Synthesis of (+)-9-Demethyl-7,8-dideoxycalopin as a Model for the Determination of the Absolute Stereochemistry of a New Group of Fungal Metabolites

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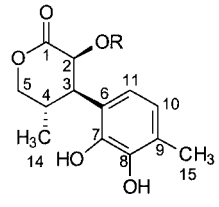
Dedicated to Prof. Lutz F. Tietze on the occasion of his 60th birthday

Keywords: Asymmetric synthesis / Calopins / Configuration determination / Ene reactions / Lactones / Natural products

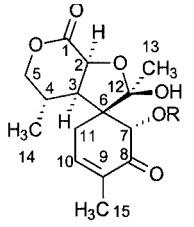
A key step in the synthesis of (+)-9-demethyl-7,8-dideoxycalopin (**3**) is the highly stereoselective ene reaction between phenylmenthyl glyoxylate **8** and β,β-dimethylstyrene (**7**). Hydroboration of the resulting homoallyl alcohol **9** afforded only the undesired epimer **10**, which was ultimately converted into target **3** by a sequence of oxidation, epimerization, and reduction steps. ^{1}H NMR comparison of the MTPA esters derived from compound **3** with those from natural calopin supported the assignment of the (2*S*,3*R*,4*S*) configuration to this new group of fungal metabolites. Further evidence of the absolute configuration was obtained by comparison of the CD spectra of calopin and of model compound **3**.

Introduction

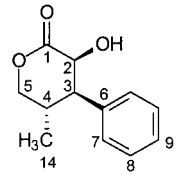
The bitter taste of *Boletus calopus* and some closely related toadstools attracted our attention and resulted in the discovery of the calopins and cyclocalopins, a new class of natural product.[1] These compounds possess some unusual structural characteristics. Common to all compounds is a δ-lactone subunit. In the cases of *O*-acetylcalopin (**1a**) and calopin (**1b**) a 3-methylcatechol residue is attached, whereas in the more complex cyclocalopins this residue forms part of a spiro substructure. Crucial for the correlation of both types of compounds is the oxidative transformation of cyclocalopin A (**2b**) into **1a**, which proves that the stereochemistries of calopins and cyclocalopins are identical.[1] However, their absolute configurations could not be determined unambiguously. To solve this problem we carried out an asymmetric synthesis of the calopin analogue (2*S*,3*R*,4*S*)-9-demethyl-7,8-dideoxycalopin (**3**) and then compared the ^{1}H NMR properties of the corresponding Mosher esters.



O-Acetylcalopin (**1a**), R = Ac
Calopin (**1b**), R = H



O-Acetylcyclocalopin A (**2a**), R = Ac
Cyclocalopin A (**2b**), R = H



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Results and Discussion

Retrosynthetic Analysis

A notable structural feature of calopin (**1b**) is the presence of three contiguous stereogenic centres. In order to simplify the synthetic problems, the unusual methylcatechol moiety of **1b** was replaced by a phenyl substituent to give the analogue **3** (Scheme 1). Retrosynthetically speaking, opening of the lactone ring should yield δ-hydroxy ester **4**,

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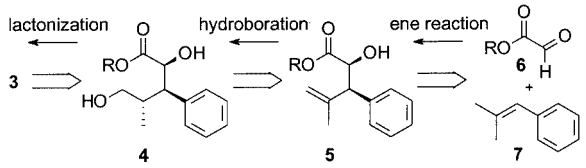
[‡] Crystal structure determination

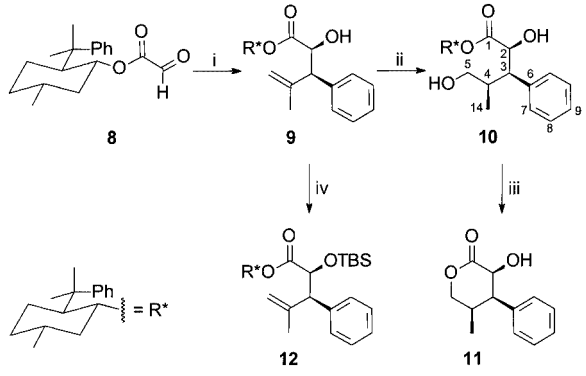
which should be obtainable by hydroboration of homoallyl alcohol **5**. The latter compound should be available by means of an enantio- and diastereoselective glyoxylate-ene reaction between compounds **6** and **7**.[2,3]



Scheme 1. Retrosynthetic analysis of model compound **3**

Synthesis of Model Compound 3

Crucial for the synthesis of model compound **3** is the simultaneous introduction of two stereocentres at C-2 and C-3 in an *anti* configuration. The glyoxylate-ene reaction developed by Whitesell et al.[2,3] would fulfill these requirements, although there has been no reported application to β,β-disubstituted styrenes. In the event, phenylmenthyl glyoxylate **8**[2,3] reacted with β,β-dimethylstyrene (**7**) in the presence of $SnCl_4$ to yield the desired α-hydroxy ester **9** as the only detectable diastereomer (as judged by GC/MS), in 81% yield (Scheme 2). The observed selectivity is explained by a transition state in which the aromatic residue adopts an equatorial orientation, as described before.[3] The absolute configuration of **9** was confirmed as (2*S*,3*R*) by a single-crystal X-ray diffraction analysis (Figure 1).



Scheme 2. Synthesis of all-*cis* δ-valerolactone **11**; reagents and conditions: i) $SnCl_4$, **7**, CH_2Cl_2, −78 °C → −25 °C (81%); ii) 9-BBN or (+)-Ipc_2BH, THF, then NaOH, H_2O_2, ultra sound (99%); iii) *p*TsOH, CH_2Cl_2, 28 °C (63%); iv) TBSOTf, 2,6-lutidine, DMAP, CH_2Cl_2 (94%); R* = (−)-8-phenylmenthyl, 9-BBN = 9-borabicyclo[3.3.1]nonane, Ipc_2BH = diisopinocampheylborane, TBS = *tert*-butyldimethylsilyl, DMAP = 4-(dimethylamino)pyridine

Unfortunately, hydroboration of the alkene **9** with 9-borabicyclo[3.3.1]nonane (9-BBN) and lactonization of the resulting alcohol **10** with *p*TsOH afforded only the undesired all-*cis* diastereomer **11**,[4] the structure of which was unambiguously determined by a single-crystal X-ray diffraction analysis (Figure 2). All attempts to form the desired epimer by the use of different hydroboration agents and either the unprotected or the TBS-protected homoallyl alcohols **9** and **12**, respectively, failed. For **9**, the stereochemical course of the reaction with (+)-diisopinocampheylborane (Ipc_2BH) was the same as described earlier (72%, matched case). In contrast, use of (−)-Ipc_2BH (mismatched) and catecholborane in combination with Wilkinson's catalyst[5,6] failed to produce any reaction whatsoever. In order to investigate the influence of the free alcohol on the stereochemical course of the hydroboration reaction, homoallyl alcohol **9** was converted into silyl ether **12** with TBSOTf (94% yield). However, this compound proved inert to hydroboration, epoxidation, transesterification or saponification reactions.

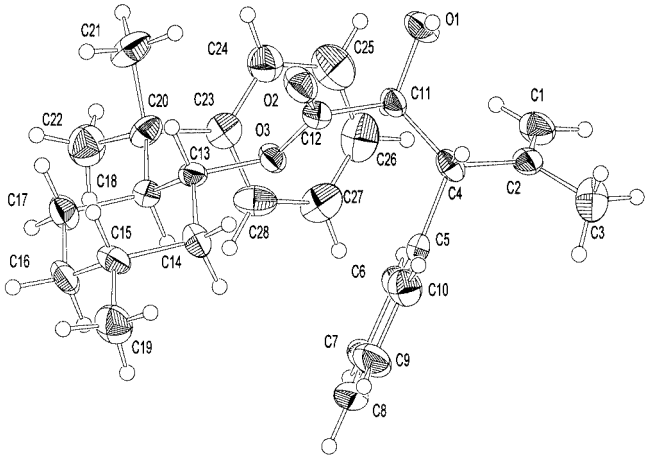


Figure 1. ORTEP plot derived from a single-crystal X-ray analysis of (−)-8-phenylmenthyl ester **9**

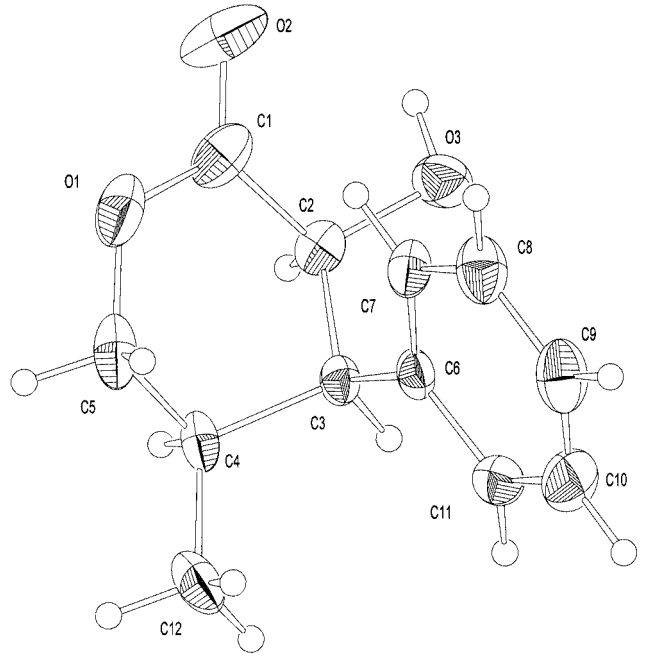
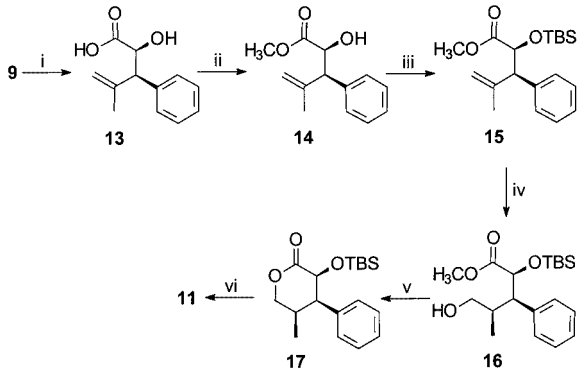


Figure 2. ORTEP plot derived from a single-crystal X-ray analysis of all-*cis*-valerolactone **11**

The highly selective but undesired stereochemical outcome of the hydroboration step might have been caused by the sterically demanding auxiliary. In an effort to eliminate this possibility, the phenylmenthyl group was cleaved by sa-

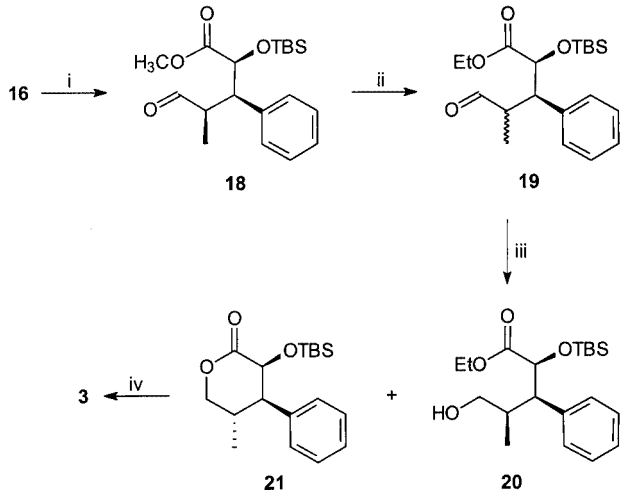
ponification (90%, Scheme 3). Esterification of the resulting carboxylic acid **13** with MeOH and protection of the carbinol **14** with TBSOTf then afforded the silyl ether **15** (protection of the α-hydroxy ester **14** was necessary, since attempts to use the free hydroxy compound for hydroboration ended in decomposition). The conversion of olefin **15** into the primary alcohol **16** with 9-BBN again provided the undesired diastereomer in 98% yield. The stereochemistry of the newly generated chiral centre was determined by NOESY experiments, after acid-catalysed lactonization to **17**. Furthermore, deprotection of **17** with concentrated HCl[7] yielded the previously described all-*cis*-valerolactone **11**. Again, no correction of the stereochemistry during the hydroboration process was possible.



Scheme 3. Alternative synthesis of all-*cis*-δ-valerolactone **11**; reagents and conditions: i) NaOH, THF, MeOH, Δ (90%); ii) $SOCl_2$, MeOH, cat. DMF, Δ (79%); iii) TBSOTf, 2,6-lutidine, DMAP, CH_2Cl_2 (85%); iv) 9-BBN, THF, then NaOH, H_2O_2, ultra sound (98%); v) TFA, $CHCl_3$ (96%); vi) concd. HCl, THF, MeOH (42%); TFA = trifluoroacetic acid (concd. = concentrated)

Other methods such as allylic oxidation of **15** with SeO_2 or reductive and regioselective ring-opening of an oxirane intermediate were examined in an effort to introduce the desired stereochemistry, but all proved unsuccessful.

The failure of standard procedures to establish the (*S*) configuration at the γ-position suggested the epimerization of this centre as an alternative. For this purpose, alcohol **16** was oxidized to aldehyde **18** by Swern's method (Scheme 4). Epimerization at C-4 by use of $NaHCO_3$ in refluxing EtOH[8] yielded a 1:1 mixture of the diastereomeric ethyl esters **19**, indicating a transesterification under these mild conditions.[9] This can be explained by hemiacetal formation, subsequent cyclization to a lactone intermediate and ring-opening with EtOH. This mechanism is supported by the observation that no transesterification occurred with olefin **15** under the same conditions. Because of their instability, the aldehydes **19** were immediately reduced with $NaBH_4$ in MeOH, which yielded two diastereomeric alcohols that could be separated by kinetic resolution techniques. Specifically, acidic workup of the reaction mixture afforded the desired δ-valerolactone **21** (23% yield from **16**) and the epimeric alcohol **20** (34% from **16**), and these were readily separated by flash chromatography. The latter product could be re-used in the epimerization sequence just described. The deprotection of silyl ether **21** to afford target **3** was accomplished by treatment of the former with concentrated HCl.[7] Overall then, the synthesis of model compound **3** proceeded in nine steps and 11% yield, starting from styrene **7** and 8-phenylmenthyl glyoxylate (**8**).

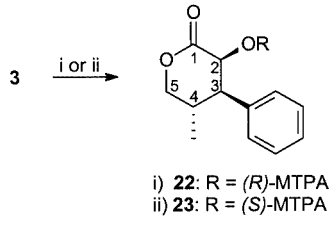


Scheme 4. Synthesis of δ-valerolactone **3**; reagents and conditions: i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; ii) $NaHCO_3$, EtOH, Δ; iii) $NaBH_4$, MeOH, 0 °C, separation of **20** [34%, steps i)−iii)] and **21** [23%, steps i)−iii)]; iv) concd. HCl, THF, MeOH (96%)

NOESY experiments performed on the δ-valerolactones **21** and **3** served to confirm the *cis* relationship between 2-H and 3-H and the *trans* arrangement of 3-H and 4-H. In addition, lactone **3** and, to a lesser extent, precursor **21** exhibited NOESY correlation signals between 2-H and 5α-H, indicating the same preference of these δ-lactones to adopt a boat conformation as seen in calopin (**1b**).[1] This observation is pivotal to the determination of the absolute configuration of **1b** as described in the following paragraph.

Assignment of Absolute Configuration

With model compound **3** of known absolute configuration to hand, the high-field NMR variant of Mosher's method[10−13] should allow the absolute configuration of calopin (**1b**) to be assigned. To this end, the MTPA esters **22** and **23** were prepared (Scheme 5) from alcohol **3** by treatment with (*S*)- and (*R*)-MTPA-Cl, respectively.



Scheme 5. Preparation of Mosher esters **22** and **23**; reagents and conditions: i) (*S*)-(+)-MTPA-Cl, NEt_3, DMAP, CH_2Cl_2; ii) (*R*)-(−)-MTPA-Cl, NEt_3, DMAP, CH_2Cl_2; MTPA = α-methoxy-α-(trifluoromethyl)phenylacetic acid

The Δδ values obtained from these compounds agree well with those for calopin[1] (Table 1), confirming the

(2*S*,3*R*,4*S*) configuration for this class of natural products. We considered the use of a model compound for the purpose of comparison to be essential, since calopin possesses protons on only one side of the MTPA plane.[14]

Table 1. ^{1}H NMR ($CDCl_3$, 600 MHz, 300 K) analysis of Mosher derivatives of **3** and **1b**

Compound	Δδ(3-H)[a]	Δδ(OCH_3)[a]
MTPA ester of **3**	−72	+222
MTPA ester of **1b**[1]	−42	+180

[a] Δδ values are given in Hz [Δδ = δ(*S*-MTPA ester) − δ(*R*-MTPA ester)].[12,13]

Independent evidence for the same absolute configuration of synthetic (+)-9-demethyl-7,8-dideoxycalopin (**3**) and (+)-calopin (**1b**) was obtained from the similarity of the CD spectra of both compounds (Figure 3).

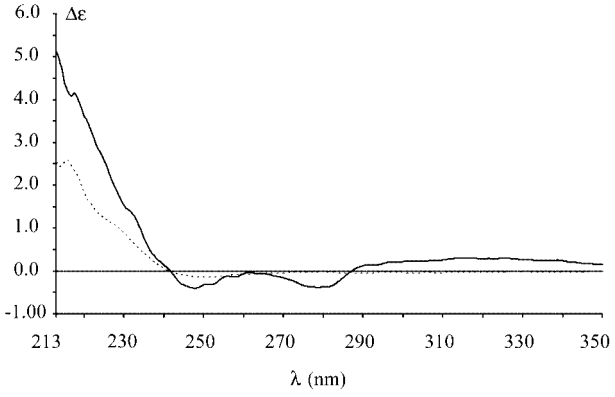


Figure 3. CD spectra of (+)-calopin (**1b**, solid line) and (+)-9-demethyl-7,8-dideoxycalopin (**3**, dotted line) (CH_3CN)

Experimental Section

General: Melting points (uncorrected): Büchi SMP 535. Optical rotations: Perkin−Elmer 241. UV/Vis: Perkin−Elmer Lambda 16. CD: S. A. Jobin Yvon CD-6-Dichrograph. FT IR: Perkin−Elmer Spectrum 1000. NMR: Varian Mercury 200, Bruker ARX 300, and AMX 600, solvent peak or TMS as internal standard. MS: Finnigan MAT 90 and MAT 95 Q. EI mass spectra were obtained at 70 eV with direct inlet. Column chromatography: silica gel 60 (40−63 μm, Merck). All solvents were distilled before use. Petroleum ether (40−60°C) was used for chromatography. (−)-8-Phenylmenthol was purchased from Aldrich, (*S*)-(+)- and (*R*)-(−)-MTPA-Cl from Fluka. The elemental analyses were carried out by the Microanalytical Laboratory of the Chemistry Department at the University of Munich.

(−)-8-Phenylmenthyl (2*S*,3*R*)-2-Hydroxy-4-methyl-3-phenylpent-4-enoate (9): $SnCl_4$ (1.64 mL, 13.93 mmol) was added to a solution of freshly prepared glyoxylate **8**[2,3] (prepared by ozonolysis of 4.65 mmol of the corresponding acrylate) and β,β-dimethylstyrene (**7**, 685 μL, 4.66 mmol) in dry CH_2Cl_2 (45 mL), maintained at −78 °C. The ensuing mixture was stirred for 2.5 h at −78 °C and for 19 h at −25 °C, and then quenched with satd. aqueous $NaHCO_3$ (150 mL) and diluted with EtOAc (300 mL). The separated organic phase was washed with satd. aqueous $NaHCO_3$ (3 × 200 mL) and brine (1 × 200 mL), and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel with EtOAc/petroleum ether (1:15, v/v) yielded **9**, which on recrystallization from hexanes gave colourless crystals, m.p. 77 °C. Yield: 1.59 g (81%) over 2 steps. $[\alpha]_D^{23}$ = +44.9 (*c* = 0.014, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 210 nm (sh, 16110), 265 (1410). IR (KBr): $\tilde{\nu}$ = 3484 cm^{-1} (s), 3060 (w), 3029 (w), 2961 (s), 2949 (s), 2923 (m), 2864 (w), 1715 (s), 1647 (w), 1600 (w), 1495 (w), 1454 (m), 1390 (w), 1375 (w), 1292 (m), 1227 (m), 1208 (m), 1182 (w), 1131 (w), 1095 (s), 984 (w), 898 (w), 764 (m), 745 (m), 699 (s), 542 (w). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.19−7.33 (m, 6 H), 7.06−7.14 (m, 4 H), 4.90 (m, 1 H), 4.88 (m, 1 H), 4.74 (td, *J* = 4.3, 10.7 Hz, 1 H), 3.54 (d, *J* = 6.3 Hz, 1 H), 3.19 (d, *J* = 6.2 Hz, 1 H), 1.91−2.01 (m, 1 H), 1.82 (dq, *J* = 3.4, 13.4 Hz, 1 H), 1.60−1.69 (m, 1 H), 1.56 (s, 3 H), 1.46−1.54 (m, 1 H), 1.31−1.45 (m, 1 H), 1.27 (s, 3 H), 1.16 (s, 3 H), 1.04−1.20 (m, 1 H), 0.75−0.90 (m, 1 H), 0.80 (d, *J* = 6.4 Hz, 3 H), 0.44 (q, *J* = 11.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 152.0, 143.9, 139.2, 128.7, 128.0, 127.9, 126.7, 125.3, 125.1, 113.2, 75.6, 72.1, 55.9, 50.2, 40.7, 39.3, 34.4, 31.1, 29.6, 26.1, 22.8, 22.3, 21.7 ppm. EI MS: *m*/*z* (%) = 420 (1) [M^+], 402 (1), 301 (1), 215 (26), 214 (23), 206 (15), 199 (17), 189 (5), 143 (16), 131 (88), 119 (100), 91 (42), 41 (10). HRMS: calcd. 420.2664; found 420.2638. $C_{28}H_{36}O_3$ (420.59): calcd. C 79.96, H 8.63; found C 80.19, H 8.67.

(−)-8-Phenylmenthyl (2*S*,3*R*,4*R*)-2,5-Dihydroxy-4-methyl-3-phenylpentanoate (10). Hydroboration with 9-BBN: A solution of **9** (250 mg, 594 μmol) in dry THF (5 mL) was treated with 9-BBN (420 mg, 3.442 mmol). After the mixture had been stirred for 12 h at room temperature, 2 M NaOH (2 mL) and 30% H_2O_2 (2 mL) were added. The mixture was sonicated in an ultrasound bath for 20 min, and then acidified with 2 M HCl, diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography on silica gel with EtOAc/petroleum ether (1:2, v/v) gave **10** (258 mg, 99%) as a colourless solid. **Hydroboration with (+)-Ipc_2BH:** A solution of **9** (50 mg, 119 μmol) in dry THF (1 mL) was treated with (+)-(Ipc_2BH) (204 mg, 713 μmol). After the mixture had been stirred for 3 h at room temperature 2 M, NaOH (0.5 mL) and 30% H_2O_2 (0.5 mL) were added. The mixture was sonicated for 20 min in an ultrasound bath, and then diluted with EtOAc (100 mL) and washed with satd. aqueous $NaHCO_3$ (3 × 50 mL) and brine (1 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography on silica gel with EtOAc/petroleum ether (1:8 → 1:3, v/v) gave **10** (38 mg, 72%) as a colourless solid; 14 mg (27%) of the starting material **9** was recovered. **Compound 10**: M.p. 90 °C. $[\alpha]_D^{23}$ = ±0. UV (CH_3CN): λ_{max} (ε) = 206 nm (15870), 265 (1410). IR (KBr): $\tilde{\nu}$ = 3464 cm^{-1} (br, s), 3060 (w), 3030 (w), 2957 (s), 2924 (s), 2879 (s), 1712 (s), 1600 (w), 1495 (m), 1455 (m), 1389 (w), 1372 (w), 1313 (w), 1210 (s), 1100 (m), 1030 (m), 984 (w), 960 (w), 766 (m), 703 (s), 646 (w), 560 (w), 518 (w). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 6.96−7.28 (m, 10 H), 4.83 (td, *J* = 4.2, 10.7 Hz, 1 H), 3.55 (d, *J* = 4.9 Hz, 1 H), 3.35 (dd, *J* = 6.0, 10.6 Hz, 1 H), 3.23 (dd, *J* = 5.0, 10.7 Hz, 1 H), 2.68 (dd, *J* = 5.9, 5.9 Hz, 1 H), 2.09−2.17 (m, 1 H), 1.93−2.04 (m, 1 H), 1.74−1.86 (m, 2 H), 1.61−1.70 (m, 2 H), 1.36−1.48 (m, 1 H), 1.25 (s, 3 H), 1.16 (s, 3 H), 1.03−1.15 (m, 1 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H), 0.67 (q, *J* = 11.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 174.0, 151.5, 139.4, 129.4, 128.0, 128.0, 126.8, 125.3, 125.2, 75.8, 72.3, 65.7, 52.9, 50.3, 41.0, 39.5, 36.5, 34.4, 31.2, 28.9, 26.3, 23.7, 21.7, 15.9 ppm. EI MS: *m*/*z* (%) = 438 (0.1) [M^+], 420 (0.1), 319 (1), 301 (1), 215 (12), 214 (11), 149 (5), 131 (33), 119 (100), 91 (54), 41 (10).

HRMS: calcd. 438.2770; found 438.2794. $C_{28}H_{38}O_4$ (438.60): calcd. C 76.68, H 8.73; found C 76.19, H 8.93.

(2*S*,3*R*,4*R*)-2-Hydroxy-4-methyl-3-phenyl-δ-valerolactone (11). Cyclization of 10: A solution of **10** (208 mg, 474 μmol) and *p*-toluenesulfonic acid (180 mg, 946 μmol) in CH_2Cl_2 (3 mL) was stirred for 40 h at 28 °C. The mixture was diluted with EtOAc (200 mL) and washed with satd. aqueous $NaHCO_3$ (2 × 100 mL) and brine (1 × 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography on silica gel with EtOAc/petroleum ether (2:5, v/v) furnished **11** (62 mg, 63%) as a colourless solid. **Deprotection of 17:** Concd. HCl (5 drops) was added to a solution of **17** (2.1 mg, 6.5 μmol) in THF (0.4 mL) and MeOH (0.5 mL). After the mixture had been stirred for 4 h at room temperature, EtOAc (20 mL) was added. The organic phase was washed with 2 M NaOH (2 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL), dried (Na_2SO_4), and filtered. The solvents were evaporated, and the residue was purified by preparative TLC on silica gel (0.25 mm, 5 × 20 cm) with EtOAc/petroleum ether (2:1, v/v) to afford **11** (0.6 mg, 45%) as a colourless solid. M.p. 142 °C. $[\alpha]_D^{23}$ = +50.8 (*c* = 0.007, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 203 nm (sh, 9600), 205 (9660), 208 (sh, 9450), 217 (sh, 5130), 258 (430). CD (CH_3CN): λ_{max} (Δε) = 219 nm (+0.3), 222 (+0.3), 224 (+0.3). IR (KBr): $\tilde{\nu}$ = 3537 cm^{-1} (s), 3476 (s), 3065 (w), 3032 (w), 2992 (w), 2969 (w), 2938 (w), 2906 (w), 1720 (s), 1604 (w), 1498 (m), 1469 (m), 1452 (m), 1411 (w), 1394 (w), 1376 (w), 1329 (w), 1244 (w), 1181 (s), 1125 (s), 1060 (m), 1031 (s), 1014 (m), 952 (w), 882 (m), 774 (w), 734 (s), 698 (s), 590 (w), 530 (w), 464 (w). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.27−7.39 (m, 3 H), 7.05−7.10 (m, 2 H), 4.53 (d, *J* = 6.4 Hz, 1 H), 4.26 (ddd, *J* = 1.2, 5.6, 11.6 Hz, 1 H), 4.00 (dd, *J* = 11.8, 11.8 Hz, 1 H), 3.58 (dd, *J* = 4.9, 4.9 Hz, 1 H), 3.15 (br., s, OH), 2.57−2.72 (m, 1 H), 0.79 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8, 133.8, 129.4, 128.6, 127.6, 72.0, 69.5, 48.8, 31.9, 14.1 ppm. EI MS: *m*/*z* (%) = 206 (20) [M^+], 188 (1), 177 (12), 131 (100), 129 (7), 120 (10), 118 (16), 117 (29), 115 (16), 91 (58). HRMS: calcd. 206.0943; found 206.0933. $C_{12}H_{14}O_3$ (206.24): calcd. C 69.89, H 6.84; found C 69.86, H 7.19.

(−)-8-Phenylmenthyl (2*S*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-methyl-3-phenylpent-4-enoate (12): TBSOTf (480 μL, 2.09 mmol), 2,6-lutidine (370 μL, 3.18 mmol), and a catalytic amount of DMAP were added at room temperature to a solution of **9** (440 mg, 1.05 mmol) in dry CH_2Cl_2 (10 mL), and the reaction mixture was stirred for 2.5 h. The mixture was diluted with EtOAc (200 mL) and washed with satd. aqueous $NaHCO_3$ (3 × 100 mL) and brine (1 × 100 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel with EtOAc/petroleum ether (1:100, v/v) yielded **12** (527 mg, 94%) as a colourless oil. $[\alpha]_D^{29}$ = +34.8 (*c* = 0.003, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 209 nm (sh, 21860), 259 (830). IR (KBr): $\tilde{\nu}$ = 3087 cm^{-1} (w), 3060 (w), 3028 (w), 2956 (s), 2928 (s), 2855 (s), 1743 (s), 1649 (w), 1600 (w), 1495 (m), 1471 (m), 1453 (m), 1389 (m), 1372 (m), 1280 (w), 1249 (s), 1204 (s), 1145 (s), 1077 (w), 1029 (m), 988 (w), 939 (w), 909 (m), 892 (m), 837 (s), 810 (m), 777 (s), 764 (m), 742 (m), 700 (s), 582 (w). ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.01−7.31 (m, 10 H), 5.26 (s, 1 H), 4.85 (s, 1 H), 4.73 (td, *J* = 4.1, 10.7 Hz, 1 H), 3.47 (d, *J* = 4.1 Hz, 1 H), 3.09 (d, *J* = 4.1 Hz, 1 H), 2.04 (td, *J* = 3.3, 11.3 Hz, 1 H), 1.71−1.81 (m, 2 H), 1.57−1.67 (m, 1 H), 1.45 (s, 3 H), 1.31−1.42 (m, 1 H), 1.24 (s, 3 H), 1.11 (s, 3 H), 1.01−1.16 (m, 1 H), 0.82−0.93 (m, 1 H), 0.78 (d, *J* = 6.5 Hz, 3 H), 0.71 (s, 9 H), 0.56−0.69 (m, 1 H), −0.14 (s, 3 H), −0.60 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 152.5, 142.5, 139.3, 129.5, 127.9, 127.7, 126.5, 125.3, 125.1, 114.0, 74.8, 74.7, 55.1, 50.1, 40.8, 39.4, 34.6, 31.2, 29.5, 26.4, 25.6, 23.9, 23.1, 21.7, 18.0, −5.1, −6.2 ppm. EI MS: *m*/*z* (%) = 534 (<< 0.1) [M^+], 477 (1), 263 (84), 219 (96), 215 (40), 214 (1), 131 (22), 119 (58), 105 (100), 91 (19). FAB MS: *m*/*z* (%) = 535 [M^+ + H], 477 [$M^+ - C(CH_3)_3$]. HR FAB MS: calcd. 535.3607 [M^+ + H]; found 535.3601. $C_{34}H_{50}O_3Si$ (534.85): calcd. C 76.35, H 9.42; found C 76.28, H 9.52.

(2*S*,3*R*)-2-Hydroxy-4-methyl-3-phenylpent-4-enoic Acid (13): NaOH (1 M, 3.4 mL) was added to a solution of **9** (475 mg, 1.13 mmol) in THF (3.5 mL) and MeOH (7 mL). The mixture was heated under reflux for 15 h and then cooled to room temperature. After addition of water (200 mL) and 2 M NaOH, the mixture was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to recover (−)-8-phenylmenthol (262 mg, quantitative). The aqueous layer was acidified with concd. HCl to pH = 1 and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (1 × 200 mL), dried (Na_2SO_4), and filtered to yield (after evaporation of the solvent) 210 mg (90%) of **13** as a colourless solid, m.p. 94−95 °C. $[\alpha]_D^{29}$ = +44.7 (*c* = 0.002, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 210 nm (sh, 10070), 261 (660). IR (KBr): $\tilde{\nu}$ = 3516 cm^{-1} (s), 3420 (m), 3089 (s), 1716 (s), 1676 (s), 1493 (m), 1451 (m), 1373 (w), 1325 (m), 1282 (m), 1231 (s), 1207 (s), 1109 (s), 1032 (w), 955 (m), 900 (s), 861 (m), 828 (m), 779 (w), 748 (m), 700 (s), 675 (w), 623 (m), 511 (w). ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.23−7.37 (m, 5 H), 5.08 (s, 1 H), 5.05 (s, 1 H), 4.68 (d, *J* = 5.2 Hz, 1 H), 3.82 (d, *J* = 5.1 Hz, 1 H), 1.70 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.7, 143.3, 138.8, 128.5, 128.5, 127.2, 114.3, 73.1, 55.5, 22.7 ppm. EI MS: *m*/*z* (%) = 206 (2) [M^+], 204 (4), 160 (5), 159 (9), 132 (34), 131 (100), 117 (32), 116 (18), 115 (28), 91 (41). HRMS: calcd. 206.0943; found 206.0958. $C_{12}H_{14}O_3$ (206.24): calcd. C 69.89, H 6.84; found C 69.42, H 6.83.

Methyl (2*S*,3*R*)-2-Hydroxy-4-methyl-3-phenylpent-4-enoate (14): DMF (3 drops) and $SOCl_2$ (96 μL, 1311 μmol) were added to a solution of **13** (180 mg, 872 μmol) in MeOH (9 mL). The mixture was heated under reflux for 4 h and then allowed to cool to room temperature and concentrated in vacuo. The residue was dissolved in toluene and the solvents were evaporated again. The crude product was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:10, v/v) to yield **14** (152 mg, 79%) as a colourless solid, m.p. 60−61 °C. $[\alpha]_D^{29}$ = +69.4 (*c* = 0.002, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 210 nm (sh, 9620), 258 (210). IR (KBr): $\tilde{\nu}$ = 3403 cm^{-1} (s), 3083 (w), 3028 (w), 2958 (w), 2931 (m), 1727 (s), 1711 (s), 1646 (w), 1493 (w), 1450 (m), 1435 (s), 1374 (w), 1353 (m), 1236 (s), 1205 (s), 1178 (m), 1089 (m), 969 (w), 893 (m), 755 (w), 734 (m), 702 (s), 609 (w), 541 (w). ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.21−7.35 (m, 5 H), 5.04 (s, 1 H), 5.03 (s, 1 H), 4.64 (dd, *J* = 5.4, 5.4 Hz, 1 H), 3.72 (d, *J* = 5.9 Hz, 1 H), 3.64 (s, 3 H), 2.76 (d, *J* = 5.3 Hz, 1 OH), 1.68 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 143.7, 139.1, 128.5, 128.4, 127.0, 113.7, 73.3, 56.2, 52.3, 22.5 ppm. EI MS: *m*/*z* (%) = 220 (<< 0.1) [M^+], 202 (2), 161 (1), 143 (6), 131 (100), 117 (4), 116 (10), 115 (11), 103 (2), 91 (23). HRMS: calcd. 220.1099; found 220.1112. $C_{13}H_{16}O_3$ (220.26): calcd. C 70.89, H 7.32; found C 70.58, H 7.48.

Methyl (2*S*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-methyl-3-phenylpent-4-enoate (15): TBSOTf (210 μL, 914 μmol), 2,6-lutidine (160 μL, 1374 μmol) and a catalytic amount of DMAP were added at room temperature to **14** (100 mg, 454 μmol) in dry CH_2Cl_2 (5 mL), and the solution was stirred for 2.5 h. The mixture was diluted with EtOAc (50 mL) and washed with satd. aqueous $NaHCO_3$ (3 × 30 mL) and brine (1 × 30 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed un-

der reduced pressure. Flash chromatography on silica gel with EtOAc/petroleum ether (1:70, v/v) yielded **15** (129 mg, 85%) as a colourless liquid. $[\alpha]_D^{29} = +48.0$ ($c = 0.002$, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 210 nm (sh, 9980), 259 (290). IR (KBr): $\tilde{\nu} = 3063\ cm^{-1}$ (w), 3028 (w), 2951 (s), 2930 (s), 2895 (m), 2857 (s), 1758 (s), 1649 (w), 1600 (w), 1492 (w), 1472 (m), 1452 (m), 1435 (m), 1389 (w), 1362 (w), 1253 (s), 1202 (m), 1147 (s), 1028 (m), 1006 (w), 954 (w), 896 (m), 886 (m), 838 (s), 810 (m), 778 (s), 742 (w), 701 (m), 618 (w). ^1H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 7.17-7.31$ (m, 5 H), 5.26 (s, 1 H), 4.98 (s, 1 H), 4.51 (d, $J = 6.3$ Hz, 1 H), 3.75 (d, $J = 6.2$ Hz, 1 H), 3.58 (s, 3 H), 1.65 (s, 3 H), 0.83 (s, 9 H), −0.05 (s, 3 H), −0.27 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.1$, 143.2, 139.2, 129.0, 128.2, 126.9, 113.4, 75.4, 56.3, 51.6, 25.6, 23.0, 18.1, −5.3, −5.9 ppm. EI MS: *m*/*z* (%) = 319 (1), 277 (96), 245 (6), 235 (9), 217 (9), 203 (4), 171 (6), 159 (12), 143 (44), 131 (100), 115 (11), 91 (19), 89 (35). HRMS: calcd. 319.1729 [$M^+ - CH_3$]; found 319.1740. $C_{19}H_{30}O_3Si$ (334.53): calcd. C 68.22, H 9.04; found C 68.35, H 9.11.

Epoxidation of 15: Compound **15** (30 mg, 90 μmol) was dissolved in dimethyldioxirane[15] (0.1 M solution in acetone, 5.0 mL) and stirred at room temperature for 6.5 h. The solvent was then evaporated, and after addition of further dimethyldioxirane solution (5.0 mL) the stirring was continued for 2 h. The reaction product was concentrated under reduced pressure to afford a spectroscopically pure epimeric mixture of methyl (2*S*,2′*RS*,3*R*)-2-(*tert*-butyldimethylsilyloxy)-3-(2′-methyloxiranyl)-3-phenylpropionate in a ratio of 2:1. Yield: 28 mg (89%), colourless liquid. ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 7.27-7.31$ (m, 5 H), 4.35 (d, $J = 5.8$ Hz, 1 H), 3.65 (s, 3 H), 3.40 (d, $J = 5.8$ Hz, 1 H), 3.36 (d, $J = 5.8$ Hz, 1 H), 2.66 (d, $J = 5.4$ Hz, 1 H), 1.25 (s, 3 H), 0.84 (s, 9 H), −0.07 (s, 3 H), −0.31 (s, 3 H); $\delta = 7.27-7.31$ (m, 5 H), 4.54 (d, $J = 6.6$ Hz, 1 H), 3.55 (s, 3 H), 2.97 (d, $J = 6.6$ Hz, 1 H), 2.72 (d, $J = 4.6$ Hz, 1 H), 2.49 (d, $J = 4.8$ Hz, 1 H), 1.48 (s, 3 H), 0.92 (s, 9 H), 0.01 (s, 3 H), −0.02 (s, 3 H) ppm. EI MS: *m*/*z* (%) = 293 (7), 275 (11), 265 (11), 263 (16), 261 (13), 233 (100), 205 (18), 169 (9), 159 (16), 131 (39), 115 (19), 91 (20), 89 (26). HRMS: calcd. 293.1209 [$M^+ - C(CH_3)_3$]; found 293.1235.

Methyl (2*S*,3*R*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-4-methyl-3-phenylpentanoate (16): A solution of **15** (56 mg, 167 μmol) in dry THF (3 mL) was treated with 9-BBN (179 mg, 1467 μmol). After the mixture had been stirred for 3.5 h at room temperature, 2 M NaOH (85 μL) and 30% H_2O_2 (1 mL) were added. The mixture was sonicated for 30 min, and then diluted with EtOAc (50 mL) and washed with satd. aqueous $NaHCO_3$ (3 × 30 mL) and brine (1 × 30 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography on silica gel with $CHCl_3$/MeOH (100:1, v/v) gave **16** (58 mg, 98%) as a colourless liquid. $[\alpha]_D^{29} = +9.8$ ($c = 0.001$, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 207 nm (8630), 208 (8600), 258 (290). IR (KBr): $\tilde{\nu} = 3452\ cm^{-1}$ (w), 3030 (w), 2953 (s), 2929 (s), 2885 (m), 2857 (s), 1754 (s), 1494 (w), 1472 (m), 1462 (m), 1454 (m), 1435 (w), 1361 (w), 1253 (s), 1206 (m), 1151 (s), 1129 (s), 1032 (m), 939 (w), 878 (m), 838 (s), 779 (s), 702 (m). ^1H NMR (600 MHz, $CDCl_3$, TMS): $\delta = 7.21-7.29$ (m, 5 H), 4.53 (d, $J = 5.2$ Hz, 1 H), 3.59 (s, 3 H), 3.53 (dd, $J = 5.6$, 10.8 Hz, 1 H), 3.30 (dd, $J = 5.9$, 10.8 Hz, 1 H), 3.10 (dd, $J = 6.0$, 6.0 Hz, 1 H), 2.32−2.39 (m, 1 H), 1.00 (d, $J = 6.9$ Hz, 3 H), 0.94 (s, 9 H), 0.01 (s, 3 H), −0.06 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 173.4$, 139.6, 129.4, 128.1, 127.0, 75.1, 65.9, 53.3, 51.6, 35.9, 25.8, 18.2, 15.9, −5.1, −5.2 ppm. EI MS: *m*/*z* (%) = 305 (< 0.1), 263 (38), 219 (100), 177 (26), 163 (10), 135 (11), 117 (7), 103 (8), 75 (60). HRMS: calcd. 305.1573 [$M^+ - CH_4O - CH_3$]; found 305.1562.

(2*S*,3*R*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-methyl-3-phenyl-δ-valerolactone (17): TFA (4.8 μL, 62.3 μmol) was added to **16** (4.4 mg, 12.5 μmol) in $CHCl_3$ (1.0 mL), and the mixture was stirred for 4 h at room temperature. Evaporation of the solvent afforded the pure product (3.9 mg, 96%) as a colourless solid, m.p. 73−75 °C. $[\alpha]_D^{30} = +40.5$ ($c = 0.001$, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 204 nm (sh, 11990), 208 (sh, 10510), 217 (sh, 6230), 257 (290). CD (CH_3CN): λ_{max} ($\Delta\varepsilon$) = 216 nm (+3.7), 227 (+2.2), 256 (0), 260 (−0.2), 268 (−0.2). IR (KBr): $\tilde{\nu} = 3454\ cm^{-1}$ (m), 3031 (w), 2954 (s), 2931 (s), 2900 (m), 2856 (s), 1743 (s), 1495 (w), 1474 (m), 1460 (w), 1452 (w), 1407 (w), 1388 (w), 1361 (w), 1334 (m), 1259 (m), 1233 (s), 1173 (s), 1157 (s), 1118 (m), 1069 (m), 1050 (m), 1033 (m), 962 (w), 905 (m), 842 (s), 778 (s), 731 (m), 700 (m), 673 (w), 583 (w). ^1H NMR (600 MHz, $CDCl_3$, TMS): $\delta = 7.23-7.33$ (m, 3 H), 7.07−7.10 (m, 2 H), 4.48 (d, $J = 6.2$ Hz, 1 H), 4.12 (dd, $J = 5.2$, 11.4 Hz, 1 H), 3.95 (dd, $J = 11.7$, 11.7 Hz, 1 H), 3.39 (dd, $J = 4.8$, 4.8 Hz, 1 H), 2.52−2.59 (m, 1 H), 0.79 (d, $J = 7.0$ Hz, 3 H), 0.70 (s, 9 H), 0.12 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 172.5$, 134.6, 129.7, 128.0, 127.0, 70.9, 70.4, 51.2, 32.1, 25.4, 18.1, 14.2, −4.6, −5.7 ppm. EI MS: *m*/*z* (%) = 305 (1), 263 (70), 219 (100), 205 (1), 177 (24), 163 (9), 161 (12), 131 (21), 117 (6), 103 (4), 91 (7), 75 (26). HRMS: calcd. 305.1573 [$M^+ - CH_3$]; found 305.1592.

(2*S*,3*R*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-methyl-3-phenyl-δ-valerolactone (21). i. Swern Oxidation of 16: DMSO (49.6 μL, 697.6 μmol) was added at −78 °C to a solution of oxalyl chloride (30.4 μL, 348.2 μmol) in dry CH_2Cl_2 (0.7 mL), and the mixture was stirred for 15 min. A solution of methyl ester **16** (41.0 mg, 116.3 μmol) in dry CH_2Cl_2 (3 × 0.2 mL) was then added by syringe, and after an additional 20 min, the mixture was treated with NEt_3 (97.0 μL, 695.7 μmol). It was stirred for 5 min, allowed to warm to room temperature and stirred for a further 40 min. After addition of water (2 mL), the mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (1 × 30 mL) and brine (1 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield aldehyde **18**, which was used without purification for the epimerization experiments. **ii. Epimerization:** $NaHCO_3$ (73.0 mg, 868.9 μmol) was added to a solution of aldehyde **18** in dry EtOH (20 mL), and the mixture was heated under reflux for 3 h. After cooling to room temperature, filtration, and evaporation of the solvent, the epimeric mixture was reduced without further purification. **iii. Reduction:** $NaBH_4$ (6.6 mg, 174.5 μmol) was added at 0 °C to a solution of epimers **19** in dry MeOH (1.1 mL). After 25 min, the mixture was quenched with 5 drops of 2 M HCl, diluted with EtOAc (50 mL) and washed with water (3 × 30 mL) and brine (1 × 30 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The products were separated by flash chromatography on silica gel with EtOAc/petroleum ether (1:15, v/v) to yield **21** (7.3 mg, 20%; 30% relative to recovered **20**) as a colourless liquid, together with unchanged **20** (15.2 mg, 36%). Starting from ethyl ester **20** (70 mg, 191 μmol), the sequence of Swern oxidation, epimerization, and reduction afforded **21** (14 mg, 23%; 35% related to recovered **20**) as a liquid, together with recovered alcohol **20** (24 mg, 34%). **21:** $[\alpha]_D^{31} = -29.0$ ($c = 0.01$, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 206 nm (7450), 208 (7370), 228 (250), 258 (200). CD (CH_3CN): λ_{max} ($\Delta\varepsilon$) = 216 nm (+4.4), 226 (sh, +0.7), 233 (0), 245 (−0.8). IR (KBr): $\tilde{\nu} = 3064\ cm^{-1}$ (w), 3031 (w), 2957 (s), 2929 (s), 2886 (m), 2857 (s), 1755 (s), 1495 (w), 1472 (m), 1462 (m), 1455 (m), 1406 (w), 1390 (w), 1361 (w), 1316 (w), 1253 (s), 1199 (w), 1151 (s), 1111 (s), 1085 (m), 1044 (m), 1001 (m), 909 (w), 890 (w), 867 (m), 839 (s), 807 (m), 780 (s), 739 (w), 700 (m), 673 (w). ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.29-7.34$ (m, 2 H), 7.23−7.26 (m, 1 H), 7.18 (d, $J =$

7.4 Hz, 2 H), 4.57 (dd, *J* = 5.4, 11.3 Hz, 1 H), 4.36 (d, *J* = 5.3 Hz, 1 H), 4.05 (dd, *J* = 9.2, 10.8 Hz, 1 H), 2.86 (dd, *J* = 5.4, 8.7 Hz, 1 H), 2.53−2.62 (m, 1 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.77 (s, 9 H), −0.02 (s, 3 H), −0.26 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.6, 139.0, 129.2, 128.3, 127.1, 72.6, 70.8, 52.3, 31.7, 25.6, 18.1, 16.7, −5.1, −5.7 ppm. EI MS: *m*/*z* (%) = 320 (0.03) [M^+], 305 (1), 263 (92), 219 (47), 205 (2), 177 (20), 163 (4), 161 (12), 131 (44), 117 (20), 103 (10), 91 (28), 75 (100). HRMS: calcd. 263.1103 [$M^+ - C(CH_3)_3$]; found 263.1113.

Ethyl (2*S*,3*R*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-4-methyl-3-phenylpentanoate (20): $[\alpha]_D^{30}$ = −4.3 (*c* = 0.01, $CHCl_3$). UV (CH_3CN): λ_{max} (ε) = 206 nm (8600), 209 (sh, 8390), 258 (270). IR (KBr): $\tilde{\nu}$ = 3436 cm^{-1} (w), 3030 (w), 2956 (s), 2929 (s), 2857 (s), 1749 (s), 1731 (m), 1494 (w), 1472 (m), 1463 (m), 1454 (m), 1389 (w), 1372 (w), 1253 (s), 1204 (m), 1182 (m), 1127 (s), 1031 (m), 939 (w), 886 (m), 838 (s), 778 (s), 702 (m). ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.20−7.29 (m, 5 H), 4.51 (d, *J* = 5.5 Hz, 1 H), 4.04 (q, *J* = 6.9 Hz, 2 H), 3.55 (dd, *J* = 5.3, 10.8 Hz, 1 H), 3.31 (dd, *J* = 5.4, 10.7 Hz, 1 H), 3.10 (dd, *J* = 6.0, 6.0 Hz, 1 H), 2.32−2.40 (m, 1 H), 1.12 (t, *J* = 7.1 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.94 (s, 9 H), 0.02 (s, 3 H), −0.05 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 173.0, 139.5, 129.5, 128.1, 127.0, 75.2, 65.9, 60.7, 53.4, 36.0, 25.8, 18.2, 16.0, 14.0, −5.0, −5.2 ppm. EI MS: *m*/*z* (%) = 366 (<< 0.1) [M^+], 309 (7), 279 (17), 263 (82), 235 (100), 219 (57), 205 (13), 177 (27), 161 (29), 143 (33), 131 (57), 117 (51). HRMS: calcd. 309.1522 [$M^+ - C(CH_3)_3$]; found 309.1492.

(2*S*,3*R*,4*S*)-2-Hydroxy-4-methyl-3-phenyl-δ-valerolactone (3): Concd. HCl (20 drops) was added to a solution of **21** (13.0 mg, 40.6 μmol) in THF (1.5 mL) and MeOH (2.0 mL). After the mixture had been stirred for 4 h at room temperature, the solvent was evaporated in vacuo. The residue was purified by preparative TLC on silica gel (0.25 mm, 10 × 20 cm) with EtOAc/petroleum ether (2:1, v/v) to afford **3** (8.1 mg, 96%) as a colourless liquid. $[\alpha]_D^{30}$ = +87.6 (*c* = 0.001, $CHCl_3$). $[\alpha]_D^{23}$ = +16.2 (*c* = 0.002, MeOH). UV (CH_3CN): λ_{max} (ε) = 206 nm (7030), 208 (sh, 6940), 257 (210). CD (CH_3CN): λ_{max} (Δε) = 216 nm (+2.6), 225 (sh, +1.2), 241 (0), 249 (−0.1). IR (KBr): $\tilde{\nu}$ = 3443 cm^{-1} (m), 3062 (w), 3030 (w), 2964 (m), 2928 (m), 2876 (w), 1747 (s), 1495 (m), 1479 (w), 1455 (s), 1387 (w), 1314 (w), 1268 (w), 1239 (m), 1188 (m), 1163 (m), 1131 (s), 1109 (s), 1072 (m), 1040 (s), 998 (w), 955 (w), 889 (w), 790 (w), 743 (s), 701 (s), 544 (w). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.25−7.37 (m, 3 H), 7.13 (d, *J* = 6.7 Hz, 2 H), 4.67 (d, *J* = 8.6 Hz, 1 H), 4.37 (dd, *J* = 5.6, 11.5 Hz, 1 H), 4.13 (dd, *J* = 11.6, 11.6 Hz, 1 H), 3.25 (dd, *J* = 6.6, 8.5 Hz, 1 H), 2.63 (s, 1 OH), 2.38−2.53 (m, 1 H), 1.12 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 175.0, 139.2, 128.8, 128.8, 127.5, 70.6, 67.2, 51.1, 37.0, 16.7 ppm. EI MS: *m*/*z* (%) = 207 (1) [M^+ + H], 206 (6) [M^+], 204 (3), 188 (< 1), 177 (17), 149 (2), 131 (100), 120 (3), 118 (16), 117 (32), 115 (10), 105 (5), 91 (46). HRMS: calcd. 206.0943; found 206.0929.

(*R*)-MTPA Ester of (2*S*,3*R*,4*S*)-2-Hydroxy-4-methyl-3-phenyl-δ-valerolactone (22): A solution of **3** (1.0 mg, 4.8 μmol), (*S*)-(+)-MTPA-Cl (1.4 μL, 7.5 μmol), NEt_3 (0.1 mL) and a catalytic amount of DMAP in CH_2Cl_2 (0.1 mL) was stirred for 3 d. After addition of water (1 mL), the stirring was continued for 3 h. The mixture was diluted with EtOAc (20 mL) and washed with aqueous $KHSO_4$ (1.1 M, 3 × 10 mL), 2 M NaOH (1 × 10 mL), satd. aqueous $NaHCO_3$ (2 × 10 mL), and brine (1 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The ^{1}H NMR spectrum of the crude product indicated that the starting material had been consumed completely. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.07−7.42 (m, 10 H), 5.87 (d, *J* = 9.1 Hz, 1 H), 4.39 (dd, *J* = 5.1, 11.5 Hz, 1 H), 4.23 (dd, *J* = 11.5, 11.5 Hz, 1 H), 3.37 (dd, *J* = 7.6, 8.7 Hz, 1 H), 3.00 (s, 3 H), 2.41−2.51 (m, 1 H), 1.14 (d, *J* = 6.7 Hz, 3 H) ppm.

(*S*)-MTPA Ester of (2*S*,3*R*,4*S*)-2-Hydroxy-4-methyl-3-phenyl-δ-valerolactone (23): The esterification was carried out with (*R*)-(−)-MTPA-Cl for 5 d as described in the above example. The ^{1}H NMR spectrum of the crude product indicated partial epimerization at C-2. The signals were unambiguously assigned to (*S*)-MTPA ester **23** by comparison of the coupling constants for 2-H and COSY experiments. ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ = 6.96−7.44 (m, 10 H), 5.84 (d, *J* = 8.9 Hz, 1 H), 4.40 (dd, *J* = 5.3, 11.7 Hz, 1 H), 4.21 (dd, *J* = 11.6, 11.6 Hz, 1 H), 3.37 (s, 3 H), 3.25 (dd, *J* = 6.9, 8.9 Hz, 1 H), 2.43−2.50 (m, 1 H), 1.12 (d, *J* = 6.9 Hz, 3 H) ppm.

X-ray Crystallographic Study: Single-crystal X-ray diffraction experiments were carried out with a STOE IPDS, area detection, and a Nonius MACH 3, four-circle, computer-controlled, single-crystal diffractometer. The structures were solved by direct methods and refined by full-matrix, least squares against F^2 of all data, using SHELXS-86 and SHELXL-93 software.[16,17] Crystal data and details of structure determinations and refinements are summarized in Table 2. CCDC-185723 and -185724 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Table 2. Crystal data and measurement conditions for compounds **9** and **11**

	9	**11**
Empirical formula	$C_{28}H_{36}O_3$	$C_{12}H_{14}O_3$
Formula mass	420.59	206.24
Crystal size [mm]	0.27×0.43×0.53	0.13×0.53×0.57
Crystal system	tetrahedral	monoclinic
Space group	$P4_12_12$	$P2_1$
Lattice parameters		
a [Å]	9.2152(5)	6.7228(12)
b [Å]	9.2152(5)	6.7025(15)
c [Å]	58.479(5)	12.184(3)
β [°]	90	102.87(2)
V [Å^3]	4966.0(6)	535.2(2)
Z	8	2
$D_{calcd.}$ [g·cm^{-3}]	1.125	1.280
F (000)	1824	220
μ [mm^{-1}]	0.071	0.091
Radiation type	Mo-K_α	Mo-K_α
λ [Å]	0.71073	0.71073
$2\Theta_{max}$ [°]	41.7	47.9
h_{min}/h_{max}	−8/9	−7/7
k_{min}/k_{max}	−8/9	−7/7
l_{min}/l_{max}	−57/56	−13/13
No. of measured reflections	11160	2068
No. of unique reflections	2551	1674
No. of observed reflections [$I > 2\sigma(I)$]	2229	1382
No. of parameters	288	141
R factor [$I > 2\sigma(I)$]	0.0357	0.0450
$wR(F^2)$ (all data)	0.0833	0.1374
Goodness of fit	0.961	0.929

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