Total Syntheses of (−)-Papuamine and (−)-Haliclonadiamine

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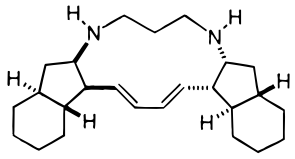
The pentacyclic marine alkaloids (−)-papuamine (**1**) and (−)-haliclonadiamine (**2**) have been prepared by total synthesis. The synthesis began with (−)-**8**, which was converted into diester **20** by way of bis-mesylate **17**, dinitrile **18**, and diacid **19**. Dieckmann cyclization of **20** provided keto ester **21**, which was transformed into acetal **22**. After hydrolysis of the acetal, ketone **25** was subjected to reductive amination with 1,3-propanediamine and sodium triacetoxyborohydride to obtain diamines **26** and **27** as a 71:29 mixture of diastereomers, favoring the symmetrical isomer having the papuamine relative configuration. After transformation of the diamines to their *t*-Boc derivatives, the benzyl ethers were cleaved and the resulting diol was oxidized to dialdehyde **30**. Application of the Seyferth procedure for conversion of aldehydes to alkynes gave a mixture of diynes **31** and **32**. After removal of the *t*-Boc protecting groups from **31**, diamino diyne **15** was treated with tributylstannane and azoisobutyronitrile to obtain the bis-vinylstannane **34**. Treatment of this compound with Pd(II) and Cu(I) in the presence of air produced (−)-papuamine (**1**). (−)-Haliclonadiamine (**2**) was obtained from the unsymmetrical isomer, **32**. The NMR spectra of the synthetic alkaloids were identical to those of authentic samples of the natural alkaloids.

The C_2-symmetric, pentacyclic alkaloid papuamine (**1**) was isolated from *Haliclona* sp., a thin red sponge that overgrows and kills coral reef, collected by Scheuer and co-workers off the coast of Papua, New Guinea.[1] Scheuer reported the major metabolite (1.3% of dry weight) to be **1** on the basis of NMR and mass spectrometry data. Shortly after the communication by Scheuer, Faulkner and co-workers[2] reported the isolation of haliclonadiamine (**2**) as the major metabolite, along with a minor amount of **1**, from *Haliclona* sp. that was obtained from Palau. The structure of **2** was determined by X-ray analysis of the *N*,*N*-diacetyl derivative. At the time they were reported, the absolute configurations of papuamine and haliclonadiamine were not known. Alkaloids **1** and **2** inhibit the growth of *Candida albicans*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Trichopyton mentagrophytes*.[1,2]



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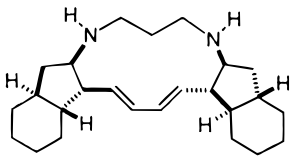

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Papuamine and haliclonadiamine are unique among the known *Haliclona* metabolites. Papuamine contains a central 13-membered ring and has a C_2-symmetry axis through the central methylene of the diaminopropane bridge and dissecting the *E*,*E*-diene. Haliclonadiamine is identical to papuamine but is epimeric at the point where the diaminopropane portion is attached to one hydrindan unit. These compounds presumably arise from the same source, but nothing is known about the biosyntheses of these unusual alkaloids.

Two syntheses of papuamine appeared in the literature in 1994. Barrett and co-workers[3] reported the total synthesis of the unnatural enantiomer of papuamine, thereby establishing the absolute stereochemistry of the naturally occurring material. A full account of Barrett's synthesis, which is conceptually very similar to our own, appears in an accompanying Article. Shortly after Barrett's original communication, Weinreb and co-workers[4] reported the total synthesis of the natural antipode of papuamine exploiting a novel imino ene reaction.

Our original retrosynthetic analysis of **1** and **2** (Scheme 1) took advantage of the fact that these compounds are nearly identical, being epimeric at a single stereocenter. We thought that by establishing the stereochemistry of this center as one of the last steps of the synthesis, both natural products would be available from a common advanced intermediate such as bis-imine **3** or the corresponding immonium ion. Reduction of **3** where hydride addition occurs exclusively in a Cram sense[5,6] would lead to **1**, while reduction where one hydride addition occurs in an anti-Cram sense would lead to **2**. The other expected product would be that resulting from anti-Cram/anti-Cram hydride addition to **3**; however, that would be a minor product if the reduction were even mildly stereospecific.

At the inception of our efforts toward the syntheses of **1** and **2**, the absolute stereochemistry of these natural products had not been established.[1,2] We arbitrarily chose as our target the enantiomer that was later shown by Barrett and Weinreb to be the unnatural enantiomer of papuamine and presumably the unnatural enantiomer of haliclonadiamine, although the latter point had not been definitively established. Our original synthetic goal, then, was diketone **4**, the retrosynthetic analysis of which is shown in Scheme 2. The requisite *E*,*E*-diene would come from metal-mediated coupling of a vinyl derivative of alkyne **5**. The alkyne would be formed by reduction of nitrile **6** followed by homologation of the resulting

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

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

(2) Faulkner, D. J.; Fahy, E.; Molinski, T. F.; Harper, M. K.; Sullivan, B. W. *Tetrahedron Lett.* **1988**, *29*, 3427.

(3) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc., Chem. Commun.* **1994**, 1881−1882.

(4) Weinreb, S. M.; Borzilleri, R. M.; Parvez, M. *J. Am. Chem. Soc.* **1994**, *116*, 9789−9790.

(5) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835.

(6) Felkin, H.; Cherest, M.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204.

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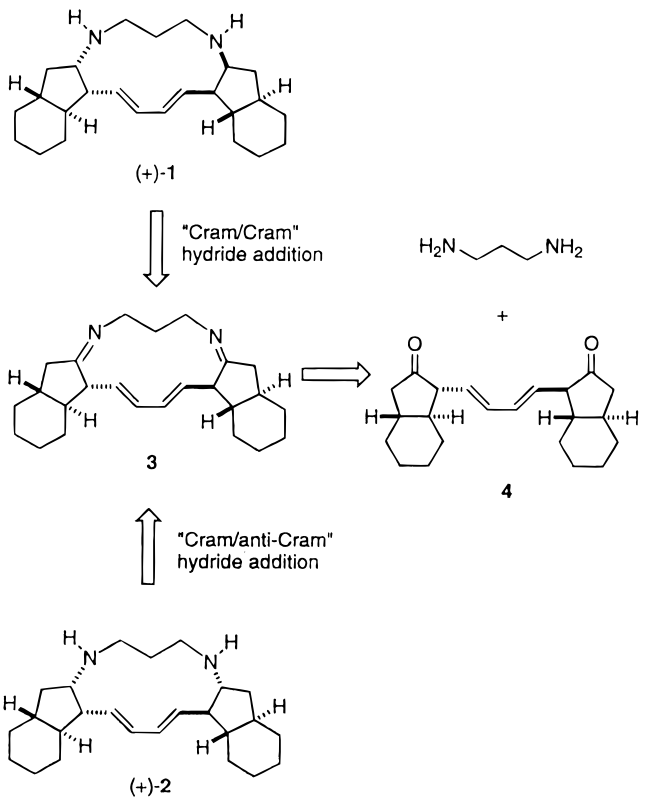
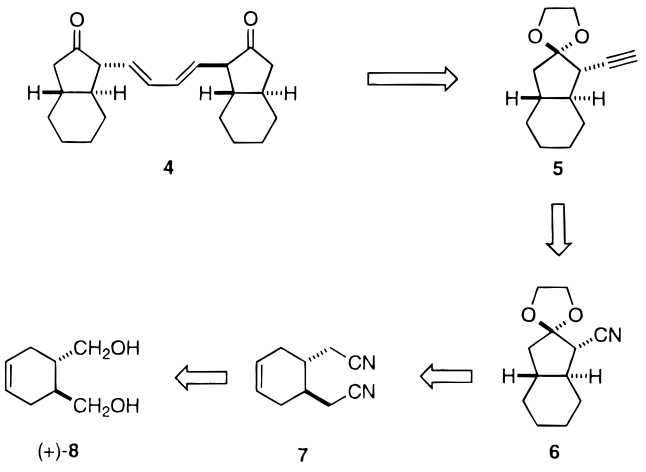
Scheme 1



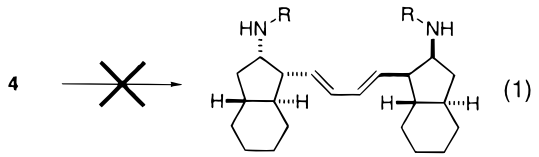
Scheme 2



aldehyde. Nitrile **6** would arise from acetal protection of the keto nitrile from a Thorpe−Ziegler cyclization of dinitrile **7**, which would come from known diol **8**.

The starting point for our synthesis is diol (+)-**8**, which was prepared in optically pure form by an asymmetric Diels−Alder reaction and a series of straightforward steps.[7] As shown in Scheme 3, diol (+)-**8** was hydrogenated to **9** followed by mesylation and displacement with cyanide to give dinitrile **7**. Thorpe−Ziegler cyclization of **7** using sodium *N*-methylanilide as a base, followed by acid hydrolysis of the intermediate imine, gave keto nitrile **11**, as a 13:1 mixture of epimers at the newly-formed stereocenter. Protection of the ketone as its acetal was followed by diisobutylaluminum hydride (DIBAL-H) reduction of the nitrile to give aldehyde **12**. Homologation to alkyne **5** was accomplished using the potassium salt of dimethyl (diazomethyl)phosphonate.[8−10] Hydrozirconation of **5** with $Cp_2ZrCl(H)$ (Schwartz's reagent)[11,12] and treatment of the resulting vinylzirconium species with CuCl[13] gave diene **13** in a 57% yield. The remainder of the material was the terminal alkene resulting from proto-demetalation of the vinylzirconium species. Deprotection of the bis-acetal **13** gave diketone **4** in quantitative yield. Although the deprotection reaction was efficient, diketone **4** was found to be unstable, decomposing upon standing at room temperature.

With diketone **4** in hand, a variety of conditions for installing the amine functionality were investigated. Reductive amination[14,15] of **4** with diaminopropane, the original synthetic plan, resulted in recovery or decomposition of starting material, depending on conditions (eq 1). Attempts to convert **4** to the corresponding primary



14: R = H
(+)-**1**: R = $(CH_2)_3$

amine[14] (**14**, R = H), with the hope of incorporating the propane bridge by a bis-alkylation reaction, also resulted in recovery of starting material or decomposition. Attempts to form the bis-imine **3** under dehydrating conditions[16] were also unsuccessful. The lack of reactivity of diketone **4** to typical reductive amination conditions may be due to tautomerization to the corresponding tetraenediol. Indeed, addition of methanol to **4** resulted in a bright yellow solution that was inert to reductive amination.

Prompted by the difficulty in functionalization of **4** and by establishment of the absolute stereochemistry of papuamine (**1**) by Barrett,[3] a new synthetic plan was devised. The new plan was focused on the synthesis of the natural enantiomer of papuamine (**1**) along with haliclonadiamine (**2**) as depicted in Scheme 4. The 13-membered ring would be formed by a vinyl coupling reaction on a derivative of dialkynes **15**/**16**. The alkyne functionality would be installed in a manner similar to that presented in the previous synthetic approach. The diaminopropane portion of the molecule would be introduced by reductive amination of a suitably functionalized hydrindanone with 1,3-diaminopropane. The synthetic plan was, again, to take advantage of the lack of complete stereocontrol of the reductive amination reaction in order to access both natural products in a convergent manner.

The starting point of the synthesis (Scheme 5) was (−)-**8**, which was prepared by a series of steps analogous to those reported[7] for the synthesis of (+)-**8**, but employing the other enantiomer of menthol. Mesylation followed

(7) Heathcock, C. H.; Davis, B. R.; Hadley, C. R. *J. Med. Chem.* **1989**, *32*, 197−202.

(8) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379.

(9) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. I* **1977**, 869.

(10) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

(11) Schwartz, J.; Hart, D. W. *J. Am. Chem. Soc.* **1974**, *96*, 8115.

(12) Buchwald, S. J.; LaMaire, S. J.; Neilsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1992**, *71*, 77.

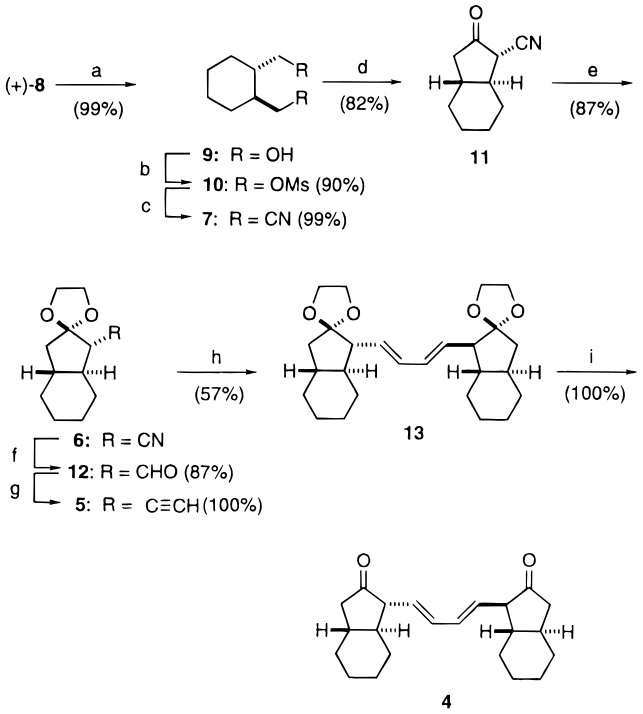
(13) Negishi, E.; Takahashi, T. *Aldrichimica Acta* **1985**, *18*, 31.

(14) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(15) Abdel-Magid, A.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595.

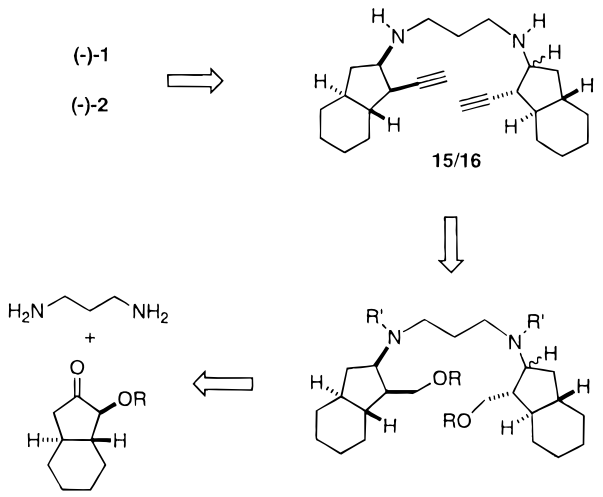
(16) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489−510.

Scheme 3



(a) H_2, Pd/C, EtOH; (b) MsCl, Et_3N, ether; (c) KCN, DMSO, Δ; (d) *N*-methylaniline, NaH, THF; H^+; (e) ethylene glycol, *p*-TsOH, Ph, Δ; (f) DIBAL-H, toluene, -78 °C; (g) $N_2CHPO(OMe)_2$, *t*-BuOK, THF, -78 °C to rt; (h) $Cp_2ZrCl(H)$, THF; CuCl; (i) *p*-TsOH, acetone/water, Δ.

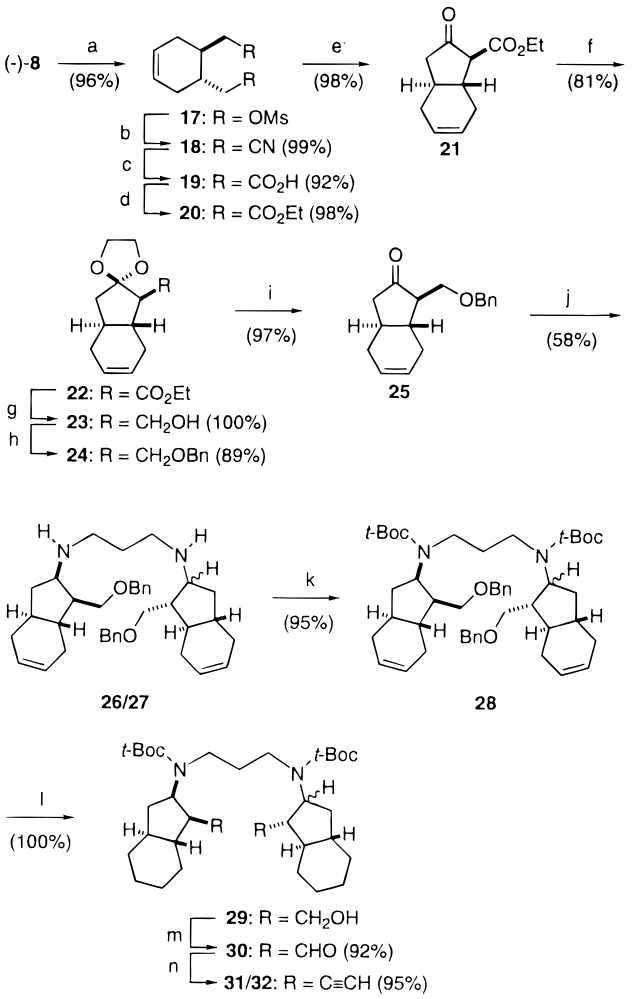
Scheme 4



by cyanide displacement gave dinitrile **18**. The moderate yield obtained for the Thorpe−Ziegler cyclization in the earlier synthetic route, along with difficulty during the reduction of a nitrile to an aldehyde on a closely-related model system, prompted us to investigate the use of a Dieckmann cyclization to construct the five-membered ring. To this end, dinitrile **18** was transformed to the corresponding diester **20**. Treatment of **20** with potassium hydride at 0 °C in THF[17] followed by quenching of the resulting enolate at 0 °C resulted in the formation of keto ester **21** in near quantitative yield as a single diastereomer. The complete stereospecificity of the Dieckmann cyclization was eroded to a 20:1 mixture of ester **22** during the subsequent acetal formation. Reduction

(17) Brown, C. A. *Synthesis* **1975**, 326−327.

Scheme 5



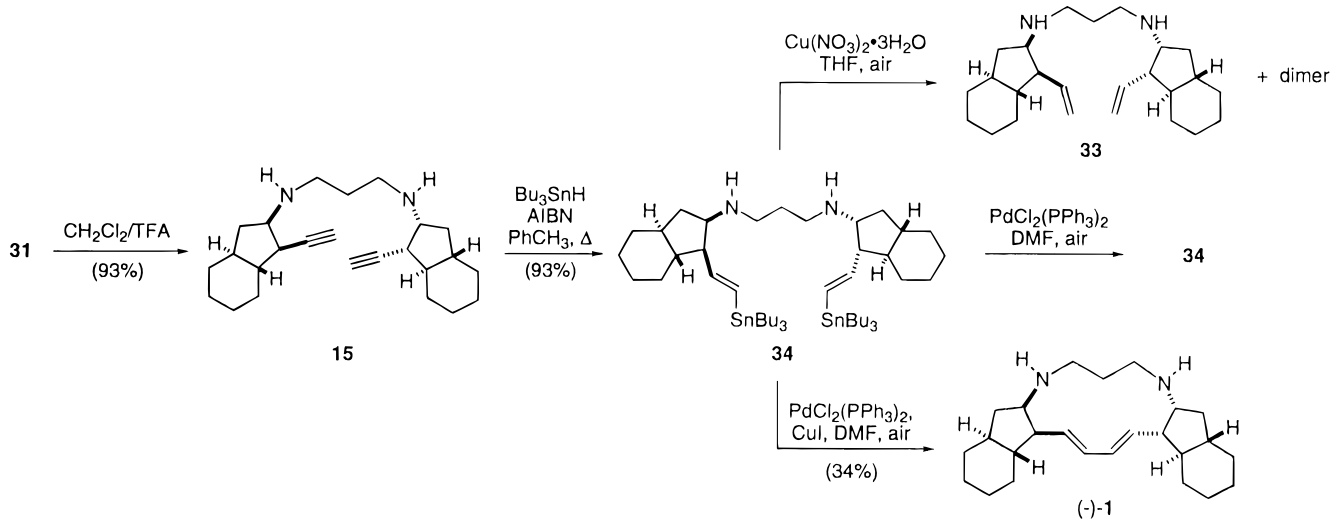
(a) MsCl, Et_3N, CH_2Cl_2; (b) KCN, DMSO, Δ; (c) KOH, ethylene glycol, water, 160 °C; (d) H_2SO_4 (cat), EtOH, Δ; (e) KH, THF, 0 °C, 20 min; (f) ethylene glycol, *p*-TsOH, benzene, Δ; (g) $LiAlH_4$, ether, 0 °C; (h) NaH, BnBr, THF, rt; (i) PPTS, acetone/water, Δ; (j) 1,3-diaminopropane, $NaBH(OAc)_3$, dichloroethane/acetic acid, rt, 72 h; (k) $(t\text{-BOC})_2O$, CH_2Cl_2, rt; (l) H_2, Pd/C, 95% EtOH; (m) TPAP, NMO, CH_2Cl_2, rt, 15 min; (n) $N_2CHPO(OMe)_2$, *t*-BuOK, THF, –78 °C to rt, 12 h.

to primary alcohol **23** was followed by conversion to its benzyl ether and removal of the acetal group to give ketone **25**. Reductive amination of **25** with 1,3-diaminopropane using sodium triacetoxyborohydride in dichloroethane/acetic acid[15,18] gave diamines **26**/**27** as a 3.4:1 mixture of diastereomers favoring the symmetrical diamine. Along with starting material, the mixture of diamines was the only product isolated from the reaction. The yield for the reductive amination based on recovered starting material was 92%. Careful chromatography allowed a minor amount of the symmetrical diamine (**26**, corresponding to the papuamine stereochemistry) to be isolated, but typically, this mixture was carried on and separated at a later stage. The amines were protected as their *tert*-butyl carbamates (*t*-Boc)[19] to give **28** as an inseparable mixture of diastereomers. The use of a *t*-Boc protecting group was ideal because of its easy installation and removal; however, NMR spectra of the *t*-Boc-protected diamines were very broad and of little or no use. Catalytic hydrogenation resulted in the removal of

(18) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* **1985**, *17*, 317.

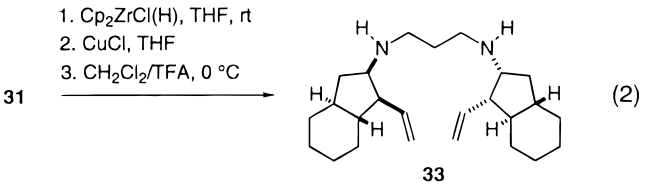
(19) Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Nat. Acad. Sci. U.S.A.* **1972**, *69*, 730−732.

Scheme 6



the benzyl ethers and reduction of the olefins to give diol **29**. Oxidation using TPAP[20] in CH_2Cl_2 gave dialdehyde **30** in good yield. This material decomposed upon standing and was immediately transformed to the corresponding dialkyne (**31**) using dimethyl (diazomethyl)phosphonate.[8−10] The symmetric (**31**) and unsymmetric (**32**) diastereomers were separated at this point.

With **31** and **32** in hand, the cyclization to the requisite diene was investigated. The coupling reaction that had proved the most successful for the formation of a diene from an alkyne in the previous approach was hydrozirconation of the alkyne followed by treatment with CuCl.[13] High-dilution variations of the vinylzirconium coupling conditions were attempted using dialkyne **31**. The only product obtained from these reactions, after removal of the *t*-Boc protecting groups,[19] was terminal alkene **33**, arising from hydrozirconation followed by proto-demetalation (eq 2). The fact that this reaction returned no



(2)

starting material and that high concentrations resulted in low mass balance, presumably due to polymerization, indicated that the hydrozirconation step was successful and that the resulting vinylzirconium species could not attain a conformation suitable for cyclization.

Weinreb's report of the successful synthesis of papuamine[4] prompted us to investigate the metal-promoted oxidative coupling of vinylstannanes. Weinreb reported that hydrostannylation of an alkyne and subsequent palladium-catalyzed coupling of the resulting vinylstannane could be accomplished in the presence of the free amines. It seemed likely that the problems with our earlier cyclization attempts were related to the *t*-Boc protecting groups. Cyclization of the free amine was an attractive option.

As shown in Scheme 6, removal of the *t*-Boc protecting group of **31** gave diamine **15**. Hydrostannylation of **15** with tributyltin hydride (Bu_3SnH) and AIBN in refluxing toluene gave bis-vinylstannane **34** in good yield.[4] Treatment of **34** with $Cu(NO_3)_2 \cdot 3H_2O$ in THF in the presence of an oxidant[21] resulted in the formation of the alkene **33**, by proto-destannylation, along with a compound tentatively identified as the uncyclized dimer. Cyclization attempts using $PdCl_2(PPh_3)_2$ in DMF open to the air[4] gave predominately starting material. It was curious that the palladium reaction gave back starting material and none of the alkene (**33**) observed from the copper-mediated reaction. It was clear that the initial step of the palladium reaction, which is presumably transmetalation to the vinylpalladium species,[22] was not occurring.

Liebeskind reported that the use of copper(I) iodide as a cocatalyst with palladium greatly increased the rate of Stille couplings[23] and of arylstannane couplings.[24] Indeed, treatment of bis-vinylstannane **34** with 10% $PdCl_2(PPh_3)_2$ and 20% CuI in DMF open to air for 30 h gave papuamine (**1**) in 34% yield. No other amine products were isolated from the reaction (Scheme 6).

The cyclization protocol was repeated with dialkyne **32** (Scheme 7). Removal of the *t*-Boc protecting groups with TFA/CH_2Cl_2 at 0 °C proceeded smoothly to give the free amine (**16**) in 92% yield. Hydrostannylation using the previously established conditions gave bis-vinylstannane **35** in 43% yield after purification. NMR analysis of the crude reaction mixture looked promising, but much of the material was lost during chromatography; however, this was not a problem for the symmetrical bis-vinylstannane **34**. Cyclization of **35** with $PdCl_2(PPh_3)_2$ and CuI in *N*,*N*-dimethylacetamide open to the air gave haliclonadiamine **2** as the free amine in 12% yield. This material is considerably more polar than papuamine, and purification by chromatography resulted in a low mass recovery. The yields in this sequence could probably be improved by optimization. However, because **32** is the minor isomer of the reductive amination reaction, we were hampered by a shortage of material for this purpose.

Samples of natural papuamine (**1**) and haliclonadiamine (**2**) were secured for comparison to our synthetic

(20) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627.

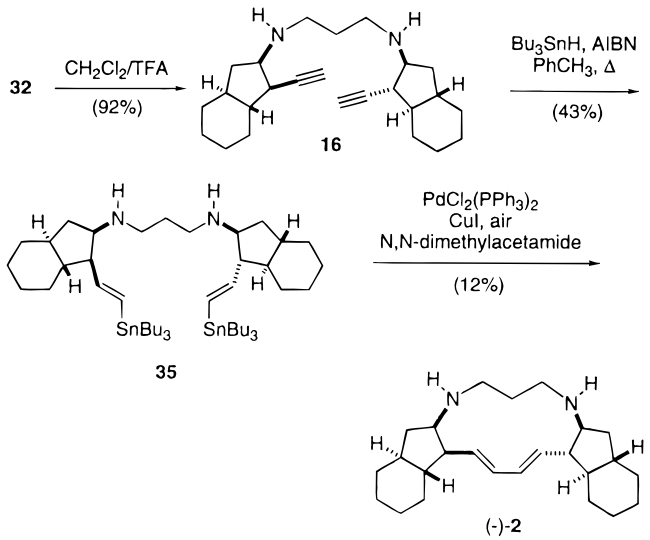
(21) Kyler, K. S.; Ghosal, S.; Luke, G. P. *J. Org. Chem.* **1987**, *52*, 4296−4298.

(22) Oshima, K.; Kanemoto, S.; Matsubara, S.; Utimoto, K.; Nozaki, H. *Chem. Lett.* **1987**, 5.

(23) Liebeskind, L. S.; Feng, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364.

(24) Liebeskind, L. S.; Riesinger, S. W. *Tetrahedron Lett.* **1991**, *32*, 5681−5682.

Scheme 7



material. In order to obtain the free amines, CH_2Cl_2 solutions of the natural materials were treated with saturated aqueous Na_2CO_3. ^1H NMR and ^{13}C NMR spectra of the synthetic and natural materials were identical. There is evidence[4] that these compounds easily form salts, and we found that careful formation of the free amines was necessary to obtain consistent NMR spectra.

There was a discrepancy between the optical rotation value reported for natural papuamine, $[\alpha]_D$ −150 (c = 1.5, MeOH),[1] and our synthetic material, $[\alpha]_D$ −346 (c = 0.46, MeOH). We suspected that partial protonation of the natural material might be responsible for this anomalous result. This situation would not be surprising as changing the stereochemistry at a single center (from papuamine to haliclonadiamine) causes the rotation to decrease from −150 to −18. In order to test our hypothesis, a sample of papuamine was contaminated with 10 mol % *p*-TsOH. The rotation of this material was found to be $[\alpha]_D$ −278 (c = 0.46, MeOH). Addition of 1 equiv of *p*-TsOH resulted in a rotation of $[\alpha]_D$ −183 (c = 0.52, MeOH).

Experimental Section

General. All starting materials were obtained from commercial suppliers and used without purification. THF and ether were distilled from sodium/benzophenone immediately prior to use. Benzene, toluene, and triethylamine (Et_3N) were distilled from CaH_2 immediately prior to use. Unless otherwise noted, all reactions were performed under an argon atmosphere. Silica gel chromatography was performed according to the method of Still.[25] Schwartz's reagent (Cp_2Zr(H)Cl) was prepared according to the literature[12] and stored at −40 °C in a glovebox under an atmosphere of dry argon. Tributyltin hydride was Kugelrohr distilled (120 °C, 0.3 mmHg) immediately prior to use. J values are given in hertz. IR spectra were measured as thin films on NaCl plates unless otherwise noted. Elemental analyses were performed at the Berkeley Microanalytical Lab, University of California.

(1*S*,2*S*)-Cyclohexane-1,2-dimethanol (9). A Parr hydrogenation flask was charged with (+)-**8** (1.07 g, 7.52 mmol) and 10 mL of absolute ethanol. Then 5% Pd/C (0.095 g, 10% by wt) was added and the flask was evacuated and back-filled with hydrogen three times. The system was filled with hydrogen to a pressure of 32 psi and was vigorously shaken for 1.5 h, at which time Celite was added and the mixture was filtered through a plug of Celite and thoroughly washed with ethanol. The filtrate was concentrated to give a thick oil that was purified by silica gel chromatography using ether as an eluent to give 1.08 g (99%) of a white solid: mp 57−58 °C; R_f 0.3 (Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.99−1.04 (m, 2), 1.19−1.31 (m, 4), 1.60 (m, 2), 1.72 (m, 2), 3.38 (br s, 2), 3.50 (dd, 2, J = 4.9, 11.0), 3.59 (dd, 2, J = 2.1, 11.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 29.8, 44.7, 67.8; IR (KBr pellet) 3610, 3400, 1445, 1050 cm^{-1}; $[\alpha]_D$ −23.0 (c = 1.63, $CHCl_3$). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.89; H, 10.91.

(1*S*,2*S*)-Cyclohexane-1,2-dimethanol Bis(methanesulfonate) (10). A dry flask was charged with diol **9** (4.90 g, 33.98 mmol) and ether (250 mL). The flask was flushed with argon and cooled to 0 °C. Triethylamine (14.2 mL, 101.94 mmol) was added, and then methansulfonyl chloride (6.31 mL, 81.55 mmol) was added dropwise over a period of 10 min. The reaction mixture was stirred at 0 °C for 20 min and at rt for 2 h. The solvent was removed in *vacuo*, and the residue was partitioned between water (100 mL) and CH_2Cl_2 (100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Filtration and evaporation gave a brown solid that was recrystallized from MeOH (two crops) to give 9.158 g (90%) of a white solid: mp 83−84 °C; R_f 0.06 (1:20 MeOH/$CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (m, 4), 1.68−1.80 (m, 6), 3.00 (s, 6), 4.15 (dd, 2, J = 3.2, 10.1), 4.25 (dd, 2, J = 4.3, 10.1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2, 29.1, 37.1, 38.4, 71.9; IR (KBr pellet) 3030, 1360, 1180, 945 cm^{-1}; $[\alpha]_D$ +16.6 (c = 1.94, $CHCl_3$). Anal. Calcd for $C_{10}H_{20}O_6S_2$: C, 39.98; H, 6.71. Found: C, 39.99; H, 6.69.

(1*R*,2*R*)-Cyclohexane-1,2-diacetonitrile (7). A dry flask was charged with dimesylate **10** (2.15 g, 7.16 mmol), potassium cyanide (1.77 g, 27.20 mmol), and freshly-distilled DMSO (35 mL). The flask was equipped with a reflux condensor, flushed with argon, and heated to 95 °C with an oil bath for 3.5 h. Water (40 mL) was added with vigorous stirring. The mixture was poured into a separatory funnel and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Filtration and concentration gave a thick yellow oil that was contaminated with DMSO. The residue was adsorbed onto silica gel using ether, and the soild was loaded directly onto a silica gel column and eluted with ether to give 1.15 g (99%) of a fluffy white solid: mp 52−53 °C; R_f 0.3 (ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (m, 4), 1.63 (m, 2), 1.79 (m, 2), 1.87 (m, 2), 2.42 (d, 4, J = 4.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 25.2, 31.7, 37.3, 117.5; IR (neat) 2260, 1440 cm^{-1}; $[\alpha]_D$ +54.5 (c = 1.67, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.91; H, 8.64; N, 16.93.

(1*R*,6*S*,7*S*)-7-Cyano-8-oxobicyclo[4.3.0]nonane (11). A dry flask was charged with sodium hydride (2.41 g, 60.16 mmol) that was rinsed (2 × 10 mL) with dry hexanes. The last of the hexanes was removed under a stream of argon. THF (130 mL) was added followed by the addition of *N*-methylaniline (6.85 mL, 63.17 mmol) with a syringe. The flask was equipped with a reflux condensor and heated to reflux with an oil bath for 1.5 h. The reaction mixture was allowed to cool to rt. Dinitrile **7** (2.44 g, 15.04 mmol) was added with a cannula as a solution in 15 mL of THF, and the reaction mixture was heated to reflux for 12 h. After cooling to rt, the mixture was poured into 200 mL of 2 N HCl and stirred for 30 min. The mixture was extracted with ether (3 × 100 mL). The combined organic layers were washed with water (75 mL) and brine (75 mL) and dried over $MgSO_4$. Filtration and concentration gave a thick brown oil that was purified by chromatography using 1:3 EtOAc/hexanes as an eluent to give 2.39 g (98%) of a yellow oil that crystallized upon standing at 0 °C overnight. The crystals were collected and washed with cold hexanes. A second recrystallization of the mother liquor gave a total of 2.021 g (82%) of white solid: mp 51−53 °C; R_f 0.3 (1:3 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.19−1.41 (m, 4), 1.62 (m, 1), 1.82−1.91 (m, 3), 1.97−2.03 (m, 2), 2.19 (dd, 1, J = 3.3, 13.0), 2.52 (dd, 1, J = 7.0, 18.6), 2.85 (d, 1, J = 13.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 25.7, 29.8, 30.8, 41.6, 43.6, 46.2, 48.4, 116.2, 204.9; IR (KBr) 2260, 1745,

(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

1422 cm^{-1}; $[\alpha]_D$ −139 (c = 1.33, $CHCl_3$). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.44; H, 8.09; N, 8.55.

(1*R*,6*S*,7*S*)-7-Cyano-8-ethylenedioxybicyclo[4.3.0]-nonane (6). A flask was charged with keto nitrile **11** (0.593 g, 3.63 mmol) and benzene (30 mL). Ehtylene glycol (0.53 mL, 9.45 mmol) was added followed by *p*-toluenesulfonic acid monohydrate (0.48 g, 2.50 mmol). The flask was equipped with a Dean−Stark trap and heated to reflux with an oil bath. After 20 h the reaction mixture was allowed to cool to rt and was diluted by the addition of ether (30 mL). The solution was poured into 75 mL of saturated $NaHCO_3$, and the layers were separated. The organic layer was washed with water (50 mL) and dried over $MgSO_4$. Filtration and concentration gave a thick oil that was purified by chromatography using 3:7 EtOAc/hexanes as an eluent to give 0.65 g (87%) of a white solid: mp 39−40 °C; R_f 0.25 (1:15 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02−1.08 (m, 2), 1.20−1.33 (m, 3), 1.55−1.58 (m, 1), 1.63 (dd, 1, J = 12.6, 13.6), 1.73−1.85 (m, 3), 2.03 (m, 1), 2.06 (dd, 1, J = 7.0, 13.6), 2.47 (d, 1, J = 12.4), 3.88 (m, 1), 4.02 (m, 2), 4.10 (m, 1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 25.7, 29.6, 30.8, 42.9, 43.9, 46.3, 49.1, 65.0, 65.3, 115.2, 118.5; IR (neat) 2260, 1290, 1175 cm^{-1}; $[\alpha]_D$ −19.4 (c = 1.56, $CHCl_3$). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.38; H, 8.19; N, 6.71.

(1*R*,6*S*,7*S*)-8,8-(Ethylenedioxy)-7-formylbicyclo[4.3.0]-nonane (12). A dry flask was charged with nitrile **6** (0.469 g, 2.26 mmol) and toluene (12 mL), and the solution was cooled to −78 °C under argon. A 1.5 M solution of diisobutylaluminum hydride in toluene (1.81 mL, 2.72 mmol) was added dropwise over a 15 min period, and the reaction solution was stirred at −78 °C for 2 h. The bath was removed, and the solution was allowed to warm to rt over 30 min. The flask was cooled to 0 °C, MeOH (0.25 mL) was added slowly followed by water (0.5 mL), and the mixture was vigorously stirred for 30 min. $MgSO_4$ was added, and the mixture was stirred for an additional 15 min and was then filtered and concentrated to give a yellow oil. The material was purified by chromatography using 1:1 ether/hexanes as eluent to give 0.425 g (89%) of a white semisolid. This material was air-sensitive and was used immediately: R_f 0.3 (1:1 Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00−1.08 (m, 2), 1.20−1.27 (m, 2), 1.38 (m, 1), 1.55 (t, 1, J = 12.8), 1.68−1.87 (m, 5), 1.97 (dd, 1, J = 6.3, 12.9), 2.43 (dd, 1, J = 3.5, 11.5), 3.71 (m, 1), 3.85 (m, 2), 3.95 (m, 1), 9.58 (d, 1, J = 3.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.9, 25.9, 30.1, 31.0, 42.9, 44.8, 45.7, 64.2, 64.7, 65.8, 117.2, 201.9; IR (neat) 1720, 1450, 1290, 1030 cm^{-1}.

(1*R*,6*S*,7*S*)-8,8-(Ethylenedioxy)-7-ethynylbicyclo[4.3.0]-nonane (5). A flask was charged with potassium *tert*-butoxide (0.87 g, 8.40 mmol) and THF (40 mL), and the mixture was cooled to −78 °C under argon. Dimethyl (diazomethyl)-phosphonate (1.26 g, 8.40 mmol) was added with a cannula as a solution in 1 mL of THF, and the resulting yellow solution was stirred for 10 min. Aldehyde **12** was added with a cannula as a solution in 6 mL of THF. Some gas evolution could be seen near the end of the addtion. The bath was packed with dry ice, and the solution was stirred for 12 h, by which time the solution had reached rt. Water (40 mL) was added followed by CH_2Cl_2 (70 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with water (50 mL) and brine (70 mL) and were dried over $MgSO_4$. Filtration and concentration gave a yellow solid that was purified by chromatography using 1:4 EtOAc/hexanes as eluent to give 1.43 g (95%) of a white solid: mp 54−55 °C; R_f 0.3 (1:5 Et_2O/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97−1.04 (m, 2), 1.20−1.35 (m, 4), 1.57 (dd, 1, J = 13.4, 14.5), 1.65−1.80 (m, 3), 2.00 (m, 2), 2.17 (d, 1, J = 2.3), 2.34 (dd, 1, J = 2.1, 11.7), 3.83 (m, 1), 3.96 (m, 1), 4.04 (m, 1), 4.11 (m, 1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.9, 26.1, 29.8, 31.2, 42.6, 44.0, 47.5, 51.1, 64.6, 65.2, 71.8, 82.3, 116.1; IR (KBr) 3320, 2120, 1450, 1175 cm^{-1}; $[\alpha]_D$ + 34.4 (c = 1.51, $CHCl_3$). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.71; H, 8.94.

(1*R*,1′*R*,6*S*,6′*S*,7*S*,7′*S*)-1,4-Bis(8,8-(ethylenedioxy)bicyclo-[4.3.0]nonan-7-yl)buta-1,3-diene (13). A flask was charged with $Cp_2Zr(H)Cl$ and THF (2.5 mL) and was protected from exposure to light. Alkyne **5** (0.110 g, 0.533 mmol) was added with a cannula as a solution in THF (1 mL), and the reaction solution was stirred for 20 min, at which time the resulting vinylzirconium species was added with a cannula to a suspension of CuI (0.063 g, 0.640 mmol) in THF (1 mL). The original flask and cannula were rinsed with 1 mL of THF that was also added to the reaction mixture. The resulting mixture was stirred at room trremperature for 2 h during which time metallic copper could be seen plated to the sides of the reaction flask. Water (5 mL) and ether (10 mL) were added, and the resulting mixture was filtered through a plug of Celite and thoroughly rinsed with ether. The filtrate was concentrated, and the residue was partitioned between water and CH_2Cl_2 (7 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 7 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration gave 0.095 g (86%) of a white solid that was purified by recrystallization from EtOAc/hexanes to give 0.063 g (57%) of a white solid: mp 188−189 °C; R_f .0.3 (1:4 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89−1.35 (m, 14), 1.49 (t, 2, J = 12.8), 1.70−1.82 (m, 6), 1.99 (dd, 2, J = 7.0, 13.3), 2.11 (dd, 2, J = 9.4, 11.6), 3.69−3.90 (m, 8), 5.51 (m, 2), 6.02 (dd, 2, J = 2.8, 11.7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 26.3, 29.9, 31.5, 42.9, 44.4, 50.5, 58.8, 64.3, 64.7, 117.5, 130.1, 132.3; IR ($CHCl_3$) 3031, 1580, 1415, 925 cm^{-1}; HRMS calcd for $C_{26}H_{38}O_4$ *m/e* 414.2770, found 414.2774.

(1*R*,1′*R*,6*S*,6′*S*,7*S*,7′*S*)-1,4-Bis(8-oxobicyclo[4.3.0]nonan-7-yl)buta-1,3-diene (4). A flask was charged with diene **13** (0.039 g, 0.094 mmol) and 25 mL of 10:1 acetone/water and *p*-TsOH (2 mg, 0.009 mmol). The flask was equipped with a reflux condensor and was heated at reflux for 16 h. The solvent was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration gave a yellow solid that was purified by silica gel chromatography using 1:4 EtOAc/hexanes to give 0.031 g (100%) of a white solid: mp 125−126 °C; R_f 0.3 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84−1.45 (m, 8), 1.51−1.62 (m, 2), 1.68−1.92 (m, 8), 1.95 (br d, 4, J = 13.6), 2.39 (dd, 2, J = 6.7, 18.0), 2.45 (dd, 2, J = 7.4, 12.1), 5.47−5.56 (m, 2), 6.04−6.11 (m, 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.3, 30.4, 31.4, 41.5, 44.6, 49.5, 59.2, 128.2, 133.1, 216.9; IR ($CHCl_3$) 3009, 1736, 1580, 1309 cm^{-1}; $[\alpha]_D$ −91.7 (c = 0.7, $CHCl_3$).

(1*R*,2*R*)-Cyclohex-4-ene-1,2-dimethanol Bis(methansulfonate) (17). A flask was charged with diol (−)-**8** (0.949g, 6.67 mmol) and 50 mL of ether, and the solution was cooled to 0 °C. Triethylamine (2.8 mL, 20.02 mmol) was added all at once. Freshly distilled methansulfonyl chloride (1.24 mL, 16.02 mmol) was added dropwise with a syringe over 5 min. A white solid began to form immediately. After 30 min the bath was removed and the mixture was allowed to warm to rt. The mixture was allowed to stir for 24 h at which time the solvent was removed and the residue was partitioned between water and CH_2Cl_2 (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL).The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration resulted in a thick yellow oil that was purified by silica gel chromatography using 1:1 ethyl acetate/hexanes as eluent to give 1.918 g (96%) of a white solid: mp 58−59 °C; R_f 0.3 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (br d, 2, J = 13.8), 2.15 (m, 4), 3.02 (s, 6), 4.23 (dq, 4, J = 4.8, 10.3), 5.63 (s, 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 33.6, 37.3, 70.7, 124.7; IR ($CHCl_3$) 3020, 1360, 1175 cm^{-1}; $[\alpha]_D$ −52.0 (c = 0.825, $CHCl_3$). Anal. Calcd for $C_{10}H_{18}O_6S_2$: C, 40.25; H, 6.08. Found: C, 40.21; H, 5.93.

(1*S*,2*S*)-Cyclohex-4-ene-1,2-diacetonitrile (18). A flask was charged with dimesylate **17** (2.15 g, 7.16 mol) and potassium cyanide (1.77 g, 27.20 mmol). Dry DMSO (35 mL) was added, and the flask was equipped with a reflux condensor and was flushed with argon. The flask was heated to 95 °C with an oil bath, and the reaction solution was allowed to stir for 4 h. Water (40 mL) was added, and the mixture was stirred for 10 min and then poured into a seperatory funnel and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic

layers were washed with brine (30 mL) and dried over $MgSO_4$. Filtration and concentration gave a thick oil that was purified by silica gel chromatography using ether as eluent to give 1.15 g (99%) of a fluffy white solid: mp 93−94 °C; R_f 0.3 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00−2.15 (m, 4), 2.26 (br d, 2, J = 13.4), 2.45 (m, 4), 5.65 (d, 2, J = 1.3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 28.4, 32.7, 117.6, 124.5; IR ($CHCl_3$) 3020, 2840, 2250, 1420 cm^{-1}; $[\alpha]_D$ −101 (c = 1.10, $CHCl_3$). Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.78; H, 7.56; N, 17.48.

(1*S*,2*S*)-Cyclohex-4-ene-1,2-diethanoic Acid (19). A flask was charged with dinitrile **18** (4.648 g, 29.01 mmol), 40 mL of ethylene glycol, and solid KOH (15.3 g, 232.08 mmol). The flask was equipped with a reflux condensor and was placed in an oil bath at 130 °C. The bath temperature was increased to 150 °C. The mixture became clear after 30 min and was stirred for an additional 4.5 h. The solution was allowed to cool to rt, and water (50 mL) was added. The solution was washed with ether (2 × 25 mL), which was discarded. The aqueous layer was acidified with concd HCl and was extracted with ether (3 × 75 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration gave 5.30 g (92%) of a pink solid. This material could be used crude. An analytical sample was purified by silica gel chromatography using 30:68:2 EtOAc/hexanes/HOAc to give a white solid: mp 148−149 °C; R_f 0.29 (3:7 EtOAc/hexanes); ^{1}H NMR (400 MHz, CD_3OD) δ 1.83 (br dquin, 2, J = 18.0, 2.3), 2.03−2.19 (m, 2), 2.23 (br dd, 2, J = 6.7, 10.0), 2.43 (dd, 2, J = 5.0, 15.0), 4.93 (br s, 2), 5.59 (d, 2, J = 1.4); ^{13}C NMR (100 MHz, CD_3OD) δ 29.6, 34.9, 39.3, 126.0, 176.8; IR (KBr pellet) 3038, 1693, 1437, 1168 cm^{-1}; $[\alpha]_D$ −52.6 (c = 0.81, EtOH). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.90; H, 7.08.

(1*S*,2*S*)-Diethyl Cyclohex-4-ene-1,2-diethanoate (20). A flask was charged with diacid **19** (3.70 g, 18.72 mmol) and 70 mL of absolute ethanol. Concd H_2SO_4 (1.0 mL, 18.72 mmol) was added as a solution in 5 mL of absolute ethanol. The flask was equipped with a reflux condensor, and the reaction solution was heated to reflux with an oil bath. After 21 h the solution was allowed to cool to rt and was concentrated *in vacuo*. The residue was partitioned between water and CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (1 × 40 mL) and brine (40 mL) and dried over $MgSO_4$. Filtration and concentration gave 4.69 g (98%) of yellow oil. This material was generally used crude, but an analytic sample was purified by silica gel chromatography using 1:4 EtOAc/hexanes as an eluent: R_f 0.4 (2:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 6, J = 7.2), 1.79−1.85 (m, 2), 2.00−2.05 (m, 2), 2.10−2.25 (m, 4), 2.40 (dd, 2, J = 5.0, 14.9), 4.11 (q, 4, J = 7.2), 5.56 (s, 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 28.4, 33.5, 38.5, 60.3, 124.9, 172.9; IR (neat) 2970, 2900, 1735, 1370 cm^{-1}; $[\alpha]_D$ −46.0 (c = 0.385, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.84; H, 8.75.

(1*S*,6*R*,7*S*)-Ethyl 8-Oxobicyclo[4.3.0]non-3-ene-7-carboxylate (21). A dry flask was charged with 35% KH in oil (0.178 g, 1.55 mmol) that was washed with dry hexanes (3 × 1.5 mL) under argon to remove the oil. The last of the hexanes was removed under a stream of argon. THF (5.5 mL) was added, and the suspension was cooled to 0 °C. Diester **20** (0.328 g, 1.29 mmol) was added as a solution in THF (0.8 mL) with a syringe over a 20 min period. An additional 0.2 mL portion of THF was used to rinse the flask and syringe and was added to the solution mixture. At the end of the addition the solution solution was clear and light brown. The solution was stirred at 0 °C for 15 min at which time the it was poured into cold 1 M HCl (20 mL) and was allowed to warm to rt. The layers were separated, and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) and were dried over $MgSO_4$. Filtration and concentration gave 0.264 g (98%) of colorless oil. ^{1}H MNR analysis of the crude product showed a single diastereomer. The material was generally used crude but could be purified by silica gel chromatography using 1:4 EtOAc/hexanes. ^{1}H NMR analysis of the purified material showed a 20:1 mixture of diastereomers: R_f 0.35 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3, J = 7.1), 1.87−2.06 (m, 4), 2.25−2.42 (m, 3), 2.57 (dd, 1, J = 6.7, 6.6), 2.86 (d, 1, J = 12.1), 4.20 (dq, 2, J = 1.4, 7.1), 5.72 (br d, 2, J = 1.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 30.3, 31.2, 36.1, 42.6, 44.8, 61.2, 61.8, 126.2, 126.2, 126.5, 168.9, 209.8; IR (neat) 2981, 1758, 1725, 1325 cm^{-1}; $[\alpha]_D$ +26.5 (c = 0.215, $CHCl_3$). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.92; H, 7.83.

(1*S*,6*R*,7*S*)-Ethyl (8,8-(Ethylenedioxy)bicyclo[4.3.0]non-3-ene-7-carboxylate (22). A flask was charged with keto ester **21** (1.022 g, 4.91 mmol), benzene (20 mL), ethylene glycol (0.82 mL, 14.7 mmol), and *p*-toluenesulfonic acid (0.093 g, 0.491 mmol). The flask was equipped with a Dean−Stark trap and condensor, and the solution was heated at reflux for 16 h. The solution was allowed to cool to rt, pyridine (1.5 mL) was added, and the solution was stirred for 30 min and poured into saturated $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic layers were washed water (20 mL) and brine (20 mL) and were dried over $MgSO_4$. Filtration and concentration gave a yellow oil that was purified by silica gel chromatography using 1:4 EtOAc/hexanes as eluent to give 1.002 g (81%) of a colorless oil. ^{1}H NMR analysis of the purified material showed a 25:1 mixture of diastereomers: R_f 0.4 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, 3, J = 7.2), 1.56−1.72 (m, 2), 1.75−1.89 (m, 2), 2.02−2.18 (m, 2), 2.23−2.30 (m, 2), 2.63 (d, 1, J = 11.3), 3.78−3.90 (m, 3), 4.06−4.25 (m, 3), 5.66 (br t, 2, J = 1.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 30.6, 31.1, 37.3, 42.3, 44.9, 60.3, 60.5, 64.4, 65.3, 116.8, 126.4, 126.6, 171.1; IR (neat) 2978, 1732, 1282, 1040 cm^{-1}; $[\alpha]_D$ −60.2 (c = 1.54, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.96; H, 8.01.

(1*S*,6*R*,7*R*)-8,8-(Ethylenedioxy)-7-(hydroxymethyl)-bicyclo[4.3.0]non-3-ene (23). A dry flask was charged with $LiAlH_4$ (0.264 g, 6.61 mmol) and ether (40 mL), and the mixture was cooled to 0 °C under argon. Ester **22** (1.39 g, 5.51 mmol) was added with a cannula as a solution in ether (10 mL) over a 20−25 min period. The mixture was stirred at 0 °C for 1 h at which time water (0.26 mL) was added slowly followed by 3 N NaOH (0.26 mL) and then water (0.79 mL). The resulting mixture was stirred for 30 min as it warmed to rt. $MgSO_4$ was added, and stirring was continued for an additional 10 min period. The mixture was filtered, and the residue was thoroughly washed with ether. Concentration gave 1.168 g (100%) of a colorless oil. This material was usually used crude, but an analytical sample was purified by silica gel chromatography using 2:3 EtOAc/hexanes as an eluent: R_f 0.4 (2:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (dd, 1, J = 12.9, 11.7), 1.58−1.73 (m, 2), 1.77−1.894 (m, 2), 2.08 (dd, 1, J = 6.3, 12.9), 2.19−2.32 (m, 2), 2.49 (dd, 1, J = 3.4, 8.3), 3.59−3.66 (m, 1), 3.79−4.03 (m, 6), 5.68 (s, 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 31.4, 37.7, 40.3, 44.2, 55.1, 60.0, 63.7, 64.5, 117.8, 126.6, 126.8; IR (neat) 3447, 2956, 1640, 1437, 1025 cm^{-1}; $[\alpha]_D$ −120 (c = 0.985, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.74; H, 8.98.

(1*S*,6*R*,7*R*)-7-(Benzyloxymethyl)-8,8-(ethylenedioxy)-bicyclo[4.3.0]non-3-ene (24). A dry flask was charged with 60% NaH in oil (0.313 g, 7.83 mmol) that was washed with hexanes (3 × 5 mL) to remove the oil. The last of the hexanes was removed under a stream of argon. THF (14 mL) was added to give a gray suspension. Alcohol **23** (1.432 g, 6.81 mmol) was added with a cannula as a solution in THF (3 mL), and the resulting gray mixture was stirred at rt for 1.5 h. Benzyl bromide (0.97 mL, 8.17 mmol) was added with a syringe over a 1 min period followed by the addition of solid tetrabutylammonium iodide (0.025 g, 0.068 mmol). The flask was flushed with argon, and the reaction solution was stirred for 72 h at rt. The solution was concentrated *in vacuo*, and the residue was taken up in CH_2Cl_2, filtered through a plug of Celite, and thoroughly washed with CH_2Cl_2. Concentration resulted in a yellow oil that was purified by silica gel chromatography using 1:5 EtOAc/hexanes as eluent to give 1.815 g (89%) of a colorless oil and 0.107 g (0.509 mmol) of recovered starting material. An analytical sample was purified by Kugelrohr distillation (150 °C at 300 mmHg): R_f 0.3

(1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (dq, 1, J = 5.1, 11.1), 1.45 (t, 1, J = 12.2), 1.64 (dquin, 1, J = 5.3, 5.8), 1.72−1.80 (m, 1), 1.86−1.93 (m, 1), 2.01 (td, 1, J = 6.6, 13.3), 2.08 (dd, 1, J = 6.5, 13.0), 2.19−2.35 (m, 2), 3.47 (dd, 1, 6.3, 9.5), 3.61 (dd, 1, J = 7.1, 9.5), 3.78−3.84 (m, 2), 3.87 (q, 1, J = 5.0), 3.95−3.97 (m, 1), 4.53 (d, 2, J = 1.3), 5.66 (br. s, 2), 7.26−7.33 (m, 5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 31.5, 37.9, 44.3, 44.7, 53.8, 64.0, 65.1, 69.9, 73.1, 116.7, 126.7, 127.0, 127.3, 127.5, 128.3, 138.7; IR (neat) 3121, 1641(w), 1537, 1366, 1094 cm^{-1}; $[\alpha]_D$ −68.9 (c = 2.29, $CHCl_3$). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.90; H, 8.14.

(1*S*,6*R*,7*R*)-7-(Benzyloxymethyl)-8-oxobicyclo[4.3.0]non-3-ene (25). A flask was charged with acetal **24** (1.623 g, 5.40 mmol) and 27 mL of 10:1 acetone/water. Pyridinium *p*-toluenesulfonate (0.136 g, 0.54 mmol) was added, and the solution was heated to reflux with an oil bath for 3.5 h. The solvent was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2 (15 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration gave a thick oil that was purified by silica gel chromatography using 1:4 EtOAc/hexanes as eluent to give 1.344 g (97%) of a colorless oil. This material solidified upon standing and was recrystallized from hexanes to give a fluffy white solid: mp 52−53 °C; R_f 0.3 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (t, 2, J = 11.8), 1.81−2.05 (m, 4), 2.36−2.55 (m, 3), 3.70 (dq, 2, J = 3.4, 9.6), 4.49 (dd, 2, J = 12.2, 17.6), 5.74 (br. s, 2), 7.25−7.35 (m, 5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 31.5, 36.6, 41.7, 45.2, 56.3, 67.4, 73.3, 126.7, 126.9, 127.4, 127.5, 128.3, 138.3, 216.9; IR (neat) 3023, 1744, 1436, 1092 cm^{-1}; $[\alpha]_D$ +51.5 (c = 0.75, $CHCl_3$). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.65; H, 7.88.

(1*S*,1′*S*,6*R*,6′*R*,7*S*,7′*S*,8*R*,8′*R*)-*N*,*N*′-Bis(7-(benzyloxymethyl)bicyclo[4.3.0]non-3-en-8-yl)-1,3-diaminopropane (26). A dry three-necked flask was charged with acetic acid (8.05 mL, 140.6 mmol) and 45 mL of dichloroethane. The flask was equipped with a stopper, a septum, and an addition elbow containing $NaBH_4$ (1.56 g, 41.35 mmol). The flask was equipped with a bubbler needle, and the solution was cooled to 0 °C. The $NaBH_4$ was added in small portions from the addition elbow over a period of 35 min. The mixture was stirred at 0 °C for 15 min and rt for 15 min and was then cooled to 0 °C. Ketone **25** (4.24 g, 16.54 mmol) was added with a cannula as a solution in 10 mL of dichloroethane followed by the addition of 1,3-diaminopropane (0.69 mL, 8.27 mmol) with a syringe. The cloudy mixture was allowed to warm to rt and was stirred for 48 h. Then 1 N HCl (50 mL) was added and the mixture was allowed to stir for 15 min. The mixture was treated with solid KOH until basic by pH paper, and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with water (75 mL) and brine (75 mL) and were dried over K_2CO_3. Filtration and evaporation gave a thick yellow oil that was purified by silica gel chromatography using 4% NH_3-saturated MeOH/$CHCl_3$ as eluent to give 2.68 g (58%) of a pale yellow oil. ^{1}H NMR analysis of this material showed a 3.4:1 mixture of diastereomers. The diastereomers could be partially separated by careful chromatography but were typically carried on as a mixture and separated at a later stage. The non-amine products were combined and chromatographed using 1:4 EtOAc/hexanes as eluent to give 1.21 g (4.74 mmol) of ketone **25** starting material. The total yield based on recovered starting material was 82%: R_f 0.3 (4% NH_3-saturated MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 1.01 (dt, 2, J = 7.6, 11.8), 134−1.51 (m, 6), 1.67 (q, 2, J = 6.7), 1.72−1.81 (m, 4), 1.88−1.92 (m, 2), 2.09−2.21 (m, 6), 2.53 (dq, 2, J = 11.2, 6.5), 2.70 (dt, 2, J = 11.1, 6, 9), 3.23 (q, 2, J = 7.4), 3.51 (dd, 2, J = 9.0, 4.8), 3.74 (t, 2, J = 8.7), 4.36 (d, 2, J = 12.0), 4.39 (d, 12.1, 2), 5.70 (br s, 4), 7.09 (t, 2, J = 7.4), 7.19 (t, 4, J = 7.5), 731 (d, 4, J = 7.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7, 31.4, 31.9, 39.7, 40.5, 42.8, 46.9, 48.2, 58.8, 70.0, 73.2, 126.8, 127.3, 127.6, 127.7, 128.4, 138.4; IR (neat) 1639 (w), 1453, 1365, 1095 cm^{-1}; $[\alpha]_D$ −138 (c = 1.29, CH_2Cl_2).

(1*S*,1′*S*,6*R*,6′*R*,7*S*,7′*S*,8*R*,8′*S*)-*N*,*N*′-Bis(7-(Benzyloxymethyl)bicyclo[4.3.0]non-3-en-8-yl)-1,3-diaminopropane (27): R_f 0.35 (4% NH_3-saturated MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (q, 1, J = 7.9), 1.19−1.25 (m, 1), 1.34−1.47 (m, 4), 1.54−1.69 (m, 4), 1.74−1.95 (m, 7), 2.16−2.23 (m, 5), 2.42−2.64 (m, 4), 2.92 (t, 1, J = 6.8), 3.23 (q, 1, J = 7.6), 3.44 (t, 1, J = 7.5), 3.51−3.59 (m, 1), 3.67 (t, 1, J = 9.0), 4.45−4.54 (m, 4), 5.29 (br s, 4), 7.26−7.34 (m, 10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 31.6, 31.9, 32.1, 38.3, 39.7, 39.8, 40.6, 42.9, 44.0, 47.0, 47.3, 48.2, 53.3, 58.8, 62.5, 70.0, 73.1, 73.3, 84.1, 126.8, 126.9, 127.1, 127.3, 127.3, 127.4, 127.6, 127.7, 128.3, 128.4, 138.4, 138.7; IR (neat) 3019, 1639 (w), 1364.0, 1096.5 cm^{-1}; $[\alpha]_D$ −94.0 (c = 0.615, $CHCl_3$).

(1*S*,1′*S*,6*R*,6′*R*,7*S*,7′*S*,8*R*,8′*R*)-*N*,*N*′-Bis(7-(benzyloxymethyl)bicyclo[4.3.0]non-3-en-8-yl)-*N*,*N*′-bis(*tert*-butoxycarbonyl)-1,3-diaminopropane (28). A flask was charged with diamine **26**/**27** (0.067 g, 0.121 mmol) and 1 mL of CH_2Cl_2. Di-*tert*-butyl dicarbonate (0.79 g, .362 mmol) was added all at once, the flask was flushed with argon, and the reaction solution was allowed to stir at rt overnight. Excess ethanolamine was added, and the mixture was stirred for 30 min. The solvent was removed *in vacuo*, and the residue was partitioned between water and ether (5 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were washed with water (3 × 10 mL) and brine (10 mL) and dried over $MgSO_4$. Filtration and concentration gave a thick oil that was purified by silica gel chromatography using 1:5 ether/hexanes as an eluent to give 0.86 g (95%) of a colorless oil. ^{1}H NMR and ^{13}C NMR analysis showed only broad signals due to the *t*-Boc protecting groups: IR (neat) 2901, 1689, 1364, 1163 cm^{-1}; $[\alpha]_D$ +4.1 (c = 0.685, $CHCl_3$). Anal. Calcd for $C_{47}H_{66}N_2O_6$: C, 74.77; H, 8.81; N, 3.71. Found: C, 74.67; H, 8.96; N, 3.51.

(1*S*,1′*S*,6*R*,6′*R*,7*S*,7′*S*,8*R*,8′*R*)-*N*,*N*′-Bis(7-(hydroxymethyl)bicyclo[4.3.0]nonan-8-yl)-*N*,*N*′-bis(*tert*-butoxycarbonyl)-1,3-diaminopropane (29). A flask was charged with benzyl ether **28** (0.547 g, 0.725 mmol), 12 mL of 95% ethanol, and 10% palladium on carbon (0.164 g, 30% by wt). The flask was equipped with a H_2 balloon and allowed to stir for 8 h. Celite and ether were added, and the mixture was filtered through a plug of Celite that was thoroughly washed with ether. The solvent was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration and concentration gave a white foam that was purified by silica gel chromatography using 3:7 EtOAc/hexanes + 2% MeOH as eluent to give 0.424 g (100%) of a white solid. ^{1}H NMR and ^{13}C NMR analysis showed only broad signals due to the *t*-Boc protecting groups: mp 205−206.5 °C; R_f 0.3 (3:7 EtOAc/hexanes + 2% MeOH); IR ($CHCl_3$) 3436, 1657, 1478, 1368, 1147 cm^{-1}; $[\alpha]_D$ +54.4 (c = 0.55, $CHCl_3$). Anal. Calcd for $C_{33}H_{58}N_2O_6$: C, 68.48; H, 10.10; N, 4.84. Found: C, 68.28; H, 10.12; N, 4.48.

(1*S*,1′*S*,6*R*,6′*R*,7*S*,7′*S*,8*R*,8′*R*)-*N*,*N*′-Bis(7-formylbicyclo[4.3.0]nonan-8-yl)-*N*,*N*′-bis(*tert*-butoxycarbonyl)-1,3-diaminopropane (30). A dry flask was charged with diol **29** (79 mg, 0.137 mmol), CH_2Cl_2 (2.7 mL), 4 Å molecular sieves (80 mg), and *N*-methylmorpholine *N*-oxide (48 mg, 0.409 mmol). Tetrapropylammonium perruthenate (TPAP) (4.8 mg, 0.014 mmol) was added all at once, the flask was flushed with argon, and the mixture was stirred at rt for 20 min. The crude reaction mixture was loaded directly onto a silica gel column and was eluted with 1:4 EtOAc/hexanes to give 72 mg (92%) of a white foam as a mixture of diastereomers. ^{1}H NMR and ^{13}C NMR analysis showed only broad signals due to the *t*-Boc protecting groups. Because of the unstable nature of this compound, it was used directly in the next reaction: R_f 0.4 (1:4 EtOAc/hexanes); IR (neat) 2973, 1712, 1690, 1680, 1366, 1143 cm^{-1}; $[\alpha]_D$ −0.93 (c = 2.05, $CHCl_3$).

(1*S*,1′*S*,6*R*,6′*R*,7*R*,7′*R*,8*R*,8′*R*)-*N*,*N*′-Bis(7-ethynylbicyclo[4.3.0]nonan-8-yl)-*N*,*N*′-bis(*tert*-butoxycarbonyl)-1,3-diaminopropane (31). A dry flask was charged with potassium *tert*-butoxide (32 mg, 0.314 mmol) and THF (1 mL). The mixture was cooled to −78 °C under argon. Dimethyl (diazomethyl)phosphonate (35 mg, 0.329 mmol) was added with a cannula as a solution in 1 mL of THF. The yellow solution

was allowed to stir for 15 min at which time a diastereomeric mixture of dialdehyde **30** (86 mg, 0.150 mmol) was added with a cannula as a solution in 1 mL of THF. The bath was packed with dry ice, and the reaction solution was allowed to stir for 12 h and to slowly warm to room temperature. Water (5 mL) was added, and the mixture was extracted with ether (3 × 7 mL). The combined organic layers were washed with brine (7 mL) and dried over $MgSO_4$. Filtration and concentrantion gave a yellow oil that was purified by silica gel chromatography using 1:3 ether/hexanes as an eluent to give 16 mg (44%) of the unsymmetrical dialkyne **32**, 11 mg (13%) of a mixture of dialkynes, and 54 mg (64%) of the C_2-symmetric dialkyne **31**. The total yield of dialkyne was 81 mg (95%). ^{1}H NMR and ^{13}C NMR analysis showed only broad signals due to the *t*-Boc protecting groups: R_f 0.3 (1:3 Et_2O/hexanes); IR (neat) 3308, 2114, 1690, 1365, 1170 cm^{-1}; $[\alpha]_D$ +61.2 (c = 1.75, $CHCl_3$). Anal. Calcd for $C_{35}H_{54}N_2O_4$: C, 74.16; H, 9.60; N, 4.94. Found: C, 74.27; H, 995; N, 4.53.

(1*S*,1′*S*,6*R*,6′*R*,7*R*,7′*R*,8*R*,8′*S*)-*N*,*N*′-Bis(7-ethynylbicyclo-[4.3.0]nonan-8-yl)-*N*,*N*′-bis(*tert*-butoxycarbonyl)-1,3-diaminopropane (32). ^{1}H NMR and ^{13}C NMR analysis showed only broad signals due to the *t*-Boc protecting groups: R_f 0.35 (1:3 Et_2O/hexanes); IR (neat) 2973, 2112, 1690, 1365, 1170 cm^{-1}; $[\alpha]_D$ +39.03 (c = 1.03, $CHCl_3$). Anal. Calcd for $C_{35}H_{54}N_2O_4$: C, 74.16; H, 9.60; N, 4.94. Found: C, 74.07; H, 9.73; N, 5.01.

(1*S*,1′*S*,6*R*,6′*R*,7*R*,7′*R*,8*R*,8′*R*)-*N*,*N*′-Bis(7-vinylbicyclo-[4.3.0]nonan-8-yl)-1,3-diaminopropane (33): R_f 0.35 (5% NH_3-saturated MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80−0.90 (m, 2), 0.95−1.35 (m, 11), 1.60−1.85 (m, 11), 2.07−2.15 (m, 4), 2.43−2.60 (m, 4), 3.14 (dd, 2, J = 7.2, 15.8), 4.98−5.10 (m, 4), 5.81 (td, 2, J = 9.8, 17.1).

(1*S*,1′*S*,6*R*,6′*R*,7*R*,7′*R*,8*R*,8′*R*)-*N*,*N*′-Bis(7-ethynylbicyclo-[4.3.0]nonan-8-yl)-1,3-diaminopropane (15). A flask was charged with dialkyne **31** (0.157 g, 0.277 mmol) and CH_2Cl_2 (1 mL). The flask was equipped with a septum, flushed with argon, and cooled to 0 °C. Trifluoroacetic acid (1 mL) was added dropwise with a syringe over a period of 5 min. The solution was stirred for 2 h at 0 °C. The solvent was removed *in vacuo*, and the residue was stirred with a 1:1 mixture of CH_2Cl_2 and 1 M NaOH for 15 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (10 mL) and were dried over K_2CO_3. Filtration and concentration gave a yellow oil that was purified by silica gel chromatography using 4% NH_3-saturated MeOH/$CHCl_3$ as eluent to give 0.096 g (94%) of a yellow oil: R_f 0.3 (4% NH_3-saturated MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92−1.07 (m, 8), 1.13−1.23 (m, 6), 1.35 (qd, 2, J = 10.7, 2.9), 1.67−1.83 (m, 8), 2.03 (dd, 2, J = 12.4, 2.8), 2.10 (t, 2, J = 6.7), 2.16 (d, 2, J = 2.5), 2.35 (ddd, 2, J = 11.7, 8.5, 2.5), 2.58−2.72 (m, 4), 3.14 (q, 2, J = 6.7); ^{13}C NMR (100 MHz, C_6D_6) δ 26.4, 26.6, 30.7, 31.4, 32.0, 40.5, 41.9, 44.6, 47.2, 50.8, 58.4, 72.2, 84.4; IR (neat) 3307, 2111, 1343, 1150 cm- 1; $[\alpha]_D$ −71.1 (c = 1.26, $CHCl_3$).

(1*S*,1′*S*,6*R*,6′*R*,7*R*,7′*R*,8*R*,8′*S*)-*N*,*N*′-Bis(7-ethynylbicyclo-[4.3.0]nonan-8-yl)-1,3-diaminopropane (16). A dry flask was charged with dialkyne **32** (0.168 g, 0.296 mmol) and 1 mL of CH_2Cl_2, and the flask was equipped with a septum, flushed with argon, and cooled to 0 °C. Trifluoroacetic acid (1 mL) was added dropwise with a syringe over a period of 10 min. The solution was allowed to stir at 0 °C for 2 h at which time the solvent was removed, and the resulting oil was stirred with a 1:1 mixture of CH_2Cl_2 and 1 M NaOH (10 mL) for 10 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water and brine and dried over K_2CO_3. Filtration and removal of the solvent gave 107 mg of yellow oil that was purified by silica gel chromatography using 5% NH_3-saturated MeOH/$CHCl_3$ as eluent to give 100 mg (92%) of a colorless oil: R_f 0.3 (5% NH_3-saturated MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 0.70−0.94 (m, 5), 0.95−1.10 (m, 4), 1.10−1.25 (m, 2), 1.28−1.50 (m, 5), 1.52−1.70 (m, 7), 1.92 (dt, 1, J = 12.2, 6.8), 1.99 (d, 1, J = 2.4), 2.02 (d, 1, J = 2.5), 2.07 (ddd, 1, J = 10.9, 6.5, 2.4), 2.12−2.15 (m, 2), 2.20 (ddd, 1, J = 11.2, 8.1, 2.5), 2.59−2.76 (m, 3), 2.78−2.84 (m, 1), 2.97 (q, 1, J = 7.1), 3.28 (ddd, 1, J = 8.8, 6.5, 2.3); ^{13}C NMR (100 MHz, C_6D_6) δ 26.3, 26.4, 26.4, 26.6, 30.4, 30.6, 31.1, 31.9, 32.0, 39.2, 40.5, 41.9, 43.9, 44.6, 44.8, 47.2, 47.4, 50.9, 52.6, 58.3, 65.3, 69.6, 72.2, 84.3, 87.4; IR (neat) 3306, 2111, 1340, 1125 cm^{-1}; $[\alpha]_D$ −20.5 (c = 1.9, $CHCl_3$).

(1*S*,1′*S*,6*R*,6′*R*,7*R*,7′*R*,8*R*,8′*R*)-*N*,*N*′-Bis(7-((*E*)-2-(tributylstannyl)-vinyl)bicyclo[4.3.0]nonan-8-yl)-1,3-diaminopropane (34). A flask was charged with dialkyne **15** (31.7 mg, 0.87 mmol) and 0.9 mL of dry toluene. The flask was equipped with a reflux condensor and was flushed with argon. AIBN (4.4 mg, 0.027 mmol) was added followed by freshly distilled tributyltin hydride (0.14 mL, 0.519 mmol), and the solution was heated from room temperature to reflux with an oil bath over a 30 min period. After an additional 3 h period, the reaction solution was allowed to cool to room temperature and the toluene was removed *in vacuo*. The residue was loaded onto a silica gel column, and 1:1 EtOAc/hexanes (100 mL) was flushed through to remove nonpolar materials and then the column was eluted with 2% Et_3N/EtOAc to give 74.6 mg (91%) of colorless oil: R_f 0.4 (1:4 EtOAc/hexanes on Et_3N-treated silica gel plates); ^{1}H NMR (500 MHz, C_6D_6) δ 0.86−1.30 (m, 40), 1.38−1.45 (m, 14), 1.58−1.74 (m, 22), 1.83−1.85 (m, 2), 1.96−1.98 (m, 2), 2.13−2.20 (m, 4), 2.63−2.74 (m, 4), 3.23 (q, 2, J = 8.2), 6.10 (d, 2, J = 19.0), 6.30 (dd, 2, J = 8.4, 19.0); ^{13}C NMR (125 MHz, C_6D_6) δ 9.9, 14.0, 26.7, 27.0, 27.7, 29.7, 30.7, 31.8, 32.4, 41.5, 44.9, 47.7, 50.0, 59.0, 60.8, 129.2, 150.8; IR (neat) 2954, 1592, 1376, 1341 cm^{-1}; $[\alpha]_D$ −61.8 (c = 1.86, C_6H_6).

(1*S*,1*S*,6*R*,6′*R*,7*R*,7′*R*,8*R*,8′*S*)-*N*,*N*′-Bis(7-((*E*)-2-(tributylstannyl)vinyl)bicyclo[4.3.0]nonan-8-yl)-1,3 diaminopropane (35). A dry flask was charged with dialkyne **16** (100 mg, 0.273 mmol), toluene (2.7 mL), and AIBN (7.5 mg). The flask was equipped with a reflux condensor and was flushed with argon. Freshly distilled Bu_3SnH (0.44 mL, 1.64 mmol) was added, and the solution was heated from room temperature to reflux over a period of 30 min and was heated at reflux for 2.5 h. The reaction solution was allowed to cool to room temperature and was loaded directly onto a silica gel column (2.2 × 10 cm), and 200 mL of 1:1 EtOAc/hexanes was run through to remove nonpolar materials. The column was eluted with 1:1 EtOAc/hexanes + 2% Et_3N to give 0.192 g (74%) of a colorless oil: R_f 0.3 (84:15:1 hexanes/EtOAc/Et_3N); ^{1}H NMR (400 MHz, C_6D_6) δ 0.96 (t, 9, J = 7.3), 0.97 (t, 9, J = 7.3), 0.99−1.12 (m, 24), 1.41 (sept, 12, J = 7.4), 1.56−1.74 (m, 21), 1.83−1.85 (m, 2), 1.97 (2.00, m, 3), 2.11 (2.12, m, 1), 2.16−2.25 (m, 1), 2.62−2.75 (m, 4), 3.00−3.03 (m, 1), 3.18−3.22 (m, 1), 6.10-6.13 (m, 2), 6.12 (d, 1, J = 19.0), 6.30 (dd, 1, J = 8.4, 19.0); ^{13}C NMR (100 MHz, C_6D_6) δ 9.8, 9.9, 14.0, 14.0, 26.6, 26.7, 26.8, 26.9, 27.7, 27.7, 29.6, 29.7, 30.5, 30.7, 31.7, 32.3, 32.4, 39.2, 41.4, 44.4, 44.8, 47.9, 48.0, 50.0, 51.4, 58.9, 60.8, 36.3, 64.2, 127.6, 129.2, 150.8, 153.2; IR (neat) 3302, 1594, 1376, 1072 cm^{-1}; $[\alpha]_D$ −7.8 (c = 1.6, $CHCl_3$).

Papuamine (1). A flask was charged with bis-vinylstannane **34** (45.2 mg, 0.0476 mmol), DMF (4.8 mL), and $PdCl_2(PPh_3)_2$ (3.3 mg, 0.0048 mmol) to give a clear, light yellow solution. CuI (1.8 mg, 0.095 mmol) was added, and the solution was stirred open to the air. The reaction solution was dark orange within 5 min and faded to light green over a period of 1 h. After a total of 22 h, an additional portion of $PdCl_2(PPh_3)_2$ (3.3 mg, 0.0048 mmol) was added, causing the reaction solution to turn from green to yellow and gradually back to green. The solution was stirred for an additional 7 h at which time it was loaded directly onto a silica gel column (2.2 × 8 cm) and was eluted with 200 mL of 5% NH_3-saturated MeOH/$CHCl_3$. Concentration *in vacuo* gave an oily residue that was partitioned between 1 M HCl and ether (20 mL). The layers were separated, and the aqueous layer was extracted with ether (20 mL). The organic layers were dried over K_2CO_3. Filtration and concentration gave a yellow semisolid that was subjected to silica gel chromatography using 1:5:94 Et_3N/EtOAc/hexanes to give 2.9 mg (0.0031 mmol) of bis-vinylstannane **34**. The acidic aquious layer was neutralized with solid Na_2CO_3 and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried over K_2CO_3. Filtration and concentration gave 6 mg (34%) of papuamine (**1**) as a white solid: mp 165−167 °C; R_f 0.35 (5% NH_3-saturated MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79−

0.92 (m, 4), 0.95−1.08 (m, 4), 1.09−1.24 (m, 6), 1.49−1.54 (m, 2), 1.67−1.73 (m, 4), 1.77−1.84 (m, 4), 2.17−2.28 (m, 6), 2.40−2.46 (m, 2), 2.96 (br q, 2, J = 8.0), 5.69−5.77 (m, 2), 6.06−6.13 (m, 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 26.4, 30.5, 31.3, 31.7, 42.1, 43.8, 45.9, 48.8, 51.2, 61.0, 129.5, 130.8; IR ($CHCl_3$) 3686, 1602, 1518, 1197.4 cm^{-1}; $[\alpha]_D$ −346 (c = 0.46, MeOH).

Haliclonadiamine (2). A flask was charged with bis-vinylstannane **35** (55.2 mg, 0.058 mmol), *N*,*N*-dimethylacetamide (5.8 mL), and $PdCl_2(PPh_3)_2$ (4.1 mg, 0.0058 mmol) to give a clear, yellow solution. CuI (1.3 mg, 0.012 mmol) was added, causing the solution to turn orange. The reaction solution was stirred for 23 h at which time an additional portion of $PdCl_2(PPh_3)_2$ (4.1 mg, 0.0058 mmol) was added and the resulting solution was stirred for 18 h. The reaction solution was loaded directly onto a silica gel column (2.2 × 8 cm) and was eluted with 200 mL of 10% NH_3-saturated MeOH/$CHCl_3$. Concentration *in vacuo* gave a yellow oil that was partitioned between 1 M HCl and ether (15 mL). The layers were separated, and the aqueous layer was extracted with ether (15 mL). The organic extracts were discarded. The aqueous layer was neutrlized with solid Na_2CO_3 and was extracted with CH_2Cl_2 (3 × 10 mL). The combined orgainc layers were washed with brine and dried over K_2CO_3. Filtration and concentration gave 10 mg of a yellow solid that was shown by ^{1}H NMR analysis to be mostly product. This material was purified by silica gel chromatography using 10% NH_3-saturated MeOH/$CHCl_3$ as eluent to give 2.5 mg (12%) of haliclonadiamine (**2**) as a light yellow solid: mp 97−102 °C dec; R_f 0.35 (10% NH_3-saturated MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85−1.40 (m, 12), 1.50−1.90 (m, 14), 1.99 (td, 1, J = 7.1, 12.1), 2.08 (ddd, 1, J = 4.9, 7.3, 12.1), 2.13−2.20 (m, 1), 2.39 (dt, 1, J = 4.2, 11.0), 2.49 (dt, 1, J = 6.1, 10.7), 2.56 (dt, 1, J = 6.0, 9.8), 2.95 (td, 1, J = 6.7, 12.5), 3.15 (br q, 1, J = 8.5), 5.30 (dd, 1, J = 9.7, 15.2), 5.55 (dd, 1, J = 10.2, 15.3), 6.11 (dd, 1, J = 10.4, 15.3), 6.23 (dd, 1, J = 10.4, 15.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 26.3, 26.5, 26.7, 30.1, 30.5, 31.6, 32.2, 32.2, 37.0, 41.0, 44.0, 44.8, 47.1, 48.7, 49.6, 51.2, 51.4, 60.1, 62.6, 68.2, 132.0, 132.5, 133.9, 134.0; IR (CH_2Cl_2) 3685, 1606, 1247 cm^{-1}; $[\alpha]_D$ −5.0 (c = 0.12, $CHCl_3$).

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