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Total synthesis of (−)-mniopetal F, a novel inhibitor of RNA-directed DNA-polymerases

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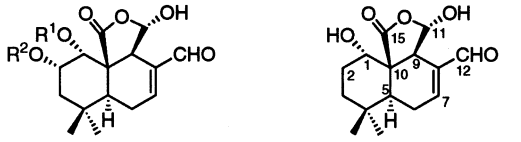
Abstract—We have achieved a total synthesis of (−)-mniopetal F, a drimane-type sesquiterpenoid which inhibits the reverse transcriptase activity of the human immunodeficiency virus (HIV)-1. The key step in our enantiospecific synthesis is a stereoselective intramolecular Diels–Alder reaction, in which the π-facial selectivity is controlled by the stereoelectronic effect of a trialkylsilyloxy substituent existing adjacent to the dienophile part.

1. Introduction

In 1994, six novel drimane-type sesquiterpenoids, mniopetals A–F (**1**–**6**) (Fig. 1) were isolated from the fermentation broth of Canadian *Mniopetalum* sp. 87256 by Steglich et al.[1] These natural products are known to inhibit the activity of the RNA-directed DNA-polymerases (RT, reverse transcriptases) of the human immunodeficiency virus (HIV)-1, avian myeloblastosis virus (AMV), and moloney murine leukemia virus (MMuLV).[1] The structures



	R^1	R^2
1 = A	H	(*R*)-$H_3C(CH_2)_7CH(OAc)CO$
2 = B	H	(*R*)-$H_3C(CH_2)_7CH(OH)CO$
3 = C	H	$H_3C(CH_2)_5CH(OH)CO$
4 = D	$H_3C(CH_2)_7CH(OH)CO$	H
5 = E	H	H

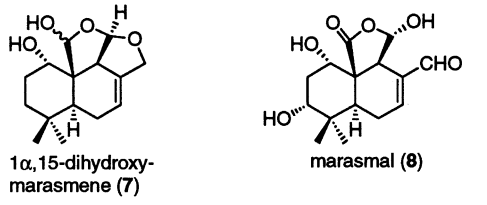


Figure 1.

of these products, all consisting of a highly oxygenated octahydronaphthalene core framework, were elucidated by a combination of chemical and spectroscopic methods (^1H and ^{13}C NMR, MS, UV, and IR).[2] The absolute stereochemistries of **1**–**6** were proposed as depicted[3] based on the correlation to the stereochemically defined 1α,15-dihydroxylmarasmene (**7**), which was isolated previously by Ayer's group.[4] In addition, a structurally similar natural product marasmal (**8**) was isolated from another fungus.[4] Recently, the absolute stereochemistries of (−)-mniopetal E (**5**) and (−)-mniopetal F (**6**) were established through their total syntheses completed by us[5] and by Jauch,[6] respectively. Because of their intriguing biological activities and structural uniqueness, a number of synthetic studies of these sesquiterpenoids have been conducted by several groups,[7] including ours.[8] In this paper, we describe an enantiospecific total synthesis of (−)-mniopetal F (**6**).

2. Results and discussion

Our retrosynthesis to **6** is shown in Scheme 1, in which the key step is the intramolecular Diels–Alder (IMDA) reaction[9] of a butenolide **C**, tethering a functionalized (*E*,*E*)-5,7-octadiene at the β-carbon, for the construction of the 6–6–5 angularly fused tricyclic skeleton in **6**. The adjustment of the oxidation states at C-11 and C-15 (mniopetal numbering) in the expected Diels–Alder adduct **A**, accompanying by the migration of the carbon–carbon double bond, would eventually provide **6**. We anticipated that the IMDA reaction of the substrate **C** would proceed favorably via a chair-like *endo*-transition state depicted as **B**, leading to the desired adduct **A**. Accordingly, we designed the trienes **C** carrying a variety of hydroxy-protecting groups (P in Scheme 1) at C-1 as the substrates for the directed Diels–Alder reaction. The synthesis of **C** could be achieved from a heptanal derivative **D** by the introduction of the diene and

Keywords: biologically active compounds; Diels–Alder reactions; Katsuki–Sharpless reactions; terpenes and terpenoids.

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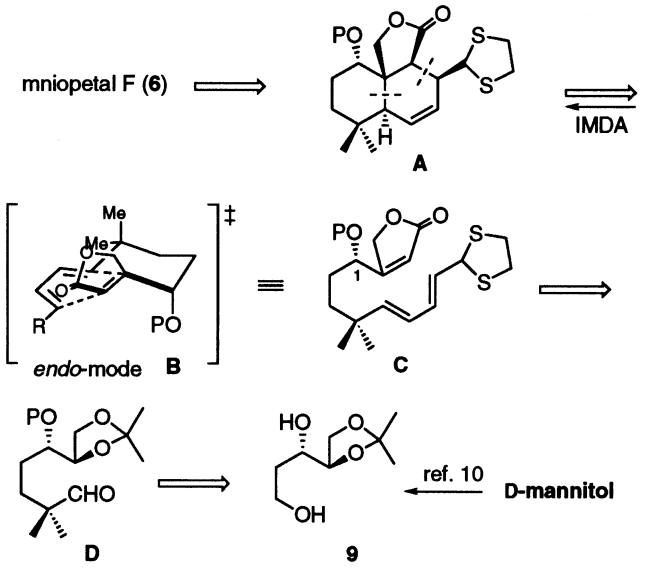
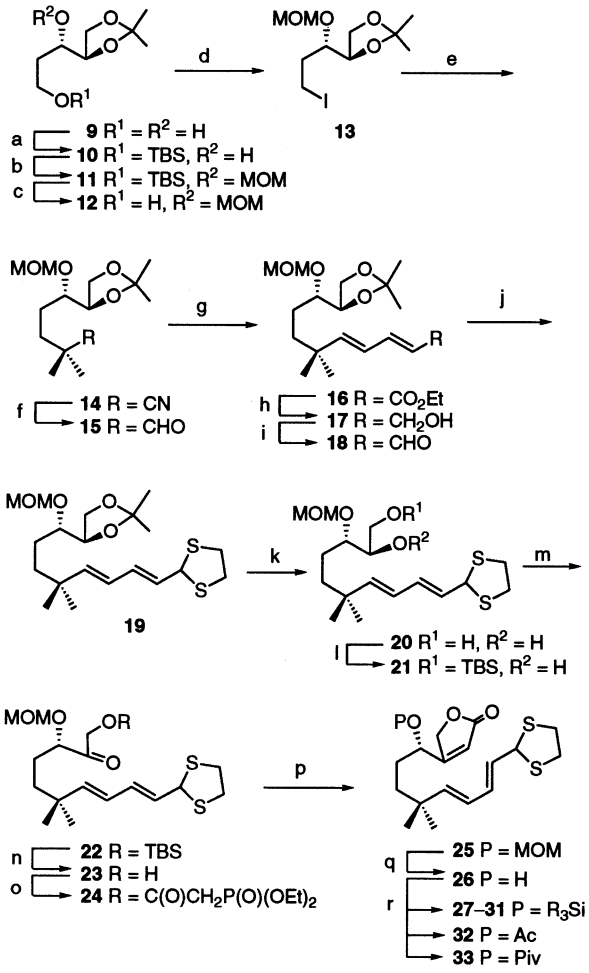


Scheme 1.

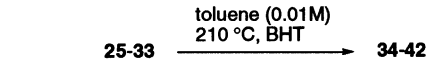
dienophile parts. Then the intermediate **D** could be prepared from known D-2-deoxy-erythritol derivative **9**, which had been prepared from D-mannitol by Sharpless et al. using their asymmetric epoxidation strategy.[10]

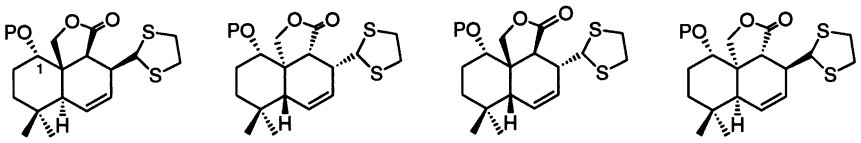
The synthesis of substrates **25**–**33** for the directed IMDA reaction is summarized in Scheme 2. The primary hydroxyl group in **9** was protected as a *tert*-butyldimethylsilyl (TBS) ether. The secondary hydroxyl group in the resulting **10** was protected as a methoxymethyl (MOM) ether to provide **11**. De-*O*-silylation of **11** with tetrabutylammonium fluoride (TBAF) afforded **12**. Treatment of **12** with I_2, PPh_3 and imidazole[11] provided iodide **13**. The substitution of the iodo group in **13** by an anion generated from 2-methylpropionitrile[12] provided, quantitatively, a heptanitrile derivative **14**. Reduction of the nitrile group in **14** with diisobutylaluminum hydride (DIBALH) followed by acidic hydrolysis provided aldehyde **15**. The Horner–Emmons reaction of **15** with triethyl 4-phosphonocrotonate using lithium hexamethyldisilazide as the base in tolune provided (*E*,*E*)-α,β/γ,δ-unsaturated ester **16** in a 66% yield with high *E*,*E*-selectivity. However, reproducibility of the Horner–Emmons recation of **15** under these conditions was problematic. This problem was overcome by conducting the reaction in the presence of $LiOH{\cdot}H_2O$ and molecular sieves (4A powder),[13] and the yield of **16** was improved to an 83% yield from **14**. Furthermore, the geometric ratio (*E*,*E*-isomer/other isomers) was determined to be >20:1 based on the ^1H NMR analysis. DIBALH reduction of **16** followed by MnO_2 oxidation of the resulting allylic alcohol **17** provided aldehyde **18**. As a masked aldehyde functionality, the formyl group in **18** was converted into a 1,3-dithiolane form, providing **19**. The de-*O*-isopropylidene derivative **20** was accompanied by **19**. Acid hydrolysis of **19** also provided the additional diol **20**. Selective protection of the primary hydroxyl group[14] in **20** provided the TBS ether **21**. Oxidation of **21** with DMSO and $SO_3{\cdot}$pyridine and subsequent de-*O*-silylation of the resulting keto derivative **22** with camphorsulfonic acid (CSA) provided α-hydroxy ketone **23**. Esterification of **23** with diethylphosphonoacetic acid by the action of water-soluble carbodiimide (WSC) provided α-phosphonoacetate **24**. The intramolecular Horner–Emmons reaction of **24** was efficiently conducted in the presence of K_2CO_3 and 18-crown-6,[15] providing the butenolide **25** in an 80% yield from **23**. The substituent at C-1 in **25** was protected by a variety of functional groups including five trialkylsilyloxy groups for investigating the effect on the π-facial selectivity in the directed IMDA reaction. Thus, hydrolysis of **25** with aqueous HCl followed by protection of the hydroxyl group in the resulting **26** with a variety of silylating reagents provided trialkylsilyl ethers **27**–**31**. We also prepared acetate **32** and pivaloate **33** by respective acylation.



Scheme 2. *Reagents and conditions*: (a) TBSCl, Et_3N, DMAP, CH_2Cl_2; (b) MOMCl, DIPEA, $CHCl_3$, 40°C; (c) TBAF, THF (89% from **9**); (d) I_2, PPh_3, imidazole, THF, −18°C (93%); (e) Me_2CHCN, LDA, THF, −18°C (99%); (f) DIBALH, PhMe, −78°C then 1 M HCl; (g) triethyl 4-phosphonocrotonate, $LiOH{\cdot}H_2O$, MS 4A, THF, reflux (83% from **14**); (h) DIBALH, CH_2Cl_2, −78°C; (i) MnO_2, CH_2Cl_2; (j) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −18°C (22% from **16** for **19** and 45% for **20**); (k) $AcOH/H_2O/THF$=3:1:1 (93%); (l) TBSCl, Et_3N, DMAP, CH_2Cl_2 (89%); (m) DMSO, $SO_3{\cdot}$pyr., Et_3N, CH_2Cl_2 (70%); (n) CSA, $MeOH/H_2O/CH_2Cl_2$ (45:7.5:1) (87%); (o) $(EtO)_2P(O)CH_2CO_2H$, WSC·HCl, Et_3N, DMAP, CH_2Cl_2; (p) K_2CO_3, 18-crown-6, PhMe (80% from **23**); (q) 4 M HCl/THF (3:7) (92%); (r) for **27**: TMSCl, Et_3N, DMAP, THF (48%, recovery of **26**, 48%); for **28**: DMIPSCl, imidazole, DMF, 0°C (87%); for **29**: TBSOTf, pyr. then 1 M HCl, THF (84%); for **30**: TESCl, DMAP, pyr. (85%); for **31**: TIPSOTf, DMAP, pyr. (93%); for **32**: Ac_2O, pyr. (99%); for **33**: PivCl, DMAP, pyr. (85%).

Table 1. Intramolecular Diels–Alder reactions of **25–33**





Entry	Triene	Products	P	Time (h)	Yield (%)[a]	*endo*/*exo*[b]	**A/B**[b]
1	**25**	**34**	MOM	40	86	>20:1	8:12
2	**26**	**35**	H	40	66	>20:1	8:12
3	**27**	**36**	TMS	40	70	>20:1	13:7
4	**28**	**37**	DMIPS	70	81	>20:1	13:7
5	**29**	**38**	TBS	50	84	>20:1	13:7
6	**30**	**39**	TES	40	78	>20:1	12:8
7	**31**	**40**	TIPS	40	50	>20:1	10:10
8	**32**	**41**	Ac	40	74	>20:1	5:15
9	**33**	**42**	Piv	40	72	>20:1	7:13

[a] Isolated yield of the diastereomeric mixture.
[b] Determined by 300 MHz ^{1}H NMR.

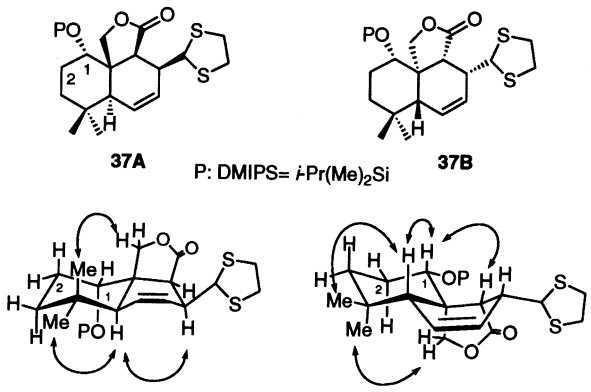


Figure 2.

The results of the thermal IMDA reactions using the substrates **25–33** are summarized in Table 1.[†] Each solution of the substrate in toluene was heated at 210°C in a sealed tube in the presence of a catalytic amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT). After chromatographic purification of the reaction mixture on silica gel, the structures of the adducts and diastereomeric ratios (*endo*/*exo* and the *endo*-adducts **A/B**) of the respective cycloadducts were determined based on ^{1}H NMR analysis. As shown in Fig. 2, the relative configurations for the diastereomeric adducts were determined by NOESY correlations, exemplified by the diastereomeric adducts **37A** and **37B** obtained from the substrate **28** carrying an isopropyldimethylsilyl (DMIPS) ether at C-1. From these NOESY correlations, it was established that both **37A** and **37B** possess a *trans*-fused octahydronaphthalene skeleton. Consequently, the cycloaddition of **28** predominantly proceeded via the anticipated *endo*-mode. Furthermore, the H-1 proton for the major adduct **37A** appeared as a narrow singlet, indicating that the ODMIPS group orients axially. On the other hand, the H-1 proton for the minor diastereomer **37B** appeared as a doublet of doublets with J=5.3 and 10.6 Hz, indicating the ODMIPS group orients equatorially. These spectral data verified the conformations of **37A** and **37B** as shown. Based on their NOESY correlations and coupling constants for ring protons, it was confirmed that all the IMDA reactions of **25–33** proceeded with high *endo*/*exo* selectivity (**A**+**B**/**C**+**D**, more than 20 to 1 in every case). In addition, the π-facial selectivity of the *endo*-adducts (**A**/**B**) depended on the substituent at C-1. The alkyloxy and acyloxy substrates at C-1, i.e. **25**, **32**, and **33**, and unprotected substrate **26** provided the undesired *endo*-cycloadduct **B** preferentially (entries 1, 2, 8, or 9). On the other hand, the silyl ethers **27–30** provided the desired *endo*-adducts **A** predominantly (entries 3–6). Among them, the subtrates **28** and **29** carrying a bulkier trialkylsilyloxy group at C-1 provided the desired *endo*-adducts **37** and **38** with the highest ratio in comparable yields (entries 4 and 5). In the case of the bulkiest silyl ether **31**, the π-facial selectivity significantly decreased, providing two *endo*-adducts **40A** and **40B** equally with a reduced combined yield (entry 7). Although we have no firm explanation for these stereochemical outcomes, the steric and/or stereoelectronic balance of the three substituents at the silicon atom seems to be crucial for the π-facial selectivity and the yield. From the steric point of view, a substituent neighboring the dienophile part would generally dispose an equatorial orientation in the transition state. Plausible transition states **TS-A**, **B**, **C**, and **D**, leading to adducts **A**, **B**, **C**, and **D**, respectively, are depicted in Fig. 3 to explain the preferential formation of the *endo*-adducts **A** and **B**. As our substrates possesses a butenolide as the dienophile, the six-membered chair-like transition states are considered as shown in Fig. 3. The *endo*-mode cyclization, as shown in the cases of **TS-A** and **B**, proceeds smoothly because of the presence of preferable secondary orbital interaction. In the *exo*-mode cyclizations (**TS-C** and **D**), severe interactions between H-6 (the diene part) and H-3 or OP-1 (or H-1) make the cyclization unfavorable. In fact,

[†] We did not conduct the IMDA reactions of **25–33** using a Lewis acid catalyst, because of our previous unfruitful results with Lewis acids obtained in the mniopetal E synthesis. See Ref. 5b.

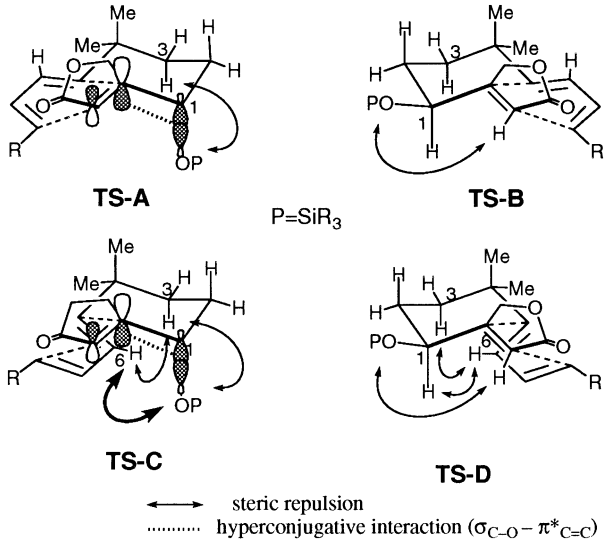
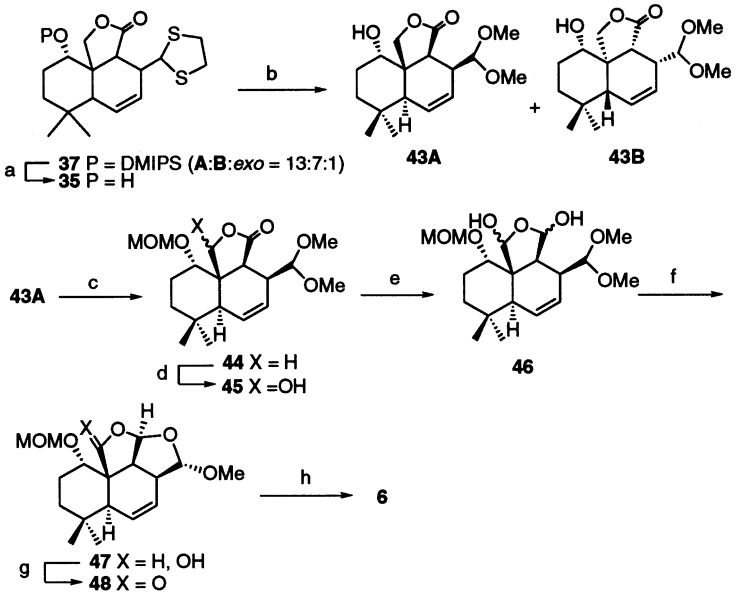


Figure 3.

in the TSs) at the neiboring site of the diene part. This may accelerate the cyclization, as a number of precedent papers described the geminal dialkyl effect.[18] However, we could not estimate the magnitude of this effect because we had no opportunity to conduct the IMDA reaction using a substrate without this geminal dimethyl substitutent. From the synthetic point of view, we chose the diastereomeric mixture **37** as the most suitable IMDA adducts for the total synthesis of **6**.[19]

Total synthesis of mniopetal F (**6**) was achieved from **37** as summarized in Scheme 3. De-*O*-silylation of **37**, as an approximately 2:1 diastereomeric mixture of **37A** and **37B**, with TBAF provided **35** as a diastereomeric mixture. Treatment of **35** with $Hg(ClO_4)_2 \cdot 3H_2O$[20] provided a diastereomeric mixture of dimethylacetal **43A**‡ (44%) and **43B** (25%), which were cleanly separated by chromatography on silica gel. The hydroxyl group in the diastereomerically pure **43A** was protected as an MOM ether. The γ-lactone in the resulting **44** was hydrolyzed under basic



Scheme 3. *Reagents and conditions*: (a) TBAF, THF, 0°C (92%); (b) $Hg(ClO_4)_2 \cdot 3H_2O$, $CaCO_3$, MeOH/$CHCl_3$ (3:1), 0°C (44% for **43A**, 25% for **43B**); (c) MOMCl, DIPEA, CH_2Cl_2, 40°C (85%); (d) 1 M KOH, Na_2RuO_4, *t*-BuOH, 80°C (100%); (e) DIBALH, PhMe, −78°C (44% for **46**, 21% for **44**, 21% for **45**); (f) $TsOH \cdot H_2O$, THF/H_2O (4:1) (43%); (g) DMSO, Ac_2O (80%); (h) 6 M HCl, THF then Et_3N, PhMe (83%).

in all IMDA reactions using **25**–**33**, only the *endo*-adducts were formed substantially. In regard to the π-facial selectivity in the formation of *endo*-adducts **A** and **B**, we made the following speculation. As shown in **TS-A** and **C**, previous reports on the stereochemical studies of IMDA reactions indicated that a trialkylsilyloxy substituent in the substrates prefers to dispose an axial orientation as a result of the maximum hyperconjugative interaction between σ_{C-O} and $\pi^*_{C=C}$ of the dienophile, which lowers the dienophile LUMO.[16,17] As mentioned above, **TS-C** suffers from a severe interaction between H-6 and the silyloxy group. In addition, the $A^{1,3}$ strain between the ring hydrogen in the butenolide and equatorially oriented silyloxy group makes **TS-B** less favorable, resulting in the preferential formation of the *endo*-A isomer as the major product. The present IMDA substrates possess a geminal dimethyl group (C-4 conditions, and the resulting open-ring γ-hydroxyl carboxylate was immediately oxidized with Na_2RuO_4,[21] providing γ-hydroxyl-γ-lactone **45** as an inseparable diastereomeric mixture. Treatment of **45** with 2 equiv. of DIBALH provided dialdehyde hydrate **46** (44%) along with **44** (21%) and recovered **45** (21%). Brief treatment of **46** with TsOH provided a tetracyclic hemiacetal mixture **47**, which was oxidized to tetracyclic lactone **48**. Finally, acid hydrolysis of the acetal moiety in **48** and subsequent base-mediated double-bond migration provided (−)-mniopetal F (**6**). In the initial stage of this step, simultaneous acid hydrolysis (6 M HCl) of the MOM ether and methyl acetal

‡ The enantiopurity of **43A** (>98% ee) was confirmed by ^1H NMR analyses of the corresponding (*R*)- and (*S*)-*O*-acetylmandelate derivatives. No racemization of the C-1 in **28** occurred under the used IMDA conditions.

in **48** occurred. Isomerization of the double bond in this intermediary hemiacetal proceeded quite slowly under the acidic conditions. On the contrary, treatment of this hemiacetal with triethylamine as the base provided the thermodynamically favorable double-bond migration product, i.e. **6**, as a sole product in a yield of 83% from **48**. The spectroscopic data (^{1}H and ^{13}C NMR, IR, MS) of the synthetic **6** were well matched with those for natural **6**.[§]

In summary, we have completed the total synthesis of (−)-mniopetal F (**6**) in its natural form. Our total synthesis features the highly *endo*-selective IMDA reaction achieved by using a variety of substrates **25**–**33**. In addition, the π-facial selectivity in the IMDA reaction was controlled by the stereoelectronic effect of the silyloxy group adjacent to the dienophile part, as in the case of **28**.

3. Experimental

3.1. General methods

Specific rotations were measured in a 10 mm cell. Infrared (IR) spectra were determined as neat unless otherwise noted. ^{1}H NMR spectra were recorded at 270 MHz or at 300 MHz in $CDCl_3$ with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 67.5 Hz or at 75 MHz in $CDCl_3$, and signal positions were measured relative to the signal for $CDCl_3$ (δ 77.0). Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel $60F_{254}$ (Merck). Extractive materials were purified by chromatography on Daisogel IR-60 (Daiso Co., Ltd) 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 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], dimethyl sulfoxide (DMSO) [CaH_2], pyridine [NaOH], and toluene [CaH_2].

3.1.1. (2*R*,3*S*)-1,2-(Isopropylidenedioxy)-3-(methoxymethoxy)-5-pentanol (12). To a cooled (0°C) solution of **9** (4.06 g, 23.0 mmol) in CH_2Cl_2 (80 mL) were added Et_3N (16.1 mL, 115 mmol), TBSCl (5.21 g, 34.6 mmol) and 4-dimethylaminopyridine (DMAP) (141 mg, 1.15 mmol). The mixture was stirred for 3.5 h and concentrated in vacuo. The residue was diluted with EtOAc, washed with 0.2 M aqueous HCl and saturated aqueous $NaHCO_3$. The organic layer was dried and concentrated in vacuo to provide crude **10** as a colorless oil, which was used in the next step without further purification. In a small-scale experiment, pure **10** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:12) as a colorless oil; TLC, R_f 0.35 (EtOAc/hexane, 1:5); $[\alpha]^{21.5}_D$=+17.5 (*c* 0.92, $CHCl_3$); IR 3500 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.35, 1.41 (2s, 3H×2), 1.59–1.74 (m, 1H), 1.78–1.89 (m, 1H), 3.41–3.68 (br, 1H), 3.76–4.12 (m, 6H); ^{13}C NMR (75 MHz) δ 5.6×2, 18.1, 25.3, 25.8×3, 26.6, 34.5, 62.4, 66.4, 72.6, 78.3, 109.1; HRMS calcd for $C_{13}H_{27}O_4Si$ (M^+-CH_3) 275.1679, found 275.1677.

To a cooled (0°C) solution of crude **10** obtained above in $CHCl_3$ (80 mL) were added diisopropylethylamine (DIPEA) (40.1 mL, 230 mmol) and chloromethyl methyl ether (MOMCl) (8.75 mL, 115 mmol). The mixture was stirred at 40°C for 19 h and concentrated in vacuo. The residue was diluted with EtOAc, washed with 1.0 M aqueous HCl and saturated aqueous $NaHCO_3$. The organic layer was dried and concentrated in vacuo to provide crude **11** as a pale yellow oil, which was used in the next step without further purification. In a small-scale experiment, pure **11** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:40) as a colorless oil; TLC, R_f 0.65 (EtOAc/hexane, 1:5); $[\alpha]^{22}_D$=−12.6 (*c* 0.57, $CHCl_3$); IR 2930 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.35, 1.41 (2s, 3H×2), 1.61–1.84 (m, 2H), 3.39 (s, 3H), 3.70–3.77 (m, 2H), 3.78–3.86 (m, 1H), 3.87 (dd, *J*=6.9, 7.9 Hz, 1H), 4.03 (dd, *J*=6.9, 7.9 Hz, 1H), 4.12–4.18 (m, 1H), 4.71, 4.74 (ABq, *J*=6.8 Hz, 1H×2); ^{13}C NMR (75 MHz) −5.43, −5.38, 18.2, 25.2, 25.9×3, 26.3, 34.6, 55.7, 59.2, 65.8, 74.9, 78.1, 96.9, 109.1; HRMS calcd for $C_{15}H_{31}O_5Si$ (M^+-CH_3) 319.1941, found 319.1950.

To a cooled (0°C) solution of crude **11** obtained above in THF (80 mL) was added tetrabutylammonium fluoride (TBAF) (30.0 mL, 1.0 M solution in THF, 30.0 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, 1:4) to provide 4.51 g (89% from **9**) of **12** as a colorless oil; TLC, R_f 0.27 (acetone/toluene, 1:3); $[\alpha]^{22}_D$=−40.1 (*c* 2.50, $CHCl_3$); IR 3440 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.36, 1.41 (2s, 3H×2), 1.61–1.75 (m, 1H), 1.77–1.90 (m, 1H), 2.31 (br-s, 1H), 3.42 (s, 3H), 3.71–3.90 (m, 4H), 4.03–4.15 (m, 2H), 4.70, 4.76 (ABq, *J*=6.7 Hz, 1H×2); ^{13}C NMR (75 MHz) δ 25.3, 26.3, 34.0, 56.0, 59.1, 66.0, 76.2, 77.8, 97.3, 109.3; HRMS calcd for $C_9H_{17}O_5$: (M^+-CH_3) 205.1076, found 205.1078.

3.1.2. (2*R*,3*S*)-5-Iodo-1,2-(isopropylidenedioxy)-3-(methoxymethoxy)pentane (13). To a cooled (−18°C) solution of **12** (1.49 g, 6.76 mmol) in THF (30 mL) were added PPh_3 (2.66 g, 10.1 mmol), imidazole (693 mg, 10.2 mmol), and I_2 (2.21 g, 8.70 mmol). After being stirred at −18°C for 1 h, the organic solvent was removed by evaporation. The residue was diluted with EtOAc, washed with 20 wt% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to provide 2.07 g (93%) of **13** as a colorless oil; TLC, R_f 0.43 (EtOAc/hexane, 1:4); $[\alpha]^{26.5}_D$=−30.9 (*c* 1.65, $CHCl_3$); IR 2990 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.35, 1.42 (2s, 3H×2), 1.97–2.19 (m, 2H), 3.22–3.42 (m, 2H), 3.41 (s, 3H), 3.63–3.73 (m, 1H), 3.85 (dd, *J*=6.1, 7.9 Hz, 1H), 4.05 (dd, *J*=6.4, 7.9 Hz, 1H), 4.06–4.16 (m, 1H), 4.72, 4.75 (ABq, *J*=7.0 Hz, 1H×2); ^{13}C NMR (75 MHz) δ 2.0,

[§] The optical rotation of our synthetic **6** ($[\alpha]^{23}_D$=−56, *c* 0.24, MeOH) was not matched with that for natural **6**[1] ($[\alpha]^{23}_D$=−29, *c* 0.22, MeOH), but was matched well with that reported by Jauch for his synthetic **6** ($[\alpha]^{20}_D$=−63, *c* 0.65, MeOH).[6]

25.1, 26.3, 35.7, 55.9, 66.1, 77.1, 78.2, 96.9, 109.3; HRMS calcd for $C_9H_{16}O_4I$ (M^+-CH_3) 315.0094, found 315.0093.

3.1.3. (5*S*,6*R*)-6,7-(Isopropylidenedioxy)-5-(methoxymethoxy)-2,2-dimethyl-1-heptanenitrile (14). The following reaction was carried out under argon. To a cooled (0°C) solution of diisopropylamine (1.67 mL, 11.9 mmol) in THF (40 mL) was added *n*-BuLi (4.8 mL, 2.46 M solution in hexane, 11.8 mmol). After being stirred at 0°C for 30 min, isobutyronitrile (1.10 mL, 12.1 mmol) was added to the solution at −78°C. After being stirred at −78°C for 1 h, a solution of **13** (1.97 g, 5.97 mmol) in THF (10 mL) was added to the mixture. The mixture was stirred at −18°C for 30 min and quenched with saturated aqueous NH_4Cl. The organic solvent was removed by evaporation. The resulting aqueous solution was diluted with 10 wt% aqueous $Na_2S_2O_3$ and the whole 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, 1:9) to provide 1.60 g (99%) of **14** as a pale yellow oil; TLC, R_f 0.22 (EtOAc/hexane, 1:4); $[\alpha]^{24}_D=-3.5$ (*c* 1.78, $CHCl_3$); IR 2240 cm^{-1}; ^1H NMR (300 MHz) δ 1.35 (s, 6H), 1.37, 1.41 (2s, 3H×2), 1.55–1.86 (m, 4H), 3.39 (s, 3H), 3.62–3.69 (m, 1H), 3.87 (dd, *J*=9.0, 10.7 Hz, 1H), 4.02–4.11 (m, 2H), 4.67, 4.72 (ABq, *J*=6.8 Hz, 1H×2); ^{13}C NMR (75 MHz) δ 25.3, 26.3, 26.5, 26.9×2, 32.2, 36.1, 55.9, 66.4, 77.1, 77.6, 96.6, 109.2, 124.8; HRMS calcd for $C_{13}H_{22}O_4N$: (M^+-CH_3) 256.1549, found 256.1552.

3.1.4. Ethyl (2*E*,4*E*,9*S*,10*R*)-10,11-(isopropylidenedioxy)-9-(methoxymethoxy)-6,6-dimethyl-2,4-undecadienoate (16). The following reaction was carried out under argon. To a cooled (−78°C) solution of **14** (1.52 g, 5.60 mmol) in toluene (30 mL) was added diisobutylaluminium hydride (DIBALH) (8.7 mL, 1.0 M solution in toluene, 8.7 mmol). After being stirred at −78°C for 30 min, the mixture was quenched with H_2O. This was diluted with 1.0 M aqueous HCl and extracted with EtOAc. The combined extracts were washed with saturated $NaHCO_3$. The organic layer was dried and concentrated in vacuo to provide crude **15** as a pale yellow oil, which was used in the next step without further purification. In a small-scale experiment, pure **15** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:10) as a colorless oil; TLC, R_f 0.57 (EtOAc/hexane, 1:2); IR 1730 cm^{-1}; ^1H NMR (300 MHz) δ 1.07 (s, 6H), 1.34, 1.39 (2s, 3H×2), 1.35–1.75 (m, 4H), 3.39 (s, 3H), 3.57–3.64 (m, 1H), 3.80–3.90 (m, 1H), 4.00–4.10 (m, 2H), 4.65, 4.72 (ABq, *J*=6.8 Hz, 1H×2), 9.46 (s, 1H).

The following reaction was carried out under argon. To a mixture of crude **15** obtained above and molecular sieves 4A powder (8.4 g) in THF (30 mL) were added triethyl 4-phosphonocrotonate (2.1 mL, 8.7 mmol) and $LiOH\cdot H_2O$ (354 mg, 8.4 mmol). The mixture was heated under reflux for 19 h. The reaction mixture was filtered through a short column of silica gel with $CHCl_3$ as eluate, and the eluate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to provide 1.72 g (83% from **14**) of **16** as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^1H NMR analysis); TLC R_f 0.53 (EtOAc/hexane, 1:3); $[\alpha]^{25}_D=+3.6$ (*c* 1.42, $CHCl_3$); IR 1715, 1640 cm^{-1}; ^1H NMR (300 MHz) δ 1.05 (s, 6H), 1.29 (t, *J*=7.2 Hz, 3H), 1.34, 1.39 (2s, 3H×2), 1.35–1.60 (m, 4H), 3.38 (s, 3H), 3.56–3.63 (m, 1H), 3.80–3.90 (m, 1H), 3.98–4.08 (m, 2H), 4.20 (q, *J*=7.2 Hz, 2H), 4.64, 4.71 (ABq, *J*=6.8 Hz, 1H×2), 5.81 (d, *J*=15.3 Hz, 1H), 6.00–6.15 (m, 2H), 7.21–7.31 (m, 1H); ^{13}C NMR (75 MHz) δ 14.3, 25.3, 26.4, 26.5, 26.6, 26.8, 36.6, 37.6, 55.8, 60.1, 66.1, 77.4, 78.0, 96.6, 109.0, 119.6, 124.8, 145.3, 153.4, 167.2; HRMS calcd for $C_{20}H_{34}O_6$ (M^+) 370.2355, found 370.2355.

3.1.5. (2*R*,3*S*,7*E*,9*E*)-10-(1,3-Dithiolan-2-yl)-3-(methoxymethoxy)-6,6-dimethyl-7,9-decadiene-1,2-diol (20). The following reaction was carried out under argon. To a cooled (−78°C) solution of **16** (11.5 g, 31.0 mmol) in CH_2Cl_2 (220 mL) was added DIBALH (78.0 mL, 1.0 M solution in toluene, 78 mmol). The mixture was stirred at −78°C for 15 min and quenched with H_2O. This was diluted with H_2O (150 mL) then with CH_2Cl_2 (150 mL). To this was added potassium sodium (+)-tartrate tetrahydrate (40 g). The whole was stirred vigorously for 15.5 h and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo to provide crude **17** (11.0 g) as a colorless oil, which was used in the next step without purification. In a small-scale experiment, pure **17** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:3) as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^1H NMR analysis); TLC, R_f 0.52 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D=+2.4$ (*c* 2.00, $CHCl_3$); IR 3430, 1660 cm^{-1}; ^1H NMR (270 MHz) δ 1.02 (s, 6H), 1.24–1.58 (m, 4H), 1.35, 1.39 (2s, 3H×2), 1.65 (br-s, 1H), 3.38 (s, 3H), 3.58–3.64 (m, 1H), 3.81–3.92 (m, 1H), 3.98–4.13 (m, 2H), 4.16 (dd, *J*=1.1, 5.9 Hz, 2H), 4.64, 4.72 (ABq, *J*=7.0 Hz, 1H×2), 5.63 (d, *J*=15.4 Hz, 1H), 5.75 (dt, *J*=5.9, 15.0 Hz, 1H), 5.96 (dd, *J*=10.3, 15.4 Hz, 1H), 6.22 (br-dd, *J*=10.3, 15.0 Hz, 1H); ^{13}C NMR (75 MHz) δ 25.3, 26.37, 26.40, 26.9, 27.2, 35.8, 37.9, 55.7, 63.4, 65.9, 77.5, 77.9, 96.5, 109.0, 125.8, 129.7, 132.2, 144.7; HRMS calcd for $C_{17}H_{29}O_5$ (M^+-CH_3) 313.2015, found 313.2018.

To a cooled (0°C) solution of the crude **17** obtained above (11.0 g) in CH_2Cl_2 (200 mL) was added MnO_2 (79.3 g, 912 mmol). The mixture was stirred for 25 min, and inorganic materials were filtered off, washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo to provide crude **18** (9.66 g) as a colorless oil, which was used in the next step without further purification. In a small-scale experiment, pure **18** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:5) (*E*,*E*-isomer/other isomers⇒20:1, determined by ^1H NMR analysis); TLC, R_f 0.49 (EtOAc/hexane, 1:2); IR 1680, 1635 cm^{-1}, ^1H NMR (300 MHz) δ 1.09 (s, 6H), 1.35, 1.39 (2s, 3H×2), 1.37–1.62 (m, 4H), 3.38 (s, 3H), 3.56–3.63 (m, 1H), 3.82–3.89 (m, 1H), 4.00–4.09 (m, 2H), 4.65, 4.72 (ABq, *J*=7.0 Hz, 1H×2), 6.11 (dd, *J*=7.7, 15.4 Hz, 1H), 6.19 (d, *J*=15.0 Hz, 1H), 6.26 (dd, *J*=8.4, 15.0 Hz, 1H), 7.09 (ddd, *J*=1.5, 8.4, 15.4 Hz, 1H), 9.54 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (75 MHz) δ 25.2, 26.2, 26.4, 26.5×2, 36.9, 37.4, 55.7, 66.1, 77.3, 78.0, 96.5, 109.0, 125.1, 130.3, 153.1, 155.9, 193.7.

To a cooled (−18°C) solution of the crude **18** obtained above (9.66 g) in CH_2Cl_2 (200 mL) were added

$HS(CH_2)_2SH$ (5.24 mL, 62.5 mmol) and $BF_3{\cdot}OEt_2$ (1.19 mL, 9.39 mmol). The mixture was stirred at −18°C for 1 h, and then $HS(CH_2)_2SH$ (1.30 mL, 15.5 mmol) and $BF_3{\cdot}OEt_2$ (0.30 mL, 2.37 mmol) were added at −18°C. The mixture was stirred for an additional 40 min and diluted with saturated aqueous $NaHCO_3$. 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, 1:13 to 1:1) to provide 2.73 g (22% from **16**) of **19** and 5.11 g (45% from **16**) of **20**. Compound **19** was obtained as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^{1}H NMR analysis); TLC, R_f 0.62 (EtOAc/hexane, 1:3); $[\alpha]^{25.5}{}_D$=+2.8 (*c* 1.77, $CHCl_3$); IR 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.00 (s, 6H), 1.35, 1.39 (2s, 3H×2), 1.25–1.54 (m, 4H), 3.20–3.38 (m, 4H), 3.38 (s, 3H), 3.58–3.63 (m, 1H), 3.81–3.91 (m, 1H), 3.98–4.09 (m, 2H), 4.64, 4.72 (ABq, *J*=6.8 Hz, 1H×2), 5.09 (d, *J*=9.4 Hz, 1H), 5.618 (d, *J*=15.4 Hz, 1H), 5.622 (dd, *J*=9.4, 14.9 Hz, 1H), 5.92 (dd, *J*=10.3, 15.4 Hz, 1H), 6.14 (dd, *J*=10.3, 14.9 Hz, 1H); ^{13}C NMR (75 MHz) δ 25.4, 26.5×2, 26.9, 27.1, 36.0, 37.9, 39.5×2, 54.3, 55.8, 66.0, 77.6, 77.9, 96.6, 109.0, 125.3, 130.2, 131.2, 145.2; HRMS calcd for $C_{20}H_{34}O_4S_2$ (M^+) 402.1899, found 402.1899.

Compound **20** was obtained as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^{1}H NMR analysis); TLC, R_f 0.56 (acetone/hexane, 1:1); IR 3420, 1650 cm^{-1}; $[\alpha]^{26.0}{}_D$=+36.6 (*c* 1.60, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.00 (s, 6H), 1.21–1.53 (m, 4H), 2.38 (br, 2H), 3.18–3.41 (m, 4H), 3.42 (s, 3H), 3.51–3.75 (m, 4H), 4.61, 4.71 (ABq, *J*=6.7 Hz, 1H×2), 5.09 (d, *J*=9.2 Hz, 1H), 5.61 (d, *J*=15.4 Hz, 1H), 5.63 (dd, *J*=9.2, 14.6 Hz, 1H), 5.92 (dd, *J*=10.3, 15.4 Hz, 1H), 6.14 (dd, *J*=10.3, 14.6 Hz, 1H); ^{13}C NMR (75 MHz) δ 26.7, 26.9, 27.0, 35.9, 38.7, 39.5×2, 54.2, 55.9, 63.0, 73.0, 83.3, 97.7, 125.4, 130.4, 131.0, 144.9; HRMS calcd for $C_{17}H_{30}O_4S_2$ (M^+) 362.1586, found 362.1585.

Compound **19** (2.73 g, 6.78 mmol) was dissolved in a mixture of AcOH, H_2O, and THF (3:1:1, v/v, 80 mL). The solution was stirred for 3.5 days then concentrated in vacuo with the aid of toluene and EtOH. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:1) to provide 2.29 g (93%) of **20**.

3.1.6. (2*R*,3*S*,7*E*,9*E*)-1-*tert*-Butyldimethylsilyloxy-10-(1,3-dithiolan-2-yl)-3-(methoxymethoxy)-6,6-dimethyl-7,9-decadien-2-ol (21). To a cooled (0°C) solution of **20** (4.86 g, 13.4 mmol) in CH_2Cl_2 (100 mL) were added Et_3N (7.50 mL, 53.8 mmol), TBSCl (3.64 g, 24.1 mmol) and DMAP (163 mg, 1.34 mmol). The mixture was stirred for 19 h and diluted with saturated brine. 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, 1:17) to provide 5.69 g (89%) of **21** as a colorless oil (*E*,*E*-isomer:-other isomers⇒20:1, determined by ^{1}H NMR analysis); TLC, R_f 0.42 (EtOAc/hexane, 1:4); $[\alpha]^{26}{}_D$=+6.4 (*c* 2.24, $CHCl_3$); IR 3470, 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.00 (s, 6H), 1.24–1.58 (m, 4H), 2.68 (br, 1H), 3.19–3.39 (m, 4H), 3.39 (s, 3H), 3.48–3.56 (m, 1H), 3.58–3.77 (m, 3H), 4.62, 4.69 (ABq, *J*=6.6 Hz, 1H×2), 5.09 (d, *J*=9.2 Hz, 1H), 5.57–5.66 (m, 2H), 5.92 (dd, *J*=10.4, 15.4 Hz, 1H), 6.14 (dd, *J*=10.4, 14.7 Hz, 1H); ^{13}C NMR (75 MHz) δ −5.4×2, 18.2, 25.7, 25.9×3, 26.9, 27.1, 35.9, 38.2, 39.5×2, 54.3, 55.8, 63.7, 72.9, 80.1, 96.8, 125.1, 130.1, 131.3, 145.4; HRMS calcd for $C_{23}H_{44}O_4SiS_2$ (M^+) 476.2450, found 476.2467.

3.1.7. (3*S*,7*E*,9*E*)-1-*tert*-Butyldimethylsilyloxy-10-(1,3-dithiolan-2-yl)-3-(methoxymethoxy)-6,6-dimethyl-7,9-decadien-2-one (22). To a stirred solution of **21** (5.69 g, 11.9 mmol) in a mixture of CH_2Cl_2 and DMSO (2.5:1 v/v, 120 mL) were added Et_3N (65.6 mL, 477 mmol) and $SO_3{\cdot}$pyridine (38.0 g, 239 mmol). The mixture was stirred for 1.5 h, then Et_3N (33.0 mL, 240 mmol) and $SO_3{\cdot}$pyridine (19.0 g, 119 mmol) were added. The mixture was stirred for 2.5 h, then Et_3N (33.0 mL, 240 mmol) and $SO_3{\cdot}$pyridine (19.0 g, 119 mmol) were added. The mixture was stirred for an additional 2 h, diluted with EtOAc and washed with H_2O. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to provide 4.02 g (70%) of **22** as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^{1}H NMR analysis); TLC, R_f 0.51 (EtOAc/hexane, 1:4); $[\alpha]^{25}{}_D$=+6.9 (*c* 1.36, $CHCl_3$); IR 1730, 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.09 (s, 6H), 0.92 (s, 9H), 0.99 (s, 6H), 1.24–1.73 (m, 4H), 3.19–3.39 (m, 4H), 3.35 (s, 3H), 4.25 (dd, *J*=4.4, 7.3 Hz, 1H), 4.34, 4.41 (ABq, *J*=18.3 Hz, 1H×2), 4.60, 4.62 (ABq, *J*=6.8 Hz, 1H×2), 5.08 (d, *J*=9.2 Hz, 1H), 5.58 (d, *J*=15.5 Hz, 1H), 5.62 (dd, *J*=9.2, 14.9 Hz, 1H), 5.90 (dd, *J*=10.3, 15.5 Hz, 1H), 6.12 (dd, *J*=10.3, 14.9 Hz, 1H); ^{13}C NMR (75 MHz) δ −5.6, −5.5, 18.3, 25.7×3, 26.8, 26.9, 27.2, 35.8, 38.0, 39.5×2, 54.2, 55.9, 67.7, 80.2, 96.4, 125.4, 130.4, 131.0, 144.7, 209.6; HRMS calcd for $C_{23}H_{42}O_4SiS_2$ (M^+) 474.2294, found 474.2300.

3.1.8. (3*S*,7*E*,9*E*)-10-(1,3-Dithiolan-2-yl)-1-hydroxy-3-(methoxymethoxy)-6,6-dimethyl-7,9-decadien-2-one (23). To a cooled (0°C) solution of **22** (4.02 g, 8.47 mmol) in a mixture of MeOH, H_2O and CH_2Cl_2 (45:7.5:1 v/v/v, 100 mL) was added CSA (197 mg, 0.848 mmol). The mixture was stirred for 19 h and diluted with saturated aqueous $NaHCO_3$, 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, 1:4) to provide 2.65 g (87%) of **23** as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^{1}H NMR analysis); TLC, R_f 0.55 (acetone/hexane, 1:2); $[\alpha]^{21.5}{}_D$=−16.3 (*c* 1.26, $CHCl_3$); IR 3460, 1720, 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.99 (s, 6H), 1.31–1.40 (m, 2H), 1.59–1.67 (m, 2H), 3.00 (br, 1H), 3.19–3.42 (m, 4H), 3.37 (s, 3H), 4.09 (t, *J*=5.9 Hz, 1H), 4.44 (s, 2H), 4.64 (s, 2H), 5.08 (d, *J*=9.1 Hz, 1H), 5.57 (d, *J*=15.5 Hz, 1H), 5.64 (dd, *J*=9.1, 14.8 Hz, 1H), 5.91 (dd, *J*=10.3, 15.5 Hz, 1H), 6.13 (dd, *J*=10.3, 14.8 Hz, 1H); ^{13}C NMR (75 MHz) δ 26.8, 26.9, 27.6, 35.8, 37.3, 39.5×2, 54.1, 56.1, 66.3, 81.1, 96.5, 125.5, 130.5, 130.8, 144.3, 211.2; HRMS calcd for $C_{17}H_{28}O_4S_2$ (M^+) 360.1429, found 360.1427.

3.1.9. 3-[(1*S*,5*E*,7*E*)-8-(1,3-Dithiolan-2-yl)-1-(methoxymethoxy)-4,4-dimethyl-5,7-octadienyl]-2-buten-4-olide (25). To a cooled (0°C) solution of **23** (2.65 g, 7.35 mmol) in

CH_2Cl_2 (50 mL) were added $(EtO)_2P(O)CH_2CO_2H$ (2.36 mL, 14.7 mmol), Et_3N (2.00 mL, 14.3 mmol), DMAP (270 mg, 2.21 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.82 g, 14.7 mmol). The mixture was stirred for 2.5 h and diluted with CH_2Cl_2. This was washed with 0.1 M aqueous HCl, 0.1 M aqueous NaOH, and H_2O, successively. The organic layer was dried and concentrated in vacuo to provide crude **24**, which was used in the next step without purification. In a small-scale experiment, pure **24** was obtained by column chromatography on silica gel (EtOAc/hexane, 1:1) as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^{1}H NMR analysis); TLC, R_f 0.31 (acetone/hexane, 1:2); $[\alpha]^{23}_D=-22.1$ (*c* 0.96, $CHCl_3$); IR 1730, 1650 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.99 (s, 6H), 1.36 (t, *J*=7.1 Hz, 6H), 1.25–1.45 (m, 2H), 1.60–1.68 (m, 2H), 3.10 (d, *J*=21.7 Hz, 2H), 3.20–3.37 (m, 4H), 3.38 (s, 3H), 4.04 (br-t, *J*=6.0 Hz, 1H), 4.20 (dq, *J*=7.1, 7.8 Hz, 4H), 4.64, 4.67 (ABq, *J*=6.6 Hz, 1H×2), 4.93, 5.01 (ABq, *J*=17.6 Hz, 1H×2), 5.08 (d, *J*=9.3 Hz, 1H), 5.59 (d, *J*=15.5 Hz, 1H), 5.63 (dd, *J*=9.3, 14.9 Hz, 1H), 5.91 (dd, *J*=10.3, 15.5 Hz, 1H), 6.13 (dd, *J*=10.3, 14.9 Hz, 1H); ^{13}C NMR (75 MHz) δ 16.3×2 (d, $^3J_{P,C}$=6.2 Hz), 26.8, 26.9, 27.4, 33.8 (d, $^1J_{P,C}$=134.3 Hz), 35.8, 37.3, 39.5×2, 54.2, 56.2, 62.8×2 (d, $^2J_{P,C}$=6.2 Hz), 67.3, 81.7, 96.6, 125.5, 130.5, 131.0, 144.6, 165.1 (d, $^2J_{P,C}$=5.0 Hz), 203.6; HRMS calcd for $C_{23}H_{39}O_8PS_2$ (M^+) 538.1824, found 538.1832.

To a cooled (0°C) solution of the crude **24** obtained above in toluene (80 mL) were added 18-crown-6 (3.50 g, 9.45 mmol) and K_2CO_3 (653 mg, 4.72 mmol). The mixture was stirred for 12 h, then 18-crown-6 (870 mg, 2.36 mmol) was added. The mixture was stirred for 1.5 h, then K_2CO_3 (162 mg, 1.17 mmol) was added. The mixture was stirred for an additional 5.5 h, diluted with saturated brine, and extracted with EtOAc. 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 2.27 g (80% from **23**) of **25** as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^{1}H NMR analysis); TLC, R_f 0.56 (acetone/hexane, 1:2); $[\alpha]^{19.5}_D=-32.8$ (*c* 1.85, $CHCl_3$); IR 1780, 1750, 1640 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.00 (s, 6H), 1.24–1.46 (m, 2H), 1.55–1.63 (m, 2H), 3.20–3.37 (m, 4H), 3.37 (s, 3H), 4.47 (br t, *J*=5.9 Hz, 1H), 4.62 (s, 2H), 4.80 (br d, *J*=1.8 Hz, 2H), 5.09 (d, *J*=9.1 Hz, 1H), 5.56 (d, *J*=15.4 Hz, 1H), 5.65 (dd, *J*=9.1, 14.8 Hz, 1H), 5.92 (dd, *J*=10.3, 15.4 Hz, 1H), 5.96–5.98 (m, 1H), 6.13 (dd, *J*=10.3, 14.8 Hz, 1H); ^{13}C NMR (75 MHz) δ 26.88, 26.93, 29.7, 35.8, 37.6, 39.5×2, 54.1, 55.9, 70.9, 73.1, 95.2, 116.4, 125.7, 130.7, 130.8, 144.2, 169.8, 173.2; HRMS calcd for $C_{19}H_{28}O_4S_2$ (M^+) 384.1429, found 384.1429.

3.1.10. 3-[(1*S*,5*E*,7*E*)-8-(1,3-Dithiolan-2-yl)-1-hydroxy-4,4-dimethyl-5,7-octadienyl]-2-buten-4-olide (26). To a cooled (0°C) solution of **25** (1.46 g, 3.80 mmol) in THF (35 mL) was added 4.0 M aqueous HCl (15 mL). The mixture was stirred for 97 h, diluted with saturated aqueous $NaHCO_3$, 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, 1:4 to 1:2) to provide 1.19 g (92%) of **26** and 93.9 mg (6%) of **25** was recovered. Compound **26** was obtained as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^{1}H NMR analysis); TLC, R_f 0.38 (EtOAc/hexane, 1:1); $[\alpha]^{26}_D=-6.4$ (*c* 1.71, $CHCl_3$); IR 3440, 1780, 1730, 1640 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.02 (s, 6H), 1.30–1.66 (m, 4H), 2.30 (br, 1H), 3.21–3.37 (m, 4H), 4.59 (br t, *J*=5.7 Hz, 1H), 4.85 (d, *J*=2.0 Hz, 2H), 5.09 (d, *J*=9.3 Hz, 1H), 5.58 (d, *J*=15.6 Hz, 1H), 5.65 (dd, *J*=9.3, 14.6 Hz, 1H), 5.93 (dd, *J*=10.3, 15.6 Hz, 1H), 5.95–5.97 (m, 1H), 6.13 (dd, *J*=10.3, 14.6 Hz, 1H); ^{13}C NMR (75 MHz) δ 26.9×2, 31.5, 35.8, 37.7, 39.5×2, 54.1, 68.8, 71.2, 114.7, 125.6, 130.6, 130.7, 144.4, 172.9, 174.0; HRMS calcd for $C_{17}H_{24}O_3S_2$ (M^+) 340.1167, found 340.1168.

3.1.11. 3-[(1*S*,5*E*,7*E*)-1-(Dimethylisopropyl)silyloxy-8-(1,3-dithiolan-2-yl)-4,4-dimethyl-5,7-octadienyl]-2-buten-4-olide (28). To a cooled (0°C) solution of **26** (521 mg, 1.53 mmol) in DMF (10 mL) were added imidazole (564 mg, 8.28 mmol) and dimethylisopropylchlorosilane (0.680 mL, 4.12 mmol). The mixture was stirred at 0°C for 50 min, diluted with EtOAc, and the whole was washed with H_2O. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:12) to provide 588 mg (87%) of **28** as a colorless oil (*E*,*E*-isomer/other isomers⇒20:1, determined by ^{1}H NMR analysis); TLC, R_f 0.50 (EtOAc/hexane, 1:3); $[\alpha]^{22}_D=-1.8$ (*c* 2.53, $CHCl_3$); IR 1780, 1750, 1645 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.05, 0.08 (2s, 3H×2), 0.73–0.89 (m, 1H), 0.96 (d, *J*=7.1 Hz, 3H), 0.97 (d, *J*=7.3 Hz, 3H), 0.99 (s, 6H), 1.25–1.35 (m, 2H), 1.48–1.56 (m, 2H), 3.20–3.38 (m, 4H), 4.58 (br t, 5.3 Hz, 1H), 4.79 (d, *J*=1.5 Hz, 2H), 5.09 (d, *J*=9.3 Hz, 1H), 5.55 (d, *J*=15.5 Hz, 1H), 5.64 (dd, *J*=9.3, 14.9 Hz, 1H), 5.88–5.90 (m, 1H), 5.90 (dd, *J*=10.4, 15.5 Hz, 1H), 6.13 (dd, *J*=10.4, 14.9 Hz, 1H); ^{13}C NMR (75 MHz) δ −4.0, −3.9, 14.6, 16.8×2, 26.9, 27.0, 32.4, 35.7, 37.2, 39.5×2, 54.2, 69.5, 70.9, 114.9, 125.6, 130.68, 130.74, 144.4, 172.8, 173.5; HRMS calcd for $C_{22}H_{36}O_3SiS_2$ (M^+) 440.1875, found 440.1869.

3.1.12. Diastereomeric mixture (13:7) of (1*S*,2*S*,6*S*,9*S*,10*S*)-(37A),(1*R*,2*S*,6*R*,9*R*,10*R*)-2-(dimethylisopropyl)-silyloxy-5,5-dimethyl-9-(1,3-dithiolan-2-yl)-12-oxatricyclo[8.3.0.0^{1,6}]tridec-7-en-11-one (37B). Compound **28** (577 mg, 1.31 mmol) was dissolved in degassed toluene (131 mL) and a crystal of 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added. The solution was transferred into **14** tubes of 20 mL sealed tube equipped with a screwed stopper. All the tubes were filled with argon. The tubes were heated to 210°C for 70 h. After being cooled to ambient temperature, the combined solutions were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to provide 466 mg (81%) of **37** as an inseparable diastereomeric mixture (the ratio of diastereomers, **37A/37B**/*exo*-isomers=ca. 13:7:1 was determined by ^{1}H NMR analysis). The mixture **37** as a colorless oil: TLC, R_f 0.47 (EtOAc/hexane, 1:4); IR 1765 cm^{-1}; ^{1}H NMR for the mixture of *endo* isomers **37A** and **37B** (300 MHz) δ 0.10 (s, 3H×7/20), 0.11 (s, 3H), 0.15 (s, 3H×13/20), 0.71–0.88 (m, 1H), 0.82 (s, 3H), 0.93 (s, 3H×7/13), 0.94 (s, 3H×7/20), 0.95 (s, 3H×7/20), 0.96 (s, 3H×13/20), 0.99 (s, 3H×13/20), 1.01 (s, 3H×13/20), 1.14–1.85 (m, 4H), 1.75 (br-s, 1H×7/20), 2.32 (br-s, 1H×13/20), 2.40–2.53 (m, 1H), 2.98 (d, *J*=7.6 Hz, 1H×7/20),

3.11–3.30 (m, 4H), 3.35 (d, J=7.3 Hz, 1H×13/20), 3.64 (dd, J=5.3, 10.6 Hz, 1H×7/20), 3.79 (d, J=8.8 Hz, 1H×7/20), 3.81 (br s, 1H×13/20), 3.88, 3.92 (ABq, J=9.5 Hz, 1H×2×13/20), 4.31 (d, J=8.8 Hz, 1H×7/20), 4.99 (d, J=11.7 Hz, 1H×13/20), 5.00 (d, J=11.2 Hz, 1H×7/20), 5.90–6.04 (m, 2H); ^{13}C NMR for the major *endo*-isomer **37A** (75 MHz) δ −4.0, −3.2, 15.0, 16.96, 17.02, 21.3, 25.8, 31.88, 31.94, 33.3, 38.0, 38.3, 43.0, 46.3, 48.7, 53.1, 53.7, 70.8, 72.7, 131.5, 132.1, 177.5; for the minor *endo*-isomer **37B** δ −3.8, −3.1, 14.8, 16.66, 16.71, 21.3, 28.2, 31.3, 31.94, 38.3, 38.4×2, 45.8, 48.2, 50.2, 53.5, 53.7, 70.2, 76.6, 131.7, 131.8, 177.1; HRMS calcd for $C_{22}H_{36}O_3SiS_2$ (M^+) 440.1875, found 444.1876.

3.1.13. Diastereomeric mixture (13:7) of (1*S*,2*S*,6*S*,9*S*,10*S*)-(35A), (1*R*,2*S*,6*R*,9*R*,10*R*)-2-hydroxy-5,5-dimethyl-9-(1,3-dithiolan-2-yl)-12-oxatricyclo[8.3.0.0^{1,6}]tridec-7-en-11-one (35B). To a cooled (0°C) solution of the 13:7 diastereomeric mixture **37** (104 mg, 0.235 mmol) in THF (2 mL) was added TBAF (0.35 mL of 1.0 M solution in THF, 0.35 mmol). The mixture was stirred at 0°C for 15 min and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:5) to provide 73.6 mg (92%) of **35** as a diastereomeric mixture (the ratio of diastereomers, **35A/35B**/*exo* isomers=ca. 13:7:1, was determined by ^{1}H NMR analysis). The mixture **35** as amorphous solids; TLC, R_f 0.68 for isomer **35A**, *Rf*0.62 for isomer **35B** (EtOAc/hexane, 1:1); IR 3450, 1760, 1750 cm^{-1}; ^{1}H NMR for the mixture of *end* isomers **35A** and **35B** (300 MHz) δ 0.83 (s, 3H), 0.95 (s, 3H×7/20), 0.98 (s, 3H×13/20), 1.23–1.90 (m, 4H), 1.82 (br-s, 1H×7/20), 2.31 (br-s, 1H×13/20), 2.49–2.56 (m, 1H), 3.17 (d, J=7.8 Hz, 1H×7/20), 3.25 (br-s, 4H), 3.51 (d, J=7.6 Hz, 1H×13/20), 3.71 (dd, J=4.8, 11.1 Hz, 1H×7/20), 3.83 (d, J=9.0 Hz, 1H×7/20), 3.89, 3.94 (ABq, J=9.5 Hz, 1H×2×13/20), 3.90 (br s, 1H×13/20), 4.32 (d, J=9.0 Hz, 1H×7/20), 4.98 (d, J=11.2 Hz, 1H×7/20), 4.99 (d, J=11.2 Hz, 1H×13/20), 5.96–6.05 (m, 2H); ^{13}C NMR for the major *endo*-isomer **35A** (75 MHz) δ 21.2, 26.2, 31.8, 32.13, 33.2, 38.3, 38.5, 42.8, 46.1, 48.3, 52.4, 53.7, 69.5, 73.1, 131.6, 131.9, 177.8; for the minor *endo*-isomer **35B** δ 21.4, 28.1, 31.3, 32.08, 38.4, 38.5×2, 45.7, 48.1, 49.8, 53.3, 53.6, 70.0, 75.7, 131.7, 131.8, 177.5; HRMS calcd for $C_{17}H_{24}O_3S_2$ (M^+) 340.1167, found 340.1160.

3.1.14. (1*S*,2*S*,6*S*,9*S*,10*S*)-(43A) and (1*R*,2*S*,6*R*,9*R*,10*R*)-2-hydroxy-9-(dimethoxy)methyl-5,5-dimethyl-12-oxatricyclo[8.3.0.0^{1,6}]tridec-7-en-11-one (43B). To a cooled (0°C) solution of the diastereomeric mixture **35** (73.6 mg, 0.216 mmol) in a mixture of MeOH and $CHCl_3$ (3:1 v/v, 6.5 mL) were added $CaCO_3$ (324 mg, 3.24 mmol) and $Hg(ClO_4)_2{\cdot}3H_2O$ (267 mg, 0.589 mmol). The mixture was stirred at 0°C for 20 h and diluted with 10 wt% aqueous KI. This was extracted with $CHCl_3$, and the organic layers were combined. The resulting inorganic precipitates were filtered off and washed well with $CHCl_3$. The combined filtrate and washings were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:6 to 1:4) to provide 29.6 mg (44%) of **43A** and 16.8 mg (25%) of **43B**. Compound **43A** as amorphous solids; mp 170–171°C (decomp.); TLC, R_f 0.35 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$=+50.0 (c 1.37, $CHCl_3$); IR (KBr disk) 3460, 1740 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.83, 0.99 (2s, 3H×2), 1.18–1.30 (m, 1H), 1.65–2.13 (m, 4H), 2.26–2.32 (m, 1H), 2.57–2.67 (m, 1H), 3.32 (d, J=8.5 Hz, 1H), 3.36, 3.50 (2s, 3H×2), 3.86 (br s, 1H), 3.90, 3.97 (ABq, J=9.4 Hz, 1H×2), 4.88 (d, J=7.8 Hz, 1H), 5.98 (dt, J=3.1, 9.4 Hz, 1H), 6.06 (dt, J=2.8, 9.4 Hz, 1H); ^{13}C NMR (75 MHz) δ 21.2, 26.1, 31.7, 32.2, 33.3, 39.2, 42.7, 45.3, 51.4, 53.1, 54.9, 69.3, 72.9, 103.1, 128.5, 131.2, 178.0; HRMS calcd for $C_{17}H_{26}O_5$ (M^+) 310.1780, found 310.1782. Compound **43B** as a colorless oil; TLC, R_f 0.39 (EtOAc/toluene, 1:1); $[\alpha]^{26}_D$=+28.7 (c 2.38, $CHCl_3$); IR 3450, 1760 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.83, 0.95 (2s, 3H×2), 1.35 (br dt, J=4.2, 13.5 Hz, 1H), 1.52 (br dt, J=3.4, 13.5 Hz, 1H), 1.61–1.83 (m, 3H), 1.87 (br, 1H), 2.53–2.61 (m, 1H), 2.99 (d, J=8.3 Hz, 1H), 3.39, 3.55 (2s, 3H×2), 3.66 (dd, J=5.0, 11.1 Hz 1H), 3.84 (d, J=9.2 Hz, 1H), 4.29 (d, J=9.2 Hz, 1H), 4.88 (d, J=8.3 Hz, 1H), 5.99 (dt, J=3.3, 9.3 Hz, 1H), 6.07 (dt, J=2.9, 9.3 Hz, 1H); ^{13}C NMR (75 MHz) δ 21.4, 28.1, 31.2, 32.1, 38.5, 39.2, 47.1, 48.2, 52.2, 53.2, 55.7, 70.0, 75.9, 103.3, 128.8, 131.4, 177.9; HRMS calcd for $C_{17}H_{26}O_5$ (M^+) 310.1780, found 310.1781.

3.1.15. (1*S*,2*S*,6*S*,9*S*,10*S*)-9-(Dimethoxy)methyl-2-(methoxymethoxy)-5,5-dimethyl-12-oxatricyclo[8.3.0.0^{1,6}]tridec-7-en-11-one (44). To a cooled (0°C) solution of **43A** (96.2 mg, 0.310 mmol) in CH_2Cl_2 (2 mL) were added DIPEA (0.870 mL, 4.99 mmol) and MOMCl (0.190 mL, 2.50 mmol). The mixture was stirred at 40°C for 19 h and diluted with saturated aqueous NH_4Cl. This was extracted with CH_2Cl_2. The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to provide 93.5 mg (85%) of **44** as a colorless oil; TLC, R_f 0.52 (EtOAc/hexane, 2:3); $[\alpha]^{23.5}_D$=+55.1 (c 1.27, $CHCl_3$); IR 1770 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.84, 0.98 (2s, 3H×2), 1.20–1.31 (m, 1H), 1.60–1.94 (m, 3H), 2.25 (br s, 1H), 2.56–2.64 (m, 1H), 3.22 (d, J=8.1 Hz, 1H), 3.38, 3.44, 3.52 (3s, 3H×3), 3.68 (br s, 1H), 3.91, 3.97 (ABq, J=9.5 Hz, 1H×2), 4.64, 4.77 (ABq, J=7.0 Hz, 1H×2), 4.90 (d, J=7.8 Hz, 1H), 5.97 (dt, J=3.3, 9.4 Hz, 1H), 6.06 (dt, J=2.9, 9.4 Hz, 1H); ^{13}C NMR (75 MHz) δ 21.4, 22.2, 31.7, 32.0, 33.7, 39.5, 43.5, 45.5, 51.0, 53.4, 55.3, 56.2, 72.7, 75.8, 95.6, 103.3, 128.8, 131.0, 177.7; HRMS calcd for $C_{19}H_{30}O_6$ (M^+) 354.2042, found 354.2042.

3.1.16. Diastereomeric mixture of (1*R*,2*S*,6*S*,9*S*,10*S*,13*R* and 13*S*)-9-(dimethoxy)methyl-13-hydroxy-2-(methoxymethoxy)-5,5-dimethyl-12-oxatricyclo[8.3.0.0^{1,6}]tridec-7-en-11-one (45). To a stirred solution of **44** (107 mg, 0.302 mmol) in *t*-BuOH (0.5 mL) were added 1.0 M aqueous KOH (1.5 mL) and a 0.015 M solution of Na_2RuO_4 in 1 M aqueous NaOH (38.8 mL, 0.582 mmol). The mixture was stirred at 80°C for 14 h, cooled to 0°C, and quenched with 2-propanol. The resulting 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. This was extracted with CH_2Cl_2. The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 113 mg (100%) of **45** as a colorless

oil (the ratio of diastereomers, ca. 5:3, was determined by ^{1}H NMR analysis); TLC, R_f 0.56 (EtOAc/hexane, 1:1); IR 3350, 1770 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.97 (s, 3H), 1.01 (s, 3H×3/8), 1.07 (s, 3H×5/8), 1.22–1.34 (m, 1H), 1.54–1.96 (m, 1H), 2.12–2.27 (m, 1H), 2.24 (br s, 1H×5/8), 2.33 (br q, J=3.1 Hz, 1H×5/8), 2.55–2.64 (m, 1H×5/8), 2.81–2.90 (m, 1H×3/8), 3.37, 3.40, 3.50 (3s, 3H×3×3/8), 3.40, 3.45, 3.51 (3s, 3H×3×5/8), 3.36–3.49 (m, 1H+1H×3/8), 4.06 (br s, 1H×5/8), 4.22 (br d, J=12.9 Hz, 1H×3/8), 4.61, 4.74 (ABq, J=6.6 Hz, 1H×2×3/8), 4.63, 4.76 (ABq, J=6.8 Hz, 1H×2×5/8), 4.66 (d, J=3.1 Hz, 1H×3/8), 4.98 (d, J=9.0 Hz, 1H×5/8), 5.41 (br d, J=12.9 Hz, 1H×3/8), 5.49 (s, 1H×5/8), 5.95 (dt, J=3.1, 9.0 Hz, 1H×5/8), 5.99–6.06 (m, 1H), 6.19 (dt, J=2.9, 10.3 Hz, 1H×3/8); ^{13}C NMR (75 MHz) for the major isomer; δ 20.7, 23.8, 32.4, 34.1, 34.5, 40.9, 44.6, 49.6, 52.0, 53.6, 54.8, 56.1, 73.9, 95.4, 100.2, 103.2, 129.6, 130.8, 176.5; HRMS calcd for $C_{19}H_{30}O_7$ (M^+) 370.1992, found 370.1992.

3.1.17. Diastereomeric mixture of (1*R*,2*S*,6*S*,9*S*,10*S*, 11*R* and 11*S*,13*R* and 13*S*)-9-(dimethoxy)methyl-2-(methoxymethoxy)-5,5-dimethyl-12-oxatricyclo[8.3.0.0^{1,6}]tridec-7-en-11,13-diol (46). The following reaction was carried out under argon. To a cooled (−78°C) solution of the mixture **45** (76.4 mg, 0.206 mmol) in toluene (1 mL) was added DIBALH (0.62 mL, 1.0 M in toluene, 0.62 mmol). The mixture was stirred at −78°C for 25 min and quenched with H_2O. The resulting gels were filtered off and washed well with CH_2Cl_2. The filtrate and washings were combined and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4 to acetone/hexane, 2:1) to provide 33.9 mg (44%) of **46** as an inseparable diastereomeric mixture, 18.4 mg (21%) of **44** and 16.4 mg (21%) of **45** was recovered. The diastereomeric mixture **46** as a colorless oil; TLC, R_f 0.48 (acetone/toluene, 1:1); IR 3420 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD, δ 3.30) δ 0.92–1.07 (m, 6H), 1.17–1.88 (m, 4H), 2.12–2.52 (m, 2H), 2.88–4.24 (m, 11H), 4.55–5.37 (m, 5H), 5.67–6.14 (m, 2H); HRMS (FAB) calcd for $C_{19}H_{31}O_7$ (M^+−H) 371.2070, found 371.2069.

3.1.18. Diastereomeric mixture (9:1) of (1*R*,2*S*,6*S*,9*S*, 10*S*,12*S*,14*R* and 14*S*,15*S*)-10-methoxy-2-(methoxymethoxy)-5,5-dimethyl-11,13-dioxatetracyclo[10.2.1.0^{1,6}.0^{9,15}]pentadec-7-en-14-ol (47). To a cooled (0°C) solution of the diastereomeric mixture **46** (23.3 mg, 62.6 μmol) in a mixture of THF and H_2O (4:1, 0.5 mL) was added *p*-toluenesulfonic acid monohydrate (TsOH) (10.4 mg, 54.7 μmol). The mixture was stirred for 2 h then TsOH (7.2 mg, 38 μmol) was added. The mixture was stirred for an additional 30 min and diluted with saturated aqueous $NaHCO_3$. This was extracted with CH_2Cl_2. The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/hexane, 1:14) to provide 9.2 mg (43%) of **47** as a colorless oil (the ratio of diastereomers, ca. 9:1, was determined by ^{1}H NMR analysis); TLC, R_f 0.53 (EtOAc/toluene, 1:1); IR 3420 cm^{-1}; ^{1}H NMR for the major isomer (300 MHz) δ 0.95, 1.01 (2s, 3H×2), 1.20–1.29 (m, 1H), 1.57–1.84 (m, 3H), 2.46–2.50 (m, 1H), 2.70–2.78 (m, 1H), 3.41, 3.42 (2s, 3H×2), 3.62 (dd, J=6.0, 11.0 Hz, 1H), 3.62–3.68 (m, 1H), 4.63, 4.75 (ABq, J=6.8 Hz, 1H×2), 4.94 (d, J=2.4 Hz, 1H), 5.19 (br d, J=9.8 Hz, 1H), 5.85 (d, J=6.0 Hz, 1H), 5.96 (dt, J=2.9, 9.9 Hz, 1H), 6.20 (dt, J=2.7, 9.9 Hz, 1H); ^{13}C NMR for the major isomer (67.5 MHz) δ 22.4, 23.3, 31.2, 32.2, 34.4, 41.4, 43.8, 45.8, 53.3, 55.5, 56.1, 75.4, 96.0, 103.9, 108.0, 109.6, 128.2, 132.6; HRMS calcd for $C_{18}H_{28}O_6$ (M^+) 340.1886, found 340.1882.

3.1.19. (1*R*,2*S*,6*S*,9*S*,10*S*,12*R*,15*S*)-10-Methoxy-2-(methoxymethoxy)-5,5-dimethyl-11,13-dioxatetracyclo[10.2.1.0^{1,6}.0^{9,15}]pentadec-7-en-14-one (48). To a stirred solution of **47** (10.9 mg, 32.0 μmol) in DMSO (1 mL) was added Ac_2O (1 mL). The mixture was stirred for 6 h and concentrated in vacuo with the aid of toluene. The residue was diluted with EtOAc and washed with brine. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to provide 8.6 mg (80%) of **48** as a colorless oil; TLC, R_f 0.47 (EtOAc/hexane, 1:2); $[\alpha]^{22}_D$=+129 (*c*0.39, $CHCl_3$); IR 1780 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.98, 1.28 (2s, 3H×2), 1.32 (dt, J=3.4, 13.4 Hz, 1H), 1.56–1.71 (m, 1H), 1.79 (dq, J=3.4, 14.8 Hz, 1H), 1.98–2.12 (m, 1H), 2.15–2.18 (m, 1H), 2.68–2.76 (m, 1H), 3.44 (s, 6H), 3.72 (br s, 1H), 3.80 (dd, J=5.4, 10.6 Hz, 1H), 4.67, 4.79 (ABq, J=6.8 Hz, 1H×2), 5.10 (d, J=2.0 Hz, 1H), 5.80 (dt, J=2.5, 9.6 Hz, 1H), 5.94 (d, J=5.4 Hz, 1H), 6.05 (dt, J=3.5, 9.6 Hz, 1H); ^{13}C NMR (67.5 MHz) δ 22.0, 22.3, 31.8, 33.1, 33.5, 42.4, 42.6, 47.0, 55.9, 56.0, 56.2, 72.6, 95.5, 104.0, 111.6, 126.7, 132.3, 174.1; HRMS calcd for $C_{18}H_{26}O_6$ (M^+) 338.1729, found 338.1732.

3.1.20. Mniopetal F (6). To a solution of **48** (8.6 mg, 25 μmol) in THF (1 mL) was added 6.0 M aqueous HCl (1 mL). The mixture was stirred for 44 h, diluted with H_2O, and extracted with $CHCl_3$. The combined extracts were dried and concentrated in vacuo. The residue was dissolved in toluene (1.5 mL) and Et_3N (25 μL, 0.18 mmol) was added. The solution was stirred for 20 h and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene/AcOH, 10:100:1) to provide 5.9 mg (83%) of **6** as a colorless oil; TLC, R_f 0.38 (acetone/toluene/AcOH, 30:70:1), $[\alpha]^{23}_D$=−55.6 (*c* 0.24, MeOH); IR 3430, 1750, 1680, 1650 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD, δ 3.30) δ 0.99, 1.23 (2s, 3H×2), 1.18–1.27 (m, 1H), 1.61 (dq, J=3.4, 13.9 Hz, 1H), 1.69 (dd, J=3.4, 12.7 Hz, 1H), 1.85 (dt, J=2.7, 13.7 Hz, 1H), 2.03–2.20 (m, 2H), 2.50 (ddd, J=3.4, 6.6, 19.0 Hz, 1H), 3.67 (br s, 1H), 4.36 (br s, 1H), 5.36 (s, 1H), 7.21 (d, J=6.6 Hz, 1H), 9.42 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD, δ 49.0) δ 23.1, 26.1, 26.4, 33.1, 33.8, 34.1, 41.6, 47.8, 54.1, 68.6, 101.5, 140.4, 156.5, 179.2, 195.3; HRMS calcd for $C_{15}H_{20}O^5$ (M^+) 280.1311, found 280.1310.

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