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TOTAL SYNTHESIS OF d,l-MESEMBRINE VIA REGIOSELECTIVE $NaBH_4$-REDUCTION OF IMIDES

by

J.B.P.A. Wijnberg and W.N. Speckamp*

Laboratory of Organic Chemistry, University of Amsterdam,

Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

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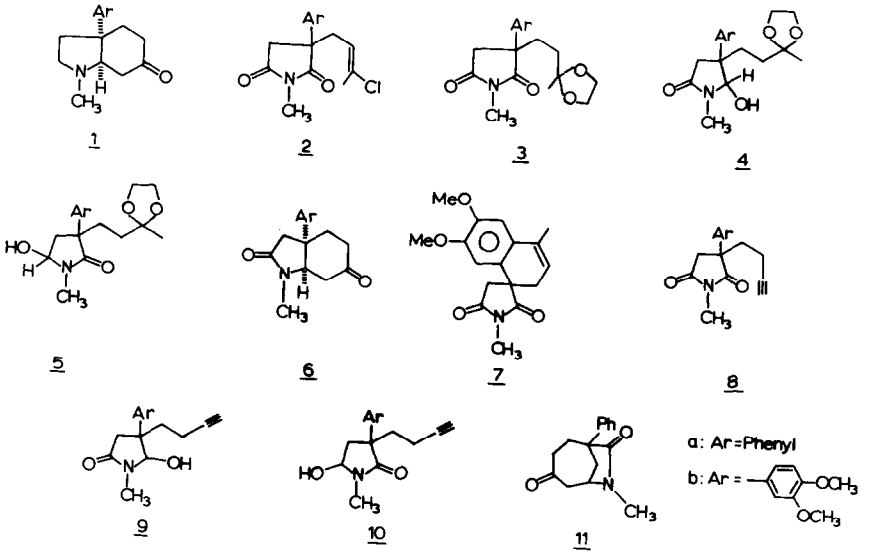
$NaBH_4/H^{\oplus}$-reduction of α,α disubstituted imides proceeds in a highly regioselective manner to afford in the corresponding ω-carbinollactams in quantitative yield[1]. Coupled with the extremely versatile synthetic utility of the cyclic acylimmonium species[2] a great number of potential applications can be designed. In this communication both principles are illustrated in a short and stereoselective synthesis of Sceletium alkaloids as exemplified for d,l-mesembrine 1b.

As a model substrate of N-methyl-phenylsuccinimide was chosen which upon coupling with 1,3-dichlorobutene-2[3] (K_2CO_3/DMF; 98%) afforded 2a. Hydrolysis of 2a (H_2SO_4 conc., r.t. 5 mn) followed by ketalization (glycol/$H^{\oplus}$) gave the imide 3a, m.p. 68-70°C in 53% yield. Upon $NaBH_4/H^{\oplus}$-reduction of 3a a 6:1 mixture of 4a and 5a (PMR) was obtained in essentially quantitative yield. Separation of the two isomers occurred readily upon chromatography to give 4a (66%) m.p. 164-168°C (EtOAc) which was cyclized (HCl/MeOH, reflux 21 hr) to 6a (77%) m.p. 126-128°C, PMR δ($CDCl_3$) 2·86 (s, 3H, N-$\underline{CH_3}$) and 4·39 (t, 1H, J = 4·5 c/s, N-C$\underline{H}$). The route employed leaves no doubts with respect to the stereochemical structure of 6a.

In applying the procedure outlined above on the synthesis of 6b, however, it was found that hydrolysis of the vinylchloride 2b could not be achieved in a satisfactory manner.



Instead of the desired transformation a cyclization to the spiroderivative 7 m.p. 150-154°C, PMR δ($CDCl_3$) 2·08 (broad s, 3H, C-$\underline{CH_3}$), 3·12 (s, 3H, N-$\underline{CH_3}$), 3·81 and 3·87 (ArO$\underline{CH_3}$), 5·67 (m, 1H, =$\underline{CH}$), 6·39 and 6·84 (s, 2x 1H, ArH) took place, which was impossible to avoid by varying the conditions.

Therefore, an alternate route was employed which was indicated to us from parallel studies on the biomimetic heterocyclization of N-alkenyl imides[4]. It appeared from these that the ethynyl moiety underwent smooth C-C bond formation with the highly reactive cyclic acylimmonium ion.

Thus N-methyl-phenylsuccinimide was coupled with 1-iodo-butyne-3 (NaH, DMSO/THF, 0°C) to give the butynylderivative 8a in 76% yield. Interestingly, $NaBH_4/H^{\oplus}$ reduction of 8a proceeded analogously as compared with 3a and afforded a mixture

of 9a and 10a in ratio 6:1 (PMR), readily separable via chromatography. Formic acid cyclization (r.t. 72 hr) of 9a directly gave 6a in 93% yield.

A similar sequence of reactions starting with N-methyl-veratrylimide[5] furnished the known[6] keto-lactam 6b through the successive compounds 8b and 9b. The actual cyclization step 9b → 6b again proceeded in nearly quantitative yield and the observed analytical data fully agree with those published before. Since 6b has been converted to d,l-mesembrine[6], the presently described procedure constitutes also a total synthesis.

It needs no further comment that the method described herein is amenable to application in the synthesis of a wide variety of Amaryllidaceae alkaloids. In addition a variety of heterocyclic and homocyclic derivatives can be obtained as is illustrated in the ready cyclization of 10a into ketone[7] 11 (HCOOH r.t. 72 hr) m.p. 168-171°C, PMR $\delta(CDCl_3)$ 3·01 (s, 3H, N-$\underline{CH_3}$) 3·84 (m, 1H, NC$\underline{H}$), Mass: M^+: m/e 243 (87%).

Other examples will be reported in our full papers.

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