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Synthesis of Guanidines From Azides: A General and Straightforward Methodology In Carbohydrate Chemistry

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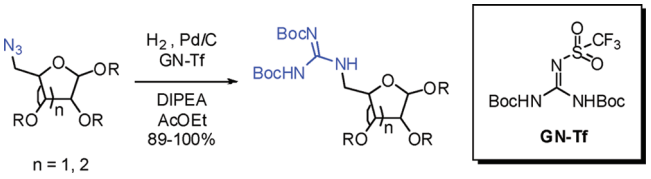

The ability of the guanidinylating reagent *N*′,*N*″-diBoc-*N*-triflyl-guanidine (GN-Tf) to react with in situ formed free amines from azides in carbohydrate scaffolds was explored. This reaction proved to be an efficient method to prepare guanidine derivatives in a one-pot manner with good to excellent yields, either with primary or secondary azides with different substitution patterns. Labile protecting groups such as benzyl ethers are not removed under these hydrogenolytic conditions.

The guanidine functional group is frequently found in bioactive compounds, either from natural sources, like marine natural products (Figure 1A),[1] or of synthetic origin (Figure 1B),[2] and constitutes an attractive building block not only in total synthesis, but also in the design of organic superbases and of new materials.[3] The relatively high pK_a value of the conjugate acids of these molecules,[4] as well as their capability to give and accept H-bonds make them very interesting targets to achieve chemical recognition and/or catalysis (Figure 1C).[5]

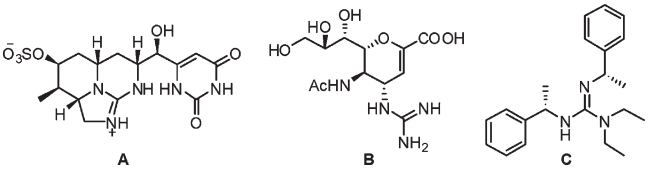

FIGURE 1. (A) Marine hepatotoxin cylindrospermopsin, (B) influenza neuraminidase inhibitor zanamivir, and (C) asymmetric nitroaldol organocatalyst.

The most commonly used methods to synthesize the guanidine moiety are multistep processes, such as the treatment of thioureas,[6] carbodiimides,[7] or cyanamides[8] with a protected primary amine (or ammonia). More recently, with the successful development of efficient guanidinylating reagents by Goodman and co-workers,[9] an alternative route has emerged. However, in some cases, the preparation of a free amine is not possible due to the presence of other reactive groups, such as esters, acetals, or aldehydes. In spite of the growing interest in guanidinylated products, there are still few general and direct methodologies to access these compounds.[10]

On the other hand, carbohydrates are the most abundant class of organic compounds in nature, being involved in almost every essential process to sustain life.[11] They have attracted

(1) (a) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095–1098. (b) El-Naggar, M.; Conte, M.; Capon, R. J. *Org. Biomol. Chem.* **2010**, *8*, 407–412. (c) O'Maley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581–3583. (d) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919–954. (e) Evans, P. A.; Qin, J.; Robinson, J. E.; Bazin, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 7417–7419. (f) Dennos, M.; Hall, L. M.; Murphy, P. J.; Thornhill, A. J.; Nash, R.; Winters, A. L.; Hursthouse, M. B.; Light, M. E.; Horton, P. *Tetrahedron. Lett.* **2003**, *44*, 3075–3080.

(2) Magano, J. *Chem. Rev.* **2009**, *109*, 4398–4438.

(3) Ishikawa, T. *Superbases for Organic Synthesis*; Wiley & Sons: Chippenham, UK, 2009.

(4) Eckert-Maksic, M.; Glasovac, Z.; Troselj, P.; Kütt, A.; Rodima, T.; Koppel, I.; Koppel, I. A. *Eur. J. Org. Chem.* **2008**, *30*, 5176–5184.

(5) (a) Takada, K.; Nagasawa, K. *Adv. Synth. Catal.* **2009**, *351*, 345–347. (b) Chinchilla, R.; Nájera, C.; Sánchez-Argullo, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393–1402.

(6) (a) Chen, C.-Y.; Lin, H.-C.; Huang, Y.-Y.; Chen, K.-L.; Huang, J.-J.; Yeh, M.-Y.; Wong, F. F. *Tetrahedron* **2010**, *66*, 1892–1897. (b) Wang, Y.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2009**, *50*, 5145–5148. (c) Ohara, K.; Vasseur, J.-J.; Smietana, M. *Tetrahedron Lett.* **2009**, *50*, 1463–1465. (d) Luan, Z.; Higaki, K.; Aguilar-Moncayo, M.; Ninomiya, H.; Ohno, K.; García -Moreno, M. I.; Ortiz Mellet, C.; García Fernández, J. M.; Suzuki, Y. *ChemBioChem* **2009**, *10*, 2780–2792. (e) Brumshtein, B.; Aguilar-Moncayo, M.; García-Moreno, M. I.; Ortiz Mellet, C.; García Fernández, J. M.; Silman, I.; Shaaltiel, Y.; Aviezer, D.; Sussman, J. L.; Futerman, A. H. *ChemBioChem* **2009**, *10*, 1480–1485. (f) Liu, Y.-H.; Cao, L.-H. *Carbohydr. Res.* **2008**, *343*, 2376–2383. (g) Liu, Y.-H.; Cao, L.-H. *Carbohydr. Res.* **2008**, *343*, 615–625. (h) Aguilar, M.; Díaz-Pérez, P.; García-Moreno, M. I.; Ortiz Mellet, C.; García Fernández, J. M. *J. Org. Chem.* **2008**, *73*, 1995–1998.

(7) (a) Perl, N. R.; Ide, N. D.; Prajapati, S.; Perfect, H. H.; Durón, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 1802–1803. (b) Zhang, L.; Pratt, R. C.; Nederberg, F.; Horn, H. W.; Rice, J. E.; Waymouth, R. M.; Wade, C. G.; Hedrick, J. L. *Macromolecules* **2010**, *43*, 1660–1664. (c) Hirota, S.; Sakai, T.; Kitamura, N.; Kubokawa, K.; Kutsumura, N.; Otani, T.; Saito, T. *Tetrahedron* **2010**, *66*, 653–662. (d) Zhu, X.; Du, Z.; Shen, Q. *J. Org. Chem.* **2009**, *74*, 6347–6349. (e) Rodríguez-Lucena, D.; Benito, J. M.; Alvarez, E.; Jaime, C.; Pérez-Miron, J.; Ortiz Mellet, C.; García Fernández, J. M. *J. Org. Chem.* **2008**, *73*, 2967–2979.

(8) (a) Larraufie, M.-H.; Ollivier, C.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2010**, *12*, 2178–2181. (b) Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3116–3120. (c) Köhn, U.; Klopfleisch, M.; Görls, H.; Anders, E. *Tetrahedron: Asymmetry* **2006**, *17*, 811–818. (d) Zahariev, S.; Guarnaccia, C.; Lamba, D.; Čemažar, M.; Pongor, S. *Tetrahedron Lett.* **2004**, *45*, 9423–9426.

(9) (a) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804–3805. (b) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432–8439. For other guanidinylating reagents, see: (c) Wojciechowski, F.; Hudson, R. H. E. *Org. Lett.* **2009**, *11*, 4878–4881. (d) Dankward, S. M.; Ferla, S.; Krstenansky, J. L.; Bhakta, S.; Osterlich, H.; Jarnagin, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1921–1926. (e) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389–3392.

(10) For substituted guanidines, a Mitsunobu route can also be used. See: Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V .P. P. *Chem. Rev.* **2009**, *109*, 2551–2651.

(11) (a) Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497–510. (b) Varki, A. *Glycobiology* **1993**, *3*, 97–130.

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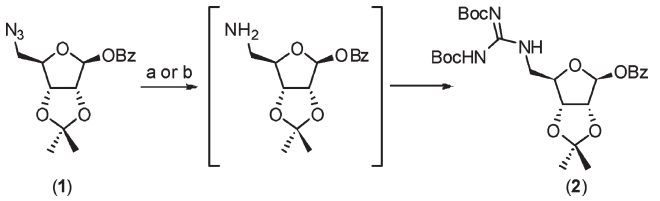
SCHEME 1. Two-Step vs One-Pot Synthesis of Guanidine 2[a]



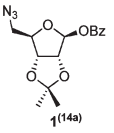
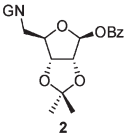
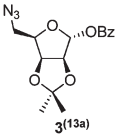
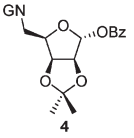
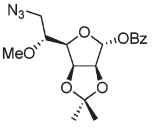
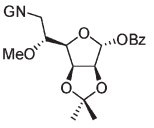
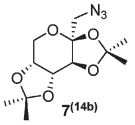
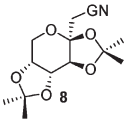
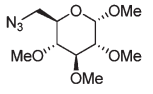
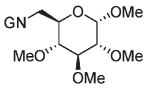
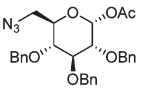
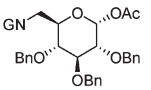
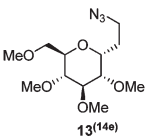
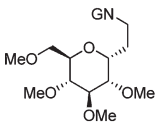
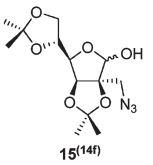
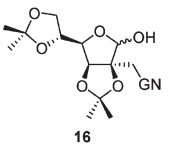
[a]Reagents and conditions: (a) (i) H_2, 10% Pd/C, AcOEt; (ii) GN-Tf, TEA, DCM, 85%. (b) H_2, 10% Pd/C, GN-Tf, DIPEA, AcOEt, overnight, 100%.

the attention of synthetic organic chemists because of their potential usefulness as easily available chiral substrates with a well-defined stereochemistry and a highly functionalized nature. These reasons make them suitable starting materials to translate their structural features into intermediates for the synthesis of more complex bioactive compounds.[12] As part of our ongoing research directed to the development of new methodologies leading to functionalized heterocycles,[13] we were interested in a rapid installation of the guanidine moiety in carbohydrate scaffolds. Herein we report on a mild and convenient method to prepare protected guanidines from azides.

As our first approach to this kind of guanidinylated sugar derivatives, we decided to prepare the azide **1**, readily available from D-ribose,[14a] which was reduced and subsequently treated, with no further purification than filtration and evaporation, with the guanidinylating reagent *N*′,*N*″-diBoc-*N*-triflyl-guanidine (**GN-Tf**, 1.0 equiv) and TEA (1.0 equiv) in DCM (0.1 M), at room temperature. The desired guanidine-derivative **2** was isolated after column chromatography in a satisfactory 85% yield (Scheme 1a).

To improve this methodology and to simplify the procedure, we tested the possibility of carrying out the two steps in a one-pot fashion, since the introduction of other *N*-protecting groups, such as Boc,[15] can be performed in this way. We were pleased to find that the hydrogenation of the same *ribo*-azide with 10% Pd/C in AcOEt in the presence of *N*′,*N*″-diBoc-*N*-triflyl-guanidine and diisopropylethylamine (DIPEA) gave the corresponding guanidine derivative in quantitative yield (Scheme 1b). This material was identical

TABLE 1. Guanidinylation of Primary Azides[a]

Entry	Substrate [(ref)]	Yield[b]	Product
1	 **1**(14a)	Quant.	 **2**
2	 **3**(13a)	98%	 **4**
3	 **5**(13a)	Quant.	 **6**
4	 **7**(14b)	Quant.	 **8**
5	 **9**(14c)	Quant.	 **10**
6	 **11**(14d)	Quant.	 **12**
7	 **13**(14e)	90%	 **14**
8	 **15**(14f)	89%	 **16**

[a]Reaction conditions: azide (1.0 mmol), 10% Pd/C (20% w/w), GN-Tf (1.0 mmol), DIPEA (1.5 mmol), AcOEt (15 mL/mmol) under H_2 atmosphere (balloon), overnight. [b]Isolated yield.

with that afforded upon sequential hydrogenation of the azide and guanidinylation of the intermediate free amine; it showed in its ^{1}H NMR the appearance of two singlets at 1.50 and 1.53 ppm, belonging to the *tert*-butyls of the Boc groups, as well as two broad singlets for the NH and NHBoc at 8.49 and 11.21 ppm, respectively. The ^{13}C NMR spectrum also featured peaks at 153.0, 156.4, and 163.5 ppm, corresponding to the three quaternary carbons of the diBoc-guanidine moiety.

This encouraging result prompted us to extend the scope of this protocol to other saccharidic primary azides.[13a,14b−f] The results are illustrated in Table 1, where the yields represent isolated pure products. Several groups that are labile to other alternative reductive methods were still stable under these conditions. Esters (benzoates: entries 1, 2, and 3; acetate: entry 6)

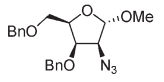
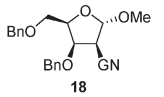
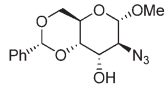
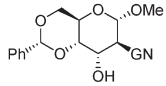
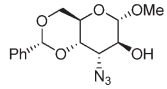
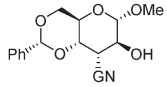
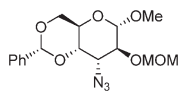
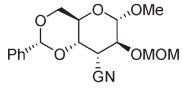
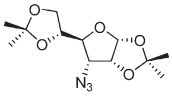
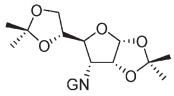
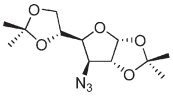
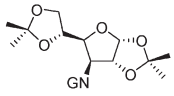
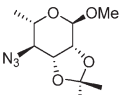
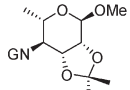
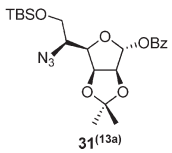
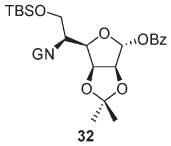
(12) Hanessian, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon Press: Oxford, UK, 1983.

(13) (a) Francisco, C. G.; Freire, R.; González, C. C.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 1861–1866. (b) Francisco, C. G.; Freire, R.; González, C. C.; Suárez, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1971–1974. (c) Francisco, C. G.; González, C. C.; Suárez, E. *Tetrahedron Lett.* **1996**, *37*, 1687–1690.

(14) (a) Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007–3018. (b) Maryanoff, B. E.; McComsey, D. F.; Costanzo, M. J.; Hochman, C.; Smith-Swintosky, V.; Shank, R. P. *J. Med. Chem.* **2005**, *48*, 1941–1947. (c) Martinez, M. B.; Mata, F. Z.; Donoso, M. T. U.; Perez, J. A. G. *Carbohydr. Res.* **1992**, *230*, 191–196. (d) Yoshimura, J.; Asano, K.; Umemura, K.; Horito, S.; Hashimoto, H. *Carbohydr. Res.* **1983**, *121*, 187–204. (e) Francisco, C. G.; Herrera, A. J.; Martin, A.; Perez-Martin, I.; Suarez, E. *Tetrahedron Lett.* **2007**, *48*, 6384–6388. (f) Mitchell, D. A.; Jones, N. A.; Hunter, S. J.; Cook, J. M. D.; Jenkinson, S. F.; Wormald, M. R.; Dwek, R. A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 1502–1510. (g) Indurugalla, D.; Bennet, A. J. *Can. J. Chem.* **2008**, *86*, 1005–1009. (h) Izawa, T.; Nishimura, Y.; Kondo, S. *Carbohydr. Res.* **1991**, *211*, 137–146. (i) Watterson, M. P.; Pickering, L.; Smith, M. D.; Hudson, S. J.; Marsh, P. R.; Mordaunt, J. E.; Watkin, D. J.; Newman, C. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1999**, *10*, 1855–1860. (j) Davis, B.; Nash, R. J.; Watson, A. A.; Smith, C.; Fleet, G. W. J. *Tetrahedron* **1999**, *55*, 4501–4520.

(15) Saito, S.; Akajima, H.; Inaba, M.; Morikawe, T. *Tetrahedron Lett.* **1989**, *30*, 837–838.

TABLE 2. Guanidinylation of Secondary Azides[a]

Entry	Substrate [(ref)]	Yield[b]	Product
1	 **17**	92%	 **18**
2	 **19**[(14g)]	90%	 **20**
3	 **21**[c (14h)]	22%	 **22**
4	 **23**[c]	54%	 **24**
5	 **25**[(14i)]	Quant	 **26**
6	 **27**[(14i)]	87%	 **28**
7	 **29**[(14j)]	92%	 **30**
8	 **31**[(13a)]	28%	 **32**

[a]Reaction conditions: azide (1.0 mmol), 10% Pd/C (20% w/w), GN-Tf (1.0 mmol), DIPEA (1.5 mmol), AcOEt (15 mL/mmol) under H_2 atmosphere (balloon), overnight. [b]Isolated yield. [c]Methyl 2,3-anhydro-4,6-benzylidene-α-D-mannopyranoside was isolated in a ca. 20% yield.

and hemiacetals (entry 8) are tolerated well, as are benzyl ethers (entry 6), which are not removed under the hydrogenolytic conditions.[16] In all the cases the yield of the combined method was almost quantitative, excepting the *C*-glycosidic azide **13** (entry 7), and the branched compound **15** (entry 8), where the anomeric alcohol was unprotected.

With the aim of further extending the scope of this methodology, we embarked on the study of this approach with a battery of secondary azides,[13a,14g−j] thus covering every position in the sugar ring, both in the furanose and the pyranose form. These results are summarized in Table 2.

As can be seen from the results shown, most of the guanidine derivatives were successfully synthesized in ca. 90% yield (entries 1, 2, 5, 6, and 7). It is worth mentioning, due to its importance in carbohydrate chemistry and in organic synthesis in general, that the benzylidene protecting group also can be employed under these conditions. In the guanidinylation of compound **21** (entry 3), concomitant formation of methyl 2,3-anhydro-4,6-benzylidene-α-D-mannopyranoside was detected,[17] showing that the installation of the bulky diBoc-guanidine group in position 3 of benzylidene-tethered pyranoses was strongly hindered. To avoid this side reaction, the free alcohol was protected as its MOM-ether. The guanidinylation of this new compound afforded the corresponding guanidine in a better yield, though it was still modest (entry 4). Finally, the reaction of compound **31** gave the desired guanidine **32** (entry 8) in poor yield, probably due to the proximity of the also bulky TBDMS-ether.[18]

This reaction was proven to tolerate a wide diversity of substitution patterns, as well as a variety of the most common protecting groups in organic synthesis. It is also noteworthy that this guanidinylation is metal-free and that it is not necessary to add any other coreagent than a neutral base in order to scavenge the residual proton.

In conclusion, we have demonstrated the ability of the guanidinylating reagent *N*′,*N*″-diBoc-*N*-triflyl-guanidine to react with in situ formed free amines from azides in carbohydrate scaffolds. We believe that the application of this protocol to the synthesis of other more general guanidine derivatives will be of interest and that this method could also be applicable to nonsaccharidic azides. Further investigation of the synthetic potential of these compounds is currently under development in our laboratory, and will be reported soon.

Experimental Section

Representative Procedure for the Hydrogenation−Guanidinylation of the Azides. A stirred solution of the corresponding azide (1.0 mmol) in ethyl acetate (15 mL) was treated with *N*′,*N*″-diBoc-*N*-triflyl-guanidine (1.0 mmol), 10% Pd/C (20% w/w), and diethylisopropylamine (DIPEA) (1.5 mmol). Three vacuum/hydrogen cycles were performed, and the mixture was further stirred under a H_2 atmosphere (balloon) overnight. The reaction mixture was then filtered over a Celite pad, which was washed twice with ethyl acetate, and the combined filtrates were evaporated. Column chromatography of the residue (hexanes/EtOAc mixtures) afforded the required guanidinylated compounds.

1-*O*-Benzoyl-5-[(*N*′,*N*″-di-*tert*-butoxycarbonyl)guanidino]-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranose (2) (Table 1, entry 1): oil; $[\alpha]_D$ +0.45 (*c* 0.44); IR 3431, 1724, 1640, 1620, 1418, 1328, 1139 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ_H 1.36 (3H, s), 1.45 (3H, s), 1.50 (9H, s), 1.53 (9H, s), 3.38 (1H, ddd, J = 3.1, 9.1, 13.2 Hz), 3.95 (1H, ddd, J = 6.3, 6.3, 13.2 Hz), 4.52 (1H, dd, J = 6.3, 9.1 Hz), 4.78 (1H, d, J = 5.7 Hz), 4.89 (1H, d, J = 5.7 Hz), 6.51 (1H, s), 7.40−7.43 (2H, m), 7.53−7.56 (1H, m), 7.98−8.00 (2H, m), 8.49 (1H, br s), 11.21 (1H, br s); ^{13}C NMR (125.7 MHz, 70 °C) δ_C 25.2 (CH_3), 26.6 (CH_3), 28.1 (3 × CH_3), 28.4 (3 × CH_3), 43.7 (CH_2), 79.2 (C), 82.4 (CH), 83.2 (C), 85.7 (CH), 85.9 (CH), 103.6 (CH), 113.4 (C), 128.4 (2 × CH), 129.8 (2 × CH), 129.9 (C), 133.2 (CH), 153.0 (C), 156.4 (C), 163.5 (C), 164.8 (C); MS (ESI)$^+$ m/z (rel intensity) 536 (M^+ + H, 100). HRMS (ESI)$^+$ Calcd for $C_{26}H_{38}N_3O_9$ 536.2608, found 536.2626. Anal. Calcd for

(16) For selective inhibition of benzyl ether hydrogenolysis, see: Sajiki, H. *Tetrahedron Lett*. **1995**, *36*, 3465–3468.

(17) For a similar result, see: (a) White, R. D.; Wood, J. L. *Org. Lett*. **2001**, *3*, 1825–1827. (b) Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem*. **1993**, *58*, 2407–2413.

(18) The use of protected thioureas with the Mukaiyama reagent seems to be superior for guanidinylation of sterically hindered and less reactive amines; see: *Organic Syntheses*; Wiley: New York, 2004; Collect. Vol. X, p 266.

$C_{26}H_{37}N_3O_9$: C, 58.31; H, 6.96; N, 7.85. Found: C, 58.47; H, 6.96; N, 7.92.

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Supporting Information Available: Experimental procedures, characterization, and copies of NMR (^{1}H and ^{13}C) spectra for all pure compounds. This material is available free of charge via the Internet at http://pubs.acs.org.