Total Synthesis of (+)-Papuamine: An Antifungal Pentacyclic Alkaloid from a Marine Sponge, *Haliclona* sp.

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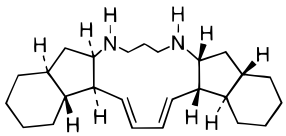
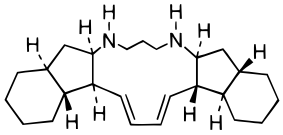
The total synthesis of (+)-papuamine, the antipode of the C_2-symmetric, optically active, pentacyclic diamine natural product, starting from a chiral diol is described. The diol is available *via* an asymmetric Diels−Alder reaction between 1,3-butadiene and di-(−)-menthyl fumarate. The key transformation in the synthesis is an intramolecular Pd(0)-catalyzed (Stille) coupling reaction to form the central 13-membered diazadiene macrocyclic ring.

Introduction

In 1988, Scheuer and co-workers reported the isolation of papuamine (**1**) from *Haliclona* sp., a marine sponge, collected at South Lion Island, Papua, New Guinea.[1] The structure was assigned as a C_2-symmetric, optically active, pentacyclic diamine from spectroscopic data although the absolute configuration was not defined at that time.[1] Papuamine (**1**) was shown to inhibit the growth of the dermatophyte *Trichophyton mentagrophytes*.[1] Subsequently, Faulkner and Clardy *et al*. reported the isolation of both papuamine (**1**) and haliclonadiamine (**2**) from a specimen of *Haliclona* collected in Palau.[2] The structure of haliclonadiamine (**2**), the major component, was assigned unequivocally from a single-crystal X-ray structure determination on the diacetamide derivative. Again, however, the absolute stereochemistry was not defined.[2] The unique C2 symmetrical structure and biological activity make papuamine (**1**) an interesting target for total synthesis.



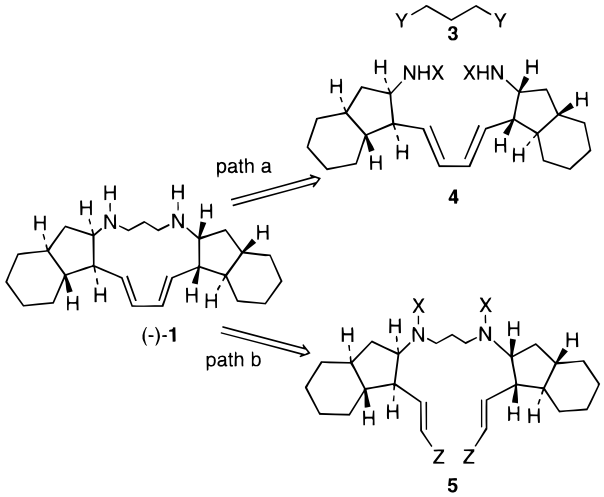
(-)-**Papuamine 1**



Haliclonadiamine 2

Herein we report a total synthesis of (+)-papuamine, the antipode of the natural product.[3] In planning our approach, it is logical to disconnect the molecule at the C2 axis to give two equivalent homochiral fragments and thus make molecular assembly simple and convergent. In the design, there are two distinct approaches to close the 13-membered diamino diene unit (Scheme 1), namely, macrocyclization, via *N,N′*-dialkylation, using a C3 dielectrophile (path a) or macrocyclization via carbon−carbon bond formation to reveal the diene entity (path b). There is much flexibility in both of these designs. The dielectrophile **3** may be simple such as a 1,3-dibromopropane or more complex such as an electronically activated allylic halide. Secondly, the nitrogen protecting/activating group X in dienes **4** and **5** may be extensively varied.[4] Finally, the Z substituents in diene **5** can be changed to accommodate a legion of organometallic approaches to close the medium size ring heterocycle. All this flexibility proved to be essential since initial approaches to close the macrocycle were unsuccessful.

Scheme 1



Results and Discussion

Nitroalkene Approach. Initially, we sought to elaborate papuamine using the Michael addition reaction of substituted alkenyl organometallic reagents to the nitroalkene **14**. Our synthesis began from the known enantiomerically pure diol **6** which was prepared from the Diels−Alder reaction of di-(−)-menthyl fumarate with 1,3-butadiene and subsequent lithium aluminum hydride mediated reduction.[5,6] The choice of the absolute stereochemistry of the isomer **6** was completely arbitrary, since the absolute configuration of papuamine (**1**) was at that time unknown. (+)-Diol **6** was converted into the unsaturated ketone **10** using methods largely similar to those reported for the corresponding racemic material

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(1) Baker, B. J.; Scheuer, P. J.; Shoolery, J. N. *J. Am. Chem. Soc.* **1988**, *110*, 965.
(2) Fahy, E.; Molinski, T. F.; Harper, M. K.; Sullivan, B. W.; Faulkner, D. J.; Parkanyi, L.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 3427.
(3) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc, Chem. Commun.* **1994**, 1881.
(4) *Protecting Groups in Organic Synthesis,* 2nd ed.; Greene, T. W., Wuts, P. G. M., Eds.; Wiley: New York, 1991.
(5) Heathcock, C. H.; Davis, B. R.; Hadley, C. R. *J. Med. Chem.* **1989**, *32*, 197.
(6) Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507.

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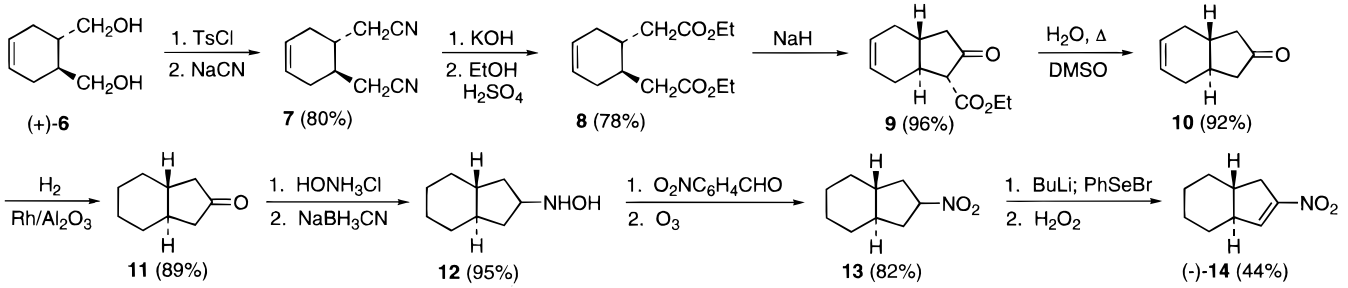
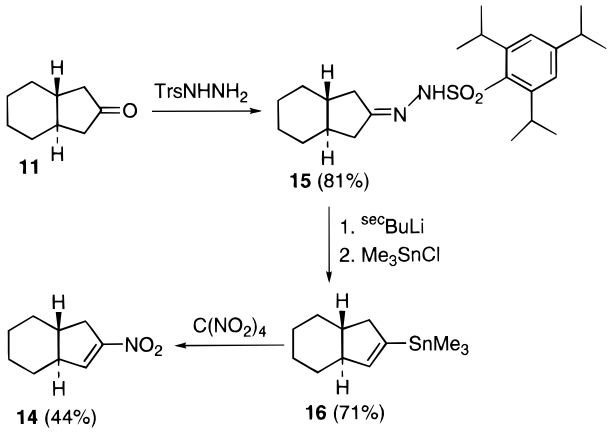
Scheme 2



Scheme 3



(Scheme 2).[7] Dieckmann cyclization of the diester **8** gave the (−)-β-keto ester **9** as a mixture of epimers (*R*:*S* = 11:1) reflecting the thermodynamic control of the reaction. Hydrolysis of the β-keto ester **9** and decarboxylation gave the corresponding tetrahydroindanone **10** (92%). Subsequent hydrogenation of alkene **10** to the saturated ketone **11** was carried out using rhodium on alumina as a catalyst to avoid any ring junction isomerization.

In principle, it should be possible to convert this ketone **11** directly into the corresponding nitroalkane **13** via oxidation of the derived oxime using pertrifluoroacetic acid.[8] However, this method requires the use of 90% hydrogen peroxide, which is no longer commercially available; thus an alternative method was developed. Ketone **11** was first converted to the oxime and then reduced to the hydroxylamine **12** using the conditions of Borch and co-workers.[9] Subsequent condensation of hydroxylamine **12** with 4-nitrobenzaldehyde gave an intermediate nitrone[10] which was not purified but directly subjected to ozonolysis[10b] to produce the nitroalkane **13** in good yield. Phenylselenenylation of the lithium nitronate derived from **13** followed by selenoxide elimination using the conditions of Sakakibara[11] gave the nitroalkene **14** (44%). In parallel, we have examined a second synthesis of the target nitroalkene **14** (Scheme 3). Condensation of the ketone **11** with (2,4,6-triisopropylbenzenesulfonyl)hydrazine gave the corresponding trisylhydrazone **15**. Following the Corey modification[12] of the Shapiro−Bond reaction,[13] lithiation of the trisylhydrazone **15** and stannylation of the derived vinyllithium reagent gave the vinylstannane **16**. This substance, in turn, was allowed to react with tetranitromethane[12] to give nitroalkene **14**. Additionally, large quantities of the nitroalkene **14** were prepared as the racemate starting from racemic *trans*-diethyl 4-cyclohexene-1,2-dicarboxylate.[7]

With nitroalkene **14** in hand, the reaction with the higher order vinylcuprate **17**[14] was investigated. When racemic **14** was allowed to react with cuprate **17** at −78 °C in THF solution and the reaction was quenched with acetic and hydrochloric acids,[15] a mixture of diastereoisomeric Michael adducts was formed in 62% yield (Scheme 4). Chromatography gave a single pure racemic isomer (**18**) in 52% yield and a fraction containing other isomers (10%). Attempts to determine the stereochemistry of **18** using both NOE and decoupling NMR experiments were inconclusive, and the material was taken on further in the synthesis. Reduction of the nitroalkane **18** under transfer hydrogenation conditions[16] gave the corresponding racemic amine **19** in good yields, as long as the reaction mixture was anhydrous. The amine **19** was successfully converted to a number of crystalline derivatives, but unfortunately none were suitable for an X-ray structure determination, to aid in the determination of the stereochemistry of **18**.

The enantiomerically pure amine **19** was synthesized by the route shown in Scheme 4 starting with (−)-nitroalkene **14**. Attempts were made to convert the amine **19** into the corresponding diene **21** using a double-alkylation strategy. Amine **19** was first protected as its *tert*-butoxycarbonyl derivative **20** and allowed to react with 1,3-diiodopropane under basic conditions to establish the 1,3-propanediyl bridge. Unfortunately, reaction of **20** with 1,3-diiodopropane in the presence of sodium hydride in DMF, lithium diisopropylamide in THF, or potassium hydride and 18-crown-6 in THF was unsuccessful. Only the allylated derivative **22** could be obtained in reasonable yields (Scheme 4).

Since alkylation of **20** failed, an alternative procedure was investigated. Reaction of amine **19** with malonyl dichloride (ca. 0.5 equiv) gave moderate yields of the malonic amide dimer **23**. Protodestannylation[17] of **23** gave **24**, which was a crystalline solid, and a single-

(7) (a) Krawczyk, A. R.; Jones, J. B. *J. Org. Chem.* **1989**, *54*, 1795. (b) Mundy, B. P.; Theodore, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 2005. (c) Turecek, F.; Vystrcil, A. *Collect. Czech. Chem. Commun.* **1976**, *41*, 1571.

(8) Emmons, W. D.; Pagano, A. S. *J. Am. Chem. Soc.* **1955**, *77*, 4557.

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

(10) (a) Inouye, Y.; Watanabe, Y.; Takahashi, S.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3763. (b) Aebischer, B.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 789.

(11) Sakakibara, T.; Takai, I.; Ohara, E.; Sudoh, R. *J. Chem. Soc., Chem. Commun.* **1981**, 261.

(12) Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1980**, *21*, 1113.

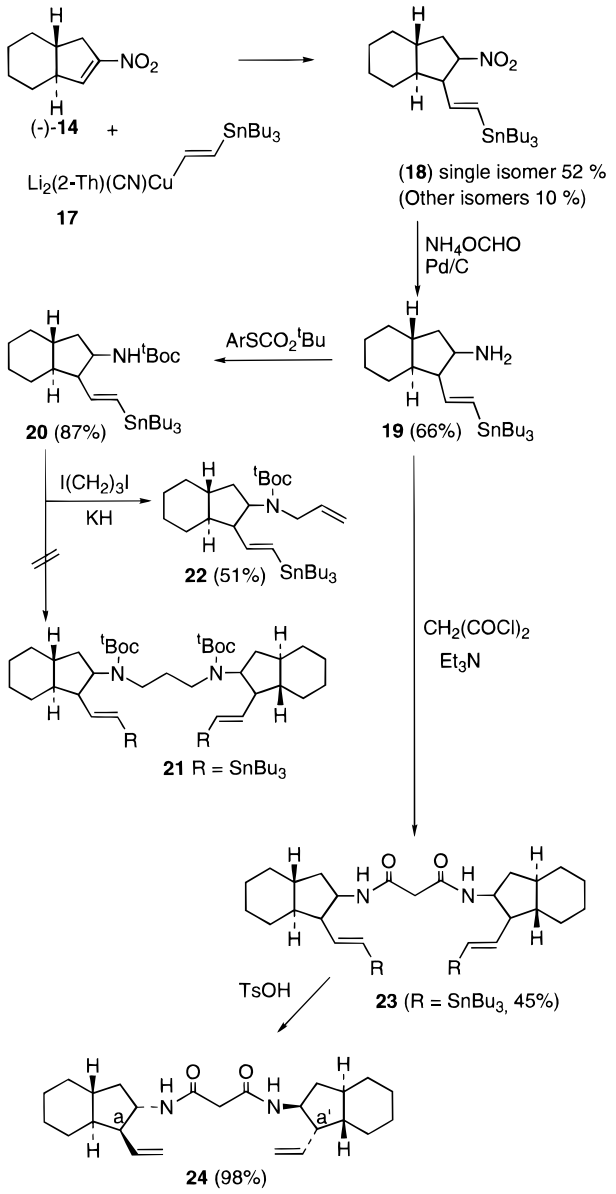
(13) (a) Chamberlain, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. (b) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.

(14) Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Elsworth, E.; Lipshutz, B. H. *Tetrahedron Lett.* **1989**, *30*, 27.

(15) Corey, E. J.; Estreicher, H. *J. Am. Chem. Soc.* **1978**, *100*, 6294.

(16) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733.

Scheme 4



crystal X-ray structure determination revealed the relative stereochemistry shown in Scheme 4.[18] As is seen in comparison with the natural product **1**, the malonamide **24** unfortunately has the incorrect relative stereochemistry of the vinyl side chains (stereocenters a and a′). This must mean that the facial selectivity in the attack of higher order vinylcuprate **17** on nitroalkene **14** is controlled by stereoelectronics rather than by steric factors (Figure 1). Thus the vinylcuprate reagent must approach the nitroalkene **14** along a pseudoaxial trajectory and *cis* to the ring carbon rather than *cis* to the ring hydrogen atom. This should produce the nitronate **25** and subsequently, on protonation, nitroalkane **18**. Several attempts were made to alter the stereochemical outcome of the Michael addition reaction by using alternative vinyl organometallic reagents. All met with unmitigated

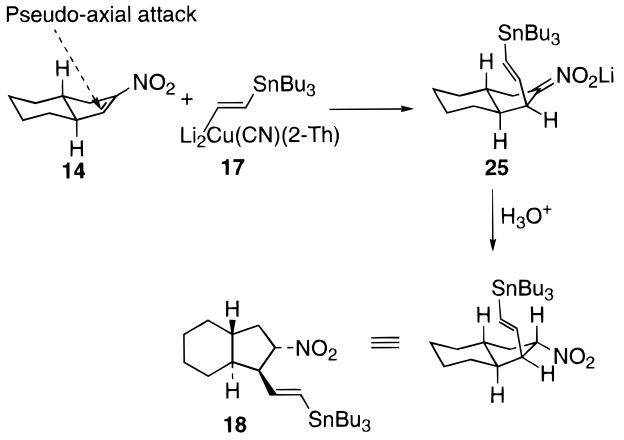


Figure 1.

failure. Additionally, attempts to isomerize the nitroalkane **18** via double lithiation[19] were also unsuccessful. On the basis of these disappointing results, an alternative strategy was investigated.

The β-Keto Ester Approach. The relative stereochemistry at C7 in the (−)-β-keto ester **9** is predominately (11:1) as is required for the natural product (**1**). It was envisioned that the direct functionalization of the hydrindan ring system of ketone **9** should proceed with the correct relative stereochemical control. Thus ketone **9** was converted into the corresponding ketal **26** by condensation with ethylene glycol. Fortuitously, this reaction, which is subject to thermodynamic control, resulted in an enhancement of the isomer ratio to 25:1. Sequential reduction of the ester **26**, *O*-benzylation, and ketal hydrolysis gave the β-benzyloxy ketone **27c**. We anticipated that reductive amination of ketone **27c** should provide the *cis* amino ether.[20] As anticipated, reductive amination of **27c** with benzylamine under mild conditions[21] gave predominately (4.5:1) the required *cis*-isomer **28** in 70% yield after chromatography (Scheme 5). In order to prove the relative stereochemistry of **28**, the secondary amine was converted into the primary amine **29** by reaction with ammonium formate in the presence of palladium on carbon.[22] It is interesting to note that this reaction proceeded with both alkene hydrogenation and selective hydrogenolysis of the *N*-benzyl substituent without loss of the benzyl ether. This chemoselectivity is unusual and warrants further study. The amine **29** was converted to its *tert*-butoxycarbonyl derivative **30** under standard conditions[23] (Scheme 5). The carbamate **30** was crystalline and a single-crystal X-ray study confirmed the stereochemical assignment.[18]

With an appropriate method for obtaining the properly substituted hydrindan ring system, a strategy was needed for homologating the protected alcohol moiety in carbamate **30** to intermediates suitable for an organometallic coupling reaction to reveal the conjugated diene unit of papuamine. Initially, it was decided to form the 1,3-diene unit of papuamine (**1**) first and to close the 13-

(17) Davies, A. G. Tin. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Davies, A. G., Eds.; Pergamon Press: Oxford, 1995; Vol. 2, pp 241−2.

(18) The author has deposited atomic coordinates for compounds **24** and **30** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(19) Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101.

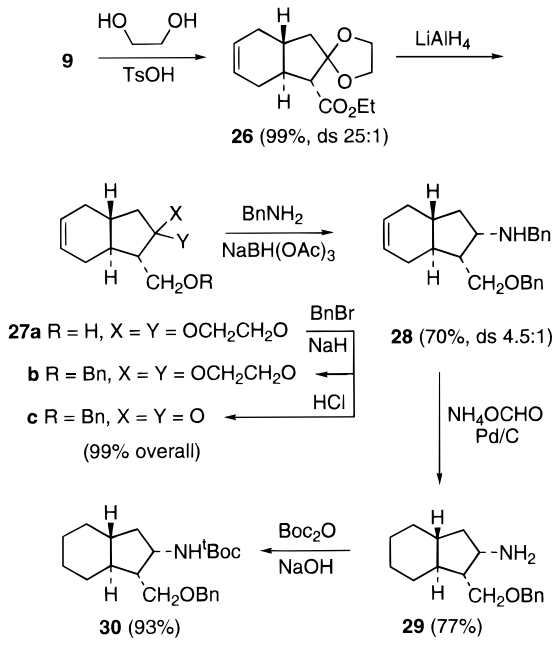
(20) (a) Hutchins, R. O.; Su, W.-Y. *Tetrahedron Lett.* **1984**, *25*, 695. (b) Hutchins, R. O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412. (c) Wrobel, J. E.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 3447.

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

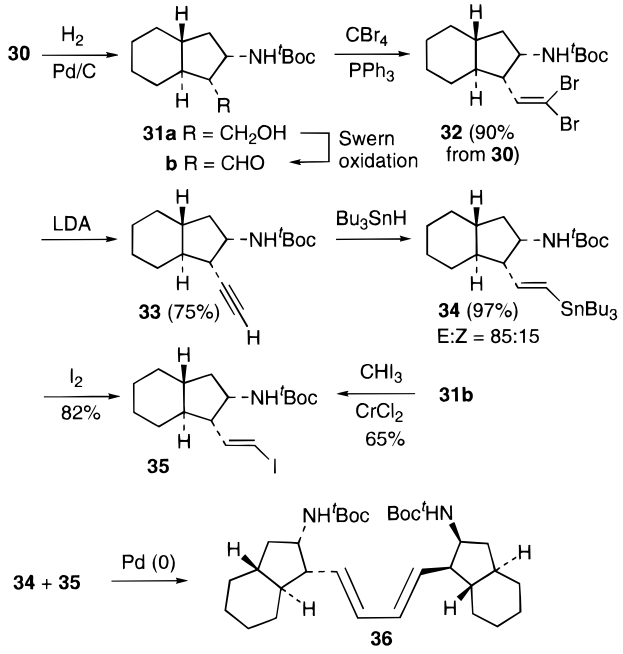
(22) Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.

(23) Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730.

Scheme 5



Scheme 6



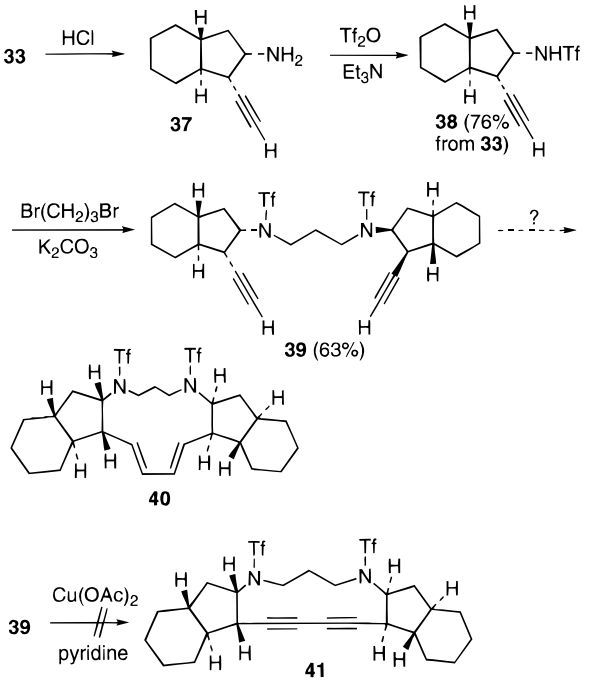
membered macrocycle by the addition of the three-carbon bridge (path a, Scheme 1). This analysis led us to target the vinylstannane **34** and vinyl iodide **35**, which would be subjected to a palladium(0)-catalyzed coupling reaction[24] to provide the desired 1,3-diene. Preparation of the coupling partners **34** and **35** is shown in Scheme 6. Deprotection of the benzyl ether **30** was effected by hydrogenolysis over palladium on carbon. Subsequent Swern oxidation[25] of the resulting alcohol **31a** to the aldehyde **31b** was followed by conversion to the terminal alkyne **33** via the dibromide **32**.[26] Hydrostannylation[27] gave the vinylstannane **34** as an 85:15 mixture of *E* and *Z* isomers. Vinylstannane **34** was iododestannylated[28] to provide the corresponding pure (*E*)-vinyl iodide **35** (82%). Alternatively, the iodide **35** was formed directly from the aldehyde **31b** using the Takai procedure.[29] With the coupling partners **34** and **35** in hand, the Stille coupling reaction was attempted. Unfortunately, this reaction proved to be problematic under a variety of conditions.[24,30] The diene synthesis was attempted using diverse catalysts [$Pd(MeCN)_2Cl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ or $Pd_2(dba)_2$] in THF, DMF, or NMP in the presence or absence of additives [Ph_3As, TBAF, or $(2\text{-Fur})_3P$]. All of these reactions did indeed provide the desired 1,3-diene; however, in most cases yields were low and the required (*E*,*E*)-diene was isolated admixed with other geometric isomers. In consequence of these unfortunate facts, the approach to papuamine based upon a late double-alkylation reaction (Scheme 1, path a) was placed aside. Instead we then sought to close the macrocycle using an intramolecular palladium(0)-catalyzed reaction to elaborate the conjugated diene unit (path b, Scheme 1).

Approaches to the Macrocycle. The carbamate **33** was converted via amine **37** into the corresponding trifluoromethanesulfonamide **38** and doubly alkylated using 1,3-dibromopropane[31] to yield dimer **39** in moderate yield. We sought to convert this intermediate into the papuamine derivative **40** using an intramolecular reductive diyne coupling. We considered that hydrozirconation and transmetalation (Zr to Cu) of the diyne **39** might provide a means to form the macrocycle **40** via a homocoupling reaction.[32] This reaction works effectively in an intermolecular sense, on unfunctionalized substrates. For example, in our hands hydrozirconation of 1-decyne with Schwartz's reagent[32] (Cp_2ZrHCl) followed by reaction with copper(I) chloride gave (*E*,*E*)-9,11-eicosadiene (79%). Sadly, attempts to form the macrocycle **40** utilizing this chemistry were unsuccessful. None of the desired cyclization product could be detected, nor indeed could diene of any description (Scheme 7). It was possible that the labile trifluoromethanesulfonamido group was interfering with the organometallic chemistry in this case. An attempt was made to carry out an intramolecular acetylenic coupling reaction. However, reaction of diyne **39** under the Eglinton conditions[33] at high dilution gave only intractable products. A 13-membered ring containing a conjugated diyne such as **41** would be extremely strained, and thus very difficult to form.[33]

Since the direct reductive macrocyclization of diyne **39** was unsuccessful, we sought to complete the synthesis of papuamine using a Stille reaction to construct the diene unit. Although the preparation of the diene **36** was complicated by poor geometric control, we considered that the palladium-catalyzed macrocyclization reaction should be more geometrically faithful. This optimism ultimately proved well founded. The amine **29** was converted to the trifluoromethanesulfonamide and toluene-4-sulfonamide derivatives[4] **42a** and **42b** (Scheme 8). Although the reaction between sulfonamide **42b** and 1,3-dichloropro-

(24) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
(25) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
(26) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
(27) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(28) Hanson, R. N.; El-Wakil, H. *J. Org. Chem.* **1987**, *52*, 3687.
(29) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2260.
(30) (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (b) Hatanaka, Y. Hiyama, T. *Synlett* **1991**, 845.
(31) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. *Tetrahedron* **1975**, *31*, 2517.
(32) Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, *18*, 1303.
(33) *Advances in Organic Chemistry*, Vol. 4; Eglinton, G., McCrea, W., Eds.; Interscience: New York, 1963; pp 225−328.

Scheme 7



pane to provide **44b** was inefficient (48%) and accompanied by extensive elimination to produce *N*-allyltoluene-4-sulfonamide derivatives, the trifluoromethanesulfonamide **42a** was coupled with 1,3-dibromopropane[31] to produce the symmetrical dimer **43** in excellent yield. Deprotection of the trifluoromethanesulfonyl groups was carried out using sodium bis(methoxyethoxy)aluminum hydride (REDAL)[31] and replaced by the more robust toluene-4-sulfonyl group[4] to give **44b**. The benzyl ether residues in **44b** were resistant to standard hydrogenolysis conditions[4] but were cleaved using W-2 Raney nickel under a hydrogen atmosphere.[4] The resulting diol **45a** was Swern oxidized[25] and the product dialdehyde **45b** converted into the diiodide **46** using the Takai method.[29] Attempted macrocyclization via lithium−halogen exchange with *n*-butyllithium at low temperature followed by the addition of a stoichiometric quantity of $Pd(PPh_3)_2Cl_2$ was unsuccessful. Macrocyclization of **46** was also attempted using nickel(0) complexes [$Ni(COD)_2$ and $Ni(PPh_3)_4$],[34] but these reactions also failed.

It is known from the work of Danilova *et al.* that 1,3-dienes can be prepared from the palladium(0)-catalyzed homocoupling of vinylstannanes.[35] Thus we sought to examine whether such a process would elaborate the required macrocycle. Reaction of diiodide **46** with excess of hexamethyldistannane in the presence of $Pd(PPh_3)_2Cl_2$ gave the bis-stannane **47**.[36] Unfortunately, all attempts to convert **47** into the macrocycle **49** by the elimination of hexamethyldistannane were unsuccessful. At this point we realized that we were obliged to run the gauntlet of desymmetrization. Reaction of the bis-stannane **47** with a stoichiometric quantity of iodine[28] resulted in the formation of a statistical mixture of starting material **47**, the desired iodostannane **48**, and regenerated diiodide **46.** Both dienes **46** and **47** were recycled. The intramolecular Stille reaction[37] was attempted using **48** as the substrate. Recently, this strategy has been applied to the total synthesis of rapamycin[38] and by Pattenden and Thom for the construction of polyene macrolactams.[39] Reaction of the iodostannane **48** with $Pd(PPh_3)_4$ (40 mol %) in THF solution under high-dilution conditions provided a product in ca. 28% yield, of which the proton NMR spectrum was consistent with formation of the macrocyclic diene **49**. High-resolution mass spectrometry confirmed that macrocyclization had indeed taken place. Efforts to improve the yield of this reaction, by varying the solvent, failed. Diene **49** appeared to be a propitious compound, but this initial optimism soon turned to dust. The material proved to be air sensitive, and we were further aggravated to find that deprotection of this material, to give the desired bis-amine, failed under a variety of conditions. At this point we decided to use a more labile amine protecting group, namely, the trifluoromethylsulfonyl residue, hoping that it could be removed more easily to reveal the desired diamine, papuamine.

Hydrogenolysis of benzyl ether **43** (Scheme 9) was carried out under standard conditions.[4] The product diol **50** was Swern oxidized,[25] and the resulting dialdehyde, which proved to be delicate and particularly prone to the β-elimination of trifluoromethanesulfonamide, was converted directly into the (*E*,*E*)-diiodide **51**, again using the Takai method.[29] Reaction of diiodide **51** with excess hexamethyldistannane in the presence of $Pd(PPh_3)_2Cl_2$ and Li_2CO_3,[36] to sequester any HI generated in the reaction, gave the (*E*,*E*)-bis-vinylstannane **52**. Again this substance was subject to desymmetrization. Treatment of the distannane **52** with a stoichiometric quantity of iodine in ether[28] provided iodostannane **53** in 44% yield along with recovered starting material **52** (24%) and regenerated diiodide **51** (24%), which were again dutifully recycled. The syringe pump addition of a solution of the iodostannane **53** in toluene to a solution of $Pd(PPh_3)_4$ in toluene at 100 °C did indeed provide the desired macrocycle **54** in 39% yield. Deprotection of **54** to the target diamine papuamine (**55**) was carried out using lithium aluminium hydride in diethyl ether at reflux. The diamine **55** was then converted to its dihydrochloride **56** in quantitative yield by treatment with concentrated hydrochloric acid in aqueous methanol, and the product salt was isolated following lyophilization.

We also considered that it should be possible to prepare the diene **54** directly from diiodide **51**. However, instead of attempting a reductive homocoupling reaction, we reasoned that if a stoichiometric quantity of hexamethylditin was reacted with **51** in the presence of a palladium(0) catalyst, then the iodostannane generated *in situ* should undergo cyclization to give the desired diene **54**. It was found that slow addition of a solution of **51** and hexamethylditin in toluene to a solution of $Pd(PPh_3)_4$ in toluene at 100 °C did indeed provide the macrocycle. Unfortunately, this material could not be readily separated by chromatography from the generated iodostan-

(34) (a) Takagi, K.; Hayama, N.; Sasaki, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1887. (b) Takagi, K.; Mimura, H.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3517. (c) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460.

(35) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. L.; Spirikhin, L. V. *Synthesis* **1989**, 633.

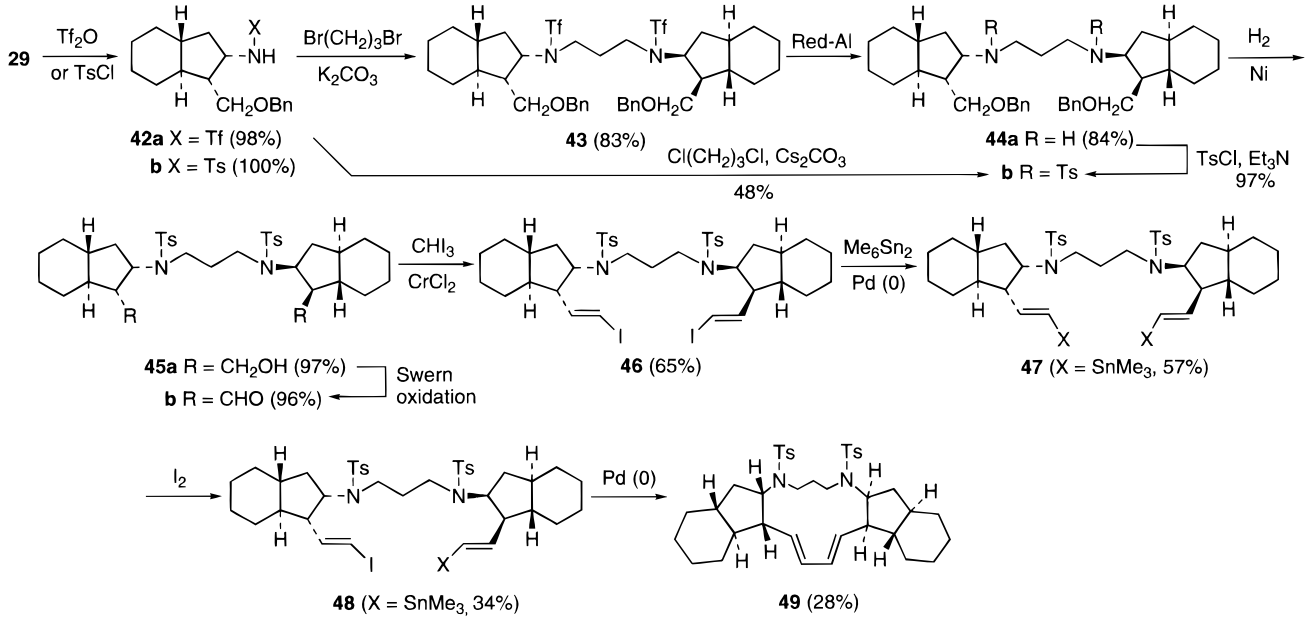
(36) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.

(37) (a) Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785. (b) Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883.

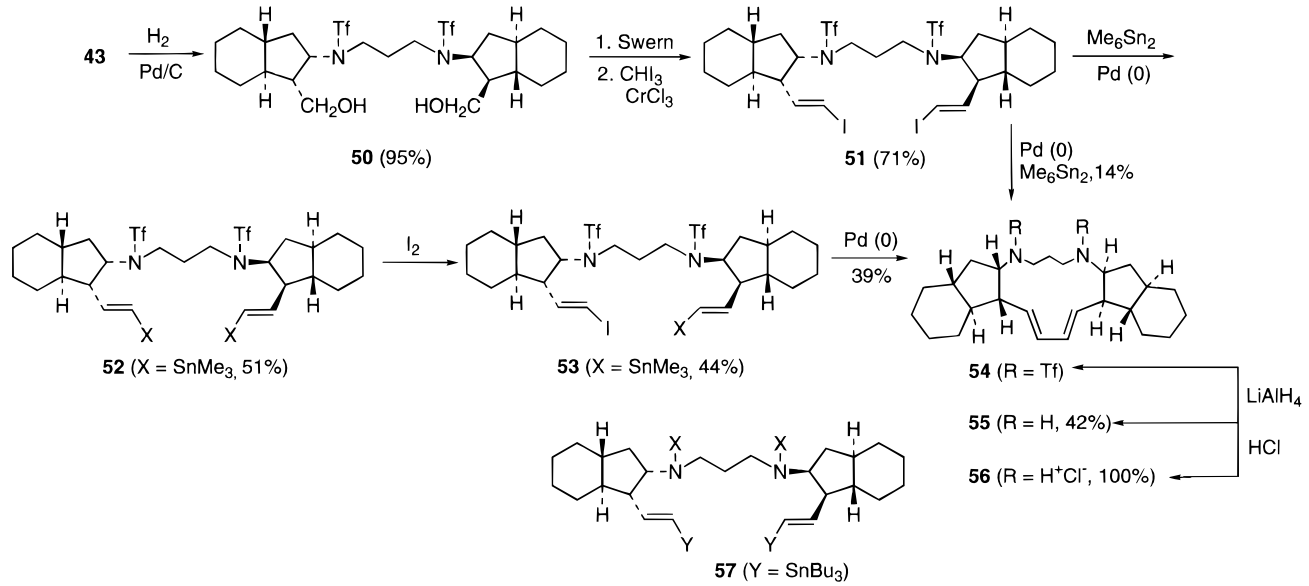
(38) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419.

(39) Pattenden, G.; Thom, S. M. *Synlett* **1993**, 215.

Scheme 8



Scheme 9



nane **53**. The desired macrocycle **54** could, however, be isolated in pure form (14% yield), if an additional portion of catalyst was added to the mixture after the addition of diiodide **51** and the hexamethylditin solution was complete.

Our synthetic (+)-papuamine **55** and its dihydrochloride **56** showed spectral characteristics (^{1}H NMR, ^{13}C NMR, HRMS, and IR) that were identical with those reported for the natural material. Additionally, our synthetic sample of the dihydrochloride **56** was identical with an authentic sample. Synthetic papuamine dihydrochloride **56** exhibited an optical rotation {$[\alpha]_D$ +139° (c = 0.34, MeOH)} which corresponds exactly, albeit antipodally, with the natural product {$[\alpha]_D$ −140° (c = 1.3, MeOH)}[1] and UV λ_{max} = 236 nm (MeOH) {lit.[1] UV λ_{max} = 241 nm (MeOH)}. Shortly after our preliminary publication,[3] Weinreb and coworkers reported the total synthesis of (−)-papuamine dihydrochloride.[40] Additionally, Heathcock and coworkers have also described the total synthesis of both (−)-papuamine and (−)-haliclonadiamine.[41] Interestingly, both these authors reported that palladium(0)-catalyzed macrocyclization of bis-stannane **57** to provide papuamine (**1**) was only successful when no secondary amine protecting group (X = H) was used!!! Weinreb also commented on difficulties in handling papuamine free base. We have observed exactly the same behavior, which is possibly due to formation of a bicarbonate salt, and recommend that papuamine is best handled as its dihydrochloride.

It is clear from our results and those from both the Weinreb and Heathcock groups that palladium(0)-catalyzed macrocyclization is a viable strategy for the synthesis of the structurally unusual natural product papuamine and its antipode.

(40) Borzilleri, R. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 9789. Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905.

(41) McDermott, T. S.; Mortlock, A.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 700.

Experimental Section

General Procedures. Solvents were dried by distillation under N_2 or Ar, from sodium benzophenone ketyl (THF, Et_2O, PhH, PhMe), CaH_2 (CH_2Cl_2, MeCN, DMF, Et_3N, pyridine), KOH (*i*-Pr_2NH), and Mg and I_2 (MeOH). Raney Ni (type W-2) was purchased from the Aldrich Chemical Co. and was used immediately after opening in order to be effective. All other reagents were used as received unless otherwise stated. All reactions were performed in oven-dried (110 °C) glassware under N_2 or Ar unless otherwise mentioned. Mass spectra and high-resolution mass spectra were obtained from the Northwestern University Analytical Services Laboratory and Imperial College Analytical Services. Combustion analyses were performed by G.D. Searle & Co., Skokie, IL, or Imperial College, London, U.K. Unless stated to the contrary, all TLC was carried out on E. Merck precoated silica gel 60 F_{254} plates. Plates were visualized using UV radiation (254 nm) or with $KMnO_4$ reagent. Unless stated to the contrary, chromatography refers to flash chromatography on E. Merck silica gel 60, 230−400 mesh ASTM. Racemic ketone **11** was prepared from diethyl fumarate following the methods described elsewhere.[7] Samples of racemic intermediates including those corresponding to **7**, **8**, **9**, and **10** showed characteristics which were identical with the spectroscopic data reported for the pure enantiomers below.

(1*R*,2*R*)-4,5-Bis(cyanomethyl)cyclohexene (7).[7a] The bis(toluene-4-sulfonate) and dinitrile **7** were prepared as described in the literature for racemic material.[7a] (1*S*,2*S*)-Cyclohex-4-ene-1,2-dimethanol[5] ((+)-**6**) (34.4 g, 0.242 mol) gave the disulfonate (91.4 g, 84%) as white crystals: mp 110−111 °C (MeOH); TLC R_f = 0.25 (hexanes:EtOAc 5:1); $[\alpha]_D$ = +43.4° (c = 1.52, $CHCl_3$); IR (neat) 2904, 1598, 1358, 1176, 1097, 940, 814, 666, 554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.5 Hz, 4H), 7.35 (d, J = 8.5 Hz, 4H), 5.51 (s, 2H), 4.00−3.90 (m, 4H), 2.47 (s, 6H), 2.02−1.97 (m, 4H), 1.88−1.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 132.7, 129.8, 127.9, 124.6, 71.2, 33.0, 25.4, 21.6. (1*S*,2*S*)-4,5-Bis[(toluene-4-sulfonyloxy)-methyl]cyclohexene (91.0 g, 0.202 mol) gave **7** (30.7 g, 95%) as a cream-colored solid: mp 97−99 °C (not recrystallized); TLC R_f = 0.23 (hexanes:EtOAc 5:1); $[\alpha]_D$ = +111° (c = 1.40, $CHCl_3$); IR (neat) 3042, 2968, 2919, 2908, 2887, 2843, 2246, 1656, 1448, 1427, 1376, 1339, 1312, 1166, 1102, 993, 909, 872, 852, 732, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (s, 2H), 2.51−2.45 (m, 4H), 2.31−2.25 (m, 2H), 2.18−2.02 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.4, 117.7, 32.7, 28.3, 21.0.

(1*R*,2*R*)-Diethyl 4-Cyclohexene-1,2-diacetate (8).[7c] Diester **8** was prepared using a combination of literature procedures for racemic material.[7a,c] A solution of **7** (9.00 g, 56.2 mmol) and aqueous KOH (6 N, 60 mL) were heated at reflux with stirring for 24 h. The resulting solution was cooled to 0 °C (ice bath), and aqueous orthophosphoric acid (85%, 60 mL) was added dropwise with stirring. The resulting solid was collected by filtration, washed with warm H_2O, and dried under vacuum to give impure diacid (10.60 g, 95%): ^1H NMR (300 MHz, DMSO-d_6) δ 12.08 (br, s, 2H), 5.57 (s, 2H), 2.40−2.23 (m, 2H), 2.20−2.00 (m, 4H), 1.98−1.83 (m, 2H), 1.82−1.65 (m, 2H). The crude diacid was taken up as a suspension in absolute EtOH (200 mL) and stirred with the addition of H_2SO_4 (98%, 5 mL). After 48 h the EtOH was removed under vacuum to ca. 50 mL, and the mixture was added to H_2O (200 mL) and extracted with Et_2O (3 × 150 mL). The extracts were combined, washed with H_2O (3 × 50 mL) and aqueous $NaHCO_3$ (50 mL), and dried ($MgSO_4$). Evaporation and chromatography of the residue (hexane:Et_2O 2:1) gave **8** (11.06 g, 82%) as a colorless oil: TLC R_f = 0.28 (hexane:Et_2O 4:1); $[\alpha]_D$ = +49.3° (c = 1.52, $CHCl_3$); IR (neat) 3026, 2981, 2906, 1734, 1446, 1373, 1346, 1264, 1155, 1096, 1029, 935, 864, 664, 457 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.57 (s, 2H), 4.10 (q, J = 6.7 Hz, 4H), 2.39 (dd, J = 13.9, 5.6 Hz, 2H), 2.29−1.97 (m, 6H), 1.89−1.72 (m, 2H), 1.22 (t, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 124.9, 60.3, 38.5, 33.6, 28.4, 14.2.

(1*R*,6*S*,7*R*)-7-(Ethoxycarbonyl)bicyclo[4.3.0]non-3-en-8-one (9). NaH (60% dispersion in mineral oil, 5.54 g, 139 mmol) was washed with dry hexane (2 × 15 mL) under Ar. Dry THF (80 mL) was added and the mixture heated to reflux. A solution of **8** (32.0 g, 126 mmol) in dry THF (50 mL) was added dropwise to the refluxing mixture. After refluxing for 2.5 h, the reaction was complete by TLC (hexane:EtOAc 4:1). The mixture was allowed to cool, and glacial AcOH (8.6 mL, 150 mmol) was added. To the resulting gelatinous mixture were added H_2O (200 mL) and Et_2O (100 mL), the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 50 mL), aqueous $NaHCO_3$ (50 mL), and brine (50 mL) and dried ($MgSO_4$). Rotary evaporation gave the crude product as a yellow oil which was chromatographed (hexane:EtOAc 4:1) to give **9** (25.2 g, 96%) as a colorless oil: TLC R_f = 0.21 (hexane:Et_2O 4:1); $[\alpha]_D$ = −24.1° (c = 1.62, $CHCl_3$); IR (neat) 2906, 1756, 1724, 1372, 1270, 1132, 1052, 1025, 668, 456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76−5.65 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H), 2.86 (d, J = 11.6 Hz, 1H), 2.57 (dd, J = 16.7, 6.4 Hz, 1H), 2.47−2.19 (m, 3H), 2.08−1.80 (m, 4H), 1.25 (t, J =7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 169.0, 126.6, 126.3, 61.9, 61.3, 44.9, 42.7, 36.2, 31.3, 30.4, 14.2.

(1*R*,6*R*)-Bicyclo[4.3.0]-3-nonen-8-one (10). A solution of **9** (25.0 g, 120 mmol) in DMSO (100 mL) and H_2O (5 mL) under Ar was heated at 155 °C for 2.5 h. The mixture was allowed to cool, added to H_2O (250 mL), and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with H_2O (3 × 100 mL), dried ($MgSO_4$), and evaporated to give a solid. This material was purified by chromatography (hexane:Et_2O 4:1) to give **10** (15.1 g, 92%) as a white solid: TLC R_f = 0.25 (hexane:Et_2O 4:1); $[\alpha]_D$ = −122° (c = 1.78, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.80−5.70 (m, 2H), 2.55−2.30 (m, 4H), 2.00−1.80 (m, 6H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 217.4, 126.5, 45.0, 38.5, 31.2.

(1*R*,6*R*)-Bicyclo[4.3.0]nonan-8-one (11). A solution of **10** (15.0 g, 110 mmol) in absolute EtOH (150 mL) was stirred with rhodium on alumina (5%, 1.4 g) under a H_2 atmosphere for 3 h. The mixture was filtered (Celite), washing with EtOH. Rotary evaporation and then distillation gave **11** (13.5 g, 89%) as a colorless oil: bp 95 °C at 20 mmHg; $[\alpha]_D$ = −308° (c = 1.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (dd, J = 17.0, 5.7 Hz, 2H), 2.00−1.91 (m, 2H), 1.90−1.75 (m, 4H), 1.62−1.50 (m, 2H), 1.42−1.30 (m, 2H), 1.28−1.11(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.3, 46.0, 44.4, 31.8, 26.7.

(1*R*,6*R*)-8-(Hydroxylamino)bicyclo[4.3.0]nonane (12). To a solution of **11** (5.00 g, 36.2 mmol) in EtOH (100 mL) and H_2O (30 mL) were added $NH_2OH{\cdot}HCl$ (2.51 g, 36.2 mmol) and KOH (2.24 g, 40.0 mmol). The mixture was stirred at room temperature for 4 h, added to H_2O (500 mL), and extracted with Et_2O (3 × 300 mL). The combined extracts were washed with H_2O (3 × 300 mL), dried ($MgSO_4$), and rotary evaporated to give the crude oxime (5.41 g, 98%) as a white solid which was used directly in the next step without purification: TLC R_f = 0.09 (hexane:Et_2O 4:1); $[\alpha]_D$ = −97.6° (c = 1.20, $CHCl_3$); IR (neat) 3247, 2926, 2850, 933, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.25 (br, s, 1H), 2.75 (dd, J = 17.4, 6.3 Hz, 1H), 2.47 (dd, J = 15.5, 5.3 Hz, 1H), 2.00−1.65 (m, 6H), 1.35−0.95 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 44.9, 44.3, 37.1, 33.7, 31.3, 31.2, 26.2, 26.1.

To a solution of the crude oxime (5.41 g, 35.5 mmol) in MeOH (70 mL) was added methyl orange indicator (several crystals). $NaBH_3CN$ (2.50 g, 39.8 mmol) was added portionwise, with simultaneous addition of hydrochloric acid (37%) to maintain ca. pH 3 (indicator red). After stirring for 30 min, MeOH was removed by rotary evaporation. The residue was taken up in H_2O (100 mL), basified to pH > 10 with aqueous KOH (6N), and extracted with CH_2Cl_2 (4 × 100 mL). The extracts were combined and dried ($MgSO_4$), and the solution was rotary evaporated to give **12** (5.33 g, 97%) as a white solid: mp 109−110 °C (not recrystallized); TLC R_f = 0.03 (hexane:Et_2O 1:1); $[\alpha]_D$ = −43° (c = 0.10, $CHCl_3$); IR (neat) 3258, 3155, 2921, 2852, 2361, 1508, 1438, 467, 455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (br, s, 2H), 3.57−3.50 (m, 1H), 2.10−1.99 (m, 1H), 1.85−1.65 (m, 5H), 1.35-0.85 (m, 8H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 60.7, 45.7, 44.0, 36.5, 36.4, 31.6, 31.5, 26.3. Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.52; H, 10.90; N, 9.00.

(1*R*,6*R*)-8-Nitrobicyclo[4.3.0]nonane (13). A solution of **12** (5.33 g, 34.3 mmol) and 4-nitrobenzaldehyde (5.19 g, 34.3

mmol) in $CHCl_3$ (75 mL) with $CaCl_2$ (1.2 g) and 3 Å molecular sieves (40 g) were heated at reflux under N_2 for 18 h. EtOH (30 mL) was added and the mixture filtered (Celite). Evaporation of solvent gave impure nitrone: TLC $R_f = 0.35$ (hexane:Et_2O 1:1); ^1H NMR (270 MHz, $CDCl_3$:CD_3OD 3:1, TMS) δ 8.40, 8.25 (AB, $J_{AB} = 9$ Hz, 4H), 7.68 (s, 1H), 4.65−4.52 (m, 1H), 2.35−2.20 (m, 2H), 2.00−1.50 (m, 7H), 1.40−0.85 (m, 5H); ^{13}C NMR (70 MHz, $CDCl_3$:CD_3OD 3:1) δ 147.5, 136.1, 131.5, 128.8, 123.5, 75.0, 45.9, 45.1, 37.8, 37.7, 31.0, 30.8, 26.0, 25.9.

The crude nitrone was taken up in MeOH (250 mL) and CH_2Cl_2 (250 mL) and cooled to −78 °C. Ozone was passed into the solution with stirring, until the color had changed from yellow through green to blue (no nitrone remaining by TLC). Me_2S (3.8 mL) was added, and the solution was allowed to warm to room temperature. The solution was rotary evaporated, and the residue was dissolved in Et_2O (150 mL). The solution was washed with H_2O (3 × 50 mL) and dried ($MgSO_4$) and the solvent evaporated. Chromatography of the residue (hexane:Et_2O 4:1) gave **13** (4.74 g, 82%) as a colorless oil: TLC $R_f = 0.60$ (hexane:Et_2O 4:1); $[\alpha]_D = +22.9°$ ($c = 1.40$, $CHCl_3$); IR (neat) 2926, 2853, 1548, 1445, 1376, 1362, 1349, 1312, 848 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.95−4.82 (m, 1H), 2.51−2.32 (m, 2H), 1.97−1.68 (m, 5H), 1.63−1.40 (m, 2H), 1.30−0.90 (m, 5H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 84.4, 45.8, 44.3, 38.8, 38.2, 31.0, 30.9, 26.00, 25.95. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.94; H, 9.02; N, 8.18.

(1*R*,6*S*)-8-Nitrobicyclo[4.3.0]non-7-ene (14). To a solution of **13** (2.00g, 11.8 mmol) in dry THF (40 mL) under N_2 at −78 °C was added *n*-BuLi (23.6 mmol, 2.5 M in hexanes), and the mixture was stirred at −78 °C for 45 min. A solution of PhSeBr (5.85 g, 24.5 mmol) in dry THF (30 mL) was added *via* cannula and the mixture allowed to reach 0 °C (ice bath). After 30 min, hydrogen peroxide (30%, 6.5 mL) was added slowly. After 20 min, the mixture was added to H_2O (200 mL) and extracted with pentane (3 × 50 mL). The combined extracts were washed with H_2O (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed (hexane:Et_2O 40:1) to give **14** (864 mg, 44%) as a pale green solid: TLC $R_f = 0.25$ (hexane:Et_2O 20:1); $[\alpha]_D = -159°$ ($c = 1.30$, $CHCl_3$); IR (neat) 2934, 2857, 1608, 1506, 1448, 1374, 1356, 1316, 1289, 1230, 1224, 1078, 1022, 911, 893, 876, 780, 758, 726, 560 cm-^{1}; ^1H NMR (270 MHz, $CDCl_3$, TMS) δ 6.99 (s, 1H), 2.81 (dd, $J = 15.1$, 6.9 Hz, 1H), 2.48 (m, 1H), 2.33−2.17 (br, m, 1H), 2.13−1.98 (m, 1H), 1.90−1.77(m, 4H), 1.42−1.27 (m, 4H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 153.6, 141.8, 50.4, 48.7, 35.1, 29.6, 29.4, 26.3, 26.1. Due to stability problems it was not possible to obtain a microanalytically pure sample of **14**, and the material was carried on to the next step without further attempts at purification.

(±)-*trans*-Bicyclo[4.3.0]nonan-8-one (2,4,6-Triisopropylbenzenesulfonyl)hydrazone (15). (2,4,6-Triisopropylbenzenesulfonyl)hydrazine[42] (7.93 g, 26.2 mmol) was dissolved in MeOH (50 mL) and THF (10 mL) under N_2. A solution of **11** (3.50 g, 25.3 mmol) in MeOH (20 mL) was added and the mixture stirred for 4 h. To the resulting white suspension was added H_2O (20 mL) dropwise, with cooling to 0 °C. The solid was collected by filtration and recrystallized from MeOH:THF:H_2O to give **15** (8.55 g, 81%) as white crystals: mp 210 °C dec; IR ($CHCl_3$) 3400, 3000, 1700, 1650, 1600, 1500, 1400, 1350, 1180, 1150, 1050, 950, 600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 2H), 6.99 (s, 1H), 4.23 (septet, $J = 6.8$ Hz, 2H), 2.90 (septet, $J = 6.8$ Hz, 1H), 2.45 (dd, $J = 17.0$, 5.7 Hz, 1H), 2.39 (dd, $J = 17.0$, 5.7 Hz, 1H), 2.20−1.85 (m, 3H), 1.80−1.55 (m, 3H), 1.26 (2d, $J = 6.8$ Hz, 18H), 1.40−1.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 153.1, 151.2 (2C), 131.8, 123.7 (2C), 44.5, 44.4, 39.8, 34.1, 31.2, 31.1, 29.9 (2C), 26.0, 25.9, 24.77 (2C), 24.75 (2C), 23.5 (2C); MS(EI) *m/e* 419 ($M + H^+$), 355, 340, 283, 282, 267, 252, 203, 152, 138, 93, 80. Anal. Calcd for $C_{24}H_{38}N_2O_2S$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.50: H, 9.08; N, 6.67.

(±)-*trans*-8-(Trimethylstannyl)bicyclo[4.3.0]non-7-ene (16). To a solution of (±)-**15** (8.30 g, 19.8 mmol) in dry THF (THF) (100 mL) at −78 °C under N_2 was added *sec*-BuLi (39.6 mmol, 1.3 M solution in cyclohexane) dropwise, maintaining an internal temperature of ≤ −70 °C. The exact volume of *sec*-BuLi added was judged from the end point color change, colorless to yellow, for monoanion formation.[13b] The resulting orange solution was stirred at −78 °C for 1 h, allowed to warm to −5 °C until evolution of N_2 had ceased (ca. 10 min), and recooled to −78 °C. A solution of Me_3SnCl (9.86 g, 49.5 mmol) in dry THF (30 mL) was added slowly *via* cannula (maintaining an internal temperature of ≤ −65 °C). The mixture was allowed up to warm to room temperature and solvent removed under vacuum. The residue was partitioned between H_2O (50 mL) and hexanes (50 mL). The organic layer was separated, dried ($MgSO_4$), and filtered through a plug of silica, washing with hexanes. Removal of solvent gave (±)-**16** (3.99 g, 71%) as a colorless oil: TLC $R_f = 0.62$ (hexane); IR (neat) 2978, 2922, 2852, 2826, 1445, 816, 766, 710, 527, 511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.98 (d, $J = 1.1$ Hz, $^3J_{Sn-H} = 41.9$ Hz, 1H), 2.39 (dd, $J = 13.6$, 5.7 Hz, 1H), 2.10−1.70 (m, 5H), 1.42−1.05 (m, 6H), 0.11 (s, $^2J_{Sn-H} = 53.6$ Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 144.5, 53.0, 50.6, 43.2, 30.7, 30.5, 27.1, 26.8, −10.2 (3C). Owing to stability problems it was not possible to obtain a microanalytically pure sample of **16**, and material was carried on to the next step without further attempts at purification.

(±)-*trans*-8-Nitrobicyclo[4.3.0]non-7-ene (14). To a solution of (±)-**16** (2.00 g, 7.02 mmol) in dry DMSO (7.5 mL) and HMPA (7.5 mL) at 0 °C were added $C(NO_2)_4$ (0.92 mL, 7.7 mmol) and AcOH (0.44 mL, 7.7 mmol). The mixture was stirred under Ar in the dark at 0 °C for 6 h, poured into H_2O (100 mL), and extracted with hexane:Et_2O (1:1, 3 × 50 mL). The combined extracts were washed with H_2O (6 × 30 mL), dried ($MgSO_4$), and filtered through a pad of silica, washing with hexane:Et_2O (20:1). After removing solvent, the residue was chromatographed (hexane:Et_2O 20:1) to give (±)-**14** (442 mg, 38%) as a pale yellow solid spectroscopically and chromatographically identical with the previously prepared material. On a scale of 100 mg, a 44% yield of (±)-**14** was obtained.

(1*R*,6*S*,7*R*,8*S*)-7-((*E*)-1-(Tri-*n*-butylstannyl)ethen-2-yl)-8-nitrobicyclo[4.3.0]nonane (18). To dry thiophene (144 μL, 1.79 mmol) in dry THF (4 mL) at 0 °C under N_2 was added *n*-BuLi (1.88 mmol, 2.5 M in hexanes). The mixture was stirred at 0 °C for 30 min, cooled to −78 °C, and added *via* cannula to a suspension of copper(I) cyanide (161 mg, 1.79 mmol) at −78 °C in THF (1 mL). The suspension was allowed to warm to near 0 °C until a beige solution formed and then recooled to −78 °C. To a solution of (*E*)-bis(tri-*n*-butylstannyl)-ethylene[43] (1.09 g, 1.79 mmol) in dry THF (6 mL) at −78 °C under N_2 was added *n*-BuLi (1.88 mmol, 2.5 M in hexanes) dropwise over 10 min. The mixture was stirred at −78 °C for 1 h and transferred, *via* cannula, into the lithium (2-thienyl)-cyanocopper solution. After 30 min at −78 °C, a solution of **14** (200 mg, 1.20 mmol) in THF (2 mL) was added *via* cannula, and the mixture was stirred for 1.5 h. A mixture of AcOH and hydrochloric acid (0.1 N) (1:2, 6 mL) was added, and the mixture was allowed to warm up to room temperature and stirred for 1 h. H_2O (40 mL) was added and the mixture extracted with Et_2O (3 × 30 mL). The combined extracts were washed with H_2O (3 × 30 mL) and aqueous $NaHCO_3$ (30 mL), dried ($MgSO_4$), and concentrated under vacuum. Chromatography (hexane:Et_2O 40:1) gave the major product **18** (302 mg, 52%) as a colorless oil containing a single diastereoisomer: TLC $R_f = 0.57$ (hexane:Et_2O 20:1); $[\alpha]_D = +70.7°$ ($c = 1.05$, $CHCl_3$); IR (neat) 2956, 2926, 1549, 1374, 1362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (d, $J = 19.0$ Hz, 1H), 5.75 (dd, $J = 19.0$, 7.8 Hz, 1H), 4.79 (ddd, $J = 8.1$, 7.5, 2.1 Hz, 1H), 3.16 (ddd, $J = 7.6$, 7.5, 2.1 Hz, 1H), 2.47 (ddd, $J = 13.2$, 8.1, 6.5 Hz, 1H), 1.90−0.75 (m, 38H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 145.2, 131.1, 90.0, 55.8, 48.2, 42.5, 38.5, 31.6, 29.2, 28.0, 27.0, 26.0, 25.9, 13.9, 9.9. Anal. Calcd for $C_{23}H_{43}NO_2Sn$: C, 57.04; H, 8.95; N, 2.89. Found: C, 57.14; H, 9.09; N, 2.85. Also isolated was a second fraction (58 mg, 10%) as a colorless oil

(42) Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157.

(43) (a) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581. (b) Bottaro, J. C.; Hanson, R. N.; Seitz, D. E. *J. Org. Chem.* **1981**, *46*, 5221.

containing a minor diastereoisomer of **18** and the product of protodestannylation of **18**: TLC $R_f = 0.29$ (hexanes:Et_2O 20:1); ^1H NMR (270 MHz, $CDCl_3$) δ 6.01 (d, $J = 18.6$ Hz, 0.5H), 5.75−5.57 (m, 1H), 5.18−5.03 (m, 1.5H), 4.78−4.69 (m, 0.5H), 3.27−3.10 (m, 1H), 2.66−2.35 (m, 1H), 2.05−0.70 (m, 38H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 141.8, 135.8, 135.2, 117.1, 90.1, 88.8, 56.4, 52.4, 49.1, 48.0, 42.4, 41.9, 38.3, 35.4, 31.9, 31.6, 29.0, 28.2, 27.6, 27.2, 26.0, 25.9, 25.8, 13.7, 9.7.

(1*R*,6*S*,7*R*,8*S*)-7-((*E*)-1-(Tri-*n*-butylstannyl)ethen-2-yl)-bicyclo[4.3.0]nonan-8-amine (19). To a solution of **18** (300 mg, 0.619 mmol) in dry THF:MeOH (1:1, 3 mL) were added dry (sublimed) ammonium formate (390 mg, 6.19 mmol) and Pd/C (10%, 60 mg). The mixture was stirred under N_2 at room temperature for 7 h, diluted with Et_2O (50 mL), and filtered (Celite), washing with Et_2O. Rotary evaporation gave a residue which was purified by chromatography (Et_2O followed by Et_2O:MeOH:NH_4OH 100:5:1) to give **19** (186 mg, 66%) as a colorless oil: TLC $R_f = 0.10$ (Et_2O:hexanes:NH_4OH 200:100:3); IR (neat) 2955, 2922, 2852, 1592, 1446, 1376, 1292, 1184, 1071, 992, 960, 866, 812, 690, 604, 505 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, TMS) δ 5.96−5.65 (m, 2H), 3.20 (ddd, $J = 7.8$, 7.8, 2.6 Hz, 1H), 2.28−2.10 (m, 2H), 1.92−1.80 (br m, 1H), 1.80−0.75 (m, 39H); ^{13}C DEPT NMR (75 MHz, $CDCl_3$) δ 150.3 (CH), 127.0 (CH), 61.4 (CH), 57.7 (CH), 47.9 (CH), 43.4(CH), 42.8 (CH_2), 32.2 (CH_2), 29.1 ($3CH_2$), 28.3 (CH_2), 27.2 ($3CH_2$), 26.5 (CH_2), 26.2 (CH_2), 13.7 ($3CH_3$), 9.5 ($3CH_2$).

(1*R*,6*S*,7*R*,8*S*)-*N*-(*tert*-Butoxycarbonyl)-7-((*E*)-1-(tri-*n*-butylstannyl)ethen-2-yl)bicyclo[4.3.0]nonan-8-amide (20). To a solution of **19** (125 mg, 0.275 mmol) in 1,4-dioxane (2 mL) and H_2O (0.25 mL) were added Et_3N (57 μL, 0.41 mmol) and *tert*-butyl *S*-(4,6-dimethylpyrimidin-2-yl) thiocarbonate (73 mg, 0.30 mmol). The mixture was stirred at 25 °C under N_2 for 10 h, added to H_2O (15 mL), and extracted into Et_2O (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated. The residue was purified by chromatography (hexanes:Et_2O 10:1) to give **20** (134 mg, 87%) as a colorless oil: TLC $R_f = 0.19$ (hexanes:Et_2O 10:1); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95−5.65 (m, 2H), 4.57 (br s, 1H), 3.80 (br s, 1H), 2.40−2.20 (m, 2H), 1.90-1.80 (m, 1H), 1.77−0.70 (m, 46H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 148.5, 128.0, 79.0, 57.3, 55.8, 48.2, 42.6, 40.9, 32.1, 29.1, 28.5, 28.0, 27.4, 26.7, 26.1, 13.9, 9.5. The material was used directly without any further purification.

Attempted Preparation of Dimer 21. A solution of **20** (20 mg, 0.036 mmol) in dry THF (0.25 mL) was added *via* cannula to KH (3 mg, 0.07 mmol) and 18-crown-6 (5 mg, 0.02 mmol). The mixture was stirred at 25 °C for 1 h and cooled to 0 °C. A solution of 1,3-diiodopropane (5.3 mg, 0.020 mmol) in THF (0.25 mL) was added *via* cannula, and stirring was continued for 1 h. The mixture was added to H_2O (10 mL) and extracted into EtOAc (2 × 10 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated. The residue was purified by chromatography (hexanes:Et_2O 20:1) to give as the major isolated product **22** (11 mg, 51%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.90−5.62 (m, 3H), 5.12−5.01 (m, 2H), 4.01−3.91 (m, 1H), 3.85−3.65 (m, 2H), 2.68−2.58 (m, 1H), 1.90−1.80 (m, 2H), 1.78−0.70 (m, 46H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 150.5, 136.0, 127.2, 115.1, 79.5, 77.2, 63.2, 53.5, 49.0, 48.7, 42.8, 37.4, 31.8, 29.2, 28.5, 27.3, 26.6, 26.1, 13.7, 9.5.

Bis[(1*R*,6*S*,7*R*,8*S*)-7-((*E*)-1-(tri-*n*-butylstannyl)ethen-2-yl)bicyclo[4.3.0]non-8-yl]malonamide (23). To a solution of **19** (100 mg, 0.220 mmol) in dry CH_2Cl_2 (3 mL) under N_2 at −78 °C were added simultaneously *via* cannula malonyl dichloride (17 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) and Et_3N (46 μL, 0.33 mmol) in CH_2Cl_2 (0.5 mL) over ca. 5 min. Further malonyl dichloride (7 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) were added, and TLC indicated complete consumption of starting material (Et_2O:NH_4OH 100:1). The reaction mixture was allowed to warm to room temperature, added to H_2O (10 mL), and extracted into Et_2O (2 × 10 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated. The residue was purified by chromatography on Et_3N-doped silica (hexanes:Et_2O 5:1) to give **23** (48 mg, 45%) as a colorless oil: TLC $R_f = 0.36$ (Et_2O); $[\alpha]_D = +34.9°$ ($c = 1.60$, $CHCl_3$); IR (neat) 3265, 2956, 2922, 2850, 1633, 1552, 1445, 1321, 988, 452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, $J = 8.9$ Hz, 2H), 5.85 (d, $J = 18.6$ Hz, 2H), 5.75 (dd, $J = 18.6$, 8.3 Hz, 2H), 4.12 (dddd, $J = 8.9$, 8.9, 8.9, 2.0 Hz, 2H), 3.05 (s, 2H), 2.45−2.30 (m, 4H), 1.80−0.75 (m, 74H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 166.5, 148.1, 128.7, 57.2, 54.8, 48.5, 43.5, 42.7, 40.4, 32.2, 29.2, 28.2, 27.2, 26.5, 26.2, 13.6, 9.7; MS(FAB) isotope cluster (abundance) ($M^+ - 57$) 911 (1.4), 912 (2.5), 913 (2.5), 914 (11.8), 915 (14.8), 916 (38.1), 917 (43.8), 918 (86.4), 919 (76.3), 920 (100.0), 921 (67.5), 922 (81.6), 923 (39.3), 924 (33.8), 925 (15.6), 926 (18.9), 927 (7.7), 928 (3.7), 929 (1.3), 930(1.4). Calcd for M^+: 968 (1.3), 969 (3.2), 970 (3.2), 971 (13.7), 972 (17.2), 973 (39.8), 974 (45.0), 975 (84.7), 976 (76.9), 977 (100.0), 978 (70.6), 979 (81.2), 980 (43.3), 981 (35.3), 982 (18.8), 983 (20.8), 984 (9.5), 985 (4.5), 986 (1.6), 987 (1.6). HRMS (FAB) calcd for $C_{49}H_{89}N_2O_2{}^{120}Sn_2$: ($M - H^+$), 977.4965. Found: 977.4791.

Bis[(1*R*,6*S*,7*R*,8*S*)-7-ethenylbicyclo[4.3.0]non-8-yl]malonamide (24). To a solution of **23** (15 mg, 0.015 mmol) in dry Et_2O (1 mL) under N_2 was added TsOH·H_2O (6.5 mg, 0.040 mmol). The solution was stirred for 30 min and rotary evaporated, and the residue was chromatographed (EtOAc) to give **24** (6 mg, 98%) as a white solid: TLC $R_f = 0.50$ (EtOAc); IR (neat) 3278, 2923, 2853, 1637, 1544, 910 cm^{-1}; $[\alpha]_D = -20.8°$ ($c = 0.25$, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 6.95 (br d, $J = 8.0$ Hz, 2H), 5.70 (ddd, $J = 18$, 13, 9.0 Hz, 2H), 4.98 (2d, overlapping, $J = 13.0$ Hz, 4H), 4.08 (dddd, $J = 8.0$, 8.0, 8.0, 2.0 Hz, 2H), 3.08 (s, 2H), 2.40−2.20 (m, 4H), 1.95−0.80 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 138.2, 115.1, 55.0, 53.8, 48.1, 43.3, 42.6, 40.0, 32.0, 27.9, 26.3, 26.0. The sample was crystallized by vapor diffusion of hexanes into an EtOAc solution to obtain crystals suitable for a single-crystal X-ray diffraction study.

(1*R*,6*S*,7*R*)-Ethyl 8,8-(Ethylenedioxy)bicyclo[4.3.0]non-3-ene-7-carbox-ylate (26). A solution of **9** (8.60 g, 41.3 mmol) in PhH (200 mL) and ethylene glycol (70 mL) with TsOH·H_2O (20 mg) was heated at reflux, with a Sohxlet thimble of molecular sieves (3 Å, 50 g) between the reaction flask and condenser. After 12 h, the mixture was allowed to cool and added to H_2O (100 mL) and Et_2O (200 mL). The organic phase was separated, washed with H_2O (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and rotary evaporated to give **26** (10.3 g, 99%) as a colorless oil: TLC $R_f = 0.21$ (hexanes:Et_2O 4:1); $[\alpha]_D = +72.7°$ ($c = 1.64$, $CHCl_3$); IR (neat) 3022, 2978, 2896, 2834, 2360, 1734, 1642, 1438, 1380, 1332, 1282, 1227, 1202, 1159, 1090, 1039, 982, 948, 904, 870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67−5.55 (m, 2H), 4.20−4.00 (m, 3H), 3.90−3.70 (m, 3H), 2.59 (d, $J = 11.2$ Hz, 1H), 2.30−2.00 (m, 4H), 1.90−1.50 (m, 4H), 1.25 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 126.5, 126.4, 116.7, 65.3, 64.4, 60.5, 60.3, 44.8, 42.2, 37.2, 31.0, 30.6, 14.2; MS(EI) *m/e* 252 ($M^{+\bullet}$), 207, 198, 169, 125, 112, 99, 91, 86. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.42; H, 8.01.

(1*R*,6*S*,7*S*)-[8,8-(Ethylenedioxy)bicyclo[4.3.0]non-3-en-7-yl]methanol (27a). A solution of **26** (10.08 g, 39.90 mmol) in dry Et_2O (100 mL) was added dropwise to $LiAlH_4$ (2.08 g, 58.1 mmol) in Et_2O (100 mL) at 0 °C under N_2 with stirring. The mixture was stirred at room temperature for 5 h and cooled to 0 °C. Saturated aqueous sodium potassium tartrate (11 mL) was added cautiously with stirring. The resulting mixture was heated at reflux for 1 h, allowed to cool, and stirred at room temperature for 18 h. The white solids were removed by filtration and the filtrate rotary evaporated to leave **27a** (8.31 g, 99%) as a colorless oil: TLC $R_f = 0.16$ (hexanes:EtOAc 2:1); $[\alpha]_D = +128.8°$ ($c = 1.40$, $CHCl_3$); IR (neat) 3449, 3019, 2956, 2887, 2832, 1641, 1473, 1437, 1401, 1359, 1314, 1276, 1231, 1202, 1151, 1085, 1024, 948, 913, 853, 662, 595, 560, 521, 487, 461, 454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70−5.55 (m, 2H), 4.00−3.50 (m, 6H), 2.50 (dd, $J = 8.9$, 4.2 Hz, 1H), 2.35−2.10 (m, 2 H), 2.06 (dd, $J = 12.8$, 6.1 Hz, 1H), 1.85−1.50 (m, 5H), 1.35 (dd, $J = 12.8$, 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.8, 126.6, 117.8, 64.5, 63.7, 60.0, 55.0, 44.2, 40.2, 37.7, 31.4, 30.4; MS(EI) *m/e* 210 ($M^{+\bullet}$), 156, 125, 91, 79, 77, 55. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.43, H, 8.54.

(1*R*,6*S*,7*S*)-7-[(Benzyloxy)methyl]-8,8-(ethylenedioxy)-bicyclo[4.3.0]non-3-ene (27b). To a solution of **27a** (8.12 g, 38.6 mmol) in dry DMF (100 mL) under Ar was added NaH

(2.16 g, 53.9 mmol, 60% dispersion in mineral oil), and the mixture was stirred at room temperature for 1 h under Ar. $PhCH_2Br$ (4.18 mL, 38.6 mmol) was added, and the mixture was stirred for 20 h. A small portion was worked up (H_2O/Et_2O), and TLC (Et_2O) indicated some starting material. Further NaH (0.20 g, 5.0 mmol, 60% dispersion in mineral oil) and $PhCH_2Br$ (0.80 mL, 7.4 mmol) were added. After a further 2 h, the reaction was complete (TLC) and the mixture was added to H_2O (300 mL) and extracted into Et_2O (3 × 100 mL). The combined extracts were washed with H_2O (3 × 50 mL) and brine (50 mL) and dried ($MgSO_4$). The solution was rotary evaporated and the residue chromatographed (hexanes, then hexanes:EtOAc gradient 1:0 to 4:1) to give **27b** (11.7 g, 100%) as a colorless oil: TLC R_f = 0.60 (Et_2O); $[\alpha]_D$ = +69.9° (c = 1.58, $CHCl_3$); IR (neat) 3021, 2957, 2883, 1641, 1496, 1453, 1436, 1366, 1306, 1286, 1202, 1153, 1094, 1028, 948, 922, 853, 735, 698, 663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 5.72−5.60 (m, 2H), 4.50 (s, 2H), 4.00−3.75 (m, 4H), 3.61 (dd, J = 9.5, 7.1 Hz, 1H), 3.48 (dd, J = 9.5, 6.2 Hz, 1H), 2.40−2.15 (m, 2H), 2.15−1.55 (m, 5H), 1.50−1.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.2, 127.4, 127.3, 126.9, 126.6, 116.6, 73.0, 69.8, 65.0, 63.9, 53.7, 44.6, 44.2, 37.8, 31.4; MS(EI) m/e 300 ($M^{+\bullet}$), 238, 209, 194, 151, 140, 125, 112, 99, 91, 79, 77. Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.32; H, 8.01.

(1*R*,6*S*,7*S*)-7-[(Benzyloxy)methyl]bicyclo[4.3.0]non-3-en-8-one (27c). A solution of **27b** (11.5 g, 38.3 mmol) in THF (220 mL) and hydrochloric acid (0.2 N, 22 mL) under Ar was stirred at 60 °C for 3 h. The mixture was allowed to cool, added to H_2O (500 mL), and extracted into Et_2O (3 × 150 mL). The combined extracts were washed with H_2O (3 × 100 mL) and brine (10 mL) and dried ($MgSO_4$). The solution was rotary evaporated to give a pale yellow oil which solidified on standing to leave **27c** (9.72 g, 99%) as a cream-colored solid: mp 43−45 °C (not recrystallized); TLC R_f = 0.20 (hexanes:Et_2O 4:1); $[\alpha]_D$ = −44.2° (c = 1.64, $CHCl_3$); IR (neat) 3023, 2893, 1743, 1641, 1496, 1453, 1436, 1408, 1363, 1315, 1230, 1203, 1152, 1093, 1027, 923, 789, 737, 698, 665, 604, 572, 535, 468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 5.79−5.68 (m, 2H), 4.50 (d, J = 3.2 Hz, 2H), 3.80−3.60 (m, 2H), 2.60−2.30 (m, 3H), 2.10−1.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.7, 138.2, 128.2, 127.4, 127.3, 126.7, 126.6, 73.1, 67.2, 56.2, 45.0, 41.5, 36.5, 31.4, 30.8. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.62; H, 8.04.

(1*R*,6*S*,7*R*,8*S*)-*N*-Benzyl-7-[(benzyloxy)methyl]bicyclo-[4.3.0]non-3-en-8-amine (28). To a solution of **27c** (5.00 g, 19.5 mmol) in dry THF under Ar were added $PhCH_2NH_2$ (2.34 mL, 21.5 mmol), $NaBH(OAc)_3$ (6.20 g, 29.3 mmol), and AcOH (2.23 mL, 39.0 mmol). The mixture was stirred with ice cooling for 1 h and at room temperature for 24 h. TLC (hexanes:Et_2O 1:1) revealed some starting material. Further $PhCH_2NH_2$ (0.25 mL, 2.3 mmol), $NaBH(OAc)_3$ (2.0 g, 9.5 mmol), and AcOH (0.75 mL, 13 mmol) were added, and mixture was stirred at room temperature for a further 24 h. The mixture was added to aqueous NaOH (1 N, 300 mL) and extracted into Et_2O (3 × 150 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated. Chromatography on silica, pretreated with 1% Et_3N in hexanes (hexanes, then hexanes:Et_2O gradient 8:1 to 5:1) gave **28** (4.72 g, 70%) as a pale yellow oil which solidified on standing to leave a cream-colored solid: mp 35−37 °C (not recrystallized); TLC R_f = 0.22 (hexanes:Et_2O:Et_3N 75:25:1); $[\alpha]_D$ = +116.3° (c = 1.16, $CHCl_3$); IR (neat) 3022, 2899, 1744, 1640, 1495, 1453, 1366, 1200, 1093, 1028, 734, 698, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 7.34−7.23 (m, 10H), 5.67 (dd, J = 1.7, 1.7 Hz, 2H), 4.48 (2d, J = 18.7 Hz, 2H), 3.84−3.72 (m, 2H), 3.63−3.56 (m, 2H), 3.32 (ddd, J = 8.9, 8.9, 7.4 Hz, 1H), 2.35−2.15 (m, 3H), 2.10−1.67 (m, 4H), 1.55−1.35 (m, 2H), 1.18−1.02 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 138.3, 128.3, 128.34, 128.27, 128.0, 127.6, 127.3, 126.7, 126.6, 73.3, 70.0, 57.7, 52.2, 48.3, 42.7, 40.3, 39.8, 31.9, 31.4; MS (CI) m/e 375 ($M + NH_4^+$), 348 ($M + H^+$), 256, 242, 198, 106, 91. Anal. Calcd for $C_{24}H_{29}NO$: C, 82.95; H, 8.41; N, 4.03. Found: C, 82.69; H, 8.51; N, 3.65. Also isolated was the minor stereoisomer (1.10 g, 15%) as a colorless oil: TLC R_f = 0.10 (hexanes:Et_2O:Et_3N 75:25:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.15 (m, 10H), 5.72−5.61 (m, 2H), 4.50 (2d, 2H), 3.81 (d, J = 13.0 Hz, 1H), 3.68 (d, J = 13.0 Hz, 1H), 3.60 (dd, J = 9.0, 5.0 Hz, 1H), 3.41 (dd, J = 9.0, 8.5 Hz, 1H), 3.04 (ddd, J = 8.6, 6.5, 2.0 Hz, 1H), 2.30−2.15 (m, 2H), 1.95−1.65 (m, 6H), 1.50−1.15 (m, 2H).

(1*R*,6*S*,7*R*,8*S*)-7-[(Benzyloxy)methyl]bicyclo[4.3.0]-nonan-8-amine (29). To a solution of **28** (4.55 g, 13.1 mmol) in dry MeOH (90 mL) under Ar were added anhydrous (sublimed) ammonium formate (4.09 g, 65.4 mmol) and Pd/C (10%, 1.37 g). The mixture was heated at reflux for 3 h, allowed to cool, and filtered (Celite), washing with EtOAc. The combined filtrate and washings were rotary evaporated and the residue chromatographed (EtOAc:EtOH:NH_4OH gradient 100:10:1 to 100:20:1) to give **29** (2.60 g, 77%) as a cream-colored solid: mp 38−40 °C (not recrystallized); TLC R_f = 0.36 (EtOAc:EtOH:NH_4OH 100:20:1); $[\alpha]_D$ = +58.6° (c = 1.23, $CHCl_3$); IR (neat) 2919, 2851, 1451, 1368, 1098, 734, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 7.40−7.21 (m, 5H), 4.52 (2d, J = 22.1 Hz, 2H), 3.63−3.54 (m, 3H), 2.30−2.23 (m, 1H), 1.90−1.71 (m, 7H), 1.26−0.90 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4,128.4, 127.7, 127.6, 73.2, 69.2, 51.4, 48.4, 46.0, 44.7, 41.9, 31.7, 30.7, 26.4, 26.1; MS(EI) m/e 259 (M^+), 169, 168, 153, 152, 136, 91; HRMS(EI) calcd for $C_{17}H_{25}NO$ (M^+) 259.1936, found (M^+) 259.1925.

(1*R*,6*S*,7*R*,8*S*)-*N*-(*tert*-Butoxycarbonyl)-7-[(benzyloxy)-methyl]bicyclo[4.3.0]nonan-8-amide (30). A solution of **29** (2.49 g, 9.58 mmol) and NaOH (588 mg, 14.7 mmol) in 1,4-dioxane (80 mL) and H_2O (20 mL) was cooled to 0 °C under Ar. Di-*tert*-butyl dicarbonate (2.64 mL, 11.5 mmol) was added and the mixture stirred at room temperature for 6 h. The reaction mixture was added to H_2O (200 mL) and extracted into Et_2O (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated. The residue was chromatographed (hexanes:Et_2O 10:1) to give **30** (3.19 g, 93%) as a white solid: mp 77−78 °C (not recrystallized); TLC R_f = 0.16 (hexanes:Et_2O 10:1); $[\alpha]_D$ = −7.6° (c = 1.48, $CHCl_3$); IR (neat) 2921, 2852, 2360, 1716, 1506, 1456, 1364, 1244, 1173, 736, 698, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 7.40−7.25 (m, 5H), 5.40 (br, d, J = 7.5 Hz, 1H), 4.49 (s, 2H), 4.25−4.00 (br, m, 1H), 3.53 (d, J = 3.5 Hz, 2H), 2.30−2.18 (m, 1H), 1.90−1.65 (m, 5H), 1.45 (s, 9H), 1.40−0.85 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 138.3, 128.3, 127.8, 127.6, 78.6, 73.5, 68.3, 51.4, 46.4, 45.8, 43.6, 41.1, 31.4, 30.4, 28.5, 26.4, 26.2. Anal. Calcd for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.59; H, 9.29; N, 3.87. A racemic sample of **30** was prepared in an identical fashion starting from racemic amine **29**. Suitable crystals were obtained for a single-crystal X-ray structure determination which proved the stereochemical assignment.

(1*R*,6*S*,7*R*,8*S*)-*N*-(*tert*-Butoxycarbonyl)-7-(hydroxy-methyl)bicyclo[4.3.0]nonan-8-amide (31a). A solution of **30** (1.50 g, 4.16 mmol) in absolute EtOH (30 mL) was stirred under a H_2 atmosphere with Pd/C (10%, 100 mg) for 6 h. Further Pd/C (100 mg) was added and stirring continued for 18 h. The mixture was filtered (Celite), washing with EtOH, and the solvent was removed by rotary evaporation. Chromatography (hexanes:EtOAc 4:1) gave **31a** (1.11 g, 99%) as a white solid: mp 88−89 °C (not recrystallized); TLC R_f = 0.33 (hexanes:EtOAc 2:1); $[\alpha]_D$ = −46.7° (c = 1.20, $CHCl_3$); IR (neat) 3327, 2923, 2853, 1677, 1534, 1449, 1391, 1366, 1315, 1286, 1249, 1173, 1090, 1027, 924, 881, 863, 734, 472, 456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (br d, J = 6.2 Hz, 1H), 4.14−4.09 (m, 1H), 3.60−3.46 (m, 2H), 3.25 (br, OH), 2.43−2.33 (m, 1H), 1.86−1.65 (m, 5H), 1.42 (s, 9H), 1.22−0.73 (m, 7H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 156.9, 79.9, 60.5, 51.9, 51.1, 45.7, 44.3, 39.9, 31.90, 31.87, 30.4, 28.4, 26.4, 26.1. Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.20. Found: C, 66.92; H, 10.03; N, 5.13.

(1*R*,6*S*,7*S*,8*S*)-*N*-(*tert*-Butoxycarbonyl)-7-formylbicyclo-[4.3.0]nonan-8-amide (31b). Oxalyl chloride (5.93 mmol, 2 M solution in CH_2Cl_2) was added to dry CH_2Cl_2 (16 mL) at −78 °C under Ar. DMSO (0.84 mL, 12 mmol) was added slowly as a solution in CH_2Cl_2 (2 mL) *via* cannula, and the mixture was stirred until effervescence had ceased (15−30 min). A solution of **31a** (1.07 g, 3.95 mmol) in CH_2Cl_2 (30 mL) was added, and the mixture was stirred at −78 °C for 30 min. Et_3N (2.8 mL, 20 mmol) was added, and the solution was

warmed to 0 °C. The mixture was added to H_2O (50 mL) and extracted into CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and rotary evaporated. The residue was chromatographed (hexanes:EtOAc 4:1) to give **31b** (1.02 g, 96%) as a white solid: mp 115−116 °C (not recrystallized); TLC R_f = 0.50 (hexanes:EtOAc 2:1); $[\alpha]_D = -92.4°$ (c = 1.08, $CHCl_3$); IR (neat) 3306, 2927, 1714, 1674, 1531, 1286, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, J = 1.6 Hz, 1H), 4.56 (br, d, J = 7.9 Hz, 1H), 4.39 (dddd, J = 8.3, 8.3, 7.9, 7.9 Hz, 1H), 2.65 (dd, J = 9.9, 9.9 Hz, 1H), 2.30−2.20 (m, 1H), 1.90−1.80 (m, 2H), 1.75−1.65 (m, 2H), 1.62−1.50 (m, 2H), 1.38 (s, 9H), 1.30−0.90 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 155.2, 79.7, 60.1, 50.9, 45.6, 43.4, 40.0, 31.3, 30.5, 28.2, 26.0, 25.9. Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.45; H, 9.29; N, 5.24.

(1*R*,6*S*,7*S*,8*S*)-*N*-(*tert*-Butoxycarbonyl)-7-(1,1-dibromoethen-2-yl)-bicyclo[4.3.0]nonan-8-amide (32). CBr_4 (7.19 g, 21.7 mmol) in dry CH_2Cl_2 (50 mL) under Ar at 0 °C was stirred with the addition of Ph_3P (11.4 g, 43.4 mmol). After 30 min, the mixture was cooled to −78 °C. A solution of **31b** (0.966 g, 3.61 mmol) in dry CH_2Cl_2 (20 mL) was added, and the mixture was stirred for 20 min at −78 °C and warmed to 0 °C. Et_3N (25 mL) was added, followed by EtOAc (50 mL). The mixture was filtered through a plug of silica, washing with EtOAc. The solution was rotary evaporated and the filtration process repeated, washing with hexanes and EtOAc (1:1). Following rotary evaporation, the residue was chromatographed (hexanes:EtOAc 10:1) to give **32** (1.45 g, 95%) as a white solid: mp 176−178 °C (not recrystallized); TLC R_f = 0.30 (hexanes:EtOAc 10:1); $[\alpha]_D = +3.1°$ (c = 1.22, $CHCl_3$); IR (neat) 3384, 2918, 2848, 1681, 1513, 1366, 1272, 1246, 1171, 1016, 870, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.24 (br d, J = 9.1 Hz, 1H), 4.34 (br s, 1H), 4.15 (br s, 1H), 2.48−2.34 (br m, 1H), 2.33-2.26 (m, 1H), 1.87−1.65 (m, 4H), 1.42 (s, 9H), 1.21−0.80 (m, 7H); ^{13}C NMR (70 MHz, $CDCl_3$) δ 155.2, 138.2, 89.4, 79.5, 53.0, 51.6, 51.5, 50.8, 44.1, 39.9, 31.7, 30.1, 28.4, 26.2. Anal. Calcd for $C_{16}H_{25}Br_2NO_2$: C, 45.41; H, 5.95; N, 3.31. Found: C, 45.44; H, 5.99; N, 3.39.

(1*R*,6*S*,7*S*,8*S*)-*N*-(*tert*-Butoxycarbonyl)-7-ethynylbicyclo[4.3.0]-nonan-8-amide (33). To a solution of dry *i*-Pr_2-NH (3.22 mL, 23.0 mmol) in dry THF (34 mL) under Ar at 0 °C was added *n*-BuLi (23.0 mmol, 2.5 M solution in hexanes). The solution was stirred for 10 min and cooled to −78 °C, and a solution of **32** (1.39 g, 3.28 mmol) in dry THF (20 mL) was added *via* cannula over 10 min. The mixture was stirred for 1 h at −78 °C, warmed to 0 °C, and stirred for a further 1 h and 15 min. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the solution was extracted into EtOAc (3 × 50 mL) and $CHCl_3$ (50 mL). The combined extracts were dried (Na_2SO_4) and rotary evaporated. The residue was chromatographed twice (hexanes:EtOAc 10:1) to give **33** (649 mg, 75%) as a pale yellow solid: mp 74−76 °C (not recrystallized); TLC R_f = 0.30 (hexanes:EtOAc 10:1); $[\alpha]_D = -20.5°$ (c = 1.30, $CHCl_3$); IR (neat) 3311, 2975, 2926, 2853, 2360, 1703, 1499, 1451, 1390, 1365, 1244, 1173, 1014, 862, 778, 624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (br s, 1H), 4.20−3.90 (br m, 1H), 2.43 (ddd, J = 9.2, 9.2, 2.5 Hz, 1H), 2.34−2.25 (m, 1H), 2.14 (d, J = 2.5 Hz, 1H), 2.10−2.00 (m, 1H), 1.90−1.60 (m, 3H), 1.40 (s, 9H), 1.30−0.80 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 83.1, 79.0, 72.2, 51.7, 50.4, 43.9, 40.6, 40.1, 31.3, 30.1, 28.4, 26.0. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 72.87; H, 9.39; N, 5.39.

(1*R*,6*S*,7*S*,8*S*)-*N*-(*tert*-Butoxycarbonyl)-7-((*E*)-1-(tri-*n*-butylstannyl)ethen-2-yl)bicyclo[4.3.0]nonan-8-amide (34). A solution of **33** (50 mg, 0.19 mmol) and Bu_3SnH (250 μL, 0.950 mmol) in dry PhMe (0.5 mL) under Ar was heated with AIBN (5 mg) at 105 °C for 2 h. The mixture was allowed to cool and directly chromatographed (hexanes, then hexanes:EtOAc 20:1) to give **34** (102 mg, 97%) as a mixture of isomers, *E*:*Z* 85:15: TLC R_f = 0.55 (hexanes:EtOAc 10:1); $[\alpha]_D = +9.0°$ (c = 0.50, $CHCl_3$); IR (neat) 2924, 2852, 1702, 1499, 1364, 1173, 459 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (d, J = 19.3 Hz, 1H), 5.77 (dd, J = 19.3, 6.7 MHz, 1H), 4.60−4.30 (br m, 1H), 4.15−3.90 (br m, 1H), 2.35−2.10 (br m, 2H), 1.90−0.65 (m, 47H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, [147.1 (*Z*), 146.9 (*E*), 1C], [132.8 (*Z*), 130.2 (*E*), 1C], 78.6, 55.2, 51.5, 49.2, [44.5 (*Z*), 44.2 (*E*), 1C], 40.6, 31.7, 30.3, 29.1 (3C), 28.4 (3C), [27.3 (*Z*), 27.2 (*E*), 3C], 26.4, 26.2, 13.6 (3C), [10.3 (*Z*), 9.4 (*E*), 3C]; MS-(EI) *m/e* 498 (M − ^{t}Bu$^+$), 442, 424, 381, 310, 177, 147, 57; HRMS(EI) calcd for $C_{24}H_{44}NO_2{}^{120}Sn$ (M − ^{t}Bu$^+$), 498.2394, found: (M − ^{t}Bu$^+$), 498.2419.

(1*R*,6*S*,7*S*,8*S*)-*N*-(*tert*-Butoxycarbonyl)-7-((*E*)-1-iodoethen-2-yl)bicyclo[4.3.0]nonan-8-amide (35). To a suspension of $CrCl_2$ (800 mg, 6.46 mmol) in dry 1,4-dioxane (6 mL) and THF (1 mL) under Ar at 25 °C were added a mixture of **31b** (288 mg, 1.08 mmol) and CHI_3 (850 mg, 2.15 mmol) in 1,4-dioxane (6 mL) and THF (1 mL) *via* cannula. The mixture was stirred at room temperature for 4 h, added to hydrochloric acid (1 N, 100 mL), and extracted into EtOAc (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated. The crude material was preabsorbed onto silica and dry loaded onto a column of silica. Elution with hexanes and EtOAc (20:1 to 10:1) gave **35** (275 mg, 65%) as a white solid: mp 129−131 °C (not recrystallized); TLC R_f = 0.49 (hexanes:EtOAc 4:1); $[\alpha]_D = -33.0°$ (c = 1.15, $CHCl_3$); IR (neat) 3368, 2918, 2852, 1678, 1519, 1389, 1366, 1316, 1278, 1245, 1171, 1018, 760 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (dd, J = 13.0 Hz, 10.0 Hz, 1H), 5.98 (d, J = 13.0 Hz, 1H), 4.45−4.26 (br m, 1H), 4.25−3.90 (br m, 1H), 2.35−2.10 (m, 1H), 1.90−1.55 (m, 4H), 1.42 (s, 9H), 1.30−0.75 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 145.5, 79.8, 76.6, 55.5, 52.0, 49.8, 44.5, 40.0, 32.0, 30.5, 29.0, 26.5; MS(FAB) *m/e* 392 (M + H$^+$), 369, 336, 307, 275, 208; HRMS(EI) calcd for $C_{12}H_{16}INO_2$ (M + H − ^{t}Bu$^+$), 335.0382, found (M·H$^+$ − ^{t}Bu), 335.0406. Anal. Calcd for $C_{16}H_{26}INO_2$: C, 49.11; H,6.70; N, 3.58. Found: C, 49.50; H, 6.80; N, 3.53.

Alternative Procedure for the Preparation of Vinyl Iodide 35. To a solution of **33** (95 mg, 0.17 mmol) in dry Et_2O (1 mL) under N_2 was added I_2 (48 mg, 0.19 mmol), and the mixture was stirred for 30 min. Aqueous $Na_2S_2O_3$ (1 mL) was added, and the mixture was added to H_2O (5 mL). The mixture was extracted into EtOAc (2 × 10 mL), and the combined extracts were dried ($MgSO_4$) and rotary evaporated. The residue was purified by chromatography (hexanes:EtOAc 10:1) to give the (*E*)-vinyl iodide **34** (55 mg, 82%) as a white solid. This material was identical to a sample prepared *via* the previous method.

(1*R*,6*S*,7*S*,8*S*)-*N*-(Trifluoromethanesulfonyl)-7-ethynylbicyclo[4.3.0]nonan-8-amide (38). The carbamate **33** (400 mg, 1.52 mmol) and HCl in MeOH (10.6 mmol, 1.6 M) were stirred at room temperature for 8 h. A further aliquot of HCl in MeOH (10.6 mmol) was added and stirring continued for 15 h. The mixture was rotary evaporated, and the residue was dissolved in a minimum volume of EtOH and basified with NH_4OH. The solution was applied to a column of silica and eluted with EtOAc:EtOH:NH_4OH (100:10:1) to give the free amine **37** (244 mg): TLC R_f = 0.43 (EtOAc:EtOH:NH_4OH 100:20:1); IR (neat) 2922, 2851, 626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.37 (ddd, J = 7.2, 7.2, 7.2 Hz, 1H), 2.35−2.19 (m, 2H), 2.16 (d, J = 2.4 Hz, 1H), 2.07−1.95 (m, 1H), 1.87−1.63 (m, 3H), 1.43 (br s, NH_2), 1.30−0.80 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.1, 72.1, 51.4, 49.9, 44.4, 43.5, 41.4, 31.7, 30.2, 26.2, 26.1. The amine was not completely characterized but was taken up in dry CH_2Cl_2 (5 mL) and Et_3N (1.25 mL) and cooled to −78 °C under Ar. $(CF_3SO_2)_2O$ (0.28 mL, 1.65 mmol) was added, and the mixture was stirred for 1 h at −78 °C. The reaction was quenched with H_2O (20 mL), and the mixture was allowed to warm to room temperature and extracted into CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with H_2O (30 mL) and brine (30 mL) and dried ($MgSO_4$). The solution was rotary evaporated and the residue chromatographed (hexanes:EtOAc 10:1) to give **38** (341 mg, 76%) as a cream-colored solid: mp 53−54 °C (not recrystallized); TLC R_f = 0.29 (hexanes:EtOAc 10:1); $[\alpha]_D = +15.1°$ (c = 1.20, $CHCl_3$); IR (neat) 3308, 2929, 2856, 2360, 1451, 1379, 1336, 1232, 1194, 1147, 1084, 963, 936, 606, 571, 504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (br s, 1H), 4.02 (ddd, J = 8.4, 8.4, 8.4 Hz, 1H), 2.60 (ddd, J = 10.4, 8.4, 2.5 Hz, 1H), 2.43−2.35 (m, 1H), 2.36 (d, J = 2.5 Hz, 1H), 2.09−2.00 (m, 1H), 1.90−1.69 (m, 3H), 1.32−0.95 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.6 (q, $^1J_{C-F}$ = 321 Hz, CF_3), 81.4, 74.7, 54.3, 52.1, 43.7, 41.2, 40.1, 30.9, 30.0, 25.9, 25.8; MS(EI) *m/e* 295 (M$^{+\bullet}$),

294 ($M - H^+$), 213, 162, 145, 105, 91; HRMS(EI) calcd for $C_{12}H_{15}F_3NO_2S$ ($M - H^+$) 294.0776, found ($M - H^+$), 294.0801. Anal. Calcd for $C_{12}H_{16}F_3NO_2S$: C, 48.80; H, 5.46; N, 4.74. Found: C, 48.99; H, 5.59; N, 4.60.

***N,N′*-Bis[(1*R*,6*S*,7*S*,8*S*)-7-ethynylbicyclo[4.3.0]non-8-yl]-*N,N′*-bis(trifluoromethanesulfonyl)-1,3-propanediamide (39).** A solution of the sulfonamide **38** (340 mg, 1.15 mmol), 1,3-dibromopropane (116 mg, 0.576 mmol) in dry MeCN (4 mL) with anhydrous K_2CO_3 (318 mg, 2.30 mmol), and KI (5 mg, 0.03 mmol) was heated at reflux under Ar for 22 h. The solvent was removed by rotary evaporation, and the residue was dissolved in $CHCl_3$ and filtered (Celite), washing with $CHCl_3$. The solvent was again removed by rotary evaporation, and the residue was chromatographed on silica (hexanes:EtOAc gradient 60:1 to 40:1) to give **39** (194 mg, 53%) (on a scale of 40 mg a yield of 63% was obtained) as a colorless gum: TLC $R_f = 0.16$ (hexanes:EtOAc 40:1); $[\alpha]_D = -15.6°$ ($c = 1.18$, $CHCl_3$); IR (neat) 3296, 2929, 2855, 1449, 1384, 1224, 1190, 1141, 1112, 1003, 962, 608, 508, 468, 462 cm^{-1}; ^1H NMR (300 MHz, CD_5CD_3 at 343 K) δ 4.27 (ddd, $J = 9.3, 9.3, 9.3$ Hz, 2H), 3.70−3.55 (m, 2H), 3.40−3.23 (m, 2H), 2.33−2.19 (m, 4H), 1.97−1.87 (m, 2H), 1.90 (d, $J = 2.6$ Hz, 2H), 1.81 (ddd, $J = 12.9, 7.5, 5.3$ Hz, 2H), 1.63−1.50 (m, 6H), 1.45−0.80 (m, 10H), 0.72−0.40 (m, 4H); ^{13}C NMR (75 MHz, CD_5CD_3 at 343 K) δ 120.8 (q, $^1J_{C-F} = 324$ Hz, $2CF_3$), 82.8 (2C), 73.6 (2C), 61.7 (2C), 53.5 (2C), 46.6 (2C), 43.3 (2C), 40.3 (2C), 37.4 (2C), 33.7, 31.2 (2C), 30.7 (2C), 26.3 (4C); MS(FAB) *m/e* 631 ($M + H^+$), 497, 363, 212, 147. Anal. Calcd for $C_{27}H_{36}N_2O_4S_2$: C, 51.42; H, 5.75; N, 4.44. Found: C, 51.65; H, 5.80; N, 4.28.

***(E,E)*-9,11-Eicosadiene.** To a suspension of Cp_2ZrHCl (98 mg, 0.38 mmol) in dry THF (1 mL) under Ar in the dark was added 1-decyne (50 mg, 0.36 mmol) in THF (1 mL) *via* cannula. The mixture was stirred for 30 min, and the resulting pale yellow solution was added *via* cannula to a suspension of copper(I) chloride (39 mg, 0.40 mmol) in dry THF (1 mL) under Ar. After stirring in the dark for 3 h, H_2O (0.5 mL) was added and stirring continued for 30 min. The mixture was filtered (Celite), and the filter pad was washed with hexanes. The solution was dried ($MgSO_4$) and rotary evaporated. The residue was purified by chromatography (hexanes) to give (*E,E*)-9,11-eicosadiene (40 mg, 79%) as a white solid: TLC $R_f = 0.56$ (hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.05−5.92 (m, 2H), 5.60−5.50 (m, 2H), 2.10−2.00 (m, 4H), 1.45−1.15 (m, 24H), 0.88 (t, $J = 6.4$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4 (2C), 130.3 (2C), 32.6 (2C), 31.9 (2C), 29.51 (2C), 29.47 (2C), 29.30 (2C), 29.26 (2C), 22.7 (2C), 14.1 (2C).

(1*R*,6*S*,7*R*,8*S*)-*N*-(Trifluoromethanesulfonyl)-7-[(benzyloxy)methyl]bicyclo[4.3.0]nonan-8-amide (42a). To a solution of **29** (2.39 g, 9.21 mmol) in dry CH_2Cl_2 (50 mL) and Et_3N (10 mL) at −78 °C under Ar was added $(CF_3SO_2)_2O$ (1.71 mL, 10.14 mmol) over 10 min. The mixture was stirred at −78 °C for 1 h, the reaction was quenched by the addition of H_2O (10 mL), and the solution was allowed to reach room temperature. The mixture was extracted into $CHCl_3$ (3 × 50 mL), and the combined extracts were washed with brine (50 mL) and dried ($MgSO_4$). The solution was rotary evaporated and the residue chromatographed (hexanes:EtOAc 10:1) to give **42a** (3.54 g, 98%) as a pale yellow oil: TLC $R_f = 0.30$ (hexanes:Et_2O 10:1); $[\alpha]_D = +9.8°$ ($c = 1.20$, $CHCl_3$); IR (neat) 2924, 2854, 1437, 1379, 1231, 1190, 1149, 1095, 700, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.26 (m, 5H), 6.40 (d, $J = 9.0$ Hz, NH), 4.55 (d, $J = 11.6$ Hz, 1H), 4.46 (d, $J = 11.6$ Hz, 1H), 4.05 (dddd, $J = 9.0, 9.0, 9.0, 9.0$ Hz, 1H), 3.68 (dd, $J = 10.3, 2.6$ Hz, 1H), 3.60 (dd, $J = 10.3, 2.6$ Hz, 1H), 2.32−2.21 (m, 1H), 1.90−1.67 (m, 5H), 1.49−1.34 (m, 1H), 1.30−0.80 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 128.6, 128.1, 128.0, 119.7 (q, $^1J_{C-F} = 321$ Hz, CF_3), 73.6, 67.1, 56.3, 46.2, 45.0, 43.3, 42.0, 31.0, 30.0, 26.1, 26.0; MS (CI) *m/e* 409 ($M + NH_4^+$), 392 ($M + H^+$), 258, 176, 152, 135, 121, 108, 91. Anal. Calcd for $C_{18}H_{24}F_3NO_3S$: C, 55.23; H, 6.18; N, 3.58. Found: C, 55.24; H, 6.37; N, 3.55.

(1*R*,6*S*,7*R*,8*S*)-*N*-(Toluene-4-sulfonyl)-7-[(benzyloxy)-methyl]bicyclo[4.3.0]nonan-8-amide (42b). To a solution of the amine **29** (250 mg, 0.964 mmol) in dry CH_2Cl_2 (5 mL) and Et_3N (1 mL) at 0 °C under Ar was added TsCl (202 mg, 1.06 mmol). The mixture was stirred at room temperature for 18 h, added to H_2O (30 mL), and extracted into EtOAc (3 × 30 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated. The residue was chromatographed (hexanes:EtOAc gradient 10:1 to 5:1) to give **42b** (400 mg, 100%) as a pale yellow gum: TLC $R_f = 0.32$ (hexanes:EtOAc 10:1); $[\alpha]_D = +12.8°$ ($c = 1.70$, $CHCl_3$); IR (neat) 3284, 2921, 2852, 2360, 1452, 1337, 1161, 1093, 815, 736, 698, 662, 548, 464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, $J = 9.7$ Hz, 2H), 7.42−7.28 (m, 5H), 7.21 (d, $J = 9.7$ Hz, 2H), 4.96 (2d, $J = 11.6$ Hz, 2H), 3.75−3.61 (m, 1H), 3.48−3.38 (m, 2H), 2.40 (s, 3H), 2.01−1.90 (m, 1H), 1.80−1.60 (m, 5H), 1.30−0.75 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.3, 137.7, 129.5 (2C), 128.5 (2C), 128.0 (2C), 127.9, 126.9 (2C), 73.5, 67.9, 54.3, 46.2, 45.5, 43.5, 41.3, 31.1, 30.2, 26.2, 26.1, 21.5.

***N,N′*-Bis[(1*R*,6*S*,7*R*,8*S*)-7-[(benzyloxy)methyl]bicyclo-[4.3.0]non-8-yl]-*N,N′*-bis(trifluoromethanesulfonyl)-1,3-propanediamide (43).** The trifluoromethanesulfonamide **42a** (3.53 g, 9.03 mmol) and 1,3-dibromopropane (504 μL, 4.96 mmol) with anhydrous K_2CO_3 (2.50 g, 18.0 mmol) and KI (15 mg, 0.09 mmol) in dry MeCN (30 mL) under Ar were heated at reflux for 3 days. The reaction mixture was allowed to cool, diluted with $CHCl_3$ (100 mL), and filtered (Celite). The solvent was removed under vacuum and the residue chromatographed (hexanes:Et_2O 20:1) to give **43** (3.09 g, 83%) as a colorless gum: TLC $R_f = 0.38$ (hexanes:Et_2O 10:1); $[\alpha]_D = -11.8°$ ($c = 1.25$, $CHCl_3$); IR (neat) 2923, 2360, 1382, 1222, 1189, 1144, 736, 698, 608, 454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.25 (m, 10H), 4.43 (s, 4H), 4.25 (br s, 2H), 3.53 (2d, $J = 4.6$ Hz, 4H), 3.30−3.10 (br m, 2H), 2.95 (br s, 2H), 2.00−1.70 (m, 14H), 1.30−0.90 (m, 14H); ^{13}C NMR (75 MHz, C_6D_6 at 335 K) δ 138.8, 128.6, 127.9, 127.8, 120.7 (q, $^1J_{C-F} = 324$ Hz, $2CF_3$), 73.6, 68.7, 61.9, 48.0, 47.8, 45.9, 43.3, 36.7, 31.3, 31.2, 26.5. Anal. Calcd for $C_{39}H_{52}F_6N_2O_6S_2$: C, 56.92; H, 6.37; N, 3.40. Found: C, 56.57; H, 6.59; N, 3.38.

***N,N′*-Bis[(1*R*,6*S*,7*R*,8*S*)-7-[(benzyloxy)methyl]bicyclo-[4.3.0]non-8-yl]-1,3-propanediamine (44a).** To a solution of **43** (3.07 g, 3.73 mmol) in dry PhMe (30 mL) under Ar was added sodium bis(methoxyethoxy)aluminum hydride (REDAL) (29.8 mmol, 3.4 M solution in PhMe). The mixture was heated at 100 °C for 18 h and allowed to cool. The solution was added to aqueous NaOH (6N, 150 mL) and extracted into Et_2O (3 × 100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and rotary evaporated. The residue was chromatographed (EtOAc:EtOH:NH_4OH 200:5:2) to give **44a** (1.75 g, 84%) as a white, waxy solid: TLC $R_f = 0.58$ (EtOAc:EtOH:NH_4OH 100:10:1); $[\alpha]_D = +84.0°$ ($c = 1.00$, $CHCl_3$); IR (neat) 2918, 2894, 1451, 1098, 734, 697, 456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.20 (m, 10H), 4.47 (2d, $J = 16.1$ Hz, 4H), 3.64 (dd, $J = 9.2, 9.2$ Hz, 2H), 3.52 (dd, $J = 9.1, 4.1$ Hz, 2H), 3.17 (ddd, $J = 7.9, 7.9, 7.9$ Hz, 2H), 2.60−2.50 (m, 2H), 2.45−2.35 (m, 2H), 2.08−1.95 (m, 2H), 1.90−1.50 (m, 14H), 1.20−0.80 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 128.3, 127.6, 127.4, 73.1, 69.6, 58.2, 47.5, 46.7, 46.5, 44.3, 40.0, 31.6, 30.8, 30.3, 26.3, 26.1; MS(EI) *m/e* 559 ($M + H^+$), 558 ($M^{+\bullet}$), 468, 286, 272, 259, 258, 210, 208, 164, 91. HRMS(EI) calcd. for $C_{37}H_{54}N_2O_2$ ($M^{+\bullet}$) 558.4185, found ($M^{+\bullet}$) 558.4188.

***N,N′*-Bis[(1*R*,6*S*,7*R*,8*S*)-7-[(benzyloxy)methyl]bicyclo-[4.3.0]non-8-yl]-*N,N′*-bis(toluene-4-sulfonyl)-1,3-propanediamide (44b).** To a solution of **44a** (1.00 g, 1.79 mmol) in dry CH_2Cl_2 (3 mL) and Et_3N (6 mL) at 0 °C under Ar was added TsCl (6.80 g, 35.8 mmol). The mixture was stirred at room temperature for 3 days, added to aqueous NaOH (2 N, 100 mL), and extracted into EtOAc (3 × 50 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed (hexanes:EtOAc gradient 20:1 to 10:1 to 7:1) to give **44b** (1.50 g, 97%) as a pale yellow gum: TLC $R_f = 0.13$ (hexanes:EtOAc 10:1); $[\alpha]_D = -20.9°$ ($c = 1.10$, $CHCl_3$); IR (neat) 2921, 2852, 1452, 1335, 1152, 1090, 814, 735, 698, 658, 547, 467 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, $J = 8.3$ Hz, 4H), 7.35−7.18 (m, 14H), 4.36 (s, 4H), 4.32−4.15 (br, m, 2H), 3.50−3.32 (m, 4H), 3.20−3.05 (m, 2H), 2.98−2.80 (m, 2H), 2.38 (s, 6H), 2.00−1.55 (m, 14H), 1.32−0.85 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.8, 138.7, 129.6, 128.3, 127.4, 127.3, 126.9, 73.0, 70.0, 59.3, 49.1, 47.0, 44.1, 43.4, 36.4, 31.3, 26.2, 21.5; MS(EI) *m/e* 776 ($M - C_7H_7^+$), 714, 713, 712, 606, 286, 91; HRMS(EI)

calcd for $C_{44}H_{59}N_2O_6S_2$ (M − $C_7H_7^+$) 775.3815, found (M − $C_7H_7^+$) 775.3815.

Alternative Procedure for the Preparation of Bis-Sulfonamide (44b). The toluene-4-sulfonamide **42b** (70 mg, 0.169 mmol) and 1,3-dichloropropane (9 μL, 0.093 mmol) with anhydrous Cs_2CO_3 (110 mg, 0.339 mmol) in dry DMF (1 mL) under Ar where heated at 90 °C for 1 day. Further 1,3-dichloropropane (1 μL, 0.011 mmol) was added, and the mixture was heated at 90 °C for a further 24 h. The reaction mixture was added to H_2O (30 mL) and extracted into EtOAc (3 × 30 mL). The combined extracts were washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed (hexanes:EtOAc gradient 10:1 to 7:1) to give bis-sulfonamide **44b** (35 mg, 48%) as a colorless oil. This material was identical to a sample prepared *via* the previous method.

***N,N′*-Bis[(1*R*,6*S*,7*R*,8*S*)-7-(hydroxymethyl)bicyclo[4.3.0]-non-8-yl]-*N,N′*-bis(toluene-4-sulfonyl)-1,3-propanediamide (45a).** A solution of **44b** (663 mg, 0.765 mmol) in EtOH (25 mL) was stirred with the addition of Raney Ni (Type W-2, 5 mL, 50% slurry in H_2O, pH > 9) under an atmosphere of H_2. After 18 h, the reaction was complete by TLC (hexanes:EtOAc 1:1). The mixture was filtered (Celite) under a flow of Ar, and the filter pad was washed with EtOAc. The solution was rotary evaporated and the residue chromatographed (hexanes:EtOAc 2:1) to give **45a** (511 mg, 97%) as a colorless oil: TLC R_f = 0.20 (hexanes:EtOAc 1:1); $[\alpha]_D$ = +47.6° (*c* = 1.05, $CHCl_3$); IR (neat) 3504, 2923, 2852, 2360, 2342, 1598, 1447, 1400, 1328, 1152, 1088, 1030, 912, 813, 732, 659, 588, 548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 4H), 7.27 (d, *J* = 8.2 Hz, 4H), 4.21 (ddd, *J* = 8.8, 8.8, 8.8 Hz, 2H), 3.67−3.56 (m, 4H), 3.37−3.27 (m, 2H), 3.08−2.98 (m, 2H), 2.75−2.10 (br, 2OH), 2.42 (s, 6H), 2.06−1.96 (m, 2H), 1.92−1.60 (m, 12H), 1.28−0.83 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.0, 129.8, 127.1, 61.1, 59.0, 51.3, 48.0, 44.7, 43.8, 34.8, 31.8, 31.3, 30.9, 26.2, 26.0, 21.6; HRMS(FAB) calcd for $C_{37}H_{54}N_2O_6S_2H$ (M + H^+) 687.3502, found (M + H^+) 687.3488.

***N,N′*-Bis[(1*R*,6*S*,7*R*,8*S*)-7-formylbicyclo[4.3.0]non-8-yl]-*N,N′*-bis(toluene-4-sulfonyl)-1,3-propanediamide (45b).** Oxalyl chloride (4.39 mmol, 2.2 M solution in CH_2Cl_2) was added to a solution of dry DMSO (0.62 mL, 8.8 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C under Ar. The mixture was stirred until effervescence had ceased (30 min), and a solution of **45a** (503 mg, 0.732 mmol) in CH_2Cl_2 (3 mL) was added. The mixture was stirred for 30 min, Et_3N (2 mL) was added, and the mixture was allowed to reach 0 °C and added to H_2O (50 mL). The organic material was extracted into EtOAc (3 × 50 mL), and the combined extracts were washed with brine (50 mL), dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed (hexanes:EtOAc gradient 10:1 to 5:1 to 2:1) to give **45b** (480 mg, 96%) as a white foam: TLC R_f = 0.40 (hexanes:EtOAc 2:1); $[\alpha]_D$ = −32.4° (*c* = 0.38, $CHCl_3$); IR (neat) 2926, 2853, 1716, 1447, 1336, 1160, 1089, 914, 815, 732, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, *J* = 1.6 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 4H), 7.30 (d, *J* = 8.2 Hz, 4H), 4.55 (ddd, *J* = 10.6, 10.6, 7.6, 2H), 3.10−2.90 (m, 2H), 2.85−2.70 (m, 2H), 2.56 (ddd, *J* = 11.1, 10.6, 1.6, 2H), 2.41 (s, 6H), 1.95−1.60 (m, 14H), 1.40−0.77 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 143.6, 137.0, 129.9, 127.1, 58.6, 58.3, 45.8, 44.1, 42.7, 36.3, 32.2, 30.9, 30.8, 25.9, 25.8, 21.6; HRMS (FAB) calcd for $C_{37}H_{50}N_2O_6S_2H$ (M + H^+) 683.3189, found (M + H^+), 683.3182.

***N,N′*-Bis[(1*R*,6*S*,7*S*,8*S*)-7-((*E*)-1-iodo-2-ethenyl)bicyclo-[4.3.0]-8-nonyl]-*N,N′*-bis(4-toluenesulfonyl)-1,3-propanediamide (46).** A mixture of **45b** (300 mg, 0.438 mmol) and CHI_3 (1.38 g, 3.51 mmol) in dry 1,4-dioxane (6 mL) and THF (1 mL) was added to a suspension of $CrCl_2$ (1.29 g, 10.5 mmol) in 1,4-dioxane (6 mL) and THF (1 mL), under Ar at room temperature. The mixture was stirred for 5 h, added to hydrochloric acid (1 N, 150 mL), and extracted into EtOAc (3 × 50 mL). The combined extracts were washed with H_2O (50 mL) and brine (50 mL) and dried ($MgSO_4$). The solvent was removed by rotary evaporation, the residue was taken up in $CHCl_3$ (10 mL) and mixed with silica (ca. 5 g), and the solvent was removed and then dry loaded onto a silica column. Elution (hexanes:EtOAc gradient 20:1 to 10:1) gave **46** (266 mg, 65%) as a white foam: TLC R_f = 0.42 (hexanes:EtOAc 4:1); $[\alpha]_D$ = −64.9° (*c* = 0.205, $CHCl_3$); IR (neat) 2922, 1335, 1156, 757, 661, 546, 456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 4H), 7.28 (d, *J* = 8.2 Hz, 4H), 6.12 (dd, *J* = 14.4, 8.5 Hz, 2H), 5.67 (dd, *J* = 14.4, 0.9 Hz, 2H), 4.35 (ddd, *J* = 10.2, 10.2, 7.8 Hz, 2H), 3.32−3.18 (m, 2H), 2.97−2.82 (m, 2H), 2.41 (s, 6H), 2.16 (ddd, *J* = 10.2, 10.2, 10.2 Hz, 2H), 2.05−1.63 (m, 12H), 1.45−1.30 (m, 2H), 1.30−0.95 (m, 10H), 0.90−0.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 143.1, 138.3, 129.9, 127.0, 76.6, 59.6, 53.7, 50.4, 45.1, 43.2, 36.9, 33.4, 31.2, 30.5, 26.1, 26.0, 21.6; MS(FAB) *m/e* 953 (M + Na^+), 931 (M + H^+), 804, 803, 776, 775, 657, 649, 648; HRMS(FAB) calcd for $C_{39}H_{52}I_2N_2O_4S_2H$ (M + H^+) 931.1540, found (M + H^+) 931.1475.

***N,N′*-Bis[(1*R*,6*S*,7*S*,8*S*)-7-((*E*)-1-(trimethylstannyl)ethen-2-yl)bicyclo[4.3.0]non-8-yl]-*N,N′*-bis(toluene-4-sulfonyl)-1,3-propanediamide (47).** A mixture of **46** (29 mg, 31 μmol) and $(Ph_3P)_2PdCl_2$ (2 mg, 2.85 μmol) was taken up in dry, oxygen free THF (2 mL) under Ar. $(Me_3Sn)_2$ (44 μL, 0.19 mmol) was added and the mixture stirred in the dark at 50 °C for 18 h. The reaction mixture was added to H_2O (20 mL) and extracted into EtOAc (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed (hexanes:EtOAc gradient 15:1 to 10:1 to 2:1) to give **47** (18 mg, 57%) as a colorless gum/foam: TLC R_f = 0.42 (hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 4H), 7.22 (d, *J* = 8.2 Hz, 4H), 5.81 (d, *J* = 19.2 Hz, 2H), 5.65 (dd, *J* = 19.2, 6.0 Hz, 2H), 4.36 (ddd, *J* = 9.4, 9.4, 9.4 Hz, 2H), 3.25−3.08 (m, 2H), 2.85−2.68 (m, 2H), 2.39 (s, 6H), 2.23 (ddd, *J* = 10.9, 10.9, 5.5 Hz, 2H), 1.90−1.60 (m, 12H), 1.35−0.75 (m, 14H), 0.06 (s, $^2J_{Sn-H}$ = 53 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 142.6, 139.1, 130.2, 129.5 126.8, 60.3, 53.2, 49.6, 45.1, 43.1, 37.1, 33.0, 31.3, 30.9, 26.2, 26.2, 21.5, −9.6 ($^1J_{Sn-C}$ = 338 Hz, 6C); HRMS(EI) calcd for $C_{44}H_{67}N_2O_4S_2{}^{118}Sn_2$ (M − Me^+), 987.2574, found (M−Me^+) 987.2595; calcd for $C_{44}H_{67}N_2O_4S_2{}^{118}Sn^{120}Sn$: (M-$Me^+$), 989.2580; Found (M-$Me^+$), 989.2596.

***N*-[(1*R*,6*S*,7*S*,8*S*)-7-((*E*)-1-Iodo-2-ethenyl)bicyclo[4.3.0]-8-nonyl]-*N′*-[(1*R*,6*S*,7*S*,8*S*)-7-((*E*)-1-(trimethylstannyl)-2-ethenyl)bicyclo[4.3.0]-8-nonyl]-*N,N′*-bis(4-toluenesulfonyl)-1,3-propanediamide (48).** To a solution of **47** (130 mg, 0.129 mmol) in dry Et_2O (3 mL) under Ar was added a solution of I_2 (32.8 mg, 0.129 mmol) in Et_2O (2 mL) *via* cannula, and the mixture was stirred for 30 min. The mixture was added to H_2O (10 mL) and extracted into Et_2O (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated. The residue was chromatographed (hexanes:EtOAc 15:1) to give the starting distannane **47** (32 mg, 25%), the desired product **48** (43 mg, 34%) as a white foam [TLC R_f = 0.38 (hexanes:EtOAc 4:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (2d, overlapping, 4H), 7.23 (2d, overlapping, 4H), 6.09 (dd, *J* = 14.4, 8.3 Hz, 1H), 5.82 (d, *J* = 19.2 Hz, 1H), 5.66 (d, *J* = 14.4 Hz, 1H), 5.65 (dd, *J* = 19.2, 6.2 Hz, 1H), 4.45−4.25 (m, 2H), 3.30−3.10 (m, 2H), 2.90−2.70 (m, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 2.30−2.10 (m, 2H), 1.95−1.60 (m, 12H), 1.40−0.70 (m, 14H), 0.07 (s, $^2J_{Sn-H}$ = 54 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 144.7, 143.0, 142.7, 139.0, 138.4, 130.4, 129.8, 129.6, 126.9, 76.5, 60.4, 59.6, 53.5, 53.3, 50.3, 49.7, 45.1, 43.1, 37.2, 36.8, 33.0, 31.3, 31.1, 30.9, 30.5, 29.7, 26.24, 26.17, 26.0, 21.54, 21.50, −9.5], and finally the diiodide **46** (37 mg, 31%) identical with the previously prepared material.

***N,N′*-Bis(toluene-4-sulfonyl)papuamine (49).** A solution of **48** (20 mg, 0.021 mmol) and $(Ph_3P)_4Pd$ (10 mg, 8.3 μmol) in dry, O_2 free THF (200 mL) was stirred under Ar at 55 °C in the dark for 24 h and rotary evaporated and the residue partitioned between H_2O (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and rotary evaporated. Chromatography (hexanes:EtOAc gradient 8:1 to 4:1) gave **49** (4 mg, 28%) as a pale yellow gum (slightly impure): TLC R_f = 0.36 (hexanes:EtOAc 4:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.5 Hz, 4H), 7.25 (d, *J* = 8.5 Hz, 4H), 6.15 (d, *J* = 14.0 Hz, 2H), 5.95 (dd, *J* = 14.0, 6.4 Hz, 2H), 4.35−4.25 (m, 2H), 3.00 (t, *J* = 6.4 Hz, 4H), 2.55 (ddd, *J* = 9.6, 9.6, 6.4 Hz, 2H), 2.40 (s, 6H), 2.15−1.60 (m, 12H), 1.45−0.70 (m, 14H); HRMS(EI) calcd for $C_{39}H_{52}N_2O_4S_2$ ($M^{+\bullet}$), 676.3369, found ($M^{+\bullet}$) 676.3364.

***N,N′*-Bis[(1*R*,6*S*,7*R*,8*S*)-7-(hydroxymethyl)bicyclo[4.3.0]-non-8-yl]-*N,N′*-bis(trifluoromethanesulfonyl)-1,3-propanediamide (50).** A solution of **43** (2.67 g, 3.24 mmol) in absolute EtOH (150 mL) was stirred under a H_2 atmosphere with Pd/C (10%, 1.30 g) for 14 h. The reaction mixture was filtered (Celite), washing with EtOH, and the filtrate rotary evaporated. The residue was chromatographed (hexanes:EtOAc 2:1) to give **50** (1.98 g, 95%) as a white foam: TLC R_f = 0.23 (hexanes:EtOAc 2:1); $[\alpha]_D = -20.1°$ (c = 1.25, $CHCl_3$); IR (neat) 3569, 3408, 3400, 3394, 2929, 2855, 1447, 1381, 1220, 1191, 1142, 1032, 759, 609 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.32 (m, 2H), 3.74 (d, J = 5.0 Hz, 4H), 3.58−3.40 (m, 2H), 3.21−3.11 (br m, 2H), 2.13−1.74 (m, 16H), 1.43−0.98 (m, 14H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 119.6 (q, $^1J_{C-F}$ = 324 Hz, $2CF_3$), 61.1, 60.6, 49.5, 47.5, 45.0, 43.2, 35.9, 31.0, 30.8, 26.0; HRMS-(EI) calcd for $C_{25}H_{40}N_2O_6S_2F_6{\cdot}NH_4$ (M + NH_4^+) 660.2576, found (M + NH_4^+) 660.2576. Anal. Calcd for $C_{25}H_{40}F_6N_2O_6S_2$: C, 46.72; H, 6.27, N, 4.36. Found: C, 47.01; H, 6.33; N, 4.19.

***N,N′*-Bis[(1*R*,6*S*,7*S*,8*S*)-7-((*E*)-1-iodo-2-ethenyl)bicyclo-[4.3.0]non-8-yl]-*N,N′*-bis(trifluoromethanesulfonyl)-1,3-propanediamide (51).** Oxalyl chloride (9.36 mmol, 2.0 M solution in CH_2Cl_2) was added to a solution of dry DMSO (1.33 mL, 18.72 mmol) in dry CH_2Cl_2 (12 mL) at −78 °C under N_2. The mixture was stirred until effervescence had ceased (30 min), and a solution of **50** (1.00 g, 1.56 mmol) in CH_2Cl_2 (12 mL) was added. The mixture was stirred at −78 °C for 30 min, Et_3N (5 mL) was added, and the mixture was slowly allowed to warm up to 0 °C. The mixture was added to ice-cold H_2O (125 mL) and extracted into EtOAc (3 × 125 mL). The combined extracts were washed with brine (125 mL), dried (Na_2SO_4), filtered, and rotary evaporated.

A mixture of the crude dialdehyde and CHI_3 (7.37 g, 18.72 mmol) in dry 1,4-dioxane (24 mL) and dry THF (4 mL) was added to a suspension of $CrCl_2$ (6.90 g, 56.16 mmol) in 1,4-dioxane (24 mL) and THF (4 mL), under N_2 at room temperature. The mixture was stirred in the dark for 2 h, then added to hydrochloric acid (1 N, 800 mL), and extracted into EtOAc (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried ($MgSO_4$), and rotary evaporated. The residue was dissolved in $CHCl_3$, absorbed onto silica gel, and chromatographed (hexanes:Et_2O 40:1) to give **51** (0.984 g, 71%) as a white foam: TLC R_f = 0.28 (hexanes:Et_2O 30:1); $[\alpha]_D = +6.4°$ (c = 1.05, $CHCl_3$); IR (neat) 2926, 2854, 1383, 1222, 1192, 1145, 1112, 758, 607, 582, 574 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.44 (dd, J = 14.4, 8.4 Hz, 2H), 6.22 (d, J = 14.4 Hz, 2H), 4.40−4.29 (m, 2H), 3.47−3.35 (m, 2H), 2.94−2.86 (br, m, 2H), 2.47−2.36 (ddd, J = 10.1, 10.1, 10.1 Hz, 2H), 2.15−1.77 (m, 12H), 1.48−0.85 (m, 14H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.7, 119.5 (q, $^1J_{C-F}$ = 324 Hz, $2CF_3$), 79.0, 61.9, 53.9, 50.6, 45.6, 43.0, 36.4, 31.0, 30.4, 25.9; HRMS (FAB) calcd for $C_{27}H_{37}F_6I_2N_2O_4S_2$ (M − H^+) 885.0189, found (M − H^+) 885.0156. Anal. Calcd for $C_{27}H_{38}F_6I_2N_2O_4S_2$: C, 36.58; H, 4.32; N, 3.16. Found: C, 36.87; H, 3.98; N, 3.20.

***N,N′*-Bis[(1*R*,6*S*,7*S*,8*S*)-7-((*E*)-1-(trimethylstannyl)ethen-2-yl)bicyclo[4.3.0]non-8-yl]-*N,N′*-bis(trifluoromethanesulfonyl)-1,3-propanediamide (52).** A mixture of **51** (0.400 g, 0.451 mmol) and $(Ph_3P)_2PdCl_2$ (32 mg, 45 μmol) and Li_2CO_3 (0.100 g, 1.35 mmol) was taken up in dry, O_2 free THF (40 mL) under N_2. $(Me_3Sn)_2$ (0.40 mL, 1.93 mmol) was added, and the mixture was stirred in the dark at 60 °C for 12.5 h. The reaction mixture was cooled and partitioned between H_2O (200 mL) and EtOAc (200 mL). The aqueous layer was further extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and rotary evaporated. The residue was dissolved in $CHCl_3$, absorbed onto silica gel, and chromatographed (silica pretreated with 1% Et_3N in hexanes, hexanes:Et_2O 60:1) to give **52** (0.223 g, 51%) as a white foam/gum: TLC R_f = 0.23 (hexanes:Et_2O 60:1); $[\alpha]_D = +5.1°$ (c = 1.30, $CHCl_3$); IR (neat) 2977, 2925, 2854, 1384, 1233, 1192, 1146, 1138, 1110, 1004, 765, 607, 582 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.17 (d, J = 19.1 Hz, 2H), 5.90 (dd, J = 19.1, 6.7 Hz, 2H), 4.46−4.35 (br m, 2H), 3.41−3.25 (br m, 2H), 3.05−2.78 (br m, 2H), 2.51−2.40 (m, 2H), 2.12−1.76 (m, 12H), 1.43−0.87 (m, 14H), 0.14 (s, $^2J_{Sn-H}$ = 55 Hz, 18H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 145.5, 133.5, 119.5 (q, $^1J_{C-F}$ = 324 Hz, $2CF_3$), 62.7, 54.2, 50.1, 45.8, 43.1, 36.7, 31.1, 30.7, 26.1, −9.8; HRMS(EI) calcd for $C_{32}H_{53}N_2O_4S_2F_6{}^{120}Sn_2$ (M − Me^+), 947.1395, found (M − Me^+), 947.1396; calcd for $C_{32}H_{53}N_2O_4S_2F_6{}^{118}Sn{}^{120}Sn$ (M − Me^+) 945.1389, found (M − Me^+) 945.1392. Anal. Calcd for $C_{33}H_{56}F_6N_2O_4S_2Sn_2$ C, 41.27; H, 5.88; N, 2.92. Found: C, 41.49; H, 5.86; N, 2.96.

***N*-[(1*R*,6*S*,7*S*,8*S*)-7-((*E*)-1-Iodo-2-ethenyl)bicyclo[4.3.0]-8-nonyl]-*N′*-[(1*R*,6*S*,7*S*,8*S*)-7-((*E*)-1-(trimethylstannyl)-ethen-2-yl)bicyclo[4.3.0]-8-non-yl]-*N,N′*-bis(trifluoromethanesulfonyl)-1,3-propanediamide (53).** To a solution of **52** (0.265 g, 0.276 mmol) in dry Et_2O (5.0 mL) under N_2 was added a solution of I_2 (0.070 g, 0.276 mmol) in Et_2O (5.0 mL) via cannula, and the mixture was stirred in the dark at room temperature for 30 min. The reaction mixture was poured into H_2O (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed (hexanes:Et_2O 60:1) to give the starting distannane **52** (61 mg, 24%), the desired product **53** (0.111 g, 44%) as a white foam: [TLC R_f = 0.39 (hexanes:Et_2O 40:1); $[\alpha]_D = +5.0°$ (c = 1.10, $CHCl_3$); IR (neat) 2927, 2855, 1383, 1223, 1192, 1146, 1111, 762, 608 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.42 (dd, J = 14.4, 8.2 Hz, 1H), 6.22 (d, J = 14.4 Hz, 1H), 6.12 (d, J = 19.8 Hz, 1H), 5.91 (dd, J = 19.1, 6.93 Hz, 1H), 4.39−4.30 (m, 2H), 3.45−3.25 (br m, 2H), 3.00−2.60 (br m, 2H), 2.45−2.35 (m, 2H), 2.13−1.76 (m, 12H), 1.43−0.87 (m, 14H), 0.15 (s, $^2J_{Sn-H}$ = 54 Hz, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 145.4, 143.7, 133.7, 119.5 (q, $^1J_{C-F}$ = 323 Hz, $2CF_3$), 78.9, 62.7, 61.9, 54.3, 53.8, 50.7, 50.0, 45.6, 43.0, 36.7, 31.0, 30.7, 30.4, 26.0, 25.9, −9.7; HRMS(FAB) calcd for $C_{29}H_{44}F_6IN_2O_4S_2{}^{120}$-Sn (M − Me^+) 909.0713, found (M − Me^+) 909.0727. Anal. Calcd for $C_{30}H_{47}F_6IN_2O_4S_2Sn$: C, 39.02; H, 5.13; N, 3.03. Found: C, 39.24; H, 4.87; N, 2.94], and finally the diiodide **51** (60 mg, 24%) identical with the previously prepared material.

***N,N′*-Bis(trifluoromethanesulfonyl)papuamine (54).** To a solution of $(Ph_3P)_4Pd$ (8.7 mg, 8 μmol) in PhMe (25 mL) under N_2 was added as a solution (0.2 mL) of **53** (35 mg, 36 μmol) in PhMe (5 mL), and the mixture was heated to 100 ± 5 °C in the dark. The remainder of the solution of **53** was added over a 6.5 h period with a syringe pump. The resulting mixture was maintained at 100 ± 5 °C for 2 h, at which time an additional portion of $(Ph_3P)_4Pd$ (4.1 mg, 4 μmol) was added. The resulting mixture was heated to 100 ± 5 °C, with stirring in the dark, under an atmosphere of N_2 for 13.5 h and allowed to cool to room temperature. The mixture was filtered (Celite), washing with EtOAc, and the combined filtrates were rotary evaporated. The residue was dissolved in Et_2O, preabsorbed onto silica gel, and chromatographed (hexanes:Et_2O 30:1) to give **54** (9 mg, 39%) as a cream-colored foam: TLC R_f = 0.17 (hexanes:Et_2O 60:1); $[\alpha]_D = +55.9°$ (c = 1.05, $CHCl_3$); IR (neat) 2927, 2854, 1382, 1223, 1186, 1144, 602, 578, 449 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.17 (d, J = 15.1 Hz, 2H), 5.87−5.75 (br m, 2H), 4.48−3.95 (br m, 2H), 3.22 (br t, 4H), 2.59−2.45 (br m, 2H), 2.01−1.58 (m, 12H), 1.46−0.82 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 147.2, 130.3, 120.1 (q, J = 324 Hz, $2CF_3$), 64.2, 47.8, 46.9, 42.5, 35.4, 30.9, 30.7, 29.7, 26.1, 26.0; MS(CI) *m/e* 650 (M + NH_4^+), 633 (M + H^+), 632, 499, 367, 121; HRMS(CI) calcd for $C_{27}H_{38}F_6N_2S_2O_4{\cdot}NH_4$ (M + NH_4^+), 650.2521, found (M + NH_4^+) 650.2547.

Alternative Procedure for the Preparation of *N,N′*-Bis(trifluoromethanesulfonyl)papuamine (54). To a solution of $(Ph_3P)_4Pd$ (4.8 mg, 4.0 μmol) and Li_2CO_3 (1.5 mg, 20 μmol) in PhMe (25 mL) under N_2, heated to 100 ± 5 °C, was added a solution of **51** (30 mg, 34 μmol) and $(Me_3Sn)_2$ (18 μL, 85 μmol) in PhMe (5.0 mL) over a 4 h period with a syringe pump. The resulting mixture was maintained at 100 ± 5 °C, for 6 h, at which time an additional portion of $(Ph_3P)_4Pd$ (5.8 mg, 5.0 μmol) was added. The resulting mixture was heated to 100 ± 5 °C, with stirring in the dark, under an atmosphere of N_2 for 13 h and allowed to cool to room temperature. The mixture was filtered (Celite), washing with EtOAc, and the combined filtrates were rotary evaporated. The residue was dissolved in Et_2O, preabsorbed onto silica gel, and chromatographed (hexanes:Et_2O 30:1) to give **54** (3 mg, 14%) as an oily residue. This material was identical to a sample prepared *via* the previous method.

(+)-Papuamine Dihydrochloride (56). To a solution of **54** (33 mg, 0.052 mmol) in Et_2O (3.0 mL), under N_2, was added a solution of $LiAlH_4$ (0.90 mmol, 1.0 M in Et_2O), and the resulting mixture was heated to reflux for 87 h. The reaction mixture was cooled to 0 °C, and then a saturated solution of potassium sodium tartrate (10 drops) was slowly added dropwise with stirring. The resulting mixture was heated at reflux for 1 h, allowed to cool to room temperature, and filtered, and the filtrate was rotary evaporated. The residue was chromatographed and subsequently further purified by preparative TLC (CH_2Cl_2:MeOH: NH_4OH (35%) 87:12:1) to give **49** (8 mg, 42%) as an off-white solid: TLC $R_f = 0.44$ (CH_2Cl_2:MeOH: NH_4OH (35%) 87:12:1); $[\alpha]_D = +179.7°$ ($c = 0.39$, MeOH); IR ($CHCl_3$) 3443, 2923, 2852, 1564, 1461, 1186 cm^{-1}; ^1H NMR (500 MHz, MeOH-d_4) δ 6.18 (ddd, $J = 15.0, 12.4, 7.0$, 2H), 5.75−5.68 (complex m, 2H), 2.98 (br ddd, $J = 8.4, 8.3, 8.2$ Hz, 2H), 2.60−2.55 (m, 2H), 2.31−2.20 (m, 6H), 2.19−2.16 (m, 2H), 1.89−1.75 (m, 8H), 1.57−1.54 (m, 2H), 1.37−0.89 (m, 14H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 130.8, 129.5, 61.00, 51.22, 48.9, 45.9, 43.8, 42.0, 31.7, 31.2, 30.5, 26.43, 26.41.

Diamine **55** (6 mg, 15.5 μmol) was dissolved in MeOH (10 mL) and H_2O (30 mL), and concentrated HCl (1 mL) was slowly added. The MeOH was removed under reduced pressure, and the H_2O was removed by lyophilization to give **56** (6.8 mg, 100%) as an off-white solid: TLC $R_f = 0.35$ (CH_2Cl_2:MeOH: NH_4OH (35%) 87:12:1); $[\alpha]_D = +138.6°$ ($c = 0.34$, MeOH); IR ($CHCl_3$) 3401, 2927, 2854, 1571, 1448, 1215, 1014, 758 cm^{-1}; UV $\lambda_{max} = 236$, MeOH; ^1H NMR (500 MHz, MeOH-d_4) δ 6.52 (complex m, 2H), 5.90−5.86 (complex m, 2H), 3.60 (m, 2H), 3.23−3.16 (m, 2H), 3.08−3.04 (m, 2H), 2.66 (ddd, $J = 10.9, 9.2, 9.1$ Hz, 2H), 2.44 (m, 2H), 2.02−1.80 (m 10H), 1.4−0.89 (m 14H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 136.1, 130.4, 62.1, 50.5, 46.8, 44.6, 39.1, 32.1, 30.7, 27.0, 24.0; HRMS(FAB) calcd for $C_{25}H_{41}N_2$: ($M^{+\bullet}$), 369.3270, found ($M^{+\bullet}$), 369.3285.

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Supporting Information Available: X-ray data for compounds **24** and **30** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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