Novel Total Synthesis of (+)-Eremantholide A

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Stereoselective total synthesis of (+)-eremantholide A (**1**), a cytotoxic furanoheliangolide sesquiterpene, was accomplished in an enantiospecific fashion. The total synthesis featured the following three key synthetic strategies. (1) Intramolecular cyclization of carbon-radicals derived from xanthates **19a** or **19b** proceeded regio- and stereoselectively in an exclusive 5-exo-dig mode to provide bicyclic lactones **20a** or **20b**. Further functional group manipulations of **20a** and **20b** efficiently afforded a highly substituted 3,7-dioxabicyclo[3.3.0]octan-2-one derivative **34**, which served as a synthetic equivalent to the A/B ring system in **1**. (2) Alkylation of the enolate of 3(2*H*)-furanone **36** with triflate **35** was thoroughly investigated to maximize formation of the C-alkylated diastereomers, either 10*R*-isomer **37** or 10*S*-isomer **38**. It was found that choice of the base, solvent, and/or additive was critical to the diastereoselectivity. Furthermore, the 10*R*-isomer **50** was also prepared in increased yield and improved diastereoselectivity by coupling **36** with A/B ring equivalent **49**. (3) In a later stage of the total synthesis, construction of the strained 11-oxabicyclo-[6.2.1]undeca-2,10-dien-9-one system (the C/D ring) was accomplished by means of an intramolecular vinylogous aldol reaction of aldehyde **52**, prepared from 10*R*-isomer **40**, followed by base-catalyzed *β*-elimination of the corresponding mesylates **54**. On the other hand, by employing analogous reaction conditions, the 10*S*-isomer **56** was transformed into unnatural (−)-10-*epi*-eremantholide A (**61**).

Introduction

In 1975, Le Quesne and co-workers isolated a modified germacranolide (furanoheliangolide) sesquiterpene, (+)-eremantholide A (**1**) (Figure 1) from the stem parts of the Brazilian plant *Eremanthus elaeagnus*, one of the rare woody composites.[1] Two structural relatives of **1**, (+)-eremantholide B (**2**) and (−)-eremantholide C (**3**), were also isolated from the same plant as minor components (absolute stereochemistries of both **2** and **3** are uncertain to date).[2] Later, compounds **1** and **2** were also isolated from other *Eremanthus* species by Herz and coworkers.[3] This structurally novel and biogenetically intriguing modified germacranolide sesquiterpene **1** was reported to exhibit a significant inhibitory activity against cells derived from human carcinoma of the nasopharynx (KB) in vitro.[1] The gross structure of **1** and its relative stereochemistry were determined by the Le Quesne group by means of extensive spectroscopic studies, and was finally confirmed by X-ray crystallographic analysis.[1,2] On the basis of literature precedent,[4] the Le Quesne group proposed the absolute stereochemistry of **1** as that depicted in Figure 1. Some novel characteristics of the structure of **1** are (1) a highly substituted 3,7-dioxabicyclo-[3.3.0]octan-2-one substructure (referred to as the A/B ring system) containing five stereogenic centers, one of which bears an angular methyl group (C11, eremantholide numbering); (2) a strained 11-oxabicyclo[6.2.1]-undeca-2,10-dien-9-one substructure possessing two conjugated double bonds (C2-C3 and C4-C5, referred to as the C/D ring system); (3) a 2,2,5-trisubstituted 3(2*H*)-furanone ring system (ring D). Two structurally related natural products of **1**, lychnophorolide A (**4**)[5] and ciliarin (**5**),[6] were reported as biologically interesting substances. That the biogenesis of **1** from the ciliarin-type precursors may involve an intramolecular conjugate addition of a hydride, which would unite its α-methylene *γ*-lactone moiety and the adjacent acyloxy side chain (A/B ring formation), was proposed by the Le Quesne group.[1,2] It was recognized that most members of the cytotoxic mono- and sesquiterpenes such as iridoids and germacranolides possess an α-methylene *γ*-lactone moiety in their struc-

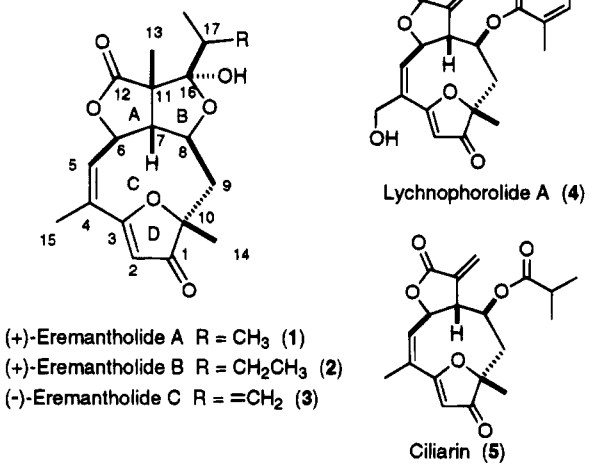


Figure 1.

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1995.

(1) Raffauf, R. F.; Huang, P.-K. C.; Le Quesne, P. W.; Levery, S. B.; Brennan, T. F. *J. Am. Chem. Soc.* **1975**, *97*, 6884.

(2) Le Quesne, P. W.; Levery, S. B.; Menachery, M. D.; Brennan, T. F.; Raffauf, R. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1572.

(3) Herz, W.; Kumar, N.; Vichnewski, W.; Blount, J. F. *J. Org. Chem.* **1980**, *45*, 2503.

(4) Kupchan, S. M.; Kelsey, J. E.; Sim, G. A. *Tetrahedron Lett.* **1967**, 2863.

(5) Le Quesne, P. W.; Menachery, M. D.; Pastore, M. P.; Kelley, C. J.; Brennan, T. F.; Onan, K. D.; Raffauf, R. F.; Weeks, C. M. *J. Org. Chem.* **1982**, *47*, 1519.

(6) (a) Bohlmann, F.; Mahanta, P. K.; Natu, A. A.; King, R. M.; Robinson, H. *Phytochemistry* **1978**, *17*, 471. (b) Chowdhury, P. K.; Sharma, R. P.; Thyagarajan, G.; Herz, W.; Govindan, S. V. *J. Org. Chem.* **1980**, *45*, 4993.

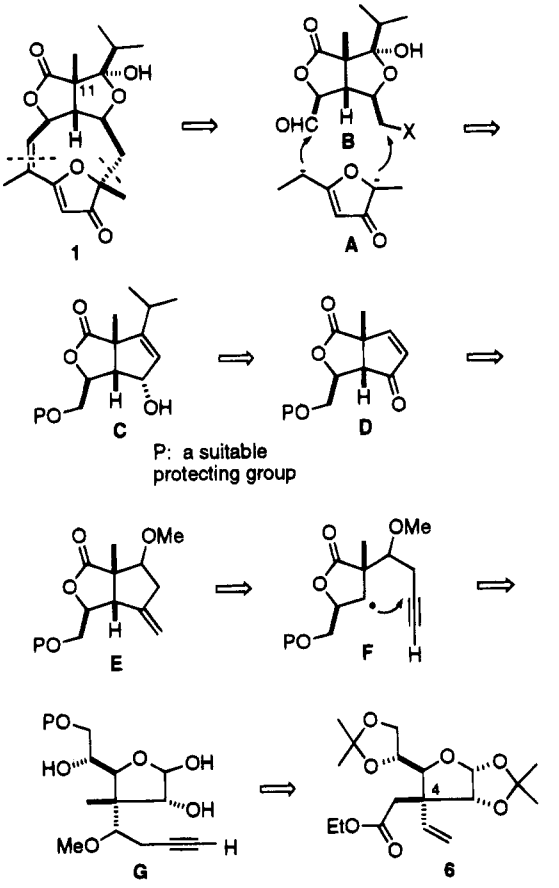
0022-3263/95/1960-8179$09.00/0

ture, which was consistently implicated as the site of nucleophilic attack by enzymes and/or nucleic acids.[7] It is particularly interesting to note, therefore, that compound **1** maintains its cytotoxic activity despite the absence of an α-methylene γ-lactone unit in its structure. To correlate the structure–cytotoxicity relationship in **1**, the Le Quesne group described an experimental result obtained by treatment of **1** with propanethiol.[2] They obtained a 1:1 mixture of propanethiolate adducts from a 1,6-Michael-type addition of the thiolate at the δ-carbon (C5) in the C-ring to the β-face of the molecule.

Owing to their structural uniqueness and cytotoxic properties, compound **1** and structurally related natural products were targets for total synthesis by several groups.[8-11] In 1991, Boeckman and co-workers completed the first total synthesis of **1**, establishing its speculated absolute stereochemistry as depicted in Figure 1.[12] Herein, we wish to disclose in detail our enantiospecific total synthesis of **1**,[13] achieved by a completely dissimilar synthetic concept from that of the Boeckman,[12] starting with our previously reported enantiopure building block **6**.[14] In addition, we describe the synthesis of the C10-diastereomer of **1**, (−)-10-*epi*-eremantholide A (**61**).

Retrosynthetic Analysis. One of the current interests in the field of synthetic carbohydrate chemistry is to investigate the stereochemical outcome of cyclization reactions initiated by a free radical[15] generated at an appropriate carbon of carbohydrate templates. In many cases, these approaches provide highly functionalized carbocycles. A number of examples manifest the utility of this strategy, especially in the context of natural products synthesis.[16] Taking into consideration this recent trend,[17] we envisaged use of this carbon-radical carbocyclization strategy as a means for stereoselective construction of the A/B rings system in **1**. Our retrosynthetic analysis is outlined in Scheme 1. First, disconnection of two carbon–carbon bonds (C4–C5 and C9–C10) in **1** leaves two fragments, the A/B ring equivalent (**B**) and a disubstituted 3(2*H*)-furanone derivative (**A**). Our planned convergent synthesis of **1** would therefore feature the coupling of **B** and **A** at a late stage in the synthesis. Hopefully, these crucial steps would be achievable, first by α′-alkylation of the enolate of **A** by displacement of X in **B** followed by an intramolecular vinylogous aldol reaction[18] to construct the carbon skeleton of **1**. Although we doubted this unprecedented strategy for the union of the A/B and D-rings, the direct connection of 3(2*H*)-furanone **A** to the A/B ring equivalent **B** seemed to be a highly attractive approach and would shorten the overall reaction sequence. The A/B ring equivalent, a 1,4,6,8,8-pentasubstituted 3,7-dioxabicyclo[3.3.0]octan-2-

Scheme 1



(7) Cassady, J. M.; Suffness, M. In *Medicinal Chemistry*; Cassady, J. M.; Douros, J. D., Eds.; Academic: New York, 1980; Volume 16 (Anticancer Agents Based on Natural Products Models), Chapter 7 (*Chem. Abstr.*, **1981**, *94*, 76386). Also, see: Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147.

(8) Tam, T. F.; Fraser-Reid, B. *J. Org. Chem.* **1980**, *45*, 1344.

(9) McDougal, P. G.; Oh, Y.-I.; VanDerveer, D. *J. Org. Chem.* **1989**, *54*, 91.

(10) Caine, D.; Venkataramu, S. D.; Kois, A. *J. Org. Chem.* **1992**, *57*, 2960. Also, see: Caine, D.; Arant, M. E. *Tetrahedron Lett.* **1994**, *35*, 6795.

(11) The total syntheses of racemic jatrophone, epijatrophone, (+)-hydroxyjatrophone A, and (+)-hydroxyjatrophone B, antileukemic macrocyclic diterpenes having a spiro-3(2*H*)-furanone substructure, were reported by Smith and co-workers in 1989: (a) Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219. (correction: *J. Am. Chem. Soc.* **1981**, *103*, 4652). (b) Smith, A. B., III; Lupo, A. T., Jr.; Ohba, M.; Chen, K. *J. Am. Chem. Soc.* **1989**, *111*, 6648.

(12) Boeckman, R. K., Jr.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682. For their early attempts to construct the A/B ring system, see: Boeckman, R. K., Jr.; Heckendorn, D. K.; Chinn, R. L. *Tetrahedron Lett.* **1987**, *28*, 3551.

(13) The total synthesis of **1** was published in preliminary form: Takao, K.; Ochiai, H.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *Tetrahedron Lett.* **1995**, *36*, 1487.

(14) Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1201.

(15) A recent leading review on free radical reactions as applied to organic synthesis: Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 715–777 and pp 779–831.

(16) Some recent publications concerning carbon-radical additions or cyclizations involving carbohydrate templates: (a) Garner, P. P.; Cox, P. B.; Klippenstein, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4183. (b) Henry, K. J., Jr.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 5128. (c) López, J. C.; Gómez, A. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1533. (d) Gómez, A. M.; López, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4048. (e) Ward, D. E.; Kaller, B. F. *J. Org. Chem.* **1994**, *59*, 4230. (f) Mootoo, D.; Wilson, P.; Jammalamadaka, V. *J. Carbohydr. Chem.* **1994**, *13*, 841. (g) Velázquez, S.; Jimeno, M. L.; Huss, S.; Balzarini, J.; Camarasa, M.-J. *J. Org. Chem.* **1994**, *59*, 7661. (h) Velázquez, S.; Camarasa, M.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 2141. (i) De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Winkler, T. *Synlett*, **1994**, 330. (j) Lesueur, C.; Nouguier, R.; Bertrand, M. P.; Hoffmann, P.; De Mesmaeker, A. *Tetrahedron* **1994**, *50*, 5369. (k) Mayon, P.; Chapleur, Y. *Tetrahedron Lett.* **1994**, *35*, 3703. (l) Ingall, A. H.; Moore, P. R.; Roberts, S. M. *Tetrahedron: Asymmetry* **1994**, *5*, 2155. (m) Marco-Contelles, J.; Bernabé, M.; Ayala, D.; Sánchez, B. *J. Org. Chem.* **1994**, *59*, 1234. (n) López, J. C.; Gómez, A. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1993**, 762. (o) Martin, O. R.; Xie, F.; Kakarla, R.; Benhamza, R. *Synlett*, **1993**, 165. (p) Malanda, J.-C.; Doutheau, A. *J. Carbohydr. Chem.* **1993**, *12*, 999. (q) Marco-Contelles, J.; Ruiz, P.; Martínez, L.; Martínez-Grau, A. *Tetrahedron* **1993**, *49*, 6669. (r) Marco-Contelles, J.; Sánchez, B. *J. Org. Chem.* **1993**, *58*, 4293.

(17) Previously, we reported carbocyclization of a carbon-radical in a carbohydrate template derived from **6** which leads to a highly functionalized cyclohexane dicarboxylate bearing a spiro carbon: Tadano, K.; Murata, T.; Kumagai, T.; Isshiki, Y.; Ogawa, S. *J. Carbohydr. Chem.* **1993**, *12*, 1187.

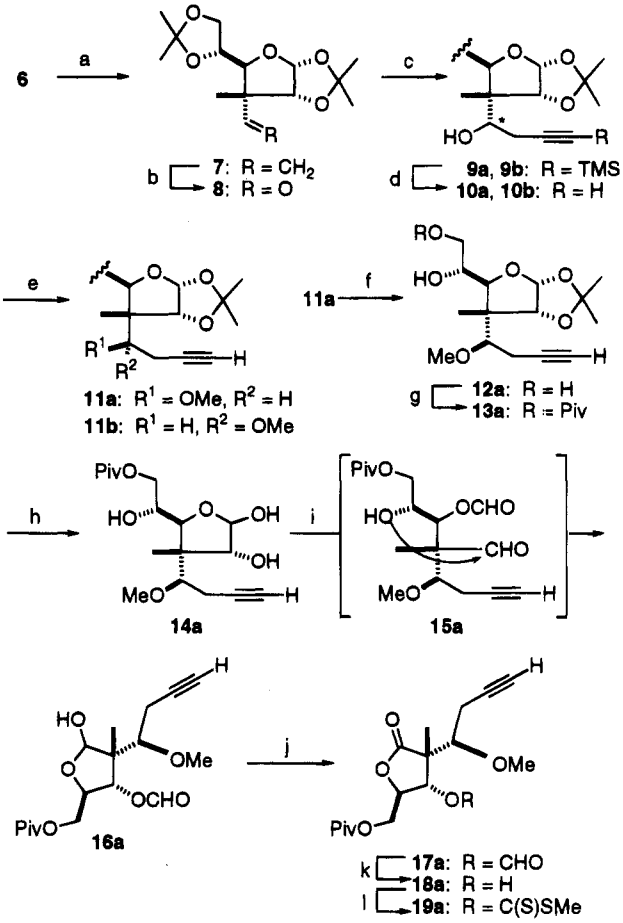
(18) A recent publication on an intramolecular vinyloguous aldol approach to natural product synthesis: Metz, P.; Bertels, S.; Fröhlich, R. *J. Am. Chem. Soc.* **1993**, *115*, 12595.

one **B**, was then expected to be obtained from bicyclic cyclopentenol γ-lactone **C** through ozonolysis followed by intramolecular ketalization of the resulting γ,δ-dihydroxy carbonyl compound. The fact that natural **1** exists solely as an α-hydroxy hemiketal suggested to us that this intramolecular ketalization would provide **B** and not the undesired C16 β-hydroxy isomer. The isopropyl group in **C** was to be introduced through a 1,4-conjugate addition of an isopropyl unit into intermediate **D** followed by regeneration of the enone system using a conventional selenylation/oxidation strategy. The latter **D** was to be prepared from γ-lactone **E**, in which the *exo*-methylene and methoxy groups would serve as precursors for introduction of the enone structure in **D**. For access to this bicyclic intermediate **E**, we anticipated that an intramolecular carbocyclization initiated by a free radical such as in **F** would be a promising approach in the sense of the regio- and stereochemical control. This radical **F** was to be obtained from a furanose derivative such as **G** via oxidative glycol cleavage, spontaneous intramolecular acetal formation, γ-lactone formation, and introduction of a xanthate group as a radical precursor. The intermediate **G**, carrying a 3-(1′-methoxy-1′-propargyl)methyl group, was to be prepared from **6**.[14] Previously, we demonstrated the versatility of **6** as an enantiopure building block in total syntheses of several natural products[19] such as (+)-asteltoxin,[20] a homolog of (+)-pantolactone,[21] and insect pheromones (−)-anastrephin and (−)-epianastrephin.[22] In the present synthetic venture, C4 in **6** would be ultimately transformed to C11 of **1**. With this conceptually novel synthetic scheme in our minds, we embarked on the total synthesis of **1**.[23]

Results and Discussion

Construction of the A/B Ring System by Intramolecular Carbon-Radical Cyclization. Preparation of the xanthate esters **19a** and **19b**, substrates for the proposed radical cyclization, began with known compound **7**, which was readily prepared from **6** in three steps.[14] Ozonolysis of the vinyl group in **7** followed by reductive workup gave aldehyde **8**, which was then treated with the anion of 1-(trimethylsilyl)propyne, prepared with *n*-BuLi in THF, resulting in the introduction of a 3-butyn-1-ol moiety at C4 of **8**. The adducts **9a** and **9b** were obtained as a 6:1 inseparable mixture of diastereomers in a combined yield of 74% from **7** (Scheme 2). Assignment of absolute stereochemistry to the newly introduced stereogenic center in **9a** and **9b** was carried out based on NOE experiments of advanced intermediates **20a** and **20b** (*vide infra*). Consequently, the *R*-configuration was assigned to the major adduct **9a**. This diastereoselective bias in the attack of the propyne anion to **8** was remarkable, but was of no consequence in our synthetic scheme since both hydroxy-bearing sp^3-carbons

Scheme 2[a]



[a] (a) Reference 14; (b) O_3 then PPh_3, CH_2Cl_2, −78 °C; (c) $MeCCSiMe_3$, *n*-BuLi, THF, −78 °C; (d) *n*-Bu_4NF, THF, −15 °C; (e) NaH, MeI, DMF; (f) 60% aqueous AcOH; (g) PivCl, pyridine; (h) 60% aqueous TFA; (i) $NaIO_4$, aqueous MeOH; (j) PCC, MS-4A, CH_2Cl_2; (k) Et_3N, MeOH; (l) NaH, imidazole, CS_2 and then MeI, THF, −15 °C.

in **9a** and **9b** were to become sp^2-carbons at a later stage. One plausible account for this diastereoselectivity is as follows. Taking into consideration the steric environment in the transition state, the formyl group in **8** is likely to be away from the neighboring *O*-isopropylidene group thus avoiding an unfavorable nonbonded interaction. This means that the formyl group would orient itself exo to the bicyclo[3.3.0]octane skeleton. Under this steric circumstance, the attack of the 3-(trimethylsilyl)propyne anion would take place preferentially from the less congested *re*-face leading to preferential formation of **9a**. Desilylation of the mixture of **9a** and **9b** with a catalytic amount of tetrabutylammonium fluoride (TBAF) in THF containing a small amount of H_2O provided **10a** and **10b** as an inseparable mixture in 93% yield. The hydroxy groups in the mixture were protected as their methyl ethers in the usual manner. At this stage, the resulting methyl ethers **11a** and **11b** were cleanly separated by chromatography in 83% and 14% yields, respectively. Subsequent reactions of **11a** to **19a** and of **11b** to **19b** were executed separately. Selective removal of the 5,6-*O*-isopropylidene group (carbohydrate numbering) in **11a** with 60% aqueous acetic acid and selective esterification of the primary hydroxy group in the resulting diol **12a** with pivaloyl chloride (PivCl) afforded monoester **13a** in 98% yield. Using 60% aqueous trifluoroacetic acid (TFA), the 1,2-*O*-isopropylidene group in **13a** was hydrolyzed to

(19) Tadano, K. In *Studies in Natural Products Chemistry*; Attaur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 10, pp 405–455 (*Chem. Abst.* **1993**, *118*, 80655).

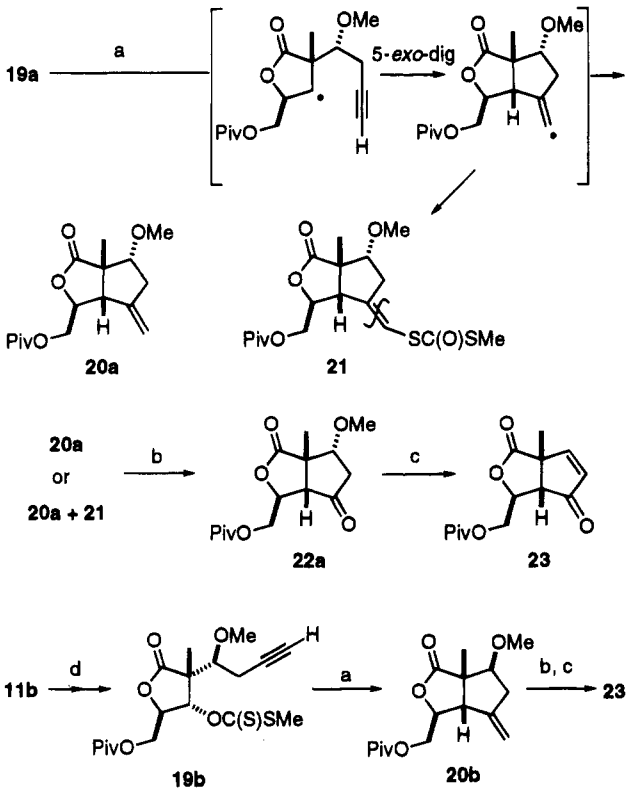
(20) Tadano, K.; Yamada, H.; Idogaki, Y.; Ogawa, S.; Suami, T. *Tetrahedron* **1990**, *46*, 2353.

(21) Tadano, K.; Kanazawa, S.; Ogawa, S. *J. Org. Chem.* **1988**, *53*, 3868.

(22) Tadano, K.; Isshiki, Y.; Minami, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 6266.

(23) In our early attempts to construct A/B ring equivalents similar to intermediate **D** in Scheme 1, we experienced much difficulty in C7–C8 carbon–carbon bond formation by means of intramolecular aldol or Wittig (Horner–Emmons) reactions: Koshimura, H. Unpublished results.

Scheme 3[a]



[a] (a) n-Bu_3SnH, AIBN, toluene (0.01 M solution), reflux; (b) O_3 and then PPh_3, CH_2Cl_2, −78 °C; (c) DBU, benzene, reflux; (d) same as f–l in Scheme 2.

afford hemiacetal **14a** in 66% yield. The starting material **13a** was also recovered in 17% yield. We were unable to identify conditions resulting in higher yields of **14a**. The vicinal diol in **14a** was oxidized with $NaIO_4$ and the resulting aldehyde **15a** underwent a spontaneous intramolecular acetalization as shown to provide a mixture of hemiacetals **16a**. Pyridinium chlorochromate (PCC) oxidation[24] of **16a** followed by brief treatment of the resulting γ-lactone **17a** with triethylamine afforded **18a** in 88% yield over three steps. Using a standard procedure, the hydroxy-lactone **18a** was converted to the xanthate ester **19a** in 95% yield.

Optimization of the reaction conditions for intramolecular cyclization of the radical derived from xanthate **19a** led to the following conditions, which were found to be reproducible on a multigram scale. To a dilute (0.01 M) solution of **19a** in refluxing toluene was added slowly (via a syringe pump) a solution of n-Bu_3SnH and a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) in toluene (Scheme 3). The reaction proceeded completely, and the cyclization product **20a** was obtained in 87% yield. When this reaction was carried out in refluxing benzene, an approximately 5:1 (^1H NMR analysis) inseparable mixture of **20a** and vinyl dithiocarbonate **21** was obtained. The structure of **21** as a 1:1 *E*/*Z*-mixture was deduced based on the ^1H NMR analysis. We have no reasonable explanation for the difference in the product distribution observed in these two solvent systems.[25] As expected, this ring closure occurred by addition of the carbon-radical generated at C4 in **19a** to the acetylenic carbon in a regio- (5-exo-dig)[26] and stereoselective (*cis*-fused) manner. The resulting vinyl radical was quenched by a hydrogen atom or underwent further reaction with **19a** to give **20a** or **21**, respectively.[25] Neither the alternative 3-oxabicyclo[4.3.0]non-6-en-2-one, formed from a 6-endo-dig mode, nor the uncyclized deoxygenated product, formed by hydrogen quenching of the initially formed C4 carbon-radical, were found in the reaction mixture. The stereochemistry of the ring juncture and configuration at C8 in **20a** were confirmed by ^1H NMR analysis and NOE experiments. As depicted in Scheme 3, significant signal enhancements at H5 and H8 were observed when the angular methyl singlet was irradiated. The *cis*-ring fusion and α-configuration of the methoxy group in **20a** (and the *R*-configuration of the methoxy-bearing carbon in precursors **11a**–**19a**) were identified at this stage. Thus, a practical and stereoselective route to a synthetic A/B-ring precursor, **20a**, was defined.

Ozonolysis of the *exo*-methylene moiety in **20a** followed by a DBU-catalyzed β-elimination of the methoxyl group in the resulting cyclopentanone **22a** gave bicyclic cyclopentenone **23** in 84% yield. Also, ozonolysis of the inseparable mixture of **20a** and **21** and subsequent β-elimination gave **23** in a less effective overall yield of 46% from **19a** (ca. 300 mg scale). On the other hand, the aforementioned minor adduct **11b** was analogously transformed into **23** using the same reaction sequence for the conversion of **11a** to **23**. In this sequence, the overall yield of **23** from **11b** was 13% (see Experimental Section). The *S*-configuration of the methoxy-bearing carbon in intermediates **11b**–**22b** was determined based on NOE experiments with **20b**, as shown in Scheme 3. After some experiments for optimizing the reaction conditions, we found that the yields of the carbon-radical cyclization (**19b** to **20b**, 66% with 16% recovery of **19b**) and the introduction of the enone system (**20b** to **23**, 56%) were somewhat lower compared to those for conversion of **19a** to **23**. In the case of conversion of **19b** to **20b** in refluxing toluene, however, formation of the vinyl dithiocarbonate corresponding to **21** was not observed. These parallel experiments showed that both **9a** and **9b** were suitable precursors for the preparation of **23**.

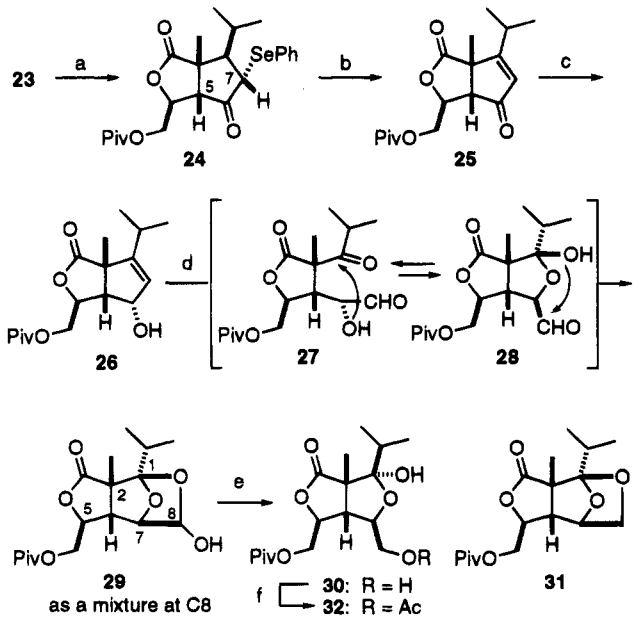
We next explored the transformation of the *cis*-fused γ-lactone cyclopentenone **23** into a 3,7-dioxabicyclo[3.3.0]-octan-2-one skeleton possessing suitable functionalities of the same oxidation states as those in the A/B ring system of **1** (Scheme 4). For installation of the isopropyl group into the B ring, 1,4-conjugate addition of an isopropyl anion equivalent and subsequent regeneration of an enone were required. This objective was efficiently achieved as follows. The addition of an isopropyl cuprate, prepared by mixing isopropylmagnesium bromide and CuBr·Me_2S complex in THF and Me_2S (4:1), to **23**

(24) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

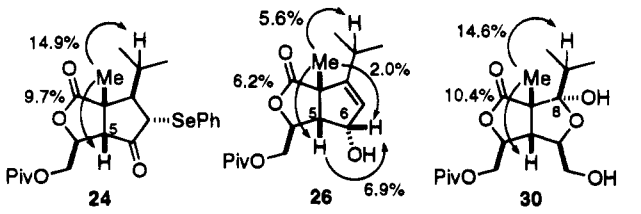
(25) For a simlar observation on the reaction of a carbon radical derived from a xanthate prepared from D-glucose, see: Marco-Contelles, J.; Ruiz-Fernández, P.; Sánchez, B. *J. Org. Chem.* **1993**, *58*, 2894.

(26) On general notation of the cyclization mode, see: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

Scheme 4[a]



NOE difference experiments of **24**, **26** and **30**



[a] (a) *i*-PrMgBr, CuBr·Me_2S, THF–Me_2S, and then PhSeCl, −78 °C; (b) $NaIO_4$, $NaHCO_3$, aqueous MeOH; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −15 °C; (d) O_3 then PPh_3, CH_2Cl_2, −78 °C; (e) $NaBH_4$, MeOH, −15 °C; (f) Ac_2O, pyridine.

followed by trapping of the resulting enolate by a selenenyl group provided **24** as a 10:1:1 diastereomeric mixture in a combined yield of 89%. On the basis of ^1H NMR analysis of the mixture, the predominant product **24** was that depicted in Scheme 4. A long range coupling between H5 and H7 ($J_{5,7}$ = 1.8 Hz) was observed. Also, 14.9% signal enhancement attributable to C*H*$(CH_3)_2$ was observed when the angular methyl was irradiated. When the reaction was carried out in the absence of Me_2S, a small amount of the 1,2-addition product (not shown) was produced, although the 1,4-adduct **24** was again the major product (33%; 32% recovery of **23**). Thus, the presence of Me_2S was essential for highest yield of **24**. Oxidative elimination of the selenoxide, prepared by $NaIO_4$ oxidation[27] of the mixture **24**, smoothly provided enone **25** in 83% yield. The keto-carbonyl in **25** was reduced chemo- and stereoselectively using Luche's conditions[28] to afford allylic alcohol **26** in 96% yield. Configuration of the newly introduced stereogenic center in **26** was determined by NOE experiments, in which 2.0% and 6.9% enhancements of the H6 signal were observed when the angular methyl and H5 were irradiated, respectively. As anticipated, hydride delivery occurred exclusively from the less-hindered β-face of the bicyclic skeleton, introducing a hydroxyl group with the desired configuration. Next, a one-step construction of the hemiketal structure in the B-ring was investigated by attempting the oxidative cleavage of the double bond in **26**. Ozonolysis of **26** followed by reductive workup (Ph_3P) resulted in the formation of tricyclic hemiacetal **29** as a 10:1 inseparable mixture of diastereomers in a combined yield of 93%. Taking into consideration the *J* value (nearly 0 Hz) between H7 and H8, it is most likely that the major hemiacetal is α-oriented. Considering the steric demands in a bicyclo[2.2.1]heptane system, the configuration at C1 of the major isomer was assumed to be that shown in Scheme 4. The formation of **29** from **26** was proposed to proceed via intermediates **27** and **28**. First, ozonolysis of **26** provided keto-aldehyde **27**, which was presumed to be in equilibrium in solution with ring-chain tautomer **28**. Further equilibration to tautomer **29** by lactol formation between the aldehyde and β-oriented hydroxy group at C8 in **28** then ensued. By exposure of **29** to $NaBH_4$ at −15 °C, the 3,7-dioxabicyclo-[3.3.0]octan-2-one **30** was isolated in quantitative yield as a single diastereomer. Under these reaction conditions, reduction of the hemiketal was not observed. Assignment of stereochemistry to the C8 hemiketal-carbon in **30** was confirmed based on NOE experiments, in which a remarkable enhancement (14.6%) of the isopropyl methine signal was observed when the angular methyl was irradiated. This exclusive formation of **30** from the reduction of **29** implies that the C-8 α-face hydroxy hemiketal structure is thermodynamically more favorable than the β-face hydroxy hemiketal epimer. Compound **30** was prone to dehydration to form tricyclic ether **31** under prolonged exposure to silica gel or in $CDCl_3$ (presumably by a trace amount of HCl contaminated). The ^1H NMR spectrum of **31**, partially formed in silica gel which was separated from **30**, verified its structure. To avoid this undesired transformation, **30** was acetylated immediately after the $NaBH_4$ reduction and gave acetate **32** in 91% yield form **29**.

Coupling of the A/B Ring Equivalents with Known 3(2*H*)-Furanone 36. Having established an efficient and stereoselective route to **32**, we next focused our attention on the coupling reaction of the A/B ring equivalent with 3(2*H*)-furanone **36**. Previously, Smith and co-workers reported[29] that several types of 2,5-disubstituted 3(2*H*)-furanones react with a wide range of alkyl halides at the α′-position (C2) preferentially under kinetically controlled deprotonation conditions, for example by using LDA as the base. They also found that the resulting 2,2,5-trisubstituted 3(2*H*)-furanones next undergo alkylation at the γ-position (C1′ of the side chain at C5) of the vinylogous enolate. Encouraged by these observations, we investigated the coupling of the A/B ring equivalent with 5-ethyl-2-methyl-3(2*H*)-furanone (**36**).[30] Prior to the coupling of the A/B ring equivalent with **36**, we searched efficient reaction conditions for the kinetic deprotonation at the α′-position of **36**. In our case, we

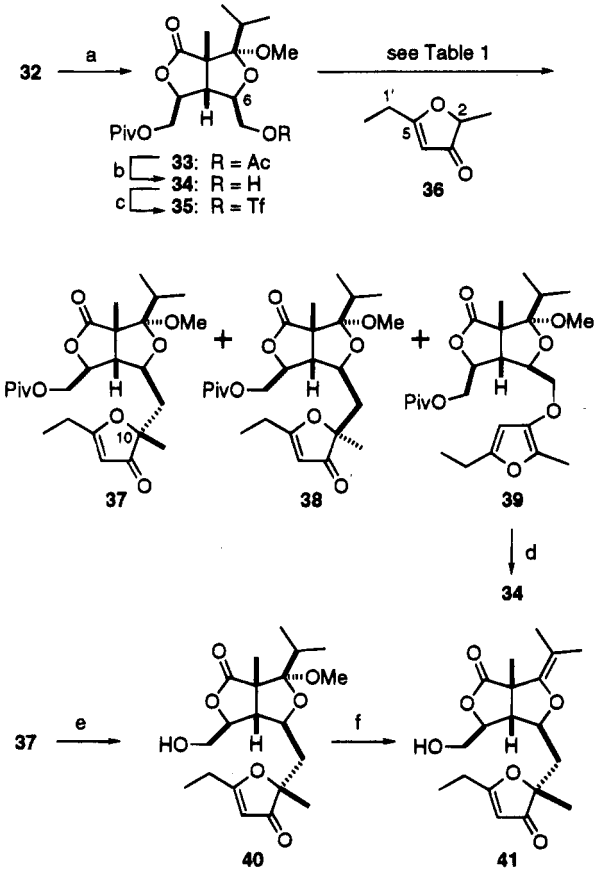
(27) (a) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813. (b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (c) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1973**, 695.

(28) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(29) (a) Smith, A. B., III.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501. (b) Smith, A. B., III.; Scarborough, R. M., Jr. *Tetrahedron Lett.* **1978**, 4193.

(30) Furanone **36** was prepared from 1-nitropropane according to the reported procedure with slight modifications in a modest overall yield. The reaction sequence for the preparation of **36** started with 1,3-dipolar cycloaddition of the corresponding silyl nitronate and methylvinyl ketone: Andersen, S. H.; Das, N. B.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G. *Acta Chem. Scand. B* **1982**, *36*, 1.

Scheme 5[a]



[a] (a) PPTS, $CH(OMe)_3$, MeOH, reflux; (b) NaOMe, MeOH, 0 °C; (c) Tf_2O, Et_3N, CH_2Cl_2, −78 °C; (d) TsOH, MeOH, 0 °C; (e) NaOMe, MeOH; (f) Amberlyst-15, MS-4A, CH_2Cl_2.

failed to alkylate the α′-position of **36** using LDA in THF at −78 °C for deprotonation and subsequent addition of ethyl iodide as an electrophile. Even after warming the reaction solution to room temparature, **36** was recovered almost quantitatively. On the other hand, alkylation of **36** using metalated bis(trimethylsilyl)amides (HMDSs), especially NaHMDS, gave the desired alkylated products. Thus, when **36** was treated with NaHMDS at −78 °C in THF and subsequently methyl iodide was added to the solution, 2,2-dimethyl-5-ethyl-3(2*H*)-furanone (24%) and 2,2-dimethyl-5-isopropyl-3(2*H*)-furanone (13%) were obtained. From these findings, we preferred to use metalated HMDSs for the coupling of the A/B ring equivalent with **36**. To convert the hydroxymethyl group at C6 of **32** to an electrophilic site, hemiketal **32** was first protected as its methyl ketal **33** in 90% yield (Scheme 5). Selective deacylation of the acetyl group in **33** was best achieved with a catalytic amount of NaOMe in MeOH providing C6 hydroxymethyl derivative **34** in 92% yield. Three typical leaving groups were introduced in the usual manner, the mesylate, bromide and iodide (not shown). We explored the coupling reaction of these electrophiles with furanone **36** under a variety of conditions, for instance using NaH and metalated HMDS as bases to generate the enolate. Unfortunately, none of the desired coupling product **37** was produced, and in many cases, unreacted starting materials were recovered intact. When the iodide was used, the C6 *exo*-methylene product (not shown) arising from elimination was obtained. To our delight, triflate **35** was found to serve as a good

Table 1. Coupling of the Triflate 35 and 3(2*H*)-Furanone 36

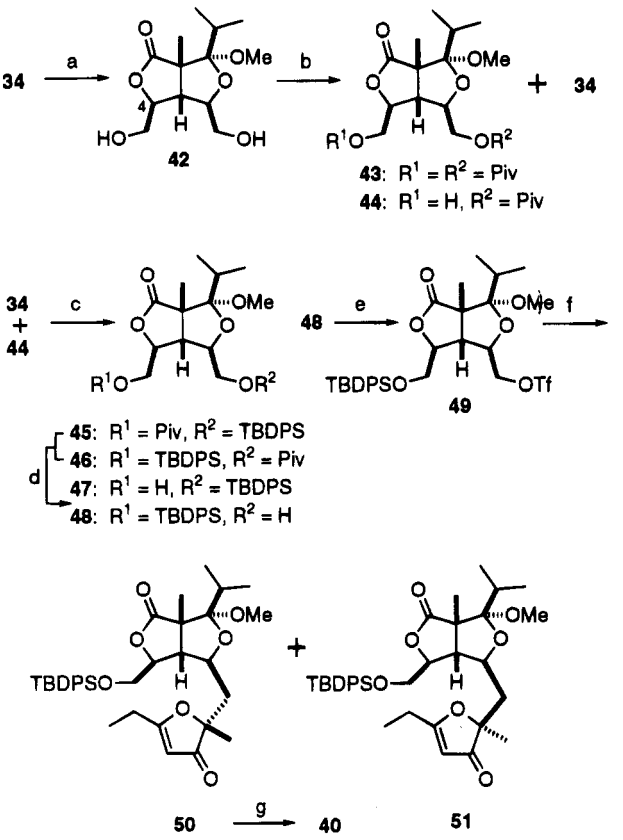
		% yield from **34**	
run	reaction conditions	**37**+**38**[a] (**37**:**38**)[b]	**39**
1	LiHMDS/toluene, −78 to 0 °C	81 (1:40)	
2	NaHMDS/toluene, −78 to −15 °C	71 (1:11)	
3	KHMDS/toluene, −78 °C	54 (1:12)	4
4	NaHMDS/ethyl ether, −78 to −15 °C	42 (1:6)	13
5	LiHMDS/THF, −78 °C to rt	29 (1:1)	33
6	NaHMDS/THF, −78 °C to rt	22 (1:1)	64
7	NaHMDS/DMF, −15 °C	9 (1:0)	10
8	LiHMDS, HMPA/toluene, −78 to 0 °C	12 (1:0)	23
9	NaHMDS, 15-crown-5/toluene, −78 °C	15 (4:1)	66
10	KHMDS, 18-crown-6/toluene, −78 °C	16 (1:0)	52

[a] Combined yield of **37** and **38**. [b] Ratios were determined based on the 270 MHz ^1H NMR analysis of the mixture.

electrophile for the desired alkylation.[31] However, triflate **35** was found to be unstable during storage at room temperature. After standing at room temperature for several hours, **35** decomposed significantly, resulting in the formation of a complex mixture. Thus, triflate **35** was used for the alkylation immediately after its preparation. Optimization of the reaction conditions to give **37** in high stereoselectivity and yield from the coupling of triflate **35** with furanone **36** was performed. For this purpose, we thoroughly investigated using a variety of metalated HMDSs in several solvents. The results are tabulated in Table 1. For instance, when the coupling reaction was carried out using LiHMDS in toluene at −78 °C followed by warming to 0 °C, C-alkylation product **38** was obtained predominantly accompanied by a small amount of desired **37** in a combined yield of 81% (run 1). The structures of **37** and **38** were unambiguously established by transforming **37** into Boeckman's synthetic intermediate[12] (*vide infra*). In this case, disappointingly, the ratio of the desired 10*R*-diastereomer **37** to the 10*S*-isomer **38** was estimated to be 1:40 based on the ^1H NMR analysis. Results from the use of other metal cations, such as sodium (run 2) and potassium (run 3) HMDSs in toluene were compared to run 1. Formation of the 10*S*-isomer **38** was slightly suppressed in both cases. However, the combined yields of **37** and **38** decreased. The solvent effect on the diastereoselectivity was investigated using Li or Na HMDS (runs 4 to 7). It was apparent that the ratio of **37** and **38** changed favorably to preferential formation of desired **37** in proportion to solvent polarity increases, i.e., from toluene to ether, THF, or DMF. However, in all cases, the use of polar solvents resulted in formation of the O-alkylation product **39**. For example, when the coupling reaction was executed using NaHMDS in THF, a 1:1 mixture of **37** and **38** was obtained in 22% yield and was accompanied by significant (64%) formation of **39** (run 6). Addition of HMPA did not dramatically affect the yield of **37**. However, crown ethers were modestly effective for preferential formation of **37** in toluene. When an equimolar amount of 18-crown-6 and KHMDS was used, the 10-*R* isomer **37** was isolated as the sole C-alkylation product, albeit in 16% yield (run 10). In this case, the O-alkylation product **39** was obtained in 52% yield. Fortunately, the O-alkylation product **39** was efficiently recycled to **34** by mild acid hydrolysis. Thus, significant quantities of **37**

(31) A previous example on the usefulness of some triflate derivatives of carbohydrate templates as good electrophiles: (a) Bruce, I.; Fleet, G. W. J.; Girdhar, A.; Haraldsson, M.; Peach, J. M.; Watkin, D. J. *Tetrahedron*, **1990**, *46*, 19. (b) Fairbanks, A. J.; Fleet, G. W. J. *Tetrahedron* **1995**, *51*, 3881.

Scheme 6[a]

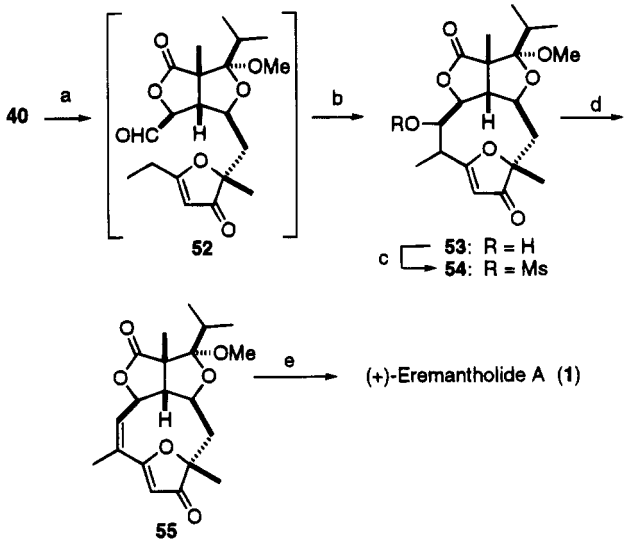


[a] (a) NaOMe, MeOH; (b) PivCl, pyridine, −15 °C; (c) TBDPSCl, DMAP, Et_3N, CH_2Cl_2; (d) NaOMe, MeOH; (e) Tf_2O, Et_3N, CH_2Cl_2, −78 °C; (f) **36**, KHMDS, toluene, −78 °C then 0 °C; (g) *n*-Bu_4NF, THF.

were accumulated from repetitive coupling/hydrolysis runs. Concerning the stereochemical outcome of the coupling reaction of triflate **35** with **36**, it could be said that the use of polar solvents or the presence of crown ethers suppressed formation of **38** at the expense of increased amounts of **39**. These results are consistent with the "naked" O-enolate being more nucleophilic than the C-enolates under these reaction conditions. The π-facial selectivity leading to predominant formation of C-alkylation product **37** using more polar conditions and crown ethers is not well understood. Depivaloylation of **37** with NaOMe gave **40**, which was converted to **41** according to Boeckman's procedure.[12] Comparison of the ^{1}H NMR and IR spectra of **41** to those of Boeckman confirmed that the configuration at C10 of **37** was *R*, and consequently that of **38** was *S*.

We also investigated the substituent effect at C4 on the diastereoselectivity in the coupling reaction. As a result, C4 silyl ether **49** was identified as a superior coupling partner (Scheme 6). This material was prepared from 4-*O*-silyl ether **48**, which in turn was prepared from **34** via diol **42**, monopivaloyl ester **44**, and silyl ether **46**. Since the regioselectivity in the monopivaloylation of **42** was not remarkable (44% of **42** was recovered for recycling), the overall yield of **48** from **34** was modest (17% over four steps). The coupling reaction of triflate **49** with **36** was executed in toluene using KHMDS as base in the absence of 18-crown-6. Fortunately, the desired 10*R*-epimer **50** and the 10*S*-isomer **51** were obtained in 57% and 22% yields from **48**, respectively, after silica gel chromatographic separation. Since the yield of the desired 10 *R*-coupling product could be

Scheme 7[a]



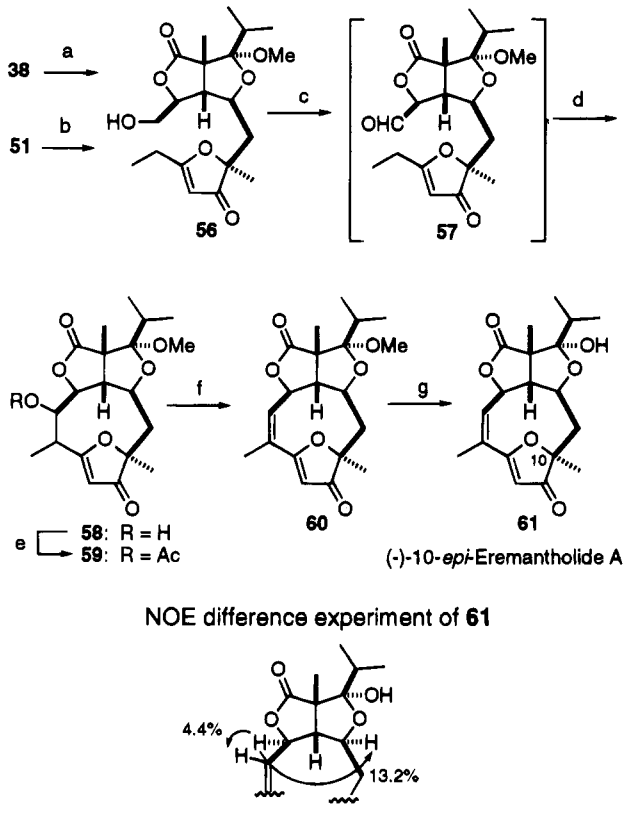
[a] (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, and then Et_3N; (b) KHMDS, 18-crown-6, THF (0.01 M solution), −78 °C; (c) MsCl, DMAP, pyridine; (d) DBU, toluene, reflux; (e) 6 M aqueous HCl−THF (1:8, v/v).

significantly improved, we did not explore the coupling of **49** with **36** further. The 10*R* configuration of **50** was confirmed by conversion to **40** by desilylation. Possible explanations for the more favorable outcome for coupling **49** with **36** (relative to **35** and **36**) might be (1) the change from a carbon-based to a silicon-based protecting group may suppress undesired side reactions at C4 arising from the former, such as depivaloylation (and possible intramolecular ether formation from displacement of triflate by the resulting alkoxide) or elimination to give an exo-olefin; (2) an overall conformational change of the electrophile's solution structure, due to the introduction of a sterically more demanding protecting group, to give a conformation from which displacement of the triflate group is more facile.[32] Consequently, by employing either **35** or **49** in the coupling reaction, access to C10-*R* diastereomers **37** or **50** was achieved in a stereoselective manner.

Total Synthesis of (+)-Eremantholide A (1). Having established preparation of **40**, an intermediate possessing all the skeletal carbons and stereochemical requirements in **1**, we needed to effect cyclization to form the C4−C5 (eremantholide numbering) double bond, thereby introducing the strained nine-membered C-ring in **1**. As mentioned earlier in the retrosynthetic analysis, it was anticipated that this ring closure would be accomplished by an intramolecular vinylogous aldol reaction using aldehyde **52** (Scheme 7). Therefore, aldehyde **52** was prepared from **40** by the oxidation procedure of Swern,[33] since pyridinium dichromate (PDC) oxidation[34] gave a complex mixture. Reaction of **52** as a dilute solution (0.01 M) in THF with NaHMDS at −78 °C resulted in the formation of an inseparable mixture of diastereomeric aldol adducts **53** in low yield (19%) from **40**. Determination of either the stereochemistry of the newly introduced stereogenic centers or the ratio of diastereomers in the mixture by ^{1}H NMR analysis was difficult due to the signal complexity observed. Other

(32) We thank a reviewer for providing us these explanations.
(33) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(34) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

Scheme 8[a]



NOE difference experiment of **61**

[a] (a) NaOMe, MeOH; (b) *n*-B_4NF, THF; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, and then Et_3N; (d) KHMDS, 18-crown-6, THF, −78 °C; (e) Ac_2O, pyridine; (f) DBU, toluene, reflux; (g) 6 M aqueous HCl−THF (1:8, v/v).

reaction products in the mixture (TLC) could not be isolated in pure form for structural identification. The yield of **53** was improved by reaction with KHMDS (as a toluene solution) in THF in the presence of 18-crown-6 at −78 °C. In this case, a mixture of two inseparable aldol adducts was obtained in 41% yield. The ratio of the diastereomers was estimated to be 3:1 based on ^1H NMR analysis; unambiguous stereochemical assignments to each diastereomer were not possible, again, owing to signal complexities. Under these basic reaction conditions, no epimerization at C6 was observed. Introduction of a leaving group into **53** was explored as a preface to introduction of the desired C4−C5 double bond. Mesylation of **53** with excess of mesyl chloride proceeded smoothly to afford a mixture of mesylates **54** in 91% yield. Previously it was reported[12] that dehydroeremantholide A is base sensitive, especially when exposed to less hindered strong base. Therefore, we used 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as a bulky base for the β-elimination. Dienone **55** was obtained uneventfully in 76% yield by refluxing **54** in toluene in the presence of an excess amount of DBU. Deblocking of the methyl ketal in **55** by acid hydrolysis ultimately provided (+)-eremantholide A (**1**) in 82% yield. Synthetic **1** was identical to an authentic sample of natural **1**, kindly provided by Professor Le Quesne, in all respects (mp, $[\alpha]_D$, IR, ^1H and ^{13}C NMR, LR and HRMS, TLC).

Synthesis of (−)-10-*epi*-Eremantholide A (61). It was recognized that C-alkylation products **38** and **51** were transformable into unnatural 10-*epi*-eremantholide A (**61**) by the analogous reaction sequence used for the synthesis of **1** from **37** and **50** (Scheme 8). Deprotection of the pivaloyl group or the TBDPS group in **38** or **51** afforded **56** in 91% or 89% yield, respectively. Swern oxidation of **56** and subsequent intramolecular vinylogous aldol reaction of the resulting aldehyde **57** under the same conditions used for **52** provided aldol product **58** in 37% yield as a single diastereomer. Again, determination of the structure of this aldol product was not possible. Mesylation of **58** was problematic, whereas acetylation proceeded uneventfully to provide acetate **59** in essentially quantitative yield.[35] DBU-mediated β-elimination of **59** provided methyl ketal **60** quantitatively. Finally, acid hydrolysis of **60** afforded (−)-10-*epi*-eremantholide A (**61**) in 88% yield. Confirmation of the stereochemistry at C6 (eremantholide numbering) in **61** was provided by the ^1H NMR analysis and NOE experiments (Scheme 8). Again, no epimerization at C6 occurred under the Swern oxidation and the aldol reaction conditions (**56** to **58**).

Conclusion. Completion of the stereoselective total syntheses of (+)-eremantholide A (**1**) and its10-epimer **61**, starting from the enantiopure chiral building block **6**, were achieved. The present syntheses showed the effectiveness of a carbon-radical carbocyclization process from enantiopure xanthates **19a** and **19b**, which were readily prepared from **6**, for access to the bicyclic templates **20a** and **20b**. These two intermediates were efficiently converted to the A/B ring equivalent **32** through oxidative cleavage of the cyclopentene ring in an advanced intermediate **26** followed by intramolecular ketalization. Also key to the syntheses was the direct attachment of the furanone **36** to the A/B ring equivalents **35** and **49**. The crucial intramolecular vinylogous aldol reactions using **52** or **57**, obtained by the coupling of triflates **35** or **49** with 3(2*H*)-furanone **36**, were also demonstrated as a feasible approach to the construction of the strained nine-membered C-ring in **1** and **61**.

Experimental Section

Melting points are uncorrected. Specific rotations were measured in a 10 mm cell. ^1H NMR spectra were recorded at 90 MHz or at 270 MHz, and ^{13}C NMR spectra were recorded at 67.5 Hz. All spectra were recorded in $CDCl_3$ as solvent, and chemical shifts are reported in δ relative to TMS. Combustion analysis was performed by the staff at our Instrumental Measurement Center. Thin-layer chromatography (TLC) was performed with a glass plate coated Kieselgel 60 GF_{254} (Merck). Organic extracts were dried over anhydrous Na_2SO_4. Crude reaction mixtures were purified by chromatography on silica gel 60 K070 (Katayama Chemicals). Reagents and solvents were removed by concentration in vacuo using an evaporator with a bath at 35−45 °C. Solvents were dried (drying reagent in parenthesis) and distilled prior to use: tetrahydrofuran (THF) ($LiAlH_4$, then Na/benzophenone ketyl), *N*,*N*-dimethylformamide (DMF) (CaH_2), CH_2Cl_2 (CaH_2), benzene (CaH_2), dimethyl sulfoxide (DMSO) (CaH_2), pyridine (NaOH) and toluene (CaH_2).

Mixture of (2*R*,3*R*,4*R*,5*S*)-4-[(1*R* and *S*)-1-Hydroxy-4-(trimethylsilyl)-3-butynyl]-2,3-(isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-4-methyltetrahydrofuran (9). To a cold (−78 °C) stirred solution of **7**[14] (14.1 g, 49.6 mmol) in CH_2Cl_2 (150 mL) was bubbled ozone (O_2 containing ca. 3% O_3) for 5 h to a persistent light blue color. To this solution was added Ph_3P (15.6 g, 59.5 mmol), and the solution was stirred for 1 h while warming to rt. The solvent was removed by evaporation in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to give 12.7 g (89%) of **8** as a colorless oil: R_f

(35) On the contrary, acetylation of the aldol mixture **53** gave a complex mixture from which the corresponding acetates could not be obtained in a pure state.

0.40 (EtOAc/hexane, 1:3); ^{1}H NMR (90 MHz) δ 1.12 (s, 3 H), 1.30, 1.31, 1.38, 1.59 (4 s, each 3 H), 4.09 (d, J = 3 Hz, 2 H), 4.10 (ddd, J = 3, 3, 8 Hz, 1 H), 4.40 (d, J = 4 Hz, 1 H), 4.54 (d, J = 8 Hz, 1 H), 5.84 (d, J = 4 Hz, 1 H), 9.74 (s, 1 H).

The following reaction was carried out under Ar. To a cold (0 °C) stirred solution of *n*-BuLi (1.6 M solution in hexane, 42 mL, 67 mmol) in THF (150 mL) was added 1-(trimethylsilyl)-1-propyne (9.9 mL, 67 mmol), and then the solution was stirred at 0 °C for 30 min and then cooled to −78 °C. To this solution was added a solution of **8** (12.7 g, 44.4 mmol) in THF (50 mL). After being stirred at −78 °C for 2 h, the solution was quenched with saturated aqueous NH_4Cl (5 mL), diluted with H_2O (1 L), and extracted with CH_2Cl_2 (500 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to give 14.7 g (83%) of an inseparable diastereomeric mixture (6:1) of **9** as colorless crystals: mp 109−110 °C; R_f 0.31 (EtOAc/hexane, 1:4); IR (neat) 3460, 2980, 2950, 2170, 1450, 1410 cm^{-1}; ^{1}H NMR (270 MHz) for major isomer δ 0.17 (s, 9 H), 0.99 (s, 3 H), 1.29, 1.37, 1.47, 1.52 (4 s, each 3 H), 1.67 (br s, 1 H), 2.56 (dd, J = 8.3, 17.2 Hz, 1 H), 2.68 (dd, J = 3.4, 17.2 Hz, 1 H), 3.86−4.22 (m, 5 H), 4.22 (d, J = 3.4 Hz, 1 H), 5.69 (d, J = 3.4 Hz, 1 H); ^{1}H NMR for minor isomer δ 0.16 (s, 9 H), 0.94 (s, 3 H), 1.32, 1.34, 1.47, 1.56 (4 s, 3 H), 2.52 (dd, J = 8.3, 17.7 Hz, 1 H), 2.88 (dd, J = 3.4, 17.7 Hz, 1 H), 4.47 (d, J = 3.4 Hz, 1 H), 5.73 (d, J = 3.4 Hz, 1 H). HRMS calcd for $C_{19}H_{31}O_6Si$ ($M^+ - CH_3$) m/z 383.1887, found 383.1883.

Mixture of (2*R*,3*R*,4*R*,5*S*)-4-[(1*R* and *S*)-1-Hydroxy-3-butynyl]-2,3-(isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-4-methyltetrahydrofuran (10). To a cold (−15 °C) stirred solution of **9** (14.7 g, 36.9 mmol) in THF (150 mL) was added *n*-Bu_4NF (TBAF) (1.0 M solution in THF including nearly 5% of H_2O, 3.7 mL, 3.7 mmol). After being stirred at −15 °C for 30 min, 3.7 mL of 1.0 M THF solution of TBAF was added. The solution was stirred at −15 °C for an additional 30 min, diluted with saturated aqueous $NaHCO_3$ (1 L), and extracted with CH_2Cl_2 (500 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to give 11.1 g (93%) of a diastereomeric mixture of **10** as colorless crystals: mp 111−113 °C; R_f 0.29 (EtOAc/hexane, 1:3); IR (neat) 3450, 3280, 2980, 2880, 2120, 1450, 1415 cm^{-1}; ^{1}H NMR (270 MHz) for major isomer δ 0.99 (s, 3 H), 1.29, 1.37, 1.47, 1.52 (4 s, each 3 H), 2.09 (t, J = 2.9 Hz, 1 H), 2.47, 2.65, 2.85 (3 m, total 2 H), 4.10 (m, 5 H), 4.21 (d, J = 3.3 Hz, 1 H), 5.70 (d, J = 3.3 Hz, 1 H); ^{1}H NMR for minor isomer δ 0.99 (s, 3 H), 1.32, 1.34, 1.47, 1.57 (4 s, each 3 H), 2.05 (t, J = 2.9 Hz, 1 H), 4.44 (d, J = 3.3 Hz, 1 H), 5.74 (d, J = 3.3 Hz, 1 H). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.21; H, 8.42.

(2*R*,3*R*,4*R*,5*S*)-2,3-(Isopropylidenedioxy)-5-[(1*R*)-1,2-(isopropylidenedioxy)ethyl]-4-[(1*R*)- and (1*S*)-1-methoxy-3-butynyl]-4-methyltetrahydrofuran (11a and 11b). To a cold (0 °C) stirred solution of **10** (11.1 g, 34.0 mmol) in DMF (110 mL) was added NaH (60% dispersion in mineral oil, 2.04 g, 51.0 mmol). The mixture was stirred at 0 °C for 15 min, and MeI (4.2 mL, 67 mmol) was added. After being stirred at rt for 2 h, the solution was quenched with EtOH (4 mL), diluted with EtOAc (600 mL), and washed with H_2O (200 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:12) to give 9.62 g (83%) of **11a** and 1.66 g (14%) of **11b**. Compound **11a** was obtained as colorless crystals: mp 67.0−68.5 °C; R_f 0.48 (EtOAc/hexane, 1:3); $[\alpha]^{20}_D$ +40.6° (*c* 0.915, $CHCl_3$); IR (neat) 3280, 2980, 2940, 2830, 2120, 1460, 1380 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.94 (s, 3 H), 1.29, 1.36, 1.44, 1.52 (4 s, each 3 H), 2.01 (t, J = 2.6 Hz, 1 H), 2.65 (m, 2 H), 3.61 (s, 3 H), 3.65 (dd, J = 4.8, 6.6 Hz, 1 H), 3.94, 4.00 (2 dd, each J = 6.6, 8.1 Hz, each 1 H), 4.15 (d, J = 5.1 Hz, 1 H), 4.22 (d, J = 3.7 Hz, 1 H), 4.31 (dt, J = 5.1, 6.6 Hz, 1 H), 5.72 (d, J = 3.7 Hz, 1 H). Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.19; H, 8.53. Compound **11b** was obtained as a colorless oil: R_f 0.51 (EtOAc/hexane, 1:3); $[\alpha]^{20}_D$ +40.9° (*c* 0.97, $CHCl_3$); IR (neat) 3290, 2980, 2940, 2120, 1455, 1380, 1370 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.95 (s, 3 H), 1.32, 1.35, 1.41, 1.54 (4 s, each 3 H), 2.00 (t, J = 2.6 Hz, 1 H), 2.40 (ddd, J = 2.6, 8.6, 17.2 Hz, 1 H), 2.98 (dt, J = 17.2, 2.6 Hz, 1 H), 3.61 (s, 3 H), 3.69 (dd, J = 2.6, 8.6 Hz, 1 H), 3.88, 3.98, 4.10 (3 m, 1 H, 2 H, 1 H), 4.32 (d, J = 3.3 Hz, 1 H), 5.64 (d, J = 3.3 Hz, 1 H). HRMS calcd for $C_{17}H_{25}O_6$ ($M^+ - CH_3$) m/z 325.1649, found 325.1644.

(2*R*,3*R*,4*R*,5*S*)-5-[(1*R*)-1-Hydroxy-2-(pivaloyloxy)ethyl]-2,3-(isopropylidenedioxy)-4-[(1*R*)-1-methoxy-3-butynyl]-4-methyltetrahydrofuran (13a). Compound **11a** (9.62 g, 28.3 mmol) was dissolved in 60% aqueous AcOH (100 mL). The solution was stirred at rt for 25 h and concentrated in vacuo with the aid of EtOH and toluene to give crude **12a** (9.78 g), which was used in the next step without further purification. In a small scale experiment, crude **12a** was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) and obtained as a colorless oil: R_f 0.27 (EtOAc/hexane, 1:1); $[\alpha]^{20}_D$ +43.9° (*c* 1.11, $CHCl_3$); IR (neat) 3360, 3280, 2980, 2940, 2110, 1460, 1380, 1370 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.07 (s, 3 H), 1.30, 1.53 (2 s, each 3 H), 2.10 (t, J = 2.8 Hz, 1 H), 2.61 (ddd, J =2.8, 4.8, 17.8 Hz, 1 H), 2.81 (ddd, J = 2.8, 4.8, 17.8 Hz, 1 H), 3.58 (s, 3 H), 3.59 (m, 1 H), 3.68 (dd, J = 4.8, 11.4 Hz, 1 H), 3.72 (t, J = 4.8 Hz, 1 H), 3.82 (dd, J = 3.8, 11.4 Hz, 1 H), 3.98 (d, J = 8.8 Hz, 1 H), 4.24 (d, J = 3.5 Hz, 1 H), 5.73 (d, J = 3.5 Hz, 1 H). HRMS calcd for $C_{15}H_{25}O_6$ ($M^+ + H$) m/z 301.1650, found 301.1654.

To a cold (0 °C) stirred solution of crude **12a** (9.78 g) in pyridine (100 mL) was added dropwise pivaloyl chloride (PivCl) (3.5 mL, 28 mmol). After being stirred at rt for 1 h, 0.35 mL of PivCl was added. The solution was stirred at rt for an additional 1 h, diluted with EtOAc (800 mL), and washed with saturated aqueous $NaHCO_3$ (400 mL) and saturated brine (400 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to give 10.7 g (98%) of **13a** as a colorless oil: R_f 0.48 (EtOAc/hexane, 1:2); $[\alpha]^{29}_D$ +34.8° (*c* 1.16, $CHCl_3$); IR (neat) 3390, 3280, 2970, 2940, 2110, 1720, 1480, 1460 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.07 (s, 3 H), 1.23 (s, 9 H), 1.30, 1.52 (2 s, each 3 H), 2.10 (t, J = 2.6 Hz, 1 H), 2.62 (ddd, J = 2.6, 5.5, 17.6 Hz, 1 H), 2.80 (ddd, J = 2.6, 4.4, 17.6 Hz, 1 H), 3.58 (s, 3 H), 3.72 (dd, J = 4.4, 5.5 Hz, 1 H), 3.73 (m, 1 H), 4.01 (d, J = 9.2 Hz, 1 H), 4.09 (dd, J = 5.1, 11.4 Hz, 1 H), 4.24 (d, J = 3.3 Hz, 1 H), 4.44 (dd, J = 2.2, 11.4 Hz, 1 H), 4.87 (br s, 1 H), 5.72 (d, J = 3.3 Hz, 1 H). Anal. Calcd for $C_{20}H_{32}O_7$: C, 62.48; H, 8.39. Found: C, 62.39; H, 8.08.

Mixture of (2*R* and *S*,3*R*,4*R*,5*S*)-2,3-Dihydroxy-5-[(1*R*)-1-hydroxy-2-(pivaloyloxy)ethyl]-4-[(1*R*)-1-methoxy-3-butynyl]-4-methyltetrahydrofuran (14a). Compound **13a** (3.36 g, 8.73 mmol) was dissolved in 60% aqueous CF_3COOH (70 mL). The solution was stirred at rt for 15 h, neutralized with 4 M aqueous NaOH, diluted with H_2O (300 mL), and extracted with CH_2Cl_2 (200 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give 1.99 g (66%) of **14a** with 584 mg (17%) recovery of **13a**. The diastereomeric mixture (2:1) of **14a** was obtained as a colorless oil: R_f 0.41 and 0.35 (acetone/toluene, 1:3); IR (neat) 3360, 3290, 2970, 2930, 2110, 1720, 1475, 1460 cm^{-1}; ^{1}H NMR (270 MHz) for major isomer δ 1.11 (s, 3 H), 1.23 (s, 9 H), 2.13 (t, J = 2.9 Hz, 1 H), 2.59 (ddd, J = 2.9, 5.5, 17.6 Hz, 1 H), 2.76 (ddd, J = 2.9, 5.5, 17.6 Hz, 1 H), 3.57 (s, 3 H),3.77 (m, 2 H), 3.86 (d, J = 3.7 Hz, 1 H), 4.04 (d, J = 9.2 Hz, 1 H), 4.12 (m, 1 H), 4.42 (dd, J = 2.2, 11.4 Hz, 1 H), 4.66 (br s, 1 H), 5.39 (d, J = 3.7 Hz, 1 H); ^{1}H NMR for minor isomer δ 1.30 (s, 3 H), 2.14 (t, J = 2.9 Hz, 1 H), 3.20 (br s, 1 H), 3.55 (s, 3 H), 3.97 (s, 1 H), 4.03 (d, J = 9.5 Hz, 1 H), 4.49 (dd, J = 2.2, 11.4 Hz, 1 H), 5.26 (s, 1 H). Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.20. Found: C, 59.13; H, 7.96.

(3*R*,4*S*,5*R*)-4-Hydroxy-3-[(1*R*)-1-methoxy-3-butynyl]-3-methyl-5-[(pivaloyloxy)methyl]tetrahydrofuran-2-one (18a). To a cold (0 °C) stirred solution of **14a** (3.43 g, 9.96 mmol) in MeOH (130 mL) was added an aqueous solution (50 mL) of $NaIO_4$ (6.39 g, 29.9 mmol). After being stirred at rt for 1 h, aqueous $NaIO_4$ [4.26 g (19.9 mmol) in H_2O (30 mL)] was added at 0 °C. The mixture was stirred at rt for an additional 1.5 h, and the precipitated solids were removed by filtration and washed well with MeOH. The combined filtrate

and washings were concentrated in vacuo, and the residue was diluted with H_2O (500 mL) and extracted with CH_2Cl_2 (300 mL × 3). The combined extracts were dried and concentrated to give crude **16a** (3.46 g), which was used directly in the next step. In a small scale experiment, crude **16a** was purified by column chromatography on silica gel (acetone/toluene, 1:5) and obtained as a colorless oil: R_f 0.63 (acetone/toluene, 1:3); IR (neat) 3450, 3280, 2970, 2940, 2110, 1720, 1480, 1460 cm^{-1}; ^1H NMR (90 MHz) δ 1.13 (s, 3 H), 1.22 (s, 9 H), 2.08 (t, J = 3 Hz, 1 H), 2.51 (dd, J = 3, 6 Hz, 2 H), 3.08 (br s, 1 H), 3.45 (s, 3 H), 3.99 (t, J = 6 Hz, 1 H), 4.32 (m, 3 H), 4.95 (s, 1 H), 5.14 (s, 1 H), 8.14 (s, 1 H). Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65. Found: C, 59.41; H, 8.01.

To a cold (0 °C) stirred solution of crude **16a** (3.46 g) in CH_2Cl_2 (70 mL) were added PCC (5.37 g, 24.9 mmol) and powdered molecular sieves 4A (3.3 g). The mixture was stirred at rt for 1.5 h followed by elution through a short column of silica gel to remove inorganic salts. The column was eluted with excess Et_2O. The combined eluates were concentrated in vacuo to give crude **17a** (3.48 g), which was used directly in the next step. In a small scale experiment, crude **17a** was purified by column chromatography on silica gel (acetone/toluene, 1:5) and obtained as a colorless oil: R_f 0.70 (acetone/toluene, 1:3); IR (neat) 3310, 3030, 2980, 2940, 2880, 2840, 2120, 1780, 1730, 1480, 1460 cm^{-1}; ^1H NMR (90 MHz) δ 1.21 (s, 9 H), 1.38 (s, 3 H), 2.07 (t, J = 3 Hz, 1 H), 2.64 (dd, J = 3, 5 Hz, 2 H), 3.55 (s, 3 H), 3.77 (t, J = 5 Hz, 1 H), 4.18 (dd, J = 13, 4 Hz, 1 H), 4.41 (dd, J = 13, 3 Hz, 1 H), 4.63 (ddd, J = 3, 4, 7 Hz, 1 H), 5.45 (d, J = 7 Hz, 1 H), 8.14 (s, 1 H).

To a cold (0 °C) stirred solution of crude **17a** (3.48 g) in MeOH (70 mL) was added Et_3N (5.6 mL, 40 mmol). The solution was stirred at rt for 1 h and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 2.73 g (88% from **14a**) of **18a** as colorless crystals: mp 101−103 °C; R_f 0.14 (EtOAc/hexane, 1:4); $[\alpha]^{25}_D$ +49.6° (c 1.16, $CHCl_3$); IR ($CHCl_3$) 3500, 3300, 3020, 2960, 2880, 2860, 2100, 1770, 1730, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.21 (s, 9 H), 1.32 (s, 3 H), 2.08 (t, J = 2.6 Hz, 1 H), 2.79 (dd, J = 2.6, 6.2 Hz, 2 H), 3.45 (br s, 1 H), 3.58 (s, 3 H), 3.91 (t, J = 6.2 Hz, 1 H), 4.10 (m, 1 H), 4.21 (dd, J = 5.9,13.3 Hz, 1 H), 4.40 (m, 2 H). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.15; H, 8.05.

(3*R*,4*S*,5*R*)-3-[(1*R*)-1-Methoxy-3-butynyl]-3-methyl-4-[(methyldithiocarbonyl)oxy]-5-[(pivaloyloxy)methyl]tetrahydrofuran-2-one (19a). To a cold (−15 °C) stirred solution of **18a** (2.13 g, 6.82 mmol) in THF (40 mL) were added imidazole (929 mg, 13.6 mmol) and NaH (60% emulsion in mineral oil, 601 mg, 15.0 mmol). The mixture was stirred at −15 °C for 15 min, and CS_2 (1.85 mL, 30.7 mmol) was added. The yellow solution was stirred for 5 min, and then MeI (1.06 mL, 17.1 mmol) was added. After being stirred for 15 min at −15 °C, the solution was quenched with H_2O (1 mL), diluted with H_2O (100 mL), and extracted with CH_2Cl_2 (100 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to give 2.61 g (95%) of **19a** as a colorless oil, which was partially decomposed upon standing at rt and used immediately in the next step: R_f 0.55 (EtOAc/hexane, 1:3); $[\alpha]^{22}_D$ +121.7° (c 0.99, $CHCl_3$); IR (neat) 3290, 2970, 2930, 2870, 2830, 2120, 1780, 1730, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.22 (s, 9 H), 1.42 (s, 3 H), 2.08 (t, J = 2.6 Hz, 1 H), 2.59 (dd, J = 2.6, 5.5 Hz, 2 H), 2.63 (s, 3 H), 3.56 (s, 3 H), 3.78 (t, J = 5.5 Hz, 1 H), 4.18 (dd, J = 4.4, 12.8 Hz, 1 H), 4.39 (dd, J = 2.9, 12.8 Hz, 1 H), 4.74 (ddd, J = 2.9, 4.4, 7.3 Hz, 1 H), 6.39 (d, J = 7.3 Hz, 1 H).

(1*S*,4*S*,5*S*,8*R*)-6-Methenyl-8-methoxy-1-methyl-4-[(pivaloyloxy)methyl]-3-oxabicyclo[3.3.0]octan-2-one (20a). The following reaction was carried out under Ar. To a refluxing solution of **19a** (2.61 g, 6.48 mmol) in toluene (620 mL) was added dropwise a solution of AIBN (213 mg, 1.30 mmol) and n-Bu_3SnH (4.36 mL, 16.2 mmol) in toluene (100 mL) over 6 h using a syringe pump. After concentration in vacuo, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to give 1.68 g (87%) of **20a** as a colorless oil: R_f 0.43 (EtOAc/hexane, 1:3); $[\alpha]^{21}_D$ −19.1° (c 0.615, $CHCl_3$); IR (neat) 2970, 2930, 2910, 2870, 2830, 1770, 1730, 1650, 1480, 1455 cm^{-1}; ^1H NMR (270 MHz) δ 1.22 (s, 9 H), 1.32 (s, 3 H), 2.72 (m, 2 H), 2.87 (d, J = 8.1 Hz, 1 H), 3.31(s, 3 H), 3.63 (dd, J = 0.7, 3.7 Hz, 1 H), 4.18 (dd, J = 5.1,12.6 Hz, 1 H), 4.38 (dd, J = 2.6, 12.6 Hz, 1 H), 4.42 (ddd, J = 2.6, 5.1, 8.1 Hz, 1 H), 5.05 (d, J = 1.8 Hz, 1 H), 5.11 (dd, J = 1.8, 1.8 Hz, 1 H). HRMS calcd for $C_{16}H_{25}O_5$ (M^+ + H) m/z 297.1700, found 297.1700.

(1*R*,4*S*,5*S*)-1-Methyl-4-[(pivaloyloxy)methyl]-3-oxabicyclo[3.3.0]oct-7-ene-2,6-dione (23). Into a cold (−78 °C) stirred solution of **20a** (1.68 g, 5.66 mmol) in CH_2Cl_2 (30 mL) was bubbled ozone (O_2 containing ca. 3% O_3) for 30 min to a persistent blue color. Then, Ph_3P (1.78 g, 6.80 mmol) was added, and the solution was maintained at −78 °C for 2 h and then stirred at rt for 3 h. The solution was diluted with saturated aqueous $NaHCO_3$ (60 mL) and extracted with CH_2Cl_2 (60 mL × 3). The combined extracts were dried and concentrated in vacuo to give crude **22a** (3.22 g), which was used directly in the next step: R_f 0.23 (EtOAc/hexane, 1:2).

To a stirred solution of crude **22a** (3.22 g) in benzene (30 mL) was added DBU (85 μL, 0.57 mmol). The solution was heated under reflux for 50 min and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 1.27 g (84%) of **23** as colorless crystals: mp 42.5−44.0 °C; R_f 0.35 (EtOAc/hexane, 1:2); $[\alpha]^{26}_D$ −131.2° (c 0.66, $CHCl_3$); IR (neat) 2980, 2940, 2880, 1770, 1730, 1720, 1590, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.24 (s, 9 H), 1.65 (s, 3 H), 2.82 (d, J = 3.7 Hz, 1 H), 4.23 (dd, J = 4.4, 12.5 Hz, 1 H), 4.39 (dd, J = 3.7, 12.5 Hz, 1 H), 4.64 (dt, J = 4.4, 3.7 Hz, 1 H), 6.23 (d, J = 5.5 Hz, 1 H), 7.61 (d, J = 5.5 Hz, 1 H). HRMS calcd for $C_{14}H_{18}O_5$ (M^+) m/z 266.1152, found 266.1151.

(2*R*,3*R*,4*R*,5*S*)-5-[(1*R*)-1-Hydroxy-2-(pivaloyloxy)ethyl]-2,3-(isopropylidenedioxy)-4-[(1*S*)-1-methoxy-3-butynyl]-4-methyltetrahydrofuran (13b). As described for the preparation of **13a**, compound **11b** (2.69 g, 7.89 mmol) was converted to 2.27 g (75%) of **13b** via **12b**. Compound **12b** was obtained as a colorless oil: R_f 0.33 (EtOAc/hexane, 1:1); $[\alpha]^{28}_D$ +29.3° (c 1.06, $CHCl_3$); IR (neat) 3400, 3290, 2980, 2940, 2110, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.04 (s, 3 H), 1.30, 1.53 (2 s, each 3 H), 2.03 (t, J = 2.6 Hz, 1 H), 2.25 (br s, 1 H), 2.55 (ddd, J =2.6, 9.5, 16.9 Hz, 1 H), 3.17 (dt, J = 16.9, 2.6 Hz, 1 H), 3.61 (m, 2 H), 3.66 (dd, J = 2.6, 9.5 Hz, 1 H), 3.69 (s, 3 H), 3.82 (m, 1 H), 4.05 (d, J = 8.8 Hz, 1 H), 4.12 (d, J = 1.5 Hz, 1 H), 4.26 (d, J = 3.7 Hz, 1 H), 5.72 (d, J = 3.7 Hz, 1 H). HRMS calcd for $C_{14}H_{21}O_6$ (M^+ − CH_3) m/z 285.1337, found 285.1342. Compound **13b** was obtained as a colorless oil: R_f 0.54 (EtOAc/hexane, 1:2); $[\alpha]^{28}_D$ +29.4° (c 0.96, $CHCl_3$); IR (neat) 3430, 3280, 2980, 2940, 2120, 1730, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.04 (s, 3 H), 1.23 (s, 9 H), 1.30, 1.52 (2 s, each 3 H), 2.03 (t, J = 2.6 Hz, 1 H), 2.56 (ddd, J = 2.6, 9.2, 16.9 Hz, 1 H), 3.12 (dt, J = 16.9, 2.6 Hz, 1 H), 3.66 (s, 3 H), 3.67 (dd, J = 2.6, 9.2 Hz, 1 H), 3.77 (m, 1 H), 3.86 (br s, 1 H), 4.11 (dd, J = 5.2, 11.4 Hz, 1 H), 4.12 (d, J = 9.2 Hz, 1 H), 4.26 (d, J = 3.7 Hz, 1 H), 4.42 (dd, J = 2.2, 11.4 Hz, 1 H), 5.71 (d, J = 3.7 Hz, 1 H). HRMS calcd for $C_{20}H_{33}O_7$ (M^+ + H) m/z 385.2224, found 385.2226.

Mixture of (2*R* and *S*,3*R*,4*R*,5*S*)-2,3-Dihydroxy-5-[(1*R*)-1-hydroxy-2-(pivaloyloxy)ethyl]-4-[(1*S*)-1-methoxy-3-butynyl]-4-methyltetrahydrofuran (14b). As described for the preparation of **14a**, compound **13b** (1.65 g, 4.28 mmol) was converted to 1.16 g (79%) of an inseparable diastereomeric mixture (3:1) of **14b** as a colorless oil: R_f 0.45 (EtOAc/hexane, 1:1); IR (neat) 3430, 3310, 2970, 2930, 2870, 2850, 2110, 1720, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) for major isomer δ 1.05 (s, 3 H), 1.24 (s, 9 H), 2.06 (t, J = 2.9 Hz, 1 H), 2.73 (m, 3 H), 3.58 (s, 3 H), 3.90 (m, 3 H), 4.22 (dd, J = 6.4, 11.2 Hz, 1 H), 4.28 (d, J = 8.3 Hz, 1 H), 4.31 (d, J = 9.8 Hz, 1 H), 4.66 (d, J = 11.2 Hz, 1 H), 5.03 (d, J = 3.4 Hz, 1 H), 5.30 (dd, J = 3.4, 11.7 Hz, 1 H); ^1H NMR for minor isomer δ 1.22 (s, 3 H), 2.05 (t, J = 2.9 Hz, 1 H), 3.56 (s, 3 H), 4.21 (dd, J = 6.4, 11.7 Hz, 1 H), 4.52 (d, J = 11.7 Hz, 1 H), 4.56 (s, 1 H), 5.21 (s, 1 H); HRMS calcd for $C_{17}H_{27}O_6$ (M^+ − OH) m/z 327.1806, found 327.1805.

(3*R*,4*S*,5*R*)-4-Hydroxy-3-[(1*S*)-1-methoxy-3-butynyl]-3-methyl-5-[(pivaloyloxy)methyl]tetrahydrofuran-2-one (18b). As described for the preparation of **18a**, compound **14b** (1.12 g, 3.25 mmol) was converted to 823 mg (81%) of **18b** as

colorless crystals: mp 133–135 °C; R_f 0.34 (EtOAc/hexane, 1:2); $[\alpha]^{29}_D$ +32.8° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3520, 3310, 3030, 2980, 2840, 1775, 1730, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.21 (s, 9 H), 1.33 (s, 3 H), 2.06 (t, J = 2.6 Hz, 1 H), 2.57 (ddd, J = 2.6, 6.6, 17.6 Hz, 1 H), 2.81 (ddd, J = 2.6, 5.1, 17.6 Hz, 1 H), 3.02 (br d, J = 7.3 Hz, 1 H), 3.56 (s, 3 H), 3.78 (dd, J = 5.1, 6.6 Hz, 1 H), 4.06 (br t, J = 7.3 Hz, 1 H), 4.25, 4.41 (2 m, 1 H, 2 H). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.35; H, 8.03.

(3*R*,4*S*,5*R*)-3-[(1*S*)-1-Methoxy-3-butynyl]-3-methyl-4-[(methyldithiocarbonyl)oxy]-5-[(pivaloyloxy)methyl]tetrahydrofuran-2-one (19b). As described for the preparation of **19a**, compound **18b** (799 mg, 2.56 mmol) was converted to 735 mg (71%) of **19b** with 139 mg (17%) recovery of **18b**. Compound **19b** was obtained as a colorless oil: R_f 0.50 (EtOAc/hexane, 1:3); $[\alpha]^{28.5}_D$ +114.4° (*c* 0.77, $CHCl_3$); IR (neat) 3300, 2980, 2940, 2920, 1780, 1740, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.22 (s, 9 H), 1.44 (s, 3 H), 2.03 (t, J = 2.6 Hz, 1 H), 2.59 (ddd, J = 2.6, 6.0, 17.6 Hz, 1 H), 2.66 (s, 3 H), 2.77 (ddd, J = 2.6, 6.0, 17.6 Hz, 1 H), 3.48 (t, J = 6.0 Hz, 1 H), 3.61 (s, 3 H), 4.20 (dd, J = 12.5, 3.7 Hz, 1 H), 4.37 (dd, 1 H, J = 12.5, 2.9 Hz, 1 H), 4.67 (ddd, J = 2.9, 3.7, 7.7 Hz, 1 H), 6.35 (d, J = 7.7 Hz, 1 H).

(1*S*,4*S*,5*S*,8*S*)-6-Methenyl-8-methoxy-1-methyl-4-[(pivaloyloxy)methyl]-3-oxabicyclo[3.3.0]octan-2-one (20b). As described for the preparation of **20a**, compound **19b** (735 mg, 1.83 mmol) was converted to 358 mg (66%) of **20b** with 115 mg (16%) recovery of **19b**. Compound **20b** was obtained as a colorless oil: R_f 0.43 (EtOAc/hexane, 1:3); $[\alpha]^{27}_D$ −13.6° (*c* 0.98, $CHCl_3$); IR (neat) 2970, 2930, 1770, 1730, 1660, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.23 (s, 9 H), 1.38 (s, 3 H), 2.60, 2.86 (2 m, 2 H, 1 H), 3.40 (s, 3 H), 3.87 (t, J = 5.5 Hz, 1 H), 4.18 (dd, J = 6.2, 12.1 Hz, 1 H), 4.29 (dd, J = 4.4, 12.1 Hz, 1 H), 4.40 (dt, J = 6.2, 4.4 Hz, 1 H), 5.01 (m, 1 H), 5.09 (m, 1 H). HRMS calcd for $C_{16}H_{23}O_5$ (M^+ − H) m/z 295.1543, found 295.1537.

Preparation of 23 from 20b. As described for the preparation of **23** from **20a**, compound **20b** (95.8 mg, 0.323 mmol) was converted to 48.1 mg (56%) of **23**.

Mixture of (1*S*,4*S*,5*S*,7*S*,8*R*)-8-Isopropyl-1-methyl-7-(phenylseleno)-4-[(pivaloyloxy)methyl]-3-oxabicyclo[3.3.0]-octane-2,6-dione (24) and Its Isomers. The following reaction was carried out under Ar and in the absence of light. To a cold (−78 °C) stirred mixture of CuBr·Me_2S (747 mg, 3.64 mmol) and **23** (484 mg, 1.82 mmol) in THF and Me_2S (4:1, 12 mL) were added *i*-PrMgBr (0.68 M solution in THF, 5.3 mL, 3.6 mmol) and a solution of PhSeCl (694 mg, 3.62 mmol) in THF (4 mL), successively. The mixture was stirred at −78 °C for 1.5 h, quenched by addition of saturated aqueous NH_4Cl (1 mL), diluted with EtOAc (100 mL), and washed with 1 M aqueous HCl (50 mL × 2), saturated aqueous $NaHCO_3$ (50 mL × 3), and saturated brine (50 mL), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to give 757 mg (89%) of an inseparable mixture of **24** and its isomers as a pale yellow solid, which was decomposed upon standing at rt thus used in the next step immediately: R_f 0.58 (EtOAc/hexane, 1:2); IR (neat) 2960, 2940, 2880, 1770, 1730, 1580, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) for major isomer: δ 0.75, 0.94 (2 d, each J = 6.8 Hz, each 3 H), 1.24 (s, 9 H), 1.46 (s, 3 H), 2.18 (d of heptets, J = 2.6, 6.8 Hz, 1 H), 2.43 (dd, J = 1.8, 2.6 Hz, 1 H), 2.60 (dd, J = 1.8, 2.9 Hz, 1 H), 3.90 (t, J = 1.8 Hz, 1 H), 4.25 (d, J = 5.4 Hz, 2 H), 4.66 (dt, J = 2.9, 5.4 Hz, 1 H), 7.37, 7.60 (2 m, 2 H, 3 H). The ratio of the diastereomers was determined based on comparative intensity of the three singlets at δ 1.22, 1.23, and 1.24 (1:1:10) attributable to the pivaloyl methyl groups.

(1*S*,4*S*,5*S*)-8-Isopropyl-1-methyl-4-[(pivaloyloxy)methyl]-3-oxabicyclo[3.3.0]oct-7-ene-2,6-dione (25). To a cold (0 °C) stirred solution of the mixture of **24** and its isomers (757 mg, 1.63 mmol) in MeOH and THF (5:1, 30 mL) was added an aqueous solution (10 mL) of $NaIO_4$ (1.39 g, 6.50 mmol) and $NaHCO_3$ (341 mg, 4.06 mmol). After being stirred at rt for 12 h, the precipitated solids were removed by filtration and washed well with MeOH. The combined filtrate and washings were concentrated in vacuo, the residue dissolved in H_2O (100 mL) and the whole extracted with CH_2Cl_2 (50 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give 415 mg (83%) of **25** as colorless crystals: mp 84.0–85.5 °C; R_f 0.40 (EtOAc/hexane, 1:2); $[\alpha]^{24}_D$ −166.7° (*c* 0.91, $CHCl_3$); IR (neat) 2970, 2930, 2870, 1770, 1730, 1710, 1600, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.18, 1.24 (2 d, each J = 6.8 Hz, each 3 H), 1.24 (s, 9 H), 1.66 (s, 3 H), 2.83 (d, J = 4.4 Hz, 1 H), 3.02 (heptet, J = 6.8 Hz, 1 H), 4.21 (dd, J = 4.4, 12.1 Hz, 1 H), 4.39 (dd, J = 3.3, 12.1 Hz, 1 H), 4.61 (dt, J = 3.3, 4.4 Hz, 1 H), 6.04 (s, 1 H). HRMS calcd for $C_{17}H_{24}O_5$ (M^+) m/z 308.1622, found 308.1637.

(1*S*,4*S*,5*R*,6*S*)-6-Hydroxy-8-isopropyl-1-methyl-4-[(pivaloyloxy)methyl]-3-oxabicyclo[3.3.0]oct-7-en-2-one (26). To a cold (−15 °C) stirred solution of **25** (415 mg, 1.35 mmol) in MeOH (16 mL) was added $CeCl_3·7H_2O$ (1.00 g, 2.68 mmol). After being stirred at −15 °C for 15 min, $NaBH_4$ (51.1 mg, 1.35 mmol) was added to the solution. After being stirred at −15 °C for an additional 15 min, the solution was diluted with saturated brine (100 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 404 mg (96%) of **26** as colorless crystals: mp 79.0–81.0 °C; R_f 0.60 (EtOAc/hexane, 1:1); $[\alpha]^{22}_D$ −68.9° (*c* 1.46, $CHCl_3$); IR (neat) 3470, 2970, 2930, 2860, 1770, 1710, 1640, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.06, 1.10 (2 d, each J = 6.8 Hz, each 3 H), 1.23 (s, 9 H), 1.37 (s, 3 H), 1.68 (br s, 1 H), 2.48 (heptet, J = 6.8 Hz, 1 H), 2.63 (dd, J = 6.3, 7.8 Hz, 1 H), 4.18 (dd, J = 5.4, 12.2 Hz, 1 H), 4.39 (dd, J = 2.4, 12.2 Hz, 1 H), 4.78 (ddd, J = 2.4, 5.4, 7.8 Hz, 1 H), 5.12 (d, J = 6.3 Hz, 1 H), 5.55 (s, 1 H). HRMS calcd for $C_{17}H_{25}O_4$ (M^+ − OH) m/z 293.1750, found 293.1742.

Mixture of (1*R*,2*S*,5*S*,6*S*,7*R*,8*R* and *S*)-8-Hydroxy-1-isopropyl-2-methyl-5-[(pivaloyloxy)methyl]-4,9,10-trioxatricyclo[5.2.1.0^{2,6}]decan-3-one (29). Into a cold (−78 °C) stirred solution of **26** (281 mg, 0.91 mmol) in CH_2Cl_2 (10 mL) was bubbled ozone (O_2 containing ca. 3% O_3) for 35 min to a persistent blue color. Then, Ph_3P (359 mg, 1.37 mmol) was added and stirring was maintained at −78 °C for 50 min. After stirring at rt for 1.5 h, the solution was diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give 289 mg (93%) of an inseparable diastereomeric mixture of **29** as a colorless oil: R_f 0.19 (EtOAc/hexane, 1:2); IR (neat) 3480, 2970, 2940, 1760, 1730, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) for major isomer δ 1.09, 1.19 (2 d, each J = 6.8 Hz, each 3 H), 1.22 (s, 9 H), 1.54 (s, 3 H), 1.68 (br s, 1 H), 2.16 (d, J = 3.9 Hz, 1 H), 2.49 (heptet, J = 6.8 Hz, 1 H), 4.12 (dd, J = 3.9, 12.2 Hz, 1 H), 4.31 (dd, J = 3.9, 12.2 Hz, 1 H), 4.37 (s, 1 H), 4.46 (q, J = 3.9 Hz, 1 H), 4.99 (br s, 1 H). HRMS calcd for $C_{17}H_{26}O_7$ (M^+) m/z 342.1676, found 342.1673. The diastereomeric ratio of **29** was determined based on comparative integration of two singlets at δ 1.22 and 1.23 (10:1) attributable to the pivaloyl methyl groups.

(1*S*,4*S*,5*R*,6*R*,8*R*)-6-(Acetoxymethyl)-8-hydroxy-8-isopropyl-1-methyl-4-[(pivaloyloxy)methyl]-3,7-dioxabicyclo-[3.3.0]octan-2-one (32). To a cold (−15 °C) stirred solution of **29** (289 mg, 0.84 mmol) in MeOH (6 mL) was added $NaBH_4$ (38.4 mg, 1.01 mmol). The solution was stirred at −15 °C for 15 min, diluted with saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried and concentrated in vacuo to give crude **30** (323 mg), which was used directly in the next step. In a small scale experiment, crude **30** was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) and obtained as a colorless oil: R_f 0.19 (EtOAc/hexane, 1:2); $[\alpha]^{26.5}_D$ −6.1° (*c* 0.21, $CHCl_3$); IR (neat) 3480, 2970, 2940, 2880, 1760, 1730, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.02, 1.10 (2 d, each J = 7.0 Hz, each 3 H), 1.22 (s, 9 H), 1.37 (s, 3 H), 1.88 (br s, 1 H), 2.10 (heptet, J = 7.0 Hz, 1 H), 2.48 (s, 1 H), 2.60 (dd, J = 4.0, 7.3 Hz, 1 H), 3.65, 3.73 (2 m, each 1 H), 4.17 (dd, 1 H, J = 4.8, 12.1 Hz, 1 H), 4.26 (dd, J = 3.7, 12.1 Hz, 1 H), 4.26 (m, 1 H), 4.71 (ddd, J = 3.7, 4.8, 7.3 Hz, 1 H).

When compound **30** was exposed to silica gel or $CDCl_3$ overnight, a significant amount of **31** was formed, which was separated from **30** by column chromatography on silica gel. Compound **31** as a colorless oil: R_f 0.50 (EtOAc/hexane, 1:2); IR (neat) 2950, 1760, 1480, 1455 cm^{-1}; ^1H NMR (270 MHz) δ 1.06, 1.18 (2 d, each J = 6.9 Hz, each 3 H), 1.22 (s, 9 H), 1.55 (s, 3 H), 2.23 (d, J = 4.4 Hz, 1 H), 2.45 (heptet, J = 7.0 Hz, 1 H), 3.63 (d, J = 7.0 Hz, 1 H), 3.70 (dd, J = 3.3, 3.7 Hz, 1 H), 4.11 (dd, J = 4.4, 7.7 Hz, 1 H), 4.31 (dd, J = 3.7, 8.8 Hz, 1 H), 4.45 (ddd, J = 3.3, 4.4, 4.4 Hz, 1 H), 4.57 (d, J = 3.7 Hz, 1 H). HRMS calcd for $C_{17}H_{26}O_6$ (M^+) m/z 326.1728, found 326.1728.

To a stirred solution of crude **30** (323 mg) in pyridine (3 mL) was added Ac_2O (3 mL). After stirring at rt for 3 h, the solution was concentrated in vacuo with the aid of toluene. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 295 mg (91% from **29**) of **32** as a colorless oil: R_f 0.32 (EtOAc/hexane, 1:2); $[\alpha]^{20}_D$ −15.0° (c 1.36, $CHCl_3$); IR (neat) 3490, 2980, 2940, 2880, 1770, 1730, 1710 cm^{-1}; ^1H NMR (270 MHz) δ 1.02, 1.09 (2 d, each J = 7.0 Hz, each 3 H), 1.22 (s, 9 H), 1.39 (s, 3 H), 2.09 (s, 3 H), 2.11 (heptet, J = 7.0 Hz, 1 H), 2.55 (dd, J = 3.7, 7.7 Hz, 1 H), 2.60 (s, 1 H), 4.10 (dd, J = 5.1, 11.4 Hz, 1 H), 4.14 (dd, J = 4.8, 12.5 Hz, 1 H), 4.18 (dd, J = 4.8, 11.4 Hz, 1 H), 4.27 (dd, J = 3.3, 12.5 Hz, 1 H), 4.35 (ddd, J = 3.7, 4.8, 5.1 Hz, 1 H), 4.72 (ddd, J = 3.3, 4.8, 7.7 Hz, 1 H). HRMS calcd for $C_{19}H_{29}O_7$ (M^+ − OH) m/z 369.1911, found 369.1915.

(1*S*,4*S*,5*R*,6*R*,8*R*)-6-(Acetoxymethyl)-8-isopropyl-8-methoxy-1-methyl-4-[(pivaloyloxy)methyl]-3,7-dioxabicyclo-[3.3.0]octan-2-one (33). To a stirred solution of **32** (295 mg, 0.76 mmol) in MeOH (6 mL) was added PPTS (96.0 mg, 0.38 mmol) and $CH(OCH_3)_3$ (0.42 mL, 3.8 mmol). The solution was heated under reflux for 3 h, diluted with saturated aqueous $NaHCO_3$ (20 mL), and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 273 mg (90%) of **33** as a colorless oil: R_f 0.43 (EtOAc/hexane, 1:2); $[\alpha]^{24}_D$ −29.0° (c 0.965, $CHCl_3$); IR (neat) 2970, 2950, 2880, 1780, 1740, 1730, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.12, 1.17 (2 d, each J = 7.3 Hz, each 3 H), 1.22 (s, 9 H), 1.37 (s, 3 H), 2.10 (s, 3 H), 2.19 (heptet, J = 7.3 Hz, 1 H), 2.50 (dd, J = 3.7, 7.7 Hz, 1 H), 3.34 (s, 3 H), 4.15 (m, 5 H), 4.47 (ddd, J = 3.9, 4.8, 7.7 Hz, 1 H). HRMS calcd for $C_{17}H_{25}O_8$ (M^+ − $CH(CH_3)_2$) m/z 357.1548, found 357.1550.

(1*S*,4*S*,5*R*,6*R*,8*R*)-6-(Hydroxymethyl)-8-isopropyl-8-methoxy-1-methyl-4-[(pivaloyloxy)methyl]-3,7-dioxabicyclo[3.3.0]octan-2-one (34). To a cold (0 °C) stirred solution of **33** (273 mg, 0.68 mmol) in MeOH (5 mL) was added MeONa (1.0 M solution in MeOH, 68 μL, 0.068 mmol). The solution was stirred at 0 °C for 1.5 h, diluted with saturated aqueous NH_4Cl (20 mL), and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give 224 mg (92%) of **34** as a colorless oil: R_f 0.26 (EtOAc/hexane, 1:2); $[\alpha]^{22}_D$ −39.2° (c 0.795, $CHCl_3$); IR (neat) 3500, 2970, 2940, 2880, 1770, 1730 cm^{-1}; ^1H NMR (270 MHz) δ 1.13, 1.17 (2 d, each J = 7.0 Hz, each 3 H), 1.22 (s, 9 H), 1.35 (s, 3 H), 1.88 (m, 1 H), 2.18 (heptet, J = 7.0 Hz, 1 H), 2.53 (dd, J = 3.7, 7.3 Hz, 1 H), 3.35 (s, 3 H), 3.66, 3.77 (2 m, each 1 H), 4.02 (dt, J = 3.7, 4.4 Hz, 1 H), 4.15 (dd, J = 5.1, 12.1 Hz, 1 H), 4.23 (dd, J = 3.7, 12.1 Hz, 1 H), 4.48 (ddd, J = 3.7, 5.1, 7.3 Hz, 1 H). HRMS calcd for $C_{18}H_{29}O_7$ (M^+ − OCH_3) m/z 327.1805, found 327.1800.

Coupling of Triflate 35 with 3(2*H*)-Furanone 36. Method A (run 10 in Table 1). The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of **34** (87.9 mg, 0.245 mmol) in CH_2Cl_2 (2 mL) were added triethylamine (0.14 mL, 0.98 mmol) and trifluoromethanesulfonic anhydride (83 μL, 0.49 mmol). The solution was stirred at −78 °C for 15 min, quenched with H_2O (10 mL), diluted with EtOAc (10 mL), and washed with saturated brine (10 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give 131 mg (>100%) of **35**, as an unstable, colorless oil which was used immediately in the next step.

The following reaction was carried out under Ar. To a cold (−78 °C) stirred mixture of KHMDS (0.5 M solution in toluene, 1.47 mL, 0.74 mmol) and 18-crown-6 (195 mg, 0.74 mmol) in toluene (2 mL) was added **36** (92.8 mg, 0.74 mmol). The solution was stirred at −78 °C for 5 min, and then a solution of **35** (131 mg) in toluene (2 mL) was added. After being stirred at −78 °C for 15 min, the solution was quenched with saturated aqueous NH_4Cl (1 mL), diluted with EtOAc (10 mL), and washed with saturated aqueous NH_4Cl (10 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) then PTLC (EtOAc/hexane, 1:2) to give 18.6 mg (16%) of **37** and 59.9 mg (52%) of **39**. Compound **37** was obtained as a colorless oil: R_f 0.27 (EtOAc/hexane, 1:2); $[\alpha]^{27}_D$ −25.1° (c 0.745, $CHCl_3$); IR (neat) 2970, 2940, 2880, 1780, 1730, 1700, 1600, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.07, 1.08 (2 d, each J = 7.1 Hz, each 3 H), 1.23 (s, 9 H), 1.24 (t, J = 7.7 Hz, 3 H), 1.31, 1.40 (2 s, each 3 H), 2.00 (dd, J = 2.6, 14.3 Hz, 1 H), 2.08 (heptet, J = 7.1 Hz, 1 H), 2.19 (dd, J = 10.6, 14.3 Hz, 1 H), 2.23 (dd, J = 4.0, 7.0 Hz, 1 H), 2.52 (q, J = 7.7 Hz, 2 H), 3.24 (s, 3 H), 3.98 (ddd, J = 2.6, 4.0, 10.6 Hz, 1 H), 4.15 (d, J = 4.6 Hz, 2 H), 4.41 (dt, J = 7.0, 4.6 Hz, 1 H), 5.43 (s, 1 H). HRMS calcd for $C_{24}H_{35}O_7$ (M^+ − OCH_3) m/z 435.2380, found 435.2395. Compound **39** was obtained as a colorless oil: R_f 0.59 (EtOAc/hexane, 1:2); $[\alpha]^{26}_D$ −23.9° (c 0.525, $CHCl_3$); IR (neat) 2980, 2940, 2880, 1770, 1730, 1680, 1650, 1580, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.13, 1.18 (2 d, each J = 7.3 Hz, each 3 H), 1.18 (t, J = 7.7 Hz, 3 H), 1.21 (s, 9 H), 1.38 (s, 3 H), 2.20 (m, 1 H), 2.16 (s, 3 H), 2.53 (q, J = 7.7 Hz, 2 H), 2.67 (dd, J = 3.7, 4.0 Hz, 1 H), 3.36 (s, 3 H), 3.86 (dd, J = 5.3, 10.1 Hz, 1 H), 3.99 (dd, J = 4.2, 10.1 Hz, 1 H), 4.11 (dd, J = 5.1, 12.0 Hz, 1 H), 4.14 (m, 1 H), 4.29 (dd, J = 3.3, 12.0 Hz, 1 H), 4.50 (m, 1 H), 5.85 (s, 1 H). HRMS calcd for $C_{25}H_{39}O_8$ (M^+ + H) m/z 467.2643, found 467.2663.

Method B (run 1 in Table 1). For this procedure, compound **34** (27.1 mg, 75.6 μmol) was converted to 43.3 mg (>100%) of triflate **35** as described in method A and used immediately.

The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of **36** (47.5 mg, 0.38 mmol) in toluene (1 mL) was added LiHMDS (1.0 M solution in hexane, 0.38 mL, 0.38 mmol). The solution was stirred at −78 °C for 10 min, and then a solution of **35** (43.3 mg) in toluene (1 mL) was added. After being stirred at 0 °C for 2 h, the solution was quenched with saturated aqueous NH_4Cl (0.2 mL), diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give 28.6 mg (81%) of a mixture (40:1) of **38** and **37**. The ratio of **38** and **37** was determined by ^1H NMR analysis. The major diastereomer **38** was separated from **37** by PTLC. Compound **38** was obtained as a colorless oil: R_f 0.30 (EtOAc/hexane, 1:2); $[\alpha]^{27}_D$ −67.3° (c 0.935, $CHCl_3$); IR (neat) 2970, 2930, 2880, 1780, 1730, 1700, 1600, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.12, 1.15 (2 d, each J = 7.1 Hz, each 3 H), 1.21 (s, 9 H), 1.25 (t, J = 7.7 Hz, 3 H), 1.34, 1.44 (2 s, each 3 H), 1.86 (dd, J = 4.0, 14.7 Hz, 1 H), 2.15 (m, 1 H), 2.17 (dd, J = 8.8, 14.7 Hz, 1 H), 2.27 (dd, J = 4.0, 7.0 Hz, 1 H), 2.53 (q, J = 7.7 Hz, 2 H), 3.28 (s, 3 H), 4.03 (m, 1 H), 4.03 (dd, J = 5.1, 12.1 Hz, 1 H), 4.25 (dd, J = 3.3, 12.1 Hz, 1 H), 4.43 (m, 1 H), 5.43 (s, 1 H). HRMS calcd for $C_{24}H_{35}O_7$ (M^+ − OCH_3) m/z 435.2380, found 435.2383.

Regeneration of 34 from 39. To a cold (0 °C) stirred solution of **39** (86.3 mg, 0.185 mmol) in MeOH (2 mL) was added *p*-TsOH (monohydrate, 6.8 mg, 0.036 mmol). After being stirred at 0 °C for 1.5 h, the solution was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give 63.2 mg (95%) of **34**. The ^1H NMR and IR spectra of this product were identical with those obtained above.

Depivaloylation of 37. Preparation of 40. To a cold (0 °C) stirred solution of **37** (76.9 mg, 0.165 mmol) in MeOH (2 mL) was added MeONa (1.0 M solution in MeOH, 0.33 mL, 0.33 mmol). The mixture was stirred at rt for 3 h, diluted with

saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:4) to give 54.7 mg (87%) of **40** as colorless crystals: mp 115–118 °C; R_f 0.17 (acetone/toluene, 1:4); $[\alpha]^{25}_D$ −38.7° (*c* 0.775, $CHCl_3$); IR (neat) 3420, 2970, 2930, 1770, 1690, 1590, 1450 cm^{-1}; ^1H NMR (270 MHz) δ 1.07, 1.09 (2 d, each *J* = 7.1 Hz, each 3 H), 1.24 (t, *J* = 7.5 Hz, 3 H), 1.31, 1.41 (2 s, each 3 H), 1.95 (br s, 1 H), 1.99 (dd, *J* = 2.9, 14.3 Hz, 1 H), 2.09 (heptet, *J* = 7.1 Hz, 1 H), 2.21 (dd, *J* = 10.3, 14.3 Hz, 1 H), 2.42 (dd, *J* = 4.0, 6.6 Hz, 1 H), 2.52 (q, *J* = 7.5 Hz, 2 H), 3.24 (s, 3 H), 3.57, 3.83 (2 m, each 1 H), 3.98 (ddd, *J* = 2.9, 4.0, 10.3 Hz, 1 H), 4.31 (ddd, *J* = 3.3, 4.0, 6.6 Hz, 1 H), 5.43 (s, 1 H). HRMS calcd for $C_{19}H_{27}O_6$ (M^+ − OCH_3) *m*/*z* 351.1805, found 351.1797.

Conversion of 40 to Boeckman's Intermediate 41. To a solution of **40** (1.8 mg, 4.7 μmol) in CH_2Cl_2 (1 mL) was added Amberlyst-15 ion-exchange resin (H^+, non-aqueous) (10 mg) and powdered molecular sieves 4A (18 mg). The mixture was stirred for 1.5 h, and the resin was removed by filtration and washed well with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:5) to give 1.6 mg (quant.) of **41** as a colorless oil: R_f 0.30 (acetone/toluene, 1:3); $[\alpha]^{21}_D$ +152° (*c* 0.06, $CHCl_3$); IR (neat) 3400, 2980, 2940, 1770, 1690, 1590, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.25 (t, *J* = 7.7 Hz, 3 H), 1.40, 1.61, 1.63, 1.75 (4 s, each 3 H), 1.87 (dd, *J* = 4.8, 14.7 Hz, 1 H), 2.04 (br s, 1 H), 2.19 (dd, *J* = 8.8, 14.7 Hz, 1 H), 2.54 (q, *J* = 7.7 Hz, 2 H), 2.70 (dd, *J* = 0.7, 6.6 Hz, 1 H), 3.63, 3.93 (2 m, each 1 H), 4.17 (m, 2 H), 5.44 (s, 1 H). HRMS calcd for $C_{19}H_{26}O_6$ (M^+) *m*/*z* 350.1728, found 350.1739.

(1*S*,4*S*,5*R*,6*R*,8*R*)-4,6-Bis(hydroxymethyl)-8-isopropyl-8-methoxy-1-methyl-3,7-dioxabicyclo[3.3.0]octan-2-one (42). To a cold (0 °C), stirred solution of **34** (15.5 mg, 0.043 mmol) in MeOH (1 mL) was added MeONa (1.0 M solution in MeOH, 87 μL, 0.087 mmol). The solution was stirred at rt for 7.5 h, diluted with saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOH/toluene, 1:5) to give 11.0 mg (92%) of **42** as a colorless oil: R_f 0.31 (EtOH/toluene, 1:5); $[\alpha]^{22}_D$ −62.2° (*c* 1.71, $CHCl_3$); IR (neat) 3400, 2980, 2940, 2890, 1760, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.12, 1.16 (2 d, each *J* = 7.1 Hz, each 3 H), 1.34 (s, 3 H), 2.17 (heptet, *J* = 7.1 Hz, 1 H), 2.55 (br s, 2 H), 2.66 (dd, *J* = 4.4, 7.0 Hz, 1 H), 3.34 (s, 3 H), 3.66 (dd, *J* = 4.4, 12.1 Hz, 1 H), 3.72 (d, *J* = 4.4 Hz, 2 H), 3.79 (dd, *J* = 4.4, 12.1 Hz, 1 H), 4.01 (q, *J* = 4.4 Hz, 1 H), 4.38 (dt, *J* = 7.0, 4.4 Hz, 1 H). HRMS calcd for $C_{12}H_{19}O_6$ (M^+ − CH_3) *m*/*z* 259.1180, found 259.1180.

(1*S*,4*S*,5*R*,6*R*,8*R*)-6-[(*tert*-Butyldiphenylsiloxy)methyl]-4-(hydroxymethyl)-8-isopropyl-8-methoxy-1-methyl-3,7-dioxabicyclo[3.3.0]octan-2-one (47) and (1*S*,4*S*,5*R*,6*R*,8*R*)-4-[(*tert*-Butyldiphenylsiloxy)methyl]-6-(hydroxymethyl)-8-isopropyl-8-methoxy-1-methyl-3,7-dioxabicyclo[3.3.0]octan-2-one (48). To a cold (−15 °C), stirred solution of **42** (55.0 mg, 0.20 mmol) in pyridine (2 mL) was added PivCl (25 μL, 0.20 mmol). The solution was stirred at −15 °C for 5 h, diluted with saturated aqueous $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2; then EtOH/toluene, 1:5) to give 9.2 mg (10%) of **43**, 33.2 mg (46%) of an inseparable mixture of monopivalates **34** and **44** (6:5), and 24.4 mg (44%) of starting **42**. The dipivalate **43** was obtained as a colorless oil: R_f 0.40 (EtOAc/hexane, 1:2); IR (neat) 2970, 2940, 2880, 1805, 1780, 1730, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.12, 1.16 (2 d, each *J* = 7.3 Hz, each 3 H), 1.21, 1.22 (2 s, each 9 H), 1.39 (s, 3 H), 2.19 (heptet, *J* = 7.3 Hz, 1 H), 2.53 (dd, *J* = 3.7, 7.3 Hz, 1 H), 3.34 (s, 3 H), 4.05 (dd, *J* = 4.8, 12.1 Hz, 1 H), 4.17 (m, 3 H), 4.30 (dd, *J* = 2.9, 12.1 Hz, 1 H), 4.49 (ddd, *J* = 2.9, 4.8, 7.3 Hz, 1 H). The mixture of **34** and **44**, R_f 0.26 (EtOAc/hexane, 1:2), was obtained as a colorless oil. The ratio of **34** and **44** was determined to be ca. 6:5 based on ^1H NMR analysis: ^1H NMR (270 MHz) for **44**: δ 1.12, 1.16 (2 d, each *J* = 7.0 Hz, each 3 H), 1.23 (s, 9 H), 1.37 (s, 3 H), 1.75 (br s, 1 H), 2.18 (heptet, *J* = 7.0 Hz, 1 H), 2.65 (dd, *J* = 4.0, 7.0 Hz, 1 H), 3.33 (s, 3 H), 3.60, 3.85 (2 m, each 2 H), 4.16 (m, 1 H), 4.34 (dt, *J* = 7.0, 3.7 Hz, 1 H).

To a cold (0 °C), stirred solution of **34** and **44** (33.2 mg, 0.093 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (52 μL, 0.37 mmol), DMAP (5.7 mg), and TBDPSCl (48 μL, 0.185 mmol). The solution was stirred at rt for 10 h, and Et_3N (26 μL), and DMAP (5.7 mg), and TBDPSCl (24 μL) were added. The solution was stirred at rt for an additional 2.5 h, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to give 83.3 mg of an inseparable mixture of **45** and **46** as a colorless oil: R_f 0.73 (EtOAc/hexane, 1:2); ^1H NMR (270 MHz) for **45**: δ 1.06 (s, 9 H), 1.13, 1.19 (2 d, each *J* = 7.1 Hz, each 3 H), 1.21 (s, 9 H), 1.33 (s, 3 H), 2.16 (heptet, *J* = 7.1Hz, 1 H), 2.71 (dd, *J* = 4.0, 7.3 Hz, 1 H), 3.33 (s, 3 H), 3.73 (d, *J* = 4.0 Hz, 2 H), 3.99 (q, *J* = 4.0 Hz, 1 H), 4.03 (dd, *J* = 5.1, 12.1 Hz, 1 H), 4.29 (dd, *J* = 2.9, 12.1 Hz, 1 H), 4.45 (ddd, *J* = 2.9, 5.1, 7.3 Hz, 1 H), 7.41, 7.68 (2 m, 6H, 4 H); ^1H NMR (270 MHz) for **46**: δ 1.06 (s, 9 H), 1.13, 1.19 (2 d, each *J* = 7.3 Hz, each 3 H), 1.18 (s, 9 H), 1.40 (s, 3 H), 2.19 (heptet, *J* = 7.3 Hz, 1 H), 2.77 (dd, *J* = 4.0, 7.0 Hz, 1 H), 3.29 (s, 3 H), 3.65 (dd, *J* = 3.3, 11.4 Hz, 1 H), 3.84 (dd, *J* = 3.7, 11.4 Hz, 1 H), 4.01 (m, 1 H), 4.12 (d, *J* = 4.0 Hz, 2 H), 4.29 (m, 1 H), 7.40, 7.68 (2 m, 6H, 4 H).

To a cold (0 °C), stirred solution of the mixture of **45** and **46** (83.3 mg) in MeOH (1 mL) was added MeONa (1 M solution in MeOH, 0.19 mL, 0.19 mmol). The solution was stirred at rt for 4.5 h, and 0.19 mL of MeONa solution was added. The solution was stirred at rt for an additional 2 h, diluted with saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 20.3 mg (20% from **42**) of **47** and 18.4 mg (18% from **42**) of **48**. Compound **47** was obtained as a colorless oil: R_f 0.35 (EtOAc/hexane, 1:2); $[\alpha]^{22}_D$ −32.7° (*c* 1.02, $CHCl_3$); IR (neat) 3440, 2960, 2880, 1760, 1590, 1470 cm^{-1}; ^1H NMR (270 MHz) δ 1.07 (s, 9 H), 1.10, 1.15 (2 d, each *J* = 7.3 Hz, each 3 H), 1.27 (s, 3 H), 2.11 (m, 1 H), 2.13 (heptet, *J* = 7.3 Hz, 1 H), 2.70 (dd, *J* = 3.7, 7.3 Hz, 1 H), 3.31 (s, 3 H), 3.56 (m, 1 H), 3.64 (dd, J = 5.9, 10.6 Hz, 1 H), 3.77 (dd, J = 4.4, 10.6 Hz, 1 H), 3.80 (m, 1 H), 3.97 (ddd, *J* = 3.7, 4.4, 5.9 Hz, 1 H), 4.33 (ddd, *J* = 3.3, 4.4, 7.3 Hz, 1 H), 7.42, 7.67 (2 m, 6H, 4 H). HRMS calcd for $C_{29}H_{41}O_6Si$ (M^+ + H) *m*/*z* 513.2669, found 513.2638. Compound **48** was obtained as a colorless oil: R_f 0.42 (EtOAc/hexane, 1:2); $[\alpha]^{22}_D$ −35.1° (*c* 0.92, $CHCl_3$); IR (neat) 3480, 2940, 2880, 1760, 1590, 1470 cm^{-1}; ^1H NMR (270 MHz) δ 1.06 (s, 9 H), 1.13, 1.17 (2 d, each *J* = 7.3 Hz, each 3 H), 1.33 (s, 3 H), 1.76 (m, 1 H), 2.17 (heptet, *J* = 7.3 Hz, 1 H), 2.72 (dd, *J* = 4.4, 7.0 Hz, 1 H), 3.31 (s, 3 H), 3.56, 3.71 (2 m, each 1 H), 3.69 (dd, *J* = 4.0, 11.0 Hz, 1 H), 3.78 (dd, *J* = 4.0, 11.0 Hz, 1 H), 3.92 (dd, *J* = 4.4, 4.4 Hz, 1 H), 4.28 (dt, *J* = 7.0, 4.0 Hz, 1 H), 7.40, 7.68 (2 m, 6H, 4 H). HRMS calcd for $C_{29}H_{39}O_6Si$ (M^+ − H) *m*/*z* 511.2513, found 511.2482.

Coupling of Triflate 49 with 3(2*H*)-Furanone 36. The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of **48** (15.9 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (17.3 μL, 0.12 mmol) and trifluoromethanesulfonic anhydride (10.4 μL, 0.06 mmol). The mixture was stirred at −78 °C for 15 min, quenched with H_2O (10 mL), diluted with EtOAc (10 mL), and washed with saturated aqueous brine (10 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give 20.4 mg (>100%) of **49** as an unstable colorless oil which was used immediately: R_f 0.72 (EtOAc/hexane, 1:2); IR (neat) 2950, 2890, 1770, 1590, 1470 cm^{-1}; ^1H NMR (270 MHz) δ 1.07 (s, 9 H), 1.12, 1.17 (2 d, each *J* = 7.3 Hz, each 3 H), 1.35 (s, 3 H), 2.20 (heptet, *J* = 7.3 Hz, 1 H), 2.75 (dd, *J* = 4.0, 6.6 Hz, 1 H), 3.31 (s, 3 H), 3.77 (d, *J* = 4.4 Hz, 2 H), 4.06 (dt, *J* = 3.3, 4.0, Hz, 1 H), 4.27 (dt, J = 6.6, 4.0 Hz, 1 H), 4.35 (dd, *J* = 4.0, 11.0 Hz, 1 H), 4.53 (dd, *J* = 3.3, 11.0 Hz, 1 H), 7.41, 7.64 (2 m, 6H, 4 H).

The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of **36** (78.2 mg, 0.62 mmol) in toluene (1 mL) was added KHMDS (0.5 M solution in toluene, 1.24 mL, 0.62 mmol). After being stirred at −78 °C for 10 min, a solution of **49** (20.4 mg, 0.03 mmol) in toluene (1 mL) was added. The solution was allowed to warm to 0 °C over 2 h with stirring, quenched with saturated aqueous NH_4Cl (5 mL), diluted with EtOAc (10 mL), and washed with saturated aqueous NH_4Cl (10 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) and then PTLC (EtOAc/hexane, 1:2) to give 10.7 mg (57%) of **50** and 4.1 mg (22%) of **51**. Compound **50** was obtained as a colorless oil: R_f 0.43 (EtOAc/hexane, 1:2); $[\alpha]^{21}_D$ −4.5° (*c* 0.31, $CHCl_3$); IR (neat) 2960, 2940, 2850, 1770, 1700, 1600, 1470, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.06 (m, 6 H), 1.07 (s, 9 H), 1.23 (t, J = 7.7 Hz, 3 H), 1.28, 1.34 (2 s, each 3 H), 1.92 (dd, J = 2.2, 14.3 Hz, 1 H), 2.06 (heptet, J = 7.1 Hz, 1 H), 2.10 (dd, J = 10.6, 14.3 Hz, 1 H), 2.40 (dd, J = 4.4, 6.6 Hz, 1 H), 2.50 (q, J = 7.7 Hz, 2 H), 3.19 (s, 3 H), 3.72 (d, J = 4.4 Hz, 2 H), 3.90 (ddd, J = 2.2, 4.4, 6.6 Hz, 1 H), 4.21 (dt, J = 6.6, 4.4 Hz, 1 H), 5.41 (s, 1 H), 7.41, 7.65 (2 m, 6H, 4H). HRMS calcd for $C_{35}H_{45}O_6Si$ ($M^+ - OCH_3$) m/z 589.2982, found 589.2971. Compound **51** was obtained as a colorless oil: R_f 0.50 (EtOAc/hexane, 1:2); $[\alpha]^{21}_D$ −32.8° (*c* 0.34, $CHCl_3$); IR (neat) 2960, 2940, 2850, 1770, 1700, 1590, 1470, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.04 (s, 9 H), 1.12, 1.14 (2 d, each J = 7.3 Hz, each 3 H), 1.17 (t, J = 7.7 Hz, 3 H), 1.31, 1.40 (2 s, each 3 H), 1.73 (dd, J = 2.9, 14.7 Hz, 1 H), 2.05 (dd, J = 9.9, 14.7 Hz, 1 H), 2.14 (heptet, J = 7.3 Hz, 1 H), 2.42 (q, J = 7.7 Hz, 2 H), 2.44 (dd, J = 4.8, 6.8 Hz, 1 H), 3.24 (s, 3 H), 3.61 (dd, J = 3.3, 11.4 Hz, 1H), 3.81 (dd, J = 4.0, 11.4 Hz, 1 H), 3.93 (ddd, J = 2.9, 4.8, 9.9 Hz, 1 H), 4.24 (ddd, J = 3.3, 4.0, 6.8 Hz, 1 H), 5.37 (s, 1 H), 7.42, 7.64 (2 m, 6H, 4H). HRMS calcd for $C_{35}H_{45}O_6Si$ ($M^+ - OCH_3$) m/z 589.2982, found 589.2957.

Desilylation of 50. To a cold (0 °C) stirred solution of **50** (19.5 mg, 0.03 mmol) in THF (1 mL) was added *n*-Bu_4NF (1.0 M solution in THF, 47 μL, 0.047 mmol). The solution was stirred at rt for 20 min, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:4) to give 12.7 mg (>100%) of **40**, which was identical with that obtained by the depivaloylation of **37**.

Swern Oxidation of 40 and Intramolecular Vinylogous Aldol Reaction of Aldehyde 52. The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of oxalyl chloride (0.034 mL, 0.39 mmol) and DMSO (0.055 mL, 0.78 mmol) in CH_2Cl_2 (1 mL) was added a solution **40** (14.9 mg, 0.039 mmol) in CH_2Cl_2 (1 mL). After being stirred at −78 °C for 1 h, triethylamine (0.16 mL, 1.2 mmol) was added and the solution was warmed gradually to 0 °C and then stirred for 30 min. The solution was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo to give crude **52** (22.9 mg), which was used immediately in the next step.

The following reaction was carried out under Ar. To a cold (−78 °C), stirred solution of 18-crown-6 (22.7 mg, 0.086 mmol) and KHMDS (0.5 M solution in toluene, 0.16 mL, 0.078 mmol) in THF (3 mL) was added a solution of **52** (22.9 mg) in THF (1 mL). The solution was stirred at −78 °C for 10 min, quenched with saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:10) to give 6.0 mg (41% from **40**) of an inseparable diastereomeric mixture **53** as a colorless powder: R_f 0.40 (acetone/toluene, 1:2); IR (neat) 3400, 2970, 2930, 1770, 1700, 1580, 1460 cm^{-1}; ^1H NMR (270 MHz) for major isomer: δ 1.09, 1.15 (2 d, each J = 7.5 Hz, each 3H), 1.30, 1.47 (2 s, each 3 H), 1.37 (d, J = 7.3 Hz, 3 H), 2.07, 2.38, 3.10 (3 m, 2 H, 1 H, 2 H), 3.22 (s, 3 H), 3.61, 4.21 (2 m, 1 H, 2 H), 5.57 (s, 1 H). The diastereomeric ratio was determined based on the comparative intensity of the two singlets at δ 5.54 and 5.57 (1:3). HRMS calcd for $C_{19}H_{25}O_6$ ($M^+ - OCH_3$) m/z 349.1648, found 349.1638.

Mesylation of Aldol Mixture 53. To a stirred solution of **53** (3.8 mg, 0.01 mmol) in pyridine (1 mL) was added mesyl chloride (16 μL, 0.21 mmol) and DMAP (12.4 mg, 0.10 mmol). After being stirred at rt for 24 h, the solution was diluted with EtOAc (20 mL) and washed with H_2O (10 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:3) to give 4.2 mg (91%) of an inseparable diastereomeric mixture **54** as a colorless oil: R_f 0.25 (EtOAc/toluene, 1:2); IR (neat) 2980, 2930, 1780, 1710, 1590, 1460 cm^{-1}; ^1H NMR (270 MHz) for major isomer: δ 1.08, 1.12 (2 d, each J = 7.1 Hz, each 3 H), 1.31, 1.48 (2 s, each 3 H), 1.45 (d, J = 7.7 Hz, 3 H), 2.02 (dd, J = 13.6, 11.7 Hz, 1 H), 2.12 (heptet, J = 7.1 Hz, 1 H), 2.41 (dd, J = 2.2, 13.6 Hz, 1 H), 3.03 (s, 3 H), 3.10 (dd, J = 4.4, 6.2 Hz, 1 H), 3.22 (s, 3 H), 3.28 (m, 1 H), 3.58 (ddd, J = 2.2, 4.4, 11.7 Hz, 1 H), 4.20 (d, J = 6.2 Hz, 1 H), 4.77 (s, 1 H), 5.61 (s, 1 H). The ratio of the diastereomers was determined based on the comparative intensity of the two singlets at δ 5.59 and 5.61 (3.8: 10). HRMS calcd for $C_{21}H_{30}O_9S$ (M^+) m/z 458.1609, found 458.1612.

β-Elimination of Mesylate 54. Preparation of 55. To a stirred solution of **54** (4.2 mg, 9.2 μmol) in toluene (2 mL) was added DBU (4 μL, 27 mmol). The solution was heated under reflux for 2 h and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give 2.5 mg (76%) of **55** as a colorless oil: R_f 0.55 (EtOAc/toluene, 1:3); $[\alpha]^{26}_D$ +38.7° (*c* 0.125, $CHCl_3$); IR (neat) 2970, 2920, 1780, 1710, 1660, 1590, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.09, 1.12 (2 d, each J = 7.3 Hz, each 3 H), 1.30, 1.49 (2 s, each 3 H), 2.04 (s, 3 H), 2.05 (m, 1 H), 2.10 (heptet, J = 7.3 Hz, 1 H), 2.38 (dd, J = 2.6, 13.6 Hz, 1 H), 2.77 (dd, J = 4.0, 7.0 Hz, 1 H), 3.22 (s, 3 H), 3.73 (ddd, J = 2.6, 4.0, 11.7 Hz, 1 H), 4.73 (dt, J = 7.0, 2.2 Hz, 1 H), 5.60 (s, 1 H), 6.00 (m, 1 H). HRMS calcd for $C_{20}H_{27}O_6$ ($M^+ + H$) m/z 363.1806, found 363.1823.

Hydrolysis of Ketal 55. Synthesis of (+)-Eremantholide A (1). A solution of **55** (3.4 mg, 9.4 μmol) in THF and 6 M aqueous HCl (8:1, v/v, 1 mL) was stirred at rt for 6 h. The solution was diluted with EtOAc (20 mL) and washed with H_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and saturated brine (10 mL), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give 2.7 mg (82%) of **1** as colorless crystals: mp 182−184 °C; $[\alpha]^{22}_D$ +65.8° (*c* 0.23, EtOH); mp and $[\alpha]_D$ of natural sample, provided by Professor Le Quesne, were measured in our laboratory for comparison, mp 184−185 °C and $[\alpha]^{28}_D$ +68.8° (*c* 0.18, EtOH); R_f 0.27 (EtOAc/hexane, 1:2); IR (neat) 3430, 2980, 2920, 1770, 1700, 1660, 1580 cm^{-1}; ^1H NMR (270 MHz) δ 0.96, 1.07 (2 d, each J = 6.8 Hz, each 3 H), 1.32, 1.48 (2 s, each 3 H), 2.00 (m, 2 H), 2.05 (m, 3 H), 2.31 (dd, J = 2.4, 13.4 Hz, 1 H), 2.36 (s, 1 H), 2.81 (dd, J = 4.0, 7.3 Hz, 1 H), 4.04 (ddd, J = 2.4, 4.0, 11.4 Hz, 1 H), 4.95 (m, 1 H), 5.60 (s, 1 H), 6.01 (m, 1 H); ^{13}C NMR (68 MHz) δ 16.6, 16.8, 20.4, 20.5, 21.0, 32.0, 43.9, 60.1, 63.6, 77.9, 81.3, 89.9, 104.4, 107.8, 130.0, 134.7, 175.5, 186.8, 205.3. HRMS calcd for $C_{19}H_{24}O_6$ (M^+) m/z 348.1571, found 348.1579.

Depivaloylation of 38. By employing the same procedure used for the depivaloylation of **37**, we converted compound **38** (66.9 mg, 0.14 mmol) to 49.5 mg (91%) of **56**, obtained as colorless crystals: mp 105−108 °C; R_f 0.45 (acetone/toluene, 1:2); $[\alpha]^{25}_D$ −97.8° (*c* 0.405, $CHCl_3$); IR (neat) 3420, 2980, 2940, 2880, 1770, 1690, 1580, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 1.11, 1.14 (2 d, each J = 7.3 Hz, each 3 H), 1.25 (t, J = 7.7 Hz, 3 H), 1.32, 1.43 (2 s, each 3 H), 1.92 (dd, J = 4.4, 15.0 Hz, 1 H), 2.14 (heptet, J = 7.3 Hz, 1 H), 2.18 (dd, J = 8.4, 15.0 Hz, 1 H), 2.26 (br s, 1 H), 2.46 (dd, J = 3.7, 7.0 Hz, 1 H), 2.54 (q, J = 7.7 Hz, 2 H), 3.26 (s, 3 H), 3.59 (dd, J = 4.0, 12.5 Hz, 1 H), 3.81 (dd, J = 3.7, 12.5 Hz, 1 H), 3.94 (ddd, J = 3.7, 4.4, 8.4 Hz, 1 H), 4.30 (ddd, J = 3.7, 4.0, 7.0 Hz, 1 H), 5.43 (s, 1 H). HRMS calcd for $C_{19}H_{27}O_6$ ($M^+ - OCH_3$) m/z 351.1805, found 351.1801.

Desilylation of 51. To a cold (0 °C) stirred solution of **51** (7.2 mg, 0.012 mmol) in THF (1 mL) was added *n*-Bu_4NF (1.0 M solution in THF, 17.4 μL, 0.017 mmol). The solution was stirred at rt for 20 min, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts

were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:4) to give 3.9 mg (89%) of **56**, which was identical with that obtained by the depivaloylation of **38** described above.

Swern Oxidation of 56 and Intramolecular Vinylogous Aldol Reaction of Aldehyde 57. Compound **56** (17.3 mg, 45 μmol) was oxidized as per the conversion of **40** to **52**, giving crude aldehyde **57** (17.2 mg) with R_f 0.23 (acetone/toluene, 1:2), which was directly used for the vinylogous aldol reaction.

The following reaction was carried out under Ar. To a cold (−78 °C), stirred solution of 18-crown-6 (39.5 mg, 149 μmol) and KHMDS (0.5 M solution in toluene, 0.27 mL, 0.14 mmol) in THF (3 mL) was added a solution of crude **57** (17.2 mg) in THF (0.5 mL × 3). After being stirred at −78 °C for 30 min, the solution was quenched with saturated aqueous NH_4Cl (1 mL), diluted with H_2O (20 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography (acetone/toluene, 1:8) to give 6.4 mg (37% from **56**) of **58** as a colorless oil: R_f 0.52 (acetone/toluene, 1:2); $[\alpha]^{27}_D$ −163.4° (*c* 0.335, $CHCl_3$); IR (neat) 3400, 2970, 2890, 2740, 1760, 1700, 1600, 1460 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.10, 1.14 (2 d, each J = 7.3 Hz, each 3 H), 1.23, 1.50 (2 s, each 3 H), 1.37 (d, J = 7.3 Hz, 3 H), 2.01 (dd, J = 11.7, 13.9 Hz, 1 H), 2.13 (heptet, J = 7.3 Hz, 1 H), 2.37 (dd, J = 3.3, 13.9 Hz, 1 H), 2.41 (t, J = 5.4 Hz, 1 H), 2.70 (dq, J = 3.9, 7.3 Hz, 1 H), 2.80 (br s, 1 H), 3.32 (s, 3 H), 4.14 (m, 2 H), 4.50 (dd, J = 1.0, 5.4 Hz, 1 H), 5.55 (s, 1 H). HRMS calcd for $C_{19}H_{25}O_6$ ($M^+ - OCH_3$) m/z 349.1649, found 349.1463.

Acetylation of 58. Preparation of 59. To a stirred solution of **58** (7.0 mg, 18 μmol) in pyridine (0.5 mL) was added Ac_2O (0.5 mL). After being stirred for 5 h at rt, the solution was concentrated in vacuo with the aid of toluene. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 7.8 mg (100%) of **59** as colorless crystals: mp 179−181 °C; R_f 0.35 (EtOAc/toluene, 1:2), $[\alpha]^{21}_D$ −244.6° (*c* 0.39, $CHCl_3$); IR (neat) 2970, 2940, 2850, 1780, 1760, 1710, 1600, 1460 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.09, 1.14 (2 d, each J = 7.0 Hz, each 3 H), 1.21, 1.53 (2 s, each 3 H), 1.24 (d, J = 7.0 Hz, 3 H), 2.03 (dd, J = 11.7, 13.9 Hz, 1 H), 2.08 (s, 3 H), 2.10 (heptet, J = 7.0 Hz, 1 H), 2.34 (t, J = 5.5 Hz, 1 H), 2.41 (dd, J = 3.7, 13.9 Hz, 1 H), 2.88 (dq, J = 4.0, 7.0 Hz, 1 H), 3.31 (s, 3 H), 4.14 (ddd, J = 3.7, 5.5, 11.7 Hz, 1 H), 4.59 (dd, J = 1.5, 5.5 Hz, 1 H), 5.52 (s, 1 H) 5.56 (dd, J = 1.5, 4.0 Hz, 1 H). HRMS calcd for $C_{22}H_{30}O_8$ (M^+) m/z 422.1938, found 422.1914.

β-Elimination of Acetate 59. Preparation of 60. By treatment of **59** (6.1 mg, 14 μmol) in refluxing toluene (1 mL) with DBU (6.5 μL) for 1.5 h, 5.2 mg (100%) of **60** was obtained as colorless crystals: mp 173−175 °C; R_f 0.53 (EtOAc/toluene, 1:3); $[\alpha]^{21.5}_D$ −136.5° (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) 3020, 2970, 2940, 2840, 1770, 1700, 1640, 1570 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.13, 1.16 (2 d, each J = 7.3 Hz, each 3 H), 1.25, 1.56 (2 s, each 3 H), 1.98 (dd, J = 11.7, 13.9 Hz, 1 H), 2.03 (d, J = 1.8 Hz, 3 H), 2.14 (t, J = 5.5 Hz, 1 H), 2.14 (heptet, J = 7.3 Hz, 1 H), 2.33 (dd, J = 2.6, 13.9 Hz, 1 H), 3.34 (s, 3 H), 4.14 (ddd, J = 2.6, 5.5, 11.7 Hz, 1 H), 5.25 (m, 1 H), 5.60 (s, 1 H), 6.07 (quintet, J = 1.8 Hz, 1 H). HRMS calcd for $C_{20}H_{25}O_6$ (M^+ − H) m/z 361.1648, found 361.1642.

Hydrolysis of Ketal 60. Synthesis of (−)-10-*epi*-Eremantholide A (61). By using the same procedure describing acid hydrolysis of **55**, compound **60** (4.3 mg, 12 μmol) was converted to 3.6 mg (88%) of 10-*epi*-eremanthoide A (**61**), obtained as colorless crystals: mp 220−223 °C; R_f 0.17 (EtOAc/hexane, 1:2); $[\alpha]^{25}_D$ −123.5° (*c* 0.195, $CHCl_3$); IR ($CHCl_3$) 3460, 2990, 2930, 1770, 1700, 1630, 1570, 1450 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.01, 1.11 (2 d, each J = 7.0 Hz, each 3 H), 1.29, 1.56 (2 s, each 3 H), 1.94 (dd, J = 11.2, 13.6 Hz, 1 H), 2.04 (d, J = 1.8 Hz, 3 H), 2.06 (heptet, J = 7.0 Hz, 1 H), 2.19 (t, J = 5.5 Hz, 1 H), 2.27 (dd, J = 2.6, 13.6 Hz, 1 H), 2.31 (s, 1 H), 4.50 (ddd, J = 2.6, 5.5, 11.2 Hz, 1 H), 5.39 (m, 1 H), 5.60 (s, 1 H), 6.09 (m, 1 H); ^{13}C NMR (68 MHz) δ 16.8, 18.9, 21.1, 21.5, 31.9, 39.7, 59.8, 66.4, 75.7, 79.7, 81.9, 86.2, 101.9, 108.6, 126.8, 139.3, 175.8, 183.3, 206.5. HRMS calcd for $C_{19}H_{24}O_6$ (M^+) m/z 348.1571, found 348.1562.

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Supporting Information Available: Copies of ^{1}H NMR spectra of **9**, **10**, **11a,b**−**14a,b**, **16a,b**−**20a,b**, **23**−**26**, **29**−**34**, **37**−**42**, **47**, **48**, **50**, **51**, **53**−**56**, **58**−**61**, synthetic **1**, and natural **1** and ^{13}C NMR spectra of synthetic **1**, natural **1**, and **61** (53 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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