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A Stereoselective Synthesis of Lentiginosine

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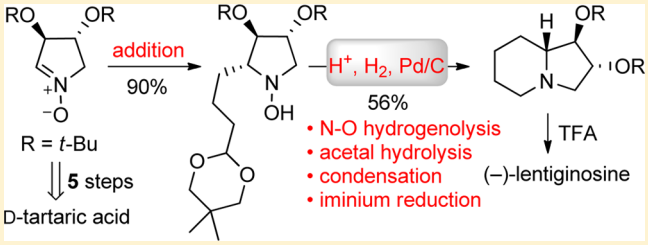
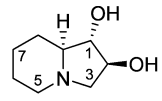
Supporting Information

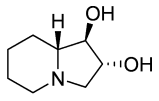
ABSTRACT: A concise stereoselective synthesis of (−)-lentiginosine, an iminosugar endowed with an interesting proapoptotic activity, has been accomplished using an enantiopure pyrroline *N*-oxide building block derived from D-tartaric acid. Key steps are a totally diastereoselective nucleophilic addition to the cyclic nitrone followed by a combination of two simultaneous and two tandem reactions occurring under the same conditions in a single laboratory operation. Natural (+)-lentiginosine can be synthesized by the same method but starting from L-tartaric acid.



INTRODUCTION

In 1990, Elbein et al. isolated two 1,2-dihydroxyindolizidine alkaloids from the leaves of *Astragalus lentiginosus* and identified their structures as (+)-lentiginosine [(+)-**1**][1] and its 2-epimer. The (1*S*,2*S*,8a*S*) absolute configuration of natural lentiginosine initially guessed on the basis of biosynthetic consideration[1] was later validated through the total synthesis of both the enantiomers and comparison of their glycosidase-inhibitory activity.[2] In fact, (+)-**1** is a potent and selective inhibitor of amyloglucosidases despite having only two hydroxyl groups. A recent study showed that natural (+)-**1** inhibits in vitro ATPase and chaperone activities of *heat shock protein 90* (*Hsp90*) by interacting with the protein middle domain.[3]


(+)-lentiginosine
(+)-**1**


(−)-lentiginosine
(−)-**1**

Synthetic (−)-lentiginosine [(−)-**1**] was shown to possess an interesting biological activity albeit different from its natural enantiomer. In particular, (−)-**1** has a good caspase-dependent proapoptotic activity against different cancer cell lines, with low toxicity toward normal cells.[4] The remarkable and specific biological activities of both the enantiomers **1**, in combination with the low abundance in nature of (+)-**1** (approximately 10 mg from 1 kg of dried plant material) and challenging indolizidine framework featuring three contiguous stereocenters, has prompted a multitude of stereoselective synthetic approaches to **1** and derivatives.[5] The inexpensive chiral pool compound tartaric acid is one of the most frequently used starting materials because it is readily available in both enantiomers and has the correct configuration for two of the three lentiginosine stereocenters.

In our previous work toward (−)-**1**, (+)-**1**, and lentiginosine derivatives, we reported on two synthetic approaches based on 1,3-dipolar cycloaddition of methylenecyclopropane and but-3-en-1-ol with dialkoxypyrroline *N*-oxide **2** and *ent*-**2** (R = TBDPS, *t*Bu, Bz) in turn derived from D- and L-tartaric acid, respectively (Figure 1).[2,6] Intermediates **3** and **4** were exploited as building blocks in the synthesis of various 7-substituted lentiginosine derivatives[7] and were converted to **1** through a suitable deoxygenation/deprotection sequence.[2,6a] To support the ongoing drug development program, a shorter synthesis of **1** was desirable. Here we describe an improved synthetic strategy based on the nucleophilic addition of a suitable Grignard reagent[8] to the same nitrone **2** followed by a domino-based approach to the indolizidine framework. The synthesis of (−)-lentiginosine is described here, but natural (+)-lentiginosine can be analogously prepared starting from L-tartaric acid.

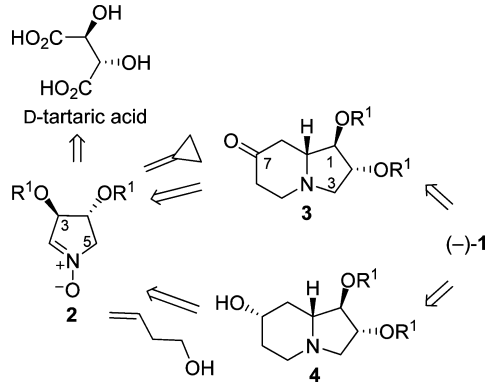


Figure 1. Previous synthetic strategies to (−)-lentiginosine [(−)-**1**] and 7-substituted derivatives.

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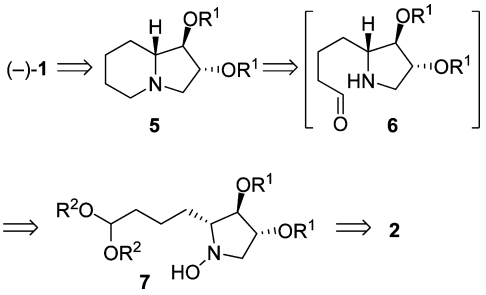
RESULTS AND DISCUSSION

Our new retrosynthesis of lentiginosine is shown in Scheme 1. It was envisaged that simultaneous N−O bond reductive cleavage and acetal hydrolysis followed by a spontaneous intramolecular condensation of amino aldehyde **6** and reduction of the formed indolizidinium ion could be used to get **5** in a single laboratory operation starting from hydroxylamine **7**. This in turn should be available with high diastereoselectivity from nitrone **2** and a Grignard reagent *ω*-functionalized with an acetal group.

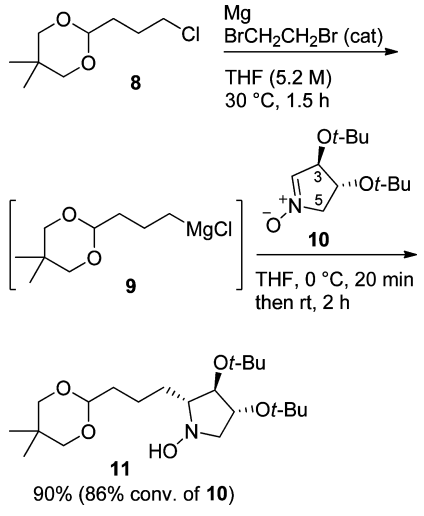
Scheme 1. New Retrosynthetic Analysis of (−)-Lentiginosine [(−)-1]



Acetal-substituted Grignard reagents can difficult to be prepare;[9] accordingly, the well-known Grignard reagent **9**[10] derived from 2-(3-chloropropyl)-5,5-dimethyl-1,3-dioxan (**8**) was chosen to establish the feasibility of the novel synthetic approach. The chloroacetal **8** is readily available in large scale by a two-step procedure employing 2,3-dihydrofuran and 2,2-dimethyl-1,3-propanediol as inexpensive starting materials (65% overall yield).[11] The corresponding Grignard reagent was generated according to the procedure of Forbes et al.[10] and immediately reacted with bis-*tert*-butoxypyrroline *N*-oxide **10**, in turn prepared by a five-step route starting from D-tartaric acid (46% overall yield).[6b]

The addition reaction afforded hydroxylamine **11** as a sole diastereoisomer in 90% yield after purification on silica gel (Scheme 2). As expected, the bulky *tert*-butoxy group on nitrone C-3 favors the exclusive addition of **9** to the *anti* (3-O*t*-Bu) face of nitrone **10**,[12] setting up the third stereocenter with the correct relative and absolute configuration. If kept in $CDCl_3$, hydroxylamine **11** is slowly oxidized to the corresponding cyclic nitrones but can be safely stored neat at low temperature for several weeks.

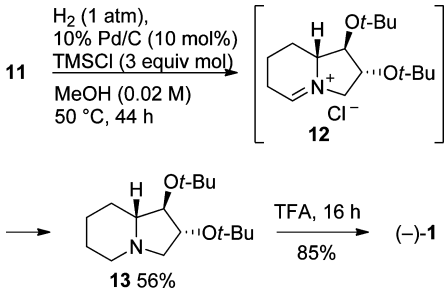
Scheme 2. Stereoselective Nucleophilic Addition of 9 to Nitrone 3



The key direct cyclization of **11** to indolizidine **13** was initially attempted using Zn/HCl in THF/H_2O. These reductive acidic conditions have been previously applied to the one-pot cyclization of nitro dimethoxyacetals,[13] but in the case of **11** the reaction breaks off after the N−O bond reduction. Hydrolysis of the relatively stable 1,3-dioxane group was observed only in traces after protracted heating. The use of TFA or acetone to favor aldehyde deprotection led to complex decomposition mixtures. The lack of product formation was attributed to the fast rate of Zn consumption in comparison with the relatively slow acetal hydrolysis. A portionwise addition of an excess of Zn was not beneficial. Consequently, a catalytic reducing system was tested.

Catalytic hydrogenation, both on Pd/C and $Pd(OH)_2/C$, is commonly used in N−O bond hydrogenolysis and reductive amination.[14] All the more, it can be carried out in the presence of an acid, therefore encompassing all the requirements for the domino-based process to **13**. After ample investigation, the optimum conditions for the reductive cyclization reaction were to heat a mixture of hydroxylamine **11** (0.02 M), Pd/C (10 mol %) and trimethylsilyl chloride (TMSCl, 3 molar equiv) in methanol at 50 °C for 44 h under a hydrogen atmosphere (1 atm)[15] (Scheme 3). Under these conditions, indolizidine **13** was smoothly formed in 56% yield after chromatography purification. Analogous results were obtained using $Pd(OH)_2/C$ as catalyst. Under the reported reaction conditions, *tert*-butyl ether hydrolysis was never detected.[16]

Scheme 3. Synthesis of (−)-Lentiginosine [(−)-1]



The effect of a different acetal protecting group on the yield of the domino-based process was also explored. In particular, when the cyclic acetal was replaced with the more acid-labile diethyl acetal, catalytic hydrogenation of the corresponding *N*-hydroxypyrrolidine **7** (R^1 = *t*-Bu; R^2 = Et) occurred faster than that for **11** (30 °C, 23 h compared to 50 °C, 44 h) but, unfortunately, gave indolizidine **13** in lower yield (49 compared to 56%).[17] The nature of the acetal group of **7** seems to be crucial for the success of the reaction, because it must secure the best timing of the proceeding of the sequential steps of the reaction, the first being, necessarily to avoid side products, the reduction of the hydroxylamine group. Hydrolysis of the *tert*-butyl ethers with TFA[6a] completed the synthesis of (−)-**1** (Scheme 3).

In summary, we have developed an improved and concise stereoselective synthesis of the proapoptotic agent (−)-lentiginosine [(−)-**1**]. The method involves a completely diaster-

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eoselective nucleophilic addition to (3*R*,4*R*)-3,4-bis(*tert*-butoxy)-3,4-dihydro-2*H*-pyrrole-1-oxide (**10**),[6b] a useful building block in turn prepared from D-tartaric acid in five steps with 46% overall yield. The formed hydroxylamine **11** featuring the requested three stereogenic centers with the correct configuration is then converted into (−)-**1** in two simple steps with 48% overall yield. The major achievement of this novel approach is the creation of the indolizidine skeleton by catalytic hydrogenation of **11** in the presence of a strong protic acid to trigger a sequence of two simultaneous and two tandem reactions, i.e., hydroxylamine N−O hydrogenolysis, acetal hydrolysis, intramolecular condensation, and reduction of the cyclic iminium ion **13** in a single laboratory operation. This strategy provides a practical and scalable access to (−)-lentiginosine to further in vitro and in vivo studies (in progress). The same sequence applied to L-tartaric acid is a novel synthesis of the natural iminosugar (+)-lentiginosine.

EXPERIMENTAL SECTION

General Information. R_f values refer to TLC on 0.25 mm silica gel plates. ^{1}H and ^{13}C NMR data are reported in δ (ppm) relative to $CDCl_3$ (7.26 and 77.0 ppm) or methanol-d_4 (3.31 and 49.05 ppm), and peak assignments were made on the basis of ^{1}H−^{1}H COSY, HSQC, and HMBC experiments.

*(2R,3R,4R)-2-[3-(5,5-Dimethyl-1,3-dioxan-2-yl)propyl]-3,4-di-tert-butoxypyrrolidin-1-ol (**11**).* A solution of chloroacetal **8**[11] (999.5 mg, 5.19 mmol) and 1,2-dibromoethane (156 mg, 0.83 mmol) in anhydrous THF (1 mL) was slowly added under stirring to magnesium turnings (354 mg, 14.57 mmol) under nitrogen atmosphere at 30 °C. The mixture was maintained at ca. 30 °C by periodic removal of the warm bath for 1.5 h and then diluted with THF (3 mL) and cooled to 0 °C. Nitrone **10**[6b] (662.5 mg, 2.89 mmol) in THF (7 mL) was added dropwise over 20 min at 0 °C. The resulting mixture was allowed to warm to rt and stirred for 2 h further. A saturated aqueous solution of NH_4Cl (9 mL) was added dropwise at 0 °C, the mixture was filtered through a cotton plug, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 8 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product (1.57 g) was purified by chromatography on silica gel [eluent: initially petroleum ether/AcOEt = 3:1 followed in sequence by petroleum ether/AcOEt = 3:2, AcOEt 100%, AcOEt/MeOH = 25:1, and AcOEt/MeOH (NH_3 1%) = 10:1] to yield hydroxylamine **11** as a colorless viscous oil (861 mg, 77%) along with unreacted nitrone **10** (93.3 mg, 14%) and chloroacetal **8** (302 mg, 30%).

11: R_f = 0.18 (petroleum ether/AcOEt = 3:1); $[\alpha]_D^{25}$ = −24 (*c* = 0.71, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz): δ = 4.48−4.44 (m, 1H, OC*H*O), 3.93 (pseudo dt, *J* = 6.8; 3.2 Hz, 1H, 4-H), 3.69−3.63 (m, 1H, 3-H), 3.56 (A part of an AB system, *J* = 11.0 Hz, 2H, OC*H*H × 2), 3.45 (B part of an AB system, *J* = 11.0 Hz, 2H, OC*H*H × 2), 3.15 (A part of an ABX system, *J* = 11.1; 2.8 Hz, 1H, 5-Ha), 3.02 (B part of an ABX system, *J* = 11.1; 6.9 Hz, 1H, 5-Hb), 2.61−2.54 (m, 1H, 2-H), 1.66−1.54 (m, 6H, $CH_2CH_2CH_2$), 1.22 (s, 9H, CH_3 × 3), 1.19 (s, 9H, CH_3 × 3), 1.16 (s, 3H, CH_3), 0.72 (s, 3H, CH_3) ppm; ^{13}C NMR (CD_3OD, 100 MHz): δ = 103.4 (d, OCHO), 82.4 (d, C-3), 78.1 (t, 2C, CH_2O × 2), 77.7 (d, C-4), 75.4 (s, Me_3CO), 75.0 (s, Me_3CO), 74.0 (d, C-2), 65.6 (t, C-5), 36.0 (t, CH_2), 31.2 (t, CH_2), 31.0 (s, Me_2C), 29.6 (q, 3C, CH_3 × 3), 29.2 (q, 3C, CH_3 × 3), 23.5 (q, CH_3), 22.1 (q, CH_3), 21.5 (t, CH_2) ppm; IR ($CDCl_3$): ν = 3690, 3580, 3378, 2978, 2853, 1472, 1463, 1394, 1366, 1190 cm^{-1}; MS ($^+$ESI): *m*/*z* = 388 $[M + H]^+$, 410 $[M + Na]^+$. $C_{21}H_{41}NO_5$ (387.6): calcd C 65.08, H 10.66, N 3.61; found C 65.09, H 10.38, N 3.28.

*(1R,2R,8aR)-1,2-Di-tert-butoxyoctahydroindolizine (**13**). Procedure A.* To a mixture of **11** (123 mg, 0.317 mmol) and Pd/C (10% in weight, 34 mg; Pd: 3.4 mg, 10 mol %) in MeOH (16 mL) under H_2 atmosphere (balloon) was added dropwise TMSCl (0.121 mL, 0.951 mmol) at 0 °C. After being stirred under H_2 atmosphere (balloon) at 50 °C for 44 h, the mixture was filtered through a pad of Celite and the filtrate was eluted through a column of Amberlyst A26 with MeOH as eluent. (The Amberlyst A26 column had been previously flushed with MeOH). MeOH was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 25:1), to yield indolizidine **13** (48 mg, 56%) along with 2,2-dimethyl-1,3-propanediol (23 mg, 70%). Under the same conditions, a little bit higher amounts of **11** (270 mg, 0.70 mmol and 400 mg, 1.03 mmol) afforded indolizidine **13** with a slightly lower but reproducible 53% yield (100 and 147 mg, respectively).

Procedure B. Following the same procedure used to prepare **11**, (2*R*,3*R*,4*R*)-2-(4,4-diethoxybutyl)-3,4-di-*tert*-butoxypyrrolidin-1-ol (**7**, R^1 = *t*-Bu; R^2 = Et) was obtained starting from 4-chloro-1,1-diethoxybutane (1 g, 5.53 mmol) and nitrone **10** (633 mg, 2.76 mmol). Purification by chromatography on silica gel (eluent: petroleum ether/EtAcOEt = 3:1) afforded hydroxylamine **7** (R^1 = *t*-Bu; R^2 = Et) as a colorless viscous oil in 89% yield (923 mg).

7 (R^1 = *t*-Bu; R^2 = Et): R_f = 0.28 (petroleum ether/EtAcOEt = 3:1); $[\alpha]_D^{21}$ = −24 (*c* = 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.48 (pseudo t, *J* = 5.6 Hz, 1H, OC*H*O), 3.92 (pseudo dt, *J* = 2.8; 4.6 Hz, 1H, 4-H), 3.67−3.57 (m, 3H, 3-H + OC*H*HMe × 2), 3.473 (dq, *J* = 9.3; 7.1 Hz, 1H, OC*H*HMe), 3.470 (dq, *J* = 9.4; 7.1 Hz, 1H, OC*H*HMe), 3.17 (d, *J* = 4.7 Hz, 2H, 5-H), 2.75 (pseudo q, *J* = 5.9 Hz, 1H, 2-H), 1.71−1.49 (m, 6H, $CH_2CH_2CH_2$), 1.19 [s, 9H, $C(CH_3)_3$], 1.18 (t, *J* = 7.1 Hz, 6H, CH_2CH_3 × 2), 1.16 [s, 9H, $C(CH_3)_3$] ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 102.9 (d, OCHO), 81.7 (d, C-3), 77.0 (d, C-4), 74.2 (s, Me_3CO), 73.8 (s, Me_3CO), 73.3 (d, C-2), 64.5 (t, C-5), 61.0 (t, CH_2Me), 60.8 (t, CH_2Me), 33.8 (t, CH_2CH_2), 30.0 (t, CH_2CH_2), 29.0 [q, 3C, $C(CH_3)_3$], 28.6 [q, 3C, $C(CH_3)_3$], 21.7 (t, CH_2CH_2), 15.3 (q, 2C, CH_2CH_3 × 2) ppm; IR ($CDCl_3$): ν = 3580, 3380, 2978, 2873, 1457, 1391, 1367, 1190 cm^{-1}; $C_{20}H_{41}NO_5$ (375.3): calcd C 63.96, H 11.00, N 3.731; found C 63.55, H 10.80, N 3.48.

To a mixture of hydroxylamine **7** (R^1 = *t*-Bu; R^2 = Et, 63.4 mg, 017 mmol) and Pd/C (10% in weight, 18 mg; Pd: 3.4 mg, 10 mol %) in EtOH (8.4 mL) under H_2 atmosphere (balloon) was added TMSCl (0.121 mL, 0.951 mmol) with a syringe below the surface of the liquid. After being stirred under H_2 atmosphere (balloon) at 30 °C for 23 h, the mixture was filtered through a pad of Celite and the filtrate was eluted through a column of Amberlyst A26 with MeOH as eluent. (The Amberlyst A26 column had been previously flushed with MeOH). MeOH was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 25:1), to yield indolizidine **13** (22.1 mg, 46%) along with (2*R*,3*R*,4*R*)-3,4-di-*tert*-butoxy-2-(4-ethoxybutyl)pyrrolidine (9 mg, 17%).

13: R_f = 0.22 (CH_2Cl_2/MeOH = 20:1); $[\alpha]_D^{23}$ = −42 (*c* = 0.58, $CHCl_3$) [lit. *ent*-**13**: $[\alpha]_D^{21}$ = +42.8 (*c* = 0.48, $CHCl_3$); $[\alpha]_D^{25}$ = +42.0 (*c* = 0.54, $CHCl_3$)];[6a,8c] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.77 (ddd, *J* = 7.2; 4.0; 1.6 Hz, 1H, 2-H), 3.62 (dd, *J* = 8.7; 4.0 Hz, 1H, 1-H), 2.95−2.88 (m, 1H, 5-Ha), 2.90 (dd, *J* = 9.9; 1.6 Hz, 1H, 3-Ha), 2.41 (dd, *J* = 9.9; 7.2 Hz, 1H, 3-Hb), 1.94−1.50 (m, 6H, 5-Hb + 6-H + 7-Ha + 8a-H + 8-Ha), 1.29−1.10 (partially obscured, m, 2H, 7-Hb + 8-Hb), 1.20 (s, 9H, CH_3 × 3), 1.16 (s, 9H, CH_3 × 3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 83.8 (d, C-1), 76.9 (d, C-2), 73.7 (s, Me_3CO), 73.5 (s, Me_3CO), 67.1 (d, C-8a), 62.2 (t, C-3), 53.6 (t, C-5), 29.3 (q, 3 C, CH_3 × 3), 28.7 (q, 3 C, CH_3 × 3) and (t, C-8), 24.9 (t, C-6), 24.1 (t, C-7) ppm. Spectral properties were identical to those reported for *ent*-**13**[6a] (the resonance of protons 7-Hb and 8-Hb, which are partially obscured by the intense singlets of the two *t*-Bu groups and were previously erroneously assigned above 1.47−1.45 ppm,[6a,8c] could be observed by ^{1}H−^{1}H COSY, HSQC, and TOCSY experiments, see copies of the corresponding spectra in Supporting Information).

*(1R,2R,8aR)-Octahydroindolizine-1,2-diol [(−)-Lentiginosine, (−)-**1**].* Indolizidine **13** (164 mg, 0.61 mmol) was dissolved in TFA (1.9 mL) at 0 °C. The mixture was stirred at rt for 16 h and then concentrated under reduced pressure. The last traces of TFA were coevaporated with MeOH, and then the residue was filtered through a column of of Amberlyst A26 with MeOH as eluent. MeOH was evaporated under reduced pressure, and the crude product (103 mg) was purified by chromatography on silica gel [eluent: CH_2Cl_2/MeOH (NH_3 33%) = 41:8. 1], to yield (−)-lentiginosine (82 mg, 85%).

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(−)-**1**: R_f = 0.33 [CH_2Cl_2/MeOH/NH_3 (33%) = 41:8:1]; $[\alpha]_D^{20}$ = −1.6 (*c* = 0.92, CH_3OH) [lit. $[\alpha]_D^{23}$ = −1.6 (*c* = 0.24, CH_3OH)];[2] ^{1}H NMR (CD_3OD, 400 MHz): δ = 3.94 (ddd, *J* = 7.2; 3.5; 1.5 Hz, 1H, 2-H), 3.59 (dd, *J* = 8.5; 3.5 Hz, 1H, 1-H), 2.95 (dm, *J* = 10.9 Hz, 1H, 5-Ha), 2.85 (dd, *J* = 10.5, 1.5 Hz, 1H, 3-Ha), 2.52 (dd, *J* = 10.5; 7.2 Hz, 1H, 3-Hb), 1.98 (pseudo dt, *J* = 3.3; 11.4 Hz, 1H, 5-Hb), 1.97−1.93 (m, 1H, 8-Ha), 1.85−1.74 (m, 2H, 7-Ha + 8a-H), 1.66−1.48 (m, 2H, 6-H), 1.33−1.17 (m, 2H, 7-Hb + 8-Hb) ppm. The spectral properties were identical to those previously reported.[2]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02804.

Copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(17) The relatively lower yield can be attributed to the formation of non-negligible amounts of the byproduct (2*R*,3*R*,4*R*)-3,4-di-*tert*-butoxy-2-(4-ethoxybutyl)pyrrolidine (17%) derived from hydrogenation of the intermediate ethyloxonium ion (see also ref 16).

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