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Highly Stereoselective Synthesis of Two Natural Olefinic Diols via *N*-Oxide [2,3]Sigmatropic Rearrangement

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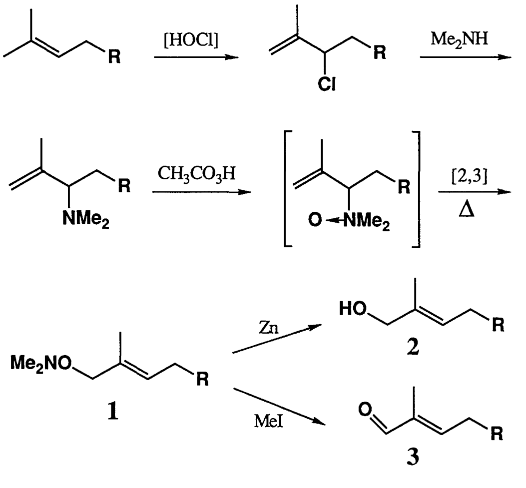
The [2,3]sigmatropic rearrangement of α-substituted *N*,*N*-dimethylmethallylamine *N*-oxides results in a highly stereoselective formation of trans olefins oxygenating at the allylic position, and providing a quite efficient synthesis of cuspidiol and plaunotol.

The allylic oxidation of *gem*-dimethyl olefins is one of the most important reactions for the synthesis of naturally occurring oxygenated terpenoids and biologically active isoprenoids. In these compounds, the stereochemistry of the double bonds has been clearly defined and the biological activity depends on the stereochemistry of the olefins. Hence, a large number of methods have been reported for the synthesis of terminal trans allylic alcohols and α,β-unsaturated aldehydes.[1] One of the more familiar methods is the Sharpless procedure,[1a] involving a catalytic amount of selenium dioxide and *t*-butyl hydroperoxide, which is an improvement in conventional oxidation using a stoichiometric amount of selenium dioxide.[1b] Although these reactions have been known to show a high *E* stereoselectivity, the product selectivity is insufficient to obtain a single product in good yield. In a preliminary communication[1c] we established the stereoselective conversion of a terminal methyl group of a terpene molecule to either an alcohol or an aldehyde via a common intermediate. The method consists of sequential ene-type chlorination, amination, *N*-oxidation, [2,3]sigmatropic rearrangement, followed by a reductive fission or a Hofmann-like elimination of the resultant allyloxyamines **1**, furnishing a trans allylic alcohol **2** and a trans α,β-unsaturated aldehyde **3**, respectively, as shown in Schme 1.

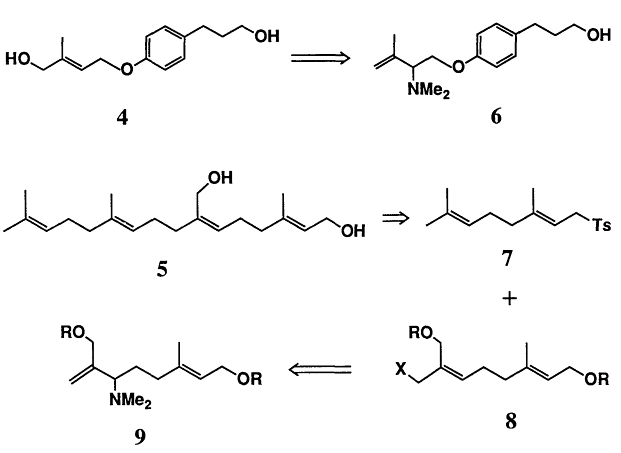


Scheme 1.

The present method has been successfully applied to two naturally occurring diols, cuspidiol (**4**) and plaunotol (**5**). Cuspidiol (**4**), one of the phenyl propanoids having an isoprenoid moiety in the molecule, was isolated from the xylem and back of *Xanthoxylum cuspidatum* Champ (*Fagara cuspidata* Engl.), a Formosan plant, as colorless needles by H. Ishii and coworkers.[2] Plaunotol (**5**), the most important component of a folk medicine named Plau-noi in Thailand, was reported to show remarkable antipeptic ulcer activities.[3]

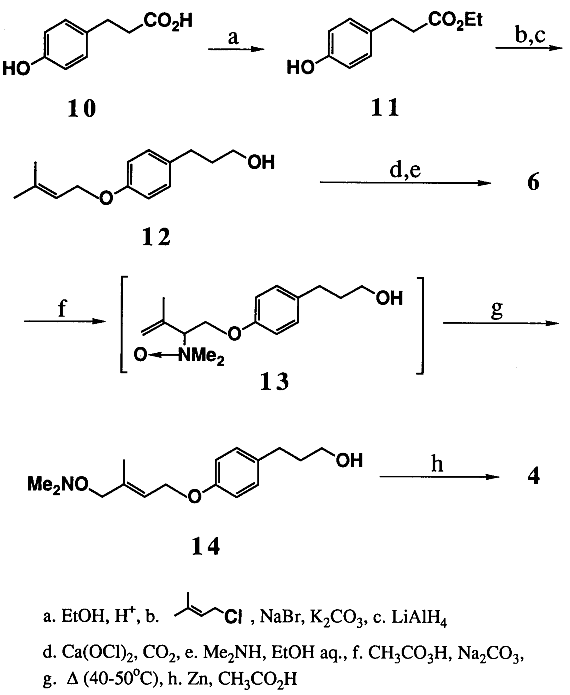
Results and Discussion

Scheme 2 shows the retrosyntheses of **4** and **5** on the basis of regio- and stereo-selective oxidation strategy.



Scheme 2.

The total synthesis of cuspidiol (**4**) is illustrated in Scheme 3. We used 3-(*p*-hydroxyphenyl)propionic acid (**10**) as an available starting material for our synthetic approach. After esterification of acid **10**, prenyl ether **12** could be efficiently prepared by the etherification of ethyl ester **11** with prenyl chloride in the presence of sodium bromide and potassium carbonate followed by a reduction with lithium aluminum hydride in excellent yield. The requisite internal allylamine **6** could be obtained by ene-type chlorination of olefin **12** using calcium hypochlorite[4] followed by amination with aqueous dimethylamine.[1c] A subsequent [2,3]sigmatropic rearrangement was carried out by the oxidation of allylamine **6** with peracetic acid followed by heating the crude allylamine *N*-oxide **13**. The resultant trans allyloxyamine **14** was treated with zinc dust in aqueous acetic acid to give the desired cuspidiol (**4**) in a good yield; its spectral data (IR and ^{1}H NMR) were identical with that in the literature.[2]

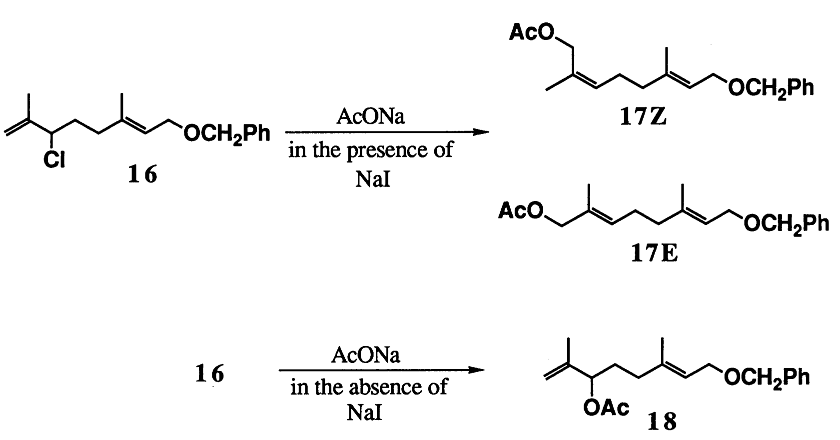


Scheme 3.

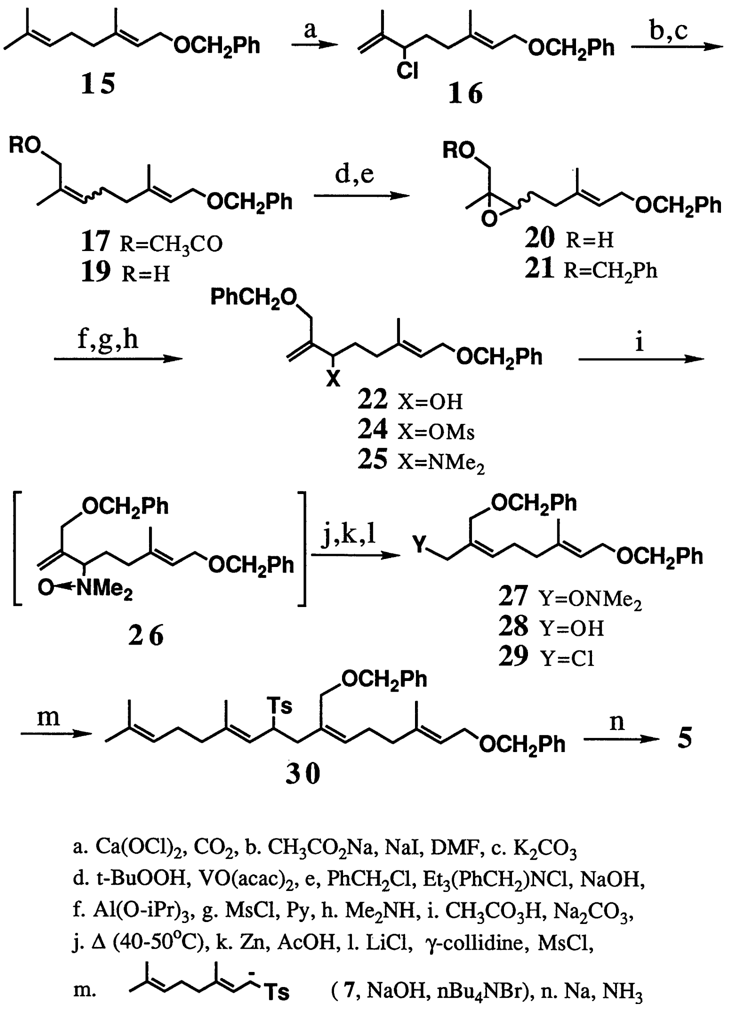
The synthesis of plaunotol (**5**) is illustrated in Scheme 4 and involves a coupling reaction of allylic chloride **29** with allylic sulfone **7** in the presence of a phase-transfer catalyst. Hypochlorous acid[4] reacted with geranyl benzyl ether (**15**) to provide allylic chloride **16** in quantitative yield. The conversion of chloride **16** into acetates is shown in Table 1. The reaction of chloride **16** was effected with sodium acetate in the presence of a catalytic amount of sodium iodide in *N*,*N*-dimethylformamide (DMF) at 80 °C for 24 h to give the S$_N$2′ displacement product **17** as a mixture of *Z* and *E* isomers in a ratio of 4:1 in a 90% combined yield. Similarly, the reaction of **16** with sodium acetate in the presence of sodium iodide in acetic acid at 60 °C for 24 h gave the S$_N$2′ product **17** in 45% yield as a mixture of *Z* and *E* isomers in a ratio of 1 : 3. To the contrary, the same reaction in the absence of sodium iodide in DMF at 80 °C resulted in the S$_N$2 displacement product **18** in 30% yield.

The hydrolysis of **17** using potassium carbonate gave terminal alcohol **19**. The ratio of the *Z* and *E* isomers remained unaltered during the hydrolysis and following epoxidation. The epoxidation of allylic alcohol **19** was efficiently achieved with *t*-butyl hydroperoxide and vanadium(IV) oxide acetylacetonate (VO(acac)$_2$) as a catalyst. After protection of the hydroxyl group as benzyl ether, epoxide **21** was subjected to isomerization with aluminum triisopropoxide (Al(O-*i*-Pr)$_3$)[6a](Scheme 5). First we anticipated[6b] that cis epoxide **21Z** should afford the desired internal allylic alcohol **22** and trans one should give undesired product **23**. Although **21Z** gave the desired product **22** completely, **21E** did not react even with excess amounts of Al(O-*i*-Pr)$_3$ and unreacted **21E** was

Table 1. Substitution Reactions of Allylic Chloride **16**

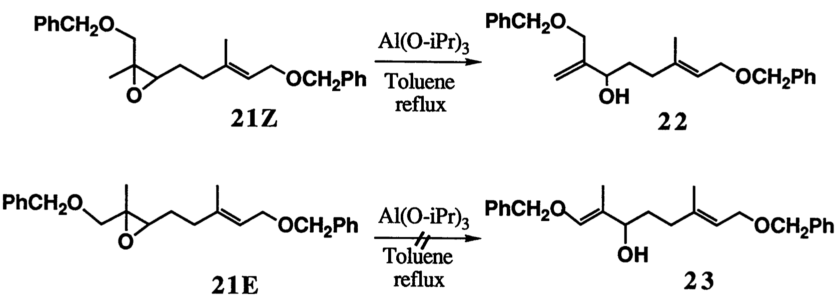


Solvent	NaI/equiv	Temp/°C	Time/h	Yield of acetate/%	**17Z**:**17E**
DMF	0.3	60	12	72	3:1
DMF	0.3	80	12	90	4:1
DMF	1.0	60	12	68	3.4:1
CH_3CO_2H	0.3	60	12	45	1:3
DMF	—	80	12	30	**18** only



a. $Ca(OCl)_2$, CO_2, b. CH_3CO_2Na, NaI, DMF, c. K_2CO_3
d. t-BuOOH, $VO(acac)_2$, e, $PhCH_2Cl$, $Et_3(PhCH_2)NCl$, NaOH,
f. $Al(O\text{-}iPr)_3$, g. MsCl, Py, h. Me_2NH, i. CH_3CO_3H, Na_2CO_3,
j. Δ (40-50°C), k. Zn, AcOH, l. LiCl, γ-collidine, MsCl,
m. Ts (7, NaOH, nBu_4NBr), n. Na, NH_3

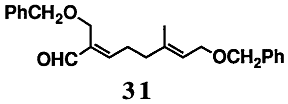
Scheme 4.



Scheme 5.

recovered.

The requisite internal allylamine **25** could be prepared by amination via mesylate **24**. Treatment of **25** with peracetic acid in dichloromethane at −50 °C in the presence of sodium carbonate resulted in the formation of the *N*-oxide intermediate **26**, which was followed by a [2,3]sigmatropic rearrangement during heating at 40—50 °C for 30 min to give trans allyloxyamine **27** in good yield. A reductive removal of the dimethylamino group was achieved with zinc dust in aqueous acetic acid at room temperature. The stereochemistry of *E* allylic alcohol **28** was confirmed by the ^{1}H NMR spectrum of aldehyde **31**, which was obtained in a quantitative yield by the treatment of either **28** with active manganese(IV) oxide in hexane at 0 °C for



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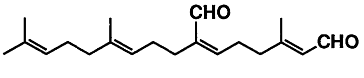
4 h or **27** with methyl iodide in chloroform under reflux for 3 h.[1c] The ^{1}H NMR spectrum of **31** exhibited a singlet at δ=9.42 attributable to the aldehyde proton of the *E* configuration and no other singlets in the formyl proton region, indicating an exclusive formation of the *E* isomer. Terminal trans alcohol **28** gave the corresponding chloride **29** by reaction with lithium chloride and 2,4,6-trimethylpyridine (γ-collidine) in the presence of methanesulfonyl chloride. *p*-Tolylsulfone **7** has been converted with sodium hydroxide in the presence of a phase-transfer catalyst[7] into its carbanion, which reacted with the chloride **29** to give C_{20} sulfone **30**. When **30** was subjected to a Na/NH_3 reduction, removal of both the sulfone residue and protective groups took place at the same time to furnish the desired plaunotol (**5**). The structure of the synthetic plaunotol was confirmed by a comparison of its spectral data (IR and ^{1}H NMR) with those in the literature.[3] Further evidence on the selective formation of the *Z* olefin was obtained as follows. The synthetic diol was treated with active manganese(IV) oxide in hexane at 0 °C for 4 h to afford dialdehyde **32** in a quantitative yield. ^{1}H NMR spectrum of **32** exhibited a singlet at δ=10.09 attributable to the aldehyde proton at C-7 of (*Z*)-double bond and no other singlets in the formyl proton region, indicating the exclusive formation of the *Z* isomer.



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The present method of stereoselective oxidation of *gem*-dimethyl olefins is very useful not only for the synthesis of trans oxygenated trisubstituted olefins, but also for an elaboration of the carbon skeletones involving *E*-olefinic bonds.

Experimental

M.p.s are uncorrected. IR spectra were measured on a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were obtained with a JEOL NM-C-60M or a JEOL FT-90Q spectrometer using tetramethylsilane as an internal standard. Column chromatography was carried out with Wako-gel C-200 (Wako Pure Chemical Industries).

3-[*p*-(3-Methyl-2-butenyloxy)phenyl]-1-propanol (12). To a round-bottomed flask was added 20.0 g (120 mmol) of 3-(*p*-hydroxyphenyl)propionic acid, 55 g (10 equiv) of ethanol, 150 mL of benzene, and 0.5 mL of concentrated sulfuric acid. A Dean and Stark trap was filled with benzene and the reaction solution was refluxed for 24 h, where the produced water remained in the trap as a bottom layer. The reaction mixture was extracted with a sodium hydrogencarbonate solution, washed with water, and then sat. brine, dried ($MgSO_4$) and evaporated, to give 23.4 g of a crude ester **11**. A solution of 6.0 g (30.9 mmol) of a crude ester **11**, 6.4 g (1.5 equiv) of potassium carbonate, 4.8 g (1.5 equiv) of sodium bromide, and 4.8 g (1.5 equiv) of prenyl chloride in acetone (80 mL) was refluxed for 24 h. Water (20 mL) was poured into the reaction mixture and extracted with ether. The ether layer was washed successively with water, brine, dried ($MgSO_4$) and evaporated, to give 8.2 g of a crude prenyl ether. To a suspension of 0.60 g (15.8 mmol) of lithium aluminum hydride in dry ether (50 mL) was added dropwise 4.0 g (15.2 mmol) of the crude prenyl ether in dry ether (10 mL) over 10 min at 0 °C. After stirring for 1 h at 0 °C, 5 mL of ice water was poured into the reaction mixture and further 40 mL of 3M hydrochloric acid (1M=1mol dm^{-3}) and extracted with ether. The ether layer was washed successively with sat. sodium hydrogencarbonate solution, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (80:20) to give 3.1 g (94%) of **12**. ^{1}H NMR ($CDCl_3$) δ=1.6—2.1 (2H, m), 1.67, 1.73 (each 3H, s), 2.55 (2H, t, *J*=7 Hz), 3.17 (1H, bs), 3.47 (2H, t, *J*=6 Hz), 4.33 (2H, d, *J*=7 Hz), 5.33 (1H, t, *J*=7 Hz), 6.40, and 6.87 (4H, ABq, *J*=8 Hz); IR (neat) 3350, 1515, 1240, and 1000 cm^{-1}. Found:C, 76.15; H, 9.2%. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%.

3-[*p*-(3-Methyl-2-dimethylamino-3-butenyloxy)phenyl]-1-propanol (6). To a suspension of 1.75 g (1.1 equiv) of 61% calcium hypochlorite in 10 mL of aqueous sat. sodium sulfate was added a solution of 3.0 g (13.6 mmol) of **12** in 90 mL of dichloromethane. Approximately 20 g of dry ice was added in small portions to this mixture with vigorous stirring over a period of 4 h. The reaction solution was filtered to remove insoluble salts. The organic layer was separated, dried ($MgSO_4$) and concentrated by a rotary evaporator to give 3.5 g of crude chloride. A solution of 3.5 g (13.6 mmol) of crude chloride in a mixed solvent of 10 mL of ethanol and 40 mL of 50% aqueous dimethylamine was stirred for 3 d at room temperature. Dilute alkaline (20 mmol) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (60:40) to give 2.72 g (77%) of allylamine **6**. ^{1}H NMR ($CDCl_3$) δ=1.6—2.1 (2H, m), 1.77 (3H, s), 2.28 (6H, s), 2.60 (2H, t, *J*=7 Hz), 2.77 (1H, s), 2.94 (1H, t, *J*=5 Hz), 3.60 (2H, t, *J*=6 Hz), 4.07 (2H, bd, *J*=7 Hz), 4.95 (2H, s), 6.80, and 7.20 (4H, ABq, *J*=8 Hz); IR (neat) 3350, 1510, 1240, and 1040 cm^{-1}. Found: C, 72.9; H, 9.5%. Calcd for $C_{16}H_{25}O_2N$: C, 72.97; H, 9.57%.

(*E*)-3-[*p*-(4-Dimethylaminooxy-3-methyl-2-butenyloxy) phenyl]-1-propanol (14). To a solution of 0.5 g (1.9 mmol) of allylamine **6**, 0.22 g of sodium carbonate in 20 mL of dichloromethane was added dropwise 0.4 g (1.1 equiv) of 40% peracetic acid at −60 °C. After stirring for 30 min at −60 °C, the reaction mixture was allowed to warm to room temperature over a 30-min period. Sat. aqueous sodium hydrogencarbonate (10 mL) was poured into the reaction mixture. After stirring for 10 min at room temperature, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure at 40—50 °C over 1 h. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (70:30) to give

0.39 g (74%) of allyloxyamine **14**. ^{1}H NMR ($CDCl_3$) δ=1.6—2.1 (2H, m), 1.68 (3H, s), 2.47 (6H, s), 2.63 (2H, t, *J*=7 Hz), 3.43 (2H, t, *J*=6 Hz), 3.97 (2H, s), 4.40 (2H, d, *J*=6 Hz), 5.3—5.7 (3H, m), 6.62, and 6.92 (4H, ABq, *J*=8 Hz); IR (neat) 3350, 1510, 1240, and 1015 cm^{-1}. Found: C, 68.6; H, 9.1%. Calcd for $C_{16}H_{25}O_3N$: C, 68.79; H, 9.02%.

Cuspidiol (4). To a round-bottomed flask was added 0.3 g (1.07 mmol) of allyloxyamine **14**, 0.5 g of zinc dust in a mixed solvent of 5 mL of acetic acid and 5 mL of water, and was stirred for 24 h at room temperature. After zinc dust was filtered, the reaction mixture was extracted with ether. The ether layer was washed successively with sat. aqueous sodium hydrogencarbonate and brine, dried ($MgSO_4$) and evaporated. The crude diol was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (50 : 50) to give 0.24 g (95%) of cuspidiol (**4**). mp 65—66 °C (65—67 °C)[2]; ^{1}H NMR ($CDCl_3$) δ=1.69 (3H, s), 1.78 (2H, s), 1.86 (2H, m), 2.59 (2H, t, *J*=7.5 Hz), 3.58 (2H, t, *J*=7 Hz), 3.99 (2H, s), 4.49 (2H, d, *J*=6 Hz), 5.72 (1H, t, *J*=6 Hz), 6.77, and 7.05 (4H, ABq, *J*=8.5 Hz); IR (KBr) 3350, 1235, 910, and 730 cm^{-1}. Found: C, 71.05; H, 8.5%. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%.

(2*Z*,6*E*)-8-Benzyloxy-2,6-dimethyl-2,6-octadienyl Acetate (17Z) and (2*E*,6*E*)-8-Benzyloxy-2,6-dimethyl-2,6-octadienyl Acetate (17E). To a suspension of 10.6 g (1.1 equiv) of 61% calcium hypochlorite in 100 mL of water was added a solution of 20 g (81.8 mmol) of geranyl benzyl ether (**15**) in 600 mL of dichloromethane. Approximately 60 g of dry ice was added in small portions to this mixture with vigorous stirring over a period of 5 h. The reaction was filtered to remove insoluble salts. The organic layer was separated, dried ($MgSO_4$) and concentrated by a rotary evaporator to give 23 g of crude chloride **16**. A solution of 23 g (81.8 mmol) of crude chloride **16**, 33.4 g (3 equiv) of sodium acetate trihydrate, 3.6 g (0.3 equiv) of sodium iodide in DMF (200 mL)was stirred for 12 h at 80 °C. The reaction mixture was partitioned between ether and water, and ether extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (90 : 10) to give 22.4 g (90%) of acetate **17** as a mixture of *Z* and *E* isomers in a ratio of 4 : 1 (by GLC). The similar substitution reactions were summarized in Table 1. ^{1}H NMR (CCl_4) δ=1.6—1.7 (6H, bs), 1.97 (3H, s), 1.9—2.3 (4H, m), 3.95 (2H, d, *J*=6 Hz), 4.42 (2H, s), 4.55 (2H, s), 5.1—5.6 (2H, m), and 7.28 (5H, s); IR (neat) 1730, 1455, 1230, 1060, 740, and 700 cm^{-1}.

(2*Z*,6*E*)-8-Benzyloxy-2,6-dimethyl-2,6-octadien-1-ol (19Z) and (2*E*,6*E*)-8-Benzyloxy-2,6-dimethyl-2,6-octadien-1-ol (19E). A solution of 20 g (66 mmol) of acetate **17**, 27.5 g (3 equiv) of potassium carbonate in a mixed solvent of 80 mL of methanol and 32 mL of water was stirred for 12 h at room temperature. After filtration of potassium carbonate and evaporation of methanol under reduced pressure, the reaction mixture was extracted with ether. The ether layers were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (80 : 20) to give 16.5 g (96%) of terminal alcohol **19** as a mixture of *Z* and *E* isomers in a ratio of 4 : 1 (by GLC). ^{1}H NMR (CCl_4) δ=1.6—1.7 (6H, bs), 2.0—2.2 (4H, m), 2.79 (1H, s), 3.83 (2H, d, *J*=6 Hz), 3.86 (2H, s), 4.33 (2H, s), 5.0—5.5 (2H, m), and 7.10 (5H, s); IR (neat) 3450, 1455, 1240, 1060, 740, and 700 cm^{-1}.

(6*E*)-8-Benzyloxy-2,3-epoxy-2,6-dimethyl-1-octenol (20). To a solution of 16.5 g (63.4 mmol) of alcohol **19** in dichloromethane (100 mL) was added portionwise 0.275 g (0.02 equiv) of $VO(acac)_2$ at 0 °C. The mixture was stirred for 5 min and 13.2 mL (1.5 equiv) of 7.18 M *t*-butyl hydroperoxide in 1,2-dichloroethane was added. The mixture was warmed to room temperature and stirred for 9 h. Aqueous sodium sulfite (20%, 50 mL) was then poured into the mixture. After stirring for 30 min, the resultant layers were separated and the aqueous layer was extracted with chloroform. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (60 : 40) to give 17 g (97%) of epoxy alcohol **20**. ^{1}H NMR ($CDCl_3$) δ=1.26 (3H, s), 1.60 (3H, s), 1.6—2.3 (4H, m), 2.5—3.1 (1H, m), 2.90 (1H, s), 3.46 (2H, s), 4.10 (2H, d, *J*=6 Hz), 4.40 (2H, s), 5.23 (1H, t, *J*=6 Hz), and 7.16 (5H, s); IR (neat) 3450, 1455, 1060, 740, and 700 cm^{-1}.

(2*E*)-1,8-Bis(benzyloxy)-6,7-epoxy-3,7-dimethyl-2-octene (21). A solution of 16 g (58 mmol) of epoxy alcohol in ether (10 mL), 11.0 g (1.5 equiv) of benzyl chloride, 50% sodium hydroxide (25 mL), and 0.7 g of triethylbenzyl ammonium chloride (TEBA) was stirred vigorously at 50 °C for 3 h. The mixture was poured into water (100 mL) and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic extracts were washed with water, then dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (80 : 20) to give 19.4 g (91%) of benzyl ether **21**. ^{1}H NMR ($CDCl_3$) δ=1.27 (3H, s), 1.57 (3H, s), 1.6—2.4 (4H, m), 2.5—2.9 (1H, m), 3.30 (2H. s), 3.83(2H, d, *J*=6 Hz), 4.33, 4.37 (each 2H, s), 5.23 (1H, t, *J*=6 Hz), and 7.07 (10H, s); IR (neat) 1455, 1090, 1060, 740, and 700 cm^{-1}. Found: C, 78.5; H, 8.15%. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25%.

(6*E*)-8-Benzyloxy-2-benzyloxymethyl-6-methyl-1,6-octadien-3-ol (22). To the round-bottomed flask with a reflux condenser was added 10 g (27.3 mmol) of benzyl ether **21** in dry toluene (60 mL), and 11.2 g (2 equiv) of $Al(O\text{-}i\text{-}Pr)_3$. The mixture was heated under reflux for 2 d with stirring, cooled, washed with 2M HCl (40 mL), water and brine, then dried ($MgSO_4$), and evaporated. The residue was purified by column chromatograph developing with a mixed solvent of hexane and ethyl acetate (70 : 30) to give 7.6 g (76%) of allylic alcohol **22** and 1.5 g of trans epoxide **21*E*** was recovered. ^{1}H NMR ($CDCl_3$) δ=1.60 (3H, s), 1.7—3.6 (5H, m), 2.90 (1H, s), 3.90 (4H, m), 4.39, 4.40 (each 2H, s), 5.07 (2H, bs), 5.34 (1H, t, *J*=6 Hz), and 7.14 (10H, s); IR (neat) 3400, 1450, 1070, 740, and 700 cm^{-1} . Found: C, 78.6; H, 8.2%. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25%.

(6*E*)-8-Benzyloxy-2-benzyloxylmethyl-3-dimethylamino-6-methyl-1,6-octadiene (25). To a solution of 5.5 g (15 mmol) of allylic alcohol **22** in dry dichloromethane(30 mL) and 5.9 g (5 equiv) of pyridine, was added dropwise 2.6 g (1.5 equiv) of methanesulfonyl chloride over 10 min at 0 °C. After stirring for 4 h at 0 °C, 10 mL of water was added to the mixture and the reaction mixture was extracted with ether. The ether layer was washed successively with 2M HCl, sat. aqueous sodium hydrogensulfate, water and brine, evaporated to give 6.7 g of a crude mesylate **24** as a pinky colored oil. A solution of 6.7 g (15 mmol) of a crude mesylate **24** in dry tetrahydrofuran (70 mL) and 70 mL of dimethylamine was stirred for 2 d at room temperature. Dilute alkaline (20 mmol) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (60 : 40) to give 4.6 g (77%) of allylamine **25**. ^1H NMR ($CDCl_3$) δ=1.57 (3H, s), 1.7—2.4 (4H, m), 2.14 (6H, s), 2.3—2.9 (1H, m), 3.86 (2H, d, *J*=6 Hz), 3.87 (2H, s), 4.34, 4.42 (each 2H, s), 4.94, 5.20 (each 1H, bs), 5.21 (1H, t, *J*=6 Hz), and 7.14 (10H, s). IR (neat) 2850, 1455, 1360, 1070, 910, 740, and 700 cm^{-1}. Found: C, 79.2; H, 8.95%. Calcd for $C_{26}H_{35}O_2N$: C, 79.35; H, 8.96%.

(2*E*,6*E*)-8-Benzyloxy-2-benzyloxymethyl-1-dimethylaminooxy-6-methyl-2,6-octadiene (27). To a solution of 1.8 g (4.6 mmol) of allylamine **25**, 0.6 g of sodium carbonate in 30 mL of dichloromethane was added dropwise 0.96 g (1.1 equiv) of 40% peracetic acid at −60 °C. After stirring for 30 min at −60 °C, the reaction mixture was allowed to warm to room temperature over a 30-min period. Sat. aqueous sodium hydrogencarbonate (25 mL) was poured into the reaction mixture. After stirring for 10 min at room temperature the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure at 40—50 °C over 1 h. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (70 : 30) to give 1.36 g (73%) of allyloxyamine **27**. ^1H NMR ($CDCl_3$) δ=1.58 (3H, s), 1.8—2.3 (4H, m), 2.45 (6H, s), 3.93 (2H, d, *J*=6 Hz), 3.95 (2H, s), 4.05 (2H, s), 4.41 (4H, s), 4.9—6.0 (2H, m), and 7.18 (10H, s); IR (neat) 1450, 1070, 1030, 740, and 700 cm^{-1}. Found: C, 76.15; H, 8.7%. Calcd for $C_{26}H_{35}O_3N$: C, 76.25; H, 8.61%.

(2*Z*,6*E*)-8-Benzyloxy-2-benzyloxymethyl-6-methyl-2,6-octadien-1-ol (28). To a round-bottomed flask was added 2.3 g (5.6 mmol) of allyloxyamine **27**, 2.0 g of zinc dust in a mixed solvent of 10 mL of acetic acid and 10 mL of water, and was stirred for 24 h at room temperatutre. After zinc dust was filtered, the reaction miture was extracted with ether. The ether layer was washed successively with sat. aqueous sodium hydrogencarbonate and brine, dried ($MgSO_4$) and evaporated. The crude diol was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (60 : 40) to give 2.05 g of alcohol **28** quantitatively. ^1H NMR ($CDCl_3$) δ=1.57 (3H, s), 1.7—2.5 (4H, m), 2.73 (1H, s), 3.90 (2H, d, *J*=6 Hz), 4.00 (4H, bs), 4.40 (4H, s), 5.0—5.8 (2H, m), and 7.20 (10H, s). IR (neat) 3450, 1450, 1070, 740, and 700 cm^{-1}. Found: C, 78.4; H, 8.15%. Calcd for $C_{24}H_{30}O_3$: C, 78.65;H, 8.25%.

(2*E*,6*E*)-1,8-Bis(benzyloxy)-2-chloromethyl-6-methyl-2,6-octadiene (29). To a solution of 1.5 g (4.1 mmol) of trans alcohol **28**, 0.35 g (2 equiv) of lithium chloride and 1 g (2 equiv) of γ-collidine in anhydrous DMF, was added portionwise 0.94 g (2 equiv) of methanesulfonyl chloride over 5 min at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was poured into 40 mL of water and extracted with ether. The ether layer was washed successively with sat. aqueous copper (II) nitrate, sat. aqueous sodium hydrogencarbonate and brine, dried ($MgSO_4$) and evaporated to give 1.58 g of a crude trans chloride **29**. ^1H NMR ($CDCl_3$) δ=1.60 (3H, s), 1.9—2.3 (4H, m), 3.97 (2H, d, *J*=6 Hz), 4.10 (4H, bs), 4.43, 4.47 (each 2H, s), 5.2—5.9 (2H, m), and 7.30 (10H, s); IR (neat) 1450, 1370, 1070, 740, and 700 cm^{-1}.

(2*E*,6*Z*,10*E*)-1-Benzyloxy-7-benzyloxymethyl-9-(*p*-tolylsulfonyl)-3,11, 15-trimethyl-2,6,10,14-hexadecatetraene (30). A mixture of 1.4 g (4.1 mmol) of geranyl sulfone (**7**), 3.5 mL of 50% aqueous sodium hydroxide, 0.13 g (10 mol%) of TEBA, and 1.58 g (4.1 mmol) of trans chloride **29** was stirred vigorously at room temperature for 4 h. The mixture was poured into water (50 mL) and extracted with ether. The ether layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (80 : 20) to give 2.12 g (75%) of C_{20} sulfone **30**. ^1H NMR ($CDCl_3$) δ=1.12 (3H, bs), 1.58 (6H, bs), 1.68 (3H, bs), 1.8—2.3 (8H, m), 2.40 (4H, bs), 3.05 (2H, bd, *J*=11 Hz), 3.90, 3.96 (each 1H, s), 3.98 (2H, d, *J*=7 Hz), 4.40, 4.43 (each 1H, s), 4.48 (2H, s), 4.8—5.1 (2H, m), 5.35 (2H, bt, *J*=7 Hz), 7.31 (10H, s), 7.25, and 7.68 (4H, ABq, *J*=8 Hz); IR (neat) 1450, 1310, 1150, 1080, 740, 700, and 670 cm^{-1}. Found: C, 76.4; H, 8.05%. Calcd for $C_{41}H_{52}O_4S$: C, 76.84; H, 8.18%.

Plaunotol(5). To 0.25 g (10.9 mmol) of sodium in ca. 15 mL of liquid ammmonia at −60 °C was added dropwise a solution of 0.5 g (0.714 mmol) of **30** in 10 mL of dry ether over a period of 10 min. After stirring for an additional 20 min at −60 °C, successively 5 mL of isoprene and 10 mL of methanol were added. The solution was allowed to gradually warm to room temperature and then poured into 50 mL of brine. After the aqueous solution was extracted with a mixture of ethyl acetate and diethyl ether (50 : 50 vol%), organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (80 : 20) to give 0.17 g (79%) of plaunotol (**5**). ^1H NMR ($CDCl_3$) δ=1.59 (3H, s), 1.60 (3H, s), 1.678, 1.683 (each 3H, s), 1.8—2.3 (14H, m), 4.09 (2H, s), 4.13 (2H, d, *J*=7.5 Hz), and 5.0—5.5 (4H, m); IR (neat) 3320, 1440, 1370, 1240, and 1000 cm^{-1}. Found: C, 78.5, H, 10.8%. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18%.

(2*E*,6*E*)-8-Benzyloxy-2-benzyloxymethyl-6-methyl-2,6-octadienal (31). (a) From Alcohol 28. To a solution of 55 mg (0.15 mg) of alcohol **28** in 5 mL of hexane was added 0.26 g (3.0 mmol) of manganese(IV) dioxide and the mixture was stirred for 3 h at 0 °C. After filtration, the solvent was evaporated to give an oil which was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (80 : 20) to give 54 mg of trans aldehyde **31** quantitatively. ^1H NMR($CDCl_3$) δ=1.64 (3H, s), 2.22 (2H, t, *J*=7 Hz), 2.61 (2H, dt, *J*=7.3 and 7 Hz), 4.03 (2H, d, *J*=7 Hz), 4.22 (2H, s), 4.49 (4H, s), 5.44 (1H, t, *J*=7 Hz), 6.68 (1H, t, *J*=7.3 Hz), 7.32 (10H, s), and 9.42 (1H, s); IR(neat) 1685 cm^{-1}. Found: C, 78.9; H, 7.9%. Calcd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74%.

(b) From Allyloxyamine 27. To a round-bottomed flask with a reflux condenser was added 0.1 g (0.24 mmol) of allyloxyamine **27** in dry chloroform (2 mL), and 0.6 mL (40 equiv) of methyl iodide. The mixture was heated under reflux for 3 h with stirring; after cooling 5 mL of water was added to the mixture. The reaction mixture was extracted with ether. The ether layer was washed with 5%

aqueous sodium thiosulfate (5 mL) and brine, then dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (80:20) to give 89 mg of trans aldehyde **31** quantitatively.

(2*E*,6*Z*,10*E*)-7-Formyl-3, 11, 15-trimethyl-2,6,10,14-hexadecatetraenal (32). To a solution of 19 mg (0.062 mmol) of the synthetic plaunotol (**5**) in 2 mL of hexane was added 0.11 g (1.24 mmol) of manganese(IV) dioxide and the mixture was stirred for 3 h at 0 °C. After filtration, the solvent was evaporated to give an oil which was purified by column chromatography developing with a mixed solvent of hexane and ethyl acetate (80:20) to give 18.7 mg of dialdehyde quantitatively. ^1H NMR ($CDCl_3$) δ=1.57 (3H, s), 1.61 (6H, s), 1.69 (3H, s), 1.9—2.9 (12H, m), 5.10 (2H, m), 5.89 (1H, d, J=8 Hz), 6.37 (1H, t, J=8.2 Hz), 10.00 (1H, d, J=8 Hz, terminal formyl proton), and 10.10 (1H, s, internal formyl proton); IR (neat) 1675 cm^{-1}. Found: C, 79.25; H, 9.85%. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%.

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