Entropy-Controlled Selectivity in the Vinylation of a Cyclic Chiral Nitrone. An Efficient Route to Enantiopure Polyhydroxylated Pyrrolidines

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Received September 19, 2000

A short synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol (LAB1) (**4**) and of 1,4-dideoxy-1,4-imino-D-galactitol (**5**), two azasugars active as enzymatic inhibitors, is reported. The key reaction is the addition of vinylmagnesium chloride to (3*S*,4*S*)-3,4-bis(benzyloxy)-3,4-dihydro-2*H*-pyrrole 1-oxide (**3**), a nitrone easily available from L-tartaric acid. Unexpectedly, the reaction affords the corresponding (2*S*,3*S*,4*S*)-1-hydroxy-2-ethenyl-3,4-bis(benzyloxy)pyrrolidine (**9**) in very good yield and in 93/7 diastereomeric ratio (dr) independently of the reaction temperature, thus representing a unique case of entropy-controlled reaction in a 100 K interval (from +20 °C to −80 °C). The trans intermediate **9** is converted in two steps (reduction, *N*-protection) into the common intermediate (2*S*,3*S*,4*S*)-1-(benzyloxycarbonyl)-3,4-bis(benzyloxy)-2-ethenylpyrrolidine (**11**). Double bond oxidation followed by reductive debenzylation opens a route to the target pyrrolidine azasugars **4** and **5**.

Introduction

Pyrrolidine azasugars of general structure **1** include members possessing interesting inhibitory activities toward glycosidases.[1] In the context of our interest in developing methods for the synthesis of biofunctional azasugars,[2] we envisaged, in (3*S*,4*S*)-3,4-bis(benzyloxy)-3,4-dihydro-2*H*-pyrrole 1-oxide (**3**), a cyclic nitrone easily accessible from L-tartaric acid,[3] an attractive starting material for the synthesis of polyhydroxylated pyrrolidines **1**. Assembly of the azasugar structure **1** was projected to arise via nucleophilic addition to **3**, since the reaction should allow the insertion of the side chain in a sterically biased fashion in favor of the trans adduct **2** (Scheme 1).

Herein we report the synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol (**4**) and 1,4-dideoxy-1,4-imino-D-galactitol (**5**) starting from **3** (see Figure 1).

Azasugar **4**, also referred to as LAB1,[4] is a powerful inhibitor of the cytopathic effect of AIDS retrovirus at noncytotoxic concentrations.[5] *ent*-**4** (DAB1), accessible through an identical sequence starting from *ent*-**3** (that means from D-tartaric acid), is, in turn, an α-glycosidase inhibitor[6] and a potential AIDS-retrovirus replication inhibitor.[8] The latter azasugar **5**, besides acting as weak α-glycosidase inhibitor,[7] was recently found to specifically inhibit the mycobacterial galactan biosynthesis, probably by inhibition of the mycobacterial UDP-Gal mutase.[8]

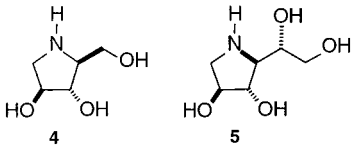
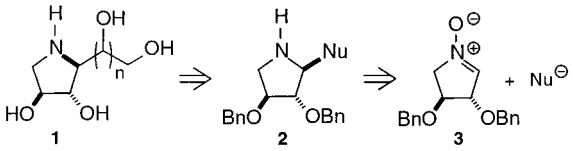


Figure 1.

Scheme 1



Results and Discussion

Several efforts have been devoted in the past decade to the use of nitrones in nucleophilic addition reactions to give *N*,*N*-disubstituted hydroxylamines.[9] Two propitious effects are displayed by the oxygen atom of the azomethine-*N*-oxide group: (i) it acts as an additional chelating center, allowing the formation of five-membered cyclic transition states in the 1,3-addition of simple organometallic reagents such as Grignard and organolithium reagents, and (ii) it strongly enhances the electrophilicity of the C=N double bond with respect to imines and other azomethines.

To achieve the synthesis of **4** and **5**, we first examined the addition of $^{-}$CN to **3**, by exploiting the procedure

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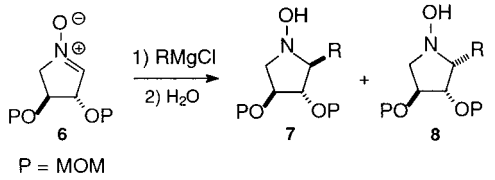
10.1021/jo0056545 CCC: $20.00
Published on Web 01/27/2001

reported by Merino et al. who made use of Et_2AlCN.[10] Unfortunately, diastereofacial selectivity was very low, affording trans adduct **2** (Nu = CN) in a dr = 3:2; moreover, purification of **2** was difficult because of the reversibility of the cyanide addition under acidic or chromatographic conditions.

Then, we turned our attention to two examples of addition of Grignard reagents to the MOM-protected nitrone **6** reported by Petrini (Scheme 2).[11,12]

Scheme 2



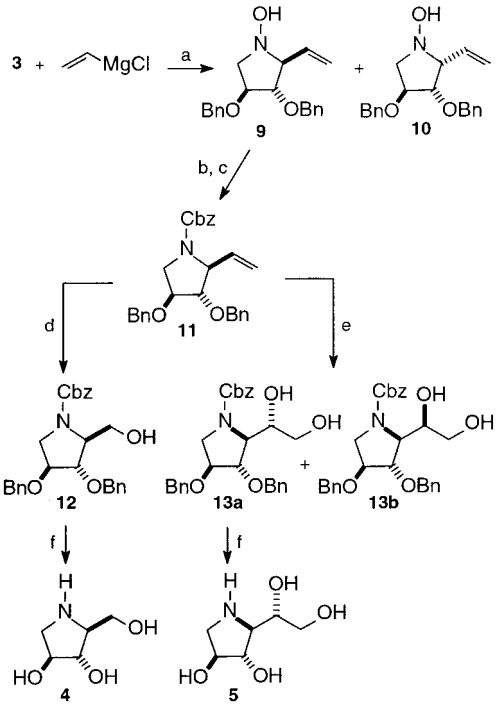
In particular, (−)-anisomycin and (+)-lentiginosine were obtained by the addition of 4-methoxybenzylmagnesium chloride and of 4-(benzyloxy)butylmagnesium bromide to **6**, respectively. The former Grignard reagent added to **6** in THF at 0 °C with modest trans selectivity to give **7** (dr = 3:2), but facial stereopreference could be reversed (**7**/**8** = 3:7) in the presence of a nitrone complexing agent, $MgBr_2$ etherate in dichloromethane. Higher facial diastereoselectivity was displayed by 4-benzyloxybutylmagnesium bromide which afforded the corresponding trans adduct **7** required for the synthesis of (+)-lentiginosine in a dr = 95:5, in THF at room temperature.

On the basis of these reports, we decided to test the direct vinylation of **3**, according to recent studies on the reaction of nitrones with vinyl organometallic reagents.[13] Our choice was based on the identification of vinylmagnesium chloride as a synthetic equivalent of d^1 synthons $^-CH_2OH$ and $^-CHOH-CH_2OH$, respectively.

Scheme 3 outlines our synthetic plan for the assembly of **4** and **5**: the key reaction was the addition of vinylmagnesium chloride to **3** to give **9** as the major diastereoisomer; completion of the sequence included conversion of **9** into the common intermediate **11** followed by oxidative manipulations of the vinyl side chain.

In our first experiment we carried out the addition of vinylmagnesium chloride to **3** in THF at 20 °C; after 1 h, the trans adduct (2*S*,3*S*,4*S*)-1-hydroxy-2-ethenyl-3,4-bis(benzyloxy)pyrrolidine (**9**) was obtained in 90% yield and in a dr = 93/7. Encouraged by the excellent facial selectivity observed at room temperature, we set about a systematic study of the dependence of dr's on temperature in the range +20/−80 °C. Reactions were quenched after 1 h with aqueous $NaHCO_3$, and the **9**/**10** relative ratio was determined by the integral ratio of the endocyclic CH_2 protons in the ^1H NMR spectrum of the crude products mixture. Chemical yields determined after flash chromatography on silica gel always lay in the 80−90% range. The stereochemical results, collected in Table 1

Scheme 3[a]



[a] Conditions: (a) THF, 20 °C, 1 h, 90%, dr = 93:7; (b) Zn/Cu, AcOH, H_2O, 70 °C, 30 min; (c) CbzCl, Et_3N, CH_2Cl_2, 12 h, 89% over two steps; (d) 1. O_3, CH_2Cl_2, −78 °C, 30 min; 2. $BH_3{\cdot}SMe_2$, −78 → 20 °C, 1 h, 67%; (e) AD-mix α, *t*-BuOH/H_2O, 24 h, 86%, dr = 83:17; (f) H_2/Pd on carbon, 2 N HCl in EtOH, 1 atm, 12 h, 85−90%.

Table 1. Stereoselectivity of the Addition of Vinylmagnesium Chloride to Nitrone 3 in THF

entry	*T* (°C)	$1/T$ (K^{-1})	**9**:**10**[a]	ln(**9**/**10**)
1	−80	5.18×10^{-3}	93:7	2.6
2	−62	4.74×10^{-3}	93:7	2.6
3	−40	4.29×10^{-3}	93:7	2.6
4	−18	3.92×10^{-3}	93:7	2.6
5	0	3.66×10^{-3}	93:7	2.6
6	+23	3.38×10^{-3}	93:7	2.6

[a] Relative values for **9** and **10** are affected by an absolute error of ±1.

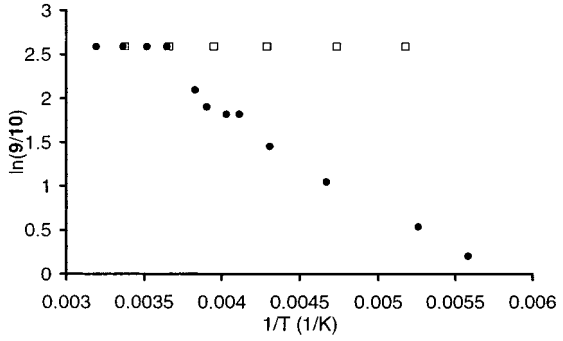


Figure 2. Eyring plots of the reaction in THF in the absence (□) and presence of diethylaluminum chloride (●).

and presented in Figure 2 in the form of an Eyring diagram (ln *S* vs reciprocal absolute temperature), were astonishing, since *no variation of selectivity was observed in the whole temperature interval examined* (ΔT = 100 K), *meaning that selectivity is dominated by entropic factors.*

The system **3**−Grignard reagent (Scheme 4) may be described as a typical irreversible addition of a nucleo-

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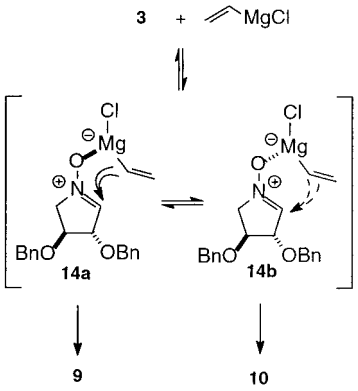
Scheme 4



phile to the diastereotopic faces of a C=X system. Nitrone magnesium precomplexation leads to two diastereomeric intermediates **14a**,**b** which open into two competing reaction channels for nucleophilic addition. According to Scharf's general kinetic scheme for selective processes,[14] selectivity *S* is expressed as the ratio between the overall rate constants k_1 and k_2 for the formation of diastereomeric 1-hydroxypyrrolidines **9** and **10**, which include all the partial steps (adduct formation, retrocleavage, interconversion, and final irreversible nucleophilic addition), and corresponds to the ratio between relative amounts I_1 and I_2 of **9** and **10** (eq 1):

$$S = k_1/k_2 = I_1/I_2 \quad (1)$$

Standard transition state theory (eq 2)[15] states that selectivity depends on temperature and $\Delta\Delta G^{\ddagger}$, namely the differences of free energies of activation of the two competing attacks to the *re* and *si* faces.

$$\ln S = \ln(k_1/k_2) = -(\Delta\Delta G^{\ddagger}/RT) = -(\Delta\Delta H^{\ddagger}/RT) + (\Delta\Delta S^{\ddagger}/R) \quad (2)$$

Applying eq 2 to results of Table 1, we may easily reckon for our reaction that $\Delta\Delta H^{\ddagger} = 0$ kcal·mol^{-1} and $\Delta\Delta S^{\ddagger} = 5.2 \pm 0.3$ cal·mol^{-1}·K^{-1}.

Usual reasoning recommends to lower the temperature in order to enjoy the best facial diastereoselectivity.[16] In fact, the lower the temperature the more restricted are internal motions and a preferred conformation is preferentially populated which differently hinders the nucleophile approach to the *re* and *si* faces. Cram, Cram-chelated, Felkin−Ahn, Karabatsos, and other models[17] sometimes help us in anticipating which is the preferred conformation and, hence, the configuration of the newly generated stereocenter relative to the preexisting ones. The main limit of the above-mentioned models is that they simply debate about face-selectivity on the basis of pure enthalpic grounds ($\Delta\Delta H^{\ddagger}$). Recently Cainelli, Giacomini et al. pointed out the importance of evaluating entropic contributions with a careful control of the dependence of selectivity on temperature, since there are cases where $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ favor different isomers.[14,18] When these conditions are found, diastereoselectivity may be inverted by a suitable change of the reaction temperature. Moreover, several examples are available in the literature where activation parameters $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ assume different values in defined temperature intervals giving rise in the corresponding Eyring plot to two (or more) linear regions intersecting at the inversion temperature.[19]

In our reaction system, the dominance of entropic factors in the +20/−80 °C temperature interval means that steric interactions between nitrone substituents and the approaching Grignard reagent along the two nitrone diastereotopic faces do not play any role in determining the stereochemical outcome of the reaction.

Considering that nitrone complexation, particularly with diethylaluminum chloride (DEAC),[20] is widely used both to increase reaction rates and to modify stereochemical outcomes of nucleophilic additions, we planned a second set of experiments in order to study the temperature/selectivity dependence of the system nitrone−DEAC complex (**15**)−Grignard reagent (Scheme 5). Results are reported in Table 2 and presented in Figure 2.

Scheme 5

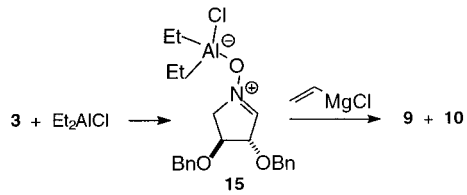


Table 2. Stereoselectivity of the Addition of Vinylmagnesium Chloride to Nitrone 1 in THF in the Presence of DEAC

entry	*T* (°C)	1/*T* (K^{-1})	**9**:**10**[a]	ln(**9**/**10**)
1	−94	5.58×10^{-3}	55:45	0.20
2	−83	5.26×10^{-3}	63:37	0.53
3	−59	4.67×10^{-3}	74:26	1.05
4	−41	4.31×10^{-3}	81:19	1.45
5	−30	4.11×10^{-3}	86:14	1.82
6	−25	4.03×10^{-3}	86:14	1.82
7	−17	3.90×10^{-3}	87:13	1.90
8	−12	3.82×10^{-3}	89:11	2.09
9	+1	3.65×10^{-3}	93:7	2.6
10	+11	3.52×10^{-3}	93:7	2.6
11	+24	3.37×10^{-3}	93:7	2.6
12	+40	3.19×10^{-3}	93:7	2.6

[a] Relative values for **9** and **10** are affected by an absolute error of ±1.

The new reactant system displays two regions in the Eyring plot: in the +40/0 °C interval, a zero slope indicates total entropic control on facial selectivity (dr = 93:7) favoring, as usual, hydroxylamine **9**. On the other hand, *a marked temperature control is exerted at T < 0 °C leading to an almost complete loss of selectivity at −94 °C*. Such a change in the enthalpy and entropy of activation probably reflects the dominance of different reaction mechanisms in different intervals of temperature when DEAC is present.

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1-Hydroxypyrrolidine **9** may be further enriched to the dr = 99:1 by chromatographic purification on silica gel. Cleavage of the N−O bond of **9** is carried out with Zn/Cu couple in aq AcOH at 70 °C, according to a protocol developed by us for the reduction of homoallylic hydroxylamines to homoallylic amines.[21] The unsaturated side chain offers further synthetic opportunities being possible, for instance, to carry out oxidative manipulations on it. With this aim we protected the amino group as Cbz and got the common intermediate **11**. First of all, we examined the ozonolysis followed by reductive quenching with $BH_3{\cdot}SMe_2$ which led to the Cbz protected (2*S*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-(hydroxymethyl)pyrrolidine **12**. The target 1,4-dideoxy-1,4-imino-L-arabinitol (**4**) may be freed by hydrogenolysis of **12** on Pd/carbon at atmospheric pressure in acidic ethanol (Scheme 3).

The synthesis of 1,4-dideoxy-1,4-imino-D-galactitol (**5**), on the other hand, requires dihydroxylation of the side-chain C=C bond of **11**. Since the hydroxylation of a closely related substrate, namely (2*S*,3*S*,4*S*)-1-benzyl-3,4-bis(benzyloxy)-2-ethenylpyrrolidine, carried out with the 4-methylmorpholine *N*-oxide/OsO_4 system was reported to occour with modest diastereoselectivity (75:25),[22] with the hope to exploit double asymmetric induction,[23] we tested the reaction of **11** with both Sharpless AD mix α and AD mix *β* systems.[24] The expected products were [2*S*-[2α(*R**),3*β*,4α]]-1-(benzyloxycarbonyl)-3,4-bis(benzyloxy)-2-(1,2-dihydroxyethyl)pyrrolidine (**13a**) and its epimer [2*S*-[2α(*S**),3*β*,4α]]-**13b**, the latter being a protected form of 1,4-dideoxy-1,4-imino-L-altritol. Surprisingly, both AD mix α and AD mix *β* afforded **13a** with epimer ratios **13a**/**13b** = 83:17 and 74:26, respectively. These results clearly indicate that **11** has an intrinsic bias that favors the production of **13a** and that the chiral ligands of Sharpless catalysts are unable to overwhelm the intrinsic preference of **11** for **13a**. Unambiguous assignment of the *S* configuration to the newly formed stereocenter on the side chain was performed by chemical correlation: hydrogenolytic debenzylation afforded 1,4-dideoxy-1,4-imino-D-galactitol (**5**) as a solid product in high yield.[22]

Conclusions

Two pyrrolidine azasugars, promising in terms of pharmacological applications, are synthesized in four steps starting from nitrone **3** in enantiopure form and in 50% overall yield. The common intermediate **11** displays a wonderful synthetic flexibility since a number of further manipulations, besides reductive ozonolysis and dihydroxylation, can be carried out, for example oxidative ozonolysis to a carboxylic acid, aminohydroxylation, epoxidation, etc., leading to a variety of target molecules.

A very relevant observation was made relative to the addition of vinylmagnesium chloride to nitrone **3**. The selectivity of the reaction was unaffected by temperature in an exceptional wide range of temperature, namely from +20 °C to −80 °C. By our knowledge, the only example in the literature of a virtually complete entropic control in a similar temperature interval was reported by Sugimura related to an intramolecular [2 + 2] cycloaddition.[25] We also examined the same temperature dependence of selectivity using diethylaluminum chloride as a nitrone activator, and we identified in the corresponding Eyring plot two regions. The best selectivity was obtained in a flat region again under complete entropic control (0 − +40 °C). When the temperature is lowered further, the selectivity decreases, reaching the de = 10% at −94 °C. It is not easy to account for the results obtained, but they represent an example of how necessary it is to replace the commonly accepted axiom "lower the temperature to increase selectivity" with the heuristic rule "always check the temperature dependence on selectivity if you are pursuing synthetic efficiency".

Experimental Section

General Methods. ^1H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively, using tetramethylsilane as an internal standard. Melting points are uncorrected. Nitrone **3** was synthesized according to the procedure described by Brandi et al.[3] All reactions were carried out in oven-dried glassware under an atmosphere of dry argon. THF was freshly distilled from lithium aluminum hydride; CH_2Cl_2 was distilled from P_2O_5. All reagents were commercially available and were used without further purification, unless otherwise stated; vinylmagnesium chloride solution (1.7 M in THF) was purchased from Fluka, AD-mix α [$(DHQ)_2PHAL$ (hydroquinine 1,4-phthalazinediyl diether), $K_3Fe(CN)_6$, K_2CO_3, and $K_2OsO_4{\cdot}2H_2O$], AD-mix *β* [$(DHQD)_2PHAL$ (hydroquinidine 1,4-phthalazinediyl diether), $K_3Fe(CN)_6$, K_2CO_3, and $K_2OsO_4{\cdot}2H_2O$] and Amberlyst A21 resin were purchased from Aldrich.

General Procedure for the Addition of Vinylmagnesium Chloride to Nitrone 3. A solution of vinylmagnesium chloride (0.94 mL, 1.7 M in THF, 1.6 mmol) was slowly added to nitrone **3** (0.43 g, 1.45 mmol) dissolved in THF (4 mL), and the reaction mixture was allowed to react for 1 h at 20 °C. The reaction was quenched with aqueous $NaHCO_3$, filtered (Celite), and extracted with ether (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated at reduced pressure to afford a crude mixture of **9** and **10** in 93:7 ratio. Flash chromatography on silica gel (cyclohexane:ethyl acetate 80/20 v/v) furnished pure **9** (0.38 g, 1.18 mmol, 81%) as a white solid and a mixture of **9** and **10** in 30:70 ratio (0.042 g, 0.13 mmol, 9%) as a yellow oil.

9: mp 64−66 °C; $[\alpha]^{20}_D$ = +51.8 (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) *δ* 3.09 (dd, *J* = 6.6/11.1 Hz, 1H), 3.27 (t, *J* = 7.5 Hz, 1H), 3.46 (d, *J* = 11.1 Hz, 1H), 3.79 (dd, *J* = 1.5/7.5 Hz, 1H), 3.98 (dd, *J* = 1.5/6.6 Hz, 1H), 4.43−4.60 (m, 4H), 5.30 (ddd, *J* = 0.6/1.8/10.2 Hz, 1H), 5.41 (ddd, *J* = 0.6/1.8/17.1 Hz, 1H), 5.46−5.56 (br s, 1H), 5.96 (ddd, *J* = 7.5/10.2/17.1 Hz, 1H), 7.25−7.40 (m, 10 H); ^{13}C NMR (APT, $CDCl_3$) *δ* 61.3 (NCH_2), 71.3 (OCH_2Ph), 72.0 (OCH_2Ph), 76.2 (NCH), 80.1 (OCH), 86.6 (OCH), 119.5 ($=CH_2$), 127.67, 127.68, 127.8, 127.9, 128.3, 128.4, 136.7 (HC=), 137.66 (C), 137.72 (C). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.88; H, 7.15; N, 4.26.

10: ^1H NMR ($CDCl_3$) *δ* 2.96 (dd, *J* = 5.4/10.5 Hz, 1H), 3.66 (dd, *J* = 5.1/8.7 Hz, 1H), 3.85 (dd, *J* = 6.6/10.5 Hz, 1H), 3.95 (dd, *J* = 1.6/5.1 Hz, 1H), 4.02 (br dt, *J* = 1.6/∼6.0 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.52−4.61 (m, 2H), 5.39 (dd, *J* = 1.5/10.2 Hz, 1H), 5.43 (dd, *J* = 1.5/17.4 Hz, 1H), 6.11 (ddd, *J* = 8.7/10.2/17.4 Hz, 1H), 7.25−7.44 (m, 10 H).

(2*S*,3*S*,4*S*)-1-(Benzyloxycarbonyl)-3,4-bis(benzyloxy)-2-ethenylpyrrolidine (11). Copper(II) acetate (0.04 g, 0.2 mmol) was added to a suspension of zinc powder (0.442 g, 6.5 mmol) in acetic acid (3.5 mL), and the mixture was stirred at room temperature for 15 min. A solution of (2*S*,3*S*,4*S*)-**9** (0.43 g, 1.3 mmol) in 3.5 mL of acetic acid/water (6/1 v/v) was added,

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and the reaction mixture was stirred at 70 °C for 30 min. After the mixture was cooled to room temperature, acetic acid was removed under reduced pressure, and the aqueous layer was adjusted to pH = 10 with 6 N NaOH and filtered (Celite). The filtrate was extracted with chloroform (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated at reduced pressure. Crude (2*S*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-ethenylpyrrolidine was dissolved in anhydrous CH_2Cl_2 (5 mL), and the solution was cooled to 0 °C. Benzyl chloroformate (0.26 mL, 1.26 mmol) and triethylamine (0.24 mL, 1.7 mmol) were added, and the reaction mixture was stirred for 12 h at room temperature. The reaction was quenched with water and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated at reduced pressure to afford 0.56 g of a viscous oil. Flash chromatography purification (cyclohexane:ethyl acetate 80/20 v/v) afforded 0.51 g of **11** (1.15 mmol, 88%) as an oil.

11: $[\alpha]^{20}_D = -11.0$ ($c = 0.2$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.62 (dd, J = 2.0/12.0 Hz, 1H), 3.74−3.94 (br m, 3H), 3.92 (s, 1H), 4.02−4.08 (m, 1H), 4.34−4.70 (br m, 5H), 5.10 (d, J = 12.5 Hz, 1H), 5.17 (d, J = 12.5 Hz, 1H), 5.12−5.36 (m, 2H), 5.90 (br quint, J = 8.1 Hz, 1H), 7.28−7.40 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 50.7, 65.2, 66.8, 71.3, 71.6, 80.0 and 81.0, 85.1 and 86.3, 116.0 and 116.5 (these three pairs of signals collapse into broad singlets when the spectra are acquired at T = 50 °C), 127.5, 127.6, 127.7, 127.8, 128.38, 128.41,136.0, 136.4, 136.7, 137.5, 154.8; IR (neat) ν: 1700 cm^{-1} (C=O). Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.74; H, 6.58; N, 3.13.

(2*S*,3*S*,4*S*)-1-(Benzyloxycarbonyl)-3,4-bis(benzyloxy)-2-(hydroxymethyl)pyrrolidine (12). A solution of **11** (0.32 g, 0.72 mmol) in CH_2Cl_2 (25 mL) was allowed to react with ozone for 30 min at −78 °C. The reaction was quenched at −78 °C with dimethyl sulfide (0.21 mL, 2.89 mmol) and allowed to reach rt. The solvent was evaporated at reduced pressure, the residue was redissolved in anhydrous THF (10 mL), and $BH_3{\cdot}S(CH_3)_2$ (0.14 mL, 1.44 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 2 h, quenched with water, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated at reduced pressure to afford 0.27 g of a viscous residue. Flash chromatography (cyclohexane/ethyl acetate 70:30 v/v) afforded 0.22 g of **12** (0.49 mmol, 68%).

12: $[\alpha]^{20}_D = +21.7$ ($c = 5.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.58−3.64 (m, 1H), 3.72−3.94 (m, 4H), 3.98−4.16 (m, 2H), 4.48−4.66 (m, 4H), 5.15 (br s, 2H), 7.28−7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 51.0, 64.5, 65.5, 67.4, 71.6 (two carbons), 80.2, 82.8, 127.7, 127.9, 128.1, 128.5, 136.3, 137.1, 137.3, 156.6. Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.64; H, 6.50; N, 3.18.

1,4-Dideoxy-1,4-imino-L-arabinitol (4). To a solution of **12** (0.19 g, 0.42 mmol) in 2 M HCl in ethanol (15 mL) was added Pd/C 10% (0.09 g, 0.09 mmol), and the heterogeneous mixture was vigorously stirred in the presence of hydrogen at atmospheric pressure for 12 h. The solution was filtered (Celite) and evaporated at reduced pressure. The title product, present in the crude residue as the hydrochloride, was purified as free base by elution with methanol on a weakly basic ion-exchange resin Amberlyst A21 packed column. Ninhydrin-positive fractions were collected and evaporated to dryness; the residue was purified by chromatography on a short path silica column (CH_2Cl_2/CH_3OH/CH_3CH_2OH/NH_4OH 50:20:20:10) to afford 0.05 g (0.38 mmol, 89%) of title compound **4**.

4: $[\alpha]^{20}D = -12.0$ ($c = 0.21$, CH_3OH); lit.:[4a] $[\alpha]^{20}_D = -11.9$, ($c = 0.044$, CH_3OH); ^{1}H NMR (CD_3OD) δ 3.00 (dd, J = 3.0/11.7 Hz, 1H), 3.14 (br dt, J = 4.5/6.9 Hz, 1H), 3.22 (dd, J = 4.7/11.7 Hz, 1H), 3.70 (dd, J = 6.9/11.5 Hz, 1H), 3.77 (dd, J = 4.5/11.5 Hz, 1H), 3.87 (br t, J = 3.0 Hz, 1H), 4.07 (dt, J = 3.0/4.7 Hz, 1H); ^{13}C NMR (APT, $CDCl_3$) δ 52.7 (NCH_2), 62.3 (CH_2OH), 68.9 (NCH), 78.1 (CHO), 79.5 (CHO). Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.16; H, 8.38; N, 10.45.

General Procedure for the Dihydroxylation with AD-mix. Synthesis of [2*S*-[2α(*R),3*β*,4α]]-1-(benzyloxycarbonyl)-3,4-bis(benzyloxy)-2-(1,2-dihydroxyethyl)pyrrolidine (13a).** To a solution of **11** (0.24 g, 0.53 mmol) in *tert*-butyl alcohol/water 1:1 (3.6 mL) was added AD-mix α (0.75 g), and the heterogeneous mixture was vigorously stirred at room temperature for 24 h. The reaction was quenched with Na_2SO_3 (0.93 g, 7.4 mmol) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated at reduced pressure, and the residue was purified by flash chromatography, eluting with cyclohexane/ethyl acetate 70:30 to afford 0.172 g of **13a** (0.36 mmol, 71%) and 0.035 g of **13b** (0.07 mmol, 15%).

[2*S*-[2α(*R),3*β*,4α]]-13a**: $[\alpha]^{20}_D = +20.5$ ($c = 0.56$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.54 (d, J = 12.3 Hz, 1H), 3.57−3.62 (m, 1H), 3.70 (d, J = 12.6 Hz, 1H), 3.76 (br d, J = 9.9 Hz, 1H), 3.84 (dd, J = 5.4/12.3 Hz, 1H), 3.98 (d, J = 9.9 Hz, 1H), 4.06 (d, J = 5.7 Hz, 1H), 4.37 (s, 1H), 4.44 (d, J = 11.7 Hz, 1H), 4.52 (d, J = 5.0 Hz, 1H), 4.56 (d, J = 5.0 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 5.12 (d, J = 12.4 Hz, 1H), 5.21 (d, J = 12.4 Hz, 1H), 7.30−7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 52.2, 62.3, 64.6, 67.7, 70.5, 71.2, 71.4, 81.1, 81.9, 127.7, 127.8, 127.87, 127.92, 128.2, 128.4, 128.5, 136.0, 137.1, 137.5, 157.4;. Anal. Calcd for $C_{28}H_{31}NO_6$: C, 70.42; H, 6.54; N, 2.93. Found: C, 70.35; H, 6.59; N, 2.97.

[2*S*-[2α(*S),3*β*,4α]]-13b**: $[\alpha]^{20}_D = +16.0$ ($c = 1.2$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.52−3.65 (m, 3H), 3.80−3.95 (m, 2H), 4.02 (s, 1H), 4.06 (br d, J = 6.0 Hz, 1H), 4.31 (br d, J = 6.0 Hz, 1H), 4.45−4.65 (m, 4H), 5.12−5.22 (m, 2H), 7.20−7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 51.8, 63.8, 64.9, 67.8, 71.4, 71.8, 73.5, 80.6, 83.1, 127.8, 127.95, 128.04, 128.2, 128.5, 128.6, 136.2, 137.3, 137.6, 157.5. Anal. Calcd for $C_{28}H_{31}NO_6$: C, 70.42; H, 6.54; N, 2.93. Found: C, 70.32; H, 6.50; N, 2.96.

1,4-Dideoxy-1,4-imino-D-galactitol (5). By applying to **13a** (0.17 g, 0.36 mmol) the same procedure used for deprotection of **12**, we obtained 0.052 g (0.32 mmol, 89%) of pure **5**.

5: mp (dec) 134−136 °C; $[\alpha]^{20}_D = +3.0$ ($c = 2.4$, H_2O); lit.:[24] $[\alpha]^{20}_D = +2.8$, ($c = 2.0$, H_2O); ^{1}H NMR (D_2O) δ: 2.77 (dd, J = 3.0/12.6 Hz, 1H), 2.82 (br d, J = 5.1/6.0 Hz, 1H), 2.97 (dd, J = 5.1/12.6 Hz, 1H), 3.17 (s, 1H), 3.42 (dd, J = 6.9/12.0 Hz, 1H), 3.56 (dd, J = 3.6/12.0 Hz, 1H), 3.60−3.65 (m, 1H), 3.91−3.94 (m, 1H), 3.98 (dt, J = 3.0/5.1 Hz); ^{13}C NMR (APT, D_2O) δ: 51.4 (NCH_2), 64.1 (CH_2OH), 66.4 (NCH), 72.2 (CHOH), 77.7 (CHOH), 78.8 (CHOH). Anal. Calcd for $C_6H_{13}NO_4$: C, 44.17; H, 8.03; N, 8.58. Found: C, 44.10; H, 8.09; N, 8.52.

Acknowledgment. The authors thank M.U.R.S.T.-Rome (National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni") and University of Bologna (funds for selected topics) for financial support.

JO0056545