An Improved Synthesis of Galanthamine

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Modifications in the total synthesis of the *Amarylidaceae* alkaloid of galanthamine from commercially available isovanillin and tyramine have resulted in a shortened reaction sequence, which is amenable to upscaling and in improved product yield.

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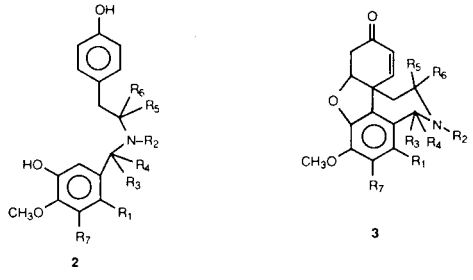
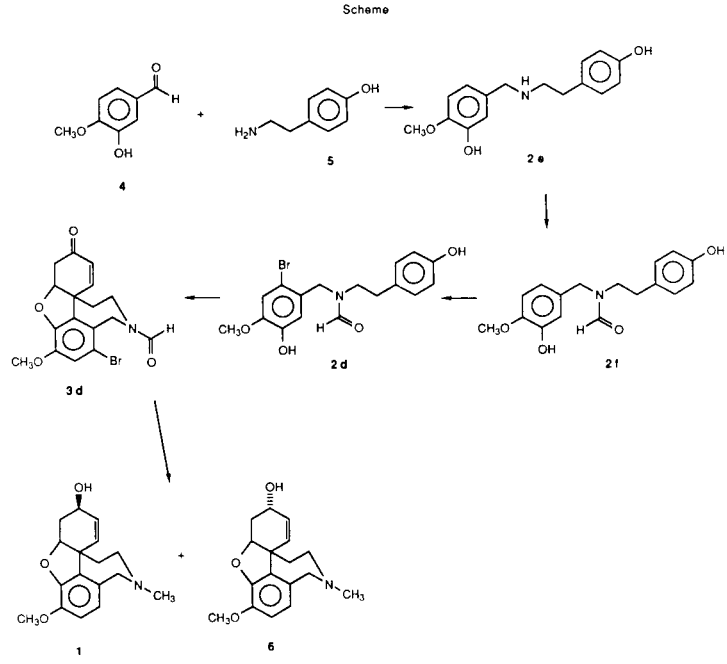
As part of a program directed toward the synthesis of galanthamine (**1**) analogs and derivatives, large quantities of this *Amarylidaceae* alkaloid were required. Examination of the literature revealed that the basic approach to the synthesis of **1** involves as a key step the oxidative coupling of an appropriate bisphenol **2** to the narwedine skeleton **3** [1-3]. It was also clear that eliminating cyclization to the *para* position by blocking the position *para* to the hydroxyl group with a bromine substituent, **2a**, [1] was advantageous and that cyclization to **3** could be carried out with bisphenols in which the carbonyl functionality was at any of the positions *alpha* to the nitrogen atom, **2a**, **2b**, **2c** [1-3]. Thus, Kametani [1] had reported synthesis of racemic galanthamine in eight steps and in 8% overall yield starting from *p*-benzyloxyphenylacetic acid and bromoisovanillin, neither of which is commercially available. Correcting for the preparation of the starting materials, the synthesis actually requires ten individual steps, and the product is obtained in 5% overall yield. In a subsequent publication Kametani [2] reported an alternative synthesis of racemic **1** involving the cyclization of the bisphenol **2b** to the enone **3b**; however, even though the number of steps was reduced to seven, the yield was also significantly lower (<1%). An alternative approach, applied by Shimizu [3] to the synthesis of (+)-galanthamine, involved oxidative cyclization of the bisphenol **2c** but had no practical synthetic value due to the extremely low yield (0.06%). Based on these literature reports, it appeared that the bisphenol **2d** may serve as a useful intermediate in the synthesis of racemic galanthamine (**1**). In this report we present a three-step synthesis of **2d** from commercially available materials and describe its conversion to galanthamine (**1**) in good yield. The synthesis, shown in the Scheme, has been found to be applicable to moderately large scale.

Starting with commercially available isovanillin (**4**) and tyramine (**5**), *N*-(*p*-hydroxyphenethyl)-*N*-(3-hydroxy-4-methoxy)benzylamine (**2e**) was prepared in quantitative yield by reductive amination. To prevent oxidation of the amine functionality, **2e** was converted to the formamide **2f**, in 80% yield, by treatment with ethyl formate. In order to avoid cyclization at the 6 position (*para* to the hydroxyl group), this position was blocked by bromination with a single equivalent of bromine at -65°C to give *N*-(*p*-hydroxyphenethyl)-*N*-(2-bromo-5-hydroxy-4-methoxy)benzylformamide (**2d**) in 85% yield. Treatment of **2d** with potassium ferricyanide in a chloroform/sodium bicarbonate biphase gave (±)-2-bromo-*N*-desmethyl-*N*-formylnarwedine (**3d**) in 21% yield. Reduction with lithium aluminum hydride gave a mixture of (±)-galanthamine (**1**) and (±)-epigalanthamine (**6**) in 85% yield; chromato-



a: R_1 = Br, R_2 = CH_3, R_3R_4 = O, R_5 = R_6 = R_7 = H
b: R_1 = Br, R_2 = CH_3, R_5R_6 = O, R_3 = R_4 = R_7 = H
c: R_2 = $C(O)CF_3$, R_7 = OH, R_1 = R_3 = R_4 = R_5 = R_6 = H
d: R_1 = Br, R_2 = C(O)H, R_3 = R_4 = R_5 = R_6 = R_7 = H
e: R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H
f: R_2 = C(O)H, R_1 = R_3 = R_4 = R_5 = R_6 = R_7 = H

Scheme



graphic separation provided the pure products in 53% and 31% yield, respectively. This synthesis has been carried out on as little as 5 mmoles of the starting material or on a one-half molar scale without significant variation in yield.

In summary, we have developed an alternative synthesis of racemic galanthamine (**1**) from commercially available isovanillin and tyramine in five steps and with a 50% increase in overall yield over the best heretofore reported synthesis. Moreover, this approach is applicable to synthesis on a large scale.

EXPERIMENTAL

Melting points were determined on a Koffler hot stage. Infrared (ir) spectra were recorded on a Perkin-Elmer 457 spectrophotometer. Proton magnetic resonance (^{1}H nmr) spectra were obtained on either a Bruker WM250 or a Varian EM390 spectrometer. Chemical shifts are reported in ppm and δ values are relative to tetramethylsilane.

N-(*p*-Hydroxyphenethyl)-*N*-(3-hydroxy-4-methoxy)benzylamine (**2e**).

A mixture of isovanillin (**4**, 48.64 g, 0.32 mole) and tyramine (**5**, 43.84 g, 0.32 mole) in 1600 ml of anhydrous methanol and 300 g of molecular sieves was stirred overnight at room temperature. After the sieves were removed by filtration and the mixture diluted to 3200 ml with methanol, sodium borohydride (24 g, 0.624 moles) was added in six equal portions at 0°, and the reaction mixture was stirred for 3 hours at room temperature. At the end of this time the solvent was evaporated, the residue suspended in 2000 ml of brine and the *p*H adjusted to 8. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (1000 ml x 2). The combined organic phase was extracted with dilute hydrochloride acid (2 x 1000 ml), and the acidic extract was brought to *p*H 8 and extracted with ethyl acetate (2 x 250 ml). The combined organic phase was dried over magnesium sulfate and evaporated. The crude product (87 g, 99%) was obtained as a yellow semi-crystalline solid; ^{1}H nmr (dimethyl sulfoxide-d_6): 90 MHz, δ 2.45 (br s, 4, CH_2CH_2N), 3.38 (s, 2, $ArCH_2N$), 3.56 (s, 3, OCH_3), 4.40-5.70 (br s, 3, 2-OH + NH), 6.40-6.86 (m, 7, ArH). To obtain an analytical sample the amine **2e** was converted to the hydrochloride by treatment with ethanolic hydrochloric acid. Recrystallization of the semicrystalline white solid from dilute aqueous hydrochloric acid gave crystals with mp 195° dec.

Anal. Calcd. for $C_{16}H_{20}ClNO_3 \cdot \frac{1}{4}H_2O$: C, 61.14; H, 6.53; N, 4.46; Cl, 11.31. Found: C, 60.88; H, 6.58; N, 4.44; Cl, 11.30.

Basification of an aqueous solution of the hydrochloride salt with 5*N* sodium hydroxide to *p*H 9 afforded the analytically pure free base as a white crystalline solid, mp 175-177° dec.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.07; H, 6.93; N, 5.11. Found: C, 69.72; H, 7.10; N, 5.21.

N-(*p*-Hydroxyphenethyl)-*N*-(3-hydroxy-4-methoxybenzyl)formamide (**2f**).

To a suspension of the amine **2e** (87 g, 0.32 mole) in 2000 ml of ethyl formate was added two drops of formic acid, and the mixture was refluxed until thin layer chromatography (7% methanol in chloroform) indicated complete consumption of the starting material. At this point any insoluble material was removed by filtration and the solvent evaporated. Flash chromatography on 2 columns (3.5% methanol in chloroform) afforded 77 g (80%) of the product **2f**. Trituration with acetone provided white crystals, mp 148-149°; ^{1}H nmr (deuteriochloroform/dimethyl sulfoxide-d_6): 250 MHz, showed the presence of two rotamers: δ 2.63-2.85 (m, 2, CH_2Ar), 3.00-3.50 (m, 4, 2-OH + NCH_2), 3.87 (s, 3, OCH_3), 4.27 (m, 2, CH_2Ar), 3.00-3.50 (m, 4, 2-OH + NCH_3), 3.87 (s, 3, OCH_3), 4.27, 4.58 (s, 2, $ArCH_2N$), 6.66, 6.97, 7.08 (m, 6 ArH), 7.86, 8.23 (s, 1, HCO).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.77; H, 6.31; N, 4.65. Found: C, 67.85; H, 6.41; N, 4.62.

N-(*p*-Hydroxyphenethyl)-*N*-(2-bromo-5-hydroxy-4-methoxybenzyl)formamide (**2d**).

To a solution of the secondary amide **2f** (37 g, 0.123 mole) in 1700 ml of a 4:1 mixture of chloroform and methanol at −65° was added a solution of bromine (197 g, 0.123 mole) in 200 ml of chloroform over a 2 hour period. The mixture was then allowed to warm up to 0° and was washed with saturated aqueous sodium bicarbonate. The organic phase was dried and the solvent removed at reduced pressure. After drying at 1 mm Hg at room temperature, the residue was recrystallized from chloroform to give 37 g of white crystals. Concentration of the mother liquor gave an additional 3 g (85% yield); ^{1}H nmr (dimethyl sulfoxide-d_6): 250 MHz, exhibited the presence of two rotamers in 55:45 ratio: δ 2.50-2.70 (m, 2, CH_2Ar), 3.15-3.45 (m, 2, NCH_2), 3.36 (s, water), 3.77 (s, 3, OCH_3), 4.34, 4.40 (s, 2, $ArCH_2N$), 6.63-6.80 (m, 3, ArH), 6.90-6.99 (m, 2, ArH), 7.10-7.35 (m, 1, ArH), 7.93, 8.25 (s, 1, HCO), 9.22 (s (br), 1, OH), 9.36, 9.44 (s (br), 1, OH).

Anal. Calcd. for $C_{17}H_{18}BrNO_4 \cdot \frac{1}{4}H_2O$: C, 53.06; H, 4.81; N, 3.64; Br, 20.81. Found: C, 53.07; H, 4.83; N, 3.66; Br, 20.94.

(4α)-4α,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-11-formyl-6*H*-benzofuran[3a,3,2-*ef*][2]benzazepin-6-one (**3d**).

To a well stirred mixture of 3000 ml of chloroform and a solution of 42 g of potassium ferricyanide in 400 ml of 5% sodium bicarbonate in a Morton flask at 60° was added, all at once, the bromoformamide **2d** (8 g, 0.021 mole). After stirring at 60° for 1.5 hours, the organic layer was separated and washed with water, dried over magnesium sulfate and evaporated, leaving 4.1 g of a yellow solid. Column chromatography with 0.4% ethanol/chloroform yielded 1.7 g (21%) of a colorless oil. A portion, 0.4 g, was crystallized from chloroform:hexane to give 0.3 g of white crystals, mp 181-183°; ir (potassium bromide): 1675, 1620, 1495, 1440, 1410, 1290, 1235 cm^{-1}; ^{1}H nmr (deuteriochloroform): 250 MHz, showed the presence of two rotamers: δ 1.97-2.19 (m, 2, CH_2CO), 2.18-2.32, 2.73-2.82, 3.01-3.18, 3.28-3.40, 3.50-4.05 (m, 4, CH_2CH_2N), 3.83, 3.84 (s, 3, OCH_3), 4.06, 5.16, 5.69 (AB, J = 15.9, 2, $ArCH_2N$), 4.54, 4.73 (m, 1, CHOC), 6.07, 6.88, 6.93 ((AB, J = 10, CH=CH), 6.96, 6.97 (s, 1, ArH), 8.15, 8.19 (s, 1, HCO).

Anal. Calcd. for $C_{17}H_{20}BrNO_3 \cdot \frac{1}{2}H_2O$: C, 52.71; H, 4.39; N, 3.62. Found: C, 52.95; H, 4.41; N, 3.59.

(4α6β)-4α,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuran-[3a,3,2-*ef*][2]benzazepin-6-ol (Galanthamine, **1**) and (4α,6α)-4α,5,9,10,-11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuran[3a,3,2-*ef*][2]-benzazepin-6-ol (Epigalanthamine, **6**).

To a stirred suspension of lithium aluminum hydride (1.0 g, 0.026 mole) in anhydrous tetrahydrofuran (30 ml) was added dropwise a solution of the enone **15** (3.0 g, 0.008 mole) in anhydrous tetrahydrofuran (40 ml) at 0°. After refluxing the mixture for 12 hours with stirring, it was cooled to 0° and quenched by the sequential addition of water (2 ml), 15% sodium hydroxide (2 ml) and water (6 ml). The precipitated inorganic salts were removed by filtration and were washed thoroughly with ethyl acetate. The combined filtrate and washings were concentrated to an oil *in vacuo*. The oil was taken up in ethyl acetate and washed with water, brine and dried over sodium sulfate. Evaporation of the solvent afforded a mixture of galanthamine (**1**) and epigalanthamine (**6**). Flash column chromatography (5% methanol/chloroform) gave 1.2 g (53%) of galanthamine (**1**), mp 117-118° (lit [1] 121-123°) and 0.7 g (31%) of epigalanthamine (**6**), mp 198-199° (lit [1] 199°).

Galanthamine (**1**) had ir (potassium bromide): 3600 (br, OH) 2950, 2800, 1600, 1595 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.56 (A part of AB, J = 14.7, 1, H9e), 2.07 (B part of AB, J = 14.7, 1, H9a), 2.08 (A part of AB, J = 13.5, 1, H5a), 2.68 (B part of AB, J = 13.5, 1, H5e), 3.03 (A part of AB, J = 12.5, 1, H10e), 3.30 (B part of AB, J = 12.5, 1, H10a), 3.75, 4.16 (AB, J = 15, 2, H12), 3.81 (s, 3, OCH_3), 4.11 (s, 1, H6), 4.59 (m, 1, H4), 5.97 (d, J = 10, 1, H7), 6.06 (d, J = 10, 1, H8), 6.61 (d, J = 8.1, 1, H2), 6.65 (d, J = 8.1, 1, H1).

Epigalanthamine (**6**), had; ir (potassium bromide): 3200 (br, OH), 2940, 2880, 1625, 1595 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.67 (A part of

AB, J = 10.5, 1, H9a), 1.73 (B part of AB, J = 10.5, 1, H9e), 2.19 (A part of AB, J = 13.6, 1, H5a), 2.77 (B part of AB, J = 13.6, 1, H9e), 2.37 (s, 3, NCH_3), 3.05 (A part of AB, J = 13.7, H10e), 3.27 (B part of AB, J = 13.7, 1, H10a), 3.63, 4.08 (AB, J = 15, 2, H12), 3.84 (s, 3, OCH_3), 4.60 (m, 2, H4, H6), 5.81 (d, J = 10.3, 1, H7), 6.06 (d, J = 10.3, 1, H8), 6.57 (d, J = 8.2, 1, H2), 6.63 (d, J = 8.2, 1, H1).

Galanthamine Hydrochloride.

A solution of galanthamine (**1**, 3.0 g, 0.01 mole) in absolute ethanol was treated with acetyl chloride (1.0 ml, 0.013 mole) at 0°. After stirring at 0° for 20 minutes the solvent was removed, and the residual solid was subjected to high vacuum. The salt (3.2 g) was recrystallized from absolute ethanol to give 3.0 g (93%) of the pure sample, mp 252-254°.

Anal. Calcd. for $C_{17}H_{22}ClNO_3 \cdot \frac{1}{3}H_2O$: C, 61.90; H, 6.70; Cl, 10.80; N, 4.20. Found: C, 62.15; H, 6.89; Cl, 10.78; N, 4.16.

Epigalanthamine Hydrochloride.

The procedure described for galanthamine hydrochloride was followed starting with 2.5 g (0.0087 mole) of the free base **6** and treating it with 1.0 ml (0.014 mole) of acetyl chloride in 70 ml of ethanol. Recrystallization from absolute ethanol gave 2.5 g (86%) of epigalanthamine hydrochloride, mp 268-269°.

Anal. Calcd. for $C_{17}H_{22}ClNO_3$: C, 63.07; H, 6.80; Cl, 10.96; N, 4.33. Found: C, 62.95; H, 6.86; Cl, 10.87; N, 4.29.

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