

ASYMMETRIC SYNTHESIS OF (*R*)-(+)-NORANICANINE

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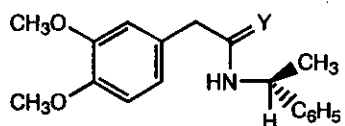
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**Abstract** - - Optically active (*R*)-(+)-noranicanine (1) was synthesized *via* stereoselective reduction of the corresponding iminium ion possessing a chiral auxiliary by Polniaszek's method.

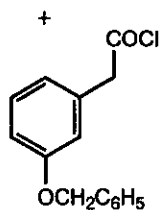
The 1-benzylisoquinoline alkaloid, (*R*)-(+)-noranicanine, which was isolated from *Aniba canelilla* H.B.K. (Lauraceae),<sup>1,2</sup> was assigned the structure, (*R*)-1-(3-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1) on the basis of spectral evidence and synthesis of the racemate. We describe here an asymmetrical synthesis of (*R*)-(+)-noranicanine *via* stereoselective reduction of the corresponding iminium ion possessing a chiral auxiliary by Polniaszek's method.<sup>3,4</sup>

The standard Schotten-Baumann reaction of (*R*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-1-phenylethylamine (3) and acid chloride (4) derived from 3-benzyloxyphenylacetic acid<sup>5</sup> afforded an 87.2 % yield of the amide (5), which was then transformed into the corresponding iminium ion possessing a chiral auxiliary (6) through the Bischler-Napieralski reaction. Stereoselective reduction of this compound (6) with sodium borohydride in methanol at -78°C afforded the (*R*)-*N*-substituted tetrahydroisoquinoline (7) in high yield based on the amide (5). In this reduction, the diastereoisomer of 7 was not isolated. *N*- And *O*-debenzylation by catalytic hydrogenation of 7 afforded (*R*)-(+)-noranicanine (1). All spectral data of this synthetic compound were identical with those of the naturally occurring (*R*)-(+)-noranicanine (1)<sup>1,2</sup> and the respective specific rotation were identified.

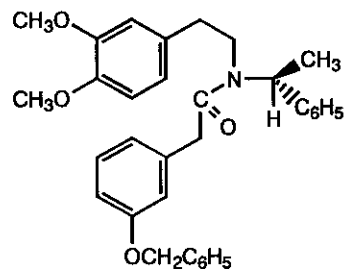
Consequently, the structure of (*R*)-(+)-noranicanine can be unequivocally



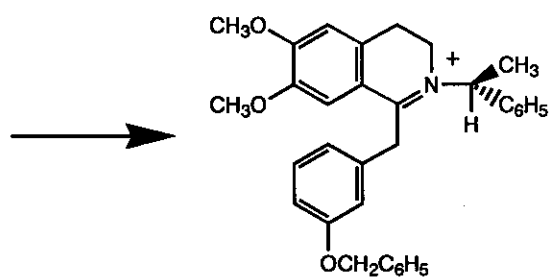
(2) Y = O    (3) Y = H<sub>2</sub>



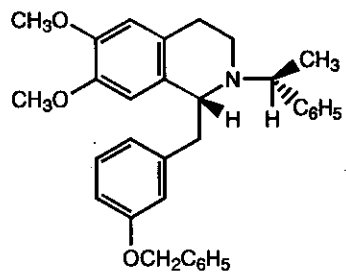
(4)



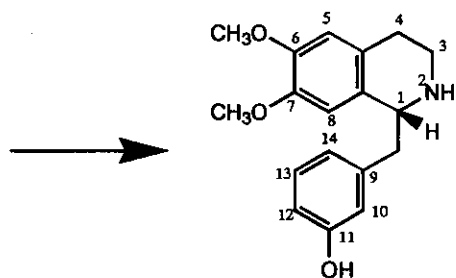
(5)



(6)



(7)



(1)

represented by formula (1). The natural base ( $[\alpha]_D +36.0^\circ$ ,  $\text{CHCl}_3$ ) was not crystallized because it was a minor product, but the synthetic compound (1) was afforded as colorless needles, mp  $182^\circ\text{C}$ ,  $[\alpha]_D +34.3^\circ$ . This synthetic route by Polniaszek *et al.* is proved to be one of the suitable method for obtaining optically active 1-benzylisoquinoline alkaloids.

#### EXPERIMENTAL

All melting points were determined using a Yanagimoto microscopic hot-stage apparatus and are uncorrected.  $^1\text{H-Nmr}$  spectra were obtained on a JEOL FX-200 spectrometer in  $\text{CDCl}_3$  solution with tetramethylsilane as an internal standard. Ir and uv spectra were recorded on a Shimadzu IR-435 and Shimadzu UV-160 spectrophotometer, respectively. Ms were obtained using a JEOL JMS DX-303 EIms spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter. All organic extracts were dried over anhydrous  $\text{MgSO}_4$ . Column chromatography and preparative thin layer chromatography (tlc) were carried out on Wakogel C-200 (100~200 mesh) and with silica gel 60F<sub>254</sub> (Merck).

(*R*)-*N*-(1-Phenyl)ethyl-2-(3,4-dimethoxyphenyl)acetamide (2) An ether solution (180 ml) of 3,4-dimethoxyphenylacetyl chloride prepared from the corresponding phenylacetic acid (11.8 g, 0.06 mol) and excess thionyl chloride (30 ml, 0.42 mol) by the usual method, and 180 ml of 5% aq.  $\text{Na}_2\text{CO}_3$  solution were alternately added dropwise to an ether solution (180 ml) of (*R*)- $\alpha$ -phenylethylamine (9.28 ml, 0.073 mol), with stirring at  $0\sim 5^\circ\text{C}$ . Stirring was continued for 1 h at the same temperature, and the precipitate was filtered off and dissolved in  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  solution was washed successively with 10% aq. HCl solution, 5% aq. NaOH solution and water, and dried. Removal of the solvent by evaporation left a residue, which was recrystallized from ethanol-hexane to furnish the optical active acetamide (2), colorless needles, mp  $101\sim 102^\circ\text{C}$  (17.6 g, 97.8%).  $[\alpha]_D^{25} -17.4^\circ$  ( $c = 0.29$ ,  $\text{CHCl}_3$ ); uv  $\lambda_{\text{max}}^{\text{EtOH}}$  nm (log  $\epsilon$ ): 204(4.71); ir  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3400(NH), 1675(C=O);  $^1\text{H-nmr}$   $\delta$ : 1.40 (3H, d,  $\text{CH}_3$ ,  $J = 7.0$  Hz), 3.52 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.84, 3.88 (3H $\times$ 2, s,  $\text{OCH}_3\times 2$ ), 5.13 (1H, m, CH), 5.64 (1H, br., NH), 6.75~6.86 (3H, m, arom.H $\times$ 3), 7.16~7.35 (5H, m, arom.H $\times$ 5); EIms  $m/z$  (rel. intensity): 299( $\text{M}^+$ , 84.0), 151[ $\text{M}^+ - \text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{NHCO}$ , 100], 105[ $\text{M}^+ - (\text{CH}_3\text{O})_2 - \text{C}_6\text{H}_3\text{CH}_2\text{CONH}$ , 32.3]; Anal. Calcd for  $\text{C}_{18}\text{H}_{21}\text{NO}_3$ : C, 72.22; H, 7.07; N, 4.68. Found: C, 72.03; H, 7.15; N, 4.72.

(*R*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenylethylamine (3)  $\text{BF}_3$  etherate (ca.47%, 0.6 ml) and 1.0 M  $\text{BH}_3$ -THF solution (12.0 ml, 0.125 mol) were carefully added dropwise to a solution of the amide (2) (1.42 g, 0.0047 mol) in anhydrous THF (24.0 ml) at room temperature and the mixture was refluxed for 2.5 h under Ar. After the excess reagent was decomposed with 5 N aq. HCl solution (35 ml), most of the solvent was evaporated off *in vacuo*. The aqueous solution was adjusted to pH 13 with 10% aq. NaOH solution, and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with water, dried and evaporated. Residual oil was converted into the hydrochloride salt, which was recrystallized from MeOH-Me<sub>2</sub>CO. Colorless needles, mp 216°C (1.12 g, 73.2%). Anal. Calcd for  $\text{C}_{18}\text{H}_{23}\text{NO}_2 \cdot \text{HCl}$ : C, 67.17; H, 7.52; N, 4.35. Found: C, 67.07; H, 7.64; N, 4.40. The hydrochloride was treated in the usual manner to give an oily free base (3).  $[\alpha]_D^{28} +39.5^\circ$  ( $c=0.56$ ,  $\text{CHCl}_3$ ); uv  $\lambda_{\text{max}}^{\text{EtOH}}$  nm (log  $\epsilon$ ): 203(4.66), 279(sh, 1.71); ir  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3280(NH);  $^1\text{H-nmr}$   $\delta$ : 1.32 (3H, d,  $\text{CH}_3$ ,  $J=6.6$  Hz), 1.46 (1H, br., NH), 2.69 (4H, m,  $\text{CH}_2 \times 2$ ), 6.67~6.81 (3H, m, arom.H $\times 3$ ), 7.22~7.35 (5H, m, arom.H $\times 5$ ); EIms  $m/z$ (rel. intensity): 285( $\text{M}^+$ , 5.2), 152[ $\text{M}^+ + 1 - \text{CH}_2\text{NHCH}(\text{CH}_3)\text{C}_6\text{H}_5$ , 50.1], 134[ $\text{M}^+ - (\text{CH}_3\text{O})_2\text{C}_6\text{H}_4\text{CH}_2$ , 71.9], 105[ $\text{M}^+ - (\text{CH}_3\text{O})_2\text{C}_6\text{H}_4\text{CH}_2\text{NH}$ , 100].

(*R*)-*N*-(1-Phenyl)ethyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-(3-benzyloxyphenyl)acetamide (5) An ether (100 ml) solution of acetyl chloride (4) prepared from 3-benzyloxyphenylacetic acid (4.0 g, 0.0165 mol) as noted above, and 5% aq. NaOH solution (100 ml) were added dropwise alternately to an ether solution (100 ml) of (*R*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-1-phenylethylamine (3) (4.27 g, 0.015 mol) with stirring at 0~5°C. After further stirring at the same temperature for 2 h, the ether layer was washed with water and dried. The solvent was evaporated off to give a pale yellow oil (5) [yield 6.65 g (87.2%)] showing a single spot on tlc.  $[\alpha]_D^{24} +6.6^\circ$  ( $c=0.15$ ,  $\text{CHCl}_3$ ); uv  $\lambda_{\text{max}}^{\text{EtOH}}$  nm (log  $\epsilon$ ): 203(4.59); ir  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 1650(C=O); EIms  $m/z$ (rel. intensity): 509( $\text{M}^+$ , 20.7), 358(4.0), 197(4.4), 164(100), 134(15.9), 105 (47.3), 91(20.4).

(*R*)-1-(3-Benzyloxybenzyl)-*N*-[(1*R*)-phenylethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7) A mixture of the amide (5) (5.25 g, 0.01 mol) and  $\text{POCl}_3$  (25.6 ml, 0.28 mol) in dry toluene (50.0 ml) was refluxed for 3.5 h. Evaporation of excess reagent and solvent left a residue, which was thoroughly washed with petroleum ether. The residual reagent was decomposed by addition of MeOH (10 ml). The solution was made alkaline with 10% aq.  $\text{NH}_4\text{OH}$  solution, and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was

washed with water, dried and evaporated, leaving the chiral iminium ion (6) (5.0 g) as a pale brown oily substance, indicating a single spot on tlc. This compound (6) was used for the following reaction without purification.

To a stirred solution of iminium ion (6) (4.9 g, 0.01 mol) in MeOH (200 ml) was gradually added NaBH<sub>4</sub> (6.70 g, 0.17 mol) at -78°C. The mixture was stirred at the same temperature for 2 h, excess NaBH<sub>4</sub> was decomposed with 10% AcOH and most of MeOH was removed by evaporation *in vacuo*. The residual solution was made alkaline with 10% aqueous NH<sub>4</sub>OH solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. Usual work-up of the CH<sub>2</sub>Cl<sub>2</sub> layer gave an oily residue, whose column chromatography on silica gel with hexane-CH<sub>2</sub>Cl<sub>2</sub> [9:1 (v/v)] gave a pale brownish oil (7), showing a single spot on tlc [4.83 g, 95.0% from 5].  $[\alpha]_D -57.6^\circ$  (c=0.59, CHCl<sub>3</sub>); uv  $\lambda_{\max}^{\text{EtOH}}$  nm (log  $\epsilon$ ): 204(4.73); <sup>1</sup>H-nmr  $\delta$ : 1.37(3H, d, CH<sub>3</sub>, J = 6.6 Hz), 2.40~3.38(6H, m, CH<sub>2</sub>×2), 3.04~3.81(2H, m, CH×2), 3.49, 3.83(3H×2, s, OCH<sub>3</sub>×2), 4.93(2H, s, OCH<sub>2</sub>), 5.87(1H, s, C-8), 6.56(1H, s, C-5), 6.53~6.58(2H, m, arom.H×2), 6.77~6.83(1H, m, arom.H×1), 7.07~7.21(6H, m, arom.H×6), 7.28~7.42(5H, m, arom.H×5); EIms  $m/z$  (rel. intensity): 493(M<sup>+</sup>, 0.21), 388(M<sup>+</sup>-C<sub>6</sub>H<sub>5</sub>CHCH<sub>3</sub>, 0.30), 296(M<sup>+</sup>-C<sub>6</sub>H<sub>5</sub>OC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>, 100), 192(M<sup>+</sup>+1-C<sub>6</sub>H<sub>5</sub>CHCH<sub>3</sub>-C<sub>6</sub>H<sub>5</sub>OC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>, 68.5), 176(192+1-CH<sub>3</sub>, 12.5), 105(C<sub>6</sub>H<sub>5</sub>CHCH<sub>3</sub>, 59.1), 91(C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, 47.8).

(R)-(+)-1-(3-Hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline [(R)-(+)-noranicanine] (1) A mixture of (7) (986 mg, 0.02 mol) and 5% Pd-C (ca.100 mg) in EtOH (ca.60 ml) containing concentrated hydrochloric acid (2 ml) was shaken at room temperature under a hydrogen atmosphere (3.0 kg/cm<sup>2</sup>) for 32 h using a medium-pressure catalytic hydrogenator. The catalyst was removed by filtration, the filtrate was made alkaline with 10% aq. NH<sub>4</sub>OH solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. Usual work-up of the extract yielded a residue which was recrystallized from Me<sub>2</sub>CO to afford colorless needles (1), mp 182°C (448 mg, 74.9 %).  $[\alpha]_D +34.3^\circ$  (c=0.2, CHCl<sub>3</sub>); uv  $\lambda_{\max}^{\text{EtOH}}$  nm (log  $\epsilon$ ): 204(4.78), 282(3.78),  $\lambda_{\max}^{\text{EtOH-KOH}}$  nm (log  $\epsilon$ ): 213(5.16), 287(3.74); ir  $\nu_{\max}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 3300~3050, 1610, 1585; EIms  $m/z$  (rel. intensity): 299(M<sup>+</sup>, 0.2), 193(16.4), 192(100), 177(3.7), 148(4.0); <sup>1</sup>H-nmr: 2.79(2H, m, C-4), 2.93(1H, dd, J = 1.5, J = 10.0 Hz, C- $\alpha$ ), 3.01(1H, dd, J = 6.0, 12.0 Hz, C-3), 3.18(1H, dd, J = 5.3, 10.0 Hz, C- $\alpha$ ), 3.24(1H, dd, J = 5.5, 12.0 Hz, C-3), 3.79, 3.86(3H×2, s, CH<sub>3</sub>O×2), 4.26(1H, dd, J = 5.0, 8.5 Hz, C-1), 6.60(1H, s, C-8), 6.66(1H, s, C-5), 6.69(1H, m, C-10), 6.69(1H, m, C-12), 6.69(1H, m, C-14), 7.14(1H, dd, J = 7.0, 9.0 Hz, C-13); <sup>13</sup>C-nmr: 56.6(C-1), 40.5(C-3), 29.0(C-4), 127.0

(C-4 $\alpha$ ), 112.1(C-5), 147.3 and 147.8 (C-6 and C-7), 109.8(C-8), 129.7(C-8 $\alpha$ ), 42.4(C- $\alpha$ ), 140.1(C-9), 116.2(C-10), 157.6(C-11), 114.4(C-12), 130.0(C-13), 121.0(C-14), 55.9 and 56.1 (2 $\times$ OCH<sub>3</sub>); Anal. Calcd for C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub>: C,72.22; H,7.07; N,4.68; Found: C,71.96; H,7.08; N,4.62.

#### ACKNOWLEDGMENT

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