An Organocatalytic One-pot Cascade Incorporating the Achmatowicz Reaction Affording 3-Pyrone Derivatives

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1. General methods

NMR spectra were acquired on a Bruker AVANCE III HD spectrometer, running at 400 MHz for $^1$H and 100 MHz for $^{13}$C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CDCl$_3$: 7.26 ppm for $^1$H NMR, 77.16 ppm for $^{13}$C NMR). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; dt, double triplet; dq, double quartet; ddd, double double doublet; ddt double double triplet; tq, triple quartet; dp, double pentet; m, multiplet; bs, broad signal. $^{13}$C NMR spectra were acquired on a broad band decoupled mode. For characterization of diastereomeric mixtures, *denotes major diastereoisomer, + denotes overlap of signals from both diastereoisomers. In cases of high diastereomeric ratios, unobservable peaks for the minor diastereomer have been omitted. Mass spectra were recorded on a Bruker MicroTOF-Q High Performance LC-MS system using electrospray (ES$^+$) ionization techniques. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation, KMnO$_4$ staining solution or vanillin staining solution. Optical rotations were measured on a Bellingham+Stanley ADP440+ polarimeter, α values are given in deg·cm$^3$·g$^{-1}$·dm$^{-1}$; concentration c in g·(100 ml)$^{-1}$. The enantiomeric excess (ee) of the products was determined by chiral stationary phase Waters ACQUITY UPC$^2$ (Daicel Chiralpak IC column), running at a column temperature of 40 °C. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Fluka) was used.
2. Synthesis of α,β-unsaturated aldehydes 1
2a. Synthesis of (E)-5-phenylpent-2-enal 1c

(E)-5-Phenylpent-2-enal 1c was synthesized from crotonaldehyde by cross-methatesis with 4-phenyl-1-butene using 2nd generation Grubbs-Hoveyda catalyst. The compound is known and the spectroscopic data were found to be in accordance with literature.¹

2b. Synthesis of (E)-3-cyclohexylacrylaldehyde 1e

Vinylcyclohexane (0.10 mL, 0.73 mmol) was dissolved in 5 ml CH₂Cl₂. Crotonaldehyde (0.12 mL, 1.47 mmol) was added to the mixture. Grubbs-Hoveyda 2nd generation catalyst (16.7 mg, 0.037 mmol) was dissolved in 1 mL CH₂Cl₂, and this was added to the reaction mixture. The reaction was stirred at 40 °C overnight. The solvent was then removed by rotatory evaporation and the crude product was purified by FC on silica gel (gradient: pentane/CH₂Cl₂ 50:50 to pentane/CH₂Cl₂ 15:85), to afford the product 1e in 64% yield as a colorless oil (E:Z >20:1).

¹H NMR (400 MHz, CDCl₃) δ ppm 9.50 (d, J = 7.9 Hz, 1H), 6.78 (dd, J = 15.7, 6.5, 1H), 6.07 (ddd, J = 15.7, 7.9, 1.4, 1H), 2.31-2.23 (m, 1H), 2.83-2.76 (m, 5H), 1.39-1.13 (m, 5H). ¹³C NMR (100 MHz, CDCl₃) δ ppm 194.5, 163.8, 130.5, 40.9, 31.5 (2C), 25.8, 25.6 (2C).

3. Enantioselective synthesis of 3-pyrones 7 – Screening Results

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<sup>a</sup>No water added in oxidation step.

Abbreviations: MTBD: methyl-1,5,7-triazabicyclo(4.4.0)dec-5-ene, CSA: camphorsulfonic acid, NMO: N-methylmorpholine-N-oxide, DMPO: 5,5-dimethyl-1-pyrroline-N-oxide.

**General procedure:** A 4 mL screw cap glass vial equipped with a magnetic stirrer bar was charged with the aminocatalyst 2 (0.01 mmol, 0.05 equiv.), which was dissolved in 0.4 mL toluene, and the aldehyde 1 (0.2 mmol, 1.0 equiv.) was added. After brief stirring, H<sub>2</sub>O<sub>2</sub> (35 wt% in water, 0.26 mmol, 1.3 equiv.) was added, and the mixture was stirred at rt for 24 h, to achieve full conversion. At this point the nucleophile 4 (0.21 mmol, 1.05 equiv.) was added together with MTBD (0.1 mmol, 0.5 equiv.). The reaction was stirred at rt for 1 h, followed by the addition of Acid (0.14 mmol, 0.7 equiv.), and stirring for another 1 h. 0.2 mL of H<sub>2</sub>O, NaOAc (0.2 mmol, 1.0 equiv.), and oxidant(0.26 mmol, 1.3 equiv.) was added. After stirring for 1 h, the layers were separated, the aqueous layer was extracted twice with 0.5 mL of toluene, and the combined organic phases were directly subjected to FC on silica gel to afford the product 7. Alternatively, the crude reaction was directly subjected to FC on silica gel to afford the product 7.
4. Enantioselective synthesis of 3-pyriones 7

General procedure: A 4 mL screw cap glass vial equipped with a magnetic stirrer bar was charged with the aminocatalyst 2 (0.01 mmol, 0.05 equiv.), which was dissolved in 0.4 mL toluene, and the aldehyde 1 (0.2 mmol, 1.0 equiv.) was added. After brief stirring, H$_2$O$_2$ (35 wt% in water, 0.26 mmol, 1.3 equiv.) was added, and the mixture was stirred at rt for 24 h, to achieve full conversion. At this point the nucleophile 4 (0.21 mmol, 1.05 equiv.) was added together with MTBD (0.1 mmol, 0.5 equiv.). The reaction was stirred at rt for 1 h, followed by the addition of TFA (0.14 mmol, 0.7 equiv.), and stirring for another 1 h. The mixture was then cooled to 5 °C, and 0.2 mL of cooled H$_2$O, NaOAc (0.2 mmol, 1.0 equiv.), and N-bromosuccinimide (0.26 mmol, 1.3 equiv.) was added. After stirring at 5 °C for 1 h, the reaction was warmed to rt. The layers were separated, the aqueous layer was extracted twice with 0.5 mL of toluene, and the combined organic phases were directly subjected to FC on silica gel to afford the product 7.

**7a (2R)-5-Acetyl-2-hexyl-6-hydroxy-6-methyl-2H-pyran-3(6H)-one (Scheme 1)**

Following the general procedure 7a was isolated by FC (gradient: acetone/pentane 5:95 to acetone/pentane 11:89) in 54% yield as a pale yellow oil (4.9:1 dr). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.44 (s, 1H), 6.38* (s, 1H), 4.52* (dd, J = 7.8, 4.0 Hz, 1H), 4.20 (dd, J = 8.3, 4.2 Hz, 1H), 3.87 (bs, 1H), 3.31* (bs, 1H), 2.45 (s, 3H), 2.45* (s, 3H), 1.98 – 1.88* (m, 1H), 1.73 (s, 3H), 1.70 – 1.68* (m, 1H), 1.63* (s, 3H), 1.50 – 1.38* (m, 2H), 1.37 – 1.22* (m, 6H), 0.87* (t, J = 6.8, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 201.3*, 200.7, 198.3*, 198.2, 154.3, 153.2*, 128.6, 127.8*, 95.6, 93.9*, 78.2, 74.2*, 31.8*, 31.8, 31.2, 29.3*, 29.2*, 29.1, 27.9, 27.7*, 27.5*, 25.4, 25.1, 25.0*, 22.7*, 14.2*. HR-MS: calculated for (M+Na$^+$): 277.1410; found: 277.1409. The ee was determined by UPC$^2$ using a Chiralpak IC column (CO$_2$/iPrOH 90:10, 3 mL min$^{-1}$). Major diastereoisomer: $\tau_{\text{major}} = 2.2$ min, $\tau_{\text{minor}} = 1.4$ min (93% ee). Minor diastereoisomer: $\tau_{\text{major}} = 1.7$ min, $\tau_{\text{minor}} = 1.9$ min (93% ee). [$\alpha$]$_D$$^{23}$: -29.1 (c = 1.01, CHCl$_3$).
7b (2R)-5-Acetyl-6-hydroxy-6-methyl-2-propyl-2H-pyran-3(6H)-one (Scheme 1)

Following the general procedure 7b was isolated by FC (gradient: acetone/pentane 7:93 to acetone/pentane 15:85) in 53% yield as a pale yellow oil (4.6:1 dr). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.45 (s, 1H), 6.39* (s, 1H), 4.54* (dd, J = 7.9, 4.0 Hz, 1H), 4.22 (dd, J = 8.4, 4.2 Hz, 1H), 3.92 (bs, 1H), 3.34* (bs, 1H), 2.46 (s, 3H), 2.45* (s, 3H), 1.96 – 1.85* (m, 1H), 1.73 (s, 3H), 1.70 – 1.64 (m, 1H), 1.63* (s, 3H), 1.53 – 1.41* (m, 2H), 0.94* (t, J = 7.4 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 201.3*, 200.8, 198.3*, 198.2, 154.2, 153.1*, 128.7, 127.9*, 95.5, 93.8*, 77.7, 73.9*, 33.1, 31.2*, 27.9, 27.7*, 27.5*, 25.4, 18.4, 18.3*, 14.0*, 13.8. HR-MS: calculated for (M+H$^+$): 213.1136; found: 213.1121.

The ee was determined by UPC$^2$ using a Chiralpak IC column (CO$_2$/iPrOH 90:10, 3 mL min$^{-1}$). Major diastereoisomer: $\tau_{\text{major}} = 1.8$ min, $\tau_{\text{minor}} = 1.2$ min (90% ee). Minor diastereoisomer: $\tau_{\text{major}} = 1.5$ min, $\tau_{\text{minor}} = 1.7$ min (90% ee). $[\alpha]_D^{19}: -15.5$ (c = 1.03, CHCl$_3$).

7c (2R)-5-Acetyl-6-hydroxy-6-methyl-2-phenethyl-2H-pyran-3(6H)-one (Scheme 1)

Following the general procedure 7c was isolated by FC (gradient: acetone/pentane 5:95 to acetone/pentane 13:87) in 49% yield as a pale yellow oil (4.6:1 dr). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.22 – 7.11* (m, 5H) 6.36 (s, 1H), 6.30* (s, 1H), 4.46* (dd, J = 8.2, 3.8 Hz, 1H), 4.09 (dd, J = 8.9, 3.9 Hz, 1H), 3.89 (bs, 1H), 3.25* (bs, 1H), 3.25 – 2.94* (m, 2H), 2.38 (s, 3H), 2.37* (s, 3H) 2.21-2.17* (m, 1H), 1.96 – 1.87* (m, 1H), 1.64 (s, 3H), 1.59* (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 201.1*, 200.8, 197.9*, 153.9, 152.9*, 141.4*, 140.9, 128.7(2C), 128.7*(2C), 128.6, 128.4(2C), 128.4*(2C), 127.7*, 126.1, 126.0*, 95.6, 93.8*, 76.6, 73.1*, 32.6, 30.9*, 30.7*, 27.7, 27.6*, 27.4*, 25.4. HR-MS: calculated for (M+Na$^+$): 297.1084; found: 297.1097. The ee was determined by UPC$^2$ using a Chiralpak IC column (CO$_2$/iPrOH 90:10, 3 mL min$^{-1}$). Major diastereoisomer: $\tau_{\text{major}} = 3.6$ min, $\tau_{\text{minor}} = 2.8$ min (94% ee). Minor diastereoisomer: $\tau_{\text{major}} = 2.2$ min, $\tau_{\text{minor}} = 3.2$ min (90% ee). $[\alpha]_D^{19}: -38.6$ (c = 0.52, CHCl$_3$).
7d (2R)-5-Acetyl-6-hydroxy-2-isopropyl-6-methyl-2H-pyran-3(6H)-one (Scheme 1)

Following the general procedure 7d was isolated by FC (gradient: acetone/pentane 5:95 to acetone/pentane 11:89) in 62% yield as a pale yellow oil (5.3:1 dr). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.43 (s, 1H), 6.36* (s, 1H), 4.38* (d, J = 3.1 Hz, 1H), 4.03 (d, J = 4.0 Hz, 1H), 3.95 (bs, 1H), 3.31* (bs, 1H), 2.45 (s, 3H), 2.44* (s, 3H), 2.43 – 2.35 (m, 1H), 1.73 (s, 3H), 1.64* (s, 3H), 1.07 – 1.03 (m, 3H), 0.95 (d, J = 6.8, 3H), 0.88* (d, J = 6.8, 3H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 201.2*, 200.7, 198.4*, 198.1, 154.5, 153.2*, 129.2, 128.2*, 95.7, 93.7*, 82.2, 78.0*, 29.6, 28.4*, 28.0, 27.7*, 27.4*, 25.2, 19.0*, 18.9, 16.8, 16.3*. HR-MS: calculated for (M+Na\(^+\)): 235.0941; found: 235.0942.

The ee was determined by UPC\(^2\) using a Chiralpak IC column (CO\(_2\)/iPrOH 90:10, 3 mL min\(^{-1}\)). Major diastereisomer: \(\tau_{\text{major}} = 1.7\) min, \(\tau_{\text{minor}} = 1.2\) min (98% ee). Minor diastereisomer: \(\tau_{\text{major}} = 1.28\) min, \(\tau_{\text{minor}} = 1.5\) min (97% ee). \([\alpha]\)\(_D\)\(^{25}\): -66.4 (c = 1.0, CHCl\(_3\)).

7e (2R)-5-Acetyl-2-cyclohexyl-6-hydroxy-6-methyl-2H-pyran-3(6H)-one (Scheme 1)

Following the general procedure using 15 mol% of the catalyst in the epoxidation step, 7e was isolated by FC (gradient: acetone/pentane 3:97 to acetone/pentane 5:95) in 46% yield as a pale yellow oil (5.7:1 dr). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.43 (s, 1H), 6.36* (s, 1H), 4.52* (d, J = 3.0 Hz, 1H), 4.01 (d, J = 4.1 Hz, 1H), 3.91 (bs, 1H), 3.24* (bs, 1H), 2.45 (s, 3H), 2.44* (s, 3H), 2.09 – 2.03 (m, 1H), 1.94-1.81 (m, 2H), 1.71 (s, 3H), 1.63* (s, 3H), 1.64 – 1.28 (m, 8H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 201.1*, 198.2*, 153.0*, 128.14*, 93.5*, 77.9*, 38.0*, 29.2*, 27.6*, 27.3*, 26.4*, 26.3*, 26.2*(2C) (minor diastereomer not observed). HR-MS: calculated for (M+Na\(^+\)): 275.1254; found: 275.1254. The ee was determined by UPC\(^2\) using a Chiralpak IC column (CO\(_2\)/iPrOH 90:10, 3 mL min\(^{-1}\)). Major diastereisomer: \(\tau_{\text{major}} = 3.2\) min, \(\tau_{\text{minor}} = 2.9\) min (95% ee). Minor diastereisomer: \(\tau_{\text{major}} = 3.0\) min, \(\tau_{\text{minor}} = 3.1\) min (97% ee). \([\alpha]\)\(_D\)\(^{25}\): -78.3 (c = 0.5, CHCl\(_3\)).
Following the general procedure 7f was isolated by FC (gradient: acetone/pentane 5:95 to acetone/pentane 11:89) in 40% yield as a pale yellow oil (7.0:1 dr). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.91 (d, J = 7.0 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 6.09 (s, 1H), 6.07 (s, 1H), 4.67 (dd, J = 7.9, 3.9 Hz, 1H), 4.31 (dd, J = 8.1, 4.9 Hz, 1H), 3.84 (bs, 1H), 3.69 (bs, 1H), 2.07 – 1.90 (m, 1H), 1.81 (s, 3H), 1.78 – 1.66 (m, 1H), 1.62 (s, 3H), 1.56 – 1.43 (m, 2H), 1.41 – 1.21 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ ppm 197.3, 197.0, 196.4, 195.8, 153.8, 134.9, 134.7, 130.3 (2C), 130.2 (2C), 129.1 (2C), 127.4, 126.9, 95.6, 94.0, 78.6, 74.6, 31.8, 31.8, 29.4, 29.3, 29.2, 29.1, 27.2, 25.7, 25.3, 25.0, 22.7, 14.2. HR-MS: calculated for (M+Na⁺): 339.1567; found: 339.1569.

The ee was determined by UPC² using a Chiralpak IC column (CO₂/iPrOH 90:10, 3 mL min⁻¹). Major diastereoisomer: τ_major = 3.7 min, τ_minor = 3.0 min (92% ee). [α]_D¹: -91.7 (c = 0.99, CHCl₃).

Following the general procedure 7g was isolated by FC (gradient: EtOAc/pentane 10:90 to EtOAc/pentane 20:80) in 57% yield as a pale yellow oil (4:4:1 dr). ¹H NMR (400 MHz, CDCl₃) δ ppm 6.61 (s, 1H), 6.58 (s, 1H), 4.53 (dd, J = 7.9, 4.0 Hz, 1H), 4.20 (dd, J = 8.3, 4.2 Hz, 1H), 3.87 (s, 3H), 3.14 (bs, 1H), 1.98 – 1.87 (m, 1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.69 – 1.57 (m, 1H), 1.50 – 1.38 (m, 2H), 1.37 – 1.22 (m, 6H), 0.87 (t, J = 6.8, 3H). ¹³C NMR (100 MHz, CDCl₃) δ ppm 197.5, 197.1, 165.9, 149.2, 146.9, 129.9, 95.4, 93.7, 78.1, 74.2, 53.1, 53.0, 31.8, 31.8, 31.0, 29.8, 29.7, 29.2, 29.1, 27.7, 25.1, 25.0, 24.8, 22.7, 14.2. HR-MS: calculated for (M+Na⁺): 293.1359; found: 293.1361. The ee was determined by UPC² using a Chiralpak IC column (CO₂/iPrOH 90:10, 3 mL min⁻¹). Major diastereoisomer: τ_major = 2.2 min, τ_minor = 1.5 min (95% ee). Minor diastereoisomer: τ_major = 1.8 min, τ_minor = 2.1 min (97% ee). [α]_D¹: -44.2 (c = 1.0, CHCl₃).
7h tert-Butyl (6R)-6-hexyl-2-hydroxy-2-methyl-5-oxo-5,6-dihydro-2H-pyran-3-carboxylate (Scheme 1)

Following the general procedure 7h was isolated by FC (gradient: acetone/pentane 2:98 to acetone/pentane 8:92) in 65% yield as a pale yellow oil (4.1:1 dr). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.49 (s, 1H), 6.44* (s, 1H), 4.51* (dd, J = 7.7, 4.0 Hz, 1H), 4.18 (dd, J = 8.2, 4.2 Hz, 1H), 3.88 (bs, 1H), 3.27* (bs, 1H), 1.97 – 1.85” (m, 1H), 1.85 – 1.77” (m, 1H), 1.76 (s, 3H), 1.71* (s, 3H), 1.69 – 1.58” (m, 2H), 1.53” (s, 9H), 1.35 – 1.23” (m, 6H), 0.87” (t, J = 6.8, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 197.8*, 197.6, 165.0*, 164.7, 150.9, 148.8*, 128.9, 128.5*, 95.5, 93.8*, 84.2, 84.0*, 78.1, 74.2*, 31.8*, 31.8, 31.1, 29.3*, 29.2*, 29.1, 28.3 (3C), 28.1 (3C)*, 28.0, 27.5*, 25.1, 25.0*, 22.7*, 14.2*. HR-MS: calculated for (M+Na$^+$): 335.1829; found: 335.1834.

The ee was determined by UPC$^2$ using a Chiralpak IC column (CO$_2$/iPrOH 95:5, 3 mL min$^{-1}$). Major diastereoisomer: $\tau_{\text{major}}$ = 3.1 min, $\tau_{\text{minor}}$ = 2.2 min (96% ee). Minor diastereoisomer: $\tau_{\text{major}}$ = 2.9 min, $\tau_{\text{minor}}$ = 1.9 min (94% ee). [$\alpha$]$_D$$^{19}$: -31.4 (c = 0.99, CHCl$_3$).

7i Ethyl (6R)-2-ethyl-6-hexyl-2-hydroxy-5-oxo-5,6-dihydro-2H-pyran-3-carboxylate (Scheme 1)

Following the general procedure 7i was isolated by FC (gradient: EtOAc/pentane 10:90 to EtOAc/pentane 20:80) in 59% yield as a pale yellow oil (5.6:1 dr). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.60 (s, 1H), 6.52* (s, 1H), 4.53* (dd, J = 7.4, 4.0 Hz, 1H), 4.32” (dq, J = 7.2, 1.8 Hz, 2H), 4.14 (dd, J = 8.7, 4.2 Hz, 1H), 3.76 (bs, 1H), 3.17* (bs, 1H), 2.20 – 2.04” (m, 1H), 1.99 – 1.86” (m, 2H), 1.75 – 1.61” (m, 1H), 1.47 – 1.37” (m, 2H), 1.34” (t, J = 7.3, 3H), 1.32 – 1.22” (m, 6H), 1.01 (t, J = 7.4, 3H), 0.89* (t, J = 7.5, 3H), 0.87” (t, J = 6.8, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 197.7*, 197.5, 165.7*, 165.6, 149.5, 147.0*, 130.7*, 129.9, 96.7, 95.9*, 78.0, 74.0*, 62.5, 62.3*, 33.1*, 31.8*, 31.8, 31.5, 30.0, 29.3*, 29.2*, 29.1, 25.3, 24.9*, 22.7*, 22.7, 14.2*, 14.2*, 8.1*, 7.1. HR-MS: calculated for (M+Na$^+$): 321.1672; found: 321.1675. The ee was determined by UPC$^2$ using a Chiralpak IC column (CO$_2$/iPrOH 90:10, 3 mL min$^{-1}$). Major diastereoisomer: $\tau_{\text{major}}$ = 2.82 min, $\tau_{\text{minor}}$ = 2.61 min (95% ee). Minor diastereoisomer: $\tau_{\text{major}}$ = 2.67 min, $\tau_{\text{minor}}$ = 2.71 min (97% ee). [$\alpha$]$_D$$^{19}$: -41.0 (c = 1.0, CHCl$_3$).
7j Methyl (6R)-6-hexyl-2-hydroxy-2-(methoxymethyl)-5-oxo-5,6-dihydro-2H-pyran-3-carboxylate (Scheme 1)

Following the general procedure, running the NBS step for 20 h, 7j was isolated by FC (gradient: acetone/pentane 5:95 to acetone/pentane 11:89) in 35% yield as a pale yellow oil (6.2:1 dr). $^1$H NMR (400 MHz, CDCl₃) δ ppm 6.70 (s, 1H), 6.66* (s, 1H), 4.56* (dd, J = 7.9, 4.0 Hz, 1H), 4.46 (dd, J = 7.9, 4.9 Hz, 1H), 3.87 (s, 3H), 3.86* (s, 3H), 3.83 (s, 2H) 3.80* (s, 2H), 3.76 (bs, 1H), 3.64* (bs, 1H), 3.43* (s, 3H), 3.40 (s, 3H), 2.02 – 1.89 † (m, 1H), 1.75 – 1.62 † (m, 1H), 1.50 – 1.38 † (m, 2H), 1.38 – 1.21 † (m, 6H), 0.87 † (t, J = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl₃) δ ppm 197.4, 197.3*, 165.7*, 165.6, 145.9, 145.3*, 131.8, 131.8*, 95.1, 94.7*, 78.6, 76.4*, 76.2, 74.4*, 60.2*, 59.9, 53.1, 53.0*, 32.1, 31.8*, 31.8, 29.3*, 29.2*, 29.1, 25.1, 25.1*, 22.7*, 14.2*. HR-MS: calculated for (M+Na⁺): 323.1465; found: 323.1468.

The ee was determined by UPC² using a Chiralpak IC column (CO₂/iPrOH 90:10, 3 mL min⁻¹). Major diastereoisomer: $\tau_{\text{major}} = 2.6$ min, $\tau_{\text{minor}} = 2.2$ min (94% ee). Minor diastereoisomer: $\tau_{\text{major}} = 1.9$ min, $\tau_{\text{minor}} = 2.1$ min (93% ee). $[\alpha]_{D}^{22} = -35.3$ (c = 1.00, CHCl₃).

7k Ethyl (6R)-2-(4-ethoxy-4-oxobutyl)-6-hexyl-2-hydroxy-5-oxo-5,6-dihydro-2H-pyran-3-carboxylate (Scheme 1)

Following the general procedure 7k was isolated by FC (gradient: acetone/pentane 7:93 to acetone/pentane 13:87) in 64% yield as a pale yellow oil (7.0:1 dr). $^1$H NMR (400 MHz, CDCl₃) δ ppm 6.60 (s, 1H), 6.60* (s, 1H), 4.52* (dd, J = 7.6, 4.0 Hz, 1H), 4.36 – 4.23 † (m, 2H), 4.19 (dd, J = 8.4, 4.0 Hz, 1H), 4.11 † (q, J = 7.2 Hz, 2H), 3.50* (bs, 1H), 2.76 – 2.70 (m, 2H), 2.36 – 2.29 † (m, 2H), 2.21 – 2.11 † (m, 1H), 2.01 – 1.85 † (m, 2H), 1.84 – 1.71 † (m, 1H), 1.69 – 1.50 † (m, 2H), 1.46 – 1.18 † (m, 14H), 0.87 † (t, J = 6.8 Hz, 3H) (Hemiketal proton of the minor diastereoisomer was not observed). $^{13}$C NMR (100 MHz, CDCl₃) δ ppm 197.5*, 197.4, 173.6*, 165.5*, 165.5, 149.4, 146.9*, 130.5*, 129.9, 96.3, 95.3*, 78.0, 74.0*, 62.5, 62.3*, 60.6, 60.5*, 41.2, 39.0*, 33.9*, 33.7, 31.8*, 31.4, 29.3*, 29.2*, 25.2, 24.9*, 22.7*, 19.1*, 18.1, 14.3*, 14.2*, 14.1*. HR-MS: calculated for (M+Na⁺): 407.2040; found: 407.2042. The ee was determined by UPC² using a Chiralpak IC column (CO₂/iPrOH 90:10, 3 mL min⁻¹). Major diastereoisomer: $\tau_{\text{major}} = 7.4$ min, $\tau_{\text{minor}} = 2.5$ min (94% ee). Minor diastereoisomer: $\tau_{\text{major}} = 3.0$ min, $\tau_{\text{minor}} = 3.5$ min (96% ee). $[\alpha]_{D}^{22} = -26.9$ (c = 0.97, CHCl₃).
Following the general procedure, using 1.0 equiv. MTBD and 20 h for cyclisation, 1.2 equiv. TFA and 2 h for aromatization, and 2.0 equiv. NaOAc and 2 h for the NBS step, 7l was isolated by FC (gradient: acetone/pentane 5:95 to acetone/pentane 15:85) in 40% yield as an amorphous white solid (13:1 dr). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.26* (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.6 Hz, 2H), 7.84 (d, J = 8.9 Hz, 2H), 7.76* (d, J = 8.8 Hz, 2H), 6.20 (s, 1H), 6.12* (s, 1H), 4.67* (dd, J = 8.0, 3.8 Hz, 1H), 4.28 (dd, J = 7.6, 5.6 Hz, 1H), 3.03 (bs, 1H), 2.90* (bs, 1H), 2.05 – 1.93* (m, 1H), 1.75 – 1.65* (m, 1H), 1.62 (s, 3H), 1.52* (s, 3H), 1.49 – 1.40* (m, 2H), 1.39 – 1.15* (m, 6H), 0.89* (t, J = 6.8, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 196.5*, 156.8*, 148.4*, 143.2*, 128.5 (2C)*, 126.5*, 124.0 (2C)*, 95.3*, 74.1*, 31.9*, 29.5*, 29.3*, 28.8*, 25.1*, 22.8*, 14.2* (minor diastereomer not observed). HR-MS: calculated for (M+H$^+$): 334.1649; found: 334.1662. The ee was determined by UPC$^2$ using a Chiralpak IC column (Gradient: CO$_2$/iPrOH 99:1 to CO$_2$/iPrOH 60:40, 3 mL min$^{-1}$). Major diastereoisomer: $\tau_{major}$ = 3.4 min, $\tau_{minor}$ = 3.5 min (84% ee). [$\alpha$]$_D$:$^{14}$ +65.1 (c = 1.03, CHCl$_3$).
A 4 mL screw cap glass vial equipped with a magnetic stirrer bar was charged with the 3-pyrone 7a (25.4 mg, 0.1 mmol, 1 equiv.), in 1.0 mL CH$_2$Cl$_2$, and cooled to -30 °C. Triethylsilane (0.5 mmol, 5.0 equiv.) and TFA (1.5 mmol, 15 equiv.) was added, and the mixture was stirred at -30 °C for 1.5 h. The reaction was quenched with 10 mL of NaHCO$_3$ (aq., sat.), extracted twice with 10 mL EtOAc and the combined organic phases were dried over Na$_2$SO$_4$. Volatiles were removed by rotatory evaporation, and the crude residue was subjected to FC on silica gel (Et$_2$O/pentane 10:90) to afford the product 8 in 48% yield as a colorless oil (10:1 dr).

8 (2R,6S)-5-Acetyl-2-hexyl-6-methyl-2H-pyran-3(6H)-one (Scheme 2)

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.51 (s, 1H), 6.21* (d, J = 2.2 Hz, 1H), 4.88 (q, J = 6.9 Hz, 1H), 4.71* (tq, J = 6.8, 2.1 Hz, 1H), 4.23 (dd, J = 8.0, 3.8 Hz, 1H), 3.82* (ddd, J = 8.0, 3.8, 1.9 Hz, 1H), 2.41+ (s, 3H), 2.01 – 1.90+ (m, 1H), 1.71 – 1.55+ (m, 1H), 1.45 (d, J = 6.9 Hz, 3H), 1.42* (d, J = 6.7 Hz, 3H), 1.37 – 1.22+ (m, 8H), 0.92 – 0.84+ (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 200.5*, 199.4, 197.8*, 157.7*, 156.2, 128.4, 128.3*, 79.9*, 77.4, 74.7, 71.1*, 67.2, 31.8*, 30.2, 29.8, 29.5*, 29.3*, 29.2, 27.6*, 26.6, 25.2*, 25.2, 22.8*, 19.7*, 17.6, 14.2* (One carbonyl carbon of minor diastereoisomer was not observed). HR-MS: calculated for (M+Na$^+$): 261.1461; found: 261.1462. The ee was determined by UPC$^2$ using a Chiralpak IC column (CO$_2$/iPrOH 90:10, 3 mL min$^{-1}$). Major diastereoisomer: $\tau_{\text{major}}$ = 1.13 min, $\tau_{\text{minor}}$ = 0.99 min (95% ee). Minor diastereoisomer: $\tau_{\text{major}}$ = 0.91 min, $\tau_{\text{minor}}$ = 1.07 min (92% ee). [$\alpha$]$_D$ $^\circ$: -36.8 (c = 1.0, CHCl$_3$).
A 4 mL screw cap glass vial equipped with a magnetic stirrer bar was charged with the 3-pyrone 7a (0.1 mmol, 1.0 equiv.), which was dissolved in 0.2 mL MeOH, and the CeCl$_3$·7H$_2$O (0.1 mmol, 1.0 equiv.) was added. The reaction mixture was cooled to -78 °C under Ar atmosphere, NaBH$_4$ (0.1 mmol, 1.0 equiv.) was added and the mixture was stirred for 1.5 h to achieve full conversion. At this point the reaction was allowed to reach rt, quenched with 1 mL of NaHCO$_3$ (aq., sat.) and extracted twice with 10 mL Et$_2$O. The combined organic layers were washed with 10 mL NaHCO$_3$ (aq., sat.) followed by 10 mL brine, dried over Na$_2$SO$_4$ and the volatiles were removed by rotatory evaporation. The crude residue was subjected to FC on silica gel (gradient: acetone/pentane 13:87 to acetone/pentane 20:80) to afford the product 9 in 71% yield as a colorless oil (>20 : 1 dr).

**9 (2R,6S)-2-Hexyl-6-hydroxy-5-((S)-1-hydroxyethyl)-6-methyl-2H-pyran-3(6H)-one (Scheme 3)**

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.21* (s, 1H), 4.80* (q, $J = 6.43$ Hz, 1H), 4.57* (t, $J = 6.96$ Hz, 1H), 2.27* (s, 3H), 1.84 – 1.78* (m, 2H), 1.60* (bs, 1H), 1.43* (d, $J = 6.43$, 3H), 1.37-1.23* (m, 8H), 0.90-0.79* (m, 3H) (minor diasteromer not observed). $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 153.8*, 146.0*, 122.9*, 103.6*, 66.8*, 61.7*, 34.4*, 30.7*, 28.1*, 24.6*, 22.9*, 21.6*, 13.0*, 10.8*(minor diasteromer not observed). HR-MS: calculated for (M+Na$^+$): 279.1567; found: 279.1580. The ee was determined by UPC$^2$ using a Chiralpak IC column (CO$_2$/iPrOH 90:10, 3 mL min$^{-1}$). Major diastereoisomer: $\tau_{\text{major}} = 5.6$ min, $\tau_{\text{minor}} = 6.5$ min (94% ee). Minor diastereoisomer: $\tau_{\text{major}} = 6.1$ min, $\tau_{\text{minor}} = 5.2$ min (91% ee). [α]$^\text{D}$: -4.6 (c = 0.5, CHCl$_3$).
7. Synthesis of dihydro 3-pyrone 10

![Chemical Structure]

A 4 mL screw cap glass vial equipped with a magnetic stirrer bar was charged with the 3-pyrone 7a (0.1 mmol, 1 equiv.), in 0.5 mL EtOAc. Pd/C (10%, 0.01 mmol, 0.1 equiv.) was added and the vial was capped with a septum. The suspension was first purged with argon, cooled to 0 °C, and subsequently purged with hydrogen for 10 min. The vial was equipped with a balloon containing hydrogen and the mixture was stirred at 0 °C for 1 h. The reaction was filtered through a HPLC-filter (0.45 µm pore size), which was flushed with EtOAc. Volatiles were removed by rotatory evaporation, and the crude residue was subjected to FC on silica gel (Et₂O/pentane 1:2) to afford the product 10 in 55% yield as a colorless oil.

10 (R)-5-acetyl-2-hexyl-6-methyl-2H-pyran-3(4H)-one (Scheme 4)

\[\text{H NMR (400 MHz, CDCl}_3\text{) } \delta \text{ ppm 4.17 (ddd, } J = 7.7 \text{ Hz, } J = 4.9 \text{ Hz, } J = 1.0 \text{ Hz, 1H), 3.23 (dp, } J = 20.9 \text{ Hz, } J = 1.5 \text{ Hz, 1H), 3.14 (dq, } J = 20.9 \text{ Hz, } J = 1.3 \text{ Hz, 1H), 2.30 (t, } J = 1.3 \text{ Hz, 3H), 2.25 (s, 3H), 1.87-1.68 (m, 2H), 1.50-1.22 (m, 8H), 0.88 (t, } J = 6.7 \text{ Hz, 3H).} \]

\[\text{^13C NMR (100 MHz, CDCl}_3\text{) } \delta \text{ ppm 206.0, 197.2, 164.4, 109.4, 81.5, 36.6, 31.7, 30.3, 29.9, 29.0, 25.0, 22.7, 20.6, 14.2. HR-MS: calculated for (M+H\text{\(^+\))}: 239.1642; found: 239.1643. The ee was determined by UPC\textsuperscript{2} using a Chiralpak IC column (CO}_2/i\text{PrOH 90:10, 3 mL min\textsuperscript{-1}). } \tau_{\text{major}} = 3.8 \text{ min, } \tau_{\text{minor}} = 4.3 \text{ min (90% ee). } [\alpha]_D^{\text{rt}}: +103.9 \text{ (c = 0.96, CHCl}_3\text{).} \]
8. NMR data

1e (E)-3-cyclohexylacrylaldehyde

$^1$H NMR

$^{13}$C NMR
7a (2R)-5-acetyl-2-hexyl-6-hydroxy-6-methyl-2H-pyran-3(6H)-one (Scheme 1)

**H NMR**

![H NMR spectrum](image)

**C NMR**

![C NMR spectrum](image)
Zoom of relevant area, showing clear 1,3-interaction for the small diastereomer, and only noise for the large diastereomer.
7b (2R)-5-acetyl-6-hydroxy-6-methyl-2-propyl-2H-pyran-3(6H)-one (Scheme 1)

$^1$H NMR

$^{13}$C NMR
7c (2R)-5-acetyl-6-hydroxy-6-methyl-2-phenethyl-2H-pyran-3(6H)-one (Scheme 1)
7d (2R)-5-acetyl-6-hydroxy-2-isopropyl-6-methyl-2H-pyran-3(6H)-one (Scheme 1)

**^1H NMR**

**^13C NMR**
$7e$ (2$R$)-5-acetyl-2-cyclohexyl-6-hydroxy-6-methyl-2H-pyran-3(6H)-one (Scheme 1)

$^1$H NMR

$^{13}$C NMR
$7f$ (2$R$)-5-benzoyl-2-hexyl-6-hydroxy-6-methyl-2$H$-pyran-3(6$H$)-one (Scheme 1)

$^1$H NMR

$^{13}$C NMR
7g methyl (6R)-6-hexyl-2-hydroxy-2-methyl-5-oxo-5,6-dihydro-2H-pyran-3-carboxylate (Scheme 1)

$^1$H NMR

$^{13}$C NMR
7h tert-butyl (6R)-6-hexyl-2-hydroxy-2-methyl-5-oxo-5,6-dihydro-2H-pyran-3-carboxylate (Scheme 1)

**1H NMR**

![1H NMR spectrum]

**13C NMR**

![13C NMR spectrum]
7i ethyl (6R)-2-ethyl-6-hexyl-2-hydroxy-5-oxo-5,6-dihydro-2H-pyran-3-carboxylate (Scheme 1)
7j methyl (6R)-6-hexyl-2-hydroxy-2-(methoxymethyl)-5-oxo-5,6-dihydro-2H-pyran-3-carboxylate (Scheme 1)

^1H NMR

^13C NMR
7k ethyl (6R)-2-(4-ethoxy-4-oxobutyl)-6-hexyl-2-hydroxy-5-oxo-5,6-dihydro-2H-pyran-3-carboxylate (Scheme 1)

$^1$H NMR

$^{13}$C NMR
7l (2R)-2-hexyl-6-hydroxy-6-methyl-5-(4-nitrophenyl)-2H-pyran-3(6H)-one (Scheme 1)

$^1$H NMR

$^{13}$C NMR
8 (2R,6S)-5-acetyl-2-hexyl-6-methyl-2H-pyran-3(6H)-one (Scheme 2)

$^1$H NMR

$^{13}$C NMR
9 (2R,6S)-2-hexyl-6-hydroxy-5-((S)-1-hydroxyethyl)-6-methyl-2H-pyran-3(6H)-one (Scheme 3)

$^1$H NMR

$^{13}$C NMR
Zoom of relevant area, showing the important long-range interactions, as well as more intense shorter range interactions.
10 (R)-5-acetyl-2-hexyl-6-methyl-2H-pyran-3(4H)-one (Scheme 4)

$^1$H NMR

$^{13}$C NMR