A General Strategy for the Synthesis of Ipecac and Heteroyohimbine Alkaloids

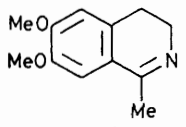
Takeaki Naito, Noriko Kojima, Okiko Miyata, and Ichiya Ninomiya*

Kobe Women's College of Pharmacy, Motoyamakita, Higashinada, Kobe 658, Japan

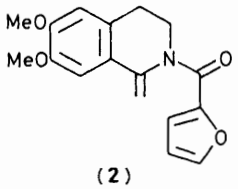
The synthesis of the ester (**6b**) and lactone (**7a**) *via* reductive photocyclisation, kinetically controlled alkylation and acylation, and reductive cleavage of γ-lactone illustrates a new general method for the preparation of the ipecac and heteroyohimbine alkaloids.

Whereas the structural and biosynthetic parallel between the ipecac and heteroyohimbine types of alkaloid has been mentioned,[1,2] only few studies have been devoted to the synthesis of 2,3-disubstituted benzo- or indolo-quinolizine derivatives as common intermediates for the synthesis of both types of alkaloid. We now describe a general strategy applicable to the total synthesis of both types of alkaloid by the efficient synthesis of compounds (**6a—d**) and (**7a** and **b**) *via* the furanoquinolizine (**3a**) as a common precursor. The ester (**6b**) is a known key intermediate for the total synthesis of emetine[3,4] and the lactone (**7a**) is an essential fragment of the C, D, and E rings of the well known key intermediate for the total synthesis of ajmalicine and other heteroyohimbine alkaloids.[5—8] The overall strategy is based on three key steps: reductive photocyclisation of enamides, kinetically controlled alkylation or acylation α to a lactam carbonyl group, and reductive cleavage of a γ-lactone ring.

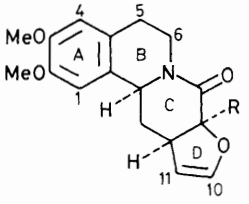
Acylation of the isoquinoline (**1**) with furan-2-carbonyl chloride in the presence of triethylamine gave the enamide (**2**) in 98% yield. Reductive photocyclisation[9] of the enamide (**2**) in the presence of sodium borohydride in MeCN–MeOH (9:1) at 5—10 °C proceeded smoothly to give the furanoquinolizine (**3a**) in 77% yield [δ_H ($CDCl_3$) 4.84 (d, *J* 10.5 Hz, 8a-H), 4.64 (br. dd, *J* 11.5 and 2.5 Hz, 12a-H), and 3.37 (m, 11a-H)]. The C/D-*cis* fusion of the lactam (**3a**) was deduced from comparison of the coupling constant (*J* 10.5 Hz) between 8a- and 11a-H with those (*J* 10—11 Hz) of analogous *cis*-compounds[10] which were also prepared by reductive photocyclisation of enamides having a furan ring and firmly characterised by both spectral and chemical means. Lithiation of (**3a**) with lithium di-isopropylamide in tetrahydrofuran at −78 °C followed by quenching with either ethyl iodide or acetic anhydride led to the formation of the corresponding 8a-ethyl (**3b**) or 8a-acetyl derivatives (**3c**) in 86 or 76% yield respectively [(**3b**) δ_H ($CDCl_3$) 3.13 (dddd, *J* 12, 5.5, 3, and 1.5 Hz, 11a-H), 1.94 (q, *J* 7.5 Hz, CH_2Me), and 0.96 (t, *J* 7.5 Hz, Me); (**3c**) δ_H ($CDCl_3$) 3.64 (dddd, *J* 12.5, 5.5, 3, and 2 Hz, 11a-H) and 2.49(s, COMe)]. The stereochemistry of both products (**3b** and **c**) thus obtained was deduced from comparison of their n.m.r. spectra, particularly signals due to protons



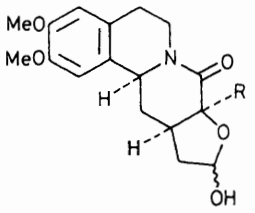
(1)



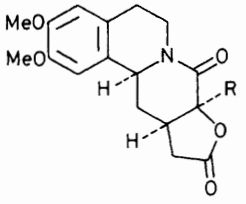
(2)



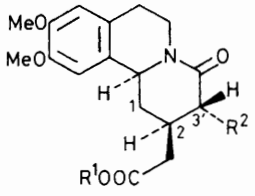
(3) a; R = H
b; R = Et
c; R = Ac



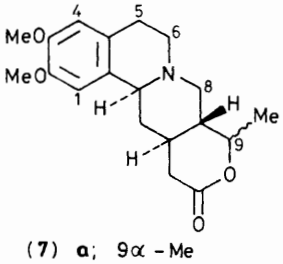
(4) a; R = Et
b; R = Ac



(5) a; R = Et
b; R = Ac



(6) a; R^1 = H, R^2 = Et
b; R^1 = Me, R^2 = Et
c; R^1 = H, R^2 = Ac
d; R^1 = Me, R^2 = Ac



(7) a; 9α-Me
b; 9β-Me

in the C- and D-rings, with the spectrum of the starting lactam (**3a**). These lactams (**3b** and **c**) both contain a versatile benzoquinolizine nucleus bearing a C_2-unit at both the 2- and 3-positions appropriate for a key precursor for conversion into ipecac alkaloids such as emetine.

The furanoquinolizine (**3b**) was then converted into the known intermediate,[3,4] the keto-ester (**6b**), as follows. The dihydrofuran (**3b**) was hydrated with 15% sulphuric acid to give the hemiacetal (**4a**) as an epimeric mixture which was then oxidised with pyridinium chlorochromate (PCC) to furnish the γ-lactone (**5a**) in 60% overall yield. Reductive cleavage of the lactone (**5a**) using methods developed for the deoxygenation of alcohols[11] was unsuccessful. However, reduction of (**5a**) with calcium in liquid ammonia[12,13] gave the desired carboxylic acid (**6a**), m.p. 186.5—188 °C (lit.,[3] 187—188 °C) in 62% yield which was converted into the corresponding methyl ester (**6b**), m.p. 54—55 °C (lit.,[3] 56—57 °C) [ν($CHCl_3$) 1735 and 1625 cm^{-1}; δ_H ($CDCl_3$) 4.67 (br. dd, *J* 12 and 4 Hz, 11b-H), 2.56 (dt, *J* 12 and 4 Hz, 1-H_{eq}), 2.37 (m, 2-H), and 1.44 (q, *J* 12 Hz, 1-H_{ax})] with diazomethane. Both the acid (**6a**) and the ester (**6b**) were identical (i.r. spectra) with the authentic samples which are known to be key intermediates[3,4] for the synthesis of emetine.

Similarly, the 8a-acetyl furan (**3c**) was converted into the acetyl lactone (**5b**) *via* the route involving hydration with 15% sulphuric acid–tetrahydrofuran (THF) (quantitatively) followed by oxidation of the resulting hemiacetal (**4b**) with either Me_2SO–Ac_2O (76%) or PCC (51%). Cleavage of the lactone ring in the 8a-acetyl lactone (**5b**) with aluminium amalgam in aqueous ethanolic THF[14] proceeded more smoothly than in the case of the ethyl lactone (**5a**) to afford the desired carboxylic acid (**6c**) in 95% yield. The stereochemistry of the acid (**6c**) was deduced from the spectral data of the corresponding methyl ester (**6d**) [ν($CHCl_3$) 1740—1720 and 1630 cm^{-1}; δ_H ($CDCl_3$) 4.74 (dd, *J* 12 and 5 Hz, 11b-H) and 3.46 (d, *J* 11 Hz, 3-H)].

Among conditions investigated for chemoselective reduction of the acetyl and lactam groups, treatment of the acetyl ester (**6d**) with diborane in THF at −10 °C for 1 h afforded a mixture of two amino lactones (**7a**) (15%) and (**7b**) (40%) which were readily separated by p.l.c. and characterised by their n.m.r. spectra [(**7a**) δ_H ($CDCl_3$) 4.76 (br. qd, *J* 7 and 4 Hz, 9-H) and 1.36 (d, *J* 7 Hz, CH*Me*); (**7b**) δ_H ($CDCl_3$) 4.23 (dq, *J* 10 and 6 Hz, 9-H), 1.88 (br. qt, *J* 11 and 5 Hz, 12a-H), 1.68 (br. qd, *J* 11 and 4 Hz, 8a-H), and 1.42 (d, *J* 6 Hz, CH*Me*)]. These two lactones (**7a** and **b**) contain the essential tricyclic skeletal structure of the C, D, and E rings of heteroyohimbine alkaloids such as ajmalicine[5] and corynantheine.[6]

Thus, we have established a new useful synthetic method for preparing a common potential intermediate for ipecac and heteroyohimbine alkaloid synthesis.

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