FORMATION OF DIHYDROBENZOXANTHONE SKELETON FROM 3-ISOPRENYLATED 2',4',5'-TRIOXYGENATED FLAVONE[1]

Miwa Aida, Yukiko Yamagami, Yoshio Hano, and Taro Nomura*

Faculty of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama,
Funabashi, Chiba 274, Japan

Abstract - Photoreaction of artonin E (**1**), 3-isoprenylated 2',4',5'-trioxygenated flavone, produced artobiloxanthone (**2**) and cycloartobiloxanthone (**3**). Furthermore, the treatment of artonin E (**1**) with a radical reagent (DPPH) resulted in the same products. These findings support that the flavone derivatives having the dihydrobenzoxanthone skeleton are biogenetically derived from the 3-isoprenylated 2',4',5'-trioxygenated flavones through the phenol oxidative cyclization.

Many kinds of isoprenylated flavonoids have been isolated from *Artocarpus* species (Moraceae) by our group[2-12] and other groups.[13-17] Some of these have shown potential inhibitory activity against the action of arachidonate 5-lipoxygenase from porcine leukocytes.[18] The flavones from *Artocarpus* plants, except some ones, are characteristic having an isoprenoid side-chain at the C-3 position of the skeleton as in the case of *Morus* flavonoids,[19] and have a 2',4',5'-trioxygenated pattern for the B ring of the skeleton. Artonins E (**1**)[11] and H (**4**)[9] are such typical flavones. In addition to the above features of *Artocarpus* flavones, some flavones such as artobiloxanthone (**2**),[15] cycloartobiloxanthone (**3**)[15] and artonin M (**5**),[10] have a unique structural feature involving a dihydrobenzoxanthone skeleton, in which the C-C linkage takes place between the C-6' position of the B ring and the C-10 position of isoprenoid moiety located at the C-3 position. Taking no optical activities into the account, the flavones having the dihydrobenzoxanthone skeleton are seemed to be biogenetically derived from the 3-isoprenylated 2',4',5'-trioxygenated flavones through the phenol oxidative cyclization. We attempt to derive the flavone having the dihydrobenzoxanthone skeleton from the 3-isoprenylated 2',4',5'-trioxygenated flavone.

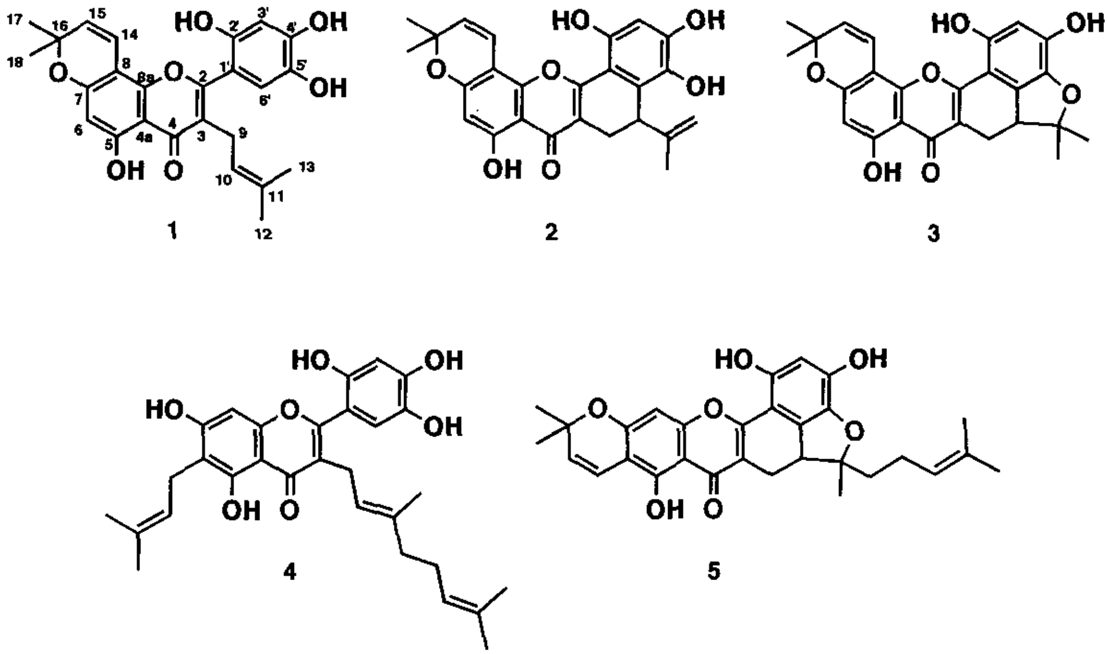

Figure 1

A solution of artonin E (**1**, 50 mg) in chloroform containing 4 % ethanol solution (50 ml) was irradiated with a high-pressure mercury lamp (100 W) for 96 h at room temperature. The products were chromatographed on a silica gel column (50 g) eluted successively with benzene, chloroform, and then ether. The chloroform fraction was rechromatographed on Sephadex LH-20 with methanol as an eluent to give cycloartobiloxanthone (**3**, 3.1 mg). The ether fraction was rechromatographed as described above to give artobiloxanthone (**2**, 16.8 mg) and artonin E (**1**, 15.0 mg). This reaction did not occur in the dark as well as in the nitrogen atmosphere. Furthermore, artonin E (**1**, 50 mg) was treated with a radical reagent, diphenyl picryl hydrazyl (DPPH, 40 mg) in chloroform containing 4 % ethanol solution in the dark for 24 h. The reaction products were purified by column chromatography as described in the case of photoreaction to give artobiloxanthone (**2**, 17.0 mg), cycloartobiloxanthone (**3**, 0.7 mg), and artonin E (**1**, 14.6 mg). These results suggest that the photo-oxidative cyclization of artonin E (**1**) may proceed through phenol oxidation *via* the semiquinone radicals described in Figure 2.

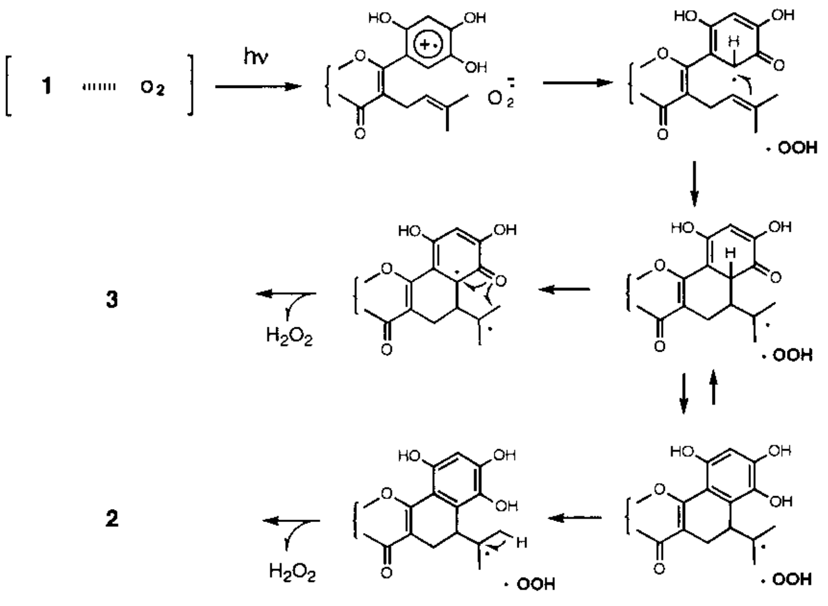

Figure 2 Mechanism of Photo-oxidative Cyclization of Artonin E (1)

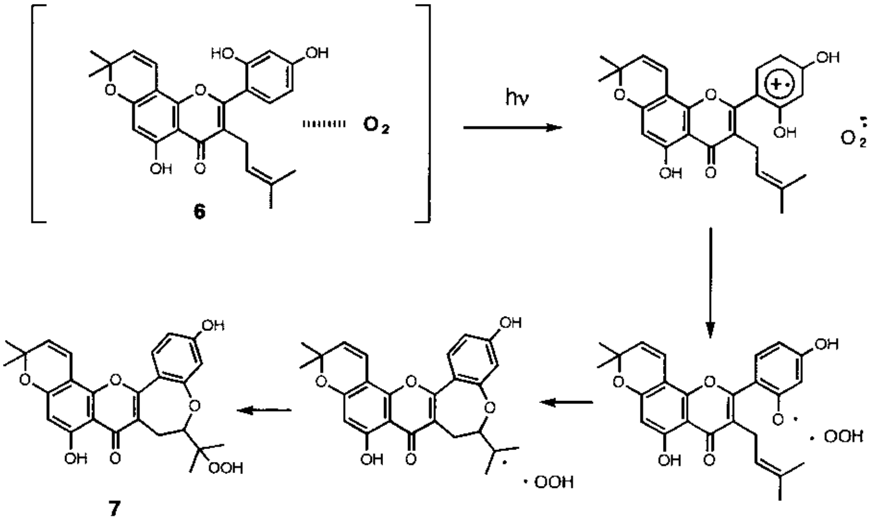

Figure 3 Mechanism of Photo-oxidative Cyclization of Morusin (6)

On the other hand, the similar oxidative cyclization had been reported by our group.[19,20] When a solution of morusin (**6**) in chloroform was irradiated using high-pressure mercury lamp, morusin hydroperoxide (**7**) was obtained in *ca.* 80 % yield. The reaction mechanism was suggested as follows : Morusin (**6**) in the ground state interacts with an oxygen molecular to form a contact charge transfer complex. On irradiation, the complex gives an excited charge transfer state that presumably leads to reactive species such as free radicals as described in Figure 3. Considering these results, the plausible reaction mechanism of the photoreaction of artonin E (**1**) can be sketched as follows: Artonin E (**1**) in the ground state interacts with an oxygen molecule to form a contact charge transfer complex as in the case of morusin (**6**). Irradiation of the complex produces the reactive species such as semiquinone radicals, and artobiloxanthone (**2**) and cycloartobiloxanthone (**3**) are derived from the radicals as described in Figure 2.

These findings support that the flavone derivatives having the dihydrobenzoxanthone skeleton, such as artobiloxanthone (**2**), cycloartobiloxanthone (**3**) and artonin M (**5**), are biogenetically derived from the 3-isoprenylated 2',4',5'-trioxygenated flavones, such as artonin E (**1**) and artonin H (**4**), through the phenol oxidative cyclization (Figure 2). On the other hand, the 3-isoprenylated 2',4'-dioxygenated flavones, such as morusin (**6**), give the hydroperoxide having a dihydrooxepin ring (**7**) under the same condition (Figure 3). These flavones having the dihydrobenzoxanthone skeleton are characteristic constituents of *Artocarpus* species, since they have never been observed in other species.

REFERENCES AND NOTES

1. Part 29 in the series "Constituents of the Moraceae Plants". Part 28 in the series: T. Fukai, Y.-H. Pei, T. Nomura, C.-Q. Xu, L.-J. Wu, Y.-J. Chen, *Heterocycles*, 1996, **43**, 425.
2. T. Nomura and Y. Hano, *Nat. Prod. Rep.*, 1994, **11**, 205, and the references cited therein.
3. Y. Hano, M. Aida, M. Shiina, T. Nomura, T. Kawai, H. Ohe, and K. Kagei, *Heterocycles*, 1989, **29**, 1447.
4. Y. Hano, M. Aida, and Taro Nomura, *J. Nat. Prod.*, 1990, **53**, 391.
5. Y. Hano, M. Aida, T. Nomura, and S. Ueda, *J. Chem. Soc., Chem. Commun.*, **1992**, 1177.
6. M. Aida, K. Shinomiya, Y. Hano, and T. Nomura, *Heterocycles*, 1993, **36**, 575.
7. M. Aida, K. Shinomiya, K. Matsuzawa, Y. Hano, and T. Nomura, *Heterocycles*, 1994, **39**, 847.
8. K. Shinomiya, M. Aida, Y. Hano, and T. Nomura, *Phytochemistry* 1995, **40**, 1317.
9. Y. Hano, R. Inami, and T. Nomura, *Heterocycles*, 1990, **31**, 2173.

10. Y. Hano, R. Inami, and T. Nomura, *Heterocycles*, 1993, **35**, 1341.

11. Y. Hano, Y. Yamagami, M. Kobayashi, R. Isohata, and T. Nomura, *Heterocycles*, 1990, **31**, 877.

12. Y. Hano, R. Inami, and T. Nomura, *J. Chem. Res.(S)*, **1994**, 348.

13. K. Venkataraman, *Recent Dev. Chem. Nat. Carbon Compd.*, 1976, **7**, 39, and the references cited therein.

14. K. Venkataraman, *Phytochemistry*, 1989, **28**, 599. and the references cited therein.

15. M.U.S. Sultanbawa and S. Surendrakumar, *Phytochemistry*, 1989, **28**, 599.

16. M.-I. Chung, C.-M. Lu, P.-L. Huang, and C.-N. Lin, *Phytochemistry*, 1995, **40**, 1279, and the references cited therein.

17. Y. Fujimoto, X.-X. Zhang, M. Kirisawa, J. Uzawa, and M. Sumata, *Chem. Pharm. Bull.*, 1990, **38**, 1787.

18. G. R. Reddy, N. Ueda, T. Hada, A. C. Sackeyfio, S. Yamamoto, Y. Hano, M. Aida, and T. Nomura, *Biochem. Pharmacol.*, 1991, **41**,115.

19. T. Nomura, " Progress in the Chemistry of Organic Natural Products", Eds by W. Herz, H. Griesebach, G. W. Kirby, and Ch. Tamm, Springer-Verlag, Viena, New York, 1988, **53**, 87, and the references cited therein.

20. T. Nomura and T. Fukai, *Heterocycles*, 1978, **9**, 635, and the references cited therein.

Received, 3rd September, 1996