Teubrevin G and Teubrevin H: The First Total Syntheses of Rearranged *neo*-Clerodanes Including Solutions to the Problems of Chirality Merger and Furan Ring Assembly

Leo A. Paquette* and Ivan Efremov

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received February 5, 2001

Abstract: Total syntheses of teubrevins G (**2**) and H (**3**) are described. The reported strategy relies on a highly regioselective cycloaddition−fragmentation approach to the construction of a 2,3,4-trisubstituted furan and features efficient ring-closing metathesis chemistry made possible through the application of a 1,3-dimesityl-4,5-dihydroimidazol-2-ylideneruthenium precatalyst. The key building blocks **39** and **48** were constructed by asymmetric processes and coupled under conditions where good remote asymmetric induction was realized. The diastereoselection observed in this alkylation reaction appears to be intimately associated with the conformational properties of the β-keto ester enolate. While the readily separated major diastereomer was transformed via a short route to **2**, the minor component served as the precursor to **3**. The efficiency of the synthesis was thereby well served.

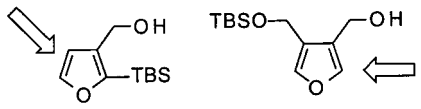
In 1995, a small group of unusual natural products was isolated by Rodriguez and co-workers during a search for new diterpenoids of the clerodane and *neo*-clerodane families in the aerial parts of *Teucrium brevifolium*.[1] Extensive spectral analysis of these metabolites exemplified by teubrevin G (**2**) and teubrevin H (**3**) identified them to be unprecedented offspring analogues. Rather than consisting of the conventional decalin framework characteristic of most members of this class,[2] **2** and **3** feature a cyclooctanone core fused and spiroannulated to smaller oxygen-containing rings. The imaginative biosynthetic proposal starting from teubrevin D (**1**) and outlined in Scheme 1 was offered as the probable route for the production of **2** and **3** in the plant.

An enantioselective synthesis of **2** and **3** was viewed as providing a setting for the formulation and evaluation of new synthetic strategies. The chemical challenges associated with the proposed biosynthesis were not taken up because of the need to generate a substrate such as **1** and the expected loss of stereocontrol and chemoselectivity following the fragmentative expulsion of acetic acid in the laboratory. Somewhat less daunting and rather more satisfying would be the development of an expeditious route that directly solves a number of key problems in the medium-ring and furan arenas.[3]

With the identification of a possible retrosynthetic pathway (Scheme 2) targeting teubrevin G (**2**), the envisioned assembly of the spirolactone moiety (**4** → **2**) was to be brought about in concert with a chirality merger event. The stereocontrolled alkylation of β-keto ester **4** with an enantiopure 3-furyl-substituted electrophile offered the prospects of an important bond construction step. The viability of ring-closing metathesis as **6** → **5** also was to play a central role. Examples of the satisfactory involvement of α,β-unsaturated ketones in this process were few.[4] Nonetheless, arrival at **5** could likely guarantee that *C*-allylation would materialize exclusively at C-9 as needed. Finally, the development of a direct and convenient means for generating the monocyclic 2,3,4-trisubstituted furans **7** and **8** was not without potential complications. As noted elsewhere,[5−7] this substitution pattern is the most difficult to elaborate in this heterocyclic class.

Results and Discussion

The envisioned need for **8** as a primary building block early in the synthesis prompted us to evaluate the possibility of effecting the regioselective lithiation[6,8] of such readily available furyl carbinols as **9**[9] and **10**.[10] The prospect offered by these



9 **10**

(1) Rodriguez, B.; de la Torre, M. C.; Jimeno, M. L.; Bruno, M.; Fazio, C.; Piozzi, F.; Savona, G.; Perales, A. *Tetrahedron* **1995**, *51*, 837.

(2) (a) Tokoroyama, T. *Synthesis* **2000**, 611. (b) Rodriguez-Hahn, L.; Esquivel, B.; Cardenas, J. *Prog. Chem. Org. Nat. Prod.* **1994**, *63*, 107. (c) Hanson, J. R. *Nat. Prod. Rep.* **1994**, *11*, 265; **1993**, *10*, 159. (d) Meritt, A. T.; Ley, S. V. *Nat. Prod. Rep*. **1992**, *9*, 243.

(3) Preliminary report of a portion of this study: Efremov, I.; Paquette, L. A. *J. Am. Chem. Soc.* **2000**, *122*, 9324.

(4) (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc*. **1993**, *115*, 9856. (b) Rutjes, P. J. T.; Schoemaker, H. E. *Tetrahedron Lett*. **1997**, *38*, 677.

(5) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955.

(6) (a) Bures, E.; Spinazzé, P. G.; Beese, G.; Hunt, I. R.; Rogers, C.; Keay, B. A. *J. Org. Chem.* **1997**, *62*, 8741. (b) Bures, E.; Nieman, J. A.; Yu, S.; Spinazzé, P. G.; Bontront, J.-L. J.; Hunt, I. R.; Rauk, A.; Keay, B. A. *J. Org. Chem.* **1997**, *62*, 8750.

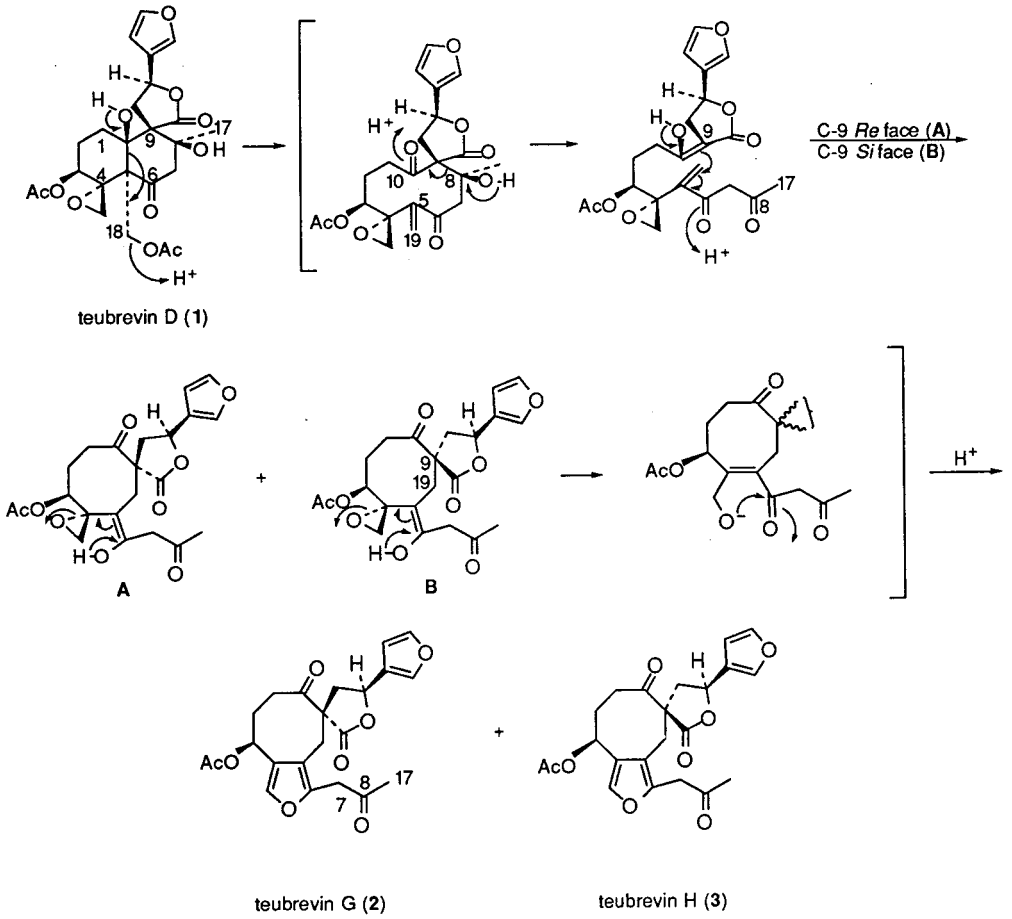
(7) (a) Efremov, I.; Paquette, L. A. *Heterocycles*, in press. (b) Brown, D. S.; Paquette, L. A. *J. Org. Chem.* **1992**, *57*, 4512.

(8) (a) Maddaford, S. P.; Andersen, N. G.; Christofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766. (b) Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501. (c) Danso-Danquah, R. E.; Scott, A. I.; Becker, D. *Tetrahedron* **1993**, *49*, 8195. (d) Keay, B. A.; Bontront, J.-L. J. *Can. J. Chem*. **1991**, *69*, 1326.

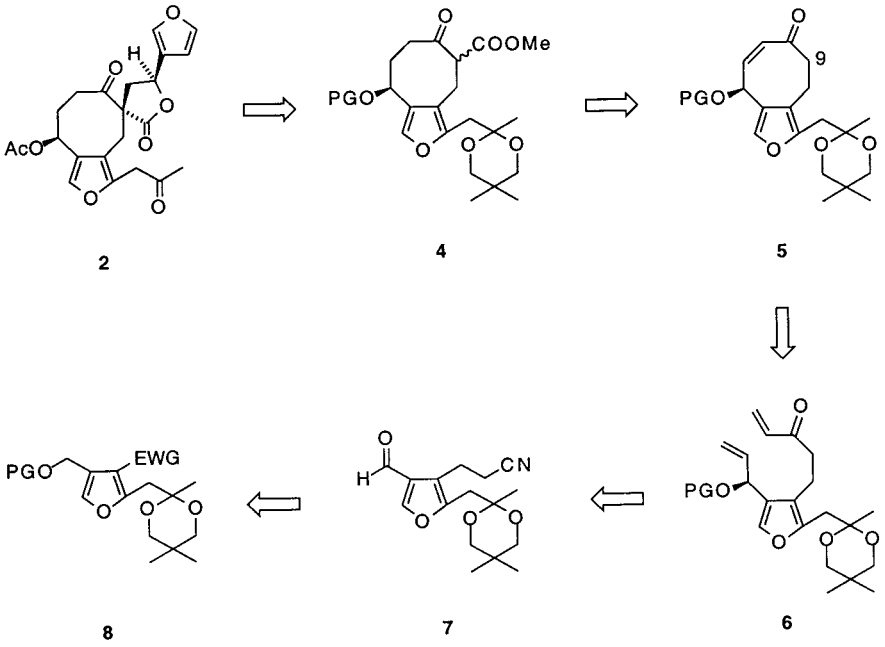
(9) Carbinol **9** was generated (74% overall yield) in a manner paralleling the known trimethylsilyl derivative from the commercially available 3-(hydroxymethyl)furan:[6] (a) TBSCl, imidazole, DMF; (b) *n*-BuLi, HMPA, −78 °C → 0 °C [Katsumura, S.; Hori, K.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett*. **1985**, *26*, 4625].

10.1021/ja010313+ CCC: $20.00
Published on Web 04/12/2001

Scheme 1



Scheme 2

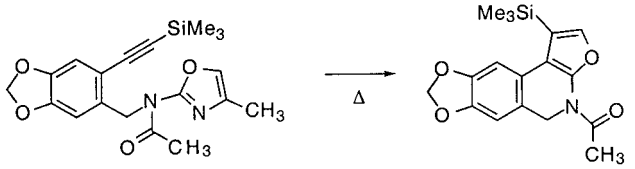


substrates and their MEM derivatives was the capability to examine the relative ease of metalation at C-4 and C-2, respectively (see arrows). When coupling to various electrophilic partners demanded by the target proved to be nonworkable,[7] recourse was made to the introduction of tributylstannyl groups at these positions. The tactic was successful in the case of **10**, but effective use of this tin reagent in palladium-catalyzed C−C bond-forming reaction was met predominantly with self-coupling to furnish dimeric furans linked at C-2.[7]

These considerations led us to investigate the possibility of realizing a regiocontrolled cycloaddition−retrograde fragmentation tactic for obtaining **8**. In this connection, we were mindful

(10) Available by sodium borohydride reduction of the known carboxaldehyde [ref 8c].

of the extensive use to which the heating of alkyne-tethered oxazoles has been used to produce polycyclic furans.[11] The conversion of **11** to **12** is exemplary. As a consequence of structural constraints in such systems, directionality options do not exist and a single regioisomer is formed efficiently. This issue likewise does not prove to be a complication with symmetrically substituted alkynes, which have consequently been utilized rather extensively to construct heavily substituted furans.[12] An obvious akwardness does, however, develop during the intermolecular [4 + 2] cycloaddition of unsymmetrical alkynes to oxazoles, such that this process has seen little use for the rapid elaboration of 2,3,4-[13] and 2,3,5-trisubstituted furans[14] in other laboratories.

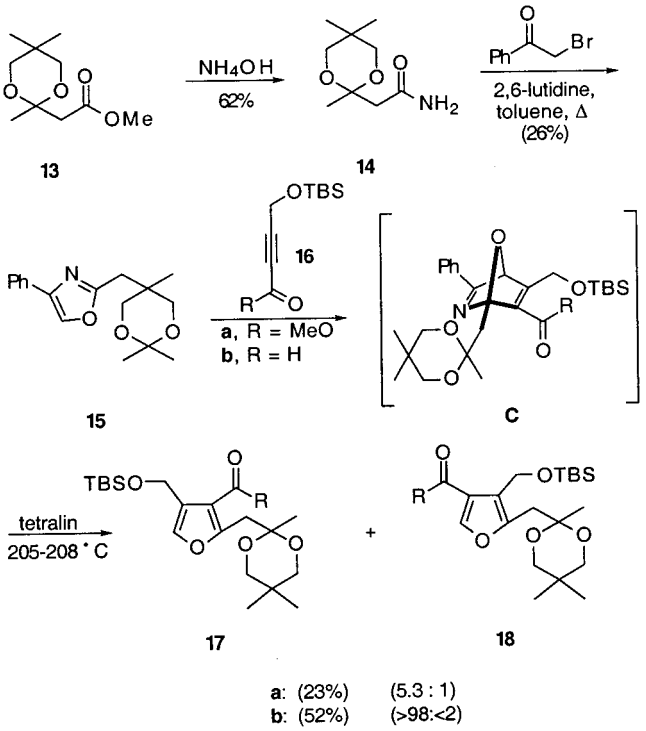


11 **12**

To determine whether acceptable levels of regiocontrol could be realized under these circumstances, oxazole **15** was formed by reacting the known acetal **13** of methyl acetoacetate[15a,b] with an ammonium hydroxide solution (Scheme 3). Arrival at **14** in this manner was followed by heating with phenacyl bromide in toluene containing 2,6-lutidine to give **15** according to general precedent.[11g] Although not particularly efficient, this sequence was easily scalable and required only a single chromatographic purification. The ability of aldehyde **16b**[15c,d] to add thermally to **15** in a highly regiocontrolled manner was particularly impressive. Only **17** was formed within our detection limits. The essentially exclusive intervention of adduct **C** conforms to expectations on the basis of the involvement of the oxazole HOMO and dienophile LUMO and indicates that steric and electronic effects may indeed be utilized to advantage in the one-step elaboration of complex furans. To our knowledge, the direct formation of **17b** constitutes the first example involving the introduction of three different carbon substituents in this manner.

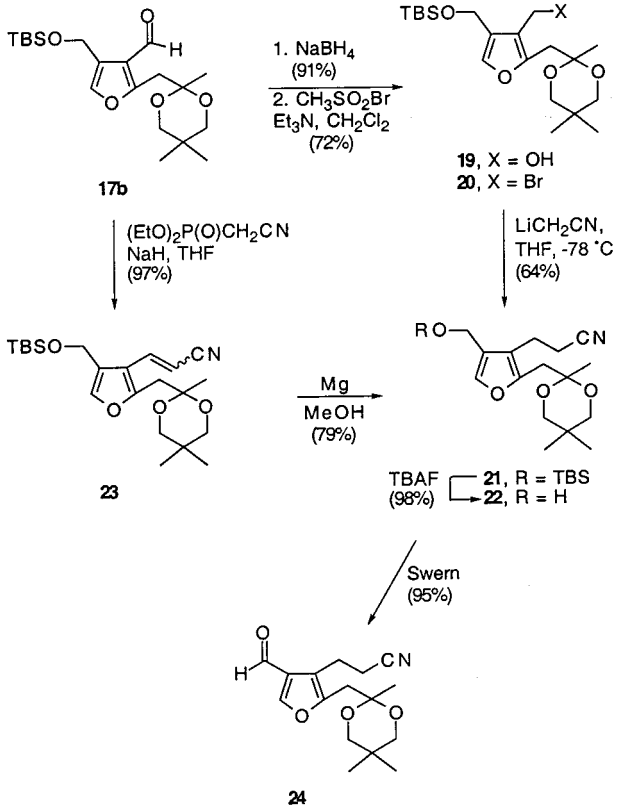
The next interim goal was to establish the C-3 propionitrile side arm resident in **7**. It was hoped that the primary alcohol **19**, easily obtained by sodium borohydride reduction of **17b**, might be transformed into **21** via the bromide **20** (Scheme 4). In practice, an array of brominating agents (Ph_3P/CBr_4,[16] Ph_3P/NBS,[17] NBS/Me_2S,[18] Me_3SiBr,[19] and Me_3SiBr/2,6-di-*tert*-butylpyridine) uniformly gave unsatisfactory results. While the adaptation of Mitsunobu-like conditions (Ph_3P, DIAD, $ZnBr_2$)[20] did furnish **20** on a small scale, this process was

Scheme 3



13 **14** **15** **C** **17** **18**

Scheme 4



17b **23** **24**

(11) (a) Liu, B.; Padwa, A. *Tetrahedron Lett.* **1999**, *40*, 1645. (b) Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc*. **1984**, *106*, 5585. (c) Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611. (d) Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem*. **1981**, *46*, 2065 (e) Iesce, M. R.; Cermola, F.; Giordano, F.; Scarpati, R.; Graziano, M. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3295. (f) Selnick, H. G.; Brookes, L. M. *Tetrahedron Lett.* **1989**, *30*, 6607. (g) *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986.

(12) (a) Caesar, J. C.; Griffiths, D. V.; Griffiths, P. A.; Tebby, J. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2329. (b) Van Aken, K.; Hoornaert, G. *J. Chem. Soc., Chem. Commun.* **1992**, 895. (c) Koenig, H.; Graf, F.; Weberndoerfer, V. *Liebigs Ann. Chem*. **1981**, 668.

(13) Yadav, J. S.; Valluri, M.; Rao, A. V. R. *Tetrahedron Lett*. **1994**, *35*, 3609.

(14) Iesce, M. R.; Cermola, F.; Graziano, M. L.; Scarpati, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 147.

(15) (a) Zamir, L. O.; Sauriol, F.; Nguen, C.-D. *Tetrahedron Lett*. **1987**, *28*, 3059. (b) Chan, T. H.; Brook, M. A.; Chaly, T. *Synthesis* **1983**, 203. (c) Motto, M. G.; Sheves, M.; Tsujimoto, K.; Balogh-Nair, V.; Nakanishi, K. *J. Am. Chem. Soc.* **1980**, *102*, 7947. (d) Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7861.

(16) Taschner, M. J. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; 1995; Vol. 8, pp 5364−5366.

(17) Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, 3937.

(18) Firouzabadi, H.; Ghaderi, E. *Tetrahedron Lett.* **1978**, 839.

(19) Jung, M. E.; Hatfield, G. L. *Tetrahedron Lett*. **1978**, 4483.

(20) Ho, P.-T.; Davies, N. *J. Org. Chem*. **1984**, *49*, 3027.

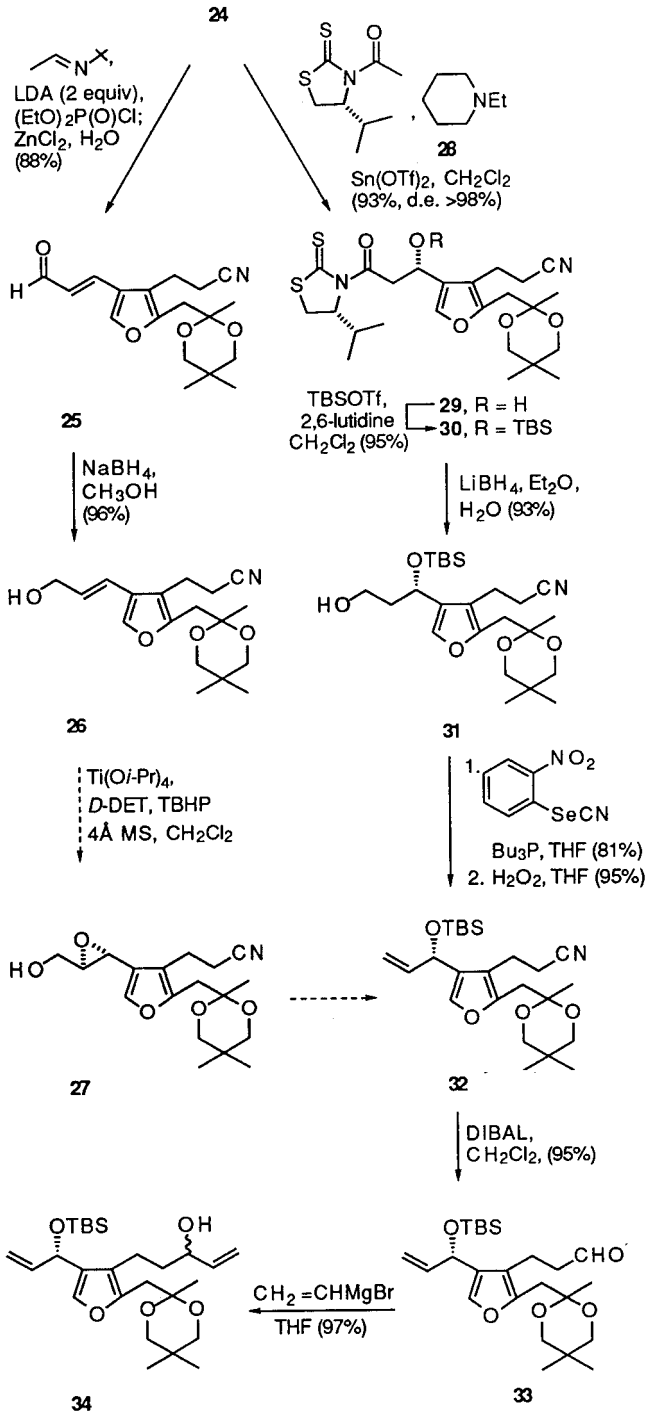
not fruitful when larger amounts were involved. The most reliable means uncovered for accessing this bromide in appropriate quantities involved the use of methanesulfonyl bromide[21] and triethylamine in CH_2Cl_2 at 0 °C (72%). We presume that the several complications with this material are due to its elevated sensitivity to decomposition, a property that complicated the serviceability of its reaction with lithioacetonitrile[22] to provide **21**.

An alternative protocol was therefore sought. When recourse was made to the anion of diethyl cyanomethylphosphonate,[23] the α,β-unsaturated nitrile was cleanly generated as an *E/Z* mixture (11:1). Saturation of the double bond occurred smoothly under the influence of magnesium in methanol[24] to give **21** in good overall yield. Desilylation and Swern oxidation[25] in the customary manner gave rise to the desired aldehyde **24**, which served as the portal of entry into the enantiopure series of advanced intermediates.

At this stage, two avenues of investigation were independently pursued. The first was programmed to utilize the Sharpless epoxidation to set the proper absolute configuration at the acetoxy-substituted carbon of both teubrevins. Because the condensation of **24** with (triphenylphosphoranylidene)acetaldehyde[26] proved troublesome, we turned instead to a procedure initially pioneered by Meyers[27] in order to arrive at **25** (Scheme 5). The activation of acetaldehyde *N-tert*-butylimine[28] by deprotonation with 2 equiv of LDA in the presence of diethyl chlorophosphate provided a reagent that gave rise to **25** exclusively as the *E* isomer in 88% yield. The outcome of exposing **25** to sodium borohydride in ethanol was to provide allylic alcohol **26** with essentially quantitative efficiency. Considerable experimentation was devoted to discovering the proper conditions for the asymmetric epoxidation of **26**. Stoichiometric and catalytic variants were both examined. These considerations convinced us that low yields could not be skirted, principally as a direct consequence of the innate lability of **27**. However, complications of this type were nicely circumvented by our second option.

The alternative approach was rendered especially feasible as a consequence of the excellent diastereoselectivity with which the chiral, enantiopure 1,3-thiazolidine-2-thione **28**[29] enters into aldol condensation with **24** in the presence of stannous triflate. Product **29**, isolated in 80% yield as the very predominant diastereomer, was in turn protected as the *tert*-butyldimethylsilyl ether and freed of the heterocyclic auxiliary by reduction with lithium borohydride. With quantities of **31** in hand, efficient dehydration to the terminal vinyl derivative **32** was accomplished by the Grieco method involving the intermediacy of an *o*-nitrophenylselenocyanate.[30] The synthesis was significantly advanced by the effectiveness with which **32** was reduced

Scheme 5

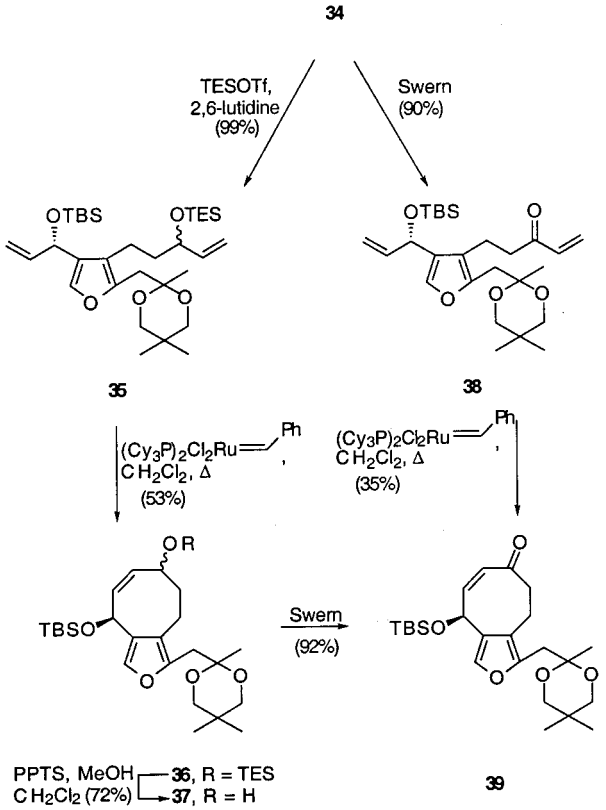


to aldehyde **33** by DIBAL reduction and the second terminal double bond introduced by 1,2-addition of vinylmagnesium bromide to the carbonyl group.

The time had now come to explore the feasibility with which **34** and related compounds would enter into the ring-closing metathesis reaction. The formation of eight-membered rings by means of this tactic has invariably held a unique position[31] because of the adverse kinetic and entropic factors associated with cyclizations to produce cyclooctanoid networks.[32] In our retrosynthetic planning, we had hoped that attachment of the reaction centers to side arms positioned at C-3 and C-4 of a furan ring would contribute to an improved state of affairs. The initial experiments did not corroborate this assumption (Scheme

(21) Sieber, G. *Justus Liebigs Ann. Chem.* **1960**, *631*, 180.
(22) Taber, D. F.; Kong, S. *J. Org. Chem.* **1997**, *62*, 8575.
(23) De Hoff, B. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; 1995; Vol. 3, pp 1806−1807.
(24) Profitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 127.
(25) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(26) McComsey, D. F.; Maryanoff, B. E. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; 1995, Vol. 4, pp 2598−2599.
(27) Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788.
(28) (a) Campbell, K. N.; Sommers, A. H.; Campbell, B. K. *J. Am. Chem. Soc.* **1944**, *66*, 82. (b) Snyder, H. R.; Matteson, D. S. *J. Am. Chem. Soc.* **1957**, *79*, 2217.
(29) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiani, M.; Inoue, T.; Hasimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.
(30) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(31) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.

Scheme 6



6). In an attempt to gain as much coverage as possible, alcohol **34** was transformed into its triethylsilyl ether **35** and oxidized under Swern conditions to ketone **38**. In the latter instance, it was quickly demonstrated that ring closure in the presence of Grubbs' benzylidene catalyst[33] was notably sluggish. Only very modest yields (20−35%) of **39** were obtained, and only after reaction times had been significantly extended (>3 days) and rather elevated catalyst loadings of 30−35 mol % had been utilized. The use of copper(I) salts has been recommended under these circumstances.[34] In the present instance, the level of conversion was indeed increased to approximately the 50% level, but the requisite proportion of catalyst remained impractically high. Since α,β-unsaturated ketones have been little used in RCM processes,[4] the possibility remained that the electron-deficient character of this particular double bond might well detract from overall metathesis efficiency.

This complication is obviated in **35**. Nonetheless, longer reaction times (>1 week) and comparably high proportions of catalyst were still required. Although yields were improved to

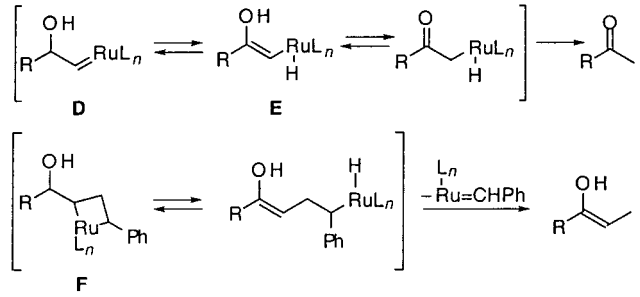
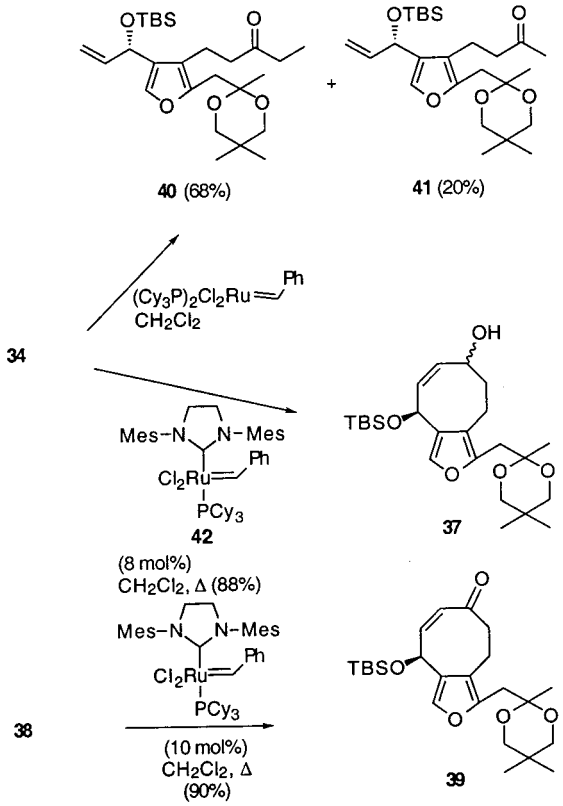


Figure 1.

Scheme 7



the 53% level, this state of affairs was not considered ideal. In light of the possibility that the slow rate of cyclization of **35** may have its origins in the steric bulk of the OTES substituent positioned adjacent to one of the reaction centers, we ultimately turned to the free alcohol **34** (Scheme 7). A recent study of the possible activating effect of allylic hydroxyls on the olefin metathesis reaction[35] lent additional support to this choice of substrate. At the experimental level, no desired product was isolated. Instead, ethyl ketone **40** (68%) and methyl ketone **41** (20%) were isolated. This outcome is presumably the end result of two competing reactions. In the first, the ruthenium carbenoid **D** is subject to tautomerism and conversion to the enolyl ruthenium hydride intermediate **E** prior to reductive elimination and generation of **41** (Figure 1).[35a] The alternative conversion to **40** can be rationalized in terms of eliminative ring opening of ruthenocycle **F** with ensuing fragmentative loss of the propagating ruthenium carbenoid. A similar observation has been reported recently.[35b]

During the period of our exploration of the RCM step, disclosure was made of the improved performance levels of the

(32) (a) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101. (b) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919. (c) Paley, R. S.; Estroff, L. A.; Gauguet, J.-M.; Hunt, D. K.; Newlin, R. C. *Org. Lett.* **2000**, *2*, 365. (d) Paquette, L. A.; Méndez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301. (e) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Méndez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259. (f) Clark, J. S.; Kettle, J. Y. *Tetrahedron Lett.* **1997**, *38*, 127. (g) Fürstner, A.; Langemann, R. *J. Org. Chem.* **1996**, *61*, 8746. (h) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548. (i) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359. (j) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (k) Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis* **2000**, 869. (l) Krafft, M. E.; Cheung, Y.-Y.; Juliano-Capucao, C. A. *Synthesis* **2000**, 1020.

(33) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202 and references therein.

(34) (a) Dias, E. L.; Nguen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (c) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(35) (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123. (b) Ackermann, L.; Tom, D. E.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195.

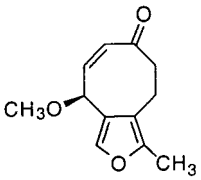
Table 1. MM3 Force Field Evaluations of Various Conformers of **G**[a]

structure	energy (kcal/mol)	ΔE (kcal/mol)	α-H/ketone angle (degrees)	γ-H/ketone angle (degrees)	enone distortion from planarity (degrees)
global minimum	27.41	0	40.0	67.4	25.6
planar enone	28.43	1.02	44.6	53.4	3.4
α-H aligned	28.97	1.56	114.8	41.5	17.7
γ-H aligned	32.04	4.36	108.0	82.0	91.0

[a] Each conformational search was allowed 1000 iterations. The conformational searching protocol was repeated three times with different starting geometry and calculation parameters. The same minimum was identified in each of the three trials.

1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted complex **42**.[36] Indeed, the use of **42** led to a very practical resolution of the predescribed problems. As indicated in Scheme 7, the conversion of free alcohol **34** to cyclooctenol **37** could now be readily achieved in 88% yield within several hours in refluxing CH_2Cl_2 at a catalyst loading of ca. 10 mol %. High RCM activity was also observed for **38**. Under comparable conditions, conversion to **39** could be realized in 90% yield within 34 h. Understandably, these developments opened up a direct access route capable of delivering significant quantities of **39**.

Following installation of the cyclooctenone ring in this manner, attention was turned to elaboration of the eastern sector of targets **2** and **3**. Since the deprotonation of **39** was envisioned to be the next necessary step, MM3 calculations were performed on the model system **G** in order to derive a prediction of the

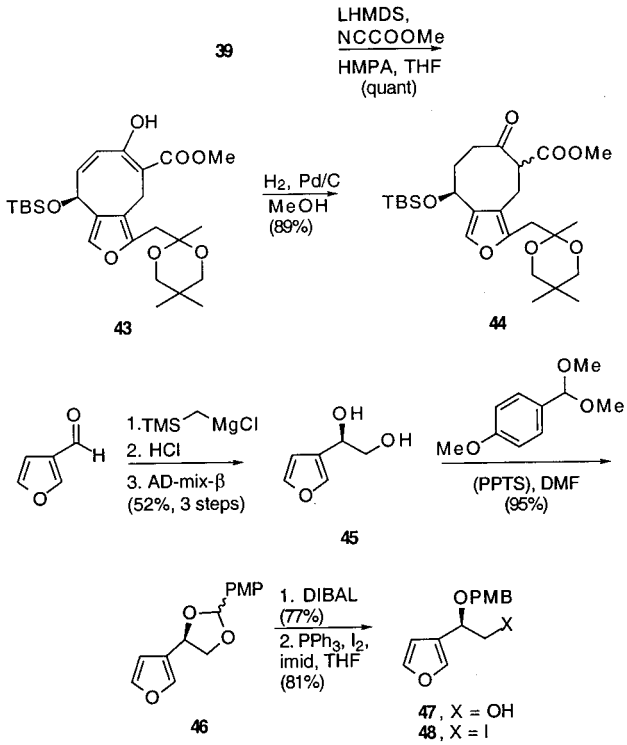


G

likely site of proton abstraction. The conformations of **G** selected for evaluation included the following: (a) the global energy minimum; (b) the lowest energy local minimum in which the enone is planar and presumably well conjugated; (c) the lowest energy local minimum with reasonable orbital alignment for α deprotonation; (d) the lowest energy local minimum with reasonable orbital alignment for γ deprotonation. The relative energy values compiled in Table 1 (for the actual conformational representations, consult Supporting Information) allow one to draw several relevant conclusions. Of particular note is the rather dramatic distortion of the enone in the lowest energy conformation that would allow proper orbital alignment of the γ C−H bond with the chromophore. The enone is likely not conjugated in this conformation, and γ-deprotonation seems entirely unlikely.

Our expectation was, therefore, that exposure of **39** to lithium hexamethyl disilazide would be directed *away from* the region of the OTBS group.[37] Conjugative overlap is absent from this conformation, and formation of an extended enolate is viewed to be unlikely. In the case at hand, treatment of the enolate anion with Mander's reagent[38] resulted in the quantitative production of the enolized β-keto ester **43** (Scheme 8). Now that regiocontrol had been realized, the superfluous double bond was

Scheme 8



saturated by conventional hydrogenation over palladium on charcoal. Bicyclic furan **44** was obtained without any sign of overreduction of the five-membered heterocyclic ring.

Any consideration of the electrophilic coupling participant for **44** carries the need to incorporate a suitably matched stereogenic center. This requirement led us to focus on iodide **48**. It is noteworthy that diol **45**, a likely precursor to this electrophilic species, has previously been accessed quite inefficiently via multistep routes starting with chiral pool substrates.[39,40] The approach outlined herein (Scheme 8), inspired by the prior work of O'Doherty,[41] is a considerable improvement. Thus, Peterson olefination of 3-furylcarboxaldehyde led conveniently to 3-vinyl furan, the dihydroxylation of which with AD-mix-β[42] provided the (2*R*)-diol **45** in 60% overall yield and >90% ee. The latter, upon acid-promoted exchange with *p*-methoxybenzaldehyde dimethylacetal, was transformed into **46** from which the selectively protected derivative **47** was obtained by regiocontrolled reduction with diisobutylaluminum hydride. Triphenylphosphine diiodide acted on **47** to give **48** without difficulty.

The key step in the concluding phase of the synthesis was the convergent, stereocontrolled alkylation of **44** with iodide **48**. The complication here was the inefficiency of the S_N2-based

(36) The improved RCM performance of ruthenum complexes with N-heterocyclic carbene ligands: (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Fürstner, A.; Thiol, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(37) Paquette, L. A.; O'Neil, S. V.; Guillo, N.; Zeng, Q.; Young, D. G. *Synlett* **1999**, 1857.

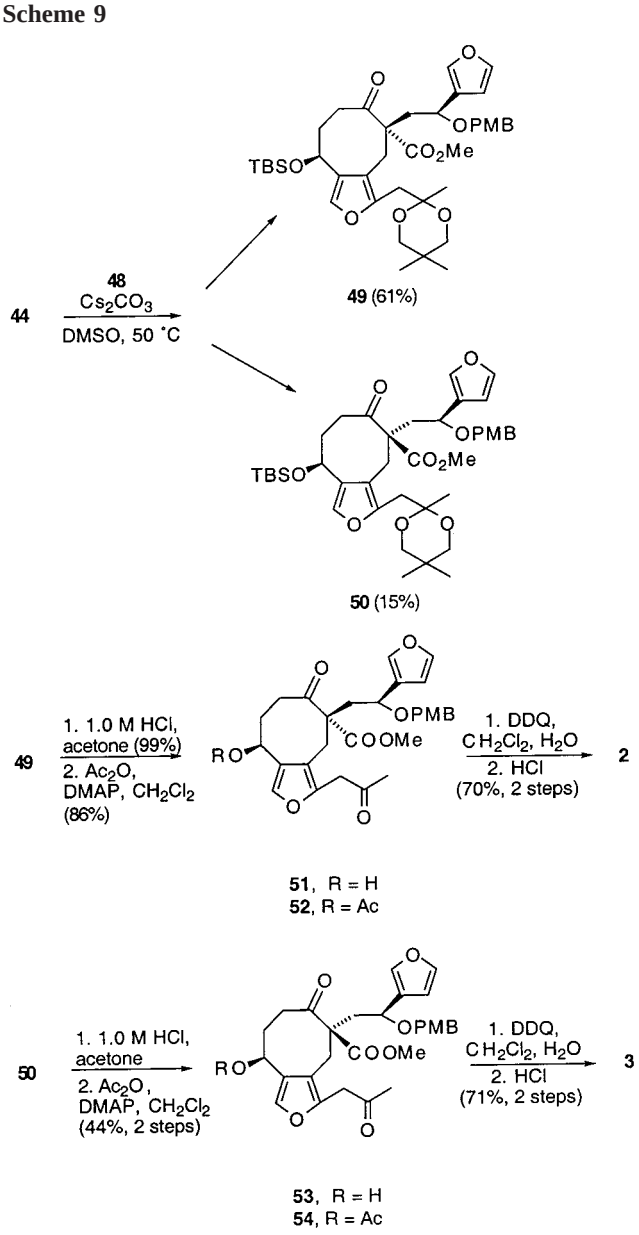
(38) Mander, L. N.; Sehti, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

(39) Marco, J. L.; Hueso-Rodriguez, J. A. *Tetrahedron Lett.* **1988**, *29*, 2459.

(40) Marco, J. L. *Tetrahedron* **1989**, *45*, 1475.

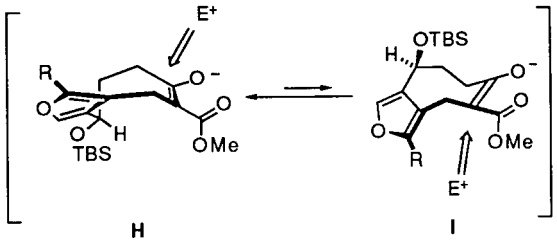
(41) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982.

Scheme 9



process. After a significant number of temperature regimes, solvents, and bases had been scrutinized, the realization was made that the desired transformation benefited from the presence of cesium salts. Ultimately it was determined that cesium carbonate in dimethyl sulfoxide at 50 °C was uniquely suitable for generating **49** and **50** in a combined yield of 76% (Scheme 9). Entry of the electrophile from the β-surface predominated by a factor of 4:1. This stereochemical outcome was anticipated on the basis of the preferred adoption by the β-keto ester anion of conformation **H**. Despite the existence of a gauche interaction between the OTBS substituent and C-5 of the furan ring in **H**, this geometry is presumably adopted in the transition state largely because the quasiequatorial projection of the siloxy functionality. In the less energetically favorable spatial arrangement **I**, the OTBS group is oriented quasiaxially, sterically shields the top face of the enolate, and generally disfavors the operation of kinetic control via this entity.

Fortunately, the chromatographic separation of **49** from **50** was readily accomplished. Hydrolysis of the major diastereomer with mineral acid in acetone brought on the selective removal of two protecting groups. The availability of **51** in this fashion made possible sequential acetylation, oxidative removal of the



PMB substituent, and acid-promoted lactonization. The IR and $^1H/^{13}C$ NMR spectra of this synthetic product were in solid agreement with the corresponding data reported for teubrevin G.[1] An $[\alpha]_D^{22}$ of -69.6 (*c* 0.46, $CHCl_3$) was determined for our isolate. The reported rotation for the natural substance is $[\alpha]_D^{22}$ -64.1 (*c* 0.382, $CHCl_3$).[1]

Entirely parallel, although nonoptimized processing of **50** resulted in the isolation of teubrevin H. The structure was confirmed by a direct matchup with the high-field (500 MHz) ^1H NMR spectrum of natural **3** provided by Professor Rodriguez. The identity extended as well to ^{13}C NMR, MS, and optical rotation data: $[\alpha]_D^{22}$ $+52.5$ (*c* 0.20, $CHCl_3$) (lit.[1] $[\alpha]_D^{17}$ $+56.6$ (*c* 0.106, $CHCl_3$)).[1]

In summary, the first total synthesis of (−)-teubrevin G has been completed over 21 steps from oxazole **15** in 5% overall yield. A second member of the family was also prepared in complementary fashion. Among the key lessons learned in the course of this investigation is the feasibility of achieving high regioselectivity in intermolecular cycloaddition−fragmentations involving oxazoles and unsymmetrically substituted alkynes. The highly functionalized nature of furan **17** so produced is noteworthy. The application of precatalyst **42** to the highly efficient formation of cyclooctenone **39** by ring-closing metathesis is quite instructive. Finally, the stereoselectivity with which **44** undergoes alkylation is viewed to be a practical extension of the concepts originally advanced by Still and Galynker regarding the influence of conformation of medium-sized rings on their capacity to achieve remote asymmetric induction.[43]

Experimental Section

9-(*S*)-*tert*-Butyldimethylsilyloxy-3-(2,5,5-trimethyl[1,3]dioxan-2-ylmethyl)-4,5-dihydro-9*H*-cycloocta[*c*]furan-6-one (39). A dry 2-L flask equipped with a condenser and a stir bar was charged with dry CH_2Cl_2 (900 mL). The solvent was brought to reflux, and a solution of catalyst **42** (56 mg, 2.8 mol %) in CH_2Cl_2 (10 mL) was added. Dienone **38** (1.120 g, 2.42 mmol) dissolved in CH_2Cl_2 (40 mL) was cannulated into the reaction mixture. Reflux was continued for 5 h when another portion of the catalyst (51 mg, 2.5 mol %) in CH_2Cl_2 (10 mL) was introduced. The reaction mixture was heated overnight when one more addition of the catalyst (40 mg in 10 mL of CH_2Cl_2) was performed. The last portion of the catalyst was added after 7 h (77 mg), and the reflux was maintained for additional 6 h. The total reaction time was 34 h. The reaction mixture was cooled, and lead tetraacetate (198 mg, 0.402 mmol) was added. The mixture was stirred overnight and filtered through a pad of silica gel, which was then washed with ethyl acetate. Chromatography of the residue (silica gel, elution with ethyl acetate/petroleum ether, 10:90) afforded **39** (848 mg, 81%) and returned unreacted **38** (97 mg, 9%).

For **39**: colorless oil; IR (neat, cm^{-1}) 1695, 1680, 1666; ^1H NMR (400 MHz, C_6D_6) δ 7.36 (d, $J = 1.0$ Hz, 1 H), 6.13 (dd, $J = 12.5$, 5.4 Hz, 1 H), 5.80 (dd, $J = 12.5$, 1.5 Hz, 1 H), 5.70 (ddd, $J = 5.4$, 1.5, 1.0 Hz, 1 H), 3.32−3.20 (m, 4 H), 2.89 (d, $J = 14.9$ Hz, 1 H), 2.85 (d, $J = 14.9$ Hz, 1 H), 2.81−2.64 (m, 4 H), 1.27 (s, 3 H), 0.91 (s, 9 H),

(42) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(43) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

0.83 (s, 3 H), 0.51 (s, 3 H), 0.00 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 148.6, 148.0, 138.1, 128.3, 126.8, 117.2, 99.1, 70.6 (2C), 66.6, 41.5, 36.3, 30.0, 25.7 (3C), 22.4, 22.3, 20.0, 19.8, 18.2, −4.96, −5.04; HRMS (EI) calcd *m*/*z* (M^+) 434.2488, obsd 434.2502; $[\alpha]_D^{21}$ +44.2 (*c* 3.85, $CDCl_3$).

Anal. Calcd for $C_{24}H_{38}O_5Si$: C, 66.32; H, 8.81. Found: C, 66.06; H, 9.04.

4-(*S*)-*tert*-Butyldimethylsilyloxy-8-carboxymethyl-1-(2,5,5-trimethyl-[1,3]dioxan-2-ylmethyl)-4,9-dihydrocycloocta[*c*]furan-7-ol (43). A 45 mg (0.104 mmol) sample of **39** was placed into a dry 25 mL flask. THF (2.0 mL) was added, and the flask was cooled to −78 °C. LHMDS (1.0 M in THF; 0.12 mL, 0.12 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 5 min, warmed to 0 °C, stirred at 0 °C for 1.5 h, returned to −78 °C, treated with a solution of dry HMPA (19 mg, 0.104 mmol) and dry methyl cyanoformate (11 mg, 0.125 mmol) in THF (0.5 mL), stirred at −78 °C for 30 min, quenched with phosphate buffer (1 mL), and allowed to warm to room temperature. Ether (10 mL) and phosphate buffer (5 mL) were added, and the separated aqueous layer was extracted with ether (4 × 5 mL). The combined organic extracts were washed with brine (10 mL) and dried. Chromatography of the residue (silica gel; ethyl acetate/petroleum ether, 10:90 → 15:85) gave 45 mg (87%) of **43** and returned (13%) unreacted **39**.

For **43**: colorless oil; IR (neat, cm^{-1}) 3494, 1658, 1651, 1602; ^{1}H NMR (400 MHz, C_6D_6) δ 11.31 (s, 1 H), 7.49 (d, J = 1.7 Hz, 1 H), 5.89 (dd, J = 11.2, 1.4 Hz, 1 H), 5.78 (dd, J = 11.2, 6.1 Hz, 1 H), 5.44, (ddd, J = 6.1, 1.7 Hz, 1 H), 3.67 (d, J = 15.9 Hz, 1 H), 3.43−3.22 (m, 6 H), 3.19 (s, 3 H), 3.00 (d, J = 15.9 Hz, 1 H), 1.42 (s, 3 H), 0.91 (s, 9 H), 0.89 (s, 3 H), 0.64 (s, 3 H), 0.04 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 172.9, 170.9, 147.4, 139.7, 137.6, 126.2, 121.5, 119.1, 100.5, 99.0, 70.4, 70.3, 67.8, 51.1, 35.7, 29.7, 25.7 (3C), 22.5, 22.1, 21.7, 20.2, 18.1, −4.9, −5.5; HRMS (EI) calcd *m*/*z* (M^+) 492.2543, obsd 492.2505; $[\alpha]_D^{21}$ +191.6 (*c* 3.00, $CHCl_3$).

Anal. Calcd for $C_{26}H_{40}O_7SI$: C, 63.38; H, 8.18. Found: C, 63.42; H, 8.32.

Compound 44. A solution of **43** (43 mg, 0.087 mmol) in dry methanol (20 mL) was treated with 5% palladium on carbon (56 mg) and stirred vigorously under a slight positive pressure of hydrogen for 15 min. After rapid filtration through Celite, the pad was rinsed with ethyl acetate and the combined filtrates were evaporated. Chromatographic purification of the residue on silica gel (elution with ethyl acetate/petroleum ether 15:85) afforded **44** as an inseparable mixture of diastereomers: colorless oil; IR (neat, cm^{-1}) 1746, 1731, 1711; ^{1}H NMR (400 MHz, C_6D_6) δ 7.30 (s, 0.36 H), 6.81 (s, 0.64 H), 4.60 (dd, J = 9.4, 4.2 Hz, 0.36 H), 4.55 (dd, J = 4.8, 2.0 Hz, 0.64 H), 4.00−3.84 (m, 1.64 H), 3.58 (t, J = 12.5 Hz, 0.36 H), 3.45−3.30 (m, 5.08 H), 3.26 (s, 1.92 H), 3.24−2.91 (m, 2.36 H), 2.84 (d, J = 14.8 Hz, 0.64 H), 2.39−1.81 (series of m, 4 H), 1.28 (s, 3 H), 0.95 (s, 5.76 H), 0.91 (s, 3.24 H), 0.91 (s, 1.92 H), 0.87 (s, 1.08 H), 0.48 (s, 3H), −0.01 (s, 1.08 H), −0.03 (s, 1.92 H), −0.06 (s, 1.08 H), −0.10 (s, 1.92 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 208.4, 170.0, 169.8, 149.4, 148.7, 137.9, 137.8, 129.3, 127.5, 116.6, 115.6, 98.6, 98.5, 70.6 (2C), 70.5 (2C), 67.8, 66.1, 62.4, 61.7, 52.24, 52.17, 37.2, 37.1, 36.9, 36.4, 36.3, 36.1, 31.9, 30.0, 29.9, 25.7 (6C), 23.3, 23.0, 22.7 (2C), 22.3, 22.2, 19.4, 19.2, 18.2, 18.1, −5.0 (2C), −5.2, −5.3; EI MS *m*/*z* (M^+) calcd 494.2700, obsd 494.2715.

Anal. Calcd for $C_{26}H_{42}O_7Si$: C, 63.13; H, 8.56. Found: C, 63.29; H, 8.65.

(1*R*)-3-Furyl-1,2-ethanediol (45). Chloromethyltrimethylsilane (1.02 g, 8.28 mmol) was added to magnesium turnings (0.24 g, 9.9 mmol) in dry ether (5 mL), and the mixture was refluxed overnight, cooled in an ice bath, and treated with a solution of 3-furaldehyde (0.69 g, 7.2 mmol) in ether (7 mL). Stirring was continued at 0 °C for 1 h and at room temperature for 11 h prior to quenching with a saturated NH_4Cl solution (5 mL). The separated aqueous phase was extracted with ether (3 × 5 mL), the combined organic phases were washed with a saturated $NaHCO_3$ solution and brine, dried, and concentrated, and the product alcohol (1.26 g, 95%) was dissolved in ether (5 mL) and stirred with 1.0 M HCl (3.4 mL) for 80 min. The phases were separated, and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic solutions were washed with a saturated $NaHCO_3$ solution (2 × 5 mL) and brine (5 mL) and then carefully concentrated to ca. 5 mL under house vacuum *with no heating*.

This solution of 3-vinylfuran was added at 0 °C to a solution containing AD-mix-β (9.24 g), *tert*-butyl alcohol (30 mL), and water (33 mL), and stirring was maintained at this temperature for 12 h. Sodium sulfite (9.90 g) was introduced, and the mixture was stirred for 45 min at 20 °C before the phases were separated and the aqueous layer was extracted with ethyl acetate (7 × 20 mL). The combined organic solutions were washed with brine and dried. Recrystallization of the residue from chloroform gave 415 mg of **45** as off-white crystals. The mother liquor was subjected to chromatography on silica gel (elution with ethyl acetate/petroleum ether 85:15) and gave an additional 71 mg of diol (52% total).[39,40]

1-(1*R*)-1-(3-Furyl)-2-(hydroxyethyl)-*p*-methoxybenzyl Ether. A mixture of **45** (457 mg, 3.56 mmol), *p*-anisaldehyde dimethylacetal (1.30 g, 7.13 mmol), pyridinium *p*-toluenesulfonate (15 mg), and dry DMF (5.0 mL) was placed on a rotary evaporator and heated at 50 °C (bath temperature) under house vacuum for 6 h. The product mixture was poured into brine and extracted with ether (4 × 20 mL). The combined extracts were washed with brine (15 mL), dried, and evaporated. The residue was dissolved in methanol (10 mL), treated with sodium borohydride (138 mg) to reduce the anisaldehyde, stirred for 2 h, and diluted with CH_2Cl_2 (50 mL) and water (50 mL). After 4 h, the separated aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic solutions were washed with water (15 mL), dried, and concentrated. The cyclic acetal **46** was purified by chromatography on silica gel (elution with ethyl acetate/petroleum ether 15:85) to yield 833 mg (95%) of a colorless oil.

This above material was dissolved in dry CH_2Cl_2 (5 mL), cooled to 0 °C, treated with Dibal-H (1.04 mL of 1 M in hexanes, 1.04 mmol), stirred at 0 °C for 30 min, cooled to −78 °C, and quenched with ethyl acetate (1 mL). The mixture was warmed to room temperature, diluted with Rochelle salt solution, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (5 mL) and dried to leave a residue, purification of which by MPLC (silica gel, elution with ethyl acetate/petroleum ether 40:60) furnished 133 mg (73% overall) of **47** as a colorless oil: IR (neat, cm^{-1}) 3443, 1613, 1514; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1 H), 7.43 (s, 1 H), 7.25−7.22 (m, 2 H), 6.90−6.87 (m, 2 H), 6.48 (d, J = 0.6 Hz, 1 H), 4.52 (d, J = 11.2 Hz, 1 H), 4.48 (dd, J = 7.9, 4.0 Hz, 1 H), 4.31 (d, J = 11.2 Hz, 1 H), 3.81 (s, 3 H), 3.76 (dd, J = 11.5, 7.9 Hz, 1 H), 3.65 (dd, J = 11.5, 4.0 Hz, 1 H), 2.10 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 143.6, 140.8, 130.0, 129.5 (2C), 122.9, 113.9 (2C), 109.0, 73.9, 70.2, 66.2, 55.3; EI MS *m*/*z* (M^+) calcd 248.1048, obsd 248.1041; $[\alpha]_D^{21}$ −82.6 (*c* 1.94, $CHCl_3$).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.60; H, 6.54.

1-(1*R*)-1-(3-Furyl)-2-(iodoethyl)-*p*-methoxybenzyl Ether (48). A mixture of imidazole (61 mg, 0.90 mmol), triphenylphosphine (0.14 mg, 0.54 mmol), and iodine (126 mg, 0.50 mmol) in dry CH_2Cl_2 (1.5 mL) was cooled in an ice bath, treated with a solution of **47** (22 mg, 0.09 mmol) in CH_2Cl_2 (5.5 mL), and concentrated to ca. 1.5 mL without exposure to air. After 3 days of stirring, water (5 mL) was introduced and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with a dilute $NaHSO_3$ solution (5 mL), dried, and concentrated. The product iodide was chromatographed on silica gel (elution with ethyl acetate/petroleum ether, 1:15): yield 26.2 mg of oil (81%); IR (neat, cm^{-1}) 1613, 1586, 1513; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.43 (m, 2 H), 7.28 (dt, J = 8.7, 2.0 Hz, 2 H), 6.88 (dt, J = 8.7, 2.0 Hz, 2 H), 6.41−6.40 (m, 1 H), 4.50 (d, J = 11.2 Hz, 1 H), 4.47 (dd, J = 7.4, 5.4 Hz, 1 H), 4.34 (d, J = 11.2 Hz, 1 H), 3.81 (s, 3 H), 3.43 (dd, J = 10.3, 7.4 Hz, 1 H), 3.32 (dd, J = 10.3, 5.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$)δ 159.4, 143.6, 140.7, 129.8, 129.6 (2C), 124.4, 113.8 (2C), 108.3, 73.0, 70.6, 55.3, 9.5; EI MS *m*/*z* (M^+) calcd 358.0025, obsd 358.0062; $[\alpha]_D^{18}$ −73.8 (*c* 1.78, $CHCl_3$).

Compounds 49 and 50. Cesium carbonate (220 mg, 0.675 mmol) was rapidly transferred into a dry 25 mL flask (closed with an all-glass three-way stopcock) and dried under vacuum by means of a heat gun. The flask was allowed to cool under N_2, and a solution of keto

ester **44** (69.8 mg, 0.141 mmol) and iodide **48** (170 mg, 0.475 mmol) in dry DMSO (2.0 mL) was added via cannula. The mixture was stirred at 50 °C for 15 h and cooled to room temperature, whereupon phosphate buffer was added (20 mL). The products were taken up into ether (5 × 15 mL). The combined extracts were washed with brine, dried, and concentrated. Initial separation was performed by flash column chromatography (silica gel; ethyl acetate/benzene, 5:95). Major product **49** was purified using an ethyl acetate/petroleum ether eluent system (silica gel; 15:85). Yield 62.3 mg (61%). Minor diastereomer **50** was similarly purified (silica gel; 2-propanol/petroleum ether, 5:95). Yield 15.0 mg (15%).

For **49**: colorless oil; IR (neat, cm^{-1}) 1746, 1715, 1614; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 2 H), 7.18 (d, J = 8.5 Hz, 2 H), 7.17 (s, 1 H), 6.83 (d, J = 8.5 Hz, 2 H), 6.45 (s, 1 H), 4.53 (br d, J = 5.4 Hz, 1 H), 4.45 (dd, J = 9.0, 2.1 Hz, 1 H), 4.27 (d, J = 10.6 Hz, 1 H), 4.03 (d, J = 10.6 Hz, 1 H), 3.78 (s, 3 H), 3.51 (dd, J = 11.2, 7.5 Hz, 2 H), 3.45 (s, 3 H), 3.40 (dd, J = 24.2, 11.2 Hz, 2 H), 3.25 (d, J = 14.9 Hz, 1 H), 3.06 (d, J = 14.9 Hz, 1 H), 2.98 (dd, J = 24.2, 15.5 Hz, 2 H), 2.67 (br t, J = 12.8 Hz, 1 H), 2.43−2.29 (m, 1 H), 2.25 (dd, J = 14.2, 2.1 Hz, 1 H), 2.08 (dd, J = 14.2, 9.0 Hz, 1 H), 2.05−2.00 (m, 2 H), 1.23 (s, 3 H), 0.87 (s, 9 H), 0.86 (s, 3 H), 0.81 (s, 3 H), 0.02 (s, 3 H), −0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 172.5, 158.9, 149.8, 143.3, 139.9, 138.1, 130.4, 129.4 (2C), 128.3, 126.3, 113.9, 113.5 (2C), 108.6, 98.6, 71.2, 70.4 (2C), 70.1, 69.4, 63.4, 55.2, 52.0, 41.7, 37.3, 36.2, 36.1, 29.8, 28.8, 25.7 (3C), 22.5, 22.3, 19.6, 18.2, −5.1, −5.4; HRMS (ES) calcd m/z $(M + Na)^+$ 747.3540, obsd 747.3503; $[\alpha]_D^{22}$ −58.0 (c 2.30, $CHCl_3$).

For **50**: colorless oil; IR (neat, cm^{-1}) 1745, 1714, 1515; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.42 (t, J = 1.6 Hz, 1 H), 7.19 (d, J = 8.6 Hz, 2 H), 7.03 (s, 1 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.52 (d, J = 1.1 Hz, 1 H), 4.76 (br s, 1 H), 4.61 (br d, J = 9.8 Hz, 1 H), 4.26 (d, J = 10.2 Hz, 1 H), 4.07 (d, J = 10.2 Hz, 1 H), 3.78−3.72 (m, 4 H), 3.59 (d, J = 11.7 Hz, 2 H), 3.51 (d, J = 11.7 Hz, 2 H), 3.42 (br d, J = 11.4 Hz, 1 H), 3.31 (s, 3 H), 3.25−3.05 (m, 1 H), 2.98−2.86 (m, 1 H), 2.62 (br d, J = 11.9 Hz, 1 H), 2.58 (br d, J = 10.9 Hz, 1 H), 2.11−1.94 (m, 3 H), 1.73 (br d, J = 5.5 Hz, 1 H), 1.25 (s, 3 H), 1.01 (s, 3 H), 0.88 (s, 3 H), 0.87 (s, 9 H), 0.00 (s, 3 H), −0.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 172.2, 159.0, 150.3, 143.6, 140.5, 138.0, 130.3, 130.0 (2C), 129.4, 125.7, 113.7, 113.4 (2C), 109.0, 71.4, 70.6, 70.4, 70.0, 69.3, 66.1, 62.7, 55.2, 51.9, 37.1, 36.2, 36.0, 29.9, 29.7, 29.2, 25.7 (3C), 22.9, 22.4, 19.6, 18.0, −5.40, −5.3; ES MS calcd m/z $(M + Na)^+$ calcd 747.3450, obsd 747.3475; $[\alpha]_D^{22}$ +33.9 (c 1.88, $CHCl_3$).

Compound 52. A solution of **49** (6.1 mg, 8.4 μmol) in acetone (2.0 mL) was stirred with 1.0 M HCl (0.25 mL) for 18 h, quenched with phosphate buffer (pH = 7, 10 mL), and extracted with CH_2Cl_2 (5 × 5 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution, dried, and evaporated. Chromatography of the residue on silica gel (elution with ethyl acetate/petroleum ether, 60:40) gave 4.4 mg (99%) of **51** as a colorless oil: IR (neat, cm^{-1}) 3461, 1742, 1715, 1614; ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.31 (d, J = 1.7 Hz, 1 H), 7.30 (s, 1 H), 7.16 (s, 1 H), 7.09 (d, J = 8.6 Hz, 2 H), 6.74 (d, J = 8.6 Hz, 2 H), 6.32 (d, J = 0.9 Hz, 1 H), 4.54 (dd, J = 9.4, 3.5 Hz, 1 H), 4.29 (dd, J = 9.7, 2.3 Hz, 1 H), 4.19 (d, J = 10.4 Hz, 1 H), 3.97 (d, J = 10.4 Hz, 1 H), 3.70−3.65 (m, 4 H), 3.54−3.46 (m, 4 H), 3.16 (d, J = 15.0 Hz, 1 H), 2.99 (d, J = 15.0 Hz, 1 H), 2.58 (br t, J = 12.9 Hz, 1 H), 2.33 (ddd, J = 13.7, 6.9, 2.7 Hz, 1 H), 2.11−1.92 (m, 5 H), 1.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 204.0, 172.0, 159.2, 147.6, 143.6, 139.8, 138.2, 130.0, 129.7 (2C), 128.3, 126.2, 114.4, 113.7 (2C), 108.5, 71.5, 70.4, 68.5, 63.9, 55.2, 52.2, 41.5, 39.3, 36.0, 35.6, 28.9, 28.1; HRMS (ES) m/z $(M + Na)^+$ calcd 547.1944, obsd 547.1923; $[\alpha]_D^{22}$ −74.7 (c 3.29, $CHCl_3$).

A solution of **51** (40 mg, 0.076 mmol) and DMAP (28 mg, 0.23 mmol) in dry CH_2Cl_2 (3.0 mL) was cooled in an ice bath, treated with acetic anhydride (12 mg, 0.11 mmol), and stirred at room temperature for 45 min prior to being quenched with phosphate buffer and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were evaporated and the residue was purified chromatographically (silica gel; ethyl acetate/petroleum ether, 40:60) to furnish 37 mg (86%) of **52**: colorless oil; IR (neat, cm^{-1}) 1739, 1731, 1715, 1614; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.40 (m, 1 H), 7.39 (s, 1 H), 7.19 (s, 1 H), 7.17 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.42−6.40 (m, 1 H), 5.69 (t, J = 6.6 Hz, 1 H), 4.37 (dd, J = 9.8, 2.2 Hz, 1 H), 4.28 (d, J = 10.3 Hz, 1 H), 4.06 (d, J = 10.3 Hz, 1 H), 3.78 (s, 3 H), 3.75 (d, J = 16.9 Hz, 1 H), 3.60 (d, J = 16.9 Hz, 1 H), 3.55 (s, 3 H), 3.23 (d, J = 15.0 Hz, 1 H), 3.15 (d, J = 15.0 Hz, 1 H), 2.74 (ddd, J = 14.5, 7.5, 7.0 Hz, 1 H), 2.41 (ddd, J = 14.0, 4.8, 4.8 Hz, 1 H), 2.18 (dd, J = 14.5, 2.3 Hz, 1 H), 2.12−1.97 (m, 6 H), 1.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 203.7, 171.8, 169.5, 159.2, 147.8, 143.6, 139.9, 138.1, 130.0, 129.7 (2C), 126.2, 125.3, 114.4, 113.7 (2C), 108.5, 71.5, 70.4, 69.7, 63.9, 55.3, 52.3, 41.5, 39.6, 35.6, 33.3, 28.9, 28.1, 21.0; HRMS (ES) m/z $(M + Na)^+$ calcd 589.2050, osbd 589.2017; $[\alpha]_D^{22}$ −94.0 (c 3.62, $CHCl_3$).

Teubrevin G (2). Acetate **52** (33.5 mg, 0.051 mmol) was dissolved in CH_2Cl_2 (1.0 mL). A solution of DDQ (26.8 mg, 0.118 mmol) in CH_2Cl_2 (1.5 mL) was introduced followed by water (0.17 mL). The reaction mixture was stirred for 8 h, quenched with a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (4 × 10 mL). The combined extracts were washed with brine, dried, and evaporated. Acetone (2.0 mL) and 1.0 M HCl (0.25 mL) were added to the residue, and the solution was stirred at room temperature for 20 h, poured into phosphate buffer, and extracted wtih CH_2Cl_2 (4 × 10 mL). The combined extracts were washed with brine, dried, and evaporated. Chromatography (silica gel; ethyl acetate/petroleum ether, 40:60) followed by preparative TLC (silica gel; 2-propanol/petroleum ether, 15:85) afforded 17.1 mg (70%) of **2**: amorphous white powder, mp 74−76 °C (lit. mp 70−80 °C); IR (film, cm^{-1}) 1737, 1722, 1713; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 0.6 Hz, 1 H), 7.45 (t, J = 1.6 Hz, 1 H), 7.23 (s, 1 H), 6.43 (t, J = 0.7 Hz, 1 H), 5.79 (dd, J = 10.7, 2.9 Hz, 1 H), 5.19 (dd, J = 10.4, 5.6 Hz, 1 H), 3.59 (d, J = 16.1 Hz, 1 H), 3.58 (d, J = 15.2 Hz, 1 H), 3.55 (d, J = 16.1 Hz, 1 H), 3.40 (br t, J = 12.4 Hz, 1 H), 3.10 (dd, J = 12.5, 5.6 Hz, 1 H), 2.78 (d, J = 15.2 Hz, 1 H), 2.37−2.33 (m, 1 H), 2.27−2.22 (m, 1 H), 2.15 (s, 3 H), 2.11 (s, 3 H), 2.09−2.02 (m, 1 H), 1.94 (dd, J = 12.5, 10.4 H, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 203.2, 172.5, 169.4, 146.6, 144.2, 140.3, 138.5, 125.6, 123.2, 114.3, 108.2, 72.9, 69.5, 65.6, 42.0, 37.8, 33.9, 33.1, 29.9, 29.4, 21.0; HRMS (ES) m/z $(M + Na)^+$ calcd 437.1212, obsd 437.1186; $[\alpha]_D^{22}$ −69.6 (c 0.46, $CHCl_3$).

Compound 54. A 15 mg (0.021 mmol) sample of **50** was hydrolyzed (0.25 mL of 1.0 M HCl) in acetone (2.0 mL) in the predescribed manner to generate **53** (6.0 mg), acetylation of which as described above afforded 5.2 mg (44%) of **54** as a colorless oil: IR (neat, cm^{-1}) 1740, 1732, 1715; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1 H), 7.44 (t, J = 1.6 Hz, 1 H), 7.23 (s, 1 H), 7.18 (d, J = 8.7 Hz, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 6.49 (d, J = 1.1 Hz, 1 H), 5.82 (br s, 1 H), 4.52 (dd, J = 10.1, 2.3 Hz, 1 H), 4.28 (d, J = 10.3 Hz, 1 H), 4.08 (d, J = 10.3 Hz, 1 H), 3.78 (s, 3 H), 3.55−3.34 (m, 3 H), 3.32 (s, 3 H), 2.91−2.75 (m, 1 H), 2.63 (dd, J = 15.2, 10.1 Hz, 1 H), 2.22−2.10 (m, 4 H), 2.09 (s, 3 H), 2.06 (s, 3 H), 1.78 (br d, J = 15.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1, 203.5, 171.8, 169.7, 159.1, 147.6, 143.9, 140.5 (2C), 130.1 (2C), 130.0, 125.4, 124.3, 115.1, 113.5 (2C), 108.9, 70.0, 68.7, 67.3, 62.6, 55.2, 52.1, 41.7, 33.3, 32.2, 29.7, 29.2, 26.0, 21.3; ES MS m/z $(M + Na)^+$ calcd 589.2050, obsd 589.2008; $[\alpha]_D^{21}$ −2.0 (c 0.46, $CHCl_3$).

Teubrevin H (3). Acetate **54** (4.9 mg, 8.7 μmol) was deprotected with DDQ (3.9 mg, 17 μmol) in CH_2Cl_2 (0.4 mL) as described earlier. The resultant product was dissolved in acetone (2.0 mL) containing 0.25 mL of 1.0 M HCl, stirred at room temperature for 20 h, and worked up in identical fashion to its epimer. There was isolated 2.4 mg (71% based on recovered **54**) of **3** as a colorless oil: IR (neat, cm^{-1}) 1767, 1738, 1731, 1713; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 1 H), 7.41 (t, J = 1.6 Hz, 1 H), 7.31 (s, 1 H), 6.40 (d, J = 0.8 Hz, 1 H), 5.93 (dd, J = 4.9, 2.2 Hz, 1 H), 5.53 (t, J = 7.5 Hz, 1 H), 3.90 (br t, J = 13.6 Hz, 1 H), 3.78 (d, J = 14.8 Hz, 1 H), 3.64 (d, J = 15.9 Hz, 1 H), 3.59 (d, J = 15.9 Hz, 1 H), 2.97 (dd, J = 13.9, 8.0 Hz, 1 H), 2.83 (d, J = 14.8 Hz, 1 H), 2.35−2.31 (m, 1 H), 2.22−2.17 (m, 4 H), 2.16−2.06 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 203.2, 173.5, 169.7, 147.2, 144.1, 141.5, 140.3, 123.7, 123.4, 115.0, 108.6, 71.9, 67.1, 63.6, 42.0, 33.6, 32.9, 31.6, 29.7, 29.6, 21.3; ES MS m/z $(M + Na)^+$ calcd 437.1212, obsd 437.1181; $[\alpha]_D^{22}$ +52.5 (c 0.20, $CHCl_3$).

Acknowledgment. We are grateful to Prof. B. Rodriguez (Madrid) for copies of the ^{1}H and ^{13}C NMR spectra of teubrevin H and John Hofferberth for the MM3 calculations. I.E. was an Evans Fellow during 2000−2001.

Supporting Information Available: Experimental procedures and spectroscopic data for those intermediates not described in the text proper, alongside the computer-generated structures for the four conformations of **G** presented in Table 1 (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

JA010313+