Pergamon

Tetrahedron Letters 40 (1999) 9129–9132

TETRAHEDRON LETTERS

Application of the TMSOTf-$AgClO_4$ Activator System to the Synthesis of Novel, Potent, C-10 Phenoxy Derivatives of Dihydroartemisinin

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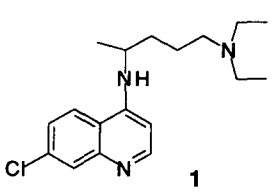
Received 17 August 1999; accepted 6 October 1999

Abstract: The combination of TMSOTf and $AgClO_4$ promotes the efficient C-10 phenoxylation of dihydroartemisinin (**3**) in good chemical yield and excellent stereoselectivity. In contrast to previous reports on other phenoxyglycoside derivatives, the phenoxy derivatives (**5a-11b**) of dihydroartemisinin do not undergo *O* to *C* rearrangement to the corresponding C-10-aryl derivatives. All of the new derivatives had potent *in vitro* antimalarial activity.

Malaria is one of the world's most deadly diseases and is becoming an increasingly serious problem as malaria parasites develop resistance to quinoline containing drugs such as chloroquine (**1**). There is, therefore, considerable urgency to develop new classes of antimalarials. [1-2] Artemisinin (**2**) (qinghaosu) is an unusual 1,2,4-trioxane which has been used clinically in China for the treatment of multidrug resistant *Plasmodium falciparum* malaria. However, the therapeutic value of **2** is limited by its low solubility in both oil and water. Consequently, in the search for more effective and soluble drugs, a number of derivatives of the parent drug have been prepared. Reduction of the lactone group of artemisinin provides dihydroartemisinin (**3**) (DHA), which in turn has enabled the preparation of a series of semisynthetic first generation analogues which include artemether (**4a**, R=-Me) and arteether (**4b**, R= -Et).



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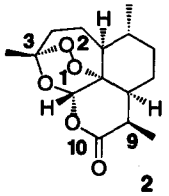

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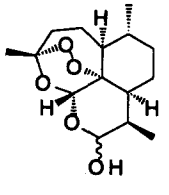

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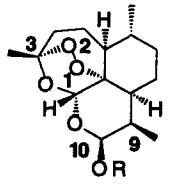


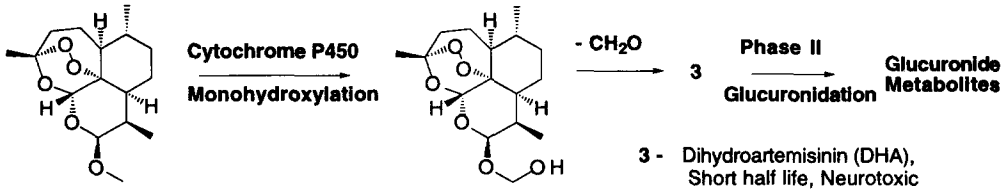
4a, R = Me
4b, R = Et

Although both of these derivatives are potent antimalarial agents *in vitro*, poor bioavailability and rapid clearance are observed with these analogues *in vivo*, principally as a result of the chemical and metabolic instability of the acetal function present in these derivatives. One of the principal routes of metabolism of artemether (**4a**), for example, involves oxidative dealkylkation to DHA, a compound associated with toxicity[3] and short half-life (Scheme 1).[4] Replacement of the oxygen at the C-10 position with carbon would be expected to produce compounds not only with greater hydrolytic stability, but also with a longer half-life and potentially lower toxicity. Consequently, several groups have developed synthetic and semi-synthetic approaches to C-10 carba analogues.[5-8] An alternative

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01891-2

approach to increasing the metabolic stability of artemisinin derivatives involves incorporation of a phenyl group in place of the alkyl group (in the ether linkage) of first generation analogues eg. (**4a**) and (**4b**).

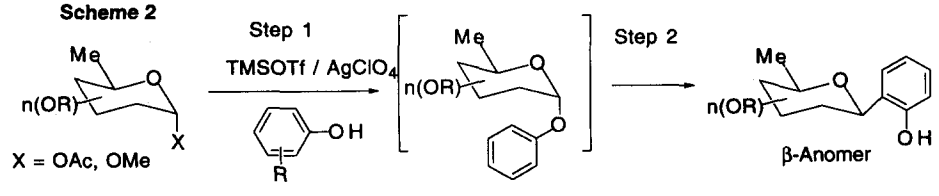
Scheme 1.



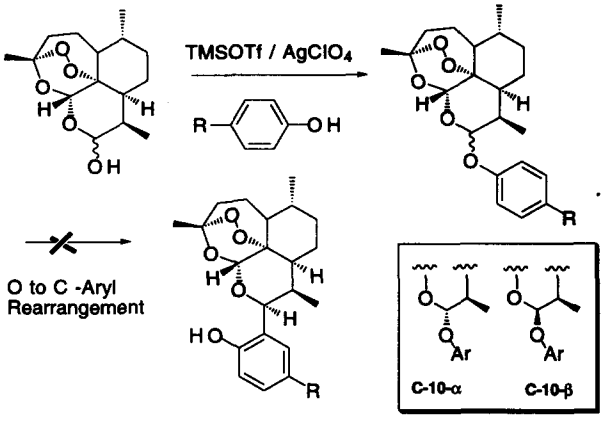
This modification would be expected to block oxidative metabolic formation of DHA *in vivo* (eg Scheme 1). This report deals with the synthesis and *in vitro* biological activity of a new series of C-10 phenoxy derivatives (alpha series, **5a-11a** and beta series, **5b-11b**). Several synthetic approaches were initially investigated for the production of target C-10 phenoxy derivatives. One of the first approaches taken was to couple DHA (1 equivalent) with various phenols (4 equivalents) using boron trifluoride diethyl etherate catalysis at room temperature. In every case, the major product obtained in the reaction was the anhydro derivative in high yield. Similar results were obtained using TMSOTf or TMSCl as Lewis acid with phenol as nucleophile. Further studies involving the use of the Mitsunobu reaction [10-11] (DEAD, Ph_3P, phenol) on (**3**) gave high stereoselectivity (12.5/1, β/α) but low overall yield (27 %).

The dihydroartemisinin lactol can be recognised as a pyranose sugar with a free anomeric hydroxyl group.[12] There are many papers detailing reactions of glycosides, including C-C bond formation at the anomeric site.[13,14] Recently, studies by Suzuki have been carried out to investigate the O to C glycoside rearrangment of phenoxy glycosides.[15] Different Lewis acid promoters have been used, including BF_3 etherate, $SnCl_4$ and Cp_2HfCl_2-$AgClO_4$ with varying success. In 1992, Toshima discovered the efficient β-stereoselective C-aryl glycosidation of 1-*O*-methylsugars by the novel use of a TMSOTf-AgClO4 catalyst system.[16] This procedure gives excellent yields and diastereoselectivity in favour of the β –isomer, by rearrangement of the pre-formed phenoxy glycoside as shown (Scheme 2). Such promising results led us to try the use of TMSOTf-$AgClO_4$ catalysis in our DHA-phenol coupling reactions. This approach involves dissolving 1 equivalent of DHA, approximately 2 equivalents of the desired phenol and one-fifth equivalent of $AgClO_4$ in anhydrous dichloromethane, under nitrogen at –78 °C. The TMSOTf (1 equivalent) is usually added to the reaction mixture last. In every case, the reaction provided excellent yields with good diastereoselectivity in favour of the beta isomers. Notably, only minor quantities of 9,10-dehydrodeoxoartemisinin were observed (Scheme 3). Notably, no *O* to *C* –aryl glycoside rearrangment was noted for any of the phenoxy derivatives obtained in contrast to the situation depicted in Scheme 2. [17]

Scheme 2



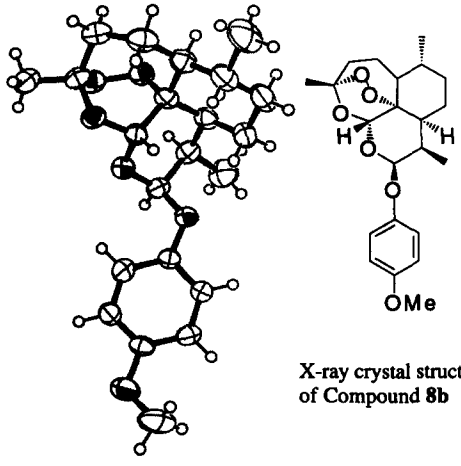
Scheme 3



R	Compounds	Yield	β/α Ratio
H	**5a & 5b**	68	4:1
Me	**6a & 6b**	84	5:1
CF_3	**7a & 7b**	68	8:1
OMe	**8a & 8b**	73	4:1
F	**9a & 9b**	60	3:1
Cl	**10a & 10b**	62	5:1
Naphthyl	**11a & 11b**	84	5:1

Compounds **5a-11a** (C-10 alpha series)
Compounds **5b-11b** (C-10 beta series)

As can be seen, compared with earlier methods described above, the increase in yield upon using the new catalyst combination was dramatic. Noticeably, when R = OMe, the yield increased by 55% (the yield was only 18% using $BF_3.Et_2O$ catalysis). There is no obvious explanation for the success of this reaction. It may be that under these conditions the oxonium ion is stabilised and therefore less likely to form the anhydro by-product. Alternatively these conditions may catalyse slow oxonium ion formation. Hence at any one time there are larger quantities of nucleophile available to react with the intermediate oxonium species.



X-ray crystal structure of Compound **8b**

The diastereoselectivity ratios were calculated from NMR data.[18] The stereochemistry of the phenoxy derivatives was also confirmed by X-ray crystallography.[19] As can be seen from Table 1 all of the new derivatives have antimalarial activity comparable to that of the clinically used derivative artemether (Table 1).

Table 1 *In Vitro* Antimalarial Activity of Selected Phenoxy Derivatives *versus Plasmodium falciparum* (K1 Strain)

Compound	IC50 (nM)	Standard Error	Compound	IC50 (nM)	Standard Error
5a	2.97	0.02	**5b**	3.66	1.88
6a	3.18	0.05	**6b**	3.92	0.11
7a	4.62	0.06	**7b**	5.29	0.08
9a	5.70	1.01	**9b**	4.58	0.04
11a	2.88	0.04	**11b**	8.89	0.05
Artemether	4.55	0.12			

Based on the excellent yield, stereochemistry and potent *in vitro* antimalarial activity, compound **7b** was selected for *in vivo* testing and drug metabolism studies *in vivo* in rodent models.

In summary, the combination of TMSOTf and $AgClO_4$ efficiently catalyses the one-step phenoxylation of dihydroartemisinin in good yield and excellent stereoselectivity. These C-10-phenoxy substituted trioxanes would be expected to be more stable towards P450 catalysed formation of DHA (**3**) and therefore should have longer half-lives than the clinically used ester and ether derivatives (eg. **4a**). Details of our drug metabolism and biomimetic Fe(II) studies on these derivatives will be published in a full paper.

Acknowledgments. We thank the Wellcome Trust (BKP [Wellcome Principal Fellow], the EPSRC (AM) and UFC LTD (AM, PON) for financial support of this work. We thank Dr A. Steiner for X-ray crystal analysis of compound **8b**.

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17 Notably, in this study, the naphthoxy derivatives **11a** and **11b** do not rearrange to the corresponding C-10-α and C-10-β-aryl derivatives. This may be on account of the low temperatures employed in our procedure. For an example of the *O* to *C* rearrangement of **11a/b** using $BF_3.Et_2O$, see ; Wang, D-Y.; Wu, Y.; Wu, Y-L.; Li, Y.; Shan, F. *J. Chem. Soc., Perkin Trans.* 1, **1999**, 1827.
18. Data for the β-isomer **5b**; mp = 104-106°C; $[\alpha]_D$ + 204° (c,1.0, $CHCl_3$); ν_{max} (nujol mull)/cm^{-1}, 2926(CH), 1463, 1193, 875(O-O), 832 (O-O); ^{1}H HMR (300 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 6.0 Hz, Me at C-9), 1.13 (3H, d, *J* = 7.4 Hz, Me at C-6), 1.44 (3H, s, Me at C-3), 1.23-2.07 (10H, m), 2.39 (1H, m), 2.81 (1H, m), 5.50 (1H, d, *J* = 3.3 Hz), 6.99 (1H, t, *J*= 7.9 Hz, 1 x aromatic), 7.22 (2H, d, *J*= 8.8 Hz, 2 x aromatic), 7.29 (2H, t, *J*= 8.8 Hz, 2 x aromatic); ^{13}C NMR (75 MHz, $CDCl_3$), δ 157, 129, 122, 116, 104, 100, 88, 81, 52, 44, 37, 36, 34, 31, 26, 25, 24, 20, 12; m/z (EI), 361 (M^+, 85%), 267 (M^+ – OPh, 33%), 221 (25%).
Data for α-isomer **5a**; mpt, 143-145°C; $[\alpha]_D$ -54.5°, (c,1.0, $CHCl_3$); ν_{max} (nujol mull)/cm^{-1}, 2925 (CH), 1040, 881 (O-O), 825 (O-O); ^{1}H HMR (300 MHz, $CDCl_3$), δ 0.97 (3H, d, *J* = 6.0 Hz, Me at C-9), 0.99 (3H, d, *J* = 7.4 Hz, Me at C-6), 1.43 (3H, s, Me at C-3), 1.26-2.10 (10H, m), 2.42 (1H, dt), 2.73 (1H, m), 5.05 (1H, d, *J*= 9.5 Hz), 5.49 (1H, s), 7.00 (1H, t, *J*= 7.1 Hz, 1 x aromatic), 7.11 (2H, d, *J*= 5.8 Hz, 2 x aromatic), 7.25 (2H, t, *J* = 4.4 Hz, 2 x aromatic); ^{13}C NMR (75 MHz, $CDCl_3$), δ 145, 129, 122, 117, 104.5, 100, 99, 91, 52, 45, 37, 36, 33, 26, 25, 22, 20, 12.5; m/z (CI, NH_3), 378 ($[M + NH_4]^+$44%), 332 (90%), 301 ($[M + NH_4]^+$ – Ph, 5%), 221 (100%); Found $[M + NH_4]^+$378.22777, $C_{21}H_{32}NO_5$ requires 378.22805.
19. Single Crystal X-ray Analysis of **8b** $C_{22}H_{30}O_6$. Wavelength 0.71073 A, Temperature, 293 K. Crystal system, space group = orthorhombic, P 2(1)2(1)2(1). Crystal size 0.75 x 0.65 x 0.5 mm, a = 10.238 (2) b = 10.720 (2) c = 18.818 (4). Volume = 2065.3 (7) $Å^3$. A total of 2645 reflections were collected in the range 2.16° to 45° . Lorentz and polarization but not absorption co-efficients were applied. The structure was solved by direct methods (SHEXS-86). R1 = 0.0272, wR2 = 0.0609