An Efficient Synthesis of Qinghaosu and Deoxoqinghaosu from Arteannuic Acid

Bin Ye and Yu-Lin Wu*

Shanghai Institute of Organic Chemistry, Acdemica Sinica, Shanghai 200032, China

Photo-oxidation of cyclic enol ether (**3**) and successive treatments with trimethylsilyl trifluoromethanesulphonate (TfOTMS) afforded three compounds, deoxoqinghaosu (**4**), (**5**), and (**6**); oxidation of (**4**) with RuO_4 gave qinghaosu (**1**).

The outstanding antimalarial activity and intriguing chemical structure of qinghaosu (**1**) have encouraged chemists to complete its total synthesis,[1] in the preparation of analogues,[2] and in model studies aimed at securing routes to the biologically active 1,2,4-trioxane component of the molecule.[3,4] Two total syntheses of qinghaosu by Zhou and Hofheinz,[1] depended on the photo-oxidation of an enol ether in methanol using Rose Bengal as a sensitizer and successive acid-catalysed transformations. Unfortunately, the yields in the key steps are low. Jung[5] failed to photo-oxidize the enol lactone to qinghaosu, and Wallace[6] was also unsuccessful in photo-oxidation of hexahydrobenzopyran to β-arte-ether. Herein we described a novel approach to the synthesis of qinghaosu.

Arteannuic acid (**2**), a relatively abundant constituent of *Artemisia annua*[7] collected from almost anywhere in the world except South China, was used as starting material for the synthesis of qinghaosu. The synthesis (Scheme 1) involved initial conversion of arteannuic acid to the key intermediate cyclic enol ether (**3**) in three steps, by previously reported procedures.[2b] Photo-oxidation of a dichloromethane solution of (**3**) in the presence of Methylene Blue at −70 to −78 °C, followed by treatment with trimethylsilyl trifluoromethanesulphonate (TfOTMS), yielded two peroxides, deoxoqinghaosu (**4**) (62%) and a compound which may have structure (**5**) (6%), together with an oxo formate (**6**) (11%). Oxidation of (**4**) with $RuCl_3$–$NaIO_4$ afforded (**1**) in 96% yield. The structure of (**4**)† was elucidated by spectroscopic analysis and confirmed by comparison of the physical data of the synthe-

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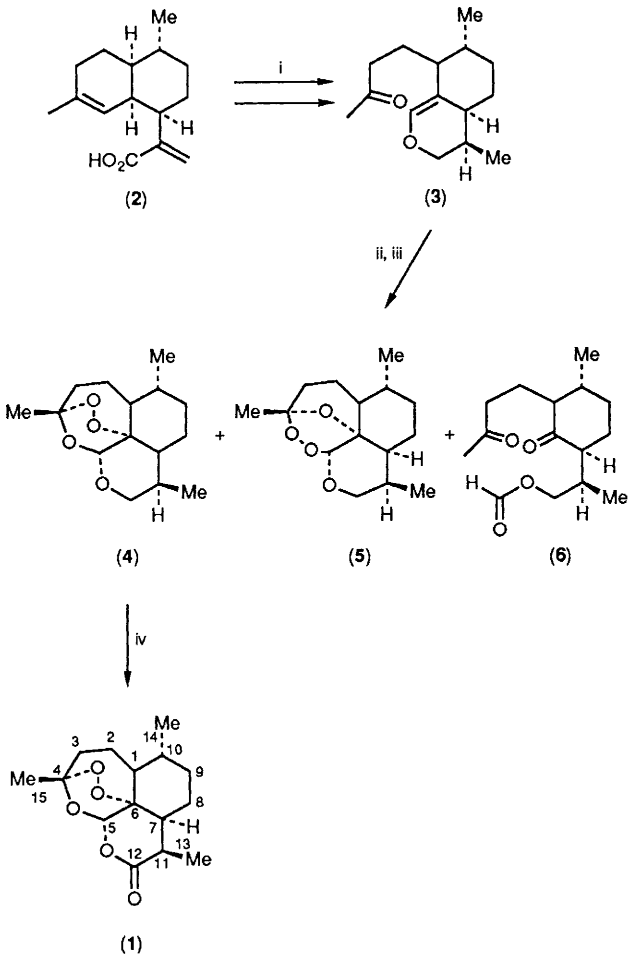
† *Selected data* for (**4**): m.p. 112 °C; $[\alpha]_D^{25}$ +86.09° (*c* 1.46, $CHCl_3$); IR, no characteristic absorptions; ^1H NMR, δ 5.08 (1H, s); 3.70 (1H, ABX, J_{AB} 13, J_{AX} 4 Hz), 3.41 (1H, ABX, J_B 13, J_{BX} 13 Hz), 1.40 (3H, s, 4-Me), 0.90 (3H, d, *J* 6 Hz, 11-Me), 0.70 (3H, d, *J* 7 Hz, 10-Me); *m/z*, 268 (M^+); 236 ($M^+ - O_2$); satisfactory elemental analyses were obtained. For synthesized ginghaosu: m.p. 154—156 °C; mixed m.p. [natural product: (**1**)] 154—156 °C; $[\alpha]_D^{25}$ +68.2 (*c* 0.97, $CHCl_3$). For (**5**): m.p. 128—130 °C; $[\alpha]_D^{25}$ −34.2° (*c* 0.66, $CHCl_3$); IR, no characteristic absorptions; ^1H NMR, δ 4.90 (1H, s), 3.75 (1H, ABX, J_{AB} 13, J_{AX} 4 Hz), 3, 41 (1H, ABX, J_{AB} 13, J_{BX} 12 Hz), 1.60 (3H, s, 4-Me), 1.0 (1H, d, *J* 4 Hz, 11-Me), 0.70 (3H, d, *J* 8 Hz, 10-Me); *m/z*, 268 (M^+); high resolution calc. for $C_{15}H_{24}O_4$ 268.1674, found 268.1657.



Scheme 1. *Reagents and conditions*: i, a, CH_2N_2; b, $NiCl_2 \cdot 6H_2O$, $NaBH_4$; c, $LiAlH_4$; d, O_3/MeOH-CH_2Cl_2; e, Me_2S; f, xylene, *p*-$MeC_6H_4SO_3H$; ii, O_2, sodium lamp, Methylene Blue, CH_2Cl_2, −70 to −78 °C; iii, TfOTMS; iv, $RuCl_3$–$NaIO_4$/MeCN–H_2O–CCl_4.

sized qinghaosu and the natural product.[8] The possible structure assigned to the minor peroxide (**5**) was deduced by comparison of its spectroscopic data† with those of (**4**), but the detail stereochemistry and the position of peroxide group have not been confirmed.

In conclusion, we have synthesized deoxoqinghaosu (**4**) and qinghaosu (**1**) from arteannuic acid in 39 and 37% overall yields, respectively.

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References

1 X.-X. Xu, J. Zhu, D.-Z. Huang, and W.-S. Zhou, *Tetrahedron*, 1986, **42**, 819; G. Schmid and W. Hofheinz, *J. Am. Chem. Soc.*, 1983, **105**, 624; M. A. Avery, C. Jennings White, and W. K. M. Chong, *Tetrahedron Lett.*, 1987, **28**, 4629.

2 (a) Y. Imakura, T. Yamagishi, J. Koyama, H. Hu, D. R. McPhail, A. T. McPhail, and K.-H. Lee, *J. Chem. Soc., Chem. Commun.*, 1988, 372; (b) Bin Ye and Yu-Lin Wu, *Tetrahedron*, 1989, **45**, 7287.

3 G. Clark, M. Nikaido, C. Fain, and J. Lin, *J. Org. Chem.*, 1985, **50**, 1994.

4 C. W. Jefford, J. Boukouvlas, S. Kohmoto, and G. Bernardinelli, *Tetrahedron*, 1985, **41**, 2081; C. W. Jefford, Y. Wang, and G. Bernardinelli, *Helv. Chim. Acta*, 1988, **71**, 2042; C. W. Jefford, J. Velarde, and G. Bernardinelli, *Tetrahedron Lett.*, 1989 **30**, 4485.

5 M. Jung, H. N. ElSohly, E. M. Croom, A. T. McPhail, and D. R. McPhail, *J. Org. Chem.*, 1986, **51**, 5417.

6 F. Binns and T. W. Wallace, *Tetrahedron Lett.*, 1989, **30**, 1125.

7 Y.-Y. Tu, M.-Y. Ni, Y.-R. Zhong, L.-N. Li, S.-L. Cui, M.-Q. Zhang, X.-Z. Wang, Z. Ji, and X.-T. Liang, *Planta Medica*, 1982, **44**, 143. D.-A. Deng, D.-Y. Zhu, Y.-L. Gao, Y.-J. Dai, and R.-S. Xu, *Kexue Tongbao*, 1981, **19**, 1209; R. J. Roth and N. Acton, *Planta Medica*, 1987, **53**, 501.

8 J.-M. Liu, M.-Y. Ni, J.-F. Fan, Y.-Y. Tou, Z.-H. Wu, Y.-L. Wu, and W.-S. Zhou, *Acta Chim. Sin.*, 1979, **37**, 129.

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‡ While this manuscript was being prepared, a direct synthesis of (**4**) from arteannuol in 18% yield appeared in the literature (M. Jung, X. Li, D. A. Bustos, H. N. ElSohly, and J. D. McChesney, *Tetrahedron Lett.*, 1989, **30**, 5973).