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# Synthesis of Optically Active (+)-Canangone, Its 6-Epimer, and Determination of Absolute Configuration

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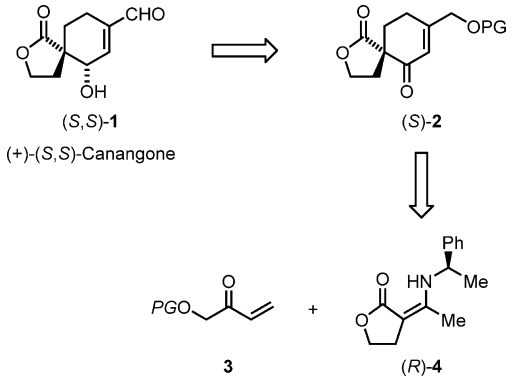
**Keywords:** Asymmetric synthesis / Lactones / Michael addition / Natural products / Spiro compounds

The first synthesis of canangone and its 6-epimer is reported. The products are obtained in optically active form by an asymmetric Robinson annulation. The relative and absolute configuration of the natural product is established for the first time.



## Introduction

Optically active (+)-canangone (**1**) was isolated by Caloprisco and coworkers from an extract of ylang-ylang (*Cananga odorata*),[1] which belongs to the family of annonaceae, a known source for biologically active natural products like acetogenins.[2] The relative configuration was elucidated by these authors to be (*R**,*R**), but the absolute configuration was so far unknown. We are interested in (+)-canangone (**1**) as a synthetic target, as it can be retrosynthetically related to spirolactone **2** with a quaternary stereocenter (Scheme 1).[3] We already prepared several optically active spirolactones and lactams by an asymmetric Michael reaction of enamines and methyl vinyl ketone.[4] In our synthetic plan, synthesis of compound **2** requires Michael acceptor **3** with a protected hydroxy functionality at the methyl group. We furthermore decided to use enamine **4**, derived from phenethylamine, as the chiral auxiliary, because the stereochemistry of the annulation reaction of this enamine with methyl vinyl ketone was already elucidated by Pfau et al.,[5] who applied a method developed by d'Angelo et al.[6] These investigations predict the configuration of spirocycle **2** to be (*S*), when enamine (*R*)-**4** is used as a starting material, and vice versa.




Scheme 1. Synthetic plan for optically active (+)-(*S*,*S*)-canangone (**1**) by an asymmetric Robinson annulation reaction with the use of (*R*)-phenethylamine as a chiral auxiliary. PG = protecting group.

## Results and Discussion

After some experimentation with other O-protecting groups, the use of 3,4-dimethoxybenzyl (DMB) finally turned out to be optimal for masking the primary alcohol functionality in methyl vinyl ketone derivative **3** (Scheme 2). This compound was prepared in three steps from dimethoxybenzyl alcohol **5**, which was first treated with bromoacetic acid (1 equiv.) in the presence of NaH (3.4 equiv.) in THF (reflux, 2 d; followed by aqueous acidic work up).[7] Resulting carboxylic acid **6** was then activated by forming mixed anhydride with pivaloyl chloride (1.0 equiv.) and $Et_3N$ (1.1 equiv.) in $CH_2Cl_2$ (0 °C, 1 h),[8] and this reaction mixture was treated with more $Et_3N$ (2.0 equiv.) and MeO(Me)$NH_2$Cl (1.0 equiv.; 5 °C, 1.5 h) to give Weinreb amide **7** after aqueous acidic work up.[9] The latter compound was converted to vinyl ketone **3** by using vinylmagnesium bromide (1.2 equiv.) in THF (23 °C, 4 h). Success of this step was highly dependent on the workup conditions, as the liberated secondary amine tends to attack the vinyl ketone by conjugate addition.[10] We recommend to quench the reaction mixture by dropwise transfer into an equal volume of hydrochloric acid (1 M) at 0 °C. The yield of vinyl ketone **3** is 64% over three steps. Compound **3** decomposes within hours, but it can be stored if hydroquinone (2 mol-%) is used as a stabilizer.

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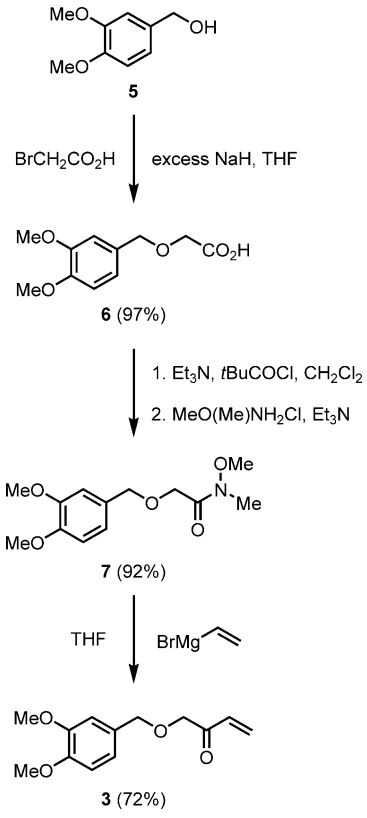
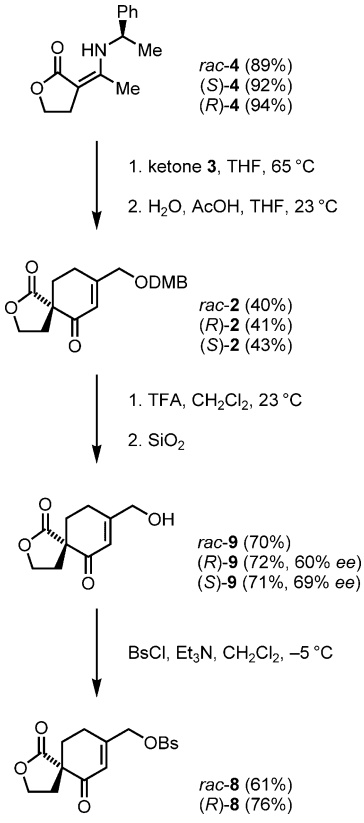



Scheme 2. Synthesis of protected Michael acceptor **3**.

The reaction sequence leading to canangone was first developed and optimized in the racemic series. Enamines **4** were prepared from α-acetylbutyrolactone by following the procedure of Pfau[5] (89–94% yield). Subsequent Michael reaction with vinyl ketone **3** (1 equiv.; THF, 65 °C, 18 h) did not stop at the stage of conjugate addition but proceeded further to give a spirocyclic imine, which was difficult to isolate and purify. Therefore, hydrolysis with aqueous acetic acid (10%; 2.0 equiv.) in THF (23 °C, 24 h) was directly performed in the same reaction flask, which gave spirocyclic ketones **2**. The yield (40–43%) after chromatographic purification remained unsatisfactory even after tedious optimization. Subsequent cleavage of the protecting group (10% TFA in $CH_2Cl_2$, 23 °C, 1.5 h)[11] gave hexamethoxytribenzocyclononane as a byproduct,[12] which made chromatographic separation necessary to give pure compound **9** (70–72% yield). Because primary alcohols **9** gave sufficient baseline resolution on chiral GLC, the stereoselectivity of the Michael reaction was determined to be 60–69% *ee*, and it was observed that the selectivity was sensitive to the reaction conditions at this stage. Selectivities in this range are often observed with phenethylamine as a chiral auxiliary in enamine-Michael reactions with methyl vinyl ketone.[13]

Work from Pfau and d'Angelo predict the (*R*) configuration when starting from (*S*)-phenethylamine.[5,6] This was confirmed by X-ray single-crystal structure determination of brosylate (*R*)-**8**, which was prepared according to a standard protocol (1.1 equiv. BsCl, 1.5 equiv. $Et_3N$, $CH_2Cl_2$, –5 °C, 12 min; Scheme 3).[14] The bromine and sulfur atom in this compound allowed for anomalous dispersion, which gave the (*R*) configuration (Figure 1) with an absolute structure parameter[15] of –0.009(5).[16] It must be pointed out, however, that the material used for the synthesis of (*R*)-**8** was only 60% *ee*, but when additional single crystals were picked from that crop and analyzed by chiral GLC, all these samples showed the (*R*) configuration. The racemate of **8**, by the way, is an oil.




Scheme 3. Robinson annulation, deprotection, and determination of absolute configuration. DMB = 3,4-$(MeO)_2C_6H_3CH_2$–, Bs = 4-$BrC_6H_4SO_2$–.

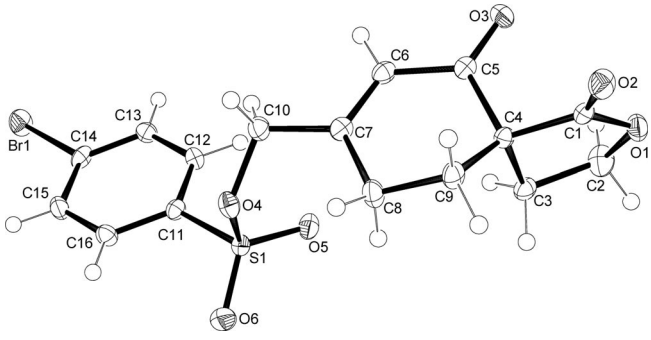


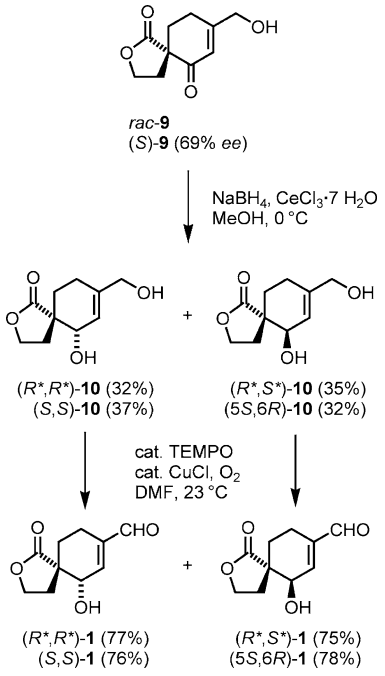

Figure 1. ORTEP view of optically active bromosulfonate **8**. The depicted enantiomer has the (*R*) configuration.

After finishing the synthesis of (*R*,*R*)-canangone (**1**; $[\alpha]_D^{20}$ = –67.0, vide infra), we realized, that this is the enantiomer of the originally isolated natural product ($[\alpha]_D^{25}$ = +58.8). Therefore, the whole synthesis had to be repeated

in the (*S*) series starting from the (*R*)-configured chiral auxiliary.

The synthesis of canangone (**1**) was finished in both the racemic as well as the (*S*) series (69% *ee* of **9**) as depicted in Scheme 4. First of all, Luche reduction[17] of the conjugated enone moiety yielded allylic alcohols **10** without any stereoselectivity (1.05 equiv. $NaBH_4$, 1.05 equiv. $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 1.5 h). The two diastereoisomers, however, could be easily separated by column chromatography. In the racemic series, single crystals could be grown from the more apolar isomer, and the crystals were suitable for another X-ray structure analysis. This confirmed the relative (*R**,*S**) configuration, which is shown in Figure 2. The primary alcohol groups of both diastereoisomers of **10** could be selectively oxidized by using TEMPO/CuCl (both 0.3 equiv., 1 atm $O_2$, DMF, 23 °C, 75 min)[18] to furnish both canangone **1** and its 6-epimer in both the racemic as well as the (5*S*) series in 75–78% yields.




Scheme 4. Synthesis of (+)-(*S*,*S*)-canangone (**1**) and (–)-6-*epi*-canangone [(5*S*,6*R*)-**1**].

Comparison of our $^1H$ and $^{13}C$ NMR spectroscopic data of (*R**,*R**)-**1** and (*R**,*S**)-**1** with the original publication confirmed the relative (*R**,*R**) configuration of canangone (**1**) as proposed by Caloprisco and coworkers.[1] Moreover, the optical rotation of our (*S*,*S*) material was $[\alpha]_D^{20}$ = +107.5 (*c* = 1.87, MeOH; 69% *ee*), which corresponds to the original literature value of the natural material: $[\alpha]_D^{25}$ = +58.8 (*c* = 0.68, MeOH; unknown *ee*). Therefore, we clearly conclude that the absolute configuration of (+)-canangone (**1**) is (*S*,*S*). Deviation of the absolute value might be due to minor differences in experimental conditions or might result from optically active impurities of the samples. Interestingly, 6-*epi*-canangone [(*S*,*R*)-**1**] showed opposite optical rotation: $[\alpha]_D^{20}$ = –71.4 (*c* = 1.56, MeOH; 69% *ee*). Having now both optically active epimers of Canangone (**1**) in hand, and being able to prepare their enantiomers, we started to confirm the results on the biological activity with all four stereoisomers of this natural product.

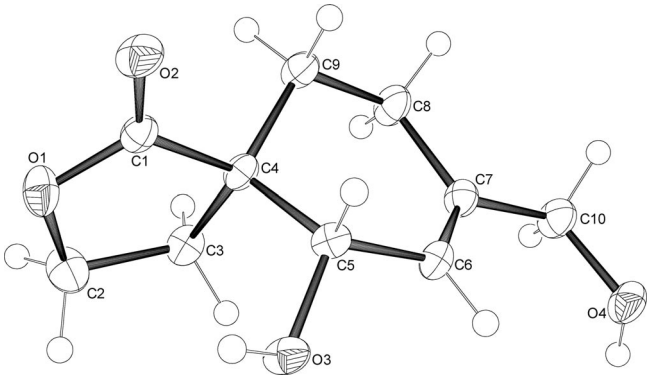



Figure 2. ORTEP view of racemic diol (*R**,*S**)-**10**. The depicted enantiomer has the (5*R*,6*S*) configuration.

## Conclusions

(+)-(*S*,*S*)-Canangone (**1**) and its 6-epimer [(5*S*,6*R*)-**1**] were prepared for the first time by the sequence of asymmetric Michael reaction, aldol condensation, reduction of the carbonyl groups, and oxidation to carbonyl groups. The absolute and relative configurations were established by X-ray crystallography. This work confirms the originally proposed relative configuration, and the so far unknown absolute configuration of this natural product was established for the first time.

## Experimental Section

**General Methods:** Preparative column chromatography was carried out by using Merck $SiO_2$ (0.035–0.070 mm, type 60 A) with hexanes (PE, b.p. 40–60 °C), ethyl acetate (EA), or $CH_2Cl_2$ as eluants. TLC was performed on Merck $SiO_2$ $F_{254}$ plates on aluminium sheets. $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker Avance DRX 500 or an Avance DPX 300 spectrometer. Multiplicities were determined with DEPT experiments. MS and HRMS spectra (EI and CI) were obtained with a Finnigan MAT 95 spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond-ATR unit. Elemental analyses were measured with an EA 1108 from Fisons Instruments. GLC analysis was performed with a Focus equipped with Triplus autosampler (Thermo Electron) and FID on a column Lipodex E (25 m × 0.25 mm, chiral phase) with hydrogen carrier gas (0.4 bar). All starting materials were commercially available. Optical rotations were measured with a Perkin–Elmer Polarimeter 343. Procedures using NaH or vinylmagnesium bromide (0.7 M in THF, Acros) were performed in flame-dried glassware and with absolute solvent under a nitrogen atmosphere.

**(3,4-Dimethoxybenzyloxy)acetic Acid (6):** A solution of 3,4-dimethoxybenzyl alcohol (**5**; 14.7 g, 87.5 mmol) in absolute THF (30 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 7.76 g, 194 mmol) in absolute THF (30 mL) under an atmosphere of nitrogen at 0 °C. After the mixture was stirred for 1 h, a solution of bromoacetic acid (8.00 g, 57.6 mmol) in absolute THF (30 mL)

was added, and the mixture was stirred for 2 h at 23 °C, after which additional absolute THF (400 mL) was added, and the mixture was heated at reflux for 2 d. The reaction mixture was cooled to 0 °C before it was diluted with ice-cold water (250 mL) and extracted with $CH_2Cl_2$ (3 × 150 mL). The aqueous layer was then acidified with concentrated hydrochloric acid (15 mL) to pH 1 and extracted with $CH_2Cl_2$ (3 × 150 mL). The combined extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo to give acid **6** (12.7 g, 56.1 mmol, 97%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 3.78 (s, 3 H), 3.80 (s, 3 H), 4.05 (s, 2 H), 4.49 (s, 2 H), 6.76 (d, $J$ = 8.0 Hz, 1 H), 6.80 (br. d, $J$ = 8.1 Hz, 1 H), 6.86 (br. s, 1 H), 10.21 (br. s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 55.51 ($CH_3$), 55.56 ($CH_3$), 65.92 ($CH_2$), 72.96 ($CH_2$), 110.69 (CH), 111.17 (CH), 120.64 (CH), 128.89 (C), 148.69 (C), 148.79 (C), 174.87 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3173 (m, br), 3085 (w), 3022 (w), 2964 (m), 2941 (w), 2870 (w), 2844 (w), 1772 (s), 1746 (s), 1609 (w), 1595 (m), 1515 (s), 1467 (m), 1456 (m), 1424 (s), 1373 (m), 1348 (w), 1322 (w), 1300 (w), 1258 (vs), 1178 (s), 1162 (vs), 1145 (vs), 1026 (vs), 969 (s), 940 (m), 927 (m), 902 (w), 816 (s), 768 (s), 744 (s) cm$^{-1}$. MS (EI, 70 eV): $m/z$ (%) = 226 (67) [M]$^+$, 167 (14), 151 (100), 139 (11). $C_{11}H_{14}O_5$ (226.23): calcd. C 58.40, H 6.24; found C 58.10, H 6.41.

**2-(3,4-Dimethoxybenzyloxy)-*N*-methoxy-*N*-methylacetamide (7):** $Et_3N$ (3.00 g, 29.6 mmol) was added to a stirred solution of acid **6** (6.11 g, 27.0 mmol) in absolute $CH_2Cl_2$ (90 mL) at –5 to 0 °C and stirred for 15 min before pivaloyl chloride (3.26 g, 27.0 mmol) was added. After 1 h, MeO(Me)$NH_2$Cl (2.63 g, 27.0 mmol) was added in one portion, followed by the dropwise addition of $Et_3N$ (5.46 g, 54.0 mmol). After additional stirring for 1.5 h (or until the disappearance of anhydride monitored by TLC; PE/EA, 2:1; $R_f$ = 0.43) at 0 to 5 °C, the reaction mixture was washed with hydrochloric acid (1 M, 20 mL), a saturated solution of $NaHCO_3$ (20 mL), and brine (20 mL), and the organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on $SiO_2$ (EA, $R_f$ = 0.44) to give Weinreb amide **7** (6.71 g, 24.9 mmol, 92%) as a light yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 3.18 (s, 3 H), 3.63 (s, 3 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 4.25 (s, 2 H), 4.60 (s, 2 H), 6.82 (d, $J$ = 8.1 Hz, 1 H), 6.90 (dd, $J$ = 1.7 Hz, $J$ = 8.1 Hz, 1 H), 6.97 (d, $J$ = 1.8 Hz, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 32.11 ($CH_3$), 55.68 ($CH_3$), 55.73 ($CH_3$), 61.20 ($CH_3$), 66.53 ($CH_2$), 72.95 ($CH_2$), 110.69 (CH), 111.25 (CH), 120.54 (CH), 129.92 (C), 148.61 (C), 148.90 (C), 170.88 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3000 (w), 2939 (m), 2913 (w), 2838 (w), 1677 (s), 1609 (w), 1594 (m), 1516 (vs), 1464 (m), 1420 (m), 1393 (w), 1330 (m), 1263 (vs), 1237 (vs), 1182 (m), 1159 (vs), 1137 (vs), 1085 (s), 1027 (vs), 993 (s), 952 (m), 923 (w), 857 (m), 812 (m), 767 (m) cm$^{-1}$. MS (EI, 70 eV): $m/z$ (%) = 269 (8) [M]$^+$, 167 (8), 152 (10), 151 (100), 107 (10), 103 (63), 73 (26). $C_{13}H_{19}NO_5$ (269.30): calcd. C 57.98, H 7.11, N 5.20; found C 58.40, H 7.24, N 5.39.

**1-(3,4-Dimethoxybenzyloxy)-3-buten-2-one (3):** A solution of vinylmagnesium bromide (38.2 mL, 26.7 mmol, 0.7 M in THF) was added dropwise to a cooled (–5 °C) solution of Weinreb amide **7** (6.00 g, 22.3 mmol) in absolute THF (180 mL) under nitrogen. The resulting mixture was slowly warmed and then stirred for 4 h at 23 °C. Subsequently, it was transferred via a cannula into a cooled (0 °C) solution of hydrochloric acid (1 M, 140 mL). The biphasic mixture was extracted with diethyl ether (3 × 30 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on $SiO_2$ (PE/EA, 1:1; $R_f$ = 0.47) to give vinyl ketone **3** (3.80 g, 16.1 mmol, 72%) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 3.76 (s, 3 H), 3.77 (s, 3 H), 4.16 (s, 2 H), 4.44 (s, 2 H), 5.71 (d, $J$ = 10.7 Hz, 1 H), 6.21 (d, $J$ = 17.6 Hz, 1 H), 6.40 (dd, $J$ = 10.7 Hz, $J$ = 17.6 Hz, 1 H), 6.73 (d, $J$ = 8.1 Hz, 1 H), 6.78 (br. d, $J$ = 8.3 Hz, 1 H), 6.84 (br. s, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 55.46 ($CH_3$), 55.51 ($CH_3$), 72.83 ($CH_2$), 73.07 ($CH_2$), 110.61 (CH), 110.99 (CH), 120.35 (CH), 128.73 ($CH_2$), 129.34 (C), 132.17 (CH), 148.54 (C), 148.75 (C), 196.78 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3001 (w), 2938 (m), 2910 (w), 2866 (w), 2836 (m), 1737 (w), 1714 (m), 1697 (s), 1613 (w), 1593 (w), 1517 (vs), 1464 (m), 1419 (m), 1403 (w), 1365 (w), 1265 (s), 1237 (m), 1216 (w), 1159 (m), 1138 (m), 1066 (w), 1027 (m), 991 (w), 891 (w), 859 (w), 809 (w), 764 (w) cm$^{-1}$. MS (EI, 70 eV): $m/z$ (%) = 236 (5) [M]$^+$, 166 (54), 151 (100), 107 (8). HRMS (CI, isobutane): calcd. for $C_{13}H_{17}O_4$ [M + H]$^+$ 237.1127; found 237.1126.

**(*Z*)-3-[1-(1-Phenylethylamino)ethylidene]dihydro-2-furanone (4):** A mixture of 2-acetylbutyrolactone (1.00 g, 7.80 mmol) and *rac*-phenethylamine (945 mg, 7.80 mmol) was stirred at 23 °C for 4 h under an atmosphere of nitrogen. It was then diluted with $CH_2Cl_2$ (20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on $SiO_2$ (PE/EA, 1:1; $R_f$ = 0.45) to give racemic enamino lactone *rac*-**4** (1.60 g, 6.91 mmol, 89%) as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.51 (d, $J$ = 6.8 Hz, 3 H), 1.78 (s, 3 H), 2.73–2.84 (m, 2 H), 4.23–4.30 (m, 2 H), 4.63 (pent, $J$ = 7.0 Hz, 1 H), 7.22–7.26 (m, 3 H) 7.32–7.34 (m, 2 H), 8.61 (br. d, $J$ = 5.7 Hz, 1 H) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 16.78 ($CH_3$), 24.87 ($CH_3$), 26.36 ($CH_2$), 52.95 (CH), 65.10 ($CH_2$), 86.10 (C), 125.42 (2 CH), 127.10 (CH), 128.79 (2 CH), 145.02 (C), 156.41 (C), 174.04 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3285 (w), 3223 (w), 3083 (w), 3061 (w), 3028 (w), 2971 (w), 2922 (w), 2907 (w), 2865 (w), 1769 (w), 1686 (s), 1618 (vs), 1476 (w), 1453 (m), 1408 (w), 1371 (m), 1279 (w), 1225 (vs), 1156 (w), 1099 (m), 1026 (m), 999 (w), 966 (m), 894 (w), 767 (m), 702 (m) cm$^{-1}$. MS (EI, 70 eV): $m/z$ (%) = 231 (82) [M]$^+$, 216 (55) [M – Me]$^+$, 145 (10), 127 (24), 105 (100). HRMS (CI, isobutane): calcd. for $C_{14}H_{18}NO_2$ [M + H]$^+$ 232.1337; found 232.1338.

In analogy, (*R*)-**4** (4.26 g, 18.4 mmol, 94%) was prepared from (*R*)-phenethylamine (2.36 g, 19.5 mmol). Colorless solid. M.p. 72–73 °C. $[\alpha]_D^{20}$ = –512.4 ($c$ = 1.15, MeOH).

In analogy, (*S*)-**4** (3.31 g, 14.3 mmol, 92%) was prepared from (*S*)-phenethylamine (1.89 g, 15.6 mmol). Colorless solid. M.p. 71–72 °C. $[\alpha]_D^{20}$ = +474.9 ($c$ = 0.86, MeOH).

**8-(3,4-Dimethoxybenzyloxymethyl)-2-oxaspiro[4.5]dec-7-ene-1,6-dione (2):** A solution of vinyl ketone **3** (1.30 g, 5.50 mmol) in absolute THF (10 mL) was added to a solution of enamino lactone *rac*-**4** (1.40 g, 6.05 mmol) in absolute THF (10 mL). The mixture was stirred at 65 °C for 18 h under an atmosphere of nitrogen. The solvent was then removed under reduced pressure, and the crude product was directly subjected to hydrolysis by dissolving it in a mixture of THF (15 mL) and aqueous acetic acid (10%, 5.5 mL). The mixture was stirred at room temperature for 24 h, and then the solvent was removed in vacuo, the residue diluted with hydrochloric acid (1 M, 5 mL) and extracted with $CH_2Cl_2$ (4 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on $SiO_2$ ($CH_2Cl_2$/EA, 4:1; $R_f$ = 0.52) to give ketone *rac*-**2** (760 mg, 2.19 mmol, 40%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.01–2.10 (m, 1 H), 2.10 (dt, $J$ = 13.1 Hz, $J$ = 8.5 Hz, 1 H), 2.29 (dt, $J$ = 18.5 Hz, $J$ = 5.8 Hz, 1 H), 2.45 (ddd, $J$ = 5.2 Hz, $J$ = 6.4 Hz, $J$ = 13.6 Hz, 1 H), 2.71–2.78 (m, 2 H), 3.88 (s, 3 H, $OCH_3$), 3.89 (s, 3 H, $OCH_3$), 4.11 (s, 2 H, 8-$CH_2$), 4.36 (dt, $J$ = 3.9 Hz, $J$ = 8.7 Hz, 1 H, 3-H), 4.42 (dt, $J$ = 7.1 Hz, $J$ = 8.7 Hz, 1 H, 3-H), 4.50 (s, 2 H, Ar$CH_2$), 6.20 (pent, $J$ = 1.5 Hz, 1 H, 7-H), 6.86–6.89 (m, 3 H, ArH) ppm. $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): $\delta$ = 23.27 ($CH_2$), 30.39 ($CH_2$), 32.41 ($CH_2$), 53.36 (C), 55.76 ($CH_3$),

55.80 ($CH_3$), 65.80 ($CH_2$), 71.12 ($CH_2$), 72.70 ($CH_2$), 110.88 (CH), 111.01 (CH), 120.36 (CH), 122.19 (CH), 129.75 (C), 148.73 (C), 148.97 (C), 162.79 (C), 175.38 (C), 194.24 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3058 (w), 2997 (w), 2935 (m), 2920 (w), 2866 (w), 2837 (w), 1770 (vs), 1715 (w), 1663 (vs), 1607 (w), 1593 (w), 1516 (s), 1464 (m), 1452 (m), 1420 (m), 1375 (m), 1341 (w), 1264 (s), 1238 (m), 1217 (m), 1187 (m), 1158 (s), 1139 (s), 1101 (w), 1083 (w), 1059 (w), 1027 (s), 961 (w), 914 (w), 869 (w), 811 (w), 765 (w), 731 (m) $cm^{-1}$. MS (EI, 70 eV): *m*/*z* (%) = 346 (40) $[M]^+$, 167 (29), 151 (100). HRMS (EI, 70 eV): calcd. for $C_{19}H_{22}O_6$ $[M]^+$ 346.1416; found 346.1415.

In analogy, (*R*)-**2** (1.17 g, 3.37 mmol, 41%) was prepared from (*S*)-**4** (2.10 g, 9.10 mmol). Colorless oil. $[\alpha]_D^{20}$ = –36.6 (*c* = 1.63, MeOH).

In analogy, (*S*)-**2** (1.94 g, 5.60 mmol, 43%) was prepared from (*R*)-**4** (3.33 g, 14.4 mmol). Colorless oil. $[\alpha]_D^{20}$ = +47.2 (*c* = 3.14, MeOH).

**8-Hydroxymethyl-2-oxaspiro[4.5]dec-7-ene-1,6-dione (9):** TFA (10% solution in $CH_2Cl_2$, 34 mL) was added to a solution of compound *rac*-**2** (213 mg, 0.614 mmol) in $CH_2Cl_2$ (2 mL) at 23 °C. After stirring for 1.5 h at the same temperature, the reaction mixture was filtered through a pad of silica (5 cm). The volatile materials were removed in vacuo, and the residue was purified by column chromatography on $SiO_2$ ($CH_2Cl_2$/EA, 1:1; $R_f$ = 0.13) to obtain a first fraction containing hexamethoxytribenzocyclononane ($R_f$ = 0.75) as a light yellow solid (10.0 mg, 0.022 mmol). The second fraction was allylic alcohol *rac*-**9** (84.0 mg, 0.428 mmol, 70%), a light yellow oil. GLC (2 min at 60 °C, then with 0.5 K $min^{-1}$ to 160 °C, then 1 min at 160 °C, then with 0.2 K $min^{-1}$ to 185 °C, finally 150 min at 185 °C): $t_R(R)$ = 325 min, $t_R(S)$ = 454 min. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.89 (t, *J* = 6.1 Hz, 1 H, OH), 2.03–2.11 (m, 1 H), 2.11 (dt, *J* = 13.0 Hz, *J* = 8.5 Hz, 1 H), 2.27 (dt, *J* = 18.5 Hz, *J* = 5.5 Hz, 1 H), 2.46 (ddd, *J* = 5.2 Hz, *J* = 6.2 Hz, *J* = 13.6 Hz, 1 H), 2.69–2.80 (m, 2 H), 4.25 (A part of an ABX system, $J_{AX}$ = 6.3 Hz, $J_{AB}$ = 16.7 Hz, 1 H, 8-CH*H*), 4.27 (B part of an ABX system, $J_{BX}$ = 5.6 Hz, $J_{AB}$ = 16.7 Hz, 1 H, 8-C*H*H), 4.36 (dt, *J* = 4.0 Hz, *J* = 8.7 Hz, 1 H, 3-H), 4.43 (dt, *J* = 7.1 Hz, *J* = 8.7 Hz, 1 H, 3-H), 6.20 (pent, *J* = 1.5 Hz, 1 H, 7-H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 23.03 ($CH_2$), 30.49 ($CH_2$), 32.51 ($CH_2$), 53.65 (C), 64.49 ($CH_2$), 66.07 ($CH_2$), 120.71 (CH), 166.26 (C), 175.94 (C), 194.67 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3447 (br. m), 2982 (w), 2927 (w), 2873 (w), 2842 (w), 1756 (vs), 1656 (vs), 1513 (w), 1479 (w), 1427 (m), 1377 (m), 1347 (m), 1323 (w), 1295 (m), 1216 (s), 1188 (s), 1159 (m), 1146 (m), 1127 (m), 1098 (w), 1052 (s), 1028 (vs), 997 (m), 960 (m), 930 (m), 866 (w), 791 (w), 731 (w), 707 (w) $cm^{-1}$. MS (CI, isobutane): *m*/*z* (%) = 393 (26) $[2M + H]^+$, 197 (100) $[M + H]^+$, 179 (8), 135 (5). HRMS (EI, 70 eV): calcd. for $C_{10}H_{12}O_4$ $[M]^+$ 196.0735; found 196.0735.

In analogy, (*R*)-**9** (740 mg, 3.77 mmol, 72%) was prepared from (*R*)-**2** (1.80 g, 5.19 mmol). Light yellow oil. GLC: $t_R(R)$ = 325 min (major), $t_R(S)$ = 454 min (minor), 60% *ee*. $[\alpha]_D^{20}$ = –60.8 (*c* = 1.54, MeOH).

In analogy, (*S*)-**9** (600 mg, 3.05 mmol, 71%) was prepared from (*S*)-**2** (1.50 g, 4.33 mmol). Light yellow solid. M.p. 84–85 °C. GLC: $t_R(R)$ = 326 min (minor), $t_R(S)$ = 446 min (major), 69% *ee*. $[\alpha]_D^{20}$ = +84.8 (*c* = 1.19, MeOH).

**(1,6-Dioxo-2-oxaspiro[4.5]-7-decen-8-yl)methyl-4-bromobenzenesulfonate: (8):** $Et_3N$ (38.7 mg, 0.382 mmol) and brosyl chloride (71.7 mg, 0.281 mmol) were subsequently added to a cooled solution of allylic alcohol *rac*-**9** (50.0 mg, 0.255 mmol) in $CH_2Cl_2$ (1 mL) at –5 °C, and the resulting mixture was stirred for 12 min at the same temperature. The reaction mixture was then washed with hydrochloric acid (1 M, 1 mL), saturated solution of $NaHCO_3$ (1 mL), and brine (1 mL), and the organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on $SiO_2$ (PE/EA, 1:1; $R_f$ = 0.24) to give *rac*-**8** (65.0 mg, 0.156 mmol, 61%) as a light yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.02 (ddd, *J* = 5.2 Hz, *J* = 7.6 Hz, *J* = 13.8 Hz, 1 H), 2.08 (dt, *J* = 12.9 Hz, *J* = 8.4 Hz, 1 H), 2.28 (dt, *J* = 18.7 Hz, *J* = 5.3 Hz, 1 H), 2.40 (ddd, *J* = 5.3 Hz, *J* = 6.2 Hz, *J* = 13.7 Hz, 1 H), 2.66–2.71 (m, 2 H), 4.31–4.39 (m, 2 H), 4.65 (A part of an AB system, *J* = 14.7 Hz, 1 H), 4.67 (B part of an AB system, *J* = 15.0 Hz, 1 H), 6.03 (pent, *J* = 1.3 Hz, 1 H, 7-H), 7.70–7.73 (m, 2 H), 7.76–7.77 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 22.94 ($CH_2$), 30.16 ($CH_2$), 32.26 ($CH_2$), 53.13 (C), 65.93 ($CH_2$), 70.07 ($CH_2$), 123.91 (CH), 129.33 (2 CH), 129.63 (C), 132.82 (2 CH), 134.36 (C), 156.30 (C), 174.79 (C), 193.51 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3102 (w), 3082 (w), 3063 (w), 3017 (w), 2983 (w), 2950 (w), 2915 (w), 2890 (w), 2872 (w), 2825 (w), 1759 (s), 1662 (s), 1632 (m), 1575 (m), 1471 (m), 1454 (w), 1443 (w), 1421 (w), 1393 (m), 1385 (m), 1363 (s), 1347 (m), 1284 (m), 1260 (m), 1217 (m), 1178 (vs), 1135 (m), 1091 (m), 1070 (m), 1057 (m), 1032 (s), 997 (m), 957 (vs), 931 (m), 889 (m), 872 (m), 792 (vs), 774 (vs), 731 (m), 721 (m), 655 (m) $cm^{-1}$. MS (CI, isobutane): *m*/*z* (%) = 829 (66) $[2M + H]^+$, 673 (8), 595 (30), 453 (10), 415 (100), 259 (14), 179 (19). HRMS (CI, isobutane): calcd. for $C_{16}H_{16}BrO_6S$ 414.9851; found 414.9850.

In analogy, (*R*)-**8** (325 mg, 0.782 mmol, 76%) was prepared from (*R*)-**9** (200 mg, 1.02 mmol). Light yellow solid. M.p. 126 °C. $[\alpha]_D^{20}$ = –44.8 (*c* = 0.59, MeOH). Single crystals were grown from $CH_2Cl_2$/pentane at 23 °C.

**6-Hydroxy-8-(hydroxymethyl)-2-oxaspiro[4.5]dec-7-en-1-one (10):** $CeCl_3 \cdot 7H_2O$ (874 mg, 2.36 mmol) was added to a cooled solution of allylic alcohol **9** (443 mg, 2.26 mmol) in MeOH (8 mL) at –5 °C. After stirring the reaction mixture for 30 min at –5 to 0 °C, $NaBH_4$ (89 mg, 2.36 mmol) was added portionwise, and the resulting mixture was stirred for 1.5 h at the same temperature. Then the reaction mixture was diluted with water (5 mL), and the solvent was removed in vacuo. The resulting residue was extracted with EtOAc (4 × 5 mL). The combined organic layer was dried with $MgSO_4$, filtered, and the solvents evaporated in vacuo. The crude product was purified by column chromatography on $SiO_2$ (EA) to obtain two fractions: first the (*R**,*S**) diastereomer (155 mg, 0.782 mmol, 35%; $R_f$ = 0.28) as a colorless solid, m.p. 99 °C (single crystals were grown from EA/pentane at 23 °C), and second the (*R**,*R**) diastereomer (142 mg, 0.716 mmol, 32%; $R_f$ = 0.20) as a colorless oil. Data for the (*R**,*S**) diastereomer (EA, $R_f$ = 0.28): $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.59 (br. s, 1 H, OH), 1.79 (ddd, *J* = 2.8 Hz, *J* = 5.2 Hz, *J* = 13.4 Hz, 1 H), 1.90–2.03 (m, 2 H), 2.07–2.15 (m, 2 H), 2.20–2.23 (m, 1 H), 2.51 (ddd, *J* = 6.2 Hz, *J* = 8.5 Hz, *J* = 14.6 Hz, 1 H), 4.06 (s, 2 H, 8-$CH_2$), 4.30 (dt, *J* = 6.1 Hz, *J* = 8.5 Hz, 1 H, 3-H), 4.38 (dt, *J* = 6.3 Hz, *J* = 8.6 Hz, 1 H, 3-H), 4.62 (br. s, 1 H, 6-H), 5.63 (sex, *J* = 1.7 Hz, 1 H, 7-H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 22.36 ($CH_2$), 26.65 ($CH_2$), 28.22 ($CH_2$), 47.90 (C), 65.42 ($CH_2$), 66.75 ($CH_2$), 70.11 (CH), 123.99 (CH), 139.30 (C), 181.99 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3395 (br. s), 2987 (w), 2925 (m), 2867 (w), 1745 (vs), 1450 (w), 1434 (w), 1382 (m), 1344 (w), 1271 (w), 1220 (s), 1193 (s), 1060 (m), 1028 (s), 893 (w), 830 (w), 745 (w), 704 (w) $cm^{-1}$. MS (EI, 70 eV): *m*/*z* (%) = 198 (8) $[M]^+$, 180 (22), 134 (18), 99 (43), 84 (100), 82 (50), 49 (65). HRMS (CI, isobutane): calcd. for $C_{10}H_{15}O_4$ $[M + H]^+$ 199.0970; found 199.0970. Data for the (*R**,*R**) diastereomer (EA, $R_f$ = 0.20): $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.56 (br. s, 1 H, OH), 1.69–1.78 (m, 1 H), 2.00–2.13 (m, 1 H), 2.10 (ddd, *J* = 4.5 Hz, *J* = 7.1 Hz, *J* = 12.8 Hz, 1 H), 2.24 (ddd, *J* = 5.0 Hz, *J* = 8.7 Hz, *J* = 19.5 Hz, 1 H), 2.19–2.30 (m, 2 H), 3.04 (d, *J* = 5.6 Hz, 1 H, 6-OH), 4.06–4.09

(m, 2 H, 8-$CH_2$), 4.15 (t, $J$ = 4.4 Hz, 1 H, 6-H), 4.31 (dt, $J$ = 7.5 Hz, $J$ = 8.8 Hz, 1 H, 3-H), 4.37 (dt, $J$ = 4.5 Hz, $J$ = 8.8 Hz, 1 H, 3-H), 5.80–5.84 (m, 1 H, 7-H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 22.55 ($CH_2$), 25.20 ($CH_2$), 32.24 ($CH_2$), 45.95 (C), 65.40 ($CH_2$), 65.77 ($CH_2$), 68.75 (CH), 121.01 (CH), 141.51 (C), 179.73 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3387 (br. s), 2922 (m), 2863 (w), 1749 (vs), 1486 (w), 1450 (w), 1431 (w), 1377 (m), 1259 (w), 1215 (s), 1188 (s), 1167 (s), 1056 (s), 1028 (vs), 962 (w) $cm^{-1}$. MS (CI, isobutane): $m/z$ (%) = 199 (2) $[M + H]^+$, 181 (100), 163 (27), 87 (5). HRMS (CI, isobutane): calcd. for $C_{10}H_{15}O_4$ $[M + H]^+$ 199.0970; found 199.0969.

In analogy, (5*R*,6*S*)-**10** (165 mg, 0.832 mmol, 36%) as a colorless oil (slowly solidifying at 5 °C), $[\alpha]_D^{20}$ = +30.6 ($c$ = 0.47, MeOH) and (*R*,*R*)-**10** (150 mg, 0.756 mmol, 33%) as a colorless solid, m.p. 105 °C, $[\alpha]_D^{20}$ = –53.2 ($c$ = 0.88, MeOH) were prepared from (*R*)-**9** (450 mg, 2.29 mmol).

In analogy, (5*S*,6*R*)-**10** (96 mg, 0.48 mmol, 32%) as a colorless solid, m.p. 78–79 °C, $[\alpha]_D^{20}$ = –32.8 ($c$ = 0.71, MeOH), and (*S*,*S*)-**10** (110 mg, 0.554 mmol, 37%) as a colorless oil (slowly solidifying at 5 °C), $[\alpha]_D^{20}$ = +66.4 ($c$ = 1.02, MeOH) were prepared from (*S*)-**9** (300 mg, 1.51 mmol).

**(*R**,*R**)-6-Hydroxy-1-oxo-2-oxaspiro[4.5]dec-7-ene-8-carbaldehyde (*R**,*R**-1):** TEMPO (4.0 mg, 0.026 mmol) and CuCl (2.6 mg, 0.026 mmol) were added to a stirred solution of (*R**,*R**)-diol **10** (17 mg, 0.086 mmol) in absolute DMF (1 mL) at 23 °C under exclusion of moisture. The reaction flask was then cooled with $N_2$(l), evacuated, filled with $O_2$ (1 atm, balloon), and the mixture was stirred at 23 °C for 75 min. Subsequently, it was diluted with a saturated aqueous solution of $CuSO_4$ (1 mL) and extracted with EA (4 × 1 mL). The combined organic layers were washed with water (2 mL) and brine (2 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on $SiO_2$ (EA, $R_f$ = 0.40) to obtain (*R**,*R**)-canangone (**1**; 13 mg, 0.066 mmol, 77%) as a colorless oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.76 (ddd, $J$ = 6.0 Hz, $J$ = 8.0 Hz, $J$ = 14.0 Hz, 1 H, 10-H), 2.07 (ddd, $J$ = 3.6 Hz, $J$ = 7.1 Hz, $J$ = 12.8 Hz, 1 H, 4-H), 2.21 (dt, $J$ = 14.0 Hz, $J$ = 5.6 Hz, 1 H, 10-H), 2.29 (dtt, $J$ = 18.7 Hz, $J$ = 5.7 Hz, $J$ = 1.4 Hz, 1 H, 9-H), 2.39 (dddt, $J$ = 18.7 Hz, $J$ = 7.9 Hz, $J$ = 5.8 Hz, $J$ = 2.1 Hz, 1 H, 9-H), 2.47 (dt, $J$ = 12.8 Hz, $J$ = 8.9 Hz, 1 H, 4-H), 3.11 (t, $J$ = 7.8 Hz, 1 H, 6-OH), 4.33 (dt, $J$ = 7.1 Hz, $J$ = 9.1 Hz, 1 H, 3-H), 4.39 (dt, $J$ = 3.6 Hz, $J$ = 9.1 Hz, 1 H, 3-H), 4.36–4.40 (m, 1 H, 6-H), 6.68 (dt, $J$ = 3.4 Hz, $J$ = 1.8 Hz, 1 H, 7-H), 9.51 (s, 1 H, 8-CHO) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 18.66 ($CH_2$), 25.59 ($CH_2$), 32.21 ($CH_2$), 46.61 (C), 65.40 ($CH_2$), 69.35 (CH), 142.07 (C), 145.81 (CH), 178.31 (C), 193.20 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3432 (br. m), 2924 (m), 2854 (w), 2726 (w), 1750 (s), 1674 (vs), 1485 (w), 1451 (w), 1429 (w), 1378 (m), 1256 (w), 1215 (m), 1176 (s), 1124 (s), 1091 (w), 1061 (m), 1024 (vs), 998 (m), 962 (m), 902 (m), 869 (w), 826 (w), 783 (w), 769 (w), 711 (m), 658 (w) $cm^{-1}$. MS (EI, 70 eV): $m/z$ (%) = 196 (3) $[M]^+$, 167 (4), 149 (12), 134 (100), 121 (19), 105 (100), 99 (88), 91 (58), 77 (65), 65 (19), 53 (28), 41 (32). HRMS (CI, isobutane): calcd. for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0814, found 197.0814.

In analogy, (*R*,*R*)-**1** (31.0 mg, 0.158 mmol, 78%) was prepared from (*R*,*R*)-**10** (40.0 mg, 0.202 mmol). Colorless solid. M.p. 92–93 °C. $[\alpha]_D^{20}$ = –67.0 ($c$ = 1.25, MeOH).

In analogy, (*S*,*S*)-**1** (36.0 mg, 0.183 mmol, 76%) was prepared from (*S*,*S*)-**10** (48.0 mg, 0.242 mmol). Colorless solid. M.p. 98–99 °C. $[\alpha]_D^{20}$ = +107.5 ($c$ = 1.87, MeOH).

**(*R**,*S**)-6-Hydroxy-1-oxo-2-oxaspiro[4.5]dec-7-ene-8-carbaldehyde (*R**,*S**-1):** TEMPO (2.80 mg, 0.018 mmol) and CuCl (1.80 mg, 0.018 mmol) were added to a stirred solution of (*R**,*S**)-diol **10** (12.0 mg, 0.061 mmol) in absolute DMF (1 mL) at 23 °C under a nitrogen atmosphere. The reaction flask was then cooled with $N_2$(l), evacuated, filled with $O_2$ (1 atm, balloon), and the mixture was stirred at 23 °C for 75 min. Subsequently, it was diluted with a saturated aqueous solution of $CuSO_4$ (1 mL) and extracted with EA (4 × 1 mL). The combined organic layers were washed with water (2 mL) and brine (2 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on $SiO_2$ (EA, $R_f$ = 0.60) to obtain (*R**,*S**)-6-*epi*-canangone (**1**; 9.00 mg, 0.046 mmol, 75%) as a colorless oil. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.80–1.94 (m, 2 H), 1.97 (ddd, $J$ = 6.1 Hz, $J$ = 8.4 Hz, $J$ = 14.4 Hz, 1 H), 2.14–2.22 (m, 1 H), 2.43–2.50 (m, 1 H), 2.50 (ddd, $J$ = 6.4 Hz, $J$ = 8.6 Hz, $J$ = 14.8 Hz, 1 H), 3.44 (d, $J$ = 6.1 Hz, 1 H, 6-OH), 4.34 (dt, $J$ = 6.3 Hz, $J$ = 8.6 Hz, 1 H, 3-H), 4.42 (dt, $J$ = 6.1 Hz, $J$ = 8.7 Hz, 1 H, 3-H), 4.83–4.87 (m, 1 H, 6-H), 6.64–6.66 (m, 1 H), 9.51 (s, 1 H, 8-H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): $\delta$ = 18.48 ($CH_2$), 26.05 ($CH_2$), 27.49 ($CH_2$), 48.22 (C), 66.77 ($CH_2$), 70.27 (CH), 140.81 (C), 149.65 (CH), 181.10 (C), 192.92 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3437 (br. m), 2986 (w), 2930 (m), 2870 (w), 2849 (w), 1759 (vs), 1683 (vs), 1485 (w), 1451 (w), 1433 (w), 1381 (m), 1342 (w), 1221 (m), 1193 (s), 1167 (m), 1059 (m), 1030 (s), 1005 (m), 954 (w), 899 (w), 871 (w), 821 (w), 784 (w), 748 (w), 707 (w) $cm^{-1}$. MS (EI, 70 eV): $m/z$ (%) = 196 (14) $[M]^+$, 178 (14), 167 (9), 150 (12), 134 (23), 121 (40), 105 (55), 99 (100), 91 (44), 77 (73), 62 (36), 51 (27), 41 (35). HRMS (CI, isobutane): calcd. for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0814; found 197.0814.

In analogy, (5*R*,6*S*)-**1** (30.0 mg, 0.153 mmol, 76%) was prepared from (5*R*,6*S*)-**10** (40.0 mg, 0.202 mmol). Colorless oil. $[\alpha]_D^{20}$ = +58.9 ($c$ = 0.43, MeOH).

In analogy, (5*S*,6*R*)-**1** (34.0 mg, 0.173 mmol, 78%) was prepared from (5*S*,6*R*)-**10** (44.0 mg, 0.222 mmol). Colorless oil. $[\alpha]_D^{20}$ = –71.4 ($c$ = 1.56, MeOH).

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