Concise Enantiospecific Synthesis of the Key Intermediate for Heteroyohimbine Alkaloids: Formal Synthesis of Ajmalicine and 19-*epi*-Ajmalicine

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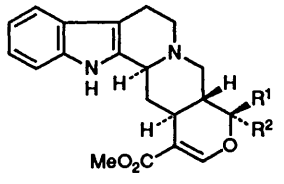
Concise enantiospecific synthesis of the key intermediate for ajmalicine **1** and 19-*epi*-ajmalicine **2** has been achieved starting from a chiral cyclopentanone derivative, easily derived from (−)-carvone.

Recently we reported an efficient procedure for the conversion of (−)- and (+)-carvones, readily accessible monoterpenes, into the corresponding cyclopentanone derivatives **3** and its enantiomer, respectively, highly functionalized chiral building blocks, and also their utilization in the synthesis of physiologically active natural products.[1] Since the cyclopentanone **3** has three contiguous stereogenic centres on its five-membered ring, it is reasonable to speculate that regioselective insertion of an oxygen atom into one of the carbon–carbon bonds at the carbonyl group by Baeyer-Villiger oxidation to form a δ-lactone moiety in combination with appropriate manipulation of the substituents would provide a suitable precursor for the mono-terpenenoid portion of heteroyohimbine alkaloids (see Scheme 1).



1 Ajmalicine: R^1 = H, R^2 = Me
2 19-*epi*-Ajmalicine: R^1 = Me, R^2 = H

Here, we describe a concise enantiospecific synthesis of the key intermediate for (−)-ajmalicine **1**,[2] the only member of the heteroyohimbine family used therapeutically, and (+)-19-*epi*-ajmalicine **2**.[3]

We first investigated the conversion of the isopropenyl group of the benzyl ether **5**, easily derived from the cyclopentanone **3** by three steps, into a carboxylic acid **7** as follows. Ozonolysis of **5**, followed by reductive work-up with dimethyl sulfide afforded quantitatively the ketone **6** and this, on treatment with calcium hypochlorite in alkaline solution,[4] followed by acidification with hydrochloric acid gave the desired acid **7** (69%).

Homologation of the acid **7** was achieved with an Arndt–Eistert reaction.[5] Thus, the reaction of the acid **7** with ethyl chloroformate in the presence of triethylamine gave the mixed anhydride **8**, which on exposure to an excess of diazomethane in ether afforded the diazo ketone **9**. Decomposition of the latter with silver(I) oxide in methanol provided the methyl ester **10** (60% yield from **7**). After deprotection of the ketal group of the ester **10** by treatment with 10% hydrochloric acid in tetrahydrofuran, the resulting ketone **11**, $[\alpha]_D$ −81 (*c* 1.2 $CHCl_3$), was oxidized to the δ-lactone **12** by Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid in dichloromethane (62% yield from **10**). The stereochemistry of the δ-lactone having the 19-*epi*-ajmalicine type configuration was established on the basis of its NMR spectrum.

Although the inversion of the methyl group stereochemistry in **12** was investigated under a variety of reaction conditions none of the desired product, ajmalicine, could be isolated. We therefore decided to exploit the δ-lactone **12** for further conversion, since the inversion of this stereogenic centre has already been achieved at a later stage of this synthesis by Hanessian and his co-workers.[2f]

Removal of the benzyl group of **12** by catalytic hydrogenation in the presence of palladium hydroxide on carbon and subsequent Swern oxidation[6] of the resulting primary alcohol **13** afforded the aldehyde **4** (66% yield from **12**). Since the monoterpenoid portion of the heteroyohimbine alkaloids was thus constructed stereoselectivity, our attention was focused on its further conversion into heteroyohimbine alkaloids.

Condensation of the aldehyde **4** with tryptamine in dichloromethane at ambient temperature in the presence of anhydrous magnesium sulfate afforded the corresponding imine which, without isolation, was reduced with sodium cyanoborohydride in methanol; treatment of the product with di-*tert*-butyl dicarbonate in dichloromethane in the presence of *N*,*N*-dimethylaminopyridine provided the lactam **14**, m.p. 140 °C (54% yield from the aldehyde **4**). The spectroscopic data of **14** including the specific optical rotation, {$[\alpha]_D$ +64.7 (*c*. 0.2 $CHCl_3$)} {lit.,[2f] $[\alpha]_D$ +63 (*c* 1.12 $CHCl_3$)} were identical with those provided by Professor Hanessian.

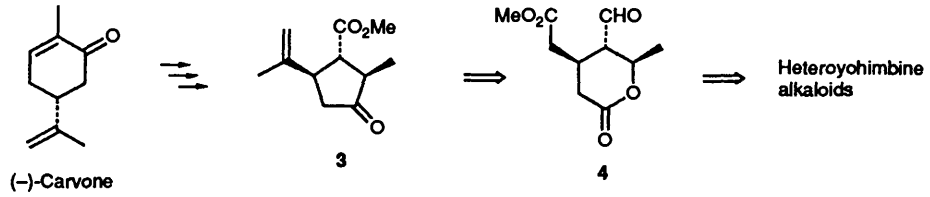
Transformation of the lactam **14** into the pentacyclic compound **15** was achieved by adopting Hanessian's procedure[2f] involving the Bischler–Napieralski reaction. Since the indolyllactone **15**, identical with an authentic specimen, had already been converted into 19-*epi*-ajmalicine and also into ajmalicine *via* compound **16**,[2f] this synthesis constitutes their formal syntheses.

Thus, the enantiospecific formal synthesis of ajmalicine and 19-*epi*-ajmalicine has been achieved by employing (−)-carvone as a starting material and this synthetic path should be applicable to the other heteroyohimbine alkaloids.

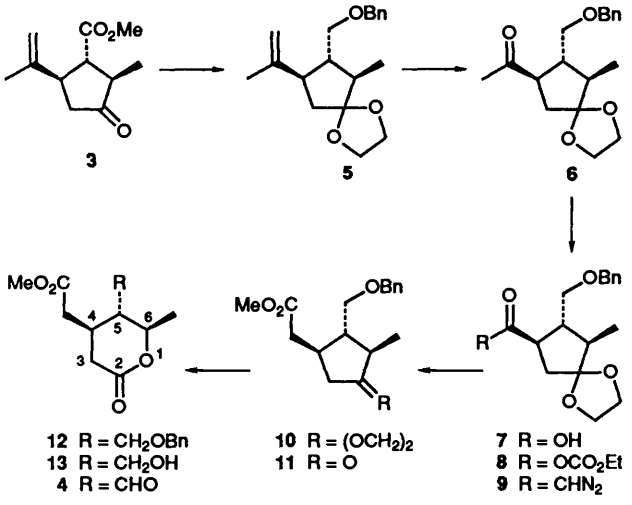
Experimental

Baeyer–Villiger Oxidation of the Cyclopentanone **11**.—To a stirred solution of **11** (0.5 g, 1.72 mmol) in dry dichloromethane (100 cm^3) in the presence of potassium hydrogen carbonate (0.52 g) was added *m*-chloroperbenzoic acid portionwise at 0 °C and the resulting mixture was further stirred for 1.5 h at the same temperature. After addition of dimethyl sulfide (0.95 cm^3), the solution was filtered through a Celite pad and the filtrate was concentrated to leave a residue, which was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (7:3, v/v) afforded the lactone **12**: $[\alpha]_D$ +20.2† (*c* 0.9 $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740; $\delta(CDCl_3)$ 1.35 (3 H, d, *J* 6.7,† 6-Me), 1.49–1.57 (1 H, m, 5-H), 2.27–2.82 (5 H, m, 3-H_2, 4-H and CH_2CO_2), 3.50 (1 H, dd, *J* 3.7 and 9.8, C*H*HOBn), 3.55 (1 H, dd, *J* 3.7 and 9.8, CH*H*OBn), 3.66 (3 H, s, OMe), 4.38–4.54 (1 H, m, 6-H), 4.45 (1 H, d, *J* 12.2, OC*H*HPh), 4.52 (1 H, d, *J* 12.2,

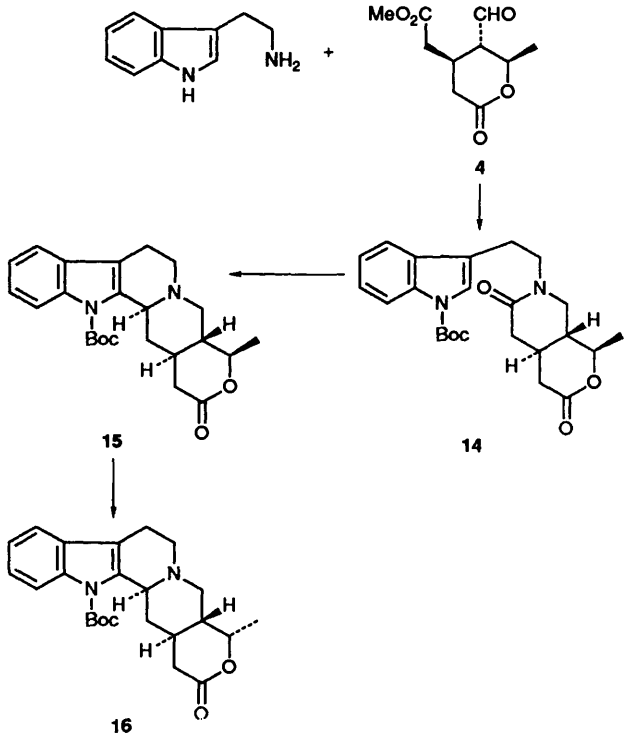
† *J* Values quoted as Hz and $[\alpha]_D$ values as 10^{-1} deg cm^3 g^{-1}.



Scheme 1



Scheme 2



Scheme 3

OCH*H*Ph) and 7.27–7.47 (5 H, m, Ph); *m/z* 306 (M^+) (Found: C, 66.4; H, 7.4. Calc. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.25%).

Acknowledgements

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