

CONVERSION OF ARTEMISINIC ACID INTO (-)-FABIANANE

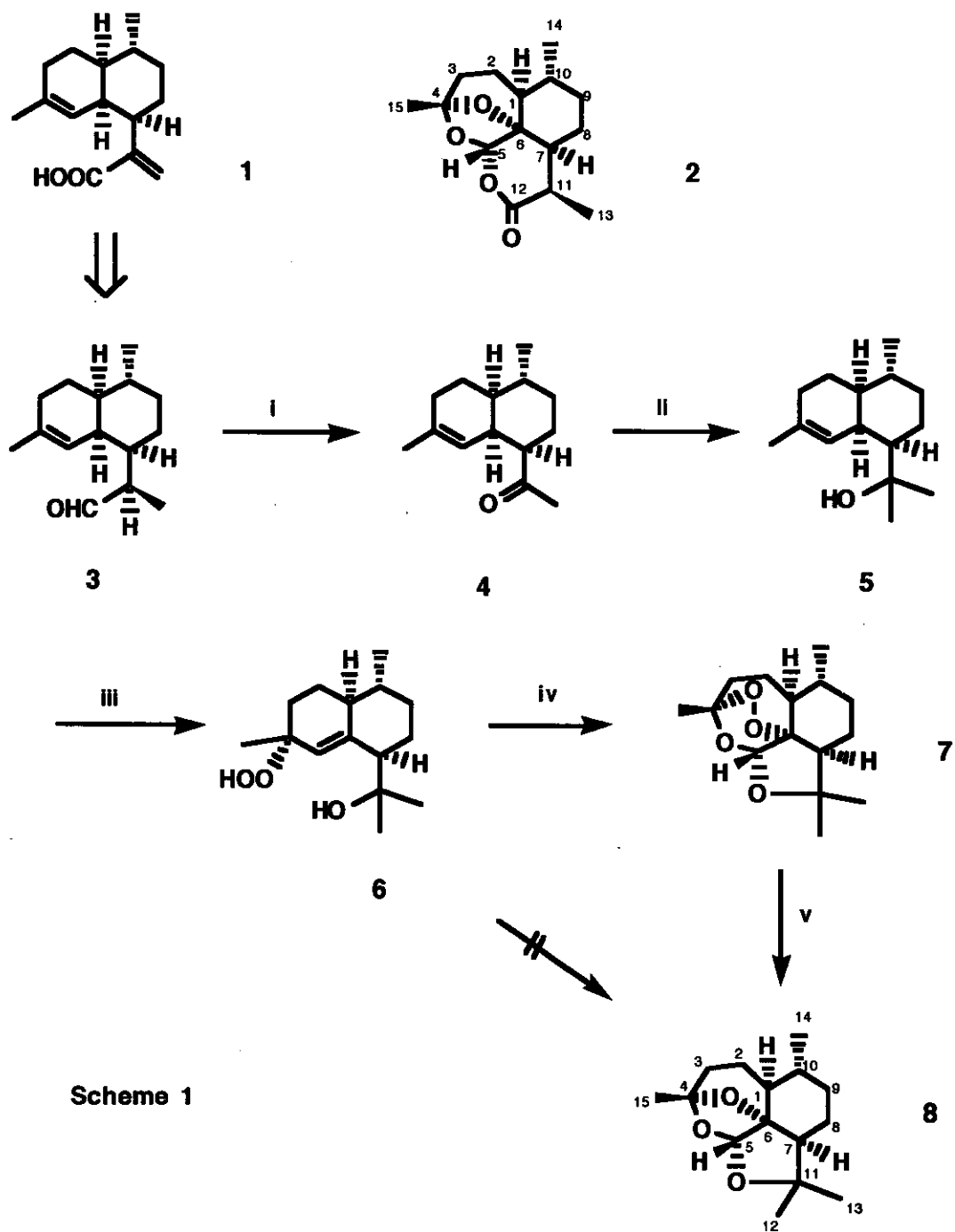
Mankil Jung* and Byoung Hee Youn

Department of Chemistry, Yonsei University, Seoul, Korea

Abstract - The conversion of (-)-fabianane from artemisinic acid was achieved in seven steps *via* photooxidative cyclization as a key step.

(-)-Fabianane (**8**) was isolated by Brown¹ from the aerial parts of *Fabiana imbricata* (Ruiz and Pavon) Romeo, a plant native to central Chile which is used by the Mapuche Indians to treat kidney and urinary afflictions. (-)-Fabianane (**8**) is novel seco-amorphane sesquiterpene. It shares several structural similarities such as overall stereochemistry and level of oxygenation at carbons 4, 5 and 6 with deoxyartemisinin (**2**),² the metabolite of artemisinin, the antimalarial principle from *Artemisia annua*. The two compounds differ in that the 5, 12 ester linkage in deoxyartemisinin (**2**) is replaced by a 5, 11 ether linkage with an additional methyl at carbon 11 in fabianane (**8**). There have been no previous reports of synthesis of fabianane to the best of our knowledge.³ The novel seco-amorphane structure as well as natural scarcity of (-)-fabianane (**8**) (0.001 % yield from *F. imbricata*) have prompted us to prepare the compound by synthesis. In this communication, we would like to report the first synthesis of (-)-fabianane.

(-)-Artemisinic acid (**1**), a versatile chiral starting material for the preparation of many novel analogs⁴ of artemisinin, was converted to dihydroartemisyl aldehyde (**3**) by literature procedures^{4a} in three steps in 65 % overall yield. The oxidative degradation⁵ of the aldehyde (**3**) with bubbling air in a dimethylformaldehyde solution of 1,4-diazabicyclo[2.2.2]octane (DABCO) and complex of cupric acetate with 2,2'-bipyridyl (70 °C, 1 h) afforded the ketone (**4**)⁶ (mp 34-36 °C) in 44 % yield (Scheme 1). Treatment of the ketone (**4**) with methylmagnesium bromide in ether (reflux, 2 h) provided 4-amorphen-11-ol (**5**)⁷ (mp 80-82 °C) in 87 % yield. The tertiary alcohol (**5**) was also isolated⁸ from *Fabiana imbricata* (Ruiz and Pav.). Photosensitized oxygenation⁹ of **5** afforded new peroxofabianane (**7**)¹² (mp 79-80 °C) in 27 % yield *via* the intermediate (**6**)^{10,11} [irradiation of **5** under oxygen atmosphere and rose bengal as photosensitizer in CH₃CN/CH₂Cl₂



Reagents and Conditions: i, air, 1,4-diazabicyclo[2.2.2]octane (0.56 equiv.), cupric acetate (cat.)/2,2'-bipyridyl(1:1), dimethylformamide, 70 °C, 1 h, 44 %; ii, methylmagnesium bromide (5.4 equiv.), anhydrous ether, reflux, 2 h, 87 %; iii, O₂, irradiation, rose bengal, CH₃CN/CH₂Cl₂(1:1), -23 °C, 2.5 h, 92 %; iv, copper triflate (0.41 equiv.), oxygen, -23 °C, 1 h then room temperature, 2 h, 27 % from 5; v, H₂, 5 % Pd/CaCO₃, ethanol, room temperature, 22h then *p*-TsOH (0.4 equiv.), room temperature, 1 h, 91 %.

(1:1), -23 °C and subsequent treatment by copper triflate at -23 °C to room temperature]. Hydrogenation of **7** with 5 % Pd/CaCO₃ in ethanol and subsequent *in situ* treatment with *p*-TsOH afforded (-)-fabianane (**8**)¹³ (oil) in 91 % yield. (-)-Fabianane (**8**) synthesized from artemisinic acid was identical by comparison of specific rotation and spectral properties with those of natural (-)-fabianane,¹ isolated from *F. imbricata*. This synthesis represents a demonstration of the potential biogenetic relationship between the tertiary alcohol (**5**) and fabianane (**8**). The intermediate (**6**)¹⁰ was obtained in 92 % yield from 4-amorphen-11-ol (**5**) and the stereoisomer was not detected in this reaction. Unfortunately, direct conversion² of the intermediate (**6**) with mCPBA in CHCl₃ to fabianane (**8**) was unsuccessful. The absolute configuration of natural fabianane has been assumed to be as shown in **8** by analogy with other amorphanes⁸ which were recently isolated from *F. imbricata*, such as the tertiary alcohol (**5**). The relative configuration of (-)-fabianane was confirmed as shown in the structure (**8**) by this conversion.

In conclusion, this first conversion of (-)-fabianane was stereoselectively established from readily available artemisinic acid in seven steps and provides this scarce natural product in quantities suitable for more extensive biological evaluation.

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3. 11 α -Hydroxydemethylfabianane was prepared from 11 β -hydroxy-11-epidihydroartemisinin in 70 % yield by silica gel-catalyzed rearrangement. See H. B. Yagen, Y. M. Pu, H. J. C. Yeh, and H. Ziffer, *J. Chem. Soc., Perkin Trans. I*, 1994, 843. Synthesis of ring-contracted artemisinin derived from artemisinin was also reported: B. Venugopalan, C. P. Bapat and P. J. Karnik, *Bioorg. & Med. Chem. Lett.*, 1994, **4**, 751.
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5. For the proposed mechanism, see V. van Rhee, *Tetrahedron Lett.*, 1969, 985.
6. Compound (4): mp 34-36 °C, $[\alpha]_D^{25} -53.5^\circ$ (c 1.0, CHCl₃); nmr (300 MHz, CDCl₃): δ 4.82 (s, 1H, 5-H), 2.95 (br s, 1H,), 2.42 (dt, J=3.4, 3.2 Hz, 1H, 6-H), 2.15 (s, 3H, CH₃CO), 1.58 (s, 3H, 14-CH₃), 0.87 (d, J=6.20 Hz, 3H, 13-CH₃); ir (CHCl₃): 2923, 2867, 1706 (C=O), 1446, 1351, 1163 cm⁻¹; Clms m/z: 224 (M+NH₄⁺, 100).
7. Compound (5): mp 80-82 °C, $[\alpha]_D^{29} -3.5^\circ$ (c 1.0, CHCl₃), [lit.⁸ $[\alpha]_D -4.5^\circ$ (c 1.54, CHCl₃)]; nmr (300 MHz, CDCl₃): δ 5.65 (s, 1H, H-5), 2.65 (s, 1H, H-6), 2.63 (s, 3H, 15-CH₃), 1.28 and 1.26 (s, 6H, 12 and 13-CH₃), 0.87 (d, J=6.6 Hz, 3H, 14-CH₃); ir (CHCl₃): 3428(OH), 2921, 2867, 1448, 1377 cm⁻¹; Clms m/z: 240 (M+NH₄⁺, 100), 222 (M+NH₄⁺ -H₂O, 46).
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(b) M. Jung, X. Li, D. A. Bustas, H. N. ElSohly, J. D. McChesney, and W. K. Milhous, *J. Med. Chem.*, 1990, 33, 1516.
10. Compound (6): oil, nmr (300 MHz, CDCl₃): δ 7.85 (br s), 5.69 (s, H-5), 1.34 (s, 3H, 15-CH₃), 1.33 (s, 3H, 12-CH₃), 1.30 (s, 3H, 13-CH₃), 0.93 (d, J=6.0 Hz, 3H, 14-CH₃); ir (CHCl₃): 3389(OOH), 2944, 2867, 1654, 1447, 1368, 1130, 756 (C=C) cm⁻¹.
11. For the proposed mechanisms, see M. Jung, H. N. ElSohly, and J. D. McChesney, *Planta Medica*, 1990, 56, 624 and (ref. 2).
12. The yield of oxidative cyclization of 5 to 7 was not optimized.
Compound (7): mp 79-80 °C, $[\alpha]_D^{23} +60^\circ$ (c 0.85, CHCl₃); nmr (300 MHz, CDCl₃): δ 5.59 (s, 1H, H-5), 2.30 (m, 1H, H-7), 2.10 (m, 1H, 2 α -H), 1.95 (dt, J=2.4, 4.0 Hz, 2H), 1.75 (m, 1H), 1.58 (s, 3H, 15-CH₃), 1.44 (s, 3H, 12-CH₃), 1.24 (s, 3H, 13-CH₃), 0.97 (d, J=6.30 Hz, 3H, 14-CH₃); C-13 nmr (75 MHz, CDCl₃): δ 19.93, 24.41, 25.42, 25.74, 26.37, 30.17, 32.72, 36.91, 37.35, 49.15, 52.14, 83.72, 87.23, 96.32, 103.41; ir (CHCl₃): 2928, 2872, 1453, 1379, 1208, 1034, 883, 828 cm⁻¹; Clms m/z: 286 (M+NH₄⁺, 100).
13. Compound (8): (oil), $[\alpha]_D^{25} -34.5^\circ$ (c 0.29, CHCl₃); nmr (300 MHz, CDCl₃): δ 5.64 (s, 1H, H-5), 1.92 (m, 1H, H-7), 1.59 (s, 3H, 12-CH₃), 1.55 (s, 3H, 4-CH₃), 1.49 (m, 1H, H-1), 1.17 (s, 3H, 13-CH₃), 1.16 (m, 1H, H-10), 0.91 (d, J=6.20 Hz, 3H, 14-CH₃); C-13 nmr (75 MHz, CDCl₃): δ 110.61, 103.78, 94.17, 87.66, 47.98, 43.89, 35.10, 34.94, 32.92, 29.82, 26.43, 25.56, 24.05, 23.49, 18.62; ir (CHCl₃): 2926, 1383, 1021 cm⁻¹; Clms m/z: 270 (M+NH₄⁺, 100).