Alkylation of *N*-Boc-1,2,3,4-tetrahydroisoquinolines in the 1-Position and its Application to the Synthesis of Isoquinoline Alkaloids

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Boc-protected 1,2,3,4-tetrahydroisoquinolines **2** can be lithiated with *t*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine. Reaction of the anion with alkyl halides provides 1-alkyl *N*-Boc-1,2,3,4-tetrahydroisoquinolines in 67-71% yield. The protecting group is easily removed in high yield with trifluoroacetic acid. The alkaloids salsolidine (**8**) and laudanosine (**11**) were synthesized in racemic form using this method.

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The functionalization of 1,2,3,4-tetrahydroisoquinolines in the 1-position has been a useful strategy for the construction of alkaloids as well as a variety of medicinally attractive synthetic intermediates.

Several investigators have successfully been able to effect substitution of the α-carbon of the isoquinoline nucleus by generating a dipole-stabilized carbanion adjacent to the amine nitrogen followed by addition of an electrophile. Suitable activating groups attached to the isoquinoline nitrogen are formamidine [1], pivaloyl [2,3,4], bis(dimethylamino)phosphinoyl [5], carbon dioxide [6], and nitroso [7], each having their own unique advantages as well as disadvantages.

Essentially, these functionalities can be considered protecting groups whose only purpose is to stabilize the incipient carbanion until reaction with the electrophile is complete. The versatility of the *t*-butoxycarbonyl (Boc) moiety as a protecting group for amines has been well documented [8,9]. It can easily be attached with several different reagents and can be removed under mild acidic conditions.

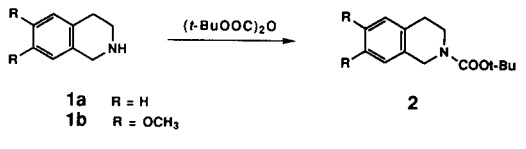
The Boc-protection of 1,2,3,4-tetrahydroisoquinoline (**1a**) can be readily accomplished in quantitative yield with di-*t*-butyl dicarbonate. The product **2a**, isolated directly from the reaction, is of sufficient purity that it can be used in the lithiation step without any further purification. In the case of the dimethoxy derivative **1b**, which is commercially supplied as the hydrochloride salt, triethylamine is added to the reaction mixture in order to generate the free base *in situ*. The product **2b**, isolated in 74% yield, can also be used in the subsequent lithiation step without further purification.

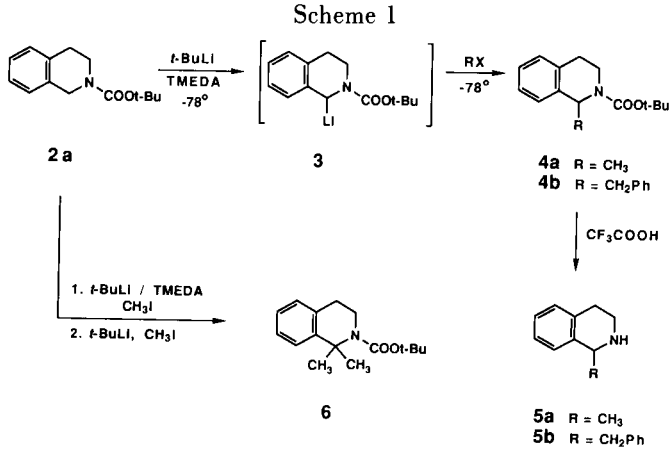
Compound **2a** can readily be deprotonated with *t*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine at -78° to form a deep-red solution of the lithiated species **3** (Scheme 1). Addition of an electrophile such as methyl iodide or benzyl bromide furnishes the 1-alkyl Boc-protected tetrahydroisoquinoline **4** in good yield. The alkylation reaction is conducted at -78° and takes approximately 2-3 hours for the red color of the anion **3** to dissipate. When the mixture turns yellow the reaction is complete.

In an effort to investigate whether this methodology is suitable for the 1,1-alkylation of tetrahydroisoquinolines, **2a** was methylated using the same conditions described above. When the first alkylation is complete, an additional equivalent of *t*-butyllithium is introduced into the reaction mixture and, after 2 hours, additional methyl iodide is added.

The second alkylation takes place very sluggishly at -78° and even raising the temperature to 25° is not sufficient to drive the reaction to completion. However, the 1,1-dimethyl derivative **6** is isolated in 26% yield along with the major product **4a** which is isolated in 35% yield. Alkylation of pure **4a** proceeds similarly and offers no particular advantage to the one-pot procedure using **2a** as the starting material.

Scheme 1



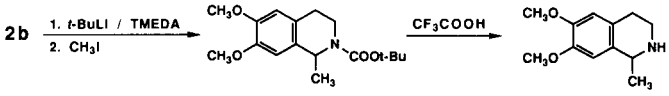


Removal of the Boc group from the monoalkylated tetrahydroisoquinoline **4** is readily accomplished with trifluoroacetic acid in methylene chloride at room temperature. The reaction is extremely clean and the resulting pure product **5** is isolated in nearly quantitative yield.

This type of substitution is exhibited in several naturally occurring isoquinolines, specifically, polymethoxylated alkaloids such as salsolidine found in the desert plant *Salsola arbuscula* (*S. richteri*) [10-13] and laudanosine isolated from opium extracts [14].

The racemic versions of these alkaloids are easily prepared employing the strategy previously outlined in Scheme 1. Salsolidine, the simpler of the two alkaloids, is synthesized in 2 steps from the Boc-protected 6,7-dimethoxytetrahydroisoquinoline **2b**. Lithiation of **2b** proceeds smoothly at -78° with *t*-butyllithium/TMEDA. Subsequent alkylation with methyl iodide furnishes the 1-methyl derivative **7** in 68% yield. Treatment of **7** with trifluoroacetic acid affords (±)-salsolidine (**8**) in quantitative yield (Scheme 2). The overall yield of the sequence starting from **1b** is 50%.

Scheme 2

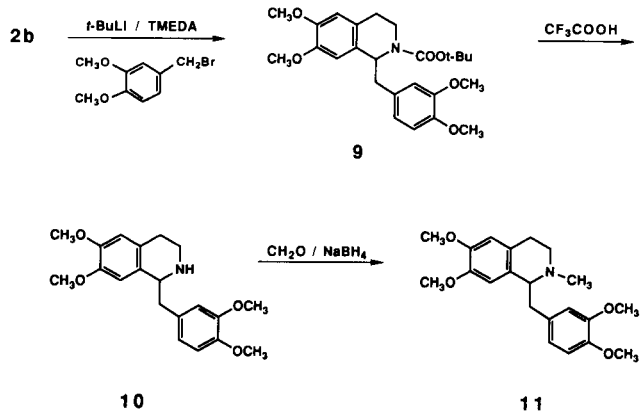


7 8

In the synthesis of laudanosine, alkylation of **2b** with 3,4-dimethoxybenzyl bromide affords the 1-benzylated derivative **9** in 62% yield. In addition to the product, 20% of unreacted **2b** is also recovered. Therefore, the actual yield of the reaction is 70% based on the amount of starting material consumed.

Deprotection of the nitrogen with trifluoroacetic acid furnishes (±)-norlaudanosine (**10**) in quantitative yield. The final transformation, *N*-methylation of **10**, is accomplished with formalin and sodium borohydride [15] to give (±)-laudanosine (**11**) in 89% yield (Scheme 3). The overall yield of **11** starting from **1b** is 46%.

Scheme 3



9 10 11

In summary, the Boc group provides efficient activation of the 1,2,3,4-tetrahydroisoquinoline nucleus for the generation of a dipole-stabilized carbanion. The resulting lithiated species reacts with alkyl halides to provide 1-alkyl tetrahydroisoquinolines in good yield. The Boc group can then be removed with trifluoroacetic acid. Reaction of the anion with other electrophiles is currently being investigated.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on an Analect FX-6200 spectrometer. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were recorded on Jeol FX-90Q and Jeol FX-200 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on either a Jeol FX-200 or a Bruker AM-500 spectrometer operating at carbon resonance frequencies of 50.1 MHz and 125.77 MHz respectively. Sample concentrations were approximately 0.1*M* in deuterated solvent and were placed in 5 mm (od) sample tubes. Acquisition parameters used were: 220 ppm spectral width, a pulse width corresponding to a 45° pulse angle (3 μsec on the Jeol FX-200 and 3.5 μsec on the Bruker AM-500), 1.8 second pulse repetition time, and 16K (Jeol FX-200) or 64K (Bruker AM-500) time-domain points. The mass spectra were determined on a Finnegan 4600 spectrometer either in EI or CI modes.

All carbanion generating reactions were conducted under an argon atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride.

Unless otherwise stated, all solutions of organic compounds were washed with saturated sodium chloride solution then were dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

3,4-Dihydro-2(1*H*)-isoquinolinecarboxylic Acid 1,1-Dimethylethyl Ester (**2a**).

To a solution of 5.0 g (0.037 mole) of 1,2,3,4-tetrahydroisoquinoline (**1a**) in 40 ml of methylene chloride was added dropwise a solution of 8.5 g (0.038 mole) of di-*t*-butyl dicarbonate in 10 ml of methylene chloride. After stirring at room temperature for 1 hour, the solvent was removed under reduced pressure to afford 9.0 g (100% yield) of **2a** as an oil. On standing the oil crystallized, mp 35-38°. The product was sufficiently pure to use in subsequent reactions without any further purification; ir (chloroform): 1701 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.10 (s, 4H), 4.55 (s, 2H), 3.64 (t, 2H), 2.82 (t, 2H), 1.50 (s, 9H).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.55; H, 8.24; N, 5.90.

3,4-Dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylic Acid 1,1-Dimethylethyl Ester (**2b**).

To a mixture of 4.2 g (0.018 mole) of **1b** and 4.1 g (0.018 mole) of di-*t*-butyl dicarbonate in 60 ml of methylene chloride was added 2.0 g (0.02 mole) of triethylamine. After stirring at room temperature for 18 hours, the solvent was removed under re-

duced pressure. Water was added to the residual solid and the mixture was extracted into methyl *t*-butyl ether. The organic phase was washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of the solvent under reduced pressure gave 4.0 g (74% yield) of pure **2b**. An analytical sample was recrystallized from methyl *t*-butyl ether, mp 123-126°; ir (chloroform): 1688 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.62 (d, J = 4.5 Hz, 2H), 4.51 (s, 2H), 3.88 (s, 6H), 3.65 (t, 2H), 2.76 (t, 2H), 1.51 (s, 9H).

Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.51; H, 7.85; N, 4.61.

3,4-Dihydro-1-methyl-2(1*H*)-isoquinolinecarboxylic Acid 1,1-Dimethylethyl Ester (**4a**).

To a solution of 2.33 g (0.01 mole) of **2a** and 1.3 g (0.011 mole) of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in 40 ml of tetrahydrofuran at -78° was added dropwise 0.72 g (0.011 mole) of *t*-butyllithium (1.7*M* solution in pentane). The mixture was stirred at -78° for 40 minutes. To the resulting red solution was added dropwise 1.5 g (0.0103 mole) of methyl iodide and the mixture was stirred at -78° for 3 hours. The resulting yellow suspension was quenched with saturated ammonium chloride solution. The mixture was extracted with methyl *t*-butyl ether (2x) and the organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to give 2.1 g of an oil. Purification was accomplished by flash chromatography using 30% ethyl acetate/hexane to elute the product, 1.7 g (67% yield) of **4a** as an oil; ir (chloroform): 1688 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.15 (m, 4H), 5.14 (m, broad, 1H), 4.10 (m, broad, 1H), 3.19 (m, broad, 1H), 3.00-2.62 (m, 2H), 1.51 (s, 9H), 1.45 (d, J = 7.5 Hz, 3H); ms (isobutane): 248 (MH^+).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.75; H, 8.69; N, 5.62.

3,4-Dihydro-1-phenylmethyl-2(1*H*)-isoquinolinecarboxylic Acid 1,1-Dimethylethyl Ester (**4b**).

To a solution of 2.0 g (0.0086 mole) of **2a** and 1.1 g (0.0095 mole) of *N,N,N',N'*-tetramethylethylenediamine in 40 ml of tetrahydrofuran at -78° was added dropwise 0.62 g (0.0097 mole) of *t*-butyllithium (1.7*M* solution in pentane). The mixture was stirred at -78° for 40 minutes. To the resulting red solution was added dropwise 1.6 g (0.0093 mole) of benzyl bromide and the mixture was stirred at -78° for 3 hours. The resulting yellow suspension was quenched with saturated ammonium chloride solution. The mixture was extracted with methyl *t*-butyl ether (2x) and the organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to give 2.9 g of an oil. Purification was accomplished by flash chromatography using 20% ethyl acetate/hexane to elute the product, 1.96 g (71% yield) of **4b**. An analytical sample was recrystallized from hexane, mp 94-96°; ir (chloroform): 1682 cm^{-1}; ^1H nmr (DMSO-d_6): 90° δ 7.16 (m, 9H), 5.23 (m, 1H), 3.96 (m, broad, 1H), 3.40-3.21 (m, 1H), 3.02 (d, J = 7.5 Hz, 2H), 2.72 (m, 2H), 1.21 (s, broad, 9H); ms (isobutane): 324 (MH^+), 285, 268, 232.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 77.75; H, 7.88; N, 4.18.

3,4-Dihydro-1,1-dimethyl-2(1*H*)-isoquinolinecarboxylic Acid 1,1-Dimethylethyl Ester (**6**).

To a solution of 2.33 g (0.01 mole) of **2a** and 1.3 g (0.011 mole) of *N,N,N',N'*-tetramethylethylenediamine in 40 ml of tetrahydrofuran at -78° was added dropwise 0.72 g (0.011 mole) of *t*-butyllithium (1.7*M* solution in pentane). The mixture was stirred at -78° for 40 minutes. To the resulting red solution was added dropwise 1.5 g (0.0103 mole) of methyl iodide and the mixture was stirred at -78° for 3 hours.

To the resulting yellow suspension was added dropwise 0.72 g (0.011 mole) of *t*-butyllithium and the mixture was stirred at -78° for 2 hours. After addition of 1.5 g (0.0103 mole) of methyl iodide the mixture was stirred at -78° for 3 hours then at room temperature for 18 hours. The reaction was quenched with saturated ammonium chloride solution and was extracted with methyl *t*-butyl ether (2x). The organic phases were combined, dried over sodium sulfate and the solvent was removed under reduced pressure to give 2.2 g of an oil. The crude mixture was chromatographed on a Waters Prep-500 apparatus using 10% ethyl acetate/hexane to elute the products, 0.87 g (35% yield) of **4a** and 0.68 g (26% yield) of **6** as an oil; ir (chloroform): 1698 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.37-7.02 (m, 4H), 3.68 (t, 2H), 2.81 (t, 2H), 1.78 (s, 6H), 1.53 (s, 9H); ms (isobutane): 262 (MH^+), 246, 206.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.50; H, 9.08; N, 5.34.

1-Methyl-1,2,3,4-tetrahydroisoquinoline (**5a**).

To a solution of 0.815 g (0.0033 mole) of **4a** in 10 ml of methylene chloride was added 1.7 ml (0.022 mole) of trifluoroacetic acid and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and 2*N* sodium hydroxide was added to the residue. The mixture was extracted with methyl *t*-butyl ether (1x) and methylene chloride (1x). The combined extracts were dried over sodium sulfate and the solvent was removed under reduced pressure to give 0.48 g (99% yield) of pure **5a** as an oil; ir (chloroform): 3313, 3270 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.14 (m, 4H), 4.13 (q, 1H), 3.36-3.22 (m, 1H), 3.12-2.66 (m, 3H), 1.90 (s, broad, 1H), 1.48 (d, J = 7.5 Hz, 3H); ms (ammonia): 148 (MH^+).

1-Phenylmethyl-1,2,3,4-tetrahydroisoquinoline (**5b**).

To a solution of 0.9 g (0.0028 mole) of **4b** in 10 ml of methylene chloride was added 2.0 ml (0.026 mole) of trifluoroacetic acid and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and 2*N* sodium hydroxide was added to the residue. The mixture was extracted with methyl *t*-butyl ether (1x) and methylene chloride (1x). The combined extracts were dried over sodium sulfate and the solvent was removed under reduced pressure to give 0.578 g (94% yield) of pure **5b** as an oil; ir (chloroform): 3328 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.33-7.02 (m, 4H), 7.24 (s, 5H), 4.31-4.07 (m, 1H), 3.40-2.70 (m, 6H), 1.80 (s, broad, 1H).

Anal. Calcd. for $C_{16}H_{17}N + 0.3H_2O$: C, 84.02; H, 7.76; N, 6.12. Found: C, 83.78; H, 8.02; N, 6.58.

3,4-Dihydro-6,7-dimethoxy-1-methyl-2(1*H*)-isoquinolinecarboxylic Acid 1,1-Dimethylethyl Ester (**7**).

To a solution of 1.0 g (0.0034 mole) of **2b** and 0.8 g (0.0068 mole) of *N,N,N',N'*-tetramethylethylenediamine in 40 ml of tetrahydrofuran at -78° was added dropwise 0.45 g (0.007 mole) of *t*-butyllithium (1.7*M* solution in pentane). The mixture was stirred at -78° for 40 minutes. To the resulting red solution was added dropwise 0.75 g (0.005 mole) of methyl iodide and the mixture was stirred at -78° for 3 hours. The resulting beige suspension was quenched with saturated ammonium chloride solution. The mixture was extracted with methyl *t*-butyl ether (2x) and the organic phases were combined and dried over sodium sulfate.

The solvent was removed under reduced pressure to give 1.1 g of an oil. Purification was accomplished by flash chromatography using 10% ethyl acetate/methylene chloride to elute the product, 0.71 g (68% yield) of **7**; ^{1}H nmr (deuteriochloroform): δ 6.61 (m, 2H), 5.09 (m, 1H), 4.17 (m, broad, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.21 (m, broad, 1H), 2.96-2.56 (m, 2H), 1.51 (s, 9H), 1.43 (d, J = 7.5 Hz, 3H), 2.72 (m, 2H), 1.22 (s, 9H).

(±)-Salsolidine (**8**).

To a solution of 0.55 g (0.0018 mole) of **7** in 7 ml of methylene chloride was added 1.0 ml (0.013 mole) of trifluoroacetic acid and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and 2*N* sodium hydroxide was added to the residue. The mixture was extracted with methyl *t*-butyl ether (1x) and methylene chloride (1x). The combined extracts were dried over sodium sulfate and the solvent was removed under reduced pressure to give 0.37 g (100% yield) of pure **8** as an oil; ir (film): 3317, 1513 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.67 (s, 1H), 6.59 (s, 1H), 4.08 (q, 1H), 3.88 (s, 6H), 3.35-3.20 (m, 1H), 3.09-2.92 (m, 1H), 2.91-2.58 (m, 2H), 1.94 (s, broad, 1H), 1.46 (d, J = 7.5 Hz, 3H); ^{13}C nmr (deuteriochloroform): δ 147.41, 147.33, 132.58, 126.90, 111.93, 109.24, 56.06, 55.90, 51.27, 41.87, 29.61, 22.88.

Anal. Calcd. for $C_{12}H_{17}NO_2$ + 0.2H_2O: C, 68.35; H, 8.32; N, 6.64. Found: C, 68.18; H, 8.59; N, 6.65.

3,4-Dihydro-6,7-dimethoxy-1-(3,4-dimethoxyphenyl)methyl)-2(1*H*)-isoquinolinecarboxylic Acid 1,1-Dimethylethyl Ester (**9**).

To a solution of 2.2 g (0.0075 mole) of **2b** and 0.9 g (0.0078 mole) of *N,N,N',N'*-tetramethylethylenediamine in 40 ml of tetrahydrofuran at -78° was added dropwise 0.5 g (0.0078 mole) of *t*-butyllithium (1.7*M* solution in pentane). The mixture was stirred at -78° for 40 minutes. To the resulting red solution was added dropwise a solution of 1.7 g (0.0074 mole) of 3,4-dimethoxybenzyl bromide [16] in 5 ml of tetrahydrofuran and the mixture was stirred at -78° for 3 hours. The mixture was quenched with saturated ammonium chloride solution and was extracted with methyl *t*-butyl ether (2x). The organic phases were combined and dried over sodium sulfate then the solvent was removed under reduced pressure to give 3.8 g of an oil. Purification was accomplished by flash chromatography using 10% ethyl acetate/methylene chloride to elute the product, 1.85 g (62% yield) of **9** as a foam; ir (chloroform): 1680, 1515 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.80 (t, 1H), 6.62 (m, 3H), 6.34 (s, 0.7H), 6.25 (s, 0.3H), 5.27 (t, 0.3H), 5.08 (t, 0.7H), 4.24-4.08 (m, 1H), 3.87 (s, 6H), 3.82 (s, 3H), 3.74 (s, 3H), 3.66 (s, 1H), 3.37-2.53 (m, 4H), 1.47 (s, 3H), 1.36 (s, 6H); ms (isobutane): 444 (MH$^+$), 388, 344, 292.

Anal. Calcd. for $C_{25}H_{33}NO_6$ + 0.3H_2O: C, 66.88; H, 7.54; N, 3.12. Found: C, 66.85; H, 7.63; N, 3.05.

In addition to the product, 0.45 g of unreacted starting material **2b** was isolated from the reaction mixture. The yield of product **9** based on the amount of **2b** consumed is 70%.

(±)-Norlaudanosine (**10**).

To a solution of 0.875 g (0.002 mole) of **9** in 25 ml of methylene chloride was added 2.0 ml (0.026 mole) of trifluoroacetic acid and the mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and 2*N* sodium hydroxide was added to the residue. The mixture was extracted with methyl *t*-butyl ether (1x) and methylene chloride (1x). The combined extracts were dried over sodium sulfate and the solvent was removed under reduced pressure to give 0.74 g (100% yield) of pure **10** as an oil; ir (film): 3320 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.92-6.62 (m, 5H), 4.17 (m, 1H), 3.91 (s, 3H), 3.89 (s, 6H), 3.88 (s, 3H), 3.31-3.13 (m, 2H), 3.00-2.65 (m, 4H), 1.78 (s, broad, 1H); ms (ammonia): 344 (MH$^+$), 192.

Anal. Calcd. for $C_{20}H_{25}NO_4$ + 0.9H_2O: C, 66.80; H, 7.51; N, 3.89. Found: C, 66.70; H, 7.12; N, 3.84.

(±)-Laudanosine (**11**).

To a solution of 0.7 g (0.002 mole) of **10** in 12 ml of methanol was added 4.0 ml of 37% formalin. After stirring at room temperature for 1 hour, 0.7 g (0.018 mole) of sodium borohydride was added slowly. After the initial vigorous reaction, the mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and saturated ammonium chloride solution was added to the residue. The mixture was extracted with methylene chloride (2x) and the combined organic phases were dried over sodium sulfate. Removal of the solvent under reduced pressure furnished 0.65 g (89% yield) of pure **11**. An analytical sample was recrystallized from methylene chloride/ether, mp 110-112° (lit [17] mp 113-114°); ^{1}H nmr (deuteriochloroform): δ 6.88-6.57 (m, 4H), 6.09 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 3.72 (m, 1H), 3.61 (s, 3H), 3.28-3.10 (m, 2H), 2.94-1.59 (m, 4H), 2.55 (s, 3H); ms (ammonia): 358 (MH$^+$), 344, 206.

Anal. Calcd. for $C_{21}H_{27}NO_4$ + 0.2H_2O: C, 69.86; H, 7.65; N, 3.88. Found: C, 69.72; H, 7.87; N, 3.90.

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