Tetrahedron Letters,Vol.26,No.25,pp 2997-3000,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain 

# STEREOCONTROL IN ISOXAZOLINE REDUCTIONS. SYNTHESIS OF AMINODEOXY-DL-XYLO- AND ARABINO-PENTOSE DERIVATIVES FROM FUROISOXAZOLINES [1]

Volker Jäger * and Ingrid Müller
Institut für Organische Chemie der Universität Würzburg, Am Hubland
D-8700 Würzburg

Erich F. Paulus
Hoechst AG, D-6230 Frankfurt a.M. 80

Summary: *Ozonolysis of furoisoxazolines furnishes* cis-*4-oxygenated isoxazolines, which by suitable derivatization and subsequent LAH reduction yield* xylo *or* arabino *aminodeoxy-pentoses, depending on the presence of a free or blocked 4-hydroxy group.*

Isoxazolines are useful intermediates in short, stereoselective syntheses of diverse natural and unnatural products,[2] notably amino compounds (by reduction).[1-5] The stereoselectivity of isoxazoline reductions effected by LAH is primarily determined by the nature, position, and number of substituents of C-4 and C-5 of the heterocyclic nucleus.[5-7] While most groups that have been checked so far are anti-directing in this respect, free 4-hydroxyl induces syn hydride addition.[3,7] Together with the remarkable additivity of substituent directing effects ($\Delta\Delta G^{+}$ values),[6] this permits stereoselective access to a large variety of γ-amino alcohols (including amino polyols, amino sugars and amino acids) in a predictable way.[5] The present letter deals with the following questions on the feasibility of exerting stereo*control* in these reductions: (i) does the strong syn-directing effect of 4-OH prevail also in the presence of other cis-substituents? (ii) is it possible to block the 4-OH group and thus convert it to an anti-directing one?

For this purpose, the isoxazolines **2** - **4** were prepared from furoisoxazolines **1** and **8**, in turn accessible in 60 - 70 % yield by nitrile oxide cycloadditions to furan and 2-methylfuran, respectively.[1,4,8] A solution of **1a** in methylene chloride/methanol (ca. 5 %)[9] was treated with ozone at -78°C [10] until complete conversion was indicated by TLC control (ca. 10 min with 10 mmol runs). Dimethylsulfide was added to destroy hydroperoxides and ozonides. The resulting yellow oil (intractable NMR spectra) was transformed in 47 % yield to the crystalline acetal **2** [11] (with neopentylglycol in refluxing benzene and TsOH catalyst), after NaOH treatment to cleave O-acyl groups and prevent the detrimental elimination to isoxazoles. On the other hand, the crude ozonation product was reduced with $NaBH_4$ in methanol/water to produce **3** (53 %) as a syrup, devoid of carbonyl absorptions (IR). The methylfuran adduct **1b** gave slightly better yields and was used therefore in subsequent experiments. Crude **3** (from **1b**, ca. 60 %) was converted by azeotropic removal of methanol to the isopropylidene derivative **4** with dimethoxypropane/p-toluenesulfonic acid (catalyst) in benzene. Filtration through basic aluminia gave pure **4** (31 %, yellow oil [11]).

The isoxazolines 2 - 4 were reduced with $LiAlH_4$ and the crude products analyzed by $^{13}C$ NMR (100.6 MHz) as usual.[5-7] From 3 a mixture of aminodeoxypentitols was isolated which, after peracetylation to furnish 6, consisted of two diastereoisomers in a 58 : 42 ratio (by NMR). However, configurational assignments (xylo/arabino) were not possible on the basis of NMR data.[11] In contrast, 2 and 4 afforded on reduction a single diastereomer (d.r. > 97 : 3) in each case, in 95 and 73 % yield, respectively. The spectroscopic data of both 5 and 7 were again inconclusive in regard to their relative configurations.[11]

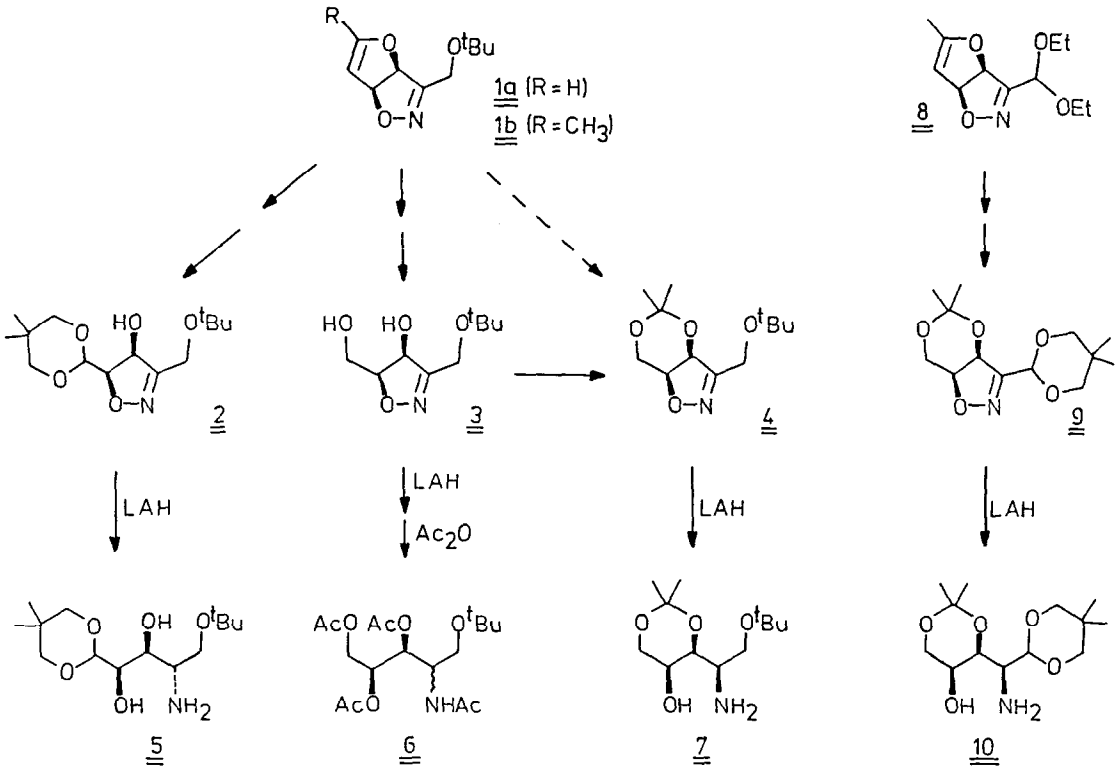
An analogous situation was met with 9 which was prepared in 34 % over-all yield from the furoisoxazoline acetal 8[1,4] by the sequence ozonolysis, $NaBH_4$ reduction, transacetalization of the diethyl acetal group with neopentyl glycol, and acetonide formation.[11-13] The reduction led to a single diastereomer (> 97 : 3) of the corresponding pentosamine derivative 10, as expected from the results for 4 → 7, in 88 % yield. The coupling constants[11] show 10 and 7 to belong to the same diastereomer series; these NMR data, however, did once more not allow to establish which one!

X-ray analysis was therefore performed on the structurally complementary aminodeoxy-pentoses 5 and 10 to elucidate the course of these highly stereoselective reductions. Single crystals of 5 were prepared by repeated crystallization[14] and suitable material from 10 was obtained in form of the O,N-diacetyl derivative.[15] The 4-amino-4-deoxy-pentose 5 proved to be the *arabino* isomer and the 2-amino-2-deoxypentose 10 turned out the *xylo* isomer!

The low selectivity in the reduction of 3, an isoxazoline with two groups individually favouring syn-addition,[7] is not expected and may be rationalized by the formation of counteracting cyclic aluminates. On the other hand, the strong anchoring effect of the 4-hydroxy group in 2 to guide hydride addition in LAH reductions is not side-tracked by the cis-5-dioxanyl substituent.[16] In addition, the stereochemical outcome of the reductions of the bicyclic isoxazolines 4 and 9, to produce xylo derivatives 7 and 10 only, exceeds *a priori* estimates based on results with related substrates.[17]

The results of this and previous[3] studies show that stereo***control*** in isoxazoline reductions can be achieved, based upon the presence of a free or blocked hydroxy group. The underlying principle may be generally useful in synthesis.[18] Specifically, the syntheses of 5, 7, and 10 - derivatives of complementary structure and configuration - provide novel examples for the utilization of the isoxazoline route[19] in amino sugar synthesis.[20]

*Acknowledgements:* Support of this work by Deutsche Forschungsgemeinschaft, Fonds der Chemischen Industrie, Bayer AG (Dr. H. Meyer, Wuppertal), and Hoechst AG (Dr. W. Bartmann, Hoechst), is gratefully acknowledged. We are obliged to Ms. D. Michel for experimental help.




## References and Notes


1. Syntheses via Isoxazolines, 17; (a) part 16: V. Jäger, I. Müller, Tetrahedron, in press; (b) part of the Dissertation of I. M., Würzburg 1984, (c) presented first at the 3rd Convegno Sulle Reazioni Pericicliche, Naples, Oct. 1984.
2. V. Jäger, R. Schohe, Tetrahedron 40, 2199 (1984) and references therein.
3. W. Schwab, V. Jäger, Angew. Chem. 93, 578 (1981); Ibid., Int. Ed. Engl. 20, 603 (1981).
4. I. Müller, V. Jäger, Tetrahedron Letters 4777 (1982).
5. Review: V. Jäger, H. Grund, V. Buß, W. Schwab, I. Müller, R. Schohe, R. Franz, R. Ehrler, Bull. Soc. Chim. Belg. 92, 1039 (1983).
6. V. Jäger, V. Buß, W. Schwab, Tetrahedron Letters 3133 (1978); V. Jäger, V. Buß, Liebigs Ann. Chem. 101 (1980); V. Jäger, V. Buß, W. Schwab, Ibid. 122 (1980).
7. V. Jäger, W. Schwab, V. Buß, Angew. Chem. 93, 576 (1981); Ibid,. Int. Ed. Engl. 20, 601 (1981).
8. Furan additions to aryl nitrile oxides: ref. 1a and P. Grünanger, I. Grasso, Gazz. Chim. Ital. 85, 1271 (1955); A. Corsico Coda, P. Grünanger, G. Veronesi, Tetrahedron Letters, 2911 (1966); P. Caramella, G. Cellerino, A. Corsico Coda, A. Gamba Invernizzi, P. Grünanger, K. N. Houk, F. Marinone Albini, J. Org. Chem. 41, 3349 (1976). Intramolecular case: O. Tsuge, K. Ueno, S. Kanemasa, Chem. Lett. 285 (1984).

9. P. S. Bailey, Ozonation in Organic Chemistry, Vol. 1, Olefinic Compounds, Academic Press, New York 1978.

10. Isoxazolines at -78 °C are rather reluctant towards ozone: cf. ref. 5; H. Grund, Dissertation, Gießen 1978; A. P. Kozikowski, M. Adamczyk, Tetrahedron Letters 3123 (1982).

11. All compounds mentioned were characterized by elemental analyses, IR, $^{1}H$ and $^{13}C$ NMR spectra ($CDCl_3$ solutions). Some characteristic data are: 2: m.p. 112 - 113 °C (from ether/p.e.); δ = 4.28 (dd, J = 5.5 and 7.5 Hz; 5-H) and 5.20 ppm (dd, broad; $J_{45}$ = 7.5, $J_{4,OH}$ = 3.8 Hz, 4-H). 3: δ = 5.25 ppm (bd, $J_{45}$ = 8 Hz; 4-H). 4: δ = 4.29 (ddd, J = 4.5, 4.5 and 7.0 Hz; 5-H), 5.11 ppm (d, J = 7.0 Hz; 4-H). 5: m.p. 120 - 122 °C; δ = 3.25 (ddd, $J_{34}$ = 5.0, $J_{45}$ = 4.0 and 7.5 Hz; 4-H), 3.78 (dd, $J_{12}$ = 4.0, $J_{23}$ = 1.0 Hz; 2-H), 3.83 (dd, $J_{23}$ = 1.0, $J_{34}$ = 5.0 Hz; 3-H). 6: 56 % crude, 42 % with d.r. 53 : 47, oil. One diastereomer was obtained pure by fractional crystallization, m.p. 133 - 134 °C. 7: light yellow oil; δ = 3.06 (ddd, $J_{12}$ = 6.5 and 6.5, $J_{23}$ = 3.0 Hz; 2-H). 9: m.p. 133 -134 °C; δ = 4.29 (ddd, J = 4.5, 4.5 and 6.5 Hz; 5-H), 5.15 ppm (d, J = 6.5 Hz; 4-H). 10: m.p. 115 - 119 °C; after two recrystallizations m.p. 123 - 125 °C (54 %); δ = 2.98 (dd, $J_{12}$ = 6.5, $J_{23}$ = 2.0 Hz; 2-H). 2-N,4-O-diacetyl derivative (with $Ac_2O$, pyridine/DMAP, 2d at room temp.; 60 % after crystallization from hexane): m.p. 142 - 143 °C; δ = 4.19 ppm (ddd, $J_{12}$ = 3.0, $J_{23}$ = 4.0, $J_{2,NH}$ = 8.1 Hz).

12. The transacetalization proved neccessary, as the diethyl acetal did not survive acid-catalyzed acetonide formation. The diethyl acetal group was chosen for the starting isoxazoline 8 in view of the considerably higher lability of cyclic acetals towards ozone.[13]

13. P. Deslongchamps, P. Atlani, D. Frehel, A. Malaval, C. Moreau, Can. J. Chem. 52, 3651 (1974).

14. X-ray of 5: single crystals, m.p. 128 °C; 8 crystallizations from heptane. a = 6.286 (1), b = 10.620 (1), c = 13.865 (2) Å, α = 71.82 (1), β = 76.94 (1), γ = 79.30 (1) °; $P\bar{1}$; Z = 2; $D_x$ = 1.138, $D_m$ = 1.13 g/cm$^3$; $R_1$ = 0.12, $R_2$ = 0.045 (R3-Nicolet diffractometer; 2θ/θ scan; $MoK_\alpha$; $\vartheta_{max}$ = 22.5 °; 1679 from 2287 independent reflexions; $F > 1\sigma(F)$; $w = 1/\sigma^2$ (F). Program system: G. M. Sheldrick, SHELXTL, Göttingen 1983; standard deviation of CC bond lengths: 0.007 Å.

15. X-ray of 10: single crystals, m.p. 144 °C; 5 crystallizations from heptane. a = 6.180 (1), b = 11.125 (1), c = 14.686 (2) Å, α = 76.56 (1), β = 85.50 (1), γ = 89.26 (2) °, $P\bar{1}$; Z = 2, $D_x$ = 1.219, $D_m$ = 1.22 g/cm$^3$; $R_1$ = 0.057, $R_2$ = 0.033 (2253 from 2563 independent reflexions); standard deviation of CC bond lengths: 0.004 Å.

16. This was confirmed independently: LAH reduction of a 5-dioxanyl isoxazoline led to a 54 : 46 mixture of corresponding amino alcohols W. Kütt, Diploma Thesis, Würzburg 1984.

17. Cf. reductions of furoisoxazolines [1,4] and of cyclopentane-annulated isoxazolines.[6]

18. For a recent case of OH-directed catalytic hydrogenation see (a) G. N. Stork, D. E. Kahne, J. Am. Chem. Soc. 105, 1072 (1983), (b) ref. 7 and references given therein.

19. V. Jäger, H. Grund, Angew. Chem. 88, 27 (1976); Ibid., Int. Ed. Engl. 15, 50 (1976).

20. For syntheses of 4-amino-4-deoxypentoses (*xylo/lyxo*) see H. Paulsen, K. Propp, J. Brüning, Chem. Ber. 102, 469 (1969); H. Paulsen, J. Brüning, K. Heyns, Chem. Ber. 103, 1621 (1970).

(Received in Germany 29 March 1985)