Pergamon

Tetrahedron Letters 42 (2001) 6433–6435

TETRAHEDRON LETTERS

Opening of a vinyl aziridine with *p*-toluenesulfonamide under TBAF catalysis: synthesis of 3,4-diamino-3,4-dideoxy-L-*chiro*-inositol

Bernhard J. Paul, Elizabeth Hobbs, Pablo Buccino and Tomas Hudlicky*

Department of Chemistry, University of Florida, PO Box 117200, Gainesville, FL 32611, USA

Received 9 July 2001; revised 17 July 2001; accepted 18 July 2001

Abstract—3,4-Diamino-3,4-dideoxy-L-*chiro*-inositol has been prepared from bromobenzene by a chemoenzymatic approach. The key chemical step was a tetrabutylammonium fluoride (TBAF) catalyzed vinyl aziridine opening employing *p*-toluenesulfonamide as a nucleophile, establishing the 1,2-*trans* relationship of the amino groups.

Unnatural inositol derivatives with amino groups substituted for one or more hydroxyl groups have attracted interest as probes for the investigation of the inositol-phosphate cycle as well as potential glycosidase inhibitors, and several diaminocyclitol aminoglycosides possess antibiotic activities. The aminocyclitol unit in the great majority of these aminoglycoside antibiotics is either 2-deoxystreptamine (**1**) or streptamine (**2**),[1] both featuring a 1,3-arrangement of the two amino groups (Fig. 1).

Several syntheses of streptamine derivatives containing either a 1,3-[2,3] or a 1,4 relationship[4] of the nitrogen atoms have been reported. The preparation of 1,2-diamino analogs has been reported for *muco*-inositol,[5] DL-*chiro*-[6] and *myo*-inositol.[7]

In this manuscript we wish to report a chemoenzymatic approach to 3,4-diamino-3,4-dideoxy-L-*chiro*-inositol by an unusual vinyl aziridine opening using *p*-toluenesulfonamide as the nucleophile and catalyzed by tetrabutylammonium fluoride (TBAF).

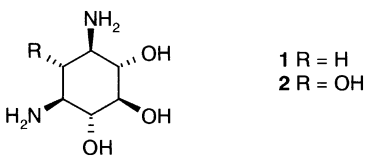


Figure 1. The structures of 2-deoxystreptamine (**1**) and streptamine (**2**).

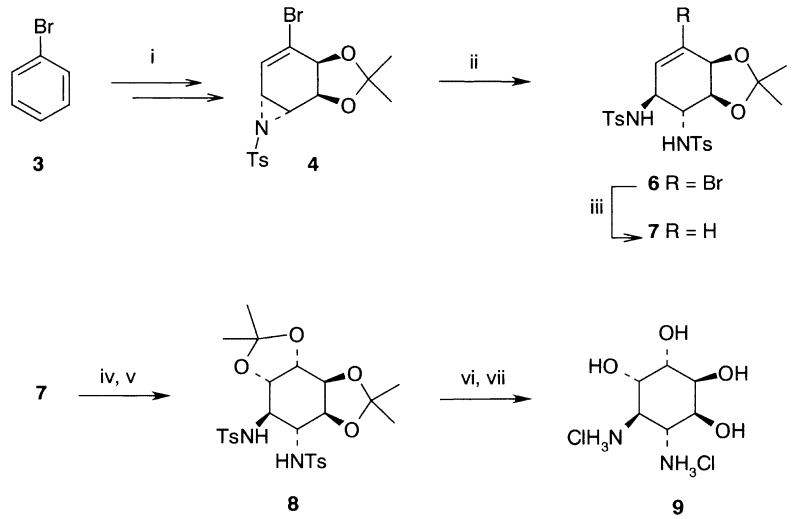
Bromocyclohexadiene-*cis*-diol **3**[8–10] was produced by whole-cell fermentation of bromobenzene with *E. coli* JM109(pDTG601) and converted in two steps to the previously reported[11–13] vinyl aziridine **4**. Because the three-step procedure for the vinyl aziridine opening with azide, reduction and subsequent protection lacked the desired brevity and was hampered by low yields, we searched for alternatives to establish the desired 1,2-*trans* relationship of the nitrogen atoms. The C_2-symmetry of the target molecule prompted us to attempt ring opening with *p*-toluenesulfonamide, despite its low nucleophilicity, thus introducing nitrogen already in its protected form and limiting deprotection to a single step for both nitrogen moieties.

TBAF[14] is a powerful catalyst for the opening of epoxides with thiols,[15] and it has been suggested that protic substances can form hydrogen-bonded complexes with fluoride ion, thus vastly enhancing the nucleophilicity of the attacking species.[16–18] TBAF has also been reported to be an excellent catalyst for the opening of aziridines with trialkylsilyl halides and pseudohalides.[19] When an equimolar solution of vinyl aziridine **4** and *p*-toluenesulfonamide (**5**) in DMSO was treated with two equivalents of TBAF,[20] the mixture was converted to bis-sulfonamide **6** in a matter of minutes in 95% yield (Scheme 1).

This transformation was also accomplished with only 0.5 equivalents of the catalyst; however, the reaction took several hours. With catalyst concentrations lower than 20 mol%, some product resulting from the opening of the vinyl aziridine with residual water was also observed.

* Corresponding author. Tel.: (352)-392-9844; fax: (352)-846-1203; e-mail: hudlicky@chem.ufl.edu

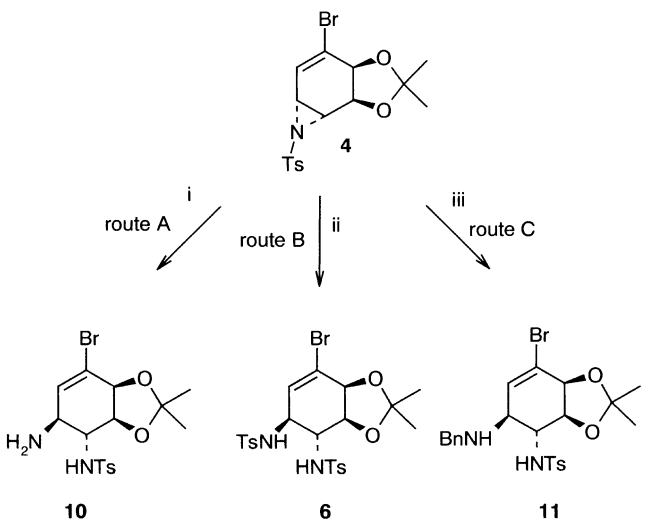
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01298-9



Scheme 1. *Reagents and conditions*: (i) Refs. 11–13; (ii) **5**, TBAF, DMSO; (iii) AIBN, Bu_3SnH, THF; (iv) $OsO_{4(cat.)}$/NMNO, acetone, H_2O; (v) DMP, H^+; (vi) Na, $NH_{3(l)}$; (vii) HCl, MeOH.

Vinyl bromide **6** was then reduced under radical conditions to provide alkene **7** (90%). The latter compound was hydroxylated ($OsO_{4(cat.)}$/NMNO) and the resulting diol protected as its acetonide to yield the fully hydroxylated species **8** in 75% yield over two steps. The sulfonamide groups in **8** were removed under the conditions of dissolving metal reduction (Na/NH_3), followed by deprotection of the ketals (HCl/MeOH) to provide the title compound (**9**) as its bis-hydrochloride (47% over two steps).[21]

This procedure further expands the scope of conditions for vinyl aziridine openings, as shown in Scheme 2. As we have recently shown,[22] the opening of vinyl aziridine **4** can be accomplished with ammonia under $Yb(OTf)_3$ catalysis to give **10** (route A). Furthermore, we have found[23] that benzylamine is also a suitable nucleophile for the $Yb(OTf)_3$-catalyzed ring opening to give **11** (route C). Finally, the (pseudo)-symmetric approach described in this manuscript allows for the construction of protected diamine **6**, which has two identical protecting groups (route B). These strategies enable us to construct differently protected diamines from the same precursor, thus allowing further functionalization of either of the two amino groups.



Scheme 2. Different strategies for vinyl aziridine opening; *reagents and conditions*: (i) $NH_{3(l)}$, $Yb(OTf)_3$, sealed tube; (ii) **5**, DMSO, TBAF; (iii) $Yb(OTf)_3$, 1,4-dioxane, $BnNH_2$.

In conclusion, we have shown that vinyl aziridine opening can be accomplished with *p*-toluenesulfonamide as the nucleophile by employing TBAF as catalyst. Diamine **9** was synthesized from vinyl aziridine **4** in four steps (six operations) in an overall yield of 34%. The current focus of our research includes expanding the scope of the TBAF-catalyzed aziridine opening, the investigation of **9** as a potential glycosidase inhibitor,[24] as well as the incorporation of derivatives of **9** into potentially water-soluble salen-type catalysts. Progress in these areas will be reported in due course.

Acknowledgements

The authors are grateful to the NSF (CHE-9615112, CHE-9910412), the US Environmental Protection Agency (R 826113) and TDC Research, Inc. for support of this work. P.B. wants to thank the Department of Chemistry at the University of Florida for support of the REU program.

References

1. Hooper, I. R. In *Aminoglycoside Antibiotics*; Umezawa, H.; Hooper, I. R., Eds.; Springer: Berlin, 1982; p. 7.

2. Schürrle, K.; Beier, B.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2407.
3. Schubert, J.; Keller, R.; Schwesinger, R.; Prinzbach, H. *Chem. Ber.* **1983**, *116*, 2524.
4. Sakairi, N.; Hayashida, M.; Amano, A.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1301.
5. Kresze, G.; Melzer, H. *Liebigs Ann. Chem.* **1981**, 1874.
6. Kresze, G.; Weiß, M. M.; Dittel, W. *Liebigs Ann. Chem.* **1984**, 203.
7. Guédat, P.; Spiess, B.; Schlewer, G. *Tetrahedron Lett.* **1994**, *35*, 7275.
8. Gibson, D. T.; Hensley, M.; Yoshika, H.; Mabry, T. T. *Biochemistry* **1970**, *9*, 1626.
9. Hudlicky, T.; Luna, H.; Barbieri, G. L.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735.
10. Hudlicky, T.; Stabile, M. R.; Gibson, D. T.; Whited, G. M. *Org. Synth.* **1999**, *76*, 77.
11. Hudlicky, T.; Tian, X. R.; Königsberger, K.; Rouden, J. *J. Org. Chem.* **1994**, *59*, 4037.
12. Tian, X. R.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643.
13. Hudlicky, T.; Tian, X. R.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752.
14. For a review about fluoride anion as a base in organic synthesis, see: Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.
15. Albanese, D.; Landini, D.; Penso, M. *Synthesis* **1994**, 34.
16. Cork, D. G.; Hayashi, N. *J. Chem. Soc., Chem. Commun.* **1993**, 527.
17. Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1989**, *54*, 328.
18. Sasson, Y.; Webster, O. W. *J. Chem. Soc., Chem. Commun.* **1992**, 1200.
19. Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2000**, *65*, 1344.
20. TBAF was used as a 1 M solution in THF (purchased from Aldrich). This solution contains about 5% water. Representative procedure: To a solution of vinylaziridine **4** (50 mg; 0.125 mmol) and *p*-tosyl sulfonamide (21.4 mg; 0.125 mmol) in DMSO (1.5 mL) was added a 1 M solution of TBAF in THF (250 μL) and the mixture was stirred for 30 min at room temperature. The solution was diluted with Et_2O (5 mL) and H_2O (1 mL) was added. The layers were separated and the aqueous layer was back-extracted with Et_2O (5×1 mL). The combined organic layers were washed with brine (1×5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **6** as a white foam (68 mg; 95%).
21. Data for bis-hydrochloride **9**: $[\alpha]_D^{31}$ −29.5 (*c* 0.2, MeOH); IR (KBr-pellet) 3413, 1618, 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.00–4.08 (m, 4H), 3.53–3.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.8, 67.3, 51.6; HRMS calcd for $C_6H_{16}N_2O_4$ $(M-H)^+$: 179.1032; found: 179.1031; anal. calcd for $C_6H_{16}Cl_2N_2O_4 \cdot H_2O$: C, 26.78; H, 6.74. Found: C, 26.45; H, 6.55.
22. Paul, B. J.; Martinot, T. A.; Willis, J.; Hudlicky, T. *Synthesis* **2001**, 952.
23. Paul, B. J.; Hobbs, E.; Hudlicky, T., unpublished results.
24. Glycosidase inhibition of *trans*-diamino conduritols has recently been reported. Arcelli, A.; Cere, V.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2001**, *57*, 3439.