JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

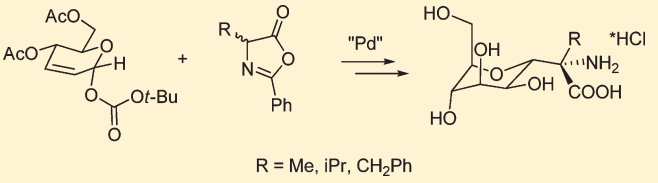
Stereoselective Pd-Catalyzed Synthesis of Quaternary α-D-*C*-Mannosyl-(*S*)-amino Acids

Marcello Di Giacomo,* Massimo Serra,* Marco Brusasca, and Lino Colombo

Dipartimento di Chimica Farmaceutica, Università degli Studi di Pavia, viale Taramelli 12, 27100 Pavia, Italy.

Supporting Information

ABSTRACT: In this paper, we report the stereoselective synthesis of α-D-*C*-mannosyl-(*S*)-amino acids exploiting, as a key step, an allylic alkylation of glycal-derived π-allyl Pd(II) intermediates, prepared by oxidative addition of Pd(0) species to 2,3-unsaturated pyranosides (pseudoglycals). The reaction of 4,6-di-*O*-acetyl α-pseudoglucal carbonate **10a** with racemic alanine-, valine-, and phenylalanine-derived azlactones gave the corresponding (4*S*)-4-α-D-*C*-mannosyl-2-phenyloxazol-5(4*H*)-ones as the major diastereoisomers in high yields. The final α-D-*C*-mannosyl-(*S*)-amino acids were obtained in a few steps comprising highly diastereoselective dihydroxylation of the glucal derivative double bond followed by the one-pot hydrolysis of the benzamido and acetate protecting groups. Main features of this method are the conciseness of the synthetic sequence, the high diastereoselection of the allylic alkylation step, the use of racemic α-amino acids as starting material, and the good overall yields.



R = Me, iPr, CH_2Ph

INTRODUCTION

Naturally occurring glycoproteins, glycopeptides, and peptidoglycans represent an extensive and important class of compounds which are widely distributed among living organisms playing a significant role in a multitude of key biological processes.[1]

Protein glycosylation not only affects their physical properties as folding and conformation[2] but also influences their biological functions.[3] Recent studies demonstrated that the carbohydrate moieties of the membrane-associated *N*- and *O*-glycoproteins are directly involved in recognition phenomena including, for example, viral and bacterial infection,[4] cancer metastasis,[5] inflammatory and immunity response,[6] and many other receptor-mediated signaling processes.

As a consequence, glycoproteins and glycopeptides[7] involved in such processes are of great pharmaceutical interest. However, these natural products are of low metabolic and chemical stability, thus limiting their use as potential drug candidates.[8]

In order to circumvent this drawback, the synthesis of *C*-glycoside derivatives[9] has been an attractive goal in recent years because of their increased stability to chemical and enzymatic cleavage[10] and favorable conformational properties[11] that allow the use of such compounds as mimics of more common, naturally occurring *N*- and *O*-glycoconjugates. Moreover, the sugar component can also modulate the biological properties of a protein, improving its water solubility as well as its bioavailability by accelerating its transport across membranes.[12]

Within this general class of compounds, *C*-glycosyl α-amino acids[13] have emerged as an important class of building blocks for the construction of *C*-glycosylated peptides.[14] The interest in this class of glycopeptide mimetics stems not only from enhanced resistance to enzymatic hydrolysis 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.[15]

Well-defined conformational constraints could also be imparted to a peptide chain by the insertion of quaternary α-amino acids.[16]

While significant research has been undertaken in the design of restricted peptides, the field of conformationally constrained glycopeptides remains relatively unexplored, and most of the restrictions studied are centered in the saccharide moiety.[17]

We reasoned that a combined effect could be derived by attaching a sugar moiety to the α-carbon of monosubstituted α-amino acids. It thus appeared interesting to combine the hydrolytic stability of carbohydrate analogues such as *C*-glycosides with conformational properties of constrained *C*-glycosylated quaternary amino acids, in order to carry out the synthesis of a new class of potential mimetics of glycopeptides.

In the course of our research project aimed at the design of novel selectin antagonists, we became interested primarily in the synthesis of quaternary *C*-α-mannosyl amino acids as building blocks for the development of a new class of conformationally restricted mimetics of tetrasaccharide Sialyl Lewis X. Indeed, α-D-mannosides have been successfully used as L-fucose equivalents in the design of SLeX mimetics.[18]

Moreover, recent studies demonstrated that *C*-D-glucopyranosides with an amino function on the carbon directly linked to the anomeric sugar center are potent inhibitors for glycosidases.[19]

Several recent syntheses of *C*-glycosyl amino acids have been recently reported in the literature, and most of them are isosteres

Received: February 8, 2011
Published: May 19, 2011

of natural *N*- or *O*-linked glycoamino acid.[13] To the best of our knowledge, there are only two examples of *C*-glycosylated α-amino acids possessing a quaternary stereocenter on the Cα of the amino acid moiety.[20] The principal reason lies in the difficulty in creating simultaneously the C−C bond between the anomeric carbon of the sugar moiety and the α-carbon of the amino acid with a high level of diastereoselectivity.

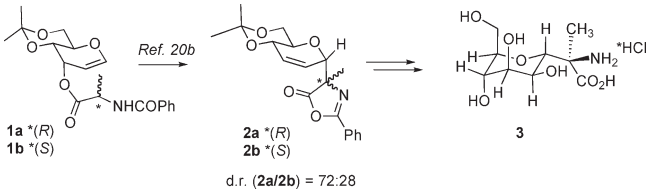
The high stereochemical control accompanying transition-metal-mediated transformations has prompted several groups to employ such methods for *C*-glycosylations. It is in this context that we describe herein a novel catalytic asymmetric synthesis of carbon-linked glycosyl-α-amino acids through the asymmetric allylic alkylation (AAA) reaction promoted by chiral palladium catalysts.[21]

In a preceding paper,[20c] we reported on the preparation of α-D-*C*-mannosyl-(*R*)-alanine **3** through an approach relying on the Steglich variant of the Claisen rearrangement of the esters **1** (Scheme 1). Although this method is practical and high yielding, it is not without limitations: (1) the starting acetonide protected D-*ribo*-hex-1-enitol must be prepared in four steps from commercially available 3,4,6-tri-*O*-acetyl-D-glucal; (2) the diastereoselection of the Claisen−Steglich rearrangement is rather low, providing the two epimeric α-*C*-glycosylated azlactones **2a** and **2b** in a 2.6:1 ratio; and (3) the method is limited to alanine derivatives as attempts to extend its scope to other amino acids such as phenylalanine and valine resulted in unacceptably low yields.

Inspired by reports by Trost[22] in which quaternary α-amino acids were prepared enantioselectively by Pd-catalyzed reaction of allylic acetates with 4-alkyl-2-phenyloxazol-5(4*H*)-ones,[23] we tried to expand this methodology to glycal derivatives. If this were successful, the last two limitations of our previous method could be obviated. The use of chiral phosphine ligands matching the stereoinduction exerted by the sugar moiety could improve the stereoselection of the process. Moreover, the wide scope of the Trost method with respect to the variation of the 4-alkyl substituent of the azlactone could allow the preparation of different *C*-glycosylated α-amino acids. However, in the Trost papers major attention was paid to the reaction of acyclic asymmetric allyl derivatives, and only two cyclic allyl acetates were studied. Moreover, the poor reactivity of glycal donors for η^3-Pd complex mediated reactions could be a challenge to this approach.[24] The use of more activated pyranone derivatives or Zn(II) activation of the glycal donors to accelerate ionization were shown to give a partial solution to this limitation.[25] As anticipated by these precedents, preliminary experiments with glycal acetonides **4**−**6** (Scheme 2, A) confirmed their reluctance to form π-allyl Pd intermediates. The *O*-acetyl and *O*-*t*-Boc derivatives **4** and **6** were recovered unchanged; only the *O*-trifluoroacetyl derivative **5** gave the desired adducts **2a**,**b** as a mixture of diastereoisomers in trace amounts, and only using the sodium enolate of the azlactone **7**. In this case, the major product was the deacylated glucal acetonide, likely arising from the attack of the nucleophilic enolate at the trifluoroacetate carbonyl. The same disappointing results were obtained starting from the corresponding epimeric acetonide-protected D-*arabino*-hex-1-enitol derivatives.

An alternative way of forming glycal-derived π-allyl Pd intermediates would be the oxidative addition of Pd(0) species to 2,3-unsaturated glycosyl carbonates (pseudoglycals). Although this reaction has received scant attention, the rare examples reported in the literature demonstrated its usefulness for the synthesis of *C*-glycosides because of its very high regio- and stereoselectivity and mild experimental conditions.[26] These considerations prompted us to study the Pd-catalyzed allylic alkylation reaction of pseudoglucal **10a** with azlactones **7**−**9** (Scheme 2, B). For any synthetic method to be useful, the substrates must be readily accessible: compound **10a** can be prepared by as few as two steps from commercial tri-*O*-acetyl-D-glucal in 76% yield and 4-alkyl-5-oxazolones in one step from *N*-benzoyl-α-amino acids.[28]

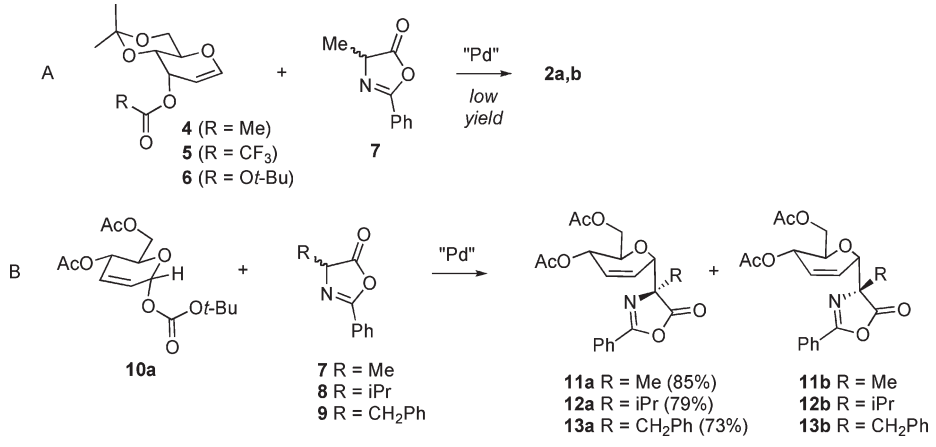
Scheme 1



RESULTS AND DISCUSSION

Exploratory experiments with simple and cheap monophosphines such as triphenyl- and tri-*O*-tolylphosphine, in the presence of $Pd(OAc)_2$ as palladium source, showed that pseudoglucal **10a** was indeed a suitable substrate for the formation of the corresponding π-allyl Pd complex as the *C*-glycosylated azlactone **11** was formed, albeit in low yields (29−45%) and as a mixture of

Scheme 2



dx.doi.org/10.1021/jo2002962 |*J. Org. Chem.* 2011, 76, 5247–5257

Table 1. Reaction of Pseudoglycal 10a with Alanine-Derived Azlactone 7

entry[a]	solvent[b]	base	$Pd_2(dba)_3$ (mol %)	phosphine	phosphine (mol %)	time (h)	isolated yield[c] (%)	dr[d] (**11a**/**11b**)
1[e]	THF	TEA	1.5	TPP	4.5	24	29	69:31
2[e]	THF	TEA	20	TPP	60	1	45	76:24
3	THF	TEA	1.5	TPP	9	1	67	72:28
4	THF	TEA	1.5	TPP	12	0.5	70	74:26
5	THF	TEA	5	dppe	15	1	64	87:13
6	THF	NaH	5	dppe	15	3	35	83:17
7	THF	TEA	5	dppe	20	0.5	82	93:7
8	THF	TEA	1.5	dppe	6	0.5	85	93:7
9	THF	DIEA	1.5	dppe	6	1	74	89:11
10	DCM	TEA	1.5	dppe	6	1	71	93:7
11	DCM	TEA	5	dppe	15	1	69	68:32
12	MeCN	TEA	1.5	dppe	6	0.5	74	87:13
13[f]	THF	TEA	1.5	dppe	6	0.5	79	87:13

[a] Reaction conditions: Reactions were performed on a 0.075−0.15 mmol scale (0.1 M) at rt using 1.0 equiv of α-pseudoglucal, 2.0 equiv of azlactone **7**, $Pd_2(dba)_3$-chloroform adduct as catalyst precursor, and 1.3 equiv of base. [b] All solvents were freshly distilled from the appropriate drying agent. [c] Isolated yield of the major diastereoisomer. [d] dr = diastereoisomeric ratio, determined by 400 MHz ^{1}H NMR analysis of the crude mixture: average from diagnostic signals of H-2′, H-3′, and H-4′. [e] Reaction performed with $Pd(OAc)_2$ as catalyst precursor. [f] Reaction performed with $[(\eta^3\text{-allyl})PdCl]_2$ as catalyst precursor.

diastereoisomers **11a** and **11b** (for configurational assignments see below) with poor selectivity (69−76%), despite the use of a large amount of catalyst (20 mol %) (Table 1, entries 1 and 2). In all cases, the major product was the dimeric adduct deriving from the attack of the azlactone enolate to the carbonyl carbon of a second azlactone molecule. Switching the palladium source to $Pd_2(dba)_3$[29] the allylic alkylation could be carried out with improved yields (70%) and a comparable diastereoselection value of 74% (Table 1, entry 4).

These results led us to consider the use of dppe (1,2-bis-(diphenylphosphino)ethane) as Pd ligand. Indeed, a paper by Hayashi[30] reports an example of allylic alkylation were the use of tetrakis (triphenylphosphine)palladium(0), "which has been used conventionally for many of the palladium-catalyzed allylation reactions" gave only 4% of the products, while a much higher yield of 96% was obtained only switching to dppe as a ligand.

As shown by the results summarized in Table 1 (entries 5−13), yields could be considerably improved by using a Pd/dppe catalyst, prepared in a separate flask by mixing $Pd_2(dba)_3$ with 1,2-bis(diphenylphosphino)ethane prior to addition to a premixed mixture of all other reagents.

Several reaction variables were then investigated including Pd source, solvent, base, and Pd to diphosphine ratio; all of the reactions were complete within 1 h at room temperature.

Comparison between the two most commonly used Pd precatalysts, $Pd_2(dba)_3$ and $[(\eta^3\text{-allyl})PdCl]_2$ (entry 8 vs entry 13), revealed that both the diastereoselection and the yield were slightly higher with the former. Taking into account this result, but also the lower cost and the better properties as to long-term storage of $Pd_2(dba)_3$, we used this precatalyst for the following optimization experiments.

The solvent effect was not extensively studied. The results in Table 1 indicate that in terms of diastereoselection either dichloromethane or tetrahydrofuran was a suitable solvent (entries 8 and 10 vs entry 12), the only remarkable difference being the increase of the reaction rate effected by the use of THF. This probably reflects also an improvement of yields as an increased reaction rate could minimize the formation of side products deriving from self-condensation of the azlactone. With regard to the base, triethylamine was superior to diisopropylethylamine and stronger inorganic bases such as NaH (entries 5 vs 6 and 8 vs 9). Finally, the most critical variable for achieving diastereoselection values higher than 90% was the Pd/diphosphine ratio. In the enantioselective allylic alkylation reactions of azlactones reported by Trost an 1/1.5 ratio was always adopted.[31] Using this same ratio yields were uniformly close to 70%, but diastereoselection was still low (entries 5 and 11). Unexpectedly, when the Pd/dppe ratio was raised to 1:4, yields were improved to 82%, and the diastereoselection reached an acceptable value of 93% (entry 7). With these optimized conditions available, we then looked to see if the Pd loading could be lowered below 5%, and we found that as little as 1.5 mol % of $Pd_2(dba)_3$ could be used with no diminution in yields and diastereoselectivity (entry 8).

In order to expand the scope of this method to other amino acid derivatives, valine- and phenylalanine-derived azlactones **8** and **9** (Scheme 2, B) were reacted with the same pseudoglycal **10a** under the optimized conditions found for the alanine derivative **7**.

Table 2 summarizes the alkylation reactions for this range of derivatives. Notably, the size of the 4-alkyl substituent did not effect the diastereoselection that was uniformly higher than 90% for all compounds. Compounds **11a**−**13a** could be isolated diastereomerically pure after chromatographic separation of the corresponding minor diastereomers **11b**−**13b** in good yields (73−85%).

An explanation of how the achiral phosphine ligands could affect the stereoinduction at the nucleophile could only be speculative since, in allylic alkylation, the attacking nucleophile is remote from the phosphine ligands. Excluding a direct interaction between the phosphine and the azlactone, we can suppose that variation of the phosphine structure reflects into a conformational change of the cyclic π-allyl-Pd complex. The sense of stereoinduction at the nucleophile could be explained taking into consideration the diastereoisomeric transition states of nucleophilic attack of azlactone enolates on the π-allyl-Pd complex as hypothesized by Trost.[22] The approach of the nucleophile could be directed by interaction between the negatively charged oxygen and the positively charged C3′ of the π-allyl-Pd intermediate,

dx.doi.org/10.1021/jo2002962 |J. Org. Chem. 2011, 76, 5247–5257

Table 2. Alkylation of Alanine-, Valine-, and Phenylalanine-Derived Azlactones under Optimized Conditions

entry[a]	azlactone	time (h)	isolated yield[b] (%)	dr[c]
1	**7** (CH_3)	0.5	85	93:7 (**11a**/**11b**)
2	**8** (iPr)	1	79	93:7 (**12a**/**12b**)
3	**9** (CH_2Ph)	2.5	73	90:10 (**13a**/**13b**)

[a] Reaction conditions: reactions were performed at rt on a 0.075−0.15 mmol scale (0.1 M) in anhydrous THF using 1.0 equiv of α-pseudoglucal, 2.0 equiv of azlactone, 1.3 equiv of TEA, 1.5 mol % of $Pd_2(dba)_3$−chloroform adduct as catalyst precursor, and 6 mol % of dppe as ligand. [b] Isolated yields of the major diastereoisomer. [c] dr = diastereoisomeric ratio, determined by 400 MHz ^{1}H NMR analysis of the crude mixture: average from diagnostic signals of H-2′, H-3′, and H-4′.

leading to chairlike (A) or boatlike (B) transition states arising from the two different spatial orientations of the azlactone (Figure 1). The observed *Si*-face selectivity of the π-allyl-Pd intermediate clearly indicates that the reaction proceeds through the more favored chairlike transition state A. Indeed, transition state B involving the attack of the π-allyl unit on the *Re*-face of the enolate becomes destabilized because of a steric interaction between the alkyl substituent of the azlactone and the pseudoaxial H5′.

Encouraged by these initial results, we further proceeded to optimize the reaction conditions in order to improve (if possible) both diastereomeric ratio and reaction yield. For this purpose, we decided to explore the use of several bidentate phosphine ligands (Figure 2) in the presence of $Pd_2(dba)_3$ as palladium source.

Since it has been reported that diphosphine ligands have a marked influence on the reactivity and selectivity of transition-metal catalysts, in our first attempts we considered the use of bis(diphenylphosphino)propane (dppp), a diphosphine ligand which is characterized by a wider bite angle than dppe. Indeed, as it is commonly accepted, a wide bite angle can both increase the effective steric bulk of the bidentate ligand and electronically favor or disfavor certain geometries of transition metal complexes.[32] Moreover, a double stereodifferentiation with chiral ligands was considered in order to determine if catalyst control could enhance the low diastereoselection exerted by the substrate alone. Keeping in mind that forcing the chiral environment to embrace the substrate by opening the bite angle is necessary for high chiral recognition,[33,21] we explored the use of both enantiomers of 2,3-bis-(diphenylphosphine)butane (dppb), and 2,4-bis-(diphenylphosphine)pentane (bdpp).

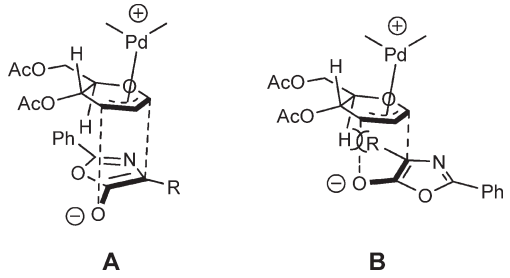


Figure 1. Possible approaches of the azlactone to the π-allyl-Pd complex.

Results reported in Table 3 (entries 1, 7, and 12) clearly indicate that the use of the more flexible dppp (bite angle 91°) caused a remarkable loss in stereoselectivity if compared to dppe (bite angle 86°).

We can only speculate on the origin of this effect and put forward the hypothesis that a more flexible ligand imparts to the Pd complex a geometry more similar to that obtained in the case of monophosphine ligands. On the basis of this result, which seemed to give the indication that a more rigid five-membered ring in the π-allyl-Pd complex coordinated with dppe would enhance the diastereoselection, we tested whether replacement of dppe by either enantiomers of a chiral ethylene diphosphine could reinforce the inherent stereodirecting effect of the sugar portion of the π-allyl complex (matching effect). Unfortunately, reaction of the most reactive azlactone **7** in the presence of both (*R*,*R*)- and (*S*,*S*)-dppb under the same previously optimized conditions afforded only trace amounts of the desired glycosyl oxazolone **11a** (entries 2 and 3).

We were then curious to see whether the "chiral shift", applied to the case of the worse performing dppp, would produce the same or even worse results.

Contrary to our expectations, reaction of azlactone **7** in the presence of (*R*,*R*)- and (*S*,*S*)-bdpp gave yields (56−65%) comparable to the achiral version (entries 4−6), and notably, a matching effect exerted by the (*R*,*R*) enantiomer was apparent, as evidenced by enhanced diastereoisomeric ratio (90:10) (entry 4 vs 1). Similar results were obtained by doubling the catalyst amount apart from an expected slight increase in yield (entry 6).

Contradictory results were obtained in the case of the least reactive isopropyl oxazolone **8** where experiments with doubled catalyst loading were needed in order to obtain more than a trace amount of the final product **12a** (entries 10 and 11). A slight matching effect by the (*R*,*R*) enantiomer was observed also in this case (entry 10) when considering the diastereoselection enhancement, but this was not accompanied by an increase in yield and reaction rate as it is common for matched pairs. Unexpectedly, the matching effect of the (*R*,*R*)-bdpp was not observed in the case of benzyl oxazolone **9** (entry 15). Even if a loss in diastereoselectivity was obtained with both bdpp enantiomers, this detrimental effect was more pronounced with (*R*,*R*)-bdpp.

These discouraging results convinced us to deeply investigate the reaction stereoselectivity testing other chiral diphosphine ligands. For this purpose, we selected three of the most representative bidentate phosphines usually employed in Pd-catalyzed

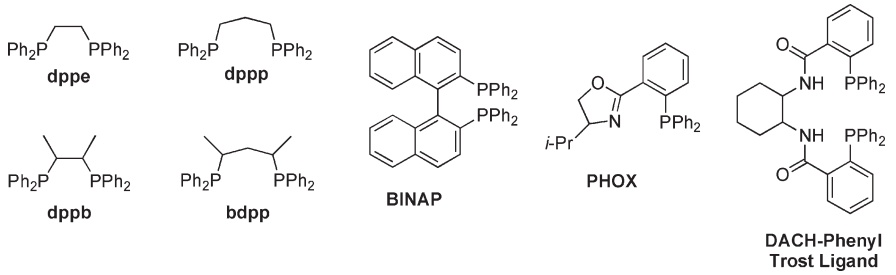


Figure 2. Employed bidentate phosphine ligands.

dx.doi.org/10.1021/jo2002962 |*J. Org. Chem.* 2011, 76, 5247–5257

Table 3. Effect of the Ligand on the Diastereoselectivity of the Allylic Alkylation of 7−9

entry[a]	azlactone	$Pd_2(dba)_3$ (mol %)	phosphine	phosphine (mol %)	time (h)	isolated yield[b] (%)	dr[c]
1	**7** (CH_3)	1.5	dppp	6	0.5	62	81:19 (**11a**/**11b**)
2		1.5	(*R*,*R*)-dppb	6	24	trace	nd
3		1.5	(*S*,*S*)-dppb	6	24	trace	nd
4		1.5	(*R*,*R*)-bdpp	6	2	56	90:10
5		1.5	(*S*,*S*)-bdpp	6	3	60	68:32
6		3	(*R*,*R*)-bdpp	12	0.3	65	90:10
7	**8** (iPr)	1.5	dppp	6	1	55	80:20 (**12a**/**12b**)
8		1.5	(*R*,*R*)-bdpp	6	24	trace	nd
9		1.5	(*S*,*S*)-bdpp	6	24	trace	nd
10		3	(*R*,*R*)-bdpp	12	18	35	85:15
11		3	(*S*,*S*)-bdpp	12	8	57	66:33
12	**9** (CH_2Ph)	1.5	dppp	6	2.5	55	77:23 (**13a**/**13b**)
13		1.5	(*R*,*R*)-bdpp	6	48	18	nd
14		1.5	(*S*,*S*)-bdpp	6	24	46	55:45
15		3	(*R*,*R*)-bdpp	12	20	60	69:31
16		3	(*S*,*S*)-bdpp	12	5	77	75:25

[a] Reaction conditions: reactions were performed at rt on a 0.075−0.15 mmol scale (0.09 M) of anhydrous THF using 1.0 equiv of α-pseudoglucal, 2.0 equiv of azlactone, 1.3 equiv of TEA, and $Pd_2(dba)_3$−chloroform adduct as catalyst precursor. [b] Isolated yield of the major diastereomer. [c] dr = diastereomeric ratio, determined by 400 MHz ^{1}H NMR analysis of the crude mixture: average from diagnostic signals of H-2′, H-3′, and H-4′. [e] nd = not determined.

Table 4. Alkylation Reactions with BINAP, PHOX, and DACH-phenyl Trost Ligand

entry[a]	azlactone	Pd catalyst (mol %)	phosphine	phosphine (mmol %)	time (h)	isolated yield[c] (%)	dr[d]
1	**7** (CH_3)	2	(*R*)-BINAP	8	6.5	47	80:20 (**11a**/**11b**)
2		2	(*S*)-BINAP	8	6.5	50	80:20
3		1.5	(*R*)-PHOX	6	1.5	59	93:7
4		1.5	(*S*)-PHOX	6	24	55	91:9
5		1.5	(*R*,*R*)-DACH	6	0.3	78	**94:6**
6		1.5	(*R*,*R*)-DACH	6	1	78[e]	**94:6**
7		1.5	(*R*,*R*)-DACH	6	1	79[e,f]	**94:6**
8		1.5	(*S*,*S*)-DACH	6	24	nd[g]	nd
9	**8** (iPr)	2	(*R*)-BINAP	8	48	40	75:25 (**12a**/**12b**)
10		2[b]	(*R*)-BINAP	8	48	26	75:25
11		2	(*S*)-BINAP	8	48	55	75:25
12		1.5	(*R*)-PHOX	6	72	50	89:11
13		1.5	(*S*)-PHOX	6	72	51	87:13
14		1.5	(*R*,*R*)-DACH	6	0.7	81	**98:2** (**12a**/**12b**)
15		1.5	(*R*,*R*)-DACH	6	2	83[e]	**98: 2**
16		1.5	(*R*,*R*)-DACH	6	2	88[e,f]	**98:2**
17		1.5	(*S*,*S*)-DACH	6	24	50	90:10
18	**9** (CH_2Ph)	2	(*R*)-BINAP	8	18	33	70:30 (**13a**/**13b**)
19		2	(*S*)-BINAP	8	6.5	54	71:29
20		2[b]	(*S*)-BINAP	8	0.7	30	50:50
21		1.5	(*R*)-PHOX	6	24	50	80:20
22		1.5	(*S*)-PHOX	6	6	49	62:38
23		1.5	(*R*,*R*)-DACH	6	1	77	**96:4**
24		1.5	(*R*,*R*)-DACH	6	1	76[e]	**96:4**
26		1.5	(*R*,*R*)-DACH	6	2	90[e,f]	**96:4**
27		1.5	(*S*,*S*)-DACH	6	1.5	67	85:15

[a] Reaction conditions: reactions were performed at rt on a 0.075−0.15 mmol scale (0.1 M) of anhydrous THF, 1.0 equiv of α-pseudoglucal, 2.0 equiv of azlactone, 0.2−1.3 equiv of TEA, 1.5 mol % of $Pd_2(dba)_3$−chloroform adduct as catalyst precursor. [b] Reaction performed with $[(\eta^3\text{-allyl})PdCl]_2$. [c] Isolated yield of the major diastereomer. [d] dr = diastereomeric ratio, determined by 400 MHz ^{1}H NMR analysis of the crude mixture: average from diagnostic signals of H-2′, H-3′, and H-4′. [e] Reaction performed with 0.2 equiv of TEA. [f] Reaction performed with 4 Å molecular sieves. [g] nd = not determined.

dx.doi.org/10.1021/jo2002962 |*J. Org. Chem.* 2011, 76, 5247–5257

enantioselective allylations[34,21b] such as BINAP,[35] PHOX,[36] and DACH-phenyl Trost ligand.[37,33]

Experiments, performed utilizing the C-2-symmetric bidentate BINAP, showed a marked decrease of yields (47−55%) and stereoselectivity (70−80%) (Table 4, entries 1, 2, 9, 11, 18, and 19). Moreover, no matching effect was exerted by either enantiomeric ligand, and only a marginal increase in yields was effected by the use of the *S*-enantiomer. Changing the palladium source from $Pd_2(dba)_3$ to $[(\eta^3\text{-allyl})PdCl]_2$ had a deleterious effect on both yields and stereoselectivity (entries 10 and 20). The major diastereoisomer has the same configuration as that obtained with achiral diphosphines showing the predominant stereodirecting effect of the sugar moiety. This behavior was substantially identical for all azlactones. Switching to the bidentate *N,P*-phosphine-oxazoline PHOX ligand led to results comparable with those obtained employing BINAP (entries 3, 4, 12, 13, 21, and 22). Much better results were finally obtained by using the more flexible and larger bite angle (110°) bidentate DACH-phenyl phosphines (Trost ligand) considered as one of the most efficient Pd catalysts for enantioselective allylic alkylation reactions.[33]

Results reported in Table 4 show that (*R,R*)-DACH gave a slightly better diastereoselection in the case of the methyl azlactone **7** (88 vs 86 de, entries 5−7), and a remarkable matching effect was observed in the case of the more sterically hindered isopropyl (>96% de) and benzyl derivatives (92% de). Notably, when a catalytic amount of base (20%) was used in combination with the presence of 4 Å molecular sieves the reaction proceeds without loss in diastereoselectivity, and in addition, yields were substantially increased to 88−90% (entries 16 and 26).

The underlying causes for the improvement of stereoselectivity observed with (*R,R*)-DACH are difficult to be rationalized. An explanation based (solely) on the enlargement of the bite angle relies on tenuous ground as it is not quite consistent with the results obtained in the case of achiral phosphines.

The "cartoon model" proposed by Trost and based on steric deactivation of the nucleophile by the pendant phenyl groups of the ligand[22] has been recently questioned by Lloyd-Jones and collaborators.[38] They demonstrated that η^3-cyclohexenyl complexes, at 2−4.2 mM concentrations, exist as monomeric *exo*-isomers, and the approach of a malonate anion is guided "by an H-bonding interaction between the enolate oxygen of the malonate and the amide NH on the concave surface of Pd-coordinated (*R,R*)-DACH". This interaction is particularly important in our case where a weakly coordinating escort ion of the enolate was used. Transposed to our substrate, this selectivity model is outlined in cartoon form in Figure 3.

Finally control experiments were performed as we have wondered whether the use of solvents other than THF and DCM, which were shown to be optimal when using achiral dppe, would further improve stereoselectivity. It was indeed fortunate that these control experiments were carried out. Conducting the reaction in toluene or dioxane had a detrimental effect on the levels of stereoselectivity while showing little impact on the reactivity (Table 5). The best results were obtained performing the allylic alkylation in MeCN which allowed the diastereoisomeric ratios to be improved to values ≥99:1.

Configurational assignments were postponed to the preparation of a more advanced lactone intermediates **14**−**16** in which the presence of a more rigid fused bicyclic system could allow to determine stereochemical correlations by NOE experiments. In the event, treatment of **11a**−**13a** with catalytic OsO_4 and NMO

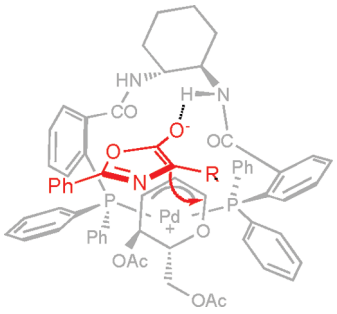


Figure 3. Cartoon model for the transition state of the allylic alkylation reaction with (*R,R*)-DACH.

Table 5. Solvent Optimization Studies

entry[a]	azlactone	solvent[b]	time (h)	isolated yield[c] (%)	dr[d] (**11a**/**11b**)
1	**7** (CH_3)	THF	0.3	78	94:6
2		DCM	1	72	95:5
3		dioxane	0.6	57	85:15
4		$PhCH_3$	0.3	71	86:14
5		MeCN	0.3	82	**99:1**
6		MeCN	0.7	82[e,f]	**99:1**
7	**8** (iPr)	MeCN	1	79	**>99:1**
8		MeCN	1	84[e,f]	**>99:1**
9	**9** (CH_2Ph)	MeCN	0.5	81	**99:1**
10		MeCN	0.7	84[e]	**99:1**

[a] Reaction conditions: reactions were performed at rt on a 0.075−0.15 mmol scale (0.1 M), 1.0 equiv of α-pseudoglucal, 2.0 equiv of azlactone, 1.3 equiv of TEA, 1.5 mol % of $Pd_2(dba)_3$−chloroform adduct as catalyst precursor, and 6 mol % of (*R,R*)-DACH phenyl Trost ligand. [b] All solvents were freshly distilled from the appropriate drying agent. [c] Isolated yield of the major diastereomer. [d] dr = diastereomeric ratio, determined by 400 MHz ^{1}H NMR analysis of the crude mixture: average from diagnostic signals of H-2′, H-3′, and H-4′. [e] Reaction performed with 0.2 equiv of TEA. [f] Reaction performed with 4 Å molecular sieves.

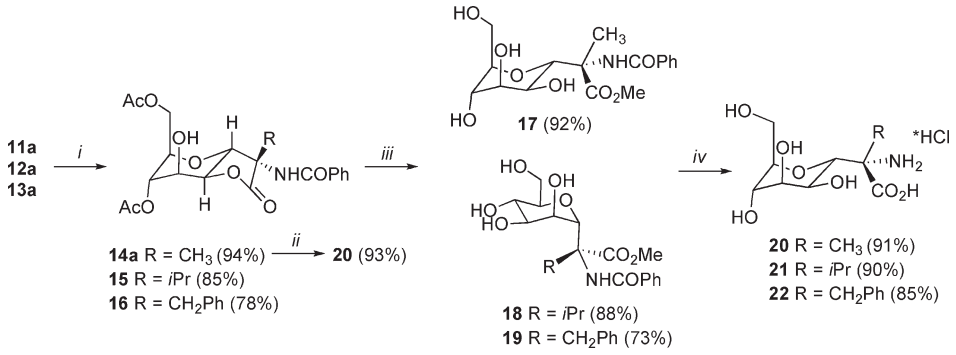
afforded directly lactones **14**−**16** as single diastereoisomers in satisfactory yields (Scheme 3).

Combined analysis of coupling constants and NOE correlations between relevant hydrogen atoms clearly demonstrated the *S* configuration of the quaternary lactone stereocenter, the α stereochemistry of the anomeric carbon, and the *β*-attack of the OsO_4 reagent from the upper face of the sugar moiety (Figure 4). Particularly diagnostic for the α anomeric configuration was the NOE between H-1′ and H-6′a or H-6′b. The *S* configuration of the quaternary stereocenter was evidenced by NOE correlation between the H-1′ and the methyl, methylene, or methine hydrogens of the α-*N*-benzoyl lactone substituents, while the benzamido proton was correlated to H-2′. Worthy of note is the preference of the pyranose ring to adopt a $^1C_4$ conformation, placing the most sterically demanding substituent at C-1′ in an equatorial position, as evidenced by the large coupling constants (9.8−10.0 Hz) between H-1′ and H-2′.

Configurational assignment of the minor diastereoisomer **11b** was made in an analogous fashion by conversion into the lactone **14b**. The α-mannosyl configuration of the anomeric center was evidenced by an NOE between H-1′ and H-6′a or H-6′b and the 10 Hz coupling constant relating H-1′ and H-2′. The opposite *R* configuration of the quaternary stereocenter was deduced by the presence of NOE between the methyl substituent and H-2′.

dx.doi.org/10.1021/jo2002962 |*J. Org. Chem.* 2011, 76, 5247–5257

Scheme 3[a]



[a] Reagents and conditions: (i) OsO_4, NMO, Me_2CO-H_2O, rt, 24 h; (ii) 6 N, HCl, 80 °C, 4 h; (iii) MeONa, MeOH, rt, few minutes; (iv) (1) LiOH, THF−MeOH, rt, 3 h, (2) 6 N, HCl, 80 °C, 4 h.

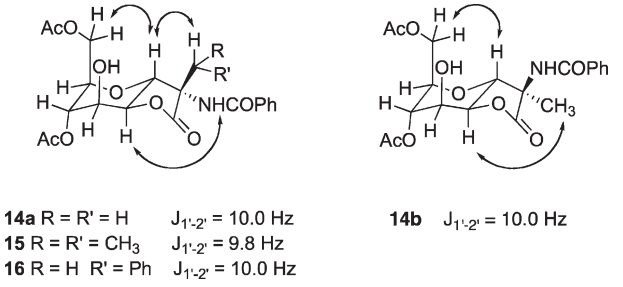


Figure 4. Relevant coupling constants and NOEs exhibited by compounds **14a**, **14b**, **15**, and **16**.

Final hydrolysis of lactone **14a** with 6 N HCl at 80 °C afforded in 93% yield the final α-D-*C*-mannosyl-(*S*)-alanine **20** completely identical (^{1}H and ^{13}C NMR, IR, ESI-MS, and α_D) with a sample previously prepared by us through the sequence reported in ref 20b.

Final acid hydrolysis proceeded uneventfully only in the case of the alanine derivative **14a**, while mannosyl lactones **15** and **16** were resistant even to harsh reaction conditions and gave only trace amounts of the desired amino acids **21** and **22**. After extensive experimentation, this lack of reactivity could be circumvented by a somewhat awkward, but high yielding, three-step sequence. Treatment of **15** and **16** with a methanol solution of sodium methoxide simultaneously removed the acetate groups and converted the lactone function into the corresponding methyl esters **18** and **19**. Saponification of **18** and **19** with LiOH followed by hydrolysis of the residual benzamido group with 6 N HCl afforded the final amino acids **21** and **22** in 90% and 85% yield, respectively. The same three sequence procedure could also be performed with high yields in the case of the alanine derivative **14a** via methyl ester intermediate **17**.

In summary, we have utilized a catalytic asymmetric allylic alkylation for the synthesis of quaternary α-D-*C*-mannosyl-(*S*)-amino acids. The synthesis proceeds in good overall yield starting from commercial tri-*O*-acetyl-D-glucal and racemic *N*-benzoyl-α-amino acids. The main features of this method are the conciseness of the synthetic sequence and the complete stereocontrol of the key allylic alkylation step leading to the generation of two new stereocenters. Experiments to explore the versatility of this methodology for the synthesis of analogues *C*-glucosyl and *C*-galactosyl amino acids are currently underway. In addition, the potential of these compounds as glycomimetics will be evaluated.

EXPERIMENTAL SECTION

Synthesis of 1′-*O*-*tert*-Butoxycarbonyl-4′,6′-di-*O*-acetyl-2′,3′-dideoxy-α/*β*-D-erythro-2′-hexenopyranosides 10a and 10b. Triacetyl glucal (10 g, 18.4 mmol) was dissolved in boiling water (180 mL, 0.1 M), and hydroquinone was added (646 mg, 2.94 mmol). The reaction was stirred for 1 h in the dark. After reaction completion was monitored by TLC analysis (hexane/AcOEt 70:30), most of the water was removed under reduced pressure. The crude was dissolved in DCM (90 mL, 0.2 M) and added with di-*tert*-butyl dicarbonate (4.4 g, 20.2 mmol), Et_3N (2.8 mL, 20.2 mmol), and DMAP (112 mg, 0.92 mmol). After reaction completion (0.5 h), the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography (hexane/ethyl acetate/chloroform 75:17:5) to obtain the pure diastereisomers **10a** (α-anomer) (76%) and **10b** (*β*-anomer) (15%). Compound **10a** was obtained as a colorless oil: R_f = 0.42 (hexane/AcOEt 75:25); $[\alpha]^{22}_D$ = +42.7 (c = 0.99, $CHCl_3$); IR (neat, cm^{-1}) 1738, 1369, 1222, 1149, 1029, 938, 844, 729; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H, *t*-Bu), 2.07 (s, 3H, AcO), 2.09 (s, 3H, AcO), 4.10−4.17 (m, 1H, H-5′), 4.19 (dd, $J_{6'a-6'b}$ = 12.3 Hz, $J_{6'a-5'}$ = 2.6 Hz, 1H, H-6′a), 4.23 (dd, $J_{6'b-6'a}$ = 12.3 Hz, $J_{6'b-5'}$ = 4.9 Hz, 1H, H-6′b), 5.39 (ddd, $J_{4'-5'}$ = 9.7 Hz, $J_{4'-3'}$ = 3.5 Hz, $J_{4'-2'}$ = 1.8 Hz, 1H, H-4′), 5.89 (ddd, $J_{2'-3'}$ = 10.2 Hz, $J_{2'-1'}$ = 2.9 Hz, $J_{2'-4'}$ = 1.9 Hz, 1H, H-2′), 6.04 (br d, $J_{3'-2'}$ = 10.2 Hz, 1H, H-3′), 6.15−6.19 (m, 1H, H-1′); ^{13}C NMR ($CDCl_3$,100 MHz) δ 21.2, 21.3, 28.1, 62.9 (t), 64.9, 69.1, 83.4 (s), 90.7, 125.8, 131.3, 152.4 (s), 170.4 (s), 171.1 (s); MS (ESI) m/z 352.9 $[M + Na]^+$, 682.6 $[2M + Na]^+$. Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.71. Found: C, 54.68; H, 6.72. Compound **10b** was obtained as a white solid: mp 45−46 °C; R_f = 0.36 (hexane/AcOEt 75:25); $[\alpha]^{22}_D$ = +89.0 (c = 0.97, $CHCl_3$); IR (neat, cm^{-1}) 1736, 1369, 1226, 1158, 1023, 936, 844, 730; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H, *t*-Bu), 2.08 (s, 6H, AcO), 4.17−4.29 (m, 3H, H-6′a + H-6′b + H-5′), 5.10−5.15 (m, 1H, H-4′), 6.00 (ddd, $J_{2'-3'}$ = 10.2 Hz, $J_{2'-1'}$ = 2.4 Hz, $J_{2'-4'}$ = 0.8 Hz, 1H, H-2′), 6.13 (ddd, $J_{3'-2'}$ = 10.2 Hz, $J_{3'-4'}$ = 4.6 Hz, $J_{3'-1'}$ = 1.3 Hz, 1H, H-3′), 6.18−6.21 (m, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 21.3, 28.1, 63.3, 63.4 (t), 73.3, 83.5 (s), 89.7, 126.5, 128.4, 152.4 (s), 170.7 (s), 170.9 (s); MS (ESI) m/z 352.9 $[M + Na]^+$, 682.6 $[2M + Na]^+$. Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.71. Found: C, 54.62; H, 6.74.

General Procedure A: Synthesis of Compounds 11a−13a. To a solution of azlactones **7**−**9** (0.79 mmol) in 2.5 mL of dry THF, under nitrogen, were added sequentially triethylamine (0.51 mmol), a solution of the α-pseudoglucal **10a** (0.39 mmol) in 1 mL of dry THF, and the palladium complex prepared by mixing $Pd_2(dba)_3CHCl_3$ (1.5 mol %) and 1,2-bis(diphenylphosphino)ethane (6 mol %) under nitrogen atmosphere in 1 mL of dry THF. The reaction mixture was stirred at room temperature (2−4 h). After reaction completion was monitored

dx.doi.org/10.1021/jo2002962 |J. Org. Chem. 2011, 76, 5247–5257

by TLC analysis, phosphate buffer was added to quench the reaction. THF was removed under reduced pressure, and the aqueous phase was extracted with DCM for **11a** and **12a** and AcOEt for **13a**. The organic phases were collected, dried with anhydrous Na_2SO_4, and evaporated in vacuo. The crude mixture was purified by flash chromatography (hexane/ethyl acetate 75:25) to obtain the pure major diastereisomers **11a** (85%), **12a** (79.0%), and **13a** (73.0%) and the corresponding minor diastereomers **11b** (5%), **12b** (5%), and **13b** (7%).

(4*S*)-4-Methyl-4-(4′,6′-di-*O*-acetyl-2′-3′-dideoxy-α-D-erythro-2′-hexenopyranosyl)-2-phenyl-5(4*H*)-oxazolone (11a). Compound **11a** was obtained as a colorless oil, following general procedure **A**: R_f = 0.25 (hexane/AcOEt 75:25); $[\alpha]^{22}_D$ = −24.4 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1816, 1737, 1654, 1580, 1544, 1494, 1451, 1369, 1321, 1291, 1226, 1153, 1106, 1085, 1070, 1031, 1003, 940, 885, 872, 850, 809, 780, 750, 721, 696, 667; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (s, 3H, CH_3), 2.02 (s, 3H, AcO), 2.07 (s, 3H, AcO), 4.18 (dd, $J_{6'a-6'b}$ = 12.0 Hz, $J_{6'a-5'}$ = 3.4 Hz, 1H, H-6′a), 4.23 (dd, $J_{6'b-6'a}$ = 12.0 Hz, $J_{6'b-5'}$ = 6.1 Hz, 1H, H-6′b), 4.38 (ddd, $J_{5'-4'}$ = 7.0 Hz, $J_{5'-6'b}$ = 6.2 Hz, $J_{5'-6'a}$ = 3.4 Hz, 1H, H-5′), 4.48 (ddd, $J_{1'-2'} = J_{1'-3'} = J_{1'-4'}$ = 2.4 Hz, 1H, H-1′), 5.14 (dddd, $J_{4'-5'}$ = 7.0 Hz, $J_{4'-3'} = J_{4'-1'}$ = 2.4 Hz, $J_{4'-2'}$ = 1.7 Hz, 1H, H-4′), 5.78 (ddd, $J_{2'-3'}$ = 10.5 Hz, $J_{2'-1'}$ = 2.5 Hz, $J_{2'-4'}$ = 1.7 Hz, 1H, H-2′), 5.95 (td, $J_{3'-2'}$ = 10.5 Hz, $J_{3'-1'} = J_{3'-4'}$ = 2.4 Hz, 1H, H-3′), 7.46−7.54 (m, 2H, ArH), 7.56−7.63 (m, 1H, ArH), 7.98−8.05 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$,100 MHz) δ 21.0, 21.1, 21.4, 63.3 (t), 64.8, 71.5, 72.9 (s), 75.8, 126.1 (s), 126.2, 128.5, 128.6, 129.2, 133.3, 160.7 (s), 170.7 (s), 171.2 (s), 178.9 (s); MS (ESI) m/z 388.0 $[M + H]^+$, 410.1 $[M + Na]^+$, 796.6 $[2M + Na]^+$. Anal. Calcd. for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.19; H, 5.47; N, 3.61

(4*R*) Epimer 11b. Compound **11b** was obtained as an oil, following general procedure **A**: R_f = 0.21 (hexane/AcOEt 75:25); $[\alpha]^{22}_D$ = −8.9 (c =1.0, $CHCl_3$); IR (neat, cm^{-1}) 1823, 1733, 1651, 1580, 1494, 1451, 1370, 1322, 1291, 1224, 1093, 1044, 1005, 883, 812, 781, 718, 699; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.56 (s, 3H, CH_3), 1.82 (s, 3H, AcO), 2.02 (s, 3H, AcO), 3.96−4.08 (m, 3H, H-5′,H-6′a, H-6′b), 4.59 (ddd, $J_{1'-2'} = J_{1'-3'} = J_{1'-4'}$ = 2.2 Hz, 1H, H-1′), 5.00−5.06 (m, 1H, H-4′), 6.06 (ddd, $J_{2'-3'}$= 10.5 Hz, $J_{2'-1'} = J_{2'-4'}$ = 2.2 Hz, 1H, H-2′), 6.13 (ddd, $J_{3'-2'}$ = 10.5 Hz, $J_{3'-1'} = J_{3'-4'}$ = 2.2 Hz, 1H, H-3′), 7.47−7.54 (m, 2H, ArH), 7.57−7.64 (m, 1H, ArH), 8.00−8.05 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$,100 MHz) δ 19.8, 20.3, 20.8, 62.7 (t), 64.2, 71.4, 73.4 (s), 74.7, 125.3, 125.6 (s), 128.0, 128.1, 128.7, 132.9, 161.5 (s), 170.2 (s), 170.6 (s), 178.9 (s); MS (ESI) m/z 388.2 $[M + H]^+$, 410.2 $[M + Na]^+$, 796.9 $[2M + Na]^+$. Anal. Calcd. for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.13; H, 5.45; N, 3.71.

(4*S*)-4-Isopropyl-4-(4′,6′-di-*O*-acetyl-2′-3′-dideoxy-α-D-erythro-2′-hexenopyranosyl)-2-phenyl-5(4*H*)-oxazolone (12a). Compound **12a** was obtained as a white solid, following general procedure **A**: R_f = 0.35 (hexane/AcOEt 75:25); mp 100−101 °C; $[\alpha]^{22}_D$ = −70.7 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1813, 1739, 1654, 1602, 1581, 1513, 1494, 1472, 1451, 1423, 1369, 1320, 1291, 1225, 1196, 1176, 1157, 1092, 1042, 1020, 975, 951, 928, 880, 834, 810, 779, 723, 697, 671; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (d, J = 6.9 Hz, 3H, CH_3iPr), 1.11 (d, J = 6.8 Hz, 3H, CH_3iPr,), 2.00 (s, 3H, AcO), 2.07 (s, 3H, AcO), 2.51 (septuplet, J = 6.9 Hz, 1H, CHiPr), 4.17 (dd, $J_{6'a-6'b}$ = 11.9 Hz, $J_{6'a-5'}$ = 3.5 Hz, 1H, H-6′a), 4.22 (dd, $J_{6'b-6'a}$ = 11.9 Hz, $J_{6'b-5'}$ = 6.0 Hz, 1H, H-6′b), 4.37 (ddd, $J_{5'-4'}$ = 7.1 Hz, $J_{5'-6'b}$ = 6.0 Hz, $J_{5'-6'a}$ = 3.5 Hz, 1H, H-5′), 4.73 (ddd, $J_{1'-2'} = J_{1'-3'} = J_{1'-4'}$ = 2.4 Hz, 1H, H-1′), 5.13 (m, 1H, H-4′), 5.76 (ddd, $J_{3'-2'}$ = 10.5 Hz, $J_{3'-1'}$ = 2.4 Hz, $J_{3'-4'}$ = 1.6 Hz, 1H, H-3′), 5.94 (ddd, $J_{2'-3'}$ = 10.5 Hz, $J_{2'-1'} = J_{2'-4'}$ = 2.4 Hz, 1H, H-2′), 7.46−7.54 (m, 2H, ArH), 7.55−7.62 (m, 1H, ArH), 7.98−8.07 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.9, 17.4, 21.1, 21.5, 32.7, 63.4 (t), 64.9, 71.5, 73.4, 79.8 (s), 126.1 (s), 126.5, 128.4, 128.5, 129.2, 133.2, 160.9 (s), 170.8 (s), 171.2 (s), 177.9 (s); MS (ESI) m/z 416.1 $[M + H]^+$, 438.1 $[M + Na]^+$, 852.7 $[2M + Na]^+$. Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.72; H, 6.06; N, 3.52

(4*R*) Epimer 12b. Compound **12b** was obtained as a colorless oil, following general procedure **A**: R_f = 0.22 (hexane/AcOEt 75:25); $[\alpha]^{22}_D$ = −68.1 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1813, 1738, 1650, 1580, 1494, 1451, 1369, 1321, 1290, 1225, 1158, 1138, 1097, 1078, 1045, 1021, 972, 881, 815, 780, 753, 722, 693, 670; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (d, J = 6.8 Hz, 3H, CH_3 iPr), 1.10 (d, J = 6.9 Hz, 3H, CH_3iPr), 1.87 (s, 3H, AcO), 2.04 (s, 3H, AcO), 2.44 (septuplet, 1H, CHiPr), 4.02 (dd, $J_{6'a-6'b}$ = 11.8 Hz, $J_{6'a-5'}$ = 3.2 Hz, 1H, H-6′a), 4.09 (dd, $J_{6'b-6'a}$ = 11.8 Hz, $J_{6'b-5'}$ = 6.9 Hz, 1H, H-6′b), 4.17 (ddd, $J_{5'-4'} = J_{5'-6'b}$ = 6.9 Hz, $J_{5'-6'a}$ = 3.2 Hz, 1H, H-5′), 4.79 (ddd, $J_{1'-2'} = J_{1'-3'} = J_{1'-4'}$ = 2.3 Hz, 1H, H-1′), 5.06 (dddd, $J_{4'-5'}$ = 6.9 Hz, $J_{4'-1'} = J_{4'-2'} = J_{4'-3'}$ = 2.3 Hz, 1H, H-4′), 6.01 (ddd, $J_{2'-3'}$ = 10.5 Hz, $J_{2'-1'} = J_{2'-4'}$ = 2.3 Hz, 1H, H-2′), 6.06 (ddd, $J_{3'-2'}$ = 10.5 Hz, $J_{3'-1'} = J_{3'-4'}$ = 2.3 Hz, 1H, H-3′), 7.49−7.57 (m, 2H, ArH), 7.59−7.66 (m, 1H, ArH), 8.01−8.09 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 17.0, 20.4, 20.9, 31.8, 62.7 (t), 64.3, 71.2, 72.1, 80.1 (s), 125.5 (s), 125.7, 128.0, 128.1, 128.7, 132.8, 161.6 (s), 170.2 (s), 170.6 (s), 177.6 (s); MS (ESI) m/z 416.1 $[M + H]^+$, 438.1 $[M + Na]^+$, 852.8 $[2M + Na]^+$. Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.47; H, 6.08; N, 3.41.

(4*S*)-4-Benzyl-4-(4′,6′-di-*O*-acetyl-2′-3′-dideoxy-α-D-erythro-2′-hexenopyranosyl)-2-phenyl-5(4*H*)-oxazolone (13a). Compound **13a** was obtained as a white solid, following general procedure **A**: R_f = 0.29 (hexane/AcOEt 75:25); mp 37−38 °C; $[\alpha]^{22}_D$ = −172.6 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1812, 1736, 1653, 1600, 1580, 1494, 1451, 1430, 1369, 1321, 1291, 1225, 1195, 1141, 1098, 1046, 1025, 976, 892, 873, 835, 798, 779, 750, 698, 667; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 6H, AcO), 3.28 (d, J = 13.5 Hz, 1H, CH_2Ph), 3.55 (d, J = 13.5 Hz, 1H, CH_2Ph), 4.25−4.29 (m, 2H, H-6′a, H-6′b), 4.58 (ddd, $J_{5'-4'}$ = 7.8, $J_{5'-6'b}$ = 5.3 Hz, $J_{5'-6'a}$ = 4.2 Hz, 1H, H-5′), 4.64 (ddd, $J_{1'-2'} = J_{1'-3'} = J_{1'-4'}$= 2.3 Hz, 1H, H-1′), 5.16−5.22 (m, 1H, H-4′), 5.75 (ddd, $J_{3'-2'}$ = 10.4 Hz, $J_{3'-1'}$ = 2.4 Hz, $J_{3'-4'}$ = 1.6 Hz, 1H, H-3′), 5.93 (td, $J_{2'-3'}$ = 10.4 Hz, $J_{2'-1'} = J_{2'-4'}$ = 2.3 Hz, 1H, H-2′), 7.08−7.19 (m, 5H, ArH), 7.38−7.46 (m, 2H, ArH), 7.49−7.57 (m, 1H, ArH), 7.81−7.88 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$,100 MHz) δ: 21.2, 21.4, 40.8 (t), 63.6 (t), 65.1, 71.6, 75.7, 78.1 (s), 125.8 (s), 126.2, 127.7, 128.3, 128.6, 129.0, 129.1, 130.6, 133.1, 134.3 (s), 160.6 (s), 170.7 (s), 171.2 (s), 177.8 (s); MS (ESI) m/z 464.0 $[M + H]^+$, 486.1 $[M + Na]^+$, 948.7 $[2M + Na]^+$. Anal. Calcd. for $C_{26}H_{25}NO_7$: C, 67.38; H, 5.44; N, 3.02. Found: C, 67.51; H, 5.33; N, 3.13

(4*R*) Epimer 13b. Compound **13b** was obtained as a white solid following general procedure **A**: R_f = 0.24 (hexane/AcOEt 7:3); mp 48−50 °C; $[\alpha]^{22}_D$ = −196.0 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1817, 1735, 1650, 1579, 1494, 1451, 1369, 1321, 1291, 1225, 1091, 1045, 994, 670; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84 (s, 3H, AcO), 2.04 (s, 3H, AcO), 3.24 (d, J = 13.2 Hz, 1H, CH_2Ph), 3.30 (d, J = 13.2 Hz, 1H, CH_2Ph), 4.03 (dd, $J_{6'a-6'b}$ = 11.9 Hz, $J_{6'a-5'}$ = 3.2 Hz, 1H, H-6′a) 4.08 (dd, $J_{6'b-6'a}$ = 11.9 Hz, $J_{6'b-5'}$ = 6.9 Hz, 1H, H-6′b), 4.17 (ddd, $J_{5'-4'} = J_{5'-6'b}$ = 6.9, $J_{5'-6'a}$ = 3.2 Hz, 1H, H-5′), 4.74 (ddd, $J_{1'-2'} = J_{1'-3'} = J_{1'-4'}$ = 2.2 Hz, 1H, H-1′), 5.08 (dddd, $J_{4'-5'}$ = 6.9 Hz, $J_{4'-2'} = J_{4'-1'}$ = 2.2 Hz, $J_{4'-3'}$ = 1.5 Hz, 1H, H-4′), 6.10 (ddd, $J_{2'-3'}$ = 10.5 Hz, $J_{2'-1'} = J_{2'-4'}$ = 2.2 Hz, 1H, H-2′), 6.16 (ddd, $J_{3'-2'}$ = 10.5 Hz, $J_{3'-1'}$ = 2.1 Hz, $J_{3'-4'}$ = 1.5 Hz, 1H, H-3′), 7.12−7.19 (m, 5H, ArH), 7.40−7.48 (m, 2H, ArH), 7.52−7.58 (m, 1H, ArH), 7.84−7.89 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$,100 MHz) δ 20.4, 20.8, 39.3 (t), 62.8 (t), 64.3, 71.3, 74.3, 78.8 (s), 125.4 (s), 125.5, 127.3, 127.9, 128.2, 128.3, 128.6, 130.1, 132.8, 133.2 (s), 161.6 (s), 170.2 (s), 170.6 (s), 177.4 (s); MS (ESI) m/z 464.0 $[M + H]^+$, 486.1 $[M + Na]^+$, 948.7 $[2M + Na]^+$. Anal. Calcd. for $C_{26}H_{25}NO_7$: C, 67.38; H, 5.44; N, 3.02. Found: C, 67.24; H, 5.37; N, 3.19

General Procedure B: Synthesis of Compounds 14a, 14b, 15, and 16. Glycosylated azlactones **11a**−**13a** and **11b** (0.73 mmol) were dissolved, under nitrogen atmosphere, in acetone (7 mL) and water (50 μL) and added with NMO (1.09 mmol) and a 2.5% w/v solution of OsO_4 in *t*-BuOH (0.07 mmol). The reaction mixture was stirred overnight at room temperature. After reaction completion by

TLC analysis, the solvent was evaporated in vacuo, and the crude mixture was purified by flash chromatography to obtain **14a** (94%), **14b** (70%), **15** (85%), and **16** (78%).

2-(4′,6′-Di-*O*-acetyl-α-D-mannopyranosyl)-2-benzamido-(2*S*)-propionic Acid 1′,2′-Lactone (14a). Compound **14a** was obtained as a white solid, following general procedure **B**: R_f = 0.35 (AcOEt/hexane 60:40); mp 90−95 °C; $[\alpha]^{22}_D$ = −78.6 (*c* = 1.5, $CHCl_3$); IR (neat, cm^{-1}) 3316, 1791, 1738, 1644, 1601, 1580, 1536, 1491, 1447, 1369, 1220, 1181, 1105.8, 1088, 1027, 970, 940, 905, 883, 851, 802, 703, 661; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (s, 3H, CH_3), 2.04 (s, 3H, AcO), 2.11 (s, 3H, AcO), 2.93−3.14 (br s, 1H, O*H*, exchanges with D_2O), 4.02 (dd, $J_{6'a-6'b}$ = 12.3 Hz, $J_{6'a-5'}$ = 4.5 Hz, 1H, H-6′a), 4.20 (dd, $J_{5'-6'b}$ = 9.7 Hz, $J_{5'-6'a}$ = 4.5 Hz, 1H, H-5′), 4.28 (d, $J_{1'-2'}$ = 10.0 Hz, 1H, H-1′), 4.43−4.50 (m, 1H, H-3′), 4.58 (dd, $J_{2'-1'}$ = 10.0 Hz, $J_{2'-3'}$ = 2.4 Hz, 1H, H-2′), 4.97 (d, $J_{4'-3}$ = 3.3 Hz, 1H, H-4′), 5.03 (dd, $J_{6'b-6'a}$ = 12.3 Hz, $J_{6'b-5'}$ = 9.7 Hz, 1H, H-6′b), 6.20 (s, 1H, N*H*), 7.40−7.49 (m, 2H, ArH), 7.50−7.57 (m, 1H, ArH), 7.74−7.83 (m, 2H, ArH); ^{13}C NMR (CDCl3, 100 MHz) δ: 21.3, 21.4, 23.0, 57.4 (s), 60.9 (t), 65.9, 71.3, 72.2, 75.8, 77.7, 127.7, 129.1, 132.6, 133.5 (s), 167.3 (s), 170.2 (s), 171.2 (s), 173.0 (s); MS (ESI) *m*/*z* 422.0 $[M + H]^+$ 444.1 $[M + Na]^+$, 864.9. $[2M + Na]^+$. Anal. Calcd. for $C_{20}H_{23}NO_9$: C, 57.00; H, 5.50; N, 3.32. Found: C, 57.23; H, 5.47; N, 3.42

2-(4′,6′-Di-*O*-acetyl-α-D-mannopyranosyl)-2-benzamido-(2*R*)-propionic Acid 1′,2′-Lactone (14b). Compound **14b** was obtained as a white solid, following general procedure **B**: R_f = 0.23 (AcOEt/hexane 60:40); mp 248 °C; $[\alpha]^{22}_D$ = +28.7 (*c* = 0.81, DMSO); IR (neat, cm^{-1}) 3341, 1783, 1722, 1707, 1661, 1517, 1283, 1269, 1244, 1116, 1072, 1044, 910, 807, 733; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.45 (s, 3H, CH_3), 1.88 (s, 3H, AcO), 2.09 (s, 3H, AcO), 4.02 (dd, $J_{6'a-6'b}$ = 11.8 Hz, $J_{6'a-5'}$ = 4.7 Hz, 1H, H-6′a), 4.10 (dd, $J_{5'-6'b}$ = 9.1 Hz, $J_{5'-6'a}$ = 4.7 Hz, 1H, H-5′), 4.26 (br t, $J_{3'-2'} = J_{3'-4'}$ = 2.8 Hz, 1H, H-3′), 4.28 (dd, $J_{2'-1'}$ = 10.0 Hz, $J_{2'-3'}$ = 2.4 Hz, 1H, H-2′), 4.64 (dd, $J_{6'b-6'a}$ = 11.8 Hz, $J_{6'b-5'}$ = 9.1 Hz, 1H, H-6′b), 4.81 (d, $J_{4'-3'}$ = 2.9 Hz, 1H, H-4′), 5.21 (d, $J_{1'-2'}$ = 10.0 Hz, 1H, H-1′), 6.27 (bs, 1H, O*H*, exchanges with D_2O), 7.48 (app t, *J* = 7.4 Hz, 2H, ArH), 7.56 (app t, *J* = 7.3 Hz, 1H, ArH), 7.86 (app d, *J* = 7.3 Hz, 2H, ArH), 8.67 (s, 1H, N*H*, partially exchanges with D_2O); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 15.0, 21.3, 21.7, 59.8 (s), 61.2 (t), 65.6, 67.6, 72.2, 75.5, 76.9, 128.5, 129.0, 132.4, 134.5 (s), 166.9 (s), 170.2 (s), 170.6 (s), 174.1 (s); MS (ESI) *m*/*z* 422.0 $[M + H]^+$ 444.1 $[M + Na]^+$, 864.9 $[2M + Na]^+$. Anal. Calcd for $C_{20}H_{23}NO_9$: C, 57.00; H, 5.50; N, 3.32. Found: C, 57.11; H, 5.43; N, 3.42

2-(4′,6′-Di-*O*-acetyl-α-D-mannopyranosyl)-2-benzamido-(2*S*)-3-methylbutanoic Acid 1′,2′-Lactone (15). Compound **15** was obtained as a white solid, following general procedure **B**: R_f = 0.56 (AcOEt/hexane 60:40); mp 47−50 °C; $[\alpha]^{22}_D$ = −50.6 (*c* = 1.0, $CDCl_3$); IR (neat, cm^{-1}) 3365, 1790, 1736, 1655, 1601, 1580, 1516, 1487, 1449, 1370, 1225, 1163, 1126, 1094, 1068, 1025, 977, 935, 906, 864, 800, 711, 694; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (d, *J* = 6.8 Hz, 3H, CH_3iPr), 1.19 (d, *J* = 6.8 Hz, 3H, CH_3iPr), 2.04 (s, 3H, AcO), 2.09 (s, 3H, AcO), 2.48 (septuplet, *J* = 6.8 Hz, 1H, C*H*iPr), 2.70−2.85 (br s, 1H, O*H*, exchanges with D_2O), 4.22 (dd, $J_{6'a-6'b}$ = 13.8 Hz, $J_{6'a-5'}$ = 4.9 Hz, 1H, H-6′a), 4.23 (dd, $J_{5'-6'b}$ = 11.3 Hz, $J_{5'-6'a}$ = 4.9 Hz, 1H, H-5′), 4.43 (d, $J_{1'-2'}$ = 9.8 Hz, 1H, H-1′), 4.46−4.50 (m, 1H, H-3′), 4.55 (dd, $J_{2'-1'}$ = 9.8 Hz, $J_{2'-3'}$ = 2.4 Hz, 1H, H-2′), 4.85 (ddd, $J_{6'b-6'a}$ = 13.9 Hz, $J_{6'b-5'} = J_{6'b-3'}$ = 11.3 Hz, 1H, H-6′b), 4.98 (d, $J_{4'-3'}$ = 3.2 Hz, 1H, H-4′), 6.37 (s, 1H, N*H*), 7.44−7.52 (m, 2H, ArH), 7.53−7.59 (m, 1H, ArH), 7.78−7.84 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.0, 18.2, 21.2, 21.3, 33.4, 60.9 (t), 63.0 (s), 66.1, 67.9, 71.1, 75.1, 77.1, 127.6, 129.2, 132.6, 133.8 (s), 167.4 (s), 170.0 (s), 171.1 (s), 171.5 (s); MS (ESI) *m*/*z* 450.1 $[M + H]^+$ 472.2 $[M + Na]^+$, 921.0 $[2M + Na]^+$. Anal. Calcd for $C_{22}H_{27}NO_9$: C, 58.79; H, 6.06; N, 3.12. Found: C, 58.53; H, 6.15; N, 3.23

2-(4′,6′-Di-*O*-acetyl-α-D-mannopyranosyl)-2-benzamido-(2*S*)-3-phenylpropanoic Acid 1′,2′-Lactone (16). Compound **16** was obtained as a white solid, following general procedure **B**: R_f = 0.44 (AcOEt/hexane 60:40); mp 155−157 °C; $[\alpha]^{22}_D$ = −101 (*c* = 1.0, Py); IR (neat, cm^{-1}) 3320, 1794, 1739, 1720, 1653, 1595, 1579, 1531, 1494, 1458, 1364, 1225, 1144, 1106, 1030, 980, 935, 881, 799, 715, 698; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.96 (s, 3H, AcO), 2.14 (s, 3H, AcO), 3.26 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 3.38 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 4.02 (dd, $J_{6'a-6'b}$ = 12.2 Hz, $J_{6'a-5'}$ = 3.8 Hz, 1H, H-6′a), 4.05 (d, $J_{1'-2'}$ = 10.0 Hz, 1H, H-1′), 4.13−4.20 (m, 2H, H-3′,H-5′), 4.31−4.40 (m, 2H, H-2′, H-6′b), 4.75 (app d, *J* = 3.6 Hz, 1H, H-4′), 5.93 (s, 1H, O*H*, exchanges with D_2O), 7.15−7.21 (m, 2H, ArH), 7.24−7.31 (m, 3H, ArH), 7.48−7.55 (m, 2H, ArH), 7.56−7.63 (m, 1H, ArH), 7.87−7.94 (m, 2H, ArH), 8.64 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.5, 21.6, 40.5 (t), 61.6 (s), 61.8 (t), 64.5, 67.8, 71.9, 75.6, 76.8, 128.1, 128.6, 129.2, 129.3, 131.5, 132.7, 134.0 (s), 135.8 (s), 167.2 (s), 170.0 (s), 171.0 (s), 172.5 (s); MS (ESI) *m*/*z* 498.1 $[M + H]^+$, 520.1 $[M + Na]^+$, 1017.0 $[2M + Na]^+$. Anal. Calcd for $C_{26}H_{27}NO_9$: C, 62.77; H, 5.47; N, 2.82. Found: C, 62.83; H, 5.46; N, 2.82.

General Procedure C: Synthesis of Compounds 17−19. A solution of NaOMe, prepared from Na (2.44 mmol) in dry MeOH (6.9 mL), was added, under nitrogen atmosphere, to a solution of compounds **14**−**16** (0.61 mmol) in dry MeOH (9.4 mL). After a few minutes, TLC (AcOEt/MeOH 9:1) showed no residual starting material. HCl (1 N, 3 mL) was added to the reaction mixture. MeOH was removed under reduced pressure, and the residue was extracted with AcOEt. The organic layers were collected, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash chromatography (ethyl acetate/MeOH 90:10) yielding **17** (92%), **18** (88%), and **19** (73%).

2-(α-D-*C*-Mannopyranosyl)-(*S*)-*N*-benzoylalanine Methyl Ester (17). Compound **17** was obtained as a white solid, following general procedure **C**: R_f = 0.30 (AcOEt/MeOH 90:10); mp 79−83 °C; $[\alpha]^{22}_D$ = +68.6 (*c* = 1.0, CH_3OH); IR (neat, cm^{-1}) 3332, 2947, 1728, 1640, 1602, 1578, 1531, 1487, 1447, 1267, 1043, 690; ^{1}H NMR (D_2O, 400 MHz) δ 1.54 (s, 3H, CH_3), 3.23 (s, 0.55 H, N*H*, partially exchanges with D_2O), 3.60 (dd, $J_{6'a-6'b}$ = 12.1 Hz, $J_{6'a-5'}$ = 3.6 Hz, 1H, H-6′a), 3.67 (s, 3H, $COOCH_3$), 3.71 (dd, $J_{4'-3'}$ = 5.1 Hz, $J_{4'-5'}$ = 3.5 Hz, 1H, H-4′), 3.73−3.78 (m, 1H, H-5′), 3.81(dd, $J_{3'-2'}$ = 3.3 Hz, $J_{3'-4'}$ = 5.1 Hz, 1H, H-3′), 3.89 (dd, $J_{6'b-6'a}$ = 12.1 Hz, $J_{6'b-5'}$ = 8.4 Hz, 1H, H-6′b), 4.12 (d, $J_{1'-2'}$ = 8.3 Hz, 1H, H-1′), 4.16 (dd, $J_{2'-1'}$ = 8.3 Hz, $J_{2'-3'}$ = 3.3 Hz, 1H, H-2′), 7.38−7.45 (m, 2H, ArH), 7.49−7.55 (m, 1H, ArH), 7.60−7.65 (m, 2H, ArH); ^{13}C NMR (D_2O, 100 MHz) δ 17.3, 53.5, 59.4 (t), 62.3 (s), 66.2, 68.7, 71.1, 73.3, 79.4, 127.3, 129.3, 132.7 (s), 133.0, 169.3 (s), 174.8 (s); MS (ESI) *m*/*z* 370.1 $[M + H]^+$, 392.2 $[M + Na]^+$, 760.9 $[2M + Na]^+$. Anal. Calcd for $C_{17}H_{23}NO_8$: C, 55.28; H, 6.28; N, 3.79. Found: C, 55.17; H, 6.31; N, 3.90.

2-(α-D-*C*-Mannopyranosyl)-(*S*)-*N*-benzoylvaline Methyl Ester (18). Compound **18** was prepared following general procedure **C** as a white amorphous solid: R_f = 0.41 (AcOEt/MeOH 90:10); mp 72−76 °C; $[\alpha]^{22}_D$ = −11.3 (*c* = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3333, 2933, 1726, 1645, 1602, 1578, 1525, 1488, 1435, 1235, 1040, 797, 690; ^{1}H NMR (D_2O, 400 MHz) δ 0.90 (d, *J* = 6.8 Hz, 3H, CH_3iPr), 1.01 (d, *J* = 6.8 Hz, 3H, CH_3iPr), 2.63 (septuplet, *J* = 6.8 Hz, 1H, C*H*iPr), 3.47 (dd, $J_{3'-4'}$ = 8.6 Hz, $J_{3'-2'}$ = 3.4 Hz, 1H, H-3′), 3.53−3.71 (m, 4H, H-4′, H-5′, H-6′a, H-6′b), 3.68 (s, 3H, $COOCH_3$), 4.41 (dd, $J_{2'-3'}$ = 3.4 Hz, $J_{2'-1'}$ = 2.4 Hz, 1H, H-2′), 4.58 (d, $J_{1'-2'}$ = 2.4 Hz, 1H, H-1′), 7.37−7.45 (m, 2H, ArH), 7.48−7.55 (m, 1H, ArH), 7.60−7.65 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.3, 18.6, 32.2, 53.0, 61.8 (t), 67.9, 68.4, 69.7 (s), 72.1, 74.7, 79.1, 127.6, 129.1, 132.3, 134.9 (s), 168.6 (s), 171.9 (s); MS (ESI) *m*/*z* 398.2 $[M + H]^+$, 420.3 $[M + Na]^+$, 817.0 $[2M + Na]^+$. Anal. Calcd for $C_{19}H_{27}NO_8$: C, 57.42; H, 6.85; N, 3.52. Found: C, 57.21; H, 6.82; N, 3.52.

2-(α-D-*C*-Mannopyranosyl)-(*S*)-*N*-benzoylphenylalanine Methyl Ester (19). Compound **19** was prepared following general procedure **C** as a white amorphous solid: R_f = 0.36 (AcOEt/MeOH 90:10); mp 163−165 °C; $[\alpha]^{22}_D$ = −13.2 (*c* = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3320, 3171, 1732, 1639, 1602, 1578, 1517, 1487, 1451, 1437, 1221, 1032, 907, 700; ^{1}H NMR (D_2O, 400 MHz) δ 3.27 (d, *J* =

13.5 Hz, 1H, CH_2Ph), 3.53 (dd, $J_{3'-4'}$ = 7.7 Hz, $J_{3'-2'}$ = 3.4, 1H, H-3′), 3.59−3.64 (m, 1H, H-4′), 3.60 (d, J = 13.5 Hz, 1H, CH_2Ph), 3.66 (s, 3H, COOCH_3), 3.68−3.73 (m, 2H, H-6′a + H-6′b), 3.74−3.80 (m, 1H, H-5′), 4.24 (dd, $J_{1'-2'}$ = 4.3 Hz, 1H, H-1′), 4.31 (br t, J = 3.7 Hz, 1H, H-2′), 7.11−7.24 (m, 5H, ArH), 7.36−7.44 (app t, J = 7.7 Hz, 2H, ArH), 7.48−7.55 (app t, J = 7.7 Hz, 1H, ArH), 7.59 (app d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.7 (t), 53.5, 61.9 (t), 67.5 (s), 67.6, 68.1, 72.1, 77.2, 78.4, 127.4, 127.5, 128.6, 129.2, 130.7, 132.2, 135.0 (s), 135.8 (s), 168.4 (s), 172.8 (s); MS (ESI) m/z 446.2 $[M + H]^+$, 468.4 $[M + Na]^+$, 913.2 $[2M + Na]^+$. Anal. Calcd for $C_{23}H_{27}NO_8$: C, 62.01; H, 6.11; N, 3.14, Found: C, 62.19; H, 6.27; N, 3.18

General Procedure for the Synthesis of Lithium Salts of Compounds 17−19 (L17−L19). A solution of methyl esters **17**−**19** (0.17 mmol) in H_2O (1.7 mL, 0.1 M) was added with LiOH·H_2O (0.70 mmol). After 3 h, the reaction was complete. The solvent was removed under reduced pressure to obtain quantitatively the corresponding lithium salts **L17**−**L19**.

2-α-D-Mannopyranosyl-2-benzamido-(2*S*)-propionic acid lithium salt (L17): white solid; mp 108 °C; $[\alpha]^{22}_D$ = 36.64 (c = 0.5, D_2O); IR (neat, cm^{-1}) 3565, 1514, 1473, 1419, 968, 861, 690; ^{1}H NMR (D_2O, 400 MHz) δ 1.47 (s, 3H, CH_3), 1.78 (s, 0.4H, N*H*, partially exchanges with D_2O), 3.56 (dd, $J_{6'a-6'b}$ = 12.1 Hz, $J_{6'a-5'}$ = 3.0 Hz, 1H, H-6′a), 3.59 (dd, $J_{4'-3'}$ = 6.4 Hz, $J_{4'-5'}$ = 5.3 Hz, 1H, H-4′), 3.66−3.73 (m, 1H, H-5′), 3.74 (dd, $J_{3'-4'}$ = 6.4 Hz, $J_{3'-2'}$ = 3.8 Hz, 1H, H-3′) 3.79 (dd, $J_{6'b-6'a}$ = 12.1 Hz, $J_{6'b-5'}$ = 7.7 Hz, 1H, H-6′b), 4.10 (d, $J_{1'-2'}$ = 6.7 Hz, 1H, H-1′), 4.19 (dd, $J_{2'-1'}$ = 6.7 Hz, $J_{2'-3'}$ = 3.8 Hz, 1H, H-2′) 7.36−7.42 (m, 2H, ArH), 7.44−7.50 (m, 1H, ArH), 7.60−7. 67 (m, 2H, ArH); ^{13}C NMR (D_2O, 100 MHz) δ 18.6, 60.7 (t), 63.7 (s), 67.4, 69.2, 71.9, 75.7, 79.0, 127.2, 129.1, 132.3, 134.1 (s), 168.7 (s), 179.1 (s), MS (ESI) (negative ion mode) m/z 354.2 $[M - Li]^-$. Anal. Calcd for $C_{16}H_{20}LiNO_8$: C, 53.19; H, 5.58; N, 3.88. Found: C, 53.29; H, 5.43; N, 3.81.

2-α-D-Mannopyranosyl-2-benzamido-(2*S*)-3-methylbutanoic Acid Lithium Salt (L18): white solid; mp 105 °C; $[\alpha]^{22}_D$ = −99.5 (c = 0.52, CH_3OH); IR (neat, cm^{-1}) 3331, 1600, 1576, 1514, 1483, 1384; ^{1}H NMR (D_2O, 400 MHz) δ 0.87 (d, J = 6.8 Hz, 3H, CH_3*i*Pr), 0.91 (d, J = 6.8 Hz, 3H, CH_3*i*Pr), 2.66 (septuplet, J = 6.8 Hz, 1H, C*H*i*P*r), 3.49−3.59 (m, 3H), 3.61−3.70 (m, 2H), 4.33 (dd, $J_{2'-1'}$ = $J_{2'-3'}$ = 4.0 Hz, 1H, H-2′), 4.76 (d, $J_{1'-2'}$ = 4.0 Hz, 1H, H-1′), 7.36−7.43 (m, 2H, ArH), 7.44−7.51 (m, 1H, ArH), 7.63−7. 69 (m, 2H, ArH); ^{13}C NMR (D_2O, 100 MHz) δ 17.9, 18.0, 30.6, 61.8 (t), 69.1, 69.2, 70.8 (s), 72.0, 77.1, 78.9, 127.1, 129.1, 132.3, 135.1 (s), 169.6 (s), 175.7 (s); MS (ESI) (negative ion mode) m/z 382.2 $[M - Li]^-$. Anal. Calcd for $C_{18}H_{24}LiNO_8$: C, 55.53; H, 6.21; N, 3.60. Found: C, 55.34; H, 6.23; N, 3.6.

2-α-D-Mannopyranosyl-2-benzamido-(2*S*)-3-phenylpropanoic Acid Lithium Salt (L19): white solid; mp 136 °C; $[\alpha]^{22}_D$ = −125.5 (c = 1.0, D_2O); IR (neat, cm^{-1}) 3340, 1510, 1481, 1418, 1030, 862, 690; ^{1}H NMR (D_2O, 400 MHz) δ 3.33 (d, J = 13.3 Hz, 1H, CH_2Ph), 3.48−3.64 (m, 4H, H-4′, H-5′, H-6′a, H-6′b), 3.53 (d, J = 13.3 Hz, 1H, CH_2Ph), 3.83 (dd, $J_{3'-4'}$ = 8.0 Hz, $J_{3'-2'}$ = 4.0 Hz, 1H, H-3′), 4.52 (app t, $J_{2'-1'}$ = $J_{2'-3'}$ = 4.0 Hz, 1H, H-2′), 4.58 (d, $J_{1'-2'}$= 4.1 Hz, 1H, H-1′), 7.05−7.16 (m, 5H, ArH), 7.31−7.38 (m, 2H, ArH), 7.42−7. 53 (m, 3H, ArH); ^{13}C NMR (D_2O, 100 MHz) δ 37.7 (t), 61.2 (t), 68.3, 68.4 (s), 68.6, 71.7, 78.4, 78.5, 126.9, 127.1, 128.6, 129.1, 130.3, 132.3, 134.8 (s), 137.1 (s), 169.5 (s), 176.3 (s); MS (ESI) (negative ion mode) m/z 430.2 $[M - Li]^-$. Anal. Calcd for $C_{22}H_{24}LiNO_8$: C, 60.41; H, 5.53; N, 3.20. Found: C, 60.62; H, 5.44; N, 3.11.

General Procedure D: Synthesis of Compounds 20−22. A solution of methyl esters **17**−**19** (0.17 mmol) in H_2O (1.7 mL, 0.1 M) was added with LiOH·•H_2O (0.70 mmol). After 3 h, the reaction was complete. The solvent was removed under reduced pressure to obtain quantitatively the corresponding lithium salts . The crude was treated with 6 N HCl (4 mL), and the resulting suspension was heated at 80 °C. After 7−8 h at 80 °C, the reaction mixture was cooled to rt, and benzoic acid crystals were allowed to precipitate. The reaction mixture was filtered, and the aqueous phase was first carefully washed with DCM to eliminate all traces of benzoic acid and then evaporated in vacuo. The crude was dried over P_2O_5 to obtain α-D-*C*-mannosyl-(*S*)-aminoacids **20** (91%), **21** (90%), and **22** (85%) as hydrochloride salt.

2-(α-D-*C*-Mannopyranosyl)-(*S*)-alanine Hydrochloride (20). Compound **20** was prepared following general procedure **D** as a white hygroscopic solid. Experimental data are in accordance with ref 20b. Preparation by acid hydrolysis of **14**: A suspension of lactone **14** (0.10 mmol) in 6 N HCl (0.7 mL) in a screw-cap vial was heated at 80 °C for 6 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. The aqueous phase was evaporated and desiccated under vacuum over P_2O_5 to a constant weight to afford **20** (93%) as hydrochloride salts.

2-(α-D-*C*-Mannopyranosyl)-(*S*)-valine Hydrochloride (21). Compound **21** was prepared following general procedure **D** as a white hygroscopic solid: mp dec >230 °C; $[\alpha]^{22}_D$ = +15.18 (c = 0.5, D_2O); IR (neat, cm^{-1}) 3379, 2488, 1727, 1637, 1411, 1203, 1050, 1014; ^{1}H NMR (D_2O, 400 MHz) δ 0.93 (d, J = 6.9 Hz, 3H, CH_3iPr), 0.96 (d, J = 6.9 Hz, 3H, CH_3iPr), 2.44 (septuplet, J = 6.9 Hz, 1H, C*H*iPr), 3.58 (dd, $J_{6'a-6'b}$ = 12.4 Hz, $J_{6'a-5'}$ = 3.0 Hz, 1H, H-6′a), 3.66 (dd, $J_{4'-3'}$ = 6.1 Hz, $J_{4'-5'}$ = 4.0 Hz, 1H, H-4′), 3.71−3.78 (m, 1H, H-5′), 3.81 (dd, $J_{3'-4'}$ = 6.1 Hz, $J_{3'-2'}$ = 3.7 Hz, 1H, H-3′), 3.91 (dd, $J_{6'b-6'a}$ = 12.4 Hz, $J_{6'b-5'}$ = 8.6 Hz, 1H, H-6′b), 4.13 (d, $J_{1'-2'}$ = 7.8 Hz, 1H, H-1′), 4.24 (dd, $J_{2'-1'}$ = 7.8 Hz, $J_{2'-3'}$ = 3.6 Hz, 1H, H-2′); ^{13}C NMR (D_2O, 100 MHz) δ 16.3, 17.1, 30.8, 59.6 (t), 65.4, 68.6, 69.7 (s), 70.8, 71.9, 80.4, 171.5 (s); HRMS (ESI) calcd for $C_{11}H_{22}O_7N$ 280.13908, found 280.13919.

Correct elemental analysis could not be obtained because of the hygroscopic character of the compound.

2-(α-D-*C*-Mannopyranosyl)-(*S*)-phenylalanine Hydrochloride (22). Compound **22** was prepared following general procedure **D** as a white hygroscopic solid: mp >205 °C dec; $[\alpha]^{22}_D$ = +42.78 (c = 0.5, D_2O); IR (neat, cm^{-1}) 3368, 2489, 1635, 1416, 1052, 1010; ^{1}H NMR (D_2O, 400 MHz) δ 3.18 (d, J = 14.5 Hz, 1H, CH_2Ph), 3.47 (d, J = 14.5 Hz, 1H, CH_2Ph), 3.60 (dd, $J_{6'a-6'b}$ = 12.4 Hz, $J_{6'a-5'}$ = 3.2 Hz, 1H, H-6′a), 3.71 (dd, $J_{4'-3'}$ = 5.4 Hz, $J_{4'-5'}$ = 3.7 Hz, 1H, H-4′), 3.79−3.86 (m, 1H, H-5′), 3.88 (dd, $J_{3'-4'}$ = 5.4 Hz, $J_{3'-2'}$ = 3.6 Hz, 1H, H-3′), 3.92−4.01 (m, 1H, H-6′b), 4.10 (d, $J_{1'-2'}$ = 8.3 Hz, 1H, H-1′), 4.26 (dd, $J_{2'-1'}$ = 8.3 Hz, $J_{2'-3'}$ = 3.6 Hz, 1H, H-2′), 7.17−7.24 (m, 2H), 7.27−7. 34 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.0 (t), 59.4 (t), 65.5, 66.8 (s), 68.7, 71.0, 73.3, 80.1, 128.7, 129.6, 130.7, 133.0 (s), 171.7 (s); HRMS (ESI) calcd for $C_{15}H_{22}O_7N$ 328.13908, found 328.13910.

Correct elemental analysis could not be obtained because of the hygroscopic character of the compound.

■ ASSOCIATED CONTENT

Supporting Information. General procedures, ^{1}H and ^{13}C spectra for all reported new compounds, and COSY and NOESY spectra for compounds **10a**, **10b**, **14a**, **14b**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: (M.D.G.) marcello.digiacomo@unipv.it; (M.S.) massimo.serra@unipv.it.

■ REFERENCES

(1) (a) Paulson, J. C. *Trends Biochem. Sci.* **1989**, *14*, 272–276. (b) Cumming, D. A. *Glycobiology* **1991**, *1*, 115–130. (c) Varki, A. *Glycobiology* **1993**, *3*, 97–130. (d) Kobata, A. *Acc. Chem. Res.* **1993**, *26*, 319–324.

(2) (a) Beeley, J. G. *Biochem. Biophys. Res. Commun.* **1977**, *76*, 1051–1055. (b) Imperiali, B.; Shannon, K. L.; Rickert, K. W. *J. Am. Chem. Soc.* **1992**, *114*, 7942–7944. (c) Lis, H.; Sharon, N. *Eur. J .Biochem.* **1993**, *218*, 1–27. (d) Andreotti, A. H.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 3352–3353. (e) O'Connor, S. E.; Imperiali, B. *Chem. Biol.* **1996**, *3*, 803–812. (f) Wyss, D. F.; Wagner, G. *Curr. Opin. Biotechnology* **1996**, *7*, 409–416. (g) Imperiali, B. *Acc. Chem. Res.* **1997**, *30*, 452–459.

(3) (a) Dweck, R. A. *Chem. Rev.* **1996**, *96*, 683–720. (b) Kihilberg, J.; Elofsson, M. *Curr. Med. Chem.* **1997**, *4*, 85–116.

(4) (a) Paulson, J. C. In *The receptors*; Conn, P. M., Ed.; Academic Press: New York, 1985; Vol. II, p 131. (b) Rostand, K. S.; Esko, J. D. *Infect. Immun.* **1997**, *65*, 1–8. (c) Mammen, M.; Choi, S. K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754–2794. (d) Schmidt, M. A.; Riley, L. W.; Benz, I. *Trends Microbiol.* **2003**, *11*, 554–561. (e) Upreti, R. K.; Kumar, M.; Shankar, V. *Proteomics* **2003**, *3*, 363–379.

(5) (a) Springer, G. F. *Science* **1984**, *224*, 1198–1206. (b) Sakamoto, J.; Furukawa, K.; Cordon-Cardo, C.; Yin, B. W. T.; Rettig, W. J.; Oettgen, H. F.; Old, L. J.; Lioyd, K. O. *Cancer Res.* **1986**, *46*, 1553–1561. (c) Itzkowitz, S. H.; Yuan, M.; Fukushi, Y.; Palekar, A.; Phelps, P. C.; Shamsuddin, A. M.; Trump, B. F.; Hakomori, S. I.; Kim, Y. S. *Cancer Res.* **1986**, *46*, 2627–2632. (d) Hakomori, S. *Adv. Cancer Res.* **1989**, *52*, 257–331. (e) Dennis, J. W.; Granowsky, M.; Warren, C. E. *Biochim. Biophys. Acta* **1999**, *1473*, 21–34. (f) Byrd, J. C.; Bresalier, R. S. *Cancer Metastasis Rev.* **2004**, *23*, 77–99.

(6) (a) Springer, T. A. *Nature* **1990**, *346*, 425–434. (b) Mc Ever, R. P.; Moore, K. L.; Cummings, R. D. *J. Biol. Chem.* **1995**, *270*, 11025–11028. (c) Kihlberg, J.; Elofsson, M. *Curr. Med. Chem.* **1997**, *4*, 85–116. (d) Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, *291*, 2370–2376. (e) Ley, K.; Kansas, G. S. *Nat. Rev. Immunol.* **2004**, *4*, 325–335.

(7) (a) Kunz, H. *Angew. Chem., Int. Ed.* **1987**, *26*, 294–308. (b) Davis, B. G. *Chem. Rev.* **2002**, *102*, 579–602. (c) Wong, C.-H. *J. Org. Chem.* **2005**, *70*, 4219–4225. (d) Buskas, T.; Ingale, S.; Boons, G. J. *Glycobiology* **2006**, *16*, 113R–136R. (e) Hojo, H.; Nakahara, Y. *Peptide Sci.* **2007**, *88*, 308–324.

(8) Kihlberg, J.; Aahman, J.; Walse, B.; Drakenberg, T.; Nilsson, A.; Soederberg-Ahlm, C.; Bengtsson, B.; Olsson, H. *J. Med. Chem.* **1995**, *38*, 161–169.

(9) (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545–8599. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995. (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC: Boca Raton, 1995. (d) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700–717. (e) Nolen, E. G.; Watts, M. M.; Fowler, D. J. *Org. Lett.* **2002**, *4*, 3963–3965.

(10) Sparks, M. A.; Williams, K. W.; Whitesides, G. M. *J. Med. Chem.* **1993**, *36*, 778–783.

(11) Kishi, Y. *Pure Appl. Chem.* **1993**, *65*, 771–778.

(12) (a) Fisher, J. F.; Harrison, A. W.; Bundy, G. L.; Wilkinson, K. F.; Rush, B. D.; Ruwart, M. J. *J. Med. Chem.* **1991**, *34*, 3140–3143. (b) Arsequell, G.; Haurum, J. S.; Elliot, T.; Dwek, R. A.; Lellouch, A. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1739–1745. (c) Mehta, S.; Meldal, M.; Duus, J. O.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1445–1451.

(13) For recent reviews, see: (a) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395–4422. (b) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230–253.

(14) Marcaurelle, L. A.; Bertozzi, C. R. *Chem.—Eur. J.* **1999**, *5*, 1384–1390 and references therein.

(15) (a) Veber, D. F.; Freidinger, R. M. *Trends Neurosci.* **1985**, *8*, 392–396. (b) Mossel, E.; Formaggio, F.; Crisma, M.; Toniolo, C.; Broxterman, Q. B.; Boesten, W. H.; Kamphuis, J.; Quaedflieg, P. J. L. M.; Temussi, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1305–1314. (c) Bellier, B.; McCort-Tranchepain, I.; Ducos, B.; Danascimento, S.; Meudal, H.; Noble, F.; Garbay, C.; Roques, B. P. *J. Med. Chem.* **1997**, *40*, 3947–3956.

(16) (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066. (b) Cativiela, C.; Daz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599 and references therein. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597.

(17) (a) Wilstermann, M.; Kononov, L. O.; Nillson, U.; Ray, A. K.; Magnusson, G. *J. Am. Chem. Soc.* **1995**, *117*, 4742–4754. (b) Navarre, N.; van Oijen, A. H.; Boons, G. J. *Tetrahedron Lett.* **1997**, *38*, 2023–2026. (c) Alibés, R.; Bundle, D. R. *J. Org. Chem.* **1998**, *63*, 6288–6301. (d) Geyer, A.; Müller, M.; Schmidt, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 6312–6313.

(18) (a) Simanek, E. E.; McGarvey, G. J.; Jablonowski, J. A.; Wong, C.-H. *Chem. Rev.* **1998**, *98*, 833–862 and references therein. (b) Sears, P.; Wong, C.-H. *Angew. Chem .Int .Ed.* **1999**, *38*, 2300–2324.

(19) (a) Maity, S. K.; Dutta, S. K.; Banerjee, A. K.; Achari, B.; Singh, M. *Tetrahedron* **1994**, *50*, 6965–6974. (b) Lopez-Herrera, F. J.; Sarabia-Garcia, F.; Heras-Lopez, A.; Pino-Gonzales, M. S. *J. Org. Chem.* **1997**, *62*, 6056–6059. (c) For C-glycomimetics of glycosyltransferase inhibitors, see: Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077–3092. (d) For α-CF_2-mannosides, see: Poulain, F.; Serre, A.-L.; Lalot, J.; Leclerc, E.; Quirion, J.-C. *J. Org. Chem.* **2008**, *73*, 2435–2438.

(20) (a) Simchen, G.; Pürkner, E. *Synthesis* **1990**, 525–527. (b) Colombo, L.; Casiraghi, G.; Pittalis, A.; Rassu, G. *J. Org. Chem.* **1991**, *56*, 3897–3900. (c) Colombo, L.; Di Giacomo, M.; Ciceri, P. *Tetrahedron* **2002**, *58*, 9381–9386.

(21) (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297.

(22) (a) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635–2637. (b) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727–10737.

(23) (a) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432–1440. (b) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755–2762.

(24) RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642–3644.

(25) For recent examples of Pd-catalyzed *O*-glycosylation using a more activated pyranone system, see: (a) Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369–4371. (b) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714–8715. (c) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406–12407. (d) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336–1337. (e) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428–3429.

(26) Engelbrecht, G. J.; Holzapfel, C. W. *Heterocycles* **1991**, *32*, 1267–1272.

(27) Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc.* **1970**, *92*, 5288–5290. Surprisingly, even if the preparation of the *tert*-butyl carbonate derivative **10a** is a well-known procedure, no characterization data for compound **10a** and the corresponding β-anomer **10b** have been previously reported.

(28) Mukerjee, A. K. *Heterocycles* **1987**, *26*, 1077–1097.

(29) Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178−180*, 511–528.

(30) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723–727.

(31) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727–10737.

(32) (a) Kramer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895. (b) Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099.

(33) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343.

(34) Trost, B. M.; Crawley, M. *Chem. Rev.* **2003**, *103*, 2921–2943.

(35) (a) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236–3237. (b) Ogasawara, M.; Ngo, H. L.; Sakamoto, T.; Takanashi, T.; Lin, W. *Org. Lett.* **2005**, *7*, 2881–2884.

(36) (a) Hemchen, G. *J. Organomet. Chem.* **1999**, *576*, 203–214. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345. For bite angle P−Pd−N, see: Kollmar, M.; Helmchen, G. *Organometallics* **2002**, *21*, 4771–4775.

(37) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem., Int. Ed.* **1995**, *34*, 2386–2388.

(38) Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945–9957.