Enantioselective Synthesis of Highly Functionalised Amides by Copper-Catalysed Vinylogous Mukaiyama Aldol Reaction

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General information:
All experiments were performed under argon and were at least repeated twice. Diethyl ether was distilled from sodium/benzophenone ketyl radical. Flash chromatography was carried out with Merck silica gel 60 (63–100 mesh). Analytical TLC was performed with aluminium sheets silica gel 60 F254 (Merck), and the products were visualised by a basic aqueous solution of KMnO4. Optical rotation measurements were conducted with a Perkin-Elmer Model 241 polarimeter (rt, \( \lambda = 589 \) nm) and are given in deg \( \cdot \) cm\(^{-1} \cdot \) g\(^{-1} \cdot \) dm\(^{-1} \); concentration \( c \) is listed in g \( \cdot \) (100 mL)\(^{-1} \). NMR spectra were recorded on a Varian Mercury 300 (\(^1\)H: 300 MHz, \(^{13}\)C: 75 MHz) or Varian Inova 400 (\(^1\)H: 400 MHz, \(^{13}\)C: 100 MHz) spectrometer. Chemical shifts (\( \delta \)) are given in ppm relative to TMS (\( \delta = 0 \) ppm) or solvent residual peak of CDCl\(_3\) (\( \delta = 7.26 \) ppm) as internal standard. Coupling constants \( J \) are reported in Hz and coupling patterns are described as br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet. IR spectra were recorded on a Spectrum 100 spectrometer with an attached UATR device Diamond KRS-5, and wave numbers \( \nu \) are reported in cm\(^{-1} \) with indicated relative intensities: w (weak, 0–33%), m (medium, 34–66%) and s (strong, 67–100%). Mass spectra were acquired on a Finnigan SSQ 7000 spectrometer (EI, 70 eV) and HRMS were recorded on a Finnigan MAT 95 spectrometer (EI). Elemental analyses were measured on an Elementar Vario EL instrument. Melting points were determined in open-end capillary tubes on a Büchi B-540 melting point apparatus. Analytical HPLC measurements were performed with an Agilent 1100-series or 1200-series system and chiral stationary phases (250 mm \( \cdot \) 4.6 mm) from Chiral Technologies Inc. (\( E \))-1-(1-Oxo-2-butenyl)-3,5-dimethyl-1\(^{1}\)H-pyrazole\(^1\), \( N,O \)-silyl ketene aminals \( 3a-c \), \( ^2 \)methyl 2-oxo-butyrate \( 5b \), \( ^3 \)isopropyl pyruvate \( 5g \), \( ^4 \)benzyl pyruvate \( 5h \)\(^5 \) and sulfoximines \( 6a-d \)\(^6 \) were synthesized by following their literature protocols. Other reagents were purchased from commercial suppliers and used without further purification.

General procedure for the Cu-catalysed VMAR:
Under argon atmosphere a dry Schlenk tube was charged with Cu(OTf)\(_2\) (0.0300 mmol, 10.9 mg, 0.1 equiv.) and sulfoximine \( 6a \) (0.0300 mmol, 13.9 mg, 0.1 equiv.). Dry Et\(_2\)O (2.0 mL) was added and the green solution was stirred at rt for 30 min. Subsequently, ketoester \( 5 \) (0.30 mmol) and 2,2,2-trifluoroethanol (0.36 mmol, 26 \( \mu \)l, 1.2 equiv.) were added. The solution was cooled to \(-78 \) °C, followed by dropwise addition of \( N,O \)-silyl ketene aminal \( 3 \) (0.33 mmol, 1.1 equiv.). The reaction mixture was stirred for 16 h and allowed to reach rt. Then, it was directly subjected to column chromatography.
(Z)-1-[1-(tert-Butyldimethylsilyloxy)-1,3-butadienyl]-3,5-dimethyl-1H-pyrazole (3d):

Prepared from (E)-1-(1-oxo-2-butenyl)-3,5-dimethyl-1H-pyrazole (10.04 mmol, 1.649 g) in analogy to the literature protocol for amide-derived silyl dienolates. The product was purified by bulb-to-bulb distillation and then kept under argon in a freezer at −24 °C. The compound showed no signs of decomposition after several weeks of storage.

Colorless oil (81%); bp (air bath temperature) 130 °C (2.8 · 10^{-2} mbar); δ_{H} (400 MHz, CDCl_{3}) −0.06 (6H, s, 2 CH_{3}), 0.94 (9H, s, 3 CH_{3}), 2.20 (3H, s, CH_{3}), 2.24 (3H, s, CH_{3}), 5.00 (1H, ddd, J 10.4 Hz, 1.9 Hz, 0.8 Hz, CH_{3}), 5.15 (1H, ddd, J 17.2 Hz, 1.9 Hz, 0.7 Hz, CH_{3}), 5.49 (1H, d, J 10.9 Hz, CH), 5.81 (1H, s, Ar-H), 6.60 (1H, dt, J 17.2 Hz, 10.6 Hz, CH); δ_{C} (100 MHz, CDCl_{3}) −5.2 (2 CH_{3}), 11.8 (CH_{3}), 13.5 (CH_{3}), 18.2 (C), 25.7 (3 CH_{3}), 106.3 (Ar-CH), 107.8 (CH), 115.3 (CH_{2}), 130.3 (CH), 139.8 (Ar-C), 142.5 (Ar-C), 148.5 (C); ν_{max} (neat) 3351 w, 2931 s, 2858 s, 1707 m, 1659 s, 1617 m, 1560 m, 1465 s, 1421 s, 1379 s, 1359 s, 1329 s, 1256 s, 1126 m, 1072 s, 1024 m, 995 m, 887 s, 841 s, 786 s; m/z (%) 278 (M^{+}, 25), 223 (51), 221 (64), 185 (22), 153 (75), 147 (100), 73 (65); HRMS for C_{15}H_{26}N_{2}OSi: calc. 278.1809, found 278.1804.

(R,E)-Methyl 2-hydroxy-2-methyl-6-morpholino-6-oxohex-4-enoate (7a):

Prepared according to the general procedure from N,O-silyl ketene aminal 3a (89.0 mg) and methyl pyruvate (5a, 27 μl). The product was purified by flash column chromatography (EtOAc). Pale yellow oil (75%); [α]_{D} 8.8 (c 0.7 in CHCl_{3}); δ_{H} (300 MHz, CDCl_{3}) 1.44 (3H, s, CH_{3}), 2.53 (1H, ddd, J 14.1 Hz, 7.8 Hz, 1.1 Hz, CH_{2}), 2.64 (1H, ddd, J 14.1 Hz, 7.2 Hz, 1.2 Hz, CH_{2}), 2.72 (1H, s br, OH), 3.54 (2H, s br, CH_{2}), 3.66 (6H, s br, 3 CH_{2}), 3.77 (3H, s, CH_{3}), 6.27 (1H, dt, J 15.2 Hz, 1.2 Hz, CH), 6.74 (1H, dt, J 15.0 Hz, 7.5 Hz, CH); δ_{C} (75 MHz, CDCl_{3}) 25.9 (CH_{3}), 42.2 (CH_{2}), 42.9 (CH_{2}), 46.1 (CH_{2}), 52.9 (CH_{3}), 66.7 (2 CH_{2}), 74.2 (C), 123.7 (CH), 139.7 (CH), 165.2 (C), 176.4 (C); ν_{max} (CHCl_{3}) 3431 s, 2962 s, 2922 s, 2858 s, 1737 s, 1659 s, 1609 s, 1441 s, 1380 m, 1266 s, 1214 s, 1116 s, 1066 m, 1036 m, 981 s, 851 m; m/z (%) 257 (M^{+}, 29), 198 (100), 180 (30), 155 (60), 154 (14), 140 (78), 125 (17), 111 (67), 86 (45); HRMS for C_{12}H_{19}NO_{5}: calc. 257.1258, found 257.1258; HPLC: t_{r} = 34.7 min [major], t_{r} = 38.7 min [minor] (Chiralpak AD column, flow rate 1.0 mL/min, heptane/iPrOH = 90:10, λ = 210 nm, 20 °C); ee = 92%.

(R,E)-Methyl 6-(dimethylamino)-2-hydroxy-2-methyl-6-oxohex-4-enoate (7b):

Prepared according to the general procedure from N,O-silyl ketene aminal 3b (75.0 mg) and methyl pyruvate (5a, 27 μl). The product was purified by flash column chromatography (EtOAc: MeOH = 19 : 1).

Pale yellow oil (45%); [α]_{D} 1.9 (c 0.4 in CHCl_{3}); δ_{H} (400 MHz, CDCl_{3}) 1.44 (3H, s, CH_{3}), 2.54 (1H, ddd, J 14.1 Hz, 7.8 Hz, 1.2 Hz, CH_{2}), 2.65 (1H, ddd, J 14.0 Hz, 7.2 Hz, 1.2 Hz, CH_{2}), 2.76 (1H, s br, OH), 2.98 (3H, s, CH_{3}), 3.05 (3H, s, CH_{3}), 3.78 (3H, s, CH_{3}), 6.31 (1H, dt, J 15.2 Hz, 1.2 Hz, CH), 6.72 (1H, dt, J 15.1 Hz, 7.5 Hz, CH); δ_{C} (100 MHz, CDCl_{3}) 26.0
S3

(CH₃), 35.7 (CH₃), 37.5 (CH₂), 43.1 (CH₃), 53.0 (CH₃), 74.3 (C), 124.4 (CH), 138.8 (CH), 166.3 (C), 176.4 (C); νₘₐₓ (CHCl₃) 3395 s, 2920 s, 2851 m, 1788 m, 1737 s, 1661 s, 1608 s, 1540 w, 1499 m, 1454 s, 1402 s, 1261 s, 1207 s, 1158 s, 1121 s, 1056 m, 981 s, 827 m, 805 m;
m/z (%) 215 (M⁺, 11), 156 (100), 138 (20), 125 (14), 113 (62), 112 (18), 111 (39), 98 (88), 72 (30; HRMS for C₁₀H₁₇NO₄: calc. 215.1152, found 215.1153; HPLC: tᵣ = 61.2 min [major], tᵣ = 68.2 min [minor] (Chiralpak AD column, flow rate 1.1 mL/min, heptane/EtOH = 96:4, λ = 210 nm, 20 °C); ee = 11%.

(R,E)-Methyl 2-hydroxy-2-methyl-6-oxo-6-(piperidin-1-yl)hex-4-enoate (7c):

Prepared according to the general procedure from N,O-silyl ketene aminal 3c (88.2 mg) and methyl pyruvate (5a, 27 μl). The product was purified by flash column chromatography (EtOAc) and then isolated by a second flash column chromatography (pentane : acetone = 1 : 1).

Pale brown oil (75%); δₛ (400 MHz, CDCl₃) 1.45 (3H, s, CH₃), 1.52–1.59 (4H, m, 2 CH₂), 1.62–1.67 (2H, m, CH₂), 2.53 (1H, ddd, J₁₄.₀ Hz, 7.9 Hz, 1.2 Hz, CΗ), 2.64 (1H, ddd, J₁₄.₀ Hz, 7.2 Hz, 1.3 Hz, CHΗΗ), 3.21 (1H, s br, OH), 3.43–3.50 (2H, m, CH₂), 3.55–3.62 (2H, m, CH₂), 3.78 (3H, s, CH₃), 6.32 (1H, dt, J₁₅.₁ Hz, 1.2 Hz, CH), 6.66 (1H, dt, J₁₅.₁ Hz, 7.5 Hz, CH); δₛ (100 MHz, CDCl₃) 24.7 (CH₂), 25.6 (CH₂), 26.0 (CH₃), 26.7 (CH₂), 34.2 (CH₂), 43.1 (CH₂), 43.2 (CH₂), 47.0 (CH₂), 53.0 (CH₃), 74.3 (C), 124.8 (CH), 138.1 (CH), 164.9 (C), 176.4 (C); νₘₐₓ (CHCl₃) 3378 s, 2923 s, 2854 s, 1790 m, 1737 s, 1657 s, 1602 s, 1445 s, 1381 m, 1266 s, 1210 s, 1120 s, 1059 w, 1021 m, 979 m, 852 m; m/z (%) 255 (M⁺, 29), 196 (64), 152 (26), 138 (100), 112 (6), 84 (74); HRMS for C₁₃H₂₁NO₄: calc. 255.1465, found 255.1468; HPLC: tᵣ = 18.2 min [major], tᵣ = 22.7 min [minor] (Chiralpak AD column, flow rate 1.0 mL/min, heptane/iPrOH = 90:10, λ = 210 nm, 20 °C); ee = 45%.

(R,E)-Methyl 2-ethyl-2-hydroxy-6-morpholino-6-oxohex-4-enoate (7e):

Prepared according to the general procedure from N,O-silyl ketene aminal 3a (89.0 mg) and methyl 2-oxo-butyrate (5b, 34.9 mg). The product was purified by flash column chromatography (EtOAc).

Pale yellow oil (66%); [α]D 18.2 (c 0.6 in CHCl₃); δₛ (300 MHz, CDCl₃) 0.83 (3H, t, J 7.4 Hz, CH₃), 1.58–1.85 (2H, m, CH₂), 2.51 (1H, ddd, J 14.1 Hz, 7.7 Hz, 1.3 Hz, CHΗΗ), 2.60 (1H, ddd, J 14.1 Hz, 7.3 Hz, 1.3 Hz, CHΗΗ), 3.36 (1H, s br, OH), 3.50 (2H, s br, CH₂), 3.64 (6H, s br, 3 CH₂), 3.75 (3H, s, CH₃), 6.24 (1H, dt, J 15.1 Hz, 1.3 Hz, CH), 6.70 (1H, dt, J 15.1 Hz, 7.5 Hz, CH); δₛ (75 MHz, CDCl₃) 7.8 (CH₃), 32.1 (CH₂), 41.9 (CH₂), 42.2 (CH₂), 46.2 (CH₂), 52.8 (CH), 66.7 (2 CH₂), 77.5 (C), 123.5 (CH), 139.9 (CH), 165.2 (C), 176.0 (C); νₘₐₓ (CHCl₃) 3430 s, 2967 s, 2922 s, 2857 s, 1735 s, 1658 s, 1610 s, 1439 s, 1384 m, 1300 m, 1267 s, 1244 s, 1206 s, 1145 m, 1116 s, 1069 m, 1039 m, 979 m; m/z (%) 271 (M⁺, 24), 242 (18), 212 (84), 194 (22), 155 (78), 140 (82), 125 (39), 86 (31); HRMS for C₁₃H₂₃NO₅: calc. 271.1414, found 271.1411; HPLC: tᵣ = 32.7 min [minor], tᵣ = 52.6 min [major] (Chiralpak AD column, flow rate 1.0 mL/min, heptane/iPrOH = 90:10, λ = 210 nm, 20 °C); ee = 87%.
(S,E)-Methyl 2-hydroxy-6-morpholino-6-oxo-2-phenylhex-4-enoate (7f):

Prepared according to the general procedure from N,O-silyl ketene aminal 3a (89.0 mg) and methyl benzoyleformate (5c, 44 µl). The product was purified by flash column chromatography (Et₂O : MeOH = 30 : 1).

Pale orange oil (36%); [α]ᵦ –4.3 (c 0.6 in CHCl₃); δ₁ (300 MHz, CDCl₃) 2.86 (1H, ddd, J 14.3 Hz, 7.6 Hz, 1.2 Hz, CH₃), 3.04 (1H, ddd, J 14.3 Hz, 7.0 Hz, 1.2 Hz, CH₃), 3.37 (2H, s br, CH₂), 3.59 (7H, s, OH and 3 CH₂), 3.75 (3H, s, CH₃), 6.20 (1H, dt, J 15.2 Hz, 1.1 Hz, CH), 6.64 (1H, dt, J 14.9 Hz, 7.3 Hz, CH), 7.22–7.35 (3H, m, Ar-H); δC (75 MHz, CDCl₃) 42.2 (CH₂), 42.8 (CH₂), 46.2 (CH₂), 53.4 (CH₃), 66.7 (2 CH₂), 77.9 (C), 124.3 (CH), 125.3 (2 Ar-CH), 128.0 (Ar-CH), 128.4 (2 Ar-CH), 139.3 (CH), 140.9 (Ar-C), 165.4 (C), 174.5 (C); νmax (CDCl₃) 3394m, 3007m, 2959m, 2853m, 1735s, 1658s, 1611s, 1438s, 1385w, 1260s, 1116s, 1070m, 1034m, 976m, 700m; m/z (%) 320 ([M + H]⁺, 8) 261 (13), 260 (72), 242 (3), 173 (14), 155 (100), 140 (51), 105 (92), 86 (9), 77 (21); HRMS for C₁₇H₂₂NO₅: calc. 319.1414, found 319.1414; HPLC: tᵦ = 35.4 min [minor], tᵦ = 42.7 min [major] (Chiralcel OD-H column, flow rate 0.8 mL/min, heptane/iPrOH = 90:10, λ = 230 nm, 20 °C); ee = 67%.

(S,E)-Ethyl 2-hydroxy-2-isopropyl-6-morpholino-6-oxohex-4-enoate (7g):

Prepared according to the general procedure from N,O-silyl ketene aminal 3a (89.0 mg) and ethyl pyruvate (3a, 5e, 45 µl). The product was purified by flash column chromatography (EtOAc) and then isolated by a second flash column chromatography (pentane : acetone = 3 : 1).

White solid (49%); mp 75–77 °C (racemic); [α]ᵦ 8.0 (c 1.0 in CHCl₃); δ₁ (300 MHz, CDCl₃) 0.85 (3H, d, J 6.8 Hz, CH₃), 0.96 (3H, d, J 6.8 Hz, CH₃), 1.29 (3H, t, J 7.1 Hz, CH₃), 1.90–2.07 (1H, m, CH), 2.49–2.67 (2H, m, CH₂), 3.20 (1H, s br, OH), 3.53 (2H, s br, CH₂), 3.65 (6H, s, CH₂), 4.15–4.32 (2H, m, CH₂), 6.26 (1H, dt, J 15.1 Hz, 1.3 Hz, CH), 6.70 (1H, dt, J 15.0 Hz, 7.5 Hz, CH); δC (75 MHz, CDCl₃) 14.3 (CH₃), 15.9 (CH₃), 17.3 (CH₃), 35.3 (CH), 39.9 (CH₂), 42.2 (CH₂), 46.2 (CH₂), 66.7 (2 CH₂), 79.2 (C), 123.4 (CH), 140.2 (CH), 165.2 (C), 175.7 (C); νmax (ATR) 3318m, 2969m, 2925 m, 2868m, 1738s, 1655s, 1601s, 1442s, 1405s, 1384m, 1320m, 1264s, 1232m, 1189s, 1116s, 1036s, 1005m, 982s, 852s; m/z (%) 299 (M⁺, 9), 256 (65), 226 (65), 155 (100), 140 (68), 114 (5), 86 (18), 71 (52); HRMS for C₁₃H₁₅NO₅: calc. 299.1727, found 299.1730; HPLC: tᵦ = 17.4 min [minor], tᵦ = 24.1 min [major] (Chiralcel OD-H column, flow rate 0.8 mL/min, heptane/iPrOH = 90:10, λ = 230 nm, 20 °C); ee = 56%.

(R,E)-Ethyl 2-hydroxy-2-methyl-6-morpholino-6-oxohex-4-enoate (7h):

Prepared according to the general procedure from N,O-silyl ketene aminal 3a (89.0 mg) and ethyl pyruvate (5e, 33 µl). The product was purified by flash column chromatography (Et₂O : MeOH = 20 : 1).

Pale yellow oil (64%); [α]ᵦ 16.6 (c 0.8 in CHCl₃); δ₁ (300 MHz, CDCl₃) 1.29 (3H, t, J 7.1 Hz, CH₃), 1.44 (3H, s, CH₃), 2.54 (1H, ddd, J 14.2 Hz, 7.8 Hz, 1.2 Hz, CH₂), 2.65 (1H, ddd,
(R,E)-Ethyl 2-hydroxy-6-morpholino-6-oxo-2-(2-phenylethyl)hex-4-enoate (7i):

![Diagram of the molecule](image)

Prepared according to the general procedure from N,O-silyl ketene aminal 3a (89.0 mg) and ethyl 2-oxo-4-phenylbutyrate (5f, 58 μl). The product was purified by flash column chromatography (EtOAc) and then isolated by a second flash column chromatography (pentane : acetone = 3 : 1).

Pale yellow solid (54%); mp 90–93 °C (racemic); [α]D 19.2 (c 1.2 in CHCl3); δH (400 MHz, CDCl3) 1.30 (3H, t, J 7.1 Hz, CH3), 2.00 (1H, ddd, J 13.8 Hz, 11.6 Hz, 5.2 Hz, CH/CH), 2.09 (1H, ddd, J 13.7 Hz, 11.3 Hz, 5.4 Hz, CH/F), 2.43 (1H, ddd, J 13.5 Hz, 11.6 Hz, 5.4 Hz, CH/F), 2.58 (1H, ddd, J 14.1 Hz, 7.8 Hz, 1.2 Hz, CH/F), 2.65 (1H, ddd, J 14.0 Hz, 7.2 Hz, 1.3 Hz, CH/F), 2.80 (1H, ddd, J 13.5 Hz, 11.4 Hz, 5.2 Hz, CH/F), 3.46 (1H, s br, OH), 3.52 (2H, s br, CH2), 3.66 (6H, s br, 3 CH2), 4.14–4.27 (2H, m, CH2), 6.27 (1H, dt, J 15.1 Hz, 1.2 Hz, CH), 6.75 (1H, dt, J 15.1 Hz, 7.5 Hz, CH), 7.12–7.21 (3H, m, Ar-CH), 7.24–7.30 (2H, m, Ar-CH); δC (100 MHz, CDCl3) δ14.4 (CH3), 30.0 (CH3), 40.9 (CH3), 42.3 (CH2), 46.2 (CH2), 62.3 (CH2), 66.8 (2 CH2), 76.5 (C), 123.6 (CH), 126.0 (Ar-CH), 128.4 (4 Ar-CH), 139.5 (CH), 141.2 (Ar-C), 165.0 (C), 175.3 (C); νmax (ATR) 3249m, 2971m, 2925m, 2862m, 1746s, 1656s, 1583s, 1461s, 1419s, 1387m, 1310w, 1262s, 1246m, 1177s, 1111s, 1083m, 1056s, 1035s, 982s, 919m, 855m, 747s, 698s; m/z (%) 361 (M+, 8) 288 (37), 257 (49), 155 (100), 140 (32), 105 (22), 91 (56); EA (%) for C20H27NO5: calc. C 66.46, H 7.53, N 3.88, found C 66.52, H 7.52, N 3.78; HPLC: tR = 31.9 min [minor], tR = 40.1 min [major] (Chiralcel OD-H column, flow rate 0.8 mL/min, heptane/iPrOH = 90:10, λ = 230 nm, 20 °C); ee = 76%.

(R,E)-Isopropyl 2-hydroxy-2-methyl-6-morpholino-6-oxohex-4-enoate (7j):

![Diagram of the molecule](image)

Prepared according to the general procedure from N,O-silyl ketene aminal 3a (89.0 mg) and isopropyl pyruvate (5g, 39.0 μg). The product was purified by flash column chromatography (EtOAc) and then isolated by a second flash column chromatography (pentane : acetone = 3 : 1 : 1).

Pale yellow oil (66%); [α]D 20.5 (c 1.2 in CHCl3); δH (400 MHz, CDCl3) 1.25 (6H, d, J 6.3 Hz, 2 CH3), 1.40 (3H, s, CH3), 2.51 (1H, ddd, J 14.1 Hz, 7.8 Hz, 1.2 Hz, CH/CH), 2.61 (1H, ddd, J 14.1 Hz, 7.2 Hz, 1.2 Hz, CH/F), 3.09 (1H, s br, OH), 3.52 (2H, s br, CH2), 3.65 (6H, s br, 3 CH2), 5.05 (1H, sept, J 6.3 Hz, CH), 6.26 (1H, dt, J 15.1 Hz, 1.2 Hz, CH), 6.74 (1H, dt, J 15.1 Hz, 7.5 Hz, CH); δC (100 MHz, CDCl3) δ21.8 (CH3), 26.0 (CH3), 42.3 (CH2), 43.0 (CH2), 46.2 (CH2), 66.8 (2 CH2), 70.0 (CH), 73.8 (C), 123.4 (CH), 139.8 (CH), 165.0 (C), 175.4 (C); νmax (CDCl3) 3430s, 2980s, 2922s, 2858s, 1729s, 1765s, 168s, 1610s, 1439s, 1375s, 1267s, 1212s, 1146m, 1109s, 1067m, 1036m, 982s; m/z (%) 285 (M+, 11), 199 (12), 207 (13), 191 (14), 173 (15), 155 (16), 137 (17), 129 (18), 111 (19), 103 (20), 95 (21), 87 (22), 79 (23), 71 (24), 63 (25), 55 (26), 47 (27), 39 (28), 31 (29), 23 (30), 15 (31), 13 (32), 11 (33), 9 (34), 7 (35), 5 (36), 3 (37), 1 (38).
198 (100), 180 (15), 155 (43), 140 (46), 111 (46), 86 (18); HRMS for C_{14}H_{23}NO_5: calc. 285.1571, found 285.1574; HPLC: \( t_r = 25.2 \text{ min} \) [major], \( t_r = 33.8 \text{ min} \) [minor] (Chiralpak AD column, flow rate 1.0 mL/min, heptane/iPrOH = 90:10, \( \lambda = 210 \text{ nm} \), 20 °C); ee = 87%.

(R,E)-Benzyl 2-hydroxy-2-methyl-6-morpholino-6-oxohex-4-enoate (7k):

Prepared according to the general procedure from \( N,O \)-silyl ketene aminal 3a (89.0 mg) and benzyl pyruvate (5h, 53.4 mg). The product was purified by flash column chromatography (EtOAc) and then isolated by a second flash column chromatography (pentane : acetone = 3 : 1 to 1 : 1).

Pale yellow oil (58%); [\( \alpha \])D 23.2 (c 1.2 in CHCl_3); \( \delta \)H(400 MHz, CDCl_3) 1.45 (3H, s, CH_3), 2.54 (1H, ddd, \( J = 14.1 \text{ Hz}, 7.7 \text{ Hz}, 1.3 \text{ Hz}, \text{ CHH} \)), 2.65 (1H, ddd, \( J = 14.1 \text{ Hz}, 7.4 \text{ Hz}, 1.3 \text{ Hz}, \text{ CHH} \)), 3.31–3.50 (3H, m, OH and CH_2), 3.63 (6H, s br, 3 CH_2), 5.17 (1H, d, \( J = 12.3 \text{ Hz}, \text{ CHH} \)), 5.21 (1H, d, \( J = 12.3 \text{ Hz}, \text{ CHH} \)), 6.18 (1H, dt, \( J = 15.1 \text{ Hz}, 1.3 \text{ Hz}, \text{ CH} \)), 6.74 (1H, dt, \( J = 15.1 \text{ Hz}, 7.5 \text{ Hz}, \text{ CH} \)), 7.30–7.39 (5H, m, Ar-CH); \( \delta \)C(100 MHz, CDCl_3) 26.1 (CH_3), 42.3 (CH_2), 42.9 (CH_2), 46.2 (CH_2), 66.7 (2 CH_2), 67.7 (CH_2), 74.2 (C), 123.7 (CH), 128.0 (2 Ar-CH), 128.5 (Ar-CH), 128.6 (2 Ar-CH), 135.1 (Ar-C), 139.5 (CH), 165.0 (C), 175.7 (C); \( \nu \) max(CHCl_3) 3409s, 2972m, 2921m, 2857m, 1736s, 1658s, 1610s, 1439s, 1381m, 1266s, 1194s, 1116s, 1067w, 1036m, 981s, 850m, 699m; m/z(%) 333 (M^+ , 11), 230 (11), 198 (61), 180 (8), 155 (31), 140 (24), 111 (18), 91 (100), 86 (16); HRMS for C_{14}H_{23}NO_5: calc. 333.1571, found 333.1578; HPLC: \( t_r = 26.1 \text{ min} \) [major], \( t_r = 33.9 \text{ min} \) [minor] (Chiralpak AS column, flow rate 0.9 mL/min, heptane/iPrOH = 85:15, \( \lambda = 210 \text{ nm} \), 20 °C); ee = 86%.

Determination of the absolute configuration of 7a by transformation into (R)-dimethyl 2-acetoxy-2-methylsuccinate (9):

(R,E)-Methyl 2-acetoxy-2-methyl-6-morpholino-6-oxohex-4-enoate (8):

Product 7a (0.100 mmol, 25.8 mg) was treated with Ac_2O (8.5 mmol, 0.80 ml). To this solution pyridine (9.9 mmol, 0.80 ml) was slowly added and the resulting mixture was stirred for 3 d. The reaction mixture was concentrated under reduced pressure and then the product was purified by column chromatography (EtOAc).

Colorless oil (94%); \( \delta \)H(300 MHz, CDCl_3) 1.54 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.67 (1H, ddd, \( J = 14.6 \text{ Hz}, 7.7 \text{ Hz}, 1.3 \text{ Hz}, \text{ CHH} \)), 2.93 (1H, ddd, \( J = 14.6 \text{ Hz}, 7.4 \text{ Hz}, 1.3 \text{ Hz}, \text{ CHH} \)), 3.53 (2H, s br, CH_2), 3.67 (6H, s br, 3 CH_2), 3.71 (3H, s, CH_3), 6.26 (1H, dt, \( J = 15.0 \text{ Hz}, 1.4 \text{ Hz}, \text{ CH} \)), 6.80 (1H, dt, \( J = 15.1 \text{ Hz}, 7.6 \text{ Hz}, \text{ CH} \)); \( \delta \)C(75 MHz, CDCl_3) 21.0 (CH_3), 22.0 (CH_3), 40.1 (CH_2), 42.3 (CH_2), 46.1 (CH_2), 52.5 (CH_3), 66.7 (2 CH_2), 79.5 (C), 123.7 (CH), 139.0 (CH), 164.9 (C), 169.9 (C), 172.1 (C); \( \nu \) max(CHCl_3) 3467w, 3000m, 2958m, 2919m, 2855m, 1743s, 1660s, 1618s, 1541w, 1473s, 1373m, 1261s, 1185m, 1117s, 1068w, 1035m, 979m; m/z(%) 299 (M^+ , 2), 268 (2), 240 (6), 239 (10), 224 (9), 198 (19), 180 (100), 171 (23), 140 (11), 125 (27), 111 (16), 86 (18); HRMS for C_{14}H_{21}NO_6: calc. 299.1363, found 299.1365.
(R)-Dimethyl 2-acetoxy-2-methylsuccinate (9):

The product was synthesised in analogy to a literature protocol.\(^7\)

Compound 8 (0.0822 mmol, 24.6 mg) was added to MeCN/H\(_2\)O (7 mL, 1 : 6) and after treatment with NaIO\(_4\) (0.416 mmol, 89.0 mg) the mixture was stirred until complete dissolution of NaIO\(_4\). A catalytic amount of RuCl\(_3\) hydrate was added, and the reaction mixture was stirred for 16 h. After extraction with DCM (three times) the organic layer was dried (MgSO\(_4\)). The aqueous phases were combined and then acidified with concentrated H\(_2\)SO\(_4\). The aqueous phase was extracted with Et\(_2\)O (three times). Two drops of dry DMF were added, and the reaction mixture was stirred for 3 h. Under reduced pressure the solvent was removed and the acid chloride was dissolved in dry THF/MeOH (4 mL, 1 : 1). The mixture was stirred for 12 h and after evaporation of the solvent the product was purified by flash column chromatography (pentane : EtOAc = 6 : 1).

Colorless oil (30%); [\(\alpha\)]\(_D\) 30.6 (c 0.5 in CHCl\(_3\)); \(\delta\)_H (400 MHz, CDCl\(_3\)) 1.66 (3H, s, CH\(_3\)), 2.07 (3H, s, CH\(_3\)), 2.88 (1H, d, J 14.4 Hz, CHH), 3.15 (1H, d, J 14.5 Hz, CHH), 3.69 (3H, s, CH\(_3\)), 3.75 (3H, s, CH\(_3\)); \(\delta\)_C (75 MHz, CDCl\(_3\)) 21.0 (CH\(_3\)), 22.5 (CH\(_3\)), 40.8 (CH\(_2\)), 51.8 (CH\(_3\)), 52.7 (CH\(_3\)), 77.8 (C), 169.4 (C), 169.9 (C), one quaternary carbon could not be resolved. The spectroscopic data for 9 matched those described in literature. For the R enantiomer [\(\alpha\)]\(_D\)\(_{20}\) 36.4 (c 1.191 in CHCl\(_3\), 96.6% ee) was reported.\(^8\)

References: