CHEMISTRY LETTERS, pp. 1433-1436, 1988.

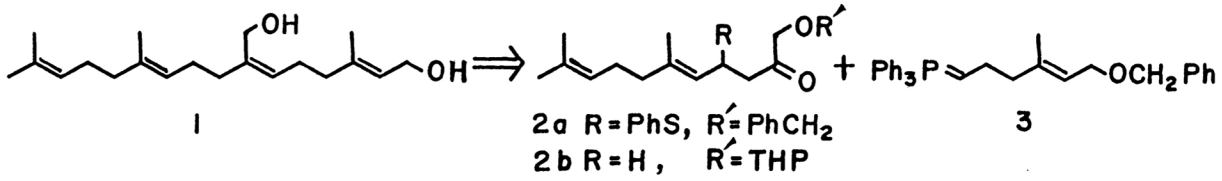
Highly Stereoselective Total Synthesis of Plaunotol

Kikumasa SATO,* Osamu MIYAMOTO, Seiichi INOUE, Norimichi IWASE,
and Kiyoshi HONDA
Department of Applied Chemistry, Faculty of Engineering,
Yokohama National University, Tokiwadai, Hodogayaku, Yokohama 240

Highly stereoselective total synthesis of plaunotol has been achieved by the application of the (Z)-stereoselective direct Wittig olefination to α-alkoxy ketones having geranylacetone skeleton.

Plaunotol(**1**), the most important component of a folk medicine named Plau-noi in Thailand, was reported to show remarkable antipeptic ulcer activities.[1] On the synthesis of this acyclic diterpene alcohol, there has been only one report by Ogiso and coworkers,[1] who prepared **1** by applying the modified indirect Wittig olefination via β-oxide phosphonium ylide, a method developed by Corey and Yamamoto.[2] This reaction is indeed highly stereoselective, but the product selectivity is insufficient to obtain a single product in a good yield. Here we report an efficient stereoselective synthesis of **1** by the direct Wittig reaction employing α-alkoxy ketones and a phosphorus ylide.

In our preceding paper, we reported that the direct Wittig reaction between unstabilized phosphorus ylides and α-alkoxyacetones lead to protected trisubstituted allylic alcohols with high stereoselectivity for the Z isomer.[3,4] Scheme 1 shows the retrosynthesis of **1** on the basis of this direct Wittig olefination strategy.

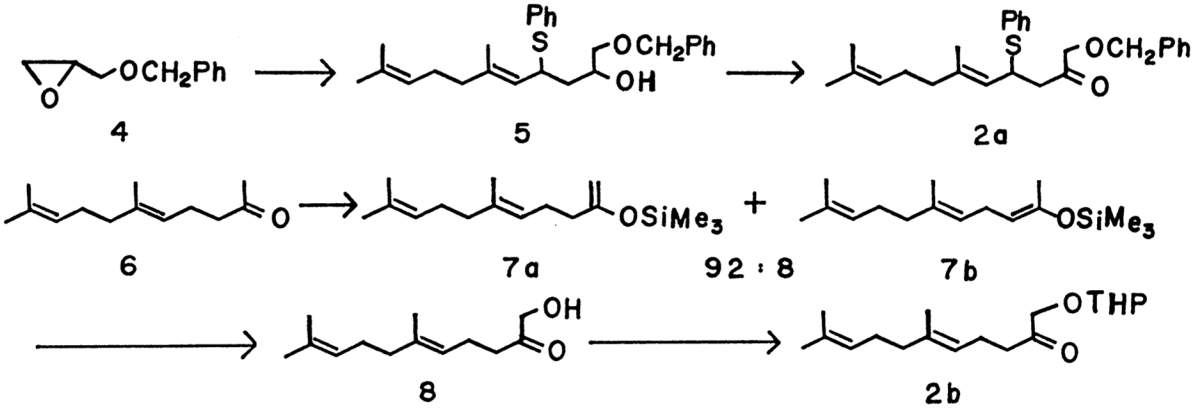


1 **2a** R=PhS, R'=PhCH$_2$ **3**
2b R=H, R'=THP

Scheme 1.

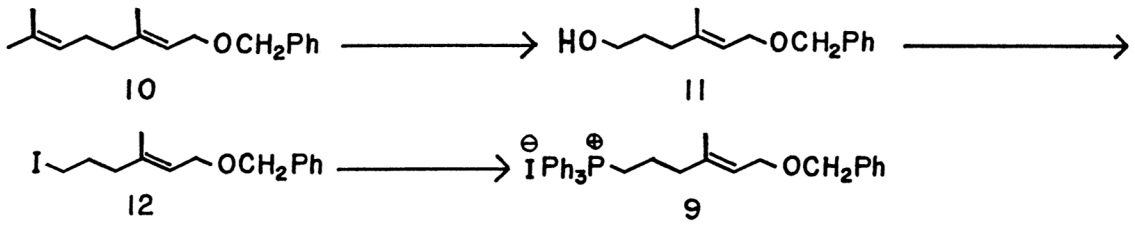
The requisite α-alkoxy ketones **2** having a geranylacetone skeleton could be prepared either by three-carbon elongation from geranyl sulfide or by regioselective oxidation of geranylacetone. As shown in Scheme 2, α-benzyloxy ketone **2a**[6] was prepared by the reaction of glycidyl benzyl ether (**4**) with α-lithiogeranyl phenyl sulfide followed by oxidation[7] in 61% yield on the basis of **4**. An alternative ketone, i. e. α-tetrahydropyranyloxy ketone **2b**, was prepared from

geranylacetone (6) in 3 steps. Lithium enolates, obtained by kinetically controlled reaction of 6 with lithiumdiisopropylamide as hindered base in THF solution at -78 °C, were quenched with trimethylsilyl chloride to form a terminal enolate 7a predominantly and inner enolate 7b in minor quantity in 90% combined yield (7a:7b = 92:8 by GLC). The mixture of two enolates 7a and 7b was subjected to oxidation with m-chloroperbenzoic acid at -78 °C to afford, after acid hydrolysis, α-hydroxy ketone 8[6] in 68% yield on the basis of 6. As kinetic inertness of the inner olefin moiety prevented 7b from undergoing oxidation, the unreacted 7b was recovered as the starting ketone 6. α-Tetrahydropyranyloxyketone 2b[6] was obtained by protection of ketol 8 in 85% yield.



Scheme 2.

Phosphonium iodide 9, a precursor of phosphorus ylide 3, was prepared from geranyl benzyl ether 10 in 65% overall yield as shown in Scheme 3. Regioselective epoxidation of the terminal double bond of 10 was effected with N-bromosuccinimide, followed by in situ treatment of the bromohydrin with potassium hydroxide. The epoxide was oxidatively cleaved with periodic acid to give an aldehyde which, without further purification, was treated with sodium borohydride to furnish benzyloxy alcohol 11 in 65% yield on the basis of 10. Phosphonium iodide 9[6] was obtained by the conventional method in 91% yield from 11 via the corresponding tosylate and iodide 12.[8]

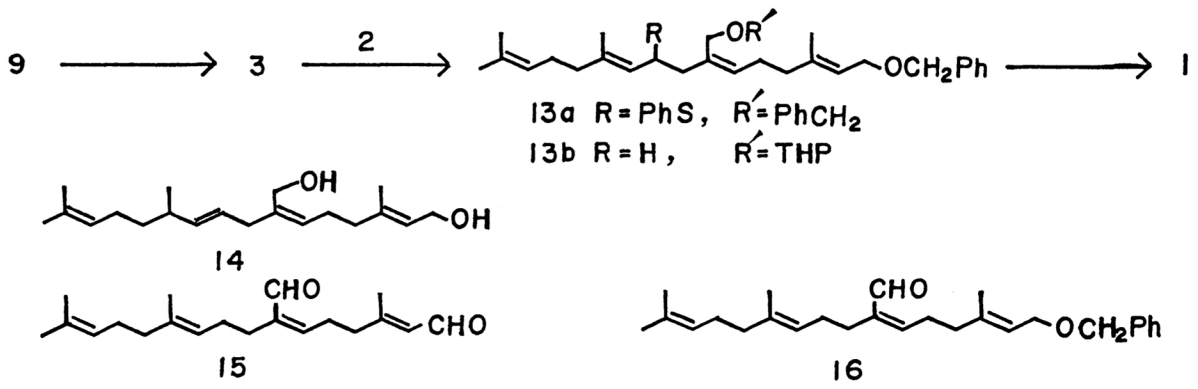


Scheme 3.

With the phosphonium salt and the counterpart ketones in hand, we then carried out the direct Wittig olefination to elaborate the plaunotol skeleton.

Phosphonium iodide **9** was converted into phosphorus ylide **3** by treatment with butyllithium in THF-HMPA (5 vol%). The direct Wittig olefination of **2a** with ylide **3** afforded a protected diterpene **13a**[6] in 62% yield, which was subjected to Na/NH_3 reduction to give the plaunotol (**1**) in 76% yield with 97-98% purity. The ^{1}H-NMR spectrum of the product indicated the presence of a very small amount (2-3%) of the conjugate reduction product **14**. The structure of the synthetic plaunotol was confirmed by the comparison of its spectral data (IR and ^{1}H-NMR) with those in the literature.[1] Further evidence for the selective formation of the Z olefin was obtained as follows. The synthetic diol **1** was treated with active manganese oxide in hexane at 0 °C for 4 hours to afford dialdehyde **15** in a quantitative yield. ^{1}H-NMR spectrum of **15**[6] 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 the Wittig reaction.

The direct Wittig olefination of an alternative ketone **2b** with **3** afforded the desired product **13b**[6] in 72% yield, which was subjected to Na/NH_3 reduction and further deprotection with dilute acid to give pure **1**[6] in 86% yield. The spectral data of the product were found to be identical with the reference ones[1] in all respects. The stereochemical outcome of the Wittig reaction was further confirmed on aldehyde **16**[6] obtained from **13b** by the removal of the THP protecting group followded by mild oxidation. The ^{1}H-NMR spectrum of **16** showed a singlet at δ 10.09 attributable to (Z)-α,β-unsaturated aldehyde proton and no signals in the aldehyde proton region (δ 9-11).



Scheme 4.

On the synthesis of plaunotol (**1**) as a single product in a good yield, an efficient stereoserective procedure was provided by the direct Wittig reaction employing α-alkoxy ketones and a phosphorus ylide.

In summary, the stereoserective preparation of oxygenated acyclic terpenoids is feasible 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.

References

1) A. Ogiso, E. Kitazawa, M. Kurabayashi, A. Sato, S. Takahashi, H. Noguchi, H. Kuwano, S. Kobayashi, and H. Mishima, Chem. Pharm. Bull., 26, 3117 (1978).
2) E. J. Corey and H. Yamamoto, J. Am. Chem. Soc., 92, 6637 (1970).
3) K. Sato, O. Miyamoto, S. Inoue, T. Kobayashi, and F. Furusawa, Chem. Lett., 1981, 1711.
4) A similar stereoselective Wittig reaction was independently reported by W. C. Still et al.[5)]
5) C. Sreekumar, K. P. Darst, and W. C. Still, J. Org. Chem., 45, 4260 (1980).
6) Spectral data for the selected compounds are as follows.
5: IR(neat) 3450, 1440, 1380, 1100, 740, and 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.28, 1.43 (3H, each s), 1.57 (3H, s), 1.66 (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 (1H, s), 4.50 (1H, s), 5.02 (2H, bt, J7), and 7.1-7.5 (10H, m). **2a**: IR(neat) 1720, 1580, 1430, 1100, 740, and 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.43 (3H, bs), 1.57 (3H, s), 1.66 (3H, s), 1.7-2.1 (4H, m), 2.72 (2H, d, J7), 3.99 (2H, s), 4.1-4.3 (1H, m), 4.53 (2H, s), 5.02 (2H, bt, J7), and 7.2-7.5 (10H, m). **8**: IR(neat) 3450, 1720, and 1070 cm^{-1}; ^{1}H-NMR(CCl_4) δ 1.60 (9H, s), 1.8-2.5 (8H, m), 3.30 (1H, bs), 4.10 (2H, s), and 4.7-5.3 (2H, m). **2b**: IR(neat) 1720, 1200, 1070, 1030, and 820 cm^{-1}; ^{1}H-NMR(CCl_4) δ 1.3-1.8 (15H, m), 1.8-2.7 (8H, m), 3.25-3.90 (2H, m), 4.00 (2H, s), 4.55 (1H, bs), and 4.7-5.3 (2H, m). **9**: mp 162.5-163.5 °C, IR(neat) 1430, 1110, 1000, 740, and 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.53 (3H, s), 1.5-2.0 (2H, m), 2.33 (2H, bt, J7), 3.3-3.7 (2H, m), 3.88 (2H, d, J7), 4.37 (2H, s), 5.25 (1H, bt, J7), 7.09 (5H, s), and 7.4-7.8 (15H, m). **13a**: IR(neat) 1450, 1380, 1065, 740, and 700 cm^{-1}; ^{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, s), 4.01 (2H, d, J7), 4.21 (1H, s), 4.48 (4H, s), 4.7-5.6 (4H, m), and 7.31 (15H, s). **13b**: IR(neat) 1200, 1030, 820, 730, and 700 cm^{-1}; ^{1}H-NMR(CCl_4) δ 1.3-1.8 (18H, m), 1.8-2.6 (12H, m), 3.3-3.8 (2H, m), 3.90 (2H, d, J7), 3.97 (2H, s), 4.37 (2H, s), 4.55 (1H, bs), 4.8-5.4 (4H, m), and 7.13 (5H, s). **15**: IR(neat) 1670, 1440, and 1380 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.57 (3H, s), 1.61 (6H, s), 1.69 (3H, s), 1.7-2.9 (12H, m), 5.0-5.2 (2H, m), 5.90 (1H, d, J8), 6.37 (1H, t, J8), 10.00 (1H, d, J8), and 10.09 (1H, s). **16**: IR(neat) 1670, 1440, 1360, 1070, 740, and 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.56 (3H, s), 1.59 (3H, s), 1.67 (6H, s), 1.7-2.8 (12H, m), 4.02 (2H, d, J7), 4.50 (2H, s), 4.9-5.2 (2H, m), 5.44 (1H, t, J7), 6.43 (1H, t, J8), 7.32 (5H, s), and 10.09 (1H, s). **1**: IR(neat) 3320, 1440, 1370, 1240, and 1000 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.59 (3H, s), 1.60 (3H, s), 1.678 (3H, s), 1.683 (3H, s), 1.8-2.3 (14H, m), 4.09 (2H, s), 4.13 (2H, d, J7), and 5.0-5.5 (4H, m).
7) E. J. Corey and C. U. Kim, J. Am. Chem. Soc., 94, 7586 (1972); J. Org. Chem., 38, 1233 (1973); D. T. W. Chu, ibid., 48, 3571 (1983).
8) For the preparation of the corresponding phosphonium bromide, see: K. Chen, J. E. Semple, and M. M. Joullié, J. Org. Chem., 50, 3997 (1985).

(Received May 19, 1988)