Synthesis of (−)-Haliclonadiamine

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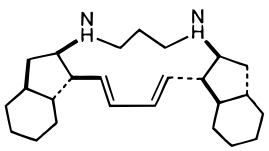
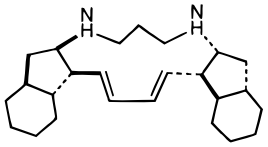
Abstract: Diastereoselective and enantioselective hydrogenation of the racemic β-keto ester **5** to give the enantiomerically pure (96% ee) ester **8** is reported. The conversion of the derived vinylstannane **11** to the antibiotic marine alkaloid (−)-haliclonadiamine (**1**) is described.

Introduction

(−)-Haliclonadiamine (**1**), a pentacyclic alkaloid isolated from the extract of a bright red encrusting marine sponge *Haliclona* sp.,[1] collected near Palau, shows antifungal and antibiotic activity. Its structure and relative configuration were established by 1- and 2-D NMR techniques and confirmed by X-ray analysis. The extract also contained papuamine (**2**), the epimer of **1**, which had previously been isolated from an extract of *Haliclona sp*.,[2] collected near Papua. We report the first stereocontrolled synthesis of (−)-haliclonadiamine (**1**).



1



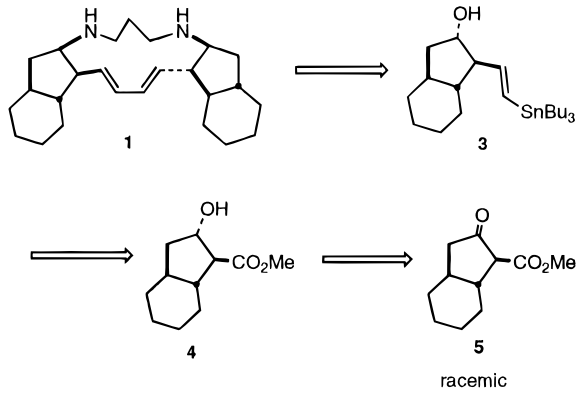
2

At the inception of our work, no synthesis of papuamine or haliclonadiamine had been reported.[3] Our retrosynthetic analysis (Scheme 1) focused on vinyl stannane **3**, which would have to be prepared in high enantiomeric and diastereomeric purity. We envisioned that **3** might be prepared from **4**, which in turn could be available by Ru−BINAP hydrogenation of the racemic β-keto ester **5**. We report here an expeditious synthesis of **5** and thus of **4** and a straightforward strategy for the diastereoselective coupling of **4** to make **1**.

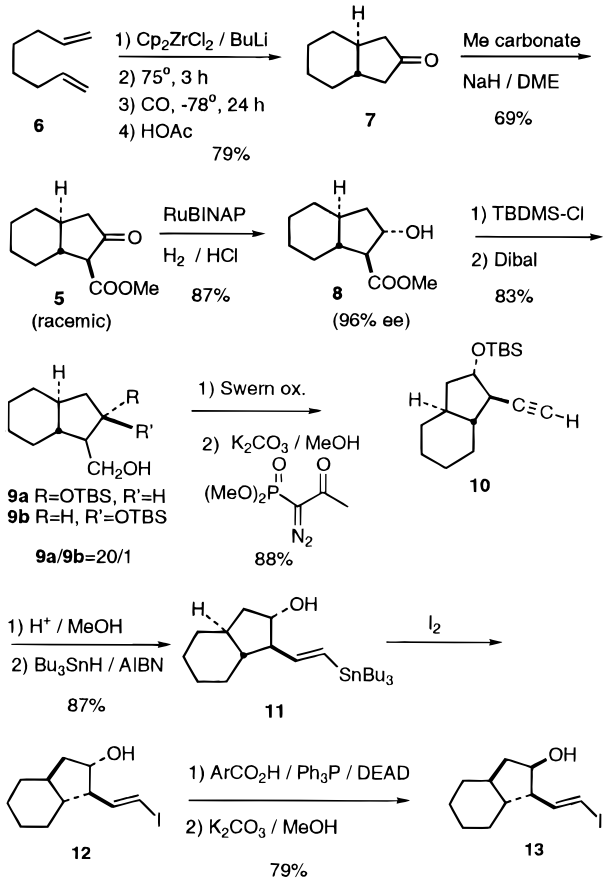
Results and Discussion

Construction of the Bicyclic β-Keto Ester 5. The key to the synthesis of **5** was the development of a facile entry to the trans-fused 6/5 ring system. We had earlier established, guided by computational analysis,[4] that under equilibrating conditions, cyclozirconation (Scheme 2) of the inexpensive 1,7-octadiene (**6**) proceeded to give cleanly the trans-fused diastereomer. By combining this procedure with those developed for carbonylation of such zirconacycles,[5] we were able to prepare the desired trans-fused ketone **7** in a single step from commercial starting materials. Carbomethoxylation of the symmetrical **7** then gave the racemic β-keto ester **5**.

Scheme 1



Scheme 2



[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1996.

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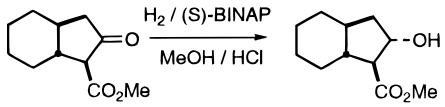
(2) Baker, B. J.; Scheuer, P. J.; Shoolery, J. N. *J. Am. Chem. Soc.* **1988**, *110*, 965.

(3) Three enantioselective syntheses of papuamine (**2**) have been reported; see: (a) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc., Chem. Commun.* **1994**, 1881. (b) Weinreb, S. M.; Borzilleri, R. M.; Parvez, M. *J. Am. Chem. Soc.* **1994**, *116*, 9789. (c) McDermott, T. S.; Mortlock, A.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 700. (−)-Haliclonadiamine was prepared as a byproduct in this synthesis of (−)-papuamine.

(4) Taber, D. F.; Louey, J. P.; Wang, Y.; Nugent, W. A.; Dixon, D. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 9457.

S0002-7863(96)02162-2 CCC: $14.00

Table 1. Hydrogenation of β-Keto Ester **5**[a]



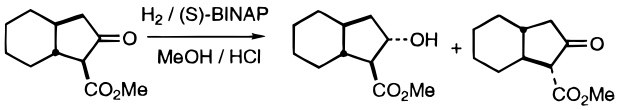
5 **4**

HCl (mol %)	conversion (%) (of racemate)	e of desired diastereomer (%)
13.0	98.4	44.7
9.5	43.5	96
8.1	33.0	100
6.2	29.9	100

[a] Hydrogenation pressure, 52 psi; temperature, 80−85 °C; time, 14 h; HCl, methanolic HCl; $RuCl_2$−BINAP, 1.2 mol %.

Kinetic Resolution by Catalytic Hydrogenation. With the racemic β-keto ester **5** in hand, we were then faced with the problem of carrying it on to the enantiomerically pure and diastereomerically defined β-hydroxy ester **4**. We thought that this might be accomplished by kinetic resolution under the conditions of Ru−BINAP hydrogenation.[6,7]

The reduction was known[6,7] to give predominantly the *trans*-β-hydroxy ester when applied to a cyclic β-keto ester. This reduction is thought to proceed by complexation of the intermediate Ru-H species with the ester carbonyl with subsequent delivery of the nucleophilic H to the ketone. As one enantiomer of the β-keto ester would fit the twist of the BINAP ligand and the other would not, we thought that one enantiomer of the ketone might reduce much more rapidly than the other. Kinetic resolution in this manner had been reported[8] but not with good diastereocontrol.



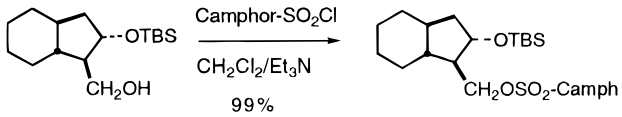
5 **4** **14**

In the event (Table 1), we found that the racemic β-keto ester **5** only hydrogenated smoothly in the presence of added HCl.[8] By optimizing the amount of HCl added, we could control the proportion of total ketone reduced. We were pleased to observe that we could convert *nearly 90%* of the "matched" ketone without significant reduction of the other enantiomer. It is interesting that if too much HCl is added initially, the (*S*)-BINAP−$RuCl_2$ will reduce the mismatched enantiomer also, to a mixture of diastereomers.

The catalyst turnover reported in these studies is lower by an order of magnitude than that previously observed.[6−8] We do not believe that this limitation is inherent. The reactions were optimized originally at the half millimole scale, and the amount of catalyst used was convenient at that scale.

The diastereoselectivity of the hydrogenation depends on the particular acid promoter[8] employed. With HCl, the trans diastereomer was dominant. With acetic acid as the promoter, the reaction was still fast, but the major product from the reduction was the cis diastereomer.

Establishment of the Enantiomeric Purity of 9a. Silylation of the hydroxy ester **4** followed by reduction gave the primary alcohols **9a,b**. The minor amount of **9b**, from the cis alcohol produced in the reduction, was removed at this stage. To establish the enantiomeric purity of **9a**, we prepared the camphorsulfonate **15**. The camphorsulfonate prepared from the racemic trans alcohol (from sodium borohydride reduction of the starting β-keto ester) showed nice resolution of the oxygenated carbons in the ^{13}C NMR (δ 74.0/73.8 and 70.0/69.9). By this measurement, **9a** was a 98:2 ratio of enantiomers.



9a **15**

Construction of the Iodo Stannane 18. Following this procedure, we were able to prepare alcohol **9a** in high enantiomeric and diastereomeric purity in just five steps from 1,7-octadiene (**6**). To move on to the haliclonadiamine precursor **18**, we had to homologate the primary alcohol of **9a** to the (*E*)-vinylstannane. We also had to construct the *N*,*N*′-diaminopropane from two equivalents of the secondary diol, with inversion of absolute configuration in one case and with retention (probably double inversion) in the other.

To effect homologation, alcohol **9a** was oxidized to the aldehyde, which was subjected without purification to the Ohira procedure[9] to give the alkyne **10**. Our experience has been that this simple procedure, which can be effected at ambient temperature, uses easily available reagents, and is not sensitive to stoichiometry, is in general the method of choice for this common transformation. Deprotection of **10** followed by radical addition of tributyltin hydride[10] then provided an 87% yield of the (*E*)-vinylstannane **11**.

We next faced the difficulty of inverting the hindered secondary alcohol of **11**. To this end, we converted a portion of the stannane **11** that we had prepared to the iodide **12**. As expected, Mitsunobu coupling[12] with 4-nitrobenzoic acid initially was sluggish. We were pleased to observe that substitution of benzene for THF as the reaction medium solved this problem. Mild transesterification then liberated the desired cis alcohol **13**, in 75% overall yield from the iodide **12**.

The final challenge that we faced was construction of the *N*,*N*′-dialkyl 1,3-diaminopropane of **18** (Scheme 3). It seemed plausible that Mitsunobu coupling could again be efficacious. The key to this approach was the selection of an activating group that would make the N-H sufficiently acidic to participate in the Mistsunobu reaction while leaving the anion sufficiently

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(6) For the first report of the reduction of Ru−BINAP-mediated hydrogenation of β-keto esters to provide the β-hydroxy esters with excellent yield and enantioselectivity, see: Noyori, R.; Ohkuma, T.; Kitamura, M. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

(7) For further studies of Ru−BINAP-mediated hydrogenation of β-keto esters, see: (a) Cesarotti, E.; Mauri, A.; Pallavicini, M.; Villa, L. *Tetrahedron Lett.* **1991**, *32*, 4381. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163. (c) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Org. Chem.* **1992**, *57*, 4053. (d) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227. (e) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689. (f) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144. (g) Genet, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Cano De Andrade, M. C.; Laffitte, J. A. *Tetrahedron* **1994**, *5*, 665. (h) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064. (i) Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423.

(8) (a) For the role of added acid in Ru−BINAP hydrogenation, see ref 7d,e. (b) The procedure described here represents a significant improvement over that previously described for kinetic resolution of a bicyclic β-keto ester: Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron: Asymmetry* **1990**, *1*, 1.

(9) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

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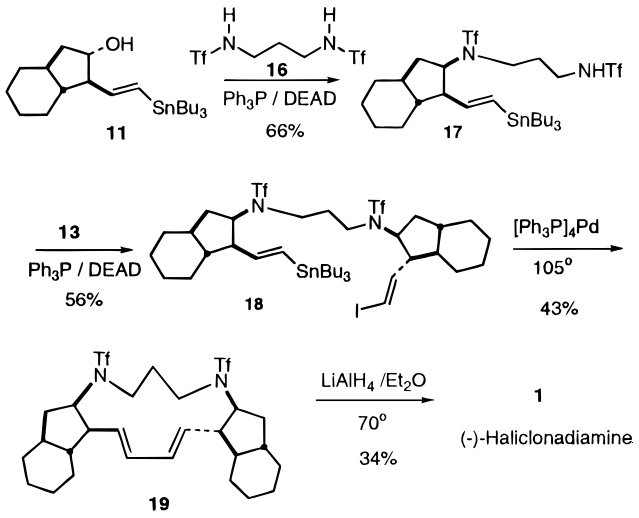
(12) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (b) Caine, D.; Kotian, P. L. *J. Org. Chem.* **1992**, *57*, 6587.

Scheme 3



nucleophilic. The activating group should also be easily removed. We found that the *N*,*N*′-bistriflamide nicely met these criteria.[13] While the Mitsunobu coupling again worked poorly in THF, reaction of **11** in benzene with two equivalents of *N*,*N*′-bistriflyl-1,3-diaminopropane (**16**) gave clean conversion to the monoalkylated diamide **17**. The final Mitsunobu coupling of **17** with **13** also proceeded smoothly in benzene, to give the desired *N*,*N*′-dialkylated diamide **18**.

Synthesis of (−)-Haliclonadiamine (1). With the iodo stannane **18** in hand, the final assembly of (−)-haliclonadiamine (**1**) was straightforward (Scheme 3). Thus, following the report by Barrett[3a] in the synthesis of (+)-papuamine, slow addition of **18** to 20 mol % of $Pd(PPh_3)_4$ at 100−105 °C in toluene followed by 36 h at reflux gave the cyclized product **19** in 43% yield. Deprotection of the bistriflamide **19** with $LiAlH_4$ in ether[14] ($LiAlH_4$ in THF was not effective) then gave the free base of (−)-haliclonadiamine (**1**). The ^{1}H NMR, ^{13}C NMR, and MS of synthetic **1** were identical with the spectra of natural (−)-haliclonadiamine.[1] The ^{1}H NMR was also identical with that recorded for a synthetic sample.[3c]

Conclusion

During the course of this total synthesis of the unusual marine alkaloid (−)-haliclonadiamine (**1**), an efficient diastereoselective preparation of the *β*-keto ester **5** via intramolecular diene cyclozirconation and carbonylation was developed. The diastereoselective and enantioselective Ru−BINAP-mediated hydrogenation of *β*-keto ester **5** to the *β*-hydroxy ester **4** was also achieved. Finally, the sequential Mitsunobu coupling with bistriflamide **16** as the nucleophile proved very efficient even with the sterically hindered secondary alcohols **11** and **13**.

Experimental Section[15]

***β*-Keto Ester 5.** To 1,7-octadiene (11.52 g, 0.105 mol) and zirconocene dichloride (36.7 g, 0.125 mol) in toluene (250 mL) was added *n*-BuLi (1.99 M, 126 mL) via syringe at −78 °C over 30 min under argon. The resulting light yellow mixture was stirred at room temperature and then warmed to 75−80 °C for 3 h. After cooling to room temperature, the dark brown reaction mixture was further cooled with liquid N_2 and evacuated to about 0.001 mmHg. The solidified reaction mixture was maintained at −78 °C, and CO was charged into the reaction container so that the pressure of CO was kept at 1.1−1.2 atm for 1 h, until no obvious CO absorbance was observed. The reaction mixture was warmed to room temperature and stirred 12 h. HOAc (25.1 mL) was added to the dark reaction mixture. The resulting yellow solution was stirred at room temperature for 30 min; then the reaction was quenched with 10% aqueous H_2SO_4. The mixture was extracted with 20% EtOAc/petroleum ether. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was distilled to give 11.5 g (79% yield) of the ketone **7**: $bp_{0.05mmHg}$ = 80−90 °C (pot); ^{1}H NMR *δ* 2.44−2.28 (m, 2 H), 2.05−1.02 (m, 12 H); ^{13}C NMR *δ* 218.3 (C), 45.6 (CH_2), 43.9 (CH), 31.3 (CH_2), 26.1 (CH_2).

To a suspension of NaH (60% in mineral oil, 579 mg, 14.5 mmol) in DME (8 mL) containing a trace of methanol was added dimethyl carbonate (978 mg, 10.9 mmol). The mixture was heated to reflux for 10 min, then the bicyclic cyclopentanone **7** (500 mg, 3.62 mmol) was added over two h. The reaction mixture at maintained at reflux overnight, then was quenched with HOAc (1.0 mL) and partitioned between H_2O and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), concentrated and chromatographed to give 489 mg (55% yield from 1,7-octadiene) of the *β*-keto ester **5**: TLC R_f = 0.34 (10% EtOAc/petroleum ether); ^{1}H NMR *δ* 3.72 (s, 3 H), 2.84 (d, J = 12.4 Hz, 1 H), 2.42 (dd, J = 17.9, 6.7 Hz, 1 H), 2.03−1.16 (m, 11 H); ^{13}C NMR *δ* u 210.1, 169.5, 44.9, 31.1, 30.2, 26.0, 25.8; d 61.7, 52.2, 47.3, 41.0; IR (neat) (cm^{-1}) 1759, 1728, 1436; MS (CI) *m*/*z* 196 (M^+, 11), 168 (58), 94 (100). HRMS: *m*/*e* calcd for $C_{11}H_{17}O_3(MH^+)$, 197.1178; found, 197.1177.

BINAP−$RuCl_2$. A 5 mL reactivial equipped with a stir vane was charged with $(RuCl_2$−cyclooctadiene$)_n$ (39 mg), (*S*)-(−)-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (100 mg), triethylamine (200 mg), and toluene (4 mL) in the dry box. The vial was capped securely and then heated in a 140−145 °C oil bath for 3 h, until a clear red solution was achieved. The contents of the vial were transferred with toluene to a 100 mL round-bottom flask under nitrogen. The reaction mixture was concentrated *in vacuo* under the Schlenk line, and the residue was taken up in THF (10 mL) in the dry box. The brown THF solution was divided into 10 × 1 mL portions, which were stored in stoppered vials under N_2.

Hydroxy Ester 8. Under N_2, a modified Parr bottle equipped with a stir bar was charged with racemic bicyclic *β*-keto ester **5** (250 mg, 1.28 mmol), methanol (1.65 mL), BINAP−$RuCl_2$ as prepared above (0.5 mL, from 5 mg of BINAP), and 1.35 mL (0.162 mmol) of a 0.12 N HCl−methanol solution (prepared by dissolving 1.0 mL of concentrated aqueous HCl in 99 mL of methanol). The bottle was flushed with hydrogen for 5 min, and hydrogenation was then carried out at 50−52 psi of H_2 for 14 h in an 80−85 °C oil bath. The reaction mixture was concentrated *in vacuo* and chromatographed to give 132 mg of residual *β*-keto ester and 110 mg (87% of theory) of the product hydroxy ester **8** as a colorless oil, which subsequent analysis showed to be 96% ee: TLC R_f = 0.19 (10% EtOAc/petroleum ether); ^{1}H NMR *δ* 4.48 (m, 1 H), 3.71 (s, 3 H), 2.75 (s, br, 1 H), 2.33 (dd, J = 11.1, 5.1 Hz, 1 H), 1.95−0.98 (m, 12 H); ^{13}C NMR *δ* u 175.3, 41.0, 31.4, 30.5, 25.9 (2); d 75.0, 59.9, 51.6, 49.2, 43.8; IR (neat) (cm^{-1}) 3445, 1733; MS (CI) *m*/*z* 199 (M^+ + H, 1), 170 (80), 74 (100). HRMS: *m*/*e* calcd for $C_{11}H_{19}O_3(MH^+)$, 199.1334; found, 199.1328.

Protected Diol 9. A mixture of the hydroxy ester (581 mg, 2.93 mmol), imidazole (999 mg, 14.7 mmol), and *tert*-butyldimethylsilyl chloride solution (2.0 M in CH_2Cl_2, 2.2 mL, 4.40 mmol) in dry CH_2Cl_2 (14 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give 920 mg of the silyl ether ester (99%) as a colorless oil: TLC R_f = 0.80 (10% EtOAc/petroleum ether); ^{1}H NMR *δ* 4.42 (m, 1 H), 3.85 (s, 3 H), 2.30 (dd, 1 H), 2.90−1.42 (m, 6 H), 1.35 (m, 4 H), 0.90 (s, 9 H), −0.02 (s, 6 H); ^{13}C NMR *δ* 175.75; IR (neat) (cm^{-1}) 2927, 2855, 2361, 1735; MS (EI) *m*/*z* 312 (M^+, 1), 255 (69), 89 (100). HRMS: *m*/*e* calcd for $C_{17}H_{31}O_3Si$ (M^+), 312.2042; found, 312.2056.

Dibal-H (1.0 M solution in CH_2Cl_2, 1.64 mL) was added dropwise via syringe to the solution of the silyl ether ester (170 mg, 0.545 mmol) in CH_2Cl_2 (5 mL) at −78 °C over 15 min. The reaction mixture was

(13) After this work was completed, an independent report of efficient Mitsunobu coupling of an alkyl triflamide appeared; see: Bell, K. E.; Knight, D. W.; Gravestock, M. B. *Tetrahedron Lett.* **1995**, *36*, 8681.

(14) (a) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett*. **1973**, 3839. (b) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. *J. Am. Chem. Soc.* **1973**, *95*, 3412.

(15) For general experimental procedures, see: Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004.

stirred at −78 °C for 1 h and then partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give 117 mg of trans-monoprotected diol **9a** (76% yield) and 6 mg (3.9%) of cismonoprotected diol **9b**.

9a: TLC $R_f = 0.53$ (10% EtOAc/petroleum ether); ^{1}H NMR δ 4.08 (m, 1 H), 3.75 (dd, $J = 10.5$, 4.6 Hz, 1 H), 3.65 (m, 1 H), 1.86−0.91 (m, 13 H), 0.88 (s, 9 H), 0.059 (s, 3 H), 0.055 (s, 3 H); ^{13}C NMR δ u 63.7, 41.4, 31.7, 30.4, 26.3, 26.2, 18.0; d 75.8, 56.9, 46.5, 43.9, 25.8, −4.4, −4.8; IR (neat) (cm^{-1}) 3359, 1471, 1446; MS (EI) *m*/*z* 269 (M^+ − Me, 1), 135 (90), 75 (100); HRMS: *m*/*e* calcd for $C_{16}H_{33}O_2Si$ (MH^+), 285.2250; found, 285.2255.

9b: TLC $R_f = 0.65$ (10% EtOAc/petroleum ether); ^{1}H NMR δ 4.38 (dd, $J = 13.4$, 7.1 Hz, 1 H), 3.85 (ddd, $J = 3.0$, 2.9, 11.5 Hz, 1 H), 3.61 (m, 1 H), 2.90 (dd, $J = 9.6$, 3.3 Hz, 1 H), 2.20−2.10 (m, 1 H), 1.92−0.98 (m, 11 H), 0.88 (s, 9 H), 0.059 (s, 3 H), 0.055 (s, 3 H).

Camphorsulfonate Derivative 15. To the trans monoprotected diol **9a** (5 mg, 0.0176 mmol) and triethylamine (5.3 mg, 0.0528 mmol) in CH_2Cl_2 (1 mL) was added (1*S*)-camphorsulfonyl chloride (6.6 mg, 0.0264 mmol). The mixture was stirred at room temperature for 24 h and then concentrated. The residue was chromatographed to give 8.5 mg (99%) of product **15**: TLC $R_f = 0.72$ (5% petroleum ether/*tert*-butyl methyl ether/CH_2Cl_2 = 8/2/1).

Racemic derivative: ^{1}H NMR δ 4.31 (m, 2 H), 4.06 (m, 1 H), 3.07 (d, $J = 15.0$ Hz, 1 H), 2.95 (d, $J = 15.0$ Hz, 1 H), 2.54−2.8 (m, 1 H), 2.12−0.90 (m, 19 H), 1.14 (s, 3 H), 0.88 (s, 9 H), 0.059 (s, 3 H), 0.055 (s, 3 H); ^{13}C NMR δ u 214.4, **70.0 + 69.9 (1:1)**, 57.9, 47.9, 46.6, 42.6, 41.6, 31.5, 30.2, 26.9, 26.2, 26.1, 24.9 (CH_2), 19.9, 17.9; d **74.0 + 73.8 (1:1)**, 54.5, 46.8, 43.6, 42.8, 25.8, 19.9, 19.7, −4.8, −4.8.

Enantiomerically enriched derivative: ^{1}H NMR δ 4.34 (dd, $J =$ 9.7, 4.6 Hz, 1 H), 4.25 (dd, $J = 9.7$, 5.1 Hz, 1 H), 3.07 (d, $J = 15.0$ Hz, 1 H), 2.95 (d, $J = 15.0$ Hz, 1 H), 2.54−2.8 (m, 1 H), 2.12−0.90 (m, 19H), 1.14 (s, 3H), 0.88 (s, 9H), 0.059 (s, 3H), 0.055 (s, 3H); ^{13}C NMR δ u 214.4, **70.0 + 69.9 (98:2)**, 57.9, 47.9, 46.6, 42.6, 41.6, 31.5, 30.2, 26.9, 26.2, 26.1, 24.9 (CH_2), 19.9, 17.9; d **74.0 + 73.8 (98:2)**, 54.5, 46.8, 43.6, 42.8, 25.8, 19.9, 19.7, −4.8, −4.8; IR (neat) (cm^{-1}) 1750, 1700, 1653, 1558.

Protected Alkyne 10. DMSO (441 mg, 5.65 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to a solution of oxalyl chloride (388 mg, 3.06 mmol) in CH_2Cl_2 (3 mL) at −78 °C. After 10 min, the alcohol **9a** (668 mg, 2.35 mmol) in CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred at −78 °C for 1 h and then warmed to −50 °C. Triethylamine (1.19 g, 11.76 mmol) was added, the ice bath was removed, and the mixture was allowed to warm to room temperature for 5 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and concentrated *in vacuo* to provide a light yellow syrup.

To the crude aldehyde in anhydrous methanol (10 mL) were added dimethyl (1-diazo-2-oxopropyl)phosphonate (903 mg, 4.70 mmol) and K_2CO_3 (811 mg, 5.88 mmol) successively at 0 °C. The reaction mixture was gradually warmed to room temperature overnight and then partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give 553 mg (85% from alcohol **9a**) of the alkyne product **10**. TLC $R_f = 0.52$ (10% EtOAc/petroleum ether); ^{1}H NMR δ 4.23 (m, 1 H), 2.09 (d, $J = 1.8$ Hz, 1 H), 2.18−0.98 (m, 13 H), 1.04 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR δ u 86.6, 69.4, 41.8, 31.5, 30.0, 26.0, 25.9, 18.1; d 78.9, 72.3, 51.9, 46.8, 43.4, 25.9, −4.5, −4.8; MS (EI) *m*/*z* 278 (1), 221 (100), 145 (27). HRMS*m*/*z* calcd for $C_{17}H_{30}OSi$, 278.2066; found, 278.2059.

Vinylstannane 11. The mixture of starting material **10** (180 mg, 0.79 mmol) and Dowex-50 sulfonic acid resin (1.0 g) in methanol (5 mL) was stirred at room temperature overnight. The reaction mixture was filtered, and the solid was washed thoroughly with methanol. The filtrate was concentrated *in vacuo*, and the residue was chromatographed to give 122 mg (95% yield) of the deprotected hydroxy alkyne: TLC $R_f = 0.52$ (10% EtOAc/petroleum ether); ^{1}H NMR δ 4.30 (m, 1 H), 2.12−0.91 (m, 16 H).

To a solution of the hydroxy alkyne (188 mg, 1.15 mmol) and AIBN (10 mg) in toluene (3 mL) was added Bu_3SnH at room temperature under argon. The reaction mixture was heated at 100−105 °C for 3 h and then stirred at room temperature overnight. The reaction mixture was concentrated and chromatographed to give 425 mg (87% yield) of the vinylstannane product **11** as a mixture of isomers (*E*:*Z* = 16:1): TLC $R_f = 0.57$ (10% EtOAc/petroleum ether); $[\alpha]_D = 5.4°$ ($c = 0.0075$, CH_2Cl_2); ^{1}H NMR δ 5.92 (d, $J = 18.8$ Hz, 1 H), 5.79 (dd, $J = 18.8$, 7.1 Hz, 1 H), 4.05 (m, 1 H), 2.02−0.77 (m, 40 H); ^{13}C NMR δ u 40.8, 31.8, 30.0, 29.1, 27.2, 26.4, 26.3, 9.5; d 150.3, 128.8, 77.7, 64.4, 50.8, 43.8, 13.6; IR (neat) (cm^{-1}) 3332, 2595; MS (EI) *m*/*z* 455 (1), 399 (100), 177 (25). HRMS: *m*/*e* calcd for $C_{19}H_{35}OSn$ (M^+ − Bu), 399.1709. found, 399.1717.

Vinyl Iodide 12. To a solution of the vinylstannane **11** (135 mg, 0.30 mmol) in Et_2O (2 mL) was added iodine (83 mg, 0.33 mmol). After 30 min, the reaction mixture was partitioned between Et_2O (20 mL) and 10% aqueous $Na_2S_2O_3$. The combined organic extract was dried (Na_2SO_4), concentrated and chromatographed to give 83 mg (96% yield) of the vinyl iodide **12** as a colorless oil. TLC $R_f = 0.29$ (5% EtOAc/petroleum ether); $[\alpha]_D = -36.4°$ ($c = 0.006$, CH_2Cl_2); ^{1}H NMR δ 6.41 (dd, $J = 13.9$, 9.0 Hz, 1 H), 6.06 (d, $J = 13.9$ Hz, 1 H), 4.06 (m, 1 H), 2.02−1.94 (m, 1 H), 1.91−0.88 (m, 12 H); ^{13}C NMR δ u 40.8, 31.6, 29.7, 26.1, 26.0; d 147.6, 143.1, 76.8, 62.5, 50.3, 43.4; IR (neat) (cm^{-1}) 3332, 1602, 1446; MS (EI) *m*/*z* 292 (3), 165 (15), 147 (42), 76 (100). HRMS: *m*/*e* calcd for $C_{11}H_{17}O_1I$ (M^+), 292.0324. found, 292.0358.

Inverted Hydroxy Vinyl Iodide 13: To the vinyl iodide **12** (45 mg, 0.15 mmol), triphenylphosphine (201 mg, 0.77 mmol), and 4-nitrobenzoic acid (113 mg, 0.68 mmol) in benzene (3 mL) was added DEAD (134 mg, 0.77 mmol) dropwise via syringe. The reaction mixture was stirred at room temperature for 14 h and then concentrated and chromatographed to give 55 mg (82%) of the 4-nitrobenzoate product as a white foam: TLC $R_f = 0.75$ (5% EtOAc/petroleum ether); ^{1}H NMR δ 8.28 (d, $J = 9.0$ Hz, 2 H), 8.14 (d, $J = 9.0$ Hz, 2 H), 6.52 (dd, $J = 14.5$, 8.9 Hz, 1 H), 6.11 (d, $J = 14.5$, 1 H), 5.45 (dt, $J = 7.4$, 4.5 Hz, 1 H), 2.56−2.45 (m, 1 H), 2.36−2.35 (m, 1 H), 1.92−1.77 (m, 4H), 1.54−0.86 (m, 7H); ^{13}C NMR δ u 165.1, 135.9, 129.0, 39.2, 31.6, 29.8, 26.2, 26.0; d 143.5, 130.6, 130.5, 129.0, 123.6, 76.9, 54.5, 48.6, 44.0.

A mixture of 4-nitrobenzoate (40 mg, 0.091 mmol) and anhydrous K_2CO_3 (0.182 mmol) in methanol (4 mL) was stirred for 24 h. The reaction mixture was concentrated, then partitioned between 50% EtOAc/petroleum ether and water. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give 25 mg (96%) of the desired vinyl iodide **13** as a white foam: TLC $R_f = 0.43$ (10% EtOAc/petroleum ether). $[\alpha]_D = -72.0°$ ($c =$ 0.0058, CH_2Cl_2); ^{1}H NMR δ 6.58 (dd, $J = 14.5$, 9.2 Hz, 1 H), 6.05 (d, $J = 14.5$ Hz, 1 H), 4.26 (m, 1 H), 2.30 (m, 1 H), 2.04−1.97 (m, 1 H), 1.85−1.71 (m, 4H), 1.58−0.80 (m, 7H); ^{13}C NMR δ u 41.5, 32.7, 29.9, 26.4, 26.1; d 145.1, 128.3, 73.1, 57.9, 47.6, 44.3; MS (EI) *m*/*z* 292 (M^+, 1), 147 (40), 76 (100). HRMS: *m*/*e* calcd for $C_{11}H_{17}O_1I$ (M^+), 292.0324; found, 292.0348.

***N,N′*-Bistriflyl-1,3-diaminopropane (16)**. To the mixture of 1,3-diaminopropane (200 mg, 2.70 mmol) and Et_3N (1.09 g, 10.8 mmol) in CH_2Cl_2 (5 mL) was added triflic anhydride (1.60 g, 5.68 mmol) at −78 °C over 5 min. The mixture was stirred at −78 °C for 1 h; then the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture partitioned between CH_2Cl_2 and water. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give 674 mg of **16**: TLC $R_f = 0.12$ (10% EtOAc/petroleum ether); ^{1}H NMR δ 5.45 (bs, 2 H), 3.45 (t, $J = 6.8$ Hz, 4 H), 1.90 (m, 2 H); ^{13}C NMR δ 119.6 (CF_3, $J = 318$ Hz), u 40.5, 31.1; MS (EI) *m*/*z* 338 (1), 162 (55), 69 (100).

Vinylstannane Bistriflamide 17. To the vinylstannane **11** (133 mg, 0.29 mmol), *N*,*N′*-bistriflyl-1,3-diaminopropane (**16**) (194 mg, 0.58 mmol), and triphenylphosphine (191 mg, 0.73 mmol) in benzene (3 mL) was added DEAD (127 mg, 0.73 mmol) via syringe dropwise at room temperature. The reaction mixture was stirred at room temperature for 20 h and then concentrated. The residual syrup was taken up in ether (5 mL), and the suspension was filtered to remove the white precipitate. The filtrate was concentrated and chromatographed to give 74 mg (66%) of the desired product **17** as a colorless oil: TLC $R_f =$ 0.69 (10% EtOAc/petroleum ether); $[\alpha]_D = 15.2°$ ($c = 0.0025$, CH_2Cl_2); ^{1}H NMR δ 6.07 (d, $J = 19.0$ Hz, 1 H), 5.86 (dd, $J = 7.0$, 19.0 Hz, 1 H), 5.03 (m, 1 H), 4.31 (m, 1 H), 3.54−3.13 (m, 6H), 2.38 (m, 1 H), 2.20−0.80 (m, 39H); ^{13}C NMR δ 119.5 (CF_3, $J = 325$ Hz); u

41.7, 31.2, 30.8, 30.6, 29.3, 29.1, 29.0, 28.9, 27.3, 26.1, 26.0, 9.4; d 145, 133.6, 50.4, 43.2, 13.6; MS (EI) *m*/*z* 455 (1), 399 (100), 285 (17). HRMS: *m*/*e* calcd for $C_{19}H_{35}OSn$ (M^+ − Bu); 397.1704; found, 397.1704.

Iodo Stannane 18. To the mixture of vinylstannane **17** (20 mg, 0.026 mmol), inverted iodo alcohol **13** (7.5 mg, 0.026 mmol), and triphenylphosphine (8.5 mg, 0.032 mmol) in benzene (0.75 mL) was added DEAD (5.6 mg, 0.032 mmol) dropwise via syringe at room temperature. The reaction mixture was stirred for 28 h and then concentrated and chromatographed to give 2.5 mg (13%) of the recovered vinyl stannane starting material and 15 mg (56% yield based on starting material not recovered) of product **18** as a white foam: TLC R_f = 0.82 (10% EtOAc/petroleum ether); $[\alpha]_D$ = 9.2° (*c* = 0.004, CH_2Cl_2); ^{1}H NMR δ 6.31 (dd, *J* = 14.6, 8.63 Hz, 1 H), 6.15 (d, *J* = 14.6 Hz, 1 H), 6.08 (d, *J* = 19.0 Hz, 1 H), 5.85 (dd, *J* = 19.0, 6.82 Hz, 1 H), 4.36 (m, 1 H), 3.42−2.82 (m, 6 H), 2.40−0.92 (m, 44 H), 0.87 (t, *J* = 7.20 Hz, 9 H); ^{13}C NMR δ 119.5 (CF_3, *J* = 320 Hz); u 60.4, 43.4, 31.5, 31.2, 30.7, 29.4, 29.1, 29.0, 27.3, 26.9, 26.2, 26.0, 25.9, 25.6, 21.0, 9.5; d 145.5, 133.2, 115.8, 64.0, 62.6, 60.4, 56.4, 54.9, 50.3, 49.1, 44.8, 43.4, 43.2, 13.7; IR (neat) (cm^{-1}) 1653, 1457, 1383; MS (EI) *m*/*z* 1049 (M^+, 1), 993 (100), 179 (64).

Bistriflylhaliclonadiamine 19. To a solution of $(PPh_3)_4Pd$ (8.4 mg, 0.0082 mmol) in toluene (20 mL) under argon was added one-twentieth of iodo stannane **18** (36 mg, 0.036 mmol) in toluene (5.0 mL), and the mixture was heated to 100−105 °C in the dark. The remaining solution of **18** was added over 6 h via syringe pump. The reaction mixture was maintained at 100−105 °C for 2 h, and additional $(PPh_3)_4Pd$ (4.2 mg, 0.0041 mmol) was added. The resulting mixture was maintained at 100−105 °C for 14 h in the dark and then cooled to room temperature. The mixture was filtered through Celite, washing thoroughly with EtOAc. The combined filtrate was concentrated and chromatographed to give 9.5 mg (43%) of the cyclized product **19** as a white foam: TLC R_f = 0.57 (4% EtOAc/petroleum ether); $[\alpha]_D$ = −7.8° (*c* = 0.005, CH_2Cl_2); ^{1}H NMR δ 6.19 (d, *J* = 14.7 Hz, 2 H), 5.51−5.45 (m, 2 H), 5.22 (m, 1 H), 4.36 (m, 1 H), 3.37−3.11 (m, 4 H), 2.59−2.52 (m, 2 H), 2.15−0.80 (m, 26 H); ^{13}C NMR δ 120.2 (CF_3, *J* = 320 Hz); u 65.3, 64.0, 39.7, 34.4, 31.9, 31.5, 31.0, 30.5, 29.7, 29.5, 29.4, 28.4, 26.4; d 1345, 127.5, 125.2, 124.2, 65.2, 52.2, 49.5, 47.6, 43.8, 43.0, 42.9, 30.0; MS (EI) *m*/*z* 632 (20), 499 (95), 191 (100).

(−)-Haliclonadiamine (1). In a 1 mL reactivial, $LiAlH_4$ (1.0 M in Et_2O, 0.5 mL, 0.5 mmol) was added to a solution of **19** (3.0 mg, 3.1 μmol) in Et_2O (0.2 mL), and the mixture was heated (sealed tube, 70 °C) for 4 days. The reaction mixture was cooled to 0 °C, and then saturated aqueous sodium potassium tartrate solution (2 drops) was added. The reaction mixture was heated to reflux for 1 h and then was cooled to room temperature and filtered with EtOAc. The combined organic was concentrated *in vacuo*. The residue was purified by reverse phase HPLC to give 0.6 mg (34% yield) of **1**: TLC R_f = 0.30 (CH_2Cl_2/MeOH/35% NH_4OH = 87/12/1); ^{1}H NMR δ 6.25−6.18 (m, 1 H), 6.14−6.06 (m, 1 H), 5.58−5.50 (m, 1 H), 5.35−5.28 (m, 1 H), 3.20−2.90 (m, 2 H), 2.65−1.90 (m, 6 H), 1.90−0.98 (m, 26 H); ^{13}C NMR δ 134.0, 133.9, 132.5, 132.0, 68.2, 62.6, 60.1, 51.5, 51.2, 49.6, 48.7, 47.1, 44.8, 44.0, 41.0, 37.0, 32.25, 32.19, 31.6, 30.5, 30.1, 26.8, 26.5, 26.34, 26.31; MS (CI) *m*/*z* 369 (12), 279 (4), 185 (100). HRMS (CI): *m*/*e* calcd for $C_{25}H_{40}N_2$ (M^+): 368.3191; found, 368.3177.

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