Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 559-576, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00040-2

Asymmetric synthesis of (-)- (2E, 4R, 5S, 11R)- Cladospolide A, induced by chiral sulfoxides.

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Abstract: an enantioselective synthesis of (-)-cladospolide in which all the chiral centers are created by asymmetric reduction of β-ketosulfoxides, is reported.

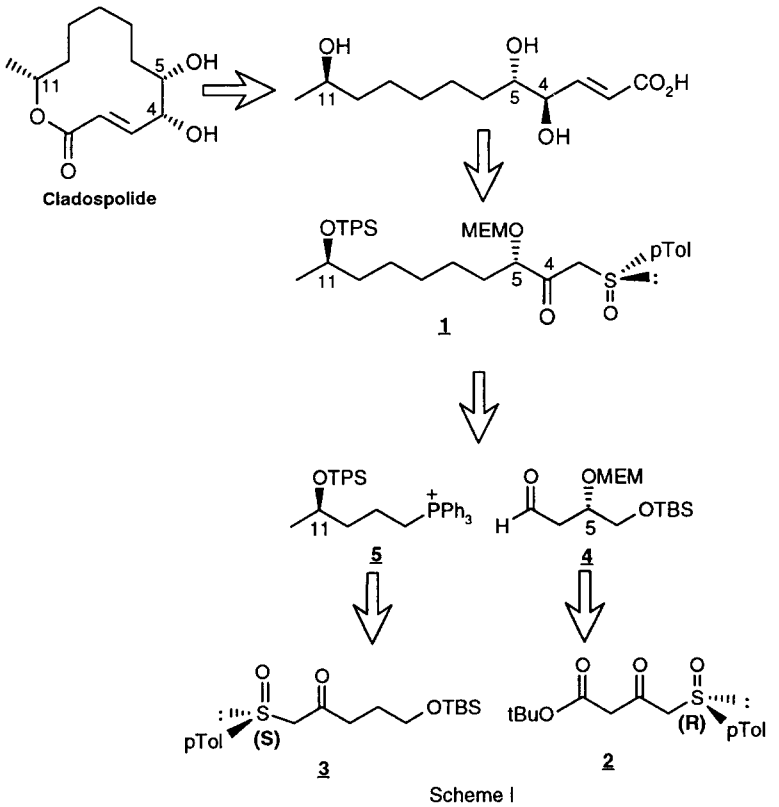
Cladospolide A, a 12-membered lactone, produced by *Cladosporium cladosporioides FI-113*[1,2] is a root-growth inhibitor of lettuce seedlings. Its structure and stereochemistry, [(2E, 4R, 5S, 11R)-4,5-dihydroxy-2-dodecen-11-olide], were elucidated by Hirota[1-4] from spectroscopic studies and X-ray analysis. Only one total synthesis of this natural product has been reported by Mori[5] from ethyl (R)-3-hydroxybutyrate, the 1,2-diol being prepared *via* a Sharpless epoxidation.

In this paper we report an enantioselective total synthesis of (-) Cladospolide-A based on chiral sulfoxide asymmetric induction. As shown in the retrosynthetic scheme I, all the hydroxylic centers of the target have been created by reduction of β-ketosulfoxides, a highly efficient diastereoselective reaction[6].

The synthesis of the (R) β-ketosulfoxide **2** and its transformation to the (S) enantiomer of the hydroxyester **6** was already reported in connection with our synthesis of 2-deoxy sugar derivatives[7]. Protection of the primary alcohol with a t-butyldimethylsilyl group (TBS) (Scheme II) and reduction of the ester to the corresponding aldehyde afforded the compound **4** in 76% overall yield.

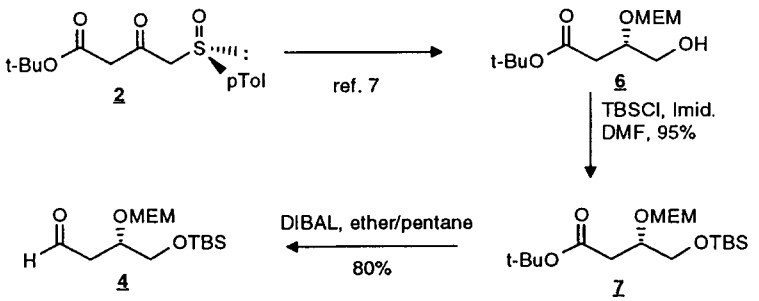
The chiral phosphonium salt **5** was prepared from γ-butyrolactone which was opened in refluxing methanol in presence of a catalytic amount of sulfuric acid. The resulting alcohol was protected with TBS. Then the anion of (-)(S) methyl p-tolylsulfoxide was then condensed with the

ester group to give (+) β-ketosulfoxide **3** in high yield. Reduction with $ZnCl_2$/DIBAL afforded the corresponding [2S, S(S)]-β-hydroxysulfoxide **8**. The diastereoselectivity was higher than 95%.



Scheme I

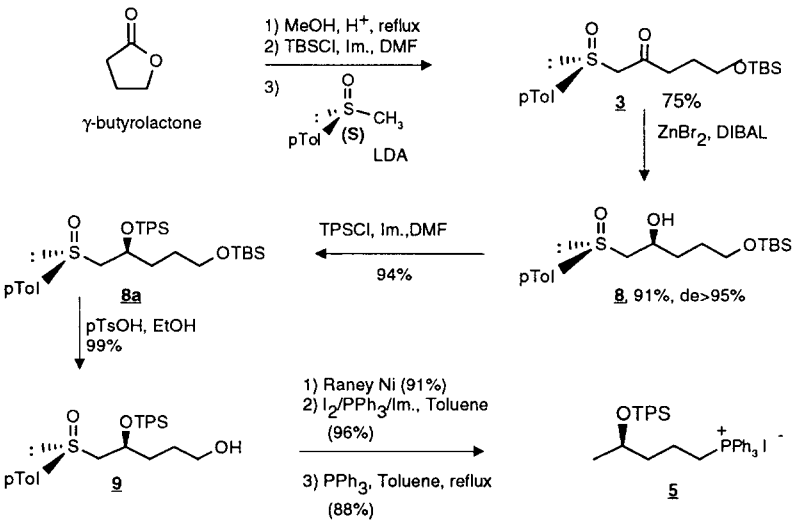
Only one diastereomer was detected by ^1H NMR from the signal of the methylene group α to sulfur.



Scheme II

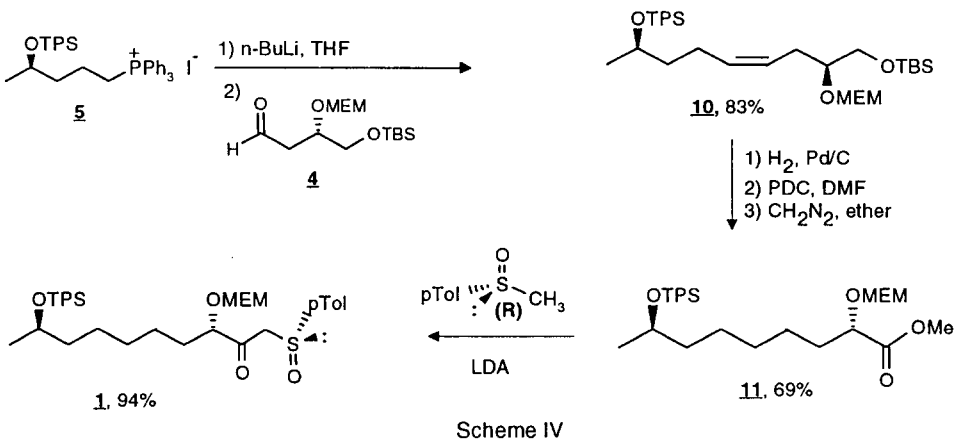
The absolute configuration (2S) was assumed from our preceeding studies and will be confirmed in the final product. Finally (scheme III) compound **8** was transformed into the phosphonium salt **5** by

protection of the alcohol with a t-butyldiphenylsilyl group (TPS), acidic deprotection of the primary alcohol, desulfurization with Raney Ni, substitution of the OH group with an iodide and finally reaction with triphenyl phosphine. All these steps were carried out in very high yields.



Scheme III

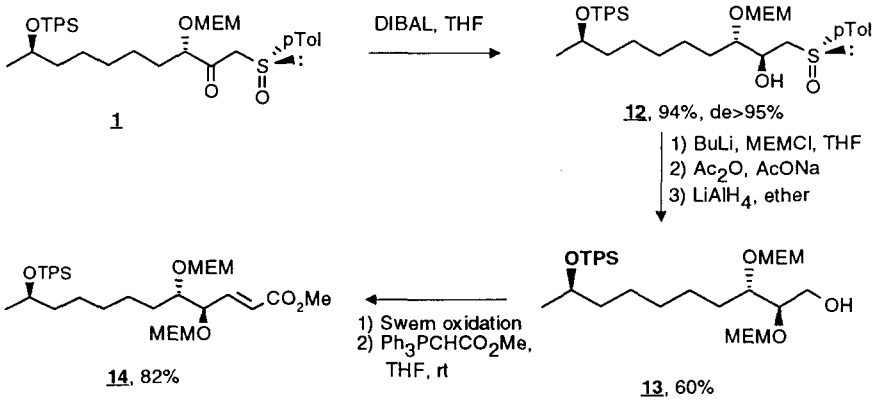
Condensation of aldehyde **4** with the ylide derived from the phosphonium salt **5** afforded in 83% yield mainly the (Z) isomer **10** (E/Z = 9/1).



Scheme IV

The (E) and (Z) isomers of **10** were identified by ^{1}H NMR from decoupling experiments showing a 10.5 Hz coupling constant between the vinylic protons in the main isomer and 18Hz in the minor

isomer. Hydrogenation of the double bond over Pd/C (scheme IV) followed by oxidative deprotection[8] of the TBS group with an excess of PDC in DMF and esterification with diazomethane afforded the α- alkoxyester **11** in 69% overall yield. Condensation of **11** with (+)(R) methyl p-tolyl sulfoxide gave the γ-alkoxy-β-ketosulfoxide **1**, in 94% yield and a d.e > 95% (determined by comparison of the ^{1}H and ^{13}C NMR spectra with those of the diastereomer obtained from (-)(S) methyl p-tolyl sulfoxide).



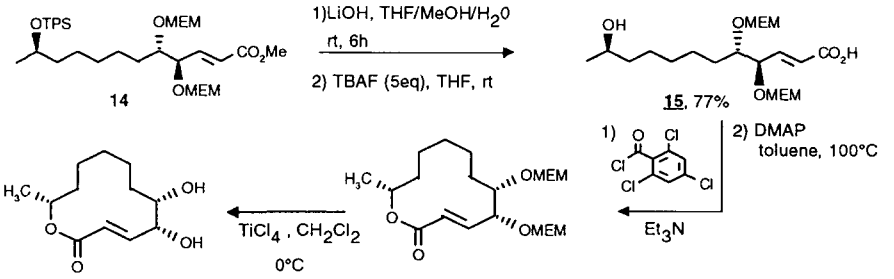
Scheme V

As expected from our results in the reduction of γ-alkoxy-β-ketosulfoxides[7,9], the reduction of **1** with DIBAL at -78°C afforded only the (2S)-hydroxysulfoxide **12** (d.e > 95%, only one diastereomer was detected by NMR, the absolute configuration deduced from our preceeding studies will be confirmed in the final product.)

The OH group of **12** (scheme V) was protected with a MEM group, the best yield being obtained by using n-BuLi as a base. Other reaction conditions gave degradation products. Pummerer rearrangement in refluxing acetic anhydride followed by $LiAlH_4$ reduction of the intermediate afforded the alcohol **13** in 60% overall yield. Swern oxidation and Wittig condensation of the commercially available triphenylphosphonoacetate gave the seco-ester **14** in 82% yield.

Finally (scheme VI) deprotection of the C-11 alcohol with TBAF and ester hydrolysis led to the seco-acid **15** in 77% yield. The lactonization was carried out following the Yamaguchi[10] methodology based on a mixed anhydride between **15** and 2,4,6-trichlorobenzoyl chloride. The lactone, obtained in 65% yield, was then treated with $TiCl_4$ to remove the MEM group to give (-)-cladospolide A showing spectroscopic and physical data identical to those of the litterature [2-5].

In conclusion it must pointed out that the methodology described in this paper to obtain natural (-) cladospolide could be used to prepare any other stereoisomer only by changing the β-ketosulfoxide reduction step conditions which allows to obtain any of the two possible configurations of the β-hydroxysulfoxide either by using DIBAL or $ZnCl_2$/DIBAL or by using only DIBAL and changing the sulfoxide configuration.



Scheme VI

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

Experimental Part.

(-)-[3(S)] t-Butyl 3-(2-methoxyethoxymethoxy)-4-(t-butyldimethylsilyloxy)butyrate , 7.

To a magnetically stirred solution of the hydroxy-ester **6**[7] (2.13 g, 8.07 mmol) in dry DMF (30 mL) was added imidazole (1.65 g, 24.2 mmol) and t-butyldimethylsilyl chloride (1.83 g, 12.1 mmol). After 15 hours at room temperature, the mixture was diluted with ether (100 mL) and water (40 mL) was added. The mixture was stirred until a clear phase-separation occured and extracted with ether (2 x 50 mL). The combined organic extracts were washed with saturated NH_4Cl (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and solvent evaporated. Silica gel chromatography of the residue (AcOEt/hexane = 1/5) gave the ester as a colourless oil (2.9 g, 95%) : Rf 0.54 (AcOEt/hexane=1/3); $[\alpha]_D$ = -3(c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 0.04 (s, 6H, MeSi), 0.87 (s, 9H, t-BuSi), 1.44 (s, 9H, t-BuO), 2.50 (ddd, AB of ABX, J_{AB} = 15Hz, J_{AX} = 5Hz, J_{BX} = 7.5Hz, Δν = 28Hz), 3.37 (s, 3H, OMe), 3.5-3.76 (m, 4H, H-2'+ H-3'), 4.02 (m, X of ABX, 1H, H-3), 4.79 (s, 2H, H-1'); ^{13}C NMR ($CDCl_3$): δ: -5.47 (MeSi), 18.24 (Me_3C-Si), 25.84 ($(CH_3)_3CSi$), 28.05 ($(CH_3)_3CO$); 38.51 (C-2), 58.96 (OMe), 64.87 (C-4), 66.88 and 71.68 (C-2'+C-3'), 75.5 (C-3), 80.40 (Me_3CO), 95.44 (C-1'), 170.75 (C-1);

IR ($CHCl_3$) 2970, 1720 cm^{-1}. Anal. Calcd for $C_{18}H_{38}O_6Si$: C, 57.11; H, 10.12. Found : C, 57.30; H, 10.23.

(-)-(S)-3-(2-methoxyethoxymethoxy)-4-(t-butyldimethylsilyloxy)-butanal, 4. To a cold (-78°C) solution of ester **7** (1.7 g, 4.54 mmol) in ether (5 mL) and pentane (45 mL), was dropwise added a 1M solution of DIBAL in toluene (4.8 mmol). After 1 hour at -78°C, the mixture was diluted with AcOEt (50 mL) and subsequently treated with methanol (0.1 mL) and a saturated sodium tartrate solution (30 mL). The mixture was stirred at room temperature until a clear phase-separation occured and extracted with AcOEt (30 mL). The combined organic layers were washed with brine prior to drying ($MgSO_4$) and solvent evaporation. The residue was column chromatographied on silica gel (ether/hexane : 1/1) to provide **(S)-4** as a colourless oil (1.1 g, 80%) : Rf 0.36 (AcOEt/hexane = 1/2) ; $[\alpha]_D$ = -28 (c 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$,, 200 MHz): δ: 0.03 (s, 6H, MeSi), 0.86 (s, 9H, t-Bu), 2.62 (m, 2H, H-2), 3.36 (s, 3H, OMe), 3.5-3.7 (m, 6H, H-4, H-2', H-3'), 4.16 (qn, 1H, H-3, J=5.5Hz), 4.77 (dd, AB, 2H, H-5, J_{AB} = 7.2Hz, Δν = 9Hz), 9.77 (t, 1H, H-1, J=2Hz) ; ^{13}C NMR ($CDCl_3$): δ: -5.56 (MeSi), 18.17 (Me_3CSi), 25.76 ($(CH_3)_3CSi$), 46.32 (C-2), 58.96 (OMe), 64.81 (C-4), 67.08 and 71.60 (C-2, C-3'), 76.38 (C-3), 95.13 (C-1'), 200.94 (C-1); IR ($CHCl_3$) 2920, 1720 cm^{-1}. Anal. Calcd for $C_{14}H_{30}O_5Si$: C, 54.87 ; H, 9.87. Found : C, 54.76; H, 9.84.

(-)-(S)-1-(p-tolylsulfinyl)-5-(t-butyldimethylsilyloxy)-2-pentanone, 3.

1). A solution of γ-butyrolactone (5 g, 58.14 mmol) in methanol (40 mL) containing a catalytical amount of sulfuric acid (5 drops) was refluxed for 12 hours. After cooling to room temperature, imidazole (0.2 g) was added and the mixture stirred for 10 min. After methanol evaporation, the residue was dissolved in dry DMF (30 mL) and treated with imidazole (9.9 g, 145.35 mmol) and t-butyldimethylsilyl chloride (13.14 g, 87.2 mmol). The mixture was stirred for 6 hours at room temperature before diluting with ether (50 mL) and water (50 mL). The mixture was stirred until a clear phase-separation occured and extracted with ether (50 mL). The combined organic layers were washed with a saturated NH_4Cl solution (4 x 30 mL) and brine (30 mL) prior to drying ($MgSO_4$) and solvent evaporation. The residue was column chromatographied on silica gel (AcOEt/hexane : 1/19) to give methyl 4-(t-butyldimethylsilyloxy)-butanoate as a pale yellow oil (10.8 g, 80%) : Rf 0.31 (AcOEt/hexane = 1/19); ^1H NMR ($CDCl_3$, 200 MHz): δ: 0.02 (s, 6H, MeSi), 0.87 (s, 9H, t-BuSi), 1.81 (qn, 2H, H-3, J = 6.5Hz), 2.38 (t, 2H, H-2, J = 7.5Hz), 3.62 (t, 2H, H-4, J = 6.5Hz), 3.65 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ: -5.50 (MeSi), 18.21 (Me_3CSi), 25.82 ($(CH_3)_3CSi$), 27.85 and 30.39 (C-2, C-3), 51.34 (OMe), 61.90 (C-4), 174.00 (C-1); IR ($CHCl_3$) 2940, 1730 cm^{-1}. Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85 ; H, 10.41. Found : C, 57.03; H, 10.38.

2) To a cold (-78°C) solution of LDA (26.36 mmol) in THF (30 mL) was added a solution of (-)(S)-methyl p-tolylsulfoxide (4.06 g, 26.36 mmol) in THF (20 mL). After stirring for 1 hour at -78°C, the anion solution was dropwise added to a cold (-78°C) solution of the preceding ester (2.9 g, 12.55 mmol) in THF (40 mL) and stirred for 1 hour at -78°C. The reaction mixture was then diluted with ether (30 mL), hydrolyzed with a saturated NH_4Cl solution (30 mL) and washed with brine (30 mL). After drying ($MgSO_4$) and solvent evaporation, a silica gel chromatography (ether/hexane : 3/1) of the residue provided the β-ketosulfoxide **(S)-3** as a pale yellow oil (4.15 g, 93%), $[\alpha]_D$ = -134 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 200MHz): δ: 0.01 (s, 6H, MeSi), 0.83 (s, 9H, t-Bu), 1.71 (tt, 2H, H-4, J = 6Hz; J = 7Hz), 2.38 (s, 3H, Me-ptol), 2.51 (td, 2H, H-3, Jt = 7Hz, Jd = 2Hz), 3.53 (t, 2H, H-5, J = 6Hz), 3.80 (dd, AB, 2H, H-1, J_{AB} = 13.5Hz, Δν = 22Hz), 7.29 and 7.50 (d, AA'BB', 4H, H arom, J = 8Hz); ^{13}C NMR ($CDCl_3$): δ: -5.48 (MeSi), 18.18 (Me_3CSi), 21.36 (Me-ptol), 25.82 ($(CH_3)_3CSi$), 26.27 (C-4), 41.39 (C-3), 61.71 (C-5), 68.17 (C-1), 123.98 and 130.02 (CH arom), 139.75 et 142.02 (Cq arom), 201.5 (C-2); IR ($CHCl_3$) 2920, 1700, 1080 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_3SSi$: C, 60.97; H, 8.53. Found : C, 60.89; H, 8.69.

(-)-[2(S), S(S)]-1-(p-tolylsulfinyl)-5-(t-butyldimethylsilyloxy)-2-pentanol, 8.

A solution of the β-ketosulfoxide **(S)-3** (2.41 g, 6.8 mmol) in THF (70 mL) was added to dried zinc bromide (1.6 g, 7.14 mmol) and the mixture stirred for 30 min. at room temperature and another 30 min. at -78°C. At -78°C, a 1M solution of DIBAL in toluene (7.14 mmol) was dropwise added. 30 min. after the addition, the reaction mixture was diluted with AcOEt (30 mL), hydrolyzed with a saturated sodium tartrate solution (30 mL) and stirred until a clear phase-separation occured. Extraction with AcOEt (2 x 30 mL) was followed by washing of the combined organic layers with brine, drying ($MgSO_4$) and solvent evaporation. The crude product was purified by silica gel chromatography (AcOEt/hexane : 1/2) to give the β-hydroxysulfoxide **8** as a white solid (2.18 g, 91%) : mp 64-65°C ; $[\alpha]_D$ = -110 (c 1, $CHCl_3$), de > 95% (only one diastereomer observed by ^1H NMR); ^1H NMR (C_6D_6, 200 MHz): δ: 0.05 (s, 6H, MeSi), 0.98 (s, 9H, t-BuSi), 1.55 (m, 4H, H-3, H-4), 1.95 (s, 3H, Me ptol), 2.50 (ddd, AB of ABX, 2H, H-1, J_{AB} = 12.5Hz, J_{AX} = 9Hz. J_{BX} = 2.5Hz, Δν = 91Hz), 3.53 (m, 2H, H-5), 4.28 (m, 1H, H-2), 4.58 (d, 1H, OH, J=2Hz), 6.84 and 7.34 (d, AA'BB', 4H, H arom, J = 8Hz); ^{13}C NMR ($CDCl_3$): δ: -5.41 (MeSi), 18.26 (Me_3CSi), 21.40 (Me ptol), 25.88 ($(CH_3)_3CSi$), 28.62 and 34.34 (C-3, C-4), 63.07 (C-1, C-5), 68.14 (C-2), 124.06 and 130.03 (CH arom), 140.65 and 141.79 (Cq arom); IR ($CHCl_3$) : 3500-3200; 2920; 1080 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_3SSi$: C, 60.63; H, 9.05; Found : C, 60.43; H, 8.83.

(-)[2(S),S(S)]-1-(p-tolylsulfinyl)-2-(t-butyldiphenylsilyloxy)-5-(t-butyldimethylsilyloxy)-pentane, 8a.

A solution of the hydroxy-sulfoxide **8** (1.84 g, 5.16 mmol) in dry DMF (15 mL) was treated with imidazole (1.05 g, 15.48 mmol) and t-butyldiphenylsilyl chloride (1.98 mL, 7.74 mmol) and stirred at room temperature for 16 hours. The reaction mixture was then diluted with ether (50 mL), water (30 mL) and stirred until a clear phase-separation occured. After extracting with ether (30 mL), the combined organic layers were washed with a saturated NH_4Cl solution (3 x 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated. Chromatography on silica gel of the residue (ether/hexane : 1/2) gave 2.88 g (94%) of **8a** as a pale yellow oil : *Rf* 0.46 (AcOEt/hexane = 1/3); $[\alpha]_D$ = -72 (c 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 0.01 and 0.02 (s, 6H, MeSi), 0.85 (s, 9H, t-Bu -TBS), 1.07 (s, 9H, t-Bu-TPS), 1.40-1.85 (m, 4H, H-3, H-4), 2.37 (s, 3H, Me ptol), 2.89 (ddd, AB of ABX, 2H, H-1, J_{AB} = 13Hz, J_{AX} = 5Hz, J_{BX} = 6Hz, Δν = 53Hz), 3.44 (m, 2H, H-5), 4.05 (qn, 1H, H-2, J=5.5Hz), 7.25-7.45 (m, 10H, H arom), 7.60-7.69 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ: -5.33 (MeSi), 18.27 and 19.33 (Me_3CSi), 21.35 (Me ptol), 25.94 and 27.01 ($(CH_3)_3CSi$), 28.02 and 32.88 (C-2, C-3), 62.81 and 64.57 (C-1, C-5), 69.03 (C-2), 124.13, 127.62, 127.72, 129.81, 135.87, 135.99 (CH arom), 133.65, 133.69, 141.26, 141.38 (Cq arom); IR ($CHCl_3$) 2920, 1100 cm^{-1}. Anal. Calcd for $C_{34}H_{50}O_3SSi_2$: C, 68.63; H, 8.47. Found : C, 68.41; H, 8.37.

(-)-[4(S), S(S)]-4-(t-butyldiphenylsilyloxy)-5-(p-tolylsulfinyl)-1-pentanol, 9.

A solution of the sulfoxide **8a** (1.62 g, 2.76 mmol) in ethanol (50 mL) containing a catalytic amount of p-toluenesulfonic acid (20 mg) was stirred at room temperature until no more starting material was detected by TLC (ether/hexane : 1/1). After evaporating the solvent, the residue was dissolved in ether (50 mL), washed with a saturated $NaHCO_3$ solution (30 mL), with brine (30 mL) and dried ($MgSO_4$). The crude product, obtained after evaporation of the solvent, was purified by silica gel chromatography (ether) to provide 1.3 g (99%) of the alcohol **9** as a pale yellow oil : *Rf* 0.26 (ether); $[\alpha]_D$ = -102 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 1.08 (s, 9H, t-BuSi), 1.50-2.00 (m, 5H, H-2, H-3, OH), 2.38 (s, 3H, Me ptol), 2.90 (ddd, AB of ABX, 2H, H-5, J_{AB} = 13.5Hz, J_{AX} = 4Hz, J_{BX} = 6.5Hz, Δν = 43Hz), 3.47 (t, 2H, H-1, J = 6Hz), 4.09 (m, 1H, H-4), 7.21-7.46 (m, 10H, H arom), 7.60-7.67 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ: 19.28 (Me_3CSi), 21.35 (Me ptol), 26.95 ($(CH_3)_3CSi$), 27.77 and 32.62 (C-2, C-3), 62.20 and 63.66 (C-1, C-5), 68.93 (C-4), 124.00, 127.66, 127.74, 129.85, 135.83, 135.93 (C-H arom), 133.37 and 133.52 (Cq arom. Phe); 140.73 and 141.31

(Cq arom ptol); IR ($CHCl_3$) 3650, 3480, 2920, 1100 cm^{-1}. Anal. Calcd for $C_{28}H_{36}O_3SSi$: C, 69.96; H, 7.55. found : C, 69.75; H, 7.58.

(+)-(R)-[4-(t-butyldiphenylsilyloxy)-pentanyl]-phosphonium iodide, 5.

1). A solution of sulfoxide **9** (3.5 g, 7.29 mmol) in ethanol was treated with Raney Nickel until no more starting material was detected by TLC (ether/hexane : 1/1). The catalyst was filtered on celite, the solvent evaporated and the crude product purified by silica gel chromatography (ether/pentane : 2/3) to provide **(+)-(R)-4-(t-butyldiphenylsilyloxy)-1-pentanol** (2.235 g, 91%) as a colourless oil : *Rf* 0.44 (ether/hexane = 1/1); $[\alpha]_D$ = + 7 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3/D_2O$, 200 MHz): δ: 1.06 (s, 9H, t-Bu), 1.08 (d, 3H, H-5, J = 6Hz), 1.56 (m, 4H, H-2, H-3), 3.55 (t, 2H, H-1, J = 6Hz), 3.91 (sext, 1H, H-4; J = 6Hz), 7.33-7.44 (m, 6H; H arom), 7.67-7.72 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ: 19.22 (Me_3CSi), 22.89 (Me ptol), 27.01 ($(CH_3)_3CSi$), 28.18 and 35.51 (C-2, C-3), 62.97 (C-1), 69.25 (C-4), 127.43, 127.53, 129.49, 129.57, 134.58, 135.86 (C-H arom), 134.25 and 134.58 (Cq arom); IR ($CHCl_3$) 3500-3200, 2940 cm^{-1}. Anal. Calcd for $C_{21}H_{30}O_2Si$: C, 73.63; H, 8.83. Found : C, 73.90; H, 8.72.

2) A solution of the preceding alcohol (2.2 g, 6.48 mmol) in toluene (60 mL) was treated with triphenylphosphine (6.8 g, 25.92 mmol), imidazole (1.7 g, 25.92 mmol), iodine (4.93 g, 19.44 mmol) and stirred at room temperature until no more starting material was detected by TLC (ether/hexane : 1/1). A saturated $NaHCO_3$ (50 mL) was added and the mixture stirred for 10 min. To the resulting mixture was added iodine in small portions until a persistent red-coloured organic layer was obtained. Stirring was continued for another 10 min. After addition of a sodium thiosulfate solution (30 mL), the mixture was extracted with toluene (2 x 30 mL) and the combined organic layers washed with brine prior to drying ($MgSO_4$) and solvent evaporation. Silica gel chromatography of the residue (hexane) provided **(+)-(R)-1-iodo-4-(t-butyldiphenylsilyloxy)-pentane** as a pale-yellow oil (2.8 g, 96%) : Rf 0.36 (hexane); $[\alpha]_D$ = + 16 (c 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 1.06 (s, 9H, t-Bu), 1.08 (d, 3H, H-5, J = 6Hz), 1.55 and 1.87 (m, 4H, H-2, H-3), 3.09 (t, 2H, H-1, J = 7Hz), 3.87 (sext, 1H, H-4, J = 6Hz), 7.34-7.44 (m, 6H, H arom), 7.66-7.71 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ: 7.23 (C-1), 19.29 (Me_3CSi), 23.30 (Me ptol), 27.07 ($(CH_3)_3CSi$), 29.33 (C-2), 40.14 (C-3), 68.51, (C-4), 127.47, 127.61, 129.52, 129.62, 135.87, 135.89 (C-H arom), 134.24 and 134.64 (Cq arom). Anal. Calcd for $C_{21}H_{29}IOSi$: C, 55.75; H, 6.46. Found : C, 55.79; H, 6.57.

3) A solution of the preceding iodide (0.85 g, 1.9 mmol) and triphenylphosphine (1.99 g, 7.6 mmol) in dry toluene (5 mL) was refluxed for 24 hours. After evaporating the solvent, **(+)-(R)-[4-(t-butyldiphenylsilyloxy)-pentanyl]-phosphonium iodide 5** was obtained as a white solid by

precipitation in dry ether, filtration and washing with ether (1.18 g, 88%) : mp 164-165°C ; $[\alpha]_D$ = + 5 (*c* 1. 5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 0.90 (s, 9H, t-Bu), 1.06 (d, 3H, H-5, J=6Hz), 1.55 and 1.84 (m, 4H, H-2, H-4), 3.58 (m, 2H, H-1), 3.89 (m, 1H, H-4), 7.23-7.83 (m, 25H, H arom); ^{13}C NMR ($CDCl_3$): δ: 18.88 (d, C-1, $^1J_{C-P}$ = 46Hz), 19.12 (Me_3CSi), 22.44 (C-2), 23.41 (C-5), 26.81 ($(CH_3)_3CSi$), 39.67 (d, C-3, $^3J_{C-P}$ = 16Hz), 68.85 (C-4), 117.85 (d, P-Carom, $^1J_{C-P}$ = 85Hz), 127.32, 127.47, 129.43, 129.46, 135.52, 135.59 (C-H arom Ph_2Si), 133.89 and 133.99 (Cq arom Ph_2Si), 130.38 (d, P-C_{ortho}, $^2J_{C-P}$ = 13Hz), 133.47 (d, P-C_{meta}, $^3J_{C-P}$ = 10Hz), 134.94 (C_{para}, $P(Ph)_3$). Anal. Calcd for $C_{39}H_{44}IOPSi$: C, 65.54; H, 6.21. Found : C, 65.73; H, 6.08.

(+)-[2(S),8(R)]-1-(t-butyldimethylsilyloxy)-2-(2-methoxyethoxymethoxy)-8-(t-butyldiphenylsilyloxy)-4-nonene, 10.

To a cold (0°C) solution of dry phosphonium salt **(R)-5** (0.55 g, 0.77 mmol) in THF (10 mL) is dropwise added a 1.47 M solution of butyllithium in hexane (0.525 mL, 0.77 mL). After stirring for 1 hour at 0°C, a solution of aldehyde **(S)-4** (192 mg, 0.627 mmol) in THF (5 mL) was dropwise added and the resulting mixture stirred for 30 min. at 0°C. Silica gel was then added, after stirring for 10 min., the solvent evaporated and the crude compound purified by silica gel chromatography (AcOEt/hexane : 1/9) to give the olefinic adduct **10** as a pale yellow oil (0.32 g, 83%) : *Rf* 0.76 (AcOEt/hexane = 1/2); $[\alpha]_D$ = + 7 (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 0.05 (s, 6H, MeSi), 0.89 (s, 9H, t-BuSiMe_2), 1.06 (s, 9H, t-BuSiPh_2), 1.06 (d, 3H, H-9, J = 6Hz), 1.50 (m, 2H, H-7), 2.06 and 2.24 (m, 4H, H-3, H-6), 3.39 (s, 3H, OMe), 3.50-3.87 (m, 8H, OCH_2CH_2O, H-1, H-2, H-8), 4.79 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 13Hz), 5.35 (m, 2H, H-4, H-5), 7.34-7.43 (m, 6H, H arom), 7.67-7.71 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ: -5.42 and -5.39 (MeSi), 18.26 and 19.23 (Me_3CSi), 23.06 (Cq), 23.26 and 29.43 (C-3, C-6), 25.89 and 27.01 ($(CH_3)_3CSi$), 39.21 (C-7), 58.78 (OMe), 65.36 (C-1), 66.72 and 71.75 (OCH_2CH_2O), 69.24 (C-8), 77.78 (C-2), 94.89 (OCH_2O), 125.20 and 131.64 (C-4, C-5), 127.38, 127.47, 129.38, 129.45, 135.84 (C-H arom), 134.44 and 134.79 (Cq arom); IR ($CHCl_3$) 2920, 1450 cm^{-1}. Anal. Calcd for $C_{35}H_{58}O_5Si_2$: C, 68.35, H, 9.51. Found : 68.37; H, 9.50.

(-)-[2(S), 8(R)] methyl 2-(2-methoxyethoxymethoxy)-8-(t-butyldiphenylsilyloxy)-nonanoate, 11.

1) A solution of the olefinic compound **10** (0.37 g, 0.6 mmol) and 10% Pd/C (40 mg) in AcOEt (20 mL), under hydrogen atmosphere (5 atm), was stirred at room temperature for 16 hours. The catalyst was then removed by filtration over celite, washed with AcOEt and the solvent evaporated. The resulting colourless oil, **(-)-[2(S), 8(R)]-1-(t-butyldimethylsilyloxy)-2-(2-methoxyethoxymethoxy)-**

8-(t-butyldiphenylsilyloxy)-nonane was pure enough to be used in the next sequence without further purification (354 mg, 96%). An analytical sample was obtained by chromatography : *Rf* 0.76 (AcOEt/hexane = 1/4); $[\alpha]_D$ = -5 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 0.06 (s, 6H, MeSi), 0.90 (s, 9H, Me_3CSiMe_2), 1.04 (s, 9H, Me_3CSiPh_2), 1.05 (d, 3H, H-9, J = 6Hz), 1.22-1.48 (m, 10H, H-3, H-4, H-5, H-6, H-7), 3.39 (s, 3H, OMe), 3.53-3.85 (m, 8H, OCH_2CH_2O, H-1, H-2, H-8), 4.81 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 22Hz), 7.32-7.43 (m, 6H, Harom), 7.66-7.71 (m, 4H, Harom); ^{13}C NMR ($CDCl_3$): δ: -5.38 (MeSi), 18.29 and 19.28 (Me_3CSi), 23.21 (C-9), 25.92 and 27.04 ($(CH_3)_3CSi$), 25.17, 25.36, 29.82, 31.64 , 39.41 (C-3, C-4, C-5, C-6, C-7), 59.00 (OMe), 65.78 (C-1), 66.86 and 71.79 (OCH_2CH_2O), 69.55 (C-8), 78.21 (C-2), 95.15 (OCH_2O), 127.36, 127.44, 129.35, 129.42, 135.87 (C-H arom), 134.61 and 134.95 (Cq arom); IR ($CHCl_3$): 2920, 1450 cm^{-1}. Anal. Calcd. for $C_{35}H_{60}O_5Si_2$: C, 68.13; H, 9.80. Found : C, 68.29; H, 9.96.

2) A solution of the preceding compound (321 mg, 0.52 mmol) and PDC (1.45 g, 3.65 mmol) in dry DMF (15mL) was stirred at room temperature for 48 hours. The reaction mixture was then diluted with ether (20 mL), water (30 mL) and stirred another 10 min. The aqueous layer was saturated with NaCl and extracted with ether (3 x 20 mL). The combined organic layers were subsequently dried ($MgSO_4$), the solvent evaporated, the residue dissolved in ether and cooled (0°C). An etheral solution of diazomethane was then dropwise added until no more starting material was detected on TLC (AcOEt). Silica gel chromatography (AcOEt/hexane : 1/3) of the crude product gave 198 mg (72%) of **11** as a pale yellow oil : *Rf* 0.42 (AcOEt/hexane = 1/2); $[\alpha]_D$ = -10 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 1.06 (d, 3H, H-9, J = 6Hz), 1.06 (s, 9H, t-Bu), 1.22-1.51 (m, 8H, H-4, H-5, H-6, H-7), 1.68 (m, 2H, H-3), 3.38 (s, 3H, OMe), 3.53 and 3.75 (m, 4H, OCH_2CH_2O), 3.74 (s, 3H, CO_2Me, 3.81 (sext, 1H, H-8, J = 6Hz), 4.14 (t, 1H, H-2, J = 6Hz), 4.78 (s, 2H, OCH_2O), 7.32-7.46 (m, 6H, Harom), 7.66-7.71 (m, 4H, H arom); ^{13}C NMR ($CDCl_3$): δ: 19.25 (MeCSi), 23.20 (C-9), 24.99, 25.11, 29.28, 32.76, 39.32 (C-3, C-4, C-5 C-6, C-7), 51.82 (CO_2Me), 59.00 (OMe), 67.46 and71.64 (OCH_2CH_2O), 69.47 (C-2), 69.47 and 75.64 (C-2, C-8), 95.17 (OCH_2O), 127.36, 127.43, 129.36, 129.43, 135.85 (C-H arom), 134.56 and 134.88 (Cq arom), 173.23 (C-1); IR ($CHCl_3$): 2940, 1740 cm^{-1}. Anal. Calcd for $C_{30}H_{46}O_6Si$: C, 67.89; H, 8.74. Found : 68.14; H, 8.81.

(+)-[3(S), 9(R), S(R)]-1-(p-tolylsulfinyl)-3-(2-methoxyethoxymethoxy)-9-(t-butyldiphenylsilyloxy)-2-decanone, 1.

To a cold (-78°C) solution of LDA (1.29 mmol) in THF (10 mL) was added a solution of (+)-(R)-methyl p-tolylsulfoxide (181 mg, 1.175 mmol) in THF (5 mL). After stirring for 1 hour at -78°C, the

anion solution was dropwise added to a cool (-78°C) solution of ester **11** (312 mg, 0.59 mmol) in THF (10 mL) and stirred for 30 min. The mixture was then hydrolyzed with a saturated NH_4Cl solution (20 mL) and extracted with AcOEt (2 x 20 mL). The combined organic layers were washed with a saturated NH_4Cl solution (20 mL), with brine (20 mL), dried ($MgSO_4$) and the solvent evaporated. Silica gel chromatography (ether/hexane : 4/1) of the crude product provided the β-ketosulfoxide **1** as a colourless oil (361 mg, 94%) : *Rf* 0.43 (ether); $[\alpha]_D$ = + 80 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 1.05 (s, 9H, t-Bu), 1.06 (d, 2H, H-10, J = 6Hz), 1.18-1.58 (m, 10H, H-4, H-5, H-6, H-7, H-8), 2.42 (s, 3H, Me ptol), 3.34 (s, 3H, OMe), 3.48 and 3.64 (m, 4H, OCH_2CH_2O), 3.82 (sext, 1H; H-9, J = 6Hz), 3.97 (t, 1H, H-3, J = 7Hz), 4.02 (dd, AB, 2H, H-1, J_{AB} = 15Hz; Δν = 35Hz), 4.67 (s, 2H, OCH_2O), 7.37 and 7.65 (m, 12H, Harom), 7.61 (d, AA'BB', 2H, Harom, ptol., J = 8Hz); ^{13}C NMR ($CDCl_3$) δ 19.20 (Me_3CSi), 21.38 and 23.16 (C-10, Me ptol), 24.78, 24.91, 29.28, 30.87 (C-4, C-5, C-6, C-7), 23.16 [$(CH_3)_3CSi$], 39.23 (C-8), 58.94 (OMe), 65.86 (C-1), 67.77 and 71.55 (OCH_2CH_2O), 69.38 and 83.15 (C-3, C-9), 95.38 (OCH_2O), 124.22, 127.32, 127.40, 129.33, 129.40, 129.97, 135.79 (C-H arom), 134.48 and 134.80 (Cq. Ph_2), 140.59 and 141.95 (Cq. ptol), 203.37 (C-2); IR ($CHCl_3$) 2920, 1710, 1040 cm^{-1}. Anal. Calcd for $C_{37}H_{52}O_6SSi$: C, 68.06; H, 8.03. Found : C, 68.10; H, 8.12.

(+)-[2(S), 3(S), 9(R), S(R)]-1-(ptolylsulfinyl)-3-(2-methoxyethoxymethoxy)-9-(t-butyldiphenylsilyloxy)-2-decanol, 12.

To a cold solution (-78°C) of β-ketosulfoxide **1** (362 mg, 0.55 mmol) in THF (30 mL) was dropwise added a 1M DIBAL solution in toluene (0.61 mL). After 15 min., the reaction mixture was diluted with AcOEt (30 mL) and hydrolyzed with a saturated sodium tartrate solution (30 mL). The stirring was continued until a clear phase-separation occured. After extraction with AcOEt (20 mL), the combined organic layers were washed with brine, dried and the solvent evaporated. The crude product was finally purified by column chromatography on silica gel (ether) to yield the β-hydroxysulfoxide **12** as a colourless oil (340 mg, 94%) : *Rf* 0.12 (ether); $[\alpha]_D$ = + 102 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3/D_2O$, 200 MHz): δ: 1.04 (s, 9H, t-Bu), 1.05 (d, 2H, H-10, J = 6Hz), 1.13-1.43 (m, 10H, H-4, H-5, H-6, H-7, H-8), 2.41 (s, 3H, Me ptol), 2.82 (ddd, AB of ABX, 2H, H-1, J_{AB} = 13.5Hz, J_{AX} = 10.5Hz, J_{XB} = 2Hz, Δν = 45Hz), 3.42 (s, 3H, OMe), 3.54-3.85 (m, 6H, OCH_2CH_2O, H-3, H-9), 4.17 (m, 1H, H-2), 4.75 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 21Hz), 7.38 et 7.67 (m, 12H, Harom), 7.54 (d, AA'BB', 2H, Harom-ptol, J = 8Hz); ^{13}C NMR ($CDCl_3$): δ: 19.25 (Me_3CSi), 21.40 and 23.21

(C-10, Me ptol), 25.05, 25.68, 29.53, 31.12 (C-4, C-5, C-6, C-7), 27.02 ($(CH_3)_3CSi$), 39.32 (C-8), 59.05 (OMe), 60.08 (C-1), 67.54 and 71.64 (OCH_2CH_2O), 68.09 and 69.47 (C-2, C-3), 84.15 (C-9), 96.40 (OCH_2O), 123.87, 127.37, 127.45, 129.37, 129.44, 129.97, 135.86; (C-H arom), 134.57 and 134.90 (Cq arom Ph_2), 141.00 and 141.24 (Cq. arom. ptol); IR ($CHCl_3$) 3500-3200, 2920, 1040 cm^{-1}. Anal. Calcd for $C_{37}H_{54}O_6SSi$: C, 67.85; H, 8.31. Found : C, 68.08; H, 8.57.

(+)-[2(R), 3(S), 9(R)]-2,3-(2-methoxyethoxymethoxy)-9-(t-butyldiphenylsilyloxy)-1-decanol, 13.

1) A cold (-78°C) solution of β-hydroxysulfoxide **12** (280 mg, 0.428 mmol) in THF (10 mL) was treated with a 1.56 M solution of butyllithium in hexane (0.3 mL, 0.45 mmol) and stirred for 30 min. 2-methoxyethoxymethyl chloride (0.1 mL, 0.856 mmol) was then added and the mixture allowed to warm to room temperature. After 15 hours, the reaction was hydrolyzed with a saturated NH_4Cl solution (20 mL) and extracted with ether (2 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent evaporated. Silica gel chromatography (ether/hexane : 4/1) of the residue provided **(+)-[2(S), 3(S), 9(R), S(R)]-1-(p-tolylsulfinyl)-2,3-di-(2-methoxyethoxymethoxy)-9-(t-butyldiphenylsilyloxy)-decane** as a pale yellow oil (232 mg, 73%) : *Rf* 0.33 (ether); $[\alpha]_D$ = + 91 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 1.04 (s, 9H, t-Bu), 1.05 (d, 3H, H-10, J = 6Hz), 1.17-1.44 (m, 10H, H-4, H-5, H-6, H-7, H-8), 2.41 (*s*, 3H, Me ptol), 2.86 (ddd, AB of ABX, 2H, H-1, J_{AB} = 13.5Hz; J_{AX} = 10Hz, J_{BX} = 2.5Hz), 3.37 and 3.40 (s, 6H, OMe), 34.2-.3.95 (m, 10H, 2 OCH_2CH_2O, H-3, H-9), 4.24 (m, 1H, H-2), 4.78 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 23Hz), 4.97 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 22Hz), 7.38 and 7.67 (m, 12H, Harom), 7.54 (d, AA'BB', 2H; Harom ptol, J = 8Hz); ^{13}C NMR ($CDCl_3$): δ: 19.22 (Me_3CSi), 21.36 and 23.20 (C-10, Me ptol), 25.06, 25.94, 29.65, 31.59 (C-4, C-5, C-6, C-7); 27.00 ($(CH_3)_3CSi$), 39.36 (C-8), 59.02 (2 OMe), 60.10 (C-1), 67.18, 67.64, 71.67, 71.75 (2 OCH_2CH_2O), 69.46 and 73.15 (C-2, C-3), 77.46 (C-9), 94.53 and 95.29 (2 OCH_2O), 123.78, 127.34, 127.43, 129.33, 129.42, 129.96, 135.82 (C-H arom), 134.50 and 134.88 (Cq arom Ph_2), 141.33 (2 Cq arom ptol); IR ($CHCl_3$) 2920, 1000 cm^{-1}. Anal. Calcd for $C_{41}H_{62}0_8SSi$: C, 66.27; H, 8.41. Found : C, 66.08; H, 8.43.

2) Pummerer rearrangement: a solution of the preceding sulfoxide (194 mg, 0.26 mmol) and sodium acetate (0.5 g) in acetic anhydride (10 mL) was refluxed for 7 hours. The excess of solvent was then evaporated under vacuum, the residue dissolved in ether and the salt removed by filtration over celite. After evaporating the solvent, the crude product was purified by column chromatogrphy (ether/hexane : 3/2) to provide **2(S), 3(S), 9(R)]-1-acetoxy-1-ptolylthio-2,3-di-(2-methoxyethoxy-methoxy)-9-(t-butyldiphenylsilyloxy)decane** as a pale yellow oil (183 mg, 90%) in a 45/55 diastereomeric mixture

determined by ^{1}H NMR from the proton (H-1) α to the sulfur : *Rf* 0.33 and 0.41 (ether/hexane = 2/1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ: 1.04 (d, 2H, H-10, J = 6Hz), 1.05 (s, 9H, t-Bu), 1.18-1.65 (m, 10H, H-4, H-5, H-6, H-7, H-8), 2.03 and 2.06 (OAc), 2.33 (Me ptol), 3.37, 3.38, 3.39 (OMe), 3.48-3.89 (m, 6H, OCH_2CH_2O, H-3, H-9), 3.97 (m, 1H, H-2), 4.80 (m, 4 AB systems, 2H, OCH_2O), 6.11 (d, 1H, H-1 of dia 1, J = 7Hz), 6.37 (d, 1H, H-1 of dia 2, J = 3.5 Hz), 7.12, 7.36, 7.67 (m, 14H, Harom); ^{13}C NMR ($CDCl_3$): δ: 19.19 (Me_3CSi), 21.01, 21.07, 23.15 (C-10, Me ptol), 24.92, 25.20, 25.88, 29.65, 29.85, 30.48 (C-4, C-5, C-6, C-7, OCOMe), 26.97 ($(CH_3)_3CSi$), 39.40 (C-8), 58.91 (OMe), 67.21, 67.40, 67.58, 71.59, 71.68 (OCH_2CH_2O), 69.48 (C-2, C-3), 77.03 and 77.57 (C-9), 93.91, 94.78, 95.46, 96.03 (OCH_2O), 127.31, 127.39, 129.07, 129.30, 129.38, 129.70, 129.83, 133.13, 134.01, 135.78 (C-H arom), 134.47 and 134.84 (Cq arom Ph_2), 138.09 and 138.68 (Cq arom ptol), 169.19 and 169.24 (OCOMe); IR ($CHCl_3$) 2920, 1730 cm-1. anal. Calcd for $C_{43}H_{64}O_9SSi$: C, 65.78; H, 8.22. Found : C, 65.56; H, 8.28.

3) To a cold (0°C) solution of the preceding product (162 mg, 0.2 mmol) in dry ether (10 mL) was added lithium aluminium hydride (31 mg, 0.826 mmol) and stirred at room temperature until no more starting material was detected by TLC (ether/hexane : 2/1). The reaction mixture was then hydrolyzed with a saturated sodium sulfate solution (0.1 mL) and stirred until a white precipitate was obtained. $MgSO_4$ was then added, the precipitate filtered over celite and washed with dry ether. After evaporating the solvent, the residue was column chromatographied on silica gel (ether) to provide the alcohol **13** as a colourless oil (115 mg, 90%) : *Rf* 0.25 (ether); $[\alpha]_D$ = + 33 (c 1; $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ: 1.04 (d, 3H, H-10, J = 6Hz), 1.05 (s, 9H, t-Bu), 1.17-1.54 (m, 10H, H-4, H-5, H-6, H-7, H-8), 3.37 and 3.38 (s, 6H, OMe), 3.52-3.86 (m, 12H, 2 OCH_2CH_2O, H-2, H-3, H-9, OH), 4.77 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 18Hz), 4.81 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 13Hz), 7.39 and 7.66 (m, 10H, Harom); ^{13}C NMR ($CDCl_3$): δ: 19.19 (Me_3CSi), 23.17, 25.11, 29.36, 29.74 (C-4, C-5, C-6, C-7), 26.97 ($(CH_3)_3CSi$), 58.91, 58.95 (OMe), 62.03 (C-1), 67.21, 67.35, 71.56, 71.64 (OCH_2CH_2O), 69.44, 77.45, 82.37 (C-2, C-3, C-9), 95.11 and 95.61 (OCH_2O), 127.29, 127.37, 129.29, 129.36, 135.77 (C-H arom), 134.48 and 134.81 (Cq arom); IR ($CHCl_3$) 3650, 3450, 2920, 1100 cm^{-1}. Anal. Calcd for $C_{34}H_{56}O_8Si$: C, 65.77; H, 9.09. Found : C, 65.99; H, 9.03.

(-)-[2(E), 4(R), 5(S), 11(R)] methyl 4,5-di-(2-methoxyethoxymethoxy)-11-(t-butyldiphenylsilyl-oxy)-2-dodecenoate, 14.

1). A cold (-78°C) solution of oxalyl chloride (0.03 mL, 0.322 mg) in CH_2Cl_2 (3 mL) was treated with dry DMSO (0.035 mL, 0.483 mmol) and stirred for 30 min. A solution of alcohol **13** (100 mg, 0.161

mmol) in 3 mL of CH_2Cl_2 was slowly added, the resulting mixture stirred for 30 min. at -78°C and finally treated with triethylamine (0.3 mL). The reaction mixture was allowed to warm to 0°C, hydrolyzed with water (5 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with a saturated NH_4Cl solution (2 x 10 mL), dried over $MgSO_4$ and the solvent evaporated. Silica gel chromatogrphy (ether/hexane : 3/1) of the residue provided (+)-**[2(S), 3(S), 9(R)] 2,3-di-(2-methoxyethoxymethoxy)-9-(t-butyldiphenylsilyloxy)-1-decanal** as a pale yellow oil (91 mg, 90%) : Rf 0.59 (ether); $[\alpha]_D$ = +7 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 1.04 (d, 3H, H-10, J = 6Hz), 1.05 (s, 9H, t-Bu), 1.14-1.72 (m, 10H, H-4, H-5, H-6, H-7, H-8), 3.37 and 3.38 (s, 6H, OMe), 3.51-3.86 (m, 9H, 2 OCH_2CH_2O, H-3), 3.95 (m, 1H, H-9), 4.12 (dd, 1H, H-2, J_{H1-H2} = 1.5Hz, J_{H2-H3} = 3Hz), 4.78 (dd, AB, OCH_2O, J_{AB} = 7Hz, Δν = 21Hz), 4.84 (s, 2H, OCH_2O), 7.40 and 7.69 (m, 10H, Harom), 9.68 (d, 1H, H-1, J = 1.5Hz); ^{13}C NMR ($CDCl_3$): δ: 19.25 (Me_3CSi), 23.20 (C-10), 25.10, 25.54, 29.58, 30.89 (C-4, C-5, C-6, C-7), 27.02 ($(CH_3)_3CSi$), 39.35 (C-8), 59.02 (OMe), 67.35, 67.53, 71.55, 71.66 (OCH_2CH_2O), 69.48, 83.31 (C-2, C-3, C-9), 94.95 and 95.65 (OCH_2O), 127.36, 127.44, 129.36, 129.43, 135.85 (C-H arom), 134.54 and 134.89 (Cq arom), 201.80 (C-1); IR ($CHCl_3$) 2920, 1740, 1000 cm^{-1}.

2) To a solution of the preceding aldehyde (136 mg, 0.22 mmol) in dry THF (5 mL) was added methyl triphenylphosphoranylideneacetate (147 mg, 0.44 mmol) and the resulting mixture stirred at room temperature for 56 hours. Evaporation of the solvent, followed by a silica gel chromatography (ether/hexane : 1/1) of the residue provided **14** as a colourless oil (135 mg, 92%) : *Rf* 0.47 (ether/hexane = 3/1; two migrations); $[\alpha]_D$ = -29 (*c* 0.5, $CHCl_3$); ^1H NMR($CDCl_3$, 200 MHz): δ: 1.04 (d, 3H, H-1, J = 6Hz), 1.05 (s, 9H, t-Bu), 1.18-1.60 (m, 10H, H-6, H-7, H-8, H-9, H-10), 3.38 (s, 6H, 2 OMe), 3.47-3.84 (m, 10H, 2 OCH_2CH_2O, H-5, H-11), 3.75 (s, 3H, CO_2Me), 4.34 (m, 1H, H-4), 4.72 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 10Hz), 4.79 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 28Hz), 6.04 (dd, 1H, H-2, J_{H2-H3} = 16Hz, J_{H2-H4} = 1Hz), 6.88 (dd, 1H, H-3, J_{H3-H2} = 16Hz, J_{H3-H4}= 6.5Hz), 7.32 and 7.69 (m, 10H, Harom); ^{13}C NMR ($CDCl_3$): δ: 19.29 (MeCSi), 23.24 (C-12), 25.22, 25.76, 29.76, 30.77 (C-6, C-7, C-8, C-9), 27.05 [$(CH_3)_3CSi$], 39.44 (C-10), 51.67 (CO_2Me), 59.05 (OMe), 67.22, 71.66, 71.74 (OCH_2CH_2O), 69.53 and 78.62 (C-4, C-5, C-11), 94.09 and 95.06 (OCH_2O), 123.19 (C-3), 127.38, 127.47, 129.38, 129.46, 135.88 (C-H arom), 134.35 and 134.95 (Cq arom), 144.80 (C-2), 166.39 (C-1); IR ($CHCl_3$) 2920, 1710, 1100 cm^{-1}. Anal. Calcd for $C_{37}H_{58}O_9Si$: C, 65.84; H, 8.66. Found : C, 65.88; H, 8.67.

(-)-[2(E), 4(R), 5(S), 11(R)]-4,5-di-(2-methoxyethoxymethoxy)-11-hydroxy-2-decenoic acid, 15.

1) To a solution of ester **14** (81 mg, 0.119 mmol) in THF (3 mL), methanol (1 mL) and water (1 mL) was added lithium hydroxide (10 mg, 0.416 mmol) and the resulting mixture stirred at room temperature for 6 hours. After diluting with ether (5 mL) and adjusting the pH of the mixture to 3 with an aqueous 5% HCl solution, the aqueous layer was saturated with Na Cl and extracted with ether (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude **(-)-[2(E), 4(R), 5(S), 11(R)]-4,5-di-(2-methoxyethoxymethoxy)-11-(t-butyldiphenylsilyloxy)-2-dodecenoic acid** (79 mg) was used in the next sequence without further purification : Rf 0.4 (AcOEt/EtOH = 8/2); $[\alpha]_D$ = -32 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3/D_2O$, 200 MHz): δ: 0.97 (*s*, 9H, t-Bu), 0.99 (d, 3H, H-12, J = 6Hz), 1.10-1.55 (m, 10H, H-6, H-7, H-8, H-9, H-10), 3.30 (OMe), 3.41-3.77 (m, 10H, 2 OCH_2CH_2O, H-5, H-11), 4.19 (m, 1H, H-4), 4.62 (*s*, 2H, OCH_2O), 4.71 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 31Hz), 5.92 (dd, 1H, H-2, J = 15.5, 1Hz), 6.53 (dd, 1H, H-3, J = 15.5, 7Hz), 7.32 and 7.61 (m, 10H, H arom); IR ($CHCl_3$) 3200-2800, 1700, 1650 cm^{-1}.

2) A solution of the preceding acid (79 mg, 0.12 mmol) in THF (5 mL) was treated with a 1.1 M solution of TBAF in THF (0.54 mL, 0.595 mmol) and stirred at room temperature for 48 hours. The reaction mixture was diluted with ether (3 mL), with water (5 mL), basified to pH 12 with an aqueous 5% NaOH solution and finally extracted with water (2 x 30 mL). The combined aqueous layers were then acidified to pH 3 with an aqueous 5% HCl solution and extracted with ether (2 x 10 mL) and AcOEt (10 mL). The combined organic layers were then dried ($MgSO_4$), concentrated and the crude product purified by column chromatography on silica gel (AcOEt/EtOH : 9/1 to 8/2) to afford the seco-acid **15** as a colourless oil (40 mg, 79% for the two steps) : *Rf* 0.32 (AcOEt/EtOH = 8/2); $[\alpha]_D$ = -103 (c 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 0.86 (d, 3H, H-12, J = 6.5 Hz), 1.12-1.50 (m, 10H, H-6, H-7, H-8, H-9, H-10), 3.37 and 3.38 (*s*, 6H, 2 OMe), 3.47-3.78 (m, 11H, 2 OCH_2OCH_2O, H-5, H-6, OH), 4.22 (m, 1H, H-4), 4.66 (dd, AB, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 10Hz), 4.78 (dd, 2H, OCH_2O, J_{AB} = 7Hz, Δν = 34 Hz), 5.96 (d, 1H, H-2, J = 15.5Hz), 6.43 (dd, 1H, H-3, J = 15.5, = 7Hz); ^{13}C NMR ($CDCl_3$): δ: 23.40 (C-12), 24.97, 25.18, 28.97, 30.07 (C-5, C-6, C-7, C-8), 38.91 (C-5), 58.96 and 59.00 (OMe), 66.77, 67.03, 71.60, 71.70 (OCH_2CH_2O), 67.45 and 78.90 (C-4, C-5, C-11), 93.40 and 94.92 (OCH_2O), 123.31 and 136.90 (C-2, C-3), 173.40 (C-1); IR ($CHCl_3$) 3650, 3550-3200, 3100-2700, 1700, 1610 cm^{-1}.

(-)-[(E), 4(R), 5(S), 11(R)]-4,5-di-(2-methoxyethoxymethoxy)-11-methyl-2-dodecenolide.

A solution of the seco-acid **15** (34 mg, 0.08 mmol) in THF (2 mL) was treated with triethylamine (0.015 mL, 0.112 mmol) and trichlorobenzoyl chloride (0.016 mL, 0.104 mmol) and stirred at room

temperature for 24 hours. The reaction mixture was diluted with dry toluene (40 mL) and slowly added (0.2 mL/min) to a refluxing solution of DMAP (39 mg, 0.32 mmol) in toluene (10 mL). The resulting mixture was refluxed for 8 hours, concentrated under vacuum and the residue dissolved in CH_2Cl_2 (10 mL) and water (5 mL). Acidification to pH 3 with a 5% HCl solution was followed by extraction with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (10 mL) and water (10 mL) prior to drying ($MgSO_4$) and solvent evaporation. Preparative chromatography on silica gel (ether) of the residue afforded the macrolactone as a colourless oil (21 mg, 65%) : Rf 0.40 (ether); $[\alpha]_D$ = -24 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 1.28 (d, 3H, H-12, J = 6.5Hz), 1.22-1.86 (m, 10H, H-6, H-7, H-8, H-9, H-10), 3.37 and 3.39 (s, 6H, 2 OMe), 3.50-3.83 (m, 9H, 2 OCH_2CH_2O, H-5), 4.62 (m, 1H, H-4), 4.75 and 4.80 (dd, 2 AB systems, 2 OCH_2O, J_{AB} = 7Hz, Δν = 10Hz), 5.06 (m, 1H, H-11), 6.13 (dd, 1H, H-2, J = 16, 1Hz), 6.81 (dd, 1H, H-3, J = 16, 6Hz); ^{13}C NMR ($CDCl_3$): δ: 19.25 (C-12), 22.58, 25.59, 27.54, 28.14, 32.41 (C-6, C-7, C-8, C-9, C-10), 59.00 (2 OMe), 66.78, 67.10, 71.60, 71.68 (2 OCH_2CH_2O), 72.88, 75.84, 78.48 (C-4, C-5, C-11), 93.48 and 94.45 (2 OCH_2O), 123.30 and 145.91 (C-2, C-3), 167.27 (C-1); IR ($CHCl_3$) 2920, 1710, 1040 cm^{-1}.

(-)-[2(E), 4(R), 5(S), 11(R)]-11-methyl-5,4-dihydroxy-2-dodecenolide or (-)-Cladospolide A.

A cold (0°C) solution of the preceding macrolactone (20 mg, 0.049 mmol) in CH_2Cl_2 (5 mL) was treated with a 1M solution of $TiCl_4$ in CH_2Cl_2 (0.147 mL, 0.147 mmol) and stirred at 0°C for 4 hours. After hydrolysis with a saturated $NaHCO_3$ solution, the mixture was extracted with AcOEt (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated and the residue purified by preparative chromatography on silica gel (ether) to provide the macrolide as a white solid (8 mg, 71%). Recrystallization in benzene (2 mL) gave Cladospolide A identical to the natural product : *Rf* 0.49 (ether, 2 migrations); mp = 91 -92°C (lit. [5] : 92-93°C); $[\alpha]_D$ = -48 (c 0.2, $CHCl_3$) (lit. [5] : -49.3 (c 0.224, $CHCl_3$)); $[\alpha]_D$ = -32 (c 0.4, MeOH) (lit. [2] : -30 (c 0.4, MeOH)); ^1H NMR ($CDCl_3/D_2O$, 200 MHz): δ: 1.28 (d, 3H, H-12, J = 6.5 Hz), 1.10-1.89 (m, 10H, H-6, H-7, H-8, H-9, H-10), 3.66 (dd, 1H, H-5, J = 3Hz, J = 9Hz), 4.55 (ddd, 1H, H-4, J = 5.5, 3, 1.5Hz), 5.13 (qdd, 1H, H-11, J = 6.5, 6.5, 2Hz), 6.21 (dd, 1H, H-2, J = 16, 1.5Hz). 6.81 (dd, 1H, H-3, J = 16, 5.5Hz); ^{13}C NMR ($CDCl_3$): δ: 18.99 (C-12), 2.57, 25.07, 28.16, 30.69, 32.47 (C-6, C-7, C-8, C-9, C-10), 72.96 and 74.69 (C-4, C-5, C-11), 122.33 and 145.59 (C-2, C-3), 167.93 (C-1), IR ($CHCl_3$) 3600-3200, 1720 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found : C, 63.34; H, 8.92.

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(*Received in UK* 1 *December* 1994)