SUPPORTING INFORMATION FOR

Halichondrin B: Synthesis of the C(1)-C(15) Subunit

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Experimental procedures for preparation of *rac*-20, *rac*-21, 24, (*S*)-20, 6(*S*)-21, 42 and 44; ¹H and/or ¹³C NMR spectra for compounds 3-6, 8, 11, 13, 14, *rac*-20, *rac*-21, 22a, 22b, 23, 25, 27-41, 43, 45, 47 and unnumbered intermediates.

General Methods. Melting points (mp) are uncorrected. Optical rotations were measured on a digital polarimeter; concentrations (*c*) are reported in g/100 mL. Infrared (IR) spectra are reported in wavenumbers (cm⁻¹) with broad signals denoted by (br). Proton nuclear magnetic resonance (¹H NMR) spectra were recorded at 300 MHz in deuterated solvents. Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded at 75 MHz. ¹³C NMR spectral assignments were aided by Distortionless Enhancement by Polarization Transfer (DEPT) experiments with a phase angle of 135°: (C) not observed; (CH) positive; (CH₂) negative; (CH₃) positive. Mass spectra (MS) were obtained using electron impact (EI) at 70eV with peak matching. Fast atom bombardment MS (FAB) were obtained on a VG Analytical ZAB-2F mass spectrometer (Ion Tech FAB gun, 8 kV, Xe carrier gas) or a Kratos MS 50 (primary beam was 1 mA of 7kV Xe carrier gas, 8 kV ion acceptance voltage).

All moisture-sensitive reactions were performed in flame-dried glassware under a stream of nitrogen, unless indicated otherwise. Bath temperatures were used to record the reaction temperature in all cases. All reactions were stirred magnetically unless otherwise indicated. When prolonged cooling was necessary, an immersion cooler was employed. Analytical thin layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates pre-coated with silica gel 60 F₂₅₄ (250 μ layer thickness). Preparative TLC was carried out using 0.5 and 2.0 mm x 10 cm x 10 cm E. Merck precoated silica gel 60 (60 F₂₅₄) plates. TLC visualization was accomplished using either a UV lamp, iodine adsorbed on silica gel, or charring solution [*p*-anisaldehyde (PAA), phosphomolybdic acid (PMA)]. Flash column chromatography (FCC) was done according to the procedure by Still¹ on EM Science silica gel 60 (230-400 mesh) or Florisil[®] (100-200 mesh) purchased from Aldrich.

Tetrahydrofuran (THF), diethyl ether (Et₂O) and benzene were distilled from sodium/benzophenone ketyl. Toluene (PhCH₃) was distilled from sodium metal. Triethylamine (Et₃N), pyridine, dichloromethane (CH₂Cl₂) and acetonitrile (CH₃CN) were distilled from calcium hydride. Dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF) were distilled under reduced pressure from calcium hydride, and stored over 4 Å molecular sieves. Deuteriochloroform (chloroform-*d*; CDCl₃), deutoacetone (acetone-*d*₆), and deuterobenzene (benzene-*d*₆; C₆D₆) were stored over 4 Å molecular sieves before use. Deuteromethanol (methanol-*d*₄) was used as received from Aldrich in glass ampules. Methanesulfonyl chloride (MsCl) was distilled under reduced pressure prior to use. Methanol (MeOH) was distilled from magnesium methoxide. Hexanes were distilled at atmospheric pressure. All other commercially obtained reagents and solvents were used as received without further purification unless indicated otherwise.

Preparation of α -Hydroxystannane *rac*-20. A solution of lithium diisopropylamide in THF (30 mL) was prepared from *N,N*-diisopropylamine (8.0 mL; 57 mmol; 1.2 eq) and a 1.7 M solution of *n*-butyllithium in hexanes (33.5 mL; 57.0 mmol; 1.2 eq) at 0 °C and allowed to stir for 20 min. Dropwise addition of tri-*n*-butyltin hydride (16.0 mL; 59.4 mmol; 1.25 eq) over the course of 30 min at 0 °C resulted in a yellow solution which was allowed to stir for 45 min to ensure complete formation of the tri-*n*-butylstannyl anion. This solution was cooled to -78 °C for the dropwise addition of a solution of 4-pentenal (4.0 g; 48 mmol) in THF (15 mL; 1.0 M total). Stirring was continued at -78 °C for 1 h, then 5% v/v aqueous HCl (20 mL) was added to quench. The reaction mixture was warmed to rt and was extracted with Et₂O. The combined ether

layers were washed with water and brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by FCC (100% hexanes to 5:1 hexanes- Et_2O) gave 9.0 g (24 mmol; 50%) of the α -hydroxystannane **rac-20** as a colorless oil. Data for **rac-20**: R_f 0.35 (5:1 hexanes- Et_2O); IR (neat) 3200-3500 (br), 1640 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.86-0.93 (m, 15 H), 1.24-1.57 (m, 12 H), 1.75-2.23 (m, 5 H), 4.10 (dt, $J = 9.1, 5.1$ Hz, 1 H), 4.94-5.09 (m, 2 H), 5.78-5.94 (m, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 8.38 (CH_2), 13.51 (CH_3), 27.36 (CH_2), 29.12 (CH_2), 31.59 (CH_2), 37.50 (CH_2), 67.75 (CH), 114.51 (CH_2), 138.33 (CH); HRMS calcd for $\text{C}_{17}\text{H}_{35}\text{OSn}$ ($\text{M}^+ - \text{H}$) 373.1704, found 373.1688.

Preparation of α -Alkoxystannane rac-21. To a solution of α -hydroxystannane **rac-20** (4.0 g; 11 mmol) and *N, N*-dimethylaniline (2.6 mL; 21 mmol; 1.9 eq) in CH_2Cl_2 (20 mL; 0.54 M) that had been cooled to -10°C was added α -chloroethyl ethyl ether (2.3 mL; ~ 21 mmol; ~ 1.9 eq) over a period of 5 min. The reaction mixture stirred between -10 and 0°C for 30 min and was quenched with water (15 mL). The layers were partitioned, and the aqueous phase was extracted with CH_2Cl_2 . The combined organic layers were washed with 5% v/v aqueous HCl, water, and saturated NaHCO_3 and dried over Na_2SO_4 . Filtration and concentration gave a yellowish oil that was purified by FCC (100% hexanes) through silica gel that had been deactivated with a 3% Et_3N -hexanes solution to give 4.6 g (10 mmol; 96%) of the α -alkoxystannane **rac-21** as a mixture of four inseparable diastereomers. Data for **rac-21**: R_f 0.62 (7:1 hexanes- Et_2O); IR (neat) 1641 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 0.85-0.92 (m, 15 H), 1.16-1.56 (m, 18 H), 1.84-2.16 (m, 4 H), 3.37-3.64 (m, 2 H), [4.02 (t, $J = 6.5$ Hz), 4.09 (dd, $J = 7.8, 5.8$ Hz), 1H], [4.54 (q, $J = 5.3$ Hz), 4.61 (q, $J = 5.3$ Hz), 1 H], 4.92-5.05 (m, 2 H), 5.75-5.92 (m, 1 H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 9.19, 13.62, 15.33, 15.37, 19.89, 20.42, 27.47, 29.18, 31.88, 32.19, 34.31, 35.11, 58.77, 60.14, 72.03, 72.85, 99.69, 99.90, 114.31, 114.38, 138.49, 138.56; HRMS calcd for $\text{C}_{17}\text{H}_{35}\text{O}_2\text{Sn}$ ($\text{M}^+ - \text{C}_4\text{H}_9$) 391.1658, found 391.1663.

Preparation of Acylstannane 24. Under an argon atmosphere, a 2.0 M solution of isopropylmagnesium chloride in Et_2O (10 mL; 20 mmol) was added at 0°C to galvinoxyl (168 mg, 0.40 mmol) dissolved in dry Et_2O (11 mL). The yellow solution was stirred at 0°C for 10 min, then tri-*n*-butyltin hydride (5.4 mL, 20 mmol) was added slowly. The reaction was warmed to rt and stirred for 2.5 h. A solution of 4-pentenal (4.0 g, 48 mmol) in dry Et_2O (15 mL) was added dropwise and after stirring at rt for 30 min, the yellow mixture was heated at reflux for 6 h. Upon cooling to 0°C , the mixture was

quenched with saturated NH_4Cl solution (30 mL), then warmed to rt and partitioned. The aqueous phase was extracted with Et_2O , and the combined organic extracts were washed with water and brine. The greenish-yellow solution was dried over MgSO_4 , filtered and concentrated *in vacuo*. Distillation under high vacuum (115–122 °C, 0.01 torr) gave acylstannane **24** (4.11 g, 11.0 mmol, 56%) as a green liquid. The product was stored immediately in a freezer under an argon atmosphere. The extremely unstable acylstannane decomposed during storage to give a white crystalline solid, but the clear green liquid portion could be drawn off *via* syringe for use in the next reaction.

Preparation of Hydroxystannane (S)-20. Under a nitrogen atmosphere, anhydrous ethanol (0.16 mL; 2.7 mmol) was added dropwise at rt to a suspension of lithium aluminum hydride (95%, 115 mg; 2.88 mmol) in dry THF (8 mL). The resulting grey suspension was stirred at rt for 10 min, then a solution of (*R*)-(+)-1,1'-bi-2,2'-naphthol (800 mg; $[\alpha]^{21}_{\text{D}} +34^\circ$ (*c* 1.00, THF); 2.79 mmol) in dry THF (5 mL) was added dropwise. After stirring for 45 min, the resulting BINAL solution was cooled to -78 °C for the slow addition of acylstannane **24** (330 mg; 0.884 mmol). The reaction was stirred at -78 °C for 4 h, then quenched with 0.6 N HCl (10 mL). Upon warming to rt, the biphasic solution was poured into a mixture of 0.6 N HCl (30 mL) and Et_2O (10 mL). The two phases were partitioned, the aqueous phase was extracted with Et_2O , and the combined organic layers were washed with water and saturated NaHCO_3 solution. The ether layers were then dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was triturated with hexanes to give solid binaphthol, which was filtered and rinsed with hexanes. The white solid binaphthol was recovered after recrystallization from Et_2O (90–95% was recovered; $[\alpha]^{24}_{\text{D}} +34.1^\circ$ (*c* 1.01, THF)). The filtrate was concentrated *in vacuo*, and FCC (5:1 hexanes- Et_2O) gave 158 mg of the desired α -hydroxystannane (*S*)-**20** as a colorless oil (0.421 mmol; 48%). Data for (*S*)-**20**: R_f 0.35 (5:1 hexanes- Et_2O); $[\alpha]^{24}_{\text{D}} -5.8^\circ$ (*c* 0.98, CHCl_3 , 86% ee); IR (neat) 3200–3500 (br), 1640 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 0.86–0.93 (m, 15 H), 1.24–1.57 (m, 12 H), 1.75–2.23 (m, 5 H), 4.10 (dd, $J = 9.1, 5.1$ Hz, 1 H), 4.94–5.09 (m, 2 H), 5.85 (ddt, $J = 17.2, 10.2, 6.9$ Hz, 1 H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 8.38, 13.51, 27.36, 29.12, 31.59, 37.50, 67.75, 114.51, 138.33; HRMS calcd for $\text{C}_{17}\text{H}_{35}\text{OSn}$ ($\text{M}^+ - \text{H}$) 373.1704, found 373.1688.

Preparation of Alkoxystannane 6(S)-21. To a solution of α -hydroxystannane (*S*)-**20** (1.65 g; 4.40 mmol) and *N,N*-dimethylaniline (1.2 mL; 9.5 mmol; 2.2 eq) in CH_2Cl_2 (12 mL; 0.37 M) that had been

cooled to -10°C was added α -chloroethyl ethyl ether (1.4 mL; ~ 12 mmol; ~ 2.2 eq) over a period of 5 min. The reaction mixture stirred at 0°C for 1 h and was quenched with water (15 mL). The layers were partitioned, and the aqueous phase was extracted with Et_2O . The combined organic layers were washed with 5% v/v aqueous HCl, water, and saturated NaHCO_3 and dried over Na_2SO_4 . Filtration and concentration gave a yellowish oil that was purified by FCC (100% hexanes) through silica gel that had been deactivated with a 3% Et_3N -hexanes solution to give 1.93 g (4.32 mmol; 98%) of the α -alkoxystannane **6(S)-21** as a colorless oil. Data for **6(S)-21**: R_f 0.62 (7:1 hexanes- Et_2O); IR (neat) 1641 cm^{-1} ; $^1\text{H NMR}$ (270 MHz, CDCl_3) δ 0.85-0.92 (m, 15 H), 1.16-1.56 (m, 18 H), 1.84-2.16 (m, 4 H), 3.37-3.64 (m, 2 H), [4.02 (t, $J = 6.5$ Hz), 4.09 (dd, $J = 7.8, 5.8$ Hz), 1 H], [4.54 (q, $J = 5.3$ Hz), 4.61 (q, $J = 5.3$ Hz), 1 H], 4.92-5.05 (m, 2 H), 5.75-5.92 (m, 1 H); $^{13}\text{C NMR}$ (67.5 MHz, CDCl_3) δ 9.19, 13.62, 15.33, 15.37, 19.89, 20.42, 27.47, 29.18, 31.88, 32.19, 34.31, 35.11, 58.77, 60.14, 72.03, 72.85, 99.69, 99.90, 114.31, 114.38, 138.49, 138.56; HRMS calcd for $\text{C}_{17}\text{H}_{35}\text{O}_2\text{Sn}$ ($\text{M}^+ - \text{C}_4\text{H}_9$) 391.1658, found 391.1663.

Preparation of Ylide 42.² To a suspension of methyltriphenylphosphonium bromide (5.3 g; 15 mmol; 2.2 eq) in THF (100 mL) at 0°C was added a 2.5 M solution of *n*-BuLi in hexanes (5.9 mL; 15 mmol; 2.2 eq). The resulting bright yellow solution was stirred for 30 min at 0°C before a solution of benzyloxyacetyl chloride (1.1 mL; 6.7 mmol; 1 eq) in THF (5 mL) was added dropwise. The reaction mixture became a milky orange color and was allowed to stir for 40 min at 0°C . The solvent was removed *in vacuo* to give an orange sludge which was stirred with ethyl acetate (200 mL) for about 20 min and filtered. The filtrate was washed with water, and the cloudy orange organic phase was dried over MgSO_4 , at which point it clarified. The orange-brown solution was concentrated to about 100 mL and placed in the freezer overnight to allow the product to crystallize. The supernatant liquid was decanted, and residual solvent was removed under reduced pressure (~ 0.25 mm Hg) to afford 1.65 g of **42** (3.89 mmol; 58%) as bright yellow crystals: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.04 (s, 2 H), 4.24 (d, $J_{\text{PH}} = 25.6$ Hz, 1 H), 4.68 (s, 2 H), 7.30-7.80 (m, 20 H).

Preparation of Ylide 44. A 2.48 M solution of *n*-butyllithium in hexanes (0.19 mL; 0.47 mmol; 1.5 eq) was added dropwise to a solution of 1-triphenylphosphoranylidene-2-propanone (100 mg; 0.314 mmol; recrystallized from benzene) in THF (1.6 mL; 0.20 M) that had been cooled to -60°C . The resulting deep red solution was stirred at this temperature for 10 min before an excess of allyl bromide (0.19 mL; 2.2

mmol; 7 eq) was added. The color slowly changed from red to orange, and when the solution was warmed to rt, it turned the characteristic yellow color of the chain extended ylide. After stirring at rt for 30 min, the reaction mixture was poured into water (10 mL). The aqueous phase was extracted with CH₂Cl₂, and the combined organic layers were washed with brine and dried over MgSO₄. Filtration and concentration *in vacuo* gave 100 mg (0.278 mmol; 90%) of **44** as a bright yellow solid which was used without further purification. Data for **44**: ¹H NMR (300 MHz, CDCl₃) δ 2.45 (s, 4 H), 3.71 (br d, *J*_{PH} = 22.2 Hz, 1 H), 4.96 (dd, *J* = 10.3, 2.5 Hz, 1 H), 5.13 (dd, *J* = 18.7, 2.5 Hz, 1 H), 5.92 (m, 1 H), 7.30-7.74 (m, 15 H).

References

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