Total Synthesis of (−)-Mniopetal E, a Novel Biologically Intriguing Drimane Sesquiterpenoid

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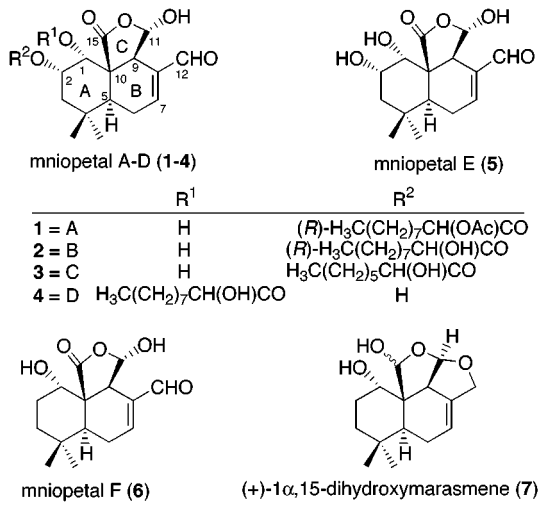
We have achieved the total synthesis of (−)-mniopetal E, a drimane sesquiterpenoid which inhibits the reverse transcriptase of human immunodeficiency virus (HIV)-1. Our enantiospecific total synthesis of this target molecule in naturally occurring form commenced with a known 2,3-anhydro-D-arabinitol derivative, which was prepared using the Sharpless asymmetric epoxidation strategy. The key steps of our total synthesis were as follows: (1) a combination of highly stereocontrolled inter- and intramolecular Horner−Emmons carbon elongations for construction of a butenolide tethering a 1,2,4,9-functionalized nona-5,7-diene moiety at the β-carbon, (2) stereoselective thermal intramolecular Diels−Alder reaction of the thus-formed trienic compound, providing preferentially an *endo*-cycloadduct with the desired π-facial selection, and (3) efficient transformation of the γ-lactone moiety in the major cycloadduct to the γ-hydroxy-γ-lactone part in mniopetal E. Our total synthesis of (−)-mniopetal E established the unsettled absolute stereochemistry of the antibiotic.

Introduction

In 1994, six novel sesquiterpenoids, mniopetals A−F (**1**−**6**), were isolated by Steglich and co-workers from the fermentation broth of a Canadian *Mniopetalum* sp. 87256.[1] Soon after, their relative stereochemistries were determined by the same authors on the basis of chemical and spectroscopic methods (^{1}H and ^{13}C NMR, MS, UV, and IR).[2] These highly oxygenated drimane-type sesquiterpenoids inhibit RNA directed DNA polymerases (reverse transcriptases) of some RNA viruses such as human immunodeficiency virus (HIV)-1.[1] The structural characteristics of the mniopetal family are (1) a 6−6−5 angularly fused tricyclic framework including a *trans*-fused octahydronaphthalene skeleton (A/B ring), (2) five or six contiguous stereogenic centers including an angular asymmetric quaternary carbon, and (3) a variety of oxygen functionalities such as a γ-hydroxy-γ-lactone ring (C ring). Although the absolute stereochemistry of the mniopetal family had not been determined, it was reasonably assumed to be those as depicted based on the correlation with (+)-1α,15-dihydroxymarasmene (**7**) isolated from the same fungus.[3,4] The absolute stereochemistry of structurally related drimane sesquiterpenoids had been established through enantiospecific total synthesis starting from, e.g., enantiopure 3-hydroxy-2,2-dimethylcyclohexanone.[5] Owing to their biological interest and structural uniqueness, mniopetals are currently selected as targets for total synthesis by several groups.[6−9]

We have recently accomplished the first total synthesis of (−)-mniopetal E (**5**), a prototype of mniopetals A−D, thereby established the unsettled absolute stereochemistry.[10] The total synthesis featured by an intramolecular Diels−Alder (IMDA) strategy for construction of the core tricyclic skeleton. We describe herein our total synthesis of **5** in detail, which involves significant improvement of our original approach[6,10] for preparation of the substrate used for the key IMDA reaction.



(1) Kuschel, A.; Anke, T.; Velten, R.; Klostermeyer, D.; Steglich, W.; König, B. *J. Antibiot.* **1994**, *47*, 733−739.
(2) Velten, R.; Klostermeyer, D.; Steffan, B.; Steglich, W.; Kuschel, A.; Anke, T. *J. Antibiot.* **1994**, *47*, 1017−1024.
(3) Ayer, W. A.; Craw, P. A. *Can. J. Chem.* **1989**, *67*, 1371−1380.
(4) Velten, R.; Steglich, W.; Anke, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1229−1232.
(5) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273−281.
(6) Murata, T.; Ishikawa, M.; Nishimaki, R.; Tadano, K. *Synlett* **1997**, 1291−1293.
(7) Jauch, J. *Synlett* **1999**, 1325−1327.
(8) Allen, Jr., A.; Gordon, D. M. *Indian J. Chem.* **1999**, *38B*, 269−273.
(9) Very recently, Jauch reported the first total synthesis of (−)-kuehneromycin A, structurally resembling natural product mniopetal F (**6**), possessing a keto functionality instead of the C-1 hydroxyl group, see: Jauch, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2764−2765.

10.1021/jo001004p CCC: $19.00
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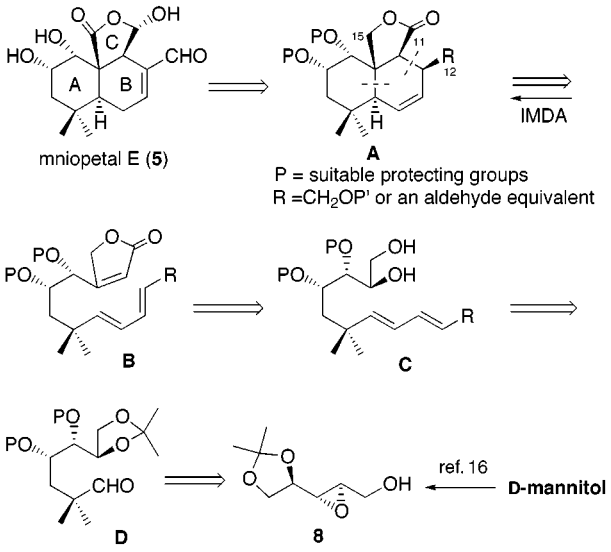
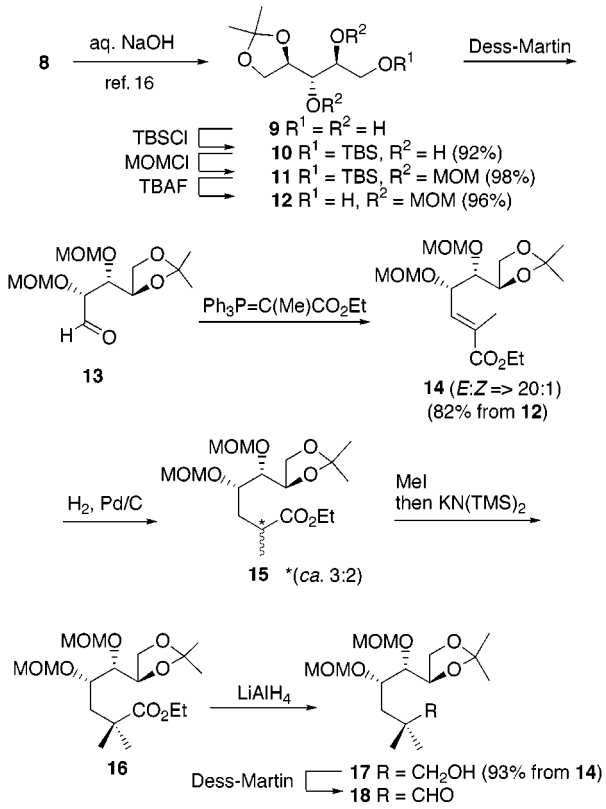
Scheme 1



Results and Discussion

Our retrosynthetic approach toward mniopetal E (**5**) is depicted in Scheme 1. For construction of the *trans*-fused octahydronaphthalene core structure[11] (the A/B ring) exemplified by **A**, we envisioned the use of IMDA reaction.[12] Adjustment of the oxidation states in the cycloadduct **A** would eventually provide the target natural product **5**. Namely, the cycloadduct **A** would be converted into **5** by modification of the oxidation states at C11, C12, and C15[13] accompanied by migration of the carbon−carbon double bond. As a properly functionalized substrate for the intended stereocontrolled IMDA reaction, we envisaged a butenolide **B** tethering an (*E*,*E*)-octa-5,7-diene-1,2-diol with a terminal aldehyde equivalent.[14] The synthesis of the substrate **B** would be achieved from 1,4-disubstituted butadiene **C** via introduction of the butenolide ring by functionalization of the terminal diol moiety. The intermediate **C** would be prepared by stereoselective introduction of an *E*,*E*-conjugate diene moiety into a 4,5,6,7-tetrahydroxyheptanal derivative **D**. This heptanal **D** could be obtained from the known epoxide **8** through the Payne rearrangement[15] followed by the epoxy ring opening by attack of an isobutyraldehyde equivalent. The enantiopure **8** had been prepared from D-mannitol by Sharpless and co-workers via the asymmetric epoxidation of (*E*)-1,2-(isopropylidenedioxy)-3-penten-5-ol.[16] According to this retrosynthesis, we embarked on the enantiospecific total synthesis of **5**.

Scheme 2



For the synthesis of a heptanal derivative **18** (**D** in the retrosynthesis) from **8**, we investigated two different approaches. The first approach[6,10] relied on the Wittig olefination of aldehyde **13** (Scheme 2). The second was based on the attack of 2-lithio-2-methylpropionitrile (α-lithiated isobutyronitrile)[17,18] on the Payne rearrangement product **25** (Scheme 4). Our original attempt for the preparation of heptanal **18** from **8** is shown in Scheme 2. Alkaline hydrolysis of **8** according to the reported procedure[16] provided a partially protected D-ribitol **9** via the Payne rearrangement followed by opening of the resulting terminal epoxy ring by a hydroxide ion. The primary hydroxyl group in **9** was selectively protected as a *tert*-butyldimethylsilyl (TBS) ether providing **10**. The secondary hydroxyl groups in **10** were protected as methoxymethyl (MOM) ethers to afford **11**. Desilylation of **11** with tetrabutylammonium fluoride (TBAF) provided **12**. Oxidation of **12** with Dess−Martin periodinane[19] gave an acyclic D-ribose derivative **13**, which was subjected to the Wittig olefination with ethylidenetriphenylphosphorane providing α,β-unsaturated ester **14** with high *E*-selectivity (>20:1, based on the ^{1}H NMR analysis). Hydrogenation of the double bond in **14** in the presence of Pd on charcoal provided a 3:2 diastereomeric mixture

(10) Suzuki, Y.; Nishimaki, R.; Ishikawa, M.; Murata, T.; Takao, K.; Tadano, K. *Tetrahedron Lett.* **1999**, *40*, 7835−7838.

(11) A recent review on the annulation route to *trans*-decalins, see: Varner M. A.; Grossman, R. B. *Tetrahedron* **1999**, *55*, 13867−13886.

(12) Some recent reviews on the IMDA reactions, see: (a) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; vol. 2, pp 91−146. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; vol. 5, pp 513−550. (d) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *42*, 14179−14233. (e) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 464−474.

(13) The numbering adapted for the mniopetals in ref 2 is used in the text.

(14) Some similar IMDA approaches for the azadirachtin synthesis, see; (a) Kanoh, N.; Ishihara, J.; Murai, A. *Synlett* **1995**, 895−897. (b) Kanoh, N.; Ishihara, J.; Murai, A. *Synlett* **1997**, 737−739. (c) Ishihara, J.; Yamamoto, Y.; Kanoh, N.; Murai, A. *Tetrahedron Lett.* **1999**, *40*, 4387−4390.

(15) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819−3822.

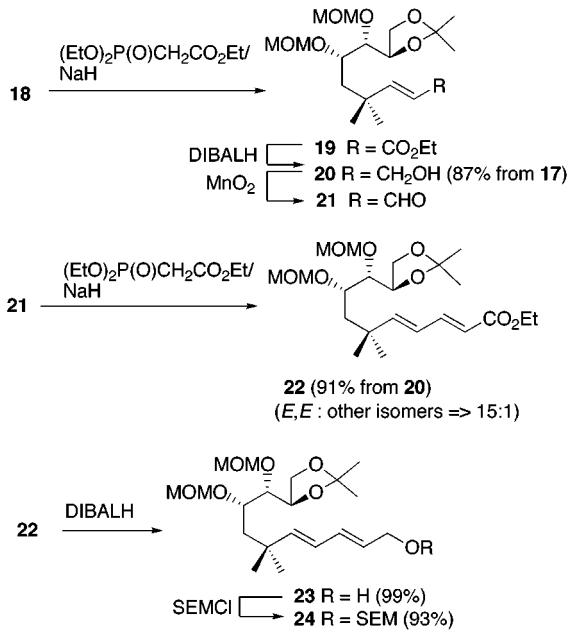
(16) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373−1380. For preparation of (*R*)-glyceraldehyde acetonide, see: Schmid, R.; Bryant, J. D. *Org. Synth.* **1993**, *72*, 6−13.

(17) (a) Borgne, J. F. L.; Cuvigny, T.; Larchevêque, M.; Normant, H. *Synthesis* **1976**, 238−240. (b) Murata, S.; Matsuda, I. *Synthesis* **1978**, 221−222. (c) Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 26−30. (d) Smith, J. G. *Synthesis* **1984**, 629−656.

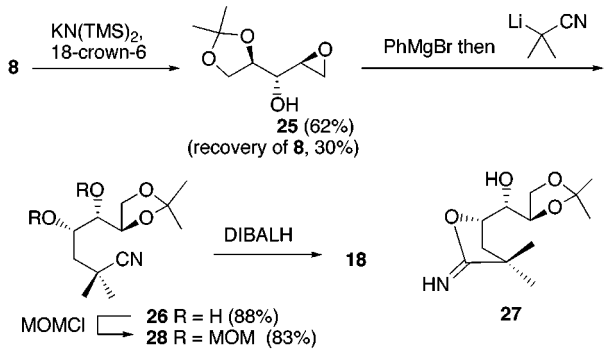
(18) Semmelhack, M. F.; Harrison, J. J.; Thebtaranonth, Y. *J. Org. Chem.* **1979**, *44*, 3275−3277.

(19) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

Scheme 3



Scheme 4



of saturated esters **15**. We did not determine the stereochemistry of the newly created stereogenic centers in the mixture. We found that the α-methylation of **15** underwent efficiently when **15** was treated with KN(TMS)$_2$ (3 equiv) in toluene−THF (6:1) at −78 °C *in the presence of* MeI (4 equiv, internal quenching), providing the desired α-dimethyl ester **16** quantitatively.[20] The ester group in **16** was reduced with $LiAlH_4$, and subsequent Dess−Martin oxidation of the neopentyl alcohol **17** provided **18** in 10 steps from **8**.

Introduction of the conjugated diene unit into **18** (**D** to **C** in the retrosynthesis) was efficiently achieved by a sequential Horner−Emmons olefination strategy as shown in Scheme 3.[21] Treatment of **18** with the carbanion generated from triethyl phosphonoacetate provided (*E*)-unsaturated ester **19** with complete geometrical stereocontrol. Reduction of **19** with diisobutylaluminum hydride (DIBALH) gave allylic alcohol **20** in 87% yield from **17**. Manganese dioxide (MnO_2) oxidation of **20** afforded unsaturated aldehyde **21**. The second Horner−Emmons olefination of **21** with triethyl phosphonoacetate provided the diene **22** in 91% yield from **20**. The geometrical stereoselection (*E*,*E* isomer:total of other isomers) was more than 15:1 (^{1}H NMR analysis). To make the anticipated IMDA reaction more electronically favorable, the ester group on the diene in **22** was reduced with DIBALH, followed by protection of the resulting allylic alcohol **23** as a 2-trimethylsilylethoxymethyl (SEM) ether providing **24**.

In view of the excessive length of the 16-step preparation of the substrate **24** from **8**, we planned to develop a more convenient route to **24**. Our improved route is depicted in Scheme 4. The Payne rearrangement of **8** with KN(TMS)$_2$ in the presence of 18-crown-6 in THF at −18 °C afforded the epoxy-migrated compound **25** in 62% yield along with 30% recovery of **8**.[22] The epoxy ring opening of **25** with 2-lithio-2-methylpropionitrile derived from isobutyronitrile using LDA as base[18] afforded an approximately 1:1 mixture of heptanenitrile **26** and a five-membered cyclic imidate **27**. The latter was presumably formed by the intramolecular attack of the alkoxide, generated after the epoxy ring opening, on the nitrile carbon.[17b,23] To avoid the formation of **27**, the epoxide **25** was treated with a Grignard reagent prior to addition of the nucleophile. We expected that the undesired cyclization would be prevented owing to the formation of a magnesium chelate between internal dialkoxide. When **25** was treated with PhMgBr (1.5 equiv) at −78 °C for 30 min and followed by addition of 2-lithio-2-methylpropionitrile (3 equiv), to our delight, the desired **26** was obtained in 88% yield.[24] The two hydroxyl groups in **26** were protected as MOM ethers providing **28**. DIBALH reduction of the nitrile group in **28** followed by hydrolytic workup of the resulting imine with 1.0 M aqueous HCl provided **18** in a four-step process from **8**. By using the aforementioned reaction sequence, **18** was converted into **20** in an overall yield of 71% from **28**.

We next explored the construction of the butenolide ring into **24** by functionalization of the terminal diol moiety (**C** to **B** in the retrosynthesis). Several initial attempts are shown in Scheme 5. Hydrolysis of **24** in aqueous AcOH afforded diol **29**, of which the primary hydroxyl group could be protected using any of three protecting groups (R = TBS, Piv, or Ac). The secondary hydroxyl group in thus-obtained silyl ether and two esters

(20) We also explored the α-methylation of **15** under the following conditions. After treating **15** with NaH, LDA, or lithium bis(trimethylsilyl)amide (LiN(TMS)$_2$), methyl iodide was added as an electrophile at −78 °C (or at −18 °C). Under these conditions, **15** was recovered almost quantitatively. Using potassium bis(trimethylsilyl)amide (KN(TMS)$_2$) as the base with subsequent addition of MeI, decomposition of **15** predominated.

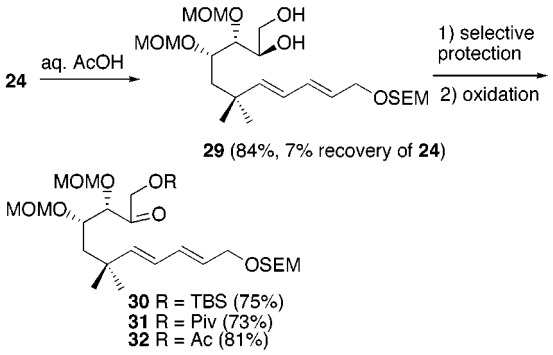
(21) The Horner−Emmons olefination of **18** with the carbanion generated from triethyl 4-phosphonocrotonate using LiN(TMS)$_2$ as base provided α,*β*:*γ*,*δ*-unsaturated ester **22** in 31% yield from **17** along with 25% recovery of **18**. The geometric ratio (the desired *E*,*E* isomer: total amount of other isomers) was approximately 8:1.

(22) This Payne rearrangement produced the equilibrium mixture of **25** and **8**. We explored this rearrangement by changing the base and reaction temperature. Most effective conditions we found were those described in the text.

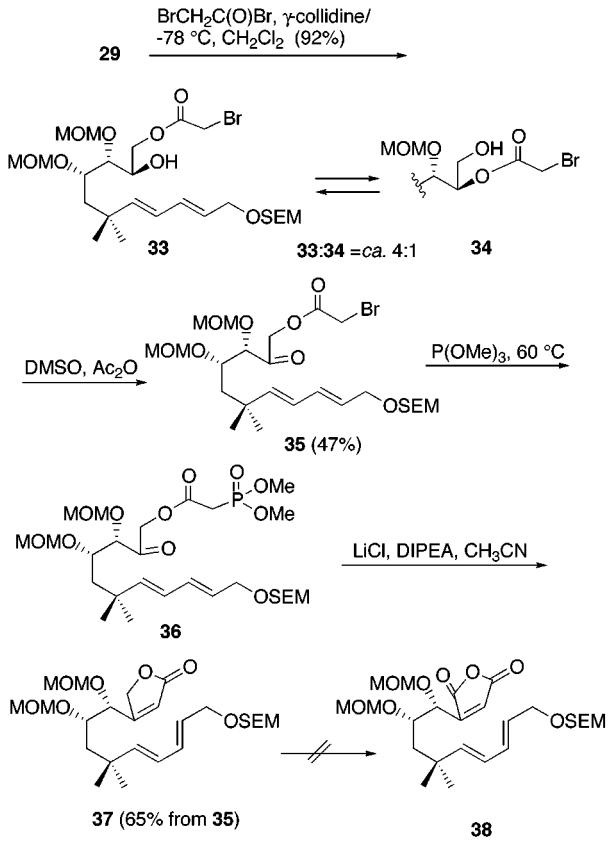
(23) As another nucleophile, the dianion of 2-methylpropanoic acid (LDA) was examined to attack to the 3-O-MOM ether of **25**. In this case, the five-membered lactone corresponding to **27** (OMOM in place of OH) was obtained in 86% yield. The lactone formation occurred quite easily during workup of the reaction mixture.

(24) We also explored a single-step conversion of **8** into **26** via a one-pot Payne rearrangement−epoxy ring opening reaction. However, we could not find any practical conditions for this purpose after trying various bases or addition of additives. For one-pot Payne rearrangement−epoxy ring opening reactions, see: (a) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687−5696. (b) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696−5704. (c) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1375−1382. Also, we examined the epoxy ring opening of **25** with the carbanions generated from *N*,*N*,2-trimethylpropionamide or 3-isobutyroyl-2-oxazolidone. The epoxy ring opening by the two nucleophiles did not proceed. For a previous example for this transformation, see: Sauriol-Lord, F.; Grindley, B. *J. Org. Chem.* **1981**, *46*, 2831−2836.

Scheme 5



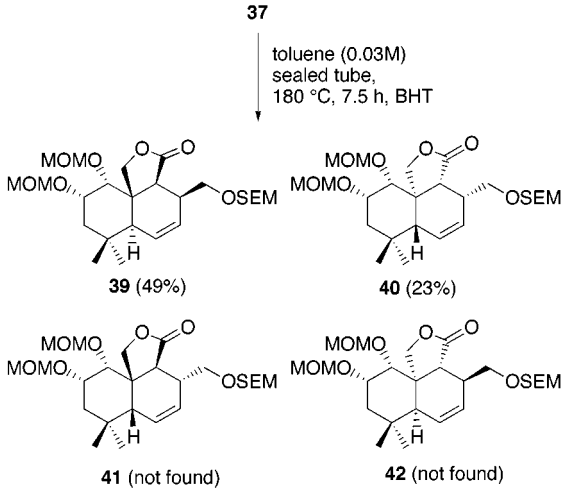
Scheme 6



was oxidized, providing the respective keto compounds **30**−**32**. A variety of carbon nucleophiles were examined for their ability to attack the carbonyl groups in **30**−**32**. Unfortunately, we could not find useful results with any of the substrates.[25]

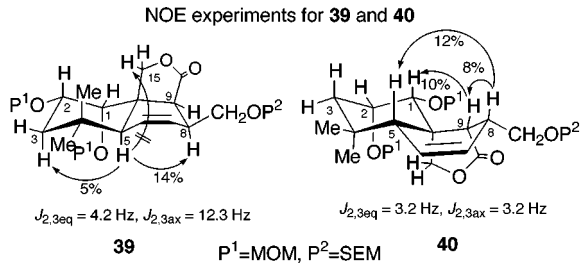
For the desired butenolide ring construction, our exploration was then focused on an intramolecular Horner−Emmons olefination approach as shown in Scheme 6. The primary hydroxyl group in **29** was selectively acylated with bromoacetyl bromide in the presence of γ-collidine,[26] affording an approximately 4:1 inseparable mixture of the desired terminal bromoacetate **33** and the regioisomeric ester **34** in a combined yield of 92%. The

Scheme 7



mixture of **33** and **34** was found to be an equilibrium mixture. Both the ^{1}H NMR spectrum ($CDCl_3$) of regioisomerically enriched **33** (>90% content) and that of **34** (>90%) revealed the same signal pattern as the 4:1 mixture. The mixture of **33** and **34** was oxidized with DMSO−Ac_2O to afford α-bromoacetoxyl ketone **35** in a moderate yield. The ketone **35** was subjected to an Arbusov phosphorylation[27] by heating in trimethyl phosphite (neat) at 60 °C providing the phosphonoacetate **36**. The intramolecular Horner−Emmons reaction of **36** under the Roush−Masamune's conditions[28] proceeded smoothly to give butenolide **37**, the substrate for the IMDA reaction, in 65% yield from **35**. We also examined converting the butenolide **37** into maleic anhydride derivative **38**, which is a superior dienophile. By using several oxidation procedures, however, we could not find any effective conditions for this conversion.

The IMDA reaction of **37** was first conducted in a protonic solvent or Lewis acid mediated conditions, involving heating in 2,2,2-trifluoroethanol at 120 °C in a sealed tube, or subjecting to Lewis acid such as BF_3·OEt_2 or Et_2AlCl in a CH_2Cl_2 solution. None of these conditions provided the desired cycloadducts.[29] Eventually, we obtained the successful result by heating a toluene solution of **37** (0.03 M concentration) in a sealed tube at 180 °C for 7.5 h in the presence of a trace of 2,6-di-*tert*-butyl-*p*-cresol (BHT). Under these conditions, two *endo*-cycloadducts **39** and **40** were isolated in 49% and 23% yields, respectively, after separation on silica gel (Scheme 7). Neither *exo*-cycloadduct **41** nor **42** was found in the reaction mixture. The stereostructures of **39** and **40** were confirmed by ^{1}H NMR analyses including NOE experiments as shown.

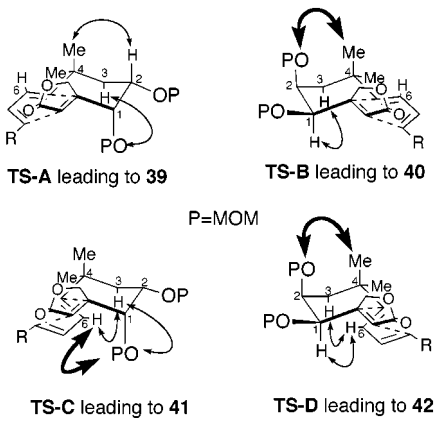


(25) We examined the following nucleophiles: (a) the enolate derived from methyl acetate for **30**−**32** (no reactions), (b) the Peterson-type acetate carbanion for **30**−**32** (no reaction), (c) the Horner−Emmons olefination with triethyl phosphonoacetate for **31** (19% yield of the adduct), and (d) the intramolecular aldol condensation using **32** (LiN(TMS)$_2$ as bases) (no reaction).

(26) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791−3793.

(27) A review on the Michaellis−Arbusov reaction, see: Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415−430.

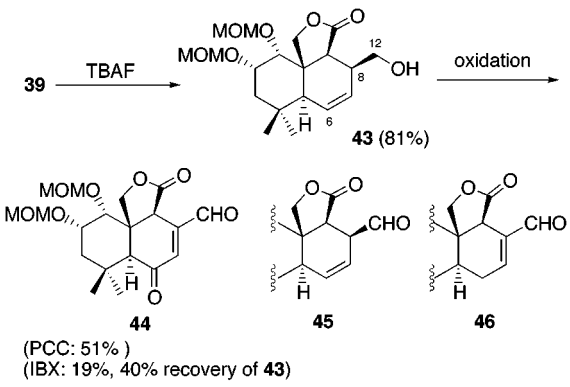
The predominant formation of the *endo*-isomers **39** and **40** can be explained as follows. On the basis of the concept of "concerted but asynchronous" cycloaddition, Roush stated that a 1,7,9-decatriene system possessing an electron-withdrawing group at the terminal position of the dienophile part can adopt a six-membered chairlike transition state.[12a,c] It seems reasonable to apply the chairlike transition state model for our substrate **37**. Therefore, four transition states **TS-A** to **TS-D** are possible as shown. Two *endo*-transition states, namely **TS-A** leading to **39** and **TS-B** leading to **40**, seem to be



more advantageous compared to the two *exo*-TSs, because of the presence of electronically favorable secondary orbital interactions in the former. In the two *exo*-transition states, **TS-C** leading to **41** and **TS-D** leading to **42**, severe steric repulsion exists between H6 and two axial substituents, i.e., OMOM at C1 and $H3_{ax}$. These unfavorable factors certainly impede the cyclization. Regarding the π-facial selectivity which affected the ratio of **39** and **40**, the total magnitude of the 1,3-diaxial repulsions in **TS-A**, i.e., those occurring between the OMOM at C1 and H3 and also between H2 and the axial methyl group at C4, is likely to be smaller than that expected in **TS-B** between the OMOM at C2 and the axial methyl at C4 and also between H1 and H3.[30,31] As a result, the cycloadduct **39** was formed preferentially.

Having established an efficient synthetic route to the tricyclic intermediate **39** with the correct stereochemistry for the mniopetals synthesis, we investigated the introduction of the α,β-unsaturated aldehyde moiety in the B-ring by oxidation of the C12 hydroxyl group in **43**, which was prepared from **39** by desilylation (Scheme 8).

Scheme 8



To the contrary of our expectation, neither the desired aldehyde **45** nor the conjugated enal **46** was obtained by pyridinium chlorochromate (PCC) oxidation or *o*-iodoxybenzoic acid (IBX) oxidation[32] of **43**. Rather γ-keto α,β-unsaturated aldehyde **44** was obtained in 51% yield with the former oxidant or in 19% yield with the latter (40% recovery of **43**). The structure of **44** was established by the ^{1}H and ^{13}C NMR analysis. Compound **44** was formed probably by successive oxidation of the intermediary enal **46**. This facile oxidation at the allylic position of **46** can be explained by high acidity of the pseudoaxial H6β in **46**.[33,34] The conformational change of the tricyclic framework accompanying migration of C6−C7 double bond to C7−C8 may enable the C6 carbon to be oxidized readily. At this stage, we concluded that it was advisable to prepare a substrate, which is equipped with an aldehyde group or its synthetic equivalent as the diene terminal, for the IMDA reaction.

We designed next a dithiolane derivative **54** as the substrate possessing a synthetic equivalent to the aldehyde group in **5**. The preparation of **54** from **23** is depicted in Scheme 9. MnO_2 oxidation of **23** provided α,β:γ,δ-unsaturated aldehyde **47**. The aldehyde group was protected as the 1,3-dithiolane under the standard conditions, providing **48** in 60% yield along with a 33% yield of de-*O*-isopropylidene derivative **49**. Acid hydrolysis of **48** in aqueous acetic acid provided additional **49**. We expected that introduction of the butenolide part into **49** could be achieved using a reaction sequence similar to that used for **29**. However, the four-step conversion of **49** to **54**, i.e., (1) bromo-acetylation of the primary hydroxyl group, (2) DMSO oxidation of the secondary hydroxyl group, (3) the Arbuzov reaction with $P(OMe)_3$, and then (4) intramolecular Horner−Emmons reaction, finally provided **54** in less effective yields of 8% to 22% without reproducibility. In some cases, the 1,3-dithiolane group was not compatible with these conditions. We explored next the butenolide construction using a direct introduction of the phosphonoacetyl group into the primary hydroxyl group. The primary hydroxyl group in **49** was protected as the TBS ether temporarily, and the secondary hydroxyl group in the resulting **50** was oxi-

(28) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.

(29) Heating of **37** in 2,2,2-trifluoroethanol or the BF_3·OEt_2-mediated conditions caused significant decomposition. In the case of the Et_2AlCl mediated reaction, the substrate **37** was recovered intact.

(30) We executed the thermal IMDA reaction of a structurally resembling substrate to **37**, in which the two OMOM groups were replaced by each pivaloyloxy group. In this case, however, the change of π-facial selectivity was not observed. Two *endo*-cycloadducts were obtained in 50% and 22% yields, respectively, with preferential formation of the adduct having the same stereochemistry as **39**.

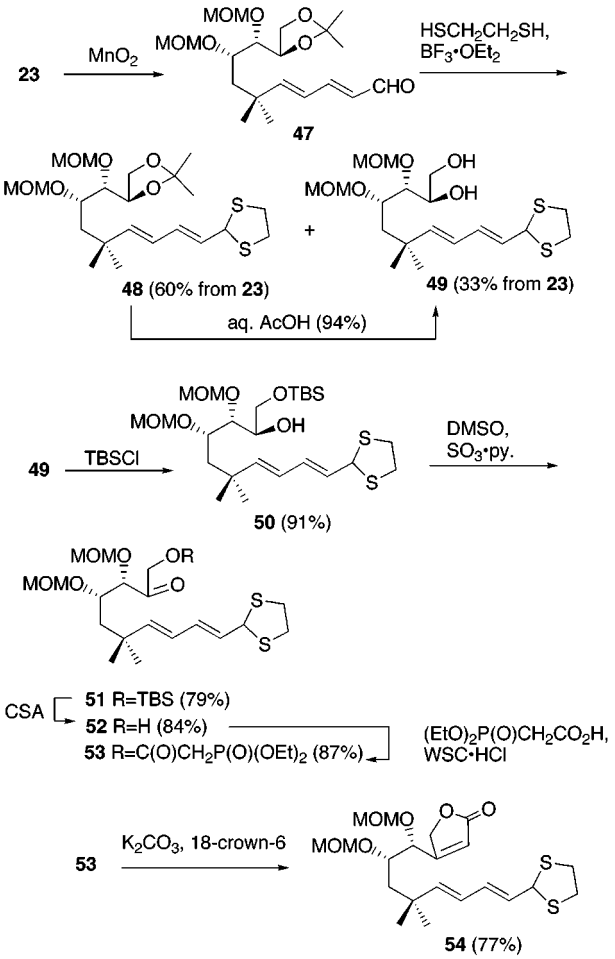
(31) An experiment further supported the effect of the 1,3-diaxial repulsion on the IMDA reaction. In our preliminary studies on a total synthesis of mniopetal F, we prepared a IMDA substrate which lacks the OMOM group at C2 (the mniopetals numbering) in **37.** The thermal IMDA reaction of this substrate provided two *endo*-cycloadducts, which correspond to **39** and **40** but lacking the OMOM group at C2, in a ratio of 2:3. Interestingly, the major adduct was one that formed as a result of the opposite π-facial selection compared to that observed in the case of **37**. Apparently, inversion of total magnitude of the 1,3-diaxial repulsion in their TSs affected.

(32) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem*. **1995**, *60*, 7272−7276.

(33) Steglich reported that the pseudoaxial H6β in mniopetal F (**6**) was smoothly exchanged against deuterium during the NMR measurement in CD_3OD, see: ref 2

(34) A drimane-type sesquiterpenoid possessing a 2-cyclohexenone substructure as the B ring in the mniopetals was isolated, see: Tabata, N.; Tomoda, H.; Masuma, R.; Iwai, Y.; Omura, S. *J. Antibiot*. **1995**, *48*, 53−58.

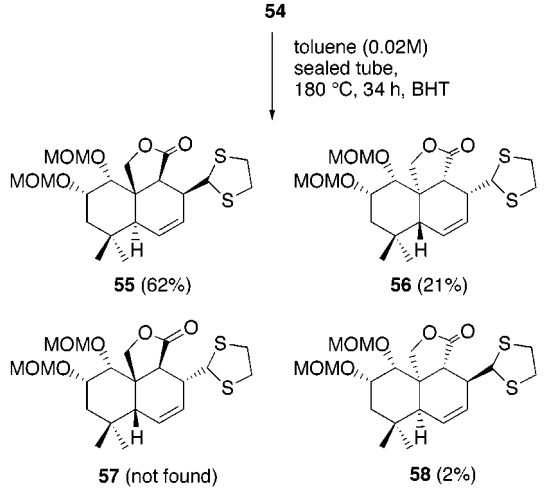
Scheme 9



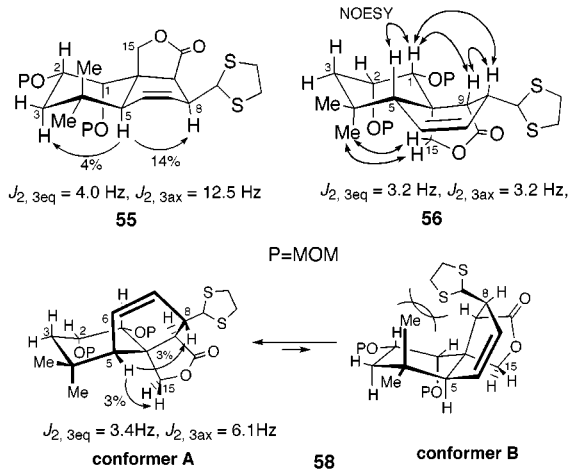
dized. Desilylation of the resulting ketone **51** was achieved in 84% yield by treatment with camphorsulfonic acid (CSA) in MeOH affording α-hydroxyketone **52**. Esterification of **52** with diethylphosphonoacetic acid was achieved efficiently in the presence of a water-soluble carbodiimide.[35] Intramolecular Horner−Emmons olefination of the resulting phosphonoacetate **53** provided the butenolide **54** in 77% yield by the action of K_2CO_3 and 18-crown-6 in toluene.[36] Under the Roush−Masamune's conditions,[28] the formation of hydrolysis product **52** accompanied the desired olefination.

We examined the IMDA reaction of **54** under Lewis acid mediated conditions. Analogously to the case of the Lewis acid mediated IMDA reaction of the substrate **37**, no good results were obtained.[37] Treatment of **54** with 5.0 M $LiClO_4$ in Et_2O[38] resulted in the formation of a complex mixture. We found that the IMDA reaction of **54** proceeded under thermal conditions as a 0.02 M toluene solution in a sealed tube in the presence of BHT. In contrast to the case of **37**, the IMDA reaction of **54** required a longer heating time for completion. Two *endo*-cycloadducts **55** and **56** were isolated in 62% and 21%

Scheme 10



yields, respectively, after separation on silica gel (Scheme 10). Furthermore, an *exo*-cycloadduct **58** was isolated in a trace amount of 2%. The stereochemistries of the cycloadducts **55**, **56**, and **58** were determined unambiguously by ^1H NMR analysis including NOE difference spectroscopy for **55** and **58** and NOESY spectroscopy for **56** as shown.



Having a practical access to the desired cycloadduct **55** in hand, the remaining tasks for the total synthesis of **5** were adjustment of the oxidation states in the γ-lactone moiety, migration of the carbon−carbon double bond, and deprotection. These requirements were solved as shown in Schemes 11 and 12. We decided to transform the 1,3-dithiolane **55** first into the dimethyl acetal **59** because of probable incompatibility of the dithioacetal with advanced oxidation reactions. This conversion was carried out using $Hg(ClO_4)_2 \cdot 3H_2O$[39] (Scheme 11). Treatment of **59** with Na_2RuO_4 as a 1.0 M aqueous NaOH solution[40] in a mixture of 1.0 M aqueous KOH and *t*-BuOH at 50 °C provided γ-hydroxy-γ-lactone **60** as an inseparable diastereomeric mixture (ca. 9:1) on the hemiacetal carbons. The oxidation of **59** to **60** presumably proceeded through saponification of the γ-lactone and subsequent oxidation of the primary hydroxyl group

(35) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522−524.

(36) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954−1957.

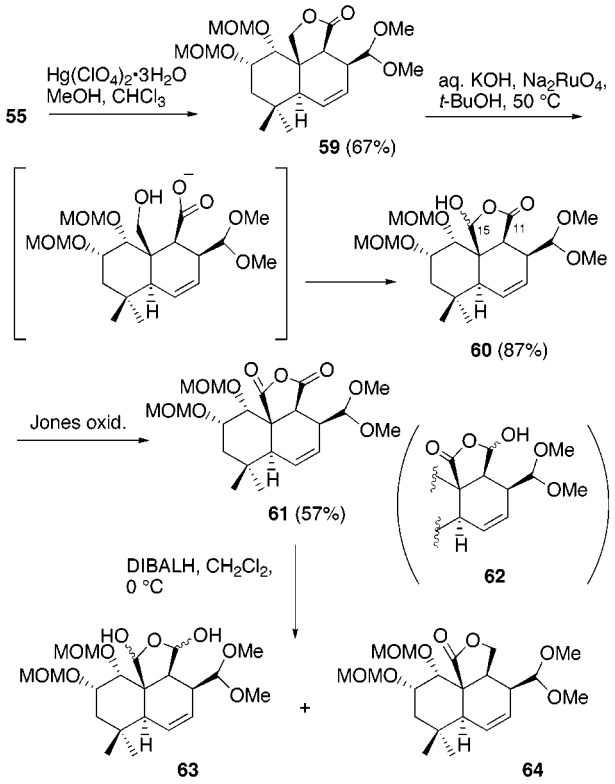
(37) The following Lewis acids were examined: Et_2AlCl/CH_2Cl_2/−78 °C (no reaction); $EtAlCl_2/CH_2Cl_2$/−78 °C (decomposition); $BF_3 \cdot OEt_2/CH_2Cl_2$/−78 °C (decomposition).

(38) (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595−4596. (b) Grieco, P. A.; Handy, S. T.; Beck, J. P.; Campaigne, E. E.; Carmack, M. *Tetrahedron Lett.* **1994**, *35*, 2663−2666.

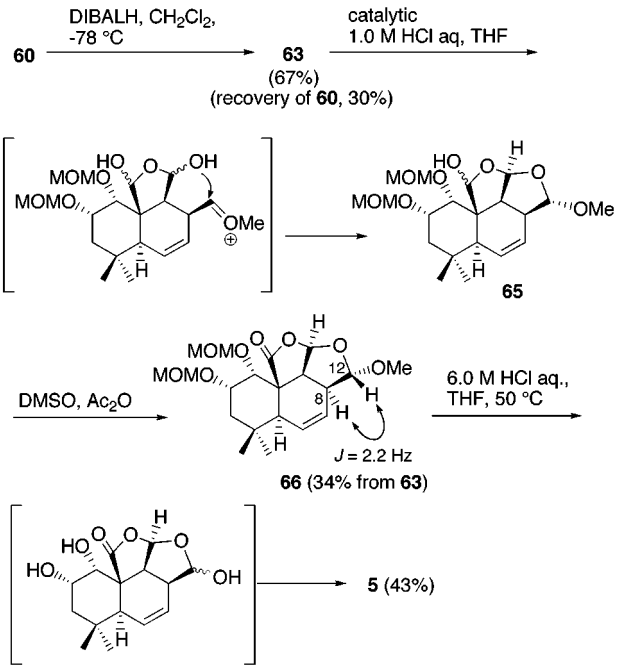
(39) Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1978**, *26*, 3743−3751.

(40) (a) Lee, D. G.; Hall, D. T.; Cleland, J. H. *Can. J. Chem.* **1972**, *50*, 3741−3743. (b) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574−5576.

Scheme 11



Scheme 12



followed by ring closure of the resulting acyclic β-formyl carboxylate. For obtaining the regioisomeric γ-hydroxy-γ-lactone **62**, we attempted the regioselective reduction of the right-hand carbonyl (C11) of the succinic anhydride moiety in anhydride **61**, which was obtained by Jones oxidation of **60**. In the case of DIBALH reduction of **61** at −78 °C, the reaction did not proceed and **61** was recovered quantitatively. The same reduction at 0 °C provided a mixture of dialdehyde hydrate **63** as a mixture of four diastereomers and γ-lactone **64**. This fact suggested that the reduction of the intermediary **62** proceeded rapidly. Reduction of **61** with other reducing reagents such as Li(*t*-BuO)$_3$AlH,[41] $Na_2Fe(CO)_4$,[42] or L-Selectride also gave unfruitful results.

The successful conversion of **60** into mniopetal E (**5**) was eventually achieved as shown in Scheme 12. DIBALH reduction of **60** at −78 °C provided an inseparable diastereomeric mixture of **63** in 67% yield along with 30% recovery of **60.** Brief treatment of **63** with a trace of 1.0 M aqueous HCl provided a tetracyclic methyl acetal **65** as a diastereomeric mixture regarding the hemiacetal carbons. This reaction presumably proceeded as shown in brackets via intramolecular attack of the right-hand hemiacetal-hydroxyl group to the oxocarbenium cation generated by elimination of 1 equiv of methanol from **63**. Consequently, the right-hand hemiacetal-hydroxyl group in **63** could be selectively protected. Oxidation of **65** with DMSO−Ac_2O provided tetracyclic γ-lactone **66** as a single diastereomer. On the basis of ^{1}H NMR analysis, the stereochemistry of C12 in **66** was confirmed as depicted. The coupling constant of H8 and H12 was 2.2 Hz, indicating their *trans*-relationship. The two-step yield of **66** from **63** was 34%. Treatment of **66** with a 1:1 mixed solution of 6.0 M aqueous HCl and THF at 50 °C caused deprotection of the MOM groups, hydrolysis of the methyl acetal, and double bond migration simultaneously to provide (−)-mniopetal E (**5**) in 43% yield. Once the double bond migrates, the resulting unsaturated aldehyde is not subject to intramolecular hemiacetal formation. The spectroscopic data of synthetic **5** were well matched with those of natural **5** kindly provided by Professor Steglich. Comparison of the optical rotation of synthetic **5** ($[\alpha]^{29.5}_D$ −58) with that of natural product ($[\alpha]^{20}_D$ −57) established the absolute stereochemistry as depicted.

In summary, we completed the total synthesis of (−)-mniopetal E (**5**), a prototype of mniopetals A−D, in its natural form. Our synthesis features the following aspects: (1) the substrate **54** for the IMDA reaction was synthesized in enantiopure form from the known building block **8**, and (2) the stereoselective IMDA reaction of **54** under thermal conditions realized a practical access to the desired *endo*-cycloadduct **55** possessing all the carbon skeleton with the correct stereochemistry. Our total synthesis of **5** as the natural form established the unambiguous absolute configuration.

Experimental Section[43]

Melting points are uncorrected. Specific rotations were measured in a 10 or 100 mm cell. ^{1}H NMR spectra were recorded at 270 MHz or at 300 MHz with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 67.5 Hz or at 75 MHz. All spectra were recorded in $CDCl_3$ as solvent, unless otherwise described. Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel 60 GF_{254} (Merck). The crude reaction mixtures and extractive materials were purified by chromatography on silica gel 60 K070 (Katayama Chemicals) or Wakogel C300 (Wako Pure Chemical Industries). Unless otherwise described, reactions were carried out at ambient temperature. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed from reaction mixture or combined organic

(41) (a) Canonne, P.; Plamondon, J.; Akssira, M. *Tetrahedron* **1988**, *44*, 2903−2912. (b) Thuring, J. W. J. F.; Nefkens, G. H. L.; Schaafstra, R.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 5047−5056.

(42) (a) Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2490−2491. (b) Bing, L. *Synth. Commun.* **1991**, *21*, 1577−1578.

(43) The numbering adopted for the nomenclatures of **55**−**66** is in accord with the IUPAC rules and is not in accord with that used in the text.

extracts by concentration under reduced pressure using an evaporator with a water bath at 35−45 °C. Commercially available solvents were dried (drying reagent in brackets) and distilled prior to use: tetrahydrofuran (THF) [$LiAlH_4$ and 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].

1-*O*-*tert*-Butyldimethylsilyl-4,5-*O*-isopropylidene-D-ribitol (10). To a cold (0 °C), stirred solution of **9**[16] (11.1 g, 57.8 mmol) in $CHCl_3$ (400 mL) were added Et_3N (40.0 mL, 287 mmol), TBSCl (15.7 g, 104 mmol), and 4-(dimethylamino)-pyridine (4-DMAP) (213 mg, 1.74 mmol). The mixture was stirred for 10 h, and then Et_3N (20.0 mL, 143 mmol), TBSCl (7.80 g, 51.7 mmol), and 4-DMAP (232 mg, 1.90 mmol) were added at 0 °C. The mixture was stirred for an additional 12 h and diluted with saturated brine (800 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 16.4 g (92%) of **10** as a colorless oil; TLC, R_f 0.42 (EtOAc/hexane, 1:2); $[\alpha]^{22}_D$ +4.5 (*c* 0.46, $CHCl_3$); IR 3460 cm^{-1}; ^1H NMR (270 MHz) δ 0.11 (s, 6H), 0.91 (s, 9H), 1.37, 1.43 (2s, 3H × 2), 2.95 (d, J = 4.8 Hz, 1H), 3.04 (d, J = 3.7 Hz, 1H), 3.62−3.77 (m, 2H), 3.81 (dd, J = 4.4, 10.3 Hz, 1H), 3.88 (dd, J = 4.8, 10.3 Hz, 1H), 4.00 (dd, J = 6.2, 8.4 Hz, 1H), 4.12 (dd, J = 6.2, 8.4 Hz, 1H), 4.20 (q, J = 6.2 Hz, 1H); ^{13}C NMR (67.5 MHz) δ −5.5 × 2, 18.1, 25.2, 25.8 × 3, 26.6, 65.0, 66.2, 71.4, 73.1, 76.9, 109.3; HRMS calcd for $C_{14}H_{31}O_5Si$ (M^+ + H) 307.1941, found 307.1930.

1-*O*-*tert*-Butyldimethylsilyl-4,5-*O*-isopropylidene-2,3-di-*O*-methoxymethyl-D-ribitol (11). To a cold (0 °C) solution of **10** (16.4 g, 53.4 mmol) in $CHCl_3$ (320 mL) were added diisopropylethylamine (DIPEA) (149 mL, 856 mmol) and chloromethyl methyl ether (MOMCl) (32.5 mL, 428 mmol). The mixture was stirred at 40 °C for 14 h, and then DIPEA (42.0 mL, 241 mmol) and MOMCl (8.1 mL, 107 mmol) were added at 0 °C. The mixture was stirred at 40 °C for an additional 3 h and diluted with saturated aqueous NH_4Cl (1000 mL). The whole was extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to provide 20.6 g (98%) of **11** as a colorless oil; TLC, R_f 0.45 (EtOAc/hexane, 1:4); $[\alpha]^{21}_D$ +32.7 (*c* 0.65, $CHCl_3$); ^1H NMR (270 MHz) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.35, 1.41 (2s, 3H × 2), 3.38, 3.40 (2s, 3H × 2), 3.68−3.80 (m, 2H), 3.84−3.96 (m, 2H), 3.96 (dd, J = 7.0, 8.1 Hz, 1H), 4.06 (dd, J = 6.2, 8.1 Hz, 1H), 4.21−4.30 (m, 1H), 4.70, 4.75 (ABq, J = 6.6 Hz, 1H × 2), 4.71, 4.80 (ABq, J = 6.6 Hz, 1H × 2);^{13}C NMR (67.5 MHz) δ −5.7 × 2, 18.0, 25.1, 25.6 × 3, 26.2, 55.3, 55.6, 62.9, 65.9, 75.0, 76.3, 78.2, 96.4, 96.8, 108.3; HRMS calcd for $C_{17}H_{35}O_7Si$ (M^+ − CH_3) 379.2152, found 379.2167.

4,5-*O*-Isopropylidene-2,3-di-*O*-methoxymethyl-D-ribitol (12). To a cold (0 °C) solution of **11** (20.6 g, 52.1 mmol) in THF (400 mL) was added tetrabutylammonium fluoride (TBAF) (68.0 mL of 1.0 M solution in THF, 68.0 mmol). The mixture was stirred for 1.5 h and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 14.1 g (96%) of **12** as a colorless oil; TLC, R_f 0.22 (EtOAc/hexane, 1:1); $[\alpha]^{22}_D$ −7.0 (*c* 0.90, $CHCl_3$); IR 3475 cm^{-1}; ^1H NMR (270 MHz) δ 1.36, 1.41 (2s, 3H × 2), 3.06 (br, 1H), 3.40, 3.43 (2s, 3H × 2), 3.72−3.80 (m, 3H), 3.84−3.89 (m, 1H), 3.94 (dd, J = 6.8, 8.2 Hz, 1H), 4.07 (dd, J = 6.4, 8.2 Hz, 1H), 4.19−4.28 (m, 1H), 4.70, 4.76 (ABq, J = 6.8 Hz, 1H × 2), 4.73, 4.79 (ABq, J = 6.6 Hz, 1H × 2); ^{13}C NMR (67.5 MHz) δ 25.3, 26.4, 55.8, 56.0, 62.2, 66.1, 75.1, 77.9, 80.6, 96.8, 97.4, 109.1; HRMS calcd for $C_{11}H_{21}O_7$ (M^+ − CH_3) 265.1287, found 265.1311.

Ethyl (2*E*,4*S*,5*S*,6*R*)-4,5-Bis(methoxymethoxy)-6,7-(isopropylidenedioxy)-2-methylhept-2-enoate (14). To a cold (0 °C) solution of **12** (8.57 g, 30.6 mmol) in CH_2Cl_2 (160 mL) was added Dess−Martin periodinane (38.9 g, 91.7 mmol).[19] The mixture was stirred while 12.8 g (30.2 mmol) and 8.50 g (20.0 mmol) of the periodinane were added after 2 and 3 h. The mixture was stirred for an additional 1 h and then diluted with saturated aqueous $Na_2S_2O_3$ (700 mL). This was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo to give crude **13**, which was used in the next step without purification. In a small-scale experiment, pure **13** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:5) as a colorless oil: TLC, R_f 0.60 (EtOAc/hexane, 1:1); IR 1730 cm^{-1}; ^1H NMR (270 MHz) δ 1.33, 1.34 (2s, 3H × 2), 3.40, 3.44 (2s, 3H × 2), 3.91 (dd, J = 2.2, 8.6 Hz, 1H), 3.94 (dd, J = 4.4, 8.6 Hz, 1H), 4.12 (dd, J = 6.1, 8.6 Hz, 1H), 4.24−4.33 (m, 2H), 4.67, 4.80 (ABq, J = 6.8 Hz, 1H × 2), 4.79, 4.82 (ABq, J = 6.8 Hz, 1H × 2), 9.65 (d, J = 1.0 Hz, 1H).

To a solution of the crude **13** obtained above in benzene (180 mL) was added $Ph_3P{=}C(Me)CO_2Et$ (37.3 g, 103 mmol). The mixture was heated under reflux for 30 min, and the solvent was removed by evaporation. The residue was triturated with excess petroleum ether. The precipitated $Ph_3P{=}O$ was removed by filtration and washed well with cold petroleum ether. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 9.09 g (82% based on **12**) of **14** as a colorless oil, which predominantly consisted of the *E*-isomer (*E*:*Z* = >20:1, ^1H NMR analysis); TLC, R_f 0.45 (EtOAc/hexane, 1:3); $[\alpha]^{21}_D$ +60.2 (*c* 1.63, $CHCl_3$); IR 1715, 1655, 1650 cm^{-1}; ^1H NMR for the major *E* isomer (300 MHz) δ 1.31 (t, J = 7.1 Hz, 3H), 1.34, 1.40 (2s, 3H × 2), 1.93 (d, J = 1.5 Hz, 3H), 3.37, 3.41 (2s, 3H × 2), 3.83−3.87 (m, 1H), 3.93−4.09 (m, 3H), 4.21 (q, J = 7.1 Hz, 2H), 4.59 (s, 2H), 4.71 (dd, J = 2.6, 9.3 Hz, 1H), 4.74, 4.88 (ABq, J = 6.6 Hz, 1H × 2), 6.67 (dd, J = 1.5, 9.3 Hz, 1H); ^{13}C NMR for the major *E* isomer (75 MHz) δ 13.0, 14.2, 25.3, 26.5, 55.4, 55.9, 60.8, 66.4, 73.3, 74.9, 79.4, 94.3, 97.4, 108.8, 131.8, 137.0, 167.4; HRMS calcd for $C_{17}H_{31}O_8$ (M^+ + H) 363.2019, found 363.2013.

(4*S*,5*S*,6*R*)-4,5-Bis(methoxymethoxy)-2,2-dimethyl-6,7-(isopropylidenedioxy)-1-heptanol (17). To a solution of **14** (12.2 g, 33.6 mmol) in EtOAc (250 mL) were added AcONa (271 mg, 3.30 mmol) and 10% Pd on charcoal (2.42 g). The mixture was stirred under atmospheric hydrogen while each 2.44 g of the catalyst was added after 13 and 16 h. The hydrogenation was conducted totally for 20 h. The catalyst was removed by filtration and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo to provide crude **15** (12.6 g) as a 3:2 diastereomeric mixture (^1H NMR analysis), which was used in the next step without purification. In a small-scale experiment, pure inseparable diastereomeric mixture **15** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:7) as a colorless oil; TLC, R_f 0.42 (EtOAc/hexane, 1:3); IR 1730 cm^{-1}; ^1H NMR (270 MHz) δ 1.20 (d, J = 7.0 Hz, 1H × 3/5), 1.21 (d, J = 7.0 Hz, 1H × 2/5), 1.26 (t, J = 7.1 Hz, 3H × 3/5), 1.27 (t, J = 7.1 Hz, 3H × 2/5), 1.34 (s, 3H), 1.40 (s, 3H × 2/5), 1.41 (s, 3H × 3/5), 1.49−1.72 (m, 1H), 1.88 (ddd, J = 2.9, 10.3, 14.3 Hz, 1H × 2/5), 2.08 (ddd, J = 6.2, 9.2, 14.3 Hz, 1H × 3/5), 2.53−2.77 (m, 1H), 3.385 (s, 3H × 3/5), 3.389 (s, 3H), 3.394 (s, 3H × 2/5), 3.80−4.00 (m, 3H), 4.03−4.20 (m, 4H), 4.59, 4.74 (ABq, J = 6.8 Hz, 1H x 6/5), 4.61, 4.72 (ABq, J = 6.8 Hz, 1H x 4/5), 4.67, 4.81 (ABq, J = 6.6 Hz, 1H × 6/5), 4.70, 4.81 (ABq, J = 6.6 Hz, 1H x 4/5); HRMS calcd for $C_{17}H_{32}O_8$ (M^+) 364.2097, found 364.2118.

The following reaction was carried out under argon. To a solution of the crude **15** obtained above (12.6 g) in a mixture of toluene and THF (6:1 v/v, 280 mL) was added MeI (8.40 mL, 135 mmol). After being stirred at −78 °C for 10 min, potassium bis(trimethylsilyl)amide ($KN(TMS)_2$) (0.5 M solution in toluene, 200 mL, 100 mmol) was added. The mixture was stirred at −78 °C for 1.5 h and quenched with saturated aqueous NH_4Cl. This was diluted with saturated brine (800 mL) and extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo to give crude **16** (15.1 g), which was used in the next step without purification. In a small-scale experiment, pure **16** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:9) as a colorless oil; TLC R_f 0.60 (EtOAc/hexane, 1:2); IR 1730 cm^{-1}; $[\alpha]^{28}_D$ +33.7 (*c* 0.74, $CHCl_3$); ^1H NMR (270 MHz) δ 1.21, 1.24 (2s, 3H × 2), 1.25 (t, J = 7.1 Hz, 3H), 1.34, 1.41 (2s, 3H × 2), 1.67 (dd, J = 3.3, 14.7 Hz, 1H), 2.02 (dd, J = 8.8 Hz, 14.7 Hz, 1H), 3.37, 3.39 (2s, 3H × 2), 3.83−4.19 (m, 7H), 4.58, 4.65 (ABq, J = 6.6 Hz, 1H × 2), 4.68, 4.86 (ABq, J = 6.6 Hz, 1H × 2); ^{13}C

NMR (67.5 MHz) δ 14.1, 24.7, 25.4, 26.5 × 2, 40.5, 40.6, 55.8, 56.2, 60.2, 66.8, 75.0, 76.9, 79.6, 96.8, 97.3, 108.8, 177.6; HRMS calcd for $C_{18}H_{33}O_8$ ($M^+ - H$) 377.2175, found 377.2199.

To a cold (0 °C), stirred suspension of $LiAlH_4$ (2.01 g, 53.0 mmol) in THF (100 mL) was added a solution of the crude **16** (15.1 g) obtained above in THF (60 mL). The mixture was stirred at 0 °C for 30 min and quenched with a small amount of H_2O. The resulting gels were filtered off and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 10.6 g (93% from **14**) of **17** as a colorless oil; TLC, R_f 0.24 (EtOAc/hexane, 1:2); $[\alpha]^{26}_D$ +14.3 (*c* 0.74, $CHCl_3$); IR 3500 cm^{-1}; ^1H NMR (270 MHz) δ 0.91, 0.97 (2s, 3H × 2), 1.35, 1.42 (2s, 3H × 2), 1.47 (dd, J = 2.6, 15.4 Hz, 1H), 1.62 (dd, J = 7.7, 15.4 Hz, 1H), 2.64 (br, 1H), 3.20−3.32 (m, 1H), 3.34−3.47 (m, 1H), 3.39, 3.43 (2s, 3H × 2), 3.85−4.14 (m, 5H), 4.67, 4.80 (ABq, J = 6.6 Hz, 1H × 2), 4.68, 4.84 (ABq, J = 6.6 Hz, 1H × 2); ^{13}C NMR (67.5 MHz) δ 24.4, 25.5, 26.4, 26.7, 35.0, 38.8, 56.0, 56.7, 67.2, 70.7, 75.2, 77.7, 80.1, 97.0, 97.2, 109.1; HRMS calcd for $C_{15}H_{29}O_6$ ($M^+ - OCH_3$) 305.1964, found 305.1969.

(2*E*,6*S*,7*S*,8*R*)-6,7-Bis(methoxymethoxy)-4,4-dimethyl-8,9-(isopropylidenedioxy)-2-nonen-1-ol (20). To a cold (0 °C), stirred solution of **17** (7.77 g, 23.1 mmol) in CH_2Cl_2 (150 mL) was added Dess−Martin periodinane (44.1 g, 104 mmol). The mixture was stirred for 1.5 h and diluted with CH_2Cl_2 (500 mL). To this solution was added an aqueous NaOH solution (28.9 g of NaOH in 350 mL of H_2O) at 0 °C. The mixture was stirred at 0 °C for 30 min, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated brine (350 mL). The aqueous layer was reextracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo to give crude **18** (10.5 g), which was used in the next step without purification. In a small-scale experiment, pure **18** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:8) as a colorless oil; TLC, R_f 0.52 (EtOAc/hexane, 1:2); IR 1730 cm^{-1}; ^1H NMR (270 MHz) δ 1.07, 1.11 (2s, 3H × 2), 1.34, 1.41 (2s, 3H × 2), 1.53 (dd, J = 2.2, 15.1 Hz, 1H), 2.15 (dd, J = 10.7, 15.1 Hz, 1H), 3.35, 3.39 (2s, 3H × 2), 3.82−4.13 (m, 5H), 4.47, 4.60 (ABq, J = 6.8 Hz, 1H × 2), 4.67, 4.85 (ABq, J = 6.8 Hz, 1H × 2), 9.40 (s, 1H).

The following reaction was carried out under argon. To a cold (0 °C), stirred suspension of NaH (3.38 g, 91.5 mmol) in THF (140 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (23.0 mL, 116 mmol). The mixture was stirred for 1 h, and a solution of the crude **18** obtained above (10.5 g) in THF (40 mL) was added at 0 °C. The mixture was stirred at 0 °C for 1 h and quenched with saturated aqueous NH_4Cl. This was diluted with saturated brine (400 mL) and extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to give crude **19** (10.0 g), which was contaminated with a small amount of $(EtO)_2P(O)CH_2CO_2Et$, but used to the next step without further purification. In a small-scale experiment, pure **19** was obtained by repeated chromatography on silica gel (EtOAc/hexane, 1:9) as a colorless oil; TLC, R_f 0.56 (EtOAc/hexane, 1:2); $[\alpha]^{29}_D$ +42.8 (*c* 0.96, $CHCl_3$); IR 1720, 1650 cm^{-1}; ^1H NMR (270 MHz) δ 1.12 (s, 6H), 1.29 (t, J = 7.0 Hz, 3H), 1.34, 1.40 (2s, 3H × 2), 1.67 (d, J = 5.1 Hz, 2H), 3.36, 3.38 (2s, 3H × 2), 3.76−3.85 (m, 2H), 3.88−3.96 (m, 1H), 3.97−4.10 (m, 2H), 4.18 (q, J = 7.0 Hz, 2H), 4.55, 4.65 (ABq, J = 6.6 Hz, 1H × 2), 4.66, 4.83 (ABq, J = 6.6 Hz, 1H × 2), 5.74 (d, J = 15.8 Hz, 1H), 6.99 (d, J = 15.8 Hz, 1H); ^{13}C NMR (67.5 MHz) δ 14.3, 25.4, 26.2, 26.5, 27.3, 36.2, 43.1, 55.7, 56.1, 60.2, 66.9, 74.8, 76.5, 80.4, 96.9 × 2, 108.8, 117.6, 157.7, 166.9; HRMS calcd for $C_{19}H_{33}O_8$ ($M^+ - CH_3$) 389.2175, found 389.2163.

The following reaction was carried out under argon. To a cold (−78 °C), stirred solution of the crude **19** obtained above (10.0 g) in CH_2Cl_2 (200 mL) was added DIBALH (61.0 mL of 1.01 M in toluene, 61.6 mmol). The mixture was stirred at −78 °C for 60 min and quenched with H_2O. The resulting gels were filtered off and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 7.25 g (87% from **17**) of **20** as a colorless oil; TLC, R_f 0.23 (EtOAc/hexane, 1:2); $[\alpha]^{20}_D$ +27.3 (*c* 0.86, $CHCl_3$); IR 3480 cm^{-1}; ^1H NMR (270 MHz) δ 1.04, 1.10 (2s, 3H × 2), 1.37, 1.40 (2s, 3H × 2), 1.48 (dd, J = 4.0, 14.8 Hz, 1H), 1.67 (dd, J = 6.2, 14.8 Hz, 1H), 2.73−2.91 (m, 1H), 3.36, 3.41 (2s, 3H × 2), 3.76 (ddd, J = 1.5, 4.0, 6.2 Hz, 1H), 3.85 (dd, J = 1.5, 3.7 Hz, 1H), 3.96−4.09 (m, 4H), 4.17−4.25 (m, 1H), 4.58, 4.63 (ABq, J = 6.8 Hz, 1H × 2), 4.67, 4.77 (ABq, J = 6.8 Hz, 1H × 2), 5.53−5.68 (m, 2H); ^{13}C NMR (67.5 MHz) δ 25.3, 26.0, 26.2, 28.5, 35.2, 44.3, 55.5 × 2, 63.7, 65.7, 74.6 × 2, 79.0, 95.3, 95.9, 108.0, 126.6, 141.3; HRMS calcd for $C_{18}H_{34}O_7$ (M^+) 362.2305, found 362.2317.

Ethyl (2*E*,4*E*,8*S*,9*S*,10*R*)-8,9-Bis(methoxymethoxy)-6,6-dimethyl-10,11- (isopropylidenedioxy)-2,4-undecadienoate (22). To a cold (0 °C), stirred solution of **20** (7.25 g, 20.0 mmol) in CH_2Cl_2 (140 mL) was added MnO_2 (36.3 g, 418.0 mmol). The mixture was stirred for 3.5 h, and the insoluble materials were filtered off and washed well with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo to give crude **21** (9.97 g) as a colorless oil, which was used in the next step without purification. In a small-scale experiment, pure **21** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:4) as a colorless oil; TLC, R_f 0.52 (EtOAc/hexane, 1:2); IR 1690, 1630 cm^{-1}; $[\alpha]^{21}_D$ +31.0 (*c* 0.76, $CHCl_3$); ^1H NMR (270 MHz) δ 1.17 (s, 6H), 1.34, 1.40 (2s, 3H × 2), 1.64−1.82 (m, 2H), 3.35, 3.38 (2s, 3H × 2), 3.78−3.85 (m, 2H), 3.93 (dd, J = 5.5, 7.3 Hz, 1H), 3.97−4.05 (m, 1H), 4.08 (dd, J = 5.5, 6.7 Hz, 1H), 4.53, 4.63 (ABq, J = 6.7 Hz, 1H × 2), 4.66, 4.82 (ABq, J = 6.7 Hz, 1H × 2), 6.05 (dd, J = 7.3, 15.9 Hz, 1H), 6.88 (d, J = 15.9 Hz, 1H), 9.53 (d, J = 7.3 Hz, 1H).

The following reaction was carried out under argon. To a cold (0 °C), stirred suspension of NaH (2.21 g, 59.9 mmol) in THF (120 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (16.0 mL, 80.6 mmol). The mixture was stirred for 1 h, and a solution of the crude **21** (9.97 g) obtained above in THF (60 mL) was added at 0 °C. The mixture was stirred for 30 min and quenched with saturated aqueous NH_4Cl. The resulting solution was concentrated in vacuo, and the residue was dissolved in $CHCl_3$ (500 mL). This was washed with saturated brine (500 mL), and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to provide 7.80 g (91% from **20**) of **22** as a colorless oil (*E*,*E*-isomer:other isomers = >15:1, was determined by ^1H NMR analysis); TLC, R_f 0.63 (EtOAc/hexane, 1:2); $[\alpha]^{28.5}_D$ +31.9 (*c* 1.00, $CHCl_3$); IR 1715, 1640, 1620 cm^{-1}; ^1H NMR (270 MHz) δ 1.112, 1.115 (2s, 3H × 2), 1.29 (t, J = 7.1 Hz, 3H), 1.34, 1.40 (2s, 3H × 2), 1.61−1.67 (m, 2H), 3.36, 3.37 (2s, 3H × 2), 3.76−3.84 (m, 2H), 3.89−4.10 (m, 3H), 4.19 (q, J = 7.1 Hz, 2H), 4.54, 4.64 (ABq, J = 6.6 Hz, 1H × 2), 4.66, 4.81 (ABq, J = 6.6 Hz, 1H × 2), 5.82 (d, J = 15.4 Hz, 1H), 6.04−6.20 (m, 2H), 7.27 (ddd, J = 2.0, 8.2, 15.4 Hz, 1H); ^{13}C NMR (67.5 MHz) δ 14.2, 25.3, 26.4, 26.8, 27.5, 36.3, 43.5, 55.7, 56.0, 60.1, 66.7, 74.8, 76.5, 80.3, 96.81, 96.87, 108.6, 119.6, 124.3, 145.2, 153.2, 167.1; HRMS calcd for $C_{22}H_{39}O_8$ ($M^+ + H$) 431.2645, found 431.2633.

(2*E*,4*E*,8*S*,9*S*,10*R*)-8,9-Bis(methoxymethoxy)-6,6-dimethyl-10,11-(isopropylidenedioxy)-2,4-undecadien-1-ol (23). The following reaction was carried out under argon. To a cold (−78 °C), stirred solution of **22** (5.26 g, 12.2 mmol) in CH_2Cl_2 (100 mL) was added DIBALH (30.5 mL, 1.0 M solution in toluene, 30.5 mmol). The mixture was stirred at −78 °C for 20 min and quenched with H_2O. This was diluted with $CHCl_3$ (100 mL), and then an aqueous solution (100 mL) of potassium sodium (+)-tartrate tetrahydrate (30 g) was added. The mixture was stirred vigorously for 2 h, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 4.70 g (99%) of **23** as a colorless oil (*E*,*E*-isomer:other isomers = >15:1, was determined by ^1H NMR analysis); TLC, R_f 0.38 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D$ +31.1 (*c* 1.23, $CHCl_3$); IR 3460, 1655 cm^{-1}; ^1H NMR (270 MHz) δ 1.07, 1.09 (2s, 3H × 2), 1.35, 1.40 (2s, 3H × 2),

1.45 (br, 1H), 1.55 (dd, J = 5.7, 14.8 Hz, 1H), 1.59−1.68 (m, 1H), 3.36, 3.38 (2s, 3H × 2), 3.74−3.83 (m, 2H), 3.91−3.98 (m, 1H), 4.01−4.20 (m, 4H), 4.56, 4.65 (ABq, J = 6.6 Hz, 1H × 2), 4.66, 4.79 (ABq, J = 6.6 Hz, 1H × 2), 5.71 (d, J = 15.4 Hz, 1H), 5.77 (dt, J = 6.0, 15.4 Hz, 1H), 6.00 (dd, J = 10.3, 15.4 Hz, 1H), 6.16−6.29 (m, 1H); ^{13}C NMR (67.5 MHz) δ 25.3, 26.3, 27.4 × 2, 35.6, 44.0, 55.5, 55.9, 63.2, 66.3, 74.8, 76.2, 80.2, 96.5, 96.6, 108.3, 125.7, 130.1, 131.9, 144.2; HRMS calcd for $C_{20}H_{36}O_7$ (M^+) 388.2461, found 388.2443.

1,2-Anhydro-4,5-*O*-isopropylidene-D-ribitol (25). The following reaction was carried out under argon. To a cold (−18 °C) solution of **8** (6.26 g, 35.9 mmol) and 18-crown-6 (12.3 g, 46.5 mmol) in THF (100 mL) was added potassium bis-(trimethylsilyl)amide (86.0 mL of 0.5 M solution in toluene, 43 mmol). The mixture was stirred at −18 °C for 1 h and quenched with saturated aqueous NH_4Cl. (20 mL). The organic solvent was removed by evaporation. The resulting aqueous solution was diluted with saturated aqueous NH_4Cl (300 mL) and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5 to 2:3) to provide 3.85 g (62%) of **25** and 1.89 g (30%) of **8** was recovered. Compound **25** was obtained as a colorless oil; TLC, R_f 0.50 (acetone/toluene, 1:2); $[\alpha]^{24.5}_D$ −28.8 (c 1.56, $CHCl_3$); IR 3450 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.37, 1.46 (2s, 3H × 2), 2.27−2.33 (m, 1H), 2.78 (dd, J = 4.2, 4.9 Hz, 1H), 2.86 (dd, J = 2.7, 4.9 Hz, 1H), 3.18−3.25 (m, 1H), 3.81−3.89 (m, 1H), 3.97−4.15 (m, 3H); ^{13}C NMR (67.5 MHz) δ 25.0, 26.5, 43.2, 52.1, 66.3, 69.1, 76.4, 109.5; HRMS calcd for $C_7H_{11}O_4$ (M^+ − CH_3) 159.0657, found 159.0657.

(4*S*,5*S*,6*R*)-4,5-Dihydroxy-2,2-dimethyl-6,7-(isopropylidenedioxy)heptanenitrile (26). The following reaction was carried out under argon. To a cold (0 °C) solution of diisopropylamine (2.90 mL, 20.7 mmol) in THF (14.5 mL) was added *n*-butyllithium (8.30 mL, 2.52 M solution in hexane, 20.9 mmol). The mixture was stirred at 0 °C for 30 min, and isobutyronitrile (1.88 mL, 20.7 mmol) was added at −78 °C. The mixture was stirred at −78 °C for 1 h to provide a 0.75 M solution of 2-lithio-2-methylpropionitrile in THF. To a cold (−78 °C) solution of **25** (1.20 g, 6.89 mmol) in THF (24 mL) was added phenylmagnesium bromide (10.3 mL, 1.00 M solution in THF, 10.3 mmol). The mixture was stirred at −78 °C for 30 min, and then the above 2-lithio-2-methylpropionitrile (27.6 mL, 0.75 M solution in THF, 20.7 mmol) was added to the mixture via cannula. The resulting mixture was stirred at −18 °C for 1 h and then quenched with saturated aqueous NH_4Cl at −78 °C. This was diluted with saturated aqueous NH_4Cl (180 mL) and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 1.47 g (88%) of **26** as white crystals, mp 44−45 °C; TLC, R_f 0.40 (acetone/toluene, 1:2); $[\alpha]^{24.5}_D$ −1.9 (c 1.64, $CHCl_3$); IR 3450, 2240 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.33, 1.39, 1.40, 1.44 (4s, 3H × 4), 1.72 (dd, J = 9.3, 14.4 Hz, 1H), 1.82 (dd, J = 2.4, 14.4 Hz, 1H), 2.57, 2.82 (2br, 1H × 2), 3.55−3.62 (m, 1H), 3.88−4.14 (m, 4H); ^{13}C NMR (75 MHz) δ 25.2, 26.5, 26.6, 27.8, 30.8, 42.0, 66.5, 70.3, 74.3, 75.9, 109.2, 125.6; HRMS calcd for $C_{11}H_{18}NO_4$ (M^+ − CH_3) 228.1236, found 228.1247.

(4*S*,5*S*,6*R*)-4,5-Bis(methoxymethoxy)-2,2-dimethyl-6,7-(isopropylidenedioxy)heptanenitrile (28). To a cold (0 °C) solution of **26** (1.47 g, 6.04 mmol) in $CHCl_3$ (30 mL) were added diisopropylethylamine (21.0 mL, 121 mmol) and chloromethyl methyl ether (4.6 mL, 61 mmol). The mixture was stirred at 40 °C for 18 h and diluted with 1.0 M aqueous HCl (350 mL). This was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to provide 1.65 g (83%) of **28** as a colorless oil; TLC, R_f 0.53 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D$ +38.2 (c 1.93, $CHCl_3$); IR 2240 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.34, 1.41, 1.42, 1.44 (4s, 3H x 4), 1.69 (dd, J = 2.7, 14.9 Hz, 1H), 1.96 (dd, J = 9.0, 14.9 Hz, 1H), 3.40, 3.45 (2s, 3H × 2), 3.84−4.14 (m, 5H), 4.67, 4.88 (ABq, J = 6.6 Hz, 1H × 2), 4.73, 4.82 (ABq, J = 6.8 Hz, 1H × 2); ^{13}C NMR (75 MHz) δ 25.3, 26.5, 26.7, 28.1, 30.4, 40.6, 55.9, 56.5, 67.1, 74.8, 76.5, 79.7, 97.0, 97.3, 109.2, 125.0; HRMS calcd for $C_{15}H_{26}NO_6$ (M^+ − CH_3) 316.1760, found 316.1760.

Compound 20 via DIBALH Reduction of 28. The following reaction was carried out under argon. To a cold (−78 °C), stirred solution of **28** (1.61 g, 4.86 mmol) in CH_2Cl_2 (40 mL) was added DIBALH (7.40 mL of 1.0 M solution in toluene, 7.40 mmol). The mixture was stirred at −78 °C for 1 h and quenched with H_2O. This was diluted with 1.0 M aqueous HCl (200 mL) and extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo to give crude **18**, which was used in the next step without purification. The Horner−Emmons reaction of **18** and subsequent DIBALH reduction of thus obtained crude **19** as described above provided 1.25 g of pure **20** (71% from **28** for three steps) after chromatographic purification on silica gel.

(2*R*,3*S*,4*S*,7*E*,9*E*)-3,4-Bis(methoxymethoxy)-6,6-dimethyl-10-(1,3-dithiolan-2-yl)-7,9-decadiene-1,2-diol (49). To a cold (0 °C), stirred solution of **23** (2.23 g, 5.74 mmol) in CH_2Cl_2 (50 mL) was added MnO_2 (11.2 g, 129 mmol). The mixture was stirred for 2 h, and then inorganic materials were filtered off and washed well with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo to provide crude **47** as a colorless oil, which was used in the next step without further purification. In a small-scale experiment, pure **47** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:5) (*E*,*E*-isomer:other isomers = >15:1, was determined by ^{1}H NMR analysis); TLC R_f 0.53 (EtOAc/hexane, 1:2); IR 1680, 1640 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.15 (s, 6H), 1.34, 1.40 (2s, 3H × 2), 1.67 (d, J = 5.4 Hz, 2H), 3.37, 3.38 (2s, 3H × 2), 3.78−3.84 (m, 2H), 3.89−4.14 (m, 3H), 4.54, 4.64 (ABq, J = 6.8 Hz, 1H × 2), 4.66, 4.81 (ABq, J = 6.8 Hz, 1H × 2), 6.12 (dd, J = 7.8, 15.1 Hz, 1H), 6.20−6.35 (m, 2H), 7.10 (ddd, J = 1.5, 8.8, 15.1 Hz, 1H), 9.54 (d, J = 8.3 Hz, 1H); ^{13}C NMR (75 MHz) δ 25.4, 26.5, 26.6, 27.5, 36.7, 43.5, 55.8, 56.1, 66.8, 74.9, 77.2, 80.3, 96.8, 96.9, 108.7, 124.6, 130.4, 153.2, 156.0, 193.9.

To a cold (−18 °C), stirred solution of the crude **47** obtained above in CH_2Cl_2 (50 mL) were added $HS(CH_2)_2SH$ (0.965 mL, 11.5 mmol) and BF_3•OEt_2 (0.22 mL, 1.74 mmol). The mixture was stirred at −18 °C for 1 h and diluted with saturated aqueous $NaHCO_3$ (250 mL). This was extracted with CH_2Cl_2. The organic layers were combined, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7 to 1:1) to provide 1.59 g (60%) of **48** and 0.80 g (33%) of **49**. Compound **48** was obtained as a colorless oil (*E*,*E*-isomer:other isomers= >15:1, was determined by ^{1}H NMR analysis); TLC R_f 0.54 (EtOAc/hexane, 1:3); $[\alpha]^{26.5}_D$ +25.5 (c 1.30, $CHCl_3$); IR 1650 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.06, 1.07 (2s, 3H × 2), 1.35, 1.40 (2s, 3H × 2), 1.50−1.66 (m, 2H), 3.19−3.40 (m, 4H), 3.37, 3.38 (2s, 3H × 2), 3.75−3.82 (m, 2H), 3.90−3.99 (m, 1H), 4.02−4.12 (m, 2H), 4.56, 4.65 (ABq, J = 6.6 Hz, 1H × 2), 4.67, 4.80 (ABq, J = 6.6 Hz, 1H × 2), 5.08 (d, J = 9.2 Hz, 1H), 5.64 (dd, J = 9.2, 14.7 Hz, 1H), 5.70 (d, J = 15.4 Hz, 1H), 5.95 (dd, J = 10.3, 15.4 Hz, 1H), 6.14 (dd, J = 10.3, 14.7 Hz, 1H); ^{13}C NMR (75 MHz) δ 25.4, 26.5, 27.4 × 2, 35.8, 39.5 × 2, 44.0, 54.3, 55.7, 56.0, 66.5, 74.9, 76.5, 80.3, 96.7, 96.8, 108.5, 125.1, 130.4, 131.0, 144.9; HRMS calcd for $C_{22}H_{38}O_6S_2$ (M^+) 462.2110, found 462.2113. Compound **49** was obtained as a colorless oil (*E*,*E*-isomer:other isomers = >15:1, was determined by ^{1}H NMR analysis); TLC R_f 0.50 (acetone/toluene, 1:2); IR 3440, 1650 cm^{-1}; $[\alpha]^{30}_D$ +32.4 (c 1.68, $CHCl_3$); ^{1}H NMR (270 MHz) δ 1.06, 1.07 (2s, 3H × 2), 1.54−1.69 (m, 2H), 2.28 (br, 2H), 3.19−3.38 (m, 4H), 3.39, 3.41 (2s, 3H × 2), 3.60−3.67 (m, 1H), 3.70−3.78 (m, 3H), 3.81−3.86 (m, 1H), 4.61, 4.66 (ABq, J = 6.4 Hz, 1H × 2), 4.65, 4.79 (ABq, J = 6.4 Hz, 1H × 2), 5.08 (d, J = 9.3 Hz, 1H), 5.64 (dd, J = 9.3, 14.6 Hz, 1H), 5.70 (d, J = 15.1 Hz, 1H), 5.95 (dd, J = 10.3, 15.1 Hz, 1H), 6.14 (dd, J = 10.3, 14.6 Hz, 1H); ^{13}C NMR (75 MHz) δ 27.4, 27.6, 35.8, 39.5 × 2, 44.1, 54.2, 56.0, 56.2, 63.6, 71.2, 77.4, 82.0, 97.2, 97.5, 125.0, 130.6, 130.9, 145.0; HRMS calcd for $C_{19}H_{34}O_6S_2$ (M^+) 422.1797, found 422.1816.

Compound **48** (1.59 g, 3.44 mmol) was dissolved in a mixture of AcOH, H_2O, and THF (3:1:1, v/v, 50 mL). The solution was stirred for 60 h and then concentrated in vacuo with aid of toluene (5 mL) and EtOH (5 mL). The residue was purified by

column chromatography on silica gel (EtOAc/toluene, 1:2) to provide 1.37 g (94%) of **49**, and 46.3 mg (3%) of **48** was recovered.

(2*R*,3*S*,4*S*,7*E*,9*E*)-3,4-Bis(methoxymethoxy)-1-*tert*-butyldimethylsilyloxy-6,6-dimethyl-10-(1,3-dithiolan-2-yl)-7,9-decadien-2-ol (50). To a cold (0 °C), stirred solution of **49** (370 mg, 0.875 mmol) in CH_2Cl_2 (8 mL) were added Et_3N (0.35 mL, 2.51 mmol), TBSCl (162 mg, 1.07 mmol), and 4-DMAP (11.2 mg, 91.7 μmol). The mixture was stirred for 20 h, and then Et_3N (0.12 mL, 0.86 mmol) and TBSCl (63.5 mg, 0.421 mmol) were added at 0 °C. The mixture was stirred for an additional 6 h and diluted with saturated brine (40 mL). The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:12) to provide 429 mg (91%) of **50** as a colorless oil (*E*,*E*-isomer:other isomers = >15:1, was determined by ^{1}H NMR analysis); TLC R_f 0.28 (EtOAc/hexane, 1:5); $[\alpha]^{22}_D$ +24.8 (*c* 1.71, $CHCl_3$); IR 3480, 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.09 (s, 6H), 0.91 (s, 9H), 1.07 (s, 6H), 1.57−1.71 (m, 2H), 1.95−2.30 (br, 1H), 3.18−3.43 (m, 4H), 3.38 (s, 6H), 3.50−3.58 (m, 1H), 3.65 (dd, J = 6.0, 9.9 Hz, 1H), 3.75 (br d, J = 8.1 Hz, 1H), 3.82 (dd, J = 3.3, 9.9 Hz, 1H), 3.87−3.93 (m, 1H), 4.59, 4.63 (ABq, J = 6.6 Hz, 1H × 2), 4.63, 4.83 (ABq, J = 6.6 Hz, 1H × 2), 5.08 (d, J = 9.3 Hz, 1H), 5.62 (dd, J = 9.3, 14.7 Hz, 1H), 5.74 (d, J = 15.4 Hz, 1H), 5.94 (dd, J = 10.3, 15.4 Hz, 1H), 6.14 (dd, J = 10.3, 14.7 Hz, 1H); ^{13}C NMR (75 MHz) δ −5.4 × 2, 18.2, 25.9 × 3, 27.1, 28.0, 35.8, 39.5 × 2, 43.3, 54.4, 55.9, 56.2, 64.1, 70.9, 77.6, 79.8, 96.9, 97.3, 124.6, 130.2, 131.2, 145.6; HRMS calcd for $C_{25}H_{48}O_6SiS_2$ (M^+) 536.2662, found 536.2662.

(3*S*,4*S*,7*E*,9*E*)-3,4-Bis(methoxymethoxy)-1-*tert*-butyldimethylsilyloxy-6,6-dimethyl-10-(1,3-dithiolan-2-yl)-7,9-decadien-2-one (51). To a stirred solution of **50** (86.9 mg, 0.16 mmol) in DMSO (4 mL) were added Et_3N (0.46 mL, 3.30 mmol) and SO_3·pyridine (263 mg, 1.65 mmol). The mixture was stirred for 20 h and diluted with EtOAc (30 mL). The resulting mixture was washed with H_2O (15 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to provide 69.2 mg (79%) of **51** as a colorless oil (*E*,*E*-isomer:other isomers = >15:1, was determined by ^{1}H NMR analysis); TLC R_f 0.49 (EtOAc/hexane, 1:3); $[\alpha]^{22}_D$ +14.2 (*c* 1.83, $CHCl_3$); IR 1730, 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.09, 0.10 (2s, 3H × 2), 0.92 (s, 9H), 1.01, 1.05 (2s, 3H × 2), 1.55 (dd, J = 3.9, 14.9 Hz, 1H), 1.63 (dd, J = 6.8, 14.9 Hz, 1H), 3.18−3.38 (m, 4H), 3.37 (s, 6H), 3.85−3.92 (m, 1H), 4.40, 4.49 (ABq, J = 18.7 Hz, 1H × 2), 4.50 (d, J = 2.0 Hz, 1H), 4.60, 4.67 (ABq, J = 6.8 Hz, 1H × 2), 4.62, 4.72 (ABq, J = 6.8 Hz, 1H × 2), 5.07 (d, J = 9.3 Hz, 1H), 5.63 (dd, J = 9.3, 14.7 Hz, 1H), 5.64 (d, J = 15.5 Hz, 1H), 5.91 (dd, J = 10.3, 15.5 Hz, 1H), 6.12 (dd, J = 10.3, 14.7 Hz, 1H); ^{13}C NMR (75 MHz) δ −5.5, −5.4, 18.5, 25.8 × 3, 27.0, 27.9, 35.5, 39.5 × 2, 42.9, 54.2, 56.0, 56.1, 68.9, 76.3, 83.0, 96.5, 96.7, 125.1, 130.5, 130.9, 144.9, 207.8; HRMS calcd for $C_{24}H_{42}O_5SiS_2$ (M^+ − CH_3OH) 502.2243, found 502.2225.

(3*S*,4*S*,7*E*,9*E*)-3,4-Bis(methoxymethoxy)-6,6-dimethyl-10-(1,3-dithiolan-2-yl)-1-hydroxy-7,9-decadien-2-one (52). To a cold (0 °C), stirred solution of **51** (149 mg, 0.28 mmol) in MeOH (4 mL) was added CSA (6.5 mg, 28 μmol). The mixture was stirred for 2 h and diluted with saturated $NaHCO_3$ (25 mL). The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 98.2 mg (84%) of **52** as a colorless oil (*E*,*E*-isomer:other isomers = >15:1, was determined by ^{1}H NMR analysis); TLC R_f 0.47 (EtOAc/hexane, 2:3); $[\alpha]^{27}_D$ +3.9 (*c* 1.17, $CHCl_3$); IR 3460, 1720, 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.03, 1.05 (2s, 3H × 2), 1.56 (dd, J = 4.6, 14.9 Hz, 1H), 1.63 (dd, J = 6.4, 14.9 Hz, 1H), 3.18−3.42 (m, 4H), 3.36, 3.39 (2s, 3H × 2), 3.84−3.91 (m, 1H), 4.34 (d, J = 2.4 Hz, 1H), 4.46 (s, 2H), 4.59, 4.64 (ABq, J = 6.8 Hz, 1H × 2), 4.64, 4.77 (ABq, J = 6.6 Hz, 1H × 2), 5.08 (d, J = 9.3 Hz, 1H), 5.64 (dd, J = 9.3, 14.7 Hz, 1H), 5.65 (d, J = 15.4 Hz, 1H), 5.92 (dd, J = 10.3, 15.4 Hz, 1H), 6.13 (dd, J = 10.3, 14.7 Hz, 1H); ^{13}C NMR (75 MHz) δ 27.2, 27.8, 35.5, 39.5 × 2, 43.6, 54.2, 56.16, 56.22, 67.8, 77.1, 83.6, 96.8 × 2, 125.3, 130.8 × 2, 144.6, 210.0; HRMS calcd for $C_{19}H_{32}O_6S_2$ (M^+) 420.1640, found 420.1643.

(3*S*,4*S*,7*E*,9*E*)-3,4-Bis(methoxymethoxy)-1-(diethylphosphono)acetoxy-6,6-dimethyl-10-(1,3-dithiolan-2-yl)-7,9-decadien-2-one (53). To a cold (0 °C), stirred solution of **52** (191 mg, 0.45 mmol) in CH_2Cl_2 (4 mL) were added $(EtO)_2P(O)CH_2CO_2H$ (0.15 mL, 0.93 mmol), Et_3N (0.16 mL, 1.15 mmol), 4-DMAP (11.0 mg, 90.0 μmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (177 mg, 0.97 mmol). The mixture was stirred for 15 h and then diluted with 0.05 M aqueous HCl (30 mL). The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with 0.05 M aqueous NaOH (30 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O (30 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:7) to provide 232 mg (87%) of **53** as a colorless oil (*E*,*E*-isomer:other isomers= >15:1, was determined by ^{1}H NMR analysis); TLC, R_f 0.44 (acetone/toluene, 1:1); $[\alpha]^{22}_D$ −4.3 (*c* 1.80, $CHCl_3$); IR 1730, 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.02, 1.05 (2s, 3H × 2), 1.35 (t, J = 7.2 Hz, 6H), 1.60 (d, J = 5.4 Hz, 2H), 3.10 (d, J = 21.5 Hz, 2H), 3.21−3.39 (m, 4H), 3.37, 3.39 (2s, 3H × 2), 3.85 (dt, J = 2.2, 5.4 Hz, 1H), 4.20 (quintet, J = 7.2 Hz, 4H), 4.30 (d, J = 2.2 Hz, 1H), 4.60, 4.64 (ABq, J = 6.8 Hz, 1H × 2), 4.68, 4.77 (ABq, J = 6.5 Hz, 1H × 2), 4.95, 5.08 (ABq, J = 17.6 Hz, 1H × 2), 5.08 (d, J = 9.3 Hz, 1H), 5.63 (dd, J = 9.3, 14.7 Hz, 1H), 5.66 (d, J = 15.2 Hz, 1H), 5.91 (dd, J = 10.3, 15.2 Hz, 1H), 6.13 (dd, J = 10.3, 14.7 Hz, 1H); ^{13}C NMR (75 MHz) δ 16.3 × 2 (d, $^3J_{P,C}$ = 6.2 Hz), 27.2, 27.7, 33.7 (d, $^1J_{P,C}$ = 134.3 Hz), 35.5, 39.5 × 2, 43.2, 54.2, 56.1, 56.2, 62.8 × 2 (d, $^2J_{P,C}$ = 6.2 Hz), 68.6, 76.9, 84.0, 96.76, 96.79, 125.1, 130.6, 130.8, 144.7, 165.1 (d, $^2J_{P,C}$ = 6.2 Hz), 202.2; HRMS calcd for $C_{25}H_{43}O_{10}S_2P$ (M^+) 598.2036, found 598.2032.

3-[(1*S*,2*S*,5*E*,7*E*)-1,2-Bis(methoxymethoxy)-4,4-dimethyl-8-(1,3-dithiolan-2-yl)-5,7-octadienyl]-2-buten-4-olide (54). To a cold (0 °C), stirred solution of **53** (172 mg, 0.29 mmol) in toluene (4 mL) were added 18-crown-6 (161 mg, 0.61 mmol) and K_2CO_3 (42.1 mg, 0.305 mmol). The mixture was stirred for 4.5 h and diluted with saturated brine (25 mL). The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 98.9 mg (77%) of **54** as a colorless oil (*E*,*E*-isomer:other isomers = >15:1, was determined by ^{1}H NMR analysis); TLC, R_f 0.58 (EtOAc/hexane, 1:1); $[\alpha]^{24.5}_D$ +6.9 (*c* 0.97, $CHCl_3$); IR 1780, 1750, 1640 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.03, 1.08 (2s, 3H × 2), 1.40 (dd, J = 4.5, 14.9 Hz, 1H), 1.57 (dd, J = 5.9, 14.9 Hz, 1H), 3.20−3.38 (m, 4H), 3.36, 3.38 (2s, 3H × 2), 3.71−3.79 (m, 1H), 4.59−4.61 (m, 1H), 4.59, 4.69 (ABq, J = 6.8 Hz, 1H × 2), 4.61, 4.70 (ABq, J = 6.6 Hz, 1H × 2), 4.81 (dd, J = 1.7, 18.1 Hz, 1H), 4.98 (dd, J = 2.0, 18.1 Hz, 1H), 5.08 (d, J = 9.3 Hz, 1H), 5.58 (d, J = 15.6 Hz, 1H), 5.67 (dd, J = 9.3, 14.8 Hz, 1H), 5.95 (dd, J = 10.3, 15.6 Hz, 1H), 6.00−6.01 (m, 1H), 6.13 (dd, J = 10.3, 14.8 Hz, 1H); ^{13}C NMR (75 MHz) δ 26.7, 28.2, 35.6, 39.5 × 2, 44.1, 54.1, 55.9, 56.2, 72.2, 76.2, 76.8, 95.3, 96.9, 118.5, 125.8, 130.4, 131.4, 143.9, 166.5, 173.1; HRMS calcd for $C_{21}H_{32}O_6S_2$ (M^+) 444.1640, found 444.1641.

(1*S*,2*R*,3*S*,6*S*,9*S*,10*S*)- (55),[43] (1*R*,2*R*,3*S*,6*R*,9*R*,10*R*)- (56), and (1*R*,2*R*,3*S*,6*S*,9*S*,10*R*)-2,3-Bis(methoxymethoxy)-5,5-dimethyl-9-(1,3-dithiolan-2-yl)-12-oxatricyclo[8.3.0.0^{1,6}]-tridec-7-en-11-one (58). Compound **54** (95.2 mg, 0.21 mmol) was dissolved in degassed toluene (7.1 mL), and a crystal of BHT was added. The solution was transferred into a 20 mL sealed tube equipped with a screwed stopper, and the tube was filled with argon. The tube was heated to 180 °C for 34 h. After being cooled to ambient temperature, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to provide 58.2 mg (62%) of **55**, 20.3 mg (21%) of **56**, and 2.1 mg (2%) of **58**. Compound **55** was obtained as colorless amorphous solids;

TLC, R_f 0.25 (EtOAc/hexane, 1:2); $[\alpha]^{23.5}_D$ +4.8 (*c* 1.78, $CHCl_3$); IR 1770 cm^{-1}; ^1H NMR (300 MHz) δ 0.89, 1.02 (2s, 3H × 2), 1.54 (dd, *J* = 4.2, 12.7 Hz, 1H), 1.81 (t, *J* = 12.7 Hz, 1H), 2.25−2.29 (m, 1H), 2.51−2.60 (m, 1H), 3.11−3.31 (m, 4H), 3.38, 3.52 (2s, 3H × 2), 3.55 (d, *J* = 7.6 Hz, 1H), 3.84−3.91 (m, 1H), 3.86 (br s, 1H), 3.92, 3.97 (ABq, *J* = 9.7 Hz, 1H × 2), 4.65 (s, 2H), 4.76, 5.00 (ABq, *J* = 6.6 Hz, 1H × 2), 5.00 (d, *J* = 10.3 Hz, 1H), 5.93−6.04 (m, 2H); ^{13}C NMR (75 MHz) δ 22.4, 31.9, 32.7, 38.3, 38.4, 39.5, 43.2, 46.2, 48.6, 53.3, 53.8, 55.6, 57.3, 72.1, 72.5, 77.7, 94.6, 98.2, 131.0, 132.2, 176.9; HRMS calcd for $C_{21}H_{32}O_6S_2$ (M^+) 444.1640, found 444.1636. Compound **56** was obtained as colorless amorphous solids; TLC, R_f 0.21 (EtOAc/hexane, 1:2); $[\alpha]^{22}_D$ +140 (*c* 1.36, $CHCl_3$); IR 1750 cm^{-1}; ^1H NMR (300 MHz) δ 0.95, 1.08 (2s, 3H × 2), 1.37 (dd, *J* = 3.2, 14.9 Hz, 1H), 1.88−1.92 (m, 1H), 1.88−1.96 (m, 1H), 2.47−2.56 (m, 1H), 3.15 (d, *J* = 7.8 Hz, 1H), 3.19−3.30 (m, 4H), 3.38, 3.48 (2s, 3H × 2), 3.64 (d, *J* = 3.9 Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 4.14 (dt, *J* = 3.2, 3.9 Hz, 1H), 4.56, 4.89 (ABq, *J* = 7.3 Hz, 1H × 2), 4.58, 4.68 (ABq, *J* = 6.8 Hz, 1H × 2), 4.98 (d, *J* = 11.5 Hz, 1H), 5.03 (d, *J* = 9.3 Hz, 1H), 6.00−6.11 (m, 2H); ^{13}C NMR (75 MHz) δ 22.7, 31.9, 32.5, 38.3, 38.5, 42.3, 46.0, 49.0, 50.4, 51.7, 53.6, 55.6, 56.8, 70.8, 72.2, 79.8, 94.0, 95.8, 131.3, 132.2, 177.4; HRMS calcd for $C_{21}H_{32}O_6S_2$ (M^+) 444.1640, found 444.1639. Compound **58** was obtained as a colorless oil; TLC, R_f 0.33 (EtOAc/hexane, 1:2); IR 1780, 1650 cm^{-1}; ^1H NMR (300 MHz) δ 1.01, 1.23 (2s, 3H × 2), 1.48 (dd, *J* = 3.3, 14.2 Hz, 1H), 1.84 (dd, *J* = 5.6, 14.2 Hz, 1H), 2.08−2.13 (m, 1H), 2.69−2.75 (m, 1H), 2.70 (d, *J* = 7.3 Hz, 1H), 3.21−3.53 (m, 4H), 3.39, 3.43 (2s, 3H × 2), 3.49 (d, *J* = 3.2 Hz, 1H), 3.94−4.01 (m, 1H), 4.33 (d, *J* = 9.4 Hz, 1H), 4.63, 4.65 (ABq, *J* = 6.9 Hz, 1H × 2), 4.65, 4.81 (ABq, *J* = 6.9 Hz, 1H × 2), 4.80 (d, *J* = 9.4 Hz, 1H), 4.99 (d, *J* = 5.9 Hz, 1H), 5.83−6.13 (m, 2H); ^{13}C NMR (67.5 MHz) δ 29.9, 31.2, 33.4, 38.6, 38.7, 38.8, 41.4 × 2, 47.9, 48.9, 55.7, 56.3, 56.8, 72.5, 72.9, 77.9, 95.7, 96.4, 128.4, 129.4, 177.8; HRMS calcd for $C_{21}H_{32}O_6S_2$ (M^+) 444.1640, found 444.1642.

(1*S*,2*R*,3*S*,6*S*,9*S*,10*S*)-2,3-Bis(methoxymethoxy)-9-(dimethoxymethyl)-5,5-dimethyl-12-oxatricyclo[8.3.0.0^{1,6}]-tridec-7-en-11-one (59). To a cold (0 °C), stirred solution of **55** (146 mg, 0.33 mmol) in a mixture of MeOH and $CHCl_3$ (3:1 v/v, 5 mL) was added a solution of $Hg(ClO_4)_2 \cdot 3H_2O$ (477 mg, 0.99 mmol) in a mixture of MeOH and $CHCl_3$ (3:1 v/v, 1 mL). The mixture was stirred for 1 h, and then Et_3N (0.69 mL, 4.95 mmol) was added at 0 °C. The resulting insoluble materials were filtered off through a pad of Celite and washed well with excess $CHCl_3$. The combined filtrate and washings were concentrated in vacuo to 10 mL. This was diluted with $CHCl_3$ (30 mL) and washed with saturated aqueous $NaHCO_3$ (30 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane/Et_3N, 10:60:1) to provide 90.6 mg (67%) of **59**, and 9.8 mg (7%) of **55** was recovered. Compound **59** was obtained as white crystals; mp 54−55 °C; TLC, R_f 0.32 (acetone/toluene, 1:9); $[\alpha]^{25.5}_D$ +54.8 (*c* 1.48, $CHCl_3$); IR 1770 cm^{-1}; ^1H NMR (300 MHz) δ 0.88, 1.01 (2s, 3H × 2), 1.54 (dd, *J* = 4.4, 12.3 Hz, 1H), 1.81 (t, *J* = 12.3 Hz, 1H), 2.21−2.26 (m, 1H), 2.55−2.64 (m, 1H), 3.37 (d, *J* = 6.4 Hz, 1H), 3.379, 3.383, 3.48, 3.56 (4s, 3H × 4), 3.84−3.87 (m, 1H), 3.84−3.92 (m, 1H), 3.95 (s, 2H), 4.66 (s, 2H), 4.71, 4.98 (ABq, *J* = 6.8 Hz, 1H × 2), 4.93 (d, *J* = 8.3 Hz, 1H), 5.93 (dt, *J* = 3.4, 9.3 Hz, 1H), 6.06 (dt, *J* = 3.2, 9.3 Hz, 1H); ^{13}C NMR (75 MHz) δ 22.5, 31.9, 32.7, 39.6, 40.2, 43.3, 46.0, 52.1, 53.4, 55.6, 56.1, 56.7, 72.0, 72.3, 78.1, 94.6, 98.3, 103.5, 129.4, 130.2, 177.3; HRMS calcd for $C_{21}H_{34}O_8$ (M^+) 414.2253, found 414.2255.

Mixture of (1*R*,2*R*,3*S*,6*S*,9*S*,10*S*,13*R* and 13*S*)-2,3-Bis-(methoxymethoxy)-13-hydroxy-9-(dimethoxymethyl)-5,5-dimethyl-12-oxatricyclo[8.3.0.0^{1,6}]-tridec-7-en-11-one (60). To a stirred solution of **59** (90.6 mg, 0.22 mmol) in *t*-BuOH (2 mL) were added 1.0 M aqueous KOH (6 mL) and Na_2RuO_4 (30.0 mL, 0.015 M solution in 1.0 M aqueous NaOH, 0.45 mmol). The mixture was stirred at 50 °C for 12 h, cooled to 0 °C, and quenched with 2-propanol (5 mL). The insoluble materials were filtered off and washed well with EtOH. The combined filtrate and washings were concentrated in vacuo to 5 mL and neutralized with 1.0 M aqueous HCl. The whole was diluted with H_2O (25 mL) and extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 81.5 mg (87%) of **60** (the ratio of inseparable diastereomers, ca. 9:1, was determined by ^1H NMR analysis) as white crystals; TLC, R_f 0.44 (acetone/toluene, 1:3); IR 3330, 1770, 1710 cm^{-1}; ^1H NMR (300 MHz) δ 1.00, 1.04 (s, 3H × 1/10), 1.02, 1.09 (2s, 3H × 9/10), 1.47−1.61 (m, 1H), 1.68−1.83 (m 1H), 1.90−2.10 (br, 1H), 2.16−2.25 (m, 1H × 9/10), 2.27−2.32 (m, 1H × 1/10), 2.50−2.65 (m, 1H × 9/10), 2.79−2.88 (m, 1H × 1/10), 3.34−3.58 (m, 13H), 3.96−4.04 (m, 1H × 1/10), 4.18−4.24 (m, 1H), 4.42 (ddd, *J* = 2.2, 4.6, 12.5 Hz, 1H × 9/10), 4.58−4.76 (m, 3H), 4.87−5.00 (m, 2H), 5.30−5.46 (m, 1H), 5.93−6.06 (m, 2H × 9/10, 1H × 1/10), 6.11−6.18 (m, 1H × 1/10); ^{13}C NMR for the major isomer (75 MHz) δ 21.7, 32.5, 32.6, 40.4, 41.4, 44.2, 49.9, 53.3, 55.2, 55.4, 55.9, 56.8, 73.5, 76.3, 94.7, 98.7, 99.8, 103.6, 130.0, 130.1, 176.3; HRMS calcd for $C_{21}H_{34}O_9$ (M^+) 430.2202, found 430.2203.

Mixture of (1*R*,2*R*,3*S*,6*S*,9*S*,10*S*,11*R* and 11*S*, 13*R*, and 13*S*)-2,3-Bis-(methoxymethoxy)-9-(dimethoxymethyl)-5,5-dimethyl-12-oxatricyclo-[8.3.0.0^{1,6}]tridec-7-ene-11,13-diol (63). The following reaction was carried out under argon. To a cold (−78 °C), stirred solution of **60** (55.7 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) was added DIBALH (0.27 mL, 1.0 M solution in toluene, 0.27 mmol). The mixture was stirred at −78 °C for 1 h and then quenched with H_2O. The resulting gels were filtered off and washed well with EtOAc. The filtrate and washings were combined and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:4) to provide 37.4 mg (67%) of **63** as an inseparable diastereomeric mixture, and 16.6 mg (30%) of **60** was recovered. The diastereomeric mixture **63** was obtained as a colorless oil; TLC, R_f 0.14 (acetone/toluene, 1:3); IR 3430, 1650 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.95−1.09 (m, 6H), 1.44−1.58 (m, 1H), 1.66−1.80 (m, 1H), 2.09−2.24 (m, 1H), 2.40−2.63 (m, 1H), 3.00−3.13 (m, 1H), 3.29−3.50 (m, 12H), 3.57−4.50 (m, 2H), 4.53−5.42 (m, 7H), 5.65−6.12 (m, 2H); HRMS (FAB) calcd for $C_{21}H_{35}O_9$ ($M^+ - H$) 431.2281, found 431.2274.

(1*R*,2*R*,3*S*,6*S*,9*S*,10*S*,12*R*,15*S*)-2,3-Bis(methoxymethoxy)-5,5-dimethyl-10-methoxy-11,13-dioxatetracyclo-[10.2.1.0^{1,6}.0^{9,15}]pentadec-7-en-14-one (66). To a cold (0 °C), stirred solution of **63** (44.8 mg, 0.10 mmol) in THF (2.5 mL) was added 1.0 M aqueous HCl (20 μL, 20 μmol). The mixture was stirred for 40 min and then diluted with saturated aqueous $NaHCO_3$ (15 mL). The resulting mixture was extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to provide 22.2 mg of **65**, which was contaminated with an unidentified product but used in the next step without further purification.

To a stirred solution of **65** (22.2 mg) obtained above in DMSO (1 mL) was added Ac_2O (1 mL). The mixture was stirred for 7 h and concentrated in vacuo with aid of toluene (5 mL). The residue was dissolved in EtOAc (30 mL) and washed with saturated brine (15 mL × 3). The combined washings were extracted with EtOAc. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:20) to provide 14.0 mg (34%) of **66** as a colorless oil; TLC, R_f 0.55 (EtOAc/hexane, 1:1); $[\alpha]^{27}_D$ +121 (*c* 0.34, $CHCl_3$); IR 1780 cm^{-1}; ^1H NMR (300 MHz) δ 1.02, 1.31 (2s, 3H × 2), 1.59 (dd, *J* = 3.7, 12.5 Hz, 1H), 1.86 (t, *J* = 12.5 Hz, 1H), 2.12−2.17 (m, 1H), 2.68−2.76 (m, 1H), 3.35, 3.44, 3.47 (3s, 3H × 3), 3.82−3.85 (m, 1H), 3.86 (dd, *J* = 5.4, 10.7 Hz, 1H), 4.20 (ddd, *J* = 2.2, 3.7, 12.5 Hz, 1H), 4.64 (s, 2H), 4.76, 4.99 (ABq, *J* = 6.3 Hz, 1H × 2), 5.10 (d, *J* = 2.2 Hz, 1H), 5.82 (dt, *J* = 2.4, 9.8 Hz, 1H), 5.99 (d, *J* = 5.4 Hz, 1H), 6.01 (dt, *J* = 3.7, 9.8 Hz, 1H); ^{13}C NMR (75 MHz) δ 23.1, 33.0, 33.5, 39.3, 42.1, 42.6, 47.4, 55.6, 56.0, 56.6, 57.4, 72.7, 75.2, 95.3, 98.7, 104.2, 111.6, 127.1, 131.4, 174.0; HRMS calcd for $C_{20}H_{30}O_8$ (M^+) 398.1940, found 398.1932.

Mniopetal E (5). To a solution of **66** (4.1 mg, 10 μmol) in THF (1 mL) was added 6.0 M aqueous HCl (1 mL). The mixture was stirred at 50 °C for 18 h and diluted with H_2O (10 mL). The resulting mixture was extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene/AcOH, 20:80:1) to provide 1.3 mg (43%) of **5** as a colorless oil; TLC, R_f 0.19 (acetone/toluene/AcOH, 30:70:1); $[\alpha]^{29.5}_D$ −58.0 (c 0.175, $CHCl_3$); IR 3410, 1770, 1680, 1650 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.02, 1.27 (2s, 3H × 2), 1.40 (dd, J = 3.9, 12.7 Hz, 1H), 1.64 (dd, J = 3.4, 12.7 Hz, 1H), 1.87 (dd, J = 12.5, 12.7 Hz, 1H), 2.06−2.20 (m, 1H), 2.50 (ddd, J = 3.4, 6.6, 19.3 Hz, 1H), 3.73 (br s, 1H), 4.09 (ddd, J = 2.4, 3.9, 12.5 Hz, 1H), 4.34 (br s, 1H), 5.39 (br s, 1H), 7.22 (br d, J = 6.6 Hz, 1H), 9.44 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 24.1, 26.0, 34.0, 34.5, 41.1, 42.3, 48.1, 55.7, 67.0, 72.5, 101.8, 140.5, 156.5, 179.1, 195.3; HRMS calcd for $C_{15}H_{20}O_6$ (M^+) 296.1260, found 296.1263.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **10**−**12**, **14**, **16, 17, 19, 20, 22**, **23**, **25**, **26**, **28**, **47**−**56**, **58**−**60**, **66**, synthetic **5**, and the experimental procedures for the preparation of **24**, **29**, **30**−**32**, **33**+**34**, **35**, **37**, **39**, **40**, **43**, **44**, **61** and their ^1H NMR spectra including ^{13}C NMR spectra for **24**, **29**, **37**, **39**, and **43.** This material is available free of charge via the Internet at http://pubs.acs.org.

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