Synthesis of C-4-Substituted Qinghaosu Analogues

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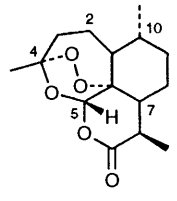
4-Demethyl- and 4-demethyl-4-ethyl-deoxoqinghaosu, analogues of the antimalarial drug qinghaosu, have been synthesized from the diketone **5**, an acidic degradation product of qinhaosu.

Qinghaosu (artemisinin) **1**,[1] extracted from the Chinese herb qinghao (*Artemisia annua.* L.), has received increasing attention because of its significant antimalarial activity against widespread drug-resistant strains of *P. falciparum* and its unique 1,2,4-trioxane sesquiterpene structure. Although a number of qinghaosu analogues have been synthesized in attempts to provide drugs with greater antimalarial activity than the parent compound,[2] few details of the molecular basis for its antimalarial activity are known.

As part of our research program, we have studied the structure–activity relationships (SAR) for various qinghaosu analogues. Recently, we reported the synthesis of, amongst others, several carba analogues of qinghaosu,[3] and showed that the peroxide bridge was a crucial feature for antimalarial activity.[4] We then synthesized a novel qinghaosu derivative, deoxoqinghaosu **2**,[5] possessing higher activity,[4] an indication that the carbonyl group was not an essential feature. Lately, a series of qinghaosu analogues lacking a lactone carbonyl group at C-12 have also been studied,[6] many of which have superior activity to qinghaosu. So far, however, nothing was known about the effect of 4-methyl group on antimalarial activity. Herein, we present a successful synthesis of 4-demethyl- **3** and 4-ethyl-4-demethyl-deoxoqinghaosu **4**, the first representatives



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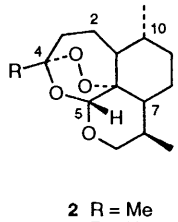
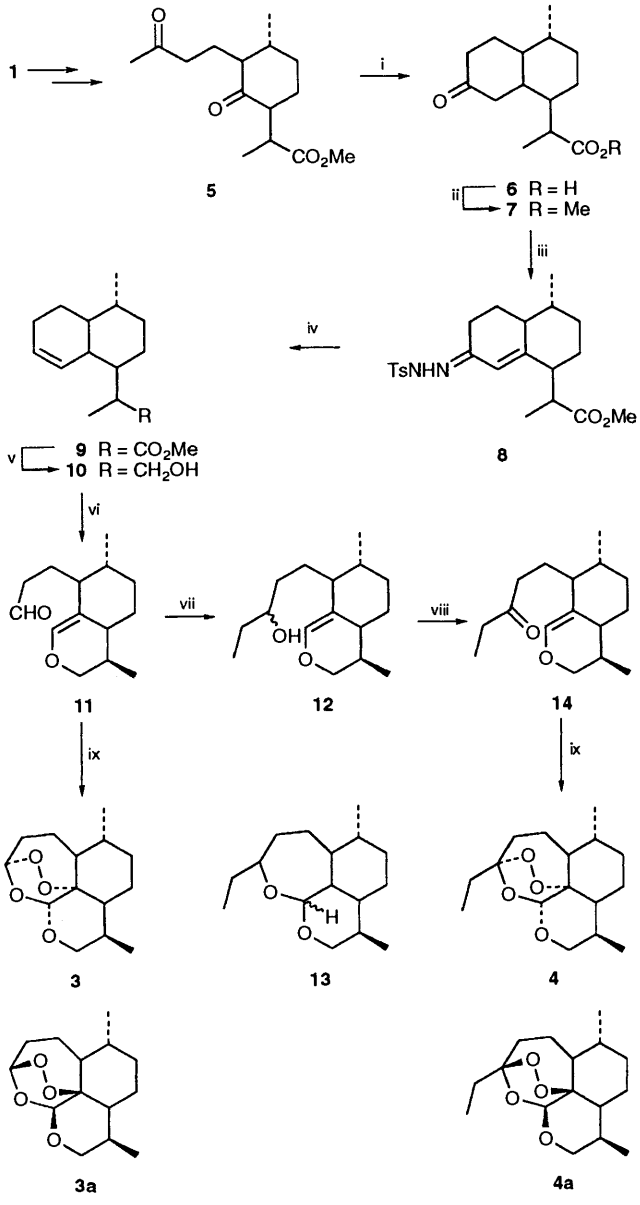


2 R = Me
3 R = H
4 R = Et

of C-4 substituted qinghaosu derivatives. Since the 4-methyl group is that nearest to the crucial 1,2,4 trioxane structure in qinghaosu, it is expected that the above-mentioned analogues will provide useful information about the SAR of qinghaosu. Furthermore, the synthetic methodology described herein may be advantageously employed in the synthesis of many other useful derivatives (*e.g.* isotopically labelled compounds).

The potential for synthesis of the diketone **5**,[7] prepared from acidic degradation of qinghaosu, makes it a useful intermediate for qinghaosu analogues, particularly so since its skeleton is of the correct configuration. A strategy for the conversion of diketone **5** into qinghaosu analogues **3** and **4** is outlined in Scheme 1.

Cyclization of the diketone **5** with $Ba(OH)_2$ as base in MeOH gave the acid **6** (86%). Methylation of **6** with CH_2N_2 in ether afforded the ester **7** (100%) which was then condensed with tosylhydrazide to give **8** quantitatively. Reduction of **8** with bis(benzoyloxy)borane[8] in alcohol-free chloroform at 0 °C furnished the methylene ester **9** (78% yield) which was further



Scheme 1 *Reagents and conditions:* i, $Ba(OH)_2$, MeOH; ii, CH_2N_2; iii, $TsNHNH_2$; iv, $BH(OCOPh)_2$, then $NaOAc{\cdot}3H_2O$; v, $LiAlH_4$, Et_2O; vi, O_3, Zn–HOAc; PPTS, toluene; vii, $EtMgBr,Et_2O$; viii, DMSO, $(COCl)_2$; ix, $^1O_2$, Methylene Blue, −78 °C, then TMSOTf

reduced with lithium aluminium hydride to afford the alcohol **10** (99% yield). Ozonolysis of a CH_2Cl_2–MeOH(1 : 1) solution of **10** at −78 °C followed by treatment with *p*-TsOH–toluene gave the enol ether **11** (34%) after flash column chromatography. Photooxidation of **11** in the presence of Methylene Blue at

−78 °C under a stream of oxygen and subsequent *in situ* treatment with trimethylsilyl trifluoromethanesulfonate (TfOTMS)[5] provided compound **3** (15%) and a by-product **3a** (11%). That the relative stereochemistry was identical was confirmed by 2D NMR (COSY and NOESY).

Treatment of **11** with ethylmagnesium bromide at 0 °C in dry ether afforded the alcohol **12** (98%) which was readily converted into **13** even by a trace acid; thus, the avoidance of oxidation reagents (*e.g.* PCC or PDC) was necessary. Careful oxidation of **12** with $(COCl)_2$–DMSO in CH_2Cl_2 at −60 °C provided **14** (62%). Irradiation of the enol ether **14** (Methylene Blue, CH_2Cl_2, O_2, −78 °C) followed by cyclization with TfOTMS yielded **4** (26%) and **4a** (9.4%).

Experimental *

Photooxidation of the Cyclic Enol Ether **11**.—Oxygen was passed into a solution of the cyclic enol ether **11** (100 mg, 0.45 mmol) and Methylene Blue (5 mg) in methylene dichloride (40 cm^3) at −78 °C, whilst it was irradiated with a sodium lamp for 1 h. To the reaction mixture was added TMSOTf (4 mm^3) under nitrogen. After neutralization with triethylamine, the reaction mixture was warmed to room temperature and concentrated under reduced pressure. Silica gel column chromatography of the oily residue gave **3** (17 mg, 15%) and **3a** (12 mg, 11%). For **3**, $[\alpha]_D^{20}$ = +26.4† (*c* 0.4, chloroform); δ_H(600 MHz, $CDCl_3$) 5.63 (d, *J* 6.7,‡ 1 H, 4-H), 5.20 (s, 1 H, 5-H), 3.72 (dd, *J* 3.3, 11.7, 1 H, 12α-H), 3.47 (t, *J* 11.7, 1 H, 12β-H), 0.98 (d, *J* 6.6, 3 H, 13-CH_3) and 0.79 (d, *J* 7.2, 3 H, 14-CH_3); δ_C(600 MHz, $CDCl_3$) 82.84 (C-4), 82.16 (C-5), 74.68 (C-6), 66.29 (C-12), 52.20 (C-1), 45.27 (C-7), 37.48 (C-10), 34.07 (C-9), 31.02 (C-3), 27.89 (C-11), 23.51 (C-2), 20.59 (C-8), 20.37 (C-14) and 13.15 (C-13). ν/cm^{-1} 1080, 870 and 840; *m/z* 255 (M^+ + 1) and 236 ($M^+ - H_2O$). [Found (HRMS): *m/z* 236.1412 ($C_{14}H_{22}O_4 - H_2O$). Calc., 236.1437]. For **3a**, m.p. 104–105 °C; $[\alpha]_D^{20}$ = +15.3 (*c* 0.1, chloroform); δ_H(600 MHz, $CDCl_3$) 5.52 (d, *J* 4.6, 1 H, 4-H), 4.79 (s, 1 H, 5-H), 4.13 (dd, *J* 11.1, 3, 1 H, 12β-H), 3.49 (dd, *J* 1.1, 11.1, 1 H, 12α-H), 1.13 (d, *J* 7.4, 3 H, 13-CH_3), 0.88 (d, *J* 6.7, 3 H, 14-CH_3); δ_C(600 MHz, $CDCl_3$) 99.69, 95.43, 86.43, 69.63, 66.82, 34.17, 31.32, 31.60, 31.06, 29.69, 24.44, 23.50, 14.22 and 13.85; ν/cm^{-1} 1090, 890 and 840; *m/z* 254 (M^+) and 236 ($M^+ - H_2O$) [Found (HRMS): *m/z* 254.1518 ($C_{14}H_{22}O_4$). Calc., 254.1543].

Photooxidation of the Cyclic Enol Ether **14**.—Oxygen was passed into a solution of the cyclic enol ether **14** (180 mg, 0.72 mmol) and Methylene Blue (5 mg) in methylene dichloride (50 cm^3) at −78 °C, whilst it was irradiated with a sodium lamp for 50 min. To the reaction mixture was added TMSOTf (20 mm^3) under nitrogen. After addition of triethylamine (0.4 cm^3), the reaction mixture was warmed to room temperature, and concentrated under reduced pressure. Silica gel column chromatography of the oily residue gave **4** (52 mg, 26%) and **4a** (19 mg, 9.4%). For **4**, m.p. 64–65 °C; $[\alpha]_D^{20}$ +89.1 (*c* 0.73, $CHCl_3$); δ_H(600 MHz, $CDCl_3$) 5.20 (s, 1 H, 5-H), 3.71 (dd, *J* 4.2, 11.7, 1 H, 12α-H), 3.44 (t, *J* 11.7, 1 H, 12β-H), 2.65 (m, 1 H, 11-H), 0.97 (d, *J* 6.4, 3 H, 14-CH_3), 0.95 (t, *J* 7.6, 3 H, 16-CH_3) and 0.78 (d, *J* 7.3, 3 H, 13-CH_3); δ_C(600 MHz, $CDCl_3$), 105.71 (C-4), 92.04 (C-5), 80.91 (C-6), 66.21 (C-12), 52.19 (C-1), 44.91 (C-7), 37.31 (C-10), 34.07 (C-15), 33.84 (C-3), 32.30 (C-9), 27.97 (C-11), 24.66 (C-2), 20.29 (C-14), 20.74 (C-8), 13.10 (C-13) and 6.95 (C-16); ν/cm^{-1} 1070, 880 and 830; *m/z* 282 (M^+), 250 ($M^+ - O_2$) [Found (HRMS) *m/z* 250.1933 ($C_{16}H_{26}O_4 - O_2$) Calc., 250.1984]. For **4a**, $[\alpha]_D^{20}$ +26.2 (*c* 0.57, $CHCl_3$); δ_H(600 MHz, $CDCl_3$) 4.80 (s, 1 H, 5-H), 4.13 (dd, *J* 11.0, 2.8, 1 H, 12β-H), 3.48 (dd, *J* 11.0, 1.2, 1 H, 12α-H), 1.13 (d, *J* 7.2, 3 H, 13-CH_3), 1.02 (t, *J* 7.2, 3 H, 16-CH_3) and 0.87 (d, *J* 6.6, 3 H, 14-CH_3); δ_C(600 MHz, $CDCl_3$) 107.72, 96.12, 85.90, 69.14, 66.80, 34.19, 33.47, 31.69, 31.29, 30.00, 29.70, 24.70, 24.45, 14.21, 13.87 and 8.14; ν_{max}/cm^{-1} 1090, 885 and 840; *m/z* 282 (M^+) and 264 ($M^+ - H_2O$) [Found (HRMS) 282.1988 ($C_{16}H_{26}O_4$). Calc., 282.2001].

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* The reaction conditions have not been optimized.
† $(\alpha]_D$ Values are recorded in units of 10^{-1} deg cm^2 g^{-1}.
‡ *J* Values are recorded in Hz.

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