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Cis Selective Wittig Olefination of α-Alkoxy Ketones and Its Application to the Stereoselective Synthesis of Plaunotol

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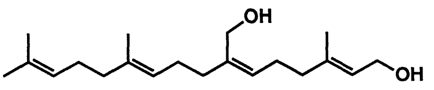
Several Wittig olefinations between α-heterosubstituted acetones and a phosphorus ylide were investigated concerning the product stereoselectivity. Benzyloxyacetone and tetrahydropyranyloxyacetone furnished trisubstituted (*Z*)-olefins exclusively. The stereoselective preparation of oxygenated acyclic terpenoids was practical by use of the direct Wittig olefination toward α-alkoxy ketones, and it facilitated a total synthesis of plaunotol from geraniol derivatives in short steps with high stereoselectivity.

Plaunotol (**1**) was isolated as the principal component of a folk medicine named Plau-noi in Thailand and it shows remarkable antipeptic ulcer activities.[1] Concerning the synthesis of this acyclic diterpene diol, there has been only one report. This was by Ogiso and co-workers,[1] who prepared **1** by applying the modified indirect Wittig olefination via a β-oxido phosphorus ylide.[2] This reaction is indeed highly stereoselective, but the product selectivity is insufficient to obtain a single product in a good yield. We previously reported another type of stereoselective Wittig olefination, in which a simple coupling between unstabilized ylides and substituted acetones furnished trisubstituted (*Z*)-olefins.[3] Because of potential versatility of this new stereoselective Wittig reaction, we report here full details of our investigation and its application to the stereoselective synthesis of plaunotol (**1**).



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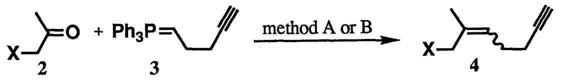
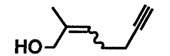
Results and Discussion

The reaction of benzyloxyacetone (**2a**) with 4-pentynylidenetriphenylphosphorane **3**[4] afforded 7-benzyloxy-6-methyl-5-hepten-1-yne (**4a**) with high (95%) *Z* stereoselectivity. Tetrahydropyranyloxyacetone (**2b**) as a carbonyl compound also gave the corresponding olefin **4b** in 95% yield with 96% *Z* stereoselectivity, but the reaction of phenoxyacetone (**2c**) and **3** took place sluggishly to yield **4c** in a low yield with diminished stereoselectivity.



a, X=BnO **b**, X=THPO **c**, X=PhO **d**, X=MeS **e**, X=PhS **f**, X=Et$_2$N

The stereochemistry of the products was confirmed by NMR spectroscopy and confirmed by the NMR spectra of the alcohol **4g** and the aldehyde **4h** derived therefrom. The ^{1}H NMR spectrum was useful in determining the *Z*:*E* ratio for the stereoisomeric pair of trisubstituted olefins. In particular the *Z* formyl proton (δ ca. 10 ppm) appears at a lower magnetic field than the *E* proton (δ ca. 9 ppm).[5] The *Z* and *E* configurations assigned to the trisubstituted double bond of the major and minor isomers of **4g** are also based upon both chemical and NMR spectral evidence of **4h**. The major isomer of **4h** slowly but completely isomerized to the minor isomer in a week in CHCl$_3$ solution in a NMR tube. ^{13}C NMR chemical shift of the methyl group is displaced upfield ($\Delta\delta=-7.15$ ppm) in the minor isomer, presumably owing to steric compression with the methylene group and magnetic anisotropy.



4g

4h

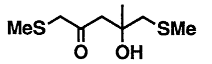
The results of the Wittig reaction of substituted acetones and ylide **3** are summarized in Table 1. The similar Wittig olefinations between **3** and other α-hetero-substituted acetones (i.e. α-methylthioacetone (**2d**) and α-diethylaminoacetone (**2f**)) afforded trisubstituted olefins in only moderate yields and, to our surprise, no stereoselectivity was observed. The

Table 1. The Wittig Reaction of Hetero-Substituted Acetones

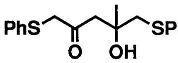
Acetone	Phosphorane	Method	Yield$^{c)}$ of **4**/%	**4***Z*/**4***E*$^{d)}$
2a	3	A$^{a)}$	89	88/12
2a	3	B$^{b)}$	92	95/ 5
2b	3	A$^{a)}$	95	92/ 8
2b	3	B$^{b)}$	95	96/ 4
2c	3	A$^{a)}$	41	72/28
2d	3	A$^{a)}$	15$^{e)}$	50/50
2e	3	A$^{a)}$	0$^{f)}$	—
2f	3	A$^{a)}$	20	60/40

a) NaOMe/DMF, 0 °C, 20 h. b) *n*-BuLi/5%HMPA-THF, −70—0 °C—rt, 20h. c) Isolated yield after column chromatography on silica gel. d) The ratio *Z*/*E* was determined by NMR analysis. e) Besides the Wittig olefination product **2d**, an aldol-type dimer **5d** was isolated in 4% yield. f) Only an aldol-type dimer **5e** was obtained in 20% yield.

attempted reaction of phenylthioacetone (**2e**) with **3** failed to give an olefin but gave an aldol-type dimer **5e** in low yield. The stereochemistry of **4f** was confirmed by NMR of an authentic sample prepared from **4b**. A similar stereoselective Wittig reaction has been independently reported by W.C.Still and co-workers,6) who described that substitutions at the α-carbon of an α-alkoxyacetone tend to improve stereoselectivity whereas α′-substitutions drastically diminish it.

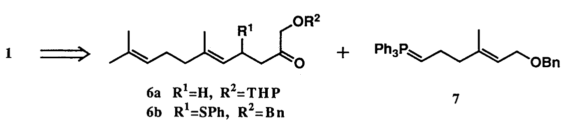


5d



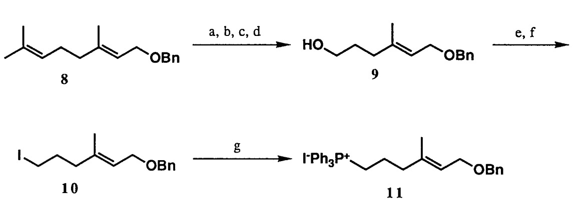
5e

On the basis of the present (*Z*)-selective Wittig reaction, the retrosynthesis of **1** can be depicted as Scheme 1. The requisite α-alkoxy ketones **6** having a geranylacetone skeleton would be prepared either by regioselective oxidation of geranylacetone or by three-carbon elongation from a geranyl sulfide. Here attention should be called to the yield and the degree of the stereoselectivity of the Wittig reaction of a highly substituted carbonyl compound such as **6b**, which possesses a bulky phenylthio group at the β′ carbon of an α-alkoxy ketone. The phosphorus ylide **7** could also be prepared from geraniol according to a sequence similar to the synthesis of the stereoisomeric ylide, which was used to prepare a difunctional *cis*-terpenoid building block in our hand.3,7)



Scheme 1.

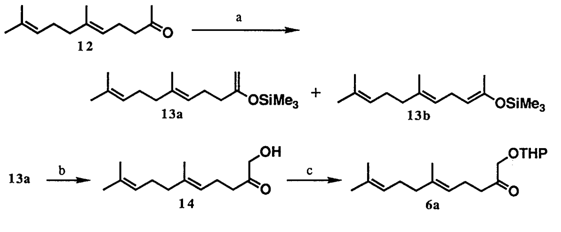
Phosphonium iodide **11**, a precursor of ylide **7**, was prepared from geranyl benzyl ether (**8**) in 53% overall yield as shown in Scheme 2. Thus, the regioselective epoxidation of the terminal double bond of **8** could be achieved in situ with *N*-bromosuccinimide followed by potassium hydroxide in aqueous 1,2-dimethoxyethane in one pot. The resulting epoxide was oxidatively cleaved with periodic acid to give a labile aldehyde which, without further purification, was treated with sodium borohydride to furnish benzyloxy alcohol **9** in 65% yield on the basis of **8**. Phosphonium iodide **11** was then obtained by the conventional method in 91% yield from **9** via the corresponding tosylate and iodide **10**.



a. NBS / DME b. KOH c. HIO_4 d. $NaBH_4$ e. TsCl, py f. NaI g. Ph_3P

Scheme 2.

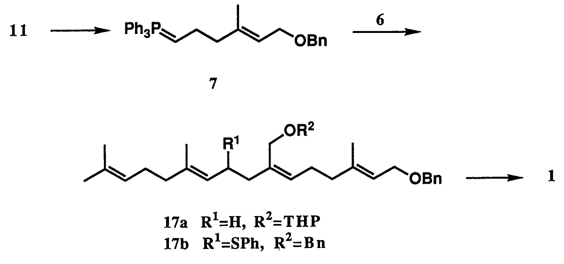
On the other hand, α-tetrahydropyranyloxy ketone **6a**, was prepared from geranylacetone (**12**) in 3 steps as shown in Scheme 3. Kinetically controlled deprotonation of **12** with lithium diisopropylamide in tetrahydrofuran (THF) and hexane (3:1) gave lithium enolates, which were quenched with chlorotrimethylsilane to afford an exo enolate **13a** predominantly and the undesired endo enolate **13b** in minor quantity in 92% combined yield (**13a**:**13b**=80:20 by GC). The same reaction, in a hexane-free THF solution, improved the kinetic regioselectivity (**13a**:**13b**=92:8) in 90% combined yield. Oxidation of the mixture of the two enolates with *m*-chloroperbenzoic acid in the presence of sodium hydrogencarbonate followed by acid hydrolysis afforded the desired α-hydroxy ketone **14** in 76% yield. The minor endo enolate **13b** did not undergo oxidation under the reaction conditions, and was subjected to hydrolysis during work-up to afford the starting ketone **12** in 20% recovery yield. Thus α-hydroxy ketone **14** could be obtained in 84% overall yield on the basis of consumed **12**. The requisite α-tetrahydropyranyloxy ketone **6a** was easily prepared by protection of ketol **14**.



a. $LiN(i\text{-}Pr)_2$, Me_3SiCl, -70°C b. MCPBA, $NaHCO_3$, -70°C c. 2,3-dihydro-2*H*-pyran, PPTS

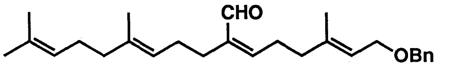
Scheme 3.

With the phosphonium salt **11** and the counterpart ketone **6a** in hand, we then carried out the Wittig olefination to generate the plaunotol skeleton (Scheme 4). Treatment of phosphonium iodide **11** with butyllithium in THF-HMPA (20:1) at −65 °C for 3.5 h afforded ylide **7**. The addition of **6a** to the ylide solution at −65 °C and stirring at the same temperature for 1 h provided the C_{20} coupling product **17a** in 72% yield, which was subjected to Na/NH_3 reduction and further deprotection with dilute acid to



Scheme 4.

give pure **1** in 86% yield. The spectral data of the product were found to be identical in all respects with the reference ones.[1] The stereochemical outcome of the Wittig reaction was further confirmed on aldehyde **18** obtained from **17a** by the removal of the tetrahydropyranyl protecting group followed by mild oxidation with active manganese dioxide in hexane at 0 °C. The ^{1}H NMR spectrum of **18** showed a singlet at δ=10.09 attributable to (*Z*)-α,β-unsaturated aldehyde proton and no other signals in the aldehyde proton region (δ=9—11). Thus, the direct Wittig reaction employing an unstabilized phosphorus ylide and an α-alkoxy ketone with geranyl substituent at the α'-position was proved to be entirely stereoselective for the *Z* isomer.



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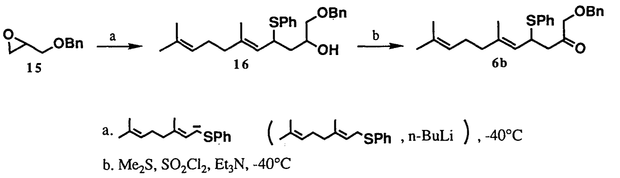
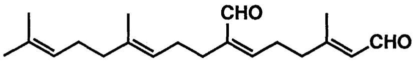
We next examined the Wittig reaction of a more highly substituted carbonyl compound such as **6b**, because **6b** can be prepared more conveniently than **6a** from readily available geranyl phenyl sulfide and glycidyl ether in two steps. As shown in Scheme 5, α-benzyloxy-β'-phenylthio ketone **6b** was prepared by the reaction of glycidyl benzyl ether (**15**) with α-lithiogeranyl phenyl sulfide followed by oxidation in 61% yield on the basis of **15**. Though a few mild oxidation methods on the basis of activated sulfonium species are well-known for converting an alcohol into a carbonyl compound, for example Swern's method[8] and Corey's method,[9] we used a combination of sulfuryl chloride and dimethyl sulfide[10] as sulfonium reagent in order to avoid the difficult removal of dimethyl sulfoxide or succinimide from the reaction product by the above-mentioned conventional methods.



Scheme 5.

The Wittig olefination of **6b** with ylide **7** provided the C$_{20}$ sulfide **17b** in 62% yield. When **17b** was subjected to Na/NH$_3$ reduction, removal of both the sulfide residue and two benzyl groups took place at the same time to furnish the desired plaunotol (**1**) in 76% yield. The structure of the synthetic plaunotol was confirmed by comparison of its spectral data with those in the literature.[1] The stereochemistry of the internal double bond formed by the Wittig reaction was again proved to be *Z* by inspection of the ^{1}H NMR spectrum of the corresponding dialdehyde **19**. This was prepared from the synthetic plaunotol by mild oxidation as described in the synthesis of **18**. The ^{1}H NMR spectrum of **19** 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 *Z* isomer in this Wittig reaction.



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The Wittig olefination between a phosphorus ylide and α-alkoxy ketones with geranyl substituent at the α'-position was found to provide high *Z* stereoselectivity, even if phenylthio functionality was present at the β'-position. General *Z*-stereoselectivity of the reaction will open its applicability to the synthesis of various compounds which possess internal *trans*-olefinic skeletons substituted with a hydroxymethyl group at the olefinic carbon.

Experimental

Mps are uncorrected. IR spectra were measured on a Hitachi 260-10 spectrometer. 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 Wakogel C-200 (Wako Pure Chemical Industries).

General procedure for the Wittig olefination with 4-pentynylidenetriphenylphosphorane (**3**) (Method A). To a suspension of 3.30 mmol of 4-pentynyltriphenylphosphonium iodide[4] in 20 mL of anhydrous *N,N*-dimethylformamide (DMF) under nitrogen was added 4.3 mmol of sodium methoxide at −2—0 °C. After stirring for 1.0 h at the same temperature, the phosphorane solution was treated with 3.0 mmol of an α-substituted acetone in 4 mL of anhydrous DMF. After stirring for 20 h at −1—0 °C, the reaction mixture was worked up by partitioning between 70 mL of methanol-water (30 : 70 by vol) and ether-hexane (50 : 50 by vol), and the organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate to give the Wittig coupling product as shown in Table 1.

General procedure for the Wittig olefination with 4-pentynylidenetriphenylphosphorane (**3**) (Method B). To a suspension of 4.20 mmol of 4-pentynyltriphenylphosphonium iodide[4] in a mixture of 65 mL of anhydrous tetrahydrofuran (THF) and 4 mL of anhydrous hexamethylphosphoric triamide (HMPA) under nitrogen was added 3.0 mL of 1.5 M *n*-BuLi in hexane at −65 °C (M=mol dm^{-3}). After stirring for 3.5 h at the same temperature, the bright red solution was treated with 4.96 mmol of an α-substituted acetone in 10 mL of anhydrous THF. After stirring for 1 h at −65 °C, the reaction mixture was allowed to warm to room temperature over a 60 min period and was further stirred for 19 h. It was worked up by partitioning between 150 mL of methanol-water (30 : 70 by vol) and ether-hexane (50 : 50 by vol), and the organic extracts were washed with brine, dried (MgSO$_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate to give the

Wittig coupling product as shown in Table 1.

The stereochemical outcome of the Wittig reaction was confirmed by the NMR spectrum of the allylic methylene protons adjacent to the heteroatom.5)

(*Z*)- and (*E*)-7-Benzyloxy-6-methyl-5-hepten-1-yne (4a) (Method A). ^{1}H NMR (CCl_4) δ=1.67, 1.77 (3H, each s, *E*:*Z*=12:88), 2.0—2.3 (5H, m) , 3.83, 3.93 (2H, each s, *E*:*Z*=12:88), 4.38 (2H, s), 5.35 (1H, t, *J*=7 Hz), 7.23 (5H, s). IR (neat) 3300, 2100, 1070 cm^{-1}. Further the stereochemical outcome was ascertained on aldehyde **4h** which was synthesized as followed. To 0.57 g (80 mmol) of lithium in ca. 30 mL of ethylamine at −70 °C was added dropwise a solution of 1.74 g (8.0 mmol) of **4a** in 1 mL of anhydrous ether over a period of 10 min. After stirring for an additional 20 min at −70 °C, 1 mL of isoprene and 2 mL of methanol were added successively. The solution was allowed to warm to room temperature gradually and poured into 50 mL of brine. After the aqueous solution was extracted with a mixture of ethyl acetate and diethyl ether (50:50 by vol), organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (70:30) to give 0.845 g (84%) of allylic alcohol **4g**. ^{1}H NMR ($CDCl_3$) δ=1.76 (4H, m), 2.20 (4H, m), 2.90 (1H, s), 4.12, 4.00 (2H, each s, *E*:*Z*=12:88), 5.23 (1H, m). IR (neat) 3300, 2100, 1000, 850 cm^{-1}. To a solution of 0.20 g (1.61 mmol) of alcohol **4g** in 45 mL of hexane was added 5.57 g (64 mmol) of active manganese dioxide and the mixture stirred for 1.5 h at 0 °C. After filtration, the solvent was evaporated to give an oil which was purified by column chromatography developing with a mixture of hexane and ethyl acetate (80:20) to give 0.198 g of aldehyde **4h** quantitatively. ^{1}H NMR ($CDCl_3$) δ=1.81 (3H, s), 2.02 (1H, t, *J*=2.6 Hz), 2.39 (2H, dt, *J*=2.6, 7.0 Hz), 2.80 (2H, q, *J*=7 Hz), 6.54 (1H, t, *J*=7.0 Hz), 9.43, 10.14 (1H, each s, formyl protons, *E*:*Z*=12:88). *Z* isomer: ^{13}C NMR ($CDCl_3$) δ=190.91, 146.05, 137.49, 82.35, 69.99, 18.64, 25.35, 16.47. *E* isomer: ^{13}C NMR ($CDCl_3$) δ=195.03, 151.58, 140.42, 82.67, 69.45, 27.85, 17.66, 9.32. IR (neat) 3300, 2100, 1685 cm^{-1}.

(*Z*)- and (*E*)-6-Methyl-7-tetrahydropyranyloxy-5-hepten-1-yne (4b) (Method A). ^{1}H NMR ($CDCl_3$) δ=1.65 (6H, s), 1.77 (3H, s), 1.83 (1H, s), 2.1—2.3 (4H, m), 3.2—3.7 (2H, m), 4.03 (2H, s), 4.3—4.7 (1H, m), 5.40 (1H, t, *J*=7 Hz). IR (neat) 3300, 2100, 1200 cm^{-1}. Tetrahydropyranyl ether **4b** suffered hydrolysis to alcohol **4g** and the ratio of *Z* and *E* isomers was determined as follows. To a solution of 0.336 g (1.61 mmol) of tetrahydropyranyl ether **4b** in 15 mL of ethanol was added 31 mg (0.16 mmol) of *p*-toluenesulfonic acid monohydrate and the mixture was allowed to stir for 10 h at room temperature. After neutralization with aqueous sodium hydrogencarbonate, the reaction mixture was concentrated under reduced pressure, and was partitioned between water and ether. Ether extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (70:30) to give 0.133 g (67%) of alcohol **4g**. ^{1}H NMR ($CDCl_3$) δ=4.12, 4.00 (2H, each s, *E*:*Z*=8:92).

(*Z*)- and (*E*)-6-Methyl-7-phenoxy-5-hepten-1-yne (4c) (Method A). ^{1}H NMR (CCl_4) δ=1.72, 1.85 (3H, each s, *E*:*Z*=28:72), 1.94 (1H, s), 2.21 (4H, s), 4.31, 4.46 (2H, s, *E*:*Z*=28:72), 5.2—5.7 (1H, m), 6.7—7.3 (5H, m). IR (neat) 3300, 2100, 1600, 1500 cm^{-1}.

(*Z*)- and (*E*)-6-Methyl-7-methylthio-5-hepten-1-yne (4d) (Method A). ^{1}H NMR ($CDCl_3$) δ=1.74, 1.83 (3H, each s, *E*:*Z*=50:50), 1.96, 2.01 (3H, each s, *E*:*Z*=50:50), 1.99 (1H, s), 2.1—2.4 (4H, m), 3.07, 3.16 (2H, each s, *E*:*Z*=50:50), 5.1—5.6 (1H, m). IR (neat) 3300, 2110, 1660 cm^{-1}. Found: C, 69.61; H, 9.24%. Calcd for $C_9H_{14}S$: C, 70.07; H, 9.15%.

Besides the Wittig olefination product **2d**, an unexpected aldol-type dimerization product, 1,5-bis(methylthio)-4-hydroxy-4-methyl-2-pentanone (**5d**), was isolated in 4% yield. ^{1}H NMR ($CDCl_3$) δ=1.32 (3H, s), 2.07 (3H, s), 2.16 (3H, s), 2.69 (2H, s), 2.87 (1H, s), 2.95 (1H, s), 3.21 (2H, s), 3.66 (1H, s). IR (neat) 3450, 1700 cm^{-1}.

1,5-Bis(phenylthio)-4-hydroxy-4-methyl-2-pentanone (5e). ^{1}H NMR ($CDCl_3$) δ=1.22 (3H, s), 2.81 (2H, ABq, *J*=8 Hz), 3.08 (2H, s), 3.36 (1H, s), 3.39 (2H, s), 7.22 (10H, s). IR (neat) 3480, 1700, 1090 cm^{-1}. Found: C, 64.91; H, 6.03%. Calcd for $C_{18}H_{20}O_2S_2$: C, 65.02; H, 6.06%.

(*Z*)- and (*E*)-7-Diethylamino-6-methyl-5-hepten-1-yne (4f). (Method A). ^{1}H NMR (CCl_4) δ=1.00 (6H, t, *J*=7 Hz), 1.63 (3H, s), 1.78 (1H, s), 2.1—2.4 (4H, m), 2.48 (4H, q, *J*=7 Hz), 2.81, 2.89 (2H, s, *E*:*Z*=45:55), 5.1—5.5 (1H, m). IR (neat) 3300, 2110, 1660 cm^{-1}.

Authentic samples of these compounds were synthesized from **4g** as follows and the ratio of *Z* and *E* isomers (*Z*:*E*=55:45) was determined by comparing with one another. To a solution of 0.85 g (6.85 mmol) of alcohol **4g** (*Z*:*E*=92:8) in 10 mL of diethyl ether at −10—5 °C was added dropwise 1.45 g (5.35 mmol) of phosphorus tribromide. After stirring for 3 h water (5 mL) was added in the reaction mixture and the reaction mixture was extracted with ether. The ether layer was washed successively with sat. aqueous sodium hydrogencarbonate and brine, dried ($MgSO_4$) and concentrated in vacuo, to give 0.95 g (74%) of a crude bromide. To a solution of 0.55 g (7.5 mmol) of diethylamine in 10 mL of anhydrous benzene was added dropwise 0.7 g (3.7 mmol) of the crude bromide at 0 °C. After stirring for 6.5 h at room temperature, the reaction mixture was poured into 10 mL of water and was extracted with ether-pentane (1:1 by vol). The organic layer was washed successively with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (70:30) to give 0.63 g (94%) of amine **4f**. ^{1}H NMR ($CDCl_3$) δ=2.81, 2.89 (2H, s, *E*:*Z*=8:92).

(*E*)-6-Benzyloxy-4-methyl-4-hexen-1-ol (9). To a solution of 40.0 g (164 mmol) of geranyl benzyl ether (**8**) in a mixture of 200 mL of 1,2-dimethoxyethane and 50 mL of water at −10—0 °C was added portionwise over several minutes 32.0 g (180 mmmol) of *N*-bromosuccinimide. After stirring for 5 h a solution of 28 g (500 mmol) of potassium hydroxide in 60 mL of water was added in the reaction mixture slowly. After stirring for 1 h at 0 °C, the reaction mixture was extracted with ether. The ether layer was washed successively with 2M hydrochloric acid and brine, dried ($MgSO_4$) and concentrated in vacuo, to give 43.0 g of a crude epoxide quantitatively. To a solution of 15.8 g (67.9 mmol) of 98% periodic acid in a mixture of 50 mL of 1,4-dioxane and 50 mL of water was added dropwise 15 g (57.6 mmol) of the crude epoxide at 0 °C. After stirring for 1 h at room temperature the reaction mixture was extracted with ether. The ether layer was washed successively with water and brine, dried ($MgSO_4$) and evaporated to give a crude aldehyde quantitatively. To a suspension of 3.70 g (97.8 mmol) of sodium borohydride in 50 mL of ethanol was added dropwise 12.6 g of the crude aldehyde in 30 mL of ethanol at room temperature. After stirring for 4 h, 20 mL of water was poured into the reaction mixture. After neutralization with 10% aqueous sulfuric acid, the reaction mixture was extracted with ether. The ether layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (80 : 20) to give 8.3 g (65%) of hydroxy compound **9**. ^{1}H NMR (CCl_4) δ=1.57 (3H, s), 1.3—1.7 (2H, m), 1.90 (1H, bs), 2.00 (2H, bt, *J*=7 Hz), 3.38 (2H, bt, *J*=6 Hz), 3.85 (2H, d, *J*=6 Hz), 4.33 (2H, s), 5.23 (1H, bt, *J*=6 Hz), 7.07 (5H, s). IR (neat) 3400, 1460, 1370, 1070, 740 cm^{-1}. Found: C, 76.25; H, 9.15%. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%.

(*E*)-1-Benzyloxy-6-iodo-3-methyl-2-hexene (10). To a solution of 9.0 g (40.9 mmol) of hydroxy compound **9** and 9.7 g (122.7 mmol) of pyridine in 20 mL of dichloromethane at 0 °C was added portionwise over several minutes 11.7 g (61.3 mmol) of *p*-toluenesulfonyl chloride. After stirring for 10 h at 0 °C, 10 mL of water was poured into the reaction mixture. After stirring for 20 min at room temperature, the reaction mixture was extracted with ether. The ether layer was washed successively with 2M hydrochloric acid and sat. aqueous sodium hydrogencarbonate and brine, dried ($MgSO_4$) and evaporated, to give 13.8 g (90%) of a crude tosylate. A solution of 13.8 g (34.8 mmol) of the tosylate in 100 mL of acetone was treated with 18 g (104 mmol) of sodium iodide. The reaction mixture was stirred for 24 h at room temperature with protection from light. The acetone was removed under reduced pressure and the residue was poured into 50 mL of water containing 1 g of sodium thiosulfate. The aqueous solution was extracted with hexane and hexane extracts were washed with brine, dried ($MgSO_4$) and evaporated, to give 11.5 g of a crude iodide **10** quantitatively. Iodide **10** was practically pure and was used in the next reaction without purification because of its lability.

(*E*)-(6-Benzyloxy-4-methyl-4-hexenyl)triphenylphosphonium Iodide (11). A solution of 11.5 g (34.8 mmol) of **10** and 27.4 g (104 mmol) of triphenylphosphine in 80 mL of anhydrous benzene was refluxed for 24 h under nitrogen. The reaction mixture was evaporated under reduced pressure and the residue suspended in diethyl ether and filtered. The filtrate was evaporated to dryness under reduced pressure to give 18.8 g (91%) of phosphonium salt **11**. ^{1}H NMR ($CDCl_3$) δ=1.53 (3H, s), 1.5—2.0 (2H, m), 2.33 (2H, bt, *J*=7 Hz), 3.3—3.7 (2H, m), 3.88 (2H, d, *J*=7 Hz), 4.37 (2H, s), 5.25 (1H, bt, *J*=7 Hz), 7.09 (5H, s), 7.4—7.8 (15H, m). IR (neat) 1430, 1110, 1000, 740, 700 cm^{-1}. mp 162.5—163.5 °C. Found: C, 64.75; H, 5.75 %. Calcd for $C_{32}H_{34}OPI$: C, 64.87; H, 5.78%.

(5*E*)-6,10-Dimethyl-2-(trimethylsiloxy)-1,5,9-undecatriene (13a). To a solution of 3.60 g (35.6 mmol) of diisopropylamine in 50 mL of anhydrous THF at 0 °C was added dropwise 31.0 mmol of a solution of *n*-BuLi in hexane. After 10 min the solution was concentrated under reduced pressure and the lithium reagent dissolved in 125 mL of anhydrous THF. The solution was cooled to −70 °C, and a solution of 5.4 g (27.8 mmol) of geranylacetone (**12**) in 18 mL of anhydrous THF was added dropwise over 5 min. After 20 min, 3.06 g (31.0 mmol) of chlorotrimethylsilane was added, and the solution was allowed to warm to room temperature over approximately 30 min. When the temperature of the reaction mixture reached around 0—15 °C, a white solid began to precipitate from the reaction mixture. After stirring for ca. 0.5—1.0 h, the reaction mixture was partitioned between pentane and sat. aqueous sodium hydrogencarbonate. The pentane extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was distilled to provide 6.64 g (90%) of trimethylsilyl enol ether **13**. (**13a** : **13b**=92 : 8 by GC). bp 102—104 °C (0.6 Torr). ^{1}H NMR (CCl_4) δ=0.20 (9H, s), 1.63 (9H, s) , 1.8—2.5 (8H, m) , 3.93 (2H, s), 4.6—5.3 (2H, m). IR (neat) 2950, 1270, 1010, 840 cm^{-1}.

(5*E*)-1-Hydroxy-6,10-dimethyl-5,9-undecadien-2-one (14). To a stirred solution of 6.64 g (25.0 mmol) of a mixture of **13a** and **13b** and 12.6 g (150 mmol) of solid sodium hydrogencarbonate in 110 mL of dichloromethane at −70 °C was added portionwise over several minutes 5.00 g (27.5 mmol) of 95% *m*-chloroperbenzoic acid. After the resulting solution was stirred for 6 h at −70 °C, 0.9 g of solid sodium sulfite was added to destroy excess peroxide, and the solution was allowed to warm to room temperature gradually. The reaction mixture was partitioned between ethyl acetate and sat. aqueous sodium hydrogencarbonate, and the ethyl acetate extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (80 : 20) to give 3.99 g (76%) of α-hydroxy ketone **14**. ^{1}H NMR (CCl_4) δ=1.60 (9H, s), 1.8—2.5 (8H, m), 3.30 (1H, bs), 4.10 (2H, s), 4.7—5.3 (2H, m). IR (neat) 3450, 1720, 1070 cm^{-1}. Found: C, 74.20; H, 10.55%. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54%. Δ^2 isomer was not obtained and 0.99 g of geranylacetone (**12**) was recovered.

(5*E*)-1-(Tetrahydro-2-pyranyloxy)-6,10-dimethyl-5,9-undecadien-2-one (6a). To a solution of 1.7 g (8.1 mmol) of α-hydroxy ketone **14** and 1.4 g (16.2 mmol) of 2,3-dihydro-2*H*-pyran in 20 mL of dichloromethane was added 0.2 g (0.81 mmol) of pyridinium *p*-toluenesulfonate (PPTS) and the mixture was allowed to stir for 15 h at room temperature. Water (10 mL) was poured into the the reaction mixture and extracted with ether. The ether layer was washed successively with sat. aqueous sodium hydrogencarbonate and brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (90 : 10) to give 2.0 g (85%) of tetrahydropyranyl ether **6a**. ^{1}H NMR (CCl_4) δ=1.60 (9H, s), 1.3—1.8 (6H, m), 1.8—2.7 (8H, m), 3.2—3.9 (2H, m), 4.00 (2H, s), 4.55 (1H, bs), 4.7—5.3 (2H, m). IR (neat) 1720, 1200, 1070, 1030, 820 cm^{-1}. Found: C, 73.40; H, 10.25%. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27%.

(2*E*,6*Z*,10*E*)-1-Benzyloxy-7-[(tetrahydro-2-pyranyloxy)-methyl]-3,11,15-trimethyl-2,6,10,14-hexadecatetraene (17a). The Wittig olefination between 1.46 g (4.96 mmol) of tetrahydropyranyloxy ketone **6a** and 4.20 mmol of ylide **7** was carried out according to the general procedure (Method B). Purification by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (90 : 10) gave 1.51 g (72%) of the Wittig coupling product **17a**. ^{1}H NMR (CCl_4) δ=1.60 (12H, s), 1.3—1.8 (6H, m), 1.8—2.6 (12H, m), 3.3—3.8 (2H, m), 3.90 (2H, d, *J*=7 Hz), 3.97 (2H, s), 4.37 (2H, s), 4.55 (1H, bs), 4.8—5.4 (4H, m), 7.13 (5H, s). IR (neat) 1200, 1030, 820, 730, 700 cm^{-1}. Found: C, 79.90; H, 10.10%. Calcd for $C_{32}H_{48}O_3$: C, 79.95; H, 10.06%.

Plaunotol (1). (From **17a**). To 1.0 g (43.5 mmol) of sodium in ca. 30 mL of liquid ammonia at −60 °C was added dropwise a solution of 1.2 g (2.4 mmol) of **17a** in 20 mL of anhydrous diethyl ether over a period of 10 min. After stirring for an additional 5 min at −60 °C, 2.3 g (43.5 mmol) of ammonium chloride was added and ammonia was replaced by ether. After filtration the ethereal solution was evaporated leaving 0.93 g (95%) of the crude tetrahydropyranyl ether as a pale yellow liquid. To a solution of 0.93 g (2.27 mmol) of crude tetrahydropyranyl ether in 40 mL of methanol was added 45 mg (0.235 mmol) of *p*-toluenesulfonic acid monohydrate and the mixture was allowed to stir for 15 h at room temperature. After neutralization with aqueous sodium hydrogencarbonate, the reaction mixture was concentrated under reduced pressure, and partitioned between water and ether. Ether extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (70 : 30) to give 0.60 g (86%) of plaunotol (**1**). ^{1}H NMR ($CDCl_3$) δ=1.59 (3H, s), 1.60 (3H, s), 1.68 (6H, s), 1.7—2.3 (14H, m), 4.09 (2H, s), 4.12 (2H, d, J=7.5 Hz), 4.9—5.4 (4H, m). IR (neat) 3320, 1445, 1365, 1240, 1000 cm^{-1}. Found: C, 78.35; H, 11.10%. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18%.

(2*E*,6*E*,10*E*)-1-Benzyloxy-7-formyl-3,11,15-trimethyl-2,6,10,14-hexadecatetraene (18). To a solution of 0.11 g (0.229 mmol) of tetrahydropyranyl ether **17a** in 4 mL of methanol was added 4.5 mg (0.023 mmol) of *p*-toluenesulfonic acid monohydrate and the mixture was allowed to stir for 16 h at room temperature. After neutralization with aqueous sodium hydrogencarbonate, the reaction mixture was concentrated under reduced pressure, and partitioned between water and ether. The ether extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 90 mg of a crude hydroxy compound quantitatively. To a solution of 90 mg (0.227 mmol) of the crude hydroxy compound in 12 mL of hexane was added 0.4 g (4.5 mmol) of active manganese dioxide and the mixture was stirred for 4 h at 0 °C. After filtration, the solvent was evaporated to give an oil which was purified by column chromatography developing with a mixture of hexane and ethyl acetate (80 : 20) to give 80 mg (89%) of aldehyde **18**. ^{1}H NMR ($CDCl_3$) δ=1.56 (3H, s), 1.59 (3H, s), 1.67 (6H, s), 1.9—2.6 (12H, m), 4.02 (2H, d, J=7 Hz), 4.50 (2H, s), 5.0—5.2 (2H, m), 5.44 (1H, t, J=7 Hz), 6.43 (1H, t, J=8 Hz), 7.32 (5H, s), 10.09 (1H, s). IR (neat) 1670 cm^{-1}. Found: C, 82.10; H, 9.70%. Calcd for $C_{27}H_{38}O_2$: C, 82.18; H, 9.71%.

(5*E*)-1-Benzyloxy-6,10-dimethyl-4-phenylthio-5,9-undecadien-2-ol (16). To a stirred solution of 10.0 g (42.6 mmol) of geranyl phenyl sulfide in anhydrous THF (50 mL) in the presence of 5.0 g of *N,N,N′,N′*-tetramethylethylenediamine, was added at −50 °C, under nitrogen, a solution of *n*-BuLi (34 mL, 51 mmol). After 1 h, was added at −40 °C over 1 h, a solution of glycidyl benzyl ether (**15**) (6.6 g, 40 mmol) in 20 mL of anhydrous THF. The reaction mixture was allowed to warm to room temperature over a 60 min period and was further stirred for 10 h. Water (20 mL) was poured into the reaction mixture and extracted with ether. The ether layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (90 : 10) to give 14.4 g (88%) of alcohol **16**. ^{1}H NMR ($CDCl_3$) δ=1.28, 1.43 (3H, each s), 1.57, 1.66 (each 3H, s), 1.8—2.1 (5H, m), 2.61 (2H, m), 3.2—3.5 (3H, m), 3.9—4.3 (1H, m), 4.48, 4.50 (each 1H, s), 5.02 (2H, bt, J=7 Hz), 7.1—7.5 (10H, m). IR (neat) 3450, 1440, 1380, 1100, 740, 700 cm^{-1}. Found: C, 75.95 ; H, 8.40%. Calcd for $C_{26}H_{34}O_2S$: C, 76.05; H, 8.35%.

(5*E*)-1-Benzyloxy-6,10-dimethyl-4-phenylthio-5,9-undecadien-2-one (6b). Sulfuryl chloride (3.61 g, 26.7 mmol) in anhydrous dichloromethane (10 mL) was added dropwise to a solution of dimethyl sulfide (2.30 g, 37 mmol) in dry dichloromethane (90 mL) at −40 °C for 5 min under a dry nitrogen atmosphere, and the mixture was stirred for 20 min. To the solution was gradually added alcohol **16** (10.0 g, 24.4 mmol) in 20 mL of anhydrous dichloromethane at −40 °C for 10 min. After the mixture had been stirred for 2 h, triethylamine (12.3 g, 122 mmol) was added to the reaction mixture at −40 °C. The solution was allowed to warm to room temperature, and poured into 100 mL of 2M hydrochloric acid. The organic layer was separated and the aqueous solution extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica-gel column (5% ethyl acetate–haxane) to give 6.9 g (69%) of benzyloxy ketone **6b**. ^{1}H NMR ($CDCl_3$) δ=1.43 (3H, bs), 1.57, 1.66 (each 3H, s), 1.7—2.1 (4H, m), 2.72 (2H, d, J=7 Hz), 3.99 (2H, s), 4.1—4.3 (1H, m), 4.53 (2H, s), 5.02 (2H, bt, J=7 Hz), 7.2—7.5 (10H, m). IR (neat) 1720, 1580, 1430, 1100, 740, 700 cm^{-1}. Found: C, 76.35; H, 7.85%. Calcd for $C_{26}H_{32}O_2S$: C, 76.43; H, 7.89%.

(2*E*,6*Z*,10*E*)-1-Benzyloxy-7-[(benzyloxy)methyl]-3,11,15-trimethyl-9-phenylthio-2,6,10,14-hexadecatetraene (17b). The Wittig olefination between 3.0 g (7.23 mmol) of benzyloxy ketone **6b** and 6.12 mmol of ylide **7** was carried out according to the general procedure (Method B). Purification by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (95 : 5) gave 1.96 g (62%) of the Wittig coupling product **17b**. ^{1}H NMR ($CDCl_3$) δ=1.30 (3H, s), 1.61 (6H, s), 1.66 (3H, s), 1.7—2.5 (10H, m), 3.97 (2H, d, J=7 Hz), 4.21 (1H, s), 4.48 (4H, s), 4.7—5.6 (4H, m), 7.31 (15H, s). IR (neat) 1450, 1380, 1065, 740, 700 cm^{-1}. Found: C, 80.60; H, 8.4%. Calcd for $C_{40}H_{50}O_2S$: C, 80.76; H, 8.47%.

Plaunotol (1) (From **17b**). To 0.25 g (10.9 mmol) of sodium in ca. 15 mL of liquid ammonia at −60 °C was added dropwise a solution of 0.5 g (0.778 mmol) of **17b** in 10 mL of anhydrous ether over a period of 10 min. After stirring for an additional 20 min at −60 °C, 5 mL of isoprene and 10 mL of methanol were added successively. The solution was allowed to warm to room temperature gradually and poured into 50 mL of brine. The aqueous solution was next extracted with a mixture of ethyl acetate and diethyl ether (50 : 50 by vol). The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel developing with a mixture of hexane and ethyl acetate (80 : 20) to give 0.167 g (70%) of plaunotol (**1**). The spectral data of the product were found to be identical in all respects with the reference data.[1)]

(2*E*,6*Z*,10*E*)-7-Formyl-3,11,15-trimethyl-2,6,10,14-hexadecatetraenal (19). To a solution of 50 mg (0.163 mmol) of the synthetic plaunotol (**1**) (from **17b**) in 6 mL of hexane was added 0.29 g (3.26 mmol) of active manganese dioxide and the mixture was stirred for 4 h at 0 °C. After filtration, the solvent was evaporated to give an oil which was purified by column chromatography developing with a mixture of hexane and ethyl acetate (80 : 20) to give 49.3 mg of dialdehyde **19** quantitatively. ^{1}H NMR (CDCl$_3$) δ=1.59 (3H, s), 1.60 (6H, s), 1.68 (3H, s), 1.9—2.7 (12H, m), 5.0—5.3 (2H, m), 5.89 (1H, d, J=8 Hz), 6.36 (1H, t, J=8.2 Hz), 9.99 (1H, d, J=8 Hz, terminal formyl proton), 10.09 (1H, s, internal formyl proton). IR (neat) 1675 cm^{-1}. Found: C, 79.2; H, 9.95%. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%

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