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Asymmetric Construction of Benzylic Quaternary Carbons from Chiral malonates : Formal Synthesis of natural (-)Aphanorphine.

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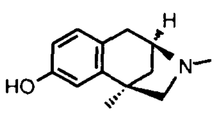
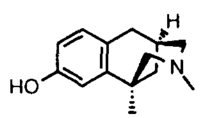
Abstract : *Enantiomerically pure (+)-dihydronaphthalene **4**, a precursor of (-)-aphanorphine, was obtained from the homochiral malonic acid ester (R)-(+)-5, via the chiral lactone (+)-12 prepared by a Wittig-Horner reaction and hydrogenation, which underwent subsequent acidic Friedel-Crafts cyclisation.*

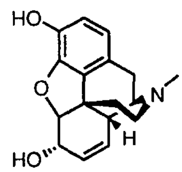
Stereogenic quaternary carbon centers are found in many naturally occuring compounds [1] and specially benzylic centers in various analgesics such as aphanorphine **1**, eptazocine **2**, and morphine **3**.[2] Convenient methods for their enantioselective construction have been investigated.[3]



(-)-**1**- aphanorphine



2- eptazocine

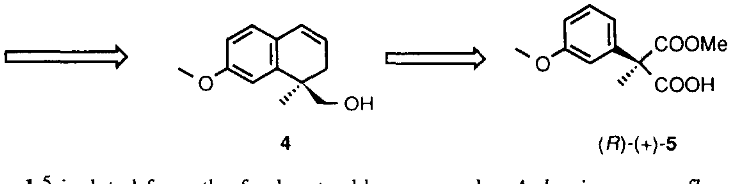


3- morphine

In previous papers, we have described the asymmetric construction of quaternary carbons from chiral malonates and their subsequent transformation into both enantiomers of cuparenones and laurene.[4]

Herein we report that this strategy can be applied to the synthesis of dihydronaphthalene derivatives **4** containing a quaternary carbon center. This approach provides a general pathway for the preparation of a wide variety of natural products containing a benzomorphan moiety. It is illustrated by the synthesis from acid ester **5** of dihydronaphthalene **4**, efficient precursors of the aphanorphine **1**.

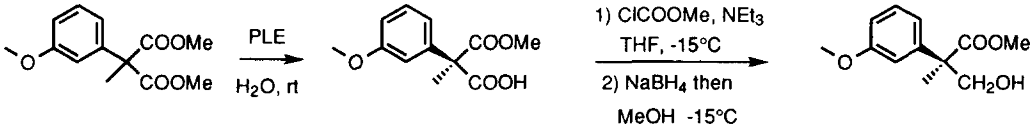
(-)-**1**



4 (*R*)-(+)-**5**

Aphanorphine **1**,[5] isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae*, has a potential analgesic activity. The relative stereochemistry of **1** was deduced spectroscopically and recently its absolute stereochemistry was determined as (1*R*,4*R*).[6,7]

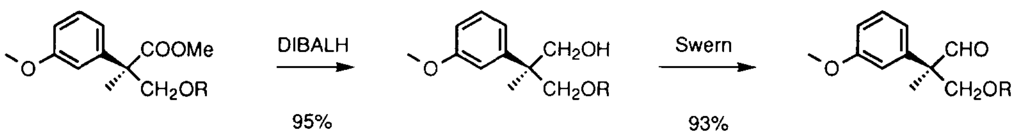
Thus, for our strategy, the prochiral dimethyl malonate **6**, obtained in 92% yield from methyl 3-methoxyphenyl acetate by successive alkylation with methyl iodide and methyl chloroformate, underwent enantioselective enzymatic hydrolysis by pig liver esterase (PLE) to provide in 88% yield the acid ester (*R*)-(+)-**5**.[8] The enantiomeric excess of **5**, determined from the ^{1}H NMR spectra of its salt with (*R*)-(+)-1-naphthylethylamine, was 91% and can be raised to 97% ee after recrystallisation with dibenzylamine ($[\alpha]_D^{20}$ +12.1 (c = 1, $CHCl_3$), 97% ee).



6 88% (*R*)-(+)-**5** 84% (*R*)-(+)-**7**

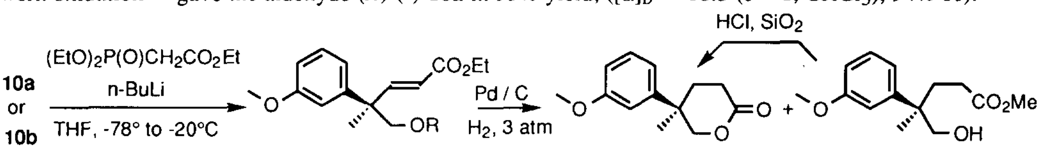
Reaction of (*R*)-(+)-**5** with 1 equiv of methyl chloroformate in the presence of triethylamine gave a mixed anhydride which, upon reduction [4d] with 3 equiv of sodium borohydride in THF then addition of MeOH [9] gave the β-hydroxy ester (*R*)-(+)-**7** in 84% overall yield ($[\alpha]_D^{20}$ +58.4 (c = 1, $CHCl_3$), 97% ee).

Hydroxy ester (*R*)-(+)-**7** was found to be a key intermediate for the preparation of dihydronaphthalene (+)- **4**. Thus its silylation with *tert*-butyldimethylsilyl chloride in the presence of imidazole led to the ester (*R*)-(+)-**8a** (92% yield ; ($[\alpha]_D^{20}$ +12 (c = 1, $CHCl_3$), 97% ee).



(*R*)-(+)-**8a** : R = TBDMS (*S*)-(+)-**9a** R = TBDMS (*R*)-(-)-**10a** : R = TBDMS
(*R*)-(+)-**8b** : R = Bn (*R*)-(+)-**10b** : R = Bn

The ester (+)-**8a** after reduction with 2 equiv of diisobutylaluminum hydride (DIBALH in hexane) [10] at -78°C gave the alcohol (*S*)-(+)-**9a** in 95% yield, ($[\alpha]_D^{20}$ +2.8 (c = 1, $CHCl_3$)). Its enantiomeric excess (94% ee) was determined by ^{1}H NMR in the presence of Eu(hfc)$_3$. The slight decrease of enantiomeric excess during reduction may be due to the labile transfer of the protecting silyl group from one oxygen atom to the other. The Swern oxidation [11] gave the aldehyde (*R*)-(-)-**10a** in 93% yield, ($[\alpha]_D^{20}$ -18.3 (c = 1, $CHCl_3$), 94% ee).



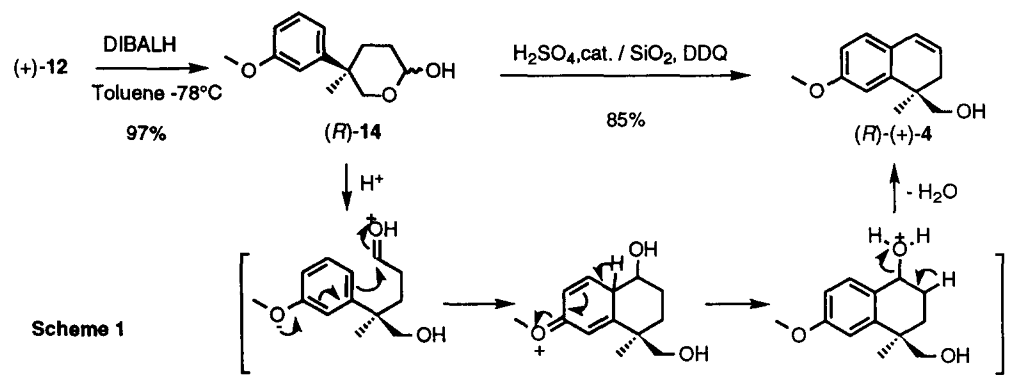
87% (-)-**11a** : R = TBDMS 98% (*R*)-(+)-**12** **13**
(+)-**11b** : R = Bn

The introduction of the two remaining carbons was carried out by Wittig-Horner reaction. Reaction of aldehyde **11a** with triethyl phosphonoacetate and n-butyllithium in tetrahydrofuran led exclusively to the *trans* ester **11a** (87% yield ; ($[\alpha]_D^{20}$ -2.45 (c = 1, $CHCl_3$), 94% ee). This ester, upon treatment with Pd/C 10% under 3 atm of hydrogen, underwent in one pot : hydrogenation of the double bond, cleavage of the protecting group and subsequent cyclisation, and gave a 1:1 mixture of lactone (*R*)-(+)-**12** and uncyclized ester **13** in 98% yield. This latter was easily transformed to the desired lactone (+)-**12** by treatment with 6N HCl on silica gel ($[\alpha]_D^{20}$ +46 (c = 1, $CHCl_3$), 94% ee).

The drawback of this sequence is in fact the slight loss of the ee during the reduction step of the ester **8a**. We subsequently found that it was possible to avoid this side reaction if the reduction was carried out on ester **8b** having a benzyl as protecting group. This ester (*R*)-(+)-**8b** was prepared [12] by reaction with benzyl 2,2,2-trichloroimidate [13] under acidic conditions (trifluoromethanesulfonic acid) ; (90% yield ; $[\alpha]_D^{20}$ +29.2 (c = 1, $CHCl_3$), 97% ee). Reduction with 1.2 equiv of DIBALH in hexane at -78°C gave directly the corresponding aldehyde (*R*)-(+)-**10b** in 85% yield as the major product ($[\alpha]_D^{20}$ +0.7 (c = 1, $CHCl_3$), 97% ee).

Wittig-Horner reaction of **10b** afforded in 80% yield pure *trans* (+)-**11b** ($[\alpha]_D^{20}$ +3.4 (c = 1, $CHCl_3$)). Further hydrogenolysis (H_2, 1 atm) in the presence of 20% $Pd(OH)_2/C$ (w/w, 9%)[14] and acidic cyclisation, furnished the expected lactone (*R*)-(+)-**12** in 85% yield, ($[\alpha]_D^{20}$ +47.5 (c = 1, $CHCl_3$), 97% ee).

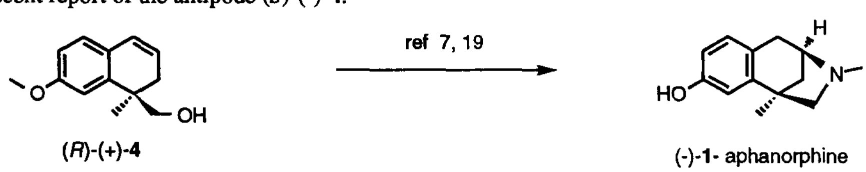
Reduction of the lactone (*R*)-(+)-**12** by 1 equiv of DIBALH in toluene at -78°C led to a 55:45 diastereoisomeric mixture of lactol (*R*)-**14** (97% yield). Treatment of this lactol under acidic conditions (catalytic amount of sulfuric acid and dichlorodicyanobenzoquinone (DDQ)[15] on silica gel) as shown in scheme 1, furnished the alcohol (*R*)-(+)-**4** in 85% yield ($[\alpha]_D^{20}$ +18.3 (c = 1, $CHCl_3$)).



Scheme 1

Other acidic conditions, ferric chloride dispersed on silica gel [16] at 90°C for 11 h, H_2SO_4/SiO_2 [17] at r.t. and $TMSCl/SiO_2$, gave unsatisfactory results : respectively 25%, 10% and 36% yields. The enantiomeric excess (97% ee) was determined by gas chromatography using a chiral column (Cydex B, 25 m, 140°C, 1 bar).

Our assignment of the (*R*)-absolute configuration of the dihydronaphthalene (+)-**4** was supported by the very recent report of the antipode (*S*)-(-)-**4**.[18]



Since the transformation of racemic dihydronaphtalene (±)-**4** into aphanorphine was reported [19] in 58% overall yield, the formal preparation of (-)-aphanorphine can be considered to be achieved.

In conclusion, from a readily available chiron (ee > 97%), we have developed, via a Wittig-Horner homologation and one pot cyclisation (cat. H_2SO_4, DDQ, SiO_2), a rapid and competitive approach to the dihydronaphthalene (*R*)-(+)-**4** (7 steps, 45.2% overall yield). This constitutes a potential precursor of aphanorphine (-)-**1**. Further synthetic applications of this approach to other alkaloids e.g. eptazocine, pentazocine and normetazocine are currently under investigation.

Experimental Section

The general experimental procedures and the analytical instruments employed have been described in detail in a previous paper.[4c] Enantiomeric excess determinations were performed on a GC (Delsi-Nermag Model DN 200) chiral column Cydex B (SGE) (25 m, 140°C, 1 bar).

Dimethyl 2-methyl-2-(3-methoxyphenyl)malonate 6

Prepared from 2-(3-methoxyphenyl)acetic acid (0.1 mol) following the procedure described in reference 4c, with 92% overall yield. As a colourless oil (23.2 g).

IR (neat) : 1750, 1610, 1590, 1260 cm^{-1}; *^{1}H NMR ($CDCl_3$) δ* : 7.34 - 7.23 (m, 1H), 7.00 - 6.80 (m, 3H), 3.82 (s, 3H, methoxy), 3.78 (s, 6H, ester), 1.89 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 171.5 (2s, COO), [6 arom. C, 159.1 (s), 139.4 (s), 128.9 (d), 119.3 (d), 113.6 (d), 112.2 (d)], 58.5 (s, C(2)), 54.8 (q, C, methoxy), 52.5 (2q, OCH_3 ester), 22.1 (q, CH_3); *MS (EI)* : 253 (M^+ +1, 16), 152, (M^+, 97), 193 (78), 192 (24), 117 (25), 165 (82), 161 (26), 134 (22), *133* (100), 91 (37), 77 (24), 59 (20), 43 (25); *Anal. calcd for $C_{13}H_{16}O_5$* : C, 61.88 ; H, 6.40. Found : C, 61.88 ; H, 6.41.

(R)-(+)-2-(Methoxycarbonyl)-2-(3-methoxyphenyl)propionic acid 5

To a stirred solution of malonate **6** (25.8 g, 102 mmol) in water (70 mL) was added, at 25°C, pig liver esterase (4 g, acetonic powder purchased from Sigma L 8251). The pH of the reaction was kept at 7.2 by regular addition of 2N aqueous NaOH via a syringe pump interfaced with a pH controller. After a stirring period of 3 h another portion of PLE (7 g) was added. When 50.1 mL of aqueous 2N NaOH (60 h) was added, the enzyme was eliminated by filtration (addition of celite to the mixture facilitates the filtration). The precipitate was washed with water (60 mL) and with ether (100 mL). After separation, the aqueous layer was acidified (2N aqueous HCl) until pH 2 and the malonate monoester **5** was extracted with ethyl acetate (6x150 mL). The combined organic extracts were whashed with brine, dried, and evaporated. Product purification was achieved by chromatography on silica gel (elution with 3:2:5 ; acetone:ethyl acetate:hexane). There was isolated 21.45 g (88.4%) of acid ester (+)-**5**, as a colourless oil : $[\alpha]_D^{20}$ +11.6 (c = 1, $CHCl_3$) ; ee = 92% from ^{1}H NMR spectra in presence of (*R*)-(+)-1-naphthylethylamine. Crystallisation of 9.52 g (40 mmol) of (+)-**5** in presence of 0.95 equiv of dibenzylamine from CH_2Cl_2/ether gave 13 g (80%) of a white solid salt, which was acidified and extracted with ethyl acetate. After drying, evaporation gave 7.6 g of pure acid (+)-**5** $[\alpha]_D^{20}$ +12.1 (c = 1, $CHCl_3$) ; ee = 97%.

IR (neat) : 1750, 1720, 1610, 1595, 1260 cm^{-1}; *^{1}H NMR ($CDCl_3$) δ* : 7.40 - 7.24 (m, 1H), 7.05 - 6.85 (m, 3H), 3.84 (s, 3H, methoxy), 3.82 (s, 3H, ester), 1.92 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 176.5 (s), 172.1 (s), [6 arom. C, 159.4 (s), 138.8 (s), 129.3 (d), 119.5 (d), 113.8 (d), 112.8 (d)], 58.4 (s), 55.2 (q), 53.1 (q), 21.9 (q); *MS (EI)* : 239 (M^+ +1, 2), 238 (M^+, 10), 162 (62), *135* (100), 134 (39), 133 (24), 105 (41), 103 (36), 92 (23), 91 (72), 89 (18), 79 (24), 78 (17), 77 (39), 65 (28); *Anal. calcd for $C_{12}H_{14}O_5$* : C, 60.50 ; H, 5.92. Found : C, 60.30 ; H, 6.02.

(R)-(+)-Methyl 3-hydroxy-2-(3-methoxyphenyl)-2-methylpropionate 7

To a cold (-15°C) stirred solution of malonate monoester **5** (9.52 g, 40 mmol) in dry THF (100 mL) was added Et_3N (6.8 mL, 44 mmol, 1.1 equiv). After 15 min., MeOCOCl (3.04 mL, 40 mmol, 1 equiv) was added dropwise and stirred for 15 min at -15°C. The mixture was then filtered under argon, and the white precipitate obtained was washed with THF (2x50 mL). To the filtrate, cooled at 0°C, was added $NaBH_4$ (4.6 g, 128 mmol, 3.2 equiv) in one portion and then MeOH (25 mL)[9a] was added dropwise over 1 h. After stirring at 0°C for a supplementary 1 h, the reaction mixture was hydrolyzed with 6N aqueous HCl (dropwise to pH 1). The hydroxy ester was extracted with CH_2Cl_2 (4x100 mL). The combined organic extracts were washed with brine, dried and concentrated. Product separation was achieved by chromatography on silica gel (elution with 15/85 ethyl acetate-hexane). There was isolated 7.525 g (84%) of the hydroxy ester (+)-**7** as a colourless oil, $[\alpha]_D^{20}$ +58.4 (c = 1, $CHCl_3$).

IR (neat) : 3500, 1740, 1610, 1595, 1260, 1050 cm^{-1}; *^{1}H NMR ($CDCl_3$) δ* : 7.35 - 7.21 (m, 1H), 6.19 - 6.78 (m, 3H), 3.85 (AB, $\Delta\nu_{AB}$ = 113 Hz), 4.07 (d, J = 11.4 Hz, 1H), 3.62 (d, J = 11.4 Hz, 1H)], 3.82 (s, 3H, methoxy), 3.73 (s, 3H, ester), 2.50 (br s, OH), 1.67 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 176.3 (s, C(1)), [6 arom. C, 159.7 (s), 141.9 (s), 129.5 (d), 118.5 (d), 112.7 (d), 112.0 (d)], 69.6 (t), 55.2 (q), 52.6 (s), 52.3 (q), 19.9 (q); *MS (EI)* : 225 (M^+ +1, 2.6), 224 (M^+, 16), 194 (20), 165 (23), 163 (18), *162* (100), 135 (11), 134 (24), 133 (17), 77 (13), 65 (12), 43 (27); *Anal. calcd for $C_{12}H_{16}O_5$* : C, 64.27 ; H, 7.19. Found : C, 64.46 ; H, 7.20.

(R)-(+)-Methyl 3-(tert-butyldimethylsiloxy)-2-(3-methoxyphenyl)-2-methylpropionate 8a

Prepared following the procedure described in ref 4c, from alcohol (+)-**7** (6,72 g, 30 mmol) imidazole (4.08 g, 60 mmol) and TBDMSCl (5.4 g, 36 mmol) in DMF. Chromatography on silica gel (5/95 ether/hexane) furnished 9.32 g (92%) of ester **8a** as a colourless oil, $[\alpha]_D^{20}$ +12 (c = 1, $CHCl_3$).

IR (neat) : 1750, 1610, 1590, 1260, 1100 cm^{-1}; *^1H NMR ($CDCl_3$) δ* : 7.30 - 7.19 (m, 1H), 6.91 - 6.74 (m, 3H), 3.97 (AB, $\Delta\nu_{AB}$ = 107.5 Hz), 4.19 (d, J = 9.25 Hz, 1H), 3.77 (d, J = 9.25 Hz, 1H)], 3.81 (s, 3H, methoxy), 3.86 (s, 3H, ester), 1.61 (s, 3H), 0.85 (s, 9H, tBu), 0.03 (s, 3H), -0.02 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 175.1 (s), [6 arom. C, 159.5 (s), 143.1 (s), 129.3 (d), 118.6 (d), 112.7 (d), 111.8 (d)], 69.0 (t), 55.2 (q), 52.8 (s), 51.9 (q), 25.7 (3q), 21.0 (q), 18.1 (s), 5.7 (2q, H_3C-Si); *MS (EI)* : no peak parent at 338, 282 (25), *281* (M^+ -tBu, 100), 221 (30), 89 (90), 75 (12), 73 (49), 59 (16); *Anal. calcd for $C_{18}H_{30}O_4Si$* : C, 63.87 ; H, 8.93 ; Si, 8.30. Found : C, 63.73 ; H, 9.03 ; Si, 8.65.

(R)-(+)-Methyl 3-benzyloxy-2-(3-methoxyphenyl)-2-methylpropionate 8b

To a stirred solution of alcohol (+)-**7** (4.48 g, 20 mmol) and benzyl 2,2,2-trichloroacetimidate [13] (7.5 mL, 40 mmol) in CH_2Cl_2 (80 mL), was added at 15°C a catalytic amount of trifluoromethanesulfonic acid (175 µl, 2 mmol). After stirring for 30 min, a saturated aqueous $NaHCO_3$ solution (28 mL) was added. Extraction with CH_2Cl_2 (4x100 mL) followed by drying and concentration of the organic layer gave a solide-liquid residue. Which was diluted in pentane (400 mL) to allow precipitation of the by product trichloroacetamide. The pentane layer concentrated and furnished, after chromatography on silica gel (100 g, elution ether-hexane : 2/8), 5.6 g (90%) of the protected ester **8b**, $[\alpha]_D^{20}$ +29.2 (c = 1, $CHCl_3$).

IR (neat) : 1740, 1605, 1590, 1260, 1100 cm^{-1}; *^1H NMR ($CDCl_3$) δ* : 7.40 - 7.20 (m, 6H), 6.75 - 6.93 (m, 3H), 4.57 (AB, $\Delta\nu_{AB}$ = 17 Hz, J_{AB} = 12.2 Hz, 2H, benzyl), 3.85 [AB, $\Delta\nu_{AB}$ = 93.8 Hz, 4.04 (d, J = 9 Hz, 1H), 3.67 (d, J = 9 Hz, 1H)], 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, ester), 1.68 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 174.9 (s), [12 arom. C, 159.5 (s), 142.7 (s), 138.2 (s), 129.4 (d), 128.2 (2d), 127.4 (3d), 118.3 (d), 112.5 (d), 111.9 (d)], 75.7 (t), 73.3 (t), 55.1 (q), 52.1 (q), 51.5 (s), 21.2 (q); *MS (EI)* : 315 (M^+ +1, 2), 314 (M^+, 5.6), 206 (12), 193 (34), 165 (23), 133 (28), *91* (100), 65 (13); *Anal. calcd for $C_{19}H_{22}O_4$* : C, 72.59 ; H, 7.05. Found : C, 72.86 ; H, 6.97.

(S)-(+)-3-(tert-butyldimethylsiloxy)-2-(3-methoxyphenyl)-2-methylpropanol 9a

To a stirred solution of silylated ester **8a** (3.38 g, 10 mmol) in dry hexane (10 mL) was added slowly via cannula at -78°C, a solution of DIBALH (20 mL of a 1M solution in hexane, 20 mmol, 2 equiv). The mixture was stirred for 30 min at -78°C before quenching with MeOH (3 mL) then allowed to warm to room temperature. The solution was poured in a 6:1 mixture of ethyl acetate-potassium sodium tartrate (140 mL). The organic layer was dried and concentrated and the residue purified by chromatography on silica gel (using 1:4 ether-hexane as eluent) to yield 2.945 g (95%) of pure alcohol (*S*)-(+)-**9a** as a colourless oil : $[\alpha]_D^{20}$ +2.8 (c = 1, $CHCl_3$). The enantiomeric excess was 94% determined from ^1H NMR spectra in the presence of $Eu(hfc)_3$.

IR (neat) : 3450, 1610, 1590, 1260, 1100, 1060, 840 cm^{-1}; *^1H NMR ($CDCl_3$) δ* : 7.34 - 7.22 (m, 1H), 7.03 - 6.92 (m, 2H), 6.82 - 6.73 (m, 1H), 3.85 (A'B', $\Delta\nu_{A'B'}$ = 73.5 Hz, 3.98 (d, J = 9.75 Hz, 1H), 3.68 (d, J = 9.75 Hz, 1H)] ; 3.88 [AB part of ABM, $\Delta\nu_{AB}$ = 47.5 Hz, 3.97 (A part, J_{AB} = 4.6 Hz, J_{AM} = 6.3 Hz, 1H), 3.78 (B part, J_{AB} = 4.6 Hz, J_{BM} = 6.3 Hz, 1H)], 3.83 (s, 3H), 2.58 (M part of ABM, J_{AM} = J_{BM} = 6.3 Hz, 1H, OH), 1.34 (s, 3H), 0.89 (s, 9H, tBu), 0.06 (s, 3H), 0.04 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 159.6 (s), [6 arom. C, 145.4 (s), 129.2 (d), 119.0 (d), 113.3 (d), 111.1 (d)], 70.9 (t), 70.4 (t), 56.2 (q), 44.4 (s), 25.8 (3q), 20.3 (q), 18.1 (s), -5.68 (q), -5.71 (q); *MS (EI)* : no peak parent at 310, 162 (17), *161* (100), 148 (20), 121 (57), 105 (10), 75 (50), 73 (36); *Anal. calcd for $C_{17}H_{30}O_3Si$* : C, 65.76 ; H, 9.75 ; Si, 9.02. Found : C, 65.46 ; H, 9.79 ; Si, 8.70.

(R)-(-)-3-(tert-butyldimethylsiloxy)-2-(3-methoxyphenyl)-2-methylpropanal 10a

This aldehyde was prepared, following Swern procedure [11] and as described in ref 4c, from alcohol **9a** (2.48 g, 8 mmol), $(COCl)_2$ (0.75 mL, 8.8 mmol, 1.1 equiv) and DMSO (1.24 mL, 17.6 mmol, 2.2 equiv) in CH_2Cl_2 (50 mL) at -60°C then Et_3N (5.22 mL, 40 mmol, 5 equiv). Chromatography on silica gel (1:99 ether-hexane as eluent) furnished 2.29 g (93%) of pure aldehyde (-)-**10a** as a colourless liquid : ($[\alpha]_D^{20}$ -18.3 (c = 1, $CHCl_3$), ee 94%). This aldehyde is not very stable at r.t. for extended periods.

IR (neat) : 1745, 1610, 1590, 1265, 1100, 840 cm^{-1}; *^1H NMR ($CDCl_3$) δ* : 9.65 (s, H), 7.34 - 7.23 (m, 1H), 6.87 - 6.75 (m, 2H), 4.01 [AB, $\Delta\nu_{AB}$ = 93 Hz, 4.20 (d, J_{AB} = 9.5 Hz, 1H), 3.82 (d, J_{AB} = 9.5 Hz, 1H)], 3.81 (s, 3H), 1.48 (s, 3H), 0.86 (s, 9H, tBu), 0.04 (s, 3H), 0.00 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 202.2 (s), [6 arom. C, 159.8(s), 140.2 (s), 129.6 (d), 119.4 (d), 113.5 (d), 112.3 (d)], 67.2 (t), 55.9 (s), 55.2 (q), 25.7 (3q), 18.1 (s), 17.6 (q), -5.65 (q), -5.72 (q); *MS (EI)* : no peak parent at 308, 251 (41), 221 (19), 207 (25), 148 (17), 136 (17), *135* (100), 115 (16), 91 (12), 89 (31), 75 (52), 73 (73), 59 (27); *Anal. calcd for* $C_{17}H_{28}O_3Si$: C, 66.19 ; H, 9.15 ; Si, 9.10. Found : C, 66.09 ; H, 9.02 ; Si, 8.80.

(R)-(+)-3-(benzyloxy)-2-(3-methoxyphenyl)-2-methylpropanal 10b

To a stirred solution of ester (+)-**8b** (3.14 g, 10 mmol) in dry CH_2Cl_2 (20 mL) was added slowly (15 min) via cannula at -78°C, a solution of DIBALH (12 mL of a 1M solution in toluene, 12 mmol, 1.2 equiv). The mixture was stirred for 30 min at -78°C before quenching with MeOH (12 mL) then allowed to warm to -20°C within 2 h. The solution was poured in a 6:1 mixture of ethyl acetate-potassium sodium tartrate (140 mL). The organic layer was dried and concentrated and the residue purified by chromatography on silica gel (using 1:9 ethyl acetate-hexane as eluent) to yield 2.415 g (85%) of pure aldehyde (*R*)-(+)-**10b** as a colourless oil : $[\alpha]_D^{20}$ +0.7 (c = 1, $CHCl_3$).

IR (neat) : 1730, 1610, 1590, 1260, 1100 cm^{-1}; *^1H NMR ($CDCl_3$) δ* : 9.63 (s, 1H), 7.45 - 7.15 (m, 6H), 6.91 - 6.77 (m, 3H), 4.57 (s, 2H, benzyl), 3.88 [AB, $\Delta\nu_{AB}$ = 59.2 Hz, 4.05 (d, J = 9 Hz, 1H), 3.74 (d, J = 9 Hz, 1H)], 3.81 (s, 3H), 1.55 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 201.4 (s), [12 arom. C, 159.9 (s), 139.9 (s), 137.9 (s), 129.7 (d), 128.3 (2d), 127.6 (2d), 127.4 (d), 119.2 (d), 113.3 (d), 112.4 (d)], 73.6 (t), 73.4 (t), 55.1 (q), 54.9 (s), 18.1 (q); *MS (EI)* : 284 (M^+, 4), 254 (9), 225 (7), 148 (11), 92 (12), *91* (100), 77 (7), 65 (9); *Anal. calcd for* $C_{18}H_{20}O_3$: C, 76.03 ; H, 7.09. Found : C, 76.33 ; H, 7.08.

(R)-(-)-Ethyl 5-(tert-butyldimethylsiloxy)-4-(3-methoxyphenyl)-4-methylpent-2-enoate trans 11a

To a cold (-78°C) stirred solution of triethyl phosphonoacetate (3.7 g, 16.4 mmol, 1 equiv) in dry THF (40 mL) was added n-BuLi (1.55M, 10.8 mL, 16.73 mmol, 1.02 equiv). After stirring at -78°C for 30 min, a solution of aldehyde (-)-**10a** (5.065 g, 16.4 mmol) in THF (30 mL) was added over 30 min. The solution was stirred at -78°C for 30 min, then allowed to warm to room temperature (2 h 30) and neutralyzed with 2N HCl. The reaction mixture was extracted with ether (4x200 mL). The combined organic extracts were washed with brine, dried and evaporated. The ester **11a** was separated by chromatography on silica gel (elution with 1:9 ether-hexane) to yield 5.385 g (87%) as a colourless oil of the *trans* (-)-**11a** : ($[\alpha]_D^{20}$ -2.45 (c = 1, $CHCl_3$), ee 94%).

IR (neat) : 1725, 1650, 1610, 1590, 1260, 1180, 1100 cm^{-1}; *^1H NMR ($CDCl_3$) δ* : 7.30 - 7.18 (m, 1H), 7.20 (d, J_{trans} = 16 Hz, 1H, olefin), 6.94 - 6.85 (m, 2H), 6.72 (m, 1H), 5.84 (d, J_{trans} = 16 Hz, 1H, olefin), 4.20 (q, J = 7 Hz, 2H, ester), 3.77 [AB, $\Delta\nu_{AB}$ = 30.8 Hz, 3.84 (d, J = 9.7 Hz, 1H), 3.70 (d, J = 9.7 Hz, 1H)], 3.81 (s, 3H), 1.45 (s, 3H), 1.30 (t, J = 7 Hz, 3H), 0.85 (s, 9H, tBu), -0.01 (s, 3H), -0.02 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 166.9 (s), [6 arom. C, 159.4 (s), 145.4 (s), 129.1 (d), 119.5 (d), 113.7 (d), 111.3 (d)], 153.9 (C olefin), 120.3 (C olefin), 70.0 (t), 60.2 (t), 55.2 (q), 46.7 (s), 25.7 (3q), 22.2 (q), 18.2 (s), 14.2 (q), -5.65 (q), -5.7 (q); *MS (EI)* : 378 (M^+, 0.5), 333 (7), 322 (40), 321(M^+ -tBu, 93), 159 (20), 135 (54), 115 (19), 89 (55), 75 (53), *73* (100), 59 (23), 57 (10); *Anal. calcd for* $C_{21}H_{34}O_4Si$: C, 66.62 ; H, 9.05 ; Si, 7.42. Found : C, 66.76 ; H, 9.23 ; Si, 7.30.

(R)-(+)-Ethyl 5-benzyloxy-4-(3-methoxyphenyl)-4-methylpent-2-enoate trans 11b

This conjugated ester was prepared following the procedure described above for **11a**, from aldehyde (+)--**10b** (855 mg, 3 mmol), triethyl phosphonoacetate (740 mg, 3.3 mmol) and n-BuLi (2.12 mL of a 1.55N solution, 3.3 mmol). Chromatography on silica gel (1:9 ether-hexane) furnished 850 mg (80%) as a colourless oil of the trans (+)-**11b** and 60 mg (7%) of starting **10b**.

$[\alpha]_D^{20}$ +3.4 (c = 1, $CHCl_3$).

IR (neat) : 3030, 1720, 1655, 1610, 1585, 1180, 1100, 1050 cm^{-1}; *^1H NMR ($CDCl_3$) δ* : 7.40 - 7.15 (m, 5H), 7.21 (d, J = 16 Hz, 1H), 7.10 - 6.70 (m, 4H), 5.85 (d, J = 16 Hz), 4.54 (s, 2H, benzyl), 4.21 (q, J = 7.3 Hz, 2H, ester), 3.79 (s, 3H), 3.65 [AB, $\Delta\nu_{AB}$ = 25.4 Hz, 3.69 (A, J = 8.9 Hz, 1H), 3.59 (B, J = 8.9 Hz, 1H)], 1.51 (s, 3H), 1.30 (t, J = 7.3 Hz, 3H); *^{13}C NMR ($CDCl_3$) δ* : 166.8 (s), [12 arom. C, 159.5 (s), 145.1 (s), 138.1 (s), 129.2 (d), 128.3 (2d), 127.5 (3d), 119.3 (d), 113.5 (d), 111.3 (d)], 153.6 (d, C=C), 120.2 (d, C=C), 76.7 (t), 73.3 (t), 60.3 (t), 55.1 (q), 45.7 (s), 22.8 (q), 14.2 (q); *MS (EI)* : 354 (M^+, 0.5), 160 (10), 159 (55), 144 (6), 129 (7), 128 (7), 127 (6), 115 (13), 92 (11), *91* (100), 65 (8); *Anal. calcd for* $C_{22}H_{26}O_4$: C, 74.55 ; H, 7.39. Found : C, 74.90 ; H, 7.12.

(R)-(+)-4-(3-Methoxyphenyl)-4-methyl-5-pentanolide 12

A solution of conjugated ester (-)-**11a** (3.830 g, 10.1 mmol) in methanol (100 mL) was hydrogenated in the presence of 10% Pd/C as catalyst (300 mg, w/w : 9%) at room temperature under hydrogen (3 atm) in a parr-hydrogenation apparatus for 24 h. After purging with argon the resulting mixture was filtered through a Celite pad and the solid washed with MeOH (3x10 mL). The combined washings concentrated, gave a crude product (2.442 g) which indicate as shown in its ^{1}H NMR spectra that only 40% conversion into the lactone **12** and 60% of the corresponding methyl ester **13**. The mixture, dissolved in CH_2Cl_2 (10 mL), was added over 1 g of SiO_2 containing 6N aqueous HCl (1 mL) and stirred at room temperature for 16 h. After evaporation of the solvent, the residue, purified by chromatography on a silica gel column (using 1:9, ether-hexane as eluent) furnished 2.170 g (97.7%) of lactone (+)-**12** as a colourless oil : ($[\alpha]_D^{20}$ +46 (c = 1, $CHCl_3$), ee 94%).

IR (neat) : 1745, 1610, 1595, 1210, 1050 cm^{-1}; *^{1}H NMR ($CDCl_3$) δ* : 7.35 - 7.23 (m, 1H), 7.20 - 6.86 (m, 2H), 4.46 [AB, $\Delta\nu_{AB}$ = 78.6 Hz, 4.66 (d.d, J_{AB} = 11.6 Hz, J_{AM} = 2.1 Hz, 1H)], 4.27 (d, J_{AB} = 11.6 Hz, 1H)], 3.83 (s, 3H), 2.70 - 2.50 (m, 1H), 2.50 - 2.20 (m, 2H), 2.16 - 1.95 (m, 1H), 1.36 (s, 3H); *^{13}C NMR ($CDCl_3$) δ* : 170.4 (s), [6 arom. C, 159.9 (s), 144.9 (s), 129.9 (d), 118.0 (d), 112.5 (d), 111.4 (d)], 76.7 (t), 55.2 (q), 36.9 (s), 33.0 (t), 27.6 (t), 25.9 (q); *MS (EI)* : 221 (M^++1, 16), 220 (M^+, 49), *148* (100), 149 (18), 147 (10), 108 (11); *Anal. calcd for $C_{13}H_{16}O_3$* : C, 70.89 ; H, 7.32. Found : C, 70.78 ; H, 7.18.

The ^{1}H NMR spectra of (*R*)-methyl 5-hydroxy-4-(3-methoxyphenyl)-4-methylpentanoate **13** read from the mixture ($CDCl_3$) δ : 7.35 - 7.22 (m, 1H), 3.83 (s, 3H, OCH_3), 3.66 [AB, $\Delta\nu_{AB}$ = 30.5 Hz, 3.73 (d.d, J_{AB} = 11 Hz, 1H), 3.58 (d.d., J_{AB} = 11 Hz, 1H)], 3.64 (s, 3H, ester), 2.30 - 1.70 (m, 4H), 1.65 (br, s, OH), 1.36 (s, 3H).

Lactone (+)-12 from conjugated ester (+)-11b (ee 97%)

This lactone was prepared following the procedure described above, from conjugated ester (+)-**11b** (1.065 g, 3 mmol), 20% $Pd(OH)_2/C$ as catalyst (95 mg, w/w : 9%) and hydrogen 1 atm for 1 h. Cyclisation with 6N HCl on SiO_2, followed by chromatography on silica gel (1:9 ether-hexane as eluent) afforded 560 mg (85%) as a colourless oil of the lactone (+)-**12** ($[\alpha]_D^{20}$ +47.5 (c = 1, $CHCl_3$), ee 97%).

If the reaction was conducted with 10% Pd/C (95 mg, w/w : 9%) and hydrogen (3 atm) for 24 h. Only 395 mg (60%) of (+)-**12** and 160 mg (15%) of starting material (+)-**11b** were isolated after chromatography.

(5R)-2-Hydroxy-5-(3-methoxyphenyl)-5-methyltetrahydropyran 14

This lactol was prepared following the procedure described above for **10b**, from lactone (+)-**12** (1.76 g, 8 mmol) and DIBALH (8 mL of a 1M solution in toluene, 8 mmol, 1 equiv). Concentration gave 1.73 g (97.3%) of a 46:54 mixture of diastereoisomers of lactol **14** as a colourless oil. This mixture was used without further purification in the next step :

IR (neat) : 3400, 1610, 1590, 1040 cm^{-1}; *^{1}H NMR (mixture of diastereoisomers **a** and **b**) ($CDCl_3$) δ* : 7.34 - 7.22 (m, 1H, **a** and **b**), 7.06 - 6.94 (m, 2H, **a** and **b**), 6.81 - 6.73 (m, 1H, **a** and **b**), 5.05 (m, 0.46H, **a**), 4.98 (m, 0.54H, **b**), 4.00 [AB, $\Delta\nu_{AB}$ = 197.4 Hz, 4.28 (d, J = 11.7 Hz, 0.46H, **a**), 3.49 (d, J = 11.7 Hz, 0.46H, **a**)], 3.90 [AB, $\Delta\nu_{AB}$ = 30 Hz, 3.96 (d, J = 11.7 Hz, 0.54H, **b**), 3.84 (d, J = 11.7 Hz, 0.54H, **b**), 3.82 (s, 3H, **a** and **b**), 2.83 (d, J = 4.2 Hz, 0.54H, OH, **b**), 2.70 (d, J = 5.3 Hz, 0.46H, OH, **a**), 2.40 - 1.40 (m, 4H, **a** and **b**), 1.27 (s, 3H, **a** and **b**); *^{13}C NMR (mixture of **a** and **b**) ($CDCl_3$) δ* : data of **a** : [6 arom. C, 159.60 (s), 148.4 (s), 129.2 (d), 118.5 (d), 112.8 (d), 110.6 (d)], 93.8 (d), 70.3 (t), 55.2 (q), 36.9 (s), 32.2 (t), 28.2 (t), 25.2 (q). Data of **b** : [6 arom. C, 159.59 (s), 148.0 (s), 129.2 (d), 118.45 (d), 112.85 (d), 110.55 (d)], 93.7 (d), 70.6 (t), 55.2 (q), 37.1 (s), 32.1 (t), 27.95 (t), 26.3 (q); *MS (EI)* : 223 (M^++1, 3), 224 (M^+, 20), 149 (25), *148* (100), 122 (11), 108 (12), 91 (12), 77 (12).

(R)-(+)-1,2-Dihydro-1-(hydroxymethyl)-7-methoxy-1-methylnaphthalene 4

To a mixture of DDQ (100 mg, 0.2 mmol) and SiO_2 (2 g) was added a solution of lactol **14** (222 mg, 1 mmol) in CH_2Cl_2 (2 mL) followed by concentrated H_2SO_4 (4 drops) and H_2O (0.5 mL). The stirred mixture was heated at 45°. The reaction was complete within 10 h as shown in TLC. Chromatography of the solid residue on silica gel (2:8 ethyl acetate-hexane as eluent) furnished 175 mg (85%) of the cyclized alcohol (+)-**4** as a colourless oil : $[\alpha]_D^{20}$ +18.3 (c = 1, $CHCl_3$). The enantiomeric excess determined from GC chiral column (Cydex B, 25 m, 140°C, 1 bar) was 97%.

IR (neat) : 3118, 1610, 1570, 1305, 1040 cm^{-1}; *^{1}H NMR ($CDCl_3$) δ* : 7.20 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 2.5 Hz, 1H), 6.73 (d.d., J = 8.2 Hz, J = 2.5 Hz, 1H), 6.38 (d, J = 9.6 Hz, 1H, olefin), 5.80 (ddd, J = 9.6 Hz, J = 1.4 Hz, J = 3.6 Hz, 1H, olefin), 3.82 (s, 3H), 3.57 [AB, J_{AB} = 17.4 Hz, J = 10.8 Hz, 2H), 2.33 (AB part of ABX, $\Delta\nu_{AB}$ = 52.2 Hz, 2.44 (ddd, J_{AB} = 17.6 Hz, J_{AX} = 5.2 Hz, J = 1Hz, 1H), 2.23 (ddd, J_{AB} = 17.6 Hz, J_{BX} = 3.5 Hz, J = 2.4 Hz, 1H), 1.58 (br. s, OH), 1.31 (s, 3H); *^{13}C NMR (CDCl3) δ* : [6 arom. C, 159.0 (s), 141.1 (s), 127.9 (d), 127.1 (s), 126.8 (d), 124.0 (d)], 112.3 (d), 110.0 (d), 68.0 (t), 55.2 (q), 39.0 (s), 33.2 (t), 23.1 (q); *MS (EI)* : 205 (M^++1, 24), *173* (100), 174 (20), 158 (32).

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