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Reagents for Stereoselective Preparation of *N*-Carbamyl β-D-Glucuronides

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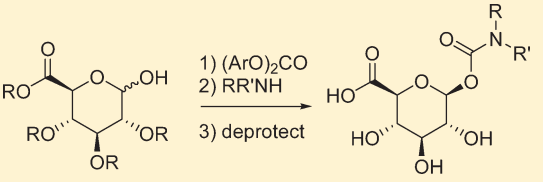
Supporting Information

ABSTRACT: Carbamyl glucuronidation is an increasingly well-recognized route of metabolism for secondary amine drugs. Proper characterization of these metabolites requires the synthesis of authentic standards. O-Protected glucuronyl *p*-nitrophenyl carbonates can be prepared with high selectivity for the β-configuration at the anomeric center and efficiently transfer the β-glucuronylcarbonyl group to secondary amines, constituting an effective and versatile method for preparation of these metabolites.



Conjugation to *N*-carbamyl β-D-glucuronides is an increasingly well-recognized metabolic fate of many amine-containing drugs.[1] The transformation is considered to proceed by reversible carboxylation of the amine with endogenous CO_2, followed by enzyme-mediated glucuronyl transfer to the intermediate carbamic acid.[1−4] Several isoforms of uridine diphosphate β-D-glucuronyl tranferase (UDPGT) are known to be competent for this process.[5] Small quantities of carbamyl glucuronides have been isolated and characterized from in vivo[4,6−8] or in vitro[2,3,9] metabolic systems, but laboratory synthesis is most practical for the larger amounts required for detailed studies of the pharmacology and toxicology,[10] distribution, recirculation, and elimination of these metabolites. Good methods for direct, stereocontrolled β-D-glucuronidation of alcohols, amines, and carboxylic acids have been developed,[11−14] but these are not suitable for preparation of glucuronyl carbamates due to the instability of the requisite carbamic acids. Activated ureas,[15] like carbamyl chlorides,[16] form glucuronyl carbamates, but with poor anomeric selectivity. On the other hand, it has been shown (Scheme 1) that isocyanates react with excellent stereoselectively with the anomeric hydroxyl of a suitably protected glucuronic acids (e.g., **1a**,[17] and even less-protected versions[18]) providing a route to β-D-glucuronyl carbamates of primary amines (**2p**).[19] Leenders and Scheeren further exploited this finding to design *N*-phenanthridinone *O*-β-D-glucuronyl carbamate (**3**) that efficiently transfers the β-D-glucuronylcarbonyl group to primary or secondary (**2s**) amines.[20] The preparation of **3**, though rather efficient, requires five steps and may limit its availability and use. Described here is methodology for stereoselective preparation of mixed p-nitrophenyl β-D-glucuronyl carbonates **4a**,**b** (Scheme 2) that transfer the glucuronylcarbamyl moiety with excellent stereochemical integrity, constituting a general method for synthesis of β-D-glucuronyl carbamates.

Reaction of methyl 2,3,4-tri-*O*-acetylglucuronate (**1a**)[15,21] (as a ∼3:1 mix of α:β anomers in solution) with *p*-nitrophenyl chloroformate in the presence of triethylamine provided the *p*-nitrophenyl glucuronyl carbonate **4a** as an 83:17 mix of α/β epimers at the anomeric center.[22] On the assumption that a less-reactive acylating agent would favor capture of the more nucleophilic β-anomeric hydroxyl group,[23] the reaction was repeated using bis(p-nitrophenyl)carbonate. Indeed, the *p*-nitrophenyl glucuronyl carbonate **4a** was formed with ca. 11:89 selectivity favoring the β-anomer. One recrystallization of the crude product provided the protected *p*-nitrophenyl β-D-glucuronyl carbonate with very high (>98:2) stereoselectivity,[24] as determined by ^{1}H NMR (sugar H-1 resonance at δ 5.80, $J_{1,2}$ = 6.1 Hz). Importantly, **4a** reacts cleanly with amines to effect transfer of the β-D-glucuronyl carbonyl group, with retention of anomeric stereochemistry to form the protected amine β-D-glucuronyl carbamate. This is illustrated by elaboration of ABT-594 (**5**),[25] a nicotinic agonist with demonstrated clinical efficacy in treating chronic neuropathic pain,[26] to its carbamyl β-D-glucuronide **7**, a putative human metabolite (Scheme 3). Thus, addition of **4a** to **5** provided the carbamate **6** in good yield after chromatographic purification. Glucuronide deprotection was accomplished with *N*,*N*-diisopropylethylamine in wet methanol to provide the carbamyl glucuronide **7** after purification by reversed-phase chromatography. The mild hydrolysis conditions were essential to minimize formation of side products, in this case resulting from methanolysis to form the methyl carbamate of **5** and elimination of the glucuronide 4-acetate providing the 4,5-dehydro glucuronide.[13] As expected, carbamate **7** was formed as the β-anomer (sugar H-1 resonance at δ 5.34, $J_{1,2}$ = 7.9 Hz), indicating retention of configuration through the glucuronyl transfer and deprotection steps.

In an effort to avoid hydrolysis side reactions in the sugar deprotection, and thereby simplify isolation of the pure glucuronyl carbamate product, benzyl protection of the sugar was investigated. Indeed, benzyl 2,3,4-tri-*O*-benzylglucuronate (**1b**,[27]

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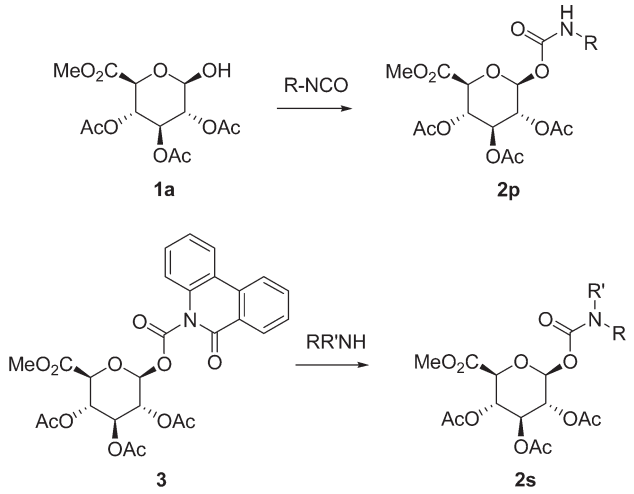
Scheme 1. Stereoselective Methods for Preparation of Glucuronylacabamates



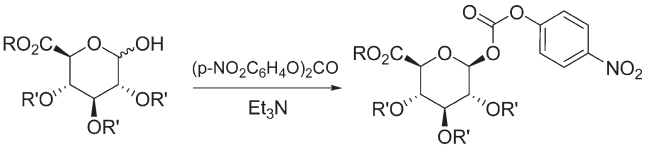
found to exist as a ca. 2:1 ratio of α:β anomers in $CDCl_3$ solution) reacted with bis(*p*-nitrophenyl)carbonate to provide the mixed carbonate **4b** with >95% β-anomeric selectivity. Similar to **4a**, the benzyl-protected glucuronyl carbonate **4b** transferred the tetra-*O*-benzyl glucuronyl carbonyl group efficiently to secondary amines. Thus, reaction with ABT-089 (**8**),[28] a nicotinic partial agonist tested clinically for treatment of ADHD,[29] provided the protected carbamate **9** in 89% yield after purification by flash chromatography (Scheme 4). In fact, since reaction of **1b** with bis(*p*-nitrophenyl)carbonate proceeds with excellent β-anomeric stereoselectivity, it was also possible to prepare **9** in a one-pot reaction from **1b** and triethylamine by sequential addition of bis(*p*-nitrophenyl)carbonate and **8**. Although related benzyl-protected glucuronides have been reported to undergo full debenzylation under mild conditions,[30] catalytic hydrogenation of **9** proceeded rather sluggishly once the benzyl ester was cleaved.[31] After screening a number of hydrogenolysis conditions (including different catalysts, hydrogen pressures, and atom-transfer conditions), it was found that full debenzylation could be accomplished using a high loading of Pearlman's catalyst, providing clean β-D-glucuronyl carbamate **10** after 2 days' reaction time with minimal workup. This deprotection is not suitable for compounds with easily hydrogenated functional groups (e.g., **7**), but reagent **4b** may be a preferred alternative to the ester-protected analogue **4a** when that is not an issue. Use of a less-protected glucuronide might be preferred in some cases, and allyl glucuronate (**4c**) has been reported[18] to undergo selective formation of β-glucuronyl carbamates and carbonates on reaction with certain isocyanates and chloroformates, respectively. Unfortunately, conditions could not be found to produce the anomeric *p*-nitrophenylcarbonate of **4c** or the related benzyl glucuronate.

In summary, the protected glucuronyl carbonates **4a** and **4b** are easily prepared in high stereochemical purity and function as glucuronylcarbonyl transfer reagents, useful for the preparation of β-D-glucuronyl carbamates.

EXPERIMENTAL SECTION

Melting ranges were determined with a capillary tube apparatus and are uncorrected. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. The ^{1}H NMR spectra of the

Scheme 2. Stereoselective Preparation of *p*-Nitrophenyl β-D-Glucuronyl Carbonates



sugar carbamates exhibited broad lines and split multiplets indicative of slow interconversion of rotamers at room temperature. At 90 °C, the signals coalesced and sharpened sufficiently to enable interpretation of the proton spectra, but the larger dispersion (Δ*Hz*) in the ^{13}C NMR made it impossible to obtain usable carbon spectra of **5**, **6**, **9**, and **10**. The stereoselectivities for **4a** and **4b** were determined from integration of the ^{1}H NMR signal for the anomeric proton for the β-glucuronide compared to the chemical shift region for the α-anomer (δ 6.4−6.2 ppm).[22]

Methyl 2,3,4-Tri-O-acetyl-1-*O*-(4-nitrophenoxycarbonyl)-β-D-glucopyranuronate (4a). A solution of bis(4-nitrophenyl) carbonate (2.40 g, 7.88 mmol) in CH_2Cl_2 (35 mL) was added dropwise over 20 min to a chilled (−5 to −10 °C) solution of methyl 2,3,4-tri-*O*-acetyl-D-glucupyranuronate (**1a**)[21] (2.51 g, 7.51 mmol) and triethylamine (1.52 g, 15.02 mmol) in CH_2Cl_2 (60 mL) under a nitrogen atmosphere. The resulting yellow solution was stirred for 30 min longer and then washed successively with 5% Na_2CO_3 (aq) (1 × 200 mL, 1 × 80 mL) and 4% H_2SO_4 (aq) (180 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum to leave an off-white, friable foam (3.68 g). The residue was crystallized from ethyl ether (80 mL) to provide a white, crystalline powder (2.89 g, 77%). If desired, further purification can be accomplished by crystallization from methanol: mp 124.5−125.5 °C (lit.[24] mp 132 °C); $[\alpha]_D^{20}$ = −20.0 (*c* 1.00, EtOAc) (lit.[24] $[\alpha]_D^{20}$ −4.4 (*c* 0.34, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3 H), 2.07 (s, 3 H), 2.11 (s, 3 H), 3.77 (s, 3 H), 4.31 (d, *J* = 8.3 Hz, 1 H, H-5), 5.21 (dd, *J* = 8.7, 6.1 Hz, 1 H, H-2), 5.33 (t, *J* = 8.3 Hz, 1 H), 5.38 (t, *J* = 8.9 Hz, 1 H), 5.80 (d, *J* = 6.1 Hz, 1 H, H-1), 7.44 (d, *J* = 9.2 Hz, 2 H), 8.29 ppm (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.4 (q), 20.5 (q), 20.6 (q), 53.1 (q), 68.1 (d), 70.1 (d), 70.9 (d), 73.1 (d), 95.6 (d), 121.7 (d), 125.4 (d), 145.7 (s), 150.7 (s), 155.0 (s), 167.0 (s), 169.1 (s), 169.3 (s), 169.7 (s); HRMS *m*/*z* 737.27009 (M + NH_4 requires 737.27049). Anal. Calcd for ($C_{20}H_{21}NO_{14}$): C, 48.10; H, 4.24; N, 2.80. Found: C, 48.10; H, 4.14; N, 2.81.

Benzyl 2,3,4-Tri-*O*-benzyl-1-*O*-(4-nitrophenoxycarbonyl)-β-D-glucopyranuronate (4b). Solid bis(4-nitrophenyl) carbonate (210 mg, 0.691 mmol) was added to an ice-cooled solution of benzyl 2,3,4-tri-*O*-benzyl-D-glucupyranuronate (**1b**)[27] (365 mg, 0.658 mmol) in triethylamine (0.183 mL, 1.32 mmol) and CH_2Cl_2 (20 mL). After 2.5 h at 0 °C, the solution was diluted with CH_2Cl_2 (25 mL) and washed successively with 5% Na_2CO_3 (aq) (2 × 20 mL) and 4% H_2SO_4 (aq) (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum. The residual pale oil (484 mg) was crystallized from ethyl ether (5 mL) and hexanes (10 mL) to provide the title compound as fine white needles (342 mg, 72%): mp 85.0−85.8 °C; $[\alpha]_D^{20}$ = −4.2 (*c* 1.00, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69−3.81 (m, 2 H), 3.92 (t, *J* = 9.0 Hz, 1 H), 4.17 (d, *J* = 9.5 Hz, 1 H, H-5), 4.47 (d, *J* = 10.5 Hz, 1 H), 4.71 (d, *J* = 10.9 Hz, 1 H), 4.75−4.88 (m, 4 H), 5.12−5.22 (m, 2 H), 5.65 (d, *J* = 6.8 Hz, 1 H, H-1), 7.12 (dd, *J* = 6.6, 3.2 Hz, 2 H), 7.21−7.37 (m, 20 H), 8.22−8.30 ppm (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.7 (t), 75.0 (t), 75.1 (d), 75.5 (t), 78.7 (d), 80.3 (d), 83.2 (d), 98.2 (d), 121.7 (d), 125.3 (d), 127.76 (d), 127.82 (d), 127.85 (d), 128.0 (d), 128.35 (d), 128.44 (d), 128.49 (d), 128.55 (d), 128.57 (d), 128.59 (d), 134.7 (s), 137.4 (s), 137.6

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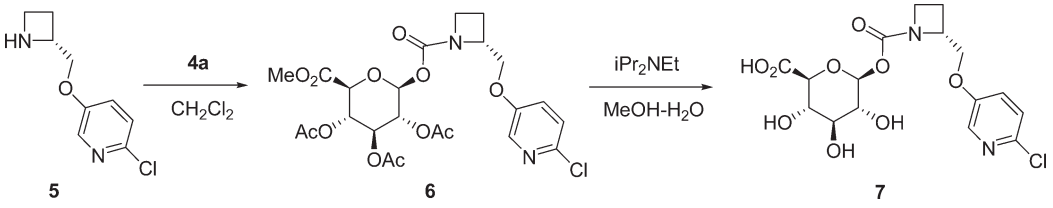
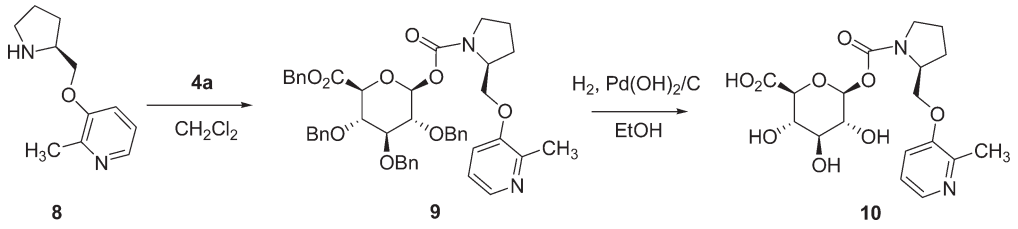
Scheme 3



Scheme 4



(s), 137.9 (s), 145.6 (s), 151.0 (s), 155.0 (s), 168.1 ppm(s), one benzylic CH_2 and two phenyl CH signals not resolved; HRMS CI/NH_3 m/z 737.27009 (M + H requires 737.27049). Anal. Calcd for ($C_{41}H_{37}NO_{11}$): C, 68.42; H, 5.18; N, 1.95. Found: C, 68.58; H, 5.11; N, 1.86.

Methyl 2,3,4-Tri-*O*-acetyl-1-(2-(*R*)-[6-chloropyridin-3-yloxymethyl]azetedin-1-ylcarboxy)-β-D-glucopyranuronate (6). Solid **4a** (99.3 mg, 0.199 mmol) was added at room temperature to a solution of the *p*-toluenesulfonate salt of **5** (74.2 mg, 0.200 mmol) in CH_2Cl_2 (5 mL) and triethylamine (0.1 mL, 0.7 mmol). The yellow solution was stirred at room temperature for 75 min, diluted with CH_2Cl_2 (10 mL) and washed successively with 5% Na_2CO_3 (aq) (15 mL) and 8% H_2SO_4 (aq) (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under vacuum to leave an off-white foam. The crude material was purified by flash chromatography (silica gel, eluted with hexanes−EtOAc, 50:50) to provide the title compound (98.4 mg, 88% yield): $[\alpha]_D^{20}$ = +33.1 (*c* 1.00, EtOH); ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C)[32] δ 1.87 (br s, 3 H), 1.94 (s, 3 H), 1.96 (s, 3 H), 2.15−2.28 (m, 1 H), 2.33−2.44 (m, 1 H), 3.65 (s, 3 H), 3.77−3.92 (m, 2 H), 4.17 (dd, *J* = 10.7, 3.3 Hz, 1 H), 4.27 (dd, *J* = 10.7, 4.4 Hz, 1 H), 4.57 (d, *J* = 9.5 Hz, 1 H, H-5), 4.56−4.63 (m, 1 H), 4.95 (dd, *J* = 9.3, 8.0 Hz, 1 H, H-2), 5.05 (t, *J* = 9.3 Hz, 1 H), 5.40 (t, *J* = 9.3 Hz, 1 H), 5.84 (d, *J* = 8.0 Hz, 1 H, H-1), 7.37 (dd, *J* = 8.8, 0.7 Hz, 1 H), 7.46 (dd, *J* = 8.8, 1.9 Hz, 1 H), 8.12 ppm (dd, *J* = 1.9, 0.7 Hz, 1 H); MS (ESI) m/z 559/561 $(M + H)^+$. Anal. Calcd for ($C_{23}H_{27}N_2O_{12}Cl$): C, 49.43; H, 4.87; N, 5.01. Found: C, 49.48; H, 5.16; N, 4.84.

1-(2-(*R*)-[6-Chloropyridin-3-yloxymethyl]azetedin-1-ylcarboxy)-β-D-glucopyranuronic Acid (7). A solution of **6** (92 mg, 0.16 mmol) in a mixture of methanol (5 mL) and water (1 mL) was stirred with ice cooling as ethyldiisopropylamine (0.5 mL) was added at once. The yellow solution was allowed to stir for 14 h, coming to room temperature as the ice bath expired overnight. The solution was concentrated under vacuum and the residue taken up in EtOAc (5 mL) and concentrated under vacuum (repeated twice to remove excess amine). The residue was purified by chromatography (Lobar RP18 column, eluting with 0.1% trifluoroacetic $acid_{(aq)}$−CH_3CN (9:1) to provide the glucuronyl carbamate as an off-white solid (55.2 mg, 67%): $[\alpha]_D^{20}$ = +49.7 (*c* 0.17, EtOH); ^{1}H NMR (300 MHz, CD_3OD) δ 2.26−2.58 (m, 2 H), 3.37−3.60 (m, 3 H), 3.88 (br d, *J* = 9.1 Hz, 1 H, H-5), 3.91−4.13 (m, 2 H), 4.21 (dd, *J* = 10.3, 2.8 Hz, 1 H), 4.40−4.53 (m, 1 H), 4.59−4.75 (m, 1 H), 5.34 (d, *J* = 7.9 Hz, 1 H, H-1), 7.35 (d, *J* = 8.7 Hz, 1 H), 7.50 (dd, *J* = 8.7, 1.6 Hz, 1 H), 8.11 ppm (brd, *J* = 1.6 Hz, 1 H); HRMS (DCI/NH_3) m/z 419.08520 (M + H requires 419.08518). Anal. Calcd for ($C_{16}H_{19}N_2O_9Cl \cdot 0.5TFA$): C, 42.91; H, 4.13; N, 5.89. Found: C, 42.97; H, 4.25; N, 5.90.

Benzyl 2,3,4-Tri-*O*-benzyl-1-(2-(*S*)-[2-methylpyridin-3-yloxymethyl]pyrrolidin-1-ylcarboxy)-β-D-glucopyranuronate (9). Solid **8** (as the dihydrochloride salt)[28] (95 mg, 0.358 mmol) was added to a solution of **4b** (100 mg, 0.139 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at 20 °C as triethylamine (100 μL, 0.717 mmol) was added, and the resulting bright yellow mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum, and the residue was purified by flash chromatography (silica gel, eluted with hexanes−EtOAc, 75:25−0:100) to provide a colorless glass (96 mg, 89%): $[\alpha]_D^{20}$ = −46.7 (*c* 1.01, EtOH); ^{1}H NMR (400 MHz, DMSO-d_6, 90 °C)[32] δ 1.76−1.88 (m, 1 H), 1.90−2.05 (m, 3 H), 2.31 (s, 3 H), 3.27−3.38 (m, 1 H), 3.38−3.50 (m, 1 H), 3.58 (dd, *J* = 8.4, 7.3 Hz, 1 H, H-2), 3.79 (t, *J* = 8.9 Hz, 1 H), 3.86 (t, *J* = 8.4 Hz, 1 H), 3.97−4.12 (m, 3 H), 4.25 (d, *J* = 9.2 Hz, 1 H, H-5), 4.44 (d, *J* = 11.0 Hz, 1 H), 4.60−4.68 (m, 3 H), 4.71 (d, *J* = 11.6 Hz, 1 H), 4.76 (d, *J* = 11.6 Hz, 1 H), 5.14 (s, 2 H), 5.71 (d, *J* = 7.3 Hz, 1 H, H-1), 7.06−7.14 (m, 4 H), 7.15−7.33 (m, 18 H), 7.99 (dd, *J* = 4.6, 1.2 Hz, 1 H); MS (ESI) m/z 413 $(M + H)^+$. Anal. Calcd for ($C_{46}H_{48}N_2O_9$): C, 71.49; H, 6.26; N, 3.62. Found: C, 71.26; H, 6.05; N, 3.58.

One-Pot Preparation of Benzyl 2,3,4-Tri-*O*-benzyl-1-(2-(*S*)-[2-methylpyridin-3-yloxymethyl]pyrrolidin-1-ylcarboxy)-β-D-glucopyranuronate (9). A solution of **1b** (270 mg, 0.487 mmol) in CH_2Cl_2 (15 mL) and triethylamine (0.117 mL, 0.84 mmol) was stirred under nitrogen with ice cooling as a solution of bis(*p*-nitrophenyl)carbonate (148 mg, 0.49 mmol) in CH_2Cl_2 (3 mL) was run in over 30 s. The yellow solution was stirred with ice cooling for 3 h, a solution of **8** (192 mg, 1 mmol) in CH_2Cl_2 (4 mL) was added to the reaction mixture, and the yellow solution was allowed to warm gradually to room temperature with stirring overnight (13 h). The solution was diluted with CH_2Cl_2 (20 mL) and washed with 20% Na_2CO_3 (aq) (2 × 15 mL). The organic phase was concentrated under vacuum, and the residue was purified by flash chromatography (SiO_2, eluted with hexanes−EtOAc 80:20−60:40) to provide the carbamate **9**, identical to that described above (276 mg, 73% yield).

1-(2-(*S*)-[2-Methylpyridin-3-yloxymethyl]pyrrolidin-1-ylcarboxy)-β-D-glucopyranuronic Acid (10). A solution of **9** (508 mg, 0.66 mmol) in ethanol (50 mL) was stirred under nitrogen

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as 20% $Pd(OH)_2/C$ (500 mg) was added. The reaction flask was evacuated and purged with nitrogen (four cycles), then with hydrogen (four cycles), and the mixture was stirred at room temperature under hydrogen (1 atm) for 46 h. The flask was evacuated and purged with nitrogen (four cycles), and the mixture was filtered through a pad of diatomaceous earth. The filter was rinsed with EtOH (15 mL), then water (10 mL), and the filtrate was concentrated under vacuum. EtOAc (20 mL) was added to the residue, and the mixture was concentrated under vacuum to leave a white solid after drying under vacuum at 45 °C (265 mg, 98% yield): $[\alpha]_D^{20} = -59.9$ (c 0.55, EtOH); ^{1}H NMR (400 MHz, D_2O, 90 °C)[32] δ 2.20−2.57 (m, 4 H), 2.87 (s, 3 H), 3.67−3.94 (m, 5 H), 4.09 (d, J = 9.4 Hz, 1 H, H-5), 4.55−4.73 (m, 3 H), 5.72 (d, J = 8.0 Hz, 1 H, H-1), 7.91 (br dd, J = 8.2, 5.5 Hz, 1 H), 8.13 (br d, J = 8.2 Hz, 1 H), 8.43 ppm (d, J = 5.5 Hz, 1 H); MS (ESI) m/z 413 $(M + H)^+$; HRMS (DCI/NH_3) m/z 413.15558 (M + H requires 413.15545). A sample (20 mg) was dissolved in water (1.5 mL) and washed with CH_2Cl_2 (2 × 2 mL). The aqueous phase was concentrated in a nitrogen stream, and the residue was dried at 50 °C under vacuum: Anal. Calcd for ($C_{18}H_{24}N_2O_9 \cdot H_2O$): C, 50.23; H, 6.09; N, 6.51. Found: C, 50.44; H, 5.81; N, 6.51.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra for **4a,b**, **6**, **7**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) In one experiment, the carbamyl chloride of **5**, formed by reaction with phosgene, reacted with **4a** to produce, in low conversion, a 1:1 mix of anomers of **6** among unidentified reaction side products.
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