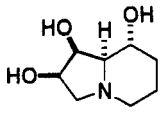
Synthesis of C-8a Hydroxyethyl-Substituted Indolizidines

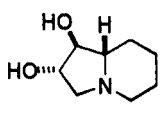
Yong Sup Lee*, Dong Woon Kim, Jae Yeol Lee, Kyu Sung Jeong†, and Hokoon Park*

Medicinal Chemistry Research Center, Korea Institute of Science & Technology, P.O. Box 131 Cheongryang, Seoul 130-650, Korea
†Department of Chemistry, Yonsei University, Seoul 120-740, Korea
Received April 25, 1998

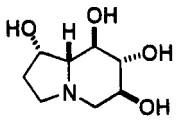
Glycosidases are a class of enzymes which catalyse the hydrolysis of glycosidic linkages and responsible for many biological phenomena such as digestion and biosynthesis of glycoprotein. Inhibitors of glycosidases have the therapeutic potential in the treatment of viral infections,[1] cancer,[2] and metabolic disorders.[3] Recently, several polyhydroxylated indolizidine alkaloids such as swainsonine,[4] castanospermine,[5] and lentiginosine[6] have been identified as naturally-occurring glycosidase inhibitors from plants or microorganisms. As a consequence, much efforts have been devoted to the synthesis of their structural analogs to design more selective and potent glycosidase inhibitors.



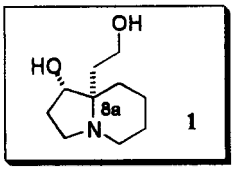
Swainsonine



Lentiginosine



Castanospermine

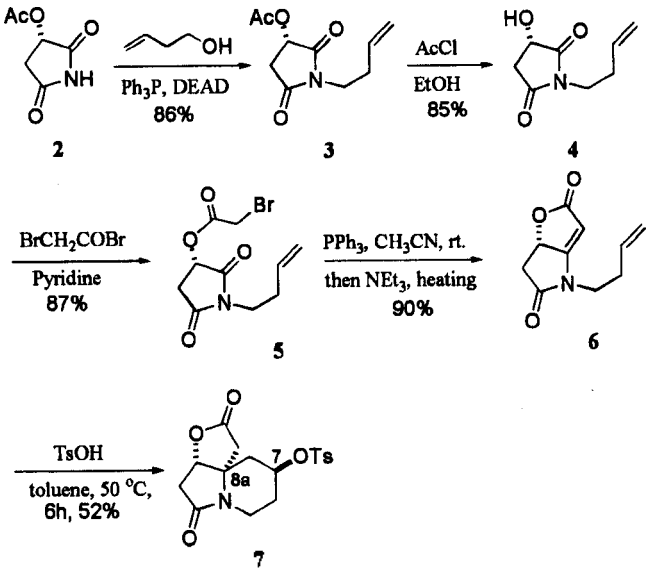


1

The hydroxyl groups in indolizidines play an important role as hydrogen bonding acceptors or donors to the active site of enzyme.[7] Therefore, most of the synthetic strategies carried out on new polyhydroxylated indolizidines so far have focused on the stereoisomers and ring-modified analogs of naturally-occurring indolizidines.[8,9] Meanwhile, Liu *et al.* have reported a synthesis of C-5 hydroxymethyl-substituted indolizidines which show quite different biological activies compared to their parent compound.[10] However, we decided to prepare unnatural indolizidine derivative with a hydroxyethyl group at C-8a position of indolizidine ring to design selective glycosidase inhibitors. Herein we wish to report our preliminary results on the synthesis of **1**, the first example of a new class of indolizidines modified at C-8a position.

We have previously shown that a quaternary-carbon center of indolizidine ring juncture can be introduced stereoselectively by an *N*-acyliminium ion cyclization of chiral enamides.[11] This strategy was extended to the synthesis of C-8a hydroxyethyl-substituted indolizidine **1**. The synthesis of enamide **6**, a key precursor for **1**, was carried out as shown in Scheme 1.[11,12]

Mitsunobu coupling[13] of (*S*)-acetoxysuccinimide (**2**) with 3-buten-1-ol afforded **3** in 86% yield. Acetoxy group in **3** was removed by treatment with acetyl chloride in ethanol and then bromoacetylated to provide **5** in 74% yield for two



Scheme 1

steps. *N*-Acyliminium ion precursor **6** was synthesized in one-pot procedure by treatment of **5** with triphenylphosphine followed by triethylamine-induced intramolecular Wittig reaction of the resulting phosphonium salt.[12] Compound **6** was subjected to *N*-acyliminium ion cyclization condition to form indolizidine ring system. When **6** was treated with 5 equivalents of anhydrous *p*-toluenesulfonic acid at 50 °C, cyclization product **7** was obtained in 52% yield.[14] The (*S*)-configuration of C-8a (indolizidine numbering) in **7** could be rationalized by the fact that the π-nucleophile would attack to the less hindered side of bicyclic ring in **6** in order to form the less-strained tricyclic compound.[11] Although the stereogenic center at C-7 will be removed at the later stage of the synthesis, the configuration of C-7 was assigned to *S* by the analogy with the previous reports[15] and further confirmed by 2D-COSY and NOE experiments. When the signal of H-7 proton was irradiated, the enhancements of protons of H-5α, H-6α, H-8α, H-9α and H-9β were observed as shown in Figure 1.

Finally, cylization product **7** was transformed to C-8a hydroxyethyl-substituted indolizidine **1** as depicted in Scheme 2. Concomitant reduction of lactam carbonyl, lactone, and tosyl group of **7** was accomplished by treatment with $LiAlH_4/AlCl_3$[16] at room temperature. Unexpectedly, eliminated product **8** was obtained in modest yield. However, compound **8** could serve as a valuable intermediate for polyhydroxylated indolizidine derivatives by hydroxylation of double bond.[17] The double bond in **8** was hydrogenated

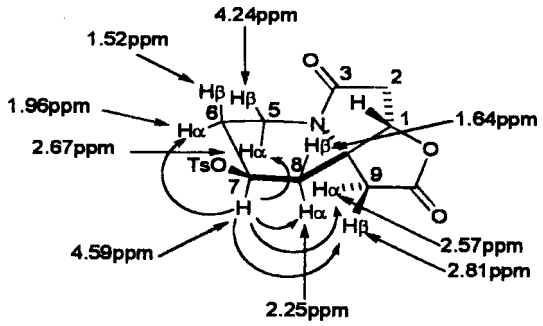
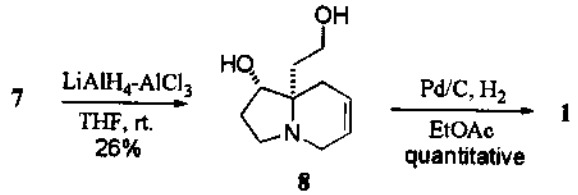


Figure 1. Observed NOE's and Chemical Shifts of 7.



Scheme 2

with Pd/C to provide **1** in quantitative yield.[18]

In conclusion, the first synthesis of C-8a hydroxyethyl-substituted indolizidines has been accomplished. Glycosidase inhibitory test of this compound and the synthesis of several polyhydroxylated indolizidines modified at C-8a position are currently in progress.

Acknowledgment. This work was supported by the Ministry of Science and Technology, Korea (2N15020).

References

1. Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl Acad. Sci.* **1988**, *85*, 9229.
2. Goss, P.; Reid, C.; Granovsky, M.; Warren, C.; Dennis, J. W. *Proc. Am. Assoc. Cancer Res.* **1995**, *36*, 393.
3. Robinson, K. M.; Begovic, M. E.; Rhinehart, B. L.; Heineke, E. W.; Ducep, J.-B.; Kastner, P. R.; Mashall, F. N.; Danzin, C. *Diabetes* **1991**, *40*, 825.
4. Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Austr. J. Chem.* **1979**, *32*, 2257.
5. Hohenschutz, L. D.; Bell, E. A.; Jewess, D. P.; Leworthy, R. J.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.
6. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbin, A. D. *Biochemistry* **1990**, *29*, 1886.
7. Khanna, I. K.; Weier, R. M.; Julien, J.; Mueller, R. A.; Lankin, D. C.; Swenton, L. *Tetrahedron Lett.* **1996**, *37*, 1355.
8. Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045.
9. Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1994**, *50*, 2131.
10. Liu, P. S.; Rogers, R. S.; Kang, M. S.; Sunkara, P. S. *Tetrahedron Lett.* **1991**, *32*, 5853.
11. Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449.
12. Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y. *J. Org. Chem.* **1987**, *52*, 2941.
13. Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
14. Spectral data for **7**: mp 156-158 °C; $[\alpha]_D^{23}$ −31.0 (*c* 0.01, $CHCl_3$); IR (KBr) 2938, 1790, 1690, 1400, 1360, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.78 (2H, d, *J*=8.2 Hz, aromatic protons), 7.37 (2H, d, *J*=8.2 Hz, aromatic protons), 4.74 (1H, dd, *J*=5.3, 2.9 Hz, H_1), 4.59 (1H, tt, *J*=11.5, 4.5 Hz, H_7), 4.24 (1H, ddd, *J*=14.3, 5.5, 1.6 Hz, H_5), 2.81 (1H, d, *J*=18.0 Hz, CH_2COO), 2.77 (2H, m, H_2), 2.67 (1H, dt, *J*=13.5, 3.3 Hz, H_5), 2.57 (1H, d, *J*=18.0 Hz, CH_2COO), 2.47 (3H, s, $-CH_3$), 2.25 (1H, ddd, *J*=12.3, 4.1, 1.6 Hz, H_8), 1.96 (1H, m, H_6), 1.64 (1H, t, *J*=11.9 Hz, H_8), 1.52 (1H, m, H_6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.84, 169.81, 145.48, 133.73, 130.18, 127.63, 79.21, 75.56, 65.78, 42.22, 41.71, 38.56, 36.88, 36.22, 34.61, 31.82, 21.01; MS (m/z) 193 [(M-TsOH)$^+$], 151, 106.
15. (a) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1987. (b) Hadly, M. S.; King, F. D.; Martin, R. T. *Tetrahedron Lett.* **1983**, *24*, 91.
16. Bernotas, R. C.; Adams, G. *Tetrahedron Lett.* **1996**, *37*, 7343.
17. Koskinen, Ari M. P.; Paul, J. M. *Tetrahedron Lett.* **1992**, *33*, 6853.
18. Spectral data for **1**: $[\alpha]_D^{23}$ +100.0 (*c* 0.01, CH_3OH); IR (KBr) 3396, 2956 cm^{-1}; ^1H NMR (CD_3OD, 600 MHz) δ 3.95 (1H, m, H_1), 3.65 (2H, m, CH_2CH_2OH), 3.04 (1H, m, H_3), 2.79 (1H, m, H_5), 2.40 (1H, m, H_3), 2.34 (1H, m, H_2), 2.22 (1H, m, H_5), 1.95 (1H, m, H_2), 1.76 (1H, m, CH_2CH_2OH), 1.62 (1H, m, CH_2CH_2OH), 1.47 (1H, m, H_6), 1.41 (1H, m, H_6), 1.22-1.34 (2H, m, H_7), 0.88 (2H, t, *J*=7.2 Hz, H_8); ^{13}C NMR (CD_3OD, 75 MHz) δ 77.84, 73.82, 61.72, 57.15, 53.56, 36.18, 34.41, 32.14, 22.63, 15.21; MS (m/z) 186 [(M+1)$^+$], 168, 156, 142, 100.