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Glycosylation-Induced and Lewis Acid-Catalyzed Asymmetric Synthesis of β-*N*-Glycosidically Linked α-Aminophosphonic Acids Derivatives

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Abstract: The diastereospecific formation of β-*N*-glycosidically linked α-aminophosphonic acids derivatives has been achieved with high yield *via* a Mannich-type reaction. The reaction was performed by using *O*-pivaloylated galactosylamine **1** as a chiral template and boron trifluoride diethyl etherate as a catalyst in THF. Imines **3** of aromatic compounds and diethyl phosphite were converted to *N*-galactosyl α-aminoalkylphosphonate **4**, giving ratios of diastereomers higher than 19:1. This procedure provides a rapid access to biologically important galactosyl α-aminophosphonic acids derivatives.

Keywords: α-aminophosphonic acids; asymmetric synthesis; carbohydrate auxiliaries; Lewis acid catalysis; Mannich-type reaction

Introduction

α-Aminophosphonic and -phosphinic acids are the phosphorus analogues of α-aminocarboxylic acids, and therefore have biological importance both in themselves and as building blocks for peptides.[1] Phosphonopeptides are a class of unnatural peptides, which act as antagonists and compete with their carboxylic counterparts for the active sites of enzymes and other cell receptors.[1,2] Several phosphonopeptides show antibiotic effects, others have been recognized as herbicides. On the basis of these biological effects a number of asymmetric syntheses of α-aminophosphonic acids derivatives have been developed during the past two decades.[3] Carbohydrates are valuable as enantiomerically pure starting materials in chiral pool syntheses of many chiral natural products and drugs.[4] The polyfunctionality of carbohydrates is useful for binding or coordinating a substrate.[5] Carbohydrate derivatives are efficient auxiliaries for stereodifferentiation in many stereoselective chiral syntheses.[5,6] Synthetic *N*- and *O*-linked glycoaminophosphonic acid derivatives are analogous to those found in naturally occurring carbohydrates linked glycosidically to the α-amino acid of a peptide or a protein (Figure 1).[7] The sugar moieties of glycopeptides define their biological activity, and thus the potential of carbohydrates for the development of new drugs is being explored. Linking peptides to carbohydrates can improve the activity and selectivity of various effects.[8,9]

The configuration at the α-carbon atom in the α-aminophosphinic acid derivatives plays a decisive role in the biological properties of these types of compound,[10] as it does similarly in α-aminocarboxylic and -phosphonic acids.[11] Typical examples for the preparation of optically active α-aminophosphonic

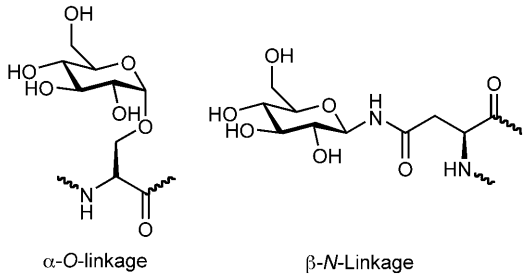


Figure 1. α-*O*-Glycosidic and β-*N*-glycosidic linkages between carbohydrate and peptides

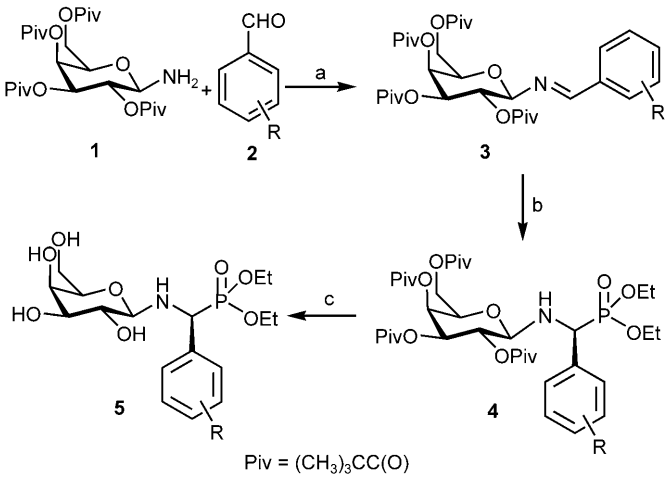
acids derivatives include the addition of a dialkyl phosphite or its lithium salt to an imine bearing a chiral auxiliary with or without Lewis acid catalysis, respectively.[12] However, studies on the synthesis and configuration of β-*N*-linked glycoaminophosphonic derivatives, which are formal α-aminophosphonic acids derivatives, are rare.[12d] Herein, we present an asymmetric and efficient synthesis of α-aminophosphonates in which *O*-pivaloylated galactosylamine serves as the stereodifferentiating auxiliary and $BF_3{\cdot}Et_2O$ as the catalyst.

Results and Discussion

The Mannich-type reaction is one of the important methods of synthesis of α-aminoalkylphosphonic acids and derivatives.[3] Chiral auxiliaries proved to be good to excellent in inducing asymmetry on the imine carbon atom resulting in enantiopure α-aminophosphinates. Lewis acid catalysts are required for induction of the enantioselectivity in the phosphorylation reaction.[13] One very versatile carbohydrate of the chiral tool is the pivalyl-protected D-galactosylaldimine **3** introduced by Kunz and co-workers.[14] This chiral auxiliary has already been used in diastereoselective Strecker,[15] Ugi,[16] Mannich,[17] and tandem Mannich–Michael reactions.[18]

The synthesis of β-*N*-glycosidically linked α-aminophosphonates started with the condensation of aryl aldehyde **2** and 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **1**. The formation of the corresponding *N*-galactosylaldimines **3**[14b] proceeded smoothly at room temperature under dehydrating conditions. Higher temperatures and longer reaction times led preferentially to the formation of the undesired conjugated enamines. In a Lewis acid-catalyzed Mannich-type reaction the aldimines **3** were reacted with diethyl phosphite to form *N*-galactosyl α-aminoalkylphosphonate **4** (Scheme 1). Removal of the protecting groups proved initially troublesome due to the high stability of the pivalate group under basic conditions. The preferred conditions that were found involved use of a freshly prepared solution of sodium methoxide in a mixture of methanol and THF. Under these conditions, the amount of deglycosylation was minimized, and no loss of anomeric purity was observed.[19]

Under these conditions, the Schiff bases **3** of aromatic aldehydes are obtained in crystalline form. The amount of the corresponding α-anomer can be restricted to less than 4%, and imines **3** of aliphatic aldehydes cannot be isolated in crystalline form by this method. Furthermore, aliphatic imines undergo anomerization at temperatures above −10 °C. Being of relatively low reactivity, the aldimines **3** do not react with diethyl phosphite at low temperature. Also

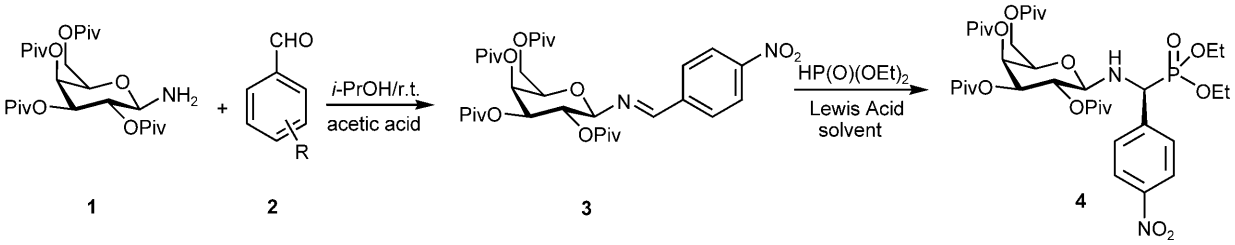


Scheme 1. *Reagents and conditions:* (a) *i*-PrOH, 2–3 drops of acetic acid, room temperature, 0.5 h; (b) 1.5 equiv. $HP(O)(OEt)_2$, 2 equiv. $BF_3{\cdot}Et_2O$, THF, room temperature, 2.5–4 h; (c) 0.5 M NaOMe/MeOH, room temperature, 2 d, 001 × 7(732), H^+.

in the presence of CuBr or CuI in THF, the reaction does not occur (Table 1 entries 1–3). When zinc chloride in THF was used, the Mannich-type reaction of the imines **3** with diethyl phosphite proceed at +4 °C to room temperature to give the *N*-galactosyl-α-aminoalkylphosphonate **4** as a mixture of four diastereomers in low yield. The results summarized in Table 1 show that besides the two β-configurated diastereomers **4**, the two α-configurated diastereomers **4** were obtained at the same time.

The reaction of the *N*-galactosylaldimines **3** with diethyl phosphite required activation by Lewis acids. Compared with $SnCl_4$ and $AlCl_3$, the best result was obtained when $BF_3{\cdot}Et_2O$ in THF at room temperature was used (Table 1). When equimolar or higher than equimolar amounts of $BF_3{\cdot}Et_2O$ were used at room temperature, the reactions were finished within four hours with very high yields (Table 1, entries 6–8). The ratios of diastereomers ranged between 9:1 and 19:1 with preponderance of the β*S*-configurated diastereomer **4**. The pure diastereomers were isolated in high yields by simple crystallization of the crude products **4** from *n*-hexane and diethyl ether. As a rule, the reaction catalyzed by $BF_3{\cdot}Et_2O$ showed the higher stereoselectivity. The crude products **4** only contained a few percent of the corresponding α-anomeric isomers presumably produced by a Lewis acid-catalyzed anomerization of the β-anomeric isomers. The ratio of diastereomers **4** was determined by ^{31}P NMR analysis. Among other Lewis acids tested, CuBr and CuI both applied in THF at room temperature, cannot catalyze this reaction (Table 1, entries 2 and 3). And also the reaction cannot work if $CHCl_3$ or toluene is used as slovent (Table 1, entries 16 and 17).

Table 1. Survey of the conditions for the formation of **4a** according to Scheme 1.[a]



Entry	Lewis acid (equi.v)	Solvent	Reaction time	Yields [%][b]	Ratio of αS:βR:βS:αR diastereomers of **4**	*de* [%][d]
1	–	THF	3 days	n.r.[c]	–	–
2	CuBr (1)	THF	3 days	n.r.	–	–
3	CuI (1)	THF	3 days	trace	–	–
4	$ZnCl_2$ (1)	THF	3.5 days	7	25.0:11.1:63.3:0.6	77
5	$BF_3{\cdot}Et_2O$ (0.5)	THF	4 h	60	10.7:9.3:80.0:0	81
6	$BF_3{\cdot}Et_2O$ (1)	THF	4 h	95	10.4:5.7:83.9:0	89
7	$BF_3{\cdot}Et_2O$ (1.5)	THF	4 h	>99	9.8:5.8:84.4:0	88
8	$BF_3{\cdot}Et_2O$ (2)	THF	4 h	>99	9.6:5.2:85.2:0	90
9	$BF_3{\cdot}Et_2O$ (2.5)	THF	4 h	87	9.0:6.9:84.1:0	86
10	$SnCl_2{\cdot}2\ H_2O$ (1)	THF	3 ays	85	9.8:6.8:83.4:0	86
11	$AlCl_3$ (1)	THF	2.5 days	75	7.3:9.7:83.0:0	81
12	$AlCl_3$ (0.5)	THF	3 days	31	7.2:27.0:65.8:0	46
13	$SnCl_4$ (0.5)	THF	3 days	82	12.3:5.4:82.3:0	89
14	$SnCl_4$ (1)	THF	3 days	78	9.2:2.7:88.1:0	94
15	$SnCl_4$ (1.5)	THF	3 days	80	11.4:4.3:84.3:0	91
16	$BF_3{\cdot}Et_2O$ (2)	$CHCl_3$	1 day	n.r.	–	–
17	$BF_3{\cdot}Et_2O$ (2)	$PhCH_3$	1 day	n.r.	–	–

[a] Unless otherwise noted all the reactions were performed with 0.5 mmol of **3**, 0.75 mmol diethyl phosphite in 5 mL solvent at room temperature.
[b] Determined from the crude product by ^{31}P NMR.
[c] No reaction.
[d] Ref.[20]

To further demonstrate the scope and flexibility of the present optimized conditions, a wide range of different aldehydes were then successfully examined with this methodology (Table 2). As expected, a number of *N*-galactosyl-α-aminoalkylphosphonates **4a–h** were prepared in a Mannich-type reaction. The reaction was conducted in THF at room temperature under mild conditions, in the presence of 2.0 equiv. of $BF_3{\cdot}Et_2O$, and the products **4** were obtained in high yields. Based on these experiments, it was found that the rates of the reaction of the electron-poor aromatic aldehydes were a little bit higher than those of the electron-rich aromatic aldehydes.

After flash chromatography (petroleum ether:ethyl acetate, 2:1) *N*-galactosyl α-aminoalkylphosphonates **4a–h** were isolated in high yields and high stereoselectivity. The diastereomeric ratio of **4** was determined by ^{31}P NMR from the crude mixture of the reaction. It should be noted that because of the anomeric carbon and one stereogenic center created at the α position of the phosphonate, the four anomeric diastereomers have the β*S*, β*R*, α*R* and α*S* configurations. Diastereomerically pure compounds **4a–h** were obtained by simple recrystallization from *n*-hexane and diethyl ether. In order to determine the absolute configuration of the main isomer of the diethyl phosphite addition to *N*-galactosylaldimines **3**, a single crystal

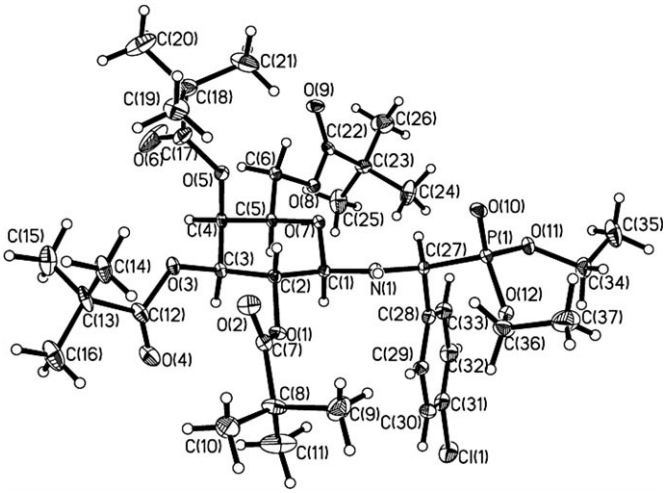
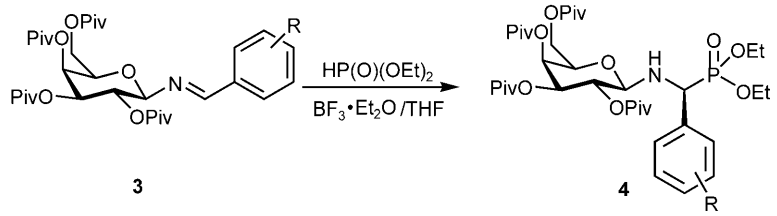


Figure 2. ORTEP presentation of the crystal structure of **4e**, with 20% probability displacement ellipsoids.

Table 2. The Mannich-type reaction of *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-galactosyl)aldimines **4a–h** at room temperature.



Entry	Product	R	Time [h]	Yield [%][a]	Ratio of αS:βR:βS:αR diastereomers[b]	*de* [%][c]
1	**4a**	*p*-NO_2	4	88	9.6:5.1:85.2:0	88
2	**4b**	*p*-Br	3	85	8.2:4.0:85.8:2.0	88
3	**4c**	*p*-F	2.5	82	8.4:4.4:84.5:2.7	86
4	**4d**	*o*-Br	3.5	90	10.3:12.0:70.7:7.0	62
5	**4e**	*p*-Cl	3	82	8.2:3.8:84.8:3.2	86
6	**4f**	*p*-CH_3	3.5	85	8.0:5.2:83.8:3.0	84
7	**4g**	*p*-OCH_3	3	80	7.0:8.1:81.4:3.5	77
8	**4h**	H	2.5	87	4.3:4.7:85.7:5.3	80

[a] After purification by chromatography and recrystallization.
[b] Diastereomeric ratio determined from the crude product by ^{31}P NMR.
[c] Ref.[20]

X-ray diffraction study of **4e** was performed.[21] The molecular structure of **4e** is shown in Figure 2, and the structure shows that the absolute configuration of α-aminoalkyl phosphonate main product can be assigned as *S*.

The possible mechanism for the reactions is shown in Figure 3. The preferred formation of the *S*-configured diastereomer of **4** can be rationalized by an attack of diethyl phosphite from the *si* side of *N*-galactosylaldimines **3**. In the transition state (Figure 3), the boron atom has tetracoordination of which the sites are occupied by the imine nitrogen and carbonyl oxygen (C-2) of the pivaloyloxy group respectively, and one of the three fluorines maybe removed when diethyl phosphite was introduced. According to this retionalization, the S_N2'-type attack of diethyl phosphite from the back side of the imine is initiated. Based on these results, the OH moiety of the diethyl phosphite is suggested to play an important role in determining the high enantioselectivity, since the required tautomeric equilibrium between the P(V) phosphinic and the P(III) phosphonous forms is still available. The mechanism indicates that the Piv4Gala group plays a significant role in controling the regio- and diastereoselective addition of diethyl phosphite to *N*-galactosylaldimines **3.**

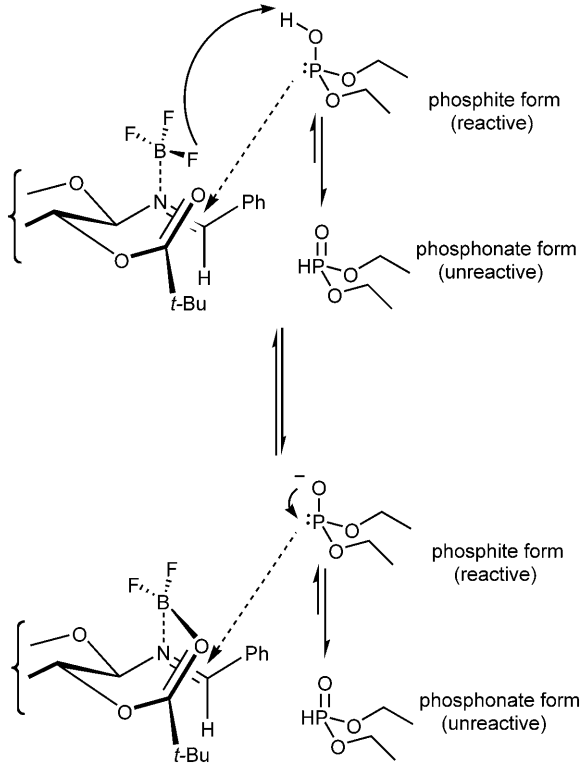


Figure 3. Plausible reaction mechanism.

Conclusions

We have found a procedure in which a highly diastereoselective addition of diethyl phosphite occurs onto the *N*-galactosylaldimines **3** to give *N*-galactosyl α-aminoalkylphosphonate **4** in high yields and high diastereoselectivity. *O*-Pivaloylated galactosylamine is an effective chiral template in this Mannich-type reaction. Boron trifluoride can form a tetra-coordination intermediate that induces the *S* configuration at the Cα center by attack at the *si* side of the C=N plane of the imine carbon atom. The deprotection of *N*-galactosyl α-aminoalkylphosphonate **4** under mild condi-

tions yields the corresponding β-*N*-glycosidically linked α-aminophosphonic acid derivatives **5**.

Experimental Section

General Comments

The spectroscopic data of all compounds are given in the Supporting Information.

General Procedure for the Synthesis of *N*-(2,3,4,6-Tetra-*O*-pivaloyl-D-galactosyl)-aldimines 3

To a solution of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **1** (0.515 g, 1 mmol) and aldehyde **2** (1.3 mmol) in 2-propanol (2.5 mL), 2–3 drops of acetic acid were added and the mixture was stirred at room temperature for about 0.5 h. The appearance of a precipitate from the solution indicated the formation of **3**, after the precipitate was filtered off, then washed with ice cold 2-propanol and dried under vacuum, *N*-galactosylaldimine **3** was isolated as a colorless solid.

General Procedure for the Synthesis of β-*N*-Glycosidically Linked α-Aminophosphonic Acid Derivatives 4

A solution of *N*-galactosylaldimine **3** (0.5 mmol) in THF (5 mL) was cooled to 0 °C, and diethyl phosphite (0.104 g, 0.75 mmol) and $BF_3{\cdot}Et_2O$ (0.142 g, 1.0 mmol) were added. The mixture was stirred for 4 h at room temperature. Then an aqueous saturated solution of sodium bicarbonate (25 mL) was added, and the mixture was stirred at room temperature for 5 min. The aqueous phase was extracted with CH_2Cl_2 (3×25 mL), and the organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum to yield the crude products **4**, which were purified by flash column chromatography on silica gel [petroleum ether/ethyl acetate, 2:1(v/v)] to provide pure products **4**.

General Procedure for the Synthesis of Compound 5

A solution of compound **4** (1.6 mmol) in dry methanol (25 mL) was treated with a freshly prepared (0.5 M) solution of sodium methoxide (5 mL), which was prepared from sodium and dry methanol. The solution was stirred for 3 days (TLC control). The mixture was neutralized with an ion-exchange resin [$001 \times 7(732)$, H^+], filtered and the solution was concentrated under vacuum, and the residue was purified by flash chromatography [EtOAc/MeOH, 10/1 (v/v)] to give **5** as a white solid.

Acknowledgements

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[21] CCDC 684637 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

