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Enantioselective synthesis of *cis*-7-methoxy-calamenene via Claisen rearrangement of an enzymatically resolved allyl alcohol

Elisabetta Brenna, Claudia Dei Negri, Claudio Fuganti, Francesco G. Gatti* and Stefano Serra

Dipartimento di Chimica dei Materiali ed Ingegneria Chimica, 'G. Natta' del Politecnico, Centro CNR per la Chimica delle sostanze Naturali, Via Mancinelli 7, 20131 Milano, Italy

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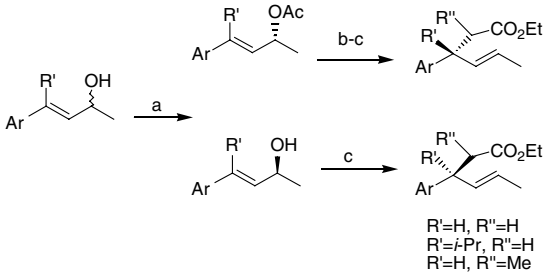
Abstract—An enantioselective synthesis of *cis*-7-methoxy-calamenene **1** has been accomplished through the following key-steps: (i) enzymatic resolution of the racemic allyl alcohol **3** to furnish the (*R*)-enantiomer (ee >99%); (ii) Claisen-orthoester rearrangement of **4** to introduce the isopropyl unit on the benzylic position (99% ee); (iii) diastereoselective reduction of dihydronaphthalene derivative **11** to give the *cis*-isomer **12** (98% de); (iv) regioselective introduction of the formyl group by a Vilsmeier reaction followed by reduction to give **1**.

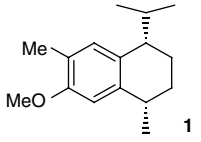
1. Introduction

The catalytic enantioselective generation of tertiary or quaternary benzylic carbons continues to remain one of the main challenges of modern organic chemistry.[1] Successful methodologies have been accomplished by means of hydrogenation,[2] metallobenzene addition,[3] benzyl lithium derivatives additions,[4] alkylations of arene rings with carbonyls and electron poor olefins[5] and intramolecular Heck reaction.[6]

Recently, Fu and co-workers have reported a new methodology based on the enantioselective isomerisation of allylic alcohols catalysed by a rhodium/phosphoferrocene complex, however the ees were modest (<87%).[7] Instead, in connection with our continuing interest in developing new synthetic strategies based on enzyme-mediated resolutions of simple and cheap starting materials, we found recently that the combination of Claisen rearrangement[8] with enzymatic asymmetric esterification of allylic alcohols furnishes an efficient and simple synthetic tool for the generation of benzylic stereocentres with excellent ee, always higher than 98% (Scheme 1).[9] Thus, we give here a further demonstration of the efficacy of our synthetic methodology culminating on the first, to our knowledge, enantioselective total synthesis of (1*S*,4*S*)-*cis*-7-methoxy-calamenene **1**.[10–12]



Scheme 1. (a) Enzymatic resolution of allylic alcohols; (b) hydrolysis of acetyl derivative; (c) Claisen rearrangement to give the benzylic stereocentre.



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Two main synthetic routes to this class of terpenoid-like compounds have been so far developed: one consists of generating the aromatic ring on a preformed chiral cyclic precursor by benzoannulation reactions.[13]

* Corresponding author. Tel.: +39-02-23993072; fax: +39-02-239930-80; e-mail: francesco.gatti@polimi.it

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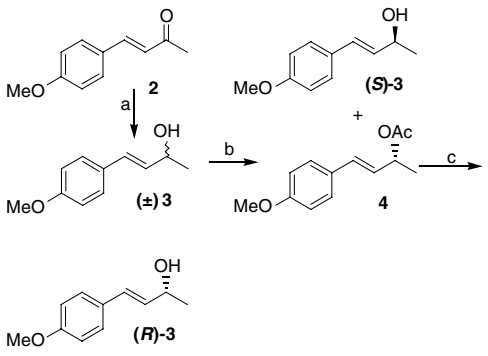
However, these reactions are not always applicable to complex systems, since either epimerisation of benzylic stereocentres or complete/partial aromatisation processes could occur.[14] Moreover, a second limitation arises from the low availability of commercial chiral precursors suitable for convenient and direct benzoannulation reactions. Alternatively, the second strategy, which is the one that we adopted for the synthesis of *cis*-calamenene, requires aromatic rings that in most of the cases are commercially available. Typically, a chiral carbon chain, is constructed on the materials by means of catalytic asymmetric syntheses, to form the final substituted tetrahydronaphthalene derivatives.[15]

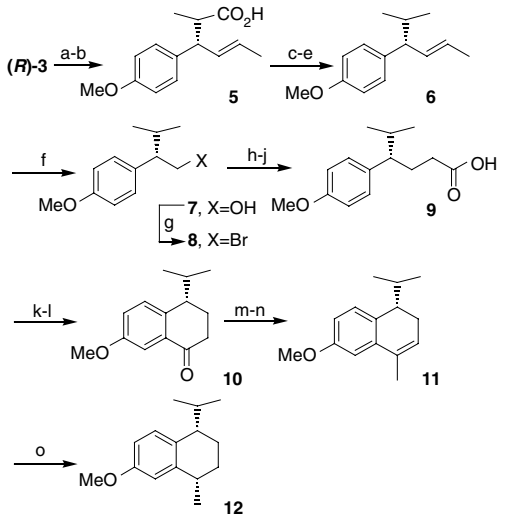
2. Synthesis of *cis*-calamene

After some preliminary optimisation experiments, the enzyme catalysed asymmetric esterification of the racemic allylic alcohols **3**, prepared by reduction of ketone **2** with $NaBH_4$,[16] gave the best results when carried out in TBME using PS as the enzyme and vinyl acetate as the acyl donor. The (*R*)-acetate derivative **4** (46%, ee >99% by chiral HPLC, for the absolute configuration vide infra) was easily separated from the (*S*)-enantiomer of **3** (ee >99%) by trituration in isopropyl ether, then, the (*R*)-alcohol was obtained by hydrolysis of **4** in an overall yield of 44% (Scheme 2).[17,18]

The synthesis of precursor to 7-methoxy-calamenenes **12** is outlined in Scheme 3. Claisen–Johnson rearrangement[19] of allylic alcohol (*R*)-**3** with triethyl orthopropionate, in the presence of a catalytic amount of propionic acid, furnished a nonchromatographically separable mixture of the alkenyl ester derivatives and their vinyl ether precursor. This mixture was hydrolysed affording the acids **5** (ratio of the two diastereoisomers 60:40, by inspection of OMe ^1H signals) in 78% yield over two steps, and some of the starting alcohol **3** which could be easily separated from the acids by an acid–base extraction. Then, the acids were processed by means of a reduction/tosylation/reduction reaction sequence in the usual way affording the hydrocarbon **6** (ee 98.9% by chiral GC) in an overall yield of 85%. The halide **8** was obtained in 84% yield in two steps by reductive ozonolysis of **6** at −78 °C followed by bromination of the alcohol **7** with NBS and PPh_3. Thus, the C_2 elongation of the aliphatic chain was achieved by malonic synthesis in the usual way. The 4-(*p*-anisyl)-5-methylexanoic acid **9** (ee 98.9% vs lit.[7] ee 82%), obtained by decarboxylation of the hydrolysed malonate derivative, was cyclised to give the tetralone **10**. The best result for cyclisation reaction of **9** to give **10**, was obtained an intramolecular Friedel–Craft reaction of the acid chloride of **9** at 0 °C (73%).[20] In contrast, the direct closure of the ring by dehydration, using polyphosphoric acid (PPA), gave rather low yields.[11] Finally, treatment of **10** with methylmagnesium chloride followed by dehydration with a catalytic amount of TsOH led to **11** in 95% yield over two steps.[21] Catalytic reduction of the double bond over Pd/C in a preformed H_2 atmosphere gave the *cis*-diastereoisomer **12** with respect to the *trans* in the ratio 99:1.



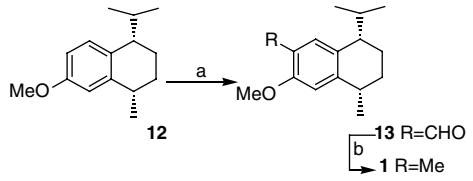
Scheme 2. Synthesis of (*R*)-**3**, reagents and conditions: (a) $NaBH_4$, MeOH, 5 h, 88%; (b) PS, TBME, 24 h, rt, (*S*)-**3** 45%, ee = 99.1%, by chiral HPLC, and **4** 46%, ee = 99.5% by chiral HPLC; (c) KOH/H_2O, MeOH, reflux, 4 h, (*R*)-**3** 95%, ee = 99.5%, by chiral HPLC.



Scheme 3. Synthesis of **12**, reagents and conditions: (a) TEOP, 5 mol% $CH_3CH_2CO_2H$, 150–155 °C, 7 h; (b) KOH/H_2O, MeOH, reflux, 4 h, 78% in two steps; (c) $LiAlH_4$, THF, 0 °C to reflux, 3 h; (d) TsCl, pyridine, 5 h; (e) $LiAlH_4$, THF, rt, 3 h, (*S*)-**6** ee 98.9%, 85% in three steps; (f) O_3, CH_2Cl_2/MeOH (9:1), −78 °C, 1 h, $NaBH_4$; (g) NBS, PPh_3, CH_2Cl_2, 84% in two steps; (h) sodium dimethyl malonate, THF, refluxing; (i) KOH/H_2O, MeOH, reflux, 4 h; (j) 150–160 °C, 1 h, 88% in three steps; (k) $SOCl_2$, reflux, 0.5 h; (l) $AlCl_3$, benzene, hexane (1:1), 1 h, 0 °C, 73 % in two steps; (m) MeMgCl, THF, rt, 1 h; (n) cat. TsOH, toluene, 60 °C, 1 h, 95% in two steps; (o) H_2, Pd/C, **12** de 98%, 95%.

Concerning compound **11**, it could adopt two different conformations: **11a** or **11b** (Fig. 1). The highly selective

Figure 1. Conformations of compound **11**.



Scheme 4. Synthesis of *cis*-7-methoxy-calamenene **1**, reagents and conditions: (a) $P_2O_3Cl_4$, DMF, 0 °C to reflux, 24 h, 56%; (b) H_2, Pd/C, MeOH, 3 h, 99%.

formation of *cis*-isomer is probably due to the predominant presence of conformer **11b**, in which the axial position of the isopropyl group should favour the reduction of the double bond from the less hindered side.

Finally, the formyl group was regioselectively added to the aromatic ring by a Vilsmeier reaction, using pyrophosphoryl chloride in DMF, to give the corresponding aldehyde, that is, **13**,[22] which was reduced over Pd/C to give the (1*S*,4*S*)-*cis*-7-methoxy-calamenene **1** in a 55% overall yield (Scheme 4). The absolute configuration was assigned by comparison of the experimental $[\alpha]_D^{20} = -30.3$ (*c* 0.92, $CHCl_3$) with the $[\alpha]_D^{20} = -29$ (*c* 0.20, $CHCl_3$) reported in literature.[10]

3. Conclusion

The first enantioselective total synthesis of *cis*-calamenene has been achieved by combining the enzymatic asymmetric esterification of racemic allylic alcohol **3** with the Claisen–Johnson rearrangement. All reaction steps are very simple and proceed with high yields. The early stereoselective introduction of the isopropyl group at the benzylic position proved crucial for the generation of the next stereocentre, since it favoured the diastereoselective reduction of double bond from the less sterically hindered face. This synthetic plan could be used for the synthesis of other related calamenenic structures.[23]

4. Experimental

All solvents and reagents were purchased from the suppliers and used without further purification. *Burkholderia cepacia* lipase (Lipase PS, Amano Pharmaceuticals Co., Japan) was employed in this work. Chiral HPLC analyses of compounds **3** was performed on a Chiralcel OD column (Daicel, Japan) installed on a Merck–Hitachi L-6200 apparatus: 0.6 mL/min, UV detector (254 nm), hexane/isopropanol 95:5. GC–MS analyses were performed on a HP 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 mm). The following temperature program was employed: 60 °C (1 min)/6 °C min^{-1}/150 °C (1 min)/12 °C min^{-1}/280 °C (5 min). ^{1}H NMR spectra were recorded in $CDCl_3$ solutions, on Bruker spectrometers; AC-250 spectrometer (250 MHz ^{1}H), DMX (400 MHz ^{1}H). The chemical shift scale was based on internal TMS. *J* values are in Hz. Optical rotations were measured on a Dr. Kernchen Propol digital automatic polarimeter. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. Microanalysis were determined on the analyser 1106 CarloErba.

4.1. (±)-*trans*-4-(4-Methoxyphenyl)-but-3-en-2-ol 3

To a stirred solution of *trans*-4-(4-methoxyphenyl)-3-buten-2-one (150 g, 0.85 mol) in methanol (1 L) at 0 °C was added $NaBH_4$ (35.3 g, 0.93 mol). After 2 h the reaction mixture was refluxed (30 min). Then, the volume of reaction mixture was concentrated to 0.3 L, poured in an ice bath and neutralised with HCl (10%). The white precipitate was filtered and dissolved in DCM (0.5 L), washed with HCl (2 × 400 mL, 0.1 M) and brine (1 × 400 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a white-yellow solid, which was triturated in isopropylether (300 mL) to afford pure **3** as white powder (133 g, 88%); mp 79 °C; ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 7.35$ (m, 2H, ArH), 6.85 (m, 2H, ArH), 6.53 (d, $J = 15.7$, 1H, C*H*Ar), 6.14 (dd, $J = 15.7$ and 6.8, 1H, CH=C*H*), 4.47 (m, 1H, C*H*OH), 3.83 (s, 3H, OMe), 1.38 (d, $J = 7.0$, 3H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 159.2$, 131.4, 129.4, 129.0, 127.6, 114.0, 69.3, 55.0, 23.2; GC/MS: $t_R = 18.69$ min; *m*/*z*: 178 (M^+, 37), 163 (15), 121 (100), 115 (15); Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.17; H, 7.94.

4.1.1. Procedure for the lipase-catalysed asymmetric esterification of (±)-*trans*-4-(4-methoxyphenyl)-but-3-en-2-ol. To a stirred solution of compound **3** (130 g, 0.73 mol) in TBME (0.5 L) was added PS (10 g) and vinyl acetate (100 mL). After 15 h the suspension was filtered and the PS was recovered as it was and it could be reused for several resolutions. The organic solution was concentrated under reduced pressure to obtain a white cream solid, which was triturated in isopropylether (2 × 200 mL) affording the (*S*)-**3** enantiomer.

The isopropyl solution was concentrated at low pressure and the resulting residue was purified on a pad of silica gel using hexane/ethyl acetate (9:1,v/v) affording in order:

(*R*)-*trans*-2-Acetoxy-4-(4-methoxyphenyl)-but-3-ene **4** as low melting point white solid (69.8 g, 46%, 99.5% ee by HPLC, (*S*) $t_R = 7.51$ min, (*R*) $t_R = 8.49$ min), $[\alpha]_D^{20} = <3$; ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 7.37$ (m, 2H, ArH), 6.83 (m, 2H, ArH), 6.47 (d, $J = 15.7$, 1H, C*H*Ar), 5.92 (dd, $J = 15.7$ and 6.8, 1H, CH=C*H*), 3.79–3.9 (m, 3H+1H, $ArOCH_3$+C*H*OAc), 3.36 (s, 3H, CO_2CH_3), 1.37 (d, $J = 7.0$, 3H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 170.1$, 159.3, 131.0, 128.9, 127.6, 127.4, 126.4, 113.8, 71.0, 55.0, 21.2, 20.2; GC/MS: $t_R = 20.45$ min; *m*/*z*: 220 (M^+, 55), 177 (80), 161 (100), 145 (75); Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32.

Found: C, 70.57; H, 7.34; and the (*S*)-*trans*-4-(4-methoxyphenyl)-but-3-en-2-ol **3** that was recombined with the other (*S*)-alcohol (59.8 g, 46%, 99.1% ee by HPLC, (*S*) $t_R = 27.98$ min, (*R*) $t_R = 25.33$ min); $[\alpha]_D^{20} = 8.9$ (*c* 1.1, $CHCl_3$) [lit.[24] $[\alpha]_D^{20} = 8.15$ and lit.[16] ee = 98%].

4.2. (*R*)-*trans*-4-(4-Methoxyphenyl)-but-3-en-2-ol 3

To a stirred solution of **4** (59 g, 0.28 mol) in EtOH/H_2O (0.5 L, 1:1) was added dropwise a solution of KOH (24 g, 0.42 mol) in H_2O (100 mL) and refluxed. After 5 h the reaction mixture was washed with DCM (2×300 mL) and the combined organic layers was washed with HCl (1×200 mL), brine (1×200 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford a solid, which was triturated in isopropylether to give compound **3** (47 g, 95%). $[\alpha]_D^{20} = -9.0$ (*c* 1.1, $CHCl_3$).

4.3. (2*RS*,3*R*)-*trans*-3-(4-Methoxyphenyl)-2-methyl-haxa-4-enoic acid 5

To a solution of (*R*)-**3** (46 g, 0.26 mol) in triethylorthopropionate TEOP (0.6 L) placed in a 1 L round bottom flask equipped with a condenser/distillation head was added propionic acid (5 mL). The reaction mixture was heated to 150–155 °C and the ethanol was continuously collected. During the reaction, propionic acid was occasionally renewed. After 6–7 h the excess of TEOP was removed by distillation to yield an orange oil residue. To a solution of the residue in EtOH/H_2O (0.5 L, 1:2) was added dropwise a solution of KOH (22 g, 0.39 mol) in H_2O (100 mL) and refluxed for 6 h. Most of TEOP was removed under reduce pressure and the residue was washed with Et_2O (2×200 mL) and dried over Na_2SO_4. The combined organic layers was dried over Na_2SO_4 and concentrated to give a yellow residue that was triturated with isopropylether (2×50 mL) to give the starting alcohol (*R*)-**3** (6 g). The water solution was neutralised with HCl (1 M) and washed with DCM (3×300 mL), the organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a yellow oil that was passed on a pad of silica gel using hexane/ethyl acetate (9:1, v/v) affording compound **5** as bright crystalline solid (47.4 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 10.9$ (br s, CO_2H), 7.05–7.12 (m, 2H, ArH), 6.79–6.86 (m, 2H, ArH), 5.4–5.6 (m, 2H, CH=CH), 3.77 (s, 2H, OMe), 3.82 (s, 3H, OMe), 2.82 (t, $J = 8.8$, C*H*Ph), (br t, $J = 7.2$, 0.4H, C*H*CO_2H), 2.63–2.82 (m, 1H, ArCH), 1.65 (dd, $J = 5.5$, 1.0, 1.8H, =CHCH_3), 1.60 (dd, $J = 5.5$, 1.0, 1.2H, =CHCH_3), 1.19 (d, $J = 6.6$, 1.8H, CHCH_3), 0.96 (d, $J = 6.6$, 1.2H, CHCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 179.5$, 177.3, 158.2, 157.8, 139.2, 138.3, 135.6, 134.2, 131.7, 130.0, 129.3, 128.7, 127.2, 125.2, 115.1, 114.4, 113.7, 55.2, 45.1, 44.7, 41.1, 40.8, 18.8, 18.0, 14.8, 14.2; GC/MS: $t_R = 22.09$ min minor diastereoisomer, *m*/*z*: 234 (M^+, 6), 161 (100), 146 (11), 91 (12); $t_R = 22.23$ min main diastereoisomer, *m*/*z*: 234 (M^+, 4), 161 (100), 146 (13), 91 (12). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.64; H, 7.64.

4.4. (*R*)-*trans*-1-(1-Isopropyl-but-2-enyl)-4-methoxy-benzene 6

To a well stirred solution of **5** (45 g, 0.19 mol) in THF (250 mL) at 0 °C was added portionwise LAH (8.7 g, 0.23 mol). After 2 h the reaction mixture was refluxed for 30 min. The usual work-up was furnished the alcohol as colourless oil. To a solution of the alcohol in pyridine (100 mL) was added TsOCl (39 g, 0.21 mol). After 16 h was added Et_2O (200 mL) and filtered the white solid. The organic solution was washed with HCl (2×200 mL, 1 N), brine (1×200 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield the tosyl derivate. To a solution of tosylate in THF (300 mL) at 0 °C was added portionwise LAH (8.7 g, 0.23 mol). After 3 h the reaction mixture was refluxed for 2 h. The usual work-up afforded a yellow oil, which was passed on a pad of silica gel with hexane to afford **6** as a low melting point white solid (32.9 g, 85%); ee 98.9% by chiral GC; $[\alpha]_D^{20} = -61.5$ (*c* 2.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.05$–7.12 (m, 2H, ArH), 6.79–6.86 (m, 2H, ArH), 5.4–5.6 (m, 2H, CH=CH), 3.81 (s, 3H, OMe), 2.73 (t, $J = 8.8$, 1H, CHPh), 1.83 (m, 1H, *CH*$(CH_3)_2$), 1.65 (d, $J = 6.6$, 3H, =CHCH_3), 0.93 (d, $J = 6.6$, 3H, CH_3CH), 0.74 (d, $J = 6.6$, 3H, CH_3CH): ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 157.7$, 137.2, 134.1, 128.6, 125.1, 113.8, 56.4, 55.1, 33.1, 21.0, 20.7, 17.9; GC/MS: $t_R = 12.31$ min; *m*/*z*: 204 (M^+, 3), 161 (100), 146 (12), 91 (13). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.47; H, 9.94.

4.5. (*S*)-2-(4-Methoxyphenyl)-3-methyl-butan-1-ol 7

Ozonolysis of a solution of **6** (31 g, 0.15 mol) in DCM/MeOH (300 mL, 7:3) at −78 °C gave, quenching with $NaBH_4$ (3 g, 0.1 mol), alcohol **7**. The reaction mixture was allowed to warm up at room temperature, then, was washed with HCl (1×200 mL), brine (1×200 mL), dried over Na_2SO_4. The solvent was removed under reduced pressure to yield **7** as colourless oil (28 g, 92%). $[\alpha]_D^{20} = +9.4$ (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.08$ (m, 2H, ArH), 6.75 (m, 2H, ArH), 3.89 (dd, $J = 4.8$, 10.6, 1H, C*H*OH), 3.75 (m, 3H+1H, OMe+C*H*OH), 2.42 (dt, $J = 5.3$, 8.8, 1H, C*H*CH_2), 1.86 (m, 1H, C*H*CH_3), 0.98 (d, $J = 6.6$, 3H, CH_3), 0.73 (d, $J = 6.6$, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 157.4$, 135.4, 128.9, 113.1, 66.1, 54.7, 48.1, 35.5, 20.6, 20.1; GC/MS: $t_R = 19.21$ min; *m*/*z*: 194 (M^+, 27), 163 (100), 151 (45), 135 (13). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.47; H 9.86.

4.6. (*S*)-1-(1-Bromomethyl-2-methoxy-propyl)-4-methoxy-benzene 8

To a solution of **7** (27.3 g, 0.14 mol) and PPh_3 (36.7 g, 0.14 mol) in DCM (0.5 L) at 0 °C was added portionwise NBS (25 g, 0.14 mol). After 1 h the reaction mixture was poured in a ice bath, washed with CH_2Cl_2 (2×300 mL), dried over Na_2SO_4 and concentrated at reduced pressure. The residue was passed trough a pad of silica gel using hexane/ethyl acetate (9:1, v/v) affording compound

8 as yellow oil (32.7 g, 91%); $[\alpha]_D^{20} = -19.6$ (*c* 1.03, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) $\delta = 7.08$ (m, 2H, ArH), 6.80 (m, 2H, ArH), 3.75 (m, 3H+1H, OMe+C*H*Br), 3.66 (dd, $J = 7.0, 10.6$, 1H, C*H*Br), 2.68 (dt, $J = 5.3, 8.8$, 1H, C*H*CH_2), 2.05 (m, 1H, C*H*CH_3), 0.98 (d, $J = 6.6$, 3H, CH_3), 0.78 (d, $J = 6.6$, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 157.5$, 135.5, 130.0, 113.2, 54.8, 48.2, 37.8, 35.6, 20.7, 20.4; GC/MS: $t_R = 20.51$ min; *m/z*: 256 (M^+, 23), 213 (70), 163 (5), 134 (100). Anal. Calcd for $C_{12}H_{17}BrO$: C, 56.04; H, 6.66. Found: C, 56.27; H, 6.54.

4.7. (*S*)-4-(4-Methoxyphenyl)-5-methylexanoic acid 9

To a solution of sodium malonate freshly prepared (26.4 g, 0.2 mol) in DMF (0.4 L) at refluxing temperature was added dropwise a solution of bromide **8** (26.0 g, 0.1 mol). After 6 h the reaction mixture was poured in an ice bath and washed with AcOEt (4×200 mL), dried over Na_2SO_4 and concentrated at reduced pressure. To a solution of the residue in MeOH/H_2O (300 mL, 1:1) was added dropwise a solution of KOH (11.2 g, 0.2 mol) in H_2O (100 mL) and refluxed. After 10 h the reaction mixture was poured in a ice bath and neutralised with HCl (1 M), washed with AcOEt, dried over Na_2SO_4 and concentrated at reduced pressure. The residue was heated at 140 °C for 1 h; then, was passed on a pad of silica gel using hexane/ethyl acetate (75:25, v/v) affording the acid **9** as colourless oil (20.6 g, 88%). $[\alpha]_D^{20} = -6.5$ (*c* 1.98, $CHCl_3$) [lit.[7] $[\alpha]_D^{20} = -3.8$ (*c* 3.01, CH_2Cl_2, ee = 82% on the alcohol derivative, by chiral HPLC)], ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.03$ (m, 2H, ArH), 6.80 (m, 2H, ArH), 3.79 (s, 3H, OMe), 2.04–2.24 (m, 4H), 1.7–1.91 (m, 2H), 0.98 (d, $J = 6.6$, 3H, CH_3), 0.74 (d, $J = 6.6$, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 179.8$, 157.5, 135.4, 128.9, 113.1, 54.9, 51.2, 33.2, 32.2, 27.9, 20.8, 20.5; GC/MS: $t_R = 22.85$ min; *m/z*: 236 (M^+, 173), 193 (70), 175 (5), 147 (50). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.02; H, 8.54.

4.8. (4*S*)-Isopropyl-7-methoxy-3,4-dihydro-2*H*-naphthalene-1-one 10

To a suspension of $AlCl_3$ (7.1 g, 53 mmol) in hexane/benzene (100 mL, 1:1) at 0 °C was added dropwise a solution of the acid chloride of the acid **9** (12 g, 51 mmol) prepared in the usual way with $SOCl_2$. After 1 h the reaction mixture was poured in an ice bath and treated with HCl (1 M, 100 mL), washed with Et_2O (3×300 mL). The combined organic layers was washed with $NHCO_3$ (satd, 2×200 mL) and brine (200 mL), dried over Na_2SO_4 and the solvent was removed at reduced pressure. The residue was passed on a pad of silica gel using hexane/AcOEt affording a yellow solid, which was crystallised in hexane yielding the tetralone **10** as bright needles (8.4 g, 73%). $[\alpha]_D^{20} = +67.9$ (*c* 1.08, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) $\delta = 7.52$ (d, $J = 2.4$, 1H, ArH), 7.20 (d, $J = 8.4$, 1H, ArH), 7.06 (dd, $J = 8.4, 2.2$, 1H, ArH), 3.83 (m, 3H, OMe), 2.48–2.87 (m, 3H), 1.9–2.2 (m, 3H), 0.98 (m, 3H+3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 198.5$, 158.1, 140.0, 133.1, 130.0, 120.9, 109.4, 55.3, 44.0, 35.2, 30.1, 24.2, 21.4, 19.6; GC/MS: $t_R = 22.69$ min; *m/z*: 218 (M^+, 17), 175 (100), 147 (20), 131 (5). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.22; H, 8.25.

4.9. (1*S*)-Isopropyl-6-methoxy-4-methyl-1,2-dihydro-naphthalene 11

To a solution of **10** (6 g, 28 mmol) in THF (100 mL) at 0 °C, under nitrogen atmosphere, was added a solution of MeMgCl (19 mL, 3 M hexane). After 1 h, the reaction was quenched with NH_4Cl (100 mL), washed with Et_2O (3×100 mL), dried over Na_2SO_4 and the solvent was removed at reduced pressure. To a solution of the residue in toluene (100 mL) was added a catalytic amount of TsOH and the reaction mixture was refluxed for 1 h. The solvent was evaporated at reduced pressure and the crude residue was purified with column chromatography using hexane/EtOAc (95:5) affording **11** as coulorless liquid (5.7 g, 95%). $[\alpha]_D^{20} = -40.5$ (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.01$ (d, $J = 8.0$, 1H, ArH), 6.80 (d, $J = 2.8$, 1H, ArH), 6.68 (dd, $J = 2.8, 8.0$, 1H, ArH), 5.74 (br s, 1H, CH=), 3.83 (s, 3H, OMe), 2.32–2.40 (m, 3H), 2.11 (2, $J = 1.8$, 3H, CH_3C=), 1.86 (dt, $J = 6.6, 7.1$, 1H, C*H*CH_3), 0.88 (d, $J = 6.6$, 3H, CH_3), 0.78 (d, $J = 6.6$, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 157.3$, 142.4, 135.3, 132.0, 129.1, 126.1, 113.3, 111.4, 55.1, 43.1, 33.2, 32.0, 25.3, 21.4, 19.7; GC/MS: $t_R = 20.52$ min; *m/z*: 216 (M^+, 10), 199 (5), 173 (100), 158 (50). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.12; H, 9.15.

4.10. (1*S*,4*S*)-1-Isopropyl-6-methoxy-4-methyl-1,2,3,4-dihydro-naphthalene 12

To a suspension of Pd/C in MeOH (50 mL) under H_2 atmosphere was added a solution **11** (3 g, 13.9 mmol) in MeOH (20 mL). After 7 h the reaction mixture was worked up in the usual way affording **12** as colourless liquid (2.97 g, ed 98% by GC and ^1H NMR, 95%). $[\alpha]_D^{20} = -34.8$; bp 110 °C at 0.8 mmHg; (*c* 2.47, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.11$ (d, $J = 9.0$, 1H, ArH), 6.68 (m, 3H, ArH), 3.78 (s, 3H, OMe), 2.85 (m, 1H), 2.57 (m, 1H), 2.20 (m, 1H), 1.60–1.83 (m, 4H, CH_2CH_2), 1.27 (d, $J = 6.6$, 3H, CH_3), 1.02 (d, $J = 6.6$, 3H, CH_3), 0.77 (d, $J = 6.6$, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 157.2$, 144.1, 131.9, 129.0, 113.2, 111.3, 55.0, 43.0, 33.1, 31.0, 28.6, 23.2, 21.3, 19.6, 17.4; GC/MS: $t_R = 20.49$ min; *m/z*: 218 (M^+, 7), 175 (100), 160 (7). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.82; H, 10.05.

4.11. (5*S*,8*S*)-8-Isopropyl-3-methoxy-5-methyl-1,2,3,4-tetrahydro-naphthalene-2-carbaldehyde 13

Pyrophosphoryl chloride (3.7 g, 14.7 mmol) was added dropwise to a stirred solution of **12** (2.0 g, 9.2 mmol) in DMF (1 g, 13.8 mmol) at 0 °C. After 30 min the resulting syrup was heated at 95–100 °C for 24 h. The cold reaction mixture was quenched with a solution AcONa

(1 M, 10 mL) extracted with Et_2O (3 × 50 mL), dried over Na_2SO_4 and concentrated at reduced pressure. Column chromatography on silica gel, eluting with hexane/AcOEt (98:2) gave in order the unreacted **12** and the aldehyde **13** as white solid, which was recrystallised in hexane as needles (2.0 g, 56%). $[\alpha]_D^{20} = -72$ (*c* 0.9, $CHCl_3$); mp 54–56 °C; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 10.40$ (s, 1H, COH), 7.69 (br s, 1H, ArH), 6.72 (s, 1H, ArH), 3.89 (s, 3H, OMe), 2.91 (m, 1H), 2.62 (m, 1H), 2.29 (m, 1H), 1.64–1.87 (m, 4H, CH_2CH_2), 1.30 (d, $J = 6.6$, 3H, CH_3), 1.02 (d, $J = 6.6$, 3H, CH_3), 0.75 (d, $J = 6.6$, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 189.7$, 159.5, 152.3, 132.4, 128.2, 122.7, 111.2, 55.5, 42.7, 33.8, 30.8, 28.2, 22.9, 21.1, 19.0, 17.1; GC/MS: $t_R = 23.87$ min; *m/z*: 246 (M^+, 5), 203 (100), 175(10). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.30; H 9.15.

4.12. (1*S*,4*S*)-*cis*-7-Methoxy-calamenene 1

To a solution of **13** (2 g, 8.1 mmol) in MeOH was added a catalytic amount of Pd/C and left under hydrogen atmosphere for 6 h. Then, the reaction mixture was worked up in the usual way affording **1** as colourless liquid, which was distilled (2.0 g, 56%). $[\alpha]_D^{20} = -30.3$ (*c* 0.9, $CHCl_3$) [lit.[9] $[\alpha]_D^{20} = -29$ (*c* 0.20, $CHCl_3$)]; bp 115 °C, 0.8 mmHg; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 6.90$ (br s, 1H, ArH), 6.58 (s, 1H, ArH), 3.80 (s, 3H, OMe), 2.85 (m, 1H), 2.15–2.25 (m, 1H+3H), 2.29 (m, 1H), 1.64–1.87 (m, 4H, CH_2CH_2), 1.27 (d, $J = 6.6$, 3H, CH_3), 1.02 (d, $J = 6.6$, 3H, CH_3), 0.76 (d, $J = 6.6$, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 155.5$, 141.2, 131.2, 130.2, 123.6, 109.6, 55.1, 42.9, 33.0, 31.0, 28.8, 23.3, 21.3, 19.5, 17.4, 16.0; GC/MS: $t_R = 20.49$ min; *m/z*: 228 (M^+, 20), 175 (100), 160 (10). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.58; H, 10.45.

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