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STEREOSELECTIVE SYNTHESIS OF ARTEMISININ[+]

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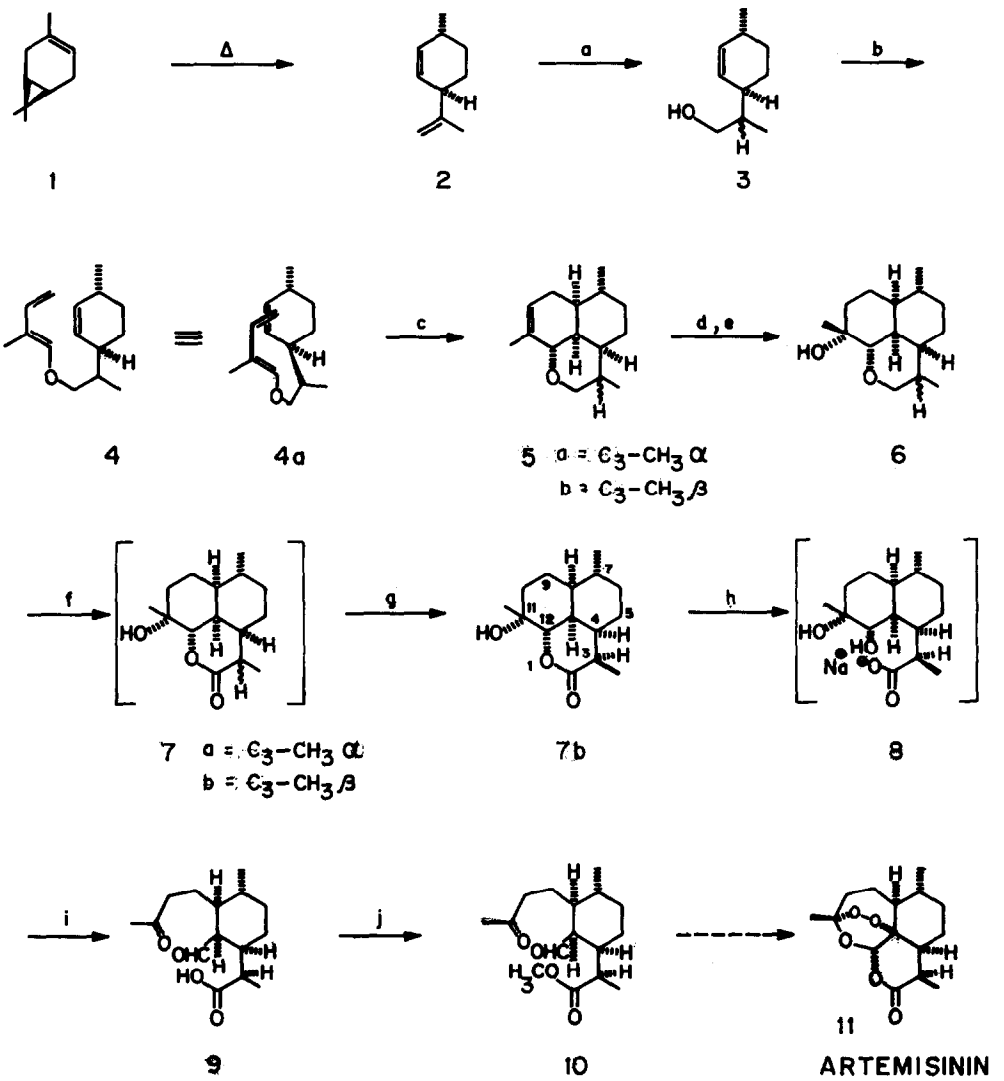
Summary: A stereoselective synthesis of artemisinin **11** based on intramolecular Diels-Alder reaction of the triene **4** derived from (+)isolimonene **2** is described.

Recently there has been a considerable interest in the chemistry[1] and total synthesis[2] of artemisinin, a promising antimalarial compound of Chinese origin isolated from the plant Artemisia annua L. This is mainly due to its effectiveness in the treatment of drug resistant strains of malaria and also due to its synthetically challenging structure. Unlike other antimalarials it does not contain nitrogen but possesses a tetracyclic structure with peroxide bridge. Considering the potential of artemisinin and/or its derivatives in antimalarial therapy, we wanted to pursue a design of synthesis which should be more practical and stereospecific than any[2] so far reported. This paper describes a stereoselective synthesis of artemisinin via intramolecular Diels-Alder approach. The starting material is (+)-isolimenene[2] which in turn can easily be derived from (+)car-3-ene **1**[3], a cheap and abundantly available monoterpene.

(+)Isolimonene **2** on regioselective hydroboration with 9BBN and oxidation furnished a mixture of diastereomeric alcohols **3** in 70% yield. Separation of this mixture was not necessary at this or the following two stages as they could be equilibrated at a later stage of the synthetic sequence (**7a** → **7b**, vide infra). The alcohol **3** was converted to the enolether **4** in 60% yield by trans-etherification[4] with 1-ethoxy-2-methyl-1,3-butadiene[4] in presence of mercuric and sodium acetates. A 0.01 M solution of this ether **4** in toluene containing a small amount of pyridine and catalytic amount of hydroquinone on heating in a sealed tube at 210°C for 72 hours

SCHEME



Reagents :

a) 1·0 equiv 9BBN; 3N NaOH ; b) 1-Ethoxy-2-methyl-1,3-butadiene, $Hg(OAc)_2$, NaOAc ; c) Toluene, 210°C, sealed tube, 72h; d) MCPBA, CH_2Cl_2, 0°C ; e) $LiAlH_4$, Et_2O; f) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $H_2O : CCl_4 : CH_3CN$; g) NaOMe, MeOH ; h) NaOH, 1·0 equiv ; i) $NaIO_4$; j) CH_2N_2

underwent intramolecular Diels-Alder reaction to furnish an epimeric mixture of ethers **5a** and **5b** (25-30% yield) approximately in the ratio of 6:4 (by chromatographic isolation). Molecular model studies on **4** revealed that the triene permits the approach of the diene to the dienophilic part only from β-side and in an exo-fashion resulting in an α-orientation of ring junction protons and β-orientation of the methine proton at C-12 (see **4a**). These observations were further evidenced by ^{1}H and ^{13}C NMR studies of 5.

The epimeric mixture of ethers 5 was epoxidised with MCPBA in dichloromethane to give a single epoxide which was then reduced by LAH to furnish the tert. alcohol **6**. Examination of molecular model for ether 5 suggested that only an α-approach is feasible for an oxidant. Hence the alcohol **6** generated after reduction will have α-orientation. This was later substantiated by the periodate cleavage of the diol **8**, obtained by $RuCl_3$-$NaIO_3$ oxidation[5] of **6** in CCl_4-CH_3CN-H_2O system which furnished an epimeric mixture (70:30) of lactone **7a** and **7b** in 60% yield. Lactones **7a** and **7b** were separated by chromatography over SiO_2 and were characterised. **7a**, m.p. 153-156°C; $[\alpha]_D$ +20.57°, $CHCl_3$; **7b**, m.p. 162-170°, $[\alpha]_D$ -11.6°, $CHCl_3$. The structures **7a** and **7b** were further supported by NMR and X-ray crystallographic studies.[7]

The lactone mixture **7a** and **7b**, and the chromatographically pure **7a** were equilibrated by heating with NaOMe - MeOH to obtain an equilibrium mixture of **7a** and **7b** [6:4, NMR ($CDCl_3$) C_{12} proton of **7a**; δ 4.18, J=12 and **7b**; δ 4.29; J=12 cps. The lactone **7b** was hydrolysed exactly with one equivalent sodium hydroxide and the resultant carboxylate anion **8** was cleaved with $NaIO_4$[6] to give the keto-aldehyde **9** in 55% yield. The methylester **10**, prepared by reaction of **9** with diazomethane was identical in its spectral properties with that reported earlier.[2c] Since the conversion of the methyl ester **10** to (+)artemisinin is reported earlier,[2c] this work described constitutes a new total synthesis of artemisinin.

This synthesis proceeded, overall, without any stereoselective problems to generate intermediate **10** in 8 steps compared to 15 steps involved in the earlier reported synthesis of Zhou et al[2c]. In contrast to other reported methods also, this method is found to be stereoselective. Intermediate **10** has to go through selective protections, singlet oxygen reaction and acid treatment as per Zhou's method to obtain artemisinin. We are looking into making these last few steps also more practical.

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