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Articles

Enantioselective Synthesis of (2*R*,4*S*)- and (2*S*,4*R*)-4-Hydroxypipecolic Acid from D-Glucoheptono-1,4-lactone

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Enantiomerically pure (2*R*,4*S*)-4-hydroxypipecolic acid [(+)-**1**] was synthesized from D-glucoheptono-1,4-lactone (**2**) via the 3,5-dideoxy-D-*xylo*-heptono-1,4-lactone (**7**). The latter was readily prepared by benzoylation of **2**, followed by β-elimination and diastereoselective hydrogenation of the resulting furanones (**4**). Compound **7** was converted into the 6,7-*O*-cyclohexylidene derivative **11**, which on treatment with tosyl chloride for long periods afforded the 2-chloro derivative **14**, the precursor of the azide **15**. Hydrogenolysis of **15** and protection of the amine gave the *N*-benzyloxycarbonyl derivative **19**, having the required configuration for the stereocenters at C-2 and C-4. Removal of the cyclohexylidene group by hydrolysis and subsequent oxidative degradation of the resulting glycol system afforded the hexurono-6,3-lactone **21** as a key intermediate. Chemoselective reduction of the aldehyde function of **21** led to the alcohol **23**, which was derivatized as the mesylate **24**. Releasing of the amino group by hydrogenation, and dissolution of resulting **25** in aqueous alkali, promoted the intramolecular nucleophilic displacement of the mesylate to give (+)-**1**. Its enantiomer [(−)-**1**] was prepared by a similar sequence starting from **2**.

Introduction

The naturally occurring (2*S*,4*R*)-4-hydroxypipecolic acid (*cis*-4-hydroxy-2-piperidinecarboxylic acid, (−)-**1**) has been isolated from leaves of *Calliandra pittieri* and *Strophantus scandeus*.[1] It was also identified as a constituent of cyclopeptide antibiotics, such as virginiamycin S_2.[2] Compound **1** was employed as precursor in the preparation of selective *N*-methyl-D-aspartate (NMDA) receptor antagonists.[3] Furthermore, (−)-**1** has served as a building block in a recent synthesis of palinavir, a potent peptidomimetic-based HIV protease inhibitor.[4] Also, substituted D- and L-pipecolic acids have been used as key intermediates in the synthesis of different types of other piperidine natural products.[5] For these reasons, *cis*-4-hydroxypipecolic acid (**1**) is an interesting target molecule for synthesis, which has attracted significant attention in recent years. In fact, racemic **1** has been

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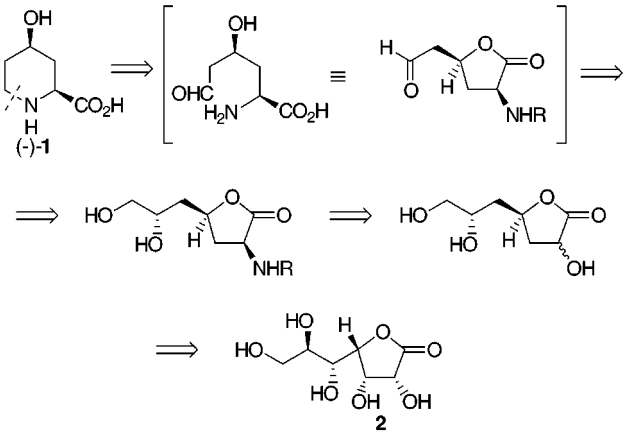
synthesized in our laboratory,[6] and some other procedures for the synthesis of racemic derivatives of **1** have appeared in the literature. These procedures include hydrogenation of 2-cyano-4-methoxypyridines at high pressures,[7] low-temperature acid-induced cyclization of a glycine cation equivalent,[8] or condensation of *N*-3-butenylbenzenemethanamine with glyoxylic acid followed by iminium ion cyclization.[3] Also, a patent on the preparation of an amide derivative of **1** from 4-hydroxypiperidine has been issued.[4b] The first synthesis of enantiomerically pure (−)-**1** was reported by Clark-Lewis and Mortimer,[9] who performed the chemical transformation of (−)-*trans*-4-hydroxypipecolic acid, isolated from leaves of *Acacia oswaldii*. Such a hydroxy acid was oxidized to the 4-oxo-L-pipecolic acid, which was then reduced to (−)-**1**. The same 4-ketoacid has been also synthesized in racemic[10] or chiral[11] forms, and it was employed as intermediate in another synthesis of (−)-**1** from L-aspartic acid.[12] Enzymatic or quinine resolution of racemic **1** led to the optically pure compound.[13] Gillard et al.[14] reported the chemical resolution of the racemic lactone prepared by the already mentioned procedure[3] consisting of the cyclization of a homoallylic iminium cation. As the lactone having the proper configuration was obtained in poor yields, an asymmetric version of this cyclization using a chiral homoallylic amine was developed. However, low levels of diastereoselective induction were observed, and a "resolving" agent was required for the separation of the resulting diastereomeric lactones.

We wish to report here an efficient synthesis of enantiomerically pure (2*S*,4*R*)- and (2*R*,4*S*)-4-hydroxypipecolic acids [(−)-**1** and (+)-**1**, respectively] using commercially available and inexpensive D-*glycero*-D-*gulo*-heptono-1,4-lactone (**2**, D-glucoheptono-1,4-lactone) as chiral template.

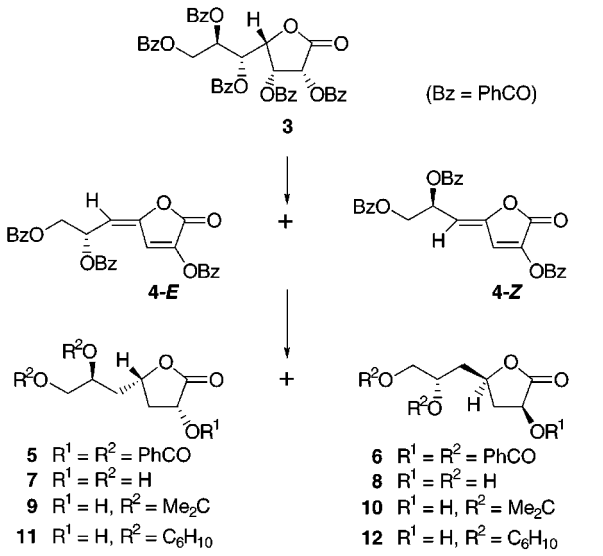
Results and Discussion

A retrosynthetic analysis for **1** (Scheme 1) suggests the disconnection of the C-6−N bond to produce a synthon equivalent to a 2-aminohexono-1,4-lactone having an aldehyde group at C-6. This function may be generated by oxidative degradation of a terminal glycol and the amino group at C-2 by substitution of HO-2 in the precursor 3,5-dideoxyheptono-1,4-lactone, which can be obtained from D-*glycero*-D-*gulo*-heptono-1,4-lactone (D-glucoheptono-1,4-lactone, **2**). We have already reported[15] that the per-*O*-benzoyl-heptonolactone **3**, when treated with 10% triethylamine in chloroform, undergoes a double β-elimination process to give a mixture of 2-furanones **4-*E*** and **4-*Z*** (∼1:1 ratio) in 90% yield (Scheme 2). Hydrogenation of the mixture of furanones, under various conditions, took place with stereocontrol induced by the stereocenter in the lateral chain to give two diastereoisomers of the four theoretically possible. The stereoisomers obtained are those which have a cis relationship for the substituents of the lactone ring. The 3,5-dideoxylactone derivative **5** (xylo configuration) was isolated pure (40% yield) by recrystallization from the reaction mixture. However, attempts to isolate the other isomer (**6**) or to separate the mixture of the free lactones (**7** and **8**) by simple chromatographic procedures were unsuccessful. Therefore, other derivatives that could facilitate the separation of the diastereoisomers and could be useful for the synthesis of **1** were prepared. The acetonation of the mixture of **7** and **8** was first attempted. The resulting acetonides **9** and **10** showed different mobility on TLC, but they were rather sensitive to the acidity of the silica gel and they underwent considerable hydrolysis during the column chromatography purification. For this reason, the isopropylidene was replaced by the cyclohexylidene group, which is known to be more stable to acidic conditions.[16] Cyclohexylidenation of **7** and **8** with cyclohexanone catalyzed by *p*-toluenesulfonic acid in the

Scheme 1



Scheme 2



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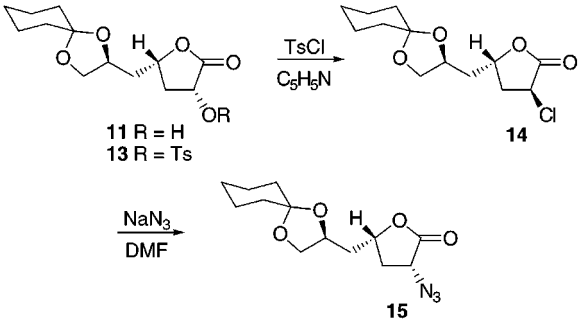
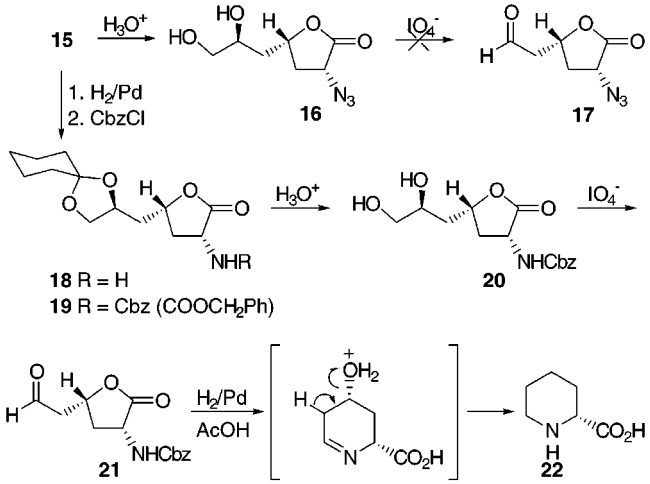
Scheme 3



Scheme 4



presence of anhydrous $CuSO_4$ afforded a mixture of **11** and **12**. These compounds were also differentiated by TLC (R_f 0.39 and 0.35, respectively) and were successfully separated by column chromatography. The 6,7-*O*-cyclohexylidene derivatives **11** and **12** are conveniently protected for the introduction of the amino group at C-2. As the ketal derivative **11** can be readily obtained from crystalline and enantiomerically pure **5**, the synthetic sequences were conducted in the first instance starting from such a compound.

The replacement of HO-2 by NH_2 in **11** should be accomplished with retention of C-2 configuration (*R*) to obtain a suitable precursor of (2*R*,4*S*)-(+)-**1**. The sulfonylation of the HO-2 of **11** (Scheme 3) was performed with tosyl chloride in pyridine, and the progress of the reaction was monitored by TLC. The tosylation took place quite rapidly, affording the less polar tosylate **13** (R_f 0.41). However, together with **13**, an even less polar product (R_f 0.61) was detected. The proportion of the latter in the mixture increased with the reaction time, and it was the very major component after 22 h. At this time, small amounts of **13** still remained, but longer periods result in incipient epimerization at C-2. Therefore, the reaction mixture was processed and the compound was isolated by column chromatography in 82% yield, and it was identified as the 2-chloro derivative **14**. The configuration of C-2 in **14** was established by ^{1}H NMR spectroscopy. As we have previously described[15,17] and in agreement with earlier studies on the elucidation of the geometry of 2,4-disubstituted butyrolactones[18] (4,5-dihydro-3,5-disubstituted-(3*H*)-furan-2-ones), the large values for the coupling constants (*J*) between H-3,3′ with H-2 and H-4 indicate a threo relationship for the substituents on C-2 and C-4. This situation is encountered in tosylate **13** ($J_{2,3} = 8.4$ Hz, $J_{2,3'} = J_{3',4} = 10.2$ Hz, $J_{3,4} = 5.2$ Hz), which bears a cis orientation for the ring substituents. On the contrary, the relatively small *J* values for the H-2 signal of **14** ($J_{2,3} = 2.6$ Hz, $J_{2,3'} = 7.0$ Hz) indicate that H-2 bisects the H-3−C-3−H-3′ angle and dictates a trans relationship for the substituents of the lactone ring at C-2 and C-4. Furthermore, the similar $J_{3,4}$ and $J_{3',4}$ values found for **13** and **14** (5.5 and 8.0 Hz, respectively) suggest that no important conformational changes have occurred.

The in situ conversion of **11** into **14**, in one step and with high yield, was very convenient for the synthesis, as the chloride at C-2 has the proper configuration for the nucleophilic substitution by azide. In fact, this reaction was readily performed by treatment of **14** with sodium azide in DMF at room temperature for 24 h. The crystalline azide derivative **15** was obtained in 89% yield. The stereochemistry at C-2 was confirmed on the basis of the ^{1}H NMR spectrum of **15**, which showed again large values for $J_{2,3}$ (8.4 Hz) and $J_{2,3'}$ (10.6 Hz) indicating a cis relationship for the substituents at C-2 and C-4 of the 1,4-lactone ring. Thus, compound **15** posseses the desired *R* configuration at C-2, and the whole transformation from **11** to **15** proceeded in a yield higher than 70%. Therefore, although it has been described that the substitution of a triflate group at C-2 of aldonolactones by azide may occur with retention of C-2 configuration,[19] in view of our satisfactory results, the alternative route via the triflate derivative of **11** was not investigated.

The aldehyde postulated as retrosynthetic precursor of (+)-**1** (Scheme 1) could be prepared from **15**, after hydrolysis of the protecting ketal followed by degradative oxidation of the glycol system (Scheme 4). The removal of the cyclohexylidene group was carried out with 0.5 N aqueous HCl in methanol. Evaporation of the solvent from the reaction mixture at 50 °C, under diminished pressure, produced also the elimination of the cyclohexanone released by hydrolysis. After five evaporations, **16** was obtained in 86% yield, after filtration through a short silica gel column. The oxidative degradation of the glycol group of **16** was conducted with sodium periodate under a variety of conditions, but the expected aldehyde **17** could not be obtained. Also, intractable mixtures were formed when sodium periodate adsorbed on silica gel[20] was employed as oxidizing agent, or when the "one-pot" removal of the ketal and oxidation with periodic acid pentahydrate[21] was attempted. Examples of unstable molecules containing both azido and aldehyde functions were found in the literature.[22] The fact that the preparation of **17** from **16** was unsuccessful was rather disappointing, as we expected to obtain (+)-**1** as product of the hydrogenolysis of the azide group of **17** to amine, followed by intramolecular reductive amination of the aldehyde.

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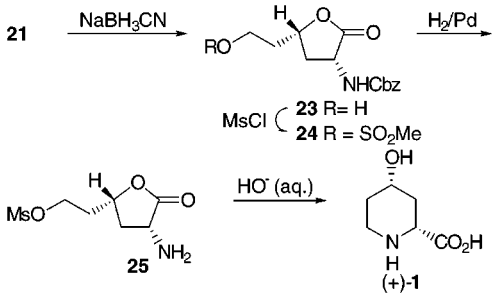
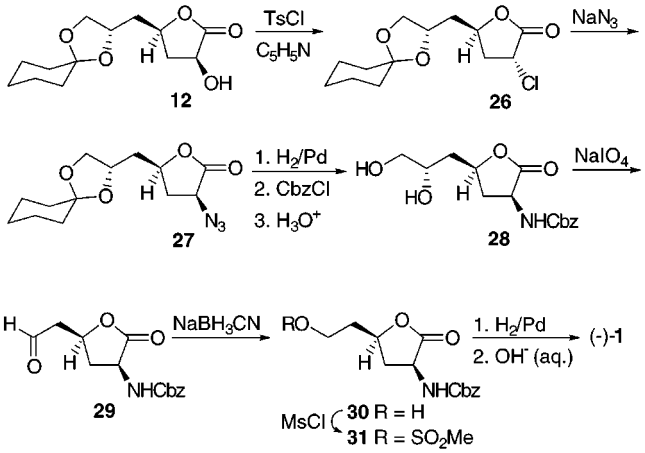
Scheme 5



Scheme 6



In view of these negative results, the original strategy was modified, and the reduction of the azide prior to the oxidation of the 1,2-diol system was studied.

Hydrogenation of **15** in EtOAc afforded the corresponding amine **18**. This crude product, dissolved in EtOAc, was treated with benzyl chloroformate in the presence of saturated aqueous $NaHCO_3$ to give the crystalline benzyl carbamate **19**. The benzyloxycarbonyl was a convenient protective group for the amine, as it may be removed during the hydrogenolysis, also required for the intramolecular reductive amination of the aldehyde. For the preparation of the aldehyde **21** from **19** the cyclohexylidene group of the latter was removed by hydrolysis with HCl in H_2O/MeOH, affording the diol **20** in crystalline form and in 94% yield. The oxidative cleavage of the glycol with sodium periodate gave the hexurono-6,3-lactone derivative **21**, which, in contrast with the azido aldehyde **17**, could be purified by flash chromatography (84% yield). This relatively higher stability of carbamates with respect to azides in molecules that also hold an aldehyde function has been previously observed.[22c] The next step of the synthesis, the hydrogenolysis of **21** to promote the cyclization to the piperidine, was attempted. Unfortunately, this reaction led to (+)-**1** as a minor product (<20%), and the major product was spectroscopically identified as pipecolic acid (**22**). The formation of this compound suggests the β-elimination of the HO group at C-4 in the intermediate imine derivative (Scheme 4), favored by the acetic acid employed as solvent, and the total hydrogenation. The conversion of **21** into (+)-**1** was also unsuccessful when milder acidic or neutral conditions were employed. Therefore, a different strategy was employed for the construction of the piperidine ring.

We still considered that **21** was a suitable precursor of (+)-**1**, as the amino and hydroxyl functions are properly located and with the required configuration. Ring closure may be promoted by the nucleophilic displacement of a leaving group at C-6 by intramolecular attack of the amine. To introduce a nucleofuge at C-6, the aldehyde group of **21** was reduced to alcohol (Scheme 5). We have previously succeeded in the chemoselective reduction of an aldehyde, without affecting the lactone carbonyl, employing a methanolic solution of $NaBH_3CN$ at pH $\sim$ 4.[23] Such a reaction when applied to **21** afforded 2-(*N*-benzyloxycarbonyl)amino-2,3,5-trideoxy-L-*threo*-hexono-1,4-lactone (**23**) in 89% yield. This compound gave the same spectral data as the corresponding racemate, previously synthesized in this laboratory.[6] Mesylation of **23** employing 1.5 molar equiv of methanesulfonyl chloride and pyridine in dichloromethane gave the 6-*O*-methanesulfonyl derivative **24** in 85% yield.

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Removal of the N-protecting benzyloxycarbonyl group was readily accomplished by hydrogenolysis with 10% Pd/C to give **25** in almost quantitative yield. Since **25** decomposes on storage, it was immediately used after the hydrogenation step. The crude syrup was dissolved in 0.1 M aqueous KOH, conditions that promoted the opening of the lactone and the cyclization by nucleophilic displacement of the mesylate by the amino group. The resulting (2*R*,4*S*)-4-hydroxypipecolic acid [(+)-**1**] was purified by ion exchange with Dowex 50W (H^+) resin. Its optical rotation ($[\alpha]_D$ +22.0) was in excellent agreement with the absolute value reported for the enantiomer,[9,14] but opposite in sign. Also, the NMR spectra were coincident with those described[6] and showed that (+)-**1** was obtained in high degree of purity.

The synthetic route described above was employed for the preparation of (−)-**1**, starting from **12** (Scheme 6). The 2-chloro derivative **26** was obtained by tosylation of **12** in pyridine, for long periods, as it was already described for the preparation of **14**. Treatment of **26** with sodium azide led to the 2-azido derivative **27** having (as **12**) the *S* configuration at C-2, because of the double configurational inversion (from **12** to **26** and from **26** to **27**). The similar pattern of chemical shifts and coupling constant values for the ^1H NMR signals of azide derivatives **15** and **27** indicated that both of them possess the same relative stereochemistry for the ring substituents at C-2 and C-4.

The azide group of **27** was reduced to amine and N-protected as the carbobenzoxy derivative. The ketal was hydrolyzed with 0.5 N HCl in H_2O−MeOH to afford crystalline **28**, the analogue of arabino configuration of **20**. Sodium periodate oxidation of the 1,2-diol system of **28** led to the aldehyde **29** in 89% yield. The removal of the stereocenter at C-6, which makes it possible to discriminate between compounds **20** and **28**, led to the enantiomeric aldehyde derivatives **21** and **29**. Therefore, compound **29** and the subsequents in the D-*threo* series (**30**, **31**) exhibited spectral properties identical to those of their respective analogues in the L-*threo* configuration (**23**, **24**).

The aldehyde function of **29** was chemoselectively reduced to the alcohol **30**, which was converted into the mesylate derivative **31**. Hydrogenolysis of the N-protecting carbamate led to the free amino group at C-2, which attacks C-6 with nucleophilic substitution of the mesylate. The resulting (2*S*,4*R*)-4-hydroxypipecolic acid [(−)-**1**] was purified by ion exchange chromatography and

isolated in 73% yield. The optical rotation ($[\alpha]_D$ −22.8) and the spectral properties were in good agreement with the reported data.[6,9,14]

Experimental Section

General Methods. Melting points are uncorrected. Optical rotations were measured at 25 °C. Column chromatographic separations were performed with silica gel 60, 240−400 mesh (Merck). Analytical TLC was performed on silica gel 60 F_{254} (Merck) precoated plates (0.2 mm). Visualization of the spots was effected by exposure to UV light or charring with a solution of 5% sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde; for amino acids, 0.25% ninhydrin in acetone was used. Solvents were reagent grade and in most cases were dried and distilled prior to use, according to standard procedures.

6,7-*O*-Cyclohexylidene-3,5-dideoxy-D-*xylo*-heptono-1,4-lactone (11). To a solution of **7** (0.59 g, 3.36 mmol) in dry cyclohexanone (5 mL) were added anhydrous $CuSO_4$ (∼2 g) and *p*-toluenesulfonic acid (10 mg). The mixture was vigorously stirred at room temperature for 20 h, when TLC showed complete conversion of starting **7** (R_f 0.45, 4:1 EtOAc−EtOH) into a less polar product (R_f 0.88). The suspension was filtered and the solvent evaporated. The resulting syrup was purified by filtration through a short column of silica gel, with 4:1 toluene−EtOAc as eluent. Fractions containing the product of R_f 0.39 (1:1 toluene−EtOAc) were collected and concentrated to afford **11** (0.77 g, 89%), which crystallized spontaneously. After recrystallization from 1:1 Et_2O−hexane it gave the following data: mp 87.5−88 °C; $[\alpha]_D$ −30.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.64−4.50 (m, 2H), 4.26 (m, 1H), 4.08 (dd, J = 5.9, 8.0 Hz, 1H), 3.54 (dd, J = 7.0, 8.0 Hz, 1H), 3.25 (bs, 1H), 2.75 (ddd, J = 5.1, 8.4, 13.0 Hz, 1H, H-3), 2.00−1.83 (m, 3H), 1.56−1.38 (m, 10 *H*-cyclohexylidene); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.4, 109.8, 74.6, 72.1, 69.1, 68.4, 40.1, 37.6, 36.6, 35.0, 25.0, 23.9, 23.8.

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.29; H, 7.73.

6,7-*O*-Cyclohexylidene-3,5-dideoxy-D-*xylo*- (11) and -D-*arabino*-heptono-1,4-lactone (12). An approximately equimolar mixture of the dideoxyheptonolactones **7** and **8** (0.87 g, 4.96 mmol) was treated with cyclohexanone (7 mL) in the presence of $CuSO_4$ (∼2 g) and *p*-toluenesulfonic acid (10 mg), in the conditions described above. After the same workup, TLC showed two main spots having R_f 0.39 and 0.35 (1:1 toluene−EtOAc). Two successive chromatographic purifications led to two pure fractions corresponding to compounds **11** (0.41 g, 32%) and **12** (0.45 g, 35%). The third fraction was a mixture of **11** and **12** (0.10 g, 7.5%; overall yield 74.5%).

Compound **11** gave the same physical and spectral properties as the acetal obtained from pure **7**, described above. Compound **12** was isolated as a syrup: $[\alpha]_D$ −18.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.54 (m, 2H), 4.22 (m, 1H), 4.07 (dd, J = 6.3, 8.0 Hz, 1H), 3.76 (bs, 1H), 3.62 (dd, J = 6.9, 8.0 Hz, 1H), 2.76 (ddd, J = 5.2, 8.4, 12.8 Hz, 1H, H-3), 2.18−1.83 (m, 3H), 1.58−1.37 (m, 10 *H*-cyclohexylidene); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.3, 109.9, 74.2, 71.3, 68.6, 68.4, 38.5, 36.8, 36.5, 35.0, 25.0, 23.9, 23.8.

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H; 7.87. Found: C, 61.36; H, 7.75.

6,7-*O*-Cyclohexylidene-3,5-dideoxy-2-*O*-(*p*-toluenesulfonyl)-D-*xylo*-heptono-1,4-lactone (13) and -2-chloro-6,7-*O*-cyclohexylidene-2,3,5-trideoxy-D-*lyxo*-heptono-1,4-lactone (14). To a solution of **12** (1.0 g, 3.90 mmol) in dry pyridine (10 mL), cooled at 0 °C, was added tosyl chloride (2.23 g, 11.70 mmol), and the mixture was allowed to warm to room temperature. A less polar product (R_f 0.41, 3:1 cyclohexane−acetone) was first formed, which was further transformed into an even faster moving compound (R_f 0.61). The latter was the major product after 22 h. The reaction mixture was diluted with dichloromethane (200 mL) and washed with aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic extract was dried ($MgSO_4$) and concentrated, affording a syrup, which was chromatographed using 8:1 cyclohexane−acetone as solvent. Fractions of the column having the product of R_f 0.61 were collected and concentrated to give syrupy **14** (0.88 g, 82%): $[\alpha]_D$ −41.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.89 (m, 1H), 4.38 (dd, J = 2.6, 7.0 Hz, 1H, H-2), 4.21 (m, 1H), 4.05 (dd, J = 5.9, 8.0 Hz, 1H), 3.50 (dd, J = 7.0, 8.0 Hz, 1H), 2.73 (ddd, J = 2.6, 5.5, 14.3 Hz, 1H, H-3), 2.36 (ddd, J = 7.0, 8.0, 14.3 Hz, 1H, H-3′), 1.86 (m, 2H), 1.53−1.37 (m, 10 *H*-cyclohexylidene); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7, 109.8, 77.1, 72.0, 69.0, 51.1, 39.4, 36.5, 34.9, 24.9, 23.8, 23.7.

Anal. Calcd for $C_{13}H_{19}ClO_4$: C, 56.83; H, 6.97. Found: C, 57.22; H, 7.05.

From later fractions of the column the compound having R_f 0.41 was obtained and spectroscopically characterized as **13** (0.08 g, 5%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84, 7.35 (d, J = 8.5 Hz, 4 *H*-aromatic), 5.10 (dd, J = 8.4, 10.2 Hz, 1H, H-2), 4.57 (m, 1H), 4.20 (m, 1H), 4.05 (dd, J = 6.2, 8.0 Hz, 1H), 3.50 (dd, J = 6.6, 8.0 Hz, 1H), 2.85 (ddd, J = 5.2, 8.4, 13.2 Hz, 1H, H-3), 2.43 (s, 3H), 2.10 (td, J = 10.2, 13.2 Hz, 1H, H-3′), 1.87 (m, 2H), 1.55−1.37 (m, 10 *H*-cyclohexylidene); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.7, 109.9, 74.7, 73.2, 71.8, 69.0, 40.1, 36.6, 36.1, 35.0, 25.0, 23.9, 23.7.

2-Azido-6,7-*O*-cyclohexylidene-2,3,5-trideoxy-D-*xylo*-heptono-1,4-lactone (15). To a solution of **14** (1.47 g, 5.36 mmol) in anhydrous DMF (10 mL) was added sodium azide (0.52 g, 8.0 mmol). The mixture was stirred at room temperature for 24 h. Then, EtOAc (20 mL) was added, and the salts were filtered off and washed with EtOAc. The filtrate and washing liquids were collected and washed with saturated aqueous NaCl (2 × 50 mL). The extract was dried ($MgSO_4$) and concentrated. The resulting syrup was filtered through a short column of silica gel, affording **15**, which crystallized upon addition of hexane (1.34 g, 89%): mp 57−57.5 °C; $[\alpha]_D$ +10.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.63 (m, 1H), 4.33 (dd, J = 8.4, 10.6 Hz, 1H, H-2), 4.25 (m, 1H), 4.05 (dd, J = 6.2, 8.0 Hz, 1H), 3.55 (dd, J = 6.6, 8.0 Hz, 1H), 2.73 (ddd, J = 5.5, 8.4, 13.0 Hz, 1H, H-3), 2.01−1.81 (m, 3H), 1.55−1.38 (m, 10 *H*-cyclohexylidene); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8, 109.8, 75.5, 72.0, 69.0, 57.6, 40.1, 36.7, 35.5, 35.0, 25.1, 24.0, 23.8.

Anal. Calcd for $C_{13}H_{19}N_3O_4$: C, 55.51; H, 6.81. Found: C, 55.73; H, 6.94.

2-Azido-2,3,5-trideoxy-D-*xylo*-heptono-1,4-lactone (16) and Its Attempted Oxidative Degradation to 5-Azido-2,4,5-trideoxy-L-*threo*-hexurono-6,3-lactone (17). To a solution of **15** (0.372 g, 1.32 mmol) in MeOH (3 mL) was added 0.5 N aqueous HCl (4 mL). The turbid mixture was concentrated at 50 °C under diminished pressure. The residue was dissolved in HCl−MeOH, and it was concentrated as before. The procedure was repeated three more times, when total consumption of the starting material was observed by TLC. The residue was purified by column chromatography (EtOAc) to give a syrup that was spectroscopically characterized as **16** (0.263 g, 86%): ^{1}H NMR (200 MHz, D_2O) δ 4.75 (m, 1H), 4.71 (dd, J = 8.7, 11.3 Hz, 1H, H-2), 3.84 (m, 1H), 3.57 (dd, J = 4.4, 11.7 Hz, 1H), 3.46 (dd, J = 6.4, 11.7 Hz, 1H), 2.83 (ddd, J = 5.5, 8.7, 12.8 Hz, 1H, H-3), 2.00−1.69 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.8, 76.5, 68.5, 65.8, 58.4, 38.3, 34.9.

To a solution of **16** (0.050 g, 0.25 mmol) in CH_2Cl_2 (3 mL) was added the $NaIO_4$−SiO_2 reactive[20] (0.76 g), and the mixture was stirred in the dark. After 6 h, no starting material was detected by TLC. The suspension was filtered and the silica gel washed with CH_2Cl_2 (20 mL). Evaporation of the solvent gave a syrup (22 mg) that was shown by NMR to be a complex mixture, which was not further analyzed.

2-Amino-6,7-*O*-cyclohexylidene-2,3,5-trideoxy-D-*xylo*-heptono-1,4-lactone (18) and 2-(*N*-Benzyloxycarbonyl)-amino-6,7-*O*-cyclohexylidene-2,3,5-trideoxy-D-*xylo*-heptono-1,4-lactone (19). Compound **15** (0.41 g, 1.46 mmol) dissolved in EtOAc (25 mL) was hydrogenated at atmospheric pressure for 1 h, in the presence of 10% Pd/charcoal. TLC showed that the starting material (R_f 0.31, 3:1 toluene−EtOAc) disappeared and a more polar product was detected (R_f 0.00). The catalyst was filtered, and the filtrate was concentrated to a syrup that was purified through a short column of silica

gel (5 g) using mixtures of EtOAc with increasing amounts of EtOH (from 0 to 25%). Fractions containing the product of R_f 0.30 (4:1 EtOAc−EtOH) were pooled and concentrated, affording **18** (0.32 g, 85%) as a colorless syrup: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.52 (m, 1H), 4.24 (m, 1H), 4.05 (dd, J = 5.8, 8.0 Hz, 1H), 3.73 (dd, J = 8.4, 12.0 Hz, 1H, H-2), 3.51 (dd, J = 7.0, 8.0 Hz, 1H), 2.70 (ddd, J = 5.1, 8.4, 13.1 Hz, 1H, H-3), 1.88−1.70 (m, 3H), 1.55−1.36 (m, 10 *H*-cyclohexylidene).

Hydrogenation of **15** (0.72 g, 2.56 mmol) was repeated as above. The catalyst was filtered and the filtrate concentrated to a final volume of about 10 mL. This EtOAc solution was energically stirred at 0 °C with saturated aqueous $NaHCO_3$ (10 mL), and benzyl chloroformate (0.55 mL, 3.84 mmol) was added. After 3 h, the mixture was diluted with EtOAc, and the organic layer was separated, washed with 5% aqueous HCl, with saturated aqueous NaCl, and then with 10% aqueous $NaHCO_3$, dried, and concentrated. The syrup was chromatographed on silica gel with 15:1 to 5:1 toluene−EtOAc as eluent. Upon evaporation of the solvent, compound **19** (0.70 g, 70%) crystallized spontaneously: mp 95−96 °C; $[\alpha]_D$ −39.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (s, 5 *H*-aromatic), 5.61 (d, J = 6,2 Hz, 1H, N*H*), 5.13 (s, 2H, PhCH_2), 4.59 (m, 1H), 4.43 (m, 1H), 4.23 (m, 1H), 4.07 (dd, J = 5.8, 8.0 Hz, 1H), 3.52 (dd, J = 7.3, 8.0 Hz, 1H), 2.82 (m, 1H), 1.96−1.80 (m, 3H), 1.57−1.39 (m, 10 *H*-cyclohexylidene); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.2, 155.9, 135.9, 128.4, 128.0, 109.7, 75.4, 72.1, 69.0, 67.2, 51.6, 39.9, 36.6, 35.0, 35.0, 23.9, 23.7.

Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64,77; H, 6.99; N, 3.50. Found: C, 64.76; H, 7.08; N, 3.55.

2-(*N*-Benzyloxycarbonyl)amino-2,3,5-trideoxy-D-*xylo*-heptono-1,4-lactone (20). To a solution of **19** (0.46 g, 1.18 mmol) in MeOH (2 mL) was added 0.5 N aqueous HCl (4 mL), and the turbid mixture was concentrated. The dissolution and evaporations were repeated four more times, as described for the preparation of **16**. The residue crystallized upon addition of MeOH−Et_2O, affording compound **20** (0.34 g, 94%): R_f 0.36 (EtOAc); mp 145 °C; $[\alpha]_D$ −29.2 (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 7.35 (s, 5 *H*-aromatic), 5.15 (s, 2H, PhCH_2), 4.77 (m, 1H), 4.60 (dd, J = 8.4, 10.2 Hz, 1H, H-2), 3.88 (m, 1H), 3.52 (m, 2H), 2.72 (ddd, J = 5.2, 8.4, 12.3 Hz, 1H, H-3), 2.13−1.69 (m, 3H); ^{13}C NMR (50 MHz, CD_3OD) δ 177.0, 158.2, 138.0, 129.5, 129.1, 128.9, 76.3, 69.8, 67.8, 67.5, 52.7, 40.5, 36.4.

Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58,25; H, 6.20; N, 4,53. Found: C, 57,96; H, 6,53; N, 4.44.

5-(*N*-Benzyloxycarbonyl)amino-2,4,5-trideoxy-L-*threo*-hexurono-6,3-lactone (21). To a solution of **20** (0.18 g, 0.58 mmol) in dry MeOH (10 mL) was added sodium periodate (0.15 g, 0.70 mmol). After 3 h, a main spot was detected by TLC (R_f 0.74, EtOAc) and no starting **20** remained. The reaction mixture was diluted with EtOAc (15 mL), and the salts were filtered. The filtrate was concentrated and the residue purified by flash chromatography. Compound **21** (0.14 g, 84%) was obtained as a rather unstable syrup that, in subsequent preparations, was used crude for the next step: ^{1}H NMR (200 MHz, $CDCl_3$) (numbered as a lactone derivative) δ 9.68 (bs, 1H, *H*CO), 7.32 (s, 5 *H*-aromatic), 5.75 (d, J = 7.0 Hz, 1H, N*H*), 5.08 (s, 2H, PhCH_2), 4.81 (m, 1H), 4.44 (m, 1H), 3.05−2.70 (m, 3H), 1.94 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.4, 174.1, 156.0, 135.9, 128.4, 128.2, 128.0, 72.0, 67.2, 51.2, 48.1, 35.0.

Hydrogenolysis of 21. Compound **21** (53 mg) dissolved in 10:1 EtOH−glacial acetic acid (10 mL) was hydrogenated at atmospheric pressure in the presence of 10% Pd−C as catalyst. The suspension was filtered, and the liquids were concentrated to a syrup, which was purified through a column of Dowex 50 W (H^+) resin. The column was washed with water and then eluted with 0.5 M aqueous pyridine. Concentration of the fractions, which showed by TLC a main spot (ninhydrin positive) having R_f 0.25 (13:4:2:1 MeCN−EtOH−H_2O−AcOH), afforded syrupy pipecolic acid (**22**, 12 mg). Its spectral properties were identical to those reported in the literature[24] for authentic **22**.

(24) (a) Johnson, R. L.; Rajakumar, G.; Mishra, R. M. *J. Med. Chem.* **1986**, *29*, 2100. (b) *Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra*; Aldrich: Milwaukee, 1992; Vol. 1, pp 889 A−C, 1085 B.

2-(*N*-Benzyloxycarbonyl)amino-2,3,5-trideoxy-L-*threo*-hexono-1,4-lactone (23). To a solution of crude **21** (97 mg, 0.35 mmol) in MeOH (7 mL) were added a small crystal of methyl orange and $NaBH_3CN$ (11 mg, 0.18 mmol). The mixture was stirred at room temperature, and the red color of the solution (pH 3.1, red; pH 4.4, yellow) was maintained by dropwise addition of 1 N methanolic HCl. After 1 h, no starting **21** was detected by TLC, and the reaction solvent was evaporated. The residue was extracted with EtOAc and the extract concentrated to afford an oil, which was chromatographed on silica gel using 1:1 toluene−EtOAc as solvent. Compound **23** (87 mg, 89%) gave $[\alpha]_D$ −29.5 (*c* 0.9, $CHCl_3$) and spectral properties identical to those of the racemic product:[6] ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.6, 156.1, 135.9, 128.5, 128.3, 128.1, 75.7, 67.3, 58.6, 51.7, 37.6, 36.1.

2-(*N*-Benzyloxycarbonyl)amino-6-*O*-methanesulfonyl-2,3,5-trideoxy-L-*threo*-hexono-1,4-lactone (24). A solution of **23** (0.17 g, 0.62 mmol) and pyridine (0.16 mL) in dry CH_2Cl_2 (5 mL) was cooled at 0 °C, and methanesulfonyl chloride (0.07 mL, 0.93 mmol) was added. The mixture was allowed to warm to room temperature, and it was stirred for 24 h, when no starting material but a faster moving spot (R_f 0.69, 1:3 toluene−EtOAc) was detected by TLC. The solution was diluted with CH_2Cl_2 (40 mL), washed with 5% aqueous HCl and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography with 1:1 toluene-EtOAc as solvent, affording **24** (0.19 g, 85%): $[\alpha]_D$ −40.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32 (s, 5 *H*-aromatic), 5.75 (d, J = 6.7 Hz, 1H, N*H*), 5.09 (s, 2H, PhCH_2), 4.50 (m, 2H), 4.33 (m, 2H), 3.00 (s, 3H), 2.73 (m, 1H), 2.14−1.80 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.9, 155.9, 135.9, 128.5, 128.3, 128.1, 73.8, 67.3, 65.7, 51.5, 37.2, 35.4, 34.7.

Anal. Calcd for $C_{15}H_{19}NO_7S$: C, 50.41; H, 5.76; S, 8.97. Found: C, 50.80; H, 5.62; S, 9.22.

(2*R*,4*S*)-4-Hydroxypipecolic Acid [(+)-1]. Compound **24** (0.10 g, 0.28 mmol) was dissolved in absolute EtOH (10 mL) and hydrogenated in the presence of 10% Pd/C (20 mg) at normal pressure and room temperature for 2 h. The reaction mixture showed by TLC a single spot having R_f 0.34 (3:1 EtOAc−MeOH) and no starting material remaining. The catalyst was filtered and the filtrate concentrated to give **25** (61 mg, 96%), which was employed without further purification for the next step. The free amine **25** (61 mg, 0.27 mmol) was dissolved in 0.1 M aqueous KOH (5 mL) and stirred at room temperature for 30 min. The solution was made neutral with 1 M aqueous HCl and concentrated to a final volume of about 0.5 mL. This solution was acidified (pH 4) with 1 M HCl and applied to a column filled with Dowex 50 W (H^+) resin. The column was washed with water and then eluted with 0.5 M aqueous pyridine. Fractions that gave the positive ninhydrin test were pooled and freeze-dried, affording (+)-**1** (32 mg, 81%), R_f 0.21 (13:4:2:1 MeCN−EtOH−H_2O−AcOH). The compound could not be induced to crystallize: $[\alpha]_D$ +22.0 (*c* 0.8, H_2O) (lit.[9] $[\alpha]_D$ −17; lit.[14] $[\alpha]_D$ −23.5 for the enantiomer); ^{13}C NMR (50 MHz, D_2O) δ 174.3, 66.4, 58.8, 42.3, 35.6, 30.8.

2-Chloro-6,7-*O*-cyclohexylidene-2,3,5-trideoxy-D-*ribo*-heptono-1.4-lactone (26). Compound **12** (0.40 g, 1.56 mmol), dissolved in pyridine (5 mL), was treated with tosyl chloride (0.89 g, 4.68 mmol) as described for the preparation of **14**. The 2-chloro derivative **26** was isolated by precipitation with cyclohexanes−EtOAc (0.36 g, 83%). Recrystallization from the same solvents gave crystals: mp 79−80 °C; $[\alpha]_D$ −1.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.89 (m, 1H), 4.45 (t, $J \approx$ 5.1 Hz, 1H, H-2), 4.19 (m, 1H), 4.06 (dd, J = 6.2, 8.0 Hz, 1H), 3.61 (dd, J = 6.6, 8.0 Hz, 1H), 2.55 (t, $J \approx$ 5.1 Hz, 2H), 2.14−1.85 (m, 2H), 1.57−1.37 (m, 10 *H*-cyclohexylidene); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 110.0, 76.4, 71.1, 68.5, 51.0, 38.6, 37.6, 36.5, 35.0, 25.0, 23.9, 23.7.

Anal. Calcd for $C_{13}H_{19}ClO_4$: C, 56.83; H, 6.97. Found: C, 57.15; H, 7.10.

2-Azido-6,7-*O*-cyclohexylidene-2,3,5-trideoxy-D-*arabino*-heptono-1,4-lactone (27). It was prepared starting from **26** (0.35 g, 1.27 mmol), employing the procedure described for **15**. Syrupy **27** was obtained in 90% yield (0.32 g): $[\alpha]_D$ −74.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.60 (m, 1H), 4.33

(dd, J = 8.8, 11.0 Hz, 1H, H-2), 4.18 (m, 1H), 4.05 (dd, J = 6.2, 8.0 Hz, 1H), 3.59 (dd, J = 6.6, 8.0 Hz, 1H), 2.70 (ddd, J = 5.5, 8.8, 12.9 Hz, 1H, H-3), 2.17−2.01 (m, 3H), 1.55−1.36 (m, 10 *H*-cyclohexylidene); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8, 109.8, 74.9, 71.1, 68.5, 57.6, 38.2, 36.5, 34.9, 34.6, 25.0, 23.9, 23.7.

Anal. Calcd for $C_{13}H_{19}N_3O_4$: C, 55.51; H, 6.81. Found: C, 55.45; H, 6.62.

2-(*N*-Benzyloxycarbonyl)amino-2,3,5-trideoxy-D-*arabino*-heptono-1,4-lactone (28). Compound **27** (0.34 g, 1.22 mmol) was hydrogenated and N-protected as described for the preparation of **19**. The resulting syrupy product (0.43 g, 91%) was treated with 0.5 N aqueous HCl in MeOH, as indicated above, affording an oil that was purified by column chromatography on silica gel with EtOAc as eluent. Evaporation of the solvent from the chromatographic fractions that showed the spot of R_f 0.36 (EtOAc) led to crystalline **28** (0.30 g, 78%), which was recrystallized from EtOAc: mp 122 °C; $[\alpha]_D$ −18.3 (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 7.33 (s, 5 *H*-aromatic), 5.10 (s, 2H, PhC*H*$_2$), 4.66 (m, 1H), 4.52 (dd, J = 8.4, 12.0 Hz, 1H, H-2), 3.75 (m, 1H), 3.50 (m, 2H), 2.68 (ddd, J = 5.6, 8.4, 12.3 Hz, 1H, H-3), 2.07−1.80 (m, 3H); ^{13}C NMR (50 MHz, CD_3OD) δ 177.1, 158.3, 138.0, 129.5, 129.1, 128.9, 76.8, 69.6, 67.8, 67.1, 52.7, 39.8, 35.9.

Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58,25; H, 6.20; N, 4.53. Found: C, 58.06; H, 6.42; N, 4.41.

5-(*N*-Benzyloxycarbonyl)amino-2,4,5-trideoxy-D-*threo*-hexurono-6,3-lactone (29). Compound **29** was prepared as described for the L-*threo* enantiomer **21**. Starting from **28** (0.10 g, 0.32 mmol), chromatographically homogeneous **29** (80 mg, 89%) was obtained. Compounds **29** and **21** showed identical spectroscopic properties.

2-(*N*-Benzyloxycarbonyl)amino-2,3,5-trideoxy-D-*threo*-hexono-1,4-lactone (30). Crude compound **29** (80 mg, 0.29 mmol) was reduced with $NaBH_3CN$ as described for the preparation of **23.** The EtOAc extract was washed with saturated aqueous solution of NaCl, which was made alkaline with $NaHCO_3$. This way the indicator is retained in the aqueous layer and the chromatographic purification could be avoided. Compound **30** (68 mg, 85%) gave $[\alpha]_D$ +28.6 (*c* 0.8, $CHCl_3$), and it showed the same spectral properties as **23**.

2-(*N*-Benzyloxycarbonyl)amino-6-*O*-methanesulfonyl-2,3,5-trideoxy-D-*threo*-hexono-1,4-lactone (31). Compound **30** (60 mg, 0.21 mmol) was mesylated as described for **24**. After identical purification, **31** (71 mg, 93%) was obtained. It gave $[\alpha]_D$ +39.5 (*c* 1.0; $CHCl_3$) and the same spectroscopic properties as **24**.

(2*S*,4*R*)-4-Hydroxypipecolic Acid [(−)-1]. Compound **31** (38 mg, 0.11 mmol) was hydrogenated as above, and the resulting syrup was also treated with 0.1 M aqueous KOH, as described in the preparation of (+)-**1**. After the same workup and purification, (−)-**1** (12 mg, 73%) was obtained: $[\alpha]_D$ −22.8 (*c* 0.38, H_2O) (lit.[9] $[\alpha]_D$ −17; lit.[14] $[\alpha]_D$ −23.5). It showed the same spectral properties as (+)-**1**.

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