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

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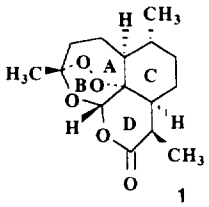
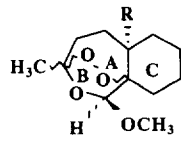
Abstract: Synthesis of optically active 2-oxo-1-alkylcyclohexane carbonitriles is described leading to access to a new bicyclic simplified analogue of artemisinin. © 1997 Elsevier Science Ltd

For twenty years, many syntheses[1] 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 relationships[2] 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.

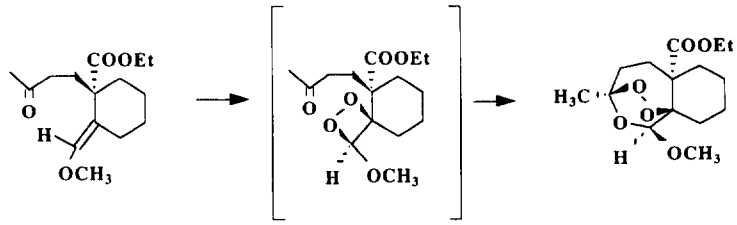


1



2 a : R = COO_2Et
b : R = CN

In a previous communication[3], 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*.



2a

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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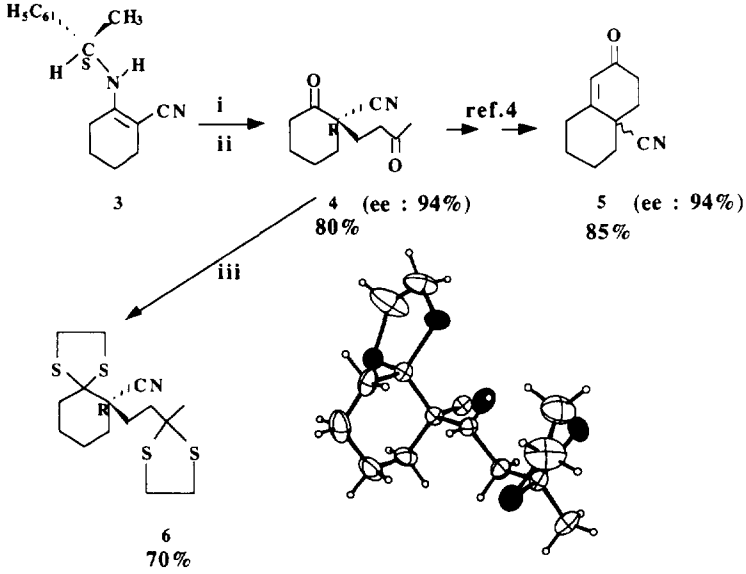
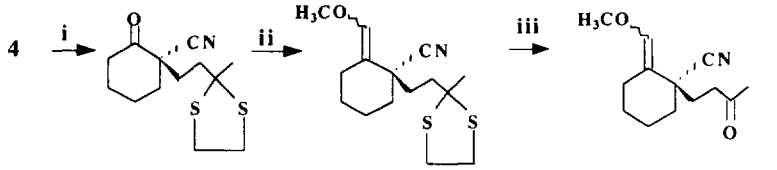
solubility of peroxides **2**. As precursors, we synthesised α,α-disubstituted cyclohexanones bearing an α nitrile group. Similar compounds have been prepared firstly in racemic form by Michael reaction[4] from 2-cyanocyclohexanone[5]. It is worthy of note that only one asymmetric synthesis of this type of compounds has been described, starting from optically active hydrazones, by Enders[6].

We chose to develop a novel application of the Michael addition to optically actives enamines[7]. The β-enaminonitrile **3** prepared from the (*S*)-α-methylbenzylamine reacts with methylvinylketone (MVK) and $ZnCl_2$ to lead, after hydrolysis, the diketone **4** in a 80% yield:



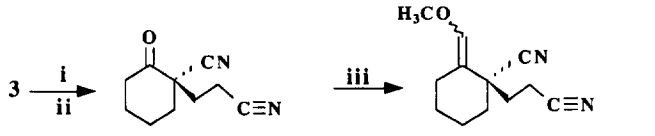
i : MVK, $ZnCl_2$, -78 °C to -40 °C, Et_2O; ii : AcOH; iii : excess of ethanedithiol, BF_3-Et_2O

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 homologation[9] and deprotection:



i = ethanedithiol, BF_3-Et_2O; ii = Φ_3P=CH-OCH_3, r.t.; iii = HgO, CH_3CN/H_2O

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:

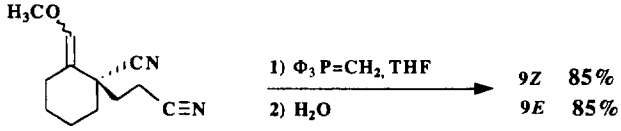


10 (ee : 99%) 71%

11 (Z /E : 63/37) 77%

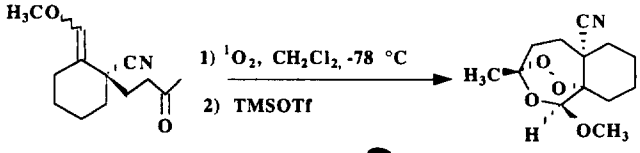
i = acrylonitrile, $ZnCl_2$, Et_2O, Δ ; ii = AcOH; iii = Φ_3P=CH-OCH_3

Transformation of **11** into **9** failed with organometallic derivatives (CH_3MgX, CH_3Li), whereas Jefford[11] 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 reaction[12] 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:

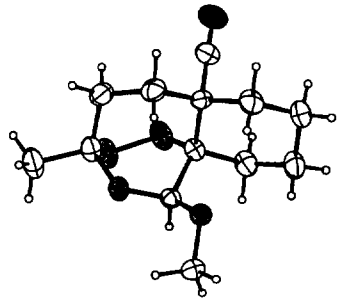


11 (*E*, Z)

The separated enol ethers **9***E* and **9***Z* 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 stereochemistry[14] as artemisinin:



9 2b



2b

In summary, two new chiral precursors with a high synthetic potential have been prepared with respectively 94 and 99% ee[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.

Acknowledgements

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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. **8***Z*, **8***E* and **11***Z*, **11***E* 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, CH_2Cl_2); $C_{13}H_{19}NO_4$, M=253.3, system orthorhombic, space group P $2_12_12_1$, 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; ^{1}H NMR (200 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz,$CDCl_3$) 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 $C_{13}H_{19}NO_4$: 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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