Tetrahedron: Asymmetry Vol. 1, No. 3, pp. 187-198, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

Asymmetric Synthesis of Orsellinic Acid Type Macrolides : The Example of Lasiodiplodin

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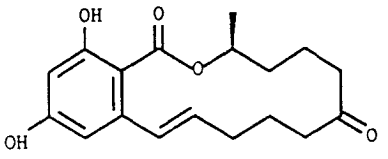
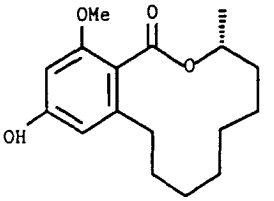
(*Received* 18 *January* 1990)

Abstract : The asymmetric synthesis of both enantiomers of methyl lasiodiplodin is described. The chiral centers were created in the very last steps of the synthesis by asymmetric induction of a chiral sulfoxide group.

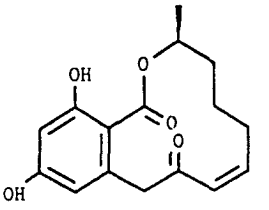
A number of naturally occurring orsellinic acid (2,4-dihydroxy-6-methylbenzoic acid) type macrolides are known. Zearalenone[1], Lasiodiplodin[2], Resorcylide[3], are typical examples. They all contain one chiral center due to the chiral methylcarbinol moiety.



Zearalenone



Lasiodiplodin

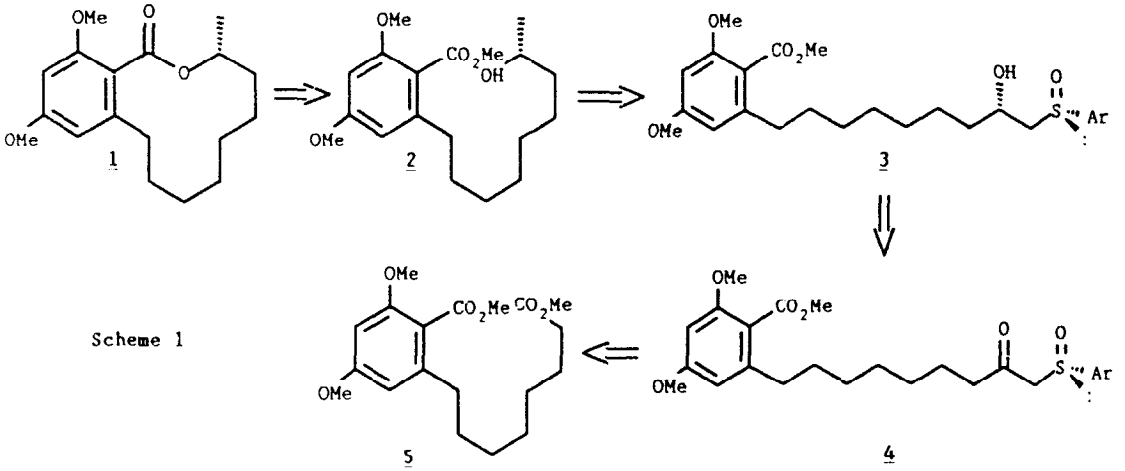


Resorcylide

We report in this paper an enantioselective synthesis of the methyl ether of Lasiodiplodin **1** in both configurations using a general asymmetric synthesis which can be applied to prepare both enantiomers of all the members of this macrolide family and based on our recent work [4] : the asymmetric synthesis of both antipodes of methyl carbinols from esters via the asymmetric reduction of ß-ketosulfoxides.

In examining the structure of these macrolides and the parent hydroxyesters, such as **2**, as shown on the retrosynthetic scheme of Lasiodiplodin methyl ether, (scheme 1) it is possible to prepare the chiral methyl carbinol moiety from the ß-hydroxysulfoxide **3**, using the stereoselective reduction of the ß-ketosulfoxide **4**.

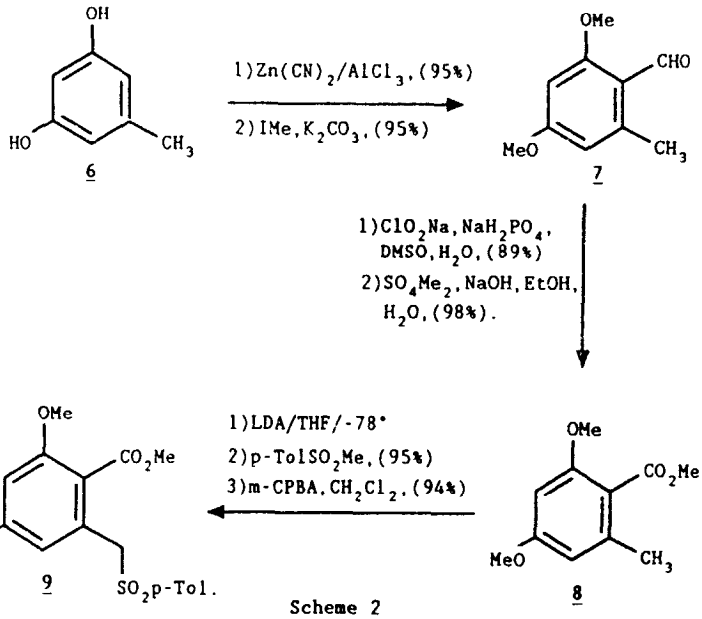
Therefore the total synthesis of these molecules can be divided in two parts : first of all the synthesis of an achiral diester **5** and then the introduction of the chiral methyl carbinol part via a ß-ketosulfoxide functionality in the very last steps of the synthesis, allowing the preparation of both configurations of the macrolide.



Scheme 1

Although three syntheses of racemic Lasiodiplodin are reported in the literature [5-7], only one from Gerlach [8] described the synthesis of the natural (+) (R)-isomer. The chirality was introduced in the first step :(+) (R)-1,2-epoxypropane was used to prepare (R)-9-hydroxydecanoic acid which was then transformed into an allenic lactone, the allenic functionality used finally to build the aromatic ring by a Diels Alder reaction.

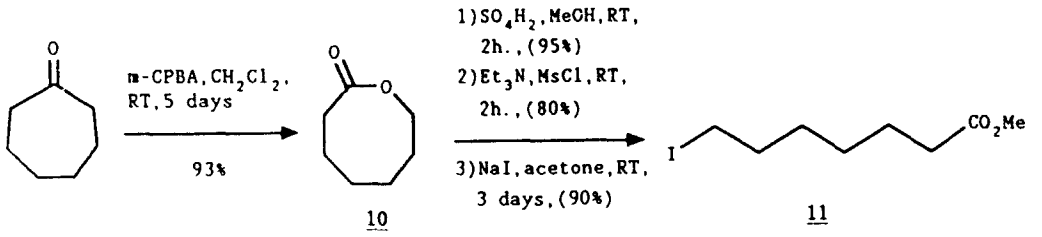
In our approach to the methyl ether of Lasiodiplodin we prepared first the diester 5.



Scheme 2

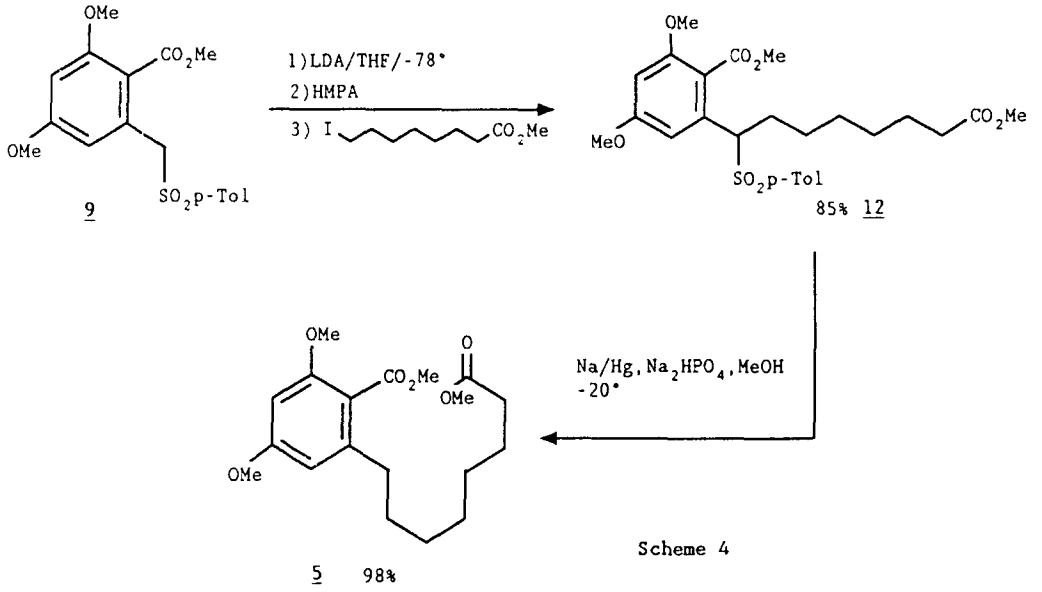
Commercially available orcinol **6** was submitted to a Gatterman reaction with zinc cyanide in presence of aluminium chloride (95% yield) and the phenols were methylated with methyl iodide.

Oxidation of the aldehyde in compound **7** with sodium chlorite (89% yield) and methylation of the resulting carboxylic acid gave the ester **8** in 98% yield. Sulfinylation of the benzylic position was obtained from the benzylic carbanion made with LDA and reaction with methyl p-toluenesulfinate (95% yld). Finally the sulfoxide group was oxidized with m-CPBA to the corresponding sulfone **9** (94% yld).



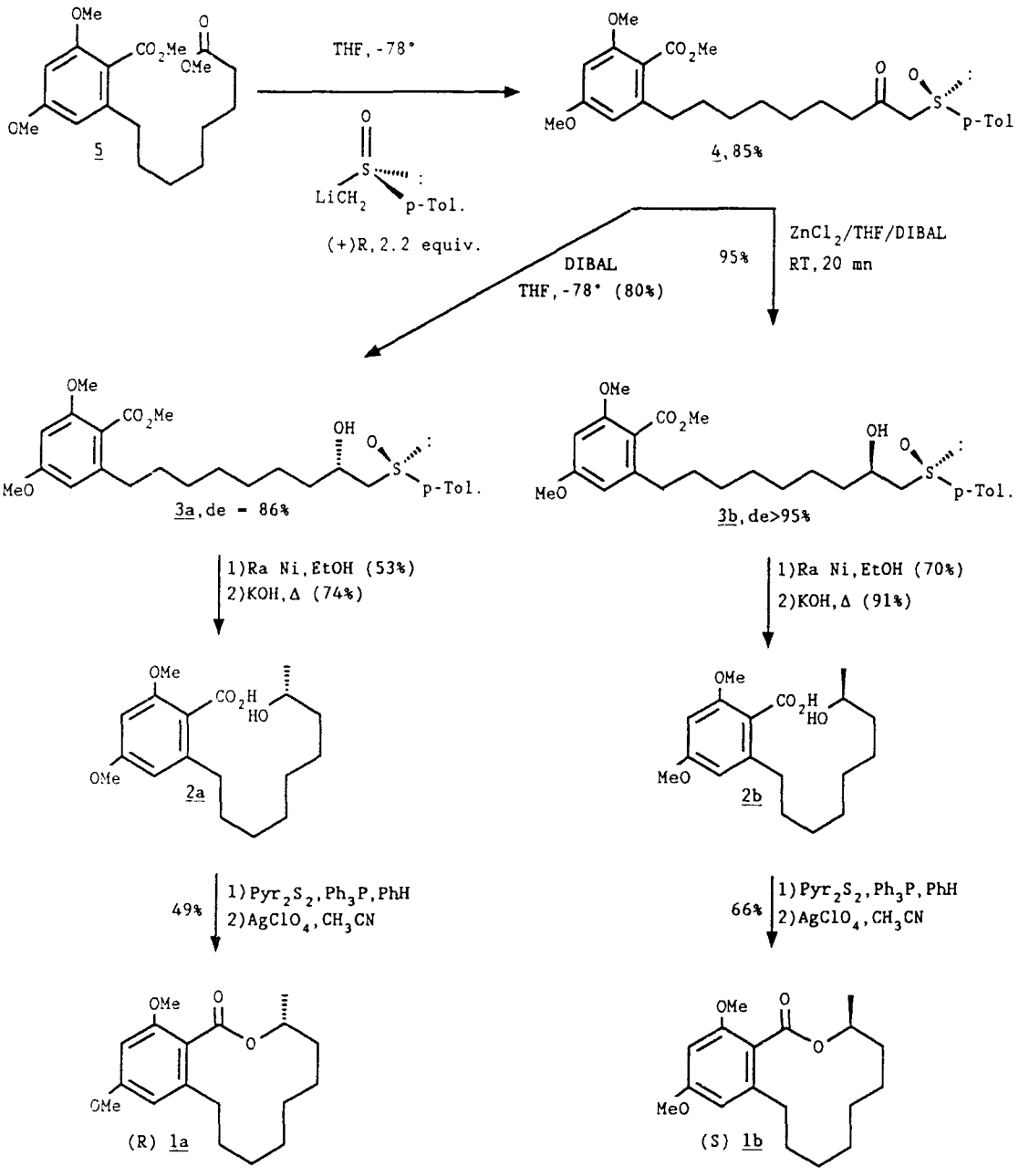
Scheme 3

The iodoester **11** was obtained from cycloheptanone which was first transformed into the lactone **10** via a Baeyer-Williger reaction (93% yld). The lactone **10** was then opened to the corresponding hydroxyester with methanol - sulfuric acid (95% yld). The corresponding mesylate obtained in 80% yield was finally displaced by sodium iodide giving **11** in 90% yield.



Scheme 4

The diester **5** was prepared by alkylation of sulfone **9** by the iodide **11** in 85% yield, followed by desulfurization with sodium amalgam (quantitative yield). The ketosulfoxide **4** was finally obtained from the ester by reaction with the carbanion of (+)(R)-methyl p-tolylsulfoxide in 85% yield.


OMe
CO2Me
OMe
O
OMe
5
THF, -78°
O
S
LiCH2
p-Tol.
(+)R, 2.2 equiv.
4, 85%
DIBAL
THF, -78° (80%)
95%
ZnCl2/THF/DIBAL
RT, 20 mn
OH
3a, de = 86%
3b, de>95%
1)Ra Ni, EtOH (53%)
2)KOH, Δ (74%)
1)Ra Ni, EtOH (70%)
2)KOH, Δ (91%)
CO2H
HO
2a
2b
49%
66%
1)Pyr2S2, Ph3P, PhH
2)AgClO4, CH3CN
(R) 1a
(S) 1b
1)BBr3
2)BnBr, CO3K2
3)IMe, acetone
4)Pd/C, EtOH, H+
(R) Lasiodiplodin

Scheme 5

Reduction of the ß-ketosulfoxide **4** with DIBAL in presence of zinc chloride yielded the (RR)-ß-hydroxysulfoxide **3b** in 95% yield. The R configuration of the hydroxylic carbon can be deduced from the reaction mechanism already published [4] 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 hydrogens α to the sulfoxide group is quite different in the two ß-hydroxysulfoxide diastereomers [4b,c] : in the RR configuration the $\Delta\nu$ value between these 2 hydrogens is around 40Hz (46Hz in **3b**) and around 80Hz in the RS configuration (83Hz in **3a**). The final correlation with natural Lasiodiplodin will indeed confirm the absolute configuration of these products. The diastereoselectivity for the reduction was higher than 95%, only one diastereomer was observed in the NMR spectrum.

The reduction of compound **4** with DIBAL alone afforded the (RS)-ß-hydroxysulfoxide **3a** in 86% de (determined by NMR from the A part of the ABX system corresponding to the methylene α to the sulfoxide).

After desulfurization with Raney Nickel and saponification of the ester group, both enantiomers **2a** and **2b** of the seco-acid were cyclized using the Gerlach's method [5] based on the macrolactonization of 2- pyridyl esters of thiocarboxylic acid.

Yields are lower in the (R) series because of the smaller quantities used with respect to the antipodal molecules.

The absolute configuration of Lasiodiplodin methyl ether **1a** was confirmed by correlation with natural (R)-Lasiodiplodin. Methyl ether hydrolysis with boron tribromide, followed by benzylation of the 4-OH group, and methylation of the 2-OH group gave after debenzylation a sample which was identical in all respects with (R)-Lasiodiplodin described in the literature [8] (Notice the positive and small value of the optical rotation at the D-line and its high and negative value at 365 nm).

Other applications of this efficient way to introduce chiral centers in the last steps of a total synthesis are in progress.

Acknowledgements : This work was partly supported by the "Action Intégrée Franco-Espagnole n°243" and Direccion General de Investigacion Cientifica y Tècnica (Grant PB 86-0120).

EXPERIMENTAL PART

7-Heptanolide, 10

15g (0.13 mol) of cycloheptanone were added to a solution of m-CPBA (0.16 mol) in chloroform (300 ml) at 0°C. The oxidation was completed after 5 days at room temperature. m-Chlorobenzoic acid was filtered and washed with chloroform. The organic phase was washed with a saturated sodium bicarbonate solution, then with water and dried over sodium sulfate. After evaporating the solvent, 16g (93% yld) of crude lactone was obtained and used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) : δ : 4.35 (m, 2 H, CH_2O), 2.56 (m, 2 H, CH_2CO), 1.00-1.50 (m, 8 H, $4CH_2$).

Methyl 7-hydroxyheptanoate

The preceeding crude lactone **10** (16g, 0.125 mol) was opened with methanol (300 ml) in presence

of concentrated sulfuric acid (1 ml) in 2 hours at room temperature. The solution was concentrated under vacuum and extracted with methylene chloride. After evaporation of the solvent, 19g (95% yld) of hydroxyester was isolated as a crude oil.

^{1}H NMR (200 MHz, $CDCl_3$) : δ : 3.67 (s, 3 H, CH_3O), 3.65 (t, 2 H, J=7.0 Hz, CH_2O), 3.50 (broad s, 1 H, OH), 2.32 (t, 2 H, J=7.0 Hz, CH_2CO), 1.63-1.25(m, 8 H, $4CH_2$).

^{13}C NMR ($CDCl_3$) : δ : 174.1, 62.1, 51.1, 33.6, 32.0, 28.6, 25.1, 24.5,

Methyl 7-methylsufonyloxyheptanoate

A solution of methylsulfonyl chloride (14g, 0.12 mol) in methylene chloride (150 ml) was slowly added to a solution of the preceeding hydroxyester (10g, 62.5 mmol) and triethylamine (19g, 0.19 mol) in methylene chloride (300 ml) at 0°C. After 2 hours at room temperature, the reaction mixture was hydrolyzed with water and the aqueous layer extracted twice with dichloromethane. The organic phase was dried over sodium sulfate and distilled : b.p. 134° (0.2 mm), yield : 11.9g, 80%.

^{1}H NMR (200 MHz, $CDCl_3$) : δ : 4.23 (t, 2 H, J=7.0 Hz, CH_2O), 3.67 (s, 3 H, CH_3O), 3.0 (s, 3 H, CH_3SO_2), 2.32 (t, 2 H, J=7.0 Hz, CH_2CO), 1.85-1.27 (m, 8 H, 4 CH_2).

^{13}C NMR ($CDCl_3$) : δ :174.4, 69.9, 51.4, 37.3, 33.8, 28.9, 28.4, 25.1, 24.6.

Methyl 7-iodoheptanoate, 11

To a solution of the preceeding mesylate (8g, 33.6 mmol) in anhydrous acetone (150 ml) were added sodium bicarbonate (8.5g) and sodium iodide (10.1g, 64.2 mmol). The reaction mixture was stirred at room temperature for 3 days. After evaporating the solvent, water was added to the residue and the mixture extracted with hexane. The organic phase was finally washed with a 5% sodium thiosulfate solution, dried over sodium sulfate and evaporated to give 8.1g (30 mmol, 90% yld) of an oily crude product which was used without further purification.

MS : 239 (51%), 155 (24%), 143 (74%), 127 (8%), 111 (91%), 83 (100%), 69 (70%), 55 (99%).

^{1}H NMR (200 MHz, $CDCl_3$) : δ : 3.67 (s, 3 H, CH_3O), 3.19 (t, 2 H, J=6.9 Hz, CH_2I), 2.32 (t, 2 H, J=7.4 Hz, CH_2CO), 1.93-1.75 (m, 2 H), 1.75-1.57 (m, 2 H), 1.55-1.25 (m, 4 H).

^{13}C NMR ($CDCl_3$) : δ : 173.3, 51.0, 33.4, 32.8, 29.7, 27.5, 24.2, 6.6.

IR (film) : 1745, 1200, 1185 cm^{-1}.

2,4-dihydroxy-6-methylbenzaldehyde

Orcinol (22g, 0.18 mol) and zinc cyanide (31.5g, 0.27 mol) were mixed in ether (500 ml). Gaseous hydrochloric acid was then added during one hour at room temperature to dissolve zinc cyanide and the reaction mixture was cooled with an ice bath. Anhydrous aluminium trichloride (57g, 0.43 mol) was slowly added under vigorous stirring. After removing the ice bath, gazeous hydrochloric acid was again added till the reaction was shown to be completed by TLC (2 hours). After cooling, the reaction mixture was poured very carefully on ice and acidified with concentrated HCl (30 ml). The organic layer was separated and the aqueous phase washed with ether. By heating for one hour the aqueous phase, one obtained the precipitation of the product : 25.5g (0.17 mol., 95% yld).

m.p. 179-180°C (lit[9] : 180°C)

M.S. : 152 (66%) M^+, 151 (100%), 123 (4%), 106 (5%), 69 (15%), 55 (8%).

^{1}H NMR (200 MHz, acetone d_6) : δ : 12.49 (s, 1 H, OH), 10.09 (s, 1 H, OH), 9.55 (s, 1 H, CHO), 6.29 (d, 1 H J=2.0 Hz, arom.), 6.16 (d, 1 H, J=2.0 Hz, arom.), 2.53 (s, 3 H, CH_3).

^{13}C NMR (acetone d_6) : δ : 194.1, 167.1, 166.1, 145.9, 113.7, 111.5, 101.3, 18.1.

IR (KBr) : 3150, 1630, 1605, 1275, 1235, 1210, 1170 cm^{-1}.

2,4-dimethoxy-6-methylbenzaldehyde 7

A mixture of the preceeding dihydroxyaldehyde (25g), potassium carbonate (150g) and methyl iodide (120 ml) in acetone, was heated under reflux for 6 hours. After filtration and evaporation of the excess of methyl iodide, the residue was extracted with ether, washed with water, dried over sodium sulfate and evaporated to give the crude dimethylether (29.3g, 99% yld).

m.p. 62-64°C (lit[10] 64-65°C)

M.S. : 181 (21%) M^++1, 180 (91%) M^+, 179 (100%), 163 (64%), 149 (16%), 121 (21%), 84 (35%), 51 (29%).

^1H NMR (200 MHz, $CDCl_3$) : δ : 10.49 (s, 1 H, CHO), 6.30 (s, 2 H, arom.), 3.88 (s, 3 H, CH_3O), 3.86 (s, 3 H, CH_3O), 2.59 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$) : δ : 189.8, 164.8, 164.0, 143.9, 116.7, 108.5, 95.1, 55.2, 54.9, 21.7.

IR (KBr) : 1680, 1610, 1580, 1215, 1160, 1105 cm^{-1}.

2,4-dimethoxy-6-methyl benzoic acid

To a solution of the preceeding aldehyde 7 (28.8g) in DMSO (460 ml) was added a solution of NaH_2PO_4 (48g) in water (60 ml). Then a solution of sodium chlorite (34.8g) in water (230 ml) was slowly added at 10°C. The reaction mixture was stirred at room temperature overnight. After the addition of a saturated sodium carbonate solution the aqueous layer was washed with ethyl acetate and then acidified with concentrated hydrochloric acid giving a white precipitate of the expected carboxylic acid (27.9g, 89% yld).

m.p. 140-142°C (dec.) (lit[10] 143-4)

M.S. : 196 (84%) M^+, 179 (64%), 178 (100%), 149 (45%), 135 (26%), 77 (29%), 69 (30%).

^1H NMR (200 MHz, $CDCl_3$) : 7.30 (broad s, 1 H, CO_2H), 6.44 (d, 1 H, J=2.4 Hz, arom.), 3.95 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 2.57 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$) : 169.6, 162.1, 159.4, 143.1, 112.6, 108.6, 96.4, 56.3, 55.3, 22.1.

IR (KBr) : 3400-2500, 1685, 1610, 1295, 1170 cm^{-1}.

Methyl 2,4-dimethoxy-6-methylbenzoate, 8

Methyl sulfate (150 ml) and a solution of sodium hydroxide (70g) in water (150 ml) were added simultaneously to a solution of the preceeding carboxylic acid (27.7g) in ethanol (130 ml). The addition was conducted in order to maintain the reaction mixture under reflux. The reaction was complete at the end of the addition (TLC, eluent : ethyl acetate/hexane 1/4). The reaction mixture was then hydrolyzed with a 5% ammonia solution in water and extracted with methylene chloride. The organic layer was dried over sodium sulfate and the solvent evaporated to give 29g of methyl ester (98% yld) of a crude product used in the next step without further purification.

m.p. 42-44°C (MeOH) (lit[11] 43-44°C)

M.S. : 210 (28%) M^+, 179 (100%), 149 (27%), 84 (47%), 69 (57%), 57 (60%)

^1H NMR ($CDCl_3$, 200 MHz) : δ : 6.32 (s, 2 H, arom.), 3.89 (s, 3 H, CH_3O), 3.80 (s, 6 H, 2 CH_3O), 2.29 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$) : δ : 168.2, 161.0, 157.8, 137.7, 116.0, 106.3, 95.6, 55.3, 54.8, 51.5, 19.0.

IR (KBr) : 1730, 1615, 1275, 1100 cm^{-1}

Methyl 2,4-dimethoxy-6-(p-tolylsulfinyl) methyl benzoate

The preceeding ester 8 (12g, 57 mmol) in THF solution (80 ml) was added at -78°C to a solution of LDA (57 mmol) in THF (80 ml). The resulting red solution was stirred at -78°C for 15 min. and

treated with methyl p-toluenesulfinate (4.4g, 26 mmol) in THF (80 ml). Five minutes after the end of the addition, the reaction mixture was hydrolyzed with a saturated solution of ammonium chloride and extracted with ether. The organic phase was washed with a saturated sodium chloride solution, dried over sodium sulfate and evaporated. The residue was chromatographed on silicagel (eluent : ethyl acetate/hexane 2/1) giving 8.5g (95% yld) of product and 5.6g of the starting ester.

m.p. 79-80°C (hexane-ethyl acetate).

M.S. : 348 (0.1%) M^+, 209 (100%), 179 (10%), 148 (5%), 135 (5%), 91 (5%).

^1H NMR (200 MHz, $CDCl_3$) : δ : 7.43 and 7.28 (AA'BB' part, 4 H, Tol.), 6.43 (d, 1 H, J=2.3 Hz, arom.), 6.13 (d, 1 H, J=2.3 Hz, arom.), 4.12 (AB part, 2 H, CH_2SO), 3.87 (s, 3 H, CH_3O), 3.81 (s, 3 H, CH_3O), 3.70 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$) : 167.3, 161.3, 158.9, 141.3, 140.1, 131.6, 129.4 (2C), 124 (2C), 115.8, 107.8, 98.8, 62.8, 55.8, 55.1, 51.9, 21.1,.

IR (KBr) : 1690, 1610, 1295, 1180 cm^{-1}.

Methyl 2,4-dimethoxy-6-(p-tolylsulfonyl) methyl benzoate, 9

A solution of m-chloroperbenzoic acid (3.83g, 18.9 mmol.) in methylene chloride (50 ml) was slowly added at 0°C to a solution of the preceeding sulfinyl ester (6.60g, 18.9 mmol.) in methylene chloride (50 ml). After stirring at room temperature for 1 hour, the reaction mixture was hydrolyzed with a saturated solution of sodium bicarbonate. After stirring for one hour, the organic layer was separated, washed with water, dried over sodium sulfate and evaporated giving 6.53g of sulfonylester (94% yld).

m.p. : 132-4°C (MeOH).

M.S. : 364 (6%) M^+, 300 (5%), 209 (100%), 179 (9%), 91 (11%).

^1H NMR (200 MHz, $CDCl_3$) : δ : 7.58 and 7.26 (AA'BB' part, 4 H, tolyl), 6.44 (d, 1 H, J=2.3 Hz, arom.), 6.30 (d, 1 H, J=2.3 Hz, arom.), 4.56 (s, 2 H, CH_2SO_2), 3.78 (s, 3 H, CH_3O), 3.75 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 2.42 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$) : δ : 167.1, 161.1, 158.9, 144.4, 135.1, 129.3 (2C), 129.2, 128.2 (2C), 116.6, 108.3, 99.2, 59.2, 55.8, 55.1, 51.9, 21.3.

IR (KBr) : 1690, 1610, 1290, 1160 cm^{-1}.

Methyl 2,4-dimethoxy-6-[1-(p-tolylsulfonyl)-7-methoxycarbonyl heptyl] benzoate, 12

The sulfonyl ester **9** (4g, 11 mmol.) in THF (50 ml) was added at -78°C to a solution of LDA (12 mmol.) in THF (50 ml). The resulting orange solution was stirred at -78°C for one hour. The unsoluble anion was then dissolved by adding HMPA (9.6 ml, 5 equiv.) and methyl 7-iodoheptanoate **11** (4g, 15 mmol.) in THF (25 ml) was slowly added. Five minutes after the end of the addition the reaction was shown to be completed (TLC, eluent : ethyl acetate/hexane 1/1). The hydrolysis of the reaction mixture was made with a 5% hydrochloric acid solution. Ether extraction followed by washing the organic layer with 5% HCl and a saturated solution of sodium bicarbonate gave, after evaporating the solvent and chromatography of the residue (eluent : ethyl acetate/hexane 1/1) 4.73g of the product (oil, 85% yld).

M.S. : 506 (1%) M^+, 475 (3%), 352 (20%), 351 (100%), 287 (19%), 259 (22%), 243 (27%), 191 (20%), 91 (21%).

^1H NMR (200 MHz, $CDCl_3$) : δ : 7.47 and 7.20 (AA'BB' part, 4 H, tolyl), 6.77 (d, 1 H, J=2.1 Hz, arom.), 6.41 (d, 1 H, J=2.1 Hz, arom.), 4.39 (dd, 1 H, J=3.6 and 11.2 Hz, $CHSO_2$), 3.84 (s, 3 H,

CH_3O), 3.73 (s, 3 H, CH_3O), 3.69 (s, 3H, CH_3O), 2.39 (s, 3H, CH_3), 2.25 (t, 2H, J=7.4 Hz, CH_2CO), 2.43-1.95 (m, 2 H, CH_2), 1.70-1.07 (m, 8 H, 4 CH_2).

^{13}C NMR ($CDCl_3$) : δ : 173.5, 167.0, 161.2, 157.8, 144.0, 134.5, 133.1, 128.9 (2C), 128.4 (2C), 118.1, 103.9, 98.4, 65.8, 55.5, 55.0, 51.5, 50.8, 33.3, 28.3 (2C), 28.2, 25.7, 24.2, 21.0.

IR (film) : 1740, 1610, 1215, 1170 cm^{-1}.

Methyl 2,4-dimethoxy-6-(7-methoxycarbonyl) heptyl benzoate, 5

To a solution of the sulfonyl ester **12** (1g, 2.0 mmol) and Na_2HPO_4 (1.14g, 8.0 mmol) in methanol (40 ml) was added at -20°C 6% sodium amalgam (3g). After stirring at -20°C for one hour, water was added and the reaction mixture extracted with methylene chloride. Evaporation of the solvent furnished the product as an oil (0.68g, 98% yld).

M.S. : 3.52 (13%) M^+, 321 (27%), 210 (100%), 191 (78%), 151 (33%), 69 (27%), 55 (34%).

^1H NMR (200 MHz, $CDCl_3$) : δ : 6.32 (s, 2 H, arom.), 3.87 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O), 3.65 (s, 3 H, CH_3O), 2.53 (m, 2 H, CH_2Ar.), 2.28 (t, 2 H, J=7.4 Hz, CH_2CO), 1.70-1.15 (m, 10 H, 5 CH_2).

^{13}C NMR ($CDCl_3$) : δ : 174.0, 161.2, 157.8, 142.7, 116.1, 105.7, 96.0, 55.7, 55.1, 51.8, 51.2, 33.9, 33.7, 30.9, 29.1, 28.9 (2C), 24.7.

IR (film) : 1730, 1610, 1205, 1100 cm^{-1}.

(+)(R) Methyl 3,5-dimethoxy-6-[8-oxo-9-(p-tolylsulfinyl) nonyl] benzoate, 4

(+)(R) methyl p-tolylsulfoxide[12] (1.56g, 10.2 mmol) in THF (20 ml) was added at -78°C to LDA (10.2 mmol) in THF (40 ml) and the resulting mixture stirred at -30°C for 0.5 hour. Then the preceeding ester **5** (1.6g, 4.6 mmol.) in THF (20 ml) was slowly added at -78°C. The reaction was shown to be completed at the end of the addition by TLC (eluent : ethyl acetate/hexane 2/1). After hydrolysis with a saturated ammonium chloride solution, the reaction mixture was extracted with methylene chloride ; the organic layer was dried and evaporated. Chromatography of the residue (eluent : ethyl acetate/ hexane 2/1) gave 1.82g of product (oil, 85% yld).

$[\alpha]_D$=+87.5° (c=1, $CHCl_3$)

M.S. : 321 (14%), 305 (32%), 210 (41%), 191 (54%), 151 (32%), 139 (82%), 91 (52%), 69 (65%), 55 (100%).

^1H NMR (200 MHz, $CDCl_3$) : δ : 7.53 and 7.33 (AA'BB', 4 H, tolyl), 6.32 (s, 2 H, arom.), 3.87 (s, 3 H, CH_3O), 3.81 (s, 3 H, CH_3O), 3.79 (s, 3 H, CH_3O), 3.80 (AB, 2 H, J_{AB}=13,5Hz, CH_2SO), 2.56-2.41 (m, 4 H, CH_2CO and CH_2Ar), 2.41 (s, 3 H, CH_3), 1.65-1.15 (m, 10H, 5 CH_2).

^{13}C NMR ($CDCl_3$) : δ : 201.5, 168.4, 161.0, 157.6, 142.5, 148.1, 139.4, 129.8 (2C), 123.7 (2C), 115.8, 105.5, 95.7, 67.7, 55.5, 55.0, 51.6, 44.5, 33.5, 30.7, 28.8, 28.7, 28.4, 22.6, 21.0.

IR (film) : 1730, 1710, 1610, 1270, 1160 cm^{-1}.

(+)(R,R) methyl 2,4-dimethoxy-6-[8-hydroxy-9-(p-tolylsulfinyl) nonyl] benzoate, 3b

Zinc chloride (0.41g, 2.96 mmol.) in THF (20 ml) was added to a solution of the preceeding ketosulfoxide **4** (1.4g, 2.96 mmol) in THF (20 ml). After stirring for 20 min., the reaction mixture was cooled at -78°C and slowly added to a 1M hexane solution of DIBAL (6 ml, 6 mmol) diluted with THF (20 ml). The reaction was shown to be completed at the end of the addition by TLC (eluent : ethyl acetate/hexane 2/1). The reaction mixture was hydrolyzed with methanol at -78°C and the solvent evaporated. The residue was treated with a 5% sodium hydroxide solution and extracted with dichloromethane. After evaporating the solvent, 1.4g (95%) of crude β-hydroxysulfoxide was obtained

as an oil.

$[\alpha]_D$=+110.6° ($CHCl_3$, c=1)

M.S. : 305 (48%), 291 (84%), 210 (35%), 191 (53%), 151 (57%), 139 (89%), 91 (100%), 77 (50%), 55 (53%).

^{1}H NMR (200 MHz, $CDCl_3$) : δ : 7.55 and 7.33 (AA'BB', 4 H, Tol.), 6.32 (s, 2H, arom.), 4.20 (m, 1 H, CHOH), 3.83 (broad s, 1 H, OH), 3.87 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O), 2.80 (AB part of ABX, 2H, J_{AB}=13,1Hz, J_{AX}=9.0Hz, J_{BX}=2,7Hz, =45,9, 2 H, CH_2SO), 2.53 (t, 1 H, J=7.2 Hz, CH_2Ar), 2.41 (s, 3 H, CH_3), 1.60-1.10 (m, 12 H, 6 CH_2).

^{13}C NMR ($CDCl_3$) : δ : 168.5, 161.0, 157.6, 142.6, 141.5, 140.2, 129.8 (2C), 123.7 (2C), 115.8, 105.5, 95.7, 68.0, 62.8, 55.5, 54.9, 51.6, 36.8, 33.5, 30.7, 28.9 (3C), 24.7, 21.0.

IR (film) : 3400, 1730, 1610, 1270, 1160 cm^{-1}.

(+)(S) methyl 2,4-dimethoxy-6-(8-hydroxynonyl) benzoate

The (+)(RR) hydroxysulfoxide **3b** (0.4g, 0.84 mmol) was desulfurized with Raney Nickel (4g) in ethanol (90 ml) over 30 min. After filtration and evaporation of the solvent, the product was chromatographed (eluent : ethyl acetate/hexane 1/1) giving 200 mg of an oily product (70% yld).

$[\alpha]_D$=+2.7° ($CHCl_3$, c=1)

M.S. : 338 (9%) M^+, 291 (12%), 210 (100%), 191 (47%), 151 (27%), 69 (45%), 57 (39%).

^{1}H NMR ($CDCl_3$) : δ : 6.32 (AB, 2 H, arom.), 5.0 (broad s, 1 H, OH), 3.87 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), ,3.79 (s, 3 H, CH_3O), 3.92-3.70 (m, 1 H, CHOH), 2.53 (m, 2 H, CH_2Ar), 1.70-1.20 (m, 12 H, 6CH_2), 1.17 (d, 3 H, J=6.2 Hz, CH_3).

^{13}C NMR ($CDCl_3$) : δ : 168.8, 161.3, 157.9, 142.9, 116.2, 105.8, 96.0, 68.0, 55.8, 55.2, 51.9, 39.2, 33.8, 31.0, 29.4, 29.2 (2C), 25.6, 23.4.

IR (film) : 3440, 1730, 1610, 1275, 1165 cm^{-1}

(+)(S) 2,4-dimethoxy-6-(8-hydroxynonyl) benzoic acid, 2b

The (+)(S) hydroxyester **2b** (192 mg, 0.57 mmol) in ethyleneglycol solution (6 ml) was saponified with a 10N potassium hydroxide solution (0.57 ml) in heating at 165°C for 4 hours. Benzene and a 2N potassium hydroxide solution were added. The aqueous phase was acidified with concentrated HCl and extracted with benzene. The organic phases were washed with water and dried with sodium sulfate. After evaporating the solvent, 167 mg of product (oil, 91% yld) were isolated.

$[\alpha]_D$=+3.5° ($CHCl_3$, c=1)

M.S. : 324 (9%) M^+, 306 (5%), 207 (24%), 196 (100%), 191 (60%), 152 (68%), 137 (26%), 120 (21%), 91 (13%).

^{1}H NMR ($CDCl_3$, 200 MHz) : δ : 6.35 (AB, 2 H, arom.), 5.95 (broad, s, 2 H, OH), 3.84 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 3.95-3.70 (m, 1 H, CHOH), 2.72 (m, 2 H, CH_2Ar),1.70-1.10 (m, 12 H, 6CH_2), 1.17 (d, 3 H, J=6.1 Hz, CH_3).

^{13}C NMR ($CDCl_3$) : δ : 170.6, 161.3, 158.1, 144.1, 115.1, 106.3, 95.9, 68.0, 55.8, 55.1, 38.7, 33.9, 30.9, 29.0 (2C), 28.9, 25.3, 22.9.

IR (film) : 3450, 1710, 1610, 1270, 1170 cm^{-1}.

(-)(S) Methyl Lasiodiplodin, 1b

The (+)(S) hydroxyacid **2b** (77 mg, 0.24 mmol) was treated with di-(2-pyridyl) disulfide (76 mg, 0.34 mmol), triphenylphosphine (90 mg, 0.80 mmol) in 1 ml of benzene. After stirring for one hour, dry acetonitrile (9ml) was added. The resulting yellow solution was added with an automatic syringe in 4

hours to a boiling solution of silver perchlorate (1.2 mmol) in acetonitrile (25 ml).

After heating the mixture at 160°C for 30 min, the solvent was evaporated and the residue dissolved in benzene and washed with a 1M sodium cyanide solution. The organic phase was dried over sodium sulfate and evaporated. After chromatography (eluent : hexane/ethyl acetate 4/1) 48 mg of (-)(S) methyl lasiodiplodine (oil, 66% yld) was obtained.

$[\alpha]_D$:-8.5° (MeOH, c=1), -8,7° ($CHCl_3$, c=1)

M.S. : 306 (67%) M^+, 196 (100%), 191 (63%), 152 (98%), 91 (21%), 77 (22%), 69 (21%).

^1H NMR ($CDCl_3$) : δ : 6.31 (AB, 2 H, arom.), 5.28 (m, 1 H, CHOH), 3.80 (s, 3 H, CH_3O), 3.79 (s, 3 H, CH_3O), 2.81-2.46 (m, 2 H, CH_2Ar), 2.00-1.20 (m, 12 H, $6CH_2$), 1.32 (d, 3 H, J=6.2 Hz, CH_3).

^{13}C NMR ($CDCl_3$) : δ : 168.5, 161.1, 157.7, 142.7, 118.1, 105.8, 96.3, 72.0, 55.8, 55.3, 32.3, 30.6, 30.1, 26.4, 25.4, 24.2, 21.2, 19.4 .

IR (film) : 1720, 1610, 1270, 1210, 1170, 1100 cm^{-1}.

(+)(R,S) methyl 2,4-dimethoxy-6-[8-hydroxy-9-(p-tolylsylfinyl) nonyl] benzoate 3a

A DIBAL 1M solution in hexane (3,5 mmol) was dropwise added at -78°C to a solution of the ß-ketosulfoxide **4** (1,5g, 3.23 mmol) in THF. After stirring at -78°C for one hour, the reaction mixture was hydrolyzed with methanol and the solvent was evaporated. The residue was diluted with a 5% sodium hydroxide solution and methylene chloride. After evaporating the solvent, the crude ß-hydroxysulfoxide was shown by RMN to be a mixture of diastereoisomers in the ratio 93/7 (for the A part of the ABX system ; corresponding to the methylene α to the sulfoxide). After chromatography (eluent : ethyl acetate/hexane 2/1) 1.2g (80%) of pure (R,S)-ß-hydroxysulfoxide **3a** was obtained.

$[\alpha]_D$=+120°C ($CHCl_3$, c=1)

^1H NMR (200MHz, $CDCl_3$) : δ : 7.53 (AA'BB', 4H, pTol.), 6.32 (s, 2H, arom.), 4.15 (m, 1H, CHOH), 3.87 (s, 3H, OMe), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.04 (A part of ABX, J_{AB}=13,5Hz, J_{AX}=9,6Hz), 2.64 (B part, J_{AB}=13,5Hz, J_{BX}=1,7Hz, CH_2SO), 2.52 (t, 2H, CH_2Ar), 2.43 (s, 3H, CH_3), 1.65-1.10 (m, 13H).

(+)(R) methyl Lasiodiplodin, 1a

All the following steps were conducted in the same conditions as in the antipodal series :

1) *(-)(R) methyl 2,4-dimethoxy-6-(8-hydroxynonyl) benzoate* **2a** obtained by desulfurization with Raney Nickel.

yld : 53%

$[\alpha]_D$=-3.1° ($CHCl_3$, c=1)

2) *(-)(R) 2,4-dimethoxy-6-(8-hydroxynonyl) benzoic acid*, obtained by saponification.

yld : 74%

$[\alpha]_D$=-3.7° ($CHCl_3$, c=1)

3) *(+)(R) methyl lasiodiplodin*, **1a**

yld : 49%

$[\alpha]_D$=+9° ($CHCl_3$, c=1)

(R) Lasiodiplodin

1) Hydrolysis of the methyl ethers in compound **1a**.To a stirred solution of (+)(R) methyl Lasiodiplodin (50mg, 0.16 mmol) in methylene chloride (0.5 ml) under nitrogen at 0°C, was added a cooled 1.26M solution of BBr_3 in methylene chloride (2.36 mmol, 1.87 ml). The reaction mixture was

stirred for 0.5 hour between 0°C and room temperature and then hydrolyzed by adding 0.1 ml of water and 20 ml of ether. The product was finally purified by chromatography (eluent : ethyl acetate/hexane 1/4) giving 7.8 mg of the pure dihydroxy compound.

yld : 17%

$[\alpha]_D$=+31.4° ($CDCl_3$, c=0.78)

^{1}HNMR (200MHz, $CDCl_3$) : δ :11.97 (s, 1H, 2-OH), 6.28 and 6.23 (AB, 2H, J_{AB}=2.7Hz, Arom.), 5.40 (broads, 1H, OH), 5.17 (m, 1H, HCOCO), 3.27 (m, 1H, benzylic H), 2.50 (m, 1H, benzylic H), 2.05-1.15 (m, 12H), 1.37 (d, 3H, J=6.2Hz, CH_3).

2) To a solution of the preceeding 2,4-dihydroxy compound (7.8 mg, 0.028 mmol) in acetone (0.2 ml) and anhydrous potassium carbonate (42 mg, 0.28 mmol) was added 4.8 mg (0.028 mmol) of benzyl bromide in acetone (0.2 ml). After 24 hours at room temperature, 0.5 ml of methyl iodide in 2 ml of acetone were added and the reaction mixture refluxed for 1 hour and filtered over silicagel. The residue obtained after evaporation of the solvent was dissolved in methanol (0.5) containing one drop of acetic acid and 20 mg of 10% Palladium on carbon were added. Under hydrogen atmosphere the reaction was followed by TLC (eluent : hexane/AcOEt 4/1). The reaction was complete after 2.5 hours ; 20 ml ether were added and the mixture was filtered over silicagel.

After evaporating the solvent, the (R) Lasiodiplodin was purified by preparative TLC (eluent : hexane/AcEt 2/1), giving 2.7 mg of pure (R) Lasiodiplodin.

Overall yield : 33%

mp=178-180°, (Lit[8], mp=183-4°)

$[\alpha]_{365}$=-83° (MeOH, c=0.27), (Lit[8], $[\alpha]_{365}$=-79°, MeOH, C=0.94, $[\alpha]_D$=+7.4)

^{1}H NMR (200MHz, $CDCl_3$) : δ : 6.25 (AB, 2H, arom.), 5.28 (m, 1H, HCOC), 3.77 (s, 3H, CH_3O), 2.77-2.43 (m, 2H, CH_2 Ar.), 2.00-1.20 (m, 12H), 1.33 (d, 3H, J=6.5Hz, CH_3)

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