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Synthesis of (2*R*,3*R*,4*S*)-2-hydroxymethylpyrrolidine-3,4-diol from (2*S*)-3,4-dehydroproline derivatives [1]

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Abstract

(2*R*,3*R*,4*S*)-2-Hydroxymethylpyrrolidine-3,4-diol (1,4-dideoxy-1,4-imino-D-ribitol) was synthesized in five steps from *N*-protected (2*S*)-3,4-dehydroproline methyl esters. The stereoselective reaction of osmium tetraoxide with dehydroproline derivatives gave high yields of (2*S*,3*R*,4*S*)-3,4-dihydroxyprolines (2,3-*trans*-3,4-*cis*-3,4-dihydroxy-L-prolines) accompanied by small amounts (< 15%) of the diastereomeric (2*S*,3*S*,4*R*)-3,4-dihydroxyprolines (2,3-*cis*-3,4-*cis*-3,4-dihydroxy-L-prolines). The mixture of the diastereomeric glycols was converted into the isopropylidene acetals, and the isomers separated efficiently on a preparative scale. The resulting protected (2*S*,3*R*,4*S*)-3,4-dihydroxyproline methyl ester was reduced ($LiBH_4$) to the 2-hydroxymethylpyrrolidine and deprotected, resulting in the production of (2*R*,3*R*,4*S*)-2-hydroxymethylpyrrolidine-3,4-diol in high yield and in high purity. The ^1H and ^{13}C NMR signals of the product have been unambiguously assigned using two-dimensional NMR techniques, and the identity of the title pyrrolidine confirmed by comparisons of its spectra with those reported for the authentic material.

1. Introduction

Certain hydroxylated pyrrolidines are biologically active as antiviral agents [2,3], immunostimulants [4], and as enzyme inhibitors [5,6]. They are a class of carbohy-

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[1] A preliminary description of this work has appeared (ref 1).

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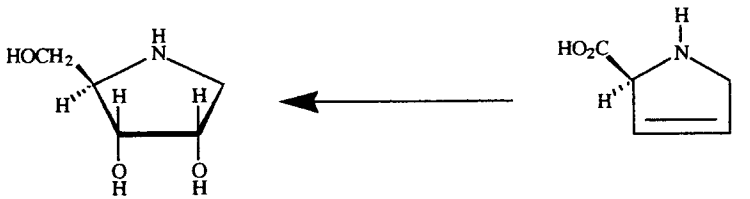
drate analogues in which the furanose oxygen is replaced by nitrogen. The protonated nitrogen of the amino sugar is envisioned to resemble an oxocarbonium-ion like transition state which may occur for certain enzyme-catalyzed glycosyl transfer reactions. The protonated pyrrolidines are considered to be a type of transition-state analogue which mimics the developing positive charge of an oxocarbonium-ion like transition state. (2*R*,3*R*,4*S*)-2-Hydroxymethylpyrrolidine-3,4-diol (1,4-dideoxy-1,4-imino-D-ribitol, **1**) is unique among the pyrrolidines in that it is the nitrogen-in-the-ring sugar analogue of D-ribofuranose. It is therefore an inhibitor of nucleoside hydrolase [7], and a potential inhibitor of nucleoside phosphorylases, pyrophosphorylases, and a variety of other enzymes which catalyze cleavage of the nucleosidyl *N*-glycosylic bond.



1
(2*R*,3*R*,4*S*)-2-hydroxymethyl pyrrolidine-3,4-diol

2
(2*S*)-3,4-dehydroproline

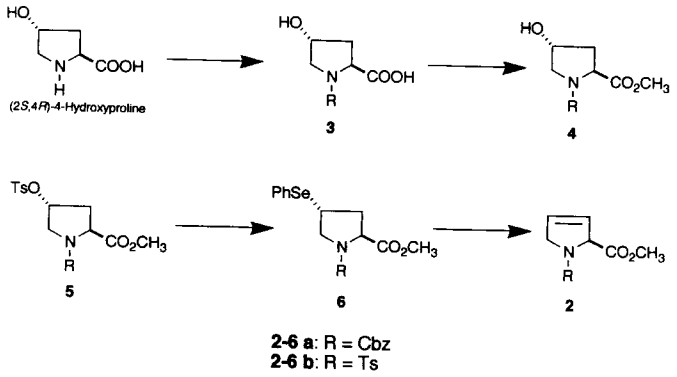
Pyrrolidine **1** in protected form is a synthetic precursor of adenosine diphosphatehydroxymethylpyrrolidine diol, a potent and specific inhibitor of poly(ADP-ribose) glycohydrolase [8]. Protected **1** is also a precursor of a number of potentially important inhibitors specific for nucleotide, dinucleotide, and polynucleotide glycohydrolases [8].

An efficient synthesis of **1** and its derivatives is of interest because of its wide variety of biological activities in the nucleotide field. We describe a short, high-yielding, and stereoselective synthesis of **1** beginning with protected derivatives of the readily available chiral amino acid, (2*S*)-3,4-dehydroproline (**2**) and rigorously prove the structure and establish the purity of the product pyrrolidines.

2. Results and discussion

(2*R*,3*R*,4*S*)-2-Hydroxymethylpyrrolidine-3,4-diol (**1**) was potentially available through multi-step synthesis from the chiral precursors L-glutamic acid [9], L-lyxose [10,11], and D-gulono-1,4-lactone [12], or via the cycloaddition reaction between an aziridine ester and vinylene carbonate [13,14]. Each of these suffers one or more disadvantages — excessive length, low yield, lack of stereoselectivity, or the production of **1** inappropriately protected for its ready conversion to the nucleoside 5′-phosphate analogue.

The chiral amino acid (2*S*)-3,4-dehydroproline (3,4-dehydro-L-proline) represented an attractive precursor for the synthesis of **1**. This amino acid already has within it the functionalized pyrrolidine skeleton. Preliminary studies of the OsO_4-

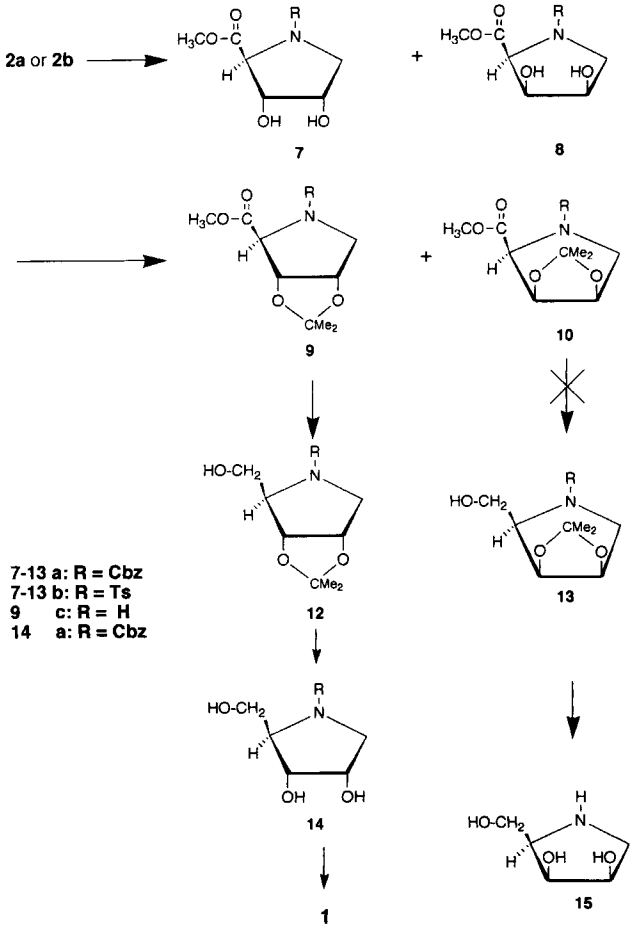


Scheme 1. Synthesis of *N*-protected (*S*)-3,4-dehydroproline methyl esters from (2*S*,4*R*)-4-hydroxyproline.

catalyzed hydroxylation of dehydroproline derivatives suggested that the reaction was stereoselective and produced the desired 2,3-*trans*-3,4-*cis*-glycol, although proof of the structure of the products was absent from the preliminary works [1,15,16]. Furthermore, (2*S*)-dehydroproline is readily available either commercially or through synthesis [17,18].

Our synthesis started with the protected amino acid derivative (2*S*)-1-benzyloxycarbonyl-3,4-dehydroproline methyl ester (**2a**), prepared from commercial (2*S*)-3,4-dehydroproline methyl ester · HCl by treatment with *N*-benzyloxycarbonyloxysuccinimide. Alternatively, **2a** was prepared in four steps and on a large scale from (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxyproline (**3a**) following the procedure of Rüeger and Benn [18] (Scheme 1). Protection of the nitrogen using the benzyloxycarbonyl-(*Z*-) group offers the stability and ease of deprotection sought for our subsequent applications of the protected pyrrolidine in nucleotide analogue synthesis. It was immediately apparent, however that *N*-benzyloxycarbonyl-protected prolines exist in two stable conformations at ordinary temperatures due to restricted rotation about the amide like N–C=O linkage [19]. This is evident in the ^{1}H NMR of the dehydro derivative **2a**, where the methyl ester signal appears as two peaks of about equal intensity separated by 0.16 ppm. Because of the difficulties in interpretation of the ^{1}H NMR spectra, the series of prolines protected using the nonamide-like *p*-tolylsulfonyl group was also investigated. (2*S*)-1-(*p*-Tolylsulfonyl)-3,4-dehydroproline (**2b**) was prepared starting from (2*S*,4*R*)-hydroxyproline (**3**, R = H) by converting it into (2*S*,4*R*)-1-(*p*-tolylsulfonyl)-4-hydroxyproline (**3b**) and applying the procedure of Rüeger and Benn [18] (Scheme 1).

Treatment of either alkene **2a** or **2b** with a catalytic quantity of OsO_4 and *N*-methylmorpholine-*N*-oxide led to the rapid consumption of starting alkene and production of a mixture of glycols (Scheme 2). Although the products appeared homogeneous on examination using TLC and reversed-phase HPLC, analysis of the ^{1}H NMR of the material resulting from hydroxylation of the *N*-tosyl methyl



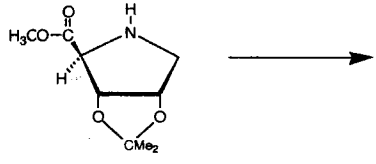
Scheme 2. Synthesis of (2*R*,3*R*,4*S*)-2-hydroxymethylpyrrolidine-3,4-diol and its protected derivatives.

ester **2b** indicated the presence of two related materials in the ratio of ca. 7:1. The major product of the OsO_4 oxidation of **2b** was assumed to be **7b** on the basis of the expectation that delivery of the oxygens would occur preferentially on the less hindered face of the alkene producing the 2,3-*trans*-3,4-*cis* compound. The ^1H NMR of the major isomer exhibited a one-proton doublet at δ 4.10 ppm (J 4 Hz) assigned to H-2. A second smaller signal of ca. 1/7 the intensity appeared as a doublet at δ 4.35 ppm (J 8 Hz), and was assigned to H-2 of the minor isomer **8b**. Conditions to separate the mixture of the glycols **7** and **8** could not be found, and the mixture was converted to a mixture of isopropylidene acetals **9** and **10** by treatment of the two *cis*-glycols with 2,2-dimethoxypropane and HCl.

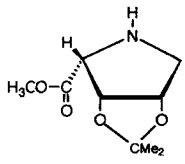
The mixture of *N*-benzyloxycarbonyl-protected isopropylidene acetals **9a** and **10a** was now separable, and examination using analytical reversed-phase HPLC revealed that two compounds were present in a ratio of 7:1. The *Z*-isopropylidene

acetals could be separated on a large scale using careful flash-column chromatography on silica gel. The analytical data for **9a** and **10a** established that the compounds were isomeric. However, the ^{1}H NMR spectra could not be interpreted in detail because of overlap of the signals and because of the complication introduced by the presence of rotamers. Although we anticipated that the major isomer would be **9a**, we sought a rigorous proof of the structures of the products.

The ^{1}H NMR spectra of the purified *Z*-protected isopropylidene acetals **9a** and **10a** were complicated primarily due to the existence of multiple signals resulting from multiple stable conformers produced from the restricted rotation about the amide-like benzyloxycarbonyl linkage. We therefore removed the *Z*-protecting group of **9a** to obtain a secondary amine **9c** which was expected to have a simplified ^{1}H NMR spectrum. The benzyloxycarbonyl group of **9a** was removed by catalytic hydrogenolysis [21]. When the hydrogenolysis product was examined immediately at the conclusion of the reaction, a single new compound was present (TLC) which was completely characterized and assigned the structure **9c**. When chloroform solutions of pure **9c** were allowed to stand for a period of weeks, or when **9c** was subjected to flash-column chromatography on silica, a second material was formed (TLC). This substance (**11**) was isolated and was shown by mass spectrometry to have the same molecular weight as **9c**, indicating that the two materials were isomeric.



9c



11: (2*R*,3*R*,4*S*)-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester

The close similarity between the ^{13}C NMR of **9c** and that of **11** also suggested that the structures were related as isomers. The major differences in the ^{1}H NMR spectra of **9c** and **11** occur in the region associated with the H-2 signals, from 3.5–3.9 ppm. We therefore proposed that **11** was the 2,3-*cis*-isomer of **9c**, produced by epimerization of the C-2 carbomethoxy group. No similar tendency to epimerize was observed for the protected amines **9a** or **9b**. The ^{1}H NMR spectra for both **9c** and **11** were first order and easily interpretable, and a set of assignments were made for the spectra and verified using two-dimensional NMR techniques. The signal assigned to H-2 in the ^{1}H NMR of **9c**, appeared as a one-proton singlet at δ 3.87 ppm, ($J_{2,3} < 0.5$ Hz). The signal assigned to H-2 in the ^{1}H NMR of **11** appeared as a one-proton doublet at δ 3.57 ppm ($J_{2,3}$ 5 Hz).

The *N*-tosyl-protected proline isopropylidene acetals **9b** and **10b** were next prepared, anticipating that the straightfoward ^{1}H NMR spectra of these derivatives would support the structural assignment of **11**. The mixture of *N*-tosyl-protected isopropylidene acetals was examined using reversed-phase HPLC and the ratio of the isomeric products determined to be 7:1. The individual *N*-tosyl isopropylidene acetals were separated on a large scale using preparative reversed-

phase HPLC, and each was fully characterized spectroscopically. In the ^{1}H NMR spectrum of the major isomer (assumed to be **9b**), the signal assigned to H-2 appeared as a slightly broadened one-proton singlet at δ 4.49 ppm, indicating that the magnitude of the H-2:H-3 coupling constant must be small ($J_{2,3} < 0.5$ Hz). The H-2 signal for the minor isomer **10b** appeared at δ 4.44 as a one-proton doublet (J 7.6 Hz). Thus, a small magnitude $J_{2,3}$ ($J < 1$ Hz) was observed in **9b** and **9c**, associated with a proposed 2,3-*trans* stereochemistry, while a large magnitude $J_{2,3}$ ($J \geqslant 5$ Hz) was observed for **10b** and **11**, associated with a proposed 2,3-*cis*-stereochemistry.

Attempts have been made to correlate the magnitudes of $J_{2,3}$ for 3-hydroxylated prolines with the stereochemistry of the substituent at C-2 relative to that of the hydroxyl group at C-3 [13,16]. A correlation of a small magnitude $J_{2,3}$ ($J < 2$ Hz) with the 2,3-*trans* stereochemistry and a large magnitude $J_{2,3}$ ($J > 4$ Hz) with the 2,3-*cis* stereochemistry was proposed from the reported ^{1}H NMR spectra of a small set of 3-hydroxylated prolines [16]. For example, the H-2 proton of the 2,3-*trans*-3-hydroxyproline appears as a singlet with $J_{2,3} < 1$ Hz, while the H-2 peak of the 2,3-*cis*-3-hydroxyproline was reported as a doublet with [20] $J_{2,3}$ 4 Hz. However, the 3,4-*cis*-dihydroxyprolines, the better models for our derivatives, refutes this proposed correlation. In the case of 2,3-*trans*-3,4-*cis*-3,4-dihydroxyproline the 2,3-*trans* coupling constant was [22] $J_{2,3}$ 5.0 Hz, while the 2,3-*cis* coupling constant for 2,3-*cis*-3,4-*cis*-3,4-dihydroxyproline [23] was $J_{2,3}$ 3.9 Hz. We therefore cannot infer relative 2,3-stereochemistry from a relation between the magnitudes of the coupling constants. Apparently the conformational flexibility of the 5-membered pyrrolidine rings permits many possible low-energy conformers to exist, and that the actual population is affected both by the substituents elsewhere on the molecule (particularly at C-4) and the steric requirements of the protecting groups present on the pyrrolidine. We therefore inferred that the major protected glycol was the 2,3-*trans*-3,4-*cis* compound **9**, and that the minor isomer was the 2,3-*cis*-3,4-*cis* compound **10**, on the basis of the expected stereoselectivity of OsO_4 hydroxylation reactions. This inference was subsequently proved here for the first time when we converted **9a** and **9b** into **1** (see following).

The protected 3,4-dihydroxyproline methyl esters **9a** and **9b** were quantitatively reduced to the 2-hydroxymethylpyrrolidine-3,4-diol isopropylidene acetals **12a** and **12b** on treatment of solutions of the methyl esters in THF with $LiBH_4$ at room temperature. Surprisingly, the 2,3-*cis*-3,4-*cis* ester **10a** was quite resistant to reduction using $LiBH_4$ under the same conditions. This is attributed to steric hindrance to hydride approach caused by the isopropylidene acetal methyl groups. The consequence of the resistance to reduction is that small amounts of **10a** which might contaminate purified batches of **9a** will not reduce to the corresponding isomeric primary alcohol **13a** and the unreacted ester will therefore be easily removed form the desired primary alcohol **12a** during purification.

(2*R*,3*R*,4*S*)-1-Benzyloxycarbonyl-2-hydroxymethylpyrrolidine-3,4-diol-3,4-isopropylidene acetal (**12a**) is thus obtained from **2a** in three steps, in 70% yield, and in high purity. It is suitably protected for its direct conversion to an analogue of a nucleotide 5′-phosphate by phosphorylation on its primary C-6 hydroxyl group.

Table 1A
^{1}H NMR chemical shifts and assignments for **1** and **1**·**HCl**

Data for **1**				Data for **1**·**HCl**		
Proton number	Chemical shift (δ, ppm)	Mult. [a]	Coupling constants (Hz)	Chemical shift (δ, ppm)	Mult. [a]	Coupling constants (Hz)
H-2	3.12	m	7.3, 6.1, 4.3	3.64	ddd	8.6, 6.0, 3.5
H-3	3.90	dd	7.3, 5.2	4.22	dd	8.6, 4.2
H-4	4.18	dt	5.2, 5.2, 3.7	4.40	dt	4.2, 4.0, 2.0
H-5	2.87	dd	12.4, 3.7	3.38	dd	13.0, 2.0
H-5′	3.20	dd	12.4, 5.2	3.51	dd	13.0, 4.0
H-6	3.65	dd	11.7, 6.1	3.84	dd	12.6, 6.0
H-6′	3.77	dd	11.7, 4.3	3.99	dd	12.6, 3.5

[a] Abbreviations: dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; m, multiplet.

Table 1B
Assignment of ^{1}H NMR coupling constants

Assignment	Compound **1** J (Hz)	Compound **1**·**HCl** J (Hz)
H-2,H-3	7.3	8.6
H-2,H-6	6.1	6.0
H-2,H-6′	4.3	3.5
H-3,H-4	5.2	4.2
H-4,H-5	3.7	2.0
H-4,H-5′	5.2	4.0
H-5,H-5′	12.4	13.0
H-6,H-6′	11.7	12.6

The completely unprotected pyrrolidine **1** was obtained from **12a** by removal of the isopropylidene acetal using aqueous acid followed by cleavage of the benzyloxycarbonyl group by catalytic hydrogenolysis. Assignments for the signals in the ^{1}H NMR spectra of **1** and its HCl salt are presented in Table 1, and the ^{13}C assignments are presented in Table 2. Assignments were made using a combina-

Table 2
^{13}C NMR chemical shifts and assignments for **1** and **1**·**HCl**

	Compound **1**	Compound **1**·**HCl**
Carbon	Chemical shift (δ [a])	Chemical shift (δ [a])
C-2	65.23	64.67
C-3	75.81	74.02
C-4	73.93	72.26
C-5	52.80	52.44
C-6	64.53	60.86

[a] Referenced to internal 1,4-dioxane (δ 69.41 with respect to DSS in dilute D_2O).

Table 3
Comparison of ^{1}H NMR of **1** to 1,4-dideoxy-1,4-imino-L-ribitol [24]

1, (2*R*,3*R*,4*S*)-2-hydroxymethyl pyrrolidine-3,4-diol					1,4-dideoxy-1,4-imino-L-ribitol				
δ (ppm)	Mult.	$\Delta\delta$ (ppm) [a]	$J_{H,H'}$ (Hz)	Assignment [b]	δ (ppm)	Mult.	$\Delta\delta$(ppm) [a]	$J_{H,H'}$ (Hz)	Assignment [b]
2.87	dd		$J_{5,5'} = 12.4$; $J_{4,5} = 3.7$	H-5	2.58	dd		$J_{5,5'} = 12.4$; $J_{4,5} = 3.9$	H-5
		0.25					0.26		
3.12	m			H-2	2.84	m			H-2
		0.08					0.10		
3.20	dd		$J_{4,5'} = 5.2$	H-5′	2.94	dd		$J_{4,5'} = 5.3$	H-5′
		0.45					0.46		
3.65	dd		$J_{6,6'} = 11.7$; $J_{2,6} = 6.1$	H-6	3.40	dd		$J_{6,6'} = 11.6$; $J_{2,6} = 6.0$	H-6
		0.12					0.11		
3.77	dd		$J_{2,6'} = 4.3$	H-6′	3.51	dd		$J_{2,6'} = 4.3$	H-6′
		0.13					0.13		
3.90	dd		$J_{3,4} = 5.2$; $J_{2,3} = 7.3$	H-3	3.64	dd		$J_{3,4} = 5.2$; $J_{2,3} = 7.3$	H-3
		0.28					0.28		
4.18	dt			H-4	3.92	dt			H-4

[a] $\Delta\delta = (\delta_{H\text{-}y}) - (\delta_{H\text{-}x})$, where x and y indicate the numbers of consecutive protons, i.e., $(\delta_{H\text{-}2}) - (\delta_{H\text{-}5})$.
[b] Numbering according to the convention used in this paper.

Table 4
Comparison of ^{1}H NMR for **1·HCl** to that of 1,4-dideoxy-1,4-imino-D-ribitol hydrochloride [12] and 1,4-dideoxy-1,4-imino-D-lyxitol hydrochloride [23]

1·HCl					1,4-dideoxy-1,4-imino-D-ribitol·HCl					1,4-dideoxy-1,4-imino-D-lyxitol·HCl				
δ (ppm)	Mult.	Δδ (ppm) [a]	$J_{H,H'}$ (Hz)	Assignment [b]	δ (ppm)	Mult.	Δδ (ppm) [a]	$J_{H,H'}$ (Hz)	Assignment [b]	δ (ppm)	Mult.	Δδ (ppm) [a]	$J_{H,H'}$ (Hz)	Assignment [b]
3.38	dd		$J_{5,5'}$ = 13.0; $J_{4,5}$ = 2.0	H-5	3.22	dd		$J_{5,5'}$ = 13.0; $J_{4,5}$ = 2.0	H-5	3.03	dd		$J_{5,5'}$ = 12.2; $J_{4,5'}$ = 7.3	H-5′
		0.13					0.11					0.33		
3.51	dd		$J_{4,5'}$ = 4.0	H-5	3.33	dd		$J_{4,5'}$ = 4.0	H-5′	3.36	dd		$J_{4,5}$ = 7.3	H-5
		0.13					0.13					0.20		
3.64	m			H-2	3.45	m			H-2	3.56	m			H-2
		0.20					0.20					0.16		
3.84	dd		$J_{6,6'}$ = 12.6; $J_{2,6}$ = 6.0	H-6	3.66	dd		$J_{6,6'}$ = 12.6; $J_{2,6}$ = 6.0	H-6	3.72dd			$J_{6,6'}$ = 12.1; $J_{2,6'}$ = 8.4	H-6′
		0.15					0.15					0.09		
3.99	dd		$J_{2,6'}$ = 3.5	H-6′	3.81	dd	$J_{2,6'}$ = 3.5	H-6′	3.81	dd		$J_{2,6}$ = 5.0	H-6	
		0.23					0.23					0.36		
4.22	dd		$J_{3,4}$ = 4.2; $J_{2,3}$ = 8.6	H-3	4.04	dd		$J_{3,4}$ = 4.1; $J_{2,3}$ = 8.5	H-3	4.17	t	$J_{2,3}$ = 4.1	H-3	
		0.18					0.18					0.14		
4.40	dt			H-4	4.22	dt			H-4	4.31	dt		$J_{3,4}$ = 4.1	H-4

[a] $\Delta\delta = (\delta_{H\text{-}y}) - (\delta_{H\text{-}x})$, where x and y indicate the numbers of consecutive protons, i.e., $(\delta_{H\text{-}2}) - (\delta_{H\text{-}5})$.
[b] Numbering according to the convention used in this paper.

Table 5
Comparison of ^{13}C NMR for **1** and **1·HCl** to that of 1,4-dideoxy-1,4-imino-D-ribitol hydrochloride [12], and 1,4-dideoxy-1,4-imino-D-lyxitol hydrochloride [23]

1				**1·HCl**				1,4-dideoxy-1,4-imino-D-ribitol hydrochloride				1,4-dideoxy-1,4-imino-D-lyxitol hydrochloride			
δ (ppm)	Mult. [a]	Δδ (ppm)	Assign-ment [b]	δ (ppm)	Mult. [a]	Δδ (ppm)	Assign-ment [b]	δ (ppm)	Mult. [a]	Δδ (ppm)	Assign-ment [b]	δ (ppm)	Mult. [a]	Δδ (ppm)	Assign-ment [b]
52.80	t		C-5	52.44	t		C-5	50.66	t		–	47.87	t		C-5
		11.73				8.42				8.38				10.51	
64.53	t		C-6	60.86	t		C-6	59.04	t		–	58.38	t		C-6
		0.7				3.81				3.82				4.84	
65.23	d		C-2	64.67	d		C-2	62.86	d		–	63.22	d		C-2
		8.7				7.59				7.56				7.33	
73.93	d		C-4	72.26	d		C-4	70.42	d		–	70.55	d		C-3
		1.88				1.76				1.75				0.15	
75.81	d		C-3	74.02	d		C-3	72.17	d		–	70.70	d		C-4

[a] Refers to multiplicity of the ^{13}C signal observed in the absence of proton decoupling.
[b] Numbering according to the convention used in this paper.

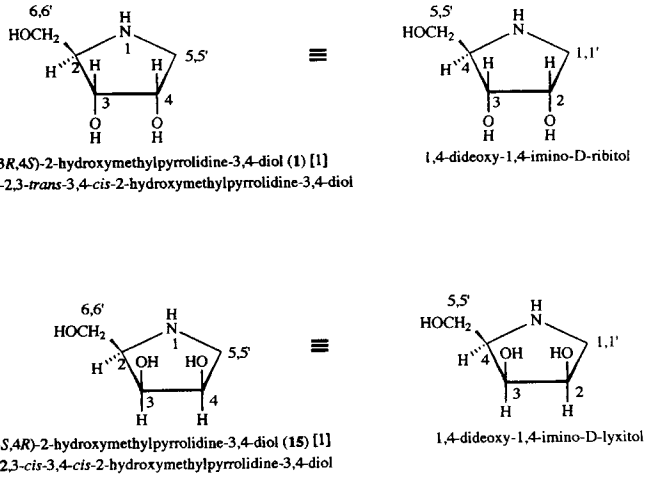
tion of one- and two-dimensional NMR techniques. The NMR spectra of **1** were compared to those reported for authentic (2*R*,3*R*,4*S*)-2-hydroxymethylpyrrolidine-3,4-diol [12,24] (see Tables 3–5 and Scheme 3) and the data agreed well in all respects. The reported values for the chemical shifts were slightly different than we observed due to the use of differing chemical shift references. We therefore compared the chemical-shift difference which separated each signal from its neighbors. These chemical shift differences ($\Delta\delta$) are independent of the chemical-shift reference. When the two data sets were compared in this way, the values for $\Delta\delta$ matched to within 0.02 ppm. In addition, the spectra of our **1** were significantly different from those reported for the isomeric (2*R*,3*S*,4*R*)-2-hydroxymethylpyrrolidine-3,4-diol (**15**) [25]. A particularly significant spectral difference between **1** · **HCl** and **15** · **HCl** is in the value for $J_{2,3}$, because this coupling constant reflects the difference between the 2,3-*trans*-linkage in **1**, and the 2,3-*cis*-stereochemistry in **15**. These values differ significantly, with $J_{2,3}$ 8.6 Hz for **1** · **HCl**, and $J_{2,3}$ 4.1 Hz for **15** · **HCl** [23]. The comparison of the NMR spectra thus unambigously identifies the product of our synthesis as **1**, and therefore proves for the first time that the major product produced in the OsO_4-catalyzed hydroxylation of **2a** was the 2,3-*trans*-3,4-*cis*-glycol **7a**.

The tosyl derivative **12b** was deprotected and converted to **1** by treatment with a solution of sodium naphthalenide anion in an apolar aprotic solvent. The isopropylidene acetal was cleaved during the aqueous and acidic workup, and the strongly basic **1** isolated by absorption on a cation-exchange resin (Dowex 50, H^+ form) followed by elution into aqueous ammonia, and conversion to the hydrochloride. Isolated yields of **1** · **HCl** from **12b** were 80–90%.

3. Experimental

General methods.—^1H NMR spectra were obtained at 300 MHz unless otherwise indicated, and ^{13}C NMR spectra were determined at 75 MHz. Two-dimensional data sets were collected on a Varian VXRA-400 MHz spectrometer at 25°C. The chemical shifts are reported in ppm from an internal standard of Me_4Si (for organic solutions) or sodium 4,4-dimethyl-4-silapentanoate[2,2,3,3-$^2H_4$] (for aqueous solutions). Optical rotations were determined on a Autopol III automatic polarimeter (Rudolf Research, Flanders, NJ) using a 2-dm cell.

Thin-layer chromatography was performed on 2.5 × 10 cm glass-supported silica gel GHLF plates (Analtech, Newark, DE) for normal phase chromatography. The positions of bands were visualized by examination under UV-light or by spraying the plate with 10% ethanolic H_2SO_4 and charring the plate at 200°C for a few minutes. Flash-column chromatography was performed using silica gel 60 (25–40 μm) (Toronto Research Chemicals, ON, Canada) packed in a 57-mm diameter pyrex tube. Analytical reversed phase HPLC was performed using a LDC system consisting of two constaMetric metering pumps, a model 400 gradient programmer, a dynamic mixer, and a Model 1203 A UV Monitor III fixed-wavelength detector operated at 254 nm. The solid phase was a 3.9 × 300 mm C-18 reversed-phase



Scheme 3. Comparison of common nomenclature and numbering schemes for 3,4-*cis*-2-hydroxymethyl pyrrolidine-3,4-diols.

column (C-18 Bondapak, 15–20 μm; Waters Associates, Milford, MA) and the separations were developed isocratically with 60:4 MeOH–H_2O at a flow rate of 1 mL/min. Preparative-scale HPLC was performed on a Delta Prep 3000 system (Waters Associates, Milford, MA) equipped with a 600E system controller, a Model 484 tuneable absorbance detector operated at 254 nm, and a PrepPak-1000 Radial Compression Module. Preparative reversed phase separations were performed using a 47 × 300 mm PrepPak cartridge (15–20 μm, C-18 Bondapak, 125 Å), developed isocratically with 1:1 MeOH–H_2O at a flow rate of 80 mL/min.

Fast-atom bombardment mass spectra were acquired on a Finnigan MAT 212 mass spectrometer in combination with an INCOS data system. An Ion Tech saddle field atom gun operating at 8 kV was used with Xe gas. The ion source temperature was ~60°C, and the accelerating voltage was 3 kV. Samples were dissolved in H_2O, 10 mg/mL, and 1 μL of the solution applied to the copper probe tip. Thioglycerol (~2 μL) was added and mixed thoroughly with the sample. The contribution of the matrix was subtracted from each spectrum.

Materials.—Reagent grade THF (tetrahydrofuran) was dried over Na and benzophenone and distilled under an atmosphere of N_2. Anhydrous DMF (*N,N*-dimethylformamide) was purchased from Aldrich Chemical Co. (Milwaukee, WI) and transferred via syringe under an atmosphere of dry N_2. Dry MeOH was distilled from over CaH_2, transferred under N_2, and stored in tightly stoppered containers. Dry pyridine was distilled from over BaO, transferred under N_2, and stored in tightly stoppered containers. *p*-Toluenesulfonyl chloride was purified by crystallization from $CHCl_3$ and hexane. All other reagents and solvents were of the highest available purity and were used without further treatment.

(2S,4R)-1-(p-Tolylsulfonyl)-4-hydroxyproline (**3b**).—(2*S*,4*R*)-4-Hydroxyproline (29.4 g, 0.224 mol; *trans*-4-hydroxy-L-proline, Aldrich) was dissolved in 448 mL of 1

M aq NaOH (0.448 mol), the solution stirred vigorously with an overhead stirring apparatus, and a solution of *p*-tolylsulfonyl chloride (46.9 g, 0.246 mol; 10% excess) in 450 mL of Et_2O added. The two phases were stirred for 7 h and allowed to stand overnight. The phases were separated and the aqueous phase washed six times with 200-mL portions of ether. Ether washings were discarded, and the pH of the aqueous phase adjusted to 2 by adding concd HCl. The solid which separated (53.7 g) was recrystallized from boiling H_2O and dried in vacuo to produce 50.5 g (80% yield) of white crystals; mp 147–152°C (reported [26] mp 157°C); R_f 0.33 (silica gel; 98:1:1 EtOAc–MeOH–AcOH); ^1H NMR (Me_2SO-d_6) δ 2.05–2.15 (m, 2 H, H-3, 3′), 2.42 (s, 3 H, tosyl-CH_3), 3.24–3.35 (m, 1 H, H-5), 3.57 (dd, 1 H, *J* 4.1, 10.8 Hz, H-5′), 4.27 (t, 1 H, *J* 7.9 Hz, H-2), 4.32–4.34 (m, 1 H, H-4), 7.38 (d, 2 H, *J* 8.4 Hz, tosyl-H), 7.75 (d, 2 H, tosyl-H); ^{13}C NMR (75 MHz, Me_2SO-d_6) δ 21.52, 40.25, 57.50, 61.12, 70.48, 128.89, 130.64, 135.84, 145.20, 175.91.

*(2S,4R)-1-(*p*-Tolylsulfonyl)-4-hydroxyproline methyl ester* (**4b**).—(2*S*,4*R*)-1-(*p*-Tolylsulfonyl)-4-hydroxyproline (**3b**) (49.75 g, 0.07 mol) was dissolved in 200 mL of dry MeOH (reagent grade, distilled from above CaH_2), cooled in an ice-bath and 10 mL of a solution of 4 N HCl in anhyd 1,4-dioxane added (0.04 mol, Pierce Chemical Co.). The solution was refluxed for 3 h until TLC (silica gel; 98:1:1 EtOAc–MeOH–AcOH) indicated that the starting material (R_f 0.33) had disappeared and that a new material (R_f 0.54) had appeared. The solution was treated with 20 g of solid $NaHCO_3$, and after vigorous mixing for 1–2 min filtered to remove solids. The filtrate and washings were evaporated in vacuo, the residue dissolved in $CHCl_3$ (200 mL), and the organic solution washed with 1 M $NaHCO_3$ (100 mL), satd aq NaCl (100 mL), and dried (anhyd Na_2SO_4). Evaporation of the solvent in vacuo left 48.9 g (96% yield), recrystallized from 1:2 EtOAc–hexanes to produce 40.7 g of white crystals; mp 97–98°C (reported [26] mp 104°C); R_f 0.14 (silica; 1:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ 2.06 (ddd, 1 H, *J* 4.5, 8.3, 13 Hz, H-3), 2.15–2.25 (m, 1 H, H-3′), 2.40 (s, 3 H, tosyl-CH_3), 2.65 (d, 1 H, *J* 3.5 Hz, -OH), 3.34 (dt, 1 H, *J* 1.4, 11.2 Hz, H-5), 3.57 (dd, 1 H, *J* 4.0, 11.2 Hz, H-5′), 3.72 (s, 3H, $-OCH_3$), 4.33 (t, 1 H, *J* 8 Hz, H-2), 4.4–4.5 (m, 1 H, H-4), 7.30 (d, 2 H, *J* 8.2 Hz, tosyl-H), 7.74 (d, 2 H, *J* 8.2 Hz, tosyl-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.53, 39.34, 52.51, 56.42, 59.51, 69.80, 127.69, 129.64, 134.55, 143.86, 172.76.

*(2S,4R)-1-(*p*-Tolylsulfonyl)-4-(*p*-tolylsulfonyl)oxyproline methylester* (**5b**).—(2*S*,4*R*)-1-(*p*-Tolylsulfonyl)-4-hydroxyproline methyl ester (**4b**) (39 g, 0.13 mol) was dissolved in 80 mL of dry pyridine in a 500 mL Erlenmeyer flask fitted with a 24/40 joint. The solution was stirred magnetically and cooled in an ice-bath as a solution of *p*-toluenesulfonyl chloride (30.1 g, 0.158 mol; 20% excess) in dry pyridine was added dropwise using an addition funnel. After the addition was complete the flask was stoppered and kept at 5°C for 7 days. The contents of the flask were poured into 500 mL of ice–H_2O and the mixture extracted with 200 mL of CH_2Cl_2. The aqueous phase was extracted three times with 50-mL portions of CH_2Cl_2, and the combined CH_2Cl_2 extracts washed with H_2O (100 mL), five times with 100-mL portions of 4 N aq HCl, once with 100 mL of 5% $NaHCO_3$ solution, and once with 100 mL of satd aq NaCl solution. Extracts were dried and

the solvent evaporated in vacuo leaving 56.8 g (96% yield) of a colorless material crystallized from EtOAc (100 mL) and Et_2O (500 mL); mp 94–96°C (reported [26] mp 94–95.5°C); $[\alpha]_D$ −50.8° (*c* 1.0, $CHCl_3$), reported [26] $[\alpha]_D^{20}$ −54.1° (*c* 1.0, $CHCl_3$); R_f 0.21 (silica gel; 3:1 hexanes–EtOAc); ^1H NMR ($CDCl_3$) δ 2.19 (ddd, 1 H, *J* 4.9, 7.9, 13 Hz, H-3), 2.3–2.4 (m, 1 H, H-3′), 2.42 (s, 3 H, tosyl-CH_3), 2.45 (s, 3 H, tosyl-CH_3), 3.57 (dt, 1 H, *J* 1.3, 12.4 Hz, H-5), 3.69 (dd, 1 H, *J* 4.3, 12.5 Hz, H-5′), 3.73 (s, 3 H, CH_3O–), 4.26 (t, 1 H, *J* 7.9 Hz, H-2), 4.90–5.05 (m, 1 H, H-4), 7.30 (d, 2 H, *J* 8 Hz, tosyl-H), 7.33 (d, 2 H, *J* 7 Hz, tosyl-H), 7.61 (d, 2 H, *J* 8 Hz, tosyl-H), 7.70 (d, 2 H, *J* 8 Hz, tosyl-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.56, 21.64, 37.29, 52.66, 53.93, 59.17, 78.27, 118.25, 127.67, 129.75, 130.02, 133.17, 134.29, 144.13, 145.36, 171.57. Anal. Calcd for $C_{20}H_{23}NO_7S_2$: C, 52.96; H, 5.11; N, 3.09; Found: C, 53.08; H, 5.16; N, 3.05.

*(2S,4S)-1-(*p*-Tolylsulfonyl)-4-phenylselenoproline methyl ester* (**6b**).—A 1-L 2-neck flask was fitted with a magnetic stirrer, a reflux condenser, and a N_2 inlet. Dry MeOH was added, followed by diphenyl diselenide (9.75 g, 0.031 mol, Aldrich). The resulting suspension was stirred and warmed slightly on a steam bath to dissolve the diphenyl diselenide. After the yellow solution had cooled somewhat, 3.5 g of solid $NaBH_4$ (0.093 mol) was added in small portions until the color of the diphenyldiselenide had disappered. (2*S*,4*R*)-1-(*p*-Tolylsulfonyl)-4-(*p*-tolylsulfonyl)oxyproline methyl ester (**5b**) (22.65 g, 0.05 mol) was added to the stirred solution, the mixture purged with N_2, and brought to reflux under N_2. The solution was refluxed for 18 h at which time TLC (silica; 1:1 EtOAc–hexanes) indicated that the starting material (R_f 0.35) had disappeared and that a new high R_f material had appeared. The product was purified by removing the MeOH in vacuo and partitioning the residue between $CHCl_3$ (500 mL) and 0.5 N aq HCl (250 mL). The organic phase was washed three times with 200-mL portions of H_2O, and dried (Na_2SO_4). Removal of the solvent in vacuo left a yellow amorphous solid from which 16.4 g of a colorless solid was isolated by crystallization from 1:3 EtOAc–hexanes. The solvent was removed from the mother liquor in vacuo and the residue purified by flash-column chromatography on silica (150 g) and development with 1:10 EtOAc–hexanes (1 L) followed by 1:3 EtOAc–hexanes (1 L). The product eluted into the 1:3 EtOAc–hexanes resulting in the isolation of an additional 2.3 g of the selenide as a colorless crystalline solid; mp 105–107°C; $[\alpha]_D^{20}$ −37.6° (*c* 1.0, $CHCl_3$); R_f 0.26 (silica, 3:1 hexanes–EtOAc); ^1H NMR ($CDCl_3$) δ 2.05 (ddd, 1 H, *J* 7.6, 9.5, 13 Hz, H-3), 2.42 (s, 3 H, tosyl-CH_3), 2.57 (dt, 1 H, *J* 7, 13 Hz, H-3′), 3.15-3.3 (m, 1 H, H-4), 3.35 (dd, 1 H, *J* 9.2, 10.9 Hz, H-5), 3.71 (s, 3 H, CH_3O–), 3.84 (dd, 1 H, *J* 7, 10.7 Hz, H-5′), 4.34 (t, 1 H, *J* 7.7 Hz, H-2), 7.23–7.46 (m, 7 H, aromatic), 7.73 (d, 2 H, *J* 8.3 Hz, tosyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.54, 36.95, 37.75, 52.51, 54.83, 60.42, 127.45, 127.61, 128.30, 129.29, 129.75, 129.99, 134.84, 135.32, 143.90, 171.70. Anal. Calcd for $C_{19}H_{21}O_4SSe$: C, 52.05; H, 4.83; N, 3.19; Found: C, 52.14; H, 4.98; N, 3.15.

(2*S*)-3,4-Dehydroproline methyl ester · HCl was purchased from Bachem Bioscience Inc. (Philadelphia, PA; product no. F-1500). The sample was a colorless amorphous solid; mp 111–114°C, $[\alpha]_D^{20}$ −195° (*c* 1.0, CH_3OH); R_f 0.65 (silica, 70:42:10:0.5 $CHCl_3$–MeOH–H_2O–AcOH).

(2S)-1-Benzyloxycarbonyl-3,4-dehydroproline methyl ester (**2a**).—This was prepared from **3a** using the procedure of Rueger and Benn [18], or from (2*S*)-3,4-dehydroproline methyl ester · HCl (Bachem). (2*S*)-3,4-Dehydroproline methyl ester · HCl, 1.05 g (6.35 mmol) was dissolved in 10 mL DMF to which 1.32 mL (0.962 g, 9.53 mmol) of Et_3N was added. The mixture was stirred magnetically and 1.80 g (7.23 mmol) of *N*-(benzyloxycarbonyloxy)succinimide was added via an addition funnel, as a solution in 2 mL of DMF. The reaction was allowed to proceed overnight under N_2, until (2*S*)-3,4-dehydroproline methyl ester was completely consumed. The mixture was added to H_2O and the mixture extracted three times with 50-mL portions of Et_2O. The organic extracts were combined and ether was removed by evaporation under diminished pressure. The residue (1.89 g) was purified by flash-column chromatography using 95 g silica gel and eluting with 1:2 EtOAc–hexane. The fractions containing the product were combined, the solvent evaporated under diminished pressure, and the last traces of solvent were removed under high vacuum affording 1.46 g of a colorless oil (88% yield); $[\alpha]_D^{20}$ −189.6° (*c* 1.0, $CHCl_3$), reported [16] $[\alpha]_D^{20}$ −210.5° (*c* 1.7, $CHCl_3$); R_f 0.65 (silica gel, 1:1 EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 3.60 and 3.76 (s, 3 H, $-OCH_3$), 4.28–4.35 (m, 2 H, H-5), 5.06–5.25 (m, 3 H, H-2 and CH_2-Ph), 5.72–5.79 (m, 1 H, H-4), 5.95–6.02 (m, 1 H, H-3), 7.24–7.36 (m, 5 H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 52.23 and 52.41, 53.36 and 53.85, 66.27 and 66.56, 67.11 and 67.17, 124.70, 127.54, 127.82 and 127.92, 127.98 and 128.02, 128.41 and 128.46, 129.06 and 129.17, 136.45 and 136.54, 153.93 and 154.37, 170.38 and 170.62. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.75; N, 5.36; Found: C, 63.96; H, 5.84; N, 5.20.

(2S)-1-(p-Tolylsulfonyl)-3,4-dehydroproline methyl ester (**2b**).—(2*S*,4*S*)-1-(*p*-Tolylsulfonyl)-4-phenylselenoproline methyl ester (**6b**) (9 g, 0.02 mol) and 2.5 mL dry pyridine (2.44 g, 0.038 mol) were dissolved in 100 mL of CH_2Cl_2, cooled in an ice-bath, and stirred vigorously with an overhead mechanical stirrer as 5.8 g of 30% aq H_2O_2 (0.051 mol) was added dropwise using a disposable pipette. The mixture was stirred with cooling for 1 h, the cooling-bath removed, and the mixture allowed to warm to room temperature over 2 h. The contents of the flask were washed into a separatory funnel with 100 mL of CH_2Cl_2, and the organic phase washed three times with 50-mL portions of H_2O, twice with 50-mL portions of 1 N HCl, twice with 50-mL portions of H_2O, and once with 50 mL of satd aq NaCl solution. The CH_2Cl_2 solution was dried (anhyd Na_2SO_4) and the solvent evaporated in vacuo leaving 7.57 g of an orange residue. The product was purified from phenylselenides by flash-column chromatography using 120 g of silica gel. The sample was applied as a solution in 15 mL CH_2Cl_2 and the chromatography developed with 2:1 hexanes–EtOAc. Fractions containing a colorless UV-positive material with R_f 0.2 (silica, 3:1 hexanes–EtOAc) were combined and the solvent evaporated in vacuo to leave 4.0 g (70% yield) of a colorless solid material crystallized from 1:4 EtOAc–hexanes; mp 106.5–107°C; $[\alpha]_D^{20}$ −253.3° (*c* 1.0, $CHCl_3$); R_f 0.21 (silica; 3:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ 2.43 (s, 3 H, tosyl-CH_3), 3.75 (s, 3 H, $-OCH_3$), 4.19–4.21 (m, 2 H, H-5), 5.12–5.14 (m, 1 H, H-2), 5.65–5.68 (m, 1 H, olefinic-H), 5.84–5.87 (m, 1 H, olefinic-H), 7.32 (d, 2 H, *J* 8.1 Hz, tosyl-H), 7.78 (d, 2 H, tosyl-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.52, 52.54, 55.13, 68.13, 124.82,

127.60, 128.58, 129.73, 135.54, 143.75, 170.20. Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98; Found: C, 55.38; H, 5.43; N, 4.90.

OsO_4-Catalyzed hydroxylation of **2a**: *(2S,3R,4S)-1-benzyloxycarbonyl-3,4-dihydroxyproline methyl ester* (**7a**) *and (2S,3S,4R)-1-benzyloxycarbonyl-3,4-dihydroxyproline methyl ester* (**8a**).—The OsO_4 reagent was prepared by dissolving 500 mg OsO_4 (Aldrich) in 25 mL of *tert*-butanol followed by addition of 1 drop of 30% H_2O_2 as a preservative. This solution was stored at 5°C in the dark. *N*-Methylmorpholine *N*-oxide (0.97 g, 7.18 mmol, Aldrich) was dissolved in a mixed solvent of 15 mL *tert*-butyl alcohol, 6 mL THF, and 1.5 mL H_2O. One mL of the above OsO_4 stock solution (20 mg) was added and the mixture was stirred magnetically in an oil bath at 50°C. A solution of 1.560 g of (2*S*)-1-*Z*-3,4-dehydroproline methyl ester (**2a**) in 5 mL THF was added dropwise via an addition funnel and the reaction was allowed to proceed overnight at 50°C. The reaction was determined to be complete when TLC indicated that the starting material had disappeared. The mixture was cooled and OsO_4 was removed by passing H_2S through the solution which was then filtered through a pad of Celite. Volatiles were removed under diminished pressure to leave a thick yellow liquid. The product was purified by flash-column chromatography using 70 g of silica gel and developing with 1000 mL of 2:1 EtOAc–hexane followed by 500 mL of 2% MeOH in EtOAc. Fractions containing **7a** and **8a** were combined and the volatiles removed under diminished pressure to afford 1.72 g (97% yield) of the mixture of **7a** and **8a**, a colorless, thick liquid; $[\alpha]_D^{20}$ −14.5° (*c* 1.0, $CHCl_3$); R_f 0.4 (silica gel, 2:1 EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 2.81 and 2.90 (d, 1 H, –OH), 3.15 and 3.22 (d, 1 H, –OH), 3.58 and 3.79 (s, 3 H, $-OCH_3$), 3.49–3.80 (m, 2 H, H-5), 4.23–4.33 (m, 3 H, H-2, H-3 and H-4), 4.98–5.22 (m, 2 H, $-CH_2$–Ph), 7.26–7.35 (m, 5 H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 50.86 and 51.18, 52.69 and 52.41, 64.34 and 64.61, 67.46, 69.78 and 70.50, 74.79 and 75.80, 127.81 and 127.86, 128.12, 128.42 and 128.45, 135.98 and 136.10, 154.58 and 155.10, 171.55 and 171.76. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.76; N, 4.75; Found: C, 56.86; H, 5.82; N, 4.74.

OsO_4-Catalyzed hydroxylation of **2b**: *(2S,3R,4S)-1-(*p*-tolylsulfonyl)-3,4-dihydroxyproline methyl ester* (**7b**) *and (2S,3S,4R)-1-(*p*-tolylsulfonyl)-3,4-dihydroxyproline methyl ester* (**8b**).—*N*-Methylmorpholine-*N*-oxide (0.69 g, 5.11 mmol) was dissolved in a mixed solvent consisting of 15 mL *tert*-butyl alcohol, 6 mL THF, and 1 mL of H_2O. A portion of an OsO_4 stock solution (0.75 mL) prepared as described above was added (15 mg of OsO_4) and the solution stirred using a magnetic stirrer and heated in a bath at 50°C. The substrate (2*S*)-1-(*p*-tolylsulfonyl)-3,4-dehydroproline methyl ester (**2b**) (1.2 g, 4.26 mmol) was added dropwise as a solution in THF (5–6 mL). Progress of the reaction was monitored by TLC (silica gel, 1:1 EtOAc–hexane). Heating was continued until starting material was consumed (18–20 h). The OsO_4 was removed by bubbling H_2S through the solution and filtering the resulting mixture through Celite to remove the precipitate. The solvent was removed by distillation in vacuo and the residue dried three times by adding 25-mL portions of toluene and evaporating the toluene under diminished pressure.

The NMR spectrum of the material revealed it to be a mixture of diols **7b** and

8b. These isomers were not separable by TLC or by HPLC. Analysis of the ^1H NMR spectrum indicated that the two isomeric compounds were present in a ratio of 7:1 with the 2,3-*trans*-3,4-*cis*-isomer **7b** being the major product; R_f 0.2 (silica, 1:1 hexane-EtOAc); ^1H NMR ($CDCl_3$) δ 2.42 (s, 3 H, tosyl-CH_3), 3.18 (d, 1 H, *J* 4 Hz, -O*H*), 3.27 (dd, 1 H, *J* 4, 10 Hz, H-5), 3.50 (d, 1 H, *J* 5 Hz, -O*H*), 3.61 (dd, 1 H, *J* 5, 10.5 Hz, H-5'), 3.76 (s, 3 H, -OCH_3), 4.10 (d, 1 H, *J* 4 Hz, H-2), 4.21–4.31 (m, 2 H, H-3 and H-4), 7.31 (d, 2 H, *J* 8 Hz, tosyl-H), 7.72 (d, 2 H, tosyl-H). A set of signals of lower intensity was observed and attributed to the minor isomer (2*S*,3*S*,4*R*)-1-(*p*-tolylsulfonyl)-3,4-dihydroxyproline methyl ester (**8b**): δ 2.43 (s, 3 H, tosyl-CH_3), 3.4 (dd, 1 H, *J* 5, 10 Hz, H-5), 3.54 (dd, 1 H, *J* 4, 11 Hz, H-5'), 3.77 (s, 3 H, -OCH_3), 4.36 (d, 1 H, *J* 8 Hz, H-2), the remaining signals could not be observed in the presence of the approximately 7-fold excess of **7b**.

(2S,3R,4S)-1-Benzyloxycarbonyl-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester (**9a**) *and (2S,3S,4R)-1-benzyloxycarbonyl-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester* (**10a**).—The unpurified mixture of glycols **7a** and **8a** (1.72 g, 5.83 mmol) was dissolved in 100 mL of 2,2-dimethoxypropane (distilled over CaH_2) to which 1.5 mL of 4 N HCl in 1,4-dioxane (Pierce Chemical Co.) was added and the mixture was stirred magnetically under an atmosphere of N_2. After 18 h, the acid was neutralized by addition of 10 mL 5% Na_2CO_3 solution and the mixture was partitioned between 50 mL of H_2O and 50 mL of ether. The ether extraction was repeated twice, the ether layers were combined, back-washed with H_2O, and dried (anhyd Na_2SO_4). Ether was removed under diminished pressure affording a residue that contained two materials: R_f 0.65 and 0.60 (TLC, silica gel, 1:2 EtOAc–hexane). The isopropylidene acetals **9a** and **10a** were separated by flash-column chromatography by applying the mixture to a column of silica gel (70 g) and eluting the products into 1:3 EtOAc–hexane. More than 90% of the major isomer **9a** eluted first, while the minor isomer, **10a**, co-eluted with the tailing fraction of **9a**. Further purification of **10a** was accomplished by column chromatography on silica gel (20 g, Camac DF-0) and development with 1:3 EtOAc–hexane. Solvents were removed under diminished pressure resulting in isolation of colorless heavy oils **9a** (1.66 g) and **10a** (0.140 g), in a combined yield of 92%.

Compound **9a**: R_f 0.80 (silica gel, 1:1 EtOAc–hexane); $[\alpha]_D^{20}$ −25.9° (*c* 1.0, $CHCl_3$), reported [16] $[\alpha]_D^{20}$ −34.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H, isopropylidene acetal-CH_3), 1.46 (s, 3 H, isopropylidene acetal-CH_3), 3.64 and 3.77 (s, 3 H, -OCH_3), 3.61–3.67 (m, 1 H, H-5), 3.88–3.98 (m, 1 H, H-5'), 4.54 and 4.63 (s, 1 H, H-2), 4.75 (m, 2 H, H-3 and H-4), 5.05–5.22 (m, 2 H, -CH_2–Ph), 7.26–7.37 (m, 5 H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.88, 26.78, 52.09, 52.55, 66.01 and 66.15, 67.23 and 67.35, 78.49 and 79.40, 82.35 and 83.31, 112.60, 127.76, 128.02, 128.46, 136.34, 154.64 and 155.23, 170.64; MS *m/z* calcd for $C_{17}H_{21}NO_6$: 335; found 335. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.27; N, 4.18; Found: C, 60.98; H, 6.32; N, 4.13.

Compound **10a**: R_f 0.75 (silica gel, 1:1 EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H, isopropylidene acetal-CH_3), 1.45 (s, 3 H, isopropylidene acetal-CH_3), 3.65 and 3.79 (s, 3H, -OCH_3), 3.58–3.95 (m, 2 H, H-5 and H-5'), 4.60 (s br, 1 H, H-2), 4.81–5.00 (m, 2 H, H-3, H-4), 5.00–5.21 (m, 2 H, -CH_2–Ph), 7.27–7.37 (m, 5

H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.92, 26.11, 51.12, 51.98, 63.43, 67.38, 78.90, 79.81, 113.80, 127.72, 127.97 and 128.10, 128.46, 136.24, 154.5, 168.98; MS m/z calcd for $C_{17}H_{21}NO_6$: 335; found 335.

Deprotection of (2S,3R,4S)-1-benzyloxycarbonyl-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester (**9a**) *by catalytic hydrogenolysis: (2S,3R,4S)-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester* (**9c**) *and (2R,3R,4S)-3,4-dihydroxyproline-3,4-*isopropylidene acetal methyl ester (**11**). Ammonium formate (320 mg, 5.08 mmol) was added to 5.0 mL of MeOH and stirred until dissolved. This solution was added to (2*S*,3*R*,4*S*)-1-*Z*-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester (**9a**) (532 mg, 1.59 mmol) in a 10-mL reaction vial, followed by 200 mg of 5% Pd–C (Aldrich Chemical Co) and the mixture was stirred magnetically for 90 min. The mixture was filtered through a pad of Celite, the solvent removed by evaporation under diminished pressure, and the residue extracted into EtOAc. The fine particles of NH_4HCO_2 were removed by filtration. The mixture initially contained a single component, (TLC, silica gel, 1% MeOH in EtOAc) (**9c**, R_f 0.40), but a second component began to appear on standing, (**11**, R_f 0.30). The amount of the second component was further increased during chromatography on silica gel. The separation and purification was accomplished using flash-column chromatography (30 g silica gel) and development with 500 mL of 3:1 EtOAc–hexane and 600 mL of 2% MeOH in EtOAc. Removal of solvents under diminished pressure resulted in the isolation of **9c** (176 mg) as a colorless oil, (2*R*,3*R*,4*S*)-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester (**11**) (26 mg) as a light-yellow solid, and a mixture of **9c** and **11** (24 mg) in a total yield of 70%.

Compound **9c**: R_f 0.40 (silica gel, 1% CH_3OH in EtOAc); $[\alpha]_D^{20}$ +27.4°; ^1H and ^{13}C NMR assignments were made using APT (attached proton test), COSY (correlated spectroscopy), and ^{13}C–^1H heteronuclear correlation experiments. ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H, isopropylidene acetal-CH_3), 1.48 (s, 3 H, isopropylidene acetal-CH_3), 1.9–2.5 (s br, 1 H, N-H), 2.96 (dd, 1 H, *J* 13.0, 4.0 Hz, H-5), 3.15 (d, 1 H, *J* 13.1 Hz, H-5′), 3.74 (s, 3 H, $-OCH_3$), 3.87 (s, 1 H, H-2), 4.73 (dd, 1 H, *J* 5.5, 4.1 Hz, H-4), 4.91 (d, 1 H, *J* 5.6 Hz, H-3); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.08 (isopropylidene acetal-CH_3), 26.21 (isopropylidene acetal-CH_3), 52.26 ($-OCH_3$), 52.75 (C-5), 67.22 (C-2), 81.37 (C-4), 84.02 (C-3), 111.51 (isopropylidene acetal quartenary-C), 172.07 (carbonyl). Anal. Calcd for $C_9H_{15}NO_4$: C, 53.73; H, 7.46; N, 6.97; Found: C, 53.52; H, 7.49; N, 6.80.

Compound **11**: mp 81–82.5°C; R_f 0.30 (1% MeOH in EtOAc); ^1H and ^{13}C NMR assignments were made as described for **9c**. ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H, isopropylidene acetal-CH_3), 1.48 (s, 3 H, isopropylidene acetal-CH_3), 2.65 (dd, 1 H, *J* 13.4, 3.4 Hz, H-5), 3.21 (d, 1 H, *J* 13.6 Hz, H-5′), 3.57 (d, 1 H, *J* 4.8 Hz, H-2), 4.71 (dd, 1 H, *J* 3.4, 5.2 Hz, H-4), 4.83 (dd, 1 H, *J* 5.1, 5.0 Hz, H-3); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.10 (isopropylidene acetal-CH_3), 25.61 (isopropylidene acetal-CH_3), 52.03 (C-5), 52.08 (O-CH_3), 66.37 (C-2), 81.69, 82.43 (C-3, C-4), 111.63 (isopropylidene acetal quarternary-C), 169.38 (carbonyl); MS m/z calcd for $C_9H_{15}NO_4$: 201, found 201. Anal. Calcd for $C_9H_{15}NO_4$: C, 53.73; H, 7.46; N: 6.97; Found: C, 52.68; H, 7.36; N: 6.97.

(2S,3R,4S)-1-(p-Tolylsulfonyl)-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester (**9b**).—The mixture of isomeric diols **7b** and **8b** (1.48 g, 4.69 mmol) was dissolved in 2,2-dimethoxypropane (40 mL, distilled from above CaH_2) and 4 M HCl in 1,4-dioxane (1 mL, Pierce Chemical Co.) was added. The mixture was vigorously stirred with a magnetic stirrer under N_2. The reaction was monitored by TLC (silica, 5% MeOH in $CHCl_3$). After 18 h, analysis indicated that all starting diol (R_f 0.45) was converted into a single new material (R_f 0.85). The acid was neutralized by adding solid Na_2CO_3 (7 g, 66 mmol) and shaking the mixture vigorously till foaming subsided. The solvent was removed in vacuo and the semisolid residue obtained was dissolved in ca. 5–7 mL MeOH. The solution was added to 0.1 M $NaHCO_3$ (100 mL). This mixture was extracted three times with 100-mL portions of 5% MeOH in $CHCl_3$. The organic extracts were combined, dried (anhyd $MgSO_4$), and the solvent removed in vacuo leaving 1.42 g (85% yield) of a white solid. The crude material was purified by flash-column chromatography on silica (150 g) using 5% MeOH in $CHCl_3$. The chromatographed material was homogeneous when examined using TLC (R_f 0.8, silica, 5% MeOH in $CHCl_3$). Analysis using reversed-phase HPLC (C-18 Bondapak) revealed two materials in a ratio of ca. 1:7, the smaller peak eluting at 5.2 min followed by the larger peak at 7.0 min. The mixture consisting of **9b** and **10b** was separated on a large scale using preparative reversed-phase HPLC. The column was equilibrated, a 250 mg sample applied, and the chromatography developed isocratically with 1:1 MeOH–H_2O at a flow rate of 80 mL/min. The minor isomer eluted first at 22–24 min followed thereafter by the major isomer at 30–32 min.

(2*S*,3*R*,4*S*)-1-(*p*-Tolylsulfonyl)-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester (**9b**) was identified as the major component present in the mixture which eluted from the preparative-HPLC column at 30–32 min; mp 123.5–124°C; R_f 0.5 (silica, 1:1 hexane–EtOAc); $[\alpha]_D^{20}$ −51.96° (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (s, 3 H, isopropylidene acetal-CH_3), 1.24 (s, 3 H, isopropylidene acetal-CH_3), 2.41 (s, 3 H, tosyl-CH_3), 3.68 (s, 3 H, $-OCH_3$), 3.72–3.73 (m, 2 H, H-5 and H-5′), 4.49 (s, 1 H, H-2), 4.73 (m, 2 H, H-3 and H-4), 7.30 (d, 2 H, *J* 8.1 Hz, tosyl-H), 7.51 (d, 2 H, tosyl-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.48, 24.65, 26.07, 52.51, 53.59, 66.91, 79.51, 83.31, 112.73, 127.32, 129.50, 136.47, 143.54, 170.03; EIMS: *m/z* (%, base), 355 [M^+] (0.04), 340 [$M^+ - CH_3$] (15), 296 (74), 200 (22), 155 (85), 91 (100); HPLC: single component, t_R 7 min (C-18, 60:40 MeOH–H_2O, 1 mL/min). Anal. Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96; N, 3.94. Found: C, 54.14; H, 6.06; N, 3.89.

(2*S*,3*S*,4*R*)-1-(*p*-Tolylsulfonyl)-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester (**10b**) was identified as the minor component in the mixture which eluted from the preparative-HPLC column at 22–24 min; mp 149–150°C; R_f 0.5 (silica, 1:1 hexane–EtOAc); $[\alpha]_D^{20}$ −16.28° (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H, isopropylidene acetal-CH_3), 1.42 (s, 3 H, isopropylidene acetal-CH_3), 2.44 (s, 3 H, tosyl-CH_3), 3.48–3.56 (m, 2 H, H-5 and H-5′), 3.71 (s, 3 H, $-OCH_3$), 4.44 (d, 1 H, *J* 7.6 Hz, H-2), 4.76 (ddd, 1 H, *J* 2.7, 5.4, 6.3 Hz, H-4), 4.90 (dd, 1 H, *J* 6.5, 7.2 Hz, H-3), 7.33 (d, 2 H, *J* 8.3 Hz, tosyl-H), 7.77 (d, 2 H, tosyl-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.55, 25.03, 25.90, 52.05, 52.47, 64.55, 78.52, 79.80,

114.02, 127.83, 129.63, 134.55, 143.40, 167.96, 167.96; EIMS: *m/z* (%base), 355[M^+] (0.04), 340[$M^+ - CH_3$] (10), 296 (60), 200 (25), 155 (70), 142 (55), 91 (100); HPLC: single component, t_R 5.2 min (C-18, 60:40 MeOH–H_2O, 1 mL/min). Anal. Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96; N, 3.94; Found: C, 53.50; H, 5.97; N, 3.96.

(2R,3R,4S)-1-Benzyloxycarbonyl-2-hydroxymethylpyrrolidine-3,4-diol-3,4-isopropylidene acetal (**12a**).—The starting ester **9a** (0.850 g, 2.54 mmol) was dissolved in 50 mL dry THF and stirred magnetically under N_2. $LiBH_4$ (0.110 g, 5.0 mmol) was added and the stirring was continued at ambient temperature for 90 min at which time the reduction was complete (TLC). The excess $LiBH_4$ was quenched by the addition of 1.0 mL of glacial AcOH, the mixture was added to 80 mL 5% $NaHCO_3$ solution and the aqueous mixture was extracted four times with 50 mL of $CHCl_3$. The combined organic extracts were back-washed with 50 mL H_2O and dried (anhyd Na_2SO_4). The solvent was removed under diminished pressure to yield 0.75 g of a residue which was further purified by flash-column chromatography on silica gel (60 g, 2:1 EtOAc–hexane). Removal of solvents under diminished pressure afforded 0.730 g (93% yield) of a colorless oil which solidified into a white solid; mp 70–71.5°C; R_f 0.60 (1:1 EtOAc–hexane); $[\alpha]_D^{20}$ −46.8° (*c* 1.0, $CHCl_3$ or MeOH), reported [16] $[\alpha]_D^{20}$ −46.0 (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H, isopropylidene acetal-CH_3), 1.45 (s, 3 H, isopropylidene acetal-CH_3), 3.60 (dd, 1 H, *J* 5, 12.6 Hz, H-5), 3.65–3.96 (m, 3 H, H-5′ and $-CH_2-OH$), 4.16 (dt br, 1 H, H-2), 4.59–4.76 (m, 2 H, H-3 and H-4), 5.16 (s, 2 H, $-CH_2-Ph$), 7.29–7.46 (m, 5 H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 24.98, 27.06, 52.72 and 53.49, 63.27, 65.02 and 65.63, 67.18, 78.76 and 79.06, 81.96 and 82.88, 111.68 and 111.91, 127.80, 128.06, 128.41, 136.48, 154.77 and 155.62. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56; Found: C, 62.35; H, 6.93; N, 4.53.

*(2R,3R,4S)-1-(*p*-Tolylsulfonyl)-2-hydroxymethylpyrrolidine-3,4-diol-3,4-isopropylidene acetal* (**12b**).—(2*S*,3*R*,4*S*)-1-(*p*-tolylsulfonyl)-3,4-dihydroxyproline-3,4-isopropylidene acetal methyl ester (**9b**) (0.2 g, 0.56 mmol) was dissolved in dry THF (5 mL), protected from moisture with N_2 and was magnetically stirred. $LiBH_4$ (15 mg, 0.68 mmol) was dissolved in THF (2 mL) and added to the methyl ester above as a single portion. After 4 h, TLC (silica, 3:2 hexane–EtOAc) indicated that all of the starting ester (R_f 0.38) was converted into a single new low R_f material (R_f 0.2). The reaction was stopped by the addition of glacial AcOH (160 μL). The solvents were evaporated in vacuo and chased three times with 5-mL portions of MeOH. The residue obtained was partitioned between 5% $NaHCO_3$ (50 mL) and $CHCl_3$ (50 mL). The aqueous layer was re-extracted twice with 50-mL portions of $CHCl_3$. The organic extracts were combined, dried (anhyd Na_2SO_4), and the solvent evaporated in vacuo. The crude product was recrystallised from EtOAc and hexane yielding 145 mg (79% yield) of white crystals; mp 110.5–112°C; R_f 0.2 (silica, 3:2 hexane–EtOAc); $[\alpha]_D^{20}$ −29.5° (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.83 (s, 3 H, isopropylidene acetal-CH_3), 1.17 (s, 3 H, isopropylidene acetal-CH_3), 2.25 (t, 1 H, –OH), 2.42 (s, 3 H, tosyl-CH_3), 3.56 (dd, 1 H), 3.70–3.81 (m, 2 H), 3.87 (t, 1 H), 3.9–3.98 (m, 1 H), 4.60 (dd, 1 H), 4.72 (dt, 1 H), 7.32 (d, 2 H, *J* 8.3 Hz, tosyl-H), 7.77 (d, 2 H, tosyl-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.44, 25.40, 25.79,

54.64, 64.29, 67.57, 79.02, 82.79, 111.47, 127.67, 129.60, 135.44, 143.66; FABMS (positive ion) m/z: 328[M + H]$^+$ (100). Anal. Calcd for $C_{15}H_{21}NO_5S \cdot 1/4C_6H_{14}$: C, 56.79; H, 7.07; N, 4.01; Found: C, 56.75; H, 7.10; N, 3.94.

(2R,3R,4S)-1-Benzyloxycarbonyl-2-hydroxymethylpyrrolidine-3,4-diol (**14a**).—The starting material, **12a** (0.520 g, 1.69 mmol), was stirred with 5 mL H_2O and 1.0 mL CF_3CO_2H was added. The dissolution of the starting material was complete on heating the mixture to 35°C for 15 min. The stirring was continued for 2 h at the end of which time TLC indicated the complete consumption of the starting material. The solvent was removed under diminished pressure and the last traces of H_2O removed by distilling off 10-mL portions of toluene three times. The residue was extracted into MeOH and further purified by flash-column chromatography on silica gel (40 g silica and 300 mL of 2:98 MeOH–EtOAc followed by 500 mL 5:95 MeOH–EtOAc). Fractions containing the product were combined and the solvent removed under diminished pressure to yield 0.435 g (96% yield) of a colorless liquid; R_f 0.35 (1:99 MeOH–EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.55–3.10 (s br, –OH), 3.51–3.72 (m, 2 H, H-5 and H-5'), 3.72–3.87 (m, 2 H, H-6), 3.88–4.02 (m, 1 H, H-2), 4.18–4.38 (m, 2 H, H-3 and H-4), 5.12 (s, 2 H, $-CH_2-$Ph), 7.28–7.43 (m, 5 H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 51.64, 63.55, 64.45, 67.47, 69.63, 73.33, 127.89–128.55, 136.11, 156.61. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.37; N, 5.24; Found: C, 58.30; H, 6.40; N, 5.18.

(2R,3R,4S)-2-Hydroxymethylpyrrolidine-3,4-diol (**1**).—*N*-Protected pyrrolidine diol **14a** (360 mg, 1.35 mmol), was hydrogenolyzed in 50 mL EtOH in the presence of 10% Pd–C catalyst, (50 mg) under an atmosphere of H_2 (25 psi) in a Parr apparatus. After 18 h, TLC indicated the complete consumption of the starting material. The mixture was filtered through a pad of celite and the solvent was removed under diminished pressure to yield a black residue which was decolorized by charcoal treatment. The residue after removal of solvent was washed with $CHCl_3$ to remove traces of the starting material, if present, and dried under high vacuum to yield a pale yellow liquid (170 mg, 95% yield); ^{1}H NMR (D_2O): see Table 1; ^{13}C NMR (75.6 MHz, D_2O): see Table 2.

(2R,3R,4S)-2-Hydroxymethylpyrrolidine-3,4-diol hydrochloride (**1 · HCl**).—This was prepared by dissolving the free base, **1** (150 mg), in H_2O (5 mL) and stirring with 1.5 mL of aq 1 N HCl. The resultant solution was freeze-dried affording 171 mg (89% yield) of a white amorphous powder; $[\alpha]_D^{20}$ +49.1° (*c* 1.0, H_2O); ^{1}H NMR (D_2O): see Table 1; ^{13}C NMR (75.6 MHz, D_2O): see Table 2. Anal. Calcd for $C_5H_{11}NO_3 \cdot HCl$: C, 35.40; H, 7.08; N, 8.26; Found: C, 35.45; H, 7.13; N, 8.19.

(2R,3R,4S)-2-Hydroxymethylpyrrolidine-3,4-diol hydrochloride (**1 · HCl**) *from (2R,3R,4S)-1-(*p*-tolylsulfonyl)-2-hydroxymethylpyrrolidine-3,4-diol-3,4-isopropylidene acetal* (**12b**).—Sodium naphthalenide solution in THF was prepared under N_2 according to the procedure of Closson et al. [27]. The protected pyrrolidine **12b** (327 mg, 1 mmol) was dissolved in 5 mL of dry THF, protected from moisture under an atmosphere of dry N_2, cooled in a dry ice–acetone bath to −78°C, and stirred magnetically as the dark green sodium naphthalenide (0.05–0.15 M) solution was added dropwise. Addition of sodium naphthalenide solution was continued until the deep-green color persisted, and stirring continued thereafter for an

additional h. Water (10 mL) was added, and the solvent removed under diminished pressure. The residue was dissolved in H_2O (5 mL) and applied to a column of cation-exchange resin (Dowex 50 X-4, H^+ form). The column was washed with H_2O, and the secondary amine eluted into 1 M NH_4OH. Fractions containing the ninhydrin-positive material were combined and the solvent evaporated under diminished pressure. The residue was dissolved in 15 mL 0.1 M HCl solution and stirred at room temperature under N_2 for 30 min to complete the removal of the isopropylidene acetal. Removal of the solvent under diminished pressure afforded 95.8 mg (72% yield) of **1 · HCl**, identical in all respects to that prepared above.

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