

## Aldonolactones as chiral templates in the synthesis of thiolactones, 1,3-polyols and hydroxy amino acids

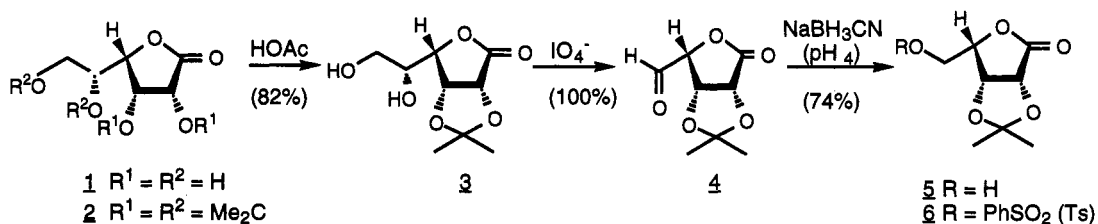
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**Abstract:** The usefulness of aldonolactones as chiral templates is shown in the synthesis of varied asymmetric molecules. For example, enantiomerically pure 4-thio-D-ribo- and 4-thio-L-lyxono-1,4-lactones have been respectively synthesized from D-gulono- and D-ribo-1,4-lactones. Seven carbon 1,3-polyol chains have been enantioselectively obtained from D-glycero-D-gulo-heptono-1,4-lactone via chiral furanone derivatives. Also, furanones and pyranones derived from D-glucosaminic acid were employed as intermediates in the synthesis of hydroxy amino acids, such as *cis*-4-hydroxypipercolic acid and (2*S*,4*S*,5*R*)-4,5,6-trihydroxynorleucine.

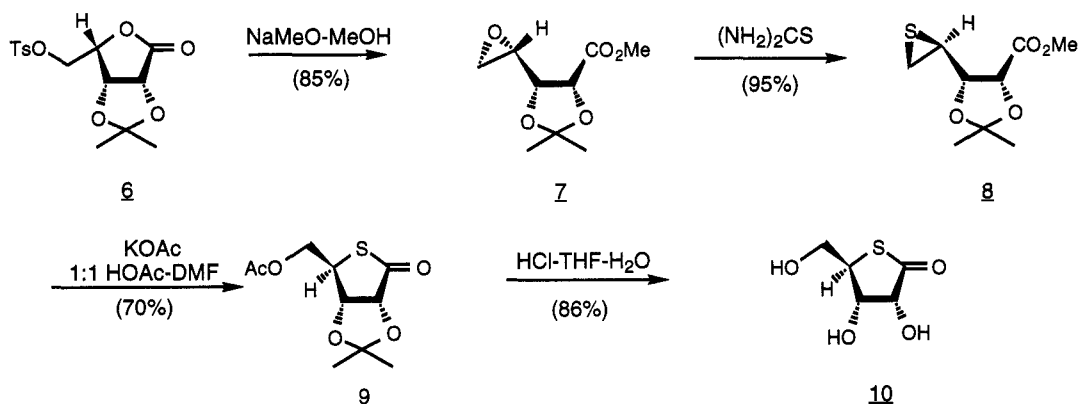
Aldonolactones are useful chiral templates in the synthesis of modified sugars and non-carbohydrate natural products (ref. 1). Many aldonolactones are commercially available products, or they can be readily obtained by oxidation of the respective monosaccharides. In our laboratory aldonolactones such as D-ribo-, D-gulono-, and D-glycero-D-gulo-heptono-1,4-lactones, as well as unsaturated lactones derived from D-glucosaminic acid have been employed in the synthesis of sugar thiolactones, 1,3-polyol systems, and hydroxy amino acids. Particularly, D-ribo-1,4-lactone has been considered a "chiral cornerstone" (ref. 2) because of its use as a chiral precursor of numerous naturally occurring, asymmetric molecules, and many derivatives have been prepared (ref. 3). However, no synthesis for its 4-thio analogue, 4-thio-D-ribo-1,4-lactone, has been reported. This together with the fact that previous attempts to prepare sugar thiolactones from aldonic acids were not satisfactory, prompted us to develop a general procedure for the synthesis of aldopentono-1,4-thiolactones.

4-Thio-D-ribo-1,4-lactone was our first target, and L-lyxono-1,4-lactone was selected as the chiral template, since the replacement of a HO group by thiol usually takes place with inversion of the configuration of the carbon involved. As this lactone is not commercial, D-gulono-1,4-lactone (**1**), which has the same stereochemistry for all the ring stereocenters as lyxonolactone, was employed as starting material. Acetonation of **1** with acetone in the presence of sulfuric acid gave the diacetone **2**, which was selectively hydrolyzed with aqueous acetic acid to the 2,3-*O*-monoisopropylidene derivative **3**. The glycol system was oxidized with sodium periodate to give the aldehyde **4**, which was in equilibrium with the hydrated form, according to the NMR spectra. Chemoselective reduction of the aldehyde function with sodium cyanoborohydride (pH 4) led to the 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (**5**) in 60% yield from **1**. The free hydroxyl group of **5** reacted with *p*-tolylsulfonyl chloride affording the tosylate **6** in 78% yield.

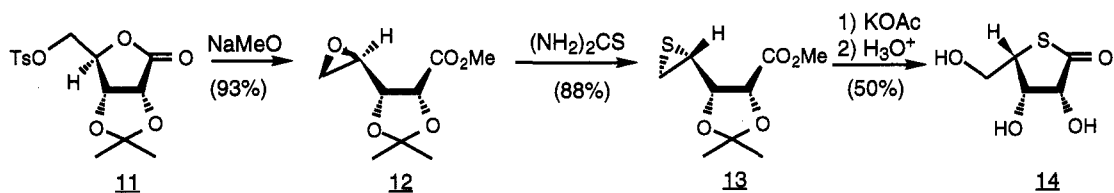


Treatment of compound **6** with sodium methoxide in methanol produces the opening of the lactone ring by methanolysis, and the resulting alkoxide at C-4 promotes the nucleophilic displacement of the tosyloxy group at C-5 to give the oxirane derivative **7**. Replacement of the epoxide oxygen atom by sulfur was achieved by reaction of **7** with thiourea, which led to the thiirane derivative **8** having inverted configuration (D-ribo) at C-4. Regioselective opening of the thiirane ring, and simultaneous thiolactonization took place when **8** was refluxed with a solution of potassium acetate in a 1:1 mixture of acetic acid and DMF. The

formation of the thiolactone ring of **9** was evident from the  $^{13}\text{C}$  NMR spectrum, which showed the thiolactone carbonyl signal at  $\delta > 200$ , and the resonance of C-4 (bonded to sulfur) at *ca* 47 ppm. Hydrolysis of the acetate and isopropylidene groups of **9** with 2% hydrochloric acid, afforded the free, crystalline 4-thio-D-ribo-1,4-lactone (**10**) in 37% overall yield from **5** (ref. 4).



The C-4 of aldonolactones is frequently employed for asymmetric induction in chiral synthesis. Therefore, a sugar thiolactone, as for example 4-thio-L-lyxono-1,4-lactone (**14**), having inverted configuration at C-4 with respect to that of **10**, will be an useful chiral building block. The thiolactone **14** was synthesized by a sequence analogous to the one employed for **10**. In this case, the starting material was the 2,3-O-isopropylidene-5-O-tosyl-D-ribo-1,4-lactone (**11**). The oxirane and thiirane derivatives **12** and **13** were intermediates in the synthetic route, as before. Thiolactonization of **13**, followed by removal of the protecting groups, afforded the crystalline 4-thio-L-lyxono-1,4-lactone (**14**) in 32% overall yield from D-ribo-1,4-lactone (ref. 4).



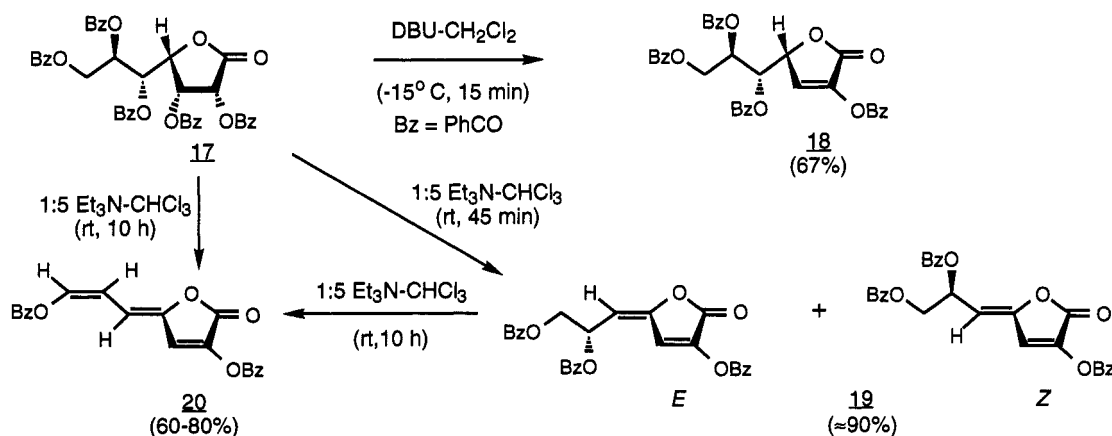
Although the conformation of aldonolactones in solution and in the crystalline state, have been intensively studied, no reports were found on the conformational analysis of aldonothiolactones. For this reason, the conformation of compound **14** was studied by means of NMR spectroscopy and by X-ray crystallography of a single crystal. For conformational assignments in solution homonuclear ( $J^1\text{H}, ^1\text{H}$ ) and heteronuclear ( $J^1\text{H}, ^{13}\text{C}$ ) coupling constants were employed. The latter were directly measured from a 2D-spectrum using the HETLOC pulse sequence, which does not require  $^{13}\text{C}$  isotopic enrichment. These experiments showed that the thiolactone ring of **14** adopts preferentially the  $E_3$  (L) conformation, both in solution as well as in the solid state (ref. 5). The conformational preferences of other heterocyclic rings were also established (ref. 6) employing a pseudorotation analysis previously reported (ref. 7).

2,3-Unsaturated thiolactone rings are structures found in thiolactonic antibiotics, as thiolactomycin (ref. 8). The (4*S*)-4-hydroxymethyl-(5*H*)-thiopenone (**16**) is the sulfur containing analogue of the aglycon of ranunculin, a precursor of the vesicant substance protoanemonine. Also, **16** could be employed for the synthesis of sulfur analogues of the antileukemic lignans *trans*-burseran, isostegane and steganacin (ref. 9). Compound **10** was considered a suitable precursor of 4-thio-2-butenolides like **16**. In order to accomplish the deoxygenation and unsaturation of **10**, its primary hydroxyl group was protected as the *tert*-butyldiphenylsilyl derivative (**15**).



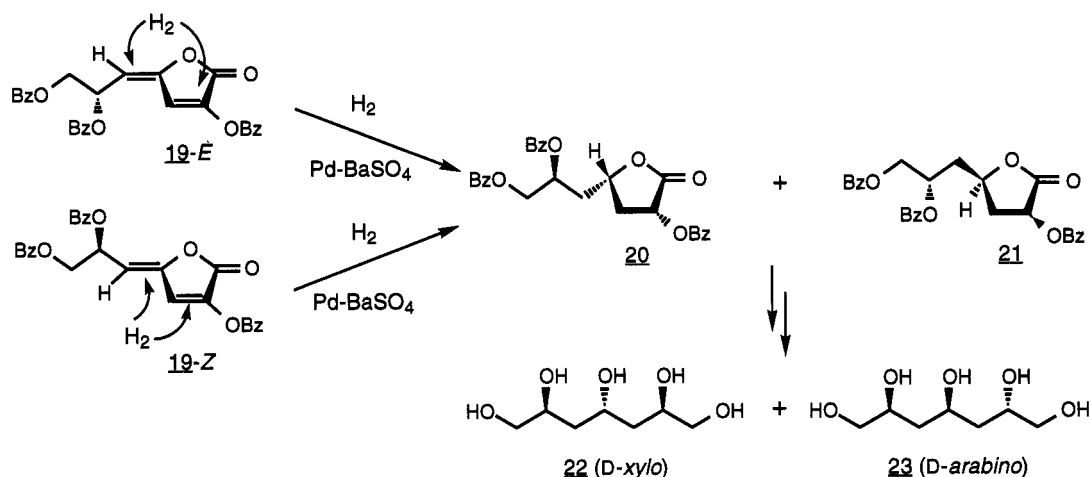
Many procedures have been reported for the conversion of a diol into an alkene, and we tried first the Hanessian method (ref.10). Reaction of **15** with *N,N*-dimethylformamide dimethyl acetal followed by reaction with methyl iodide and pyrolysis gave a complex mixture, which was not further analyzed. The Corey-Winter procedure, modified by Ireland (ref.11), was then attempted. Treatment of **15** with 1,1'-thiocarbonyldiimidazole gave the corresponding 2,3-*O*-thiocarbonyl derivative, which reacted with Raney nickel in refluxing THF to give the 5-*O*-*tert*-butyldiphenylsilyl derivative of **16** in about 60% yield. The same procedure when applied to the 5-*O*-silylated derivative of **14** afforded the corresponding (5*H*)-thiofenone in 70% yield. Other alternative routes for the preparation of **16** and its enantiomer are in course. Also, in order to determine conclusively the optical purity of the products, reactions of **16** with chiral reagents are being attempted.

The  $\beta$ -elimination is an interesting and synthetically useful reaction of aldonolactones, which takes place under smooth conditions, as for example on prolonged acylation in an alkaline medium (ref. 1). Aldono-1,4-lactones can undergo successive eliminations affording polyunsaturated products. Thus, prolonged benzylation of *D*-glycero-*D*-gulo-heptono-1,4-lactone gave a mixture of mono, di, and triunsaturated lactones (**18**, **19**, and **20**, respectively). The extent of the elimination can be controlled starting from the per-*O*-benzoylated heptonolactone derivative **17** (ref. 12, 13). The reagents and reaction conditions employed for each individual case, and the yields obtained, are shown in the next scheme. The configurations for the exocyclic double bonds were determined by means of H,H-coupling constants and nuclear Overhauser enhancement (nOe) experiments. The diunsaturated derivative **19** was isolated as an approximately 1:1 mixture of the *E* and *Z* isomers; which could be separated by column chromatography or, more efficiently, by preparative HPLC.



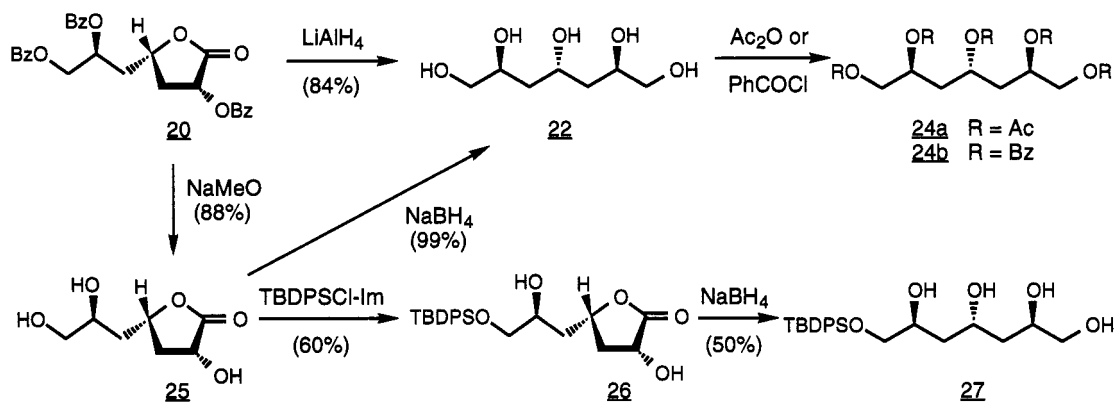
The stereocenter located in the lateral chain of furanones **19** was employed for inducing asymmetry. Thus, the stereocontrolled hydrogenation of **19** gave chiral dideoxylactones, which were appropriate precursors of optically pure 1,3-polyols. In recent years, a number of strategies have been described for the synthesis of extended 1,3-polyol chains (ref. 14). This kind of polyols are found, in varied stereochemical arrays, as constituents of polyene macrolide antibiotics, such as amphotericin, mycoticin, roxaticin and roflamycin. We described a carbohydrate approach for the synthesis of polyol fragments found in those antibiotics, starting from **19-E,Z** (ref. 15). For the diastereoselective hydrogenation of this mixture, and of each pure isomer, Pd/C or Pd/BaSO<sub>4</sub> were used as heterogeneous catalysts. A somewhat higher selectivity was observed when the latter was employed. For example, hydrogenation of **19-E** afforded a 3:1 mixture of the 3,5-dideoxylactones having the *D*-xylo (**20**) and *D*-arabino (**21**) configurations, respectively. Interestingly, although less selective, hydrogenation of **19-Z** led to the *D*-arabino isomer as the major product (ratio **20:21** 1:1.4).

The observed diastereofacial selectivity was explained assuming that hydrogenation of the furanones **19-E** and **19-Z** takes place under conformational control. The large *J* values observed for the allylic and vinylic protons indicated an *anti* relationship, and a conformation having the C-H bond eclipsing the exocyclic double bond. If this conformational preference is reflected in the transition state, the stereochemistry of the major product arises from the approach of hydrogen from the face which is opposite to that containing the allylic benzyloxy group. This result is in good agreement with the Kishi's empirical rule on osmilation of allylic systems. As previously reported for other 2-enolactones (ref. 16), the hydrogenation of the endocyclic double bond was also diastereoselective. In this case, the sterical hindrance of the lateral chain at C-4 induces the addition of hydrogen from the opposite side, affording the dideoxylactone having a *threo* relationship for the substituents at C-2 and C-4.



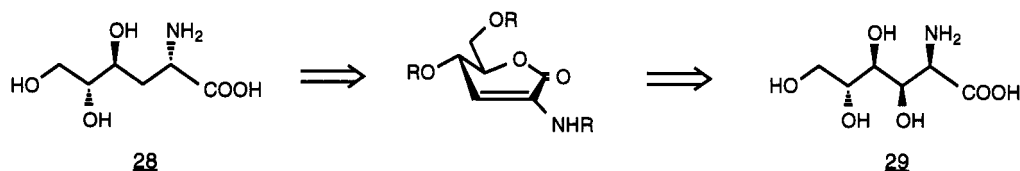
When the hydrogenation of an approximately equimolar mixture of furanones **19-E,Z** was conducted on preparative scale, compound **20** crystallized from the reaction mixture and it was obtained pure in about 40% yield, after three successive recrystallizations from methanol. A remarkable advantage of this synthesis is the easy purification of **20** by recrystallization, as commonly tedious chromatographic separations of diastereoisomers are avoided. In order to obtain the polyol, compound **20** was reduced with  $\text{LiAlH}_4$  to give the 3,5-dideoxy-*meso*-xylo-heptitol (**22**). The same product was alternatively synthesized by  $\text{NaBH}_4$  reduction of the free 3,5-dideoxylactone **25**, obtained by sodium methoxide *O*-debenzoylation of **20**. The perbenzoylated (**24a**) and peracetylated (**24b**) derivatives of the alditol were also prepared for its full characterization.

A polyol derivative having one of the primary hydroxyl groups selectively protected would be useful for the chain elongation by known procedures (ref. 14). Therefore, the 1-*O*-silyl derivative **27** was synthesized from the dideoxylactone **25**. Treatment of **25** with 1.2 equivalents of *tert*-butylchlorodiphenylsilane - imidazole gave the 7-*O*-silyl derivative (**26**, 60%) together with the 2,7-di-*O*-silyl derivative as a byproduct (22%). The lactone group of **26** was reduced with  $\text{NaBH}_4$  to give the desired 1-*O*-silylated polyol **27**. Also, a modified polyol chain with a carbonyl group in one of the extremes was prepared by chemoselective reduction of the carbonyl lactone of **20** with diisooamylborane. The resulting lactol is a partially benzoylated derivative of a rare sugar (3,5-dideoxy-D-xylo-heptofuranose), which has the anomeric hydroxyl group unprotected.

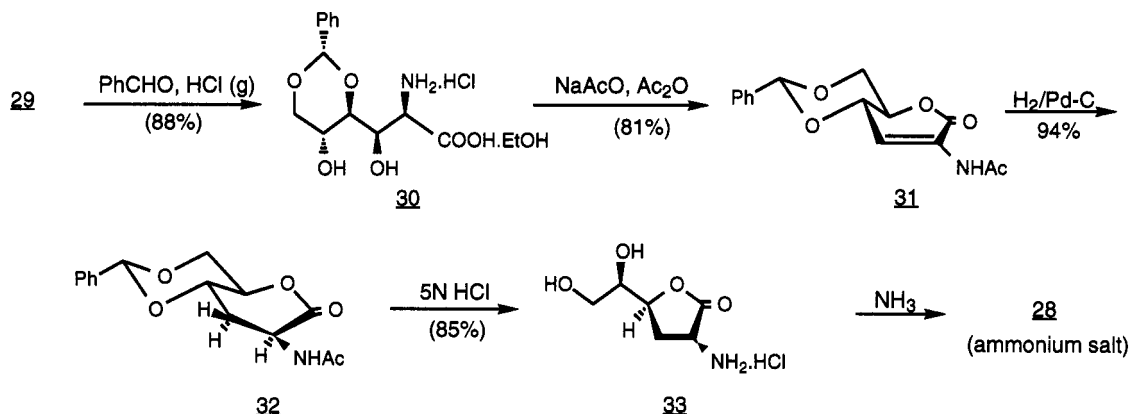


In order to obtain the free alditol of D-*arabino* configuration (**23**), the crude mixture of hydrogenation of the furanones **19-E,Z**, containing almost equal proportions of **20** and **21**, was subjected to *O*-debenzoylation followed by sodium borohydride reduction. At this stage the mixture of *meso*-xylo-(**22**) and D-*arabino*-(**23**)-3,5-dideoxyalditols could be readily accomplished by HPLC. Compound **22** is identified as the C-16-C-22 and C-18-C-24 fragments of the polyene macrolide antibiotics roxaticin (ref. 14a,b) and roflamycoin (ref. 14c), respectively. The polyol **23** is also found as the unit constituent of the C-20-C-26 segment of the latter antibiotic.

On the other hand, we have employed unsaturated aldonolactones as precursors of hydroxy amino acids. The synthesis of these compounds constitutes an area of intensive current research because of the varied biological activities displayed by hydroxy amino acids, mainly as enzyme inhibitors and antimetabolites. Also, they occur naturally in free form like in fruits, seeds, microorganisms, etc., or combined, taking part of large molecules, such as peptides and antibiotics (ref. 17). Several synthetic strategies have employed carbohydrates as convenient starting materials. In our laboratory we have shown the utility of furanones or pyranones, derived from sugars, for the synthesis of hydroxylated analogs of norleucine (ref. 18). For example, (2*S*,4*S*,5*R*)-4,5,6-trihydroxynorleucine (**28**) was synthesized from D-glucosamine, via unsaturated lactones of D-glucosaminic acid (**29**). Compound **29** was prepared, in multigram scale, by mercury (II) oxide oxidation of D-glucosamine. The synthesis of **28** requires the deoxygenation of C-3 and inversion of the configuration of C-2 of the glucosaminic acid, in order to obtain an amino acid in the L-series, generally found in nature.



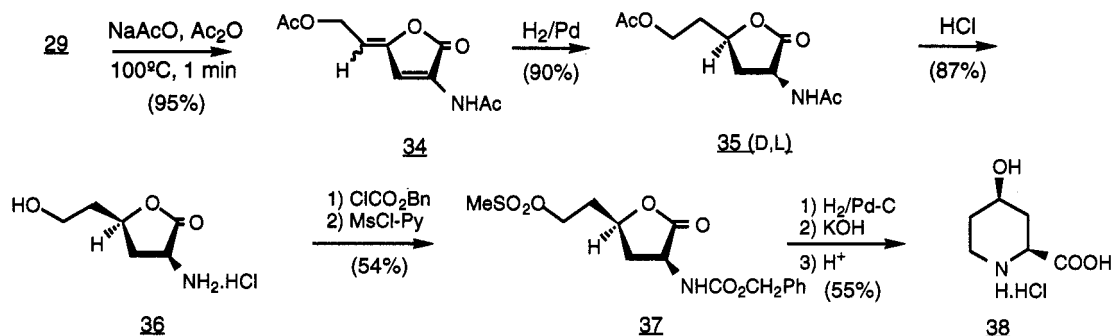
We have previously observed (ref. 19) that acylation of **29**, with an acyl chloride in pyridine, gave mono-unsaturated 1,4- and 1,5-lactones. Hydrogenation of the double bond of the 2-enonolactones led diastereoselectively to acylated lactic derivatives of **28**. This compound was obtained in free form by an alternative route, in which the ring size of the intermediate lactones was maintained. This could be achieved by blocking the HO-4 of **29** by preparation of its 4,6-*O*-benzylidene derivative **30**, isolated as the hydrochloride ethanol solvate. Compound **30** reacted with a hot mixture of sodium acetate in acetic anhydride to give the unsaturated pyranone **31**, which was diastereoselective hydrogenated affording the 3-deoxylactone **32**. Upon removal of the benzylidene and *N*-acetyl groups by acid hydrolysis, the 1,4-lactonic form of **30** was obtained as the crystalline hydrochloride, in 57% overall yield. The ammonium salt of (2*S*,4*S*,5*R*)-4,5,6-trihydroxynorleucine was also prepared, as an example of an open chain derivative of the amino acid.



A biologically interesting cyclic hydroxy amino acid is the *cis*-4-hydroxypiperolic acid (**38**), a natural product which has been isolated from leaves of *Calliandra pittieri* and *Strophantus scandeus*. The 4-phosphonoxy derivative of **38** has shown antagonist activity for the NMDA subtype of excitatory amino acids receptors, probably involved in certain neuropathologies. Furthermore, an amide of **38** is a constituent of palinavir, a highly potent inhibitor of the HIV protease. For all these reasons, the *cis*-4-hydroxypiperolic acid was an attractive target molecule (ref. 20). The retrosynthetic analysis for **38** suggested the disconnection of the C-6-N bond, affording a synthon equivalent of a 2-amino-2,3,5-trideoxylactone, which can be prepared from D-glucosamine via the D-glucosaminic acid (**29**). The required stereochemistry for the chiral centers of **38** was readily generated by two high yielding steps: the  $\beta$ -elimination and catalytic hydrogenation. A double elimination took place on acetylation of **29** with a hot mixture of sodium acetate and acetic anhydride affording the furanone **34** in 95% yield. Hydrogenation of this compound led to the 3,5-dideoxylactone **35**, as a single racemic diastereoisomer having *threo* configuration. Compound **35** was *O*- and *N*-deacetylated in acidic conditions, to give the lactone **36** as the hydrochloride derivative.

The synthetic strategy for the construction of the piperidine ring involved the nucleophilic displacement of the conveniently substituted HO-6 by the amino function at C-2. This group was protected as the carbobenzyloxy derivative, prior to the conversion of HO-6 into a good leaving group by sulfonylation. The mesylate **37** was obtained in 54% yield from **36**. Removal of the carbobenzyloxy protecting group by

hydrogenolysis, followed by alkaline treatment, led to the free amino acid **38**, which was purified through a column of Dowex 50 W (H<sup>+</sup>) resin, and isolated as its hydrochloride derivative (ref. 21).



The *cis*-4-hydroxypipercolic acid was prepared in an overall yield > 20%, by means of a short and completely diastereoselective synthesis. However, the product obtained was racemic. In order to overcome this inconvenience, an enantioselective synthesis of **38** is currently in progress in our laboratory. The previously mentioned 3,5-dideoxy-D-xylo-heptono-1,4-lactone (**25**), derived from D-glycero-D-gulo-heptono-1,4-lactone, was selected as the chiral intermediate which will lead to the stereochemistry and functionalization required for the stereocenters of **38**.

## ACKNOWLEDGMENTS

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