Tetrahedron Asymmetry Vol. 2, No. 8, pp. 801-819, 1991
Printed in Great Britain

0957-4166/91 $3.00+00
Pergamon Press plc

Asymmetric Synthesis of the Macrolide (-)-Aspicilin

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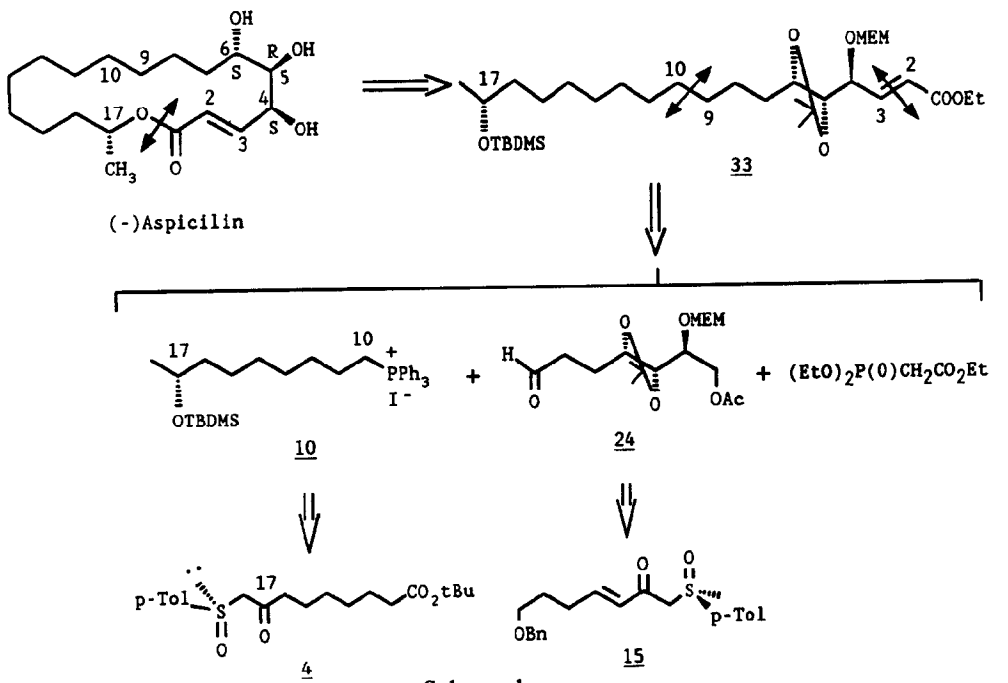
(*Received* 4 *June* 1991)

Abstract : *The asymmetric synthesis of 4(S), 5(R), 6(S), 17(R)-(-)- Aspicilin is described. The chiral parts of the molecule were obtained by asymmetric synthesis monitored by a chiral sulfoxide group.*

Aspicilin is a macrocyclic lactone which was isolated from the lichen *Aspicilia Gibbosa* at the beginning of this century[1,2]. The basic structure was elucidated in 1973[3] and its absolute configuration 4R, 5S, 6R, 17S-(+)- was recently determined by two independent total syntheses[4,5] and by X-ray analysis[6].



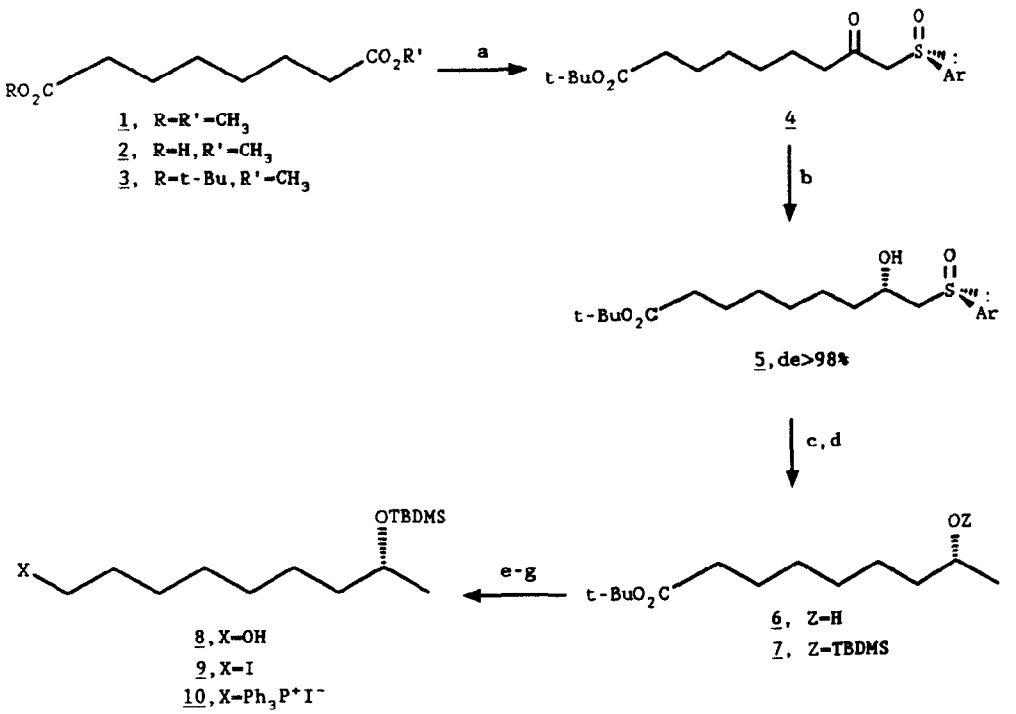
Scheme 1

We report in this paper the asymmetric synthesis of the unnatural (-) isomer, based essentially on the asymmetric induction of a chiral sulfoxide group.

As shown on the retrosynthetic scheme (scheme 1), the secoester **33** can be prepared by Wittig reaction from the chiral phosphonium salt **10** and the aldehyde **24**.

It will be shown that molecules **10** and **24** can be readily made from the two ß-ketosulfoxides **4** and **15** with a high stereoselectivity.

The ß-ketosulfoxide **4** prepared in 88% yield from the diester **3** and the anion of (R)(+) methyl p-tolylsulfoxide, was reduced with DIBAL to give the (8S)-hydroxysulfoxide **5** in 90% yield. The *S* configuration of the hydroxylic carbon can be deduced from the reaction mechanism already published[7] but also from the NMR characteristics of the product. From the numerous examples of the reduction of ß-ketosulfoxides we reported, we noticed that the non-equivalence of the methylene protons α to the sulfoxide group is quite different in the two diastereoisomers[7b,c,d] : in the RR configuration the $\Delta\nu$ value between the two hydrogens is around 40Hz and around 80Hz in the RS configuration (86Hz in **5**). The final correlation with the known (-)-Aspicilin will indeed confirm this absolute configuration. The diastereoselectivity for the reduction was higher than 98%, only one diastereoisomer being observed in the NMR spectrum of the crude reaction mixture.

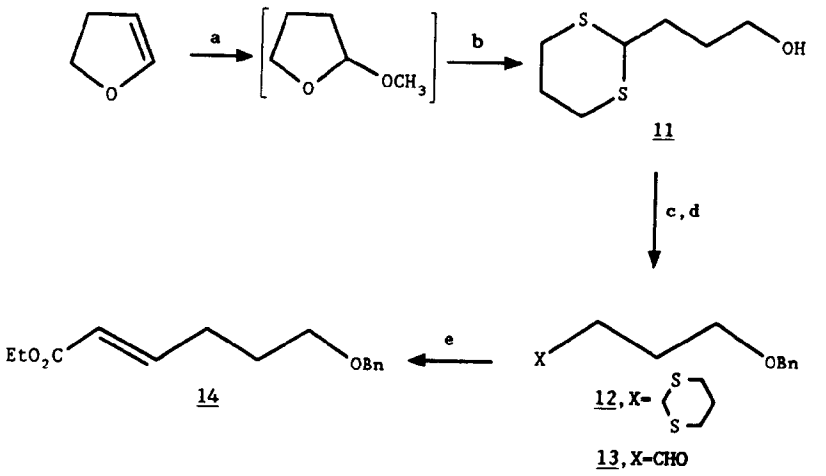


a) (R)(+) methyl p-tolylsulfoxide, LDA, -78°, 88% yld ; b) DIBAL, THF, -75°, 90% yld, de>98% ; c) H_2, RaNi, EtOH, 96% yld ; d) TBDMSCl, imidazole, DMF, 95% yld ; e) $LiAlH_4$, THF, 97% yld ; f) PPh_3, imidazole, I_2, PhMe, 10 mn, 92% yld ; g) PPh_3, CH_3CN, 24h, 70°, 87% yld.

Scheme 2

Compound **5** was then desulfurized with Raney Nickel and the hydroxyl group protected with TBDMS in high yield. Finally the ester group was reduced to the corresponding alcohol which was then transformed into the iodide **9** and into the phosphonium salt **10**. Each step gave a very high yield (scheme 2).

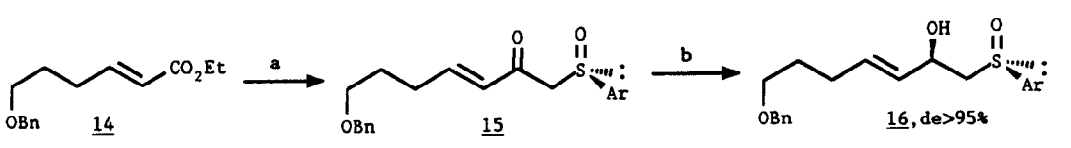
The α,β- unsaturated ester **14**, precursor of the β-ketosulfoxide **15** was prepared from dihydrofuran which was opened in two steps into the hydroxythioacetal **11**. After benzylation, the thioacetal was hydrolyzed and submitted to a Wittig-Horner reaction to give in high yield the ester **14** (scheme 3).



a) TsOH, MeOH ; b) BF_3 Et_2O, $HS(CH_2)_3SH$, 79% yield ; c) BnBr, TBAI, rt, 12h, quantitative yld ; d) MeI, CO_3Ca, CH_3CN-H_2O, rt, 12h, 85% yld ; e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°, 15 mn, 75% yld.

Scheme 3

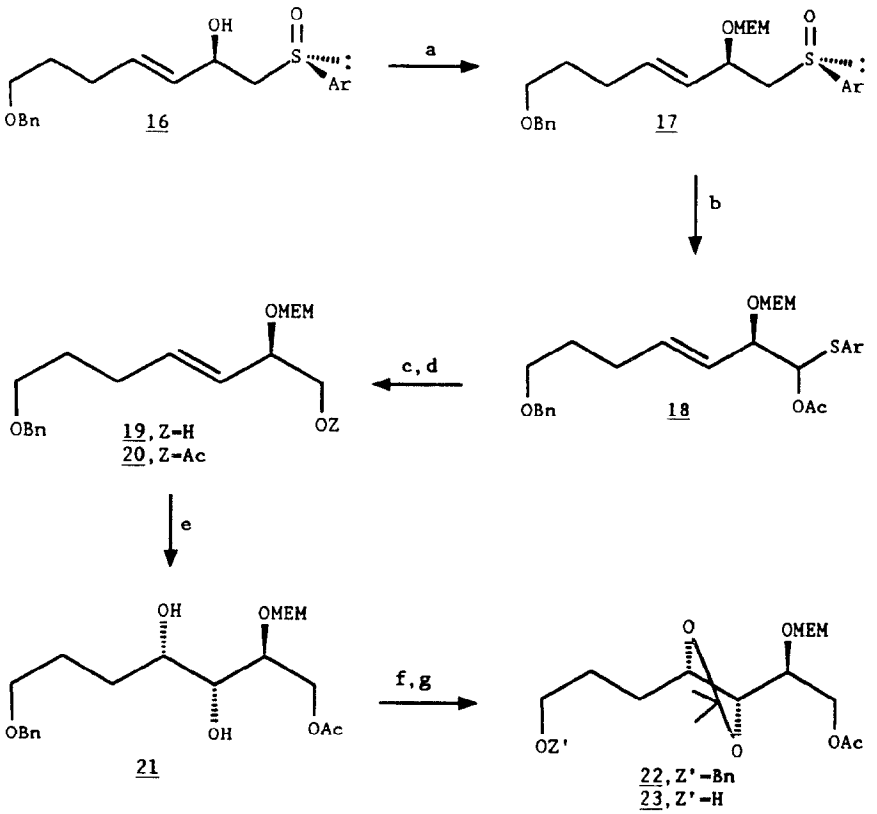
The β-ketosulfoxide **15** was obtained in 80% yield from the reaction of the ester **14** with the carbanion of (R)(+) methyl p-tolyl sulfoxide (a coupling constant of 16Hz between the two vinylic protons H_3 and H_4 confirmed the E stereochemistry of the double bond). Reduction with DIBAL in presence of zinc chloride afforded in 90% the (R,R) β-hydroxysulfoxide **16** as the sole diastereoisomer[7] [the non-equivalence in NMR, ($\Delta\nu$=55Hz), between the methylene protons α to the sulfoxide group is consistent with the *RR* configuration] (scheme 4).



a) (R)(+) methyl p-tolyl sulfoxide, LDA, THF, 0°, 15 mn, 80% yld ; b) DIBAL, $ZnCl_2$, THF, -78°, 90% yld.

Scheme 4

The two last chiral hydroxylic centers on carbons 3 and 4 were created by hydroxylation of the double bond. We already reported in a preliminary communication[8] two different approaches for the hydroxylation step. We describe in this paper only the best one which gave the highest chemical yield and a good stereoselectivity.

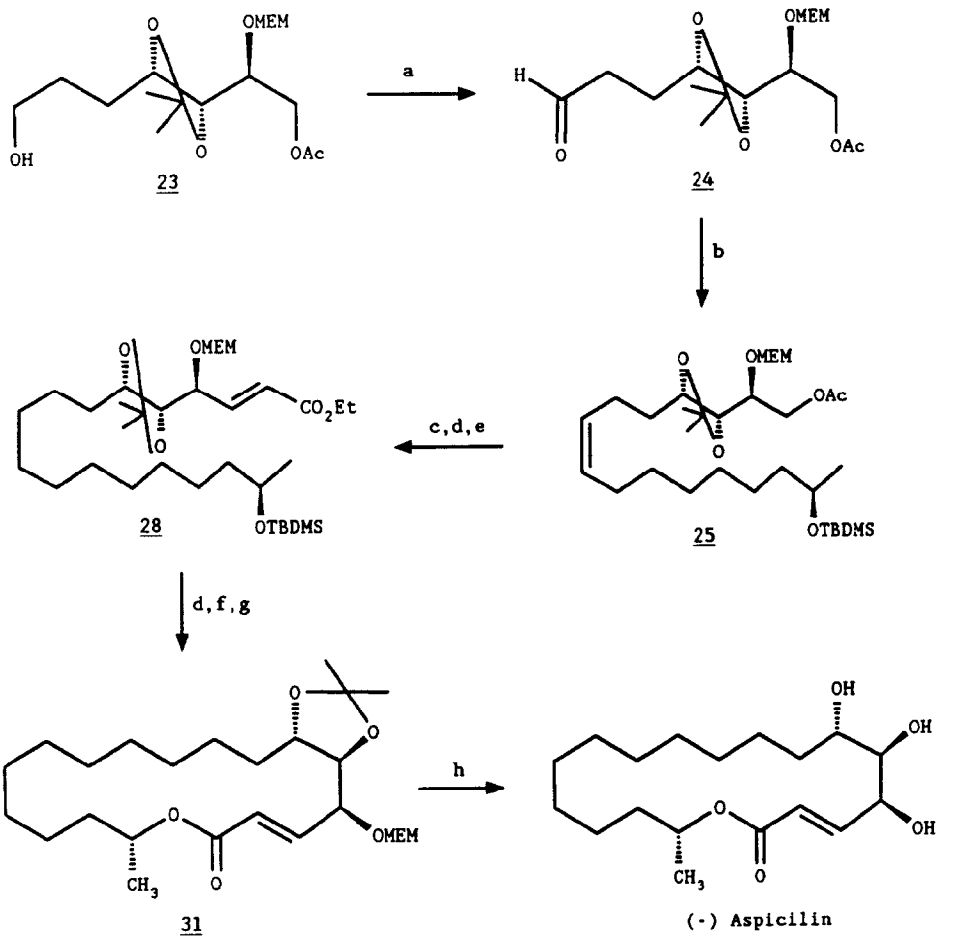


a) Et(i-Pr)$_2$N, MEM Cl, CH_2Cl_2, 95% yld ; b) Ac_2O, AcONa, 130°, 12h, 99% yld ; c) $LiAlH_4$, 92% yld ; d) Ac_2O, AcONa, rt, 98% yld ; e) OsO_4 catal., $Me_3N(O)$, THF-H_2O, rt, 12h, 85% yld ; dr:80/20, 71% in pure isolated **21** ; f) $Me_2C(OMe)_2$, pTsOH, DME, 60°, 6h, 93% yld ; g) RaNi, EtOH, 98% yld.

Scheme 5

The MEM ether **17** of the ß-hydroxysulfoxide **16**, was converted into acetate **20** by Pummerer rearrangement in acetic anhydride, reduction with lithium aluminium hydride and acetylation. The acetate **20**, was transformed into diol **21** in 85% yield by catalytic osmylation with a stereoselectivity of 80:20 (determined by NMR from the acetyl signal). The absolute configuration of the main diastereoisomer was deduced from our previous results[8,9,10] and was eventually confirmed by the final correlation with known (-) aspicilin.

The main diastereoisomer **21** was first separated by column chromatography (71% isolated yield) and then converted into the corresponding acetonide and finally debenzylated to give molecule **23** (scheme 5).



23 24 28 25 31

a) Swern oxidation, 93% yld ; b) **10**, n-BuLi, THF, rt, 2h, 64% yld ; c) H_2, Pd/C, EtOAc, 90% yld ; d) LiOH, MeOH-H_2O, rt, 4h, 90% yld ; e) Swern oxidation followed by Wittig-Horner with $(EtO)_2P(O)CH_2CO_2Et$, n-BuLi, 0°, 85% yld ; f) TBAF, THF, 0°, 48h, 95% yld ; g) 2,5-dichlorobenzoyl chloride, Et_3N, THF, rt, 8h, then DMAP, 12h, 55%yld ; h) BF_3-Et_2O, HS-$(CH_2)_2$SH, CH_2Cl_2, 0°, 74% yield.

Scheme 6

The aldehyde **24** derived from alcohol **23** underwent a Wittig reaction with the phosphonium **salt 10** and gave the Z olefin **25** in 64% yield (an 11Hz coupling constant was observed between the two vinylic hydrogens). Reduction of the double bond, saponification of the acetate, Swern oxidation followed by a Wittig-Horner reaction gave the secoester **28**.

After saponification of the ester and removal of the TBDMS group the secoacid **30** was cyclized using 2,6-dichlorobenzoyl chloride with the conditions described by Zwanenburg[5].

After removing the protecting groups, (-) aspicilin was obtained as a white solid [m.p. 149-151°C, $[\alpha]_D$ -33 (c=4.1, $CHCl_3$)] identical in all respects with the known macrolide [m.p. 150-152[2,3,5], $[\alpha]_D$ -34 (c=0.85, $CHCl_3$)[5]]. The NMR and IR data are identical with those of the literature[3].

EXPERIMENTAL SECTION

Melting points have been determined with a Reichert microscope. IR spectra have been recorded in $CHCl_3$ solution unless otherwise indicated on a Perkin-Elmer 1310 ^1H and ^{13}C NMR spectra were recorded at 200.1 and 50.3 MHz in $CDCl_3$ on a Bruker WM 200 SY spectrometer. Signals are reported in δ units. High resolution mass spectra were recorded on a Krabs MS-80 RFA spectrometer using the electron impact technique.
Optical rotations were recorded using a Perkin-Elmer 241 MC polarimeter at 25°C. Thin layer chromatography (TLC) was performed by using precoated sheets of silica gel 60 and flash column chromatography was carried out with silica gel 60 (230-400 mesh). Eluting solvents are indicated in the text. Dry THF was distilled from sodium-benzaphenone ketyl, dichloromethane and chloroform were dried over phosphorus peutoxide. Diisopropylamine was freshly distilled over potassium hydroxide. Apparatus for all experiments carried out under inert atmosphere, was dried by flaming in a stream of dry argon.

Tert-butyl methyl octadioate, 3

1) To a solution of 9.50 g (50.54 mmol) of acid **2** in 15 ml of benzene under argon was added 20 ml of thionyl chloride. The reaction mixture was refluxed during 4 h. Elimination of benzene and of the excess of thionyl chloride under vacuum gave the corresponding acid chloride of **2**, which was used without further purification. ^1H NMR : δ : 3.68 (s, 3H, CO_2CH_3), 2.90 (t, J=7Hz, 2H, H_2), 2.31 (t, J=7Hz, 2H, H_7), 1.67 (m, 4H, H_3 and H_6), 1.37 (m, 4H, H_4 and H_5).

2) The obtained acid chloride of **2**, in 12 ml of dimethylaniline was added to a mixture of 25 ml of tert-butanol and 11 ml of dimethylaniline and refluxed during 3 h. The reaction mixture was diluted with methylene chloride (100 ml), washed with 10% aqueous H_2SO_4 solution (10x30 ml), 5% aqueous Na_2CO_3 solution (2x30 ml) and saturated NaCl solution (50 ml), and dried (Na_2SO_4). Removal of the solvent, followed by distillation afforded the diester **3** (9.86 g, 80%) : liquid ; bp 120°C/1.5 mmHg ; IR : 2980, 2940, 2860, 1720, 1440, 1370, 1260, 1160 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) : δ : 3.67 (s, 3H, CO_2CH_3), 2.31 (t, J=7Hz, 2H, H_7), 2.21 (t, J=7Hz, 2H, H_2), 1.62 (m, 4H, H_3 and H_6), 1.44 (s, 9H, $C(CH_3)_3$), 1.33 (m, H4, H_4 and H_5). Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.91 ; H, 9.90. Found : C, 64.00 ; H, 10.01.

t-butyl [(S)*R*]-8-oxo-9-p-tolylsulfinyl nonanoate, 4

To a cold (-78°C) solution of 45 mmol of lithium diisopropylamine (LDA) in 50 ml of THF under argon was dropwise added 6.62 g (43 mmol) of (+)-(R)-methyl p-tolyl sulfoxide in 50 ml of THF. After stirring for 30 min, this solution was added to a cold (-78°C) solution of diester **3** (3.30 g, 21.5 mmol) in 150 ml of THF. The temperature was then allowed to reach room temperature and, stirred for 1 h. The reaction mixture was then hydrolyzed with 200 ml of a saturated ammonium chloride solution. The organic layer was separated and the aqueous solution was acidified with 5% aqueous H_2SO_4 solution to pH 3-4 and extracted with ether (3x70 ml). The organic phase was washed with a saturated NaCl solution (100 ml), dried (Na_2SO_4), concentrated, and column chromatographed on silica gel using a 80:20 mixture of ether and hexane as eluent to give 6.92 g (88% yield) of **4** : oil ; $[\alpha]_D$ + 118.3 (c 1.47, acetone) ; IR ($CHCl_3$) 2960, 2920, 2860, 1715, 1365, 1250, 1150 cm^{-1}. ^1H NMR : δ : 7.93 (d, J=8Hz, 2H, C_6H_4 Me), 7.73 (d, J=8Hz, 2H, C_6H_4 Me), 3.80 (AB system, J=-13Hz, $\Delta\nu$=23Hz, 2H, H_9), 2.46 (m, 2H, H_7), 2.43 (s, 3H, C_6H_4 CH_3), 2.19 (t, J=7Hz, 2H, H_2), 1.56 (m, 4H, H_3 and H_6), 1.44 (s, 9H, Bu^t), 1.28 (m, 4H, H_4 and H_5). ^{13}C NMR : δ : 193.43, 173.56, 142.65, 140.15, 130.60 (2C of p-tol), 124.63 (2C of p-tol), 80.43, 68.47, 45.26, 35.88, 29.20, 29.02, 28.58, 25.29, 23.13 and 21.91. Anal. Calcd. for $C_{20}H_{30}O_4S$: C, 65.54 ; H, 8.25. Found : C, 65.70 ; H, 8.33.

Tert-butyl [8S, (S)*R*]-hydroxy-9--p-tolylsulfinyl nonanoate, 5

To a cold (-75°C) solution of 3 g (8.19 mmol) of ketosulfoxide **4** in 175 ml of THF under argon was dropwise added 12.5 ml (12.5 mmol) of a 1M solution of DIBAL in hexane diluted with 25 ml of THF. After stirring at -75°C for 2 h, the reaction mixture was quenched with 50 ml of MeOH. The solvent was then evaporated and the residue was diluted with 5% aqueous HCl solution and extracted with CH_2Cl_2 (5x60 ml). The organic layer was washed with 5% aqueous NaOH solution (2x50 ml), and saturated NaCl solution (100 ml), dried (Na_2SO_4) and evaporated.

The ^1H NMR of the crude product showed that there was only one diastereomer. Finally, the product was purified by column chromatography using a 80:20 mixture of ether and hexane as eluent to give 2.71 g (90% yield) of **5** : solid ; m.p. 58-59°C ; $[\alpha]_D$ + 142 (c 0.8, acetone) ; IR (film) 3330, 2950, 2910, 2840, 1715, 1360, 1145, 1080, 1020, 1005 cm^{-1}. ^1H NMR : δ : 7.44 (AB system, J=8.1Hz, $\Delta\nu$=32Hz, 4H, -C_6H_4-Me), 4.14 (m, X fragment from an ABX system, 1H, H_8), 2.84 (AB fragment from an ABX system, J=9.7Hz, 1.7Hz and -13.5Hz, $\Delta\nu$=86Hz, 2H, H_9), 2.43 (s, 3H, -C_6H_4-CH_3), 2.17 (t, J=7Hz, 2H, H_2), 1.53 (m, 4H, H_3 and H_6), 1.43 (s, 9H, Bu^t), 1.25 (m, 6H, H_4, H_5 and H_7). Anal. Calcd. for $C_{20}H_{32}O_4S$: C, 65.18 ; H, 8.75. Found : C, 65.45 ; H, 8.53.

t-butyl (8R)-hydroxynonanoate, 6

A solution of 5.6 g (15.2 mmol) of hydroxysulfoxide **5** in 100 ml of EtOH under argon was added to a suspension of 1 g of Raney Ni in 100 ml of EtOH. After stirring the mixture at 25°C for 2 h, it was filtered through a fritted funnel. After eliminating the solvent, the residue was column chromatographed on silica gel, using a 50:50 mixture of ether and hexane as eluant to give 3.35 g (96% yield) of **6** : an oil ; $[\alpha]_D$ - 6 (c 1.6, acetone) ; IR (film) 3400, 2950, 2910, 2840, 1720, 1360, 1250, 1145 cm^{-1}. ^1H NMR : δ : 3.78 (m, 1H, H_8), 2.21 (t, J=7.3Hz, 2H H_2), 1.53 (m, 6H, H_4, H_5 and H_6), 1.45 (s, 9H, Bu^t), 1.32 (m, 4H, H_3 and H_7), 1.19 (d, J=6.2Hz, 3H, H_9). Anal. Calcd. for $C_{13}H_{26}O_3$: C, 67.79 ; H, 11.38. Found : C, 67.85 ; H, 11.46.

Tert-butyl (8R)-8-(tert-butyldimethylsilyloxy) nonanoate, 7

To a solution of 622 mg (2.7 mmol) of alcohol **6** in 5.5 ml of DMF, 460 mg (6.76 mmol, 2.5 eq) of imidazole and 510 mg (3.38 mmol, 1.25 eq) of tert-butylchlorodimethylsilane were successively added. After stirring the reaction mixture overnight, 25 ml of saturated ammonium chloride solution was added and extracted with pentane (4x50 ml). The organic phase was washed with water, dried (Na_2SO_4), concentrated and column chromatographied with a 5:95 mixture of ether and hexane as eluent to give 882 mg (95% yield) of **7** : an oil ; $[\alpha]_D$ - 12 (c 2.5, acetone) ; IR (film) 2940, 2910, 2840, 1720, 1450, 1360, 1245, 1140, 825, 770 cm^{-1}. ^1H NMR : δ : 3.75 (m, 1H, H_8), 2.21 (t, J=7Hz, 2H H_2), 1.58 (m, 4H, H_3 and H_7), 1.45 (s, 9H, CO_2Bu^t), 1.34 (m, 6H, H_4, H_5 and H_6), 1.11 (d, J=6Hz, 3H, H_9), 0.89 (s, 9H, $OSiBu^t$), 0.05 (s, 6H, $OSiMe_2$). Anal. Calcd. for $C_{19}H_{40}O_3Si$: C, 66.28 ; H, 11.63. Found : C, 66.18 ; H, 11.80.

(8R)-8-(tert-butyldimethylsilyloxy) nonanol, 8

To a cold (-78°C) LAH ether solution (2.2 ml of a 1.3M solution in ether, diluted with 20 ml of ether), under argon, a solution of 880 mg (2.56 mmol) of ester **7** in 20 ml of THF was dropwised added. The reaction mixture was allowed to stir at room temperature for 2 h and then quenched with a saturated Na_2SO_4 solution (0.89 ml). After stirring for 30 mn, the precipitate was removed by filtration and the solvent evaporated under vacuum. The residue was purified by column chromatography using a 25/75 mixture of ether and hexane as eluent to give 680 mg (97% yield) of alcohol **8** :oil, ^1H NMR : δ : 3.77 (m, 1H, H_8), 3.65 (t, J=6Hz, 2H, H_1), 1.51 (m, 4H, H_2, and H_7), 1.31 (m, 8H, H_3, H_4, H_5 and H_6), 1.11 (d, J=6Hz, 3H, H_9), 0.89 (s, 9H, $OSiBu^t$), 0.05 (s, 6H, $OSiMe_2$).

(2R)-(tert-butyldimethylsilyloxy)-9-iodononane, 9

To a solution of 100 mg (0.36 mmol) of alcohol **8** in 10 ml of toluene, 335 mg (1.28 mmol, 3.5 eq) of Ph_3P, 87 mg (1.28 mmol, 3.5 eq) of imidazole and 370 mg (1.46 mmol, 4 eq) of **12** are subsequently added with stirring, at room temperature. After stirring for 15 min, 10 ml of

saturated $NaHCO_3$ aqueous solution is added and stirred for 10 mn. The organic layer is separated, treated with sodium thiosulphate aqueous solution, washed with water and saturated NaCl aqueous solution, dried (Na_2SO_4), concentrated and column chromatographed on silica gel (eluent : ether/hexane : 2/98), giving 127 mg (92% yield) of iodide **9** : oil ; IR (film) 2920, 2900, 2830, 1445, 1360, 1240, 820, 764 cm^{-1}. ^1H NMR : δ : 3.76 (m, 1H, H_2), 3.19 (t, J=7Hz, 2H H_9), 1.83 (m, 1H, H_8), 1.31 (s, 10H, H_3, H_4, H_5, H_6 and H_7), 1.12 (d, J=6Hz, 3H, H_1), 0.89 (s, 9H, $OSiBu^t$), 0.05 (s, 6H, $OSiMe_2$). Anal. Calcd. for $C_{15}H_{33}OSi$ I : C, 46.86 ; H, 8.64. Found : C, 46.97 ; H, 8.80.

[(8R)-(tert-butyldimethylsilyloxy) nonanyl] triphenyl phosphonium iodide, 10

To a solution of 366 mg (0.95 mmol) of iodide **9** in 10 ml of CH_3CN, was added 300 mg (1.14 mmol, 1.2 eq) of triphenylphosphine and the reaction mixture was stirred at 60°C for 48 h. After removing the solvent, the residue was treated with anhydrous ether in order to remove the excess of Ph_3P. Recrystallization from a mixture of AcOEt and hexane yielded 536 mg (87% yield) of the pure phosphonium salt **10** : solid, m.p. 102-103°C ; [α] = - 3.82 (489 nm), - 4.70 (500 nm), - 5.50 (540 nm) (c 1.49, methylene chloride). ^1H NMR : δ : 7.8 (m, 15H, Ph_3P), 3.72 (m, 3H, H_1 and H_8), 1.66, 1.31 (2m, 12H, H_2, H_3, H_4, H_5, H_6 and H_7), 1.09 (d, J=6Hz, 3H, H_9), 0.87 (s, 9H, $OSiBu^t$), 0.03 and 0.02 (2s, 6H, $SiMe_2$). ^{13}C NMR : δ : 135.76 (d, J=2.8Hz, 3C), 134.35 (d, J=9.9Hz, 6C), 131.20 (d, J=12.5Hz, 6C), 118.84 (d, J=85.6Hz, 3C), 69.23, 40.26, 33.10 (d, J=15.4Hz), 29.90, 26.56 (3C), 26.31, 24.42, 24.30, 23.31, 23.30, 18.79, -3.76, -4.03. Anal. Calcd. for $C_{33}H_{48}OSiPI$: C, 61.30 ; H, 7.43. Found : C, 61.39 ; H, 7.30.

2-(3'-hydroxypropyl)-1,3-dithiane, 11[12]

A three-necked round-bottomed flask equipped with a condenser and a magnetic stirring bar was charged with a solution of 2,3-dihydrofuran (7.0 g, 0.1 mol) and methanol (8 ml, 0.2 mol) in dichloromethane (30 ml). Freshly distilled boron trifluoride etherate (4.0 g, 28 mol) was dropwise added to the stirred solution at room temperature and the reaction left 10 min before 1,3-propanedithiol (10.8 g, 0.1 mol) addition. Reaction course was monitorized by TLC (hexane:ether 3:2). After 2 h with stirring at room temperature, the reaction mixture was diluted with dichloromethane (80 ml) and washed with water (30 ml), a 20% sodium carbonate aqueous solution (20 ml) and water (3x15 ml). The organic phase was dried and the solvent evaporated to afford the crude hydroxydithiane (17.11 g), which was distilled to yield pure **11** (14.06 g, 79%). B.p. 110-111°C (0.5 mmHg).

2-(3'-benzyloxypropyl)-1,3-dithiane, 12

To a sodium hydride (193 mg, 8.02 mmol) stirred suspension in THF (20 ml) at room temperature was added a solution of alcohol **11** (1.36 g, 7.64 mmol) in THF. After 30 min with stirring, benzyl bromide (1.34 g, 7.83 mmol) and tetra n-butylammonium bromide (28 mg, 0.076 mmol) were added. Starting compound conversion was TLC monitorized (hexane:ether

1:1). The reaction mixture was stirred overnight at room temperature, filtered through Celite and dried. Solvent evaporation yields compound **12** (2.05 g, quantitative) suitable for the next step. ^{1}H NMR : δ : 7.33 (m, 5H, Ph) ; 4.50 (s, 2H, CH_2-Ph) ; 4.03 (m, 1H, H_2) ; 3.50 (m, 2H, $H_{3'}$) ; 2.85 (m, 4H, H_4 and H_6) ; 1.85 (m, 6H, $H_{1'}$, $H_{2'}$, H_5).

4-benzyloxybutanal, 13[13]

To a stirred solution of dithiane **12** (2.05 g, 7.64 mmol) in 80% aqueous acetonotrile (30 ml), calcium carbonate (0.76 g, 7.64 mmol) and iodomethane (2.85 ml, 45.84 mmol) were added. Dithiane consumption was monitorized by TLC (ether:hexane 1:4). The reaction mixture was kept overnight at room temperature and then diluted with dichloromethane and passed through a silica gel column. The solvent was evaporated in vacuo to yield aldehyde **13** (1.16 g, 85%) suitable for the next step. ^{1}H NMR : δ : 9.80 (t, J=1.6Hz, 1H, CHO) ; 7.33 (m, 5H, C_6H_5) ; 4.50 (s, 2H, CH_2-C_6H_5) ; 3.52 (t, J=6Hz, 2H, H_4) ; 2.56 (dt, J=1.6 and 7Hz, 2H, H_2) ; 1.96 (q, J=6Hz, 2H, H_3).

Ethyl (2E)-6-benzyloxy-2-hexenoate, 14

To a cold (0°C) stirred suspension of 1.51 g (34.60 mmol, 1.3 eq) of NaH (55% in oil) in 40 ml of THF, 6.10 ml (29.16 mmol, 1.1 eq) of $(EtO)_2$ P(O) CH_2 CO_2Et under argon was dropwise added. After stirring for 20 min. at 0°C, 4.72 g (26.51 mmol) of aldehyde **13** in 20 ml of THF was quickly introduced and stirring was continued for 15 min. The reaction mixture was then hydrolyzed with 400 ml of water and extracted with hexane (2x200 ml). The organic phase was washed with 10% aqueous sodium bisulfite solution (50 ml), water (50 ml) and brine (50 ml) before drying (Na_2SO_4). Evaporation followed by column chromatography on silica gel using a 94:6 mixture of hexane : ethyl acetate as eluent, afforded 4.93 g (75% yield) of alkene **14** : oil ; IR(film) 3090-3030, 2980, 2930, 2860, 1715, 1650, 1450, 1370, 1265, 1205, 1165, 1110, 1040, 735 and 700 cm^{-1}. ^{1}H NMR : δ : 7.34 (m, 5H, C_6H_5), 6.97 (dt, J=7.0Hz and 15.5Hz, 1H, H_3), 5.83 (dt, J=1.5Hz and 15.5Hz, 1H, H_2), 4.51 (s, 2H, $PhCH_2O$), 4.19 (q, J=7Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.50 (t, J=6Hz, 2H, H_6), 2.32 (dq, J=7Hz and 1.5Hz, 2H, H_4), 1.79 (tt, J=6.3Hz and 6.7Hz, 2H, H_5), 1.29 (t, J=7Hz, 3H, $CO_2CH_2C\underline{H}_3$) ; Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55 ; H, 8.12. Found : C, 72.71 ; H, 8.10.

[(S)*R*, 3E]-7-benzyloxy-1--p-tolylsulfinyl-3-hepten-2-one, 15

To a cold (-50°C) solution of 47.67 mmol of lithium diisopropylamine (LDA) in 60 ml of THF under argon was dropwise added 6.96 g (45.16 mmol) of (+)-(R)-methyl p-tolylsulfoxide in 30 ml of THF. After stirring for 30 min., this solution was quickly added to a cold (0°C) solution of 5.6 g (22.58 mmol) of ester **14** in 30 ml of THF and was stirred for 15 min. The reaction mixture was then hydrolyzed with 250 ml of a saturated ammonium chloride solution. The organic layer was separated and the aqueous solution was acidified with 5% aqueous H_2SO_4 solution to pH 5-4 and extracted with ethyl acetate (3x200 ml). The organic phase was

washed with a saturated NaCl solution (100 ml), dried (Na_2SO_4), concentrated and column chromatographied on silica using a 94:6 mixture of ether and ethyl acetate as eluent to give 6.4 g (80% yield) of ketosulfoxide **15** : oil ; $[\alpha]_D$ + 171.6 (c 2.48, acetone) ; IR(film) 3080-3020, 2940-2900, 2850, 1705, 1650, 1620, 1485, 1445, 1370, 1265, 1080, ^1H NMR : δ : 7.54 (d for an AA'BB' system, J=8.2Hz, 2H, $C_6H_4CH_3$), 7.33 (m, 5H of OCH_2 C_6H_5 and 2H of AA'BB' system of C_6H_4 CH_3) ; 6.85 (dt, J=7Hz and 16Hz, 1H, H_4), 6.12 (dt, J=1.5Hz and 16Hz, 1H, H_3), 4.50 (s, 2H, $OCH_2C_6H_5$), 3.96 (AB system, J=13Hz, $\Delta\nu$=42Hz, 2H, H_1), 3.48 (t, J=6Hz, 2H, H_7), 2.42 (s, 3H, $SOC_6H_4CH_3$), 2.35 (m, 2H, H_5), 1.75 (dt, J=6.1Hz and 6.8Hz, 2H, H_6) ; Anal. Calcd. for $C_{21}H_{24}O_3S$: C, 70.76 ; H, 6.79. Found : C, 70.89 ; H, 6.87.

[2R, (S)*R*, 3E]-7-benzyloxy-1-[(R)-p-tolylsulfinyl]-3-hepten-2-ol, 16

To 1.37 g (11.9 mmol) of anhydrous $ZnCl_2$ in 30 ml of THF, a solution of 3.52 g (9.88 mmol) of ketosulfoxide **15** was added. After stirring during 30 min at room temperature, the solution was cooled at -78°C and 14.8 ml (14.8 mmol) of a 1M solution of DIBAL in hexane, diluted with 20 ml of THF, was dropwise added and stirred for 2 h. The reaction mixture was quenched with 75 ml of MeOH. The solvent was then evaporated and the residue was diluted with 5% aqueous HCl solution and extracted with CH_2Cl_2 (4x50 ml). The organic layer was washed with 5% aqueous NaOH solution (2x50 ml), saturated NaCl solution (50 ml), dried (Na_2SO_4) and evaporated. The crude was column chromatographed using a 50:50 mixture of ethyl acetate and hexane as eluent to give 3.18 g (90% yield) of **16** : oil ; $[\alpha]_D$ + 98 (c 2.06, acetone) ; IR(film) 3350, 3080-3020, 2910, 2850, 1485, 1445, 1090, 1020, 965, 810, 730, 700 cm^{-1}. ^1H NMR : δ : 7.55 (d, J=7.5Hz, 2H of AA'BB' system of p-tol), 7.32 (m, 7H, 5H of $OCH_2C_6H_5$ and 2H of p-tol), 5.81 (dt, J=7Hz and 15Hz, 1H, H_4), 5.47 (ddt, J=1Hz, 6.5Hz and 15Hz, 1H, H_3), 4.74 (m, X fragment of an ABX system, 1H, H_2), 4.49 (s, 2H, OCH_2-C_6H_5), 3.46 (t, J=6.4Hz, 2H, H_7), 2.88 (AB fragment of an ABX system, J=3Hz, 9Hz and 13Hz, $\Delta\nu$=55Hz, 2H, H_1), 2.43 (s, 3H, C_6H_4-CH_3), 2.15 (m, 2H, H_5), 1.69 (dt, J=6.4Hz and 14Hz, 2H, H_6). Anal. Calcd. for $C_{21}H_{26}O_3S$: C, 70.36 ; H, 7.31. Found : C, 70.19 ; H, 7.18.

[2R, (S)*R*, 3E]-7-benzyloxy-2-(2'-methoxyethoxy) methoxy]-3-hept-1-enyl p-tolylsulfoxide, 17

To a solution of 2.3 g (6.42 mmol) of alcohol **16** in 25 ml of methylene chloride were added 1.67 ml (9.63 mmol, 1.5 eq) of diisopropylethylamine and 1.1 ml (9.63 mmol, 1.5 eq) of β-methoxyethoxymethyl chloride (MEMCl) under argon. After stirring overnight at room temperature, 100 ml of water was added and the aqueous layer was extracted with methylene chloride (3x50 ml). The organic phases were combined and washed with saturated NaCl solution (50 ml) before drying (Na_2SO_4). Evaporation followed by column chromatography, using a mixture 20:10:1 of ether, hexane and isopropanol as eluent, afforded 2.72 g (95% yield) of **17** : oil ; $[\alpha]_D$ + 28.1 (c 1.91, acetone) ; IR(film) 3060-3020, 2910, 2860, 1485, 1445, 1100, 1030 cm^{-1}. ^1H NMR : δ : 7.57 (d, J=8Hz, 2H of AA'BB' system of p-tol), 7.33 (m, 7H, 5H of $C_6H_5CH_2O$ and 2H of AA'BB' system of p-tol), 5.77 (dt, J=6Hz and 15Hz, 1H, H_4), 5.37 (ddt, J=1Hz, 8Hz and 15Hz, 1H, H_3), 4.68 (AB system, J=7Hz, $\Delta\nu$=23Hz, 2H, O-CH_2-O),

4.50 (s, 2H, $PhCH_2O$), 4.35 (dd, J=7Hz and 6.4Hz, 1H, X fragment of ABX system, H_2), 3.51-3.89 (m, 4H, OCH_2CH_2O), 3.47 (t, J=6.5Hz, 2H, H_7), 3.39 (s, 3H, OCH_3), 3.02 (AB fragment of ABX system, J=6.4Hz, 7Hz and 13Hz, $\Delta\nu$=87Hz, 2H, H_1), 2.42 (s, 3H, $C_6H_4CH_3$), 2.18 (m, 2H, H_5), 1.70 (m, 2H, H_6). ^{13}C NMR : δ : 142.17, 141.87, 139.12, 137.06, 130.57, 128.96, 128.20, 128.16, 128.13, 124.83, 93.09, 73.50, 73.01, 72.31, 70.02, 67.91, 64.55, 59.61, 29.55, 29.39, 22.01. Anal. Calcd. for $C_{25}H_{34}O_5S$: C, 67.23 ; H, 7.67. Found : C, 67.07 ; H, 7.80.

(2R, 3E)-1-acetoxy-7-benzyloxy-2 [(2'-methoxyethoxy) methoxy]-3-hepten-1-yl p-tolyl sulfide, 18

1.96 g (4.4 mmol) of sulfoxide **17** and 3 g of anhydrous sodium acetate in 31 ml of Ac_2O are heated at 130-135°C overnight. The reaction mixture is cooled and the solvent is evaporated under vacuum by adding benzene several times. The residue obtained is treated with ether (200 ml) and filtered to remove the salts. Evaporation of solvent yields 2.17 g (quantitative yield) of compound **18** as a mixture of two diastereomers that is used for the following reaction without further purification : oil ; IR(film) 3080-3020, 2910-2840, 1740, 1485, 1445, 1365, 1220, 1100, 1020, 810, 730, 700 cm^{-1}. ^1H NMR : δ : 7.41-7.30 (m, 7H, 5H of C_6H_5-CH_2O and 2H of p-tol), 7.11 (d, J=8Hz, 2H of AA'BB' system of p-tol), 6.17-6.16 (m, 1H, H_1), 5.92-5.70 (m, 1H, H_4), 5.56-5.25 (m, 1H, H_3), 4.80-4.67 (m, 2H, OCH_2O), 4.49 and 4.50 (2s, 2H, $OCH_2C_6H_5$), 4.41-4.29 (m, 1H, H_2), 4.00-3.48 (m, 6H, H_7, OCH_2CH_2O), 3.38 and 3.39 (2s, 3H, OCH_3), 2.33 (s, 3H, C_6H_4-$C\underline{H}_3$), 2.29-2.10 (m, 2H, H_5), 2.02 and 2.04 (2s, 3H, $OCOCH_3$), 1.82-1.60 (m, 2H, H_6).

(2R, 3E)-7-benzyloxy-2-[(2'-methoxyethoxy) methoxy]-3-hepten-1-ol, 19

To a cold (0°C) solution of 450 mg (0.92 mmol) of compound **18** in 4 ml of anhydrous ether under argon, was added 1.28 ml (1.42 mmol) of a 1.12M solution of LAH in ether. After stirring at 0°C for 2 h, the reaction mixture was quenched with 0.5 ml of saturated aqueous Na_2SO_4 solution, and stirred for 30 min, at room temperature. The white precipitate (aluminium salts) formed is filtered and washed with ether (3x10 ml). The organic phases were combined, dried (Na_2SO_4), concentrated and column chromatographed on silica gel, using a 80:20 mixture of ethyl acetate and hexane as eluent to give 224 mg (92% yield) of alcohol **19** : oil ; $[\alpha]_D$ - 81.5 (c 1.15, acetone) ; IR(film) 3450, 3080-3020, 2910-2840, 1445, 1360, 1100, 1080, 970, 730 and 695 cm^{-1}. ^1H NMR : δ : 7.33 (m, 5H, C_6H_5), 5.77 (dt, J=6.0Hz and 15.0Hz, 1H, H_4), 5.33 (ddt, J=1.4Hz, 7.0Hz and 15.0Hz, 1H, H_3), 4.74 (AB system, J=7.0Hz, $\Delta\nu$=12.7Hz, 2H, OCH_2O), 4.50 (s, 2H, OCH_2Ph), 4.13 (m, 1H, H_2), 3.54-3.90 (m, 6H, O-CH_2-CH_2-O and H_1), 3.47 (t, J=6.0Hz, 2H, H_7), 3.40 (s, 3H, OCH_3), 2.16 (q, J=6.0Hz, 2H, H_5), 1.70 (quint., J=6.0Hz, 2H, H_6). ^{13}C NMR : δ : 139.08, 135.72, 128.89 (2C of Ph), 128.16, 128.07, 127.18 (2C of Ph), 93.76, 79.56, 73.42, 72.34, 70.04, 67.78, 66.17, 59.47, 29.62 and 29.52. Anal. Calcd. for $C_{18}H_{28}O_5$: C, 66.64 ; H, 8.70. Found : C, 66.53 ; H, 8.63.

(2R, 3E)-7-benzyloxy-2-[(2'-methoxyethoxy) methoxy]-3-hepten-1-yl acetate, 20

268 mg (0.82 mmol) of alcohol **19** and 826 mg of sodium acetate in 16.5 ml of Ac_2O are stirred overnight at room temperature. The solvent is evaporated under vacuum by adding benzene several times and the residue is treated with ether (150 ml) and filtered to remove the salts. Evaporation of solvent and purification by column chromatography using a 80:20 mixture of hexane and ethyl acetate as eluent yiels 296 mg (98% yield) of acetate **20** : oil ; $[\alpha]_D$ - 74.5 (c 1.33, acetone) ; IR(film) 3080, 3060, 3020, 2920, 2870, 1735, 1450, 1365, 1235, 1105, 1030, 970, 730, 695 cm^{-1}. ^1H NMR : δ : 7.33 (m, 5H, C_6H_5), 5.79 (dt, J=6.6Hz and 15.4Hz, 1H, H_4), 5.32 (ddt, J=1.3Hz, 7.7Hz and 15.4Hz, 1H, H_3), 4.72 (AB system, J=6.9Hz, $\Delta\nu$=19Hz, 2H, OCH_2O), 4.49 (s, 2H, OCH_2Ph), 4.31-4.24 (m, X fragment of an ABX system, 1H, H_2), 4.10 (AB fragment of ABX system, J=-11.5Hz, 7.0Hz and 4.0Hz, $\Delta\nu$=17Hz, 2H, H_1), 3.87-3.52 (m, 4H, OCH_2CH_2O), 3.46 (t, J=6.7Hz, 2H, H_7), 3.39 (s, 3H, OCH_3), 2.16 (qd, J=6.7Hz and 1.3Hz, 2H, H_5), 2.07 (s, 3H, $OCOCH_3$), 1.70 (quint, J=6.7Hz, 2H, H_6). ^{13}C NMR : δ : 171.28, 139.06, 136.48, 128.88 (2C of Ph), 128.14, 128.06, 126.47 (2C of Ph), 93.05, 74.78, 73.43, 72.24, 69.96, 67.35, 67.04, 59.47, 29.58, 29.43 and 21.36. Anal. Calcd. for $C_{20}H_{30}O_6$: C, 65.55 ; H, 8.25. Found : C, 65.59 ; H, 8.28.

(2*S*, 3*R*, 4*S*)-1-acetoxy-7-benzyloxy-2 [(2'-methoxyethoxy) methoxy]-3,4-heptane diol, 21

To 219 mg (0.87 mmol) of alkene **20** in 17 ml of methylene chloride, 128 mg (1.14 mmol, 1.3 eq) of dihydrated trimethyl amine N-oxide and 89 µl ($8.7x10^{-3}$ mmol, 0.01 eq) of a 2.5% solution of osmium tetroxide in CCl_4 were added. After stirring for 48 h, a small quantity of sodium bisulfite was added (to decompose the excess of Me_3 N(O) and the organic phase is washed with water (2x10 ml), dried (Na_2SO_4), evaporated and column chromatographed using a 24:71:5 mixture of ethyl acetate, hexane and iso-propanol as eluent to give 247 mg (71% yield) of diol **21** (and 62 mg of the other possible diol) : oil ; [α] = - 3 (589 nm), - 4 (524.5 nm), - 5 (489 nm), (c 1.42, acetone). IR(film) : 3440, 3080-3020, 2920, 2870, 1730, 1450, 1365, 1240, 1100, 1025, 740 and 700 cm^{-1}. ^1H NMR : δ : 7.35-7.30 (m, 5H, OCH_2 $C_6\underline{H}_5$), 4.81 (AB system, J=7.1Hz, $\Delta\nu$=22.0Hz, 2H, OCH_2O), 4.51 (s, 2H, C_6H_5 $C\underline{H}_2O$), 4.29 (AB fragment of ABX system, J=12.0Hz, 5.0Hz and 3.0Hz, 2H, H_1), 4.02-3.68 (m, 5H, H_2, H_3, H_4 and H_7), 3.54, 3.46 (m, 4H, OCH_2CH_2O), 3.38 (s, 3H, OCH_3), 2.08 (s, 3H, CH_3CO), 1.85-1.61 (m, 4H, H_5 and H_6). ^{13}C NMR : δ : 171.70, 138.95, 128.95, 128.34, 128.15 (Three last signals for 5C of Ph), 95.23, 76.20, 73.56, 72.79, 72.24, 71.02, 69.17, 68.05, 64.01, 59.56, 31.28, 26.98 and 21.49. Anal. Calcd. for $C_{20}H_{32}O_8$: C, 59.98 ; H, 8.05. Found : C, 60.12 ; H, 8.12.

(2*S*, 3*S*, 4*S*)-7-benzyloxy-3,4-isopropylidenedioxy-2-[(2'-methoxyethoxy)methoxy]-heptyl acetate, 22

p-TsOH (3 mg) was added to a solution of 753 mg (1.88 mmol) of diol **21** in 20 ml of a 50:50 mixture of acetone and 2,2-dimethoxypropane and the reaction mixture was stirred for 20 min at room temperature. Successive addition of aqueous saturated $NaHCO_3$ solution,

shaking with a 50:50 mixture of Cl_2CH_2 and water, washing the organic phase with saturated aqueous NaCl solution, drying (Na_2SO_4) and evaporation, furnished the corresponding acetonide **22**, that was column chromatographed using a 50:50 mixture of ethyl acetate and hexane to yield 800 mg (93% yield) of pure compound **22** : oil ; [α] = - 18.7 (589 nm), - 26.4 (500 nm), - 33.3 (450 nm) ; (c 1.84, acetone) ; IR(film) 3090, 3060, 3030, 2980, 2920, 2870, 1740, 1450, 1380, 1370, 1240, 1160, 1100-1040, 740, 700 cm^{-1}. ^1H NMR : δ : 7.33 (m, 5H, $OCH_2C_6H_5$), 4.81 (AB system, J=7.1Hz, $\Delta\nu$=22.0Hz, 2H, OCH_2O), 4.51 (s, 2H, $C_6H_5CH_2O$), 4.29 (AB fragment of ABX system, J=12Hz, 5Hz and 3Hz, 2H, H_1), 4.02-3.68 (m, 5H, H_2, H_3, H_4 and H_7), 3.54-3.46 (m, 4H, OCH_2CH_2O), 3.38 (s, 3H, OCH_3), 2.08 (s, 3H, CH_3CO_2), 1.85-1.61 (m, 4H, H_5 and H_6), 1.39 and 1.36 (2s, 6H, $OC(CH_3)_2O$). ^{13}C NMR : δ : 171.32, 139.17, 128.90, 128.16, 128.08 (Three last signals for 5C of Ph), 109.58, 95.23, 80.21, 79.56, 76.33, 73.40, 72.23, 70.64, 68.03, 64.21, 59.59, 31.44, 28.02, 27.60, 26.92 and 21.46.

(2*S*,3*S*,4*S*)-7-hydroxy-3,4-isopropylidenedioxy-2-[(2'-methoxyethoxy) methoxy] heptyl acetate, 23

A solution of 780 mg (1.76 mmol) of O-benzyl derivative **22** in 15 ml of EtOH under argon was added to a suspension of 200 mg of Raney Ni (previously activated) in 50 ml of EtOH. The mixture was stirred at 25°C for 5 h, and filtered through a fritted funnel. After elimination of the solvent under vacuum, the residue was column chromatographed on silica gel, using ethyl acetate as eluent to give 604 mg (98% yield) of **23** : oil ; [α] = - 21 (589 nm), - 25 (540 nm), (500 nm), - 30.8 (489 nm) ; (c 2.35, acetone) ; IR(film) 3460, 2980, 2920, 2870, 1735, 1445, 1375, 1240 cm^{-1}. ^1H NMR : δ : 4.82 (AB system, J=7Hz, $\Delta\nu$=22.1Hz, 2H, OCH_2O), 4.30 (AB fragment of ABX system, J=-11.5Hz, 5Hz and 3Hz, $\Delta\nu$=11.5Hz, 2H, H_7), 4.06-3.55 (m, 9H, OCH_2CH_2O, H_2, H_3 H_4 and H_7), 3.39 (s, 3H, OCH_3), 2.09 (s, 3H, CH_3CO_2), 1.80-1.64 (m, 4H, H_5 and H_6), 1.41 and 1.37 (2s, 6H, $OC(CH_3)_2O$). ^{13}C NMR : δ : 171.38, 109.71, 95.63, 80.28, 79.71, 76.40, 72.30, 68.11, 64.29, 63.01, 59.64, 31.36, 30.01, 27.96, 27.58, and 21.47. Anal. Calcd. for $C_{16}H_{30}O_8$: C, 54.84 ; H, 8.63. Found : C, 54.63 ; H, 8.51.

(2*S*, 3*S*, 4*S*)-7-oxo-3,4-isopropylidenedioxy-2-[(2'-methoxyethoxy) methoxy] heptyl acetate, 24

To a cold (-50°C) solution of 1 ml (11 mmol) of oxalyl chloride $(COCl)_2$ in 13 ml of CH_2Cl_2, 1.7 ml, 24 mmol) of dimethyl sulfoxide are added. After stirring 10 min, a solution of 232 mg (1.09 mmol) of alcohol **23** in 10 ml of CH_2Cl_2 is added, the temperature allowed is to reach at -10°C and it is stirred for 15 min. Then, 3.5 ml (25 mmol) of triethylamine are added and after stirring for 5 min, the temperature is left to arrive at room temperature and 20 ml of water added. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (2x25 ml). The combined organic phase was washed with a saturated NaCl solution (25 ml), dried (Na_2SO_4), concentrated and column chromatographied on silica gel using a 50:50 mixture of hexane and ether as eluent to give 352 mg (93% yield) of aldehyde **24** : oil ; [α] - 14.5 (589 nm), - 17.4 (540 nm), - 20.5 (500 nm), - 21.5 (489 nm) [c 1.51, acetone] ; IR (film) 2970, 2920, 2880, 1730, 1370, 1235 cm^{-1}. ^1H NMR : δ : 4.81 (AB system, J=7.1Hz, $\Delta\nu$=23Hz,

2H, OCH_2O), 4.29 (AB fragment of ABX system, J=12.0Hz, 4.5Hz and 3.0Hz, 2H, H_1), 3.52-4.04 (m, 7H, H_2, H_3, H_4, OCH_2CH_2O), 3.38 (s, 3H, OCH_3), 2.64 (m, 2H, H_6), 2.08 (s, 3H, $OCOCH_3$), 1.83 (m, 2H, H_5), 1.38 and 1.35 (2s, 6H, $OC(CH_3)_2O$). ^{13}C NMR : δ : 201.86, 171.10, 109.66, 95.46, 79.73, 78.67, 76.34, 72.13, 68.01, 63.92, 59.42, 40.70, 27.74, 27.38, 26.96, 21.26.

(2*S*,3*S*,4*S*,7*Z*,15*R*)-15-(tert-butyldimethylsilyloxy)-3,4-isopropylidenedioxy-2-[(2'-methoxy-ethoxy) methoxy]-7-hexadecen-1-yl acetate, 25

To 939 mg (1.45 mmol) of dry, recrystallized phosphonium salt **10** in 30 ml of anhydrous THF under argon, 973 µl (1.46 mmol) of a 1.5M solution of n-BuLi in toluene was added with stirring at 0°C. The temperature was allowed to reach 25°C and stirring was continued for 1 h to obtain a complete formation of the corresponding ylide. 350 mg (1 mmol) of aldehyde **24** dissolved in 30 ml of anhydrous THF was added via a cannula to the freshly prepared ylide at room temperature and stirring was continued for 2 h. The reaction mixture was quenched with 30 ml of water and extracted with ether (5x40 ml). The combined organic extract was washed with saturated NaCl solution (40 ml), dried (Na_2SO_4), concentrated and column chromatographied on silica gel using a 75:25 mixture of hexane and ether as eluent to give 377 mg (64% yield) of alkene **25** : oil ; IR(film) : 2920, 2850, 1740, 1450, 1375, 1240, 835 and 775 cm^{-1}. ^1H NMR : δ : 5.37 (m, 2H, H_7 and H_8), 4.81 (AB system, J=7.0Hz, $\Delta\nu$=23.0Hz, 2H, OCH_2O), 4.29 (AB fragment of ABX system, J=-12.0Hz, 5.0Hz and 3.0Hz, $\Delta\nu$=66Hz, 2H, H_1), 4.00-3.53 (m, 8H, OCH_2CH_2O, H_2, H_3, H_4 and H_{15}), 3.39 (s, 3H, OCH_3), 2.27-1.18 (m, 25H, $OC(CH_3)_2O$, $OCOCH_3$, H_5, H_6, H_9, H_{10}, H_{11}, H_{12}, H_{13} and H_{14}), 1.11 (d, J=6.0Hz, 3H, H_{16}), 0.89 (s, 9H, $SiBu^t$), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR : δ : 171.41, 131.54, 129.25, 109.67, 95.65, 80.30, 79.21, 76.40, 72.36, 69.31, 68.13, 64.30, 59.71, 40.42, 34.96, 30.37, 30.31, 30.25, 28.13, 27.89, 27.67, 26.59, 26.41, 24.51, 24.46, 21.56, 18.83, -3.73, -4.02.

(2*S*,3*S*,4*S*,15*R*)-15-(tert-butyldimethylsilyloxy)-3,4 isopropylidenedioxy-2-[(2'-methoxyethoxy) methoxy]-hexadecyl acetate, 26

253 mg (0.43 mmol) of alkene **25** was dissolved in 15 ml of ethyl acetate and the flask was flushed with argon. Then, 40 mg of 10% Pd/C was introduced, the flask was flushed with argon again, and the mixture was stirred under hydrogen atmosphere at 5 bars of pressure and 25°C overnight. The reaction mixture was then filtered through celite, the solvent was evaporated and the residue was column chromatographed using a 75:25 mixture of ether and hexane as eluent to give 228 mg (90% yield) of compound **26** : oil ; [α] = - 19 (589 nm), - 23 (540 nm), - 27 (500 nm), - 28 (489 nm) (c 1.09, acetone). ^1H NMR : δ : 4.82 (AB system, J=7.0Hz, $\Delta\nu$=21Hz, 2H, OCH_2O), 4.28 (AB fragment of ABX system, J=-11.5Hz, 5.0Hz and 3.0Hz, $\Delta\nu$=64Hz, 2H, H_1), 3.88-3.53 (m, 8H, OCH_2CH_2O, H_2, H_3, H_4 and H_{15}), 3.39 (s, 3H, OCH_3), 2.09 (s, 3H, $OCOCH_3$), 1.61-1.23 (m, 26H, $OC(CH_3)_2O$ from H_5 to H_{14}), 1.12 (d, J=6.0Hz, 3H, H_{16}), 0.89 (s, 9H, $SiBu^t$), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR ($CDCl_3$, 50 MHz) : δ : 171.44, 109.61,

95.67, 80.42, 79.85, 76.38, 72.33, 69.32, 68.08, 64.35, 59.72, 40.42, 34.98, 30.37, 30.32, 30.27, 30.23, 30.02 (Five last signals for 6 methylenic C), 28.10, 27.70, 26.84, 26.59, 26.47, 24.48, 21.57, 18.83, -3.75, -4.04. Anal. Calcd. for $C_{31}H_{62}O_8Si$: C, 63.01 ; H, 10.58. Found : C, 63.25 ; H, 10.73.

(2*S*,3*S*,4*S*,15*R*)-15-(tert-butyldimethylsilyloxy)-3,4-isopropylidenedioxy-2-[(2'-methoxy-ethoxy) methoxy] hexadecanol, 27

To 170 mg (0.28 mmol) of acetate **26** dissolved in 20 ml of a 95:5 mixture of methanol and water, an small quantity of lithium hydroxide was added, and the mixture was stirred for 4 h at room temperature. The solvent was then concentrated under vacuum and 30 ml of a 50:50 mixture of ether and water was added to the residue. Both phases were separated and the aqueous layer was extracted with ether (5x25 ml). The ether extract was washed with saturated NaCl solution (30 ml), dried (Na_2SO_4), and concentrated under vacuum to give a crude oil which was column chromatographed on silica gel using a 75:25 mixture of ether and hexane as eluent to give 142 mg (90% yield) of alcohol **27** : oil ; [α] = - 22 (589 nm), - 27 (540 nm), - 32 (500 nm), - 33 (489 nm) (c 2.78, acetone) ; IR(film) 3460, 2920, 2840, 1450, 1370, 1250, 830, 770 cm^{-1} ^1H NMR : δ : 4.82 (AB system, J=7.0Hz, $\Delta\nu$=15.0Hz, 2H, OCH_2O), 4.00-3.55 (m, 10H, OCH_2CH_2O, H_1, H_2, H_3, H_4 and H_{15}), 3.40 (s, 3H, OCH_3), 1.65-1.23 (m, 26H, $OC(CH_3)_2O$ from H_5 to H_{14}), 1.12 (d, J=6.0Hz, 3H, H_{16}), 0.89 (s, 9H, $SiBu^t$), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR : δ : 109.44, 96.66, 83.29, 80.71, 80.04, 72.22, 69.29, 68.27, 63.30, 59.59, 40.37, 34.84, 30.34, 30.31, 30.28, 30.22, 30.18 (Five last signals for 6 methylenic C), 28.06, 27.66, 26.76, 26.55, 26.43, 24.45, 18.79, -3.78 and -4.08.

(2*E*,4*S*,5*S*,6*S*,17*R*)-17-(tert-butyldimethylsilyloxy)-5,6-isopropylidenedioxy-4-[(2'-methoxy-ethoxy) methoxy]-2-octadecenoate, 28

To a cold (-50°C) solution of 226 µl (2.54 mmol) of $(COCl)_2$ in 7 ml of anhydrous methylene chloride under argon, 283 µl (3.98 mmol) of DMSO are added. After stirring 15 min, a solution of 139 mg (0.25 mmol) of alcohol **27** in 7 ml of methylene chloride are added to the above mixture and stirred for 1 h. Then, 1.85 ml of Et_3N is added and the temperature is allowed to reach 0°C under stirring for 90 min.

To a cold (0°C) solution of 1.6 ml (7.64 mmol) of $(EtO)_2P(O)CH_2CO_2Et$ in 5 ml of methylene chloride under argon, 5.15 ml (7.72 mmol) of a 1.5M solution of n-BuLi in toluene is added. After stirring for 20 min, this solution is added to the aldehyde solution. The mixture is stirred for 10 min, 20 ml of saturated NaCl solution are then added, the two phases are separated and the aqueous layer is extracted with methylene chloride (5x25 ml). The organic extracts are dried (Na_2SO_4), evaporated under vacuum and column chromatographed on silica gel using a 70:30 mixture of hexane and ether as eluent, to give 132 mg (85% yield) of alkene **28** : oil ; [α] = + 10 (589 nm), + 12 (540 nm), + 14 (500 nm), + 15 (489 nm) (c 3.06, acetone). ^1H NMR : δ : 6.90 (dd, J=16.0Hz and 6.5Hz, 1H, H_3), 6.05 (dd, J=16.0Hz and 1.0Hz, 1H, H_2), 4.74 (s, 2H, OCH_2O), 4.41-4.23 (m, 1H, H_4), 4.21 (q, J=7.0Hz, 2H,

$CO_2CH_2CH_3$), 3.95-3.45 (m, 7H, OCH_2CH_2O, H_5, H_6, H_{17}), 3.38 (s, 3H, OCH_3), 1.80-1.18 (m, 29H, $OC(CH_3)_2O$, $CO_2CH_2CH_3$ from H_7 to H_{16}), 1.11 (d, J=6.0Hz, 3H, H_{18}), 0.88 (s, 9H, $SiBu^t$), 0.04 (s, 6H, $SiMe_2$). ^{13}C NMR : δ : 166.39, 144.38, 124.95, 109.81, 94.43, 82.71, 79.02, 76.25, 72.31, 69.33, 68.05, 61.22, 59.69, 40.41, 34.62, 30.38, 30.33, 30.27, 30.19 (Four last signals for 6 methylenic C), 28.11, 27.46, 26.75, 26.58, 26.48, 24.49, 18.83, 14.87, -3.73, -4.03.

(2*E*,4*S*,5*S*,6*S*,17*R*)-17-(tert-butyldimethylsilyloxy)-5,6-isopropylidenedioxy-4-[(2'-methoxy-ethoxy) methoxy]-2-octadecenoic acid, 29

To 130 mg (0.21 mmol) of ethyl ester **28** in 20 ml of a 95:5 mixture of methanol and water, a small quantity of lithium hydroxide was added and stirring was maintained overnight. The solvent was then concentrated under vacuum and 30 ml of a 50:50 mixture of ether and water was added to the residue. Both phases were separated and the aqueous layer was extracted with ether (5x25 ml). The ethereal extract was washed with saturated NaCl solution (40 ml), dried (Na_2SO_4), and concentrated under vacuum to give a crude oil which was column chromatographed on silica gel using a 95:5 mixture of methylene chloride and methanol as eluent to give 105 mg (85% yield) of acid **29** : oil ; $[\alpha]_D$ + 66 (c 0.5, methylene chloride). ^1H NMR : δ : 7.00 (dd, J=16.0Hz and 6.5Hz, 1H, H_3), 6.08 (d, J=16.0Hz, 1H, H_2), 4.76 (s, 2H, OCH_2O), 4.35 (t, J=6.5Hz, 1H, H_4), 4.00-3.55 (m, 7H, OCH_2CH_2O, H_5, H_6 and H_{17}), 3.39 (s, 3H, OCH_3), 1.65-1.18 (m, 26H, $OC(CH_3)_2O$ from H_7 to H_{16}), 1.12 (d, J=6.1Hz, 3H, H_{18}), 0.89 (s, 9H, $SiBu^t$), 0.05 (s, 6H, $SiMe_2$).

(2*E*, 4*S*, 5*S*, 6*S*, 17*R*)-17-hydroxy-5,6-isopropylidenedioxy-4-[(2'-methoxy-ethoxy) methoxy]-2-octadecenoic acid, 30

98 mg (0.17 mmol) of the acid **29** was dissolved in 2 ml of anhydrous THF and treated with 0.85 ml (0.85 mmol, 5 eq) of a 1M solution of n-Bu_4NF in THF, under argon and at 0°C. Stirring was continued for 48 h at room temperature and then the reaction mixture was diluted with ether (150 ml), washed with water (20 ml) and saturated NaCl solution (20 ml), and dried (Na_2SO_4). Evaporation of solvent and purification by column chromatography using a 93:7 mixture of methylene chloride and methanol as eluent gave 76 mg (95% yield) of alcohol **30** : oil ; [α] = + 17 (589 nm), + 19 (540 nm), + 23 (500 nm), + 25 (489 nm) (c 0.22, methylene chloride) ; IR(film) 3420, 2920, 2850, 1700, 1450, 1375, 1250, 1170, 1110 and 1030 cm^{-1}. ^1H NMR : δ : 6.90 (dd, J=16.0Hz and 6.5Hz, 1H, H_3), 6.05 (d, J=16.0Hz, 1H, H_2), 4.75 (s, 2H, OCH_2O), 4.35 (t, J=6.5Hz, 1H, H_4), 4.00-3.50 (m, 7H, OCH_2CH_2O, H_5, H_6 and H_{17}), 3.39 (s, 3H, OCH_3), 1.80-1.10 (m, 29H, H_{18}, $OC(CH_3)_2O$ from H_7 to H_{16}).

(2*E*, 4*S*, 5*S*, 6*S*, 17*R*)-5,6-isopropylidenedioxy-4-[(2'-methoxyethoxy) methoxy]-17-methyl-2-heptadecenolide, 31

75 µl (0.52 mmol, 3.25 eq) of 2,5-Dichlorobenzoyl chloride was added to a mixture of 76 mg (0.16 mmol) of hydroxy acid **30** and 0.1 ml (0.71 mmol, 4.4 eq) of Et_3N in 3 ml of THF. The mixture was stirred for 8 h at room temperature. After filtration of triethylamine hydrochloride, the filtrate was diluted with toluene (120 ml) and added under high-dilution conditions to a refluxing solution of 117 mg (0.96 mmol, 6 eq) of 4-dimethylaminopyridine in 40 ml of toluene over a period of 2 h.
The reaction mixture was diluted with ether (200 ml), washed successively with 3% aqueous sodium hydrogenocarbonate solution (40 ml), and water (40 ml), dried ($MgSO_4$) and purified by column chromatography using a 50:50 mixture of ether and hexane as eluent to give 39 mg (55% yield) of lactone **31** : oil ; $[\alpha] = +10$ (589 nm), + 13 (540 nm), + 15 (500 nm), + 16 (489 nm) (c 0.96, methylene chloride). ^1H NMR : δ : 6.90 (dd, J=7.6Hz and 16.0Hz, 1H, H_3), 6.03 (dd, J=1.0Hz and 16.0Hz, 1H, H_2), 5.05 (m, 1H, H_{17}), 4.78 (AB system, J=7.1Hz, $\Delta\nu$=6.0Hz, 2H, OCH_2O), 4.41 (d, J=7.6Hz, 1H, H_4), 3.9-3.5 (m, 6H, H_5, H_6, OCH_2CH_2O), 3.38 (s, 3H, OCH_3), 1.70-1.15 (m, 29H from H_7 to H_{16}, C(17)-CH_3, $OC(Me)_2O$). ^{13}C NMR : δ : 165.03, 142.26, 125.79, 108.76, 93.81, 81.91, 74.91, 73.94, 71.63, 71.10, 67.14, 58.96, 35.30, 31.65, 27.92, 27.69, 27.49, 27.36, 27.16, 26.87, 26.53, 26.15, 24.66, 23.51, 20.49.
HRMS (EI) 456.3077M+ ; Calcd. for $C_{25}H_{44}O_7$: 456.3087.

(-)(2*E*, 4*S*, 5*R*, 6*S*, 17*R*) Aspicilin

8.3 µl (66.10^{-3} mmol, 2 eq) of boron trifluoride-ethyl ether complex was added to a mixture of 15 mg (33.10^{-3} mmol) of compound **31** and 11 µl (0.131 mmol, 4 eq) of 1,2-ethanedithiol in 17 ml of methylene chloride, under argon and at 0°C. After stirring 45 min., the mixture was diluted with methylene chloride (20 ml) and saturated $NaHCO_3$ (20 ml) was added. Both phases were separated and the aqueous layer was extracted with methylene chloride (5x25 ml). The organic extract was washed with saturated NaCl solution (25 ml), dried (Na_2SO_4), and concentrated in vacuo to give a crude solid which was column chromatographed on silica gel using ether as eluent to give 8 mg (74% yield) of (-)-Aspicilin as a white solid. The spectroscopic characteristics for this compound were the same as those reported[3].

(-) Aspicilin : a white solid, m.p. 149-151°C (lit[2,3,5] 150-152°) ; $[\alpha]_D$ - 33 (c=4.1, chloroform, lit[5] - 34) ; IR (KBr) : 3450, 3275, 2927, 2855, 1716, 1459, 1364, 1245, 1180, 1076 and 988 cm^{-1}. ^1H NMR ($CDCl_3$, 80 MHz) : δ : 6.89 (dd, J=5.0Hz and 15.8Hz, 1H, H_3) ; 6.08 (dd, J=1.5Hz and 15.8Hz, 1H, H_2) ; 5.05 (m, 1H, H_{17}) ; 4.56 (m, 1H, H_4) ; 3.85-3.33 (m, 2H, H_6 and H_5) ; 1.75-1.05 (m, 22H, from H_7 to H_{17} and CH_3).
HRMS(EI) 328.2247M+, Calcd for $C_{18}H_{32}O_5$: 328.2249.

Acknowledgments : The help of NATO is gratefully acknowledged for a grant to Dr. Fernandez as well as that of the spanish "Direccion General de Investigacion Cientifica y Tecnica" for a grant to Dr. Maestro.

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a) on leave from the University of Sevilla (Faculty of Pharmacy).

b) on leave from the University Autonoma of Madrid.

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