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SIMPLE SYNTHSIS OF RACEMIC PYRROLO[2,3-*b*]INDOLES: FORMAL TOTAL SYNTHESIS OF (±)-PHYSOSTIGMINE

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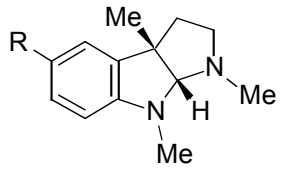
Abstract - Racemic pyrrolo[2,3-*b*]indoles were efficiently synthesized by the reaction of aromatic hydrazines with 4-chloro-2-methylbutanal. A formal total synthesis of physostigmine was achieved.

Physostigmine (**1**), which is isolated from *Physostigma venenosum* (Balf.) seeds (Calabar beans),[1] is a highly potent acetylcholinesterase inhibitor.[2]



(-)-Pysostigmine (**1**): R=OCONHMe
(-)-Phenserine (**2**): R=OCONHPh
(-)-Esermethol (**3**): R=OMe
(-)-Eseroline (**4**): R=OH
(-)-Desoxyeseroline (**5**): R=H

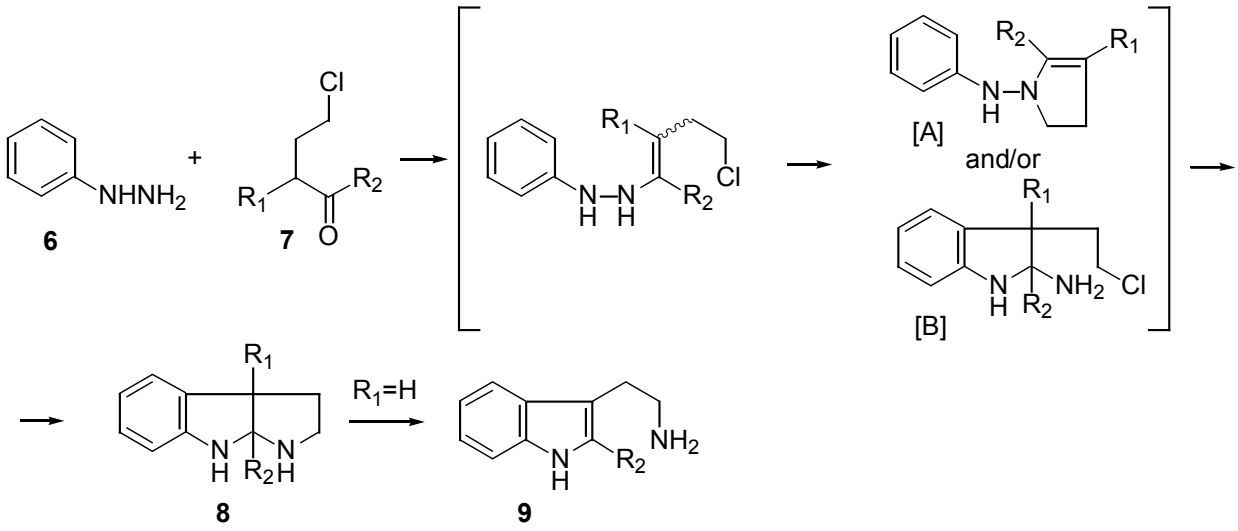
Figure 1. Physostigmine and related alkaloids.

Much attention has been focused on this molecule and its derivatives because of its therapeutic potential in Alzheimer's disease (AD), the most common neurodegenerative disorder. Among these derivatives, phenserine (**2**) has been recognized to reduce β-amyloid peptide precursor protein, which is an important target in the treatment of AD, and is currently in phase II efficacy trials.[3] Physostigmine is also an important tool in neuroscience. The binding ability of (-)-eseroline (**4**), a metabolite of physostigmine, and its enantiomer to opiate receptors is alto an important topic in neuroscience in connection with the potent morphine-like narcotic agonist activity of (-)-eserine *in vivo*.[4]

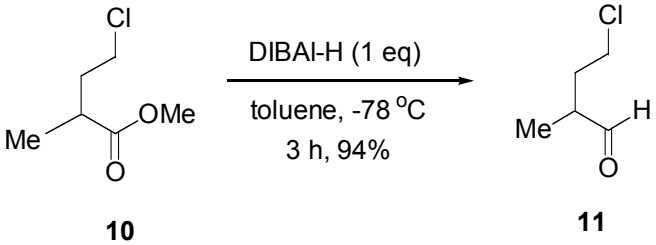
Based on the potential utility of **1** and its derivatives, considerable effort has been applied to develop methods for synthesizing chiral and racemic pyrrolo[2,3-*b*]indoles.[5] These syntheses are classified in three categories, such as 1) synthesis via 3-alkyloxindoles,[5e,h] which is the most popular route for the synthesis, 2) reductive cyclization of 3-(2-aminophenyl)-2-pyrrolidinones,[5i,j] 3) modification of Fischer indole synthesis.[5a,b] We report here a simple and practical synthesis of racemic pyrrolo[2,3-*b*]indoles via a modified Grandberg tryptamine synthesis and a formal total synthesis of racemic physostigmine.

In 1967, Grandberg and co-workers reported an efficient synthesis of tryptamines by Fischer indole synthesis.[6] The reaction most likely give dihydropyrrol intermediates (A) or aminoindoline intermediates (B) to give pyrroloindole intermediates (**8**), which spontaneously deprotonated to afford tryptamines (**9**) when R_1=H. On the other hand, when R_1 is not a hydrogen, **8** becomes a product that can be isolated, and

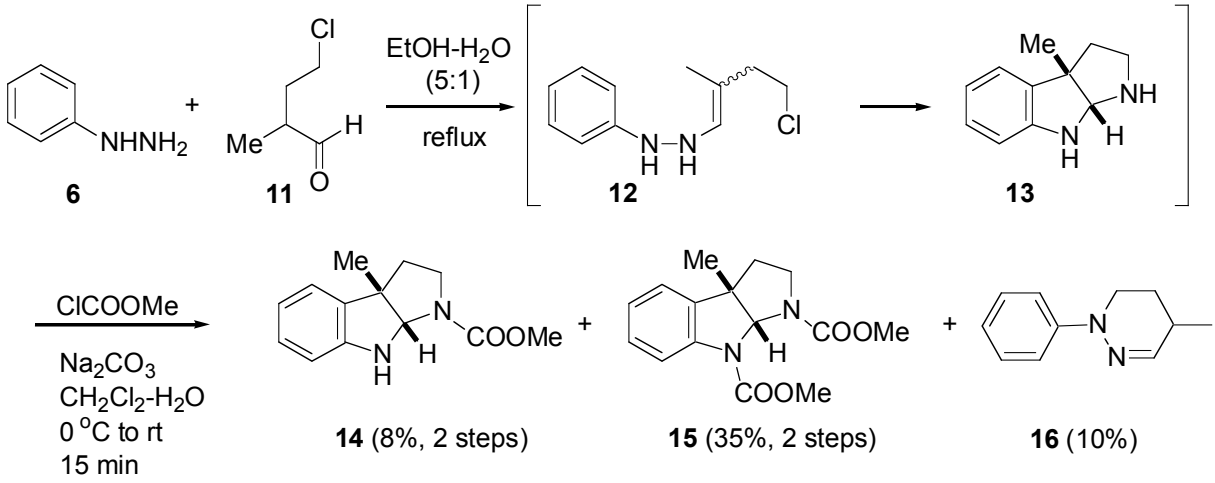
this would represent a new method for synthesizing of pyrroloindoles. In fact, they also reported deoxydinor-9-methyleseroline was synthesized by the reaction of phenylhydrazine (**6**) with 5-chloro-3-methyl-2-pentanone (**7**, R_1=R_2=Me). Grandberg and colleagues did not, however, study the reaction using 5-chloro-3-methylbutanal (**11**). Therefore, we first tested the similar reaction of **6** with the aldehyde (**11**), which was readily prepared by the DIBALH reduction of commercially available methyl 4-chloro-2-methylbutanoate (**10**) (**Scheme 2**).[7]



Scheme 1



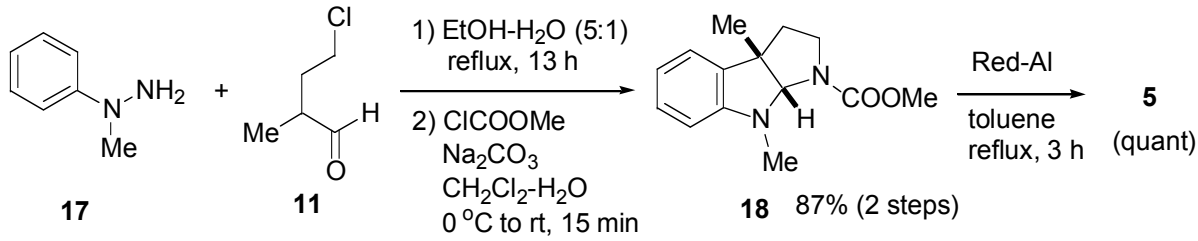
Scheme 2



Scheme 3

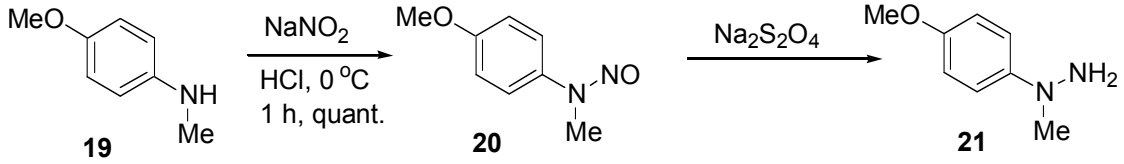
The reaction of phenylhydrazine (**6**) with **11** (1.0 eq.) proceeded smoothly under reflux conditions in

EtOH-H_2O (5:1). Subsequent acylation of the reaction mixture with methyl chloroformate gave **14** and **15** in respective yields of 8% and 35% (**Scheme 3**). The structure of a newly formed by-product (*ca.* 10%) was elucidated to be 4-methyl-1-phenyl-1,4,5,6-tetrahydropyridazine (**16**), which was probably formed after nucleophilic attack by an *Na* nitrogen atom of the ene-hydrazine intermediate (**12**) to the terminal carbon. Therefore, we examined the reaction of *Na*-methylphenylhydrazine (**17**), instead of **6**, with **11** to prevent the formation of undesired **16**.

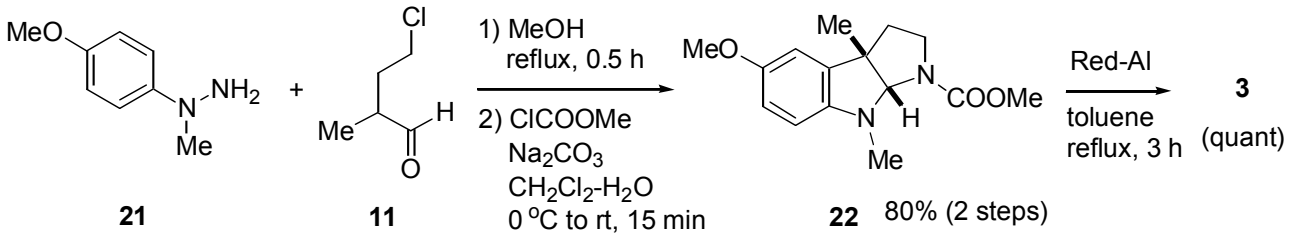


Scheme 4

Heating a mixture of **17** and **11** (2.0 eq.) in EtOH-H_2O (5:1) for 13 h and subsequent acylation gave **18** in 87% yield. The carbamate (**18**) was readily converted to desoxyeseroline (**5**) in quantitative yield by reduction with Red-Al in toluene (**Scheme 4**). Thus, we developed a highly efficient method for the synthesis of racemic physostigmine derivatives.



Scheme 5



Scheme 6

We next applied this reaction to the hydrazine (**21**) to obtain **3**, which has been known to convert to **1**. However, **21**, which was synthesized from *N*-methyl-*p*-anisidine (**19**) in 2 steps (**Scheme 5**), did not give **22** under similar reaction conditions. The reaction did not proceed at all in benzene and the product decomposed at elevated temperature (THF and CF_3CH_2OH). The best result was obtained when the reaction was performed in MeOH. The reaction of **21** with **11** was completed within 0.5 h and gave **22** in 80% yield after acylation. The reaction of **21** proceeded much faster than that of **17** because of the higher nucleophilicity of the hydrazine (**21**) due to an electron–donating substituent on the benzene ring. Product (**22**) was easily converted to esermethol (**3**) in excellent yield by reduction with Red-Al.

Racemic desoxyeseroline (**5**) and esermethol (**3**) were synthesized in 3 steps from **17** and **21**, respectively. The synthesis of physostigmine (**1**) from esermethol (**3**) has already been established,[5h] and therefore a

formal synthesis of racemic physostigmine (**1**) was achieved.
In combination with optical resolution methodologies,[8] this should also give a highly efficient method for the synthesis of chiral physostigmine derivatives. Further studies on its application in asymmetric processes are underway.

EXPERIMENTAL

4-Chloro-2-methylbutanal (11):[8] To a solution of methyl 4-chloro-2-methylbutanoate (**10**) (4.2 mL, 30 mmol) in toluene (50 mL) at –78 °C was slowly added DABALH (1.00 M solution in toluene, 30 mL) over 30 min. After the mixture was stirred for 1.2 h at the same temperature, MeOH (3.0 mL) was added and stirring was continued for an additional 30 min. A saturated aqueous solution of Rochelle salt (100 mL) was then added and the mixture was stirred at rt for several hours. The resulting mixture was diluted with ether (50 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3 times) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt / *n*-hex = 1 / 10) to give **11** (3.4 g , 94%).
^{1}H NMR ($CDCl_3$): δ 1.17 (d, 3H, *J* = 7.3 Hz), 1.74-1.82 (m, 1H), 2.20-2.29 (m, 1H), 2.62-2.71 (m, 1H), 3.56-3.67 (m, 2H), 9.68 (d, 1H, *J* = 0.9 Hz); ^{13}C NMR ($CDCl_3$): δ 12.98, 32.86, 42.30, 43.58, 203.59.

1-Methoxycarbonyl-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (14) and 1,8-bis(methoxycarbonyl)-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (15): A mixture of phenylhydrazine (**6**) (108 mg, 1.0 mmol) and **11** (120 mg, 1.0 mmol) in 12 mL of EtOH-H_2O (5:1) was heated at reflux temperature for 2 h. After the solvent was evaporated, the residue was dissolved in a mixture of CH_2Cl_2 (5 mL) and water (1 mL). To this mixture were added ClCOOMe (283 mg, 3.0 mmol) and Na_2CO_3 (211 mg, 2.0 mmol) at 0 °C, and the solution was stirred at rt for 15 min. The product was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (AcOEt/*n*-hexane=1/10 to 1/5) to afford **14** (18 mg, 8%) and **15** (100 mg, 35%).
14: ^{1}H NMR (DMSO-d_6, 130 °C) δ 1.35 (3H, s), 2.00 (1H, ddd, *J*= 7.8, 9.8, 12.4 Hz), 2.30 (1H, ddd, *J*= 2.7, 6.6, 12.4 Hz), 3.58 (1H, ddd, *J*= 2.7, 7.8, 10.5 Hz), 3.65 (3H, s), 5.04 (1H, s), 6.56 (1H, d, *J*= 7.8 Hz), 6.63 (1H, t, *J*= 7.4 Hz), 6.96 (1H, dt, *J*= 1.0, 7.8 Hz), 7.05 (1H, d, *J*= 7.3 Hz); ^{13}C NMR (DMSO, 130 °C) δ 23.85, 36.76, 40.12, 44.75, 51.01, 52.18, 81.48, 107.97, 117.21, 121.38, 126.95, 133.09, 148.40, 153.85; IR ν_{max} (neat) 3363, 2956, 2869, 1770, 1695, 1454, 1384, 1201, 744 cm^{-1}; LRMS (EI) m/z 232 (M^+, 100%); HRMS (FAB) calcd for $C_{13}H_{16}N_2O_2$ 232.1212, found 232.1226. **15:** ^{1}H NMR ($CDCl_3$) δ 1.43 (3H, s), 1.98 (1H, dt, *J*= 7.8, 12.2 Hz), 2.18 (1H, dd, *J*= 5.6, 12.2 Hz), 2.91 (1H, dt, *J*= 5.6, 11.9 Hz), 3.72 (3H, s), 3.80 (1H, m), 3.86 (3H, s), 5.92 (1H, s), 7.03-7.07 (1H, m), 7.12-7.14 (1H, m), 7.21-7.26 (1H, m), 7.68 (1H, *J*= 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 24.88, 37.72, 46.03, 52.47, 52.70, 52.73, 81.92, 116.14, 122.27, 123.70, 128.23, 129.07, 136.08, 141.42, 154.06, 155.05; IR ν_{max} (neat) 3363, 2956, 2867, 1695, 1610, 1454, 1384, 1201, 744 cm^{-1}; LRMS (EI) m/z 290 (M^+, 88%), 231 (100% base peak); HRMS (FAB) calcd for $C_{15}H_{19}N_2O_4$ 291.1345, found 291.1353.

3a,8-Dimethyl-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (18): A mixture of *N*-methylphenylhydrazine (**17**) (122 mg, 1.0 mmol) and **11** (240 mg, 2.0 mmol) in 12 mL of EtOH-H_2O (5:1) was heated at reflux temperature for 13 h. After the solvent was evaporated, the resulting residue was dissolved in a mixture of CH_2Cl_2 (5 mL) and water (1 mL). To this mixture were added ClCOOMe (283 mg, 2.0 mmol) and Na_2CO_3 (211 mg, 2.0 mmol) at 0 ℃. The solution was stirred at rt for 15 min, and the product was then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent *in vacuo* gave a residue which was purified by silica gel chromatography (AcOEt/*n*-hexane=1/2) to give **18** (213 mg, 87%).
^{1}H-NMR (DMSO-d_6, 150 ℃) □1.38 (3H, s), 1.95 (1H, ddd, *J* = 7.8, 8.8, 12.5 Hz), 2.04 (1H, ddd, *J*= 3.9, 6.6, 12.5 Hz), 2.90 (3H, s), 3.00 (1H, ddd, *J* = 6.7, 8.8, 10.7 Hz), 3.68 (3H, s), 3.73 (1H, ddd, *J*= 3.9, 7.8, 10.6 Hz), 5.09 (1H, s), 6.39 (1H, d, *J* = 7.8 Hz), 6.63 (1H, t, *J* = 7.3 Hz), 7.02-7.06 (2H, m); ^{13}C-NMR (DMSO-d_6, 150 ℃) □23.80, 32.01, 37.80, 42.05, 45.02, 51.05, 88.22, 105.19, 116.55, 120.88, 127.15, 127.69, 133.66, 149.49; IR □$_{max}$ (neat) 2953, 1713, 1608, 1494, 1446, 1386, 1234, 1201, 1107, 745 cm^{-1}; LRMS (EI) m/z 246 (M^+, 100%), 247 (M^++1, 50%); HRMS (FAB) calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1367.

Desoxyeseroline (5): A solution of Red-Al (70% in toluene, 1.4 mL, 4.8 mmol) was added to a solution of **18** (112 mg, 0.47 mmol) in 5 mL of toluene at rt. The mixture was heated at reflux temperature for 3 h. The reaction was quenched with 2 mL of 5% NaOH aq at 0 ℃ and the mixture was diluted with 2 mL of AcOEt. The reaction mixture was filtered through a Celite pad and the filtrate was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent *in vacuo* gave a residue which was purified by silica gel chromatography (AcOEt/*n*-hexane=2/1) to give **5** (94 mg, 100%).
^{1}H-NMR ($CDCl_3$) □1.43 (3H, s), 1.94-1.97 (2H, m), 2.55 (3H, s), 2.60-2.74 (2H, m), 2.95 (3H, s), 4.10 (1H, s), 6.40 (1H, d, *J*= 7.8 Hz), 6.66 (1H, t, *J*= 7.4 Hz), 6.98 (1H, d, *J*= 7.8 Hz), 7.07 (1H, t, *J*= 7.6 Hz); ^{13}C-NMR ($CDCl_3$) □27.32, 36.46, 38.45, 40.81, 52.57, 53.18, 97.47, 106.49, 117.43, 122.14, 127.61, 136.63, 151.90; IR □$_{max}$ (neat) 2957, 2864, 1605, 1492, 1451, 1346, 1299, 1255, 1191, 1124, 1034, 957, 897, 737 cm^{-1}; LRMS (EI) m/z 202 (M^+, 20%), 158 (100% base peak); HRMS (FAB) calcd for $C_{13}H_{18}N_2$ 202.1470, found 202.1465.

4-Methoxy-*N*-methyl-*N*-nitrosoaniline (20): A solution of $NaNO_2$ (1.38 g, 20 mmol) in 8 mL of water was added dropwisely to a stirred solution of **19** (2.74 g, 20 mmol) in 2.9 mL of concentrated HCl at 0 to 3 ℃. After stirring for 1 h, the mixture was poured into water and the product was extracted with benzene. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give **20** (3.31 g, 100%). This compound was used without further purification.
^{1}H-NMR ($CDCl_3$) □3.44 (3H, s), 3.85 (3H, s), 6.94-7.01 (2H, m), 7.42-7.46 (2H, m); ^{13}C-NMR ($CDCl_3$) □33.25, 55.56, 114.56, 121.12, 135.70, 158.91; IR □$_{max}$ (KBr) 3465, 3421, 2935, 1650, 1606, 1513, 1450, 1247, 1213, 1027, 833 cm^{-1}; LRMS (EI) m/z 136 (M^+-NO_2, 100%); HRMS (FAB) calcd for $C_8H_{10}N_2O_2$ 166.0742, found 166.0735.

4-Methoxy-*Na*-methylphenylhydrazine (21): To a solution of **20** (5.50 g, 33 mmol) in a mixture of 73 mL of 20% NaOH and 108 mL of EtOH at 58 ℃ under Ar was added $Na_2S_2O_4$ (23.0 g, 132 mmol) in a single portion. The mixture was stirred at 90 ℃ for 2 h and then poured into water. The product was extracted with ether and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane=1/2 to 1/1) to give **21** (4.74 g, 94%).
^{1}H-NMR ($CDCl_3$) δ 2.99 (3H, s), 3.55 (2H, br s), 3.73 (3H, s), 6.79-6.84 (2H, m), 6.94-6.98 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 45.74, 55.43, 114.12, 115.54, 147.21, 153.02; IR ν_{max} (KBr) 3338, 2952, 2832, 2362, 1508, 1243, 678 cm^{-1}; LRMS (EI) m/z 152 (M^+, 50%), 149 (100%); HRMS (FAB) calcd for $C_8H_{12}N_2O$ 152.0950, found 152.0938.

3a,8-Dimethyl-5-methoxy-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]-indole (22): A mixture of *p*-methoxy-*Na*-methylphenylhydrazine (**21**) (152 mg, 1.0 mmol) and **11** (240 mg, 2.0 mmol) in 10 mL of MeOH was heated at reflux temperature for 0.5 h. After the solvent was evaporated, the resulting residue was dissolved in a mixture of CH_2Cl_2 (5 mL) and water (1 mL). To this mixture were added ClCOOMe (283 mg, 2.0 mmol) and Na_2CO_3 (211 mg, 2.0 mmol) at 0 ℃. The solution was stirred at rt for 15 min and the product was then extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent *in vacuo* gave a residue which was purified by silica gel chromatography (AcOEt/*n*-hexane=1/4) to give **22** (222 mg, 80%).
^{1}H-NMR ($CDCl_3$, 55 ℃) δ 1.40 (3H, br s), 1.86-2.11 (2H, m), 2.90 (3H, br s), 3.13-3.20 (1H, m), 3.73 (7H, m), 5.10 (1H, br s), 6.30 (1H, d, *J*= 8.0 Hz), 6.66 (1H, d, *J*= 2.4 Hz), 6.66 (1H, dd, *J*= 2.4, 8.0 Hz), 7.07 (1H, t, *J*= 7.6 Hz); ^{13}C-NMR ($CDCl_3$, observed as two sets of rotomers) δ (24.01, 24.33), (33.61, 34.30), (38.22, 38.71), (46.14, 46.38), 51.64, (52.34, 52.82), 55.92, (89.14, 89.91), (106.70, 106.84), 109.65, 112.31, (135.58), (144.59, 144.75), 152.86, (155.52, 156.41); IR ν_{max} (neat) 2954, 2885, 2829, 1700, 1597, 1498, 1446, 1385, 1281, 1198, 1092, 1032, 995, 856, 800, 769, 723, 692 cm^{-1}; LRMS (EI) m/z 276 (M^+, 100% base peak); HRMS (FAB) calcd for $C_{15}H_{20}N_2O_3$ 276.1474, found 276.1488.

Esermethol (3): A solution of Red-Al (70% in toluene, 0.6 mL, 2.0 mmol) was added to a solution of **22** (108 mg, 0.40 mmol) in 5 mL of toluene at rt. The mixture was heated at reflux temperature for 3 h. The reaction was quenched with 2 mL of 5% NaOH aq. at 0 °C and diluted with 2 mL of AcOEt. The reaction mixture was filleted through a Celite pad and the product was extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent *in vacuo* gave a residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane=2/1) to give **3** (86 mg, 96%).
^{1}H-NMR ($CDCl_3$) δ 1.43 (3H, s), 1.97 (2H, m), 2.53 (3H, s), 2.64 (1H, m), 2.72 (1H, m), 2.89 (3H, s), 3.75 (3H, s), 4.05 (1H, s), 6.36 (1H, d, *J*= 8.1 Hz), 6.63 (1H, s), 6.65 (1H, d, *J*= 8.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 27.38, 37.90, 38.14, 40.78, 52.69, 53.01, 55.96, 98.32, 107.39, 109.75, 112.12, 138.22, 146.53, 152.90; IR ν_{max} (neat) 2955, 1595, 1495, 1423, 1346, 1280, 1220, 1121, 1066, 1032, 958, 866, 798, 707 cm^{-1}; LRMS (EI) m/z 232 (M^+, 100% base peak) 149 (80%); HRMS (FAB) calcd for $C_{14}H_{20}N_2O$ 232.1576, found 232.1577.

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