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Multiple Component Approaches to C-Glycosyl β-Amino Acids by Complementary One-Pot Mannich-Type and Reformatsky-Type Reactions

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Dedicated to Professor S. V. Ley on the occasion of his 60th birthday

Abstract: The development of new methods for the preparation of C-glycosyl β-amino acid libraries with chemical and stereochemical diversity levels was investigated and the results are described herein. Two complementary one-pot three-component Mannich-type and Reformatsky-type synthetic strategies have been developed for the construction of chiral 3-amino propanoate fragments (eventually bis-substituted at C-2) directly linked to the anomeric carbon of pyranose and furanose residues. Both methods involved as the initial step the coupling of a sugar aldehyde to *p*-methoxybenzylamine but differed in the nucleophile (a d^2 synthon equivalent) which was successively added: a ketene silyl acetal (Mannich route) or a bromozinc enolate (Reformatsky route). Individual C-glycosyl β-amino esters were isolated as single 3*R* diastereoisomers in fair to excellent yield (60–90%) and their structure assigned by NMR spectroscopy (Riguera protocol) supported by X-ray crystallography. A tentative explanation of the observed stereochemical outcome based on transition-state models is provided. A preliminary study on the synthesis of α,α-difluoro C-glycosyl β-amino acids via a more traditional Reformatsky route is also reported.

Keywords: amino acids · glycosides · Mannich reaction · multicomponent reactions · Reformatsky reaction

Introduction

C-Glycosyl amino acids belong to a class of glycosides most of which are non-natural products, featuring carbohydrates anomerically linked to amino acid residues through one or more carbon–carbon bond(s). The interest in synthetic methods[1] which are amenable to the production of these compounds in usable quantities orginates from their subsequent incorporation into peptides. Both co- and post-translational synthetic strategies are used for this task.[2] The resulting materials display carbohydrate residues which are linked to the polyamide backbone through a carbon–carbon bond (C-glycopeptides). Hence, unlike native peptides carrying oligosaccharides through carbon–oxygen or carbon–nitrogen linkages (O- and N-glycopeptides),[3] these artificial glycopeptides are more resistant toward enzymatic and chemical degradation. Given the central role exerted by O- and N-glycopeptides in glycoprotein biological functions at the cellular level[4] (cellular recognition, adhesion, cell-growth regulation, cancer cell metastasis, and inflammation), the introduction of structurally defined, metabolically stable C-glycopeptides is expected to provide the opportunity to probe and intervene in critical biological processes. The final goal of these studies is the development of glycopeptide-based drugs for the control of bacterial and viral diseases, cancer therapy, and treatment of inflammatory processes.[5] Consequently, a variety of C-glycosyl α-amino acids have been prepared thus far; particular attention has been paid to methylene isosteres of O-glycosyl serine and threonine and ethylene isosteres of N-glycosyl asparagines,[1,2,6] because these glycosyl amino acids are the most common components of natural glycopeptides. However, it appears of some importance to opening viable routes also to C-glycosyl β-amino acids in order to introduce a further diversification in newly designed C-glycopeptides. In fact, in the recent decade there has been a great interest in β-amino acid synthesis[7] not only for their own pharmacological activities[8] and structural properties[9] but especially for their use as α-

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amino acid surrogates in the construction of hybrid α- and β-peptidic materials, which display enhanced stability toward proteolysis[10] and possess interesting folding patterns in the form of well defined and stable helical, turn, and pleated-sheet conformations in solution.[11] However, at present, there are only three accounts describing multistep routes to sugar β-amino acids. The approaches by Tripathi[12] and Sharma[13] and their co-workers were both based on the Michael-type addition of amines to sugar derived γ-alkoxy α,β-unsaturated esters; the route by Palomo[14] and co-workers involved the reaction of α-amido glycoalkyl sulfones (prepared from C-glycosyl propionaldehydes) with the lithium enolate derived from 2-acetylisoborneol, followed by the elaboration of the resulting β-amino ketone. However, the Tripathi[12] and Sharma[13] route afforded compounds of type **I** (Figure 1) which cannot be considered C-glycosyl β-amino

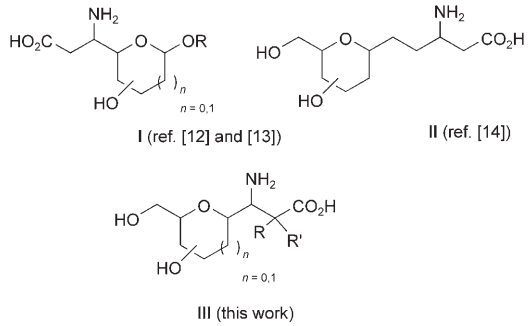
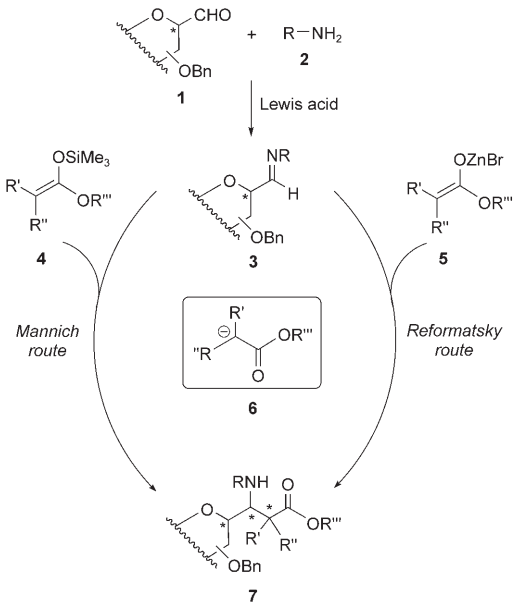


Figure 1. Three different types of sugar β-amino acids.

acids because the amino acid residue is linked to the C-4 or C-5 of furanose or pyranose ring, respectively, rather than to the anomeric carbon of the sugar fragment.[15] The method of Palomo[14] allowed for the synthesis of a few compounds of type **II** in which the sugar and the amino acid fragments are linked through an ethylene bridge. Therefore two years ago we became particularly interested in developing efficient routes to a new class of genuine C-glycosyl β-amino acids such as those of type **III** featuring the amino acid residue directly linked to the sugar fragment. We reported preliminary results of a successful approach to those target molecules based on a one-pot, three-component cross-Mannich-type reaction of sugar aldehydes.[16,17] We have now set for ourselves a goal to broadening the scope of the Mannich-type approach to C-glycosyl β-amino acids **7** from aldehydes **1**, amines **2** and silyl ketene acetals **4** as well as developing a complementary route based on the Reformatsky reaction using as nucleophiles the bromozinc enolates **5** (Scheme 1). Apparently, the reagents **4** and **5** serve as the equivalents of the d^2 synthon **6**, a carboxylate stabilized α-carbanion, that by addition to the C-glycosyl imine intermediate **3**, completes the assembly of the three reaction partners via carbon–carbon bond formation. Delighted by the high diastereoselectivity levels registered in an earlier exploratory work,[16] we hoped that similar stereochemical control would result in new reactions. For many years the Mannich[18] and



Scheme 1. Complementary Mannich and Reformatsky one-pot routes to C-glycosyl β-amino esters.

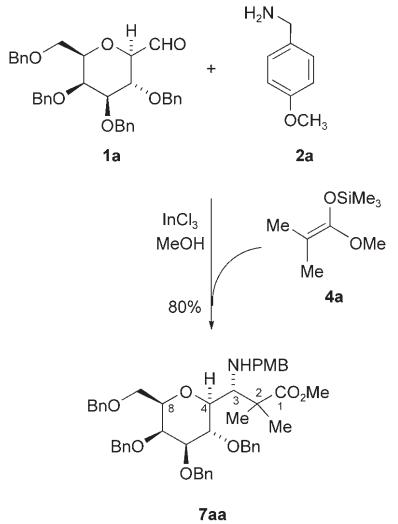
the Reformatsky[19] reactions have represented the most common routes to β-amino carbonyl compounds. Both reactions involved an aldehyde, an amine, and a carbonyl-stabilized nucleophile and were performed stepwise. Our approach consists of performing the reactions in a three-component manner (3-CR) by adding successively the amine, then aldehyde and finally the nucleophile to the resulting imine.[20,21] The design of multicomponent syntheses often relies on the integration of multiple individual reactions to give a one-pot synthetic operation. In recent years there has been an increasingly awareness among the synthetic organic chemistry community on the great potential of multicomponent reactions as step-economical strategies in target-oriented synthesis.[22,23] It can be foreseen that from the 3-CRs shown in Scheme 1 large libraries of C-glycosyl β-amino acids should be accessible by the use of a wide range of reagents. Structural and stereochemical diversity can be achieved by changing the sugar residue in aldehydes **1**, the group R in the amine **2**, as well as the substituents R′ and R″ in the nucleophiles **4** and **5**. The results of this investigation are presented in the following.

Results and Discussion

While efficiency and scope of synthetic methodologies are quite often evaluated by the use of simple model reagents, in the target oriented synthesis of C-glycosyl β-amino esters **7** we needed as starting materials rather special aldehydes, such as formyl C-glycosides **1**. Earlier studies were carried out in our laboratory on the stereoselective anomeric formylation of pyranoses and furanoses via thiazole and benzothiazole chemistry.[24] Hence, a collection of sugar aldehydes

1 was at hand for the present study. Also the choice of the amine **2** was carefully considered because this reagent had to be sufficiently reactive towards sugar aldehyde **1** and at the same time bear a group R; this residue should be easily removable from the final product **7** and replaceable by another amino protecting group, such as Boc and Fmoc, suitable for peptide synthesis. The primary amine *p*-methoxybenzylamine (PMBA, **2a**) appeared to be endowed with the required properties since it is a good nucleophile and the N-PMB group can be readily cleaved under both oxidative and mild acid conditions.

One-pot Mannich route to β-amino esters 7: In a model system suitable for optimization studies we started with perbenzylated β-linked C-galactosyl formaldehyde **1a**, PMBA **2a**, and the commercially available ketene silyl acetal 1-methoxy-2-methyl-1-trimethylsilyloxypropene (**4a**) (Scheme 2). The promoter was $InCl_3$, an active catalyst of the Mannich reaction both in water and methanol which was recently introduced in multicomponent approaches by Loh and coworkers.[20a] As we anticipated to perform the reaction under one-pot stepwise conditions, a solution in methanol of the aldehyde **1a**, amine **2a** (1.0 equiv), and catalytic $InCl_3$ (0.2 equiv) was stirred at room temperature for 30 min and then the nucleophile **4a** (1.5 equiv) was added in one portion. Work up of the reaction mixture after 12 h afforded the three-component coupling product C-galactosyl β-amino ester **7aa**[25] as the sole diastereoisomer as observed by ^{1}H NMR analysis of the crude reaction mixture. Pure product **7aa** was isolated by chromatography in 80% yield. Noteworthy, the same high diastereoselectivity and yield were registered in different scale reactions starting from 100 mg up to one gram of the aldehyde **1a**. The β-linkage at the sugar anomeric center of **7aa** was easily established by estimating the $J_{4,5}$ value of about 9.0 Hz in the ^{1}H NMR spectrum. On the other hand, the configuration at the newly formed C-3 stereocenter carrying the NHPMB group was more laboriously assigned after transformations of **7aa** into Mosher's amides (see below) as being *R*.



Scheme 2. Model synthesis of a C-glycosyl β-amino acid via the one-pot three-component Mannich approach.

The assembly of the sugar aldehyde **1a**, amine **2a**, silyl ketene acetal **4a** was examined under the light of amount and promoter changes while maintaining the same reaction conditions, that is, 12 h at room temperature in methanol as the solvent (Table 1). The results obtained in this study indicated that the best performing catalyst was by far $InCl_3$ since only 0.2 equiv of this Lewis acid served to perform the aminocarbonylation with very good yields (80%) of the target product **7aa**. However, the inexpensive and environmentally friendly $FeCl_3{\cdot}6H_2O$ appears to be promising in this endeavor although it is less effective than $InCl_3$. Also $Yb(OTf)_3$ showed good activity but the high costs constitute a serious limitation. In comparison to these promoters, TMSOTf was much less efficient and $BF_3{\cdot}OEt_2$ was practically ineffective. With all catalysts, the (3*R*)-epimer **7aa** was observed as the sole product in the crude reaction mixtures.

Table 1. Mannich reaction of **1a**, **2a**, **4a**, and different promoters.[a]

Entry	Promoter	% mol promoter	Yield **7aa** [%][b]
1	$InCl_3$	20	80
2	$InCl_3$	100	85
3	$Yb(OTf)_3$	20	60
4	$Yb(OTf)_3$	100	70
5	TMSOTf	20	25
6	TMSOTf	100	60
7	$BF_3{\cdot}Et_2O$	20	< 5
8	$BF_3{\cdot}Et_2O$	100	10
9	$FeCl_3{\cdot}6H_2O$	20	60
10	$FeCl_3{\cdot}6H_2O$	100	70

[a] All reactions were run with 1.0 mmol **1a** and 1.0 mmol **2a** in 3 mL MeOH in the presence of the promoter and 4 Å molecular sieves. Then **4a** (1.5 mmol) was added in one portion after 30 min. [b] Isolated yields.

The Mannich-type 3-CR under the $InCl_3$ catalysis was then applied to other β-linked C-glycosyl aldehydes **1b–e** (D-*gluco*, D-*manno*, D-*ribo*, D-*arabino* series)[26] to give the corresponding three-component coupling products C-glycosyl β-amino esters **7ba–ea** as single 3*R* diastereoisomers (see below for the configurational assignments) in fair to excellent isolated yields (60–90%) (Table 2). These results demonstrated the applicability of this approach to different sugar aldehydes. However, the synthesis of β-amino ester **7ca** (*manno* series) required some experimental adjustments. In fact, dichloromethane was chosen as the solvent because of the insolubility of the intermediate imine in methanol and the whole synthetic sequence was performed at 0°C for 16 h (overall time) to limit the formation (30%) of the two epimeric (1:1 ratio) glycal amino esters **8** (see below) resulting from the elimination of BnOH from C-1 and C-2 of the sugar moiety. This side reaction occurred later than the imine formation as

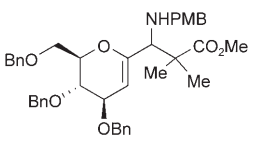
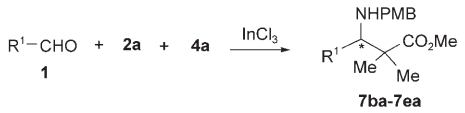
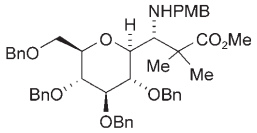
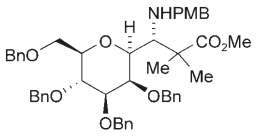
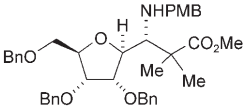
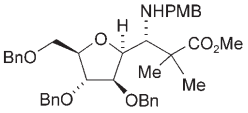


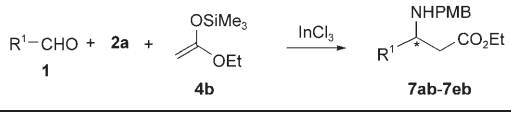
Table 2. Three-component Mannich reactions of the β-linked C-glycosyl aldehydes **1b–e** with PMBA **2a** and silyl ketene acetal **4a** in the presence of $InCl_3$ (0.2 equiv).[a]

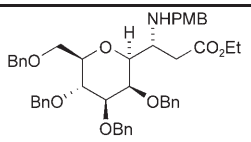
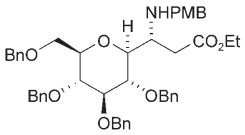
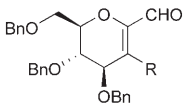
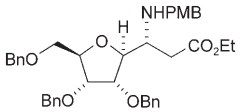
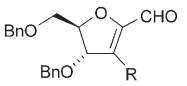


R^1	β-amino ester	Yield[b] [%]	*de*[c] [%]
β-glucosyl, **1b**	 **7ba**	90	100
β-mannosyl, **1c**	 **7ca**	60[d]	100
β-ribosyl, **1d**	 **7da**	85	100
β-arabinosyl, **1e**	 **7ea**	75	100

[a] All reactions were performed in MeOH at room temperature with 1.0 mmol **1**, 1.0 mmol **2a**, and 0.2 mmol $InCl_3$ in the presence of 4 Å molecular sieves. Then **4a** (1.5 mmol) was added in one portion after 30 min. [b] Isolated yields. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Reaction run at 0 °C in CH_2Cl_2.

Table 3. Three-component Mannich reactions of the β-linked C-glycosyl aldehydes **1a–e** with PMBA **2a** and the silyl ketene acetal **4b** in the presence of $InCl_3$ (0.2 equiv).[a]



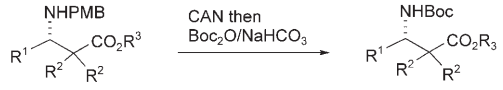
R^1	β-amino ester	Yield[b] [%]	*de*[c] [%]
β-galactosyl, **1a**	 **7ab**	60	100
β-glucosyl, **1b**	 **7bb**	58	100
β-mannosyl, **1c**	 **9**: R = H **10**: R = OBn		50[d,e]
β-ribosyl, **1d**	 **7db**	62	100
β-arabinosyl, **1e**	 **11**: R = H **12**: R = OBn		55[e]

[a] All reactions were performed in EtOH at room temperature with 1.0 mmol **1**, 1.0 mmol **2a**, and 0.2 mmol $InCl_3$ in the presence of 4 Å molecular sieves. Then **4b** (5.0 mmol) was added in one portion after 30 min. [b] Isolated yields. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Reaction run at 0 °C in CH_2Cl_2. [e] Isolated as a ca. 1:1 mixture of glycals.

confirmed by ^1H NMR analysis of the crude reaction mixture before **4a** was added. This experiment showed the absence of glycal derivatives of **1c** and its corresponding imine. The elimination pathway was very likely favored in the *manno* series by the *trans*-diaxial disposition of the anomeric proton and the OBn group at C-2 of the carbohydrate unit.[27]

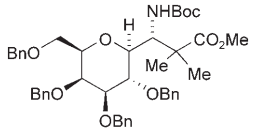
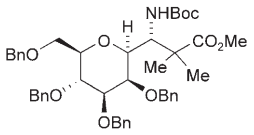
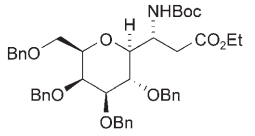
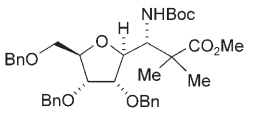
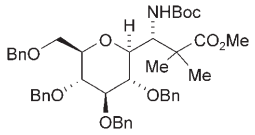
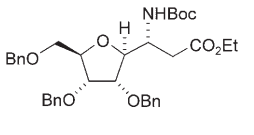
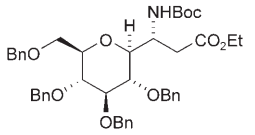
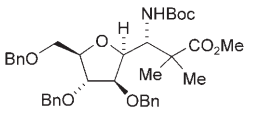
Reagent diversity was next considered in respect to the silyl ketene acetal **4** since this component served to modulate the extent and the type of substitution at C-2 of the amino acid side chain. Thus, the construction of a C-α unsubstituted fragment was examined by the use of (1-ethoxyvinyloxy)trimethylsilane (**4b**), a known ketene silyl acetal for which an optimized preparation from lithium diisopropylamide/ethyl acetate/trimethylsilyl chloride was available.[28] Unfortunately, this enol silane was found to isomerize to the corresponding α-silylated or desilylated acetate due to the migration of the $SiMe_3$ group from oxygen to carbon.[28a] The consequence of this undesirable behavior became manifested by the low yield, even when using 5.0 equiv of **4b**, for three new C-glycosyl β-amino propionates **7ab**, **7bb**, and **7db** synthesized from the corresponding aldehydes **1a**, **1b**, and **1d** (Table 3). In addition the reactions showed a remarkably high stereochemical control as only one single Mannich adduct (see below for the configurational assignment at C-3) was observed in the crude reaction mixture and briefly characterized. Quite disappointing was the unexpected lack of Mannich adduct formation starting from the mannopyranosyl and arabinofuranosyl aldehydes **1c** and **1e**, respectively. The only products isolated were PMBA **2a**, and the C-formyl glycals **9–10** (*manno* series) and **11–12** (*arabino* series). It can be speculated that these products arise from the retro-Mannich reaction of the expected glycosyl β-amino esters **7cb** and **7eb** (see Table 5). Accordingly, the formation of glycals **9** and **11** can be explained by the hydrolysis of the water-sensitive imine intermediates (the retro-Mannich products along with **2a** and ethyl acetate) to the aldehydes **1c** and **1e**, followed by the ready 1,2-*trans* elimination of BnOH. The route leading to compounds **10** and **12** is instead open to various interpretations.

Table 4. Transformation of the N-PMB amino esters **7aa–ea** and **7ab–eb** into their corresponding N-Boc derivatives **13aa–ea** and **13ab–eb**.



7aa-ea: R^2 = Me; R^3 = Me
7ab-eb: R^2 = H; R^3 = Et

13aa-ea: R^2 = Me; R^3 = Me
13ab-eb: R^2 = H; R^3 = Et

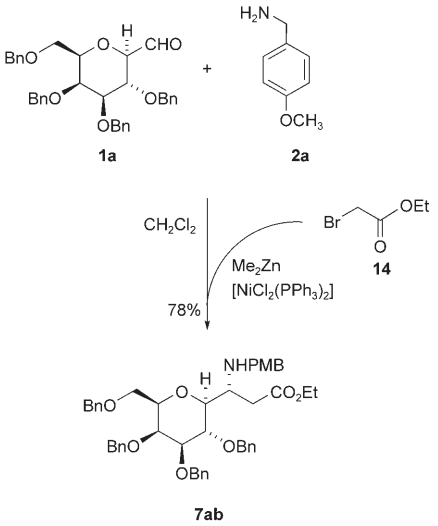
N-PMB derivative	N-Boc derivative	Yield [%][a]	N-PMB derivative	N-Boc derivative	Yield [%][a]
7aa	 **13aa**	85	**7ca**	 **13ca**	78
7ab	 **13ab**	81	**7da**	 **13da**	82
7ba	 **13ba**	78	**7db**	 **13db**	80
7bb	 **13bb**	71	**7ea**	 **13ea**	76

[a] Isolated yields.

In view of the synthetic application of the newly prepared amino esters as precursors to glycopeptides, compounds **7aa–7ea** and **7ab–eb** were transformed into their corresponding N-Boc derivatives **13aa–ea** and **13ab–eb**, all of which are expected to be suitable for co-translational introduction into peptides by Boc-based peptide synthesis. The N-protecting group modification required removing of the PMB group under oxidative conditions using ammonium cerium nitrate (CAN) and then treatment with di-*tert*-butyl dicarbonate (Boc_2O) under mild basic conditions for the formation of the carbamate-type protection. The overall yield of this optimized one-pot transformation varied in the range 70–85% and was carried out both in milligram and gram scale. The compounds thus obtained are presented in Table 4. It is at this point worth mentioning that the attempt to obtain the N-Boc protected amino esters **13** directly from the Mannich 3-CR using the *tert*-butyl carbamate ($BocNH_2$) as the amine component, failed in our hands. This unfortunate finding can be ascribed to the lack of imine formation in the first step of the Mannich reaction. The reluctance of carbamates to take part in Mannich reactions is well known and appears to be attributable to their low nucleophilicity.[29] However, a successful reaction of this type has been reported quite recently by Xia and co-workers.[23y]

One-pot Reformatsky route to β-amino esters 7: Having pointed out some limitations in the Mannich-type approach to the desired C-glycosyl β-amino esters **7**, it became quite obvious to us exploring the complementary Reformatsky reaction to see whether new molecular diversity could be achieved for the compilation of a small yet significant collection of these amino acids. Only three examples were reported up to 2002 on the Reformatsky-type reaction carried out under the light of a three-component technique.[21a–c] Very recently, Adrian and Snapper reported on an efficient, nickel-catalyzed, Reformatsky-type three-component condensation that allowed to prepare a library of 64 β-amino carbonyl compounds constituted of β-amino esters, amides, and ketones.[21d] Consistent with earlier observations of Périchon and co-workers,[30] the key element in this technique was the use a nickel-based catalyst which was identified as $NiCl_2$ to which were added two equivalents of PPh_3. Thus, substantial experimentation led Adrian and Snapper to the preparation of the Reformatsky reagent from ethyl 2-bromoacetate, a dialkyl zinc and $[NiCl_2(PPh_3)_2]$ and perform the 3-CR in a one-pot reaction but with the addition of the reagents in a successive manner. While the aldehydes that we intended to use in our target-oriented synthesis were more complex substrates than those tested by Adrian and Snapper in their

model systems, we decided to apply the optimized conditions established by these authors to our own chemistry. Adopting once again as starting material the perbenzylated β-linked C-galactopyranosyl aldehyde **1a**, we proceeded in the following way (Scheme 3). Aldehyde **1a** and PMBA **2a**



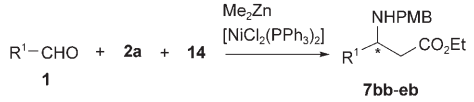
Scheme 3. Model synthesis of a C-glycosyl β-amino acid via the one-pot three-component Reformatsky approach.

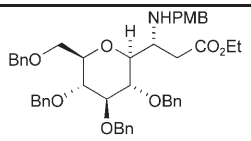
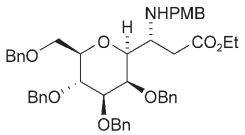
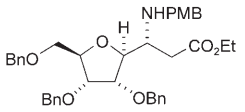
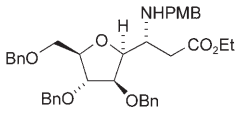
(1 equiv) were stirred in CH_2Cl_2 at room temperature for 30 min and then a toluene solution of the zinc donor Me_2Zn (3.5 equiv) was added followed, after 15 min, by ethyl bromoacetate **14** (3.0 equiv) and a dichloromethane solution of the catalyst $[NiCl_2(PPh_3)_2]$ (0.05 equiv). The latter three species served to form in situ the Reformatsky reagent $BrZnCH_2CO_2Et$ (**5b**) very likely through the catalytic cycle propose by Adrian and Snapper.[21d] These conditions worked beautifully because after 12 h of stirring the reaction mixture the Reformatsky three-component adduct **7ab** was afforded as one single stereoisomer (crude ^1H NMR analysis) and in much higher isolated yield (78 vs 60%) of the identical Mannich product reported in Table 3.

Encouraged by this result, the same strategy was tested with C-glycosyl aldehydes **1b–e** (D-*gluco*, D-*manno*, D-*ribo*, D-*arabino* series).[26] The corresponding C-glycosyl β-amino esters **7bb**, **7cb**, **7db**, and **7eb** were obtained as single observable diastereoisomers (Table 5). The yields of the two glucosyl **7bb** and ribosyl **7db** derivatives (70 and 72%) were higher by about 10% of those registered in the Mannich-type route (Table 3). Also quite gratifyingly was the successful access, although in low yield, to the mannosyl **7cb** and arabinosyl **7eb** derivatives, which cannot be synthesized via the Mannich-type route. Hence the power of the Reformatsky route in this chemistry appears to be sufficiently demonstrated.

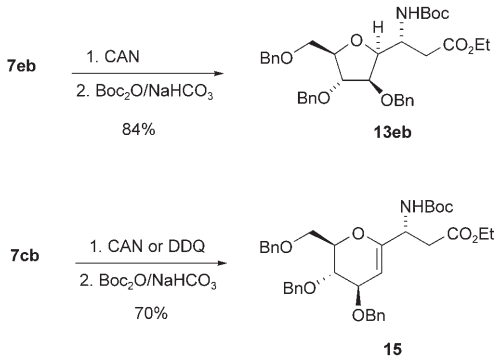
Although the substitution of the N-PMB group with the N-Boc was demonstrated to be performable easily with the compounds previously prepared, we decided to test the feasibility of this transformation also with the newly prepared amino esters **7cb** and **7eb**. Hence we observed that the N-protective group replacement was readily carried out in **7eb** using CAN and then Boc_2O to give the target amino ester **13eb** in 84% yield (Scheme 4). Glycal **15** was obtained instead starting from **7cb** under the same conditions. In this case the BnOH elimination which was concomitant to the PMB group removal was not prevented even by using the neutral oxidant 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

Table 5. Three-component Reformatsky reactions of the β-linked C-glycosyl aldehydes **1b–e** with PMBA **2a** and ethyl bromoacetate **14** in the presence of Me_2Zn and $[NiCl_2(PPh_3)_2]$.[a]



R^1	β-amino ester	Yield [%][b]	*de* [%][c]
β-glucosyl, **1b**	 **7bb**	70	100
β-mannosyl, **1c**	 **7cb**	60	100
β-ribosyl, **1d**	 **7db**	72	100
β-arabinosyl, **1e**	 **7eb**	45	100

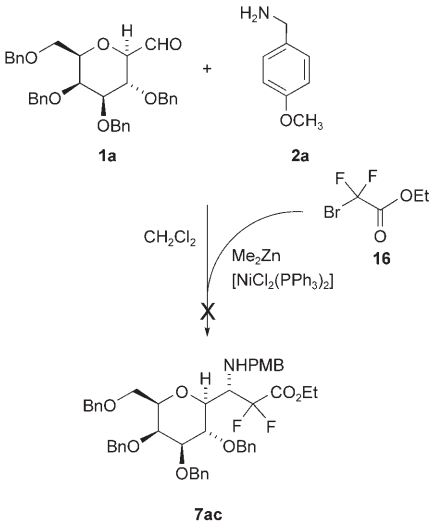
[a] All reactions were run in CH_2Cl_2 at room temperature for 12 h (see Experimental Section). [b] Isolated yields. [c] Determined by ^1H NMR analysis of the crude reaction mixture.



Scheme 4. N-Protective group replacement.

(DDQ). This is a typical case of an unexpected event, thus stressing the view on the highly experimental basis of our chemical discipline. From the practical standpoint this may serve to alert on the ease of trans-elimination of BnOH in the *manno* series not only in the starting reagent C-formyl glycoside **1c** or in the corresponding imine, but also in the final amino ester C-glycoside **7cb**.

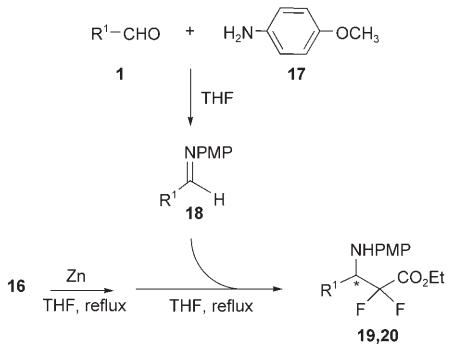
Applications of fluorinated amino acids, especially *gem*-difluoro derivatives[31] in biological and medicinal studies as well as in pharmaceutical research toward the development of new drugs, are of great interest. It is well known that compounds in which hydrogen atoms are replaced by fluorine atoms represent bioisosteres of great importance.[32] Hence isosteric changes represent another element of diversity in the target-oriented preparation of special libraries for life science. We anticipated that a route to α,α-difluoro C-glycosyl β-amino acids by the Reformatsky-type synthesis as described above would now be possible. The preference for this route over the Mannich-type route was dictated by the ready access to the α,α-difluoro Reformatsky reagent $BrZnCF_2CO_2Et$ (**5c**); this reagent could be conveniently prepared from ethyl bromodifluoroacetate (**16**) and has also been successfully implemented in addition reactions to imine derivatives both under classical[33] and catalytic[34] conditions. On the other hand, the synthesis of difluoroketene ethyl trimethylsilyl acetal $F_2C{=}C(OSiMe_3)OEt$ (**4c**), that is reported to occur in only 12% yield from **16**,[35] failed in our hands thus precluding us from exploring a Mannich-type approach. Quite disappointingly, the application of optimized conditions to the one-pot three-component Reformatsky reaction of the perbenzylated β-linked C-galactopyranosyl aldehyde **1a**, PMBA **2a**, and ethyl bromodifluoroacetate **16** in the presence of Me_2Zn and $[NiCl_2(PPh_3)_2]$ resulted in no formation of the target α,α-difluoro C-galactosyl β-amino ester **7ac** (Scheme 5).

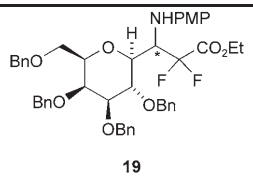
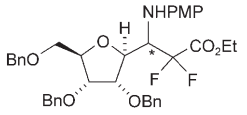


Scheme 5. Abortive synthesis of a α,α-difluoro C-glycosyl β-amino acid via the one-pot three-component Reformatsky approach.

Although we were aware of the crucial role of catalyst and solvent in the Reformatsky-type addition involving ethyl bromodifluoroacetate (**16**),[36] we did not carry out a systematic screening of reaction conditions to opening a successful one-pot route to derivatives of type **7ac**. Nevertheless, the need for sufficient amounts of these compounds for biological and structural studies led us to consider an alternative and more straightforward access to this class of fluorinated β-amino acids. Hence, since the fluorinated Reformatsky reagent **5c**, due to its instability,[37] is usually generated and reacted in refluxing THF we focused our attention on the use of traditional Reformatsky conditions. Accordingly, galactosyl imine **18a**, which was separately prepared from the corresponding aldehyde **1a** and *p*-anisidine **17** (THF, room temperature, 45 min), was added to a suspension of ethyl bromodifluoroacetate (**16**; 4.0 equiv) and activated zinc powder in boiling THF. The reaction was completed under reflux conditions in 45 min and furnished the *gem*-difluoro *N*-*p*-methoxyphenyl (PMP)-β-amino ester **19** in 30% yield after purification by column chromatography (Table 6). Compound **19** was isolated as a single diastereoisomer along with uncharacterized byproducts arising from the thermal decomposition of the imine **18a**. The precautionary use of *p*-anisidine **17** as amine component was suggested by earlier studies reporting on the preferential formation of β-lactam derivatives in the addition reactions

Table 6. Classical Reformatsky reactions of the β-linked C-glycosyl imines **18a** and **18d** with ethyl bromodifluoroacetate **16** in the presence of activated zinc powder.

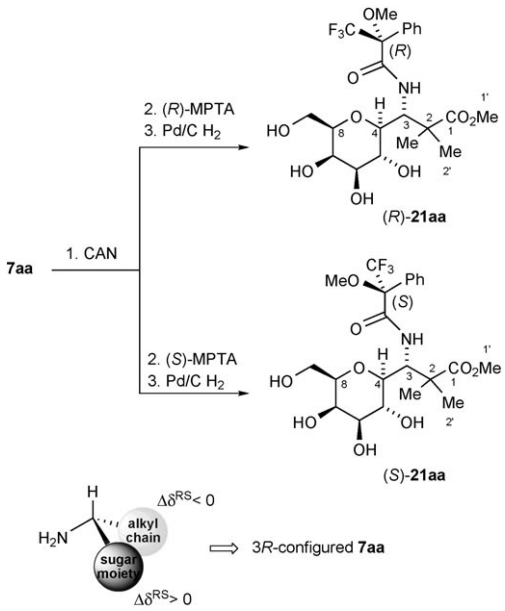


R^1	β-amino ester	Yield [%][b]	*de* [%][c]
β-galactosyl, **1a**	 **19**	30	100
β-ribosyl, **1d**	 **20**	32	100

[a] Isolated yields. [b] Determined by ^1H NMR analysis of the crude reaction mixture.

of zinc enolates to N-PMB imines under conventional Reformatsky conditions.[38] A complete diastereoselectivity and a comparable moderate yield (32%) was also observed for the synthesis of β-amino ester **20** prepared under the above reaction conditions from the corresponding C-ribosyl formaldehyde **1d** (Table 6). Any attempts to assign the absolute configuration at C-3 of derivatives **19** and **20** (see next section) as well as to improve the chemical yield of the above transformations have been fruitless so far.[39] Evidently, this exploratory work on the synthesis and structural analysis of α,α-difluoro C-glycosyl β-amino acids needs further research. In our laboratory both issues are intensely pursued by addressing effective catalytic Reformatsky conditions and exhaustive crystallographic and NMR investigations.

Structure assignments: Structure and absolute configuration assignments of β-amino esters **7** were performed by using one- and two-dimensional ^{1}H and ^{13}C NMR spectroscopic analysis supported by X-ray crystallographic data. The β-linkage at the anomeric carbon (C-4) of the sugar moieties was confirmed for all compounds by estimating the $J_{4,5}$ values or by the aid of NOE measurements, as appropriate. In fact, as anticipated, galactopyranosyl and glucopyranosyl derivatives showed $J_{4,5}$ values around 9.0 Hz. The ribofuranosyl and arabinofuranosyl derivatives instead displayed NOE values between H-4 and H-7, the mannopyranosyl derivatives between H-4 and H-8. These results indicate that the stereochemical integrity at the anomeric carbon of the sugar aldehydes **1** and intermediate imines **3** was retained in the course of the three-component reactions in agreement with previous studies in our laboratory.[16,17,22l,23h,i] The assignment of the absolute configuration at the newly formed C-3 stereocenter of β-amino esters **7** was a crucial problem of this research and we thought to conveniently solve it by means of X-ray crystallography. Nevertheless, the reluctance of most of these compounds to give suitable crystals for X-ray analysis prompted us to consider an alternative methodology. In this regard, we focused out attention on NMR methods for the determination of the absolute configuration of chiral primary amines.[40] These methods usually involve a double derivatization of the substrate of unknown configuration with the two enantiomers of a chiral auxiliary. Then the chemical shifts of the signals due to protons in the resulting diastereoisomers are determined and the corresponding differences expressed as $\Delta\delta^{RS}$. Accordingly, compound **7aa** was transformed into the corresponding hydroxy-free (*R*)- and (*S*)-methoxytrifluoromethylphenylacetic (MTPA) amides (*R*)-**21aa** and (*S*)-**21aa** (Mosher's amides)[41] by means of a simple reaction sequence involving N-PMB group removal, (*R*)- or (*S*)-Mosher's acid condensation, and benzyl groups hydrogenolysis (Scheme 6).[42] The assignment of the configuration at C-3 was then straightforward from the analysis of the ^{1}H NMR spectra of (*R*)-**21aa** and (*S*)-**21aa** and determination of $\Delta\delta^{RS}$ signs in agreement with the protocol developed by Riguera and co-workers.[40d] In fact, a positive $\Delta\delta^{RS}$ value was observed for the protons of the sugar moiety (from H-4 to H-9) while a negative $\Delta\delta^{RS}$ value



Scheme 6. NMR method for the determination of the absolute configuration at β-carbon.

was found for the protons of the alkyl chain (H-2′ and H-1′). This result allowed us to pinpoint the spatial location of the substituents (the sugar moiety and the alkyl chain) around the C-3 stereocenter and therefore assign the 3*R* configuration on the basis of the proposed configurational model.[40d] Fortunately enough, this structure assignment was confirmed by the X-ray crystallographic analysis of a derivative of **7aa** which was obtained in a suitable crystalline form (see Supporting Information and ref. [16]). Having thus validated the above NMR methodology for this class of glycosylated β-amino esters, we applied the same protocol to the Mosher's amides arising from the α,α-dimethyl β-amino esters **7ba–ea** and to the representative α-unsubstituted β-amino ester **7ab** (see Experimental Section).[43] The results of this NMR investigation led us to assign the 3*R* configuration to all β-amino esters **7** and therefore postulate an identical steric course for all relevant reactions.

Mechanistic considerations: The astonishing stereoselectivity observed in the three-component Mannich and Reformatsky reactions of sugar aldehydes **1a–e**, PMBA **2a**, and ketene silyl acetals **4a**,**b** or bromozinc enolate **5b**, respectively, which afforded exclusively β-amino esters **7** with 3*R* configuration, can be explained in terms of attack of the above C-nucleophiles from the less hindered *Re* face of the α-chelate formed by the simultaneous coordination of indium (Mannich route) or zinc (Reformatsky route) to the nitrogen of the intermediate imine **3** and the α-endocyclic oxygen of the carbohydrate moiety (Figure 2). The observed stereochemical outcome is in accordance with that previously described by Gálvez and Díaz-de-Villegas and co-workers[44] for the Lewis acid-promoted addition of ketene silyl acetals to imines derived from D-glyceraldehyde. Also in that case, the

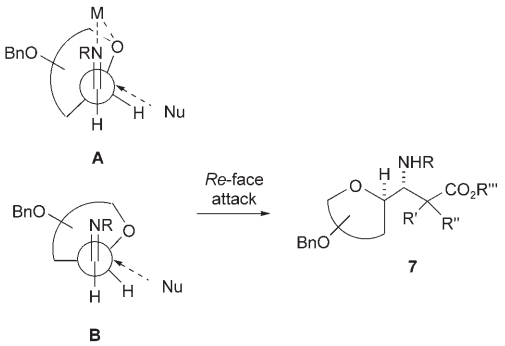


Figure 2. α-Chelate (**A**) and Felkin-Anh (**B**) models explaining the formation of 3*R*-configured β-amino esters **7**.

stereodifferentiation at the C=N double bond of imines was explained with a α-chelate model. Nevertheless, the formation of β-amino esters **7** is also consistent with a Felkin–Anh model[45] (Figure 2) in agreement with the formation of **7aa** via the Mannich route promoted by the non-chelating Lewis-acid TMSOTf (Table 1, entries 5 and 6). On the contrary, the polar Felkin–Anh model,[46] which is commonly accepted as the preferred explanation for 1,2-asymmetric induction in α-heteroatom-substituted aldehydes, predicted the opposite 3*S* configuration. Currently, the proposal of transition-state models that take into account the above-mentioned features (Figure 2) and rationalize the observed stereochemical outcome is highly speculative. We feel that more information on the imine structure as well as the complexing ability of all the oxygen functions of the carbohydrate toward Lewis acids is needed for a better understanding of the reasons of the strong stereocontrol. The need for more detailed studies is also justified by the paucity of any in depth systematic investigations reported in the literature examining the addition of C-nucleophiles to imine derivatives containing an adjacent stereocenter.[18a,44]

Conclusion

In summary, it has been shown that the implementation of the valuable sugar aldehydes **1** as key components in the one-pot Mannich and Reformatsky 3-CR allows for an efficient and straightforward entry to the class of C-glycosyl β-amino esters **7**. It is noteworthy that both Mannich-type and Reformatsky-type routes occur with complete asymmetric induction furnishing the target β-amino esters **7** with 3*R* configuration. We believe that both strategies, which are also applicable to parallel synthesis programs, are of great value for the rapid generation of structurally related compound libraries. Studies on the insertion of unnatural amino acids of type **7** into glycopeptides of biological relevance and evaluation of the pharmacological activity of the resulting C-glyco-β-peptide mimetics are currently underway.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere by using oven-dried glassware. Solvents were dried over standard drying agent and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (5 μm average particle size) were used without further activation. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Melting points were determined with a capillary apparatus. Optical rotations were measured at 20±2°C in the solvent given; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H (300 MHz), ^{19}F (282 MHz), and ^{13}C (75 MHz) NMR spectra were recorded for $CDCl_3$ solutions at room temperature unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. Aldehydes **1a**–**e**[24] and (1-ethoxyvinyloxy)trimethylsilane (**4b**)[28] were synthesized as described.

General procedure for the Mannich-type synthesis of C-glycosyl β-amino esters 7aa, 7ba, 7ca, and 7ea: A mixture of aldehyde **1** (1.00 mmol), *p*-methoxybenzylamine **2a** (131 μL, 1.00 mmol), activated 4 Å powdered molecular sieves (150 mg), and anhydrous MeOH (3 mL) was stirred at room temperature for 15 min; then $InCl_3$ (44 mg, 0.20 mmol) was added in one portion. The mixture was stirred at room temperature for 30 min; then 1-methoxy-2-methyl-1-trimethylsilyloxypropene (**4a**; 304 μL, 1.50 mmol) was added slowly. The mixture was stirred at room temperature for an additional 12 h, then diluted with AcOEt (10 mL), filtered through a pad of Celite, and concentrated. The residue was suspended in AcOEt (100 mL) and washed with H_2O (2×10 mL). The organic phase was dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel with the suitable elution system to give the corresponding β-amino ester.

Methyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*p*-methoxybenzylamino)-D-*threo*-L-*galacto*-nonanoate (7aa): Column chromatography with cyclohexane/AcOEt 5:1 afforded **7aa** (619 mg, 80%) as a white foam; $[\alpha]_D=-12.0$ (c = 1.3, $CHCl_3$); ^{1}H NMR (C_6D_6): δ=7.40–6.70 (m, 24H, Ph), 5.02, 4.65 (2d, J=11.0 Hz, 2H, PhCH_2), 4.98, 4.50 (2d, J=11.5 Hz, 2H, PhCH_2), 4.42, 4.32 (2d, J=11.8 Hz, 2H, PhCH_2), 4.24, 4.16 (2d, J=12.0 Hz, 2H, PhCH_2), 4.15 (dd, $J_{4,5}$=9.0, $J_{5,6}$=9.5 Hz, 1H, H-5), 4.04, 3.72 (2d, J=12.5 Hz, 2H, PhCH_2), 3.86 (dd, $J_{6,7}$=3.0, $J_{7,8}$~0.5 Hz, 1H, H-7), 3.58–3.53 (m, 2H, H-9a, H-3 or H-9b), 3.45–3.40 (m, 3H, H-4, H-8, H-9b or H-3), 3.42 (s, 3H, OCH_3), 3.36 (dd, 1H, H-6), 3.29 (s, 3H, OCH_3), 1.43 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR: δ= 178.2, 158.4, 139.1, 138.6, 138.3, 137.9, 133.8, 129.1, 129.0, 128.5–127.3 (12C), 113.5, 113.4, 85.7, 77.5, 77.4, 76.1, 75.1, 74.4, 73.7, 73.5, 72.0, 68.9, 61.4, 55.3, 54.2, 51.5, 48.2, 23.1, 20.9; MALDI-TOF MS: m/z: 773.3 [M^+], 796.9 [M^++Na]; elemental analysis calcd (%) for $C_{48}H_{55}NO_8$ (773.95): C 74.49, H 7.16, N 1.81; found: C 74.47, H 7.12, N 1.80.

Methyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*p*-methoxybenzylamino)-D-*erythro*-L-*galacto*-nonanoate (7ba): Column chromatography with cyclohexane/AcOEt 5:1 afforded **7ba** (697 mg, 90%) as a white foam; $[\alpha]_D=-17.7$ (c = 0.4, $CHCl_3$);^{1}H NMR: δ=7.40–6.80 (m, 24H, Ph), 4.95, 4.71 (2d, J=11.0 Hz, 2H, PhCH_2), 4.94, 4.87 (2d, J=10.5 Hz, 2H, PhCH_2), 4.84, 4.65 (2d, J=10.8 Hz, 2H, PhCH_2), 4.53, 4.46 (2d, J=12.0 Hz, 2H, PhCH_2), 3.80, 3.61 (2d, J=12.5 Hz, 2H, PhCH_2), 3.76 (s, 3H, OCH_3), 3.73–3.59 (m, 5H, H-5, H-6, H-7, 2H-9), 3.62 (s, 3H, OCH_3), 3.42 (ddd, $J_{7,8}$=9.0, $J_{8,9a}$=1.5, $J_{8,9b}$=3.5 Hz, 1H, H-8), 3.37 (d, $J_{3,4}$~0.5 Hz, 1H, H-3), 3.34 (dd, $J_{4,5}$=9.5 Hz, 1H, H-4), 1.60 (br s, 1H, NH), 1.21 (s, 3H, CH_3), 1.19 (s, 3H, CH_3); ^{13}C NMR: δ=178.2, 159.3, 139.0, 138.8, 138.7, 138.5, 134.5, 129.3–127.6 (14C), 112.2, 112.1, 88.1, 79.8, 78.7, 78.2, 77.3, 75.8, 75.3, 75.2, 73.8, 69.4, 61.2, 55.7, 54.0, 51.9, 48.0, 23.9, 20.7; MALDI-TOF MS: m/z: 774.3 [M^++H], 796.3 [M^++Na]; elemental analysis calcd (%) for $C_{48}H_{55}NO_8$ (773.95): C 74.49, H 7.16, N 1.81; found: C 74.45, H 7.20, N 1.85.

Methyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*p*-methoxybenzylamino)-D-*glycero*-D-*altro*-octanoate (7da): Column chromatography with cyclohexane/AcOEt 5:1 afforded **7da** (556 mg, 85%) as a white foam; $[\alpha]_D=-43.0$ (c = 1.1, $CHCl_3$); ^{1}H NMR: δ=7.40–6.70 (m,

20H, Ph, NH), 4.62, 4.40 (2d, $J=11.8$ Hz, 2H, PhCH_2), 4.58, 4.54 (2d, $J=12.0$ Hz, 2H, PhCH_2), 4.36, 4.31 (2d, $J=11.5$ Hz, 2H, PhCH_2), 4.16 (ddd, $J_{6,7}=6.0$, $J_{7,8a}=4.0$, $J_{7,8b}=4.5$ Hz, 1H, H-7), 4.13 (dd, $J_{3,4}\sim0.5$, $J_{4,5}=4.5$ Hz, 1H, H-4), 3.90 (dd, $J_{5,6}=2.5$ Hz, 1H, H-6), 3.79 (dd, 1H, H-5), 3.75 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.55, 3.42 (2d, $J=13.0$ Hz, 2H, PhCH_2), 3.46 (dd, $J_{8a,8b}=10.0$ Hz, 1H, H-8a), 3.38 (dd, 1H, H-8b), 3.06 (d, $J_{3,4}=\approx0.5$ Hz, 1H, H-3), 1.23, 1.21 (2s, 6H, 2CH_3); ^{13}C NMR: $\delta=$ 178.4, 158.3, 138.0, 137.8, 137.7, 133.7, 129.0–127.6 (11C), 113.4, 113.3, 81.6, 80.6, 79.1, 76.3, 73.1, 71.9, 71.6, 70.0, 63.1, 55.2, 54.2, 51.6, 48.0, 23.1, 21.3; MALDI-TOF MS: m/z: 653.9 [M^+]; elemental analysis calcd (%) for $C_{40}H_{47}NO_7$ (653.80): C 73.48, H 7.25, N 2.14; found: C 73.53, H 7.22, N 2.18.

Methyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*p*-methoxybenzylamino)-D-*glycero*-D-*ido*-octanoate (7ea): Column chromatography with cyclohexane/AcOEt 5:1 afforded **7ea** (490 mg, 75%) as a white foam; $[\alpha]_D=1.1$ (c = 1.2, $CHCl_3$); ^{1}H NMR: $\delta=7.40$–6.70 (m, 19H, Ph), 4.60 (s, 2H, PhCH_2), 4.58, 4.51 (2d, $J=11.0$ Hz, 2H, PhCH_2), 4.48, 4.42 (2d, $J=12.0$ Hz, 2H, PhCH_2), 4.08–4.01 (m, 2H, H-6, H-7), 3.98 (dd, $J_{3,4}=2.5$, $J_{4,5}=4.5$ Hz, 1H, H-4), 3.91 (dd, $J_{5,6}=4.5$ Hz, 1H, H-5), 3.88, 3.49 (2d, $J=12.5$ Hz, 2H, PhCH_2), 3.78 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.58 (dd, $J_{7,8a}=5.0$, $J_{8a,8b}=10.0$ Hz, 1H, H-8a), 3.52 (dd, $J_{7,8b}=5.5$ Hz, 1H, H-8b), 3.32 (d, $J_{3,4}$ = 2.5 Hz, 1H, H-3), 1.80 (brs, 1H, NH), 1.21 (s, 3H, CH_3), 1.14 (s, 3H, CH_3); MALDI-TOF MS: m/z: 654.6 [M^++H]; elemental analysis calcd (%) for $C_{40}H_{47}NO_7$ (653.80): C 73.48, H 7.25, N 2.14; found: C 73.52, H 7.22, N 2.20.

Methyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*p*-methoxybenzylamino)-D-*erythro*-L-*gluco*-nonanoate (7ca): A mixture of aldehyde **1c** (552 mg, 1.00 mmol), *p*-methoxybenzylamine **2a** (132 μL, 1.00 mmol), activated 4 Å powdered molecular sieves (150 mg), and anhydrous CH_2Cl_2 (3 mL) was stirred at room temperature for 15 min and then cooled to 0°C. To the mixture was then added $InCl_3$ (44 mg, 0.20 mmol) in one portion. The mixture was stirred at 0°C for 30 min then 1-methoxy-2-methyl-1-trimethylsilyloxypropene (**4a**; 304 μL, 1.50 mmol) was slowly added. The mixture was stirred at 0°C for an additional 16 h, then diluted with CH_2Cl_2 (10 mL), filtered through a pad of Celite, and concentrated. The residue was suspended in CH_2Cl_2 (100 mL) and washed with H_2O (2×10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with cyclohexane/AcOEt 2:1 (containing 3% Et_3N) to afford first byproduct **8** (200 mg, 30%) as a 1:1 mixture of 3*R* and 3*S* epimers.

Second eluted compound was **7ca** (464 mg, 60%) as a white foam $[\alpha]_D=-30.7$ (c = 0.8, $CHCl_3$); ^{1}H NMR: $\delta=7.40$–7.10, 6.90–6.60 (2m, 24H, Ph), 5.26, 4.72 (2d, $J=11.5$ Hz, 2H, PhCH_2), 4.90, 4.67 (2d, $J=11.0$ Hz, 2H, PhCH_2), 4.80 (s, 2H, PhCH_2), 4.63, 4.42 (2d, $J=12.0$ Hz, 2H, PhCH_2), 4.07 (dd, $J_{6,7}=9.2$, $J_{7,8}=9.5$ Hz, 1H, H-7), 3.87, 3.34 (2d, $J=$ 12.5 Hz, 2H, PhCH_2), 3.80 (dd, $J_{8,9a}=4.5$, $J_{9a,9b}=11.5$ Hz, 1H, H-9a), 3.78 (dd, $J_{4,5}\sim0.5$, $J_{5,6}=2.5$ Hz, 1H, H-5), 3.72 (s, 3H, OCH_3), 3.69 (dd, $J_{8,9b}=$ 1.5 Hz, 1H, H-9b), 3.66 (dd, 1H, H-6), 3.60 (s, 3H, OCH_3), 3.42 (ddd, 1H, H-8), 3.18 (dd, $J_{3,4}=2.5$ Hz, 1H, H-4), 3.00 (d, $J_{3,4}$ = 2.5 Hz, 1H, H-3), 1.61 (brs, 1H, NH), 1.20 (s, 3H, CH_3), 1.07 (s, 3H, CH_3); ^{13}C NMR: $\delta=178.2$, 158.1, 139.4, 139.3, 139.2, 139.1, 134.1, 129.7–127.2 (14C), 113.2, 113.1, 85.3, 79.8, 77.9, 76.9, 75.1, 75.0, 74.7, 73.3, 72.8, 69.6, 63.5, 55.2, 54.2, 51.5, 49.1, 22.1, 20.0; MALDI-TOF MS: m/z: 774.4 [M^++H]; elemental analysis calcd (%) for $C_{48}H_{55}NO_8$ (773.95): C 74.49, H 7.16, N 1.81; found: C 74.55, H 7.19, N 1.85.

Analytical samples of each epimeric **8** were obtained by preparative TLC (cyclohexane/AcOEt 2:1 containing 3% Et_3N). First eluted compound: ^{1}H NMR: $\delta=7.40$–6.80 (m, 19H, Ph), 4.83 (d, $J_{5,6}=3.0$ Hz, 1H, H-5), 4.82, 4.69 (2d, $J=11.5$ Hz, 2H, PhCH_2), 4.65, 4.55 (2d, $J=11.5$ Hz, 2H, PhCH_2), 4.56 (s, 2H, PhCH_2), 4.25 (dd, $J_{6,7}=5.5$ Hz, 1H, H-6), 4.14 (ddd, $J_{7,8}=8.0$, $J_{8,9a}=4.5$, $J_{8,9b}=3.0$ Hz, 1H, H-8), 3.88 (dd, 1H, H-7), 3.82 (dd, $J_{9a,9b}=10.5$ Hz, 1H, H-9a), 3.81 (s, 3H, OCH_3), 3.76 (dd, 1H, H-9b), 3.74, 3.50 (2d, $J=13.0$ Hz, 2H, PhCH_2), 3.62 (s, 3H, OCH_3), 3.22 (s, 1H, H-3), 1.62 (brs, 1H, NH), 1.24 (s, 3H, CH_3), 1.19 (s, 3H, CH_3); MALDI-TOF MS: m/z: 666.3 [M^++H];, elemental analysis calcd (%) for $C_{41}H_{47}NO_7$ (665.81): C 73.96, H 7.12, N 2.10; found: C 74.00, H 7.16, N 2.12.

Second eluted compound: ^{1}H NMR: $\delta=7.40$–6.70 (m, 19H, Ph), 4.84, 4.71 (2d, $J=11.0$ Hz, 2H, PhCH_2), 4.80 (d, $J_{5,6}=3.0$ Hz, 1H, H-5), 4.68, 4.59 (2d, $J=11.5$ Hz, 2H, PhCH_2), 4.56 (s, 2H, PhCH_2), 4.23 (dd, $J_{6,7}=$ 5.5 Hz, 1H, H-6), 4.13 (ddd, $J_{7,8}=8.0$, $J_{8,9a}=4.5$, $J_{8,9b}=3.0$ Hz, 1H, H-8), 3.92 (dd, 1H, H-7), 3.88 (dd, $J_{9a,9b}=11.0$ Hz, 1H, H-9a), 3.80, 3.54 (2d, $J=13.0$ Hz, 2H, PhCH_2), 3.79 (s, 3H, OCH_3), 3.74 (dd, 1H, H-9b), 3.60 (s, 3H, OCH_3), 3.15 (s, 1H, H-3), 1.62 (brs, 1H, NH), 1.18 (s, 6H, 2CH_3); MALDI-TOF MS: m/z: 666.5 [M^++H].

General procedure for the Mannich-type synthesis of C-glycosyl β-amino esters 7ab, 7bb, and 7db: A mixture of aldehyde **1** (1.00 mmol), *p*-methoxybenzylamine **2a** (132 μL, 1.00 mmol), activated 4 Å powdered molecular sieves (150 mg), and anhydrous MeOH (3 mL) was stirred at room temperature for 15 min; then $InCl_3$ (44 mg, 0.20 mmol) was added in one portion. The mixture was stirred at room temperature for 30 min; then (1-ethoxyvinyloxy)trimethylsilane (**4b**)[28] (801 mg, 5.00 mmol) was slowly added. The mixture was stirred at room temperature for an additional 12 h, then diluted with AcOEt (10 mL), filtered through a pad of Celite, and concentrated. The residue was suspended in AcOEt (100 mL) and washed with H_2O (2×10 mL). The organic phase was dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel with the suitable elution system to give the corresponding β-amino ester.

Ethyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-3-(*p*-methoxybenzylamino)-D-*threo*-L-*galacto*-nonanoate (7ab): Column chromatography with cyclohexane/AcOEt 3:1 (containing 3% Et_3N) afforded **7ab** (456 mg, 60%) as a colorless syrup; $[\alpha]_D=1.5$ (c = 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$ + D_2O): $\delta=7.40$–6.70 (m, 24H, Ph), 5.01, 4.61 (2d, $J=$ 11.5 Hz, 2H, PhCH_2), 4.88, 4.48 (2d, $J=10.5$ Hz, 2H, PhCH_2), 4.77, 4.68 (2d, $J=11.5$ Hz, 2H, PhCH_2), 4.48, 4.44 (2d, $J=11.5$ Hz, 2H, PhCH_2), 4.30 (brdd, $J_{4,5}=9.5$, $J_{5,6}=9.2$ Hz, 1H, H-5), 4.14 (q, $J=7.0$ Hz, 2H, OCH_2CH$_3$), 4.01 (dd, $J_{6,7}=2.5$, $J_{7,8}\sim0.5$ Hz, 1H, H-7), 3.86, 3.62 (2d, $J=$ 12.5 Hz, 2H, PhCH_2), 3.72 (s, 3H, OCH_3), 3.62 (dd, 1H, H-6), 3.58–3.51 (m, 3H, H-8, H-9a, H-9b), 3.50 (ddd, $J_{2a,3}=5.5$, $J_{2b,3}=6.0$, $J_{3,4}\sim0.5$ Hz, 1H, H-3), 3.31 (dd, 1H, H-4), 2.72 (dd, $J_{2a,2b}=14.0$ Hz, 1H, H-2a), 2.62 (dd, 1H, H-2b), 1.24 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR: $\delta=$ 172.4, 158.5, 138.9–137.8 (5C), 129.6, 129.5, 128.4–127.3 (12C), 113.6, 113.5, 85.0, 81.1, 76.8, 75.1, 74.9, 74.3, 73.7, 73.4, 72.2, 68.7, 60.3, 55.1, 52.6, 50.0, 36.4, 14.2; MALDI-TOF MS: m/z: 760.1 [M^++H], 798.1 [M^+ +K]; elemental analysis calcd (%) for $C_{47}H_{53}NO_8$ (759.93): C 74.28, H 7.03, N 1.84; found: C 74.00, H 7.10, N 1.80.

Ethyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-3-(*p*-methoxybenzylamino)-D-*erythro*-L-*galacto*-nonanoate (7bb): Column chromatography with cyclohexane/AcOEt 3:1 (containing 3% Et_3N) afforded **7bb** (441 mg, 58%) as a white foam; $[\alpha]_D=-8.7$ (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ + D_2O): $\delta=7.40$–6.80 (m, 24H, Ph), 4.88 (s, 2H, PhCH_2), 4.83, 4.56 (2d, $J=11.0$ Hz, 2H, PhCH_2), 4.81, 4.50 (2d, $J=12.0$ Hz, 2H, PhCH_2), 4.59, 4.51 (2d, $J=10.5$ Hz, 2H, PhCH_2), 4.13 (q, $J=7.0$ Hz, 2H, OCH_2CH$_3$), 3.97 (dd, $J_{4,5}=9.5$, $J_{5,6}=9.2$ Hz, H-5), 3.88, 3.58 (2d, $J=$ 13.0 Hz, 2H, PhCH_2), 3.72 (s, 3H, OCH_3), 3.71–3.66 (m, 3H, H-6, 2 H-9), 3.61 (dd, $J_{6,7}=9.0$, $J_{7,8}=9.2$ Hz, 1H, H-7), 3.47 (ddd, $J_{2a,3}=6.5$, $J_{2b,3}=7.5$, $J_{3,4}\sim0.5$ Hz, 1H, H-3), 3.42–3.38 (m, 1H, H-8), 3.32 (dd, 1H, H-4), 2.74 (dd, $J_{2a,2b}=14.0$ Hz, 1H, H-2a), 2.67 (dd, $J_{2b,3}$ = 7.5 Hz, 1H, H-2b), 1.22 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR: $\delta=172.4$, 158.6, 138.8, 138.7, 138.6, 138.5, 138.4, 129.6–127.5 (14C), 113.7, 113.6, 87.3, 80.9, 78.9, 78.3, 78.1, 75.5, 74.9, 74.7, 73.3, 69.1, 60.4, 55.1, 52.5, 50.0, 35.0, 14.2; MALDI-TOF MS: m/z: 760.3 [M^++H], 782.3 [M^++Na], 798.3 [M^++K]; elemental analysis calcd (%) for $C_{47}H_{53}NO_8$ (759.93): C 74.28, H 7.03, N 1.84; found: C 74.30, H 7.10, N 1.87.

Ethyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-3-(*p*-methoxybenzylamino)-D-*glycero*-D-*altro*-octanoate (7db): Column chromatography with cyclohexane/AcOEt 5:2 (containing 3% Et_3N) afforded **7db** (397 mg, 62%) as a white foam; $[\alpha]_D=2.3$ (c = 0.6, $CHCl_3$); ^{1}H NMR: $\delta=7.40$–6.70 (m, 19H, Ph), 4.58, 4.51 (2d, $J=11.8$ Hz, 2H, PhCH_2), 4.50 (s, 2H, PhCH_2), 4.48, 4.42 (2d, $J=12.0$ Hz, 2H, PhCH_2), 4.20–4.08 (m, 4H, H-4, H-7, OCH_2CH$_3$), 4.04 (dd, $J_{5,6}=4.5$, $J_{6,7}=5.0$ Hz, 1H, H-6), 3.93 (dd, $J_{4,5}=4.5$ Hz, 1H, H-5), 3.80 (s, 3H, OCH_3), 3.72, 3.54 (2d, $J=13.0$ Hz, 2H, PhCH_2), 3.60 (dd, $J_{7,8a}=3.5$, $J_{8a,8b}=10.5$ Hz, 1H, H-8a), 3.48 (dd, $J_{7,8b}=4.0$ Hz, 1H, H-8b), 3.10 (brs, 1H, H-3), 2.57 (d, $J=6.5$ Hz, 2H, 2H-2), 1.61 (brs, 1H, NH), 1.26 (t, $J=7.0$ Hz, 3H, OCH$_2$CH_3); ^{13}C NMR: $\delta=172.3$, 158.6, 138.0, 137.9, 137.8, 137.7, 129.3–127.6 (11C), 113.6, 113.5,

83.8, 80.6, 78.0, 77.3, 73.2, 71.8, 71.6, 71.5, 69.8, 60.5, 55.2, 55.1, 50.2, 14.2; MALDI-TOF MS: *m/z*: 640.4 [M^++H], 662.4 [M^++Na], 678.3 [M^++K]; elemental analysis calcd (%) for $C_{39}H_{45}NO_7$ (639.78): C 73.22, H 7.09, N 2.19; found: C 73.27, H 7.11, N 2.14.

General procedure for the synthesis of N-Boc derivatives 13aa–ab, 13ba–bb, 13ca, 13da–db, 13ea–eb, and 15: CAN (1.10 g, 2.00 mmol) was added in one portion to a cooled (0 °C) stirred solution of N-PMB-derivative (0.50 mmol) in CH_3CN (20 mL) and H_2O (5 mL). The resulting mixture was vigorously stirred at room temperature for 6 h, quenched with a few drops of saturated aqueous Na_2SO_3 solution, and then concentrated to remove most of the CH_3CN.

The above mixture was diluted with dioxane (10 mL) then Boc_2O (546 mg, 2.50 mmol) and a few drops of saturated aqueous $NaHCO_3$ solution (until basic pH) were added. The solution was stirred at room temperature for 12 h then diluted with Et_2O (100 mL) and washed with a 10% aqueous solution of citric acid (2×10 mL). The organic phase was separated, washed with brine (2×10 mL), dried (Na_2SO_4) and concentrated. The residue was then purified by column chromatography on silica gel with the suitable elution system to give the corresponding N-Boc derivative.

Methyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-nonanoate (13aa): Column chromatography with cyclohexane/AcOEt 6:1 afforded **13aa** (320 mg, 85%) as a white foam; $[\alpha]_D$=31.4 (c = 1.5, $CHCl_3$); ^{1}H NMR: δ=7.50–7.25 (m, 20H, 4Ph), 5.42 (d, $J_{3,NH}$=10.5 Hz, 1H, NH), 5.01, 4.58 (2d, J=12.0 Hz, 2H, PhCH_2), 4.86, 4.77 (2d, J=10.5 Hz, 2H, PhCH_2), 4.78, 4.71 (2d, J=11.5 Hz, 2H, PhCH_2), 4.47, 4.42 (2d, J=11.8 Hz, 2H, PhCH_2), 4.26 (dd, $J_{3,4}$~0.5 Hz, 1H, H-3), 4.00 (dd, $J_{6,7}$=2.8, $J_{7,8}$~0.5 Hz, 1H, H-7), 3.73 (dd, $J_{4,5}$=9.0, $J_{5,6}$=9.1 Hz, 1H, H-5), 3.61 (dd, 1H, H-6), 3.59 (ddd, $J_{8,9a}$=6.5, $J_{8,9b}$=5.0 Hz, 1H, H-8), 3.56 (s, 3H, OCH_3), 3.52 (dd, $J_{9a,9b}$=11.5 Hz, 1H, H-9a), 3.45 (dd, 1H, H-9b), 3.44 (dd, 1H, H-4), 1.42 (s, 9H, *t*Bu), 1.22 (s, 6H, 2CH_3); ^{13}C NMR: δ=176.8, 156.3, 139.4, 138.7, 138.3, 137.8, 128.6–127.2 (12C), 84.9, 79.0, 77.2, 76.2, 75.4, 75.3, 74.3, 73.6, 73.4, 72.3, 68.3, 55.2, 51.6, 45.5, 28.4 (3C), 23.5, 23.0; MALDI-TOF MS: *m/z*: 754.5 [M^++H], 776.2 [M^++Na], 792.8 [M^++K]; elemental analysis calcd (%) for $C_{45}H_{55}NO_9$ (753.92): C 71.69, H 7.35, N 1.86; found: C 71.65, H 7.32, N 1.80.

Ethyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-3-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-nonanoate (13ab): Column chromatography with cyclohexane/AcOEt 5:2 afforded **13ab** (300 mg, 81%) as a white syrup $[\alpha]_D$=26.2 (c = 0.8, $CHCl_3$); ^{1}H NMR: δ=7.45–7.20 (m, 20H, 4Ph), 5.16 (d, $J_{3,NH}$=10.0 Hz, 1H, NH), 5.02, 4.60 (2d, J=11.5 Hz, 2H, PhCH_2), 4.87, 4.70 (2d, J=10.0 Hz, 2H, PhCH_2), 4.80, 4.74 (2d, J=12.0 Hz, 2H, PhCH_2), 4.58 (dddd, $J_{2a,3}$=8.0, $J_{2b,3}$=8.0, $J_{3,4}$~0.5 Hz, 1H, H-3), 4.49, 4.45 (2d, J=11.0 Hz, 2H, PhCH_2), 4.20–4.02 (m, 2H, OC$H_2$$CH_3$), 4.02 (dd, $J_{6,7}$=2.5, $J_{7,8}$~0.5 Hz, 1H, H-7), 3.87 (dd, $J_{4,5}$=9.0, $J_{5,6}$=9.5 Hz, 1H, H-5), 3.65 (dd, 1H, H-6), 3.62–3.50 (m, 3H, H-8, 2H-9), 3.35 (dd, 1H, H-4), 2.58 (d, J = 8.0 Hz, 2H, 2H-2), 1.44 (s, 9H, *t*Bu), 1.25 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=171.1, 155.3, 138.4, 138.2, 138.0, 137.8, 128.7–127.4 (12C), 84.5, 79.5, 79.2, 76.4, 75.5, 75.1, 74.3, 73.7, 73.5, 72.3, 68.6, 60.4, 46.9, 38.2, 28.3 (3C), 14.1; MALDI-TOF MS: *m/z*: 762.5 [M^++Na], 778.5 [M^++K]; elemental analysis calcd (%) for $C_{44}H_{53}NO_9$ (739.89): C 71.43, H 7.22, N 1.89; found: C 71.40, H 7.28, N 1.82.

Methyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-nonanoate (13ba): Column chromatography with toluene/AcOEt 14:1 afforded **13ba** (294 mg, 78%) as a white foam; $[\alpha]_D$=26.6 (c = 1.2, $CHCl_3$); ^{1}H NMR: δ=7.50–7.05 (m, 20H, 4Ph), 5.40 (d, $J_{3,NH}$=10.5 Hz, 1H, NH), 4.93 (s, 2H, PhCH_2), 4.84, 4.62 (2d, J=11.0 Hz, 2H, PhCH_2), 4.82, 4.79 (2d, J=10.0 Hz, 2H, PhCH_2), 4.57, 4.51 (2d, J=12.0 Hz, 2H, PhCH_2), 4.24 (dd, $J_{3,4}$~0.5 Hz, 1H, H-3), 3.74 (dd, $J_{8,9a}$=4.0, $J_{9a,9b}$=11.0 Hz, 1H, H-9a), 3.71 (dd, $J_{4,5}$=6.5 Hz, 1H, H-4), 3.62 (dd, $J_{6,7}$=9.0, $J_{7,8}$=9.2 Hz, 1H, H-7), 3.61 (dd, $J_{8,9b}$=1.5 Hz, 1H, H-9b), 3.57 (s, 3H, OCH_3), 3.50–3.38 (m, 2H, H-5, H-6), 3.35 (ddd, 1H, H-8), 1.51 (s, 9H, *t*Bu), 1.26 (s, 6H, 2CH_3); ^{13}C NMR: δ=176.6, 156.1, 138.5, 138.3, 138.2, 138.1, 128.5–127.2 (12C), 87.4, 79.3, 78.5, 77.9, 76.9, 75.7, 75.2, 74.9, 73.2, 68.7, 55.8, 55.0, 51.6, 45.5, 28.4 (3C), 23.4, 23.2; MALDI-TOF MS: *m/z*: 774.6 [M^++Na]; elemental analysis calcd (%) for $C_{45}H_{55}NO_9$ (753.92): C 71.69, H 7.35, N 1.86;; found: C 71.73, H 7.37, N 1.80.

Ethyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-3-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-nonanoate (13bb): Column chromatography with cyclohexane/AcOEt 5:2 afforded **13bb** (263 mg, 71%) as a white foam; $[\alpha]_D$=24.5 (c = 0.6, $CHCl_3$); ^{1}H NMR: δ=7.50–7.10 (m, 20H, 4 Ph), 5.05 (d, $J_{3,NH}$=10.0 Hz, 1H, NH), 4.94, 4.90 (2d, J=11.0 Hz, 2H, PhCH_2), 4.83, 4.59 (2d, J=10.5 Hz, 2H, PhCH_2), 4.79, 4.68 (2d, J=10.0 Hz, 2H, PhCH_2), 4.58 (dddd, $J_{2a,3}$=8.0, $J_{2b,3}$=8.0, $J_{3,4}$~0.5 Hz, 1H, H-3), 4.56, 4.52 (2d, J=11.0 Hz, 2H, PhCH_2), 4.16–4.08 (m, 2H, OC$H_2$$CH_3$), 3.72 (dd, $J_{8,9a}$=5.0, $J_{9a,9b}$=11.0 Hz, 1H, H-9a), 3.71 (dd, $J_{5,6}$=9.0, $J_{6,7}$=9.2 Hz, 1H, H-6), 3.68 (dd, $J_{8,9b}$=2.8 Hz, 1H, H-9b), 3.62 (dd, $J_{7,8}$=9.0 Hz, 1H, H-7), 3.50 (d, $J_{4,5}$=9.2 Hz, 1H, H-5), 3.40 (ddd, 1H, H-8), 3.32 (dd, $J_{3,4}$ ≈0.5, $J_{4,5}$ = 9.2 Hz, 1H, H-4), 2.60 (d, J=8.0 Hz, 2H, 2H-2), 1.44 (s, 9H, *t*Bu), 1.26 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=171.0, 155.1, 138.5, 138.4, 138.1, 138.0, 128.7–127.7 (12C), 87.0, 79.4, 78.8, 78.3, 78.1, 75.6, 75.3, 75.0, 73.4, 69.0, 60.5, 46.6, 38.4, 29.7, 28.3 (3C), 14.1; MALDI-TOF MS: *m/z*: 762.6 [M^++Na], 778.4 [M^++K]; elemental analysis calcd (%) for $C_{44}H_{53}NO_9$ (739.89): C 71.43, H 7.22, N 1.89; found: C 71.50, H 7.18, N 1.92.

Methyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*gluco*-nonanoate (13ca): Column chromatography with cyclohexane/AcOEt 5:1 afforded **13ca** (294 mg, 78%) as a white foam; $[\alpha]_D$=1.5 (c = 0.8, $CHCl_3$); ^{1}H NMR: δ=7.40–7.10 (m, 20H, 4 Ph), 5.37 (d, $J_{3,NH}$=9.5 Hz, 1H, NH), 4.88, 4.80 (2d, J=11.5 Hz, 2H, PhCH_2), 4.84, 4.57 (2d, J=11.0 Hz, 2H, PhCH_2), 4.69, 4.65 (2d, J=11.8 Hz, 2H, PhCH_2), 4.66, 4.51 (2d, J=12.0 Hz, 2H, PhCH_2), 4.18 (dd, $J_{3,4}$~0.5 Hz, 1H, H-3), 3.96 (dd, $J_{6,7}$=9.5, $J_{7,8}$=9.0 Hz, 1H, H-7), 3.87 (dd, $J_{4,5}$~0.5, $J_{5,6}$=2.5 Hz, 1H, H-5), 3.77 (dd, $J_{8,9a}$=5.0, $J_{9a,9b}$=11.0 Hz, 1H, H-9a), 3.67 (dd, $J_{8,9b}$=1.5 Hz, 1H, H-9b), 3.60 (s, 3H, OCH_3), 3.55 (dd, $J_{5,6}$ = 2.5, $J_{6,7}$ = 9.5 Hz, 1H, H-6), 3.40 (ddd, 1H, H-8), 3.27 (dd, $J_{3,4}$ ≈0.5, $J_{4,5}$ ≈0.5 Hz, 1H, H-4), 1.25 (s, 9H, *t*Bu), 1.22 (s, 3H, CH_3), 1.17 (s, 3H, CH_3); ^{13}C NMR: δ=177.1, 156.1, 139.2, 138.6, 138.4, 138.3, 128.3–126.9 (12C), 84.7, 79.5, 78.9, 78.0, 75.4, 75.1, 74.7, 74.1, 73.1, 72.3, 69.5, 56.6, 51.8, 47.8, 28.1 (3C), 23.7, 20.3; MALDI-TOF MS: *m/z*: 774.6 [M^++Na], 792.6 [M^++K]; elemental analysis calcd (%) for $C_{45}H_{55}NO_9$ (753.92): C 71.69, H 7.35, N 1.86; found: C 71.75, H 7.32, N 1.78.

Methyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-D-*glycero*-D-*altro*-octanoate (13da): Column chromatography with toluene/AcOEt 14:1 afforded **13da** (260 mg, 82%) as a white foam; $[\alpha]_D$=2.6 (c = 1.2, $CHCl_3$); ^{1}H NMR: δ=7.41–7.20 (m, 15H, 3Ph), 5.70 (d, $J_{3,NH}$=10.0 Hz, 1H, NH), 4.60, 4.53 (2d, J=12.0 Hz, 2H, PhCH_2), 4.53, 4.47 (2d, J=11.5 Hz, 2H, PhCH_2), 4.51, 4.41 (2d, J=11.8 Hz, 2H, PhCH_2), 4.21 (dd, $J_{3,4}$~0.5, $J_{4,5}$=5.0 Hz, 1H, H-4), 4.06 (ddd, $J_{6,7}$=5.0, $J_{7,8a}$=4.5, $J_{7,8b}$=4.5 Hz, 1H, H-7), 3.97 (dd, $J_{3,NH}$ = 10.0, $J_{3,4}$ ≈0.5 Hz, 1H, H-3), 3.79 (dd, $J_{5,6}$=4.8 Hz, 1H, H-6), 3.74 (dd, 1H, H-5), 3.60 (s, 3H, OCH_3), 3.46 (dd, $J_{8a,8b}$=10.5 Hz, 1H, H-8a), 3.35 (dd, 1H, H-8b), 1.40 (s, 9H, *t*Bu), 1.20 (s, 6H, 2CH_3); ^{13}C NMR: δ=176.8, 156.2, 138.1, 138.0, 137.9, 128.4–127.6 (9C), 81.3, 80.5, 79.8, 79.0, 77.1, 73.1, 72.8, 72.0, 69.3, 57.4, 51.8, 45.6, 28.4 (3C), 23.1, 22.8. MALDI-TOF MS: *m/z*: 656.2 [M^++Na], 672.0 [M^++K]; elemental analysis calcd (%) for $C_{37}H_{47}NO_8$ (633.77): C 70.12, H 7.47, N 2.21; found: C 70.15, H 7.45, N 2.25.

Ethyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-3-(*tert*-butoxycarbonylamino)-D-*glycero*-D-*altro*-octanoate (13db): Column chromatography with toluene/AcOEt 14:1 afforded **13db** (248 mg, 80%) as a white foam; $[\alpha]_D$=14.9 (c = 0.7, $CHCl_3$); ^{1}H NMR: δ=7.40–7.20 (m, 15H, 3Ph), 5.70 (d, $J_{3,NH}$=9.5 Hz, 1H, NH), 4.66, 4.56 (2d, J=11.5 Hz, 2H, PhCH_2), 4.60, 4.48 (2d, J=12.0 Hz, 2H, PhCH_2), 4.55, 4.42 (2 d, J=11.5 Hz, 2H, PhCH_2), 4.34–4.04 (m, 5H, H-3, H-5, H-7, OC$H_2$$CH_3$), 4.00–3.88 (m, 2H, H-4, H-6), 3.62 (dd, $J_{7,8a}$=3.5, $J_{8a,8b}$=10.5 Hz, 1H, H-8a), 3.42 (dd, $J_{7,8b}$=3.0 Hz, 1H, H-8b), 2.61 (d, J=8.0 Hz, 2H, 2H-2), 1.41 (s, 9H, *t*Bu), 1.28 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR: δ=171.1, 155.5, 137.8, 137.7, 137.6 128.5–127.6 (9C), 83.0, 81.1, 78.6, 77.7, 73.1, 72.3, 72.1, 69.0, 60.5, 49.2, 38.1, 35.3, 29.7, 28.4 (3C), 14.2; MALDI-TOF MS: *m/z*: 642.6 [M^++Na], 658.5 [M^++K]; elemental analysis calcd (%) for $C_{36}H_{45}NO_8$ (619.74): C 69.77, H 7.32, N 2.26; found: C 69.80, H 7.27, N 2.28.

Methyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(*tert*-butoxycarbonylamino)-D-*glycero*-D-*ido*-octanoate (13ea): Column chromatography with toluene/AcOEt 14:1 afforded **13ea** (241 mg, 76%) as a white foam; $[\alpha]_D = 14.4$ (c = 0.5, $CHCl_3$); ^{1}H NMR ([D$_6$]DMSO): $\delta =$ 7.40–7.20 (m, 15H, 3Ph), 6.10 (d, $J_{3,NH} = 9.0$ Hz, 1H, NH), 4.50, 4.44 (2d, $J = 11.0$ Hz, 2H, PhCH_2), 4.49 (s, 2H, PhCH_2), 4.46 (s, 2H, PhCH_2), 4.13 (dd, $J_{3,4} = 2.5$ Hz, 1H, H-3), 4.02 (dd, $J_{5,6} = 5.0$, $J_{6,7} = 3.5$ Hz, 1H, H-6), 3.98 (dd, $J_{4,5} = 5.0$ Hz, 1H, H-5), 3.96 (dd, $J_{3,4} = 2.5$, $J_{4,5} = 5.0$ Hz, 1H, H-4), 3.83 (ddd, $J_{7,8a} = 5.0$, $J_{7,8b} = 4.5$ Hz, 1H, H-7), 3.50 (s, 3H, OCH_3), 3.48 (dd, $J_{8a,8b} = 10.5$ Hz, 1H, H-8a), 3.43 (dd, 1H, H-8b), 1.35 (s, 9H, *t*Bu), 1.24, 1.22 (2s, 6H, 2CH_3); ^{13}C NMR: $\delta = 177.3$, 156.0, 137.9, 137.8, 137.7, 128.4–127.2 (9C), 84.1, 81.7, 80.9, 78.2, 77.5, 77.1, 73.2, 72.5, 71.8, 69.0, 54.1, 51.8, 28.4 (3C), 23.9, 20.5; MALDI-TOF MS: m/z: 656.5 [M^++Na]; elemental analysis calcd (%) for $C_{37}H_{47}NO_8$ (633.77): C 70.12, H 7.47, N 2.21; found: C 70.18, H 7.53, N 2.25.

Ethyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-3-(*tert*-butoxycarbonylamino)-D-*glycero*-D-*ido*-octanoate (13eb): Column chromatography with toluene/AcOEt 14:1 afforded **13eb** (260 mg, 84%) as a white foam; $[\alpha]_D = -2.0$ (c = 0.3, $CHCl_3$); ^{1}H NMR: $\delta =$ 7.40–7.12 (m, 15H, 3Ph), 5.64 (br d, $J_{3,NH} = 8.5$ Hz, 1H, NH), 4.47 (s, 2H, PhCH_2), 4.46, 4.40 (2d, $J = 12.0$ Hz, 2H, PhCH_2), 4.41 (s, 2H, PhCH_2), 4.25 (bdddd, $J_{2a,3} = 7.5$, $J_{2b,3} = 6.0$, $J_{3,4} = 4.0$ Hz, 1H, H-3), 4.14 (dd, $J_{4,5} = 3.5$ Hz, 1H, H-4), 4.06 (dd, $J_{5,6} = 5.5$, $J_{6,7} = 5.0$ Hz, 1H, H-6), 4.04 (q, $J = 7.0$ Hz, 2H, OCH_2CH$_3$), 3.97 (dd, 1H, H-5), 3.91 (dddx, $J_{7,8a} = 5.0$, $J_{7,8b} = 4.5$ Hz, 2H, H-7), 3.50 (dd, $J_{8a,8b} = 10.5$ Hz, 1H, H-8a), 3.46 (dd, $J_{7,8a} = 5.0$, $J_{8a,8b} = 10.5$ Hz, 1H, H-8b), 2.57 (dd, $J_{2a,2b} = 15.5$ Hz, 1H, H-2a), 2.48 (dd, $J_{2a,2b} = 15.5$, $J_{2b,3} = 6.0$ Hz, 1H, H-2b), 1.30 (s, 9H, *t*Bu), 1.26 (t, $J = 7.0$ Hz, 3H, OCH$_2$CH_3); ^{13}C NMR selected data: $\delta =$137.8, 83.2, 82.0, 81.3, 73.1, 71.8, 69.2, 60.4, 37.2, 29.7, 28.4 (3C), 14.2; MALDI-TOF MS: m/z: 642.6 [M^++Na], 659.3 [M^++K]; elemental analysis calcd (%) for $C_{36}H_{45}NO_8$ (619.74): C 69.77, H 7.32, N 2.26; found: C 69.80, H 7.35, N 2.22.

Ethyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3,5-trideoxy-3-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*gluco*-nonan-4-enoate (15): Column chromatography with cyclohexane/AcOEt 3:1 (containing 3% Et_3N) afforded **15** (221 mg, 70%) as a white foam; ^{1}H NMR of a 1.5:1 mixture of conformers: $\delta =$ 7.40–7.20 (m, 15H, Ph), 5.25, 5.24 (2br d, $J_{3,NH} = 8.0$ Hz, 1H, NH), 4.97 (d, $J_{5,6} = 3.5$ Hz, 0.4H, H-5), 4.96 (d, $J_{5,6} = 3.0$ Hz, 0.6H, H-5), 4.80, 4.64 (2d, $J = 11.5$ Hz, 1.2H, PhCH_2), 4.79, 4.63 (2d, $J = 11.5$ Hz, 0.8H, PhCH_2), 4.62, 4.48 (m, 5H, H-3, PhCH_2), 4.21–4.04 (m, 4H, H-6, H-8, OCH_2CH$_3$), 3.84–3.60 (m, 3H, H-7, 2 H-9), 2.75–2.50 (m, 2H, 2H-2), 1.42, 1.41 (2s, 9H, *t*Bu), 1.21, 1.20 (2t, $J = 7.0$ Hz, 3H, OCH$_2$CH_3); MALDI-TOF MS: m/z: 670.5 [M^++K]; elemental analysis calcd (%) for $C_{37}H_{45}NO_8$ (631.76): C 70.34, H 7.18, N 2.22; found: C 70.40, H 7.15, N 2.25.

General procedure for the Reformatsky-type synthesis of C-glycosyl β-amino esters 7ab–eb: *p*-Methoxybenzylamine **2a** (131 μL, 1.00 mmol) was added to a stirred solution of aldehyde **1** (1.00 mmol) in anhydrous CH_2Cl_2 (8 mL) at room temperature. After 30 min, a solution of dimethylzinc (1.75 mL, 2M, 3.50 mmol) in toluene was added all at once. After another 15 min, ethyl bromoacetate **14** (333 μL, 3.00 mmol) was added, followed immediately by a freshly prepared solution of bistriphenylphosphine nickel(II) dichloride (2.5 mL, 0.02M, 0.05 mmol) in CH_2Cl_2. The mixture was stirred for an additional 12 h and then quenched by the addition of aqueous HCl (2.0 mL, 2M). The organic phase was separated, washed sequentially with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was then purified by column chromatography on silica gel with the suitable elution system to give the corresponding β-amino ester.

Compound 7ab: Column chromatography with cyclohexane/AcOEt 3:1 (containing 3% Et_3N) afforded **7ab** (593 mg, 78%) as a colorless syrup.

Compound 7bb: Column chromatography with cyclohexane/AcOEt 3:1 (containing 3% Et_3N) afforded **7bb** (532 mg, 70%) as a white foam.

Ethyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-3-(*p*-methoxybenzylamino)-D-*erythro*-L-*gluco*-nonanoate (7cb): Column chromatography with cyclohexane/AcOEt 3:1 (containing 3% Et_3N) afforded **7cb** (456 mg, 60%) as a white foam; $[\alpha]_D = -3.6$ (c = 0.4, EtOH); ^{1}H NMR ([D$_6$]DMSO, 120°C): $\delta =$7.40–6.80 (m, 24H, Ph), 4.98 (dd, $J_{4,5} = 4.0$, $J_{5,6} =$ 4.5 Hz, 1H, H-5), 4.74, 4.68 (2d, $J = 12.0$ Hz, 2H, PhCH_2), 4.63, 4.55 (2d, $J = 11.5$ Hz, 2H, PhCH_2), 4.60, 4.56 (2d, $J = 12.5$ Hz, 2H, PhCH_2), 4.54 (s, 2H, PhCH_2), 4.20–4.10 (m, 2H, H-6, H-8), 4.06 (q, $J = 7.0$ Hz, 2H, OCH_2CH$_3$), 3.84–3.66 (m, 4H, H-4, H-7, 2 H-9), 3.74 (s, 3H, OCH_3), 3.71, 3.59 (2d, $J = 13.0$ Hz, 2H, PhCH_2), 3.48–3.40 (m, 1H, H-3), 2.60–2.40 (m, 2H, 2H-2), 1.20 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3); MALDI-TOF MS: m/z: 760.6 [M^++H]; elemental analysis calcd (%) for $C_{47}H_{53}NO_8$ (759.93): C 74.28, H 7.03, N 1.84; found: C 74.33, H 7.10, N 1.85.

Compound 7db: Column chromatography with cyclohexane/AcOEt 5:2 (containing 3% of Et_3N) afforded **7db** (461 mg, 72%) as a white foam.

Ethyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-3-(*p*-methoxybenzylamino)-D-*glycero*-D-*ido*-octanoate (7eb): Column chromatography with cyclohexane/AcOEt 5:2 (containing 3% Et_3N) afforded **7eb** (288 mg, 45%) as a white foam. $[\alpha]_{436} = 6.9$ (c = 1.2, $CHCl_3$); ^{1}H NMR: $\delta =$7.40–6.70 (m, 19H, Ph), 4.58, 4.54 (2d, $J = 12.0$ Hz, 2H, PhCH_2), 4.56, 4.51 (2d, $J =$ 11.5 Hz, 2H, PhCH_2), 4.47, 4.29 (2d, $J = 11.8$ Hz, 2H, PhCH_2), 4.10 (ddd, $J_{6,7} = 3.5$, $J_{7,8a} = 5.5$, $J_{7,8b} = 6.5$ Hz, 1H, H-7), 4.08 (q, $J = 7.0$ Hz, 2H, OCH_2CH$_3$), 4.04 (dd, $J_{3,4} = 8.0$, $J_{4,5} = 3.5$ Hz, 1H, H-4), 4.00 (dd, $J_{5,6} \sim$ 0.5 Hz, 1H, H-6), 3.93 (dd, $J_{4,5} = 3.5$, $J_{5,6} \approx 0.5$ Hz, 1H, H-5), 3.78 and 3.73 (2d, $J = 12.5$ Hz, 2H, PhCH_2), 3.76 (s, 3H, OCH_3), 3.63 (dd, $J_{8a,8b} =$ 10.0 Hz, 1H, H-8a), 3.51 (dd, 1H, H-8b), 3.49 (ddd, $J_{2a,3} = 4.5$, $J_{2b,3} =$ 6.5 Hz, 1H, H-3), 2.44 (dd, $J_{2a,2b} = 14.5$ Hz, 1H, H-2a), 2.35 (dd, $J_{2a,2b} =$ 14.5, $J_{2b,3} = 6.5$ Hz, 1H, H-2b), 1.80 (br s, 1H, NH), 1.24 (t, $J = 7.0$ Hz, 3H, OCH$_2$CH_3); ^{13}C NMR: $\delta =$172.0, 158.6, 138.2, 137.7, 137.3, 132.2, 129.6 (2C), 128.4–127.6 (9C), 113.7 (2C), 82.3 (4C), 73.3, 71.4, 71.0, 70.4, 60.4, 55.2, 53.9, 50.7, 36.3, 14.1. MALDI-TOF MS: m/z: 640.4 [M^++H], 662.4 [M^++Na], 678.3 [M^++K]; elemental analysis calcd (%) for $C_{39}H_{45}NO_7$ (639.78): C 73.22, H 7.09, N 2.19; found: C 73.25, H 7.15, N 2.22.

Ethyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2,2-difluoro-3-(*p*-methoxyphenylamino)-D-*threo*-L-*galacto*-nonanoate (19): *p*-Anisidine (126 mg, 1.02 mmol) in one portion was added to a stirred solution of aldehyde **1a** (552 mg, 1.00 mmol) in anhydrous THF (8 mL) at room temperature. The reaction mixture was stirred at room temperature for 45 min. In a separate flask, to a freshly activated suspension of zinc dust (327 mg, 5.00 mmol) in anhydrous THF (2 mL) heated under reflux, a few drops of ethyl bromodifluoroacetate **16** were added. After the green colour had appeared (ca. 15 min), the above C-galactosyl imine solution was slowly added. The remaining ethyl bromodifluoroacetate **16** was added dropwise over 30 min (total amount of ethyl bromodifluoroacetate **16**: 513 μL, 4.00 mmol). The reaction mixture was stirred under reflux for an additional 15 min then cooled to room temperature, treated with saturated aqueous $NaHCO_3$ solution (5 mL), and filtered through a pad of Celite. The filtrate was extracted with Et_2O (3×75 mL); the combined organic layers were dried (Na_2SO_4), concentrated, and purified on a silica gel column with toluene/cyclohexane/AcOEt 6:0.5:0.5 to afford **19** (235 mg, 30%) as a yellow syrup. $[\alpha]_D = 3.2$ (c = 1.1, $CHCl_3$); ^{1}H NMR ([D$_5$]pyridine): $\delta =$7.90–7.10 (m, 24H, Ph), 5.89 (d, $J_{3,NH} = 10.5$ Hz, 1H, NH), 5.45, 5.07 (2d, $J = 11.0$ Hz, 2H, PhCH_2), 5.37, 4.62 (2d, $J = 11.5$ Hz, 2H, PhCH_2), 5.23 (dddd, $J_{Fa,3} = 6.5$, $J_{Fb,3} = 18.0$, $J_{3,4} \sim 0.5$ Hz, 1H, H-3), 5.16, 5.0 (2d, $J = 11.8$ Hz, 2H, PhCH_2), 4.92, 4.82 (2d, $J = 12.0$ Hz, 2H, PhCH_2), 4.65 (dd, $J_{6,7} = 2.5$, $J_{7,8} \sim 0.5$ Hz, 1H, H-7), 4.56–4.48 (m, 4H, H-4, H-5, OCH_2CH$_3$), 4.32 (ddd, $J_{8,9a} = 7.5$, $J_{8,9b} = 5.5$ Hz, 1H, H-8), 4.28 (ddd, $J_{4,6} = 2.0$, $J_{5,6} = 8.0$ Hz, 1H, H-5), 4.14 (dd, $J_{9a,9b} = 9.5$ Hz, 1H, H-9a), 4.03 (dd, 1H, H-9b), 3.80 (s, 3H, OCH_3), 1.40 (t, $J = 7.0$ Hz, 3H, OCH$_2$CH_3); ^{13}C NMR: $\delta =$163.9 (dd, $^2J_{C,Fa} = 32.3$ Hz, $^2J_{C,Fb} = 32.3$ Hz), 153.0, 141.7, 138.9, 138.5, 137.9, 137.8, 128.4–127.3 (12C), 116.2 (2C), 115.2 (dd, $^1J_{C,Fa} = 260.0$ Hz, $^1J_{C,Fb} = 261.0$ Hz), 114.7 (2C), 84.8, 76.5, 75.6, 74.8, 74.5, 74.4, 73.5, 73.3, 72.0, 68.2, 62.7, 57.6 (dd, $^2J_{C,Fa} = 25.1$ Hz, $^2J_{C,Fb} = 25.2$ Hz), 55.6, 13.8; ^{19}F NMR ([D$_5$]pyridine): $\delta = -107.9$ (dd, $J_{Fa,H} = 6.5$, $J_{Fa,Fb} =$ 253.3 Hz, 1F, Fa), −115.4 (dd, $J_{Fb,H} = 18.0$ Hz, 1F, Fb). MALDI-TOF MS: m/z: 781.1 [M^+], 804.1 [M^++Na], 820.1 [M^++K]; elemental analysis calcd (%) for $C_{46}H_{49}F_2NO_8$ (781.88): C 70.66, H 6.32, F 4.86, N 1.79; found: C 70.68, H 6.35, F 4.90, N 1.78.

Ethyl 4,7-anhydro-5,6,8-tri-*O*-benzyl-2,3-dideoxy-2,2-difluoro-3-(*p*-methoxyphenylamino)-D-*glycero*-D-*altro*-octanoate (20): Treatment of aldehyde **1d** (432 mg, 1.00 mmol) as described for the preparation of **19** gave, after column chromatography with cyclohexane/AcOEt 4:1, **20** (212 mg, 32%) as a yellow syrup. $[\alpha]_D = -18.2$ (c = 0.8, $CHCl_3$); ^{1}H NMR: $\delta =$

7.40–7.10, 6.70–6.30 (2m, 19H, Ph), 5.58, 4.44 (2d, J=12.0 Hz, 2H, PhCH_2), 4.47 (dd, $J_{3,4}$~0.5, $J_{4,5}$=6.0 Hz, 1H, H-4), 4.45, 4.41 (2d, J=11.8 Hz, 2H, PhCH_2), 4.32, 4.22 (2d, J=11.5 Hz, 2H, PhCH_2), 4.21 (ddd, $J_{6,7}$=4.0, $J_{7,8a}$=3.5, $J_{7,8b}$=3.0 Hz, 1H, H-7), 4.20 (q, J=7.0 Hz, 2H, OCH_2CH$_3$), 4.05 (ddd, $J_{Fa,3}$=5.0, $J_{Fb,3}$=21.0 Hz, 1H, H-3), 3.79 (dd, $J_{5,6}$= 5.0 Hz, 1H, H-6), 3.72 (s, 3H, OCH$_3$), 3.66 (dd, $J_{4,5}$ = 6.0, $J_{5,6}$ = 5.0 Hz, 1H, H-5), 3.62 (dd, $J_{8a,8b}$=10.5 Hz, 1H, H-8a), 3.46 (dd, $J_{7,8b}$ = 3.0, $J_{8a,8b}$ = 10.5 Hz, 1H, H-8b), 1.22 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR: δ=163.8 (dd, $^2J_{C,Fa}$=32.3, $^2J_{C,Fb}$=32.2 Hz), 152.6, 140.9, 137.6, 137.5, 137.4, 128.5–127.8 (9C), 115.0 (dd, $^1J_{C,Fa}$=260.0, $^1J_{C,Fb}$=261.0 Hz), 114.8 (4C), 82.3, 78.5, 77.9, 76.3, 73.5, 72.3, 72.1, 69.6, 62.9, 57.1 (dd, $^2J_{C,Fa}$= 25.1, $J_{C,Fb}$=25.0 Hz), 55.7, 13.8; ^{19}F NMR: δ=−107.9 (dd, $J_{Fa,H}$=5.0, $J_{Fa,Fb}$=256.3 Hz, 1F, Fa), −118.6 (dd, $J_{Fb,H}$=21.0 Hz, 1F, Fb); MALDI-TOF MS: m/z: 662.0 [M^++H], 684.1 [M^++Na], 700.0 [M^++K]; elemental analysis calcd (%) for $C_{38}H_{41}F_2NO_7$ (661.73): C 68.97, H 6.25, F 5.74, N 2.12; found: C 68.94, H 6.22, F 5.77, N 2.15.

General procedure for the synthesis of Mosher's amides 21aa–ea and 21ab: CAN (1.10 g, 2.00 mmol) was added in one portion to a cooled (0°C) stirred solution of N-PMB-derivative (0.50 mmol) in CH_3CN (20 mL) and H_2O (5 mL). The resulting mixture was vigorously stirred at room temperature for 6 h, and quenched with saturated aqueous Na_2SO_3 solution (15 mL). The aqueous layer was extracted with AcOEt (3× 30 mL), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (3×10 mL), dried (Na_2SO_4), and concentrated to give the corresponding unprotected β-amino ester.

To a stirred solution of the above crude β-amino ester (~0.25 mmol) in anhydrous CH_2Cl_2 (2 mL) were added either (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (73 mg, 0.30 mmol), 1,3-dicyclohexylcarbodiimide (63 mg, 0.30 mmol), and a catalytic amount of 4-*N*,*N*-(dimethylamino)pyridine. The mixture was stirred for an additional 12 h at room temperature then concentrated. The residue was taken into AcOEt, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with the suitable elution system affording the corresponding benzylated Mosher's amide in almost quantitative yield.

A vigorously stirred mixture of the above crude Mosher's amide (~0.25 mmol), 20% palladium hydroxide on carbon (50% w/w of substrate), AcOEt (2 mL), and EtOH (2 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. After stirring under a slightly positive pressure of hydrogen (balloon) at room temperature for 3–5 h, palladium hydroxide on carbon was filtered off through a plug of cotton and washed thoroughly with MeOH (2 mL), H_2O (0.5 mL), and DMF (2 mL). The combined filtrates were concentrated to give the corresponding deprotected Mosher's amide in almost quantitative yield. This debenzylation step was unnecessary starting from **7ba** (*gluco* series) since a homogeneous distribution of $\Delta\delta^{RS}$ signs was already observed in the ^{1}H NMR spectra of the corresponding benzylated Mosher's amides (see ref. [42]).

(2′*R*)-Methyl 4,8-anhydro-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenyl-propionylamino)-D-*threo*-L-*galacto*-nonanoate ((*R*)-21aa): ^{1}H NMR ($CDCl_3$ + D_2O): δ=8.70 (d, $J_{3,NH}$=9.0 Hz, 1H, NH), 7.63–7.43 (m, 5H, Ph), 4.06 (dd, $J_{3,4}$~0.5 Hz, 1H, H-3), 4.02 (dd, $J_{6,7}$=3.0, $J_{7,8}$~0.5 Hz, 1H, H-7), 3.86 (dd, $J_{8,9a}$=7.0, $J_{9a,9b}$=12.0 Hz, 1H, H-9a), 3.76 (s, 3H, OCH$_3$), 3.70 (dd, $J_{8,9b}$=3.0 Hz, 1H, H-9b), 3.66 (dd, $J_{5,6}$=9.0 Hz, 1H, H-6), 3.55 (q, J=0.7 Hz, 3H, OCH$_3$), 3.51 (dd, $J_{4,5}$=8.5 Hz, 1H, H-4), 3.50 (dd, $J_{4,5}$ = 8.5, $J_{5,6}$ = 9.0 Hz, 1H, H-5), 3.49 (ddd, $J_{7,8}$ ≈0.5, $J_{8,9a}$ = 7.0, $J_{8,9b}$ = 3.0 Hz, 1H, H-8), 1.34 (s, 3H, CH$_3$), 1.16 (s, 3H, CH$_3$).

(2′*S*)-Methyl 4,8-anhydro-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenyl-propionylamino)-D-*threo*-L-*galacto*-nonanoate ((*S*)-21aa): ^{1}H NMR ($CDCl_3$ + D_2O): δ=8.93 (d, $J_{3,NH}$=9.0 Hz, 1H, NH), 7.64–7.43 (m, 5H, Ph), 4.06 (dd, $J_{3,4}$~0.5 Hz, 1H, H-3), 3.97 (dd, $J_{6,7}$=2.5, $J_{7,8}$~0.5 Hz, 1H, H-7), 3.86 (dd, $J_{8,9a}$=7.0, $J_{9a,9b}$=12.0 Hz, 1H, H-9a), 3.79 (s, 3H, OCH$_3$), 3.69 (dd, $J_{8,9b}$=3.0 Hz, 1H, H-9b), 3.57 (dd, $J_{5,6}$=9.0 Hz, 1H, H-6), 3.47 (dd, $J_{4,5}$=9.0 Hz, 1H, H-4), 3.45 (ddd, 1H, H-8), 3.42 (q, J=0.7 Hz, 3H, OCH$_3$), 3.28 (dd, $J_{4,5}$ = 9.0, $J_{5,6}$ = 9.0 Hz, 1H, H-5), 1.36 (s, 6H, CH$_3$).

(2′*R*)-Methyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenylpropionylamino)-D-*erythro*-L-*galacto*-nonanoate ((*R*)-benzylated-21ba): ^{1}H NMR ([D$_6$]acetone): δ= 7.75–7.20 (m, 25H, 5Ph), 7.60 (d, $J_{3,NH}$=10.0 Hz, 1H, NH), 4.94, 4.91 (2d, J=11.0 Hz, 2H, PhCH_2), 4.88, 4.83 (2d, J=10.0 Hz, 2H, PhCH_2), 4.86, 4.69 (2d, J=10.5 Hz, 2H, PhCH_2), 4.64, 4.59 (2d, J=12.0 Hz, 2H, PhCH_2), 4.60 (dd, $J_{3,4}$~0.5 Hz, 1H, H-3), 3.80 (dd, $J_{8,9a}$=3.5, $J_{9a,9b}$= 11.0 Hz, 1H, H-9a), 3.75 (dd, $J_{4,5}$=9.0, $J_{5,6}$=9.5 Hz, 1H, H-5), 3.71 (dd, $J_{8,9b}$=1.5 Hz, 1H, H-9b), 3.65 (dd, $J_{3,4}$ ≈0.5, $J_{4,5}$ = 9.0 Hz, 1H, H-4), 3.63 (dd, $J_{6,7}$=9.0, $J_{7,8}$=9.2 Hz, 1H, H-7), 3.53 (s, 3H, OCH$_3$), 3.51 (ddd, $J_{7,8}$ = 9.2, $J_{8,9a}$ = 3.5, $J_{8,9b}$ = 1.5 Hz, 1H, H-8), 3.48 (q, J=0.7 Hz, 3H, OCH$_3$), 3.27 (dd, $J_{5,6}$ = 9.5, $J_{6,7}$ = 9.0 Hz, 1H, H-6), 1.20 (s, 3H, CH$_3$), 1.02 (s, 3H, CH$_3$).

(2′*S*)-Methyl 4,8-anhydro-5,6,7,9-tetra-*O*-benzyl-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenyl-propionylamino)-D-*erythro*-L-*galacto*-nonanoate ((*S*)-benzylated-21ba): ^{1}H NMR ([D$_6$]acetone): δ= 7.79–7.22 (m, 25H, 5Ph), 7.60 (d, $J_{3,NH}$=10.5 Hz, 1H, NH), 4.88, 4.82 (2d, J=11.5 Hz, 2H, PhCH_2), 4.76, 4.62 (2d, J=11.0 Hz, 2H, PhCH_2), 4.70, 4.64 (2d, J=10.0 Hz, 2H, PhCH_2), 4.59, 4.55 (2d, J=11.5 Hz, 2H, PhCH_2), 4.46 (dd, $J_{3,4}$~0.5 Hz, 1H, H-3), 3.68 (dd, $J_{8,9a}$=3.5, $J_{9a,9b}$= 11.0 Hz, 1H, H-9a), 3.63 (dd, $J_{8,9b}$=2.0 Hz, 1H, H-9b), 3.62 (s, 3H, OCH$_3$), 3.57 (dd, $J_{5,6}$=9.5, $J_{6,7}$=9.0 Hz, 1H, H-6), 3.55 (q, J=0.7 Hz, 3H, OCH$_3$), 3.53 (dd, $J_{4,5}$=9.0 Hz, 1H, H-4), 3.40 (ddd, $J_{7,8}$=9.0 Hz, 1H, H-8), 3.17 (dd, $J_{6,7}$ = 9.0, $J_{7,8}$ = 9.0 Hz, 1H, H-7), 2.75 (dd, $J_{4,5}$ = 9.0, $J_{5,6}$ = 9.5 Hz, 1H, H-5), 1.25 (s, 3H, CH$_3$), 1.22 (s, 3H, CH$_3$).

(2′*R*)-Methyl 4,8-anhydro-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenylpropionylamino)-D-*erythro*-L-*gluco*-nonanoate ((*R*)-21ca): ^{1}H NMR ($CDCl_3$ + D_2O): δ=7.92 (d, $J_{3,NH}$=9.5 Hz, 1H, NH), 7.65–7.40 (m, 5H, Ph), 4.11 (dd, $J_{3,4}$=2.5 Hz, 1H, H-3), 3.85 (dd, $J_{4,5}$~0.5, $J_{5,6}$=3.5 Hz, 1H, H-5), 3.79–3.62 (m, 2H, H-9a, H-9b), 3.72 (dd, $J_{6,7}$=8.5, $J_{7,8}$=9.0 Hz, 1H, H-7), 3.71 (s, 3H, OCH$_3$), 3.54 (dd, $J_{3,4}$ = 2.5, $J_{4,5}$ ≈0.5 Hz, 1H, H-4), 3.48 (dd, $J_{5,6}$ = 3.5, $J_{6,7}$ = 8.5 Hz, 1H, H-6), 3.30 (q, J=0.7 Hz, 3H, OCH$_3$), 3.19 (ddd, $J_{7,8}$ = 9.0, $J_{8,9a}$ = 3.5, $J_{8,9b}$ = 2.0 Hz, 1H, H-8), 1.24 (s, 6H, 2CH$_3$).

(2′*S*)-Methyl 4,8-anhydro-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenylpropionylamino)-D-*erythro*-L-*gluco*-nonanoate ((*S*)-21ca): ^{1}H NMR ($CDCl_3$ + D_2O): δ=8.06 (d, $J_{3,NH}$=10.0 Hz, 1H, NH), 7.60–7.38 (m, 5H, Ph), 4.28 (dd, $J_{3,4}$=2.0 Hz, 1H, H-3), 3.83 (dd, $J_{4,5}$~0.5, $J_{5,6}$=3.0 Hz, 1H, H-5), 3.78–3.60 (m, 2H, H-9a, H-9b), 3.72 (s, 3H, OCH$_3$), 3.68 (dd, $J_{6,7}$=9.0, $J_{7,8}$=9.5 Hz, 1H, H-7), 3.52 (dd, $J_{3,4}$ = 2.0, $J_{4,5}$ ≈0.5 Hz, 1H, H-4), 3.45 (dd, $J_{5,6}$ = 3.0, $J_{6,7}$ = 9.0 Hz, 1H, H-6), 3.32 (q, J=0.7 Hz, 3H, OCH$_3$), 3.17 (ddd, $J_{8,9a}$=3.0, $J_{8,9b}$=3.5 Hz, 1H, H-8), 1.26 (s, 6H, 2CH$_3$).

(2′*R*)-Methyl 4,7-anhydro-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenylpropionylamino)-D-*glycero*-D-*altro*-octanoate ((*R*)-21da): ^{1}H NMR ($CDCl_3$ + D_2O): δ=8.63 (d, $J_{3,NH}$=9.0 Hz, 1H, NH), 7.60–7.40 (m, 5H, Ph), 4.18 (dd, $J_{3,4}$=2.5, $J_{4,5}$=7.5 Hz, 1H, H-4), 4.11 (dd, $J_{3,NH}$ = 9.0, $J_{3,4}$ = 2.5 Hz, 1H, H-3), 4.08 (dd, $J_{5,6}$=6.0, $J_{6,7}$=8.5 Hz, 1H, H-6), 3.92 (ddd, $J_{7,8a}$=3.5, $J_{7,8b}$=5.0 Hz, 1H, H-7), 3.81 (dd, $J_{4,5}$ = 7.5, $J_{5,6}$ = 6.0 Hz, 1H, H-5), 3.74 (dd, $J_{8a,8b}$=12.5 Hz, 1H, H-8a), 3.68 (s, 3H, OCH$_3$), 3.58 (dd, $J_{7,8b}$ = 5.0, $J_{8a,8b}$ = 12.5 Hz, 1H, H-8b), 3.42 (q, J= 0.7 Hz, 3H, OCH$_3$), 1.35 (s, 3H, CH$_3$), 1.23 (s, 3H, CH$_3$).

(2′*S*)-Methyl 4,7-anhydro-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenylpropionylamino)-D-*glycero*-D-*altro*-octanoate ((*S*)-21da): ^{1}H NMR ($CDCl_3$ + D_2O): δ=8.36 (d, $J_{3,NH}$=9.0 Hz, 1H, NH), 7.62–7.40 (m, 5H, Ph), 4.10 (dd, $J_{3,4}$=4.5 Hz, 1H, H-3), 4.09 (dd, $J_{4,5}$= 6.0 Hz, 1H, H-4), 3.76 (ddd, $J_{6,7}$=5.5, $J_{7,8a}$=3.0, $J_{7,8b}$=3.5 Hz, 1H, H-7), 3.68 (s, 3H, OCH$_3$), 3.61 (dd, $J_{5,6}$=4.5 Hz, 1H, H-6), 3.59 (dd, $J_{8a,8b}$= 12.5 Hz, 1H, H-8a), 3.54 (q, J=0.7 Hz, 3H, OCH$_3$), 3.52 (dd, $J_{4,5}$ = 6.0, $J_{5,6}$ = 4.5 Hz, 1H, H-5), 3.35 (dd, $J_{7,8b}$ = 3.5, $J_{8a,8b}$ = 12.5 Hz, 1H, H-8b), 1.34 (s, 3H, CH$_3$), 1.29 (s, 3H, CH$_3$).

(2′*R*)-Methyl 4,7-anhydro-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenylpropionylamino)-D-*glycero*-D-*ido*-octanoate ((*R*)-21ea): ^{1}H NMR ($CDCl_3$ + D_2O): δ=8.17 (d, $J_{3,NH}$=10.5 Hz, 1H, NH), 7.62–7.40 (m, 5H, Ph), 4.48 (dd, $J_{3,4}$=8.0 Hz, 1H, H-3), 4.25 (dd, $J_{5,6}$= 1.5, $J_{6,7}$=5.0 Hz, 1H, H-6), 4.08 (dd, $J_{4,5}$=4.5 Hz, 1H, H-4), 3.98 (dd, $J_{4,5}$ = 4.5, $J_{5,6}$ = 1.5 Hz, 1H, H-5), 3.90 (ddd, $J_{7,8a}$=3.5, $J_{7,8b}$=2.0 Hz, 1H, H-7), 3.73 (dd, $J_{8a,8b}$=13.5 Hz, 1H, H-8a), 3.68 (s, 3H, OCH$_3$), 3.64 (dd, $J_{7,8b}$ = 2.0, $J_{8a,8b}$ = 13.5 Hz, 1H, H-8b), 3.57 (q, J=0.7 Hz, 3H, OCH$_3$), 1.28 (s, 3H, CH$_3$), 1.14 (s, 3H, CH$_3$).

(2′*S*)-Methyl 4,7-anhydro-2,3-dideoxy-2,2-dimethyl-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenyl-propionylamino)-D-*glycero*-D-*ido*-octanoate ((*S*)-21ea): ^{1}H NMR ($CDCl_3$ + D_2O): $\delta = 8.59$ (d, $J_{3,NH} = 10.0$ Hz, 1H, NH), 7.62–7.40 (m, 5H, Ph), 4.46 (dd, $J_{3,4} = 7.5$ Hz, 1H, H-3), 4.09 (dd, $J_{5,6} = 1.5$, $J_{6,7} = 4.0$ Hz, 1H, H-6), 4.08 (dd, $J_{4,5} = 3.5$ Hz, 1H, H-4), 3.92 (dd, $J_{4,5} = 3.5$, $J_{5,6} = 1.5$ Hz, 1H, H-5), 3.83 (ddd, $J_{7,8a} = 1.5$, $J_{7,8b} = 3.0$ Hz, 1H, H-7), 3.74 (s, 3H, OCH_3), 3.46 (dd, $J_{8a,8b} = 12.0$ Hz, 1H, H-8a), 3.40 (dd, $J_{7,8b} = 3.0$, $J_{8a,8b} = 12.0$ Hz, 1H, H-8b), 3.33 (q, $J = 0.7$ Hz, 3H, OCH_3), 1.21 (s, 3H, CH_3), 1.30 (s, 3H, CH_3).

(2′*R*)-Ethyl 4,8-anhydro-2,3-dideoxy-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenyl-propionylamino)-D-*threo*-L-*galacto*-nonanoate ((*R*)-21ab): ^{1}H NMR ($CDCl_3$ + D_2O): $\delta = 7.98$ (d, $J_{3,NH} = 8.0$ Hz, 1H, NH), 7.60–7.40 (m, 5H, Ph), 4.74 (dddd, $J_{2a,3} = 7.5$, $J_{2b,3} = 5.0$, $J_{3,4} \sim 0.5$ Hz, 1H, H-3), 4.20–4.00 (m, 2H, OCH_2CH_3), 4.07 (dd, $J_{6,7} = 3.0$, $J_{7,8} \sim 0.5$ Hz, 1H, H-7), 3.92 (dd, $J_{8,9a} = 6.0$, $J_{9a,9b} = 12.0$ Hz, 1H, H-9a), 3.80 (dd, $J_{8,9b} = 3.5$ Hz, 1H, H-9b), 3.66 (dd, $J_{5,6} = 9.0$ Hz, 1H, H-6), 3.58–3.51 (m, 2H, H-5, H-8), 3.46 (q, $J = 0.7$ Hz, 3H, OCH_3), 3.28 (dd, $J_{4,5} = 9.0$ Hz, 1H, H-4), 2.76 (dd, $J_{2a,2b} = 15.0$ Hz, 1H, H-2a), 2.64 (dd, $J_{2a,2b} = 15.0$, $J_{2b,3} = 5.0$ Hz, 1H, H-2b), 1.23 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3).

(2′*S*)-Ethyl 4,8-anhydro-2,3-dideoxy-3-(3′,3′,3′-trifluoro-2′-methoxy-2′-phenyl-propionylamino)-D-*threo*-L-*galacto*-nonanoate ((*S*)-21ab): ^{1}H NMR ($CDCl_3$ + D_2O): $\delta = 8.20$ (d, $J_{3,NH} = 9.0$ Hz, 1H, NH), 7.60–7.40 (m, 5H, Ph), 4.70 (dddd, $J_{2a,3} = 6.5$, $J_{2b,3} = 6.0$, $J_{3,4} \sim 0.5$ Hz, 1H, H-3), 4.30–4.10 (m, 2H, OCH_2CH_3), 4.01 (dd, $J_{6,7} = 3.0$, $J_{7,8} \sim 0.5$ Hz, 1H, H-7), 3.90 (dd, $J_{8,9a} = 5.5$, $J_{9a,9b} = 12.0$ Hz, 1H, H-9a), 3.76 (dd, $J_{8,9b} = 4.0$ Hz, 1H, H-9b), 3.57 (ddd, $J_{5,6} = 8.5$, $J_{4,6} = 1.5$ Hz, 1H, H-6), 3.51 (ddd, $J_{7,8} \approx 0.5$, $J_{8,9a} = 5.5$, $J_{8,9b} = 4.0$ Hz, 1H, H-8), 3.40 (q, $J = 0.7$ Hz, 3H, OCH_3), 3.28 (dd, $J_{4,5} = 9.0$ Hz, 1H, H-5), 3.24 (ddd, $J_{3,4} \approx 0.5$, $J_{4,5} = 9.0$, $J_{4,6} = 1.5$ Hz, 1H, H-4), 2.77 (dd, $J_{2a,2b} = 14.5$ Hz, 1H, H-2a), 2.70 (dd, $J_{2a,2b} = 14.5$, $J_{2b,3} = 6.0$ Hz, 1H, H-2b), 1.32 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3).

Acknowledgements

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[26] The use of α-linked C-glycosyl aldehydes (D-*gluco* and D-*arabino*) in the three-component Mannich-type and Reformatsky-type reactions resulted, under different reaction conditions, in no formation of the corresponding β-amino esters **7** very likely because of the intrinsic instability of these α-configured sugar aldehydes. The synthesis of α-linked C-glycosyl β-amino acids by a different route is the subject of a forthcoming paper.

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