Dimetalation of Pyrazines. A One-Pot Synthesis of Multisubstituted Pyrazine *C*-Nucleosides

Weimin Liu,† Dean S. Wise,‡ and Leroy B. Townsend*

Department of Medicinal Chemistry, College of Pharmacy, and Department of Chemistry, College of Literature, Science, and the Arts, The University of Michigan Ann Arbor, Michigan 48109

ltownsen@umich.edu

Received November 2, 2000

As a part of our efforts to pursue direct, convergent, and concise methodologies for the synthesis of pyrazine *C*-nucleosides, we have successfully established a sequential dilithiation−addition method, which allows one to introduce two different functional groups to a pyrazine ring in a one-pot fashion. 2,6-Dichloropyrazine was dilithiated at −100 °C and then allowed to react with an electrophile, such as bromine, iodine, or disulfides, followed by a reaction with a protected ribonolactone to afford *C*-nucleosides. After reduction and deprotection, tetrasubstituted pyrazine *C*-nucleosides, including 2,6-dichloro-3-iodo-5-(β-D-ribofuranosyl)pyrazine and 2-bromo-3,5-dichloro-6-(β-D-ribofuranosyl)pyrazine, were obtained. A tandem reaction sequence occurred when disulfides were used, resulting in the formation of 5,6-bis-methylthio-2-chloro-3-(β-D-ribofuranosyl)pyrazine and 6-(β-D-ribofuranosyl)-2,3,5-tris-phenylthiopyrazine.

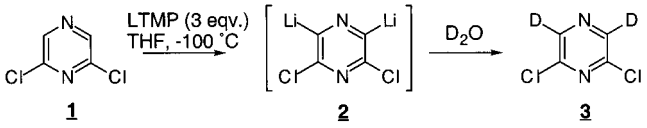
Introduction

The reactions between lithiopyrazines and benzyl-protected ribonolactones have yielded a number of pyrazine *C*-nucleosides.[1] As an extension of this study, we have developed a sequential dilithiation−addition method to synthesize a number of multisubstituted pyrazine *C*-nucleosides. Unlike aliphatic dimetalation which has been used extensively in organic synthesis,[2] dimetalation of aromatic compounds, especially aromatic heterocycles, has remained relatively understudied and underutilized, except in isolated examples.[3,4] Although the lithiation of pyrazines has been studied by several groups,[5,6] no proven dilithiation of this heterocycle has been reported.

Results and Discussion

In our studies, as shown in Scheme 1, 2,6-dichloropyrazine (**1**) was treated with 3 equiv of LTMP at −100 °C for 1 h to give an orange-colored solution, which was visually distinct from the monolithiopyrazine obtained[1] in our previous studies. The reaction was quenched with excess deuterium oxide, and a dideuterated product was detected by GC-MS. Since excess deuterium oxide would react with LTMP, the dideuterated pyrazine must have resulted from a simultaneous dilithiation of 2,6-dichloropyrazine, i.e., the dilithiopyrazine **2**. To the best of our knowledge, this is the first example of a dilithiopyrazine being formed by direct lithiation on the ring. This result is contrary to other findings,[6] where only monodeuterated products were obtained.

Scheme 1



1 **2** **3**

After establishing the conditions for pyrazine dilithiation, we investigated reactions between the corresponding dilithiopyrazines and a number of electrophiles. The results are illustrated in Scheme 2. The addition of 2,3,5-tri-*O*-benzyl-D-ribono-1,4-lactone (**4**) to the dilithiated pyrazine **2** led to the formation of a tetrasubstituted pyrazine (**5a**), which, upon reduction with triethylsilane in the presence of boron trifluoride diethyl etherate, gave 3,5-bis-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-2,6-dichloropyrazine (**6a**). The *C*-2 symmetry of this compound was established by an inspection of the ^{1}H NMR spectrum, which displayed only one set of peaks representing the carbohydrate portion.

Next, we investigated the possibility of introducing sequentially two different electrophiles. Thus, dilithiopyrazine **2** was subjected to the sequential treatment of a variety of electrophiles. In the first reaction sequence, 1 equiv of iodine was added to **2**, followed by 1 equiv of lactone **4** 2 h later to provide the hemiketal **5b**. Reduction of this hemiketal was accomplished with triethylsilane in the presence of boron trifluoride diethyl etherate to give the protected iodopyrazine C-nucleoside, 2,6-dichloro-

† Present address: Boehringer Ingelheim Pharmaceuticals, Inc., P.O. Box 368, Ridgefield, CT 06877.

‡ Berry and Associates, Inc., 2434 Bishop Circle E, Dexter, MI 48130.

(1) (a) Liu, W.; Walker, J. A., II.; Chen, J. J.; Wise, D. S.; Townsend, L. B. *Tetrahedron Lett.* **1996**, *37*, 5325−5328. (b) Walker, J. A., II.; Liu, W.; Wise, D. S.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1236−1241. (c) Liu, W. Ph.D. Thesis, University of Michigan, Ann Arbor, Michigan 1997.

(2) For reviews, see: (a) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, 1994. (b) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1976**, 509−555. (c) Stowell, J. C. *Carbanions in Organic Synthesis;* J. Wiley & Sons: New York, 1979.

(3) (a) Wilson, W. D.; Tanious, F. A.; Watson, R. A.; Baron, H. J.; Strekowska, A.; Harden, D. B.; Srekowski, L. *Biochemistry* **1989**, *28*, 1984−1992. (b) Feringa, B. L.; Hulst, R.; Rikers, R.; Brandsma, L. *Synthesis* **1988**, 316−318.

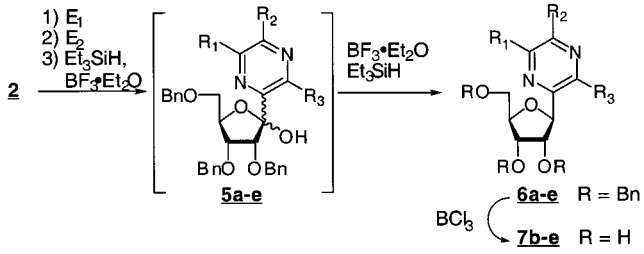
(4) Plé, N.; Turck, A.; Heynderickx, A.; Quéguiner, G. *Tetrahedron* **1998**, *54*, 4899−4912.

(5) Turck, A.; Trohay, D.; Mojovic, L.; Plé, N.; Quéguiner, G. *J. Organomet. Chem.* **1991**, *412*, 301−310.

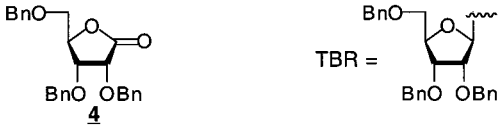
(6) Plé, N.; Turck, A.; Couture, K.; Quéguiner, G. *J. Org. Chem.* **1995**, *60*, 3781−3786.

10.1021/jo001555f CCC: $20.00
Published on Web 06/16/2001

Scheme 2



	E_1	E_2	R_1	R_2	R_3
a	**4**	–	TBR	Cl	Cl
b	I_2	**4**	I	Cl	Cl
b	**4**	I_2	I	Cl	Cl
c	Br_2	**4**	Br	Cl	Cl
d	Ph_2S_2	**4**	PhS-	PhS-	PhS-
e	Me_2S_2	**4**	MeS-	MeS-	Cl



3-iodo-5-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)pyrazine (**6b**). In a second reaction, the addition order was reversed, i.e., lactone **4** was introduced first followed by iodine, and the same product[6b] was obtained. Compound **6b** was then debenzylated with boron trichloride in dichloromethane to furnish 2,6-dichloro-3-iodo-5-(*β*-D-ribofuranosyl)pyrazine (**7b**).

Attempts to access **5b** with *N*-iodosuccinimide (NIS) were unsuccessful. Although NIS has been used as an electrophile in similar reactions, it is not reactive enough to iodinate the lithiopyrazines. We later found that this is a general phenomenon among most of the halogenated succinimides. No halogenation was achieved with *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) when either was allowed to react with dilithiopyrazine **2**. The bromopyrazine C-nucleoside was eventually obtained by reacting dilithiopyrazine **2** with 1 equiv of bromine followed by the introduction of lactone **4** 2 h later. The tetrasubstituted pyrazine hemiketal (**5c**) was isolated and then reduced to give 2-bromo-3,5-dichloro-6-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)pyrazine (**6c**). Debenzylation of this compound afforded 2-bromo-3,5-dichloro-6-(*β*-D-ribofuranosyl)pyrazine (**7c**).

In our search for other electrophiles, we found a literature report[7] where 6-lithiouridines were reacted with phenyl disulfide. We followed this procedure by treating **2** first with 1 equiv of phenyl disulfide then with 1 equiv of lactone **4**. This afforded a complex reaction mixture from which a sugar adduct (**5d**) was isolated in 37% yield. Treatment of this material with triethylsilane in the presence of boron trifluoride diethyl etherate in dichloromethane afforded a protected *C*-nucleoside (**6d**). The ^{1}H NMR spectrum of this compound indicated that the product contained multiple phenylthio group substitutions. Unfortunately, the aromatic peaks for the *O*-benzyl groups on the sugar moiety also appear in the same region, making it difficult to identify the number of phenylthio groups on the molecule. This problem was resolved by removing the benzyl groups on the sugar moiety. The treatment of **6d** with boron trichloride furnished the free nucleoside **7d** as a light yellow crystalline product. That a complete removal of the protecting groups had been accomplished was apparent from the absence of benzylic signals in the ^{1}H NMR spectrum of the compound. However, the ^{1}H NMR spectrum of this compound indicated that there were still three phenyl groups in the aromatic region. This result suggested that, instead of the expected single phenylthio group, three phenylthio groups had been introduced onto the pyrazine ring. The ^{13}C NMR spectrum and elemental analysis of **6d** also supported this structure. Evidently, compound **5d** was a result of a nucleophilic substitution by phenylthiolithium, the byproduct of the first nucleophilic reaction between the pyrazine dianion and phenyl disulfide. Thus, compound **6d** and **7d** were identified as 2,3,5-tris-phenylthio-6-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)pyrazine and 2,3,5-tris-phenylthio-6-(*β*-D-ribofuranosyl)pyrazine, respectively. Because phenyl disulfide is a very reactive electrophile, it is possible that the pyrazine dianion may react with two molecules of the disulfide, especially toward the end of the addition when the majority of the dianion has been consumed. The disproportionate consumption of pyrazine dianion could generate excess phenylthiolithium, which, in return, would serve as a nucleophile. This hypothesis could also explain the low yield of the nucleoside and the formation of the less polar byproducts.

The secondary nucleophilic substitution which had occurred in the above reaction presented us a new prospect for this type of synthesis. To understand the above reaction sequence better, we chose methyl disulfide and repeated the above sequence. In this instance the methyl peak of the methylthio group is very distinct in the ^{1}H NMR spectra, which would make it easy for us to follow the reaction. Therefore, dilithiopyrazine **2** was first treated with 1 equiv of methyl disulfide at −100 °C, and 2 h later with 1 equiv of lactone **4** to afford **5e**. Unlike the reaction of phenyl disulfide, only two peaks representing methyl groups were detected in the ^{1}H NMR spectrum of the hemiketal, indicating the presence of only two methylthio groups in this compound. Reduction of the hemiketal **5e** by triethylsilane and boron trifluoride diethyl etherate gave 2-chloro-5,6-bis-methylthio-3-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)pyrazine (**6e**). The free nucleoside, 2-chloro-5,6-bis-methylthio-3-(*β*-D-ribofuranosyl)pyrazine (**7e**) was obtained by debenzylation of **6e** with boron trichloride. The ^{1}H NMR of **7e** confirmed that only two methylthio groups were introduced in this reaction sequence. The regiochemistry of these two groups was determined by a NOE experiment on **6e**. When either methyl peak was irradiated, an enhancement was observed on the other methyl peak. This result established the ortho relationship between the two methyl peaks.

Conclusion

In conclusion, we have prepared and studied the chemistry of a dilithopyrazine. This dilithiopyrazine has

(7) Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Tetrahedron* **1982**, *38*, 2635−2642.

been successfully used in sequential addition reactions, allowing two different functional groups to be introduced onto the pyrazine ring. This reaction sequence provides an efficient method to access multisubstituted pyrazine *C*-nucleosides. When the first nucleophilic substitution between the dianion and an electrophile releases a nucleophilic byproduct, a secondary nucleophilic substitution reaction might occur at the pyrazine, thus allowing up to four new functional groups to be added to the pyrazine ring.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used as provided. Acetonitrile (calcium hydride), dichloromethane (phosphorus pentoxide), dimethylformamide (calcium oxide), nitromethane (phosphorus pentoxide), and tetrahydrofuran (sodium/benzophenone) were distilled from the indicated drying agent and stored over activated 4 Å molecular sieves under a positive pressure of argon prior to use (if not used immediately). The phrase "evaporated in vacuo" describes the use of a rotary evaporator with a bath temperature not exceeding 40 °C using a water aspirator. Thin-layer chromatography (TLC) was carried out on Analtech 60F-254 silica gel plates, and detection of components on TLC was made by UV light absorption at 254 nm, 365 nm, staining with iodine vapor, or heating to a char following treatment with 10% sulfuric acid in methanol. Solvent systems are expressed as a ratio of the more polar component with respect to total volumes (v/v%). Mallinckrodt SilicAR 230−400 mesh (40−63 μm) was used for chromatography. Melting points are uncorrected. The ^{1}H (300, 360, or 500 MHz) and ^{13}C (67.5, 90, or 125 MHz) NMR spectra were recorded, and the chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard for ^{1}H NMR, and relative to the standard chemical shift of the solvent for ^{13}C NMR. Mass spectroscopy and elemental analyses were performed by the University of Michigan Chemistry Department or by MHW Laboratories, Phoenix, AZ.

3,5-Bis(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-2,6-dichloropyrazine (6a). To a solution of *n*-butyllithium (1.6 M solution in hexane, 7.5 mL, 12.0 mmol) in 40 mL of dry THF at 0 °C under argon was added 2,2,6,6-tetramethylpiperidine (2.0 mL, 12.0 mmol). The reaction mixture was stirred at 0 °C for 30 min at which time the pale yellow solution was cooled to −78 °C. A solution of 2,6-dichloropyrazine[8] (0.75 g, 5.0 mmol) in 30 mL of dry THF was then added dropwise, and the reaction mixture was stirred at −78 °C for 1 h to give an orange-colored solution. 2,3,5-Tri-*O*-benzyl-D-ribono-1,4-lactone (4.18 g, 10.0 mmol) was dissolved in 40 mL of dry THF and then transferred dropwise into the lithiopyrazine solution at −78 °C. The mixture was stirred at −78 °C for 3 h, and the reaction was then warmed to room temperature and stirred for an additional 10 h. The reaction mixture was quenched by the addition of a saturated ammonium chloride solution and then extracted with diethyl ether (3 × 30 mL). The combined extracts were dried over magnesium sulfate, and after filtration, the solvent was removed in vacuo. The resultant orange oil was purified by silica gel flash chromatography (5 × 18 cm) and eluted with ethyl acetate/hexane (1:4, R_f = 0.4) to give **5a** as a clear oil (3.16 g, 64% yield). This oil was then dissolved in 60 mL of dry dichloromethane. Boron triflouride diethyl etherate (1.20 mL, 9.0 mmol) and triethylsilane (1.44 mL, 9.0 mmol) were added to this solution at −78 °C, under argon. The mixture was allowed to stand at 5 °C for 5 days, quenched with a saturated sodium bicarbonate solution, and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was purified by silica gel flash chromatography (4 × 10 cm) and eluted with ethyl acetate/hexane (1:19, R_f = 0.3) to give **6a** as a clear oil (2.09 g 69% yield). ^{1}H NMR ($CDCl_3$) δ 7.31−7.15 (m, 30H), 4.97 (d, J = 6.2 Hz, 2H), 4.72−4.44 (m, 16H), 4.09 (m, 2H), 3.66 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 150.1, 145.8, 138.2, 137.8, 137.6, 137.3, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 128.0, 127.7, 83.0, 80.8, 78.6, 77.8, 73.6, 72.8, 72.5, 70.4. Anal. Calcd for $C_{60}H_{54}Cl_2N_2O_8$: C, 70.50; H, 5.71; N, 2.94. Found: C, 70.85; H, 6.04; N, 2.84.

2,6-Dichloro-3-iodo-5-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)pyrazine (6b). Method A: To a solution of *n*-butyllithium (1.6 M solution in hexane, 10 mL, 16.0 mmol) in 50 mL of dry THF at 0 °C under argon was added 2,2,6,6-tetramethylpiperidine (2.70 mL, 16.0 mmol). The mixture was stirred at 0 °C for 30 min at which time the pale yellow solution was cooled to −100 °C. A solution of 2,6-dichloropyrazine (0.90 g, 6.0 mmol) in 30 mL of dry THF was then added dropwise, and the mixture was stirred at −100 °C for 1 h to give an orange-colored solution. Iodine (1.52 g, 6.0 mmol) in 30 mL of dry THF was added dropwise while the temperature was maintained at −100 °C for 2 h. 2,3,5-Tri-*O*-benzyl-D-ribono-1,4-lactone (2.51 g, 6.0 mmol) was dissolved in 30 mL of dry THF and then transferred dropwise into the lithiopyrazine solution at −100 °C. The mixture was stirred at −100 °C under argon for 3 h and then warmed to room temperature and stirred for 10 h. The reaction was quenched by the addition of a saturated ammonium chloride solution (30 mL). The reaction mixture was extracted with diethyl ether (3 × 50 mL), and the combined extracts were dried over magnesium sulfate. After filtration, the solvent was removed in vacuo, and the resultant orange oil was purified by silica gel flash chromatography (4 × 10 cm) and eluted with ethyl acetate/hexane (1:5, R_f = 0.45) to give **5b** as a clear oil (3.05 g, 73% yield). This oil was dissolved in 60 mL of dry dichloromethane. To this solution at −78 °C, under argon, were added boron trifluoride diethyl etherate (3.60 mL, 30.0 mmol) and triethylsilane (4.60 mL, 20.0 mmol). The mixture was allowed to stand at 0 °C for 24 h, quenched with a saturated sodium bicarbonate solution, and extracted with diethyl ether (3 × 40 mL). The combined extracts were dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was purified by silica gel flash chromatography (4 × 8 cm) and eluted with ethyl acetate/hexane (1:9, R_f = 0.3) to give **6b** as a clear oil (2.40 g, 79% yield). ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 15H), 5.34(d, 1H, J = 6.0 Hz), 4.69−4.38 (m, 6H), 4.37 (ABq, J = 4.5 Hz, 1H), 4.32 (dd, J = 5.8 Hz, 1H), 4.11 (dd, J = 4.8 Hz, 1H), 3.56 (d, J = 4.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 152.0, 150.8, 146.8, 138.3, 137.7, 128.7, 128.6, 128.6, 128.4, 128.1, 127.9, 127.8, 115.4, 83.1, 80.9, 78.8, 77.9, 73.7, 72.9, 72.6, 70.5. Anal. Calcd for $C_{30}H_{27}Cl_2IN_2O_4$: C, 53.20; H, 4.02; N, 4.14. Found: C, 53.46; H, 4.15; N, 4.11.

Method B: The dilithiopyrazine was prepared as in method A. 2,3,5-Tri-*O*-benzyl-D-ribono-1,4-lactone was dissolved in 30 mL of dry THF and then transferred dropwise into the dilithiopyrazine solution at −100 °C. The reaction mixture was stirred at −100 °C for 1.5 h, and then the iodine solution was added. The reaction was worked up as described in method A to give the intermediate **5b** in 74% yield.

3,5-Dichloro-2-iodo-6-(β-D-ribofuranosyl)pyrazine (7b). Compound **6b** (2.40 g, 3.54 mmol) was dissolved in 30 mL of dry dichloromethane. At −78 °C, under argon, boron trichloride (1.0 M, 20 mL, 20 mmol) was added. The reaction mixture was kept at 0 °C for 10 h and then quenched with 5 mL of water and 0.5 g of sodium bicarbonate. The solvent was removed in vacuo, and the residue was purified by silica gel flash chromatography (4 × 7 cm) and eluted with methanol/dichloromethane (1:19, R_f = 0.2) to give **7b** as a white crystalline product (1.20 g, 83% yield). mp 154−155 °C. ^{1}H NMR (acetone-d_6) δ 5.24 (d, J = 3.8 Hz, 1H), 4.44 (dd, J = 3.1 Hz, 1H), 4.29 (dd, J = 3.90 Hz, 1H), 4.06−4.11 (m, 1H), 3.75−3.85 (m, 1H), 3.62−3.65 (m, 1H). ^{13}C NMR (acetone-d_6) δ 152.8, 151.6, 145.8, 115.8, 85.6, 81.3, 76.0, 71.4, 62.0. Anal. Calcd for $C_9H_9Cl_2IN_2O_4$: C, 26.56; H, 2.23; N, 6.88. Found: C, 26.34; H, 2.26; N, 6.80.

(8) Purchased from Pyrazine Specialties, Inc. or prepared from chloropyrazine as described: Cheeseman, G. W. H.; Törzs, E. S. G. Pyrazines. *J. Chem. Soc. (C)* **1965**, 6681−6688.

2-Bromo-3,5-dichloro-6-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)pyrazine (6c). This was prepared following a similar procedure described in method A. ^{1}H NMR ($CDCl_3$) δ 7.15−7.37 (m, 15H), 5.37 (d, J = 6.2 Hz, 1H), 4.69−4.32 (m, 9H), 4.12 (dd, J = 4.6 Hz, 1H), 3.57 (d, J = 4.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 150.1, 145.8, 138.2, 137.8, 137.6, 137.3, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 128.0, 127.7, 83.0, 80.8, 78.6, 77.7, 73.6, 72.8, 72.5, 70.4. Anal. Calcd for $C_{30}H_{27}BrCl_2N_2O_4$: C, 57.16; H, 4.12; N, 4.44. Found: C, 57.42; H, 4.54; N, 4.47.

2-Bromo-3,5-dichloro-6-(*β*-D-ribofuranosyl)pyrazine (7c). This was prepared following a similar procedure described in **7b**. ^{1}H NMR (DMSO-d_6) δ 5.26 (d, J = 4.8 Hz, 1H), 5.05 (dd, J = 5.9 Hz, 2H), 4.59 (dd, J = 5.0 Hz, 1H), 4.21 (ddd, J = 4.8 Hz, 1H), 3.94 (ddd, J = 5.5 Hz, 1H), 3.88 (ddd, J = 5.3 Hz, 1H), 3.40−3.58 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 151.3, 146.1, 144.4, 136.9, 85.1, 80.2, 74.5, 71.1, 61.9. Anal. Calcd for $C_9H_9BrCl_2N_2O_4$: C, 30.03; H, 2.52; N, 7.78. Found: C, 30.19; H,2.29; N,7.58.

2,3,5-Tris-phenylthio-6-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)pyrazine (6d). To a solution of *n*-butyllithium (1.6 M solution in hexane, 4.5 mL, 7.2 mmol) in 40 mL of dry THF at 0 °C under argon was added 2,2,6,6-tetramethylpiperidine (1.2 mL, 7.2 mmol). The mixture was stirred at 0 °C for 30 min at which time the pale yellow solution was cooled to −100 °C. A solution of 2,6-dichloropyrazine (0.45 g, 3.0 mmol) in 30 mL of dry THF was then added dropwise, and the mixture was stirred at −100 °C for 1 h to give an orange colored solution. Phenyl disulfide (0.655 g, 3.0 mmol) was added, and then the reaction mixture was kept at −100 °C for 2 h. 2,3,5-Tri-*O*-benzyl-D-ribono-1,4-lactone (1.26 g, 3.0 mmol) was dissolved in 30 mL of dry THF and then transferred dropwise into the lithiopyrazine solution at −100 °C. The mixture was stirred at −100 °C under argon for 3 h and then warmed to room temperature and stirred for an additional 10 h. The reaction was quenched by the addition of a saturated ammonium chloride solution. The reaction mixture was extracted with diethyl ether (3 × 30 mL), and the combined organic phase was dried over magnesium sulfate. After filtration, the solvent was removed in vacuo, and the resultant yellow oil was purified by silica gel flash chromatography (4 × 8 cm) and eluted with ethyl acetate/hexane (1:6, R_f = 0.4) to give **5d** as a clear oil (0.424 g, 35% yield). This oil was then dissolved in 60 mL of dry dichloromethane. To this solution at −78 °C, under argon, were added boron trifluoride diethyl etherate (1.90 mL, 15.8 mmol) and triethylsilane (2.00 mL, 8.70 mmol). The mixture was allowed to stand at 5 °C for 72 h, quenched with a saturated sodium bicarbonate solution, and extracted with diethyl ether (3 × 30 mL). The combined extracts were dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified by silica gel flash chromatography (2 × 10 cm) and eluted with ethyl acetate/hexane (1:19, R_f = 0.5) to give **6d** as an oil (0.351 g, 84% yield). ^{1}H NMR ($CDCl_3$) δ 7.41−7.10 (m, 30H), 5.40 (d, J = 4.8 Hz, 1H), 4.50−4.25 (m, 7H), 4.04 (dd, J = 4.8 Hz, 1H), 3.68 (dd, J = 5.7 Hz, 1H), 3.32−3.25 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 152.9, 150.6, 149.2, 146.2, 138.6, 138.3, 138.2, 135.6, 135.2, 134.7, 130.2, 129.4, 129.3, 129.2, 129.1, 129.1, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 81.5, 80.2, 79.8, 78.9, 77.6, 73.4, 72.2, 70.9. Anal. Calcd for $C_{48}H_{42}N_2O_4S_3$: C, 71.43; H, 5.25; N, 3.47. Found: C, 71.18; H, 5.35; N, 3.33.

2,3,5-Tris-phenylthio-6-(*β*-D-ribofuranosyl)pyrazine (7d). This was prepared following a similar procedure described in **7b**. ^{1}H NMR (DMSO-d_6) δ 7.56−7.21 (m, 15H), 4.96 (d, J = 5.2 Hz, 2H), 4.75 (d, J = 5.7 Hz, 1H), 4.46 (dd, J = 5.7 Hz, 1H), 3.95 (ddd, J = 5.0 Hz, 1H), 3.67 (ddd, J = 5.1 Hz, 1H), 3.55 (ddd, J = 5.5 Hz, 1H), 3.00−3.21 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 151.7, 149.7, 148.4, 147.5, 134.2, 134.1, 133.5, 129.6, 129.5, 129.4, 129.3, 129.1, 128.5, 127.5, 85.1, 80.4, 73.9, 71.8, 62.3. HRMS calcd for $C_{27}H_{24}N_2O_4S_3$: 536.0898. Found 536.0897.

2-Chloro-3,5-bis-methylthio-6-(2,3,5-tri-*O*-benzyl-*β*-D-ribofuranosyl)pyrazine (6e). To a solution of *n*-butyllithium (1.6 M solution in hexane 13.0 mL, 20.8 mmol) in 100 mL of dry THF at 0 °C under argon was added 2,2,6,6-tetramethylpiperidine (3.40 mL, 20.0 mmol). The mixture was stirred at 0 °C for 30 min at which time the pale yellow solution was cooled to −100 °C. A solution of 2,6-dichloropyrazine (1.50 g, 10.0 mmol) in 30 mL of dry THF was then added dropwise, and the mixture was stirred at −100 °C for 1 h to give an orange-colored solution. Methyl disulfide (0.90 mL, 10.0 mmol) was added, and the reaction mixture was kept at −100 °C for 2 h. 2,3,5-Tri-*O*-benzyl-D-ribono-1,4-lactone (4.18 g, 10.0 mmol) was dissolved in 50 mL of dry THF and then transferred dropwise into the lithiopyrazine solution at −100 °C. The mixture was stirred at −100 °C under argon for 3 h and then warmed to room temperature and stirred for 10 h. The reaction was quenched by the addition of a saturated ammonium chloride solution. The reaction mixture was extracted with diethyl ether (3 × 50 mL), and the combined extracts were dried over magnesium sulfate. After filtration, the solvent was removed in vacuo and the resultant yellow oil was purified by silica gel flash chromatography (5 × 12 cm) and eluted with ethyl acetate/hexane (1:5, R_f = 0.5) to give **5e** as a clear oil (4.25 g, 68% yield). This oil was then dissolved in 60 mL of dry dichloromethane. To this solution at −78 °C, under argon, were added boron trifluoride diethyl etherate (5.0 mL, 50.2 mmol) and triethylsilane (10.0 mL, 40.0 mmol). The mixture was allowed to stand at 5 °C for 72 h, quenched with a saturated sodium bicarbonate solution, and extracted with diethyl ether (3 × 50 mL). The combined extracts were dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was purified by silica gel flash chromatography (4 × 10 cm) and eluted with ethyl acetate/hexane (1:19, R_f = 0.5) to give **6e** as a crystalline solid (2.68 g, 65% yield). mp 78−79 °C. ^{1}H NMR ($CDCl_3$) δ 7.34−7.21 (m, 15H), 5.51(d, 1H, J = 4.8 Hz), 4.70−4.51 (m, 6H), 4.44−4.41 (m, 1H), 4.33−4.31 (m, 1H), 4.24−4.21 (m, 1H), 3.60−3.65 (m, 2H), 2.60 (s, 3H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 154.5, 452.9, 143.7, 142.9, 138.5, 138.2, 138.0, 128.9, 128.7, 128.4, 128.3, 128.3, 128.1, 128.0, 81.9, 80.3, 79.9, 77.9, 77.9, 73.9, 73.5, 72.4, 70.6, 13.9, 13.6. Anal. Calcd for $C_{32}H_{33}N_2O_4S_2$: C, 63.09; H, 5.46; N, 4.60. Found: C, 62.89; H, 5.36; N, 4.71.

2-Chloro-5,6-bis-methylthio-3-(*β*-D-ribofuranosyl)pyrazine (7e). This was prepared following a similar procedure described in **7b**. ^{1}H NMR ($CDCl_3$) δ 5.37 (d, J = 5.7 Hz, 1H), 4.57 (m, J = 5.7 Hz, 1H), 4.44 (m, J = 4.6 Hz, 1H), 4.21 (m, 1H), 3.92 (m, J = 12.0, 2.7 Hz, 1H), 3.74 (ddd, J = 11.8, 10.2, 2.0 Hz, 1H), 2.83 (dd. J = 7.4, 2.6 Hz, 1H), 2.60 (s, 3H). 2.58 (s, 3H), 2.53 (m, 2H). ^{13}C NMR (acetone-d_6) δ 154.5, 153.5, 145.6, 143.3, 86.2, 81.8, 76.3, 73.3, 63.2, 13.5, 13.4. Anal. Calcd for $C_{11}H_{15}ClN_2O_4S_2$: C, 38.99; H, 4.46; N, 8.27. Found: C, 38.75; H, 4.36; N, 8.12.

Acknowledgment. The authors would like to thank Mr. Jack Hinkley for the large-scale preparation of compounds and Ms. Kimberly Barrett for assistance in the preparation of this manuscript. This research was supported by research grant 5-R01-AI-36872 from the National Institute of Allergy and Infectious Diseases, the National Institutes of Health.

JO001555F