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

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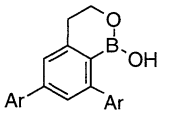
A terphenylboronic acid **1** and its silylated derivative **2** are prepared from (2-nitrophenyl)acetic acid for the purpose of controlling stereochemistry of synthetic organic reactions. These boronic acids are found to recognize α and β-anomers of 2-deoxyribofuranosides. That is, when these boron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

Hydroxyboranes smoothly react with alcohols at ambient temperature, yielding the corresponding boronic esters reversibly.[1] We have applied this characteristic feature of boronic acids to control the efficiency and the selectivity of some reactions.[2] 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-tetra- hydro-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-deoxy-ribofuranoside) derivatives.

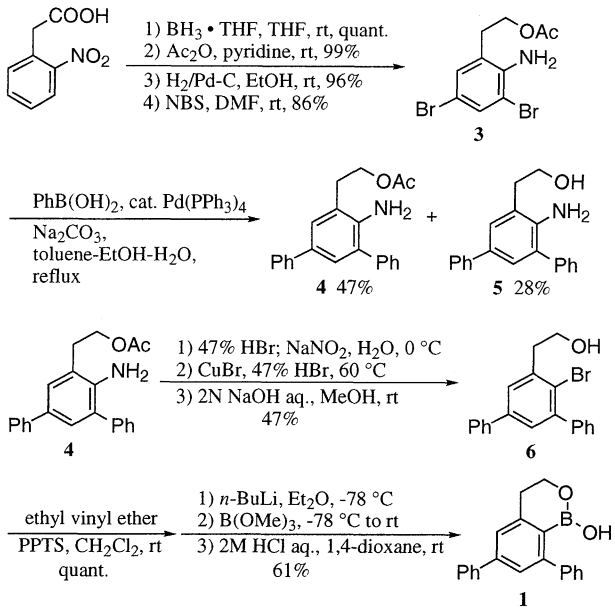


1 Ar = Phenyl
2 Ar = 3,5-Bistrimethylsilylphenyl

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[3] 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,[4] 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**[5] afforded a bromide **6** after removal of the acetyl group. The hydroxyl group of **6** was protected as its 1-ethoxyethyl ether.[6] Then, a boron functionality was introduced by successive treatment with butyllithium at -78 °C, trimethoxyborane,[7] 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 α and β-anomers of 2-deoxyribofuranosides **7** and **8**.[8] It is known that there is no generally applicable method



Scheme 1.

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

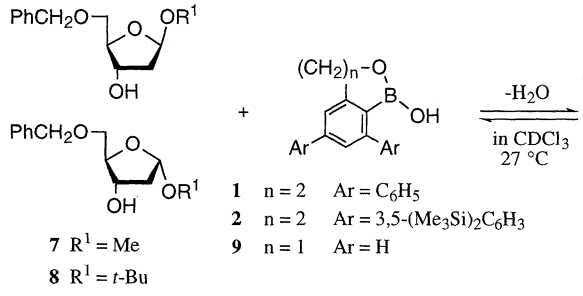
It was supposed that in the boronic esters between **1** and 3-hydroxyl group of 2-deoxyribofuranosides, 8-phenyl group of the terphenyl moiety would cover the α-face of the furanoside ring as depicted in scheme 2. Accordingly, the boronic acid **1** and **2** would form the boronates with the β-anomers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

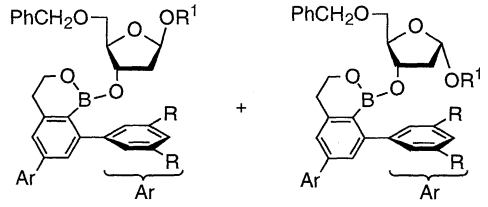
At first, the generation of boronates between **1** and each anomer of *t*-butyl 5-*O*-benzyl-2-deoxyribofuranoside (**8**) was studied. The boronic acid **1** was added to an equimolar amount of β-*t*-butyl 5-*O*-benzyl-2-deoxyribofuranoside (**8**β) in $CDCl_3$ at room temperature in the presence of Molecular Sieves 4A. By the ^{1}H-NMR spectrum at 300 K, complete formation of the boronate **11**β was observed. The anomeric α-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 α-face of the furanoside ring as expected. By the same esterification study with the bis-silyl boronic acid **2**, the anomeric proton of **12**β also appeared at higher field ($\Delta\delta$ = -0.48). By contrast, in boronic esters **11**α

and **12**α of α-anomer of the *t*-butyl furanoside (**8**α), the β-anomeric protons of **11**α and **12**α exhibited smaller highfield shifts, $\Delta\delta$ = -0.25 and -0.24 respectively, than those of the β-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 α and β-*t*-butyl 5-*O*-benzyl-2-deoxyribofuranosides (**8**) in $CDCl_3$ at room temperature in the presence of Molecular Sieves 4A. The esterification was monitored by observing ^{1}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 β : α-anomers was estimated as 6.2 : 1 (**11**β : **11**α) and this ratio was constant one day later and after a week.





R = H	R^1 = Me	**10**β	4.5	:	1	**10**α
R = H	R^1 = *t*-Bu	**11**β	6.2	:	1	**11**α
R = $SiMe_3$	R^1 = *t*-Bu	**12**β	7.9	:	1	**12**α

Scheme 2.

The alkoxy-exchange of the boronic ester **11**β consisting of **1** and the β-anomer **8**β was also examined by addition of the α-anomer **8**α. To the $CDCl_3$ solution of **11**β, an equimolar amount of α-*t*-butyl 5-*O*-benzyl-2-deoxyribofuranoside (**8**α) was added. After one day, the boronate of the α-anomer was observed along with the generation of the free β-anomer by ^{1}H-NMR spectrum at 300 K. The ratio of the boronates **11**β and **11**α was 5.1 : 1.

The esterification of the silylated terphenylboronic acid **2** was also examined with a 1 : 1 mixture of α- and β-*t*-butyl 5-*O*-benzyl-2-deoxyribofuranoside (**8**). The boron esters was formed more preferentially with the β-anomers (**12**β : **12**α = 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 α and β-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**β : **10**α was 4.5 : 1. As a reference experiment, the esterification of 1-hydroxy-2-oxa-1-boraindane (**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**β and **7**α 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 α and β-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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