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Enantioselective synthesis of methyl (+)-(R)-11-hydroxy-8(E)-dodecenoate, the seco-ester of (+)-(R)-recifeiolide, from [2(S), S(R)] 2-(p-tolylsulfinyl)methyl oxirane.

Guy Solladié*, José Kovenski[a], Françoise Colobert

Ecole Européenne des Hautes Etudes des Industries Chimiques,
Laboratoire de Stéréochimie associé au CNRS, 1 Rue B. Pascal, 67008-Strasbourg, France.

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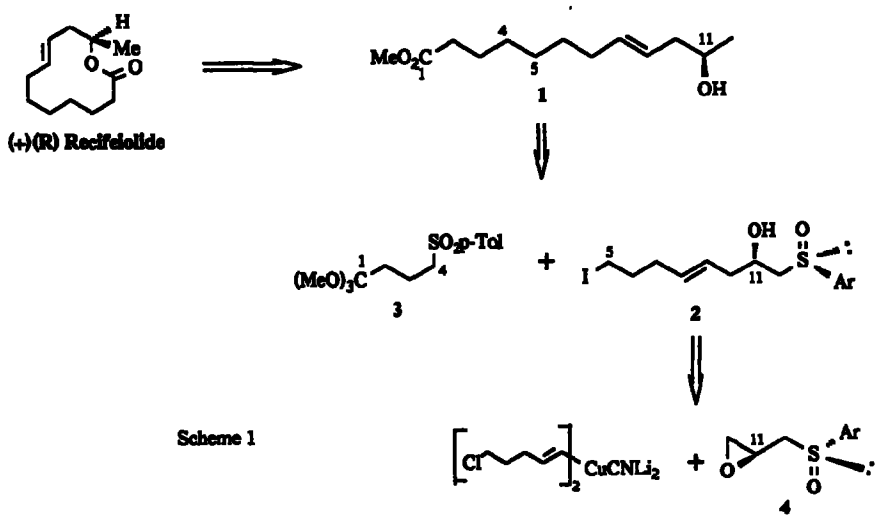
Abstract : a short and enantioselective synthesis of the seco-ester of (+)-(R)-recifeiolide from the readily available [2(S), S(R)]-2-(p-tolylsulfinyl)methyl oxirane is described.

(+)-(R)-recifeiolide, a 12-membered lactone, is a metabolite isolated from the fungus *cephalosporium recifei* [1]. Although many total syntheses of the racemic molecule were reported [2], only three have described the synthesis of the optically active natural compound [3].

We report now the synthesis of the seco-ester 1 from [2(S),S(R)] 2-(p-tolylsulfinyl) methyl oxirane 4 readily obtained by asymmetric synthesis from methyl α-chloroacetate and (+)-(R)-methyl p-tolylsulfoxide [4,5].

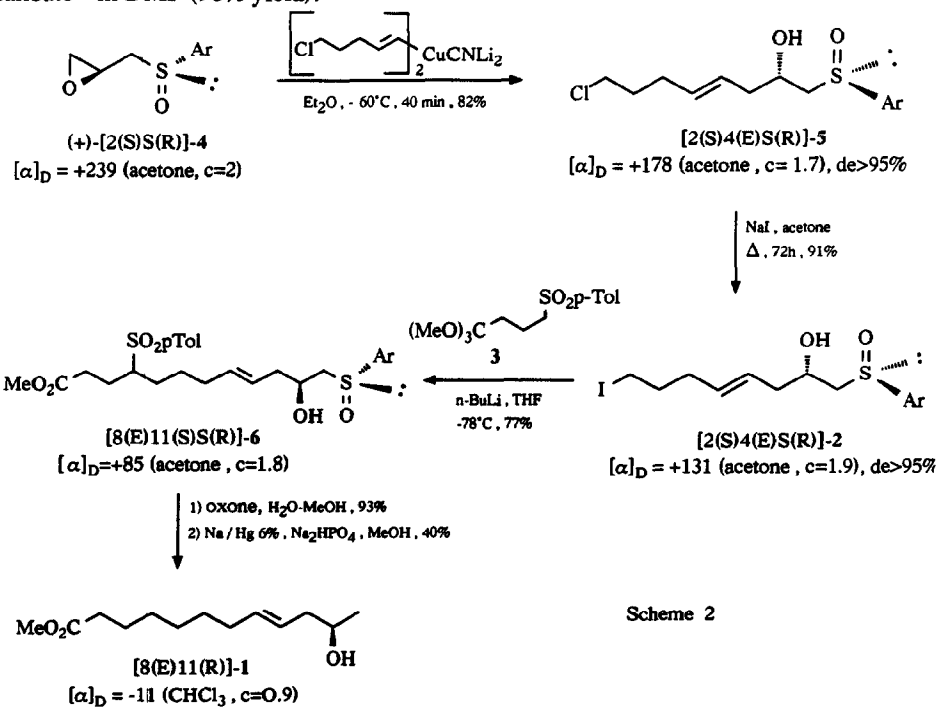
As shown in the retrosynthetic scheme 1, the seco-ester can be made by coupling the 4-sulfonyl orthoester 3 with the optically active iodide 2 which can be obtained from [2(S),S(R)]-2-(p-tolylsulfinyl) methyl oxirane 4.

(+)-[2(S),S(R)]-2-(p-tolylsulfinyl) methyl oxirane [4,5], 4 was allowed to react with the cyanocuprate made from (E)-1-iodo-5-chloropentene [6] in ether to yield (+)-[2(S),4(E),S(R)]-8-chloro-1-(p-tolylsulfinyl)-4-octene-2-ol, 5, in 82% yield (Scheme 2).



Scheme 1

Only one diastereomer could be detected by ^{1}H and ^{13}C NMR [7]. The halogen exchange was carried out with NaI in acetone yielding the iodide 2 in 91% yield[8]. Then trimethyl 4-(p-tolylsulfonyl)-orthobutanoate 3 was prepared by adding sodium p-toluenesulfinate to trimethyl 4-bromo-orthobutanoate [9] in DMF (96% yield).



Scheme 2

The crude sulfonyl orthoester 3 was treated with BuLi and added to the iodide 2 to give [8(E),11(S),S(R)]-6, in 77% yield. The crucial step was to remove the sulfoxide and the sulfone groups in 6. After several unsuccessfull attempts, we oxidized the sulfinyl group to a sulfonyl group with potassium persulfate (oxone) and hydrogenolyze the two sulfonyl groups with sodium amalgam giving the secoester 1 which showed all the characteristics of the literature [3b] and a slightly higher optical rotation.

These results showed that chiral sulfinyl methyl oxirane is a very useful synthetic tool to introduce an optically active homoallylic moiety in total synthesis.

Experimental.

(E)-1-Iodo-5-chloropentene

Diisobutyl aluminium hydride (19.8 mL of a 1M solution in toluene, 19.8 mmol) is added to a solution of 1-chloro-4-pentyne (2g, 18.9 mmol) in 10 mL of hexane at room temperature. After heating at 50°C for 2h, the mixture is cooled to -40°C and 10 mL of THF are added, followed by a dropwise addition of iodine (5.28 g, 20.8 mmol) in 20 mL THF. The mixture is warmed gradually to -10°C and hydrolyzed with dilute sulfuric acid. The organic layer is washed with aqueous sodium

thiosulfate (2x20 mL), brine (2x20 mL) and dried over anhydrous sodium sulfate. The solvents are evaporated under vacuum and the residue distilled giving pure iodo alkene (3.19 g, 71%). Bp 49°C/0.9 mmHg [6]. ^{1}H NMR ($CDCl_3$), δ : 6.50 (dt, 1H, J=7.5Hz), 6.10 (d, 1H, J_{trans}=15Hz), 3.52 (t, 2H, J=7.5Hz), 2.23 (m, 2H), 1.85 (m, 2H).

[2(S),4(E),S(R)]-8-chloro-1-(p-tolylsulfinyl)-4-octene-2-ol,(5).

To a solution of (E)-1-iodo-5-chloropentene (4.34 g, 18.84 mmol) in 25 mL of anhydrous ether under argon, 11.78 mL of n-butyllithium (1.6 M, 18.84 mmol) were added at -78°C. The mixture was stirred 45 min at -78°C. Copper cyanide (928 mg, 10.4 mmol) was then added and the mixture warmed to -25°C and stirred 30 min at this temperature, whereupon a green solution resulted. The flask was recooled to -60°C, and 924 mg (4.71 mmol) of [2(S), S(R)]-p-tolylsulfinyl-2-methyloxirane, dissolved in 10 mL of anhydrous ether, were added with a canula. The mixture was stirred at -60°C during 40 min and quenched with 10% conc. NH_4OH in saturated aq. NH_4Cl, followed by an extractive workup (ethyl acetate). After drying over sodium sulfate, filtration and evaporation of solvents, the resulting yellow oil was chromatographed on silica gel (ethyl acetate-hexane, 2:1), affording 1.16 g (82%) of the title compound as a pale yellow oil. Rf= 0.32 (silica gel, ethyl acetate/hexane 3:1). $[\alpha]_D$= + 178 (c=1,7, acetone), d.e. > 95%. IR : 3600-3400 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$), δ : 1.73 (q, 2H, H-6), 2.07 (m, 2H, H-7), 2.21 (m, 2H, H-3), 2.36 (s, 3H, CH_3, p-tolyl), 2.8 (AB of an ABX system, 2H, J_{AB}=13Hz, J_{AX}=9.5Hz, J_{BX}=2.5Hz, Δν=36Hz, H-1,), 3.43 (t, 2H, J=6.5Hz, H-8), 4.19 (m, 1H, part X of an ABX system, H-2), 4.61 (broad s, 1H, OH), 5.39 (m, 2H, H-4, H-5), 7.38 (AA'BB', 4 arom.H). ^{13}C NMR ($CDCl_3$) : 141.2, 139.6, 129.8, 126 (arom.C), 131.1 (C-4), 123.7 (C-5), 65.3 (C-2), 63 (C-1), 44.1 (C-8), 40.1 (C-3), 31.7 (C-7), 29.4 (C-6) 21.1 (CH_3, ptolyl). Anal. Calcd. for $C_{15}H_{21}O_2ClS$: C 59.89%, H 7.04%; Found : C 59,88%, H 6.92%.

[2(R),4(E),S(R)]-8-chloro-1-(p-tolylsulfinyl)-4-octene-2-ol, (5a).

Was prepared according the procedure used for 5 from [2(R),S(R)]-p-tolylsulfinyl-2-methyloxirane. Yield 80%. $[\alpha]_D$: +110.9 (C=2, acetone); d.e.>95%. IR (neat) : 3600-3400 cm^{-1}(OH). ^{1}H NMR ($CDCl_3$), δ : 1.8 (m, 2H, H-6), 2.18 (m, 2H) and 2.33 (m, 2H) (H-3, H-7), 2.45 (s, 3H, CH_3, p-tolyl), 2.9 (AB of ABX system, 2H, J_{AB}=13Hz, J_{AX}=9Hz, J_{BX}=3Hz, Δν=41Hz H-1), 3.53 (t, 2H, J=6.25Hz, CH_2Cl), 4.09 (d, 1H, OH), 4.2 (m, 1H, part X of an ABX system, H-2), 5.5 (m, 2H, H-4, H-5), 7.4 (AA'BB', 4 arom.H). ^{13}C NMR ($CDCl_3$): 142.5, 140.9, 130.6, 126.6 (arom.C), 133.1 (C-4), 124.6 (C-5), 62.8 (C-1), 68.5 (C-2), 40.8 (C-3), 30.2 (C-6), 32.4 (C-7), 44.8 (C-8), 22.0 (CH_3, p-tolyl). Anal. calcd for $C_{15}H_{21}O_2ClS$: C 59.89%, H 7.04%; found : C 59.69%, H 7.13%.

[2(S),4(E),S(R)]-8-iodo-1-(p-tolylsulfinyl)-4-octene-2-ol,(2).

1.16 g (3.86 mmol) of [2(S), 4(E), S(R)] 8-chloro-1-(p-tolylsulfinyl)-4-octene-2-ol, 5, are added, at room temperature to a solution of 2.9 g (19.3 mmol, 5 eq.) of sodium iodide in 30 mL of acetone. The mixture is stirred at reflux for 72h (and at room temperature overnight). The cooled mixture is poured into ether-water 1:1 (100 mL) and the ethereal phase is washed with water and dried (sodium sulfate). Evaporation of solvents afforded the iodide 2 (1.37 g, 91%). $[\alpha]_D$=+131 (c=1.9, acetone), d.e > 95%. ^{1}H NMR (200MHz, $CDCl_3$): δ: 1.8 (q, 2H, H-6), 2.1 (m, 2H, H-7), 2.23 (m, 2H, H-3), 2.41 (s, 3H, CH_3 , ptolyl), 2.81 (AB of an ABX system, 2H, J_{AB}=14Hz, J_{AX}=10Hz, J_{BX}=2Hz, Δν=52Hz, H-1), 3.12 (t, 2H, J=7Hz, H-8), 4.23 (m, 2H, OH and part X of ABX, H-2), 5.4 (m, 2H, H-4, H-5), 7.4 (AA, BB', 4 arom.H). ^{13}C NMR ($CDCl_3$) : 141.3, 139.57, 129.90, 126.2 (C arom.), 131.4 (C-4), 123.7 (C-

5), 65.5 (C-2), 62.4 (C-1), 40.1 (C-3), 32.9 et 32.4 (C-6, C-7), 21.3 (CH_3, ptolyl), 6.4 (C-8). Anal. calcd for $C_{15}H_{21}O_2IS$: C 45.9%, H 5.4%, Found : C 45.83%, H 5.54%.

[2(R),4(E),S(R)]-8-iodo-1-(p-tolylsulfinyl)-4-octene-2-ol, (2a).

Was prepared from **5a** by the procedure used for **5**, yield 88%.$[\alpha]_D$: +89.7 (c=2, acetone), d.e. > 95%. ^1H NMR ($CDCl_3$) : δ : 1.8 (m, 2H, H-6), 2.12 (m, 2H), 2.3 (m, 2H, H-3, H-7), 2.43 (s, 3H, p-tol), 2.85 (AB of an ABX system, 2H, J_{AB}=13.5Hz, J_{AX}=8.75Hz, J_{BX}=3Hz, Dn=29.5Hz, H-1), 3.16 (t, 2H, J=6.75Hz, CH_2I), 3.76 (broad s, 1H, OH), 4.3 (m, 1H, part X of ABX, H-2), 5.48 (m, 2H, H-4, H-5), 7.4 (AA'BB', 4H, arom). ^{13}C NMR ($CDCl_3$) : δ : 142.7, 141.0, 130.9, 126.9 (C arom.), 133.1 (C-4), 124.6 (C-5), 69.2 (C-2), 62.3 (C-1), 41.0 (C-3), 33.8 and 33.2 (C-6, C-7), 22.1 (p-tolyl), 7.1 (C-8, CH_2I).

Methyl-4-bromo-1-butane imidate hydrochloride.

To a solution of 8g (54 mmol) of 4-bromobutane nitrile in 50 mL of dry dichloromethane was added 4.6 mL (3.6g, 113.4 mmol, 2.1 eq.) of dry methanol followed by 4.22 mL (4.66 g, 59.4 mmol, 1.1 eq.) of acetyl chloride at 0°C under stirring. After 5 min. at this temperature, the solution was maintained at 4°C without stirring for 48h. The precipitate was collected by filtration, washed with hexane (2x20 mL) and dried in an argon stream, leading to 5g of the title compound (42% yield) which was directly used in the next step.

Trimethyl-4-bromo-orthobutanoate.

To 5 g (23 mmol) of methyl-4-bromo-1-butane imidate hydrochloride was added 100 mL of hexane and 3 mL (2.4 g, 74 mmol, 3.2 eq.) of dry methanol at 0°C. After 48h at 4°C, the mixture was filtrated in order to separate the NH_4Cl formed, which was exhaustively washed with hexane (5x50 mL). Evaporation of solvents gave a crude pale yellow oil which was partitioned between ether and $NaHCO_3$ 8% (1:1, 100 mL). The ethereal phase was dried (sodium sulfate). Evaporation of solvent gave 4.2 g (80%) of pure bromo orthoester[9]. ^1H NMR ($CDCl_3$) : δ: 1.9 (m, 4H, H-2, H-3), 3.25 (s, 9H, OMe), 3.49 (m, 2H, CH_2Br).

Trimethyl 4-(p-tolylsulfonyl)-orthobutanoate, (3).

To a solution of 3.2 g (14.1 mmol) of trimethyl-4-bromo-orthobutanoate in 30 mL of freshly distilled DMF was added 3.65 g (17.0 mmol, 1.2 eq.) of sodium p-tolylsulfinate. The mixturre was stirred 24h at room temperature, and partitioned in ether-water (1:1, 100 mL). The ethereal phase was washed with water (2x50 mL), dried (Na_2SO_4) and evaporated to yield 4.1 g (96%) of crude sulfone orthoester, which was used as such in the following step. ^1H NMR ($CDCl_3$) : δ: 1.4-1.9 (m, 4H), 2.45 (s, 3H, p-tolyl), 3.1-3.3 (s, 9H, OMe and t, 2H, CH_2-SO_2), 7.55 (AA'BB', 4H, arom.). ^{13}C NMR ($CDCl_3$) : 144.7 (C-4) 136.2, 129.9, 128.1, 115.1 (C arom.), 55.8 (C-1), 49.5 (C-5), 29 (C-3), 21.7 CH_3, p-tolyl), 17.0 (C-2).

Methyl-[8(E),11(S),S(R)]-4-(p-tolylsulfonyl)-11-hydroxy-12-(p-tolylsulfinyl)-8-dodecenoate, (6).

A solution of trimethyl-4-(p-tolylsulfonyl)-orthobutanoate **3** (906 mg, 3.mmol) in 24 mL of anhydrous THF in a dry 50 mL round-bottomed flask under argon was cooled to -78°C. n-Butyllithium (2.17 mL, 3 mmol, 1.38 M in hexane, 1.0 eq.) was added dropwise with a syringe. After 30 min at -78°C, a solution of [2(S), 4(E), S(R)]-8-iodo-1-(p-tolylsulfinyl)-4-octene-2-ol ,2, (300 mg, 0.75 mmol, 0.25 equiv.) in 3 mL of THF, previously cooled to -78°C, was added dropwise with a canula. The solution was stirred 1h at -78°C and slowly warmed to -30°C, and carefully quenched with saturated aqueous NH_4Cl. The pH of the mixture was adjusted to 2 and stirred 5 min. at room

temperature. The product was extracted into ether (4x50 mL), washed with brine and dried (sodium sulfate). Evaporation of solvent yielded a crude yellowish oil that was subjected to flash chromatography on silica gel using ethyl acetate/hexane (3:1) as eluant. After removal of less polar compounds, 300 mg (77%) of the title product was obtained, Rf: 0.2 (ethyl acetate/hexane 3:1). $[\alpha]_D$=+85 (c=1.8, acetone). ^{1}H NMR (200MHz), $CDCl_3$): δ : 1.45 (m, 2H, H-6), 1.7-2.1 (m, 6H, H-3, H-5, H-7), 2.19 (t, 2H, H-10), 2.42 (S, 3H, CH_3, ptolyl sulfoxide) 2.45 (s, 3H, CH_3, ptolyl sulfone), 2.55 (m, 2H, H-2), 2.82 (AB of an ABX system, 2H, J_{AB}=13.6Hz, J_{AX}=9.8Hz, J_{BX}=1.9Hz, Δν=66Hz, H-12), 3 (m, 1H, H-4), 3.65 (s, 3H, COOMe), 4.17 (m, 1H, part X of ABX, H-11), 5.34 (m, 2H, H-8, H-9), 7.43 (AA'BB', 4H, J_{AB}=8.2Hz, Δν=33.5Hz, H arom, ptolyl sulfoxyde), 7.55 (AA'BB', 4H, J_{AB}=8.26Hz, Δν=75.2Hz, H arom ptolyl sulfone). ^{13}C NMR ($CDCl_3$) : 172.9 (CO) 144.7, 141.4, 139.7, 134.5, 130, 129.7, 128.7, 123.9 (C arom.), 133 (C-9), 125.7 (C-8), 65.9 (C-11), 62.9 (C-4), 61.7 (C-12), 51.6 (OMe), 40.2 (C-10, 32 (C-2), 30.7 (C-7), 27.1 (C-3), 25.8 (C-5), 23 (C-6), 21.5 et 21.3 (Me-ptolyl). Anal Calcd for $C_{27}H_{36}O_6S_2$: C: 62.4%, H : 6.96%; Found : C : 61.97%; H : 6.94%.

Methyl-[8(E),11(R),S(R)]-4-(p-tolylsulfonyl)-11-hydroxy-12-(p-tolylsulfinyl)-8-dodecenoate, (6a).

Was prepared from 2a by the procedure described for 6, yield 65%., Rf : 0.2 (ethylacetate/hexane 3:1). ^{1}H NMR (200MHz, $CDCl_3$) : δ : 1.45 (m, 2H, H-6), 1.95-1.65 (m, 6H, H-3, H-5, H-7), 2.25 (m, 2H, H-10), 2.43 (s, 3H, CH_3 p-tolylsulfoxide), 2.45 (s, 3H, CH_3 p-tolylsulfone), 2.5 (m, 2H, H-2), 2.85 (AB of an ABX system, 2H, J_{AB}=13Hz, J_{AX}=9Hz, J_{BX}=3Hz, Δν=32.4Hz, H-12), 3.0 (m, 1H, H-4), 3.64 (s, 3H, COOMe), 3.8 (broad s, 1H, OH), 4.25 (m, 1H, part X of ABX, H-11), 5.4 (m, 2H, H-8, H-9), 7.35-7.75 (m, 8H, 2 overlapped systems AA'BB', H arom.). ^{13}C NMR ($CDCl_3$) : 173.7 (CO), 145.5, 142.7, 141.2, 135.2, 130.8, 130.5, 129.5, 126.3 (C arom.), 134.1 (C-9), 124.7 (C-8), 69.1 (C-11), 63.7 (C-12), 62.3 (C-4), 52.4 (OMe), 41.0 (C-10), 32.7 (C-2), 31.4 (C-7), 27.9 (C-3, 26.6 (C-5), 23.8 (C-6), 22.3 and 22.1 (Me, p-tolyl).

Methyl [8(E),11(S)]-4, 12-bis-(p-tolylsulfonyl)-11-hydroxy-8-dodecenoate.

233 mg of oxone in H_2O (1 mL) are added to a solution of 100 mg (0.19 mmol) of methyl [8(E), 11(S), S(R)] 4-(p-tolylsulfonyl)-11-hydroxy-12-(p-tolylsulfinyl)-8-dodecenoate, 6, in 1.5 mL of MEOH at 0°C. The mixture was then stirred 1h at room temperature and hydrolyzed with water and aqueous sodium thiosulfate. The product was extracted with $CHCl_3$ (3x10 mL), washed with water and brine and dried over magnesium sulfate. Evaporation of the solvant yielded a crude yellowish oil that was purified by flash chromatography on silica gel (ethyl acetate / hexane : 1.5 / 1) affording 95 mg (93%) of the title compound as a yellow oil, Rf=0.75 (ethylacetate/hexane 3:1), $[\alpha]_D$= -1.5 (c=1.7, acetone). ^{1}H NMR (200MHz, $CDCl_3$) : δ : 1.45 (m, 2H, H-6) 1.7-2.1 (m, 6H, H-3, H-7, H-5), 2.17 (t, 2H, H-10), 2.42 (s, 6H, 2 CH_3, p-tolylsulfone), 2.54 (m, 2H, H-2), 2.97 (m, 1H, H-4), 3.15 (d, 2H, J=5.7Hz, H-12), 3.62 (s, 3H, COOMe), 4.1 (m, 1H, H-11), 7.34 (m, 2H, H-8, H-9), 7.52 (AA'BB', J_{AB}=8.2Hz, Δν=72Hz, 4H, H arom., p-tolylsulfone), 7.55 (AA'BB', 4H, J_{AB}=8.2Hz, Δν=86Hz, H arom., p-tolylsulfone). ^{13}C NMR ($CDCl_3$) : 172.9 (CO), 144.9, 144.6, 136.1, 134.4, 129.9, 129.7, 128.6, 127.8 (C arom.), 133.5 (C-9), 125 (C-8), 65.6 (C-11), 62.8 (C-4), 61.4 (C-12), 51.6 (OMe), 39.4 (C-10), 31.9, 30.6, 27.1, 25.8, 22.9 (C-2, C-3, C-5, C-6, C-7), 21.5 (2 CH_3, p-tolyl).

Methyl [8(E),11(R)]-11-hydroxy-8-dodecenoate, (1).

To a solution of methyl [8(E), 11(S)]-4, 12 bis-(p-tolylsulfonyl)-11-hydroxy-8-dodecenoate, 65 mg (0.12 mmol) in 2 mL of MeOH, 170 mg (1.2 mmol) of Na_2HPO_4 were added at room temperature. Then 919 mg (2.4 mmol) of 6% NaHg were added at -30°C under stirring. The mixture was stirred at -30°C during 3 hours and quenched with a few mL of water. The product was extracted with AcOEt (4x10 mL), washed with brine and dried over magnesium sulfate. Evaporation of the solvent yielded a crude oil that was subjected to flash chromatography on silica gel using ethyl acetate/hexane (1:3) as eluant, affording 11 mg (40%) of **1**. Rf : 0.3 (ethyl acetate/hexane 1:4), $[\alpha]_D$= -11 (c=0.9, $CHCl_3$), [lit[3b] $[\alpha]_D$= -9 ($CHCl_3$, c=1)]. ^1H NMR (200MHz, $CDCl_3$) : δ : 1.19 (d, J=6.2Hz, 3H, H-12), 1.22-1.4 (m, 6H, H-4, H-5, H-6) 1.55-1.72 (m, 2H, H-7), 1.9-2.2 (m, 4H, H-3, H-10), 2.3 (m, 2H, H-2), 3.67 (s, 3H, COOMe), 3.8 (m, 1H, H-11), 5.47 (m, 2H, H-8, H-9). ^{13}C NMR ($CDCl_3$) : 174.3 (CO), 134.5 (C-8), 125.9 (C-9), 67.2 (C-11), 51.6 (OMe), 42.5 (C-11), 34, 32.5, 29.2, 28.9, 28.7, 24.8, 22.5, (C-12, C-2, C-3, C-4, C-5, C-6, C-7).

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a) On leave from the University of Buenos Aires, Argentina.

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7) The synthesis was partially carried out from (+)-[2(R),S(R)]-4, giving [2(R),4(E),S(R)]-**5a** : $[\alpha]_D$= +111 (acetone, C=2). In ^1H NMR (200MHz, $CDCl_3$), the 2(S) isomer showed a singlet for the benzylic methyl at 2.36 ppm and the 2(R) at 2.45 and in ^{13}C NMR, the vinylic carbons gave two signals at 131.1 and 123.7 in the 2(S) isomer and at 133.1 and 124.6 in the 2(R).

8) Isomer (+)-[2(R),4(E),S(R)]-**2a** : $[\alpha]_D$ = +89.7 (c=2, acetone). In ^1H NMR (200MHz, $CDCl_3$), the methylene α to the sulfoxide group gave an AB system in the 2(S) isomer at 2.81 ppm (J_{AB}=14Hz, J_{AX}= 10Hz, J_{BX}= 2Hz, Δν=52Hz) and in the 2(R) isomer at 2.85 ppm (J_{AB}= 13.5Hz, J_{AX}= 8.7Hz, J_{BX}=3Hz, Δν=29Hz).

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