## SHORT COMMUNICATIONS

# Total Synthesis of (−)-Artemisin

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The key compound chosen in our total synthesis of (±)-artemisin (**1**)[1] was racemic 3-oxo-8$\beta$(H), 11$\alpha$(H)-eudesm-4-en-8,13-olide (**2**); and its dextrorotatory modification mp 142°, $[\alpha]_D^{18}$ +19.4° was derived from (+)-isoalantolactone or (+)-alantolactone as described in our preceding communication.[2] Since this (+)-**2** from the natural sources was converted into (−)-artemisin,[2] any optically active intermediate compound between (+)-**2** and isoalantolactone or alantolactone could be the relay substance in the total synthesis of natural (−)-artemisin.

Our choice was unsaturated ketoester (**3**), preparation of which is dealt in the present communication.

To make unsaturated ketoester (**3**) by enamine alkylation required the preparation of unsaturated ketone (**8**), which was accomplished following the general synthesis route employed previously.[1]

From the reaction mixture of Robinson's annelation of *cis*-2-methyl-4-acetoxycyclohexanone with diethylaminopentan-3-one methiodide in the presence of sodium methoxide, *cis*-bicyclic ketoalcohol (**4**), mp 101°C and its *trans* form (**5**), mp 82—83°C in ratio of 7 : 3, were isolated.

To remove the keto group without affecting the double bond, *cis*-ketoalcohol (**4**) was first converted into thioketal (**6**) with ethanedithiol and $BF_3$-etherate.

Desulfurization of thioketal (**6**) with sodium in liquid ammonia[3] gave unsaturated alcohol (**7**), mp 72°C which was then oxidized with chromic acid anhydride in acetone[4] to the requisite unsaturated ketone (**8**), bp 130—132°C/15 mmHg.

The oily enamine (**9**) obtained by refluxing unsaturated ketone (**8**) with piperidine in benzene solution, was dissolved in methanol and treated with ethyl $\alpha$-bromopropionate. After being decomposed with water, the reaction mixture was saponified to furnish a mixture of esters, bp 120—125°C/0.1 mmHg. Inspection of thin layer and vapor chromatograms revealed the presence (1 : 1) of the two epimers (**10**) and (**11**) differing at $C_{11}$-center, whose chromatography on silica gel led to isolation of the unsaturated ketoester (**10**) as a fast moving elute.

Infrared and NMR spectra data together with vapor phase chromatogram established the identity of this unsaturated ketoester (**10**) with the intermediate (**3**) from the natural sources.

In order to complete the total synthesis, there only remained the optical resolution which was accomplished by working with brucine as the resolving agent.

Crystallization from methanol-water of brucine salt of acid (**12**) obtained by alkaline hydrolysis of **10** furnished the salt, $[\alpha]_D^{22}$ −15.7° (*c* 0.5, ethanol). The acid regenerated from the salt was esterified with diazomethane to ester (**3**), bp 118—121°C/0.1 mmHg, $[\alpha]_D^{22}$ +42.9° (*c* 0.3, in ethanol) (**3** from the natural sources: bp 116—122°C/0.1 mmHg, $[\alpha]_D^{18}$ +41.4°).[2] Comparison of their infrared and NMR spectra established their identity which was further supported by a mixed melting point determination of their semicarbazone, mp 165—166°C.

(−)-Artemisin has been obtained therefore by total synthesis.

1) M. Nakazaki and K. Naemura, *Tetrahedron Letters*, **1966**, 2615.
2) M. Nakazaki and K. Naemura, *ibid.*, **1969**, 33.
3) D. C. Humber, A. R. Pinder and R. A. Williams, *J. Org. Chem.*, **32**, 2335 (1967).
4) J. A. Marshall, N. Cohen and A. R. Hochstetler, *J. Am. Chem. Soc.*, **88**, 3408 (1966).