An Approach to the Chiral Synthesis of Heteroyohimbine Alkaloids

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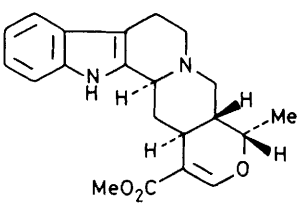
Methyl α-D-mannopyranoside is used as a chiral starting material to prepare two epimeric substituted indolo[2,3-*a*]quinolizidines which could serve as chiral synthons for the total synthesis of (−)-ajmalicine (**1**) and the heteroyohimbine alkaloids in general.

Of the eight naturally occurring heteroyohimbine alkaloids, (−)-ajmalicine (**1**) is the most important commercially. The total synthesis of racemic ajmalicine has been reported by many workers.[1–4] Uskokovic *et al.*[5] have described an asymmetric synthesis of *allo*-heteroyohimbine alkaloids, the chirality being obtained by microbiological reduction of an 3-acetylpyridine intermediate.

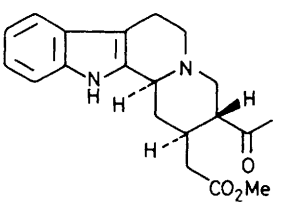
We describe here the use of carbohydrates as chiral starting materials in a new approach towards the synthesis of (−)-ajmalicine (**1**) *via* the chiral synthon (**3a**).

The unsaturated ester (**5**),[6] obtained from methyl α-D-mannopyranoside in three steps *via* the 3-ulose compound,[7] (**4**), was reduced to the branched-chain methyl glycoside (**6**) (Raney Ni, H_2, MeOH). Subsequent hydrolysis of the benzylidene group in acid medium afforded the furanoside (**7**) in 75% yield. Oxidation by $NaIO_4$ then yielded the aldehyde which was in turn reduced to the primary alcohol (**8**) in 82% yield.

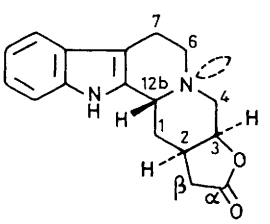
Conversion of this furanoside compound (**8**) into the corresponding pyranose sugar (**10**), and condensation with N^b-benzyltryptamine (**9**) by the Pictet–Spengler reaction, afforded the chiral 3-epimeric substituted tetrahydro-β-



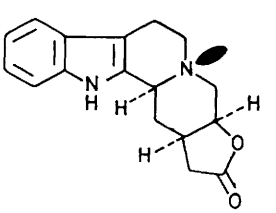
(1) (−)ajmalicine



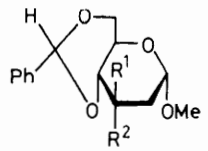
(2)



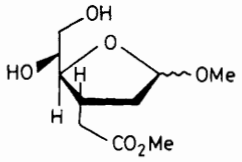
(3a)



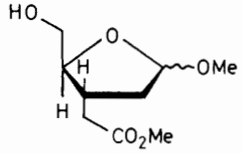
(3b)



(4) $R^1 R^2 = =O$
(5) $R^1 R^2 = =CHCO_2Me$
(6) $R^1 = H$, $R^2 = CH_2CO_2Me$



(7)



(8)

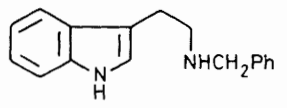
carbolines (**11a**) in 56% yield. The two epimeric products (**11a**) were then treated with methanesulphonyl chloride or toluene-*p*-sulphonyl chloride in pyridine; the ammonium salts (**12a** or **b**) obtained after cyclisation of (**11 b** or **c**) were hydrogenolysed to give the two chromatographically separable indolo[2,3-*a*]quinolizidines in 60% yield from (**5a**): (**3a**), m.p. 208—209 °C, $[\alpha]_D$ + 65° (*c* 0.79, Me_2CO), u.v. (EtOH) 226 (log ϵ 4.65), 276 (3.91), 282 (3.95), and 291 nm (3.87); (**3b**), m.p. 249—251 °C, $[\alpha]_D$ −110° (*c* 0.77, Me_2CO), u.v. (EtOH) 227 (log ϵ 4.55), 277 (3.86), 283 (3.88), and 291 nm (3.79). The structures and conformations of (**3a**) and (**3b**) were assigned by analysis of their 400 MHz ^1H and ^{13}C n.m.r. spectra.†

The elaboration of the chiral products (**3a**) and (**3b**) to the van Tamelen synthon (**2**) and (−)-ajmalicine (**1**) is under investigation.

We thank Mr. S. K. Kan, Institut d'Electronique Fondamentale, Université de Paris-Sud, for use of a 400 MHz n.m.r. spectrometer.

Received, 17th November 1982; Com. 1313

† N.m.r. data ($CDCl_3$): (**3a**), ^1H δ 4.83 (ddd, 3-H) and 3.61 (dd, 12b-H); ^{13}C δ 176.2 (C-α), 75.7 (C-3), 55.9 (C-4), 53.9 (C-12b), 53.2 (C-6), 32.9 (C-2), 30.1 (C-1), 29.8 (C-β), and 21.3 p.p.m. (C-7); (**3b**), ^1H δ 4.53 (ddd, 3-H) and 3.32 (dd, 12b-H); ^{13}C δ 176.8 (C-α), 78.2 (C-3), 58.1 (C-12b), 56.9 (C-4), 53.3 (C-6), 38.3 (C-2), 34.5 (C-β), 33.4 (C-1), and 22.5 p.p.m. (C-7).



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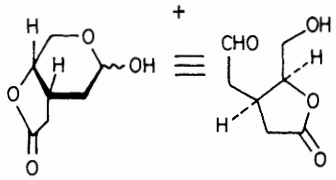
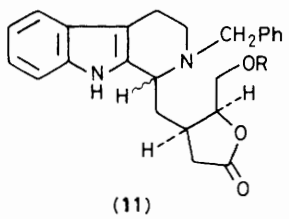
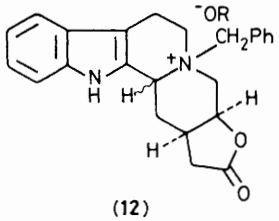


(10)



(11)

a; R = H
b; R = SO_2Me
c; R = $SO_2C_6H_4Me$-*p*



(12)

a; R = SO_2Me
b; R = $SO_2C_6H_4Me$-*p*

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