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The absolute configuration of the mushroom metabolites involutin and chamonixin

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Dedicated to Professor Peter Welzel on the occasion of his 65th birthday

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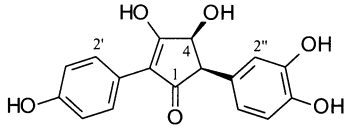
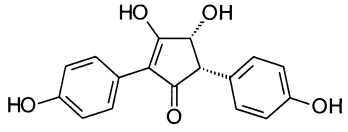
Abstract—The absolute configurations of the cyclopentanoid fungal metabolites involutin (**1**) and chamonixin (**2**) have been determined by application of the high-field ^{1}H NMR variant of Mosher's method. The experimental results are supported by quantum chemical calculations.

1. Introduction

2,5-Diarylcyclopentenones are characteristic constituents of certain mushrooms of the order Boletales (Basidiomycetes).[1,2] Typical examples are (−)-involutin (**1**)[3,4,5] and (+)-chamonixin (**2**),[6] which are responsible for the conspicuous brown and blue color reactions observed when the fruit bodies of *Paxillus involutus* and *Chamonixia caespitosa* are bruised. From the vicinal coupling constant $^3J_{4H,5H}$=7 Hz in the ^{1}H NMR spectra of **1** and **2**, a relative *cis*-configuration of the substituents at the cyclopentane ring can be assigned.[3,4,6] The CD spectra of **1** and **2** are effectively mirror images of one another,[6] suggesting that the compounds should be near-enantiomeric. In this publication we describe the determination of the absolute configurations of these cyclopentanoid fungal metabolites.



(-)-involutin (**1**)

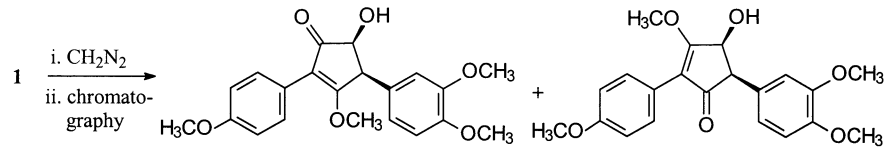


(+)-chamonixin (**2**)

2. Results and discussion

2.1. Determination of the absolute configuration by Mosher derivatization and NMR analysis

(−)-Involutin (**1**) was isolated from fresh or freeze-dried fruit bodies of *P. involutus* by acetone extraction followed by chromatography on acetylated polyamide. Its absolute configuration was determined by Kakisawa's[7] high-field NMR variant of Mosher's method. In order to achieve a selective esterification of the 4-OH group with methoxy(trifluoromethyl)phenylacetyl (MTPA) chloride,[8] the phenolic and enolic OH functions had to be first protected as methyl ethers. For this purpose, a solution of **1** in methanol was



3 (25%) **4** (12%)

Scheme 1. *O*-Methylation of (−)-involutin (**1**).

Keywords: involutin; chamonixin; basidiomycetes; natural products; stereochemistry; CD calculations.
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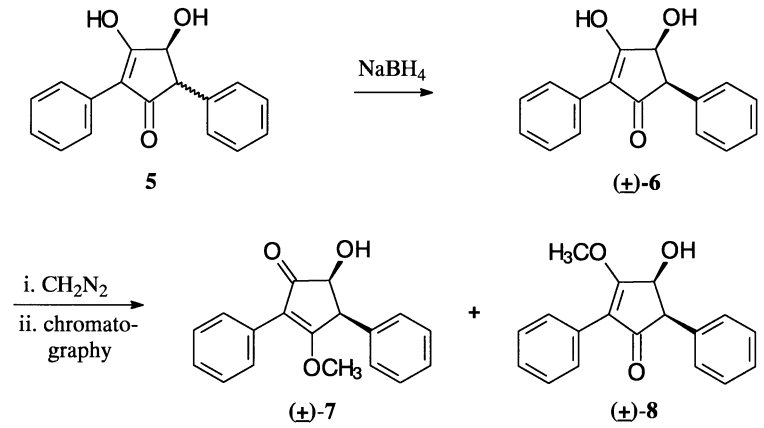


Scheme 2. Synthesis of model compounds **7** and **8**.

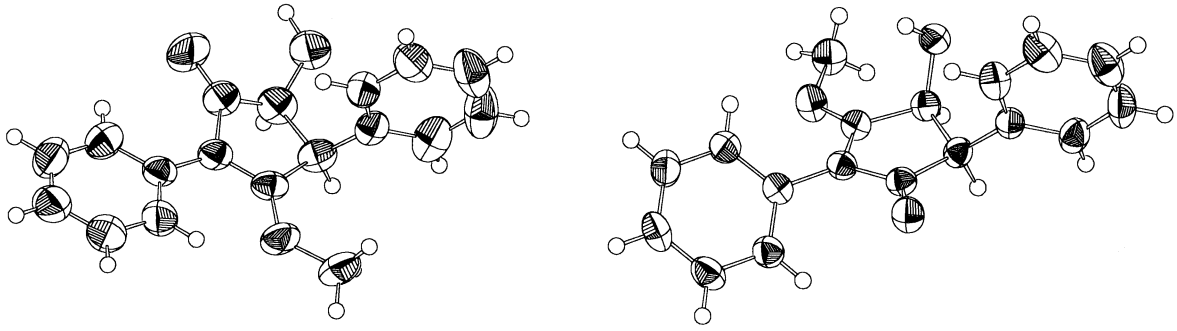


Figure 1. Crystal structures of **7** and **8**.

treated with diazomethane in the presence of silica gel (Scheme 1). Chromatographic separation of the reaction products yielded two isomeric tetramethyl ethers, **3** and **4**, in a 2:1 ratio. These isomers exhibit a characteristic chemical shift difference of the protons at C-4 and C-5. In **3** the signals of C*H*(OH) and C*H*(Ar) are close to each other (δ 4.57 and 4.51, respectively), whereas in isomer **4** they exhibit a much larger difference in chemical shift (δ 5.13 and 4.06, respectively). A similar effect is observed in the ^{1}H NMR spectra of the related model compounds **7** and **8**, which were obtained by *cis*-selective reduction of 3-hydroxy-2,5-diphenyl-2-cyclopentene-1,4-dione (**5**) with sodium borohydride, followed by methylation of the resulting product, **6**, with diazomethane (Scheme 2). The structures of **7** and **8** were confirmed by X-ray crystallography (Fig. 1).

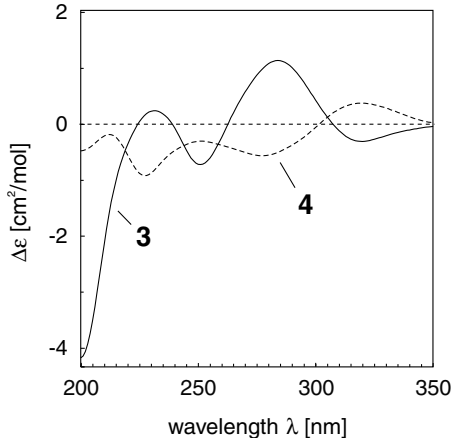
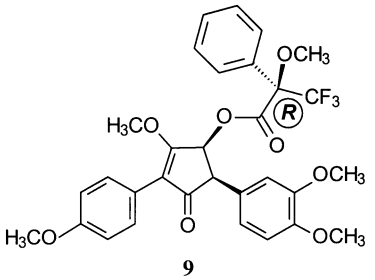


Figure 2. CD spectra of involutin tetramethyl ethers **3** (—) and **4** (···) (in MeOH).

Interestingly, the isomeric tetramethyl ethers **3** and **4** exhibit opposite CD curves (Fig. 2) despite their joint synthetic origin from **1**. This phenomenon can be explained by the assumption that **3** and **4** possess near-enantiomeric chromophores, which, as shown below, was supported by quantum chemical CD calculations. These calculations independently confirm the assignment of the absolute configuration as determined by the modified Mosher's method mentioned above and detailed below.

For the preparation of the MTPA ester, alcohol **4** was selected, since it contains protons on both sides nearby the carbinol group, a necessary prerequisite for the application of the high-field NMR variant of Mosher's method.[9] Thus, treatment of **4** with (*S*)- and (*R*)-MTPA chloride, DMAP, and *N*-ethylmorpholine yielded the (*R*)- and (*S*)-MTPA esters **9** and **10**, respectively.



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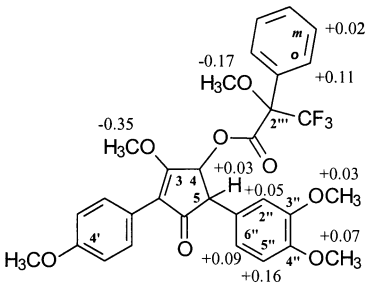


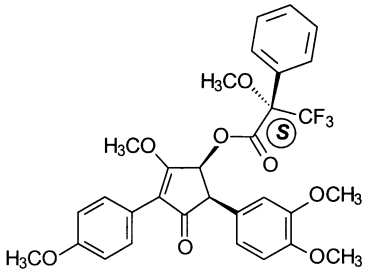
Figure 3. $\Delta\delta_{R-S}$ values determined from the MTPA esters **9** and **10**.

Table 1. Temperature dependence of the shift differences $\Delta\delta_{R-S}$ of MTPA esters **9** and **10** (in $CDCl_3$, 400 MHz)

T (K) esters **9**/**10** ($\Delta\delta_{R-S}$)	273	253	233	213
5-H	+0.034	+0.040	+0.050	+0.060
5″H	+0.182	+0.198	+0.218	+0.220
6″H	+0.112	+0.131	–	–
2″H	+0.066	+0.098	–	–
o-H	+0.141	+0.161	+0.219	+0.265
m-H	+0.030	+0.057	+0.069	+0.073
3-OCH_3	−0.393	−0.434	−0.475	−0.519
3″-OCH_3	+0.045	+0.049	+0.059	+0.081
4″-OCH_3	+0.086	+0.095	+0.106	+0.116
2‴-OCH_3	−0.214	−0.259	−0.309	−0.369

The shift differences $\Delta\delta_{R-S}$ shown in Fig. 3 were determined from the ^{1}H NMR spectra of **9** and **10**.

From the sign of the $\Delta\delta_{R-S}$ values and the assumption of a 'Mosher plane', the absolute configuration of (−)-involutin is (4*S*,5*R*).[10] This assignment is supported by the proton shifts of the MTPA moiety caused by the reciprocal shielding effect of the 3,4-dimethoxyphenyl residue.



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The conformation of compounds **9** and **10** was confirmed by ^{1}H NMR experiments at different temperatures as proposed by Riguera.[11] The spectra of the diastereomeric MTPA esters **9** and **10** recorded at reduced temperatures exhibited increasing shift differences in the expected directions (Table 1).

In summary, the absolute configuration of (−)-*cis*-involutin (**1**) from *P. involutus* (Batsch: Fr.) Fr. was established as (4*S*,5*R*). The (4*R*,5*S*) configuration of (+)-chamonixin (**2**) from *C. caespitosa* Roll. follows from its mirror-symmetrical CD spectrum. The enantiomer of **2**, (−)-chamonixin,[12] is present in *P. involutus* as a minor constituent and could be isolated in 0.03% yield from lyophilised fruit bodies (see Section 3).

2.2. Configurational assignment by quantum chemical CD calculation

To explain the mirror-like CD curves of the isomeric permethyl ethers **3** and **4** and to confirm the configurational

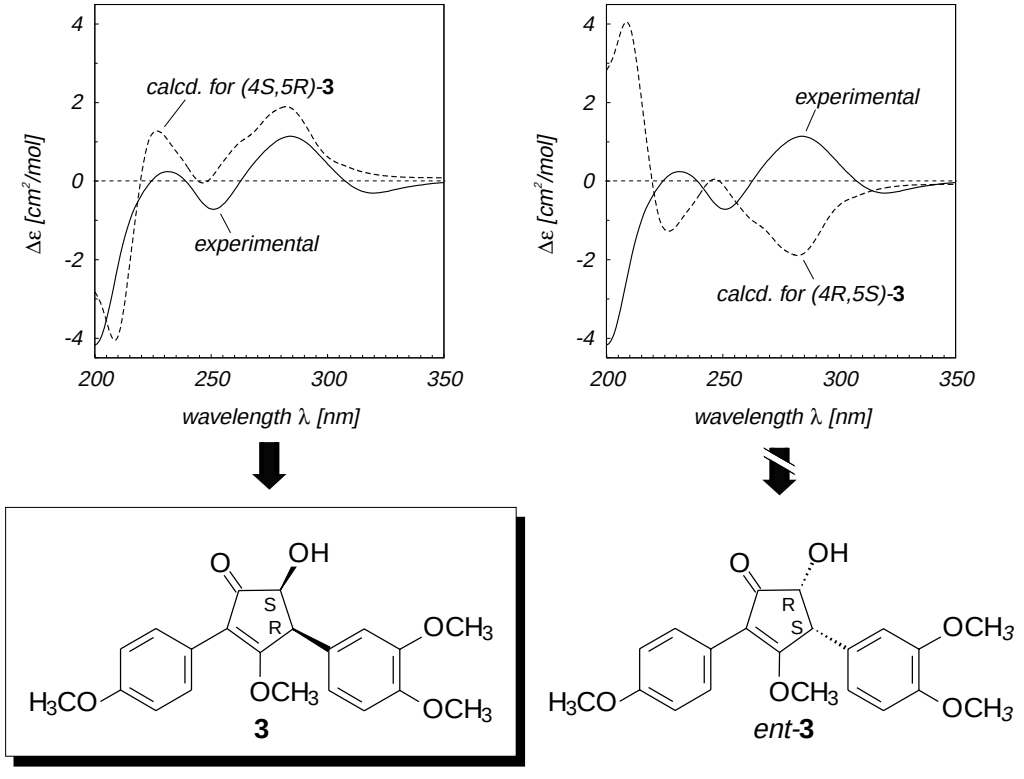

Figure 4. Calculated CD spectra for **3** and *ent*-**3** in comparison with the experimental one.

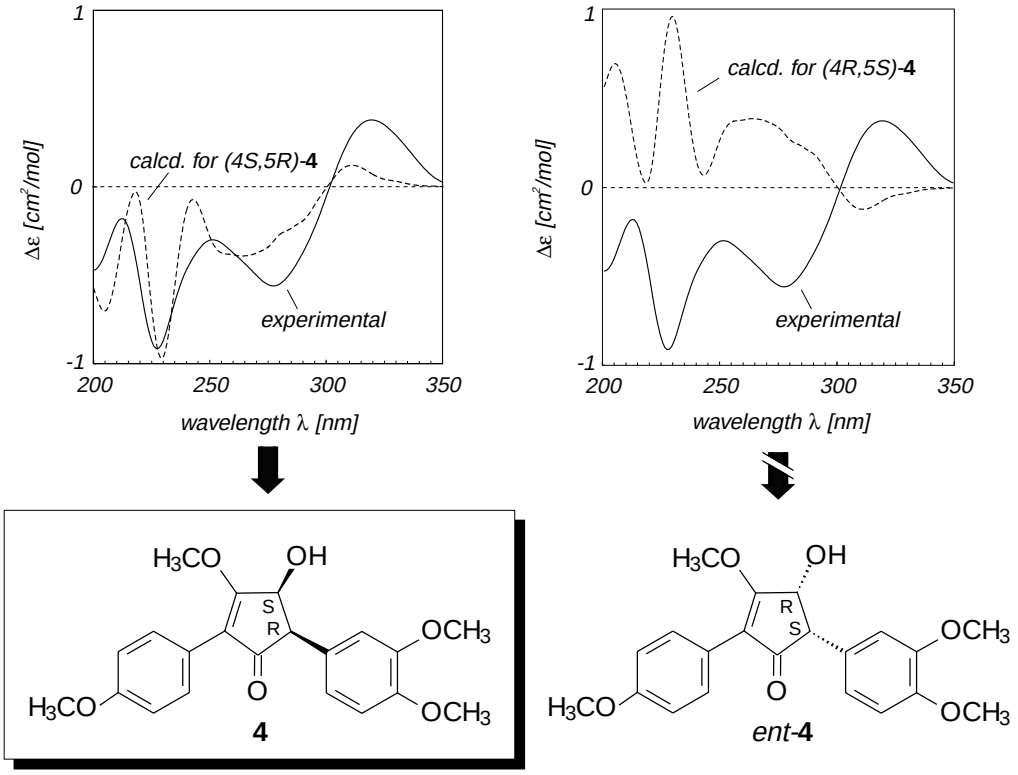

Figure 5. CD spectra calculated for **4** and *ent*-**4** in comparison with the experimental one.

assignments of involutin (**1**) and chamonixin (**2**) derived from analysis of the NMR spectra of the MTPA esters, we have independently determined the absolute configuration of **3** and **4** by quantum chemical calculations and comparison of the calculated CD spectra with the experimental ones, a valuable tool as shown by numerous previous examples.[13,14]

Considering the molecular flexibility of the relevant chromophores, the CD calculations were based on molecular dynamics simulations using the Tripos force field,[15] arbitrarily starting with the (4*S*,5*R*)-enantiomer of **3** and the (4*S*,5*R*)-enantiomer of **4**. The simulations were performed for a total time period of 500 ps, recording the structure every 0.5 ps for further calculations.

For the 1000 structures thus collected, single CD spectra were calculated and then averaged arithmetically to give theoretical overall spectra. In order to take into account systematic shifts of the calculated CD spectra, a 'UV correction' was carried out for each calculated spectrum as introduced earlier.[13] The good agreement between the calculated overall CD spectrum for (4*S*,5*R*)-**3** with the experimental one of **3** (Fig. 4) and the overall CD spectrum calculated for (4*S*,5*R*)-**4** with the experimental one of **4** (Fig. 5) permits an accurate attribution of the absolute configuration of both, **3** and **4**, as (4*S*,5*R*), despite their mirror-image like experimental CD curves.

3. Experimental

3.1. General

Melting points (uncorrected): Reichert Thermovar. Optical rotations: Perkin–Elmer 214. UV/Vis and CD: S.A. Jobin Yvon CD-6-Dichrograph. IR: Bruker FTIR spectrophotometer IFS 45 or IFS 48. NMR: Varian VXR-400S and Bruker ARX 300 with solvent peak as internal reference ($CDCl_3$: δ_H 7.24, δ_C 77.0; CD_3OD: δ_H 3.35, δ_C 49.0; [D_6]acetone: δ_H 2.04, δ_C 29.8). TLC: Silica gel Merck G plates. Column chromatography: silica gel Merck 60; acetylated polyamide Macherey–Nagel SC 6-Ac. HPLC was carried out on a Waters Millenium equipped with two Waters 510 pumps, a Waters 717 plus autosampler and a photodiode array detector Waters 996. Analytical column: Nucleosil 100 RP-18, 5 μm, 250×4 mm; preparative column: Nucleosil 100 RP-18, 7 μm, 250×16 mm, and Merck LiChrosorb DIOL, 7 μm, 250×25 mm. Preparative HPLC (RP-18), solvent system A: acetonitrile/water 1:9+ 0.1% TFA, solvent system B: acetonitrile; gradient 100% A to 100% B within 60 min, flow rate 6 mL/min. MS and HRMS were performed on a Finnigan MAT 95 double focusing mass spectrometer equipped with an EI ion source operated at 70 eV.

P. involutus was collected in autumn 1996 and 1998 near Regensburg, Bavaria, Germany.

3.2. Isolation of (−)-involutin and (−)-chamonixin

Fresh or frozen fruit bodies (34 g) of *P. involutus* were cut and shaken for 20 h with a mixture of acetone (0.5 L), 2 M HCl (5 mL) and ascorbic acid (0.3 g). After filtration, the extract was concentrated under reduced pressure, and the remaining brown aqueous phase was extracted with petroleum ether (2×100 mL) and EtOAc (3×200 mL). The combined EtOAc extracts were dried (Na_2SO_4) and

concentrated under reduced pressure. The residue (0.2 g, 0.6%) was chromatographed on acetylated polyamide (column 400×30 mm, acetone/MeOH 3:1) to yield **1** (35 mg, 0.1%) as a pale brown solid. According to HPLC, the material was 95% pure and could be further purified by preparative HPLC on DIOL-phase (elution with *n*-hexane/*t*-BuOMe 9:1, *t*-BuOMe/*i*-PrOH 1:9) or on RP-18 (elution with acetonitrile/water/0.1% TFA). In the same manner, **1** (450 mg, 1%) and (−)-**2** (15 mg, 0.03%) were obtained from 45 g of lyophilised fruit bodies [HPLC on RP-18, **1**: t_R=11 min, (−)-**2**: t_R=14 min].

3.2.1. (−)-Involutin [(−)-1]. Mp 172–174°C (dec)., Lit.[3] 171–174°C; R_f 0.1 (toluene/ethyl formate/formic acid 10:5:3), brown spot with $K_3[Fe(CN)_6]$/$NaHCO_3$); $[\alpha]_D^{25}$=−23 (*c* 1, 96% EtOH), Lit.3 −23; UV/Vis (MeOH): λ_{max} (log ϵ) 258.5 nm (4.39), 270.5 (4.38); IR (KBr): 3300 (br.), 2500, 1672, 1631, 1606, 1518, 1452, 1390, 1290, 1271, 1251, 1217, 1200, 1174, 1122, 1103, 1035, 960, 932, 897, 882, 843, 804, 777, 748 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 290 K): δ 3.98 (d, ^3J=6.9 Hz, 1H, 5-H), 4.70 (d, ^3J=6.9 Hz, 1H, 4-H), 5.52 (dd, ^3J=8.1 Hz, ^4J=2.0 Hz, 1H), 6.61 (d, ^4J=2.0 Hz, 1H), 6.78 (d, ^3J=9.0 Hz, 2H), 6.72 (d, ^3J=8.1 Hz, 1H), 7.71 (d, ^3J=9.0 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD, 290 K): δ 58.3 (C-5), 68.7 (C-4), 115.7 (CH), 116.2 (CH), 118.0 (CH), 122.9 (CH), 123.6 (C), 128.5 (C), 130.6 (CH), 145.7, 146.1, 157.4 (each C), signals for C-1, C-2 and C-3 not visible; MS (EI): *m/z* (%)=314 (1) [M^+], 296 (100), 163 (56), 134 (30), 106 (10); Anal. calcd for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49. Found: C, 64.70; H, 4.60.

3.2.2. (−)-Chamonixin [(−)-2]. Mp >130°C (dec)., R_f 0.2 (toluene/ethyl formate/formic acid 10:5:3, blue spot with aqueous $K_3[Fe(CN)_6]$/$NaHCO_3$); $[\alpha]_D^{25}$=−28 (*c* 1, 96% EtOH), Lit.[12] −28.7; UV/Vis (MeOH): λ_{max} (log ϵ) 228 nm (4.27), 245 (4.29), 275 (sh, 4.14); IR (KBr): 3430–3330 (br.), 2930, 1682, 1607, 1516, 1444, 1368, 1344, 1249, 1228, 1174, 1004, 836 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 290 K): δ 4.07 (d, ^3J=6.7 Hz, 1H, 5-H), 4.78 (d, ^3J=6.7 Hz, 1H, 4-H), 6.78 (d, ^3J=8.7 Hz, 2H), 6.83 (d, ^3J=9.0 Hz, 2H), 7.03 (d, ^3J=8.7 Hz, 2H), 7.75 (d, ^3J=9.0 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD, 290 K): δ 56.0 (C-5), 72.6 (C-4), 116.0 (CH), 116.4 (CH), 117.1 (C-2), 123.7 (C), 128.2 (C), 130.9 (CH), 132.5 (CH), 157.7, 157.9 (each C), 163.6 (C-3), 195.11 (C-1); MS (EI): *m/z* (%)=298 (3) [M^+], 280 (51), 252 (4), 224 (4), 147 (100), 134 (13), 119 (11), 107 (6), 91 (6); HRMS (EI):): *m/z* 298.0836 (298.0841 calcd for $C_{17}H_{14}O_5$).

3.3. Methylation of (−)-involutin

A stirred solution of **1** (200 mg, 0.64 mmol) in 96% MeOH (5 mL) and silica gel (20 mg) was slowly titrated at 0°C with a freshly prepared solution of diazomethane in Et_2O until no more gas evolution was observed. The mixture was allowed to warm to room temperature and, after the addition of a small excess of CH_2N_2/Et_2O, was stirred for 20 h. After evaporation, the crude brown oil was separated by flash chromatography on silica gel ($CHCl_3$/MeOH 30:1) to yield the ethers **3** (52 mg, 25%) and **4** (28 mg, 12%).

3.3.1. (+)-*cis*-5-Hydroxy-3-methoxy-2-(4-methoxyphenyl)-4-(3,4-dimethoxyphenyl)-2-cyclopenten-1-one (3). Pale yellow oil; R_f 0.32 ($CHCl_3$/MeOH, 30:1); $[\alpha]_D^{25}$=+19 (*c* 1.6, 96% EtOH); UV/Vis (MeOH): λ_{max} (log ϵ) 230 nm (sh, 2.61), 250, 285 (sh, 2.35); CD (MeOH, 0.4 mg/mL): λ_{max} ($\Delta\epsilon$) 320 nm (−0.3), 284 (+1.3), 251 (−0.7), 231 (+0.2); IR (KBr): 3425 (br.), 2935, 2838, 1689, 1600 (s), 1513 (ss), 1463, 1420, 1353, 1251 (s), 1176, 1142, 1026, 837, 810, 767, 574 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.83, 3.85 (each s, 2 OCH_3, 6H), 4.51 (d, ^3J=7.2 Hz, 1H, 4-H), 4.57 (d, ^3J=7.2 Hz, 1H, 5-H), 6.68 (d, ^4J=2.1 Hz, 1H), 6.72 (dd, ^3J=8.4 Hz, ^4J=2.1 Hz, 1H), 6.84 (d, ^3J=8.4 Hz, 1H), 6.94, 7.83 (each d, ^3J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.8 (C3–O*C*H_3), 55.2 (C3″–O*C*H_3), 55.8/55.9 (C4′–O*C*H_3/C4″–O*C*H_3), 57.5 (C-4), 74.1 (C-5), 111.6 (CH), 111.7 (C-2), 113.6 (2 CH), 116.6 (C), 120.7 (C), 122.3 (CH), 126.6 (CH), 129.4 (CH), 148.9/149.5 (C-4′/C-4″), 158.8 (C-3″), 179.8 (C-3), 203.4 (C-1); MS (EI): *m/z* (%) 370 (100) [M^+], 341 (28), 325 (9), 281 (12), 267 (6), 233 (15), 191 (7), 165 (10), 119 (6); HRMS (EI): *m/z* 370.1411 (370.1416 calcd for $C_{21}H_{22}O_6$).

3.3.2. (−)-*cis*-4-Hydroxy-3-methoxy-2-(4-methoxyphenyl)-5-(3,4-dimethoxyphenyl)-2-cyclopenten-1-one (4). Pale yellow oil; R_f 0.41 ($CHCl_3$/MeOH, 30:1); $[\alpha]_D^{25}$=−26 (*c* 0.5, 96% EtOH); UV/Vis (MeOH): λ_{max} (log ϵ)=232 nm (sh, 2.31), 250, 280 (sh, 2.17); CD (MeOH, 0.2 mg/mL): λ_{max} ($\Delta\epsilon$)=320 nm (+0.4), 277 (−0.5), 251 (−0.3), 227 (−0.9), 212 (−0.2); IR (KBr): 3435 (br.), 2934, 2838, 1686, 1603 (s), 1514 (ss), 1463, 1421, 1349, 1252 (s), 1170, 1143, 1025 (s), 838, 810, 766, 569 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.82, 3.84, 3.86, 4.20 (each s, 3H, OCH_3), 4.06 (d, ^3J=6.6 Hz, 1H, 5-H), 5.13 (d, ^3J=6.6 Hz, 1H, 4-H), 6.71 (d, ^4J=1.8 Hz, 1H), 6.74 (dd, ^3J=8.1 Hz, ^4J=1.8 Hz, 1H), 6.86 (d, ^3J=8.1 Hz, 1H), 6.93 (d, ^3J=8.7 Hz, 2H), 7.79 (d, ^3J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 55.9 (2×) (each OCH_3), 56.5 (C-5), 58.2 (C1–O*C*H_3), 67.5 (C-4), 111.6 (C-2), 113.5 (3×CH), 119.3, 122.3 (each C), 122.5, 126.1 (each CH), 129.9 (2×CH), 148.9, 149.3, 158.9 (each C), 180.0 (C-3), 200.7 (C-1); MS (EI): *m/z* (%)=370 (100) [M^+], 338 (18), 325 (37), 324 (33), 310 (10), 294 (12), 262 (28), 191 (18), 151 (14); HRMS (EI): *m/z*=370.1410 (370.1416 calcd for $C_{21}H_{22}O_6$).

3.3.3. (±)-*cis*-3,4-Dihydroxy-2,5-diphenyl-2-cyclopenten-1-one (6). To a suspension of $NaBH_4$ (0.38 g, 10 mmol) in 50 mL of anhydrous EtOH in a dried Schlenk apparatus under argon were slowly added 0.36 mL (20 mmol) of water in dry EtOH (5 mL). The suspension was homogenized in an ultrasound bath, refluxed for 30 min and then cooled to 0°C. The resulting solution was then added dropwise at 0°C to a stirred solution of 3-hydroxy-2,5-diphenyl-2-cyclopentene-1,4-dione (**5**)[16] (1.32 g, 5 mmol) in EtOH (50 mL). The formation of **6** was monitored by TLC (R_f 0.34, toluene/ethyl formate/formic acid, 10:5:3). After completion (ca. 30 min), acetic acid (10 mL) was added and the mixture hydrolyzed with ice-cooled 2 M HCl. The solution was concentrated, and the aqueous residue was extracted with Et_2O (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to yield a light yellow oil. Compound **6** was obtained as a colorless powder (1.20 g, 90%) on recrystallization from EtOAc/petroleum ether. Mp >190°C (dec.); ^1H NMR (300 MHz, [D_6]acetone, 290 K): δ 4.10 (br., 1H, 5-H), 4.90 (br., 1H, 4-H), 7.14–7.26 (m, 6H),

7.33–7.38 (m, 2H), 7.99 (m, 2H); ^{13}C NMR (75 MHz, [D$_6$]acetone, 290 K): δ 55.0, 71.0, 115.0, 126.7, 126.8, 127.8, 127.9, 128.1, 128.5, 128.6, 130.1, 131.4, 136.5; MS (EI): *m/z* (%) 266 (M^+, 34), 248 (100); $C_{17}H_{14}O_3$ (266.3).

3.4. Methylation of 6

The alcohol **6** (1.06 g, 4 mmol) was dissolved in 96% MeOH (5 mL) and treated at 0°C with a five-fold excess of an etheric diazomethane solution. The mixture was stirred for 10 min and then treated with a few drops of acetic acid. Evaporation of the solvent yielded the crude product in form of an amorphous, yellowish solid. Chromatography on silica gel (petroleum ether/EtOAc 2:1) yielded **8** (0.45 g, 40%), followed by **7** (0.56 g, 50%). **8** could also obtained as a first fraction by fractional crystallisation of the mixture from petroleum ether/EtOAc (4:1). Both products **7** and **8** were diastereomerically pure (de>99%).

3.4.1. (±)-*cis*-5-Hydroxy-3-methoxy-2,4-diphenyl-2-cyclopenten-1-one (7). Mp 158–161°C; R_f 0.41 (petroleum ether/EtOAc, 4:1); UV/Vis (MeOH): λ_{max} (log ϵ) 202.5 nm (4.18), 249.3 (3.86); IR (KBr): 3399 (br.), 3026, 2954, 1677 (s), 1591 (s), 1362 (s), 1136, 1052, 711, 700 cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]acetone): δ 3.88 (s, 3H, OCH$_3$), 4.15 (d, ^3J=7.1 Hz, 1H, 4-H), 4.63 (d, ^3J= 3.0 Hz, 1H, OH), 4.82 (dd, ^3J=7.2 Hz, ^3J=3.0 Hz, 1H, 5-H), 7.31–7.38 (m, 8H), 7.89–7.92 (m, 2H); ^{13}C NMR (75 MHz, [D$_6$]acetone): δ 50.2 (C-4), 58.3 (OCH$_3$), 75.5 (C-5), 119.4 (C-2), 128.1, 128.6, 129.0, 129.5, 129.9, 130.5 (each CH), 132.4, 137.3 (each C), 182.6 (C-3), 203.5 (C-1); MS (EI): *m/z* (%) 280 (100) [M^+], 251 (16), 234 (14), 220 (9), 191 (25), 185 (6), 178 (5), 131 (7), 105 (6), 91 (8), 89 (9); Anal. calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.52; H, 5.89.

3.4.2. (±)-*cis*-4-Hydroxy-3-methoxy-2,5-diphenyl-2-cyclopenten-1-one (8). Mp 142–144°C; R_f 0.53 (petroleum ether/EtOAc, 4:1); UV/Vis (MeOH): λ_{max} (log ϵ) 202.5 nm (4.18), 249.3 (3.86); IR (KBr): 3378 (br.), 3031, 2961, 1659 (s), 1614 (s), 1593 (s), 1494 (s), 1358 (s), 1238 (s), 1047, 949, 711, 700 cm^{-1} (s); ^{1}H NMR (300 MHz, [D$_6$]-acetone): δ 4.04 (d, ^3J=6.6 Hz, 1H, 5-H), 4.25 (s, 3H, OCH$_3$), 5.41 (d, ^3J=6.6 Hz, 1H, 4-H), 7.21–7.38 (m, 8H), 7.84–7.87 (m, 2H); ^{13}C NMR (75 MHz, [D$_6$]acetone): δ 58.5 (OCH$_3$), 58.7 (C-5), 68.6 (C-4), 119.4 (C-2), 127.9, 128.2, 128.9, 129.0, 129.8, 132.4 (each CH), 132.5, 137.5 (each C), 183.0 (C-3), 202.0 (C-1); MS (EI): *m/z* (%) 280 (31) [M^+], 262 (7), 248 (11), 234 (100), 220 (19), 203 (25), 191 (19), 185 (21), 131 (20), 118 (8), 91 (17), 89 (17); Anal. calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.70; H, 5.84.

3.5. Preparation of the MTPA esters 9 and 10

To a solution of **4** (12.0 mg, 0.03 mmol) in anhydrous CH_2Cl_2 (3 mL) was added at 0°C *N*-ethylmorpholine (6.8 mg, 2.0 equiv.) and catalytic amounts of DMAP (0.5 mg). After the addition of (*S*)- or (*R*)-MTPA chloride (14.4 mg, 0.06 mmol), the solution was warmed to room temperature and stirred for 12 h. The reaction mixture was hydrolysed with saturated NH_4Cl solution, washed with cold 2 M HCl, aqueous $NaHCO_3$ and water. Preparative TLC (silica gel, Merck, 0.25 mm, petroleum ether/EtOAc 4:1) yielded the diastereomeric (*R*)- or (*S*)-MTPA esters, **9** (9 mg, 50%) and **10** (12 mg, 60%) respectively, as yellow oils.

3.5.1. (*R*)-MTPA ester 9. Yellow oil; R_f 0.15 ($CHCl_3$/MeOH, 30:1); UV/Vis (MeOH): λ_{max} 204 nm (sh), 232 (sh), 278 (sh); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (q, J=1.1 Hz, through-space H–F coupling, 3H, C2‴–OCH$_3$), 3.60 (s, 3H,C3–OCH$_3$), 3.77 (s, 3H, C3″–OCH$_3$), 3.82 (s, 3H, C4′–OCH$_3$), 3.83 (s, 3H, C4″–OCH$_3$), 4.24 (d, ^3J= 7.2 Hz, 1H, 5-H), 6.36 (d, ^3J=7.2 Hz, 1H, 4-H), 6.66 (d, ^4J=1.6 Hz, 1H, 2″-H), 6.74 (dd, ^3J=8.4 Hz, ^4J=1.6 Hz, 1H, 6″-H), 6.75 (d, ^3J=8.4 Hz, 1H, 5″-H), 6.93 (d, ^3J= 8.8 Hz, 2H, 3′,5′-H), 7.12 (d, ^3J=8.0 Hz, 2H, *o*-Ph-H), 7.25 (dd, ^3J=8.0 Hz, ^3J=7.6 Hz, 2H, *m*-Ph-H), 7.32 (dd, ^3J=7.6 Hz, ^4J=1.2 Hz, 1H, *p*-Ph-H), 7.60 (2H, d, ^3J= 8.8 Hz, 2′,6′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.8 (OCH$_3$), 55.0 (C-5), 55.3, 56.0, 55.7, 58.7 (each OCH$_3$), 71.8 (C-4), 111.4 (CH), 113.6 (2×CH), 113.7 (CH), 121.7 (C), 122.3 (C), 122.9 (CH), 126.0 (C), 127.3, 128.2, 129.6 (each CH), 131.3 (C), 130.5 (2×CH), 148.8/149.0 (C-4′/C-4″), 159.5 (C-3″), 166.0 (COO), 175.1 (C-3), 199.8 (C-1); MS (EI): *m/z* (%) 586 (7) [M^+], 542 (7), 510 (7), 384 (10), 368 (11), 354 (33), 353 (92), 352 (100), 337 (29), 293 (12), 281 (17), 189 (61), 175 (20), 170 (28), 165 (19), 147 (11), 135 (19), 119 (16), 105 (28), 91 (14), 77 (21), 44 (12); HRMS (EI): *m/z* 586.1802 (586.1814 calcd for $C_{31}H_{29}F_3O_8$).

3.5.2. (*S*)-MTPA ester 10. Yellow oil; R_f 0.19 ($CHCl_3$/MeOH, 30:1); UV/Vis (MeOH): λ_{max} 204 nm (sh), 232 (sh), 278 (sh); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.21 (q, J=1.0 Hz, through-space H–F coupling, 3H, C2‴–OCH$_3$), 3.74 (s, 3H, C3″–OCH$_3$), 3.76 (s, 3H, C4″–OCH$_3$), 3.83 (s, 3H, C4′–OCH$_3$), 3.95 (s, 3H, C3–OCH$_3$), 4.21 (d, ^3J= 7.2 Hz, 1H, 5-H), 6.39 (d, ^3J=7.2 Hz, 1H, 4-H), 6.59 (d, ^3J=8.4 Hz, 1H, 5″-H), 6.61 (d, ^4J=1.8 Hz, 1H, 2″-H), 6.65 (dd, ^3J=8.4 Hz, ^4J=1.8 Hz, 1H, 6″-H), 6.94 (d, ^3J= 8.8 Hz, 2H, 3′,5′-H), 7.01 (d, ^3J=8.0 Hz, 2H, *o*-Ph-H), 7.23 (dd, ^3J=7.2 Hz, ^3J=8.0 Hz, 2H, *m*-Ph-H), 7.33 (dd, ^3J=7.2 Hz, ^4J=1.2 Hz, 1H, *p*-Ph-H), 7.67 (d, ^3J=8.8 Hz, 2H, 2′,6′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.0 (OCH$_3$), 55.1 (C-5), 55.3 (OCH$_3$), 55.7 (2×OCH$_3$), 58.8 (OCH$_3$), 71.5 (C-4), 111.0 (CH), 113.7 (2×CH), 121.6 (C), 121.8 (C), 122.2 (C), 122.9 (CH), 124.4 (C), 125.5 (C), 127.4 (CH), 127.6 (C), 128.3 (CH), 128.6 (C), 129.6 (CH), 130.2 (C), 130.4 (2×CH), 148.8/148.7 (C-4′/C-4″), 159.5 (C-3″), 166.0 (COO), 175.0 (C-3), 199.9 (C-1); MS (EI): *m/z* (%) 586 (7) [M^+], 510 (9), 368 (7), 354 (61), 352 (60), 337 (14), 293 (10), 281 (19), 207 (16), 189 (50), 170 (40), 149 (16), 119 (34), 105 (100), 91 (30), 77 (92), 58 (23), 51 (25); HRMS (EI): *m/z* 586.1812 (586.1814 calcd for $C_{31}H_{29}F_3O_8$).

3.6. X-Ray analyses

3.6.1. Crystal data for 7. $C_{18}H_{16}O_3$, M=280.31, monoclinic, space group $P2_1/n$, a=10.345(2) Å, b=8.952(2) Å, c=16.106(5) Å, β=105.98(2)°, V=1433.9(6) Å^3, Z=4, D_c=1.298 Mg/m^3, μ=0.088 mm^{-1}, crystal dimensions 0.37×0.43×0.53 mm^3, F(000)=592, T=295(2) K, θ= 3.06–23.97°, reflections measured 2335, unique reflections

2246, R_{int}=0.0103, min. and max. transmission coefficient 0.9594, 0.9988, $R1$=0.0490 and $wR2$=0.1080 for all 1622 observed reflections with $I>2\sigma(I)$, $R1$=0.0711 and $wR2$= 0.1208 for all reflections and 191 parameters. Final electron density 0.199 and −0.195 e/Å^3; S=1.103.

3.6.2. Crystal data for 8. $C_{18}H_{16}O_3$, M=280.31, monoclinic, space group $P2_1/c$, a=10.293(5) Å, b=10.084(2) Å, c=13.802(5) Å, β=97.56(3)°, V=1420.1(9) Å^3, Z=4, D_c= 1.311 Mg/m^3, μ=0.089 mm^{-1}, crystal dimensions: 0.33× 0.40×0.53 mm^3, F(000)=592, T=295(2) K, θ=2.51–24.97°, reflections measured 2605, unique reflections 2491, R_{int}=0.0181, min. and max. transmission coefficient 0.9206, 0.9992, $R1$=0.0414 and $wR2$=0.1004 for all 1981 observed reflections with $I>2\sigma(I)$, $R1$=0.0556 and $wR2$= 0.1101 for all reflections and 192 parameters. Final electron density 0.121 and −0.165 e/Å^3, S=1.100.

For the compounds **7** and **8** the data were collected on a Nonius MACH3 kappa diffractometer with MoK$_\alpha$ radiation (λ=0.71073 Å). The structures were solved by direct methods using SHELXS-86[17] and refined by full matrix least squares on F^2 by SHELXL-93.[18] The molecular views were realised by ZORTEP.[19]

Crystal and data collection parameters, relevant structure refinement parameters, atomic coordinates for the non-hydrogen atoms, positional and isotropic displacement coefficients for hydrogen atoms, a list of anisotropic displacement coefficients for the non-hydrogen atoms and a full list of bond distances and bond angles have been deposited with the Cambridge Crystallographic Data Center. The crystallographic data will be sent on quoting the CCDC numbers 163731 for **7** and 163730 for **8** (e-mail: deposit@ccdc.cam.ac.uk).

3.7. Computational details

3.7.1. Molecular dynamics (MD). The MD simulations were performed on Silicon Graphics Octane (R10000) workstations using the Tripos[15] force field as implemented in the molecular modeling package Sybyl.[15] The molecules were weakly coupled to a thermal bath at T=400 K,[20] with a temperature relaxation time of τ=0.1 ps.

3.7.2. CD calculations. The wave functions for the calculation of the rotational strength for the electronic transitions from the ground state to excited states were obtained by a CNDO/S-CI[21,22] calculation, in which the CI expansion[21,22] takes into account the ground state and all n and π orbitals. These calculations were carried out on Linux *i*PII workstations using the BDZDO/MCDSPD[21] program package. For a better comparison of the theoretical CD spectrum with the experimental one, a Gaussian band shape function was generated over the calculated rotational strength values.

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