The Stereochemical Assignment and Conformational Analysis of the V/W-Ring Juncture of Maitotoxin

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Abstract: The unambiguous stereochemical assignment of the V/W-ring juncture of maitotoxin, as shown in Figure 1, was accomplished using a two-step approach: (1) the synthesis of two diastereomeric models **Me-A** and **Me-B** and (2) the comparison of the NMR spectroscopic data for each model with those of maitotoxin. Furthermore, the fact that the NMR characteristics observed for **Me-A** were remarkably close to those reported for maitotoxin makes a strong case for the accurate extrapolation of the conformational properties of maitotoxin from those of the model **Me-A**. Using $^1H-^1H$ NOESY experiments and MM3 calculations, the solution conformations of **Me-A** and **Me-B** were studied in aprotic and protic solvents. In aprotic solvents such as benzene, both **Me-A** and **Me-B** preferentially adopt the conformations **Me-Aa** and **Me-Ba**, respectively, due to intramolecular hydrogen bond stabilization. On the other hand, in a protic solvent such as a 1:1 mixture of methanol and pyridine both **Me-A** and **Me-B** exist as mixtures of all of their possible rotamers.

Introduction

Maitotoxin (MTX; **1**, Figure 1), a toxin found in the surgeonfish *Ctenochaetus striatus*, was first mentioned in the literature in 1976[1] and later found to be a product of epiphytic dinoflagellate *Gambierdiscus toxicus*.[2a] With a molecular weight of 3422 Da, it is the largest natural product known to date besides biopolymers.[2b] Except for a few proteins maitotoxin is the most potent natural product, having a minimum lethal dose in mice of 0.17 μg/Kg when injected intraperitoneally. The mode of action of MTX on the cell was studied by Yasumoto, and in 1982 he published that MTX causes an increase in the intracellular Ca^{2+}-concentration in PC12h cells, derived from a rat pheochromocytoma, and that the effect of MTX can be counter-acted by Ca^{2+}-channel blockers and local anesthetics.[2c] MTX's unusual size and toxicity have attracted the attention of many pharmocologists and biochemists.

The complete gross structure of MTX was disclosed in 1993[3] followed by a partial relative stereochemical assignment a year later focusing on the fused ring portions of MTX.[4] The relative stereochemistry of the four acyclic fragments, C.1-C.15, C.35-C.39, C.63-C.68, and C.134-C.142, was recently published independently by Yasumoto and by us.[5−8]

The stereochemistry of the K/L-, O/P-, and V/W-ring junctures were assigned by Yasumoto and co-workers in 1994.[4] Based on the NOE and vicinal spin coupling constant data supported by molecular mechanics calculations (MM2), they assigned the relative stereochemistry of the K/L- and O/P-ring junctures as shown in Figure 1. However, the presence of C.155 methyl group precluded the use of vicinal spin coupling constant between ring-juncture protons in assigning the relative stereochemistry at the V/W-ring juncture, and Yasumoto relied on NOE data in 1:1 $C_5D_5N-CD_3OD$ in combination with MM2 force field calculations to distinguish between the two possible diastereomers, cf. **A** and **B** (Figure 2). NOEs between the C.101-C.99 protons and the C.155-C.98 protons were observed in the NOESY spectrum for MTX in 1:1 $C_5D_5N-CD_3OD$. Then MM2 force field calculations indicated that, in order for **B** to exhibit the observed NOEs, it must be 1.2 kcal/mol higher in energy than its lowest energy conformation. Based on these data, they assigned the relative stereochemistry of the V/W-ring juncture of MTX as shown in Figure 1.

The NOE and computational data were very informative, and at the time there might have been no other way available to firmly establish the stereochemistry of the V/W-ring juncture. Nevertheless, the stereochemical assignment for the V/W-ring juncture is, in our view, less conclusive than that for the K/L- and O/P-ring junctures. We addressed this issue with a two-step approach: (1) synthesizing the two possible diastereomers of an appropriate model compound and (2) comparing their proton and carbon NMR chemical shifts with those of the natural product. We originally chose to use $\mathbf{H_2}$**-A** and $\mathbf{H_2}$**-B**[9] as the diastereomeric models because of the ease of synthesis (Figure 3). The NMR chemical shifts for the C.104-C.95 protons and

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(1) Yasumoto, T.; Bagnis, R.; Vernoux, J. P. *Bull. Jpn. Soc. Sci. Fish.* **1976**, *42*, 359−365.

(2) (a) Yasumoto, T.; Nakajima, I.; Oshima, Y.; Bagnis, R. In *Toxic Dinoflagellate Blooms*; Taylor, D. L., Seliger, H., Eds.; Elsevier: North Holland, 1979; pp 65−70. (b) Yokoyama, A.; Murata, M.; Oshima, Y.; Iwashita, T.; Yasumoto, T. *J. Biochem.* **1988**, *104*, 184−187. (c) Takahashi, M.; Ohizumi, Y.; Yasumoto, T. *J. Biol. Chem.* **1982**, *257*, 7287−7289.

(3) Murata, M.; Naoki, H.; Iwashita, T.; Matsunaga, S.; Sasaki, M.; Yokoyama, A.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 2060−2062.

(4) Murata, M.; Naoki, H.; Matsunaga, S.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1994**, *116*, 7098−7107.

(5) (a) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1994**, *35*, 5023−5026. (b) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 9007−9010. (c) Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 9011−9014. (d) Matsumori, N.; Nonomura, T.; Sasaki, M.; Murata, M.; Tachibana, K.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1996**, *37*, 1269−1272. (e) Sasaki, M.; Matsumori, N.; Maruyama, T.; Nonomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1672−1675. (f) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1675−1678.

(6) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946−7968.

(7) The absolute stereochemistry of MTX has been assigned: (a) ref 5f. (b) Oinuma, H.; Kim, H.; Kishi, Y. Unpublished work. Also, see the note added in the proof of ref 6.

(8) The numbering used throughout this paper corresponds to the position of the corresponding carbon atom of MTX. Because of availability of chiral starting material for both the $\mathbf{H_2}$**-** and the **Me-**model series we opted to study the stereochemical assignment and conformational analysis of the V/W-ring juncture with the antipode of MTX.

S0002-7863(97)01259-6 CCC: $14.00

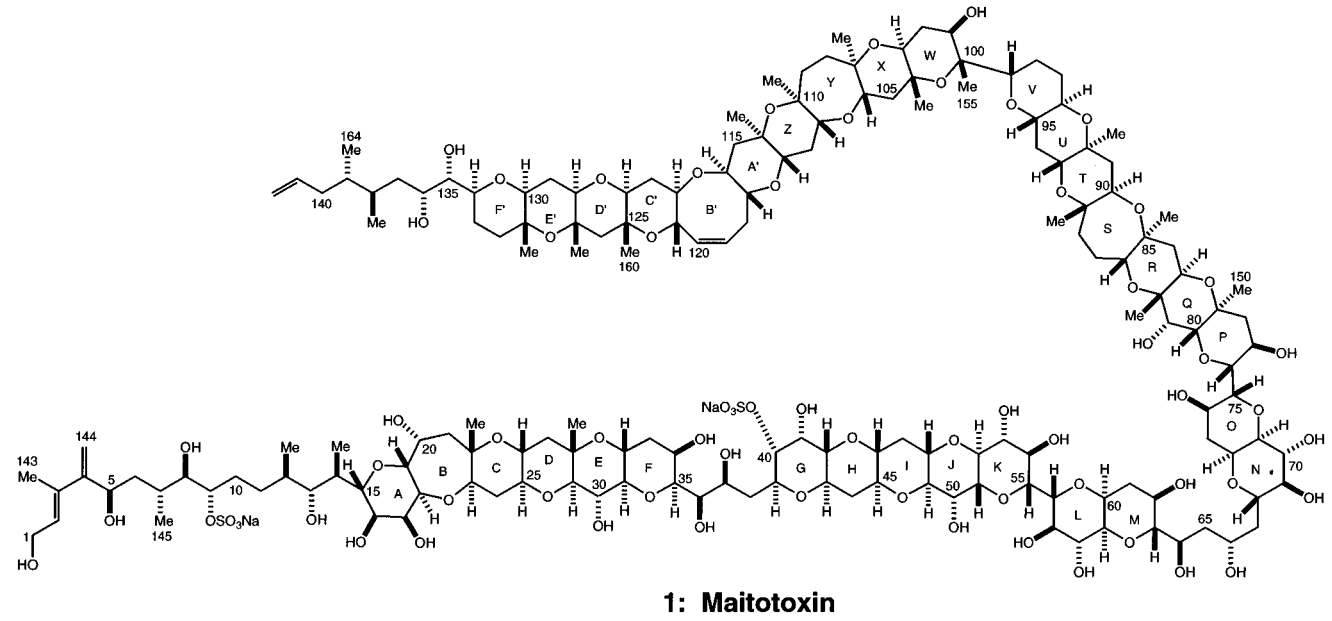


Figure 1. Complete structure of maitotoxin (**1**).

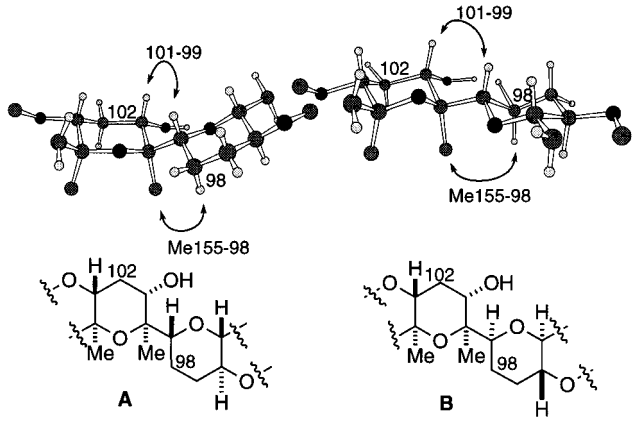


Figure 2.[4] Both possible diastereomers of the V/W-ring juncture of MTX, **A** and **B**, with Chem 3D drawings of their conformations which would exhibit the observed NOEs in 1:1 $C_5D_5N-CD_3OD$.

carbons of **H_2-A** and **H_2-B** were compared to the NMR chemical shifts of the corresponding protons and carbons of MTX (Chart 1). This exercise demonstrated that the relative stereochemistry of the V/W-ring juncture was represented by **H_2-A**,[10] corresponding to the stereochemistry suggested by Yasumoto.

Although we were able to make the assignment of the stereochemistry of the V/W-ring juncture with models **H_2-A** and **H_2-B**, we did recognize the large discrepancy in NMR chemical shifts for the C.103 and C.96 protons and carbons of both **H_2-A** and **H_2-B** relative to MTX as seen in Chart 1. Therefore, we did not consider them to be ideal models with which to study the conformational characteristics associated with this portion of MTX. We felt that these differences in NMR chemical shifts might be largely due to the absence of angular methyl groups at the C.107 and C.92 positions in **H_2-A** and **H_2-B**. In this paper we describe the synthesis of the improved models **Me-A** and **Me-B**, the comparison of their NMR spectroscopic data with that of MTX, the unambiguous assignment of the relative stereochemistry of V/W-ring juncture of MTX, and the conformational properties observed for these models in protic and aprotic solvents.

(9) The synthesis of these two models is described in detail in the Supporting Information, and the results of the NMR spectroscopic study were added to the 1996 publication as the note added in the proof. See ref 6.

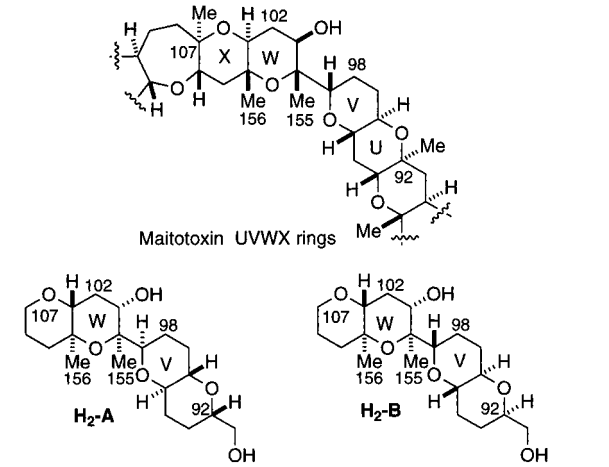


Figure 3.[8] The structures of V/W-juncture of MTX and models **H_2-A and H_2-B.**

Results and Discussion

Relative Stereochemistry of the V/W-Ring Juncture. Scheme 1 outlines the convergent synthetic plan for both models **Me-A** and **Me-B**. It was envisioned that ring V could be formed by reductive cyclization[11] of hydroxy ketones **11** and **12**, which

(10) The stereochemistry of model **H_2-A** was established by the crystal structure of its bis-3′,5′-dinitrobenzoate derivative as shown below.The DNBz groups were removed from the representation for clarity.

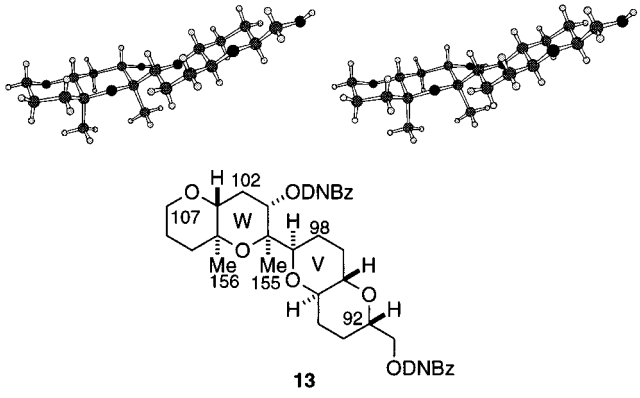
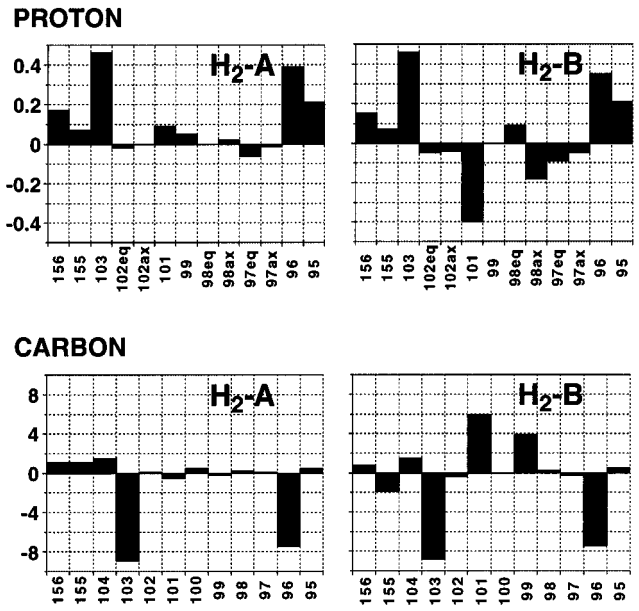
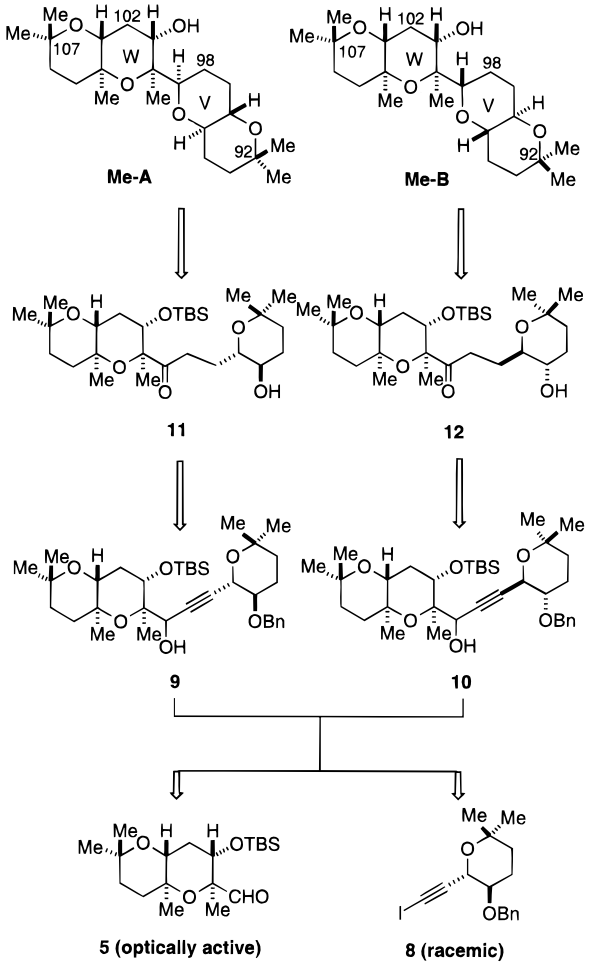


Chart 1. Difference in Proton (500 MHz, 1:1 $C_5D_5N-CD_3OD$) and Carbon (125 MHz, 1:1 $C_5D_5N-CD_3OD$) Chemical Shifts between MTX and Each of **H_2-A** and **H_2-B**[a]



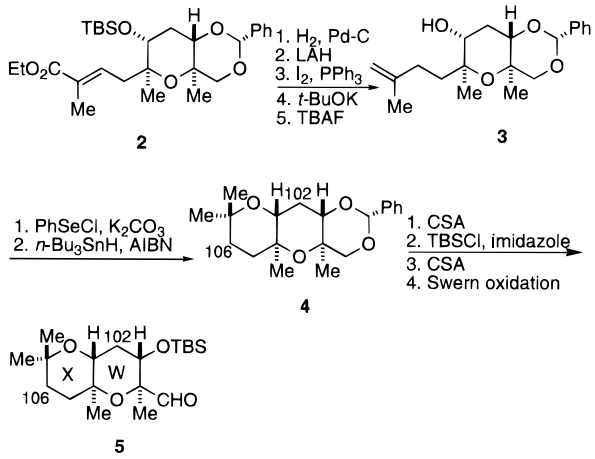
[a] The *x*- *y*-axes represent carbon number and $\Delta\delta$ ($\Delta\delta = \delta$MTX $- \delta$Synthetic Model in ppm), respectively. The chemical shift assignment of the C.98 axial versus the C.98 equatorial protons of MTX was not established.[4] However, in this work the chemical shift assignments of these protons are made by analogy to the model.

Scheme 1



in turn could be derived from **9** and **10**, respectively. The propargyl alcohols **9** and **10** could be obtained through a coupling of the aldehyde **5** with the anion generated from an acetylene, for example, a Ni(II)/Cr(II)-mediated coupling[12] of **8** with **5**. This coupling was purposely carried out with a racemic form of **8** and an optically active form of **5** so that both models could be available in one synthesis, provided that they were chromatographically separable at some stage of the synthesis.

Scheme 2



The synthesis of aldehyde **5** began with unsaturated ester **2**,[13] which was converted to the hydroxy olefin **3** in five steps (Scheme 2). Cationic cyclization promoted by phenylselenyl chloride[14] followed by reduction of the phenyl selenide with tributyltin hydride[15] furnished **4**, the stereochemistry of which was established by X-ray crystallography.[16] Deprotection of the benzylidene, followed by the two-step selective protection of the secondary alcohol and then Swern oxidation,[17] yielded aldehyde **5**.

The synthesis of racemic iodoacetylene **8** is shown in Scheme 3. 2-Methyl-5-hexen-2-ol[18] was converted to the acid **6** in six steps, and the lactone **7** was formed in two steps by deprotection of the tertiary alcohol[19] followed by treatment with ethyl

(11) There are numerous examples known for this type of reduction with ionic or radical conditions. For example, see: (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978. (b) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 2468−2469.

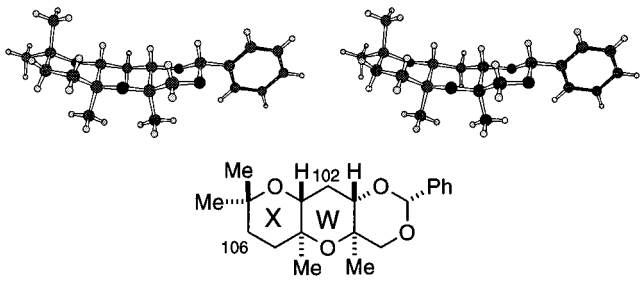
(12) (a) Jin, H.; Uenishi, J.-i.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281−5284.

(13) (a) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517−4552. (b) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6676−6682.

(14) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Tetrahedron Lett.* **1990**, *31*, 5917−5920.

(15) Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438−4447.

(16) The X-ray crystal structure of **4** is shown below.



4

(17) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660. (c) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297−299.

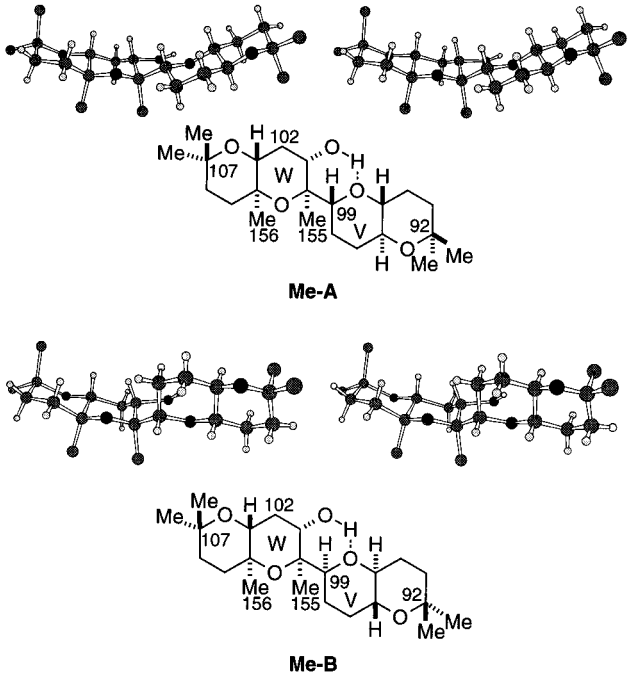
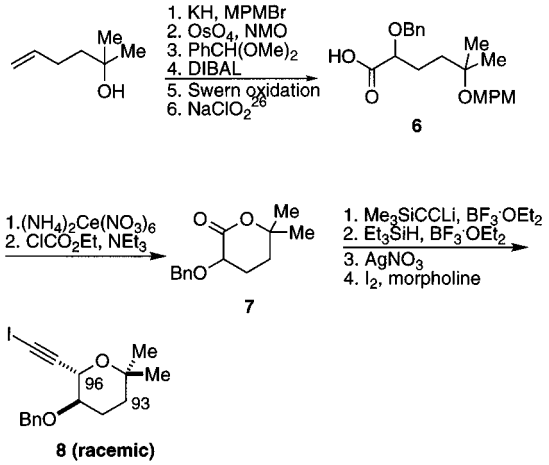


Figure 4.[8] X-ray crystal structure of dimethyl models, **Me-A** and **Me-B**, shown in stereoview.

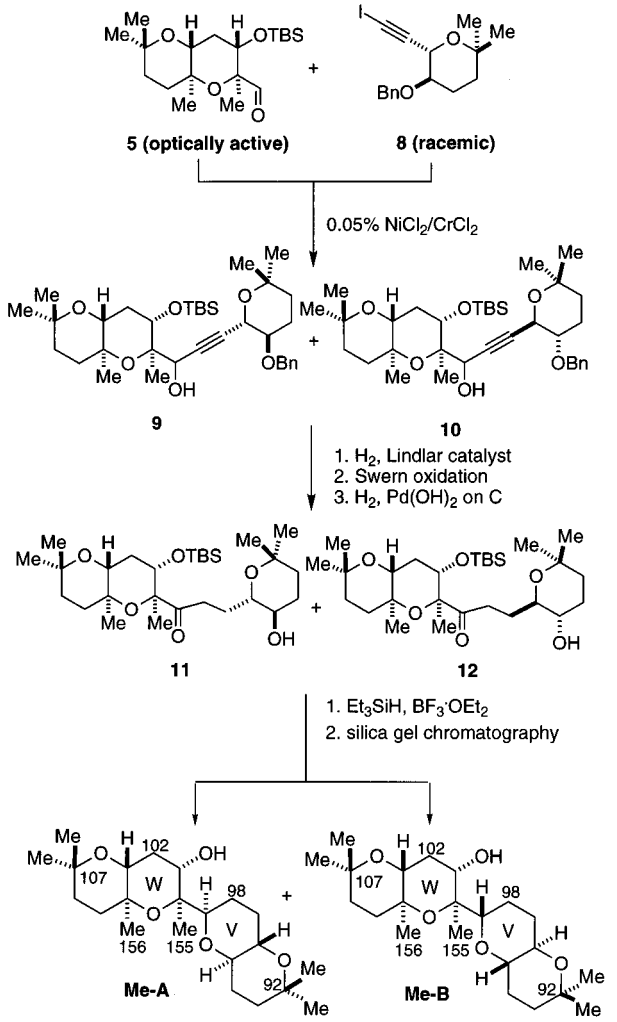
Scheme 3



chloroformate. Alkyne addition to the lactone **7** and then reduction of the hemiketal with triethylsilane set the two stereocenters at C.95 and C.96, placing both the alkyne and the benzyl ether in the equatorial positions on the ring.[11a] Replacement of the trimethylsilyl group with iodide was accomplished in two steps to furnish racemic **8**. The relative stereochemistry for C.95 and C.96 was established based on the vicinal spin coupling constant (9.3 Hz) between H.95 and H.96.[20]

The Ni(II)/Cr(II)-mediated coupling[12] of the racemic iodoacetylene **8** with optically active aldehyde **5** gave a 1:1 mixture of diastereomers **9** and **10** (Scheme 4). Interestingly, only two out of the four possible diastereomers[21] were formed in this coupling.[22] Selective hydrogenation of the alkyne in the presence of the benzyl ether with Lindlar catalyst, followed by

Scheme 4



Swern oxidation of the hydroxyl group and deprotection of the benzyl ether gave a mixture of two ketones, **11** and **12**. One-pot reductive cyclization/TBS ether deprotection yielded a mixture of **Me-A** and **Me-B**. As predicted, the hydride preferentially added axially in the reductive cyclization due to stereoelectronic effects,[11a] thereby yielding **Me-A** and **Me-B.** There were no other diastereomers detected in this reductive cyclization, and the two diastereomeric models **Me-A** and **Me-B** were readily separable by silica gel chromatography. The structures of **Me-A** and **Me-B** were confirmed by X-ray crystallography (Figure 4).

The two diastereomeric models **Me-A** and **Me-B** were subjected to the NMR spectroscopic study, and the proton and carbon chemical shifts for C.104-C.95 of each diastereomer were compared to the NMR chemical shifts of the corresponding protons and carbons of MTX (Chart 2). As predicted, the inclusion of the angular methyl groups at C.107 and C.92 dramatically improved the correlation of the chemical shifts for C.103 and C.96 protons and carbons of both **Me-A** and **Me-B** with those of MTX.[23] This study demonstrates that each model exhibits distinct NMR characteristics and that only **Me-A**

(18) 2-Methyl-5-hexen-2-ol is commercially available, but for this work it was prepared in two steps from 4-pentenoic acid: 1. esterification with methanol in the presence of CSA and 2. methyl magnesium iodide addition to the methyl ester.

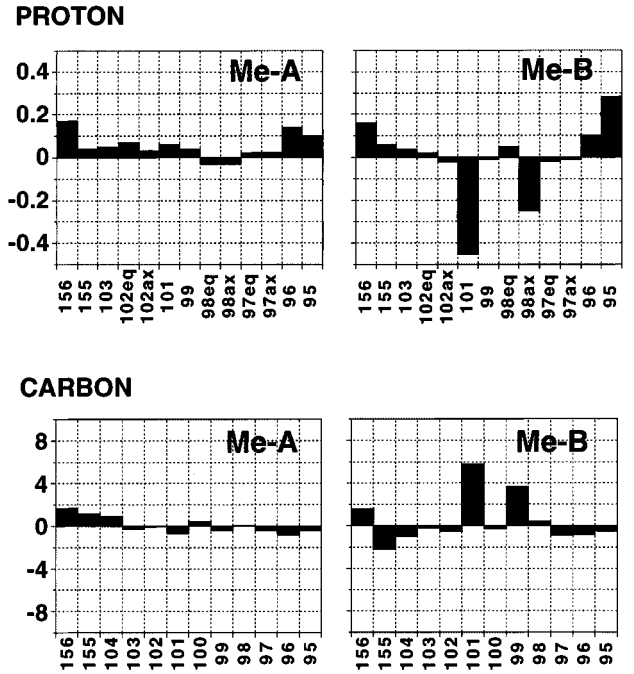
(19) (a) Classon, B.; Garegg, P. J.; Samuelsson, B. *Acta. Chem. Scand. Ser. B.* **1984**, *B38*, 419−422. (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. I* **1984**, 2371−2374.

(20) Based on the large H.96-H.95 coupling constant, it was demonstrated that both H.96 and H.95 must be axial on the pyran ring.

(21) The stereochemistry at the carbinol center of **9** and **10** was not assigned.

(22) There are several cases known where the Ni(II)/Cr(II)-mediated coupling reactions are highly stereoselective or even stereospecific. For example, see: (a) Ref 12a. (b) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735−2737. (c) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162−3164.

Chart 2. Difference in Proton (500 MHz, 1:1 $C_5D_5N-CD_3OD$) and Carbon (125 MHz, 1:1 $C_5D_5N-CD_3OD$) Chemical Shifts between MTX and Each of **Me-A** and **Me-B**[a]



[a] The *x*- *y*-axes represent carbon number and $\Delta\delta$ ($\Delta\delta = \delta$MTX $-$ δSynthetic Model in ppm), respectively. The chemical shift assignment of the C.98 axial versus the C.98 equatorial protons of MTX was not established.[4] However, in this work the chemical shift assignments of these protons are made by analogy to the model.

displays virtually identical NMR characteristics to those of MTX. Therefore, the relative stereochemistry of the V/W-ring juncture of MTX is represented by **Me-A**, confirming the results obtained with the original model study of **H_2-A** and **H_2-B**.

Solution Conformations of Me-A and Me-B. As shown in Chart 2, the NMR characteristics observed for **Me-A** are remarkably close to those reported for maitotoxin itself, which makes a strong case for the accurate extrapolation of the conformational properties of maitotoxin from those of the model **Me-A**. For this reason, we conducted the solution conformational studies on **Me-A** as well as **Me-B**.

NOESY data were acquired in 1:1 $C_5D_5N-CD_3OD$ for both **Me-A** and **Me-B**.[24] Both diastereomers exhibit NOEs corresponding to all the three possible rotamers around the C.100-C.99 bond (Figure 5), indicating that in protic solvents they both exist as a mixture of these rotamers. As previously mentioned, Yasumoto relied on the NOESY cross peaks in 1:1 $C_5D_5N-CD_3OD$ representing NOEs between the C.101-C.99 protons and the C.155-C.98 protons to assign the relative stereochemistry of the V/W-ring juncture of MTX, cf. the ring-juncture stereochemistry of **Me-A** over that of **Me-B**. This experiment disproves Yasumoto's reasonings because *both* **Me-A** and **Me-B** clearly exhibit the NOE cross peaks in question.[24] MM3 force field calculations also confirm this conclusion. When water was chosen as the solvent for the calculations for **Me-A**, the **Me-Aa** rotamer (corresponding to the crystal structure) that would exhibit the mentioned NOEs was found to be the highest energy rotamer (Figure 5). For **Me-B**, the MM3 calculations in water showed that the rotamer **Me-Bc** which has a close proximity between the C.99 and C.101 protons and the C98(axial) and C155 protons is the second highest energy rotamer.[25]

NOESY data for both **Me-A** and **Me-B** in C_6D_6 were also collected. For both diastereomers the only NOEs observed were those expected for their crystal structure conformations **Me-Aa** and **Me-Ba**, respectively. **Me-A** showed cross peaks representing NOEs between the C.101-C.99 protons and the C.155-C.98(axial) protons. **Me-B** showed cross peaks representing NOEs between the C.101-C.98(axial) protons and between the C.155-C.99 protons. This change in conformational preference for both **Me-A** and **Me-B** in C_6D_6 is consistent with the results of MM3 force field calculations. In chloroform **Me-Aa** was calculated to be the lowest energy rotamer by at least 2 kcal/mol, whereas **Me-Ba** was calculated to be the lowest energy rotamer by at least 0.7 kcal/mol.

The solvent effect on the NOESY experiments and MM3 calculations can be explained by hydrogen bond stabilization. In both **Me-Aa** and **Me-Ba** it is possible for a hydrogen bond to exist between the C.101 hydroxyl and the V-ring oxygen as depicted in Figure 4. In an aprotic solvent such as benzene, hydrogen bonding stabilizes **Me-Aa** and **Me-Ba**; therefore, they are the lowest energy rotamers in aprotic solvents. On the other hand, in a protic solvent such as methanol, this intramolecular hydrogen bond is disrupted and becomes much less significant in determining the relative stability among these conformers.

Conclusions

The comparison of the NMR chemical shifts in 1:1 $C_5D_5N-CD_3OD$ for the two improved models **Me-A** and **Me-B** with the NMR chemical shifts of the corresponding carbons and protons of MTX allowed for the unambiguous assignment of the stereochemistry of the V/W-ring juncture of MTX as shown in Figure 1. Namely, **Me-A** and **Me-B** exhibited distinct NMR characteristics, and only **Me-A** exhibited virtually identical proton and carbon NMR chemical shifts to those of MTX. The fact that the NMR characteristics observed for **Me-A** were remarkably close to those reported for maitotoxin indicates that the conformational characteristics of this portion of maitotoxin could be accurately extrapolated from those of the model **Me-A**. Using $^1H-^1H$ NOESY experiments and MM3 calculations, the solution conformations of **Me-A** as well as **Me-B** were studied in aprotic and protic solvents. In aprotic solvents such as benzene, both **Me-A** and **Me-B** preferentially adopt the conformations **Me-Aa** and **Me-Ba**, respectively, due to the intramolecular hydrogen bond stabilization. On the other hand, in protic solvents such as a 1:1 mixture of methanol and pyridine their conformational properties are described as a mixture of all the possible rotamers.

Experimental Section

Transformation of Ester 2 to Olefin 3. Hydrogenation of Ethyl Ester. To a solution of unsaturated ester **2**[13] (3.47 g, 6.87 mmol) in EtOAc (50 mL) was added Pd on C (10%, 1.50 g), and the mixture was stirred vigorously under a H_2 atmosphere for 40 h. The catalyst was removed by filtration through Celite washing with EtOAc (100 mL), and the filtrate was concentrated to give the saturated ester as a

(23) The difference between the conformation of ring W in **H_2-A** and **Me-A** is also evident in their crystal structures. The ring W appears to be in a bent chair conformation in **Me-A** due to the repulsion between the angular methyl group on C.107, and the angular proton on C.103. The distance between H.101 and H.103 is 1.7 Å in **Me-A**, whereas the distance between H.101 and H.103 is 2.5 Å in **H_2-A**.

(24) $^1H-^1H$ NOESY spectra for both **Me-A** and **Me-B** in 1:1 $C_5D_5N-CD_3OD$ and C_6D_6 are included in the supporting information.

(25) Chloroform and water were the only solvent choices for MM3 calculations.

(26) (a) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096. (b) Hillis, L. R.; Ronald, R. C., Jr. *J. Org. Chem.* **1985**, *50*, 470−473.

(27) Stamos, D. P. Ph.D. Thesis, Harvard University, 1997.

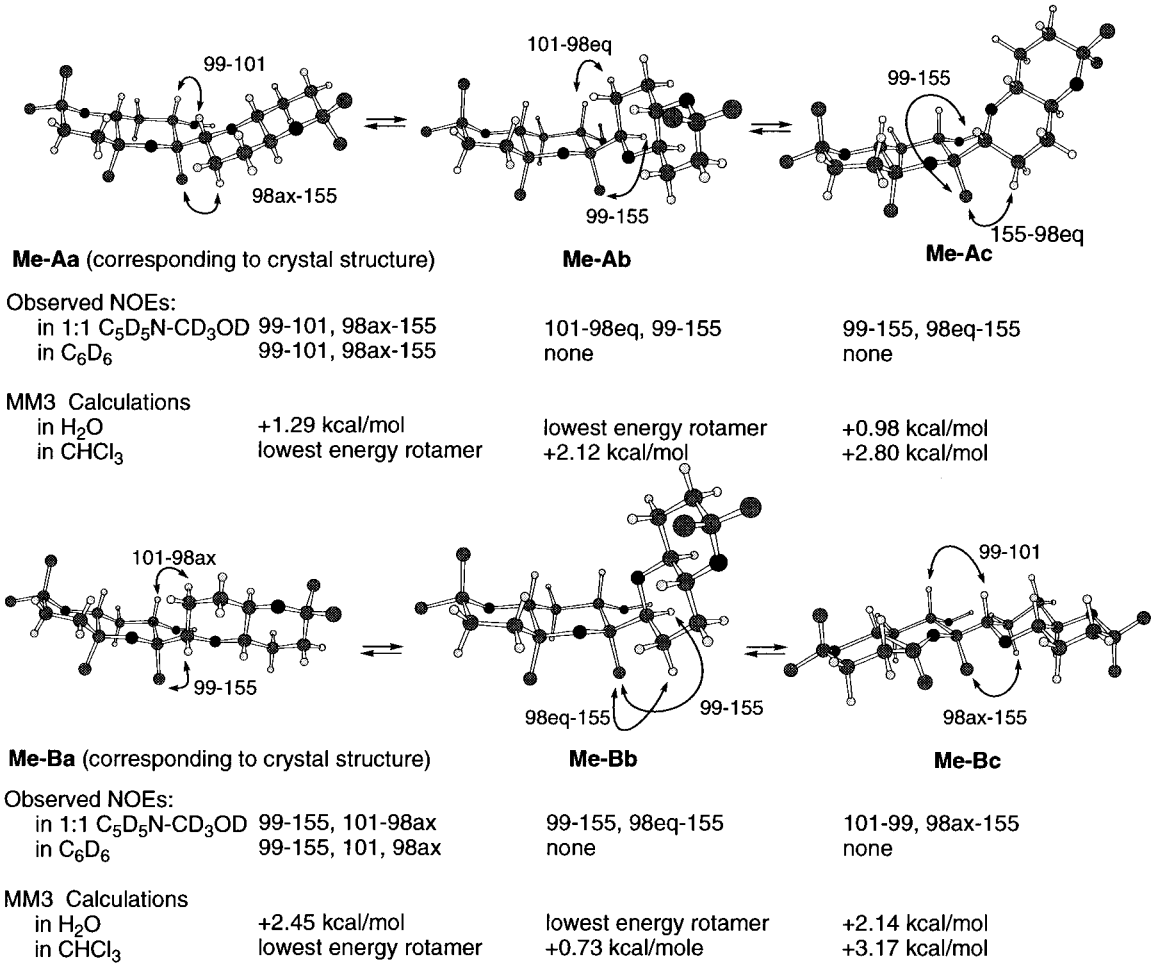


Figure 5.[8] Three possible conformations of **Me-A** and **Me-B** represented by Chem 3-D structures with NOEs and the results of the NOESY experiments and MM3 Force Field Calculations.

1:1 mixture of diastereomers (3.16 g, 97%). The residue was used for the next step without further purification. Data for the 1:1 mixture of saturated esters: IR: 2960 cm^{-1}, 2933, 2868, 1737, 1479, 1374, 1262. ^1H NMR (500 MHz, C_6D_6): δ 7.67 ppm (4H, d, J = 7.1 Hz), 7.20 (4H, t, J = 7.8 Hz), 7.13 (2H, t, J = 7.4 Hz), 5.44 (1H, s), 5.43 (1H, s), 4.03 (2H, q, J = 7.2 Hz), 4.00 (2H, q, J = 7.2 Hz), 3.86 (1H, d, J = 10.0 Hz), 3.81 (1H, d, J = 10.0 Hz), 3.71 (1H, dd, J = 10.4, 5.5 Hz), 3.65 (1H, dd, J = 10.4, 5.5 Hz), 3.44 (1H, d, J = 10.6 Hz), 3.41 (1H, d, J = 10.6 Hz), 3.34 (1H, dd, J = 11.2, 4.3 Hz), 3.32 (1H, dd, J = 11.2, 4.3 Hz), 2.43 (1H, m), 2.42 (1H, m), 2.07−1.90 (8H, m), 1.76−1.47 (4H, m), 1.50 (6H, s), 1.25 (3H, s), 1.24 (3H, s), 1.19 (3H, d, J = 7.0 Hz), 1.17 (3H, d, J = 7.0 Hz), 0.94 (9H, s), 0.93 (9H, s), 0.11 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.02 (3H, s). HRMS (FAB): $C_{28}H_{46}O_6Si$ $(M + Na)^+$ calcd 529.2961, found 529.2936.

Reduction of the Saturated Ester. The saturated ester (3.15 g, 6.23 mmol) was dissolved in Et_2O (40 mL), and $LiAlH_4$ (0.354 g, 1.50 equiv) was added in several portions at 0 °C. The mixture was stirred at room temperature for 40 min and then cooled to 0 °C. H_2O (0.437 mL) and 3 N NaOH aqueous (0.437 mL) were slowly added to the mixture, and it was stirred for 10 min. The resultant gray suspension was diluted with EtOAc (70 mL), dried with $MgSO_4$ (2.62 g), and filtered through Celite. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (SGC) (9:1 → 8:2 hexanes/EtOAc) to give the primary alcohol as a 1:1 mixture of diastereomers (2.74 g, 95%). Data for the 1:1 mixture of primary alcohols: IR: 3400 cm^{-1} (br), 2953, 2927, 2861, 1466, 1374, 1255. ^1H NMR (500 MHz, C_6D_6): δ 7.64 ppm (4H, d, J = 7.2 Hz), 7.20 (4H, t, J = 7.7 Hz), 7.13 (2H, t, J = 7.2 Hz), 5.43 (2H, s), 3.87 (2H, d, J = 9.8 Hz), 3.70 (2H, m), 3.45 (2H, br d, J = 9.0 Hz), 3.37−3.24 (6H, m), 2.03−1.96 (4H, m), 1.73 (2H, m), 1.65 (2H, m), 1.53−1.32 (4H, m), 1.52 (6H, s), 1.29 (2H, m), 1.27 (3H, s), 1.26 (3H, s), 0.93 (9H, s), 0.93 (9H, s), 0.92 (3H, d, J = 6.9 Hz), 0.91 (3H, d, J = 6.9 Hz), 0.07 (3H, s), 0.06 (3H, s), 0.04 (3H, s), 0.03 (3H, s). ^{13}C NMR (125 MHz, C_6D_6): δ 138.8 ppm, 128.9, 128.3 (×2), 126.8 (×2), 102.8, 80.7, 77.2, 74.2, 69.0, 68.0, 39.8, 36.6, 31.7, 26.4, 25.9, 19.2, 18.0, 16.8. HRMS (FAB): $C_{26}H_{44}O_5Si$ $(M + Na)^+$ calcd 487.2856, found 487.2855.

Iodide Formation. Iodine (0.826 g, 1.35 equiv) was added in two portions at 0 °C to a suspension of the 1:1 mixture of alcohols (2.82 g, 6.07 mmol), PPh_3 (3.18 g, 2.00 equiv), and imidazole (0.826 g, 2.00 equiv) in benzene, and the mixture was stirred vigorously at room temperature for 20 min. The reaction was quenched with MeOH (20.0 mL) at 0 °C, and the mixture was concentrated. The residue was purified by SGC (67:33 hexanes/CH_2Cl_2 → 67:30:3 hexanes/CH_2Cl_2/EtOAc) to give a 1:1 mixture of iodides as a colorless oil (3.36 g, 97%). Data for the 1:1 mixture of iodides: IR: 2960 cm^{-1}, 2927, 2854, 1459, 1374, 1262. ^1H NMR (400 MHz, C_6D_6): δ 7.66 ppm (4H, d, J = 7.1 Hz), 7.20 (4H, t, J = 7.1, Hz), 7.13 (2H, t, J = 7.5 Hz), 5.45 (1H, s), 5.44 (1H, s), 3.87 (2H, d, J = 9.8 Hz), 3.66 (1H, dd, J = 10.2, 5.3 Hz), 3.63 (1H, dd, J = 10.2, 5.3 Hz), 3.46 (1H, d, J = 9.2 Hz), 3.45 (1H, d, J = 9.2 Hz), 3.34 (1H, dd, J = 11.8, 4.6 Hz), 3.34 (1H, dd, J = 11.8, 4.6 Hz), 2.92−2.83 (4H, m), 2.03−1.91 (4H, m), 1.64−1.35 (4H, m), 1.51 (6H, s), 1.36−1.25 (2H, m), 1.25 (3H, s), 1.22 (3H, s), 1.23−1.06 (2H, m), 0.94 (9H, s), 0.93 (9H, s), 0.85 (3H, d, J = 6.4 Hz), 0.84 (3H, d, J = 6.4 Hz), 0.07 (3H, s), 0.06 (3H, s), 0.04 (3H, s), 0.03 (3H, s). HRMS (EI): $C_{26}H_{43}IO_4Si$ $(M - H)^-$ calcd 573.1897, found 573.1900.

Elimination of the Iodide. To a solution of the iodides (3.36 g, 5.85 mmol) in THF (36 mL) was added *t*-BuOK (1.0 M in THF, 15.2 mL, 2.62 equiv) at −35 °C, and the mixture was slowly warmed to 0 °C during 2 h. After quenching with saturated NH_4Cl aqueous (30 mL), the mixture was diluted with Et_2O (50 mL), and the aqueous layer was extracted with Et_2O (2 × 20 mL). The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the olefin as a colorless oil (2.83 g). The residue was used for the next step without further purification. Data for the olefin: IR: 2960

cm^{-1}, 2933, 2868, 1472, 1374, 1255. ^{1}H NMR (400 MHz, C_6D_6): δ 7.66 ppm (2H, d, J = 7.3 Hz), 7.20 (2H, t, J = 7.4 Hz), 7.13 (1H, t, J = 7.5 Hz), 5.47 (1H, s), 4.91 (1H, s), 4.85 (1H, s), 3.87 (1H, d, J = 9.8 Hz), 3.69 (1H, dd, J = 8.6, 7.3 Hz), 3.43 (1H, d, J = 9.7 Hz), 3.35 (1H, dd, J = 10.3, 5.8 Hz), 2.32 (1H, ddd, J = 12.7, 12.7, 4.2 Hz), 2.22 (1H, ddd, J = 12.3, 12.3, 4.0 Hz), 2.00 (2H, m), 1.88 (1H, ddd, J = 12.9, 12.9, 4.5 Hz), 1.74 (3H, s), 1.67 (1H, ddd, J = 13.1, 13.1, 4.9 Hz), 1.53 (3H, s), 1.26 (3H, s), 0.92 (9H, s), 0.04 (3H, s), 0.02 (3H, s). HRMS (FAB): $C_{26}H_{42}O_4Si$ (M + Na)$^+$ calcd 469.2750, found 469.2727.

TBS Deprotection. To a solution of the TBS ether (2.83 g, crude) in THF (10 mL) was added *n*-Bu_4NF (1.0 M in THF, 12.1 mL, 2.10 equiv) at room temperature, and the mixture was stirred at room temperature for 1.5 h. The mixture was concentrated and the residue was purified by SGC (10:5:1 → 10:5:3 hexanes/CH_2Cl_2/EtOAc) to give alcohol **3** as a colorless oil (1.33 g, 68% overall yield for two steps). Data for **3**: IR: 3400 cm^{-1} (br), 2973, 2927, 2854, 1459, 1374. ^{1}H NMR (500 MHz, C_6D_6): δ 7.62 ppm (2H, d, J = 7.0 Hz), 7.19 (2H, t, J = 7.2 Hz), 7.12 (1H, t, J = 7.2 Hz), 5.41 (1H, s), 4.87 (1H, s), 4.83 (1H, s), 3.82 (1H, d, J = 9.8 Hz), 3.38 (1H, d, J = 9.7 Hz), 3.35 (1H, m), 2.25 (1H, ddd, J = 12.6, 12.6, 4.6 Hz), 2.14 (1H, ddd, J = 12.3, 12.3, 4.7 Hz), 1.83−1.77 (2H, m), 1.75 (1H, q, J = 11.8 Hz), 1.72 (3H, s), 1.63 (1H, ddd, J = 12.1, 12.1, 4.8 Hz), 1.46 (3H, s), 1.11 (3H, s). ^{13}C NMR (125 MHz, C_6D_6): δ 146.4 ppm, 138.9, 129.0, 126.8 (×2), 109.8, 102.9, 80.9, 78.1, 77.1, 69.0, 40.7, 31.4, 31.0, 22.9, 21.7, 19.2. HRMS (CI): $C_{20}H_{28}O_4$ (M + H)$^+$ calcd 333.2066, found 333.2065.

Transformation of Olefin 3 to Benzylidene 4. Cationic Cyclization.[14] To a suspension of olefin **3** (1.33 g, 4.00 mmol) and K_2CO_3 (8.39 g, 15.0 equiv) in CH_2Cl_2 (50 mL) was added PhSeCl (3.83 g, 5.00 equiv) in three portions at 2 min intervals at 0 °C. The mixture was stirred at 0 °C for 10 min and then at room temperature for 1.5 h. Additional K_2CO_3 (8.39 g) and PhSeCl (3.83 g) were added at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with H_2O (40 mL) and Et_2O (50 mL), and the aqueous layer was extracted with Et_2O (2 × 20 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residual oil was dissolved in CH_2Cl_2 (20 mL). $PhCH(OCH_3)_2$ (20 mL) and *(1R)*-(−)-10-camphorsulfonic acid (CSA) (0.30 g, 1.2 mmol) were added sequentially to the solution at room temperature, and the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with 50% K_2CO_3 aqueous (5 mL), and the mixture was extracted with Et_2O (2 × 20 mL). The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by SGC (98:2 → 7:3 hexanes/EtOAc) to give a 2:1 mixture of the tricyclic selenides as a pale yellow oil (0.932 g, 48%). Data for the less polar isomer: ^{1}H NMR (500 MHz, C_6D_6): δ 7.62 ppm (2H, d, J = 7.1 Hz), 7.50 (2H, dd, J = 8.1, 1.8 Hz), 7.22−7.10 (4H, m), 6.98 (2H, m), 5.43 (1H, s), 3.85 (1H, d, J = 9.7 Hz), 3.47 (1H, d, J = 9. 7 Hz), 3.42 (1H, dd, J = 11.4, 4.3 Hz), 3.41 (1H, dd, J = 11.1, 2.1 Hz), 3.11 (1H, d, J = 12.1 Hz), 2.79 (1H, d, J = 12.1 Hz), 1.95 (1H, ddd, J = 11.4, 11.4, 11.4 Hz), 1.98−1.90 (2H, m), 1.62−1.55 (2H, m), 1.56 (3H, s), 1.36 (3H, s), 1.30 (1H, m), 1.13 (1H, ddd, J = 13.8, 3.7, 3.7 Hz). Data for the more polar isomer: ^{1}H NMR (500 MHz, C_6D_6): δ 7.61 ppm (2H, d, J = 7.2 Hz), 7.46 (2H, dd, J = 7.7, 2.4 Hz), 7.22−7.00 (4H, m), 6.98 (2H, m), 5.37 (1H, s), 3.84 (1H, d, J = 9.8 Hz), 3.72 (1H, d, J = 12.0 Hz), 3.46 (1H, d, J = 9.8 Hz), 3.42 (1H, dd, J = 11.8, 3.7 Hz), 2.61 (1H, d, J = 11.9 Hz), 2.07 (1H, ddd, J = 11.2, 3.6, 3.6 Hz), 1.96 (1H, dddd, J = 11.6, 11.6, 11.6, 11.6 Hz), 1.61−1.52 (2H, m), 1.55 (3H, s), 1.36−1.27 (2H, m), 1.30 (3H, s), 1.23 (s, 3H). MS of the selenides (FAB): *m/z* (M + H)$^+$ 488.

Reduction of the Selenide.[15] To a suspension of the selenides (0.864 g, 1.77 mmol) in benzene (10 mL) were added *n*-Bu_3SnH (4.77 mL, 10.0 equiv) and 2,2′-azobisisobutyronitrile (AIBN) (50 mg, 0.17 equiv) at room temperature, and the mixture was heated to 80 °C for 2.5 h. After cooling, the reaction mixture was concentrated, and the residue was purified by SGC (98:2 → 7:3 hexanes/EtOAc) to give the *gem*-dimethyl derivative **4** as white crystals (0.450 g, 76%). Data for benzylidene **4**: mp 167 ∼168 °C. IR: 2979 cm^{-1}, 2966, 2854, 1466, 1380. ^{1}H NMR (400 MHz, C_6D_6): δ 7.63 ppm (2H, d, J = 7.1 Hz), 7.19 (2H, t, J = 7.2 Hz), 7.12 (1H, t, J = 7.2 Hz), 5.43 (1H, s), 3.87 (1H, d, J = 9.5 Hz), 3.49 (1H, d, J = 9.6 Hz), 3.50−3.43 (2H, m), 2.05−1.98 (2H, m), 1.60 (1H, br t, J = 11.3 Hz), 1.58 (3H, s), 1.53 (1H, ddd, J = 13.7, 13.7, 5.3 Hz), 1.29 (1H, m), 1.28 (3H, s), 1.18 (1H, m), 1.15 (3H, s), 1.14 (3H, s). ^{13}C NMR (100 MHz, C_6D_6): δ 138.8 ppm, 128.9, 126.8 (×2), 103.0, 83.0, 77.1, 75.03, 74.98, 72.8, 70.6, 35.9, 35.0, 31.5, 28.3, 23.2, 21.0, 19.2. HRMS (CI): $C_{20}H_{28}O_4$ (M + H)$^+$ calcd 333.2066, found 333.2066.

Transformation of Benzylidene 4 to Aldehyde 5. Benzylidene Deprotection. To a solution of benzylidene **4** (0.440 g, 1.32 mmol) in MeOH (5.0 mL) was added CSA (61.3 mg, 0.20 equiv) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with Et_3N (0.10 mL), and the mixture was concentrated. The residue was purified by SGC (99:1 → 90:10 $CHCl_3$/MeOH) to give the diol as a white solid (0.295 g, 91%). Data for the diol: IR: 3400 cm^{-1} (br), 2979, 2947, 2881, 1466, 1387. ^{1}H NMR (400 MHz, C_6D_6): δ 3.89 ppm (1H, ddd, J = 11.5, 5.0, 5.0 Hz), 3.45 (1H, t, J = 9.5 Hz), 3.36 (1H, d, J = 10.5 Hz), 3.24 (1H, dd, J = 12.1, 3.6 Hz), 1.95 (1H, br d, J = 9.3 Hz), 1.81 (1H, ddd, J = 11.7, 3.1, 3.1 Hz), 1.73 (1H, ddd, J = 11.8, 11.8, 11.8 Hz), 1.52−1.37 (3H, m), 1.20 (3H, s), 1.13 (3H, s), 1.11 (3H, s), 1.04 (3H, s). HRMS (CI): $C_{13}H_{24}O_4$ (M + H)$^+$ calcd 245.1753, found 245.1753.

TBS Protection. To a solution of the diol (0.290 g, 1.19 mmol) in DMF (5.0 mL) were added imidazole (0.324 g, 4.00 equiv) and TBSCl (0.591 g, 3.30 equiv) at room temperature, and the mixture was heated to 50−60 °C for 14 h. After cooling, the excess TBSCl was quenched with MeOH (0.2 mL), and the mixture was diluted with Et_2O (8 mL). The aqueous layer was extracted with Et_2O (5 mL), and the organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by SGC (98:2 → 96:4 hexanes/EtOAc) to give the bis-TBS ether as a white solid (0.541 g, 96%). Data for the bis-TBS ether: IR: 2960 cm^{-1}, 2933, 2861, 1466, 1387. ^{1}H NMR (400 MHz, C_6D_6): δ 4.34 ppm (1H, dd, J = 11.2, 5.4 Hz), 3.53 (1H, dd, J = 12.0, 3.6 Hz), 3.52 (1H, d, J = 10.5 Hz), 3.47 (1H, d, J = 10.6 Hz), 2.04 (1H, ddd, J = 8.7, 5.5, 5.5 Hz), 1.96 (1H, ddd, J = 11.6, 11.6, 11.6), 1.77 (1H, ddd, J = 12.7, 12.7, 4.4 Hz), 1.61 (1H, ddd, J = 12.3, 4.7, 2.2 Hz), 1.55 (1H, ddd, J = 13.9, 13.9, 4.9 Hz), 1.30 (3H, s), 1.19 (3H, s), 1.18 (3H, s), 1.07 (3H, s), 0.92 (9H, s), 0.21 (3H, s), 0.16 (3H, s), 0.10 (3H, s), 0.03 (3H, s). HRMS (CI): $C_{25}H_{52}O_4Si_2$ (M + H)$^+$ calcd 473.3482, found 473.3471.

Selective Deprotection. A solution of the bis-TBS ether (0.531 g, 1.12 equiv) in Et_2O/MeOH (1:1, 10 mL) was treated with CSA (53.0 mg, 0.20 equiv) at room temperature for 1 h. Additional two portions of CSA (30 mg each) were added at 1 h intervals, and the mixture was stirred at room temperature for 4 h. The mixture was quenched with Et_3N (0.2 mL) and concentrated, and the residue was purified by SGC (98:2 → 85:15 hexanes/EtOAc) to give the mono-TBS ether as a white solid (0.308 g, 77%). Bis-TBS ether (50.9 mg, 10%) and the diol (50.9 mg, 18%) were recovered as less polar and more polar products, respectively. Data for the mono-TBS ether: IR: 3400 cm^{-1} (br), 2960, 2927, 2854, 1466, 1387, 1262. ^{1}H NMR (500 MHz, C_6D_6): δ 4.27 ppm (1H, dd, J = 11.4, 5.3 Hz), 3.48 (1H, t, J = 11.0 Hz), 3.41 (1H, dd, J = 11.0, 2.5 Hz), 3.34 (1H, dd, J = 12.2, 3.5 Hz), 2.11 (1H, dd, J = 10.9, 2.4 Hz), 1.98 (1H, ddd, J = 12.3, 4.2, 4.2 Hz), 1.89 (1H, ddd, J = 11.7, 11.7, 11.7 Hz), 1.53−1.45 (1H, m), 1.38 (1H, ddd, J = 13.8, 13.8, 4.9 Hz), 1.24 (3H, s), 1.15 (3H, s), 1.14 (3H, s), 1.04 (3H, s), 0.89 (9H, s), 0.08 (3H, s), 0.00 (3H, s). ^{13}C NMR (125 MHz, C_6D_6): δ 78.8 ppm, 73.1, 72.4, 69.0, 67.6, 65.7, 35.9, 34.8, 32.2, 31.6, 25.9 (× 3), 22.9 (×2), 20.4, 18.0, −4.0, −5.1. HRMS (CI): $C_{19}H_{38}O_4Si$ (M + NH_4)$^+$ calcd 376.2883, found 376.2893.

Swern Oxidation.[17] DMSO (2.22 mL, 60.0 equiv) was slowly added to a solution of $(COCl)_2$ (1.36 mL, 30.0 equiv) in CH_2Cl_2 (20 mL) at −78 °C, and the resultant mixture was stirred for 10 min. A solution of the alcohol (187 mg, 1.00 equiv) in CH_2Cl_2 (10 mL) was added dropwise, and the resultant mixture was stirred at −35 °C for 1 h and then warmed to −15 °C for 1.5 h. The reaction mixture was cooled again to −78 °C, and Et_3N (8.71 mL, 120 equiv) was slowly added to the mixture. After having been stirred at −78 °C for 10 min, the mixture was warmed to 0 °C and stirred for additional 10 min. Et_2O (50 mL) and 50% $NaHCO_3$ aqueous (40 mL) were added, and the aqueous layer was extracted with Et_2O (20 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by SGC (95:5 → 80:20 hexanes/EtOAc) to give the aldehyde **5** as a colorless oil (323 mg, 100%). Data for **5**: ^{1}H

NMR (500 MHz, C_6D_6): δ 9.40 ppm (1H, s), 3.98 (1H, dd, J = 5.8, 9.7 Hz), 3.38 (1H, dd, J = 3.9, 12.3 Hz), 2.00 (1H, m) 1.85 (1H, m), 1.61 (1H, m), 1.46 (1H, ddd, J = 7.1, 12.8, 12.8 Hz), 1.39 (3H, s), 1.25 (3H, s), 1.14 (3H, s), 1.06 (3H, s), 0.89 (9H, s), 0.80 (1H, m), −0.02 (3H, s), −0.07 (3H, s).

Transformation of 2-Methyl-5-hexen-2-ol to Carboxylic Acid 6. MPM Protection. To a 0 °C solution of 2-methyl-5-hexen-2-ol[18] (17.0 g, 0.150 mole) in THF/DMF (4:1, 1.25 L) was added 4-methoxyphenylmethyl bromide (MPMBr) (6.83 M in benzene, 90 mL, 5.00 equiv) and KH (51.4 g, 35% dispersion in mineral oil, 3.00 equiv). The reaction was completed in 45 min, and the excess MPMBr was quenched with additional KH (51.4 g, 35% dispersion in mineral oil, 3.00 equiv) and MeOH (36 mL, 6.00 equiv). This mixture was warmed slowly to room temperature for 15 min, then cooled back to 0 °C, and quenched with H_2O (500 mL). The mixture was extracted with Et_2O (3 × 700 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to yield the crude olefin, which was taken onto the next step without further purification.

Osmylation. To a solution of the crude olefin (35.0 g, crude) in acetone/H_2O (10:1, 1.1 L) was added 4-methylmorphorine *N*-oxide (NMO)·hydrate (70.0 g, 4.00 equiv), DABCO (34.0 g, 2.00 equiv), and OsO_4 (1.00 g, 0.05 equiv). The reaction was stirred at room temperature overnight in the dark, then quenched with saturated Na_2SO_3 aqueous (500 mL), and extracted with EtOAc (3 × 600 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by SGC (10% MeOH/EtOAc) to yield the diol (22.0 g, 74% overall yield for two steps). Data for the diol: IR: 3391 cm^{-1} (br), 2972, 2919, 2866, 2835, 1617, 1526, 1473, 1389, 1374, 1305, 1260. ^1H NMR (500 MHz, C_6D_6): δ 7.26 ppm (2H, d, J = 8.4 Hz), 6.82 (2H, d, J = 8.4 Hz), 4.23 (1H, d, J = 11.0 Hz), 4.21 (1H, d, J = 10.9 Hz), 3.51 (1H, m), 3.40 (1H, br d, J = 8.7 Hz), 3.31 (1H, m), 3.31 (3H, s), 2.96 (1H, br s), 1.68 (1H, m), 1.45 (3H, m), 1.09 (6H, s). ^{13}C NMR (125 MHz, C_6D_6): δ 159.5 ppm, 132.1, 129.2, 114.1, 74.8, 72.7, 67.1, 63.7, 54.8, 37.3, 28.0, 25.5, 25.4. HRMS (FAB): $C_{15}H_{24}O_4$ $(M + Na)^+$ calcd 291.1572, found 291.1571.

Benzylidene Formation. A solution of the diol (15.5 g, 60.0 mmol), $PhCH(OMe)_2$ (43.5 mL, 5.00 equiv), and CSA (1.25 g, 0.10 equiv) in DMF (400 mL) was heated at 50 °C for 12 h. The reaction mixture was then cooled to 0 °C and quenched with saturated $NaHCO_3$ aqueous (200 mL), extracted with hexanes (3 × 500 mL), dried with $MgSO_4$, and concentrated. SGC yielded the benzylidene as a 1:1 mixture of diastereomers (18.0 g, 87%). Data for the 1:1 mixture of benzylidenes: IR: 3064 cm^{-1}, 3034, 2972, 2930, 2836, 1613, 1586, 1513, 1459. ^1H NMR (500 MHz, $CDCl_3$): δ 7.47 ppm (2H, m), 7.35 (3H, m), 7.24 (2H, m), 6.85 (2H, m), 5.91 (1H, s), 5.79 (1H, s), 4.35 (2H, d, J = 11 Hz), 4.32 (2H, d, J = 10.8 Hz), 4.23 (2H, m), 4.09 (2H, t, J = 7 Hz), 3.78 (6H, s), 3.69 (1H, t, J = 7.2 Hz), 3.62 (1H, t, J = 7.0 Hz), 1.90 - 1.50 (8H, m), 1.26 (6H, s), 1.25 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0 ppm, 129.4, 129.2, 128.9, 128.5, 126.8, 126.5, 113.9, 104.2, 103.3, 77.8, 74.7, 70.9, 70.3, 63.5, 55.4, 44.4, 36.7, 36.6, 28.2, 27.9, 25.9, 25.7. HRMS (FAB): $C_{22}H_{28}O_4$ $(M + Na)^+$ calcd 379.1885, found 379.1875.

Benzylidene Reduction. To a −78 °C solution of the benzylidene (18.0 g, 52.0 mmol) in CH_2Cl_2 (400 mL) was slowly added diisobutylaluminum hydride (DIBAL) (1.0 M in hexanes, 800 mL, 14.0 equiv), and the reaction was warmed to room temperature overnight. The excess DIBAL was quenched with MeOH (50 mL) at O °C and then slowly warmed to room temperature. The aluminum salts were dissolved with saturated NH_4Cl aqueous (500 mL), and the aqueous layer was extracted with EtOAc (3 × 500 mL). The organic extracts were dried over $MgSO_4$ and concentrated. SGC (3:1 hexanes/EtOAc) yielded the alcohol (15.8 g, 87%). Data for the alcohol: IR: 3427 cm^{-1} (br), 3062, 3031, 2921, 2852, 1613, 1587, 1575, 1513, 1464, 1454, 1247. ^1H NMR (500 MHz, C_6D_6): δ 7.37 ppm (3H, m), 7.05 (1H, m), 6.85 (2H, d, J = 8.4 Hz), 4.40 (1H, d, J = 11.9 Hz), 4.35 (1H, d, J = 11.9 Hz), 4.26 (2H, s), 3.51 (1H, m), 3.46 (1H, m), 3.31 (3H, s), 3.29 (1H, m), 1.77−1.61 (2H, m), 1.55 (1H, ddd, J = 13.5, 11.7, 4.8 Hz), 1.46 (1H, ddd, J = 13.5, 11.7, 4.8 Hz), 1.11 (6H, s). ^{13}C NMR (125 MHz, C_6D_6): δ 159.4 ppm, 139.5, 128.9, 128.5, 128.3, 127.6, 114.0, 80.4, 74.6, 71.4, 64.4, 63.6, 54.8, 36.1, 25.7, 25.7, 25.4. HRMS (FAB): $C_{22}H_{30}O_4$ $(M + Na)^+$ calcd 381.2042, found 381.2040.

Swern Oxidation. To a −78 °C solution of $(COCl)_2$ (6.00 mL, 1.20 equiv) in CH_2Cl_2 (300 mL) was added DMSO (9.00 mL, 2.20 equiv) in CH_2Cl_2 (45 mL). This mixture was stirred for 20 min and then treated with the alcohol (15.8 g, 45.0 mmol) in CH_2Cl_2 (28 mL). The reaction was stirred at −78 °C for 45 min and then quenched with Et_3N (50.0 mL, 5.00 equiv). This mixture was stirred for 10 min at −78 °C and 30 min at 0 °C, and then the resultant precipitate was dissolved with saturated NH_4Cl aqueous (400 mL) and extracted with CH_2Cl_2 (3 × 400 mL). The combined organic layers were dried over $MgSO_4$ and concentrated, and the aldehyde was taken onto the next step without further purification.

$NaClO_2$ Oxidation.[26] To a solution of the aldehyde (∼45.0 mmol) in *t*-BuOH (410 mL) and 2-methyl-2-butene (100 mL) at 0 °C was added dropwise a solution of $NaClO_2$ (10.0 g, 10.0 equiv) and $NaH_2PO_4·H_2O$ (11.0 g, 7.00 equiv) in H_2O (160 mL). The reaction was stirred at 0 °C for 1 h and then extracted with $CHCl_3$ (3 × 500 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. SGC (EtOAc) yielded the carboxylic acid **6** (7.90 g, 48% overall yield for two steps). Data for **6**: IR: 3247 cm^{-1} (br), 3073, 3039, 2968, 2921, 2852, 1718, 1613, 1513, 1455, 1301. ^1H NMR (500 MHz, C_6D_6): δ 7.27 ppm (3H, br t, J = 8.8 Hz), 7.13 (3H, m), 7.06 (1H, br t, J = 7.3 Hz), 6.85 (2H, br d, J = 8.6 Hz), 4.62 (1H, d, J = 11.6 Hz), 4.24 (1H, d, J = 11.4 Hz), 4.23 (2H, s), 3.96 (1H, t, J = 5.7 Hz), 3.31 (3H, s), 2.05 (2H, m), 1.73 (2H, m), 1.90 (6H, s). ^{13}C NMR (125 MHz, C_6D_6): δ 159.4 ppm, 132.4, 129.1, 128.6, 114.0, 78.4, 74.4, 72.4, 63.5, 60.1, 54.8, 35.7, 31.1, 27.5, 25.7, 25.5, 20.5, 14.1. HRMS (FAB): $C_{22}H_{28}O_5$ $(M - H)^-$ calcd 371.1858, found 371.1857.

Transformation of Carboxylic Acid 6 to Lactone 7. MPM Deprotection.[19] A 0 °C solution of **6** (7.42 g, 20.0 mmol) in MeCN/H_2O (10:1, 220 mL) was treated with $(NH_4)_2Ce(NO_3)_6$ (CAN) (38.0 g, 3.50 equiv) and stirred for 1 h. The reaction mixture was then filtered through a pad of Celite which was washed with EtOAc (1.3 L). The filtrate was concentrated, and the crude hydroxy carboxylic acid was submitted to lactonization conditions.

Lactonization. To a 0 °C solution of the hydroxy carboxylic acid (∼20.0 mmol, crude) in THF (600 mL) were added ethyl chloroformate (40.0 mL, 21.0 equiv) and then slowly Et_3N (80.0 mL, 29.0 equiv). The reaction mixture was warmed to room temperature overnight and then filtered through silica gel washing with EtOAc (1.0 L). The filtrate was concentrated, and SGC yielded lactone **7** (3.48 g, 75% overall yield for two steps). Data for **7**: IR: 3096 cm^{-1}, 3067, 3038, 2977, 2922, 2853, 1737, 1454, 1389, 1373. ^1H NMR (500 MHz, C_6D_6): δ 7.36 ppm (2H, d, J = 8.0 Hz), 7.16 (2H, m), 7.09 (1H, t, J = 8.0 Hz), 5.07 (1H, d, J = 12.0 Hz), 4.67 (1H, d, J = 12.0 Hz), 3.54 (1H, dd, J = 8.6, 6.1 Hz), 1.69 (1H, m), 1.55 (1H, m), 1.30 (1H, ddd, J = 14.0, 7.3, 4.1 Hz), 1.03 (1H, m), 0.96 (3H, s), 0.93 (3H, s). ^{13}C NMR (125 MHz, C_6D_6): δ 176.0 ppm, 128.5, 128.3, 81.5, 72.9, 72.6, 32.2, 28.8, 28.2, 25.5. HRMS (CI): $C_{14}H_{18}O_3$ $(M + NH_4)^+$ calcd 252.1600, found 252.1600.

Transformation of Lactone 7 to Iodoacetylene 8. Alkyne Addition. To a solution of (trimethylsilyl)acetylene (9.50 mL, 4.50 equiv) in THF (130 mL) at −78 °C was added *n*-BuLi (2.4 M in hexanes, 18.8 mL, 3.00 equiv). This mixture was stirred at −78 °C for 5 min, warmed to 0 °C during 15 min, and then cooled back down to −78 °C. To this solution was added $BF_3·Et_2O$ (5.50 mL, 3.00 equiv), and then the mixture was stirred at −78 °C for 30 min. A solution of lactone **7** (3.48 g, 15.0 mmol) in THF (20 mL) was added to the reaction mixture, and then it was stirred for 30 min. The reaction mixture was poured into saturated NH_4Cl aqueous (150 mL), extracted with Et_2O (3 × 200 mL), dried over $MgSO_4$, and concentrated. The residual crude hemiketal was submitted to the next step without further purification.

Hemiketal Reduction.[11] To a solution of the hemiketal (∼15.0 mmol, crude) in MeCN/CH_2Cl_2 (5:1, 150 mL) at 0 °C were added Et_3SiH (14.4 mL, 6.00 equiv) and $BF_3·OEt_2$ (2.40 mL, 1.30 equiv), sequentially. The reaction mixture was stirred at 0 °C for 1 h and then quenched with saturated $NaHCO_3$ aqueous (150 mL), extracted with CH_2Cl_2 (4 × 150 mL), and dried over $MgSO_4$. The organic layers were concentrated and SGC (5:1 hexanes/EtOAc) yielded the alkyne (4.25 g, 86% overall yield for two steps). Data for the alkyne: IR: 3059 cm^{-1}, 3026, 2921, 2851, 2367, 2334, 2186, 1454, 1371, 1311. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 ppm (2H, d, J = 7.3 Hz), 7.32 (2H, t, J = 7.4 Hz), 7.26 (1H, t, J = 7.3 Hz), 4.78 (1H, d, 11.6 Hz),

4.68 (1H, d, J = 11.6 Hz), 4.23 (1H, d, J = 9.3Hz), 3.36 (1H, ddd, J = 9.8, 9.8, 4.6 Hz), 1.96 (1H, m), 1.65−1.52 (3H, m), 1.25 (3H, s), 1.22 (3H, s), 0.17 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.3 ppm, 127.8, 127.6, 105.0, 77.6, 72.8, 72.3, 65.9, 35.1, 30.6, 26.5, 21.7, 4.3, −0.1. HRMS (FAB): $C_{19}H_{28}O_2Si$ $(M + Na)^+$ calcd 339.1756, found 339.1763.

TMS Deprotection. To a 0 °C solution of the alkyne (4.25 g, 13.0 mmol) in EtOH/H_2O (4:1, 200 mL) was added $AgNO_3$ (5.00 g, 2.00 equiv) in EtOH/H_2O (3:1, 50 mL). The mixture was stirred for 25 min, then was treated with NaI (9.00 g, 4.00 equiv) in H_2O (50 mL), stirred for an additional 1 h, and then filtered through Celite with Et_2O (250 mL). The water layer was separated and washed with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. SGC (5:1 hexanes/EtOAc) yielded the terminal alkyne (2.60 g, 84%). Data for the terminal alkyne: IR: 3287 cm^{-1}, 3101, 3071, 3041, 2974, 2939, 2871, 1454, 1372, 1352, 1254. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (2H, d, J = 7.3 Hz), 7.32 (2H, t, J = 7.2 Hz), 7.26 (1H, t, J = 7.2 Hz), 4.75 (1H, d, J = 11.6 Hz), 4.67 (1H, d, J = 11.6 Hz), 4.21 (1H, dd, J = 9.4, 1.9 Hz), 3.38 (1H, ddd, J = 10.6, 9.5, 4.7 Hz), 2.44 (1H, d, J = 2.2 Hz), 1.98 (1H, m), 1.65−1.50 (3H, m), 1.25 (3H, s), 1.23 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4 ppm, 128.3, 127.9, 127.7, 77.4, 72.8, 72.7, 72.2, 65.2, 35.0, 30.6, 26.3, 21.6. HRMS (CI): $C_{16}H_{20}O_2$ $(M + NH_4)^+$ calcd 262.1807, found 262.1806.

Iodoacetylene Formation. To a solution of morpholine (13.0 mL, 10.0 equiv) in benzene (130 mL) was added iodine (4.60 g, 1.20 equiv), and the mixture was heated at 45 °C for 1.3 h. A solution of the terminal alkyne (2.60 g, 11.0 mmol) in benzene (60 mL) was added *via canula*, and the reaction was stirred at 45 °C overnight. The reaction was cooled to room temperature, diluted with Et_2O (200 mL), and filtered through cotton wool. The filtrate was washed with saturated Na_2SO_3 aqueous (100 mL), H_2O (100 mL), and saturated NH_4Cl aqueous (100 mL) and then dried over Na_2SO_4. The organic layers were concentrated and SGC (9:1 hexanes/EtOAc) yielded the iodoacetylene **8** (2.50 g, 63%). Data for **8**: IR: 3087 cm^{-1}, 3062, 3029, 2973, 2938, 2869, 2190, 1496, 1454, 1371. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.25 ppm (5H, m), 4.70 (1H, d, J = 11.7 Hz), 4.66 (1H, d, J = 11.7 Hz), 4.34 (1H, d, J = 9.3 Hz), 3.35 (1H, ddd, J = 9.9, 9.6, 4.6 Hz), 1.99 (1H, m), 1.64−1.48 (3H, m), 1.24 (3H, s), 1.21 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3 ppm, 128.4, 128.0, 127.7, 93.5, 77.4, 73.0, 72.1, 66.8, 34.9, 30.5, 26.3, 21.6. HRMS (FAB): $C_{16}H_{19}IO_2$ $(M + Na)^+$ calcd 393.0328, found 393.0324.

Coupling of Aldehyde 5 with Iodoacetylene 8. $NiCl_2$-$CrCl_2$ Coupling. This coupling was carried out in a drybox. To a mixture of aldehyde **5** (crude 323 mg, 0.688 mmol) and iodoacetylene **8** (1.27 g, 5.00 equiv) in THF/DMF (7:3, 8.0 mL) was added 0.05% $NiCl_2$-$CrCl_2$ (750 mg, 8.94 equiv) in one portion, and the mixture was stirred at room temperature for 24 h. The reaction mixture was taken out from the drybox, quenched with 1.0 M serin potassium salt aqueous (20 mL)[27] at 0 °C, and diluted with EtOAc (50 mL). After stirring 20 min at room temperature, the aqueous layer was extracted with EtOAc (3 × 40 mL). Then the aqueous layer was acidified with 2.0 M HCl aqueous, and the solution was extracted again with EtOAc (40 mL). The organic extracts were combined, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by SGC (95:5 → 80:20 hexanes:EtOAc) to give a 1:1 mixture of two isomers, **9** and **10**, as colorless oil (384 mg, 93%). Data for the 1:1 mixture of **9** and **10**: IR: 3450 cm^{-1} (br), 3092, 3060, 2980, 2964, 2924, 2853, 2343, 1467, 1379, 1244. ^{1}H NMR (400 MHz, C_6D_6): δ 7.48 ppm (4H, br d, J = 7.3 Hz), 7.26−6.94 (6H, m), 4.85 (2H, d, J = 11.9 Hz), 4.67 (2H, d, J = 11.9 Hz), 4.48 (6H, m), 3.64 (2H, ddd, J = 12.5, 12.5, 3.4 Hz), 3.43 (2H, m), 2.67 (2H, t, J = 10.7 Hz), 2.02 (4H, ddd, J = 11.8, 5.1, 3.4 Hz), 1.92 (4H, ddd, J = 11.8, 11.8, 11.8 Hz), 1.84 (2H, m), 1.76 (4H, ddd, J = 13.0, 4.2, 4.2 Hz), 1.52 (3H, s), 1.52 (4H, m), 1.35 (2H, m), 1.25 (3H, s), 1.25 (5H, m), 1.24 (3H, s), 1.20 (3H, s), 1.19 (3H, s), 1.19 (6H, m), 1.17 (3H, s), 0.97 (3H, s), 0.87 (9H, s), 0.86 (9H, s), 0.10 (3H, s), 0.09 (3H, s), 0.02 (3H, s), -0.02 (3H, s). ^{13}C NMR (125 MHz, C_6D_6): 128.5 ppm, 128.3, 128.1, 127.9, 127.7, 80.5, 78.1, 78.0, 73.2, 72.6, 72.5, 72.2, 72.0, 71.8, 66.1, 35.6, 35.0, 35.0, 32.6, 31.6, 30.7, 30.6, 25.9, 23.1, 22.1, 22.0, 20.4, 18.0, 17.8. HRMS (FAB): $C_{35}H_{56}O_6Si$ $(M + Na)^+$ calcd 623.3744, found 623.3739.

Transformation of Alcohols 9 and 10 to Hydroxy Ketones 11 and 12. Selective Hydrogenation. To a solution of alkynes, **9** and **10** (384 mg, 0.639 mmol), in EtOAc (10 mL) was added Lindlar catalyst (3.60 g), and the mixture was vigorously stirred at room temperature under a H_2 atmosphere for 16 h. The catalyst was filtered off through Celite washing with EtOAc, and the filtrate was concentrated to give a 1:1 mixture of saturated alcohols as a colorless oil (0.338 g, 87%). Data for the 1:1 mixture of saturated alcohols. IR: 3555 cm^{-1}(br), 3090, 3064, 3028, 2959, 2928, 2855, 1461, 1380, 1363. ^{1}H NMR (500 MHz, C_6D_6): δ 7.37 ppm (4H, m), 7.18 (6H, m), 4.48 (2H, d, J = 11.8 Hz), 4.33 (4H, m), 3.66 (4H, m), 3.35 (2H, ddd, J = 11.5 3.4, 1.2 Hz), 3.21 (1H, m), 3.06 (2H, dddd, J = 10.1, 10.1, 10.0, 4.6 Hz), 3.00 (1H, br d, J = 2.9 Hz) 2.76 (1H, m), 2.34 (1H, m), 2.15 (2H, m), 2.03 (3H, m), 1.88 (2H, ddd, J = 11.6, 11.6, 11.6 Hz), 1.83 (4H, m), 1.72 (2H, m), 1.54−1.44 (8H, m), 1.41 (3H, s), 1.40 (3H, s), 1.38−1.27 (8H, m), 1.26 (3H, s), 1.24 (3H, s), 1.22 (3H, s), 1.21 (3H, s), 1.15 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.04 (3H, s), 1.03 (3H, s), 0.94 (9H, s), 0.93 (9H, s), 0.43 (3H, s), 0.11 (3H, s), 0.10 (3H, s), 0.03 (3H, s). ^{13}C NMR (125 MHz, C_6D_6): δ 139.7 ppm, 128.5 (×2), 128.3, 128.1, 127.9, 127.5, 116.2, 80.9, 80.8, 79.8, 79.5, 78.6 (×2), 74.3, 74.0, 72.7, 72.6 (×2), 71.2 (×2), 71.1, 70.9, 70.9, 36.0, 35.9, 34.9, 33.0, 31.6 (×2), 31.3, 27.6, 27.5, 26.2, 22.9, 22.0, 21.9, 19.9, 19.7, 18.2, 18.0, −3.0. HRMS (FAB): $C_{35}H_{60}O_6Si$ $(M + Na)^+$ calcd 627.4057, found 627.4073.

Swern Oxidation. DMSO (2.38 mL, 60.0 equiv) was slowly added to a solution of $(COCl)_2$ (1.46 mL, 30.0 equiv) in CH_2Cl_2 (20 mL) at −78 °C, and the resultant mixture was stirred for 10 min. A solution of the alcohols (338 mg, 0.559 mmol) in CH_2Cl_2 (10 mL) was added dropwise, and the resultant mixture was stirred at −35 °C for 1 h and then warmed to −15 °C for 40 min. The reaction mixture was cooled again to −78 °C, and Et_3N (9.34 mL, 120 equiv) was slowly added to the mixture. After having been stirred at −78 °C for 10 min, the mixture was warmed up to 0 °C and stirred for additional 10 min. Et_2O (100 mL) and saturated $NaHCO_3$ aqueous (20 mL) were added to the mixture, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by SGC (95:5 → 90:10 hexanes/EtOAc) to give a 1:1 mixture of ketones as a colorless oil (408 mg, 100%). Data for a 1:1 mixture of the ketones: IR: 2923 cm^{-1}, 2852, 1721, 1462, 1453, 1379, 1363. ^{1}H NMR (500 MHz, C_6D_6): δ 7.33 ppm (4H, m), 7.15 (6H, m), 4.44 (2H, m), 4.40 (1H, dd, J = 9.0, 6.2 Hz), 4.27 (2H, t, J = 12.5 Hz), 3.59 (2H, m), 3.48 (2H, ddd, J = 12.2, 4.2, 1.0 Hz), 3.24 (1H, ddd, J = 17.9, 9.7, 4.8 Hz), 3.07 (2H, m), 2.97 (4H, m), 2.63 (1H, m), 2.49 (1H, m), 2.14 (3H, m), 1.86 (3H, m), 1.79 (1H, dddd, J = 12.9, 4.3, 4.3, 4.3 Hz), 1.72 (1H, ddd, J = 13.3, 13.3, 4.3 Hz), 1.61 (2H, br d, J = 10.4 Hz), 1.49 (3H, s), 1.48 (8H, m), 1.48 (3H, s), 1.36 (3H, s), 1.34 (3H, s), 1.30 (6H, m), 1.17 (3H, s), 1.16 (3H, s), 1.16 (4H, m), 1.14 (6H, s), 1.09 (3H, s), 1.08 (3H, s), 0.94 (9H, s), 0.94 (9H, s), 0.40 (3H, s), 0.10 (3H, s), 0.10 (3H, s), 0.03 (3H, s), 0.02 (3H, s). ^{13}C NMR (125 MHz, C_6D_6): δ 128.5 ppm, 128.3, 128.1, 127.9, 127.6, 84.0, 73.5, 73.5, 73.4, 73.1, 72.5, 71.8, 71.5, 70.7, 69.9 (×2), 56.1, 41.8, 36.0, 35.9, 35.7, 35.0, 33.1, 33.1, 32.4, 32.2, 31.5, 31.3, 28.1, 26.1 (×2), 26.0, 22.8, 22.0 (×3), 21.2, 18.5, 18.4, 18.2, −4.5. HRMS (FAB): $C_{35}H_{58}O_6Si$ $(M + Na)^+$ calcd 625.3900, found 625.3901.

Benzyl Deprotection. A suspension of the 1:1 mixture of the ketones (408 mg crude, 0.559 mmol) and 20% $Pd(OH)_2$ on C (1.40 g) in EtOAc (6 mL) was stirred under H_2 at room temperature for 2 h. The reaction mixture was filtered through Celite washing with EtOAc (15 mL), and the filtrate was concentrated to give a 1:1 mixture of alcohols, **11** and **12**, as a colorless oil (290 mg, 100% overall yield for two steps), which was used for the next step without further purification.

Transformation of Hydroxyl Ketones 11 and 12 to Me-A and Me-B. Reductive Cyclization.[11] To a mixture of ketoalcohols, **11** and **12** (86.1 mg, 0.168 mmol), and Et_3SiH (0.540 mL, 20.0 equiv) in CH_3CN (10 mL) at −20 °C was slowly added BF_3·OEt_2 (0.100 mL, 5.00 equiv), and the mixture was stirred at −20 °C for 1 h. To the reaction mixture was added saturated $NaHCO_3$ aqueous (10 mL) at 0 °C, and the mixture was stirred vigorously for 10 min. The resultant mixture was extracted with Et_2O (3 × 5 mL), and the organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to SGC (95:5 → 70:30 hexanes/EtOAc) to

give the separated dimethyl models **Me-A** and **Me-B**. Data for less polar isomer **Me-A** (22.0 mg, 34%): mp 165−167 °C. IR: 3529 cm^{-1} (br), 2972, 2941, 2870, 1462, 1380, 1366. ^{1}H NMR (500 MHz, 1:1 CD_3OD/C_5D_5N): δ 3.78 ppm (1H, dd, J = 11.4, 5.0 Hz), 3.35 (1H, dd, J = 12.2, 3.5 Hz), 3.27 (1H, dd, J = 11.2, 1.9), 3.15 (1H, ddd, J = 10.0, 10.0, 4.1), 2.93 (1H, ddd, J = 9.8, 9.8, 4.5 Hz), 1.81 (3H, m), 1.74 (2H, ddd, J = 11.8, 11.8, 11.8 Hz), 1.64−1.42 (8H, m), 1.35 (1H, m), 1.28 (3H, s), 1.16 (6H, s), 1.10 (3H, s), 1.09 (3H, s), 1.07 (3H, s). ^{13}C NMR (125 MHz, 1:1 CD_3OD/C_5D_5N): δ 88.2 ppm, 80.6, 78.4, 75.5, 73.7, 73.6, 72.9, 72.2, 36.8, 36.3, 35.5, 31.8, 31.5, 31.1, 30.7, 27.1, 25.0, 23.3, 22.4, 18.5, 18.4. HRMS (CI): $C_{22}H_{38}O_5$ $(M + NH_4)^+$ calcd 400.3063, found 400.3059. $[\alpha]_D$: +7.0° (*c* 0.50, $CHCl_3$).

Data for more polar isomer **Me-B** (29.1 mg, 46%): mp 172−174 °C. IR: 3537 cm^{-1} (br), 2971, 2925, 2870, 2852, 1572, 1462, 1378. ^{1}H NMR (500 MHz, 1:1 CD_3OD/C_5D_5N): δ 4.30 ppm (1H, dd, J = 11.5, 5.1 Hz), 3.36 (1H, dd, J = 12.1, 3.6 Hz), 3.32 (1H, m), 3.19 (1H, ddd, J = 10.0, 10.0, 4.4 Hz), 2.81 (1H, ddd, J = 12.4, 12.4, 4.8 Hz), 1.87 (2H, m), 1.80 (1H, ddd, J = 11.9, 11.9, 11.9 Hz), 1.73 (1H, m), 1.58 (3H, m), 1.48 (1H, m), 1.43−1.29 (6H, m), 1.26 (3H, s), 1.17 (3H, s), 1.09 (3H, s), 1.08 (3H, s), 1.06 (3H, s), 1.06 (3H, s). ^{13}C NMR (125 MHz, 1:1 CD_3OD/C_5D_5N): δ 84.1 ppm, 80.6, 79.0, 73.6, 73.5, 72.8, 72.2, 68.9, 36.9, 36.1, 35.5, 31.8, 31.7, 31.5, 31.2, 27.1, 24.7, 23.3, 22.5, 21.7, 18.6. HRMS (FAB): $C_{22}H_{38}O_5$ $(M + H)^+$ calcd 383.2797, found 383.2799. $[\alpha]_D$: +21.2° (*c* 0.65, $CHCl_3$).

X-ray Structures. X-ray data was collected using a Siemens SMART CCD (charge coupled device) based diffractometer equipped with an LT-2-low-temperature apparatus at 213 K, and the crystal structures of **4**, **13**, **Me-A**, and **Me-B**, along with the relevant information were deposited *via* e-mail in Crystallographic Information File format.

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Supporting Information Available: The general procedures and methods, the experimentals for the synthesis of models **H_2-A** and **H_2-B**, and the 2D ^{1}H−^{1}H NOESY spectra for **Me-A** and **Me-B** in C_6D_6 and 1:1 CD_3OD/C_5D_5N are included (23 pages). X-ray crystallographic files, in CIF format, are available for **4**, **13**, **Me-A**, and **Me-B** through the Internet only. See any current masthead page for ordering and Internet access instructions.

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