

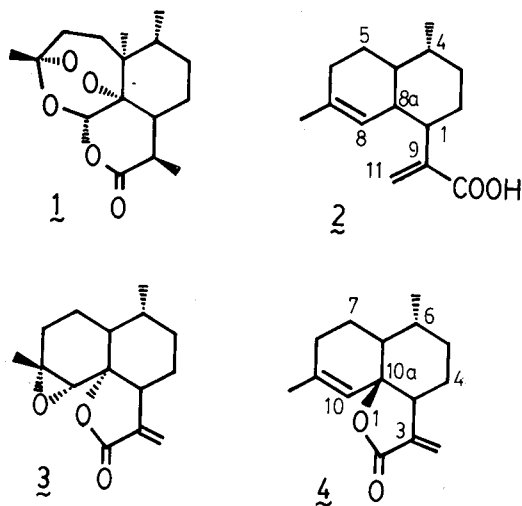
Efficient conversion of arteannuic acid into *epi*-deoxyarteannuin B

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Abstract : Oxidation of artemisinic acid was attempted with chromium trioxide-pyridine complex. *Epi*-Deoxyarteannuin B was formed almost quantitatively, while expected keto artemisinic acid was not the major product. The physical and spectral data of the product are presented (Received March 9, 1990, Accepted May 25, 1990)

Recent interest in antimalarial drug resulted in the discovery of a new placimocidal agent, artemisinin (1), from a traditional chinese herbal, *Artemisia annua*¹. The compound possesses a unique structure of cycloendoperoxide sesquiterpene². The syntheses of 1 have been attempted but usually resulted in a poor yield.



A. annua also has been found to contain several sesquiterpenes whose structures are related to 1. Arteannuic acid (2), among them, has been considered as possible biosynthetic precursor³⁻⁷ and, interestingly, could serve as a synthetic starting material for 1³. The acid was reported to occur more abundantly compared to 1 in up to 8 to 1 ratio⁸. It appears thus very attractive to

find a way to convert 2 to 1 through chemical synthesis. The attempts usually resulted in a rather low yield involving several steps⁴. However, Acton and Roth recently achieved this feat with 9, 11-dihydro-2 through simple photochemical reaction utilizing singlet oxygen at low reaction temperature followed by incubation at room temperature⁹. It is of note, nevertheless, that the similar reaction at ordinary room temperature yielded not 1, but arteannuin B³, and *epi*-deoxyarteannuin B (4) in various ratios depending on the reaction conditions^{10, 11}.

Recently, compound 4 was isolated from the leaves of *A. annua*^{12, 13}. Since ethanolic solution of 2 formed 4 spontaneously when allowed to stand at room temperature for several days, it is possible that 4 was an artefact. The compound 4 also has been obtained through chemical oxidation with pyrimidium chlorochromate in low yield, 23 percent¹². Here, we would like to report almost quantitative conversion of 2 into 4 with chromium trioxide-pyridine complex.

Materials and Methods

Arteannuic acid : The acid was isolated from *A. annua* as described previously¹⁴.

Oxidation of arteannuic acid : To the stirred solution of CrO₃-pyridine complex (60 mmol) in 100ml of dry CH₂Cl₂¹⁵ was added with 5 mmol of artemisinic acid in 20ml of the same solvent. The solution was stirred for 24 hours under dry N₂ atmosphere at room temperature. The re-

sulting dark brown solution was decanted, and the residue was triturated with ethyl ether. The combined solution was washed with 100ml of 2N HCl and subsequently with saturated brine. Resulting clear solution was dried over MgSO₄ and concentrated under reduced pressure to give brown residue. Thin layer chromatography of the residue showed trace of arteannuic acid and almost quantitative conversion of **3** into a product (R_f=0.90 in 7.5percent EtOAc in CHCl₃ on silica gel, while that of the acid was 0.69). The product was isolated through VLC using increasing EtOAc in CH₂Cl₂. The fractions containing the product were concentrated to give the crystalline product in 57 percent yield.

Results and Discussion

Physical data of the product are as follows : mp 72~73°C, literature, 81~82°C : $[\alpha]_D^{20} = +123^{\circ}$ (C=0.05, MeOH) : IR(KBr) ν_{\max} 1765(C=O), 2965(C-H), 1680(C=C), carboxylic O-H missing : MS(EL, 70eV), m/e(relative intensity) 232(100), 217(16.7), 188(43.5), 173(59.0), 159(27), 145(32.5), 131(27.3), 123(34.2), 109(44.1), 91.0(36.8), 79.1(23.7), 67(15.9), 53(25.9) ; PMR(200MHz, CDCl₃, TMS) δ 0.97(br. d, 6.5Hz, 3H), 1.71(s, 3H), 2.73(t, 6.7Hz, 1H), 5.28(br. d, 1.4Hz, 1H), 5.58(s, 1H), 6.16(s, 1H) ; CMR(50.3MHz, CDCl₃, TMS) δ 19.7, 21.4, 28.2, 29.7, 30.8, 43.9, 44.6, 83.2, 120.4, 123.5, 140.9, 142.6, 170.2. Analysis, calculated for C₁₅H₂₀O₂ : C, 76.92, H, 8.56 ; found : C, 77.58 ; H, 8.62.

The physical data are consistent with the structure of *epi*-deoxyarteannuin B (**4**). Although melting point of the product was somewhat lower than the published

data, other spectroscopic data strongly indicate the structure of **4**. Among them, triplet PMR signal at δ 2.73 (H3a) especially suggests disappearance of hydrogen at C8a of the acid, and CMR signal at δ 83.2 is typical of oxygenated quaternary carbon(C10a). Stereochemistry at C10a was unequivocally verified with specific rotation measurement^{12, 13}.

The outcome of the reaction is rather unexpected, though not impossible, since the chromium trioxide reagent is known to principally oxidize allylic position to yield keto functional group⁶. It is also worthwhile to mention that *O*-methyl arteannuic acid was converted into the product through the same reaction condition. It seems very likely that the methoxy group was hydrolyzed during work-up. Comparison of the reaction mechanism between the photooxidation and the chromium trioxide reaction, which yielded only the *epi* isomer, and occurrence of all the photochemical reaction products in the plant should receive further attention in regards to the *in vivo* synthesis of these compounds.

Acknowledgments

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References

1. Klayman, D.L. : Science, 228 : 1049 (1985)
2. Qinghaosu Research Group : Sci. Sin., 23 : 380 (1980)
3. Schmid, G. and Hofheinz, W. : J. Am. Chem. Soc., 105 : 624 (1983)
4. Xu, X.-X., Zhu, J., Huang, D.-Z. and Zhou, W.-S. : Tetrahedron, 42 : 819 (1986)
5. El-Feraly, F. S., Al-Meshal, I. A., Al-Yahya, M.A. and HifNawy, M. S. : Phytochemistry, 25 : 2777 (1986)
6. Akhila, A., Thakur, R. S. and Popli, S.P. : Phytochemistry, 26 : 1927 (1987)
7. Wang, Y., Xia, Z.-Q., Zhou, F.-Y., Wu, Y.-L., Hunag, J.-J. and Wang Z.-Z. : Acta Chim. Sin (Chinese version), 46 : 1152 (1988)
8. Jung, M., ElSohly, H. N. and Croom E. M. : J. Org. Chem., 51 : 5417 (1986)
9. Roth, R.J. and Acton, N. : J. Nat. Prod., 52 : 1183 (1986)
10. Xu, X.-X., Zhu, J. and Zhou, W.-S. : Acta Chim. Sin. (Chinese version), 43 : 48 (1985)

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11. Jung, M., Yoo, Y., ElSohly, H.N. and McChesney, J. D. : J. Nat. Prod., 50 : 972 (1987)
 12. El-Feraly, F. S., Al-Meshal, I. A. and Khalifa, S. I. : J. Nat. Prod., 52 : 196 (1989)
 13. Roth, R. J. and Acton, N. : Planta Med., 575 (1987)
 14. Kim, S.-U. and Lim, H.-J. : J. Korean Agric. Chem. Soc., 32 : 178 (1989)
 15. Ratcliffe, R. and Rodehorst, R. : J. Org. Chem., 35 : 4000 (1970)
 16. Dauben, W. G., Lorber, M. and Fullerton, D.S. : J. Org. Chem., 34 : 3587 (1969)

Arteannic acid에서 *epi*-deoxyarteannuin B의 효과적 합성

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