

## Synthesis of Terphenylboronic Acid Derivatives and Recognition of Anomers of 2-Deoxyribofuranoside

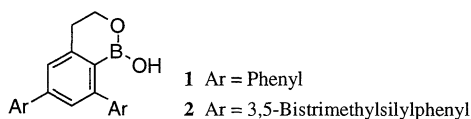
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A terphenylboronic acid **1** and its silylated derivative **2** are prepared from (2-nitrophenyl)acetic acid for the purpose of controlling stereochemistry of synthetic organic reactions. These boronic acids are found to recognize  $\alpha$  and  $\beta$ -anomers of 2-deoxyribofuranosides. That is, when these boron compounds are added to a 1 : 1 mixture of  $\alpha$  and  $\beta$ -*t*-butyl 5-*O*-benzyl-2-deoxy-D-ribofuranosides, the boronic acids **1** and **2** form the corresponding boronates preferentially with the  $\beta$ -anomer.

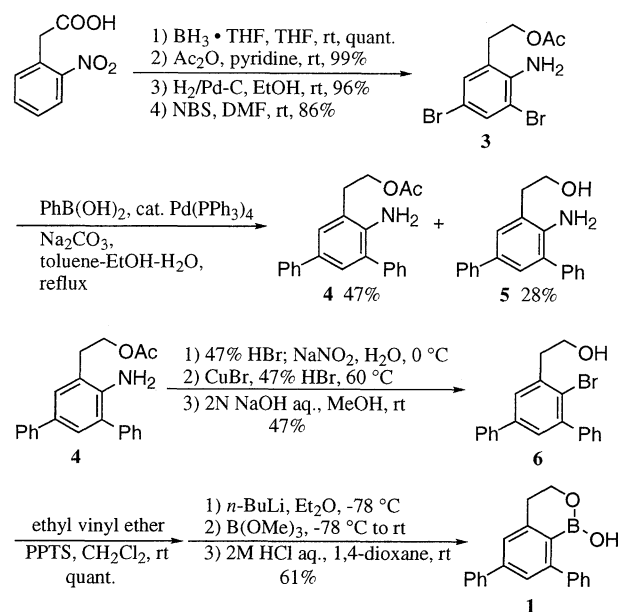
Hydroxyboranes smoothly react with alcohols at ambient temperature, yielding the corresponding boronic esters reversibly.<sup>1</sup> We have applied this characteristic feature of boronic acids to control the efficiency and the selectivity of some reactions.<sup>2</sup> To use boronic acids for stereocontrol of organic reactions of hydroxyl compounds, we designed terphenylboronic acids such as 1-hydroxy-6,8-diphenyl-1,2,3,4-tetrahydro-2-oxa-1-boranaphthalene (**1**) and its tetrakis(trimethyl silyl) derivative **2**. In this report are described the preparation of these boronic compounds and their application to the recognition of anomers of 2-deoxy-D-erythro-pentofuranoside (2-deoxyribofuranoside) derivatives.



The terphenylboronic acid **1** was synthesized as shown in Scheme 1. (2-Nitrophenyl)acetic acid was reduced and acetylated to give a nitro ester. After hydrogenation of the nitro group, the resulting aniline derivative was brominated with *N*-bromosuccinimide in DMF<sup>3</sup> to give a 2,4-dibromoaniline derivative **3**. Terphenyl structure was constructed by treatment of the dibromide **3** with phenylboronic acid under the Suzuki coupling conditions,<sup>4</sup> giving a terphenyl derivative **4** with a deacetylated product **5**, which was converted to the acetate **4** with acetic anhydride in pyridine. Sandmeyer reaction of **4**<sup>5</sup> afforded a bromide **6** after removal of the acetyl group. The hydroxyl group of **6** was protected as its 1-ethoxyethyl ether.<sup>6</sup> Then, a boron functionality was introduced by successive treatment with butyllithium at -78 °C, trimethoxyborane,<sup>7</sup> and 2M HCl, to give the terphenylboronic acid **1**.

For the synthesis of the tetrakis-silyl derivative **2**, bis(trimethylsilyl)phenylboronic acid was employed for the Suzuki coupling with the dibromide **4**. By following the same route in the synthesis of **1**, the tetrakis(trimethylsilyl)terphenyl derivative **2** was obtained in a 14% total yield from the silylated phenylboronic acid.

Next, the ability of these boronic acids **1** and **2** for stereochemical recognition was examined by the formation of their boronates with  $\alpha$  and  $\beta$ -anomers of 2-deoxyribofuranosides **7** and **8**.<sup>8</sup> It is known that there is no generally applicable method



Scheme 1.

to obtain  $\beta$ -isomers of 2-deoxyribofuranosides stereoselectively as there is no 2- $\alpha$ -hydroxyl group for the neighboring group participation.<sup>9</sup> Furthermore, the separation of  $\alpha$  and  $\beta$ -anomers of 2-deoxyribofuranoside derivatives is a difficult problem, which was performed by high-performance liquid chromatography (HPLC).<sup>10</sup> We supposed that terphenylboronic acids synthesized as above would enable the separation of anomers of 2-deoxyribofuranosides and  $\beta$ -selective glycosylation by forming the boronates with 3-hydroxyl group.

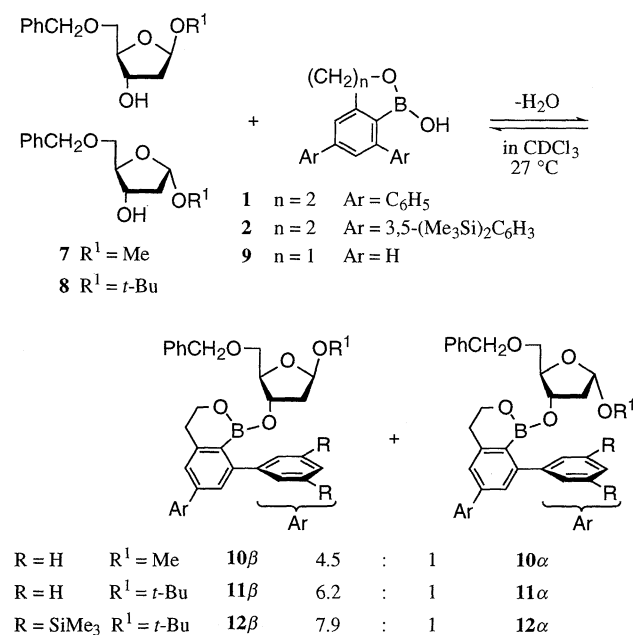
It was supposed that in the boronic esters between **1** and 3-hydroxyl group of 2-deoxyribofuranosides, 8-phenyl group of the terphenyl moiety would cover the  $\alpha$ -face of the furanoside ring as depicted in scheme 2. Accordingly, the boronic acid **1** and **2** would form the boronates with the  $\beta$ -anomers in preference to the  $\alpha$ -anomers.

At first, the generation of boronates between **1** and each anomer of *t*-butyl 5-*O*-benzyl-2-deoxyribofuranoside (**8**) was studied. The boronic acid **1** was added to an equimolar amount of  $\beta$ -*t*-butyl 5-*O*-benzyl-2-deoxyribofuranoside (**8** $\beta$ ) in CDCl<sub>3</sub> at room temperature in the presence of Molecular Sieves 4A. By the <sup>1</sup>H-NMR spectrum at 300 K, complete formation of the boronate **11** $\beta$  was observed. The anomeric  $\alpha$ -proton shifted to higher field and the shift value,  $\Delta\delta = \delta$  (boronate) -  $\delta$  (free anomer), was -0.46 ppm. This highfield shift indicates that the 8-phenyl group covers the  $\alpha$ -face of the furanoside ring as expected. By the same esterification study with the bis-silyl boronic acid **2**, the anomeric proton of **12** $\beta$  also appeared at higher field ( $\Delta\delta = -0.48$ ). By contrast, in boronic esters **11** $\alpha$

and  $12\alpha$  of  $\alpha$ -anomer of the *t*-butyl furanoside ( $8\alpha$ ), the  $\beta$ -anomeric protons of  $11\alpha$  and  $12\alpha$  exhibited smaller highfield shifts,  $\Delta\delta = -0.25$  and  $-0.24$  respectively, than those of the  $\beta$ -anomers.

The recognition of the anomers of 2-deoxyribofuranoside was then studied. A half molar amount of the boronic acid **1** and **2** was added to a 1 : 1 mixture of  $\alpha$  and  $\beta$ -*t*-butyl 5-*O*-benzyl-2-deoxyribofuranosides (**8**) in  $\text{CDCl}_3$  at room temperature in the presence of Molecular Sieves 4A. The esterification was monitored by observing  $^1\text{H-NMR}$  spectra at 300 K.

After one day, the boronic acid **1** was completely consumed for the boronate formation with the 2-deoxyribofuranosides **8**. The ratio of the boronates with the  $\beta$  :  $\alpha$ -anomers was estimated as 6.2 : 1 ( $11\beta$  :  $11\alpha$ ) and this ratio was constant one day later and after a week.



Scheme 2.

The alkoxy-exchange of the boronic ester  $11\beta$  consisting of **1** and the  $\beta$ -anomer  $8\beta$  was also examined by addition of the  $\alpha$ -anomer  $8\alpha$ . To the  $\text{CDCl}_3$  solution of  $11\beta$ , an equimolar amount of  $\alpha$ -*t*-butyl 5-*O*-benzyl-2-deoxyribofuranoside ( $8\alpha$ ) was added. After one day, the boronate of the  $\alpha$ -anomer was observed along with the generation of the free  $\beta$ -anomer by  $^1\text{H-NMR}$  spectrum at 300 K. The ratio of the boronates  $11\beta$  and  $11\alpha$  was 5.1 : 1.

The esterification of the silylated terphenylboronic acid **2** was also examined with a 1 : 1 mixture of  $\alpha$ - and  $\beta$ -*t*-butyl 5-*O*-benzyl-2-deoxyribofuranoside (**8**). The boron esters were formed more preferentially with the  $\beta$ -anomers ( $12\beta$  :  $12\alpha = 7.9$  : 1) as compared with the ester formation by the non-silylated boronic acid **1**.

The important role of the phenyl substituents on the recognition of the  $\alpha$  and  $\beta$ -anomers was shown in the following experiments. In the case of esterification of the boronic acid **1**

with methyl 5-*O*-benzyl-2-deoxyribofuranosides (**7**), the ratio of  $10\beta$  :  $10\alpha$  was 4.5 : 1. As a reference experiment, the esterification of 1-hydroxy-2-oxa-1-borindane (**9**), which has no phenyl substituent, was examined with methyl 5-*O*-benzyl-2-deoxyribofuranoside (**7**) in a similar manner. The boron esters was formed with  $7\beta$  and  $7\alpha$  in the ratio of 3.0 : 1. These results indicate that phenyl substituents in the terphenyl boronic acids **1** and **2** considerably influence the recognition of  $\alpha$  and  $\beta$ -anomers by forming the boron ester with 3-hydroxy group.

Thus, the boronic acids **1** and **2** can be utilized in the stereochemical recognition of alcohols such as ribofuranosides, even though the boryl group is attached to the remote hydroxyl group.

## References and Notes

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