Notes

Synthesis of β-L-Lyxofuranosyl Benzimidazoles by an Unexpected Intramolecular Displacement Reaction

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Anhydro nucleosides are useful intermediates in a number of reaction pathways. These anhydro bonds are commonly formed between two hydroxyl groups[1,2] or between the heterocyclic moiety of a nucleoside analogue and the 5′-hydroxyl[3,4] or the 2′-hydroxyl[5−10] group. Only a few anhydro nucleosides have been described with the anhydro bridge linking the purine heterocyclic base and the 3′-hydroxyl group of a nucleoside.[11] These 2′-, 3′-, and 5′-anhydro nucleosides were generally formed in the presence of a strong base or a good leaving group on the sugar moiety.[12]

During our previous work with 2,5,6-trichlorobenzimidazole (TCB) derivatives, the 2-position proved to be quite sensitive to nucleophilic attacks.[13,14] On several occasions, our group has reported an intramolecular substitution of the 2-halogen by the 2′-hydroxyl group in the α-ribofuranosyl series.[10,15] As part of our ongoing research effort to establish a SAR for these polyhalogenated benzimidazole nucleosides, we initiated a study designed to prepare the β-L-analogue of the recently reported[14] α-L-lyxofuranosyl analogues. We anticipated some problems with the formation of a 2′,2-anhydro derivative. We were not very concerned with a 3′,2-anhydro derivative since the synthesis of 2,5,6-trichloro-1-(β-L-xylofuranosyl)benzimidazole was accomplished[16] without a displacement of the 2-chloro group by either the 5′-hydroxyl group or the 3′-hydroxyl group. However, we now report an unexpected intramolecular attack of the 3′-hydroxyl group on the 2-chloro- and 2-bromobenzimidazole derivatives in the β-L-lyxofuranosyl series.

The Vorbrüggen type condensation[17] of TCB and 2-bromo-5,6-dichlorobenzimidazole (BDCB) with 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-xylofuranose (**1**)[18] gave 2,5,6-trichloro-1-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-xylofuranosyl)-benzimidazole (**2a**) and 2-bromo-5,6-dichloro-1-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-xylofuranosyl)benzimidazole (**2b**). A selective removal of the 2′-acetyl group with hydrazine hydrate afforded 2,5,6-trichloro-1-(3,5-di-*O*-benzoyl-β-L-xylofuranosyl)benzimidazole (**3a**) and 2-bromo-5,6-dichloro-1-(3,5-di-*O*-benzoyl-β-L-xylofuranosyl)benzimidazole (**3b**). The free 2-hydroxyl group was protected using triflic anhydride to give the proposed unstable intermediates which were hydrolyzed with water (Scheme 1). This type of reaction was first described by Herdewijn for the synthesis of 9-β-D-lyxofuranosyladenine.[19] In our case, with 2-bromo- and 2-chlorobenzimidazoles, two major compounds were revealed on TLC [R_f (system 2): 0.26 and 0.40] after the water hydrolysis. These two compounds were still present after the workup which consisted of an extraction, drying the organic layer over sodium sulfate, filtration, and an evaporation to dryness of the organic layer. However, after silica gel chromatography of the mixture, we obtained almost exclusively one compound (R_f: 0.40), which we assigned the structure of **6**, and a small amount of another compound that we did not identify (one exchangeable proton, probably **4** or **5**, R_f: 0.26). The ratio of these two compounds was 13:1 w/w. Evidence for the formation of the anhydro bond at this early stage was as follows: the major compound (R_f: 0.40) did not have any exchangeable protons as determined by ^{1}H NMR, and it did not char when exposed to sulfuric acid and heat, while the minor compound (R_f: 0.26) did char. Formation of this 2,3′-*O*-anhydro compound may be due to a favorable conformation of the intermediate **5** as illustrated in Figure 1. In the β-L-ribofurano and β-L-xylofurano series, the C-2′ endo conformation is most likely favored[20] and places the heterocyclic base in a pseudoequatorial position. However, in the β-L-lyxofurano series, a bulky substituent like

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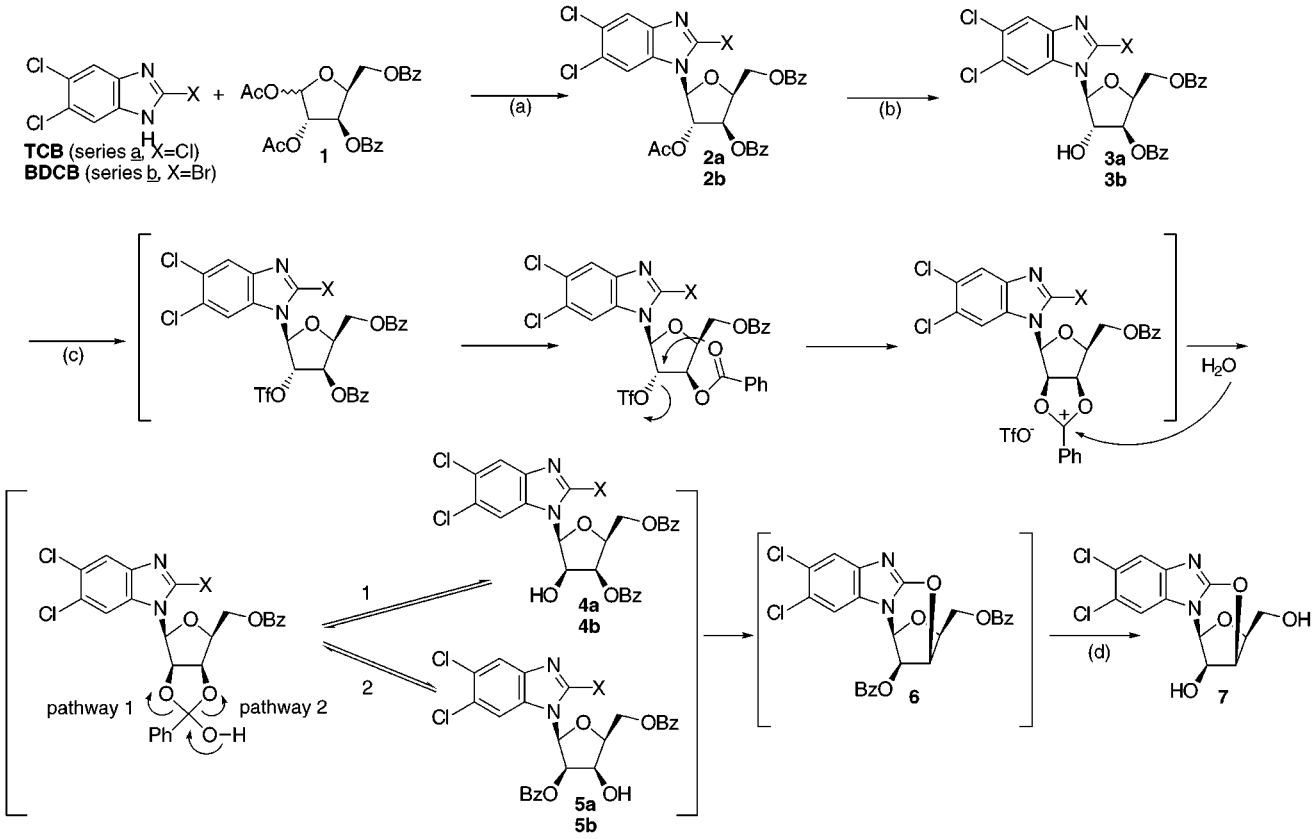
Scheme 1[a]



[a] (a) BSA, TMSOTf, CH_3CN, △; (b) $NH_2NH_2 \cdot H_2O$, pyr/CH_3COOH; (c) Tf_2O, pyr/CH_2Cl_2; (d) Na_2CO_3, EtOH/H_2O 90:10.

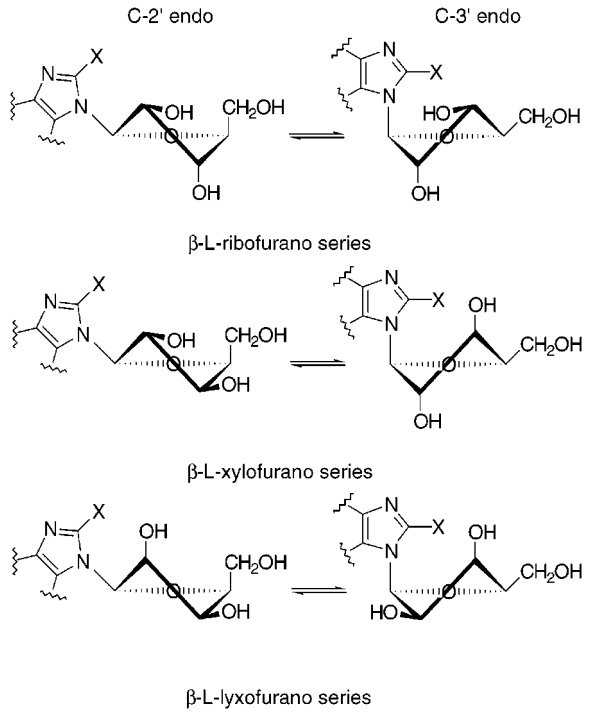


Figure 1.

a benzoyl group on the OH-2′ may favor the C-3′ endo conformation. This C-3′ endo conformation brings the 3′-hydroxyl group and the heterocyclic base, which are both in pseudoaxial positions, into a very close proximity. This close proximity favors an intramolecular substitution of the 2-halogen group by the 3′-hydroxyl group. No substitution of the 2-halogen group by the 2′-hydroxyl group has been observed during our studies of this reaction. Compound **6** was deprotected with sodium carbonate in a mixture of ethanol and water to give 2,3′-*O*-anhydro-5,6-dichloro-1-(*β*-L-lyxofuranosyl)benzimidazole (**7**) in 43% and 40% yield, respectively, from **3a** and **3b**. The structure and absolute stereochemistry of compound **7** was unequivocally determined by X-ray crystallography (Figure 2).[21] The reaction of **7** with isopropylamine in ethanol at 80 °C gave 5,6-dichloro-2-isopropylamino-1-(*β*-L-lyxofuranosyl)benzimidazole (**8**) in 71% yield (Scheme 2).

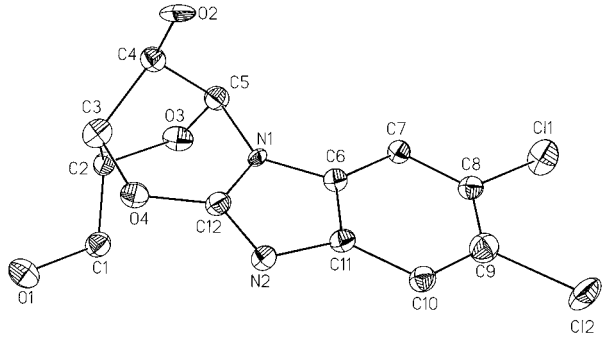
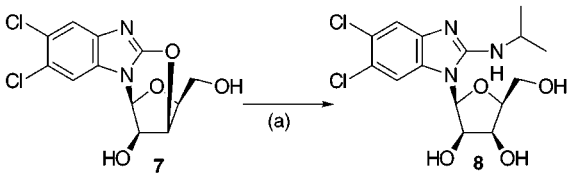


Figure 2. ORTEP diagram of **7**.

(21) An ORTEP diagram and other crystallographic data are included in the Supporting Information. The small, colorless needles (monoclinic) were grown from a methanol/water mixture at room temperature and the X-ray obtained from the X-ray laboratory of the Department of Chemistry at the University of Michigan.

Scheme 2[a]



[a] (a) Isopropylamine, EtOH, △.

Experimental Section

General Chemical Procedures. Melting points were determined on a melting point apparatus and are uncorrected. Silica gel, SilicAR 40−63 μm, 230−400 mesh (Mallinckrodt), was used for column chromatography. Thin-layer chromatography (TLC) was performed on prescored SilicAR 7GF plates (Analtech, Newark, DE). TLC plates were developed in the following solvent systems: system 1 (35% EtOAc/hexanes, v/v), system 2 (50% EtOAc/hexanes, v/v), system 3 (10% MeOH/CH_2Cl_2, v/v). Compounds were visualized by illuminating with UV light (254 nm) or by treatment with 10% methanolic sulfuric acid followed by charring on a hot plate. Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature not exceeding 50 °C, unless specified otherwise. ^{1}H NMR spectra were recorded at 300, 360, or 500 MHz. Chemical shifts are expressed in δ values (ppm) relative to the chemical shift of the residual DMSO-d_5 (δ 2.50 ppm) contained in the solvent DMSO-d_6. All ^{1}H NMR assignments reported were made by homonuclear decoupling experiments. Microanalytical results were performed by the University of Michigan, Department of Chemistry, and are within ±0.4% of the theoretical values, unless otherwise specified. Unless otherwise noted, all materials were obtained from commercial suppliers.

2,5,6-Trichloro-1-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-xylofuranosyl)benzimidazole (2a). 2,5,6-Trichlorobenzimidazole[22] (500 mg, 2.3 mmol) was suspended in acetonitrile (60 mL), and the mixture was stirred at 50 °C. BSA (0.83 mL, 3.4 mmol) was added, and the reaction mixture stirred for an additional 15 min. Compound **1**[18] (1.0 g, 2.3 mmol) in acetonitrile (10 mL) and TMSOTf (0.65 mL, 3.4 mmol) were added to the clear solution. The mixture was allowed to stir at 50 °C for 16 h. The mixture was concentrated under reduced pressure and the residue dissolved with ethyl acetate (75 mL). The solution was washed with a saturated aqueous solution of sodium bicarbonate (10 mL) and with water (3 × 10 mL) and then dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel chromatography [2.5 × 15 cm, eluent: gradient of methanol (0−1%) in dichloromethane] to give **2a** (1.1 g, 80%) as a foam. Compound **2a** was used in the following reaction without further purification.

R_f (system 1): 0.20; ^{1}H NMR (DMSO-d_6): δ 8.1−7.5 (m, 12 H, phenyl, H-4 and H-7), 6.37 (d, 1 H, H-1′, J = 5.3 Hz), 5.9 (m, 1 H, H-3′), 5.6−5.5 (m, 1 H, H-2′), 5.0−4.9 (m, 1 H, H-4′), 4.8−4.7 (m, 2 H, H-5′,5″), 2.12 (s, 3 H, acetyl).

2-Bromo-5,6-dichloro-1-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-xylofuranosyl)benzimidazole (2b). The reaction was performed as described for **2a**, using 2-bromo-5,6-dichlorobenzimidazole[13] (530 mg, 2.0 mmol), BSA (0.73 mL, 3.0 mmol), compound **1**[18] (0.88 g, 2.0 mmol), and TMSOTf (0.58 mL, 3.0 mmol) to give **2b** (1.1 g, 83%) as a foam. Compound **2b** was used in the following reaction without further purification.

R_f (system 2): 0.45; ^{1}H NMR (DMSO-d_6): δ 8.1−7.5 (m, 12 H, phenyl, H-4 and H-7), 6.33 (d, 1 H, H-1′, J = 5.3 Hz), 5.9 (m, 1 H, H-3′), 5.6−5.5 (m, 1 H, H-2′), 5.0−4.9 (m, 1 H, H-4′), 4.8−4.7 (m, 2 H, H-5′,5″), 2.12 (s, 3 H, acetyl).

2,5,6-Trichloro-1-(3,5-di-*O*-benzoyl-β-L-xylofuranosyl)-benzimidazole (3a). Hydrazine hydrate (0.27 mL, 5.5 mmol) was added to a solution of **2a** (1.1 g, 1.8 mmol) in a mixture of pyridine (12.6 mL) and acetic acid (3.2 mL). After stirring the mixture at room temperature for 20 h, acetone (4.1 mL) was added, and the reaction mixture was stirred for an additional 2 h. The mixture was concentrated under reduced pressure, and the residue was dissolved with ethyl acetate (20 mL). The solution was washed with a saturated aqueous solution of sodium bicarbonate (5 mL) and with water (3 × 5 mL) and then dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel chromatography [2.5 × 15 cm, eluent: methanol (1%) in dichloromethane] to give **3a** (0.82 g, 80%) as a foam. Compound **3a** was used in the following reaction without further purification.

R_f (system 2): 0.42; ^{1}H NMR (DMSO-d_6): δ 8.0−7.5 (m, 12 H, H-4, H-7 and phenyl), 6.44 (bs, 1 H, OH-2′), 6.11 (d, 1 H, H-1′, J = 5.2 Hz), 5.7−5.6 (m, 1 H, H-3′), 4.9 (m, 1 H, H-4′), 4.8−4.6 (m, 3 H, H-2′, H-5′ and H-5″).

2-Bromo-5,6-dichloro-1-(3,5-di-*O*-benzoyl-β-L-xylofuranosyl)benzimidazole (3b). The reaction was performed as described for **3a**, using hydrazine hydrate (0.15 mL, 3.0 mmol), **2b** (0.65 g, 1.0 mmol), pyridine (7 mL), and acetic acid (1.8 mL) to give **3b** (0.52 g, 85%) as a foam. Compound **3b** was used in the following reaction without further purification.

R_f (system 2): 0.42; ^{1}H NMR (DMSO-d_6): δ 8.0−7.4 (m, 12 H, H-4, H-7 and phenyl), 6.43 (d, 1 H, OH-2′, J = 5.7 Hz), 6.09 (d, 1 H, H-1′, J = 5.2 Hz), 5.7−5.6 (m, 1 H, H-3′), 4.9 (m, 1 H, H-4′), 4.8−4.6 (m, 3 H, H-2′, H-5′ and H-5″).

2,3′-*O*-Anhydro-5,6-dichloro-1-(β-L-lyxofuranosyl)benzimidazole (7). Triflic anhydride (0.37 mL, 2.2 mmol) in a solution of dichloromethane (4.5 mL) was added to a solution of **3a** (820 mg, 1.5 mmol) in a mixture of dichloromethane (7.5 mL) and pyridine (0.75 mL). The reaction was stirred at 0 °C and monitored by TLC (system 1). After 30 min, water (1.5 mL) was added, and the temperature of the reaction mixture was increased to 40 °C. After an additional 15 h of stirring, the mixture was diluted with dichloromethane (10 mL) and water (10 mL). The organic extract was washed with water (5 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness. The residue was subjected to silica gel chromatography [2.5 × 15 cm, eluent: gradient of methanol (0−2%) in dichloromethane] to give one major compound [R_f (system 2): 0.40, 590 mg] as a foam. ^{1}H NMR (DMSO-d_6): δ 7.9−7.5 (m, 12 H, phenyls, H-4 and H-7), 6.61 (d, 1 H, H-1′, J = 5.4 Hz), 6.27 (t, 1 H, H-2′, J = 5.5 Hz), 5.88 (t, 1 H, H-3′, J = 5.5 Hz), 4.9 (m, 1 H, H-4′), 4.6−4.5 (m, 1 H, H-5′), 4.3−4.2 (m, 1 H, H-5″). This foam was dissolved in a solution of ethanol and water (9:1, v/v, 20 mL), and sodium carbonate (0.45 g, 4.2 mmol) was added. The reaction mixture was stirred 4 days, and then acetic acid (1 mL) was added and the mixture evaporated to dryness. Water (10 mL) and ethyl acetate (20 mL) were added to the residue. The organic extract was washed with water (2 × 5 mL), dried over sodium sulfate, and filtered, and the filtrate was evaporated to dryness. The residue was suspended in boiling dichloromethane, (10 mL) and methanol was added until complete dissolution had occurred. Compound **7** (200 mg, 43%) crystallized from this solution.

Mp: 255−257 °C (decomp); R_f (system 3): 0.18; ^{1}H NMR (DMSO-d_6): δ 7.96 and 7.62 (2 s, 2 H, H-4 and H-7), 6.36 (d, 1 H, OH-2′, J = 2.9 Hz), 6.18 (d, 1 H, H-1′, J = 4.0 Hz), 5.04 (t, 1 H, H-3′, J = 2.9 Hz), 5.01 (t, 1 H, OH-5′, J = 5.4 Hz), 4.7 (m, 1 H, H-2′), 4.4 (m, 1 H, H-4′), 3.5−3.4 (m, 1 H, H-5′), 3.4−3.3 (m, 1 H, H-5″); *Anal.* Calcd for $C_{12}H_{10}Cl_2N_2O_4$: C, 45.45; H, 3.18; N, 8.83. Found: C, 45.08; H, 3.15; N, 8.74. Compound **7** (0.12 g, 40%) was also obtained from **3b** (0.55 g, 0.9 mmol). Structure and absolute stereochemistry of **7** was determined by X-ray crystallography.

5,6-Dichloro-2-isopropylamino-1-(β-L-lyxofuranosyl)benzimidazole (8). Compound **7** (150 mg, 0.47 mmol) was dissolved in ethanol (3.3 mL). Isopropylamine (2.0 mL, 24 mmol) was added, the flask was sealed, and the reaction mixture was stirred at 70 °C for one week. At this time, the reaction was checked by TLC (system 3). Because only a partial reaction had occurred, the reaction mixture was stirred at 80 °C for an additional week. The mixture was then evaporated to dryness, and the residue was dissolved in ethyl acetate (20 mL) and water (5 mL). The organic extract was washed with water (2 × 5 mL), dried over Na_2SO_4, and filtered, and the filtrate was evaporated to dryness. The residue was subjected to silica gel chromatography [2.5 × 15 cm, eluent: methanol (6%) in dichloromethane]. Fractions

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that contained the major spot (R_f (system 3): 0.24) were evaporated to dryness. The resulting solid was suspended in boiling dichloromethane (5 mL), and methanol was added until complete dissolution occurred. Compound **8** (127 mg, 71%) crystallized from this solution.

R_f (system 3): 0.24; mp: 197−199 °C; ^{1}H NMR (DMSO-d_6): δ 7.60 and 7.31 (2 s, 2 H, H-4 and H-7), 7.21 (d, 1 H, NH, J = 7.1 Hz), 6.02 (d, 1 H, H-1′, J = 6.6 Hz), 5.84 (bs, 1 H, OH-3′), 5.32 (d, 1 H, OH-2′, J = 5.9 Hz), 4.85 (t, 1 H, OH-5′, J = 4.9 Hz), 4.4 (m, 1 H, H-2′), 4.2 (bs, 1 H, H-3′), 4.0−3.9 (m, 1 H, C*H*(CH_3)$_2$), 3.8−3.7 (m, 3 H, H-4′, H-5′ and H-5″), 1.18 (d, 6 H, CH(C*H*$_3$)$_2$, J = 6.4 Hz); *Anal*. Calcd for $C_{15}H_{19}Cl_2N_3O_4$: C, 47.89; H, 5.09; N, 11.17. Found: C, 47.91; H, 5.08; N, 11.02.

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Supporting Information Available: An ORTEP diagram and other crystallographic data for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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