Catalytic asymmetric conjugate addition of Grignard reagents to chromones

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Catalytic asymmetric conjugate addition of Grignard reagents to chromones
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General Methods:

Column chromatography was performed on silica gel (Silica-P flash silica gel from Silicycle, size 40-63 μm). TLC was performed on silica gel 60/Kieselguhr F254. Components were visualized by UV and staining with a solution of a mixture of KMnO4 (10 g) and K2CO3 (10 g) in H2O (500 mL). Mass spectra were recorded on a AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). 1H- and 13C-NMR were recorded on a Varian AMX400 (400 and 101 MHz, respectively) using CDCl3 as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl3: δ 7.26 for 1H, δ 77.0 for 13C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured in CHCl3 on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). Conversion of the reaction was determined by GC (GC, HP6890: MS HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Enantiomeric excess values were determined by HPLC analysis using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. All solvents were reagent grade and were dried and distilled prior to use, if necessary. Tetrahydrofuran (THF), tert-butyl methyl ether (t-BuOMe) and diethylether (Et2O) were distilled over Na/benzophenone. Toluene and dichloromethane (CH2Cl2) were distilled over calcium hydride. All the ligands, copper salts and chromanones were purchased from Aldrich, ABCR and Acros and used as received. Grignard reagents RMgBr (R = Et, n-pentyl, n-hexyl, i-Bu, 3-pentyl, dodecyl, cyclopentyl) were purchased from Aldrich. Phenethylmagnesium bromide and but-3-en-1-ylmagnesium bromide were prepared from the corresponding alkyl bromides and magnesium turnings in Et2O following standard procedures. Grignard reagents were titrated using sec-BuOH and catalytic amounts of 1,10-phenanthroline.
General procedure for the synthesis of the racemic product of the copper catalyzed 1,4-addition of Grignard reagents to chromones

CuBr·SMe₂ (0.01 mmol, 2.02 mg) and PPh₃ (0.012 mmol, 6.3 mg) were dissolved in dry DCM (2.0 mL) and the mixture was stirred at room temperature for 10 min. The mixture was cooled to -80 °C and subsequently the corresponding Grignard reagent solution (1.25 equiv.) were added dropwise. The reaction mixture was stirred at -80 °C for another 10 min. Then a solution of chromonone (0.2 mmol) in DCM (1.0 mL) was added dropwise. The reaction mixture was stirred until TLC (n-pentane:EtOAc 9:1) showed full conversion and quenched with saturated aqueous NH₄Cl solution (2 mL). The mixture was separated and the water layer was extracted with DCM (3×5 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was evaporated under vacuo. Purification by flash chromatography over silica gel, using n-pentane:Et₂O 9:1 afforded the desired compounds. (The reaction in some cases shown 1,2 and 1,4 addition products)

General procedure for the asymmetric 1,4-addition of Grignard reagents to chromones:

CuBr·SMe₂ (0.01 mmol, 2.02 mg) and L₄ (R,S)-Rev-Josiphos (0.012 mmol, 7.2 mg) were dissolved in dry DCM (2.0 mL) and the mixture was stirred at room temperature for 10 min. The mixture was cooled to -80 °C and subsequently the corresponding Grignard reagent solution (1.25 equiv.) was added dropwise. The reaction mixture was stirred at -80 °C for another 10 min. Then a solution of chromonone (0.4 mmol) in DCM (1.0 mL) was added slowly over 1h using a syringe pump. The reaction was stirred until TLC (n-pentane:EtOAc 9:1) showed full conversion and quenched with saturated aqueous NH₄Cl solution (2 mL). The mixture was separated and the water layer was extracted with DCM (3×5 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was evaporated under vacuo. Purification by flash chromatography over silica gel, using n-pentane:Et₂O 9:1 afforded the desired compounds.

Characterization of products 2, 3, 4, 5, 6, 7

(R)-2-ethylchroman-4-one (2a)

Synthesized according the general procedure, obtained in 98% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer tᵣ = 14.2 min, minor enantiomer tᵣ = 16.0 min, ee= 95%; [α]D²₅ = +51.5 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.85 (dd, J = 7.8, 1.3 Hz, 1H), 7.44 (td, J = 7.8, 1.6 Hz, 1H), 7.03-6.88 (m, 2H), 4.45-4.29 (m, 1H), 2.66 (d, J = 7.8 Hz, 2H), 1.88 (d, J = 14.7, 7.4 Hz,
1H), 1.81-1.69 (m, 1H), 1.05 (t, J = 7.5 Hz, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 192.5, 161.6, 135.8, 126.8, 121.0, 120.9, 117.8, 78.9, 42.4, 27.9, 9.2 ppm; HRMS (ESI) calculated for C\(_{11}\)H\(_{13}\)O\(_2\) [M + H] 177.0910 found 177.0910.

**(R)-2-pentylchroman-4-one (2b)**

![Structure](image)

Synthesized according the general procedure, obtained in 80% yield; oil; enantiomeric excess was determined by HPLC (Chiracel OBH), hexane:i-PrOH 99:1, 0.5 mL/min, minor enantiomer \(t_r = 12.3\) min, major enantiomer \(t_r = 12.9\) min, ee = 96%; \([\alpha]^{25}_D = +48.9\) (c 1.05, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.87 (dd, \(J = 7.8, 1.7\) Hz, 1H), 7.46 (td, \(J = 8.0, 1.6\) Hz, 1H), 7.02-6.94 (m, 2H), 4.43 (qd, \(J = 7.6, 5.2\) Hz, 1H), 2.68 (d, \(J = 7.5\) Hz, 2H), 1.88 (dddd, \(J = 12.8, 10.1, 7.4, 5.3\) Hz, 1H), 1.75-1.64 (m, 1H), 1.61-1.41 (m, 2H), 1.39-1.29 (m, 4H), 0.91 (t, \(J = 7.5\) Hz, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 192.6, 161.7, 135.9, 126.9, 121.1, 121.0, 117.8, 77.9, 43.0, 34.9, 31.5, 24.5, 22.5, 14.0 ppm; HRMS (ESI) calculated for C\(_{14}\)H\(_{19}\)O\(_2\) [M + H] 219.1380 found 219.1379.

**(R)-2-hexylchroman-4-one (2c)**

![Structure](image)

Synthesized according the general procedure, obtained in 87% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer \(t_r = 12.1\) min, minor enantiomer \(t_r = 12.8\) min, ee = 96%; \([\alpha]^{25}_D = +51.3\) (c 1.09, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86 (dd, \(J = 7.8, 1.6\) Hz, 1H), 7.44 (td, \(J = 7.8, 1.5\) Hz, 1H), 7.00-6.94 (m, 2H), 4.42 (qd, \(J = 7.6, 5.4\) Hz, 1H), 2.67 (d, \(J = 7.9\) Hz, 2H), 1.93-1.81 (m, 1H), 1.69 (ddd, \(J = 13.9, 10.4, 5.4\) Hz, 1H), 1.60-1.40 (m, 2H), 1.39-1.21 (m, 6H), 0.89 (t, \(J = 6.7\) Hz, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 192.6, 161.7, 135.9, 126.9, 121.1, 121.0, 117.9, 77.9, 43.0, 34.9, 31.5, 24.8, 22.6, 14.0 ppm; HRMS (ESI) calculated for C\(_{15}\)H\(_{21}\)O\(_2\) [M + H] 233.1536 found 233.1537.

**(R)-2-dodecylchroman-4-one (2d)**

![Structure](image)
Synthesized according the general procedure, obtained in 53% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer $t_r = 10.6$ min, minor enantiomer $t_r = 11.5$ min, ee= 86%; $\left[\alpha\right]^{25}_D= +24.5$ (c 0.85, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.82 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.41 (td, $J = 7.8$, 2.0 Hz, 1H), 6.96-6.91 (m, 2H), 4.41-4.35 (m, 1H), 2.63 (d, $J = 7.9$ Hz, 2H), 1.89-1.77 (m, 1H), 1.71-1.60 (m, 1H), 1.55-1.35 (m, 2H), 1.33-1.10 (m, 18H), 0.83 (t, $J = 6.8$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.6, 161.6, 135.8, 126.9, 121.0, 117.8, 77.9, 42.9, 34.9, 31.9, 29.63, 29.59, 29.57, 29.49, 29.43, 29.32, 29.29, 24.8, 22.6, 14.0 ppm; HRMS (ESI) calculated for C$_{21}$H$_{33}$O$_2$ [M + H] 317.2475 found 317.2477.

(R)-2-isobutylchroman-4-one (2e)

Synthesized according the general procedure, obtained in 82% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer $t_r = 12.4$ min, minor enantiomer $t_r = 13.2$ min, ee= 98%; $\left[\alpha\right]^{25}_D= +57.2$ (c 0.97, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.76 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.34 (td, $J = 7.8$, 1.6 Hz, 1H), 6.90-6.83 (m, 2H), 4.45-4.36 (m, 1H), 2.61-2.48 (m, 2H), 1.88-1.71 (m, 2H), 1.34 (dd, $J = 13.8$, 7.9, 4.6 Hz, 1H), 0.864 (d, $J = 6.4$ Hz, 3H), 0.857 (d, $J = 6.4$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.5, 161.6, 135.9, 126.9, 121.1, 121.0, 117.9, 76.3, 43.9, 43.4, 24.2, 23.0, 22.2 ppm; HRMS (ESI) calculated for C$_{13}$H$_{17}$O$_2$ [M + H] 205.1223 found 205.1223.

(R)-2-(but-3-en-1-yl)chroman-4-one (2f)

Synthesized according the general procedure, obtained in 79% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer $t_r = 15.3$ min, minor enantiomer $t_r = 17.1$ min, ee= 87%; $\left[\alpha\right]^{25}_D= +44.4$ (c 0.9, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.82 (d, $J = 7.3$ Hz, 1H), 7.41 (t, $J = 7.3$ Hz, 1H), 6.98-6.90 (m, 2H), 5.79 (ddt, $J = 16.9$, 10.1, 6.6 Hz, 1H), 5.03 (d, $J = 17.1$ Hz, 1H), 4.97 (d, $J = 10.2$ Hz, 1H), 4.45-4.37 (m, 1H), 2.64 (d, $J = 7.7$ Hz, 2H), 2.33-2.16 (m, 2H), 1.95 (td, $J = 14.2$, 8.0 Hz, 1H), 1.74 (ddd, $J = 13.9$, 8.9, 6.7 Hz, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.3, 161.5, 137.2, 135.9, 126.9, 121.2, 121.0, 117.8, 117.5, 77.0, 42.9, 34.0, 29.0 ppm; HRMS (ESI) calculated for C$_{13}$H$_{15}$O$_2$ [M + H] 203.1067 found 203.1066.
(R)-2-phenethylchroman-4-one (2g)

Synthesized according the general procedure, obtained in 77% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 95:5, 0.5 mL/min, major enantiomer \( t_r = 29.2 \) min, minor enantiomer \( t_r = 12.5 \) min, ee= 75%; \([\alpha]^{25}_D = +56.7 \) (c 0.8, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 7.89 (dd, \( J = 8.1, 1.7 \) Hz, 1H), 7.49 (td, \( J = 7.8, 1.6 \) Hz, 1H), 7.32-7.29 (m, 2H), 7.26-7.19 (m, 3H), 7.03-7.00 (m, 2H), 4.44 (dtd, \( J = 11.0, 8.6, 4.5 \) Hz, 1H), 2.96-2.81 (m, 2H), 2.77-2.65 (m, 2H), 2.23 (dtd, \( J = 13.9, 9.2, 4.4 \) Hz, 1H) ppm; \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) 192.3, 161.5, 140.9, 136.0, 128.5, 128.4, 127.0, 126.2, 121.3, 117.9, 76.8, 43.0, 36.5, 31.1 ppm; HRMS (ESI) calculated for C₁₇H₁₇O₂ [M + H] 253.1223 found 253.1224.

(S)-2-(pentan-3-yl)chroman-4-one (2h)

Synthesized according the general procedure, obtained in 68% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer \( t_r = 11.4 \) min, minor enantiomer \( t_r = 12.3 \) min, ee= 84%; \([\alpha]^{25}_D = +53.5 \) (c 0.92, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 7.87 (dd, \( J = 7.9, 1.5 \) Hz, 1H), 7.44 (dd, \( J = 8.4, 7.3, 1.8 \) Hz, 1H), 7.01-6.94 (m, 2H), 4.43 (dd, \( J = 13.5, 4.9, 2.70 \) Hz, 1H), 2.75 (dd, \( J = 16.6, 13.5 \) Hz, 1H), 2.60 (dd, \( J = 16.6, 2.7 \) Hz, 1H), 1.69-1.59 (m, 2H), 1.58-1.49 (m, 2H), 1.36 (dt, \( J = 15.7, 7.9 \) Hz, 1H), 0.96 (t, \( J = 7.3 \) Hz, 3H), 0.95 (t, \( J = 7.4 \) Hz, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) 193.2, 162.1, 135.8, 126.9, 121.0, 117.9, 79.5, 44.8, 40.0, 21.5, 21.3, 11.4 ppm; HRMS (ESI) calculated for C₁₄H₁₉O₂ [M + H] 219.1380 found 219.1380.

(S)-2-cyclopentylchroman-4-one (2i)

Synthesized according the general procedure, obtained in 79% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer \( t_r = 13.8 \) min, minor enantiomer \( t_r = 14.5 \) min, ee= 97%; \([\alpha]^{25}_D = +72.1 \) (c 0.9,
CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.86 (dd, J = 7.8, 1.3 Hz, 1H), 7.45 (td, J = 7.8, 1.7 Hz, 1H), 7.00-6.93 (m, 2H), 4.22 (ddd, J = 9.6, 7.8, 5.7 Hz, 1H), 2.74-2.64 (m, 2H), 2.28-2.20 (m, 1H), 1.97-1.89 (m, 1H), 1.79-1.74 (m, 1H), 1.72-1.50 (m, 5H), 1.37-1.25 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 192.8, 161.8, 135.9, 126.9, 121.0, 117.9, 81.7, 44.1, 42.2, 28.8, 28.4, 25.5, 25.4 ppm; HRMS (ESI) calculated for C₁₄H₁₇O₂ [M + H] 217.1223 found 217.1223.

(R)-2-ethyl-6-methylchroman-4-one (3)

![Structure of 2-ethyl-6-methylchroman-4-one (3)](image)

Synthesized according the general procedure, obtained in 93% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer τᵣ = 13.8 min, minor enantiomer τᵣ = 15.2 min, ee= 92%; [α]⁰DG = +69.6 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.64 (d, J = 1.3 Hz, 1H), 7.25 (dd, J = 8.4, 2.1 Hz, 1H), 6.86 (s, J = 8.4, 1H), 4.32 (qd, J = 7.6, 5.6 Hz, 1H), 2.64 (d, J = 8.0 Hz, 2H), 2.28 (s, 3H), 1.87 (dp, J = 14.4, 7.3 Hz, 1H), 1.80-1.68 (m, 1H), 1.05 (t, J = 7.5 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 192.8, 159.7, 137.0, 130.5, 126.4, 120.6, 117.6, 79.0, 42.6, 28.0, 20.4, 9.3 ppm; HRMS (ESI) calculated for C₁₂H₁₅O₂ [M + H] 191.1067 found 191.1065.

(R)-2-ethyl-6-fluorochroman-4-one (4)

![Structure of 2-ethyl-6-fluorochroman-4-one (4)](image)

Synthesized according the general procedure, obtained in 75% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer τᵣ = 12.9 min, minor enantiomer τᵣ = 14.3 min, ee= 92%; [α]⁰DG = +72.3 (c 1.11, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.45 (dd, J = 8.3, 3.1 Hz, 1H), 7.12 (td, J = 8.6, 3.2 Hz, 1H), 6.89 (dd, J = 9.0, 4.2, 1H), 4.29 (m, 1H), 2.66-2.62 (m, 2H), 1.83 (dp, J = 14.7, 7.4 Hz, 1H), 1.77-1.65 (m, 1H), 1.01 (t, J = 7.5 Hz, 3H) ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -121.9 (td, J_H-F = 8.0, 4.3) ¹³C NMR (100 MHz, CDCl₃) δ 191.8 (d, J_C-F = 1.8), 158.0 (d, J_C-F = 31.6), 156.9 (d, J_C-F = 208.6), 123.4 (d, J_C-F = 24.6), 121.4 (d, J_C-F = 6.5), 119.5 (d, J_C-F = 7.3), 111.8 (d, J_C-F = 23.2), 79.3, 42.2, 27.8, 9.2 ppm; HRMS (ESI) calculated for C₁₁H₁₂FO₂ [M + H] 195.0816 found 195.0815.
(R)-6-chloro-2-ethylchroman-4-one (5)

Synthesized according the general procedure, obtained in 85% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 13.6 min, minor enantiomer t_r = 15.2 min, ee = 90%; [α]_D^25 = +78.2 (c 1.0, CHCl_3); ¹H NMR (400 MHz, CDCl_3): δ 7.82 (d, J = 2.7 Hz, 1H), 7.40 (dd, J = 8.8, 2.7 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 4.36-4.28 (m, 1H), 2.72-2.61 (m, 2H), 1.89 (dp, J = 14.7, 7.4 Hz, 1H), 1.83-1.71 (m, 1H), 0.97 (t, J = 7.5 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl_3) δ 191.4, 160.1, 138.5, 129.3, 122.2, 120.0, 113.7, 79.3, 42.1, 27.9, 9.2 ppm; HRMS (ESI) calculated for C₁₁H₁₂ClO₂ [M + H] 211.0520 found 211.0519.

(R)-6-bromo-2-ethylchroman-4-one (6)

Synthesized according the general procedure, obtained in 81% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 14.4 min, minor enantiomer t_r = 15.9 min, ee = 89%; [α]_D^25 = +64.3 (c 1.15, CHCl_3); ¹H NMR (400 MHz, CDCl_3): δ 7.88 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.8, 2.1 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 4.32-4.24 (m, 1H), 2.65-2.52 (m, 2H), 1.81 (dp, J = 14.7, 7.4 Hz, 1H), 1.75-1.54 (m, 1H), 0.99 (t, J = 7.5 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl_3) δ 191.3, 160.5, 138.5, 129.3, 122.2, 120.0, 113.7, 79.3, 42.1, 27.8, 9.2 ppm; HRMS (ESI) calculated for C₁₁H₁₂BrO₂ [M + H] 255.0015 found 255.0016.

(R)-2-ethyl-7-methoxychroman-4-one (7)

Synthesized according the general procedure, obtained in 81% yield; oil; enantiomeric excess was determined by HPLC (Chiracel OJH), hexane:i-PrOH 99:1, 0.5 mL/min, minor enantiomer t_r = 28.9 min, minor enantiomer t_r = 30.3 min, ee = 92%; [α]_D^25 = +50.9 (c 0.82, CHCl_3); ¹H NMR (400 MHz, CDCl_3): δ 7.78 (d, J = 8.8 Hz, 1H), 6.53 (dd, J = 8.8, 2.4 Hz, 1H), 6.40 (d, J = 2.3 Hz, 1H), 4.38-4.29 (m, 1H), 3.81 (s, 3H), 2.66-2.54 (m, 2H), 1.86 (dp, J = 14.7, 7.3 Hz, 1H), 1.80-1.68 (m, 1H), 1.05 (t, J = 7.5 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl_3) δ
191.2, 166.0, 163.6, 128.6, 114.9, 109.7, 100.6, 79.4, 55.6, 42.2, 28.0, 9.3 ppm; HRMS (ESI) calculated for C_{12}H_{15}O_{3} [M + H] 207.1016 found 207.1016.

**(2R,3R)-2-ethyl-3-(hydroxy(phenyl)methyl)chroman-4-one (9)**

![Chemical Structure Image]

CuBr·SMe\(_2\) (0.01 mmol, 2.02 mg) and L4 (R,S)-Rev-Josiphos (0.012 mmol, 7.2 mg) were dissolved in dry DCM (2.0 mL) and the mixture was stirred at room temperature for 10 min. The mixture was cooled to -80 °C and subsequently the corresponding Grignard reagent solution (1.25 equiv.) was added dropwise. The reaction mixture was stirred at -80 °C for another 10 min. Then a solution of chromonone 2a (0.4 mmol, 58.4 mg) in DCM (1.0 mL) was added slowly over 1 h using a syringe pump. The reaction was stirred until TLC (n-pentane:EtOAc 9:1) showed full conversion. PhCHO (1.6 mmol, 150 μL) was added and the mixture was stirred at room temperature for 3 h. After that the reaction mixture was quenched with saturated aqueous NH\(_4\)Cl solution (2 mL). The mixture was separated and the water layer was extracted with DCM (3×5 mL). The combined organic layers were dried over MgSO\(_4\), filtered and the solvent was evaporated under vacuo. Purification by flash chromatography over silica gel, using n-pentane:Et\(_2\)O 9:1 afforded the desired compound 9 was obtained as an oil (101.5 mg, 0.36 mmol, 90% yield, dr: 1:1.1); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.90 (dd, \(J = 7.8, 1.5\) Hz, 1H), 7.75 (d, \(J = 7.8\) Hz, 1H), 7.54-7.20 (m, 12H), 7.01 (t, \(J = 7.5\) Hz, 1H), 6.99-6.92 (m, 3H), 5.15 (d, \(J = 6.7\) Hz, 1H), 4.98\(^*\) (d, \(J = 9.1\) Hz, 1H), 4.72-4.63 (m, 1H), 4.04\(^*\) (ddd, \(J = 9.4, 5.0, 2.3\) Hz, 1H), 2.90 (dd, \(J = 6.6, 4.8\) Hz, 1H), 2.73\(^*\) (dd, \(J = 9.1, 2.3\) Hz, 1H), 1.87-1.67 (m, 2H), 1.63-1.51 (m, 1H), 1.50-1.39\(^*\) (m, 1H), 0.95 (t, \(J = 7.3\) Hz, 3H), 0.84\(^*\) (t, \(J = 7.3\) Hz, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 193.8, 193.4, 159.6, 158.9, 141.4, 141.1, 136.6, 136.4, 128.7, 128.5, 128.43, 128.39, 128.0, 127.22, 127.0, 126.8, 126.8, 126.3, 121.3, 121.1, 118.20, 118.17, 79.7, 79.3, 72.9, 72.6, 57.9, 57.0, 25.1, 24.7, 9.84, 9.75 ppm; HRMS (ESI) calculated for C\(_{18}\)H\(_{19}\)O\(_3\) [M + H] 283.1329 found 283.1328.

**(R)-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]dioxepin-2-one (10)**

![Chemical Structure Image]

(R)-2-ethylchroman-4-one (2a) (0.25 mmol, 44.1 mg) and MCPBA (0.625 mmol, 107.9 mg) were dissolved in 5 mL of ClCH\(_2\)CH\(_2\)Cl, and the mixture was heated to 60 °C. The reaction mixture was stirred until TLC (n-pentane:EtOAc 9:1) showed full conversion and quenched with...
saturated aqueous NaHCO₃ solution (10 mL) and 15 mL of DCM. The mixture was separated and the organic layer was washed with aq. NaHCO₃ (2×7 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was evaporated under vacuo. Purification by flash chromatography over silica gel, using n-pentane:Et₂O 9:1 afforded the desired compound 10 as an oil (33.7 mg, 0.178 mmol, 71% yield); oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer tᵣ = 30.9 min, minor enantiomer tᵣ = 23.7 min, ee = 93%; [α]²⁵°D = +67.1 (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.19-7.08 (m, 4H), 4.62-4.53 (m, 1H), 2.83 (dd, J = 13.2, 5.5 Hz, 1H), 2.65 (dd, J = 13.2, 7.5 Hz, 1H), 1.93-1.80 (m, 1H), 1.67-1.55 (m, 1H), 1.08 (t, J = 7.4 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 168.2, 145.9, 144.8 126.7, 125.5, 124.1, 120.2, 84.0, 37.5, 27.5, 10.0 ppm; HRMS (ESI) calculated for C₁₁H₁₃O₃ [M + H] 193.0859 found 193.0858.

References:


NMR Spectra of Characterized Compounds

(R)-2-ethylchroman-4-one
(R)-2-pentylchroman-4-one
(R)-2-hexylchroman-4-one
(R)-2-dodecylchroman-4-one
(R)-2-isobutylchroman-4-one
(R)-2-(but-3-en-1-yl)chroman-4-one
(R)-2-phenethylchroman-4-one
(S)-2-(pentan-3-yl)chroman-4-one
(S)-2-cyclopentylchroman-4-one
(R)-2-ethyl-6-methylchroman-4-one
(R)-2-ethyl-6-fluorochroman-4-one
(R)-6-chloro-2-ethylchroman-4-one
(R)-6-bromo-2-ethylchroman-4-one
(R)-2-ethyl-7-methoxychroman-4-one
(2R,3R)-2-ethyl-3-(hydroxy(phenyl)methyl)chroman-4-one
(R)-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]dioxepin-2-one
HPLC data of the compounds

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