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Carbohydrate Research 339 (2004) 1565–1568
Carbohydrate RESEARCH

Note

Facile route for the synthesis of the iminosugar nucleoside (3*R*,4*R*)-1-(pyren-1-yl)-4-(hydroxymethyl)pyrrolidin-3-ol

Allam A. Hassan,[a] Per T. Jørgensen,[a] Paul C. Stein,[a] M. E. Abdel Fattah,[b] Ibrahim I. A. El Gawad[c] and Erik B. Pedersen[a,*]

[a]*Nucleic Acid Center*[†]*, Department of Chemistry, University of Southern Denmark, Odense University, DK-5230 Odense M, Denmark*
[b]*Department of Chemistry, Faculty of Science, Suez Canal University, Ismailia, Egypt*
[c]*Department of Chemistry, Faculty of Education, Suez Canal University, Suez, Egypt*

Received 14 January 2004; received in revised form 12 March 2004; accepted 24 March 2004

Abstract—*N*-(Pyren-1-yl)-(3*R*,4*S*)-4-[(1*S*,2*R*)-1,2,3-trihydroxypropyl]pyrrolidin-3-ol (**4**) was obtained in 36% yield from 3-deoxy-3-*C*-formyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**) by combined hydrolysis and aminoalkylation reactions with 1-aminopyrene in a one-pot reaction. Cleavage reactions of the exocyclic triol chain in **4** with $NaIO_4$ and $NaBH_4$ resulted in iminosugars **7** and **8**, which are analogues of the furanose forms of 2-deoxy-D-allose and of 2-deoxy-D-ribose, the latter analogue *N*-(pyren-1-yl)-(3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol (**8**) being formed in 83% yield.

Keywords: Aza-C-nucleoside; Iminosugar; Pyrene nucleoside; Reductive amination reaction; Pyrrolidinol sugar

The discovery of the glycosidase inhibitor activity of natural product nojirimycin initiated the synthesis of hydroxylated pyrrolidines called azasugars or iminosugars,[1] which have potential applications as anticancer[2] and antidiabetic agents.[3] We have recently synthesized a pyrrolidine analogue of 2-deoxy-D-ribofuranose having a nitrogen in place of the anomeric carbon and a methylene group instead of the ring oxygen.[4,5] The key step in the synthesis was a one-pot reaction consisting in reduction of a nitro, cyano or azido group in an aldehydo sugar and subsequent intramolecular reductive aminoalkylation reaction. This iminosugar has been used in the synthesis of transition state analogue inhibitors for purine nucleoside phosphorylase, which were reported active in picomolar range.[6,7]

However, the synthesis outlined above for the pyrrolidine analogue of 2-deoxy-D-ribofuranose is not suitable for the synthesis of its corresponding derivatives with substituted aryl groups on the ring nitrogen atom.

We found it interesting to modify the synthetic strategy in order to prepare such a derivative with a 1-pyrenyl group on the ring nitrogen. This compound we considered an iminosugar analogue of the pyrene deoxynucleoside prepared by Kool and co-workers who used it for DNA synthesis.[8,9]

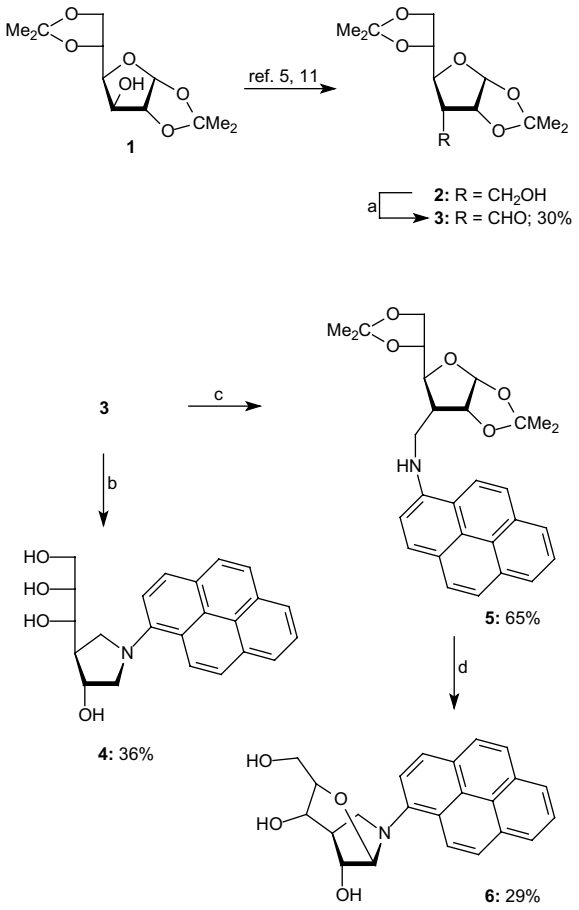
In the present work, the key step for obtaining the *N*-aryl iminosugars was a double aminoalkylation reaction of 1-aminopyrene with the branched masked sugar dialdehyde in its form of 3-deoxy-3-*C*-formyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**). This compound was obtained from the corresponding alcohol **2** by oxidation with pyridinium chlorochromate (PCC), which turned out to give a lower yield than the previously reported oxidation under Swern reaction conditions for the same step.[10] The alcohol **2** in turn is readily available in four steps from D-glucose diacetonide.[5,11] The iminosugar **4** was obtained in a one-pot reaction by condensing the aldehyde **3** with 1-aminopyrene followed by reductive amination, deprotection and performing a

* Corresponding author. Tel.: +45-6550-2555; fax: +45-6615-8780; e-mail: ebp@chem.sdu.dk
[†] A research center funded by The Danish National Research Foundation for studies on nucleic acid chemical biology.

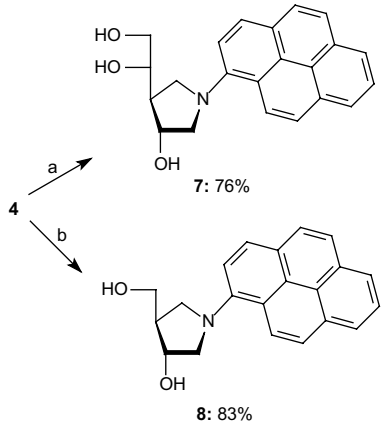
0008-6215/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2004.03.022

subsequent intramolecular reductive amination reaction utilizing the previously masked furanoside aldehyde group. In this way, the iminosugar **4** was obtained in 36% yield from aldehyde **3**. The intermediate after the first aminoalkylation reaction could be filtered off in 65% yield from the reaction mixture before the hydrolysis with aqueous HCl and it was identified as compound **5**. When this compound was hydrolyzed with aqueous HCl, the anhydro iminosugar **6** of a 2-hydroxy iminosugar was obtained in 29% yield. This compound was distinguished from its open form and other possible anhydro forms by standard NMR experiments (^{1}H, ^{13}C, DEPT, DQ-COSY and HSQC) (Scheme 1).

The iminosugar **4** was a suitable starting material for preparation of the corresponding lower homologous azasugars **7** and **8**, which were obtained by sodium periodate oxidation of the iminosugar **4** followed by reduction with sodium borohydride. Using 2.2 equiv of sodium periodate only one carbon was cleaved off and **7** was obtained in 76% yield whereas 6.9 equiv of sodium periodate afforded **8** in 83% yield (Scheme 2).



Scheme 1. Reagents and conditions: (a) NaOAc, PCC, dry CH_2Cl_2; (b) (1) 1-aminopyrene, MeOH, 6 h; (2) HOAc, 2×14 equiv $Na[BH_3(CN)]$; (3) 2 M HCl, MeOH, 2 h; (c) (1) 1-aminopyrene, MeOH, 6 h; (2) HOAc, $Na[BH_3(CN)]$, filtration; (d) 2 M HCl, MeOH, 6 h.



Scheme 2. Reagents and conditions: (a) (1) 2.2 equiv $NaIO_4$, EtOH; (2) $NaBH_4$; (b) (1) 6.9 equiv $NaIO_4$, EtOH; (2) $NaBH_4$.

1. Experimental

1.1. General

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^{1}H NMR and at 75.5 MHz for ^{13}C NMR. Internal standards used in ^{1}H NMR spectra were Me_4Si (δ: 0.00) for $CDCl_3$ and Me_2SO-d_6; in ^{13}C NMR were $CDCl_3$ (δ: 77.0) and Me_2SO-d_6 (δ: 39.5). ^{1}H 2D experiment for compound **6** was recorded on a Varian Unity Inova at 500 MHz. Accurate ion mass determination was performed on a Fourier transform ion cyclotron resonance (FTICR) mass spectrometry (IonSpec, IRVINE, CA, USA). The $[M+H]^+$ ions were peakmatched using ions derived from the glycerol matrix. Thin layer chromatography (TLC) analyses were carried out with the use of TLC plates 60 F_{254} purchased from E. Merck and were visualized in an UV light (254 nm) and/or with a 5% solution of H_2SO_4 in MeOH for sugar derivatives and azasugars. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from E. Merck. All solvents were distilled before use.

1.2. 3-Deoxy-3-*C*-formyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (3)

To a cold solution of **2**[5,11] (0.18 g, 0.69 mmol) in dry CH_2Cl_2 (40 mL), anhyd NaOAc (0.56 g, 6.87 mmol) and pyridinium chlorochromate (PCC, 1.5 g, 6.87 mmol) in dry CH_2Cl_2 (10 mL) were added at 0 °C under N_2 with stirring. After complete addition of PCC, stirring was continued at rt for 15 min followed by TLC. Then the mixture was filtered through a silica-gel column (30 g) using EtOAc elution (200 mL), and the eluted product was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated under diminished pressure to give an oily residue, which was subjected to silica-gel column chromatography

using 2:5 EtOAc–petroleum ether (60–80 °C) to afford **3** in 30% yield as a yellow oil: R_f 0.5; IR (film): ν max 1728 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.25 (s, 6H, 2×CH_3), 1.33 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.82–2.88 (m, 1H, 3-H), 3.85–4.09 (m, 3H, 5-H, 6-H), 4.49–4.54 (m, 1H, 4-H), 4.92–4.96 (m, 1H, 2-H), 5.81 (d, 1H, J 3.6 Hz, 1-H), 9.66 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 24.38, 25.90, 25.95, 26.22 (4×CH_3), 57.44 (3-C), 66.09 (6-C), 76.16 (5-C), 77.72 (4-C), 81.07 (2-C), 105.24 (1-C), 109.25 (CMe_2), 112.76 (CMe_2), 196.97 (CHO); HRMS (MALDI) m/z 295.1152 ($[MNa]^+$ calcd for $[C_{13}H_{20}NaO_6] = 295.1152$).

1.3. *N*-(Pyren-1-yl)-(3*R*,4*S*)-4-[(1*S*,2*R*)-1,2,3-trihydroxypropyl]pyrrolidin-3-ol (4)

Compound **3** (0.12 g, 0.5 mmol) was dissolved in MeOH (30 mL), and 1-aminopyrene (0.09 g, 0.5 mmol) was added under N_2 and the mixture was stirred at rt for 6 h. $Na[BH_3(CN)]$ (0.47 g, 7.0 mmol) was added to the reaction mixture at pH 2 (HOAc). The mixture was stirred at rt overnight and excess of $Na[BH_3(CN)]$ (0.47 g, 7.0 mmol) was added. HCl (2 M, 50 mL) was added dropwise followed by addition of MeOH (30 mL) in one portion, and the mixture was stirred for 2 h. The solvent was evaporated under diminished pressure and the aq phase was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2 (4 × 50 mL), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica-gel column chromatography (1:9 MeOH–CH_2Cl_2) to afford azasugar **4** (50 mg, 36%) as a pale green solid: mp 140–145 °C; R_f 0.4 (1:9 MeOH–CH_2Cl_2); ^1H NMR (Me_2SO-d_6): δ 2.53–2.61 (m, 2H, 2×OH), 3.50–3.75 (m, 7H, 2-H, 4-H, 5-H, 1′-H, OH), 4.54–4.57 (m, 2H, 3′-H); 4.76–4.78 (m, 1H, OH), 4.93–4.95 (m, 1H, 2′-H), 5.16–5.17 (m, 1H, 3-H), 7.63–8.46 (m, 9H, H_{arom}); ^{13}C NMR (Me_2SO-d_6): δ 48.5 (4-C), 54.5 (5-C), 60.8 (2-C), 63.3 (3′-C), 70.1 (1′-C), 71.1 (3-C), 73.8 (2′-C), 114.3, 120.7, 123.4, 124.6, 125.8, 127.4, 130.9, 131.5, 145.7 (arom); HRMS (MALDI) m/z 377.1622 ($[M]^{+\cdot}$ calcd for $[C_{23}H_{23}NO_4] = 377.1630$).

1.4. 3-Deoxy-3-*C*-(pyrene-1-yl-aminomethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (5)

A soln of compound **3** (0.1 g, 0.36 mmol) and 1-aminopyrene (0.086 g, 0.39 mmol) in MeOH (20 mL) was stirred at rt for 6 h. Acetic acid was added to pH 2 followed by addition of $Na[BH_3(CN)]$ (0.3 g, 5 mmol) and the reaction mixture was stirred overnight at rt. The solid obtained was filtered off and washed with MeOH to give **5** (0.11 g, 65%) as a yellow solid: mp 155 °C; R_f 0.8 (1:9 MeOH–CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 1.35 (s, 6H, 2×CH_3), 1.48 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.33 (br s, 1H, 3-H), 3.64–3.82 (m, 2H, 5-H), 3.84–3.97 (m, 2H, 6-H), 4.01–4.16 (m, 1H, 4-H), 4.71 (br s, 1H, 2-H), 5.92 (br s, 1H, 1-H), 7.36–8.03 (m, 9H, H_{arom}); ^{13}C NMR (Me_2SO-d_6): δ 25.5, 26.4, 26.7, 26.95 (4×CH_3), 41.21 (3-C), 48.28 (CH_2–NH), 68.17 (6-C), 77.48 (5-C), 82.15 (4-C), 82.97 (2-C), 104.71, 108.77, 110.10, 112.32, 116.88, 120.04, 123.08, 123.69, 125.42, 125.88, 126.43, 127.71, 131.70, 132.40, 142.83 (arom); HRMS (MALDI) m/z 473.2197 ($[M]^+$ calcd for $[C_{29}H_{31}NO_5] = 473.2212$).

1.5. (1*S*,3*R*,4*S*,5*R*,8*R*)-3-Hydroxymethyl-7-pyren-1-yl-2-oxa-7-aza-bicyclo[3.2.1]octane-4,8-diol (6)

HCl (2 M, 50 mL) was added dropwise to a soln of compound **5** (0.1 g, 0.2 mmol) in MeOH (30 mL), the reaction mixture was stirred for 6 h. MeOH was evaporated and the aq phase was neutralized with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (4 × 50 mL) dried over Na_2SO_4 and evaporated till dryness. The crude product was purified by silica-gel column chromatography using 1:9 MeOH–CH_2Cl_2 to afford **6** (22 mg, 29%) as a greenish brown foam: R_f 0.14 (1:9 MeOH–CH_2Cl_2); ^1H NMR (Me_2SO-d_6): δ 2.58 (m, 1H, 5-H), 3.15–4.25 (m, 7H, 8-H, 4-H, 3-H, 9-H, 6-H), 5.10 (1-H), 4.65, 5.80, 5.15 (3×s, 3×OH), 7.79–8.75 (m, 9H, H_{arom}); ^{13}C NMR (Me_2SO-d_6): δ 46.79 (5′-C), 48.34 (6′-C), 60.89 (9′-C), 65.98 (4′-C), 73.75 (3′-C), 74.29 (8′-C), 92.72 (1′-C), 114.88–143.49 (arom); HRMS (MALDI) m/z 376.1543 ($[MH]^+$ calcd for $[C_{23}H_{21}NO_4] = 376.1545$).

1.6. (3*R*,4*S*)-1-(Pyren-1-yl)-4-[(1*S*)-1,2-dihydroxyethyl]pyrrolidin-3-ol (7)

To a soln of **4** (0.1 g, 0.29 mmol) in abs. EtOH (20 mL) was added a soln of $NaIO_4$ (0.137 g, 0.64 mmol) in water (10 mL) and the soln was stirred for 3 h. The resultant soln was immediately reduced with $NaBH_4$ (0.03 g, 0.87 mmol), then diluted with water (20 mL) and extracted with CH_2Cl_2 (4 × 40 mL), and the combined CH_2Cl_2 layers were dried (Na_2SO_4) and evaporated under diminished pressure. The crude product was purified by silica-gel column chromatography (1:9 MeOH–CH_2Cl_2) to give **7** (70 mg, 76%) as a pale green foam: R_f 0.52 (1:9 MeOH–CH_2Cl_2); ^1H NMR (Me_2SO-d_6): δ 2.36–2.42 (m, 2H, 2×OH), 3.57–3.98 (m, 8H, 2-H, 4-H, 5-H, 1′-H, 2′-H), 4.43–4.58 (m, 1H, 3-H), 4.84 (br s, 1H, OH), 7.58–8.48 (m, 9H, H_{arom}); ^{13}C NMR (Me_2SO-d_6): δ 49.4 (4-C), 53.9 (5-C), 60.9 (2-C), 64.8 (2′-C), 70.5 (1′-C), 71.5 (3-C), 114.3, 120.9, 123.4, 124.7, 125.8, 127.4, 130.9, 131.5, 145.7 (arom); HRMS (MALDI) m/z 347.1516 ($[M]^+$ calcd for $[C_{22}H_{21}NO_3] = 347.1516$).

1.7. (3*R*,4*R*)-1-(Pyren-1-yl)-4-(hydroxymethyl)pyrrolidin-3-ol (8)

A soln of $NaIO_4$ (0.2 g, 0.9 mmol) in water (10 mL) was added to a soln of **4** (0.05 g, 0.13 mmol) in abs. EtOH (50 mL) and the soln was stirred for 3 h. $NaBH_4$ (0.1 g,

2.6 mmol) was added with stirring for 2 h. The resultant soln was diluted with water (20 mL) and extracted with CH_2Cl_2 (4×40 mL), dried (Na_2SO_4) and evaporated under diminished pressure. The crude product was purified by silica-gel column chromatography with 1:9 MeOH–CH_2Cl_2 to give **8** (40 mg, 83%) as a pale green foam: R_f 0.58 (1:9 MeOH–CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 2.04–2.50 (m, 1H, 4-H), 3.08–3.98 (m, 8H, 2-H, 5-H, CH_2, 2×OH), 4.15–4.38 (br s, 1H, 3-H), 7.59–8.20 (m, 9H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 49.4 (4-C), 54.3 (5-C), 60.5 (2-C), 63.6 (*C*H_2), 73.6 (3-C), 114.8, 122.8, 123.5, 124.1, 125.4, 126.0, 127.3, 131.2, 131.8, 144.5 (C_{arom}); HRMS (MALDI) m/z 317.1410 ($[M]^+$ calcd for $[C_{21}H_{19}NO_2] = 317.1401$).

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