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Metal-Free One-Pot Oxidative Amidation of Aldoses with Functionalized Amines

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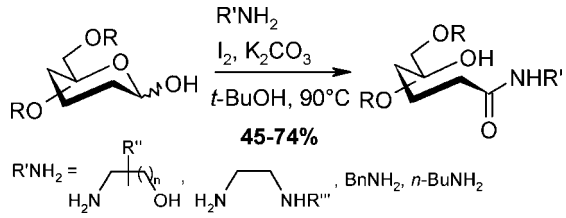
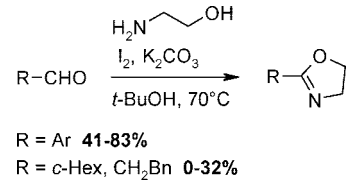


Metal-free one-pot oxidative amidation of aldoses with functionalized amines using iodine provides a rapid access to functionalized aldonamides. The main advantage of this approach relies on the fact that aldehyde oxidation and C−N bond formation are performed in a single synthetic operation.

The amide is one of the most fundamental functional groups in organic chemistry and biochemistry, from natural products to synthetic pharmaceuticals. It has been reported that more than 25% of known drugs present in the Comprehensive Medicinal Chemistry (CMC) database contain an aminocarbonyl group.[1] The amide function is the link between amino acids in peptides and proteins and thus is key to the structure of many biological systems. Most of the preparative methods for amide bond formation are based on the reaction between an amine and an activated carboxylic acid derivative without change in the oxidation level.[2] These methods often require the use of coupling agents such as carbodiimides from free carboxylic acids or the prior synthesis of acid chlorides or anhydride derivatives. In this context, direct oxidative amidation of aldehydes[3] and alcohols[4] has recently attracted much attention. The main advantage of this approach relies on the fact that oxidation and C−N bond formation are performed in a single step. This challenging one-pot process is thus environmentally and economically attractive and makes use of readily available starting materials. Despite these advantages, few direct oxidative amidation methods have been reported in the literature.[3,4] Most of them suffer from limitations such as the use of an excess amount of expensive transition-metal catalyst and poor substrate scope. It is important to note that such oxidative amidation reactions have been successfully performed almost exclusively on aryl aldehydes to date.

SCHEME 1. Oxidative Conversion of Aldehydes to 2-Oxazolines[6]



In connection with our work on bicyclic iminosugars[5] related to nagstatin,[5e] we were interested in a method recently described by Togo et al. concerning the direct oxidative conversion of aldehydes to 2-oxazolines.[6] In this process, aryl aldehydes react with 2-aminoethanol in the presence of iodine and potassium carbonate to provide the corresponding 2-oxazolines in 41−83% yield, whereas enolizable aldehydes give much lower yields or lead only to degradation products (Scheme 1).[6] As this process could significantly shorten the synthesis of polyhydroxylated 1-oxaindolizidine derivatives, we decided to apply it to tetra-*O*-benzyl-D-glucopyranose (**1**).

In a first attempt, reaction of **1** with ethanolamine (**2**) following Togo's protocol[6] did not lead to the formation of the expected 2-oxazoline derivative but to gluconamide **3** in 45% yield (Table 1, entry 1). To our knowledge, this reaction constitutes a rare example of metal-free one-pot oxidative amidation of aldehydes. Till very recently, no such process without metal catalyst was reported in the literature.[3a,b,7] In addition, its application to aldoses is also of interest for the direct synthesis of relevant complex glycoconjugates including calixsugars, synthetic carbohydrate polymers, neoglycopeptides, or sugar-modified oligonucleotides.[8]

(1) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55.

(2) (a) Bailey, P. D.; Collier, I. D.; Morgan, K. M. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Elsevier Science Inc.: New York, 1995; Vol. 5, pp 258−391. (b) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1999. (c) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: New York, 2007. (d) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.

(3) (a) Gao, J.; Wang, G.-W. *J. Org. Chem.* **2008**, *73*, 2955. (b) Ekoue-Kovi, K.; Wolf, C. *Org. Lett.* **2007**, *9*, 3429. (c) Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 13064. (d) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523. (e) Naota, T.; Murahashi, S.-I. *Synlett* **1991**, 693. (f) Tamaru, Y.; Yamada, Y.; Yoshida, Z.-I. *Synthesis* **1983**, 474. (g) Fukuoka, S.; Ryang, M.; Tsutsumi, S. *J. Org. Chem.* **1971**, *36*, 2721. (h) Nakagawa, K.; Onoue, H.; Minami, K. *Chem. Commun.* **1966**, 17.

(4) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790.

(5) (a) Godin, G.; Compain, P.; Masson, G.; Martin, O. R. *J. Org. Chem.* **2002**, *67*, 6960. (b) Godin, G.; Compain, P.; Martin, O. R. *Org. Lett.* **2003**, *5*, 3269. (c) Compain, P.; Martin, O. R.; Boucheron, C.; Godin, G.; Yu, L.; Ikeda, K.; Asano, N. *ChemBioChem* **2006**, *7*, 1356. (d) Toumieux, S.; Compain, P.; Martin, O. R. *J. Org. Chem.* **2008**, *73*, 2155. (e) *Iminosugars: from Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; Wiley-VCH: Weinheim, 2007.

(6) Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474.

(7) Recently, Fang et al. reported the synthesis of aldonamide derivatives by direct oxidation of aldoses by iodine in aqueous ammonia: Chen, M.-Y.; Hsu, J.-L.; Shie, J.-J; Fang, J.-M. *J. Chin. Chem. Soc.* **2003**, *50*, 129.

(8) See for example: (a) Fujimoto, K.; Miyata, T.; Aoyama, Y. *J. Am. Chem. Soc.* **2000**, *122*, 3558. (b) Budka, J.; Tkadlecova, M.; Lhotak, P.; Stibor, I. *Tetrahedron* **2000**, *56*, 1883. (c) Narain, R.; Armes, S. P. *Macromolecules* **2003**, *36*, 4675. (d) Kim, K.; Matsuura, K.; Kimizuka, N. *Bioorg. Med. Chem.* **2007**, *15*, 4311. (e) Kida, T.; Tanaka, T.; Nakatsuji, Y.; Akashi, M. *Chem. Lett.* **2006**, *35*, 112.

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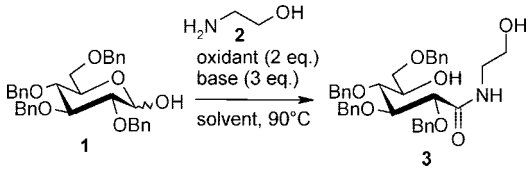
TABLE 1. Optimization of the Oxidative Amidation of Aldoses.



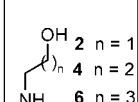
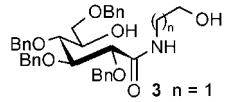
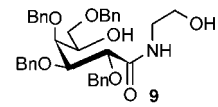
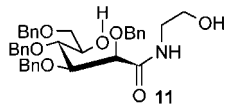
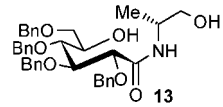
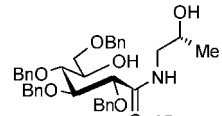
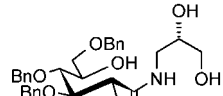
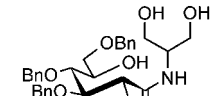
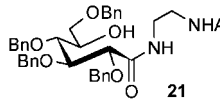
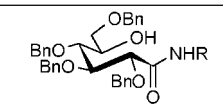
entry	oxidant	base	2 (equiv)	solvent	T1 (h)[a]	yield (%)[b]
1	I_2	K_2CO_3	1.1	*t*-BuOH	0.5	45
2	I_2	K_2CO_3	1.1	*t*-BuOH[c]	1	27
3	I_2	K_2CO_3	1.1	MeCN	1	46
4	**I_2**	**K_2CO_3**	**1.1**	*t*-BuOH	**1**	**74**
5	I_2	K_2CO_3	2.2	*t*-BuOH	1	47
6	I_2	K_2CO_3	3.3	*t*-BuOH	1	62
7	I_2	Na_2CO_3	1.1	*t*-BuOH	1	58
8	$PhI(OAc)_2$[d]		1.1	MeCN	1	trace
9	$PhI(OAc)_2$[e]		1.1	MeCN	1	trace
10	$PhI(OAc)_2$[d]		1.1	*t*-BuOH	1	trace

[a] T1 refers to reaction time between **2** and **1** before addition of oxidant and base to the reaction mixture. [b] Isolated yield. [c] Aqueous *t*-BuOH containing 25% of water. [d] 1.1 equiv of $PhI(OAc)_2$ was used. [e] 2.2. equiv of $PhI(OAc)_2$ was used.

In this paper, we wish to report our exploration of the synthetic scope of this reaction and to provide some insights into its mechanism for rationalizing the unexpected formation of the amide product. The effect of various experimental parameters was examined to improve the yield. The reaction was first studied with the I_2/K_2CO_3 system. It appeared that an increase in the reaction time (T1) between the aldose **1** and ethanolamine (**2**) before introduction of the oxidant and the base was critical for the efficiency of the process (Table 1, entries 1 and 4); following these conditions, the desired gluconamide **3** was indeed obtained after 3 h in 74% yield. No improvement was observed when the solvent was switched from *t*-BuOH to MeCN or to aqueous *t*-BuOH, although **1** appeared to be more soluble under both conditions (entries 2 and 3). The addition of more equivalents of ethanolamine (**2**) was found to decrease the yield in amide **3** (entries 4−6). Contrary to what was observed by Togo et al.[6] for the formation of 2-oxazoline derivatives (Scheme 1), the use of Na_2CO_3 instead of K_2CO_3 did not improve the product yield (entry 7). $PhI(OAc)_2$ was then evaluated as a different source of electrophilic iodine. In a recent report, it was shown that $PhI(OAc)_2$ could be a better oxidizing agent than the I_2/K_2CO_3 system for the formation of 2-oxazoline derivatives from enolizable aldehydes and 2-amino alcohols.[9] However, $PhI(OAc)_2$ was found to be unsuitable to produce amide **3** in any acceptable yield (entries 8−10).

We then tested the oxidative amidation reaction of various aldoses and amines under the optimized reaction conditions to evaluate its synthetic scope (Table 2). Ethanolamine (**2**) reacted with tetra-*O*-benzyl-D-galactopyranose (**8**) or tetra-*O*-benzyl-D-mannopyranose (**10**) to produce the desired amides, however, in lower yields compared to substrate **1** (entries 1, 4, and 5). Further screening revealed that our optimized amidation procedure tolerated a wide range of amino alcohol derivatives. The amidation reaction proceeded smoothly to provide the expected amides from **1** in reasonable to good yields using 3-amino-1-propanol (**4**), 4-amino-1-butanol (**6**) (entries 2 and 3), or substituted ethanolamine derivatives (entries 6−13). Interestingly, the amidation reaction could be performed with unprotected amino-diol derivatives (entries 11−13). As a general feature, it should be noted that better yields were observed with ethanolamine derivatives carrying a substitutent α to the hydroxyl group rather than α to the amino group (entries 6−13). When aldose **1** reacted with ethylenediamine derivative **20**, instead of amino alcohol substrates, the corresponding amide **21** was obtained in moderate yield (entry 14).[10] Finally, we explored the reactivity of simple amine derivatives to evaluate if the absence of a hydroxyl group was detrimental to the amidation reaction (entries 15 and 16). Remarkably, the reaction

TABLE 2. Oxidative Amidation of Aldoses with Amines[a]

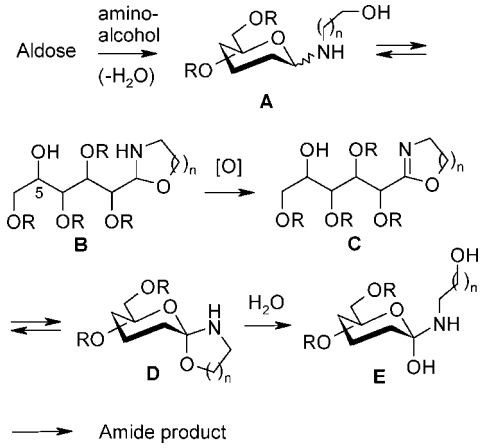
Entry	Aldose	Amine	Product	Yield[b]
1 2 3	**1** **1** **1**			74% (n=1) 63% (n=2) 58% (n=3)
4	**8**			51%
5	**10**			50%
6 7 8	**1** **1** **1**			45%[c] 25%[d] 41%[e]
9 10	**1** **1**			71%[c] 42%[d]
11 12	**1** **1**			58%[c] 51%[d]
13	**1**			46%[c]
14	**1**			45%[c]
15 16	**1** **1**	*n*-$BuNH_2$ $BnNH_2$		58%[c] 53%[c]

[a] Reaction conditions: *t*-BuOH, 90 °C, 2−6 h, aldose/amine/I_2/K_2CO_3 1:1.1:2:3. [b] Isolated yield. [c] 3.3 equiv of amine substrate were used. [d] 2.2 equiv of amine substrate were used. [e] 4.4 equiv of amine substrate were used.

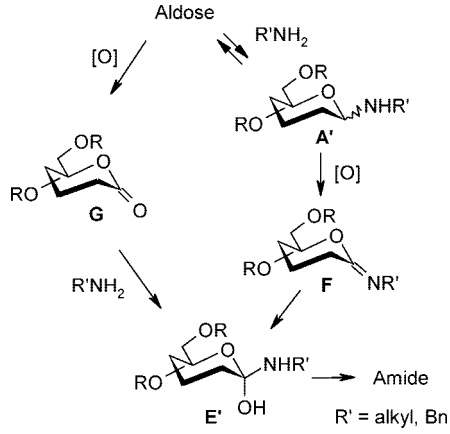
(9) Karade, N. N.; Tiwari, G. B.; Gampawar, S. V. *Synlett* **2007**, 1921.

(10) The amidation reaction performed with ethylenediamine afforded the expected amide in low yields along with side products.

SCHEME 2. Tentative Mechanism for the Oxidative Amidation of Aldoses with Amino Alcohol Substrates



SCHEME 3. Tentative Mechanisms for the Oxidative Amidation of Aldoses with Simple Amine Substrates

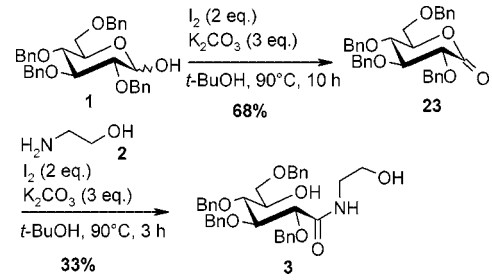


proceeded well with *n*-butylamine or benzylamine to give compounds **22a** and **22b**,[11] respectively, although longer reaction time and a larger number of equivalents of amine were required. However, arylamines including aniline, 4-nitroaniline, and *p*-toluidine were found to be unsuitable substrates for this amidation reaction as were also *N*-methyl- and *N*-benzyl ethanolamine. First attempts to perform the reaction under our typical amidation conditions with fully unprotected monosaccharide substrates were found to be unsuccessful to date.

A tentative mechanism for the oxidative amidation of aldoses is proposed in Schemes 2 and 3.

First it is important to note that the 5-*O*-benzyl analog of **1**[12] was not a substrate of the amidation reaction, since only products corresponding possibly to 2-oxazoline or imidate derivatives were observed by IR ($\upsilon = 1646$ cm^{-1}) and MS on the crude reaction mixture. In addition to the work described by Togo et al.[6] (Scheme 1), this result strongly suggested that the free hydroxyl group at C-5 in the aldose substrate was crucial for the process. On the other hand, the hydroxyl group in the amine substrate seemed to facilitate the reaction but was not absolutely required as indicated by results obtained with benzylamine and

SCHEME 4. Lactone 23 as Possible Intermediate in the One-Pot Synthesis of Gluconamide 3



n-butylamine. Consequently, we envisioned two main pathways depending on the presence or the absence of a hydroxyl group on the amine substrate (Schemes 2 and 3). We believe that the first step of the process is the favored formation[13] of the glycosylamine derivative **A** by way of the corresponding open-chain imine and the release of 1 equiv of water (Scheme 2). With amino alcohol derivatives, the corresponding glycosylamine **A** is in equilibrium with oxazolidine **B**, which is oxidized by iodine to afford the corresponding oxazoline **C**.[6] Then, the next step might involve an intramolecular nucleophilic addition to yield the reactive spiranic orthoamide **D**, which is hydrolyzed to afford **E**. This intermediate is expected to exist predominantly in a $^4C_1$ chair conformation in which the hydroxyl group is axial because of the anomeric effect. Finally, stereoelectronic control in the cleavage of hemiorthoamide **E** would lead to the amide product.[14] In the intermediate **E**, lone pair orbitals of the nitrogen and exocyclic oxygen atoms can be properly oriented antiperiplanar to the leaving OR group, promoting the formation of the amide. The formation of the lactone is disfavored by the β-orientation of the amino group: because of the resulting nonantiperiplanar orientation of the endocyclic oxygen lone pairs in **E**, the ejection of the amino group is not facilitated.

In the case of simple amine substrates with no hydroxyl group, two pathways could be conceived. The first one involves the oxidation of glycosylamine **A′** by iodine to yield the corresponding imidate intermediate **F**[15] and, after nucleophilic addition of water, the key intermediate **E′**. Alternatively, the aldose may be directly oxidized to give the lactone **G** and then the imidate intermediate **F**. This latter pathway was partly experimentally verified. It was demonstrated that aldose **1** could be oxidized to give lactone **23**[16] in 68% yield by treatment with molecular iodine and potassium carbonate in refluxing *t*-BuOH (Scheme 4). This process required relatively long reaction time (10 h). Treatment of lactone **23** with ethanol amine (**2**) in refluxing *t*-BuOH under our classical oxidation conditions afforded the amide **3** in 33% yield. These qualitative results argue in favor of the hypothetical mechanism described in Scheme 3.

In conclusion, we report a metal-free one-pot oxidative amidation of aldoses with functionalized amines using molecular iodine as the oxidant. Experimental data appear to indicate that the hydroxyl group at C-5 in the aldose substrate is crucial for

(11) Fleet, G. W. J.; Ramsden, N. G.; Carpenter, N. M.; Petursson, S.; Apli, R. T. *Tetrahedron Lett.* **1990**, *31*, 405.

(12) (a) The 5-*O*-benzyl analog of **1** was prepared by deprotection of the corresponding diethyl dithioketal according to the procedure described by Doutheau et al.: Malanda, J.-C.; Doutheau, A. *J. Carbohydr. Chem.* **1993**, *12*, 999. (b) Pozsgay, V.; Jennings, H. J. *J. Org. Chem.* **1988**, *53*, 4042.

(13) See for example: Pigman, W.; Cleveland, E. A.; Couch, D. H.; Cleveland, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 1976 and ref. cited.

(14) (a) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463. (b) Deslongchamps, P. *Pure. Appl. Chem.* **1975**, *43*, 351.

(15) For examples of related glycosylamine oxidation see: (a) Ferris, J. P.; Devadas, B. *J. Org. Chem.* **1987**, *52*, 2355. (b) Somsak, L.; Praly, J. P.; Descotes, G. *Synlett* **1992**, 119.

(16) (a) Hoos, R.; Naughton, A. B.; Vasella, A. *Helv. Chim. Acta* **1993**, *76*, 1802. (b) Kuzuhara, H.; Flechter, H. G. *J. Org. Chem.* **1967**, *32*, 2531.

the process and may greatly facilitate the hydrolysis step according to the proposed mechanistic rational. The hydroxyl group in the amine substrate seems to accelerate the reaction by facilitating the oxidation step via an oxazolidine intermediate. The synthetic application of this reaction for the preparation of complex glycoconjugates are currently under investigation in our laboratory.

Experimental Section

General Experimental Procedure for the Oxidative Amidation of Aldoses. To a solution of aldose (200 mg, 0.37 mmol) in *t*-butyl alcohol (4 mL) was added the amine (1.1−3.3 equiv). The mixture was stirred at reflux under an argon atmosphere for 1 h, and then K_2CO_3 (154 mg, 3 equiv) and I_2 (188 mg, 2 equiv) were added. The solution was stirred at reflux until TLC indicated total conversion of starting material (2−6 h). The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and was extracted with Et_2O (2 × 10 mL). The organic layer was washed with brine (7 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (PE/AcOEt) to give the amide.

***N*-2-Hydroxyethyl-2,3,4,6-tetra-*O*-benzyl-D-gluconamide (3).** Aldose **1** (200 mg, 0.37 mmol) was treated as described in the general procedure using 2-aminoethanol **2** (25 mg, 0.41 mmol, 1.1 equiv), K_2CO_3 (154 mg, 1.1 mmol, 3 equiv) and I_2 (188 mg, 0.74 mmol, 2 equiv). The resulting crude product was purified by silica gel chromatography (PE/AcOEt gradient) to provide **3** (163 mg, 74%) as a white solid: mp 102−103 °C; $[\alpha]^{20}_D$ +24.5 (*c* 1, CH_2Cl_2); IR (neat) 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.46 (br t, 1H, J = 4.9 Hz, NH-CH_2-CH_2-O<u>H</u>), 2.95 (d, 1H, J = 3.8 Hz, OH-5), 3.31 (m, 2H, NH-C<u>H</u>$_2$-CH_2-OH), 3.53 (m, 2H, NH-CH_2-C<u>H</u>$_2$-OH), 3.58 (dd, 1H, J = 5.3 Hz, J = 9.8 Hz, H-6b), 3.66 (dd, 1H, J = 2.8 Hz, J = 9.9 Hz, H-6a), 3.86 (dd, 1H, J = 5.8 Hz, J = 7.5 Hz, H-4), 3.93 (m, 1H, H-5), 4.08 (dd, 1H, J = 3.5 Hz, J = 5.5 Hz, H-3), 4.29 (d, 1H, J = 3.3 Hz, H-2), 4.44−4.58 (m, 6H, -O-C<u>H</u>$_2$-Ph), 4.71 (d, 2H, J = 11 Hz, -O-C<u>H</u>$_2$-Ph), 7.00 (t, 1H, J = 5.9 Hz, NH), 7.24−7.33 (m, 20H, H-Ar); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 42.1 (NH-<u>C</u>H_2-CH_2-OH), 62.0 (NH-CH_2-<u>C</u>H_2-OH), 71.1 (C-6), 71.4 (C-4), 73.4−75.1 (4 × -O-<u>C</u>H_2-Ph), 77.4 (C-3), 80.1 (C-5), 80.7 (C-2), 127.6−128.6 (CH-Ar), 136.7−138.1 (Cq-Ar), 172.1 (C-1); MS $[M + H]^+$ 600.5. Anal. Calcd for $C_{36}H_{41}NO_7$: C, 72.10; H, 6.89; N, 2.34. Found: C, 71.80; H, 6.86; N, 2.40.

***N*-2-Hydroxy-1-(hydroxymethyl)ethyl-2,3,4,6-tetra-*O*-benzyl-D-gluconamide (19).** Aldose **1** (200 mg, 0.37 mmol) was treated as described in the general procedure using aminoalcohol **18** (111 mg, 1.22 mmol, 3.3 equiv), K_2CO_3 (154 mg, 1.11 mmol, 3 equiv). and I_2 (184 mg, 0.74 mmol, 2 equiv). The resulting crude product was purified by silica gel chromatography (PE/AcOEt gradient) to provide **19** (107 mg, 46%) as a white solid: mp 72−73 °C; $[\alpha]^{20}_D$ +29.5 (*c* 1.2, CH_2Cl_2); IR (neat) 1661 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.84 (br t, 1H, NH-CH(CH_2-O<u>H</u>)-CH_2-OH), 2.95 (br t, 1H, NH-CH(CH_2-OH)-CH_2-O<u>H</u>), 3.07 (d, 1H, J = 5 Hz, OH-5), 3.50 (m, 4H, NH-CH(C<u>H</u>$_2$-OH)-C<u>H</u>$_2$-OH), 3.58 (dd, 1H, J = 5.5 Hz, J = 9.8 Hz, H-6b), 3.65 (dd, 1H, J = 3 Hz, J = 10 Hz, H-6a), 3.79 (m, 1H, NH-C<u>H</u>(CH_2-OH)-CH_2-OH), 3.84 (dd, 1H, J = 5.8 Hz, J = 7.5 Hz, H-4), 3.94 (m, 1H, H-5), 4.09 (dd, 1H, J = 3.6 Hz, J = 5.4 Hz, H-3), 4.28 (d, 1H, J = 3.5 Hz, H-2), 4.45 - 4.61 (m, 6H, -O-C<u>H</u>$_2$-Ph), 4.70 (2 d, 2H, J = 11.2 Hz, -O-C<u>H</u>$_2$-Ph), 7.20 (m, 1H, NH), 7.18−7.34 (m, 20H, H-Ar); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 52.3 (NH-<u>C</u>H(CH_2-OH)-CH_2-OH), 62.87, 62.94 (NH-CH(<u>C</u>H_2-OH)-<u>C</u>H_2-OH), 71.1 (C-6), 71.4 (C-4), 73.4−75.1 (4 × -O-<u>C</u>H_2-Ph), 77.4 (C-3), 80.1 (C-5), 80.6 (C-2), 127.6−128.6 (CH-Ar), 136.6−137.9 (Cq-Ar), 171.6 (C-1); MS $[M + H]^+$ 631.0. Anal. Calcd for $C_{37}H_{43}NO_8$: C, 70.57; H, 6.88; N, 2.22. Found: C, 70.56; H, 6.99; N, 2.22.

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Supporting Information Available: Additional procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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