Synthesis of the α,β-Unsaturated δ-Lactones (+)-Anhydrocalopin and (+)-Dehydrocalopin

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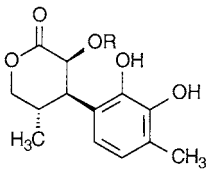
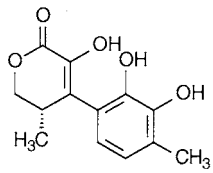
Abstract: During our investigations on the calopin group of mushroom metabolites, a synthesis of 3,4-disubstituted α,β-unsaturated δ-lactones has been developed. It was applied to the synthesis of optically active dehydrocalopin (**2**) and anhydrocalopin (**3**).

Key words: natural products, δ-lactones, cyclizations, epoxides, Horner–Emmons reaction

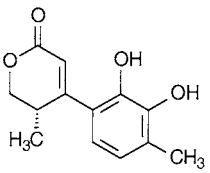
Compounds of the calopin group are responsible for the bitter taste of the mushrooms *Boletus calopus, B. radicans*, and *B. coniferarum*. They represent a new class of natural products possessing a δ-lactone moiety and, in the case of *O*-acetylcalopin (**1a**) and calopin (**1b**) (Figure 1), a rare methylcatechol residue.[1] The absolute configuration of these metabolites has been determined by synthetic studies[2] including the total synthesis of (+)-**1b**.[3]



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



Dehydrocalopin (**2**)

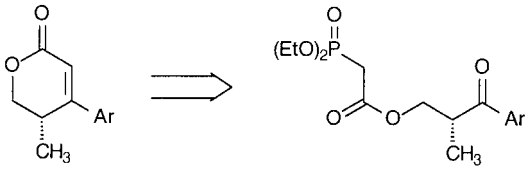


Anhydrocalopin (**3**)

Figure 1 Structures of calopins and synthetic derivatives **2** and **3**

Our interest in the properties of these and related δ-lactones[4] prompted us to synthesize dehydrocalopin (**2**) and anhydrocalopin (**3**), which could not be obtained directly from calopin (**1b**) by selective oxidation or dehydration, respectively. In this communication we describe a strategy for the synthesis of unsaturated calopin derivatives.

Key step in our retrosynthetic planning is the intramolecular Horner–Emmons reaction of phosphonate ester **5**, which should yield the anhydrocalopin system **4** (Scheme 1).



4 **5**

Scheme 1 Retrosynthetic analysis of **4**

In our first synthesis of the phosphonate ester **5**, we started from commercially available 2,3-dimethoxybenzoic acid (**6**) (Scheme 2). Conversion of **6** to the acid chloride followed by treatment with *N*,*O*-dimethylhydroxylamine/Et_3N afforded the Weinreb amide **7** in 85% yield. Reaction of **7** with 2-propenyllithium, prepared by halogen-metal exchange from 2-bromopropene, led to ketone **8** in 94% yield.[5] Epoxidation of **8** with aqueous NaOH and H_2O_2 (95%) followed by regioselective ring cleavage of the resulting oxirane **9** with tributyltin hydride gave the racemic β-hydroxy ketone **10b** in quantitative yield.[6,7]

Despite its high efficiency, the synthesis of **10b** via Weinreb amide **7** is not suitable for the synthesis of optically active compounds. We therefore developed an alternative strategy that commences from 3-methylcatechol. The latter compound was doubly MOM-protected to give **11** (90%),[3] *ortho*-lithiated,[3,8] and coupled with the known optically pure Weinreb amide **12**[9] to afford alcohol **10a** in 47% yield (Scheme 3).

For the synthesis of (+)-anhydrocalopin (**3**) the optically pure building block **10a** was converted to the phosphonate ester **5a** by treatment with the acyl chloride **13**[10] under acidic conditions (91%, Scheme 4). In order to prevent elimination, the intramolecular Horner–Emmons reaction had to be performed under mild conditions. In accordance with the literature,[11,12] ring closure of **5a** with Et_3N in the presence of LiBr produced the lactone **4a** in 38% yield. The low yield may be caused by the lability of the MOM groups under the given reaction conditions. This is supported by the observation that the cyclization of the methyl-protected catechol **5b** (Scheme 4) afforded the lactone

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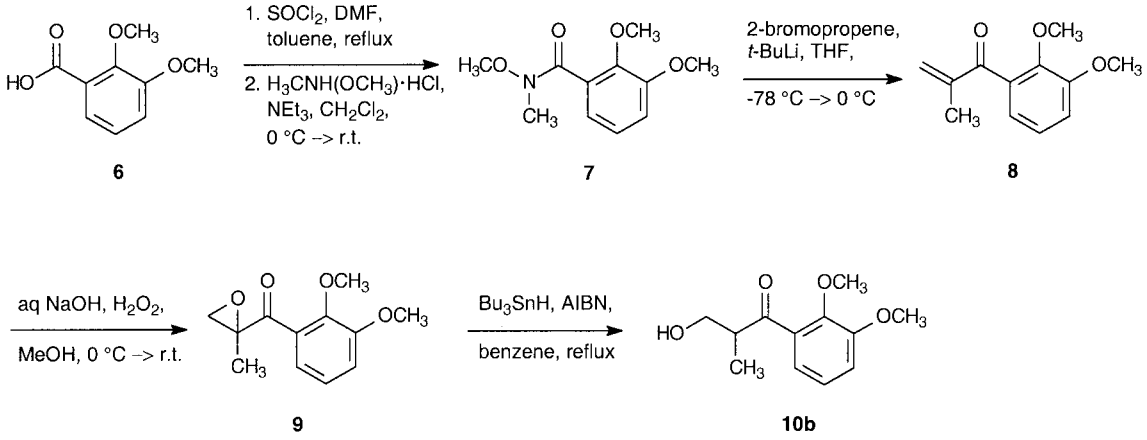
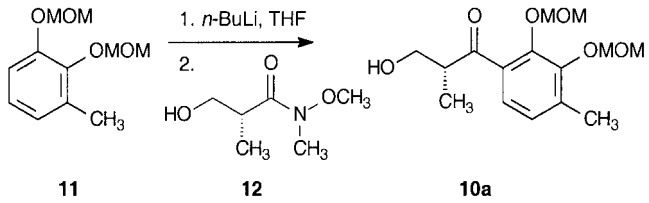
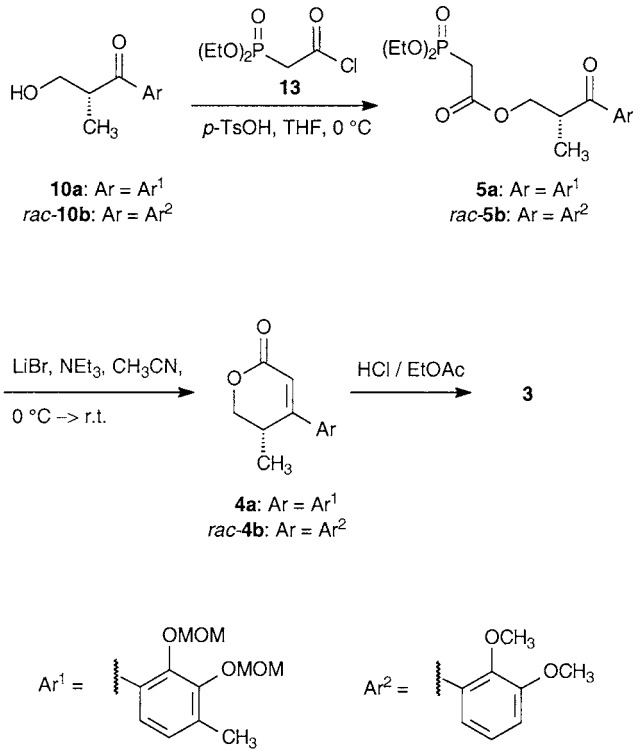


Scheme 2 Synthesis of racemic building block *rac*-**10b**



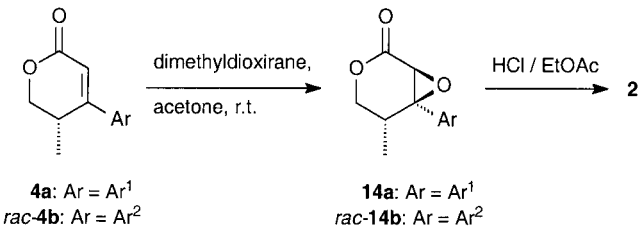
Scheme 3 Chiral pool synthesis of building block **10a**

4b in 63% yield. Deblocking of the optically active lactone **4a** with HCl in EtOAc gave (+)-anhydrocalopin (**3**) in 97% yield. The same sequence of reactions was applied to the racemic building block **10b** to produce racemic demethylanhydrocalopin dimethyl ether (**4b**) (Scheme 4).



Scheme 4 Synthesis of anhydrocalopin (**3**)

In order to prepare dehydrocalopin (**2**), the MOM-protected (+)-anhydrocalopin (**4a**) was treated with dimethyldioxirane[13,14] to give exclusively the oxirane **14a** in 97% yield (Scheme 5). In the same manner, epoxide **14b** was obtained from the racemic analogue **4b**. The steric influence of the γ-methyl group is responsible for the selective formation of the *anti*-diastereomer. The relative configuration of the products was confirmed by a single-crystal X-ray diffraction analysis of **14b** (Figure 2). A comparison of the ^{1}H NMR data as well as NOESY experiments proved that both oxiranes **14a**,**b** have the same configuration. Treatment of **14a** with HCl in EtOAc induced rearrangement and deprotection to deliver (+)-dehydrocalopin (**2**) (97%).



Scheme 5 Synthesis of dehydrocalopin (**2**)

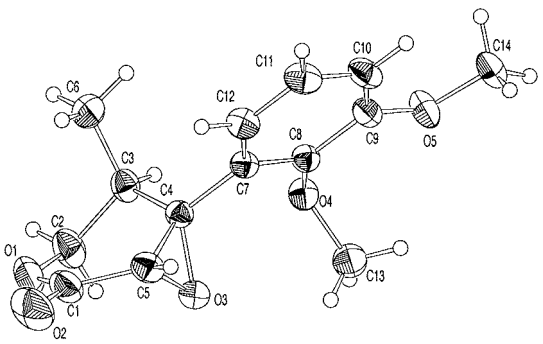


Figure 2 X-ray structure of **14b**

Reductive ring opening of epoxide **14a** with palladium on charcoal and subsequent deprotection of the catechol with HCl in EtOAc yielded only traces of calopin (**1b**) that

were detected by mass spectroscopy and HPLC comparison with the natural product.

All solvents were distilled before use. Petroleum ether (PE, 40–60 °C) was used for chromatography. The reactions were monitored by TLC prior to workup. Solvents were removed from the reaction mixtures at 40 °C using a rotavapor. TLC was run on silica gel plates 60 F_{254} (Merck) and visualized with UV fluorescence (254 and 366 nm). Flash chromatography was performed on silica gel 60 (40–63 μm, Merck). Mps were determined with a Büchi SMP 535 apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 spectrometer. UV/Vis spectra were measured with a Perkin–Elmer Lambda 16 spectrometer. CD spectra were measured with a S. A. Jobin Yvon CD-6-Dichrograph. All IR spectra were measured as KBr pellets using a Perkin–Elmer Spectrum 1000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury 200, Bruker ARX 300, and AMX 600 instruments. Chemical shifts are given as δ values from solvent peak or internal TMS. The mass spectra were recorded at 70 eV on Finnigan MAT 90 and MAT 95 Q instruments. 3-Methylcatechol was purchased from Aldrich. Elemental analyses were carried out by the Microanalytical Laboratory of the Department Chemie, Universität München.

2,3,*N*-Trimethoxy-*N*-methylbenzamide (7)

To a suspension of 2,3-dimethoxybenzoic acid (**6**; 9.10 g, 50.0 mmol) in toluene (20 mL) were added DMF (5 drops) and $SOCl_2$ (5.50 mL, 75.4 mmol), and the mixture was heated to 60 °C for 50 min. The mixture was cooled to r.t. and concentrated under reduced pressure. The resulting acid chloride was dissolved in CH_2Cl_2 (50 mL), and *N*,*O*-dimethylhydroxylamine hydrochloride (4.88 g, 50.0 mmol) was added at 0 °C. Then, a solution of Et_3N (14.6 mL, 104.8 mmol) in CH_2Cl_2 (10 mL) and a catalytic amount of 4-dimethylaminopyridine (DMAP) were added, and the reaction mixture was stirred at r.t. overnight. After dilution with EtOAc (400 mL), the solution was subsequently washed with aq HCl (2 N, 3 × 200 mL), sat. aq $NaHCO_3$ (3 × 200 mL), and brine (200 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography on silica gel with EtOAc–PE (1:5 → 1:2) yielded **7** (9.62 g, 85% over 2 steps) as a colorless solid; mp 57 °C.

IR (KBr): 2970 (m), 2938 (m), 2837 (w), 1655 (s), 1599 (w), 1582 (m), 1480 (s), 1427 (s), 1381 (s), 1304 (m), 1268 (s), 1230 (s), 1173 (m), 1102 (w), 1085 (m), 1051 (s), 1003 (s), 923 (w), 837 (w), 796 (m), 785 (w), 752 (m), 734 (w), 683 (w), 617 (w), 569 (w), 536 (w), 474 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 3.33 (br s, 3 H), 3.50 (s, br, 3 H), 3.88 (s, 6 H), 6.87 (dd, *J* = 7.6, 1.1 Hz, 1 H), 6.95 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.08 (dd, *J* = 8.1, 7.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 32.2 (br), 55.9, 61.1, 61.6, 113.4, 119.1, 124.1 (br), 130.7, 145.5, 152.6, 169.0.

EI-MS: *m*/*z* (%) = 225 (1, [M^+]), 195 (1), 165 (100), 122 (11).

HRMS: *m*/*z* calcd for $C_{11}H_{15}NO_4$: 225.1001; found: 225.1000.

UV/Vis (MeCN): λ_{max} (ε) = 201 (33600), 222 (sh, 11470), 278 nm (2190).

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N 6.22. Found: C, 58.49; H, 6.75; N, 6.20.

1-(2,3-Dimethoxyphenyl)-2-methylprop-2-en-1-one (8)

To a solution of 2-bromopropene (1.97 mL, 22.2 mmol) in anhyd THF (5 mL) was added *t*-BuLi (1.7 M in pentane, 13.10 mL, 22.3 mmol) at –78 °C, and the mixture was stirred for 10 min. Then, this suspension was added to a solution of **7** (1.00 g, 4.44 mmol) in anhyd THF (5 mL) at 0 °C and stirred for 90 min at 0 °C and for 1 h at r.t. The reaction was quenched by the addition of sat. aq NH_4Cl (100 mL), and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash chromatography on silica gel with EtOAc–PE (1:20) yielded **8** (858 mg, 94%) as a colorless liquid.

IR (KBr): 3310 (w), 3088 (w), 2937 (m), 2838 (m), 1666 (s), 1629 (w), 1580 (m), 1477 (s), 1426 (s), 1372 (w), 1333 (s), 1301 (m), 1268 (s), 1230 (s), 1179 (m), 1149 (w), 1086 (m), 1024 (s), 1004 (s), 987 (m), 942 (w), 883 (w), 847 (m), 788 (m), 769 (m), 752 (m), 674 (w), 658 (w), 604 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 2.03 (s, 3 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 5.62 (s, 1 H), 5.94 (s, 1 H), 6.80 (dd, *J* = 7.4, 1.7 Hz, 1 H), 6.97 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.06 (dd, *J* = 8.2, 7.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 17.1, 55.9, 61.6, 113.9, 120.0, 123.7, 129.4, 134.6, 145.1, 146.5, 152.7, 198.2.

EI-MS: *m*/*z* (%) = 207 (10, [M^+ + H]), 206 (76) [M^+], 191 (6), 175 (12), 165 (100), 151 (12), 122 (19).

HRMS: *m*/*z* calcd for $C_{12}H_{14}O_3$: 206.0943; found: 206.0953.

UV/Vis (MeCN): λ_{max} (ε) = 219 (17480), 255 nm (sh, 3030).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.83; H, 7.12.

(*rac*)-(2,3-Dimethoxyphenyl) (2-Methyl-2-oxiranyl)methanone (9)

To a solution of **8** (1.03 g, 5.0 mmol) in MeOH (50 mL) were added NaOH (2 M, 0.25 mL, 0.5 mmol) and aq H_2O_2 (30%, 0.66 mL, 6.5 mmol) at 0 °C, and the mixture was stirred overnight. Sat. aq NH_4Cl (5 mL) was added, and the mixture was concentrated under reduced pressure. After the addition of H_2O (50 mL) and extraction with EtOAc (3 × 50 mL), the combined organic layers were dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography on silica gel with CH_2Cl_2–acetone (200:1) to yield **9** (1.06 g, 95%) as a colorless liquid.

IR (KBr): 2982 (m), 2940 (m), 2838 (w), 1696 (s), 1581 (m), 1478 (s), 1443 (m), 1427 (s), 1380 (w), 1322 (m), 1269 (s), 1225 (s), 1178 (m), 1147 (w), 1086 (m), 1020 (s), 1002 (s), 972 (m), 920 (w), 864 (w), 843 (w), 793 (m), 752 (m), 669 (w), 603 (w), 569 (w), 543 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.65 (s, 3 H), 2.86 (s, 2 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 6.90 (dd, *J* = 7.2, 2.0 Hz, 1 H), 7.00 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.06 (dd, *J* = 8.2, 7.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 17.2, 52.5, 55.9, 60.1, 61.6, 115.1, 119.8, 123.8, 131.7, 147.1, 152.4, 203.0.

EI-MS: *m*/*z* (%) = 223 (5, [M^+ + H]), 222 (52, [M^+]), 191 (1), 177 (3), 165 (100), 150 (8), 122 (28).

HRMS: *m*/*z* calcd for $C_{12}H_{14}O_4$: 222.0892; found: 222.0889.

UV/Vis (MeCN): λ_{max} (ε) = 218 (14570), 250 (3410), 283 nm (1620).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.89; H, 6.36.

(*rac*)-3-Hydroxy-1-(2,3-dimethoxyphenyl)-2-methylpropan-1-one (10b)

A mixture of **9** (510 mg, 2.3 mmol), AIBN (37 mg, 225 μmol) and tributyltin hydride (0.72 mL, 2.7 mmol) in anhyd benzene (15 mL) was refluxed for 45 min. The mixture was cooled to r.t., and the solvent was removed under reduced pressure. Flash chromatography on silica gel with EtOAc–PE (1:3) gave **10b** (510 mg, 99%) as a colorless liquid.

IR (KBr): 3437 (br, s), 3079 (w), 2937 (s), 2876 (m), 2838 (m), 1681 (s), 1579 (s), 1475 (s), 1426 (s), 1371 (m), 1307 (s), 1266 (s),

1187 (m), 1075 (m), 991 (s), 879 (w), 836 (w), 799 (m), 753 (m), 693 (w), 644 (w), 567 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.16 (d, *J* = 7.3 Hz, 3 H), 2.31 (t, *J* = 6.4 Hz, 1 H, OH), 3.47−3.58 (m, 1 H), 3.75−3.86 (m, 2 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 7.02−7.13 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 13.5, 47.9, 56.0, 61.8, 64.6, 115.4, 120.4, 124.3, 134.0, 147.4, 152.9, 207.9.

EI-MS: *m*/*z* (%) = 224 (2, $[M^+]$), 206 (4), 194 (8), 165 (100), 150 (5), 122 (13).

HRMS: *m*/*z* calcd for $C_{12}H_{16}O_4$: 224.1049; found: 224.1049.

UV/Vis (MeCN): λ_{max} (ε) = 221 (sh, 20900), 264 nm (4050).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.33.

(2*R*)-1-[2,3-Bis(methoxymethoxy)-4-methylphenyl]-3-hydroxy-2-methylpropan-1-one (10a)

To a solution of **11**[3] (5.77 g, 27.2 mmol) in anhyd THF (35 mL) was added BuLi (2.5 M solution in hexanes, 11.1 mL, 27.8 mmol) at 0 °C. The mixture was stirred for 2 h at r.t. and cooled to 0 °C again. The resulting red suspension was added to a pre-cooled (0 °C) solution of **12**[9] (1.00 g, 6.8 mmol) in anhyd THF (6.5 mL) and stirred for 30 min. Then, the mixture was warmed to r.t. and stirred for another 15 h. The reaction was quenched by the addition of aq $KHSO_4$ (1.1 M, 30 mL), diluted with sat. aq NH_4Cl (200 mL), and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography on silica gel with EtOAc–PE (1:8 → 1:2) gave **10a** (0.96 g, 47%) as a colorless liquid, together with **11** (3.57 g); $[\alpha]_D^{23}$ +0.1 (*c* = 0.048, $CHCl_3$).

IR (KBr): 3469 (br, w), 2936 (m), 1683 (s), 1601 (m), 1455 (m), 1426 (m), 1389 (m), 1251 (s), 1207 (m), 1159 (s), 1083 (s), 964 (s), 924 (s), 824 (w), 787 (w), 756 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.14 (d, *J* = 7.2 Hz, 3 H), 2.35 (s, 3 H), 2.49–2.56 (m, 1 H), 3.46 (s, 3 H), 3.60 (s, 3 H), 3.73–3.79 (m, 1 H), 3.82–3.89 (m, 1 H), 5.08 (s, 2 H), 5.12 (s, 2 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 13.8, 16.9, 47.2, 57.7, 58.0, 64.7, 99.4, 100.2, 124.3, 126.6, 132.8, 137.4, 148.2, 149.1, 206.6.

EI-MS: *m*/*z* (%) = 298 (2, $[M^+]$), 222 (1), 192 (37), 163 (38), 150 (16), 45 (100).

HRMS: *m*/*z* calcd for $C_{15}H_{22}O_6$: 298.1416; found: 298.1417.

UV/Vis (MeCN): λ_{max} (ε) = 214 (18460), 250 (6690), 291 nm (970).

Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.60; H, 7.57.

(2*R*)-3-[2,3-Bis(methoxymethoxy)-4-methylphenyl]-2-methyl-3-oxopropyl (Diethoxyphosphinyl)acetate (5a); Typical Procedure

To a solution of **10a** (940 mg, 3.14 mmol) in anhyd THF (13 mL) were added a solution of freshly prepared (diethylphosphinyl)acetyl chloride (**13**;[10] 1.35 g, 6.28 mmol) in anhyd THF (5 mL) and a catalytic amount of *p*-toluenesulfonic acid at 0 °C. After stirring for 2 h at 0 °C followed by the addition of sat. aq NH_4Cl (100 mL), the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Flash chromatography on silica gel with EtOAc–PE (10:1) yielded **5a** (1.37 g, 91%) as a colorless liquid; $[\alpha]_D^{23}$ +9.5 (*c* = 0.051, $CHCl_3$).

IR (KBr): 3470 (br, w), 2982 (m), 2936 (m), 1739 (s), 1687 (m), 1600 (w), 1456 (m), 1427 (m), 1390 (m), 1265 (s), 1208 (m), 1160 (s), 1054 (s), 1025 (s), 965 (s), 827 (w), 786 (w), 614 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.19 (d, *J* = 7.2 Hz, 3 H), 1.33 (t, *J* = 7.0 Hz, 6 H), 2.35 (s, 3 H), 2.91 (d, *J* = 21.6 Hz, 2 H), 3.45 (s, 3 H), 3.60 (s, 3 H), 3.76−3.88 (m, 1 H), 4.09−4.17 (m, 4 H), 4.20 (dd, *J* = 11.1, 6.2 Hz, 1 H), 4.47 (dd, *J* = 11.1, 6.6 Hz, 1 H), 5.06 (d, *J* = 5.8 Hz, 1 H), 5.09 (d, *J* = 5.8 Hz, 1 H), 5.12 (s, 2 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 14.0, 16.3 (d, *J* = 6.2 Hz, CH_3), 17.0, 34.2 (d, *J* = 134.7 Hz, PCH_2), 44.2, 57.7, 58.0, 62.7 (d, *J* = 6.2 Hz, CH_2), 62.7 (d, *J* = 6.2 Hz, CH_2), 66.7, 99.5, 100.2, 124.5, 126.6, 132.4, 137.6, 148.2, 149.0, 165.7 (d, *J* = 5.9 Hz, CO_2), 203.1.

EI-MS: *m*/*z* (%) = 476 (9, $[M^+]$), 431 (10), 400 (36), 399 (100), 385 (27), 371 (6), 285 (15), 204 (55), 197 (67), 191 (28), 183 (21), 179 (77), 163 (83), 151 (24), 137 (15), 123 (16), 45 (99).

HRMS: *m*/*z* calcd for $C_{21}H_{33}O_{10}P$: 476.1811; found: 476.1772.

UV/Vis (MeCN): λ_{max} (ε) = 214 (21190), 251 (8950), 292 nm (2300).

Anal. Calcd for $C_{21}H_{33}O_{10}P$: C, 52.94; H, 6.98. Found: C, 52.81; H, 7.03.

(*rac*)-3-(2,3-Dimethoxyphenyl)-2-methyl-3-oxopropyl (Diethoxyphosphinyl)acetate (5b)

Prepared as described above from **10b** (2.00 g, 8.9 mmol), freshly prepared (diethylphosphinyl)acetyl chloride (**13**;[10] 3.83 g, 17.8 mmol), and a catalytic amount of *p*-toluenesulfonic acid. Flash chromatography of the crude product on silica gel with EtOAc–PE (2:1) afforded **5b** (3.30 g, 92%) as a colorless liquid.

IR (KBr): 3471 (w), 2983 (m), 2939 (m), 2840 (w), 1738 (s), 1693 (m), 1579 (m), 1476 (s), 1427 (m), 1392 (w), 1369 (w), 1267 (s), 1164 (w), 1118 (m), 1095 (m), 1051 (s), 1026 (s), 973 (s), 839 (w), 800 (w), 754 (w), 615 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.20 (d, *J* = 7.1 Hz, 3 H), 1.32 (t, *J* = 7.1 Hz, 6 H), 2.92 (d, *J* = 21.6 Hz, 2 H), 3.68−3.79 (m, 1 H), 3.89 (s, 3 H), 3.89 (s, 3 H), 4.09−4.19 (m, 4 H), 4.23 (dd, *J* = 10.9, 5.9 Hz, 1 H), 4.46 (dd, *J* = 10.9, 7.0 Hz, 1 H), 7.02−7.13 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 13.8, 16.3 (d, *J* = 6.2 Hz), 34.2 (d, *J* = 134.4 Hz, PCH_2), 44.8, 56.0, 61.7, 62.7 (d, *J* = 6.1 Hz, CH_2), 62.7 (d, *J* = 6.4 Hz, CH_2), 66.7, 115.6, 120.7, 124.2, 133.7, 147.6, 152.9, 165.7 (d, *J* = 6.2 Hz, CO_2), 204.3.

EI-MS: *m*/*z* (%) = 402 (3, $[M^+]$), 206 (10), 165 (100), 151 (5), 122 (5).

HRMS: *m*/*z* calcd for $C_{18}H_{27}O_8P$: 402.1444; found: 402.1432.

UV/Vis (MeCN): λ_{max} (ε) = 216 (19880), 247 (5320), 298 nm (2230).

Anal. Calcd for $C_{18}H_{27}O_8P$: C, 53.73; H, 6.76. Found: C, 53.70; H, 6.84.

(4*S*)-3-[2,3-Bis(methoxymethoxy-4-methylphenyl]-4-methyl-2,3-didehydro-δ-valerolactone (4a)

Et_3N (0.42 mL, 3.00 mmol) was added to a stirred solution of **5a** (1.30 g, 2.73 mmol) and LiBr (710 mg, 8.18 mmol) in anhyd MeCN (50 mL) at 0 °C, and the stirring was continued for 9 h. After the addition of Et_3N (0.21 mL, 1.50 mmol), the mixture was warmed to r.t. overnight. Sat. aq NH_4Cl (200 mL) was then added followed by extraction of the mixture with EtOAc (3 × 250 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography on silica gel with EtOAc–PE (1:2) yielded **4a** (336 mg, 38%) as a colorless liquid together with elimination product (200 mg, 26%) and alcohol **10a** (117 mg, 14%); $[\alpha]_D^{29}$ +280.2 (*c* = 0.003, $CHCl_3$).

IR (KBr): 3522 (w), 2966 (m), 2933 (m), 2829 (w), 1715 (s), 1620 (w), 1454 (m), 1427 (m), 1391 (m), 1348 (w), 1306 (w), 1286 (m), 1265 (s), 1223 (s), 1159 (s), 1083 (s), 1062 (s), 1014 (m), 966 (s), 925 (s), 826 (w), 813 (w), 784 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.08 (d, *J* = 7.1 Hz, 3 H), 2.34 (s, 3 H), 3.14−3.27 (m, 1 H), 3.46 (s, 3 H), 3.60 (s, 3 H), 4.23 (dd, *J* = 11.1, 5.0 Hz, 1 H), 4.54 (dd, *J* = 11.1, 4.2 Hz, 1 H), 5.04 (s, 2 H), 5.10 (s, 2 H), 6.09 (s, 1 H), 6.88 (d, *J* = 7.9 Hz, 1 H), 6.98 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 15.5, 16.7, 32.1, 57.7, 57.9, 72.0, 99.3, 99.5, 117.9, 124.2, 126.7, 130.3, 135.0, 147.3, 149.1, 161.7, 164.7.

EI-MS: *m*/*z* (%) = 322 (17, [M^+]), 307 (11), 291 (1), 277 (19), 246 (35).

HRMS: *m*/*z* calcd for $C_{17}H_{22}O_6$: 322.1416; found: 322.1419.

UV/Vis (MeCN): λ_{max} (ε) = 214 (19320), 271 nm (9550).

CD (MeCN): λ_{max} (Δε) = 217 (–2.6), 224 (–2.0), 230 (–0.2), 232 (0), 234 (+0.5), 257 (+3.1), 292 nm (+4.7).

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.52; H, 6.75.

(*rac*)-3-(2,3-Dimethoxyphenyl)-4-methyl-2,3-didehydro-δ-valerolactone (4b)

Prepared as described above from **5b** (990 mg, 2.46 mmol), LiBr (432 mg, 4.97 mmol), and Et_3N (0.55 mL, 3.96 mmol). Flash chromatography on silica gel with EtOAc–PE (1:2) yielded **4b** (388 mg, 63%) as a colorless solid; mp 53−54 °C, together with elimination product **8** (151 mg, 29%) and alcohol **10b** (17 mg, 3%).

IR (KBr): 3430 (m), 2968 (m), 2934 (m), 2839 (w), 1718 (s), 1617 (w), 1575 (m), 1471 (s), 1426 (m), 1401 (m), 1375 (w), 1349 (w), 1306 (m), 1262 (s), 1229 (s), 1170 (w), 1135 (w), 1095 (s), 1063 (m), 1001 (s), 959 (w), 898 (w), 882 (w), 794 (m), 753 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.08 (d, *J* = 7.1 Hz, 3 H), 3.11−3.21 (m, 1 H), 3.79 (s, 3 H), 3.90 (s, 3 H), 4.24 (dd, *J* = 11.1, 5.0 Hz, 1 H), 4.56 (dd, *J* = 11.1, 4.2 Hz, 1 H), 6.04 (s, 1 H), 6.77 (dd, *J* = 7.7, 1.2 Hz, 1 H), 6.98 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.09 (dd, *J* = 8.1, 7.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 15.5, 32.3, 55.9, 61.1, 72.2, 113.6, 117.8, 120.9, 124.5, 131.8, 146.3, 152.9, 162.3, 164.7.

EI-MS: *m*/*z* (%) = 248 (100) [M^+], 230 (7), 217 (13), 203 (9), 189 (19).

HRMS: *m*/*z* calcd for $C_{14}H_{16}O_4$: 248.1049; found: 248.1043.

UV/Vis (MeCN): λ_{max} (ε) = 222 (53290), 263 nm (26330).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.68; H, 6.42.

(4*S*)-3-[2,3-Dihydroxy-4-methylphenyl]-4-methyl-2,3-didehydro-δ-valerolactone (Anhydrocalopin, 3)

Compound **4a** (4.5 mg, 13.9 μmol) was dissolved in a sat. solution of HCl in EtOAc (0.7 mL) and stirred for 30 min at r.t. Removal of the solvent under reduced pressure afforded spectroscopically pure **3** (3.2 mg, 97%) as a colorless solid; mp 152−153 °C (dec.); $[\alpha]_D^{30}$ +88.5 (*c* = 0.002, $CHCl_3$).

IR (KBr): 3454 (m), 3194 (m), 2970 (m), 2930 (w), 2560 (w), 2373 (w), 1667 (s), 1614 (s), 1595 (s), 1466 (s), 1409 (m), 1376 (m), 1354 (m), 1309 (m), 1296 (m), 1269 (s), 1219 (s), 1132 (m), 1088 (m), 1061 (m), 1006 (m), 889 (m), 804 (m), 760 (w), 735 (w), 707 (w) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$, TMS): δ = 1.17 (d, *J* = 7.1 Hz, 3 H), 2.29 (s, 3 H), 3.14−3.20 (m, 1 H), 4.27 (dd, *J* = 10.6, 3.1 Hz, 1 H), 4.57 (dd, *J* = 10.6, 2.7 Hz, 1 H), 5.25 (s, 1 OH), 6.10 (s, 1 OH), 6.22 (s, 1 H), 6.73 ('s', 2 H).

^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 15.7, 16.0, 31.8, 72.1, 116.9, 120.1, 121.3, 122.2, 125.9, 142.0, 142.2, 160.9, 165.4.

EI-MS: *m*/*z* (%) = 234 (25, [M^+]), 216 (48), 201 (22), 190 (61), 175 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{14}O_4$: 234.0892; found: 234.0885.

UV/Vis (MeCN): λ_{max} (ε) = 219 (14880), 283 nm (11720).

CD (MeCN): λ_{max} (Δε) = 218 (–1.1), 220 (–1.1), 226 (0), 227 (+0.1), 235 (+0.4), 259 (+1.3), 273 (sh, +0.2), 277 (0), 280 (–0.2), 283 (0), 287 (+0.3), 308 nm (+2.0).

(2*S*,3*R*,4*R*)-3-[2,3-Bis(methoxymethoxy-4-methylphenyl]-2,3-epoxy-4-methyl-δ-valerolactone (14a)

Compound **4a** (238 mg, 740 μmol) was dissolved in dimethyldioxirane[14] (0.1 M solution in acetone, 22.0 mL, 2.2 mmol) and stirred for 18 h at r.t. Then, the solution was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel with EtOAc–PE (1:4) to yield **14a** (242 mg, 97%) as a colorless liquid; $[\alpha]_D^{29}$ –6.2 (*c* = 0.003, $CHCl_3$).

IR (KBr): 3624 (w), 3470 (w), 2971 (m), 2830 (w), 1747 (s), 1607 (w), 1455 (s), 1429 (m), 1392 (s), 1318 (w), 1266 (s), 1232 (m), 1210 (m), 1160 (s), 1061 (s), 1005 (m), 964 (s), 927 (s), 869 (m), 811 (m), 782 (w), 718 (w), 570 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.06 (d, *J* = 7.2 Hz, 3 H), 2.33 (s, 3 H), 2.84−2.96 (m, 1 H), 3.60 (s, 3 H), 3.61 (s, 3 H), 3.83 (s, 1 H), 4.01 (d, *J* = 10.8 Hz, 1 H), 4.77 (dd, *J* = 10.8, 3.1 Hz, 1 H), 5.08 (d, *J* = 6.0 Hz, 1 H), 5.11 (d, *J* = 6.0 Hz, 1 H), 5.12 (d, *J* = 5.1 Hz, 1 H), 5.18 (d, *J* = 5.1 Hz, 1 H), 6.91 (d, *J* = 7.9 Hz, 1 H), 6.95 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 13.8, 16.7, 33.0, 54.4, 57.7, 58.0, 66.3, 69.6, 99.2, 99.8, 124.9, 126.2, 126.9, 135.0, 149.1, 149.1, 167.8.

EI-MS: *m*/*z* (%) = 338 (1, [M^+]), 322 (1), 262 (3), 246 (5), 234 (9), 232 (12), 219 (7), 218 (6), 188 (20), 45 (100).

HRMS: *m*/*z* calcd for $C_{17}H_{22}O_7$: 338.1366; found: 338.1364.

UV/Vis (MeCN): λ_{max} (ε) = 202 (4511090), 220 (sh, 10260), 271 nm (1090).

CD (MeCN): λ_{max} (Δε) = 218 (0), 221 (+4.1), 224 (sh, +2.9), 228 (0), 233 (–3.9), 266 (0), 274 nm (+0.2).

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55. Found: C, 60.49; H, 6.63.

(*rac*-2*S*,3*R*,4*R*)-3-(2,3-Dimethoxyphenyl)-2,3-epoxy-4-methyl-δ-valerolactone (14b)

Prepared as described above from **4b** (300 mg, 1.21 mmol) and dimethyldioxirane[14] (0.1 M solution in acetone, 36.0 mL, 3.6 mmol). Purification by flash chromatography on silica gel with EtOAc–PE (1:4) yielded **14b** (300 mg, 94%, 98% related to recovered **4b**) as a colorless solid; mp 82−83 °C, together with recovered starting material **4b** (13 mg, 4%).

IR (KBr): 3462 (m), 2972 (m), 2942 (m), 1741 (s), 1584 (w), 1479 (s), 1412 (m), 1378 (w), 1320 (m), 1304 (m), 1282 (m), 1264 (s), 1229 (m), 1185 (w), 1106 (m), 1076 (m), 1062 (s), 1005 (s), 956 (w), 867 (w), 823 (m), 792 (m), 755 (m) cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$, TMS): δ = 1.04 (d, *J* = 7.3 Hz, 3 H), 2.81−2.85 (m, 1 H), 3.77 (s, 1 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 4.00 (d, *J* = 10.7 Hz, 1 H), 4.80 (dd, *J* = 10.7, 3.0 Hz, 1 H), 6.82 (d, *J* = 7.5 Hz, 1 H), 6.97 (d, *J* = 8.2 Hz, 1 H), 7.06 (dd, *J* = 8.2, 7.5 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ = 13.8, 33.0, 54.4, 55.8, 61.3, 66.4, 69.7, 113.6, 121.3, 124.1, 128.7, 148.5, 153.0, 167.9.

EI-MS: *m*/*z* (%) = 264 (40, [M^+]), 207 (100), 165 (40).

HRMS: *m*/*z* calcd for $C_{14}H_{16}O_5$: 264.0998; found: 264.0997.

UV/Vis (MeCN): λ_{max} (ε) = 201 (41110), 220 (sh, 5590), 279 nm (1010).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.68; H, 6.12.

(4*S*)-3-[2,3-Dihydroxy-4-methylphenyl]-2-hydroxy-4-methyl-2,3-didehydro-δ-valerolactone (Dehydrocalopin, 2)

Compound **14a** (25 mg, 73.9 μmol) was dissolved in a sat. solution of HCl in EtOAc (1.5 mL) and stirred for 30 min at r.t. After concentration of the reaction mixture under reduced pressure, the residue was purified by flash chromatography on reversed phase (RP-18) with MeOH–H_2O (3:2) to afford **2** (18 mg, 97%) as a colorless foam; $[\alpha]_D^{30}$ +54.9 (*c* = 0.003, $CHCl_3$).

IR (KBr): 3418 (s), 2971 (m), 2930 (m), 1713 (s), 1694 (s), 1626 (w), 1574 (w), 1463 (s), 1415 (m), 1353 (s), 1260 (s), 1189 (s), 1112 (w), 1096 (w), 1037 (w), 1020 (w), 1007 (m), 949 (w), 911 (m), 824 (w), 800 (w), 782 (m), 755 (m), 732 (m), 650 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.17 (d, *J* = 7.0 Hz, 3 H), 2.29 (s, 3 H), 3.02−3.13 (m, 1 H), 4.33 (dd, *J* = 11.1, 3.0 Hz, 1 H), 4.64 (dd, *J* = 11.1, 3.6 Hz, 1 H), 6.12 (s, 1 OH), 6.68 (d, *J* = 8.1 Hz, 1 H), 6.81 (d, *J* = 8.1 Hz, 1 H), 6.99 (br s, 2 OH).

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 15.6, 17.0, 33.0, 72.8, 117.8, 119.4, 123.6, 125.8, 128.2, 132.1, 141.2, 145.4, 164.0.

EI-MS: *m*/*z* (%) = 250 (100, $[M^+]$), 232 (5), 222 (3), 205 (30), 204 (32), 189 (11), 177 (34), 176 (23), 175 (21), 164 (18), 161 (38), 159 (43).

HRMS: *m*/*z* calcd for $C_{13}H_{14}O_5$: 250.0841; found: 250.0833.

UV/Vis (MeCN): λ_{max} (ε) = 202 (23360), 285 nm (9220).

CD (MeCN): λ_{max} (Δε) = 222 (–4.1), 241 (–2.4), 254 (0), 277 (+6.8), 294 (+3.3), 339 nm (+0.2).

Crystallographic Data

The single-crystal X-ray diffraction experiment was carried out with a Nonius MACH 3, four-circle, computer-controlled, single-crystal diffractometer. The structure was solved by direct methods and refined by full-matrix least squares against F^2 of all data, using SHELXS-86 and SHELXL-93 software.[15,16] Crystal data and measurement conditions for compound **14b**: Formula: $C_{14}H_{16}O_5$; Formula mass: 264.27; Crystal size: 0.13 × 0.47 × 0.53 mm; Crystal system: monoclinic; Space group: $P2_1/n$; Lattice parameters: *a* = 8.8020(7) Å, *b* = 8.0244(10) Å, *c* = 18.903(3) Å, β = 97.142(9)°; V = 1324.8(3) $Å^3$; *Z* = 4; D_{calcd} 1.325 g/cm^3; F(000) 560; μ: 0.101 mm-1; Radiation type: Mo-K_α, λ = 0.71073 Å; $2\theta_{max}$ = 48.0°; h_{min}/h_{max} = –9/10, k_{min}/k_{max} = 0/9, l_{min}/l_{max} = –21/0; No. of measured reflections: 2136, No. of unique reflections: 2071, No. of observed reflections: 1594 [$I > 2\sigma(I)$]. Final *R*-values for data with $I > 2\sigma(I)$ *R*1 = 0.0439, *wR*2 = 0.1169, and *R*1 = 0.0613, *wR*2 = 0.1315 for all data and 175 variables. Goodness-of-fit: 1.126.[17]

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(17) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-195296. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].