Synthesis of Potential Inhibitors of Glycosidases and Glycohydrolases
I. 1,4-Imino-1,4-dideoxyribose

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A stereoselective synthesis of D or L form of 1,4-imino-1,4-dideoxyribose has been achieved by two different approaches. The first begins with resolution of the inexpensive 3,4-dehydroproline. Key steps are a stereoselective dihydroxylation followed by reduction of the carboxylate group to a hydroxymethyl. Alternately, 4-tosyl-2,3-*O*-isopropylidene derivatives of D- or L-lyxose were converted to the azides. Acid hydrolysis of the methyl glycoside followed by catalytic hydrogenation produces 1,4-imino-1,4-dideoxyribose. These aminoribose derivatives should serve as the basis for the development of specific inhibitors of glycosidases and potentially of NAD glycohydrolases.

Our interest in the design of specific potent inhibitors of ADP-ribose transferases and related enzymes had prompted us to prepare the amino sugars 4-amino-4-deoxy- and 1,4-imino-1,4-dideoxyribose in order to incorporate them into ADP—ribose and NAD analogues.

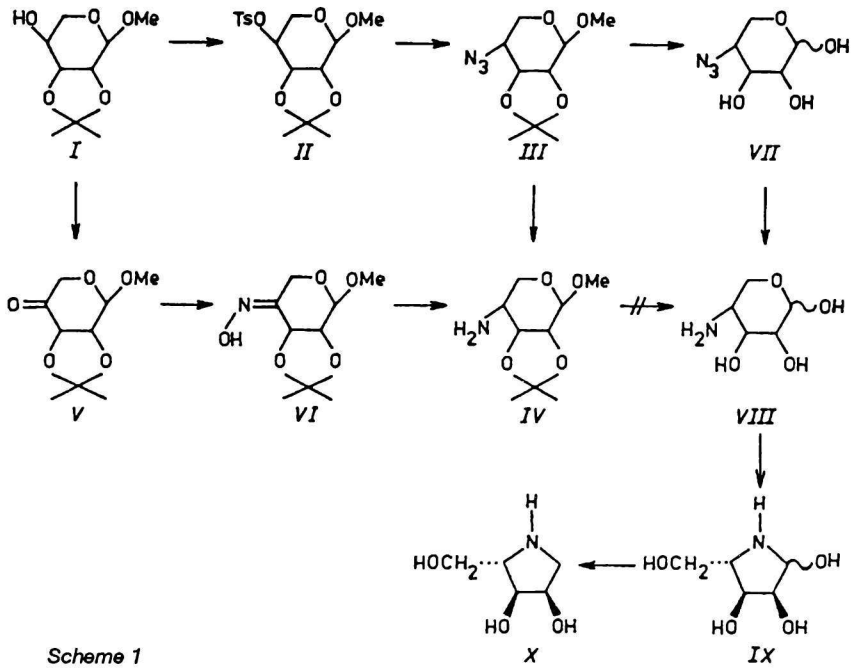
The protonated amino group is envisioned to resemble the oxocarbonium ion intermediate proposed as inhibitor of the NAD glycohydrolases. Carbohydrate derivatives in which the ring oxygen is replaced by nitrogen have already found extensive application as specific inhibitors of mannosidases and glucosidases. By analogy, the aminoribose may constitute a specific transition state inhibitor of nucleotidases and poly(ADP—ribose) glycohydrolases. Recently, 1,4-imino-1,4-dideoxy-D-lyxitol and -D-arabinitol [1], 1,4-imino-1,4-dideoxy-D-xylitol and -L-arabinitol [2] have been prepared.

The synthesis of 4-acetamido-4-deoxy-D-ribose by deacetylation of its pentaacetate derivative has been reported in [3]. We have duplicated this synthesis, and introduced a number of modifications to improve the yields and to direct it towards the preparation of our objective compounds 4-amino-4-deoxy- and 1,4-imino-1,4-dideoxyribose. Therefore, methyl 2,3-*O*-isopropylidene-α-L-lyxopyranoside (*Ia*) and its D isomer (*Ib*) were prepared from L- and D-lyxose, respectively, according to the known procedure [4], and purified by chromatography before subsequent tosylation to compound *II* (Scheme 1).

Azide displacement of the tosyl group using sodium azide at 118 °C is reported to proceed with merely 39 % yield [3]. We have achieved a higher yield (56 %) using lithium azide as a nucleophile. This yield improvement most probably is due to the better solubility of lithium azide in organic solvents. After completion of this work a recent publication [1] reported a comparable high yield (54 %) using sodium azide for displacement of trifluoromethanesulfonate group. Catalytic hydrogenation of 4-azido-4-deoxyribopyranoside *III* in methanol using 5 % Pd/C afforded 4-amino derivative *IV* in 92 % yield.

An alternative route for the synthesis of *IV* was accomplished by the oxidation of the lyxopyranoside *I* using DMSO—acetic anhydride [5] or DMSO—DCC—pyridinium trifluoroacetate [6] mixtures to afford the 4-keto derivative *V* in 47 % and 49.5 % yields, respectively. Treatment of *V* with hydroxylamine at pH 9 afforded 4-(hydroxyimino)ribopyranoside *VI* in 64 % yield. Lithium aluminium hydride reduction of the oxime *VI* afforded the 4-amino compound *IV* identical in its spectral properties to the product obtained by the catalytic hydrogenation of the azide compound *III*.

Acid hydrolysis of methyl glycoside grouping in *IV* resulted in the formation of a dark-brown polymeric residue. This is similar to the attempt of acid hydrolysis of the isomeric methyl 4-aminoxylopyranoside [7]. On the other hand, when compound *III* is subjected to acid hydrolysis 4-azido-4-deoxyribopyranose (*VII*) is obtained. Upon catalytic



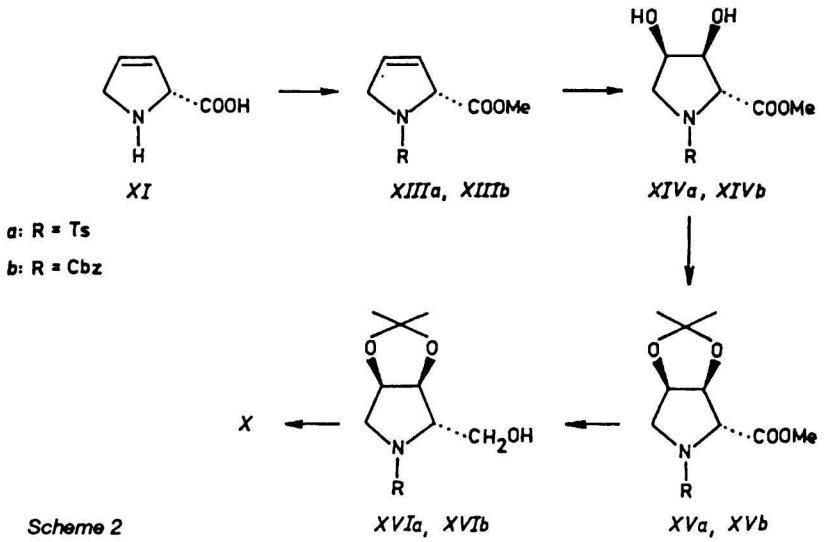
Scheme 1

hydrogenation this afforded 1,4-imino-1,4-dideoxyribofuranose (*X*), presumably *via* the intermediate 4-amino-4-deoxyribose (*VIII*), which is reduced under the reaction conditions into *X*.

Eventhough the above synthesis is a viable one to prepare the required aminoribose, it nonetheless suffers from some disadvantages. It starts with an expensive starting material (L-lyxose), requires multi-steps, and the intermediates are usually amorphous requiring difficult chromatographic purification due to the absence of a UV chromophore. We sought an alternative synthesis of those compounds, starting with the amino acid 3,4-dehydroproline (*XI*) [8]. Resolution of *XI* is achieved by treatment with L-tartaric acid according to the described procedure [9]. (*S*)-(–)-3,4-Dehydroproline (dehydro-L-proline) will be the suitable precursor for the potentially bioactive aminoribose [10]. The dehydroproline amino group is protected with *N*-tosyl (*XIIa*) or *N*-benzoyloxycarbonyl (*XIIb*) groups [11]. The tosylate offers the advantage that its derivatives have the tendency to be more stable and crystallizable [12]. On the other hand, *N*-benzoyloxycarbonyl group is much easier to remove. Treatment of 3,4-dehydroproline protected with *N*-tosyl or *N*-benzoyloxycarbonyl (both prepared in almost quantitative yield) with excess ethereal solution of diazomethane afforded the methyl ester *XIII* quantitatively (Scheme 2).

Osmium tetraoxide dihydroxylation of *XIII* was shown [12] to proceed stereoselectively with exclusive production of the 2,3-*trans*-3,4-*cis*-dihydroxy isomer *XIV*. Methyl ester of dihydroxy-*N*-tosylproline obtained according to this procedure has only one isomer as proved by HPLC and ^{1}H NMR measurements. Its sharp melting point at 83 °C is in agreement with that reported for this compound in [12]. From ^{1}H NMR spectrum a coupling constant for C-2—C-3 equal to 3.3 Hz has been found, which is supportive of a *trans* isomer. However, the most conclusive support is the complete agreement between the spectroscopic data obtained for 4-amino-1,4-dideoxyribose prepared from this compound and for that obtained from L-lyxose. The two hydroxyl groups in *XIV* were protected with isopropylidene group by treatment with dimethoxypropane in HCl. Reduction of the carboxylate group in *XV* into hydroxymethyl was affected by $LiBH_4$, to afford the isopropylidenedioxyprolinol derivative *XVI*.

The ^{1}H NMR spectra in the benzoyloxycarbonyl series were complicated by the presence of the compounds in two stable conformations of approximately equal population resulting from hindered rotation of N—C=O bond of N—CBz. This was less noticeable in ^{13}C NMR spectra except for compounds *IVb* and *XIVb*, where two of the carbons appeared as doublets. On the other hand, ^{1}H NMR analysis in the tosyl series is much simpler and again the only complicated spectrum was that of compound *XVa* where each of the isopropylidene, tosyl, and ester methyls appeared as an unsymmetrical doublet of relative ratio of the two branches 5 : 1. The aromatic protons also were more complicated as dddd. This may indicate the presence of two conformers of different stability and chemical shift. However, in the tosyl series this phenomenon was restricted only to compound



Scheme 2

XVa and it could not be detected in its precursor and completely disappeared from the spectrum of the following compounds. *N*-Benzoyloxycarbonyl protecting group is removed by catalytic hydrogenation to afford *XVII*. The usual methods for removal of *N*-tosyl group like HBr in acetic acid or treatment with sodium in liquid ammonia result in extensive decomposition and poor yields. However, treatment with sodium naphthalenide afforded 72 % yield of compound identical to *X* obtained in the carbohydrate series in all spectroscopic properties.

EXPERIMENTAL

NMR spectra were run on spectrometers FX 90 (Jeol) or QE-300 (General Electric), IR spectra on a Perkin–Elmer apparatus in $CHCl_3$ solution using cavity cell. Optical rotation was measured on a polarimeter 241 (Perkin–Elmer) using 10 cm tube. Melting points were determined with Thomas–Hoover apparatus and were not corrected. Composition analyses were performed by Gallbreath Laboratories (Knoxville, Tenn.) and are within 0.4 % of the calculated values. The commercial preparations dehydro-DL-proline (Adams Chemicals or Sigma), L- and D-lyxose, and L-tartaric acid (Aldrich) were used. Thin-layer chromatography was run on Kieselgel 60 using solvent systems: *A* (MeOH–$CHCl_3$, φ_r = 9 : 1), *B* (chloroform–ether, φ_r = 3 : 1), *C* ($CHCl_3$–hexane, φ_r = 2 : 1). Spots were detected by visual examination under UV light, iodine, dinitrophenylhydrazine or ninhydrin spray and subsequent heat at 75 °C for 10 min. HPLC were run on Whatman Partisil-10 silica gel column with 2-propanol–hexane (φ_r = 1 7) as eluting solvent system. DEAE-32 is a product of Whatman.

4-Azido-4-deoxy-D-ribopyranose (*VII*)

A suspension of methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-α-D-ribopyranoside (*III*) (229 mg; 1 mmol) in 0.5 M-HCl (10 cm^3) was heated with stirring under nitrogen at 75 °C. Optical rotation was read every 30 min until it became constant (about 18 h). The acid was neutralized with 10 % sodium carbonate solution. The solvent was removed under reduced pressure and the residue was purified by chromatography (system *A*; R_f = 5.8) to afford 138 mg of *VII* (73 % yield). IR spectrum, $\tilde{\nu}_{max}/cm^{-1}$: 2100 (azide). ^1H NMR spectrum (D_2O), δ: 4.99 (s, 2H), 5.37 (d, 1H), 5.8 (d, 1H), 5.9 (s, 2H). ^{13}C NMR spectrum (D_2O), δ: 55.39 (C-4, CHN_3), 57.55 (C-5, CH_2), 64.82 (C-2, HCOH), 67.79 (C-3, HCOH), 91.02 (C-1, OCOH).

1,4-Imino-1,4-dideoxy-D-ribose (*X*)

A solution of *VII* (350 mg; 2 mmol) in methanol (40 cm^3) was treated with 5 % Pd/C (90 mg) and hydrogenated at room temperature for 6 h.

The reaction mixture was filtered and the filtrate concentrated under reduced pressure to afford *X* as off-white crystals. The product in water (5 cm^3) was applied to a Dowex 50 x 4 (H^+ form) column, washed with water and eluted with 1 M-NH_4OH. The relevant fractions (ninhydrin) were combined and evaporated. The product was purified further on a cellulose column (90 cm x 3.4 cm) and fractionation was carried out with BuOH–pyridine–H_2O (φ_r = 1 1 1). The pure fractions were combined and concentrated, adequate amount of 1 M-HCl was added to make it weakly acid. Evaporation of the solvent yielded crude crystals which were recrystallized from ethanol–ether (m.p.

= 134 °C). [α](D, 20 °C, ρ = 6.1 g dm^{-3}, water) = + 57.0°. IR spectrum, $\tilde{\nu}_{max}$/cm^{-1}: 3320 (no azide at 2100). Mass spectrum, *m/z* (I_r/%): 133 (M^+, 7.2), 132 (7.2), 105 (32), 104 (16.5), 102 (100, $M^+ - CH_2OH$), 55 (78.4). ^{1}H NMR spectrum (D_2O), δ: 3.32 (ddd, 1H, *J* = 4.5, 8.4, and 3.3 Hz, CHNH), 3.41 (dd, 1H, *J* = 11.6 and 5.5 Hz, CH_2NH), 3.50 (dd, 1H, *J* = 12.4 and 8.4 Hz, CH_2OH), 3.78 (dd, 1H, *J* = 12.4 and 4.5 Hz, CH_2OH), 3.84 (dd, 1H, *J* = 11.6 and 8.1 Hz, CH_2NH), 4.17 (m, 1H), 4.24 (dd, 1H, *J* = 3.3 and 4.1 Hz, CHOH). ^{13}C NMR spectrum (D_2O, acetonitrile), δ: 52.1 (CH_2N), 59.2 (CHN), 59.6 (CH_2OH), 69.1 (CHOH), 69.8 (CHOH).

Methyl 2,3-*O*-Isopropylidene-4-oxoribopyranoside (*V*)

Methyl 2,3-*O*-isopropylidene-α-L-lyxopyranoside (*I*) (408 mg; 2 mmol) in dry DMSO (6 cm^3) was treated with acetic anhydride (0.9 cm^3). The reaction mixture was stored overnight at room temperature. The obtained yellow solution was added to cooled water (15 cm^3) containing sodium hydrogen carbonate (1 g) and stirred for 1 h. After extraction with chloroform (3 x 10 cm^3 each) the extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by chromatography (system *B*) to afford 190 mg of *V* (47 % yield) which gave a positive carbonyl test upon spraying with 0.2 % dinitrophenylhydrazine in 1 M-HCl. IR spectrum, $\tilde{\nu}_{max}$/cm^{-1}: 1750 (CO). ^{1}H NMR spectrum ($CDCl_3$), δ: 1.35 (s, 3H, isopropylidene), 1.55 (s, 3H, isopropylidene), 3.40 (3H, methoxy), 3.63 (m, 1H), 4.11 (m, 2H),. 4.73 (d, 1H, anomeric H), 4.78 (s, 1H).

Methyl 2,3-*O*-Isopropylidene-4-(hydroxyimino)ribopyranoside (*VI*)

Potassium hydrogen carbonate (540 mg) and hydroxylammonium chloride (285 mg; 4 mmol) were stirred in the methanol—water mixture (26 cm^3, φ_r = 25 : 1) at 50 °C. The ketone *V* (202 mg; 1 mmol) in methanol (5 cm^3) was added dropwise. Saturated potassium hydrogen carbonate solution was added to keep the mixture alkaline (pH > 9). After reflux for 15 min, the solvent was removed under vacuum. The residue was extracted in methylene dichloride and purified by chromatography (silica gel, system *B*) to afford 139 mg of *VI* (64 % yield). This compound gave negative dinitrophenylhydrazine test. IR spectrum, $\tilde{\nu}_{max}$/cm^{-1}: 1730 (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ: 1.35 (s, 3H, isopropylidene CH_3), 1.55 (s, 3H, isopropylidene CH_3), 3.40 (methoxy CH_3), 3.64 (br s, 1H), 4.11 (m, 2H), 4.73 (d, 1H, anomeric H), 4.78 (s, 1H).

Methyl 2,3-*O*-Isopropylidene-4-amino-4-deoxyribopyranoside (*IV*)

Method A. The azide *III* (600 mg; 2.64 mmol) in methanol (10 cm^3) was treated with 5 % Pd/C (240 mg) and hydrogenated at room temperature for 4 h. The catalyst was removed by filtration and the solvent evaporated. The residue was chromatographed (system *B*). Upon spray with ninhydrin it gave a positive primary amine test. IR spectrum, $\tilde{\nu}_{max}$/cm^{-1}: 3300 and 1620 (NH) (no azide at 2100). ^{1}H NMR spectrum ($CDCl_3$), δ: 1.37 (s, 3H, isopropylidene CH_3), 1.59 (s, 3H, isopropylidene CH_3), 3.48 (s, 3H, methoxy CH_3), 3.65 (d, 1H), 3.92 (br s, 2H), 4.27 (d, 2H), 4.76 (d, 1H, anomeric H). Acetolysis according to the known procedure [3] afforded the pentaacetate derivative. Its ^{1}H NMR spectrum ($CDCl_3$), δ: 2.0—2.3 (15H, acetyl CH_3), 3.49 (d, 2H), 4.15 (d, 2H), 5.30 (d, 1H, anomeric H), 5.42 (m, 1H). The acetamide was also prepared according to the known procedure [3]. Its ^{1}H NMR spectrum ($CDCl_3$), δ: 1.18 (s, 3H, isopropylidene CH_3), 1.81 (s, 3H, acetyl CH_3), 3.26 (s, 3H, methoxy CH_3), 3.55 (dd, 2H), 4.01 (m, 1H), 4.32 (d, 2H), 4.67 (hidden d, 1H, anomeric H). Final proof of the structure is the acid hydrolysis with 0.1 M-HCl for 10 min at 50 °C which afforded methyl 4-ammonio-4-deoxyribopyranoside chloride, its free base was obtained by the treatment of the chloride with the ion-exchange resin AG 1 x 8 (OH^- form) and its m.p. = 109 °C (according to Ref. [3] m.p. = 109—111 °C).

Method B. To a suspension of $LiAlH_4$ (480 mg) in ether (18 cm^3), the oxime *VI* (108 mg; 0.5 mmol) in ether (6 cm^3) was added dropwise with stirring at room temperature. After completing the addition, the mixture was refluxed for 4 h. Ice-cooled water (10 cm^3) and ethyl acetate (5 cm^3) were added, and the precipitate was removed by filtration. The product was extracted in ether, dried, and evaporated. The residue was purified by chromatography (system *B*) affording 46 mg of *IV* (45 % yield). This compound showed a positive ninhydrin test and has the same IR and ^{1}H NMR spectral data as the product obtained from the reduction of the 4-azide derivative described in the method *A*.

Methyl Ester of 2,3-*trans*-3,4-*cis*-Isopropylidenedioxy-*N*-tosylproline (*XVa*)

Methyl ester of 2,3-*trans*-3,4-*cis*-dihydroxy-*N*-tosylproline (*XIVa*) (315 mg; 1 mmol) in dimethoxypropane (9 cm^3, distilled) and 4 M-HCl in dioxane (0.1 cm^3) were stirred overnight at room temperature. The reaction mixture was neutralized with solid sodium hydrogen carbonate and filtered through a cellite pad. The filtrate was evaporated

in vacuo and the residue purified by medium-pressure chromatography (silica gel; ethyl acetate—hexane, φ_r = 2 : 1), TLC (system *C*) R_f = 0.6, HPLC retention time 7 min. The product (348 mg, 98 % yield) was crystallized from CH_3OH as white crystals with m.p. = 98 °C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ: 1.42—1.79 (d, d of a relative ratio 1 : 4.5, 6H, isopropylidene CH_3), 2.41—2.43 (unsymmetrical d of a relative ratio between the branches 1 : 5.2, 3H, tosyl CH_3), 3.68—3.73 (unsymmetrical d with a relative ratio between the branches 1 : 5, 3H, ester CH_3), 3.45—3.80 (m, 2H), 4.40—8.82 (m, 3H), 7.28—7.76 (dddd, 4H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ: 21.0 ($TsCH_3$), 24.5 (isopropylidene CH_3), 26.2 (isopropylidene CH_2), 52.5 (ester CH_3), 52.7 (NCH_2), 67.2 (NCH), 79.4 (HCO), 83.2 (HCO), 117.1 (CCH_3), 128.4—129.1 (C_{arom}), 143.4 ($C_{arom}—SO_2$), 171.1 (carboxyl CO).

2,3-*trans*-3,4-*cis*-Isopropylidenedioxy-*N*-tosylprolinol (*XVIa*)

XVa (355 mg; 1 mmol) in dry THF (10 cm^3; dried over sodium) was treated with $LiBH_4$ (40 mg) at 0 °C with stirring for 3 h at room temperature. Acetic acid (1 cm^3) was added and the mixture basified with 10 % aqueous $NaHCO_3$ solution and evaporated under reduced pressure. The residue was partitioned between water (2 cm^3) and ethyl acetate (10 cm^3). The aqueous layer was saturated with NaCl and reextracted with THF (3 times, 10 cm^3 each). The organic extracts were combined and dried over anhydrous $MgSO_4$ and evaporated. Thin-layer chromatography (system *A*; R_f = 0.4) afforded *XVIa* (284 mg, 85 % yield) as a pale yellow oil which was crystallized from $CHCl_3$ as white prisms with m.p. = 102 °C. IR spectrum, $\tilde{\nu}_{max}$/cm^{-1}: 3370, 3610. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ: 0.84 (s, 3H, isopropylidene CH_3), 1.17 (s, 3H, isopropylidene CH_3), 2.41 (s, 3H, $TsCH_3$), 3.44—3.98 (m, 5H, CH_2OH, 2 x HCO, NCH), 4.60 (ddd, 1H, NCH_2), 4.70 (dd, 1H, NCH_2), 7.32—7.78 (dd, 4H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ: 20.86 ($TsCH_3$), 29.8 (CCH_3), 30.2 (CCH_3), 55.37 (H_2CN), 62.73 (H_2COH), 67.7 (NCH), 79.39 (HCO), 82.5 (HCO), 116.9 ($C(CH_3)_2$), 143.3—144.1 (C_{arom}).

2,3-*trans*-3,4-*cis*-Dihydroxyprolinol (Identical with *X*)

Sodium naphthalenide solution [13, 14] in THF was prepared under nitrogen and was added to a stirred solution of *XVIa* (327 mg; 1 mmol) in dry THF (5 cm^3) in dry-ice bath at − 80 °C under nitrogen. Addition was continued until a deep green colour persisted and stirring was continued for an additional hour. Water (10 cm^3) was added and the solvent was removed under vacuum. The residue was taken in $CHCl_3$ and purified by chromatography on a Dowex 50 x 4 (H^+ form) as described for compound *X*. The ninhydrin positive fractions were collected and evaporated. The residue was suspended in 0.1 M-HCl (15 cm^3) and stirred at room temperature under nitrogen for 30 min. Evaporation of the solvent under reduced pressure afforded the compound (95.8 mg, 72 % yield) with indentical ^{1}H and ^{13}C NMR, resp. mass spectra, melting point and optical rotation to *X* obtained above.

2,3-*trans*-3,4-*cis*-Isopropylidenedioxyprolinol (*XVII*) and 2,3-*trans*-3,4-*cis*-Dihydroxyprolinol (*X*)

2,3-*trans*-3,4-*cis*-Isopropylidenedioxy-*N*-benzoyloxycarbonyl-D-prolinol (*XVIb*) (50 mg; 0.163 mmol) [15] in methanol (10 cm^3) was treated with 5 % Pd/C catalyst (20 mg) and hydrogenated at room temperature for 4 h. The reaction mixture was filtered and the filtrate evaporated *in vacuo* to afford *XVII* (26 mg, 90 % yield). The product in 20 % aqueous pyridine (10 cm^3) was refluxed for 30 min, the solvent was evaporated under vacuum and the residue afforded compound *X*.

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