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Access to Complex C2-Branched Glycoconjugates via Palladium-Catalyzed Aminocarbonylation Reaction of 2-Iodoglycals

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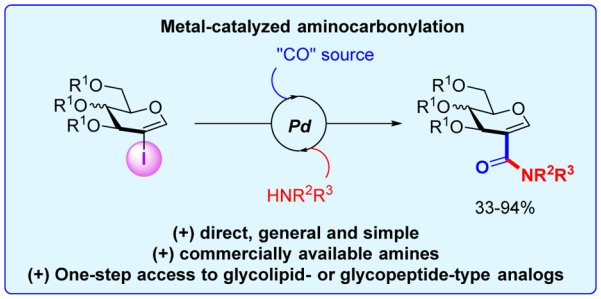
Supporting Information

ABSTRACT: A convenient and straightforward synthesis of 2-amidoglycals through a palladium-catalyzed aminocarbonylation reaction between 2-iodoglycal partners and diverse amines in the presence of a "CO" source has been developed. Several amines such as aliphatics, benzylics, or aromatics are compatible with our reaction conditions as well as sulfonamides. Further deprotection steps have been successfully applied, leading to glycoside mimics. This method constitutes a new route to access original glycopeptide- and glycolipid-type analogues possessing a C−C bond at the C2-position.



The well-known ubiquity of carbohydrates and glycoconjugates (glycopeptides and glycolipids) in biological processes such as cell adhesion, cell recognition, or immunity led chemists to develop new synthetic methodologies to build them or their analogues efficiently.[1] In particular, the replacement of natural glycosidic linkages by mimic carbon−carbon bonds (C-branched sugars) is widely explored due to the discovery of interesting natural bioactive C-glycosides such as Palytoxin or Spongistatin.[2] Moreover, the enzymatic and chemical stability of C−C bonds and conformational similarity compared to C−O and C−N links are major strengths in carbohydrate-type mimic design, in particular, as sugar processing enzyme inhibitors.[2c] These promising properties led our laboratory to develop new synthetic access to C-branched glycoside and nucleoside analogues.[3] A few years ago, we described the synthesis of a potential antiviral C-nucleoside mimic of Ribavirin via a key indium-mediated alkynylglycosylation step.[3b] Recently, C2-branched carbohydrates have been proven to mimic *N*-acetylglycosides, which are key intermediates of lipid biosynthesis.[4] In the literature, the preparation of C2-branched analogues of carbohydrates have been extensively described.[5] However, access to C2-amidoglycoconjugates is still limited despite their proven potential inhibitory activity as stable glycoside mimics.[6] Indeed, scarce C2-amidosugar examples are described where the amide link was generally inserted by cycloaddition reactions between a glycal-type starting material and an isocyanate or an azomethine imine partner (Figure 1).[6,7] However, these methods require the synthesis of a suitable isocyanate or azomethine imine compound. In recent decades, the development of versatile methods to build amide function via metal-catalyzed reactions became more and more attractive. In particular, an aminocarbonylation process was proven to be a useful and powerful tool to insert amide parts.[8] In glycoside chemistry, the formation of C2-branched analogues by metal-catalyzed cross-coupling steps is less explored. Indeed, only a few examples of Suzuki−Miyaura, Sonogashira, Heck, or Stille cross-coupling reactions were described on 2-halogenated compounds.[9] However, to the best of our knowledge, access to C2-branched glycoconjugate analogues by an aminocarbonylation strategy has not been described so far despite its usefulness. We describe thus a new convenient access to C2-amidoglycosides by a palladium-catalyzed aminocarbonylation reaction from 2-iodoglycals and commercially available amines, leading to original C2-branched glycoconjugates (Figure 1).

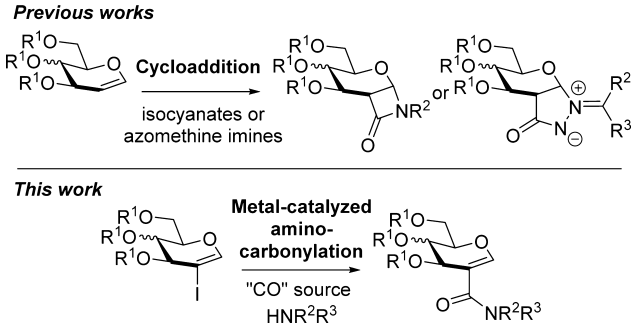


Figure 1. Synthesis of C2-amidoglycal scaffolds.

We started our aminocarbonylation methodological study using a classical catalytic system: $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (2 equiv) in DMF.[9] To these conditions were added an amine partner ($BnNH_2$) and a "CO" source (molybdenum hexacarbonyl, $Mo(CO)_6$).

The choice of $Mo(CO)_6$ as "CO" tank was motivated by its solid state, which is easy to handle compared to gaseous carbon monoxide and its well-known efficiency in this type of

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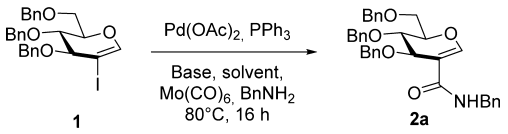
reaction.[10] However, these first conditions furnished only a trace of the desired compounds **2a** (Table 1, entry 1). The change of solvent modified drastically the outcome of the reaction, leading to the desired products in 94% in the case of dioxane (Table 1, entries 2 and 3) but in a moderate 43% in the case of toluene (Table 1, entry 4). On the other hand, the nature of the base seems to be inconsequential because both trimethylamine and potassium *tert*-butylate gave **2a** in very good yields (Table 1, entries 5 and 6). Nevertheless, the absence of base decreases drastically the reactivity (Table 1, entry 7). Therefore, the excess of basic amine as a unique base source in the reaction medium is not sufficient to perform the reaction. The loading of palladium could be reduced to 2.5 mol % without major loss of yield (Table 1, entry 8). It was shown that the presence of $Mo(CO)_6$ as the sole catalyst can be sufficient to perform the aminocarbonylation process.[10a,c,d] In our case, the presence of the palladium species is essential to the reaction because no trace of **2a** was observed without $Pd(OAc)_2$ (Table 1, entry 9). Other "CO" sources as the system ($CHCl_3$, $CsOH{\cdot}H_2O$ in toluene)[8d] could be successfully used, leading to excellent yield, generating CO gas in a separate flask than the reaction vessel (Table 1, entry 10). In the scope of this investigation, the system of $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (2 equiv), amine (2 equiv), and $Mo(CO)_6$ (4.2 equiv) in dioxane at 80 °C was chosen. Various amines were then engaged with **1** (Table 2). Aliphatic primary and secondary amines were well-tolerated, leading in all cases to good to excellent yields (Table 2, **2a**–**f**). In the case of **2f**, only

Table 1. Optimization of the Aminocarbonylation Reaction[a]

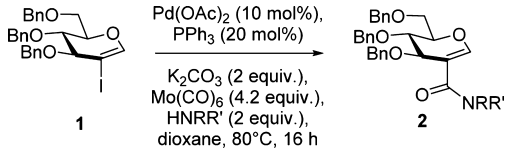


1 2a

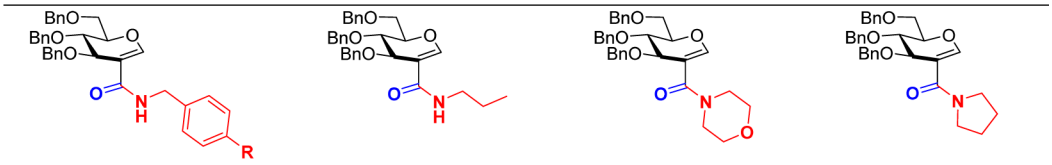
entry	$Pd(OAc)_2$ (mol %)	base (2 equiv)	solvent	yield[b] (%)
1	10	K_2CO_3	DMF	<10
2	10	K_2CO_3	dioxane	94
3	10	K_2CO_3	MeCN	93
4	10	K_2CO_3	toluene	43
5	10	NEt_3	dioxane	80
6	10	*t*BuOK	dioxane	87
7	10		dioxane	28
8	2.5	K_2CO_3	dioxane	73
9		K_2CO_3	dioxane	0
10[c]	10	K_2CO_3	dioxane	84

[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (*x* mol %), PPh_3 (20 mol %), base (2 equiv), $Mo(CO)_6$ (4.2 equiv), $BnNH_2$ (2 equiv), solvent (1 mL) at 80 °C for 16 h under air. [b]Yields were determined on isolated products. [c]The reaction was conducted using the system of $CHCl_3$ (9 equiv), $CsOH{\cdot}H_2O$ (28 equiv) in toluene as "CO" source in a two-pot process.

Table 2. Amine Scope[a]



1 2



R = H **2a** /94%
R = Cl **2b** / 79%

2c /73%

2d /88%

2e /79%

2f /55%

R = OMe **2g** /50%
R= F **2h** /51%

2i /36%

2j /67%

2k /55%

2l /60%[b]

2m /33%[b,c]

2n /53%[b,c]

[a]Yields were determined on isolated products. [b]The corresponding aminoester was used as its hydrochloride form, and the amount of base was increased to 4 equiv. [c]With 30% epimerization.

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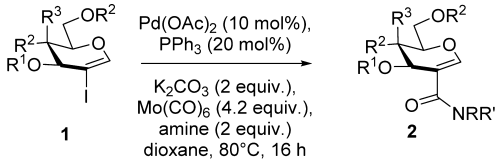
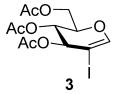
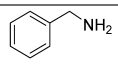
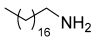
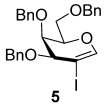
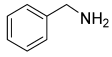
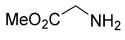
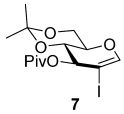
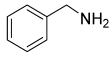
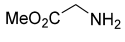
one diastereoisomer was obtained, certifying that the two stereocenters of the norephedrine moiety remained untouched.

Moderate to good yields could also be obtained with differently substituted anilines (Table 2, **2g–i**) as well as with a sulfonamide-type substrate (Table 2, **2j**). Since our goal is to exploit this methodology to the synthesis of glycopeptide or glycolipid mimics, long-chain amine (Table 2, **2k**) and amino acid partners were finally tested. Both led to the corresponding C2-amidoglycal compounds in moderate to good yields despite a partial epimerization in the case of amino acid partners (Table 2, **2l–n**). Different glycal starting materials were then tested (Table 3). Peracetylated glucals led to corresponding amides in good yields (Table 3, entry 1), showing the mildness of the developed conditions. Perbenzylated galactals were also successfully coupled without loss of reactivity compared to glucal analogues and furnished the corresponding glycoconjugates in good yields (Table 3, entry 2). Acetylidene protecting groups were also tolerated (Table 3, entry 3), but the corresponding C2-amidoglycals were obtained with slightly lower yields.

Table 3. Glycal Scope



Entry	Starting material	Amine	Product/ Yield[a]
1	 3		**4a** / 70%
			**4b** / 62%
2	 5		**6a** / 75%
			**6b** / 71%
3	 7		**8a** / 65%
			**8b** / 45%

[a]Yields were determined on isolated products.

From a mechanistic point of view, the reaction is expected to follow a classical catalytic cycle involving first the action of Pd(0) (obtained by in situ reduction of $Pd(OAc)_2$), which could activate the carbon–halogen bond of the glycal starting material to form a Pd(II) complex (**A**). After CO insertion in **A**, the acyl–Pd complex **B** could undergo a nucleophilic attack of the amine partner to liberate the product and a palladium hydride complex **C**, which was finally reduced in Pd(0) by the base (Figure 2).

Finally, in order to obtain glycoside mimics, deprotection of four obtained 2-amidoglycal compounds was performed

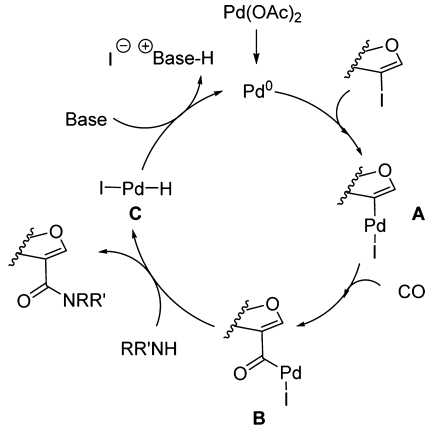


Figure 2. Proposed mechanism.

(Figure 3). Benzyl protecting groups of **2a**, **2k**, **2g**, and **6b** could be removed via a hydrogenolysis reaction leading to compounds **9a–d** with moderate to good yields (Figure 3). Curiously, these reductive conditions left the glycal double bond untouched as well as the benzylamide part of **9b**. Peracetylated compound **4b** or substrate **8a** could be deprotected in good yields.

In summary, C2-branched amidoglycal compounds were synthesized via a palladium-catalyzed aminocarbonylation cross-coupling reaction between 2-iodoglycals and amines using molybdenum hexacarbonyl as the "CO" source. Six examples could be successfully deprotected. Complex glycoconjugates, as glycolipid- or glycopeptide-type analogues, could thus be obtained. Post-translational modifications of complex peptides using this methodology are currently under investigation. Recently, *N*-acetylaminoglycal substrates were shown to be interesting ligands of hexosaminidases.[11] Given the structural analogy of these compounds with glycals **6**, the biological profile of these C2-branched glycoanalogues will also be explored.

EXPERIMENTAL SECTION

General Experimental Methods. All chemical operations were carried out using standard Schlenk tubes. Acetonitrile was purified before use by distillation under argon atmosphere. Others solvents were used without further purification. Commercially available chemicals were used as received unless otherwise stated. Reactions were monitored by thin-layer chromatography on silica gel plates (60 F254 aluminum sheets), which were rendered visible by ultraviolet and/or spraying with vanillin (15%) + sulfuric acid (2.5%) in EtOH followed by heating. ^{1}H NMR (400 MHz), ^{13}C NMR (100.5 MHz), and ^{19}F NMR spectra (376.2 MHz) were recorded at 298 K unless otherwise stated. Chemical shifts are given in parts per million (δ) and are referenced to the internal solvent signal or to TMS used as an internal standard. Multiplicities are declared as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), m (multiplet). Coupling constants *J* are given in hertz. Infrared (IR) spectra were recorded on a FT-IR system using diamond window Dura SamplIR II, and the data are reported in reciprocal centimeters (cm^{-1}) in the range of 4000–600 cm^{-1}. Optical rotations were measured on a polarimeter at 589 nm. $[\alpha]$ is expressed in $deg{\cdot}cm^3{\cdot}g^{-1}{\cdot}dm^{-1}$, and *c* is expressed in g/100 cm^3. HRMS were determined on a TOF mass analyzer coupled with electrospray ionization or atmospheric pressure chemical ionization.

Compounds **1**, **3**, and **5** were prepared according to the literature:[9e] corresponding glycal was dissolved in dry acetonitrile (8 mL/mmol), and the resulting mixture was heated to 80 °C. At this temperature, *N*-

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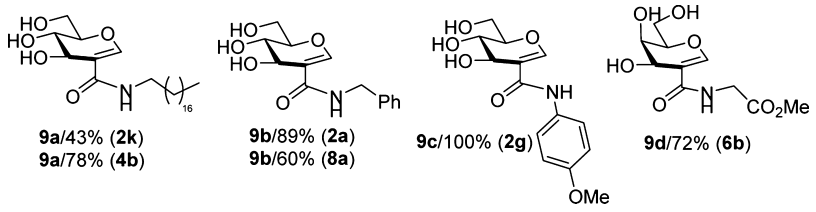

Figure 3. Deprotected glycals.

iodosuccinimide (1.2 equiv) and silver nitrate (20 mol %) were added. The resulting mixture was stirred at 80 °C for 2−7 h. The mixture was filtrated on Celite and concentrated. The obtained crude was purified on silica gel and furnished the corresponding 2-iodoglycal.

General Procedure for the Aminocarbonylation Reaction. $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), $Mo(CO)_6$ (4.2 equiv), K_2CO_3 (2 equiv), and the corresponding 2-iodoglycal (50 mg, 1 equiv) were introduced in a Schlenk tube. Dioxane (1 mL) and the amine (2 equiv) were then added. The mixture was stirred at 80 °C overnight and then concentrated under vacuum. The crude was finally purified on silica gel.

*(2R,3S)-N-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-carboxamide (**2a**):* White solid, 47.5 mg, 94%; eluent, EtOAc/cyclohexane 2:8; mp 126−128 °C; $[\alpha]_D^{20}$ = +44.3 (*c* = 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.61 (s, 1H), 7.36−7.02 (m, 20H), 6.39 (t, *J* = 5.5 Hz, 1H), 4.67 (s, 2H), 4.53 (s, 2H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.43 (m, 1H), 4.34−4.29 (m, 4H), 4.09 (t, *J* = 4.3 Hz, 1H), 3.79 (dd, *J* = 10.4 and 5.9 Hz, 1H), 3.71 (dd, *J* = 10.5 and 4.8 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 166.6, 153.7, 138.6, 137.8, 137.6, 136.9, 128.8, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.4, 107.3, 76.5, 73.6, 72.4, 71.7, 70.4, 69.7, 67.5, 43.4; IR (ν, cm^{-1}) 3352, 3063, 3030, 2916, 2867, 1656, 1607, 1526, 1496, 1454, 1194, 1071, 1028, 736, 669; HRMS calcd $[C_{35}H_{35}NO_5Na]^+$ 572.2413, found 572.2429.

*(2R,3S,4S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-N-(4-chlorobenzyl)-3,4-dihydro-2H-pyran-5-carboxamide (**2b**):* White solid, 42 mg, 79%; eluent, EtOAc/cyclohexane 2:8 then 3:7; mp 131−134 °C; $[\alpha]_D^{20}$ +51.5 (*c* = 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.54 (s, 1H), 7.35−7.05 (m, 16H), 7.05−6.85 (m, 3H), 6.28 (t, *J* = 5.5 Hz, 1H), 4.61 (s, 2H), 4.47 (s, 2H), 4.42 (d, *J* = 11 Hz, 1H), 4.36 (dd, *J* = 10.0 and 4.6 Hz, 1H), 4.28−4.12 (m, 4H), 4.02 (t, *J* = 4.2 Hz, 1H), 3.72 (dd, *J* = 10.8 and 6.2 Hz, 1H), 3.65 (dd, *J* = 10.6 and 5.0 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 166.6, 154.0, 137.7, 137.5, 137.2, 136.7, 129.2, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 107.0, 76.5, 73.6, 72.4, 71.7, 70.3, 69.6, 67.5, 42.6; IR (ν, cm^{-1}) 3268, 3030, 2859, 1652, 1622, 1540, 1453, 1319, 1182, 1089, 1058, 1027, 747, 668; HRMS calcd $[C_{35}H_{34}ClNO_5Na]^+$ 606.2023, found 606.2045, 608.2044.

*(2R,3S,4S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-N-propyl-3,4-dihydro-2H-pyran-5-carboxamide (**2c**):* White solid, 33 mg, 73%; eluent, EtOAc/cyclohexane 2:8 then 3:7; mp 66−68 °C; $[\alpha]_D^{20}$ +30.1 (*c* = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.49 (s, 1H), 7.33−7.10 (m, 15H), 6.00 (t, *J* = 5.5 Hz, 1H), 4.61 (s, 2H), 4.47 (s, 2H), 4.44 (s, 1H), 4.36−4.24 (m, 3H), 4.00 (t, *J* = 4.6 Hz, 1H), 3.72 (dd, *J* = 10.5 and 6.0 Hz, 1H), 3.65 (dd, *J* = 10.5 and 4.6 Hz, 1H), 3.01 (q, *J* = 7.3 Hz, 2H), 1.25 (q, *J* = 7.3 Hz, 2H), 0.71 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 166.6, 153.4, 137.8, 137.7, 137.2, 128.9, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 107.6, 76.6, 73.6, 72.5, 72.0, 70.5, 69.6, 67.6, 41.1, 22.9, 11.6; IR (ν, cm^{-1}) 3354, 3063, 3030, 2960, 2930, 2871, 1653, 1609, 1533, 1454, 1194, 1087, 736; HRMS calcd $[C_{31}H_{35}NO_5Na]^+$ 524.2413, found 524.2419.

*((2R,3S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-yl)(morpholino)methanone (**2d**):* Colorless oil, 43.0 mg, 88%; eluent, EtOAc/cyclohexane 2:8 then 3:7; $[\alpha]_D^{20}$ = −20.3 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.32−7.20 (m, 15H), 6.59 (s, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.63−4.55 (m, 5H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.32−4.28 (m, 1H), 3.94−3.91 (m, 1H), 3.82 (dd, *J* = 10.8 and 5.7 Hz, 1H), 3.68−3.65 (m, 3H), 3.56−3.44 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 168.3, 145.9, 138.2, 137.8, 128.6, 128.5, 128.4, 128.0, 127.9, 127.9, 127.8, 109.4, 77.1, 74.0, 73.6, 73.4, 73.2, 73.1, 67.9, 67.0, 45.6; IR (ν, cm^{-1}) 3062, 3031, 2958, 2917, 2899, 2858, 1623, 1454, 1427, 1182, 1114, 1091, 1070, 1027, 740, 698; HRMS calcd $[C_{32}H_{35}NO_6Na]^+$ 552.2362, found 552.2372.

*((2R,3S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-yl) (pyrrolidin-1-yl)methanone (**2e**):* Colorless oil, 37.0 mg, 79%; eluent, EtOAc/cyclohexane 2:8 then 3:7; $[\alpha]_D^{21}$ = −0.1 (*c* = 1.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.32−7.20 (m, 15H), 6.78 (s, 1H), 4.73 (d, *J* = 11.6 Hz, 1H), 4.66−4.51 (m, 6H), 4.34−4.31 (m, 1H), 3.89 (t, *J* = 5.2 Hz, 1H), 3.84 (dd, *J* = 10.8 and 6.2 Hz, 1H), 3.66 (dd, *J* = 10.8 and 3.1 Hz, 1H), 3.61−3.33 (br m, 4H), 1.95−1.83 (br m, 2H), 1.83−1.68 (br m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 167.4, 147.0, 138.6, 137.9, 128.6, 128.5, 128.4, 127.9, 127.8, 127.8, 127.7, 111.4, 77.1, 73.5, 73.1, 72.9, 72.8, 68.0, 47.5, 25.4; IR (ν, cm^{-1}) 3062, 3030, 2950, 2871, 1643, 1610, 1453, 1426, 1185, 1088, 1071, 1028, 738; HRMS calcd $[C_{32}H_{35}NO_5Na]^+$ 536.2413, found 536.2408.

*(2R,3S,4S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-N-((1S,2R)-1-hydroxy-1-phenylpropan-2-yl)-3,4-dihydro-2H-pyran-5-carboxamide (**2f**):* White solid, 30 mg, 55%; eluent, EtOAc/cyclohexane 3:7 then 5:5; mp 87−90 °C; $[\alpha]_D^{20}$ −24.1 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.48 (s, 1H), 7.33−7.10 (m, 18H), 6.88−7.00 (m, 2H), 6.13 (d, *J* = 7.4 Hz, 1H), 4.67 (d, *J* = 2.7 Hz, 1H) 4.60 (s, 2H), 4.44 (s, 2H), 4.38 (d, *J* = 9.9 Hz, 1H) 4.37−4.34 (m, 1H), 4.25−4.19 (m, 2H), 4.12 (d, *J* = 9.9 Hz, 1H), 3.98 (t, *J* = 8.7 Hz, 1H), 3.69 (dd, *J* = 10.6 and 5.9 Hz, 1H), 3.62 (dd, *J* = 10.6 and 5.9 Hz, 1H), 0.69 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 168.1, 153.7, 140.8, 137.7, 137.5, 137.0, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 126.8, 107.2, 77.6, 76.7, 73.6, 72.4, 72.4, 70.6, 70.2, 67.4, 51.1, 15.0; IR (ν, cm^{-1}) 3374, 3029, 2866, 1654, 1602, 1520, 1453, 1193, 1068, 737, 697; HRMS calcd $[C_{37}H_{40}NO_6]^+$ 594.2856, found 594.2877.

*(2R,3S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-N-(4-methoxyphenyl)-3,4-dihydro-2H-pyran-5-carboxamide (**2g**):* Yellowish oil, 26.0 mg, 50%; eluent, EtOAc/cyclohexane 2:8; $[\alpha]_D^{21}$ = +43.5 (*c* = 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.08 (s, 1H), 7.67 (s, 1H), 7.36−7.24 (m, 15H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 4.73 (s, 2H), 4.63 (d, *J* = 11.2 Hz, 1H), 4.57 (s, 2H), 4.51−4.50 (m, 1H), 4.46−4.43 (m, 2H), 4.18−4.16 (m, 1H), 3.84 (dd, *J* = 10.4 and 5.5 Hz, 1H), 3.79−3.75 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 164.7, 156.1, 154.5, 137.7, 137.5, 136.9, 131.3, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 121.8, 114.0, 107.6, 76.8, 73.7, 72.9, 72.6, 70.5, 70.0, 67.5, 55.6; IR (ν, cm^{-1}) 3324, 3030, 2931, 2908, 2866, 2835, 1661, 1615, 1509, 1454, 1244, 1192, 1068, 1028, 827, 737, 697; HRMS calcd $[C_{35}H_{35}NO_6Na]^+$ 588.2362, found 588.2350.

*(2R,3S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-N-(4-fluorophenyl)-3,4-dihydro-2H-pyran-5-carboxamide (**2h**):* Yellowish oil, 26.0 mg, 51%; eluent, EtOAc/cyclohexane 1:9 and washing with HCl 10%; $[\alpha]_D^{20}$ = +40.1 (*c* = 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.20 (s, 1H), 7.69 (s, 1H), 7.38−7.25 (m, 15H), 7.08−7.04 (m, 2H), 6.91−6.86 (m, 2H), 4.74−4.58 (m, 6H), 4.51−4.50 (m, 1H), 4.45−4.42 (m, 2H), 4.20−4.17 (m, 1H), 3.85 (dd, *J* = 10.6 and 5.4 Hz, 1H), 3.78 (dd, *J* = 10.5 and 4.7 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 164.8, 159.1 (d, *J* = 242.4 Hz), 155.0, 137.6, 137.4, 136.9, 134.1, 129.1, 128.8, 128.6, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 121.8, 121.7, 115.5, 115.3, 107.3, 76.8, 73.7, 73.1, 72.7, 70.5, 70.1, 67.4; ^{19}F-NMR (376.2 MHz, $CDCl_3$) δ [ppm] = −122.0-(−122.1) (m, 1F); IR (ν, cm^{-1}) 3323, 3064, 3031, 2923, 2866, 1665,

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1615, 1538, 1508, 1454, 1193, 1071, 832, 737, 698; HRMS calcd $[C_{34}H_{32}NO_5FNa]^+$ 576.2162, found 576.2172.

(2R,3S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-N-(2-methoxyphenyl)-3,4-dihydro-2H-pyran-5-carboxamide (**2i**): Yellowish oil, 19.0 mg, 36%; eluent, EtOAc/cyclohexane 1:9; $[\alpha]_D^{20}$ = +13.7 (*c* = 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 8,74 (s, 1H), 8.42 (d, *J* = 7.7 Hz, 1H), 7.67 (s, 1H), 7.35−7.21 (m, 15H), 7.02−6.93 (m, 2H), 6.79 (d, *J* = 7.7 Hz, 1H), 4.71−4.60 (m, 4H), 4.52−4.41 (m, 4H), 4.07−4.06 (m, 1H), 3.80 (dd, *J* = 10.3 and 6.3 Hz, 1H), 3.66 (dd, *J* = 10.3 and 4.9 Hz, 1H), 3.46 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 165.0, 153.7, 148.1, 137.7, 137.6, 137.5, 128.7, 128.5, 128.2, 128.2, 128.1, 127.9, 127.8, 127.1, 123.4, 121.1, 120.2, 109.8, 108.1, 76.5, 73.6, 72.2, 71.7, 70.5, 70.1, 67.5, 55.3; IR (ν, cm^{-1}) 3351, 3063, 3030, 2930, 2866, 1677, 1619, 1602, 1525, 1459, 1289, 1194, 1121, 1070, 1048, 1028, 745, 697; HRMS calcd $[C_{35}H_{35}NO_6Na]^+$ 588.2362, found 588.2361.

(2R,3S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-N-tosyl-3,4-dihydro-2H-pyran-5-carboxamide (**2j**): Colorless oil, 38.0 mg, 67%; eluent, EtOAc/cyclohexane 2:8 then 3:7 and precipitation of the residual *para*-toluenesulfonamide with cold toluene several times; $[\alpha]_D^{20}$ = +4.7 (*c* = 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.83−7.81 (m, 2H), 7.55 (s, 1H), 7.39−7.24 (m, 17H), 4.65 (s, 2H), 4.56−4.45 (m, 5H), 4.32−4.31 (m, 1H), 4.09 (t, *J* = 4.3 Hz, 1H), 3.73 (dd, *J* = 10.4 and 5.7 Hz, 1H), 3.65 (dd, *J* = 10.5 and 5.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 163.9, 156.9, 144.8, 137.5, 137.1, 136.2, 136.0, 129.8, 129.5, 129.1, 128.8, 128.6, 128.6, 128.4, 128.1, 127.9, 126.6, 105.8, 77.1, 73.6, 72.4, 71.0, 70.6, 70.0, 67.1, 21.8; IR (ν, cm^{-1}) 3254, 3064, 3031, 2954, 2923, 2866, 1684, 1623, 1496, 1453, 1340, 1293, 1198, 1164, 1090, 1054, 1028, 877, 813, 737, 697, 660; HRMS calcd $[C_{35}H_{35}NO_7SNa]^+$ 636.2032, found 636.2061.

(2R,3S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-N-octadecyl-3,4-dihydro-2H-pyran-5-carboxamide (**2k**): White solid, 36.0 mg, 55%; eluent, EtOAc/cyclohexane 1:9 then 2:8; mp 73−77 °C; $[\alpha]_D^{20}$ = +32.4 (*c* = 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.57 (s, 1H), 7.36−7.22 (m, 15H), 6.08 (t, *J* = 5.4 Hz, 1H), 4.69 (s, 2H), 4.56−4.53 (m, 3H), 4.43−4.36 (m, 3H), 4.10−4.08 (m, 1H), 3.81 (dd, *J* = 10.5 and 5.7 Hz, 1H), 3.73 (dd, *J* = 10.5 and 4.7 Hz, 1H), 3.14−3.09 (m, 2H), 1.26−1.20 (m, 32H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 166.5, 153.5, 137.8, 137.6, 137.2, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.9, 107.4, 76.6, 73.6, 72.4, 72.1, 70.5, 69.5, 67.6, 39.5, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 27.1, 22.8, 14.3; IR (ν, cm^{-1}) 3284, 2926, 2850, 1653, 1620, 1540, 1454, 1179, 1110, 1088, 1077, 1028, 748, 696; HRMS calcd $[C_{46}H_{65}NO_5Na]^+$ 734.4760, found 734.4775.

Methyl ((2R,3S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-carbonyl)glycinate (**2l**): Four equivalents of K_2CO_3 (42 mg) was used since the glycine methyl ester was used in this hydrochloride form; colorless oil, 29.0 mg, 60%; eluent, EtOAc/cyclohexane 2:8 then 3:7; $[\alpha]_D^{20}$ = +13.5 (*c* = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.58 (s, 1H), 7.37−7.25 (m, 15H), 6.55 (t, *J* = 5.1 Hz, 1H), 4.66 (s, 2H), 4.57−4.44 (m, 5H), 4.37−4.36 (m, 1H), 4.06−4.04 (m, 1H), 3.96 (d, *J* = 5.3 Hz, 2H), 3.78 (dd, *J* = 10.6 and 6.1 Hz, 1H), 3.72 (s, 3H), 3.68 (dd, *J* = 10.5 and 4.8 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 170.6, 167.0, 153.8, 137.8, 137.5, 137.2, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 107.0, 76.6, 73.6, 72.3, 71.4, 70.5, 70.1, 67.6, 52.4, 41.2; IR (ν, cm^{-1}) 3385, 3064, 3031, 2951, 2868, 1748, 1661, 1616, 1526, 1454, 1367, 1196, 1161, 1091, 1071, 1028, 739, 699; HRMS calcd $[C_{31}H_{33}NO_7Na]^+$ 554.2155, found 554.2150.

tert-Butyl ((2R,3S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-carbonyl)-L-phenylalaninate (**2m**): Four equivalents of K_2CO_3 (42 mg) was used since the phenylalanine *tert*-butyl ester was used in this hydrochloride form; colorless oil as a mixture of two diastereoisomers (30% of epimerization on the phenylalanine part), 20.0 mg, 33%; eluent, EtOAc/cyclohexane 2:8; data correspond to the major isomer; $[\alpha]_D^{20}$ = +18.5 (*c* = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.46 (s, 1H), 7.34−7.07 (m, 20H), 6.65 (d, *J* = 7.6 Hz, 1H), 4.82−4.77 (m, 1H), 4.65−4.57 (m, 2H), 4.53−4.39 (m, 6H), 3.97−3.95 (m, 1H), 3.76 (dd, *J* = 10.6 and 6.5 Hz, 1H), 3.64−3.61 (m, 1H), 3.01 (d, *J* = 6.0 Hz, 2H), 1.38 (s, 9H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 170.9, 166.3, 152.6, 137.8, 137.6, 137.6, 137.5, 129.6, 128.7, 128.6, 128.3, 128.1, 128.0, 128.0, 127.9, 126.9, 107.8, 82.2, 76.7, 73.5, 72.1, 71.3, 70.9, 70.7, 67.6, 53.7, 38.2, 28.1; IR (ν, cm^{-1}) 3367, 3063, 3030, 2977, 2930, 2866, 1727, 1661, 1606, 1516, 1497, 1454, 1367, 1193, 1151, 1069, 1028, 737, 697; HRMS calcd $[C_{41}H_{45}NO_7Na]^+$ 686.3094, found 686.3117.

(S)-tert-Butyl 2-((2R,3S,4S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-carboxamido)-3-methylbutanoate (**2n**): Four equivalents of K_2CO_3 (42 mg) was used since the valine *tert*-butyl ester was used in this hydrochloride form; colorless oil, 29 mg, 53%, with a partial epimerization of the α proton of the valine (20% by ^{1}H NMR); eluent, EtOAc/cyclohexane 3:7; $[\alpha]_D^{20}$ +21.8 (*c* = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.52 (s, 1H), 7.36−7.25 (m, 15H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.64 (d, *J* = 7.3 Hz, 2H), 4.59 (d, *J* = 5.5 Hz, 2H), 4.55−4.51 (m, 1H), 4.50 (d, *J* = 4.6 Hz, 2H), 4.49−4.45 (m, 2H), 4.03 (t, *J* = 7.3 Hz, 1H), 3.78 (dd, *J* = 10.5 and 6.4 Hz, 1H), 3.67 (dd, *J* = 10.5 and 4.6 Hz, 1H), 2.15−2.04 (m, 1H), 1.47 (s, 9H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 166.6, 161.8, 148.0, 133.0, 132.7, 132.6, 123.8, 123.7, 123.6, 123.4, 123.3, 123.2, 123.1, 123.0, 102.9, 77.0, 71.7, 68.7, 67.3, 67.0, 65.9, 65.8, 62.7, 52.5, 26.9, 23.4, 14.1, 13.0; IR (ν, cm^{-1}) 3392, 2966, 2871, 1727, 1670, 1617, 1497, 1368, 1193, 1151, 1090, 737, 668; HRMS calcd $[C_{37}H_{46}NO_7]^+$ 616.3274, found 616.3293.

(2R,3S)-2-(Acetoxymethyl)-5-(benzylcarbamoyl)-3,4-dihydro-2H-pyran-3,4-diyl Diacetate (**4a**): Colorless oil, 36.0 mg, 70%; eluent, EtOAc/cyclohexane 3:7 then 4:6; $[\alpha]_D^{20}$ = −5.5 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.70 (s, 1H), 7.33−7.23 (m, 5H), 6.66−6.65 (m, 1H), 5.63−5.62 (m, 1H), 5.12−5.11 (m, 1H), 4.54−4.49 (m, 2H), 4.41−4.33 (m, 2H), 4.24−4.20 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 171.1, 170.5, 169.6, 164.6, 154.5, 138.3, 128.8, 127.9, 127.6, 127.5, 105.5, 74.3, 66.3, 62.4, 61.2, 43.7, 20.9; IR (ν, cm^{-1}) 3335, 3064, 3030, 2926, 2855, 1740, 1653, 1540, 1368, 1219, 1184, 1146, 1049, 1026, 913, 700; HRMS calcd $[C_{20}H_{23}NO_8Na]^+$ 428.1321, found 428.1322.

(2R,3S)-2-(Acetoxymethyl)-5-(octadecylcarbamoyl)-3,4-dihydro-2H-pyran-3,4-diyl Diacetate (**4b**): White solid, 44.0 mg, 62%; eluent, EtOAc/cyclohexane 2:8 then 3:7; mp 66−68 °C; $[\alpha]_D^{20}$ = −6.9 (*c* = 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.71 (s, 1H), 6.34−6.31 (m, 1H), 5.62−5.61 (m, 1H), 5.11 (t, *J* = 2.7 Hz, 1H), 4.56−4.53 (m, 1H), 4.39 (dd, *J* = 12.1 and 7.9 Hz, 1H), 4.25 (dd, *J* = 12.1 and 4.5 Hz, 1H), 3.36−3.29 (m, 1H), 3.24−3.18 (m, 1H), 2.11 (s, 6H), 2.10 (s, 3H), 1.28−1.25 (m, 32H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 171.2, 170.5, 169.6, 164.6, 154.3, 105.4, 74.2, 66.4, 62.3, 61.3, 39.9, 32.1, 29.8, 29.7, 29.5, 29.4, 27.1, 22.8, 21.1, 21.0, 20.9, 14.3; IR (ν, cm^{-1}) 3335, 2917, 2850, 1744, 1718, 1653, 1540, 1369, 1224, 1190, 1150, 1048, 1026; HRMS calcd $[C_{31}H_{53}NO_8Na]^+$ 590.3669, found 590.3667.

(2R,3R,4S)-N-Benzyl-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-carboxamide (**6a**): White solid, 38 mg, 75%; eluent, EtOAc/cyclohexane 2:8 then 3:7; mp 125−127 °C; $[\alpha]_D^{20}$ +29.0 (*c* = 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.32 (s, 1H), 7.33−7.00 (m, 20H), 6.52 (br s, 1H), 4.76 (d, *J* = 11 Hz, 1H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H) 4.43−4.34 (m, 4H), 4.32 (dd, *J* = 14.6 and 5.5 Hz, 1H), 4.19 (dd, *J* = 14.6 and 5.5 Hz, 1H), 3.97 (t, *J* = 3.7 Hz, 1H), 3.82 (dd, *J* = 11.0 and 7.8 Hz, 1H), 3.75 (dd, *J* = 11.0 and 4.1 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 166.8, 152.4, 138.6, 137.9, 137.6, 137.2, 128.8, 128.7, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.4, 108.4, 76.4, 73.6, 73.3, 73.2, 72.5, 70.5, 67.6, 43.5; IR (ν, cm^{-1}) 3303, 3029, 2919, 1655, 1617, 1541, 1212, 1137, 1058, 733, 695; HRMS calcd $[C_{35}H_{36}NO_5]^+$ 550.2593, found 550.2616.

Methyl ((2R,3R)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-carbonyl)glycinate (**6b**): Four equivalents of K_2CO_3 (42 mg) was used since the glycine methyl ester was used in this hydrochloride form; white solid, 35.0 mg, 71%; eluent, EtOAc/cyclohexane 3:7; mp 98−100 °C; $[\alpha]_D^{20}$ = +22.0 (*c* = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39 (s, 1H), 7.34−7.26 (m,

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15H), 6.70−6.66 (m, 1H), 4.91 (d, J = 11.2 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.71−4.65 (m, 2H), 4.57 (d, J = 11.8 Hz, 1H), 4.51−4.45 (m, 3H), 4.07−4.01 (m, 2H), 3.93−3.82 (m, 3H), 3.72 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 170.5, 167.0, 152.8, 137.9, 137.7, 137.6, 128.7, 128.6, 128.6, 128.3, 128.2, 128.1, 128.1, 127.9, 127.9, 108.1, 76.5, 73.6, 73.3, 73.1, 72.7, 70.1, 67.6, 52.3, 41.3; IR (ν, cm^{-1}) 3362, 3063, 3030, 2950, 2925, 2866, 1748, 1653, 1603, 1522, 1454, 1203, 1159, 1090, 1027, 736, 697; HRMS calcd $[C_{31}H_{33}NO_7Na]^+$ 554.2155, found 554.2162.

*(4aR,8aS)-7-(Benzylcarbamoyl)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl Pivalate (**8a**):* **7** was synthesized following the described procedure:[9e] tri-*O*-benzyl-3,4,6-D-glucal (555 mg, 2 mmol) was dissolved in dry acetonitrile (18 mL), and the resulting mixture was heated to 80 °C. At this temperature, *N*-iodosuccinimide (542 mg, 2.4 mmol, 1.2 equiv) and silver nitrate (80 mg, 0.4 mmol, 20 mol %) were added. The resulting mixture was stirred at 80 °C for 4 h. The mixture was filtrated on Celite and concentrated. The obtained crude was purified on silica gel (eluent, EtOAc/cyclohexane 0:100 then 10:90) and furnished the corresponding compound **7** as a colorless solid (215 mg, 0.54 mmol, 27%), which was directly engaged in the next step: $[\alpha]_D^{20}$ = +73.3 (c = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.69 (s, 1H), 5.62 (d, J = 7.4 Hz, 1H), 4.06−3.92 (m, 3H), 3.83−3.77 (m, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 177.4, 149.4, 100.0, 70.5, 70.3, 70.2, 69.8, 61.5, 39.2, 28.9, 27.3, 19.1; IR (ν, cm^{-1}) 2975, 2904, 3030, 2875, 1739, 1616, 1603, 1270, 1202, 1171, 1162, 1148, 1132, 1087, 887. **8a** was synthesized following the general procedure: White solid, 33 mg, 65%; eluent, EtOAc/cyclohexane 2:8 then 3:7; mp 158−162 °C; $[\alpha]_D^{20}$ = +37.8 (c = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.49 (s, 1H), 7.33−7.10 (m, 5H), 6.43 (t, J = 4.6 Hz, 1H), 5.71 (d, J = 7.4 Hz, 1H), 4.46 (dd, J = 14.7 and 6.4 Hz, 1H), 4.25 (dd, J = 14.7 and 5.5 Hz, 1H), 4.03−3.90 (m, 2H)), 3.85−3.70 (m, 2H), 1.39 (s, 3H), 1.29 (s, 3H), 0.95 (s, 9H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 180.3, 163.9, 155.0, 138.3, 128.7, 128.1, 127.5, 109.3, 100.0, 70.5, 67.7, 61.4, 43.5, 39.0, 28.8, 27.0, 26.7, 18.9. IR (ν, cm^{-1}) 3314, 2957, 1737, 1647, 1537, 1496, 1480, 1325, 1217, 1189, 1171, 10841, 885, 753, 697; HRMS calcd $[C_{22}H_{30}NO_6]^+$ 404.2073, found 404.2068.

*(4aR,8aS)-7-((2-Methoxy-2-oxoethyl)carbamoyl)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl Pivalate (**8b**):* **7** was synthesized following the described procedure:[9e] tri-*O*-benzyl-3,4,6-D-glucal (555 mg, 2 mmol) was dissolved in dry acetonitrile (18 mL) and the resulting mixture was heated to 80 °C. At this temperature, *N*-iodosuccinimide (542 mg, 2.4 mmol, 1.2 equiv) and silver nitrate (80 mg, 0.4 mmol, 20 mol %) were added. The resulting mixture was stirred at 80 °C for 4 h. The mixture was filtrated on Celite and concentrated. The obtained crude was purified on silica gel (eluent, EtOAc/cyclohexane 0:100 then 10:90) and furnished the corresponding compound **7** as a colorless solid (215 mg, 0.54 mmol, 27%) which was directly engaged in the next step: $[\alpha]_D^{20}$ = +73.3 (c = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.69 (s, 1H), 5.62 (d, J = 7.4 Hz, 1H), 4.06−3.92 (m, 3H), 3.83−3.77 (m, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 177.4, 149.4, 100.0, 70.5, 70.3, 70.2, 69.8, 61.5, 39.2, 28.9, 27.3, 19.1; IR (ν, cm^{-1}) 2975, 2904, 3030, 2875, 1739, 1616, 1603, 1270, 1202, 1171, 1162, 1148, 1132, 1087, 887. **8b** was synthesized following the general procedure: 4 equiv of K_2CO_3 (42 mg) was used since the glycine methyl ester was used in this hydrochloride form: White solid, 22.0 mg, 45%; eluent, EtOAc/cyclohexane 2:8; mp 77−79 °C; $[\alpha]_D^{20}$ = +29.8 (c = 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.52 (s, 1H), 6.52 (t, J = 5.0 Hz, 1H), 5.85 (d, J = 7.3 Hz, 1H), 4.07−3.99 (m, 4H), 3.90−3.85 (m, 2H), 3.72 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 180.4, 170.0, 164.5, 155.4, 108.9, 100.1, 70.6, 67.5, 61.4, 52.4, 41.2, 39.3, 28.9, 26.9, 19.0; IR (ν, cm^{-1}) 3357, 2957, 2940, 2908, 2875, 1739, 1652, 1532, 1370, 1202, 1186, 1169, 1137, 1087, 847; HRMS calcd $[C_{18}H_{27}NO_8Na]^+$ 408.1634, found 408.1654.

Deprotection Steps. General Procedure A: The glycal starting material (1 equiv) was dissolved in EtOH. $PdCl_2$ (20 mol %) was added. The vial was placed in an autoclave, and the atmosphere was replaced by dihydrogen. The resulting mixture was stirred at room temperature under 8 bar of H_2 for the corresponding time and then filtered on Celite and concentrated.

General Procedure B: The glycal starting material (1 equiv) was dissolved in MeOH. K_2CO_3 was added. The resulting mixture was stirred at the corresponding temperature for the corresponding time. DOWEX 50WX8 was added, and the resulting mixture was stirred at room temperature for the corresponding time and then filtered and concentrated.

*(2R,3S,4S)-3,4-Dihydroxy-2-(hydroxymethyl)-N-octadecyl-3,4-dihydro-2H-pyran-5-carboxamide (**9a**).* General procedure A: **2k** (40 mg, 0.056 mmol), $PdCl_2$ (2.0 mg, 0.011 mmol, 20 mol %), and EtOH (2.0 mL). The resulting mixture was stirred at room temperature under 8 bar of H_2 for 24 h. **9a** was obtained as a white solid (10.5 mg, 43%) after being washed with dichloromethane. General procedure B: **4b** (105 mg, 0.185 mmol), K_2CO_3 (26 mg, 0.037 mmol, 20 mol %), and MeOH (3.0 mL). The resulting mixture was stirred at room temperature overnight. DOWEX 50WX8 was added, and the resulting mixture was stirred at room temperature for 1 h and then filtered and concentrated. **9a** was obtained as a white solid (64.0 mg, 78%): mp 156−159 °C; $[\alpha]_D^{20}$ +50.0 (c = 0.70, C_5H_5N); ^{1}H NMR (400 MHz, C_5D_5N) δ [ppm] = 8.47−8.45 (m, 1H), 8.11 (s, 1H), 5.13 (d, J = 6.2 Hz, 1H), 4.68−4.65 (m, 1H), 4.49−4.46 (m, 3H), 3.59−3.51 (m, 2H), 1.60−1.56 (m, 2H), 1.28−1.19 (m, 32H), 0.88−0.85 (m, 3H); ^{13}C NMR (100.5 MHz, C_5D_5N) δ [ppm] = 168.1, 153.0, 112.2, 82.6, 70.4, 70.0, 61.9, 40.0, 32.6, 30.8, 30.5, 30.4, 30.1, 27.9, 23.4, 14.8; IR (ν, cm^{-1}) 3328, 2916, 2850, 1652, 1589, 1550, 1467, 1192, 1150, 1033, 721; HRMS calcd $[C_{25}H_{48}NO_5]^+$ 442.3532, found 442.3530.

*(2R,3S)-N-Benzyl-3,4-dihydroxy-2-(hydroxymethyl)-3,4-dihydro-2H-pyran-5-carboxamide (**9b**):* General procedure A: **2a** (35 mg, 0.064 mmol), $PdCl_2$ (2.3 mg, 0.013 mmol, 20 mol %), and EtOH (2.0 mL). The resulting mixture was stirred at room temperature under 8 bar of H_2 for 24 h. **9b** was obtained as a white solid (16 mg, 89%) after being washed with dichloromethane. General procedure B: **8a** (24 mg, 0.059 mmol) and K_2CO_3 (6 mg, 0.059 mmol, 1 equiv) in MeOH (1 mL) were stirred overnight at 40 °C. The reaction was allowed to come at rt, and DOWEX 50WX8 was added. The mixture was stirred for an additional 2 h and filtered, and the solvent was removed under vacuum. **9b** was obtained as an amorphous solid (10 mg, 65%) after purification by silica gel (DCM/MeOH 95:5): $[\alpha]_D^{20}$ +42.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.42 (s, 1H), 7.18−7.30 (m, 5H), 4.48 (d, J = 14.6, 1H), 4.42 (d, J = 14.6, 1H), 4.32 (d, J = 5.5, 1H), 3.93−3.98 (m, 1H), 3.83 (d, J = 4.1, 2H), 3.75 (dd, J = 7.8 and 6.0, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 169.6, 153.8, 140.2, 129.6, 128.5, 128.1, 110.9, 81.8, 70.0, 68.4, 61.7, 49.2, 43.9. IR (ν, cm^{-1}) 3317, 2928, 1651, 1594, 1543, 1454, 1189, 1146, 1028, 730, 698; HRMS calcd $[C_{14}H_{18}NO_5]^+$ 280.1185, found 280.1183.

*(2R,3S,4S)-3,4-Dihydroxy-2-(hydroxymethyl)-N-(4-methoxyphenyl)-3,4-dihydro-2H-pyran-5-carboxamide (**9c**):* **9c** was synthesized following the general procedure A: **2g** (26 mg, 0.046 mmol), $PdCl_2$ (1.8 mg, 0.0092 mmol, 20 mol %), and EtOH (2.0 mL). The resulting mixture was stirred at room temperature under 8 bar of H_2 for 48 h. **9c** was obtained as a white solid (14.0 mg, 100%) after purification by silica gel (DCM/MeOH 95:5 then 90:10): mp 137−140 °C; $[\alpha]_D^{20}$ +24.1 (c = 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.48 (s, 1H), 7.40 (d, J = 9.2 Hz, 2H), 6.82−6.90 (m, 2H), 4.42 (d, J = 6.0, 1H), 3.95−4.01 (m, 1H), 3.90−3.79 (m, 2H), 3.75 (s, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ [ppm] = 166.2, 156.6, 152.7, 131.0, 122.0, 113.7, 109.5, 80.5, 68.5, 67.2, 60.3, 54.6. IR (ν, cm^{-1}) 3317, 2929, 2848, 1652, 1603, 1511, 1414, 1244, 1190, 1105, 1051, 1033, 830; HRMS calcd $[C_{14}H_{18}NO_6]^+$ 296.1134, found 296.1126.

*Methyl ((2R,3R,4S)-3,4-Dihydroxy-2-(hydroxymethyl)-3,4-dihydro-2H-pyran-5-carbonyl)glycinate (**9d**):* **9d** was synthesized following the general procedure A: **6b** (31 mg, 0.058 mmol), $PdCl_2$ (2.1 mg, 0.012 mmol, 20 mol %), and MeOH (2.0 mL). The resulting mixture was stirred at room temperature under 8 bar of H_2 for 24 h. **9d** was obtained as a white solid (11.0 mg, 72%) after purification by silica gel (DCM/MeOH 9:1): $[\alpha]_D^{20}$ +78.0 (c = 0.60, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ [ppm] = 7.44 (s, 1H), 4.65 (s, 1H), 4.60 (d, J = 4.3 Hz, 1H), 4.09−4.04 (m, 1H), 4.04 (s, 2H), 3.99 (dd, J = 4.4 and 1.8

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Hz, 1H), 3.89 (dd, J = 11.8 and 6.9 Hz, 1H), 3.83−3.78 (m, 1H), 3.74 (s, 3H); ^{13}C NMR (100.5 MHz, CD_3OD) δ [ppm] = 172.2, 170.2, 154.9, 109.9, 80.4, 66.3, 65.0, 61.8, 52.7, 41.9; IR (ν, cm^{-1}) 3341, 2951, 2918, 2850, 1740, 1651, 1592, 1541, 1439, 1408, 1374, 1204, 1165, 1057, 1033, 1020, 691; HRMS calcd $[C_{10}H_{16}NO_7]^+$ 262.0927, found 262.0914.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02278.

^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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