THE ASYMMETRIC TOTAL SYNTHESIS OF (+)-RETICULINE†

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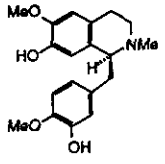
Abstract - The synthesis of the title compound was accomplished *via* chiral formamidines in 5 steps (30.4% overall) and 98.6% ee.

The isoquinoline alkaloid, reticuline **1** was first isolated in 1930[1] and again in 1939.[2] The absolute configuration was reported in 1959[3] and total syntheses have been numerous.[4] However, except for studies by Yamada[5a] and Noyori[5b] all syntheses of **1** yielded racemic products. We now describe an efficient route to this important alkaloid (a biosynthetic precursor to thebaine, codeine, and morphine[6-8]) using asymmetric methodology previously developed in our laboratory. Although Brossi[4] has described an expedient synthesis of (±)-1 and norreticuline (NH-analog) the method requires a resolution, *via* the tartaric acid salt.[9] The



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present synthesis will provide (+)-1 in the natural configuration (S) and in greater than 98.6% enantiomeric excess thus making this pivotal alkaloid available in optically active form.

The scheme utilized is a further extension of methodology involving chiral formamidines to reach a number of isoquinoline,[10] morphinan,[11] indole,[12] and pyrrolidine[13] alkaloids.

Starting with the phenethylamine **2**, derived from vanillin, nitromethane, and lithium aluminum hydride, the known[14] tetrahydroisoquinoline **3** was formed in 75% yield. The valinol *t*-butyl ether formamidine[13] was then introduced by heating with tetrahydroisoquinoline **3** in toluene affording **4** in 88% yield. The key stereoselective step was accomplished by treating **4** with *t*-butyllithium at -78°C to generate the lithiated species **5** to which the benzyl bromide was then introduced at -100°C. *In situ* removal of the chiral auxiliary gave the 1-benzylisoquinoline **6** in 70% yield for the process.

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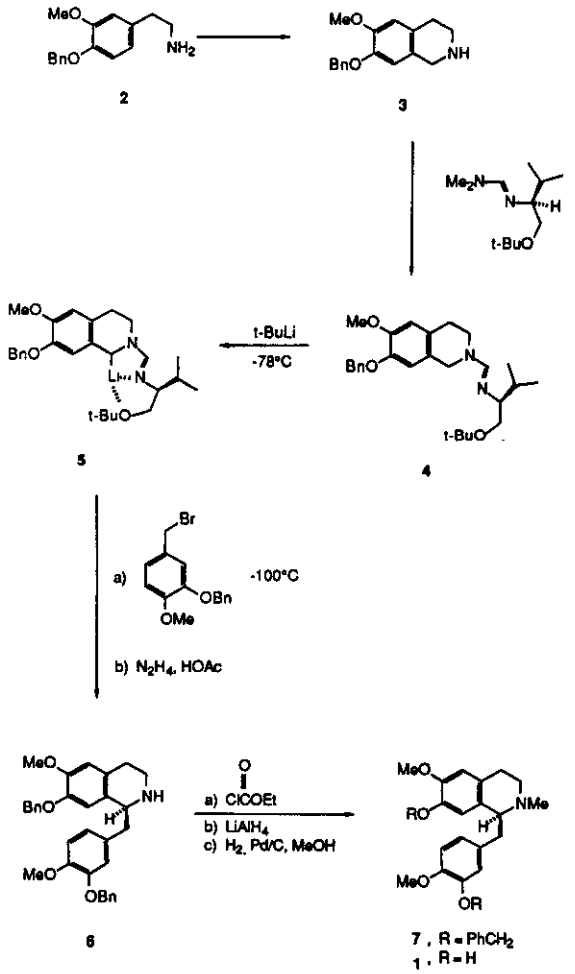
†*This paper is dedicated to Professor* D.H.R. Barton on the occasion of his 70th birthday.

The introduction of the N-methyl group was accomplished by reduction of the formamide derivative to give **7** and hydrogenolysis of the benzyl ethers led to (+)-reticuline. Comparison of the specific rotation to that of the natural material (+43.4° and +44.0° respectively) indicated that the synthetic material was obtained in



98.6% ee. This five step sequence (from **2**) was accomplished in 30.4% overall yield and constitutes an efficient preparation of the natural alkaloid.

EXPERIMENTAL

4-Benzyloxy-3-methoxybenzaldehyde

To a stirred solution of vanillin (39.03 g, 0.258 mol) in ethanol (200 ml) was added K_2CO_3 (38.9 g, 0.292 mol), and benzyl bromide (44.11 g, 0.258 mol), and the mixture was maintained under an argon atmosphere overnight. The solution was filtered through celite and washed with CH_2Cl_2 (2 x 200 ml), and then

concentrated under vacuum. The residue is dissolved in 250 ml of CH_2Cl_2 and washed with 5% NaOH solution, dried over K_2CO_3, concentrated and crystallized from ethanol (55.4 g, 88% yield), mp 62-63°C (lit[13] mp 63-65°C).

3-Benzyloxy-4-methoxybenzaldehyde

To a stirred solution of isovanillin (7.7 g, 50.67 mmol) in water (50 ml) was added KOH (3.4 g, 60.0 mmol, 1.2 eq.). After 10 minutes the mixture was homogenous, benzyl bromide (8.66 g, 50.67 mmol) was added, followed by heating at reflux for 5 h. The mixture was cooled and the layers were seprated, the organic layer was dissolved in dichloromethane (200 ml), washed with water (100 ml), and dried over K_2CO_3 (0.5 g). This oil was crystallized from ethanol to afford (9.14 g, 40.0 mmol, 75%), mp 61-62°C (lit[14] 61-64°C).

3-Benzyloxy-4-methoxybenzyl bromide

To a stirred solution of 3-benzyloxy-4-methoxybenzaldehyde (1.034 g, 4.27 mmol) in ethanol (15 ml) was added $NaBH_4$ (0.255 g, 6.7 mmol) and maintained at room temperature under an argon atmosphere for 18 h. The solution was brought to reflux for 1 h, cooled to room temperature and decanted into 20% NH_4Cl (50 ml). This was extracted with ether (3 x 20 ml), the ether washes were combined and washed with brine (20 ml), followed by drying over K_2CO_3 (0.5 g). The solvent was removed to provide 3-benzyloxy-4-methoxybenzyl alcohol (0.97 g, 3.97 mmol, 93%) as a sharp melting white solid, mp 69.5-70.5°C. To a stirred solution of this alcohol (0.717 g, 2.94 mmol) in tetrahydrofuran (5 ml) at 0°C was added PBr_3 (0.40 g, 1.5 mmol) and the mixture was maintained at 0°C under an argon atmosphere for 90 min, before gradual warming to room temperature for 30 min. The solvent was removed under vacuum at 0°C, and the oil crystallized from CH_2Cl_2/hexane to yield the title compound (0.87 g, 2.83 mmol, 96%) as a sharp melting solid, mp 86-87°C.

2-(4-Benzyloxy-3-methoxyphenyl)ethylamine 2

Prepared according to the method of Kessar, Kumar, and Jogi,[15] a mixture of ammonium acetate (1.5 g, 20.4 mmol), nitromethane (2.9 g, 48 mmol), and 4-benzyloxy-3-methoxybenzaldehyde (6.6 g, 27.25 mmol) was refluxed for 1.5 h. Upon cooling, the reaction deposited 5.24 g of 4-benzyloxy-3-methoxy-β-nitrostyrene as yellow crystals, the mother liquor was collected, concentrated, and crystallized from methanol giving another 0.4 g of yellow needles (5.64 g, 20 mmol, 73%), mp 126-128°C.

To a stirred solution of the above nitrostyrene (4.5 g, 15.8 mmol) in 1:1 ether/tetrahydrofuran (100 ml) was slowly added a suspension of lithium aluminum hydride (2.1 g, 54 mmol) in ether (55 ml). The solution was refluxed for 2 h then stirred overnight at room temperature. To this solution was added water (8 ml), then 15% sodium hydroxide (8 ml), then water (24 ml) and the solution was stirred 30 min before filtering. The phases were separated and the aqueous phase was extracted with ether (3 x 20 ml), the ether washes were combined and concentrated. The oily residue was dissolved in 10% HCl (12 ml) and washed with ether (10 ml), the aqueous layer was made basic and extracted with ether (2 x 20 ml). These two ether washes were combined and washed with water (10 ml), and brine (10 ml) before drying over K_2CO_3. Removal of the

solvent produced the title compound as a sharp melting white solid (2.2 g, 10.0 mmol, 55%), mp 60-62°C: ^{1}H Nmr 270 MHz ($CDCl_3$ δ 1.25 (s, 2 H), 2.67 (t, 3 H, J = 6.74 Hz), 3.08 (t, 3 H, J = 6.71 Hz), 3.84-3.85 (s, 5 H), 5.09 (s, 2 H), 6.53 (s, 1 H), 6.6 (s, 1 H), 7.35 (s, 1 H) ppm; ^{13}C nmr 300 MHz ($CDCl_3$) δ 149.48, 146.45, 137.21, 132.95, 128.34, 127.6, 127.1, 120.57, 114.12, 112.48, 71.0, 55.81, 43.44, 39.84 ppm; ir ($CHCl_3$) 3372, 3032, 2925, 2871, 2244, 2197, 1588, 1507, 1464, 1411, 1384, 1260, 1214, 1157, 1140, 1033, 1020, 910, 850, 803 cm-1.

7-Benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline 3

Prepared according to the procedure of Ruchirawat[16] with the following modifications. To a stirred solution of 2-(4-benzyloxy-3-methoxy)phenethylamine 2 (4.95 g, 19.2 mmol) in formic acid (20 ml) at 50°C was added paraformaldehyde (0.57 g, 19.2 mmol). The solution was stirred at 50°C under argon for 48 h. The solvent was removed under vacuum and the residue dissolved in ethanol (50 ml) and added dropwise to an ethanol solution (50 ml) of oxalic acid (3.6 g, 40.0 mmol) to yield (5.17 g, 75%) of the title compound as its oxalic acid salt, mp 216-217°C (lit[14] 214-216°C). ^{1}H Nmr 270 MHz ($CDCl_3$) δ 1.8 (s, 1 H), 2.69 (t, 2 H, J = 5.85 Hz), 3.08 (t, 2 H, J = 5.9 Hz), 3.85-3.86 (s, 5 H), 5.10 (s, 2 H), 6.50 (s, 1 H), 6.60 (s, 1 H), 7.35 (s, 1 H) ppm.

(S)-Valinol-tert-butyl ether formamidine of 7-Benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline 4

To a stirred solution of 3 (4.85 g, 18.01 mmol) in toluene (20 ml) was added (4.24 g, 19.8 mmol) of the dimethylformamidine[13] and a catalytic amount of ammonium sulfate. This solution was heated to reflux and continuously purged with argon for 48 h, followed by removal of the solvent to yield an oily residue that was dissolved in ethyl acetate (75 ml) and washed with saturated $NaHCO_3$ (10 ml) and brine (10 ml). The ethyl acetate solution was dried over K_2CO_3 (0.5 g) and the solvent was removed to give 7.2 g of a yellow oil. The resulting material was purified by chromatography on silica (deactivated with 5% triethylamine, eluent hex:EtOAc 55:40) to give the title compound as a yellow oil (6.7 g, 15.3 mmol, 88%); $[\alpha]_D^{22}$ -23.5° (c 1.5, $CHCl_3$); ^{1}H nmr 270 MHz ($CDCl_3$) δ 0.86 (d, 6 H, J = 6.71 Hz), 1.13 (s, 9 H), 1.85 (m, 1 H), 2.76 (m, 3 H), 3.16-3.26 (m, 1 H), 3.43-3.55 (m, 3 H), 3.86 (s, 3 H), 4.26 (ABq, 1 H, J = 16.8 Hz), 4.41 (ABq, 1 H, J = 16.43 Hz), 5.11 (s, 2 H), 6.62 (s, 1 H), 6.63 (s, 1 H), 7.26-7.44 (m, 6 H) ppm. Ir (film) 3020, 2970, 2860, 1630, 1450, 1375, 1250, 1180, 1100, 1070, 1000, 865, 740 cm^{-1}.

1-(3'Benzyloxy-4'-methoxybenzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline 6

To a stirred solution of 4 (264 mg, 0.60 mmol, 1.0 eq.) in tetrahydrofuran (12 ml) at -78°C was added *t*-butyllithium (0.391 ml of a 1.85 M solution in hexanes, 0.723 mmol, 1.2 eq.) resulting in a deep red solution, which was stirred for an additional 30 min. The temperature was lowered to -100°C and 231 mg (0.753 mmol, 1.3 eq.) of the benzyl bromide in tetrahydrofuran (2 ml) was added dropwise with subsequent stirring for 4 h resulting in a light yellow solution. The temperature was raised to -78°C and 20% NH_4Cl (1 ml) was added. After warming to room temperature the solvent was removed, the oily residue was dissolved in ethyl acetate

(15 ml) and washed with 20% NH_4Cl (2 x 10 ml), and with brine (10 ml). The ethyl acetate solution was dried over K_2CO_3 (0.5 g) and the solvent was removed to give an orange oil. This oil was not purified but carried on to the next step by treatment with ethanol (4 ml), water (0.5 ml), acetic acid (0.5 ml) and hydrazine (1 ml). This solution was stirred at room temperature for 12 h, followed by removal of the solvent to yield an oily residue that was dissolved in ethyl acetate (20 ml) and washed with water (5 ml) and brine (5 ml). The ethyl acetate solution was dried over K_2CO_3 (0.5 g) and the solvent was removed to give 210 mg of yellow oil. The resulting material was purified by chromatography on silica (deactivated with 5% TEA, eluent CH_2Cl_2:hex:EtOAc 40:30:25) to give the title compound (200 mg, 0.414 mmol, 69% overall): Ir (neat) 3062, 3027, 3009, 2932, 2834, 1606, 1588, 1512, 1461, 1452, 1442, 1424, 1261, 1232, 1219, 1137, 1112, 1024, 753 cm^{-1}; ^1H nmr (270 MHz, $CDCl_3$) δ 7.44-7.27 (m, 10 H), 6.88-6.59 (m, 5 H), 5.10 (s, 2 H), 5.07 (s, 2 H), 3.99-3.94 (m, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.14-3.06 (m, 1 H), 3.0-2.93 (m, 1 H), 2.85-2.65 (m, 2 H) ppm.

1-(3'-Benzyloxy-4'-methoxybenzyl)-7-benzyloxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 7

Prepared according to the method of Corey.[17] To a stirred solution of **6** (42 mg, 0.087 mmol, 1.0 eq.) in acetone (2 ml) was added K_2CO_3 (72 mg, 0.52 mmol, 6 eq.) and ethyl chloroformate (38 mg, 0.35 mmol, 4 eq.). The solution was refluxed for 14 h, then cooled to room temperature and the solvent was removed. The solid residue was dissolved in ethyl acetate (10 ml) and washed with water (5 ml) and brine (5 ml). The ethyl acetate solution was dried over K_2CO_3 (0.5 g) and the solvent was removed to give a yellow oil. This material showed a carbonyl stretch at 1690 cm^{-1}. To a stirred solution of this yellow oil in tetrahydrofuran (10 ml) was added lithium aluminum hydride (80 mg, 2.1 mmol) at 0°C. The solution was refluxed overnight, then cooled to 0°C and diluted with diethyl ether (10 ml), before adding water (1 ml), sodium hydroxide (1.3 ml, 15% solution), and water (3 ml). The phases were separated and the ethereal layer was washed with brine (5 ml). The ether layer was dried over K_2CO_3 (0.5 g) and the solvent was removed to give 38 mg of a clear oil. The resulting material was purified by chromatography on silica (deactivated with 5% TEA, CH_2Cl_2:hex:EtOAc 50:25:20) to give the title compound (30 mg, 0.06 mmol, 70%) as a sharp melting white solid, mp 91-91.5°C (lit[18] 90-91°C): Ir (neat) 3060, 3030, 3010, 2930, 2830, 1605, 1585, 1510, 1460, 1450, 1260, 1230, 1216, 1134, 1110, 1020, 750 cm^{-1}; ^1H nmr (270 MHz, $CDCl_3$) δ 7.42-7.23 (m, 10 H), 6.76-6.50 (m, 4 H), 6.07 (s, 1 H), 5.04 (s, 2 H), 4.87-4.74 (ABq, 2 H, J = 8.3 Hz), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.54-3.5 (t, 1 H), 3.14-2.94 (m, 2 H), 2.81-2.51 (m, 4 H), 2.45 (s, 3 H) ppm; ^{13}C nmr (300 MHz, $CDCl_3$) δ 148.8, 148.7, 148.4, 146.5, 137.6, 137.4, 131.8, 131.0, 128.7, 128.4, 127.7, 127.4, 16.4, 113.2, 112.8, 71.9, 71.4, 56.8, 56.3, 56.2, 42.2, 41.0, 29.7 ppm, $[\alpha]_D^{22}$ +43.4° (c 0.8, $CHCl_3$); {lit[14] $[\alpha]_D^{22}$ +44° (c 1.0, $CHCl_3$)}; Anal. Calcd for $C_{33}H_{35}NO_4$: C, 77.77; H, 6.92; N, 2.74. Found: C, 77.61; H, 6.96; N, 2.88.

1-(3'-Hydroxy-4'-methoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, Reticuline (+)-1

To a solution of **7** (42 mg, 0.084 mmol, 1.0 eq.) in methanol (7 ml) was added Pd/C (10 mg, 10% by wt) and acetic acid (20 µl). This solution was kept under a H_2 (50 psi atmosphere) for 6 h, and was then filtered through a thick pad of Celite with repeated methanol (3 x 20 ml) washings. The methanol was removed under vacuum and the residue was dissolved in CH_2Cl_2 (10 ml) and washed with 10% $NaHCO_3$ (5 ml) then brine (5 ml). The CH_2Cl_2 solution was dried over K_2CO_3 and the solvent removed under vacuum to yield 26 mg of a yellow solid. ^1H Nmr ($CDCl_3$, 300 MHz) δ 2.45 (s, 3 H), 2.52-2.69 (m, 1 H), 2.74-2.82 (m, 3 H), 2.96-3.03 (m, 1 H), 3.11-3.15 (m, 1 H), 3.65-3.67 (m, 1 H), 3.85 (s, 1 H), 3.86 (s, 3 H), 6.53-6.78 (m, 5 H) ppm. ^{13}C Nmr ($CDCl_3$, 300 MHz) δ 25.09, 40.99, 42.49, 46.85, 55.80, 55.87, 64.51, 110.42, 110.58, 113.68, 115.62, 120,83, 125.39, 130.49, 133.33, 143.34, 144.96, 145.06, 145.31 ppm. Ir ($CHCl_3$) 3679, 3539, 3012, 2938, 2845, 2398, 1588, 1508, 1458, 1444, 1371, 1271, 1224, 1200, 1127, 1097, 1027, 787, 720 cm^{-1}; $[\alpha]_D^{25}$ +46.2° (c 1.6, $CHCl_3$). The hydrochloride of **1** was made by bubbling HCl gas through a CH_2Cl_2 (5 ml) of **1** (10 mg), the solid was collected on a glass fritted funnel and washed with ether (2 x 5 ml). The crystals were dissolved in H_2O and passed through a Sep-pak (C-18) column, yielding 2 mg of white solid, mp 122-124°C. $[\alpha]_D^{22}$ +72.3° (c 0.2, H_2O), lit[18] $[\alpha]_D$ +73.1°, -75° (no solvent given).

ACKNOWLEDGEMENTS

The authors are grateful to the National Science Foundation whose financial support made this work possible.

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Received, 25th July, 1988