SYNTHESIS OF 2-IMINO-3-[1-(β-D-RIBOFURANOSYL)OXO]-1*H*,5*H*-1,5-BENZODIAZEPINE THROUGH CONDENSATION OF *o*-PHENYLENEDIAMINE WITH FORMYLISOXAZOLE GLYCOSIDE

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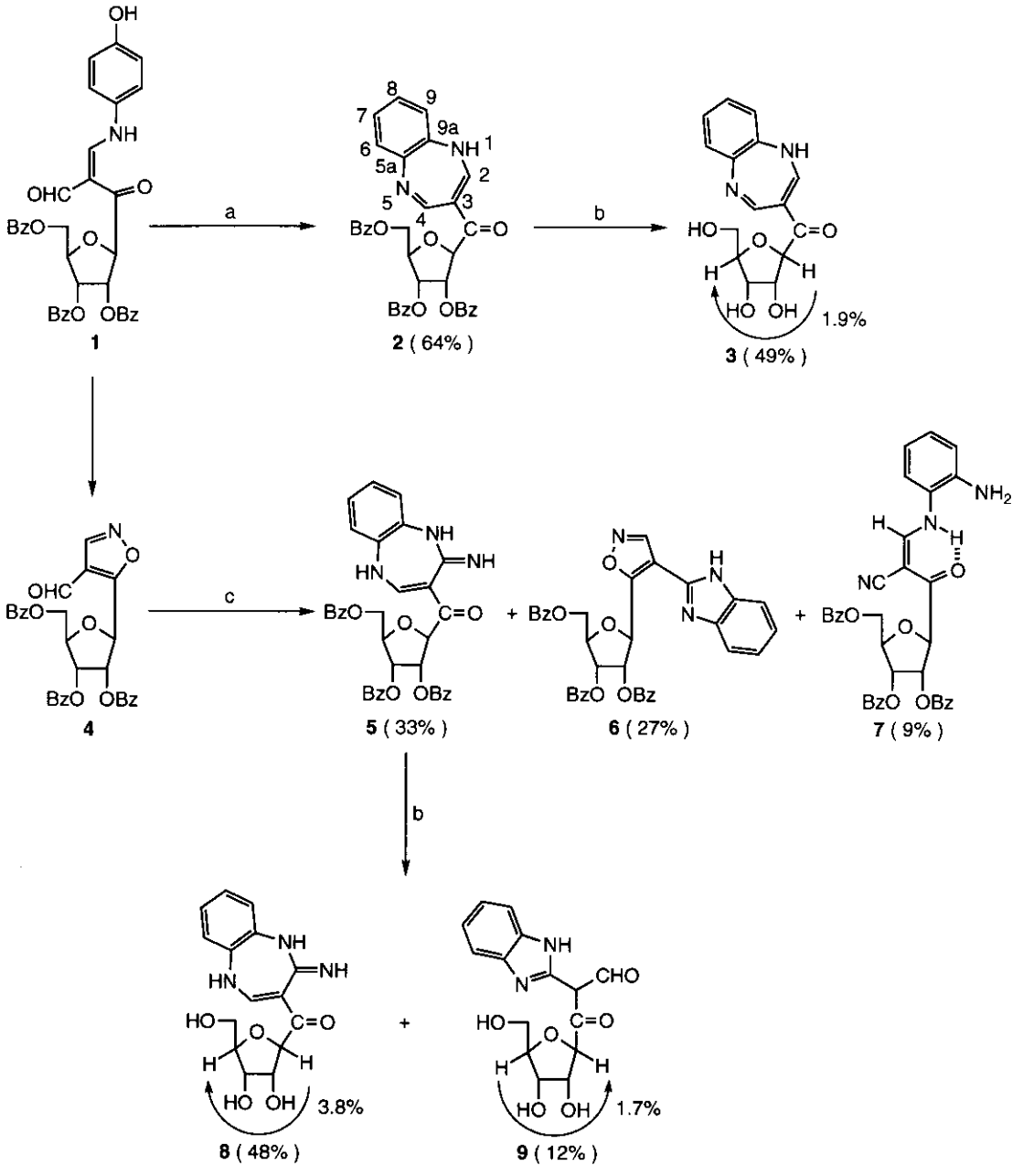
Abstract— The synthesis of 3-[1-(β-D-ribofuranosyl)oxo]-1*H*-1,5-benzodiazepine (**3**) and 2-imino-3-[1-(β-D-ribofuranosyl)oxo]-1*H*,5*H*-1,5-benzodiazepine (**8**) is described. The cyclocondensation of enaminone glycoside (**1**) with *o*-phenylenediamine afforded benzodiazepine (**2**) in 64% yield. The reaction of formylisoxazole (**4**) with *o*-phenylenediamine led to three products, iminobenzodiazepine (**5**), benzimidazole (**6**), and enaminone nitrile (**7**) in 33%, 27%, and 9% yields, respectively. Removal of the sugar protecting groups in **2** and **5** with aqueous sodium carbonate in methanol gave the deprotected *C*-nucleosides (**3** and **8**).

Recently we have reported the syntheses of the 4-[1-(β-D-ribofuranosyl)oxo]-1,3-dihydro-2*H*-1,5-benzodiazepin-2-ones through condensation of 1,2-diaminobenzenes with furanone glycoside.[1] In this paper, we want to describe the novel synthesis of 3-[1-(β-D-ribofuranosyl)oxo]-1*H*-1,5-benzodiazepines through the condensation of the enaminone aldehyde (**1**) and isoxazole aldehyde (**4**) with *o*-phenylenediamine. Compounds (**1** and **4**) can be obtained from enaminone glycoside by our previously published procedure.[2]

Condensation of the enaminone aldehyde (**1**) with o-phenylenediamine in methanol-chloroform (10:1) at room tempetrature for 9 days gave 3-[1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)oxo]-1*H*-1,5-benzodiazepine (**2**) in 64% yield. Higher reaction temperatures gave lower yields. **2** was characterized by the elemental analysis and $^{1}H/^{13}C$ NMR spectra. The ^{1}H NMR spectrum of **2** exhibited signals at δ 14.37 (d, J = 6.6 Hz, NH) and δ 8.82 (d, J = 6.6 Hz, diazepine ring proton). The removal of the sugar protecting groups in compound (**2**) was readily accomplished with

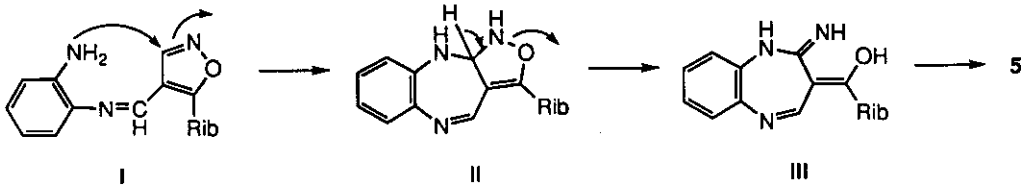
aqueous sodium carbonate to produce benzodiazepine (**3**) in 49% yield. The stereochemistry of the C-1' position in compound (**3**) was confirmed as to be β by NOE experiment (Scheme 1).



Reagents and conditions: a. *o*-phenylenediamine, MeOH/$CHCl_3$, rt, 9 days; b. aq.Na_2CO_3, MeOH, rt, 23 h; c. *o*-phenylenediamine, $CHCl_3$, rt, 3 days.

Scheme 1.

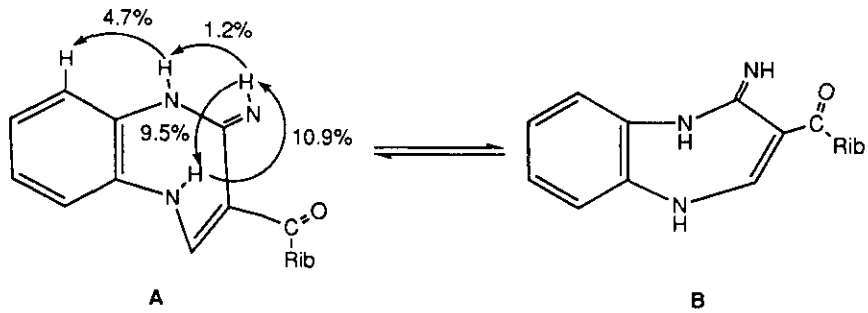
Condensation of isoxazole aldehyde (**4**) with *o*-phenylenediamine in chloroform at room temperature gave 2-imino-3-[1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)oxo]-1*H*,5*H*-1,5-benzodiazepine (**5**) and 4-(2-benzimidazolyl)-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)isoxazole (**6**) in 33% and 27% yields as the major products and small amounts of *Z*-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-(2-amino)anilino-1-oxo-2-propene-2-carbonitrile (**7**) in 9% yield. Structure assignment of **5**, **6**, and **7** was supported by ^{1}H and ^{13}C NMR spectra. In particular, ^{1}H NMR spectrum of **5** showed three NH protons at δ 9.00, 10.97, and 12.39 (disappear on the addition of deuterium oxide). The proton signal on diazepine ring at δ 8.47 (H-4) showed HMBC correlations to the carbon at δ 152 (C-2) and δ 189 (carbonyl). These data indicate the ring system of 1,5-benzodiazepine in **5**. In the ^{1}H NMR spectrum of **7** the signal for olefinic proton appeared at δ 7.82 (d, J=13.3 Hz). The presence of an intramolecular NH chelated proton is clearly observed at δ 12.30 (d, J=13.3 Hz). The IR spectrum of **7** showed an absorption band at 2212 cm^{-1} due to the nitrile group. A plausible explanation for the formation of **5** involves nucleophilic attack by *o*-phenylenediamine on the aldehyde carbon of the isoxazole moiety of **4** with subsequent formation of Schiff's base [**I**] which then undergoes cyclization to tricyclic compound [**II**]. Ring opening of **II** produce benzodiazepine [**III**], which is converted to **5** by hydrogen shift (Scheme 2).



I II III

Scheme 2

Removel of protecting groups in compound (**5**) with aqueous sodium carbonate in methanol was readily accomplished and afforded the benzodiazepine (**8**) and benzimidazole (**9**) in 48% and 12% yields, respectively. From a stereochemical point of view the diazepine ring of **8** can be regarded as a cycloheptadiene system, oscillating between two limiting pseudo-boat conformations, which interconvert through a quasi-planar transition state. In the NOE experiment of **8**, strong NOE correlations were observed between the N_5 proton and imino proton, between N_1 proton and benzene ring proton as shown in Figure 1. These data indicated the preference of conformation (**8 A**). In the ^{1}H NMR spectrum of **9**, the signal corresponding to the methine proton of position 2 was not observed. The missing signal may be attributed to exchange occurring between tautomeric forms.[3] The ring contraction of 1,5-benzodiazepine into benzimidazole under basic condition was reported by Okamoto and Ueda.[4] The stereochemistry of the C-1' position in compounds (**8** and **9**) was confirmed as to be β by NOE experiments (Scheme 1). Thus, the NOE indicates that the β-ribofuranoside configuration has been preserved during the reaction sequence.



A B

Figure 1 *NOE experiment of* ***8***

ACKNOWLEDGEMENT

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EXPERIMENTAL

Fast-atom bombardment MS spectra (FABMS) were run on a JMS-HX 110 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with a JNM-A-400 or an A-600 (JEOL) spectrometer, with tetramethylsilane as an internal standard. Optical rotations were measured with a Jasco DIP-370 polarimeter (10-cm cell) at 25 °C. The IR spectra were measured with a FT/IR-230 (Jasco) spectrophotometer. Analytical TLC was performed on glass plates coated with a 0.5-mm layer of Silica Gel GF_{254} (E. Merck). The compounds were detected by UV light (254 nm).

3-[1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)oxo]-1*H*-1,5-benzodiazepine (2): To a solution of **1** (224.5 mg, 0.36 mmol) in 10:1 MeOH-$CHCl_3$ (20 mL) was added *o*-phenylenediamine (40 mg, 0.36 mmol). The mixture was stirred at rt for 9 days, and then the reaction mixture was evaporated. The residue was purified by PTLC with $CHCl_3$ as eluent. This afforded 108.5 mg (64%) of **2** as an orange yellow solid (from methanol); mp 165-166℃; ^{1}H NMR ($CDCl_3$): δ 4.58 (dd, 1 H, *J* = 4.2, 12.1 Hz, H-5'a), 4.81 (m, 1 H, H-4'), 4.92 (dd, 1 H, *J* = 4.2, 12.1 Hz, H-5'b), 5.35 (d, 1 H, *J* = 2.4 Hz, H-1'), 5.80 (dd, 1 H, *J* = 4.9, 7.1 Hz, H-3'), 6.20 (dd, 1 H, *J* =2.4, 4.9 Hz, H-2'), 7.14-8.08 (m, 19 H, Ph), 8.82 (d, 2 H, *J* = 6.6 Hz, H-2, 4), 14.37 (dd, 1 H, *J* = 6.6 Hz, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$): δ 63.8 (C-5'), 72.7, 74.5, 79.7, 83.1 (C-1', 2', 3', 4'), 107.8 (C-3), 115.9, 126.7, 128.3-133.6 (C-6, 7, 8, 9, 5a, 9a, Ph), 137.0, 151.9 (C-2, C-4), 165.3, 165.6, 166.1, 190.6 (C=O). Anal. Calcd for $C_{36}H_{28}N_2O_8 \cdot 0.5 H_2O$; C, 69.11; H, 4.67; N, 4.48. Found: C, 69.31; H, 4.60; N, 4.61.

3-[1-(β-D-Ribofuranosyl)oxo]-1*H*-1,5-benzodiazepine (3): To a solution of **2** (64.2 mg, 0.105 mmol)

in 2:1 MeOH-$CHCl_3$ (4 mL) was added 10% aq. Na_2CO_3 (0.4 mL). The mixture was stirred at rt for 23 h, and then the reaction mixture was evaporated. The residue was chromatographed on a column of silica gel with 99:1 $CHCl_3$-MeOH as eluent. This afforded 15.6 mg (49%) of **3** as an orange yellow solid (methanol); mp 133-135℃; $[\alpha]_D$ -1.3° (*c* 0.1, Me_2SO); ^1H NMR [$(CD_3)_2SO$]: δ 3.58 (m, 2 H, H-5'), 3.85 (m, 2 H, H-3', 4'), 4.10 (dd, 1 H, *J* = 5.0, 5.0 Hz, H-2'), 5.08 (d, 1 H, *J* = 5.0 Hz, H-1'), 7.24, 7.60 (each m, each 2 H, H-6, 7, 8, 9), 8.90 (d, 2 H, *J* = 6.3 Hz, H-2, 4), 14.90 (dd, 1 H, *J* = 6.3, 6.3 Hz, NH, exchanged with D_2O); ^{13}C NMR [$(CD_3)_2SO$]: δ 61.7 (C-5'), 71.3, 83.0 (C-3', 4'), 74.0 (C-2'), 79.2 (C-1'), 108.0 (C-3), 115.6, 124.2, 126.7, 126.8 (C-6, 7, 8, 9), 136.5, 136.6 (C-5a, 9a), 152.5, 162.0 (C-2, C-4), 194.4 (C=O). Anal. Calcd for $C_{15}H_{16}N_2O_5$; C, 59.21; H, 5.30; N, 9.21. Found: C, 60.06; H, 5.05; N, 9.15.

2-Imino-3-[1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)oxo]-1*H*,5*H*-1,5-benzodiazepine (5), 4-(2-Benzimidazolyl)-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)isoxazole (6) and *E*-1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3-(2-amino)anilino-1-oxo-2-propene-2-carbonitrile (7). To a solution of **4** (131.1 mg, 0.24 mmol) in $CHCl_3$ (10 mL) was added *o*-phenylenediamine (26 mg, 0.24 mmol). The mixture was stirred at rt for 3 days, and then the reaction mixture was evaporated. TLC ($CHCl_3$) showed that the dark yellow syrup contained three major components (R_f 0.25, 0.20, and 0.22). The mixture was separated by PTLC with $CHCl_3$ as eluent.

Compound (5): yellow foam; yield 40.0 mg (33%); R_f 0.25; IR (KBr) 1726 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$]: δ 4.55 (dd, 1 H, *J* = 3.5, 12.3 Hz, H-5'a), 4.63 (dd, 1 H, *J* = 3.5, 12.3 Hz, H-5'b), 4.79 (m, 1 H, H-4'), 5.65 (d, 1 H, *J* = 4.8 Hz, H-1'), 5.83 (dd, 1 H, *J* = 4.8, 4.8 Hz, H-3'), 6.12 (dd, 1 H, *J* = 4.8, 4.8 Hz, H-2'), 7.13-7.99 (m, 19 H, Ph), 8.47 (dd, 1 H, *J* = 7.1, 14.8 Hz, H-4), 9.00 (dd, 1 H, *J* = 7.1, 7.1 Hz, H-5, exchanged with D_2O),10.97 (dd, 1 H, *J* = 7.1, 14.8 Hz, =NH, exchanged with D_2O), 12.39 (s, 1 H, H-1, exchanged with D_2O); ^{13}C NMR [$(CD_3)_2SO$]: δ 63.6 (C-5'), 72.4, 75.4, 78.9, 80.7 (C-1', 2', 3', 4'), 97.8 (C-3), 111.8 (C-9), 116.9 (C-6), 121.1, 121.6 (C-7, 8), 128.6-133.7 (Ph) , 132.1, 141.2 (C-5a, 9a), 151.5 (C-2), 157.6 (C-4), 164.8, 164.8, 165.5, 189.3 (C=O). FABMS (nitrobenzyl alcohol as matrix). Found: $[M + H]^+$ *m/z* 632.2028. Calcd for $C_{36}H_{30}N_3O_8$: [M + H] 632.2033.

Compound (6): colorless foam; yield 32.5 mg (27 %); R_f 0.20; ^1H NMR (CD_3COCD_3): δ 4.77 (dd, 1 H, *J* = 4.0, 12.2 Hz, H-5'a), 4.88 (dd, 1 H, *J* = 4.0, 12.2 Hz, H-5'b), 4.98 (m, 1 H, H-4'), 6.18 (dd, 1 H, *J* = 5.5, 5.5 Hz, H-3'), 6.25 (dd, 1 H, *J* = 5.5, 5.5 Hz, H-2'), 6.58 (d, 1 H, *J* = 5.5 Hz, H-1'), 7.23-8.13 (m, 19 H, imidazole ring, Ph), 9.07 (s, 1 H, H-3), 12.00 (br, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$): δ 63.4 (C-5'), 71.8, 74.6, 76.3, 81.3 (C-1', 2', 3', 4'), 111.3 (C-4), 123.2-134.0 (imidazole ring, Ph), 141.8 (C-2 imidazole), 150.8 (C-3), 163.0 (C-5), 165.3, 165.8, 166.3 (C=O). Due to the unstable nature of this compound, a good elemental analysis could not be obtained.

Compound (7): yellow foam; yield 10.5 mg (9%); R_f 0.22; IR (KBr) 2212 (CN), 1728 (C=O) cm^{-1}; ^1H NMR

($CDCl_3$): δ 3.70 (br, 2 H, NH_2, exchanged with D_2O), 4.63 (dd, 1 H, *J*= 4.3, 11.3 Hz, H-5'a), 4.78 (m, 2 H, H-4', 5'b), 5.34 (d, 1 H, *J*= 4.3 Hz, H-1'), 5.83 (dd, 1 H, *J*= 5.6, 5.6 Hz, H-3'), 5.98 (dd, 1 H, *J*= 4.3, 5.6 Hz, H-2'), 6.86 (m, 2 H, Ph), 7.05 (d,1 H, *J*=7.8 Hz, Ph), 7.13 (dd,1 H, *J*= 7.8, 7.8 Hz, Ph), 7.33-7.58 (m, 9 H, Ph), 7.82 (d, 1 H, *J*= 13.3 Hz, H-3), 7.91-8.10 (m, 6 H, Ph), 12.30 (d, 1 H, *J*= 13.3 Hz, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$): δ 64.0 (C-5'), 72.7, 73.7, 80.3, 82.7 (C-1', 2', 3', 4'), 83.4 (C-2), 118.3 (CN), 118.0, 119.5, 120.3, 125.9, 128.2-138.1 (Ph), 155.4 (C-3), 165.3, 166.2, 193.1 (C=O). FABMS (nitrobenzyl alcohol as matrix). Found: $[M + H]^+$ *m/z* 632.2063. Calcd for $C_{36}H_{30}N_3O_8$: [M + H] 632.2033.

2-Imino-3-[1-(β-D-ribofuranosyl)oxo]-1*H*,5*H*-1,5-benzodiazepine (8) and 2-(β-D-Ribofuranosyl)-oxo-2-formylethane-2-benzimidazole (9): To a solution of **5** (145.5 mg, 0.23 mmol) in 5:1 MeOH-$CHCl_3$ (15 mL) was added 10% aq. Na_2CO_3 (4.5 mL) and $CHCl_3$ (5 mL). The mixture was stirred at rt for 1 day, and then the reaction mixture was evaporated. TLC ($CHCl_3$) showed that the dark yellow syrup contained two major components (R_f 0.22, and 0.31). The mixture was separated by PTLC with 99:1 $CHCl_3$-MeOH as eluent.

Compound (8): yellow solid; yield 35.5 mg (48%); mp 197-199℃ (from methanol); R_f 0.22; $[\alpha]_D$ -80.1° (*c* 0.7, Me_2SO); ^1H NMR [$(CD_3)_2SO$]: δ 3.49 (dd, 1 H, *J*= 3.9, 11.7 Hz, H-5'a), 3.61 (dd, 1 H, *J*= 3.9, 11.7 Hz, H-5'b), 3.92 (m, 2 H, H-3', 4'), 4.17 (dd, 1 H, *J*= 4.7, 4.7 Hz, H-2'), 4.87 (br, 1 H, OH, exchanged with D_2O), 4.91 (d, 1 H, *J*= 4.7 Hz, H-1'), 4.97 (br, 1 H, OH, exchanged with D_2O), 5.22 (br, 1 H, OH, exchanged with D_2O), 7.11 (m, 2 H, Ph), 7.53 (dd, 1 H, *J*= 2.7, 6.3 Hz, Ph), 7.61 (dd, 1 H, *J*= 2.7, 6.3 Hz, Ph), 8.35 (dd, 1 H, *J*= 6.8, 14.6 Hz, H-4), 8.81 (dd, 1 H, *J*= 6.8, 6.8 Hz, H-5, exchanged with D_2O), 10.87 (dd, 1 H, *J*= 6.8, 14.6, =NH, exchanged with D_2O), 12.32 (s, 1 H, H-1, exchanged with D_2O); ^{13}C NMR [$(CD_3)_2SO$]: δ 61.9 (C-5'), 71.6, 74.1, 82.1, 84.7 (C-1', 2', 3', 4'), 98.2 (C-3), 111.7, 116.9, 121.1, 121.2 (C-6, 7, 8, 9), 132.0, 141.2 (C-5a, 9a), 151.8, 156.2 (C-2, 4), 192.8 (C=O). Anal. Calcd for $C_{15}H_{17}N_3O_5 \cdot 0.5\ H_2O$; C, 54.87; H, 5.53; N, 12.80. Found: C, 54.94; H, 5.58; N, 12.34.

Compound (9): colorless foam; yield 9.0 mg (12%); R_f 0.31; $[\alpha]_D$ -68.1° (*c* 0.2, Me_2SO); ^1H NMR [$(CD_3)_2SO$]: δ 3.69 (dd, 1 H, *J*= 3.2, 12.1 Hz, H-5'a), 3.90 (dd, 1 H, *J*= 3.2, 12.1 Hz, H-5'b), 4.05 (m, 1 H, H-4'), 4.16 (dd, 1 H, *J*= 4.9, 4.9 Hz, H-3'), 4.28 (dd, 1 H, *J*= 4.9, 4.9 Hz, H-2'), 4.97 (br, 2 H, OH, exchanged with D_2O), 5.18 (d, 1 H, *J*= 4.9 Hz, H-1'), 5.24 (br, 1 H, OH, exchanged with D_2O), 7.31, 7.73 (each dd, each 2 H, *J*= 3.2, 6.1 Hz, H-4, 5, 6, 7), 9.88 (s, 1 H, CHO), 13.15 (br, 1 H, benzimidazole H-1, exchanged with D_2O); ^{13}C NMR [$(CD_3)_2SO$]: δ 61.8 (C-5'), 71.3, 74.5, 82.5, 84.1 (C-1', 2', 3', 4'), 79.2 (C-2), 99.0, 113.0, 123.6, 128.3, 129.2 (benzimidazole C-4, 5, 6, 7, 8, 9), 148.9 (benzimidazole C-2), 184.5 (CHO), 192.5 (C=O). FABMS (nitrobenzyl alcohol as matrix). Found: $[M + H]^+$ *m/z* 321.1072. Calcd for $C_{15}H_{17}N_2O_6$: [M + H] 321.1087.

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