A HIGHLY STEREOSELECTIVE SYNTHESIS OF (±)-NORMALINDINE

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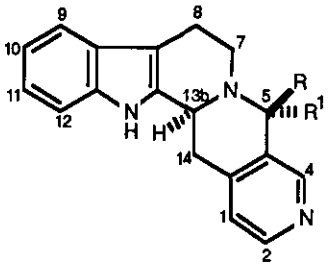
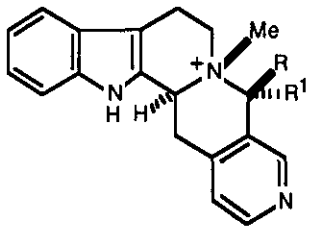
Abstract — Methyllithium reacted with (±)-dihydronaucléfine (**5**) to form, upon alkaline processing, a mixture of compounds, one having an exocyclic methylene group at C-5 (**9**) and the other, a C-5—N iminium compound having a methyl group at C-5 (**10**). Treatment of this mixture with either hydrogen over palladium catalyst or cyanoborohydride provided (±)-normalindine [(±)-**1**] in a highly stereoselective and efficient manner.

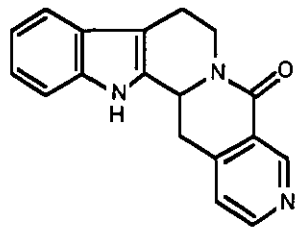
A number of indole alkaloids containing the indolo[2':3',3:4]pyrido[1,2-*b*][2,7]naphthyridine ring system have been isolated[1] and synthesized.[2] They generally occur as lactams, except for the recently isolated alkaloids normalindine (**1**), norisomalindine (**2**), malindine (**3**), and isomalindine (**4**), which have a methyl group at C-5. The latter compounds were isolated from *Strychnos johnsonii* [3] (**1** and **2**), *Strychnos decussata* [4] (**3**), and *Strychnos usambarensis* [5] (**4**). We now describe an efficient synthesis of (±)-**1** by way of (±)-dihydronaucléfine (**5**).[6]



1 R=Me; R^1=H
2 R=H; R^1=Me

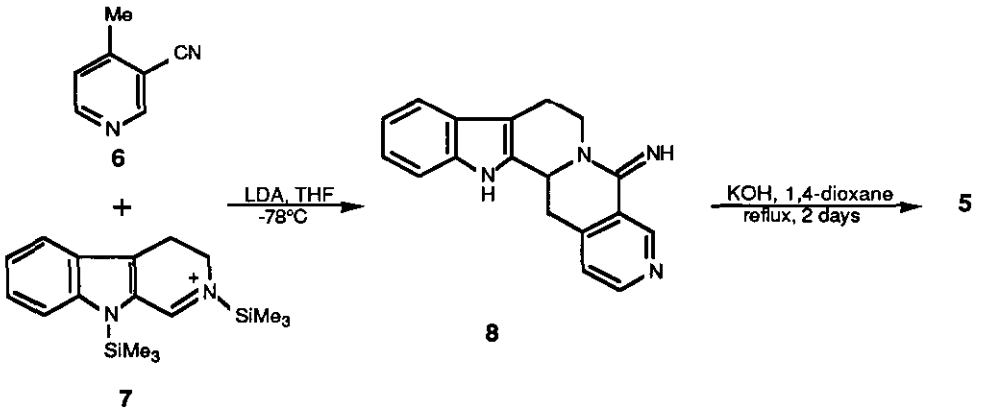


3 R=Me; R^1=H
4 R=H; R^1=Me



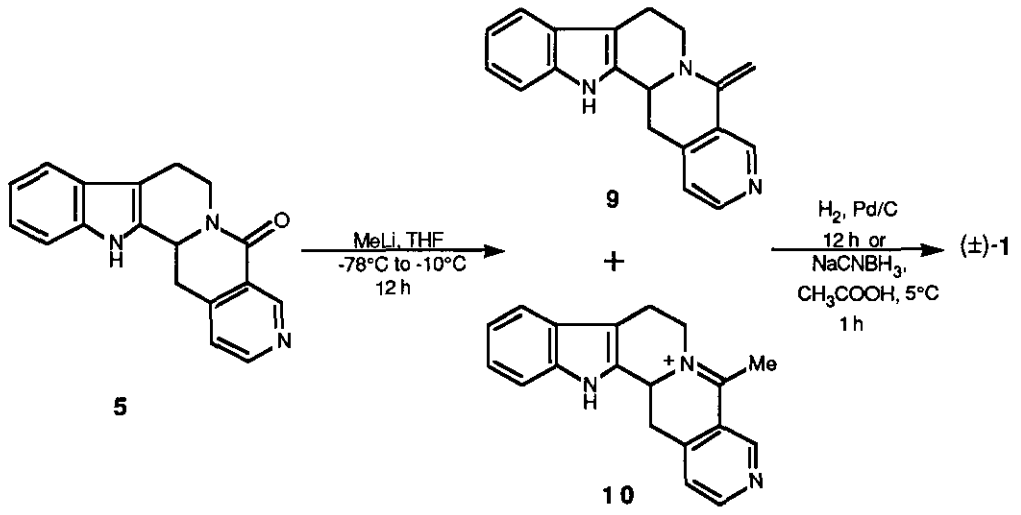
5

(±)-Dihydronaucléfine (**5**) was obtained in high yield by a recently reported procedure.[7] Thus, addition of the lithiated derivative of 3-cyano-4-methylpyridine (**6**) to trimethylsilyl trifluoromethanesulfonate-activated 3,4-dihydro-β-carboline (**7**) gave the amidine (**8**) in 78% yield. Alkaline hydrolysis of **8** then afforded the lactam (**5**) (see Scheme 1) in 89% yield.



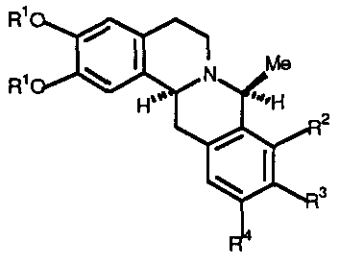
Scheme 1

The addition of methyllithium to the lactam (**5**) in THF yielded a mixture of two products (^{1}H nmr), namely compound (**9**), having an exocyclic methylene group at C-5, and the C-5—N iminium compound (**10**) (see Scheme 2), in the ratio of 8.2:1, respectively; the combined yield of these crude products was 95%.

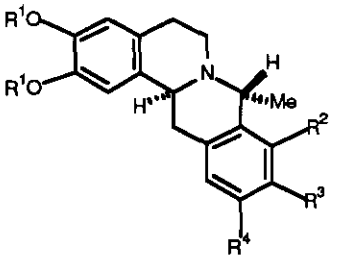


Scheme 2

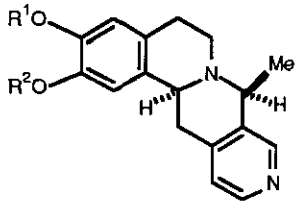
Without isolation, these intermediates were hydrogenated over palladium catalyst to form (±)–**1** in 48% overall yield. The crude reaction product did not show any evidence (tlc, ^{1}H nmr) of the compound epimeric at C-5, namely (±)-norisomalindine [(±)-**2**]. In another experiment, the crude reaction mixture was taken up in glacial acetic acid and treated with sodium cyanoborohydride at 5°C. Again, (±)-normalindine was obtained as the sole product in 44% overall yield. This methodology is analogous to that developed for the conversion of various 8-oxoberberines into 8-methylberberines[8] (**11**—**14**, see Figure 1) and their aza analogs[8] (**15**—**18**, see Figure 1).



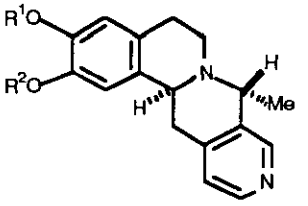
11 R^1=Me; R^2=H; R^3=R^4=OMe
(Coralydine)
13 R^1=CH_2; R^2=R^3=OMe; R^4=H
(8β-Methylcanadine)



12 R^1=Me; R^2=H; R^3=R^4=OMe
(*O*-Methylcorytenchirine)
14 R^1=CH_2; R^2=R^3=OMe; R^4=H
(8α-Methylcanadine)



15 R^1=R^2=Me
(8-epi-*O*-Methylalamaridine)
17 R^1=Me; R^2=H
(8-epi-Alamaridine)

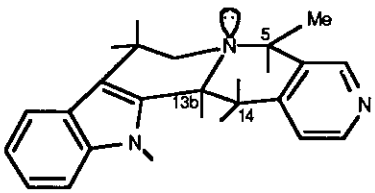


16 R^1=R^2=Me
(*O*-Methylalamaridine)
18 R^1=Me; R^2=H
(Alamaridine)

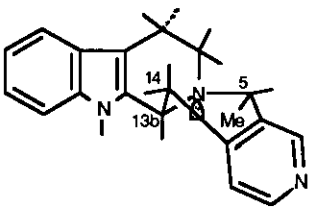
Figure 1

(±)-Normalindine [(±)-**1**] has been assigned the *trans*-quinolizidine ring system (Structure I, see Figure 2) on the basis of ^{1}H nmr and ir spectral data,[3,9] whereas the C-5 epimer, namely (±)-norisomalindine [(±)-**2**], has been assigned the *cis*-quinolizidine ring system; in the latter case, conformation II has been shown to be preferred over conformation III on the basis of the values of

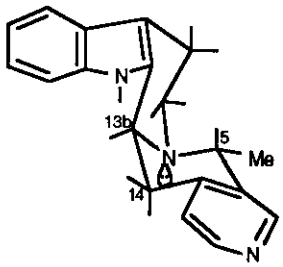
$J_{13b,14ax}$ (10 Hz) and $J_{13b,14eq}$ (4 Hz). In the case of the *cis*-stucture III, the vicinal dihedral angles involving H-13*b*, H-14ax and H-13*b*, H-14eq are each ~55°, a value inconsistent with the observed doublet of doublets. Examination of Dreiding models of **9** or **10** suggests that there should be little steric difference between attack from either the *re*– [leading to (±)-**1**] or the *si*–face [leading to (±)-**2**]. Thus, the high diastereoselectivity observed in the course of this reaction appears to be a consequence of the greater product stability of the *trans*-quinolizidine ring relative to the *cis*-quinolizidine ring. This hypothesis assumes a late-stage transition state. A stereoselective reduction of this type was utilized by us in the asymmetric synthesis of coralydine.[10]



I
trans–Quinolizidine
[(±)-Normalindine]



II
cis–Quinolizidine
[(±)-Norisomalindine]



III
cis–Quinolizidine
[(±)-Norisomalindine]

Figure 2

As indicated above, assignment of (±)-**1** as having a *trans*-quinolizidine ring fusion was based upon spectral evidence. For instance, the presence of Bohlmann bands in the ir spectrum of (±)-**1** (2740–2840 cm^{-1}) is typical of a *trans*-quinolizidine system.[11] These bands were absent in the spectrum of (±)-**2**.[3,9] Also diagnostic of the configuration and conformation of (±)-**1** are the values of the ^1H nmr chemical shifts of the signals of H-13*b*, H-5, and the methyl group attached to C-5, and of $J_{H\text{-}5,Me}$, relative to the corresponding values for (±)-**2**. It has been noted[12] that, for various 8-methylberberines and 8-methylazaberberines, the signals of the relevant protons vary in a

predictable manner depending on the configuration and conformation of the quinolizidine ring. A comparison of the relevant ^{1}H nmr data for the isomeric pair of compounds discussed in this study with data selected from other studies further substantiates the proposed *trans*-quinolizidine structure for (±)-**1**. These data are given in Table 1.

Table 1. Correlation between stereochemistry and ^{1}H nmr signals of various alkaloids containing a quinolizidine ring system

Configuration of quinolizidine ring	Compound	^{1}H nmr parameter[a] δ C-Me	δ HC-Me	δ R_2CHN	$J_{C\text{-}Me,H}$ (Hz)
trans	Normalindine [(±)-**1**][b]	1.59	3.83	3.79	6.3
	Coralydine (**11**)[10,12]	1.54	3.72	3.71	6.2
	8β-Methylcanadine (**13**)[8]	1.50	3.81	3.53	6.1
	8-epi-*O*-Methylalamaridine (**15**)[8]	1.60	3.83	3.75	6.4
	8-epi-Alamaridine (**17**)[8]	1.60	3.79	3.71	6.4
cis	Norisomalindine (**2**)[3,9]	1.42	4.40	4.34	7.0
	O-Methylcorytenchirine (**12**)[12]	1.40	4.10	4.24	6.6
	8α-Methylcanadine (**14**)[8]	1.37	4.30	4.19	6.7
	O-Methylalamaridine (**16**)[8]	1.42	4.23	4.27	6.9
	Alamaridine (**18**)[8]	1.41	4.24	4.21	6.9

[a]For a solution in $CDCl_3$. [b]Values obtained in this study.

The spectroscopic and physical data obtained for (±)-normalindine [(±)-**1**] are identical with the data provided by Maiti *et al.* [9] and Massiot *et al.* [3] Attempts have been made to methylate (±)-**1** directly to form (±)–malindine [(±)-**3**], however, methylation at the pyridine nitrogen occurred in most cases. Attempts to circumvent this course by way of selective protection of the pyridine nitrogen (for instance, as its benzyl salt), and subsequent methylation and deprotection, have also been unsuccessful. This observation has been noted by others.[13]

EXPERIMENTAL

General Methods. The ^1H nmr spectra were recorded at 200 and 400 MHz on Bruker AC-F200 and AM-400 spectrometers, respectively. The samples were dissolved in $CDCl_3$ or CD_3OD (as indicated). The chemical shifts are quoted in parts per million (ppm) downfield relative to the internal standard, tetramethylsilane (δ scale). The ^{13}C nmr spectra were recorded at 100.6 MHz on a Bruker A-400 spectrometer. Chemical shifts are reported in ppm with reference to $CDCl_3$ (77.00 ppm). The multiplicity of signals was determined by JMOD experiments. The numbering system used for both ^{13}C and ^1H nmr assignments refers to normalindine numbering, as shown in the text. Mass spectra were recorded on a VG-7070E instrument (ei-ms 70 eV; ci-ms 70 eV ionizing potential, using ether as reagent gas). The peak intensities are given as a percent of the base peak (100%) intensity. High-resolution mass spectra (hrms) were recorded on the above instrument. The ir spectra were determined using KBr disks on a BOMEM MB-120 ft-ir spectrophotometer. The uv–visible spectra were measured on a CARY-3 double beam spectrophotometer in CH_3OH. Melting points were determined using a Fisher—Johns apparatus, and are uncorrected.

All reaction flasks and equipment were dried at 140°C for at least 12 h and assembled hot while cooling under a stream of argon. Tetrahydrofuran (THF) was distilled over sodium—benzophenone ketyl under an argon atmosphere just prior to use. Preparative layer chromatography (ptlc) separations were performed on PSC-Fertigplatten Kieselgel 60 F_{254} precoated silica gel plates (Merck 5717) of 2 mm thickness.

Treatment of (±)-dihydronaucléfine (**5**) with methyllithium

To a stirred solution of (±)-dihydronaucléfine (**5**) (115 mg, 0.398 mmol) in dry THF (15 ml) at -78°C was added a solution of MeLi (1.4 M in ether; 2.84 ml, 3.98 mmol) under an argon atmosphere. The mixture was stirred at -78°C for 1 h, the temperature was raised to -10°C and the stirring was continued a further 12 h. The excess of MeLi was destroyed by addition of saturated Na_2CO_3 (aq.) (1 ml) and the mixture was diluted with $CHCl_3$ (50 ml), filtered, and the residue was washed several times with $CHCl_3$. The combined $CHCl_3$ extracts were washed with saturated NaCl (aq.) (20 ml). The aqueous layer was extracted with $CHCl_3$ (20 ml) and the combined organic layers were dried over $MgSO_4$ (anhydrous). Removal of the solvent *in vacuo* provided a red powder (110 mg; 95%

yield) which was identified by ^{1}H nmr spectroscopy as a 8.2:1 mixture of the C-5 exocyclic methylene and iminium salt compounds (**9** and **10**, respectively).

For purposes of characterization, the exocyclic methylene compound (**9**) was isolated by ptlc [9:1 (v/v) ether—methanol]. It was then converted into the iminium salt (**10**) by treatment of a methanolic solution of **9** with 48% HBr (aq.). The reaction mixture was stirred for 5 min at room temperature and then evaporated to dryness *in vacuo* to give a quantitative yield of the quaternary bromide which was crystallized from methanol—ethyl acetate.

(±)-5,7,8,13,13*b*,14-Hexahydro-5-methyleneindolo[2',3':3,4]pyrido[1,2-*b*][2,7]naphthyridine (**9**) has R_f [1:9 (v/v) methanol—ether] 0.35; ^{1}H nmr (200 MHz, $CDCl_3$): δ 8.96 (1H, s, H-4), 8.68 (1H, br s, exchangeable, NH), 8.33 (1H, d, *J* = 5.0 Hz, H-2), 7.55 (1H, d, *J* = 8.5 Hz, H-9 or H-12), 7.02–7.36 (3H, m, H-10, H-11, H-9 or H-12), 7.00 (1H, d, *J* = 5.0 Hz, H-1), 5.06 (1H, d, *J* = 1.8 Hz, $=CH_2$), 4.48 (1H, d, *J* = 1.8 Hz, $=CH_2$), 4.28 (1H, app d, *J* = 11.3 Hz, H-13*b*), 3.65–3.92 (2H, m, H-8eq, H-14eq), 3.23 (1H, dd, *J* = 3.5, 16.4 Hz, H-7ax), 2.90–3.15 (3H, m, H-7eq, H-8ax, H-14ax); ms (ci) *m/z* (relative intensity): 288 (M^++1).

(±)-8,13,13*b*,14-Tetrahydro-5[7*H*]-methylindolo[2',3':3,4]pyrido[1,2-*b*][2,7]naphthyridinium bromide (**10**) has R_f [15:85 (v/v) methanol—methylene chloride] 0.62; mp 215-220°C (dec.); ^{1}H nmr (400 MHz, CD_3OD): δ 9.63 (1H, s, H-4), 9.09 (1H, d, *J* = 5.4 Hz, H-2), 8.16 (1H, d, *J* = 5.4 Hz, H-1), 7.40 (1H, d, *J* = 7.8 Hz, H-9 or H-12), 7.35 (1H, d, *J* = 7.8 Hz, H-9 or H-12), 7.12 (1H, t, *J* = 7.8 Hz, H-10 or H-11), 7.03 (1H, t, *J* = 7.8 Hz, H-10 or H-11), 5.16 (1H, app d, *J* = 12.6 Hz, H-13*b*), 4.09 (1H, dd, *J* = 5.1, 17.0 Hz, H-7ax), 4.01 (1H, ddd, *J* = 5.1, 12.6, 17.0 Hz, H-7eq), 2.96–3.57 (4H, m, H-8, H-14), 3.26 (3H, s, C-5–Me); ms (ei) *m/z* (relative intensity): 288 [(M^+), 8], 287 (9), 273 (12), 272 (24), 84 (100); ms (ci) *m/z* (relative intensity): 289 (M^++1).

Reduction of **9** and **10** using $NaCNBH_3$

A 40-mg portion of the crude material obtained above was dissolved in glacial acetic acid (2 ml) and the solution was treated with an excess of $NaCNBH_3$ at 5°C. After being stirred for 1 h at this temperature, the mixture was evaporated to dryness *in vacuo* and basified to pH 10 using concentrated NH_4OH solution (aq.). The oil was thoroughly extracted with $CHCl_3$ (5 X 10 ml) and the combined $CHCl_3$ extracts were washed with saturated NaCl (aq.) (20 ml), dried over $MgSO_4$ (anhydrous) and the solvent was removed *in vacuo*. The crude material was purified by ptlc [9:1

(v/v) ether—methanol] to furnish (±)-normalindine [(±)-**1**] (18.3 mg, 44% overall yield from **5**) as pale-red crystals.

Catalytic hydrogenation of **9** and **10**

The crude material (70 mg) obtained from the reaction with MeLi was taken up in 95% ethanol (10 ml) and three drops of concentrated NH_4OH solution (aq.) were added. The solution was transferred to a Parr flask and 10% Pd on activated carbon (80 mg) was added. This mixture was treated with hydrogen (4 atm) at room temperature for 12 h and the catalyst was removed by filtration. Removal of the solvent *in vacuo* and purification by ptlc [9:1 (v/v) ether—methanol] afforded (±)-normalindine [(±)-**1**] (35 mg, 48% overall from **5**) as pale-red crystals.

(±)-Normalindine {(5S*,13*b*S*)-5,7,8,13,13*b*,14-Hexahydro-5-methylindolo[2',3':3,4]pyrido[1,2-*b*][2,7]naphthyridine} [(±)-**1**] has R_f [1:9 (v/v) methanol—ether] 0.32; mp 195-198°C; ir (KBr) υ: 3400, 3183, 2921, 2840, 2810, 2740, 1637, 1590, 1453, 1302, 1057, 741 cm^{-1}; uv (methanol) λ_{max}: 290, 282, 268, 223 nm; ^1H nmr (400 MHz, $CDCl_3$): δ 8.50 (1H, s, H-4), 8.35 (1H, d, *J* = 5.0 Hz, H-2), 7.85 (1H, br s, exchangeable, NH), 7.52 (1H, d, *J* = 7.8 Hz, H-9 or H-12), 7.34 (1H, d, *J* = 7.8 Hz, H-9 or H-12), 7.17 (1H, t, *J* = 7.8 Hz, H-10 or H-11), 7.11 (1H, t, *J* = 7.8 Hz, H-10 or H-11), 7.07 (1H, d, *J* = 5.0 Hz, H-1), 3.83 (1H, q, *J* = 6.3 Hz, H-5), 3.79 (1H, app d, *J* = 11.6 Hz, H-13*b*), 3.51–3.62 (2H, m, H-8ax, H-14eq), 2.89–3.09 (2H, m, H-7eq, H-14ax), 2.81 (1H, app d, *J* = 15.5 Hz, H-8eq), 2.55 (1H, dt, *J* = 3.8, 11.6 Hz, H-7ax), 1.59 (1H, d, *J* = 6.3 Hz, CH-Me); ^{13}C nmr (100.6 MHz, $CDCl_3$): δ 148.4 (C-4), 146.3 (C-2), 142.8 (C-14*a*), 136.4 (C-4*a*), 136.0 (C-12*a*), 134.2 (C-13*a*), 127.0 (C-8*b*), 123.1 (C-1), 121.7 (C-11), 119.5 (C-10), 118.3 (C-9), 110.8 (C-12), 109.0 (C-8*a*), 57.1 (C-5), 54.9 (C-13*b*), 48.6 (C-7), 34.7 (C-14), 22.2 (CH-Me), 21.9 (C-8); ms (ei) *m/z* (relative intensity): 289 [(M^+), 58], 288 (51), 287 (25), 274 (64), 169 (71), 89 (100); ms (ci) *m/z* (relative intensity): 290 (M^++1); hrms (ei) *m/z* (M^+) calcd for $C_{19}H_{19}N_3$ 289.1579; found 289.1574.

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6. In each of the cases of racemic mixtures, only one enantiomer is shown. In the cases of **1**—**4**, the structures depict only the relative stereochemistry; the absolute stereochemistry has not been established.

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