Synthesis of Enamides Related to the Salicylate Antitumor Macrolides Using Copper-Mediated Vinylic Substitution

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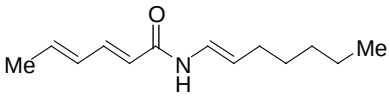
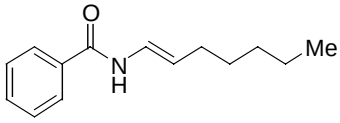
Supporting Information

^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on a 75.0 MHz spectrometer (unless otherwise stated) at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.24; ^{13}C, δ 77.0). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad) and coupling constants. All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Perkin-Elmer 1800 series FTIR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200-4—mesh silica gel (Natland International Corporation). Yields refer to chromatographically pure materials, unless otherwise stated. Tetrahydrofuran was freshly distilled under argon from sodium/benzophenone ketyl. Copper (I) thiophenecarboxylate (CuTC) was prepared according the procedure of Allred and Liebeskind.[1] *E*-(1)-iodoheptene was prepared by the method of Stille and Simpson.[2] (*E*)-β-iodostyrene was prepared according to the method of Takai.[3] 2,4-Hexadienamide (sorbamide) was prepared according to the method reported by Pellegata.[4] Dimethylacetamide (DMA) was distilled from barium oxide and stored over 4Å molecular sieves prior to use. All other reagents were used as supplied by Sigma-Aldrich, Fluka, and Strem Chemicals. All reactions were performed under a dry argon or nitrogen atmosphere in oven dried glassware.

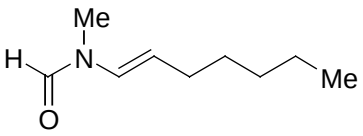
General Procedure for Enamide Formation Illustrated for Compound 3b:



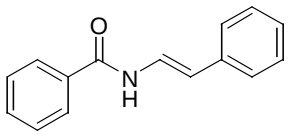
2,4-Hexadienamide (sorbamide) (83 mg, 0.75 mmol), copper (I) thiophenecarboxylate (CuTC) (28.6 mg, 0.15 mmol), and cesium carbonate (245 mg, 0.75 mmol) were placed in an oven-dried 10 mL Schlenk flask equipped with a stir bar. Anhydrous NMP (2 mL) was added to the Schlenk flask using an oven dried syringe. The suspension was degassed using high vacuum until gas evolution ceased. *E*-(1)-iodoheptene (112 mg, 0.5 mmol, 79 μL) was added to the flask using a microliter syringe. The mixture was degassed with high vacuum until no further gas evolution was observed. The suspension was stirred at 90^{o}C for 12 h under argon. The red slurry was cooled to room temperature, diluted with ether and the ether extracts washed with pH 7 buffer. The aqueous layer was extracted twice further with ether. The organic layers were combined, dried with anhydrous sodium sulfate, and concentrated. The pure enamide **3b** was obtained as a white solid (71 mg, 69 % yield) after flash chromatography on silica gel (hexane: ethyl acetate= 4:1, 1% Et_3N). mp. 116~117^{o}C; IR (neat): 3247, 2921, 1654, 1629, 1534, 1350 cm^{-1}; ^{1}H NMR: δ 7.23 (1H, dd, J=14.8, 10 Hz), 7.16 (1H, d, J=9.6 Hz), 6.82 (1H, dd, J=14, 10.8 Hz), 6.12 (2H, m), 5.71 (1H, d, J=14.8 Hz), 5.16 (1H, dt, J=14, 7.2 Hz), 1.82 (3H, d, J=5.6 Hz), 1.30 (6H, m), 2.01 (2H, m), 0.86 (3H, t, J=6 Hz) ppm; ^{13}C NMR (67.5 MHz): δ 163.1, 142.4, 138.6, 129.7, 122.6, 120.7, 113.6, 31.3, 29.7, 29.5, 22.5, 18.6, 14.0 ppm; HRMS (EI): calcd. for $C_{13}H_{21}NO$ 207.1623, found 207.1588.



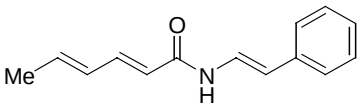
Enamide 3a: mp. 83~84 ^{o}C; IR (neat): 3272, 2961, 1635, 1529, 1319 cm^{-1}; ^{1}H NMR: δ 7.77 (2H, d, J=7.2 Hz), 7.50~7.39 (3H, m), 6.93 (1H, dd, J=14, 10 Hz), 5.30 (1H, dt, J=14, 7.2 Hz), 2.05 (2H, dt, J=7.2, 7.2 Hz), 1.39~1.27 (6H, m), 0.87 (3H, t, J=6.8 Hz) ppm; ^{13}C NMR (67.5 MHz) δ 164.3, 133.9, 131.7 (2C), 128.6 (2C), 127.1, 122.8, 114.4, 31.2, 29.7, 29.5, 22.5, 14.0 ppm; HRMS (EI): calcd. for $C_{14}H_{19}NO$ 217.1467, found 217.1450.



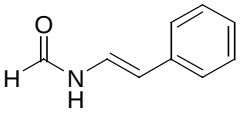
Enamide 3c: IR (neat): 2957, 1695, 1660, 1388, 1077 cm^{-1}; ^{1}H NMR: δ 8.21 and 8.00 (each 1H, s, major and minor rotamers), 7.06 (1H, d, J=14 Hz, minor rotamers), 6.40 (1H, d, J=14 Hz, major rotamers), 5.04 (1H, dt, J=14, 7 Hz), 2.95 and 2.99 (each 3H, s, major and minor rotamers), 2.02 (2H, dt, J=7, 7 Hz), 1.38~1.23 (6H, m), 0.85 (3H, t, J=6.4 Hz) ppm; ^{13}C NMR (major and minor rotamers): δ 163.0, 161.7, 129.2, 125.3, 114.3, 112.6, 34.0, 32.3, 31.2, 31.0, 30.8, 30.7, 28.5, 23.5, 15.0 ppm; HRMS (EI): calcd. for $C_9H_{17}NO$ 155.1310, found 155.1325.



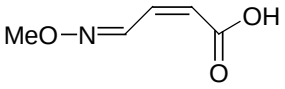
Enamide 3d: mp. 169~170°C; IR (neat): 3308, 1661, 1639, 1521 cm^{-1}; ^{1}H NMR: δ 7.83 (2H, d, J=8 Hz), 7.73 (1H, dd, J=14.4, 10.8 Hz), 7.55~7.46 (3H, m), 7.37~7.19 (5H, m), 6.24 (1H, d, J=14.4 Hz) ppm; ^{13}C NMR δ 165.5, 137.1, 134.6, 133.2, 129.9 (2C), 129.8 (2C), 128.1 (2C), 127.8, 126.7 (2C), 124.1, 114.7 ppm; HRMS (EI): calcd. for $C_{15}H_{13}NO$ 223.0997, found 223.1007.



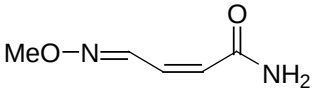
Enamide 3e: IR (neat): 3279, 1646, 1627, 1528, 1345, 1255 cm^{-1}; ^{1}H NMR: δ 7.64 (2H, m), 7.34~7.15 (6H, m), 6.15 (2H, m), 5.81 (1H, d, J=15.2 Hz), 1.83 (3H, d, J=5.2 Hz) ppm; ^{13}C NMR δ 164.5, 144.2, 104.3, 137.2, 130.7, 129.7 (2C), 127.6, 126.6 (2C), 124.1, 121.4, 113.9, 19.7 ppm; HRMS (EI): calcd. for $C_{14}H_{15}NO$ 213.1154, found 213.1176.



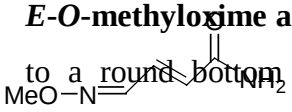
Enamide 3f: IR (neat): 3025, 1685, 1641, 1311, 1249, 1069 cm^{-1}, ^{1}H NMR: δ 8.41 and 8.14 (each 1H, s, major and minor rotamers), 7.86 (1H, d, J=14.8 Hz, minor rotamers), 7.15 (1H, d, J=14.0Hz, major rotamers), 7.36~7.17 (5H, m), 6.04 (1H, d, J=14.8 Hz), 3.13 and 3.16 (each 3H, s, major and minor rotamers) ppm; ^{13}C NMR (major and minor rotamers): δ 162.5, 161.1, 135.9, 128.7, 126.6, 125.7, 125.3, 124.2, 112.4, 110.9, 33.0, 27.5 ppm; HRMS(EI): calcd. for C_9H_9NO 161.0841, found 161.0842.



***Z*-*O*-methyloxime acid 4**: 5-hydroxy-2 (*5H*)-furanone (1.5 g, 15 mmol), methoxylamine hydrochloride (1.378 g, 16.5 mmol) was added to a 50 mL round bottom flask equipped with a stir bar. Distilled water (36 mL) was added to the flask to dissolve the solid. The solution was stirred at room temperature for 1h. To the solution was added solid sodium chloride (5 g) and the mixture extracted 3 × 40 mL ethyl acetate. The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated. The product was obtained as pale yellow crystals (1.78 g, 92% yield). IR (neat): 3000 (br s), 1700, 1617, 1444, 1257, 1041 cm^{-1}; ^1H NMR: δ 8.80 (1H, d, J=10.4 Hz), 6.17 (1H, dd, J=11.6, 10.4 Hz), 6.00 (1H, d, J=11.6 Hz), 3.96 (3H, s) ppm; ^{13}C NMR δ 170.8, 147.2, 139.1, 122.0, 62.5 ppm.

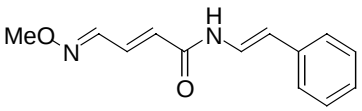


***Z*-*O*-methyloxime amide 5**: Z-*O*-methyloxime acid **4** (770 mg, 6.0 mmol) was placed in an oven dried round bottom flask equipped with a stir bar. The solid was dissolved in 20 mL anhydrous THF. Ethyl chloroformate (716.2 mg, 6.6 mmol) and triethylamine (920 μL, 6.6 mmol) were added to the flask sequentially at 0°C. The mixture was stirred at 0°C for 30 minutes. Ammonium hydroxide (28~30%) (1213 μL, 9.0 mmol) was added to the flask dropwise. The mixture was stirred at room temperature for 1.5 h. The suspension was filtered using a fritted funnel, and the filtrate was concentrated and redissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2 further and the CH_2Cl_2 layers were combined, dried with anhydrous Na_2SO_4, and concentrated. Amide **5** was obtained as a yellow solid in 95% yield. IR (neat): 3397, 1669, 1617, 1437, 1341, 1043 cm^{-1}; ^1H NMR: δ 8.95 (1H, d, J=10 Hz), 6.49 (1H, dd, J=11.6, 10 Hz), 5.95 (1H, d, J=11.6 Hz), 5.56 (2H, br s), 3.92 (3H, s) ppm; ^{13}C NMR (67.5 MHz) δ 167.2, 147.5, 134.8, 124.6, 62.3 ppm; HRMS (EI): calcd. for $C_5H_8N_2O_2$ 128.0586, found 128.0608.

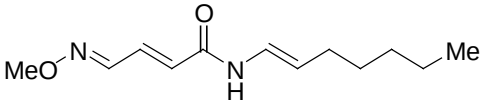


***E*-*O*-methyloxime amide 6**: Z-*O*-methyloxime amide **5** (150 mg, 1.17 mmol) was added to a round bottom flask and dissolved in 2.4 mL methanol. 1.2 mL concentrated

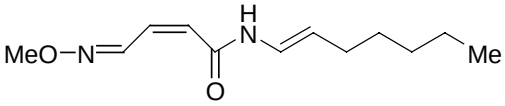
hydrochloric acid (37%) was added to the flask. The mixture was stirred at room temperature for 4 h. The reaction solution was neutralized and further basified to pH 12 with saturated Na_2CO_3 solution. The mixture was extracted with ethyl acetate 4 × 5 mL. The organic layers were combined, washed with saturated NaCl solution, dried with anhydrous Na_2SO_4 and concentrated. Amide **6** was obtained as a white solid (121 mg, 81% yield). IR (neat): 3147, 1669, 1616, 1405, 1037 cm^{-1}; ^1H NMR (DMSO): δ 7.94 (1H, d, J=10 Hz), 7.64 (1H, br s), 7.20 (1H, br s), 6.85 (1H, dd, J=16, 10 Hz), 6.30 (1H, d, J=16 Hz), 3.80 (3H, s) ppm; ^{13}C NMR δ 168.0, 151.1, 135.1, 134.1, 64.1 ppm; HRMS (EI): calcd. for $C_5H_8N_2O_2$ 128.0586, found 128.0608.



Enamide 7: The general procedure for enamide formation was employed except that the solvent used was dimethylacetamide (DMA). IR (neat): 3240, 1642, 1617, 1521, 1050 cm^{-1}; ^1H NMR: δ 7.79 (1H, d, J=10 Hz), 7.60 (1H, dd, J=14.4, 10.8 Hz), 7.37~7.18 (6H, m), 6.16 (1H, d, J=14.8 Hz), 6.14 (1H, d, J=14.8 Hz), 3.95 (3H, s) ppm; ^{13}C NMR (DMSO) δ 162.7, 143.9, 137.3, 134.1, 131.1, 129.7 (2C), 127.4, 126.3 (2C), 124.4, 114.1, 63.0 ppm; HRMS (EI): calcd. for $C_{13}H_{14}N_2O_2$ 230.1055, found 230.1061.



Enamide 8: The general procedure for enamide formation was employed except that the solvent used was dimethylacetamide (DMA). IR (neat): 3172, 2922, 1646, 1533, 1350, 1264 cm^{-1}; ^1H NMR: δ 7.76 (1H, d, J=10 Hz), 7.26 (1H, dd, J=15.2, 10 Hz), 7.05 (1H, d, J=10 Hz), 6.81 (1H, dd, J=14, 10 Hz), 6.06 (1H, d, J=15.6 Hz), 5.21 (1H, dt, J=14, 7 Hz), 3.93 (3H, s), 2.02 (2H, dt, J=7, 7 Hz), 1.37~1.23 (6H, m), 0.86 (3H, t, J=6.8 Hz) ppm; ^{13}C NMR δ 162.7, 147.7, 134.7, 128.5, 122.2, 115.0, 62.4, 31.2, 29.7, 29.4, 22.4, 13.9 ppm; HRMS (EI): calcd. for $C_{12}H_{20}N_2O_2$ 224.1525, found 224.1571.



Enamide 9: The general procedure for enamide formation was employed except that the solvent used was dimethylacetamide (DMA), the base used was rubidium carbonate (Rb_2CO_3)

and the reaction time was 1.5 h. IR (neat): 3255, 2928, 1635, 1521, 1054 cm^{-1}; ^{1}H NMR (DMSO): δ 10.09 (1H, d, J=10 Hz), 8.93 (1H, d, J=10.4 Hz), 6.60 (1H, dd, J=14.4, 10 Hz), 6.46 (1H, dd, J=10.8, 10.8 Hz), 6.06 (1H, d, J=11.6 Hz), 5.21 (1H, dt, J=14.4, 7.2 Hz), 3.81 (3H, s), 1.94 (2H, dt, J=7.2, 7.2 Hz), 1.30~1.18 (6H, m), 0.81 (3H, s, 7.2 Hz) ppm; ^{13}C NMR δ 162.8, 148.9, 136.2, 125.8, 123.3, 116.2, 63.4, 32.3, 30.9, 30.3, 23.6, 15.0 ppm; HRMS (EI): calcd. for $C_{12}H_{20}N_2O_2$ 224.1525, found 224.1519.

References and Notes

[1] Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.
[2] Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc*. **1987**, 109, 2138
[3] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc*. **1986**, *108*, 7408.
[4] Pellegata, R.; Italia, A.; Villa, M. *Synthesis*, **1985**, 517