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A DIHYDROISOXAZOLE-BASED ROUTE TO 2,3,6-TRIDEOXY-3-AMINOHEXOSE DERIVATIVES

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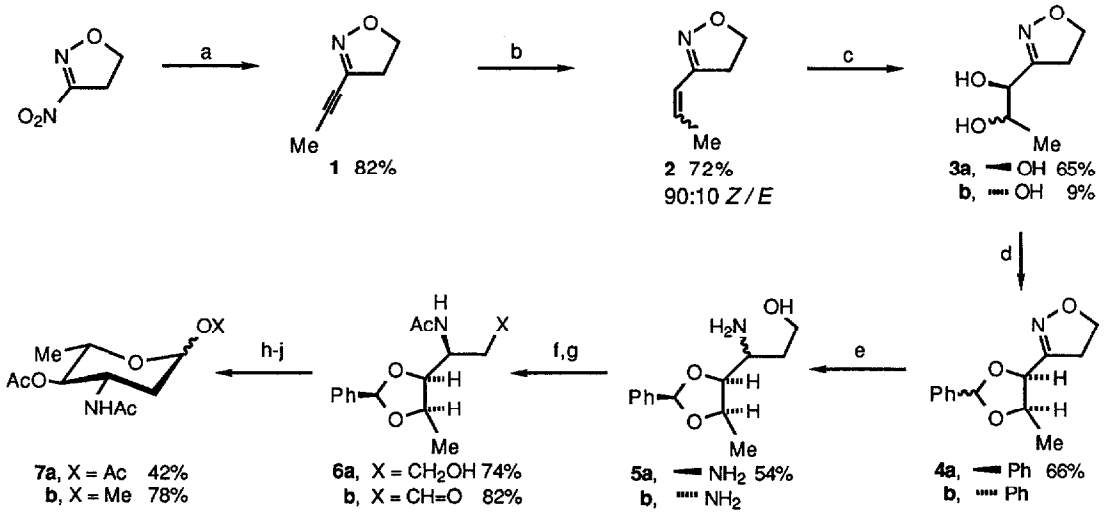
Summary: Acosamine and ristosamine derivatives were prepared via stereoselective reductive cleavage reactions of a benzylidenated dihydroisoxazolyl diol; the diol was prepared from 3-nitro-4,5-dihydroisoxazole via sequential propynylation, Lindlar reduction, and catalytic hydroxylation.

A number of aminosugar derivatives have now been prepared from dihydroisoxazole (isoxazoline) precursors.[1] The key reaction, conversion of the dihydroisoxazole to a γ-aminoalcohol, has been extensively studied: the stereochemical outcome is typically dictated by substituents at the 4- and 5-positions of the heterocyclic ring. Oxygenated substituents attached at the 3-position of a dihydroisoxazole appear to diminish the stereoselectivity normally imparted by 4- and 5-substituents,[1a, c] but extensive studies are lacking. Although dihydroisoxazoles have previously been prepared in optically active form,[1c, 2] we are unaware of any procedure used to enantioselectively transform an achiral dihydroisoxazole to a chiral one.

Scheme 1.



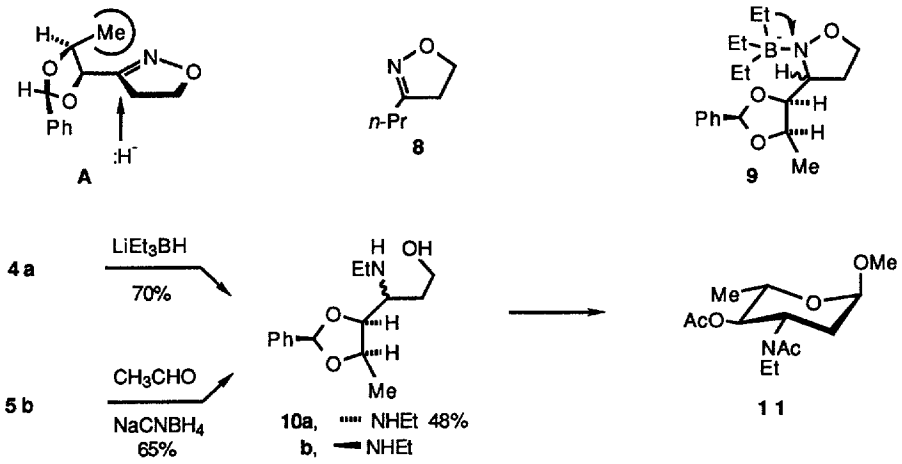
[a] $CH_3C{\equiv}CLi$. [b] 1 atm. H_2, Lindlar cat.,quinoline. [c] $Me_3N{\rightarrow}O$, cat. OsO_4,wet THF. [d] PhCH=O, $ZnCl_2$. [e] $LiBH_4$, THF, 40 °C, 3 d. [f] *p*- $AcOC_6H_4NO_2$, *N*-hydroxybenztriazole, DMSO. [g] $COCl_2$, Et_3N, DMSO. [h] aq. HOAc. [i] Ac_2O, pyr. [j] MeOH, TsOH.

We wish to describe a diastereoselective total synthesis of racemic methyl N,O-diacetylacosaminide (**7b**)[3] from 3-nitro-4,5-dihydroisoxazole and the potential for extending the approach to enantioselective aminosugar synthesis. Also, initial work on extending the synthesis to ristosamine derivatives will be described.

Reaction of 3-nitro-4,5-dihydroisoxazole[4] with excess propynyllithium, prepared *in situ* by the method of Roush[5], afforded the alkyne **1** in 82% yield (Scheme 1). Catalytic hydrogenation of the triple bond could be carried out in the presence of the dihydroisoxazole N,O-bond using Lindlar catalyst: a 72% yield of alkene **2** was obtained as a 90:10 inseparable *Z/E* mixture. Catalytic *cis*-hydroxylation of **2** by the Upjohn procedure[6] afforded a separable mixture of diols from which **3a**[7] could be isolated in 65% yield. Benzylidenation of **3a** gave the acetal **4** as a mixture of two diastereomers: rapid reaction (30 min) provided largely the diastereomer **4a**[7,8] (90:10 **a/b** ratio, kinetic product) which could be obtained pure by chromatography in 66% yield. Longer reaction times in the presence of excess $ZnCl_2$ favored diastereomer **4b** (30:70 **a/b** ratio at 10 hr). Reduction of **4a** with lithium borohydride (LBH) was slow at 40 °C but provided the γ-aminoalcohol **5** (90:10 **a/b** ratio); reduction with LAH gave a 70:30 mixture of the same stereoisomers. The aminoalcohol **5a**[7] was obtained in 54% yield from LBH reduction after chromatographic separation from **5b** (chromatography did not cleanly separate products obtained from benzylidene isomer **4b**!).

Examination of molecular models has led to a likely explanation of the diastereoselectivity. Reductive cleavage preferentially on conformation **A** where the 3α H-atom is "inside" [9] and the O-atom is "outside" would afford **5a** as the major product: the terminal methyl group appears to be the stereodiscriminator, protecting one face (the top as shown in Scheme 2) of the C,N-double bond. Presumably the Li-atom of the attacking LBH is coordinated to the dihydroisoxazole O-atom and / or N-atom. The stereochemical assignment for **5a** is based on the acosamine product obtained at the end of the synthesis.

Scheme 2.



To complete the synthesis, **5a** was first *N*-acetylated[10] to **6a** in 74% yield. Oxidation of **6a** by Swern's procedure gave the open-chain acosamine derivative **6b**[7] in 82% yield. Removal of the benzylidene group with aqueous acetic acid, *in situ* cyclization, and exhaustive acetylation provided acosamine triacetate (**7a**)[7] in 42% yield; the anomers (58:42 α/β-ratio) were separable. Treatment of **7a** with methanol and catalytic acid gave the glycoside **7b** (20:80 α/β-ratio), with spectra of the major anomer matching those previously published.[11]

The Sharpless catalytic asymmetric *cis*-hydroxylation[12] procedure was applied to the *Z*-isomer of alkene **2** (90:10 *Z/E* ratio) with only modest success. Thus, the diol **3a**, obtained using Et_4NOAc and slow addition at 0 °C, exhibited only 34% enantiomer excess (e.e.).[13] Asymmetric hydroxylation of *Z*-4,4-dimethyl-2-pentene has been reported to proceed with much lower enantioselectivity than the *E*-isomer.[14] Consequently, asymmetric hydroxylation of the *E*-isomer of **2b** (5:95 *Z/E* ratio) was examined. Here the *trans*-diol **3b** was obtained with 76% e.e. (absolute configuration not assigned) under conditions similar to those used for the *Z*-isomer. A 50:50 mixture of the *E*-alkene **2** (>95:5 *E/Z* ratio) and the over-reduced product **8** was prepared via reduction of alkyne **1** using 50% by weight Lindlar catalyst. The byproduct **8** was easily removed after hydroxylation which was performed in 30% overall yield.

Reductive cleavage of dihydroisoxazole **4a** with lithium triethylborohydride ($LiBEt_3H$) took an unusual path. Cleavage was accompanied by *N*-ethylation to give aminoalcohol **10** in 70% yield as a separable mixture of isomers (70:30 **a/b** ratio). Here, the predominant product was **10a**, a precursor to ristosamine. Conversion to ristosamine triacetate and glycoside derivatives analagous to the syntheses of **7a-b** is currently under study. The minor aminoalcohol **5b** obtained in the LBH reaction was ethylated[15] to produce **10a**, the same isomer as the major product obtained from $LiBEt_3H$ reduction. The minor product **10b** was converted to acosamine derivative **11** as evidenced by H_3-H_4 and H_4-H_5 axial - axial coupling constants ($J_{3,4} \approx J_{4,5} \approx 9.8$ Hz) of the major anomer, comparable to the homologous non-ethylated product **7b**.

Alkylations with $LiBEt_3H$ are rare. The *N*-ethylation observed with $LiBEt_3H$ can be rationalized by assuming the intermediacy of **9**. Thus, triethylborane first coordinates with the dihydroisoxazole N-atom: subsequent intramolecular (B → N)-ethide migration affords N,O-bond cleavage. The changed stereoselectivity might arise from chelation prior to hydride reduction of the C,N-double bond: chelation would alter the preference for "outside" placement of the 3α O-atom.

Application of this chemistry to 4-oxygenated (3-alkenyl)dihydroisoxazoles is currently under study. The synthesis of optically active daunosamine derivatives from diol **3b** is also planned.

References and Footnotes

1 (a) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79 and references cited therein. (b) Wade, P. A.; Price, D. T. *Tetrahedron Lett.* **1989**, *30*, 1185. (c) Jäger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199 and references cited therein. (d) See also: Torssell, K. B. G.; Hazell, A. C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569.

2. Kozikowski, A. P.; Chen, Y.-Y. *Tetrahedron* **1984**, *40*, 2345.

3. Acosamine and ristosamine have been synthesized by numerous routes. For a review, see: Hauser, F. M.; Ellenberger, S. R. *Chem. Rev*, **1986**, *86*, 35.

4. Wade, P. A. *J. Org. Chem.*, **1978**, *43*, 2020.

5. Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.*, **1987**, *52*, 5127.

6. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

7. Representative ^{1}H-NMR spectra in $CDCl_3$: **3a** δ 1.22 (d, 3H, *J* = 6.5 Hz), 2.43 (d, variable, 1H, *J* = 5.3 Hz, 3α O<u>H</u>), 2.74 (d, variable, 1H, *J* = 5.9 Hz, 3β O<u>H</u>), 3.08 (m, 2H, C-4<u>H</u>), 4.05 (m [apparent sx], 1H, 3β <u>H</u>), 4.32 (t, 2H, *J* = 10.1 Hz, C-5<u>H</u>), 4.41 (t, 1H, *J* = 5.3 Hz, 3α <u>H</u>); **4a** δ 1.35 (d, 3H, *J* = 6.5 Hz), 2.75-3.1 (m, 2H, C-4<u>H</u>), 4.15-4.4 (m , 2H, C-5<u>H</u>), 4.51 (quin, 1H, *J* ≈ 6.6Hz, 3β <u>H</u>), 5.1 (d, 1H, *J* = 7 Hz, 3α <u>H</u>), 5.89 (s, 1H, PhC<u>H</u>), 7.36-7.5 (m, 5H); **5a** δ 1.27 (d, 3H, *J* = 6.5 Hz), 1.57 (m, 2H, C-2<u>H</u>), 2.55 (bs, variable, 3H, N<u>H</u>, O<u>H</u>), 3.13 (m, 1H, C-3<u>H</u>), 3.86 (m, 2H, C-1<u>H</u>), 3.91 (t, 1H, *J* = 6.5 Hz, C-4<u>H</u>), 4.37 (quin, 1H, *J* ≈ 6.4 Hz, C-5<u>H</u>), 5.82 (s, 1H, PhC<u>H</u>), 7.3-7.55 (5H, m); **6b** δ 1.36 (d, 3H, *J* = 6.4 Hz), 1.73 (s, 3H, NHAc), 2.65 (m, 2H, C-2<u>H</u>), 4.21 (d, 1H, *J* = 7 Hz, C-4<u>H</u>), 4.3-4.55 (m, 2H, C-3<u>H</u>,5<u>H</u>), 5.65 (bd, 1H, N<u>H</u>), 5.79 (s, 1H, PhC<u>H</u>), 7.36-7.46 (m, 5H), 9.66 (m, 1H, C<u>H</u>O); **7a** δ [α-anomer] 1.17 (d, 3H, *J* = 6.2 Hz), 1.55 (m, 1H, ax C-2<u>H</u>), 1.87 (s, 3H, NHAc), 2.03 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.29 (ddd, 1H, *J* = 2.1, 5.9, 12.5 Hz, eq C-2<u>H</u>), 3.63 (m, 1H, C-5<u>H</u>), 4.12 (m, 1H, C-3<u>H</u>), 4.41 (t , 1H, *J* = 9.8 Hz, C-4<u>H</u>), 5.63 (bd, 1H, *J* = 8 Hz, N<u>H</u>), 5.70 (dd, 1H, *J* = 10, 2.1 Hz, C-1<u>H</u>); **7a** δ [β-anomer] 1.12 (d, 3H, *J* = 6.2 Hz), 1.65 (m, 1H, ax C-2<u>H</u>), 1.87 (s, 3H, NHAc), 2.03 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.18 (m, 1H, eq C-2<u>H</u>), 3.93 (m, 1H, C-5<u>H</u>), 4.3-4.5 (m, 2H, C-3<u>H</u>,4<u>H</u>), 5.50 (bd, 1H, N<u>H</u>), 6.07 (d, 1H, *J* = 2.53 Hz, C-1<u>H</u>); **10a** δ 1.08 (t, 3H, *J* = 7.1 Hz, $CH_3C\underline{H}_2$),1.35 (d, 3H, *J* = 6.4 Hz, $C\underline{H}_3CH$), 1.77 (m, 2H, C-2<u>H</u>), 2.6-2.8 (m, 2H, $CH_3C\underline{H}_2$), 2.92 (m, 1H, C-3<u>H</u>), 3.20 (bs, variable, 2H, N<u>H</u>,O<u>H</u>), 4.27 (dd, 1H, *J* = 6.8, 4.9 Hz, C-4<u>H</u>), 4.4 (quin, 1H, *J* ≈ 6.6 Hz, C-5<u>H</u>), 5.75 (s, 1H, PhC<u>H</u>), 7.3-7.5 (m, 5H).

8. Assigned by analogy to 2-phenyl-*cis*-4,5-dimethyl-2,4-dioxolanes: Willy, W. E.; Binsch, G.; Eliel, E. E. *J. Am. Chem. Soc.*, **1970**, *92*, 5394. The isomer with the *upfield* ^{1}H-NMR signal for the dioxolane 2-proton was assigned as *syn*.

9. Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Houk, K. N.; Schohe, R.; Jäger, V.; Fronczek, F. R. *J. Am. Chem. Soc.*, **1984**, *106*, 3880. Attack anti-periplanar to the α-C,O-bond would be inconsistent with the observed major product: Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788 and references cited therein.

10. Steinfeld, A. S.; Naider, F.; Becker, J. M. *J. Chem. Res. (S)* **1979**, 129.

11. (a) Lee, W. W.; Wu, H. Y.; Christensen, J. E.; Goodman, L.; Henry, D. W. *J. Med. Chem.*, **1975**, *18*, 768. (b) Boivin, J.; Pais, M.; Monneret, C. *Carbohyd. Res.* **1978**, *64*, 271.

12. (a) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1989**, *111*, 1123. (b) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1988**, *110*, 1968.

13. Best determined using $Eu(tfc)_3$ in $CDCl_3$ after conversion of the diol to the benzylidene acetal.

14. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1980**, *102*, 4264.

15. Using 1 mol. equiv. of $NaBH_3CN$ and 1 mol. equiv. of acetaldehyde in acetonitrile: Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.*, **1970**, *93*, 2897; Unangst, P. C.; Connor, D. T.; Stabler, S. R. *J. Med. Chem.*, **1987**, *24*, 817.

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