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Stereoselective access to α-azido aldehydes and a new synthetic route to myriocin

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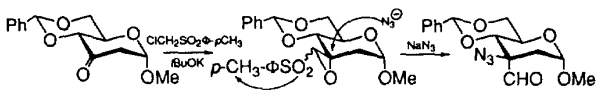
Summary — Reaction of dichloromethyllithium with six-membered carbohydrate ketones followed by azide ion treatment furnished stereoselectively α-azido aldehydes, potential intermediates in the synthesis of α-substituted α-amino acids. The same reaction sequence applied to an acyclic ketone **10a** allowed the preparation of an α-azido aldehyde **12** which could be converted in four steps into a known intermediate **14b** of the total synthesis of the immunosuppressant myriocin **16**.

α-azido aldehyde / Darzens' condensation / myriocin / immunosuppressant

Résumé — Approche stéreosélective vers les α-azido aldéhydes et un nouveau chemin synthétique vers la myriocine. *La réaction du dichlorométhyllithium sur des cétones d'hydrates de carbone à six chaînons suivie par le traitement à l'azoture de sodium permet d'accéder stéréosélectivement à des α-azido aldéhydes, intermédiaires potentiels dans la synthèse d'acides α-aminés α-substitués. La même suite de réactions appliquée à la cétone acyclique* **10a** *conduit à l'α-azido aldéhyde* **12** *qui, en 4 étapes, peut être transformé en l'intermédiaire* **14b** *connu dans la synthèse totale de l'immunosuppresseur myriocine* **16**.

α-azido aldéhyde / condensation de Darzens / myriocine / immunosuppresseur

In an attempt to synthesize α-substituted α-amino acids of biological interest [1] from carbohydrates, a few years ago we were interested in preparing α-azido aldehydes [2], potential intermediates towards the target molecules. We have shown during these studies that some carbohydrate ketones undergo Darzens' condensations, in the presence of potassium *t*-butoxide, with chloromethyl *p*-tolylsulfone. Thus, α,β-epoxy sulfones that are sterically pure at the quaternary center could be obtained in good yields [2]. These α,β-epoxy sulfones reacted readily in the presence of a variety of nucleophiles, allowing the preparation of branched-chain carbohydrates [2, 3] (scheme 1).



Scheme 1

The use of the azide ion was of particular interest since this reaction permitted access to α-azido aldehydes. However, the good yields obtained for α,β-epoxy sulfones could not be reproduced for carbohydrate ketones substituted simultaneously at both α- and α′-positions with respect to the carbonyl group. Application of Darzens' condensation to ketone **1** led to its decomposition while ketone **4** afforded only the elimination product **5**. Therefore, a recently published new procedure [4, 5] involving the reaction of dichloromethyllithium with carbonyl compounds was investigated. Carbohydrate ketones **1** [6], **2** [7], **3** [8] and **4** [9], prepared using published methods, were submitted to the action of dichloromethyllithium, and without isolation the reaction products were treated with azide nucleophile. Although the yields were moderate, this procedure appeared to be quite efficient for preparing, the following α-azido aldehydes: **6** (52%), **7** (46%), **8** (50%) and **9** (54%) (scheme 2).

Unambiguous determination of the stereochemistry at the quaternary carbon center of the new compounds proved difficult by ^{13}C NMR spectroscopy alone using the technique applied in our earlier studies [2]. Quantitative interpretation of the chemical shifts became complicated in the highly crowded systems, exhibiting several gauche interactions, due to the presence of substituents on both sides of the quaternary carbon centers. Therefore, the stereochemistry for all the new branched-chain sugars was ascertained by means of nuclear Overhauser effects (nOe). Selective irradiation of the axial aldehyde protons revealed nOes on the axial protons at the β-position with respect to the quaternary center.

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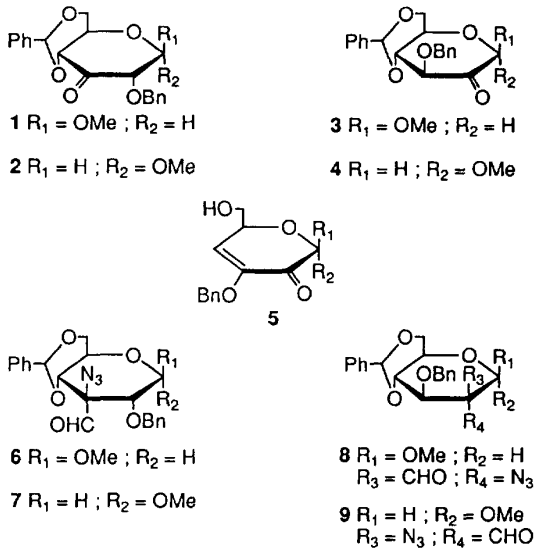


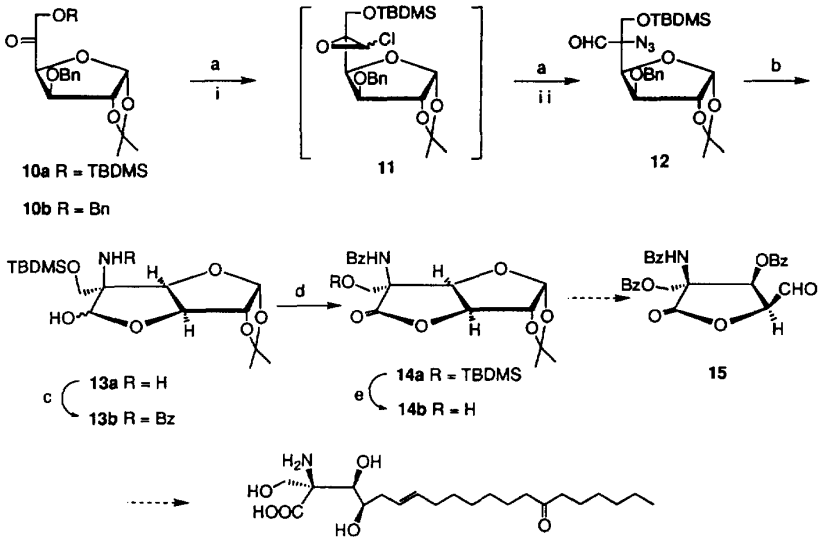
Scheme 2

Thus, in the cases of **6**, **7** and **8** the following hydrogens exhibited, nOe effects: (H_1, H_5), (H_5) and (H_4) respectively. The same experiment on the equatorial aldehyde **9** revealed an nOe effect on the *cis*-hydrogen H_3 but not on H_4.

These results prompted us to consider a stereoselective access via α-azido aldehyde **12** to the immunosuppressant myriocin **16**, which is of considerable biological interest (scheme 3). This metabolite [10], originating from the thermophilic fungus *Myriococcum albomyces*, appears to be two orders of magnitude more efficient [11, 12] than cyclosporine A and its clinical applications are being considered [13]. Several groups have already reported the total synthesis of myriocin [14].

We were interested in improving the very elegant formal synthesis of **16** reported by Rama Rao et al [15]. Our efforts were directed towards the stereoselective synthesis of compound **14b** [16]. The preparation of **14b** from **10a** by the Indian group requires 13 steps, and we were hoping to considerably shorten the synthesis of myriocin **16** via the α-azido aldehyde **12**.

Darzens' condensation with chloromethyl *p*-tolylsulfone on ketones **10a** and **10b** failed to produce α,β-epoxy sulfones due to rapid decomposition of the starting material. The same starting ketones **10a** and **10b** were then treated with dichloromethyllithium according to Sato's procedure [4, 5] and the resulting material, without isolation, was submitted to the action of azide ion. Both ketones **10a** and **10b** furnished, via the intermediate α,β-epoxy chloride **11**, the required α-azido aldehyde **12** by SN_2 reaction at the β-carbon relative to the halogen atom. While the reaction from **10a** afforded a unique α-azido aldehyde **12** of (*S*) configuration (55% overall yield), a mixture of epimers at C-5 (2:1) resulted from ketone **10b**. In the light of earlier contradictory results of the Sakurai reaction on related systems [17], no unambiguous interpretation can be furnished to explain the C-5 stereochemistry of **11**, the unique addition product from **10a**. Transformation of **12** into the known **14b** could be performed in only four steps. Hydrogenolysis of **12** was followed by benzoylation of the intermediate **13a** giving **13b** as a mixture of two anomers (46% overall yield from **12**). Swern oxidation of **13b** led to the lactone **14a** (86%). The structure of the latter was unambiguously established on the basis of a Noesy experiment at 400 MHz (fig 1).



a) (i) 2 equiv LDA, 4 equiv CH_2Cl_2, THF, −78 °C, (ii) 10 equiv NaN_3, 0.1 equiv 15-crown-5,5 equiv DMPU, 70 °C; b) H_2 (3 bar, Pd/C, EtOH; c) 3 equiv BzO_2, MeOH, rt; d) 1.3 equiv $(COCl)_2$, 2.6 equiv DMSO, 5.9 equiv NEt_3, CH_2Cl_2, −78 °C; e) 2 equiv Bu_4NF, THF, 0 °C.

Scheme 3

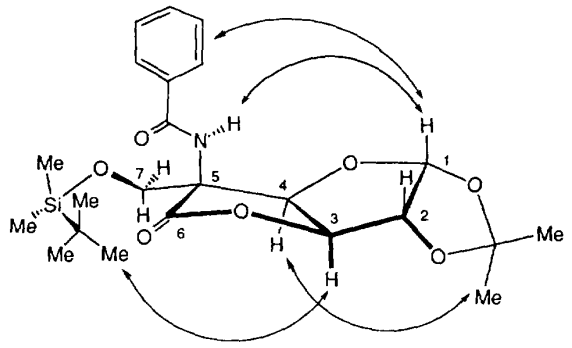


Fig 1

Desilylation of **14a** gave **14b** (97%) whose ^{1}H NMR spectrum exhibited chemical shifts and coupling constants absolutely identical with its reported spectrum [15].

The Indian group described the conversion of **14b** into the aldehyde **15**, transformation of which into myriocin has been described by Banfi et al [14a, 14b]. Our synthetic scheme represents a considerably improved stereoselective formal synthesis of myriocin **16**.

Experimental section

General

All reactions were carried out under argon. Solvents were purified and dried by standard techniques. Thin layer chromatography (TLC) was performed using Merck plates of silica gel 60 with fluorescent indicator. Column chromatography was carried out on the same support. Visualization was effected by spraying plates with 5% H_2SO_4 in ethanol, followed by heating at 120–140 °C. The term 'usual work-up' means CH_2Cl_2 extraction, followed by washing with a saturated NaCl water solution, drying the organic layer over Na_2SO_4, filtration and evaporation under reduced pressure. ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometers (WP 250, WP 300 or WP 400). Chemical shifts are expressed in ppm relative to tetramethylsilane; aromatic ^{13}C NMR shifts are not given. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Mass spectra (MS) were run on an MS50 for the EI mass spectra and on an AEIMS59 for the CI mass spectra.

General method of preparation of α-azido aldehydes from ketones via α,β-epoxy chlorides

To a solution of diisopropylamine (210 μL, 1.50 mmol) in tetrahydrofuran (1 mL) was added at −78 °C a 1.6 M solution of *n*-butyllithium (940 μL, 1.50 mmol) in hexane. After stirring this mixture at −78 °C for 30 min, anhydrous dichloromethane (192 μL, 3 mmol) was added. Further stirring at −78 °C for 30 min was followed by addition of the ketone (0.75 mmol) in tetrahydrofuran (2 mL). The mixture was stirred for an additional 40 min at −78 °C and then the temperature was allowed to rise slowly to room temperature. To the mixture was then added sodium azide (488 mg, 7.5 mmol), 15-crown-5 (14 μL, 0.075 mmol) and *N,N'*-dimethylpropyleneurea (453 μL, 3.75 mmol). The solution was heated to 70 °C and stirring was applied for 12 h. After cooling, addition of water and dilution with CH_2Cl_2, the usual work-up followed.

• *Methyl 3-O-benzyl-3-ene-α-D-glycero-hex-3-eno-pyranosid-2-ulose* **5**

Ketone **4** (196 mg, 0.52 mmol) and chloromethyl *p*-tolylsulfone (114 mg, 0.55 mmol) were dissolved in a mixture of tetrahydrofuran (4 mL) and *t*-butyl alcohol (0.12 mL). After cooling to +5 °C potassium *t*-butoxide (62 mg, 0.55 mmol) was added to the mixture. Stirring was applied at +5 °C for 10 min and then for 4 h at room temperature. The usual work-up gave **5** (60 mg, 43%) as a foam.

R_f = 0.42 with ether.

$[\alpha]_D$ = +36° (*c* = 0.74, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.35 (m, 5H, Ph), 5.83 (d, 1H, $J_{4,5}$ = 2 Hz, H-4), 4.89 (s, 3H, H-1 and OCH_2Ph), 4.75 (m, 1H, H-5), 3.79 and 3.71 (2 dd, 2H, $J_{5,6}$ = 3.8 Hz, $J_{5,6'}$ = 5.7 Hz, J_{gem} = 11.5 Hz, H-6,6'), 3.54 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$, 62.91 MHz): δ 184.3 (C-2), 147.5 (C-3), 116.2 (C-4), 99.5 (C-1), 70.0 (O*C*H_2Ph), 69.8 (C-5), 65.3 (C-6), 57.0 (OMe).

MS (EI): *m/z* 264 (M^+).

Anal calc for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.71, H, 6.03.

• *Methyl 3-azido-2-O-benzyl-4,6-O-benzylidene-3-deoxy-3-C-formyl-β-D-glucopyranoside* **6** *(see general method)*

(52%), foam.

R_f = 0.36 with CH_2Cl_2/heptane 7:3.

$[\alpha]_D$ = −54° (*c* = 0.98, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.81 (s, 1H, CHO), 7.38–7.32 (m, 10H, 2Ph), 5.48 (s, 1H, H-7), 4.98 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.84 and 4.73 (2d, 2H, J_{gem} = 11.2 Hz, OCH_2Ph), 4.40 (dd, 1H, $J_{5,6eq}$ = 4.9 Hz, J_{gem} = 10.2 Hz, H-6eq), 4.07 (td, 1H, $J_{5,6eq}$ = 4.9 Hz, $J_{5,6ax}$ = $J_{4,5}$ = 9.7 Hz, H-5), 3.78 (d, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 3.69 (t, 1H, $J_{5,6ax}$ = J_{gem} = 10.2 Hz, H-6ax), 3.57 (s, 3H, OMe), 3.51 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-2).

^{13}C NMR ($CDCl_3$, 62.91 MHz): δ 196.5 (CHO), 103.2 (C-1), 102.1 (C-7), 82.3 (C-2), 81.9 (C-4), 75.2 (O*C*H_2Ph), 73.0 (C-3), 69.3 (C-6), 64.2 (C-5), 57.5 (OMe).

MS (CI): *m/z* 426 $(M + H)^+$.

Anal calc for $C_{22}H_{23}N_3O_6$: C, 62.10; H, 5.45; N, 9.87. Found: C, 62.25; H, 5.62; N, 9.71.

• *Methyl 3-azido-2-O-benzyl-4,6-O-benzylidene-3-deoxy-3-C-formyl-α-D-glucopyranoside* **7** *(see general method)*

(46%), foam.

R_f = 0.37 with CH_2Cl_2.

$[\alpha]_D$ = −22° (*c* = 1.03, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.0 (s, 1H, CHO), 7.39–7.32 (m, 10H, 2Ph), 5.50 (s, 1H, H-7), 4.80 and 4.62 (2d, 2H, J_{gem} = 12.1 Hz, OCH_2Ph), 4.63 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 4.34 (dd, 1H, $J_{5,6eq}$ = 4.9 Hz, J_{gem} = 10.2 Hz, H-6eq), 4.19 (td, 1H, $J_{5,6eq}$ = 4.9 Hz, $J_{5,6ax}$ = $J_{4,5}$ = 10.2 Hz, H-5), 3.75 (d, 1H, $J_{4,5}$ = 10.2 Hz, H-4), 3.69 (t, 1H, $J_{5,6ax}$ = J_{gem} = 10.2 Hz, H-6ax), 3.65 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-2), 3.42 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$, 62.91 MHz): δ 194.4 (CHO), 102.0 (C-7), 98.2 (C-1), 82.1 (C-4), 80.1 (C-2), 73.8 (O*C*H_2Ph), 73.3 (C-3), 69.5 (C-6), 60.7 (C-5), 56.0 (OMe).

MS (CI): *m/z* 426 $(M + H)^+$.

Anal calc for $C_{22}H_{23}N_3O_6$: C, 62.10; H, 5.45; N, 9.87. Found: C, 61.87; H, 5.63; N, 9.61.

• *Methyl 2-azido-3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-C-formyl-β-D-glucopyranoside* **8** *(see general method)*

(50%), foam.

R_f = 0.40 with ether/heptane 1:1.

$[\alpha]_D$ = −119° (c = 1.03, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.74 (s, 1H, CHO), 7.41–7.17 (m, 10H, 2Ph), 5.55 (s, 1H, H-7), 4.73 (s, 2H, OCH_2Ph), 4.46 (s, 1H, H-1), 4.36 (dd, 1H, $J_{5,6eq}$ = 4.9 Hz, J_{gem} = 10.5 Hz, H-6eq), 4.07 (t, 1H, $J_{4,5} = J_{3,4}$ = 9.7 Hz, H-4), 3.82 (t, 1H, $J_{5,6ax} = J_{gem}$ = 10.2 Hz, H-6ax), 3.71 (d, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 3.49 (td, 1H, $J_{5,6eq}$ = 4.9 Hz, $J_{5,6ax} = J_{4,5}$ = 10.0 Hz, H-5), 3.46 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$, 75.49 MHz): δ 193.9 (CHO), 105.2 (C-1), 101.7 (C-7), 80.7 (C-3), 80.1 (C-4), 75.1 (C-2), 75.0 (OCH_2Ph), 68.5 (C-6), 66.9 (C-5), 57.9 (OMe).

MS (CI): m/z 426 $(M + H)^+$.

Anal calc for $C_{22}H_{23}N_3O_6$: C, 62.10; H, 5.45; N, 9.87. Found: C, 62.37; H, 5.68; N, 9.62.

• *Methyl 2-azido-3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-C-formyl-α-D-mannopyranoside* **9** *(see general method)*

(54%), foam.

R_f = 0.31 with ether/heptane 1:2.

$[\alpha]_D$ = +43° (c = 0.95, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.23 (s, 1H, CHO), 7.50–7.25 (m, 10H, 2Ph), 5.66 (s, 1H, H-7), 4.94 and 4.71 (2d, 2H, J_{gem} = 11.8 Hz, OCH_2Ph), 4.53 (d, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 4.49 (s, 1H, H-1), 4.29 (m, 1H, H-6eq), 4.22 (t, 1H, $J_{4,5} = J_{3,4}$ = 9.2 Hz, H-4), 3.93–3.85 (m, 2H, H-5, H-6ax), 3.33 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$, 62.91 MHz): δ 196.0 (CHO), 101.8 (C-7), 101.1 (C-1), 80.5 (C-4), 74.8 and 74.6 (C-3 and OCH_2Ph), 73.9 (C-2), 68.6 (C-6), 63.8 (C-5), 55.4 (OMe).

MS (CI): m/z 426 $(M + H)^+$.

Anal calc for $C_{22}H_{23}N_3O_6$: C, 62.10; H, 5.45; N, 9.87. Found: C, 61.93; H, 5.38; N, 9.73.

• *5-Azido-3-O-benzyl-6-O-(*tert*-butyldimethylsilyl)-5-deoxy-5-C-formyl-1,2-O-isopropylidene-β-L-ido-furanose* **12**

To a solution of diisopropylamine (666 μL, 4.75 mmol) in tetrahydrofuran (3 mL) was added at −78 °C a 1.6 M solution of n-butyllithium (3 mL, 4.75 mmol) in hexane. After stirring this mixture at −78 °C for 30 min, anhydrous dichloromethane (610 μL, 9.50 mmol) was added. Further stirring at −78 °C for 30 min was followed by addition to the mixture of the ketone **10a** (1.003 g, 2.37 mmol) in tetrahydrofuran (5 mL). The mixture was stirred for an additional 90 min at −78 °C and then the temperature was allowed to rise slowly to room temperature. To the mixture was then added sodium azide (1.54 mg, 23.76 mmol), 15-crown-5 (47 μL, 0.23 mmol) and N,N'-dimethylpropyleneurea (1.4 mL, 11.88 mmol). The solution was heated to 70 °C and stirring was applied for 12 h. After cooling, addition of water and dilution with CH_2Cl_2 was followed by the usual work-up. After purification by flash chromatography, **12** (623 mg, 55%) was obtained as a foam.

R_f = 0.42 with heptane/ethyl acetate 8:2.

$[\alpha]_D$ = −25° (c = 1.03, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.60 (s, 1H, CHO), 7.42–7.28 (m, 5H, Ph), 6.00 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.66 and 4.45 (2d, 2H, J_{gem} = 11.7 Hz, OCH_2Ph), 4.64 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-2), 4.49 and 4.05 (2d, 2H, $J_{3,4}$ = 3.8 Hz, H-3 and H-4), 4.07 and 3.90 (2d, 2H, J_{gem} = 10.8 Hz, H-6, 6′), 1.47 and 1.34 [2s, 6H, $C(CH_3)_2$] 0.86 [s, 9H, $SiC(CH_3)_3$], 0.03 and 0.01 [2s, 6H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$, 62.91 MHz): δ 196.7 (CHO), 112.5 [$C(CH_3)_2$], 105,1 (C-1), 82.1, 82.1 and 81.0 (C-2, C-3 and C-4), 72.3 (OCH_2Ph), 71.6 (C-5), 64.2 (C-6), 27.0 and 26.6 [$C(CH_3)_2$], 25.7 [$SiC(CH_3)_3$], 18.1 [$SiC(CH_3)_3$], −5.6 [$Si(CH_3)_2$].

MS (CI): m/z 478 $(M + H)^+$.

Anal calc for $C_{23}H_{35}O_6N_3Si$: C, 57.84; H, 7.39; N, 8.80; Si, 5.88. Found: C, 57.59; H, 7.45; N, 8.71; Si, 6.12.

• *5-Benzamido-5-C-[(*tert*-butyldimethylsilyl)oxymethyl]-5-deoxy-1,2-O-isopropylidene-β-L-ido-furanose, 3,6-hemiacetal* **13b**

A solution of **12** (580 mg, 1.21 mmol) in ethanol (20 mL) was stirred for 17 h in a hydrogen atmosphere (3 bars) in the presence of Pd/C (60 mg, 10%). After filtration and evaporation, the residue was dissolved in methanol (6 mL) and the solution cooled to 0 °C before the addition of benzoic anhydride (825 mg, 3.64 mmol). The mixture was stirred at room temperature for 48 h, then neutralized with sodium hydrogenocarbonate and the solution concentrated. The usual work-up gave **13b** as a mixture of isomers (260 mg, 46%) as a foam.

R_f = 0.21 with heptane/ethyl acetate 7:3.

Chemical shifts are given only for the major isomer:

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77–7.38 (m, 5H, Ph), 6.91 (s, 1H, NH), 6.04 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 5.53 (s, 1H, H-6), 5.08 and 4.75 (2m, 3H, H-2, H-3, H-4), 4.26 and 3.63 (2d, 2H, J_{gem} = 10.5 Hz, H-7, 7′), 1.53 and 1.36 [2s, 6H, $C(CH_3)_2$], 0.86 [s, 9H, $SiC(CH_3)_3$], 0.01 [2s, 6H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$, 75.49 MHz): δ 168.2 (NHCOPh), 113.5 [$C(CH_3)_2$], 107.0 (C-1), 98.8 (C-6), 86.7, 84.2 and 82.5 (C-2, C-3 and C-4), 68.4 (C-5), 61.6 (C-7), 27.7 and 27.0 [$C(CH_3)_2$], 25.8 [$SiC(CH_3)_3$], 18.3 [$SiC(CH_3)_3$], −5.3 [$Si(CH_3)_2$].

MS (CI): m/z 466 $(M + H)^+$.

• *5-Benzamido-5-C-[(*tert*-butyldimethylsilyl)oxymethyl]-5-deoxy-1,2-O-isopropylidene-β-L-ido-furanose, 3,6-lactone* **14a**

A solution of dichloromethane (1.2 mL) containing DMSO (91 μL, 1.27 mmol) was added at −78 °C to a solution of dichloromethane (1.2 mL) containing oxalyl chloride (56 μL, 0.63 mmol) and the mixture was stirred for 10 min at −78 °C. Then, a solution of lactol **13** (228 mg, 0.49 mmol) in dichloromethane (1.5 mL) was added drop by drop. Stirring was continued for 30 min at −78 °C and then triethylamine (406 μL, 2.89 mmol) was added and the stirring maintained for another 90 min. The temperature was then allowed to rise slowly and after dilution with CH_2Cl_2 and addition of water the usual work-up followed giving **14a** (195 mg, 86%) as a foam.

R_f = 0.34 with heptane/ethyl acetate 7:3.

$[\alpha]_D$ = +32° (c = 0.72, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.80–7.42 (m, 5H, Ph), 6.47 (s, 1H, NH), 5.90 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.34 (d, 1H, $J_{3,4}$ = 3.8 Hz, H-4), 5.02 (d, 1H, $J_{3,4}$ = 3.8 Hz, H-3), 4.86 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-2), 4.43 and 3.86 (2d, 2H, J_{gem} = 9.4 Hz, H-7, 7′), 1.53 and 1.34 [2s, 6H, $C(CH_3)_2$] 0.90 [s, 9H, $SiC(CH_3)_3$], 0.10 and 0.08 [2s, 6H, $Si(CH_3)_2$].

^{13}C NMR ($CDCl_3$, 62.91 MHz): δ 174.9 (C-6), 167.0 (NH*C*OPh), 113.2 [*C*$(CH_3)_2$], 106.3 (C-1), 85.0, 83.3 and 81.5 (C-2, C-3 and C-4), 65.5 (C-5), 65.1 (C-7), 27.3 and 26.9 [C(*C*$H_3)_2$], 25.8 [SiC(*C*$H_3)_3$], 18.3 [Si*C*$(CH_3)_3$], −5.5 [Si(*C*$H_3)_2$].

MS (CI): m/z 464 $(M + H)^+$.

Anal calc for $C_{23}H_{33}NO_7Si$: C, 59.59; H, 7.18; N, 3.02; Si, 6.06. Found: C, 60.13; H, 7.27; N, 3.18; Si, 6.09.

• *5-Benzamido-5-C-(hydroxymethyl)-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose, 3,6-lactone* **14b** *[18]*

To a solution of **14a** (112 mg, 0.24 mmol) in tetrahydrofuran (2 mL) was added at 0 °C a 1M solution of tetrabutylammonium fluoride (485 μL, 0.48 mmol) in tetrahydrofuran and the mixture was stirred at 0 °C for 10 min. After dilution with water and the usual work-up **14b** (82 mg, 97%) was obtained as a foam.

R_f = 0.16 with heptane/ethyl acetate 1:1.

$[\alpha]_D$ = +33° (c = 1.0, $CHCl_3$); $[\alpha]_D$ lit = +19° (c = 0.3, $CHCl_3$) [15].

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79–7.38 (m, 5H, Ph), 6.79 (s, 1H, NH), 5.92 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.27 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-4), 5.07 (d, 1H, $J_{3,4}$ = 3.6 Hz, H-4), 4.86 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-2), 4.43 (bs, 1H, OH), 4.15 and 3.91 (2d, 2H, J_{gem} = 11.4 Hz, H-7, 7′), 1.50 and 1.33 [2s, 6H, C$(CH_3)_2$].

^{13}C NMR ($CDCl_3$, 50.33 MHz): δ 173.6 (C-6), 168.5 (NH*C*OPh), 113.5 [*C*$(CH_3)_2$], 106.6 (C-1), 83.9 (C-3), 83.2 (C-2), 80.3 (C-4), 66.4 (C-5), 64.2 (C-7), 27.1 and 26.7 [C(*C*$H_3)_2$].

MS (CI): m/z 350 $(M + H)^+$.

Anal calc for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.58; H, 5.43; N, 3.94.

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18 The discrepancy between our value and the reported $[\alpha]_D$ value for **14b** is due to a less precise measurement at lower concentration. The ^{1}H-^{1}H NMR Noesy experiment on **14a** revealed a reversed signal assignment for H-3 and H-4 relative to the signal attribution proposed earlier [15]. For carbon numbering, see figure 1.