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Isolation and Structure of Antipeptic Ulcer Diterpene from Thai Medicinal Plant

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A potent antipeptic ulcer substance, acyclic diterpene alcohol, was isolated from a Thai medicinal plant identified with *Croton sublyratus* Kurz. The structure was determined by the spectral data and stereospecific synthesis to be (*E*,*Z*,*E*)-7-hydroxymethyl-3,11,15-trimethyl-2,6,10,14-hexadecatetraen-1-ol.

Keywords——diterpene; isolation; structure; synthesis; *Croton sublyratus*; antipeptic ulcer

In the course of our research for finding antipeptic ulcer substances of plant origin, we found that extract of a crude drug named Plau-noi in Thailand showed significant inhibitory activities against Shay-ulcer in rat and reserpine-induced ulcer in mouse. Plau-noi is a folk medicine used for anthelmintic and dermatologic agent and can be identified with stems of *Croton sublyratus* Kurz (Euphorbiaceae).[2]

As shown in Chart 1, acetone extract of the crude drug was separated into *n*-hexane layer and 80% aqueous methanol fraction. Benzene solution of the latter having the phar-

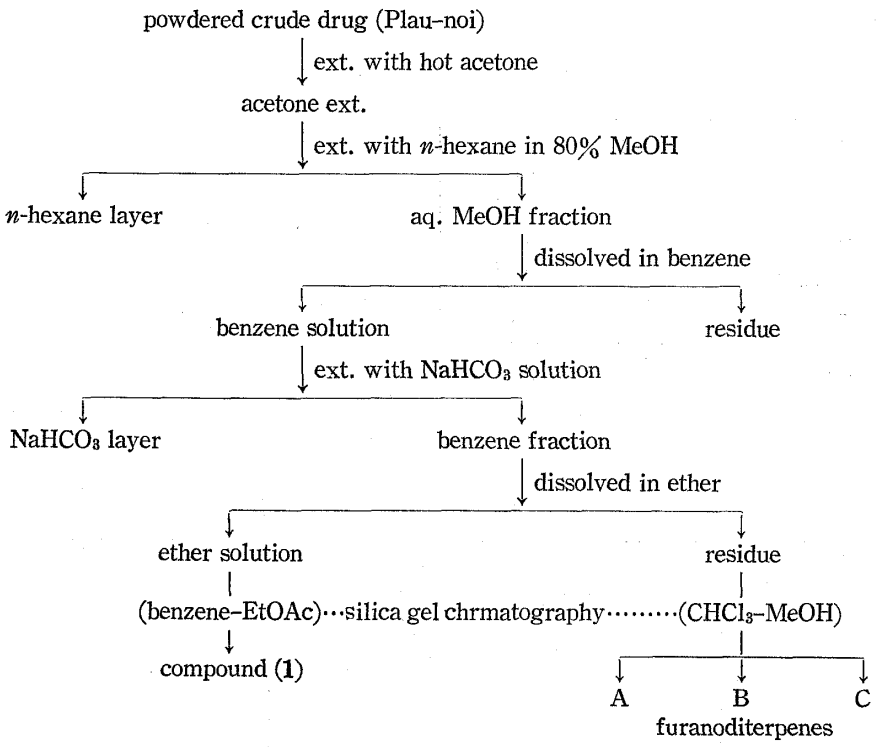


Chart 1. Extraction and Isolation of Antiulcer Substances

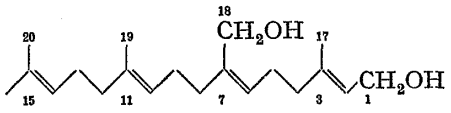
1) Location: *1-2-58 Hiromachi, Shinagawa-ku, Tokyo.*

2) The authors are indebted to Dr. H. Tsuyama, Professor Emeritus of Ochanomizu University, for his valuable suggestion for identification of the original plant.

macological activities was washed with sodium bicarbonate solution to remove inactive acidic substances and evaporated. From ether soluble part of the residue, compound (**1**) was isolated as anti-reserpine ulcer factor, and ether insoluble part gave several furanoditerpenoids[3] exhibiting anti-Shay ulcer activity.

The oily anti-reserpine ulcer substance (**1**) possesses a molecular composition of $C_{20}H_{34}O_2$ as shown by high resolution mass spectrometry. The infrared spectrum of **1** exhibits absorption bands at 3300, 1665 and 1000 cm^{-1}. The proton magnetic resonance (PMR) spectrum of **1** shows signals due to four vinyl methyl groups at δ 1.58 (6H, s) and δ 1.66 (6H, s), six allyl methylene groups at δ 1.9—2.3 (12H, m), two hydroxymethyl groups at δ 3.94 (2H, s) and δ 3.97 (2H, d), and four olefinic protons at δ 5.0—5.3 (4H, m). In addition to the above spectral data, the results of giving a diacetate and a bis-3,5-dinitrobenzoate suggest that **1** possesses an acyclic tetraprenyl structure having two hydroxyl groups. Comparing with the PMR spectrum of geranylgeraniol, it is clear that one of the five vinyl methyl groups of geranylgeraniol is oxidized into hydroxymethyl moiety in **1** revealing a singlet at δ 3.94. In order to determine the position of the hydroxyl group, decoupling experiments of PMR spectrum were carried out by using tris(dipivalomethano)europium as a shift reagent and all of the protons on **1** were able to assign as described in Table I. Since the signals due to protons attached to the carbons C-1 to C-9, C-17 and C-18 are strongly affected by the shift reagent as shown in Table I, it is suggested that the extra hydroxyl group of **1** must be at C-17 or C-18 position. PMR spectrum of the aldehyde obtained by oxidation of **1** with manganese dioxide shows a triplet at δ 6.38 and a doublet at δ 5.88 attributable to

Table I. PMR Spectrum and Effect of Shift Reagent



1

	CCl_4	$Eu(DPM)_3$[a]	$\Delta\delta$		CCl_4	$Eu(DPM)_3$[a]	$\Delta\delta$
16-CH_3	1.66	1.67	0.01	18-CH_2	3.94	9.89	5.95
20-CH_3	1.58	1.60	0.06	6-CH	5.14	7.68	2.54
14-CH	5.05	5.12	0.06	5-CH_2	(2.3—1.9)	4.86	2.96
13-CH_2	(1.95)	2.15	0.20	4-CH_2		4.29	2.02
12-CH_2		2.15	0.20	17-CH_3	1.67	4.25	2.45
19-CH_3	1.58	1.93	0.35	2-CH	5.30	11.20	5.90
10-CH	5.05	5.90	0.85	1-CH_2	3.97	11.66	7.69
9-CH_2	(2.01)	3.75	1.65				
8-CH_2		4.90	2.80				

	Geraniol			Nerol		
	CCl_4	$Eu(DPM)_3$[a]	$\Delta\delta$	CCl_4	$Eu(DPM)_3$[a]	$\Delta\delta$
8-CH_3	1.66	2.16	0.50	1.67	2.36	0.69
10-CH_3	1.59	2.06	0.47	1.59	2.13	0.54
6-CH	5.03	6.13	1.10	5.05	6.63	1.58
5-CH_2	2.10	3.60	1.50	2.05	4.07	2.02
4-CH_2	2.10	3.80	1.70	2.05	5.35	3.30
9-CH_3	1.65	4.51	2.86	1.72	3.54	1.82
2-CH	5.33	12.12	6.79	5.36	12.48	7.12
1-CH_2	4.01	15.30	11.29	3.96	15.85	11.89

a) Taken in the presence of 50% molar equivalent of tris (dipivalomethano)europium in CCl_4.

3) Report of structural studies is in preparation.

olefinic protons on the double bond conjugated with the aldehyde, therefore the extra hydroxyl group must not be at C-17 position.

Geometry of the double bonds of **1** was also presumed on the basis of the PMR spectrum. Chemical shift of the C-4 methylene protons of nerol are more strongly affected than that of the C-9 methyl protons in the presence of the shift reagent, while in the case of geraniol, signal of the C-9 methyl group are shifted more than that of C-4 methylene protons as shown in Table I. Effect of the shift reagent on **1** is the same feature as geraniol indicating that the double bond at C-2 should be *E*-configuration. Configuration of the double bonds at C-6 and C-10 might be assigned by the chemical shifts of the C-6 olefinic proton at δ 5.14 and C-19 methyl protons at δ 1.58 to *Z* and *E* respectively.[4]

Furthermore, structure and stereochemistry of the anti-reserpine ulcer substance (**1**) were clarified by an unambiguous synthesis. Total synthesis of the compound bearing (*E,Z,E*)-configuration was successfully ashieved by application of the method developed by E. J. Corey and H. Yamamoto[5] as depicted in Chart 2. This synthetic route involves a stereospecific sequence for trisubstituted olefine having an allylic alcohol *via* β-oxido phosphonium ylide. Reaction of phosphonium iodide (**2**), prepared by Coates' procedure,[6] with aldehyde (**3**) obtained by ozonolysis of geranyl 2-tetrahydropyranyl ether, in the presence of *n*-butyllithium in tetrahydrofuran gave a Wittig betaine (**4**). Subsequent reaction of the betaine with *sec*-butyllithium and dried paraformaldehyde followed by treatment of the resulting tetrahydropyranyl ether (**5**) with acid furnished the desired compound bearing (*E,Z,E*)-configuration.

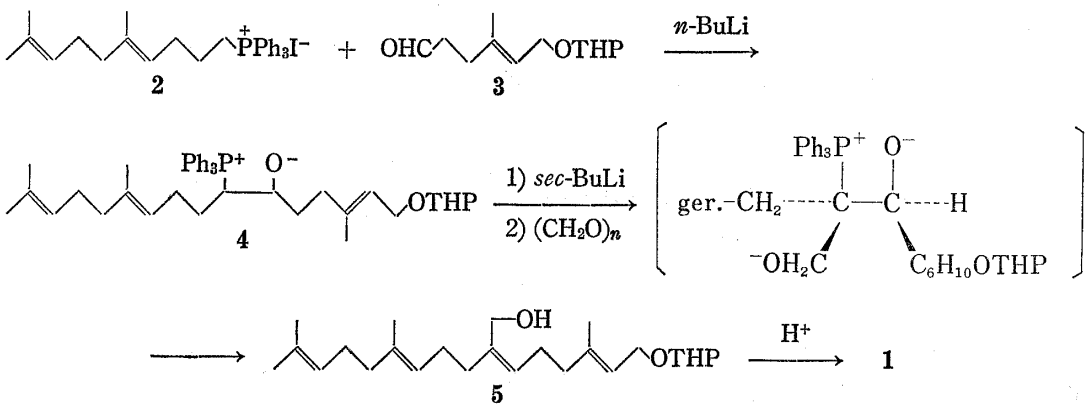


Chart 2

On the other hand a geometric isomer having (*E,E,E*)-configuration was synthesized by the method of [2,3] sigmatropic rearrangement of allylic sulfoxide developed by D.A. Evans.[7] As shown in Chart 3, geranylacetone was converted into allylalcohol (**7**) by oxirane formation followed by treatment of the oxirane (**6**) with base.[8] Sulfenyl ester prepared from the allyl alcohol (**7**) and phenylsulfenyl chloride was rearranged into the desired starting material (**8**) in aprotic solvent.[9] In order to synthesize another unit of the starting material, homoisopentenyl

4) K.C. Chan, R.A. Jewell, W.H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968); R.B. Bates and D.M. Gale, *J. Am. Chem. Soc.*, **82**, 5749 (1960); R.B. Bates and B.J. Gruner, *J. Org. Chem.*, **28**, 1086 (1963).
5) E.J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 6637 (1970); *idem*, *ibid.*, **92**, 6638 (1970).
6) R.M. Coates and W.H. Robinson, *J. Am. Chem. Soc.*, **93**, 1785 (1971).
7) D.A. Evans, G.C. Andrews, T.T. Fujimoto, and D. Wells, *Tetrahedron Lett.*, **1973**, 1385; *idem*, *ibid.*, **1973**, 1389.
8) B. Rickborn and K.R. Thummel, *J. Org. Chem.*, **34**, 3583 (1969); C.L. Kissel and B. Rickborn, *ibid.*, **37**, 2060 (1972).
9) P. Bickart, F.W. Carson, J. Jacobus, E.G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4869 (1968); R. Tang and K. Mislow, *ibid.*, **92**, 2100 (1970).

iodide (**11**), isopentenyl derivative (**9**) converted from 1-chloro-2-methyl-4-acetoxy-2-butene,[10] was treated with phenylthiomethyllithium and cuprous iodide to give sulfide (**10**), the phenylthio group of this compound was then replaced by iodine by treatment with excess of methyl iodide.[11] The allylic sulfoxide (**8**) was alkylated with **11** in the presence of lithium diisopropylamide to give sulfoxide (**12**), which was converted into the (*E,E,E*)-isomer by treatment with trimethyl phosphite in protic solvent and removal of the protecting group of **13**.

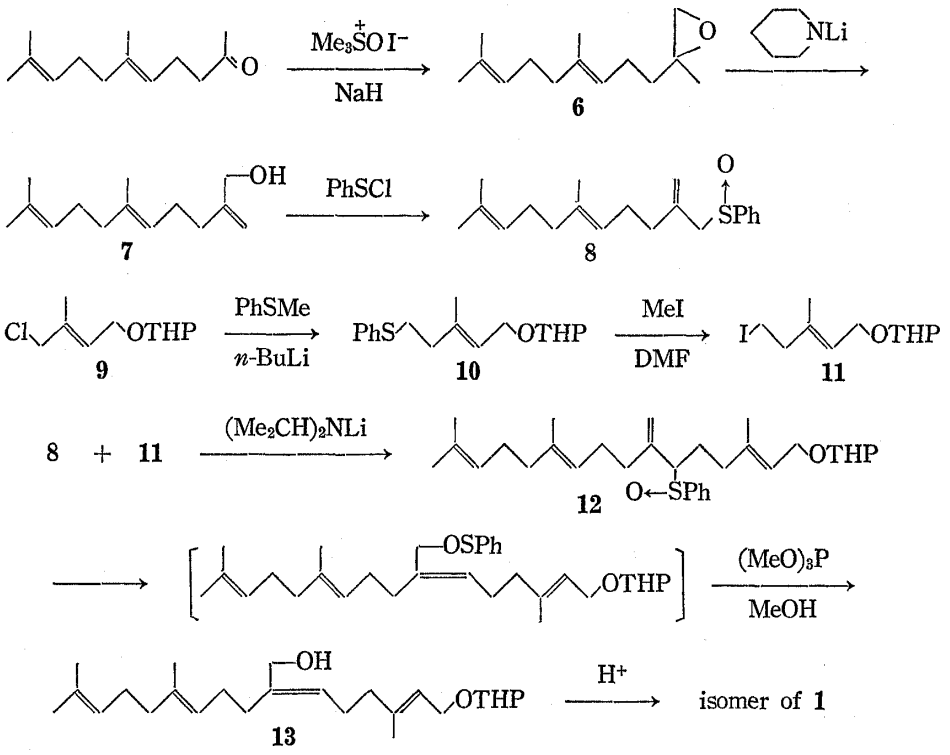


Chart 3

Differences of the chemical shifts on the PMR spectra between the both isomers were observed at the hydroxymethylene protons at C-18 and the olefinic proton at C-6 position (*vide* experimental part). Consequently, (*E,Z,E*)-isomer was found to be identical with the natural product in all respects including PMR spectral data.

Antipeptic ulcer activities[12] were summarized in Table II indicating that (*E,Z,E*)-7-hydroxymethyl-3,11,15-trimethyl-2,6,10,14-hexadecatetraen-1-ol isolated from the herbal medicine, Plau-noi, showed remarkable inhibitory activities agenst several ulcers including reserpine-induced ulcer.

Table II. Antiulcer Effect of Compound (**1**)

Ulcer	Animal	Route	Compound (**1**) ID_{50} (mg/kg)	Gefarnate ID_{50} (mg/kg)
Reserpine	Mouse	*i.p.*	<10	300
Stress	Mouse	*p.o.*	195	275
Stress	Rat	*p.o.*	73	300
Aspirin	Rat	*p.o.*	190	350

10) W. Oroshnik and R.A. Mallory, *J. Am. Chem. Soc.*, **72**, 4608 (1950).
11) E.J. Corey and M. Jautelat, *Tetrahedron Lett.*, **1968**, 5787.
12) S. Kobayashi, A. Morita, C. Ishibashi, M. Miyamoto, and A. Ogiso, in preparation.

Experimental[13]

Bioassay——Anti-Shay ulcer activity was tested in rats.[14] Male Donryu rats, weighing 130—150 g and fasted for 48 hr, underwent ligation of the pylorus under ether anesthesia and were killed 18 hr after ligation. Through macro-scopic examination of the stomach, the severity of the lesions of the fore-stomach was classified according to an arbitrary scale (0—5). The test sample was intraperitoneally administered immediately after ligation.

Anti-reserpine ulcer activity was tested in mice.[15] The test compound was intraperitoneally administered to male DDY mice, weighing 28—33 g, and 30 min later, reserpine was subcutaneously administered in the dose of 10 mg/kg. After 18 hr from the reserpine administration, the animal was sacrificed, and the stomach was isolated. This stomach was inflated with 2 ml of 0.5% formalin and wax fixed. Then the stomach was opened by cutting along the greater curvature, and the ulcer area was measured with a stereoscopic microscope. The ulcer areas of the treated group and the control group were compared, and the inhibitory ratios were calculated.

Extraction and Isolation of Active Components——A crushed crude drug (81.5 kg of commercial Plau-noi) was extracted three times with acetone under reflux. After evaporation of the solvent, the residue was dissolved in 10 l of 80% aqueous methanol and washed with *n*-hexane. The concentrated methanol layer was poured into 40 l of benzene under vigorous stirring. After washing with an aqueous sodium hydrogen carbonate solution, the benzene solution was evaporated and the residue was extracted with ether. The ether soluble fraction was chromatographed on silica gel (3 kg) using benzene and ethyl acetate as eluent. Each fraction was checked by bioassay against experimental ulcer to isolate 53 g of the anti-reserpine ulcer substance (**1**): IR $\nu_{max}^{liq.}$ cm^{-1}: 3300, 1665, 1440, 1380, 1000. PMR (CCl_4) δ: 1.58 (6H, s), 1.66 (6H, s), 1.9—2.3 (12H, m), 3.94 (2H, s), 3.97 (2H, d), 5.05 (2H, m), 5.14 (1H, t), 5.30 (1H, t). MS *m/e*: 306.255 (M^+, Calcd. for $C_{20}H_{34}O_2$ 306.256), 288, 270, 121, 81, 69 (base).

The ether insoluble fraction was chromatographed on silica gel (5 kg) using chloroform and methanol as eluent. Fractionation guided by bioassay led to isolate 12 g of anti-Shay ulcer furanoditerpene A and 28 g of furanoditerpene B showing the same activity.

Furanoditerpene A: mp 180—181° $[\alpha]_D^{20}$ −142° (*c*=1.0, acetone). IR ν_{max}^{Nujol} cm^{-1}: 3380, 1750, 1720, 1675, 1635, 1505, 1235, 1210, 1040, 875, 760. PMR (acetone-d_6) δ: 2.02 (3H, s), 2.0—3.5 (7H, m), 3.31 (1H, d), 4.01 (1H, d), 4.68 (1H, q), 4.75 (1H, m), 4.76 (1H, s), 5.06 (1H, d), 5.39 (1H, d), 5.95 (1H, q), 6.42 (1H, t), 6.68 (1H, d), 7.48 (2H, m). *Anal.* Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.54; H, 5.78.

Furanoditerpene B: mp 170—172°. $[\alpha]_D^{20}$ −144° (*c*=1.0, acetone). IR ν_{max}^{Nujol} cm^{-1}: 3450, 3320, 1680, 1640, 1600, 1505, 1040, 885, 770. PMR (acetone-d_6) δ: 1.8—3.3 (7H, m), 3.23 (1H, d), 4.01 (1H, d), 4.60—5.15 (4H, m), 4.95 (1H, s), 5.32 (1H, d), 6.40 (1H, m), 6.73 (1H, s), 7.49 (2H, m). *Anal.* Calcd. for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 63.93; H, 6.00.

Compound (1) Diacetate——A solution of 1.0 g of the compound (**1**) in 5 ml of pyridine and 2 ml of acetic anhydride was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed successively with an aqueous sodium hydrogen carbonate solution, dilute hydrochloric acid and water. Upon evaporation, 1.1 g of the desired diacetate was obtained. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1235, 960. PMR ($CDCl_3$) δ: 1.58 (3H, s), 1.62 (3H, s), 1.70 (6H, s), 2.07 (6H, s), 1.8—2.4 (12H, m), 4.60 (2H, d), 4.67 (2H, s), 4.9—5.6 (4H, m).

Compound (1) Bis-3,5-dinitrobenzoate——To a solution of 1.0 g of the compound (**1**) in 25 ml of pyridine was added 2.5 g of 3,5-dinitrobenzoyl chloride and the mixture was allowed to stand for 5 hr. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed successively with an aqueous sodium hydrogen carbonate solution, dilute hydrochloric acid and water. Evaporation of the solvent and recrystallization from ether–methanol gave the desired bis-3,5-dinitrobenzoate. mp 83—84°. PMR ($CDCl_3$) δ: 1.60 (9H, s), 1.67 (3H, s), 1.8—2.3 (12H, m), 4.98 (2H, d), 5.01 (2H, s), 5.0—5.7 (4H, m), 9.17 (6H, s). *Anal.* Calcd. for $C_{34}H_{38}N_4O_{12}$: C, 58.84; H, 5.52; N, 8.06. Found: C, 58.69; H, 5.59; N, 7.97.

Oxidation of Compound (1)——To a solution of 300 mg of compound (**1**) in 10 ml of *n*-hexane was added 2 g of manganese dioxide and the mixture was stirred for 5 days at room temperature. After filtration, the solvent was evaporated to give an oil which was purified by a preparative thin-layer chromatography on silica gel developing with a mixed solvent of benzene and ethyl acetate (2: 1) to give 24.0 mg of dialdehyde.

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13) The PMR spectra were measured with Varian T-60 and HA-100 spectrometer using tetramethylsilane as an internal reference. The IR spectra were determined on JASCO IRA-2 spectrophotometer. The UV spectra were measured in 99% ethanol using Hitachi Model 624 Digital spectrophotometer. Mass spectra (MS) were measured on JEOL JMS-01SG spectrometer. Preparative thin-layer chromatography was performed by use of TLC-plates Silica gel 60 F_{254} (thickness 2 mm, E. Merk). For column chromatography, silica gel 60—110 mesh (Kanto Chemical Co., Inc., Tokyo) was used.

14) H. Shay, S.A. Komarov, S.S. Fels, D. Meranze, M. Gruenstein, and H. Spielt, *Gastroenterology*, **5**, 43 (1945).

15) J.C. Blackmann, D.S. Campion, and F.N. Fastier, *Brit. J. Pharmacol.*, **14**, 112 (1959).

IR $\nu_{max}^{liq.}$ cm^{-1}: 1676. PMR (CCl_4) δ: 1.57 (9H, s), 1.67 (3H, s), 1.9—3.0 (12H, m), 5.10 (2H, m), 5.88 (1H, d), 6.38 (1H, t), 10.07 (1H, d), 10.19 (1H, s). UV λ_{max} nm (ε): 237 (15600).

Total Synthesis of Compound (1)——To a suspension of 9.0 g of (*E*)-5,9-dimethyl-4,8-decadien-1-yltriphenylphosphonium iodide (**2**) in 60 ml of anhydrous tetrahydrofuran was added dropwise the equimolar amount of *n*-butyllithium at 0° in a stream of argon. After stirring for 30 min at room temperature, the reaction mixture was cooled to −78°, and to this mixture was added a solution of 3.3 g of (*E*)-4-methyl-6-(2′-tetrahydropyranyloxy)-4-hexenal (**3**) in 20 ml of anhydrous tetrahydrofuran. After stirring for 30 min, the mixture was maintained at −50° and to this was added the equimolar amount of a *sec*-butyllithium–pentane solution. The temperature was slowly raised to −10°, 1.5 g of dry paraformaldehyde was added at once thereto. The reaction mixture was then stirred at room temperature for 2 hr, and after addition of ice-water, extracted with *n*-hexane. From the *n*-hexane extract was obtained 7.2 g of an oil, which was then chromatographed on a silica gel column (20 g). The resulting oil (5.8 g) was dissolved in 50 ml of methanol containing 100 mg of *p*-toluenesulfonic acid and allowed to stand overnight. After addition of an aqueous sodium hydrogen carbonate solution, the mixture was extracted with ether. The crude product obtained from the ether layer was further purified by a silica gel column (30 g), yielding 1.8 g of the desired product, whose spectrum data were coincided with that of the compound (**1**) isolated from crude drug.

2,6,10-Trimethyl-1,2-epoxy-5,9-undecadiene (6)——To a mixture of 1.02 g of 52% sodium hydride and 4.7 g of trimethyloxosulfonium iodide was added 30 ml of dimethyl sulfoxide at 15° under nitrogen atmosphere. After evolution of hydrogen ceased, a solution of 3.8 g of geranylacetone in 30 ml of dry tetrahydrofuran was added to the reaction mixture at room temperature. After stirring for 15 min at room temperature, the mixture was warmed to 50° for 1 hr, cooled, diluted with water and the product was extracted with *n*-hexane. The desired compound was purified by distillation, bp 87° (3 mmHg). PMR (CCl_4) δ: 1.27 (3H, s), 1.6 (9H, m), 2.43 (2H, s), 5.1 (2H, m).

2-Methyl-6,7-dimethyl-5,9-undecadien-1-ol (7)——To a solution of 4 ml of piperidine in 45 ml of dry tetrahydrofuran was added 25 ml of 1.6 M *n*-butyllithium at 0° under nitrogen atmosphere. After 10 min, a solution of 4.16 g of the oxirane (**6**) in 10 ml of tetrahydrofuran was added to the reaction mixture and stirring was continued for 12 hr at room temperature. After addition of water, the mixture was extracted with ether, the ether extract was washed successively with dilute hydrochloric acid and water. The product was chromatographed on silica gel and eluted with benzene to give 2.25 g of the allylalcohol (**7**). IR $\nu_{max}^{liq.}$ cm^{-1}: 3350, 1650, 1060, 1020, 900. PMR (CCl_4) δ: 1.6 (9H, m), 4.00 (2H, s), 4.90 (2H, d), 5.10 (2H, m).

1-(Phenylsulfinyl)-2-methyl-6,10-dimethyl-5,9-undecadiene (8)——To a solution of 1.12 g of the allylalcohol (**7**) in 50 ml of dry ether was added 4 ml of 1.6 M *n*-butyllithium at 0° under nitrogen. After stirring for 30 min, a solution of 940 mg of phenylsulfenyl chloride in 10 ml of ether was added to the mixture and stirring was continued for 30 min at room temperature. The reaction mixture was diluted with ether and washed with water. The product obtained from the ether layer was chromatographed on silica gel to give 754 mg of the desired phenylsulfoxide (**8**). IR $\nu_{max}^{liq.}$ cm^{-1}: 1640, 1080, 1070, 1040, 900, 740, 690. PMR (CCl_4) δ: 1.65 (6H, m), 3.37 (2H, s), 4.90 (2H, d), 5.1 (2H, m), 7.50 (5H, m).

4-Chloro-3-methyl-2-buten-1-ol Tetrahydropyranyl Ether (9)——To a solution of 5.0 g of 1-chloro-2-methyl-4-acetoxy-2-butene in 50 ml of methanol was added 5.0 g of potassium carbonate and the mixture was stirred for 3 hr under ice-cooling. After filtration and removal of the solvent, the residue was dissolved in benzene and washed with water. The benzene layer was dried over potassium carbonate and evaporated to dryness. The residue was dissolved in 20 ml of dihydropyran containing 50 mg of *p*-toluenesulfonic acid and the solution was stirred for 5 hr under ice-cooling. After evaporation of the excess dihydropyran, the product was dissolved in benzene and washed with aqueous sodium carbonate solution. The benzene layer was dried over potassium carbonate and evaporated to dryness. Distillation of the resulting product yielded 5.2 g of the desired compound (**9**). bp 90° (1.0 mmHg). PMR (CCl_4) δ: 1.76 (3H, s), 3.96 (2H, s), 4.05 (2H, t), 5.66 (1H, t).

5-Iodo-3-methyl-2-penten-1-ol Tetrahydropyranyl Ether (11)——To a solution of 1.35 g of triethylenediamine and 1.4 ml of thioanisol in 30 ml of dry tetrahydrofuran was added 8.3 ml of 1.6 M *n*-butyllithium–hexane solution at 0° under nitrogen. After stirring for 45 min at room temperature, the reaction mixture was cooled to −50° and 3.2 g of cuprous iodide was added. To this mixture a solution of 2.05 g of **9** in 5 ml of tetrahydrofuran was added and stirring was continued for 3 hr at −25°. The reaction mixture was gradually warmed to room temperature and extracted with *n*-hexane. The product obtained from the *n*-hexane layer was purified by column chromatography to give 1.6 g of the phenylsulfide (**10**). A mixture of 1.6 g of **10**, 4.3 ml of methyl iodide, one drop of mercury and 30 mg of calcium carbonate was refluxed for 20 hr under stirring. After removal of the excess methyl iodide, the mixture was extracted with *n*-hexane. Work-up as usual gave 920 mg of the desired iodide (**11**). PMR (CCl_4) δ: 1.67 (3H, s), 3.15 (2H, t), 4.13 (2H, d), 5.43 (1H, t).

6-(Phenylsulfinyl)-7-methylene-3,11,15-trimethyl-2,10,14-hexadecatrien-1-ol Tetrahydropyranyl Ether (12)——A solution of 630 mg of the sulfoxide (**8**) in 5 ml of dry tetrahydrofuran was added to a solution of lithium diisopropylamide in 6 ml of tetrahydrofuran prepared from 0.285 ml of diisopropylamine and 1.35 ml of 1.6 M *n*-butyllithium–hexane solution. The reaction was carried out at −50° under nitrogen. After 15 min, a solution of 790 mg of the iodide (**11**) in 3 ml of tetrahydrofuran was added at the same temperature

and stirring was continued for 5 hr at −30°. After addition of water, the reaction mixture was extracted with ether. The product was purified by a preparative thin-layer chromatography on silica gel developing with a mixed solvent of benzene and ethyl acetate (5: 1) to yield 700 mg of the crude desired compound (**12**).

(*E*,*E*,*E*)-Isomer of Compound (1)——A solution of 200 mg of the crude sulfoxide (**12**) in 2 ml of methanol containing 0.2 ml of trimethyl phosphite was allowed to stand 1 week at room temperature. The resulting material obtained by an usual work-up was dissolved in 2 ml of methanol containing 2 mg of *p*-toluenesulfonic acid and the solution was kept at room temperature for 2 hr. The product was purified by a preparative thin-layer chromatography on silica gel developing with a mixed solvent of benzene and ethyl acetate (1: 1) to yield 60 mg of the isomer of compound (**1**). PMR (CCl_4) δ: 1.57 (6H, s), 1.65 (6H, s), 1.9—2.3 (12H, m), 3.88 (2H, s), 3.98 (2H, d), 5.05 (2H, m), 5.28 (1H, t), 5.30 (1H, t).

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