CONVERSION OF ARTEMISINIC ACID INTO (-)-FABIANANE

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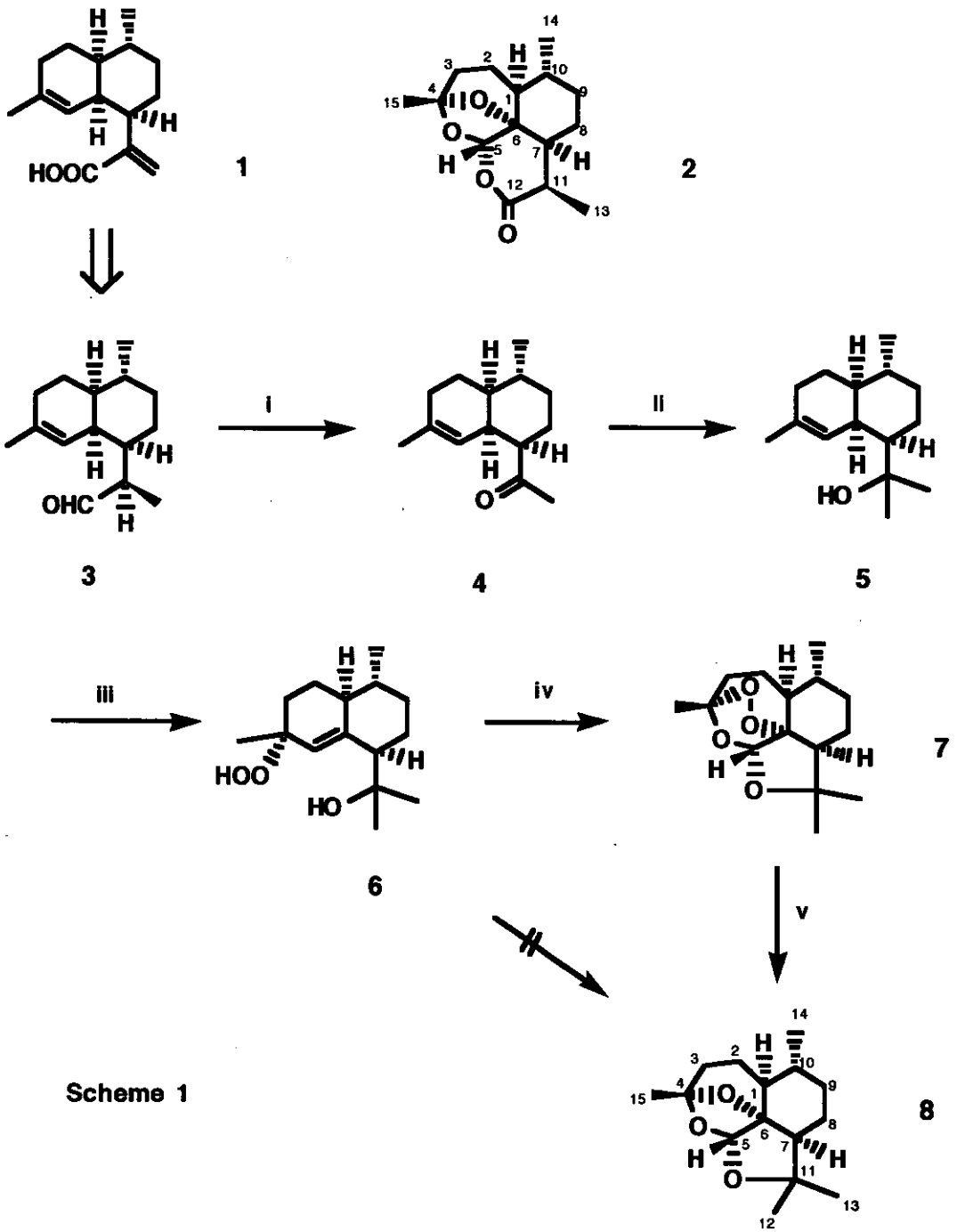
Abstract - The conversion of (-)-fabianane from artemisinic acid was achieved in seven steps *via* photooxidative cyclization as a key step.

(-)-Fabianane (**8**) was isolated by Brown[1] 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 analogs[4] of artemisinin, was converted to dihydroartemisinyl aldehyde (**3**) by literature procedures[4a] in three steps in 65 % overall yield. The oxidative degradation[5] 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 isolated[8] from *Fabiana imbricata* (Ruiz and Pav.). Photosensitized oxygenation[9] 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 atomosphere and rose bengal as photosensitizer in CH_3CN/CH_2Cl_2



Scheme 1

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, O_2, irradiation, rose bengal, CH_3CN/CH_2Cl_2(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, H_2, 5 % Pd/$CaCO_3$, 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 % $Pd/CaCO_3$ 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 comparision 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 conversion[2] of the intermediate (**6**) with mCPBA in $CHCl_3$ to fabianane (**8**) was unsuccessful. The absolute configuration of natural fabianane has been assumed to be as shown in **8** by analogy with other amorphanes[8] 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. 11α-Hydroxydemethylfabianane was prepared from 11β-hydroxy-11-epidihydroartemisinin in 70 % yield by silica gel-catalized 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 Rheenen, *Tetahedron Lett.*, 1969, 985.
6. Compound (**4**): mp 34-36 °C, $[\alpha]_D^{25}$ -53.5° (c 1.0, $CHCl_3$); nmr (300 MHz, $CDCl_3$): 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, CH_3CO), 1.58 (s, 3H, 14-CH_3), 0.87 (d, J=6.20 Hz, 3H, 13-CH_3); ir ($CHCl_3$): 2923, 2867, 1706 (C=O), 1446, 1351, 1163 cm^{-1}; CIms m/z: 224 ($M+NH_4^+$, 100).
7. Compound (**5**): mp 80-82 °C, $[\alpha]_D^{29}$ -3.5 ° (c 1.0, $CHCl_3$), [lit.,[8] $[\alpha]_D$ -4.5 ° (c 1.54, $CHCl_3$)]; nmr (300 MHz, $CDCl_3$): δ 5.65 (s, 1H, H-5), 2.65 (s, 1H, H-6), 2.63 (s, 3H, 15-CH_3), 1.28 and 1.26 (s, 6H, 12 and 13-CH_3), 0.87 (d, J=6.6 Hz, 3H, 14-CH_3); ir ($CHCl_3$): 3428(OH), 2921, 2867, 1448, 1377 cm^{-1}; CIms m/z: 240 ($M+NH_4^+$, 100), 222 ($M+NH_4^+ - H_2O$, 46).
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10. Compound (**6**): oil, nmr (300 MHz, $CDCl_3$): δ 7.85 (br s), 5.69 (s, H-5), 1.34 (s, 3H, 15-CH_3), 1.33 (s, 3H, 12-CH_3), 1.30 (s, 3H, 13-CH_3), 0.93 (d, J=6.0 Hz, 3H, 14-CH_3); ir ($CHCl_3$): 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 ° (c 0.85, $CHCl_3$); nmr (300 MHz, $CDCl_3$): δ 5.59 (s, 1H, H-5), 2.30 (m, 1H, H-7), 2.10 (m, 1H, 2α-H), 1.95 (dt, J=2.4, 4.0 Hz, 2H), 1.75 (m, 1H), 1.58 (s, 3H, 15-CH_3), 1.44 (s, 3H, 12-CH_3), 1.24 (s, 3H, 13-CH_3), 0.97 (d, J=6.30 Hz, 3H, 14-CH_3); C-13 nmr (75 MHz, $CDCl_3$): 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 ($CHCl_3$): 2928, 2872, 1453, 1379, 1208, 1034, 883, 828 cm^{-1}; CIms m/z: 286 ($M+NH_4^+$, 100).
13. Compound (**8**): (oil), $[\alpha]_D^{25}$ -34.5° (c 0.29, $CHCl_3$); nmr (300 MHz, $CDCl_3$): δ 5.64 (s, 1H, H-5), 1.92 (m, 1H, H-7), 1.59 (s, 3H, 12-CH_3), 1.55 (s, 3H, 4-CH_3), 1.49 (m, 1H, H-1), 1.17 (s, 3H, 13-CH_3), 1.16 (m, 1H, H-10), 0.91 (d, J=6.20 Hz, 3H, 14-CH_3); C-13 nmr (75 MHz, $CDCl_3$): 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 ($CHCl_3$): 2926, 1383, 1021 cm^{-1}; CIms m/z: 270 ($M+NH_4^+$, 100).

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