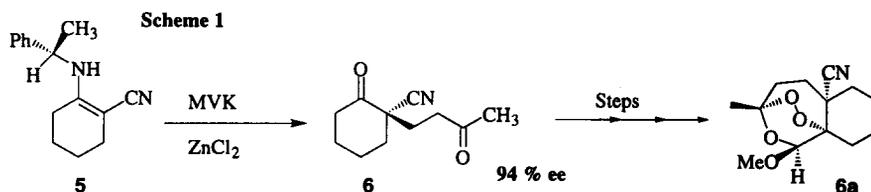
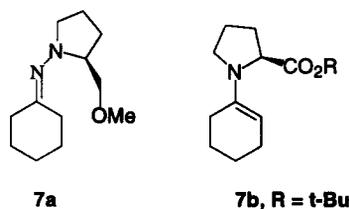




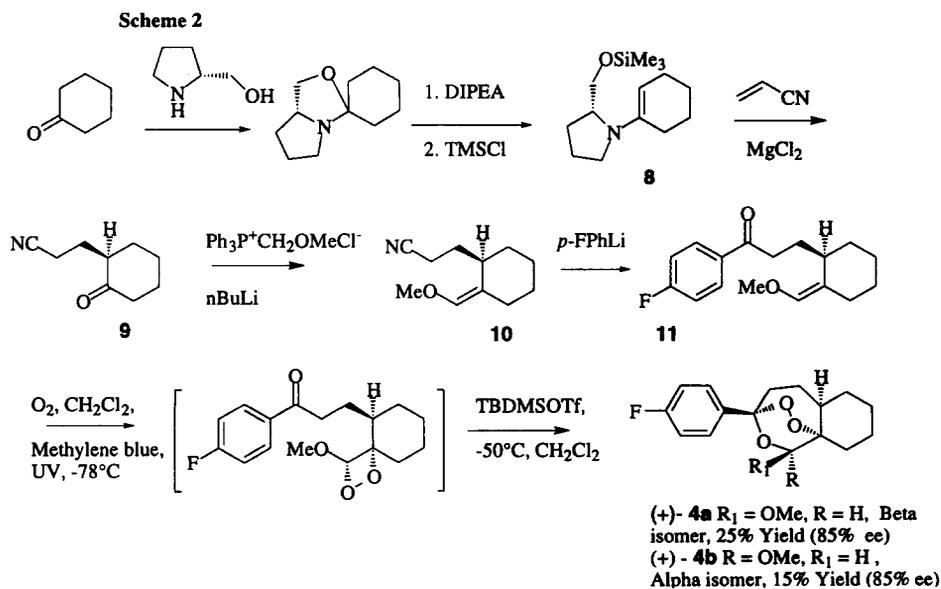
lead derivative **4**, R' = *p*-fluoro). Previous work on the enantioselective synthesis of 1,2,4-trioxane analogues by Mayrargue *et al.* (Scheme 1) involved the use of the  $\beta$ -enaminonitrile **5** in an asymmetric Michael reaction with methyl vinyl ketone. Subsequent synthetic elaboration of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



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**<sup>6</sup> to acrylonitrile gave only moderate chemical and optical yields of product.

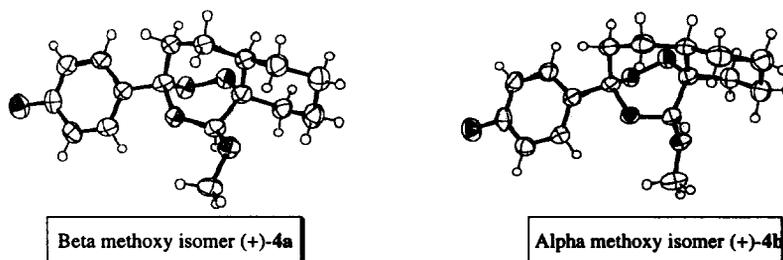


Our new approach to the synthesis of enantiomerically enriched 1,2,4-trioxanes is shown in Scheme 2. Studies by Ito *et al.* in 1985 revealed that enamines derived from *R* or *S*-pyrrolidinemethanol react with Michael acceptors such as methyl acrylate with excellent enantiomeric excesses.<sup>7</sup>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



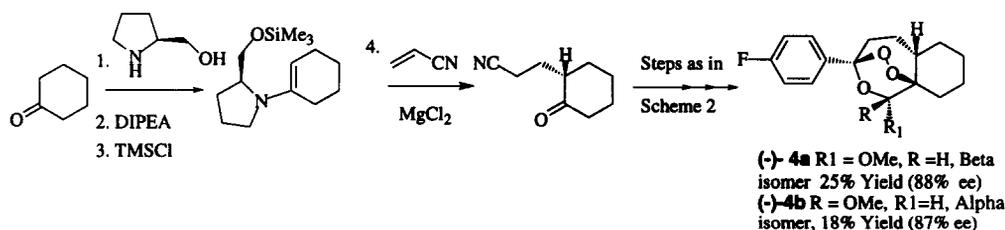
The enantiomerically pure enamine **8** was prepared by condensation of *R*-(+)-2-pyrrolidinemethanol with cyclohexanone in the presence of tosic acid. The resultant oxazolidine was then treated *in situ* with diisopropylethylamine (DIPEA) and TMSCl to give **8** in good yield. Reaction of **8** with 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).<sup>5</sup> 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 rearrangement 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).<sup>9</sup> As clearly shown, (+)-**4a** and (+)-**4b** have the same stereochemistry as the natural product, artemisinin.

Scheme 3



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.

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8. Data for the  $\beta$ -isomer **4a**; mp = 81-84°C;  $[\alpha]_D + 96^\circ$  (c, 1.0, CHCl<sub>3</sub>); HPLC Chiralpak AD, 0.5 % IPA in hexane, Rt = 22.37 min (254 nm);  $\nu_{\max}$  (nujol mull)/cm<sup>-1</sup>, 2934(CH), 1600, 1512, 875(O-O), 832 (O-O); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>17</sub>H<sub>22</sub>O<sub>4</sub>F requires C = 66.22, H = 6.86, found C = 66.28, H = 6.88  
Data for the  $\alpha$ -isomer **4b**; mp = 85-87°C;  $[\alpha]_D + 27^\circ$  (c, 1.0, CHCl<sub>3</sub>);  $\nu_{\max}$  (nujol mull)/cm<sup>-1</sup>, 3035, 2863, 1602, 1513, 835 (O-O); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>17</sub>H<sub>22</sub>O<sub>4</sub>F requires C = 66.22, H = 6.86, found C = 66.21, H = 6.88
9. Single Crystal X-ray Analysis of **4a** (C<sub>17</sub>H<sub>21</sub>O<sub>4</sub>F) Wavelength 0.71073 Å, 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<sup>3</sup>. 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<sub>17</sub>H<sub>21</sub>O<sub>4</sub>F) 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<sup>3</sup>. 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