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A Short and Highly Stereocontrolled Total Synthesis of (*3R,5R,8aR*)-3-*n*-Butyl-5-methylindolizidine

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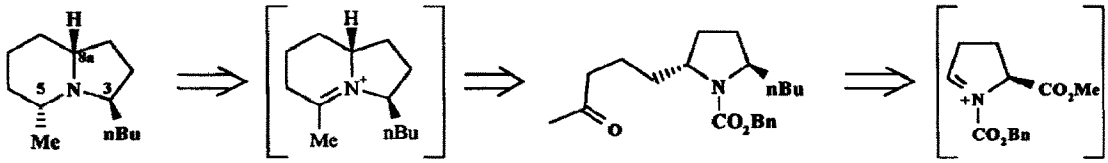
Abstract: Total synthesis of (-) (*3R,5R,8aR*)-3-*n*-Butyl-5-methylindolizidine is described in 9 steps (22% overall yield) from *L*-proline.

Most reported syntheses[1] of indolizidine alkaloids begin with the 2,5-disubstituted pyrrolidine ring elaboration. Untill now our interest in this field has been focused on the (S)-pyroglutamic acid as starting chiral material for the construction of *trans* (or *cis*) 2,5-dialkylpyrrolidines[2].

The purpose of the present communication is to describe a short and highly diastereoselective route to the levogyre (*3R,5R,8aR*)-3-*n*-butyl-5-methylindolizidine **1** starting from (S)-proline as chiral precursor.

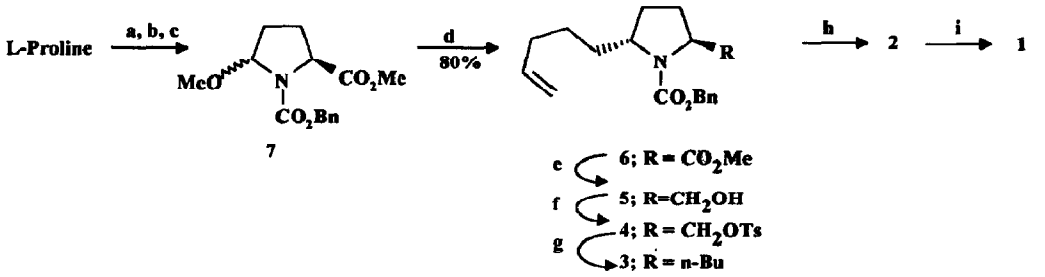
As illustrated in scheme 1 our synthetic strategy involves two key steps during which the C-5 and C-8a configurations should be controlled. It is well established that the 5-substituted indolizidines formation by intramolecular catalytic reductive amination leads selectively to *cis* relative arrangement of C-5 and C-8a hydrogen atoms regardless of C-3 configuration. The construction of the *trans* pyrrolidine **2** can be achieved by diastereoselective adequate organocopper addition to the homochiral acyliminium **8** as reported by Wistrand and Skrinjar[3]. The absolute configuration at C-3 which should induce that at C-8a is supplied by the natural *L*-proline.



1 **2** **8**

Scheme 1

With these considerations in mind, we started our synthetic work by preparing the aminoether **7** in bulk form from *L*-proline (in 69% overall yield) *via* two protection steps[4], then anodic α-electromethoxylation following the Shono procedure[5]. Compound **7** was treated with BF_3,OEt_2 (2 equiv.) at -78°C in order to generate the acyliminium **8** which was subjected to the organocopper (CH_2=$CHCH_2CH_2CH_2Cu$; 2 equiv.) addition in dry ethyl ether at -78°C. Analysis of the crude product showed a high diastereoselectivity for this reaction (*trans*/*cis* = 96/4). The diastereoisomers separation on column chromatography was done after chemoselective reduction of the ester group which took place without detectable epimerization, leading to **5** in 63% yield from **7**.



Reagents: a) $ClCO_2Bn/NaOH$, 0°C; b) $MeOH/BF_3,OEt_2$, reflux; c) $-2e^-/MeOH$, -20°C; d) $BF_3,OEt_2/CH_2=CH(CH_2)_3Cu$, -78°C; e) $NaBH_4/CaCl_2$, THF/EtOH, -5°C; f) $TsCl/NEt_3$, rt; g) n-Pr_2CuLi, -40°C; h) $PdCl_2(PhCN)_2$-$CuCl_2$-O_2, H_2O/DMF; 70°C i) $H_2/Pd/BaSO_4$.

Scheme 2

Carbon-chain elongation of the homochiral alcohol **5** was carried out through tosylation, then cross coupling reaction with n-Pr_2CuLi to afford compound **3** in 72% yield for the two steps. Oxidation of **3** under the Wacker procedure smoothly proceeded to give the methyl ketone **2** in 78% yield. Finally one-pot carbamate cleavage and subsequent reductive amination under hydrogen atmosphere and over $Pd/BaSO_4$ catalysts in methanol gave the desired (-) indolizidine **1** in 86% yield after column chromatography on alumina (hexane-$CHCl_3$/3:1). Our synthetic sample exhibits spectral data[6] in agreement with the reported ones[7].

Compared to the reported methods, our synthesis of the unatural enantiomer (-) 195B contitutes a straightforward and highly stereoselective route to the levogyre 3,5- disubstituted indolizidines.

Compound **6** is a potential chiral building block for construction of *trans*-2,5-pyrrolidines. Further transformations of **6** are going on for the synthesis of (-) 195B gephyrotoxin homologues[8] having the same configurations at C-3,C-5 and C-8a chiral centers.

Acknowledgement. We are grateful to DEGUSSA compagny for a generous gift of *L*-proline.

References and notes

1. Except for two methods: a) Takahata, H.; Bandoh, H.; Momose, T. *Tetrahedron* **1993**, *49*, 11205-11212. b) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 1515-1518.
2. a) Rosset, S.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.***1991**,*51*, 7521-7524. b) Fleurant, A.; Célérier, J.-P.; Lhommet,G. *Tetrahedron: Asymmetry* **1993**, *4*, 1429-1430.
3. Wistrand, L.G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573-582.
4. a) Berger, A.; Kurtz, J.; Katchalski, E. *J. Am. Chem. Soc.* **1954**,*76*, 5552-5554. b) Yamada, T.; Isono, N.; Inui, A.; Miyazawa, T.Kuwata S.; Watanabe, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1897-1898.
5. Shono, T.; Matsumura, Y.; Tsubata, K. *Organic Syntheses* **1985**, *63*, 206-213.
6. Satisfactory NMR data were obtained for (-) **1**: ^{1}H-NMR (200MHz, $CDCl_3$)δ : 0.87(3H, t, J= 7.2Hz), 0.96-1.98(16H, m), 1.07(3H, d, J= 6.4Hz), 2.24-2.26(2H, m), 3.24(1H, m) ppm; ^{13}C-NMR (50MHz, $CDCl_3$) δ : 14.29, 20.55, 23.09, 24.80, 24.93, 26.40, 29.27, 30.11, 32.51, 34.64, 52.01, 58.81, 59.01ppm. $[\alpha]_D^{22}$ -99 (c= 0.215, MeOH); Lit.[7], $[\alpha]_D^{22}$ -101 (c= 0.15, MeOH)
7. Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178-5189.
8. Tokuyama, T.; Nishimori, N.; Karle, I.; Edwards, M.; Daly, J. *Tetrahedron* **1986**, *42*, 3453-3460.

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