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Synthetic Studies on Biscembranoids. Asymmetric Total Synthesis of the 14-Membered Diene Unit of Methyl Sarcophytoate#

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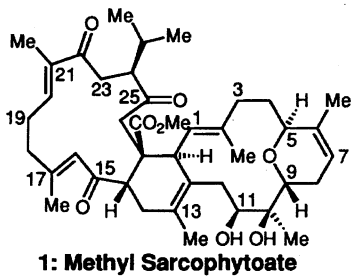
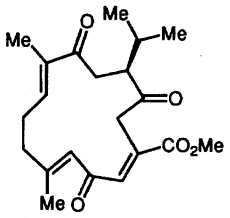
An asymmetric total synthesis of the 14-membered diene unit, (1*S*,2*S*,4*E*,6*E*,10*S*,11*Z*,14*R*)-10,14-epoxy-4-isopropenyl-1,7,11-trimethyl-4,6,11-cyclotetradecatriene-1,2-diol (**3**), of methyl sarcophytoate (**1**) has been achieved. Methyl ketone, (3*S*,4*S*)-3,4-(isopropylidenedioxy)-3,7-dimethyl-6-octen-2-one (**6**), was enantioselectively prepared from geraniol via Sharpless asymmetric epoxidation and a regioselective epoxide-opening reaction. The aldol coupling between the lithium enolate of **6** and aldehyde, (2*E*,6*E*)-2,6-dimethyl-8-(2,2-dimethylpropanoyloxy)-2,6-octadienal (**7**), which was also prepared from geraniol, gave a 1 : 1 separable mixture of the adducts (**17** and **18**). Reduction of the carbonyl group in **17** and **18**, followed by regioselective oxidation of the allylic hydroxy group, afforded α,β-unsaturated ketone, (2*E*,6*E*,10*R*,11*R*,12*S*)-1-(2,2-dimethylpropanoyloxy)-10-hydroxy-11,12-(isopropylidenedioxy)-3,7,11,15-tetramethyl-2,6,14-hexadecatrien-8-one (**5**). The intramolecular oxy-Michael addition of **5** followed by regioselective enol triflation and deoxygenation gave dihydropyran, (2*E*,6*S*,7*Z*,10*R*,11*R*,12*S*)-1-(2,2-dimethylpropanoyloxy)-6,10-epoxy-11,12-(isopropylidenedioxy)-3,7,11,15-tetramethyl-2,7,14-hexadecatriene (**31**). The regioselective epoxidation of **31** and a subsequent functional-group transformation gave (2*E*,6*S*,7*Z*,10*R*,11*R*,12*S*,14*RS*)-6,10 : 14,15-diepoxy-11,12-(isopropylidenedioxy)-3,7,11,15-tetramethyl-1-(phenylthio)-2,7-hexadecadiene (**4**). The 14-membered ring formation was achieved by the treatment of **4** with the *n*-BuLi–Bu_2Mg complex to give (1*Z*,3*S*,6*E*,8*RS*,9*RS*,11*S*,12*R*,13*R*)-3,13-epoxy-9-(1-hydroxy-1-methylethyl)-11,12-(isopropylidenedioxy)-2,6,12-trimethyl-8-(phenylthio)-1,6-cyclotetradecadiene (**33**), which was transformed to **3** through triene construction and deacetonidation.

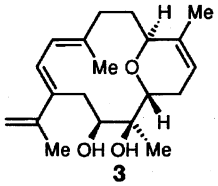
Methyl sarcophytoate (**1**) was isolated from the Okinawan soft coral *Sarcophyton glaucum*, and exhibits cytotoxic activities against KB cells.[1] It belongs to biscembranoids (tetraterpenoids) and four other members, methyl chlorosarcophytoate,[1] methyl isosartortuoate,[2] methyl sartortuoate,[3] and methyl neosartortuate acetate[4] have been identified so far. Biogenetically, they are considered to be formed by a Diels–Alder reaction of two cembranes (e.g. **2** and **3**) (Fig. 1).[1—4] Methyl sarcoate (**2**) is the common dienophile unit of methyl sarcophytoate (**1**), methyl chlorosarcophytoate, and methyl neosartortuate acetate, and has been isolated from the same coral;[4,5] however, diene units have not been isolated, except for the diene unit of methyl neosartortuate acetate, probably because of their highly reactive nature.[4] The absolute configuration of **1** was elucidated by the difference CD spectrum.[6] We have been interested in synthesizing these biscembranoids, and recently reported on model studies of the intermolecular Diels–Alder reaction of a 14-membered diene–dienophile pair.[7] In this full article[8] we wish to describe the total synthesis of the 14-membered diene unit **3** of **1** based on Sharpless asymmetric epoxidation, the aldol reaction, intramolecular oxy-Michael addition, and modified Ito–Kodama cyclization as the key steps; all of the carbon skeleton of **3** was derived from only geraniol.



1: Methyl Sarcophytoate



2: Methyl Sarcoate



3

Fig. 1.

Dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.

Results and Discussion

Synthetic Plan. Figure 2 reveals a plan for the synthesis of **3**. We anticipated that the crucial cyclization to secure the 14-membered ring would be realized by using the Ito–Kodama cyclization[9] of epoxy allyl sulfide **4**. The dihydropyran portion of **4** would be obtained by the intramolecular oxy-Michael addition[10] of α,β-unsaturated ketone **5**, followed by regioselective double-bond construction. The α,β-unsaturated ketone **5** would be obtained by the aldol reaction of ketone **6** and aldehyde **7**, followed by a stereoselective reduction of the carbonyl group of the aldol adducts and regioselective oxidation of the allylic hydroxy group of the resulting diol. Ketone **6** was derived from geraniol via Sharpless asymmetric epoxidation[11] in an enantioselective manner. Aldehyde **7** was also prepared from geraniol by the well-known regioselective oxidation.[12]

Synthesis of Ketone 6. The synthesis of the C8—C14[13] portion **6** of **3** began with the known epoxide **8** (91%ee), which was derived from geraniol by Sharpless asymmetric epoxidation[11] (Scheme 1). Epoxide-ring opening was first attempted under Noyori's conditions:[14] the treatment of **8**

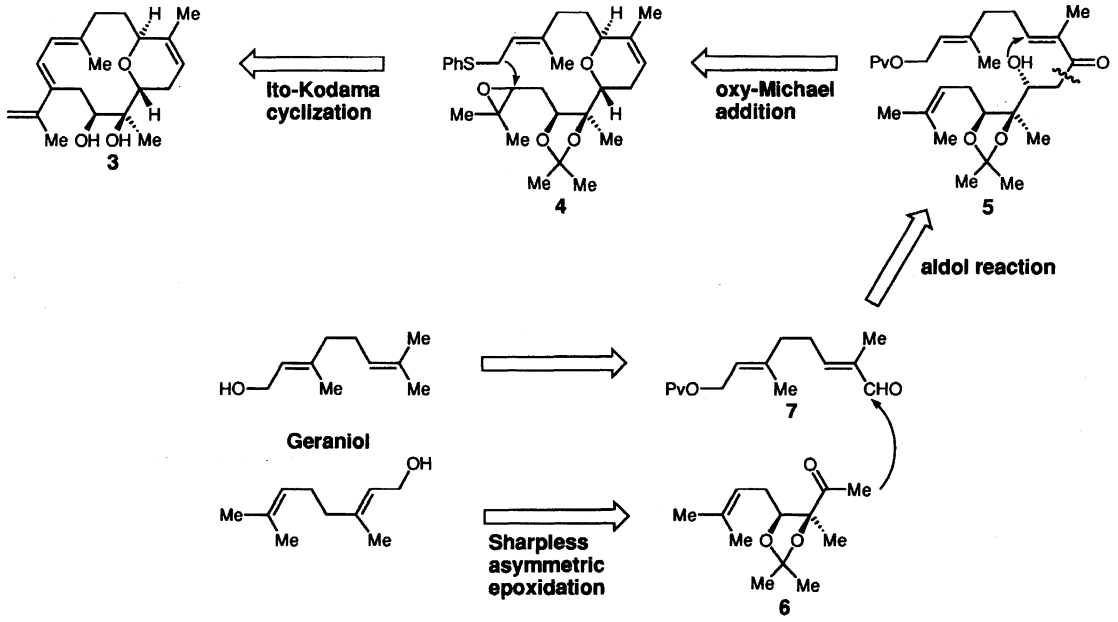
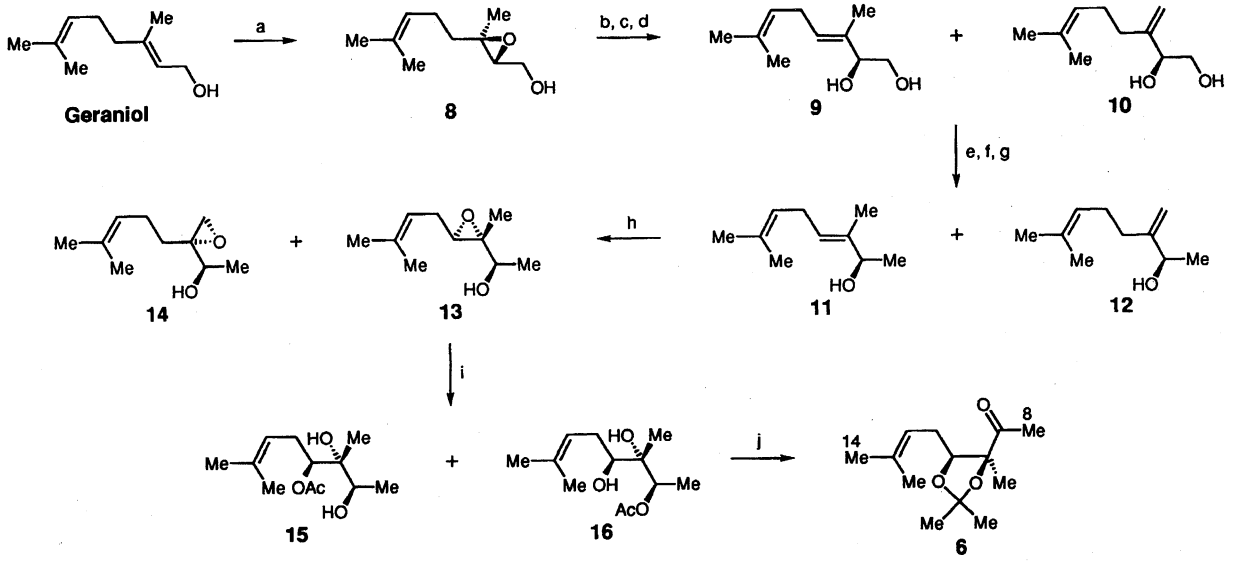


Fig. 2.

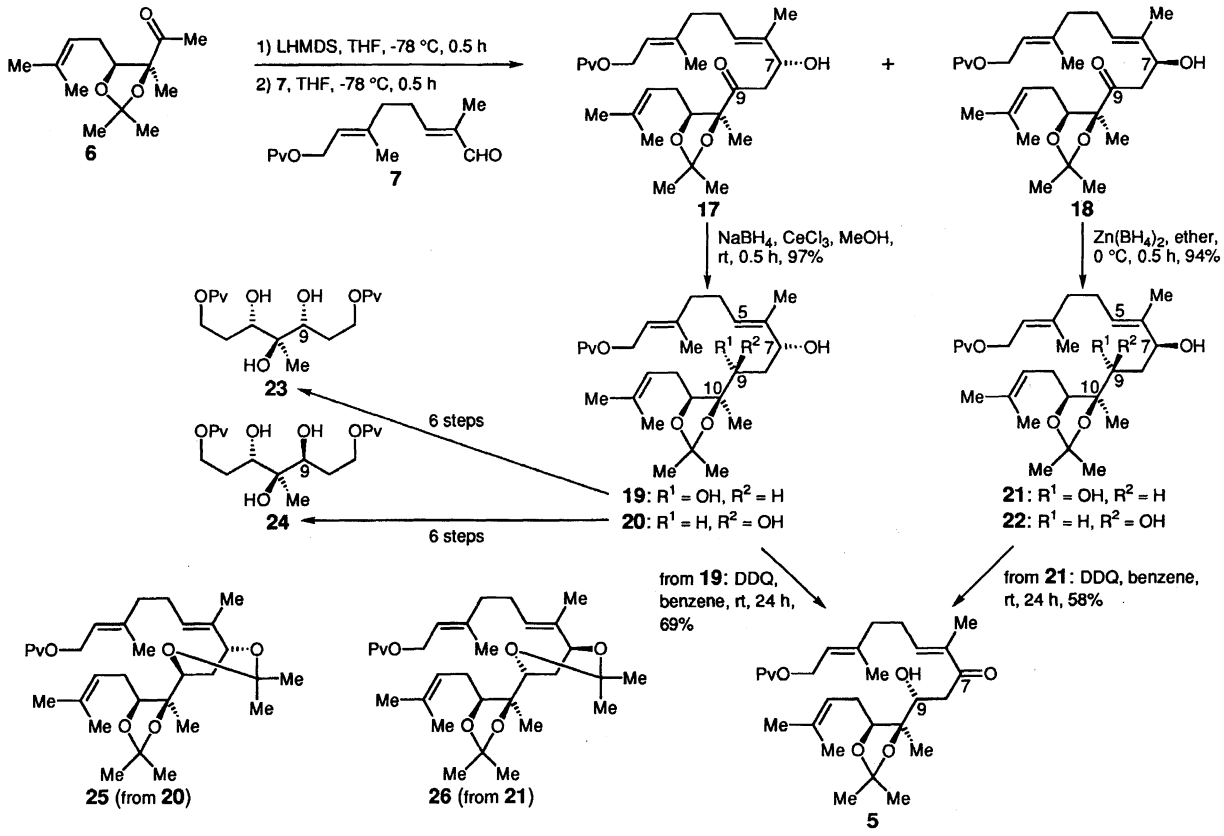


(a) TBHP, (-)-DET, $(i\text{-PrO})_4$Ti, MS 4AP, CH_2Cl_2, -30 °C, 2 h, 96%; (b) TMSCl, Et_3N, DMF, rt, 1 h; (c) TMSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 3 h, then DBU, rt, 60 h; (d) excess KF, 4:1 MeOH-H_2O, rt, 3 h; (e) TsCl, Et_3N, CH_2Cl_2, rt, 3 h; (f) *n*-BuLi, THF, -78 °C, 0.5 h; (g) $LiAlH_4$, 0 °C, 1 h, 69% from **8**; (h) TBHP/2,2,4-trimethylpentane, (-)-DIPT, $(i\text{-PrO})_4$Ti, MS 4AP, CH_2Cl_2, -30 °C, 2 h, 65%; (i) NH_4OAc, $(i\text{-PrO})_4$Ti, THF, rt, 15 h, 50% for **15**, 23% for **16**; (j) from **15**: (1) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 0.5 h, then Et_3N, -78 to 0 °C, 1 h; (2) NaOMe, MeOH, rt, 1 h; (3) DMP, CSA, CH_2Cl_2, rt, 0.5 h, 86% for three steps. from **16**: (1) DMP, PPTS, CH_2Cl_2, rt, 0.5 h; (2) DIBALH, CH_2Cl_2, -78 °C, 0.5 h; (3) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 0.5 h, then Et_3N, -78 to 0 °C, 1 h, 82% for three steps.

Scheme 1.

with 2 molar amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 2,6-lutidine at −78 °C, and then DBU at r.t. However, in a large-scale preparation, effective stirring of the reaction mixture was difficult due to a large amount of precipitates. Therefore, an alternative two-step procedure was chosen. Namely, the primary alcohol in **8** was silylated with 1.2 molar amounts of chlorotrimethylsilane (TMSCl) and 1.8 molar amounts of triethylamine in DMF. After a workup, the resulting silyl ether was treated with 1.2 molar amounts of TMSOTf and 1.7 molar amounts of 2,6-lutidine in CH_2Cl_2 at −78 °C, and then DBU at r.t. An excess KF workup afforded a 7 : 1 inseparable mixture of **9** and **10**.[14,15] In the original report,[14] the authors did not describe the presence of the exomethylene compound **10**. Selective tosylation of the primary hydroxy group in this mixture with *p*-toluenesulfonyl chloride (TsCl) and triethylamine in CH_2Cl_2 and subsequent epoxidation with *n*-BuLi in THF followed by the epoxide-ring opening with $LiAlH_4$ afforded an inseparable mixture of **11** and **12** in 69% yield from **8**. This mixture was subjected to Sharpless asymmetric epoxidation[11] using diisopropyl D-tartrate ((−)-DIPT), titanium(IV) isopropoxide, and *t*-butyl hydroperoxide (TBHP) in 2,2,4-trimethylpentane to afford an inseparable mixture of **13** and **14** in 65% yield. As anticipated from a kinetic resolution (a matched pair),[11] the enantiomeric excess of **13** was determined to be > 98% by ^{1}H NMR analysis of the (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA esters)[16] of a mixture of **13** and **14**. The epoxide-ring opening of a mixture of **13** and **14** by ammonium acetate in the presence of titanium(IV) isopropoxide[17] gave, after silica-gel column chromatography, diol **15** and its acetyl-migration product **16** in 50 and 23% yields, respectively, along with as-yet-unidentified by-products derived mainly from **14**. Diol **15** could be easily converted to the desired C8—C14 portion **6** by the following three-step sequence: 1) Swern oxidation; 2) deacetylation with NaOMe in MeOH; 3) acetonidation with 2,2-dimethoxypropane (DMP) and *d*-10-camphorsulfonic acid (CSA) in CH_2Cl_2, in 86% overall yield. Diol **16**, as well as **15**, could be converted to the same ketone **6** by acetonidation, deacetylation (diisobutylaluminium hydride (DIBALH) in CH_2Cl_2), and Swern oxidation in 82% overall yield.

Synthesis of α,β-Unsaturated Ketone 5. We chose aldehyde **7** as the remaining carbon skeleton required for the synthesis of **3**. Aldehyde **7** was obtained[12] in 37% overall yield from geranyl acetate by successive oxidation with SeO_2–TBHP and pyridinium dichromate (PDC) followed by a protecting-group change from the acetyl group to 2,2-dimethylpropanoyl (pivaloyl, Pv) group (NaOMe in MeOH and PvCl, triethylamine in CH_2Cl_2) (Scheme 2). Direct oxidation of geranyl pivaloate (2,2-dimethylpropanoate) under the above oxidation conditions resulted in a low yield. The aldol reaction was realized by the lithiation of **6** with lithium bis(trimethylsilyl)amide in THF at −78 °C followed by the addition of the above aldehyde **7**, giving a separable 1 : 1 mixture of the aldol adducts **17** and **18** in 72% combined yield. The C7-stereochemistry in **17** and **18** was established

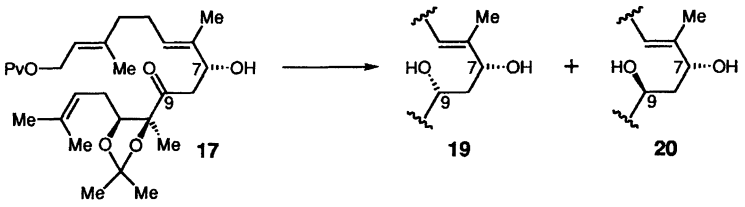


Scheme 2.

by conversion to acetonides **25** and **26** via **20** and **21**, respectively (vide infra).

To construct the C9-stereocenter, a stereoselective reduction of the carbonyl group was examined. A variety of reduction conditions were attempted, and some examples are displayed in Tables 1 and 2. Reduction of the separated adduct **17** with $NaBH_4$ in the presence of $CeCl_3$ in MeOH[18] gave a separable 1.2 : 1 mixture of the desired diol **19** and the undesired diol **20** in 53 and 44% yields, respectively (Entry 6, Table 1). The newly formed C9-stereocenter was verified by ^{1}H NMR analysis of the degradation products **23** (*meso*-compound) and **24** derived from **19** and **20**, respectively: 1) ozonolysis; 2) $NaBH_4$ reduction; 3) oxidative scission with $NaIO_4$; 4) $NaBH_4$ reduction; 5) protection as bis(pivaloate); 6) deacetonidation, 20% overall yield (see Experimental). On the other hand, reduction of the adduct **18** with $Zn(BH_4)_2$ in ether[19] gave a separable 1 : 1 mixture of **21** and **22** in 94% combined yield (Entry 1, Table 2). The stereochemical assignment of the C9-stereocenter in **21** was confirmed by its transformation to ketone **5** (vide infra). The stereochemistry of the C7-stereocenter in **20** was established by ^{1}H NMR analysis of its acetonide **25**: $J_{7,8}$ = 2.0 and 11.8 Hz, $J_{8,9}$ = 2.0 and 11.2 Hz. The stereochemistry of the C7-stereocenter in **21** was also established by ^{1}H NMR analysis of its acetonide **26**: $J_{7,8}$ = 3.0 and 10.8 Hz, $J_{8,9}$ = 3.0 and 11.2 Hz. These results confirm the C7-stereocenter in **17** and **18**. The

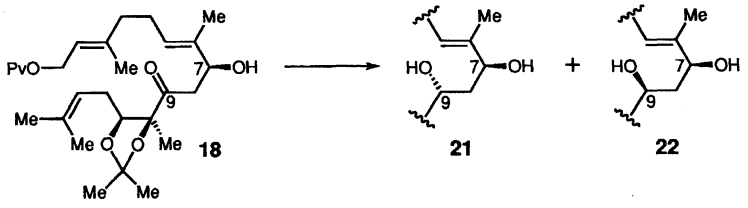
Table 1. Reduction of the Carbonyl Group in **17**



Entry	Reductant (molar amt.)	Solvent	Temp/°C	Time/h	Ratio[a] **19/20**
1	$Zn(BH_4)_2$ in ether (2)	Ether	0	1	0 : 100
2	$LiAlH_4$ (1)	THF	0	0.5	1 : 6.8
3	DIBALH in CH_2Cl_2 (5)	CH_2Cl_2	−78	2	1 : 40[b]
4	$LiBH_4$ (3)	MeOH	R.T.	5	1 : 8.3
5	$NaBH_4$ (2)	MeOH	R.T.	2	1 : 13
6	$NaBH_4$ (2), $CeCl_3$ (2)	MeOH	R.T.	0.5	1.2 : 1
7	$Me_4NBH(OAc)_3$ (3)[c]	CH_3CN–AcOH	0	4	1.5 : 1[d]
8	$LiBH(s\text{-}Bu)_3$ in THF (3)	THF	0	3	0 : 100

a) Product ratio was based on ^{1}H NMR analysis of the crude products after usual workup. All reactions proceeded cleanly without decomposition (checked by TLC). b) Product ratio as the depivaloylation products. c) D. A. Evans and K. T. Chapman, *Tetrahedron Lett.*, **27**, 5939 (1986); D. A. Evans, K. T. Chapman, and E. M. Carreira, *J. Am. Chem. Soc.*, **110**, 3560 (1988). d) Compound **17** remained.

Table 2. Reduction of the Carbonyl Group in **18**



Entry	Reductant (molar amt.)	Solvent	Temp/°C	Time/h	Ratio[a] **21/22**
1	$Zn(BH_4)_2$ in ether (2)	Ether	0	0.5	1 : 1
2	$Zn(BH_4)_2$ in ether (2)	THF	0	1	1 : 2.3
3	$Zn(BH_4)_2$ in ether (2)	DME	0	1	1 : 4.2
4	$LiAlH_4$ (1)	THF	0	0.5	1 : 2.0
5	DIBALH in CH_2Cl_2 (5)	CH_2Cl_2	−78	2	1 : 5.9[b]
6	$LiBH_4$ (3)	MeOH	R.T.	5	1 : 14
7	$NaBH_4$ (2)	MeOH	R.T.	2	1 : 6.7
8	$NaBH_4$ (2), $CeCl_3$ (2)	MeOH	R.T.	2	0 : 100
9	$Me_4NBH(OAc)_3$ (3)	CH_3CN–AcOH	0	4	0 : 100
10	$LiBH(s\text{-}Bu)_3$ in THF (3)	THF	0	3	0 : 100

a) Product ratio was based on ^{1}H NMR analysis of the crude products after usual workup. All reactions proceeded cleanly without decomposition (checked by TLC). b) Product ratio as the depivaloylation products.

data in Tables 1 and 2 show that the reduction of **17** and **18** proceeded at a high level of stereoselectivity to afford the undesired diastereomers (**20** and **22**). A rationale for this disappointing diastereoselectivity is not unequivocally assumed, because it is difficult to predict the transition-state conformation in these reductions.

Although we initially aimed at a direct construction of the dihydropyran skeleton from **19** and **21** by using S_N2'-type cyclization, all attempted cyclization, including base-promoted and Pd-catalyzed[20] cyclization, failed. The next candidate at this stage was intramolecular oxy-Michael addition.[10] Therefore, diol **19** was regioselectively oxidized to α,β-unsaturated ketone **5** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene in 69% yield. Diol **21** was also converted to the same ketone **5** with DDQ in 58% yield (10% of the recovered **21**).

Synthesis of Dihydropyran 31. After an extensive variation of base and/or acid, solvent, and temperature, crucial intramolecular oxy-Michael addition[10] of **5** was best achieved by using CSA in *t*-BuOH at r.t. for 50 h to afford the desired **27** and the undesired **28** in 47 and 10% yields, respectively (Scheme 3). *t*-BuOH was the best solvent to prevent hydrolysis of the acetonide. The desired **27** consists of a 3 : 1 mixture at the C6-position, while **28** consists of a single equatorial isomer at the C6-position. The six-membered ring configuration of **28** was verified by NOE experiments; irradiation of H-5 at 3.19 ppm produced a 10.5% NOE enhancement of the H-9 doublet of a doublet at 3.68 ppm, indicating that both substituents at C5 and C9 lie in equatorial positions. To finish the dihydropyran construction, it was necessary to introduce a double bond at the C6–C7 position. We selected the Stille's methodology: reduction of vinyl triflates.[21] Regioselective, thermodynamically-controlled vinyl triflate formation was investigated; some representative examples are given in Table 3. Treatment of **27** with 1.2 molar amounts of sodium bis(trimethylsilyl)amide in THF at 0 °C for 0.5 h; to this was added 1 molar amount of $PhNTf_2$ and the mixture was stirred at r.t. for 1 h, giving a 1 : 3.6 separable mixture of the desired **29** and the undesired regioisomer **30** in 84% combined yield (Entry 1, Table 3). When the amount of base was reduced to 0.9 molar amounts, the product ratio was reversed: **29**/**30** = 2 : 1 (Entry 2, Table 3). Furthermore, when 0.7 molar amounts of the base was used, the product ratio increased to 4 : 1 in favor of **29** (Entry 3, Table 3). Elongation of the enolate-formation time (1.5 h) did not have any effect on the product ratio, but caused a lower yield. These results suggest that some amount of the starting material **27** in the reaction mixture probably plays an important role as a proton source for shifting the equilibrium toward the thermodynamically-controlled enolate. The use of lithium and potassium bis(trimethylsilyl)amides was less satisfactory (Entries 4 and 5, Table 3). Reduction of vinyl triflate **29** with Et_3SiH in the presence of $[Pd(Ph_3P)_4]$ and LiCl in DMF at 60 °C for 12 h[21] gave, in 74% yield, dihydropyran **31**.

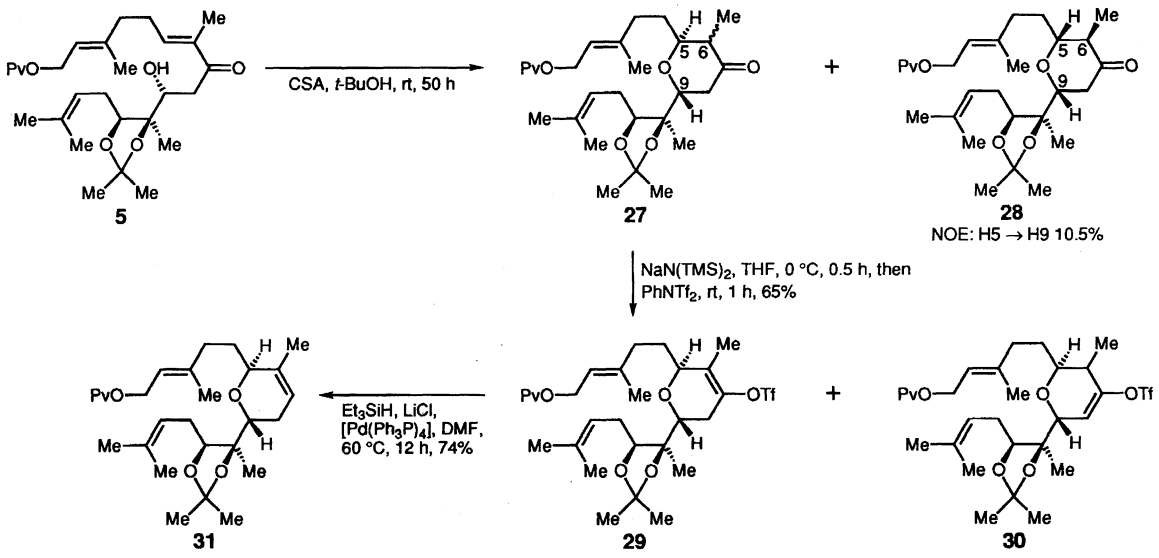
Table 3. Formation of the Enol Triflates **29** and **30**

27 $\xrightarrow{a)}$ **29** + **30**

Entry	Base (molar amt. for **27**)	Product ratio[b] **29**/**30**	Combined yield/%[c]
1	$NaN(SiMe_3)_2$ (1.2)	1 : 3.6	84
2	$NaN(SiMe_3)_2$ (0.9)	2 : 1	87
3	$NaN(SiMe_3)_2$ (0.7)	4 : 1	65[d]
4	$LiN(SiMe_3)_2$ (0.7)	1 : 4.9	44[e]
5	$KN(SiMe_3)_2$ (0.7)	—	0[f]

a) Base was added to a solution of **27** in THF at −78 °C. After 10 min at −78 °C and 0.5 h at 0 °C, $PhNTf_2$ was added and the mixture was stirred at r.t. for 1 h. b) Product ratio was based on ^1H NMR analysis of the purified mixture of products. c) Isolated yield. d) Recovered **27**: 31%. e) Recovered **27**: 50%. f) Recovered **27**: 100%.

14-Membered Ring Formation. Our next concern was the 14-membered ring formation.[22] We chose the Ito–Kodama cyclization methods,[9] which feature in-



Scheme 3.

tramolecular reactions of phenylthio-stabilized allylic anions with epoxides. Dihydropyran **31** was subjected to a variety of epoxidation conditions, including magnesium monoperoxyphthalate (MMPP),[23] and chiral (salen)Mn(II) complexes;[24] however, none of them was satisfactory with respect to the regioselectivity and isolated yield. Fortunately, we found that regioselective epoxidation of **31** with 3-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at −78 °C initially, and then at −78 to 0 °C over 3 h, gave **32** in 50% yield as a 2 : 1 inseparable mixture of diastereomers along with the recovered **31** (27%) (Scheme 4). Small amounts of regioisomeric epoxides and diepoxides were obtained. In order to carry out Ito–Kodama cyclization, epoxide **32** was transformed to phenyl sulfide **4** by the following three-step sequence: 1) $LiAlH_4$, THF, −78 °C, 4 h; 2) methanesulfonyl chloride (MsCl), 2,4,6-collidine, LiBr, CH_2Cl_2, r.t., 1 h; 3) sodium benzenethiolate, DMF, r.t., 2 h, 88% overall yield. First, we applied the original Ito–Kodama cyclization conditions: *n*-BuLi was added to a solution of **4** in THF and 1,4-diazabicyclo[2.2.2]octane (DABCO) at −78 °C. After 1 h at −78 °C, the reaction mixture was warmed to 0 °C and stirred for 3 h. After workup, **33** was obtained in 30% yield. However, substantial decomposition took place, especially while the reaction mixture was warming and the reproducibility of the method was poor. The use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), hexamethylphosphoric triamide (HMPA) instead of DABCO and *s*-BuLi instead of *n*-BuLi showed no improvement. We considered that it was necessary for this cyclization to obtain a thermally-stable anion, at least above 0 °C, or to activate the epoxide function. After extensive variations of the reaction conditions, we found *n*-BuLi–Bu_2Mg-mediated cyclization to be the best so far. Namely, to a solution of 1.6 M *n*-BuLi in hexane (3 molar amt., 1 M = 1 mol dm^{-3}) was added at r.t. a solution of 1.0 M Bu_2Mg in heptane (*n*-Bu : *s*-Bu = 1 : 1, Aldrich, 6 molar amt.). This was added at 0 °C to a solution of **4** (1 molar amt.) in THF and the mixture was stirred at r.t. for 5 h, yielding **33a** and **33b** in 76% combined yield as a 2.5 : 1 separable mixture of diastereomers. The unambiguous structure of **33b** was confirmed by X-ray crystallographic analysis (Fig. 3 and see Experimental); therefore, although the configuration of the C12a in the major **33a** was also confirmed, that of the phenylthio-bearing carbon could not be determined at this stage. Although the precise role is not clear, this is the first example, to the best of our knowledge,[25] of the mixed-reagents system (*n*-BuLi–Bu_2Mg) used for Ito–Kodama cyclization and/or the Biellmann-type reaction.[9]

Final Stage. The major **33a** led to **34** by $NaIO_4$-oxidation in MeOH and subsequent triethylamine-treatment in toluene in 61% yield; this result shows that the major **33a** had the desirable configuration of the phenylthio-bearing carbon for *syn* elimination of the intermediate sulfoxide. On the other hand, the minor **33b**, which seems to have a suitable structure for elimination (Fig. 3), led to **34** in only 6% yield under the same reaction conditions. The obtained **34**

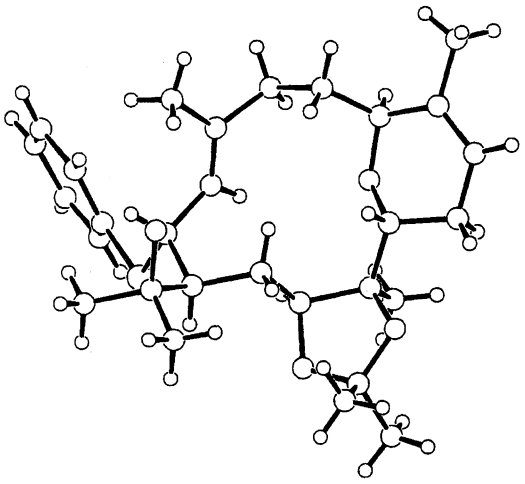
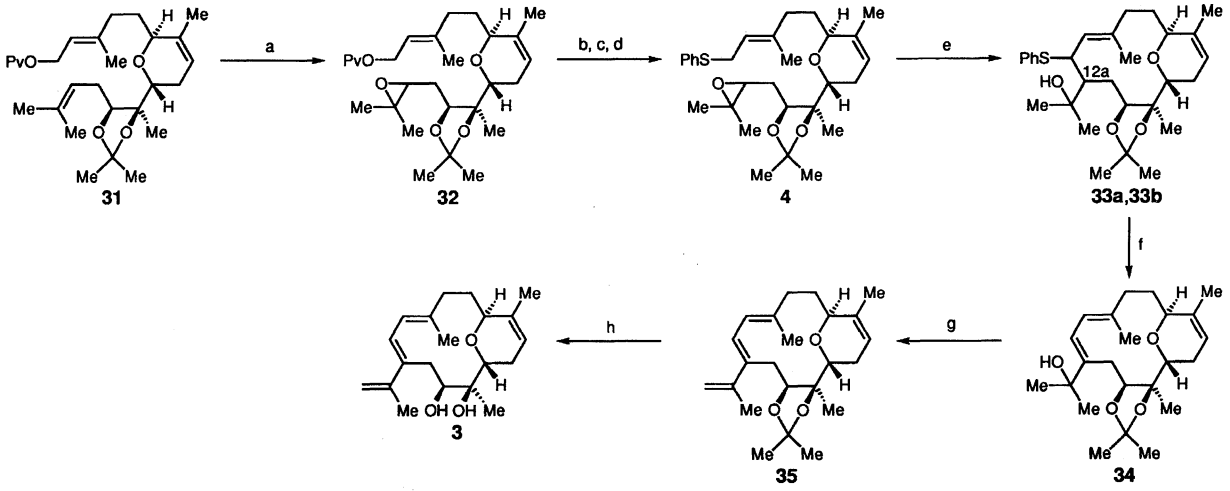


Fig. 3. X-ray crystal structure of **33b**.



(a) *m*-CPBA, CH_2Cl_2, -78 to 0 °C, 4 h, 50% (recovered **31**: 27%); (b) $LiAlH_4$, THF, -78 °C, 4 h; (c) MsCl, 2,4,6-collidine, LiBr, CH_2Cl_2, rt, 1 h; (d) PhSNa, DMF, rt, 2 h, 88% for three steps; (e) *n*-BuLi-Bu_2Mg, THF, rt, 5 h, 76%; (f) $NaIO_4$, MeOH, rt, 12 h, Et_3N, toluene, 80 °C, 3 h, 61%; (g) SiO_2, toluene, 35 °C, 12 h, 32% (recovered **34**: 37%); (h) PPTS, MeOH, rt, 12 h, 11% (recovered **35**: 64%).

Scheme 4.

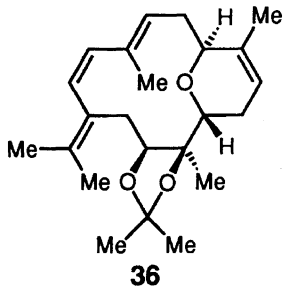


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Fig. 4.

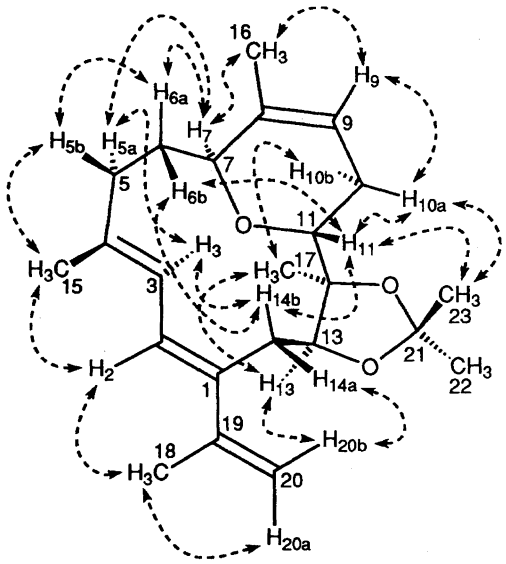

Fig. 5. NOEs observed in NOESY and NOEDIF spectra of **35**. NOEs between geminal protons are omitted. The special numbering system applied to this figure.

Table 4. ^{1}H and ^{13}C NMR Data for **35** in C_6D_6[a)]

Position		^{1}H/ppm (mult, J (Hz))	^{13}C/ppm	HMBC
1			138.9	
2		6.39 (br d, 5.4)	125.8	C1, 3, 4, 14, 19
3		6.18 (br d, 5.4)	124.3	C1, 2, 4, 5, 15
4			137.6	
5	a	2.06 (br ddd, 13.9, 10.7, 2.0)	39.3	C3, 4, 6, 7, 15
	b	2.19 (br dd, 13.9, 7.1)		C3, 4, 6, 7, 15
6	a	1.55 (dddd, 15.2, 7.1, 2.0, 2.0)	29.0	C4, 5, 7
	b	1.64 (dddd, 15.2, 10.7, 8.5, 2.0)		C4, 5, 7
7		4.05 (br d, 8.5)	80.0	C5, 6, 8, 11
8			134.5	
9		5.59 (br dq, 5.6, 1.7)	121.3	C7, 10, 11, 16
10	a	2.27 (m)	26.6	C8, 9
	b	2.44 (ddq, 18.0, 10.0, 2.4)		C9
11		4.13 (dd, 10.0, 4.2)	68.4	C7, 12, 13, 17
12			84.2	
13		4.21 (dd, 8.8, 1.2)	83.7	C1, 11, 12, 14,17
14	a	2.85 (br dd, 14.4, 1.2)	26.7	C1, 2, 12, 13, 19
	b	3.44 (dd, 14.4, 8.8)		C1, 2, 12, 13, 19
15		1.63 (br s)	18.6	C3, 4, 5
16		1.51 (m)	20.2	C7, 8, 9
17		1.37 (s)	20.6	C11, 12, 13
18		1.97 (br d, 1.0)	21.4	C1, 19, 20
19			143.0	
20	a	5.15 (br s)	113.2	C1, 18, 19
	b	5.57 (br s)		C1, 18, 19
21			105.6	
22		1.38 (s)	26.6	C21, 23
23		1.43 (s)	28.2	C21, 22

a) The special numbering system in Fig. 5 applied to this table.

underwent dehydration when treated with SiO_2 in toluene at 35 °C for 12 h, giving unstable **35** in 32% yield along with the recovered **34** (37%) and the double-bond isomer **36** (8%) (Fig. 4). When the reaction mixture was heated at 100 °C for 30 min, the starting material disappeared and the combined yield of trienes **35** and **36** increased to 81%; however, the ratio of **35/36** decreased to 1.2 : 1. The structure of **35** was confirmed by extensive NMR experiments (^{1}H, ^{13}C, H–H COSY, HSQC, NOEDIF, NOESY, HMBC). ^{1}H and ^{13}C NMR data are shown in Table 4. NOEs observed in NOESY and NOEDIF are shown in Fig. 5. Finally, the deprotection of **35** with pyridinium *p*-toluenesulfonate (PPTS) in MeOH at r.t. for 12 h afforded the unstable 14-membered diene unit **3** in 11% yield along with the recovered **35** (64%).

Although the last two steps in the synthetic sequence resulted in low yields, due to the instability of the triene portion, we succeeded in the first asymmetric synthesis of the 14-membered diene unit **3** of methyl sarcophytoate (**1**). Studies toward the syntheses of methyl sarcoate (**2**) and methyl sarcophytoate (**1**) as well as efforts to rationalize the role of the mixed reagents system (*n*-BuLi–Bu_2Mg) in Ito–Kodama cyclization are now in progress.

Experimental

The melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-360 photoelectric polarimeter in chloroform, unless otherwise noted. IR spectra were recorded on a BIO RAD DIGI-LAB FTS-165 spectrometer in $CHCl_3$ or neat at 25 °C and ^{1}H NMR spectra were on a JEOL GSX270 or a JEOL LA400 spectrometer in $CDCl_3$ at 25 °C using TMS as an internal standard, unless otherwise noted. Mass spectra (EI) were recorded on a JEOL JMS-DX302 mass spectrometer. Silica-gel TLC and column chromatography were performed on a Merck TLC 60F-254 and a Fuji-Davison BW-820MH, respectively. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, the organic solvents were purified and dried by appropriate procedures, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

(2*R*,3*R*,4*S*)-4-Acetoxy-3,7-dimethyl-6-octene-2,3-diol (15) and (2*R*,3*R*,4*S*)-2-Acetoxy-3,7-dimethyl-6-octene-3,4-diol (16). To a stirred solution of **8**[11)] (211 g, 1.24 mol) in dry DMF (1.1 l) were added at 0 °C triethylamine (311 ml, 2.23 mol) and TMSCl (189 ml, 1.49 mol). After 1 h at 25 °C, water (1.5 dm^3) was added and the mixture was extracted with hexane. The extracts were washed

with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (2 kg) with 4 : 1 hexane–ethyl acetate to afford a colorless syrup (286 g, 95%). A solution of this syrup (207 g, 0.854 mol) in dry CH_2Cl_2 (414 ml) was slowly added at −78 °C to a stirred solution of TMSOTf (228 g, 1.03 mol) and 2, 6-lutidine (165 ml, 1.42 mol) in dry CH_2Cl_2 (1.0 dm^3). After 3 h at −78 °C, DBU (169 mL, 1.13 mol) was added; the resulting suspension was stirred at 25 °C for 60 h. To this was added 2.0 M aqueous HCl (1.0 dm^3) (M = mol dm^{-3}); the mixture was extracted with $CHCl_3$ and the extracts were concentrated. To a stirred solution of this residue in 10 : 3 MeOH–H_2O (1.3 dm^3) was added at 25 °C KF (100 g, 1.72 mol). After 1 h at 25 °C, water was added and the new mixture was extracted with ethyl acetate. The extracts were concentrated and the residue was chromatographed on silica gel (2 kg) with ethyl acetate to afford a mixture of **9** and **10** (145 g, 100%, **9** : **10** = 7 : 1) as a colorless syrup. To a stirred solution of this syrup (145 g, 0.852 mol) in dry CH_2Cl_2 (727 ml) were added at 0 °C triethylamine (262 ml, 1.88 mol) and TsCl (179 g, 0.939 mol). After 2 h at 0 °C, saturated aqueous $NaHCO_3$ was added; the mixture was extracted with $CHCl_3$. The extracts were concentrated and the residue was chromatographed on silica gel (2 kg) with 2 : 1 hexane–ethyl acetate to afford a colorless syrup (236 g, 85%). To a stirred solution of this syrup (121 g, 0.373 mol) in THF (610 ml) was added over 15 min at −78 °C 1.65 M *n*-BuLi in hexane (220 ml, 0.363 mol). After 0.5 h at −78 °C, $LiAlH_4$ (12.8 g, 0.337 mol) was added; the mixture was warmed to 0 °C. After 1 h at 0 °C, water (12.8 ml) was slowly added. This was diluted with water (200 ml) and ethyl acetate (500 ml) and the mixture was stirred at 25 °C for 15 min. The mixture was separated and the aqueous layer was extracted with ethyl acetate (500 ml×5). The combined organic layers were concentrated and the residue was chromatographed on silica gel (1 kg) with 5 : 1 hexane–ethyl acetate to afford a mixture of **11** and **12** (48.9 g, 85%) as a colorless syrup. To a solution of this syrup (85.0 g, 551 mmol) in dry CH_2Cl_2 (1.1 dm^3) were added at 25 °C D-(−)-DIPT (19.4 g, 82.8 mmol) and molecular sieves (MS) 4AP (17.0 g); to this was added at −30 °C (i-PrO)$_4$Ti (16.0 ml, 54.2 mmol). After 0.5 h at −30 °C, 0.47 M TBHP in 2,2,4-trimethylpentane (129 ml, 60.6 mmol) was added; the mixture was stirred at −30 °C for 1 h. To this were added a solution of $FeSO_4 \cdot 7H_2O$ (76.6 g, 0.276 mol) and tartaric acid (20.7 g, 0.108 mol) in water (230 ml). The mixture was stirred at 25 °C for 0.5 h and separated. The aqueous layer was filtered through Celite and the filtrate was extracted with ethyl acetate. The combined organic layers were concentrated and the residue was dissolved in 30% aqueous NaOH (551 ml). The mixture was stirred at 25 °C for 1 h and extracted with $CHCl_3$. The extracts were concentrated and the residue was chromatographed on silica gel (1 kg) with 6 : 1 hexane–ethyl acetate to afford a mixture of **13** and **14** (61.0 g, 65%, **13** : **14** = 9 : 1) as a colorless syrup. To a stirred solution of this syrup (60 g, 0.352 mol) in dry THF (705 ml) were added at 25 °C NH_4OAc (40.7 g, 0.528 mol) and (i-PrO)$_4$Ti (134 ml, 0.454 mol). After 21 h at 25 °C, ether (300 ml) and 5% aqueous H_2SO_4 (870 ml) were added; the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (2 kg) with 2 : 1 hexane–ethyl acetate to afford **15** (40.4 g, 50%) as a colorless syrup and **16** (18.4 g, 23%) as colorless crystals.

15: R_f = 0.40 (1 : 1 hexane–ethyl acetate); $[\alpha]_D^{31}$ +20.5, $[\alpha]_{435}^{31}$ +43.4 (*c* 1.27); IR (neat) 3450, 2980, 2930, 1720, 1450, 1380, 1260, 1090, and 1030 cm^{-1}; ^{1}H NMR (270 MHz) δ = 1.20 (3H, s), 1.21 (3H, d, J = 6.0 Hz), 1.63 (3H, br s), 1.68 (3H, br s), 1.96 (1H, d, J = 6.0 Hz), 2.04 (3H, s), 2.18 (1H, s), 2.28—2.55 (2H, m), 3.73 (1H, quintet, J = 6.0 Hz), 5.02 (1H, dd, J = 3.8, 9.2 Hz), and 5.11 (1H, t with a small long-range coupling, J = 7.2, 1.0 Hz). Found: C, 62.38; H, 10.03%. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63%.

16: R_f = 0.53 (1 : 1 hexane–ethyl acetate); mp 46—47 °C (pillars from hexane); $[\alpha]_D^{31}$ −25.7, $[\alpha]_{435}^{31}$ −53.7 (*c* 1.02); IR (neat) 3470, 2990, 2920, 1720, 1450, 1380, 1260, and 1050 cm^{-1}; ^{1}H NMR (270 MHz) δ = 1.22 (3H, s), 1.28 (3H, d, J = 6.4 Hz), 1.65 (3H, br s), 1.75 (3H, br s), 2.07 (3H, s), 2.10—2.30 (2H, m), 3.53 (1H, br d, J = 9.8 Hz), 5.03 (1H, q, J = 6.4 Hz), and 5.17 (1H, t with a small long-range coupling, J = 7.0, 1.0 Hz). Found: C, 62.43; H, 9.93%. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63%.

Formation of MTPA Ester of a Mixture of 13 and 14. To a solution of a mixture of **13** and **14** (2.0 mg, 0.0117 mmol, **13** : **14** = 9 : 1) in dry CH_2Cl_2 (0.177 ml) were added at 25 °C triethylamine (0.0246 ml, 0.167 mmol), (+)-MTPACl (0.0044 ml, 0.024 mmol), and 4-dimethylaminopyridine (DMAP) (1.4 mg, 0.012 mmol). After 1 h at 25 °C, saturated aqueous $NaHCO_3$ was added; the mixture was extracted with hexane. The extracts were concentrated and the residue was chromatographed on silica gel (1.5 g) with 20 : 1 hexane–ethyl acetate to afford MTPA ester (4.4 mg, 96%) as a colorless syrup. By using (−)-MTPACl, MTPA ester of a mixture of **13** and **14** was obtained (98%) as a colorless syrup.

MTPA Ester from (+)-MTPACl: ^{1}H NMR (270 MHz) δ = 1.29 (3H, s), 1.32 (3H, d, J = 7.0 Hz), 1.63 (3H, br s), 1.70 (3H, br s), 2.09 (1H, m), 2.40 (1H, m), 2.94 (1H, dd, J = 6.0, 7.0 Hz), 3.53 (3H, m), 4.86 (1H, q, J = 7.0 Hz), 5.09 (1H, m), and 7.35—7.57 (5H, m).

MTPA Ester from (−)-MTPACl: ^{1}H NMR (270 MHz) δ = 1.18 (3H, s), 1.39 (3H, d, J = 6.4 Hz), 1.63 (3H, br s), 1.71 (3H, br s), 2.10 (1H, m), 2.33 (3H, m), 2.89 (1H, t, J = 6.4 Hz), 3.56 (3H, m), 4.82 (1H, q, J = 6.4 Hz), 5.07 (1H, m), and 7.34—7.58 (5H, m).

(3*S*,4*S*)-3,4-(Isopropylidenedioxy)-3,7-dimethyl-6-octen-2-one (6) from 15. A solution of DMSO (50.0 ml, 0.705 mol) in dry CH_2Cl_2 (250 ml) was added at −78 °C to a stirred solution of oxalyl dichloride (30.5 ml, 0.350 mol) in dry CH_2Cl_2 (606 ml). After 15 min at −78 °C, a solution of **15** (40.4 g, 0.175 mol) in dry CH_2Cl_2 (120 ml) was added; the resulting suspension was stirred at −78 °C for 0.5 h. After the addition of triethylamine (147 ml, 1.05 mol), the mixture was gradually warmed to 0 °C during 0.5 h. The reaction mixture was quenched with water and extracted with $CHCl_3$. The extracts were concentrated and the residue was chromatographed on silica gel (1 kg) with 3 : 1 hexane–ethyl acetate to afford ketone (38.3 g, 96%) as a colorless syrup. To a stirred solution of this ketone (38.3 g, 0.168 mol) in dry MeOH (383 ml) was added at 25 °C 5 M NaOMe in MeOH (1.68 ml, 8.40 mmol). After 2 h at 25 °C, the reaction mixture was neutralized with Amberlite CG50 and the insoluble materials were filtered and washed with MeOH. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (500 g) with 4 : 1 hexane–acetone to afford diol (29.8 g, 95%) as a colorless syrup. To a stirred solution of this diol (28.2 g, 0.151 mol) in dry CH_2Cl_2 (141 ml) were added at 25 °C DMP (185 ml, 1.50 mol) and CSA (600 mg, 2.58 mmol). After 1.5 h at 25 °C, the reaction mixture was neutralized with triethylamine; the mixture was concentrated. The residue was chromatographed on silica gel (600 g) with 20 : 1 hexane–ethyl acetate to afford **6** (30.8 g, 90%) as a colorless syrup: R_f = 0.40 (15 : 1 hexane–ethyl acetate); $[\alpha]_D^{31}$ −41.6, $[\alpha]_{435}^{31}$ −82.9 (*c* 1.10); IR ($CHCl_3$) 3020, 2990, 1710, 1380, 1230, 1100, 1050, 790, 740, and 670 cm^{-1}; ^{1}H NMR (270 MHz) δ = 1.38 (3H, s), 1.45 (3H, s), 1.60 (3H, br s), 1.62 (3H, s), 1.71 (3H, br s), 2.01 (1H, m), 2.18 (1H, m), 2.27 (3H, s), 3.91 (1H, dd, J = 4.4, 9.2 Hz), and 5.16 (1H, t with a small long-range coupling, J = 7.0, 1.0 Hz). Found:

C, 68.88; H, 10.09%. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80%.

Preparation of 6 from 16. To a stirred solution of **16** (18.0 g, 78.2 mmol) in dry CH_2Cl_2 (90 ml) were added at 25 °C DMP (48.1 ml, 0.391 mol) and PPTS (0.98 g, 3.9 mmol). After 2 h at 25 °C, the reaction mixture was neutralized with triethylamine; the mixture was concentrated. The residue was chromatographed on silica gel (400 g) with 2 : 1 hexane–ethyl acetate to afford a colorless syrup (20.9 g, 99%). To a stirred solution of this syrup (20.9 g, 77.3 mmol) in dry CH_2Cl_2 (210 ml) was added at −78 °C 0.99 M DIBALH in toluene (121 ml, 0.120 mol). After 1 h at −78 °C, potassium sodium tartrate·$4H_2O$ (103 g, 0.365 mol) in water (310 ml) was added and the mixture was separated. The aqueous layer was extracted with hexane and the combined organic layers were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (1 kg) with 7 : 1 hexane–ethyl acetate to afford alcohol (17.1 g, 92%) as a colorless syrup. A solution of DMSO (18.1 ml, 0.255 mol) in dry CH_2Cl_2 (80 ml) was added at −78 °C to a stirred solution of oxalyl dichloride (11.1 ml, 0.127 mol) in dry CH_2Cl_2 (257 ml). After 15 min at −78 °C, a solution of this alcohol (17.1 g, 74.9 mmol) in dry CH_2Cl_2 (86 ml) was added; the resulting suspension was stirred at −78 °C for 0.5 h. After the addition of triethylamine (53.2 ml, 0.382 mol), the mixture was gradually warmed to 0 °C for a period of 0.5 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (1 kg) with 16 : 1 hexane–ethyl acetate to afford **6** (15.3 g, 90%) as a colorless syrup.

(2*E*,6*E*)-2,6-Dimethyl-8-(2,2-dimethylpropanoyloxy)-2,6-octadienal (7). To a stirred solution of geranyl acetate (176 g, 0.897 mol) in dry CH_2Cl_2 (230 ml) were added at 25 °C SeO_2 (1.99 g, 17.9 mmol), salicylic acid (12.4 g, 89.8 mmol), and 70% aqueous TBHP (246 ml, 1.80 mol). After 24 h at 25 °C, 10% aqueous KOH (246 ml) was added; the mixture was extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was dissolved in water (750 ml) and to this were added at 25 °C $FeSO_4$·$7H_2O$ (249 g, 0.896 mol) and acetic acid (2.57 ml, 44.9 mmol). After 0.5 h at 25 °C, the mixture was extracted with hexane and the extracts were concentrated. The residue was chromatographed on silica gel (2 kg) with 2 : 1 hexane–ethyl acetate to afford alcohol (90.1 g, 48%) as a colorless syrup and aldehyde (2.01 g, 9.7%) as a pale yellow syrup. To a stirred solution of this alcohol (90.1 g, 0.424 mol) in dry CH_2Cl_2 (630 ml) were added at 0 °C PDC (160 g, 0.425 mol) and MS 4AP (212 g). After 0.5 h at 0 °C, the reaction mixture was diluted with hexane and the insoluble materials were filtered through a pad of silica gel and washed with 1 : 1 hexane–ethyl acetate. The combined filtrate and washings were concentrated. The residue (90.0 g, 100%) was dissolved in dry MeOH (500 ml), and to this was added at 25 °C 5 M NaOMe in MeOH (9.5 ml, 42.4 mmol). After 2 h at 25 °C, the reaction mixture was neutralized with CG50 and the insoluble materials were filtered and washed with ethyl acetate. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (1 kg) with 1.5 : 1 hexane–ethyl acetate to afford alcohol (53.6 g, 67%) as a colorless syrup. To a stirred solution of this alcohol (53.6 g, 0.319 mol) in dry CH_2Cl_2 (268 ml) were added at 0 °C triethylamine (70.9 ml, 0.509 mol) and PvCl (46.5 ml, 0.378 mol). After 2 h at 25 °C, saturated aqueous $NaHCO_3$ and the mixture was extracted with $CHCl_3$; the extracts were concentrated. The residue was chromatographed on silica gel (1 kg) with 10 : 1 hexane–ethyl acetate to afford **7** (77.9 g, 97%) as a pale yellow syrup: R_f = 0.70 (2 : 1 hexane–ethyl acetate); IR (neat) 2970, 2930, 2880, 1730, 1690, 1280, 1150, and 770 cm^{-1}; ^1H NMR (270 MHz) δ = 1.19 (9H, s), 1.74 (3H, br s), 1.75 (3H, br s), 2.24 (2H, t, J = 7.8 Hz), 2.50 (2H, q, J = 7.8 Hz), 4.58 (2H, d, J = 7.0 Hz), 5.37 (1H, t with a small long-range coupling, J = 7.0, 1.0 Hz), 6.45 (1H, t with a small long-range coupling, J = 7.8, 1.0 Hz), and 9.38 (1H, s). Found: *m/z* 252.1752. Calcd for $C_{15}H_{24}O_3$: M^+, 252.1726.

(5*S*,6*S*,9*R*,10*E*,14*E*)-16-(2,2-Dimethylpropanoyloxy)-9-hydroxy-5,6-(isopropylidenedioxy)-2,6,10,14-tetramethyl-2,10,14-hexadecatrien-7-one (17) and Its (9*S*)-Epimer (18). To a stirred solution of **6** (25.1 g, 0.111 mol) in dry THF (555 ml) was added at −78 °C 1.0 M lithium bis(trimethylsilyl)amide in THF (111 ml, 0.111 mol). After 15 min at −78 °C, a solution of **7** (30.8 g, 0.122 mol) in dry THF (216 ml) was added and the new mixture was stirred at −78 °C for 0.5 h. The reaction mixture was poured into saturated aqueous NH_4Cl and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (2 kg) with 6 : 1 hexane–ethyl acetate to afford **17** (19.6 g, 37%) and **18** (18.7 g, 35%) as colorless syrups.

17: R_f = 0.52 (5 : 1 hexane–ethyl acetate); $[\alpha]_D^{29}$ −2.2, $[\alpha]_{435}^{29}$ −11.6 (*c* 1.20); IR ($CHCl_3$) 3530, 3020, 2980, 1710, 1450, 1380, 1210, 1160, 1100, 1050, 790, 730, and 670 cm^{-1}; ^1H NMR (270 MHz) δ = 1.19 (9H, s), 1.39 (3H, s), 1.44 (3H, s), 1.60 (6H, s), 1.63 (3H, s), 1.70 (6H, s), 2.00—2.20 (6H, m), 2.70 (1H, dd, J = 9.2, 18.0 Hz), 2.74 (1H, d, J = 3.2 Hz), 3.00 (1H, dd, J = 2.0, 18.0 Hz), 3.92 (1H, dd, J = 4.8, 9.0 Hz), 4.44 (1H, br d, J = 9.2 Hz), 4.56 (2H, d, J = 7.0 Hz), 5.14 (1H, br t, J = 7.0 Hz), 5.32 (1H, br t, J = 7.0 Hz), and 5.43 (1H, t with a small long-range coupling, J = 6.4, 1.0 Hz). Found: C, 70.19; H, 9.99%. Calcd for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69%.

18: R_f = 0.41 (5 : 1 hexane–ethyl acetate); $[\alpha]_D^{29}$ −22.5 (*c* 1.38); IR ($CHCl_3$) 3490, 3020, 2980, 1710, 1450, 1380, 1230, 1160, 1100, 1050, 790, 770, 740, and 670 cm^{-1}; ^1H NMR (270 MHz) δ = 1.19 (9H, s), 1.39 (3H, s), 1.45 (3H, s), 1.59 (3H, s), 1.61 (3H, s), 1.64 (3H, s), 1.70 (3H, s), 1.72 (3H, s), 1.90—2.20 (6H, m), 2.64 (1H, dd, J = 3.0, 17.6 Hz), 3.04 (1H, dd, J = 9.8, 17.6 Hz), 3.15 (1H, d, J = 3.0 Hz), 3.92 (1H, dd, J = 4.0, 9.2 Hz), 4.37 (1H, br d, J = 9.8 Hz), 4.57 (2H, d, J = 7.0 Hz), 5.14 (1H, br t, J = 7.0 Hz), 5.32 (1H, br t, J = 7.0 Hz), and 5.44 (1H, br t, J = 6.6 Hz). Found: C, 70.02; H, 9.84%. Calcd for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69%.

(5*S*,6*R*,7*R*,9*R*,10*E*,14*E*)-7,9-Dihydroxy-16-(2,2-dimethylpropanoyloxy)-5,6-(isopropylidenedioxy)-2,6,10,14-tetramethyl-2,10,14-hexadecatriene-7,9-diol (19) and Its (7*S*)-Epimer (20). To a stirred solution of **17** (9.20 g, 19.2 mmol) and $CeCl_3$·$7H_2O$ (10.7 g, 28.7 mmol) in MeOH (180 ml) was added at 25 °C $NaBH_4$ (1.1 g, 29 mmol). After 10 min at 25 °C, saturated aqueous NH_4Cl (5 ml) was added and the mixture was concentrated. The residue was dissolved in water and this was extracted with ethyl acetate. The extracts were concentrated and the residue was chromatographed on silica gel (1 kg) with 3 : 1 hexane–ethyl acetate to afford **19** (4.90 g, 53%) and **20** (4.07 g, 44%) as colorless syrups.

19: R_f = 0.42 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{32}$ +19.2, $[\alpha]_{435}^{32}$ +37.5 (*c* 0.78); IR (neat) 3490, 2980, 2930, 2870, 1730, 1460, 1380, 1280, 1240, 1220, 1160, 1080, and 1050 cm^{-1}; ^1H NMR (270 MHz) δ = 1.19 (9H, s), 1.26 (3H, s), 1.35 (3H, s), 1.37 (3H, s), 1.62 (3H, br s), 1.65 (3H, br s), 1.70 (3H, br s), 1.72 (3H, br s), 1.97—2.50 (6H, m), 2.54 (1H, d, J = 4.0 Hz), 3.79 (1H, dd, J = 5.0, 8.2 Hz), 3.96 (1H, ddd, J = 2.0, 4.0, 10.0 Hz), 4.32 (1H, m), 4.57 (2H, d, J = 7.0 Hz), 5.25 (1H, t with a small long-range coupling, J = 7.0, 1.0 Hz), 5.32 (1H, t with a small long-range coupling, J = 7.0, 1.0 Hz), and 5.47 (1H, br t, J = 7.0 Hz). Found: C, 69.70;

H, 10.40%. Calcd for $C_{28}H_{48}O_6$: C, 69.96; H, 10.06%.

20: $R_f = 0.34$ (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{32}$ +3.6, $[\alpha]_{435}^{32}$ +10.7 (*c* 0.72); IR (neat) 3500, 2980, 2940, 2880, 1730, 1460, 1380, 1240, 1160, 1090, and 1050 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.20$ (9H, s), 1.40 (3H, s), 1.50 (3H, s), 1.57 (3H, s), 1.63 (6H, br s), 1.70 (3H, br s), 1.73 (3H, br s), 2.00—2.45 (6H, m), 3.07 (1H, br d, $J = 2.0$ Hz), 3.66 (1H, br s), 3.78 (1H, dt, $J = 9.8$, 2.0 Hz), 3.88 (1H, dd, $J = 5.8$, 8.0 Hz), 4.24 (1H, dd, $J = 3.0$, 9.0 Hz), 4.57 (2H, d, $J = 7.0$ Hz), 5.16 (1H, br t, $J = 5.8$ Hz), 5.32 (1H, br t, $J = 7.0$ Hz), and 5.44 (1H, br t, $J = 7.0$ Hz). Found: *m/z* 463.3412. Calcd for $C_{28}H_{47}O_5$: $(M-OH)^+$, 463.3424.

(5*S*,6*R*,7*R*,9*S*,10*E*,14*E*)-7,9-Dihydroxy-16-(2,2-dimethylpropanoyloxy)-5,6-(isopropylidenedioxy)-2,6,10,14-tetramethyl-2,10,14-hexadecatriene-7,9-diol (21) and Its (7*S*)-Epimer (22). To a stirred solution of **18** (10.4 g, 21.7 mmol) in dry ether (200 ml) was added at 0 °C 0.145 M $Zn(BH_4)_2$ in ether (254 ml, 36.8 mmol). After 0.5 h at 0 °C, water was added and the mixture was extracted with 1 : 1 hexane–ethyl acetate. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (500 g) with 20 : 1 $CHCl_3$–acetone to afford **21** (4.88 g, 47%) and **22** (4.87 g, 47%) as colorless syrups.

21: $R_f = 0.29$ (10 : 1 $CHCl_3$–acetone); $[\alpha]_D^{32}$ +7.7, $[\alpha]_{435}^{32}$ +19.1 (*c* 0.68); IR (neat) 3460, 2980, 2930, 2870, 1730, 1450, 1380, 1280, 1220, 1160, 1080, 1050, and 770 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.19$ (9H, s), 1.25 (3H, s), 1.35 (3H, s), 1.37 (3H, s), 1.62 (3H, br s), 1.65 (3H, br s), 1.69 (3H, br s), 1.72 (3H, br s), 1.93—2.58 (8H, m), 3.55 (1H, br s), 3.78 (1H, dd, $J = 4.8$, 9.0 Hz), 3.92 (1H, br d, $J = 9.8$ Hz), 4.23 (1H, dd, $J = 2.0$, 10.0 Hz), 4.55 (2H, d, $J = 7.0$ Hz), 5.25 (1H, t with a small long-range coupling, $J = 7.0$, 1.0 Hz), 5.29 (1H, t with a small long-range coupling $J = 7.0$, 1.0 Hz), and 5.37 (1H, br t, $J = 7.0$ Hz). Found: C, 69.84; H, 10.48%. Calcd for $C_{28}H_{48}O_6$: C, 69.96; H, 10.06%.

22: $R_f = 0.40$ (10 : 1 $CHCl_3$–acetone); $[\alpha]_D^{33}$ −0.1, $[\alpha]_{435}^{33}$ −0.1 (*c* 0.69); IR (neat) 3490, 2980, 2940, 2880, 1730, 1450, 1380, 1280, 1210, 1160, and 1050 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.19$ (12H, s), 1.40 (3H, s), 1.50 (3H, s), 1.62 (3H, br s), 1.65 (3H, br s), 1.70 (3H, br s), 1.73 (3H, br s), 2.00—2.55 (6H, m), 2.68 (1H, d, $J = 4.0$ Hz), 3.80—3.92 (2H, m), 4.33 (1H, m), 4.57 (2H, d, $J = 7.0$ Hz), 5.17 (1H, t with a small long-range coupling, $J = 6.0$, 1.0 Hz), 5.32 (1H, t with a small long-range coupling, $J = 7.0$, 1.0 Hz), and 5.47 (1H, br t, $J = 6.8$ Hz). Found: *m/z* 463.3439. Calcd for $C_{28}H_{47}O_5$: $(M-OH)^+$, 463.3424.

Degradation of 19 and 20. A solution of **19** (50.0 mg, 0.104 mmol) in MeOH (2.5 ml) was bubbled with O_3/O_2 gas at −78 °C. After 2 h at −78 °C, argon gas was bubbled for a few min and then Me_2S (0.0768 ml, 1.05 mmol) was added. The mixture was warmed to 25 °C and concentrated. The residue was dissolved in MeOH (2.5 ml); to this was added at 25 °C $NaBH_4$ (11.8 mg, 0.312 mmol). After 10 min at 25 °C, the mixture was neutralized with dry ice and diluted with $CHCl_3$; the resulting suspension was transferred to a column filled with silica gel (2 g). The column was eluted with 5 : 1 $CHCl_3$–MeOH and the eluate was concentrated. The residue (27 mg) was dissolved in MeOH (1.5 ml); to this was added at 25 °C $NaIO_4$ (65.5 mg, 0.306 mmol). After 1 h at 25 °C, the reaction mixture was diluted with $CHCl_3$; the resulting suspension was transferred to a column filled with silica gel (2 g). The column was eluted with 5 : 1 $CHCl_3$–MeOH and the eluate was concentrated. The residue was dissolved in MeOH (2.5 ml); to this was added at 25 °C $NaBH_4$ (11.8 mg, 0.312 mmol). After 10 min at 25 °C, the mixture was neutralized with dry ice and diluted with $CHCl_3$; the resulting suspension was transferred to a column filled with silica gel (2 g). The column was eluted with 5 : 1 $CHCl_3$–MeOH and the eluate was concentrated. The residue (20 mg) was dissolved in dry CH_2Cl_2 (0.60 ml); to this were added at 0 °C triethylamine (0.0952 ml, 0.683 mmol), PvCl (0.0415 ml, 0.337 mmol), and a tiny amount of DMAP. After 3 h at 25 °C, 1 M aqueous NaOH was added and the mixture was extracted with 1 : 1 hexane–ether. The extracts were washed successively with saturated aqueous NH_4Cl and saturated aqueous NaCl. The organic layer was concentrated and the residue was chromatographed on silica gel (3 g) with 3 : 1 hexane–ethyl acetate to afford a colorless syrup (25.7 mg, 61% for five steps). To a stirred solution of this syrup (10 mg, 24.8 mmol) in dry MeOH (0.3 ml) was added at 25 °C CSA (5.8 mg, 25.0 mmol). After 14 h at 25 °C, the reaction mixture was neutralized with triethylamine. The mixture was concentrated and the residue was chromatographed on silica gel (2 g) with 1 : 1 hexane–ethyl acetate to afford **23** (7.5 mg, 26%) as a colorless syrup. Degradation of **20** by the same procedure described for degradation of **19** gave **24** (20% for six steps).

23: $R_f = 0.32$ (1 : 1 hexane–ethyl acetate); ^1H NMR (270 MHz) $\delta = 1.22$ (21H, s), 1.72 (2H, m), 2.07 (2H, m), 2.23 (1H, s), 2.99 (2H, d, $J = 4.4$ Hz), 3.62 (2H, ddd, $J = 2.0$, 4.4, 11.4 Hz), 4.17 (2H, dt, $J = 11.8$, 5.6 Hz), and 4.43 (2H, ddd, $J = 4.2$, 9.0, 11.4 Hz). MS M^+, 362.

24: $R_f = 0.28$ (1 : 1 hexane–ethyl acetate); ^1H NMR (270 MHz) $\delta = 1.06$ (3H, s), 1.21 (9H, s), 1.22 (9H, s), 1.61—2.00 (4H, m), 2.99 (1H, s), 3.28 (1H, d, $J = 8.0$ Hz), 3.49 (1H, d, $J = 4.0$ Hz), 3.57 (1H, ddd, $J = 2.0$, 8.0, 11.2 Hz), 3.71 (1H, dt, $J = 9.0$, 4.0 Hz), and 4.10—4.51 (4H, m). MS M^+, 362.

Preparation of 25 and 26. To a stirred solution of **21** (6.9 mg, 0.0144 mmol) in dry CH_2Cl_2 (0.21 ml) were added at 25 °C DMP (0.0177 ml, 0.144 mmol) and PPTS (0.36 mg, 0.0014 mmol). After 2 h at 25 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with hexane. The extracts were concentrated and the residue was chromatographed on silica gel (2 g) with 20 : 1 hexane–ethyl acetate to afford **26** (5.3 mg, 70%) as a colorless syrup. Protection of **20** under the same conditions gave **25** (70%).

25: ^1H NMR (270 MHz) $\delta = 1.17$ (3H, s), 1.20 (9H, s), 1.37 (3H, s), 1.44 (3H, s), 1.47 (3H, s), 1.52 (3H, s), 1.65 (6H, br s), 1.70 (3H, br s), 1.73 (3H, br s), 2.00—2.67 (6H, m), 3.74 (1H, dd, $J = 2.0$, 11.2 Hz), 3.85 (1H, dd, $J = 5.0$, 8.0 Hz), 4.18 (1H, dd, $J = 2.0$, 11.8 Hz), 4.56 (2H, d, $J = 7.0$ Hz), 5.20 (1H, br t, $J = 6.0$ Hz), 5.32 (1H, br t, $J = 7.0$ Hz), and 5.41 (1H, br t, $J = 6.0$ Hz).

26: ^1H NMR (270 MHz) $\delta = 1.19$ (9H, s), 1.24 (3H, s), 1.36 (3H, s), 1.37 (3H, s), 1.40 (3H, s), 1.47 (3H, s), 1.64 (6H, br s), 1.69 (3H, br s), 1.72 (3H, br s), 2.02—2.46 (6H, m), 3.76 (1H, dd, $J = 4.0$, 9.2 Hz), 3.98 (1H, dd, $J = 3.0$, 11.2 Hz), 4.21 (1H, dd, $J = 3.0$, 10.8 Hz), 4.57 (2H, d, $J = 7.0$ Hz), 5.24 (1H, br t, $J = 6.6$ Hz), 5.32 (1H, br t, $J = 7.0$ Hz), and 5.44 (1H, br t, $J = 6.8$ Hz).

(2*E*,6*E*,10*R*,11*R*,12*S*)-1-(2,2-Dimethylpropanoyloxy)-10-hydroxy-11,12-(isopropylidenedioxy)-3,7,11,15-tetramethyl-2,6,14-hexadecatrien-8-one (5). To a stirred solution of **19** (10.0 g, 20.8 mmol) in 1 : 1 benzene–H_2O (170 ml) was added at 25 °C DDQ (7.00 g, 30.9 mmol). After 24 h at 25 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The extracts were concentrated and the residue was chromatographed on silica gel (300 g) with 5 : 1 hexane–ethyl acetate to afford **5** (6.90 g, 69%) as a pale yellow syrup. Oxidation of **21** under the same conditions gave **5** (58%) along with the recovered **21** (10%).

5: $R_f = 0.51$ (5 : 1 hexane–ethyl acetate); $[\alpha]_D^{31}$ +34.3, $[\alpha]_{435}^{31}$ +72.2 (*c* 0.81); IR (neat) 3530, 2980, 2930, 2870, 1730, 1660, 1460, 1380, 1280, 1150, and 1080 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.19$ (9H, s), 1.26 (3H, s), 1.35 (3H, s), 1.36 (3H, s), 1.64 (3H, br s),

1.72 (6H, br s), 1.79 (3H, br s), 2.18 (2H, br t, J = 7.2 Hz), 2.30—2.60 (4H, m), 2.67 (1H, dd, J = 10.2, 17.8 Hz), 3.22 (1H, d, J = 3.0 Hz), 3.23 (1H, dd, J = 2.0, 17.8 Hz), 3.79 (1H, dd, J = 4.0, 9.2 Hz), 4.21 (1H, ddd, J = 2.0, 3.0, 10.2 Hz), 4.57 (2H, d, J = 6.8 Hz), 5.24 (1H, br t, J = 7.0 Hz), 5.34 (1H, t with a small long-range coupling, J = 6.8, 1.0 Hz), and 6.67 (1H, t with a small long-range coupling, J = 6.8, 1.0 Hz). Found: C, 70.27; H, 10.11%. Calcd for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69%.

(2*E*,6*S*,10*R*,11*R*,12*S*)-1-(2,2-Dimethylpropanoyloxy)-6,10-epoxy-11,12-(isopropylidenedioxy)-3,7,11,15-tetramethyl-2,14-hexadecadien-8-one (27). To a stirred solution of **5** (6.80 g, 14.2 mmol) in dry *t*-BuOH (82 ml) was added at 25 °C CSA (2.31 g, 9.94 mmol). After 50 h at 25 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with hexane. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (1 kg) with 7 : 1 hexane–ethyl acetate to afford **27** (3.20 g, 47%, 3 : 1 mixture at the C7-position) and **28** (680 mg, 10%) as colorless syrups.

27: R_f = 0.42 (2 : 1 hexane–ether); ^{1}H NMR (270 MHz) δ = 0.97 (3/4H, d, J = 6.6 Hz), 1.14 (9/4H, d, J = 7.0 Hz), 1.19 (9H, s), 1.25—1.40 (9H, m), 1.61—1.75 (9H, m), 2.00—2.70 (7H, m), 3.73—3.90 (3/2H, m), 3.96 (1/2H, dd, J = 4.2, 10.0 Hz), 4.12 (1H, dd, J = 5.0, 8.8 Hz), 4.57 (2H, d, J = 6.8 Hz), and 5.15—5.40 (2H, m).

28: R_f = 0.47 (2 : 1 hexane–ether); ^{1}H NMR (270 MHz) δ = 1.01 (3H, d, J = 6.6 Hz), 1.19 (9H, s), 1.32 (3H, s), 1.34 (3H, s), 1.37 (3H, s), 1.63 (3H, br s), 1.70 (3H, br s), 1.73 (3H, br s), 1.83 (1H, m), 1.98—2.50 (6H, m), 2.60 (1H, dd, J = 2.8, 13.2 Hz), 3.19 (1H, ddd, J = 2.6, 8.0, 10.2 Hz), 3.68 (1H, dd, J = 2.8, 12.0 Hz), 3.79 (1H, dd, J = 4.0, 10.0 Hz), 4.57 (2H, d, J = 7.0 Hz), 5.24 (1H, t with a small long-range coupling, J = 6.2, 1.0 Hz), and 5.33 (1H, t with a small long-range coupling, J = 7.0, 1.0 Hz).

(2*E*,6*S*,7*Z*,10*R*,11*R*,12*S*)-1-(2,2-Dimethylpropanoyloxy)-6,10-epoxy-11,12-(isopropylidenedioxy)-3,7,11,15-tetramethyl-2,7,14-hexadecatriene (31). To a stirred solution of **27** (3.20 g, 6.69 mmol) in dry THF (96 ml) was added at −78 °C 1.0 M sodium bis(trimethylsilyl)amide in THF (4.68 ml, 4.68 mmol) and the mixture was warmed to 0 °C. After 0.5 h at 0 °C, $PhNTf_2$ (1.91 g, 5.35 mmol) was added and the mixture was stirred at r.t. for 1 h. 1 M Aqueous NaOH (50 ml) was added and the mixture was extracted with hexane. The extracts were washed with 1 M aqueous HCl and then saturated aqueous $NaHCO_3$. The organic layer was concentrated and the residue was chromatographed on silica gel (400 g) with 20 : 1 hexane–ethyl acetate to afford **29** (2.06 g, 52%) and **30** (514 mg, 13%) as pale yellow syrups along with the recovered **27** (992 mg, 31%).

29: ^{1}H NMR (270 MHz) δ = 1.19 (9H, s), 1.27 (3H, s), 1.36 (3H, s), 1.40 (3H, s), 1.64 (3H, br s), 1.69 (3H, br s), 1.73 (6H, br s), 2.00—2.65 (6H, m), 3.77 (1H, dd, J = 4.2, 9.0 Hz), 3.94 (1H, dd, J = 4.0, 10.2 Hz), 4.10 (1H, m), 4.57 (2H, d, J = 6.8 Hz), and 5.16—5.40 (2H, m).

30: ^{1}H NMR (270 MHz) δ = 1.19 (9H, s), 1.21 (3H, s), 1.25 (3H, d, J = 6.8 Hz), 1.37 (3H, s), 1.40 (3H, s), 1.64 (3H, br s), 1.71 (3H, br s), 1.73 (3H, br s), 1.82 (1H, m), 2.00—2.55 (5H, m), 3.72 (1H, ddd, J = 1.6, 5.2, 8.4 Hz), 3.82 (1H, dd, J = 4.0, 9.2 Hz), 4.28 (1H, t, J = 1.8 Hz), 4.57 (2H, d, J = 6.8 Hz), 5.22 (1H, br t, J = 5.8 Hz), 5.34 (1H, t, J = 6.6 Hz), and 6.0 (1H, d, J = 1.8 Hz).

To a stirred solution of **29** (1.24 g, 2.10 mmol) in dry DMF (25 ml) were added at 25 °C LiCl (178 mg, 4.20 mmol), PPh_3 (110 mg, 0.419 mmol), Et_3SiH (0.469 ml, 2.94 mmol), and [Pd(PPh_3)$_4$] (242 mg, 0.209 mmol). After 12 h at 60 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with hexane. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (100 g) with 10 : 1 hexane–ether to afford **31** (718 mg, 74%) as a colorless syrup: R_f = 0.63 (10 : 1 hexane–acetone); $[\alpha]_D^{31}$ +16.1, $[\alpha]_{435}^{31}$ +38.3 (*c* 0.74); IR (neat) 2980, 2940, 2870, 1730, 1450, 1380, 1220, 1150, 1100, 1050, and 760 cm^{-1}; ^{1}H NMR (270 MHz) δ = 1.19 (9H, s), 1.27 (3H, s), 1.35 (3H, s), 1.39 (3H, s), 1.63 (3H, br s), 1.64 (3H, br s), 1.68 (3H, br s), 1.73 (3H, br s), 1.95—2.55 (6H, m), 3.70—3.80 (2H, m), 3.92 (1H, br d, J = 8.4 Hz), 4.56 (2H, d, J = 7.0 Hz), 5.27 (1H, br t, J = 7.0 Hz), 5.33 (1H, br t, J = 7.0 Hz), and 5.56 (1H, m). Found: C, 72.52; H, 10.41%. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02%.

(2*E*,6*S*,7*Z*,10*R*,11*R*,12*S*,14*RS*)-6,10 : 14,15-Diepoxy-11,12-(isopropylidenedioxy)-3,7,11,15-tetramethyl-1-(phenylthio)-2,7-hexadecadiene (4). To a stirred solution of **31** (620 mg, 1.34 mmol) in dry CH_2Cl_2 (62 ml) was added at −78 °C *m*-CPBA (231 mg, 1.34 mmol) and the mixture was gradually warmed to 0 °C during 3 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were concentrated and the residue was chromatographed on silica gel (40 g) with 8 : 1 hexane–ethyl acetate to afford epoxide (321 mg, 50%) as a colorless syrup along with the recovered **31** (167 mg, 27%). A stirred solution of this epoxide (565 mg, 1.18 mmol) in dry THF (11 ml) was added at −78 °C $LiAlH_4$ (44.8 mg, 1.18 mmol). After 4 h at −78 °C, water (0.045 ml), 10% aqueous NaOH (0.045 ml), and then water (0.135 ml) were slowly added. After 0.5 h at 25 °C, the insoluble materials were filtered and washed with ethyl acetate. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (15 g) with 15 : 1 hexane–ethyl acetate to afford alcohol (466 mg, 100%) as a colorless syrup. To a stirred solution of this alcohol (466 mg, 1.18 mmol) in dry CH_2Cl_2 (7.0 ml) were added at 0 °C 2,4,6-collidine (0.933 ml, 7.06 mmol), MsCl (0.274 ml, 3.54 mmol), and then LiBr (512 mg, 5.90 mmol). After 1 h at 0 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with $CHCl_3$. The extracts were concentrated and the residue was chromatographed on silica gel (15 g) with 2 : 1 hexane–ethyl acetate to afford a pale yellow syrup (522 mg, 96%). To a stirred solution of this syrup (522 mg, 1.14 mmol) in dry DMF (7.8 ml) was added at 0 °C a solution of NaH (54.8 mg, 2.28 mmol) and PhSH (0.288 ml, 2.85 mmol) in dry DMF (3.65 ml). After 1 h at 25 °C, saturated aqueous NH_4Cl was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (100 g) with 10 : 1 hexane–ethyl acetate to afford **4** (509 mg, 92%, a 2 : 1 mixture of the epoxide isomers) as a colorless syrup: R_f = 0.55 (5 : 1 hexane–ethyl acetate); IR (neat) 2980, 2940, 2870, 1740, 1440, 1380, 1240, 1220, 1100, 1050, 740, and 690 cm^{-1}; ^{1}H NMR (270 MHz) δ = 1.23—1.41 (15H, m), 1.59 (6H, m), 1.75—2.30 (6H, m), 2.95—3.02 (1H, m), 3.55 (2H, d, J = 7.2 Hz), 3.67—3.88 (2H, m), 3.91 (1/3H, dd, J = 5.6, 8.4 Hz), 3.97 (2/3H, dd, J = 3.2, 10.0 Hz), 5.32 (1H, m), 5.54 (1H, m), and 7.13—7.36 (5H, m). Found: C, 71.28; H, 8.95%. Calcd for $C_{29}H_{42}O_4S$: C, 71.57; H, 8.70%.

(1*Z*,3*S*,6*E*,8*S*,9*R*,11*S*,12*R*,13*R*)-3,13-Epoxy-9-(1-hydroxy-1-methylethyl)-11,12-(isopropylidenedioxy)-2,6,12-trimethyl-8-(phenylthio)-1,6-cyclotetradecadiene (33a) and Its (8*R*,9*S*)-Diastereomer (33b). 1.0 M Bu_2Mg in heptane (5.55 ml, 5.55 mmol) was added at 25 °C to 1.66 M *n*-BuLi in hexane (1.11 ml, 1.84 mmol). This mixture was added at 0 °C to a solution of **4** (300 mg, 0.616 mmol, a 2 : 1 mixture of the epoxide isomers) in dry THF (62 ml). After 3 h at 25 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with hexane. The extracts were washed with saturated aqueous NaCl and concentrated. The

residue was chromatographed on silica gel (40 g) with 20 : 1 hexane–acetone to afford **33a** (162 mg, 54%) as a colorless syrup and **33b** (65 mg, 22%) as colorless crystals.

33a: $R_f = 0.34$ (8 : 1 hexane–acetone); $[\alpha]_D^{27}$ +50.5, $[\alpha]_{435}^{27}$ +112 (*c* 0.32); IR (neat) 3470, 2980, 2940, 2870, 1740, 1440, 1380, 1240, 1220, 1170, 1100, 1060, 1020, and 760 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.21$ (3H, s), 1.37 (3H, br s), 1.40 (6H, s), 1.48 (6H, s), 1.61 (3H, br s), 1.64—1.80 (3H, m), 1.90—2.30 (4H, m), 2.45 (1H, dt, $J = 13.2$, 2.8 Hz), 3.72—3.85 (3H, m), 3.91 (1H, m), 4.00 (1H, dd, $J = 2.4$, 11.2 Hz), 5.16 (1H, dt, $J = 10.4$, 1.0 Hz), 5.51 (1H, m), and 7.20—7.42 (5H, m). Found: C, 71.35; H, 8.92%. Calcd for $C_{29}H_{42}O_4S$: C, 71.57; H, 8.70%.

33b: $R_f = 0.30$ (8 : 1 hexane–acetone); mp 135—136 °C (pillars from hexane); $[\alpha]_D^{34}$ −79.8, $[\alpha]_{435}^{34}$ −164 (*c* 0.61); IR (neat) 3450, 2980, 2940, 2860, 1440, 1370, 1250, 1220, 1100, 1060, and 760 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.29$ (3H, s), 1.33 (3H, s), 1.38 (9H, s), 1.51 (3H, br s), 1.63 (3H, br s), 1.77—2.45 (7H, m), 3.33 (1H, s), 3.69 (1H, dd, $J = 4.2$, 9.4 Hz), 3.81 (1H, dd, $J = 7.0$, 11.0 Hz), 3.89 (1H, dd, $J = 2.0$, 8.6 Hz), 4.00 (1H, br d, $J = 10.4$ Hz), 5.29 (1H, br d, $J = 11.0$ Hz), 5.57 (1H, m), and 7.14—7.37 (5H, m). Found: C, 71.31; H, 8.99%. Calcd for $C_{29}H_{42}O_4S$: C, 71.57; H, 8.70%.

Single-Crystal X-Ray Diffraction Analysis of 33b: Orthorhombic, $P2_12_12_1$, $a = 10.807(4)$, $b = 27.783(8)$, $c = 9.256(4)$ Å, $V = 2778(1)$ Å^3, $Z = 4$, $M_r = 486.71$, λ (Cu $K\alpha$) = 1.54178 Å, $\mu = 12.70$ cm^{-1}, $D_x = 1.163$ g cm^{-3}, $R = 0.070$ for 2398 reflections. Tables of positional parameters, bond lengths, bond angles, and structure factors are deposited as Document No. 71032 at the Office of the Editor of Bull. Chem. Soc. Jpn.

(1*E*,3*E*,7*S*,8*Z*,11*R*,12*R*,13*S*)-7,11-Epoxy-1-(1-hydroxy-1-methylethyl)-12,13-(isopropylidenedioxy)-4,8,12-trimethyl-1,3,8-cyclotetradecatriene (34). To a stirred solution of **33a** (141 mg, 0.290 mmol) in MeOH (4.2 ml) was added at 25 °C $NaIO_4$ (186 mg, 0.870 mmol). After 12 h at 25 °C, water was added and the mixture was extracted with 1 : 1 hexane–ethyl acetate. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was dissolved in toluene (5.8 ml) and to this was added at 25 °C triethylamine (0.122 ml, 0.875 mmol). After 3 h at 80 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with hexane. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (10 g) with 6 : 1 hexane–ethyl acetate to afford **34** (66.6 mg, 61%) as a colorless syrup: $R_f = 0.48$ (4 : 1 hexane–ethyl acetate); $[\alpha]_D^{31}$ −7.0, $[\alpha]_{435}^{31}$ −11.6 (*c* 0.29); IR (neat) 3450, 2980, 2940, 1650, 1450, 1380, 1250, 1220, 1100, 1050, 950, and 760 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.25$ (3H, s), 1.39 (3H, s), 1.41 (3H, s), 1.45 (6H, s), 1.62 (3H, br s), 1.65 (3H, br s), 1.72 (1H, m), 1.86 (1H, m), 1.97—2.11 (2H, m), 2.18 (1H, m), 2.37 (1H, br dd, $J = 7.6$, 14.2 Hz), 2.48 (1H, dd, $J = 7.0$, 14.2 Hz), 2.95 (1H, dd, $J = 5.0$, 14.2 Hz), 3.21 (1H, s), 3.94 (1H, dd, $J = 4.6$, 8.8 Hz), 4.00 (1H, dd, $J = 4.8$, 6.4 Hz), 4.07 (1H, br d, $J = 8.6$ Hz), 5.59 (1H, m), 5.80 (1H, d, $J = 4.0$ Hz), and 6.06 (1H, d, $J = 4.0$ Hz) Found: *m/z* 377.2695. Calcd for $C_{23}H_{37}O_4$: $(M+H)^+$, 377.2692.

(1*E*, 3*E*, 7*S*, 8*Z*, 11*R*, 12*R*, 13*S*)- 7, 11- Epoxy- 1- isopropenyl- 12, 13- (isopropylidenedioxy)- 4, 8, 12- trimethyl- 1, 3, 8- cyclotetradecatriene (35). To a stirred solution of **34** (58.8 mg, 0.156 mmol) in dry toluene (5.9 ml) was added at 25 °C silica gel (1.2 g: dried at 120 °C for 3 h). After 12 h at 35 °C, the insoluble materials were filtered and washed with ethyl acetate. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (10 g) with 20 : 1 hexane–ether to afford **35** (17.9 mg, 32%), **36** (4.5 mg, 8%) as colorless syrups, and the recovered **34** (21.7 mg, 37%).

35: $R_f = 0.35$ (10 : 1 hexane–ether); $[\alpha]_D^{29}$ +246, $[\alpha]_{435}^{29}$ +615 (*c* 0.51); IR (neat) 2980, 2940, 2860, 1730, 1660, 1610, 1450, 1380, 1250, 1220, 1100, 1050, 890, and 760 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, $C_6H_6 = 7.20$ ppm) $\delta = 1.37$ (3H, s), 1.38 (3H, s), 1.43 (3H, s), 1.51 (3H, m), 1.55 (1H, dddd, $J = 2.0$, 2.0, 7.1, 15.2 Hz), 1.63 (3H, br s), 1.64 (1H, dddd, $J = 2.0$, 8.5, 10.7, 15.2 Hz), 1.97 (3H, br d, $J = 1.0$ Hz), 2.06 (1H, br ddd, $J = 2.0$, 10.7, 13.9 Hz), 2.19 (1H, br dd, $J = 7.1$, 13.9 Hz), 2.27 (1H, m), 2.44 (1H, ddq, $J = 10.0$, 18.0, 2.4 Hz), 2.85 (1H, br dd, $J = 1.2$, 14.4 Hz), 3.44 (1H, dd, $J = 8.8$, 14.4 Hz), 4.05 (1H, br d, $J = 8.5$ Hz), 4.13 (1H, dd, $J = 4.2$, 10.0 Hz), 4.21 (1H, dd, $J = 1.2$, 8.8 Hz), 5.15 (1H, br s), 5.57 (1H, br s), 5.59 (1H, br dq, $J = 5.6$, 1.7 Hz), 6.18 (1H, br d, $J = 5.4$ Hz), and 6.39 (1H, br d, $J = 5.4$ Hz); ^{13}C NMR (100 MHz, C_6D_6, $C_6H_6 = 128.0$ ppm) $\delta = 18.6$, 20.2, 20.6, 21.4, 26.6, 26.6, 26.7, 28.2, 29.0, 39.3, 68.4, 80.0, 83.7, 84.2, 105.6, 113.2, 121.3, 124.3, 125.8, 134.5, 137.6, 138.9, and 143.0. Found: *m/z* 358.2510. Calcd for $C_{23}H_{34}O_3$: M^+, 358.2508.

36: $R_f = 0.42$ (10 : 1 hexane–ether); ^1H NMR (270 MHz) $\delta = 1.17$ (3H, s), 1.41 (1H, s), 1.47 (3H, s), 1.69 (3H, m), 1.88 (3H, br s), 1.90 (3H, br s), 1.93 (3H, br s), 2.06 (1H, m), 2.16 (1H, m), 2.28 (1H, m), 2.64 (1H, m), 2.76 (1H, dd, $J = 3.0$, 15.2 Hz), 2.99 (1H, dd, $J = 6.8$, 15.2 Hz), 3.68 (1H, dd, $J = 2.8$, 6.8 Hz), 3.95 (1H, br d, $J = 11.2$ Hz), 4.20 (1H, dd, $J = 4.0$, 10.0 Hz), 5.51 (1H, t, $J = 8.0$ Hz), 5.63 (1H, m), 6.47 (1H, d, $J = 16.0$ Hz), and 6.79 (1H, d, $J = 16.0$ Hz).

(1*S*,2*S*,4*E*,6*E*,10*S*,11*Z*,14*R*)-10,14-Epoxy-4-isopropenyl-1,7,11-trimethyl-4,6,11-cyclotetradecatriene-1,2-diol (3). To a stirred solution of **35** (35.6 mg, 0.0993 mmol) in dry MeOH (3.6 ml) was added at 25 °C PPTS (45.2 mg, 0.180 mmol). After 12 h at 25 °C, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with 1 : 1 hexane–ethyl acetate. The extracts were washed with saturated aqueous NaCl and concentrated. The residue was chromatographed on silica gel (5 g) with 3 : 1 hexane–ethyl acetate to afford **3** (3.5 mg, 11%) as colorless crystals along with the recovered **35** (22.8 mg, 64%).

3: $R_f = 0.40$ (2 : 1 hexane–ethyl acetate); mp 102—103 °C (decomp); $[\alpha]_D^{30}$ +209 (*c* 0.12, MeOH); UV (EtOH) λ 274 (sh, ε 25600), 282.5 (ε 26700), and 293 nm (sh, ε 21100); IR (neat) 3410, 2990, 2930, 2880, 1730, 1710, 1650, 1600, 1450, 1370, 1220, 1100, and 1050 cm^{-1}; ^1H NMR (400 MHz) $\delta = 1.24$ (3H, s), 1.68 (3H, m), 1.76 (1H, m), 1.77 (3H, br s), 2.01 (3H, br d, $J = 0.7$ Hz), 2.03 (1H, m), 2.08 (1H, m), 2.17 (1H, br dd, $J = 10.5$, 18.6 Hz), 2.27 (1H, ddq, $J = 10.2$, 17.3, 2.5 Hz), 2.51 (1H, br dd, $J = 8.5$, 18.6 Hz), 2.51 (1H, br), 2.95 (1H, br d, $J = 14.9$ Hz), 3.83 (1H, br d, $J = 8.8$ Hz), 3.94 (1H, br d, $J = 10.0$ Hz), 4.15 (1H, dd, $J = 4.4$, 10.2 Hz), 5.00 (1H, br s), 5.30 (1H, br s), 5.58 (1H, m), 6.15 (1H, br d, $J = 10.0$ Hz), and 6.44 (1H, d, $J = 10.0$ Hz). Found: *m/z* 318.2189. Calcd for $C_{20}H_{30}O_3$: M^+, 318.2195.

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