Tetrahedron: Asymmetry Vol. 3, No. 8, pp. 999-1000, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

An Asymmetric Synthesis of an Acetonide Form of (-)-*cis*-1,2-Dihydroxyindolizidine

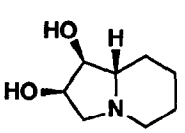
Hiroki Takahata,* Yasunori Banba, and Takefumi Momose*

Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

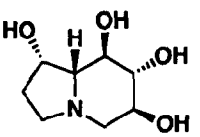
(*Received* 9 *April* 1992)

Abstract: An enantiospecific synthesis of an acetonide (4) of *cis*-1,2-dihydroxyindolizidine (1) starting from the known pyrrolidine 6 has been achieved in a stereoselective manner.

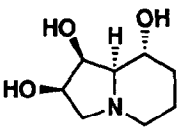
Polyhydroxylated indolizidine alkaloids isolated from plants and microorganisms offer fascinating targets for synthesis because of their unique structure and intriguing biological activities such as inhibition of glycosidase enzymes and suppression of viral replication.[1] Accordingly, much attention is focussed on their asymmetric synthesis.[2,3] Tetra- or tri-hydroxylated indolizidines, as exemplified by castanospermine (2)[4] or swainsonine (3)[5], are frequently encountered as natural products. Recently a dihydroxylated indolizidine (1) has been isolated from *Rhizoctonia leguminicola*[6] and *Astragalus lentignosus*.[7] In addition, this alkaloid has been demonstrated to be a biosynthetic precursor to swainsonine (3).[8] Following earlier work on the preparation of racemic 1,[9] a single example of the synthesis of both 1 and its enantiomer has recently been reported by Overman.[10] In connection with our program directed towards the development of methodology for the synthesis of biologically active nitrogen-containing compounds, we wish to disclose an enantiospecific synthesis of a ketal form (4) of (-)-*cis*-1,2-dihydroxyindolizidine (1) starting with the chiral (*S*)-*N*-benzyloxycarbonyl-3-hydroxy-4-pentenylamine (5) readily available from the Katsuki-Sharpless asymmetric oxidation developed by us.[11]



1



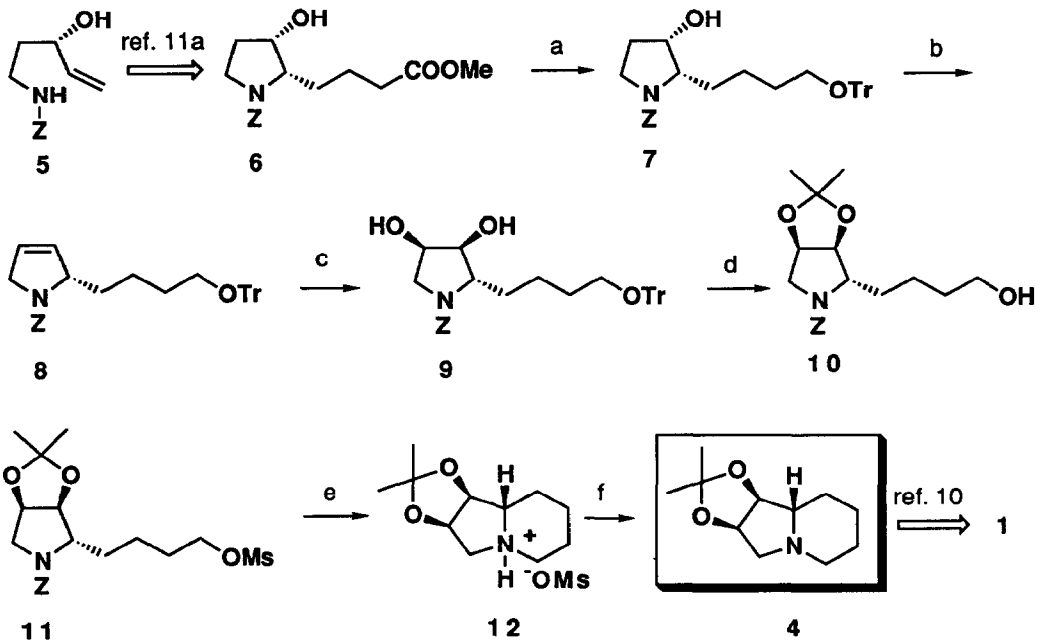
2



3

Our approach to 1 was built on previous work concerning the synthesis of 1-hydroxyindolizidines,[11a] which act as biosynthetic precursors to 1 and 3,[12] *via* a stereoselective intramolecular amidomercuration of 5. The synthesis started with the intermediate 6 (two steps from 5). Reduction of 6 with DIBAL-H followed by selective monotritylation provided the 3-hydroxypyrrolidine 7 in 37% yield. The elimination of the hydroxyl in 7 aimed at enabling the pyrrolidine to glycolize at C_3 and C_4 was performed by the Chugaev reaction (1. xanthation; 2. thermolysis) to furnish the desired 3-pyrroline 8 in 52% yield. *cis*-Dihydroxylation of 8*via* catalytic osmylation provided the diol 9 as a single diasteroisomer in 86% yield. Apparently, the attack of osmium tetroxide occurs mainly on the opposite side to the ring appendage at C_2. After acid hydrolysis of 9 at the trityl moiety, the resulting triol was protected to give the acetonide 10 in 84% yield from 9. Mesylation of the hydroxyl in 10 followed by hydrogenolytic debenzyloxycarbonylation afforded the indolizidine hydromesylate 12, which upon treatment with aq. K_2CO_3, yielded the desired acetonide 4 {$[\alpha]_D^{25}$ -48.3 (*c* 0.32, $CHCl_3$), lit.[10] $[\alpha]_D$ -49.7 (*c* 0.49, $CHCl_3$)} in 70% yield from 10. Its spectral data (^1H and ^{13}C NMR)

were consistent with the values reported.[10] The acetonide **4** has been transformed by deprotection (2M HCl at 80 °C) into **1** by Overman *et al.*[10]



a) 1. DIBAL-H; 2. TrCl/NEt_3; b) 1. NaH/CS_2/MeI; 2. 170 °C; c) cat. OsO_4/NMO;
d) 1. HCl/MeOH; 2. $Me_2C(OMe)_2$/TsOH; e) 1. MsCl/Py; 2. H_2/$Pd(OH)_2$; f) aq. K_2CO_3

This synthesis provides an efficient entry into the asymmetric total synthesis of **1**. Further investigation to transform **4** into swainsonine (**3**) is currently ongoing.[13]

References and notes

1. Elbein, A. D.; Molyneux, R. J. "Alkaloids: Chemical and Biological Perspectives," Pelleitier, S. W., Ed,: Wiley, New York, 1987, Vol 5, chapter 1.
2. Howard, A. S.; Michael, J. P. "The Alkaloids," Brossi, A. Ed., Academic Press, New York, 1986, Vol 28, chapter 3.
3. Most of the syntheses of polyhydroxylated indolizidines are based on the use of sugars as starting materials and involve a large number of steps.
4 Hohenschultz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.
5. Molyneux, R. J.; James, L. F. *Science (Washington, D. C.)* **1982**, *216*, 190.
6. Harris, T. M.; Harris, C. M.; Hill, J. E.; Ungemach, F. S.; Broquist, H. P.; Wickwire, B. M. *J. Org. Chem.* **1987**, *52*, 3094.
7. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886.
8. Harris, C. M.; Campbell, B. C.; Molyneux, R. J.; Harris, T. M. *Tetrahedron Lett.* **1988**, *29*, 4815.
9. Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1984**, *37*, 1503.
10. Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591.
11. a) Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron: Asymmetry* **1990**, *1*, 763. b) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240. c) Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron: Asymmetry* **1991**, *2*, 445. d) Idem. *Tetrahedron* **1991**, *47*, 7635.
12. Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940.
13. Pearson, W. H.; Lin, K.-C.; *Tetrahedron Lett.* **1990**, *31*, 7571.