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Efficient Synthesis of 2′-*C*-*β*-Methylguanosine

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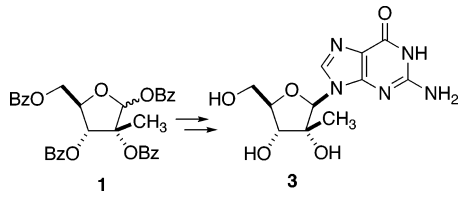

2′-*β*-Methyl nucleosides have potential value as therapeutic agents and as nucleoside analogues for exploring RNA biology. Here we develop a strategy for efficient synthesis for 2′-*C*-*β*-methylguanosine (**3**). Starting from 1,2,3,5-tetra-*O*-benzoyl-2-*C*-*β*-methyl-D-ribofuranose (**1**) and N^2-acetylguanine, we obtained the title compound in two steps (78% overall yield) with high stereoselectivity (β/α > 99:1) and high regioselectivity (N9/N7 > 99:1). Extension of this strategy to the classic synthesis of guanosine also resulted in high stereoselectivity (β/α = 99:1) and improved regioselectivity (N9/N7 = 97:3).

2′-*C*-Branched nucleosides have attracted much attention as potential anticancer and antiviral agents and as probes to study nucleic acid biology.[1−3] Recently, Eldrup et al. identified 2′-*C*-*β*-methylribonucleosides as potent nucleoside inhibitors of Hepatitis C virus RNA replication.[2,3] Considering their ability to impart nuclease resistance to oligonucleotides, *β*-branched nucleosides also hold promise as components of oligonucleotide regulators of gene expression via antisense, ribozyme, or small interfering RNAs. Our interest in *β*-branched nucleosides emanates from their potential to reveal structural and mechanistic features of RNA-mediated biological processes.[4] For example, the strong preference of 2′-*β*-methyl nucleosides for the 3′-endo sugar pucker provides a strategy to probe the conformation of specific residues within a functional RNA.[5] Additionally, *β*-branched nucleosides present a structural context in which to install substituents of varying electron-withdrawing power, thereby enabling systematic variation of the 2′-hydroxyl group pK_a.[6−9] Here we focus on the synthesis of 2′-*C*-*β*-methylguanosine, which we hope to use for mechanistic investigations of group I intron self-splicing.[10]

Two syntheses of 2′-*C*-*β*-methylguanosine have been reported in the literature, both involving glycosylation of purines with an appropriately protected 2′-*C*-*β*-methylribose derivative.[2,11] In a 1968 patent, Walton described the synthesis of 2′-*C*-*β*-methylguanosine via the reaction of 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-*β*-D-ribofuranosyl chloride with chloromercuripurine. Preparation of the glycosylating agent required eight steps from 2,3-*O*-isopropylidene-D-glyceraldehyde and gave low overall yield.[11,12] Additionally, the yield and selectivity of the glycosylation reactions with this reagent were not disclosed.

Recently, Harry-O'kuru et al. reported an efficient synthesis of the 2′-*C*-*β*-methyl ribofuranosylating agent, 1,2,3,5-tetra-*O*-benzoyl-2-*C*-methyl-D-ribofuranose (**1**), in three steps (43% overall yield) starting from commercially available 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (Pfanstiehl Laboratories, Inc.).[1,13] This reagent glycosylates persilylated nucleobases (uracil, 6-azauracil, N^6-benzoyladenine, and 6-methylthiopurine), but the reaction with guanine was not reported. Franchetti et al. used **1** in reactions with 6-chloropurine and 2,6-dichloropurine and obtained the corresponding nucleoside derivatives in high yields.[14] Isis Pharmaceuticals and Merck Research Laboratories extended this approach to 2-amino-6-chloropurine, leading to the synthesis of 2′-*C*-*β*-methylguanosine in three steps from **1** with 34% overall yield.[2] Here we show by systematic investigation of reaction conditions that **1** reacts directly with persilylated N^2-acetylguanine, resulting in an efficient two-step synthetic approach to 2′-*C*-*β*-methylguanosine.

In 1981, Vorbrüggen et al. described the synthesis of guanosine by glycosylation of persilylated N^2-acetylguanine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (**4**).[15] Under thermodynamic conditions (trimethylsilyl triflate as catalyst/1,2-dichloroethane as solvent/at reflux), the glycosylation gave N9 and N7 products in a ∼6:1 ratio (79% yield).[16] To improve the regioselectivity for the N9 isomer, Robins and co-workers[17,18] used persilylated N^2-acetyl-6-*O*-diphenylcarbamoylguanine, which bears a bulky protecting group at the 6-oxygen atom. Reaction

(1) Harry-O'kuru, R. E.; Smith, J. M.; Wolfe, M. S. *J. Org. Chem.* **1997**, *62*, 1754 and references therein.
(2) Eldrup, A. B.; Allerson, C. R.; Bennett, C. F.; Bera, S.; Bhat, B.; Bhat, N.; Bosserman, M. R.; Brooks, J.; Burlein, C.; Carroll, S. S.; Cook, P. D.; Getty, K. L.; MacCoss, M.; McMasters, D. R.; Olson, D. B.; Prakash, T. P.; Prhavc, M.; Song, Q.; Tomassini, J. E.; Xia, J. *J. Med. Chem.* **2004**, *47*, 2283.
(3) Eldrup, A. B.; Prhavc, M.; Brooks, J.; Bhat, B.; Prakash, T. P.; Song, Q.; Bera, S.; Bhat, N.; Dande, P.; Cook, P. D.; Bennett, C. F.; Carroll, S. S.; Ball, R. G.; Bosserman, M.; Burlein, C.; Colwell, L. F.; Fay, J. F.; Flores, O. A.; Getty, K.; LaFemina, R. L.; Leone, J.; MacCoss, M.; McMasters, D. R.; Tomassini, J. E.; Langen, D. V.; Wolanski, B.; Olson, D. B. *J. Med. Chem.* **2004**, *47*, 5284.
(4) Gordon, P. M.; Fong, R.; Deb, S.; Li, N.-S.; Schwans, J. P.; Ye, J.-D.; Piccirilli, J. A. *Chem. Biol.* **2004**, *11*, 237.
(5) Li, N.-S.; Piccirilli, J. A. *J. Org. Chem.* **2003**, *68*, 6799.
(6) Li, N.-S.; Tang, X.-Q.; Piccirilli, J. A. *Org. Lett.* **2001**, *3*, 1025.
(7) Tang, X.-Q.; Liao, X.; Piccirilli, J. A. *J. Org. Chem.* **1999**, *64*, 747.
(8) Ye, J.-D.; Liao, X.; Piccirilli, J. A. *J. Org. Chem.* **2005**, *70*, 7902.
(9) Dai, Q.; Piccirilli, J. A. *Org. Lett.* **2003**, *5*, 807.
(10) Cech, T. R.; Herschlag, D. In *Catalytic RNA*, 2nd ed.; Lilley, D. M. J., Eckstein, F., Eds.; Springer: New York, 1997.
(11) Walton, E. France Patent 1521076, 1968.
(12) Lopez-Herrera, F. J.; Sarabia-Garcia, F.; Pino-Gonzalez, M. S.; Garcia-Aranda, J. F. *J. Carbohydr. Chem.* **1994**, *13*, 767.
(13) Cook, G. P.; Greenberg, M. M. *J. Org. Chem.* **1994**, *59*, 4704.
(14) Franchetti, P.; Cappellacci, L.; Marchetti, S.; Trincavelli, L.; Martin, C.; Mazzoni, M. R.; Lucacchini, A.; Grifantini, M. *J. Med. Chem.* **1998**, *41*, 1708.
(15) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
(16) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1988**, *53*, 1294.
(17) Zou, R.; Robins, M. J. *Can. J. Chem.* **1987**, *65*, 1436.
(18) Robins, M. J.; Zou, R.; Guo, Z.; Wnuk, S. F. *J. Org. Chem.* **1996**, *61*, 9207.

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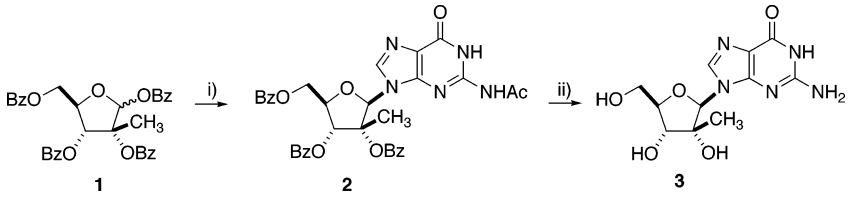
SCHEME 1[a]



[a] Reagents and conditions: (i) persilylated N^2-acetylguanine (2.5 equiv), TMSOTf (2.5 equiv), *p*-xylene, reflux, 6 h, 80%; (ii) NH_3/MeOH, 0−4 °C, 48 h, 98%.

with 1,2,3,5-tetra-*O*-acetyl-*β*-D-ribofuranose in toluene (80 °C) gave the 9-glycosyl guanine derivative exclusively (91% yield).

To construct 2′-*C*-*β*-methylguanosine, we began with persilylated N^2-acetyl-6-*O*-diphenylcarbamoylguanine, hoping to direct regiochemistry (N-9) in the same manner as Robins et al.[17,18] We investigated the reaction of this nucleobase with **1** using trimethylsilyl triflate as catalyst. After being stirred overnight either in toluene at 80 °C or in refluxing benzene, the reaction mixture produced no glycosylation product, as judged by TLC. Although some **1** remained, the protected nucleobase decomposed completely. Refluxing the reaction mixture overnight in toluene resulted in decomposition of both **1** and the nucleobase. Refluxing the reaction mixture in 1,2-dichloroethane for 8 h completely consumed **1** and generated the N9 and N7 regioisomers in ∼40% yield, isolated as a ∼7:3 mixture of N^2-acetyl-2′,3′,5′-tri-*O*-benzyl-2′-*C*-*β*-methylguanosine and the N^2-acetyl-2′,3′,5′-tri-*O*-benzyl-2′-*C*-*β*-methyl-7-guanosine.[19] However, these products lacked the diphenylcarbamyl group, apparently precluding its regioselective advantage during the reaction.

We therefore considered the use of N^2-acetylguanine directly in reactions with **1** (Scheme 1). We carried out reactions under a range of conditions (varying molar ratio of reactants and catalyst, solvent, reaction temperature, and time). The results are summarized in Table 1. For optimization of conditions, all reactions contained 0.1 mmol sugar substrate. Under the conditions used by Harry-O'Kuru et al. (refluxing acetonitrile with trimethylsilyl triflate as catalyst[1]) the reaction gave the regioisomers in lower yield and with weaker stereoselectivity relative to other conditions (Table 1, entries 1 and 2). In refluxing benzene, the reaction remained incomplete after 24 h (Table 1, entry 3). We varied solvent and found the N9-regioselectivity to increase in the following order: MeCN < 1,2-dichloroethane < benzene < toluene < *o*-xylene < *m*-xylene < *p*-xylene, mirroring the polarity and boiling point (reaction temperature) orders. Apparently, nonpolar solvents and higher reaction temperatures favor the thermodynamic product (N9), as described previously for the synthesis of guanosine.[16] Without silylation, N^2-acetylguanine exhibited no regioselectivity in the reaction with **1** (Table 1, entry 10). Use of *tert*-butyldimethylsilyl triflate instead of trimethylsilyl triflate as catalyst had no significant effect on the reaction (Table 1, entries 8 and 9). We achieved the highest N9-regioselectivity (N9/N7 = 98:2) using *p*-xylene at 140 °C for 5 h (Table 1, entry 12). Shorter reaction times (Table 1, entries 12 and 15) or less nucleobase and catalyst (Table 1, entries 12 and 16) decreased the formation of the 9-*β*-isomer. After we adjusted the reaction time and the reagent amount appropriately, we carried out the glycosylation on a 1.0 mmol scale in refluxing *p*-xylene for 6 h using a molar ratio of sugar:nucleobase:catalyst = 1:2.5:2.5. The reaction proceeded with N9-isomer regioselectivity and gave the 2′-*C*-*β*-methylguanosine derivative **2** in 80% yield.

TABLE 1. Reaction of Persilylated N^2-Acetylguanine with 1,2,3,5-Tetra-*O*-benzoyl-2-*C*-*β*-methyl-D-ribofuranose (1)

entry[a]	molar ratio[b]	solvent	temp (°C)	time (h)	ratio[c]	yield (%)[d]
1	1:4:4	MeCN	reflux (82)	5	74:26	43
2	1:4:4	MeCN	reflux (82)	22	90:10	44
3	1:4:4	benzene	reflux (80)	24	91:9	27
4	1:4:4	$ClCH_2CH_2Cl$	reflux (84)	5	90:10	68
5	1:4:4	$ClCH_2CH_2Cl$	reflux (84)	16	89:11	64
6	1:4:4	$ClCH_2CH_2Cl$	reflux (84)	22	90:10	74
7	1:4:4	toluene	100	24	93:7	63
8	1:4:5.5	toluene	reflux (111)	19	96:4	65
9[e]	1:4:5.5	toluene	reflux (111)	22	95:5	65
10[f]	1:4:5.5	toluene	reflux (111)	24	50:50	50
11	1:4:4	*m*-xylene	100	22	94:6	58
12	1:4:4	*p*-xylene	140	5	98:2	89
13	1:4:4	*o*-xylene	140	5	96:4	57
14	1:4:4	*m*-xylene	140	5	97:3	72
15	1:4:4	*p*-xylene	140	3	95:5	88
16	1:2:2	*p*-xylene	140	8	94:6	91
17[g]	1:2.5:2.5	*p*-xylene	reflux (140)	6	>99:1	80

[a] All reactions were carried out on a 0.1 mmol scale of sugar substrate except entry 17, which was carried out on a 1.0 mmol scale. [b] Sugar: nucleobase:catalyst. [c] Ratio calculated by the integration of 1′-H (*δ* 6.72 and 6.98) from ^{1}H NMR spectra. [d] Isolated yield of 7- and 9-*β*-isomers. [e] *tert*-Butyldimethylsilyl triflate as a catalyst. [f] In this experiment, the base was not persilylated. [g] 1.0 mmol scale.

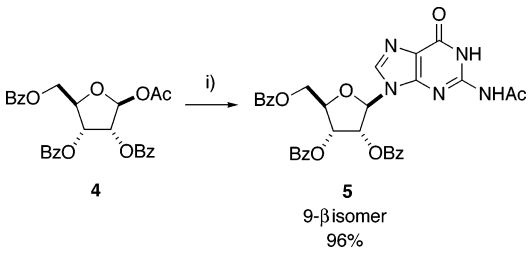
Deprotection of **2** with ammonia in methanol gave 2′-*C*-*β*-methylguanosine (**3**) in 98% yield. The structure of **3** was confirmed by a 1D NOE difference experiment. When the 2′-methyl (*δ* 0.80) was irradiated, we observed NOEs for 3′-H (3.9%), 8-H (1.9%), 1′-H (4.5%), and 2′-OH (5.9%). These results indicate that the 2′-*C*-methyl group, 3′-H, and guanine base are on the same side of the ribose ring. The NOE between the 2′-methyl group and 1′-H and the large $J_{3'-4'}$ coupling constant (9.1 Hz) suggest that **3** populates the 3′-endo configuration predominantly. For nucleosides that populate the 2′-endo configuration, the 3′-H and 4′-H usually exhibit significantly smaller $J_{3'-4'}$ values (∼2.0−2.5 Hz).[20]

The high regioselectivity, stereoselectivity, and yield achieved for the reaction of N^2-acetylguanine with **1** prompted us to examine the effect of different solvents on the classic Vorbrüggen reaction, which involves the glycosylation of persilylated N^2-acetylguanine with ribofuranose **4** to give **5** (Scheme 2). We carried out the reaction in refluxing 1,2-dichloroethane, toluene, and *p*-xylene (Table 2). Refluxing the reactants in toluene for 6 h (Table 2, entry 4) gave the highest 9-*β* regioselectivity (9-*β*/7-*β* 96:3), significantly higher than the literature conditions (9-*β*/7-*β* 6:1, Table 2, entry 3).[16] At the

(19) The ratio was determined by the ^{1}H NMR of the product (1′-H of N7 isomer *δ* 6.98; 1′-H of N9 isomer *δ* 6.72).

(20) Schmit, C.; Bevierre, M.-O.; Mesmaeker, A. D.; Altmann, K.-H. *Bioorg., Med. Chem. Lett.* **1994**, *4*, 1969.

SCHEME 2 [a]



[a] Reagents and conditions: (i) persilylated N^2-acetylguanine (4.0 equiv), TMSOTf (4.0 equiv), toluene, 6 h.

TABLE 2. Reaction of N^2-Acetylguanine with 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (4)

entry[a]	solvent	temp (°C)	time (h)	ratio[b]	yield (%)[c]
1	$ClCH_2CH_2Cl$	reflux (84)	2	87:13:0	66
2	$ClCH_2CH_2Cl$	reflux (84)	6	92:8:0	88
3[d]	$ClCH_2CH_2Cl$	reflux (84)	1.5	6:1:0	79
4	toluene	reflux (111)	6	96:3:1	>99
5	*p*-xylene	reflux (140)	5	94:3:3	99

[a] All Reactions were carried out with 0.1 mmol sugar and a molar ratio of sugar:nucleobase:catalyst (1:4:4). Trimethylsilyl triflate (89 mg, 0.40 mmol) was added slowly with vigorous stirring at room temperature. [b] Ratio of 9-β/7-β/9-α isomers calculated from ^{1}H NMR. [c] Combined isolated yield of isomers. [d] Literature result (molar ratio of sugar:nucleobase:catalyst = 1:1.4−1.7:2.1−2.4).[16]

higher temperatures allowed by toluene or *p*-xylene (Table 2, entries 4 and 5), the reaction produces a small amount of the α-isomer (possibly 9-α), consistent with previous observations for trimethylsilyl triflate catalyzed glycosylation reactions.[6] Kiss et al. also reported that at room temperature, trimethylsilyl triflate catalyzed β to α epimerization of uridine derivatives over the course of a week.[21] The guanosine derivative **5** may epimerize more rapidly at the higher reaction temperatures used in our study.

In summary, systematic variation of reaction conditions has led to an efficient, straightforward synthesis of 2′-*C*-β-methylguanosine with high regio- and stereoselectivity. This strategy also improved regioselectivity in the synthesis of guanosine and may provide a generally useful approach for the synthesis of other guanosine nucleosides by glycosylation.

Experimental Section

***N*^{2}-Acetyl-2′,3′,5′-tri-*O*-benzoyl-2′-*C*-β-methylguanosine (2).** The procedure for Table 1, entry 12 (0.10 mmol scale synthesis), is representative. Under an argon atmosphere, a mixture of N^2-acetylguanine (77 mg, 0.40 mmol), dry pyridine (0.50 mL), and 1,1,1,3,3,3-hexamethyldisilazane (1.5 mL) was heated to reflux for 30 min to obtain a clear solution. The solvent was removed carefully under vacuum, and the residue was dried under high vacuum for 1 h. To the flask containing persilylated N^2-acetylguanosine (0.40 mmol) was added *p*-xylene (5.0 mL) and 1,2,3,5-tetra-*O*-benzoyl-2-*C*-β-methylribofuranose (58 mg, 0.10 mmol). To the resulting mixture was added trimethylsilyl triflate (89 mg, 0.40 mmol) slowly with vigorous stirring at room temperature. After the reaction mixture was stirred under an argon atmosphere at 140 °C for 5 h, TLC showed that the reaction was complete. The reaction mixture was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The organic layers were combined, washed with brine, and dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered off, and the solvent was removed by evaporation under vacuum. The residue was purified by silica gel chromatography, eluting with 2% methanol in chloroform, to give product as a white foam: 58 mg (89% yield). ^{1}H NMR of the product showed that the ratio of 9-β-isomer to 7-β-isomer was 98:2.

Table 1, entry 17 (1.0 mmol scale synthesis): persilylated N^2-acetylguanosine (2.47 mmol) was prepared from N^2-acetylguanosine (477 mg, 2.47 mmol), dry pyridine (3.0 mL), and 1,1,1,3,3,3-hexamethyldisilazane (10 mL) according to the procedure described above. To the flask containing persilylated N^2-acetylguanine (2.47 mmol) was added 1,2,3,5-tetra-*O*-benzoyl-2-*C*-β-methylribofuranose (580 mg, 1.0 mmol), *p*-xylene (30 mL), and trimethylsilyl triflate (0.45 mL, 2.5 mmol) under argon. The reaction mixture was stirred at reflux for 6 h. After workup, the residue was purified by silica gel chromatography to give product as a white foam: 520 mg (80% yield).^{1}H NMR of the product showed that the ratio of the 9-β-isomer to 7-β-isomer was greater than 99:1. ^{1}H NMR ($CDCl_3$/TMS) δ 10.34 (s, 1H), 8.15−7.22 (m, 16H), 6.72 (s, 1H), 6.55 (d, 1H, J = 8.0 Hz), 5.77 (m, 1H), 4.88 (m, 1H), 4.49 (dd, 1H, J = 5.6, 10.8 Hz), 2.47 (s, 3H), 1.50 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.4, 167.0, 165.4, 165.1, 155.6, 147.7, 147.2, 138.7, 133.8, 133.48, 133.45, 129.8, 129.7, 129.5, 128.8, 128.6, 128.5, 128.3, 128.2, 122.6, 89.5, 87.3, 77.3, 76.5, 63.0, 24.3, 17.7; HRMS cacld for $C_{34}H_{30}N_5O_9$ [MH^+] 652.2044, found 652.2047.

***N*^{2}-Acetyl-2′,3′,5′-tri-*O*-benzoyl-β-guanosine (5).**[16] The reaction (0.1 mmol scale) was carried out in refluxing toluene for 6 h (Table 2, entry 3) following the procedure described above. The product (64 mg, 100%) was isolated by silica gel chromatography, eluting with 2% methanol in chloroform as a white foam. ^{1}H NMR of the product showed that the ratio of the 9-β-isomer to 7-β-isomer to 9-α-isomer was 96:3:1.^{1}H NMR ($CDCl_3$/TMS) δ 12.07 (s, 1H), 10.15 (s, 1H), 7.91−7.86 (m, 7H), 7.54−7.52 (m, 3H), 7.35−7.32 (m, 6H), 6.35 (m, 1H), 6.29 (m, 1H), 6.25 (m, 1H), 4.92 (dd, 1H, J = 5.1, 11.7 Hz), 4.79 (m, 1H), 4.65 (dd, 1H, J = 5.7, 11.7 Hz), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.3, 166.6, 165.3, 165.2, 155.5, 147.7, 147.6, 138.8, 133.8, 133.6, 133.5, 129.7, 129.6, 129.5, 129.0, 128.5, 128.42, 128.41, 128.3, 122.4, 88.3, 80.0, 73.8, 71.5, 63.2, 24.2.

2′-*C*-β-Methylguanosine (3).[2] N^2-Acetyl-2′,3′,5′-tri-*O*-benzoyl-2′-*C*-β-methylguanosine (146 mg, 0.224 mmol) in methanol (20 mL) was saturated with ammonia for 30 min at 0 °C, then sealed and kept in a refrigerator (4 °C) for 48 h. The solvent was removed by evaporation under vacuum, and the residue was isolated by silica gel chromatography, eluting with 20% methanol in chloroform, to give product as a white powder: 65 mg (98% yield). ^{1}H NMR (D_2O/CD_3OD) δ 8.01 (s, 1H), 5.91 (s, 1H), 4.83 (br s, 5H), 4.16 (s, 1H, J = 9.1 Hz), 4.07 (m, 1H), 4.02 (dd, 1H, J = 12.9, 2.1 Hz), 3.88 (dd, 1H, J = 12.9, 3.80 Hz), 0.97 (s, 3H); ^{1}H NMR (DMSO-d_6) δ 10.62 (br s, 1H), 8.05 (s, 1H), 6.52 (br s, 2H), 5.73 (s, 1H), 5.27 (d, 1H, J = 6.6 Hz), 5.16 (t, 1H, J = 4.9 Hz), 5.07 (s, 1H), 3.97 (m, 1H), 3.85 (m, 1H), 3.81 (dd, 1H, J = 12.4, 5.0 Hz), 3.64 (dd, 1H, J = 12.4, 3.0 Hz), 0.80 (s, 3H); ^{13}C NMR (D_2O/CD_3OD) δ 159.8, 154.9, 152.0, 138.1, 117.1, 92.0, 83.1, 80.2, 73.4, 61.0, 19.9; HRMS cacld for $C_{11}H_{16}N_5O_5$ [MH^+] 298.1151, found 298.1140.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of **2**, **3**, and **5** and the NOE difference spectra of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Kiss, J.; D'Souza, R.; van Koeveringe, J. A.; Arnold, W. *Helv. Chim. Acta* **1982**, *65*, 1522.