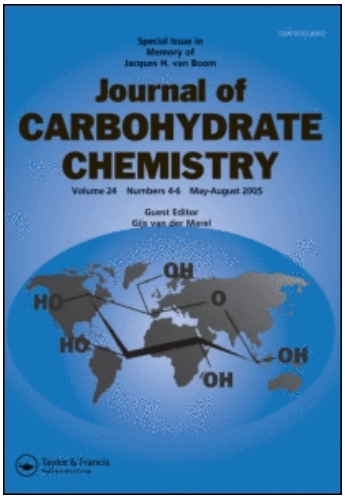


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# 2-Amino-2-Deoxytetrose Derivatives. 2. Preparation from d-Glyceraldehyde Acetonide: A Reinvestigation

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# 2-AMINO-2-DEOXYTETROSE DERIVATIVES. 2. PREPARATION FROM D-GLYCERALDEHYDE ACETONIDE: A REINVESTIGATION

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## ABSTRACT

A diastereomeric mixture of nitriles **1a,b** was prepared by a Strecker synthesis from D-glyceraldehyde acetonide and benzylamine. The reported selective hydrolysis of the acetonide group of **1a** could not be accomplished. Nitrile diastereomers **1a,b** were carried forward as a mixture to amines **3a,b** where the diastereomers were readily separable. The hydrochloride of **3a** was transformed via sequential debenzylation, *N*-acetylation, reduction, and exhaustive acetylation to the 2-amino-2-deoxy-D-threose derivatives **5** and **6**. The corresponding 2-amino-2-deoxy-D-erythrose derivatives **10a** and **11** were prepared similarly from amine **3b**.

## INTRODUCTION

Many derivatives of the two tetroses erythrose and threose are common chemicals. However, 2-amino-2-deoxytetrose derivatives have been little studied.[1, 2] This is in part due to a lack of published syntheses. Indeed, only two general approaches to the synthesis of 2-amino-2-deoxythreose and 2-amino-2-deoxyerythrose have been reported. One approach, first employed by Kuhn and Fisher,[1a] involved chain extension of D-glyceraldehyde acetonide via a Strecker synthesis. The resulting nitriles were subsequently converted to the amino sugars, isolated as hydrochloride salts and as acetamides including the 1-*O*-acetylfuranose **5**.[1a] Yoshimura et al.[1b] subsequently reported a very similar Strecker synthesis ultimately affording the 2-amino-2-deoxy-D-

tetroses. We have very recently reported a dihydroisoxazole-based approach to racemic 2-amino-2-deoxytetrose derivatives.[3] We have also attemped to repeat Kuhn and Fisher's synthesis of **5**, but were unsuccessful. Here we report on the difficulties encountered and a successful alternate approach.

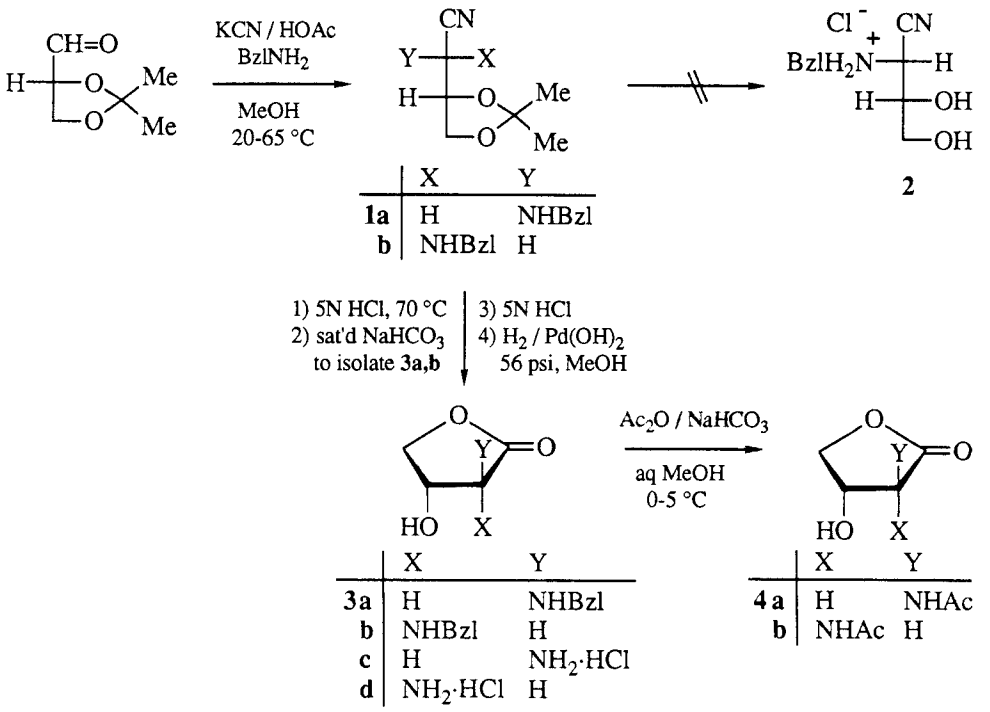
## RESULTS AND DISCUSSION

The previously employed Strecker syntheses used liquid hydrogen cyanide. Kuhn and Fisher reported formation of a diastereomeric mixture of the nitriles **1a,b** from which **1a** was isolated by recrystallization. We chose to carry out the Strecker synthesis of nitriles **1a,b** under general conditions recommended by Weinges et al.[4] so as to avoid liquid hydrogen cyanide (Scheme 1). After chromatographic purification, a 60:40 mixture of **1a,b** was obtained in 85% yield whereas it appears that Kuhn and Fisher obtained a greater percentage of isomer **1a** under their conditions. The difference likely arises from epimerization at the C-2 center during heating under the conditions employed by us: Kuhn and Fisher noted substantial isomerization of **1a** to **1b** in refluxing 1-propanol.[1a]

All attempts to separate the 60:40 isomer mixture of **1a,b** by column chromatography and preparative thin-layer chromatography were unsuccessful, but the *threo*-isomer **1a** could be obtained in 17% yield by simple recrystallization. We were unable to obtain pure *erythro*-isomer **1b** via recrystallization as previously reported[1a] but were able to effect small-scale HPLC separation of the **1a,b** mixture. Pure **1b** obtained in this way exhibited a substantially higher melting point and rotation than published values.[1a] However, after the initial studies, it proved expeditious to take the **1a,b** mixture onward for separation at a later stage in the synthesis.

Kuhn and Fisher reported a selective hydrolysis procedure for removal of the acetonide group of **1a** affording nitrile **2**, isolated in 80% yield. Yoshimura et al.[1b] reported difficulty with this procedure, claiming that the acetonide group of **1a** was not easily removed. We, too, were unable to selectively hydrolyze nitrile **1a** to nitrile **2**. In our hands, the acetonide was readily removable but concomitant hydrolysis of the cyano group to amido group occurred, as indicated by the $^{13}C$ NMR spectrum of the crude hydrolysate. The hydrochloride salt of amine **3a** was also obtained here in varying amounts. Consequently, and only after numerous attempts, selective hydrolysis of **1a** was abandoned.

More vigorous conditions for hydrolysis of **1a** have been reported to remove both the acetonide and cyano groups, cleanly affording the hydrochloride salt of amine **3a**.[1a] This procedure was repeated with no difficulties and the salt was converted to the



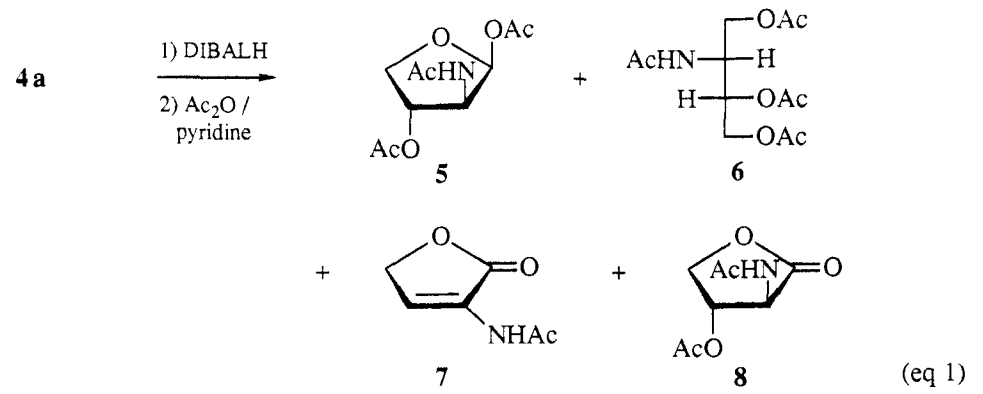

**Scheme 1**



free amine in 70% yield. For preparative purposes, it proved efficient to hydrolyze crude **1a,b** as the isomer mixture or as a recrystallized mixture partially enriched in **1a**. Thus, an 87:13 **1a,b** mixture was converted to the hydrochloride salts of amines **3a,b** (76% yield). The amine hydrochloride mixture was neutralized, and the free amines separated by column chromatography to afford pure *threo*-amine **3a** in 46% yield and pure *erythro*-amine **3b** in 7% yield from **1a,b**. The free amines were then reconverted separately to their hydrochloride salts. Subsequent debenzylation of the hydrochloride salt of **3a** under Kuhn and Fisher's conditions afforded amine hydrochloride **3c**, isolated in 70% overall yield from **3a**.

Acetylation of **3c** quantitatively afforded the crude *threo*-acetamide **4a**. Low recoveries of purified **4a** from both chromatography (< 20% recovery) and recrystallization (55% recovery) were obtained. Therefore, the crude acetamide **4a** was employed in the following reduction studies.

Reduction of the *threo*-acetamide **4a** with diisobutylaluminum hydride (DIBALH) and subsequent acetylation afforded four products (eq 1). In a typical run, the 1-*O*-acetylfuranose **5** was isolated in 26% yield accompanied by the open-chain triacet-

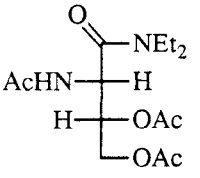



(eq 1)

ate (18% yield). Also obtained were lactone **8** and its elimination product, the conjugated lactone **7**. 1-*O*-Acetylfuranose **5** had similar melting point and optical rotation to values published by Kuhn and Fisher[1a] confirming the identity of their sample and our sample. The anomeric configuration for **5** having the C-1 acetoxy group *cis* to the C-2 *N*-acetyl group was implicated by NMR spectra.[3a]

The open-chain triacetate **6** must have arisen from overreduction of the hemiacetal intermediate, a pesky side reaction which could not be circumvented. The lactone **8** was simply the acetylation product of unspent starting material: this was confirmed by direct acetylation of **4a** to afford **8** in quantitative crude yield. The conjugated lactone **7** arose from acetic acid elimination[5] from **8**, at least in part during the acetylation step. On chromatography, lactone **8** was further converted to **7** so that the ratio of these two products was variable. The typical crude product showed substantial amounts of **8**, but after chromatography mostly **7** was obtained. Fortunately, there was no detectable epimerization during the reduction of **4a** and thus no concomitant conversion to *erythro*-products **10a,b**.

Alternative reducing agents were investigated. Overreduction of **4a** using lithium tris(diethylamino)hydride[6] was less severe but an additional side product was formed. Thus, 1-*O*-acetylfuranose **5** was obtained in 25% yield, open-chain triacetate **6** in only 4% yield, and open-chain amide **9** in 29% yield. The open-chain amide is presumably

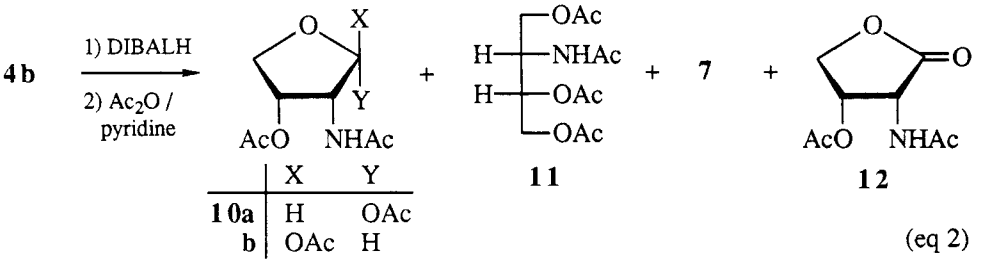



**9**

the product of lactone amidation and subsequent acetylation. Reduction of acetamide **4a** with sodium bis(2-methoxyethoxy)aluminum hydride / ethanol[7] gave more **6** than **5**.

Reduction of **4a** with sodium borohydride and subsequent acetylation gave the open-chain triacetate **6** cleanly in 78% yield. This synthesis of the previously unreported open-chain triacetate **6** was efficient and uncomplicated by side reactions. Thus, **6** proved to be the most easily obtained derivative of 2-amino-2-deoxy-D-threose in the current work.

Results obtained for reactions in the *erythro*-series paralleled the results obtained for the *threo*-series. Thus, reaction of *erythro*-amine **3b** with hydrochloric acid and subsequent catalytic hydrogenolysis afforded amine hydrochloride **3d** in 66% overall yield. The salt **3d** was acetylated to afford **4b** in quantitative crude yield. Reduction of *erythro*-**4b** with DIBALH afforded the anomeric 1-*O*-acetylfuranoses **10a,b** (80:20 ratio) and side products **11**, **7**, and **12** (eq 2). The major anomer **10a** was isolated in 30%




(eq 2)

yield. Here overreduction was a less severe problem than in the *threo* series: open-chain triacetate **11** was obtained in only trace amounts. In one run, the *erythro*-1-*O*-acetylfuranose **10a** was contaminated by a small amount of *threo*-1-*O*-acetylfuranose **5** (98:2, **10a** / **5**) but in all other runs there was no detectable amount of **5**. The trace of **5** is attributed to partial isomerization under reduction conditions of **4b** to **4a** which is then subsequently reduced and acetylated. It should be noted that this problem was inconsequential in most runs.

A racemic sample of **10a,b** was synthesized from dihydroisoxazole intermediates.[3a] The optically active crude anomeric 1-*O*-acetylfuranose **10a,b** mixture exhibited spectra identical to racemic **10a,b** when peaks for the identified side products were subtracted. The ratio (**10a** / **10b**, 80:20) was the same for the optically active and racemic samples. The major optically active isomer, **10a**, was obtained pure by repetitive preparative thin-layer chromatography but **10b** could not be freed of side products. Also, racemic **10b** was noticeably less stable than **10a**.[3a]

It is noteworthy that Fujii and Maruoka[1c] have published a $^1H$ NMR spectrum for one of the 1-*O*-acetylfuranoses **10a,b** which is inconsistent with our observations. The sample used for their spectrum was reportedly prepared by acetylation of 2-amino-2-deoxy-D-erythrose, apparently obtained via the synthesis of Yoshimura et al. Fujii and Maruoka assigned the structure **10b** to their product based on H-1, H-2 coupling constants. This spectrum shows a signal attributed to H-1 at δ 5.44 whereas authentic **10b** gave signals at δ 6.08 and δ 5.83 which we attribute to H-1 and the amide N-H, respectively. The corresponding signals for isomer **10a** were at δ 6.21 and δ 5.77, respectively. Fujii and Maruoka's spectrum shows no signal which can be attributed to the amide N-H, although the coupling constant (J = 8 Hz) of the signal at δ 5.44 in their spectrum more closely matches the amide N-H signal of our samples than the H-1 signal. Furthermore, the remainder of Fujii and Maruoka's spectrum does not agree with either of our spectra for **10b** and **10a**. Based on these observations, it would seem that Fujii and Maruoka's spectrum was obtained neither for authentic **10b** nor for **10a**.

The lactone **12** was particularly sensitive to elimination affording **7**. Very little of **12** was observed as a product in the reduction of lactone **4b** and its synthesis by direct acetylation of **4b** gave material heavily contaminated with **7** (**12** / **7**, 70:30). Thus, *erythro*-lactone **12** eliminated acetic acid more readily than the *threo*-lactone **8**. Presumably, H-2 is more open in **12** permitting more rapid deprotonation. The more open H-2 of *erythro*-lactone **4b** compared to **4a** also explains why a small amount of *erythro* → *threo* isomerization was noted but not the reverse.



## CONCLUSIONS

Work presented here documents a practical, reproducible route to 2-amino-2-deoxy-D-threose and 2-amino-2-deoxy-D-erythrose derivatives. The 2-amino-2-deoxy-D-threose derivatives are somewhat easier to obtain, but diastereoselectivity is relatively poor. Thus, the overall yield from starting aldehyde was 8% for 1-*O*-acetylfuranose **5** and 22% for open-chain triacetate **6**.

## EXPERIMENTAL

**General.** D-Glyceraldehyde acetonide was prepared by the procedure of Schmid et al.:[8] $[\alpha]^{25}_D$ = +80.3° (*c* 1.18, benzene) {lit[8] $[\alpha]_D$ = +80.1° (*c* 1.53, benzene)}. Combined organic layers were typically dried over anhydrous $Na_2SO_4$ followed by concentration at reduced pressure. The $^1H$ NMR spectra and $^{13}C$ NMR spectra were determined (TMS internal / external standard) on a Bruker WM-250 instrument.

Preparative TLC (elution solvent) was performed on 0.25 and 1.0 mm Analtech silica gel GF plates.

**Preparation of (α*R*, 4*S*)-2,2-dimethyl-α-(phenylmethyl)amino-1,3-dioxolane-4-acetonitrile (1a) and (α*S*, 4*S*)-2,2-dimethyl-α-(phenylmethyl)-amino-1,3-dioxolane-4-acetonitrile (1b).** In an efficient fume hood (*caution*: *HCN!* ), acetic acid (9.9 mL, 172 mmol) was added to a stirred solution of KCN (5.05 g, 77.5 mmol), D-glyceraldehyde acetonide (10 g, 76.9 mmol), and benzylamine (9.4 g, 87.9 mmol) in methanol (200 mL). Stirring was continued at 60-65 °C for 2 h and at ambient temperature for 22 h. The reaction solution was then concentrated; $CH_2Cl_2$ (250 mL) and water (100 mL) were added to the residue. The layers were separated, the aqueous layer was extracted with $CH_2Cl_2$ (two 100-mL portions), and the organic layers were combined and washed with water (100 mL). Further work-up gave crude product which was purified by flash chromatography on silica gel ($CHCl_3$/*i*-PrOH, 98.5:1.5) to give pure **1a,b** (16.15 g, 85% yield) as a 60:40 **a / b** isomer mixture. The first two crops (3.3 g, 17% yield) obtained by crystallization from methanol consisted of pure **1a**: mp 86.5-87 °C (lit[1a] 87 °C); $[\alpha]^{26}_D$ = -99.6° (*c* 2.32, EtOH) {lit[1a] $[\alpha]_D$ = -99.4° (*c* 2.32, EtOH)}; IR (KBr) 3373 (NH), 2226 (C≡N), 1601 $cm^{-1}$ (NH); $^1H$ NMR ($CDCl_3$) δ 7.25-7.4 (m, 5 H), 4.39 (apparent q, 1 H, J = 5.4 Hz), 4.18 (d, 1 H, J = 13.2 Hz) on 4.1-4.2 (m) [total 2 H], 4.02 (dd, 1 H, J = 5.6, 8.7 Hz), 3.86 (d, 1 H, J = 13.2 Hz), 3.55 (typically broad d, 1 H, J = 4.8 Hz), 2.17 (broad s, 1 H), 1.44 (s, 3 H), 1.36 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 137.6, 128.4, 128.1, 127.5, 117.8, 110.4, 75.2, 65.8, 51.3, 51.2, 26.2, 24.9; mass spectrum *m/z* 246 ($M^+$).

A 95-mg portion of the mother liquor from another run (50:50, **1a / 1b**) was subjected to HPLC (Rainin Microsorb™ 5 mm spherical silica column; hexanes/$CHCl_3$, 80:20). Three fractions were isolated and concentrated: pure **1a** (15 mg), a **1a / 1b** mixture (41 mg), and pure **1b** (last to be eluted, 31 mg). Compound **1b** was a solid: mp 61-61.5 °C (lit[1a] 53 °C); $[\alpha]^{26}_D$ = +74.7° (*c* 0.75, MeOH) {lit[1a] $[\alpha]_D$ = +52° (*c* 0.75, MeOH)}; IR (KBr) 3305 (NH), 2227 (C≡N), 1604 $cm^{-1}$ (NH); $^1H$ NMR ($CDCl_3$) δ 7.3-7.45 (m, 5 H), 4.24 (apparent q, 1 H, J = 5.4 Hz), 4.11 (d, J = 13 Hz) on 4.1-4.2 (m) [total 2 H], 3.9 (dd, 1 H, J = 5.4, 8.9 Hz), 3.84 (d, 1 H, J = 13 Hz), 3.49 (d, 1 H, J = 5 Hz), 2.18 (broad s, 1 H), 1.50 (s, 3 H), 1.36 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 137.7, 128.3, 128.2, 127.4, 117.6, 110.4, 75.4, 66.6, 53.2, 51.4, 26.5, 25.0; mass spectrum *m/z* 246 ($M^+$).

**Synthesis of amine 3a,b.** An 87:13 mixture of nitrile **1a,b** (7.01 g, 28 mmol) and 5N HCl (82 mL) was heated at 70 °C for 3.5 h followed by concentration in vacuo. The crude product was recrystallized from ethanol/ether to give 5.26 g (76% yield) of the hydrochloride salts of **3a,b**. The salts were dissolved in water, neutralized with

saturated $NaHCO_3$ and extracted several times with ethyl acetate to give 4.15 g of the free amine **3a,b**. Flash chromatography of the free amine on silica gel (*i*-PrOH/$CHCl_3$, from 1:99 to 6:94) afforded *erythro*-isomer **3b** as the first material to be eluted. Recrystallization of this material from acetone/hexanes gave pure **3b** (0.41 g, 7% yield): mp 91-92 °C; $[\alpha]_D$ = -29.2° (*c* 0.72, MeOH); IR (KBr) 3288, 3159 (NH), 1769 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) δ 7.3-7.4 (m, 5 H), 4.40 (d, 1 H, J = 10.4 Hz), 4.21 (dd, 1 H, J = 2.9, 10.4 Hz), 4.1-4.15 (m, 1 H), 3.93 (d, 1 H, J = 13.6 Hz), 3.88 (d, 1 H, J = 13.6 Hz), 3.51 (d, 1 H, J = 4.7 Hz), 1.7-2.2 (broad s, 2 H); $^{13}C$ NMR ($CDCl_3$) δ 175.3, 137.8, 128.7, 128.0, 127.7, 72.7, 66.2, 59.8, 52.5; mass spectrum *m/z* 207 ($M^+$).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.39; H, 6.21; N, 6.55.

The *threo*-isomer **3a** was isolated from later chromatography fractions. Recrystallization of the chromatographed material from acetone/hexanes afforded pure **3a** (2.71 g, 46% yield): mp 122.5-123 °C; $[\alpha]_D$ = -53.0° (*c* 0.72, MeOH); IR (KBr) 3262, 3139 (NH), 1772 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) δ 7.25-7.4 (m, 5 H), 4.30-4.45 (m, 2 H), 4.11 (d, 1 H, J = 13.2 Hz), 3.85-3.95 (m, 2 H), 3.47 (d, 1 H, J = 7.3 Hz), 2.1-2.2 (broad s, 2 H); $^{13}C$ NMR ($CDCl_3$) δ 174.7, 139.1, 128.7, 128.2, 127.6, 73.4, 69.9, 63.8, 52.3; mass spectrum *m/z* 207 ($M^+$).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.60; H 6.18; N, 6.61.

**Synthesis of the hydrochloride salt of 3a. Run A: from 3a.** Sufficient 5N aqueous HCl was added dropwise to a solution of the amine **3a** (0.46 g, 2.2 mmol) in ether (85 mL) to attain a pH of 1-3. The solution was then concentrated in vacuo to give the crude product which was recrystallized from methanol/ether and dried overnight over $P_2O_5$ in a desiccator to furnish 0.48 g (89% yield) of the hydrochloride salt: mp 169-170 °C (lit[1a] 170-171 °C); $[\alpha]_D$ = -36.6° (*c* 1.08, water); {lit[1a] $[\alpha]_D$ = -36° (*c* 1.0, water)}; $^1H$ NMR (acetone-$d_6$) δ 7.65-7.75 (m, 2 H), 7.4-7.55 (m, 3 H), 6.29 (broad s, 2 H), 5.09 (apparent q, 1 H, J = 8.5 Hz), 4.75 (d, 1 H, J = 12.8 Hz), 4.56 (d, J = 12.8 Hz) on 4.5-4.65 (m) [total 2 H], 4.34 (d, 1 H, J = 8.7 Hz), 4.06 (apparent t, 1 H, J = 8.7 Hz), 2.85 (broad s, 1 H); $^{13}C$ NMR ($D_2O$/ acetone-$d_6$) δ 170.5, 130.2, 130.1, 129.5, 71.0, 68.6, 60.0, 50.2.

**Run B: from 1a.** A solution of the nitrile **1a** (0.24 g, 0.98 mmol) in 5N HCl (2.8 mL) was heated at 60-70 °C for 3.5 h and was then concentrated in vacuo. The crude product was recrystallized from ethanol/ether to give 0.17 g (72% yield) of **1a**.

**Synthesis of the hydrochloride salt of 3b.** Prepared in 80% yield from **3b** similarly to the preparation (Run A) of the hydrochloride salt of **3a**: mp 200-201 °C (lit[1a] 196-198 °C); $[\alpha]_D$ = -28.8° (*c* 1.0, water) {lit[1a] $[\alpha]_D$ = -27.3° (*c* 1.0, water)}; $^1H$

NMR (acetone-$d_6$) δ 7.7-7.8 (m, 2 H), 7.4-7.45 (m, 3 H), 6.1 (broad s, 2 H), 4.9-4.95 (m, 1 H), 4.72 (d, 1 H, J = 13.1 Hz), 4.55-4.65 (m, 2 H), 4.35-4.45 (m, 2 H), 2.9 (broad s, hydroxylic H); $^{13}C$ NMR ($D_2O$/acetone-$d_6$) δ 172.4, 130.4, 130.2, 129.7, 75.4, 66.2, 57.5, 50.6.

**Synthesis of amine hydrochloride salt 3c.** A mixture of $Pd(OH)_2$ (1.19 g) and methanol (40 mL) was placed under hydrogen in a Parr hydrogenator for 5 min. A solution of the hydrochloride salt of **3a** (0.98 g, 4.04 mmol) in methanol (200 mL) was added and a hydrogen atmosphere (56 psi) was maintained with shaking for 6.5 h. The reaction mixture was filtered and concentrated to give the crude product which was recrystallized from ethanol/ether to give 0.48 g (78% yield) of the hydrochloride salt **3c**: mp 178-179 °C (lit[1a] 163 °C); $[\alpha]_D$ = -30.2° (*c* 1.15, water) (lit[1a] $[\alpha]_D$ = -29.5° (*c* 1.05, water); $^1H$ NMR (acetone-$d_6$) δ 5.45 (apparent q, 1 H, J = 8 Hz), 5.21 (d, 1 H, J = 8.4 Hz), 4.67 (dd, 1 H, J = 7.4, 8.5 Hz), 4.11 (apparent t, 1 H, J = 8.5 Hz), 2.88 (broad s, hydroxylic H) ($N\underline{H}_3^+$ not observed); $^{13}C$ NMR ($D_2O$/acetone-$d_6$) δ 171.6, 71.2, 69.2, 55.4.

**Synthesis of amine hydrochloride salt 3d.** Prepared in 82% yield from the hydrochloride salt of **3b** similarly to the preparation of **3c**: mp 172.5-173.5 °C (lit[1a] 174-175 °C); $[\alpha]_D$ = -56.4° (*c* 0.97, water) {lit[1a] $[\alpha]_D$ = -52° (*c* 1.0, water)}; $^1H$ NMR (acetone-$d_6$) δ 5.40 (d, 1 H, J = 4.2 Hz), 4.9-4.92 (m, 1 H), 4.60 (dd, 1 H, J = 2.9, 9.9 Hz), 4.37 (d, 1 H, J = 9.9 Hz), 2.84 (broad s, hydroxylic H) ($N\underline{H}_3^+$ not observed); $^{13}C$ NMR ($D_2O$/acetone-$d_6$) δ 172.7, 75.2, 66.4, 52.1.

**Synthesis of lactone 4a.** Acetic anhydride (149 μL, 1.6 mmol) was added to a cold (0-5 °C) solution of the hydrochloride salt of **3b** (129 mg, 0.8 mmol) and $NaHCO_3$ (100 mg, 1.2 mmol) in aqueous 70% MeOH (3.8 mL). The resulting mixture was kept cold and was stirred for 3 h. Filtration followed by concentration gave a residue which was dissolved in acetone, stirred vigorously, and filtered to give **4a** in quantitative yield, pure enough for preparative purposes. An analytical sample of **4a** was obtained by recrystallization from acetone/hexanes: mp 165-166 °C; $[\alpha]_D$ = -89.8° (*c* 1.08, MeOH); IR (KBr) 3352, 1777 (C=O), 1660 $cm^{-1}$(O=CN); $^1H$ NMR (acetone-$d_6$) δ 7.78 (broad m, 1 H), 4.58 (apparent q, 1 H, J = 7.3 Hz), 4.47 (dd, 1 H, J = 7.3, 8.5 Hz), 4.28 (dd, 1 H, J = 5.6, 7.6 Hz), 3.94 (dd, 1 H, J = 7.3, 8.5 Hz), 2.86 (broad s, 1 H), 1.95 (s, 3 H). $^{13}C$ NMR ($D_2O$/acetone-$d_6$) δ 175.8, 174.7, 71.8, 70.8, 57.0, 21.9; HRMS (EI) Calcd for $C_6H_9NO_4$ ($M^+$) 159.0532, found 159.0529.

Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.16; H, 5.74; N, 8.66.

**Reduction of 4a using DIBALH.** DIBALH (1.9 mL of a 1M solution in toluene; 1.9 mmol) was added dropwise over 2 min to a cooled (Dry Ice-acetone)

solution of the amide **4a** (59 mg, 0.37 mmol) in THF (10 mL) and the resulting solution was stirred for 90 min with cooling. The reaction was quenched with glacial HOAc (110 μL) followed by water (0.5 mL). The reaction mixture was concentrated in vacuo and to the ensuing residue was added $Ac_2O$ (3 mL) and pyridine (3 drops). This reaction mixture was stirred for 12 h and was then concentrated in vacuo. The solid residue was treated with water (3 mL) and ether (10 mL) and the mixture was made neutral with $NaHCO_3$. The organic layer was separated, the aqueous layer was extracted with ethyl acetate (three 30-mL portions) and the combined organic layers were worked up to give crude product. The crude product was treated with acetone, solids were filtered off, and the filtrate was concentrated. The resulting residue was purified by preparative TLC (benzene/MeOH, 88:12) to give 1 mg (2% yield; from a trace to 7% yield in other runs) of **8** as the most polar fraction: the $^1H$ NMR spectrum matched an authentic sample.

Preparative TLC also afforded 24 mg (26% yield) of **5** from the second most polar fraction: mp 129-130.5 °C (lit[1a] 129-130 °C); $[\alpha]_D$ = -135.8° (*c* 0.64, water) (lit[1a] $[\alpha]_D$ = -135° (*c* 0.63, water); IR (film) 3292 (NH), 1740 (C=O), 1654 $cm^{-1}$ (O=CN); $^1H$ 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.

Preparative TLC afforded 19 mg (18% yield) of the triacetate **6**, an oil, obtained from the third most polar fraction. Spectral data for **6** matched a sample prepared by reduction of **4a** using sodium borohydride.

Preparative TLC also afforded 4 mg (7% yield) of **7** from the least polar fraction: mp 152-153.5 °C; IR (film) 1768, 1755 $cm^{-1}$ (C=O);$^1H$ NMR ($CDCl_3$) δ 7.64 (broad s, 1 H), 7.51, (t, 1 H, J = 2.0 Hz), 4.92 (d, 2 H, J = 2.0 Hz), 2.19 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 170.2, 168.6, 125.5, 70.3, 23.5; HRMS (EI) Calcd for $C_6H_7NO_3$ ($M^+$) 141.0426, found 141.0428.

**Preparation of 8.** Pyridine (3 drops) was added to a solution of amide **4a** (35 mg, 0.22 mmol) in acetic anhydride (3 mL) and the resulting solution was stirred for 12 h. Volatiles were removed in vacuo to afford 46 mg (quantitative) of a residue containing **8** and **7** (**8** / **7**, 90:10). Recrystallization from acetone-hexanes afforded 23 mg (53% yield) of pure **8**: mp 126-127 °C; $[\alpha]_D$ = -48.0° (*c* 0.69, MeOH); IR (film) 3300 (NH), 1790, 1730 $cm^{-1}$ (C=O), 1652 $cm^{-1}$ (O=CN); $^1H$ NMR ($CDCl_3$) δ 6.27 (broad d, 1 H), 5.3-5.4 (m, 1 H), 4.83 (dd, 1 H, J = 7.3, 10.1 Hz), 4.20 (dd, J = 5, 10.1 Hz) on 4.16 (dd, J = 5.5, 7.1 Hz) [total 2 H], 2.13 (s, 3 H), and 2.07 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 171.7, 170.6, 170.3, 74.2, 70.0, 55.4, 22.4, 20.6; HRMS (FAB) Calcd for $C_8H_{12}NO_5$ ($M+H^+$) 202.0715, found 202.0717.

**Reduction of 4a using sodium borohydride: synthesis of open-chain triacetate 6.** Sodium borohydride (0.68 g, 14 mmol) was added to a cold (-10 °C) solution of **4a** (90 mg, 0.57 mmol) in methanol (10 mL) and dichloromethane (4 mL) and the resulting mixture was stirred for 3 h at ambient temperature. The reaction was quenched by addition of 10% $KH_2PO_4$ (6 mL) and concentrated. Acetic anhydride (3 mL) and pyridine (3 drops) were added and the resulting solution was stirred for 12 h. Volatiles were removed under high vacuum and the solid residue was treated with water (3 mL) and ether (10 mL). Sufficient $NaHCO_3$ was added to neutralize acid and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (three 30-mL portions). The combined organic layers were worked up to give a residue which was purified by preparative TLC (benzene/MeOH, 88:12) affording 127 mg (78% yield) of **6** as an oil: $[\alpha]_D$ = +40.3° (*c* 1.12, MeOH); IR (film) 3292 (NH), 1744 (C=O), 1661 $cm^{-1}$ (O=CN); $^1H$ NMR ($CDCl_3$) δ 5.68, (broad d, 1 H, J = 9.4 Hz), 5.25-5.35 (m, 1 H), 4.5-4.65 (m, 1 H), 4.25 (dd, 1 H, J = 4.8, 12 Hz), 4.0-4.15 (m, 3 H), 2.11 (s, 3 H), 2.08 (s, 3 H), 2.07 (s, 3 H), 2.03 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 170.5, 170.3, 169.8, 169.7, 69.9, 62.9, 62.5, 48.2, 23.1, 20.6, 20.5; HRMS (EI) Calcd for $C_{12}H_{19}NO_7$ ($M^+$) 289.1162, found 289.1158.

**Reduction of 4a using lithium tris(diethylamino)aluminum hydride.** Diethylamine (6.7 mL, 4.6 g) was added to a cold (0-5 °C) THF solution of $LiAlH_4$ (1 M, 20 mL) and the resulting solution was stirred for 3 h. A portion (0.8 mL, 0.6 mmol of $LiAlH(Et_2N)_3$) of this solution was added to a cooled (Dry Ice-acetone) solution of **4a** (26 mg, 0.16 mmol) in THF (5 mL) and the resulting solution was stirred for 3 h with cooling. Quenching, work-up, and preparative TLC were carried out similarly to the DIBALH procedure. The products included **5** (9 mg, 25% yield), **6** (2 mg, 4% yield), and **7** (4 mg, 16% yield). Also obtained from a fraction between **6** and **7** was 15 mg (29% yield) of (2*S*, 3*S*)-3,4-diacetoxy-2-acetylamino-*N*, *N*-diethylbutanamide (**9**): $[\alpha]_D$ = -4.35° (*c* 0.92, MeOH); IR (film) 3300 (NH), 1746 (C=O), 1637 $cm^{-1}$ (O=CN); $^1H$ NMR ($CDCl_3$) δ 6.52 (d, 1 H, J = 8.9 Hz), 5.4-5.5 (m, 1 H), 5.20 (dd, 1 H, J = 3.5, 8.9 Hz), 4.36 (dd, 1 H, J = 4.4, 11.9 Hz), 3.97 (dd, 1 H, J = 7.1, 11.9 Hz), 3.35-3.6 (m, 3 H), 3.16 (dt, 1 H, J = 7.1, 13.6 Hz), 2.07 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.26 (t, 3 H, J = 7.1 Hz), 1.09 (t, 3 H, J = 7.1 Hz); $^{13}C$ NMR ($CDCl_3$) δ 170.3, 169.9, 167.9, 71.0, 63.0, 48.9, 42.0, 40.7, 23.0, 20.6, 14.2, 12.5; HRMS (FAB, NaBr) Calcd for $C_{14}H_{24}N_2O_6Na$ ($M+Na^+$) 339.1532, found 339.1531.

**Synthesis of lactone 4b.** Crude **4b**, pure enough for preparative purposes, was prepared in quantitative yield from **3d** similarly to the preparation of lactone **4a**. In one run, crude product (171 mg) was recrystallized from acetone/hexanes to give 154 mg (90% yield) of **4b**: mp 170-171 °C; $[\alpha]_D$ = -86.6° (*c* 1.38, MeOH); IR (KBr) 3364 (NH),

1762 (C=O), 1654 $cm^{-1}$ (O=CN); $^1H$ NMR (acetone-$d_6$) δ 7.35 (broad m, 1 H), 4.91 (dd, 1 H, J = 4.4, 8.3 Hz), 4.5-4.6 (m, 2 H), 4.24 (d, 1 H, J = 9.9 Hz), 2.91 (broad s, 1 H), 2.01 (s, 3 H); $^{13}C$ NMR ($D_2O$/acetone-$d_6$) δ 177.0, 174.9, 74.8, 68.2, 53.4, 21.9; mass spectrum *m/z* 159 ($M^+$).

Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 44.99 H, 5.76; N, 8.63.

**Reduction of 4b using DIBALH.** DIBALH (3.5 mL of a 1M solution in toluene; 3.5 mmol) was added dropwise over 2 min to a cooled (Dry Ice-acetone) solution of the amide **4b** (0.11 g, 0.69 mmol) in THF (20 mL) and the resulting solution was stirred for 90 min with cooling. The reaction was quenched with glacial HOAc (205 μL) followed by water (0.7 mL). The reaction mixture was concentrated in vacuo and to the ensuing residue was added $Ac_2O$ (3 mL) and pyridine (3 drops). Further reaction and work-up as described for reduction of **4a** afforded an acetone soluble residue. This residue was purified by preparative TLC (benzene-acetone, 60:40) to give 51 mg (30% yield) of **10a** as the most polar fraction: mp 127-128 °C; $[\alpha]_D$ = +15.9° (*c* 0.66, water); IR (film) 3363, 1727 (C=O), 1667 $cm^{-1}$ (O=CN); $^1H$ 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.

A mixture (38.4 mg) was isolated from less polar fractions. This mixture contained **7**, **10b**, and **12** (**7** / **10b** / **12**, 67:14:19). Also present was a trace of the triacetate **11**, identified by comparison of the $^1H$ NMR spectra to a sample obtained by reduction of **4b** with sodium borohydride. Peaks attributed to **10b** matched the $^1H$ NMR spectrum of a racemic sample obtained in an alternate route.[3a]

**Preparation of lactone 12.** Pyridine (3 drops) was added to a solution of amide **4b** (17 mg, 0.1 mmol) in acetic anhydride (3 mL) and the resulting solution was stirred for 12 h. Volatiles were removed in vacuo to afford 21 mg (quantitative) of a residue containing **12** and **7** (**12** / **7**, 65:35). Recrystallization from acetone-hexanes afforded 12 mg of impure **12** (**12** / **7**, 70:30) as a solid: IR (film) 3340 (NH), 1768, 1750 (C=O), 1691 $cm^{-1}$ (O=CN); $^1H$ NMR ($CDCl_3$, peaks attributed to **7** were subtracted) δ 5.94 (broad d, 1 H, J = 7.4 Hz), 5.52 (dd, 1 H, J = 3.0, 5.3 Hz), 5.03 (dd, 1 H, J = 5.3, 7.4 Hz), 4.51 (dd, 1 H, J = 3.0, 11.5 Hz), 4.42 (d, 1 H, J = 11.5 Hz), 2.13 (s, 3 H), and 2.07 (s, 3 H); $^{13}C$ NMR ($CDCl_3$, peaks attributed to **7** were subtracted) δ 173.3, 170.7, 169.6, 71.0, 70.4, 50.7, 22.6, 20.7; HRMS (FAB) Calcd for $C_8H_{12}NO_5$ ($M+H^+$) 202.0715, found 202.0716.

**Reduction of 4b using sodium borohydride: synthesis of open-chain triacetate 11.** Reduction of **4b** was carried out similar to reduction of **4a** to afford **11** in 65% yield. An analytical sample of **11** was obtained by recrystallization from acetone/hexanes: mp 135-135.5 °C; $[\alpha]_D$ = +10.4° (*c* 1.09, MeOH); IR (film) 3320 (NH), 1734 (C=O), 1654 $cm^{-1}$ (O=CN); $^1H$ NMR ($CDCl_3$) δ 5.94 (broad d, 1 H, J = 9.5 Hz), 5.05-5.15 (m, 1 H), 4.3-4.4 (m, 2 H), 4.12 (dd, 1 H, J = 6.3, 12.3 Hz), 4.0 (dd, 1 H, J = 3.5, 11.7 Hz), 2.10 (s, 3 H), 2.08 (s, 6 H), 2.03 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 170.7, 170.5, 170.1, 169.7, 70.5, 63.0, 62.8, 48.1, 23.2, 20.7, 20.6; HRMS (FAB) Calcd for $C_{12}H_{20}NO_7$ ($M+H^+$) 290.1240, found 290.1240.

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