

Enantioselective synthesis of functionalized 2-oxo-cyclohexane carbonitriles. Access to a trioxane analogue of artemisinin

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Abstract: Synthesis of optically active 2-oxo-1-alkylcyclohexane carbonitriles is described leading to access to a new bicyclic simplified analogue of artemisinin. © 1997 Elsevier Science Ltd

For twenty years, many syntheses¹ of artemisinin 1 and derivatives have been undertaken and numerous modifications of artemisinin have been made, principally on the lactone ring, in order to increase biological activity against drug resistant forms of malaria, notably *Plasmodium falciparum*. Examination of the structure–activity relationships² suggests that the 1,2,4-trioxane system is essential and we have synthesised simplified analogous trioxane compounds with substituted A/C ring junction. We now describe an access to new optically active intermediates and their use in this field.



In a previous communication³, we described the synthesis of an analogue bearing an ester group at the A-C ring junction 2a. But the singlet oxygen attack took place on the face opposite to this bulky substituent and the 1,2-dioxetane precursor led, after rearrangement, to a compound presenting a reverse stereochemistry of the peroxidic bridge in comparison with artemisinin: compound 2a was inactive against *Plasmodium falciparum*.



In order to obtain compounds with the stereochemistry of artemisinin, we looked for a compound bearing a less bulky substituent at the A-C ring junction. We decided to replace the ethyl ester group by a nitrile function. Apart from the decrease of the bulkiness, the nitrile group constitutes a reactive site, which could later be transformed into a polar substituent in order to increase the

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solubility of peroxides 2. As precursors, we synthesised α, α -disubstituted cyclohexanones bearing an α nitrile group. Similar compounds have been prepared firstly in racemic form by Michael reaction⁴ from 2-cyanocyclohexanone⁵. It is worthy of note that only one asymmetric synthesis of this type of compounds has been described, starting from optically active hydrazones, by Enders⁶.

We chose to develop a novel application of the Michael addition to optically actives enamines⁷. The β -enaminonitrile 3 prepared from the (S)- α -methylbenzylamine reacts with methylvinylketone (MVK) and ZnCl₂ to lead, after hydrolysis, the diketone 4 in a 80% yield:



i : MVK, ZnCl_{2,} -78 °C to -40 °C, Et₂O; ii : AcOH; iii : excess of ethanedithiol, BF₃-Et₂O

In attempts to establish the enantiomeric excess of compound 4, we failed to transform the angular nitrile into an ester, acid or amine group leading to known compounds. However, enantiomeric excess (94%) has been evaluated by chiral HPLC on compound 5 after Robinson annellation and subsequent dehydration. The absolute configuration was determined by X-ray diffraction on crystalline compound 6^8 . Enol ethers 9, precursors of 1,2,4-trioxane 2b, were obtained by selective protection with 1,2-ethanedithiol, Wittig homologation⁹ and deprotection:





In order to increase the yield and to avoid protection and deprotection of the unstable diketone 4, we used another reaction sequence using acrylonitrile, a less reactive Michael acceptor than MVK^{10} , to obtain compound 11^9 which could be transformed into 9 owing to a chemoselective reaction:



i = acrylonitrile, $ZnCl_2$, Et_2O , Δ ; ii = AcOH; iii = Φ_3P =CH-OCH₃

Transformation of 11 into 9 failed with organometallic derivatives (CH₃MgX, CH₃Li), whereas Jefford¹¹ readily obtained methylketone in the case of analogous compound without the angular nitrile. Nevertheless, we have succeeded in getting the enol ethers 9 by an unusual reaction¹² of the triphenylmethylene ylide on the more accessible nitrile function of 11^{13} . Absolute configuration and enantiomeric excess of compound 10 (*R*, ee=99%) were determined after chemical correlation. So, this shorter synthesis allowed both yield and enantiomeric excess to be increased:





The separated enol ethers 9E and 9Z lead to the same 1, 2, 4-trioxane 2b (R=CN, 50% and 58% yield respectively) in a diastereoselective cyclisation reaction. As expected, the compound 2b has the same stereochemistry¹⁴ as artemisinin:



In summary, two new chiral precursors with a high synthetic potential have been prepared with respectively 94 and 99% e^{15} , leading to a trioxane, analogue of artemisinin. The antimalarial properties of **2b** are under investigation and these results will be published elsewhere in a full paper.

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- 8. $C_{15}H_{23}NS_4$, M=345.61, system orthorhombic, space group P $2_12_12_1$, a=7.363(4), b=14.500(8), c=16.434(9), Z=4, 5085 measured reflections (-8<h<8, -14<k<17, 0<19). R=0.044, R_w=0.063 for 2579 reflections. The absolute configuration was established by comparison of 78 Bijvoet's pairs.
- 9. 8Z, 8E and 11Z, 11E isomers were easily separated by column chromatography on silicagel and then transformed separately.
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- 13. This reaction is under study in view of others applications.
- 14. **2** (R=CN) $[\alpha]_D$ =+50 (c=0.5, CH₂Cl₂); C₁₃H₁₉NO₄, M=253.3, system orthorhombic, space group P 2₁2₁2₁, a=6.735(2), b=13.698(4), c=14.476(4), Z=4, 1373 measured reflections, R=0.063, R_w=0.099 for 999 observed reflections; ¹H NMR (200 MHz, CDCl₃) δ 5.00 (1H, s), 3.50 (3H, s), 2.60–2.50 (1H, m), 2.30–2.20 (1H, m), 2.20–2.00 (2H, m), 1.95–1.85 (3H, m), 1.80–1.55 (5H, m), 1.40 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 121.9, 104.6, 103.0, 80.9, 57.0, 50.4, 36.3, 34.4, 33.4, 31.4, 25.9, 22.6, 22.6, 21.5. Anal. Calcd for C₁₃H₁₉NO₄: C, 61.64; H, 7.56; N, 5.52. Found: C, 61.51; H, 7.66; N, 5.37.
- 15. All new compounds were characterised by satisfactory spectroscopic and elemental analysis.

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