2-Amino-2-deoxytetrose Derivatives. Preparation from 4,5-Dihydroisoxazoles via Reductive Cleavage

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The 4-alkoxy-3-nitro-4,5-dihydroisoxazoles **2a,b** were prepared by condensation of nitromethane and chloroacetaldehyde, protection of the resulting nitroaldol **1c**, and subsequent nitrosative cyclization. Multistep replacement of the nitro group of **2a,b** by a 2-(1,3-dithiolanyl) group gave **7a,b**. Reaction of **7b** with lithium borohydride afforded reductive cleavage of the dihydroisoxazole ring to produce the open-chain diastereomeric amino alcohols **6a,b**. A reproducible ratio of >90:10 **6a/6b** was obtained using freshly prepared hydride reagent. The amino alcohols were converted to the corresponding (*R**,*R**)-amide **6c** and (*R**,*S**)-amide **6d** which were chromatographically separated. The (*R**,*R**)-amide was transformed into the 2-amino-2-deoxythreose derivatives **11a,b** and hence to **12** while the (*R**,*S**)-amide was similarly transformed to 2-amino-2-deoxyerythrose derivative **14a** and its anomeric isomer **14b**.

Introduction

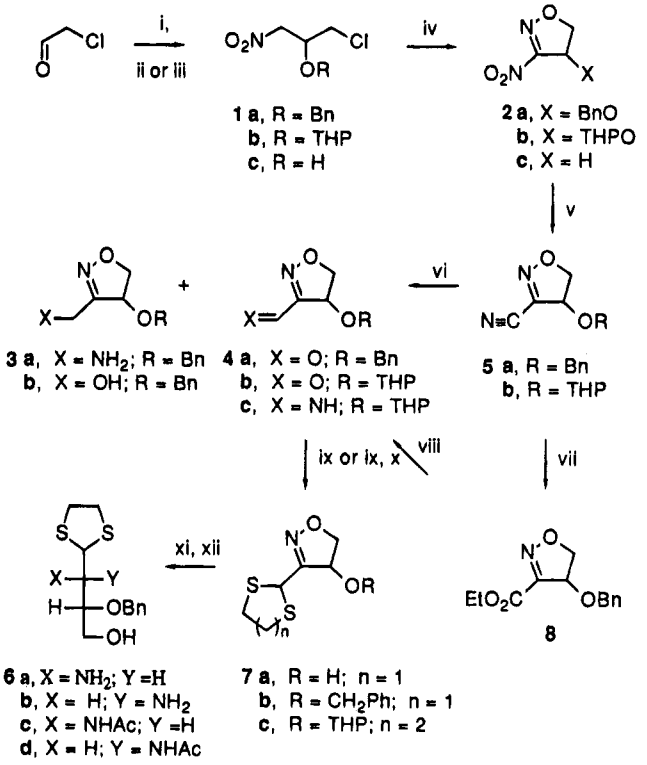
The 4,5-dihydroisoxazoles (DHIs) are versatile synthetic intermediates which have been extensively used for the construction of carbohydrates.[1] The C,N double bond present in DHIs is readily amenable to diastereoselective reduction with concomitant N,O bond cleavage. Thus, DHIs are latent 3-amino alcohol synthons and are especially useful in amino sugar synthesis.

To prepare a desired DHI, resort is often made to nitrile oxide cycloaddition on an appropriate alkene.[1] We have previously reported an alternate nitrosative cyclization approach well-suited to the preparation of DHIs which contain alkoxy groups at the 4-position and which lack substituents at the 5-position.[2] The nitrosative cyclization approach has recently been extended to encompass carbohydrate-derived γ-iodo *p*-toluenesulfonates.[3] Here we present the completion of a general synthesis of racemic 2-amino-2-deoxythreose derivatives. These compounds have been little studied to date: since other amino sugars have important biological activity,[4] one might anticipate similar activity for 2-amino-2-deoxythreose derivatives.

Results and Discussion

Access to the DHI derivatives **2a,b** was gained by a nitroaldol reaction.[5] Condensation of a 55% aqueous solution of chloroacetaldehyde with excess nitromethane followed by either acid-catalyzed benzylation[6] or THP-protection of the hydroxyl group of the resulting crude nitroaldol **1c** gave nitro compounds **1a,b** which were isolated in 38% and 42% yield, respectively, after column chromatography on silica gel (Scheme 1). Nitrosative cyclization using a DMSO solution of sodium nitrite and *n*-propyl nitrite afforded DHIs **2a,b** in 82% and 71% yield, respectively, after chromatography. In large scale runs of **2a**, it was possible to avoid chromatography in both preparative steps. Kugelrohr distillation afforded **1a** in 49% yield and, subsequently, **2a** in 70% yield. Here *N*-benzyltrichloroacetamide was a contaminant which

Scheme 1[a]



[a] Key: (i) 4 equiv of CH_3NO_2, Na_2CO_3, aqueous EtOH; (ii) $Cl_3CC(=NH)OBn$, cat. CF_3SO_3H, CH_2Cl_2; (iii) DHP, TsOH, CH_2Cl_2; (iv) $NaNO_2$, PrONO, DMSO, 50–52 °C; (v) NaCN, DMSO; (vi) DIBAH, CH_2Cl_2, −5 to 0 °C then H_3O^+; (vii) NaOEt, EtOH; (viii) DIBAH, CH_2Cl_2, −78 °C then aqueous HCl; (ix) $HSCH_2CH_2SH$, BF_3,CH_2Cl_2; (x) NaH, BnI, cat. Bu_4NI, THF; (xi) $LiBH_4$, THF, 42–45 °C; (xii) *p*-$O_2NC_6H_4O_2CCH_3$, 1-hydroxybenzotriazole, DMSO.

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(3) Wade, P. A.; Shah, S. S.; Govindarajan, L. *J. Org. Chem.* **1994**, *59*, 7199.

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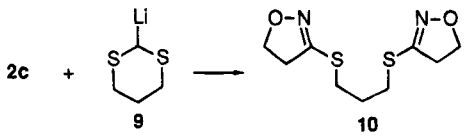
codistilled with **1a**, partially crystallizing in the distillate. However, the amide contaminant was easily removed at the next stage, being destroyed in the preparation of **2a**. Thus, **2a**, a 4-alkoxy DHI with a readily replaceable 3-substituent, could be prepared in two synthetic steps in greater than 30% overall yield and in 50-g lots. The benzyl ether **2a** could be stored for months without noticeable decomposition. However, the THP derivative **2b** significantly decomposed in 1−2 weeks even when stored in the freezer: it seems that **2b** is particularly acid sensitive. Thus, the preferred synthetic intermediate is the benzyl ether **2a**.

Four routes were investigated for synthesis of the sulfur heterocycles **7a-c** from **2a,b**. The most obvious route, direct displacement of the nitro group by 2-(1,3-dithianyl)lithium (**9**), was unsuccessful for **2b**, none of the desired dithiane **7c** being obtained. Model studies of this displacement reaction were conducted by allowing **9** to react with 3-nitro-4,5-dihydroisoxazole (**2c**). Again, none of the desired dithiane was obtained, although the bis(DHI) **10** was obtained in variable yield. It seems that the dianion of 1,3-propanedithiol was formed from decomposition of **9**, and it, rather than **9**, displaced the nitro group of the heterocycle.[7]



9 **10**

Successful multi-step routes were developed involving the initial conversion of **2b** to nitrile **5b** in 77% yield and **2a** to nitrile **5a** in 84% yield. Initially, dithiolane **7a** was prepared from nitrile **5b** via a three-step sequence beginning with the reduction of **5b** to aldehyde **4b** in 30% yield. Aldehyde **4b** was allowed to react with 1,2-ethanedithiol in the presence of an acid catalyst to give an 85% yield of dithiolane **7a** in which the THP group had been lost and 1,3-dithiolane-2-butanol[8] was obtained as a side product. Benzylation of **7a** then afforded DHI **7b** in 63% yield. A more efficient route employed nitrile **5a** as the aldehyde precursor, affording benzyl ether **4a** from the nitrile reduction step in 34% yield which was directly converted to **7b** in 85% yield, eliminating the need for reprotection. However, both of these routes are disadvantageous because the nitriles **5a,b** afford aldehydes only in modest yield. Nor did the nitrile reduction scale up well, the yield of both **4a** and **4b** falling under 20% for a 5fold increase in starting materials. The intermediate imines present here were rather more stable than usual. Thus, imine **4c** was present as a relatively stable initial reduction product of **5b**: its selective hydrolysis to afford **4b** in the presence of the THP ether proved difficult. Amine **3a**, a product derived from imine reduction, was isolated as a byproduct of the DIBALH reduction of **5a**.

Reduction of a nitrile with DIBALH usually proceeds in higher yield than reduction of the corresponding ester. However, the best synthesis of dithiolane **7b** involved conversion of nitrile **5a** to ester **8** prior to reduction. Accordingly, nitrile **5a** was treated with sodium ethoxide in ethanol to produce **8**. This reaction was best run just short of completion to maximize yield. In this way, an 88% yield of **8** could be obtained (2% recovery of **5a**). Ester **8** was subsequently reduced to aldehyde **4a** in 71% yield which was converted to **7b** in 85% yield. This route was readily amenable to scale-up: gram quantities of **7b** were prepared in 53% overall yield from nitrile **5a**. It was possible to avoid chromatographic purification of ester **8** and aldehyde **4a**: Kugelrohr distillation provided pure **8** but **4a** was contaminated with alcohol **3b** which codistilled. Fortunately, chromatographic separation of **3b** was straightforward after conversion of **4a** to **7b**.

Reduction of **7b** with lithium borohydride provided the open-chain dithiolanes **6a,b** routinely in 65−80% yield. However, considerable variability was noted in the diastereoselectivity of this reaction. In the preliminary publication,[2] we indicated that a 95:5 **6a/6b** ratio was present when THF was used as solvent and a 75:25 **6a/6b** ratio was present when ether was used as solvent. Since that time, numerous runs have been performed with the following results. The use of freshly prepared[9] lithium borohydride in THF solution typically provides **6a,b** in a 90:10 to 95:5 **6a/6b** ratio on a small (<250 mg of **7b**) scale. On the other hand, if aged lithium borohydride solution is used, and oftentimes with commercially prepared material, much lower diastereoselectivity (often *ca.* 70:30) is observed. Lower diastereoselectivity (*ca.* 70:30 **6a/6b**) was observed in large scale (>1g of **7b**) runs even with freshly prepared lithium borohydride solution. A reaction run in ether solution (91:9, **6a/6b**) showed no reproducible difference from a simultaneously run control reaction in THF. Thus, our previous report of lower diastereoselectivity in ether is now attributed to aged commercial lithium borohydride which was used in the earlier work.

A number of experiments were tried to determine the cause of the variability of diastereoselectivity in the lithium borohydride reductions. Reaction temperature, quantity of hydride reagent, added traces of water, and $MgBr_2$ all had no major reproducible effect. For related reactions, the presence of air or addition of 1-butanol gave no reproducible effect.[10] It is hypothesized that there are two competing reduction mechanisms. The more stereoselective reaction is slow (4 days) while the competing reaction is variable in rate, presumably catalyzed by an impurity in lithium borohydride solutions. Quite possibly the reduction involves a delicate balance between initial C=N reduction and N−O cleavage. If N−O cleavage precedes C=N reduction, low diastereoselectivity would be expected.[1a, 11]

The isomer assignments for **6a** and **6b** were originally based in part on their respective ^{1}H-NMR coupling constants for the 2-H, 3-H ($CHNH_2$−$CHOCH_2Ph$) signals: $J_{2,3}$ = 1.4 Hz for **6a** and 8.8 Hz for **6b**.[2] Assuming a chairlike conformation imposed by H-bonding between the hydroxyl and amino groups,[12] the 2-H, 3-H protons must be *cis* in **6a** (threo) and *trans* in **6b** (erythro). The

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(10) The effect of air and 1-butanol on diastereoselectivity was examined for lithium borohydride reduction of chiral DHIs lacking a 4-substituent: Wade, P. A.; D'Ambrosio, S. G. Unpublished studies.
(11) Reduction of C=N normally precedes N−O cleavage using $LiBH_4$ as the reducing agent. Thus, isoxazolidine intermediates have been observed where there is incomplete reduction: Wade, P. A.; Rao, J. A. unpublished studies.
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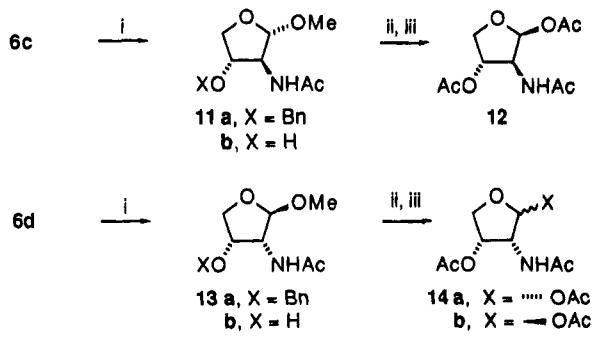
Scheme 2[a]



[a] Key: (i) $HgClO_4 \cdot 3H_2O$, MeOH, $CHCl_3$; (ii) $Pd(OH)_2$, H_2 (60 psi), MeOH; (iii) 1 N HCl then Ac_2O, cat. pyridine.

original assignment for **6a** and **6b** was also based on the spectra of cyclic carbamates to which mixtures of **6a,b** were converted.[2]

The diastereomeric mixtures of **6a,b** obtained from hydride reduction were selectively *N*-acetylated using *p*-nitrophenyl acetate and 1-hydroxybenzotriazole.[13] The resulting diastereomeric acetamides **6c,d**, typically obtained in 80–85% combined yield, were readily separable by chromatography.

Acetamide **6c** was treated with mercuric perchlorate[14] in methanol to remove the dithiolane protecting group (Scheme 2). The product, methyl furanoside **11a**, was obtained in 57% yield after chromatographic purification. Debenzylation of **11a** via hydrogenolysis using a palladium hydroxide catalyst afforded methyl furanoside **11b** in 85% yield. Both **11a** and **11b** exhibit ^{13}C-NMR spectral data consistent with assignment of the C-1 methoxy group *trans* to the C-2 *N*-acetylamino group. Thus, a signal at δ 108.0 was assigned to C-1 of **11a** and a signal at δ 107.9 to C-1 of **11b**. In related methyl furanosides, the C-1 signals occurred at δ 106–110 for compounds with C-1, C-2 *trans*-substituents and at δ 101–104 for compounds with C-1, C-2 *cis*-substituents.[15] The lack of strong H-1, H-2 coupling ($J_{1,2}$ < 2 Hz) is also consistent with C-1 , C-2 *trans*-substituents.[16]

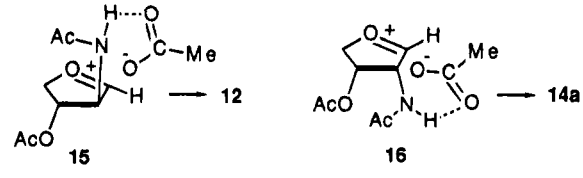
The crude furanoside **11b** was treated with dilute acid and then acetylated to provide **12** in 68% yield from **11b**. This material had NMR spectra identical to optically active material produced by an alternate route,[17] thus confirming the structure assignment. It is noteworthy that the anomeric configuration was inverted: the C-1 acetoxy group was *cis* to the C-2 *N*-acetylamino group.

In the *erythro*-series, acetamide **6d** was treated with mercuric perchlorate to afford methyl furanoside **13a**, obtained in 72% yield after chromatographic purification. Debenzylation of **13a** afforded methyl furanoside **13b** in 90% yield. Both **13a** and **13b** exhibited NMR spectral data consistent with assignment of the C-1 methoxy group *trans* to the C-2 *N*-acetylamino group.

Hydrolysis of **13b** and subsequent exhaustive acetylation provided 2-amino-2-deoxyerythrose derivative **14a,b** as an anomeric mixture (**14a/14b**, 80:20) in 70% yield from **13b**. The major isomer **14a** was obtained pure by preparative thin-layer chromatography. The minor anomer **14b** could only be obtained as an enriched sample (**14b/14a**, 70:30) owing to its limited stability. Thus, samples containing **14b** decomposed on standing several days in deuteriochloroform. An optically active mixture of **14a,b** was synthesized by an alternate route[17] and pure optically active **14a** compared to racemic **14a** in order to confirm the structure assignment. The optically active **14a,b** exhibited similar spectra and a similar ratio to the racemic sample of **14a,b** produced here. Again, the configuration at C-1 was inverted for the major anomer: the acetoxy group was *cis* to the *N*-acetylamino group at C-2 of **14a**.

The assignment of *cis*-orientation for the C-1 acetoxy and C-2 amide groups of **12** and **14a** is based on NMR spectra. The ^{13}C-NMR spectra[17] of **12** and **14a** exhibit signals at δ 95.2 and 94.5, respectively, attributed to C-1. Conversely, the minor anomer **14b** exhibited a signal at δ 100.5 attributed to C-1. There is ample precedence for a 5–6 ppm upfield shift for C-1 signals arising from *cis*-1,2 substituent compression in related furanose acetates.[18] Thus, *cis*-C-1, C-2 diacetates give signals attributable to C-1 at δ 93–94 while *trans*-diacetates give signals at δ 98–99. Similarly, the ^{1}H-NMR spectra support the assignments. Signals observed at δ 6.21 and 6.08, respectively, for **14a** and **14b** were assigned to H-1. The more downfield chemical shift is typically observed for related furanose *cis*-1,2-diacetates. Stronger H-1, H-2 coupling was observed for the major anomer **14a** ($J_{1,2}$ = 5.1 Hz) than for **14b** ($J_{1,2}$ = 3.3 Hz). Stronger coupling for the *cis*-isomer is typical in many related tetrahydrofuran derivatives.[16]

It is somewhat surprising that the configuration at the anomeric center is altered in going from the methyl furanoside **11b** to the 1-*O*-acetylfuranose **12** and from the methyl furanoside **13b** to the 1-*O*-acetylfuranose **14a**. Perhaps the amide proton of cations **15** and **16** hydrogen bonds to the approaching acetate ion directing attack on the same face as the amide group. This effect is most pronounced for the *threo*-cation **15** where only the *cis*-1,2-isomer **12** is produced. For the *erythro*-cation **16**, a



1,3-pseudodiaxial interaction between the C-3 acetoxy group and entering *cis* C-1 acetoxy group should lower the *cis*-1,2-preference, and thus, the *trans*-1,2-isomer **14b** is produced as a minor anomer. Similar internal hydrogen bonding interactions might also be responsible for stabilizing the *cis*-isomers once formed.

Summary

A useful, diastereoselective route involving DHI intermediates has been developed for the synthesis of racemic 2-amino-2-deoxythreose derivatives. Thus, chloroacetaldehyde can be converted to 1-*O*-acetylfuranose **12** in 3% overall yield. The corresponding 2-amino-2-deoxyerythrose derivatives were also obtained as minor products.

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Experimental Section

General. Reactions were routinely run under argon. Lithium borohydride (LBH) solutions were prepared[9] from $NaBH_4$ and LiBr and were titrated[19] by published procedures. Combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure (procedure A) or dried over anhydrous Na_2SO_4 followed by concentration at reduced pressure (procedure B). Preparative TLC (elution solvent) was performed on 0.25 and 1.0 mm Analtech silica gel GF plates; predried silica gel plates were obtained by baking commercial plates in the oven at 140–150 °C. *n*-Propyl nitrite was prepared by the published procedure[20] for *n*-butyl nitrite: bp 49–50 °C. Chloroform was passed through alumina to remove the ethanol preservative prior to use.

Preparation of [[1-(Chloromethyl)-2-nitroethoxy]methyl]benzene (1a). Run A. Nitromethane (17 mL, 0.29 mol), Na_2CO_3 (0.52 g, 5 mmol), ethanol (8 mL), and water (10 mL) were combined and stirred for 35 min. Chloroacetaldehyde (9 mL, 50–55% w/w aqueous solution, 0.07 mol C_2H_3ClO) was added dropwise (syringe pump) over 1 h while a pH 7-9 was maintained by concomitant addition of anhydrous Na_2CO_3 (two 0.1-g portions were added at 30 and 45 min, respectively). After addition was complete, the mixture was stirred for 15 min, poured into ice-water (150 mL), and extracted with CH_2Cl_2 (four 50-mL portions). The combined organic layers were worked up (procedure A) to afford 7 g of crude alcohol as a yellow oil. Cyclohexane (120 mL), CH_2Cl_2 (60 mL), benzyl 2,2,2-trichloroacetimidate (15.52 g, 0.06 mol), and trifluoromethanesulfonic acid (0.63 mL, 7 mmol) were added, and the solution was stirred for 8 h. The resulting mixture was filtered to partially remove the trichloroacetamide byproduct, and the filtrate was washed with aqueous 10% $NaHCO_3$ (two 150-mL portions) followed by 10% brine (two 150-mL portions). Further workup (procedure A) gave 12.5 g of an oily residue. This was chromatographed on silica gel (benzene/hexanes/HOAc, from 50:49:1 to 99:0:1) to give 6.09 g of **1a** (38% yield). An analytical sample was obtained by Kugelrohr distillation: bp 100–105 °C (0.03 mmHg); IR (film) 1555 and 1383 cm^{-1} (NO_2); ^{1}H-NMR δ 7.3–7.4 (m, 5 H), 4.55–4.72 (m, 4 H), 4.37–4.46 (m, 1 H), 3.64 (dd, 1 H, J = 4.4, 11.8 Hz), 3.61 (dd, 1 H, J = 6.9, 11.8 Hz); ^{13}C-NMR δ 136.4, 128.5, 128.2, 127.8, 76.5, 75.3, 72.9, 42.1; mass spectrum m/z 231 (M+2), 229 (M^+). Anal. Calcd for $C_{10}H_{12}ClNO_3$: C, 52.29; H, 5.27. Found: C, 52.29; H, 5.28.

Run B. Run A was repeated at triple scale using chloroacetaldehyde solution (27 mL) to give 39.5 g of crude benzylated product which was Kugelrohr distilled. Two fractions were collected: 3.7 g of mostly solid forecut, bp 20–104 °C (0.04 mmHg), and 23.84 g (49% yield) of mostly liquid main fraction, bp 110–165 °C (0.04 mmHg). The ^{1}H-NMR of the main fraction showed **1a** (>95% pure) contaminated with a trace of *N*-benzyltrichloroacetamide. This material was sufficiently pure for nitrosative cyclization.

Preparation of 2-[1-(Chloromethyl)-2-nitroethoxy]tetrahydro-2*H*-pyran (1b). Nitromethane (13.4 mL, 0.25 mol), water (9 mL), ethanol (7 mL), and Na_2CO_3 (0.44 g, 4.2 mmol) were combined and stirred for 15 min. Chloroacetaldehyde (7.6 mL, 50–55% w/w aqueous solution, 62 mmol C_2H_3ClO) was added dropwise over 1 h while more Na_2CO_3 (0.2 g, to maintain pH 7-9) was added at 40 min reaction time. Stirring was continued for 10 min after the chloroacetaldehyde addition was complete, and then the reaction mixture was poured into ice–water and extracted with CH_2Cl_2 as in the preparation of **1a**. The crude aldol was dissolved in CH_2Cl_2 (170 mL), and the solution was cooled (0–5 °C). Dihydropyran (14.5 mL, 0.16 mol) and *p*-toluenesulfonic acid monohydrate (76 mg, 0.4 mmol) were introduced, and the resulting solution was stirred for 15 min in the cold and subsequently for 75 min at ambient temperature. The reaction solution was washed with water/brine/saturated $NaHCO_3$ (50:25:25, three 200-mL portions). Further workup (procedure A) gave the crude product which was column chromatographed (hexanes/CH_2Cl_2, from 100:0 to 30:70) to give 5.81 g (42% yield) of **1b** as a mixture of diastereomers: IR (film) 1555 and 1382 cm^{-1} (NO_2); ^{1}H-NMR δ 4.5–4.9 (m, 4 H), 3.5–4.0 (m, 4 H), 1.4–1.7 (m, 6 H). Anal. Calcd for $C_8H_{14}NO_4Cl$: C, 42.96; H, 6.31. Found: C, 43.11; H, 6.33.

Nitrosative Cyclization To Afford 4,5-Dihydro-3-nitro-4-(phenylmethoxy)isoxazole (2a). Run A. A stirred solution containing **1a** (12.46 g, 0.05 mol), sodium nitrite (19.18 g, 0.28 mol), and *n*-propyl nitrite (27.0 g, 0.30 mol) in DMSO (440 mL) was heated at 50–52 °C for 4 h and was then poured into ice-cold 10% brine (2 L). The resulting mixture was extracted with CH_2Cl_2 (five 400-mL portions), and the combined organic extracts were washed with water (three 500-mL portions). Further workup (procedure B) afforded 13.2 g of a yellow oil which was chromatographed on a column of silica gel (benzene/hexanes/HOAc, from 50:49:1 to 99:0:1) to give 9.84 g (82% yield) of **2a**. An analytical sample was obtained by Kugelrohr distillation: bp 108–115 °C (0.03 mmHg); IR (film) 1537 and 1367 cm^{-1} (NO_2); ^{1}H-NMR δ 7.3–7.45 (m, 5 H), 5.31 (dd, 1 H, J = 3.3, 7.7 Hz), 4.82 (d, 1 H, J = 11.9 Hz), 4.6–4.8 (m, 3 H); ^{13}C-NMR δ 164.3, 136.0, 128.5, 128.4, 128.0, 81.5, 76.8, 73.6; mass spectrum m/z 222 (M^+). Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.03; H, 4.53. Found: C, 54.24; H, 4.57.

Run B. In a duplicate run, the crude product was Kugelrohr distilled to give 3.26 g of forecut consisting predominantly of benzaldehyde and DMSO followed by 8.46 g (70% yield, >95% pure by NMR) of **2a**: bp 110–160 °C (0.05 mmHg). This product was sufficiently pure for preparative purposes.

Nitrosative Cyclization To Afford 4,5-Dihydro-3-nitro-4-[(tetra-hydro-2*H*-pyran-2-yl)oxy]isoxazole (2b). A stirred solution containing **1b** (13.4 g, 0.060 mol), sodium nitrite (20.7 g, 0.30 mol), and *n*-propyl nitrite (26.7 g, 0.30 mol) in DMSO (200 mL) was heated at 50–52 °C for 90 min and was then poured into ice/water (1 L). Further workup was as described for **2a**. Column chromatography of the crude product (benzene/hexanes, from 50:50 to 80:20) gave DHI **2b** (9.16 g, 71% yield) as a mixture of diastereomers: IR (film) 1540 and 1365 cm^{-1} (NO_2); ^{1}H-NMR δ 5.4–5.6 (m, 1 H), 4.6–4.95 (m, 3 H), 3.45–3.95 (m, 2 H), 1.5–1.8 (m, 6 H); mass spectrum m/z 216 (M^+). Anal. Calcd for $C_8H_{12}N_2O_5$: C, 44.45; H, 5.59. Found: C, 44.89; H, 5.64.

Preparation of 4,5-Dihydro-4-(phenylmethoxy)-3-isoxazolecarbonitrile (5a). In the hood, sodium cyanide (2.39 g, 48.8 mmol) was added to a solution of DHI **2a** (7.93 g, 35.7 mmol) in DMSO (200 mL), and the resulting mixture was stirred for 25 min. The reaction solution was then poured into ice-cold 10% brine (2 L) and extracted with CH_2Cl_2 (four 600-mL portions). The combined organic extracts were washed with water (three 700-mL portions). Further workup (procedure B) afforded 6.56 g of an oil which was Kugelrohr distilled to give **5a** (6.06 g, 84% yield) as an oil: bp 100–125 °C (0.04 mmHg). This oil was crystallized from toluene/hexanes to give crystalline **5a**: mp 49–49.5 °C; IR (melt) 2238 cm^{-1} (C≡N); ^{1}H-NMR δ 7.3–7.45 (m, 5 H), 5.08 (dd, 1 H, J = 3.5, 8.2 Hz), 4.77 (d, 1 H, J = 11.7 Hz), 4.65 (d, 1 H, J = 11.7 Hz), 4.58 (dd, 1 H, J = 3.5, 11 Hz), 4.37 (dd, 1 H, J = 8.2, 11 Hz); ^{13}C-NMR δ 136.1, 135.6, 128.5, 128.3, 127.8, 110.6, 81.2, 76.9, 72.3; mass spectrum m/z 202 (M^+). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.30; H, 4.98. Found: C, 65.54; H, 4.87.

Preparation of 4,5-Dihydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-3-isoxazolecarbonitrile (5b). Prepared from **2b** in 77% yield similarly to **5a** but at 1/16 scale. The crude product was purified by preparative TLC (CH_2Cl_2) to give a mixture of diastereomers: IR (film) 2237 cm^{-1} (C≡N); NMR δ 5.2–5.35 (m, 1 H), 4.3–4.9 (m, 3 H), 3.55–4.0 (m, 2 H), 1.3–1.85 (m, 6 H) [of the two diastereomers, one gave peaks at 5.26 (dd, 1 H, J = 2.8, 7.9 Hz), 4.62 (dd, 1 H, J = 2.8, 11 Hz), and 4.41 (dd, 1 H, J = 7.9, 11 Hz)]; mass spectrum m/z 196 (M^+). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16. Found: C, 54.75; H, 6.17.

Preparation of Ethyl 4,5-Dihydro-4-(phenylmethoxy)-3-isoxazolecarboxylate (8). Nitrile **5a** (0.54 g, 2.65 mmol) was added to a cool (20 °C) alcoholic solution of sodium

(19) Brown, H. C. *Organic Synthesis via Boranes*; Wiley Interscience: New York, 1975; p 244.

(20) Noyes, W. A. In *Organic Syntheses*; Blatt, A. H., Ed.; Wiley: New York, 1943; Collect. Vol. 2, p 108.

ethoxide, prepared by reaction of Na^0 (0.33 g, 14.4 mmol) with absolute ethanol (25 mL) under reflux, and the resulting solution was stirred for 20 min. The reaction mixture was cooled and quenched by addition of 10% H_2SO_4 (15 mL). After the mixture was stirred for an additional 10 min, water (25 mL) was added, and organic products were extracted with CH_2Cl_2 (four 30-mL portions). The combined organic layers were washed with 10% brine (125 mL); further workup (procedure B) gave a clear oil. The crude product was column chromatographed on silica gel (80 g, CH_2Cl_2 elution) to give recovered **5a** (0.01 g) followed by ester **8** (0.57 g) in 88% yield. An analytical sample was obtained by Kugelrohr distillation: bp 125–140 °C (0.04 mmHg); IR (film) 1722 cm^{-1} (C=O); ^{1}H-NMR δ 7.3–7.4 (m, 5 H), 5.15 (dd, 1 H, J = 2.9, 7.9 Hz), 4.76 (d, 1 H, J = 11.9 Hz), 4.66 (d, 1 H, J = 11.9 Hz), 4.53 (dd, 1 H, J = 2.9, 11 Hz), 4.38–4.44 (q, 2 H, J = 7.1 Hz) on 4.30 (dd, 1 H, J = 7.9, 11 Hz), 1.40 (t, 3 H, J = 7.1 Hz); ^{13}C-NMR δ 160.1, 151.8, 136.9, 128.3, 127.9, 127.7, 80.5, 77.1, 72.5, 62.1, 14.1; mass spectrum (CI) 250 ($M + 1^+$). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.06. Found: C, 62.75; H, 6.14.

In a run performed at 15 times the previous scale, the crude product was not chromatographed prior to Kugelrohr distillation. After a forecut enriched in nitrile **5a**, the main fraction was obtained consisting of **8** (>95% pure, 82% yield) contaminated by a small amount of **5a**. This material was suitable for preparation of aldehyde **4a**. An attempt to bring the reaction further to completion resulted in a very low yield.

Preparation of 4,5-Dihydro-4-(phenylmethoxy)-3-isoxazolecarboxaldehyde (4a). Run A: From Ester 8. A 1.5 M toluene solution of DIBALH (0.8 mL, 1.2 mmol DIBALH) was added dropwise over 3 min to a cooled (dry ice-acetone) solution of ester **8** (149 mg, 0.6 mmol) in CH_2Cl_2 (7 mL), and the resulting solution was stirred and kept cold for 1 h. Water (2.5 mL) was added and after 10 min aqueous 3% HCl (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (four 18-mL portions). The combined organic layers were washed with 10% brine (75 mL). Further workup (procedure B) gave a yellow oil which was purified by preparative TLC (CH_2Cl_2 elution) to afford aldehyde **4a** (87 mg, 71% yield) as the less polar fraction. An analytical sample of **4a** was obtained by Kugelrohr distillation: bp 150–158 °C (0.04 mmHg); IR (film) 1696 (C=O); ^{1}H-NMR δ 10.07 (s, 1 H), 7.35–7.4 (m, 5 H), 5.10 (dd, 1 H, J = 2.9, 7.8 Hz), 4.75 (d, 1 H, J = 11.8 Hz), 4.64 (d, 1 H) on 4.58 (dd, 1 H, J = 2.9, 11.1 Hz), 4.35 (dd, 1 H, J = 7.8, 11.1 Hz); ^{13}C-NMR δ 185.0, 159.1, 136.7, 128.3, 127.9, 127.7, 78.2, 78.0, 72.7; mass spectrum m/z 205 (M^+). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.36; H, 5.40. Found: C, 64.24; H, 5.34.

Also isolated by preparative TLC from a more polar fraction was alcohol **3b** (20 mg, 16% yield) which exhibited spectra identical to an independently prepared sample.

Run B: From Nitrile 5a. A 1.5 M toluene solution of DIBALH (0.5 mL, 0.7 mmol DIBALH) was added dropwise over 15 min to a cold (−5 to 0 °C) solution of nitrile **5a** (100 mg, 0.5 mmol) in CH_2Cl_2 (15 mL), and the resulting solution was stirred and kept cold for 30 min. Water (15 mL) was added and after 5 min aqueous 10% H_2SO_4 (18 mL). Stirring at ambient temperature was continued for 3 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (three 15-mL portions). The combined organic layers were washed with water (50 mL); further workup (procedure B) gave a yellow oil which was purified by preparative TLC (hexanes–ethyl acetate, 75:25) to afford aldehyde **4a** (34 mg, 34% yield).

The aqueous layer was neutralized with 10% aqueous $NaHCO_3$ (pH > 7) and was again extracted with CH_2Cl_2. Further workup (procedure B) afforded an oil (3 mg, 3% yield) identified as amine **3a**: IR (film) 3317 cm^{-1} (NH_2); ^{1}H-NMR δ 7.25–7.4 (m, 5 H), 5.01 (dd, 1 H, J = 3.6, 7.9 Hz), 4.52 (m, 2 H), 4.32 (dd, 1 H, J = 3.6, 10.2 Hz), 4.14 (dd, 1 H, J = 7.9, 10.2 Hz), 3.76 (d, 1 H, J = 16.1 Hz), 3.59 (d, 1 H, J = 16.1 Hz), 2.05 (broad s, 2 H).

Preparation of 4,5-Dihydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-3-isoxazolecarboxaldehyde (4b). Diisobutylaluminum hydride (0.64 mL of a 1 M solution in CH_2Cl_2, 0.64 mmol DIBALH) was added via syringe pump over 15 min to a cold (0–5 °C) solution of nitrile **5b** (0.1 g, 0.51 mmol) in CH_2Cl_2 (15 mL). Stirring was continued for 25 min, and then water (2 mL) was added and stirring continued for another 10 min. Aqueous 5% HCl (7 mL) was added, and the layers were separated. The aqueous layer was extracted once with CH_2Cl_2 (15 mL), and the combined organic layers were worked up according to procedure B. The residue (largely imine **4c** at this stage: ^{1}H-NMR δ 8.38 (s, C*H*=NH)) was dissolved in glacial HOAc (1 mL), and the resulting solution was applied to a preparative TLC plate. After being allowed to stand for 15 min, the plate was eluted (CH_2Cl_2/MeOH, 98:2) to give aldehyde **4b** (30 mg, 30% yield) as the more mobile component. An analytical sample of aldehyde **4b** was obtained by preparative TLC (CH_2Cl_2/MeOH, 98:2) on predried silica gel plates: IR (film) 1700 cm^{-1} (C=O); ^{1}H-NMR δ 10.02 (s, 1 H), 5.25–5.45 (m, 1 H), 4.25–4.9 (m, 3 H), 3.45–3.95 (m, 2 H), 1.3-1.85 (m, 6 H). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58. Found: C, 54.19; H, 6.61.

A small amount of the imine (5% yield) persisted and was present as a less mobile TLC fraction.

Preparation of 4,5-Dihydro-4-(phenylmethoxy)-3-isoxazolemethanol (3b). Sodium borohydride (0.85 g, 22 mmol) was added to a cold (−10 °C) solution of ester **8** (175 mg, 0.70 mmol) in CH_2Cl_2 (5 mL) and absolute methanol (12 mL). Stirring was continued in the cold for 1 h and at ambient temperature for 2 h. Aqueous 10% KH_2PO_4 (7 mL) and CH_2Cl_2 (5 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (two 15-mL portions), and the combined organic layers were washed with 10% brine (35 mL). Further workup (procedure B) followed by preparative TLC (CH_2Cl_2/MeOH, 97:3) gave **3b** (141 mg, 97% yield). An analytical sample was obtained by Kugelrohr distillation: bp 140–145 °C (0.05 mmHg); IR (film) 3412 cm^{-1} (OH); ^{1}H-NMR δ 7.25–7.4 (m, 5 H), 5.09 (dd,1 H, J = 3.7, 7.9 Hz), 4.57 (s, 2 H) on 4.57 (d, 1 H, J = 14.1 Hz), 4.47 (d, 1 H, J = 14.1 Hz), 4.36 (dd, 1 H, J = 3.7, 10.5 Hz), 4.18 (dd, 1 H, J = 7.9, 10.5 Hz), 2.04 (broad s, 1 H); ^{13}C-NMR δ 157.7, 136.8, 128.4, 128.0, 127.7, 82.6, 73.3, 71.8, 56.2; mass spectrum m/z 207 (M^+). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.74; H, 6.32. Found: C, 63.47; H, 6.07.

Preparation of 4,5-Dihydro-3-(1,3-dithiolan-2-yl)-4-(phenylmethoxy)isoxazole (7b). Run A: From Aldehyde 4a. A solution of aldehyde **4a** (0.17 g, 0.83 mmol), 1,2-ethanedithiol (0.24 mL, 2.8 mmol), and boron trifluoride etherate (23 μL, 0.2 mmol) in CH_2Cl_2 (10 mL) was stirred for 1 h. The resulting solution was washed with 5% aqueous NaOH (25 mL) and then 10% brine (10 mL). Further workup (procedure B) followed by preparative TLC (CH_2Cl_2) gave **7b** (0.2 g, 85% yield) as an oil which crystallized after several days: mp 33–34 °C; ^{1}H-NMR δ 7.3–7.4 (m, 5 H), 5.44 (s, 1 H), 5.18 (dd, 1 H, J = 3.4, 7.8 Hz), 4.58 (d, 1 H, J = 11.5 Hz), 4.51 (d, 1 H, J = 11.5 Hz), 4.43 (dd, 1 H, J = 3.4, 10.7 Hz), 4.20 (dd, 1 H, J = 7.8, 10.7 Hz), 3.25–3.5 (m, 4 H); ^{13}C-NMR δ 157.8, 136.6, 128.1, 127.7, 127.5, 82.2, 74.0, 70.6, 45.9, 39.2, 38.4; mass spectrum m/z 281 (M^+). Anal. Calcd for $C_{13}H_{15}NO_2S_2$: C, 55.49; H, 5.37. Found: C, 55.52; H, 5.43.

Run B: From Dithiolane 7a. A solution of dithiolane **7a** (0.14 g, 0.73 mmol) in THF (2 mL) was introduced over 30 s to a cold (0–5 °C) mixture of sodium hydride (70 mg, 2.9 mmol) and THF (18 mL). The mixture was stirred for 15 min, $Bu_4N^+I^-$ (27 mg, 0.07 mmol) was added, and the mixture was again stirred for 10 min. Benzyl iodide (0.16 g, 0.95 mmol) was added and the reaction mixture stirred for 70 min at ambient temperature. Water/THF (50:50, 2 mL) and subsequently water (20 mL) were added and the resultant extracted with CH_2Cl_2 (three 40-mL portions). The combined organic layers were washed with saturated sodium thiosulfate (50 mL). Further workup (procedure A) followed by preparative TLC (CH_2Cl_2/MeOH, 99:1) gave 0.13 g (63% yield) of pure dithiolane **7b**.

Preparation of 4,5-dihydro-3-(1,3-dithiolan-2-yl)-4-isoxazolol (7a). A solution of aldehyde **4b** (0.45 g, 2.3 mmol), 1,2-ethanedithiol (0.6 mL, 6.8 mmol), and boron trifluoride etherate (56 μL, 0.5 mmol) in CH_2Cl_2 (20 mL) was stirred for 1 h. The resulting solution was washed with 5% aqueous NaOH (10 mL) and then 10% brine (5 mL). Further workup (procedure B) followed by preparative TLC on predried silica

gel plates (ethyl acetate/hexanes, 35:65) gave 0.37 g (85% yield) of dithiolane **7a** as an oil: IR (film) 3420 cm^{-1} (OH); ^{1}H-NMR δ 5.61 (s, 1 H), 5.28–5.31 (m, 1 H), 4.39 (dd, 1 H, J = 2.8, 10.5 Hz), 4.28 (dd, 1 H, J = 7.1, 10.5 Hz), 3.3–3.45 (m, 4 H), and 3.21 (d, 1 H, J = 3.8 Hz); mass spectrum m/z 191 (M^+). Anal. Calcd for $C_6H_9NO_2S_2$: C, 37.68; H, 4.98. Found: C, 37.81; H, 4.74.

Also obtained by preparative TLC from a less polar fraction was 0.34 g (82% yield) of an oil identified as 1,3-dithiolane-2-butanol: IR (film) 3384 cm^{-1} (OH); ^{1}H-NMR δ 4.48 (t, 1 H, J = 7.1 Hz), 3.66 (t, 2 H, J = 6.2 Hz), 3.15–3.3 (m, 4 H), 1.85 (q, 2 H, J = 7.1 Hz), 1.75 (s, 1 H), 1.45–1.65 (m, 4 H); ^{13}C-NMR δ 61.3, 53.0, 38.5, 37.7, 31.4, 24.9; HRMS (EI) calcd for $C_7H_{14}S_2O$ (M^+) 178.0486, found 178.0482.

An authentic sample of 1,3-dithiolane-2-butanol was prepared[8] by reaction of DHP (0.71 g, 8 mmol), 1,2-ethanedithiol (2.5 g, 26.5 mmol), and boron trifluoride etherate (0.2 mL, 1.6 mmol) in CH_2Cl_2 (50 mL) under reflux for 150 min. The reaction solution was washed with 5% aqueous NaOH (25 mL) and water (10 mL). Further workup (procedure B) followed by preparative TLC (ethyl acetate/hexanes, 25:75) gave 1.27 g (85% yield) of an oil identical with the above sample of 1,3-dithiolane-2-butanol.

Reductive Cleavage of 7b Affording (*R,*R**)-γ-Amino-β-(phenylmethoxy)-1,3-dithiolane-2-propanol (6a) and (*R**,*S**)-γ-Amino-β-(phenylmethoxy)-1,3-dithiolane-2-propanol (6b).** Freshly prepared LBH (1.4 mL of a 0.94 M solution in THF, 1.3 mmol) was added to a solution of dithiolane **7b** (18 mg, 0.07 mmol) in THF (1.6 mL) and the resulting stirred solution heated at 42–45 °C for 4 days. Volatiles were removed at reduced pressure, and the residue was taken up in CH_2Cl_2 (30 mL). The solution was cooled (0–5 °C), and 10% aqueous NaH_2PO_4 (11 drops) was added. After 2 min, the resulting mixture was washed with 10% brine (three 20-mL portions). Further workup (procedure B) gave a residue which was dissolved in benzene (30 mL). Ethanolamine (5 drops) was added, and the solution was stirred for 30 min, concentrated, diluted with CH_2Cl_2 (60 mL), and washed with 10% brine (three 20-mL portions). Further workup (procedure B) followed by preparative TLC (CH_2Cl_2/MeOH, 97:3) gave 15 mg (80% yield) of an inseparable mixture of **6a,b** (**6a/6b**, 92:8): IR (film) 3362, 3262 cm^{-1} (broad; NH_2, OH); ^{1}H-NMR (500 MHz) δ 7.25–7.4 (m, 5 H of **6a,b**), 5.15 (d, 1 H of **6b**, J = 3.2 Hz), 4.77 (d, 1 H of **6a**, J = 11.5 Hz), 4.64 (d, 1 H of **6b**, J = 11.1 Hz), 4.57 (d, 1 H of **6a**, J = 9.2 Hz), 4.51 (d, 1 H of **6b**, J = 11.1 Hz), 4.48 (d, 1 H of **6a**, J = 11.5 Hz), 4.08 (dd, 1 H of **6a**, J = 3.6, 12.5 Hz), 3.91 (dd, 1 H of **6b**, J = 3.3, 11.7 Hz), 3.7–3.8 (m, 1 H of **6a,b** and 1 H of **6a**), 3.25–3.3 (m, 1 H of **6b**), 3.1–3.25 (m, 4 H of **6a,b**), 3.07 (dd, 1 H of **6b**, J = 3.2, 8.8 Hz), 2.78 (dd, 1 H of **6a**, J = 1.4, 9.2 Hz), 2.6 (broad s, 3 H of **6a,b**); ^{13}C-NMR **6a** δ 137.8, 128.4, 128.0, 127.8, 76.7, 71.0, 63.3, 61.9, 58.4, 38.7, 37.7; ^{13}C-NMR **6b** [peaks not obscured by **6a**] δ 137.5, 80.4, 72.3, 63.3, 59.1, 56.8, 39.1, 39.0; mass spectrum m/z 285 (M^+). Anal. Calcd for $C_{13}H_{19}NO_2S_2$: C, 54.71; H, 6.71. Found: C, 54.77; H, 6.79.

Reactions run with freshly prepared LBH solution gave reproducible stereochemical results: **6a:6b** > 90:10 at the above scale and at 10 times the scale. However, reactions run using LBH solutions stored for longer than 1 week typically gave reduced diastereoselectivity. Several runs afforded **6a/6b** isomer ratios of *ca.* 70:30 (50:50 in one case!). Commercially prepared LBH solutions gave variable results. Reduced stereoselectivity was noted in large scale runs (>1 g of **7b**). A reaction in which diethyl ether was used as solvent gave a 91:9 ratio, similar within the experimental error (±5%) to a simultaneously run control reaction in THF.

Preparation of (*R,*R**)-γ-(Acetylamino)-β-(phenylmethoxy)-1,3-dithiolane-2-propanol (6c) and (*R**,*S**)-γ-(Acetylamino)-β-(phenylmethoxy)-1,3-dithiolane-2-propanol (6d).** A solution containing amino alcohol **6a,b** (63 mg, 0.2 mmol, **6a/6b**, 70:30), *p*-nitrophenyl acetate (85 mg, 0.5 mmol), and 1-hydroxybenzotriazole (31 mg, 0.2 mmol) in DMSO (23 mL) was stirred for 20 h. Ice-water (75 mL) was added, and the mixture was extracted with CH_2Cl_2 (three 100-mL portions). The combined organic layers were washed with 5% aqueous NaOH (25 mL) followed by water (25 mL). Further workup (procedure B) and subsequent preparative TLC (ethyl ether/MeOH, 95:5) gave 45 mg (63% yield) of **6c** as the less polar component. Recrystallization from ethyl acetate/hexanes gave the analytical sample of **6c**: mp 123–123.5 °C; IR (KBr) 3273, 3100–3600 (broad) (NH, OH), 1653 cm^{-1} (C=O); ^{1}H-NMR δ 7.3–7.4 (m, 5 H), 5.93 (broad d, 1 H, J = 9.8 Hz), 4.66 (d, 1 H, J = 7.8 Hz), 4.61 (d, 1 H, J = 11.2 Hz), 4.54 (d, 1 H, J = 11.2 Hz), 4.2–4.35 (m, 1 H), 3.90 (ddd, 1 H, J = 1.6, 5.3, 9.2 Hz), 3.73 (dd, 1 H, J = 5.3, 11.7 Hz), 3.33 (dd, 1 H, J = 9.2, 11.7 Hz), 3.21 (apparent s, 4 H), 2.41 (broad s, 1 H), 2.08 (s, 3 H); ^{13}C-NMR δ 171.5, 137.4, 128.3, 128.1, 127.9, 79.2, 73.1, 60.6, 55.0, 54.4, 38.4, 38.4, 23.0; mass spectrum m/z 327 (M^+). Anal. Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.01; H, 6.46. Found C, 54.77; H, 6.19.

Preparative TLC also afforded 16 mg (21% yield) of **6d** as the more polar component. Recrystallization from ethyl acetate/hexanes gave the analytical sample of **6d**: mp 111–112 °C; IR (KBr) 3364, 3279, 3100–3600 (broad) (NH, OH), 1655 cm^{-1} (C=O); ^{1}H-NMR δ 7.25–7.4 (m, 5 H), 6.11 (broad d, 1 H, J = 9.2 Hz), 5.27 (d, 1 H, J = 2.8 Hz), 4.73 (d, 1 H, J = 11.5 Hz), 4.51 (d, 1 H, J = 11.5 Hz) on 4.45 (td, 1 H, J = 2.8, 9.2 Hz), 3.85 (dd, 1 H, J = 2.4, 13.2 Hz), 3.54 (dd, 1 H, J = 1.9, 13.2 Hz), 3.15–3.3 (m, 6 H), 2.07 (s, 3 H); ^{13}C-NMR δ 171.5, 137.3, 128.3, 127.9, 127.7, 80.6, 71.5, 59.4, 53.7, 52.4, 39.2, 38.8, 23.2; mass spectrum m/z 327 (M^+). Anal. Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.01; H, 6.46. Found C, 54.85; H, 6.19.

Preparation of Methyl Furanoside 11a. A solution of mercuric perchlorate trihydrate (280 mg, 0.6 mmol) in methanol (2.4 mL) was added to a solution of acetamide **6c** (78 mg, 0.24 mmol) in chloroform (4 mL), and the resulting mixture was stirred for 5 min. Aqueous 10% sodium carbonate (0.8 mL) was added, bringing the pH to 7-8, and the mixture was then extracted with chloroform (four 10-mL portions). The combined organic layers were washed with 10% brine (10 mL) and were further worked up (procedure B) to give crude **11a**. Preparative TLC (ethyl ether/MeOH, 97:3) gave 36 mg (57% yield) of **11a**: IR (film) 3278 (NH), 1651 cm^{-1} (C=O); ^{1}H-NMR δ 7.3–7.4 (m, 5 H), 5.62 (broad d, 1 H, J = 8 Hz), 4.81 (s, 1 H) on 4.80 (d, 1 H, J = 12.3 Hz), 4.59 (d, 1 H, J = 12.3 Hz), 4.39 (apparent d, 1 H, J = 8 Hz), 4.1–4.2 (m, 1 H), 3.8–3.95 (m, 2 H), 3.38 (s, 3 H), 1.98 (s, 3 H); ^{13}C-NMR δ 169.3, 138.0, 128.4, 127.9, 127.7, 108.0, 83.2, 71.9, 71.0, 60.4, 54.8, 23.1; HRMS (FAB, NaBr) calcd for $C_{14}H_{19}NO_4Na$ (M + Na^+) 288.1212, found 288.1214.

Preparation of Methyl Furanoside 11b. A solution of **11a** (21 mg, 0.08 mmol) in methanol (120 mL) was added to a preequilibrated mixture of $Pd(OH)_2$ (98 mg) and methanol (20 mL), and the mixture was placed under a hydrogen atmosphere (60 psi) for 29 h. The mixture was then filtered and the filtrate concentrated to give 12 mg (85% yield) of **11b**: IR (film) 3416 (broad; NH, OH), 1644 cm^{-1} (C=O); ^{1}H-NMR δ 5.76 (broad s, 1 H), 4.85 (apparent s, 1 H), 4.1–4.3 (m, 4 H), 3.89 (dd, 1 H, J = 3.8, 9.4 Hz), 3.40 (s, 3 H), 2.02 (s, 3 H); ^{13}C-NMR (D_2O/acetone-d_6) δ 174.2, 107.9, 74.4, 72.8, 62.5, 55.2, 22.1; HRMS (FAB) calcd for $C_7H_{14}NO_4$ (M + H^+) 176.0923, found 176.0925.

Preparation of 1-*O*-Acetylfuranose 12. A solution of **11b** (12 mg, 0.07 mmol) in aqueous 1 N HCl (3.2 mL) was stirred for 30 min and was then concentrated at reduced pressure. To the residue was added acetic anhydride (6 mL) and pyridine (4 drops), and the mixture was stirred for 12 h. Volatiles were then removed at reduced pressure followed by preparative TLC (benzene/acetone, 60:40) to give 11 mg (68% yield) of pure racemic **12** as an oil. Spectra were identical to spectra obtained for a levorotatory sample of **12**.[17] Crystallization of racemic **12** was effected from hexanes/acetone: mp 126.5–127 °C; IR (film) 3292 (NH), 1740 (C=O), 1654 cm^{-1} (O=CN); ^{1}H-NMR ($CDCl_3$) δ 6.28, (d, 1 H, J = 4.8 Hz), 5.79 (broad d, 1 H), 5.2–5.3, (m, 1 H), 4.7–4.8 (m, 1 H), 4.33 (dd, 1 H, J = 7.3, 10.1 Hz), 3.84 (dd, 1 H, J = 5.1, 10.1 Hz), 2.11 (s, 3 H), 2.10 (s, 3 H), 2.01 (s, 3 H); ^{13}C-NMR ($CDCl_3$) δ 171.1, 169.9, 169.1, 95.2, 75.5, 70.2, 56.5, 23.0, 21.0, 20.7; HRMS (FAB, NaBr) calcd for $C_{10}H_{15}NO_6Na$ (M + Na^+) 268.0797, found 268.0799.

Preparation of Methyl Furanoside 13a. A solution of mercuric perchlorate trihydrate (132 mg, 0.29 mmol) in methanol (1.2 mL) was added to a solution of acetamide **6d**

(33 mg, 0.1 mmol) in chloroform (1.4 mL), and the resulting mixture was stirred for 5 min. Aqueous 10% sodium carbonate (0.4 mL) was added, bringing the pH to 7–8, and the mixture was then extracted with chloroform (four 10-mL portions). The combined organic layers were washed with 10% brine (10 mL) and further worked up (procedure B) to give crude **13a**. Preparative TLC (ethyl ether/MeOH, 97:3) gave 19 mg (72% yield) of **13a**: IR (film) 3287 (NH), 1655 cm^{-1} (C=O); ^{1}H-NMR δ 7.3–7.4 (m, 5 H), 6.05 (broad d, 1 H), 4.88 (apparent s, 1 H), 4.53 (d, 1 H, J = 11.1 Hz), 4.46 (d, 1 H, J = 11.1 Hz), 4.3–4.45 (m, 2 H), 4.07 (dd, 1 H, J = 5.5, 9.8 Hz), 3.87 (dd, 1 H, J = 3.5, 9.8 Hz), 3.33 (s, 3 H), 2.00 (s, 3 H); ^{13}C-NMR δ 170.0, 137.3, 128.6, 128.1, 127.8, 108.3, 77.2, 72.6, 69.9, 55.6, 54.9, 23.1. HRMS (FAB) calcd for $C_{14}H_{20}NO_4$ (M + H^+) 266.1392, found 266.1393.

Preparation of Methyl Furanoside 13b. A solution of **13a** (23 mg, 0.09 mmol) in methanol (120 mL) was added to a preequilibrated mixture of $Pd(OH)_2$ (107 mg) and methanol (20 mL), and the mixture was placed under a hydrogen atmosphere (60 psi) for 26 h. The mixture was then filtered and the filtrate concentrated to give 14 mg (90% yield) of **13b**: IR (film) 3379, 3249, 3095 (broad; NH, OH), 1611 cm^{-1} (C=O); ^{1}H-NMR δ 6.38 (broad d, 1 H, J = 6.5 Hz), 4.86 (d, 1 H, J = 2.1 Hz), 4.5–4.6 (m, 1 H), 4.2–4.3 (m, 2 H), 4.11 (dd, 1 H, J = 4.9, 9.9 Hz), 3.85 (dd, 1 H, J = 2.5, 9.9 Hz), 3.36 (s, 3 H), 2.05 (s, 3 H); ^{13}C-NMR (D_2O/acetone-d_6) δ 174.7, 107.8, 73.1, 70.2, 58.5, 56.0, 22.2. HRMS (FAB) calcd for $C_7H_{14}NO_4$ (M + H^+) 176.0923, found 176.0919.

Preparation of 1-*O*-Acetylfuranoses 14a,b. A solution of **13b** (14 mg, 0.08 mmol) in aqueous 1 N HCl (4 mL) was stirred for 30 min and was then concentrated at reduced pressure. To the residue was added acetic anhydride (6 mL) and pyridine (4 drops), and the mixture was stirred for 12 h. Volatiles were then removed at reduced pressure, and the residue was purified by preparative TLC (benzene/acetone, 60:40) to give 13 mg (70% yield) of racemic **14a,b** as an oil (80:20 **14a/14b**). The ^{1}H-NMR spectrum of the racemic **14a,b** mixture matched peak for peak to spectra of an impure optically active **14a,b** mixture.[17] Repetitive preparative TLC (benzene/acetone, 60:40) followed by crystallization from hexanes/acetone gave 8 mg (42% yield) of pure **14a**: mp 138–138.5 °C; IR (film) 3363, 1727 (C=O), 1667 cm^{-1} (O=CN); ^{1}H-NMR ($CDCl_3$) δ 6.21, (d, 1 H, J = 5.1 Hz), 5.77 (broad d, 1 H, J = 9.0 Hz), 5.2–5.3 (m, 1 H), 4.8–4.9 (m, 1 H), 4.33 (dd, 1 H, J = 5.2, 11.2 Hz), 4.02 (dd, 1 H, J = 1.8, 11.2 Hz), 2.16 (s, 3 H), 2.14 (s, 3 H), 2.07 (s, 3 H); ^{13}C-NMR ($CDCl_3$) δ 169.8, 169.5, 94.5, 73.6, 70.5, 51.8, 23.0, 21.1, 20.8; HRMS (FAB, NaBr) calcd for $C_{10}H_{15}NO_6Na$ (M + Na^+) 268.0797, found 268.0798.

Repetitive preparative TLC of the **14a,b** mixture also gave a sample enriched in **14b** (70:30 **14b/14a**). Spectral data for **14b** were obtained for this sample: ^{1}H-NMR (subtraction of **14a** from spectrum): δ 6.08 (d, 1 H, J = 3.3 Hz), 5.83 (broad d, 1 H, J = 8.1 Hz), 5.3–5.4 (m, 1 H), 4.8–4.9 (m, 1 H), 4.27 (dd, 1 H, J = 4.5, 10.9 Hz), 4.01 (dd, 1 H, J = 2.1, 10.9 Hz), 2.14 (s, 3 H), 2.10 (s, 3 H), 2.05 (s, 3 H); ^{13}C-NMR (subtraction of **14a** from spectrum): δ 100.5, 72.5, 72.0, 56.0, 21.0; HRMS (FAB, NaBr) calcd for $C_{10}H_{15}NO_6Na$ (M + Na^+) 268.0797, found 268.0789.

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