Dihydropyridine *C*-Glycoconjugates by *Hantzsch* Cyclocondensation. Synthesis of a *C*(6)-Glycosylated Nifedipine Analogue

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Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

The use of glycosylated reagents in *Hantzsch*-type cyclocondensation reactions leading to *C*-glycosylated dihydropyridines (DHPs) has been investigated. A three-component approach with an anomeric sugar aldehyde (*galacto*, *manno*, and *ribo* derivatives), a β-keto ester, and an aminocrotonate afforded *C*(4)-glycosylated DHPs in high yield (70–90%). A two-component cyclocondensation approach based on different glycosylated β-amino acrylates (sugar enamines) and an enone derived from the *Knoevenagel* condensation between benzaldehyde and ethyl acetoacetate was followed for the preparation of *C*(6)-glycosylated 4-phenyl-substituted DHPs in fair yields (60–70%). The latter compounds were obtained as mixtures of diastereoisomers owing to the asymmetric induction of the sugar moiety in the formation of the C(4)-stereogenic center of the DHP ring. The diastereomer excess of the major products varied from 30 to 60%. The structure of selected compounds was determined by X-ray crystallography and by chiroptical measurements. The two-component cyclocondensation method was also employed for the preparation of a *C*(6)-ribofuranosyl-containing analogue of the well-known hypotensive agent *nifedipine*.

Introduction. – There is continuous interest in the pharmacology of 1,4-dihydropyridines (DHPs), because, in addition to their classical profile as cardiovascular and antihypertensive agents (calcium channel antagonists) [1], recent studies suggest several other medicinal applications including neurotropic, antidiabetic, membrane-protecting, as well as anticancer, antibacterial, and antiviral activities [2]. For example, while nifedipine [3] **1** and several congeners, *e.g.*, the trifluoromethylanalogue SKF 24260 (**2**), have been introduced on the market since the 1970s as drugs for the treatment of coronary diseases [4], cerebrocrast (**3**) [5] is a novel, highly active drug with antidiabetic, neuroprotectant, cognition- and memory-enhancing properties. Hence, great progress has been made in recent years in DHP synthesis [2][6] and in understanding the relation between pharmacological properties and chemical structure, especially chirality and nature of the substituents at C(4) and at the C(3) and C(5) ester groups of the DHP ring [1]. However, quite surprisingly, the synthesis of DHP glycoconjugates is an issue that has been almost ignored so far. One paper from 1989

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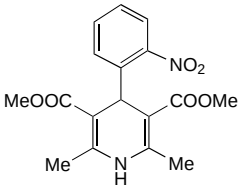
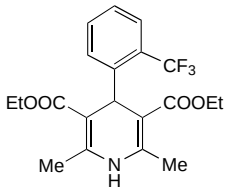
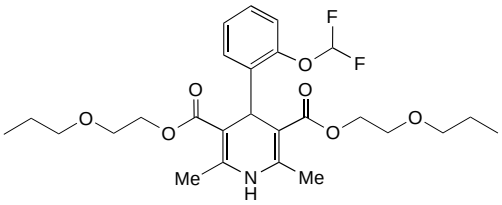
described the introduction of sugar residues at C(4) through a non-anomeric linkage [7], another paper [8] dealt with the preparation of simple polyalkoxy aldehyde derivatives. The introduction of carbohydrates on pharmacophores can be quite beneficial, because these residues often improve the pharmacokinetic and dynamic properties of drugs without leading to a loss in activity or selectivity. In addition, new biological properties may appear due to specific interactions between glycoside residues and bioreceptors. Moreover, it is expected that *Hantzsch*-type cyclocondensations [9] with glycosylated reagents will occur with some degree of asymmetric induction with respect to C(4). The preparation of enantiomerically pure DHPs is especially important, because in several cases optical antipodes of DHPs display opposite pharmacological profiles (calcium agonist *vs.* antagonist; hypotensive *vs.* hypertensive activity) [10]. Asymmetric chemical synthesis of DHPs with chiral auxiliary groups linked to one of the reagents are scanty [1b], and most of the methods employed for the preparation of individual enantiomers are based on the resolution of racemates *via* diastereoisomers, or on the chemoenzymatic resolution of diesters [2b][6a,d,e]. These methods, naturally, provide 50% of the undesired enantiomer. However, an interesting method has been described that allows the conversion of the 'wrong' enantiomer into the desired one [11]. Hence, for all these reasons, we were spurred to examine in deeper detail the *Hantzsch* cyclocondensation of suitable *C*-glycosylated reagents leading to C(4) and C(6) glycoconjugates of DHPs. A preliminary account of this work has already been reported elsewhere [12].



1
Nifedipine



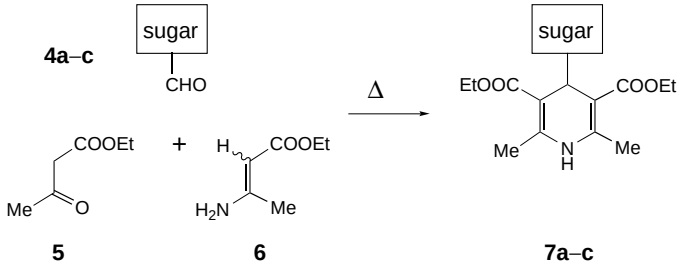
2
SKF 24260



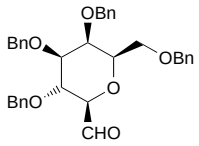
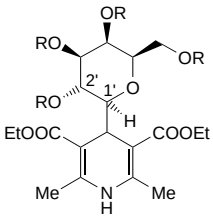
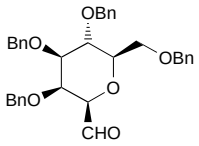
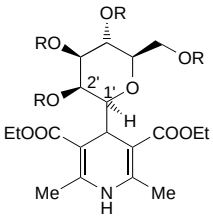
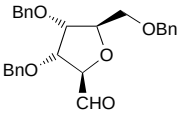
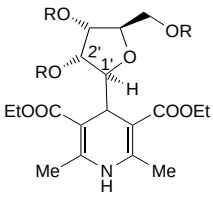
3
Cerebrocrast

Synthesis of *C*(4)-glycosylated DHPs. – The three-component variant of the *Hantzsch* cyclocondensation [1] was considered for the synthesis of the *C*(4)-glycosylated DHP derivatives **7** starting from the anomeric sugar aldehyde **4** [13], ethyl 3-oxobutanoate (**5**), and ethyl 3-aminobut-2-enoate (**6**) as components (*Table 1*).

Table 1. *Cyclocondensation of Formylcarbohydrates* **4a**–**c** *in the Presence of Ethyl 3-Oxobutanoate* (**5**) *and Ethyl 3-Aminobut-2-enoate* (**6**)



5 **6** **7a**–**c**

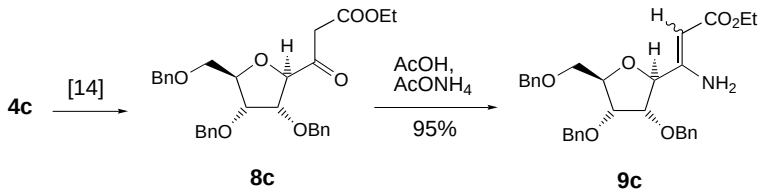
Aldehyde[a])	Product	Yield[b,c]) Solvent: EtOH	Yield[b,d]) Solvent: THF
 **4a**	 **7a** R = Bn **7a'** R = H	88%	95%
 **4b**	 **7b** R = Bn **7b'** R = H	70%	28%
 **4c**	 **7c** R = Bn **7c'** R = H	71%	40%

[a]) All reactions were run with **4**/**5**/**6** in a 1 : 1 : 1 ratio. [b]) Isolated yield after chromatography. [c]) Reaction carried out at 90°. [d]) Reaction carried out at 90° in the presence of $Yb(OTf)_3$.

Although various anomeric carbohydrate aldehydes are available on a multigram scale by the thiazole-based formylation of the corresponding lactones [13], we considered the use of compounds **4a–c** containing *galacto*, *manno*, and *ribo* residues. In a model reaction, the perbenzylated galactosyl derivative **4a**, the keto ester **5**, and the amino ester **6** (1:1:1) were heated in EtOH for 48 h. The reaction afforded the *C*(4)-galactosyl DHP derivative **7a** in high yield. The β-configuration at the anomeric center of **7a** was assigned based on the ^{1}H-NMR coupling constant ($J(1',2') = 9.2$ Hz), which confirmed the retention of configuration of **4a** during the cyclocondensation. Under similar conditions, the *manno* and *ribo* aldehydes **4b** and **4c**, respectively, afforded the corresponding *C*-glycosylated *Hantzsch* products **7b** and **7c** in good yields. The retention of configuration at the anomeric center was further corroborated by NOE experiments. Succinctly, NOEs were observed in compound **7b** and **7c** between H–C(1′) and H–C(5′) and between H–C(1′) and H–C(4′), respectively. Subsequently, compounds **7a–c** were transformed into the deprotected alcohols **7a′–c′**. Debenzylation was carried out in almost quantitative yield by hydrogenation over $Pd(OH)_2$. Nevertheless, different conditions were applied to shorten the reaction time. Considering that the established mechanism of the *Hantzsch* reaction involves, as a first step, the condensation between the active methylene compound, *i.e.*, the keto ester, and the aldehyde to yield an enone, the reaction of **4a** with **5** and **6** was carried out in the presence of 1 equiv. of $Yb(OTf)_3$ in refluxing THF for 12 h. The choice of the *Lewis* acid was suggested by parallel work in our [14] and other [15] laboratories, which have shown the high efficiency of lanthanide(III) *Lewis* acids in catalyzing homogenous condensation reactions, such as the *Biginelli* reaction. Thus, we were pleased to observe that the above reaction afforded **7a** in higher yields (95%) than in the absence of $Yb(OTf)_3$ (88%). However, the less stable *manno*- and *ribo*-derived aldehydes **4b** and **4c** afforded **7b** and **7c** in much lower yields than in the absence of $Yb(OTf)_3$. We found that, in these cases, the catalyst induced the 1′,2′-elimination of BnOH to yield the corresponding unsaturated aldehydes, which, however, also participated in the cyclocondensation process to afford the corresponding 1′,2′-dehydro-DHP derivatives of **7b** and **7c**.

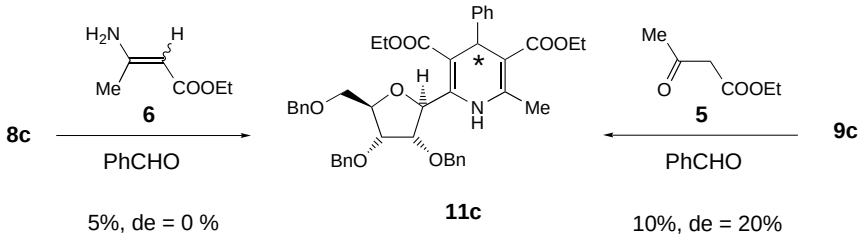
Synthesis of *C*(6)-glycosylated DHPs. – We prepared two types of reagents for the synthesis of this class of C(6)-substituted DHPs, one in which the carbohydrate moiety is part of a ketoester, *e.g.*, **8c**, the other where it is part of a β-amino acrylate (enamine), *e.g.*, **9c** (*Scheme 1*). These reagents were prepared from the ribofuranosyl aldehyde **4c**. When reacted with ethyl diazoacetate, the glycosyl ketoester **8c** was obtained [14b], which, in turn, by treatment with $AcONH_4$/AcOH in refluxing toluene provided the

Scheme 1



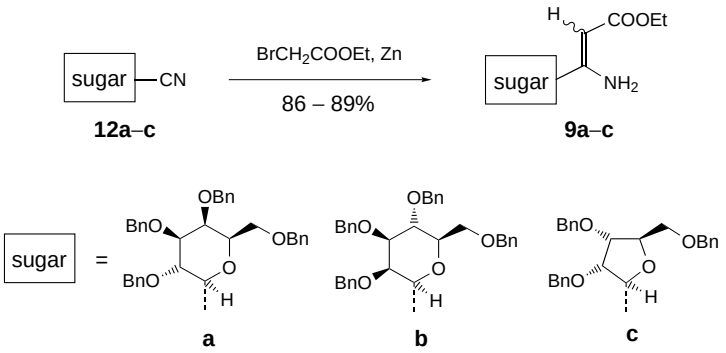
enamine **9c** [16]. We first considered the three-component *Hantzsch*-type reaction between **8c**, benzaldehyde (**10**), and 3-aminobut-2-enoate **6** under non-catalyzed, standard conditions. This reaction afforded the *C*(6)-glycosylated DHP **11c** in very low yield (5%) as a 1:1 mixture of epimers (diastereoisomer excess (de) = 0%) (*Scheme 2*). Comparable, yet unsatisfactory results were obtained in an alternative reaction between enamine **9c**, benzaldehyde, and keto ester **5**. Unfortunately, the results of these three-component cyclocondensations could not be improved by the use of acidic promoters ($Yb(OTf)_3$, AcOH) or higher temperatures (DMF, 150°).

Scheme 2



The two-component variant of the *Hantzsch* reaction, which involves the cyclocondensation of amino crotonates and enones (*Knoevenagel* condensation product of aldehyde and keto ester) was considered next. To this aim, we first examined a more straightforward entry to carbohydrate enamines of type **9** avoiding the use of valuable formylcarbohydrates as starting materials. An alternative method [17] could in fact be employed by coupling the nitriles **12a–c** [18] with $BrCH_2COOEt \cdot Zn$ couple (*Scheme 3*). By this reaction, the galactosyl, mannosyl, and ribosyl enamines **9a–c** were conveniently prepared in 86–89% yield, each product being present as a single (unidentified) stereoisomer.

Scheme 3



Michael-type addition of the enamine **9c** to the *Knoevenagel* enone **13** (Ar = C_6H_5, 5 equiv.) in DMF at 150° for 48 h led to 71% of (*S*)-**11c** and (*R*)-**11c** (not shown) in a 60:40 ratio (*Table 2*). It is worth pointing out that the excess of **13** in the crude reaction mixture was conveniently removed by treatment with aminomethylated polystyrene

(AM-*resin*). This operation substantially facilitated product purification. Subsequent catalytic hydrogenation over $Pd(OH)_2/C$ afforded the deprotected 4-phenyl-substituted *C*(6)-ribofuranosyl DHP derivative (*S*)-**11c′** and its (*R*)-epimer in almost quantitative yield. The absolute configuration of these compounds was assigned with the aid of circular dichroism (CD) (see below). The cyclocondensation of **9c** and **13** carried out in refluxing toluene for 12 h in the presence of AcOH (2 equiv.) also afforded (*S*)-**11c** and (*R*)-**11c**, in slightly lower yield (65%), though, but in a higher diastereoisomer ratio (75:25). Similar results were obtained in either DMF or toluene for the reaction of the galactosyl and mannosyl enamines **9a** and **9b** with **13**, as well as of the ribosyl enamine **9c** with **14** (Ar = 2-$(CF_3)C_6H_4$) (*Table 2*). This demonstrates that the cyclocondensation nicely proceeds even with *ortho*-substituted aryl groups in the enone. Please notice that the products (*S*)-**15c′** and (*R*)-**15c′** are glycosylated analogues of SKF 24260 (**2**) in which the Me group at C(6) is replaced by a ribofuranosyl residue. These results also clearly demonstrate that an asymmetric induction can be achieved in the construction of the DHP ring when chiral glycosylated reagents are used. Compounds **11a′–c′** and **15c′** are DHP derivatives that can be considered C-nucleosides, a class of glycoconjugates of current interest for their antitumor and antiviral activity [19].

The assignment of the structure of 4-aryl-substituted asymmetric DHPs is a general problem that can be most conveniently solved by X-ray crystallography. However, most of these compounds are reluctant to give suitable crystals for X-ray analysis. Fortunately enough, the mannopyranosyl derivative (*S*)-**11b′** (*Table 2*) crystallized from $AcOEt/H_2O$ in nice plates and was subjected to X-ray-analysis (*Fig. 1*)[3]). The stereocenter at C(4) of the DHP ring has the (*S*)-configuration, the β-linkage at the anomeric center of the mannopyranosyl residue (which is in the chair conformation) being retained. As in other known solid-state structures of 4-aryl-substituted DHPs [1b], the heterocyclic ring of (*S*)-**11b′** is in a flattened boat conformation, with the 4-Ph substituent in pseudoaxial position orthogonal to the plane of the DHP ring.

None of the other products shown in *Table 2* nor their minor isomers crystallized in a suitable form for X-ray analysis. Thus, based on the above X-ray structure, the (*S*)-configuration was tentatively assigned by analogy to the C(4)-stereocenter of the major isomers of the other three pairs of DHP derivatives, *i.e.*, compounds (*S*)-**11a′**, (*S*)-**11c′**, and (*S*)-**15c′**. Additional support for this assignment came from circular dichroism (CD) measurements. The CD spectra of the structurally known stereoisomer (*S*)-**11b′** and its epimer (*R*)-**11b′** are shown in *Fig. 2*. The spectrum of the (*S*)-isomer features a first absorption band with a negative sign at 210 nm and a second band of higher intensity and positive sign at 240 nm. The spectrum of the minor isomer (*R*)-**11b′** is characterized by four bands with alternative signs at 210 nm (pos.), 230 nm (neg.), 250 nm (pos.), and 290 nm (neg.). Quite gratifyingly, the CD spectra of the major and minor stereoisomers of the other three (*S*)- and (*R*)-pairs of **11a′**, **11c′**, and **15c′** display similar trends. Hence, these *Cotton* effects appear to support the assigned absolute

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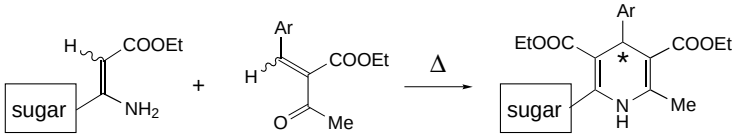
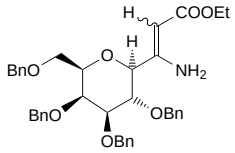
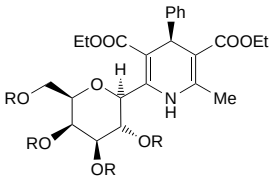
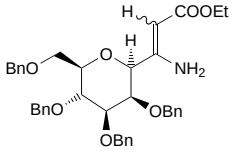
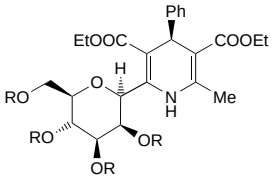
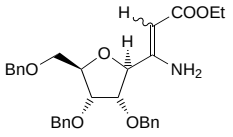
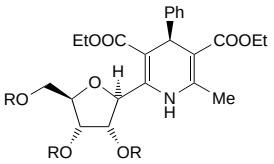
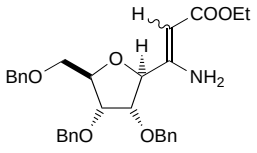
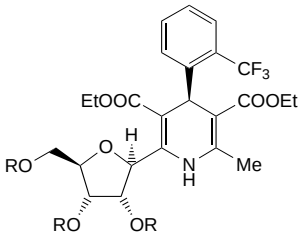
[3]) Crystallographic data (excluding structure factors) have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication number CCDC 182892. Copies of the data can be obtained, free of charge, on application to CCDC, Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 2. *Cyclocondensation*[a]) *between Glycosylated Enamines* **9a**–**c** *and Enones* **13** *and* **14**



9 **13** Ar = C_6H_5; **14** Ar = 2-$(CF_3)C_6H_4$ **11, 15**

Enamine	Product	Yield, de [%][b]) Solvent: DMF	Yield, de [%][b]) Solvent: toluene
 **9a**	 (*S*)-**11a** R = Bn; (*S*)-**11a'** R = H	61, 30	20, 30
 **9b**	 (*S*)-**11b** R = Bn; (*S*)-**11b'** R = H	66, 0	39, 60
 **9c**	 (*S*)-**11c** R = Bn; (*S*)-**11c'** R = H	71, 20	65, 50
 **9c**	 (*S*)-**15c** R = Bn; (*S*)-**15c'** R = H	62, 10	40, 30

[a]) All reactions were run with a five-fold excess of the enones **13** and **14**. [b]) Overall yield of the mixture of diastereoisomers. Yield and diastereoisomeric excess (de) refer to purified products.

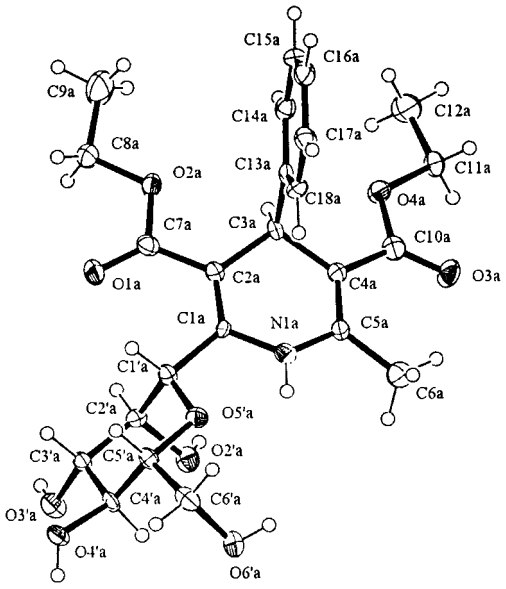


Fig. 1. *ORTEP View of compound (*S*)*-**11b**′. Thermal ellipsoids are dispayed at a 40% probability level.

configurations. However, this conclusion should be taken with care, because CD analogies are not always unequivocal [20].

Synthesis of Glycosylated Analogues of Nifedipine. – Given the successful cyclocondensation between the enamine **9c** and the *ortho*-aryl-substituted enone **14**, we decided to prepare a glycosylated DHP analogue of Nifedipine (**1**). The replacement of the Me group at C(6) by a carbohydrate residue might improve the compound's bioavailability while retaining its pharmacological properties, which are known to be related to the nature of the aryl group at C(4). The cyclocondensation between **16** and the nitrophenyl-substituted enone **19** (5 equiv.) run in DMF at 150°, afforded the glycosylated DHP **20** in low yield (15%) and as a 1:1 mixture of diastereoisomers (*Scheme 4* and *Table 3*). In refluxing toluene, in the presence of AcOH, a complex mixture of products was obtained, with traces of **20**, as shown by TLC (*Table 3*). Condensation in MeOH produced the desired cycloadduct in fair yield (64%), but still with no stereoselectivity. The removal of the *O*-Bn groups of **20** proved to be problematic. Hydrogenolysis in the presence of $Pd(OH)_2/C$ did not afford the deprotected ribosyl DHP **21** but several products most likely arising from the reduction of the NO_2 group. Attempted debenzylation with BCl_3 at low temperature [21] afforded the desired product **21** in poor yield. In order to overcome this problem, we used a *C*-glycosylated enamine whose carbohydrate moiety was protected with a group that can be removed under nonreductive conditions. Hence, the *O*-benzoylated *C*-ribosyl enamine **17**, prepared from 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide [17] and $BrCH_2COOMe \cdot Zn$, was allowed to react with **19** (5 equiv.) in refluxing MeOH. The usual workup, *i.e.*, sequestering the excess of **19** with the AM-resin followed by chromatography led to a mixture of products constituted by the deprotected nifedipine

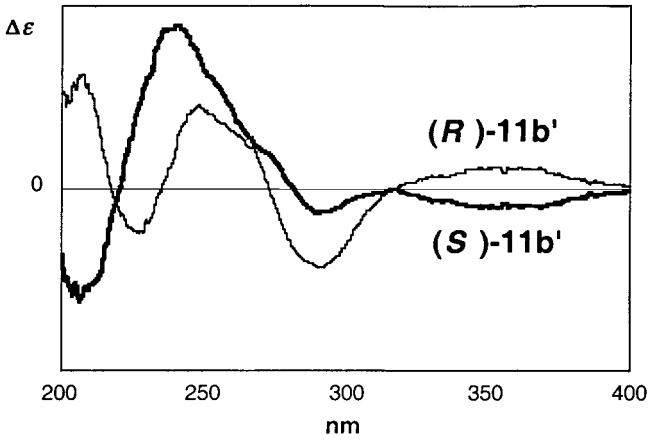
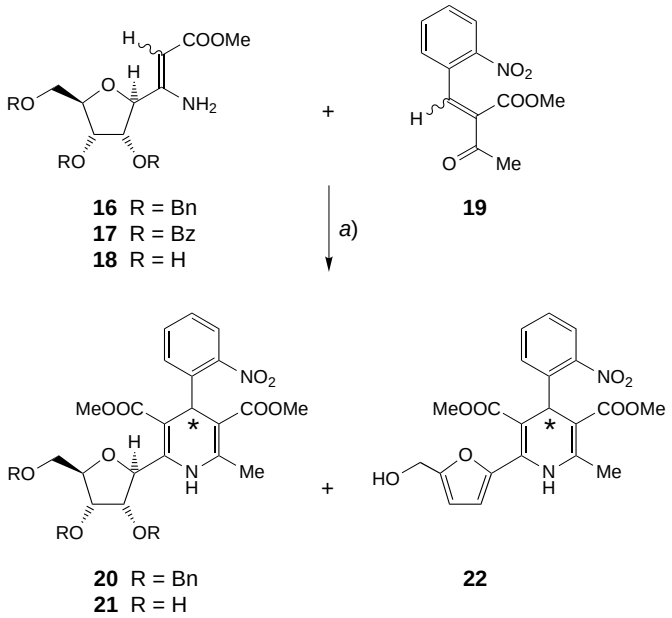


Fig. 2. *Circular-dichroism spectra of* (R)-**11b**′ *and* (S)-**11b**′

Scheme 4



a) For reaction conditions, *cf. Table 3*.

analogue **21** and partially benzoylated precursors. A modified workup, especially addition of a solution of MeONa in MeOH finally afforded **21** as a 1.2 : 1 mixture of diastereoisomers in 30% overall yield, together with the furyl derivative **22**, which was also isolated in 30% yield. The latter was the only product obtained in almost quantitative yield when **17** was treated with 10 equiv. of **19**, both in MeOH at 90° and in DMF at 150°. We think that, under these conditions, **19** promotes the elimination of

Table 3. *Synthesis of a C(6)-Ribofuranosyl Nifedipine Analogue* (*cf. Scheme 4*)

Enamine	Equiv. of **19**	Solvent	T [°]	Time [h]	Product(s)	Yield [%]
16	5	DMF	150	48	**20**	15
16	5	Toluene[a])	120	12	–	–
16	5	MeOH	90	48	**20**	64
17	5	MeOH[b])	90	48	**21**/**22** (1:1)	60 (total)
17	10	DMF[b])	150	24	**22**	95
17	10	MeOH[b])	90	24	**22**	95
18	5	MeOH	90	48	**21**	40
18	10	MeOH	90	48	**21**	53

[a]) In the presence of AcOH. [b]) Workup with 0.1M MeONa in MeOH.

PhCOOH from **17** before coupling. A driving force for this elimination can be the coordination of **19** to the PhCO groups of **17**. However, it is also possible that **19** tends to induce the elimination of PhCOOH from the final product **21**.

In order to solve all the problems described above, a final approach was made with the deprotected enamine **18** obtained from **17** by debenzoylation (0.1M soln. of MeONa in MeOH). Treatment of **18** with 5 or 10 equiv. of **19** in MeOH at 90° exclusively afforded **21** in 40% and 53% yield, respectively, as a 1.2:1 mixture of diastereoisomers. Thereby, the chromatographic isolation of the product was facilitated by the high ΔR_f value (EtOAc/MeOH 10:1) between **21** and **19**, which helped avoiding the use of AM-resin.

Conclusions. – We have demonstrated that three- and two-component *Hantzsch* reactions can be successfully applied to the synthesis of *C*(4)- and *C*(6)-glycosylated 1,4-dihydropyridines (DHPs) with suitable carbohydrate-based reagents. The first asymmetric synthesis of 4-aryl-substituted DHPs has been achieved in which carbohydrate residues act as 'chirality inducers' at C(4) of the heterocyclic ring. Now, further studies will be required to establish the scope and limitations of this method with respect to both chemical efficiency and degree of asymmetric induction. Moreover, due to the importance of chiral 4-aryl-substituted DHPs as pharmacologically active compounds, the preparation of an extensive number of *C*(6)-glycosylated analogues and the exploration of their biological activities will be targeted in the near future. Thereby, it is likely that novel biological properties of DHPs in general [2] and of *C*(4)- and *C*(6)-glycosylated derivatives will be found and that these interesting compounds will prove valuable in drug discovery.

We gratefully acknowledge *MURST* and the University of Ferrara for financial support. We would also like to thank *P. Formaglio* for assistance in NMR spectroscopy.

Experimental Part

General. All moisture-sensitive reactions were performed under a N_2 atmosphere with oven-dried glassware. Solvents were dried over standard drying agents and freshly distilled prior to use. Commercially available powdered molecular sieves (4 Å, 5 μm average particle size) were used without further activation. AM-resin was purchased from *Novabiochem*. Reactions were monitored by TLC on silica-gel *60* F_{254}, with detection by charring with H_2SO_4. Column chromatography (CC) was performed on silica-gel *60*

(230–400 mesh). Melting points (m.p.) were determined with a capillary apparatus. Optical rotations were measured at $20 \pm 2°$ in the solvent stated; $[\alpha]_D$ values are given in 10^{-1} deg · cm^2 · g^{-1}. ^{1}H- and ^{13}C-NMR spectra (300 and 75 MHz, resp.) were recorded in $CDCl_3$ at r.t., unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments. MALDI-TOF (*matrix-assisted-linear-desorption-ionization time-of-flight*) mass spectra were acquired with α-cyano-4-hydroxycinnamic acid as the matrix, unless otherwise specified. CD Measurements were carried out with a 0.1 cm cell at 20° in MeOH. Spectra were recorded twice between 400 and 200 nm with 1 nm resolution at a scan speed of 10 nm/min and were averaged and baseline-corrected. Compounds **4a–c** [13], **8c** [14], and **12a–c** [18] were synthesized as described. The compounds **13**, **14**, and **19** were prepared by standard *Knoevenagel* condensation of the corresponding aryl aldehydes and β-keto esters.

General Procedures for the Synthesis of the C(4)-Glycosylated Compounds **7a–c.** – *Method A*. A screw-capped vial, containing a magnetic bar, was charged with **4** (1.00 mmol), **5** (127 µl, 1.00 mmol), **6** (129 mg, 1.00 mmol), molecular sieves (300 mg), and anh. EtOH (5 ml). The mixture was vigorously stirred, degassed *in vacuo*, and saturated with Ar (3×). The mixture was stirred at 90° for 48 h, cooled to r.t., filtered through a pad of *Celite*, concentrated, and subjected to CC.

Method B. A screw-capped vial, containing a magnetic bar, was charged with **4** (1.00 mmol), **5** (127 µl, 1.00 mmol), **6** (129 mg, 1.00 mmol), $Yb(OTf)_3$ (620 mg, 1.00 mmol), and anh. THF (7 ml). The mixture was vigorously stirred, degassed *in vacuo*, and saturated with Ar (3×). The mixture was stirred at 90° for 12 h, cooled to *r.t.*, filtered through a pad of *Celite*, and concentrated. The residue was diluted with CH_2Cl_2 (100 ml) and washed with H_2O (2 × 10 ml). The org. layer was dried (Na_2SO_4), concentrated, and subjected to CC.

*Diethyl 4-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-*D*-galactopyranosyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate* (**7a**): *Method A* and CC (cyclohexane/AcOEt 3:1) afforded **7a** (683 mg, 88%) as a yellow oil. $[\alpha]_D = +72.1$ ($c = 1.4$, $CHCl_3$). ^{1}H-NMR: 7.50–7.20 (*m*, 20 arom. H); 5.48 (br. *s*, NH); 5.07, 4.76 (2*d*, *J* = 11.2, PhCH_2); 5.00, 4.53 (2*d*, *J* = 11.8, PhCH_2); 4.76, 4.59 (2*d*, *J* = 11.5, PhCH_2); 4.66 (*d*, *J*(4,1′) = 1.8, H–C(4)); 4.42 (*s*, PhCH_2); 4.28, 3.98 (*m*, 2 MeCH_2); 3.94 (*dd*, *J*(3′,4′) = 2.8, *J*(4′,5′) ≈ 0.5, H–C(4′)); 3.85 (*dd*, *J*(1′,2′) = 9.2, *J*(2′,3′) = 9.0, H–C(2′)); 3.58 (*dd*, H–C(3′)); 3.50 (*ddd*, *J*(5′,6′a) = 4.2, *J*(5′,6′b) = 3.8, H–C(5′)); 3.49 (*dd*, *J*(6′a,6′b) = 12.0, H–C(6′a)); 3.44 (*dd*, H–C(6′b)); 3.20 (*dd*, H–C(1′)); 2.26 (*s*, Me); 2.24 (*s*, Me); 1.20 (*t*, *J* = 7.0, *Me*CH_2); 1.18 (*t*, *J* = 7.0, *Me*CH_2). Anal. calc. for $C_{47}H_{53}NO_9$ (775.93): C 72.75, H 6.88, N 1.81; found: C 72.74, H 6.82, N 1.78.

Method B and CC (cyclohexane/AcOEt 3:1) afforded **7a** (737 mg, 95%) as a yellow oil.

*Diethyl 4-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-*D*-mannopyranosyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate* (**7b**): *Method A* and CC (cyclohexane/AcOEt 2:1) afforded **7b** (543 mg, 70%) as a yellow oil. $[\alpha]_D = -69.7$ ($c = 1.2$, $CHCl_3$). ^{1}H-NMR: 7.60–7.10 (*m*, 20 arom. H); 5.69 (br. *s*, NH); 5.33, 4.55 (2*d*, *J* = 12.0, PhCH_2); 4.84, 4.73 (2*d*, *J* = 11.8, PhCH_2); 4.83, 4.61 (2*d*, *J* = 11.5, PhCH_2); 4.82 (*d*, *J*(4,1′) = 9.0, H–C(4)); 4.79, 4.45 (2*d*, *J* = 11.2, PhCH_2); 4.28, 4.00 (*m*, 2 MeCH_2); 3.88 (*dd*, *J*(5′,6′a) = 4.2, *J*(6′a,6′b) = 12.0, H–C(6′a)); 3.82 (*dd*, *J*(3′,4′) = 9.2, *J*(4′,5′) = 9.1, H–C(4′)); 3.81 (*d*, *J*(2′,3′) = 2.5, H–C(2′)); 3.73 (*dd*, *J*(5′,6′b) = 1.0, H–C(6′b)); 3.55 (*dd*, H–C(3′)); 3.28 (*ddd*, H–C(5′)); 2.98 (*d*, H–C(1′)); 2.32 (*s*, Me); 2.28 (*s*, Me); 1.16 (*t*, *J* = 7.0, *Me*CH_2); 1.08 (*t*, *J* = 7.0, *Me*CH_2). Anal. calc. for $C_{47}H_{53}NO_9$ (775.93): C 72.75, H 6.88, N 1.81; found: C 72.77, H 6.89, N 1.83.

Method B and CC (cyclohexane/AcOEt 2:1) afforded **7b** (217 mg, 28%) as a yellow oil.

*Diethyl 4-(2′,3′,5′-Tri-*O*-benzyl-β-*D*-ribofuranosyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate* (**7c**). *Method A* and CC (cyclohexane/AcOEt 3:1) afforded **7c** (466 mg, 71%) as a yellow oil. $[\alpha]_D = +38.6$ ($c = 0.9$, $CHCl_3$). ^{1}H-NMR: 7.40–7.20 (*m*, 15 arom. H); 5.42 (br. *s*, NH); 4.57, 4.51 (2*d*, *J* = 12.0, PhCH_2); 4.53, 4.37 (2*d*, *J* = 11.5, PhCH_2); 4.49, 4.42 (2*d*, *J* = 11.2, PhCH_2); 4.25 (*d*, *J*(4,1′) = 7.0, H–C(4)); 4.21 (*ddd*, *J*(4′,5′a) = 4.5, *J*(4′,5′b) = 6.2, H–C(4′)); 4.18–4.02 (*m*, H–C(3′), 2 MeCH_2); 3.92 (*dd*, *J*(1′,2′) = 5.0, *J*(2′,3′) = 3.8, H–C(2′)); 3.59 (*dd*, H–C(1′)); 3.52 (*dd*, *J*(5′a,5′b) = 10.8, H–C(5′a)); 3.39 (*dd*, H–C(5′b)); 2.22 (*s*, Me); 2.18 (*s*, Me); 1.26 (*t*, *J* = 7.0, *Me*CH_2); 1.21 (*t*, *J* = 7.0, *Me*CH_2). Anal. calc. for $C_{39}H_{45}NO_8$ (655.78): C 71.43, H 6.92, N 2.14; found: C 71.45, H 6.94, N 2.17.

Method B and CC (cyclohexane/AcOEt 3:1) afforded **7c** (262 mg, 40%) as a yellow oil.

*Ethyl 3-Amino-3-(2′,3′,4′,6′-tetra-*O*-benzyl-β-*D*-galactopyranosyl)propenoate* (**9a**). A suspension of Zn dust (588 mg, 9.0 mmol) in anh. THF (8 ml) was brought to reflux, then a few drops of ethyl bromoacetate were added. After a green color had appeared (*ca.* 15 min), a soln. of **12a** [18] (825 mg, 1.5 mmol) in anh. THF (2 ml) was added in one portion. The remaining bromoacetate was added dropwise over 40 min (total amount: 0.66 ml, 6 mmol). The mixture was cooled to r.t., treated with sat. $NaHCO_3$ soln. (10 ml), and filtered through a pad of *Celite*. The filtrate was extracted with Et_2O (3 × 75 ml), the combined org. layers were dried (Na_2SO_4) and concentrated. CC (cyclohexane/AcOEt 7:1 containing 0.5% of Et_3N) afforded **9a** (823 mg, 86%) as an oil. $[\alpha]_D = -9.3$ ($c = 0.9$, $CHCl_3$). ^{1}H-NMR ($CDCl_3/D_2O$): 7.42–7.20 (*m*, 20 arom. H);

4.99, 4.60 (2*d*, *J* = 11.5, PhC*H*$_2$); 4.88 (*s*, H–C(2)); 4.78 (*s*, PhC*H*$_2$); 4.74, 4.60 (2*d*, *J* = 10.8, PhC*H*$_2$); 4.50, 4.44 (2*d*, *J* = 11.8, PhC*H*$_2$); 4.26–4.06 (*m*, MeC*H*$_2$); 3.99 (*dd*, *J*(3′,4′) = 2.8, *J*(4′,5′) ≈ 0.5, H–C(4′)); 3.94 (*dd*, *J*(1′,2′) = 9.1, *J*(2′,3′) = 9.0, H–C(2′)); 3.69 (*d*, H–C(1′)); 3.66–3.56 (*m*, H–C(3′), H–C(5′), 2 H–C(6′)); 1.30 (*t*, *J* = 7.0, *Me*CH$_2$). Anal. calc. for $C_{39}H_{43}NO_7$ (637.76): C 73.45, H 6.80, N 2.20; found: C 73.41, H 6.80, N 2.18.

*Ethyl 3-Amino-3-(2′,3′,4′,6′-tetra-*O*-benzyl-β-*D*-mannopyranosyl)propenoate* (**9b**). Compound **12b** [18] (825 mg, 1.5 mmol) was treated as described for the preparation of **9a**. CC (cyclohexane/AcOEt 7:1 containing 0.5% of Et$_3$N) yielded **9b** (823 mg, 86%) as an oil. $[\alpha]_D = +12.7$ (*c* = 1.4, CHCl$_3$). ^{1}H-NMR (CDCl$_3$/D$_2$O): 7.45–7.10 (*m*, 20 arom. H); 4.92, 4.68 (2*d*, *J* = 11.2, PhC*H*$_2$); 4.84, 4.59 (2*d*, *J* = 11.5, PhC*H*$_2$); 4.73, 4.66 (2*d*, *J* = 11.0, PhC*H*$_2$); 4.63, 4.56 (2*d*, *J* = 12.0, PhC*H*$_2$); 4.47 (*s*, H–C(2)); 4.15 (*q*, *J* = 7.0, MeC*H*$_2$); 4.00 (*dd*, *J*(1′,2′) ≈ 0.5, *J*(2′,3′) = 3.0, H–C(2′)); 3.93 (*dd*, *J*(3′,4′) = 9.1, *J*(4′,5′) = 9.0, H–C(4′)); 3.91 (*d*, H–C(1′)); 3.77 (*dd*, *J*(5′,6′a) = 2.5, *J*(6′a,6′b) = 10.8, H–C(6′a)); 3.73 (*dd*, *J*(5′,6′b) = 4.8, H–C(6′b)); 3.66 (*dd*, H–C(3′)); 3.51 (*ddd*, H–C(5′)); 1.30 (*t*, *Me*CH$_2$). Anal. calc. for $C_{39}H_{43}NO_7$ (637.76): C 73.45, H 6.80, N 2.20; found: C 73.48, H 6.82, N 2.23.

*Ethyl 3-Amino-3-(2′,3′,5′-tri-*O*-benzyl-β-*D*-ribofuranosyl)propenoate* (**9c**). *Method C.* Compound **12c** [18] (644 mg, 1.5 mmol) was treated as described for the preparation of **9a**. CC (cyclohexane/AcOEt 6:1 containing 0.5% of Et$_3$N) yielded **9c** (691 mg, 89%) as an oil. $[\alpha]_D = +18.7$ (*c* = 1.1, CHCl$_3$). ^{1}H-NMR (CDCl$_3$/D$_2$O): 7.50–7.10 (*m*, 15 arom. H); 4.72, 4.61 (2*d*, *J* = 12.0, PhC*H*$_2$); 4.58, 4.42 (2*d*, *J* = 11.8, PhC*H*$_2$); 4.56 (*d*, *J*(1′,2′) = 3.0, H–C(1′)); 4.54, 4.45 (2*d*, *J* = 11.2, PhC*H*$_2$); 4.52 (*s*, H–C(2)); 4.27 (*ddd*, *J*(3′,4′) = 7.5, *J*(4′,5′a) = 2.8, *J*(4′,5′b) = 2.0, H–C(4′)); 4.13 (*q*, *J* = 7.0, MeC*H*$_2$); 4.11 (*dd*, *J*(2′,3′) = 4.5, H–C(3′)); 3.98 (*dd*, H–C(2′)); 3.85 (*dd*, *J*(5′a,5′b) = 10.8, H–C(5′a)); 3.59 (*dd*, H–C(5′b)); 1.28 (*t*, *Me*CH$_2$). Anal. calc. for $C_{31}H_{35}NO_6$ (517.61): C 71.93, H 6.82, N 2.71; found: C 71.91, H 6.80, N 2.69.

Method D. A screw-capped vial, containing a magnetic bar, was charged with **8c** [14] (138 mg, 0.27 mmol), AcONH$_4$ (103 mg, 1.33 mmol), AcOH (15 µl, 0.27 mmol), molecular sieves (100 mg) and anh. toluene (3 ml). The mixture was stirred at 120° for 1.5 h, cooled to r.t., filtered through a pad of *Celite*, and concentrated. The residue was diluted with CH$_2$Cl$_2$ (50 ml) and washed with H$_2$O (2 × 5 ml). The org. phase was dried (Na$_2$SO$_4$), concentrated, and subjected to CC (cyclohexane/AcOEt 6:1 containing 0.5% of Et$_3$N) to afford **9c** (131 mg, 95%) as an oil.

Procedures for the Three-Component Hantzsch *Reaction Leading to Diethyl (4*R*)- and (4*S*)-2-(2′,3′,5′-Tri-*O*-benzyl-β-*D*-ribofuranosyl)-6-methyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate* (**11c**). *Method E.* A screw-capped vial, containing a magnetic bar, was charged with PhCHO (102 µl, 1.00 mmol), **8c** (259 mg, 0.50 mmol), **6** (129 mg, 1.00 mmol), molecular sieves (200 mg), and anh. EtOH (5 ml). The mixture was vigorously stirred, degassed *in vacuo*, and saturated with Ar (3×). The mixture was stirred at 90° for 48 h, cooled to r.t., filtered through a pad of *Celite*, and concentrated. The residue was purified by CC (cyclohexane/AcOEt 9:1) to yield **11c** (18 mg, 5%) as a 1:1 mixture of the (4*R*)- and (4*S*)-diastereoisomers (for anal. data, see the two-component procedure below).

Method F. A screw-capped vial, containing a magnetic bar, was charged with benzaldehyde (102 µl, 1.00 mmol), **5** (127 µl, 1.00 mmol), **9c** (259 mg, 0.50 mmol), molecular sieves (200 mg), and anh. EtOH (5 ml). The mixture was vigorously stirred, degassed *in vacuo*, and saturated with Ar (3×). The mixture was stirred at 90° for 48 h, cooled to r.t., filtered through a pad of *Celite*, and concentrated. CC (cyclohexane/AcOEt 9:1) afforded **11c** (36 mg, 10%) as a 1.5:1 mixture of the (4*R*)- and (4*S*)-diastereoisomers (for analytical data, see the two-component procedure below).

General Procedures for the Two-Component Hantzsch *Reaction Leading to the C(6)-Glycosylated Compounds* **11a–c** *and* **15c**. *Method G.* A screw-capped vial, containing a magnetic bar, was charged with **13** or **14** (2.50 mmol), **9** (0.50 mmol), molecular sieves (200 mg), and anh. DMF (4 ml). The mixture was vigorously stirred, degassed *in vacuo*, and saturated with Ar (3×). The mixture was stirred at 150° for 48 h, cooled to r.t., filtered through a pad of *Celite*, and concentrated. The residue was diluted with CH$_2$Cl$_2$ (5 ml) and treated with aminomethylated polystyrene (1.0 g, *ca.* 2.50 mmol). The suspension was stirred for an additional 2 h. The resin was filtered off and washed thoroughly with CH$_2$Cl$_2$. The combined filtrates were concentrated and subjected to CC to yield the corresponding dihydropyridines.

Method H. A screw-capped vial, containing a magnetic bar, was charged with **13** or **14** (2.50 mmol), AcOH (57 µl, 1.00 mmol), **9** (0.50 mmol), molecular sieves (200 mg), and anh. toluene (4 ml). The mixture was vigorously stirred, degassed *in vacuo* and saturated with Ar (3×). The mixture was stirred at 120° for 12 h, cooled to r.t., filtered through a pad of *Celite*, and concentrated. The residue was diluted with CH$_2$Cl$_2$ (5 ml), and treated with aminomethylated polystyrene (1.0 g, *ca.* 2.50 mmol). The suspension was stirred for an additional

2 h. The resin was filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated and subjected to CC to afford the corresponding dihydropyridines.

*Diethyl (4*S*)- and (4*R*)-2-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-*D*-galactopyranosyl)-1,4-dihydro-6-methyl-4-phenylpyridine-3,5-dicarboxylate* (**11a**). *Method G* and CC (toluene/cyclohexane/(i-Pr)$_2$O 2:1:1) afforded (*S*)-**11a** (166 mg, 40%) as a yellow foam. $[\alpha]_D = +32.6$ ($c = 1.1$, $CHCl_3$). ^{1}H-NMR: 7.40–7.10 (*m*, 25 arom. H); 6.58 (br. *s*, NH); 5.61 (*d*, $J(1',2') = 9.0$, H–C(1′)); 5.03 (*s*, H–C(4)); 5.01, 4.57 (2*d*, $J = 11.5$, PhCH_2); 4.79 (*s*, PhCH_2); 4.73, 4.57 (2*d*, $J = 11.0$, PhCH_2); 4.54, 4.50 (2*d*, $J = 11.8$, PhCH_2); 4.20–3.88 (*m*, 2 MeCH_2);4.07 (*dd*, $J(3',4') = 2.8$, $J(4',5') \approx 0.5$, H–C(4′)); 3.84 (*dd*, $J(2',3') = 9.0$, H–C(2′)); 3.74 (*dd*, H–C(3′)); 3.74–3.54 (*m*, H–C(5′), 2 H–C(6′)); 2.15 (*s*, Me); 1.26 (*t*, $J = 7.0$, OCH_2*Me*); 1.14 (*t*, $J = 7.0$, *Me*CH_2). Anal. calc. for $C_{52}H_{55}NO_9$ (837.99): C 74.53, H 6.62, N 1.67; found: C 74.55, H 6.67, N 1.68. Eluted second was (*R*)-**11a** (90 mg, 21%) slightly contaminated by the major isomer; ^{1}H-NMR (selected data): 6.62 (br. *s*, NH); 5.77 (*d*, $J(1',2') = 9.1$, H–C(1′)); 5.05 (*s*, H–C(4)); 4.03 (*dd*, $J(3',4') = 2.8$, $J(4',5') \approx 0.5$, H–C(4′)); 3.85 (*dd*, $J(2',3') = 9.0$, H–C(2′)); 2.36 (*s*, Me).

Method H and CC (toluene/cyclohexane/(i-Pr$_2$)O 2:1:1) afforded first (*S*)-**11a** (55 mg, 13%) as a yellow foam and, second, (*R*)-**11a** (29 mg, 7%, slightly contaminated by the major isomer).

*Diethyl (4*S*)- and (4*R*)-2-(2′,3′,4′,6′-Tetra-*O*-benzyl-β-*D*-mannopyranosyl)-1,4-dihydro-6-methyl-4-phenylpyridine-3,5-dicarboxylate* (**11b**). *Method G* and CC (cyclohexane/(i-Pr$_2$)O 1:1) afforded (*S*)-**11b** (138 mg, 33%) as yellow foam. $[\alpha]_D = +49.0$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR: 7.60–7.00 (*m*, 25 arom. H); 5.21 (*d*, $J(1',2') \approx 0.5$, H–C(1′)); 4.94, 4.62 (2*d*, $J = 11.2$, PhCH_2); 4.92 (*s*, H–C(4)); 4.82, 4.46 (2*d*, $J = 11.5$, PhCH_2); 4.79, 4.74 (2*d*, $J = 11.8$, PhCH_2); 4.67, 4.57 (2*d*, $J = 12.0$, PhCH_2); 4.42 (*dd*, $J(2',3') = 2.5$, H–C(2′)); 4.22–4.00 (*m*, 2 *Me*CH_2); 4.00 (*dd*, $J(3',4') = 9.0$, $J(4',5') = 9.2$, H–C(4′)); 3.86–3.74 (*m*, H–C(3′), 2 H–C(6′)); 3.60 (*ddd*, $J(5',6'a) = 3.0$, $J(5',6'b) = 3.2$, H–C(5′)); 2.07 (*s*, Me); 1.30 (*t*, $J = 7.0$, OCH_2*Me*); 1.22 (*t*, $J = 7.0$, OCH$_2$CH_3). Anal. calc. for $C_{52}H_{55}NO_9$ (837.99): C 74.53, H 6.62, N 1.67; found: C 74.51, H 6.59, N 1.65. Eluted second was (*R*)-**11b** (137 mg, 33%) as a yellow foam; $[\alpha]_D = +82.8$ ($c = 1.6$, $CHCl_3$). ^{1}H-NMR: 7.50–7.00 (*m*, 25 arom. H); 5.30 (*d*, $J(1',2') \approx 0.5$, H–C(1′)); 5.12 (*s*, H–C(4)); 4.92, 4.60 (2*d*, $J = 12.0$, PhCH_2); 4.83, 4.42 (2*d*, $J = 11.8$, PhCH_2); 4.73, 4.65 (2*d*, $J = 11.5$, PhCH_2); 4.65, 4.57 (2*d*, $J = 11.2$, PhCH_2); 4.29 (*dd*, $J(2',3') = 2.5$, H–C(2′)); 4.22–4.00 (*m*, 2 MeCH_2); 3.98 (*dd*, $J(3',4') = 9.2$, $J(4',5') = 9.5$, H–C(4′)); 3.84 (*dd*, H–C(3′)); 3.80 (*dd*, $J(5',6'a) = 3.0$, $J(6'a,6'b) = 11.8$, H–C(6′a)); 3.74 (*dd*, $J(5',6'b) = 4.0$, H–C(6′b)); 3.61 (*ddd*, H–C(5′)); 2.32 (*s*, Me); 1.31 (*t*, $J = 7.0$, *Me*CH_2); 1.20 (*t*, $J = 7.0$, *Me*CH_2). Anal. calc. for $C_{52}H_{55}NO_9$ (837.99): C 74.53, H 6.62, N 1.67; found: C 74.54, H 6.63, N 1.65.

Method H and CC (cyclohexane/(i-Pr$_2$)O 1:1) afforded first (*S*)-**11b** (130 mg, 31%) as a yellow foam. Eluted second was (*R*)-**11b** (33 mg, 8%), yellow foam.

*Diethyl (4*R*)- and (4*S*)-2-(2′,3′,5′-Tri-*O*-benzyl-β-*D*-ribofuranosyl)-1,4-dihydro-6-methyl-4-phenylpyridine-3,5-dicarboxylate* (**11c**). *Method G* and CC (cyclohexane/AcOEt 9:1) afforded (*S*)-**11c** (153 mg, 43%) as yellow foam. $[\alpha]_D = +103.3$ ($c = 1.5$, $CHCl_3$). ^{1}H-NMR: 8.19 (br. *s*, NH); 7.50–7.00 (*m*, 20 arom. H); 5.83 (*s*, H–C(1′)); 5.00 (*s*, H–C(4)); 4.97, 4.90 (2*d*, $J = 11.8$, PhCH_2); 4.63, 4.53 (2*d*, $J = 12.0$, PhCH_2); 4.51, 4.25 (2*d*, $J = 11.5$, PhCH_2); 4.31 (*ddd*, $J(3',4') = 7.5$, $J(4',5'a) = 2.5$, $J(4',5'b) = 1.0$, H–C(4′)); 4.20–4.04 (*m*, 2 OCH_2Me); 4.04–4.00 (*m*, H–C(2′), H–C(3′)); 3.97 (*dd*, $J(5'a,5'b) = 10.8$, H–C(5′a)); 3.66 (*dd*, H–C(5′b)); 2.05 (*s*, Me); 1.26 (*t*, $J = 7.0$, OCH_2*Me*); 1.24 (*t*, $J = 7.0$, OCH_2*Me*). Anal. calc. for $C_{44}H_{47}NO_8$ (717.85): C 73.62, H 6.60, N 1.95; found: C 73.64, H 6.59, N 1.93. Eluted second was (*R*)-**11c** (102 mg, 28%) as a yellow foam. $[\alpha]_D = +136.2$ ($c = 0.8$, $CHCl_3$). ^{1}H-NMR: 8.17 (br. *s*, NH); 7.50–7.10 (*m*, 20 arom. H); 5.88 (*s*, H–C(1′)); 5.05 (*s*, H–C(4)); 4.95, 4.76 (2*d*, $J = 11.8$, PhCH_2); 4.60, 4.50 (2*d*, $J = 12.0$, PhCH_2); 4.49, 4.20 (2*d*, $J = 11.5$, PhCH_2); 4.32 (*ddd*, $J(3',4') = 9.0$, $J(4',5'a) = 2.5$, $J(4',5'b) = 1.0$, H–C(4′)); 4.24–4.00 (*m*, H–C(3′), H–C(5′a), 2 MeCH_2); 3.94 (*d*, $J(2',3') = 4.0$, H–C(2′)); 3.65 (*dd*, $J(5'a,5'b) = 10.8$, H–C(5′b)); 1.95 (*s*, Me); 1.28 (*t*, $J = 7.0$, *Me*CH_2); 1.23 (*t*, $J = 7.0$, *Me*CH_2). Anal. calc. for $C_{44}H_{47}NO_8$ (717.85): C 73.62, H 6.60, N 1.95; found: C 73.67, H 6.63, N 1.97.

Method H and CC (cyclohexane/AcOEt 9:1) afforded (*S*)-**11c** (175 mg, 49%) as a yellow foam. Eluted second was (*R*)-**11c** (58 mg, 16%), yellow foam.

*Diethyl (4*R*)- and (4*S*)-2-(2′,3′,5′-Tri-*O*-benzyl-β-*D*-ribofuranosyl)-1,4-dihydro-6-methyl-4-[2-(trifluoromethyl)phenyl]pyridine-3,5-dicarboxylate* (**15c**). *Method G* and CC (cyclohexane/AcOEt 6:1) afforded (*S*)-**15c** (139 mg, 35%) as a yellow foam. $[\alpha]_D = +90.4$ ($c = 1.4$, $CHCl_3$). ^{1}H-NMR: 8.18 (br. *s*, NH); 7.60–7.10 (*m*, 19 arom. H); 5.80 (*s*, H–C(1′)); 5.62 (br. *q*, $J(4,CF_3) = 1.0$, H–C(4)); 4.96, 4.88 (2*d*, $J = 11.8$, PhCH_2); 4.65, 4.53 (2*d*, $J = 12.0$, PhCH_2); 4.50, 4.26 (2*d*, $J = 11.5$, PhCH_2); 4.32 (*ddd*, $J(3',4') = 9.0$, $J(4',5'a) = 2.5$, $J(4',5'b) \approx 0.5$, H–C(4′)); 4.28–4.12 (*m*, MeCH_2); 4.10–3.94 (*m*, OCH_2Me, H–C(2′), H–C(3′)); 3.98 (*dd*, $J(5'a,5'b) = 10.8$, H–C(5′a)); 3.67 (*dd*, H–C(5′b)); 2.05 (*s*, Me); 1.22 (*t*, $J = 7.0$, *Me*CH_2); 1.19 (*t*, $J = 7.0$, *Me*CH_2). Anal. calc. for $C_{45}H_{46}F_3NO_8$ (785.84): C 68.78, H 5.90, F 7.25, N 1.78; found: C 68.76, H 5.92, F 7.24, N 1.76. Eluted second was (*R*)-**15c** (105 mg, 27%), yellow foam. $[\alpha]_D = +106.0$ ($c = 1.2$, $CHCl_3$). ^{1}H-NMR: 8.17 (br. *s*, NH);

7.60–7.10 (*m*, 19 arom. H); 5.79 (*s*, H–C(1′)); 5.66 (br. *q*, *J*(4,CF_3) = 1.0, H–C(4)); 4.97, 4.76 (2*d*, *J* = 11.8, PhCH_2); 4.64, 4.55 (2*d*, *J* = 12.0, PhCH_2); 4.53, 4.24 (2*d*, *J* = 11.5, PhCH_2); 4.34 (*ddd*, *J*(3′,4′) = 9.0, *J*(4′,5′a) = 2.0, *J*(4′,5′b) ≈ 0.5, H–C(4′)); 4.28–3.92 (*m*, 2 MeCH_2, H–C(2′), H–C(3′), H–C(5′a)); 3.69 (*dd*, *J*(5′a,5′b) = 10.8, H–C(5′b)); 1.91 (*s*, Me); 1.24 (*t*, *J* = 7.0, *Me*CH_2); 1.19 (*t*, *J* = 7.0, *Me*CH_2). Anal. calc. for $C_{45}H_{46}F_3NO_8$ (785.84): C 68.78, H 5.90, F 7.25, N 1.78; found: C 68.806, H 5.92, F 7.27, N 1.79.

Method H and CC (cyclohexane/AcOEt 6:1) afforded (*S*)-**15c** (102 mg, 26%) as yellow foam. Eluted second was (*R*)-**15c** (55 mg, 14%), yellow foam.

General Procedure for the Synthesis of the C(4)- and C(6)-Glycosylated Compounds **7a′–c′**, **11a′–c′**, *and* **15c′**. A vigorously stirred mixture of 20% $Pd(OH)_2$/C (50 weight-% of substrate), AcOEt (2 ml), and EtOH (4 ml) was degassed *in vacuo* and saturated with H_2 (3×): To this mixture was added a degassed and H_2-sat. soln. of benzylated DHP (0.30 mmol) in AcOEt (2 ml). After stirring in a H_2 atmosphere (balloon) at r.t. for 3–5 h, the catalyst 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 yield the corresponding deprotected DHPs in almost quantitative yield.

*Diethyl 4-(β-*D*-Galactopyranosyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate* (**7a′**). White foam. $[\alpha]_D = -26.4$ (*c* = 0.8, MeOH). ^{1}H-NMR (CD_3OD): 4.24 (*q*, *J* = 7.0, MeCH_2); 4.23 (*d*, *J*(4,1′) = 3.2, H–C(4)); 4.18 (*q*, *J* = 7.0, MeCH_2); 3.82 (*dd*, *J*(3′,4′) = 3.0, *J*(4′,5′) ≈ 0.5, H–C(4′)); 3.61 (*dd*, *J*(5′,6′a) = 6.5, *J*(6′a,6′b) = 11.2, H–C(6′a)); 3.53 (*dd*, *J*(5′,6′b) = 6.0, H–C(6′b)); 3.48 (*dd*, *J*(1′,2′) = 9.0, *J*(2′,3′) = 9.1, H–C(2′)); 3.42 (*dd*, H–C(3′)); 3.27 (*ddd*, H–C(5′)); 2.93 (*dd*, H–C(1′)); 2.29 (*s*, Me); 2.28 (*s*, Me); 1.34 (*t*, *Me*CH_2); 1.31 (*t*, *Me*CH_2). ^{13}C-NMR: 170.8; 167.9; 150.1; 148.0; 98.5; 95.4; 84.5; 84.3; 74.1; 69.7; 66.5; 62.0; 60.9; 60.0; 34.1; 20.5; 19.1; 14.4; 14.3. MALDI-TOF-MS: 438.6 ($[M+Na]^+$), 454.0 ($[M+K]^+$). Anal. calc. for $C_{19}H_{29}NO_9$ (415.43): C 54.93, H 7.04, N 3.37; found: C 54.94, H 7.03, N 3.39.

*Diethyl 1,4-Dihydro-4-(β-*D*-mannopyranosyl)-2,6-dimethylpyridine-3,5-dicarboxylate* (**7b′**). White foam: $[\alpha]_D = -73.9$ (*c* = 1.6, MeOH). ^{1}H-NMR (CD_3OD): 4.30–4.10 (*m*, 2 MeCH_2); 4.22 (*d*, *J*(4.1′) = 9.5, H–C(4)); 3.73 (*dd*, *J*(5′,6′a) = 3.0, *J*(6′a,6′b) = 11.5, H–C(6′a)); 3.62 (*dd*, *J*(5′,6′b) = 5.5, H–C(6′b)); 3.60 (*dd*, *J*(3′,4′) = 9.2, *J*(4′,5′) = 9.1, H–C(4′)); 3.60 (*dd*, *J*(1′,2′) ≈ 0.5, *J*(2′,3′) = 3.5, H–C(2′)); 3.32 (*dd*, H–C(3′)); 2.99 (*dd*, H–C(1′)); 2.98 (*ddd*, H–C(5′)); 2.32 (*s*, Me); 2.25 (*s*, Me); 1.34 (*t*, *J* = 7.0, *Me*CH_2); 1.32 (*t*, *J* = 7.0, *Me*CH_2). ^{13}C-NMR (CD_3OD): 171.7; 171.4; 150.7; 144.3; 103.8; 96.7; 82.1; 81.8; 76.3; 69.7; 69.1; 63.5; 61.8; 61.1; 36.1; 19.5; 17.7; 14.7; 14.7; 14.6. MALDI-TOF-MS: 438.7 ($[M+Na]^+$), 454.5 ($[M+K]^+$). Anal. calc. for $C_{19}H_{29}NO_9$ (415.43): C 54.93, H 7.04, N 3.37; found: C 54.94, H 7.03, N 3.39.

*Diethyl 1,4-Dihydro-2,6-dimethyl-4-(β-*D*-ribofuranosyl)pyridine-3,5-dicarboxylate* (**7c′**). White foam. $[\alpha]_D = +3.9$ (*c* = 1.0, MeOH). ^{1}H-NMR (CD_3OD): 4.28–4.12 (*m*, 2 MeCH_2); 4.10 (*d*, *J*(4,1′) = 7.5, H–C(4)); 3.99 (*dd*, *J*(2′,3′) = 5.0, *J*(3′,4′) = 7.0, H–C(3′)); 3.94 (*dd*, *J*(1′,2′) = 2.5, H–C(2′)); 3.73 (*ddd*, *J*(4′,5′a) = 3.0, *J*(4′,5′b) = 4.5, H–C(4′)); 3.68 (*dd*, *J*(5′a,5′b) = 10.8, H–C(5′a)); 3.66 (*dd*, H–C(1′)); 3.51 (*dd*, H–C(5′b)); 2.33 (*s*, Me); 2.30 (*s*, Me); 1.33 (*t*, *J* = 7.0, OCH_2*Me*); 1.32 (*t*, *J* = 7.0, OCH_2*Me*). ^{13}C-NMR (CD_3OD): 170.7; 170.2; 148.9; 148.7; 99.9; 99.3; 88.4; 83.2; 73.4; 72.2; 63.0; 61.2; 61.0; 37.7; 19.2; 18.5; 14.8; 14.7. MALDI-TOF-MS: 386.6 ($[M+H]^+$), 392.9 ($[M+Li]^+$), 408.9 ($[M+Na]^+$), 424.8 ($[M+K]^+$). Anal. calc. for $C_{18}H_{27}NO_8$ (385.41): C 56.09, H 7.06, N 3.63; found: C 56.12, H 7.09, N 3.65.

*Diethyl (4*S*)-2-(β-*D*-Galactopyranosyl)-1,4-dihydro-6-methyl-4-phenylpyridine-3,5-dicarboxylate* ((*S*)-**11a′**). White foam. $[\alpha]_D = +4.9$ (*c* = 1.7, MeOH). ^{1}H-NMR (CD_3OD): 8.35 (br. *s*, NH); 7.40–7.00 (*m*, 5 arom. H); 5.35 (*d*, *J*(1′,2′) = 9.1, H–C(1′)); 5.05 (*s*, H–C(4)); 4.14–4.02 (*m*, 2 MeCH_2); 3.98 (*dd*, *J*(3′,4′) = 2.8, *J*(4′,5′) ≈ 0.5, H–C(4′)); 3.82 (*dd*, *J*(5′,6′a) = 6.5, *J*(6′a,6′b) = 11.5, H–C(6′a)); 3.74 (*dd*, *J*(5′,6′b) = 5.0, H–C(6′b)); 3.65 (*ddd*, H–C(5′)); 3.64 (*dd*, *J*(2′,3′) = 9.2, H–C(2′)); 3.55 (*dd*, H–C(3′)); 2.38 (*s*, Me); 1.21 (*t*, *J* = 7.0, *Me*CH_2); 1.20 (*t*, *J* = 7.0, *Me*CH_2). ^{13}C-NMR (CD_3OD): 170.1; 169.7; 148.9; 147.7; 144.1; 129.1; 129.0; 128.9; 128.8; 127.2; 108.1; 103.1; 81.2; 76.9; 76.4; 71.1; 71.0; 62.6; 61.3; 60.7; 41.6; 18.6; 14.6; 14.4. MALDI-TOF-MS: 478.1 ($[M+H]^+$), 500.7 ($[M+Na]^+$), 516.9 ($[M+K]^+$). Anal. calc. for $C_{24}H_{31}NO_9$ (477.50): C 60.37, H 6.54, N 2.93; found: C 60.33, H 6.50, N 2.91.

*Diethyl (4*S*)-1,4-Dihydro-2-(β-*D*-mannopyranosyl)-6-methyl-4-phenylpyridine-3,5-dicarboxylate* ((*S*)-**11b′**). White solid. M.p. 88–90° dec. (EtOAc/H_2O). $[\alpha]_D = +57.7$ (*c* = 1.0, MeOH). ^{1}H-NMR (CD_3OD): 7.40–7.10 (*m*, 5 arom. H); 5.33 (*d*, *J*(1′,2′) ≈ 0.5, H–C(1′)); 5.00 (*s*, H–C(4)); 4.18 (*dd*, *J*(2′,3′) = 3.0, H–C(2′)); 4.16–4.02 (*m*, 2 MeCH_2); 3.93 (*dd*, *J*(5′,6′a) = 2.8, *J*(6′a,6′b) = 11.8, H–C(6′a)); 3.89 (*dd*, *J*(5′,6′a) = 4.0, H–C(6′b)); 3.78 (*dd*, *J*(3′,4′) = 9.5, *J*(4′,5′) = 9.2, H–C(4′)); 3.61 (*dd*, H–C(3′)); 3.34 (*ddd*, H–C(5′)); 2.38 (*s*, Me); 1.23 (*t*, *J* = 7.0, OCH_2*Me*); 1.21 (*t*, *J* = 7.0, OCH_2*Me*). ^{13}C-NMR (CD_3OD): 169.6; 168.6; 149.0; 148.2; 146.9; 129.3; 129.2; 128.9; 128.8; 127.2; 104.2; 102.6; 82.1; 77.0; 75.9; 72.8; 67.7; 62.1; 61.0; 60.8; 40.7; 19.0; 14.6; 14.5. MALDI-TOF-MS: 477.5 (M^+), 500.7 ($[M+Na]^+$), 516.9 ($[M+K]^+$). Anal. calc. for $C_{24}H_{31}NO_9$ (477.50): C 60.37, H 6.54, N 2.93; found: C 60.33, H 6.50, N 2.91.

*Diethyl (4*R*)-1,4-Dihydro-2-(β-*D*-mannopyranosyl)-6-methyl-4-phenylpyridine-3,5-dicarboxylate* ((*R*)-**11b**′). Amorphous solid. $[\alpha]_D = +100.0$ ($c = 1.0$, MeOH). ^{1}H-NMR (CD_3OD): 7.40–7.10 (*m*, 5 arom. H); 5.41 (*d*, *J*(1′,2′) = 1.0, H–C(1′)); 5.03 (*s*, H–C(4)); 4.16–4.00 (*m*, 2 MeCH_2); 4.11 (*dd*, *J*(2′,3′) = 3.5, H–C(2′)); 3.92 (*dd*, *J*(5′,6′a) = 2.5, *J*(6′a,6′b) = 11.8, H–C(6′a)); 3.86 (*dd*, *J*(5′,6′a) = 4.5, H–C(6′b)); 3.76 (*dd*, *J*(3′,4′) = 9.5, *J*(4′,5′) = 9.2, H–C(4′)); 3.62 (*dd*, H–C(3′)); 3.34 (*ddd*, H–C(5′)); 2.34 (*s*, Me); 1.25 (*t*, *J* = 7.0, *Me*CH_2); 1.20 (*t*, *J* = 7.0, *Me*CH_2). ^{13}C-NMR (CD_3OD): 169.7; 168.7; 149.3; 147.8; 145.7; 129.3; 129.2; 128.9; 128.8; 127.2; 104.1; 102.2; 82.3; 76.3; 76.1; 73.4; 67.7; 62.2; 61.0; 60.8; 40.8; 19.0; 14.6; 14.5. MALDI-TOF-MS: 478.4 ($[M+H]^+$), 500.5 ($[M+Na]^+$), 516.7 ($[M+K]^+$). Anal. calc. for $C_{24}H_{31}NO_9$ (477.50): C 60.37, H 6.54, N 2.93; found: C 60.33, H 6.50, N 2.91.

*Diethyl (4*S*)-1,4-Dihydro-2-methyl-4-phenyl-6-(β-*D*-ribofuranosyl)pyridine-3,5-dicarboxylate* ((*S*)-**11c**′). White foam. $[\alpha]_D = +11.0$ ($c = 1.7$, MeOH). ^{1}H-NMR (CD_3OD): 9.10 (br. *s*, NH); 7.40–7.00 (*m*, 5 arom. H); 5.51 (*d*, *J*(1′,2′) = 1.0, H–C(1′)); 4.95 (*s*, H–C(4)); 4.22–3.90 (*m*, 2 MeCH_2, H–C(2′), H–C(3′), H–C(4′), H–C(5′a)); 3.84 (*dd*, *J*(4′,5′b) ≈ 0.5, *J*(5′a,5′b) = 11.0, H–C(5′b)); 2.30 (*s*, Me); 1.24 (*t*, *J* = 7.0, *Me*CH_2); 1.23 (*t*, *J* = 7.0, *Me*CH_2). ^{13}C-NMR (CD_3OD): 168.4; 167.6; 148.5; 148.0; 145.6; 128.1; 128.0; 127.8; 127.7; 126.1; 103.6; 101.5; 82.1; 82.0; 78.4; 69.4; 59.9; 59.7; 59.1; 39.7; 17.2; 13.5; 13.4. MALDI-TOF-MS: 470.8 ($[M+Na]^+$), 486.9 ($[M+K]^+$). Anal. calc. for $C_{23}H_{29}NO_8$ (447.48): C 61.73, H 6.53, N 3.13; found: C 61.70, H 6.51, N 3.12.

*Diethyl (4*R*)-1,4-Dihydro-2-methyl-4-phenyl-6-(β-*D*-ribofuranosyl)-pyridine-3,5-dicarboxylate* ((*R*)-**11c**′). White foam. $[\alpha]_D = +84.4$ ($c = 1.0$, MeOH). ^{1}H-NMR (CD_3OD): 9.08 (br. *s*, NH); 7.40–7.10 (*m*, 5 arom. H); 5.55 (*d*, *J*(1′,2′) = 1.0, H–C(1′)); 5.00 (*s*, H–C(4)); 4.28–3.90 (*m*, 2 MeCH_2, H–C(2′), H–C(3′), H–C(4′), H–C(5′a)); 3.85 (*dd*, *J*(4′,5′b) ≈ 0.5, *J*(5′a,5′b) = 11.2, H–C(5′b)); 2.32 (*s*, Me); 1.24 (*t*, *J* = 7.0, *Me*CH_2); 1.22 (*t*, *J* = 7.0, *Me*CH_2). ^{13}C-NMR (CD_3OD): 169.6; 168.8; 149.7; 149.6; 146.2; 129.3; 129.0; 128.9; 128.8; 127.3; 104.2; 102.7; 82.9; 82.4; 79.6; 70.5; 61.0; 60.8; 60.2; 41.1; 18.7; 14.6; 14.5. MALDI-TOF-MS: 470.4 ($[M+Na]^+$), 486.4 ($[M+K]^+$). Anal. calc. for $C_{23}H_{29}NO_8$ (447.48): C 61.73, H 6.53, N 3.13; found: C 61.75, H 6.57, N 3.15.

*Diethyl (4*S*)-4-[2-(trifluoromethyl)phenyl]-1,4-dihydro-2-methyl-6-(β-*D*-ribofuranosyl)pyridine-3,5-dicarboxylate* ((*S*)-**15**′). White foam. $[\alpha]_D = +3.7$ ($c = 0.9$, MeOH). ^{1}H-NMR (CD_3OD): 7.70–7.20 (*m*, 4 arom. H); 5.54 (br. *q*, *J*(4,CF_3) = 1.0, H–C(4)); 5.46 (*d*, *J*(1′,2′) = 1.5, H–C(1′)); 4.22–3.94 (*m*, 2 MeCH_2, H–C(2′), H–C(3′), H–C(4′), H–C(5′a)); 3.85 (*dd*, *J*(4′,5′b) ≈ 0.5, *J*(5′a,5′b) = 10.8, H–C(5′b)); 2.25 (*s*, Me); 1.18 (*t*, *J* = 7.0, *Me*CH_2); 1.15 (*t*, *J* = 7.0, OCH_2*Me*). ^{13}C-NMR (CD_3OD): 169.5; 168.5; 149.9; 148.7; 145.9; 133.4; 132.3; 132.2; 127.8; 127.3; 127.2; 105.8; 103.5; 83.3; 83.2; 79.5; 70.6; 60.9; 60.8; 60.3; 39.6; 18.2; 14.5; 14.4. MALDI-TOF-MS: 516.1 ($[M+H]^+$), 538.9 ($[M+Na]^+$), 554.9 ($[M+K]^+$). Anal. calc. for $C_{24}H_{28}F_3NO_8$ (515.48): C 55.92, H 5.47, F 11.06, N 2.72; found: C 55.90, H 5.44, F 11.08, N 2.71.

*Diethyl (4*R*)-4-[2-(Trifluoromethyl)phenyl]-1,4-dihydro-2-methyl-6-(β-*D*-ribofuranosyl)pyridine-3,5-dicarboxylate* ((*R*)-**15c**′). White foam. $[\alpha]_D = +25.8$ ($c = 1.0$, MeOH). ^{1}H-NMR (CD_3OD): 7.70–7.20 (*m*, 4 arom. H); 5.62 (br. *q*, *J*(4,CF_3) = 1.0, H–C(4)); 5.47 (*d*, *J*(1′,2′) ≈ 0.5, H–C(1′)); 4.32–3.90 (*m*, 2 MeCH_2, H–C(2′), H–C(3′), H–C(4′), H–C(5′a)); 3.87 (*dd*, *J*(4′,5′b) ≈ 0.5, *J*(5′a,5′b) = 11.5, H–C(5′b)); 2.29 (*s*, Me); 1.20 (*t*, *J* = 7.0, *Me*CH_2); 1.16 (*t*, *J* = 7.0, *Me*CH_2). ^{13}C-NMR (CD_3OD): 169.4; 168.7; 148.8; 148.7; 145.9; 133.3; 132.3; 129.0; 127.9; 127.8; 127.4; 105.0; 103.4; 83.0; 82.5; 79.4; 70.5; 61.0; 60.8; 60.2; 37.2; 18.6; 14.5; 14.4. MALDI-TOF-MS: 515.2 (M^+), 538.7 ($[M+Na]^+$), 554.3 ($[M+K]^+$). Anal. calc. for $C_{24}H_{28}F_3NO_8$ (515.48): C 55.92, H 5.47, F 11.06, N 2.72; found: C 55.94, H 5.47, F 11.08, N 2.75.

*Methyl 3-Amino-3-(2′,3′,5′-tri-*O*-benzyl-β-*D*-ribofuranosyl)propenoate* (**16**). A suspension of Zn dust (588 mg, 9.0 mmol) in anh. THF (8 ml) was heated under reflux, then a few drops of methyl bromoacetate were added. After a green color had appeared (*ca.* 15 min), a soln. of ribofuranosyl cyanide **12c** [18] (643 mg, 1.5 mmol) in anh. THF (2 ml) was added in one portion. The remaining bromoacetate (total amount: 0.57 ml, 6 mmol) was added dropwise over 40 min. The mixture was cooled to r.t. treated with $NaHCO_3$ soln. (10 ml), and filtered through a pad of *Celite*. The filtrate was extracted with Et_2O (3 × 75 ml), and the combined org. layers were dried (Na_2SO_4), concentrated, and subjected to CC (cyclohexane/AcOEt 6:1 containing 0.5% of Et_3N) to afford **16** (672 mg, 89%) as an oil. $[\alpha]_D = +11.2$ ($c = 2.4$, $CHCl_3$). ^{1}H-NMR ($CDCl_3/D_2O$): 7.45–7.15 (*m*, 15 arom. H); 4.71, 4.60 (2*d*, *J* = 12.0, PhCH_2); 4.58, 4.42 (2*d*, *J* = 11.5, PhCH_2); 4.54, 4.44 (2*d*, *J* = 11.2, PhCH_2); 4.55 (*d*, *J*(1′,2′) = 3.0, H–C(1′)); 4.53 (*s*, H–C(2)); 4.27 (*ddd*, *J*(3′,4′) = 7.0, *J*(4′,5′a) = 3.0, *J*(4′,5′b) = 2.5, H–C(4′)); 4.10 (*dd*, *J*(2′,3′) = 4.5, H–C(3′)); 3.97 (*dd*, H–C(2′)); 3.85 (*d*, *J*(5′a,5′b) = 10.8, H–C(5′a)); 3.67 (*s*, MeO); 3.59 (*dd*, H–C(5′b)). Anal. calc. for $C_{30}H_{33}NO_6$ (503.59): C 71.55, H 6.61, N 2.78; found: C 71.50, H 6.60, N 2.75.

*Methyl 3-Amino-3-(2′,3′,5′-tri-*O*-benzoyl-β-*D*-ribofuranosyl)propenoate* (**17**). 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl cyanide [17] (707 mg, 1.5 mmol) was treated as described for the preparation of **16**. CC (cyclohexane/Et_2O 1.5:1 containing 0.5% of Et_3N) afforded **17** (507 mg, 62%) as an oil. $[\alpha]_D = -70.5$ ($c = 1.1$, $CHCl_3$). ^{1}H-NMR ($CDCl_3/D_2O$): 8.20–7.90 (*m*, 6 arom. H); 7.70–7.30 (*m*, 9 arom. H); 5.68 (*dd*, *J* = 5.0, *J* = 5.1,

H–C(2′) or H–C(3′)); 5.59 (*dd*, *J* = 4.8, *J* = 5.0, H–C(2′) or H–C(3′)); 4.92 (*s*, H–C(2)); 4.86–4.67 (*m*, H–C(1′), H–C(4′), 2 H–C(5′)); 3.65 (*s*, OMe). Anal. calc. for $C_{30}H_{27}NO_9$ (545.54): C 66.05, H 4.99, N 2.57; found: C 66.08, H 4.91, N 2.53.

*Methyl 3-Amino-3-(β-*D*-ribofuranosyl)propenoate* (**18**). To a stirred soln. of **17** (500 mg, 0.92 mmol) in MeOH (4 ml) was added MeONa (0.5M in MeOH, 10 ml), and stirring was continued at r.t. for 12 h. The soln. was neutralized with AcOH and concentrated. The residue was diluted with 2-butanone (100 ml) and washed with sat. $NaHCO_3$ soln. (2 × 10 ml). The org. layer was dried (Na_2SO_4) and concentrated. The residue was diluted with MeOH (5 ml) and treated with aminomethylated polystyrene (368 mg, *ca.* 0.92 mmol) to remove methyl benzoate. The suspension was stirred for an additional 2 h, the resin was filtered off and washed thoroughly with MeOH. The combined filtrates were concentrated to yield **18** (148 mg, 69%) as a foam. An analytical sample was purified by CC (CH_2Cl_2/MeOH/NH_4OH (28%) 9:1:0.1). $[\alpha]_D = -86.9$ (*c* = 2.3, MeOH). ^{1}H-NMR (CD_3OD): 4.62 (*s*, H–C(2)); 4.20 (*d*, *J*(1′,2′) = 5.5, H–C(1′)); 4.07 (*dd*, *J*(2′,3′) = 5.0, *J*(3′,4′) = 4.5, H–C(3′)); 3.96 (*dd*, H–C(2′)); 3.93 (*ddd*, *J*(4′,5′a) = 3.5, *J*(4′,5′b) = 4.0, H–C(4′)); 3.82 (*dd*, *J*(5′a,5′b) = 10.8, H–C(5′a)); 3.70 (*dd*, H–C(5′b)); 3.62 (*s*, MeO). Anal. calc. for $C_9H_{15}NO_6$ (233.22): C 46.35, H 6.48, N 6.01; found: C 46.32, H 6.49, N 6.05.

*Dimethyl (4*R*)- and (4*S*)-6-(2′,3′,5′-Tri-*O*-benzyl-β-*D*-ribofuranosyl)-1,4-dihydro-2-methyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate* (**20**). A screw-capped vial, containing a magnetic bar, was charged with **19** (623 mg, 2.50 mmol), **16** (252 mg, 0.50 mmol), molecular sieves (200 mg), and anh. MeOH (4 ml). The mixture was vigorously stirred, degassed *in vacuo* and saturated with Ar (3×). The mixture was stirred at 90° for 48 h, cooled to r.t., filtered through a pad of *Celite*, and concentrated. The residue was diluted with CH_2Cl_2 (5 ml) and treated with aminomethylated polystyrene (1.0 g, *ca.* 2.50 mmol). The suspension was stirred for an additional 2 h. The resin was filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated and subjected to CC (cyclohexane/AcOEt 4:1) to afford **20** (235 mg, 64%) as a 1:1 mixture of diastereoisomers. ^{1}H-NMR (first diastereoisomer): 8.24 (br. *s*, NH); 7.80–7.10 (*m*, 19 arom. H); 5.77, 5.75 (2*s*, H–C(1′), H–C(4)); 4.96, 4.89 (2*d*, *J* = 11.8, PhCH_2); 4.64, 4.53 (2*d*, *J* = 12.0, PhCH_2); 4.52, 4.25 (2*d*, *J* = 11.5, PhCH_2); 4.31 (*ddd*, *J*(3′,4′) = 9.0, *J*(4′,5′a) = 2.5, *J*(4′,5′b) ≈ 0.5, H–C(4′)); 4.06–3.94 (*m*, H–C(2′), H–C(3′), H–C(5′a)); 3.66 (*dd*, *J*(5′a,5′b) = 10.8, H–C(5′b)); 3.64 (*s*, MeO); 3.61 (*s*, MeO); 2.07 (*s*, Me). ^{1}H-NMR (second diastereoisomer): 8.24 (br. *s*, NH); 7.80–7.10 (*m*, 19 arom. H); 5.82, 5.75 (2*s*, H–C(1′), H–C(4)); 4.96, 4.76 (2*d*, *J* = 11.8, PhCH_2); 4.64, 4.55 (2*d*, *J* = 12.0, PhCH_2); 4.55, 4.27 (2*d*, *J* = 11.5, PhCH_2); 4.35 (*ddd*, *J*(3′,4′) = 9.0, *J*(4′,5′a) = 2.0, *J*(4′,5′b) ≈ 0.5, H–C(4′)); 4.11 (*dd*, *J*(2′,3′) = 3.5, H–C(3′)); 4.08 (*dd*, *J*(5′a,5′b) = 10.8, H–C(5′a)); 3.90 (*d*, H–C(2′)); 3.69 (*dd*, H–C(5′b)); 3.66 (*s*, MeO); 3.60 (*s*, MeO); 1.93 (*s*, Me). Anal. calc. for $C_{42}H_{42}N_2O_{10}$ (734.79): C 68.65, H 5.76, N 3.81; found: C 68.63, H 5.71, N 3.84.

*Dimethyl (4*R*)- and (4*S*)-1,4-Dihydro-2-methyl-4-(2-nitrophenyl)-6-(β-*D*-ribofuranosyl)pyridine-3,5-dicarboxylate* (**21**). *Method I.* A screw-capped vial, containing a magnetic bar, was charged with **19** (1.25 g, 5.00 mmol), **18** (117 mg, 0.50 mmol), molecular sieves (200 mg), and anh. MeOH (4 ml). The mixture was vigorously stirred, degassed *in vacuo*, and saturated with Ar (3×). The mixture was stirred at 90° for 48 h, cooled to r.t., filtered through a pad of *Celite*, and concentrated. The residue was subjected to CC (AcOEt/MeOH 10:1) to afford **21** (123 mg, 53%) as a 1.2:1 mixture of diastereoisomers slightly contaminated by unknown byproducts. An analytical sample was purified by prep. TLC (CH_2Cl_2/MeOH/NH_4OH (28%) 9:1:0.1). ^{1}H-NMR (CD_3OD): 7.80–7.20 (*m*, 4 arom. H); 5.70 (*s*, H–C(4)(maj.)); 5.67 (*s*, H–C(4)(min.)); 5.52 (*d*, *J*(1′,2′) = 1.0, H–C(1′)(maj.)); 5.42 (*d*, *J*(1′,2′) = 1.0, H–C(1′)(min.)); 4.25 (*dd*, *J*(2′,3′) = 4.0, *J*(3′,4′) = 9.0, H–C(3′)(maj.)); 4.17 (*dd*, *J*(2′,3′) = 4.0, *J*(3′,4′) = 9.0, H–C(3′)(min.)); 4.08–3.95 (*m*, H–C(2′)(min.), H–C(4′)(maj.), H–C(4′)(min.), H–C(5′a)(maj.), H–C(5′a)(min.)); 3.92 (*dd*, H–C(2′)(maj.)); 3.86 (*dd*, *J*(4′,5′b) = 3.5, *J*(5′a,5′b) = 10.8, H–C(5′b)(maj.), H–C(5′b)(min.)); 3.60 (*s*, MeO(maj.)); 3.59 (*s*, MeO (min.)); 3.57 (*s*, MeO(maj.)); 3.56 (*s*, MeO(min.)); 2.31 (*s*, Me(maj.), Me(min.)). ^{13}C-NMR (CD_3OD) (selected data): 169.4; 168.7; 168.6; 168.4; 150.9; 150.0; 149.3; 149.1; 147.7; 147.3; 104.2; 103.5; 102.1; 101.9; 36.4; 35.7. MALDI-TOF-MS (without matrix): 471.2 ($[M + Li]^+$), 487.3 ($[M + Na]^+$). Anal. calc. for $C_{21}H_{24}N_2O_{10}$ (464.42): C 54.31, H 5.21, N 6.03; found: C 54.33, H 5.22, N 6.07.

Method J. A screw-capped vial, containing a magnetic bar, was charged with **19** (623 mg, 2.50 mmol), **17** (273 mg, 0.50 mmol), molecular sieves (200 mg), and anh. MeOH (4 ml). The mixture was vigorously stirred, degassed *in vacuo*, and saturated with Ar (3×). The mixture was stirred at 90° for 48 h, cooled to r.t., filtered through a pad of *Celite*, and concentrated. The residue was diluted with CH_2Cl_2 (5 ml) and treated with aminomethylated polystyrene (1.0 g, *ca.* 2.50 mmol). The suspension was stirred for an additional 2 h. The resin was filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated and diluted with a 0.1M soln. of MeONa in MeOH (10 ml). The soln. was stirred at r.t. for 12 h. Once neutralized with AcOH, a minimal amount of SiO_2 was added, and the solvent was evaporated. The compound (absorbed on SiO_2) was

subjected to CC (AcOEt/cyclohexane 4:1–4:0) to afford *dimethyl 1,4-dihydro-2-[5-(hydroxymethyl)furan-2-yl]-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate* (**22**) (70 mg, 30%) as a racemic mixture. $[\alpha]_D = 0.0$ ($c = 1.5$, $CHCl_3$); $[\alpha]_D = 0.0$ ($c = 1.2$, MeOH). ^{1}H-NMR: 7.80–7.20 (*m*, 4 arom. H); 7.00, 6.43 (2*d*, $J = 3.5$, H–C(3′), H–C(4′)); 6.50 (br. *s*, NH); 5.88 (*s*, H–C(4)); 4.68 (*s*, CH_2OH); 3.67 (*s*, MeO); 3.62 (*s*, MeO); 2.43 (*s*, Me). Anal. calc. for $C_{21}H_{20}N_2O_8$ (428.39): C 58.88, H 4.71, N 6.54; found: C 58.86, H 4.73, N 6.51. Eluted second was **21** (70 mg, 30%) as a 1.2:1 mixture of diastereoisomers.

Method K. To a stirred soln. of **20** (213 mg, 0.29 mmol of a 1:1 mixture of diastereoisomers) in anh. CH_2Cl_2 was dropwise added at $-70°$ BCl_3 (1.0M soln. in CH_2Cl_2, 2.64 ml, 2.64 mmol), and stirring was continued at that temp. for 10 min. The soln. was warmed to 0° and stirred for 1.5 h. The excess of BCl_3 was quenched at $-70°$ with MeOH/CH_2Cl_2 1:1 (5 ml). The soln. was warmed to 5°, adjusted to pH 5 with cold 3N aq. NaOH soln., and concentrated. The residue was diluted with AcOEt (100 ml) and washed with H_2O (2 × 10 ml). The org. layer was dried (Na_2SO_4), concentrated, and subjected to CC (AcOEt/MeOH 10:1) to yield **21** (23 mg, 17%) as a 1:1 mixture of diastereoisomers.

X-Ray Crystal-Structure Analysis of (S)-**11b′**. $2\,(C_{24}H_{31}NO_9)\cdot C_4H_8O_2\cdot 6\,H_2O$; $M_r = 1151.20$; colorless crystal (0.08 × 0.28 × 0.40 mm); monoclinic; space group $P2_1$ (no. 4); $a = 8.5036(1)$, $b = 37.4870(5)$, $c = 9.1210(2)$ Å; $\beta = 102.789(1)°$; $V = 2835.41(8)$ Å^3; $Z = 2$, $D_c = 1.348\ g\cdot cm^{-3}$; 13410 reflections measured, 5970 independent; $R_{int} = 0.038$, range: $2.17 < \theta < 27.45°$; $T = 150$ K; MoK_α radiation ($\lambda = 0.71073$ Å) on a *Nonius Kappa CCD* diffractometer. The structure was solved by direct methods (SIR92) [22] and refined on F^2 (SHELXL-97) [23]. The asymmetric unit contains two independent molecules of compound (*S*)-**11b′** (which differ in the conformation of OH groups), one molecule of AcOEt, and six molecules of H_2O. The refinement converged at a final wR_2 value of 0.1034 (all reflections), $R_1 = 0.0451$ (for 4545 reflections with $I > 2\sigma(I)$), $s = 1.049$. All non-H-atoms were refined anisotropically, the NH and OH H-atoms were refined isotropically; all other H-atoms were included on calculated positions, riding on their carrier atoms. A final difference *Fourier* transformation showed no residual density outside -0.24 and 0.36 Å^{-3}. An ORTEP [24] view of the molecule is shown in *Fig. 1*. Crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* (*cf. Footnote 3*).

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