ELSEVIER

Carbohydrate Research 337 (2002) 273–277

CARBOHYDRATE RESEARCH

www.elsevier.com/locate/carres

Note

Reinvestigation of the iodocyclization of 4,5,7-tri-*O*-benzyl-3-(*N*-benzylacetamido)-1,2,3-trideoxy-D-*gluco*-hept-1-enitol: unexpected formation of a 1,3-imino-heptitol derivative

Adewale Eniade, Olivier R. Martin*

Department of Chemistry, State University of New York, PO Box 6016, Binghamton, NY 13902-6016, USA

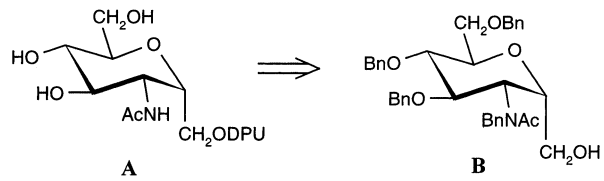
Received 18 September 2001; accepted 28 November 2001

Abstract

The NIS-mediated iodocyclization of 4,5,7-tri-*O*-benzyl-3-(*N*-benzylacetamido)-1,2,3-trideoxy-D-*gluco*-hept-1-enitol gave unexpectedly a 1,3-imino-heptitol derivative, namely 2-*O*-acetyl-*N*-benzyl-4,5,7-tri-*O*-benzyl-1,3-dideoxy-1,3-imino-D-*glycero*-D-*ido*-heptitol. This compound is a new example of a rare class of azetidine imino alditol derivatives which have interesting properties such as glycosidase inhibitors. The physical and spectral data for this imino heptitol were essentially identical to those reported for 2,6-anhydro-4,5,7-tri-*O*-benzyl-3-(*N*-benzylacetamido)-3-deoxy-D-*glycero*-D-*ido*-heptitol, a derivative of *C*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)methanol obtained from the same precursor [Lay, L.; Nicotra, F.; Panza, L.; Verani, A. *Gazz. Chim. Ital.* **1992**, *122*, 345–348]; these findings cast doubts on the structure reported for the latter product.

Keywords: Azetidines, polyhydroxylated; 1,3-Imino heptitols; *C*-Glycosides

In the course of our investigations on glycoside mimics,[1] we became interested in the synthesis of non-transferable analogs of UDP-GlcNAc for the study of the mechanism of biosynthesis of chitin.[2] In particular, we designed as target compound the homo analog of UDP-GlcNAc (**A**, Scheme 1), a potential inhibitor of chitin synthase and of related glycosyl transferases. Although *C*-glycosyl derivatives of GlcNAc are notoriously difficult to prepare,[3] we considered that the *C*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)methanol derivative **B** reported in 1992 by Nicotra and coworkers[4] would constitute a convenient precursor of the desired homoglycosyl phosphate and the corresponding sugar nucleotide analog. We now report that the NIS-mediated iodocyclization of 4,5,7-tri-*O*-benzyl-3-(*N*-benzylacetamido)-1,2,3-trideoxy-D-*gluco*-hept-1-enitol (**4**) did not give **B**, but an unexpected 1,3-dideoxy-1,3-imino heptitol derivative **5**; this compound has properties nearly identical to those reported for **B**, which suggests that the product reported as **B**[4] may not have the correct structure. A synthesis of the homo-analog of UDP-GlcNAc **A** has recently been achieved by Thiem and Schäfer[5] by way of a different route.

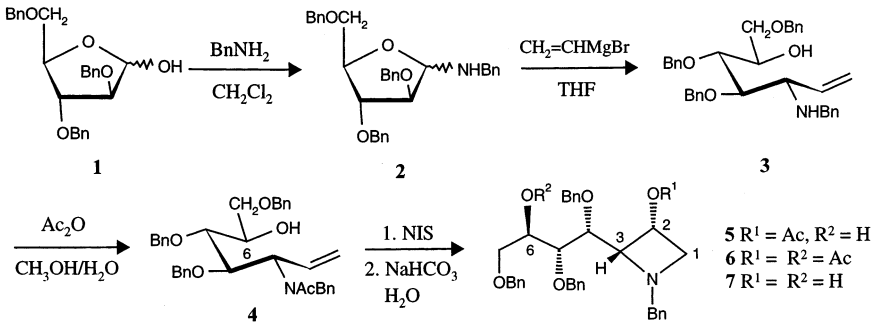


Scheme 1.

* Corresponding author. Present address: ICOA, Université d'Orléans, BP 6759, F-45067 Orléans, France; tel.: +33-23-8494581; fax: +33-23-8417281.

E-mail address: olivier.martin@univ-orleans.fr (O.R. Martin).

0008-6215/02/$ - see front matter
PII: S0008-6215(01)00314-7



Scheme 2.

Heptenitol derivative **4** was prepared from tri-*O*-benzyl-D-arabinofuranose (**1**) using Nicotra's approach[4] under slightly modified conditions (Scheme 2). In particular, we confirmed the high degree of stereoselectivity of the addition of vinylmagnesium bromide to the furanosylamine **2**: the D-gluco epimer **3** could be obtained exclusively by reversing the mode of addition and using a smaller excess of reagent. The procedure was completed by the selective N-acetylation of **3**, thus affording the interesting chain-extended derivative of GlcNAc **4**. The NMR spectra of **4** were complicated by the presence of signals of the two amide conformers. Compound **4** was then reacted with NIS (instead of iodine[4]), with the goal of promoting iodocyclization,[6] and the reaction mixture was treated, after disappearance of the starting material, with aqueous $NaHCO_3$ for several hours. This sequence of reactions afforded a major product, isolated in 41% yield, whose physical and spectral properties were essentially identical to those reported for **B**[4] (see for example Table 1 for a comparison of ^{13}C NMR chemical shifts). The detailed study of the spectral parameters of the isolated product, as well as its chemical behavior, led us however to conclude that this product was the isomeric 2-*O*-acetyl-*N*-benzyl-4,5,7-tri-*O*-benzyl-1,3-dideoxy-1,3-imino-D-*glycero*-D-*ido*-heptitol (**5**).

Several features indicated that **5** did not contain an acetamido function any more, but an acetate ester: the C=O absorption band appearing at 1735 cm^{-1} and the ready cleavage of the acetyl group under Zemplén conditions to give compound **7**. Furthermore, the acetylation of **5**, to give the diacetate **6**, promoted a large downfield shift of the signal of H-6 (see ^1H NMR data in Table 2), thus providing strong evidence that the 6-OH group of precursor **4** did not participate in the iodocyclization reaction. The chemical shift of C-1 (δ 58.0 ppm in **5**) suggested a bond to nitrogen rather than to oxygen. Chemical shift changes on (de)-acetylation also indicated that the acetate group in **5** was at C-2. The four-membered ring constitution of the new product was firmly established on the basis of long-range H,H-COSY correlations: one of the N-benzylic protons was found to exhibit strong correlations with both H-1A and H-1B as well as a weaker one with H-3 (see Fig. 1). Finally, the cis-stereochemistry of the azetidine ring system was determined on the basis of a series of unambiguous NOE correlations (Fig. 1) and by comparison of the $^3J_{H,H}$ coupling constants with those reported for related cis-configured azetidines (1,3-dideoxy-1,3-imino-hexitol derivatives[7]).

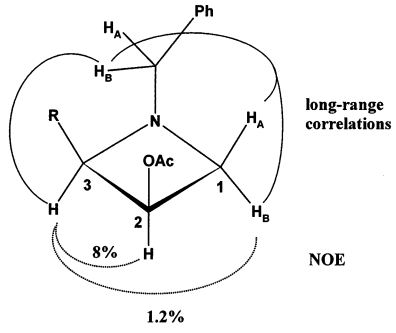


Fig. 1. Long-range H,H-COSY correlations and NOE's in **5**.

Table 1
^{13}C NMR spectral data for **5**–**7** (90 MHz) [a]

Position	**5**	Lit. data[4]	**6** [b]	**7** [b]
C-1	58.0 (−)	58.7	58.2 (−)	59.3 (−)
C-2	67.2 [c]	67.8	67.4	65.3
C-3	67.6 [c]	68.3	67.3	69.5
C-4	78.6 [d]	79.2	79.1	80.4
C-5	77.3 [d]	77.8	76.8	76.8
C-6	70.0	70.6	73.7	71.0
C-7	71.3 (−)	71.8	68.6 (−)	71.0 (−)
O–CH_2Ph	73.4 (−)	74.0	73.1 (−)	73.4 (−)
	73.4 (−)	74.0	73.8 (−)	73.6 (−)
	74.9 (−)	75.6	75.4 (−)	74.1 (−)
N–CH_2Ph	62.6 (−)	63.3	62.7 (−)	62.6 (−)
CH_3CO	20.9	21.6	20.9	
			21.2	
CH_3CO	170.5	171.3	170.2	
			170.4	

[a] Chemical shifts in ppm (δ_{TMS} 0). Solvent $CDCl_3$.
[b] Assignments confirmed by HETCOR experiments.
[c] These assignments can be interchanged.
[d] These assignments can be interchanged.

Table 2
^{1}H NMR spectral data for **5**–**7** (360 MHz) [a]

Position	**5** [b]	**6** [c,d]	**7** [c]
H-1A (*pro-R*)	3.04, dd	3.02 dd	2.99 dd
($J_{1A,1B}$, $J_{1A,2}$)	(9.9, 6.1)	(9.9, 6.1)	(9.0, 6.0)
H-1B (*pro-S*)	3.26 d	3.23 d	3.24 d
($J_{1B,2}$)	(~1)	(1.4)	(<1)
H-2	4.79 td	4.62 td	~4.23 m
($J_{2,3}$)	(6.5)	(6.5)	(5.7)
H-3	3.75 dd	3.67 dd	3.56 dd
($J_{3,4}$)	(9.4)	(9.7)	(8.7)
H-4	4.35 dd	4.20 dd	~4.23 m
($J_{4,5}$)	(2.3)	(2.5)	(3.5)
H-5	3.47 dd	3.64 dd	3.83 dd
($J_{5,6}$)	(7.6)	(5.5)	(8.0)
H-6	4.01 m	5.22 td	3.98 q
($J_{6,7A}$, $J_{6,7B}$)	(5.2, 3.3)	(5.9, 2.4)	(?)
H-7A	3.63 dd	3.78 dd	3.71 ~d
($J_{7A,7B}$)	(9.8)	(11.2)	(?)
H-7B	3.70 dd	3.91 dd	3.71 ~d
N–CH_A	3.41 d	3.37 d	3.45 d
($J_{A,B}$)	(13.3)	(13.3)	(13.2)
N–CH_B	4.17 d	4.16 d	4.13 d
O–CH_{A1}	4.51 d	4.46 AB	4.57 d
($J_{A,B}$)	(11.7)	(12.0)	(11.9)
O–CH_{B1}	4.59 d	~4.50 AB	4.65 d
O–CH_{A2}	4.53 AB	4.51 d	4.57 AB
($J_{A,B}$)		(11.8)	(10.8)
O–CH_{B2}	4.53 AB	4.68 d	4.57 AB
O–CH_{A3}	4.86 d	4.70 d	4.75 AB
($J_{A,B}$)	(11.1)	(10.7)	(11.1)
O–CH_{B3}	5.00 d	5.00 d	4.75 AB

[a] Chemical shifts in ppm (δ_{TMS} 0) and coupling constants in Hz. Solvent: $CDCl_3$.
[b] δ CH_3CO: 2.00 (s).
[c] Assignments confirmed by H,H-COSY.
[d] δ CH_3CO: 2.04, 2.05 (2s).

What is the origin of this unexpected product? Although no detailed mechanistic investigations have been undertaken, the mechanism described in Scheme 3 provides a working hypothesis. The NIS-mediated iodocyclization might involve, as the internal nucleophile, the carbonyl oxygen of the neighboring amide function, to give iodinated intermediate **II**. Upon hydrolytic treatment, the resulting orthoamide **III** could evolve either by regeneration of the acetamido group with formation of a 1,2-epoxide or by cleavage of the C–N bond to form the ester function at O-2 and the azetidine ring by an internal S_N2 process. The factors responsible for the unexpected evolution of **III** remain to be elucidated.

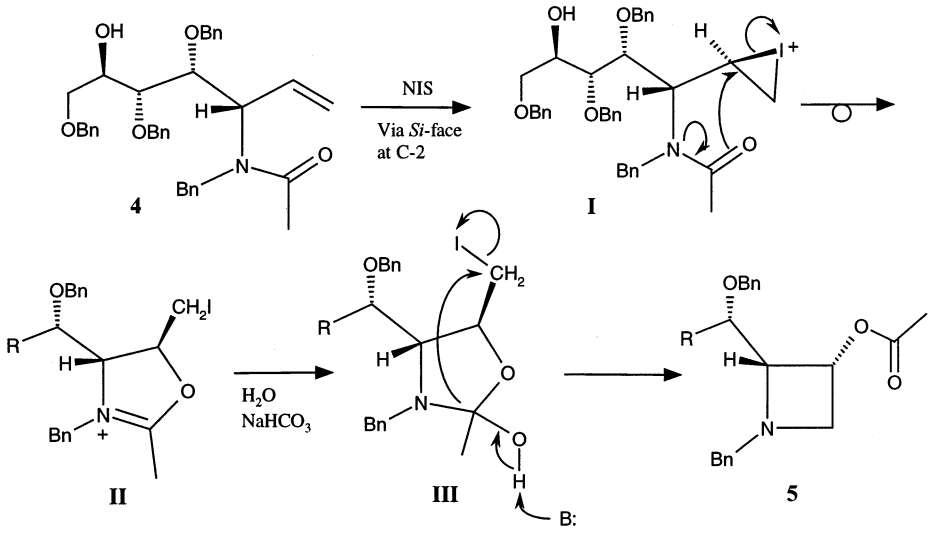
In conclusion, the NIS-mediated reaction of the unsaturated heptenitol **4**, a derivative of 2-acetamido-2-deoxy-D-glucose, did not give the expected six-membered *C*-glycosyl compound. This behavior is in marked contrast with that of hexose-derived heptenitols which constitute convenient precursors of various pyranoid *C*-glycosyl compounds under the same conditions.[8] The process reported herein provides an unusual access to 1,3-imino-alditols, a rare class of azetidine-containing imino sugars. The related, five-carbon 1,3-dideoxy-1,3-imino-L-xylitol was shown recently to be a potent and very selective glucoamylase inhibitor.[9] Finally, our study suggests that the product obtained by Nicotra from **4** under similar conditions is actually **5** and not a *C*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)methanol derivative as reported.[4]

1. Experimental

General methods.—Solvents were evaporated under reduced pressure and below 40 °C. Optical rotations were measured with an automatic polarimeter for solutions in a 0.1 dm cell at 22 ± 3 °C. ^{1}H and ^{13}C NMR spectra were recorded at 360 and 90 MHz, respectively, on a Bruker AM-360 instrument using chloroform-*d* as the solvent unless otherwise indicated and TMS as the internal reference (δ_{TMS} 0.00 ppm). For ^{13}C NMR spectra in $CDCl_3$, the signal of the solvent (δ 77.00) was used as the reference. Chemical shifts (in ppm) and coupling constants (in Hz) were obtained from first-order analysis of the spectra. A (−) sign is used to indicate negative ^{13}C NMR-signals in the DEPT mode (θ_y 135°). Assignments were generally made on the basis of 2D H,H-COSY and HETCOR correlation spectra. IR spectra were recorded using a Perkin–Elmer 1600 FT-IR instrument. Analytical TLC was performed on glass plates precoated with Silica Gel 60 F-254 as the adsorbent (layer thickness: 0.25 mm). The developed plates were air-dried, exposed to UV light for inspection, sprayed with a solution of ammonium phosphomolybdate, and heated to 120–140 °C. Flash chromatography was performed using Silica Gel 60 (230–400 mesh). Mass spectral analyses were carried out at Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE 68588. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA 30091.

N-*Benzyl-2,3,5-tri*-O-*benzyl*-D-*arabinofuranosylamine* (**2**).—Prepared from 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**1**) as described by Nicotra.[4] The product was recrystallized from EtOH (yield: 87%): mp 75–77 °C (lit.[4] 72–74 °C). ^{13}C NMR ($CDCl_3$, mixture of anomers, main signals): δ 49.1, 49.9 (N–CH_2Ph), 70.7, 71.0, 71.6, 71.7, 71.9, 72.1 (OCH_2Ph), 73.3 (C-5), 79.6, 80.5, 82.6, 83.0, 83.5, 86.5 (C-2–4), 90.4 and 93.5 (C-1).

4,5,7-Tri-O-*benzyl-3-benzylamino-1,2,3-trideoxy*-D-gluco-*hept-1-enitol* (**3**).—The procedure[4] was modified as follows: to compound **2** (2.5 g, 4.9 mmol) in THF (5



Scheme 3.

mL) was added, at rt and under nitrogen, a 1 M solution of vinyl magnesium bromide in THF (25 mL, 5 equiv). The mixture was stirred overnight. The solution was then carefully added to aq NH_4Cl (50 mL). THF was partially evaporated under reduced pressure. Ethyl acetate (50 mL) was then added, the aqueous phase was separated, washed with EtOAc (25 mL), and the combined organic phases were dried and concentrated, thus affording essentially pure **3** (2.7 g, quant); $[\alpha]_D$ +12° (*c* 1, $CHCl_3$) {lit.[4] $[\alpha]_D$ +12.3° (*c* 1, $CHCl_3$)}. The D-manno epimer could not be detected in the reaction mixture.

4,5,7-Tri-O-*benzyl*-*3*-(N-*benzylacetamido*)-*1,2,3-trideoxy*-D-gluco-*hept*-*1*-*enitol* (**4**).—Prepared from **3** in 94% yield by the procedure described.[4] $[\alpha]_D$ +14.6° (*c* 1, $CHCl_3$) {lit.[4] $[\alpha]_D$ +14° (*c* 1, $CHCl_3$)}; IR: ν_{max} (KBr) 3405 (OH), 1625 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$, 25°C; mixture of two amide rotamers): δ 22.7, 22.9 ($NCOCH_3$), 46.3, 54.3 (NCH_2Ph), 61.9 (C-3), 70.1, 70.6 (C-6), 71.1, 71.3 (C-7), 73.4, 73.5, 73.6, 74.8, 74.9 (OCH_2Ph), 78.3, 78.7, 79.7, (C-4,5), 119.8, 121.0 (C-2), 126.6–128.5 (Ar-CH), 134.0–134.9 (Ar-C), 171.4, 172.0 ($NCOCH_3$).

2-O-*Acetyl*-N-*benzyl*-*4,5,7*-*tri*-O-*benzyl*-*1,3*-*dideoxy*-*1,3*-*imino*-D-glycero-D-ido-*heptitol*† (**5**).—To a solution of **4** (350 mg, 0.6 mmol) in anhyd THF (10 mL) was added, under N_2 at 0 °C, *N*-iodosuccinimide (290 mg, 1.3 mmol). The reaction mixture was stirred at rt until complete disappearance of **4** (~2 h). Saturated aq $Na_2S_2O_3$ was then added dropwise until the brown color had disappeared. The phases were then separated and the organic layer was transferred into a reaction flask. Saturated aq $NaHCO_3$ (4 mL) was added and the mixture was stirred vigorously overnight. Ethyl acetate (20 mL) was then added and the aqueous phase was separated. The organic phase was washed successively with aq $Na_2S_2O_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (3:1 hexane–EtOAc) which afforded compound **5** as a syrup (150 mg, 41%). $[\alpha]_D$ −21.3° (*c* 1, $CHCl_3$) {reported[4] $[\alpha]_D$ for **B**: −20.8° (*c* 1, $CHCl_3$)}; IR: ν_{max} 3455 (OH), 1735 cm^{-1} (C=O); NMR: see Tables 1 and 2. FAB-MS: *m*/*z* 596 (100%, $[M+H]^+$).

2,6-Di-O-*acetyl*-N-*benzyl*-*4,5,7*-*tri*-O-*benzyl*-*1,3*-*dideoxy*-*1,3*-*imino*-D-glycero-D-ido-*heptitol*† (**6**).—Compound **5** was acetylated in essentially quantitative yield using DMAP in Ac_2O. An analytical sample was obtained by flash chromatography (4:1 hexane–EtOAc): $[\alpha]_D$ −29.9° (*c* 1, $CHCl_3$); IR: ν_{max} 1736 cm^{-1} (C=O); NMR: see Tables 1 and 2. FAB-MS: *m*/*z* 638 (100%, $[M+H]^+$). Anal. Calcd for $C_{39}H_{43}NO_7$: C, 73.45; H, 6.80; N, 2.20. Found: C, 73.40; H, 7.11; N, 2.07.

N-*Benzyl*-*4,5,7*-*tri*-O-*benzyl*-*1,3*-*dideoxy*-*1,3*-*imino*-D-glycero-D-ido-*heptitol*† (**7**).—Compound **5** (260 mg, 0.44 mmol) was deacetylated in MeOH (20 mL) containing a catalytic amount of MeONa. The solvent was evaporated, the residue was taken into EtOAc (20 mL), the solution was washed with water, then with brine, dried ($MgSO_4$) and concentrated, thus affording homogeneous **7** (240 mg, 99%): $[\alpha]_D$ −22.9° (*c* 1, $CHCl_3$); IR: ν_{max} 3433 cm^{-1} (OH); NMR: see Tables 1 and 2. FAB-MS: *m*/*z* 554 (30%, $[M+H]^+$). Anal. Calcd for $C_{35}H_{39}NO_5$: C, 75.92; H, 7.10; N, 2.53. Found: C, 75.33; H, 7.15; N, 2.49.

† Strictly, these compounds should be named as derivatives of a 5,7-dideoxy-5,7-imino-D-*glycero*-L-*gulo*-heptitol.

Acknowledgements

This work was supported, in part, by a grant from the National Institutes of Health (grant DK 35766).

References

1. (a) Martin, O. R. In *Carbohydrate Mimics*: *Concepts and Methods*; Chapleur, Y., Ed.; Wiley–VCH: Weinheim, 1997; pp. 259–282;
   (b) Spak, S. J.; Martin, O. R. *Tetrahedron* **2000**, *56*, 217–224.
2. Saxena, I. M; Brown, R. M., Jr.; Fevre, M.; Geremia, R. A.; Henrissat, B. *J. Bacteriol.* **1995**, *177*, 1419–1424 and references cited therein.
3. Xie, J. *Recent Res. Dev. Org. Chem.* **1999**, *3*, 505–523.
4. Lay, L.; Nicotra, F.; Panza, L.; Verani, A. *Gazz. Chim. Ital.* **1992**, *122*, 345–348.
5. Schäfer, A.; Thiem, J. *J. Org. Chem.* **2000**, *65*, 24–29.
6. Harding, K. E.; Tiner, T. H In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, pp. 363–421.
7. Michaud, T.; Chanet-Rey, J.; Chou, S.; Gelas, J. *Carbohydr. Res.* **1997**, *303*, 123–127.
8. (a) Lancelin, J.-M.; Pougny, J.-R.; Sinaÿ, P. *Carbohydr. Res.* **1985**, *136*, 369–375;
   (b) Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1988**, *53*, 4181–4185;
   (c) Freeman, F.; Robarge, K. D. *J. Org. Chem.* **1989**, *54*, 346–359.
9. Krämer, B.; Franz, T.; Picasso, S.; Pruschek, P.; Jäger, V. *Synlett* **1997**, 295–297.