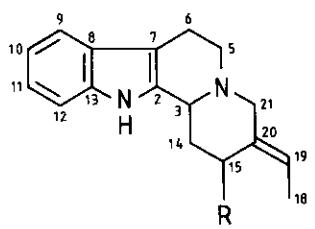
HETEROYOHIMBINE ALKALOID SYNTHESIS

Reija Jokela, Tuula Taipale, Kari Ala-Kaila, and Mauri Lounasmaa*

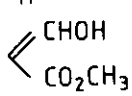
Technical University of Helsinki, Department of Chemistry,
Laboratory for Organic and Bioorganic Chemistry, SF-02150 Espoo, Finland

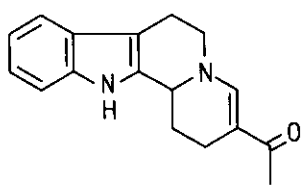
Abstract - Preparation of the heteroyohimbine analogues 6 and 7 and a new short stereoselective total synthesis of (±)-3-iso-19-epiajmalicine 12 are described.

There are eight deplancheine (1) syntheses,[1-8] of which that introduced by Hämeilä and Lounasmaa[4] is a short and rapid method based on $LiAlH_4$-reduction of the easily accessible indoloquinolizidine (3) which is a vinylogous amide. To examine the applicability of the method for the synthesis of formal geissoschizine (2)[9] analogues, compound 5 was chosen as a model. This was prepared from salt 4 using our modification (dimethyl sodiomalonate, THF, DME, -15°C) of the Kröhnke procedure[10] to afford the corresponding 1,4-dihydropyridine, which was immediately cyclized to the indoloquinolizidine 5 (yield 4→5 ~40%). The main products of the $LiAlH_4$-reduction of 5 were the heteroyohimbine analogues 6 (yield 47%) and 7 (17%). Geissoschizine analogues with the ethylidene side chain were not detected (vide infra).

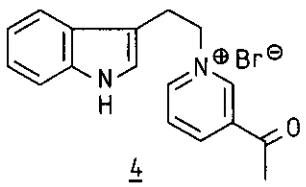


1 R = H

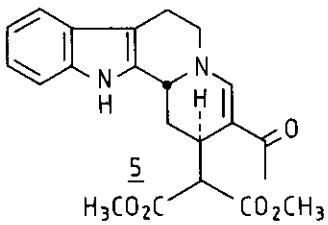
2 R = 



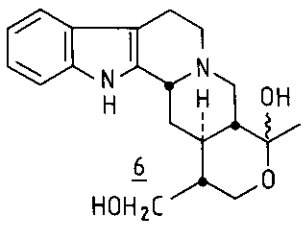
3



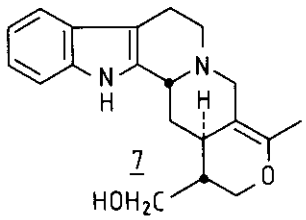
4



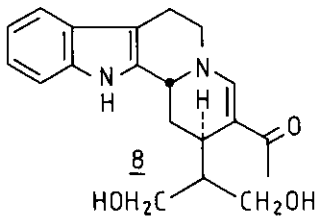
5



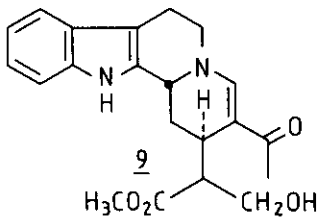
6



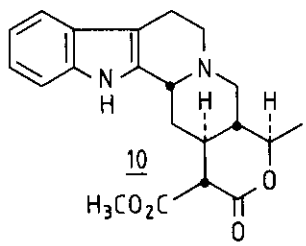
7



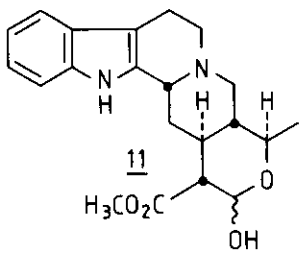
8



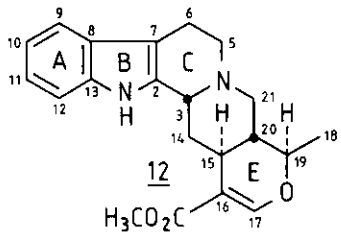
9



10



11



12

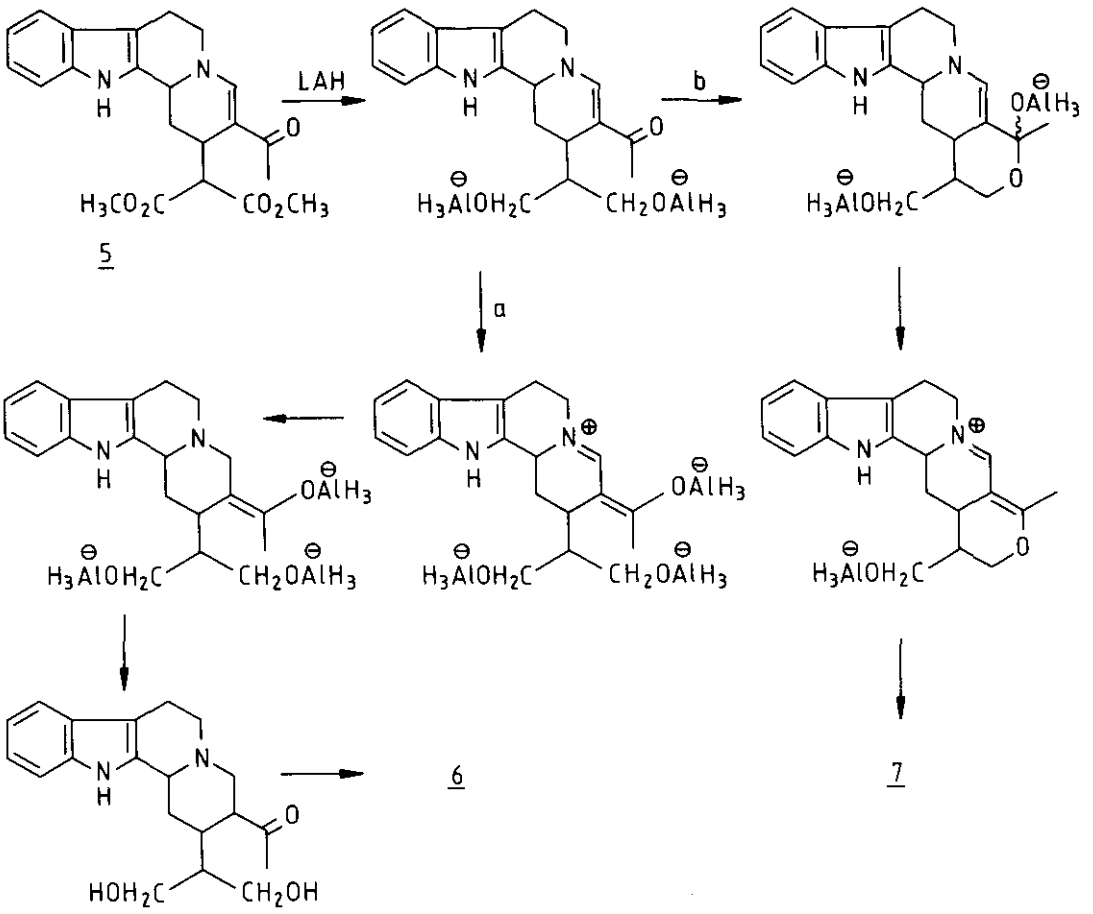
The mechanism of the formation of the five-ring compounds 6 and 7 is interpreted in Scheme 1. After the initial reduction of the methoxycarbonyl groups to the corresponding alcohol derivatives, the reaction proceeds by two paths (cf. ref. 11).

Path a. Formation of an enolic iminium ion derivative, which is reduced to the corresponding enol derivative, leads after hydrolysis (during the work-up) and hemiacetal formation to compound 6.

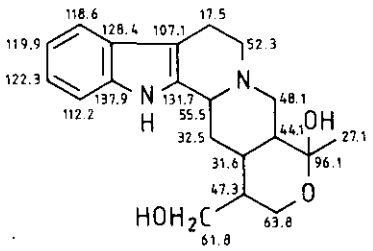
Path b. Hemiacetal formation (due to the sufficient ketonic character of the present vinylogous amide system), which is followed by the iminium ion formation and simultaneous cleavage, leads after the reduction of the iminium group to compound 7.

The possibility that 6 was formed from 7 by addition of H_2O during the work-up was excluded by using abs. methanol instead of H_2O (see Experimental). But even with abs. methanol the only products formed were 6 and 7. No C(19)-OMe analogue of compound 6 was detected.

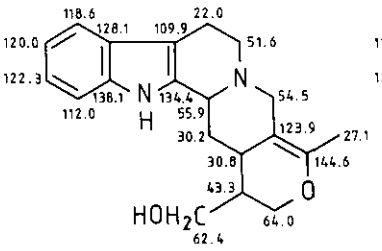
In considering the stereochemistry of heteroyohimbine alkaloid analogues of the above type, several conformations due to nitrogen inversion and cis-decalin type ring interconversion between rings C and D have to be taken into account.[12,13] The pseudo configuration of compound 6 (confirmed with ^1H and ^{13}C NMR spectral data) implies exclusively the cis C/D ring juncture. Trans-fusion of D and E rings causes conformational rigidity which does not permit cis-decalin type ring interconversion between the C and D rings.



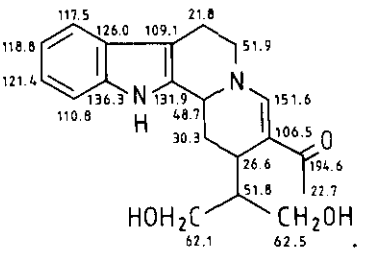
Scheme 1.



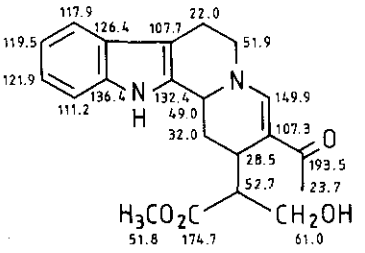
6



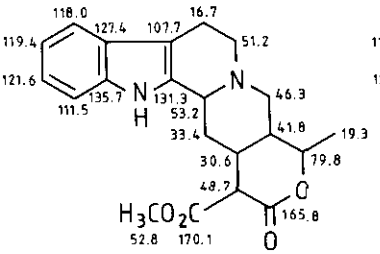
7



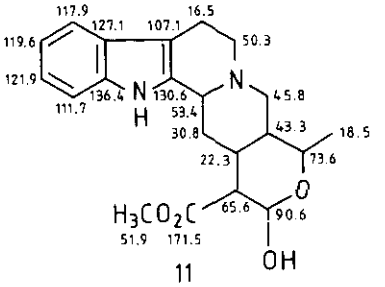
8



9

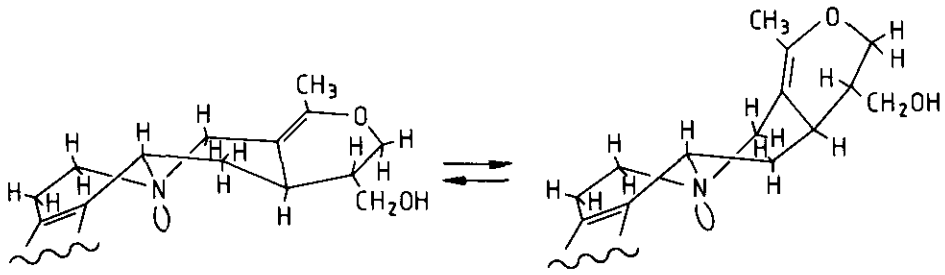


10



11

In the case of compound 7 the above mentioned nitrogen inversion and cis-decalin type ring interconversion between rings C and D are in principle possible. However, the ^{13}C NMR shift of C(6) (δ 22.0), in particular, indicates an overwhelming preponderance of the trans C/D ring juncture in the conformational equilibrium. This finding, combined with the known trans C(3)H - C(15)H relationship,[14] points to the predominance of the following conformations (where ring D is in modified boat conformations) for compound 7.



The behaviour of compound 5 was also investigated in the presence of $NaBH_4$. Under strictly neutral conditions only the ester functions were reduced, totally (8) or partially (9), confirming thereby the stability of the vinylogous amide system under the used conditions. Under acidic conditions (CH_3COOH), however, the corresponding iminium ion was formed in the first stage of the reaction. The thus formed iminium ion and the normal keto function were both then reduced, enabling a further reaction of the formed alcohol to yield lactone 10. No further reduction of the lactone could be observed in acidic media. However, when the solution was neutralised by the addition of excess methanol followed by addition of $NaBH_4$, the lactonic carbonyl function was reduced to afford 11 (see Experimental). Polyphosphoric acid treatment of 11 finally yielded 12 in nearly quantitative yield. Thus, a new short stereoselective total synthesis of (±)-3-iso-19-epi-ajmalicine 12[9] was accomplished.[15]

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 700 Spectrophotometer using liquid film between NaCl crystals. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}) using polystyrene calibration. Bands yielding structural information are reported. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (compounds 8, 9, 10 and 11) or CD_3OD (compounds 6 and 7) (TMS as internal standard δ=0) on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS where s, d, t, q and m

designate singlet, doublet, triplet, quartet and multiplet, respectively. Coupling constants J are given in Hz. Mass spectrometry was performed on a Jeol DX 303/DA 5000 instrument.

For column chromatography, Aluminium oxide Merck (act. II-III) and Silica Woelm TSC were used. TLC plates were coated with either Silica gel 60 $PF_{254+366}$ or Aluminium oxide $PF_{254+366}$, both from Merck. Dragendorff-Munier reagent was used to locate reaction components.

Compound 5

Dimethyl malonate (400 mg, 3.0 mmol, 0.35 ml) was added during 0.5 h to a suspension of NaH (100 mg, 4.16 mmol) and 18 ml of dry solvent (8 ml of THF + 10 ml of DME). The mixture was stirred under nitrogen for 0.5-1 h. Salt 4[14] (500 mg, 1.45 mmol) was added slowly at -15°C and the temperature was gradually allowed to reach rt (3-5 h). The solvents were evaporated and methanol (50 ml) presaturated with dry HCl gas was added. Stirring was continued for 20 h. The solution was then slowly poured into a suspension of $NaHCO_3$ in dichloromethane. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum to give essentially pure 5. Y: 227 mg (40%). Mp 245-248°C. Analytical data (ir, pmr, cmr, ms) were identical with those given in the literature.[14]

Compounds 6 and 7

$LiAlH_4$ (300 mg) and dry THF (20 ml) were refluxed for 15 min (Ar-atm) and then cooled to rt. Diester 5 (45 mg, 0.1 mmol) in THF (10 ml) was added during 1 h and stirring was continued for 2 h at rt and 15 min under reflux. To the cooled solution saturated aq Na_2SO_4 (or abs. MeOH, vide supra) and finally diethyl ether were added. The precipitate formed was washed with ether and the combined extracts were dried over Na_2SO_4. After preparative TLC on silica, compounds 6 and 7 were obtained.

6. Y: 47%, ir 3320 (OH), pmr (CD_3OD) 2.02 (3H, s, CH_3), 2.50 (1H, dd, H-21 ax), 3.13 (1H, dd, H-21 eq), 3.65 (4H, m, CH_2-O-, CH_2OH), 4.49 (1H, dm, H-3), 6.7-7.5 (4H, m, arom. H), 10.40 (1H, br s, NH), m/z 342 (M^+, 100%), 324, 293, 281, 251, 223, 184, 170, 169, 156. Found 342.1936 (mass spectrometry). Calc. for $C_{20}H_{26}O_3N_2$: 342.1944.

7. Y: 17%, ir 3320 (OH), pmr (CD_3OD) 1.93 (3H, s, CH_3), 3.65 (4H, CH_2-O-, CH_2OH), 6.9-7.5 (4H, m, arom. H), m/z 324 (M^+, 100%), 293, 281, 265, 251, 223, 184, 170, 169, 156. Found 324.1829 (mass spectrometry). Calc. for $C_{20}H_{24}O_2N_2$: 324.1838.

Compounds 8 and 9

Compound 5 (150 mg, 0.38 mmol) was dissolved in 25 ml of abs. ethanol. $NaBH_4$ (500 mg, 13 mmol) was added and stirring was continued under argon for 6 h. Thereafter 2N HCl was added and the mixture was extracted several times with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4 and evaporated to dryness. After preparative TLC on silica, two main products, 8 and 9, were obtained.

8. Y: 25 mg (20%), ir 3300 (OH), 1630 (C=O), pmr 2.26 (3H, s, $COCH_3$), 7.05-7.40 (4H, m, arom. H), 7.69 (1H, s, H-21), 9.02 (1H, br s, NH), m/z 340 (M^+), 322, 265, 263 (100%), 221, 170, 169, 156, 143. Found: 340.1780 (mass spectrometry). Calc. for $C_{20}H_{24}O_3N_2$: 340.1788.

9. Y: 20 mg (15%), ir 3350 (OH), 1720 (CO_2CH_3), 1630 (C=O), pmr 2.21 (3H, s, $COCH_3$), 3.61 (3H, s, CO_2CH_3), 7.06-7.39 (4H, m, arom. H), 7.52 (1H, s, H-21), 9.14 (1H, br s, NH), m/z 368 (M^+), 350, 325, 265 (100%), 263, 221, 170, 169, 156, 143. Found: 368.1729 (mass spectrometry). Calc. for $C_{21}H_{24}O_4N_2$: 368.1737.

Compound 10

Compound 5 (209 mg, 0.53 mmol) was dissolved in glacial acetic acid (40 ml). $NaBH_4$ (2.1 g, 55 mmol) was added during 1.5 h while the mixture was cooled in a cold water bath. Stirring was continued for 5 h. The mixture was then neutralised with $NaHCO_3/CH_2Cl_2$, the inorganic salts were filtered off and the dried filtrate was evaporated under vacuum. After purification of the crude product through a column of alumina (Woelm TSC), compound 10 was obtained. Mp 205-206°C (lit. 203°C dec[17], 208-211°C[14]). Y: 38% (contaminated with a small amount of another isomer). Ir 1730-1700 (C=O, ester + lactone), pmr 1.48 (3H, d, J = 7.0 Hz, CH_3), 3.80 (3H, s, CO_2CH_3), 4.40 (1H, br, H-3), 7.01-7.50 (4H, m, arom. H), 8.23 (1H, br s, NH), m/z 368 (M^+, 100%), 309, 251, 223, 184, 170, 169, 156, 143. Found: 368.1739 (mass spectrometry). Calc. for $C_{21}H_{24}O_4N_2$: 368.1737.

Compound 11

Compound 5 (300 mg, 0.76 mmol) was dissolved in glacial acetic acid (40 ml), $NaBH_4$ (2.5 g, 65 mmol) was added during 45 min and stirring was continued for 3 h. Methanol (100 ml) and $NaBH_4$ (1.1 g, 29 mmol) were added. The mixture was stirred for 20 h. Water was then added and methanol and the methyl acetate formed were evaporated. The rest was neutralised by pouring the mixture into a suspension of $NaHCO_3$ in CH_2Cl_2. After usual workup and preparative TLC (silica, 10% MeOH/$CHCl_3$), 134 mg (48%) 11 (contaminated with a small amount of the OH-epimer) was obtained. Ir 3300 (OH), 1730 (C=O), pmr 1.17 (3H, d, J = 6.5 Hz, CH_3), 3.74 (3H, s, CO_2CH_3), 7.06-7.53 (4H, m,

arom. H), 8.54 (1H, br s, NH), m/z 370 (M^+, 100%), 369, 352, 339, 225, 223, 184, 169, 156. Found: 370.1896 (mass spectrometry). Calc. for $C_{21}H_{26}N_2O_4$: 370.1894.

Compound 12

Compound 11 (42 mg, 0.11 mmol), ethylene glycol dimethyl ether and 1 drop of polyphosphoric acid were stirred (65°C, Ar-atm) for 1 h. The mixture was neutralised with conc. aq Na_2CO_3 and extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried over Na_2SO_4. The yield of pure 12 was 39 mg (98%). Analytical data (ir, pmr, cmr, ms) were identical with the data given in refs. 13, 14 and 17.

REFERENCES AND NOTES

1. D. Thielke, J.W. Wegener and E. Winterfeldt, Chem. Ber., 1975, 108, 1791.
2. R. Besselièvre, J.-P. Cosson, B.C. Das and H.-P. Husson, Tetrahedron Lett., 1980, 21, 63.
3. W.R. Ashcroft and J.A. Joule, Tetrahedron Lett., 1980, 2341.
4. M. Hämeilä and M. Lounasmaa, Acta Chem. Scand., Ser. B, 1981, 35, 5.
5. L. Calabi, B. Danieli, G. Lesma and G. Palmisano, Tetrahedron Lett., 1982, 2139.
6. I.E. Overman and T.C. Malone, J. Org. Chem., 1982, 47, 5297.
7. P. Rosenmund and M. Casutt, Tetrahedron Lett., 1983, 1771.
8. G. Lesma, G. Palmisano and S. Tollari, J. Chem. Soc., Perkin Trans. I, 1984, 1593.
9. Biogenetic numbering; see J. Le Men and W. Taylor, Experientia, 1965, 21, 508.
10. F. Kröhnke, K. Ellegast and E. Bertram, Liebigs Ann. Chem., 1956, 600, 176 (for earlier applications see refs. 14 and 16).
11. M. Hämeilä and M. Lounasmaa, Heterocycles, 1982, 19, 1517.
12. M. Lounasmaa and M. Hämeilä, Tetrahedron, 1978, 34, 437.
13. M. Lounasmaa and S.-K. Kan, Tetrahedron, 1980, 36, 1607. See also E. Yamahaka, N. Saito, Y. Suzuki and S. Sakai, Chem. Pharm. Bull., 1982, 30, 2068, Note 16.
14. E. Wenkert, C.-J. Chang, H. Chawla, D. Cochran, E. Hagaman, J. King and K. Orito, J. Am. Chem. Soc., 1976, 98, 3645.
15. M. Lounasmaa and R. Jokela, Tetrahedron Lett., in press.
16. M. Lounasmaa and A. Koskinen, Tetrahedron Lett., 1982, 23, 349.
17. E. Winterfeldt, A. Gaskell, T. Korth, H. Radunz and M. Walkowiak, Chem. Ber., 1969, 102, 3558.

Received, 21st April, 1986