Stereoselective Assembly of a 1,3-Diene via Coupling between an Allenic Acetate and a (*B*)-alkylborane: Synthetic Studies on Amphidinolide B1.

Amit K. Mandal[¶], John S. Schneekloth, Jr.[§] and Craig M. Crews[§¶#*]

Experimental Procedures and Characterization Data

General. Unless otherwise indicated, reactions were carried out under a nitrogen atmosphere in flame- or oven-dried glassware using freshly distilled solvents. THF was distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride. Triethylamine was distilled from calcium hydride, and stored over potassium hydroxide. Reactions were monitored by thin layer chromatography (TLC) with 0.25-mm E. Merck pre-coated silica gel plates. Silica gel for flash chromatography (particle size 32-63 μm) was supplied by Silicycle. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. ^{1}H and ^{13}C spectra were recorded on Bruker Avance DPX-500 or Bruker Avance DPX-400 spectrometers. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C). Infrared spectra were recorded on a Midac M-1200 FTIR. Optical rotations were measured on a Perkin-Elmer model 341 polarimeter. High resolution mass spectra were measured at the University of Illinois Mass Spectrometry Center. Low resolution mass spectra were acquired on a Waters Micromass ZQ mass Spectrometer.

Compound 8: $^{l}Ipc_2BH$ (2.25 g, 7.8 mmol) in dry CH_2Cl_2 (15 ml) was cooled to 0 °C. In another flask, allenyl boronate (3.24 g, 7.8 mmol) was dissolved in dry CH_2Cl_2 (15 ml) at room temperature. The resulting mixture was added *via* cannula to the borane and stirred vigorously for 2 h. The borane does not easily go into solution. After 90 min., the reaction was warmed to room temperature until the reaction was homogeneous and then

recooled to 0 °C in an ice bath. The ice bath was removed, and the reaction mixture was cooled to −78 °C. Benzyloxyacetaldehyde (0.895 ml, 6.39 mmol) was added dropwise and the mixture stirred at −78 °C for 2 h. Then distilled acetaldehyde (0.73 ml, 13.24 mmol) was added dropwise and the reaction was stirred for an additional 2 h. The cold bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for an additional 24 h. The reaction was cooled in an ice bath and diluted with CH_2Cl_2 (50 ml), followed by addition of NaOH (23.2 ml, 1.0 M aqueous solution) and H_2O_2 (3.0 ml, 30%). A thick white precipitate formed. The mixture was stirred for 3 h at room temperature. It was diluted with CH_2Cl_2 (50 ml), aqueous saturated $NaHCO_3$ and brine (50 ml). The biphasic mixture was stirred for 30 min or until the precipitate has dissolved. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50ml). The organic layers were combined, washed with brine (1 x 150 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (65% EtOAc/hexane) gave **8** as a colorless oil (1.43 g, 6.07 mmol, 95%).

FT-IR ν_{max}(neat, cm^{-1}) 3187-3600.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.26 (5 H, m), 5.57 (1 H, m), 5.48 (1 H, t, *J* 8.2), 4.55 (1 H, m), 4.49 (2 H, s), 3.77 (1 H, m), 3.40 (1 H, dd, *J* 4.4 and 9.5), 3.35 (1 H, dd, *J* 7.4 and 9.4), 2.25 (1 H, m), 2.18 (1 H, m) and 1.11 (3 H, d, *J* 6.5).

^{13}C NMR δ_c (125.7 MHz; $CDCl_3$) 136.74, 130.17, 128.78, 127.45, 126.77, 72.64, 72.38, 65.93, 65.59, 36.24 and 21.87.

FABHRMS *m/z* found 237.1490 (M^+ + H). $C_{14}H_{20}O_3H$ requires 237.1491.

$[\alpha]_D^{20}$ (c 0.30, $CHCl_3$) +30.0

Compound 9. The diol **8** (506 mg, 2.14 mmol) was dissolved in dry CH_2Cl_2 (50 ml) and cooled to 0 °C. It was treated subsequently with Na_2HPO_4 (912.3 mg, 6.4 mmol) and *m*CPBA (1.055 g, ~77%, 4.7 mmol). The mixture was stirred at 0 °C for 30 min., then warmed to r.t. and stirred for 6 h. The reaction was quenched by adding aqueous saturated $NaHCO_3$ (50 ml). It was stirred until organic layer became clear. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml). The

organic layers were combined, washed with brine (1 x 100 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (65% EtOAc/hexane) gave **9** as a colorless oil (512.9 mg, 2.03 mmol, 95%).

FT-IR ν_{max}(neat, cm^{-1}) 3175-3571.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.34 (5 H, m), 4.58 (2 H, s), 4.01 (1 H, m), 3.76 (1 H, m), 3.58 (2 H, d, *J* 5.7), 3.22 (1 H, m), 3.05 (1 H, dd, *J* 4.4 and 7.7), 1.73 (1 H, m), 1.65 (1 H, m) and 1.22 (3 H, d, *J* 5.9).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 137.55, 128.48, 127.92, 73.61, 71.37, 68.90, 65.85, 58.46, 55.15, 53.74, 37.41 and 23.99,

LRMS *m/z* (EI) 275.2 (M^+ + Na, 100%). $C_{14}H_{20}O_4Na$ requires 275.1.

$[\alpha]_D^{20}$ (c 0.23, $CHCl_3$) +21.0

Compound 10: The hydroxyl epoxide (1.247 g, 4.988 mmol) was dissolved in dry CH_2Cl_2 (50 ml) and cooled to −78 °C, and subsequently treated with 2,6-lutidine (4.64 ml, 39.90 mmol) and TBSOTf (4.55 ml, 19.95 mmol). It was stirred at the same temperature for 1 h. It was quenched with aqueous saturated $NaHCO_3$ solution at −78 °C, and warmed to room temperature. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 ml). The organic layers were combined, washed with brine (1 x 100 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (10% EtOAc/hexane) gave bis-silylether as a colorless oil (2.28 g, 4.74 mmol, 95%).

FT-IR ν_{max}(neat, cm^{-1}) 2925.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.25 (5 H, m), 4.55 (2 H, s), 3.95 (1 H, m), 3.55 (1 H, m), 3.43 (2 H, d, *J* 5.3), 3.03 (1 H, m), 2.86 (1 H, dd, *J* 4.5 and 8.2), 1.76 (1 H, ddd, *J* 2.6, 8.2 and 14.4), 1.25 (1 H, ddd, *J* 4.7, 8.8 and 14.4), 1.10 (3 H, d, *J* 6.0), 0.83 (9 H, s), 0.81 (9 H, s), 0.01 (3 H, s), 0.00 (3 H, s), −0.004 (3 H, s) and −0.011 (3 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 137.18, 128.64, 126.53, 72.64, 71.38, 70.57, 65.94, 57.97, 53.38, 38.11, 24.85, 22.46, 17.13, −4.5 and −4.7.

LRMS *m/z* (EI) 503.5 (M^+ + Na, 100%). $C_{26}H_{49}O_4Si_2Na$ requires 503.3.

$[\alpha]_D^{20}$ (c 0.33, $CHCl_3$) +6.1

To a solution of Me_3Al (2.49 ml, 4.99 mmol, 2.0M solution in hexane) in dry hexane (30 ml) at room temperature was added methyllithium (1.55 ml, 2.49 mmol, 1.6 M solution in Et_2O). The solution was then stirred at the same temperature for 10 min., followed by addition of bis-silylether (1.615 g, 3.33 mmol) in dry hexane (2 ml). It was heated to 50 °C for 6 h, cooled to room temperature and quenched with aqueous saturated NH_4Cl (30 ml). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 x 30 ml). The organic layers were combined, washed with brine (1 x 50 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (gradient 1%, then 3% to 25% EtOAc/hexane) gave alcohol as a colorless oil (1.49 g, 2.99 mmol, 90%).

FT-IR ν_{max} (neat, cm^{-1}) 3618-3484, 2933.

^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.35 (5 H, m), 4.53 (2 H, s), 3.92 (2 H, m), 3.52 (1 H, dd, *J* 5.2 and 9.7), 3.43 (1 H, dd, *J* 5.8 and 9.5), 3.36 (1 H, m), 2.40 (1 H, br s), 1.64 (1 H, m), 1.54 (1 H, m), 1.39 (1 H, m), 1.13 (3 H, d, *J* 6.2), 0.96 (3 H, d, *J* 6.4), 0.91 (9 H, s), 0.89 (9 H, s), 0.12 (3 H, s), 0.10 (3 H, s), 0.07 (3 H, s) and 0.05 (3 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 137.04, 127.31, 126.63, 73.73, 72.38, 71.66, 71.18, 65.93, 42.94, 31.58, 24.92, 22.48, 17.17, 13.72, −4.94, −5.33, −5.60 and −5.81.

LRMS *m/z* (EI) 519.5 (M^+ + Na, 100%). $C_{27}H_{52}O_4Si_2Na$ requires 519.3.

$[\alpha]_D^{20}$ (c 0.33, $CHCl_3$) −6.7

The alcohol (977 mg, 1.95 mmol) was dissolved in dry CH_2Cl_2 (20 ml) and cooled to −78 °C, and subsequently treated with 2,6-lutidine (1.81 ml, 7.80 mmol) and TBSOTf (1.78 ml, 3.90 mmol). It was stirred at the same temperature for 1 h. It was quenched with aqueous saturated $NaHCO_3$ solution at −78 °C, and warmed to room temperature. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 ml). The organic layers were combined, washed with brine (1 x 50 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash

chromatography (10% EtOAc/hexane) gave tris-silylether **10** as a colorless oil (1.11 g, 1.83 mmol, 94%).

FT-IR ν_{max} (neat, cm^{-1}) 2929, 1254.

^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.34 (5 H, m), 4.54 (1 H, d, *J* 12.5), 4.49 (1 H, d, *J* 12.4), 3.89 (1 H, m), 3.84 (1 H, m), 3.73 (1 H, dd, *J* 1.6 and 9.4), 3.43 (2 H, m), 1.79 (1 H, m), 1.52 (2 H, m), 1.11 (3 H, d, *J* 5.8), 0.905 (9 H, s), 0.902 (9 H, s), 0.900 (9 H, s), 0.79 (3 H, d, *J* 6.6), 0.092 (3 H, s), 0.084 (3 H, s), 0.080 (3 H, s), 0.070 (3 H, s), 0.066 (3 H, s) and 0.062 (3 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$)

LRMS *m/z* (EI) 633.7 (M^+ + Na, 100%). $C_{33}H_{66}O_4Si_3Na$ requires 633.4.

$[\alpha]_D^{20}$ (c 0.16, $CHCl_3$) +9.0

Fragment 2. A mixture of benzyl ether **10** (938 mg, 1.5 mmol) and 20% $Pd(OH)_2$ on charcoal (224.97 mg) in absolute EtOH (30 ml) was stirred for 30 min. under hydrogen atmosphere at room temperature. The mixture was filtered through celite and the filtrate evaporated under reduced pressure. The crude product was purified by flash chromatography (40% EtOAc/hexane) to give primary alcohol alcohol as colorless oil. A mixture of Dess-Martin Periodinane (1.83 g, 4.34 mmol) in dry CH_2Cl_2 (15 ml) was stirred at room temperature for 15 min. A solution of alcohol (727 mg, 1.39 mmol) in dry CH_2Cl_2 (5 ml) was then added dropwise and the resulting mixture stirred at the same temperature for 45 min. The mixture was the diluted with ether (20 ml) and the resulting white suspension treated with a 1:7 mixture of $NaHCO_3/Na_2S_2O_3$ (30 ml). Stirring was continued at room temperature until the mixture became clear (~15 min). The two layers were separated, and the aqueous layer was extracted with Et_2O (2 x 30 ml). The organic layers were combined, washed with brine (1 x 50 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude aldehyde (521 mg, 1.0 mmol) was taken up in dry THF (10 ml) and cooled to −78 °C. The mixture was then treated with MeMgBr (0.83 ml, 2.5 mmol, 3.0 M solution in Et_2O) and stirred for 1.5 h. The reaction was quenched with aqueous saturated NH_4Cl (15 ml), and warmed to room temperature. The two layers were separated, and the aqueous layer was extracted with EtOAc (2 x 15 ml). The organic layers were combined, washed with brine (1 x 30 ml), dried (Na_2SO_4),

filtered and evaporated under reduced pressure to give secondary alcohol (~1.0 mmol, ~100%). A mixture of Dess-Martin Periodinane (655.2 mg, 1.56 mmol) in dry CH_2Cl_2 (10 ml) was stirred at room temperature for 15 min. A solution of alcohol (1.0 mmol) in dry CH_2Cl_2 (5 ml) was then added dropwise and the resulting mixture stirred at the same temperature for 1.5 h. The mixture was the diluted with ether (20 ml) and the resulting white suspension treated with a 1:7 mixture of $NaHCO_3/Na_2S_2O_3$ (30 ml). Stirring was continued at room temperature until the mixture became clear (~15 min). The two layers were separated, and the aqueous layer was extracted with Et_2O (2 x 25 ml). The organic layers were combined, washed with brine (1 x 50 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (5% EtOAc/hexane) gave compound Fragment A (**2**) as a colorless oil (479.7 mg, 0.9 mmol, 60%).

FT-IR ν_{max} (neat, cm^{-1}) 2933, 1728, 1258

^{1}H NMR δ_H (400 MHz; $CDCl_3$) 4.11 (1 H, d, J 4.5), 3.80 (1 H, m), 3.64 (1 H, t, *J* 4.0), 2.23 (3 H, s), 1.75 (1 H, m), 1.52 (2 H, m), 1.11 (3 H, d, *J* 5.9), 0.95 (9 H, s), 0.94 (9 H, s), 0.89 (9 H, s), 0.82 (3 H, d, *J* 6.9), 0.11 (3 H, s), 0.10 (3 H, s), 0.06 (3 H, s), 0.07 (6 H, s) and 0.05 (3 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 209.68, 81.09, 79.41, 67.61, 45.28, 32.62, 28.59, 25.91, 23.05, 18.19, 14.78, −3.95, −4.46, −4.53, −4.66, −4.94.

LRMS *m/z* (EI) 555.5 (M^+ + Na, 30%). $C_{27}H_{60}O_5Si_3Na$ requires 555.4.

$[\alpha]_D^{20}$ (c 0.22, $CHCl_3$) +9.0

Compound 15. The alcohol **14** (2.37 g, 10.60 mmol) in dry THF (100 ml) was cooled to 0 °C. Then BH_3•THF (26.5 ml, 26.50 mmol, 1.0 M solution in THF) was introduced slowly. The mixture was stirred at 0 °C for 1 h, and then warmed to room temperature over 12 h. It was recooled to 0 °C, and subsequently treated with NaOH (8.8 ml, 26.50 mmol, 3.0 M aqueous solution) and H_2O_2 (8.92 ml, 26.50 mmol, aqueous 30%). The reaction mixture was stirred at room temperature for 2 h and at 50 °C for 6 h. Then it was cooled to room temperature, and diluted with aqueous saturated NH_4Cl (100 ml). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 ml). The organic layers were combined, washed with brine (1 x 150 ml), dried (Na_2SO_4), filtered

and evaporated under reduced pressure. Purification of the crude product by flash chromatography (gradient 30% to 90% EtOAc/hexane) gave diol as a colorless oil (1.88 g, 7.84 mmol, 74%).

FT-IR ν_{max} (neat, cm^{-1}) 3336, 2909.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.17 (2 H, d, *J* 8.6), 6.8 (2 H, d, *J* 8.6), 4.33 (1 H, d, *J* 11.6), 4.32 (1 H, d, *J* 11.6), 3.73 (1 H, m), 3.72 (3 H, s), 3.64 (1 H, m), 3.60 (1 H, d, *J* 11.6), 3.44 (1 H, d, *J* 11.6), 2.58 (2 H, br s), 1.83 (2 H, m), 1.21 (3 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 159.22, 130.71, 129.11, 67.99, 64.57, 58.56, 55.32, 38.86 and 21.02.

LRMS *m/z* (EI) 263.3 (M^+ + Na, 100%). $C_{13}H_{20}O_4Na$ requires 263.1.

$[\alpha]_D^{20}$ (c 0.20, $CHCl_3$) −3.0

A mixture of diol (1.608 g, 6.69 mmol), imidazole (716.6 mg, 10.54 mmol) and a catalytic amount DMAP (75 mg, 0.67 mmol) was dissolved in dry CH_2Cl_2 (70 ml) and cooled to 0 °C. *tert*-Butyldiphenylsilyl chloride (1.79 ml, 7.02 mmol) was added and the mixture was stirred overnight. The reaction mixture was quenched with aqueous saturated NaHCO3 (70 ml) and brine (40 ml). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 ml). The organic layers were combined, washed with brine (1 x 150 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (gradient 10% to 25% EtOAc/hexane) gave monosilyl protected alcohol **15** as a colorless oil (3.04 g, 6.35 mmol, 95%).

FT-IR ν_{max} (neat, cm^{-1}) 3500-3185.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.78 (4 H, m), 7.49 (6 H, m), 7.27 (2 H, d, *J* 8.6), 6.92 (2 H, d, *J* 8.6), 4.43 (1 H, d, *J* 10.5), 4.37 (1 H, d, *J* 10.5), 3.96 (1 H, m), 3.84 (3 H, s), 3.82 (1 H, m), 3.70 (1 H, d, *J* 11.8), 3.64 (1 H, d, *J* 11.8), 2.89 (1 H, br s), 2.03 (2 H, m), 1.34 (3 H, s) and 1.15 (9 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 159.06, 135.66, 133.31, 131.30, 129.87, 129.07, 127.86, 113.86, 67.80, 63.43, 60.16, 55.33, 53.50, 38.63, 26.91, 21.33 and 19.15.

LRMS *m/z* (EI) 501.5 (M^+ + Na, 100%). $C_{29}H_{38}O_4SiNa$ requires 501.2.

$[\alpha]_D^{20}$ (c 0.30, $CHCl_3$) +10

Ketone 16. To a solution of oxalyl chloride (3.70 ml, 41.73 mmol) in CH_2Cl_2 (80 ml) was added dropwise DMSO (3.79 ml, 51.73 mmol) at −70 °C. After the mixture was stirred for 15 min., alcohol **15** (4.46 g, 9.31 mmol) in CH_2Cl_2 (10 ml) was introduced. Stirring was continued for another 30 min. After addition of Et_3N (9.36 ml, 65.8 mmol), the mixture was warmed to room temperature over a period of 30 min. Water (80 ml) was added. The two layers were separated, and the aqueous layer was extracted with Et_2O (2 x 80 ml). The organic layers were combined, washed with water (150 ml), brine (1 x 150 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (gradient 10% EtOAc/hexane) gave aldehyde as a colorless oil (9.31 mmol, ~100%). It was taken up in Et_2O (80 ml) and cooled to −78 °C. MeMgBr (10.07 ml, 16.12 mmol, 1.6 M solution in Et_2O) was added dropwise, followed by slow warming to 0 °C over 40 min. The reaction was quenched with aqueous saturated NH_4Cl (15 ml), and warmed to room temperature. The two layers were separated, and the aqueous layer was extracted with EtOAc (2 x 15 ml). The organic layers were combined, washed with brine (1 x 30 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give secondary alcohol (8.06 mmol, 86%). To a solution of oxalyl chloride (3.15 ml, 36.11 mmol) in CH_2Cl_2 (60 ml) was added dropwise DMSO (3.3 ml, 45.91 mmol) at −70 °C. After the mixture was stirred for 15 min., diastereomeric alcohols (4.0 g, 8.06 mmol) in CH_2Cl_2 (20 ml) was introduced. Stirring was continued for another 30 min. while the bath temperature was warmed from −70 °C to −30 °C. After addition of Et_3N (8.2 ml, 57.96 mmol), the mixture was warmed to room temperature over a period of 10 min. Water (80 ml) was added. The two layers were separated, and the aqueous layer was extracted with Et_2O (2 x 80 ml). The organic layers were combined, washed with water (150 ml), brine (1 x 150 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (gradient 10% EtOAc/hexane) gave ketone **16** as a colorless oil (2.86 g, 6.04 mmol, 75%)

FT-IR ν_{max} (neat, cm^{-1}) 2253, 1713.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.71 (4 H, m), 7.42 (6 H, m), 7.23 (2 H, d, *J* 8.7), 6.91 (2 H, d, *J* 8.7), 4.30 (1 H, d, *J* 11.0), 4.26 (1 H, d, *J* 10.8), 3.84 (3 H, s), 3.76 (2 H, m), 2.26 (3 H, s), 2.17 (1 H, m), 2.09 (1 H, m), 1.39 (3 H, s) and 1.08 (9 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 212.57, 159.50, 136.04, 134.00, 130.91, 130.09, 129.16, 128.11, 114.24, 83.54, 65.69, 59.95, 55.72, 53.87, 39.61, 27.23, 25.52, 20.97 and 19.52.

LRMS *m/z* (EI) 513.5 (M^+ + Na, 40%). $C_{30}H_{38}O_4SiNa$ requires 513.2.

$[\alpha]_D^{20}$ (c 0.30, $CHCl_3$) +7.0

Allenic acetate 18. The ketone (40 mg, 0.08 mmol) was dissolved in Et_2O (1 ml). Ethylnylmagnesium bromide (0.8 ml, 0.40 mmol, 0.5 M solution in THF) was then slowly introduced. After the reaction mixture was heated to reflux for 45 min., it was cooled to room temperature. The reaction was quenched with aqueous saturated NH_4Cl (2 ml). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 x 3 ml). The organic layers were combined, washed with brine (1 x 5 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (25% EtOAc/hexane) gave ethynyl carbinol as a colorless oil (36.7 mg, 0.07 mmol, 89%) as a 9:1 diastereoisomeric mixture.

FT-IR ν_{max} (neat, cm^{-1}) 3293, 2929.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.71 (4 H, m), 7.43 (6 H, m), 7.19 (2 H, d, *J* 8.6), 6.86 (2 H, d, *J* 8.8), 4.58 (1 H, d, *J* 10.7), 4.41 (2 H, d, *J* 10.7), 3.91 (2 H, obs. m), 3.85 (3 H, s), 2.48 (1 H, s), 2.12 (1 H, m), 2.05 (1 H, m), 1.47 (3 H, s) and 1.09 (9 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 159.30, 136.03, 135.99, 135.95, 131.64, 130.11, 129.15, 128.29, 114.09, 80.81, 73.92, 92.78, 68.37, 65.43, 61.02, 55.67, 38.15, 27.23, 24.83, 19.50 and 18.95.

LRMS *m/z* (EI) 539.5 (M^+ + Na, 100%). $C_{32}H_{40}O_4SiNa$ requires 539.3.

$[\alpha]_D^{20}$ (c 0.16, $CHCl_3$) +5.0

Ethynyl carbinol (2.26 g, 4.27 mmol), paraformaldehyde (762.6 mg, 25.40 mmol), cuprous bromide (305 mg, 2.14 mmol), and diisopropylamine (0.72 ml, 5.10 mmol) were refluxed in dry dioxane (40 ml) for 48 h. The dioxane was carefully evaporated, and water (50 ml) was added to the residue. The two layers were separated, and the aqueous layer was extracted with Et_2O (2 x 30 ml). The organic layers were combined, washed with brine (1 x 50 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (25% EtOAc/hexane) gave allenic alcohol **17** as a colorless oil (1.59 g, 2.99 mmol, 70%).

FT-IR ν_{max} (neat, cm^{-1}) 3410, 2925, 1955.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.62 (4 H, m), 7.32 (6 H, m), 7.06 (2 H, d, *J* 8.6), 6.77 (2 H, d, *J* 8.6), 5.39 (1 H, t, *J* 6.5), 4.73 (2 H, m), 4.31 (1 H, d, *J* 10.7), 4.23 (2 H, d, *J* 10.7), 3.86 (1 H, m), 3.75 (3 H, s), 3.70 (1 H, m), 3.08 (1 H, s), 1.97 (2 H, m), 1.22 (3 H, s), 1.20 (3 H, s) and 1.05 (9 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 212.55, 159.76, 135.98, 133.96, 130.88, 130.07, 129.45, 128.28, 114.43, 83.52, 65.66, 59.93, 55.70, 53.84, 39.58, 27.29, 25.49, 20.94 and 19.60.

LRMS *m/z* (EI) 553.6 (M^+ + Na, 100%). $C_{33}H_{42}O_4SiNa$ requires 553.3.

$[\alpha]_D^{20}$ (c 0.15, $CHCl_3$) +11.0

The allenic alcohol (1.2 g, 2.28 mmol) was treated with Ac_2O (10 ml) and pyridine (1 ml) and 4-pyrrolidinopyridine (506 mg) at room temperature. After the reaction mixture was heated to 40 °C for 4 h, it was cooled to 0 °C. MeOH (5 ml) was added and the mixture was stirred at 0 °C for 5 min. and at room temperature for 30 min. Then MeOH was removed under reduced pressure. The residue was taken up in Et_2O (30 ml) and saturated aqueous $NaHCO_3$ (30 ml) was added. The two layers were separated, and the aqueous layer was extracted with Et_2O (2 x 30 ml). The organic layers were combined, washed with brine (1 x 50 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography (5% EtOAc/hexane) gave allenic acetate **17** as a colorless oil (653 mg, 1.14 mmol, 50 %).

FT-IR ν_{max} (neat, cm^{-1}) 2933, 1958, 1763, 1724.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.58 (4 H, m), 7.30 (6 H, m), 7.02 (2 H, d, *J* 8.6), 6.73 (2 H, d, *J* 8.6), 5.24 (1 H, t, *J* 6.8), 4.82 (1 H, dd, *J* 6.7 and 11.0), 4.73 (1 H, dd, *J* 7 and 11.0), 4.36 (1 H, d, *J* 11.0), 4.33 (1 H, d, *J* 10.8), 3.79 (2 H, m), 3.72 (3 H, s), 2.23 (3 H, d, *J* 0.9), 2.10 (3 H, s), 1.98 (1 H, m), 1.82 (1 H, m), 1.19 (3 H, s) and 0.97 (9 H, s).

^{13}C NMR δ_C (125.7 MHz; $CDCl_3$) 207.85, 168.11, 164.16, 158.76, 135.61, 133.97, 131.73, 129.58, 128.60, 127.65, 113.65, 110.99, 93.79, 87.00, 81.09, 77.95, 65.63, 60.61, 55.29, 26.92, 21.14, 19.15, 18.53 and 18.00.

$[\alpha]_D^{20}$ (c 0.12, $CHCl_3$) +15.0

Fragment 3. Acetic acid (0.3 ml) was added to the allenic acetate (8 mg, 0.014 mmol) and LiI (5.2 mg, 0.038 mmol). The solution was stirred for 40 °C for 30 min. Water (0.5 ml) and hexane (0.5 ml) was added, and the aqueous layer was extracted with hexane (2 x 1 ml). The organic layers were combined, washed with brine (1 x 5 ml), dried (Na_2SO_4), filtered (drying and filtration was performed in the dark) and evaporated under reduced pressure. Purification of the crude product by flash chromatography (silica column was neutralized by running 10:20:70 Et_3N-EtOAc-Hexane, 3% EtOAc/hexane) gave iodide Fragment B (**3**) as a colorless oil (8.3 mg, 0.013 mmol, 96%).

FT-IR ν_{max}

^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.68 (4 H, m), 7.41 (6 H, m), 7.18 (2 H, d, *J* 8.7), 6.86 (2 H, d, *J* 8.7), 6.09 (1 H, br s), 5.94 (1 H, s), 5.87 (1 H, s), 4.19 (1 H, d, *J* 10.9), 4.05 (1 H, d, *J* 11.1), 3.81 (3 H, s), 3.70 (2 H, m), 2.01 (2 H, m), 1.71 (3 H, d, *J* 0.4), 1.37 (3 H, s) and 1.06 (9 H, s).

MALDI *m/z* 663.4086 (M^+ + Na, 100%). $C_{33}H_{41}IO_3SiNa$ requires 663.1760.

Compound 21. To a solution of alcohol **20** (1.950 g, 12.34 mmol) in dry CH_2Cl_2 (60 ml) was added imidazole (3.850 g, 49.36 mmol) and *tert*-butyldimethylsilyl chloride (3.702 g, 24.68 mmol) at room temperature. The reaction mixture was stirred for 2 h, after which it was quenched with aqueous saturated NH_4Cl (60 ml). The aqueous layer was extracted three times with CH_2Cl_2 (2 x 50 ml). The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was

purified by flash chromatography to afford silyl ether (3.156 g, 94%) as a clear colorless oil.

FT-IR ν_{max} (neat, cm^{-1}) 2930, 2858, 1756.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 4.76 (1 H, s), 4.72 (1 H, s), 4.26 (1 H, dd, *J* 5.7 and 7.6), 4.13 (2 H, m), 2.37 (1 H, d, *J* 5.7), 2.36 (1 H, d, *J* 7.6), 1.72 (3 H, s), 1.22 (3 H, t, *J* 6.3), 0.84 (9 H, s), 0.024 (3 H, s) and 0.00 (3 H, s).

^{13}C NMR δ_C (125 MHz; $CDCl_3$) 173.75, 141.49, 114.31, 71.90, 61.05, 43.94, 26.02, 23.02, 18.65, 14.56, –4.63 and –4.95.

FABHRMS $[M+1]^+$ calculated for $C_{14}H_{28}O_3Si$: 273.1808, observed: 273.1888

$[\alpha]_D^{20}$ (c 0.54, $CHCl_3$) +13.6

To a solution of ester (1.885 g, 6.91 mmol) in THF (69 ml) was added (*N*,*O*)-dimethylhydroxylamine hydrochloride (1.417 g, 14.53 mmol). The slurry was cooled to 0 °C, and ^{i}PrMgCl (13.83 ml, 27.66 mmol, 2.0 M solution) was added dropwise. The reaction was stirred for 1 h at 0 °C, after which it was quenched with aqueous saturated NH_4Cl (60 ml). EtOAc (50 ml) was added and stirred for 3 h. The aqueous layer was extracted with EtOAc (3 x 50 ml), and combined organic layers were washed with brine (100 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography to afford **21** (1.825 g, 92%) as a clear colorless oil.

FT-IR ν_{max} (neat, cm^{-1}) 2929, 2856, 1624.

^{1}H NMR δ_H (400 MHz; $CDCl_3$) 4.75 (1,H, s), 4.71 (1 H, s), 4.59 (1 H, brs), 3.64 (3 H, s), 3.12 (3 H, brs), 2.29 (1 H, d, *J* 4.0), 2.28 (1 H, d, *J* 7.0), 1.707 (3 H, s), 0.815 (9 H, s), 0.00 (3 H, s) and -0.02 (3 H, s).

^{13}C NMR δ_C (125 MHz; $CDCl_3$) 141.88, 114.16, 70.23, 61.57, 43.39, 26.16, 23.15, 18.74, –4.38 and –4.90.

FABHRMS $[M+1]^+$ calculated for $C_{14}H_{29}NO_3Si$: 288.1995, observed: 288.1988.

$[\alpha]_D^{20}$ (c 0.32, $CHCl_3$) +5.2

Vinyl iodide 23. A solution of alcohol **22** (750 mg, 3.34 mmol) in DMF (20 ml) was cooled to 0 °C and treated with NaH (172 mg, 2.15 mmol). After stirring for 30 minutes,

$^{n}Bu_4NI$ (61 mg, 0.17 mmol) and *p*-methoxybenzyl chloride (1.048 g, 6.69 mmol) were added. The reaction was warmed to room temperature and stirred for 12 h. The reaction was quenched by adding water (20 ml). EtOAc (30 ml) was added. The aqueous layer was extracted with EtOAc (3 x 20 ml), and the organic layers were combined, washed with brine (50 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography to afford **23** (776 mg, 70%) as a clear colorless oil.

FT-IR ν_{max} (neat, cm^{-1}) 2934, 2852.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.09 (2 H, d, *J* 7.8), 6.72 (2 H, d, *J* 7.8), 6.33 (1 H, dt, *J* 7.2 and 14.4), 5.80 (1 H, d, *J* 14.4), 4.25 (2 H, s), 3.64 (3 H, s), 3.27 (2 H, t, *J* 6.4), 1.98 (2 H, q, *J* 7.2) and 1.57 (2 H, m).

^{13}C NMR δ_C (125 MHz; $CDCl_3$) 159.59, 146.29, 131.12, 129.68, 114.43, 75.34, 72.76, 69.11, 55.69, 33.13 and 28.81.

FABHRMS $[M+Na]^+$ calculated for $C_{13}H_{17}IO_2$: 355.0171, observed: 355.0166.

α,β-unsaturated ketone 24. A flame dried 25 ml round bottom flask was charged with a solution of iodide **23** (25 mg, 0.08 mmol) in anhydrous THF (0.8 ml) and cooled to –78 °C. ^{t}BuLi (97 µl, 1.7 M solution in pentane) was added dropwise. After stirring for 30 min., a solution of Weinreb amide **21** (24 mg, 0.082 mmol) in THF (1 ml) was introduced slowly. The reaction mixture was stirred for 30 min. at –78 °C, after which it was warmed to 0 °C and stirred for 2 h. The reaction was quenched with aqueous saturated NH_4Cl (2 ml). EtOAc (2 ml) was added. The aqueous layer was extracted with EtOAc (2 x 2 ml). The combined organic layers were washed with water (5 ml) and brine (5 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography to afford ketone **24** (28 mg, 86%) as a clear colorless oil.

FT-IR ν_{max} (neat, cm^{-1}) 2931, 2856, 1685.

^{1}H NMR δ_H (400 MHz; $CDCl_3$) 7.22 (2 H, d, *J* 8.6), 6.98 (1 H, dt, *J* 7.2 and 15.7), 6.85 (2 H, d, *J* 8.6), 6.54, (1 H, d, *J* 15.7), 4.78 (1 H, s), 4.70 (1 H, s), 4.40 (3 H, s), 4.18 (1 H, dd, *J* 7.9 and 5.0), 3.77 (3 H, s), 3.43 (2 H, t, *J* 6.2), 2.27 (4 H, m), 1.74 (2 H, m), 1.72 (3 H, s), 0.87 (9 H, s), 0.00 (3 H, s) and –0.03 (3 H, s).

^{13}C NMR δ_C (125 MHz; $CDCl_3$) 201.13, 159.22, 148.20, 140.81, 130.49, 129.26, 124.80, 114.23, 113.83, 72.69, 69.13, 55.29, 43.61, 29.44, 28.24, 25.77, 22.74, 18.20, –4.68 and –4.88.

FABHRMS $[M+1]^+$ calculated for $C_{25}H_{40}O_4Si$: 433.2774, observed: 433.2790.

$[\alpha]_D^{20}$ (c 0.57, $CHCl_3$) +2.4

Fragment 4. A slurry of ketone **24** (53 mg, 0.13 mmol) and $CeCl_3$ (31 mg, 0.13 mmol) in MeOH (1.3 ml) was stirred and cooled to –78 °C. $NaBH_4$ (5 mg, 0.13 mmol) was added slowly. The solution was stirred for 15 min., after which it was warmed to 0 °C, and water (2 ml) was added. The reaction mixture was warmed to room temperature and quenched with water (2 ml). Then EtOAc (2 ml) was added. The aqueous layer was extracted with EtOAc (2 x 2 ml). The organic layers were combined, washed with water (3 ml), brine (3 ml), and dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography to afford alcohol (52 mg, 96%) as a clear colorless oil.

FT-IR ν_{max} (neat, cm^{-1}) 3509, 2930, 2856.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.26 (2 H, d, *J* 8.5), 6.87 (2 H, d, *J* 8.5), 5.69 (1 H, dt, *J* 7.4, 15.4), 5.47 (1 H, dd, *J* 6.6 and 15.4), 4.82 (1 H, s), 4.76 (1 H, s), 4.42 (3 H, s), 3.94 (1 H, m), 3.81 (3 H, s), 3.72 (2 H, m), 3.45 (2 H, t, *J* 6.8), 2.41 (1 H, d, *J* 6.8), 2.38 (1 H, d, *J* 7.4), 1.74 (3 H, s), 1.70 (2 H, m), 0.83 (9 H, s), 0.01 (3 H, s) and 0.00 (3 H, s).

^{13}C NMR δ_C (125MHz; $CDCl_3$) 159.15, 141.95, 131.81, 131.03, 130.78, 130.72, 129.24, 113.78, 73.32, 72.56, 72.46, 69.74, 55.29, 42.31, 29.72, 29.42, 25.89, 18.18, –4.02 and –4.53.

FABHRMS $[M+1]^+$ calculated for $C_{25}H_{42}O_4Si$: 435.2931, observed: 435.2907.

$[\alpha]_D^{20}$ (c 0.52, $CHCl_3$) +1.6

A solution of alcohol (85 mg, 0.203 mmol) in CH_2Cl_2 (2.0 ml) was cooled to 0 °C. To this solution was added 2,6-lutidine (94 µl, 0.812 mmol) and triisopropylsilyl triflate (108 µl, 0.41 mmol). The reaction was warmed to 7 °C, where it was held for 18 h. The reaction was quenched with aqueous saturated NH_4Cl (2 ml), and the aqueous layer was

extracted with CH_2Cl_2 (2 x 2.0 ml). The organic layers were combined, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography to afford Fragment **4** (98 mg, 82%) as a clear viscous oil.

FT-IR ν_{max} (neat, cm^{-1}) 2943, 2865.

^{1}H NMR δ_H (500 MHz, $CDCl_3$) 7.28 (2 H, d, *J* 8.3), 6.89 (2 H, d, *J* 8.4), 5.63 (1 H, dt, *J* 16.8 and 15.8), 5.53 (1 H, dd, *J* 5.6 and 15.8), 4.77 (1 H, s), 4.71 (1 H, s), 4.44 (2 H, s), 4.23 (1 H, t, *J* 5.2), 3.81 (3 H, s), 3.47 (2 H, t, *J* 6.5), 2.37 (1 H, d, *J* 13.6), 2.15 (5 H, m), 1.91 (1 H, dd, *J* 11.7 and 13.6), 1.69 (3 H, s), 1.07 (21 H, s), 0.88 (9 H, s), 0.04 (3 H, s) and 0.01 (3 H, s).

^{13}C NMR δ_C (125 MHz; $CDCl_3$) 159.14, 143.39, 131.28, 130.78, 129.26, 129.09, 113.79, 112.85, 75.35, 74.16, 72.68, 69.68, 60.41, 55.28, 39.54, 29.50, 29.06, 25.93, 22.78, 18.10, 12.30, –4.23 and –4.54.

FABHRMS $[M+Na]^+$ calculated for $C_{34}H_{62}O_4Si_2$: 613.4060, observed: 613.4066.

$[\alpha]_D^{20}$ (c 0.27, $CHCl_3$) +7.0

Compound 26. Styrene (0.229 ml, 2 mmol) in THF (10 ml) at 0 °C was treated with 9-BBN-dimer (488 mg, 2 mmol) in THF (4 ml), and warmed to room temperature. Overall concentration is 0.14 M. It was stirred for 4 h. Another flask was charged with acetate **18** (5 mg, 8.6 μmol), $Pd(dppf)Cl_2$ (0.7 mg, 0.86 μmol) and K_3PO_4 (2.7 mg, 12.9 μmol). THF (0.2 ml) and DMF (0.1 ml) was added, followed by borane (8.5 μl, 12.9 μmol) and H_2O (0.43 mmol, 7.74 μl, an aliquot was taken from the 0.14 M solution in THF prepared before). The reddish solution was heated to 65 °C for 14 h during which it turned black. It was cooled to room temperature, diluted with Et_2O, and partitioned between aqueous saturated NH_4Cl (2 ml). The aqueous layer was extracted with Et_2O (2 x 2.0 ml). The organic layers were combined, washed with brine (5 m), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (25% EtOAc/hexane) to afford 26 (2.5 mg, 4.04 μl, 47%) as an oil.

FT-IR ν_{max} 2957, 2930, 2857, 2362 and 2337.

^{1}H NMR δ_H (500 MHz; $CDCl_3$) 7.58 (4 H, m), 7.27 (6 H, m), 7.19 (5 H, m), 7.09 (2 H, d, *J* 8.7), 6.76 (2 H, d, *J* 8.7), 5.73 (1 H, s), 4.94 (1 H, br s), 4.67 (1 H,

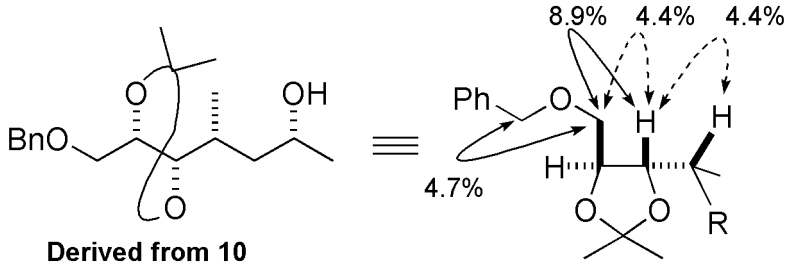
s), 4.08 (1 H, d, *J* 11.0), 3.97 (1 H, d, *J* 11.0), 3.71 (3 H, s), 3.63 (2 H, m), 2.57 (2 H, m), 2.28 (2 H, m), 1.96 (2 H, m), 1.60 (3 H, d, *J* 0.9), 1.46 (3 H, s) and 0.96 (9 H, s).

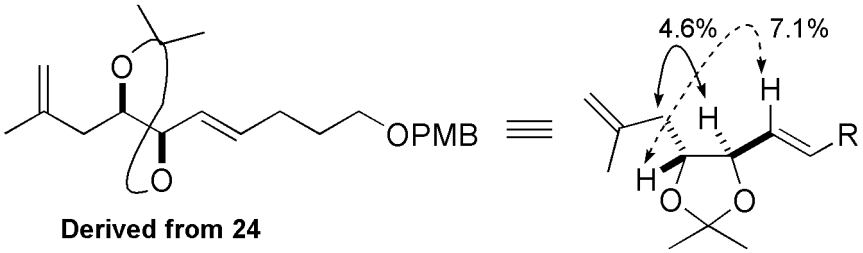
^{13}C NMR δ_C (125 MHz; $CDCl_3$) 158.82, 141.88, 140.44, 136.23, 135.58, 133.96, 133.91, 129.56, 129.55, 128.79, 128.38, 127.56, 126.49, 125.22, 113.91, 79.36, 63.68, 60.61, 55.31, 41.39, 39.52, 34.85, 32.32, 30.01, 28.89, 26.89, 22.54, 19.14, 15.86 and 13.91.

MALDI *m/z* 641.5 ((M^+ + Na, 100%),$C_{41}H_{50}O_3SiNa$ requires 641.3

$[\alpha]_D^{20}$ (c 0.12, $CHCl_3$) +3.0

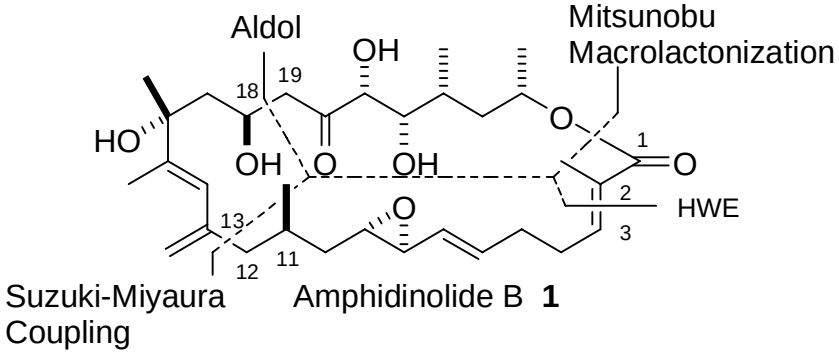
Stereochemical assignment by NOE experiment





Short text for the Table of contents

The preparation of three fragments for the total synthesis of amphidinolide B1 has been described. The C16 stereochemistry was set by asymmetric allylic alkylation, C21 & C25 stereogenic centers by an enantioselective/diastereoselective double allylation reaction and the C9 stereochemistry by an asymmetric heteroene reaction. A differentially substituted stereodefined 1,3-diene iodide was synthesized by iodide mediated S_N2' reaction. A novel stereoselective method to assemble a 1,3-diene by coupling an allenic acetate and (*B*)-alkylborane is also reported.



Key words: Asymmetic Alkylation, Asymmetric Synthesis, Anti-cancer Agents, Amphidinolide B1, Partial Synthesis.