Tetrahedron Vol 45, No 7, pp 2057 to 2065, 1989
Printed in Great Britain

0040-4020/89 $3.00+.00

TOTAL ENANTIOSPECIFIC SYNTHESES OF 13(S)-HYDROXY 9Z, 11E-OCTADECADIENOIC (CORIOLIC) ACID AND 13(S)-N-TOSYLAMINO ANALOGUE

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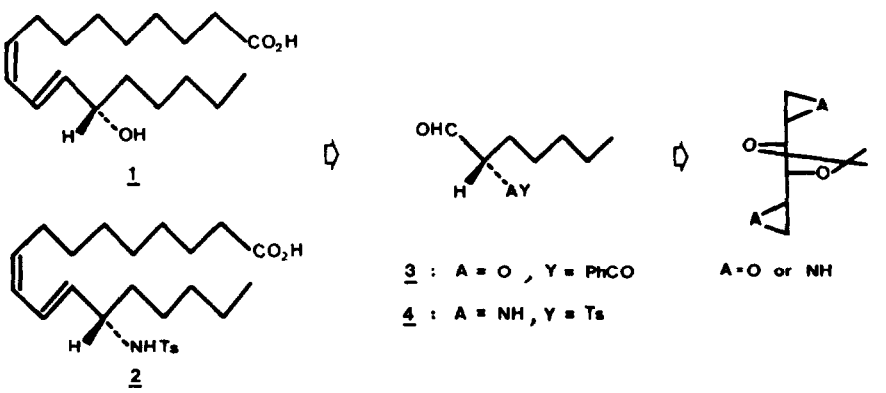
(*Received in Belgium 7 December* 1988)

Summary : The total syntheses of 13(S)-hydroxy 9Z, 11E-octadecadienoic (coriolic) acid and its 13(S)-N-tosylamino analogue are reported via a short, efficient, enantiospecific route from D-mannitol.

Coriolic acid[1] 1 is an oxygenated unsaturated fatty acid. This metabolite of linoleic acid in plants andanimals, exhibits interesting biological activities. Coriolic acid has been isolated from rice plant cultivations and has shown to be active in the plants natural defense against rice blast desease[2]. Present in bovine heart mitochondria it was shown to possess cation-specific ionophoric activity[3]. In addition recent studies have demonstrated that this metabolite stimulates prostacyclin production by cultured bovine endothelial cells and inhibits platelet adhesion to cultured human endothelium[4]. These findingsevoke considerable interest in its total synthesis[5] as an aid to further pharmacological evaluation. Furthermore, structural analogues of coriolic acid could prove useful as specific inhibitors of the lipoxygenases involved in the metabolism of fatty acids. Thus, we have incorporated at the C-13 position of octadecadienoic acid an N-tosylamino group, a potential bidentate ligand which could chelate the iron atom in the active site of a lipoxygenase[6].

We report here a short enantiospecific synthesis of coriolic acid 1 and of its N-tosylamino analogue 2 following the retrosynthetic pathway depicted in scheme I.

Scheme I



The chiral α-hydroxyaldehyde 3 and α-aminoaldehyde 4 are the key targets of these syntheses. Diepoxide 5 or bis-aziridine 6 readily obtained from D-mannitol following a method previously described,[7] are respectively precursors of aldehydes 3 and 4 of S configuration.

Nucleophilic opening of the enantiomerically pure diepoxide[8a] or N-tosyl bis-aziridine[8a,b] by dibutylcopperlithium, followed by hydrolysis of the acetonide and oxidative cleavage of the 3,4-diols respectively 8 or 10 leads to α-hydroxyaldehyde 3 or α-aminoaldehyde 4 without any racemisation (scheme II).

Reaction of 3 or 4 with formylmethylene triphenylphosphorane resulted in unsaturated aldehydes 11 and 12 [9] (scheme III).

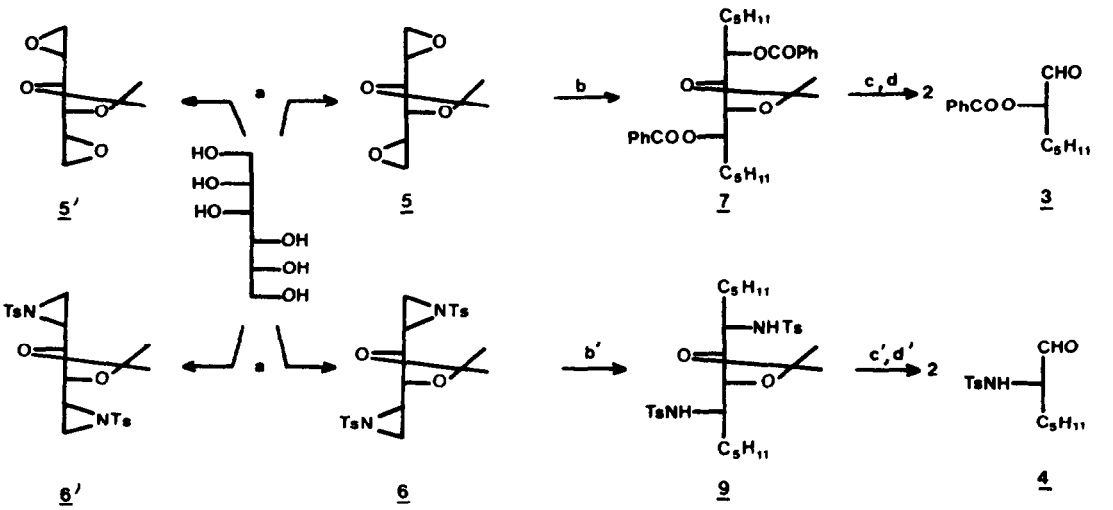
Condensation of 11 with the ylidederived from 8-carboxymethyl octyltriphenylphosphonium bromide 15 provided Z,E isomers of 13 in a 85:15 ratio. In fact it is necessary to raise the temperature to RT for the reaction to be complete. Separation of the isomers by HPLC followed by saponification leads to coriolic acid 1[11]. Enantiomeric purity of coriolic acid methyl ester (methyl coriolate) has been confirmed by HPLC on chiral phase column.

When reacted with the same ylideat -78°C, aminoaldehyde 12 leads to ester 14 (precursor of acid 2) in 70 % yield. The configuration of the 9-10 double bond is exclusively Z.

The (R)-enantiomers of 1 or 2 could be obtained by the same method starting from 5' or 6' [7].

Biological investigations of these compounds are currently in progress.

Scheme II

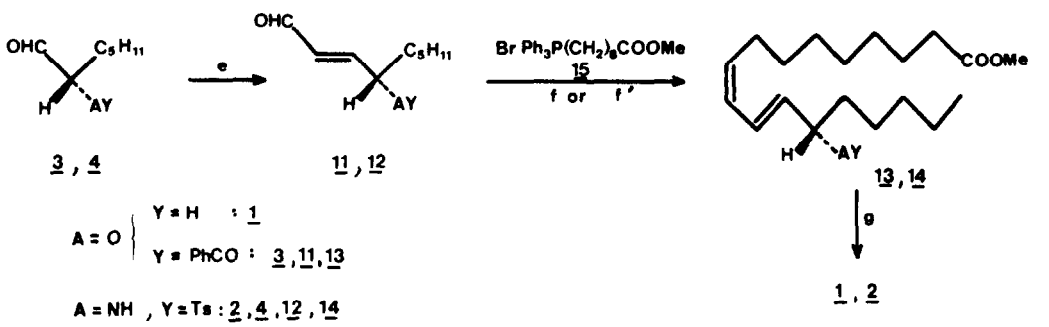


(a) : ref.7

(b) : nBu_2CuLi, Et_2O, -5°C followed by PhCOCl, 0°C ; 83 % - (c) : TFA/H_2O 9:1, 0°C, 15min ; 76 % - (d) : $Pb(OAc)_4$, CH_2Cl_2, -10°C, 1h ; 90 %.

(b') : nBu_2CuLi, THF, -30°C ; 95 % - (c') : TFA/H_2O 9:1, 0°C, 1h ; 92 % - (d') : $Pb(OAc)_4$, CH_2Cl_2, -20°C, 15min ; 100 % crude 4.

Scheme III



A=O - (e) : $OHCCH_2PPh_3Cl$ (1.2 eq.), Et_3N(1.5 eq.), C_6H_6, RT, 24h ; 85 % - (f) : 15, $LiN(SiMe_3)_2$, THF/HMPA 4:1, -78°C ⟶ RT ; 55 % - (g) : K_2CO_3, MeOH/H_2O 4:1, RT.

A=NH 60 % yield of 12 for (d') and (e) - (f') : 15, $KN(SiMe_3)_2$, THF, -78°C, 1h ; 70 %.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian EM 390 (90 MHz) or a Bruker AM 250 (250 MHz). All signals were expressed as ppm downfield from tetramethylsilane used as an internal standard (δ-value). ^{13}C NMR spectra were obtained on a Bruker AM 250. To facilitate the notation of ^1H and ^{13}C NMR data in the experimental section, only half of symmetrical molecules are numbered. Infrared spectra were obtained with a Perkin-Elmer 783 spectrophotometer. Optical rotations were obtained with the indicated solvent and concentration by using a Perkin-Elmer 241-C polarimeter. Mass spectrometry (MS,70eV) was performed on a Riber 10-10 instrument. All reactions were carried out under an inert atmosphere of nitrogen or argon and were monitored by thin layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Flash chromatography[12] was performed with Merck Kieselgel 60 (230-400 mesh ASTM) silica.

To the phosphonium salt (15) :

9-Bromo nonanoic acid. To chromic anhydride (5g, 50mmol) in water (7.2 ml) at 0°C were added dropwise concentrated sulfuric acid (4.35 ml, 78.6 mmol) followed by water (14.3 ml). The resulting mixture was then slowly added to a solution of 9-bromo nonanol[13] (7.6g, 34.2 mmol) in acetone (20.5 ml) at -5°C. After stirring for 2h at 0°C, then for 2h at room temperature, 30ml of ether were added and the mixture was extracted several times (3x30 ml). The combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (30 % ethyl acetate in cyclohexane) gave the 9-bromo nonanoïc acid, as a colorless oil (5.70g, 70 % yield). IR (neat) cm^{-1} : 3100 (OH), 1710 (C=O) ; ^1H NMR (90 MHz, $CDCl_3$) δ 3.40 (t,2H,$-CH_2-Br$), 2.35 (t,2H,$\underline{CH_2}-COOH$), 2.00-1.20 (m,12H).

Methyl 9-bromo nonanoate. To 9-bromo nonanoïc acid (1.79g, 7.5 mmol) in methanol (3.7ml) was added sulfuric acid (50 µl) at room temperature. The reaction mixture was then heated at reflux for 7h, poured into 5 ml of ice water and extracted several times with ether. The combined organic extracts were washed with 3 % aqueous $NaHCO_3$, then with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (5 % ethyl acetate in cyclohexane) gave the methyl ester as a colorless oil (1.80g, 95 % yield) : ^1H NMR (90 MHz, $CDCl_3$) δ 3.65 (s,3H,$COOCH_3$), 3.40 (t,2H,J=7Hz,CH_2Br), 2.30 (t,2H,J=7Hz,$\underline{CH_2}-COOCH_3$), 2.00-1.20 (m,12H).

8-Carboxymethyl octyltriphenylphosphonium bromide (15). To triphenylphosphine (2.35g, 8.9 mmol) was added methyl 9-bromo nonanoate (1.80g, 7.14 mmol) in acetonitrile (54 ml). The solution was heated at reflux for 5 days, after which the solvent was evaporated. Flash chromatography of the residue on silica gel (100 % ethyl acetate then 10 % ethanol in ethyl acetate) gave a thick, hygroscopic syrup (3g, 82 % yield) : IR (neat) cm^{-1} : 1730 (C=O) ; ^1H NMR (90 MHz, $CDCl_3$) δ 8.00-7.50 (m,15H,PPh_3Br), 3.70 (m,2H,$\underline{CH_2}-PPh_3Br$), 3.60 (s,3H,COOMe), 2.20 (t,2H,$\underline{CH_2}-COOCH_3$), 1.80-1.00 (m,12H).

To the coriolic acid (1) :

6(S),9(S)-Dibenzoyloxy-7(R),8(R)-O-methylethylidene-7,8-tetradecanediol (7). To a suspension of cuprous iodide (571 mg ; 3mmol) in Et_2O (14ml) at -30°C was added dropwise n-butyllithium (3.75ml, 1.6M in hexane solution, 6mmol). After stirring 1h at this temperature, the "L iditol diepoxide" 5 (186mg, 1mmol) in THF (1ml) was introduced. After addition was complete, stirring was continued

for 3h at -25°C, then the mxiture was recooled to -40°C and the benzoylchloride (700µl, 6mmol) was added. After 30 min. at 0°C, the reaction was quenched with water (30 ml) and the resulting mixture was filtered through Celite and extracted with ether. The combined organic extracts were washed with a saturated aqueous NH_4Cl solution, with brine, dried over $MgSO_4$ and evaporated in vacuo. Flash chromatography on silica gel (CH_2Cl_2-hexane 3:2) gave 7 (424 mg, 83 % yield) : $[\alpha]_D^{20}$ -2° (c 1.55, $CHCl_3$) ; ^1H NMR (250 MHz, $CDCl_3$) δ 8.05, 7.45 (m,10H,Ph), 5.3 (m,2H,H-6), 4.0 (s,2H,H-7), 1.8 (m,4H,H-5), 1.4 (s,6H,$C(CH_3)_2$), 1.31-0.85 (m,18H) ; MS m/e (relative intensity) 510 : M^+ (<1), 495 (10), 305 (20), 266 (23), 247 (62), 209 (27), 183 (74), 105 (100), 77 (37). Anal. Calcd. for $C_{31}H_{42}O_6$: C, 72.91 ; H, 8.28. Found : C, 72.8 ; H, 8.2.

6(S),9(S)-Dibenzoyloxy-7(S),8(S)-tetradecanediol (8). A solution of 7 (2.44g, 5.19 mmol) in trifluoroacetic acid (35 ml) and water (3.5ml) was stirred at -5°C for 15 min. After addition of water (40 ml), the mixture was extracted with CH_2Cl_2 (4x50 ml). The organic extracts were washed with 3 % aqueous $NaHCO_3$, then with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (CH_2Cl_2/AcOEt 95:5) gave 8 as white cristals (1.71g, 76 % yield) : mp 67°C ; $[\alpha]_D^{20}$ -13° (c 1.55, CH_2Cl_2) ; ^1H NMR (90 MHz, $CDCl_3$) δ 8.2-7.5 (m,10H,Ph), 5.3 (m,2H,H-6), 3.85 (m,2H,H-7), 1.85 (m,4H,H-5), 1.25-0.85 (m,18H) ; SM m/e (relative intensity) 470 : M^+ (<1), 265 (3), 235 (8), 123 (11), 105 (100), 77 (30).

2(S)-Benzoyloxy-heptanal (3). To a solution of diol 8 (307mg, 0.65 mmol) in CH_2Cl_2 (6ml), lead tetraacetate (348mg, 0.783 mmol) was added at -10°C. After stirring for 45 min, the reaction mixture was filtered and evaporated. Flash chromatography of the residue on silica gel (CH_2Cl_2) gave aldehyde 3 as a colorless oil (276mg, 90 % yield) : $[\alpha]_D^{20}$ -31° (c 1.4, CH_2Cl_2) ; ^1H NMR (90 MHz, $CDCl_3$) δ 9.65 (s,1H,H-1), 8.2-7.5 (m,5H,Ph), 5.2 (t,1H,J=6Hz,H-2), 1.85 (m,2H,H-3), 1.4-0.85 (m,9H).

4(S)-Benzoyloxy-2(E)-nonenal (11). To a benzene solution (9ml) of formylmethyltriphenylphosphonium chloride (580mg, 1.72 mmol) at room temperature was added triethylamine (297 µl, 2.13 mmol). After stirring for 45 min (obtention of a yellow coloration), the freshly prepared aldehyde 3 (332 mg, 1.42 mmol) was added and the mixture was stirred for 24h at room temperature. The solvent was evaporated and crude 11 was purified by flash chromatography on silica gel (CH_2Cl_2) giving a colorless oil (307 mg, 83 % yield) : $[\alpha]_D^{20}$ +67° (c 1.0, CH_2Cl_2) ; ^1H NMR (250 MHz, $CDCl_3$) δ 9.55 (d,1H,$J_{1,2}$=7.5Hz,H-1), 8.05-7.5 (m,5H,Ph), 6.83 (dd,1H,$J_{3,4}$=4.5Hz,$J_{2,3}$=15.5Hz,H-3), 6.26 (ddd,1H, $J_{1,2}$=7.5Hz,$J_{2,3}$=15.5Hz ,$J_{2,4}$=1.5Hz,H-2), 5.74 (m,1H,H-4), 1.85 (m,2H,H-5), 1.5-0.88 (m,9H) ; ^{13}C NMR ($CDCl_3$) δ 13.9 (C-9), 22.4, 24.7, 31.5, 33.7 (C-5→8), 72.8 (C-4), 128.5, 129.6, 131.5, 133.3 (C-2,Ph), 153.8 (C-3), 165.5 (PhCO), 192.8 (C-1) ; Anal. Calcd. for $C_{10}H_{20}O_3$: C, 73.82 ; H, 7.74. Found : C, 73.5 ; H, 7.9.

Methyl-13(S)-benzoyloxy-9(Z),11(E)-octadecadienoate (13). To the phosphonium salt 15 (781mg, 1.52 mmol) in THF (12.5ml) and HMPA (3.12ml) at -78°C was added LiHMDS (1.52 ml, 1M in THF solution, 1.52 mmol). The solution rapidly became bright orange and stirring was continued for 45 min, after which the α,β-unsaturated aldehyde (264mg, 1.02mmol) in THF (2ml) was added. After stirring 1h at -78°C, the temperature was allowed to slowly warm to 20°C (30 min). The reaction mixture was hydrolyzed with a 25 % solution of ammonium acetate (pH=7) then extracted with pentane (3x50ml). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography of the residue (CH_2Cl_2) gave Z,E isomers of 13 in a 85:15 ratio (231 mg, 55 % yield). The separation of the Z isomer was carried out by HPLC chroma-

tography through a μ-PORASIL (length 30 cm, i.d. 7.9 mm, eluent : hexane-Et_3N 2 %, flow rate 3 ml/min, retention time of Z isomer : 21.6 min ; E isomer : 25.2 min).
Z isomer : $[\alpha]_D^{20}$ + 74° (c 0.4, $CHCl_3$), Lit[5a] : $[\alpha]_D$ +64.1° (c 1.5, $CHCl_3$)[14] ; ^1H NMR (250 MHz, $CDCl_3$) δ 8.1-7.3 (m,5H,Ph), 6.57 (dd,1H,$J_{10,11}$=11Hz,$J_{11,12}$=15.5Hz,H-11), 5.94 (t,1H,$J_{9,10}$=$J_{10,11}$=11Hz, H-10), 5.66 (dd,1H,$J_{12,13}$=7.5Hz,$J_{11,12}$=15.5Hz,H-12), 5.55 (m,1H,H-13), 5.46 (m,1H,H-9), 3.65 (s, 3H,COOMe), 2.27 (t,2H,H-2), 2.14 (q,2H,$J_{8,9}$=7.5Hz,H-8), 1.9-0.87 (m,21H) ; ^{13}C NMR ($CDCl_3$) δ 13.9 (C-18), 29.1, 29.4, 31.6, 34.1, 34.7 (C-2→8, C-14→17), 51.3 (COOMe), 75.4 (C-13), 127.6, 128.0, 128.2, 129.5, 130.9, 132.7, 133.6 (C-9→12,Ph), 165.8 (PhCO), 174.2 (C-1).

Methyl-13(S)-hydroxy-9(Z),11(E)-octadecadienoate, (methyl coriolate). A mixture of benzoate 13 (7 mg, 16.8 μmol) and K_2CO_3 (2.4 mg, 16.9 μmol) in methanol (250 μl) was stirred at 50°C for 2h. After careful acidification with 5 % methanolic acetic acid, the methanol was evaporated. The resulting mixture was then diluted with CH_2Cl_2, filtered through Celite, and the solvent was removed under reduced pressure. Methyl coriolate was obtained after Flash chromatography on silica gel (5 % AcOEt in cyclohexane). Analysis of methyl coriolate using a Baker dinitrobenzoylphenylglycine (covalent) chiral phase HPLC column (250x4.6mm) eluting with n-hexane : 2-propanol (100: 0.5) and a flow rate of 0.8ml/min revealed the presence of a single enantiomer having a retention time of 32 min. (retention time for (±)-methyl coriolate[11] was 32 and 32.9 min) : ^1H NMR (250 MHz, $CDCl_3$) δ 6.46 (dd,1H,$J_{10,11}$=11Hz,$J_{11,12}$=15Hz,H-11), 5.95 (t,1H,$J_{9,10}$=$J_{10,11}$=11Hz,H-10), 5.64 (dd,1H,$J_{11,12}$=15Hz,$J_{12,13}$=7Hz,H-12), 5.41 (dt,1H,$J_{8,9}$=7Hz,$J_{9,10}$=11Hz,H-9), 4.15 (q,1H,J=7Hz,H-13), 3.65 (s,3H,COOMe), 2.27 (t,2H,J=7Hz,H-2), 2.14 (q,2H,J=7Hz,H-8), 1.8-0.8 (m,21H).

13(S)-Hydroxy-9(Z),11(E)-octadecadienoic acid (1). A mixture of ester 13 (17mg, 4.1 10^{-5}mol) and K_2CO_3 (56mg, 10 eq) in aqueous methanol (0.83ml, 4:1) was stirred at room temperature for 60h. Then it was diluted with water, carefully acidified with 5 % methanolic acetic acid and extracted with ether. The combined organic extracts were washed with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (CH_2Cl_2/ MeOH 9:1) gave pure coriolic acid : ^1H NMR (250 MHz, $CDCl_3$) δ 6.47 (dd,1H,$J_{10,11}$=11Hz,$J_{11,12}$=15Hz, H-11), 5.95 (t,1H,$J_{9,10}$=$J_{10,11}$=11Hz,H-10), 5.64 (dd,1H,$J_{11,12}$=15Hz,$J_{12,13}$=6.5Hz,H-12), 5.42 (dt, 1H,$J_{8,9}$=7Hz,$J_{9,10}$=11Hz,H-9), 4.16 (q,1H,J=6.5Hz,H-13), 2.35 (t,2H,J=7Hz,H-2), 2.15 (q,2H,J=7Hz, H-8), 1.8-0.8 (m,21H).

To the amino coriolic acid (2) :

6(S),9(S)-Di-N-ptoluenesulfonylamino-7(R),8(R)-O-methylethylidene-7,8-tetradecanediol (9). To a suspension of cuprous iodide (1.165g, 6.1mmol) in THF (6.3ml) at -40°C was added dropwise n-butyllithium (7.6ml, 1.6M in hexane solution, 12.2 mmol). After stirring 30min at this temperature, the heterogeneous mixture was recooled to -60°C and the N-tosyl bis-aziridine 6 (0.75g, 1.52mmol) in 16 ml of THF was introduced. After addition was complete, the temperature was warmed to -30°C over 2h and stirring was continued for an additional 2h at this temperature.The reaction was then quenched with a mixture composed of 10 % concentrated NH_4OH/saturated aqueous NH_4Cl solution (20ml) and allowed to stir at room temperature for 30 min. The resulting mixture was then filtered through Celite and extracted with ether (3x30ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (20 % ethyl acetate in cyclohexane) gave 9 as white cristals (882mg, 95 % yield) : m.p. 102°C ; $[\alpha]_D^{20}$ -60° (c 1.1, CH_2Cl_2) ; IR (nujol) cm^{-1} : 3300 (NH) ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.74, 7.28 (AB,8H,$J_{(AB)}$=8Hz,C_6H_4), 4.64 (d,2H,$J_{NH,6}$=10Hz,NH), 3.99 (s,2H,H-7),

3.32 (dt,2H,$J_{2,1}$=7Hz,$J_{6,NH}$=10Hz,H-6), 2.39 (s,6H,C_6H_4-CH_3), 1.37 (s,6H,$C(CH_3)_2$), 1.40-0.70 (m,22H); Anal. Calcd for $C_{31}H_{48}N_2O_6S_2$: C, 61.15 ; H, 7.94 ; N, 4.60. Found : C, 61.2 ; H, 8.0 ; N, 4.8.

6(R),9(R)-Di-N-ptoluenesulfonylamino-7(R),8(R)-O-methylethylidene-7,8-tetradecanediol (9'). Diopening of N-tosyl bis-aziridine 6' by dibutylcuprate was performed using the same conditions as for 6, described previously, giving a colorless oil 9'. $[\alpha]_D^{20}$ +44° (c 1.0, CH_2Cl_2) ; IR (neat) cm^{-1} : 3280 (NH), ^1H NMR (250 MHz, $CDCl_3$) δ 7.74, 7.28 (AB,8H,J_{AB}=8Hz,C_6H_4), 4.99 (d,2H,$J_{NH,6}$=10Hz, NH), 3.95 (m,2H,H-7), 3.39 (m,2H,H-6), 2.38 (s,6H,C_6H_4-CH_3), 1.30 (s,6H,$C(CH_3)_2$), 1.36-0.64 (m,22H)

6(S),9(S)-Di-N-ptoluenesulfonylamino-7(R),8(R)-tetradecanediol (10). A solution of 9 (792mg, 1.3 mmol) in trifluoroacetic acid (9.36 ml) and water (1.04ml) was stirred at 0°C for 1h. After addition of water (8ml) the mixture was extracted with CH_2Cl_2 (3x10ml). The organic extracts were washed with 3 % aqueous $NaHCO_3$, then with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (50 % ethyl acetate in cyclohexane) gave 10 as white cristals (740mg, 92 % yield) : mp 140°C ; $[\alpha]_D^{20}$ -83° (c 1.0, CH_2Cl_2); IR (nujol) cm^{-1} 3470(OH), 3170 (NH) ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.80, 7.23 (AB,8H,J_{AB}=8Hz,C_6H_4), 6.50 (d,2H,$J_{NH,6}$=10Hz,NH), 3.81 (s,2H,H-7), 3.55 (m,2H,H-6), 2.34 (s,6H,C_6H_4-CH_3), 1.35-0.54 (m, 22H) . Anal. Calcd for $C_{28}H_{44}N_2O_6S_2$: C, 59.13 ; H, 7.79 ; N, 4.92. Found : C, 59.3 ; H, 7.7 ; N, 5.0.

6(R),9(R)-Di-N-ptoluenesulfonylamino-7(R),8(R)-tetradecane diol (10'). Deacetalisation of 9' was carried out under identical conditions as for 9, described beforehand, giving a colorless oil 10'. $[\alpha]_D^{20}$ +33° (c 1.0, CH_2Cl_2) ; IR (neat) cm^{-1} : 3480 (OH),3280 (NH) ; ^1H NMR (250MHz, $CDCl_3$) δ 7.77, 7.27 (AB,8H,J_{AB}=9Hz,C_6H_4), 5.45 (d,2H,$J_{NH,6}$=9.5Hz,NH), 3.73 (d,2H,$J_{7,6}$=6.5Hz,H-7), 3.25 (m,2H,H-6), 2.40 (s,6H,C_6H_4-CH_3), 1.60-0.55 (m,22H).

2(S)-N-pToluenesulfonylamino-heptanal (4). To a solution of diol 10 (227.6mg, 0.4mmol) in CH_2Cl_2 (6ml), lead tetraacetate (213mg, 0.48mmol) was added at -20°C. After stirring for 15min, the reaction mixture was rapidly filtered through a small silica gel column (ether elution). Evaporation of the solvent gave aldehyde 4 quantitatively (226mg) as a colorless oil, which was not further purified, due to its relative instability : ^1H NMR (250 MHz, $CDCl_3$) δ 9.39 (s,1H,H-1), 7.71, 7.27 (AB,4H,J_{AB}=7.5Hz,C_6H_4), 5.24 (d,1H,$J_{NH,2}$=7.5Hz,NH), 3.85 (m,1H,H-2), 2.40 (s,3H,C_6H_4-CH_3), 1.70-0.70 (m,11H,C_5H_{11}). The enantiomeric purity of aldehyde 4 was proved by ^1H NMR spectroscopy (250 MHz),using (+)$Eu(tfc)_3$ as a chiral shift reagent. A 50-50 mixture of the 2(R) and 2(S)-N-ptoluenesulfonylamino-heptanals showed two distinct aldehyde signals in the presence of 2 equivalents of $Eu(tfc)_3$ (ΔΔδ 0.03ppm), whereas the aldehyde signal of 4 always appeared as a single peak. The (R) enantiomer 4' of aldehyde 4 was synthetized starting from diol 10' according to the same conditions as for 4.

4(S)-N-pToluenesulfonylamino-2(E)-nonenal (12). Wittig reaction on 4 was carried out under identical conditions as for 3, described beforehand. Flash chromatography of the residue on silica gel (30 % ethyl acetate in cyclohexane) gave 12 as a light yellow oil (60 % yield calculated from diol 10) :$[\alpha]_D^{20}$ -48° (c 1.0 ; CH_2Cl_2) ; IR (neat) cm^{-1} : 3280 (NH), 1690 (C=O), 1640 (C=C), 975 (H-C=C-H) ; ^1H NMR (250 MHz, $CDCl_3$) δ 9.34 (d,1H,$J_{1,2}$=7.5Hz,H-1), 7.72, 7.27 (AB,4H,J_{AB}=7.5Hz,C_6H_4), 6.48 (dd,1H,$J_{2,1}$=7.5Hz,$J_{2,3}$=15.5Hz,H-2), 5.99 (dd,1H , $J_{3,2}$=15.5Hz,$J_{3,4}$=8Hz,H-3), 5.07 (d,1H,$J_{NH,4}$=7.5Hz NH), 3.95 (m,1H,H-4), 2.42 (s,3H,C_6H_4-CH_3), 1.60-0.70 (m,11H). ^{13}C NMR ($CDCl_3$) δ 13.7 (C_9), 21.4 (C_6H_4-CH_3), 22.2, 24.8, 31.1, 34.6 (C_5→C_8), 54.8 (C_4), 127.1, 129.6, 137.4, 143.7 (-C_6H_4), 131.9,

155.6 (C_2,C_3), 192.8 (C_1). Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.10 ; H, 7.49 ; N, 4.52. Found : C, 61.6 ; H, 7.6 ; N, 4.5.

Methyl-13(S)-N-ptoluenesulfonylamino-9(Z),11(E)-octadecadienoate (14). To the phosphonium salt 15 (458mg, 0.89mmol) in THF (5.35 ml) at -78°C was added KHMDS (1.78ml, 0.89mmol). The solution rapidly became bright orange and stirring was continued for 15 min,after which the α,β-unsaturated aldehyde 12 (110mg, 0.36 mmol) in 0.7ml of THF was added, quickly giving a yellow coloration. After 1h at -78°C, the reaction mixture was hydrolyzed at 0°C with a 25 % solution of ammonium acetate (pH=7) then extracted with pentane (3x15ml). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (15 % ethyl acetate in cyclohexane) gave 14 as a yellow oil (115mg, 70 % yield) : $[\alpha]_D^{20}$ +5° (c 2.0, CH_2Cl_2) ; IR (neat) cm^{-1} : 3280 (NH), 1740 (C=O) ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70, 7.22 (AB,4H,J_{AB}=7.5Hz,C_6H_4), 6.12 (dd,1H,$J_{11,10}$=11Hz,$J_{11,12}$=15Hz,H-11), 5.70 (t,1H,$J_{10,9}$=11Hz,$J_{10,11}$=11Hz H-10), 5.34 (m,1H,H-9), 5.23 (dd,1H,$J_{12,13}$=7Hz,$J_{12,11}$=15Hz,H-12), 4.40 (d,1H,$J_{NH,13}$=7.5Hz,NH), 3.80 (m,1H,H-13), 3.65 (s,3H,COOMe), 2.38 (s,3H,C_6H_4-$\underline{CH_3}$), 2.30 (t,2H,H-2), 2.02 (m,2H,H-8), 1.70-0.80 (m,21H). ^{13}C NMR ($CDCl_3$) δ 13.9 (C_{18}), 21.4 (C_6H_4-$\underline{CH_3}$),22.4, 24.9, 25.0, 27.5, 28.9, 29.0,29.4, 31.3, 34.0, 35.9 (C_2→C_8, C_{14}→C_{17}), 51.3 (OCH_3), 56.0 (C_{13}), 126.7, 127.4, 132.3, 132.6 (C_9→C_{12}), 127.2, 129.3, 138.4, 142.9 (C_6H_4), 174.1 (C_1). Anal. Calcd for $C_{26}H_{41}NO_4S$: C, 67.35 ; H, 8.91 ; N, 3.02. Found : C, 67.5 ; H, 9.1 ; N, 3.1.

(9Z,11E,13S)-13-N-pToluenesulfonylamino octadecadienoic acid (2). A mixture of ester 14 (20mg, 4.3 10^{-5}mol) and K_2CO_3 (60mg, 10eq) in aqueous methanol (0.86ml, 4:1) was stirred at room temperature for 24h. Then at 0°C it was diluted with water, carefully acidified with 5 % methanolic acetic acid and extracted with ether (3x20ml). The combined organic extracts were washed with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (30 % ethyl acetate in cyclohexane) gave 2 as a yellow oil (17.5mg, 85 % yield) : $[\alpha]_D^{20}$ -2°5 (c 1.6, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$) δ 7.70, 7.22 (AB,4H,J_{AB}=7.5Hz,C_6H_4), 6.17 (dd,1H,$J_{11,12}$=15Hz,$J_{11,10}$=11Hz,H-11), 5.72 (t,1H,$J_{10,9}$=11Hz,$J_{10,11}$=11Hz,H-10), 5.43-5.20 (m, 2H,H-9,H-12), 4.92 (d,1H,$J_{NH,13}$=8Hz,NH), 3.81 (m,1H,H-13), 2.43-2.32 (m,5H,H-2,C_6H_4-$\underline{CH_3}$), 2.04 (m,2H,H-8), 1.80-0.70 (m,21H).

REFERENCES AND NOTES

1. Tallent,W.H.; Harries,J.; Wolff,I.A. Tetrahedron Lett. 1966, 4329.
2. Kato,T.; Yamaguchi,Y.; Hirano,T.; Yokayama,T.; Ugehara,T.; Namai,T.; Yamanaka,S.; Harada,N. Chem. Letters, 1984, 409.
3. Blondin,G.A. Ann. N.Y. Acad. Sci. 1975, 264, 98.
4. Setty,B.N.Y.; Berger,M.; Stuart,M.J. Biochem. Biophys. Res. Commun., 1987, 148, 528.
5. Chiral syntheses : (a) Suemune,H.; Hayashi,N.; Funakoshi,K.; Akita,H.; Oishi,T.; Sakai,K. Chem. Pharm. Bull., 1985, 33, 2168 ; (b) Moustakis,C.A.; Weerasinghe,D.K.; Mosset,P.; Falck,J.R.; Mioskowski,C., Tetrahedron Lett., 1986, 27, 303 ; (c) Kobayashi,Y.; Okamoto,S.; Shimazaki,T.; Ochiai,Y.: Sato,F. Tetrahedron Lett., 1987, 28, 3959 ; (d) de Montarby,L.; Mosset,P.; Gree,R., Tetrahedron Lett., 1988, 29, 3937 ; (e) Chan,C.; Cox,P.B.; Roberts,S.M., J. Chem. Soc.,Chem. Commun., 1988, 971.
6. Kerdesky,F.A.J.; Schmidt,S.P.; Holms,J.H.; Dyer,R.D.; Carter,G.W.; Brooks,D.W., J. Med. Chem., 1987, 30, 1177.
7. (a) Le Merrer,Y.; Duréault,A.; Greck,C.; Micas-Languin,D.; Gravier,C.; Depezay,J.C., Heterocycles,1987, 25, 541 ; (b) Duréault,A.; Greck,C.; Depezay,J.C., Tetrahedron Lett., 1986, 27, 4157.
8. (a) Le Merrer,Y.; Duréault,A.; Gravier,C.; Languin,D.; Depezay,J.C., Tetrahedron Lett., 1985, 26, 319 ; (b) Duréault,A.; Tranchepain,I.; Greck,C.; Depezay,J.C., Tetrahedron Lett., 1987, 28, 3341.
9. In the olefination conditions we use, no racemisation occurs. The question of racemisation in the Wittig olefination of the optically sensitive α-aminoaldehydes has been addressed : Luly,J.R.; Dellaria,J.F.; Plattner,J.J.; Soderquist,J.L.; Yi,N., J. Org. Chem., 1987, 52, 1487.
10. Prepared in four steps as follows :

$$HO(CH_2)_9OH \xrightarrow{HBr\ 48\ \%} Br(CH_2)_9OH \xrightarrow[2)\ MeOH,HCl]{1)\ CrO_3} Br(CH_2)_8COOMe \xrightarrow[CH_3CN]{Ph_3P} \underline{15}$$

11. We thank Dr. R. Gree for kindly providing us with a sample of (±)-coriolic acid methyl ester for HPLC comparison.
12. Still,W.C.; Kahn,M.; Mitra,A., J. Org. Chem., 1978, 43, 2923.
13. Kang,Suk-Ku; Kim,Won-Sup; Moon,Byoung-Ho, Synthesis, 1985, 1161.
14. Comparison of the $(\alpha)_D$ values of methyl-13(S)-benzoyloxy-9(Z),11(E)-octadecadienoate suggests that Sakai has obtained this compound with about 86 % ee. Comparison of the $(\alpha)_D$ values of coriolic acid reported by Sato and by Sakai suggests also the same enantiomeric excess for the Sakai's compound : $(\alpha)_D^{25}$ + 9.3° (c 1.29, $CHCl_3$)[5c], $(\alpha)_D^{23}$ + 7.8 (c 1.15, $CHCl_3$)[5a].