New Approach to 1'*C*-Modified Riboside Scaffold Via Stereoselective Functionalization of D-(+)-Ribonic-γ-lactone [1]

Arnaldo Alzérreca

Department of Chemistry, Metropolitan Campus, Inter American University of Puerto Rico,
P.O. Box 19-1293, San Juan, Puerto Rico 00919
Received September 24, 2002

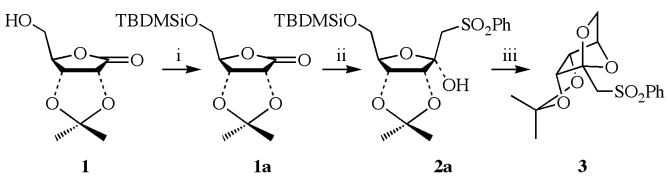
We describe the preparation and spectroscopic properties of a novel class of nucleoside analogues in which a phenyl sulfonyl methylene group is attached to the 1'-carbon atom of β-D-ribofuranose. The glycosylation of 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-ribofuranolactone **1b** with phenyl methyllithium sulfone in THF at -60° C afforded 5-*O*-(*tert*-butyldiphenylsilyl)-1'-(benzenesulfonylmethylene)-2',3'-*O*-isopropylidene-α-D-ribofuranose **2b**. When subjected to deoxydative reaction conditions with boron trifluoride etherate in the presence of triethylsilane at -45° C, lactol **2b** was converted into 2',3'-*O*-isopropylidene-1'-deoxy-1'-(benzenesulfonylmethylene)-β-D-ribofuranose **4b** with excellent stereocontrol over the anomeric carbon in moderate yield. This method has the potential for the development of a wider array of useful probes derived from 1'-deoxy-β-D-ribofuranose for nucleic acid research and for antisense therapeutic agents through further functionalization of the coupled sulfonyl group.

J. Heterocyclic Chem., **40**, 317 (2003).

Synthetic methods for the preparation of base-modified glycosides are of current interest primarily because of their application in antisense technology of therapeutic oligonucleotides with improved properties such as enzymatic stability, binding specificity or cellular uptake [2], and for the study of aromatic stacking as a contributing factor with respect to the thermodynamic stability of nucleic acids in protic media [3]. Glycosylation reactions starting from protected sugar lactones or from 1-chloro derivatives of protected sugars as the glycosyl donors have not been an easy task mainly because of problems related with α/β-anomer stereoselectivity, glycosyl donor activation, and the often-dual role of the protecting functionalities. For example, mono-and polycyclic aromatic hydrocarbons as the DNA "base analogue", such as phenyl, naphthalene- or phenanthrene-residues were successfully incorporated at the α-1'-C-position of D-ribose and 2-deoxy-D-ribose *via* coupling reactions of organometallic derivatives of these aromatic compounds with Hoffer's chlorosugar [4]. Although the coupling was reported to work efficiently, the α-anomers were obtained as the major products, and the β-anomers were prepared by acid-catalyzed isomerization of the α-compounds [5]. Also, earlier attempts for the glycosylation of benzyl-protected sugar lactones with phenyllithium, and deoxydation with boron trifluoride etherate and triethylsilane were successful in the pyrano series but failed to afford the corresponding D-ribose derivatives since debenzylation was found to proceed with opening of the tetrahydrofuran ring [6]. Subsequently, it was also reported that glycosylation of protected D-(+)-ribonic-γ-lactone with phenyllithium afforded a 1:3 α/β mixture of the corresponding lactols, which were then reduced to yield the anomeric mixture of protected phenyl ribosides [7].

In a previous paper, we described the phenylsulfonyl methylenation of 2,3-isopropylidene-D-erythronolactone to give the corresponding lactols of type **2** with good stereocontrol of the anomeric atom and its subsequent Lewis-acid catalyzed dehydration to the corresponding 2-benzenesulfonylmethylene derivatives. We also reported that when a similar procedure was applied to the 5-*O*-(*tert*-butyldimethylsilyl)-2',3'-*O*-isopropylidene-D-ribofuranolactone **1a**, lactol **2a** was obtained in good yields and high stereoselection [Scheme1]. However, under Lewis-acid promoted dehydration conditions lactol **2a** was converted into its 1',5'-anhydro derivative **3** *via* competing intramolecular substitution after cleavage of the *tert*-butyldimethylsilyl (TBDMS) protecting group [8]. On the basis of our previous experience, changing the protecting devise at the 5'-hydroxyl group and modifying reaction conditions were necessary to avoid exclusive formation of the 1',5'-anhydro derivative **3**. Therefore, we examined the potential of other protecting devises under similar reaction conditions for allowing both a stereoselective nucleophilic attack by the organometallic species to D-ribofuranolactone **1b** from the β-face, and the Lewis acid-promoted deoxydation of **2b** with retention of the β-stereochemistry of the 1'-C-coupled methyl phenyl sulfone functionality. To our knowledge, there were no reports on the synthesis of this class of ^{1}C-riboside derivatives.

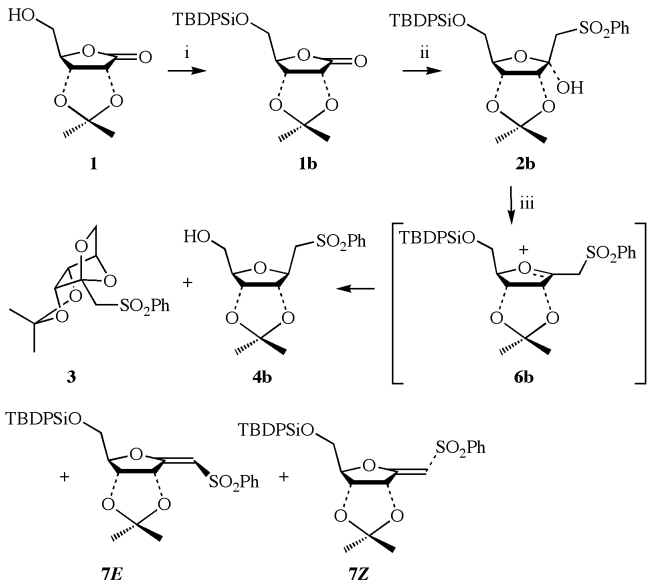
Scheme 1



Reagents and conditions [12]: (i) TBDMSiCl, imidazole, DMF, 35 °C, 15 h, 95%; (ii) $LiCH_2SO_2Ph$, THF, -60 °C to -35 °C, 5 h, 62%; (iii) $BF_3{\cdot}Et_2O$, CH_3CN, -40 °C, 1 h, 67%.

In this paper, we describe the highly stereoselective phenylsulfonyl methylenation of 5-*O*-(*tert*-butyldiphenylsilyl)-2',3'-*O*-isopropylidene-D-ribofuranolactone **1b** and the subsequent deoxydation to afford the β-1'-*C*-coupled riboside analogue **4b** [Scheme 2]. The addition of lithiated methyl phenyl sulfone to 5-*O*-(*tert*-butyldiphenylsilyl)-2',3'-*O*-isopropylidene-D-ribofuranolactone **1b** [9,10] in tetrahydrofuran at –60 °C leads exclusively to α-lactol **2b**, which can be isolated as a white foam in 84%

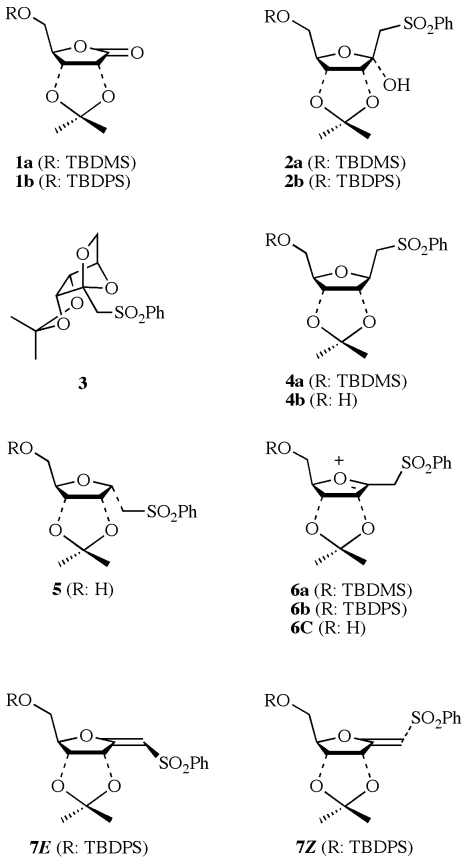
Scheme 2



Reagents and conditions [12]: (i) TBDPSiCl, imidazole, DMF, 22 °C, 24 h, 95%; (ii) $LiCH_2SO_2Ph$, THF, -60 °C to 22 °C, 6 h, 84%; (iii) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_3CN, -45 °C, 1.5 h, 4b (48%), 3 (29%), 7*Z*/*E* (traces).

yield after silica gel column chromatography. Structure assignments are based on infrared, ^1H nmr, ^{13}C nmr, ^1H-^1H COSY, mass spectral and elemental analysis. When lactol **2b** is subsequently treated with boron trifluoride etherate in the presence of 2.5 equivalents of triethylsilane in acetonitril at -45 °C, the major diastereomer β-D-ribofuranose derivative **4b** is isolated as a crystalline and colorless solid after column chromatographic separation on silica gel using EtOAc-petroleum ether mixtures as eluent in 48% yield.

The β-stereochemistry of the 1'carbon atom of **4b** is tentatively assigned on the basis of its proton nmr spectrum. It shows two doublets at 4.87 and 4.49 ppm for $H_{3'}$ and $H_{2'}$, respectively, with a coupling constant of 5.7 Hz for both vicinal protons. Protons $H_{4'\alpha}$ and $H_{1'\alpha}$ appear as multiplets centered at 4.23 and 3.33 ppm due to vicinal coupling to both of their respective vicinal proton pairs $H_{5'a}$-$H_{5'b}$, and H_{1a}-H_{1b}. Karplus-Conroy approximation for vicinal coupling with dihedral angles of 102.9°, 106.0° and 2.6° for $H_{2'}$,$H_{1'\alpha}$, $H_{3'}$,$H_{4'\alpha}$ and $H_{2'}$,$H_{3'}$, estimated by conformational optimization with MM2 Force Field Method [11] for **4b** suggests a coupling constant of



8.2 Hz between $H_{2'}$ and its vicinal $H_{3'}$ proton. The same approximation predicts a very weak coupling of less than 1.0 Hz for the near orthogonal relationships between $H_{2'}$,$H_{1'\alpha}$ and $H_{3'}$,$H_{4'\alpha}$ By comparison, although smaller than expected coupling constants are expected between protons on vicinal oxygenated carbon atoms in rigid ring systems [8], the $H_{2'}$ resonance of the α-anomer **5** should appear as a doublet of doublets with coupling constants larger than 1 Hz. The β-stereochemistry assignment is confirmed by 2D ^1H-^1H correlation analysis, which shows only three sets of cross peaks between $H_{2'}$-$H_{3'}$, $H_{4'\alpha}$ -$H_{5'a}$- $H_{5'b}$, and $H_{1'\alpha}$ -H_{1a}- H_{1b}. In contrast, the presence of only very small amounts of the 1'-deoxy-1'-(benzenesulfonylmethylene)-α-D-ribofuranose anomer **5** could be detected in the proton nmr spectrum of the crude reaction mixture for which the integration of nmr signals shows a α/β ratio of 4/96, thus establishing the highly stereoselective course of this two step *C*-glycosylation sequence.

The combined steric demands of the phenyl sulfonyl methylene group and the appropriately selected protecting *tert*-butyldiphenylsilyl group imposed on the intermediate oxocarbenium ion **6b** may strongly limit the approach of triethyl silane to the 1'C-atom from the β-face and thus determine the stereochemical outcome of the reaction.

Alternatively, the intermediate oxocarbenium ion **6c** may be formed *via* Lewis-acid assisted cleavage of the TBDPS protecting group prior to the reaction with triethyl silane. According to preliminary geometry optimization of molecular models [11] **6c** may adopt a conformation in which the 5'-hydroxyl group and the sulfonyl group are close enough to undergo hydrogen-bonding, and prevent formation of anomer **5** to a greater extent.

In addition to the desired **4b** riboside, the 1',5'-anhydro derivative **3** was obtained after column chromatographic separation on silica gel with EtOAc-Petroleum ether mixtures as eluent in 29% yield. Thus, the competitive intramolecular substitution of the 5'-hydroxyl group in **6c** could not be completely suppressed under these reaction conditions. However, these results contrast with the exclusive formation of compound **3** under similar reaction conditions when the 5'-hydroxyl group carries a TBDM protecting devise, instead. On the other hand, the infrared spectrum of the crude reaction mixture of **4b** shows two very small absorption bands at 1646 and 1636 cm^{-1}, which are preliminarily assigned to the geometric isomers **7*Z*** and **7*E***, formed only in trace amounts *via* elimination of the methylen hydrogen atoms 1a and 1b from the intermediate oxocarbenium ion **6b**. Isomers of this type were the major products when the α-lactol derived from 1'-(benzenesulfonylmethylene)-2',3'-*O*-isopropylidene-D-erythronolactone was dehydrated with $BF_3 \cdot Et_2O$ at low temperatures [8].

In conclusion, we have developed a convenient protocol for the synthesis of novel β–1'-C-coupled riboside analogues with excellent stereoselectivity in moderate yield. The synthetic approach involves low temperature coupling of phenyl methyllithium sulfone to 5-*O*-(*tert*-butyldiphenylsilyl)-2',3'-*O*-isopropylidene-D-ribofuranolactone **1b**, and Lewis-acid catalyzed deoxydation of the intermediate lactol **2b**. Current work to increase the overall yield of **4b**, and further functionalization of the attached phenylmethylene sulfonyl functional group to provide access to a wider variety of synthetic derivatives is now in progress.

EXPERIMENTAL

General.

Melting points were determined on an Electrothermal apparatus and are uncorrected. Commercially available reagents and solvents were used without further purification. *N*,*N*-Dimethylformamide was purified by fractional distillation *in vacuo*. Tetrahydrofuran was distilled from sodium metal in the presence of benzophenone under dry argon; acetonitrile was refluxed over phosphorus pentoxide and distilled with a Vigreaux column. 2',3'-*O*-Isopropylidene-D-ribofuranolactone was purchased from Aldrich and used without further purification. Infrared spectra were recorded on a Perkin-Elmer 1620 FT-IR spectrophotometer in carbon chloride and methylene chloride solutions. ^1H and ^{13}C nmr spectra were recorded on a 200 MHz Varian spectrometer at the nominal frequency of 199.97 MHz for hydrogen. The 7.26 ppm resonance of residual chloroform and 77.0 ppm of deuterochloroform were used as internal references for ^1H and ^{13}C nmr spectra, respectively. Mass spectral analysis and combustion analysis were performed by Oneida Research Services, Whitesboro, NY 13492. For thin layer chromatography (TLC) Riedel-de-Haen plates with fluorescence indicator (SiO_2-60, F-254), and for flash column chromatography purifications E. Merck silica gel grade 9385 (230-400 mesh) were used.

5-*O*-(*tert*-Butyldiphenylsilyl)-1'-(benzenesulfonylmethylene)-2',3'-*O*-isopropylidene-α-D-ribofuranose (**2b**).

Commercially available 2',3'-*O*-isopropylidene-D-ribofuranolactone **1** (2.5 g, 0.013 mol), *tert*-butyldiphenylsilyl chloride (5.47 g, 0.019 mol), and imidazole (2.21 g, 0.032 mol) were dissolved in dimethylformamide (5.0 ml) and stirred at room temperature for 24 hours to afford 5-*O*-(*tert*-butyldiphenylsilyl)-2',3'-*O*-isopropylidene-D-ribofuranolactone [10]. The crude product was recrystallized from isopropyl alcohol to give a colorless solid, 5.4 g (95%), mp 99-100°. To a magnetically stirred solution of methyl phenyl sulfone (1.09 g, 0.007 mol) in dry tetrahydrofuran (60 ml) under argon *n*-butyllithium (3.2 ml of a 2.5 *M* solution in hexanes, 0.008 mol) was added at -60°, warmed up to -10° and stirred for 1 hour. The solution was then cooled again to -60°, and a solution of 5-*O*-(*tert*-butyldiphenylsilyl)-2',3'-*O*-isopropylidene-D-ribofuranolactone **1b** (3.0 g, 0.007 mol) was added over a period of 10 minutes. After addition, the solution was warmed up to -35° and stirred for three hours, warmed up again to room temperature and stirred for 3 more hours. The reaction mixture was then quenched with a saturated solution of ammonium chloride (20 ml). After extraction with ethyl acetate the organic layer was dried with magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the remaining crude reaction mixture using silica gel column chromatography with EtOAc/petroleum ether mixtures as eluent afforded **2b** (3.4 g, 84%), as a white foam; ir ($CHCl_3$): 3461 (-OH), 3068 (=C-H), 2940 (aliphatic C-H), 1380 (*tert*-butyl), 1320 (ν_{as} -SO_2-), 1141 and 1108 (ν_{sym} -SO_2-) cm^{-1}; ^1H nmr: δ 7.98-7.26 (m, 15H, ArH), 5.10 (s, 1H, OH), 4.70 (dd, 1H, $J_{3',2'}$ = 5.9 Hz, $J_{3',4'}$ = 1.5 Hz, $H_{3'}$), 4.45 (d, 1H, $J_{2',3'}$ = 5.9 Hz, $H_{2'}$), 4.13 (m, 1H, $H_{4'\alpha}$), 3.70 (m, 4H, $H_{5'a}$,$H_{5'b}$,H_{1a},H_{1b}), 1.38 (s, 3H), 1.26 (s, 3H), 1.05 (s, 9H); ^{13}C nmr: δ 140.8, 135.5, 133.4, 132.3, 130.0, 128.6, 127.8 (ArC), 112.8 ($C_{1'}$), 104.4 (O-C-O), 86.8 ($C_{2'}$), 86.6 ($C_{5'}$), 81.8 ($C_{3'}$), 64.9 ($C_{4'}$), 59.9 (C-SO_2Ph), 27.0 (CH_3)$_3$, 26.6 (CH_3), 25.2 (CH_3), 19.3 (CMe_3). Ms: m/z 565 (M^+ - OH, 100% relative intensity).

Anal. Calcd. for $C_{31}H_{38}O_7SSi$: C, 63.89; H, 6.57; S, 5.50. Found: C, 63.50; H, 6.46; S, 5.15.

2',3'-*O*-Isopropylidene-1'-deoxy-1'-(benzenesulfonylmethylene)-β-D-ribofuranose (**4b**).

5-*O*-(*tert*-Butyldiphenylsilyl)-1'-(benzenesulfonylmethylene)-2',3'-*O*-isopropylidene-α-D-ribofuranose **2b** (2.0 g, 0.003 mol) was dissolved in dry acetonitrile (45 ml) and cooled down to -45° under argon. Then, triethylsilane (0.87 g, 0.007 mol) was added followed by the dropwise addition of boron trifluoride-diethyl etherate (0.46 g, 0.003 mol) and the reaction mixture was stirred at -40° for 1.5 hour. After warming up to room temperature, the solution was quenched with saturated aqueous potassium carbonate (40 ml). The reaction mixture was extracted with ethyl acetate and the organic layer dried with magnesium sulfate and concentrated under reduced pressure. Purification of the crude reaction mixture using silica gel column chromatography

with EtOAc/petroleum ether mixtures afforded first **3** (0.32 g, 29%) [8], and then **4b** (0.53 g, 48%), as colorless crystals, mp 161-162° (isopropyl alcohol); ir ($CHCl_3$): 3436 (-OH), 3083 (=C-H), 2954 (aliphatic C-H), 1384 (*gem*-dimethyl), 1319 (ν_{as} -SO_2-), 1161 and 1084 (ν_{sym} -SO_2-) cm^{-1}; ^1H nmr: δ 7.98-7.93 (m, 2H, ArH), 7.69-7.50 (m, 3H, ArH), 5.95 (s, 1H, OH), 4.87 (d, 1H, $J_{3',2'}$ = 5.7 Hz, $H_{3'}$), 4.49 (d, 1H, $J_{2',3'}$ = 5.7 Hz, $H_{2'}$), 4.23 (m, 1H, $H_{4'\alpha}$), 3.68 (m, 4H, $H_{5'a}$,$H_{5'b}$,H_{1a},H_{1b}), 3.33 (m, 1H, $H_{1'\alpha}$), 1.37 (s, 3H), 1.24 (s, 3H); ^{13}C nmr: δ 140.2 ($ArCSO_2$), 133.9 (ArC_p), 128.9 (ArC_o), 128.1 (ArC_m), 112.7 (O-C-O), 104.4 ($C_{1'}$), 87.7 ($C_{2'}$), 87.3 ($C_{4'}$), 81.4 ($C_{3'}$), 63.7 ($C_{5'}$), 59.6 (C_1), 26.2 (CH_3), 24.5 (CH_3); Ms: m/z 327 (100%), 328 (M^+, 17 % relative intensity).

Anal. Calcd. for $C_{15}H_{20}O_6S$: C, 54.86; H, 6.14; S, 9.76. Found: C, 54.23; H, 6.06; S, 9.31.

Acknowledgement.

NIGMS-MBRS-SCORE Grant S06 RR08159 from the National Institutes of Health supported this work.

REFERENCES AND NOTES

[*] Author email: aalzerre@inter.edu.

[1] Presented in part at the American Chemical Society Meeting, Puerto Rico Section, San Juan, Puerto Rico, August 6, 2002.

[2] H. An, T. Wang, M. A. Maier, M. Manoharan, Bruce S. Ross, and P. D. Cook, *J. Org. Chem.*, **66**, 2789 (2001); C. A. Stein and Y.-C. Cheng, in "Cancer: Principles & Practice of Oncology", 5th Edition, V. T. DeVita, Jr., S. Hellman, S. A. Rosenberg, Editors. Lippincott-Raven Publishers, Philadelphia, Chapter 63,1997; A. De Mesmaeker, R. Häner, P. Martin and H. E. Moser, *Acc. Chem. Res.*, **28**, 366 (1995).

[3] K. M. Guckian, B. A. Schweitzer, R. X.-F. Ren, C. J. Sheils, D. C. Tahmassebi, and E. T. Kool, *J. Am. Chem. Soc.*, **122**, 2213 (2000); E. T. Kool, J. C. Morales, and K. M. Guckian, *Angew. Chem. Int. Ed.*, **39**, 990 (2000).

[4] M. Hoffer, *Chem. Ber.*, **93**, 2777 (1960).

[5] C. Strässler, N. E. Davis, and E. T. Kool, *Helv. Chim. Acta*, **82**, 2160 (1999).

[6] S. Czernecki and G. Ville, *J. Org. Chem.*, **54**, 610 (1989).

[7] J. Matulic-Adamic, L. Beigelman, S. Portman, M. Egli and N. Usman, *J. Org. Chem.*, 3909, **61** (1996).

[8] A. Alzérreca, E. Hernández, E. Mangual and J. A. Prieto, *J. Heterocyclic Chem.*, **36**, 555 (1999).

[9] M. G. B. Drew, J. Mann and A. Thomas, *J. Chem. Soc. Perkin Trans. 1*, 2279 (1986).

[10] E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

[11] N. L. Allinger and U. Burkert, *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington DC, 1982.

[12] Yields are given after column chromatographic purification.