**Note**

Boronic Acid-Catalyzed Final-Stage Site-Selective Acylation for the Total Syntheses of O-3’-Acyl Bisabolol β-D-Fucopyranoside Natural Products and Their Analogues

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The first concise total syntheses of O-3’-senecioyl α-bisabolol β-D-fucopyranoside (4a) and O-3’-isovaleroyl α-bisabolol β-D-fucopyranoside (4b) were achieved through final-stage site-selective acylation via the activation of cis-vicinal diols by imidazole-containing boronic acid catalysts as a key step. This synthetic method was also effective for the syntheses of unnatural analogues with modified acyl side chains or carbohydrate moieties.

**Key words** boronic acid catalysis; site-selective acylation; bisabolol; carbohydrate; total synthesis

**Introduction**

In the synthesis of biologically active complex molecules with many functional groups, site-selective molecular transformations which could avoid complicated protection and de-protection sequences are powerful synthetic methodologies.1,2) From the viewpoint of atom efficiency, the development of direct catalytic site-selective reactions is required.3–6) Polyols with many hydroxy groups represented by carbohydrates are ubiquitous in nature and often have a structure in which only a part of the hydroxy groups is acylated. Thus far, there are many examples of site-selective acylation of carbohydrates using metal complex catalysts (e.g., chiral copper,7,8) organotin,9) molybdenum complex,10) and iron11)) and organocatalysts (e.g., chiral 4-pyrrolidinopyridine,12,13) peptides,14) chiral imidazole,15) chiral N-heterocyclic carbene (NHC),16) chiral benzo-triamisole (BTM),17) borinic acid,18) and benzoxaborole19)). In fact, there are reports in which site-selective acylation has been considered a powerful means for synthesizing partially acylated polyol natural products with focus on structure–activity relationships.20–25) In this regard, we have recently reported that imidazole-containing boronic acid acts as a highly active catalyst for the site-selective acylation of carbohydrates26) (Chart 1). Our catalytic reaction allows us to introduce a wide variety of acyl functional moieties in the equatorial position of cis-vicinal diol of carbohydrates in a highly selective manner.

α-Bisabolol2,27) a type of sesquiterpene alcohol, is known as a major anti-inflammatory component contained in chamomile oil, but its mechanism of action is not clarified (Fig. 1). Recent biological studies have revealed that α-bisabolol exhibits anti-inflammatory, anticholinesterase, and anticoagulant activities.28–31) However, α-bisabolol exhibits poor solubility in biological fluids owing to its highly lipophilic property, which makes it difficult to apply it to pharmacological applications. It is known that the physicochemical and pharmacokinetic properties can be improved by glycosidation owing to an increase in water solubility. In fact, according to a study on the structure–activity relationship of glycosidic α-bisabolol derivatives, α-bisabolol α-1-rhamnoside exhibited a better physicochemical and pharmacokinetic profile compared with α-bisabolol.32) More recently, α-bisabolol β-D-fucopyranoside 3(33) isolated from Carthamus lanatus has exhibited acetylcholinesterase (AChE) inhibitory activity, antioxidant capacity, antiaggregation, and disaggregation property of amyloid β (Aβ), which is attracting attention as a promising multitarget agent for the treatment of Alzheimer’s disease34) (Fig. 1).

**Chart 1. Boronic Acid-Catalyzed Site-Selective Acylation of Carbohydrates**

Fig. 1. Structures of (–)-α-Bisabolol (2), α-Bisabolol β-D-Fucopyranoside (3), and O-3’-Acyl α-Bisabolol β-D-Fucopyranoside Natural Products 4a and 4b

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lated from the aerial parts of the Mediterranean weed *Carthamus glaucus* in 2012 by the group of Appendino and Taglialetela-Scafati, and their structures were characterized by the fact that only the O-3'-position of α-bisabolol β-D-fucopyranoside was acylated15) (Fig. 1). Although O-3'-senecioyl α-bisabolol β-D-fucopyranoside (4a) exhibits moderate activity for the tumor necrosis factor (TNF) α-mediated activation of nuclear factor-kappa B (NF-κB) as well as bisabolol, there are currently no reports on its total synthesis. We envisioned that the O-3'-acyl side chains required for 4a and 4b can be introduced into the common precursor 3 in the final stage by our boronic acid-catalyzed site-selective acylation26) as a key step (Chart 2). Herein, we report the first total synthesis of 4a and 4b by boronic acid catalysis. In addition, we demonstrated that the boronic acid-catalyzed site-selective acylation in the final step was highly effective for the synthesis of acyl side chain-modified or sugar part-modified unnatural analogues.

### Results and Discussion

We started the synthesis by the preparation of α-bisabolol β-D-fucopyranoside 3 as a precursor of site-selective acylation from D-fucose (5)25) (Chart 3). The benzoylation of D-fucose (5) using benzoyl chloride in the presence of a catalytic amount of 4-dimethyl aminopyridine (DMAP) afforded a perbenzoylated product, which was subjected to the selective deprotection of the anomeric position by two step sequences of bromination with HBr/AcOH and hydrolysis using silver carbonate, which afforded alcohol 6 in 87% yield (three steps). The exposure of 6 to cesium carbonate under an excess amount of trichloroacetonitrile afforded imidate glycosyl donor 7 in 95% yield (78% of α-isomer and 17% of β-isomer). The glycosidation of α-bisabolol (2) with each isomer of 7 was performed by employing trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a promotor, which formed the desired product with a β-glycosydic linkage as a single isomer, followed by the hydrolysis of the benzoyl groups using NaOH to provide α-bisabolol β-D-fucopyranoside 3 with high yields over 87% in two steps (92% from 7-α and 87% from 7-β in two steps).36)

After obtaining the desired precursor 3, next, we examined the final-stage site-selective acylation of α-bisabolol β-D-fucopyranoside 3 toward the total synthesis of natural product 4a (Table 1). The reaction of 3 with senecioyl chloride (8) (2.0 equivalent (equiv)) in 1,4-dioxane at room temperature in the absence of a catalyst afforded a mixture of monoacylated products in 53% yield with poor site selectivity (3’-O-acylated product 4a: 2’-O-acylated product 9 = 1.2:1) along with undesired diacylated products 10 in 6% yield (entry 1). When using 1.0 mol% of boronic acid 1a as a catalyst, improved site selectivity was observed (4a:9 = 3.4:1), although almost no difference in product yield was observed (entry 2). By contrast, a change in the catalyst to boronic acid 1b containing a methoxy substituent on benzene ring resulted in a considerable improvement in site selectivity, which afforded the desired natural product 4a in 85% isolated yield as a single isomer (4a:9 = 99:1) (entry 3). The boronic acid 1b with electron-donating methoxy group is expected to produce a more nucleophilic tetra-coordinated boronate intermediate. Hence, it is considered that 1b accelerated the reaction rate at the acylation step more than 1a and suppressed the non-catalytic low site-selective reaction. The 1H-NMR spectra of O-3’-acylated synthetic and natural products showed good agreement.37) On the other hand, the use of 10 mol% of diphenyl boronic acid (11) or cyclic boronic acid 12 as a catalyst decreased site selectivity with 4a:9 = 1.4:1 (entries 4 and 5). Of note, even when DMAP, which is widely used as a catalyst for the acylation reaction, was used as a catalyst, regioselectivity was hardly observed despite the reduction in the amount of acylation reagent (entries 6 and 7). These results clearly indicate the superior catalytic performance of imidazole-containing boronic acid 1b in the site-selective acylation of 3.

If various acyl functional groups could be introduced directly from the same precursor at the final stage, it would be a powerful strategy focused on the structure–activity relationship studies. Consequently, to demonstrate the synthetic utility of boronic acid-catalyzed site-selective acylation, next, we conducted the synthesis of natural product 4b with an isovaleryl acyl side chain together with the analogues 13–15 having unnatural acyl side chains (Chart 4). Using only 0.5 mol% of boronic acid 1b, the site-selective acylation of common precursor 3 with isovaleryl chloride (16) proceeded to give natural product 4b in an extremely high yield of 98% with perfect site selectivity. The introduction of unnatural acyl side chains to 3 at the O-3’-position was easily accomplished by changing acylation reagents to 3-phenylpropionyl chloride (17), cinnamoyl chloride (18), or galloyl chloride derivative 19, which formed the corresponding derivatives 13, 14, and 15.
in high yields (88–92%). Thus, we demonstrated that boronic acid-catalyzed site-selective acylation would be effective in synthesizing various analogues from the common precursor 3 by final-stage manipulation.

To demonstrate the applicability of our methodology, we planned to investigate the syntheses of \(O\)-3'-acyl \(\alpha\)-bisabolol \(\beta\)-\(\alpha\)-fucopyranoside analogues containing different carbohydrate moieties. Before examining boronic acid-catalyzed site-selective acylation, precursor 23 was synthesized from \(L\)-rhamnose monohydrate (20) (Chart 5). Using the same protocols for precursor 3 in linear sequences of six steps from 20, 23 was successfully obtained in 83% overall yield.

Next, we examined the site-selective acylation of 23 (Chart 6).

### Table 1. Optimization of the Catalytic Site-Selective Acylation for \(\alpha\)-Bisabolol \(\beta\)-\(\alpha\)-Fucopyranoside (3) toward the Synthesis of Natural Product 4a

| Entry | Catalyst [x mol%] | Yield (4a:9:10) [%] \(^a\) | Total [%] \(^a\) | 4a:9 | 3 [%] \(^b\) |
|-------|-------------------|----------------------------|-----------------|-----|------|
| 1     | —                 | 29/24/6                    | 59              | 1.2:1 | 17   |
| 2     | 1a [1.0]          | 41/12/2                    | 55              | 3.4:1 | 34   |
| 3     | 1b [1.0]          | 86 [85\(^b\)] — 9         | 95              | \(99 : 1\) | — |
| 4     | 11 [10]           | 33/24/9                    | 66              | 1.4:1 | 17   |
| 5     | 12 [10]           | 34/24/9                    | 67              | 1.4:1 | 17   |
| 6     | DMAP [1.0]        | 33/24/6                    | 63              | 1.4:1 | 19   |
| 7\(^c\) | DMAP [1.0]     | 26/19/2                    | 47              | 1.4:1 | 42   |

\(4a\) Determined by 'H-NMR. \(b\) Isolated yield. \(c\) 1.1 equiv of 8 and collidine were used.
The purpose of structure–activity relationship studies is a powerful method for constructing compound libraries. The direct site-selective acylation using boronic acid catalysis is applicable to the syntheses of natural acyl side chains. In addition, site-selective acylation to achieve concise syntheses of various analogues with excellent site selectivity values. This approach allows us to introduce various acyl functional groups into a carbohydrate precursor at final manipulation with high yield. This synthetic route allows the direct synthesis of natural products and their analogues, such as fucopyranoside natural products, from a mon carbohydrate precursor.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Supplementary Materials**

The online version of this article contains supplementary materials.

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Attempts at the glycosidation of 2 with 2,3,4-tri-O-benzoyl-α-D-

fucopyranosyl bromide followed by deprotection resulted in lower

yield of 3 (20% over 2 steps) compared with results shown in

Chart 3.

See the Supplementary Materials for details.

In the absence of boronic acid catalyst, the reaction of rhamnopy-

ranoside 23 with senecioyl chloride (8) gave O-3′-acylated product

24 in 43% yield along with O-4′-acylated product in 21% yield,

showing low site-selectivity. See the Supplementary Materials for
details.