Tetrahedron Letters, Vol.31, No.49, pp 7157-7158, 1990
Printed in Great Britain

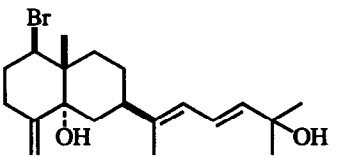
0040-4039/90 $3.00 + .00
Pergamon Press plc

A BIOGENETIC-TYPE SYNTHESIS OF (±)-APLYSIADIOL, A BROMINATED DITERPENE ISOLATED FROM THE MARINE MOLLUSC *APLYSIA KURODAI*

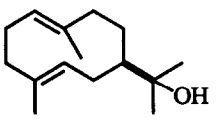
Haruki Niwa,* Shigeru Ieda, Hideaki Inagaki, and Kiyoyuki Yamada
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464, Japan

Summary: (±)-Aplysiadiol (**1**), a brominated diterpene having a rare, prenylated eudesmane skeleton was synthesized starting with (±)-hedycaryol (**2**) in a biogenetic manner.

Aplysiadiol (**1**) isolated from the Japanese marine mollusc *Aplysia kurodai* is a brominated diterpene having a rare, prenylated eudesmane skeleton.[1] A biogenesis of aplysiadiol (**1**) is shown in Scheme I. A prenylated germacrene-like precursor (**A**) biosynthesized from geranylgeranyl pyrophosphate (GGPP) may be converted into **1** through an intermediate (**B**) formed by a bromine(I) cation induced stereospecific transannular cyclization. Described herein is a stereocontrolled synthesis of racemic aplysiadiol (**1**) on the lines of the biogenesis.

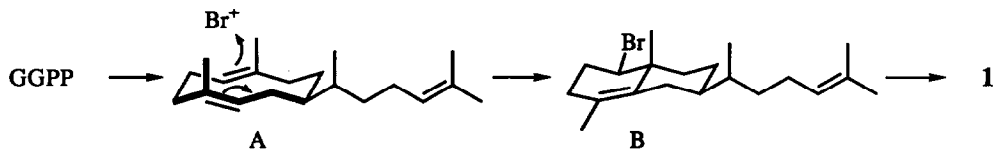


1 aplysiadiol

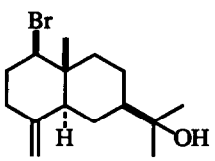


2 hedycaryol

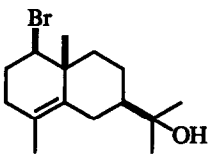
Scheme I. Biogenesis of Aplysiadiol (**1**)



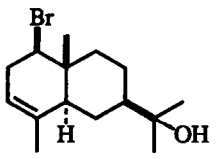
We have chosen (±)-hedycaryol (**2**) as the starting material, which was easily prepared from (*E,E*)-farnesol by the Kodama-Ito method with slight procedural modifications.[2] The bromine(I) cation induced stereospecific transannular cyclization of hedycaryol (**2**) proceeded smoothly on reaction with *N*-bromosuccinimide (1 equiv) in *t*-BuOH (25 °C, 1 h) to provide a mixture of brominated bicyclic alcohols **3**-**5**.[3] HPLC separation of the mixture[4] furnished pure **3**, **4**, and **5** in 33%, 24%, and 33% yield, respectively.[5] Of the three bicyclic alcohols, spectral properties of **3** (mp 71-72 °C) were identical with those reported for natural brasudol,[6] establishing the relative stereochemistry of **4** and **5** as depicted below. For the synthesis of **1**, bicyclic alcohol **4** was converted into diene **6** in 72% yield by dehydration with $SOCl_2$ (3 equiv) in Py-toluene (-78 °C, 1.5 h). Selective hydroboration of the disubstituted double bond in diene **6** with BH_3·THF (0.5 mol equiv) in THF (0 °C, 1.5 h) followed by H_2O_2-NaOH oxidation (25 °C, 30 min) provided alcohol **7** in 83% yield as a 1:1 mixture of the diastereomers concerning the secondary methyl group. Photosensitized oxygenation[7] of **7** proceeded stereoselectively. An oxygen-bubbled pyridine solution of **7** containing hematoporphyrin was irradiated with a 400 W tungsten-halogen lamp (25 °C, 6 h). Reduction of the crude oxygenated products with



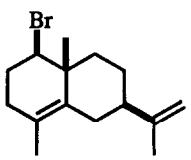
3 brasudol



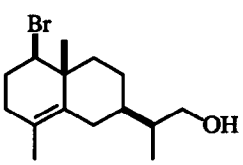
4



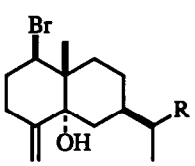
5



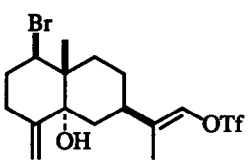
6



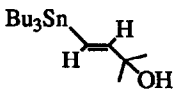
7



8 R = CH_2OH
9 R = CHO



(*E*)-**10**



11

Ph_3P (1.3 equiv) in acetone (25 °C, 2 h) gave the desired, angularly oxygenated diol **8** in 45% yield, which upon Swern oxidation gave aldehyde **9** in 80% yield. Carbon chain elongation of **9** was performed by utilizing Stille's method.[8] Thus, aldehyde **9** reacted with trifluoromethanesulfonic anhydride (1.6 equiv) and 2,6-di-*t*-butyl-4-methylpyridine (4 equiv) in CH_2Cl_2 (25 °C, 36 h) to provide the desired (*E*)-enol triflate **10** (58%) as the major product along with the isomeric (*Z*)-enol triflate (10%).[9] The stereochemistry of the triflates was unambiguously determined by comparison of the ^{13}C NMR spectral data of (*E*)-**10** with those of the (*Z*)-isomer. Stille's coupling[8] of (*E*)-enol triflate **10** and vinylstannane **11** (3 equiv)[10] was effected with $Pd(Ph_3P)_4$ (0.036 equiv), CsF (1 equiv), and LiCl (0.17 equiv) in THF (25 °C, 60 h) to give (±)-aplysiadiol (**1**) in 31% yield along with the 55% recovery of the starting (*E*)-**10**. Spectral and chromatographic properties of synthetic (±)-**1** were identical with those of natural **1** in all respects.

Acknowledgment: We are cordially grateful to Professor Ryoji Noyori of this department for permitting us to use the photochemical reaction apparatus, and to Professor Mitsuaki Kodama of Tokushima Bunri University for providing us with the spectral data of hedycaryol and valuable information on preparation of hedycaryol.

References and Notes

1) M. Ojika, Y. Yoshida, M. Okumura, S. Ieda, and K. Yamada, *J. Natl. Prod.*, in press.
2) M. Kodama, Y. Matsuki, and S. Ito, *Tetrahedron Lett.*, **1976**, 1121. See also R. E. K. Winter, F. Dorn, and D. Arigoni, *J. Org. Chem.*, **45**, 4786 (1980).
3) The stereochemical results in the transannular reactions of hedycaryol (**2**) and the related compounds are well documented: E. D. Brown, M. D. Solomon, J. K. Sutherland, and A. Torre, *J. Chem. Soc., Chem. Commun.*, **1967**, 111; R. V. H. Jones and M. D. Sutherland, *J. Chem. Soc., Chem. Commun.*, **1968**, 1229; M. Kodama, S. Yokoo, Y. Matsuki, and S. Ito, *Tetrahedron Lett.*, **1979**, 1687; Y. Shizuri, S. Yamaguchi, Y.Terada, and S. Yamamura, *Tetrahedron Lett.*, **27**, 57 (1986).
4) Deverosil ODS-10 (250 mm x 20 mm ID); solvent MeOH-H_2O (80:20); flow rate 8 ml/min; detection UV 215 nm; recycled twice. Retention time (t_R): **3**, t_R 107 min; **4**, t_R 114 min; **5**, t_R 121 min.
5) Satisfactory spectral (^1H NMR, IR, mass) and analytical (exact mass) data were obtained for all new compounds. Yields refer to the isolated, chromatographically homogeneous materials.
6) R. K. Dieter, R. Kinnel, J. Meinwald, and T. Eisner, *Tetrahedron Lett.*, **1979**, 1645. No authentic sample nor the copies of the spectral data were available.
7) I. Kitagawa, Y. Yamazoe, H. Shibuya, R. Takeda, H. Takeno, and I. Yoshioka, Chem. Pharm. Bull., **22**, 2662 (1974).
8) W. I. Scott and J. K. Stille, *J. Am. Chem. Soc.*, **108**, 3033 (1986).
9) P. J. Stang and W. Treptow, *Synthesis*, **1980**, 283.
10) H. E. Ensley, R. R. Buescher, and K. Lee, *J. Org. Chem.*, **47**, 404 (1982).

(Received in Japan 24 August 1990)