Rhodium Catalyzed [5+2] Cycloadditions of Allenes and Vinylcyclopropanes: Asymmetric Total Synthesis of (+)-Dictamnol

Paul A. Wender,* Masahiro Fuji, Craig O. Husfeld, and Jennifer A. Love

Department of Chemistry, Stanford University, Stanford, California, 94305-5080
Wenderp@leland.stanford.edu

General methods. Air and moisture sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry nitrogen from a manifold or balloon, unless otherwise indicated. Similarly sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Reactions were run using Teflon-coated magnetic stir bars. Elevated temperatures were maintained using Thermowatch-controlled silicone oil baths. Organic solutions were concentrated using a Buchi rotary evaporator with a water aspirator or recirculating aspirator pump. Tetrahydrofuran was distilled from sodium benzophenone prior to use. Toluene was distilled from sodium prior to use. Analytical TLC was performed with 0.25 mm silica gel 60F plates with 254 nm fluorescent indicator from Merck. Plates were visualized by ultraviolet light and treatment with acidic *p*-anisaldehyde stain followed by gentle heating. Chromatographic purification of products was accomplished by flash chromatography, as described by Still and co-workers.[1] Silica gel 60, 230-400 mesh was purchased from EM. The enantiomeric purity was determined by chiral GLP analysis using a Cyclosil B (30 m length × 0.25 mm I.D. × 0.25 μm film, J&W Scientific) column. The temperature program used the initial temperature of 140 °C for 2 min and then ramped at 3 °C min^{-1} to 215 °C.

NMR spectra were measured on a Varian INOVA 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz), Varian XL-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz), Varian Gem-300 (^{1}H at 300

MHz, ^{13}C at 75 MHz), or Varian Gem-200 (^{1}H at 200 MHz, ^{13}C at 50 MHz) magnetic resonance spectrometer. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet), integration, and coupling constant (Hz). Data for ^{13}C are reported in terms of chemical shift. Infrared spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer (FTIR) and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were recorded at the NIH regional mass spectrometry facility at the University of California, San Francisco. Reported mass values are with error limits of ±13 millimass units. Elemental analyses (%C, %H) were determined by Desert Analytics, Tucson, Arizona. Reported atomic percentages are within error limits of ±0.4%.

Weinreb Amide 4: Diethyl (*N*-methoxy-*N*-methyl-carbamoylmethyl)phosphonate (11.6 mL, 41.8 mmol) was added dropwise to a stirred suspension of sodium hydride (2.43g, 60.8mmol) in THF (150mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 1 h at room temperature. Cyclopropanecarboxaldehyde (3.75g, 53.5mmol) was added to the solution over 10 min. via syringe. The reaction was allowed to stir for 2 h. The reaction was quenched by the addition of saturated ammonium chloride (40 mL). The aqueous layer was separated and washed with ether (4 x 40mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was solvent was evaporated under reduced pressure to yield the crude product, which was purified by flash silica gel chromatography to afford Weinreb amide **4** as a colorless oil (7.48g, 90%). (^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.52 (d, *J* = 15.2 Hz, 1H), 6.44 (dd, *J* = 15.2 Hz, 9.7 Hz, 1H), 3.73 (s, 3H), 1.63 (m, 1H), 0.95 (m, 2H), 0.66 (m, 2H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 167.81, 153.32, 116.34, 62.36, 33.09, 15.44, 9.20 (2C) ppm.

(FT-IR, film): ν = 3493 (m), 3006 (m), 2963 (m), 2936 (m), 1687 (s), 1621 (s), 1463 (s), 1424 (s), 1386 (s), 1351 (s), 1297 (m), 1179 (s), 1097 (s), 1007 (s), 959 (s), 939 (s), 879 (s), 832 (m), 811 (m), 705 (m) cm^{-1}. MS (70 ev): m/z (%) = 155 (5), 96 (12), 95 (100), 68 (5), 67 (81), 66 (4), 65 (14). HRMS calcd for $C_8H_{13}NO_2$: 155.0946. Found: 155.0943.

Allenyl Enone 5: 1-Iodo-3,4 pentandiene (2.01 mL, 10.4 mmol) was added dropwise to a stirred solution of *tert*-butyl lithium (8.0 mL, 1.7 M in hexane, 13.6mmol) in Et_2O (85 mL) at -78 °C. The solution was allowed to stir for 1 h at -78 °C. To the solution was added Weinreb amide **4** (1.31g, 8.44 mmol) dropwise via syringe. The reaction was allowed to stir for 1 h at -78 °C. The reaction was quenched by the addition of saturated ammonium chloride (30 mL). The aqueous layer was separated and washed with ether (3 x 50mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure to yield the crude product, which was purified by flash silica gel chromatography (5% Et_2O in pentane) to afford Allenyl Enone **5** as a colorless oil (1.12g, 82%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.32 (dd, *J* = 15.6 Hz, *J* = 9.7 Hz, 1H), 6.23 (d, *J* = 15.8, 1H), 5.15-5.20 (m, 1H), 4.68-4.71 (m, 2H), 2.62 (t, *J* = 7.3 Hz, 2H), 2.27-2.33 (m, 2H), 1.54-1.79 (m, 1H), 0.96-1.00 (m, 2H), 0.65-0.68 (m, 2H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 208.25, 198.61, 152.42, 127.10, 89.25, 75.75, 39.00, 22.34, 14.69, 8.92 ppm. (FT-IR, film): ν = 3086 (w), 3008 (w), 2919 (w), 1956 (m), 1690 (s), 1665 (s), 1620 (s), 1433 (w), 1382 (m), 1265 (w), 1197 (m), 1094 (m), 939 (s), 847 (s) cm^{-1}. MS (70 ev): m/z (%) = 162 (13), 147 (20), 133 (14), 121 (26), 105 (34), 95 (100), 79 (21), 77 (18), 67 (89), 65 (20), 55 (15). HRMS calcd for $C_{11}H_{14}O$: 162.1045. Found: 162.1041.

Alcohol 6: Allene enone **5** (500 mg, 3.08 mmol) was added to a stirred solution of (*R*)-2-methyl-CBS-oxazaborolidine (0.617 mL, 1.0 M in toluene, 0.617 mmol) in THF (100 mL) at -30 °C. To the solution was added BH_3 (3.08 mL, 1.0 M in THF, 3.08 mmol). The reaction was allowed to stir for 1 h at -30 °C and then allowed to warm to room temperature. The reaction was quenched with MeOH (5 mL). To the solution was added saturated ammonium chloride (40 mL). The aqueous layer was separated and washed with ether (2 x 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure to yield the crude product, which was purified by flash silica gel chromatography (20 % Et_2O in pentane) to afford alcohol **6** as a colorless oil (390 mg, 78%). $[\alpha]^{23}_D$ +26.3 (c 3.0, $CDCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.54 (dd, *J* = 15.3 Hz, *J* = 7.3 Hz, 1H), 5.14 (m, 2H), 4.67 (m, 2H), 4.08 (dd, *J* = 12.4 Hz, *J* = 5.5 Hz, 1H), 2.07 (m, 2H), 1.64 (m, 2H), 1.44 (s, 1H), 1.38 (m, 1H), 0.72 (m, 2H), 0.37 (m, 2H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 208.47, 136.19, 130.21, 89.58, 75.10, 72.41, 36.38, 24.18, 13.36, 6.79, 6.76 ppm. (FT-IR, film): ν = 3360 (s), 3004 (m), 2925 (s), 2858 (m), 1955 (m), 1665 (w), 1438 (w), 1097 (w), 1047 (m), 1019 (m), 962 (s), 842 (w) cm^{-1}. MS (70 ev): m/z (%) = 163 (1), 149 (3), 145 (2), 131 (9), 117 (11), 110 (10), 109 (12), 105 (32), 97 (37), 95 (35), 94 (10), 93 (31), 92 (22), 91 (33), 81 (14), 80 (14), 79 (100), 77 (27), 69 (14), 67 (62), 66 (11), 65 (14). Anal. calcd for $C_{11}H_{14}O$: C: 80.44, H: 9.82. Found: C: 80.28, H: 9.92.

Cycloadduct 7: $[Rh(CO)_2Cl]_2$ (12.1 mg, 0.031 mmol) is added in one batch to a based-washed, oven-dried Schlenk flask under an argon atmosphere and is dissolved in oxygen-free dichloroethane (50 mL). The solution is stirred for 5 min. at room temperature, after which allene-vinylcyclopropane **6** (204 mg, 1.24 mmol) is added over 10 s and the solution is heated to 80 ^{0}C for 7 h. After cooling, the reaction mixture is filtered through a plug of alumina and concentrated. Flash chromatography (silica gel, 10% ethyl acetate in hexane) gives 154.1 mg of cycloadduct **7** in 76% yield as a colorless oil. $[\alpha]^{24}_{D}$ +180.1 (c 1.0, $CDCl_3$); ^1H-NMR (500 MHz, $CDCl_3$): δ = 5.59-5.64 (m, 1H), 5.33-5.36 (m, 1H), 4.80 (dd, *J* = 0.9 Hz, 1H), 4.76 (dd, *J* = 1.5 Hz, 1H), 4.09 (q, *J* = 4.8 Hz, 1H), 3.14 (q, *J* = 8.4 Hz, 1H), 2.76 (s, 1H), 2.25-2.40 (m, 3H), 2.15-2.20 (m, 1H), 2.04-2.14 (m, 1H), 1.90-1.96 (m, 1H), 1.66-1.74 (m, 1H), 1.54-1.61 (m, 2H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 152.02, 129.91, 129.65, 110.20, 79.85, 50.34, 47.09, 33.79, 33.06, 30.20, 27.06 ppm. (FT-IR, film): ν = 3346 (m, br), 3075 (w), 3008 (w), 2934 (s), 2887 (m), 1638 (m), 1458 (w), 1430 (w), 1347 (w), 1166 (w), 1070 (w), 1034 (m), 885 (m) cm^{-1}. MS (70 ev): m/z (%) = 164 (23), 149 (15), 146 (35), 145 (13), 135 (11), 131 (76), 120 (33), 119 (14), 118 (34), 117 (45), 109 (10), 107 (26), 106 (16), 105 (90), 104 (35), 97 (11), 96 (16), 95 (14), 94 (10), 93 (31), 92 (54), 91 (100), 83 (11), 80 (20), 79 (74), 78 (22), 77 (31), 67 (22), 65 (13), 55 (10). HRMS calcd for $C_{11}H_{16}O$: 164.1201. Found: 164.1197. Anal. calcd for $C_{11}H_{16}O$: C: 80.44, H: 9.82. Found: C: 80.11, H: 9.82.

Ketone 8: Alcohol **7** (55 mg, 0.335 mmol) was added to a stirred solution of Dess-Martin periodinane (0.284 mL, 0.669 mmol) in CH_2Cl_2 (5.4 mL) at room temperature. The reaction was allowed to stir for 2 h at room temperature. The reaction was quenched with 1:1 saturated $NaHCO_3$: saturated NaS_2O_3 (10 mL). The aqueous layer was separated and washed with ether (2 x 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure to yield the crude product, which was purified by flash silica gel chromatography (10 % Et_2O in pentane) to afford ketone **8** as a colorless oil (43 mg, 80%). $[\alpha]^{26}_{D}$ +187.9 (c 4.0, MeOH); ^1H-NMR (500 MHz, $CDCl_3$): δ = 5.92-5.99 (m, 2H), 4.91 (t, *J* = 1.29 Hz, 1H), 4.83 (s, 1H), 2.46-2.50 (m, 4H), 2.32-2.39 (m, 1H), 2.18-2.27 (m, 3H), 2.08-2.15 (m, 1H), 1.84-1.94 (m, 1H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 217.15, 151.83, 127.45, 108.03, 55.06, 47.39, 37.38, 36.39, 28.70, 24.85 ppm. (FT-IR, film): ν = 3022 (w), 2961 (m), 2844 (w), 1742 (s), 1640 (m), 1439 (w), 1406 (w), 1146 (m), 894 (m), 716 (m) cm^{-1}.

Dictamnol (1): Methyl magnesium bromide (54 µg, 1.0 M in Et_2O, 0.054 mmol) was added to a stirred solution of ketone **8** (8 mg, 0.049 mmol) in THF (4 mL) at 0 °C. The reaction was allowed to stir for 2 h at 0 °C. The reaction was quenched with saturated ammonium chloride (10 mL). The aqueous layer was separated and washed with ether (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure to yield the crude product, which was purified by flash silica gel chromatography (10 % Et_2O in pentane) to afford a 1:1 mixture of dictamnol **1** and *epi*-dictamnol **9** in 50% yield. Dictamnol **1**: $[\alpha]^{25}_{D}$ +54.2 (lit: +55)[2] (c 1.0, MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.86-5.90 (m, 1H), 5.78-5.81 (m, 1H), 4.84 (s, 1H), 4.76 (s, 1H), 2.56-2.61 (m, 1H), 2.38-2.45 (m, 2H), 2.27-2.31 (m, 1h), 2.28-2.31 (m,1H) 2.19-2.24 (m, 1H), 2.11-2.17 (m, 1H), 1.90-1.93 (m, 1H), 1.77-1.85 (m, 3H), 1.41 (s, 1H), 1.25 (s, 3H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 153.38, 131.66, 129.73, 107.16, 80.37, 55.40, 47.01, 40.06, 36.75, 28.74, 25.27, 24.13 ppm. (FT-IR, film): ν = 3292 (m, br), 3233 (m, br), 2958 (m), 2928 (m), 1638 (m), 1560 (m), 1437 (m), 1368 (m), 1270 (m), 1078 (m) cm^{-1}. *epi*-Dictamnol **9**: $[\alpha]^{26}_{D}$ +20.52 (c 2.0, $CDCl_3$); (^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.97-6.03 (m, 1H), 5.78-5.80 (m, 1H), 4.83 (s, 1H), 4.77 (s, 1H), 2.79-2.81 (m, 1H), 2.49-2.58 (m, 2H), 2.32-2.36 (m, 1h), 2.20-2.25 (m,1H) 2.10-2.16 (m, 2H), 1.96-2.02 (m, 1H), 1.77-1.86 (m, 2H), 1.35 (s, 3H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 153.67, 133.45, 128.61, 107.33, 80.51, 55.01, 47.66, 39.39, 36.86, 28.86, 26.89, 26.06 ppm. (FT-IR, film): ν = 3439 (m, br), 2958 (s), 2928 (s), 1697 (m), 1638 (m), 1456 (m), 1437(m), 1373 (m), 1260 (m), 1088 (m), 886(m) cm^{-1}.

References

1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

2. Takeuchi, N.; Fujita, T.; Goto, K.; Morisaki, N.; Osone, N.; Tobinaga, S. *Chem. Pharm. Bull.* **1993**, *41*, 923-925.