SUPPORTING INFORMATION

Asymmetric Conjugate Addition of Grignard Reagents to Pyranones

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1. General Remarks:

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) or a Varian Unity Plus Varian-500 (500 and 125 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, 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). Enantioselectivities 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 pyranones were purchased from Aldrich and used without as received. Grignard reagents RMgBr (R = Me, Et, n-Hexyl, i-Bu) were purchased from Aldrich. Hept-6-en-1-ylmagnesium 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.
2. Experimental Section

Table S1. Influence of copper salts in the optimization process$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>[Cu]</th>
<th>conversion$^b$ (%)</th>
<th>er$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr·SMe$_2$</td>
<td>100</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>100</td>
<td>90:10</td>
</tr>
<tr>
<td>3</td>
<td>CuTC</td>
<td>&lt;10</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>(CuOTf)$_2$·C$_6$H$_6$</td>
<td>&lt;10</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

$^a$ General conditions for ACA: 5.0 mol % of CuBr·SMe$_2$, 6.0 mol % of L4, 2 equiv of EtMgBr in 2 mL t-BuOMe at -72 °C.
$^b$ Conversion was determined by $^1$H NMR spectroscopy of the crude mixture.
$^c$ Determined by chiral HPLC analysis.

![Diagram of ligands L1-L4]

2.1 General procedure for the synthesis of racemic product of the copper catalyzed 1,4-addition of Grignard reagents to 2H-pyran-2-one:

CuBr·SMe$_2$ (0.0175 mmol, 3.6 mg) and PPh$_3$ (0.042 mmol, 11.0 mg) were dissolved in dry t-BuOMe (5.0 mL) and stirred at room temperature for 15 min. The mixture was cooled to -72 °C and subsequently 2.0 equiv of the appropriate Grignard reagent was added dropwise. The reaction mixture was stirred at -72 °C for another 15 min. Then a solution of 2H-pyran-2-one (0.35 mmol, 37.0 mg) in 2 mL t-BuOMe added slowly over 1 h by a syringe pump. The reaction mixture was stirred until TLC (Et$_2$O/n-pentane 1/3) showed full conversion and quenched by saturated aqueous NH$_4$Cl solution (2 mL). The mixture was
separated and the water layer was extracted by ether (3×5 mL). The organic layer was dried over MgSO$_4$, filtered and the solvent was evaporated under vacuo (Note: in some cases products are very volatile). Purification by flash chromatography over silica gel, using Et$_2$O/n-Pentane 1/9 afforded the pure racemic product as colorless oil.

2.2 General procedure for the enantioselective copper catalyzed 1,4-addition of Grignard reagents to 2-Pyrene:

\[
\text{O} \quad \text{RMgBr} + \text{O} \quad \text{O} \quad \text{R} \\
1 \quad \text{CuBr-SMe$_2$, 6.0 mol %} \quad \text{L} \quad \text{CuBr-SMe$_2$, 5.0 mol %} \\
\text{R = alkyl} \quad \text{L} \quad \text{L} \quad \text{Fe PCy$_2$PPh$_2$} \\
\quad \text{t-BuOMe, -72 °C} \quad \text{L} \quad \text{(R,S)-Rev-Josiphos} \quad \text{L} \quad \text{(R,S)-Rev-Josiphos} \\
\quad \quad \text{2 equiv} \quad \quad \text{L} \quad \text{L} \\
2 \quad \text{CuBr-SMe$_2$ (0.0175 mmol, 3.6 mg) and L$_4$ (R,S)-Rev-Josiphos (0.021 mmol, 12.5 mg) were} \\
\quad \quad \text{dissolved in dry t-BuOMe (5.0 mL) and the mixture was stirred at room temperature for 15} \\
\quad \quad \text{min. The mixture was cooled to -72 °C and subsequently the corresponding Grignard reagent} \\
\quad \quad \text{solution (2.0 equiv) were added dropwise. The reaction mixture was stirred at -72 °C for} \\
\quad \quad \text{another 15 min. Then a solution of 2$H$-pyran-2-one 1 (0.35 mmol, 37.0 mg) in t-BuOMe} \\
\quad \quad \text{(2.0 mL) was added slowly over 1h using a syringe pump. The reaction was stirred until} \\
\quad \quad \text{TLC (Et$_2$O/n-pentane 25%) showed full conversion and quenched with saturated aqueous} \\
\quad \quad \text{NH$_4$Cl solution (2 mL). The mixture was separated and the water layer was extracted with} \\
\quad \quad \text{ether (3×5 mL). The combined organic layers were dried over MgSO$_4$, filtered and the} \\
\quad \quad \text{solvent was evaporated under vacuo (Note: in some cases products are very volatile).} \\
\quad \quad \text{Purification by flash chromatography over silica gel, using Et$_2$O/n-Pentane 1/9 afforded the} \\
\quad \quad \text{pure product 2 as colorless oil.}
\]

(-)-(R)-4-Ethyl-3,4-dihydro-2$H$-pyran-2-one (2a)

Colorless oil obtained after column chromatography (SiO$_2$, Et$_2$O/n-pentane 1/9), [67% yield, 95:5 er]. [α]$^0_{D}$ = -1.0 (c 1.7, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.48 (dd, $J$ = 6.0, 1.5 Hz, 1H), 5.35 – 5.12 (m, 1H), 2.81 – 2.61 (m, 1H), 2.51 – 2.39 (m, 1H), 1.55 – 1.39 (m, 2H), 1.37 – 1.24 (m, 2H), 0.94 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.6, 140.6, 110.1, 34.6, 32.0, 27.5, 10.7. HRMS (ESI+, m/z): calcd for C$_7$H$_{11}$O$_2$ [M+H]$^+$: 127.07536, found 127.07546. Enantiomeric ratio was determined by chiral HPLC, Chiralpak AS-H (Heptane/i-Propanol = 99/1, 0.5 mL/min, 211 nm, column temperature 40 °C), retention times: $t_R$ (major) 18.23 min, $t_R$ (minor) 20.62 min.
(-)-(R)-4-Hexyl-3,4-dihydro-2H-pyran-2-one (2b)

Colorless oil obtained after column chromatography (SiO₂, Et₂O/n-pentane 1/9), [82% yield, 94:6 er]. [α]²⁰ = -4.1 (c 0.8, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 6.47 (dd, J = 6.0, 1.5 Hz, 1H), 5.25 (dd, J = 5.9, 4.0 Hz, 1H), 2.70 (dd, J = 15.3, 6.0 Hz, 1H), 2.55 – 2.47 (m, 1H), 2.40 (dd, J = 15.3, 8.1 Hz, 1H), 1.35 – 1.20 (m, 10H), 0.92 – 0.83 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.7, 140.5, 110.5, 35.0, 34.7, 31.6, 30.5, 29.1, 26.3, 22.5, 14.0. HRMS (ESI+, m/z): calcd for C₁₁H₁₉O₂ [M+H]⁺: 183.13796, found 183.13813. Enantiomeric ratio was determined by chiral HPLC, Chiralpak AD-H (Heptane/i-Propanol = 99.5/0.5, 0.5 mL/min, 213 nm, column temperature 40 °C), retention times: tᵣ (major) 21.16 min, tᵣ (minor) 19.50 min.

(-)-(R)-4-(Hept-6-en-1-yl)-3,4-dihydro-2H-pyran-2-one (2c)

Colorless oil obtained after column chromatography (SiO₂, Et₂O/n-pentane 1/9), [85% yield, 95:5 er]. [α]²⁰ = -7.8 (c 0.9, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 6.46 (dd, J = 6.0, 1.4 Hz, 1H), 5.78 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.24 (dd, J = 5.8, 4.1 Hz, 1H), 4.98 (dd, J = 17.1, 1.6 Hz, 1H), 4.93 (d, J = 9.5 Hz, 1H), 2.70 (dd, J = 15.3, 6.0 Hz, 1H), 2.56 – 2.45 (m, 1H), 2.40 (dd, J = 15.4, 8.0 Hz, 1H), 2.03 (dd, J = 14.1, 6.9 Hz, 2H), 1.50 – 1.27 (m, 8H). ¹³C NMR (101 MHz, CDCl₃) δ 168.5, 140.6, 138.8, 114.4, 110.4, 35.0, 34.6, 33.6, 30.4, 28.9, 28.7, 26.2. HRMS (ESI+, m/z): calcd for C₁₂H₁₉O₂ [M+H]⁺: 195.13796, found 195.13802. Enantiomeric ratio was determined by chiral HPLC, Chiralpak AD-H (Heptane/i-Propanol = 99.5/0.5, 0.5 mL/min, 223 nm, column temperature 40 °C), retention times: tᵣ (major) 33.64 min, tᵣ (minor) 28.83 min.

(-)-(R)-4-Isobutyl-3,4-dihydro-2H-pyran-2-one (2d)

Colorless oil obtained after column chromatography (SiO₂, Et₂O/n-pentane 1/9), [55% yield, 94:6 er]. [α]²⁰ = -6.5 (c 1.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 6.44 (dd, J = 6.0, 1.5 Hz, 1H), 5.23 (dd, J = 5.9, 4.0 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.60 – 2.51 (m, 1H), 2.35 (dd, J = 15.4, 7.8 Hz, 1H), 1.66 (dt, J = 13.8, 6.7 Hz, 1H), 1.36 – 1.26 (m, 1H), 1.25 – 1.17 (m, 1H), 0.88 (dd, J = 6.6, 4.3 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 168.6, 140.5, 110.6, 43.9, 35.2, 28.3, 25.0, 22.5, 22.3. HRMS (ESI+, m/z): calcd
for C₃H₅O₂ [M+H]+: 155.1067, found 155.1064. Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 50 °C (hold for 20 min), then 10 °C/min to 180 °C for 5 min, then 10 °C/min to 50 °C (final temp), retention times (min.): 28.16 (major) and 28.24 (minor).

2.3 General procedure for the synthesis of (R)-methyl 3-(2-oxoethyl)nonanoate:

\[
\begin{array}{c}
\text{1} \quad \text{2 equiv} \\
\text{CuBr-SMe₂ (0.0175 mmol, 3.6 mg) and L4 (R,S)-Rev-Josiphos (0.042 mmol, 11.0 mg) were dissolved in dry } \text{t-BuOMe (5.0 mL) and the mixture was stirred at room temperature for 15 min. The mixture was cooled to -72 °C and subsequently the hexylmagnesium bromide solution (c = 2.0 M in Et₂O, 0.7 mmol, 0.35 mL) was added dropwise. The reaction mixture was then stirred at -72 °C for another 15 min. Then a solution of 2-pyrene 1 (0.35 mmol, 37.0 mg) in 2 mL t-BuOMe was added slowly over 1h using a syringe pump. The reaction mixture was stirred until TLC (Et₂O/n-pentane 1/3) showed full conversion and then MeOH (1.75 mmol, 71 μL) was added in one portion. The reaction mixture was warmed to room temperature and stirred at that temperature for 12h. Then the reaction was quenched by the addition of saturated aqueous NH₄Cl solution (2 mL). The mixture was separated and the water layer was extracted by ether (3×5 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was evaporated under vacuo. (Note: in some cases products are very volatile). Purification by flash chromatography over silica gel, using Et₂O/n-pentane 1/9 afforded the pure product 4 as colorless oil.}
\end{array}
\]

(-)-(R)-Methyl 3-(2-oxoethyl)nonanoate (4)

Colorless oil obtained after column chromatography (SiO₂, Et₂O/n-pentane 1/9), [66% yield, 94:6 er], [α]°D = -25.4 (c 1.0, CHCl₃). H NMR (400 MHz, CDCl₃) δ 9.75 (s, 1H), 3.68 – 3.62 (m, 2H), 3.50 – 3.42 (m, 1H), 2.49 – 2.40 (m, 2H), 1.40 – 1.18 (m, 10H), 0.93 – 0.78 (m, 3H). C NMR (101 MHz, CDCl₃) δ 201.8, 172.9, 65.8, 51.5, 48.2, 38.4, 34.1, 31.7, 30.0, 29.2, 22.3, 14.0. HRMS (APCI, m/z): calcd for C₁₂H₂₃O₃ [M+H]+: 215.16417; found: 215.16422.
Enantiomeric ratio was determined by chiral GC analysis, Chiraldex G-TA (30 m x 0.25 mm), initial temp. 40 °C (hold for 15 min), then 10 °C/min to 150 °C (hold for 10 min), then 10 °C/min to 40 °C (final temp), retention times (min.): 32.9 (major) and 33.2 (minor).

2.4 General procedure for the synthesis of (-)-(R)-methyl 3-((S)-1-bromo-2-hydroxyethyl) nonanoate

(R)-4-Hexyl-3,4-dihydro-2H-pyran-2-one 2b (0.4 mmol, 72.8 mg) was dissolved in 4 mL of MeOH at rt. Ammonium acetate (0.1 mmol, 7.7 mg) was added as a catalyst. The solution was cooled to −78 °C, and N-bromosuccinimide (0.48 mmol, 85.4 mg) was added in one portion. The yellow mixture was allowed to warm to 0 °C over 4 h. Sodium borohydride (1.2 mmol, 45.3 mg) was then added. The resulting solution was warmed up to room temperature and then quenched with saturated aqueous NH₄Cl solution (2 mL) until GC-MS analysis showed full conversion. The mixture was separated and the water layer was extracted by ether (3×5 mL). The combine organic layers were dried over MgSO₄, filtered and the solvent was evaporated under vacuo. Purification by flash chromatography over silica gel, using Et₂O/n-pentane 1/9 afforded the pure product 6 as colorless oil.

(-)-(R)-Methyl 3-((S)-1-bromo-2-hydroxyethyl)nonanoate (6)

Colorless oil obtained after column chromatography (SiO₂, Et₂O/n-Pentane 1/9), [71% yield, 93:7 er]. [α]D²⁰ = -3.0 (c 1.6, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 5.37 (bs, 2H), 4.23 (bs, 1H), 3.58 (s, 3H), 2.61 (d, J = 14.9 Hz, 1H), 2.46 – 2.35 (m, 2H), 1.36 – 1.21 (m, 10H), 0.95 – 0.83 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 168.4, 104.4, 57.1, 51.2, 33.2, 33.2, 31.7, 31.6, 29.0, 25.7, 22.5, 14.0. HRMS (APCI+, m/z): calcd for C₁₂H₂₂BrO₃ [M+H]⁺: 293.07468; found: 293.07290.

Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 50 °C (hold for 20 min), then 10 °C/min to 180 °C for
5 min, then 10 °C/min to 50 °C (final temp), retention times (min.): 34.3 (major) and 34.6 (minor).

2.5 General procedure for the synthesis of racemic product of the copper catalyzed 1,4-addition of Grignard reagents to 5,6-dihydro-2H-pyran-2-one:

\[
\begin{align*}
\text{7} + \text{RMgBr} & \quad \text{CuI 1.0 equiv, Et}_2\text{O, 0 °C} \\
\text{1} & \quad \text{2 equiv} \\
\text{8} & \quad \text{(±)R}
\end{align*}
\]

A solution of the appropriate Grignard reagent in ether (1.2 equiv) was slowly added to a suspension of CuI (57.0 mg, 0.3 mmol) in Et₂O (5 mL) at 0 °C. After stirring for 15 min at 0 °C, 5,6-dihydro-2H-pyran-2-one 7 (0.3 mmol) was added dropwise. The reaction mixture was stirred for 2h and quenched by saturated aqueous NH₄Cl solution (2 mL). The mixture was warmed up to room temperature and partitioned between ether and water. The organic layer was dried over MgSO₄, filtered and the solvent was evaporated under vacuo. Purification by flash chromatography over silica gel, using Et₂O/n-pentane 1/1 afforded the pure racemic product 8 as pale yellow oil.

2.6 General procedure for the copper catalyzed 1,4-addition of Grignard reagents to 5,6-dihydro-2H-pyran-2-one:

\[
\begin{align*}
\text{7} + \text{RMgBr} & \quad \text{CuBr-SMe} \quad \text{L₄, 6.0 mol %, t-BuOMe, -72 °C} \\
\text{1} & \quad 1.5 \text{ equiv} \\
\text{8} & \quad \text{R = alkyl}
\end{align*}
\]

CuBr-SMe₂ (0.0175 mmol, 3.6 mg) and L₄ (R,S)-Rev-Josiphos (0.021 mmol, 12.5 mg) were dissolved in dry t-BuOMe (5.0 mL) and stirred at room temperature for 15 min. The mixture was cooled to -72 °C and subsequently the appropriate Grignard reagent (1.5 equiv) was added dropwise. The reaction mixture was stirred at -72 °C for another 15 min. Then a solution of 5,6-dihydro-2H-pyran-2-one 7 (0.35 mmol, 34 mg) in 2 mL t-BuOMe was added slowly over 1h by a syringe pump. The reaction mixture was stirred until TLC (Et₂O/n-Pentane 1/1) showed full conversion and quenched with saturated aqueous NH₄Cl solution (2 mL). The mixture was warmed up to room temperature and partitioned between ether and water. The organic layer was dried over MgSO₄, filtered and the solvent was
evaporated under \textit{vacuo}. Purification by flash chromatography over silica gel, using Et$_2$O/n-pentane 1/1 afforded the pure product 8 as colorless oil.

\textbf{(-)-(S)-4-Ethyl-tetrahydro-2H-pyran-2-one (8a)}

Pall yellow oil obtained after column chromatography (SiO$_2$, Et$_2$O/n-pentane 1/1), [81\% yield, 95:5 er]. The physical data were identical in all respects to those previously reported.$^1$ [\alpha]$_{D}^{20}$ = -14.8 (c 0.50, CHCl$_3$), [lit.$^1$ (R isomer, 99:1 er): [\alpha]$_{D}^{20}$ = +21.9 (c 0.51, CHCl$_3$)]. Enantiomeric ratio was determined by chiral GC analysis, Chiraldex G-TA (30 m x 0.25 mm), initial temp. 50 $^\circ$C, then 10 $^\circ$C/min to 90 $^\circ$C, then 0.3 $^\circ$C/min to 105 $^\circ$C (hold for 5 min), then 10 $^\circ$C/min to 50$^\circ$C (final temp), retention times (min.): 107.2 (major) and 109.6 (minor).

\textbf{(-)-(S)-4-Hexyltetrahydro-2H-pyran-2-one (8b)}

Pall yellow oil obtained after column chromatography (SiO$_2$, Et$_2$O/n-pentane 1/1), [88\% yield, 96:4 er]. [\alpha]$_{D}^{20}$ = -8.8 (c 1.0, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.39 (dt, $J = 11.3, 4.3$ Hz, 1H), 4.23 (td, $J = 10.9, 3.5$ Hz, 1H), 2.67 (ddd, $J = 17.3, 6.8, 1.3$ Hz, 1H), 2.12 (dd, $J = 17.3, 9.7$ Hz, 1H), 2.00 – 1.87 (m, 2H), 1.55 – 1.44 (m, 1H), 1.38 – 1.18 (m, 10H), 0.87 (t, $J = 6.6$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.5, 68.5, 36.6, 36.2, 31.7, 31.4, 29.2, 28.9, 26.3, 22.5, 14.0. HRMS (APCI+, m/z): calcd for C$_{11}$H$_{21}$O$_2$ [M+H]$^+$: 185.15361; found: 185.15425. Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 40 $^\circ$C, then 10 $^\circ$C/min to 85 $^\circ$C, then 0.5 $^\circ$C/min to 160 $^\circ$C, then 10 $^\circ$C/min to 40 $^\circ$C (final temp), retention times (min.): 85.5 (major) and 86.2 (major).

\textbf{(-)-(S)-4-(But-3-en-1-yl)-tetrahydro-2H-pyran-2-one (8c)}

Pall yellow oil obtained after column chromatography (SiO$_2$, Et$_2$O/n-pentane 1/1), [85\% yield, 97:3 er]. [\alpha]$_{D}^{20}$ = -15.0 (c 1.0, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.75 (ddt, $J = 16.9, 10.2, 6.7$ Hz, 1H), 5.05 – 4.92 (m, 2H), 4.39 (dt, $J = 11.3, 4.4$ Hz, 1H), 4.23 (td, $J = 11.2, 3.6$ Hz, 1H), 2.67 (ddd, $J = 17.2, 9.7$ Hz, 1H), 2.00 – 1.87 (m, 2H), 1.55 – 1.44 (m, 1H), 1.38 – 1.18 (m, 10H), 0.87 (t, $J = 6.6$ Hz, 3H).

5.7, 1.5 Hz, 1H), 2.16 – 2.05 (m, 3H), 2.02 – 1.89 (m, 2H), 1.57 – 1.37 (m, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.2, 137.6, 115.3, 68.4, 36.4, 35.2, 30.8, 30.5, 28.8. HRMS (APCI+, $m$/z): calcd for C$_9$H$_{15}$O$_2$ [M+H]$^+$: 155.10666; found: 155.10684. Enantiomeric ratio was determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 40 °C, then 10 °C/min to 85 °C, then 0.5 °C/min to 160 °C, then 10 °C/min to 40 °C (final temp), retention times (min.): 54.9 (major) and 56.1 (minor).

(-)-(S)-4-Isobutyl-tetrahydro-2H-pyran-2-one (8d)

Pale yellow oil obtained after column chromatography (SiO$_2$, Et$_2$O/n-pentane 1/1), [84% yield, >99:1 er]. $[\alpha]_D^{20}$ = -25.4 (c 1.0, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.38 (dt, $J$ = 11.3, 4.5 Hz, 1H), 4.23 (td, $J$ = 10.9, 3.7 Hz, 1H), 2.64 (ddd, $J$ = 16.6, 5.1, 1.2 Hz, 1H), 2.11 – 1.96 (m, 2H), 1.94 – 1.85 (m, 1H), 1.69 – 1.54 (m, 1H), 1.52 – 1.41 (m, 1H), 1.26 – 1.10 (m, 2H), 0.87 (d, $J$ = 6.6 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.4, 68.5, 45.5, 36.7, 29.1, 24.6, 22.5, 22.5. HRMS (ESI+, $m$/z): calcd for C$_9$H$_{17}$O$_2$ [M+H]$^+$: 157.1250; found: 157.1228. Enantiomeric ratio was determined by chiral GC analysis, Chiralaldex G-TA (30 m x 0.25 mm), initial temp. 50 °C, then 10 °C/min to 110 °C, then 0.3 °C/min to 140 °C (hold for 5 min), then 10 °C/min to 50 °C (final temp), retention times (min.): 74.9 (minor) and 76.0 (major).

(-)-(S)-4-methyltetrahydro-2H-pyran-2-one (8e)

Pale yellow oil obtained after column chromatography (SiO$_2$, Et$_2$O/n-pentane 1/1), [68% yield, 75:25 er]. $[\alpha]_D^{20}$ = -11.7 (c 1.0, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.35 (dt, $J$ = 11.4, 4.4 Hz, 1H), 4.21 (td, $J$ = 11.0, 3.8 Hz, 1H), 2.61 (q, $J$ = 10.0 Hz, 1H), 2.20 – 1.96 (m, 2H), 1.86 (dd, $J$ = 13.6, 3.9 Hz, 1H), 1.58 – 1.37 (m, 1H), 1.01 (d, $J$ = 6.4 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) 171.1, 68.4, 38.1, 30.5, 26.4, 21.3. Enantiomeric ratio was determined by chiral GC analysis, Chiralaldex G-TA (30 m x 0.25 mm), initial temp. 60 °C (hold for 15 min), then 5 °C/min to 150 °C (hold for 25 min), then 10 °C/min to 40 °C (final temp), retention times (min.): 34.8 (major) and 35.0 (minor).

3. NMR Spectroscopy

(-)-(R)-4-Ethyl-3,4-dihydro-2H-pyran-2-one (2a)

$^1$H NMR

$^1$C NMR
(-)-(R)-4-Hexyl-3,4-dihydro-2H-pyran-2-one (2b)

$^1$H NMR

$^{13}$C NMR
(-)-(R)-4-(Hept-6-en-1-yl)-3,4-dihydro-2H-pyran-2-one (2c)

$^1$H NMR

$^{13}$C NMR
(-)-(R)-4-Isobutyl-3,4-dihydro-2H-pyran-2-one (2d)

$^1$H NMR

$^{13}$C NMR
(-)-(R)-Methyl 3-(2-oxoethyl)nonanoate (4)

$^1$H NMR

$^{13}$C NMR
(-)-(R)-methyl 3-((S)-1-bromo-2-hydroxyethyl)nonanoate (6)

$^1$H NMR

$^{13}$C NMR
(-)-(S)-4-Hexyltetrahydro-2H-pyran-2-one (8b)

$^{1}H$ NMR

$^{13}C$ NMR
(-)-(S)-4-(But-3-en-1-yl)-tetrahydro-2H-pyran-2-one (8c)

$^1$H NMR

$^{13}$C NMR
(-)-(S)-4-Isobutyl-tetrahydro-2H-pyran-2-one (8d)

$^1$H NMR

$^{13}$C NMR
(-)-(S)-4-methyltetrahydro-2H-pyran-2-one (8e)

$^1$H NMR

$^{13}$C NMR
4. HPLC Data

(±)-4-Ethyl-3,4-dihydro-2H-pyran-2-one ((±)-2a)

(-)-(R)-4-Ethyl-3,4-dihydro-2H-pyran-2-one (2a)
(±)-4-Hexyl-3,4-dihydro-2H-pyran-2-one ((±)-2b)

(-)-(R)-4-Hexyl-3,4-dihydro-2H-pyran-2-one (2b)
(±)-4-(Hept-6-en-1-yl)-3,4-dihydro-2H-pyran-2-one ((±)-2c)

1: 210 nm, 2 nm Results

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(-)-(R)-4-(Hept-6-en-1-yl)-3,4-dihydro-2H-pyran-2-one (2c)

1: 220 nm, 2 nm Results

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(±)-4-Isobutyl-3,4-dihydro-2H-pyran-2-one ((±)-2d)

(-)-(R)-4-Isobutyl-3,4-dihydro-2H-pyran-2-one (2d)

S23
(±)-Methyl 3-(2-oxoethyl)nonanoate ((±)-4)

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(-)-(R)-Methyl 3-(2-oxoethyl)nonanoate (4)

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(±)-Methyl 3-(1-bromo-2-hydroxyethyl)nonanoate ((±)-6)

(-)-(R)-Methyl 3-((S)-1-bromo-2-hydroxyethyl)nonanoate (6)

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(±)-4-Ethyl-tetrahydro-2H-pyran-2-one (±)-8a

(-)-(S)-4-Ethyl-tetrahydro-2H-pyran-2-one (8a)
(±)-4-Hexyltetrahydro-2H-pyran-2-one ((±)-8b)

(-)-(S)-4-Hexyltetrahydro-2H-pyran-2-one (8b)
(±)-4-(But-3-en-1-yl)-tetrahydro-2H-pyran-2-one ((±)-8c)

![Graph for (±)-4-(But-3-en-1-yl)-tetrahydro-2H-pyran-2-one ((±)-8c)]

<table>
<thead>
<tr>
<th>#</th>
<th>Meas.RT</th>
<th>Main Pe</th>
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(-)-(S)-4-(But-3-en-1-yl)-tetrahydro-2H-pyran-2-one (8c)

![Graph for (-)-(S)-4-(But-3-en-1-yl)-tetrahydro-2H-pyran-2-one (8c)]

<table>
<thead>
<tr>
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<th>Meas.RT</th>
<th>Main Pe</th>
<th>Exp.RT</th>
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<th>Resp. Main Pe</th>
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<tbody>
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(±)-4-Isobutyl-tetrahydro-2\textit{H}-pyran-2-one ((±)-8d)

<table>
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<th>Peak #</th>
<th>RT [min]</th>
<th>Type</th>
<th>Name</th>
<th>Width [min]</th>
<th>Area</th>
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(-)-(S)-4-Isobutyl-tetrahydro-2\textit{H}-pyran-2-one (8d)

<table>
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<th>RT [min]</th>
<th>Type</th>
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<th>Width [min]</th>
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(±)-4-Methyl-tetrahydro-2H-pyran-2-one ((±)-8e)

(−)-(S)-4-Methyl-tetrahydro-2H-pyran-2-one ((−)-8e)