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A NEW ROUTE TO 4-OXYGENATED ISOXAZOLINES. APPLICATION TO THE SYNTHESIS OF 2-DEOXY-2-AMINOBUTOSE DERIVATIVES

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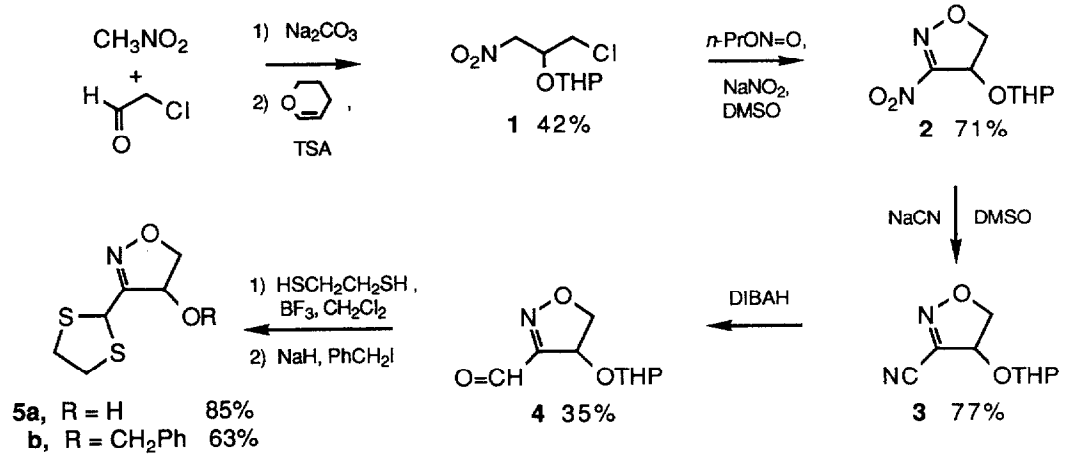
Summary: The THP ether of 4,5-dihydro-3-nitro-4-isoxazolol, prepared by a sequential nitroaldol nitrosative cyclization strategy, was converted to a 4,5-dihydro-3-(dithiolanyl)isoxazole; subsequent LBH reduction gave a 95:5 diastereomeric mixture of 2-deoxy-2-aminothreose and -erythrose derivatives, respectively, which was cyclized to a mixture of tetrahydro-2*H*-1,3-oxazine-2-ones.

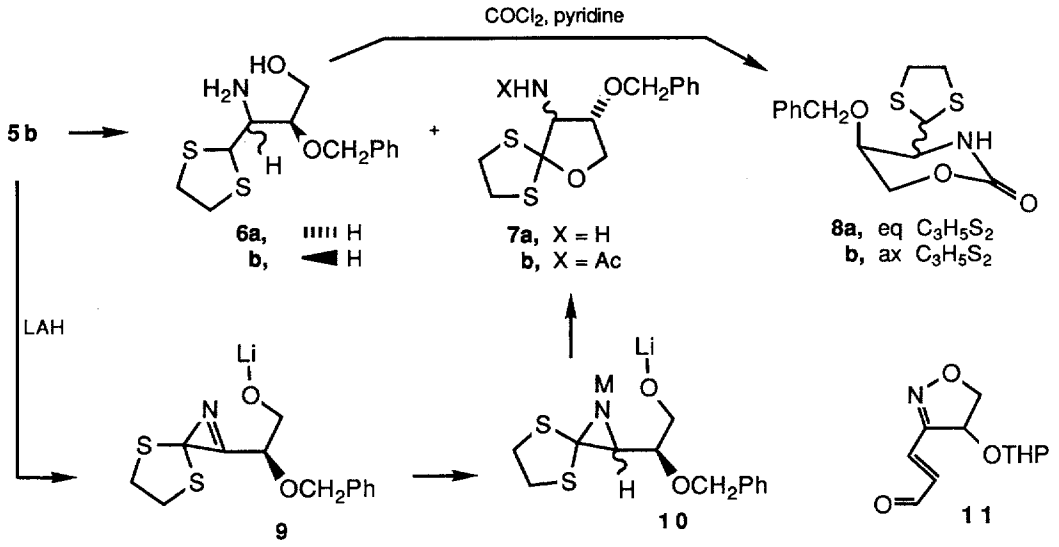
An impressive array of natural products have now been synthesized from isoxazoline intermediates.[1, 2] In a number of these syntheses[2a-b, 3], a 4-oxygenated isoxazoline has been required. Preparation of 4-oxygenated isoxazolines by direct cycloaddition is only successful using furan and its derivatives as the dipolarophile: enolic dipolarophiles typically give the 5-oxygenated regioisomer.[1b] Access to 4-oxygenated isoxazolines can also be gained by oxidation of the corresponding anion; however, optimization is often necessary to obtain a satisfactory yield.[1c]

We wish to describe a simple nitroaldol-based approach to 4-oxygenated isoxazolines which is particularly well-suited to obtaining materials without a 5-substituent. Condensation of a 55% aqueous solution of chloroacetaldehyde with excess nitromethane followed by THP-protection of the hydroxyl group of the resulting crude nitroaldol[4] gave nitro compound **1**[5] which was isolated in 42% yield after column chromatography on silica gel (Scheme 1). Nitrosative cyclization using a DMSO solution of sodium nitrite and *n*-propyl nitrite afforded isoxazoline **2**[5,6] in 71% yield. Thus, a 4-oxygenated isoxazoline with a readily replaceable 3-substituent could be prepared in two synthetic steps in 28% overall yield.

Scheme 1.



Scheme 2.



A variety of substitution reactions of 4,5-dihydro-3-nitroisoxazole have previously been reported.[7] However, attempts to install a 1,3-dithianyl group via direct substitution on **2** were unsuccessful: reaction with 2-lithio-1,3-dithiane gave none of the desired product, possibly owing to a redox reaction with the nitro group of **2.** Instead, the 1,3-dithiolane **5a** was prepared indirectly by a three-step sequence. First, reaction of **2** with a DMSO solution of sodium cyanide gave the nitrile **3**[5,8] in 77% yield. Reduction of **3** at 0°C with di-*iso*-butylaluminum hydride provided the corresponding imine which was hydrolyzed during purification[9] to isoxazoline-3-carboxaldehyde **4** in 35% yield from **3**. Boron trifluoride-catalyzed reaction of **4** with 1,2-ethanedithiol gave a 1,3-dithiolane with concomitant removal of the THP group; thus, **5a**[5,10] was obtained in 85% yield. Benzylation of the free hydroxyl group of **5a** gave the benzyl ether **5b**[5,10] in 63% yield.

Highly stereoselective conversion of isoxazolines to γ-aminoalcohols has been reported using either lithium aluminum hydride (LAH)[1,3] or di-*iso*-butylaluminum hydride (DIBAH).[11] DIBAH offers the advantage of mild conditions, but studies with LAH have been much more extensive: LAH has been shown to coordinate with a 4-hydroxyl substituent delivering hydride *syn* to the substituent.

Reductive cleavage (Scheme 2) of isoxazoline **5b** with DIBAH gave a 67% yield of aminoalcohols **6a** and **6b**, but with virtually no stereoselectivity (52:48, **6a** / **6b** ratio, Table). Reduction with LAH gave only a 13% yield of the same aminoalcohols[5,10] but with a much improved stereoselectivity (96:4, **6a** / **6b** ratio); an additional product **7a**[10] was obtained as two easily separable isomers (77:23 ratio) in 18% and 4% yield, respectively. The configurations of **7a** were not assigned but the isomers were separately acetylated to the monoacetates **7b**[10]. Thus, LAH lacked the necessary chemoselectivity for successful completion of the synthesis. Fortunately, lithium borohydride (LBH) provided both high stereoselectivity and high chemoselectivity[12]: reduction of **5b** in THF gave the desired aminoalcohols in 69% yield with a strong preference for the *threo*-isomer **6a** (95:5, **6a** / **6b** ratio). A pronounced solvent effect was noted on stereoselectivity: in ether the diastereomer ratio was much lower (75:25, **6a** / **6b** ratio).

Table. Stereoselectivity of Reduction of Isoxazoline 5b.

Hydride Reagent	6a / 6b	Solvent	Temp	Yield
DIBAH	52:48	THF	0-5 °C	67%
$LiAlH_4$	96:4	THF	0-5 °C	13%
$LiBH_4$	95:5	THF	20 °C	69%
$LiBH_4$	75:25	ether	20 °C	59%

The isomer assignments for **6a** and **6b** are based partly on ^{1}H-NMR coupling constants for the 4H, 5H ($CHNH_2$ - $CHOCH_2Ph$) signals: j = 1.4 Hz for **6a** and 8.8 Hz for **6b**. Assuming a chair-like conformation imposed by H-bonding between the hydroxyl and amino groups[13, 1b], the 4H, 5H protons must be *cis* in **6a** (*threo*) and *trans* in **6b** (*erythro*). The mixtures of **6a** and **6b** were converted to cyclic carbamate mixtures. The carbamate **8a**[10] was the major product from mixtures containing predominantly **6a**: thus, the carbamate **8a** was formed from **6a** and **8b** from **6b**, respectively. Large ax-ax proton coupling constants were absent in the 250 MHz ^{1}H-NMR spectrum of carbamate **8a** ($j_{4,5}$ = 3.6 Hz, $j_{5,6}$ = 2.5 Hz, and $j_{5,6'}$ too small to measure), consistent with the *cis*-isomer having a preference for the conformation with an axial benzyloxy group. Large ax-ax proton coupling constants were also absent for carbamate **8b** ($j_{4,5} \cong j_{5,6} \cong j_{5,6'} \cong$ 3.9 Hz), consistent with the *trans*-isomer, but largely in a diaxial conformation![14] Accordingly, the configurational assignments for the carbamates are based on two rather subtle points. First, contribution from a small amount of *trans*-diequatorial conformation should give rise to the larger 4-H, 5-H coupling constant (ax-ax protons): **8b** (j = 3.9 Hz in $CDCl_3$; 5.7 Hz in C_6D_6) versus **8a** (j = 3.6 Hz in $CDCl_3$; 3.7 Hz in C_6D_6). Also, a 4H, 6-H coupling constant (j = 1.2 Hz; W-coupling, observable in C_6D_6) was noted for **8b** only, requiring an axial dithiolanyl substituent. It should be noted that preferential formation of **8a** requires delivery of hydride ion *anti* to the benzyloxy substituent in **5b**, counter to observations with the 4-hydroxyl substituent, although the stereoselectivity is higher than expected for a simple steric effect[1b]. It is possible that O---Li---S chelation shields the top face of the isoxazoline while a second molecule of the reducing agent attacks *anti*.

Concerning the formation of the spirotetrahydrofuran **7a**, it is probable that the spiroaziridine **10** is an intermediate. Kotera et al[15] have observed aziridine formation with concomitant dehydroxylation in the reduction of isoxazolines with LAH in refluxing THF: an intermediate azirine was postulated. We propose deprotonation of **5b** to a dithiolanyl anion, displacement of alkoxide to afford spiroazirine **9**, and subsequent reduction to afford spiroaziridine **10**; rearrangement of **10** would then afford the more stable **7a**. Since stereoselectivity differs markedly in the formation of spirofuran **7a** and aminoalcohol **6a-b**, it is unlikely that C=N reduction occurs on a common intermediate.

The methodology described here is extendable to other aminosugars. Reaction of aldehyde **4** with the lithium enolate of acetaldehyde affords dehydrated aldol product **11**; elaboration of the sidechain of **11** would be expected to provide a 4-aminohexose. Propynyllithium displaces the nitro group of 4,5-dihydro-3-nitroisoxazole and application of this reaction to isoxazoline **2** is under investigation.

References and Footnotes

1. Reviews: (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (b) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79. (c) Jäger, V.; Grund, H.; Buß, V.; Scwab, W.; Müller, I.; Schohe, R.; Franz, R.; Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039.

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4. Using 4 eq. of CH_3NO_2 to diminish self condensation of $ClCH_2CHO$ and sufficient Na_2CO_3 to keep the reaction basic. Two diastereomers were obtained which could be chromatographically separated but which were used as a mixture.

5. Correct elemental analyses ± 0.45% were obtained.

6. The product decomposes on long-term storage and should be used shortly after preparation. Nitrosative cyclization of the unprotected nitroaldol also gave the isoxazoline but in very low yield: separation from DMSO was a major problem.

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8. Obtained as a mixture of two diastereomers partially separable by TLC: ^{1}H-NMR (isomer with larger r_f) δ 5.27 (dd, 1H, j = 2.8, 8 Hz, $C_4\underline{H}$), 4.77 (m, 1H, C$\underline{H}$OO), 4.61 (dd, 1H, j = 2.8, 10.8 Hz, $C_5\underline{H}$H'), 4.43 (dd, 1H, j = 8, 10.8 Hz, C_5H$\underline{H}$'), 3.9-4.0 (m, 1H), 3.5-3.7 (m, 1H), 1.5-1.9 (m, 6H); ^{1}H-NMR (isomer with smaller r_f) δ d 5.28 (dd, 1H, j = 4.1, 8.4 Hz), 4.88 (m, 1H), 4.61 (dd, 1H, j = 4.1, 11 Hz), 4.52 (dd, 1H, j = 8.4, 11 Hz), 3.8-3.9 (m, 1H), 3.5-3.7 (m, 1H), 1.5-1.9 (m, 6H).

9. Applied as an acetic acid solution to a silica gel TLC plate.

10. Representative ^{1}H-NMR data: **5a** δ 5.61 (s, 1H), 5.28 (m, 1H; dd, j = 2.8, 7.1 Hz on saturation of O$\underline{H}$), 4.39 (dd, 1H, j = 2.8, 10.5 Hz), 4.28 (dd, 1H, j = 7.1, 10.5 Hz), 3.3-3.6 (m, 4H), 3.21 (d, 1H, j = 3.8 Hz, O$\underline{H}$); **5b** δ 7.2-7.4 (m, 5H), 5.44 (s, 1H), 5.18 (dd, 1H; j = 3.5, 7.8 Hz), 4.57 (d, 1H, j = 11.4 Hz), 4.51 (d, 1H, j = 11.4 Hz), 4.43 (dd, 1H, j = 3.5, 10.7 Hz), 4.20 (dd, 1H, j = 7.8, 10.7 Hz), 3.2-3.5 (m, 4H); **6a** δ 7.2-7.5 (m, 5H), 4.77 (d, 1H, j = 11.6 Hz, PhC$\underline{H}$H'), 4.58 (d, 1H, j = 9.2 Hz, SC$\underline{H}$S), 4.48(d, 1H, j = 11.6 Hz), 4.13 (dd, 1H, j = 3.6, 12.5 Hz, C$\underline{H}$H'OH), 3.7-3.85 (m, 2H), 3.1-3.3 (m, 4H), 2.74 (dd, 1H, j = 1.4, 9.2 Hz, C$\underline{H}$N$\underline{H}_2$), 2.6 (bs, 3H, N$\underline{H}_2$ and O$\underline{H}$); **7a** (major isomer) δ 7.2-7.5 (m, 5H), 4.68 (d, 1H, j = 12 Hz, PhC$\underline{H}$H'), 4.59 (d, 1H; j = 12 Hz), 3.9-4.2 (m, 3H), 3.61 (d, 1H, j = 4.7 Hz, C$\underline{H}$N$\underline{H}_2$), 3.4-3.6 (m, 2H), 3.2-3.4 (m, 2H), 1.7 (bs, 2H, N$\underline{H}_2$); **7b** (major isomer) δ 7.2-7.5 (m, 5H), 6.21 (bd, 1H, j = 9.1 Hz, N$\underline{H}$), 4.90(dd, 1H, j = 5, 9.2 Hz, C$\underline{H}$NH), 4.64 (d, 1H, j = 12 Hz, PhC$\underline{H}$H'), 4.48 (d, 1H, j = 12 Hz), 3.5-3.7 (m, 3H), 3.2-3.6 (m, 4H), 2.05 (s, 3H); **8a** (500 MHz) δ 7.2-7.4 (m, 5H), 5.41 (bs, 1H, N$\underline{H}$), 4.68(d, j = 10.1 Hz, SC$\underline{H}$S) on 4.67 (d, j = 11.4 Hz, PhC$\underline{H}$H') (2H total), 4.47 (dd, j = 2.5, 12.5 Hz, C$\underline{H}$H'OCO) on 4.45 (d, j = 11.4 Hz, PhCH$\underline{H}$') (total 2H), 4.02 (d, 1H, j = 12.5 Hz, CH$\underline{H}$'OCO), 3.92 (m, 1H), 3.26 (dd, 1H, j = 3.6, 10.1 Hz, C$\underline{H}$NH), 2.9-3.3 (m, 4H, SC$\underline{H}_2$C$\underline{H}_2$S).

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12. Similarly, 3-α-oygenated isoxazolines can be reduced with LBH at 40 °C. Here LBH offers substantially higher stereoselectivity than LAH (90:10 vs 70:30 in the one case examined): Wade, P. A.; Rao, J. A. unpublished studies.

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