New Route to 1-(5-Imidazolyl)ribofuranoid Glycals from Ribofuranosyl Chloride and 5-Lithio-imidazole

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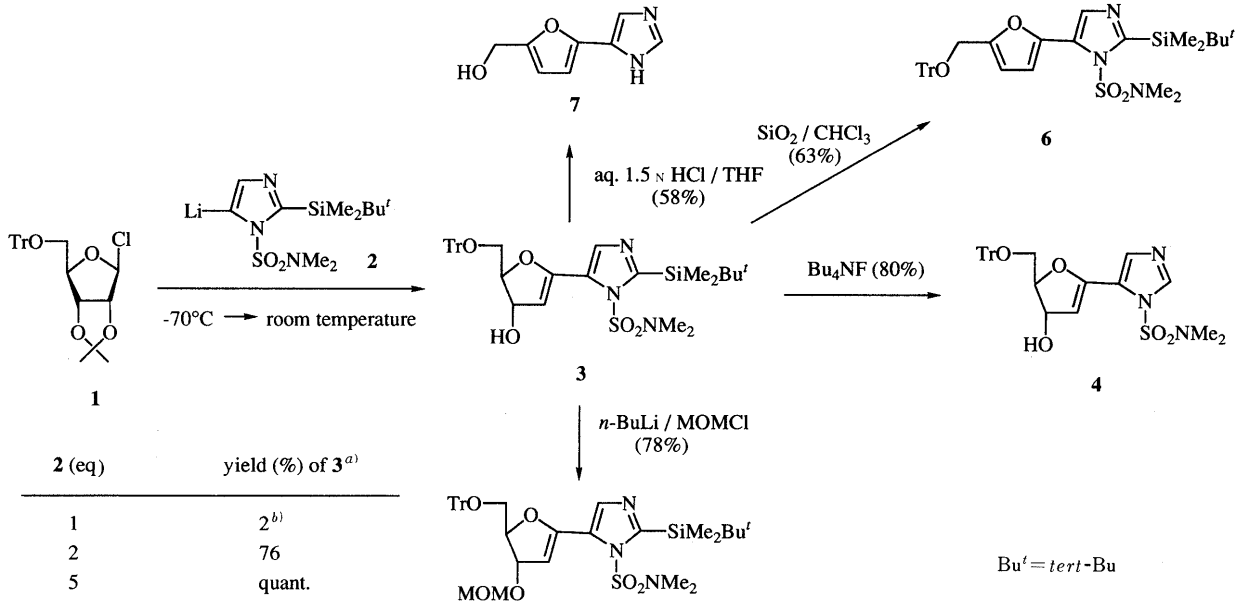
Reaction of ribofuranosyl chlorides with 2 eq of 5-lithio-imidazole afforded 1-(5-imidazolyl)ribofuranoid glycals in good yields. Hydrolysis of the glycal (3) with hydrochloric acid led to 4-(5-hydroxymethylfuran-2-yl)imidazole (7), which contains both hydrophilic and hydrophobic aromatic heterocycles.

Keywords glycal; furanoid glycal; ribofuranosyl chloride; furylimidazole; 2-phenylfuran

Recently, natural C-nucleosides have received considerable attention due to their remarkable antiviral and antitumor activities.[1] Although imidazoles play an important role in many biologically interesting processes,[2] and many useful therapeutic agents[3] contain the imidazole moiety, only a few imidazole C-nucleosides have been reported in the literature.[1,4] Thus we became interested in the possibility of synthesizing novel imidazole C-nucleosides with histamine-H_2 receptor antagonist activities.[5] During the course of this investigation, we developed a new synthetic procedure for furanoid glycals bearing the imidazole moiety at the C-1 position. Few C-nucleoside analogues (glycals) possessing a 1,2-double bond in the sugar are known,[6,7] and some of those were obtained only as the result of an undesired side reaction involving the elimination of a protecting group on the sugar moiety under basic conditions. Recently, Daves and co-workers[8] reported an efficient synthesis of 1-substituted furanoid glycals by palladium-mediated coupling reactions of stannylated furanoid glycals and complex nitrogen-heterocyclic iodo derivatives. Two 1-glycals having aromatic heterocycles were reported to have cytotoxic activity.[7,9]

We first tried a synthesis of the imidazole C-nucleoside by direct reaction of protected D-ribosyl chlorides with 5-lithio-imidazoles. Although such a reaction is known,[10] it suffers from poor reactivity or many side reactions.[11] The reaction of 2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl chloride (**1**)[12] with 1 eq of 5-lithium salt (**2**),[3] which was prepared *in situ* from 1-*N*,*N*-dimethylsulfamoyl-2-*tert*-butyldimethylsilylimidazole, did not afford any of the desired imidazole C-nucleosides. However, trace amounts of an unexpected material (**3**) (2%) were isolated from the reaction mixture, together with recovery of **1** (84%) (Table in Chart 1). Inspection of the ^{1}H-NMR spectrum showed the presence of an allylic proton and a vinyl proton at δ 4.93 (1H, br) and δ 5.55 (1H, d, J=3.0 Hz), respectively. Examination of the MS exhibited a parent peak at m/z 646 ($M^+ + 1$). These results indicated that **3** might be a furanoid glycal, as shown in Chart 1.



2 (eq)	yield (%) of 3[a]
1	2[b]
2	76
5	quant.

a) Isolated yield.
b) The starting material (**1**, 84%) was recovered.

Chart 1

Desilylation of **3** with tetrabutylammonium fluoride (TBAF) led to the corresponding glycal (**4**) in 80% yield. Treatment of a lithium salt of **3** with chloromethyl methyl ether (MOMCl) afforded a 3-*O*-protected glycal (**5**) in 78% yield. On the other hand, when the product (**3**) was treated with silica gel in CH_2Cl_2, a furan derivative (**6**) was obtained in 63% yield. It has been reported that, unlike pyranoid,[11b] furanoid glycals are characterized by easy elimination of the 3-hydroxy group to yield the corresponding furan derivatives.[6,7] Thus, the structure of **3** was confirmed as 1-*N*,*N*-dimethylsulfamoyl-2-*tert*-butyldimethylsilyl-5-(5-*O*-trityl-2-deoxy-D-*erythro*-pent-1-enofuranosyl)-1*H*-imidazole.

When 2 eq of the lithium salt (**2**) were used, the yield of **3** was remarkably improved from 2% to 76% (Table in Chart 1). Moreover, use of five equivalents of **2** resulted in a quantitative yield of **3**. Accordingly, at least 2 eq of the lithium salt were required for the effective formation of **3**. A possible mechanism is illustrated in Chart 2. A carbanion generated from **1** by proton abstruction of the first lithium salt might cause elimination of acetone. Then, addition of the second lithium salt to the resulting 1-chloroglycal intermediate followed by elimination of lithium chloride would give the product (**3**). The product (**3**) was also obtained quantitatively in a one-pot operation from the readily available 1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazole without isolation of the bis-protected imidazole (Chart 3). To our knowledge, no example of the synthesis of 1-(heterocyclic)ribofuranoid glycals from D-ribosyl halides has been reported so far.

We were further interested in a synthesis of 4-(5-hydroxymethylfuran-2-yl)-1*H*-imidazole (**7**), in which hydrophilic and hydrophobic heterocycles are directly linked. Hydrolysis of **3** with 1.5 N aqueous HCl in tetrahydrofuran (THF) resulted in double deprotection and furan formation to give **7** in 58% yield (Chart 1).

Reaction of α-D-ribofuranosyl chloride (**8**),[13] whose hydroxy group at C-5 was protected with a *tert*-butyldimethylsilyl (TBDMS) group, with **2** was similarly carried out. In this case, the formed glycal (**9**) could not be isolated by the usual column chromatography owing to its instability. However, **9** was derived to 3-*O*-protected glycals (**10** and **11**), which were reasonably stable during chromatographical purification, by a treatment of its lithium salt with MOMCl or by silylation with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) (Chart 4).

In conclusion, we have developed a synthetically useful

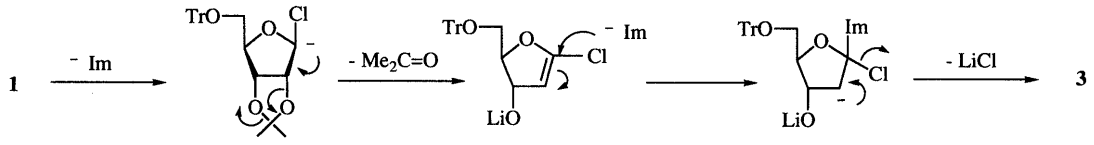


Chart 2

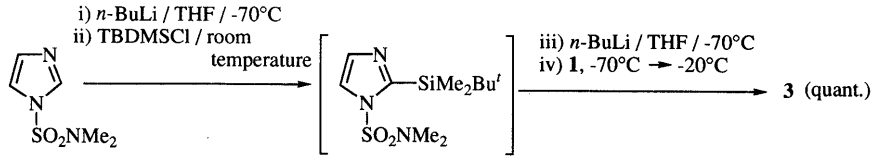


Chart 3

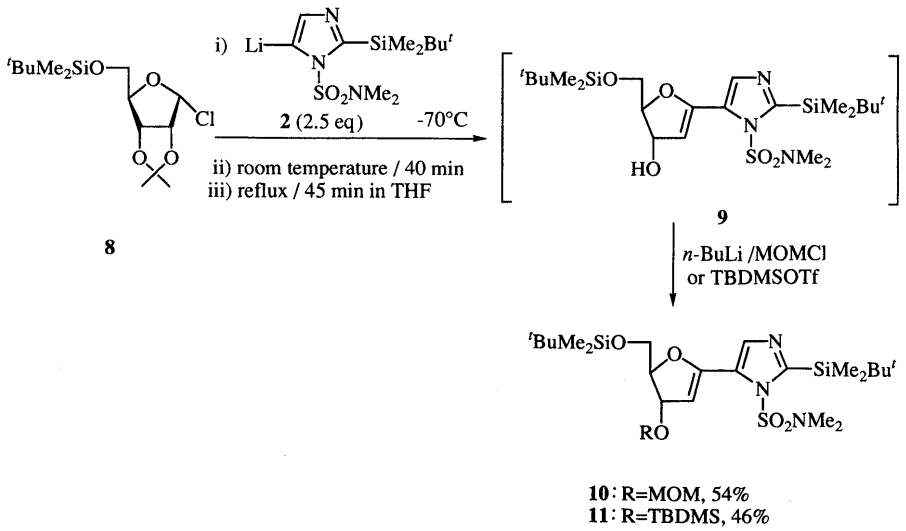


Chart 4

method[14] for 1-(5-imidazoyl)ribofuranoid glycals. Hydrolysis of the glycals afforded a new route to the furylimidazoles. Conversion of the 1-(5-imidazole)ribofuranoid glycals to imidazole C-glycosides is being investigated in our laboratories.

Experimental

The melting point of **7** was determined on a Yanagimoto micromelting point apparatus and is uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were taken with tetramethylsilane as an internal standard on a Varian Gemini-200 spectrometer in $CDCl_3$ unless otherwise noted. Low-resolution and high-resolution mass spectra (HR-MS) were determined with Hitachi M-80 and M-4000H instruments. Optical rotations were measured with a JASCO DIP-181 digital polarimeter. All reactions were carried out under a nitrogen atmosphere. For column chromatography, SiO_2 (Merck 7734 or 9385) was used. THF was distilled from sodium-benzophenone.

1-*N*,*N*-Dimethylsulfamoyl-2-*tert*-butyldimethylsilyl-5-(5-*O*-trityl-2-deoxy-D-*erythro*-pent-1-enofuranosyl)-1*H*-imidazole (3) A solution of 1.6 M BuLi in hexane (0.25 ml, 0.4 mM) was added to a solution of 1-*N*,*N*-dimethylsulfamoyl-2-*tert*-butyldimethylsilylimidazole (116 mg, 0.4 mM) in THF (1.5 ml) with stirring at −70 °C. After being stirred for 15 min, a solution of **1** (90 mg, 0.2 mM) in THF (1.5 ml) was added and the mixture was stirred for 20 min at this temperature, whereupon the solution changed from orange to yellow. The temperature of the reaction mixture was then elevated to −20 °C over 2 h. The reaction was quenched with H_2O and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified by column chromatography (15% EtOAc in hexane) to give **3**[15] (98 mg, 76%) as an oil. IR (film) cm^{-1}: 1384, 1170 (SO_2). ^{1}H-NMR δ: 0.39 [6H, s, $Si(CH_3)_2$], 1.00 [9H, s, $C(CH_3)_3$], 2.74 [6H, s, $N(CH_3)_2$], 3.19 (1H, dd, J=9.6, 5.2 Hz, $C_{5'}$-$\underline{H}_a H_b$), 3.30 (1H, dd, J=9.6, 5.9 Hz, $C_{5'}$-$H_a\underline{H}_b$), 4.51 (1H, ddd, J=5.9, 5.2, 3.0 Hz, $C_{4'}$-H), 4.93 (1H, br, $C_{3'}$-$\underline{H}_a H_b$), 5.55 (1H, d, J=3.0 Hz, $C_{3'}$-$H_a\underline{H}_b$), 7.18—7.47 (16H, m, ArH and imidazole C_5-H). CI-MS m/z: 646 (M^++1). SI-MS m/z: 646 (M^++1).

1-*N*,*N*-Dimethylsulfamoyl-5-(5-*O*-trityl-2-deoxy-D-*erythro*-pent-1-enofuranosyl)-1*H*-imidazole (4) A 1 M solution of TBAF (0.1 ml, 0.1 mM) in THF was added to a solution of **3** (65 mg, 0.1 mM) in THF (1.5 ml) at 0 °C and the mixture was stirred for 1 h at this temperature. The reaction was quenched with H_2O and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in EtOAc–hexane (3 : 1) and the solution was washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified by column chromatography [EtOAc–hexane (1 : 1)] to give **4** (42 mg, 80%) as a colorless oil. ^{1}H-NMR δ: 2.81 [6H, s, $N(CH_3)_2$], 3.23 (1H, dd, J=10.0, 5.7 Hz, $C_{5'}$-$\underline{H}_a H_b$), 3.30 (1H, dd, J=10.0, 6.7 Hz, $C_{5'}$-$H_a\underline{H}_b$), 4.54 (1H, ddd, J=6.7, 5.7, 3.3 Hz, $C_{4'}$-H), 4.88 (1H, dd, J=3.3, 3.0 Hz, $C_{3'}$-H), 5.63 (1H, d, J=3.0 Hz, $C_{2'}$-H), 7.10—7.49 (16H, m, ArH and imidazole C_4-H), 7.98 (1H, s, imidazole C_2-H). EI-MS m/z: 513 ($M^+ - H_2O$). FD-MS m/z: 532 (M^++1). HR-MS Calcd for $C_{29}H_{27}N_3O_4S$ ($M^+ - H_2O$): 513.1721. Found: 513.1723.

1-*N*,*N*-Dimethylsulfamoyl-2-*tert*-butyldimethylsilyl-5-(3-*O*-methoxymethyl-5-*O*-trityl-2-deoxy-D-*erythro*-pento-1-enofuranosyl)-1*H*-imidazole (5) A solution of 1.6 M BuLi in hexane (3.13 ml, 5.0 mM) was added to a solution of **3** (3.225 g, 5.0 mM) in THF (20 ml) with stirring at 0 °C. The mixture was stirred for 10 min, then chloromethyl methyl ether (0.76 ml, 10.0 mM) was added at the same temperature and the whole was stirred for 2.5 h at room temperature. The reaction was quenched with H_2O and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified by column chromatography (5% EtOAc in hexane) to give **5**[15] (2.640 g, 78%) as an oil, $[\alpha]_D^{21}$ +47.1° (c=1.43, $CHCl_3$). IR (film) cm^{-1}: 1022 (C–O–C). ^{1}H-NMR δ: 0.38 [6H, s, $Si(CH_3)_2$], 1.00 [9H, s, $C(CH_3)_3$], 2.75 [6H, s, $N(CH_3)_2$], 3.18 (1H, dd, J=11.0, 6.2 Hz, $C_{5'}$-$\underline{H}_a H_b$), 3.30 (1H, overlapped, $C_{5'}$-$H_a\underline{H}_b$), 3.32 (3H, s, OCH_3), 4.55—4.65 (1H, m, $C_{4'}$-H), 4.66 (2H, s, OCH_2O), 4.84 (1H, t, J=4.0 Hz, $C_{3'}$-H), 5.52 (1H, d, J=4.0 Hz, $C_{2'}$-H), 7.20—7.48 (16H, m, ArH and imidazole C_4-H). CI-MS m/z: 590 (M^++1).

1-*N*,*N*-Dimethylsulfamoyl-2-*tert*-butyldimethylsilyl-5-(5-trityloxymethylfuran-2-yl)-1*H*-imidazole (6) A suspension of **3** (98 mg, 0.15 mM) with silica gel (Merck 7734) (100 mg) in CH_2Cl_2 (5 ml) was stirred at room temperature for 2 d. Evaporation of the solvent left silica gel coated with a crude oil, which was subjected to column chromatography (30% EtOAc in hexane) to give **6** (59 mg, 63%) as a colorless oil. ^{1}H-NMR δ: 0.44 [6H, s, $Si(CH_3)_2$], 1.08 [9H, s, $C(CH_3)_3$], 2.60 [6H, s, $N(CH_3)_2$], 4.11 (2H, s, CH_2), 6.34 and 6.63 (each 1H, each d, J=3.6 Hz, furan-H), 7.30—7.50 (16H, m, ArH and imidazole 4-H). EI-MS m/z: 628 (M^++1). HR-MS Calcd for $C_{35}H_{42}N_3O_4SSi$: 628.2663. Found: 628.2666.

Synthesis of 3 by One-Pot Conversion from 1-*N*,*N*-Dimethylsulfamoyl-*H*-imidazole A solution of 1.6 M BuLi in hexane (8.6 ml, 13.75 mM) was added to a solution of 1-*N*,*N*-dimethylsulfamoyl-1*H*-imidazole (2.19 g, 12.5 mM) in THF (100 ml) with stirring at −70 °C. The mixture was stirred for 15 min, then a solution of TBDMSCl (2.27 g, 15.0 mM) in THF (20 ml) was added at the same temperature and the whole was allowed to warm to room temperature over 1 h. It was again cooled to −70°C and a solution of 1.6 M BuLi in hexane (8.6 ml, 13.75 mM) was added. The solution was stirred for 15 min, a solution of **1** (2.25 g, 5 mM) in THF (30 ml) was added and the temperature was elevated to −20 °C over 2 h. The reaction was quenched with H_2O and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude oil (5.8 g). Flash chromatography (15% EtOAc in hexane) of the oil gave **3** (3.20 g, quantitative yield), which was identical with **3** synthesized in the stepwise manner.

4-(5-Hydroxymethylfuran-2-yl)-1*H*-imidazole (7) A solution of **3** (441 mg, 0.68 mM) in 1.5 N aqueous HCl (10 ml) was stirred at room temperature for 12 h. The solution was basified with 30% NH_4OH, saturated with NaCl, and extracted with EtOAc. The extract was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified by column chromatography (1% MeOH in EtOAc) to give **7** (65 mg, 58%) as a white wax. Recrystallization of the wax from $CHCl_3$–MeOH gave colorless prisms, mp 143—144 °C. IR (KBr): 1632, 1578, 1200, 1072, 1008 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 4.55 (2H, s, CH_2O), 6.35 and 6.53 (each 1H, each d, J=5.0 Hz, furan-H), 7.30 and 7.70 (each 1H, each s, imidazole-H). ^{13}C-NMR (CD_3OD) δ: 57.5 (t), 106.1 (d), 110.5 (d), 115.7 (d), 133.0 (s), 137.4 (d), 150.5 (s), 155.0 (s). EI-MS m/z: 164 (M^+), 148 ($M^+ - OH$). HR-MS Calcd for $C_8H_8N_2O_2$: 164.0585. Found: 164.0606. *Anal.* Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.47; H, 4.92; N, 16.94.

1-*N*,*N*-Dimethylsulfamoyl-2-*tert*-butyldimethylsilyl-5-(3-*O*-methoxymethyl-5-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-erythro-pent-1-enofuranosyl)-1*H*-imidazole (10) A solution of 1.6 M BuLi in hexane (0.31 ml, 0.5 mM) was added to a solution of 1-*N*,*N*-dimethylsulfamoyl-2-*tert*-butyldimethylsilylimidazole (144.5 mg, 0.5 mM) in THF (2 ml) with stirring at −70 °C. The mixture was stirred for 15 min, then a solution of **8** (65 mg, 0.2 mM) in THF (3 ml) was added and the whole was stirred for 5 min at this temperature. The reaction mixture was further stirred at room temperature for 40 min and refluxed for 45 min. Extractive work-up gave crude **9** as a brown oil. A solution of 1.6 M BuLi in hexane (0.137 ml, 0.22 mM) was added to a solution of **9** thus obtained in THF (5 ml) at 0 °C. The mixture was stirred for 15 min, then MOMCl (0.06 ml, 0.8 mM) was added at this temperature and the whole was stirred for 2.5 h at room temperature. Extractive work-up and purification by column chromatography (5—10% EtOAc in hexane) gave **10**[15] (60 mg, 54% from **8**) as an oil, $[\alpha]_D^{21}$ +64.00 (c=0.83, $CHCl_3$). ^{1}H-NMR δ: 0.08 [6H, s, $OSi(CH_3)_2$)], 0.40 [6H, s, C_2–$Si(CH_3)_2$], 0.90 [9H, s, $OSi(CH_3)_3$], 1.02 (9H, C_2–$Si(CH_3)_3$], 2.83 [6H, s, $N(CH_3)_2$], 3.38 (3H, s, OCH_3), 3.60 (1H, dd, J=16.4, 6.7 Hz, $C_{5'}$-$\underline{H}_a H_b$), 3.81 (1H, dd, J=16.4, 5.1 Hz, $C_{5'}$-$H_a\underline{H}_b$), 4.50 (1H, m, $C_{4'}$-H), 4.70 (2H, s, OCH_2O), 4.88 (1H, t, J=2.5 Hz, $C_{3'}$-H), 5.51 (1H, d, J=2.5 Hz, $C_{2'}$-H), 7.30 (1H, s, imidazole C_4-H).

1-*N*,*N*-Dimethylsulfamoyl-2-*tert*-butyldimethylsilyl-5-(3,5-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-*erythro*-pent-1-enofuranosyl)-1*H*-imidazole (11) TBDMSOTf (0.14 ml, 0.6 mM) was added to a solution of crude **9**, prepared on a 0.2 mM scale as above, in pyridine (3 ml) with stirring at 0 °C. The mixture was stirred for 15 min, quenched with H_2O and extracted with EtOAc. The extract was washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified by column chromatography (5% EtOAc in hexane) to give **11**[12] (58 mg, 46% from **8**) as an oil, $[\alpha]_D^{21}$ +68.6°

($c=1.83$, $CHCl_3$). ^{1}H-NMR δ: 0.08 [12H, s, $2\times OSi(CH_3)_2$], 0.39 [6H, s, imidazole C_2-$Si(CH_3)_2$], 0.88 [18H, s, $2\times OSi(CH_3)_3$], 1.03 [9H, s, imidazole C_2-$Si(CH_3)_3$], 2.87 [6H, s, $N(CH_3)_2$], 3.55 (1H, dd, $J=16.4$, 8.2 Hz, $C_{5'}$-$\underline{H}_a\underline{H}_b$), 3.78 (1H, dd, $J=16.4$, 5.1 Hz, $C_{5'}$-$H_a\underline{H}_b$), 4.37 (1H, m, $C_{4'}$-H), 4.99 (1H, t, $J=2.5$ Hz, $C_{3'}$-H), 5.40 (1H, d, $J=2.5$ Hz, $C_{2'}$-H), 7.27 (1H, s, imidazole C_4-H). SI-MS m/z: 632 ($M^+ + 1$). Negative SI-MS m/z: 630 ($M^+ - 1$).

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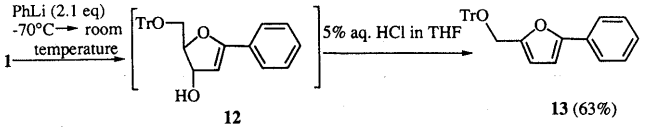
14) In addition, **1** was derived to a 1-phenylribofuranoid glycal (**12**) by treatment with phenyllithium (2.1 eq). Subsequent treatment of the crude **12** with 5% HCl afforded the 2-phenylfuran derivative (**13**) in 63% yield from **1**. IR (film) cm^{-1}: 1030, 1050. ^{1}H-NMR δ: 4.16 (2H, s), 7.37 and 7.62 (each 1H, each d, $J=3.5$ Hz, furan-H), 7.20—7.90 (20H, m, ArH).



15) The EI-MS data were not obtained because of the thermal instability of this product.