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 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\(_3\)CN/CH\(_2\)Cl\(_2\).
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, 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, 22 h 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.

ACKNOWLEDGMENTS

This study was supported in part by a research grant from Bioproducts Research Center of Yonsei University (Project No. 96-K3-04-12) - Korea Science and Engineering Foundation (KOSEF).

REFERENCES AND NOTES


6. Compound (4): mp 34-36 °C, [α]D 25 -53.5 ° (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, [α]D 25 -3.5 ° (c 1.0, 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(0H), 2921, 2867, 1448, 1377 cm⁻¹; Clms m/z: 240 (M+NH₄⁺, 100), 222 (M+NH₄⁺ -H₂O, 46).


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(0H), 2944, 2867, 1654, 1447, 1368, 1130, 756 (C=C) cm⁻¹.

11. For the proposed mechanisms, see M. Jung, H. N. ElSohliy, 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, [α]D 25 +60 ° (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, 2α-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), [α]D 25 -34.5 ° (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).

Received, 30th January, 1996