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Practical stereoselective synthesis of α-D-*C*-mannosyl-(*R*)-alanine

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Abstract—α-D-*C*-Mannosyl-(*R*)-alanine **2** was synthesized in only four steps starting from the known acetonide protected D-*ribo*-hex-1-enitol **4** and *N*-benzoylalanine. The key C–C bond formation between the sugar and the amino acid moieties was effected through a Claisen rearrangement of the intermediate oxazole **7**, derived from the ester **6**.

C-Glycoside derivatives[1] have been the subject of intensive research effort in recent years due to their chemical stability, protection against glycosidases, and favorable conformational properties that allow the use of such compounds as mimics of more common, naturally occurring *N*- and *O*-glycoconjugates. Recent studies have demonstrated that C-linked glycoconjugates bind biological targets with nearly identical conformation and affinities as natural O-linked glycoconjugates, in spite of a seemingly dramatic difference in chemical structure.[2]

Within this general class of compounds, *C*-glycosyl α-amino acids[3] have emerged as an important class of building blocks for the construction of *C*-glycosylated peptides.[4] The interest in this class of glycopeptide mimetics stems not only from enhanced resistance to enzymatic hydrolysis[5] but also from potential superior properties for specific therapeutic or biological applications. It has been reported, for example, that C-linked carbohydrates exert conformational restrictions on a peptide backbone and this effect was ascribed to unfavorable steric interactions and limitations of the conformational space of the glycosyl side chain.[6] Well defined conformational constraints could also be imparted to a peptide chain by the insertion of quaternary α-amino acids.[7] We reasoned that a combined effect could be derived by attaching a sugar moiety to the α-carbon of a monosubstituted α-amino acid.

Only a few examples of *C*-pyranosyl α-amino acids of the general structure **1** (Fig. 1) have been reported.[8–12] All of them are β-*C*-glycosyl derivatives and only in two cases, reported by one of us,[12] a quaternary carbon atom is adjacent to the sugar anomeric center. The synthetic strategy applied to the preparation of **1** (R=Me) relied on the Steglich variant of the Claisen transposition.[13] Rearrangement reactions have found a limited application in the synthesis of *C*-glycosides,[14] in spite of the fact that the intramolecular and concerted character of such reactions should entail a stereoselective formation of the *C*-glycosidic bond. In this paper we report that the Steglich rearrangement can be applied to a practical and stereoselective synthesis of α-D-*C*-mannosyl-(*R*)-alanine **2**. The use of *N*-benzoylalanine in racemic form, the conciseness of the synthetic sequence, and the need, in all steps, of rather inexpensive shelf-reagents contribute to the practical value of the method. Moreover, an appreciable amount of the (*S*)-diastereomer **3** could also be obtained (Fig. 1).

The synthesis started from the known acetonide protected D-*ribo*-hex-1-enitol **5**,[15] prepared in four steps from commercially available tri-*O*-acetyl-D-glucal **4**. Esterification with racemic *N*-benzoylalanine to give the esters **6** turned out to be an unexpectedly difficult operation. Using the experimental conditions that were shown to be effective for the same transformation on the epimeric 3-β-OH compound,[12] the desired ester **6** was obtained in very low yields, the rearranged *N*-acylurea being the major product. Other methods for the activation of the carboxyl function

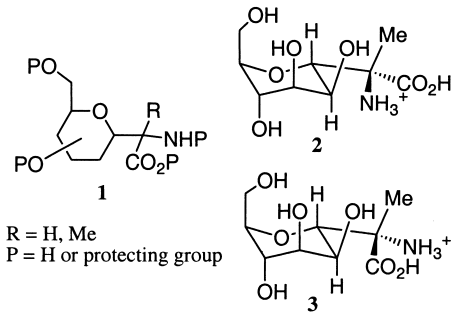

Figure 1.

Keywords: *C*-glycosyl α-amino acids; quaternary α-amino acids; Claisen rearrangement.

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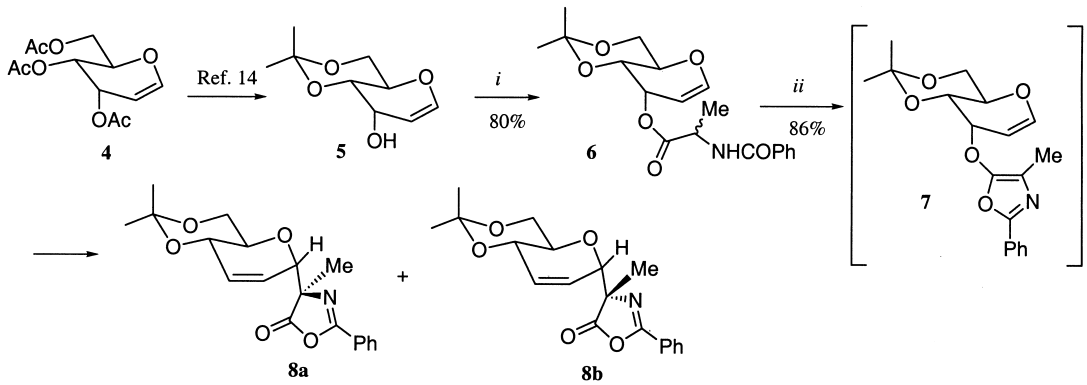
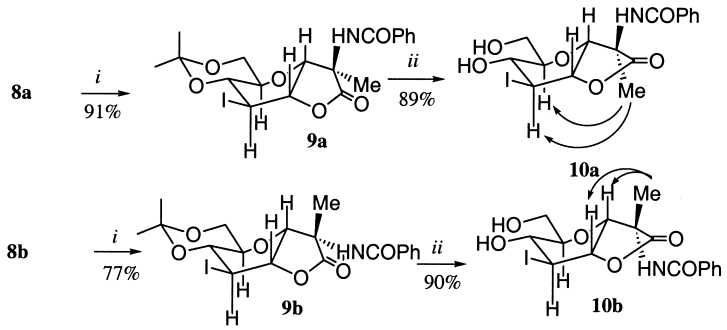


Scheme 1. *Reagents and conditions*: (i) *N*-Benzoylalanine, DCC, DMAP, DMAP–HCl, $CHCl_3$, reflux, 9 h; (ii) PPh_3, CCl_4, Et_3N, rt, 12 h.



Scheme 2. *Reagents and conditions*: (i) (1) 1 M NaOH, THF/H_2O, rt, 30 min; (2) I_2, rt, 48 h; (ii) 5 M HCl, THF, rt, 3 h. (Arrows indicate nOe correlations).

proved equally ineffective, producing 2-phenyl-4-benzyl-5(4*H*)-oxazolone as a major product.[16] After extensive experimentation we returned to the DCC activation protocol, modified by the addition of a mixture of a stoichiometric amount of DMAP and a two-fold excess of its hydrochloride salt.[17] Application of the above conditions allowed the preparation of the diastereomeric mixture of esters **6** in an acceptable 80% yield. (Scheme1).

Treatment of the esters **6** with PPh_3, CCl_4, and Et_3N at room temperature directly provided a 2.6:1 mixture of two diastereomeric oxazolones **8a** and **8b**, deriving from the Claisen rearrangement of the intermediate oxazole **7**, which could not be detected neither by TLC nor by any standard spectroscopic means. The intramolecular, concerted nature of the rearrangement reaction should lead to the stereoselective formation of α-*C*-glycosyl derivatives, epimeric at the oxazolone stereocenter. This stereochemical result was easily demonstrated by comparing the physical and spectroscopic properties of **8a** and **8b** with those of the epimeric β-*C*-glycosyl analogous compounds previously synthesized by us following a similar procedure.[12] Furthermore, nOe experiments carried out on advanced intermediates confirmed the above results (see below).

Configurational assignment of the oxazolone stereocenter required conversion of **8a** and **8b** into conformationally constrained compounnds in order to correlate, by nOe difference experiments, the spatial arrangement of the oxazolone methyl substituent with some proton of defined stereochemistry in the sugar moiety. To this end **8a** and **8b** were easily separated by flash chromathography (ΔR_f=0.13, 4:1 hexane–EtOAc) and individually converted into iodolactones **9a** and **9b** by NaOH hydrolysis of the oxazolone nucleus to *N*-benzoyl α-amino acid carboxylates, followed by one pot treatment with iodine. The acetonide protecting group was then removed in order to make an unequivocal assignment of the NMR signal corresponding to the oxazolone methyl group. (Scheme 2)

Irradiation of the methyl signal of the major diastereoisomer **10a** caused an intensity enhancement of peaks corresponding to H3′ (2.3%) and H5′ (4.8%), thus establishing the configuration of the iodolactone stereocenter as (*R*). This result was confirmed by performing the same experiment on the minor stereoisomer **10b**, where the methyl signal presented nOe correlations with resonances attributed to H2′ and H1′.

It is interesting to note that an (*R*) configured stereocenter would be formed if the Claisen rearrangement were to proceed via a boat-like transition state. One can only speculate on the factors disfavoring the usually more stable chair-like transition state. Inspection of molecular models suggests a steric interaction between H5′ and the oxazolone

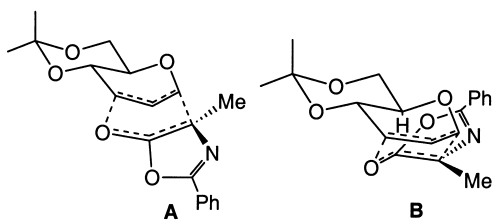
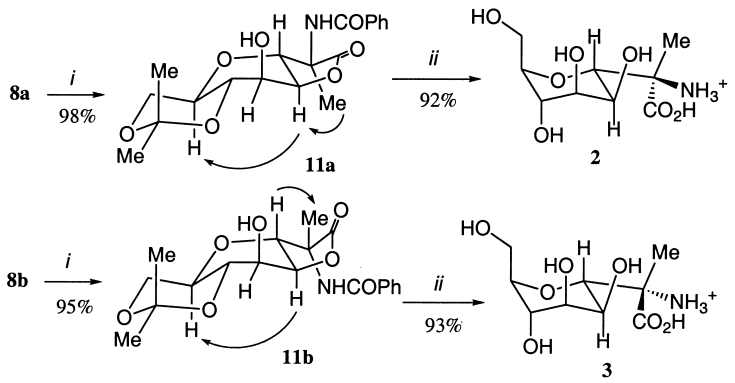


Figure 2. Boat-like **A** and chair-like **B** transition states leading to **8a** and **8b**, respectively.



Scheme 3. *Reagents and conditions*: (i) OsO_4, NMO, Me_2CO–H_2O, rt, 24 h; (ii) 6N, HCl, 80°C, 4 h. (Arrows indicate nOe correlations).

nucleus projecting toward the bottom face of the sugar moiety as a likely factor destabilizing the chair-like transition state. (Fig. 2)

Dihydroxylation of **8a** by treatment with catalytic OsO_4 under standard conditions furnished directly, as a single isomer, the mannosyl lactone **11a**, plausibly arising from intramolecular attack of the C2′-OH group of the intermediate diol on the carbonyl carbon of the oxazolone. The formation of a γ-lactone was evidenced by the presence of only one OH resonance and a low field chemical shift of the C2′-H in the proton NMR spectrum as well as by a strong IR absorbance at 1771 cm^{-1}. The stereochemical outcome of the dihydroxylation reaction was easily proven by NMR data. A 10.2 Hz coupling constant correlating H1′ an H2′ is diagnostic of a *trans* relationship between these two protons. Moreover, an nOe correlation between H2′ and H5′ corroborated the assigned stereochemistry. (Scheme 3).

Final treatment of the lactone **11a** with 6N HCl at 80°C brought about three discrete hydrolysis reactions involving the acetonide, the lactone, and the benzamide functions affording in excellent yield and purity α-*C*-mannosyl-(*R*)-alanine **2**. Repetition of the two-step sequence on the minor oxazolone **8b** proceeded uneventfully to give the epimeric mannosylated amino acid **3** in comparable yields.

In summary, we have developed a concise, practical, and high-yielding synthesis of α-D-*C*-mannosyl-(*R*)- and (*S*)-alanine. The above mannosylated compounds will be exploited as fucose mimics in glycoconjugated compounds in which an appropriate scaffold is attached to the carboxyl function of the amino acid unit. Such constructs, characterized by a properly positioned carboxylic function that should play the role of the carboxylate present in the sialic acid, will be tested as sialyl Lewis X mimics in binding assays with selectins.[18]

1. Experimental

1.1. General

THF was distilled from sodium/benzophenone ketyl and MeCN from P_2O_5 under nitrogen. TLC was performed on Kieselgel 60 F_{254} (Merck) glass plates with detection by UV light, iodine, and a solution of $(NH_4)_4MoO_4$ and Ce_2SO_4 in dilute H_2SO_4. Flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Melting points were determined on a Kofler apparatus and are uncorrected. Optical rotations were measured at room temperature with a Perkin–Elmer 343 polarimeter. The ^1H (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded with Bruker Avance 300 and 400 instruments respectively. In the peak listing of ^{13}C spectra abbreviations s, d, t, and q refer to zero, one, two, and three protons attached to the carbons, as determined by DEPT experiments. Infrared spectra were recorded on a Perkin–Elmer FTIR 1600 series spectometer. Mass spectra were recorded on a Finnigan LCQ-DECA mass spectrometer. Elemental analyses were performed on a Carlo Erba Elemental Analyzer Mod. 1106.

1.1.1. 1,5-Anhydro-4,6-*O*-isopropylidene-2-deoxy-3-*O*-(2-benzamidopropionyl)-D-*ribo*-hex-1-enitol (6). To a solution of the protected glycal **5** (2.224 g, 11.94 mmol) in ethanol free $CHCl_3$ (40 mL) were added sequentially DMAP (1.459 g, 11.94 mmol), DMAP hydrochloride (3.788 g, 23.88 mmol), DCC (4.927 g, 23.88 mmol), and racemic *N*-benzoylalanine (2.307 g, 11.94 mmol) under a nitrogen atmosphere. After refluxing for 3 h, one additional equivalent of *N*-benzoylalanine was added followed by a 3 h reflux period. After that time one more equivalent of both DCC and *N*-benzoylalanine were added and the mixture refluxed for 3 h. The reaction mixture was diluted with EtOAc, filtered and evaporated. The resulting oily residue was purified by flash chromatography (*n*-hexane–EtOAc 65:35) to give pure **6** as a white powder (3.452 g, 80%). For sake of characterization, the two epimeric esters were separately prepared from enantiomerically enriched (L)- and (D)-benzoylalanine (92 and 85% e.e., respectively) and purified by flash chromatography (*n*-hexane–EtOAc 65:35).

Ester **6** from (L)-benzoylalanine: white amorphous solid. $[\alpha]_D$=+219.1 (*c* 1.3, $CDCl_3$). IR (KBr, cm^{-1}): 3325, 3000, 1741, 1637, 1533, 1242, 1165, 1087. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.39 (s, 3H), 1.52 (s, 3H), 1.59 (d, *J*=7.1 Hz, 3H), 3.81–3.91 (m, 1H), 3.95–4.10 (m, 3H), 4.85 (quintet, *J*=7.2 Hz, 1H), 4.94 (t, *J*=6.0 Hz, 1H), 5.42 (dd, *J*=6.0, 3.1 Hz, 1H), 6.51 (d, *J*=6.0 Hz, 1H), 6.85 (bd, *J*=7.2 Hz, 1H), 7.41–7.56 (m, 3H), 7.78–7.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.8 (s), 166.7 (s), 147.9 (d), 133.9 (s), 131.6 (d), 128.5 (d), 127.0 (d), 99.8 (s), 97.8 (d), 69.0 (d), 65.8 (d), 63.2 (d), 61.6 (t), 48.6 (d), 28.7 (q), 19.1 (q), 18.9 (q). MS (ESI) *m/z* 384.1 $(M+Na)^+$, 745 $(2M+Na)^+$. Anal. calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.28; H, 6.22; N, 3.94.

Ester **6** from (D)-benzoylalanine: white crystals, mp 123–125°C (EtOAc–*n*-hexane). $[\alpha]_D$=+212.9 (*c* 1.1, $CDCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.40 (s, 3H), 1.52 (s, 3H), 1.55 (d, *J*=7.1 Hz, 3H), 3.95–4.10 (m, 3H), 4.89 (quintet, *J*=7.1 Hz, 1H), 4.99 (t, *J*=6.0 Hz, 1H), 5.32 (dd, *J*=6.0, 3.6 Hz, 1H), 6.49 (d, *J*=6.0 Hz, 1H), 6.81 (bd, *J*=7.1 Hz, 1H), 7.41–7.56 (m, 3H), 7.78–7.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.5 (s), 166.6 (s), 147.8 (d), 134.1 (s), 131.6 (d), 128.5 (d), 126.9 (d), 99.9 (s), 97.8 (d), 68.8 (d), 65.9 (d), 63.9 (d), 61.6 (t), 48.6 (d), 28.7 (q), 18.9 (q), 18.7 (q). MS (ESI) *m/z* 384.1 $(M+Na)^+$. Anal. calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.40; H, 6.18; N, 3.98.

1.1.2. (4*R*)-4-Methyl-4-(4′,6′-*O*-isopropylidene-2′-3′-dideoxy-α-D-erythro-2′-hexenopyranosyl)-2-phenyl-5(4*H*)-oxazolone (8a) and (4*S*) epimer (8b). To a solution of **6** (1.508 g, 4.17 mmol) in anhydrous acetonitrile (14 mL) were added triethylamine (1.6 mL, 11.26 mmol), CCl_4 (9.38 mmol, 0.905 mL), and triphenylphosphine (2.196 g, 8.34 mmol) and the mixture was stirred under nitrogen at room temperature overnight, becoming dark brown and producing a heavy precipitate. The solvent was removed at reduced pressure and the residue diluted with EtOAc, washed with saturated NH_4Cl and the aqueous phase extracted with EtOAc. The organic phases were collected, dried, and evaporated. The resulting reddish oily residue was flash chromatographed (*n*-hexane–EtOAc 83:17) to give 0.889 g of **8a** (62%) and 0.342 g of **8b** (24%).

Oxazolone **8a**: white crystals, mp 152–153°C (EtOAc–Et_2O). $[\alpha]_D$=−69.0 (*c* 0.9, $CDCl_3$). IR (KBr, cm^{-1}): 2990, 1826, 1653, 1323, 1095, 1006. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (s, 3H), 1.47 (s, 3H), 1.56 (s, 3H), 3.45 (q, *J*=8.0 Hz, 1H), 3.62 (d, AB part of an ABX system, *J*=8.0 Hz, 2H), 4.07–4.13 (m, 1H), 4.59 (dd, *J*=5.1, 2.6 Hz, 1H), 5.98 (dt, *J*=10.6, 2.4 Hz, 1H), 6.19 (dq, *J*=10.6, 1.4 Hz, 1H), 7.48–7.55 (m, 2H), 7.57–7.65 (m, 1H), 8.01–8.06 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 179.3 (s), 161.5 (s), 133.0 (d), 131.9 (d), 128.9 (d), 128.0 (d), 125.5 (s), 122.2 (d), 99.5 (s), 76.3 (d), 74.2 (s), 68.4 (d), 67.1 (d), 62.9 (t), 29.0 (q), 19.7 (q), 18.8 (q). MS (ESI) *m/z* 366.1 $(M+Na)^+$. Anal. calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.72; H, 5.95; N, 4.12.

Oxazolone **8b**: white solid, mp 84–86°C. $[\alpha]_D$=−121.8 (*c* 1.0, $CDCl_3$). IR (KBr, cm^{-1}): 2930, 1790, 1649, 1450, 1103. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.45 (s, 3H), 1.53 (s, 3H), 1.65 (s, 3H), 3.72–3.87 (m, 2H), 4.01 (dd, *J*=9.5, 4.1 Hz, 1H), 4.18 (ddt, *J*=8.3, 1.5, 2.7 Hz, 1H), 4.45 (q, *J*=2.5 Hz, 1H), 5.55 (dt, *J*=10.5, 2.4 Hz, 1H), 6.00–6.05 (m, 1H), 7.47–7.54 (m, 2H), 7.57–7.64 (m, 1H), 7.99–8.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 179.0 (s), 160.2 (s), 132.8 (d), 132.1 (d), 128.8 (d), 128.1 (d), 125.6 (s), 123.1 (d), 99.7 (s), 76.7 (d), 73.1 (s), 68.2 (d), 67.4 (d), 63.2 (t), 29.2 (q), 20.9 (q), 19.0 (q). MS (ESI) *m/z* 366.1 $(M+Na)^+$. Anal. calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.63; H, 5.99; N, 3.90.

1.1.3. 2-(4′,6′-*O*-Isopropylidene-3′-deoxy-3′-iodo-α-D-mannopyranosyl)-2-benzamido-(2*R*)-propionic acid 1′,2′-lactone (9a) and (2*S*) epimer (9b). To a solution of the oxazolone **8a** (0.300 g, 0.87 mmol) in THF distilled on sodium (3 ml) (reagent grade THF inhibits the reaction) was added a 1 M aqueous solution of NaOH (2.2 mL). After 30 min, sublimed iodine (0.665 g, 2.62 mmol) was added in one portion and the solution stirred at room temperature under nitrogen for 24 h. Two additional equivalents of iodine (0.443 g) were added and stirring continued for 24 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with an equal volume of saturated NH_4Cl. The organic phase was washed with a 0.1N solution of $Na_2S_2O_3$ until disappearance of the brown color. The aqueous layer was extracted with EtOAc and the organic extracts were combined, dried, and evaporated. The crude reaction mixture was purified by flash chromatography (*n*-hexane–EtOAc 60:40) to give pure **9a** (0.380 g, 89%). The same procedure was applied to the oxazolone **8b** giving pure **9b** in 77% yield

Iodolactone **9a**: white needles, mp 193–194°C (EtOAc–*n*-hexane). $[\alpha]_D$=+23.3 (*c* 0.8, $CDCl_3$). IR (nujol, cm^{-1}): 1765, 1652, 1538, 1264, 1199, 1142, 1110, 1054. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.49 (s, 3H), 1.55 (s, 3H), 1.68 (s, 3H), 3.60–3.77 (m, 3H), 3.84–3.92 (m, 1H), 3.97 (dd, *J*=11.2, 9.5 Hz, 1H), 5.20 (d, *J*=9.1 Hz, 1H), 5.26–5.34 (m, 1H), 6.48 (s, 1H), 7.43–7.49 (m, 2H), 7.53–7.59 (m, 1H), 7.76–7.80 (m, 2H). ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ: 173.2 (s), 166.2 (s), 132.7 (s), 132.2 (d), 128.5 (d), 127.8 (d), 100.2 (s), 79.8 (d), 76.7 (d), 71.7 (d), 71.0 (d), 62.0 (t), 59.4 (s), 31.5 (d), 28.8 (q), 19.1 (q), 18.4 (q). MS (ESI) *m/z* 488 $(M+H)^+$, 510 $(M+Na)^+$, 997 $(2M+Na)^+$. Anal. calcd for $C_{19}H_{22}INO_6$: C, 46.83; H, 4.55; N, 2.87. Found: C, 46.71; H, 4.39; N, 2.95.

Iodolactone **9b**: white prisms, mp 166–167°C (EtOAc–*n*-hexane). $[\alpha]_D$=+21.1 (*c* 0.8, $CDCl_3$)). IR (nujol, cm^{-1}): 1779, 1711, 1653, 1529, 1260, 1197, 1132, 1033. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.42 (s, 3H), 1.47 (s, 3H), 1.70 (s, 3H), 3.49 (ddd, *J*=9.6, 9.6, 5.6 Hz, 1H), 3.58 (dd, *J*=10.8, 9.6 Hz, 1H), 3.67 (dd, *J*=10.8, 5.6 Hz, 1H), 4.07 (t, *J*=9.6 Hz, 1H), 4.36 (dd, *J*=9.6, 2.8 Hz, 1H), 5.01 (d, *J*=4.1 Hz, 1H), 5.31 (dd, *J*=4.1, 2.8 Hz, 1H), 6.50 (s, 1H), 7.46–7.51 (m, 2H), 7.54–7.60 (m, 1H), 7.78–7.82 (m, 2H). ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ: 174.2 (s), 167.6 (s), 133.7 (s), 132.9 (d), 129.4 (d), 128.5 (d), 100.7 (s), 81.9 (d), 77.4 (d), 72.4 (d), 71.3 (d), 62.6 (t), 57.2 (s), 29.9 (d), 29.6 (q), 25.9 (q), 19.8 (q). MS (ESI) *m/z* 488 $(M+H)^+$, 510 $(M+Na)^+$. Anal. calcd for $C_{19}H_{22}INO_6$: C, 46.83; H, 4.55; N, 2.87. Found: C, 46.85; H, 4.31; N, 2.91.

1.1.4. 2-(3′-Deoxy-3′-iodo-α-D-mannopyranosyl)-2-benzamido-(2*R*)-propionic acid 1′,2′-lactone (10a) and (2*S*) epimer (10b). A 0.3 M solution of iodolalactone **9a** (0.135 g, 0.28 mmol) in THF was treated with a 5 M solution of aqueous HCl (0.9 mL) and left aside at room temperature for 3 h. The solution was reduced to a volume of ca. 1 mL, diluted with 3 mL of saturated brine and extracted three times with EtOAc. The combined organic layers were dried and evaporated, giving **10a** as a white solid (0.110 g, 89%). The same procedure was applied to the iodolactone **9b** giving pure **10b** in 90% yield.

Iodolactone **10a**: white needles, mp 192–194°C (MeOH–EtOAc). $[\alpha]_D$=+52.4 (*c* 0.6, MeOH). IR (nujol, cm^{-1}): 3483, 3166, 1766, 1625, 1314, 1126, 1079, 1020. ^1H NMR

($(CD_3)_2SO$, 400 MHz) δ: 1.45 (s, 3H), 3.51 (m, 1H, after exchange with D_2O: dd, J=12.0, 2.3 Hz), 3.57–3.71 (m, 3H), 4.17 (dd, J=11.3, 10.1 Hz, 1H), 4.61 (d, J=6.9 Hz, 1H), 4.86 (t, J=4.8 Hz, 1H, exchanges with D_2O), 5.03 (dd, J=10.1, 6.9 Hz, 1H), 5.87 (d, J=7.1 Hz, 1H, exchanges with D_2O), 7.56 (m, 2H), 7.59 (m, 1H), 7.89–7.83 (m, 2H), 9.10 (s, 1H). ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ: 175.7 (s), 167.4 (s), 133.1 (s), 132.9 (d), 129.2 (d), 128.6 (d), 84.3 (d), 82.3 (d), 76.7 (d), 68.7 (d), 61.6 (t), 60.9 (s), 36.6 (d), 19.2 (q). MS (ESI) m/z 448 $(M+H)^+$, 470 $(M+Na)^+$. Anal. calcd for $C_{16}H_{18}INO_6$: C, 42.97; H, 4.06; N, 3.13. Found: C, 42.91; H, 4.17; N, 3.11.

Iodolactone **10b**: white prisms, mp 98–100°C (MeOH–EtOAc). $[\alpha]_D$=+105.1 (c 0.4, MeOH). IR (nujol, cm^{-1}): 3378, 1784, 1643, 1308. ^1H NMR ($(CD_3)_2SO$, 400 MHz) δ: 1.52 (s, 3H), 3.42–3.51 (m, 2H), 3.52–3.66 (m, 2H), 4.35 (dd, J=11.3, 9.1 Hz, 1H), 4.43 (d, J=6.4 Hz, 1H), 4.68 (t, J=5.2 Hz, 1H, exchanges with D_2O), 5.04 (dd, J=9.2, 6.5 Hz, 1H), 5.77 (d, J=7.5 Hz, 1H, exchanges with D_2O), 7.47 (m, 2H), 7.56 (m, 1H), 7.85 (m, 2H), 8.46 (s, 1H). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ: 174.5 (s), 166.8 (s), 133.5 (s), 131.8 (d), 128.5 (d), 127.9 (d), 82.8 (d), 80.9 (d), 74.1 (d), 68.4 (d), 60.9 (t), 58.4 (s), 35.6 (d), 23.2 (q)). MS (ESI) m/z 448 $(M+H)^+$, 470 $(M+Na)^+$. Anal. calcd for $C_{16}H_{18}INO_6$: C, 42.97; H, 4.06; N, 3.13. Found: C, 43.02; H, 4.01; N, 3.09.

1.1.5. 2-(4′,6′-*O*-Isopropylidene-α-D-mannopyranosyl)-2-benzamido-(2*R*)-propionic acid 1′,2′-lactone (11a) and 2*S* epimer (11b). To a 0.2 M solution of the oxazolone **8a** (0.200 g) in 5% aqueous acetone was added 4-methylmorpholine *N*-oxide (0.102 g, 0.87 mmol) and 0.58 mL of a 0.1 M solution of OsO_4 in *tert*-butyl alcohol (0.06 mmol). The pale yellow solution was stirred at room temperature under nitrogen for 24 h. The solvent was evaporated at reduced pressure and the residue filtered through a short pad of silica gel eluting with EtOAc to give 0.216 g of **11a** (98%). The same procedure was adopted for the preparation of the epimeric lactone **11b** (95%).

Lactone **11a**: white crystals, mp 251–252°C (EtOAc–Et_2O). $[\alpha]_D$=+8.3 (c 0.9, acetone). IR (KBr, cm^{-1}): 3402, 1771, 1658, 1537, 1060. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.44 (s, 3H), 1.51 (s, 3H), 1.58 (s, 3H), 2.61 (bs, 1H, exchanges with D_2O), 3.73 (dd, J=10.5, 10.0 Hz, 1H), 3.78–3.86 (m, 1H), 3.96 (dd, J=10.5, 5.6 Hz, 1H), 4.21 (dd, J=11.2, 4.0 Hz, 1H), 4.37 (dd, J=5.0, 4.0 Hz, 1H), 4.52 (dd, J=10.6, 5.0 Hz, 1H), 5.28 (d, J=10.6 Hz, 1H), 6.40 (bs, 1H), 7.43–7.48 (m, 2H), 7.53–7.58 (m, 1H), 7.80–7.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.8 (s), 166.6 (s), 133.9 (s), 132.7 (d), 129.2 (d), 128.5 (d), 99.8 (s), 77.8 (d), 73.4 (d), 71.3 (d), 67.6 (d), 67.5 (d), 63.6 (t), 60.8 (s), 29.7 (q), 19.7 (q), 15.2 (q). MS (ESI) m/z 378 $(M+H)^+$, 390 $(M+Na)^+$, 777 $(2M+Na)^+$. Anal. calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.52; H, 6.31; N, 3.82.

Lactone **11b**: white crystals, mp 235–236°C (EtOAc–Et_2O). $[\alpha]_D$=−44.0 (c 0.8, $CDCl_3$). IR (nujol, cm^{-1}): 3439, 1770, 1666, 1531, 1062. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.42 (s, 3H), 1.54 (s, 3H), 1.67 (s, 3H), 2.33 (bs, 1H, exchanges with D_2O), 3.75 (t, J=10.0 Hz, 1H), 3.77–3.84 (m, 1H), 3.95 (dd, J=10.0, 4.5 Hz, 1H), 4.15 (dd, J=10.7, 3.8 Hz, 1H), 4.18 (d, J=10.6 Hz, 1H), 4.34–4.37 (m, 1H), 4.93 (dd, J=10.6, 5.1 Hz, 1H), 6.15 (s, 1H), 7.46–7.51 (m, 2H), 7.55–7.60 (m, 1H), 7.77–7.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.0 (s), 167.2 (s), 133.9 (s), 132.6 (d), 129.1 (d), 128.6 (d), 99.8 (s), 78.1 (d), 75.9 (d), 75.1 (d), 68.0 (d), 67.3 (d), 63.5 (t), 57.5 (s), 29.7 (q), 24.3 (q), 19.7 (q). MS (ESI) m/z 378 $(M+H)^+$, 390 $(M+Na)^+$, 777 $(2M+Na)^+$. Anal. calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.42; H, 6.32; N, 3.81.

1.1.6. 2-(α-D-*C*-Mannopyranosyl)-(*R*)-alanine hydrochloride (2) and 2*S* epimer (3). A suspension of lactone **11a** (0.216 g, 0.57 mmol) in 6N HCl (4 mL) in a screw-cap vial was heated at 80°C for 4 h. The suspended solid dissolved after ca. 30 min. The pale yellow solution was cooled to room temperature and the precipitated benzoic acid extracted with methylene chloride (2×4 mL). The aqueous phase was evaporated and dessicated under vacuum to a constant weight to afford **2** (0.160 g, 92%) as a white solid monohydrated salt, as revealed by the elemental analysis. The same procedure was applied to the lactone **11b** to give **3** (93%).

(2*R*) Epimer **2**: white hygroscopic solid, dec. >200°C. $[\alpha]_D$=+33.1 (c 0.8, MeOH). IR (nujol, cm^{-1}): 3359, 2361, 1735, 1376, 1051. ^1H NMR (D_2O, 400 MHz) δ: 1.53 (s, 3H), 3.54 (dd, J=3.5, 12.4 Hz, 1H), 3.72 (dd, J=2.7, 4.8 Hz, 1H), 3.77–3.84 (m, 2H), 3.92 (dd, J=3.6, 9.6 Hz, 1H), 3.96 (dd, J=9.1, 12.4 Hz, 1H), 4.05 (d, J=9.6 Hz, 1H). ^{13}C NMR (D_2O, 100 MHz) δ: 172.7 (s), 80.2 (d), 71.4 (d), 70.6 (d), 68.7 (d), 65.2 (d), 62.9 (s), 59.2 (t), 17.4 (q). MS (ESI) m/z 252.1 $(M-Cl)^+$. Anal. calcd for $C_9H_{18}NO_7H_2O$: C, 35.36; H, 6.59; N, 4.58. Found: C, 35.01; H, 6.71; N, 4.26. (2*S*).

Epimer **3**: white hygroscopic solid, dec. >205°C. $[\alpha]_D$=+71.0 (c 0.5, MeOH). IR (nujol, cm^{-1}): 3359, 1735, 1622, 1376, 1054. ^1H NMR (D_2O, 400 MHz) δ: 1.58 (s, 3H), 3.56 (dd, J=3.4, 12.5 Hz, 1H), 3.72 (dd, J=2.9, 5.0 Hz, 1H), 3.79–3.85 (m, 2H), 3.97 (d, J=9.1 Hz, 1H), 3.98 (dd, J=9.0, 12.5 Hz, 1H), 4.05 (dd, J=3.5, 9.1 Hz, 1H). ^{13}C NMR (D_2O, 100 MHz) δ: 172.4 (s), 80.1 (d), 72.4 (d), 70.7 (d), 68.9 (d), 65.1 (d), 61.9 (s), 59.2 (t), 19.9 (q). MS (ESI) m/z 252.1 $(M-Cl)^+$. Anal. calcd for $C_9H_{18}NO_7H_2O$: C, 35.36; H, 6.59; N, 4.58. Found: C, 35.12; H, 6.84; N, 4.38.

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