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Asymmetric Synthesis of Polyhydroxy α-Amino Acids with the Sulfinimine-Mediated Asymmetric Strecker Reaction: 2-Amino 2-Deoxy L-Xylono-1,5-lactone (Polyoxamic Acid Lactone)

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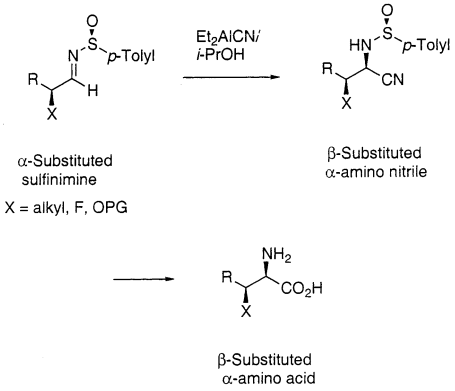
Received May 1, 2002

Polyhydroxylated sulfinimines derived from protected 1,2-*O*-isopropyliden-L-threoses undergo the sulfinimine-mediated Strecker syntheses to give α-amino nitriles in good yield and de. A double stereodifferentiation effect was not observed and the diastereoselectivity is controlled by the absolute configuration of the sulfinyl group. Hydrolysis of the amino nitriles afforded the lactone rather than polyoxamic acid.

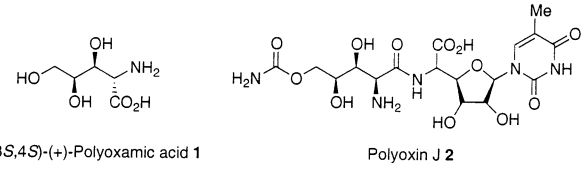
As part of a program aimed at the asymmetric synthesis of functionalized and polyfunctionalized α-amino acids we have been examining the sulfinimine (*N*-sulfinyl imine) mediated asymmetric Strecker synthesis. This protocol entails the addition of ethylaluminumcyanoisopropoxide [EtAl(CN)O-*i*-Pr], generated in situ from diethylaluminum cyanide and isopropyl alcohol, to functionalized sulfinimines (Scheme 1).[1] Hydrolysis of the resultant α-amino nitriles, obtained diastereomerically pure either by crystallization or chromatography, affords directly the enantiopure α-amino acids. In this regard highly efficient asymmetric synthesis of functionalized α-amino acids, including *β*-alkyl (alloisoleucine),[2] *β*-fluoro (3-fluorophenylalanine, 3-fluoroleucine)[3], and *β*-hydroxy (phenylserine, *β*-hydroxyleucine)[4] amino acids, have resulted. Other examples include bis-α-amino acids (DAP and actionidic acid)[5,6] and oxo α-amino acids.[7] In general the de values of the α-amino nitriles were >90% with the stereochemistry being controlled by the sulfinyl group and consistent with intramolecular delivery of CN via a six-membered transition state. A modest double-stereodifferentiation effect was noted only for the protected *β*-hydroxy sulfinimines.[4]

The only limitation of this protocol would appear to be the ability to prepare the sulfinimine and the compatibility of the functional groups with the hydrolysis conditions. A rigorous test of this idea is the asymmetric synthesis of polyoxamic acid (**1**), an amino acid having three contiguous hydroxyl groups, two of which are attached to stereogenic centers (Scheme 2). Numerous lengthy synthesis of **1** or advanced precursors have been reported starting from chiral pool sources such as carbohydrates, amino acids, and tartaric acid.[8] Surprisingly, the study by Merino and co-workers of the hydrocyanation of chiral nitrones is the only reference to a Strecker-like process for **1**.[9] However, the resultant α-(hydroxyami-

SCHEME 1



SCHEME 2



† Temple University.
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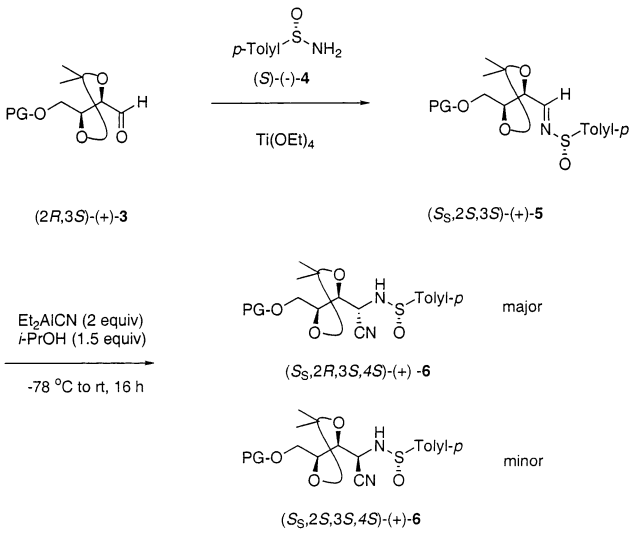
10.1021/jo020302e CCC: $22.00
Published on Web 10/10/2002

SCHEME 3



a: PG = Bn, b: PG = TBDMS, c: PG = TBDPS

no) nitriles were not transformed into the amino acids, perhaps because of the sensitivity of the substrate under the hydrolysis conditions. (+)-(2*S*,3*S*,4*S*)-2-Amino-3,4,5-trihydroxypentanoic acid (polyoxamic acid **1**) is a key constituent of polyoxins such as **2**, novel nucleosides that are toxic to phytopathogenic fungi while being nontoxic to bacteria, plants, or animals.[10]

Our synthesis begins with the preparation of the requisite sulfinimines **5** by the $Ti(OEt)_4$ assisted condensation of commercially available (*S*)-(−)-*p*-toluenesulfinamide (**4**) with the known protected 1,2-*O*-isopropylidene-L-threoses **3a**−**c** (Scheme 3).[11,12] These aldehydes are readily prepared, on a large scale, from commercially available (+)-2,3-*O*-isopropylidene-L-threitol or (+)-diethyl-L-tartrate.[13−15] The modest yields of (S_S,2*S*,3*S*)-(+)-**5** may reflect partial hydrolysis of the ketal by the Lewis acid $Ti(OEt)_4$ (Table 1).

Hydrocyanation of **5a**−**c** with 2.0 equiv of Et_2AlCN and 1.5 equiv of *i*-PrOH gave the corresponding α-amino nitriles in 70−78% isolated yield. The diastereoselectivity varied from a low of 66% for the *O*-benzyl protected sulfinimine **5a** to a high of 82% for the *tert*-butyldiphenylsilyl derivative **5c** (Table 1: entries 1 and 3). Fewer equivalents of Et_2AlCN/*i*-PrOH resulted in incomplete reaction (Table 1, entry 4), and in the absence of added *i*-PrOH the de decreased to 36% (Table 1, entry 5). Surprisingly running the reaction at 40 °C did not diminish the diastereoselectivity as is normally observed (Table 1: entry 6). Both diastereoisomers were isolated by flash chromatography, affording the major diastereoisomers (S_S,2*R*,3*S*,4*S*)-(+)-**6** in 66−71% yield (Table 1).

To examine the possibility of a match-mismatched situation (double stereodifferentiation) and to determine the effect of the tartrate moiety on diastereoselectivity, sulfinimine (R_S,2*S*,3*S*)-(+)-**7** was prepared starting with sulfinamide (*R*)-(+)-**4** and aldehyde (+)-**3** (Scheme 4). The only difference between sulfinimines (+)-**5** and (+)-**7** is the configuration of the sulfinyl group (Schemes 3 and 4). If CN addition is controlled by the tartrate moiety then addition, under standard conditions, will furnish amino nitrile (R_S,2*R*,3*S*,4*S*)-(+)-**8** as the major product. Conversely, if the sulfinyl group controls the asymmetric induction, amino nitrile (R_S,2*S*,3*S*,4*S*)-(+)-**8** will be the major product. Indeed, the latter was observed, confirming that the sulfinyl group determines the stereoselectivity for CN addition to sulfinimines. Noteworthy is the fact that the ratio of the major and minor amino nitrile products was 91:9, which is identical with that observed for hydrocyanation of (+)-**5c** (Table 1, compare entries 3 and 7). Thus there was an absence of any double stereodifferentiation effect. The absolute stereochemistry of the major product (R_S,2*S*,3*S*,4*S*)-(+)-**8** was established by X-ray crystallography.

With the *N*-sulfinyl amino nitriles in hand, all that was necessary to obtain polyoxamic acid was hydrolysis. This is usually easily accomplished by refluxing the amino nitrile in 2−6 N HCl, which results in concomitant removal of the *N*-sulfinyl auxiliary and hydrolysis of the nitrile, to furnish the α-amino acids. Application of this protocol to the *N*-sulfinyl amino nitrile (S_S,2*R*,3*S*,4*S*)-(+)-**6a**, 2 N HCl-reflux, resulted in decomposition. However, smooth deprotection of the sulfinyl group and isopropylidene ketal moiety followed by hydrolysis of the nitrile was achieved with moist ethereal HCl, affording, after 16 h, hydrochloride (−)-**9** in 95% yield (Scheme 5). Unfortunately, all attempts to reductively remove the benzyl group failed.

We thought that deprotection of the silyl ether would prove easier and would give (−)-**1** in one pot. However, refluxing (S_S,2*R*,3*S*,4*S*)-(+)-**6b** in 2 N HCl resulted in decomposition and similar results were found with Et_2O/HCl/H_2O. Sequential deprotection, where the TBDPS group is first removed followed by the sulfinyl auxiliary, proved to be successful. Thus treatment of (+)-**6b** with tetrabutylammonium fluoride (TBAF) afforded alcohol (+)-**10** in 77% yield (Scheme 6). On exposure to Et_2O/HCl the alcohol underwent instantaneous sulfinyl deprotection to the amino cyanide hydrochloride **11**. Hydrolysis of (−)-**11** with moist ethereal HCl ($Et_2O/HCl/H_2O$) gave a hydrochloride that on treatment with propylene oxide furnished lactone (2*S*,3*S*,4*S*)-(−)-**12** in 36% yield for the two steps. All attempts to isolated polyoxamic acid (**1**) by using milder hydrolysis conditions failed. The structure of lactone **12** was established by comparison of its spectral properties with literature values.[16] Precedent exists for formation of the enantiomer of **15** under related hydrolysis conditions.[16] Surprisingly, attempts to remove the TBDMS group in amino nitrile **6b** with HCl led to decomposition.

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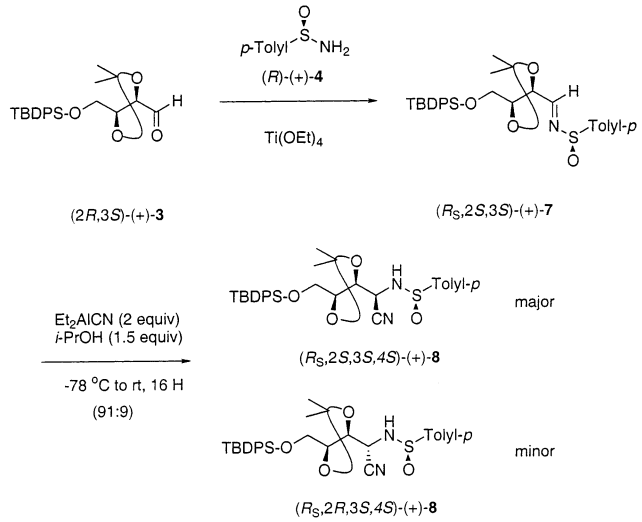
TABLE 1. Hydrocyanation of Sulfinimines 5 to α-Amino Nitriles 6 at −78 °C to Room Temperature.

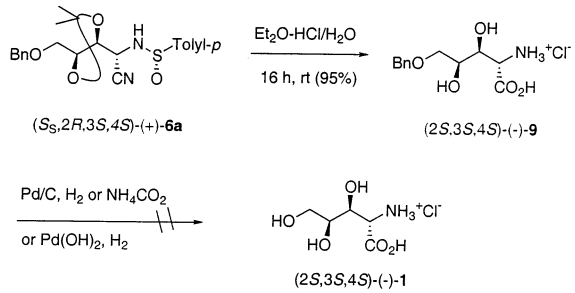
			α-amino nitrile **6**dr	
entry	sulfinimine **5** (% yield)[a]	conditions[b]	dr (% de)[c]	% yield major (minor)[a]
1	(+)-**5a**, PG = Bn (48)		83:17 (66)	67 (11)
2	(+)-**5b**, PG = TBDMS (53)		89:11 (78)	66 (4)
3	(+)-**5c**, PG = TBDPS (59)		91:9 (82)	71 (6)
4		1.5Et_2AlCN/ 1.0 equiv of *i*-PrOH	90:10 (80)	44 (5)[d]
5		2 equiv of Et_2AlCN	68:32 (36)	
6		40 °C	91:9 (82)	66 (6)
7	(+)-**7**		91:9 (82)	65 (5)

[a] Isolated yield of pure material. [b] 2.0 equiv of Et_2AlCN and 1.5 equiv of *i*-PrOH used unless otherwise noted. [c] Determined by NMR on the crude reaction mixture. [d] **5c** recovered in 18% yield.

SCHEME 4



SCHEME 5



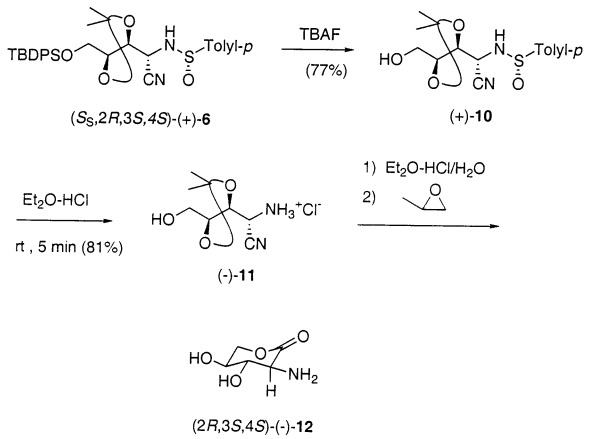
Applying the same sequential deprotection-hydrolysis technology to (R_S,2*S*,3*S*,4*S*)-(+)-**8**, as outlined in Scheme 7, for **6** furnished lactone (2*R*,3*S*,4*S*)-(−)-(**15**).

In summary, we have shown that functionalized sulfinimines derived from the chiral pool source tartaric acid undergo the sulfinimine-mediated Strecker synthesis to afford the corresponding α-amino nitriles in good yield and de. The absolute stereochemistry of the amino nitrile product was found to be consistent with that found in other applications of the sulfinimine-mediated asymmetric Strecker synthesis. Careful hydrolysis of the amino nitriles afforded polyoxamic acid lactones **12** and **15**.

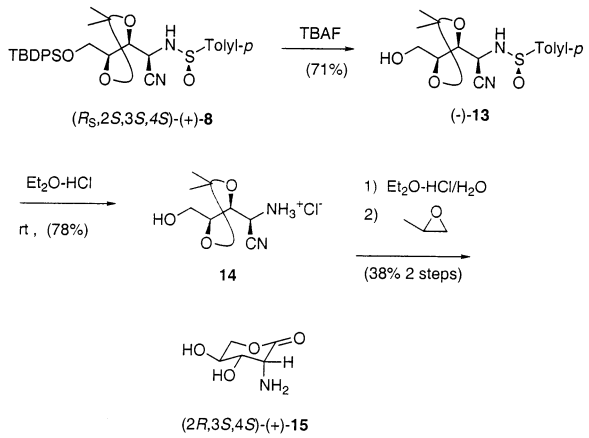
Experimental Section

General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless noted otherwise. ^1H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively.

SCHEME 6



SCHEME 7



THF and Et_2O were freshly distilled under argon from a purple solution of sodium and benzophenone. Unless stated otherwise, all the reagents were purchased from commercial sources and used without additional purification. (2*S*,3*S*)-(+)-(1-Benzyloxy-2,3-isopropylidenedioxy)butyraldehyde (**3a**),[13] (2*S*,3*S*)-(−)-1-*tert*-butyldimethylsilyloxy-2,3-isopropylidenedioxybutyraldehyde (**3b**),[14] and (2*S*,3*S*)-(−)-1-*tert*-butyldiphenylsilyloxy-2,3-isopropylidenedioxybutyraldehyde (**3c**)[15] were prepared from 2,3-*O*-isopropylidene-L-threitol as previously described. (*S*)-(+)- and (*R*)-(−)-*p*-toluenesulfinamide (**4**) were prepared according to a literature procedure.[11]

Typical Procedure for the Synthesis of Sulfinimines: (S_S,2*S*,3*S*)-(+)-*N*-(4-Benzyloxy-2,3-isopropylidenedioxy)-butylidine-*p*-toluenesulfinamide (5a). In a two-neck, 100-

mL, round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon-filled balloon was placed aldehyde (+)-**3a** (0.25 g, 1.0 mmol) and sulfinamide (*S*)-(+) **4** (0.16 g, 1.1 mmol) in CH_2Cl_2 (25 mL). To this solution was added titanium tetraethoxide (1 mL, 5 mmol) and the reaction mixture was stirred at room temperature for 3 h. At this time the solution was cooled to 0 °C, quenched with ice-cold H_2O (5 mL), and filtered through a pad of Celite, and the pad was washed with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (hexane/EtOAc 90:10) gave 0.19 g (48%) of (+)-**5a** as a viscous oil; $[\alpha]^{20}_D$ +176.2 (*c* 0.6, $CHCl_3$); IR (neat) 2987, 2867, 1627, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (d, J = 4.3 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.26−7.17 (m, 7H), 4.52 (dd, J = 4.3, 7.7 Hz, 1H), 4.42 (s, 2H), 4.06 (m, 1 H), 3.47 (m, 2H), 2.3 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.75, 142.36, 141.49, 138.12, 130.29, 128.80, 128.13, 124.96, 111.69, 79.17, 78.35, 73.93, 69.76, 27.30, 26.92, 21.85; HRMS calcd for $C_{12}H_{25}NO_4SNa$ (M + Na) 410.1402, found 410.1421.

(*S*$_S$,2*S*,3*S*)-(+)-*N*-(4-*tert*-Butryldimethylsilyloxy-2,3-isopropylidenedioxy)butrylidine-*p*-toluenesulfinamide (5b). Chromatography (hexane/EtOAc 90:10) gave 0.21 g (51%) of a viscous oil; $[\alpha]^{20}_D$ +164.1 (*c* 1.5, $CHCl_3$); IR (neat) 2932, 2865, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (d, J = 4.2 Hz, 1H), 7.54 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.80 (dd, J = 4.2, 7.5 Hz, 1H), 3.99 (m, 1H), 3.72 (dd, J = 4.2, 11.3 Hz, 1H), 3.66 (dd, J = 4.2, 11.3 Hz, 1H), 2.4 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3 H), 0.85 (s, 3H), 0.00 (d, J = 3.1 Hz, 6H); ^{13}C NMR δ 165.03, 142.25, 141.54, 130.25, 124.90, 111.40, 79.86, 78.69, 62.82, 32.96, 30.72, 26.26, 21.81, 18.72, −5.00; HRMS calcd for $C_{20}H_{34}NO_4SiS$ (M + H) 412.1978, found 412.1990.

(*S*$_S$,2*S*,3*S*)-(+)-*N*-(4-*tert*-Butryldiphenylsilyloxy-2,3-isopropylidenedioxy)butryilylidine-*p*-toluenesulfinamide (5c). Chromatography (hexane/EtOAc 90:10) gave 0.31 g (59%) of a viscous mass; $[\alpha]^{20}_D$ +103.1 (*c* 0.6, $CHCl_3$); IR (neat) 2931, 2858, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 4.0 Hz, 1H), 7.5−7.56 (m, 4H), 7.41 (d, J = 8.1 Hz, 2H), 7.34−7.24 (m, 6H), 7.15 (d, J = 8.0 Hz, 2H), 4.80 (dd, J = 4.0, 7.3 Hz, 1H), 3.96 (m, 1H), 3.72 (dd, J = 4.1, 11.2 Hz, 1H), 3.58 (dd, J = 11.2, 3.6 Hz, 1H), 2.29 (s, 3 H), 1.40 (s, 3H), 1.31 (s, 3H), 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.20, 142.20, 141.59, 136.00, 133.45, 130.26, 128.13, 124.55, 111.39, 79.74, 78.47, 63.10, 27.14, 21.83, 19.65; HRMS calcd for $C_{30}H_{37}NO_4SiSNa$ (M + Na) 558.2110, found 558.2115.

(*S*$_R$,2*S*,3*S*)-(−)-*N*-(4-*tert*-Butryldiphenylsilyloxy-2,3-isopropylidenedioxy)butrylidine-*p*-toluenesulfinamide (7). Chromatography (hexane/EtOAc 90:10) afforded 0.27 g (51%) of a viscous oil; $[\alpha]^{20}_D$ −150.5 (*c* 0.5, $CHCl_3$); IR (neat) 2930, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 (d, J = 4.5 Hz, 1H), 7.61−7.57 (m, 4 H), 7.46 (d, J = 8.2 Hz, 2H), 7.35−7.29 (m, 6H), 7.21 (d, J = 7.9 Hz, 2H), 4.67 (dd, J = 4.4, 7.38 Hz, 1H), 4.11−4.07 (m, 1H), 3.80−3.65 (m, 2H), 2.34 (s, 3H), 1.37 (s, 3 H), 1.31 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.88, 142.38, 141.31, 136.04, 133.43, 130.26, 128.15, 124.84, 111.51, 79.71, 63.69, 27.32, 27.18, 21.85, 19.65; HRMS calcd for $C_{30}H_{38}NO_4SiS$ (M + H) 536.2291, found 536.2288.

Typical Procedure for the Addition of Et[Al(O-*i*-Pr)CN] to Sulfinimines: (*S*$_S$,2*R*,3*S*,4*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-2-amino-3,4-isopropylidenedioxy-5-benzyloxypentane Nitrile (6). In a two-neck, 100-mL, round-bottom flask fitted with a magnetic stirring bar and an argon-filled balloon was placed (+)-**5a** (0.39 g, 1.0 mmol) in THF (15 mL) and the reaction mixture was cooled to −78 °C. In a separate 100-mL, single-neck, round-bottom flask equipped with a magnetic stirring bar under an argon-filled balloon was placed a solution of diethyl aluminum cyanide (2 mmol, 2 mL of 1 M solution in toluene) in THF (10 mL). The clear solution was cooled to −78 °C and *i*-PrOH (0.11 mL, 1.5 mmol) was added. The reaction mixture was stirred at −78 °C for 15 min and warmed to room temperature, and after 5 min it was cannulated to the sulfinimine solution at −78 °C. The reaction mixture was stirred at −78 °C for 6 h, warmed to room temperature, stirred for 16 h, cooled to −78 °C, and cautiously quenched with saturated NH_4Cl (5 mL). The turbid solution was diluted with EtOAc (25 mL) and filtered through a pad of Celite, and the pad was washed with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (hexane/EtOAc, 75:25) gave 0.28 g (67%) of a thick viscous mass; $[\alpha]^{20}_D$ +25.5 (*c* 0.5 $CHCl_3$); IR (neat) 3234, 2922, 2361 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (d, J = 8.2 Hz, 2H), 7.22−7.05 (m, 7H), 5.94 (d, J = 6.3 Hz, 1H), 4.43 (s, 2H), 4.10 (dd, J = 3.8, 8.68 Hz, 1H), 4.04 (dt, J = 3.9, 8.9 Hz, 1H), 3.83 (dd, J = 3.8, 7.8 Hz, 1H), 3.69 (dd, J = 3.9, 9.0 Hz, 1H), 3.37 (t, J = 9.1 Hz, 1H), 2.21 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.66, 139.45, 136.78, 130.45, 129.23, 128.92, 128.71, 126.69, 117.40, 110.86, 81.44, 76.38, 74.72, 70.50, 43.02, 27.38, 27.03, 21.81; HRMS calcd for $C_{22}H_{27}N_2O_4S$ (M + H) 415.1691, found 415.1691.

(*S*$_S$,2*R*,3*S*,4*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-2-amino-5-*tert*-butyldimethylsilyloxy-3,4-isopropylidenedioxypentane Nitrile (6b). Chromatography (hexane/EtOAc, 70:30) afforded 0.29 g (66%) of the major diastereomer as a white solid: mp 66−68 °C; $[\alpha]^{20}_D$ +43.5 (*c* 0.5, $CHCl_3$); IR (KBr) 2922, 2354, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.23 (d, J = 8.4 Hz, 1H), 4.17 (dd, J = 3.8, 8.5 Hz, 1H), 3.95−3.88 (m, 2H), 3.86−3.76 (m, 1H), 3.49 (dd, J = 9.1, 9.8 Hz, 1H), 2.25 (s, 3 H), 1.23 (s, 3H), 1.17 (s, 3 H), 0.79 (s, 9H), 0.00 (d, J = 3.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 142.74, 139.44, 130.49, 126.77, 117.40, 110.73, 81.62, 78.33, 64.18, 42.67, 27.39, 27.04, 21.81, 18.83, −5.07; HRMS calcd for $C_{21}H_{34}N_2O_4SiSNa$ (M + Na) 461.1925, found 461.1906.

Minor isomer **(*S*$_S$,2*S*,3*S*,4*S*)-(+)-*N*-*p*-(toluenesulfinyl)-2-amino-5-*tert*-butyldimethylsilyloxy-3,4-isopropylidenedioxypentane nitrile (6b)**: 0.02 g (4%), mp 128−130 °C; $[\alpha]^{20}_D$ +141.18 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 5.07 (d, J = 10.0 Hz, 1H), 4.50−4.22 (br m, 1H), 3.99 (br s, 1 H), 3.74−3.71 (m, 1H), 3.59−3.53 (m, 1H), 2.44 (s, 3 H), 1.48 (s, 3H), 1.41 (s, 3H), 0.85 (s, 9H), 0.00 (d, J = 0.8 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 142.69, 140.34, 130.38, 126.29, 117.31, 111.33, 81.11, 77.76, 63.85, 47.14, 28.56, 27.55, 26.23, 21.80, 18.60, −5.27.

(*S*$_S$,2*R*,3*S*,4*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-2-amino-5-*tert*-butyldiphenylsilyloxy-3,4-isopropylidenedioxypentane nitrile (6c). Chromatography (hexane/EtOAc 75:25) gave 0.4 g (71%) of viscous mass; $[\alpha]^{20}_D$ +25.7 (*c* 0.7, $CHCl_3$); IR (neat) 3208, 2931, 2859, 1471 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62−7.59 (m, 4H), 7.49 (d, J = 8.2 Hz, 2H), 7.38−7.34 (m, 6H), 7.26 (d, J = 8.0 Hz, 2H), 5.98 (d, J = 8.4 Hz, 1H), 4.39 (dd, J = 3.4, 7.8 Hz, 1H), 4.23 (dd, J = 3.4, 8.4 Hz, 1H), 4.09 (dt, J = 3.5, 7.9 Hz, 1H), 3.87 (dd, J = 3.5, 10.5 Hz, 1H), 3.67 (dd, J = 8.1, 10.5 Hz, 1H), 2.35 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 142.75, 139.49, 135.99, 135.96, 132.42, 132.29, 130.67, 130.49, 128.52, 126.66, 117.51, 110.78, 80.75, 77.99, 64.72, 42.39, 27.53, 27.44, 27.11, 21.84, 19.61. Anal. Calcd: C, 66.16; H, 6.81; N, 4.98. Found: C, 66.33; H, 7.16; N, 4.93.

Minor diastereomer **(*S*$_S$,2*S*,3*S*,4*S*)-(+)-*N*-(*p*-toluenesulfinyl)-2-amino-5-*tert*-butyldiphenylsilyloxy-3,4-isopropylidenedioxypentane nitrile (6c)**: 0.03 g (6%); $[\alpha]^{20}_D$ +96.8 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.50−7.53 (m, 5H), 7.39−7.30 (m, 7H), 7.19 (d, J = 6.8 Hz, 2H), 4.79 (d, J = 10.4 Hz, 1H), 4.50−4.4 (m, 1H), 4.2 (dd, J = 3.4, 10.4 Hz, 1H), 4.01 (dd, J = 3.3, 7.9 Hz, 1H), 3.93 (dt, J = 3.9, 7.4 Hz, 1H) 3.7 (dd, J = 4.0, 10.4 Hz, 1H), 3.55 (dd, J = 7.0, 10.5 Hz, 1H), 2.27 (s, 3 H), 1.36 (s, 3H), 1.3 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.72, 140.35, 135.92, 132.95, 132.82, 130.49, 130.38, 128.38, 128.33, 126.18, 117.26, 111.31, 80.41, 78.06, 64.22, 47.15, 27.53, 27.25, 21.80, 19.48.

(*S*$_R$,2*S*,3*S*,4*S*)-(−)-*N*-(*p*-Toluenesulfinyl)-2-amino-5-*tert*-butyldiphenylsilyloxy, 3,4-isopropylidenedioxypentane Nitrile (8). Chromatography afforded 0.36 g (65%) of a white solid; mp 118−119 °C; $[\alpha]^{20}_D$ −30.14 (*c* 0.7, $CHCl_3$); IR (KBr)

3020, 2337, 1576 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.58−7.51 (m, 5H), 7.40−7.31 (m, 7H), 7.23 (d, J = 8.0 Hz, 2H), 5.21 (d, J = 8.2 Hz, 1H), 4.28 (d, J = 3.4, 8.2 Hz, 1H), 4.1 (dd, J = 4.2, 7.8 Hz, 1H), 3.97 (dt, J = 4.1, 7.9 Hz, 1H), 3.75 (dd, J = 4.1, 10.1 Hz, 1H), 3.54 (dd, J = 8.1, 10.1 Hz, 1H), 2.33 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 0.91 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 142.71, 139.55, 136.00, 132.78, 132.58, 130.49, 128.36, 126.69, 117.04, 111.22, 81.42, 78.34, 64.63, 44.66, 27.45, 27.26, 21.83, 19.44; HRMS calcd for $C_{31}H_{38}N_2O_4SSiNa$ (M + Na) 585.2219, found 585.2239.

Minor diastereomer **(*S*$_R$,2*R*,3*S*,4*S*)-(+)-*N*-(*p*-toluenesulfinyl)-2-amino-5-*tert*-butyldiphenylsilyloxy-3,4-isopropylidenedioxypentane nitrile (8)**: 0.03 g (5%) of a white solid; mp 120−121 °C; $[\alpha]^{20}_D$ +7.58 (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.67−7.62 (m, 5H), 7.53 (d, J = 8.2 Hz, 2H), 7.42−7.38 (m, 5H), 7.28 (d, J = 8.0 Hz, 2H), 6.38 (d, J = 8.1 Hz, 1H), 4.42 (t, J = 5.6 Hz, 1H), 4.34−4.30 (m, 2H), 4.28−4.21 (m, 2H), 3.90−3.82 (m, 1H), 2.36 (s, 3H), 1.32 (s, 3H), 1.18 (s, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 142.54, 139.27, 135.85, 135.79, 132.22, 130.59, 130.52, 130.29, 128.32, 126.58, 118.02, 109.91, 61.69, 42.25, 27.20, 26.93, 24.98, 21.67, 19.41.

Preparation of (2*S*,3*S*,4*S*)-(−)-5-Benzyloxy-3,4-dihydroxy-2-amino pentanoic Acid Hydrochloride (9). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar was placed 0.21 g (0.5 mmol) of (+)-**6a**. Saturated ethereal HCl (20 mL) was added with vigorous stirring, which resulted in the immediate formation of white precipitate. A few drops of H_2O was added and the reaction mixture was stirred at room temperature for 12 h. At this time the solution was diluted with ether (25 mL), and the precipitated hydrochloride was filtered and dried under vacuum to give 0.12 g (95%) of a white solid: mp 145−150 °C; $[\alpha]^{20}_D$ −57.5 (*c* 0.2 MeOH); IR (KBr) 3410, 1690, 1458 cm^{-1}; ^{1}H NMR (CD_3OD) 7.36−7.25 (m, 5H), 4.77−4.71 (m, 2H), 4.57 (q, J = 11.7, 22 Hz, 2H), 4.37 (d, J = 9.7 Hz, 1H), 3.94 (d, J = 11.3 Hz, 1H), 3.79 (dd, J = 2.3, 11.2 Hz, 1H); ^{13}C NMR (CD_3OD) 169.84, 137.62, 127.95, 127.33, 127.26, 79.42, 73.14, 70.01, 66.40, 54.27; HRMS calcd for $C_{12}H_{18}NO_5$ (M + 1) 256.1185, found 256.1178.

(*S*$_S$,2*R*,3*S*,4*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-2-amino-5-hydroxy-3,4-isopropylidenedioxypentane Nitrile (10). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar and argon-filled balloon was placed (+)-**6c** (0.28 g, 0.5 mmol) in THF (10 mL). The solution was cooled to 0 °C, tetrabutylammonium fluoride (0.75 mmol, 0.75 mL of a 1 M solution in THF) was added, and the reaction mixture was stirred for 2 h until the reaction was complete as indicated by TLC. The reaction mixture was diluted with ether (30 mL) and washed with 1 N HCl (20 mL). The organic phase was separated, washed with water (20 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexane/ethyl acetate, 75:25) gave 0.12 g (77%) of a viscous oil; $[\alpha]^{20}_D$ +6.61 (*c* 1.9, $CHCl_3$); IR (neat) 3420, 2918, 2360 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.99 (d, J = 8.5 Hz, 1H), 4.27 (dd, J = 3.1, 8.6 Hz, 1H), 4.1 (dt, J = 3.9, 8.2 Hz, 1H), 3.99 (dd, J = 3.2, 8.0 Hz, 1H), 3.94 (br dd, J = 3.8, 10.8 Hz, 1H), 3.60 (br t, J = 9.2 Hz, 1H), 3.11 (br s, 1H), 2.37 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 143.07, 138.84, 130.67, 130.41, 126.69, 126.12, 117.34, 110.73, 80.29, 77.75, 62.69, 42.94, 27.36, 27.16, 21.84; HRMS calcd for $C_{15}H_{20}N_2O_4SNa$ (M + Na) 347.1042, found 347.1052.

(*S*$_R$,2*S*,3*S*,4*S*)-(−)-*N*-(*p*-Toluenesulfinyl)-2-amino-5-hydroxy-3,4-isopropylidenedioxypentane Nitrile (13). Purification by chromatography (hexane/ethyl acetate, 75:25) gave 0.11 g (71%) of a viscous oil; $[\alpha]^{20}_D$ −17.77 (*c* 1.4, $CHCl_3$); IR (neat) 3420, 2935, 2334 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.36 (d, J = 8.1 Hz, 1H), 4.16 (dd, J = 4.4, 8.1 Hz, 1H), 4.09 (dd, J = 4.4, 7.8 Hz, 1H), 3.98−3.93 (m, 1H), 3.76 (dd, J = 4.1, 11.3 Hz, 1H), 3.64 (dd, J = 6.4, 11.24 Hz, 1H), 2.37 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 142.58, 139.60, 129.92, 127.65, 117.01, 110.48, 78.67, 61.85, 45.46, 29.63, 26.95, 26.62, 21.36; HRMS calcd for $C_{15}H_{20}N_2O_4SNa$ (M + Na) 347.1042, found 347.1047

(2*R*,3*S*,4*S*)-(+)-2-Amino-5-hydroxy-3,4-isopropylidenedioxypentane Nitrile (11). In a 50-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar was placed (+)-**10** (0.10 g, 0.31 mmol) in ether (10 mL). Saturated ethereal HCl (5 mL) was introduced to the reaction mixture with vigorous stirring and resulted in the formation of a white precipitate. After the reaction mixture was stirred for 15 min, the precipitate was allowed to settle and most of the ether was decanted. The residue was washed with dry ether (2 × 20 mL) and dried under vacuum to give 0.055 g (81%) of the hydrochloride salt; mp 95−98 °C dec; $[\alpha]^{20}_D$ −10.73 (*c* 1.8, MeOH); IR (KBr) 3417, 2918, 2338 cm^{-1}; ^{1}H NMR (CD_3OD) δ 4.80 (d, J = 7.0 Hz, 1H), 4.29 (t, J = 7.5 Hz, 1H), 4.19−4.17 (m, 1H), 3.76 (t, J = 4 Hz, 2H), 1.44 (d, J = 3.0 Hz, 6H); ^{13}C NMR (D_2O) δ 113.99, 112.71, 78.68, 74.85, 61.06, 44.62, 26.53, 26.41; HRMS cacld for $C_8H_{17}N_2O_3$ (M + H) 187.1083, found 187.1075.

(2*S*,3*S*,4*S*)-(−)-2-Amino-3,4-isopropylidenedioxy-5-hydroxypentane nitrile (14). A similar procedure as above afforded 0.052 g (78%) of the hydrochloride salt as a white hydroscopic solid; mp 85−90 °C dec; $[\alpha]^{20}_D$ −2.11 (*c* 0.5, MeOH); IR (KBr) 3408, 2911, 2360 cm^{-1}; ^{1}H NMR (CD_3OD) δ 4.60 (d, J = 4.4 Hz, 1H), 4.18 (dd, J = 2.7, 8.1 Hz, 1H), 4.02−3.99 (m, 1H), 3.76−3.69 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (CD_3OD) δ 112.94, 111.65, 77.61, 73.79, 62.47, 45.97, 27.82, 27.57; HRMS calcd for $C_8H_{15}N_2O_3$ (M + H) 187.1083, found 187.1084.

(3*S*,4*S*,5*S*)-(−)-3-Amino-4,5-dihydroxytetrahydropyran-2-one (12). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar was placed 0.05 g (0.22 mmol) of hydrochloride (−)-**11** in ethereal HCl (10 mL). A few drops (4−5) of H_2O was added and the solution was vigorously stirred at room temperature for 12 h. At this time the reaction mixture was concentrated and the white precipitate was dried under high vacuum for 2 h. The residue was suspended in dry ethanol (5 mL) and 0.15 g (2.5 mmol) of isopropylene oxide was added under an argon atmosphere. After being stirred for 5 h at room temperature the solution was concentrated, dry ether (25 mL) was added, and most of the solvent was decanted. The solid residue was washed with ether (2 × 20 mL) and dried under high vacuum to give 0.013 g (36%) of a brown hydroscopic solid; mp 65−72 °C; $[\alpha]^{20}_D$ −4.2 (*c* 1.0, H_2O); IR (KBr) 3400−3100, 1787 cm^{-1}; ^{1}H NMR (D_2O) δ 4.17 (t, J = 3.3 Hz, 1H), 3.90−3.83 (m, 2H), 3.60 (dq, J = 7.0, 11.7 Hz, 2H); ^{13}C NMR (D_2O) δ 73.49, 68.41, 62.79, 58.35; the lactone has spectra properties identical with those reported for the enantiomer;[16,17] HRMS calcd for $C_5H_{10}NO_4$ (M + H) 148.0610, found 148.0610.

(3*R*,4*S*,5*S*)-(−)-3-Amino-4,5-dihydroxytetrahydropyran-2-one (15). A similar procedure gave 0.014 g (38%) of a viscous mass: $[\alpha]^{20}_D$ −2.3 (*c* 0.6, H_2O); ^{1}H NMR (D_2O) δ 4.17 (t, J = 3.3 Hz, 1H), 3.90−3.83 (m, 2H), 3.60 (dq, J = 7.0, 11.7 Hz, 2H); ^{13}C NMR (D_2O) δ 72.07, 67.44, 62.75, 59.13; spectral properties were nearly identical with those of (3*S*,4*S*,5*S*)-(−)-**12**.

Acknowledgment. This work was supported by a grant from the National Institutes of Health General Medical Sciences (NIGMS 57870).

Supporting Information Available: ^{1}H NMR spectra of compounds **5a**, **5b**, **5c**, **6a**, **6b**, **6c**, **8**, **9**, **10**, **11**, **12**, and **13** and an ORTEP view of (*S*$_S$,2*S*,3*S*,4*S*)-(+)-**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020302E

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