2), 139897-30-6; (±)-**58**, 139897-33-9; **59**, 139897-31-7; (±)-**60** (isomer 1), 139913-91-0; (±)-**60** (isomer 2), 139897-32-8; (±)-**61**, 126822-62-6; (±)-**61** alcohol, 139896-15-4; (±)-**62**, 126822-63-7; (±)-**64**, 139897-38-4; (±)-**67**, 139897-34-0; (±)-**68**, 139897-35-1; (±)-**68** phenylselenide, 139897-44-2; **69**, 139897-36-2; **70**, 139897-37-3; (±)-**71**, 139896-05-2; CH_2=$C(CH_3)MgBr$, 13291-18-4; $OHC(CH_2)_2CO_2Me$, 13865-19-5; $(CH_3)_2C$=$CHMgBr$, 38614-36-7; (±)-$Br(CH_2)_2OTHP$, 59146-56-4; (±)-$I(CH_2)_2OTHP$, 139897-17-9; $Br(CH_2)_2OH$, 540-51-2; t-BuO_2CCH_3, 540-88-5; $(CH_3)_2C$=$CHSnMe_3$, 20484-24-6.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **30** (4 pages). Ordering information is given on any current masthead page.

Total Synthesis of Furanocembranolides. 2. Macrocyclization Studies Culminating in the Synthesis of a Dihydropseudopterolide and Gorgiacerone, Related Furanocembranolide Interconversions[1]

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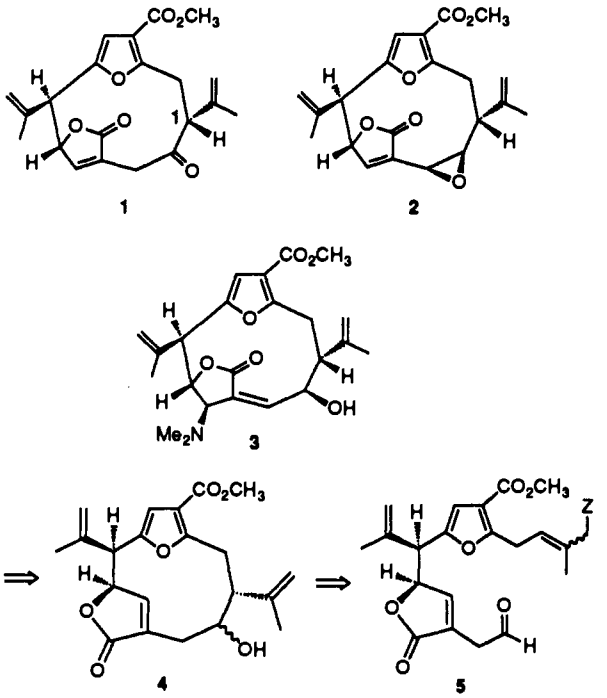
Abstract: The acetaldehydes **7**, **14**, **22**, and **29** were screened for their ability to undergo macrocyclization. These substrates were made available as a consequence of the generality of Pd(0)-catalyzed vinylstannane couplings to bromides **12**. Although molecular mechanics calculations indicated there to be no conformational deterrent to ring closure, **7** failed to undergo intramolecular Prins reaction and **14** did not enter into allylsilane–carboxaldehyde condensation. Fortunately, while **22** gave no evidence for ring closure under conditions of reductive coupling, its *E* isomer **29** was stereoselectively transformed into the dihydropseudopterolide **17**, the stereochemical features of which were unequivocally established by X-ray crystallography. The overall course of this reaction was determined to be in good accord with the results of MODEL calculations of product stabilities. The availability of **17** made possible a total synthesis of gorgiacerone (**1**). A related approach to tobagolide (**3**) was also investigated. When initial experiments established the feasibility of transforming pseudopterolide (**2**) into tobagolide, the dimethylamino group was directly incorporated into several butenolides. Of these, **34b** was sufficiently stable to be converted to **35**. Still more impressive was the successful conversion of **37** into bromo aldehyde **40**. However, these intermediates proved to be too sensitive for eventual crafting into furanocembranolide derivatives.

Gorgiacerone (**1**),[3] pseudopterolide (**2**),[4] tobagolide (**3**),[5] and structurally related cembranoids[6] represent important synthetic targets.[7] A unique opportunity for developing new technologies for molecular construction is thereby offered.[8] Furthermore, accomplishments in this area may also hold application for assault on other biomedically important furanocembranolides represented by pukalide[6a,c] and lophotoxin.[6b,d] In the preceding paper in this series,[1] the details of a possible synthetic entry into this class of compounds via **4** and **5** were given. In particular, a suitably stereocontrolled assembly of the key heterocyclic building blocks was described, and the feasibility of gaining access to **5** (Z = H) was demonstrated.



(1) Part 1: Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.*, preceding article in this issue.

(2) NATO Postdoctoral Fellow of the Science and Engineering Research Council, 1987–1989.

(3) Tinto, W. F.; John, L.; Reynolds, W. F.; McLean, S. *Tetrahedron*, in press.

(4) Bandurraga, M. M.; Fenical, W.; Donovan, S. F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463.

(5) Tinto, W. F.; Chan, W. R.; Reynolds, W. F.; McLean, S. *Tetrahedron Lett.* **1990**, *31*, 465.

(6) (a) Missakian, M. G.; Burreson, B. J.; Scheuer, P. G. *Tetrahedron* **1975**, *31*, 2513. (b) Fenical, W.; Okuda, R. K.; Bandurraga, M. M.; Culver, P.; Jacobs, R. S. *Science* **1981**, *212*, 1512. (c) Ksebati, M. B.; Ciereszko, L. S.; Schmitz, F. J. *J. Nat. Prod.* **1984**, *47*, 1009. (d) Jacobs, R. S.; Culver, P.; Langdon, R.; O'Brien, T.; White, S. *Tetrahedron* **1985**, *41*, 981. (e) Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741. (f) Williams, D.; Andersen, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332. (h) D'Ambrosio, M.; Fabbri, D.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta.* **1987**, *70*, 63. (h) Bowden, B. F.; Coll, J. C.; Wright, A. D. *Aust. J. Chem.* **1989**, *42*, 757. (i) Coll, J. C.; Bowden, B. F.; Heaton, A.; Scheuer, P. J.; Li, M. K. W.; Clardy, J.; Schulte, G. K.; Finer-Moore, J. *J. Chem. Ecol.* **1989**, *15*, 1177. (j) Wright, A. E.; Burres, N. S.; Schulte, G. K. *Tetrahedron Lett.* **1989**, *30*, 3491. (k) Chan, W. R.; Tinto, W. F.; Laydoo, R. S.; Manchand, P. S.; Reynolds, W. F.; McLean, S. *J. Org. Chem.* **1991**, *56*, 1773. (l) Tinto, W. F.; John, L.; Lough, A. J.; Reynolds, W. F.; McLean, S. *Tetrahedron Lett.*, in press.

(7) Tius, M. A. *Chem. Rev.* **1988**, *88*, 719. (b) Pietra, F. *Gazz. Chim. Ital.* **1985**, *115*, 443.

(8) (a) Tius, M. A.; Trehan, S. *J. Org. Chem.* **1986**, *51*, 765. (b) Kondo, A.; Ochi, T.; Iio, H.; Tokoroyama, T.; Siro, M. *Chem. Lett.* **1987**, 1491. (c) Leonard, J.; Ryan, R. *Tetrahedron Lett.* **1987**, *28*, 2525. (d) Marshall, J. A.; Nelson, D. J. *Tetrahedron Lett.* **1988**, *29*, 741. (e) Paterson, I.; Gardner, M.; Banks, B. J. *Tetrahedron* **1989**, *45*, 5283. (f) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450. (g) Astley, M. P.; Pattenden, G. *Synlett* **1991**, 335.

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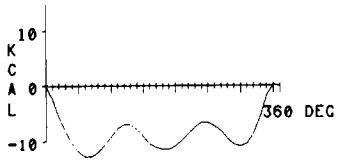


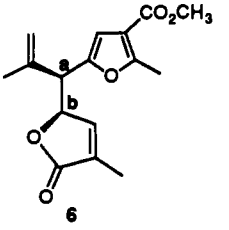
Figure 1. Approximate variation of energy with H–C(a)–C(b)–H bond angle in **6**.

With a reliable synthesis of **5** achieved, our efforts were next directed to the rather formidable challenge of macrocyclization. Described herein is the successful realization of this goal, which culminates in the synthesis of **1**.[9] Systematic studies are necessary to achieve the appropriate C–C bond construction as in **5** → **4**, and these issues are addressed first. Subsequently, the reversible conversion of **2** to **3** is described, showing that a direct chemical link exists between hydroxylated pseudopteranes and activated epoxides.[10]

Results and Discussion

Evaluation of Prins Chemistry. The preparative utility of intramolecular Lewis acid-catalyzed condensations of aldehydic carbonyl groups with distal double bonds (the Prins reaction[11]), as surveyed by Snider,[12] has been creatively applied by numerous research groups to highly varied carbocycle construction. The ability to accomplish ring closure with formation of five-,[13] six-,[14] and seven-membered homoallylic alcohols[15] has been recognized for some time. The important issue of the relative configuration of the hydroxyl and neighboring alkenyl substituent, where relevant, has also been given attention. To date, however, we are unaware of an application of such an intramolecular ene reaction in a macrocyclization context.[11,12,16] On the other hand, the systematic investigation of Kitahara and his co-workers of successful 14-membered polyene cyclizations via acid chlorides under Friedel–Crafts-like conditions was considered to be constructive precedent.[17]

Since conformational factors are known to play an important role in facilitating ring closure reactions, our work begins by computational analysis of the low-energy conformations of **6**, a structurally less complex prototype of **5** possessing the key C_a–C_b bond (the ancillary appendages are remote from these centers and do not have an impact on the relative ordering of the energetics).



6

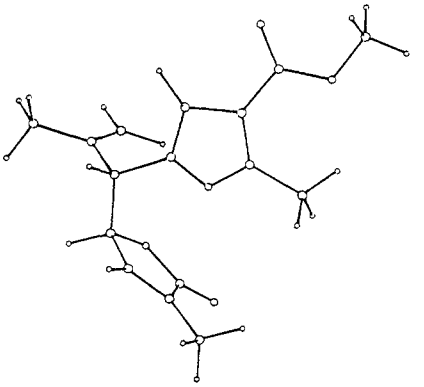


Figure 2. Minimum energy conformation of **6** (for angle H–C(a)–C(b)–H = 66°).

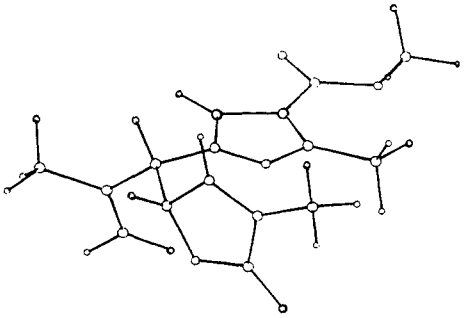
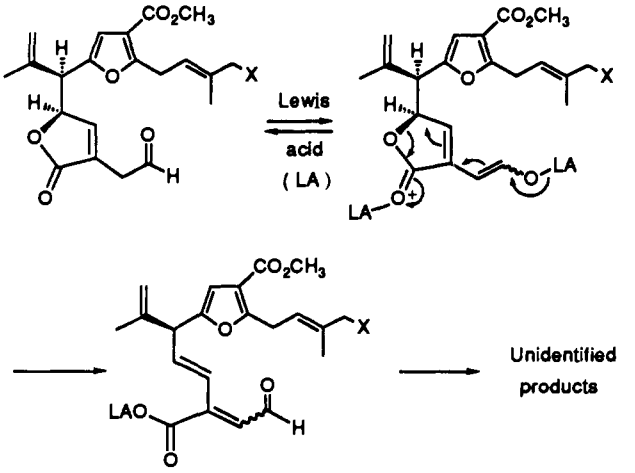


Figure 3. Conformation of **6** considered near-ideal for engaging the two proximal methyl groups in bonding (for angle H–C(a)–C(b)–H = 30°).

Scheme I



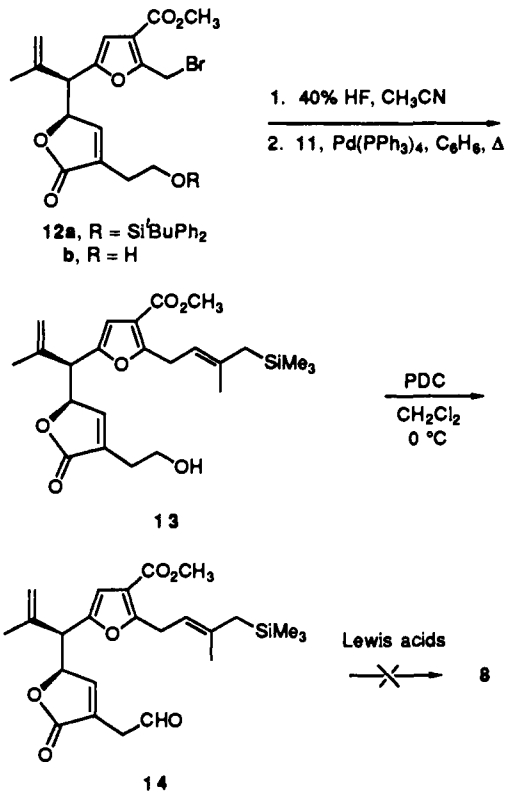
Should **6** (and **5**) strongly prefer adoption of that antiplanar arrangement in which the hydrogen atoms on C_a and C_b are oriented 180° apart, the relevant side chains would be directed to the maximum extent possible away from each other. Under these circumstances, cyclization would not be likely. However, this situation does not pertain.

A rough minimization of **6** was first carried out in MACROMODEL[18] to adjust bond angles and distances. The multiconformer mode of this program was then used to generate a set of possible conformers by rotation about the C_a–C_b bond, as well as those bonds linked to the isopropenyl group and furan ring. A basis set of 46 possible conformers was used. Following batch minimization of these structures with the MM2 force field, those of highest energy were eliminated. Eight conformers resided within 3 kcal of the minimum conformer, and that of lowest energy was selected for further refinement. The program MODEL[19] was next

(9) Preliminary communication: Paquette, L. A.; Rayner, C. M.; Doherty, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 4078.
(10) Paquette, L. A.; Astles, P. *Tetrahedron Lett.* **1990**, *31*, 6505.
(11) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661 and relevant references cited therein.
(12) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426 and relevant references cited therein.
(13) For example: (a) Piers, E.; Isenring, H.-P. *Synth. Commun.* **1976**, *6*, 221. (b) Andersen, N. H.; Hadley, S. W.; Kelly, J. D.; Bacon, E. R. *J. Org. Chem.* **1985**, *50*, 4144. (c) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424.
(14) For example: (a) Nakatani, Y.; Kawashima, K. *Synthesis* **1978**, 147. (b) Niwa, M.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3148.
(15) For example: (a) Marshall, J. A.; Andersen, N. H.; Johnson, P. C. *J. Org. Chem.* **1970**, *35*, 186. (b) Andersen, N. H.; Uh, H. S.; Smith, S. E.; Wuts, P. G. M. *J. Chem. Soc., Chem. Commun.* **1972**, 956. (c) Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858. (d) Snider, B. B.; Ke, Y. *Tetrahedron Lett.* **1989**, *30*, 2465.
(16) (a) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (b) Oppolzer, W. *Pure Appl. Chem.* **1981**, *53*, 1181.
(17) (a) Kobayashi, T.; Kumazawa, S.; Kato, T.; Kitahara, Y. *Chem. Lett.* **1975**, 301. (b) Kato, T.; Kobayashi, T.; Kitahara, Y. *Tetrahedron Lett.* **1975**, 3299. (c) Kitahara, Y.; Kato, T.; Kobayashi, T. *Chem. Lett.* **1976**, 219. (d) Kato, T.; Suzuki, M.; Nakazima, Y.; Shimizu, K.; Kitahara, Y. *Chem. Lett.* **1977**, 705. (d) Kato, T.; Suzuki, M.; Kobayashi, T.; Moore, B. P. *J. Org. Chem.* **1980**, *45*, 1126.

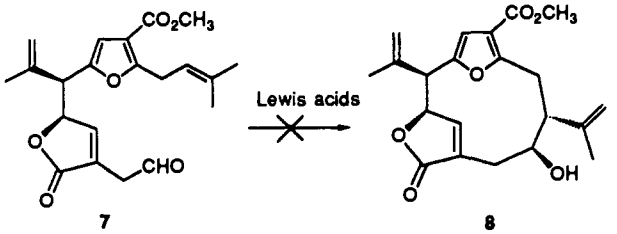
(18) We thank Professor W. C. Still (Columbia University) for making his program available for use and Professor K. Steliou (University of Montreal) for providing us with updates of this software package.

Scheme II



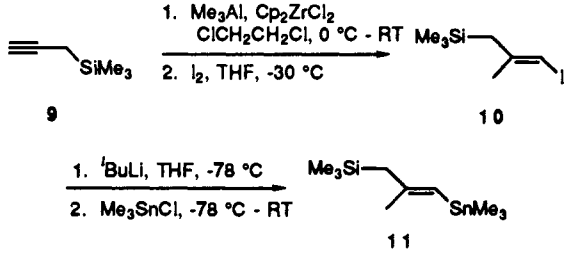
employed to construt an energy versus dihedral angle plot for rotation about the C_a–C_b bond. As can be seen in Figure 1, the spatial orientations of lowest energy occur at approximately 60° (−12.8 kcal/mol), 180° (−11.4 kcal/mol), and 300° (−10.8 kcal/mol). Relevantly, the deepest well seen at 66° three-dimensionally corresponds (Figure 2) rather closely to the conformation deemed most appropriate for the hypothetical cyclization (ca. 30°, −8.0 kcal/mol; see Figure 3). On this basis, we conclude that *the rotational barrier about the C_a–C_b bond is insufficient to preclude macrocyclization.* In actuality, the energy required to adopt the conformation depicted in Figure 3 is less than that required to rotate between the three energy minima. While these calculations are approximations, with no attempt to account for either mechanism or possible atomic distortions at the height of the appropriate transition state, every indication exists that **5** should have minimal difficulty in aligning itself for arrival at the pseudopterane framework.

Despite this prognosis, submission of **7** to the full range of conditions that proved effective earlier, i.e., catalysis with Et_2AlCl, $EtAlCl_2$, $BF_3{\cdot}OEt_2$,[13b] $ZnBr_2$,[14] $SnCl_4$,[20] or Dowex H^+ resin,[11] failed to bring about the desired ring closure. Recourse to harsher conditions destroyed **7** without producing identifiable compounds. This is not totally unexpected, since pathways exist (see Scheme I) for butenolide fragmentation and ultimate polymerization.



Assessment of the Intramolecular Allylsilane–Carboxaldehyde Condensation Pathway. The lack of success described above hints that the isopentenyl side chain in **7** may perhaps be insufficiently reactive to engage in a suitably accelerated Prins reaction. This conclusion receives support from the fact that no example of ring formation involving more than seven atoms has been reported for this process. In contrast, intramolecular additions to allylsilanes are recognized to be able to form rings containing up to eight carbon atoms.[21,22] Consequently, the synthesis of **13** was next undertaken.

In analogy with the all-carbon process,[1] we hoped to realize appendage of the side chain in **13** by means of Pd(0)-catalyzed vinylstannane coupling to bromide **12**. Accordingly, propargyltrimethylsilane (**9**)[23] was carbometalated and transformed with excellent stereoselectivity into vinyl iodide **10** by the method of Negishi.[27] Lithium–halogen exchange followed by condensation with trimethyltin chloride afforded **11** with full preservation of double bond geometry in 60% overall yield.



Although interconnective bonding between **11** and **12a**[1] could be realized, subsequent attempted unmasking of the hydroxyl group under normal conditions could not be accomplished without concomitant protodesilylation of the allylsilane subunit. Condensations promoted by Pd(0) have been reported to occur satisfactorily in the presence of many functional groups including hydroxyl.[28] Consequently, **12a** was first transformed into **12b**, and reaction of this alcohol with **11** was examined (Scheme II). Although this coupling could never be brought to total completion, **13** could be isolated in 51% yield when the level of recovered starting material was taken into account.

Oxidation of **13** to aldehyde **14** provided the target cyclization precursor. However, all attempts to effect the intended ring closure ($EtAlCl_2$, $BF_3{\cdot}OEt_2$, $ZnCl_2$, $SnCl_4$, etc.)[21,29] resulted either in no reaction or in rapid decomposition of **14**. The sensitivity of **14** also precluded recourse to sources of F^-. Accordingly, a still milder synthetic protocol had to be devised.

Stereochemical Dependence to Ring Closure via Cr(II)-Promoted Reductive Coupling. The chromium(II) chloride-mediated condensation of allylic halides with aldehydes has found past ap-

(19) (a) Still, W. C.; MacPherson, L. J.; Harada, T.; Rheingold, A. *Tetrahedron* **1984**, *40*, 2275. (b) Still, W. C.; Golynker, I. *Tetrahedron* **1981**, *37*, 3981.

(20) Andersen, N. H.; Golec, F. A., Jr. *Tetrahedron Lett.* **1977**, 3783.

(21) Schinzer, D. *Synthesis* **1988**, 263.

(22) Failure to achieve intramolecular cyclization of an allylsilane onto an aldehyde for the purpose of generating a 14-membered cembranoid ring has been mentioned by Still and Mobilio [Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785].

(23) After repeated attempts to generate propargylmagnesium bromide by means of the standard methods for activating magnesium metal,[24,25] all of which failed to produce the reagent, recourse was made to use of mercury(II) chloride for this purpose. The results were striking. Initiation was virtually immediate and exothermic. This methodology has been used previously for the preparation of **9**, although experimental details were sparse.[26]

(24) Review: Lai, Y. H. *Synthesis* **1981**, 585.

(25) (a) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775. (b) Chapman, O. L.; Mattes, K. C.; Sheridan, R. S.; Klun, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 4878.

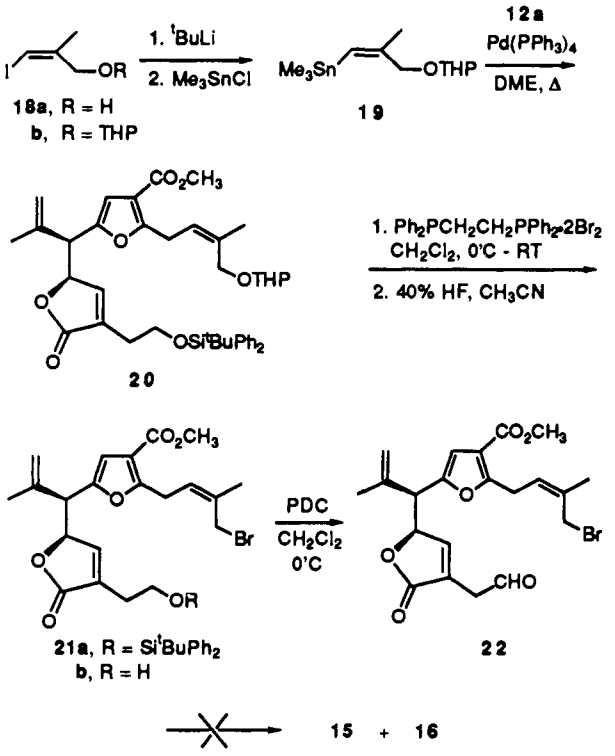
(26) Slutsky, J.; Kwart, H. *J. Am. Chem. Soc.* **1973**, *95*, 8678.

(27) Negishi, E.; Luo, F.-T.; Rand, C. L. *Tetrahedron Lett.* **1982**, *23*, 27.

(28) (a) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500. (b) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173. (c) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833.

(29) For additional examples, consult the following: (a) Itoh, A.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1979**, 1783. (b) Andersen, N. H.; McCrae, D. A.; Grotjohn, D. B.; Gabhe, S. Y.; Theodore, L. J.; Ippolito, R. M.; Sarkar, T. K. *Tetrahedron* **1981**, *37*, 4069. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (d) Denmark, D. E.; Weber, E. *J. Am. Chem. Soc.* **1984**, *106*, 7970. (e) Denmark, S. E.; Weber, E. *Helv. Chim. Acta* **1983**, *66*, 1655. (f) Paquette, L. A.; Ladouceur, G. *J. Org. Chem.* **1989**, *54*, 4278. (g) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57.

Scheme III

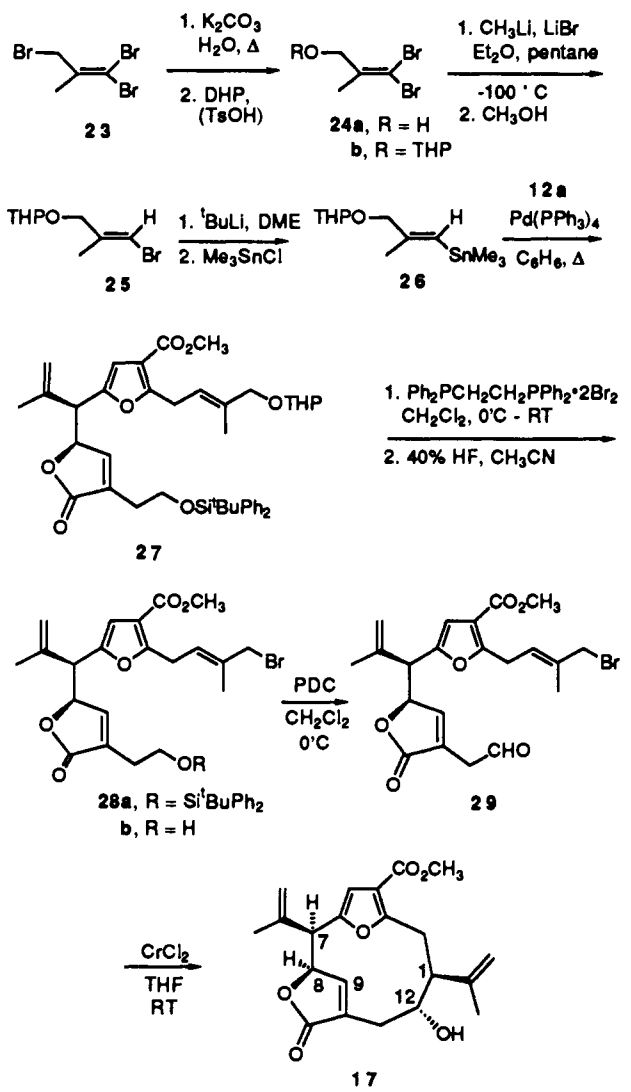


plication in synthesis because of its threo selectivity,[30,31] ability to promote macrocyclization in the presence of the sensitive epoxide functionality,[22] suitability for itramolecular C–C bond formation under conditions where the corresponding allylsilane reaction failed,[22] and relative ease of operation.[32] The high stereoselectivity of this process has been rationalized.[30b] Extension of these concepts to our objectives required that proper attention be given to the inherent stereochemistry of the side chain positioned at C-2 of the furan ring. As illustrated in Figure 4, utilization of the *E* stereoisomer should eventuate in the formation of either **15** or **16**, furanocembranolide systems that are diastereomerically related to **1**. In contrast, recourse to the *Z* allylic bromide can be expected to proceed preferably in a manner that would deliver **8** and/or **17**.

The intriguing structural and stereochemical interrelationships described above prompted examination of both alternatives. We proceeded first to prepare **22** because vinyl iodide **18a** was a known entity[33] (Scheme III). The conversion of **18a** to its tetrahydropyranyl ether **18b** was undertaken not only for hydroxyl protection purposes but more specifically because of our projected requirement that the allyl bromide residue be generated under the mildest conditions available.

Once **20** had been acquired, its exposure to the action of 1,2-bis(diphenylphosphino)ethane tetrabromide in dichloromethane[34] resulted in rapid conversion to **21a** (63% isolated). Thus, this reagent is capable of effecting this useful transformation on a sensitive substrate, as advertised. Desilylation of **21a** was accomplished with aqueous hydrofluoric acid in acetonitrile.[35] The

Scheme IV



oxidation of **21b** to **22** was again best accomplished with pyridinium dichromate.[36]

The transition-state models for the cyclization of **22** (**A** and **B** in Figure 4) contemplate intramolecular π-facially selective attack at the aldehyde carbonyl by a flanking π-bond such that one large substituent is oriented axially on the oxa chromium six-membered ring. The extent to which these arrangements are more costly in energy than those embodied in **C** and **D** is not without its own questions of detail and nuance. Suffice it to say that, at the limits represented by **A** and **B**, no cyclization was observed under a variety of conditions known to be effective in other contexts.[22,30-32,37] In addition, efforts to promote ring closure by means of tin(II) chloride[38] proved equally unsuccessful.

At the other extreme, the transoid, all-equatorial variants (**C** and **D** in Figure 4) might be sufficiently better transition-state stereoalignments to permit ready joining of the indicated carbon atoms. To assess these alternatives, 1,1-dibromo-2-methylpropane[39] was monobrominated under free radical conditions[40]

(30) (a) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. (b) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (c) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.

(31) (a) Reference 22. (b) Shibuya, H.; Ohashi, K.; Kawashima, K.; Hori, K.; Murakami, N.; Kitagawa, I. *Chem. Lett.* **1986**, 85. (c) Mulzer, J.; Kattner, L.; Strecker, A. R.; Schröder, C.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 4218. (d) Wender, P. A.; Grissom, J. W.; Hoffmann, U.; Ma, R. *Tetrahedron Lett.* **1990**, *31*, 6605. (e) Wender, P. A.; McKinney, J. A.; Mukai, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369.

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(35) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(36) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.

(37) (a) Still, W. C. Private communication. (b) Kato, N.; Nakanishi, K.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1109. (c) Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354.

(38) (a) Mukaiyama, T.; Harada, T.; Shoda, S. *Chem. Lett.* **1980**, 1507. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(39) (a) Rule, M.; Mondo, J. A.; Berson, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2209. (b) Posner, G. H.; Loomis, G. L.; Sawaya, H. S. *Tetrahedron Lett.* **1975**, 1373.

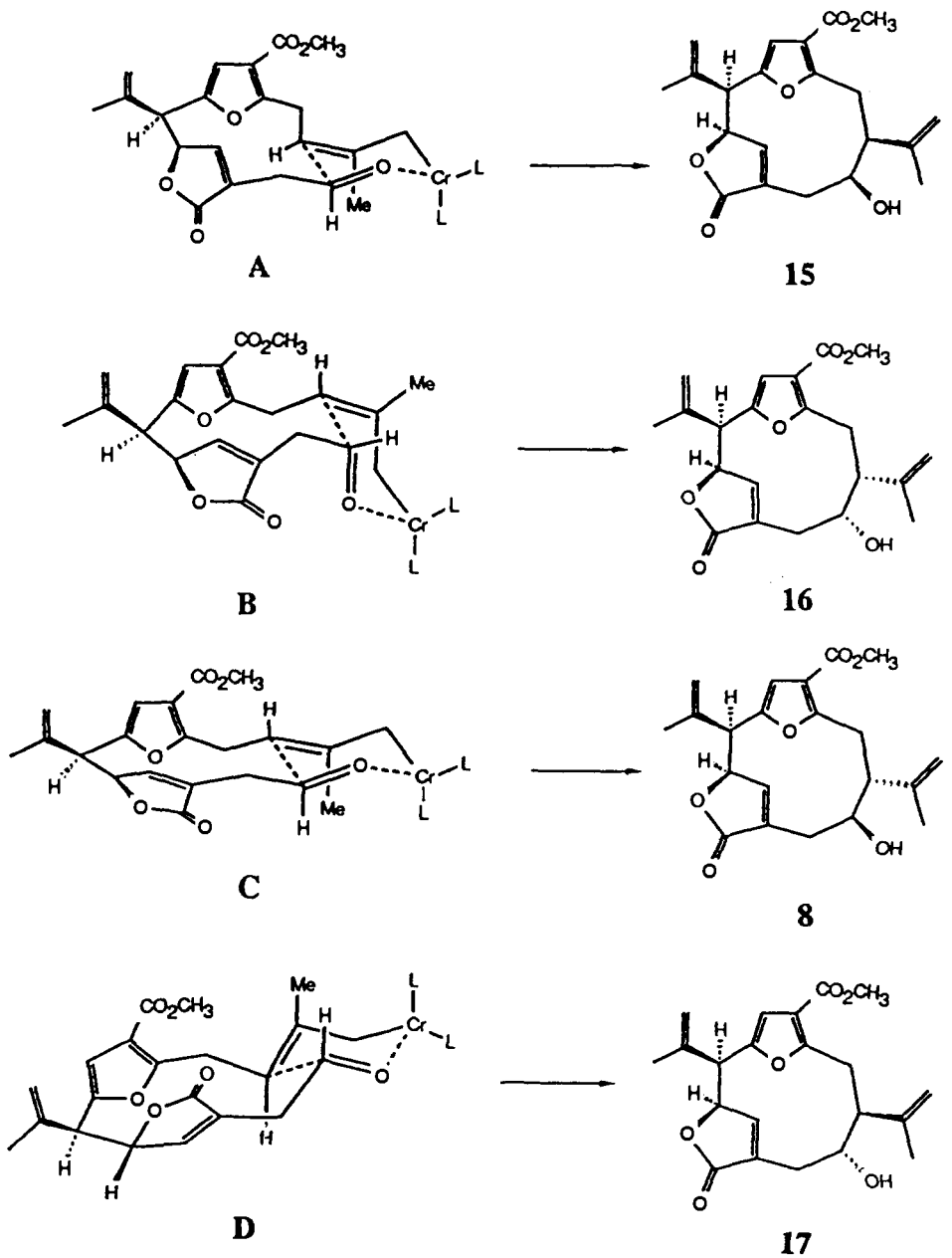


Figure 4. Diastereomeric transition states for Cr(II)-mediated macrocyclization.

and then hydrolyzed and converted to **24b** (Scheme IV). In order to establish the proper *E* relationship between the functional groups in **25**, use was made of the ability of the neighboring tetrahydropyranyl ether to direct lithium–bromide exchange[41] upon treatment of **24b** with the methyllithium–lithium bromide complex in cold 1:1 pentane–ether (a solvent system of low Lewis basicity). When this reaction was performed at −100 °C, regioselectivity levels in excess of 100:1 could be reproducibly attained.[42]

The transformation of **25** into **26** proved to be simple, although it was found necessary to use 1,2-dimethoxyethane as solvent. Recourse instead to tetrahydrofuran resulted in competitive formation of significant (~20%) amounts of unidentified decomposition products. Butenolide **27** was the sole characterizable product of the Pd(0)-promoted coupling of **12a** with **26**. Access to bromo alcohol **28b** was gained without complication as before, thereby setting the stage for oxidation to **29** (52%).

Of the various means examined for reductive cyclization of this unstable intermediate, only the Hiyama reaction[30,31] proved successful. Admixture of **29** with 20 equiv of chromium(II) chloride and activated 4-Å molecular sieves in anhydrous THF under nitrogen at room temperature resulted in stereoselective formation of a single identifiable product (25%). The spectroscopic characteristics of this homoallylic alcohol indicated the anticipated gross structure to be present. A series of 2-D NMR experiments, including $^{1}H/^{13}C$ correlation studies, led to the identification of all carbons and their attached hydrogens. The established array of connectivities proved insufficient to rigorously define the relationship between the configurations at C-1, C-7 (or C-8), and C-12 because of the need to assume a specific conformation, information about which was lacking.[43] Ultimately, the acquisition of product crystals suitable for X-ray structure analysis permitted its unequivocal identification as **17** (Figure 5).

Since questions persisted as to why **8** had not also been formed, the pair of stereoisomers were evaluated by means of the MODEL software package (version KS 2.96).[18] A multiconformer run on the macrocyclic ring with simultaneous rotation of the propenyl

(40) Fischetti, W.; Mak, K. T.; Stakem, F. G.; Kim, J.-I.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948.
(41) Corey, E. J.; Ulrich, P. *Tetrahedron Lett.* **1975**, 3685.
(42) Attempted debromination of **22a** cleanly gave rise to 2-butyn-1-ol, possibly via a vinylidene carbene[40] or a Fritsch–Buttenberg–Wiechell reaction (March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons, Inc.: New York, 1985; pp 978–980).

(43) This vexing problem has been encountered previously in furanocembranolide systems. See especially refs 4 and 6k.

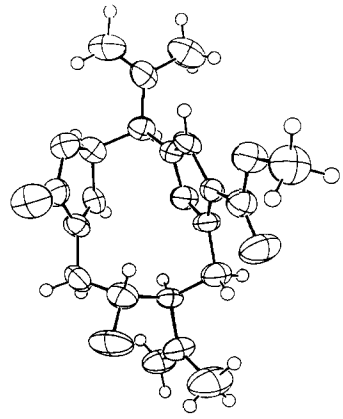
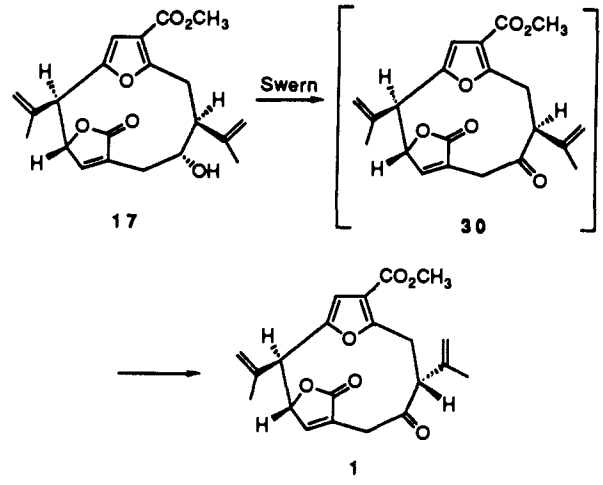


Figure 5. ORTEP drawing of **17**. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids. The hydrogen atoms are drawn with an artificial radius.

Scheme V



substituents was performed, leading to over 150 orientations for each alcohol. All were minimized to ensure discovery of the global minimum energy conformer, the further optimization of which was accomplished within MMX (Figure 6). The resulting energies of the methyl counterparts, compiled in Table I, showed **17** to be approximately 1.9 kcal/mol more thermodynamically stable than **8**. Although this energy gap is probably too small on which to base predictions, it is interesting that the experimental findings are reproduced. Perhaps transition states **C** and D in Figure 4 are productlike and mirror the energetics of the related macrocyclic alcohols.

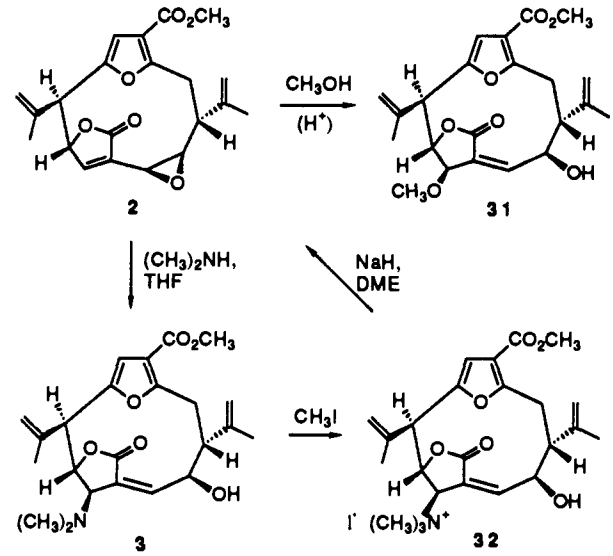
Oxidation of **17** to the ketone level proved not to be a straightforward process. Chromium(VI) reagents induced decomposition, while milder reagents such as TPAP[44] and the Dess–Martin periodinane[45] led to the loss of starting material but not to generation of a new carbonyl group. The solid-state structure of **17** (Figure 5) suggests a possible reason for this difficulty. The C-12 methine proton that must be abstracted during the requisite oxidation is positioned within the macrocyclic cavity and is sterically inaccessible to any bulky reagent.[46] Recourse was therefore made to the less sterically demanding Swern reagent (Scheme V). These conditions furnished gorgiacerone (**1**) directly in 17% yield after chromatography. The spectral properties of the product were identical with those of natural gorgiacerone,[3] and no trace of the 1-epimer **30** was detected. Epimerization of α-substituents has often been encountered during Swern oxidation,[47] and complete enolization toward an α-isopropenyl group has previously been observed, resulting in conjugation of the double bond.[48,49]

Table I. Computed Energies and Heats of Formation of Macrocyclic Alcohols **8** and **17** and Ketones **1** and **30**

compd	ΔE_{strain}, kcal/mol	ΔH, kcal/mol	ΔE_{total}, kcal/mol
	A. Alcohols		
8	36.2	−105.6	43.1
17	34.3	−108.5	41.2
	B. Ketones		
1	27.7	−100.1	32.8
30	29.2	−99.0	34.4
CI[a]	31.3	−103.6	35.5

[a] The α,β-unsaturated isomer interconnecting **1** and **30**.

Scheme VI



Our failure to detect a conjugated enone product and the stability of **1** to K_2CO_3 in refluxing methanol (12 h) or to Et_3N in CH_2Cl_2 at 20 °C (36 h) suggest that a thermodynamic bias in favor of gorgiacerone may be an underlying control element. To shed light on this issue, the strain energies of **1**, **30**, and the corresponding conjugated isomer (again as their methyl counterparts for simplification purposes) were evaluated in MODEL[18] in the manner described earlier. For each of the compounds, over 305 conformers were generated and minimized. Final MMX optimization of the three global minima provided the energy values compiled in Table I. The corresponding MACROMODEL values are 19.6, 20.5, and 24.7 kcal/mol, respectively. In line with the experimental observations, therefore, **1** is approximately 1–2 kcal/mol more stable than **30**. The α,β-unsaturated isomer is least stable, presumably beause yet another trigonal center must be accommodated by the macrocyclic ring.

Furanocembranolide Interconversions and an Attempted Synthesis of Tobagolide. The small energy differences that distinguish **8** and **17** suggested that modest structural modifications in the bromo aldehyde precursors might promote cyclization to macrocyclic alcohols having the stereochemical features shared in common by **1–3**. The tolerance of yet additional functional groups to the threo-selective Cr(II)-mediated cyclization had to be demonstrated. If successful, however, a means for incorporating

(44) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. (b) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(45) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

(46) See also: Buckle, D. R.; Houge-Frydrych, C. S. V.; Pinto, I. L.; Smith, D. G.; Tedder, J. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 63.

(47) (a) Tidwell, T. T. *Synthesis* **1990**, 857. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.

(48) Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046.

(49) More hindered bases (e.g., diisopropylethylamine) have been reported[48] to circumvent problems due to epimerization. Such modifications were not examined.

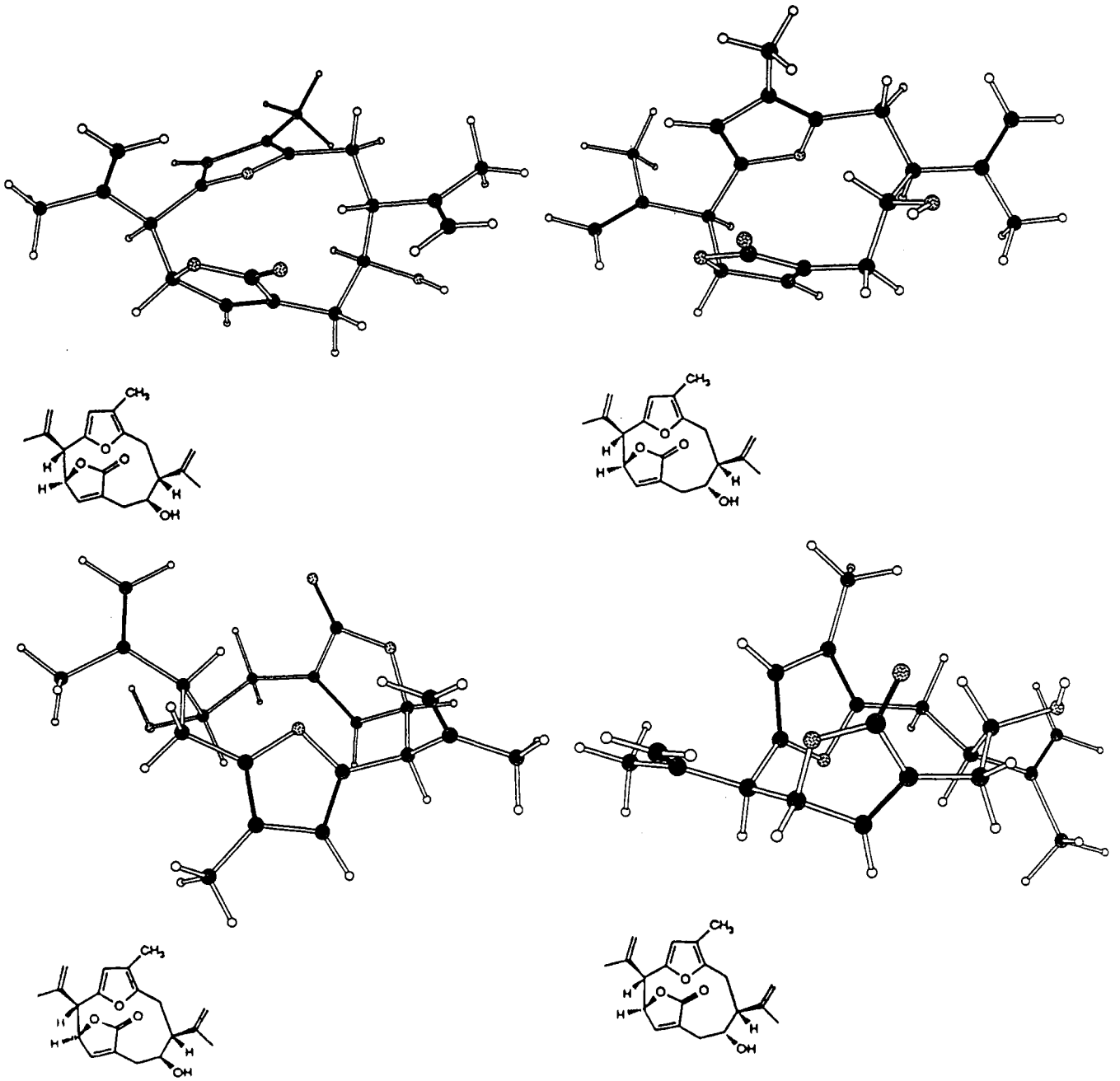


Figure 6. Global minimum energy conformations of **8** (left) and **17** (right) as determined by molecular mechanics calculations (3-D output). The top views are along a plane roughly parallel to those of the two heterocyclic rings. The views from the orthogonal direction (below) provide a better perspective of the substituents projecting from the macrocyclic ring.

the unusual arrays present in the southeastern sectors of pseudopterolide (**2**) and tobagolide (**3**) might become available.

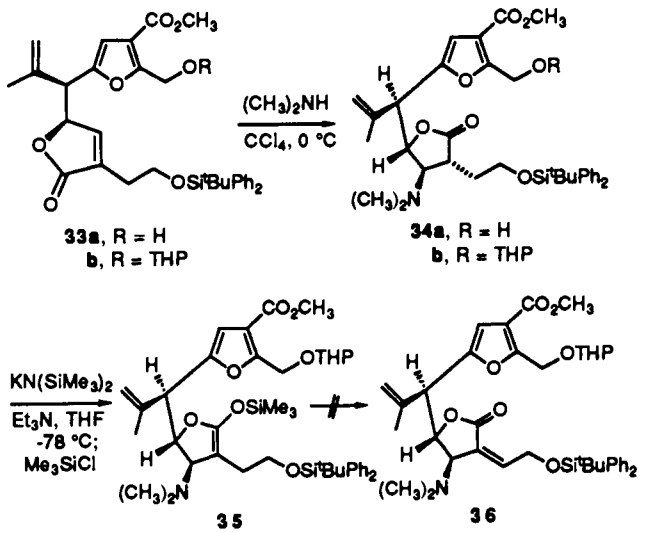
A singular prior observation by Fenical and co-workers[4] proved especially relevant to the preceding strategic analysis. This group recognized that the storage of **2** in methanol led to the formation of **31**, the nucleophilic attack being subject to acid catalysis (Scheme VI). By analogy, we reasoned that **2** should be sufficiently activated to accept dimethylamine and give rise directly to tobagolide (**3**) with concurrent release of oxirane ring strain. Indeed, exposure of **2** to anhydrous dimethylamine in tetrahydrofuran solution afforded **3** in 90% yield.[10] The reversibility of this process was accomplished as readily, provided that chemical activation was first implemented. For this purpose, **3** was reacted with methyl iodide to give the quaternary ammonium iodide **32**. Since molecular models of **32** showed its HO and $(CH_3)_3N^+$ groups to adopt a synclinal relationship, a predisposition for facile intramolecular S_N' displacement was anticipated. In actuality, treatment of **32** with sodium hydride in 1,2-dimethoxyethane at room temperature gave pseudopterolide in 90% overall yield.

An important aspect of these developments is recognized in the fact that molecules such as **17**, which lack the vinyl epoxide moiety, are remarkably inert toward dimethylamine.[50] Steric shielding inhibits the desired Michael addition, which is now no longer fostered by strain release. Consequently, functionalization at C-9 needs to be accomplished in advance of cyclization if this strategy is to be useful in the present context.

To this end, **33a**,[1] **33b**,[1] and the advanced butenolide intermediate **27** were determined to undergo highly steroselective 1,4-addition in the presence of dimethylamine to deliver **34a**, **34b**, and **37**, respectively (Scheme VII).[51] The latter condensation was accompanied by a competing isomerization leading to **38**. The trans relationship of the dimethylamino group at C-4 and the larger furyl substituent at C-5 was evident on the basis of the small degree of coupling between H-4 and H-5.[52] The relative stere-

(50) Astles, P. Unpublished findings.
(51) Farina, F.; Martin, V. M.; Sanchez, F.; Maestro, M. C.; Martin, M. R. *Heterocycles* **1983**, *20*, 1761.

Scheme VII



ochemistry at C-3 could not be comparably deduced, but is also considered to be trans as shown.

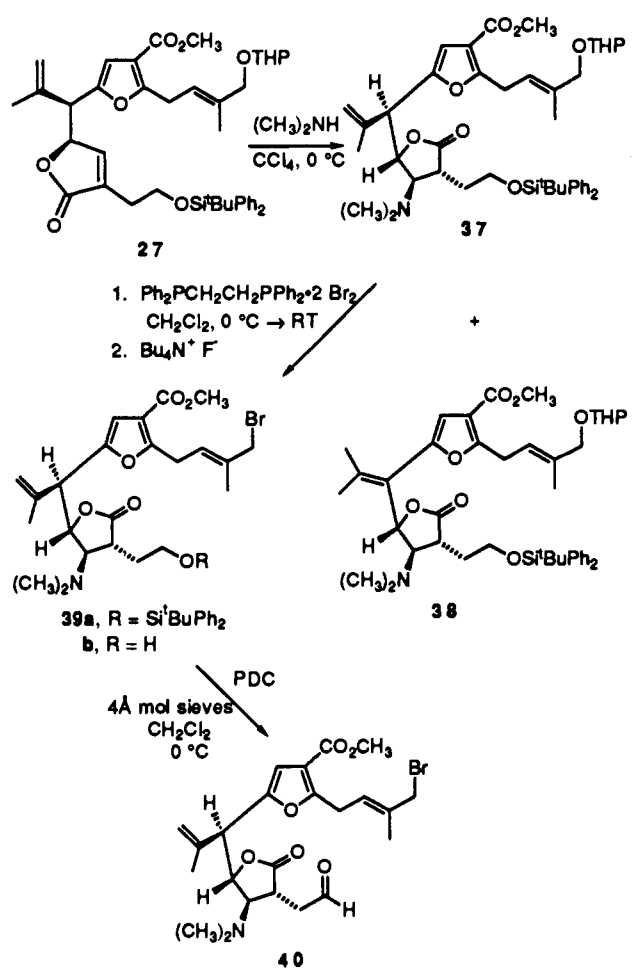
As anticipated, the enolate of **34b** could be successfully generated at low temperatures without inducing β-elimination of the amino substituent. However, the reactivity of this species was seriously limited. Thus, while conversion to silyl ketene acetal **35** could be accomplished,[53] electrophilic capture at carbon (such as phenylselenenylation or bromination) could not be successfully achieved. Loss of dimethylamine was invariably observed. All attempts to oxidize **35**[54] to **36** were similarly thwarted. In an effort to circumvent these complications, **33b** was treated with *N,N*-dimethylbenzeneselenenamide ($PhSeNMe_2$) in order to achieve direct conversion to the α-(phenylseleno)-β-(dimethylamino) lactone.[55] Unfortunately, the desired addition reaction was not observed under various conditions.

A more expedient synthesis of tobagolide was sought by converting **37** to bromide **39a** and then to **39b** and aldehyde **40** (Scheme VIII). Success in the last step was dependent on the use of freshly prepared PDC.[56] The extreme lability of **40** required its immediate use for cyclization purposes. Perhaps because of this sensitivity, the desired homoallylic alcohol was never observed following exposure of **40** to chromium(II) chloride.

Summary. Outlined herein is a practical means for appending to 2-furylmethyl bromides functionalized side chains of various types. In this context, recourse to coupling with vinylstannanes under catalysis by Pd(0) is both efficient and highly stereoselective. These attractive features permitted direct examination of several approaches for effecting ring closure by intramolecular capture of an aldehyde group. Although only one of these was successful, the particular macrocyclization proved to be a much more stereoselective process than expected. The single homoallylic alcohol so produced is the one computed by molecular mechanics methods to be thermodynamically most stable. Its availability made possible the total synthesis of gorgiacerone.

The facility with which pseudopterolide is transformed into tobagolide by reaction with dimethylamine is remarkable, especially since allied molecules lacking the activating oxirane unit are unreactive to this reagent. When sequential treatment of tobagolide with methyl iodide and sodium hydride was found to

Scheme VIII



reconstruct pseudopterolide by intramolecular S_N' displacement, effort as delineated herein was directed to accomplishing a related de novo preparation of tobagolide. While several open-chain butenolide precursors were found to undergo the necessary Michael addition of dimethylamine, the labilizing effect of this substituent adversely affected key steps later in the synthetic schemes. Alternative protocols necessarily need to be developed and are currently under investigation.

Experimental Section

Desilylation of 12a. Bromide **12a** (185 mg, 0.29 mmol) was dissolved in CH_3CN (2 mL) and treated with a 5% solution of 40% aqueous hydrofluoric acid in CH_3CN (4 mL). After 2.5 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and water (5 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic solutions were washed with brine (10 mL), dried, and concentrated in vacuo. Purification of the residue by silica gel chromatography (elution with 5–20% ethanol in petroleum ether) gave **12b** as a colorless oil (98 mg, 85%): IR (neat, cm^{-1}) 3460 (br), 2960, 1760, 1720, 1565, 1445, 1250, 1220, 1070, 785; ^1H NMR (300 MHz, C_6D_6) δ 6.46 (s, 2 H), 4.76 (s, 2 H), 4.62 (dd, J = 1.5, 7.3 Hz, 1 H), 4.47 (AB, $\Delta\nu$ = 31.6 Hz, J = 11.1 Hz, 2 H), 3.41 (t, J = 6.1 Hz, 2 H), 3.35 (s, 3 H), 3.05 (d, J = 7.3 Hz, 1 H), 2.20 (t, J = 5.9 Hz, 2 H), 1.44 (s, 3 H), hydroxyl proton not observed; ^{13}C NMR (75 MHz, C_6D_6, ppm) 173.1, 162.9, 155.0, 153.2, 147.8, 140.8, 132.9, 116.9, 115.7, 109.5, 80.1, 60.2, 51.3, 50.2, 29.1, 21.4, 21.3; MS m/z (M^+ – Br) calcd 319.1181, obsd 319.1240; MS (CI) m/z (M^+ – 1) calcd 399.04, obsd 399.00.

(*E*)-[2-Methyl-3-(trimethylsilyl)-1-propenyl]trimethylstannane (11). A solution of **10**[27] (940 mg, 3.7 mmol) in cold (–78 °C) tetrahydrofuran (20 mL) was treated dropwise with *tert*-butyllithium (4.4 mL of 1.7 M in pentane, 7.5 mmol). After 45 min at this temperature, the yellow solution was transferred via cannula into a precooled (–78 °C) solution of trimethyltin chloride (740 mg, 3.7 mmol) in THF (10 mL). The reaction mixture was stirred at –78 °C for 1 h and then allowed to warm slowly to room temperature over 2 h. After an additional hour, saturated aqueous NH_4Cl solution (1 mL) was introduced, followed by water (10

(52) (a) Haasnoot, C. A. G.; deLeeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783. (b) Haasnoot, C. A. G.; deLeeuw, F. A. A. M.; de Leeuw, H. P. M.; Altona, C. *Org. Magn. Res.* **1981**, *15*, 43.

(53) Dell, C. P.; Khan, K. M.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1989**, 1812.

(54) For example, see: (a) Kawabata, T.; Grieco, P. A.; Sham, H.-L.; Kim, H.; Jaw, J. Y.; Tu, S. *J. Org. Chem.* **1987**, *52*, 3346. (b) Van Hijfte, L.; Little, R. D.; Petersen, J. L.; Moeller, K. D. *J. Org. Chem.* **1987**, *52*, 4647.

(55) Reich, H. J.; Renga, J. M. *J. Org. Chem.* **1975**, *40*, 3313.

(56) (a) Reference 36. (b) Czernecki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakurnaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699.

mL) and petroleum ether (50 mL). The separated organic phase was washed with water (20 mL), saturated $NaHCO_3$ solution (20 mL), and water (2 × 20 mL) and then dried. Volatiles were removed by distillation through an 8-in. Vigreux column at atmospheric pressure. Kugelrohr distillation of the residue at 100–120 °C and 20 Torr gave **11** as a colorless liquid (650 mg, 60%): IR (neat, cm^{-1}) 2960, 2915, 1595, 1380, 1250, 1155, 860, 840, 770, 700; ^1H NMR (300 MHz, C_6D_6) δ 5.47 (s, 1 H), 1.86 (s, 3 H), 1.80 (s, 2 H), 0.32 (s, 9 H), 0.13 (s, 9 H) (the smaller satellite signals due to ^1H–Sn coupling are not reported); ^{13}C NMR (75 MHz, C_6D_6, ppm) 153.1, 120.7, 33.6, 26.8, -1.3, 8.7; MS m/z ($M^+ - CH_3$) calcd 275.0431, obsd 275.0436.

Palladium(0)-Catalyzed Coupling of 11 to 12b. A solution of **12b** (130 mg, 0.326 mmol) in benzene (10 mL) was treated in turn with **11** (140 mg, 0.49 mmol) and tetrakis(triphenylphosphine)palladium (11 mg, 9.7 μmol). The reaction mixture was flushed with nitrogen, heated under reflux at 70–75 °C for 33 h, cooled, and diluted with ether (50 mL). Filtration of this material through a thin pad of Florisil with ether rinsing (30 mL) gave a filtrate that was concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 5–20% isopropyl alcohol in petroleum ether). There was recovered 37.5 mg (29%) of **12b** in addition to 32.5 mg of **13** (51% based on unreacted starting material) as a colorless oil: IR (neat, cm^{-1}) 3410, 2960, 2920, 1765, 1715, 1565, 1440, 1250, 1225, 1070, 850; ^1H NMR (300 MHz, C_6D_6) δ 6.57 (d, J = 1.3 Hz, 1 H), 6.56 (s, 1 H), 5.25 (t, J = 7.5 Hz, 1 H), 4.80 (d, J = 3.9 Hz, 2 H), 4.73 (dd, J = 1.5, 7.5 Hz, 1 H), 3.82 (d, J = 7.4 Hz, 2 H), 3.55–3.38 (m, 5 H), 3.20 (d, J = 7.3 Hz, 1 H), 2.25 (t, J = 6.0 Hz, 2 H), 1.84 (br s, 1 H), 1.69 (s, 3 H), 1.49 (s, 3 H), 1.44 (s, 2 H), -0.30 (s, 9 H); MS (CI) m/z (M + 1) calcd 447.22, obsd 447.00.

Oxidation of 13. To a magnetically stirred suspension of crushed 4-Å molecular sieves (30 mg) and pyridinium dichromate (16 mg, 43 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added a solution of **13** (9.5 mg, 21 μmol) in the same solvent (0.5 mL). The reaction mixture was stirred at 0 °C for 2.5 h, diluted with ether (20 mL), and filtered through a thin pad of Florisil. The precipitate was rinsed with ether (40 mL), and the combined filtrates were concentrated. The product was dried by azeotropic distillation with benzene (30 mL) to give **14** as a colorless oil (6 mg, 64%), which was used directly: IR ($CHCl_3$, cm^{-1}) 2950, 2920, 2870, 2850, 1755, 1710, 1445, 1435, 1250, 1215, 1110, 1075, 1040, 850; ^1H NMR (300 MHz, C_6D_6) δ 9.01 (s, 1 H), 6.70 (d, J = 1.4 Hz, 1 H), 6.55 (s, 1 H), 5.26 (t, J = 7.2 Hz, 1 H), 4.85–4.70 (m, 3 H), 3.82 (d, J = 7.2 Hz, 2 H), 3.47 (s, 3 H), 3.18 (d, J = 7.5 Hz, 1 H), 2.70 (d, J = 0.8 Hz, 2 H), 1.69 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 2 H), -0.03 (s, 9 H).

(*Z*)-1-Iodo-2-methyl-3-(2-tetrahydropyranyloxy)-1-propene (18b). To a cold (-10 °C), mechanically stirred slurry of propargyl alcohol (4.48 g, 0.08 mol) and cuprous iodide (1.52 g, 8 mmol) in ether (100 mL) was added methylmagnesium bromide (67 mL of 3.0 M in ether, 0.20 mol) dropwise during 1 h. After 20 h at -10 °C, a solution of iodine (54 g, 0.21 mol) in THF (20 mL) was introduced dropwise, and the reaction mixture was stirred at -10 °C for 1 h and at 0 °C for 5 h. Following treatment with saturated NH_4Cl solution (20 mL), warming to room temperature was allowed to occur, excess iodine was removed by washing with sodium thiosulfate solution, and the layers were separated. The aqueous phase was extracted with ether (3 × 50 mL), and the combined organic solutions were washed with brine (30 mL), dried, and filtered. Volatiles were removed by distillation through a 12-in. Vigreux column at atmospheric pressure, and the residue was distilled in a Kugelrohr apparatus at 100–150 °C and 20 Torr to give a brown oil. This was redistilled at 25–70 °C and 0.5 Torr (collector at -78 °C) to give iodo alcohol **18a** as a yellowish oil (3.41 g, 21%): ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (s, 1 H), 4.24 (s, 2 H), 1.98 (s, 3 H), 1.71 (br s, 1 H).[33]

A solution of the above alcohol (3.40 g, 17.2 mmol) in CH_2Cl_2 (30 mL) at 0 °C was treated with dihydropyran (1.59 g, 18.9 mmol) followed by *p*-toluenesulfonic acid (50 mg). After 20 min, the reaction mixture was allowed to warm to room temperature, stirred for 2 h, and diluted with petroleum ether (50 mL). This solution was washed with 1 M NaOH solution (2 × 10 mL) and brine (10 mL) prior to drying and solvent evaporation. The residue was chromatographed on silica gel (elution with 100% petroleum ether → 100% ether) to give 3.81 g (79%) of **18b** as a colorless liquid: IR (neat, cm^{-1}) 2940, 2870, 2850, 1455, 1440, 1350, 1285, 1265, 1205, 1120, 1080, 1055, 1035, 1025, 980, 910, 875; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (d, J = 1.1 Hz, 1 H), 4.62 (t, J = 3.0 Hz, 1 H), 4.20 (AB, $\Delta\nu$ = 30.1 Hz, J = 12.3 Hz, 2 H), 4.0–3.80 (m, 1 H), 3.65–3.45 (m, 1 H), 1.94 (d, J = 1.3 Hz, 3 H), 1.85–1.50 (series of m, 6 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 144.4, 98.1, 75.2, 71.8, 62.1, 30.5, 25.4, 21.8, 19.3; MS m/z ($M^+ - I$) calcd 155.1072, obsd 155.1077.

(*Z*)-[2-Methyl-3-(2-tetrahydropyranyloxy)-1-propenyl]trimethylstannane (19). A solution of **18b** (2.03 g, 7.19 mmol) in THF (10 mL) at -78 °C was treated dropwise with *tert*-butyllithium (8.5 mL of 1.7 M in pentane, 14.4 mmol). After 45 min at this temperature, this solution was transferred via cannula into a cold (-78 °C) solution of trimethyltin chloride (1.43 g, 7.20 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h at -78 °C and allowed to warm to room temperature over 1 h. After an additional hour, saturated aqueous NH_4Cl solution (5 mL) and petroleum ether (20 mL) were introduced, and the separated organic phase was washed with water (2 × 20 mL) and saturated $NaHCO_3$ solution (20 mL). The combined aqueous layers were extracted with petroleum ether (2 × 40 mL), and the organic phases were combined and dried. After solvent removal in vacuo, the residue was distilled at 110 °C and 0.3 Torr in a Kugelrohr apparatus to give **19** as a colorless oil (1.38 g, 60%): IR (neat, cm^{-1}) 2950, 2875, 2850, 1445, 1205, 1185, 1160, 1125, 1080, 1040, 1020, 980, 910, 770; ^1H NMR (300 MHz, C_6D_6) δ 5.77 (s, 1 H), 4.53 (t, J = 3.7 Hz, 1 H), 4.30 (d, J = 12.4 Hz, 1 H), 3.90 (d, J = 12.4 Hz, 1 H), 3.82–3.70 (m, 1 H), 3.37–3.25 (m, 1 H), 1.91 (s, 3 H), 1.80–1.50 (m, 3 H), 1.40–1.15 (m, 3 H), 0.24 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 151.3, 127.0, 98.3, 72.1, 62.3, 31.0, 25.8, 24.5, 20.0, -8.0; MS m/z (M^+) calcd 318.0794, obsd 318.0802.

Palladium(0)-Catalyzed Coupling of 12a to 19. To a solution of **12a** (260 mg, 0.41 mmol) in deoxygenated 1,2-dimethoxyethane (5 mL) was added **19** (156 mg, 0.49 mmol) followed by tetrakis(triphenylphosphine)palladium (43 mg, 0.041 mmol). The reaction mixture was flushed with nitrogen, heated under reflux at 75–80 °C for 16 h, and allowed to cool. Ether (50 mL) was introduced, and the insolubles were removed by filtration through a thin pad of anhydrous $MgSO_4$. The filtrate was evaporated and the residue purified by column chromatography on silica gel (elution with 5–20% ethyl acetate in petroleum ether). There was isolated 172 mg (59%) of **20** as a colorless oil: IR (neat, cm^{-1}) 2930, 2860, 1765, 1720, 1570, 1440, 1430, 1220, 1115, 1080, 1030, 705; ^1H NMR (300 MHz, C_6D_6) δ 7.80–7.65 (m, 4 H), 7.30–7.15 (m, 6 H), 6.67 (s, 1 H), 6.58 (s, 1 H), 5.56 (t, J = 7.0 Hz, 1 H), 4.90–4.75 (m, 3 H), 4.66 (t, J = 3.2 Hz, 1 H), 4.30 (AB, $\Delta\nu$ = 11.8 Hz, J = 11.8 Hz, 2 H), 3.90 (d, J = 7.1 Hz, 2 H), 3.85–3.75 (m, 1 H), 3.74 (t, J = 6.2 Hz, 2 H), 3.47 (s, 3 H), 3.45–3.35 (m, 1 H), 3.15 (d, J = 7.9 Hz, 1 H), 2.40 (t, J = 6.2 Hz, 2 H), 1.79 (s, 3 H), 1.65–1.55 (m, 2 H), 1.47 (s, 3 H), 1.40–1.15 (series of m, 4 H), 1.12 (s, 9 H); MS (FAB) m/z ($M^+ - C_5H_9O_2$) calcd 611.28, obsd 611.27.

Bromide 21a. A cold (0 °C) solution of 1,2-bis(diphenylphosphino)-ethane (144 mg, 0.362 mmol) in CH_2Cl_2 (3 mL) was treated dropwise with bromine (37 μL, 115 mg, 0.725 mmol). After 5 min, a solution of **20** (172 mg, 0.241 mmol) in the same solvent (2 mL) was added via cannula, and any residual material was washed in with more CH_2Cl_2 (2 mL). The reaction mixture was allowed to warm to room temperature, stirred for 6 h, diluted with ether (50 mL), and filtered through a thin pad of anhydrous $MgSO_4$. Following solvent evaporation, the residue was purified by column chromatography on silical gel (elution with 5–20% ethyl acetate in petroleum ether) to give **21a** as a colorless oil (105 mg, 63%): IR (neat, cm^{-1}) 2950, 2930, 2860, 1765, 1720, 1570, 1470, 1440, 1430, 1220, 1115, 1080, 745, 700; ^1H NMR (300 MHz, C_6D_6) δ 7.80–7.65 (m, 4 H), 7.30–7.15 (m, 6 H), 6.65 (s, 1 H), 6.55 (s, 1 H), 5.38 (t, J = 7.6 Hz, 1 H), 4.90–4.70 (m, 3 H), 3.82 (s, 2 H), 3.73 (t, J = 6.1 Hz, 2 H), 3.65 (d, J = 7.5 Hz, 2 H), 3.46 (s, 3 H), 3.12 (d, J = 7.8 Hz, 1 H), 2.39 (t, J = 5.0 Hz, 2 H), 1.60 (s, 3 H), 1.48 (s, 3 H), 1.12 (s, 9 H); MS (CI) m/z ($M^+ + 1$) calcd 691.20, obsd 691.00.

Desilylation of 21a. To a solution of **21a** (16 mg, 23 mmol) in CH_3CN (1 mL) was added a 5% solution of 40% aqueous hydrofluoric acid in CH_3CN (2 mL). After 1.75 h, CH_2Cl_2 (20 mL) and water (5 mL) were introduced, and the separated aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic solutions were washed with brine (5 mL), dried, and evaporated. The residue was subjected to silica gel chromatography (elution with 5 → 20% ethanol in petroleum ether) to give **21b** as a colorless oil (7 mg, 67%): IR (neat, cm^{-1}) 3450 (br), 2950, 2920, 1765, 1715, 1610, 1570, 1440, 1220, 1075; ^1H NMR (300 MHz, C_6D_6) δ 6.51 (s, 1 H), 6.47 (d, J = 1.3 Hz, 1 H), 5.39 (t, J = 7.5 Hz, 1 H), 4.90–4.70 (m, 2 H), 4.67 (dd, J = 1.4, 7.0 Hz, 1 H), 3.82 (AB, $\Delta\nu$ = 7.1 Hz, J = 10.0 Hz, 2 H), 3.66 (d, J = 7.5 Hz, 2 H), 3.45 (s, 3 H), 3.38 (t, J = 6.0 Hz, 2 H), 3.12 (d, J = 7.0 Hz, 1 H), 2.17 (t, J = 6.0 Hz, 2 H), 1.62 (s, 3 H), 1.48 (s, 3 H) (no hydroxyl proton seen); ^{13}C NMR (75 MHz, C_6D_6, ppm) 173.0, 163.9, 159.3, 151.1, 147.8, 141.2, 134.6, 132.9, 124.9, 115.3, 114.3, 108.8, 80.4, 60.2, 51.1, 50.1, 31.6, 29.1, 26.7, 21.8, 21.5; MS (CI) m/z ($M^+ - 1$) calcd 455, obsd 455.

Oxidation of 21b. To a suspension of crushed activated 4-Å molecular sieves (50 mg) and pyridinium dichromate (30 mg, 0.105 mmol) in CH_2Cl_2 (1 mL) at 0 °C under nitrogen was added a solution of **21b** (19 mg, 42 mmol) in the same solvent (2 mL) via cannula. Residual alcohol was rinsed in with additional CH_2Cl_2 (1 mL), and the reaction mixture was stirred at 0 °C for 2.5 h. Ether (50 mL) was introduced, and the insolubles were removed by filtration through a thin pad of anhydrous $MgSO_4$. The solvent was evaporated, and the residue was azeotroped with benzene (20 mL) to give **22** (15 mg, 79%) as a colorless oil, which was used without further purification: ^1H NMR (300 MHz, C_6D_6) δ

9.00 (s, 1 H), 6.69 (s, 1 H), 6.59 (s, 1 H), 5.41 (t, J = 7.0 Hz, 1 H), 4.90–4.65 (m, 3 H), 3.83 (AB, $\Delta\nu$ = 6.9 Hz, J = 10.2 Hz, 2 H), 3.60 (d, J = 7.0 Hz, 2 H), 3.45 (s, 3 H), 3.11 (d, J = 7.0 Hz, 1 H), 2.68 (br s, 2 H), 1.61 (s, 3 H), 1.48 (s, 3 H).

1,1-Dibromo-2-methyl-1-propen-3-ol (24a). A mixture of tribromide **23**[40] (15.1 g, 51.5 mmol), water (100 mL), and K_2CO_3 (9.30 g, 67.4 mmol) was heated at 80 °C for 22 h. The cooled reaction mixture was saturated with NaCl and extracted with ether (5 × 30 mL). The combined organic phases were washed with brine (20 mL), dried, and evaporated. Distillation of the residue in a Kugelrohr apparatus at 80–100 °C and 1 Torr gave **24a** as a colorless oil (7.94 g, 67%): IR (neat, cm^{-1}) 3340, 2930, 2890, 1595, 1435, 1380, 1240, 1210, 1015, 810; ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (s, 2 H), 1.99 (s, 3 H), 1.85–1.70 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 141.00, 87.87, 66.03, 20.77; MS m/z (M^+) calcd 227.8785, obsd 227.8779.

The tetrahydropyranyl ether **24b** was prepared by treating a cold (0 °C) solution of **24a** (19.08 g, 82.9 mmol) in CH_2Cl_2 (150 mL) with dihydropyran (10.5 g, 124 mmol) followed by *p*-toluenesulfonic acid (500 mg). After 20 min, the reaction mixture was allowed to warm to room temperature and stirred overnight. Following dilution with ether (100 mL), the solution was washed with 1 M NaOH (3 × 30 mL) and brine (50 mL) prior to drying and solvent evaporation in vacuo. Purification of the residue by silica gel chromatography (elution with 5 → 20% ether in petroleum ether) furnished the desired product as a colorless liquid (18.2 g, 70%): IR (neat, cm^{-1}) 2950, 2880, 2860, 1470, 1455, 1445, 1390, 1375, 1350, 1330, 1290, 1265, 1205, 1190, 1155, 1135, 1080, 1060, 1035, 1025, 975, 910, 875, 820; ^1H NMR (300 MHz, $CDCl_3$) δ 4.65–4.55 (m, 1 H), 4.24 (s, 2 H), 3.92–3.78 (m, 1 H), 3.60–3.45 (m, 1 H), 1.95 (s, 3 H), 1.85–1.50 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 139.2, 98.1, 88.1, 69.6, 62.2, 30.5, 25.4, 20.9, 19.3; MS m/z ($M^+ - C_5H_9O_2$) calcd 210.8757, obsd 210.8804.

(*E*)-1-Bromo-2-methyl-3-(2-tetrahydropyranyloxy)propene (25). To a cold (−100 °C), magnetically stirred solution of **24b** (500 mg, 1.60 mmol) in anhydrous ether (10 mL) and pentane (10 mL) under nitrogen was added a solution of the methyllithium–lithium bromide complex (1.70 mL of 1.30 M in ether, 2.30 mmol) in ether (5 mL) dropwise over 5 min. After an additional 2 min at −100 °C, methanol (1 mL) was introduced, and the reaction mixture was allowed to warm to room temperature. Ether (20 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic solutions were washed with brine (20 mL), dried, and concentrated. Kugelrohr distillation of the residue at 100 °C and 1 Torr furnished **25** as a clear colorless liquid (300 mg, 88%), the ^1H NMR analysis of which showed the isomeric ratio to be approximately 135 to 1: IR (neat, cm^{-1}) 2950, 2880, 2860, 1640, 1470, 1460, 1445, 1385, 1350, 1295, 1205, 1125, 1080, 1060, 1040, 1025, 980, 910, 875, 820, 790, 630; ^1H NMR (300 MHz, $CDCl_3$) δ 6.24 (quintet, J = 1.3 Hz, 1 H), 4.61 (t, J = 3.4 Hz, 1 H), 4.15 (d, J = 12.6, 1 H), 3.93 (dd, J = 12.6, 1.0 Hz, 1 H), 3.90–3.88 (m, 1 H), 3.60–3.45 (m, 1 H), 1.82 (s, 3 H), 1.90–1.40 (series of m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 138.6, 104.7, 97.6, 70.2, 62.1, 30.5, 25.4, 19.3, 17.1; MS m/z ($M^+ - C_5H_9O_2$) calcd 132.9652, obsd 132.9683.

(*E*)-[2-Methyl-3-(2-tetrahydropyranyloxy)-1-propenyl]trimethylstannane (26). To a cold (−78 °C) solution of **25** (330 mg, 1.40 mmol) in 1,2-dimethoxyethane (10 mL) and tetrahydrofuran (5 mL) was added *tert*-butyllithium (1.82 mL of 1.7 M in pentane, 3.09 mmol) dropwise. After 1 h at −78 °C, a solution of trimethyltin chloride (335 mg, 1.69 mmol) in THF (2 mL) was introduced, and the reaction mixture was stirred for 1 h at −78 °C and 1 h at room temperature. After recooling to −10 °C, a saturated NH_4Cl solution (5 mL) and petroleum ether (20 mL) were added, followed by further dilution with water (5 mL) and extraction of the aqueous layer with petroleum ether (2 × 20 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated in vacuo. The residue was purified by bulb-to-bulb distillation (100–130 °C, 0.3 Torr) to give **26** as a colorless oil (280 mg, 63%): IR (neat, cm^{-1}) 2950, 2880, 2860, 1620, 1470, 1455, 1445, 1380, 1355, 1345, 1325, 1205, 1130, 1115, 1080, 1040, 1030, 910, 875, 805, 775; ^1H NMR (300 MHz, C_6D_6) δ 6.04 (s, 1 H), 4.67 (t, J = 3.3 Hz, 1 H), 4.27 (dd, J = 0.6, 13.1 Hz, 1 H), 3.93 (dd, J = 1.1, 13.0 Hz, 1 H), 3.81 (dt, J = 3.1, 11.4 Hz, 1 H), 3.45–3.33 (m, 1 H), 1.76 (s, 3 H), 1.90–1.50 (series of m, 4 H), 1.45–1.20 (m, 2 H), 0.16 (s, 9 H) (the smaller satellite signals due to ^1H–Sn coupling are not reported); ^{13}C NMR (75 MHz, C_6D_6, ppm) 151.1, 123.8, 97.4, 72.9, 61.2, 30.7, 25.6, 21.0, 19.3, −6.6; MS m/z ($M^+ - CH_3$) calcd 303.0559, obsd 303.0519.

Palladium(0)-Catalyzed Coupling of 12a to 26. To a solution of **12a** (235 mg, 0.369 mmol) in benzene (10 mL) was added **26** (141 mg, 0.443 mmol) followed by tetrakis(triphenylphosphine)palladium (21 mg, 18 μmol). The reaction mixture was flushed with nitrogen, heated at the reflux temperature for 36 h, and allowed to cool. Concentration in vacuo followed by column chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether) provided 146 mg (56%) of **27** as a colorless oil: IR (neat, cm^{-1}) 2940, 2860, 1765, 1720, 1570, 1440, 1430, 1220, 1115, 1075, 1040, 1025, 710; ^1H NMR (300 MHz, C_6D_6) δ 7.77–7.65 (m, 4 H), 7.30–7.20 (m, 6 H), 6.68 (d, J = 1.2 Hz, 1 H), 6.56 (s, 1 H), 5.76 (t, J = 6.4 Hz, 1 H), 4.85–4.65 (m, 3 H), 4.58 (br s, 1 H), 4.13 (d, J = 12.1 Hz, 1 H), 3.90–3.70 (m, 6 H), 3.46 (s, 3 H), 3.40–3.28 (m, 1 H), 3.14 (d, J = 8.0 Hz, 1 H), 2.40 (t, J = 6.1 Hz, 2 H), 1.73 (s, 3 H), 1.65–1.55 (m, 3 H), 1.47 (s, 3 H), 1.45–1.20 (m, 3 H), 1.16 (s, 9 H); MS (FAB) m/z ($M + Na^+$) calcd 735.34, obsd 735.39.

Bromide 28a. A solution of 1,2-bis(diphenylphosphino)ethane (480 mg, 1.2 mmol) in CH_2Cl_2 (16 mL) at 0 °C was treated dropwise with bromine (125 μL, 2.16 mmol). After 5 min, a solution of **27** (560 mg, 0.79 mmol) in the same solvent (8 mL) was added via cannula. The reaction mixture was stirred at 0 °C for 2 h, diluted with ether (50 mL), and filtered through a thin pad of silica gel. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) to give **28a** as a light tan oil (92 mg, 77%); IR (neat, cm^{-1}) 2970, 2950, 2880, 1770, 1725, 1445, 1435, 1230, 1120, 1090, 715; ^1H NMR (300 MHz, C_6D_6) δ 7.80–7.65 (m, 4 H), 7.30–7.17 (m, 6 H), 6.66 (d, J = 1.5 Hz, 1 H), 6.54 (s, 1 H), 5.51 (t, J = 6.7 Hz, 1 H), 4.88–4.70 (m, 3 H), 3.73 (t, J = 6.3 Hz, 2 H), 3.59 (d, J = 7.4 Hz, 2 H), 3.54 (s, 2 H), 3.45 (s, 3 H), 3.13 (d, J = 8.0 Hz, 1 H), 2.39 (t, J = 6.1 Hz, 2 H), 1.66 (s, 3 H), 1.48 (s, 3 H), 1.12 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 172.4, 163.8, 159.5, 151.4, 147.3, 141.3, 135.9, 135.2, 134.8, 132.9, 130.1, 129.7, 124.9, 115.2, 114.2, 108.7, 80.1, 61.9, 51.0, 50.5, 40.4, 28.9, 27.1, 26.8, 21.3, 19.4, 14.8; MS (FAB) m/z ($M + 1$) calcd 691.21, obsd 691.34.

Desilylation of 28a. To a solution of **28a** (143 mg, 0.206 mmol) in CH_3CN (3 mL) was added a 5% solution of 40% aqueous hydrofluoric acid in CH_3CN (2 mL). After 2.25 h of stirring, CH_2Cl_2 (20 mL) and water (5 mL) were introduced, and the separated aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic solutions were dried and concentrated to leave a residue; purification of the residue by chromatography on silica gel (elution with 10% isopropyl alcohol in petroleum ether) gave **28b** as a colorless oil (58 mg, 62%): IR (neat, cm^{-1}) 3420, 2920, 2900, 2830, 1745, 1700, 1555, 1430, 1370, 1300, 1210, 1060, 770; ^1H NMR (300 MHz, C_6D_6) δ 6.54 (d, J = 1.5 Hz, 1 H), 6.51 (s, 1 H), 5.53 (t, J = 7.0 Hz, 1 H), 4.90–4.65 (m, 3 H), 3.60 (d, J = 7.3 Hz, 2 H), 3.57 (s, 2 H), 3.50–3.35 (m, 2 H), 3.45 (s, 2 H), 3.14 (d, J = 7.2 Hz, 1 H), 2.23 (t, J = 6.0 Hz, 2 H), 1.67 (s, 3 H), 1.49 (s, 3 H) (hydroxyl proton not observed); ^{13}C NMR (75 MHz, C_6D_6, ppm) 173.0, 163.8, 159.5, 151.1, 147.6, 141.2, 134.9, 132.9, 124.9, 115.3, 114.3, 108.8, 80.4, 60.2, 51.0, 50.2, 40.5, 29.1, 27.1, 21.5, 14.8; MS (CI) m/z ($M + 1$) calcd 453.08, obsd 453.00.

Oxidation of 28b. To a suspension of crushed activated 4-Å molecular sieves (70 mg) and freshly prepared pyridinium dichromate (62 mg, 0.166 mmol) in CH_2Cl_2 (1 mL) at 0 °C under nitrogen was added a solution of **28b** (30 mg, 66 mmol) in CH_2Cl_2 (2 mL) via cannula. The reaction mixture was stirred at 0 °C for 2.5 h. Ether (50 mL) was introduced, and the insolubles were separated by filtration through a thin pad of Florisil. The filtrate was concentrated in vacuo and azeotroped with benzene (20 mL) to give **29** (15.6 mg, 52%) as an unstable colorless oil, which was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1 H), 6.68 (d, J = 1.4 Hz, 1 H), 6.50 (s, 1 H), 5.52 (t, J = 7.0 Hz, 1 H), 4.79 (m, 2 H), 4.69 (m, 1 H), 3.60 (d, J = 7.4 Hz, 2 H), 3.56 (s, 2 H), 3.44 (s, 3 H), 3.12 (d, J = 7.2 Hz, 1 H), 2.72 (s, 2 H), 1.66 (s, 3 H), 1.48 (s, 3 H).

Cyclization of 29. A solution of **29** (35 mg, 0.08 mmol) in dry THF (10 mL) was added to a suspension of chromium(II) chloride (184 mg, 1.5 mmol) and crushed activated 4-Å molecular sieves (500 mg) in the same solvent (90 mL). The reaction mixture was stirred vigorously at room temperature under nitrogen for 6 h before being quenched with water (10 mL). The supernatant was decanted, concentrated to a volume of ca. 20 mL, and extracted with ether (3 × 20 mL). The combined organic phases were washed with water (10 mL) and brine (15 mL), dried, and concentrated. The residue was chromatographed on silica gel (elution with 40% ethyl acetate in petroleum ether) to give 7.5 mg (25%) of **17**; slow crystallization of the product from chloroform–hexane afforded colorless cubic crystals, mp 151–152 °C: IR ($CHCl_3$, cm^{-1}) 3460, 1760, 1710, 1560, 1440, 1220, 1170, 1075, 900, 780; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1 H), 6.42 (s, 1 H), 5.45 (br s, 1 H), 5.39 (s, 1 H), 5.21 (s, 1 H), 5.17 (br s, 1 H), 4.96 (br s, 1 H), 3.77 (s, 3 H), 3.75 (s, 1 H), 3.65 (dd, J = 13.2, 15.0 Hz, 1 H), 3.01 (m, 1 H), 2.87 (dd, J = 2.6, 13.2 Hz, 1 H), 2.67 (dd, J = 2.9, 15.1 Hz, 1 H), 2.55 (m, 2 H), 1.97 (s, 3 H), 1.93 (s, 3 H) (hydroxyl proton not observed); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 171.9, 163.8, 158.8, 150.5, 148.5, 144.5, 139.4, 128.7, 116.5, 115.6, 114.1, 80.7, 69.3, 57.4, 49.4, 47.7, 35.3, 30.4, 24.0, 23.4; MS (M^+) calcd 372.1551, obsd 372.1571.

Oxidation of 17. Gorgiacerone (1). A solution of freshly distilled oxalyl chloride (20 μL, 0.23 mmol) in dry CH_2Cl_2 (1.5 mL) was cooled

to −60 °C under N_2. Dimethyl sulfoxide (40 μL, 0.60 mmol) in CH_2Cl_2 (50 μL) was introduced dropwise, and the reaction mixture was stirred for 20 min before being treated with a solution of **17** (6 mg, 0.016 mmol) in CH_2Cl_2 (50 μL). After 30 min, triethylamine was added for quenching purposes, followed 30 min later by water (0.5 mL) and ether (10 mL). The separated organic phase was washed sequentially with 1-mL portions of 5% $KHSO_4$ solution, water, and brine prior to filtration through a small pad of Florisil. Concentration gave a residue that was purified by silica gel chromatography (elution with 30% ethyl acetate in petroleum ether) to give 2 mg of material. Further purification by HPLC afforded 1 mg (17%) of gorgiacerone (**1**), identical by IR, ^1H NMR (300 MHz), ^{13}C NMR (500 MHz), and TLC to an authentic sample of the natural material.

Addition of Dimethylamine to 33a. A solution of **33a** (360 mg, 0.62 mmol) in dry CCl_4 was cooled to 0 °C, and approximately 0.5 mL of dimethylamine was condensed into the flask. The reaction mixture was stirred at 0 °C for 24 h, and the solvent was removed in vacuo. The residue was chromatographed on silica gel (elution with 5:5:1 petroleum ether–ethyl acetate–methanol) to give 240 mg (61%) of **34a** as a pale yellow oil: IR (neat, cm^{-1}) 3400, 2940, 2860, 1720, 1630, 1570, 1435, 1390, 1230, 1110, 1090, 825, 780; ^1H NMR (300 MHz, C_6D_6) δ 7.73 (m, 4 H), 7.23 (m, 6 H), 6.63 (s, 1 H), 4.77 (m, 4 H), 4.05 (m, 1 H), 3.68 (m, 2 H), 3.37 (s, 3 H), 3.36 (m, 2 H), 3.23 (m, 2 H), 2.65 (s, 3 H), 2.00 (m, 2 H), 1.63 (s, 3 H), 1.14 (s, 9 H); MS m/z (M^+ − H) calcd 618.2768, obsd 618.2786.

Addition of Dimethylamine to 33b. A solution of **33a** (4.9 g, 8.5 mmol) and *p*-toluenesulfonic acid (150 mg, 0.8 mmol) in CH_2Cl_2 (40 mL) at 0 °C was treated with dihydropyran (0.9 mL, 9.9 mmol) and stirred for 2 h. The solvent was removed in vacuo and replaced with CCl_4 (25 mL). This solution was cooled to 0 °C, and excess dimethylamine (ca. 5 mL) was condensed into the flask. The reaction mixture was stored at 0 °C for 48 h and then concentrated. The residue was chromatographed on silica gel (elution with 1:1 → 3:1 ethyl acetate–petroleum ether containing 1% triethylamine) to give 3.88 g (65% overall) of **34b** as a colorless foam: IR (CCl_4, cm^{-1}) 2920, 2860, 1715, 1630, 1420, 1390, 1220, 1110, 1080, 1020, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H), 7.39 (m, 6 H), 6.50 (s, 1 H), 4.88 (m, 4 H), 4.75 (m, 1 H), 3.98 (m, 1 H), 3.86 (m, 1 H), 3.81 (s, 3 H), 3.67 (m, 2 H), 3.49 (m, 1 H), 3.28 (br m, 2 H), 3.08 (s, 3 H), 2.92 (s, 3 H), 2.46 (dd, J = 5, 8.3 Hz, 1 H), 1.68 (s, 3 H), 1.95–1.45 (series of m, 8 H), 1.05 (s, 9 H); MS m/z (M^+) calcd 703.3540, obsd 703.3544.

O-Silylation of 34b. A solution of **34b** (70 mg, 0.1 mmol) in dry THF (2 mL) containing triethylamine (30 μL) was cooled to −78 °C under nitrogen, treated with potassium hexamethyldisilazide (0.4 mL of 0.5 M in toluene, 0.2 mmol), stirred for 1 h, quenched with trimethylsilyl chloride (50 μL, 0.4 mmol), and allowed to warm to room temperature. Following the addition of saturated $NaHCO_3$ solution (2 mL) and ether (10 mL), the separated organic layer was dried, filtered through a short pad of silica gel, and concentrated to furnish **35** (80 mg) as a less polar pale yellow oil, which was used without further purification.

Addition of Dimethylamine to 27. Into a cooled (0 °C) solution of **27** (550 mg, 0.73 mmol) in dry CCl_4 (30 mL) was condensed approximately 1 mL of dimethylamine. The reaction mixture was stirred for 24 h at this temperature, freed of excess amine by purging with nitrogen for 15 min, and freed of solvent in vacuo. The residue was chromatographed on silica gel (elution with 3:2 petroleum ether–ethyl acetate) to give 130 mg of **37**, 80 mg of **38**, and 330 mg of unreacted **27**. The yield of **37** based on recovered starting material was 55%.

Data for **37**: colorless oil; IR (neat, cm^{-1}) 2920, 2860, 1720, 1640, 1430, 1420, 1390, 1240, 1120, 1080, 710; ^1H NMR (300 MHz, C_6D_6) δ 7.80 (m, 4 H), 7.29 (m, 6 H), 6.73 (m, 1 H), 5.84 (m, 1 H), 4.95 (br s, 1 H), 4.85 (br s, 1 H), 4.63 (m, 1 H), 4.19 (m, 1 H), 4.08 (m, 1 H), 3.90–3.75 (m, 6 H), 3.52 (s, 3 H), 3.45–3.30 (m, 3 H), 2.78 (m, 1 H), 2.74 (s, 6 H), 2.15–1.90 (m, 2 H), 1.78 (s, 3 H), 1.78 (m, 2 H), 1.67 (s, 3 H), 1.60 (m, 2 H), 1.30 (br m, 2 H), 1.20 (s, 9 H); MS (FAB) m/z (M^+) calcd 757.401, obsd 757.403.

Data for **38**: colorless oil; ^1H NMR (300 MHz, C_6D_6) δ 7.80 (m, 4 H), 7.30 (m, 6 H), 6.70 (s, 1 H), 5.87 (m, 1 H), 4.64 (m, 1 H), 4.23 (m, 2 H), 3.92 (m, 2 H), 3.83 (m, 1 H), 3.67 (m, 2 H), 3.50 (s, 3 H), 3.40 (m, 2 H), 2.89 (s, 3 H), 2.77 (s, 3 H), 2.75 (m, 1 H), 2.57 (m, 1 H), 1.95 (s, 3 H), 1.82 (s, 3 H), 1.77 (m, 2 H), 1.63 (s, 3 H), 1.61 (m, 2 H), 1.45–1.25 (m, 4 H), 1.20 (s, 9 H).

Brominative Substitution of 37. A solution of 1,2-bis(diphenylphosphino)ethane (52 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C, and bromine (13 μL, 0.26 mmol) was introduced dropwise. After 5 min, a solution of **37** (85 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added slowly, and the reaction mixture was allowed to warm to room temperature, stirred for 3 h, and diluted with ether prior to filtration through a pad of Celite. The filtrate was evaporated, and the residue was purified on a short silica gel column (elution with petroleum ether–ethyl acetate, 3:2) to give **39a** as a yellow oil (38 mg, 50%): IR (neat, cm^{-1}) 1720, 1620, 1440, 1430, 1390, 1220, 1110, 1080, 900, 820, 780, 740, 710; ^1H NMR (300 MHz, C_6D_6) δ 7.80 (m, 4 H), 7.29 (m, 6 H), 6.74 (s, 1 H), 5.63 (m, 1 H), 4.98 (br s, 1 H), 4.88 (br s, 1 H), 4.10 (m, 1 H), 3.85–3.60 (m, 5 H), 3.59 (s, 2 H), 3.51 (s, 3 H), 3.40–3.25 (m, 2 H), 2.71 (s, 6 H), 2.05 (m, 2 H), 1.73 (s, 3 H), 1.70 (s, 3 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 176.1, 159.1, 153.9, 143.7, 135.9, 134.6, 134.1, 130.0, 125.2, 114.3, 108.4, 97.0, 71.1, 62.0, 54.6, 50.8, 40.5, 37.7, 36.8, 36.0, 35.6, 35.5, 27.1, 21.1, 19.4, 14.7; MS m/z (M^+ − Br) calcd 656.3407, obsd 656.3413.

Desilylation–Oxidation of 39a. A solution of **39a** (50 mg, 0.07 mmol) in THF (2 mL) was treated with tetra-*n*-butylammonium fluoride (0.1 mL of 1 M in THF), stirred at 20 °C for 3 h, diluted with ethyl acetate (10 mL), and washed with water (2 × 25 mL). The aqueous washings were extracted with ethyl acetate (2 × 5 mL), and the combined organic solutions were washed with brine (10 mL), dried, and concentrated. The resulting viscous yellow oil (30 mg) was found to decompose rapidly on standing. It was therefore used without further purification.

The above material was dissolved in dry CH_2Cl_2 (2 mL) and stirred with crushed activated 4-Å molecular sieves (160 mg) for 15 min under N_2 with cooling to 0 °C. Freshly prepared pyridinium dichromate (50 mg, 0.13 mmol) was introduced, and the reaction mixture was stirred vigorously for 3 h, at which time the alcohol was totally consumed (TLC analysis). Ether (20 mL) and ethyl acetate (20 mL) were added, and the mixture was filtered through a thin pad of Florisil and concentrated. The residue (15 mg) was immediately taken up in THF (20 mL) and stirred with 4-Å molecular sieves (100 mg) under nitrogen for 10 min before anhydrous $CrCl_2$ (30 mg) was added. The usual extractive workup yielded no identifiable product.

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Supplementary Material Available: A listing of experimental crystallographic details for **17**, ORTEP drawing for the second conformation of this molecule in the crystal, stereodrawing of the unit cell, listings of crystallographic details, and tables of bond lengths and angles, intermolecular distances, final and calculated positional and anisotropic thermal intramolecular bond angles, and torsion angles for **17**, together with the final calculated (MM2) atomic coordinates for the macrocyclic alcohols and ketones in Table I (27 pages).