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Asymmetric Syntheses of Enantiomeric 3-*p*-Fluorophenyl 1,2,4-Trioxane Analogues of the Antimalarial Artemisinin

Paul M. O' Neill *,[a] Alison Miller,[a] Jamie F. Bickley,[a] Feodor Scheinmann,[b] Chang Ho Oh[c,d] and Gary H. Posner *[c]

[a] Department of Chemistry, The Robert Robinson Laboratories, University of Liverpool, Liverpool, L69 7ZD

[b] UFC Ltd, Synergy House. Guildhall Close, Manchester Science Park, Manchester M15 6SY

[c] The Johns Hopkins University, Baltimore MD 21218

[d] On leave, Department of Chemistry, Hayang University, Seoul 131-791, Korea

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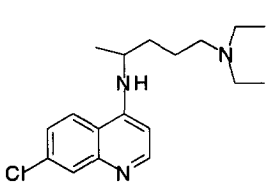
Abstract: We have devised an asymmetric synthesis of chiral artemisinin analogues (+)-**4a** and (-)-**4a** that retain the tricyclic ring system found in the natural product. The key step in the preparation of (+)-**4a** involves an asymmetric $MgCl_2$ promoted Michael addition of the (*R*)-(-)pyrrolidinemethanol-derived enamine **8** to acrylonitrile. This gives the corresponding ketone **9** in 50% yield (>95% ee). Subsequent elaboration of **9** provides the trioxane target (+)-**4a** in greater than 85% ee. Enantiomeric trioxane (-)-**4a** was prepared in a similar manner using (*S*)-(+)-pyrrolidinemethanol in the first step of the sequence.

The frightening spread of malaria parasite resistance to chloroquine (**1**) has led the WHO to predict that without new antimalarial drug intervention, the number of cases of malaria will double by the year 2010.[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 to a great extent 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 artemisinin to the lactone-reduced dihydroartemisinin (**3a**, R = H, DHA) has in turn led to the preparation of a series of semisynthetic first generation analogues which include artemether (**3b**, R= Me) and arteether (**3c**, R= Et).



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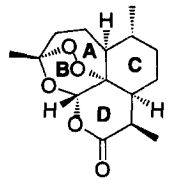

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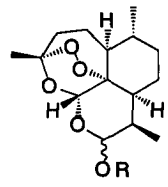
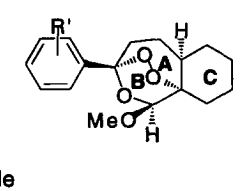


3a, R = H
3b, R = Me
3c, R = Et



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Examination of structure-activity relationships in this class of drugs suggests that the 1,2,4-trioxane system is essential and recently several simplified analogues have been prepared that retain the A, B and C ring system present in the natural product.[3] Based on evidence obtained from biomimetic Fe(II) decomposition of simplified 1,2,4-trioxanes, racemic C-3-aryl 1,2,4-trioxanes of general formula **4** were prepared and shown to have potent antimalarial activity *in vitro* against chloroquine resistant *Plasmodium falciparum* and excellent oral activity versus *Plasmodium berghei in vivo* in mice.[4] In order to determine the importance of chirality for antimalarial activity, metabolism and transport studies we required an efficient method of preparing enantiopure 1,2,4-trioxane analogues of

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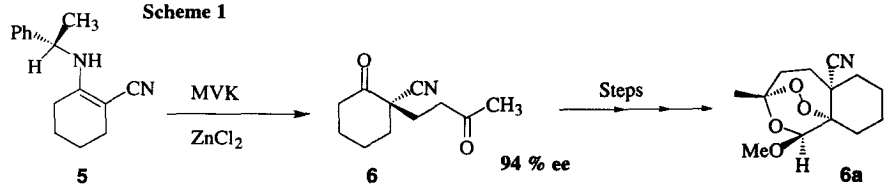
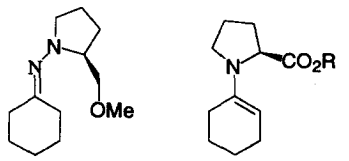
lead derivative **4**, R' = *p*-fluoro). Previous work on the enantioselective synthesis of 1,2,4-trioxane analogues by Mayrargue *et al.* (Scheme 1) involved the use of the β-enaminonitrile **5** in an asymmetric Michael reaction with methyl vinyl ketone. Subsequent synthetic elaboration of **6** led to the nitrile containing 1,2,4-trioxane **6a** with excellent enantiomeric excess.[5] However, analogues of this type, which contain functionality at the A-C ring junction have poor antimalarial activity *in vitro*.[5]

Scheme 1

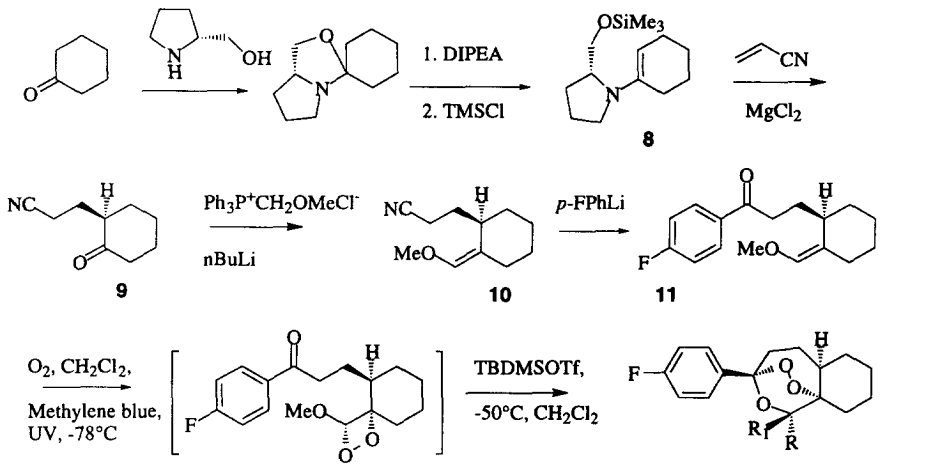


Initial attempts to prepare key nitrile **9** by the conjugate addition of the cyclohexanone derived SAMP hydrazone **7a** to acrylonitrile were prevented by the rapid polymerisation of acrylonitrile in the presence of LDA. Alternatively, the conjugate addition of enamine L-proline ester derivatives **7b** [6] to acrylonitrile gave only moderate chemical and optical yields of product .



Our new approach to the synthesis of enantiomerically enriched 1,2,4-trioxanes is shown in Scheme 2. Studies by Ito *et al.* in 1985 revealed that enamines derived from *R* or *S*-pyrrolidinemethanol react with Michael acceptors such as methyl acrylate with excellent enantiomeric excesses.[7] The presence of the $MgCl_2$ is crucial for the success of this reaction. We decided to apply this methodology to the synthesis of key nitrile **9**.

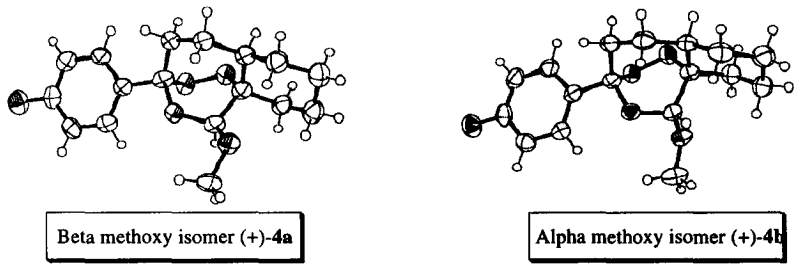
Scheme 2



(+)- **4a** R_1 = OMe, R = H, Beta isomer, 25% Yield (85% ee)
(+) - **4b** R = OMe, R_1 = H , Alpha isomer, 15% Yield (85% ee)

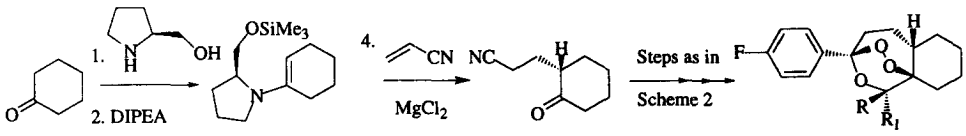
The enatiomerically pure enamine **8** was prepared by condensation of *R*-(+)-2-pyrrolidinemethanol with cyclohexanone in the presence of tosic acid. The resultant oxazolidine was then treated *in situ* with diisopropylethylamine (DIPEA) and TMSCl to give **8** in good yield. Reaction of **8** with acrylonitrile in refluxing benzene furnished the key chiral nitrile **9** in 48 % yield (90% ee). Methoxymethylenation of ketone **9** was accomplished in 70% yield without appreciable racemisation to provide the *Z*-configured alkene **10**, accompanied by the *E*-isomer. Separation of the two geometric isomers was easily accomplished by column chromatography, and on the basis of previous work on the racemic synthesis of **4a**, the *Z*-isomer was taken on to complete the synthesis. Addition of *p*-fluorophenyllithium to nitrile **10** provided the trioxane precursor **11** in 72% yield following chromatography. With the chiral precursor in hand, photo-oxygenation was carried out using methylene blue as sensitiser. Following low temperature formation of the dioxetane as shown, TBDMSOTf was added to induce the known rearrangement to our target chiral 1,2,4-trioxanes (+)-**4a** and (+)-**4b** (85 % ee by chiral HPLC).[8] The beta isomer (+)- **4a** was always the major product in these reactions.

Figure 1 **X-ray crystal structures of (+)-4a and (+)-4b**



Several aspects of Scheme 2 are noteworthy. The control of the stereochemistry in the first step of the synthetic sequence ultimately provides the alkene **11** which undergoes addition of singlet oxygen on *si* face of the double bond. Lewis acid-catalysed dioxetane rupture and rearrangment to the target 1,2,4-trioxane **4a** are also stereoselective. The stereochemistry of the 1,2,4-trioxanes (+)-**4a** and (+)-**4b** were confirmed by single crystal X-ray analysis (Figure 1).[9] As clearly shown, (+)-**4a** and (+)-**4b** have the same stereochemistry as the natural product, artemisinin.

Scheme 3



(-)- 4a R1 = OMe, R =H, Beta isomer 25% Yield (88% ee)
(-)-4b R = OMe, R1=H, Alpha isomer, 18% Yield (87% ee)

The enantiomers of methoxy isomers (+)-**4a** and (+)-**4b** were prepared as shown in Scheme 3 using (*S*)-(+)-pyrrolidinemethanol in the first step of the sequence. The chiral trioxanes (-)-**4a** and

4b were obtained in 43 % yield and 88% ee. The enantiomeric excesses were determined by chiral HPLC. We are currently investigating potential differences in the *in vitro* antimalarial potency, drug metabolism and neurotoxicity of enantiomeric 1,2,4-trioxanes (-)-**4a** and (+)-**4a**. The results of these findings will be of fundamental importance to the future design and synthesis of synthetic 1,2,4-trioxane antimalarials and will be reported shortly in a full paper.

Acknowledgments We thank the EPSRC and UFC LTD (AM, PON) and the US NIH (AI-34885) (GHP) for financial support of this work.

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   For an investigation of the effects of chemical substitution at the C-5a position of artemisinin tricyclic analogues see; Zouhiri, F.; Desmaële, D.; d'Angelo, J.; Riche, C.; Gay, F.; Cicéron, L. *Tetrahedron Lett.*, **1998**, *39*, 2969.
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8. Data for the β-isomer **4a**; mp = 81-84°C; $[\alpha]_D$ + 96° (c, 1.0, $CHCl_3$); HPLC Chiralpak AD, 0.5 % IPA in hexane, Rt = 22.37 min (254 nm); ν_{max} (nujol mull)/cm^{-1}, 2934(CH), 1600, 1512, 875(O-O), 832 (O-O); ^1H HMR (300 MHz, $CDCl_3$) δ 1.23 (m, 1H), 1.30 (m, 1H), 1.60-1.80 (m, 7H), 1.87-2.03 (m, 2H), 2.28 (1H, m), 2.79 (1H, m), 3.62 (3H, s, OMe), 5.15 (1H, d, *J* = 1.3 Hz), 7.03 (2H, m,), 7.50 (2H, m,); Analysis, $C_{17}H_{22}O_4F$ requires C = 66.22, H= 6.86, found C= 66.28, H= 6.88
   Data for the α-isomer **4b**; mp = 85-87°C; $[\alpha]_D$ + 27° (c, 1.0, $CHCl_3$); ν_{max} (nujol mull)/cm^{-1}, 3035, 2863, 1602, 1513, 835 (O-O); ^1H HMR (300 MHz, $CDCl_3$) δ 1.14-1.33 (m, 4H), 1.62 (m, 1H), 1.70-2.83 (m, 4H), 1.90 (1H, m), 2.25 (1H, m), 2.45 (1H, m), 2.83 (1H, m), 3.60 (3H, s, OMe), 5.18 (1H, s), 7.03 (2H, m), 7.52 (2H, m); Analysis, $C_{17}H_{22}O_4F$ requires C = 66.22, H= 6.86, found C= 66.21, H= 6.88
9. Single Crystal X-ray Analysis of **4a** ($C_{17}H_{21}O_4F$) Wavelength 0.71073 A, Temperature, 213 K. Crystal system, space group = monoclinic, P 2(1). Crystal size 0.70 x 0.60 x 0.55 mm, a = 7.4196 (19) b = 8.7037 (13) c = 12.282 (3). Volume = 792.7 (3) $Å^3$. A total of 4205 reflections were collected in the range 2.75° to 22.49°. Lorentz and polarization but not absorption co-efficients were applied. The structure was solved by direct methods (SHEXS-86). R1 = 0.0710, wR2 = 0.1674
   Single Crystal X-RAY Analysis of **4b** ($C_{17}H_{21}O_4F$) Wavelength 0.71073 Å, Temperature, 213 K. Crystal system, space group = orthorhombic, P 2(1)2(1)2(1). Crystal size 0.70 x 0.60 x 0.50 mm, a = 8.0736 (8) b = 10.4646 (15) c = 18.277 (2). Volume = 1544.2 (3) $Å^3$. A total of 8313 reflections were collected in the range 2.24° to 22.50°. Lorentz and polarization but not absorption co-efficients were applied. The structure was solved by direct methods (SHEXS-86). R1 = 0.0291, wR2 = 0.0697