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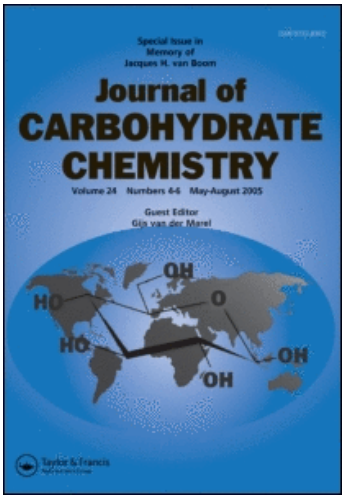

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José A. Serrano[a]; M. Jiménez[a]; Emilio Román[a]
[a] Departamento de Química Orgánica, Universidad de Extremadura, Badajoz, Spain

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PREPARATION OF NEW NUCLEOSIDE ANALOGUES FROM 3,6-ANHYDROSUGARS[1]

José A. Serrano, M. Jiménez, and Emilio Román*

Departamento de Química Orgánica, Universidad de Extremadura
06071 Badajoz (Spain)

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ABSTRACT

2-(3,6-Anhydro-2-deoxy-α-D-glucofuranosylamino)pyridine (**2α**), 1-*N*,3-*N*-(*o*-phenylene)-2-deoxy-α-D-allofuranosylamine (**4**) and 2-(2,5-anhydro-1-deoxy-D-*arabino*-pentitol-1-yl)benzimidazole (**8**) were synthesized by reaction of 2-aminopyridine or *o*-phenylenediamine with 3,6-anhydro-2-deoxy-D-glucose. Formation of compound (**4**) is explained through a Michael-type addition of the *o*-phenylenediamine on the intermediate α,β-unsaturated carbohydrate aldehyde (**7**).

INTRODUCTION

The synthesis of nucleoside analogues has received great attention due to their use as therapeutic agents, especially as antiviral and antitumoral agents. In particular, 2′,3′-dideoxy nucleosides are among the most potent and selective compounds for the treatment of acquired immunodeficiency syndrome (AIDS).[2-5] One of the routes to prepare this class of compounds is based on a Michael-type addition of nucleophiles to either *in situ* generated or preformed α,β-unsaturated carbohydrate aldehydes; thus, in early studies, J. A. Carbon[6] reported on the addition of purine to 2-deoxy-D-*erythro*-

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pentose to yield 2,3-dideoxy-3-(9-purinyl)-D-*erythro-* (and *threo-*)pentoses. More recently, extensive studies on this subject with several nucleobases have been performed, mainly by Danish researchers.[4,7] Furthermore, 1,2-dinucleophiles (such as diamino-compounds, aminophenols, aminothiols, etc.) have been used in a similar way in additions on α,β-unsaturated lactones or lactams.[8-11]

In a previous work,[12] we reinvestigated on the preparation of 3,6-anhydro-2-deoxy-D-glucose (isoglucal, **1**), through intramolecular cyclization of (2*E*)-4,6-di-*O*-acetyl-2,3-didehydro-*aldehydo*-D-*erythro*-hex-2-enose, easily available in just one step by mercuric salt catalyzed hydrolysis of tri-*O*-acetyl-D-glucal.[13] In connection with this investigation, we describe now in full the preparation of new nucleoside analogues, by reaction of 2-aminopyridine or *o*-phenylenediamine with 3,6-anhydro-2-deoxy-D-glucose.

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RESULTS AND DISCUSSION

Reaction of 3,6-anhydro-2-deoxy-D-glucose (**1**) with 2-aminopyridine in methanol at reflux for 24 h yielded 2-(3,6-anhydro-2-deoxy-α-D-glucofuranosylamino)pyridine (**2**α) as the only crystalline product. On dissolution in dimethyl sulfoxide at room temperature, compound **2**α reached equilibration (^{1}H NMR), after 140 h, with its β-anomer (**2**β) (**2**α: **2**β ratio 4.8:1.0). Acetylation of **2**α with pyridine/acetic anhydride afforded the corresponding monoacetate **3**α, which equilibrated in chloroform solution at room temperature after 96 h (**3**α:**3**β ratio 1.0:1.2). Assignment of anomeric configurations are based on the values of the coupling constants $J_{1,2a}$ and $J_{2a,3}$ (≈ 0 Hz) observed for **3**β, indicative of a *trans*-relationship for H-1, H-2a, and H-3.[14,15] Furthermore, it is noteworthy that in the ^{1}H NMR spectrum of the anomer **3**β (not isolated) was observed an "abnormal" upfield shift (1.42 ppm) of its *O*-acetyloxy methyl group at C-5, possibly due[16] to its proximity with the shielding aromatic region of the pyridine nucleus (thus also supporting the assigned β-anomeric configuration). On the other hand, the fact that the optical rotations for **2**α (or its acetate **3**α) have values more

positive than their respective α/β-equilibration mixtures is in agreement with the assigned anomeric configurations, according to Hudson's Isorotation Rules.[17,18]

Treatment of 3,6-anhydro-2-deoxy-D-glucose (**1**) with *o*-phenylenediamine yielded 1-*N*,3-*N*-(*o*-phenylene)-2-deoxy-α-D-allofuranosylamine (**4**) and the benzimidazole derivative (**8**); the former crystallized spontaneously from the reaction mixture, whereas the second was isolated from the mother liquor by column chromatography. The ^{1}H NMR spectrum of compound **4** (as well as those of its di- and tri-*O*-acetyl derivatives **5** and **6**) showed coupling constants $J_{1,2b}$, $J_{2b,3}$, and $J_{3,4}$ with values of *ca.* 0 Hz, thus demonstrating[14,15] a *trans*-relationship between H-1, H-2b, H-3, and H-4. These results indicate that the configuration at the anomeric center is α and that both nitrogen atoms are *cis*-connected to the furanoid ring. The presence of the *N*-acetyl group on C-3 in compound **6** is supported by the downfield shift (*ca.* 1.4 ppm) of H-3, compared to H-3 of **4** and **5**.

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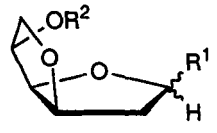

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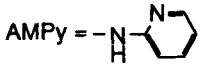
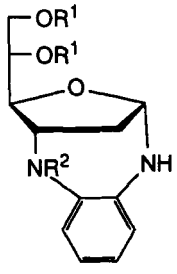
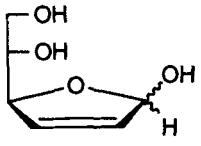
2α, 2β: R^1 = AMPy, R^2 = H
3α, 3β: R^1 = AMPy, R^2 = Ac





4; R^1 = R^2 = H
5; R^1 = Ac, R^2 = H
6; R^1 = R^2 = Ac



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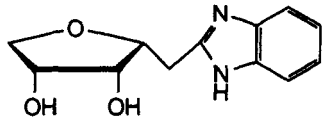

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The formation of the new 2,3-dideoxy nucleoside analogue **4** can be explained through a Michael-type addition of the *o*-phenylenediamine,[19] as a 1,2-dinucleophile, on the unisolated intermediate α,β-unsaturated carbohydrate aldehyde **7** (whose formation may be promoted by the amine). This mechanism is similar to that proposed by Allevi *et al*,[20] for the anomerization of α-*C*-glucosidic ketones by treatment with potassium

carbonate or other bases. However, as far as we are aware, there are no antecedents about a similar process on 3,6-anhydro-2-deoxy-sugars.

Compounds **2α** and **4** were evaluated at the National Cancer Institute (Bethesda, Maryland) for in vitro anti-cancer and anti-HIV screening programs but did not show significant activity.

EXPERIMENTAL

General Procedures. Solvents were evaporated under reduced pressure below 40 °C bath temperature. Melting points were determined with an Electrothermal 8100 apparatus and are uncorrected. Optical rotations were obtained at 20±2 °C with a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded in the range 4000-600 cm^{-1} with a Perkin-Elmer 399 or Midac FT-IR spectrophotometers. NMR spectra were recorded at 20 °C on Bruker spectrometers AM 400 or AC 200 (400 MHz and 200 MHz for ^1H, 100.6 and 50.3 MHz for ^{13}C) with tetramethylsilane and deuteriochloroform as internal references. NMR assignments were confirmed by homo- and heteronuclear double-resonance experiments, and DEPT. TLC was performed on precoated plates of silica gel 60 GF_{254} (Merck), with visualisation of spots by UV light or iodine vapour, and the solvent systems specified. Column chromatography was performed in the flash mode using silica gel 60 (particle size 0.2-0.063 mm, Merck). FAB mass spectroscopic analyses were performed with a VG Autospec mass spectrometer. Elemental analyses were determined by the Servicio de Microanálisis, CSIC, Barcelona.

2-(3,6-Anhydro-2-deoxy-α-D-glucofuranosylamino)pyridine (2α). To a solution of 3,6-anhydro-2-deoxy-D-glucose[12] (**1**; 3.95 g, 27.05 mmol) in methanol (160 mL) was added 2-aminopyridine (2.55 g, 27.13 mmol), and the mixture was refluxed for 24 h. Evaporation of the solvent yielded an oil that was crystallized from ethyl acetate-diethyl ether, affording **2α** as a white solid (2.9 g, 48%), mp 92-94 °C, R_F 0.42 (solvent ethyl acetate-ethanol, 6:1), $[\alpha]_D$ +150° (*c* 0.60, dimethyl sulfoxide); ν_{max} (KBr)/cm^{-1} 3290 (NH, OH), 1605 and 1575 (C=C); δ_H (DMSO-d_6) 8.01 (1 H, d, $J_{5Ar,6Ar}$ = 4.2 Hz, H-6Ar), 7.46 (1 H, td, $J_{4Ar,5Ar} = J_{3Ar,4Ar}$ = 7.8 Hz, $J_{4Ar,6Ar}$ = 1.5 Hz, H-4Ar), 7.16 (1 H, d, $J_{1,NH}$ = 9.3 Hz, D_2O exchangeable NH), 6.60 (2 H, m, H-3Ar

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and H-5Ar), 5.85 (1 H, ddd, $J_{1,2a}$ = 5.0 Hz, $J_{1,2b}$ = 7.7 Hz, H-1), 4.71 (1 H, d, $J_{H,OH}$ = 6.0 Hz, D_2O exchangeable OH), 4.58 (1 H, t, $J_{2b,3} = J_{3,4}$ = 4.4 Hz, H-3), 4.37 (1 H, t, $J_{4,5}$ = 4.8 Hz, H-4), 4.04 (1 H, m, H-5), 3.68 (1 H, dd, $J_{5,6a}$ = 6.4 Hz, $J_{6a,6b}$ = 8.3 Hz, H-6a), 3.48 (1 H, t, $J_{5,6b}$ = 7.7 Hz, H-6b), 2.14 (1 H, dd, $J_{2a,2b}$ = 12.9 Hz, H-2a) and 2.02 (1 H, ddd, H-2b); δ_C (DMSO-d_6) 157.7 (C-2Ar), 147.6 (C-6Ar), 137.2 (C-4Ar), 113.4 (C-5Ar), 108.3 (C-3Ar), 84.1 (C-1), 81.3, 80.6 (C-3,4), 71.9 (C-5), 71.3 (C-6) and 39.4 (C-2).

On standing in dimethyl sulfoxide for 140 h at room temperature, anomeric equilibration was reached between α- and β-anomers (**2α** and **2β**, 4.8:1.0 ratio); $[\alpha]_D$ +104° (*c* 0.60, dimethyl sulfoxide). The following NMR signals for **2β** could be observed from the mixture; δ_H (DMSO-d_6) 7.09 (1 H, d, $J_{1,NH}$ = 9.3 Hz, D_2O exchangeable NH), 5.75 (1 H, ddd, H-1), 4.63 (1 H, d, $J_{H,OH}$ = 6.1 Hz, D_2O exchangeable OH), 4.20 (1 H, t, $J_{4,5}$ = 4.8 Hz, H-4), 2.40 (1 H, m, $J_{2a,2b}$ = 13.7 Hz, $J_{1,2b} = J_{2b,3}$ = 6.8 Hz, H-2b) and 1.86 (1 H, ddd, $J_{1,2a}$ = 7.1 Hz, $J_{2a,3}$ = 3.5 Hz, H-2a); δ_C (DMSO-d_6) 157.6 (C-2Ar), 147.5 (C-6Ar), 108.6 (C-3Ar), 84.0 (C-1), 81.7, 80.6 (C-3,4), 71.5 (C-6), 70.2 (C-5) and 39.0 (C-2).

2-(5-*O*-Acetyl-3,6-anhydro-2-deoxy-α-D-glucofuranosylamino)pyridine (3α). Compound **2α** (0.2 g, 0.9 mmol) was acetylated (Ac_2O/Py) to give **2α** as a syrup, that crystallized from diethyl ether:petroleum ether (1:1). Yield: 0.19 g (80%), mp 117-119 °C, R_F 0.14 (solvent ethyl acetate-hexane, 2:1), $[\alpha]_D$ +188° (*c* 0.45, chloroform); ν_{max} (KBr)/cm^{-1} 3340 (NH), 1715 (C=O ester), 1590, 1565 (C=C), 1240 and 1030 (C-O-C); δ_H ($CDCl_3$) 8.09 (1 H, dd, $J_{5Ar,6Ar}$ = 5.0 Hz, $J_{3Ar,6Ar}$ = 1.2 Hz, H-6Ar), 7.46 (1 H, td, $J_{4Ar,5Ar} = J_{3Ar,4Ar}$ = 7.8 Hz, $J_{4Ar,6Ar}$ = 1.8 Hz, H-4Ar), 6.69 (1 H, m, H-5Ar), 6.58 (1 H, d, H-3Ar), 5.87 (1 H, td, $J_{1,NH} = J_{1,2b}$ = 9.6 Hz, $J_{1,2a}$ = 4.8 Hz, H-1), 5.15 (1 H, m, H-5), 5.11 (1 H, br d, D_2O exchangeable NH), 4.83 (1 H, t, $J_{4,5}$ = 5.4 Hz, H-4), 4.57 (1 H, t, $J_{2b,3} = J_{3,4}$ = 5.4 Hz, H-3), 3.97 (1 H, dd, $J_{5,6a}$ = 3.6 Hz, $J_{6a,6b}$ = 10.4 Hz, H-6a), 3.82 (1 H, dd, $J_{5,6b}$ = 5.2 Hz, H-6b), 2.42 (1 H, dd, $J_{2a,2b}$ = 13.7 Hz, H-2a), 1.86 (1 H, ddd, H-2b) and 2.22 (3 H, s, OAc); δ_C ($CDCl_3$) 170.4 ($OCOCH_3$), 157.1 (C-2Ar), 148.0 (C-6Ar), 137.5 (C-4Ar), 114.8 (C-5Ar), 107.9 (C-3Ar), 84.8 (C-1), 81.5 (C-3), 79.9 (C-4), 73.9 (C-5), 70.8 (C-6), 39.5 (C-2) and 20.7 ($OCOCH_3$).

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Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.16; H, 6.10; N, 10.58.

On standing in chloroform for 96 h at room temperature, anomeric equilibration was reached between α- and β-anomers (**3**α and **3**β, 1.0:1.2 ratio); $[\alpha]_D$ +72° (*c* 0.45, chloroform). The following NMR signals for **3**β could be observed from the mixture; δ_H ($CDCl_3$) 8.13 (1 H, dd, $J_{5Ar,6Ar}$ = 5.0 Hz, $J_{3Ar,6Ar}$ = 1.2 Hz, H-6Ar), 6.61 (1 H, d, H-3Ar), 5.90 (1 H, dd, $J_{1,NH}$ = 10.6 Hz, $J_{1,2b}$ = 6.7 Hz, H-1), 5.82 (1 H, br d, D_2O exchangeable NH), 5.06 (1 H, td, $J_{5,6a}$ = 2.1 Hz, H-5), 4.78 (1 H, t, $J_{4,5}$ = 5.7 Hz, H-4), 4.53 (1 H, t, $J_{2b,3} = J_{3,4}$ = 4.7 Hz, H-3), 4.12 (1 H, dd, $J_{6a,6b}$ = 10.7 Hz, H-6a), 3.80 (1 H, dd, $J_{5,6b}$ = 5.2 Hz, H-6b), 2.33 (1 H, ddd, H-2b), 2.25 (1 H, br d, $J_{2a,2b}$ = 14.1 Hz, H-2a) and 1.42 (3 H, s, OAc); δ_C ($CDCl_3$) 170.5 ($OCOCH_3$), 157.4 (C-2Ar), 148.2 (C-6Ar), 114.3 (C-5Ar), 107.6 (C-3Ar), 84.8, 84.4, 82.5 (C-1,3,4), 74.0 (C-5), 72.2 (C-6), 38.0 (C-2) and 19.5 ($OCOCH_3$).

1-*N*,3-*N*-(*o*-phenylene)-2-deoxy-α-D-allofuranosylamine (4) and 2-(2,5-Anhydro-1-deoxy-D-*arabino*-pentitol-1-yl)benzimidazole (8). To a solution of 3,6-anhydro-2-deoxy-D-glucose[12] (**1**; 0.2 g, 1.37 mmol) in methanol (8 mL) was added *o*-phenylenediamine (0.148 g, 1.37 mmol). On refluxing the reaction mixture for 24 h, the title compound (**4**) precipitated as a white solid, that was filtered and washed with methanol. Yield: 0.1 g (31%), mp 192-194 °C (dec.), R_F 0.47 (solvent ethyl acetate-ethanol, 6:1), $[\alpha]_D$ +3.5° (*c* 0.45, dimethyl sulfoxide); ν_{max} (KBr)/cm^{-1} 3430, 3230 (NH, OH), 1600 and 1506 (C=C); δ_H (DMSO-d_6) 6.66 (2 H, m, 2H-Ar), 6.47 (2 H, m, 2H-Ar), 6.29 (1 H, d, D_2O exchangeable anomeric NH), 5.84 (1 H, d, D_2O exchangeable 3-NH), 5.16 (1 H, t, $J_{1,2a}$ = 6.2 Hz, $J_{1,NH}$ = 6.1 Hz, H-1), 4.72 (1 H, d, $J_{5,OH}$ = 5.1 Hz, D_2O exchangeable 5-OH), 4.33 (1 H, t, D_2O exchangeable 6-OH), 3.96 (1 H, t, $J_{3,NH}$ = 6.0 Hz, H-3), 3.47 (1 H, ddd, $J_{6a,6b}$ = 9.7 Hz, $J_{5,6a}$ = 3.6 Hz, $J_{6a,OH}$ = 5.7 Hz, H-6a), 3.29 (1 H, m, H-6b), 3.26 (1 H, m, $J_{4,5}$ = 7.8 Hz, H-4), 3.13 (1 H, td, H-5), 2.28 (1 H, m, $J_{2a,3}$ = 6.3 Hz, H-2a) and 1.41 (1 H, d, $J_{2a,2b}$ = 11.9 Hz, H-2b); δ_C (DMSO-d_6) 134.4, 132.4 (C-1Ar and C-2Ar), 119.2, 118.9, 118.4, 117.4 (C-3Ar, C-4Ar, C-5Ar, and C-6Ar), 85.1 (C-1), 82.3 (C-4), 72.7 (C-5), 63.2 (C-6), 52.8 (C-3) and 41.5 (C-2).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.90; N, 11.85. Found: C, 60.93; H, 6.91; N, 11.76.

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Column chromatography (solvent ethyl acetate:ethanol, 6:1) of the mother liquor of **4** afforded the benzimidazole derivative **8** as a colorless oil (0.041 g, 13%), R_F 0.32, $[\alpha]_D$ +41° (*c* 0.54, methanol); ν_{max} (film)/cm^{-1} 3300 (NH, OH), 1610 and 1525 (C=C); δ_H (DMSO-d_6) 7.45 (2 H, m, H-4Ar and H-7Ar), 7.07 (2 H, m, H-5Ar and H-6Ar), 4.74 (1 H, m, D_2O exchangeable NH), 4.03 (1 H, m, H-2'), 4.00 (1 H, m, H-4'), 3.91 (1 H, dd, $J_{4',5'}$ = 4.9 Hz, $J_{5',5''}$ = 9.2 Hz, H-5'), 3.76 (1 H, dd, $J_{2',3'}$ = 5.1 Hz, $J_{3',4'}$ = 6.8 Hz, H-3'), 3.53 (1 H, dd, $J_{4',5''}$ = 3.2 Hz, H-5"), 3.40 (2 H, m, D_2O exchangeable 3'-OH and 4'-OH), 3.11 (1 H, dd, $J_{1',1''}$ = 14.8 Hz, $J_{1',2'}$ = 5.1 Hz, H-1') and 2.93 (1 H, dd, $J_{1'',2'}$ = 7.4 Hz, H-1"); δ_C (DMSO-d_6) 152.7 (C-2Ar), 142.2, 139.4 (C-3aAr and C-7aAr), 121.9 (C-4Ar, C-5Ar, C-6Ar, and C-7Ar), 79.8 (C-2'), 72.6 (C-5'), 75,4, 70.5 (C-3' and C-4') and 33.3 (C-1'); HRFABMS Calcd for $C_{12}H_{14}N_2O_3$: 234.1003. Found: 235.1080 $[M+H]^+$.

5,6-Di-*O*-acetyl-1-*N*,3-*N*-(*o*-phenylene)-2-deoxy-α-D-allofuranosylamine (5) and 5,6-Di-*O*-acetyl-1-*N*,3-*N*-acetyl-(*o*-phenylene)-2-deoxy-α-D-allofuranosylamine (6). A suspension of compound **4** (0.2 g, 0.85 mmol) in acetic anhydride (1 mL) and pyridine (2 mL) was stirred at room temperature until dissolution (*ca.* 1 h). Then, the mixture was poured onto ice cold water (25 mL) and extracted with chloroform (3 x 25 mL). The organic extracts were washed with water, dried, and concentrated to an oil which was subjected to column chromatography (solvent ethyl acetate-ethanol, 20:1). Fractions of R_F 0.8 were pooled and concentrated, to give oily diacetate **5** (0.054 g, 20%): $[\alpha]_D$ +41° (*c* 0.46, chloroform); ν_{max} (film)/cm^{-1} 3350 (NH), 1720 (C=O), 1590, 1480 (C=C), 1230 and 1030 (C-O-C); δ_H ($CDCl_3$) 6.72 (4 H, m, 4H-Ar), 5.40 (1H, d, $J_{1,2a}$ = 6.6 Hz, H-1), 4.83 (1 H, ddd, H-5), 5.0-4.5 (2 H, m, D_2O exchangeable 1- and 3-NH), 4.48 (1 H, dd, $J_{5,6a}$ = 3.1 Hz, $J_{6a,6b}$ = 12.1 Hz, H-6a), 4.03 (1 H, dd, $J_{5,6b}$ = 5.7 Hz, H-6b), 3.88 (1 H, d, $J_{2a,3}$ = 6.7 Hz, H-3), 3.77 (1 H, d, $J_{4,5}$ = 8.2 Hz, $J_{3,4}$ ≈ 0 Hz, H-4), 2.42 (1 H, m, $J_{2a,2b}$ = 12.8 Hz, H-2a), 1.83 (1 H, d, H-2b), 2.13 (3 H, s, 1 OAc) and 2.04 (3 H, s, 1 OAc); δ_C ($CDCl_3$) 170.6, 170.3 ($OCOCH_3$), 132.5, 131.0 (C-1Ar and C-2Ar), 120.3, 120.2, 119.7, 119.6 (C-3Ar, C-4Ar, C-5Ar, and C-6Ar), 86.5 (C-1), 80.1 (C-4), 71.8 (C-5), 62.6 (C-6), 54.6 (C-3), 40.9 (C-2), 21.0 and 20.8 ($OCOCH_3$); HRFABMS Calcd for $C_{16}H_{20}N_2O_5$: 320.1371. Found: 321.1451 $[M+H]^+$.

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Fractions of R_F 0.6 yielded compound **6** as an oil (0.186 g, 60%): $[\alpha]_D$ -6.5° (*c* 0.6, chloroform); ν_{max} (film)/cm^{-1} 3350 (NH), 1735 (C=O), 1640 (C=O amide), 1590, 1485 (C=C), 1220 and 1040 (C-O-C)); δ_H ($CDCl_3$) 7.17 (2 H, m, 2 H-Ar), 6.93 (1 H, t, J = 7.4 Hz, 1 H-Ar), 6.85 (1 H, d, J = 7.7 Hz, 1 H-Ar), 5.31 (2 H, m, H-1 and H-3), 4.90 (1 H, d, $J_{1,NH}$ = 6.6 Hz, D_2O exchangeable NH), 4.81 (1 H, m, H-5), 4.36 (1 H, dd, $J_{5,6}$ = 2.5 Hz, $J_{6a,6b}$ = 12.5 Hz, H-6a), 3.99 (1 H, dd, $J_{5,6b}$ = 5.6 Hz, H-6b), 3.89 (1 H, d, $J_{4,5}$ = 7.6 Hz, H-4), 2.38 (1 H, m, $J_{2a,2b}$ = 11.6 Hz, $J_{1,2a}$ = $J_{2a,3}$ = 5.3 Hz, H-2a), 1.98 (1 H, d, H-2b), 2.10 (3 H, s, 1 OAc), 2.00 (3 H, s, 1 OAc) and 1.91 (3 H, s, NAc); δ_C ($CDCl_3$) 170.5, 170.0 ($OCOCH_3$), 141.1 (*C*Ar-NH), 130.5, 128.0, 121.3, 120.6 (4 C-Ar), 127.8 (*C*Ar-NAc), 86.7 (C-1), 79.8 (C-4), 70.9 (C-5), 62.5 (C-6), 52.6 (C-3), 40.5 (C-2), 23.7 ($NCOCH_3$), 20.9 and 20.6 ($OCOCH_3$); HRFABMS Calcd for $C_{18}H_{22}N_2O_6$: 362.1477. Found: 363.1578 $[M+H]^+$.

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