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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.

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 cancer[2] 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 retrosynthetic 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 reaction[14] with the readily known available aldose **A**.

According to our previous work,[14] Strecker conditions, using 2 equiv of $HCOONH_3Bn$ 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 **2b*R***) 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**–**6c*R*** 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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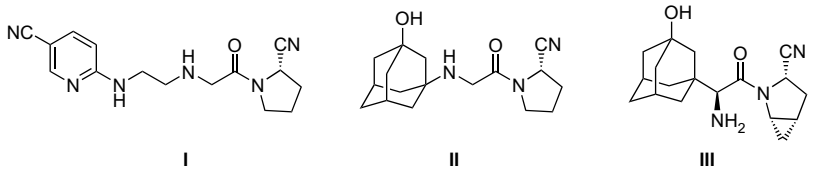
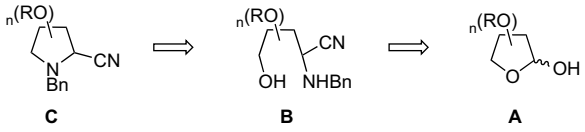


Figure 1. Structures of selected DPPIV inhibitors.



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]

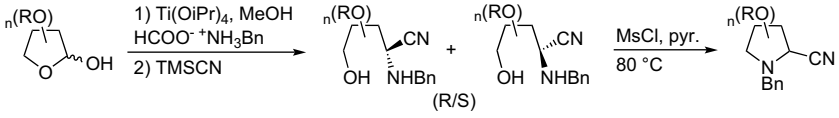
In order to obtain the proline analogues, we selected the (*R*)-derivatives **1c*R***, **2c*R*** and **3c*R*** to be submitted to acidic hydrolysis (concentrated HCl at 100 °C in a sealed tube) followed by hydrogenolysis (H_2 atmosphere, Pd/C) to afford the corresponding hydroxyprolines **1d**, **2d** and **3d** in 78%, 76% and 77%, respectively (Table 2).

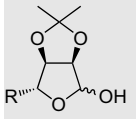
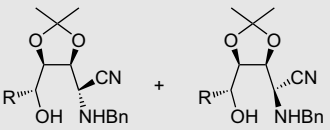
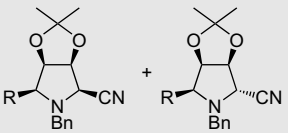
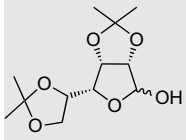
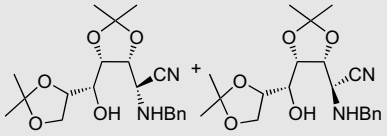
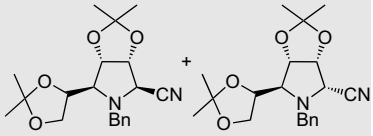
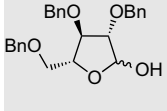
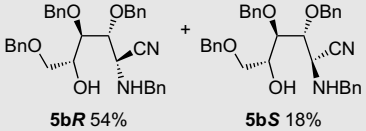
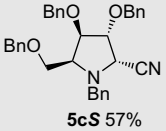
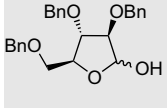
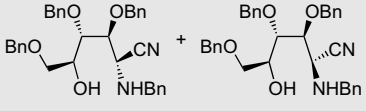
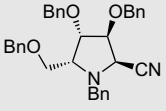
With these derivatives in our hands, we tested the polyhydroxyprolines **1d**, **2d** and **3d** versus natural L-proline in organocatalysis since the pioneering work of List, Barbas and their coworkers[29] have demonstrated that L-proline or functionalized 4-hydroxyproline[30] could work as a catalyst 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 reported[32] 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_2OTr **3a**, R= CH_2N_3	**1b*R*** 80% **2b*R*** 86% **3b*R*** 50%	**1b*S*** 5% - **3b*S*** 13%	**1c*R*** 85% **2c*R*** 84% **3c*R*** 77%	**1c*S*** 6% **3c*S*** 4%
		
4a	**4b*R*** 24%	**4b*S*** 74%	**4c*R*** 16%	**4c*S*** 44%
		
5a	**5b*R*** 54%	**5b*S*** 18%	**5c*S*** 57%	
		
6a	**6b*R*** 70%	**6b*S*** 8%	**6c*R*** 84%	

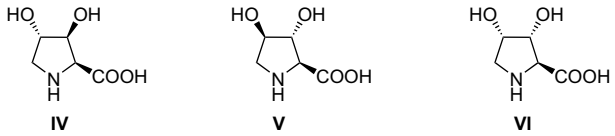
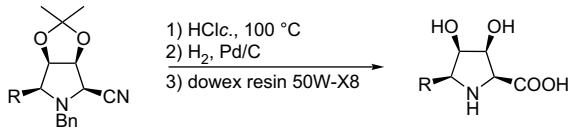
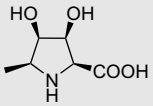
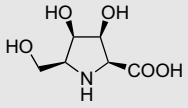
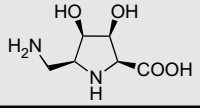


Figure 2. 3,4-Dihydroxyprolines from natural sources.

Table 2
Synthesis of polyhydroxyprolines



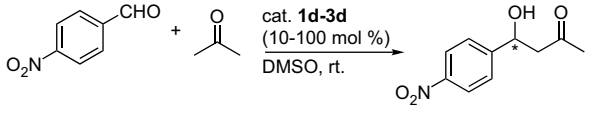
Substrate	Product		Yield
1c*R*		**1d**	78%
2c*R*		**2d**	76%
3c*R*		**3d**	77%

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 hypothetic 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 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 literature[33] and is attributed to a poor reactivity when L-proline was used below 20 mol %.

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.

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 literature[33] 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

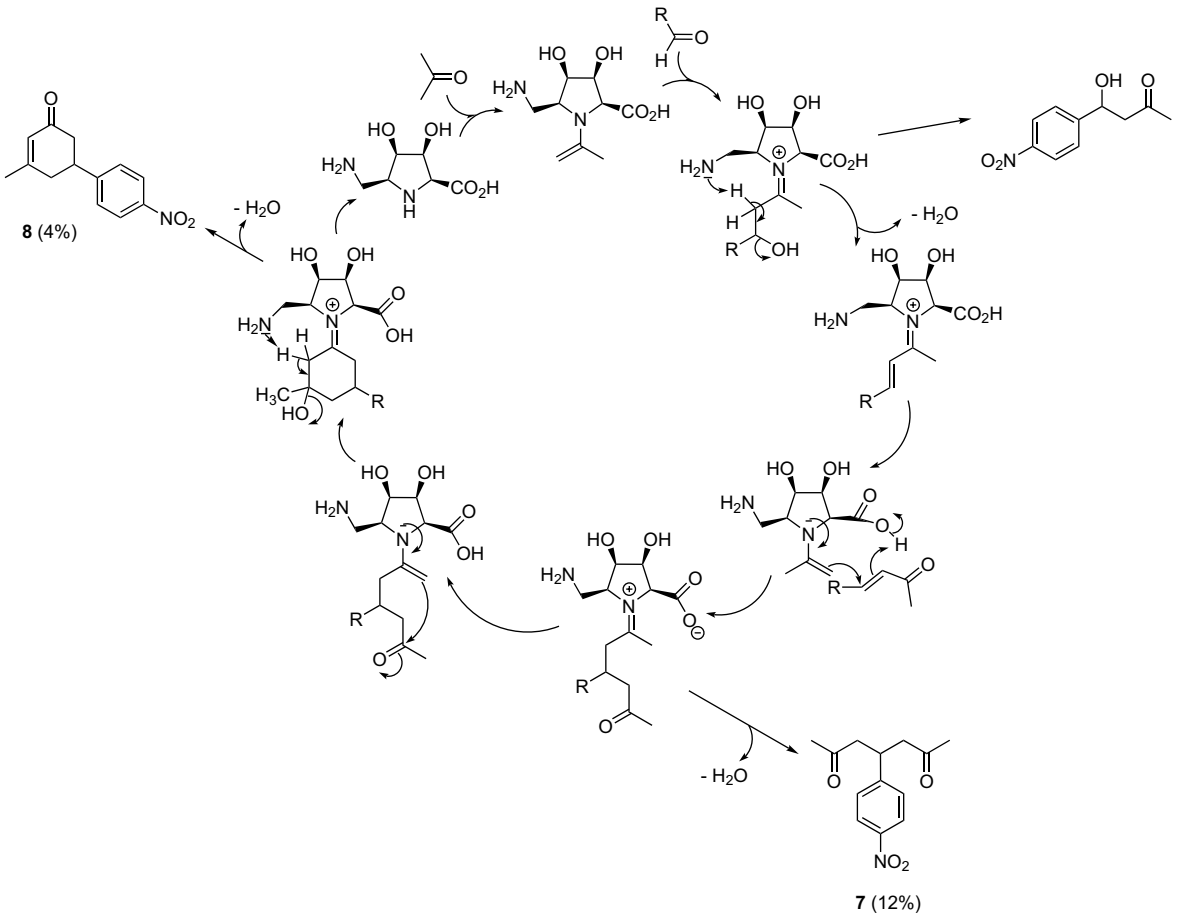
Materials and methods. Melting points are uncorrected. Optical rotations were recorded in $CHCl_3$ or MeOH solutions. ^1H NMR (300.13 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded in $CDCl_3$, DMSO-d_6 or MeOD-d_4 (internal Me_4Si), respectively. TLC was performed on Silica F_{254} and detection 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-TOFF 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)

$Ti(OiPr)_4$ (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.



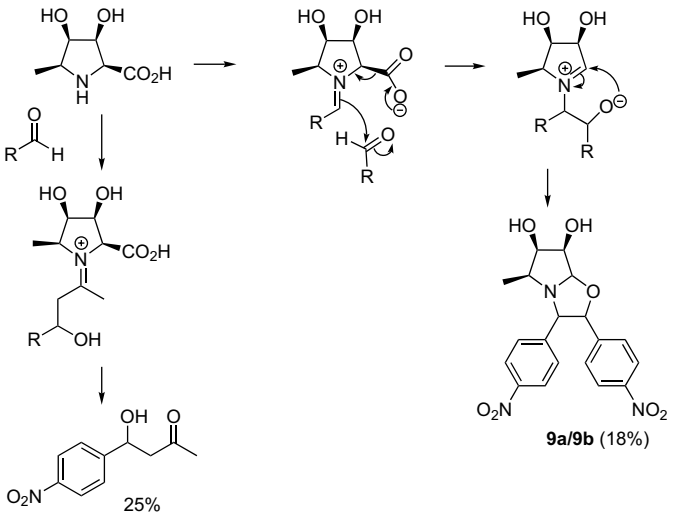
Scheme 2. Aldol–aldol reaction and cyclodehydration.

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 $1H_2$ 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 NH_4OH 0.1 M. After removal of the solvent, the solid was lyophilisated 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), $HCOONH_3Bn$ (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 **1b*R*** and **1b*S*** (12.1 g, 90%) as a white syrup. A pure fraction of **1b*R*** has been isolated for analysis: $[\alpha]_D^{20}$ −77 (*c* 0.05, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H, C_6H_5), 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, $J_{4,CH3}$=6.1 Hz, 1H, H-4), 4.10 (q, $J_{OH,CH3}$=7.1 Hz, 1H, OH), 4.08 (d, $J_{A,B}$=12.8 Hz, 1H, H-A NCH_2Ph), 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 NCH_2Ph), 1.46 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.26 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 129.3–128.2 (C_6H_5), 118.7 (CN), 109.3 [$OC(CH_3)_2$], 81.7 (C-3), 76.9 (C-2), 65.5 (C-4), 52.0 (NCH_2Ph), 50.2 (C-1), 27.4, 25.2, 21.5 (3×CH_3). HRMS: $C_{16}H_{22}O_3N_2Na$ 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), $HCOONH_3Bn$ (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, CH_2Cl_2); IR (ATR) ν 3059, 3032, 2985, 2926, 2850, 1491, 1448, 1373, 1213, 1157, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47–7.32 (m, 20H, 4×C_6H_5), 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 NCH_2Ph), 4.04 (d, $J_{1,2}$=2.7 Hz, 1H, H-1), 3.82 (d, $J_{A,B}$=12.8 Hz, 1H, H-B NCH_2Ph), 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, CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.0, 138.2, 129.0–127.6 (4×C_6H_5), 118.9 (CN), 109.5 [$OC(CH_3)_2$], 87.4 [$OC(C_6H_3)_3$], 77.2 (C-2, C-3), 69.0 (C-4), 65.5 (C-5), 52.0 (NCH_2Ph), 50.2 (C-1), 27.1, 24.9 (2×CH_3). HRMS: $C_{35}H_{36}O_4N_2Na$ 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), $HCOONH_3Bn$ (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, CH_2Cl_2); IR (ATR) ν 2988, 2934, 2102, 1454, 1382, 1214, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.28 (m, 5H, C_6H_5), 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 NCH_2Ph), 4.01 (d, $J_{1,2}$=2.7 Hz, 1H, H-1), 3.82 (d, $J_{A,B}$=12.8 Hz, 1H, H-B NCH_2Ph), 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, CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7, 129.2–128.4 (C_6H_5), 118.5 (CN), 109.8 [$OC(CH_3)_2$], 77.1, 76.6 (C-2, C-3), 68.7 (C-4), 54.9 (C-5), 52.0 (NCH_2Ph), 49.7 (C-1), 27.3, 25.0 (2×CH_3). HRMS: $C_{16}H_{21}O_3N_5Na$ 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), $HCOONH_3Bn$ (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 ($CDCl_3$, 300 MHz) δ 7.36 (m, 5H, C_6H_5), 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 NCH_2Ph), 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 NCH_2Ph), 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, CH_3), 1.42 (s, 3H, CH_3), 1.35 (s, 6H, 2×CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.4, 129.3–128.7 (C_6H_5), 117.9 (CN), 109.9, 109.8 (2×[$OC(CH_3)_2$]), 76.8, 76.7 (C-2, C-3), 75.8 (C-5), 70.5 (C-4), 68.1 (C-6), 51.9 (NCH_2Ph), 49.1 (C-1), 27.2, 26.4, 25.6, 24.9 (4×CH_3). HRMS: $C_{20}H_{28}O_5N_2Na$ 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), $HCOONH_3Bn$ (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 ($CDCl_3$, 300 MHz) δ 7.44–7.28 (m, 40H, 8×C_6H_5), 4.92–4.59 (m, 12H, 6×OCH_2Ph), 4.19–3.65 (m, 16H, 2×H-1, 2×H-2, 2×H-3, 2×H-4, 4×H-5, 2×NCH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 129.1–128.1 (8×C_6H_5), 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×OCH_2Ph), 61.0, 60.2 (2×C-5), 52.1, 51.9 (NCH_2Ph), 52.7, 51.8 (2×C-1). HRMS: $C_{34}H_{36}O_4N_2$ 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), $HCOONH_3Bn$ (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 ($CDCl_3$, 300 MHz) δ 7.45–7.31 (m, 20H, 4×C_6H_5), 4.95–4.62 (m, 6H, 3×OCH_2Ph), 4.16–3.70 (m, 8H, H-1, H-2, H-3, H-4, 2×H-5, NCH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8–138.2, 129.2–127.9 (4×C_6H_5), 119.4 (CN), 81.0, 80.7, 79.3 (C-2, C-3, C-4), 75.9, 75.1, 72.6 (3×OCH_2Ph), 61.6 (C-5), 52.2 (C-1), 52.0 (NCH_2Ph). HRMS: $C_{34}H_{36}O_4N_2$ 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, $CHCl_3$); IR (ATR) ν 3031, 2987, 2936, 2812, 1454, 1380, 1211, 1147, 1127, 1076, 1001 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (m, 5H, C_6H_5), 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, NCH_2Ph), 3.19 (d, $J_{2,3}$=5.4 Hz, 1H, H-2), 2.42 (dd, $J_{5,CH3}$=6.2 Hz, $J_{4,5}$=4.5 Hz, 1H, H-5), 1.62 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.28 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.8, 130.2–128.2 (C_6H_5), 116.4 (CN), 113.6 [$OC(CH_3)_2$], 81.7 (C-3), 77.9 (C-4), 59.6 (C-5), 57.8 (C-2), 52.5 (NCH_2Ph), 26.6 (CH_3), 26.2 (CH_3), 12.8 (CH_3). HRMS: $C_{16}H_{20}O_2N_2Na$ calcd 295.1422, found 295.1422. Compound **1cS**: $[\alpha]_D^{20}$ −78 (*c* 0.1, $CHCl_3$); IR (ATR) ν 3019, 2986, 2966, 2937, 2864, 2246, 1454, 1376, 1267, 1243, 1207, 1123, 1104, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 5H, C_6H_5), 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 NCH_2Ph), 3.75 (s, 1H, H-2), 3.36 (d, $J_{A,B}$=13.2 Hz, 1H, H-B NCH_2Ph), 2.77 (dd, $J_{5,CH3}$=6.2 Hz, $J_{4,5}$=4.3 Hz, 1H, H-5), 1.53 (s, 3H, CH_3), 1.32 (m, 6H, 2×CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.6, 129.0–127.9 (C_6H_5), 115.3 (CN), 113.0 [$OC(CH_3)_2$], 82.1 (C-4), 81.0 (C-3), 61.0 (C-5), 59.6 (C-2), 52.7 (NCH_2Ph), 26.7, 26.2 (2×CH_3), 12.8 (CH_3). HRMS: $C_{16}H_{20}O_2N_2Na$ 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, CH_2Cl_2); IR (ATR) ν 3056, 2986, 2932, 2847, 2373, 1491, 1448, 1380, 1213, 1163, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.59–7.08

(m, 20H, 4×C_6H_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×C_6H_5), 116.4 (CN), 113.7 [$OC(CH_3)_2$], 87.6 [$OC(C_6H_5)_3$], 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×CH_3). HRMS: $C_{35}H_{34}O_3N_2Na$ 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**, **3b*R*/3b*S*** (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 **3c*S*** (5.82 g, 77%) as a white solid. Compound **3c*R***: 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}; ^{1}H 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 [$OC(CH_3)_2$], 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×CH_3). HRMS: $C_{16}H_{19}O_2N_5Na$ calcd 336.1436, found 336.1440. Compound **3c*S***: $[\alpha]_D^{20}$ +122 (*c* 0.59, CH_2Cl_2); IR (ATR) ν 2989, 2936, 2102, 1454, 1373, 1274, 1210 cm^{-1}; ^{1}H 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 [$OC(CH_3)_2$], 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×CH_3). HRMS: $C_{16}H_{19}O_2N_5Na$ 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**, **4b*R*/4b*S*** (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, **4c*S*** (990 mg, 43.5%) as an orange solid followed by **4c*R*** (370 mg, 16.3%) as a white solid. Compound **4c*S***: 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}; ^{1}H 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×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×[$OC(CH_3)_2$]), 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×CH_3). HRMS: $C_{20}H_{26}O_4N_2$ calcd 381.1790, found 381.1799. Compound **4c*R***: 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}; ^{1}H 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, $J_{5,6}$=$J_{6,7b}$=$J_{6,7a}$=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×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×[$OC(CH_3)_2$]), 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×CH_3). HRMS: $C_{20}H_{26}O_4N_2$ calcd 381.1790, found 381.1793.

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

Following the general method **B**, **5b*R*/5b*S*** (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, **5c*S*** (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}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.23 (m, 20H, 4×C_6H_5), 4.89–4.59 (m, 6H, 3×OCH_2Ph), 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×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×C_6H_5), 115.2 (CN), 80.2 (C-4), 75.3 (C-3), 74.0, 73.3, 71.9 (3×OCH_2Ph), 72.9 (C-5), 59.7 (C-6), 57.8 (C-2), 50.1 (NCH_2Ph). HRMS: $C_{34}H_{34}O_3N_2$ calcd 519.2666, found 519.2657.

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

Following the general method **B**, **6b*R*/6b*S*** (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, **6c*R*** (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}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50–7.27 (m, 20H, 4×C_6H_5), 4.88–4.53 (m, 6H, 3×OCH_2Ph), 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×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×C_6H_5), 115.2 (CN), 80.2 (C-4), 75.3 (C-3), 74.0, 73.3, 71.9 (3×OCH_2Ph), 73.0 (C-5), 59.7 (C-6), 57.8 (C-2), 50.2 (NCH_2Ph). HRMS: $C_{34}H_{34}O_3N_2$ 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 **1c*R***, 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}; ^{1}H 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, $J_{5,CH3}$=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: $C_6H_{12}O_4N$ 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 **2c*R***, 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}; ^{1}H 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: $C_6H_{11}O_5NNa$ 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 **3c*R***, 80 mL of HCl*c*. (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}; ^{1}H 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: $C_6H_{13}O_4N_2$ 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 (×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}; ^{1}H 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×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: $C_{13}H_{13}O_3NNa$ 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}; ^{1}H 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, $J_{H,HA}$=6.5 Hz, $J_{HA,HB}$=17.3 Hz, 2H, 2×H-A CH_2), 2.80 (dd, $J_{H,HB}$=7.5 Hz, $J_{HA,HB}$=17.3 Hz, 2H, 2×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×CH_2), 36.1 (CH), 30.6 (2×CH_3). HRMS: $C_{13}H_{15}O_4NNa$ 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 (×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}; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.96, 7.34, 7.18 (m, 8H, 2×C_6H_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, $J_{5,CH3}$=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×C_6H_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: $C_{19}H_{19}O_7N_3$ 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}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22, 7.42 (m, 8H, 2×C_6H_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, $J_{5,CH3}$=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×C_6H_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: $C_{19}H_{19}O_7N_3$ calcd 402.1301, found 402.1301.

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