AN ASYMMETRIC SYNTHESIS OF *S*-(-)-NORANICANINE†

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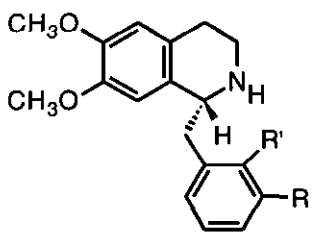
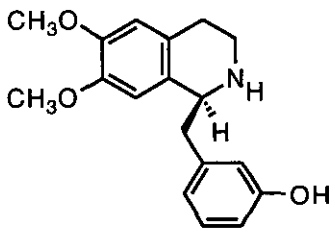
Abstract *- The absolute configuration of the titled natural alkaloid has been confirmed as R-(+) through a chiral formamidine-assisted total synthesis.*

The (*R*)-(+)-noranicanines (**1a**,**1b**) are isoquinoline alkaloids first isolated from Bolivian Lauraceae, *Aniba canelila*, by Guinaudeau *et al.*[1] The absolute configuration of the (+)-noranicanines was determined from the CD curve which gave a negative Cotton effect at 284 nm



(+)-Noranicanines

1a R' = H, R = OH
b R' = OH, R =H



(-)-Noranicanine

2

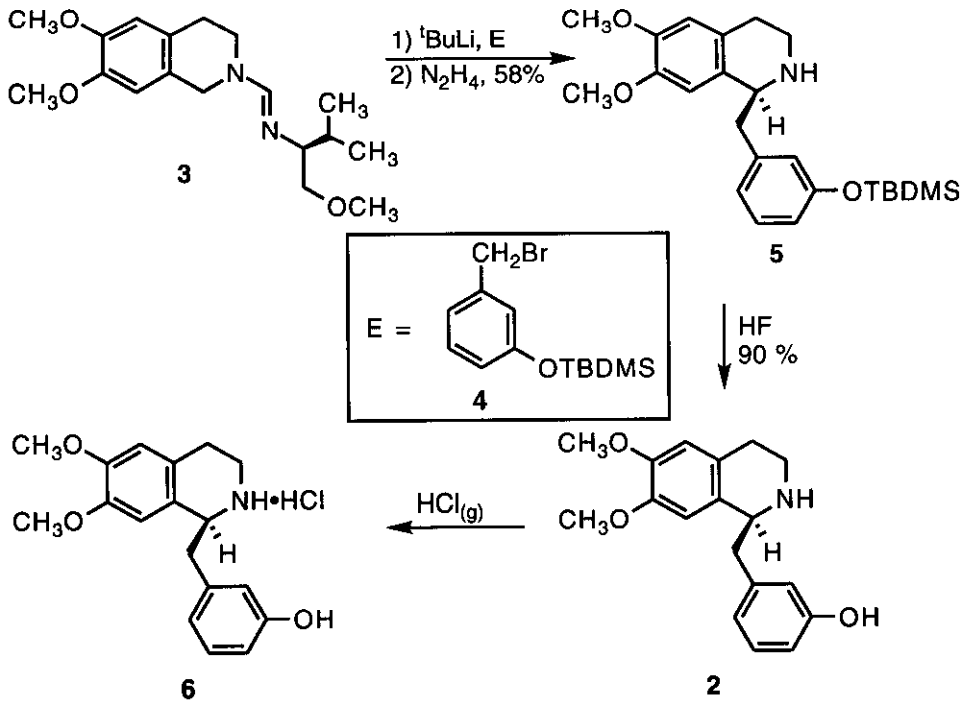
and a negative tail at 240 nm.[2] We were somewhat concerned that the absolute configuration, designated as *R*-(+) was unusual since most, if not all, of the isoquinoline alkaloids possessed the *S*-configuration at C-1. We have now confirmed the absolute configuration of the naturally

† Dedicated to Dr. Arnold Brossi on the occasion of his 70th birthday.

occurring noranicanine by the total asymmetric synthesis of (*S*)-(-)-noranicanine (**2**) using chiral formamidines. This route has been shown over and over again to provide predictable absolute configuration[3] of isoquinoline alkaloids.[4]

The synthesis was initiated when the previously employed chiral formamidine (**3**)[4] was metalated and alkylated with the *O*-silylated benzyl bromide (**4**) in THF at low temperature. Treatment of the crude product with hydrazine gave the (*S*)-amine (**5**) in >96% ee as assessed by chiral hplc (Scheme I). Desilylation of **5** using hydrofluoric acid gave (*S*)-noranicanine (**2**) in 89% yield, or 54% overall based on formamidine (**3**).

Scheme I



Attempts to secure an optical rotation of **2** uncovered a discrepancy with Guinaudeau's work. In our hands (*S*)-(-)-noranicanine (**2**) proved to be less soluble in chloroform than previously reported.[1] The optical rotation of natural (*R*)-(-)-noranicanine (**1b**) was reported to be $[\alpha]_D = +36°$ at a concentration of 10 mg/ml in chloroform. Attempts to prepare a solution of (*S*)-(-)-noranicanine (**2**) at this same concentration for optical rotation proved unsuccessful. A

concentration of 5 mg/ml in chloroform was eventually obtained by warming and gave an absolute optical rotation of $[\alpha]^{25}_D = -25.6°$.

Synthetic (*S*)-(-)-noranicanine (**2**) exhibited a melting point of 188-189.5 °C which was not reported earlier. The structure of noranicanine was verified by comparing ^1H and ^{13}C nmr spectra with that of natural noranicanine (**1b**) kindly provided by Professor Guinaudeau. The hydrochloride of **2** was prepared using hydrogen chloride and provided **6**, mp 140 °C (decomp.). This was also compared to that prepared earlier and reported[1] to have a mp 155-156 °C.

EXPERIMENTAL

***S*-(3-*tert*-Butyldimethylsilyloxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5):** The valinol-derived formamidine (**3**)[5] (100 mg, 0.3 mmol) was weighed into an oven dried 50 ml round-bottomed flask and evacuated under reduced pressure (0.5 mmHg) overnight. This cycle was repeated (3 x) then dry THF (10 ml) was added and cooled to -78 °C. The solution was treated with ^{t}BuLi (1.53 M, 0.23 ml) slowly to give an orange solution. After stirring for 30 min at -78 °C, it was cooled to -100 °C followed by slow addition of benzyl bromide (**4**) (99 mg, 0.33 mmol) as a solution in THF (5 ml). The reaction mixture was stirred for an additional 3 h, warmed to -78 °C and quenched with methanol. The solvent was removed under reduced pressure, diluted with water and extract with ethyl acetate (3 x 10 ml). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give a yellow oil. The crude oil was then taken up in 1 ml (8:1:1) of EtOH, HOAc and H_2O and cooled to 0 °C. Hydrazine hydrate (0.2 ml) was then added dropwise and the mixture was stirred overnight. The crude orange solution was diluted with 10 ml of water and extracted with dichloromethane (3 x 10 ml). The organic layers were combined, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give an orange oil, which was purified by radial chromatography (hexanes: ethyl acetate: triethylamine, 90: 5: 5) to give a clear oil (72 mg, 58%). Ir (film): 1464, 1600 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 0.16 (6H, s), 0.96 (9H, s), 1.65 (1H, br s), 2.68-2.78 (2H, m), 2.88-3.00 (2H, m), 3.08-3.24 (2H, m), 3.77 (3H, s), 3.83 (3H, s), 4.13 (1H, dd, J = 4.1, 9.4 Hz), 6.57 (1H, s), 6.62 (1H, s), 6.67-6.75 (2H, m), 6.83 (1H, m), 7.16 (1H, dd, J = 7.6, 15.2 Hz); ^{13}C nmr ($CDCl_3$): δ -4.51, -4.43, 18.2, 25.6, 25.7, 29.5, 40.7, 42.5, 55.8, 109.4, 111.8, 118.1, 121.1, 122.5, 127.3, 129.4, 130.5, 140.6, 147.0, 147.4, 155.8. The material was carried on to the next step without further purification.

(*S*)-(-)-Noranicanine (2): 3-Silyloxybenzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5**) (355 mg, 0.86 mmol) was dissolved in 3 ml of a solution of HF-acetonitrile (2.0 ml 49% HF, 1.5 ml H_2O, 22 mL CH_3CN) and stirred overnight at ambient temperature. The reaction solution was quenched with aqueous $NaHCO_3$ (10 ml) and extracted with chloroform (3 x 20 ml). The solvent (after drying) was removed under reduced pressure to give a pale solid, which was crystallized from ethyl acetate to give white flakes of (*S*)-noranicanine (**2**) (230 mg, 89%). mp 188-189.5 °C; $[\alpha]^{25}_D$ = -25.6° (c = 0.5, $CHCl_3$); ir (thin film): 3289 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.78 (2H, dd, *J* = 5.3, 10.7 Hz), 2.88-3.02 (2H, m), 3.12-3.26 (2H, m), 3.77 (3H, s), 3.84 (3H, s), 4.23 (1H, dd, *J* = 5.0, 8.7 Hz), 6.58 (1H, s), 6.59 (1H, s), 6.67 (3H, m), 7.12 (1H, dd, *J* = 7.5, 8.7 Hz); ^{13}C nmr ($CDCl_3$): δ 28.4, 40.2, 42.0, 55.8, 55.9, 56.4, 109.4, 111.7, 114.7, 116.1, 120.7, 126.4, 128.7, 130.1, 139.4, 147.2, 147.8, 157.5; *CIMS*(NH_3) m/z Calcd for $C_{18}H_{21}NO_3$ = 299: 300 ($[MH]^+$, 31.2%), 193 (10.2%), 192 (82.6%), 190 (100%); Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 71.97; H, 7.12; N, 4.63.

(*S*)-Noranicanine Hydrochloride (6): (*S*)-Noranicanine (**2**) (40 mg, 0.134 mmol) was dissolved in dichloromethane (20 ml) and cooled to 0 °C. Hydrogen chloride gas was passed through the solution for 30 min. The solvent was removed under reduced pressure to give a yellow solid (40 mg, 84%), which was recrystallized from acetone and ether to give an off white solid, mp 140 °C (decomp.) (lit.,[1] mp 155-156 °C); ^1H nmr (acetone-d_6): δ 2.95-3.05 (1H, m), 3.05-3.22 (1H, m), 3.22-3.33 (2H, m), 3.42-3.52 (2H, m), 3.61 (3H, s), 3.77 (3H, s), 4.62 (1H, t, *J* = 7.5 Hz), 6.60 (1H, s), 6.70-6.88 (3H, m), 6.95-7.00 (1H, m), 6.67 (3H, m), 7.12 (1H, t, *J* = 7.8 Hz), 8.79 (1H, s), 10.05 (1H, br); Anal. Calcd for $C_{18}H_{22}NO_3Cl \cdot H_2O$: C, 61.10; H, 6.84; N, 3.96. Found: C, 60.70; H, 6.77; N, 3.91.

3-*tert*-Butyldimethylsilyloxybenzyl bromide (4):

a) 3-tert-Butyldimethylsilyloxybenzaldehyde: 3-Hydroxy benzaldehyde (9.00 g, 73.7 mmol), *tert*-butyldimethylsilyl chloride (12.22 g, 81.1 mmol) and 4-dimethylaminopyridine (4.50 g, 36.9 mmol) were dissolved in dichloromethane (270 ml) and stirred under argon. Triethylamine (18.9 mmol, 25.74 ml) was added dropwise and the solution was allowed to stir overnight. The mixture was diluted with saturated $NaHCO_3$ solution and the organic layer was separated. The aqueous layer was back extracted with dichloromethane (2 x 50 ml). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to give an oil, which was

filtered through a plug of silica gel with 15% ethyl acetate in hexanes to give a yellow oil (17.17 g, 99%). This product is suitable for further reaction without purification. Ir (neat): 1704, 2724 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.19 (6H, s), 0.97 (9H, s), 7.04-7.46 (4H, m), 9.93 (1H, s); ^{13}C nmr ($CDCl_3$): δ -4.49, 18.14, 25.57, 38.97, 46.13, 106.53, 119.82, 123.52, 126.50, 130.03, 137.88, 149.61, 192.05.

b) 3-tert-Butyldimethylsilyloxybenzyl alcohol: In 125 ml Erlenmeyer flask, 3-*tert*-butyldimethylsilyloxybenzaldehyde (1.27 g, 5.37 mmol) was dissolved in ethanol (40 ml). Sodium borohydride (2.03 g, 53.7 mmol) was added and the mixture stirred for 10 min. Water (20 ml) was then added and the reaction was heated to reflux for 5 min and then cooled to room temperature. The solution was extracted with chloroform (3 x 50 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure to give a pale oil (1.20 g, 94%). This product is suitable for further reaction without purification. Ir (neat): 1083, 3100-3700 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.15 (6H, s), 0.97 (9H, s), 2.05 (1H, br s), 4.52 (2H, s), 6.62-6.88 (3H, m), 7.10 (1H, t, J = 7.8 Hz); ^{13}C nmr ($CDCl_3$): δ -4.43, -3.62, 18.16, 25.65, 65.09, 106.55, 118.58, 119.19, 119.73, 123.52, 129.47, 142.53, 148.92, 155.85.

c) 3-tert-Butyldimethylsilyloxybenzyl bromide: Using a modified procedure by Corey,[4] *N*-bromosuccinimide was dissolved in dichloromethane (120 ml) and cooled to 0 °C. Dimethyl sulfide (21.4 mmol, 1.57 ml) was added dropwise to give a yellow precipitate. The mixture was cooled to -20 °C (ethylene glycol/Dry Ice) and 3-*tert*-butyldimethylsilyloxybenzyl alcohol (1.49 g, 6.35 mmol) in dichloromethane (4 ml) was added slowly. After 1 h, the reaction was warmed to room temperature, and allowed to stir overnight. The product was filtered, taken up in aqueous $NaHCO_3$ (20 ml) and extracted with dichloromethane (3 x 50 ml). The organic layers were combined, dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to give a pale oil. This was then filtered through a plug of silica gel with hexanes to give a clear oil (1.62 g, 86%). This product is suitable for further reaction without purification. GCms R_t = 8.55 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C), Elms m/z (rel int) 302 (M^+), 245 (M - ^{t}Bu); ir (film): 1442, 1603 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.19 (6H, s), 1.01 (9H, s), 4.40 (2H, s), 6.68-6.98 (3H, m), 7.20 (1H, t, J = 7.8 Hz); Anal. Calcd for $C_{13}H_{21}OBrSi$: C, 51.82; H, 7.03. Found: C, 51.97; H, 7.07.

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REFERENCES

1. J. M. Olger, O. Duvall, P. Richomme, J. Bruneton, H. Guideneau, and A. Fournet, *Heterocycles,* 1992, **34**, 17.
2. J. C. Craig, M. Martin-Smith, S. K. Roy, and J. B. Stenlake, *Tetrahedron,* 1966, **22**, 1335.
3. For a recent review of total syntheses using chiral formamidines, see T. K. Highsmith and A. I. Meyers, 'Advances in Heterocyclic Natural Product Synthesis', Vol. 1, ed. by W. H. Pearson, JAI Press Inc., Connecticut, 1990, p. 95.
4. A. I. Meyers, D. A. Dickman, and M. Boes, *Tetrahedron,* 1987, **43**, 5095.
5. J. Guiles and A. I. Meyers, *J. Org. Chem.,* 1991, **56**, 6873; A. I. Meyers and T. R. Elworthy, *J. Org. Chem.,* 1992, **57**, 4732; A. I. Meyers and R. H. Hutchings, *Tetrahedron,* 1993, **49**, 1807.
6. E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Lett.,* 1972, 4339.

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