

Acyclic C-nucleosides: synthesis of chiral 1,1-diheteroaryl-alditols and X-ray crystal structure of 2,3,5-tri-*O*-benzyl-1,1-di-(2'-pyrryl)-1-deoxy-D-arabinitol

Mara Cornia^{*,a,*} Silvia Capacchi,^b Monica Del Pogetto,^a Giorgio Pelosi^b and Giovanna Gasparri Fava^{* b}

^a Dipartimento di Chimica Organica e Industriale dell'Università, Università di Parma, Viale delle Scienze, I-43100 Parma, Italy

^b Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica e Centro di Studio per la Strutturistica Diffattometrica del CNR, Università di Parma, Viale delle Scienze, I-43100 Parma, Italy

Abstract: Tetra-*O*-acetyl-D-ribose, penta-*O*-acetyl-D-glucose, 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose, 2,3,5-tri-*O*-benzyl-D-arabinofuranose and 2,3,5,6-tetra-*O*-benzyl-D-glucose react with pyrrole and indole, in presence of Lewis acids, to afford C-glycosylpyrroles and indoles in position 2 and 3 respectively (acyclic C-nucleosides, 1–7). The crystal structure of 4 was determined by X-ray crystallography. © 1997 Published by Elsevier Science Ltd

It is known that a large number of drugs used in the treatment of neoplastic diseases and viral infections are nucleoside analogues,¹ therefore in this field the search for new or improved drugs (safer and stronger) is a stimulating purpose. Moreover the synthesis of modified nucleosides has received great attention from the discovery of the potent antiviral activity of Acyclovir and overall AZT:² in particular many efforts are directed to C-nucleoside synthesis.³

Our previous work in the C-glycosides and C-nucleosides area has been characterized by a simple synthetic method, consisting of a direct, Lewis acid promoted arylation and hetero-arylation of glycosidic protected compounds.⁴ Thus, all these findings taken together prompted us to prepare and characterise, in the present paper, a series of acyclic C-nucleoside analogues, as 1,1-dipyrrylalditols 1–4 and 1,1-diindolylalditols 5–7, for testing and structure–activity studies. From our previous work, it emerged that when protected sugars were allowed to react with 1:4 or 1:5 molar ratio of phenols or pyrroles, in dichloromethane, the metallic promoter played a fundamental role in the reaction pathway to perform a selective reaction, and its choice strictly depended on the substrate, the sugar nature and the protecting group.

In this paper we have analysed a number of Lewis acids, (including blends), and protected sugars to obtain a series of dinuclear (dipyrrolic and diindolic) alditols. First, we studied the direct synthesis of the new acetyl-protected C-glyco-dipyrrolic compounds (1 and 2, 15% and 20% yields, Figure 1), starting from two sugars protected at the anomeric carbon C-1, as tetra-*O*-acetyl-D-ribose and penta-*O*-acetyl-D-glucose, with pyrrolylmagnesiumbromide (5:1 molar ratio) in CH₂Cl₂ under ultrasonic irradiation for 30 minutes. The reactions also produced alditolic intermediates (not isolated), but using a 1:1 blend between pyrrolylmagnesiumbromide and SnCl₄ the yields were enhanced to 35% and 40% respectively for compounds 1 and 2.

The compounds 3 and 4 (Figure 1) were respectively synthesised from 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose and from 2,3,5-tri-*O*-benzyl-D-arabinofuranose with pyrrolylmagnesiumbromide in toluene at 80°C for 12 h. Using only MgBr⁺, at 80°C, instead of SnCl₄, as the metallic promoter, the synthesis of compounds 3 and 4, proceeded very cleanly under the same reaction conditions.⁵ In the

* Corresponding author. Email: marac@vaimo.cce.unipr.it and chemic8@ipruniv.cce.unipr.it

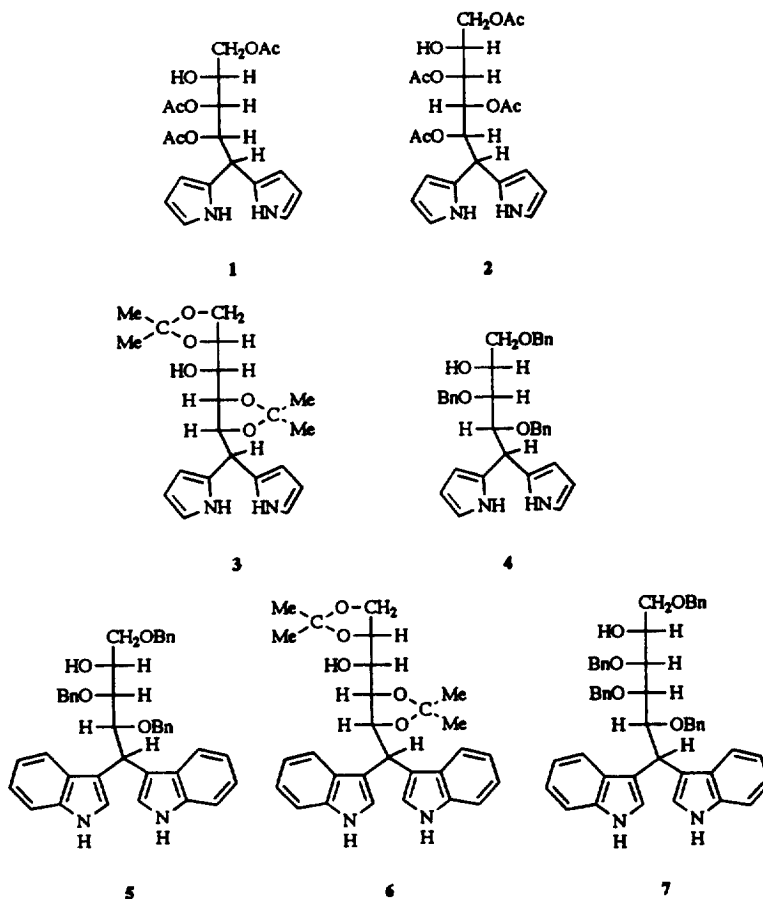


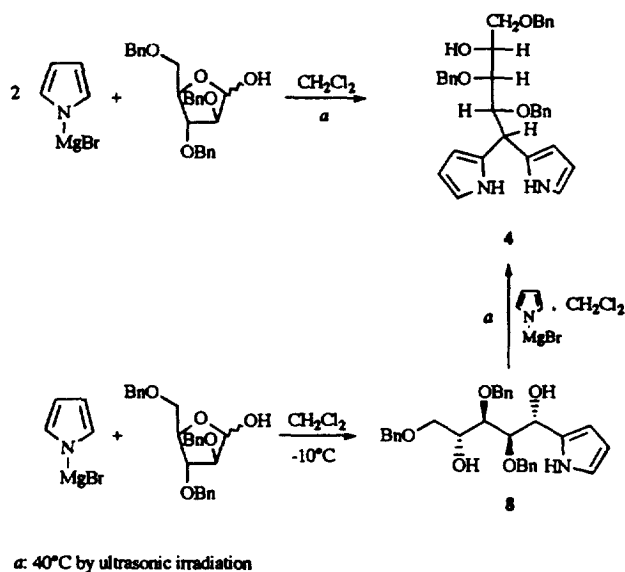
Figure 1.

case of compound **4** a direct crystallisation from the crude mixture was also possible. An alternative procedure for compound **4** started from the alcoholic intermediate **8** that could be separated when the reaction was carried out in the range between -18°C and 0°C : compound **8** was able to react with an equimolar amount of pyrrolylmagnesiumbromide in CH_2Cl_2 (sonication) or toluene at 80°C to produce the corresponding dinuclear compound **4** in 40% yield (Scheme 1).

The synthesis of compounds **5** and **7** (Figure 1), acyclic C-nucleoside analogues in which the aglycon moiety is an indolyl residue, was performed using another Lewis acid, $\text{ClTi}(\text{OPr}^i)_3$, with pyrrolylmagnesiumbromide (1:1), in toluene at 80°C (35% yield), while for the isopropylidene protected compound **6** (Figure 1) the best yield (50%) was obtained with MgBr^+ . The reactions showed the same pathway: it was possible to isolate the corresponding alcoholic intermediates⁶ at -5°C in this case too, and to produce the dimeric compounds in the subsequent step with indolylmagnesiumbromide in CH_2Cl_2 under ultrasonic irradiation.

All the compounds (**1**–**7**) were separated from the crude mixture by flash chromatography, after usual work up with hexane/acetone or CH_2Cl_2 /acetone (in variable ratio), and in acceptable yields (30–50%). The structures of all these C-nucleosidic compounds were assigned by elemental analysis, EI or CI mass spectrometry and ^1H NMR spectroscopy, while compound **4** was also confirmed by X-ray diffraction.

^1H NMR studies show that the resonance for H-1 of the carbohydrate residue of all the compounds



Scheme 1. Reaction pathway of pyrrolylmagnesiumbromide and 2,3,5-tri-*O*-benzyl-D-arabinofuranose. The alcoholic intermediate **8** can evolve in one step to the dipyrrolic compound **4** (40°C). The same mechanism occurs for the other glycosidic reagents and to the indolic substrates here considered.

(1–7) appears as a doublet at 4.1–5.1 ppm, and the two pyrrolic rings show non-equivalent resonances in the aromatic region. The steric hindrance, due to the bulky substituents at the centre C-1, hinders the free rotation of the two pyrrole rings and of the alditolic chain, and this could give the aromatic hydrogens a diastereotopic behaviour. This fact can justify the lack of symmetry in the aromatic pattern of the NMR spectra, where each pyrrolic proton shows its own resonance. Moreover, these ^1H magnetic resonance experiments, carried out in CDCl_3 , can be compared with the data obtained by structural X-ray analysis, where an evident and different surrounding situation for the two pyrrolic moieties is present. Furthermore, the two dimensional ^1H – ^1H COSY and NOESY experiments made it possible to establish the complete assignments of the non-equivalent protons of the two pyrrolic rings and overall of the alditolic chain.

The X-ray determination shows that the molecular conformation of compound **4** is determined by strong intramolecular hydrogen bonds $\text{O3-H} \cdots \text{O4} = 2.763(6) \text{ \AA}$ and $\text{N2-H} \cdots \text{O1} = 2.804(6) \text{ \AA}$ and by one interaction between C5-H5 and O2 [$2.897(6) \text{ \AA}$] (crystallographic numbering). An ORTEP view of the molecule in its correct absolute configuration (10R,18R,26R), corresponding to that of its sugar precursor, is shown in Figure 2.

Long interactions between the nitrogen atom N1 and the π -delocalized charge of the other pyrrole ring are also present (the C6 and C7 atoms are closer than the others to N1: $\text{N1} \cdots \text{C6} = 3.283(7) \text{ \AA}$ and $\text{N1} \cdots \text{C7} = 3.462(7) \text{ \AA}$) probably as a consequence of the steric hindrance. The orientation of the OH group is shown by the following torsion angles: O4C27C26O3 $62.5(5)^\circ$, O2C18C26O3 $-171.6(4)^\circ$ and C10C18C26O3 $-51.0(5)^\circ$. The distance $\text{H1O3} \cdots \text{H26} = 2.12(9) \text{ \AA}$ and the related torsion angle of $-68(5)^\circ$ corresponds to a nearly synclinal conformation. The $\text{H26} \cdots \text{H18}$, $\text{H10} \cdots \text{H18}$ and $\text{H10} \cdots \text{H5}$ distances are $2.97(8)$, $2.35(5)$ and $2.97(9) \text{ \AA}$ respectively, and the related torsion angles are $-179(4)$, $57(4)$ and $176(5)^\circ$ showing therefore an antiperiplanar, synclinal and antiperiplanar conformation respectively. The relative position of the O1 and O2 atoms is defined by the O2C18C10O1 torsion angle of $66.3(5)^\circ$. The orientation of the phenyl rings with respect to the O ether atoms is evidenced by the three torsion angles: O1C11C12C13 $66.4(7)^\circ$, O2C19C20C21 $87.9(7)^\circ$ and O4C28C29C30 $71.2(8)^\circ$.

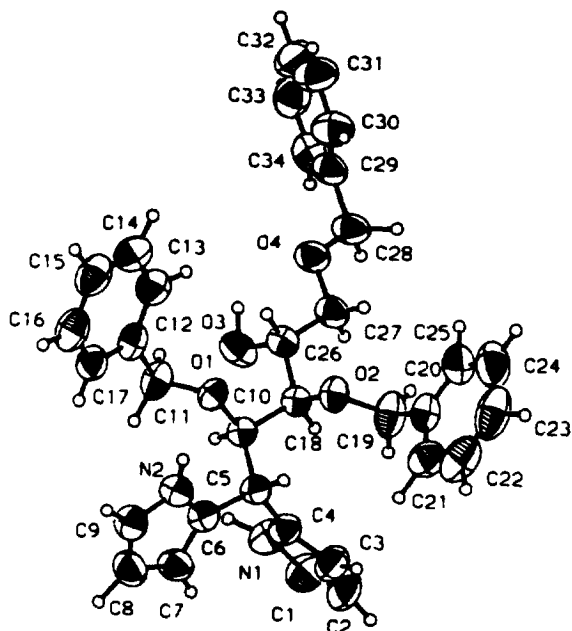


Figure 2. ORTEP drawing of **4** in its correct absolute configuration with thermal ellipsoid plot (50% probability). Selected bond lengths (Å): N1–C1 1.362(9), N1–C4 1.371(8), C3–C4 1.383(7), C2–C3 1.42(1), C1–C2 1.36(1), N2–C9 1.373(7), N2–C6 1.372(7), C6–C7 1.37(1), C7–C8 1.430(8), C8–C9 1.35(1), C6–C5 1.511(6), O1–C10 1.425(6), O1–C11 1.438(6), O2–C18 1.436(4), O2–C19 1.428(6), O3–C26 1.426(6), O4–C27 1.419(8), O4–C28 1.440(6).

For the first time, to our knowledge, two pyrrole rings have been structurally characterized bonded to the same tetrahedral carbon atom. The N2C6C7C8C9 pyrrole ring is perfectly planar, while the N1C1C2C3C4 one shows a small distortion from planarity probably owing to the presence of intra- and intermolecular interactions with the second pyrrole moiety. The two pyrrole rings are tilted by $77.4(3)^\circ$ with respect to each other. The carbon–carbon distances opposite to the nitrogen atoms in both pyrrole rings [1.415(1), 1.430(8) Å] are longer than the corresponding average lengths [1.395(3) Å] observed in analogous pyrrole moieties.⁷

The packing is mainly determined by intermolecular hydrogen bonds involving the pyrrole nitrogen atoms of both pyrrole rings: N2–H \cdots O3($x+1, y, z$)=2.967(8) Å and N1–H \cdots M($x-1, y, z$)=3.286(7) Å (H \cdots M=2.39(8) Å, N1–H \cdots M=142(6) $^\circ$, where M is the midpoint of the N2–C9 bond). This feature generates linear chains in the *a* direction, which are joined together by Van der Waals interactions between the phenyl and pyrrole rings (Figure 3).

Experimental

General

All the materials and solvents were obtained from commercial suppliers and used without further purification. 2,3,5-Tri-*O*-benzyl-D-arabinofuranose and 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose were from Sigma; 1,2,3,5-tetra-*O*-acetyl-D-ribose and 1,2,3,4,6-penta-*O*-acetyl-D-glucose were from Fluka. Flash chromatography was performed on 40–60 μm silica gel Merck no. 9385, using the indicated solvent mixtures. ¹H NMR were obtained on a Bruker AMX-400 spectrometer, and ¹³C NMR spectra were recorded on a Bruker AC 100 spectrometer (25.14 MHz), and are reported in part per million (δ) relative to tetramethylsilane as the internal standard. Low resolution mass spectra were obtained on a Finnigan 1020 6c mass spectrometer. Optical rotations were measured on a Rudolph Autopol III polarimeter. Melting points were recorded on an Electrothermal apparatus and were

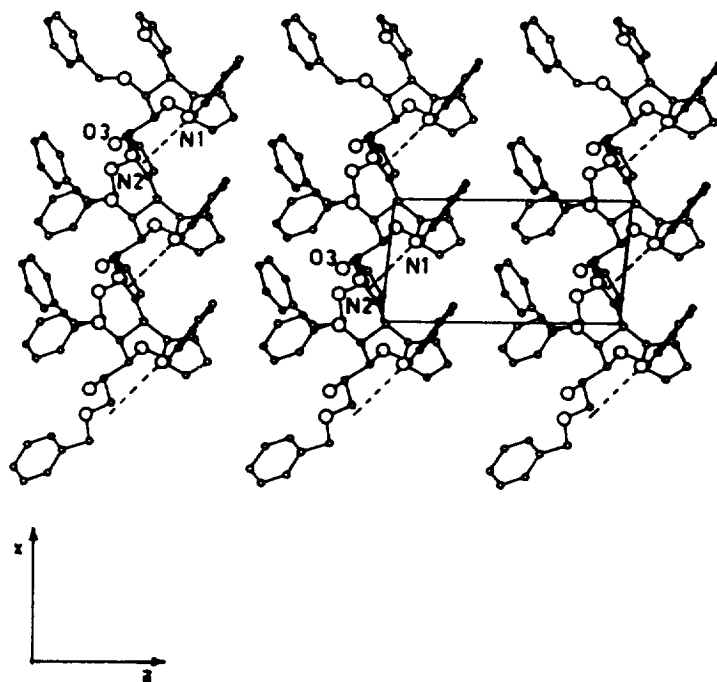


Figure 3. The packing arrangement of **4** showing the different situation of the two pyrrole rings and the chains running along the *a* direction.

uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the University of Parma (Dipartimento di Chimica Generale ed Inorganica).

Synthesis of 1,1-dipyrrolylditols

Procedure A

2,3,5-Tri-O-acetyl-1,1-di-(2'-pyrryl)-1-deoxy-D-ribose 1. To a solution of pyrrolylmagnesium-bromide (0.35 ml, 5 mmol) and tetra-O-acetyl-D-ribose (1590 mg, 5 mmol) in CH_2Cl_2 (50 ml), at room temperature under N_2 , with stirring, was added a solution of SnCl_4 (0.60 ml, 5 mmol) in CH_2Cl_2 (5 ml). After 60 minutes under ultrasonic irradiation, the orange reaction mixture was quenched by addition of a saturated NaHCO_3 solution (50 ml) and then with solid NH_4Cl (5 g). The resulting light yellow mixture was extracted with diethyl ether (3×30 ml) and the combined extracts were dried on MgSO_4 , filtered, evaporated and purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{acetone}$ 6:1) to give **1** (35% yield) as a colourless oil. $[\alpha]_{\text{D}}^{20} + 41.6$ ($c=0.055$, CHCl_3). $^1\text{H NMR}$ (CDCl_3) δ 8.81 and 8.39 (2H, 2 br s, 1H each, NH), 6.74 (1H, m, H-5'a), 6.68 (1H, m, H-5'b), 6.18 (1H, m, H-4'b), 6.15 (1H, m, H-4'a), 6.09 (1H, m, H-3'b), 5.98 (1H, m, H-3'a), 5.43 (1H, ddd, $J=2.6, 5.1, 7.7$ Hz, H-2), 5.02 (1H, dd, $J=2.6, 5.1$ Hz, H-3), 4.44 (1H, dd, $J=2.6, 11.5$ Hz, H-5 α), 4.33 (1H, m, H-4), 4.25 (1H, dd, $J=7.7, 11.5$ Hz, H-5 β), 4.22 (1H, d, $J=2.6$ Hz, H-1), 2.80 (1H, m, $J=5.1$ Hz, OH), 2.07 (3H, s, OCH_3), 2.04 (6H, s, OCH_3). MS (EI) m/z 393 (M+1), 392, 326, 266, 206, 145. Anal. calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_7$: C 58.15, H 6.17, N 7.14; found: C 58.20, H 6.23, N 7.07.

2,3,4,6-Tetra-O-acetyl-1,1-di-(2'-pyrryl)-1-deoxy-D-glucitol 2. The crude mixture, obtained as above described, was purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{acetone}$ 9:1) to give **2** (40% yield) as a colourless oil. $[\alpha]_{\text{D}}^{20} + 50.0$ ($c=0.024$, CHCl_3). $^1\text{H NMR}$ (CDCl_3) δ 8.75 and 8.25 (2H, 2 br s, 1H each, NH), 6.80 (1H, br s, H-5'a), 6.62 (1H, br s, H-5'b), 6.12 (4H, m, H-3' and H-4'), 5.7 (1H, d, $J=2$ Hz, H-1), 5.12 (1H, m, H-2), 4.58 (1H, m, H-4), 4.22 (3H, m, H-3 and H-6), 3.82 (1H, m, H-5),

3.15 (1H, br s, OH), 2.08 (6H, s, OCH₃), 2.04 (6H, s, OCH₃). MS (EI) *m/z* 465 (M+1), 464, 398, 338, 145. Anal. calcd for C₂₂H₂₈N₂O₉: C 56.89, H 6.08, N 6.03; found: C 57.03, H 6.12, N 5.88.

Procedure B

2,3,5,6-Di-O-isopropylidene-1,1-di-(2'-pyrryl)-1-deoxy-D-mannitol 3. To a solution of pyrrolylmagnesiumbromide (3 mmol) in CH₂Cl₂ (20 ml), under N₂, with stirring, was added a solution of 2,3,5,6-di-O-isopropylidene-D-mannofuranose (260 mg, 1 mmol). After 24 h under ultrasonic irradiation (40°C), the reaction mixture was treated as previously described and purified by flash chromatography (hexane/acetone 7:3) to give **3** (30% yield) as a colourless oil. $[\alpha]_D^{20} + 5.5$ (*c*=0.220, CHCl₃). ¹H NMR (CDCl₃) δ 8.57 and 8.05 (2H, 2 br s, 1H each, NH), 6.61 (2H, m, H-5'a and H-5'b), 6.05 (1H, dd, *J*=2.9, 5.8 Hz, H-3'a), 5.99 (1H, m, H-4'a), 5.98 (1H, dd, *J*=2.9, 5.4 Hz, H-3'b), 5.58 (1H, m, H-4'b), 4.68 (1H, dd, *J*_{1,2}=10.1 Hz, *J*_{2,3}=6.9 Hz, H-2), 4.50 (1H, d, *J*_{1,2}=10.1 Hz, H-1), 4.28 (1H, d, *J*_{2,3}=6.9 Hz, H-3), 3.9–3.7 (3H, m, H-5 and H-6), 3.12 (1H, d, *J*_{4,5}=7.8 Hz, H-4), 1.96 (1H, br s, OH), 1.48, 1.31, 1.17, 1.05 (12H, 4 s, 3H each, CH₃). ¹³C NMR (CDCl₃) δ 132.66 (C), 128.31 (C), 109.27 (C), 108.30 (C), 117.53 (CH), 117.03 (CH), 108.74 (CH), 107.76 (CH), 106.93 (CH), 106.06 (CH), 79.32 (CH), 76.17 (2 CH), 69.54 (CH), 38.04 (CH), 66.60 (CH₂), 26.86 (CH₃), 26.64 (CH₃), 25.45 (CH₃), 24.54 (CH₃). MS (EI) *m/z* 377 (M+1), 376, 375, 361, 301, 145. Anal. calcd for C₂₀H₂₈N₂O₅: C 63.81, H 7.50, N 7.44; found: C 63.95, H 7.54, N 7.38.

2,3,5-Tri-O-benzyl-1,1-di-(2'-pyrryl)-1-deoxy-D-arabinitol 4. The crude mixture obtained as above described was purified by flash chromatography using hexane/acetone 7:3 as a white solid (30% yield). M.p. 146–148°C. $[\alpha]_D^{20} + 24.2$ (*c*=0.095, CHCl₃). CD (CHCl₃) $[\theta]_{284} = 14200$ deg cm² dmol⁻¹, $[\theta]_{260} = 11500$ deg cm² dmol⁻¹. ¹H NMR (CDCl₃) δ 8.72 and 7.70 (2H, 2 br s, 1H each, NH), 7.4–7.0 (15H, m, CH₂Ph), 6.61 (1H, dd, *J*_{4',5'}=4.5 Hz, *J*_{3',5'}=2.5 Hz, H-5'a), 6.44 (1H, dd, *J*_{4',5'}=4.4 Hz, *J*_{3',5'}=2.6 Hz, H-5'b), 6.07 (1H, dd, *J*_{3',4'}=5.6 Hz, *J*_{3',5'}=2.5 Hz, H-3'a), 6.05 (1H, dd, *J*_{3',4'}=5.5 Hz, *J*_{3',5'}=2.6 Hz, H-3'b), 5.96 (1H, m, H-4'a), 5.90 (1H, m, H-4'b), 4.49 (1H, 1/2 AB quartet, *J*=10.3 Hz, CH₂Ph), 4.5–4.4 (4H, m, CH₂Ph), 4.37 (1H, d, *J*_{1,2}=4.5 Hz, H-1), 4.16 (1H, dd, *J*_{1,2}=4.5 Hz, *J*_{2,3}=5.6 Hz, H-2), 4.04 (1H, 1/2 AB quartet, *J*=10.3 Hz, CH₂Ph), 3.92 (1H, m, H-4), 3.63 (1H, dd, *J*_{2,3}=5.6 Hz, *J*_{3,4}=9.5 Hz, H-3), 3.6–3.5 (2H, m, H-5), 2.48 (1H, br s, OH). ¹³C NMR (CDCl₃) δ 138.38 (C), 138.21 (C), 137.80 (C), 131.63 (C), 129.50 (C), 130.0–127.0 (15 CH), 117.45 (CH), 116.41 (CH), 108.38 (CH), 108.02 (2 CH), 105.52 (CH), 83.81 (CH), 80.79 (CH), 70.71 (CH), 39.63 (CH), 75.34 (CH₂), 74.55 (CH₂), 73.61 (CH₂), 71.08 (CH₂). MS (EI) *m/z* 538, 537 (M+1), 536, 470, 428, 362. Anal. calcd for C₃₄H₃₆N₂O₄: C 76.09, H 6.76, N 5.22; found: C 76.20, H 6.79, N 5.20.

Synthesis of indolyl derivatives

Procedure C

This method is the same as Procedure A except SnCl₄ is exchanged with CITi(OPr^{*i*})₃.

2,3,5-Tri-O-benzyl-1,1-di-(3'-indolyl)-1-deoxy-D-arabinitol 5. 35% yield; colourless oil. $[\alpha]_D^{20} + 42.5$ (*c*=0.040, CHCl₃). ¹H NMR (CDCl₃) δ 10.85 and 10.15 (2H, 2 br s, 1H each, NH), 7.98 (1H, m, H-6'a), 7.88 (1H, m, H-6'b), 7.70 and 7.62 (2H, 2 d, 1H each, *J*=7.7 Hz, H-4'a and H-4'b), 7.4–7.0 (9H, m, CH₂Ph, H-2'a+H-2'b and H-7'a+H-7'b), 6.99 (2H, m, H-5'a and H-5'b), 5.07 (1H, d, *J*=6.4 Hz, H-1), 4.55 (1H, dd, *J*_{1,2}=6.4 Hz, *J*_{2,3}=4.4 Hz, H-2), 4.4–3.9 (7H, m, CH₂Ph and H-4), 3.83 (1H, dd, *J*_{3,4}=6.4 Hz, *J*_{2,3}=4.4 Hz, H-3), 3.67 (1H, dd, *J*_{4,5α}=3.4 Hz, *J*_{5α,5β}=9.6 Hz, H-5α), 3.50 (1H, dd, *J*_{4,5β}=6.1 Hz, *J*_{5α,5β}=9.6 Hz, H-5β), 2.66 (1H, br s, OH). ¹³C NMR (CDCl₃) δ 138.7 (C), 138.0 (C), 136.4 (C), 136.0 (C), 117.6 (C), 116.2 (C), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 123.6 (CH), 122.9 (CH), 121.6 (CH), 119.9 (CH), 119.3 (CH), 111.2 (CH), 111.0 (CH), 82.8 (CH), 80.5 (CH), 71.0 (CH), 74.8 (CH₂), 74.3 (CH₂), 73.4 (CH₂). MS (CI/CH₄) 637 (M+1). Anal. calcd for C₄₂H₄₀N₂O₄: C 79.22, H 6.33, N 4.40; found: C 79.38, H 6.37, N 4.31.

2,3,5,6-Di-O-isopropylidene-1,1-di-(3'-indolyl)-1-deoxy-D-mannitol 6. The method is the same as Procedure B. 50% yield; colourless oil. $[\alpha]_D^{20} - 115.6$ ($c=0.032$, CHCl_3). $^1\text{H NMR}$ (CDCl_3) δ 8.08 and 8.04 (2H, 2 br s, 1H each, NH), 7.88 (1H, d, $J=7.2$ Hz, H-7'a), 7.53 (1H, d, $J=7.3$ Hz, H-7'b), 7.42 and 7.10 (4H, m, H-6'a+H-6'b and H-5'a+H-5'b), 7.05 and 7.02 (2H, 2 s, H-2'a and H-2'b), 6.99 (1H, d, $J=7.3$ Hz, H-4'a), 6.90 (1H, d, $J=7.3$ Hz, H-4'b), 5.48 (1H, br s, H-1), 5.19 (1H, d, $J=5.54$ Hz, H-2), 4.40 (1H, d, $J=5.54$ Hz, H-3), 4.11 (1H, m, H-4), 3.92 (2H, m, H-6), 3.65 (1H, m, H-5), 2.80 (1H, br s, OH), 1.51, 1.41, 1.25, 1.20 (12H, 4 s, 3H each, CH_3). MS (CI/CH_4) 477 (M+1). Anal. calcd for $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_5$: C 70.57, H 6.77, N 5.88; found: C 70.69, H 6.81, N 5.82.

2,3,4,6-Tetra-O-benzyl-1,1-di-(3'-indolyl)-1-deoxy-D-glucitol 7. 35% yield; colourless oil. $[\alpha]_D^{20} + 57.2$ ($c=0.034$, CHCl_3). $^1\text{H NMR}$ (CDCl_3) δ 8.81 (1H, d, $J=7.0$ Hz, H-7'a), 8.70 and 8.19 (2H, 2 br s, 1H each, NH), 7.77 (1H, d, $J=7.0$ Hz, H-7'b), 7.62 (2H, m, H-6'), 7.40 and 7.00 (17H, m, CH_2Ph and H-2'), 6.92 (1H, d, $J=7.2$ Hz, H-4'a), 6.82 (1H, d, $J=7.2$ Hz, H-4'b), 6.50 (2H, m, H-5'), 5.82 (1H, d, $J=6.1$ Hz, H-1), 4.6–4.4 (5H, m, CH_2Ph), 4.38 (1H, d, $J=6.1$ Hz, H-2), 4.21 (4H, m, CH_2Ph and H-3), 4.07 (1H, m, H-4), 3.7–3.5 (2H, m, H-5 and H-6 α), 3.21 (1H, m, H-6 β), 3.00 (1H, br s, OH). MS (CI/CH_4) 757 (M+1). Anal. calcd for $\text{C}_{50}\text{H}_{48}\text{N}_2\text{O}_5$: C 79.34, H 6.39, N 3.70; found: C 79.46, H 6.43, N 3.65.

X-Ray crystal structure determination of compound 4

Crystals suitable for X-ray analysis were obtained by slow evaporation from the saturated solution of 4 in CDCl_3 . Data were collected on a Siemens AED three circle diffractometer with Ni-filtered $\text{Cu-K}\alpha$ radiation at room temperature using a colourless prismatic crystal. Crystal data: $\text{C}_{34}\text{H}_{36}\text{N}_2\text{O}_4$, $M=536.67$, dimensions $0.23 \times 0.32 \times 0.47$ mm, triclinic space group $P1$ ($N^\circ 1$), $a=6.021(2)$, $b=11.069(3)$, $c=12.553(3)$ Å, $\alpha=65.74(3)$, $\beta=89.64(3)$, $\gamma=76.49(3)^\circ$, $V=737.8(4)$ Å³, $F(000)=286$, $Z=1$, $D_c=1.208$ g cm^{-3} , $\text{Cu-K}\alpha$, $\lambda=1.54184$ Å, μ ($\text{Cu-K}\alpha$)=6.29 cm^{-1} , θ range=3–70°.

A total of 2798 reflections were collected using the $\theta-2\theta$ scan technique within the range $3 < \theta < 70^\circ$. The structure was solved by direct methods using SIR 92^{8a} and refined anisotropically by full matrix least squares on F^2 using SHELXL-93.^{8b} 1968 observed reflections with $I > 2\sigma(I)$, were used in the refinement of 505 parameters. Hydrogen atoms were located with a difference Fourier map and isotropically refined. The weighting scheme adopted was $w=1/[\sigma^2(F_o^2)+(0.1250 P)^2]$, where $P=[\text{Max}(F_o^2, 0)+2 F_o^2]/3$. Final R and wR_2 values were 0.048 and 0.178 respectively; residual electronic density $-0.26 < \Delta\rho < +0.17$ eÅ⁻³. Scattering factors for C, H, N and O were taken from the literature.^{8c} Molecular geometry calculations were carried out by using the computer program PARST^{8d} and the structure drawings by using the ORTEP^{8e} and PLUTO^{8f} programs. The fractional atomic coordinates, thermal parameters obtained from the crystallographic analysis, and the subsequently derived interatomic distances and bond angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

Acknowledgements

This work was supported by Ministero dell'Università e della Ricerca Scientifica. The authors acknowledge the Centro Interfacoltà di Misure "Giuseppe Casnati" dell'Università di Parma for NMR and MS instrumental facilities.

References

- (a) Hacksell U., Daves, G. D., *Progr. Med. Chem.* **1985**, 22, 1. (b) Buchanan J. G., Craven D. A., Wightman R. H., Harnden M. R., *J. Chem. Soc. Perkin Trans. 1* **1991**, 195. (c) Bera S., Sakthivel K., Pathak T., Langley G. J., *Tetrahedron*, **1995**, 51, 7857.
- (a) Piantadosi C., Marasco J. C. J., *J. Med. Chem.* **1991**, 34, 1408. (b) Steim J. M., Neto C. C., *Biochem. Biophys. Res. Commun.* **1990**, 171, 451. (c) Chu C., Bhadti V. S., *J. Med. Chem.* **1991**, 33, 2188. (d) Robins M. J., Manfredini S., Wood S. G., Wanklin R. J., Rennie B. A., Sacks S. L.,

- J. Med. Chem.* **1991**, *34*, 2275. (e) Lefebvre I., Périgaud C., Pompon A., Aubertin A. M., Girardet J. L., Kirn A., Gosselin G., Imbach J. L., *J. Med. Chem.* **1995**, *38*, 3941. (f) Stubbe J., *Nature*, **1994**, *370*, 502. (g) Samano V., Robins M. J., *J. Am. Chem. Soc.* **1992**, *114*, 4007. (h) Baker C. H., Banzon J., Bollinger J. M., Stubbe J., *J. Med. Chem.* **1991**, *34*, 1879. (i) Manfredini S., Baraldi P. G., Bazzanini R., Marangoni M., Simoni D., Balzarini J., De Clercq E., *J. Med. Chem.* **1995**, *38*, 199.
3. (a) Yokoyama M., Tanabe T., Toyoshima A., Togo H., *Synthesis*, **1993**, 517. (b) Girgis N. S., Smee D. F., Robins R. K., Cottam H. B., *J. Med. Chem.* **1990**, *112*, 2750.
4. (a) Cornia M., Casiraghi G., *Tetrahedron*, **1989**, *45*, 2869. (b) Cornia M., Casiraghi G., *Tetrahedron*, **1990**, *46*, 3071. (c) Casiraghi G., Cornia M., Rassu G., Del Sante C., Spanu P., *Nat. Prod. Lett.* **1992**, *1*, 45. (d) Casiraghi G., Cornia M., Zanardi F., Rassu G., E. Ragg E., Bortolini R., *J. Org. Chem.* **1994**, *59*, 1801.
5. Casiraghi G., Cornia M., Rassu G., Del Sante C., Spanu P., *Tetrahedron*, **1992**, *48*, 5619.
6. Cornia M., Casiraghi G., Zetta L., *J. Org. Chem.* **1991**, *56*, 5466.
7. (a) Barral M. C., Jimenez-Aparicio R., Royer E. C., Ruiz-Valero C., Saucedo M. J., Urbanos F. A., *Inorg. Chem.* **1994**, *33*, 2692. (b) Castro J., Romero J., Garcia-Vazquez A., Sousa A., Castineiras A., *J. Chem. Cryst.* **1994**, *24*, 469. (c) Linden A., Wright A. D., Konig G. M., *Acta Cryst. C (Cr. Str. Comm.)*, **1995**, *51*, 744. (d) Castro J. A., Romero J., Garcia-Vazquez J. A., Castineiras A., Sousa A., *Z. Anorg. Allg. Chem.* **1993**, *619*, 601. (e) Castro J., Romero J., Garcia-Vazquez J. A., Castineiras A., Sousa A., *Transition Met. Chem.* **1994**, *19*, 343. (f) Morgan G. F., Deblaton M., Hussein W., Thornback J. R., Evrard G., Durant F., Stach J., Abram U., Abram S., *Inorg. Chim. Acta* **1991**, *190*, 257. (g) Castro J. A., Romero J., Garcia-Vazquez J. A., Macias A., Sousa A., Englert U., *Acta Cryst. C (Cr. Str. Comm.)*, **1994**, *50*, 369. (h) Fulop F., Sillanpaa R., Dahlqvist M., Pihlaja K., Vainiotalo P., *Heterocycles*, **1994**, *37*, 1093. (i) Kwiatkowski E., Kwiatkowski M., Olechnowicz A., Bandoli G., *J. Cryst. Spectrosc.* **1993**, *23*, 473. (j) Castro J. A., Romero J., Garcia-Vazquez J. A., Sousa A., Castellano E. E., Zukerman-Schpector J., *J. Coord. Chem.* **1993**, *30*, 165. (k) Jones R. A., Powell A. K., Whitmore A. P., *Acta Cryst. C (Cr. Str. Comm.)*, **1996**, *52*, 1002.
8. (a) Altomare A., Burla M. C., Camalli, M., Cascarano G., Giacovazzo C., Guagliardi A., Polidori G., *J. Appl. Crystallography*, **1994**, *27*, 435. (b) Sheldrick G. M., SHELXL-93, a program for crystal-structure refinement, University of Goettingen, 1993. (c) *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham, 1975, 4. (d) Nardelli M., *Comput. Chem.* **1983**, *7*, 95. (e) Johnson C. K., ORTEP Report ORNL 3794, Oak Ridge National Laboratory, Tennessee, 1965. (f) Motherwell W. D. S., PLUTO, a program for plotting molecular and crystal structures, University Chemical Laboratory Cambridge, England, 1976.

(Received in UK 11 June 1997; accepted 22 July 1997)