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Concise Total Synthesis of (−)-Deoxocuscohygrine and (−)-Dihydrocuscohygrine†

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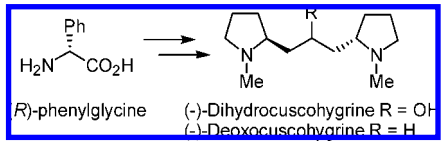
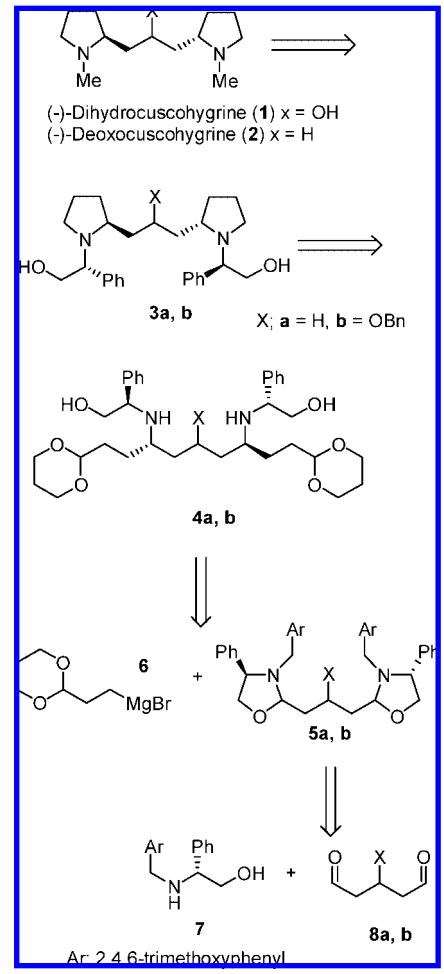


The concise enantioselective total synthesis of C_2-asymmetrical (−)-deoxocuscohygrine and (−)-dihydrocuscohygrine are described. Double-diastereoselective additions of normal Grignard reagent to bis(1,3-oxazolidine) have been deployed to construct chiral diamine fragments as a key step.

Since (−)-dihydrocuscohygrine **1** was isolated from the leaves of *Erythroxylon coca* by Turner in 1981,[1] it has been found distributed in some Erythroxylaceae families.[2,3] Compound **1** has been inferred from other included alkaloids to be a byproduct in the biosynthesis pathway of tropane alkaloids, but there is no report on its biological activity. Alkaloids having a tropane skeleton, for example, cocaine, atropine, and scopolamine, have some physiological activities that have attracted considerable attention in medicinal chemistry. Cuscohygrine, which has frequently been seen in their alkaloids, has some biological activity.[4] These compounds were found to be C_2-symmetrical diamines with a propane side chain attached to two pyrrolidine heterocyclic moieties. In connection with establishing absolute configuration, the only total synthesis of antipode of **1** has been accomplished in nine steps with a 30% overall yield starting from the chiral compound derived from the enzymatic desymmetrization of *meso*-diol.[5] In this paper, we describe the first total synthesis of naturally occurring (−)-dihydrocuscohygrine **1** using a C_2-asymmetric approach.

SCHEME 1. Total Retrosynthesis of 1 and 2



The retrosynthetic plan for dihydrocuscohygrine **1** and deoxocuscohygrine **2** is outlined in Scheme 1. We envisaged obtaining dihydrocuscohygrine and deoxocuscohygrine from the C_2-symmetrical dipyrrolidine derivatives **3a**,**b**. Dipyrrolidine **3a**,**b** could be derived from linear diamines **4a**,**b** via a ring-closure reaction. The key intermediate **4a**,**b** is delivered through double-diastereoselective addition of alkylmagnesium bromide **6** to bis(1,3-oxazolidine) **5a**,**b**, which was expected to establish the requisite asymmetric carbon center. In addition to our work on the synthesis of piperidines[6] related to the pyrrolidines, we have previously demonstrated that easily available Grignard reagents are especially effective as nucleophiles in double diastereoselective addition to bis(1,3-oxazolidine).[7] For the synthesis of bis(1,3-oxazolidine) **5a**,**b** we relied on our development that involves the condensation of N-substituted phenylglycinol **7** as a chiral auxiliary and dial **8a**,**b**.

† This paper is dedicated to the memory of late A. I. Meyers.

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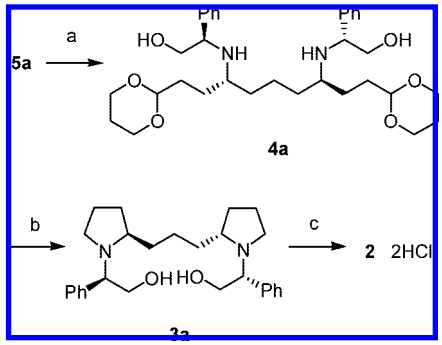
SCHEME 2. Asymmetrical Synthesis of (−)-Deoxocuscohygrine[a]

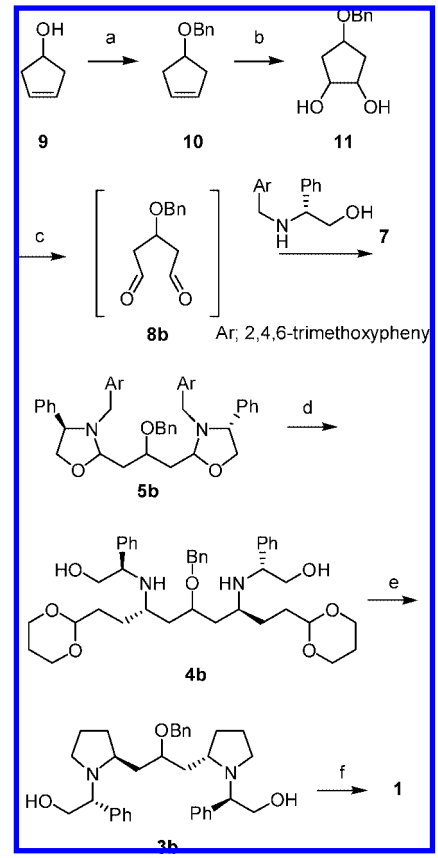


[a] Reagents and conditions: (a) 2-[2-(1,3-dioxanyl)]ethylmagnesium bromide (**6**), THF, 60 °C, 92%; (b) HCl, then $NaBH_3CN$, 65%; (c) Raney Ni, MeOH, then HCl, 56%.

Our first target was deoxocuscohygrine **2**; our aim was to prove the utility of our methodology and also confirm the C_2-symmetrical dipyrrolidine skeleton. The synthesis of compound **2** started from the known bis(1,3-oxazolidine) **5a**,[7a] which was readily prepared from the enantiomerically pure (*R*)-*N*-2,4,6-trimethoxybenzylphenylglycinol **7** and pentanedial **8a** with no need for chromatographic purification (Scheme 2). Double-diastereoselective addition of nucleophile **6**, prepared in situ from alkyl bromide, to bis(1,3-oxazolidine) **5a** provided the desired diamine **4a** in 95% yield as the sole isolable product. There is nothing surprising to estimate the high diastereoselectivity by our previous reports.[6−8] It is noteworthy that cleavage of the 2,4,6-trimethoxybenzyl moiety occurred during the addition at 60 °C for 2 d. Subsequent compound **4a** was subjected to acidic cyclization followed by reduction with $NaBH_3CN$ to give the requisite C_2-symmetrical dipyrrolidine **3a** in 65% yield through a two-step sequence. Finally, reductive methylation of a secondary amine with Raney nickel (W-2) in methanol furnished deoxocuscohygrine **2** as dihydrochloride in 56% yield.[9]

Our second target was dihydrocuscohygrine **1**, which we envisioned could be synthesized by a route similar to that described above, introducing oxygen function into dial **8a**. The synthesis of compound **1** began with known alcohol **9** derived from cyclopentadiene.[10] Standard benzyl protection of **9** gave benzyl ether **10** in 83% yield that was dihydroxylated under Tsuji dihydroxylation condition (cat. OsO_4, K_2CO_3, DABCO, $K_3Fe(CN)_6$ in *t*-BuOH−H_2O) to afford **11** in 73% yield.[11] After screening under several reaction conditions, the desired bis(1,3-oxazolidine) **5b** was obtained by one-pot synthesis following condensation of dial **8b**, generated in situ by a $NaIO_4$ oxidation of diol **11**, with a double portion of amino alcohols **7**. The crude product **5b** was confirmed to be pure by ^{1}H NMR analysis. The conversion of compound **5b** into dipyrrolidine **3b** was accomplished in a manner analogous to the protocol described in Scheme 2. Thus, double-diastereoselective addition of Grignard reagent **6** to compound **5b** was successfully achieved from

SCHEME 3. Asymmetrical Synthesis of (−)-Dihydrocuscohygrine[a]



[a] Reagents and conditions: (a) BnBr, NaH, TBAI, 70%; (b) OsO_4, DABCO, K_2CO_3, 74%; (c) $NaIO_4$, then (*R*)-*N*-(2,4,6-trimethoxybenzyl)phenylglycinol, (d) 2-[2-(1,3-dioxanyl)]ethylmagnesium bromide (**6**), THF, 60°C, 60% (from **11**); (e) HCl, then $NaBH_3CN$, 66%; (f) (1) $Pd(OH)_2/H_2$, (2) 10% HCl, HCHO, then $NaBH_3CN$, 67%.

compound **11** in three steps with high diastereoselectivity in 60% yield. Simultaneous deprotection of acetal function and annulation by nitrogen concerted an attack under acidic conditions, followed by treatment with $NaBH_3CN$ to afford the desired C_2-symmetrical dipyrrolidine **3b** in 66% yield through a two-step sequence. X-ray structural analysis of compound **3b** unequivocally proved the expected absolute configurations of the new stereogenic centers (see the Supporting Information). Finally, the above reductive methylation of compound **3b** resulted in low yield. This could be circumvented by hydrogenation of the three-benzyl portion with $Pd(OH)_2$ catalysis, followed by aldimination with HCHO and subsequent $NaBH_3CN$ reduction, leading to the formation of the target dihydrocuscohygrine **1** in 67% yield in three steps. The ^{1}H NMR spectral data of synthetic product **1** was fully identical with that of natural product **1** and unnatural synthetic product **1**. The magnitude of the optical rotation of our synthetic product **1** $[\alpha]^{26}_D$ −105.5 (*c* 1.67, $CHCl_3$) was in strict accordance with that of antipode synthetic product **1** $[\alpha]^{20}_D$ +105 (*c* 2.05, acetone)[5] but not that of natural product **1** $[\alpha]^{22}_D$ −68 (*c* 2.5, acetone).[1]

In conclusion, stereoselective total synthesis of C_2-asymmetrical (−)-dihydrocuscohygrine **1** and (−)-deoxocuscohygrine **2** was accomplished starting from (*R*)-phenylglycinol derivative **7**. The key step in the synthesis involved the stereocontrolled construction of the convertible secondary diamines via double-

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diastereoselective additions of Grignard reagent to bis(1,3-oxazolidine) and was a highly effective means for preparing C_2-asymmetrical chiral diamines.

Experimental Section

(2*R*,2′*R*)-[1,9-Bis(1,3-dioxan-2-yl)nonane-(3*S*,7*S*)-diamino]bis-(2-phenylethanol) (4a). A solution of **5a** (21.30 g, 30.52 mmol) in THF (150 mL) was treated with a freshly prepared Grignard reagent **6**, derived from 2-(2-bromoethyl)-1,3-dioxane (30.37 mL, 183.12 mmol) and magnesium (7.27 g, 244.16 mmol) in THF (150 mL), heated at 60 °C for 2 d, and allowed to cool to rt. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (200 mL) and extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography (200:10:1 CH_2Cl_2/CH_3OH/NH_4OH) to furnish **4a** (16.52 g, 95%) as a dark yellow gum: $[\alpha]^{26}D$ −55.2 (*c* 3.06, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28−1.71 (m, 18H), 1.95−2.13 (m, 2H), 2.44 (m, 2H), 3.01 (br, 2H), 3.40−3.47 (dd, J = 9.0, 10.5 Hz, 2H), 3.62−3.68 (dd, J = 4.4, 10.5 Hz, 2H), 3.69−3.74 (dt, J = 2.1, 11.0 Hz, 4H), 3.78−3.83 (dd, J = 4.4, 9.0 Hz, 2H), 4.03−4.09 (dd, J = 4.8, 11.0 Hz, 4H), 4.35−4.38 (t, J = 4.8 Hz, 2H), 7.23−7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 19.2, 25.7, 29.0, 31.6, 33.5, 53.4, 61.8, 66.8, 66.9, 102.2, 127.3, 127.4, 128.5, 141.3; IR (film) cm^{-1}; 3440, 2930, 2850, 1455, 1140, 700; MS (EI) 570 (M^+); HRMS calcd for $C_{33}H_{50}N_2O_6$ 570.3668, found 570.3675.

(1*S*,3*S*)-Bis[(2-hydroxy-(1*R*)-phenethyl)pyrrolidin-2-yl]propane (3a). A solution of **4a** (3.90 g, 6.84 mmol) in CH_3OH (30 mL) was treated with 10% HCl (10 mL), heated to reflux for 3 h, and allowed to cool to rt. The reaction mixture was treated with sodium cyanoborohydride (1.29 g, 20.53 mmol) and stirred for an additional 2.5 h before concentration of CH_3OH. The product was alkalized with 1 M NaOH and extracted with CH_2Cl_2 three times. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (150:10:1 CH_2Cl_2/CH_3OH/NH_4OH) to furnish **3a** (1.88 g, 65%) as a light yellow oil: $[\alpha]^{23}_D$ −136.1 (*c* 2.62, EtOH); ^1H NMR ($CDCl_3$) δ 1.38−1.88 (m, 14H), 2.16−2.25 (dd, J = 8.5, 16.0 Hz, 2H), 2.60−2.63 (m, 2H), 2.87−2.94 (dt, J = 2.6, 9.0 Hz, 2H), 3.25 (br, 2H), 3.63−3.68 (dd, J = 4.5, 9.4 Hz, 2H), 3.93−4.00 (dd, J = 9.4, 10.6 Hz, 2H), 4.03−4.09 (dd, J = 4.5, 10.6 Hz, 2H), 7.16−7.39 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.2, 29.5, 34.2, 45.3, 58.7, 60.9, 62.2, 127.5, 127.9, 129.0, 135.1; IR (film) cm^{-1} 3410, 3020, 2940, 2880, 1240, 1030, 910; MS (EI) 422 (M^+); HRMS calcd for $C_{27}H_{37}N_2O_2$ 421.2855, found 421.2853.

(−)-Deoxocuscohygrine (2) Dihydrochloride. A solution of **3a** (357 mg, 0.846 mmol) in CH_3OH (5 mL) was treated with Raney Ni (W-2) (ca. 4 g), heated for refluxing for 16 h, allowed to cool to rt, and concentrated. The product was diluted with 10% HCl (5 mL), washed with ether (10 mL), alkalized with 1 M NaOH, extracted with CH_2Cl_2 for three times. The combined organic layers were dried over Na_2SO_4, a few drops of saturated hydrogen chloride ethanol solution was added, and the mixture was concentrated in vacuo. The residue was purified by recrystalization with ethyl acetate to furnish **2** dihydrochloride (134 mg, 56%) as a colorless solid: $[\alpha]^{22}D$ −14.4 (*c* 0.56, EtOH); ^1H NMR ($CDCl_3$) δ 1.52−1.70 (m, 2H), 1.86−2.11 (m, 12H), 2.23−2.32 (m, 2H), 2.84 (m, 6H), 2.91−3.10 (dt, J = 8.4, 11.5 Hz, 2H), 3.21−3.40 (m, 2H), 3.66−3.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 23.2, 29.6, 31.0, 39.2, 56.2, 67.2; IR (film) cm^{-1} 3390, 2960, 2560, 1460, 1240; MS (EI) 210 (M^+); HRMS (CI) calcd for $C_{13}H_{29}N_2Cl_2$ 283.1708, found 283.1685.

4-Benzyloxycyclopentane-1,2-diol (11). A solution of **10** (12.2 g, 71 mmol) in *t*-BuOH (700 mL) was treated with H_2O (700 mL), $K_3Fe(CN)_6$ (70.0 g, 212 mmol), K_2CO_3 (29.4 g, 212 mmol), 1,4-diazabicyclo[2.2.2]octane (2.10 g, 17.8 mmol), and 5% aqueous OsO_4 (17.6 mL) at rt. After the reaction mixture was stirred for 18 h, the product was quenched with anhydrous sodium sulfite and extracted with ethyl acetate three times. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography (1:1 ethyl acetate/hexane) to furnish **11** (10.9 g, 73.8%) as an amorphous white solid: ^1H NMR ($CDCl_3$) δ 2.00 (dd, J = 5.3, 5.8 Hz, 4H), 2.96 (br, 2H), 4.14−4.22 (m, 3H), 4.42 (s, 2H), 7.25−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 37.6, 70.2, 71.9, 76.2, 126.9, 127.0, 127.7, 137.7; IR (film) cm^{-1}; 3400, 3000, 2940, 1600, 1500, 1460, 1350, 1240, 1200, 1170, 1070, 1020, 700; MS (EI) 208 (M^+); HRMS calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1105.

(2*R*,2′*R*)-[5-Benzyloxy-1,9-bis(1,3-dioxan-2-yl)nonane-(3*S*,7*S*)-diamino]bis(2-phenylethanol) (4b). A solution of **11** (4.41 g, 21.2 mmol) in CH_2Cl_2 (110 mL) and H_2O (22 mL) was treated with sodium periodate (4.53 g, 21.2 mmol) and stirred for 10 min, and *N*-2,4,6-trimethoxybenzylphenylglycinol (12.1 g, 38.16 mmol) was added. The reaction mixture was stirred for 16 h before being separated, dried, and concentrated. The crude product **5b** was unstable and used without further purification: ^1H NMR ($CDCl_3$) δ 1.83−2.05 (m, 4H), 3.54 (s, 6H), 3.66 (s, 6H), 3.74 (s, 3H), 3.76 (s, 3H), 3.50−3.83 (m, 6H), 3.92−4.07 (m, 5H), 4.40−4.51 (m, 2H), 4.58−4.73 (m, 2H), 5.95 (s, 2H), 6.00 (s, 2H), 7.18−7.44 (m, 15H). A solution of crude **5b** (16.08 g) in THF (90 mL) and Grignard reagent [2-(2-bromoethyl)-1,3-dioxane (27.3 mL, 20.0 mmol) and magnesium (4.86 g, 20.0 mmol) in THF (90 mL)] were reacted at 60 °C for 3 d and worked up as described for **4b** to give **4b** (8.60 g, 60%) as a dark yellow oil: $[\alpha]^{26}_D$ −55.4 (*c* 3.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26−1.62 (m, 14H), 1.99−2.04 (m, 2H), 2.54−2.69 (m, 2H), 3.45 (dd, J = 8.4, 10.7 Hz, 2H), 3.61−3.83 (m, 12H), 4.01−4.09 (m, 5H), 4.24 (t, J = 4.8 Hz, 1H), 4.29 (t, J = 4.8 Hz, 1H), 4.38 (d, J = 11.2 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 7.20−7.34 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 25.7, 29.4, 29.7, 31.1, 31.1, 39.2, 39.4, 51.6, 51.9, 61.8, 62.3, 66.7, 70.2, 74.3, 102.0, 102.1, 127.1, 127.3, 127.4, 127.8, 128.2, 128.4, 138.4, 141.5, 141.8; IR (film) cm^{-1} 3440, 3020, 2960, 2940, 2860, 1600, 1500, 1450, 1220, 1140, 750; MS (EI) 676 (M^+); HRMS calcd for $C_{40}H_{56}N_2O_7$ 676.4072, found 676.4087.

3-Benzyloxy-(1*S*,3*S*)-bis[(2-hydroxy-(1*R*)-phenethyl)pyrrolidin-2-yl]propane (3b). A solution of **4b** (7.04 g, 10.4 mmol) in CH_3OH (165 mL), 15% HCl (55 mL), and sodium cyanoborohydride (2.62 g, 41.6 mmol) were reacted and worked up as described for **3a** to give **3b** (4.66 g, 85%) as a colorless crystal: mp 122−123 °C (ether/ethyl acetate); $[\alpha]^{26}D$ −155.1 (*c* 0.63, EtOH); ^1H NMR ($CDCl_3$) δ 1.28−1.78 (m, 10H), 2.05−2.29 (m, 4H), 2.63 (m, 1H), 2.84−2.94 (m, 3H), 3.26 (br, 2H), 3.44 (m, 1H), 3.63−3.70 (m, 2H), 3.94−4.08 (m, 4H), 4.38 (d, J = 11.4 Hz, 1H), 4.67 (d, J = 11.4 Hz, 1H), 7.16−7.39 (m, 15H,); ^{13}C NMR ($CDCl_3$) δ 22.1, 30.3, 30.6, 39.2, 40.4, 45.1, 45.4, 55.6, 56.1, 60.9, 61.2, 62.0, 62.4, 70.8, 75.7, 127.5, 127.6, 127.8, 128.0, 128.2, 128.3, 129.3, 129.4, 135.1, 138.5; IR (film) cm^{-1} 3100, 2920, 2880, 1600, 1450, 1100, 1060, 740, 700; MS (EI) 528 (M^+). Anal. Calcd for $C_{34}H_{44}N_2O_3$: C, 77.23; H, 8.89; N, 5.30. Found: C, 77.01; H, 8.27; N, 5.27. X-ray crystal data: $C_{34}H_{44}N_2O_3$, M = 528.73; monoclinic, space group $P2_1$(#4), a = 16.481(4) Å, b = 7.997(3) Å, c = 11.861(3) Å, β = 105.21(2)°, V = 1508.6(7) A^3, Z = 2, and D_{calc} = 1.16 g/cm^3; R = 0.050 and R_w = 0.057 for 2726 reflections with $I > 3.00\sigma(I)$. A crystal of 0.20 × 0.30 × 0.30 mm was used.

Dihydrocuscohygrine (1). A solution of **3b** (115 mg, 0.218 mmol) in CH_3OH (5 mL) was treated with 20% palladium hydroxide on carbon under hydrogen atmosphere for 3 d. The reaction mixture was filtrated with celite pad, and concentrated in vacuo. The residue was diluted with CH_3OH (2 mL), formaldehyde (0.5 mL), and 10% HCl (0.5 mL) before being stirred for 1 h and treated with sodium cyanoborohydride (200 mg, 3.18 mmol) for an additional 30 min. The product was diluted with water, washed with ether at twice, alkalized with 1 M NaOH, and extracted with CH_2Cl_2 at 5 times. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (10:4:1 hexane/CH_2Cl_2/Et_2NH) to furnish 33 mg

(67%) of **1** as colorless oil: $[\alpha]^{24}_{D}$ −105.5 (*c* 1.67, acetone); ^{1}H NMR ($CDCl_3$) δ 1.18−1.25 (m, 1H), 1.41−1.48 (m, 2H), 1.71−1.97 (m, 8H), 2.03−2.23 (m, 3H), 2.30−2.39 (m, 7H), 2.59 (m, 1H), 3.04−3.29 (m, 2H), 3.99−4.07 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.3, 28.5, 30.8, 36.7, 40.6, 40.7, 42.5, 56.9, 57.0, 63.1, 64.7, 67.1; MS (EI) 226 (M^+); HRMS calcd for $C_{13}H_{26}N_2O$ 226.2045, found 226.2034.

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Supporting Information Available: X-ray structure of compound **3b**, NMR spectra for all new compounds synthesized, and CIF file of compound **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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