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'-seneciroyl 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 moiety.

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 deprotection 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 benzotetramisole (BTM),¹⁷ boronic 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 -Bisabolol **2**,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 **2** 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 -L-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 (A β), which is attracting attention as a promising multitarget agent for the treatment of Alzheimer's disease³⁴ (Fig. 1).

O-3'-Seneciroyl α -bisabolol β -D-fucopyranoside (**4a**) and *O*-3'-isovaleroyl α -bisabolol β -D-fucopyranoside (**4b**) were iso-

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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Chart 2. Synthetic Plan of α -Bisabolol β -D-Fucopyranosides **4**

lated from the aerial parts of the Mediterranean weed *Carthamus glaucus* in 2012 by the group of Appendino and Tagliabue-Scafati, and their structures were characterized by the fact that only the *O*-3'-position of α -bisabolol β -D-fucopyranoside was acylated³⁵ (Fig. 1). Although *O*-3'-senecieryl α -bisabolol β -D-fucopyranoside (**4a**) exhibits moderate activity for the tumor necrosis factor (TNF) α -mediated activation of nuclear factor-kappa B (NF- κ B) 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**)³² (Chart 3). The benzylation of D-fucose (**5**) using benzoyl chloride in the presence of a catalytic amount of 4-dimethyl aminopyridine (DMAP) afforded a per-benzoylated 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 -glycosidic 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 senecieryl 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 me-

Chart 3. Preparation of α -Bisabolol β -D-Fucopyranoside (**3**) from D-Fucose (**5**)

thoxy 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**

Table 1. Optimization of the Catalytic Site-Selective Acylation for α -Bisabolol β -D-Fucopyranoside (**3**) toward the Synthesis of Natural Product **4a**

Entry	Catalyst [x mol%]	Yield (4a / 9 / 10) [%] ^{a)}	Total [%] ^{a)}	4a : 9	3 [%] ^{a)}
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

a) Determined by ¹H-NMR. b) Isolated yield. c) 1.1 equiv of **8** and collidine were used.

Chart 4. Syntheses of Natural Product **4b** and Unnatural Analogues **13–15** Using Boronic Acid **1b**-Catalyzed Final-Stage Site-Selective Acylation of α -Bisabolol β -D-Fucopyranoside (**3**)

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 α -bisabolol α -L-rhamnopyranoside 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).

The reaction with senecieryl chloride (**8**) as acylation reagent proceeded smoothly under the influence of 1.0 mol% of **1b**, providing *O*-3'-acylated α -bisabolol α -L-rhamnopyranoside analogue **24** in 86% yield. However low site-selectivity with moderate conversion yield was observed in the absence of catalyst **1b**.³⁸⁾ These results clearly showed that boronic acid **1b** improves not only the reaction rate but also the site-selectivity. The reaction with isovaleryl chloride (**16**) also gave analogue **25** in 96% yield within a short time. These results reveal that boronic acid catalysis can be applied not only to the synthesis of acyl side chain-modified analogues but also to the synthesis of carbohydrate-modified analogues.

Chart 5. Preparation of α-Bisabolol α-L-Rhamnopyranoside (**23**) from L-Rhamnose (**20**)

Chart 6. Synthesis of O-3'-Acyl α-Bisabolol α-L-Rhamnopyranosides **24** and **25** Using Boronic Acid **1b**-Catalyzed Final-Stage Site-Selective Acylation

Conclusion

The first total syntheses of O-3'-acyl α-bisabolol β-D-fucopyranoside natural products and their analogues were achieved by using boronic acid-catalyzed site-selective acylation in the final stage. This synthetic route allows the direct introduction of various acyl functional groups into a common carbohydrate precursor at final manipulation with high to excellent site selectivity values. This approach allows us to achieve concise syntheses of various analogues with unnatural acyl side chains. In addition, site-selective acylation is applicable to the syntheses of O-3'-acyl α-bisabolol α-L-rhamnopyranosides containing different carbohydrate moieties. The direct site-selective acylation using boronic acid catalysis is a powerful method for constructing compound libraries for the purpose of structure–activity relationship studies.

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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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- 36) 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.
- 37) See the Supplementary Materials for details.
- 38) In the absence of boronic acid catalyst, the reaction of rhamnopyranoside **23** with senecioid 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.