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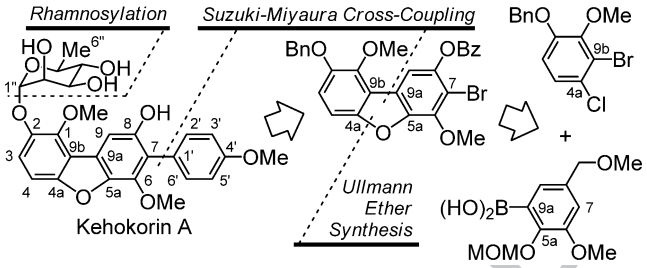

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Total synthesis of kehokorins A and B

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ABSTRACT

The total synthesis of a dibenzofuran rhamnoside, kehokorin A, and its aglycone, kehokorin B, was achieved via a route including Suzuki-Miyaura cross-coupling followed by Ullmann ether synthesis to form a dibenzofuran, stepwise bromination at C7 of the dibenzofuran, a second Suzuki-Miyaura cross-coupling to install a 4-methoxyphenyl group at C7, and rhamnosylation.

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A dibenzofuran rhamnoside, kehokorin A (**1**), and its aglycone, kehokorin B (**2**), were isolated as cytotoxins from the myxomycete *Trichia favoginea* var. *persimilis* by Ishibashi (Figure 1).[1] The kehokorins are structurally highlighted by a *p*-terphenyl core skeleton, which is highly oxygenated and cyclized with an oxygen atom to form a dibenzofuran. While many dibenzofuran *p*-terphenyl natural products are known to date,[2] kehokorin A (**1**) belongs to a rare class of glycoside derivatives. From the IC_{50} values of **1** and its congeners against HeLa epithelial carcinoma cell line (1.5 and 7.2 μg/mL for **1** and **2**, respectively), Ishibashi also suggested the importance of the rhamnose unit of **1** in cytotoxicity. Prompted by the unique structure and cytotoxicity against cancer cells, we started our program toward the total synthesis of **1** and **2**. During the course of our study, the Takahashi group achieved the total synthesis of **1**, **2** and other congeners[3] in 2017 via a route including *p*-terphenyl construction followed by dibenzofuran cyclization.[4] Here, we describe our recent results on the total synthesis of **1** and **2** by a different strategy based on dibenzofuran formation followed by *p*-terphenyl construction.[5]

Our plan for the synthesis of **1** and **2** is shown in Scheme 1. First, *p*-terphenyl **4**, having different protecting groups for the oxygen atoms at C2 and C8, was designed as a common intermediate for **1** and **2**. In the final stage of the synthesis of **1**, a process including the removal of the benzyl group of **4** followed by glycosylation with known rhamnosyl donor **3**[6] and full deprotection was scheduled. *p*-Terphenyl **4** would also produce **2** through a simple two-step deprotection process. The 4-methoxyphenyl group at C7 of **4** would be installed by the Suzuki-Miyaura cross-coupling[7] of 7-bromodibenzofuran **5** with boronic acid **6**. Intermediate **5** was planned to be constructed from dibenzofuran carbaldehyde **7** via Baeyer-Villiger oxidation to form an oxygen functional group at C8 and regioselective bromination at C7. Since the regio-controlled bromination of a dibenzofuran having multiple oxygen functional groups was a difficult challenge, an exhaustive study on the basis of an ample supply of **7** was required to solve the challenge. Therefore, a reliable synthesis of **7** was designed as follows. The furan of **7** would be formed via the Ullmann ether synthesis from **8**, which would be assembled by the Suzuki-Miyaura cross-coupling of bromide **9** with boronic acid **10**, prepared from known bromide **11**.[8]

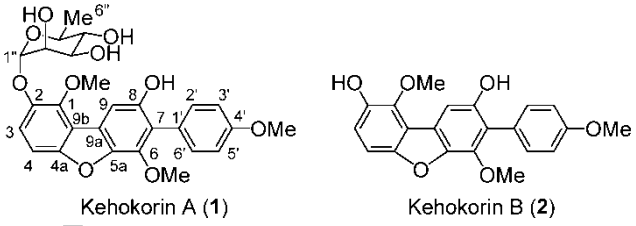
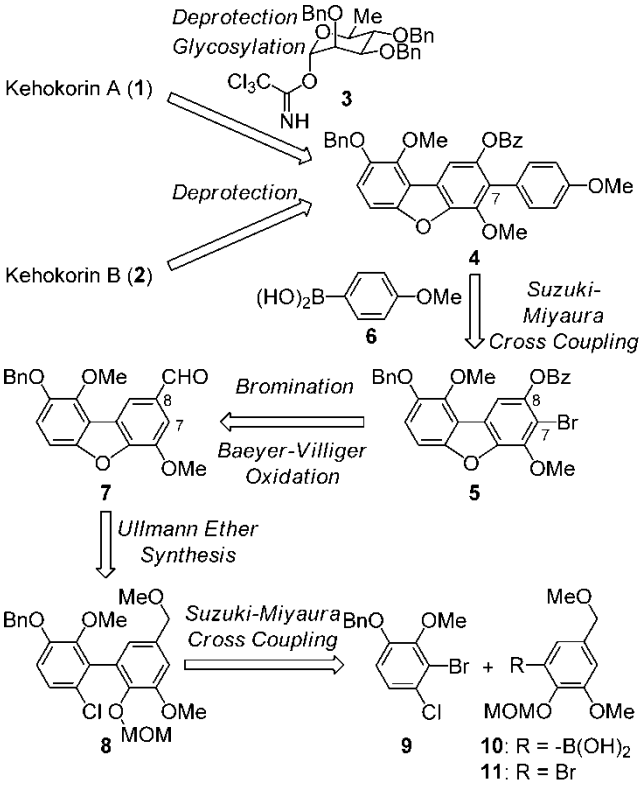
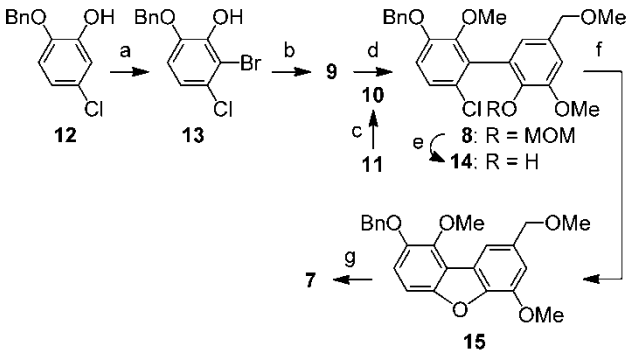


Figure 1. Kehokorins A and B



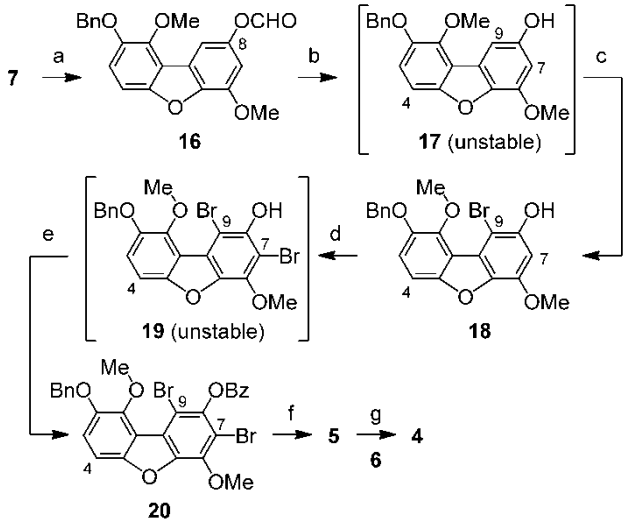
Scheme 1. Plan for the synthesis of kehokorins A and B



Scheme 2. Reagents and conditions: (a) $(i\text{-Pr})_2NH$, NBS, CH_2Cl_2, 0 °C, 45 min, 81%; (b) $TMSCHN_2$, MeOH-toluene (1.45:1), 22 °C, 25 min, 95%; (c) BuLi, THF, –78 °C, 5 min, then $B(Oi\text{-Pr})_3$, –78 → 0 °C, 1 h; (d) **10**, $Pd_2(dba)_3$, SPhos, K_3PO_4, toluene, 105 °C, 24 h, 94%; (e) $TsOH{\bullet}H_2O$, MeOH, 21 °C, 1 h; (f) CuI, $MeNHCH_2CH_2NHMe$, K_2CO_3, DMF, reflux, 4 h; (g) DDQ, CH_2Cl_2-H_2O (9:1), 21 °C, 1 h, 83% from **8**.

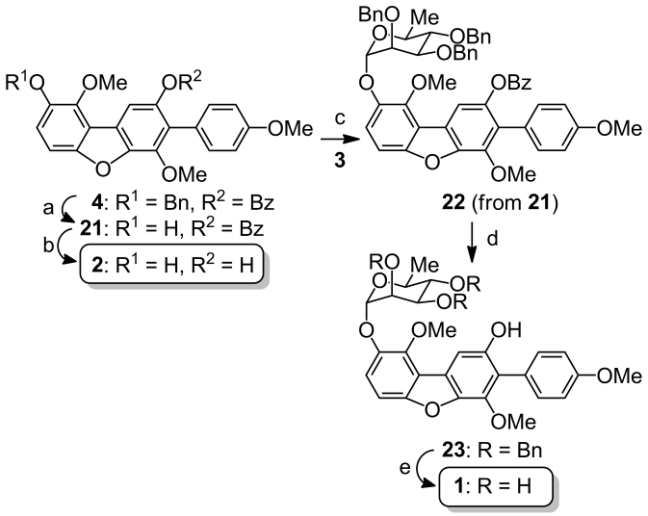
As a first step of the synthesis of dibenzofuran **7**, the conversion of known phenol **12**[9] to intermediate **9** was examined (Scheme 2). While a simple reaction of **12** with *N*-bromosuccinimide (NBS) gave only an undesired mixture of 4-bromophenol and 2,4-dibromophenol derivatives, the treatment of **12** with NBS in the presence of diisopropylamine, according to Fujisaki's selective *ortho*-bromination method,[10] produced **13** predominantly (81%). The phenolic hydroxy group of **13** was methylated with trimethylsilyldiazomethane ($TMSCHN_2$) to afford **9** (95%). The boronic acid **10** was prepared from bromide **11**[8] by a process including lithiation, reaction with $B(Oi\text{-Pr})_3$ and hydrolysis. The Suzuki-Miyaura coupling of **9** with **10** successfully furnished diphenyl **8** (94%) under the Buchwald conditions using $Pd_2(dba)_3$, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) and K_3PO_4.[11] The MOM group of **8** was removed with acidic methanol to give **14**, which was then

treated with CuI, *N*,*N*'-dimethylethylenediamine and K_2CO_3 in refluxing DMF for 4 h to afford dibenzofuran **15** successfully.[12,13] The methoxymethyl group of **15** was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to furnish aldehyde **7** (83% over 3 steps).[14] Thus, dibenzofuran **7** was synthesized in 6 steps and 60% overall yield from known phenol **12**.



Scheme 3. Reagents and conditions: (a) *m*CPBA, $Sc(OTf)_3$ (cat.), BHT, CH_2Cl_2, 20 °C, 1 h; (b) NaOMe, MeOH, 20 °C, 15 min, then AcOH, 0 °C, 9 min; (c) NBS, MeOH, 0 °C, 15 min, 61% from **7**; (d) *i*-Pr_2NH, Br_2, CH_2Cl_2, 21 °C, 15 min, then 2-methylbut-2-ene, 0 °C, 5 min; (e) BzCl, DMAP, CH_2Cl_2, 0 °C, 80 min, 64% from **18**; (f) $Pd(PPh_3)_4$ (cat.), BuOH, K_2CO_3, BuOAc, 90 °C, 6 h; repeated once again: 13 h, **5**: 34%, benzoate of **17**: 32%; (g) **6**, $Pd_2(dba)_3$, SPhos, K_3PO_4, toluene, 105 °C, 5 h; repeated once again: 14 h, 55%.

With the desired dibenzofuran **7** in hand, we next examined the regioselective installation of a bromine group at C7 for the preparation of intermediate **5** (Scheme 3). The formyl group of **7** was first rearranged to a formate ester via Baeyer-Villiger oxidation under Kotsuki's conditions[15] to give **16**. Although the basic methanolysis of **16** facilely produced phenol **17**, the difficulty in the isolation of **17** due to its instability urged us to use **17** *in situ* for the next reaction. After intensive exploration of the reaction conditions for the regioselective monobromination at C7 of **17**, it was found that the positional reactivity of **17** was decreased in the order: C9 > C4 > C7. Since the high reactivity at C9 could not be suppressed, we revised our plan, taking an alternative route including dibromination at C9 and C7 followed by debromination at C9. Thus, phenol **17**, generated *in situ*, was reacted with NBS to afford C9-bromide **18** as a stable product (61% over 3 steps). Regioselective bromination at C7 of **18** was achieved by Fujisaki's method[10] with a modification using Br_2 instead of NBS to produce **19** predominantly. Because dibromophenol **19** was unstable under the isolation conditions, the phenol was protected *in situ* as a benzoate to give stable **20** (64% over 2 steps). The conditions for the reductive removal of the Br group at C9 of **20** were extensively screened. It was found that C9-Br was more reactive than C7-Br under palladium-catalyzed conditions, though the difference was small. At present, the best production of the desired **5** was observed under Zhang's conditions[16] with a modification using a decreased amount of reductant. Thus, dibromophenol **20** was treated with K_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$ in the presence of 2 equiv. of BuOH as a reductant in butyl acetate at 90 °C. However, the reaction tended to stop without completion to give an inseparable mixture of **5** and unreacted **20** along with a small amount of an over-reduced product, the benzoate of **17**. Therefore, in order to consume **20**, the resulting mixture was subjected to the same reaction with reduced amounts of reagents to provide a reasonable yield of **5** (34%) along with the benzoate of **17** (32%). Bromide **5** showed decreased reactivity in the Suzuki-Miyaura coupling with **6** even under the Buchwald conditions.[11] Therefore, the coupling was repeated once again to give the desired *p*-terphenyl dibenzofuran **4** in 55% yield. Thus, key intermediate **4** was synthesized from dibenzofuran **7** via a process including dibromination at C9 and C7, debromination at C9 and the Suzuki-Miyaura coupling at C7.



Scheme 4. Reagents and conditions: (a) H_2, Pd/C, MeOH-EtOAc (2:1), 21 °C, 15–17 h; (b) K_2CO_3, 1,4-dioxane-BuOH (25:1), 90 °C, 13 h, 70% from **4**; (c) **3**, TMSOTf, MS4A, CH_2Cl_2, –20 °C, 45 min; repeated once again: –20 °C → 0 °C, 45 min; (d) K_2CO_3, 1,4-dioxane-BuOH (25:1), 90 °C, 15.5 h, 40% from **4**; (e) H_2, Pd/C, MeOH-EtOAc (3:1), 25 °C, 63 h, 48%.

At the final stage, the synthesis of kehokorins A and B from **4** was examined via a route including rhamnosylation and removal of the protecting groups (Scheme 4). The benzyl group of **4** was first removed by hydrogenolysis to give common intermediate **21**. The removal of the benzoate ester of **21** by transesterification with BuOH under basic conditions produced kehokorin B (**2**) (70% over 2 steps). Because the rhamnosylation of **21** using imidate **3**[6] in the presence of TMSOTf was sluggish to afford a mixture of desired **22** and unreacted **21**, the mixture was again reacted with **3** under the same conditions for the completion of the rhamnosylation to provide **22** and byproducts from **3** as an inseparable mixture. Treatment of the mixture with K_2CO_3 and BuOH at 90 °C converted benzoate **22** to phenol **23**,[17] which was separated from the byproducts (40% over 3 steps from **4**). The benzyl groups of **23** were removed by hydrogenolysis to furnish kehokorin A (**1**) (48%). The spectral data of synthetic **1** and **2** as well as the specific optical rotation of synthetic **1** were in accordance with those reported in the literature,[1,4] thereby confirming the completion of the total synthesis of kehokorins A and B.

In conclusion, the total synthesis of a dibenzofuran rhamnoside, kehokorin A, and its aglycone, kehokorin B, was achieved via a route including Suzuki-Miyaura cross-coupling followed by Ullmann ether synthesis to form a dibenzofuran, stepwise bromination at C7 of the dibenzofuran, a second Suzuki-Miyaura cross-coupling to install a 4-methoxyphenyl group at C7, and rhamnosylation. Further optimization of the synthesis of kehokorins A and B and biological studies on the synthetic kehokorins and their derivatives are in progress.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/##.####/j.tetlet.#####.##.###

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Successful total synthesis of kehokorins A and B
A strategy based on dibenzofuran formation
followed by *p*-terphenyl construction
Construction of the dibenzofuran unit by Suzuki
coupling and Ullmann ether synthesis
7-Bromodibenzofuran formation via dibromination
of the core followed by debromination