Tetrahedron Letters,Vol.25,No.2,pp 165-168,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

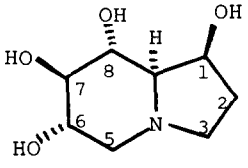
TOTAL SYNTHESES OF (+)-CASTANOSPERMINE AND (+)-DEOXYNOJIRIMYCIN

Ronald C. Bernotas and Bruce Ganem*[1]

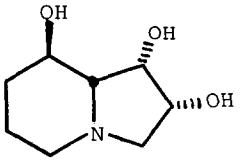
Department of Chemistry
Baker Laboratory
Cornell University
Ithaca, New York 14853

Summary: The absolute configuration of castanospermine has been determined by total synthesis to be as shown in 1.

Interest continues to grow in the indolizidine alkaloids castanospermine (1) and swainsonine (2), two potent inhibitors of numerous carbohydrate processing enzymes. Castanospermine, whose structure and relative stereochemistry were determined by x-ray crystallography,[2] has been shown to inhibit α- and β-glucosidases in fibroblast extracts[3] as well as the processing of oligosaccharide portions of influenza viral hemagglutinin.[4] Swainsonine inhibits lysosomal and jack bean α-mannosidase and disrupts processing of glycoproteins containing asparagine-linked oligosaccharides.[5] Although the absolute configuration of 2 has been assigned on the basis of chiroptical and biosynthetic studies,[6] the absolute stereostructure of castanospermine remains unknown, thus hampering efforts by biochemists to develop well-defined structure-activity relationships in this family of glycosidase inhibitors. Here we report an enantiospecific total synthesis of (+)-castanospermine from D-glucose which unambiguously establishes its absolute configuration as shown in 1.



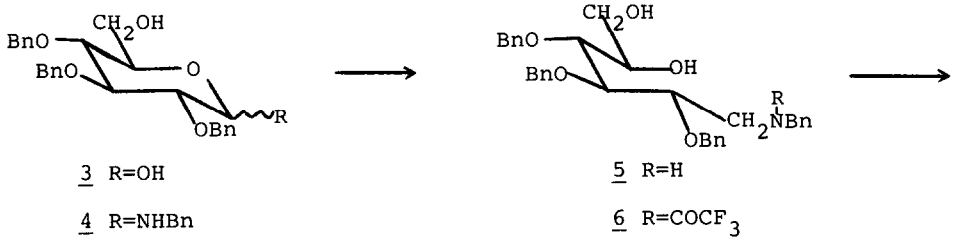
1



2

Condensation of 2,3,4-tri-O-benzyl-D-glucopyranose 3[7] with benzylamine (10 equiv, $CHCl_3$) afforded glucosylamine(s) 4 as an anomeric mixture (77% yield after recrystallization; mp 141.5-142.5^{0}C).[8] After reduction ($LiAlH_4$, THF, reflux, 5h), the crude amine 5 was trifluoroacetylated to furnish amide 6 (78%). In order to form an epoxide with inverted configuration at C5, diol 6 was protected (t-$BuMe_2SiCl$-imidazole), mesylated, deprotected and cyclized (Bu_4NF-THF; CH_3ONa-CH_3OH) to give 7 in 75% overall yield.

Cleavage of the amide group in 7 was best accomplished by reduction with $NaBH_4$ in ethanol at 40^{0}C. Under these conditions, aminoepoxide 8 cyclized spontaneously and in quantitative yield to a mixture of piperidine 9 (45%) and azepane 11 (55%) which were readily separated by chromatography. Hydrogenolysis of 9 afforded pure (+)-deoxynojirimycin 10 whose 300MHz NMR spectrum matched the published spectrum.[9] Similar deprotection of 11 produced 12, a tetraol previously prepared by Paulsen and Todt from 6-amino-6-deoxy-L-idose.[10]

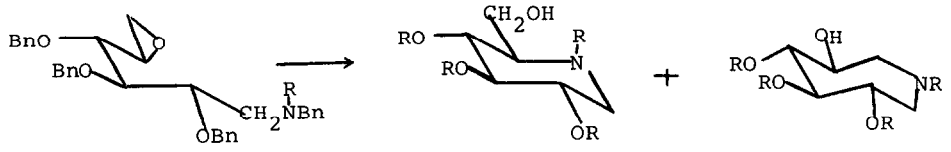


3 R=OH

4 R=NHBn

5 R=H

6 R=$COCF_3$



7 R=$COCF_3$

8 R=H

9 R=Bn

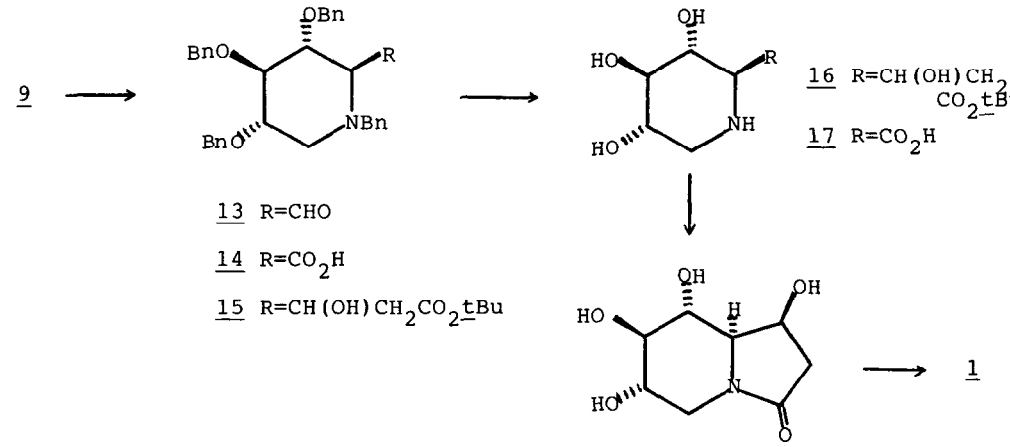
10 R=H

11 R=Bn

12 R=H

Oxidation of 9 by the method of Swern (DMSO-oxalyl chloride)[11] furnished the sensitive aldehyde 13 in 90% yield. This substance was immediately condensed with lithio t-butylacetate[12] and furnished 15 as a 1:1 mixture of separable diastereomers. The less polar diastereomer was transformed by hydrogenolysis, then acid treatment (TFA-H_2O, 60^0C, 3h) into lactam 18. Reduction with diisobutylaluminum hydride gave castanospermine, whose 300MHz ^{1}H-NMR spectrum was superimposable with that of natural material. The specific rotation of synthetic (+)-1 [observed: $+71^0$ (c=0.27, H_2O); reported: $+80^0$ (c=0.93, H_2O)] further defined its structure as (1S,6S,7R,8R,8aR)-1,6,-7,8-tetrahydroxyindolizidine. The same reaction sequence transformed the more polar form of 15 into 1-epicastanospermine, $[\alpha]_D$ $+6^0$ (c=0.45, H_2O).

In vitro inhibition of β-glucosidase (almond emulsion) by synthetic (+)-1 matched that of natural castanospermine.[13]



Although the biosynthesis of indolizidines commonly involves condensation of pipecolic acid with one acetyl (i.e. malonyl CoA) unit,[6] trihydroxypipecolate 17, accessible synthetically via 14, may be an intermediate in the biosynthesis of 1. Castanospermine, its C1-epimer, azepane 12, and acid 17 are presently being screened for activity against glycosidases and for inhibition of viral glycoprotein processing reactions. Those results will be reported elsewhere.

ACKNOWLEDGMENT: We are indebted to the National Institutes of Health for a predoctoral traineeship to R.C.B. on Grant GM 97273. We thank Professor J.C. Clardy for a sample of authentic castanospermine, and acknowledge helpful discussions with Professor J.R. Rasmussen. Support of the Cornell Nuclear Magnetic Resonance Facility by the National Science Foundation (CHE 7904825;PCM 8018643) is greatly appreciated.

REFERENCES AND NOTES

1. Camille and Henry Dreyfus Teacher Scholar Grant Awardee, 1978-83.
2. L.D. Hohenschutz, E.A. Bell, P.J. Jewess, D.P. Leworthy, R.J. Pryce, E. Arnold, J. Clardy, Phytochemistry, 20, 811 (1981).
3. R. Saul. J.P. Chambers, R.J. Molyneux, A.D. Elbein, Arch. Biochem. Biophys., 221, 593 (1983).
4. Y.T. Pan, H. Hori, R. Saul, B.A. Sanford, R.J. Molyneux, A.D. Elbein, Biochem., 22, 3973 (1983).
5. (a) S.M. Colegate, P.R. Dorling, C.R. Huxtable, Aust. J. Chem., 32, 2257 (1979); (b) P.R. Dorling, C.R. Huxtable, S.M. Colegate, Biochem. J.,191, 649 (1980); (c) A.D. Elbein, R. Solf, P.R. Dorling, K. Vosbeck, Proc. Nat. Acad. Sci. USA, 78, 7393 (1981); (d) A.D. Elbein, P.R. Dorling, K. Vosbeck, M. Horrisberger, J. Biol. Chem., 257, 1573 (1982).
6. (a) M.J. Schneider, F.S. Ungemach, H.P. Broquist, T.H. Harris, Tetrahedron, 39, 29 (1983); (b) idem., J. Am. Chem. Soc.,104, 6863 (1983).
7. G. Zemplen, Z. Csuros, S. Angyal, Chem. Ber., 70, 1848 (1937).
8. All new compounds gave satisfactory IR, NMR and mass spectra.
9. S. Inouye, T. Tsuruoka, T. Niida, Tetrahedron, 24, 2125 (1968).
10. H. Paulsen, K. Todt, Chem. Ber., 100, 512 (1967).
11. (a) S.L. Huang, K. Omura, D. Swern, J. Org. Chem., 41, 3329 (1976). (b) A.J. Mancuso, D. Swern, Synthesis, 165 (1981).
12. M.W. Rathke, D.F. Sullivan, J. Am. Chem. Soc., 95, 3050 (1973).
13. We thank Dr. J.R. Rasmussen and Mr. David Hsu for performing this assay.

(Received in USA 18 October 1983)