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Total synthesis of the mushroom metabolite (+)-calopin

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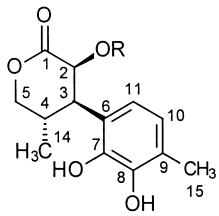
Abstract—A synthesis of (+)-calopin (**1a**) was achieved employing a highly stereoselective ene reaction between 8-phenylmenthyl glyoxylate (**3**) and the β,β-dimethylstyrene **4c**. Transesterification of the resulting homoallylic alcohol **5c**, followed by allylic oxidation and hydrogenation yielded the δ-lactone **13** which was deprotected to the natural product **1a**.

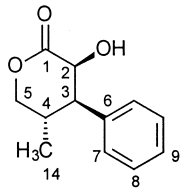
1. Introduction

The calopins and cyclocalopins constitute a new class of mushroom metabolites, which are in part responsible for the bitter taste of *Boletus calopus* (German: Schönfussröhrling) and related mushrooms.[1] Common to all compounds is a δ-lactone ring with three contiguous stereogenic centres. In addition, calopin (**1a**) and its *O*-acetyl derivative **1b** contain a 3-methylcatechol unit, a structural motif rarely encountered in natural products. The absolute configuration of these compounds was determined by the synthesis of (+)-(2*S*,3*R*,4*S*)-9-demethyl-7,8-dideoxycalopin (**2**) and comparison of its CD spectra and Mosher esters with those of natural **1a**.[2] In this communication we report on the asymmetric synthesis of (+)-calopin (**1a**).



Calopin (**1a**), R = H

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



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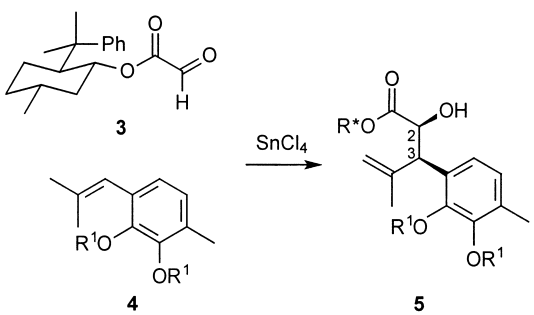
2. Results and discussion

The synthesis of (+)-calopin (**1a**) employed a similar approach to that used in preparing analogue **2**.[2] It relies on the ene reaction between 8-phenylmenthyl glyoxylate (**3**)[3,4] and a suitably protected 3-methyl-6-(2-methylpropenyl)-catechol **4**, which should deliver the homoallylic alcohols **5** exclusively with the desired configuration at C-2 and C-3 (Scheme 1).[2–4]

To prepare building block **4**, 3-methylcatechol (**6**) was transformed into the MOM ether **7**,[5] which after *ortho*-lithiation[6] and subsequent treatment with dimethyl formamide afforded aldehyde **8** (Scheme 2). Wittig reaction of **8** with *i*-PrP(Ph)$_3$I gave the styrene derivative **4a** in excellent overall yield. As expected, the MOM groups did not survive the Lewis acidic conditions of the ene reaction and had therefore to be replaced by a less acid-labile protecting group. After unsuccessful experiments with benzyl, isopropyl and methylene residues, the problem was finally solved with the 3,4-dichlorobenzyl group.[7–10] To prepare the desired derivative, the MOM acetals in **4a** were cleaved quantitatively with a saturated solution of HCl in EtOAc to yield the free catechol **4b**,[11] which was then converted into the bis-3,4-dichlorobenzyl ether **4c**.

The styrene derivative **4c** was subjected to the ene reaction with glyoxylate **3**[3,4] in the presence of $SnCl_4$ to afford the δ-hydroxy ester **5c** as a single diastereomer in 81% yield (Scheme 3). In order to prevent cleavage of the protecting



3 **4** **5**

Scheme 1. Stereoselective formation of the crucial intermediate **5** by an ene reaction.

Keywords: natural product synthesis; calopin; lactones; asymmetric synthesis; ene reaction.

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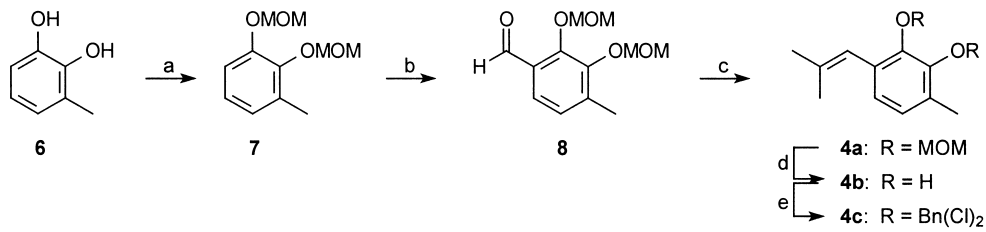
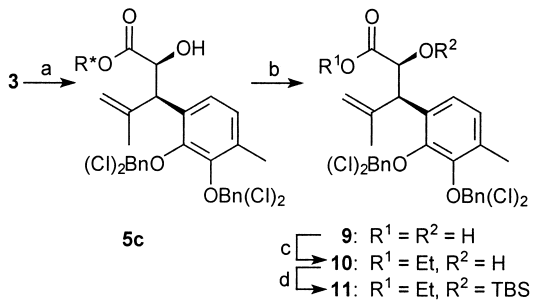


Scheme 2. *Reagents and conditions*: (a) MOMCl, NaH, K_2CO_3, DMF, 0°C (90%); (b) *n*-BuLi, THF, 0°C→rt, then DMF (96%); (c) *n*-BuLi, *i*-PrP(Ph)$_3$I, THF, 0°C→rt (87%); (d) HCl, EtOAc (99%); (e) 3,4-dichlorobenzyl chloride, K_2CO_3, KI, DMF, reflux (67%). MOM=methoxymethyl; Bn(Cl)$_2$=3,4-dichlorobenzyl.

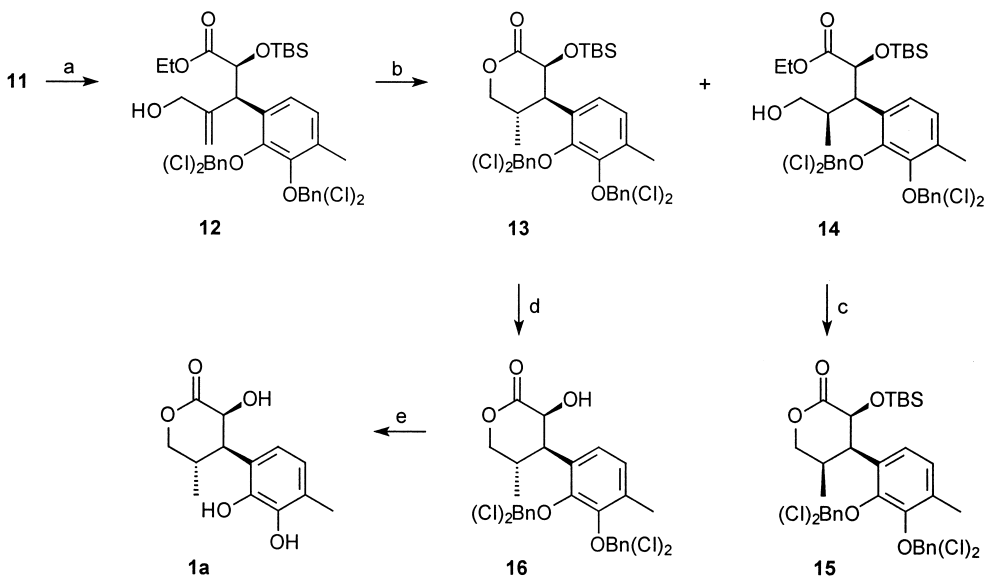


Scheme 3. *Reagents and conditions*: (a) $SnCl_4$, CH_2Cl_2, −78°C, then **4c**, −78→−47°C (81%); (b) KOH, EtOH, DME, H_2O, 65°C (81%); (c) $SOCl_2$, DMF, EtOH (83%); (d) TBSOTf, 2,6-lutidine, CH_2Cl_2 (90%). DME=dimethoxyethane; DMF=*N*,*N*-dimethylformamide; R*=(−)-8-phenylmenthyl; TBS=*t*-butyldimethylsilyl; Bn(Cl)$_2$=3,4-dichlorobenzyl.

groups, the styrene derivative was added to the reaction mixture after coordination of $SnCl_4$ to the glyoxylate. In analogy to the stereochemical outcome of the ene reaction with β,β-dimethylstyrene,[2] the absolute configuration of **5c** was assigned as (2*S*, 3*R*).

With the optically pure alcohol **5c** to hand, the introduction of the third stereocentre by conversion of the terminal isopropenyl residue into the desired (*S*)-HOCH$_2$CH(CH$_3$)– moiety was addressed. As a prerequisite for this transformation, the sterically demanding phenylmenthyl group had to be removed by alkaline hydrolysis (Scheme 3). The resulting acid **9** was then converted into ethyl ester **10** the carbinol group of which was protected with TBS-triflate. In accord with prior experience,[2] hydroboration of the TBS ether **11** yielded only the undesired (4*R*)-alcohol **14**. To circumvent this problem, a sequence of allylic oxidation and subsequent hydrogenation of the resulting allylic alcohol was applied. Thus, allylic oxidation of **11** with stoichiometric amounts of SeO_2 delivered the desired alcohol **12** (Scheme 4),[12] although in maximising the yield (29% at 47% conversion) the reaction had to be stopped at ~50% conversion because of over oxidation to the corresponding aldehyde (4%). Reduction of the unstable aldehyde yielded some additional alcohol **12**. In this manner, the allylic alcohol **12** could be obtained in 32% yield from **11** (61% related to recovered **11**).

Hydrogenation of **12** with Wilkinson's catalyst and hydrogen (15 bar) in the presence of Hünig's base,[13] afforded two diastereomeric alcohols that could be easily separated due to their different tendency towards lactonization.[2] Treatment of the crude product with TFA yielded the desired δ-lactone **13** (52% yield) and the epimeric alcohol **14** (14%) that were readily separated by flash chromatography. The stereochemistry of the newly generated stereogenic centres of **13** (4*S*) and **14** (4*R*) was determined by NOESY experiments,



Scheme 4. *Reagents and conditions*: (a) SeO_2, *t*-BuO_2H, CH_2Cl_2, then Me_2S (32%); (b) $(Ph_3P)_3RhCl$, H_2 (15 bar), benzene, then TFA, $CHCl_3$, separation of **13** (52%) and **14** (14%); (c) TFA, CH_2Cl_2 (79%); (d) 5% HF–CH_3CN (92%); (e) 10% Pd–C, H_2 (40 bar), MeOH (68%). TFA=trifluoroacetic acid; Bn(Cl)$_2$=3,4-dichlorobenzyl.

in the latter case after conversion to the corresponding lactone **15**. Attempts to avoid the formation of the undesired (4*R*)-epimer by varying the conditions for the hydrogenation failed.

The silyl ether **13** was deprotected with HF to yield alcohol **16**.[14,15] Deblocking of the catechol groups in **16** was accomplished by hydrogenolysis with palladium on charcoal and hydrogen (40 bar) in dry MeOH to afford (+)-calopin (**1a**) in 68% yield. The physical and spectroscopic properties of the synthetic compound were identical with those of authentic (+)-calopin (**1a**).[1]

Overall, the synthesis of (+)-calopin was accomplished from 3-methylcatechol (**6**) in 14 steps and 3% yield.

3. Experimental

3.1. General

Silica gel 60 (40–63 μm, Merck) and RP 18 (Lichroprep®) were used for column chromatography. R_f values were measured on silica gel 60 F_{254} TLC plates (Merck). Melting points (uncorrected) were determined on a Büchi SMP 535. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. UV/VIS spectra were recorded on a Perkin–Elmer Lambda 16 instrument. CD spectra were measured on a S. A. Jobin Yvon CD-6-Dichrograph. FT IR spectra were determined on a Perkin–Elmer Spectrum 1000 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX 300, Varian VXR 400S and Bruker AMX 600 instruments. ^{1}H and ^{13}C chemical shifts are given with respect to the solvent or TMS as internal standard. Mass spectra were measured with a Finnigan MAT 90 or Finnigan MAT 95Q sector mass spectrometer. Elemental analyses were carried out by the Microanalytical Laboratory of the Chemistry Department at the Universität München. All solvents were destilled before use. For chromatography petroleum ether 40–60° was used. (−)-8-Phenylmenthol was purchased from Aldrich.

3.1.1. 2,3-Bis(methoxymethoxy)toluene (7). To a solution of 3-methylcatechol (**6**) (8.00 g, 64.44 mmol) in dry DMF (64 mL) were added, at 0°C, NaH (2×1.63 g, 135.83 mmol) and further MOMCl (6 M solution in MeOH, 2×12 mL, 144.00 mmol). After addition of K_2CO_3 (26.7 g) and MOMCl (6 M solution in MeOH, 18 mL, 108.00 mmol), the mixture was stirred for 30 min, then poured into ice-cold aqueous ammonia, diluted with EtOAc (400 mL) and washed with aqueous ammonia (3×200 mL), water (3×200 mL) and brine (1×200 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 1:15) yielded **7** (12.28 g, 90%) as a colourless liquid. R_f=0.13 (EtOAc/petroleum ether, 1:15). UV (CH_3CN) λ_{max} ε 216 (sh, 7610), 270 nm (570). IR (KBr) $\tilde{\nu}$ 2956 (m), 2931 (m), 2901 (m), 2826 (m), 1604 (w), 1586 (w), 1483 (s), 1440 (m), 1401 (w), 1310 (w), 1265 (s), 1223 (w), 1206 (m), 1187 (m), 1155 (s), 1076 (s), 1044 (s), 976 (s), 924 (m), 774 (m), 749 (w), 693 cm^{-1} (w). ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.32 (s, 3H), 3.49 (s, 3H), 3.60 (s, 3H), 5.11 (s, 2H), 5.18 (s, 2H), 6.83 (d, J=7.1 Hz, 1H), 6.90–7.00 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 16.6, 56.2, 57.4, 95.2, 98.9, 114.3, 124.1, 124.4, 132.6, 145.4, 149.8. EI MS *m/z* (%) 212 (10) $[M]^+$, 149 (5), 136 (100), 45 (78). HRMS calcd for $C_{11}H_{16}O_4$ $[M]^+$ 212.1049; found 212.1043. Anal. calcd for $C_{11}H_{16}O_4$ C 62.25, H 7.60; found C 62.11, H 7.82.

3.1.2. 2,3-Bis(methoxymethoxy)-4-methylbenzaldehyde (8). To a solution of **7** (4.59 g, 21.63 mmol) in dry THF (80 mL) was added *n*-butyllithium (2.5 M solution in hexane, 9.5 mL, 23.75 mmol) at 0°C, and the mixture was stirred for 2 h. Dry DMF (5.0 mL, 64.84 mmol) was then added, and the mixture was stirred for additional 1 h. The reaction was quenched with aqueous $KHSO_4$ (1.1 M, 30 mL), the resulting mixture diluted with saturated aqueous NH_4Cl (200 mL) and extracted with EtOAc (3×200 mL). The combined organic layers were washed with water (3×300 mL) and brine (1×100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 1:4) yielded **8** (5.00 g, 96%) as a colourless solid, mp 55–56°C. R_f=0.25 (EtOAc/petroleum ether, 1:4). UV (CH_3CN) λ_{max} ε 215 (20890), 261 (12660), 303 nm (2780). IR (KBr) $\tilde{\nu}$ 3435 (w), 2910 (m), 1688 (s), 1598 (m), 1487 (m), 1458 (m), 1429 (m), 1380 (s), 1254 (s), 1195 (m), 1159 (s), 1078 (s), 1046 (s), 957 (s), 917 (s), 891 (s), 813 (w), 775 (m), 602 (w), 547 (w), 487 (w), 436 cm^{-1} (w). ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 2.37 (s, 3H), 3.56 (s, 3H), 3.59 (s, 3H), 5.11 (s, 2H), 5.20 (s, 2H), 7.06 (d, J=8.0 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 10.34 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 17.3, 57.8, 58.1, 99.3, 100.2, 123.5, 126.9, 129.3, 140.7, 148.8, 152.8, 189.8 (CHO). EI MS *m/z* (%) 240 (1) $[M]^+$, 208 (4), 195 (23), 164 (37), 45 (100). HRMS calcd for $C_{12}H_{16}O_5$ $[M]^+$ 240.0998; found 240.0995. Anal. calcd for $C_{12}H_{16}O_5$ C 59.99, H 6.71; found C 59.97, H 6.83.

3.1.3. 2,3-Bis(methoxymethoxy)-4-(2-methylpropenyl)-toluene (4a). To a suspension of isopropyltriphenylphosphonium iodide (58.24 g, 134.73 mmol) in dry THF (340 mL), was added *n*-butyllithium (2.5 M solution in hexane, 53.4 mL, 133.50 mmol) at 0°C, and the mixture was stirred for 1 h. A solution of **8** (24.90 g, 103.64 mmol) in dry THF (2×22 mL) was then added via syringe and the stirring was continued for 30 min. The reaction mixture was poured into petroleum ether (450 mL) and water (450 mL). The separated aqueous phase was extracted with petroleum ether (3×300 mL) and the combined organic layers then dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 1:25) yielded **4a** (24.10 g, 87%) as a colourless liquid. R_f=0.44 (EtOAc/petroleum ether 1:4). UV (CH_3CN) λ_{max} ε 214 (23170), 247 nm (10580). IR (KBr) $\tilde{\nu}$ 3522 (w), 2956 (s), 2931 (s), 1658 (w), 1605 (w), 1566 (w), 1488 (w), 1453 (m), 1425 (m), 1390 (m), 1277 (m), 1201 (w), 1159 (s), 1084 (m), 1040 (s), 977 (s), 926 (s), 824 (w), 806 (w), 791 cm^{-1} (w). ^{1}H NMR (300 MHz, $CDCl_3$ TMS) δ 1.77 (s, 3H), 1.90 (s, 3H), 2.30 (s, 3H), 3.53 (s, 3H), 3.58 (s, 3H), 5.00 (s, 2H), 5.10 (s, 2H), 6.29 (s, 1H), 6.85 (d, J=8.1 Hz, 1H), 6.88 (d, J=8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 19.5, 26.4, 57.4, 57.5, 98.9, 99.2, 120.9, 125.6, 125.6, 130.7, 131.3, 135.8, 147.5, 148.6. FAB MS *m/z* (%) 266 (26) $[M]^+$, 235 (27), 221 (15), 190 (100). ESI MS *m/z* (%) 289 $[M+Na]^+$. HRMS (ESI) calcd for $C_{15}H_{22}O_4Na$ $[M+Na]^+$

289.1416; found 289.1430. Anal. calcd for $C_{15}H_{22}O_4$ C 67.65, H 8.33; found C 67.95, H 8.64.

3.1.4. 3-Methyl-6-(2-methylpropenyl)benzene-1,2-diol (4b). 4a (504 mg, 1.892 mmol) was dissolved in a saturated solution of HCl in EtOAc (10 mL) and stirred for 45 min. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on RP 18 with MeOH/water (3:2) to yield **4b** (334 mg, 99%) as a colourless solid, mp 75–76°C. UV (CH_3CN) λ_{max} ε 215 (26360), 247 (9980), 284 nm (1320). IR (KBr) $\tilde{\nu}$ 3448 (s), 3274 (s), 2979 (w), 2913 (w), 2859 (w), 1628 (w), 1573 (w), 1502 (w), 1464 (s), 1348 (m), 1322 (s), 1278 (s), 1250 (s), 1235 (s), 1192 (m), 1148 (m), 1072 (w), 1039 (s), 933 (m), 840 (w), 805 (w), 782 (w), 592 cm^{-1} (w). ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.68 (s, 3H), 1.92 (s, 3H), 2.24 (s, 3H), 5.01 (s, 1OH), 5.35 (s, 1OH), 6.10 (s, 1H), 6.52 (d, J=7.7 Hz, 1H), 6.65 (d, J=7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 19.5, 25.8, 118.6, 120.2, 121.9, 122.5, 122.8, 139.7, 140.0, 142.0. EI MS m/z (%) 178 (100) $[M]^+$, 163 (42), 145 (25), 137 (14), 136 (12), 135 (11), 117 (13). HRMS calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178.0994; found 178.0998. Anal. calcd for $C_{11}H_{14}O_2$ C 74.13, H 7.92; found C 74.32, H 8.00.

3.1.5. 2,3-Bis(3,4-dichlorobenzyloxy)-4-(2-methylpropenyl)toluene (4c). To a solution of freshly prepared catechol **4b** (5.15 g, 28.90 mmol) in dry DMF (280 mL) were added 3,4-dichlorobenzyl chloride (10.00 mL, 72.25 mmol), anhydrous K_2CO_3 (24 g) and KI (960 mg, 5.70 mmol). The resulting mixture was heated under reflux for 10 h, cooled to room temperature then concentrated under reduced pressure. The residue was dissolved in EtOAc (1 L) and washed with water (3×0.5 L), 2 M NaOH (3×0.5 L) and brine (1×0.5 L). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 1:100) yielded **4c** (9.61 g, 67%) as a colourless oil. R_f=0.33 (EtOAc/petroleum ether, 1:4). UV (CH_3CN) λ_{max} ε 202 (sh, 90400), 219 (sh, 42910), 248 nm (sh, 11620). IR (KBr) $\tilde{\nu}$ 3023 (w), 2967 (w), 2926 (m), 2860 (w), 1596 (w), 1564 (w), 1472 (s), 1423 (m), 1397 (s), 1360 (m), 1278 (s), 1212 (s), 1181 (w), 1131 (m), 1082 (s), 1050 (m), 1032 (s), 898 (w), 824 (w), 720 (w), 687 cm^{-1} (w). ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.75 (s, 3H), 1.90 (s, 3H), 2.25 (s, 3H), 4.82 (s, 2H), 4.91 (s, 2H), 6.23 (s, 1H), 6.89 (s, 2H), 7.12 (dd, J=8.2, 1.5 Hz, 1H), 7.19 (dd, J=8.2, 1.5 Hz, 1H), 7.35–7.43 (m, 2H), 7.45 (d, J=1.4 Hz, 1H), 7.49 (d, J=1.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.6, 26.5, 73.3, 73.7, 120.2, 125.7, 125.8, 127.1, 127.3, 129.8, 130.2, 130.3, 130.4, 130.6, 131.4, 132.0, 132.5, 132.6, 136.4, 137.8, 137.9, 149.4, 149.9 one signal obscured. EI MS m/z (%) 500 (0.1) $[M(^{37}Cl_3^{35}Cl)]^+$, 498 (0.3) $[M(^{37}Cl_2^{35}Cl_2)]^+$, 496 (0.6) $[M(^{37}Cl^{35}Cl_3)]^+$, 494 (0.4) $[M(^{35}Cl_4)]^+$, 339 (2), 337 (12), 335 (17), 163 (9), 161 (61), 159 (100). HRMS calcd for $C_{25}H_{22}^{37}Cl^{35}Cl_3O_2$ $[M]^+$ 496.0291; found 496.0298. Anal. calcd for $C_{25}H_{22}Cl_4O_2$ C 60.51, H 4.47, Cl 28.58; found C 60.71, H 4.42, Cl 28.51.

3.1.6. (−)-8-Phenylmenthyl (2*S*,3*R*)-3-[2,3-bis(3,4-dichlorobenzyloxy)-4-methylphenyl]-2-hydroxy-4-methylpent-4-enoate (5c). To a solution of freshly prepared glyoxylate **3**[3,4] (prepared by ozonolysis of 12.12 mmol of the corresponding acrylate) in dry CH_2Cl_2 (70 mL) was added $SnCl_4$ (4.27 mL, 36.40 mmol) at −78°C, and the mixture was stirred for 10 min. Then, a solution of **4c** (5.00 g, 10.10 mmol) in dry CH_2Cl_2 (28 mL) was added via syringe. The mixture was stirred for 22 h at −47°C, then quenched with saturated aqueous $NaHCO_3$ (0.8 L) and diluted with Et_2O (0.8 L). The organic layer was washed with saturated aqueous $NaHCO_3$ (3×400 mL) and brine (1×300 mL), then dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 1:15) yielded **5c** (6.42 g, 81%) as a colourless oil. R_f=0.45 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{23}$=+32.2 (c 0.007, $CHCl_3$). UV (CH_3CN) λ_{max} ε 202 (sh, 106450), 221 (sh, 36170), 271 nm (1570). IR (KBr) $\tilde{\nu}$ 3501 (w), 3058 (w), 2957 (s), 2870 (m), 1723 (s), 1643 (w), 1599 (w), 1564 (w), 1472 (s), 1455 (s), 1398 (m), 1368 (m), 1276 (s), 1215 (s), 1130 (m), 1110 (m), 1070 (m), 1031 (s), 983 (w), 954 (w), 903 (m), 874 (w), 816 (m), 762 (s), 700 cm^{-1} (m). ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 0.60 (q, J=11.8 Hz, 1H), 0.83 (d, J=6.4 Hz, 3H), 0.85–0.94 (m, 1H), 1.02–1.23 (m, 2H), 1.17 (s, 3H), 1.26 (s, 3H), 1.33–1.47 (m, 1H), 1.56 (s, 3H), 1.60–1.70 (m, 1H), 1.72–1.82 (m, 1H), 1.89–2.00 (m, 1H), 2.26 (s, 3H), 2.62 (d, J=5.7 Hz, 1OH), 3.54 (dd, J=5.7, 5.0 Hz, 1H), 3.85 (d, J=5.0 Hz, 1H), 4.77–4.92 (m, 7H), 6.89–7.02 (m, 3H), 7.12–7.24 (m, 6H), 7.36–7.50 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 21.8, 22.5, 23.7, 26.3, 28.8, 31.1, 34.3, 39.5, 41.1, 48.0, 50.4, 72.1, 73.0, 73.2, 75.6, 114.2, 125.0, 125.1, 125.3, 126.0, 126.7, 127.0, 127.9, 129.4, 129.7, 130.4, 130.4, 131.1, 131.8, 132.0, 132.1, 132.6, 137.6, 137.9, 143.5, 149.4, 149.6, 151.5, 173.5 three signals obscured. FAB MS m/z (%) 811 (0.2) $[M(^{37}Cl_3^{35}Cl)+Na]^+$, 809 (0.8) $[M(^{37}Cl_2^{35}Cl_2)+Na]^+$, 807 (1.5) $[M(^{37}Cl^{35}Cl_3)+Na]^+$, 805 (1.1) $[M(^{35}Cl_4)+Na]^+$. HRMS (FAB) calcd for $C_{43}H_{46}^{37}Cl^{35}Cl_3O_5Na$ $[M+Na]^+$ 807.1975; found 807.2033.

3.1.7. (2*S*,3*R*)-3-[2,3-Bis(3,4-dichlorobenzyloxy)-4-methylphenyl]-2-hydroxy-4-methylpent-4-enoic acid (9). To a solution of **5c** (2.72 g, 3.47 mmol) in DME (18 mL) and EtOH (27 mL) were added water (2.6 mL) and KOH (584 mg, 10.41 mmol). The mixture was stirred for 20 h at 65°C, then cooled to room temperature and concentrated under reduced pressure. The residue was poured into a mixture of petroleum ether (100 mL) and 0.5 M NaOH (300 mL) and the aqueous layer washed with petroleum ether (4×100 mL), acidified with concentrated HCl (pH 1), then extracted with $CHCl_3$ (4×100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography on silica gel (formic acid/EtOAc/petroleum ether, 1:10:30) yielded **9** (1.60 g, 81%) as a colourless oil. R_f=0.22 (formic acid/EtOAc/petroleum ether, 1:1:10). $[\alpha]_D^{23}$=+35.0 (c 0.005, $CHCl_3$). UV (CH_3CN) λ_{max} ε 221 (sh, 139150), 271 nm (4560). IR (KBr) $\tilde{\nu}$ 3436 (s), 2924 (m), 1718 (m), 1647 (m), 1595 (s), 1472 (m), 1398 (m), 1363 (m), 1275 (m), 1212 (m), 1130 (m), 1066 (m), 1031 (m), 899 (s), 873 (s), 812 (m), 701 (s), 592 cm^{-1} (s). ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3H), 2.23 (s, 3H), 4.27 (d, J=4.0 Hz, 1H), 4.51 (d, J=4.0 Hz, 1H), 4.76–5.02 (m, 6H), 6.91 (d, J=8.3 Hz, 1H), 7.12 (d, J=8.3 Hz, 1H), 7.31–7.41 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 23.3, 48.5, 72.0, 73.0, 73.5, 114.6, 124.9, 126.2, 126.8, 127.4, 130.1, 130.1, 130.8, 130.8, 131.8, 132.0, 132.0, 132.1, 132.6, 137.3, 131.4,

143.3, 144.2, 149.8, 150.1, 177.7. EI MS *m/z* (%) 574 (0.02) $[M(^{37}Cl_3^{35}Cl)]^+$, 572 (0.1) $[M(^{37}Cl_2^{35}Cl_2)]^+$, 570 (0.3) $[M(^{37}Cl^{35}Cl_3)]^+$, 568 (0.3) $[M(^{35}Cl_4)]^+$, 500 (0.1), 498 (0.6), 496 (1.2), 494 (1), 411 (0.1), 409 (0.4), 163 (9), 161 (59), 159 (100). HRMS calcd for $C_{27}H_{24}^{37}Cl^{35}Cl_3O_5$ $[M]^+$ 570.0348; found 570.0320. Anal. calcd for $C_{27}H_{24}Cl_4O_5$ C 56.86, H 4.24, Cl 24.87; found C 56.98, H 4.24, Cl 24.94.

3.1.8. Ethyl (2*S*,3*R*)-3-[2,3-bis(3,4-dichlorobenzyloxy)-4-methylphenyl]-2-hydroxy-4-methylpent-4-enoate (10). To a solution of **9** (1.78 g, 3.12 mmol) in EtOH (40 mL) were added DMF (0.10 mL) and $SOCl_2$ (381 μL, 5.21 mmol). The mixture was stirred for 6 h at room temperature and then concentrated under reduced pressure. The residue was dissolved in toluene and the solvents were evaporated again. The crude product was purified by flash chromatography on silica gel (EtOAc/MeOH/petroleum ether, 2:3:50) to yield **10** (1.55 g, 83%) as a colourless oil. R_f=0.34 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{23}$=+52.9 (*c* 0.001, $CHCl_3$). UV (CH_3CN) λ_{max} ε 225 nm (sh, 24050). IR (KBr) $\tilde{\nu}$ 3500 (m), 3073 (w), 2980 (s), 2928 (s), 2872 (m), 1898 (w), 1732 (s), 1647 (m), 1596 (m), 1565 (m), 1471 (s), 1398 (s), 1367 (s), 1275 (s), 1130 (s), 1068 (s), 1031 (s), 947 (m), 900 (s), 873 (s), 817 (s), 735 (m), 688 (m), 673 (w), 657 (m), 592 (w), 537 cm^{-1} (w). ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J*=7.1 Hz, 3H), 1.64 (s, 3H), 2.26 (s, 3H), 2.86 (d, *J*=5.2 Hz, 1OH), 4.16–4.26 (m, 3H), 4.54 (dd, *J*=5.2, 4.7 Hz, 1H), 4.81–5.03 (m, 6H), 6.96 (d, *J*=8.0 Hz, 1H), 7.14–7.19 (m, 2H), 7.21 (d, *J*=8.0 Hz, 1H), 7.39 (d, *J*=8.2 Hz, 1H), 7.41 (d, *J*=8.2 Hz, 1H), 7.45 (d, *J*=2.0 Hz, 1H), 7.48 (d, *J*=2.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 16.0, 23.1, 48.1, 61.8, 73.3, 73.4, 73.8, 114.8, 125.3, 126.7, 127.3, 127.5, 130.0, 130.2, 130.8, 130.8, 131.5, 131.8, 132.0, 132.1, 132.6, 132.6, 137.5, 137.7, 143.2, 149.6, 149.7, 173.9. EI MS *m/z* (%) 600 (0.3) $[M(^{37}Cl_2^{35}Cl_2)]^+$, 598 (0.6) $[M(^{37}Cl^{35}Cl_3)]^+$, 596 (0.5) $[M(^{35}Cl_4)]^+$, 497 (5), 495 (9), 493 (7), 441 (0.2), 439 (0.8), 437 (1.1), 163 (10), 161 (62), 159 (100). HRMS calcd for $C_{29}H_{28}^{35}Cl_4O_5$ $[M]^+$ 596.0691; found 596.0694. Anal. calcd for $C_{29}H_{28}Cl_4O_5$ C 58.21, H 4.72, Cl 23.70; found C 58.12, H 4.62, Cl 23.70.

3.1.9. Ethyl (2*S*,3*R*)-3-[2,3-bis(3,4-dichlorobenzyloxy)-4-methylphenyl]-2-(*tert*-butyldimethylsilyloxy)-4-methylpent-4-enoate (11). To **10** (902 mg, 1.507 mmol) in dry CH_2Cl_2 (14 mL) were added 2,6-lutidine (530 μL, 4.522 mmol) and TBSOTf (690 μL, 3.015 mmol) at −15°C, and the solution was stirred for 30 min. After additional stirring for 3 h at room temperature, the mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ (3×100 mL), then brine (1×100 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 1:100) yielded **11** (968 mg, 90%) as a colourless oil. R_f=0.40 (EtOAc/petroleum ether, 1:10). $[\alpha]_D^{23}$=−1.1 (*c* 0.002, $CHCl_3$). UV (CH_3CN) λ_{max} ε 222 (sh, 33700), 274 nm (1440). IR (KBr) $\tilde{\nu}$ 2929 (s), 2857 (s), 1753 (s), 1565 (w), 1472 (s), 1398 (m), 1362 (m), 1274 (s), 1251 (s), 1211 (s), 1144 (s), 1068 (m), 1031 (s), 939 (w), 899 (m), 875 (m), 838 (s), 778 (s), 733 (w), 687 cm^{-1} (w). ^1H NMR (300 MHz, $CDCl_3$) δ −0.38 (s, 3H), −0.06 (s, 3H), 0.81 (s, 9H), 1.21 (t, *J*=7.2 Hz, 3H), 1.56 (s, 3H), 2.25 (s, 3H), 4.07–4.22 (m, 2H), 4.17 (d, *J*=5.0 Hz, 1H), 4.49 (d, *J*=5.0 Hz, 1H), 4.76 (d, *J*=11.4 Hz, 1H), 4.91 (d, *J*=11.3 Hz, 1H), 4.93 (d, *J*=11.4 Hz, 1H), 5.00 (s, 1H), 5.04 (d, *J*=11.3 Hz, 1H), 5.36 (s, 1H), 6.90 (d, *J*=8.0 Hz, 1H), 7.01 (d, *J*=8.0 Hz, 1H), 7.19 (dd, *J*=8.2, 2.0 Hz, 1H), 7.25 (dd, *J*=8.2 Hz, 2.0 Hz, 1H), 7.42 (d, *J*=8.2 Hz, 1H), 7.42 (d, *J*=8.2 Hz, 1H), 7.49 (d, *J*=2.0 Hz, 1H), 7.51 (d, *J*=2.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −6.0, −5.2, 14.2, 16.0, 18.1, 23.5, 25.6, 48.6, 60.6, 73.1, 73.7, 74.2, 114.6, 125.9, 125.9, 127.1, 127.5, 129.8, 130.1, 130.5, 130.5, 131.2, 131.4, 132.1, 132.2, 132.6, 137.6, 137.7, 142.5, 142.5, 149.6, 149.8, 172.6. FAB MS *m/z* (%) 713 (0.03) $[M^+(^{37}Cl_2^{35}Cl_2)-H]$, 711 (0.03) $[M^+(^{37}Cl^{35}Cl_3)-H]$, 709 (0.02) $[M^+(^{35}Cl_4)-H]$, 699 (0.1), 697 (0.1), 695 (0.1), 659 (0.3), 657 (1.2), 655 (2.2), 653 (1.6), 611 (0.2), 609 (0.3), 607 (0.2), 163 (9), 161 (48), 159 (80), 73 (100). EI MS *m/z* (%) 712 (<0.1) $[M(^{37}Cl_3^{35}Cl)]^+$, 701 (<0.1), 699 (0.1), 697 (0.2), 695 (0.1), 659 (3), 657 (11), 655 (20), 653 (15), 609 (2), 163 (10), 161 (68), 159 (100). HRMS (EI) calcd for $C_{34}H_{39}^{37}Cl^{35}Cl_3O_5Si$ $[M-CH_3]^+$ 697.1291; found 697.1292. Anal. calcd for $C_{35}H_{42}Cl_4O_5Si$ C 58.99, H 5.94; found C 59.08, H 6.16.

3.1.10. Ethyl (2*S*, 3*R*)-3-[2,3-bis(3,4-dichlorobenzyloxy)-4-methylphenyl]-2-(*tert*-butyldimethylsilyloxy)-4-(hydroxymethyl)pent-4-enoate (12). To a stirred suspension of SeO_2 (234 mg, 2.11 mmol) in CH_2Cl_2 (1.5 mL) was added *t*-butyl hydroperoxide (5.5 M solution in nonane, 1.68 mL, 9.24 mmol) and the mixture was stirred for 30 min. Then, a solution of **11** (3.000 g, 4.22 mmol) in CH_2Cl_2 (1.5 mL) was added and the stirring was continued for 48 h. The reaction was quenched by addition of dimethylsulfide (1.0 mL, 13.65 mmol). After 2 h, the mixture was diluted with Et_2O (250 mL) and washed with 2 M NaOH (4×200 mL) then brine (1×200 mL). The organic layer 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 (1:8) to yield the allylic alcohol **12** (900 mg, 29%) and the corresponding aldehyde (123 mg, 4%; R_f=0.35, EtOAc/petroleum ether, 1:4) as colourless oils, together with unreacted **11** (1.594 g, 53%).

For the conversion of the undesired aldehyde into additional alcohol **12**, a solution of the aldehyde (123 mg, 134 μmol) in dry MeOH (2 mL) was treated with $NaBH_4$ (12.80 mg, 338 μmol) at −15°C. The mixture was stirred for 30 min at this temperature, then quenched with water (2 mL) and 2 M HCl (0.2 mL), diluted with Et_2O (100 mL) and washed with water (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 (EtOAc/petroleum ether, 1:10) yielded **12** (97 mg) as a colourless oil. Total yield of **12**: 997 mg (32%). R_f=0.28 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{23}$=+32.2 (*c* 0.003, $CHCl_3$). UV (CH_3CN) λ_{max} ε 223 (sh, 36630), 273 nm (1630). IR (KBr) $\tilde{\nu}$ 3488 (s), 2953 (s), 2929 (s), 2882 (m), 2857 (s), 1851 (m), 1731 (m), 1712 (m), 1643 (w), 1565 (w), 1472 (s), 1397 (m), 1367 (m), 1276 (s), 1250 (s), 1214 (s), 1141 (s), 1066 (s), 1032 (s), 1003 (m), 937 (w), 896 (m), 872 (w), 826 (s), 779 (s), 745 (w), 689 (w), 658 (w), 595 cm^{-1} (w). ^1H NMR (600 MHz, $CDCl_3$) δ −0.41 (s, 3H), −0.06 (s, 3H), 0.81 (s, 9H), 1.23 (t, *J*=7.1 Hz, 3H), 2.25 (s, 3H), 3.86

(d, J=13.3 Hz, 1H), 3.89 (d, J=13.3 Hz, 1H), 4.11–4.16 (m, 1H), 4.17–4.22 (m, 1H), 4.45 (d, J=4.5 Hz, 1H), 4.53 (d, J=4.5 Hz, 1H), 4.77 (d, J=11.4 Hz, 1H), 4.92 (d, J=11.4 Hz, 1H), 4.94 (d, J=11.4 Hz, 1H), 5.03 (d, J=11.4 Hz, 1H), 5.31 (s, 1H), 5.62 (s, 1H), 6.90 (d, J=7.9 Hz, 1H), 7.01 (d, J=7.9 Hz, 1H), 7.21 (dd, J=8.2, 2.0 Hz, 1H), 7.27 (dd, J=8.2, 2.0 Hz, 1H), 7.43 (d, J=8.0 Hz, 2H), 7.50 (d, J=1.8 Hz, 1H), 7.53 (d, J=1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −6.1, −5.3, 14.2, 16.0, 18.1, 25.7, 43.9, 60.9, 66.6, 73.2, 73.9, 74.6, 114.7, 126.0, 126.0, 127.1, 127.7, 129.8, 130.3, 130.5, 130.5, 131.1, 131.5, 132.1, 132.3, 132.6, 132.7, 137.4, 137.6, 146.4, 149.6, 150.0, 172.4. EI MS m/z (%) 673 (0.3) $[M(^{37}Cl^{35}Cl_2)-C(CH_3)_3]^+$, 671 (0.5) $[M(^{37}Cl^{35}Cl_3)-C(CH_3)_3]^+$, 669 (0.4) $[M(^{35}Cl_4)-C(CH_3)_3]^+$, 629 (0.5), 627 (2), 625 (4), 623 (3), 599 (0.2), 597 (0.5), 595 (0.5), 495 (4), 493 (7), 491 (5), 335 (6), 333 (9), 163 (10), 161 (64), 159 (100). HRMS calcd for $C_{31}H_{33}^{35}Cl_4O_6Si$ $[M-C(CH_3)_3]^+$ 669.0801; found 669.0798. Anal. calcd for $C_{35}H_{42}Cl_4O_6Si$ C 57.70, H 5.81, Cl 19.46; found C 57.69, H 5.64, Cl 19.56.

3.1.11. (2*S*,3*R*,4*S*)-3-[2,3-Bis(3,4-dichlorobenzyloxy)-4-methylphenyl]-2-(*tert*-butyldimethylsilyloxy)-4-methyl-δ-valerolactone (13). To a solution of **12** (120.0 mg, 164.7 μmol) in dry benzene (5 mL) was added $(Ph_3P)_3RhCl$ (15.3 mg, 16.5 μmol) under an argon atmosphere. Hydrogenation then was carried out at 15 bar hydrogen pressure for 4 h. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (5 mL), TFA (63.0 μL, 817.8 μmol) was added and the mixture was stirred for 10 min. Then, the products were concentrated under reduced pressure and separated by flash chromatography on silica gel (EtOAc/petroleum ether, 1:12) to yield **13** (57.5 mg, 52%) and **14** (17.0 mg, 14%) as colourless oils. **13**: R_f=0.36 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{23}$=−34.5 (c 0.001, $CHCl_3$). UV (CH_3CN) λ_{max} ε 217 (27800), 231 (sh, 18740), 272 nm (1490). CD (CH_3CN) λ_{max} $\Delta\varepsilon$ 224 (−3.6), 232 (−0.7), 237 (0), 243 (+0.7), 274 (+0.4) 288 (0), 294 nm (−0.1). IR (KBr) $\tilde{\nu}$ 3470 (w), 3021 (w), 2954 (s), 2982 (s), 2884 (m), 2856 (m), 2737 (w), 1750 (s), 1596 (w), 1564 (w), 1493 (w), 1472 (s), 1429 (m), 1398 (m), 1379 (m), 1360 (m), 1317 (w), 1277 (m), 1254 (s), 1235 (m), 1214 (s), 1195 (m), 1151 (s), 1129 (s), 1067 (s), 1044 (m), 1032 (s), 1004 (m), 940 (w), 875 (m), 839 (s), 817 (s), 781 (s), 758 (s), 687 (w), 668 (w), 639 (w), 584 (w), 558 (w), 536 cm^{-1} (w). ^{1}H NMR (600 MHz, $CDCl_3$) δ −0.23 (s, 3H), 0.00 (s, 3H), 0.77 (s, 9H), 0.88 (d, J=6.7 Hz, 3H), 2.25 (s, 3H), 2.45–2.54 (m, 1H), 3.26 (dd, J=9.2, 5.8 Hz, 1H), 3.99 (dd, J=11.3, 9.4 Hz, 1H), 4.31 (d, J=5.8 Hz, 1H), 4.49 (dd, J=11.3, 5.3 Hz, 1H), 4.74 (d, J=11.3 Hz, 1H), 4.86 (d, J=11.4 Hz, 1H), 4.94 (d, J=11.9 Hz, 1H), 4.98 (d, J=11.9 Hz, 1H), 6.88 (d, J=7.8 Hz, 1H), 6.93 (d, J=7.8 Hz, 1H), 7.10–7.15 (m, 2H), 7.37–7.42 (m, 4H). NOESY (600 MHz, $CDCl_3$, selected correlations) 2-H/5α-H, 2-H/3-H, 3-H/14-H, 3-H/5α-H, 4-H/5β-H, 4-H/11-H, 5α-H/14-H. ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.7, −5.0, 16.0, 16.3, 18.1, 25.6, 31.2, 45.1, 69.8, 72.6, 73.0, 73.9 125.6, 126.0, 126.9, 127.0, 129.5, 129.7, 130.4, 130.5, 130.6, 131.5, 132.1, 132.6, 132.6, 137.4, 137.5, 149.5, 150.0, 171.4 one signal obscured. EI MS m/z (%) 669 (0.2) $[M(^{37}Cl^{35}Cl_3)-CH_3]^+$, 631 (2) $[M(^{37}Cl_3^{35}Cl)-C(CH_3)_3]^+$, 629 (10) $[M(^{37}Cl_2\,^{35}Cl_2)-C(CH_3)_3]^+$, 627 (18) $[M(^{37}Cl^{35}Cl_3)-C(CH_3)_3]^+$, 625 (13) $[M(^{35}Cl_4)-C(CH_3)_3]^+$, 609 (3), 507 (2), 468 (2), 466 (4), 423 (3), 421 (3), 349 (4), 347 (5), 337 (4) 335 (7), 333 (2), 163 (11), 161 (63), 159 (100). HRMS calcd for $C_{29}H_{29}Cl_4O_5Si$ $[M-C(CH_3)_3]^+$ 625.0538; found 625.0549. Anal. calcd for $C_{33}H_{38}Cl_4O_5Si$ C 57.90, H 5.60; found C 57.20, H 5.60.

3.1.12. Ethyl (2*S*,3*R*,4*R*)-3-[2,3-bis(3,4-dichlorobenzyloxy)-4-methylphenyl]-2-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methylpentanoate (14). R_f=0.27 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{23}$=−24.8 (c 0.006, $CHCl_3$). UV (CH_3CN) λ_{max} ε 223 (sh, 128590), 273 nm (8770). IR (KBr) $\tilde{\nu}$ 3467 (w), 2929 (s), 2857 (s), 1747 (m), 1565 (w), 1472 (s), 1398 (m), 1361 (m), 1275 (s), 1252 (s), 1211 (m), 1130 (s), 1064 (m), 1032 (s), 877 (m), 837 (s), 778 (s), 687 cm^{-1} (w). ^{1}H NMR (600 MHz, $CDCl_3$) δ −0.10 (s, 3H), 0.02 (s, 3H), 0.94 (s, 9H), 1.03 (d, J=7.0 Hz, 3H), 1.18 (t, J=7.1 Hz, 3H), 1.87 (s, 1OH), 2.23 (s, 3H), 2.22–2.28 (m, 1H), 3.26 (dd, J=10.8, 4.8 Hz, 1H), 3.46 (dd, J=10.8, 4.7 Hz, 1H), 3.73–3.80 (m, 1H), 4.06–4.17 (m, 2H), 4.37 (d, J=3.9 Hz, 1H), 4.85 (d, J=11.5 Hz, 1H), 4.89 (d, J=11.5 Hz, 1H), 4.93 (d, J=11.1 Hz, 1H), 4.97 (d, J=11.1 Hz, 1H), 6.90 (d, J=8.0 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 7.14 (dd, J=8.1, 1.8 Hz, 1H), 7.27 (dd, J=8.1, 1.8 Hz, 1H), 7.39 (d, J=8.3 Hz, 1H), 7.42 (d, J=8.3 Hz, 1H), 7.44 (d, J=1.7 Hz, 1H), 7.53 (d, J=1.7 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.1, −4.8, 14.1, 15.7, 16.0, 18.3, 25.8, 36.7, 43.6, 60.9, 66.3, 73.1, 73.7, 75.1, 124.9, 126.2, 127.2, 127.4, 129.9, 130.0, 130.4, 130.5, 131.1, 132.1, 132.6, 132.6, 133.2, 137.5, 137.6, 149.5, 149.8, 173.2 one signal obscured. EI MS m/z (%) 671 (0.1) $[M(^{37}Cl^{35}Cl_3)-C(CH_3)_3]^+$, 669 (0.2) $[M(^{35}Cl_4)-C(CH_3)_3]^+$, 657 (0.3), 655 (0.6), 653 (0.4), 631 (1), 629 (6), 627 (11), 625 (7), 601 (0.5), 599 (1), 597 (0.8), 163 (10), 161 (64), 159 (100). HRMS calcd for $C_{31}H_{35}^{37}Cl^{35}Cl_3O_6Si$ $[M-C(CH_3)_3]^+$ 671.0957; found 671.0948. Anal. calcd for $C_{35}H_{44}Cl_4O_6Si$ C 57.54, H 6.07; found C 57.67, H 5.95.

3.1.13. (2*S*,3*R*,4*R*)-3-[2,3-Bis(3,4-dichlorobenzyloxy)-4-methylphenyl]-2-(*tert*-butyldimethylsilyloxy)-4-methyl-δ-valerolactone (15). To **14** (33.0 mg, 45.2 μmol) in CH_2Cl_2 (4 mL) was added TFA (16.0 μL, 207.7 μmol), and the mixture was stirred for 6 h at room temperature. Then, the solvent was removed under reduced pressure and the residue flash chromatographed on silica gel (EtOAc/petroleum ether, 1:10) to yield **15** (24.4 mg, 79%) as a colourless oil. R_f=0.36 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{23}$=−17.9 (c 0.003, $CHCl_3$). UV (CH_3CN) λ_{max} ε 216 (24870), 229 (sh, 16460), 271 nm (1200). CD (CH_3CN) λ_{max} $\Delta\varepsilon$ 223 (+3.0), 226 (0), 228 (−2.7), 233 (0), 240 (+0.6), 273 (+0.2) 284 (0), 293 nm (−0.1). IR (KBr) $\tilde{\nu}$ 3436 (s), 2927 (m), 1746 (m), 1636 (w), 1473 (m), 1398 (w), 1359 (w), 1320 (w), 1297 (m), 1212 (w), 1129 (m), 1065 (m), 1031 (m), 874 (w), 815 (m), 783 (w), 687 cm^{-1} (w). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.13 (s, 3H), 0.74 (s, 9H), 0.77 (d, J=6.7 Hz, 3H), 2.26 (s, 3H), 2.56–2.61 (m, 1H), 3.82–3.94 (m, 1H), 4.00 (dd, J=11.5, 11.5 Hz, 1H), 4.15 (dd, J=11.5, 4.8 Hz, 1H), 4.48 (d, J=6.7 Hz, 1H), 4.77 (d, J=11.9 Hz, 1H), 4.78–4.99 (m, 3H), 6.77 (d, J=7.7 Hz, 1H), 6.93 (d, J=7.7 Hz, 1H), 7.11–7.19 (m, 2H), 7.32–7.46 (m, 4H). NOESY (600 MHz, $CDCl_3$, selected correlations) 2-H/3-H, 3-H/4-H, 4-H/5α-H, 5β-H/14-H, 11-H/14-H. ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.8, −4.6, 13.9, 16.0, 18.2, 25.5, 32.3, 42.6, 70.1, 71.2, 73.0, 73.1, 126.1, 126.9, 128.7,

128.7, 129.6, 129.8, 130.3, 130.5, 131.6, 132.0, 132.0, 132.5, 132.5, 137.3, 137.5, 149.5, 151.3, 174.95 one signal obscured. EI MS *m/z* (%) 684 (<0.1) $[M(^{37}Cl^{35}Cl_3)]^+$, 673 (<0.1), 671 (0.2), 669 (0.4), 667 (0.3), 631 (2), 629 (9), 627 (16), 625 (11), 468 (1), 466 (1), 163 (9), 161 (61), 159 (100). HRMS calcd for $C_{29}H_{29}^{35}Cl_4O_5Si$ $[M-C(CH_3)_3]^+$ 625.0538; found 625.0518.

3.1.14. (2*S*,3*R*,4*S*)-3-[2,3-Bis(3,4-dichlorobenzyloxy)-4-methylphenyl]-2-hydroxy-4-methyl-δ-valerolactone (16). To a solution of **13** (89.7 mg, 131 μmol) in CH_3CN (6.5 mL) was added aqueous HF (40%, 0.35 mL), and the mixture was stirred for 18 h. Then, the solution was concentrated under reduced pressure and the residue partitioned between Et_2O (50 mL) and water (40 mL). The organic layer was washed with water (2×40 mL) and brine (1×40 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether, 1:1) afforded **16** (68.7 mg, 92%) as a colourless oil. R_f=0.10 (EtOAc/petroleum ether, 1:3). $[\alpha]_D^{23}$=+2.3 (*c* 0.002, $CHCl_3$). UV (CH_3CN) λ_{max} ε 223 nm (sh, 123570). CD (CH_3CN) λ_{max} Δε 228 (−1.6), 230 (−0.5), 232 (0), 233 (+1.1), 236 (+0.3), 239 (0), 247 (−0.34) 272 nm (−0.3). IR (KBr) $\tilde{\nu}$ 3458 (m), 3019 (w), 2962 (m), 2928 (m), 1747 (s), 1596 (w), 1564 (w), 1493 (m), 1472 (s), 1428 (m), 1398 (s), 1360 (m), 1319 (w), 1279 (s), 1214 (s), 1162 (w), 1130 (s), 1065 (s), 1032 (s), 875 (w), 816 (m), 793 (w), 757 (s), 688 (w), 667 (w), 637 (w), 591 (w), 536 cm^{-1} (w). ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, *J*=6.8 Hz, 3H), 2.24 (s, 3H), 2.29–2.41 (m, 1H), 2.82 (s, 1OH), 3.79 (dd, *J*=9.5, 7.0 Hz, 1H), 4.13 (dd, *J*=11.6, 11.6 Hz, 1H), 4.33 (dd, *J*=11.6, 5.3 Hz, 1H), 4.63 (d, *J*=9.5 Hz, 1H), 4.81 (d, *J*=11.5 Hz, 1H), 4.90 (d, *J*=11.5 Hz, 1H), 4.97 (s, 2H), 6.75 (d, *J*=8.0 Hz, 1H), 6.94 (dd, *J*=8.0, 0.6 Hz, 1H), 7.12 (dd, *J*=8.2, 2.0 Hz, 1H), 7.18 (dd, *J*=8.2, 2.0 Hz, 1H), 7.38 (d, *J*=8.2 Hz, 1H), 7.39 (d, *J*=8.2 Hz, 1H), 7.40 (d, *J*=1.9 Hz, 1H), 7.47 (d, *J*=1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 16.6, 36.8, 42.9, 66.7, 70.6, 73.0, 73.9, 123.6, 126.7, 126.9, 127.0, 129.5, 129.7, 130.3, 130.4, 130.5, 131.3, 131.9, 132.0, 132.5, 132.5, 137.4, 137.8, 149.6, 150.9, 175.2. EI MS *m/z* (%) 572 (3) $[M(^{37}Cl_2^{35}Cl_2)]^+$, 570 (6) $[M(^{37}Cl^{35}Cl_3)]^+$, 568 (5) $[M(^{35}Cl_4)]^+$, 542 (2), 540 (2), 411 (3), 410 (4), 409 (5), 408 (5), 366 (3), 365 (2), 364 (5), 363 (2), 235 (2), 233 (28), 206 (13), 163 (12), 161 (66), 159 (100). HRMS calcd for $C_{27}H_{24}^{35}Cl_4O_5$ $[M]^+$ 568.0378; found 568.0357.

3.1.15. (+)-Calopin (1a). Palladium on charcoal (10.0 mg, 10% Pd) was added to a solution of **16** (15.0 mg, 26.3 μmol) in dry MeOH (3 mL). Hydrogenation was carried out at 40 bar hydrogen pressure for 2 h. The catalyst was removed by filtration, and the mixture was diluted with Et_2O (75 mL) and washed with water (2×50 mL) and brine (1×50 mL). After the solvent was removed under reduced pressure, the crude product was purified by flash chromatography on RP 18 (CH_3CN/H_2O, 3:2), to yield **1a** (4.5 mg, 68%) as a colourless oil. R_f=0.42 (EtOAc/petroleum ether, 2:1). $[\alpha]_D^{23}$=−15.3 (*c* 0.003, $CHCl_3$); +19.9 (*c* 0.002, MeOH). UV (CH_3CN) λ_{max} ε 210 (7250), 222 (4920), 277 nm (650). CD (CH_3CN) λ_{max} Δε 222 (+2.3), 224 (sh, +0.8), 227 (0), 238 (−0.6), 279 nm (−0.5). IR (KBr) $\tilde{\nu}$ 3369 (s), 3019 (m), 2965 (m), 2928 (m), 1738 (s), 1588 (m), 1470 (s), 1435 (m), 1378 (m), 1359 (m), 1315 (s), 1277 (s), 1216 (s), 1123 (s), 1066 (m), 1042 (m), 1015 (w), 982 (w), 949 (w), 919 (w), 891 (w), 853 (w), 806 (w), 756 (s), 667 (w), 597 (w), 565 (w), 543 cm^{-1} (w). ^1H NMR (600 MHz, $CDCl_3$) δ 1.10 (d, *J*=6.7 Hz, 3H), 2.22 (s, 3H), 2.72–2.80 (m, 1H), 3.52 (dd, *J*=7.6, 5.3 Hz, 1H), 4.02 (dd, *J*=11.6, 11.6 Hz, 1H), 4.51 (dd, *J*=11.6, 6.7 Hz, 1H), 4.71 (d, *J*=7.6 Hz, 1H), 6.53 (d, *J*=7.8 Hz, 1H), 6.71 (d, *J*=7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 17.3, 31.9, 45.0, 69.0, 71.3, 119.3, 123.3, 123.9, 123.9, 141.8, 144.0, 173.9. EI MS *m/z* (%) 253 (14) $[M+H]^+$, 252 (83) $[M]^+$, 234 (6), 207 (17), 206 (100), 191 (25), 177 (56), 164 (12), 163 (16), 161 (16), 159 (28), 149 (14), 147 (10), 145 (13), 137 (76), 136 (17), 131 (15), 124 (5), 121 (11), 91 (20). HRMS calcd for $C_{13}H_{16}O_5$ $[M]^+$ 252.0998; found 252.1002.

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