess (>95%).

Scheme III



In order to confirm the absolute configuration of compound **7**, the free hydroxyl group was protected by a TBS group and the resulting product **10** was desulfurized with Raney Nickel giving the known 3(S), 4(R)-dihydroxy pentanal[4] derivative **12**. (scheme III).

Scheme IV



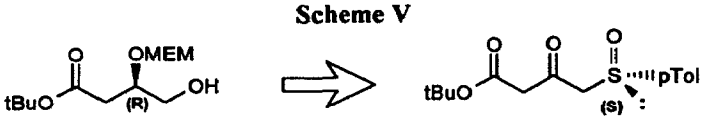
The dihydroxy sulfinyl pentanoate derivative **10** can be considered as a good precursor of 2-deoxy D-ribose. One example of such a transformation is shown on scheme III. Compound **10** was

first submitted to a Pummerer rearrangement and the resulting product desulfurized to **14** which is an oxidated form of 2-deoxy-D-ribose having each hydroxyl group protected differently.

Similarly compound **9** can be transformed into the oxidated form of 2-deoxy-L-xylose **17** (Scheme IV) *via* a Pummerer rearrangement which lead to the intermediate **15**. Desulfurization with Raney Nickel afforded the diacetate **16** which was easily transformed into the acetonide **17**.

The enantiomers of **14** and **17** can also be prepared in a similar manner from the β-hydroxy ester derivative **(R)-4** easily made from (S)-t-butyl-4-[p-tolylsulfinyl]-3-oxobutyrate *via* DIBAL reduction [2] (Scheme V).

Scheme V



(R)-4

In conclusion, this ''iterative stereoselective β-ketosulfoxide reduction'' route is very efficient in terms of diastereoselectivity (de>95% for the DIBAL reduction) and chemical yields, affording diastereomerically pure and highly functionalized *syn* and *anti*-1,2-diols. The strength of this method has been demonstrated by the synthesis of 2-deoxypentose derivatives, which can be obtained in all four possible configurations.

Acknowledgements : one of us (A.A.) gratefully thanks the Spanish Ministery of Education and Sciences for a scholarship.

EXPERIMENTAL PART.

(+)[3(S), S(R)] t-butyl 3-hydroxy-4-(p-tolylsulfinyl)butyrate, 1.

A 1M DIBAL solution in toluene (6 mL, 6 mmol.) is dropwise added to a solution of (+)(R)-t-butyl 3-oxo-4-(p-tolylsulfinyl) butyrate[2] (1.48g, 5 mmol.) in THF (40 mL) at -78°C. After stirring for 30 min., the reaction mixture was hydrolyzed with methanol (1 mL) and sat. sodium tartrate (25 mL). EtOAc (50 mL) was then added and the mixture stirred at room temperature until the phases were clearly separated. The aqueous phase was extracted with EtOAc (2x30 mL). The combined organic phases were then washed with sat. NaCl (30 mL), dried (Na_2SO_4) and solvents evaporated. The crude product was finally purified by chromatography on silica gel (EtOAc/hexane : 1/1). Yield : 78% (1.15 g) ; m.p = 92-93°C ; $[\alpha]_D$+191 (c=0.8, $CHCl_3$) ; Rf : 0.24 (EtOAc/hexane : 1/1). ^1H NMR (200 MHz, $CDCl_3$) : δ : 1.42 (s, 9H, tBu), 2.42 (s, 3H, Me of p-tolyl), 2.46 (d, 2H, H-2, J=6.5Hz), 2.87 (AB of ABX, H-4, J_{AB}=13.5Hz, J_{AX}=10Hz, J_{BX}=2.5Hz : Δν=45Hz), 4.12 (d, 1H, OH, J=3.5Hz), 4.50 (m, X of ABX, 1H, H-3), 7.34 and 7.54 (d, AA'BB', 4H, J=8Hz, arom. H). ^{13}C NMR ($CDCl_3$) : δ : 21.41 (Me of p-Tol), 28.02 [($\underline{C}H_3)_3C$], 42.04 (C-2), 61.84 (C-4), 63.63 (C-3), 81.62 ($Me_3\underline{C}$), 123.95 and 130.10 (arom. $\underline{C}H$), 139.88 and 141.64 (arom. $\underline{C}$), 170.65 (C-1). Anal. Calc. for $C_{15}H_{22}O_4S$: C, 60.38 ; H, 7.43. Found : C, 60.31 ; H, 7.33.

(+) 3(S) t-butyl 3-(2-methoxyethoxymethoxy)-4-acetoxybutyrate, 3.

1) [3(S), S(R)] t-butyl 3-(2 methoxyethoxymethoxy)-4-(p-tolylsulfinyl) butyrate, 2.

To a solution of the β-hydroxysulfoxide **1** (3.882 g, 13 mmol.) in CH_2Cl_2 (200 mL) were added diisopropylethyl amine (9.2 mL, 52 mmol.) and 2-methoxyethoxymethyl chloride (5.9 mL, 52 mmol.). After stirring at room temperature for 48h, the reaction mixture was hydrolyzed with sat. NH_4Cl and extracted with CH_2Cl_2 (3x70 mL). The organic phases were washed with sat. NaCl (70 mL), dried (Na_2SO_4) and evaporated to give crude **2** , slightly contaminated by some starting material (having the same Rf).

2) Pummerer rearrangement of compound 2.

The preceeding crude product was dissolved in acetic anhydride (40 mL), sodium acetate (1 g) was added and the mixture refluxed for 8h. The excess of acetic anhydride was evaporated under vacuum, the residue dissolved in ether, filtered on celite and the solid washed with ether. After evaporating the solvent, the product was purified by chromatography on silica gel (EtOAc/hexane : 1/4, Rf 0.26) to yield 4.52 g (81% overall yield) of a 1/1 mixture of the 2 diastereomers (resulting from C-4 and determined from the H-4 signal). ^{1}H NMR (200MHz, $CDCl_3$) : δ : 1.39 and 1.40 (s, 9H, tBu), 2.00 (s, 3H, CH_3), 2.28 (s, 3H, Me of p-tol), 2.64 (m, 2 AB of ABX overlapped, 2H, H-2), 3.22 and 3.33 (s, 3H, OCH_3), 3.44-3.66 (m, 4H, H-2', H-3'), 4.22 and 4.32 (m, X of ABX, 1H, H-3), 6.24 (d, 1H, J=3Hz, H-4 of one dia.), 6.26 (d, 1H, J=5Hz, H-4 of the other dia.), 7.06 and 7.35 (d, AA'BB', J=8Hz, arom.H).

3) Desulfurization of the Pummerer product to 3.

To a solution of the preceeding compound (4 g, 9.346 mmol.) in ethanol (50 mL) was added Raney Nickel and the mixture stirred at room temperature (TLC monitoring : AcOEt/hexane : 1/2, Rf=0.51). The mixture was then filtered on celite, the solid washed with ethanol and after evaporating the solvent, the product was purified by chromatography on silica gel (EtOAc/hexane : 1/3). Yield : 2.6 g (91%), $[\alpha]_D$+10 (c=2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 1.42 (s, 9H, tBu), 2.04 (s, 3H, H-6), 2.48 (AB of ABX, J_{AB}=16Hz, J_{AX}=7Hz, J_{BX}=5.5Hz, Δν=18Hz, H-2), 3.36 (s, 3H, H-4'), 3.50-3.72 (m, 4H, H-2', H-3'), 4.15 (m, 3H, H-3, H-4), 4.77 (bs, 2H, H-1'). ^{13}C NMR ($CDCl_3$) : 20.77 (C-6), 27.98 [($\underline{C}H_3)_3C$], 38.49 (C-2), 58.95 (C-4'), 65.59 (C-4), 67.07 and 71.58 (C-2', C-3'), 72.31 (C-3), 80.91 ($Me_3\underline{C}$), 95.21 (C-1'), 169.78 and 170.66 (C-1, C-5). Anal. calcd. for $C_{14}H_{26}O_7$: C, 54.89 ; H, 8.55. Found : C, 55.07 ; H, 8.45.

(+) 3(S) t-butyl 3-(2-methoxyethoxymethoxy)-4-hydroxybutyrate, 4.

To a solution of **3** (2.7 g, 8.9 mmol.) in THF (100 mL) at -78°C was added dropwise a 1M DIBAL solution in toluene (18 mL, 18 mmol.). After stirring at -78°C for 30 min., the reaction mixture was allowed to reach 0°C and stirred for 15 minutes. After cooling at -78°C, the solution was hydrolyzed with sat. sodium tartrate (25 mL) and diluted with EtOAc (50 mL) before stirring until a clear separation of the 2 phases. The organic layers were washed with sat. NaCl, dried (Na_2SO_4) and evaporated. The product **4** was finally purified by column chromatography on silica gel (EtOAc/hexane : 1/1, Rf=0.3). Yield 2.17 g (92%) ; $[\alpha]_D$+50 (c=1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 1.43 (s, 9H, tBu), 2.44 (AB of ABX, 2H, J_{AB}=16Hz, J_{AX}=8Hz, J_{BX}=6Hz, Δν=17Hz, H-2), 3.37 (s, 3H, H-4'), 3.50-3.90 (m, 7H, H-2', H-4, OH), 4.00 (m, 1H, H-3), 4.79 (s, 2H, H-1'). ^{13}C NMR ($CDCl_3$): δ: 27.86 [($\underline{C}H_3)_3C$], 38.30 (C-2), 58.71 (C-4'), 64.58 (C-4), 67.22 and 71.43 (C-2',

C-3'), 78.32 (C-3), 80.49 (C-1'), 170.13 (C-1). Anal. calcd for $C_{12}H_{24}O_6$: C, 54.53 ; H, 9.15. Found : C, 54.49 ; H, 9.18.

(-)2(S) -Methyl 2-(2-methoxyethoxymethoxy)-3-(t-butoxycarbonyl) propanoate, 5.

To a solution of (+)(S)-4 (796 mg, 3 mmol.) in DMF (30 mL) was added pyridinium dichromate (5.6 g, 15 mmol.) and the reaction mixture stirred at room temperature for 15h. Water (40 mL) and ether (40 mL) were added before stirring for 10 min. After separation of the organic phase, the aqueous layer was saturated with NaCl and extracted with ether (2x40 mL). Solvent was evaporated after drying ($MgSO_4$). The resulting crude carboxylic acid was dissolved in ether (50 mL), cooled at 0°C and treated by an ether solution of diazomethane until a persistent yellow color was obtained. A spoon of silica gel was then added to the reaction mixture which was stirred for 5 min. Filtration and solvent evaporation gave the crude ester which was purified by column chromatography on silica gel /ether/hexane : 1/1, Rf 0.37). Yield 700 mg (80%) ; $[\alpha]_D$ -35 (c=1.2, $CHCl_3$). ^1H NMR (200MHz, $CDCl_3$) : δ : 1.41 (s, 9H, tBu), 2.68 (d, 2H, H-2, J=6Hz), 3.35 (s, 3H, H-4'), 3.40-3.70 (m, 4H, H-2', H-3'), 3.72 (s, 3H, CO_2Me), 4.49 (t, 1H, H-3, J=6Hz), 4.78 (AB, 2H, J_{AB}=6Hz, Δν=4Hz, H-1'). ^{13}C NMR ($CDCl_3$) : δ : 27.93 [$(C\underline{H}_3)_3C$), 38.93 (C-2), 52.05 ($CO_2\underline{C}H_3$), 58.92 (C-4'), 67.43 and 71.56 (C-2', C-3'), 72.13 (C-3), 81.17 ($Me_3\underline{C}$), 95.32 (C-1'), 168.91 (C-1), 171.78 (C-4). Anal. calcd for $C_{13}H_{24}O_7$: 53.40 ; H, 8.28. Found : C, 53.48 ; H, 8.11.

(+)-[3(S), S(R)]-t-butyl 3-(2-methoxyethoxymethoxy)-4-oxo-5-(p-tolylsulfinyl) pentanoate, 6.

To a solution of LDA (1.5 mmol.) in THF (20 mL) cooled at -78°C, was added a solution of (+)-(R)-methyl p-tolyl sulfoxide (224 mg, 1.45 mmol.) in THF (20 mL). After stirring for one hour at -78°C, this solution was dropwise added to a solution of the ester 5 (212 mg, 0.73 mmol.) in THF (20 mL) cooled at -78°C. 15 mn after the end of the addition, the reaction mixture was hydrolyzed with sat. NH_4Cl (20 mL) and extracted with EtOAc (2x30 mL). The organic layers were washed with sat. NH_4Cl (30 mL), sat. NaCl (30 mL), dried ($MgSO_4$) and the solvents evaporated. The crude product was purified by column chromatography on silica gel (Ether/hexane : 9/1, Rf 0.36 in 100% ether). Yield : 236 mg (79%), $[\alpha]_D$+91 (c=0.7, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ : 1.41 (s, 9H, tBu), 2.41 (s, 3H, Me of p-Tol), 2.74 (AB of ABX, 2H, J_{AB}=15.5Hz, J_{AX}=5.5Hz, J_{BX}=5Hz, Δν=11Hz, H-2), 3.35 (s, 3H, OCH_3), 3.48-3.72 (m, 4H, H-2', H-3'), 4.18 (t, 1H, J=5Hz, H-3), 4.2 (AB, 2H, J_{AB}=15Hz, Δν=35Hz, H-5), 4.77 (AB, 2H, J_{AB}=7Hz, Δν=13Hz, H-1'), 7.32-7.57 (AA'BB', 4H, J=8Hz, arom. H.). ^{13}C NMR ($CDCl_3$): δ : 21.29 (Me of p-tol), 27.87 [$(\underline{C}H_3)_3C$], 37.96 (C-2), 58.81 (C-4'), 65.48 (C-5), 67.70 and 71.44 (C-2', C-3'), 79.82 (C-3), 81.32 ($Me_3\underline{C}O$), 96.11 (C-1'), 124.15 and 129.84 (arom. CH), 140.50 and 141.83 (arom.C), 168.97 (C-1), 202.09 (C-4). Anal. calcd. For $C_{20}H_{30}O_7S$: C, 57.95 ; H, 7.30. Found : C, 57.91 ; H, 7.41.

(+)-[3(S), 4(S), S(R)]-t-butyl 3-(2-methoxyethoxymethoxy)-4-hydroxy-5-(p-tolylsulfinyl) pentanoate, 7.

To a solution of the β-ketosulfoxide 6 (365 mg, 0.88 mmol.) in THF (60 mL) cooled at -78°C, was dropwise added a 1M DIBAL solution in toluene (0.970 mL, 0.97 mmol.). 10 min. after the end of the addition, the reaction mixture was hydrolyzed with sat. sodium tartrate (30 mL), diluted with EtOAc (40 mL), and extracted once with EtOAc (30 mL). The organic layers were washed with sat. NaCl, dried ($MgSO_4$) and solvents evaporated. The crude product was purified by column chromatography

on silica gel (Ether). Yield : 322 mg (88%), Rf : 0.53 (AcOEt), mp 72-3°C, d.e > 95% (only one set of signals in ^1H and ^{13}C NMR), $[\alpha]_D$ + 150 (C=0.6, $CHCl_3$). ^1H NMR (200 MHz, C_6D_6) : δ : 1.33 (s, 9H, tBu), 1.96 (s, 3H, CH_3 of p-Tol), 2.40 (AB of ABX, 2H, J_{AB}=16Hz, J_{AX}=8.5Hz, J_{BX}=4Hz, Δν=37Hz, H-2), 2.81 (AB of ABX, 2H, J_{AB}=13Hz, J_{AX}=10Hz, J_{BX}=2Hz, Δν=35Hz, H-5), 3.08 (s, 3H, OCH_3), 3.1-3.6 (m, 4H, H-2', H-3'), 4.14 (td, 1H, J=4Hz, J=8.5Hz, H-3), 4.5 (m, 1H, H-4), 4.7 (AB, 2H, J_{AB}=7Hz, Δν=26Hz, H-1'), 4.86 (d, 1H, J=6Hz, OH), 6.87-7.46 (AA'BB', 4H, J=8Hz, arom. H). ^{13}C NMR ($CDCl_3$)) : d : 21.34 (CH_3 of p-Tol), 27.94 [($\underline{C}H_3)_3C$]. 37.77 (C-2), 58.93 (C-4'), 60.06 (C-5), 67.56 and 71.56 (C-2', C-3'), 67.74 (C-4), 80.28 (C-3), 80.87 (Me_3C), 96.42 (C-1'), 123.82 and 129.95 (arom. CH), 140.61 and 141.31 (arom. C), 170.08 (C-1). Anal. Calcd. for $C_{20}H_{32}O_7S$: C, 57.67 ; H, 7.75. Found : C, 57.91 ; H, 7.88.

[3(S), 4(R), S(R)]-t-butyl 3-(2-methoxyethoxymethoxy)-4-hydroxy-5-(p-tolylsulfinyl) pentanoate, 7a.

The β-ketosulfoxide **6** (56 mg, 0.135 mmol.) in THF (20 mL) was added to dried $ZnBr_2$ (33 mg, 0.148 mmol). The mixture was stirred at 0°C for 30 min. and at -78°C for 30 min. Then a 1M DIBAL solution in toluene (0.150 mL, 0.150 mmol.) was dropwise added at -78°C. Ten min. after the addition , the reaction mixture was hydrolyzed with sat. sodium tartrate (10 mL), diluted with EtOAc (20 mL), and extracted once with EtOAc (20 mL). The organic layers were washed with sat. NaCl, dried ($MgSO_4$) and evaporated. The crude product was purified by silica gel column chromatography (ether). Yield : 46 mg (82%) of a 93/7 mixture of diastereomers determined by ^1H NMR from the signals of H-2 and H-3. Rf 0.39 (AcOEt). ^1H NMR (200 MHz, C_6D_6) : δ : 1.34 (s, 9H, tBu), 1.96 (s, 3H, CH_3 of p-Tol), 2.56 (AB of ABX, 2H, J_{AB}=16Hz, J_{AX}=4Hz, J_{BX}=9Hz, Δν=68Hz, H-2), 2.90 (d, 2H, J=6Hz, H-5), 3.08 (s, 3H, OCH_3), 3.20-3.60 (m, 4H, H-2', H-3'), 4.34 (td, 1H, J=9Hz, J=4Hz, H-3), 4.55 (m, 2H, H-4, OH), 4.73. (AB, 2H, J_{AB}=7Hz, Δν=31Hz, H-1'), 6.86 and 7.41 (AA'BB', 4H, J=8Hz, arom. H). ^{13}C NMR ($CDCl_3$) of the major dia.:δ: 21.44 (Me of p-tol.), 28.03 [($\underline{C}H_3)_3CO$], 36.99 (C-2), 59.02 (C-4'), 59.26 (C-5), 67.77 and 71.61 (C-2', C-3'), 69.56 (C-4), 77.95 (C-3), 80.93 ($Me_3\underline{C}O$), 96.41 (OMe), 124.06 and 130.10 (arom.C), 140.56 and 141.95 (arom.C), 170.28 (C-1)..

(-) -[3(S), S(S)] -t-butyl 3-(2-methoxyethoxymethoxy)-4-oxo-5-(p-tolylsulfinyl)pentanoate, 8

The β-ketosulfoxide **8** was obtained from (-)-(S)-methyl p-tolsulfoxide (216 mg, 1.4 mmol.) and the diester **5** (205 mg, 0.7 mmol.) by the procedure described for the synthesis of **6**. The product **8** was purified by chromatography on silica gel (EtOAc/hexane : 7/3). Yield : 231 mg (80%) ; Rf=0.32 (ether) ; $[\alpha]_D$ -149 (c=1.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ : 1.39 (s, 9H, tBu), 2.41 (s, 3H, Me of p-Tol.), 2.74 (AB of ABX, 2H, J_{AB}=16.5Hz, J_{AX}=5Hz, J_{BX}=5Hz, Δν=11Hz, H-2), 3.36 (s, 3H, OCH_3), 3.50-3.70 (m, 4H, H-2', H-3'), 4.17 (AB, 2H, J_{AB}=15Hz, Δν=66Hz, H-1'), 4.24 (t, 1H, J=5Hz, H-3), 4.76 (AB, 2H, J_{AB}=7Hz, Δν=10Hz, H-1'), 7.32-7.57 (AA'BB'), 4H, J=8Hz, arom. H). ^{13}C NMR ($CDCl_3$) : δ : 21.38 (Me of p-Tol), 27.92 [($\underline{C}H_3)_3C$], 38.01 (C-2), 58.94 (C-4'), 66.26 (C-5), 67.73 and 71.49 (C-2', C-3'), 79.45 (C-3), 81.45 ($Me_3\underline{C}$), 95.77 (C-1'), 124.18 and 129.94 (arom. CH), 140.34 and 141.90 (arom. C), 169.08 (C-1), 202.59 (C-4). Anal. Calcd. for $C_{20}H_{30}O_7S$: C, 57.95 ; H, 7.30. Found : C, 57.83 ; H, 7.38.

(-)-[3(S), 4(R), S(S)]-t-butyl 3-(2-methoxyethoxymethoxy)-4-hydroxy-5-(p-tolylsulfinyl) pentanoate, 9.

The β-hydroxysulfoxide **9** was obtained by reduction of **8** (187 mg, 0.51 mmol.) with DIBAL following the procedure described for the synthesis of **7**. The crude product was purified by chromatography on silica gel (EtOAc/hexane : 7/3). Yield : 170 mg (91%) ; Rf 0.45 (EtOAc) ; $[\alpha]_D$ -132 (c=1.8, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ : 1.40 (s, 9H, tBu), 2.41 (s, 3H, Me of p-Tol.), 2.51 (AB of ABX, 2H, J_{AB}=16Hz, J_{AX}=5Hz, J_{BX}=8Hz, Δν=29Hz, H-2), 2.88 (AB of ABX, 2H, J_{AB}=13Hz, J_{AX}=10Hz, J_{BX}=1.5Hz, Δν=63Hz, H-3), 3.36 (s, 3H, OCH_3), 3.40-3.60 (m, H-2', H-3'), 3.94 (td, 1H, J=5Hz, J=8Hz, H-3'), 4.20 (m, 2H, H-4, OH), 4.70 (AB, 2H, J_{AB}=7Hz, Δν=15Hz, H-1'), 7.33 and 7.52 (AA'BB', 4H, J=8Hz, arom. H). ^{13}C NMR ($CDCl_3$) : δ : 21.29 (Me of p-Tol), 27.90 [($\underline{C}H_3)_3C$], 37.32 (C-2), 58.87 (C-4'), 59.07 (C-5), 67.32 (C-4), 67.46 and 71.47 (C-2', C-3'), 78.09 (C-3), 80.82 (Me_3C), 96.07 (C-1'), 123.90 and 129.92 (arom. CH), 139.97 and 141.36 (arom. C), 170.29 (C-1). Anal. calcd for $C_{20}H_{32}O_7S$: C, 57.67 ; H, 7.75. Found : C, 57.83 ; H, 7.79.

(+)-[3(S), 4(S), S(R)]-t-butyl 3-(2-methoxyethoxymethoxy)-4-(t-butyldimethyl silyloxy)-5-(p-tolyl sulfinyl) pentanoate, 10.

To a solution of the β-hydroxysulfoxide **7** (360 mg, 0.865 mmol.) in DMF was added at room temperature imidazole (206 mg, 3 mmol.) and t-butyldimethylsilyl chloride (260 mg, 1.73 mmol.). The reaction mixture was heated at 50°C for 36h, hydrolyzed with water (20 mL) and diluted with ether (40 mL). After extraction with ether (20 mL), the organic layers were washed with sat. NH_4Cl (3x30 mL), sat. NaCl and dried ($MgSO_4$). After evaporating the solvent, the crude product was purified by column chromatography (ether/hexane : 1/1, Rf 0.25). Yield : 361 mg (79%) ; $[\alpha]_D$+98 (c=1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ : 0.19 and 0.25 (s, 6H, Me_2Si), 0.97 (s, 9H, tBuSi), 1.42 (s, 9H, tBuO), 2.39 (AB of ABX, 2H, J_{AB}=15Hz, J_{AX}=7Hz, J_{BX}=5.5Hz, Δν=16Hz, H-2), 2.39 (s, 3H, Me of p-Tol.), 2.77 (dd, 2H, J=5.5Hz, J=1.5Hz, H-5), 3.37 (s, 3H, OCH_3), 3.5-3.7 (m, 4H, H-2', H-3'), 4.1 (m, 1H, H-3), 4.32 (m, 1H, H-4), 4.81 (s, 2H, H-1'). Anal. Calcd. for $C_{26}H_{46}O_7SSi$: 58.84 ; H, 8.74. Found : C, 58.72 ; H, 8.67.

(-)-[3(S), 4(R)]-t-butyl 3-(2-methoxyethoxymethoxy)-4-(t-butyldimethylsilyloxy) pentanoate, 11.

Compound **10** (105 mg, 0.198 mmol.) in ethanol (20 mL) was desulfurized with Raney Nickel at room temperature. The reaction was monitored by TLC (ether/hexane : 1/2, Rf 0.42). After filtration of the catalyst over celite and evaporation of the solvent, the product was purified by column chromatography on silica gel (ether/hexane : 1/3). Yield : 71 mg (92%) ; $[\alpha]_D$-24 (c=1.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) : δ : 0.06 (s, 6H, Me_2Si), 0.88 (s, 9H, tBuSi), 1.13 (d, 3H, J=6Hz, CH_3), 1.45 (s, 9H, tBuO), 2.45 (d, 2H, J=6Hz, H-2), 3.39 (s, 3H, OCH_3), 3.50-3.70 (m, 4H, H-2', H-3'), 3.9 (m, 2H, H-3, H-4), 4.81 (s, 2H, H-1').

(-)-[3(S), 4(R)]-3-(2-methoxyethoxymethoxy)-4-(t-butyldimethylsilyloxy) pentanal, 12.

To a solution of ester **11** (73 mg, 0.186 mmol.) in a mixture of ether/pentane (3 mL/21 mL) at -78°C under argon, was dropwise added DIBAL (0.205 mL of a 1M solution in toluene, 0.205 mmol.). After 1h at -78°C, the reaction mixture was hydrolyzed with sat. sodium tartrate and diluted with EtOAc (2x20 mL). The aqueous layer was extracted with EtOAc (20 mL). The organic phases were washed with sat. NaCl, dried ($MgSO_4$) and the solvent evaporated. The product was purified by column chromatography on silica gel (ether/hexane : 1/3). Yield : 42 mg (71%) ; Rf 0.45 (ether/hexane : 1/2) ; $[\alpha]_D$-40 (c=2.1, $CHCl_3$) (lit.[4], -39.1 (c=1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ : 0.06 (s, 6H,

Me_2Si), 0.88 (s, 9H, tBuSi), 1.14 (d, 3H, J=6Hz, H-5), 2.61 (AB of ABXY, 2H, J_{AB}=16.5Hz, J_{AX}=6Hz, J_{BX}=5.5Hz, J_{AY}=J_{BY}=3Hz), 3.39 (s, 3H, OCH_3), 3.50-3.70 (m, 4H, H-2', H-3'), 3.90 (m, 2H, H-3, H-4), 4.80 (AB, J_{AB}=7Hz, Δν=13Hz), 9.81 (t, 1H, H-1, J=3Hz). ^{13}C NMR ($CDCl_3$) : δ : -4.76 and -4.54 (Me_2Si), 18.00 (Me_3CSi), 20.06 (C-5), 25.76 [($\underline{C}H_3)_3CSi$], 44.63 (C-2), 59.04 (C-4'), 67.32 and 71.66 (C-2', C-3'), 69.89 (C-4), 77.55 (C-3), 95.08 (C-1'), 201.69 (C-1). Anal. Calcd. for $C_{15}H_{32}O_5Si$: C, 56.22 ; H, 10.07. Found : C, 56.42 ; H, 10.21.

(-)-[3(S), 4(R)]- t-butyl 3-(2-methoxyethoxymethoxy)-4-(t-butyldimethylsilyloxy)-5-acetoxy penta noate, 14.

1) Pummerer rearrangement of sulfoxide 10

To a solution of sulfoxide **10** (260 mg, 0.49 mmol.) in acetic anhydride (10 mL), was added sodium acetate (500 mg) and the reaction mixture refluxed for 15h. The excess of acetic anhydride was then evaporated under vacuum, the residue dissolved in ether and filtrated over celite. After evaporating the solvent, the crude product **13** was purified by column chromatography on silica gel (ether/hexane : 1/4). Yield : 229 mg (82%) ; Rf 0.47 and 0.57 (ether/hexane : 1/1) for the two diastereomers in 1/1 ratio. ^1H NMR (200 MHz, $CDCl_3$) : δ : 0.03, 0.06, 0.10, 0.16 (s, 6H, Me_2Si), 0.87 and 0.94 (s, 9H, tBuSi), 1.45 (s, 9H, tBuO), 2.04 and 2.07 (s, 3H, $OCOCH_3$), 2.31 and 2.33 (s, 3H, Me of p-tol in the 2 dia.), 2.52 (AB of ABX, 2H, J_{AB}=16Hz, J_{AX}=3Hz, J_{BX}=6Hz, Δν=48Hz, H-2 in one dia.), 2.51 (d, 2H, J=6Hz, H-2 in the other dia.), 3.36 and 3.39 (s, 3H, OCH_3), 3.42-3.80 (m, 4H, H-2', H-3'), 4.02 (dd, 1H, J=1.5Hz, J=8Hz, H-4, in one dia.), 4.18 (m, 1H, H-3, H-4 in one dia), 4.49 (td, 1H, J=1.5Hz, H-3, one dia), 4.70 and 4.76 (dd, AB, 2H, J=7Hz, Δν=8Hz, H-1', one dia.), 4.76 (dd, AB, 6.34 (d, 1H, J=2.5Hz, H-5, one dia.), 7.08, 7.12, 7.38, 7.42 (AA'BB', 4H, J=8Hz, arom. H).

2) Desulfurization of the compound 13 to the acetate 14.

Following the procedure used for the synthesis of **3**, the compound **13** (115 mg, 0.2 mmol.) was desulfurized with Raney Ni.Yield : 75 mg (83%), Rf=0.34 (ether/hexane : 1/2). $[\alpha]_{D=}$ -6 (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) : δ : 0.08 and 0.09 (s, 6H, Me_2Si), 0.88 (s, 9H, tBuSi), 1.45 (s, 9H, tBuO), 2.07 (s, 3H, $OCOCH_3$), 2.52 (d, 2H, J=6Hz, H-2), 3.38 (s, 3H, OMe), 3.50-3.70 (m, 4H, H-2', H-3'), 4.05-4.22 (m, 2H, H-2, H-3), 4.79 (s, 2H, H-1'). Anal. calcd. for $C_{21}H_{42}O_8Si$: C, 55.97 ; H, 9.40. Found : C, 55.81 ; H, 9.33.

(+)-[3(S), 4(S)]-t-butyl 3-(2-methoxyethoxymethoxy)-4.5-diacetoxypentanoate, 16.

1) Pummerer rearrangement of sulfoxide 9 to 15.

To a solution of sulfoxide **9** (160 mg, 0.385 mmol.) in acetic anhydride (10 mL), was added sodium acetate (300 mg) and the mixture refluxed for 16h. The acetic anhydride was then evaporated under vacuum, the residue dissolved in ether and filtrated on celite and the solvent evaporated. The product **15** was purified by chromatography on silica gel (EtOAc/hexane : 3/7). Yield : 156 mg (81%), Rf 0.52 (EtOAc/hexane : 1/1) for the diastereomeric mixture. ^1H NMR (200 MHz, $CDCl_3$) : δ : 1.41 and 1.43 (s, 9H, tBu), 2.05, 2.08, 2.15 ($OCOCH_3$), 2.33 (CH_3 of p-tol.), 2.49 [AB of ABX, 2H (1 dia.), J_{AB}=16Hz, J_{AX}=5Hz, J_{BX}=7Hz, Δν=46Hz, H-2], 2.55 [AB of ABX, 2H (1 dia), J_{AB}=16Hz, J_{AX}=5Hz, J_{BX}=7Hz, Δν=35Hz, H-2], 3.36 and 3.38 (s, 3H, OCH_3), 3.50-3.80 (m, 4H, H-3, H-4), 4.23 [td, 1H (1 dia), J_t=6.5Hz, J_d=3.5Hz, H-3), 4.54 [td, 1H (1 dia), J_t=6.5Hz, J_d=3Hz, H-3], 4.74 [AB, 2H (1 dia), J_{AB}=7Hz, Δν=12Hz, H-1'), 4.79 [s, 2H (1 dia), H-1'), 5.23 [dd, 1H (1 dia), J=3Hz,

J=8Hz, H-4], 5.28 [dd, 1H (1 dia), J=3.5Hz, J=7.5Hz, H-4], 6.13 [d, 1H (1 dia), J=7.5Hz, H-5], 6.29 [d, 1H (1 dia), J=8Hz, H-5], 7.15, 7.36, 7.44 [AA'BB', 4H, H arom.).

2) Desulfurization of compound 15 to 16.

To a solution of the diacetate **15** (114 mg, 0.228 mmol.) in EtOH (20 mL) was added Raney Nickel at room temperature. The reaction was monitored by TLC. The mixture was then filtrated on celite, the solvent evaporated and the product purified by chromatography on silica gel (EtOAc/hexane : 3/7). Yield : 55 mg (64%), Rf=0.51 (EtOAc/hexane : 1/1) ; $[\alpha]_D$ + 3 (c=1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ : 1.45 (s, 9H, tBu), 2.05 and 2.10 (2s, $OCOCH_3$), 2.51 (AB of ABX, 2H, J_{AB}=16Hz, J_{AX}=7Hz, J_{BX}=6Hz, Δν=14Hz, H-2), 3.38 (s, 3H, Ome), 3.50-3.80 (m, 4H, H-2', H-3'), 4.21 (td, 1H, J_t=6.5Hz, J_d=4H, H-3), 4.26 (AB of ABX, 2H, J_{AB}=12Hz, J_{AX}=4Hz, J_{BX}=7Hz, Δν=39Hz, H-5), 4.79 (AB, 2H, J_{AB}=7Hz, Δν=12Hz, H-1'), 5.28 (td, 1H, J_t=4Hz, J_d=7Hz, H-4). ^{13}C NMR ($CDCl_3$) : δ : 20.77 and 20.89 ($OCOCH_3$), 28.01 [$(CH_3)_3CO$], 37.39 (C-2), 59.04 (C-4'), 62.64 (C-5), 67.69 and 71.63 (C-2', C-3'), 71.40 and 73.46 (C-3, C-4), 81.21 (Me_3CO), 96.02 (C-1'), 169.68, 170.07 and 170.64 (C-1, C-6, C-8). Anal. Calcd for $C_{17}H_{30}O_9$: C, 53.94 ; H, 7.99. Found : C, 54.13 ; H, 8.08.

(+)-[3(S), 4(S)]-t-butyl 3-(2-methoxyethoxymethoxy)-4.5-(isopropylidenedioxy) pentanoate, 17.

To as solution of the diacetate **16** (50 mg, 0.132 mmol.) in THF (20 mL) at -78°C was added a 1M solution of DIBAL in toluene (0.53 mL, 0.53 mmol). After stirring 1h at -78°C, the temperature was revised to 0°C and after 15 min., the reaction mixture was cooled at -78°C and hydrolyzed with sat. sodium tartrate (20 mL), diluted with EtOAc (30 mL) and stirred vigorously untill phases separation. After extraction with EtOAc (2x20 mL), the organic phases were washed with sat. NaCl and dried ($MgSO_4$). After evaporating the solvent, the residue was dissolved in acetone (20 mL) and at 0°C were added 2.2-dimethoxypropane (0.033 mL, 0.264 mmol.) and a catalytic amount of PPTS. After stirring 24h at room temperature, acetone was evaporated, the residue dissolved in ether (40 mL), washed with sat. NH_4Cl and dried ($MgSO_4$). The product was purified by silica gel chromatography (EtOAc/hexane : 1/4). Yield : 25 mg (57%), Rf 0.25 (EtOAc/hexane : 1/3), $[\alpha]_D$ +6 (c=0.8, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) : δ : 1.34 and 1.43 [s, 6H, $(CH_3)_2C$], 1.45 (s, 9H, tBu), 2.47 (AB of ABX, 2H, J_{AB}=16Hz, J_{AX}=4.5Hz, J_{BX}=7.5Hz, Δν=22Hz, H-2), 3.39 (s, 3H, OCH_3), 3.50-3.70 (m, 4H, H-2', H-3'), 3.91 (AB of ABX, 2H, J_{AB}=8.5Hz, J_{AX}=7Hz, J_{BX}=6.5Hz, Δν=41Hz, H-5), 4.20 (m, 1H, H-3), 4.34 (td, 1H, J_t=6.5Hz, J_d=6Hz, H-4), 4.83 (AB, 2H, J_{AB}=7Hz, Δν=10Hz, H-1'). ^{13}C NMR ($CDCl_3$) : δ : 24.95 and 26.31 [$(\underline{C}H_3)_2C$], 28.07 [$(\underline{C}H_3)_3CO$], 37.15 (C-2), 59.03 (C-4'), 65.33 (C-5), 67.26 and 71.67 (C-2', C-3'), 75.33 and 76.48 (C-3, C-4), 80.79 ($Me_3\underline{C}O$), 95.98 (C-1'), 170.36 (C-1).

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3) The hydroxyl group of **1** has also been successfully protected by different silyl groups (TBDMS: 89% yield; TBDPS: 93% yield). The protection of the alcohol as the corresponding benzyl ether could not be achieved in a satisfactory manner (yields < 25%).

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