First Asymmetric Synthesis of Stigmolone: The Fruiting Body Inducing Pheromone of the Myxobacterium *Stigmatella Aurantiaca*

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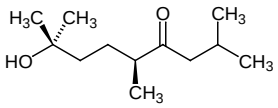
Abstract: The asymmetric synthesis of *(S)*- and *(R)*-stigmolone [*(S)*- and *(R)*-**1**], an aggregation pheromone of the myxobacterium *Stigmatella aurantiaca*, starting from 4-methylpentan-2-one is described. The stereogenic centre at the C-5 position of the pheromone was generated via the SAMP/RAMP hydrazone method with high enantiomeric purity. It could be shown again that both enantiomers induce the fruiting body formation of the myxobacterium at concentrations of 1.0−30.0 nM.

Key words: asymmetric synthesis, pheromones, hydrazones, natural products, *Stigmatella aurantiaca*

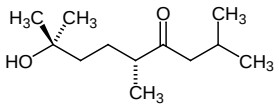
Myxobacteria like *Stigmatella aurantiaca* are Gram-negative, sticklike soil bacteria, which live in swarms on insoluble polymer surfaces like rotten wood. Gliding in a swarm has an immense profit for the food intake. This is due to an increase in the local density of secreted hydrolytic enzymes and therefore the amount of available soluble nutrients. The swarm and also the secreted slime serves as a carpet which prevents the loss of enzymes and nutrients. Typically for myxobacteria, *S. aurantiaca* exists in two different life cycles. In the vegetative growth cycle the population rises like normal bacteria through cell division, but under conditions of starvation the bacteria form multicellular fruiting bodies.[1,2] These fruiting bodies have a treelike structure and contain the myxospores, which are dormant cells. The change from the vegetative growth to the so-called development cycle is induced by the aggregation pheromone 8-hydroxy-2,5,8-trimethylnonan-4-one, which is named stigmolone after its biological origin and structure according to Plaga et al. Furthermore, this group published the first isolation[3,4] as well as a synthesis[5] of the racemate of this pheromone.

The natural product was isolated in racemic form perhaps due to the extensive isolation and purification procedures and the sensitivity of α-substituted ketones to racemisation. Plaga et al. also discovered an active concentration of 1.0 nM for the fruiting body formation, which makes this pheromone one of the most effective, non-peptidic bacterial pheromones known.[4] Mori et al. reported an 'exchiral-pool' synthesis starting either with *(R)*- or *(S)*-citronellol shortly after the first publication of stigmolone.[6,7] The bioassay of the enantiomers showed the same active concentration for the fruiting body formation as for the racemate and therefore the natural product seemed to be an enantiomeric mixture.[8] For further biological tests Mori et al. developed a new and short synthesis of the racemic pheromone.[9]

We now want to present the first asymmetric synthesis of *(S)*- and *(R)*-stigmolone [*(S)*- and *(R)*-**1**] and describe the results for the bioassays, which were carried out by Plaga.



(*S*)-**1**



(*R*)-**1**

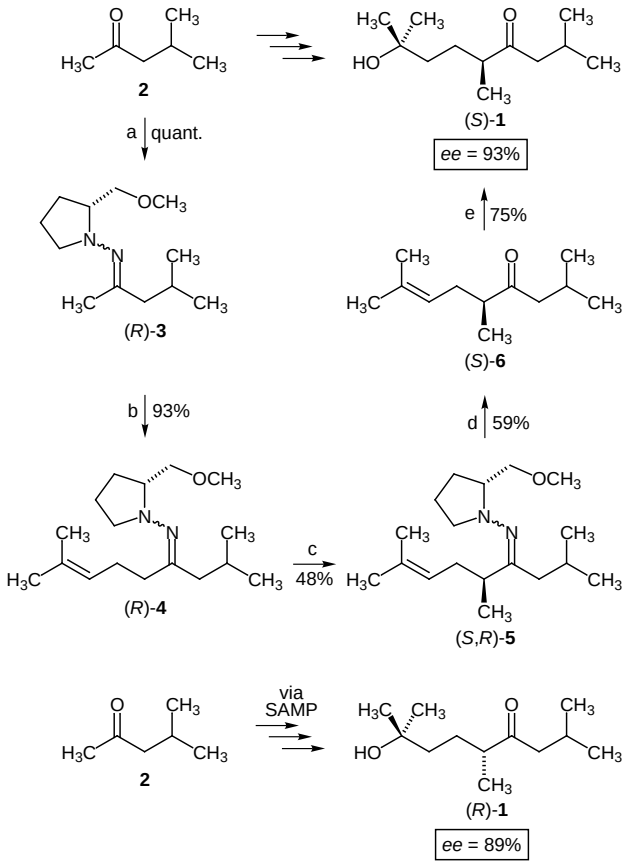
The target molecule contains one stereogenic centre resulting from the methyl branching at the C-5 position α to the carbonyl group. Therefore, the RAMP/SAMP hydrazone method[10] was chosen to generate both enantiomers of the pheromone based on either enantiomer of the chiral auxiliary. As shown in the Scheme, 4-methylpentan-2-one (**2**) was treated with *(R)*-1-amino-2-(methoxymethyl)pyrrolidine (RAMP), both commercially available, under azeotropic removal of water giving the corresponding RAMP-hydrazone *(R)*-**3** in virtually quantitative yield after distillation.[11] The regioselective deprotonation of *(R)*-**3** was achieved with LDA at 0 °C and after reaction with 1-bromo-3-methylbut-2-ene at −78 °C RAMP-hydrazone *(R)*-**4**, was isolated in an excellent 93% yield. The regioselective introduction of the C-5 stereogenic centre was next investigated. As expected from steric and stereoelectronic effects, the homoallylic methylene group at C-5 and not the methylene group at C-3 was regioselectively metalated with LDA for 24 h and alkylated with methyl iodide at −100 °C. The hydrazone (*S*,*R*)-**5** was obtained after chromatographic purification in 48% yield. For the regioselective metalation the use of a sterically demanding base is as important as the metalation temperature of −78 °C. Product hydrazones may be isomerised to the thermodynamically more stable *E*-form, prior to determining the de. In this case such isomerisation did not readily occur. Therefore the epimer (*R*,*R*)-**5** was synthesised through synthon control[10] in a test run by reversing the order of the electrophile addition. Comparative ^{13}C NMR analysis established the diastereomeric excess of (*S*,*R*)-**5** to be greater than 85%. In addition the de-value could be increased by HPLC to ≥ 99%.

The formation of ketone *(S)*-**6** was attained by hydrolytic cleavage using copper(II) chloride.[12] The product was isolated in 59% yield and an enantiomeric excess greater than 93%, attributed to partial racemisation during cleav-

age. This ketone was also an intermediate in the synthesis of racemic **1** by Plaga et al.[5] In this work, *rac*-**6** was converted to the Markovnikov alcohol by treatment with trifluoroacetic acid followed by alkaline workup, which is not compatible with our asymmetric synthesis. In addition, under these conditions there was always a partial formation of a dihydropyran via a lactol intermediate, which was also discovered in Mori's approaches.[5, 7, 9] Yamada et al. recently published a neutral oxidation−reduction hydration using oxygen and bis(1,1,1-trifluoropentane-2,4-dionato)cobalt(II) ($Co(tfa)_2$)[13] as catalyst for the hydration of various alkenes according to the Markovnikov rules.[14, 15] Pleasingly, application of these conditions to unsaturated ketone *(S)*-**6** yielded *(S)*-stigmolone in 75% yield without detectable racemisation. No dihydropyran and no lactol formation was detected by NMR analysis. As Yamada et al. noted, it must be reiterated that an efficient azeotropic removal of the reaction water is necessary to obtain a good yield. Furthermore, our system needs a higher amount of catalyst (50 mol%), perhaps due to partial chelation. Similarly, we synthesised the enantiomer *(R)*-**1** with 89% ee starting from 4-methylpentan-2-one (**2**) using SAMP as chiral auxiliary. In this case the diastereoisomeric excess of the alkylation was also excellent. (*R*,*S*)-**5** was isolated in 71% yield and ≥ 95% de. The SAMP-hydrazone cleavage was achieved using ammonium dihydrogen phosphate buffer according to a method developed by Carlsen et al. for dimethylhydrazone cleavage.[16] This method afforded the ketone *(R)*-**6** in 23% yield and 92% ee. Finally, comparison of the rotation values with those given in the literature[7] confirms the absolute configurations given and is in accordance with the established mechanism for the SAMP/RAMP-hydrazone alkylations.

The biological tests of the two enantiomers *(S)*- and *(R)*-**1** were carried out by Plaga under normal bioassay conditions[4] and showed again that both enantiomers induced the fruiting body formation at concentrations of 1.0−30.0 nM in the same way as the racemate. Due to the high enantiomeric purity of the pheromones we concluded that there are two possible interpretations for the biotest results. Firstly, the bacterium does not differ between the enantiomers or secondly, there is a racemisation during the biotest. At this moment we are not able to give a final answer.

In conclusion, we have achieved the first asymmetric synthesis of both enantiomers of the fruiting body inducing pheromone from the myxobacterium *S. aurantiaca*. The yield over five steps of *(S)*-**1** (ee = 93%) was 18% (20% based on recovered starting material) and of *(R)*-**1** (ee = 89%) was 6% (18% based on recovered starting material) from **2**.



Reagents and conditions: (a) RAMP/benzene, *p*-TsOH (cat.), reflux (b) LDA/THF, 0 °C, 5 h then 1-bromo-3-methylbut-2-ene, −78 °C to r.t. (c) LDA/THF, −78 °C, 24 h then CH_3I, −100 °C to r.t. (d) 1M $CuCl_2$/THF (e) $Co(tfa)_2$, O_2, *i*-PrOH, reflux, 5 h.

Scheme

All reagents were of commercial quality used from freshly opened containers. Solvents were dried and purified by conventional methods prior to use. THF was freshly distilled from sodium/lead alloy under Ar. BuLi (1.5 M in hexane) was purchased from Merck, Darmstadt. Cobalt(II) chloride hexahydrate was purchased from Aldrich. Preparative column chromatography: Merck silica gel 60, particle size 0.040−0.063 mm (230−400 mesh, flash). Analytical TLC: Silica gel 60 F_{254} plates, Merck, Darmstadt. Optical rotation values were measured on a Perkin-Elmer P241 polarimeter, solvents used were of Merck UVASOL-quality. Microanalyses were obtained from a Heraeus CHN-O-RAPID element analyzer. HR-MS: Finnigan MAT 95. Mass spectra: Finnigan MAT 212 (CI 100 eV; EI 70 eV). IR spectra: Perkin-Elmer FT/IR 1750. ^{1}H NMR spectra (300 and 400 MHz), ^{13}C NMR (75 and 100 MHz): Gemini 300 or Varian Inova 400 ($CDCl_3$ as solvent, TMS as internal standard).

***(R)*-*N*2-[2-Methoxymethyltetrahydro-1*H*-1-pyrrolyl]-4-methyl-2-pentan-2-imine [*(R)*-3]**

To a solution of RAMP (6.51 g, 50 mmol) and *p*-TsOH (0.05 g, cat.) in benzene (50 mL) was added 4-methylpentan-2-one (**2**) (12.52 mL, 100 mmol) and the mixture was refluxed overnight using a Dean−Stark trap. After cooling the mixture, the solvent and excess of **2** were evaporated and the crude product purified by distillation under reduced pressure to yield hydrazone *(R)*-**3** as a colourless liquid; yield: 10.62 g (quantitative); bp 82 °C/1mbar (Lit.[17]: 83 °C/1Torr).

^{1}H NMR (400 MHz) (*E*/*Z*-isomeric mixture): δ = 0.88−0.95 (m, 6 H, $CH(CH_3)_2$), 1.60−1.71 (m, 1 H, $CH(CH_3)_2$), 1.77−1.86 (m, 2 H, $NCHCH_2CH_2$), 1.89, 1.91 (2 s, 3 H, $NCCH_3$), 1.90−2.53 (m, 5 H, $NCHHCH_2CH_2$, $NCCH_2CH$, $NCHHCH_2CH_2$), 3.08−3.26 (m, 3 H,

NC*H*, C*H*HO, NCH*H*CH_2CH_2), 3.32, 3.33 (2 s, 3 H, OCH_3), 3.35−3.45 (m, 1 H, CH*H*O).

^{13}C NMR (100 MHz) (*E*/*Z*-major isomer): δ = 17.84 (NCCH_3), 22.07 (NCH_2CH_2), 22.19, 22.54 ($CH(CH_3)_2$), 26.30 ($CH(CH_3)_2$), 26.61 ($NCHCH_2CH_2$), 48.04 ($NCCH_2$), 53.98 (NCH_2), 59.17 (OCH_3), 66.16 (NCH), 75.54 (CH_2O), 166.02 (NC).

The other analytical data were consistent with the data given in the literature.[17]

(*S*)-*N*2-[2-Methoxymethyltetrahydro-1*H*-1-pyrrolyl]-4-methylpentan-2-imine [(*S*)-3]

In the same manner as described above **2** (4.70 g, 36.1 mmol) was converted to *(S)*-**3** (7.10 g, 93%) using SAMP as chiral auxilary. The analytical data were identical with those of the *(R)*-isomer.

(*R*)-*N*4-[2-Methoxymethyltetrahydro-1*H*-1-pyrrolyl]-2,8-dimethylnon-7-en-4-imine [(*R*)-4]

To a cooled solution (0 °C) of diisopropylamine (0.78 mL, 5.5 mmol) in anhyd THF (30 mL) under Ar was slowly added BuLi (1.5 M in hexane, 3.67 mL, 5.5 mmol) and the mixture was stirred for 30 min. *(R)*-**3** (1.061 g, 5.0 mmol) was added slowly and stirring maintained at 0 °C for 5 h. The resulting yellow solution was cooled to −78 °C and 1-bromo-3-methylbut-2-ene (0.82 g, 5.5 mmol) was added dropwise. The mixture was allowed to warm to r.t. over a period of 15 h and was quenched with sat. aq NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O (3 x 75 mL), the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. Distillative purification gave hydrazone *(R)*-**4** as a colourless liquid; yield: 1.30 g (93%); bp 92 °C/0.02mbar.

IR (capillary in $CHCl_3$): ν = 3775, 2957, 2925, 2871, 2827, 2730, 1630, 1461, 1383, 1344, 1282, 1198, 1128, 1054, 973, 923, 532 cm^{-1}.

^{1}H NMR (300 MHz) (*E*/*Z*-isomeric mixture): δ = 0.90 (d, 3 H, $^3J_{H-H}$ = 6.6 Hz, CH_3CHCH_3), 0.91 (d, 3 H, $^3J_{H-H}$ = 6.6 Hz, CH_3CHCH_3), 1.62 (broad s, 3 H, CC$H_{3,(Z)}$), 1.62−2.54 (m, 12 H, NCHCH_2CH_2, NCHCH_2CH_2, CCHCH_2, NCCH_2CH_2, NCCH_2CH, CH(CH_3)$_2$, NC*H*H), 1.69 (broad d, 3 H, $^4J_{H-H}$ = 1.1 Hz, CC$H_{3,(E)}$), 3.03 (m, 1 H, NCH*H*), 3.09−3.17 (m, 1 H, NC*H*), 3.17−3.24 (m, 1 H, C*H*HO), 3.33 (s, 3 H, OCH_3), 3.37−3.42 (m, 1 H, CH*H*O), 5.09 (t/m, 1 H, $^3J_{H-H}$ = 7.0 Hz, CC*H*).

^{13}C NMR (100 MHz) (*E*/*Z*-major isomer): δ = 17.65 (C$CH_{3,(Z)}$), 21.94 (NCH_2CH_2), 22.27, 22.66 ($CH(CH_3)_2$), 24.90 ($CCHCH_2$), 25.63 (C$CH_{3,(E)}$), 26.32 ($CH(CH_3)_2$), 26.71 ($NCH_2CH_2CH_2$), 30.73 ($NCCH_2CH_2$), 44.98 ($NCCH_2CH$), 54.89 (NCH_2), 59.06 (OCH_3), 65.80 (NCH), 75.57 (CH_2O), 123.49 (CCH), 131.97 (CCH), 170.90 (NC).

MS (CI, isobutane): *m*/*z* (%) = 282 (15), 281 (100, M^+ +1), 279 (7), 249 (7, $-CH_3O$), 235 (18), 167 (11), 125 (6), 70 (1, $M^+_{\text{dihydropyrrole}}$ +1).

HRMS: *m*/*z* calcd for $C_{15}H_{27}N_2^+$ (M $-CH_2OCH_3$): 235.2174. Found: 235.2174.

(*S*)-*N*4-[2-Methoxymethyltetrahydro-1*H*-1-pyrrolyl]-2,8-dimethylnon-7-en-4-imine [(*S*)-4]

In the same manner as described above *(S)*-**3** (1.0 g, 4.71 mmol) was converted to *(S)*-**4** (1.18 g, 89%). The analytical data were identical to those of the *(R)*-isomer.

(2'*R*,5*S*)-*N*4-[2'-Methoxymethyltetrahydro-1*H*-1-pyrrolyl]-2,5,8-trimethylnon-7-en-4-imine [(*S*,*R*)-5]

To a cooled solution (0 °C) of diisopropylamine (1.37 mL, 9.9 mmol) in anhyd THF (50 mL) under Ar was added slowly BuLi (1.5 M in hexane, 6.7 mL, 9.9 mmol) and the mixture was stirred for 30 min before cooling to −78 °C. *(R)*-**4** (2.521 g; 8.99 mmol) was added slowly and the yellow solution was maintained for 24 h at this temperature. Afterwards the solution was cooled to −100 °C and then CH_3I (2.55 g, 17.98 mmol) was gradually added to the solution. The mixture was maintained for 5 h at this temperature, then was allowed to warm to r.t. over a period of 15 h and finally was quenched with sat. aq NH_4Cl (4.5 mL). The aqueous phase was extracted with Et_2O (3 x 75 mL), the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel; pentane/Et_2O, 10:1, containing 1% Et_3N; R_f 0.23) gave *(S,R)*-**5**; yield: 1.271 g (48%); de ≥ 85% (^{13}C NMR); further purification by HPLC (Merck Fertigsäule) gave *(R)*-**6** in ≥ 99% de.

IR (capillary in $CHCl_3$): ν = 3372, 2956, 2925, 2870, 1627, 1459, 1377, 1365, 1278, 1198, 1185, 1129, 1101, 1048, 974, 950, 922, 879, 758 cm^{-1}.

^{1}H NMR (400 MHz) (*E*/*Z*-isomeric mixture): δ = 0.91 (d, 6 H, $^3J_{H-H}$ = 6.6 Hz, CH(CH_3)$_2$), 1.00 (d, 3 H, $^3J_{H-H}$ = 7.1 Hz, NCCHCH_3), 1.60 (broad d, $^4J_{H-H}$ = 0.8 Hz, 3 H, CC$H_{3,(Z)}$), 1.61−2.08 (m, 8 H, NCHCH_2CH_2, NCHCH_2CH_2, CHCH_2CH, NCCH_2), 1.68 (broad d, 3 H, $^4J_{H-H}$ = 1.1 Hz, CC$H_{3,(E)}$), 2.10−2.15 (m, 1 H, CH(CH_3)$_2$), 2.43 (q, 1 H, $^3J_{H-H}$ = 8.8 Hz, NC*H*H), 2.97 (m, 1 H, NCH*H*), 3.09−3.21 (m, 2 H, NC*H*, C*H*HO), 3.34 (s, 3 H, OCH_3), 3.39 (m, 1 H, CH*H*O), 3.53 (broad s, 1 H, NCC*H*CH_3), 5.01 (t/m, 1 H, $^3J_{H-H}$ = 6.9 Hz, CC*H*).

^{13}C NMR (100 MHz) (*E*/*Z*-major isomer): δ = 17.09 (NCCHC*H*$_3$), 17.86 (C$CH_{3,(Z)}$), 21.76 (NCH_2CH_2), 22.52, 22.90 ($CH(CH_3)_2$), 25.49 (C$CH_{3,(E)}$), 25.71 ($CH(CH_3)_2$), 26.38 ($NCH_2CH_2CH_2$), 32.15 ($CHCH_2CH$), 35.05 (NCCH), 40.14 ($NCCH_2$), 55.11 (NCH_2), 59.02 (OCH_3), 65.85 (NCH), 75.30 (CH_2O), 122.37 (CCH), 132.31 (CCH), 174.95 (NC).

MS (CI, isobutane): *m*/*z* (%) = 296 (16), 295 (100, M^++1), 293 (5), 263 (4, $-CH_3O$), 249 (2), 181 (6).

HRMS: *m*/*z* calcd for $C_{16}H_{29}N_2^+$ (M $-CH_2OCH_3$): 249.2331. Found: 249.2334.

(2'*S*,5*R*)-*N*4-[2'-Methoxymethyltetrahydro-1*H*-1-pyrrolyl]-2,5,8-trimethylnon-7-en-4-imine [(*R*,*S*)-5]

In the same manner as described above *(S)*-**4** (1.84 g, 6.57 mmol) was converted to (*R*,*S*)-**5** (1.38 g, 71%); de ≥ 95% (^{13}C NMR). The analytical data were identical to those of the (*S*,*R*)-isomer.

***(S)*-2,5,8-Trimethylnon-7-en-4-one [(*S*)-6]**

To a cooled solution (0 °C) of (*S*,*R*)-**5** (0.842 g, 2.86 mmol) in THF (30 mL) was added slowly 1 M copper(II) chloride (3.43 mL) and the mixture was stirred for an additional 15 min at this temperature. The mixture was allowed to warm to r.t., stirred for 15 h and quenched with sat. aq NH_4Cl (30 mL). The aqueous phase was extracted with Et_2O (3 x 75 mL), the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the reddish crude product by flash chromatography (silica gel; pentane/Et_2O, 20:1; R_f 0.64) gave the colourless liquid *(S)*-**6**; 0.308 g (59%); ee ≥ 93%; GC-CSP (column: Lipodex G 25 m, 60-1-140, H_2 = 1 bar, t_R = 16.6 min). Further elution gave (*S*,*R*)-**5** (0.070 g, 8%). The yield based on recovered starting material was 64%. $[\alpha]_D^{25}$ = +28.2 (c = 1.26, $CHCl_3$).

^{1}H NMR (300 MHz): δ = 0.90 (d, 6 H, $^3J_{H-H}$ = 6.6 Hz, CH(CH_3)$_2$), 1.04 (d, 3 H, $^3J_{H-H}$ = 6.9 Hz, COCHCH_3), 1.60 (broad s, 3 H, CC$H_{3,(Z)}$), 1.69 (broad d, 3 H, $^4J_{H-H}$ = 1.1 Hz, CC$H_{3,(E)}$), 2.02 (broad quin, 1 H, $^3J_{H-H}$ = 7.4 Hz, CCHC*H*H), 2.15 (sep, 1 H, $^3J_{H-H}$ = 6.7 Hz, CH(CH_3)$_2$), 2.29 (broad quin, 1 H, CCHCH*H*), 2.31 (d, 2 H, $^3J_{H-H}$ = 6.6 Hz, COCH_2), 2.50 (sep, 1 H, $^3J_{H-H}$ = 6.9 Hz, COC*H*CH_3), 5.04 (t/m, 1 H, $^3J_{H-H}$ = 7.4 Hz, CC*H*).

^{13}C NMR (75 MHz): δ = 16.08 (COCH*C*H$_3$), 17.90 (C$CH_{3,(Z)}$), 22.73 (CH_3CHCH_3), 22.75 ($COCH_2CH$), 24.31 (CH_3CHCH_3),

25.87 (C*C*H$_{3,(E)}$), 31.56 (CCH*C*H$_2$), 46.96 (CO*C*H), 50.67 (CO*C*H$_2$), 121.76 (C*C*HCH$_2$), 133.49 (*C*CHCH$_2$), 214.32 (*C*O).

Anal. calcd. for $C_{12}H_{22}O$ (182.2): C 79.06, H 12.16. Found: C 79.24, H 12.26.

The other analytical data were consistent with those given in the literature.[5]

***(R)*-2,5,8-Trimethylnon-7-en-4-one [*(R)*-6]**

Hydrazone (*R*,*S*)-**5** (1.296 g, 4.40 mmol) was dissolved in THF (4.4 mL), sat. aq ammonium dihydrogen phosphate (176 mL) was added and the solution was stirred at r.t. for 94 h. The aqueous phase was extracted with Et_2O (4 x 100 mL), the combined organic extracts washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel; pentane/Et_2O, 20:1; R_f 0.64) yielded the colourless liquid *(R)*-**5**; 0.183 g (23%); ee ≥ 92%; GC-CSP (column: Lipodex G 25 m, 60-1-140, H_2 = 1 bar, t_R = 16.2 min). Further elution gave (*R*,*S*)-**5** (0.932 g, 72%). The yield based on recovered starting material was 81%. $[\alpha]_D^{25} = -26.9$ (*c* = 1.30, $CHCl_3$).

The other analytical data were identical with those of the *(S)*-isomer.

Bis(1,1,1-trifluoropentane-2,4-dionato)cobalt(II) [Co(tfa)$_2$]

To a emulsion of 1,1,1-trifluoropentane-2,4-dione (3.08 g, 20 mmol) in H_2O (29 mL) was added aq NaOH (2 M, 10 mL). After stirring for 30 min at r.t. an aqueous solution (10 mL) of cobalt(II) chloride hexahydrate (2.38 g, 10.0 mmol) was added and stirring was maintained for 1 h. The resulting precipitate was filtered and washed with H_2O (3 x 30 mL). The resulting red powder was dried in vacuo at 90 °C for 6 h to give Co(tfa)$_2$, which was used in the next step without any further purification; yield: 1.849 g (51%).

IR (KBr): ν = 3431, 1619, 1535, 1460, 1367, 1297, 1232, 1192, 1142, 862, 789, 731, 581 cm^{-1}.

MS (CI, isobutane): *m*/*z* (%) = 406 (6), 367 (7), 366 (100, M^+ +1), 295 (5), 155 (7, ligand +1).

The other analytical data were consistent with those given in the literature.[13]

***(S)*-8-Hydroxy-2,5,8-trimethylnonan-4-one [*(S)*-1]**

To a solution of Co(tfa)$_2$ (0.183 g, 0.5 mmol) in *i*-PrOH (20 mL) was added a solution of *(S)*-**6** (0.182 g, 1.0 mmol) in *i*-PrOH (10 mL). A Soxhlet apparatus with a thimble containing molecular sieves (4 Å, 1.0 g) was fitted and compressed air was bubbled through the mixture at reflux. After 5 h the volatiles were removed in vacuo. Purification by flash chromatography (silica gel; pentane/Et_2O, 1:1; R_f 0.41) gave *(S)*-**1**; yield: 0.151 g (75%); ee ≥ 93%; GC-CSP (column: Lipodex G 25 m, 50-1-80-3-190, H_2 = 1 bar, t_R = 176.4 min); $[\alpha]_D^{25} = +8.3$ (*c* = 1.05, $CHCl_3$). (Lit.[7] $[\alpha]_D^{22} = +7.63$ (*c* = 0.51, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 0.90, 0.91 (2 x d, 6 H, $^3J_{H-H}$ = 6.6 Hz and $^3J_{H-H}$ = 6.8 Hz, C*H*$_3$CHC*H*$_3$), 1.08 (d, 3 H, $^3J_{H-H}$ = 7.1 Hz, COCHC*H*$_3$), 1.21 (d, 6 H, $^4J_{H-H}$ = 1.1 Hz, C*H*$_3$COHC*H*$_3$), 1.32 (s, 1 H, CO*H*), 1.35−1.46 (m, 3 H, HOCC*H*$_2$CHH, HOCCH$_2$C*H*H), 1.66−1.78 (m, 1 H, HOCCH$_2$CH*H*), 2.16 (sep/m, 1 H, $^3J_{H-H}$ = 6.6 Hz, CH$_3$C*H*CH$_3$), 2.26−2.38 (m, 2 H, COC*H*$_2$), 2.42−2.51 (m, 1 H, COC*H*).

^{13}C NMR (75 MHz): δ = 16.47 (COCH*C*H$_3$), 22.62, 22.69 (*C*H$_3$CH*C*H$_3$), 24.21 (CH$_3$*C*HCH$_3$), 27.30 (COCH*C*H$_2$), 29.20 (HOC*C*H$_{3,(Z)}$), 29.26 (HOC*C*H$_{3,(E)}$), 41.19 (HOC*C*H$_2$), 46.80 (CO*C*HCH$_3$), 50.30 (CO*C*H$_2$), 70.77 (HO*C*), 214.41 (*C*O).

MS (EI): *m*/*z* (%) = 185 (16, $M^+ - CH_3$), 182 (38, $M^+ - H_2O$), 167 (11), 164 (5), 149 (5), 141 (8, $M^+ - C_3H_7O^+$), 127 (37), 125 (39), 115 (14), 114 (52), 111 (13), 109 (10), 103 (41), 99 (6), 98 (9), 97 (67), 95 (5), 91 (10), 86 (5), 85 (84), 74 (7), 73 (9), 72 (36), 71 (25), 70 (15), 69 (32), 59 (59), 58 (19), 57 (97), 56 (100), 55 (42), 49 (5), 45 (25).

The other analytical data were consistent with those given in the literature.[5,7]

***(R)*-8-Hydroxy-2,5,8-trimethylnonan-4-one [*(R)*-1]**

In the same manner as described above *(R)*-**5** (0.115 g; 0.631 mmol) was converted to *(R)*-**1** (0.059 g, 47%); ee ≥ 89%; GC-CSP (column: Lipodex G 25 m, 50-1-80-3-190, H_2 = 1 bar, t_R = 175.7 min). $[\alpha]_D^{25} = -9.1$ (*c* = 0.69, $CHCl_3$). (Lit.[7] $[\alpha]_D^{22} = -7.85$ (*c* = 0.53, $CHCl_3$).

The other analytical data were identical with those of the *(S)*-enantiomer.

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