



Synthesis of 5-substituted-3,4-dihydroxycyanopyrrolidines. An easy access to polyhydroxyprolines

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ABSTRACT

A novel procedure for the synthesis of cyanopyrrolidines is presented. Starting from conveniently functionalized D-ribose, D-mannose, D-(L)-arabinose, the compounds were efficiently synthesised in four steps in overall good yields. Transformation into proline derivatives and preliminary evaluation of these derivatives in organocatalysis is also described.

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1. Introduction

A great interest in new synthetic procedures giving access to chiral non-racemic pyrrolidines has regained attention.¹ These small molecules, densely functionalized and rich in stereochemistry make them attractive for their chemotherapeutic properties against cancer² and as potent glycosidases.³ Amongst these derivatives, 2-cyanopyrrolidine could be found in peptide sequence as dipeptidyl peptidase IV (DPPIV) inhibitors as a potential treatment of diabetes and obesity. For example, **I** (DPP728), **II** (LAF-237), **III** (BMS-477118) have entered into human clinical trials in diabetic patients (Fig. 1).^{4–7}

One of the most interesting applications of 2-cyanopyrrolidines in organic synthesis is their transformation to proline analogues. Synthetically, the interest in this reaction lies in the cyanide adducts being precursors of proline derivatives^{8,9} and chiral 1,2-diamines.¹⁰ Therefore, general methods for the synthesis of 2-cyanopyrrolidines are of great interest. In most cases these compounds are chiral, and stereoselective approaches to their synthesis are often required.^{11–13}

As a part of our ongoing program to utilise glyco- α -aminonitriles derivatives,¹⁴ we wish now to report a detailed account of our approach and its extension to the synthesis of 5-substituted-polyhydroxy-2-cyanopyrrolidine starting from conveniently functionalized pentoses and their transformation to proline derivatives. Preliminary results in organocatalysis will also be disclosed.

2. Results and discussion

Our approach to the synthesis of 5-substituted-polyhydroxy-2-cyanopyrrolidine **C** could be planned according to the retro-synthetic paths outlined in Scheme 1.

It could be envisioned that the pyrrolidines could be generated from aminonitriles **B** by cyclisation. The diastereomeric mixture (in major cases) of aminonitrile **B** could be easily prepared by our modified Strecker reaction¹⁴ with the readily known available aldehyde **A**.

According to our previous work,¹⁴ Strecker conditions, using 2 equiv of HCOONH₃Bn and 2 equiv of Ti(OiPr)₄ as the Lewis acid, applied to the anomeric position of derivatives **1a**,¹⁵ **2a**,¹⁶ **3a**,¹⁷ and commercially available **4a**, **5a**, **6a**, followed by TMSCN addition gave the α -aminonitriles **1b–6b** (Table 1). The α -aminonitriles derivatives were obtained with yields ranging from 63% to 90%, in an unseparable diastereomeric mixture (except for **2bR**) or with a ratio in favour of the desired 2-(*R*)-derivatives. The stereoselectivity of TMSCN addition could be easily explained by a Cram-chelate model between [Ti], the iminium and the substituent in position 2 leaving a preferential attack of the anion [−]CN from the side of the smallest remaining substituent, hence favouring the *R*-configuration for derivatives **1b**, **2b**, **3b**, **5b**, **6b** and *S*-configuration for compound **4b**.

Next, we investigated the two steps cyclisation. Compounds **1b–6b** reacting with methanesulfonyl chloride, in pyridine at 80 °C afforded the key cyanopyrrolidines **1c–6cR** in 57–91% overall yield (Table 1). Interestingly, at room temperature, competition between the formation of cyanopyrrolidine and dimesylation occurred in favour of the *O,N*-dimesyl derivatives.

Purification by flash chromatography afforded each stereoisomer where the major compound derivative is (*R*) with a ratio *R/S* consistent with our previous results.

Among the various functional groups resulting from the chemical transformation of a cyano group, the hydrolysis into carboxylic

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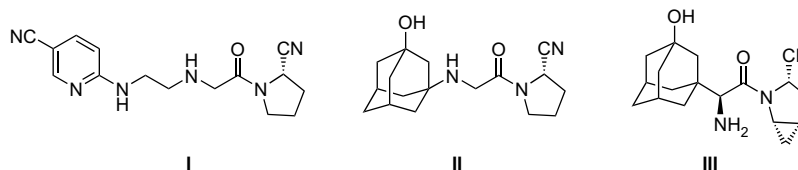
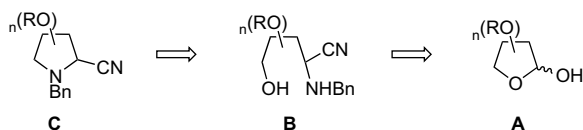


Figure 1. Structures of selected DPPIV inhibitors.



Scheme 1. Retrosynthetic analysis.

acid is easily accessible. Indeed, it is well established that hydroxylated prolines influence the polypeptide secondary structure in antibiotics.¹⁸ Furthermore, 3,4-*trans* or *cis* dihydroxyprolines (DHP, **IV**,¹⁹ **V**,²⁰ **VI**,²¹ Fig. 2) are also found as substructures in bioactive natural compounds and an effective methodology for their synthesis has been the subject of much attention in recent years.^{22–28}

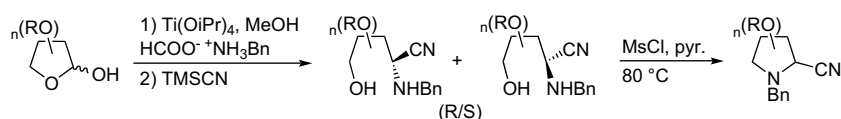
In order to obtain the proline analogues, we selected the (*R*)-derivatives **1cR**, **2cR** and **3cR** to be submitted to acidic hydrolysis (concentrated HCl at 100 °C in a sealed tube) followed by hydrogenolysis (H₂ atmosphere, Pd/C) to afford the corresponding hydroxyprolines **1d**, **2d** and **3d** in 78%, 76% and 77%, respectively (Table 2).

With these derivatives in our hands, we tested the polyhydroxyprolines **1d**, **2d** and **3d** versus natural L-proline in organocatalysis since the pioneering work of List, Barbas and their co-workers²⁹ have demonstrated that L-proline or functionalized 4-hydroxyproline³⁰ could work as a catalyst in the intermolecular direct aldol reaction.

Despite a number of effective chiral organocatalytic systems have emerged and particularly the concept of small organic molecules as highly efficient and enantioselective catalysts, few examples were exploiting the introduction of hydroxyl groups in proline with a substituent in position 5,³¹ and consequently examined their influence. We disclose now some preliminary results in the known direct aldol reaction catalysed by polyhydroxyprolines using 4-nitrobenzaldehyde and acetone (Table 3).³²

In our initial experiment, the reaction was performed in DMSO using a catalytic amount (20 mol %) of catalyst as previously reported³² for direct asymmetric aldol reaction and the results are summarised in Table 3. It is interesting to find out that the aldol products were obtained with similar enantioselectivity than L-proline but with decreased yields. These results demonstrated that the catalytic process is not affected by the presence of the

Table 1
Formation of cyanopyrrolidines



A	B	C
 1a , R= CH ₃ 2a , R= CH ₂ OTr 3a , R= CH ₂ N ₃	 1bR 80% 2bR 86% 3bR 50% 1bS 5% 2bS 13% 3bS 13%	 1cR 85% 2cR 84% 3cR 77% 1cS 6% 2cS 4% 3cS 4%
 4a	 4bR 24% 4bS 74%	 4cR 16% 4cS 44%
 5a	 5bR 54% 5bS 18%	 5cR 57% 5cS 57%
 6a	 6bR 70% 6bS 8%	 6cR 84%

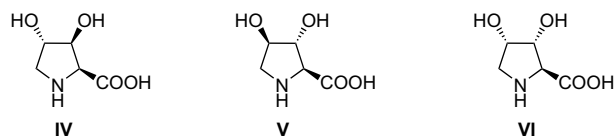


Figure 2. 3,4-Dihydroxyprolines from natural sources.

Table 2
Synthesis of polyhydroxyprolines

Substrate	Product	Yield
1cR		1d 78%
2cR		2d 76%
3cR		3d 77%

hydroxyl groups in the proline scaffold. Nevertheless, an amino group seems to act as a basic catalytic centre leading and probably performing the dehydration of the γ -hydroxyiminium intermediate during the first addition step.

Then using an equimolar quantity of catalyst **3d**, the aldol derivative (entry 3) was submitted to an hypothetical dehydration followed by a Michael addition (Scheme 2) to afford **7** in 12% yield. Interestingly, the process can be pursued probably due to the basicity of the -NH_2 group leading to the unexpected Robinson

Table 3
Catalyst screen for the direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone

Entry	Time [h]	Cat. (equiv)	Yield ^a [%]	ee ^b [%]
1	19	Proline (0.2)	69	76
2	72	3d (0.2)	11	69
3	24	3d (1)	— ^c	—
4	72	1d (0.2)	Traces	nd
5	48	1d (1)	25 ^d	85
6	72	2d (0.2)	Traces	nd
7	72	2d (1)	40	71

^a Isolated yield.

^b Enantiomeric excess was determined by chiral HPLC. The absolute configuration was determined by comparison of the HPLC retention time of the product with reported data.³¹

^c See Scheme 2.

^d Bicyclic 1,3-oxazolidine **9a/9b** were isolated as a by-product in 18% overall yield.

annelation product **8** in 4% yield. This process did not occur with catalyst **1d** or **2d** emphasising our hypothesis.

Moreover, we were delighted to observe that catalyst **1d** presenting a methyl group led to the aldol derivative in 25% yield and also to the bicyclic 1,3-oxazolidine **9a** and **9b** (Scheme 3). Similar results leading to the formation of oxazolidine with L-proline is well known in literature³³ and is attributed to a poor reactivity when L-proline was used below 20 mol %.

3. Conclusion

In conclusion, a synthesis of 2-cyanopyrrolidine **1c–6c** was achieved via a simple reaction sequence in four steps starting from D-ribose, D-mannose, D-(L)-arabinose involving a cyclisation step of a mesyl intermediate. This approach is helpful in obtaining proline derivatives by simple conversion of the nitrile group into the carboxylic acid. This methodology will be applied to the other substrates in order to obtain configurationally and conformationally diversified polyhydroxyprolines to get insights into the influence of the OH groups compared to L-proline pattern. This study will be reported in due course. Furthermore, these catalysts showed unusual reactivity (Scheme 2) and paved the way for further improvements.

4. Experimental

4.1. General

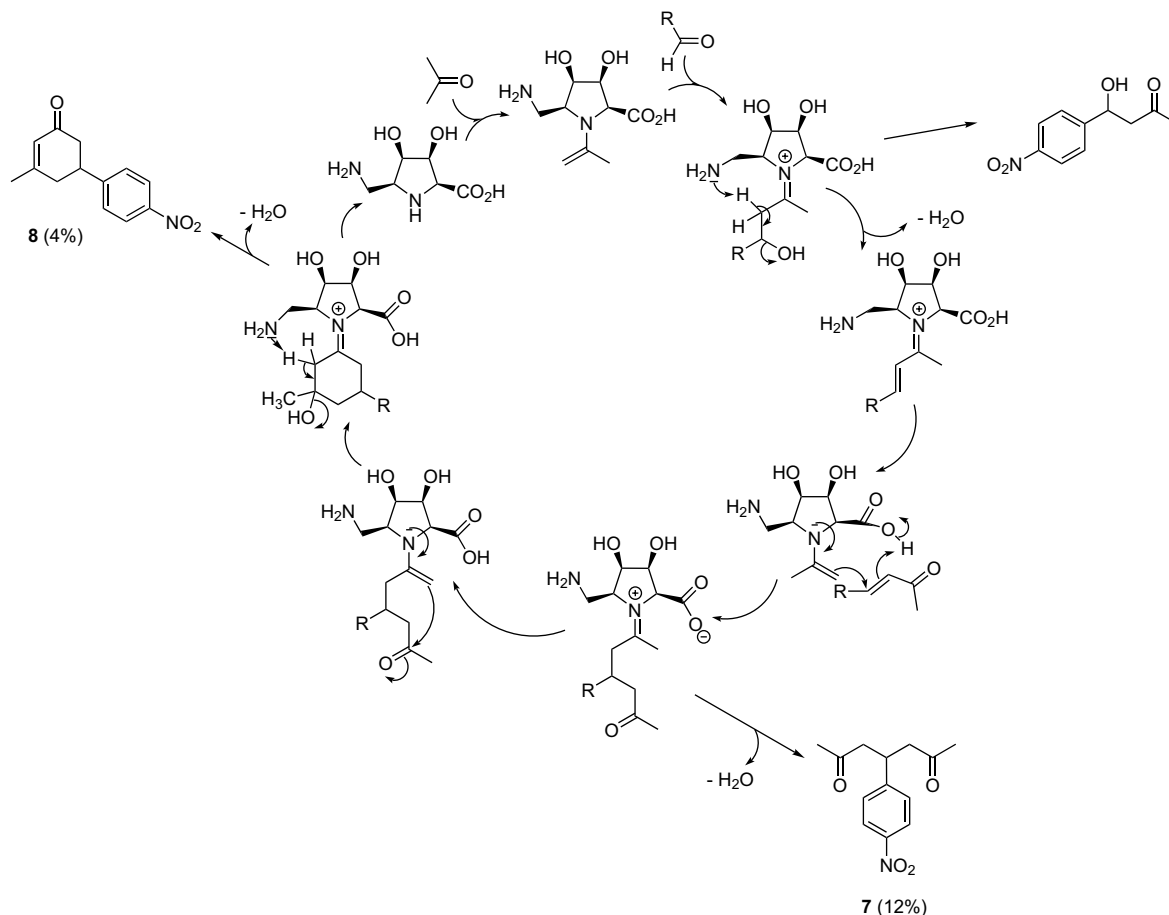
Materials and methods. Melting points are uncorrected. Optical rotations were recorded in CHCl_3 or MeOH solutions. ^1H NMR (300.13 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded in CDCl_3 , $\text{DMSO}-d_6$ or $\text{MeOD}-d_4$ (internal Me_4Si), respectively. TLC was performed on Silica F₂₅₄ and detection by UV light at 254 nm or by charring with phosphomolybdic- H_2SO_4 reagent. FTIR spectra were obtained on an AVATAR™ 320 neat using ATR and are reported in cm^{-1} . Mass spectral data were acquired on a WATERS Micromass ZQ spectrometer or a WATERS Micromass Q-TOF spectrometer. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AS columns were purchased from Daicel Chemical Industries. Column chromatography was effected on Silica Gel 60 (230 mesh). Cyclohexane and ethyl acetate were distilled before use.

4.2. General method for the synthesis of α -aminonitriles (A)

$\text{Ti}(\text{OiPr})_4$ (2 equiv) was added to a solution of aldose and HCOONH_3Bn (2 equiv) in MeOH. The reaction mixture was stirred at room temperature overnight, and then TMSCN (1.2 equiv) was added and the mixture stirred for 5 h. Water (5 mL) and EtOAc were added until oxidation of the titanium residue was complete. The solvent was evaporated to dryness and the crude was triturated in EtOAc and filtered through a silica pad. After elimination of the solvent, the crude was purified by flash chromatography (EtOAc/cyclohexane).

4.3. General method for the synthesis of imino-pyrrolidines (B)

Methanesulfonyl chloride (5 equiv) was added dropwise to a solution of α -aminonitrile in pyridine at 80 °C. The reaction mixture was stirred at 80 °C for 1–2 h. After cooling, water and CH_2Cl_2 were added. The organic layer was separated, dried over Na_2SO_4 , and removed under vacuum. The crude product was purified by flash chromatography.



Scheme 2. Aldol-aldol reaction and cyclodehydration.

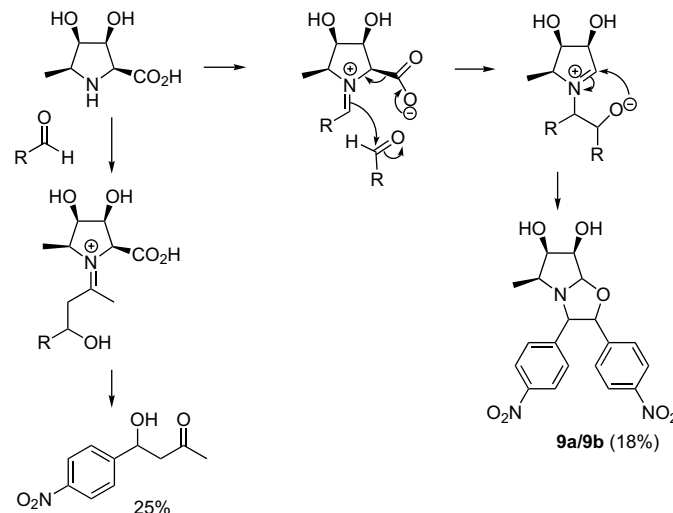
4.4. General method for the synthesis of polyhydroxyprolines (C)

The cyanopyrrolidine was placed into a reinforced flask. Concentrated HCl was added to the flask, and the flask was sealed. The reaction mixture was heated at 80 °C for 1–2 days then cooled to room temperature. The solvent was removed under vacuum then the crude mixture was redissolved in water, washed with a spatula of Pd/C and filtered. Pd/C (wet, 10 mol %) was added to the water layer and the mixture was vigorously stirred under 1H₂ atmosphere for 2 days at rt. After filtration, the filtrate was concentrated in vacuo. The residue was purified by ion exchange resin (Dowex 50W-X8, 100–200 mesh) and eluted with NH₄OH 0.1 M. After removal of the solvent, the solid was lyophilised to afford pure polyhydroxyproline as a brownish solid.

4.4.1. (1R)-1-N-Benzylamino-1-C-cyano-1,5-dideoxy-2,3-O-isopropylidene-D-ribose (**1bR**) and (1S)-1-N-benzylamino-1-C-cyano-1,5-dideoxy-2,3-O-isopropylidene-D-ribose (**1bS**)

Following the general method A, **1a** (8.0 g, 45.97 mmol), HCOONH₃Bn (14.06 g, 91.95 mmol), Ti(OiPr)₄ (27.5 mL, 91.95 mmol) and TMSCN (7.39 mL, 55.16 mmol) in MeOH (100 mL) gave, after flash chromatography (EtOAc/cyclohexane, 25/75) an unseparable mixture of **1bR** and **1bS** (12.1 g, 90%) as a white syrup. A pure fraction of **1bR** has been isolated for analysis: $[\alpha]_D^{20}$ –77 (c 0.05, MeOH); ¹H NMR (CDCl₃, 300 MHz) δ 7.34 (m, 5H, C₆H₅), 4.36 (dd, $J_{1,2}$ =3.1 Hz, $J_{2,3}$ =6.1 Hz, 1H, H-2), 4.21 (dd, $J_{3,4}$ =8.9 Hz, J_{4,CH_3} =6.1 Hz, 1H, H-4), 4.10 (q, J_{OH,CH_3} =7.1 Hz, 1H, OH), 4.08 (d, $J_{A,B}$ =12.8 Hz, 1H,

H-A NCH₂Ph), 3.96 (d, $J_{1,2}$ =3.1 Hz, 1H, H-1), 3.89 (dd, $J_{2,3}$ =6.1 Hz, $J_{3,4}$ =8.9 Hz, 1H, H-3), 3.80 (d, $J_{A,B}$ =12.8 Hz, 1H, H-B NCH₂Ph), 1.46 (s, 3H, CH₃), 1.34 (s, 3H, CH₃), 1.26 (m, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 137.8, 129.3–128.2 (C₆H₅), 118.7 (CN), 109.3 [OC(CH₃)₂], 81.7 (C-3), 76.9 (C-2), 65.5 (C-4), 52.0 (NCH₂Ph), 50.2 (C-1), 27.4, 25.2, 21.5 (3×CH₃). HRMS: C₁₆H₂₂O₃N₂Na calcd 313.1528, found 313.1527.



Scheme 3. Formation of bicyclic 1,3-oxazolidine.

4.4.2. (1R)-1-N-Benzylamino-1-C-cyano-1-deoxy-2,3-O-isopropylidene-5-O-trityl-D-ribose (**2bR**)

Following the general method **A**, **2a** (1.83 g, 4.23 mmol), HCOONH₃Bn (1.29 g, 8.47 mmol), Ti(OiPr)₄ (2.53 mL, 8.47 mmol) and TMSCN (0.68 mL, 5.07 mmol) in MeOH (20 mL) gave, after flash chromatography (EtOAc/cyclohexane, 20/80) **2bR** (1.8 g, 77%) as a white solid. Mp=46–48 °C; $[\alpha]_D^{20}$ –48 (c 0.13, CH₂Cl₂); IR (ATR) ν 3059, 3032, 2985, 2926, 2850, 1491, 1448, 1373, 1213, 1157, 1060 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 7.47–7.32 (m, 20H, 4×C₆H₅), 4.45 (dd, $J_{1,2}$ =2.7 Hz, $J_{2,3}$ =6.4 Hz, 1H, H-2), 4.34 (m, 1H, H-4), 4.27 (dd, $J_{2,3}$ =6.4 Hz, $J_{3,4}$ =8.5 Hz, 1H, H-3), 4.12 (d, $J_{A,B}$ =12.8 Hz, 1H, H-A NCH₂Ph), 4.04 (d, $J_{1,2}$ =2.7 Hz, 1H, H-1), 3.82 (d, $J_{A,B}$ =12.8 Hz, 1H, H-B NCH₂Ph), 3.38 (dd, $J_{4,5a}$ =3.3 Hz, $J_{5a,5b}$ =9.6 Hz, 1H, H-5a), 3.31 (dd, $J_{4,5b}$ =5.3 Hz, $J_{5a,5b}$ =9.6 Hz, 1H, H-5b), 1.43 (s, 3H, CH₃), 1.36 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 144.0, 138.2, 129.0–127.6 (4×C₆H₅), 118.9 (CN), 109.5 [OC(CH₃)₂], 87.4 [OC(C₆H₅)₃], 77.2 (C-2, C-3), 69.0 (C-4), 65.5 (C-5), 52.0 (NCH₂Ph), 50.2 (C-1), 27.1, 24.9 (2×CH₃). HRMS: C₃₅H₃₆O₄N₂Na calcd 571.2573, found 571.2585.

4.4.3. (1R)-1-C-Cyano-5-azido-1-N-benzylamino-1,5-dideoxy-2,3-O-isopropylidene-D-ribose (**3bR**) and (1S)-1-C-cyano-5-azido-1-N-benzylamino-1,5-dideoxy-2,3-O-isopropylidene-D-ribose (**3bS**)

Following the general method **A**, **3a** (15.8 g, 73.4 mmol), HCOONH₃Bn (22.4 g, 146.8 mmol), Ti(OiPr)₄ (43.9 mL, 146.8 mmol) and TMSCN (11.8 mL, 88.1 mmol) in MeOH (200 mL) gave, after flash chromatography (EtOAc/cyclohexane, 20/80) an unseparable mixture of **3bR/3bS** (15.5 g, 56%) as a slight yellow syrup. A pure fraction of **3bR** has been isolated for analysis: $[\alpha]_D^{20}$ –74 (c 0.4, CH₂Cl₂); IR (ATR) ν 2988, 2934, 2102, 1454, 1382, 1214, 1062 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 7.43–7.28 (m, 5H, C₆H₅), 4.41 (dd, $J_{1,2}$ =2.7 Hz, $J_{2,3}$ =6.3 Hz, 1H, H-2), 4.26 (ddt, $J_{4,5a}$ =2.7 Hz, $J_{4,5b}$ =5.8 Hz, $J_{3,4}$ =9.1 Hz, 1H, H-4), 4.10 (m, 2H, H-3, H-A NCH₂Ph), 4.01 (d, $J_{1,2}$ =2.7 Hz, 1H, H-1), 3.82 (d, $J_{A,B}$ =12.8 Hz, 1H, H-B NCH₂Ph), 3.56 (dd, $J_{4,5a}$ =2.7 Hz, $J_{5a,5b}$ =12.7 Hz, 1H, H-5a), 3.39 (dd, $J_{4,5b}$ =5.8 Hz, $J_{5a,5b}$ =12.7 Hz, 1H, H-5b), 1.48 (s, 3H, CH₃), 1.36 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 137.7, 129.2–128.4 (C₆H₅), 118.5 (CN), 109.8 [OC(CH₃)₂], 77.1, 76.6 (C-2, C-3), 68.7 (C-4), 54.9 (C-5), 52.0 (NCH₂Ph), 49.7 (C-1), 27.3, 25.0 (2×CH₃). HRMS: C₁₆H₂₁O₃N₅Na calcd 354.1542, found 354.1539.

4.4.4. (1R)-1-N-Benzylamino-1-C-cyano-2,3:5,6-di-O-isopropylidene-D-mannose (**4bR**) and (1S)-1-N-benzylamino-1-C-cyano-2,3:5,6-di-O-isopropylidene-D-mannose (**4bS**)

Following the general method **A**, **4a** (5.0 g, 19.23 mmol), HCOONH₃Bn (5.88 g, 38.46 mmol), Ti(OiPr)₄ (10.91 mL, 38.46 mmol) and TMSCN (3.09 mL, 23.07 mmol) in MeOH (50 mL) gave, after flash chromatography (EtOAc/cyclohexane, 35/65) a mixture of **4bR** and **4bS** (25/75) (7.09 g, 98%); IR (ATR) ν 3297, 2980, 2960, 2935, 2906, 1454, 1378, 1266, 1254, 1205, 1157, 1136, 1061 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 7.36 (m, 5H, C₆H₅), 4.56 (dd, $J_{1,2}$ =1.5 Hz, $J_{2,3}$ =7.7 Hz, 1H, H-2), 4.48 (d, $J_{2,3}$ =7.7 Hz, 1H, H-3), 4.17–4.06 (m, 4H, H-4, H-5, H-6a, H-A NCH₂Ph), 4.06 (dd, $J_{5,6b}$ =4.5 Hz, $J_{6a,6b}$ =7.7 Hz, 1H, H-6b), 3.87 (d, $J_{A,B}$ =12.4 Hz, 1H, H-B NCH₂Ph), 3.74 (d, $J_{1,2}$ =1.5 Hz, 1H, H-1), 3.27 (d, $J_{4,5}$ =8.3 Hz, 1H, H-4), 1.52 (s, 3H, CH₃), 1.42 (s, 3H, CH₃), 1.35 (s, 6H, 2×CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 136.4, 129.3–128.7 (C₆H₅), 117.9 (CN), 109.9, 109.8 (2×[OC(CH₃)₂]), 76.8, 76.7 (C-2, C-3), 75.8 (C-5), 70.5 (C-4), 68.1 (C-6), 51.9 (NCH₂Ph), 49.1 (C-1), 27.2, 26.4, 25.6, 24.9 (4×CH₃). HRMS: C₂₀H₂₈O₅N₂Na calcd 399.1896, found 399.1902.

4.4.5. (1R)-1-N-Benzylamino-1-C-cyano-2,3,5-tri-O-benzyl-D-arabinose (**5bR**) and (1R)-1-N-benzylamino-1-C-cyano-2,3,5-tri-O-benzyl-D-arabinose (**5bS**)

Following the general method **A**, **5a** (2.0 g, 4.93 mmol), HCOONH₃Bn (1.51 g, 9.86 mmol), Ti(OiPr)₄ (2.95 mL, 9.86 mmol)

and TMSCN (0.79 mL, 5.92 mmol) in MeOH (20 mL) gave, after flash chromatography (EtOAc/cyclohexane, 25/75) an unseparable mixture of **5bR** and **5bS** (1.90 g, 72%) as a white solid; IR (ATR) ν 3433, 3288, 3068, 3030, 2920, 2878, 1496, 1453, 1213, 1129, 1086, 1055, 1028 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 7.44–7.28 (m, 40H, 8×C₆H₅), 4.92–4.59 (m, 12H, 6×OCH₂Ph), 4.19–3.65 (m, 16H, 2×H-1, 2×H-2, 2×H-3, 2×H-4, 4×H-5, 2×NCH₂Ph); ¹³C NMR (CDCl₃, 75 MHz) δ 138.8, 129.1–128.1 (8×C₆H₅), 119.7, 119.5 (2×CN), 80.5, 80.4, 80.3, 79.8, 78.5, 78.1 (2×C-2, 2×C-3, 2×C-4), 76.1, 75.5, 75.4, 75.2, 72.3, 71.9 (6×OCH₂Ph), 61.0, 60.2 (2×C-5), 52.1, 51.9 (NCH₂Ph), 52.7, 51.8 (2×C-1). HRMS: C₃₄H₃₆O₄N₂ calcd 537.2753, found 537.2758.

4.4.6. (1R)-1-N-Benzylamino-1-C-cyano-2,3,5-tri-O-benzyl-L-arabinose (**6bR**) and (1R)-1-N-benzylamino-1-C-cyano-2,3,5-tri-O-benzyl-L-arabinose (**6bS**)

Following the general method **A**, **6a** (5.2 g, 12.38 mmol), HCOONH₃Bn (3.78 g, 24.76 mmol), Ti(OiPr)₄ (7.40 mL, 24.76 mmol) and TMSCN (1.99 mL, 14.85 mmol) in MeOH (30 mL) gave, after flash chromatography (EtOAc/cyclohexane, 20/80) **6bR** (2.47 g, 37%) and a mixture of **6bR** and **6bS** (4/1) (2.73 g, 41%); IR (ATR) ν 3429, 3288, 3064, 3030, 2921, 2878, 1496, 1453, 1128, 1086, 1055, 1028 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 7.45–7.31 (m, 20H, 4×C₆H₅), 4.95–4.62 (m, 6H, 3×OCH₂Ph), 4.16–3.70 (m, 8H, H-1, H-2, H-3, H-4, 2×H-5, NCH₂Ph); ¹³C NMR (CDCl₃, 75 MHz) δ 138.8–138.2, 129.2–127.9 (4×C₆H₅), 119.4 (CN), 81.0, 80.7, 79.3 (C-2, C-3, C-4), 75.9, 75.1, 72.6 (3×OCH₂Ph), 61.6 (C-5), 52.2 (C-1), 52.0 (NCH₂Ph). HRMS: C₃₄H₃₆O₄N₂ calcd 537.2753, found 537.2752.

4.4.7. (2R,3S,4R,5S) 1-N-Benzyl-2-cyano-3,4-O-isopropylidene-5-methylpyrrolidine (**1cR**) and (2S,3S,4R,5S) 1-N-benzyl-2-cyano-3,4-O-isopropylidene-5-methylpyrrolidine (**1cS**)

Following the general method **B**, **1bR/1bS** (6.69 g, 23.06 mmol), MsCl (8.92 mL, 115.34 mmol) in pyridine (100 mL) for 1 h 20 min gave, after flash chromatography (EtOAc/cyclohexane, 20/80), **1cS** (430 mg, 6%) as an orange syrup and **1cR** (5.37 g, 85%) as a slight yellow solid. Compound **1cR**: mp=73–75 °C; $[\alpha]_D^{20}$ –85 (c 0.2, CHCl₃); IR (ATR) ν 3031, 2987, 2936, 2812, 1454, 1380, 1211, 1147, 1127, 1076, 1001 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 7.31 (m, 5H, C₆H₅), 4.59 (t, $J_{2,3}$ = $J_{3,4}$ =5.4 Hz, 1H, H-3), 4.47 (dd, $J_{4,5}$ =4.5 Hz, $J_{3,4}$ =5.4 Hz, 1H, H-4), 3.98 (s, 2H, NCH₂Ph), 3.19 (d, $J_{2,3}$ =5.4 Hz, 1H, H-2), 2.42 (dd, J_{5,CH_3} =6.2 Hz, $J_{4,5}$ =4.5 Hz, 1H, H-5), 1.62 (s, 3H, CH₃), 1.44 (s, 3H, CH₃), 1.28 (t, 3H, CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 133.8, 130.2–128.2 (C₆H₅), 116.4 (CN), 113.6 [OC(CH₃)₂], 81.7 (C-3), 77.9 (C-4), 59.6 (C-5), 57.8 (C-2), 52.5 (NCH₂Ph), 26.6 (CH₃), 26.2 (CH₃), 12.8 (CH₃). HRMS: C₁₆H₂₀O₂N₂Na calcd 295.1422, found 295.1422. Compound **1cS**: $[\alpha]_D^{20}$ –78 (c 0.1, CHCl₃); IR (ATR) ν 3019, 2986, 2966, 2937, 2864, 2246, 1454, 1376, 1267, 1243, 1207, 1123, 1104, 1026 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 7.36 (m, 5H, C₆H₅), 4.73 (d, $J_{3,4}$ =6.2 Hz, 1H, H-3), 4.63 (dd, $J_{4,5}$ =4.3 Hz, $J_{3,4}$ =6.2 Hz, 1H, H-4), 4.12 (d, $J_{A,B}$ =13.2 Hz, 1H, H-A NCH₂Ph), 3.75 (s, 1H, H-2), 3.36 (d, $J_{A,B}$ =13.2 Hz, 1H, H-B NCH₂Ph), 2.77 (dd, J_{5,CH_3} =6.2 Hz, $J_{4,5}$ =4.3 Hz, 1H, H-5), 1.53 (s, 3H, CH₃), 1.32 (m, 6H, 2×CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 137.6, 129.0–127.9 (C₆H₅), 115.3 (CN), 113.0 [OC(CH₃)₂], 82.1 (C-4), 81.0 (C-3), 61.0 (C-5), 59.6 (C-2), 52.7 (NCH₂Ph), 26.7, 26.2 (2×CH₃), 12.8 (CH₃). HRMS: C₁₆H₂₀O₂N₂Na calcd 295.1422, found 295.1421.

4.4.8. (2R,3S,4R,5S)-1-N-Benzyl-2-cyano-3,4-O-isopropylidene-5-trityloxymethylpyrrolidine (**2cR**)

Following the general method **B**, **2bR** (600 mg, 1.09 mmol), MsCl (0.48 mL, 5.45 mmol) in pyridine (20 mL) for 2 h gave, after flash chromatography (EtOAc/cyclohexane, 15/85) through a silica pad, **2cR** (458 mg, 79%) as a slight yellow solid. Mp=53–55 °C; $[\alpha]_D^{20}$ +16 (c 0.15, CH₂Cl₂); IR (ATR) ν 3056, 2986, 2932, 2847, 2373, 1491, 1448, 1380, 1213, 1163, 1074 cm^{–1}; ¹H NMR (CDCl₃, 300 MHz) δ 7.59–7.08

(m, 20H, $4\times\text{C}_6\text{H}_5$), 4.82 (dd, $J_{3,4}=6.0$ Hz, $J_{4,5}=4.7$ Hz, 1H, H-4), 4.65 (dd, $J_{2,3}=5.0$ Hz, $J_{3,4}=6.0$ Hz, 1H, H-3), 3.93 (d, $J_{A,B}=14.8$ Hz, 1H, H-A NCH_2Ph), 3.86 (d, $J_{A,B}=14.8$ Hz, 1H, H-B NCH_2Ph), 3.67 (dd, $J_{5,6a}=7.6$ Hz, $J_{6a,6b}=9.1$ Hz, 1H, H-6a), 3.42 (dd, $J_{5,6b}=4.7$ Hz, $J_{6a,6b}=9.1$ Hz, 1H, H-6b), 3.26 (d, 1H, H-2), 2.62 (m, 1H, H-5), 1.58 (s, 3H, CH_3), 1.46 (s, 3H, CH_3); ^{13}C NMR (CDCl_3 , 75 MHz) δ 144.3, 133.9, 130.3–127.5 ($4\times\text{C}_6\text{H}_5$), 116.4 (CN), 113.7 [$\text{OC}(\text{CH}_3)_2$], 87.6 [$\text{OC}(\text{C}_6\text{H}_5)_3$], 80.4 (C-4), 78.0 (C-3), 64.5 (C-5), 61.3 (C-6), 58.2 (C-2), 53.8 (NCH_2Ph), 26.7, 26.6 ($2\times\text{CH}_3$). HRMS: $\text{C}_{35}\text{H}_{34}\text{O}_3\text{N}_2\text{Na}$ calcd 553.2467, found 553.2462.

4.4.9. (2R,3S,4R,5S) 5-Azidomethyl-1-N-benzyl-2-cyano-3,4-O-isopropylidenepyrrolidine (3cR) and (2S,3S,4R,5S) 5-azidomethyl-1-N-benzyl-2-cyano-3,4-O-isopropylidenepyrrolidine (3cS)

Following the general method **B**, **3bR/3bS** (8.0 g, 24.16 mmol), MsCl (9.35 mL, 120.84 mmol) in pyridine (150 mL) for 3 h gave, after flash chromatography (EtOAc/cyclohexane , 2/8) through a silica pad, **3e** (300 mg, 4%) as an orange syrup followed by **3cS** (5.82 g, 77%) as a white solid. Compound **3cR**: mp=78 °C; $[\alpha]_D^{20} +1$ (c 0.9, CHCl_3); IR (ATR) ν 2991, 2978, 2944, 2108, 2092, 1454, 1373, 1272, 1203, 1095 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.34 (m, 5H, C_6H_5), 4.80 (dd, $J_{3,4}=6.2$ Hz, $J_{4,5}=4.1$ Hz, 1H, H-4), 4.76 (d, $J_{3,4}=6.2$ Hz, 1H, H-3), 4.12 (d, $J_{A,B}=13.4$ Hz, 1H, H-A NCH_2Ph), 3.81 (s, 1H, H-2), 3.74 (dd, $J_{5,6a}=7.8$ Hz, $J_{6a,6b}=12.2$ Hz, 1H, H-6a), 3.53 (d, $J_{A,B}=13.4$ Hz, 1H, H-B NCH_2Ph), 3.54 (dd, $J_{5,6b}=4.8$ Hz, $J_{6a,6b}=12.2$ Hz, 1H, H-5b), 2.90 (m, 1H, H-4), 1.54 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (CDCl_3 , 75 MHz) δ 136.9, 129.1–128.2 (C_6H_5), 114.9 (CN), 113.5 [$\text{OC}(\text{CH}_3)_2$], 80.7, 80.4 (C-3, C-4), 64.9 (C-5), 59.8 (C-2), 53.7 (NCH_2Ph), 49.8 (C-6), 26.6, 25.9 ($2\times\text{CH}_3$). HRMS: $\text{C}_{16}\text{H}_{19}\text{O}_2\text{N}_5\text{Na}$ calcd 336.1436, found 336.1440. Compound **3cS**: $[\alpha]_D^{20} +122$ (c 0.59, CH_2Cl_2); IR (ATR) ν 2989, 2936, 2102, 1454, 1373, 1274, 1210 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.41–7.28 (m, 5H, C_6H_5), 4.67 (m, 2H, H-3, H-4), 4.04 (d, $J_{A,B}=14.8$ Hz, 1H, H-A NCH_2Ph), 3.90 (d, $J_{A,B}=14.8$ Hz, 1H, H-B NCH_2Ph), 3.64 (dd, $J_{5,6a}=8.6$ Hz, $J_{6a,6b}=12.0$ Hz, 1H, H-6a), 3.48 (dd, $J_{5,6b}=4.8$ Hz, $J_{6a,6b}=12.0$ Hz, 1H, H-6b), 3.36 (d, $J_{2,3}=4.4$ Hz, 1H, H-2), 2.63 (m, 1H, H-5), 1.63 (s, 3H, CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR (CDCl_3 , 75 MHz) δ 134.2, 129.9–128.5 (C_6H_5), 116.0 (CN), 114.1 [$\text{OC}(\text{CH}_3)_2$], 79.9, 77.7 (C-3, C-4), 64.2 (C-5), 58.6 (C-2), 54.1 (NCH_2Ph), 49.6 (C-6), 26.5, 26.0 ($2\times\text{CH}_3$). HRMS: $\text{C}_{16}\text{H}_{19}\text{O}_2\text{N}_5\text{Na}$ calcd 336.1436, found 336.1444.

4.4.10. (2S,3R,4S,5S,6R)-1-N-Benzyl-2-cyano-3,4,6,7-di-O-isopropylidenepyrrolidine (4cS) and (2R,3R,4S,5S,6R)-1-N-Benzyl-2-cyano-3,4,6,7-di-O-isopropylidenepyrrolidine (4cR)

Following the general method **B**, **4bR/4bS** (1/1.5) (2.39 g, 6.35 mmol), MsCl (2.45 mL, 31.75 mmol) in pyridine (100 mL) for 1 h 10 min gave, after flash chromatography (EtOAc/cyclohexane , 3/7) through a silica pad, **4cS** (990 mg, 43.5%) as an orange solid followed by **4cR** (370 mg, 16.3%) as a white solid. Compound **4cS**: mp=108–109 °C; $[\alpha]_D^{20} +140$ (c 0.19, MeOH); IR (ATR) ν 2986, 2877, 2843, 2813, 2357, 1454, 1384, 1373, 1260, 1210, 1146, 1102, 1069, 1015 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.43–7.28 (m, 5H, C_6H_5), 4.88 (dd, $J_{2,3}=3.8$ Hz, $J_{3,4}=6.3$ Hz, 1H, H-3), 4.41 (dd, $J_{3,4}=6.3$ Hz, $J_{4,5}=2.4$ Hz, 1H, H-4), 4.25 (d, $J_{A,B}=13.7$ Hz, 1H, H-A NCH_2Ph), 4.23 (d, $J_{A,B}=13.7$ Hz, 1H, H-B NCH_2Ph), 4.05–3.98 (m, 2H, H-6, H-7a), 3.75 (dd, $J_{6,7b}=7.0$ Hz, $J_{7a,7b}=8.3$ Hz, 1H, H-7b), 3.60 (d, $J_{2,3}=3.8$ Hz, 1H, H-2), 3.25 (dd, $J_{4,5}=2.4$ Hz, $J_{5,6}=6.8$ Hz, 1H, H-5), 1.49, 1.43, 1.36, 1.30 (s, 12H, $4\times\text{CH}_3$); ^{13}C NMR (CDCl_3 , 75 MHz) δ 136.0, 129.7–128.3 (C_6H_5), 118.6 (CN), 114.1, 110.4 ($2\times[\text{OC}(\text{CH}_3)_2]$), 82.5, 81.4, 75.9, 69.7 (C-3, C-4, C-5, C-6), 66.8 (C-7), 59.3 (C-2), 55.4 (NCH_2Ph), 27.4, 26.9, 25.6, 25.4 ($4\times\text{CH}_3$). HRMS: $\text{C}_{20}\text{H}_{26}\text{O}_4\text{N}_2$ calcd 381.1790, found 381.1799. Compound **4cR**: mp=87–88 °C; $[\alpha]_D^{20} +1$ (c 0.46, MeOH); IR (ATR) ν 2989, 2947, 2891, 2850, 2242, 1375, 1251, 1210, 1157, 1084, 1071, 1047, 1028 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.33 (m, 5H, C_6H_5), 4.58 (t, $J_{2,3}=J_{3,4}=6.7$ Hz, 1H, H-3), 4.42 (dd, $J_{4,5}=4.0$ Hz, 1H,

H-4), 4.41 (d, $J_{A,B}=13.6$ Hz, 1H, H-A NCH_2Ph), 4.34 (q, $J_{5,6}=J_{6,7b}=J_{7a,7b}=6.7$ Hz, 1H, H-6), 4.13 (dd, $J_{6,7a}=6.7$ Hz, $J_{7a,7b}=8.6$ Hz, 1H, H-7a), 3.98 (d, 1H, H-2), 3.90 (dd, $J_{6,7b}=6.7$ Hz, $J_{7a,7b}=8.6$ Hz, 1H, H-7b), 3.68 (d, $J_{A,B}=13.6$ Hz, 1H, H-B NCH_2Ph), 3.19 (dd, 1H, H-5), 1.49, 1.44, 1.38, 1.34 (s, 12H, $4\times\text{CH}_3$); ^{13}C NMR (CDCl_3 , 75 MHz) δ 137.3, 129.2–128.1 (C_6H_5), 116.1 (CN), 114.5, 110.6 ($2\times[\text{OC}(\text{CH}_3)_2]$), 81.0 (C-4), 77.4 (C-3), 76.8 (C-6), 69.9 (C-5), 66.7 (C-7), 59.0 (C-2), 54.7 (NCH_2Ph), 26.9, 26.2, 25.6, 25.5 ($4\times\text{CH}_3$). HRMS: $\text{C}_{20}\text{H}_{26}\text{O}_4\text{N}_2$ calcd 381.1790, found 381.1793.

4.4.11. (3S,4R,5R,6S)-1-Cyano-2,3,5-tri-O-benzyl-1-N-benzylpyrrolidine (5cS)

Following the general method **B**, **5bR/5bS** (5.9 g, 11.0 mmol), MsCl (4.26 mL, 55.03 mmol) in pyridine (100 mL) for 1 h 30 min gave, after flash chromatography (EtOAc/cyclohexane , 25/75) through a silica pad, **5cS** (3.28 g, 57%) as a white solid. Mp=132–133 °C; $[\alpha]_D^{20} -50$ (c 0.21, MeOH); IR (ATR) ν 3063, 3031, 2877, 2809, 1496, 1452, 1368, 1153, 1114, 1090, 1059, 1027 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.43–7.23 (m, 20H, $4\times\text{C}_6\text{H}_5$), 4.89–4.59 (m, 6H, $3\times\text{OCH}_2\text{Ph}$), 4.15 (dd, $J_{2,3}=5.3$ Hz, $J_{3,4}=9.5$ Hz, 1H, H-3), 4.00 (d, $J_{2,3}=5.3$ Hz, 1H, H-2), 3.77 (m, 1H, H-5), 3.70 (dd, $J_{3,4}=9.5$ Hz, $J_{4,5}=3.3$ Hz, 1H, H-4), 3.66 (s, 2H, $2\times\text{H-6}$), 2.96 (dt, $J_{A,B}=13.2$ Hz, $J_{1,A}=J_{4,A}=1.5$ Hz, 1H, H-A NCH_2Ph), 2.42 (d, $J_{A,B}=13.2$ Hz, 1H, H-B NCH_2Ph); ^{13}C NMR (CDCl_3 , 75 MHz) δ 138.9–136.8, 129.3–128.0 ($4\times\text{C}_6\text{H}_5$), 115.2 (CN), 80.2 (C-4), 75.3 (C-3), 74.0, 73.3, 71.9 ($3\times\text{OCH}_2\text{Ph}$), 72.9 (C-5), 59.7 (C-6), 57.8 (C-2), 50.1 (NCH_2Ph). HRMS: $\text{C}_{34}\text{H}_{34}\text{O}_3\text{N}_2$ calcd 519.2666, found 519.2657.

4.4.12. (3R,4S,5S,6R)-1-Cyano-2,3,5-tri-O-benzyl-1-N-benzylpyrrolidine (6cR)

Following the general method **B**, **6bR/6bS** (2.59 g, 4.83 mmol), MsCl (1.87 mL, 24.16 mmol) in pyridine (50 mL) for 1 h gave, after flash chromatography (EtOAc/cyclohexane , 15/85) through a silica pad, **6cR** (2.12 g, 84%) as a white solid. Mp=129–130 °C; $[\alpha]_D^{20} +50$ (c 0.23, MeOH); IR (ATR) ν 3064, 3031, 2852, 2809, 1496, 1452, 1368, 1153, 1114, 1090, 1059, 1027 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.50–7.27 (m, 20H, $4\times\text{C}_6\text{H}_5$), 4.88–4.53 (m, 6H, $3\times\text{OCH}_2\text{Ph}$), 4.15 (dd, $J_{2,3}=5.3$ Hz, $J_{3,4}=9.6$ Hz, 1H, H-3), 4.00 (d, $J_{2,3}=5.3$ Hz, 1H, H-2), 3.76–3.66 (m, 4H, H-4, H-5, $2\times\text{H-6}$), 2.97 (d, $J_{A,B}=13.3$ Hz, 1H, H-A NCH_2Ph), 2.43 (d, $J_{A,B}=13.3$ Hz, 1H, H-B NCH_2Ph); ^{13}C NMR (CDCl_3 , 75 MHz) δ 138.9–136.8, 129.3–128.0 ($4\times\text{C}_6\text{H}_5$), 115.2 (CN), 80.2 (C-4), 75.3 (C-3), 74.0, 73.3, 71.9 ($3\times\text{OCH}_2\text{Ph}$), 73.0 (C-5), 59.7 (C-6), 57.8 (C-2), 50.2 (NCH_2Ph). HRMS: $\text{C}_{34}\text{H}_{34}\text{O}_3\text{N}_2$ calcd 519.2648, found 519.2655.

4.4.13. (2S,3S,4R,5S)-3,4-Dihydroxy-5-methylproline (1d)

Following the general method **C**, 800 mg (2.94 mmol) of compound **1cR**, 20 mL of concd HCl (37%) for 24 h followed by addition of Pd/C (500 mg) in water (10 mL) gave after lyophilisation 370 mg (78%) of compound **1d** as a slight brown solid. Mp=220 °C; $[\alpha]_D^{20} -9$ (c 0.32, H_2O); IR (ATR) ν 3367, 3064, 2949, 2532, 2465, 1599, 1438, 1394, 1367, 1319, 1157, 1132, 1049, 1022, 985, 877, 808 cm^{-1} ; ^1H NMR (D_2O , 300 MHz) δ 4.49 (dd, $J_{2,3}=6.3$ Hz, $J_{3,4}=4.5$ Hz, 1H, H-3), 4.25 (t, $J_{3,4}=4.5$ Hz, $J_{4,5}=4.5$ Hz, 1H, H-4), 4.04 (d, $J_{2,3}=6.3$ Hz, 1H, H-2), 3.72 (m, 1H, H-5), 1.34 (d, $J_{5,\text{CH}_3}=6.9$ Hz, 3H, CH_3); ^{13}C NMR (D_2O , 75 MHz) δ 170.6 (CO), 70.9, 70.8 (C-3, C-4), 62.4 (C-2), 56.4 (C-5), 12.0 (CH_3). HRMS: $\text{C}_6\text{H}_{12}\text{O}_4\text{N}$ calcd 162.0766, found 162.0767.

4.4.14. (2S,3S,4R,5S)-3,4-Dihydroxy-5-hydroxymethylproline (2d)

Following the general method **C**, 645 mg (1.21 mmol) of compound **2cR**, 20 mL of concd HCl (37%) for 2 days followed by addition of Pd/C (300 mg) in water (10 mL) gave after lyophilisation 164 mg (76%) of compound **2d** as a slight brown solid. Mp=223 °C; $[\alpha]_D^{20} -41$ (c 0.17, H_2O); IR (ATR) ν 3196, 3113, 1622, 1562, 1417, 1396, 1319, 1282, 1132, 1041, 1018, 902, 873 cm^{-1} ; ^1H NMR (D_2O , 300 MHz) δ 4.42 (m, 2H, H-3, H-4), 4.05 (m, 1H, H-2), 3.86–3.76 (m,

3H, H-5, H-6a, H-6b); ^{13}C NMR (D_2O , 75 MHz) δ 170.0 (CO), 70.7, 70.3 (C-2, C-3), 62.7, 60.8 (C-2, C-5), 57.6 (C-6). HRMS: $\text{C}_6\text{H}_{11}\text{O}_5\text{NNa}$ calcd 200.0535, found 200.0535.

4.4.15. (2S,3S,4R,5S)-5-Aminomethyl-3,4-dihydroxyproline (**3d**)

Following the general method **C**, 5.0 g (15.97 mmol) of compound **3cR**, 80 mL of HClc. (37%) for 2 days followed by addition of Pd/C (500 mg) in water (100 mL) gave after lyophilisation 2.17 g (77%) of compound **3d** as a slight brown solid. Mp=99–100 °C; $[\alpha]_D^{20}$ –17 (c 0.45, H_2O); IR (ATR) ν 3151, 3105, 3014, 2160, 2034, 1979, 1624, 1560, 1417, 1398, 1354, 1321, 1284, 1120, 1043, 1018, 902, 875 cm^{-1} ; ^1H NMR (D_2O , 300 MHz) δ 4.64 (m, 2H, H-2, H-3), 4.49 (m, 1H, H-4), 4.16 (m, 1H, H-5), 3.59 (dd, $J_{5,6a}=6.5$ Hz, $J_{6a,6b}=13.9$ Hz, 1H, H-6a), 3.46 (dd, $J_{5,6b}=5.7$ Hz, $J_{6a,6b}=13.9$ Hz, 1H, H-6b); ^{13}C NMR (D_2O , 75 MHz) δ 168.2 (CO), 70.5 (C-3), 70.0 (C-4), 62.7 (C-2), 56.5 (C-5), 37.0 (C-6). HRMS: $\text{C}_6\text{H}_{13}\text{O}_4\text{N}_2$ calcd 177.0875, found 177.0875.

4.4.16. 4-para-Nitrophenylhepta-2,6-dione (**7**) and 3-methyl-5-para-nitrophenylcyclohex-3-enone (**8**)

4-Nitrobenzaldehyde (100 mg, 0.66 mmol) and catalyst **3d** (116 mg, 0.66 mmol) were dissolved in DMSO (5.3 mL) and acetone (1.3 mL) and stirred overnight at room temperature. Addition of NH_4Cl (20 mL) followed by extraction with EtOAc ($\times 2$) led successively after flash chromatography (EtOAc/cyclohexane, 3/7) to **8** (6 mg, 4%) and **7** (19 mg, 12%, EtOAc/cyclohexane, 4/6) as slight yellow solid. Compound **8**: mp=115–116 °C; $[\alpha]_D^{20}$ –2 (c 0.09, CHCl_3); IR (ATR) ν 2925, 1656, 1605, 1596, 1518, 1510, 1339, 1313, 1298, 1254 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 8.28 (d, $J_{o,m}=6.8$ Hz, 2H, C_6H_4), 7.45 (m, 2H, C_6H_4), 6.04 (s, 1H, CH=), 3.49 (m, 1H, CH), 2.74–2.55 (m, 4H, $2\times\text{CH}_2$), 2.06 (s, 3H, CH_3); ^{13}C NMR (CDCl_3 , 75 MHz) δ 197.6 (CO), 160.8 (C=), 150.5, 127.7, 126.7, 124.1 (CH=, C_6H_4), 43.2 (CH_2), 40.5 (CH), 38.2 (CH_2), 24.3 (CH_3). HRMS: $\text{C}_{13}\text{H}_{13}\text{O}_3\text{NNA}$ calcd 254.0793, found 254.0798. Compound **7**: mp=49–50 °C; IR (ATR) ν 3403, 2907, 1704, 1597, 1501, 1341, 1219, 1158 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 8.15 (d, $J_{o,m}=8.6$ Hz, 2H, C_6H_4), 7.42 (m, 2H, C_6H_4), 3.83 (m, 1H, CH), 2.88 (dd, $J_{\text{H,HA}}=6.5$ Hz, $J_{\text{HA,HB}}=17.3$ Hz, 2H, $2\times\text{H-A CH}_2$), 2.80 (dd, $J_{\text{H,HB}}=7.5$ Hz, $J_{\text{HA,HB}}=17.3$ Hz, 2H, $2\times\text{H-B CH}_2$), 2.09 (s, 3H, CH_3); ^{13}C NMR (CDCl_3 , 75 MHz) δ 206.4 (CO), 151.8, 147.1, 128.8, 124.2 (C_6H_4), 49.2 ($2\times\text{CH}_2$), 36.1 (CH), 30.6 ($2\times\text{CH}_3$). HRMS: $\text{C}_{13}\text{H}_{15}\text{O}_4\text{NNA}$ calcd 272.0899, found 272.0905.

4.4.17. 5-Methyl-2,3-bis-(4-nitrophenyl)-hexahydro-pyrrolo[2,1-b]oxazole-6,7-diol (**9a**) and 5-methyl-2,3-bis-(4-nitrophenyl)-hexahydro-pyrrolo[2,1-b]oxazole-6,7-diol (**9b**)

4-Nitrobenzaldehyde (100 mg, 0.66 mmol) and catalyst **1** (106 mg, 0.66 mmol) were dissolved in DMSO (5.3 mL) and acetone (1.3 mL) and stirred for 48 h at room temperature. Addition of NH_4Cl (20 mL) followed by extraction with EtOAc ($\times 2$) led successively after flash chromatography (EtOAc/cyclohexane, 4/6) to the known aldol derivative (34 mg, 25%) followed by **9a** (24 mg, 9%, EtOAc/cyclohexane, 6/4) and **9b** (24 mg, 9%, EtOAc/cyclohexane, 1/0). Compound **9a**: mp=65–66 °C; $[\alpha]_D^{20}$ +92 (c 0.15, MeOH); IR (ATR) ν 3308, 2925, 1729, 1600, 1514, 1343, 1108, 1041 cm^{-1} ; ^1H NMR (CD_3OD , 300 MHz) δ 7.96, 7.34, 7.18 (m, 8H, $2\times\text{C}_6\text{H}_4$), 5.50 (d, $J_{7,8}=4.8$ Hz, 1H, H-8), 5.46 (d, $J_{2,3}=5.7$ Hz, 1H, H-2), 4.62 (d, $J_{2,3}=5.7$ Hz, 1H, H-3), 4.19 (t, $J_{6,7}=J_{7,8}=4.7$ Hz, 1H, H-7), 4.08 (dd, $J_{5,6}=3.0$ Hz, $J_{6,7}=4.7$ Hz, 1H, H-6), 3.43 (m, 1H, H-5), 1.25 (d, $J_{5,\text{CH}_3}=6.4$ Hz, 3H, CH_3); ^{13}C NMR (CD_3OD , 75 MHz) δ 147.0, 144.8, 128.6, 127.3, 122.5, 122.1 ($2\times\text{C}_6\text{H}_4$), 103.2 (C-8), 78.0, 69.8 (C-2, C-3), 77.3 (C-7), 74.1 (C-6), 62.6 (C-5), 14.5 (CH_3). HRMS: $\text{C}_{19}\text{H}_{19}\text{O}_7\text{N}_3$ calcd 402.1301, found 402.1301. Compound **9b**: mp=49–50 °C; $[\alpha]_D^{20}$ +72 (c 0.10, MeOH); IR (ATR) ν 3382, 2929, 1733, 1600, 1516, 1343, 1244, 1105, 1044 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 8.22, 7.42 (m, 8H, $2\times\text{C}_6\text{H}_4$), 5.26 (d, $J_{7,8}=3.0$ Hz, 1H, H-8), 4.80 (d, $J_{2,3}=7.9$ Hz, 1H, H-2), 4.52 (dd, $J_{5,6}=3.0$ Hz, $J_{6,7}=5.0$ Hz, 1H, H-6), 4.30 (dd,

$J_{6,7}=5.0$ Hz, $J_{7,8}=3.0$ Hz, 1H, H-7), 3.82 (d, $J_{2,3}=7.9$ Hz, 1H, H-3), 3.34 (m, 1H, H-5), 1.06 (d, $J_{5,\text{CH}_3}=6.5$ Hz, 3H, CH_3); ^{13}C NMR (CDCl_3 , 75 MHz) δ 147.8, 144.8, 127.9, 127.1, 124.0 ($2\times\text{C}_6\text{H}_4$), 104.0 (C-8), 88.8 (C-2), 76.6, 76.4, 76.2 (C-6, C-7, C-3), 65.2 (C-5), 14.7 (CH_3). HRMS: $\text{C}_{19}\text{H}_{19}\text{O}_7\text{N}_3$ calcd 402.1301, found 402.1301.

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