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New Concise Total Synthesis of (+)-Lentiginosine and Some Structural Analogues

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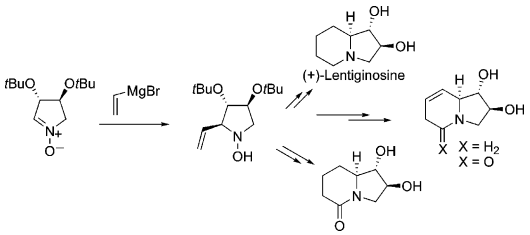

An efficient and concise total synthesis of (+)-lentiginosine (**1**) starting from an L-tartaric acid-derived nitrone using organometallic addition, indium-catalyzed reduction, and ring-closing metathesis reaction as the key steps is reported. Structural analogues of (+)-**1** have been also synthesized, and their inhibitory activity toward 22 commercially available glycosidases has been evaluated.

(+)-Lentiginosine (**1**), a dihydroxylated indolizidine alkaloid, was isolated in 1990 from the leaves of *Astragalus lentiginosus*.[1] It was reported to be a potent and selective inhibitor of amyloglucosidase, an enzyme that hydrolyzes 1,4- and 1,6-α-glucosidic linkages. Isolated lentiginosine was found to be weakly levorotatory ($[\alpha]_D$ −3.3 in MeOH). The absolute configuration (1*S*,2*S*,8a*S*) was tentatively assigned on the basis of biosynthetic considerations.[1] Later on, numerous syntheses of (1*S*,2*S*,-8a*S*)-lentiginosine have been reported, all leading to samples with small positive rotations.[2−4] We have reported the synthesis of both (+)- and (−)-lentiginosine[2b,d,g,j] based on stereoselective 1,3-dipolar cyloaddition reactions of dihydroxylated pyrroline nitrones to suitable dipolarophiles. Comparison of inhibitory activity data of both (+)- and (−)-lentiginosine allowed us to confirm the assignment of the absolute configuration (1*S*,2*S*,8a*S*) for natural lentiginosine.[2d] Moreover, a molecular dynamic simulation performed on the complex of glucoamylase II (471) from *Aspergillus awamori* var.X100 with all (*S*)-lentiginosine showed that this enantiomer perfectly fits within the enzyme cavity, forming strong H-bonds with the key residues for bioactivity.[5]

Apart from a recent controversial article,[3] all subsequent contributors concurred on the fact that natural lentiginosine has the (1*S*,2*S*,8a*S*) absolute configuration and that it is dextrorotatory. The negative rotation initially reported can be ascribed to impurities present in the natural product, also evident from the published ^{1}H NMR spectrum.[1]

Despite the plethora of synthetic methods, the interest in the synthesis of (+)-lentiginosine and its analogues remains undiminished. Development of methods having enough flexibility to allow also the construction of non-natural analogues continues to be an important topic, in particular to investigate the structure−activity relationships of this class of inhibitors.

The majority of the reported enantiospecific syntheses of lentiginosine relies upon the chiral pool. Among the chiral starting material used, the low-cost L-tartaric acid is the most widely employed, since it allows the straightforward installation of the (1*S*,2*S*) configuration of the final compound.

As part of our research on organometallic addition to chiral hydroxylated cyclic nitrones,[6,7] we report here a concise and straightforward synthesis of (+)-lentiginosine (**1**) and its structural analogues **2**−**4** (Figure 1) based on a highly stereoselective addition of vinylmagnesium

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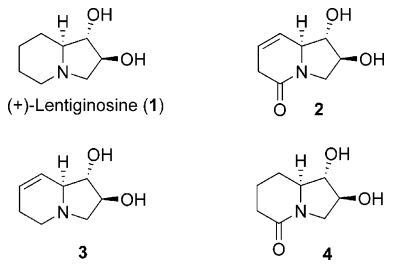
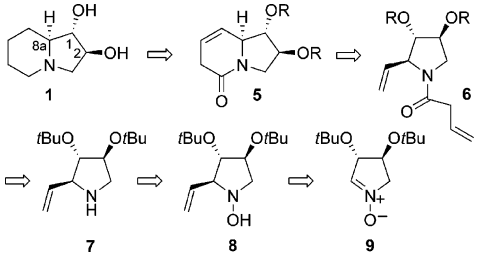


FIGURE 1. (+)-Lentiginosine and its structural analogues.

SCHEME 1. Retrosynthetic Analysis for (+)-Lentiginosine (1)

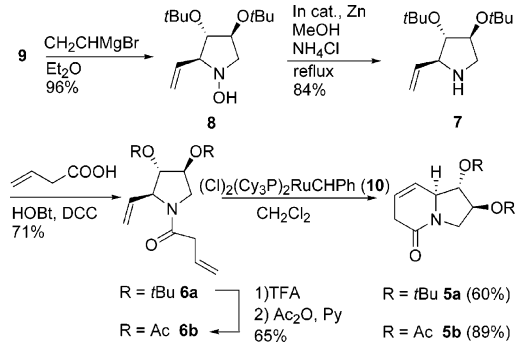


bromide on an L-tartaric acid-derived nitrone as the key step. This allowed the totally diastereoselective installation of the (8a*S*) stereogenic center. The cyclization step has been performed using a ring-closing metathesis (RCM) reaction that has been diffusely applied in the past few years for the construction of a variety of nitrogen-containing ring systems,[8,9] including pyrrolizidines, indolizidines, and other compounds related to iminosugars. Analogues **2**−**4** of (+)-lentiginosine have been tested toward 22 commercially available glycosidases. We report that dehydrolentiginosine **3** is a moderate inhibitor of amyloglucosidases from *Aspergillus niger* and from *Rhizopus mold*, not as potent as (+)-lentiginosine. It is also a weak inhibitor of *β*-glucosidases from almonds and from *Saccharomyces cerevisiae*.

Our retrosynthetic strategy for the synthesis of (+)-lentiginosine (**1**) is outlined in Scheme 1. We envisioned that indolizidine lactam **5**, from which (+)-**1** may derive by simple reduction−deprotection sequences, could be prepared by RCM reaction of amide **6**, in turn accessible from amine **7**. Compound **7**, in turn, may be prepared by indium-catalyzed reduction of hydroxylamine **8**, which may finally derive from a stereoselective addition of vinylmagnesium bromide to the L-tartaric acid-derived nitrone **9**.

Thus, nitrone **9**[10] reacted with 1.2 equiv of vinylmagnesium bromide in diethyl ether at room temperature, affording hydroxylamine **8** in 96% yield (Scheme 2).

SCHEME 2



Product **8** derived from an anti attack of the organometallic reagent with respect to the vicinal alkoxy group, as a result of combined steric and stereoelectronic effects.[11] No other stereoisomers could be detected by ^{1}H NMR of the crude reaction mixture. The possible alternative strategy for the synthesis of the indolizidine skeleton, namely allylmagnesium bromide addition to nitrone **9** followed by coupling with acrylic acid, was discarded, since the addition lacked any selectivity (two diasteroisomers were formed in ca. 1:1 ratio). This behavior of allylmagnesium bromide was an exception, since a broad range of Grignard reagents (either sp^3, sp^2, or sp type) invariably gave a high anti diastereoselectivity.[6,12] We have recently recorded a similar inversion of selectivity in the addition of allylmagnesium bromide to another class of nitrones.[13]

Reduction of **8** with powdered Zn (4 equiv) and catalytic indium (18%), according to a methodology we have recently introduced for the reduction of hydroxylamines to amines,[14] afforded the pyrrolidine **7** (84% yield). Both steps did not require purification by chromatography and could be performed on a multigram scale. Amine **7** was then reacted with but-3-enoic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) as the coupling agents, leading to amide **6a** (71%). This compound consisted of a mixture of two rotamers, clearly visible in the ^{1}H NMR spectrum recorded at 25 °C. The RCM reaction was performed on **6a** using first-generation Grubbs' catalyst **10** in refluxing dichloromethane. Three sequential additions of the catalyst (for a 12% total molar amount) and 50 h of heating under reflux were necessary to reach complete conversion of **6a**.[15] This led to lactam **5a**, isolated in 60% yield after column chromatography. We supposed that the bulky *tert*-butoxy groups might be responsible for the low reactivity of **6a** in the RCM reaction. Thus, it was converted into the acetyl-protected amide **6b** by treatment with trifluoroacetic acid, followed by an excess of

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(12) A full account on nucleophilic additions of organometallic reagents to 3-alkoxy-substituted pyrroline *N*-oxides is under preparation and will be published in due time.

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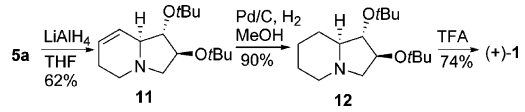
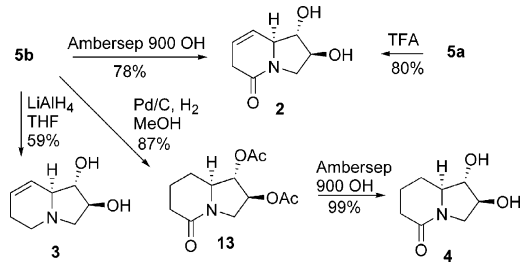
(15) Attempts were made using second-generation Grubb's catalyst or even higher temperature (80 °C or refluxing temperature in toluene as solvent), but the rate of conversion and the recovered yield could not be improved.

SCHEME 3. Synthesis of (+)-Lentiginosine



SCHEME 4. Synthesis of Analogues 2−4



acetic anhydride in pyridine. To our delight, the RCM reaction on amide **6b** was faster and higher yielding than that of **6a**. A 15% molar amount of the Grubbs' catalyst **10** was required to react **6b** completely after 20 h under reflux. This provided lactam **5b** in 89% yield (Scheme 2).

Reduction of **5a** with an excess of $LiAlH_4$ (3.2 equiv) in refluxing THF led to **11** (62%). Catalytic hydrogenation of the alkene moiety afforded the protected lentiginosine **12**[2g,j] (Scheme 3). After treatment with trifluoroacetic acid at room temperature,[2g,l] (+)-lentiginosine (**1**) was obtained in 74% yield. The spectroscopical data of the product were identical to those of (+)-lentiginosine. Its specific optical rotation ($[\alpha]_D^{25}$ +2.6, *c* 0.4, MeOH) was in excellent agreement to those reported for (+)-**1**.[16] In conclusion, (+)-lentiginosine was obtained in seven steps and 14% overall yield starting from nitrone **9**.

The analogues **2**−**4** of (+)-lentiginosine were derived from lactams **5** in a few steps (Scheme 4). Treatment of **5a** with trifluoracetic acid at room temperature or of **5b** with strongly basic Ambersep 900 OH provided **2** in comparable yields (80 and 78%, respectively). Reduction of **5b** with an excess of $LiAlH_4$ in dry THF afforded **3** in good yield.[17] On its turn, catalytic hydrogenation of **5b** and subsequent treatment with strongly basic Ambersep 900 OH produced dihydroxylactam **4** (86%, overall yield).

At 1 mM concentration, compounds **2**−**4** did not inhibit α-fucosidase from bovine epididymis, α-galactosidase from coffee bean and from *Escherichia coli*, β-galactosidase from *E. coli*, *A. niger* and from *Aspergillus orizae*, α-glucosidase from yeast and from rice, α-mannosidase from jack bean and from almond, β-mannosidase from *Helix pomatia*, β-xylosidase from *A. niger*, α-*N*-acetylgalactosamidase from chicken liver, and β-*N*-acetylglucosamidase from jack bean and from bovine epididymis A and B. Table 1 reports the inhibitory activities of 7,8-didehydrolentiginosine (**3**) to five glycosidases together with those evaluated for lactams **2** and **4** toward the same enzymes.

As for (+)-lentiginosine (**1**), **3** displays similar specificity as inhibitor toward the 22 glycosidases assayed. Thus,

TABLE 1. Inhibition Rate (in %) toward Glycosidases at 1 mM Concentration of Inhibitors 2−4[a]

	2	**3**	**4**	**1**
β-galactosidase EC 3.2.1.23 from bovine liver	0	36%	0	
β-glucosidase EC 3.2.1.21 from almonds	56%	74%	31%	
β-glucosidase EC 3.2.1.21 from *Saccharomyces cerevisiae*	0	75%	0	
amyloglucosidase EC 3.2.1.3 from *Aspergillus niger*	0	94% (63) 28	0	2[b]
amyloglucosidase EC 3.2.1.3 from *Rhizopus mold*	0	80% (41) 25	0	3[b]

[a] IC_{50} (in Parentheses) and K_i values are given in micromolar concentrations. [b] Reference 2d.

3 inhibits amyloglucosidase (1,4-α-D-glucan glucohydrolase EC 3.2.1.3), an important industrial enzyme used to produce glucose from starch.[18] The inhibitory activity of **3** is about 1 order of magnitude lower than that of **1**, thus indicating that the "flattening" of the six-membered ring of the indolizidine unit due to the unsaturation is detrimental to the inhibitory activity of **3** toward amyloglucosidases.

Nonbasic sugar analogues such as glycals, epoxides, halides, sulfonium salts, and lactams can be potent glycosidase inhibitors.[19] For instance, D-manno-δ-lactam, a natural product found in the broth of *Streptomyces lavendulae* SF435, inhibits α-mannosidases.[20] D-Manno-δ-lactam is known to be a better glucosidase inhibitor than D-glucono-δ-lactam.[21] The glucono-δ-lactone analogue 6-deoxy-4-*O*-methyl-D-glucono-δ-lactam is a slightly better inhibitor than deoxynojirimycin toward α-glucosidases from brewer's yeast and from sweet almonds.[22] Isofagomine lactams have been found to be glycosidase inhibitors with micro- and nanomolar inhibition constants.[23] We were therefore keen to see how our new lactams **2** and **4** would behave toward the 22 glycosidases assayed in this work. To our dismay, except for a weak inhibitory activity of **2** toward β-glucosidase from almonds (56% inhibition at 1 mM concentration), these two bicyclic lactams were devoid of inhibitory activity. The tautomeric form of the lactams might be involved in the enzyme recognition by a lactam as shown for a xylobiose-derived isofagomine lactam.[24] It is thus not excluded that the inability of lactams **2** and **4** to recognize any glycosidases tested here might be due to their inability to equilibrate with the corresponding tautomers of the

(16) Literature values: +3.2 (ref 2d), +2.2 (ref 2g), +3.1 (ref 2n), +2.9 (ref 2s), +1.06 (ref 2t).

(17) For the synthesis of a diastereoisomer of **3** via a RCM−ROM sequence, see: Ovaa, H.; Stragies, R.; van der Marel, G. A.; van Boom, J. H.; Blechert, S. *Chem. Commun.* **2000**, 1501.

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hydroxyimine type. Alternatively, their lack of inhibitory activity might be because their conjugate acid is not stable and cannot be formed on penetration into the active site of the enzymes.

In conclusion, a practical and enantioselective synthesis of (+)-lentiginosine (**1**) has been realized. It relies on a highly stereoselective addition of an organometallic nucleophile onto the L-tartaric acid-derived nitrone **9**, an indium-catalyzed reduction, and a ring-closing metathesis. The method has also afforded novel 7,8-didehydrolentiginosine (**3**) and the analogues of **1**, namely lactams **4** and **2**. Didehydrolentiginosine **3** is a slightly weaker inhibitor of amyloglucosidase than (+)-lentiginosine (**1**). Both compounds showed, however, the same selectivity pattern toward 22 glycosidases assayed.

Experimental Section

(1*S*,2*S*,8a*S*)-1,2-Diacetyloxy-2,3,6,8a-tetrahydro-5(1*H*)-indolizinone (5b). To a stirred solution of **6b** (342 mg, 1.22 mmol) in dry CH_2Cl_2 (60 mL) at 20 °C, under nitrogen atmosphere, a solution of benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (Grubbs' catalyst, 167 mg, 0.202 mmol) in dry CH_2Cl_2 (40 mL) was added. The reaction was heated under reflux and monitored by TLC. After 22 h, the solvent was evaporated. FC (AcOEt) afforded pure **5b** (R_f = 0.3, 275 mg, 1.09 mmol, 89%) as a light brown solid. **5b**: mp 98−100 °C; $[\alpha]^{26}_D$ +8.7 (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.96 (dq, J = 10.1, 1.8 Hz, 1H, H-7), 5.91−5.86 (m, 1H, H-8), 5.22 (ddd, J = 7.8, 3.9, 3.8 Hz, 1H, H-2), 5.07 (dd, J = 7.8, 4.3 Hz, 1H, H-1), 4.14−4.12 (m, 1H, H-8a), 4.09 (dd, J = 13.4, 3.4 Hz, 1H, Ha-3), 3.67 (dd, J = 13.7, 7.0 Hz, 1H, Hb-3), 2.98−2.96 (m, 2H, H-6), 2.14 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.3 (s), 170.0 (s), 166.1 (s, C-5) 124.1 (d, C-7), 121.9 (d, C-8), 79.1 (d, C-2), 74.5 (d, C-1), 61.5 (d, C-8a), 48.0 (t, C-3), 32.2 (t, C-6), 20.8 (q), 20.7 (q); MS (70 eV): *m/z* (%): 253 (M^+, 4), 151 (89), 134 (100), 96 (83), 57 (56); IR (KBr) ν (cm^{-1}) 2977, 1755, 1739, 1651, 1636, 1242. Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.91; H, 5.87; N, 5.50.

(1*S*,2*S*,8a*S*)-1,2-Dihydroxyoctahydroindolizine ((+)-Lentiginosine), (1). Trifluoroacetic acid (3 mL) was added at 0 °C under stirring to **12** (100 mg, 0.372 mmol). The mixture was stirred at 20 °C overnight. Then, CF_3COOH was evaporated under reduced pressure, the residue was dissolved in MeOH, and strongly basic Ambersep 900 OH was added. After filtration, the solvent was evaporated under reduced pressure. FC (CH_2Cl_2/MeOH/NH_4OH 41:8:1) afforded (+)-**1** as a white solid (43 mg, 0.274 mmol, 74%): mp 106−107 °C, $[\alpha]^{25}_D$ +2.6 (*c* 0.4, MeOH). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.32; H, 9.64; N, 8.66.

(1*S*,2*S*,8a*S*)-1,2-Dihydroxy-2,3,6,8a-tetrahydro-5(1*H*)-indolizinone (2). From **5a**: CF_3COOH (2 mL) was added at 0 °C under stirring to **5a** (63 mg, 0.22 mmol). The mixture was stirred at 20 °C overnight. The solvent was evaporated under reduced pressure. FC (AcOEt/MeOH 5:1) gave pure **2** (R_f = 0.44, 29.7 mg, 0.176 mmol, 80%) as a white solid: mp 100−104 °C; $[\alpha]^{26}_D$ −27.6 (*c* 0.34, MeOH); ^{1}H NMR (D_2O, 400 MHz) δ 5.93 (m, 1H, H-8), 5.82 (dddd, J = 12.5, 5.0, 2.5, 2.3 Hz, 1H, H-7), 4.18 (dt, J = 8.0, 6.4 Hz, 1H, H-2), 3.98−3.96 (m, 1H, H-8a), 3.67 (m, 2H, H-1, Ha-3), 3.39 (dd, J = 12.5, 6.4 Hz, 1H, Hb-3), 2.96−2.89 (m, 1H, Ha-6), 2.84−2.77 (m, 1H, Hb-6); ^{13}C NMR (D_2O, 50 MHz) δ 172.4 (s), 125.6 (d), 124.5 (d), 81.3 (d), 75.6 (d), 64.1 (d), 51.2 (t), 34.1 (t); MS (70 eV): *m/z* (%): 169 (M^+, 61), 151 (3), 150 (6), 109 (84), 96 (92), 80 (100); IR (KBr) ν (cm^{-1}) 3195, 2890, 1635, 1480, 1205. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.92; H, 6.45; N, 8.52. From **5b**: to a solution of **5b** (23 mg, 0.09 mmol) in MeOH (1.5 mL), basic Ambersep 900 OH (25 mg) was added. After 2 h under stirring at 20 °C, the precipitate was filtered off and washed with MeOH. The solution was concentrated under vacuum and purified by FC (AcOEt/MeOH 5:1) to give pure **2** (R_f = 0.4, 12 mg, 0.07 mmol, 78%) as a colorless oil.

(1*S*,2*S*,8a*S*)-1,2-Dihydroxy-1,2,3,5,6,8a-hexahydroindolizine (3). To a solution of **5b** (116 mg, 0.46 mmol) in dry THF (2 mL) a 1 M solution of $LiAlH_4$ in THF (5.5 mL) was added dropwise at 0 °C under nitrogen atmosphere. After 2 h under reflux, the mixture was cooled to 20 °C and an aqueous saturated solution of Na_2SO_4 (0.5 mL) was added dropwise. After filtration through Celite and Na_2SO_4 (washing with AcOEt), the solvent was evaporated under reduced pressure. FC (CH_2Cl_2/MeOH/NH_4OH 41:8:1) gave pure **3** (R_f = 0.26, 42 mg, 0.27 mmol, 59%) as a white solid: mp 105−107 °C; $[\alpha]^{25}_D$ −39.8 (*c* 0.99, MeOH); ^{1}H NMR (D_2O, 400 MHz) δ 5.81 (ddq, J = 10.2, 1.0, 2.9 Hz, 1H, H-7), 5.73 (dq, J = 10.2, 2.0 Hz, 1H, H-8), 4.06 (dt, J = 7.2, 4.9 Hz, 1H, H-2), 3.72 (dd, J = 6.8, 4.5 Hz, 1H, H-1), 3.05 (dquint, J = 7.0, 2.5 Hz, 1H, H-8a), 2.98 (dd, J = 11.1, 7.2 Hz, 1H, Ha-3), 2.80 (ddd, J = 12.3, 5.7, 3.9 Hz, 1H, Ha-5), 2.71 (dd, J = 11.1, 4.9 Hz, 1H, Hb-3), 2.61 (ddd, J = 12.3, 9.0, 5.1 Hz, 1H, Hb-5), 2.21−2.10 (dm, J = 18.2 Hz, 1H, Ha-6), 1.98−1.90 (dm, J = 18.2 Hz, 1H, Hb-6); ^{13}C NMR (D_2O, 50 MHz) δ 129.2 (d, C-7), 127.7 (d, C-8), 84.6 (d, C-1), 79.4 (d, C-2), 66.6 (d, C-8a), 59.3 (t, C-3), 48.8 (t, C-5), 24.5 (t, C-6); MS (70 eV): *m/z* (%): 155 (M^+, 38), 138 (7), 95 (100), 80 (65), 67 (77); IR (KBr) ν (cm^{-1}) 3369, 3033, 2960, 2938, 2916, 2873, 2835, 1383, 1141. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.48; H, 8.49; N, 8.80.

(1*S*,2*S*,8a*S*)-1,2-Dihydroxy-hexahydro-5(1*H*)-indolizinone (4). To a solution of **13** (58 mg, 0.23 mmol) in MeOH (4 mL) strongly basic Ambersep 900 OH (60 mg) was added, and the mixture was stirred for 2 h at 20 °C. After filtration and solvent evaporation under reduced pressure, FC (AcOEt/MeOH 5:1) afforded pure **4** (R_f = 0.3, 39 mg, 0.228 mmol, 99%) as a white solid: mp 109−111 °C; $[\alpha]^{25}_D$ −3.7 (*c* 0.15, MeOH); ^{1}H NMR (D_2O, 400 MHz) δ 4.09 (qd, 1H, J = 7.0, 1.0 Hz, H-2), 3.62 (dd, J = 12.6, 8.2, 1H, Ha-3), 3.61 (dd, J = 8.8, 7.2 Hz, 1H, H-1), 3.29 (td, J = 10.0, 3.8 Hz, 1H, H-8a), 3.22 (dd, J = 12.6, 7.0 Hz, 1H, Hb-3), 2.29 (dd, J = 18.3, 6.5 Hz, 1H, Ha-6), 2.19 (ddd, J = 18.3, 11.3, 7.2 Hz, 1H, Hb-6), 2.10−2.04 (m, 1H, Ha-8), 1.88−1.81 (m, 1H, Ha-7), 1.63−1.51 (m, 1H, Hb-7), 1.29 (qd, J = 13.3, 3.3 Hz, 1H, Hb-8); ^{13}C NMR (D_2O, 50 MHz) δ 175.1 (s), 82.4 (d), 75.3 (d), 64.2 (d), 51.3 (t), 32.4 (t), 28.1 (t), 21.9 (t); MS (70 eV): *m/z* (%): 171 (M^+, 21), 128 (72), 111 (71), 83 (60), 56 (63), 55 (100); IR (KBr) ν (cm^{-1}) 3369, 2931, 1694, 1602, 1464, 1105. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.45; H, 7.35; N, 8.23.

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Supporting Information Available: Characterization data and full experimental procedures for compounds **8**, **7**, **6a**, **5a**, **6b**, **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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