Ruthenium-Catalyzed Alkylative Lactonization and Carbocyclization

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Supplemental Information

Table of Contents:

General Experimental:	S2
Synthesis of Substrates:	S2-S6
Ruthenium-Catalyzed Reactions:	S6-S12
Spectra for Compounds:	S13-S46

Experimental

1. General

Melting points were recorded using a Thomas Hoover Capillary Melting Point Apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 500 FT-IR spectrometer. ^1H NMR spectra were recorded on a Varian Gemini GEM-300 (300 MHz), a Varian Mercury Merc-400 (400 MHz), or a Varian Inova UI-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (acetone: δ 2.05 ppm, chloroform: δ 7.26 ppm, dimethylsulfoxide: δ 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sep = septet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Gemini GEM-300 (75 MHz), a Varian Mercury Merc-400 (100 MHz), or a Varian Inova UI-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (acetone: δ 206.0 ppm, chloroform: δ 77.0 ppm, dimethylsulfoxide: δ = 39.5 ppm). Analytical thin layer chromatography was performed on pre-coated EM silica gel 60-F₂₅₄ plates. Flash chromatography employed ICN silica gel (Kieselgel 60, 230-400 mesh). Solvents for extraction and chromatography were used as received. Unless otherwise noted, all reactions were conducted in flame-dried glassware with magnetic stirring under an inert atmosphere of dry argon. Dimethyl sulfoxide, dioxane, and N,N-dimethylformamide were used as received. Diisopropylamine, hexanes, and methanol were distilled from the appropriate drying reagents. Cuprous iodide was purified according to a published procedure.¹ Cerium (III) chloride heptahydrate and paraformaldehyde were used as received. *All other organic reagents were distilled or recrystallized prior to use.* The complex $[\text{CpRu}(\text{NCCH}_3)_3]\text{PF}_6$ was prepared according to a published procedure.² Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Resource, School of Pharmacy, University of California-San Francisco on a Kratos MS9 spectrometer. HRMS data are reported with accurate mass for the molecular ion (M^+) or suitable fragments.

2. Synthesis of Substrates

Sodium metal was thinly sliced and washed with hexanes. The resulting sodium (0.241 g, 10.5 mmol) was added portionwise to methanol (6.6 mL) at 0°C. Dimethyl propargyl

¹ Dieter, R. K. et al. *J. Am. Chem. Soc.* **1985**, 107, 4679.

² Gill, T. P. & Mann, K. R. *Organometallics*. **1982**, 1, 485.

malonate (1.00 mL, 6.57 mmol) was added to the resulting clear solution, followed by benzyl bromide (0.86 mL, 7.23 mmol) and the reaction was refluxed for 24 hours. The reaction was cooled to 25°C and poured into ice water (100 mL). The solution was acidified with 1M HCl (aq., 50 mL) and extracted with diethyl ether (3 x 50 mL). The combined organics were washed with brine, dried with MgSO₄ (anh.), filtered, and evaporated *in vacuo*. Purification by flash chromatography (gradient: pet ether / diethyl ether 50:50...25:75) provided the product **2** as white, cubic crystals. Yield: 1.25 g (73%). MP: 55-56.5°C. IR (CHCl₃): 3290, 3087, 3064, 3032, 3005, 2954, 2844, 1740, 1605, 1496, 1455, 1436, 1333, 1281, 1244, 1210, 1118, 1086, 1063, 1046, 978, 961, 937, 919, 892, 856, 816, 764, 744, 704 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.30-7.23 (m, 3H), 7.16-7.13 (m, 2H), 3.75 (s, 6H), 3.41 (s, 2H), 2.68 (d, J=2.7 Hz, 2H), 2.16 (t, J=2.7 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 170.0, 135.3, 129.7, 128.4, 127.2, 79.1, 72.2, 58.2, 52.7, 37.4, 22.1.

The malonate substrate **2** (1.11 g, 4.26 mmol) was dissolved in dimethyl sulfoxide (4.3 mL). Water (0.153 mL, 8.52 mmol) was added, followed by sodium chloride (0.261 g, 4.47 mmol). The resulting mixture was heated at 150°C for 12 hours. The reaction was cooled to 25°C, poured into brine (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined organics were washed with brine, dried with MgSO₄ (anh.), filtered, and evaporated *in vacuo*. The pale yellow oil was purified by flash chromatography (pet ether / diethyl ether 95:5) to give the product **3** as a clear oil. Yield: 0.706 g (82%). IR (CHCl₃): 3293, 3086, 3064, 3029, 3003, 2952, 2846, 2120, 1739, 1604, 1585, 1496, 1455, 1436, 1371, 1268, 1231, 1195, 1169, 1080, 1033, 969, 915, 871, 834, 803, 746, 702, 646 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.31-7.16 (m, 5H), 3.65 (s, 3H), 3.07-2.81 (m, 3H), 2.44-2.41 (m, 2H), 2.05 (t, J=2.7 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 174.0, 138.2, 128.9, 128.4, 126.5, 81.1, 70.3, 51.7, 46.0, 36.7, 20.3.

The alkyne **3** (0.588 g, 2.91 mmol) was dissolved in dioxane (11.6 mL). Diisopropylamine (0.816 mL, 5.82 mmol) was added, followed by paraformaldehyde (0.175 g, 5.82 mmol) and cuprous iodide (0.185 g, 0.970 mmol). The mixture was refluxed for 12 hours. The resulting brown solution was cooled to 25°C, diluted with diethyl ether (30 mL), and acidified with 0.1M NaHSO₄ (aq., 30 mL). The phases were separated and the aqueous phase was washed with diethyl ether (3 x 50 mL). The combined organic washes were washed with 0.1M NaHSO₄ (10 mL), dried with MgSO₄ (anh.), filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography (gradient: pet ether / diethyl ether 97:3...95:5) to provide the intermediate allenyl ester as a clear oil. Yield: 0.506 g (80%).

The above ester (0.471 g, 2.18 mmol) was dissolved in methanol (1.60 mL). Water (0.60 mL) was added, followed by lithium hydroxide monohydrate (0.101 g, 2.40 mmol). The resulting mixture was stirred at 75°C for 20 hours. The reaction was cooled to 25°C, diluted with diethyl ether, and acidified with 1M HCl (aq., 25 mL). The phases were separated and the aqueous phase was washed with diethyl ether (3 x 20 mL). The combined organic washes were washed with 0.1M NaHSO₄ (aq., 10 mL), dried with MgSO₄ (anh.), filtered, and evaporated *in vacuo* to provide the product **4** as a clear, green-tinged oil. Yield: 0.436 g (99%). IR (CHCl₃): 3500-2250, 1956, 1707, 1604, 1585, 1496, 1446, 1282, 1245, 1198, 1081, 1030 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 12.00 (bs, 1H), 7.30-7.16 (m, 5H), 5.14-5.05 (m, 1H), 4.72-4.67 (m, 2H), 3.04-2.95 (m, 1H), 2.87-2.75 (m, 2H), 2.38-2.17 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 208.8, 181.3, 138.5, 128.8, 128.3, 126.4, 86.8, 75.6, 46.9, 37.3, 29.8. Anal. Calcd. For C₁₃H₁₄O₂: C, 77.20; H, 6.98; Found: C, 76.97; H, 6.73.

Clear oil. IR (CHCl₃): 3500-2250, 1957, 1709, 1643, 1444, 1420, 1343, 1280, 1249, 1212, 1180, 1116 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 11.66 (bs, 1H), 5.81-5.73 (m, 1H), 5.13-5.05 (m, 3H), 4.72-4.69 (m, 2H), 2.62-2.57 (m, 1H), 2.46-2.31 (m, 3H), 2.27-2.20 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 209.0, 181.5, 134.7, 117.4, 86.9, 75.5, 44.8, 35.4, 29.7. Anal. Calcd. For C₉H₁₂O₂: C, 71.03; H, 7.95; Found: C, 70.79; H, 7.76.

Clear oil. IR (CHCl₃): 3400-2250, 1956, 1707, 1612, 1584, 1514, 1465, 1443, 1301, 1248, 1179, 1109, 1036 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 11.71 (bs, 1H), 7.09 (d, J=8.8 Hz, 2H), 6.81 (d, J=8.8 Hz, 2H), 5.14-5.05 (m, 1H), 4.72-4.68 (m, 2H), 3.76 (s, 3H), 2.98-2.89 (m, 1H), 2.82-2.71 (m, 2H), 2.35-2.16 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 209.0, 181.4, 158.2, 130.6, 129.9, 113.8, 86.9, 75.6, 55.1, 47.1, 36.4, 29.7. Anal. Calcd. For C₁₄H₁₆O₃: C, 72.39; H, 6.94; Found: C, 72.45; H, 6.74.

Pale yellow crystals. MP: 94-96°C. IR (CHCl₃): 3400-2500, 1956, 1707, 1606, 1519, 1492, 1447, 1415, 1347, 1279, 1244, 1202, 1110, 1016 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 8.15 (d, J=8.3 Hz, 2H), 7.37 (d, J=8.3 Hz, 2H), 5.14-5.09 (m, 1H), 4.76-4.74 (m, 2H), 3.11-3.06 (m, 1H), 3.00-2.96 (m, 1H), 2.89-2.83 (m, 1H), 2.42-2.35 (m, 1H), 2.30-2.23 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 209.1, 180.4, 146.8, 146.5, 129.8, 123.7, 86.4, 76.0, 46.3, 36.6, 30.0. Anal. Calcd. For C₁₃H₁₃NO₄: C, 63.15; H, 5.30; N, 5.67; Found: C, 63.16; H, 5.22; N, 5.60.

Light yellow oil. IR (CHCl₃): 3600-2250, 1956, 1732, 1708, 1442, 1415, 1360, 1275, 1234, 1163, 1094 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 11.34 (bs, 1H), 5.14-5.05 (m, 1H), 4.73-4.69 (m, 2H), 2.58-2.47 (m, 3H), 2.43-2.33 (m, 1H), 2.26-2.16 (m, 1H), 2.17 (s, 3H), 1.93-1.85 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 208.6, 208.0, 180.8, 86.7, 75.5, 44.0, 40.8, 30.5, 30.0, 25.0. Anal. Calcd. For C₁₀H₁₄O₃: C, 65.91; H, 7.74; Found: C, 65.78; H, 7.70.

Clear, sweet-smelling, non-viscous oil. IR (CHCl₃): 3600-2250, 1956, 1736, 1706, 1454, 1379, 1346, 1248, 1221, 1171, 1143, 1109, 1064 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 10.86 (bs, 1H), 5.12-5.07 (m, 1H), 4.71-4.68 (m, 2H), 3.98-3.91 (m, 4H), 2.53-2.48 (m, 1H), 2.39-2.33 (m, 1H), 2.25-2.19 (m, 1H), 1.78-1.66 (m, 4H), 1.32 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 208.9, 181.3, 109.6, 86.9, 75.3, 64.5, 44.8, 36.2, 30.4, 25.6, 23.7.

Viscous clear oil. IR (CHCl₃): 3600-2000, 1956, 1707, 1438, 1406, 1343, 1275, 1236, 1182, 1057, 1035 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 6.35 (bs, 2H), 5.12-5.06 (m, 1H), 4.71-4.68 (m, 2H), 3.65 (t, J = 6.5 Hz, 2H), 2.52-2.47 (m, 1H), 2.39-2.32 (m, 1H), 2.22-2.16 (m, 1H), 1.72-1.53 (m, 4H), 1.47-1.37 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 208.9, 180.6, 87.1, 75.3, 62.3, 45.1, 32.1, 31.2, 30.5, 23.3. Anal. Calcd. For C₁₀H₁₆O₃: C, 65.19; H, 8.75; Found: C, 64.93; H, 8.69.

Yellow crystals. MP 126-132°C. IR: 3200-2300, 1937, 1691, 1569, 1491, 1422, 1407, 1309, 1283, 1257, 1060 cm⁻¹. ¹H NMR (CDCl₃): δ 11.90 (bs, 1H), 8.07 (dd, J = 8.1, 1.2 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.51 (dt, J = 7.7, 1.3 Hz, 1H), 7.3 (m, 1H), 7.28 (m, 1H), 5.17 (d, J = 6.6 Hz, 2H). ¹³C NMR (CDCl₃): δ 211.1, 173.3, 136.3, 133.0, 131.8, 128.8, 126.6, 126.0, 91.7, 78.4. Anal. Calcd. For C₁₀H₈O₂: C, 74.99; H, 5.03; Found: C, 74.78; H, 5.00.

Clear, pale yellow oil. Mixture of epimers (*ca.* 2:1). IR: 3400-2300, 2934, 2857, 2671, 1956, 1705, 1449, 1421, 1289, 1260, 1205, 1105, 1026 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.21-5.13 (m, 1H), 4.73-4.69 (m, 2H), 2.84-2.82 (m, 0.33H), 2.65-2.61 (m,

0.33H), 2.29-2.17 (m, 1.33H), 2.03-1.99 (m, 0.66H), 1.89-1.84 (m, 1H), 1.79-1.70 (m, 2.33H), 1.61-1.41 (m, 2H), 1.37-1.12 (m, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 208.4, 207.6, 182.0, 180.9, 93.4, 90.3, 76.4, 75.7, 49.2, 45.5, 37.9, 35.9, 31.6, 31.6, 29.9, 29.8, 25.4, 25.1, 24.4, 21.8. HRMS. Calcd. For $\text{C}_{10}\text{H}_{14}\text{O}_2$: 166.0994; Found: 166.0994.

Clear oil. IR: 3500-2300, 1958, 1712, 1433, 1413, 1334, 1281, 1251, 1214, 1172, 1047 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 11.78 (bs, 1H), 5.21-5.16 (m, 1H), 4.75-4.72 (m, 2H), 2.50(t, $J = 7.1$ Hz, 2H), 2.34-2.29 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 208.2, 179.8, 88.5, 76.2, 33.0, 22.7. Anal. Calcd. For $\text{C}_6\text{H}_8\text{O}_2$: C, 64.27; H, 7.19; Found: C, 64.19; H, 7.03.

Clear oil. IR: 3400-2300, 1956, 1711, 1413, 1288, 1242, 1206, 1159, 1055 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 11.40 (bs, 1H), 5.11-5.06 (m, 1H), 4.70-4.68 (m, 2H), 2.41 (t, $J = 7.5$ Hz, 2H), 2.09-2.04 (m, 2H), 1.80-1.74 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 208.6, 180.3, 88.9, 75.2, 33.3, 27.4, 23.8. Anal. Calcd. For $\text{C}_7\text{H}_{10}\text{O}_2$: C, 66.65; H, 7.99; Found: C, 66.75; H, 7.91.

Clear, pale brown oil. IR: 3002, 2944, 2872, 1956, 1785, 1748, 1458, 1439, 1395, 1384, 1327, 1296, 1266, 1206, 1099, 1062 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 5.13-5.06 (m, 1H), 4.69-4.66 (m, 2H), 3.57 (t, $J = 5.2$ Hz, 1H), 2.16-2.11 (m, 2H), 2.10-2.04 (m, 2H), 1.80 (s, 3H), 1.76 (s, 3H), 1.64-1.56 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 208.5, 165.4, 104.8, 89.0, 75.0, 45.9, 28.3, 28.0, 25.8, 25.8.

3. Ruthenium-Catalyzed Alkylative Lactonization

The following two procedures were used. Yields represent the average of 2 runs.

Method A: The allene acid substrate (0.25 mmol) was weighed into a 1 mL vial. To this was added N,N-dimethylformamide (0.25 mL), followed by methyl vinyl ketone (0.026 mL, 0.31 mmol), cerium (III) chloride heptahydrate (0.0047 g, 0.013 mmol), and ruthenium complex $[\text{CpRu}(\text{NCCH}_3)_3]\text{PF}_6$ (0.0055 g, 0.013 mmol). The resulting clear dark orange solution was stirred for 30 min at 25°C , then purified by flash chromatography to give the product.

Method B: The allene acid substrate (0.25 mmol) was weighed into a 1 mL vial. To this was added N,N-dimethylformamide (0.25 mL), followed by methyl vinyl ketone (0.031 mL, 0.38 mmol), cerium (III) chloride heptahydrate (0.0090 g, 0.025 mmol), and ruthenium complex $[\text{CpRu}(\text{NCCH}_3)_3]\text{PF}_6$ (0.011 g, 0.025 mmol). The resulting clear

dark orange solution was stirred for 2 hours at 60°C, then cooled to 25°C and purified by flash chromatography to give the product.

Method B was used to provide the title compound as a clear oil. Mixture of 2 diastereomers (1:1). Purification by flash chromatography (gradient: pet ether / diethyl ether 66:33...50:50). Yield: 0.043 g (77%). IR (CHCl₃): 3080, 2980, 2920, 1774, 1716, 1643, 1438, 1418, 1359, 1323, 1281, 1223, 1164, 1116, 1056 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.82-5.74 (m, 1H), 5.17-5.09 (m, 3H), 4.91-4.88 (m, 1.5H), 4.82-4.79 (m, 0.5H), 2.81-2.62 (m, 3.5H), 2.60-2.48 (m, 1H), 2.36-2.24 (m, 3.5H), 2.21-2.15 (m, 0.5H), 2.18 (s, 1.5H), 2.18 (s, 1.5H), 1.82-1.75 (m, 0.5H). ¹³C NMR (125 MHz, CDCl₃): δ 207.5, 207.4, 178.4, 177.6, 145.3, 145.0, 134.3, 134.1, 117.9, 117.6, 111.4, 110.2, 80.2, 79.5, 41.5, 41.2, 40.3, 38.2, 34.4, 34.0, 33.6, 31.7, 29.9, 29.9, 24.8, 24.5. Anal. Calcd. For C₁₃H₁₈O₃: C, 70.24; H, 8.16; Found: C, 70.13; H, 7.90.

Method A was used to provide the title compound as a clear oil. Mixture of 2 diastereomers (1:1). Purification by flash chromatography (gradient: pet ether / diethyl ether 66:33...50:50). Yield: 0.054 g (79%). IR (CHCl₃): 3087, 3063, 3028, 2925, 1772, 1716, 1652, 1604, 1497, 1454, 1433, 1359, 1325, 1276, 1202, 1167, 1029, 975, 914, 753, 702 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.33-7.19 (m, 5H), 5.11 (s, 0.5H), 5.04 (s, 0.5H), 4.88 (s, 0.5H), 4.84 (s, 0.5H), 4.77-4.73 (m, 0.5H), 4.72-4.69 (m, 0.5H), 3.30 (dd, J=9.9, 4.2 Hz, 0.5H), 3.19 (dd, J=9.4, 4.4 Hz, 0.5H), 2.99-2.89 (m, 1H), 2.82-2.71 (m, 1H), 2.68-2.56 (m, 2H), 2.39-2.34 (m, 0.5H), 2.29-2.18 (m, 2H), 2.17-2.11 (m, 3.5 H), 1.82-1.75 (m, 0.5H), 1.26 (s, 0.5H). ¹³C NMR (125 MHz, CDCl₃): δ 207.8, 207.7, 178.7, 177.9, 145.6, 145.3, 138.7, 138.4, 129.2, 129.1, 129.0, 129.0, 127.1, 127.0, 112.0, 110.6, 80.7, 79.7, 43.1, 41.9, 41.6, 40.7, 36.5, 36.3, 34.3, 32.1, 30.3, 30.3, 25.2, 24.8. Anal. Calcd. For C₁₇H₂₀O₃: C, 74.97; H, 7.40; Found: C, 74.86; H, 7.61.

Method A was used to provide the title compound as a clear oil. Mixture of 2 diastereomers (1:1). Purification by flash chromatography (gradient: pet ether / diethyl ether 50:50...25:75). Yield: 0.059 g (78%). IR (CHCl₃): 2997, 2932, 2837, 1772, 1716, 1653, 1612, 1584, 1514, 1442, 1358, 1324, 1302, 1248, 1176, 1112, 1032 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.13-7.10 (m, 2H), 6.86-6.83 (m, 2H), 5.10 (s, 0.5H), 5.04 (s, 0.5H), 4.87 (s, 0.5H), 4.84 (s, 0.5H), 4.76-4.73 (m, 0.5H), 4.69-4.66 (m, 0.5H), 3.79 (s, 1.5H), 3.78 (s, 1.5H), 3.21 (dd, J = 4.3, 14.0 Hz, 0.5H), 3.09 (dd, J = 4.4, 13.8 Hz, 0.5H), 2.95-2.85 (m, 1H), 2.80-2.55 (m, 3H), 2.39-2.33 (m, 0.5H), 2.28-2.11 (m, 3H), 2.15 (s, 1.5H), 2.14 (s, 1.5H), 1.81-1.74 (m, 0.5H). ¹³C NMR (125 MHz, CDCl₃): δ 207.4, 207.3,

178.4, 177.6, 158.4, 158.2, 145.3, 144.9, 130.2, 129.9, 129.8, 129.7, 114.0, 113.9, 111.6, 110.2, 80.3, 79.4, 55.1, 55.1, 42.8, 41.5, 41.2, 40.5, 35.2, 34.9, 33.7, 31.7, 29.9, 29.8, 24.8, 24.4. HRMS. Calcd. For C₁₈H₂₂O₄: 302.1518; Found: 302.1515.

Method A was used to provide the title compound as a clear oil. Mixture of 2 diastereomers (1:1). Purification by flash chromatography (gradient: pet ether / diethyl ether 50:50...25:75). Yield: 0.064 g (81%). IR (CHCl₃): 3080, 2926, 1773, 1715, 1673, 1604, 1519, 1494, 1433, 1347, 1169, 1110 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 8.19-8.17 (m, 2H), 7.42-7.40 (m, 2H), 5.12 (s, 0.5H), 5.06 (s, 0.5H), 4.90 (s, 0.5H), 4.88 (s, 0.5H), 4.84-4.79 (m, 1H), 3.38 (dd, J = 4.5, 13.9 Hz, 0.5H), 3.29 (dd, J = 3.2, 12.1 Hz, 0.5H), 3.06-2.89 (m, 2H), 2.73-2.60 (m, 2H), 2.46 (m, 0.5H), 2.31-2.13 (m, 3H), 2.17 (s, 1.5H), 2.16 (s, 1.5H), 1.85-1.77 (m, 0.5H). ¹³C NMR (125 MHz, CDCl₃): δ 207.4, 207.3, 177.5, 176.8, 146.9, 146.8, 146.1, 145.8, 144.9, 144.6, 129.8, 129.7, 123.8, 123.8, 111.7, 110.3, 80.3, 79.1, 42.2, 41.3, 41.2, 39.5, 35.8, 35.7, 33.8, 31.7, 29.9, 29.6, 24.8, 24.3. Anal. Calcd. For C₁₇H₁₉NO₅: C, 64.34; H, 6.03; N, 4.41; Found: C, 64.23; H, 5.96; N, 4.22.

Method A was used to provide the title compound as a clear oil. Mixture of 2 diastereomers (1:1). Purification by flash chromatography (gradient: pet ether / diethyl ether 50:50...0:100). Yield: 0.048 g (76%). IR (CHCl₃): 3094, 2995, 2928, 1770, 1715, 1652, 1416, 1359, 1320, 1288, 1229, 1165 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.16 (s, 0.5H), 5.08 (s, 0.5H), 4.93-4.89 (m, 1.5H), 4.79-4.76 (m, 0.5H), 2.75-2.51 (m, 5.5H), 2.35-2.25 (m, 2.5H), 2.18 (s, 1.5H), 2.18 (s, 1.5H), 2.18 (s, 1.5H), 2.17 (s, 1.5H), 2.14-1.94 (m, 1.5H), 1.90-1.71 (m, 1.5H). ¹³C NMR (100 MHz, CDCl₃): δ 207.6, 207.5, 207.4, 207.3, 178.4, 177.8, 145.0, 144.8, 111.3, 110.2, 80.0, 79.2, 41.3, 41.1, 40.2, 40.2, 39.5, 37.3, 34.4, 32.9, 29.8, 29.8, 29.8, 29.7, 24.7, 24.4, 24.0, 23.7. Anal. Calcd. For C₁₄H₂₀O₄: C, 66.65; H, 7.99; Found: C, 66.44; H, 7.82.

Method A was used to provide the title compound as a clear oil. Mixture of 2 diastereomers (1:1). Purification by flash chromatography (gradient: pet ether / diethyl ether 25:75...0:100). Yield: 0.058 g (78%). IR (CHCl₃): 2983, 2936, 2885, 1771, 1716, 1654, 1450, 1433, 1377, 1319, 1252, 1220, 1164, 1107, 1066, 1036 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.16 (s, 0.5H), 5.09 (s, 0.5H), 4.91-4.89 (m, 1.5H), 4.80-4.77 (m, 0.5H), 3.98-3.92 (m, 4H), 2.74-2.52 (m, 3.5H), 2.37-2.30 (m, 2.5H), 2.18 (s, 1.5H), 2.18 (s,

1.5H), 2.15-1.92 (m, 1.5H), 1.84-1.68 (m, 2.5H), 1.62-1.51 (m, 1H), 1.33 (s, 1.5H), 1.32 (s, 1.5H). ^{13}C NMR (125 MHz, CDCl_3): δ 207.5, 207.3, 178.8, 178.1, 145.3, 145.0, 111.3, 110.2, 109.4, 109.3, 80.1, 79.3, 64.6, 64.5, 41.5, 41.3, 40.6, 38.3, 26.5, 36.4, 34.5, 32.6, 29.9, 29.9, 24.8, 24.8, 24.5, 24.5, 23.8, 23.7. Anal. Calcd. For $\text{C}_{16}\text{H}_{24}\text{O}_5$: C, 64.84; H, 8.16; Found: C, 64.82; H, 8.13.

Method A was used to provide the title compound as a clear viscous oil. Mixture of 2 diastereomers (1:1). Purification by flash chromatography (gradient: pet ether / ethyl acetate 50:50...25:75). Yield: 0.052 g (82%). IR (CHCl_3): 3453, 3094, 2937, 2864, 1769, 1714, 1653, 1433, 1420, 1360, 1239, 1167, 1057, 1030, 1007 cm^{-1} . ^1H NMR (500 MHz, DMSO-d_6): δ 5.07-4.84 (m, 3H), 4.40-4.39 (m, 1H), 3.41-3.36 (m, 3H), 2.78-2.71 (m, 0.5H), 2.69-2.63 (m, 2H), 2.59-2.50 (m, 1H), 2.25-2.19 (m, 2.5H), 2.15-2.08 (m, 0.5H), 2.12 (s, 3H), 1.75-1.58 (m, 1H), 1.48-1.32 (m, 4.5H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 207.5, 178.9, 178.3, 146.4, 145.9, 110.3, 109.3, 79.6, 79.0, 60.5, 40.5, 40.5, 38.1, 33.8, 32.2, 31.9, 29.9, 29.7, 29.5, 24.6, 24.3, 23.3, 23.2. HRMS. Calcd. For $\text{C}_{14}\text{H}_{22}\text{O}_4$: 254.1518; Found: 254.1518.

Method A was used to provide the title compound as off-white crystals. Purification by flash chromatography (gradient: pet ether / diethyl ether 75:25...50:50...33:66). Yield: 0.039 g (67%). MP: 56-57°C. IR (CHCl_3): 2920, 1764, 1715, 1651, 1612, 1599, 1466, 1419, 1359, 1335, 1284, 1232, 1209, 1188, 1162, 1100, 1063 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.92 (d, J = 7.7 Hz, 1H), 7.70 (dt, J = 1.1, 7.6 Hz, 1H), 7.57 (dt, J = 0.6, 8.2 Hz, 1H), 7.42 (dd, J = 0.7, 7.6 Hz, 1H), 5.89 (s, 1H), 5.37 (s, 1H), 5.15 (t, J = 1.2 Hz, 1H), 2.64-2.52 (m, 2H), 2.12-2.06 (m, 2H), 2.10 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 207.3, 170.3, 148.0, 143.5, 134.2, 129.5, 126.0, 125.6, 122.4, 116.3, 84.8, 41.6, 29.8, 23.5. Anal. Calcd. For $\text{C}_{14}\text{H}_{14}\text{O}_3$: C, 73.03; H, 6.13; Found: C, 73.16; H, 5.98.

Method A was used to provide the title compound as a clear oil. Mixture of 4 diastereomers. Purification by flash chromatography (gradient: pet ether / diethyl ether 75:25...50:50). Yield: 0.045 g (76%). IR (CHCl_3): 3091, 2936, 2859, 1780, 1716, 1651, 1447, 1415, 1364, 1327, 1302, 1271, 1234, 1221, 1165, 1134, 1116, 1084, 1054, 1031 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 5.23-4.46 (m, 3H), 2.84-0.89 (m, 17H). ^{13}C NMR (125 MHz, CDCl_3): δ 207.7, 207.4, 207.4, 207.3, 178.2, 177.6, 177.3, 176.5, 143.8, 143.4, 142.7, 140.9, 113.8, 110.8, 110.3, 109.9, 87.1, 84.1, 82.1, 81.7, 47.4, 46.1, 45.8, 42.0, 41.8, 41.7, 41.4, 41.1, 39.9, 38.2, 38.1, 37.2, 30.0, 29.9, 29.5, 27.6, 27.6, 26.2, 25.3,

25.2, 25.1, 25.1, 24.8, 24.7, 24.5, 23.3, 23.0, 22.8, 22.8, 22.6, 22.5, 22.3. Anal. Calcd. For $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; Found: C, 71.52; H, 8.28.

Method A was used to provide the title compound as a clear oil. Purification by flash chromatography (diethyl ether). Yield: 0.026 g (63%). IR ($CHCl_3$): 3094, 2925, 2837, 2732, 1776, 1721, 1653, 1459, 1419, 1392, 1327, 1298, 1273, 1220, 1181, 1145, 1057, 1026, 1002 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 9.81 (t, J = 1.2 Hz, 1H), 5.18-5.17 (m, 1H), 4.96-4.93 (m, 2H), 2.78-2.67 (m, 2H), 2.61-2.55 (m, 2H), 2.47-2.34 (m, 3H), 2.14-2.06 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.1, 176.7, 144.6, 111.5, 81.8, 41.6, 28.4, 27.2, 23.0. Anal. Calcd. For Corresponding Oxime $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65; Found: C, 58.86; H, 6.97; N, 7.52.

Method B was used to provide the title compound as a clear oil. Purification by flash chromatography (gradient: pet ether / ethyl acetate 66:33...50:50). Yield: 0.025 g (55%). IR ($CHCl_3$): 2956, 2731, 1728, 1652, 1439, 1415, 1390, 1345, 1240, 1189, 1161, 1094, 1041 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 9.80 (t, J = 1.3 Hz, 1H), 5.17 (d, J = 1.0 Hz, 1H), 4.96-4.95 (m, 1H), 4.80-4.77 (m, 1H), 2.75-2.60 (m, 3H), 2.53-2.37 (m, 3H), 2.03-1.85 (m, 3H), 1.81-1.73 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 171.1, 145.1, 112.6, 82.6, 41.9, 29.4, 26.9, 23.4, 18.3. Anal. Calcd. For Corresponding Oxime $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10; Found: C, 60.68; H, 7.48; N, 6.87.

Method A was used to provide the title compound as a clear oil. Purification by flash chromatography (gradient: pet ether / diethyl ether 50:50...20:80). Yield: 0.036 g (78%). IR ($CHCl_3$): 3093, 2996, 2925, 1778, 1715, 1652, 1460, 1421, 1360, 1327, 1298, 1273, 1220, 1181, 1162, 1144, 1056, 1028, 1003 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 5.14-5.13 (m, 1H), 4.94-4.91 (m, 2H), 2.75-2.64 (m, 2H), 2.58-2.55 (m, 2H), 2.46-2.39 (m, 1H), 2.38-2.28 (m, 2H), 2.18 (s, 3H), 2.15-2.05 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.5, 176.8, 145.1, 110.9, 81.9, 41.3, 29.9, 28.3, 27.2, 24.5. Anal. Calcd. For $C_{10}H_{14}O_3$: C, 65.91; H, 7.74; Found: C, 65.76; H, 7.74.

Method B was used to provide the title compound as a clear oil. Purification by flash chromatography (gradient: pet ether / diethyl ether 50:50...20:80). Yield: 0.032 g (65%). IR ($CHCl_3$): 3091, 2956, 2913, 1733, 1714, 1651, 1437, 1415, 1360, 1240, 1189, 1163, 1092, 1041, 1009 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 5.13 (s, 1H), 4.93 (s, 1H), 4.78-4.75 (m, 1H), 2.74-2.59 (m, 3H), 2.53-2.45 (m, 1H), 2.42-2.29 (m, 2H), 2.18 (s, 3H), 2.02-1.84 (m, 3H), 1.80-1.73 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.8, 171.2,

145.6, 112.1, 82.7, 41.7, 29.9, 29.4, 26.8, 24.9, 18.2. HRMS. Calcd. For $C_{11}H_{16}O_3$: 196.1100; Found: 196.1097.

Method A was used to provide the title compound as a clear oil. Purification by flash chromatography (gradient: pet ether / diethyl ether 75:25...33:66). Yield: 0.038 g (75%). IR ($CHCl_3$): 3093, 2978, 2939, 1777, 1714, 1653, 1460, 1418, 1376, 1327, 1298, 1272, 1218, 1181, 1143, 1114, 1040, 1004 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 5.13-5.12 (m, 1H), 4.94-4.90 (m, 2H), 2.68-2.62 (m, 2H), 2.58-2.55 (m, 2H), 2.49-2.39 (m, 3H), 2.35-2.30 (m, 2H), 2.14-2.06 (m, 1H), 1.07 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.2, 176.8, 145.3, 110.8, 81.9, 40.0, 35.9, 28.3, 27.2, 24.6, 7.6. Anal. Calcd. For $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; Found: C, 67.49; H, 8.24.

Method B was used to provide the title compound as a clear oil. Purification by flash chromatography (gradient: pet ether / diethyl ether 50:50...30:70). Yield: 0.031 g (58%). IR ($CHCl_3$): 3091, 2968, 2932, 1735, 1714, 1651, 1460, 1440, 1415, 1346, 1240, 1189, 1161, 1114, 1094, 1043, 1010 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 5.13 (s, 1H), 4.93 (s, 1H), 4.78-4.76 (m, 1H), 2.71-2.59 (m, 3H), 2.52-2.30 (m, 5H), 2.03-1.84 (m, 3H), 1.80-1.73 (m, 1H), 1.06 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.4, 171.2, 145.8, 112.0, 82.6, 40.4, 35.9, 29.4, 26.8, 25.0, 18.2, 7.7. Anal. Calcd. For $C_{12}H_{18}O_3$: C, 68.54; H, 8.63; Found: C, 68.43; H, 8.41.

Method B was used to provide the title compound as a clear oil. Purification by flash chromatography (gradient: pet ether / diethyl ether 70:30...30:70). Yield: 0.048 g (79%). IR ($CHCl_3$): 3088, 3062, 2926, 1770, 1682, 1652, 1597, 1580, 1449, 1418, 1360, 1324, 1297, 1249, 1206, 1180, 1143, 1037 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 7.99-7.97 (m, 2H), 7.59-7.56 (m, 1H), 7.49-7.46 (m, 2H), 5.17-5.16 (m, 1H), 4.99-4.96 (m, 2H), 3.28-3.17 (m, 2H), 2.59-2.55 (m, 2H), 2.52-2.41 (m, 3H), 2.18-2.10 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.8, 176.8, 145.4, 136.5, 133.1, 128.6, 127.9, 111.0, 82.0, 36.5, 28.3, 27.3, 25.0. Anal. Calcd. For $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; Found: C, 73.88; H, 6.52.

Method B was used to provide the title compound as a clear oil. Purification by flash chromatography (gradient: pet ether / diethyl ether 50:50...25:75). Yield: 0.046 g (71%). IR ($CHCl_3$): 3061, 2955, 1733, 1685, 1652, 1597, 1580, 1448, 1413, 1359, 1328, 1240, 1205, 1184, 1161, 1092, 1043 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 7.99-7.97 (m, 2H), 7.59-7.55 (m, 1H), 7.49-7.45 (m, 2H), 5.17 (s, 1H), 5.01 (s, 1H), 4.84-4.81 (m, 1H), 3.28-

3.15 (m, 2H), 2.65-2.46 (m, 4H), 2.07-2.01 (m, 1H), 2.00-1.93 (m, 1H), 1.92-1.75 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 199.0, 171.2, 145.8, 136.6, 133.1, 128.5, 127.9, 112.0, 82.6, 36.8, 29.4, 26.9, 25.4, 18.2. HRMS. Calcd. For $\text{C}_{16}\text{H}_{18}\text{O}_3$: 258.1256; Found: 258.1254.

Method B was used to provide the title compound as a clear oil. Purification by flash chromatography (gradient: pet ether / diethyl ether 75:25...50:50). Yield: 0.033 g (58%). IR (CHCl_3): 2969, 2873, 1779, 1704, 1652, 1479, 1463, 1420, 1395, 1366, 1325, 1297, 1272, 1216, 1180, 1142, 1084, 1050, 1026, 1004 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 5.13-5.12 (m, 1H), 4.94-4.90 (m, 2H), 2.80-2.68 (m, 2H), 2.58-2.55 (m, 2H), 2.47-2.40 (m, 1H), 2.31-2.27 (m, 2H), 2.15-2.08 (m, 1H), 1.16 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ 214.7, 176.9, 145.7, 110.5, 82.0, 44.0, 34.5, 28.3, 27.3, 26.4, 24.7. Anal. Calcd. For $\text{C}_{13}\text{H}_{20}\text{O}_3$: C, 69.61; H, 8.99; Found: C, 69.80; H, 9.03.

Method B was used to provide the title compound as a clear oil. Purification by flash chromatography (gradient: pet ether / diethyl ether 75:25...50:50). Yield: 0.030 g (50%). IR (CHCl_3): 2966, 2874, 1736, 1704, 1652, 1479, 1465, 1440, 1415, 1394, 1366, 1343, 1238, 1189, 1161, 1083, 1042 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 5.13 (s, 1H), 4.93 (s, 1H), 4.79-4.76 (m, 1H), 2.79-2.59 (m, 3H), 2.53-2.45 (m, 1H), 2.40-2.28 (m, 2H), 2.05-1.98 (m, 1H), 1.98-1.92 (m, 1H), 1.91-1.83 (m, 1H), 1.81-1.73 (m, 1H), 1.16 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ 214.9, 171.2, 146.1, 111.6, 82.7, 44.0, 34.8, 29.5, 26.9, 26.4, 25.1, 18.2. HRMS. Calcd. For $\text{C}_{14}\text{H}_{22}\text{O}_3$: 238.1569; Found: 238.1571.

Method B was used to provide the title compound as white crystals. MP: 62-63.5°C. Purification by flash chromatography (gradient: pet ether / diethyl ether 66:33...33:66). Yield: 0.049 g (66%). IR (CHCl_3): 3093, 2947, 2876, 1772, 1740, 1717, 1646, 1440, 1394, 1382, 1359, 1287, 1245, 1205, 1162, 1104, 1068, 1014 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 4.95 (s, 1H), 4.90 (s, 1H), 3.49-3.45 (m, 1H), 2.63-2.47 (m, 2H), 2.40-2.27 (m, 4H), 2.19-1.96 (m, 4H), 2.14 (s, 3H), 1.74 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 207.4, 172.5, 169.3, 144.1, 113.1, 104.7, 59.5, 57.0, 41.7, 39.0, 30.8, 29.9, 29.8, 29.4, 27.8, 24.7.