A PRACTICAL AND GENERAL SYNTHESIS OF (+)-CARBOXYALKYLDEOXOARTEMISININS+

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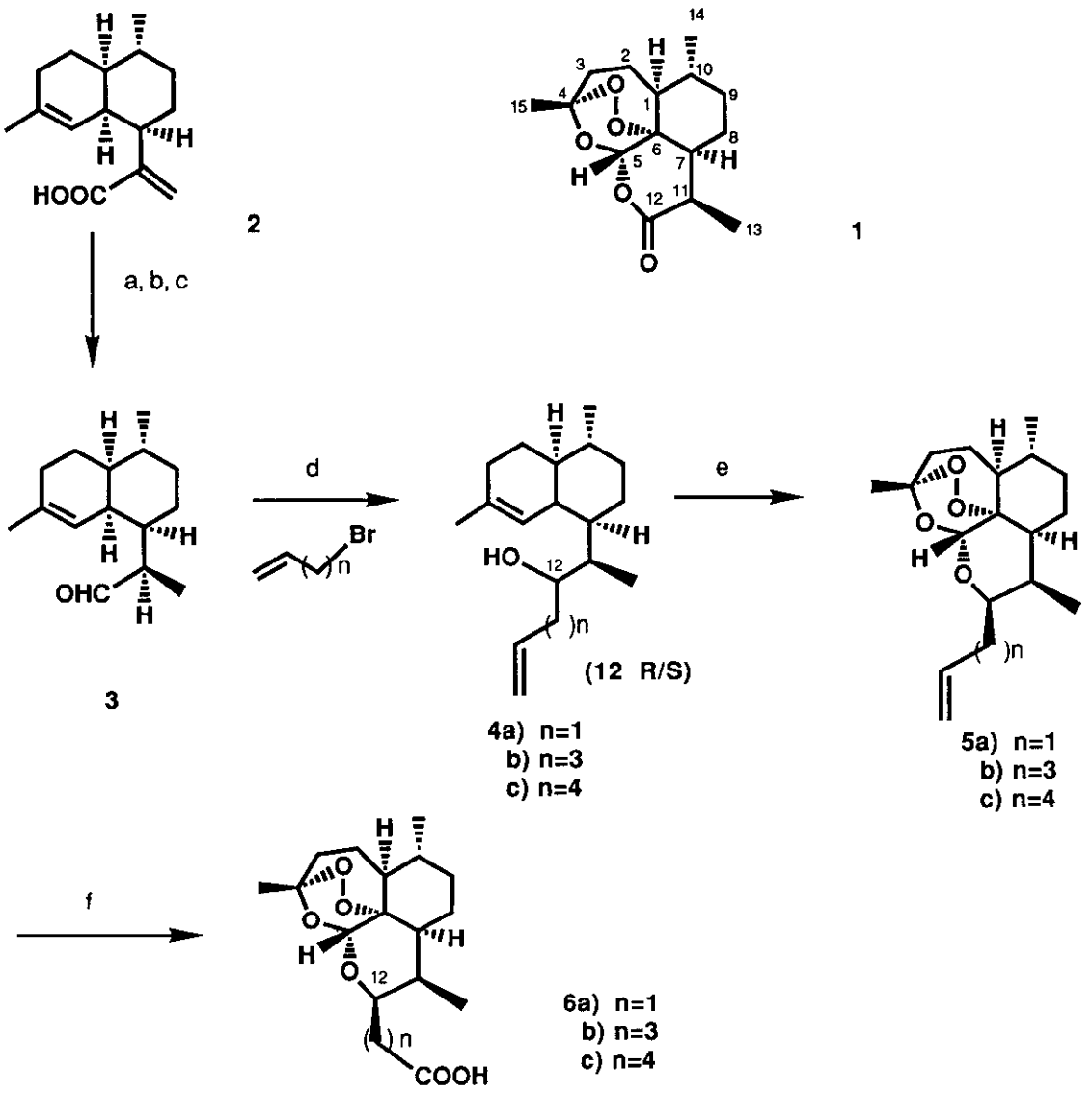
Abstract- Dye-sensitized photoxygenation of olefinic alcohols of dihydroartemisinates (**4a-c**) and direct oxidation of olefinic deoxoartemisinins (**5a-c**) have led to the preparation of carboxyalkyldeoxoartemisinins (**6a-c**), which are water-soluble and chemically more stable antimalarial agents.

+*Dedicated to Professor Arnold Brossi on the occasion of his 70th birthday.*

Malaria is the most widespread infectious disease in the world today. Worldwide, 200 million people are newly infected and over 2 million people die each year of malaria. Artemisinin (Qinghaosu) (**1**), a sesquiterpene lactone endoperoxide, is one of the most promising new antimalarials known.[2] In view of its novel structure and antimalarial activity against chloroquine-resistant malaria, the chemistry of artemisinin and its derivatives has been subject of intense study for more than 10 years.[2] Partial[3] and total[4] syntheses of artemisinin and its analogs have been reported. In addition to potent antimalarial activity, an ideal artemisinin-related drug candidate should possess (1) an external C-C bond at C-12 for increased

chemical stability, providing a longer half-life in the body, and (2) water-solubilizing functional groups such as carboxylates.[5,6] We have described a short synthesis of deoxoartemisinin as a first analog lacking the carbonyl function at C-12.[3b,7] Compounds (**6a-c**) represent some novel antimalarial agents containing both an external C-C bond and carboxyalkyl side chains at C-12. Synthesis of compounds (**6a-c**) has remained, for a long time, elusive because their direct synthesis from artemisinin (**1**) is very difficult due to the chemically sensitive functional groups within the molecule. We now report a first practical and general synthesis of (+)-carboxyalkyl deoxoartemisinins (**6a-c**), which fulfill the above requirements (1) and (2) for the discovery of urgently needed artemisinin-related antimalarial drugs. Our general synthesis is outlined in Scheme I. Since artemisinic (qinghao) acid (**2**) is more abundant than artemisinin in the plant *Artemisia annua*,[3a,8] there is commercial advantage in using it for preparing water-soluble artemisinin derivatives. The dihydroartemisinylaldehyde (**3**) was prepared easily in three steps from artemisinic acid (**2**).[3d,f] Thus, treatment of **2** with CH_2N_2 (yield 98 %) and subsequent reduction of the terminal double bond of methyl artemisinate by $NaBH_4$ afforded dihydro-methylartemisinate (yield 95 %). A second reduction of the methyl ester group with DIBAL-H gave **3** (11*R*/*S*=5/1, yield 70 %), providing in overall yield from **2** to **3** of 65 %. Aldehyde (**3**) serves as a versatile chiral intermediate to various homologs of these series.[3d,f,h] Grignard reactions of **3** (11*R*) can introduce the external C-C bond at C-12, as previously shown.[3f,h] Thus, coupling of **3** (11*R*) with the corresponding olefinic bromides [allyl bromide (n=1), 5-bromo-1-pentene (n=3), 6-bromo-1-hexene (n=4)] cleanly afforded olefinic alcohols (**4a-c**) [yields, 80 % (12*R*/*S*=2/1) for **4a** (n=1), 95 % (12*R*/*S*=3/1) for **4b** (n=3), 97 % (12*R*/*S*=5/1) for **4c** (n=4)] respectively. In this reaction, extention of the alkyl group of the olefinic bromides generally increases stereoselectivity. The terminal double bond was introduced in this reaction to serve as a masked equivalent for the carboxyl group of the target compounds (**6a-c**). We found that separation of 12*R*-isomers from 12*S*-isomers of



Scheme I. Reagents and Conditions: (a) CH_2N_2 (2.34 equiv.), anhydrous ether, 0°C, 30 min, 98 %. (b) $NaBH_4$ (2.0 equiv.), $NiCl_2$ (cat.), CH_3OH, room temperature, 1.5 h, 95 %. (c) DIBAL-H (1.5 equiv.), CH_2Cl_2, -78 °C, 2 h, 70 %. (d) allyl bromide (5 4 equiv) for **4a**, 5-bromo-1-pentene (5.4 equiv.) for **4b**, 6-bromo-1-hexene (5.4 equiv.) for **4c**, magnesium (2.5 equiv.), anhydrous ether, N_2, room temperature, 1h, 80-97 %. (e) oxygen, irradiation, rose bengal, CH_3CN-CH_2Cl_2 (1:1), -23 °C, 4 h, then copper triflate (0.41 equiv.), oxygen, CH_3CN, -23 °C to room temperature, 5 h, 30-62 %. (f) $KMnO_4$ (2.91 equiv.), $NaHCO_3$ (0.5 equiv.), acetone, room temperature, 4h, 68-84 %.

4a-c was difficult. Dye-sensitized photoxygenation-cyclization[9] of the diastereomers of **4a-c** (-23 °C, irradiation, rose bengal in CH_2Cl_2/ CH_3CN=1/1, followed by treatement of the intermediates with copper triflate[3e,i] in CH_3CN under oxygen at room temperature, 4 h.) afforded **5a-c** [yields, 30 % for **5a** (n=1), 32 % for **5b** (n=3), 62 % for **5c** (n=4)] stereospecifically in natural configuration respectively. The predominate 12*R*-isomers were easily separated from their 12*S*-isomers by column chromatography (silica gel, $CHCl_3$ as eluent). The trisubstituted double bond of **4a-c** *was selectively oxidized by the photoxygenation while the monosubstituted* terminal double bond was left intact. Although the yield for this key step was only moderate (30-62 %), this reaction represents one of the best methods to date to prepare these novel compounds in one step.[3] Final oxidation of the double bond of **5a-c** *into the (+)-carboxyalkyldeoxoartemisinins* (**6a-c**)[10] *was achieved with* $KMnO_4$ in the presence of $NaHCO_3$ in acetone (4 h at room temperature) in one step [yields: 84 % for **6a** (n=1), 73 % for **6b** (n=3), 68 % for **6c** (n=4)], respectively. The relative configuration at the new chiral centers, C-4, 5, 6, 11, and 12, was unambiguously determined to be as depicted in **6a-c** by utilization of two dimensional nOe (NOSEY) techniques.[11] The C-12 configuration of all three compounds (**6a-c**) was found to be *R*. Compounds (**6b**) and (**6c**) were found to show approximately equal *in vitro* antimalarial activity (IC_{50}=1.30 and <1.28 ng/ml, respectively) as artemisinin against chloroquine-resistant malaria.

In conclusion, this synthesis represents the first practical and general methodology to prepare new carboxyalkyl deoxoartemisinins, which hold promise as water-soluble (sodium salts) and chemically more stable anti-malarial agents.

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REFERENCES AND NOTES

1. (a) Research Institute of Pharmaceutical Sciences. (b) Department of Medicinal Chemistry. (c) Department of Pharmacognosy.
2. For a review of chemistry and pharmacology of artemisinin and its derivatives, see: (a) D. L. Klayman, *Science*,1985, **228**, 1049. (b) X-D. Luo and C-C.Shen, *Med. Res. Rev.*, 1987, **7**, 29. (c) P. I. Trigg, *Economic & Med. Plant Res.*,1989, *3*, 19. (d) S. S. Zaman and R. P. Sharma, *Heterocycles*,1991, **32**,1593.
3. For partial syntheses of artemisinin and other analogs, see: (a) M. Jung, H. N. ElSohly, E. M. Croom, A. T. McPhail,and D. R. McPhail, *J. Org. Chem.*,1986, **51**, 5417. (b) M. Jung, X. Li, D. A. Bustos, H. N. ElSohly, and J. D. McChesney, *Tetrahedron Lett.*, 1989, **30**, 5973. (c) R. J. Roth and N. Acton, *J. Nat. Prod.*, 1989, **52**, 1183. (d) D. A. Bustos, M. Jung, H. N. ElSohly, and J. D. McChesney, *Heterocycles,* 1989, **29**, 2273. (e) R. K. Haynes and S. C. Vonwiller, *J. Chem. Soc., Chem. Comm.,* 1990, 451. (f) M. Jung, D. A. Bustos, H. N. ElSohly, and J. D. McChesney, *Synlett,* 1990, 743. (g) B. Ye and Y-L. Wu, *J.Chem.Soc.,Chem. Comm.*,1990, 726. (h) M. Jung, D. Yu, D. A. Bustos, H. N. ElSohly, and J. D. McChesney, *Bioorg. Med. Chem. Lett.*, 1991, **1**, 741. (i) R. K. Haynes and S. C. Vonwiller, *Synlett*, 1992, 481. (j) S. S. Zaman, J. Debnath, P. Sarmah, N. C. Barua, and R. P. Sharma, *J. Chem. Soc., Chem. Comm.*, 1992, 329.
4. For total syntheses of artemisinin and other analogs, see: (a) G. Schmid and W. Hofheinz, *J. Am. Chem. Soc.*, 1983,**105**, 624. (b) X. Xu, J. Zhu, D. Huang, and W. Zhou, *Tetrahedron*,1986,**42**, 818. (c)M. A. Avery, C. Jennings-White, and W. K. M. Chong, *Tetrahedron Lett.*,1987,**28**, 4629. (d) Y. Imakura, T. Yokoi, T. Yamagishi, J. Koyama, H. Hu, D. R. McPhail, A. T. McPhail, and K-H. Lee, *J. Chem. Soc., Chem. Comm.*, 1988, 372. (e) M. A. Avery, C. Jennings-White, and W. K. M. Chong, *J. Org. Chem.*,1989, **54**, 1792. (f)C. W. Jefford, J. Velarde, and G. Bernardinelli, *Tetrahedron Lett.*,1989, **30**,

4485 (g) T. Ravindranathan, M. A. Kumar, R. B. Menon, and S. V. Hiremath, *Tetrahedron Lett.,* 1990, **31**, 755. (h)M. A. Avery, W. K. M. Chong, and J. E. Bupp, *J. Chem. Soc., Chem. Comm.*, 1990, 1487. (i) Y. Imakura, K. Hachiya, T. Ikemoto, S. Kobayashi, S. Yamashita, J. Sakakibara, F. T. Smith, and K-H. Lee, *Heterocycles,* 1990, **31**, 2125. (j) G. H. Posner, C. H. Oh, and W. K. Milhous,*Tetrahedron Lett.*, 1991, **32**, 4235. (k)G. H. Posner, C. H. Oh, L. Gerena, and W. K. Milhous, *J. Med. Chem.*,1992, **35**, 2459.

5. (a) Cooperative Research Group, *J. Trad. Chin. Med.*, 1982, **2**, 9. (b) A. J. Lin, D. L. Klayman, and W. K. Milhous, *J. Med. Chem.,* 1987, **30**, 2147.
6. The water-soluable analogs bearing an external C-O bond at C-12 such as sodium artesunnate and sodium artelinate have been prepared from dihydroartemisinin. See ref. (5). Sodium artesunnate is used as an antimalarial drug. However, its efficacy is impaired by its rapid decomposition in solution.
7. M. Jung, X. Li, D. A. Bustos, H. N. ElSohly, J. D. McChesney, and W. K. Milhous, *J. Med. Chem.*, 1990, **33**, 1516.
8. For isolation of artemisinic acid, see (a) Y.Tu, M. Ni, Y. Zhong, L. Li, S.Cui, M. Zhang, X. Wang, and Z. Ji, *Planta Medica,* 1982, **44,** 143. (b) R. J. Roth and N. Acton, *ibid.*, 1987,**53**, 501. (c) H. N. ElSohly, E. M. Croom, Jr., F. S. ElFeraly, and M. M. ElSherei, *J. Nat. Prod.*, 1990, **53**, 1560.
9. For a proposed mechanism, see: ref. (3e) and (a) M. Jung, H. N. ElSohly, and J. D. McChesney, *Planta Medica,* 1990, **56**, 624. (b) N. Acton and R. J. Roth, *J. Org. Chem.*, 1992, **57**, 3610.
10. Compd **6a**: $[\alpha]_D^{25}$= +105.2° (c 0.5, $CHCl_3$), ^1H nmr(300 MHz) δ 5.36 (s, 1H, 5-H), 4.84 (m, 1H, 12-H), 2.69 (m, 3H, 11-H, 1'-H), 1.41 (s, 3H, 15-CH_3), 0.96 (d, J 6 Hz, 3H, 13-CH_3), 0.87 (d, J 6 Hz, 3H, 14-CH_3). Ir ($CHCl_3$) 3400-2700 (OH), 2940, 1710 (C=O), 1380,1220. Clms m/z 344 ($M+NH_4^+$,100), 327($M+H^+$,18), 312($M+NH_4^+-O_2$, 9). Compd **6b**: $[\alpha]_D^{25}$= +134° (c 0.5, $CHCl_3$), ^1H nmr(300 MHz) δ 5.30 (s, 1H, 5-H), 4.19

(m, 1H, 12-H), 2.66(m, 1H, 11-H), 2.43(t, J 7.8 Hz, 2H, 3'-H), 1.41 (s, 3H, 15-CH_3), 0.95 (d, J 5.9 Hz, 3H, 13-CH_3), 0.85 (d, J 7.5 Hz, 3H, 14-CH_3). Ir ($CHCl_3$) 3300-2800 (OH), 2960, 1720 (C=O), 1210. Clms m/z 372 ($M+NH_4^+$, 100), 355 ($M+H^+$, 11). Compd **6c** :$[\alpha]_D^{25}$=+75.4° (c 0.5, $CHCl_3$), ^1H nmr (300 MHz) δ 5.29 (s, 1H, 5-H), 4.15 (m, 12-H), 2.36 (m, 2H, 4'-H), 1.41 (s, 3H, 15-CH_3), 0.95 (d, J 6 Hz, 3H, 13-CH_3), 0.85 (d, J 7.5 Hz, 3H, 14-CH_3). Ir($CHCl_3$) 3300-2800 (OH), 2960, 1710 (C=O), 1210. Clms m/z 386 ($M+NH_4^+$,100), 369 ($M+H^+$,9).

11. For NOESY experiments of artemisinin analogs, see: ref. (3d), (4e) and (a) A. Brossi, B. Venugopalan, L. Dominguez Gerpe, H. J. C. Yeh, J. L. Flippen-Anderson, P. Buchs, X. D. Luo, W. K. Milhous, and W. Peters, *J. Med. Chem.*,1988, **31**, 645. (b) J. K. Baker, H. N. ElSohly, and C. D. Hufford, *Spectrosc. Lett.*, 1990, **23**, 111.

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