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Total Synthesis of Kehokorins A−E, Cytotoxic *p*-Terphenyls

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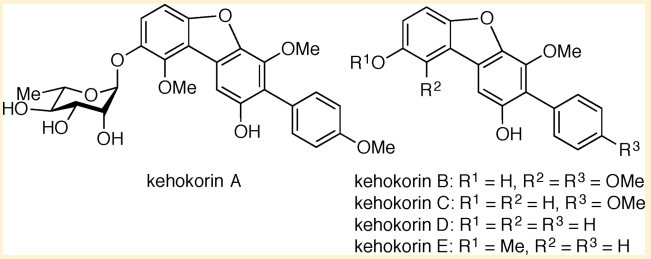
Supporting Information

ABSTRACT: This paper describes a general method for the synthesis of kehokorins A−E, novel cytotoxic *p*-terphenyls. 2,4,6-Trihydroxybenzaldehyde served as a common building block for preparation of the central aromatic ring. Construction of their *p*-terphenyl skeletons was achieved by a stepwise Suzuki−Miyaura coupling, whereas the phenyldibenzofuran moiety was built up by an intramolecular Ullmann reaction. Introduction of an L-rhamnose residue into partly protected kehokorin B was performed by the trichloroacetimidate method.



INTRODUCTION

Terphenyls are a group of aromatic hydrocarbons consisting of a chain of three benzene rings. Most of natural products belonging to this family are *p*-terphenyls, in which two terminal aromatic rings connect to the central ring at the *p*-position, and are known to be present in fungi and lichens.[1] Although their research history is derived from the discovery of polyporic acid as a pigment in 1877,[2] recent studies have been mainly focused on their diverse biological activities, such as potent immunosuppressive,[3] neuroprotective,[4] antitumor,[5] antiallergic,[6] and 5-lipoxygenase[7] inhibitory activities. On the other hand, the presence of many aromatic sp^2 carbons existing in these molecules makes it difficult to study their structures, and several papers on structural revision may emphasize the significance of synthetic studies.[8−12] Kehokorins A−E (**1**−**5**) are novel *p*-terphenyls carrying a dibenzo[*b*,*d*]furan as a common structural motif which were isolated from field-collected fruit bodies of the myxomycetes *Trichia favoginea* by Ishibashi et al. (Figure 1).[13] Their *p*-terphenyl structures were mainly determined by extensive NMR analyses, and the presence of the L-rhamnose residue in **1** was confirmed by enzymatic degradation studies. These natural products exhibit cytotoxic activity against the HeLa human epithelial carcinoma cell line, and the IC_{50} value of the most potent compound **1** was shown to be 1.5 μg/mL. In the antimicrobial assay, only **1** was reported to show a weak activity against *Staphylococcus aureus*. These results suggest the importance of the sugar residue. Although there are many *p*-terphenyls in nature, a phenyldibenzofuran glycoside such as **1** was virtually unknown.[14] In connection with our studies on bioactive *p*-terphenyls,[15] the unique structure stimulated our interest. Described herein is the first total synthesis of kehokorins A−E (**1**−**5**), thus confirming the structures of the natural products.

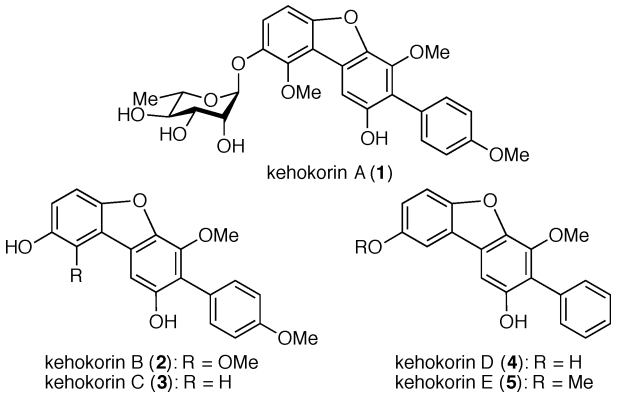


Figure 1. Structures of kehokorins A−E (**1**−**5**).

RESULTS AND DISCUSSION

As the most complex molecule in the kehokorin series is kehokorin A (**1**), we initially designed a synthetic strategy directed toward **1** as illustrated in Scheme 1. Removal of the L-rhamnose residue in the target molecule leads to a benzoylated L-rhamnose derivative **6** and 8-*O*-protected kehokorin B **7**. Cleavage of the internal ether linkage can revert **7** back to the *p*-terphenyl **8**. This could be synthesized by a stepwise Suzuki−Miyaura coupling[16] of **10** with a couple of boronic acid derivatives, **9** and **11**. The formyl group in **10** was introduced for a regioselective functionalization of the central ring as well as for an equivalent of a masked hydroxyl group, and 2,4,6-trihydroxybenzaldehyde (**12**) was envisaged as the common starting material. In addition, these retrosynthetic analyses would enable us to prepare kehokorin C−E (**3**-**5**) by changing the boronic acid derivatives employed in the Suzuki−Miyaura coupling.

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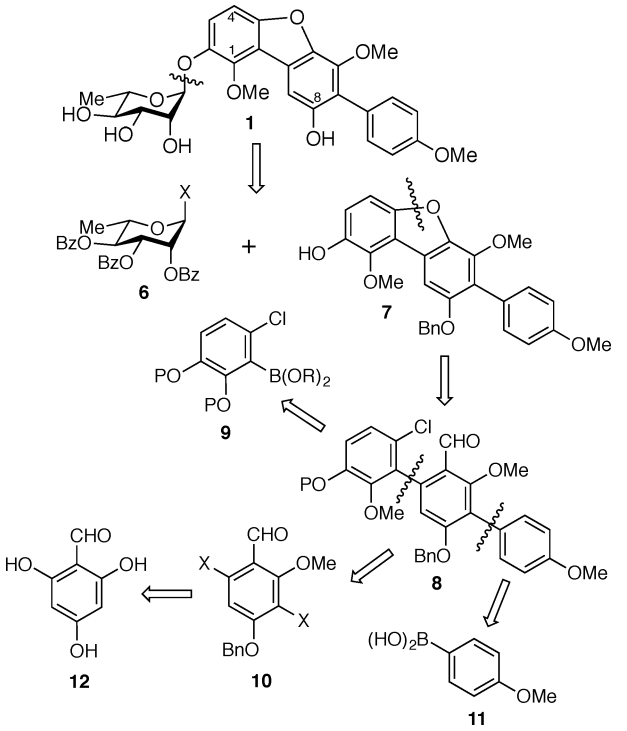
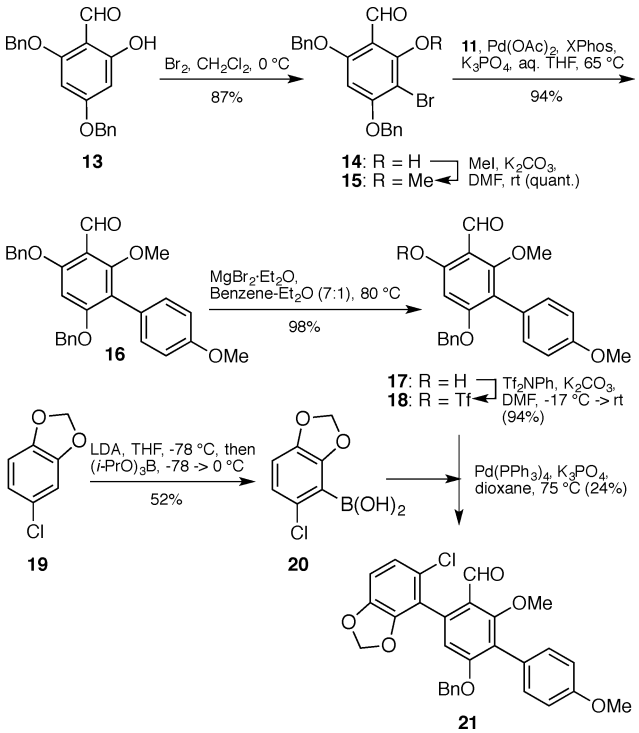
Scheme 1. Synthetic Plan for Kehokorin A (1)



The synthesis of **1** began with preparation of the central part **15**. The dibenzyl ether **13** obtained by benzylation[17] of 2,4,6-trihydroxybenzaldehyde (**12**) was transformed into **14** (Scheme 2) via bromination. The structure, in particular the position of the newly introduced bromine atom, was confirmed by 2D NMR analyses.[18] The free hydroxyl group was changed to the corresponding methyl ether to afford the central part **15**. The first Suzuki–Miyaura coupling of **15** with boronic acid **11** was performed by the action of $Pd(OAc)_2$ in the presence of XPhos and potassium phosphate in aqueous THF, giving a biphenyl **16** in high yield. Its 6-*O*-benzyl group was removed by magnesium bromide etherate[19] giving **17** quantitatively. Its triflation afforded a biphenyl block **18** in good yield. Prior to the second Suzuki–Miyaura coupling, chloroboronic acid **20** was prepared from 5-chlorobenzo[*d*][1,3]dioxole (**19**) via ortho-lithiation[20] with LDA followed by trapping with triisopropylborate. The selection of **20** as a coupling partner stemmed from the ready availability of the starting material **19** and the expectation of an easy hydrolysis of the methylene acetal moiety at a later stage.[15] The coupling of **18** with **20**, however, gave unsatisfactory results. Among the conditions tried (Table 1), a combination of $Pd(PPh_3)_4$ and potassium phosphate in anhydrous 1,4-dioxane afforded the desired *p*-terphenyl **21** in 24% yield. The low yield made us change the boronic acid employed in the coupling.

Scheme 2. Synthesis of the Central Part 15 and Its Conversion into *p*-Terphenyl 21



Next, as another precursor of the terminal aromatic ring, methoxyphenylboronic acid derivavtive **28** with an acyclic protecting group was designed that would be obtained easily from 3-bromo-4-chloro-2-methoxyphenol (**25**)[21] (Scheme 3). It was obtained by a 1,4-addition of HCl to 5-bromo-6,6-dimethoxycyclohexa-2,4-dien-1-one, but we found this method to be unsuitable for our purpose because of the low yield (2%). Therefore, direct chlorination of **22** was attempted. Treatment with sulfuryl chloride in $CHCl_3$ at 50 °C afforded a ca. 1:1 mixture of a *p*-chlorophenol derivative **25** and its *o*-isomer **24** in 78% yield, whereas Gustafson's method using NCS–Ph_3P=S[22] improved the selectivity (**25**/**24** = 82/18, total 84% yield). As the authors reported, the use of a BINAP derivative **23**[23] (0.1 mol equiv) instead of Ph_3P=S gave the desired product **25** in high selectivity (**25**/**24** = 93/7). When a small excess of NCS (~1.5 mol equiv) was employed according to the original paper, the ratio of **25** was revealed to decrease due to the formation of the corresponding dichloride by the ^1H NMR analysis. Therefore, 1.0 equiv of NCS was employed in this reaction. The phenol **25** thus obtained was transformed into the corresponding MOM ether **26**. Preparation[24] of **28** from **26** was a troublesome step. As a Pd-catalyzed cross-coupling of **26** with bis(pinacolato)diboron[25] resulted in a low yield of **28**, a route via transmetalation was examined. Different from the case of its regioisomer,[15b] the anion generated by treatment of **26** with *n*-BuLi was found to be unstable. Consequently, a brief (<5 min, −78 °C) treatment with the base followed by immediate addition of **27** was needed to obtain **28** in a practical yield. The second Suzuki–Miyaura coupling of **18** with the boronate **28** was also effected by treatment with $Pd(PPh_3)_4$ in the presence of potassium phosphate to give **29** in good yield. Although the reaction was completed in a short time at a higher temperature (100–110 °C), hydrolysis of **18** into **17** was observed. In order to suppress the side reaction, the reaction was conducted at a low temperature (~75 °C) for a long time. Construction of the dibenzo[*b*,*d*]furan skeleton was accomplished by the method[15b] previously reported. Thus, **29** was initially oxidized with *m*CPBA in the presence of $NaHCO_3$, and then the resulting formate, without purification, was heated with Cu_2O[26] in pyridine to furnish the desired dibenzofuran derivative **30**. Treatment with HCl led to **7**. The benzyl group in **7** was removed by hydrogenolysis with 10% Pd/C to give kehokorin B (**2**), the spectral data of which were identical with those of the natural product.[13a] On the other hand, the

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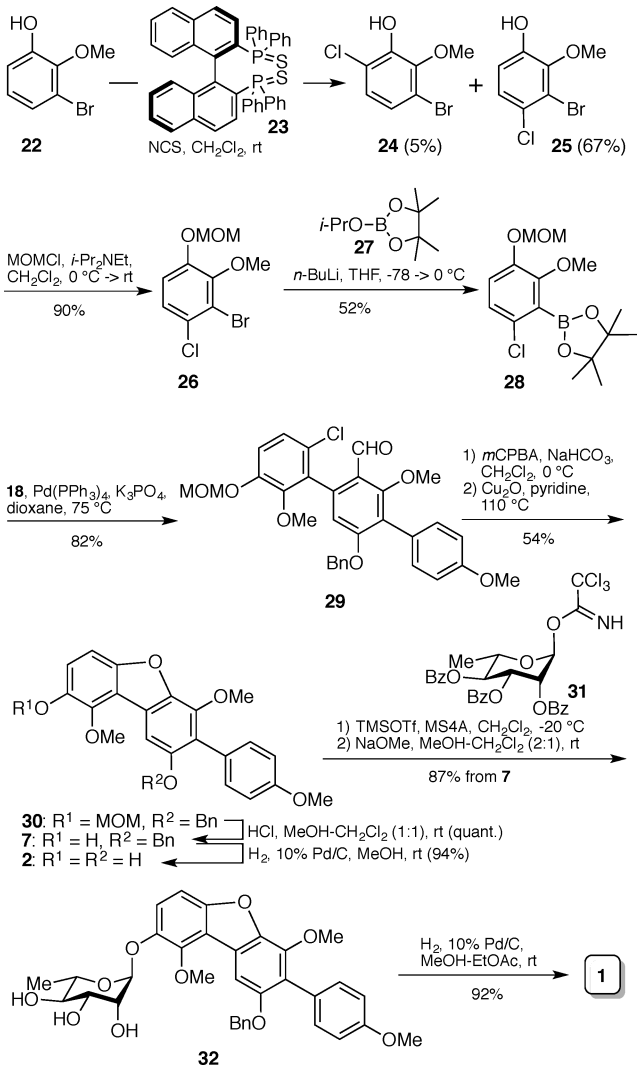
Table 1. Suzuki–Miyaura Coupling of 18 and 20[a]

entry	catalyst (mol %)	ligand[b]	base (equiv)	solvent	temp (°C)	products (% yield)
1	$Pd(PPh_3)_4$ (10)	–	Cs_2CO_3 (2.0)	toluene	110	**17** (60), **21** (20)
2	$Pd(PPh_3)_4$ (5)	–	K_3PO_4 (1.5)	1,4-dioxane	100	complex mixture
3	$Pd(PPh_3)_4$ (5)	–	K_3PO_4 (1.5)	1,4-dioxane	75	**21** (24)
4	$PdCl_2$(dppf) (5)	–	Cs_2CO_3 (2.0)	1,4-dioxane	100	**17** (23), **21** (10)
5	$Pd(OAc)_2$ (5)	PPh_3	K_3PO_4 (2.0)	THF	65	no reaction[c]
6	$Pd(OAc)_2$ (5)	PCy_3	KF (3.3)	THF	rt	no reaction[c]
7	$Pd(OAc)_2$ (5)	PCy_3	KF (3.3)	THF	55	no reaction[c]

[a]Boronic acid (1.3 equiv) was employed. [b]A 15 mol % portion of ligand was employed. [c]Triflate **18** was recovered in 86–95% yield.

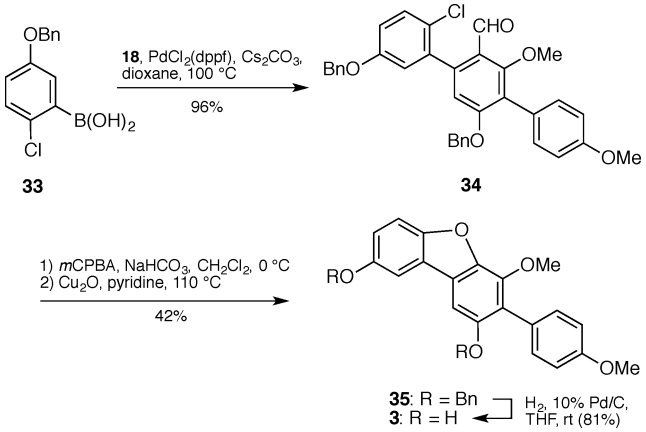
Scheme 3. Total Synthesis of Kehokorins A (1) and B (2)



introduction of an L-rhamnose unit into **7** was needed for the preparation of kehokorin A (**1**). Although several groups reported the glycosidation employing a phenol with a benzofuran moiety as a glycosyl acceptor,[27−32] no paper has appeared dealing with such reaction of a dibenzofuran derivative. We adopted Schmidt's procedure using 2,3,4-tri-*O*-benzoyl-L-rhamnosyl trichloroacetimidate (**31**)[33] as a glycosyl donor. Reaction of **7** and **31** (2.2 equiv) in the presence of TMSOTf (0.001 equiv) and MS4A in dichloromethane at −20 °C proceeded nicely to provide a glycosylated product[34] in high yield. This contained a considerable amount of the inseparable imidate-derived byproducts so that the glycosylated product was isolated as **32** after debenzoylation.[35] Finally, debenzylation of **32** afforded kehokorin A (**1**). The physical and spectral data of **1** matched well those of natural kehokorin A.[13a]

As we could establish a synthetic route to kehokorins A (**1**) and B (**2**), we next turned our attention to kehokorin C (**3**). Kehokorin C (**3**) lacks the 1-methoxy group of kehokorin B (**2**). Therefore, boronic acid **33** instead of **28** was employed for the second Suzuki–Miyaura coupling (Scheme 4). Reaction of

Scheme 4. Total Synthesis of Kehokorin C (3)



18 with **33** was effected by the use of $PdCl_2$(dppf) in the presence of Cs_2CO_3 (Table 2) to give *p*-terphenyl **34** in high yield. Baeyer–Villiger oxidation of **34** followed by the Ullmann reaction afforded **35**, which underwent debenzylation to give **3**, the spectral data of which were consistent with those of natural kehokorin C.[13a]

In a similar way, kehokorins D (**4**) and E (**5**) were synthesized from **15** and **36** (Scheme 5). Thus, a mixture of both compounds was treated with $Pd(OAc)_2$ in the presence of XPhos and potassium phosphate, affording biphenyl **37** in good yield. Debenzylation and triflation of the resulting phenol **38** gave a pivotal intermediate **39**. A Pd-catalyzed coupling of **39** with **33** or **40** provided **41** or **42**, respectively. Upon the indicated functionalization, each compound was transformed into **43** and **44** and then kehokorins D (**4**) and E (**5**), respectively. Spectral data for both compounds were identical in all respects to those previously reported.[13b]

In conclusion, we achieved the total synthesis of kehokorin A (**1**) through a stepwise Suzuki–Miyaura coupling, Ullmann reaction, and stereoselective glycosidation as key steps. This strategy also enabled us to prepare its congeners (**2**–**5**) and therefore would be useful for preparing kehokorin A analogs with a variety of sugars in aid of SARs. Furthermore, the structures of the natural products were unambiguously established by our synthetic work.

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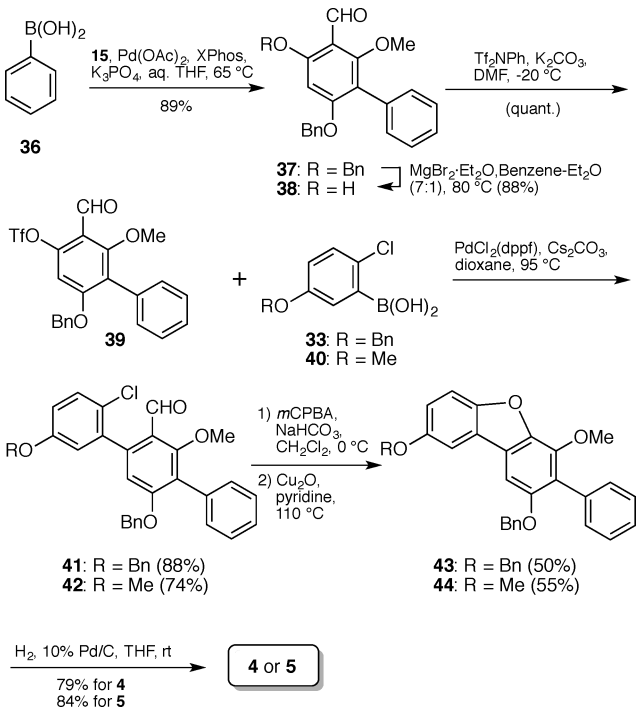
Table 2. Suzuki–Miyaura Coupling of 18 and 33[a]

entry	catalyst (mol %)	ligand[b]	base (equiv)	solvent	temp (°C)	products (% yield)
1	$Pd(PPh_3)_4$ (10)	–	Cs_2CO_3 (2.0)	toluene	110	no reaction[c]
1	$Pd(PPh_3)_4$ (5)	–	K_3PO_4 (1.5)	1,4-dioxane	75	**34** (41), **18** (43)
2	$PdCl_2$(dppf) (5)	–	Cs_2CO_3 (2.0)	1,4-dioxane	100	**34** (96)
3	$Pd(OAc)_2$ (5)	PCy_3	KF (3.3)	THF/H_2O (v/v; 12/1)	65	no reaction[c]

[a]Boronic acid (1.2 equiv) was employed. [b]A 15 mol % portion of ligand was employed. [c]Triflate **18** was recovered in 82–98% yield.

Scheme 5. Total Synthesis of Kehokorins D (4) and E (5)



EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under an argon atmosphere, unless otherwise noted. Melting points are uncorrected. IR spectra were recorded by the ATR method. The NMR spectra were recorded at 500 or 600 MHz for ^1H and 125 or 150 MHz for ^{13}C. The ^1H chemical shift was referenced to the residual solvent signal (δ_H 7.26 for $CDCl_3$ or δ_H 2.04 for acetone-d_6). The ^{13}C chemical shift was referenced to the solvent signal (δ_C 77.0 for $CDCl_3$ or δ_C 29.8 for acetone-d_6). High-resolution mass spectra (HRMS) were acquired in electron-impact mode (EI) or field desorption mode (FD) using a time-of-flight mass spectrometer or gas chromatograph time-of-flight mass spectrometer, respectively. The solvent extracts were dried with magnesium sulfate, and the solutions were evaporated under diminished pressure at 35–40 °C.

4,6-Bis(benzyloxy)-3-bromo-2-hydroxybenzaldehyde (14). To a stirred solution of **13** (1.23 g, 3.69 mmol) in dichloromethane (12 mL) was added dropwise bromine (0.19 mL, 3.7 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After being quenched with addition of saturated aqueous $Na_2S_2O_3$, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed successively with saturated aqueous $NaHCO_3$, water, and brine and concentrated. The residue was treated with *n*-hexane–dichloromethane to give **14** (1.33 g, 87%) as a crystalline solid: mp 149–150 °C (*n*-hexane–ethyl acetate); IR (ZnSe) 3031, 2880, 1634, 1604, 1411, 1384, 1293, 1217, 1123, 1092, 722 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 12.94 (1H, s), 10.15 (1H, s), 7.41–7.36 (10H, m), 6.12 (1H, s), 5.19 (2H, s), 5.09 (2H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.8, 162.7, 162.2, 161.5, 135.4, 135.3, 128.9, 128.8, 128.6, 128.4, 127.4, 126.9, 106.8, 91.8, 90.1, 71.1, 71.0; HRMS (EI^+) calcd for $C_{21}H_{17}BrO_4$ $[M]^+$ 412.0310, found 412.0309.

4,6-Bis(benzyloxy)-3-bromo-2-methoxybenzaldehyde (15). To a stirred suspension of **14** (100 mg, 0.24 mmol) and potassium carbonate (60.2 mg, 0.435 mmol) in *N*,*N*-dimethylformamide (0.5 mL) was added iodomethane (40 μL, 0.61 mmol) at rt, and the mixture was stirred at rt for 16 h, diluted with water, and then extracted with ether. The combined organic layers were washed successively with water and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane–ethyl acetate–dichloromethane = 4:1:1) to give **15** (103 mg, quant.) as a crystalline solid: mp 91–92 °C (*n*-hexane–ethyl acetate); IR (ZnSe) 2942, 2871, 1672, 1578, 1198, 1168, 1101, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.36 (1H, s), 7.43–7.33 (10H, m), 6.40 (1H, s), 5.15 (2H, s), 5.11 (2H, s), 3.91 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9, 161.8, 160.7, 160.5, 135.5, 135.2, 128.6, 128.5, 128.22, 128.20, 126.9, 126.8, 114.2, 100.3, 95.2, 71.0, 62.2; HRMS (EI^+) calcd for $C_{22}H_{19}BrO_4$ $[M]^+$ 426.0467, found 426.0469.

4,6-Bis(benzyloxy)-3-(*p*-methoxyphenyl)-2-methoxybenzaldehyde (16). To a stirred mixture of **15** (4.08 g, 9.54 mmol), **11** (2.10 g, 13.8 mmol), potassium phosphate (6.10 g, 28.7 mmol), and XPhos (685 mg, 1.43 mmol) in THF–water (12:1, 165 mL) was added palladium acetate (107 mg, 0.476 mmol), and the mixture was stirred at 65 °C for 7 h, cooled, diluted with water, and then extracted with ethyl acetate. The combined organic layers were washed successively with water and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane–ethyl acetate–dichloromethane = 25:5:1 → 8:2:1) to give **16** (4.07g, 94%) as a crystalline solid: mp 127–128 °C (*n*-hexane–ethyl acetate); IR (ZnSe) 2932, 1683, 1588, 1452, 1373, 1246, 1153, 1097, 1028, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.44 (1H, s), 7.44–7.28 (10H, m), 7.20 (2H, brd, J = 7.3 Hz), 6.95 (2H, brd, J = 8.9 Hz), 6.39 (1H, s), 5.13 (2H, s), 5.04 (2H, s), 3.86 (3H, s), 3.42 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 162.0, 161.8, 161.5, 158.6, 136.08, 136.06, 132.0, 128.7, 128.6, 128.3, 128.1, 128.0, 127.0, 126.5, 124.6, 118.3, 113.3, 94.6, 70.8, 70.4, 61.8, 55.2; HRMS (EI^+) calcd for $C_{29}H_{26}O_5$ $[M]^+$ 454.1780, found 454.1778.

6-(Benzyloxy)-4-hydroxy-2,4′-dimethoxy-[1,1′-biphenyl]-3-carbaldehyde (17). To a stirred solution of **16** (912 mg, 2.00 mmol) in benzene-ether (7:1, 16 mL) was added magnesium bromide ethyl etherate (622 mg, 2.41 mmol) and the mixture was stirred at 80 °C for 2.5 h and then cooled to rt. After addition of 4 M HCl at 0 °C, the resulting mixture was stirred at 0 °C → rt for 12 h and then extracted with ethyl acetate. The combined organic layers were washed successively with water and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane–ether = 6:1 → 4:1) to give **17** (719 mg, 98%) as an amorphous solid: IR (ZnSe) 3027, 2933, 1632, 1607, 1578, 1289, 1245, 1176, 1095, 800, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.26 (1H, s), 10.10 (1H, s), 7.34–7.23 (7H, m), 6.96 (2H, d, J = 8.8 Hz), 6.32 (1H, s), 5.09 (2H, s), 3.86 (3H, s), 3.40 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 164.43, 164.39, 162.0, 158.7, 135.8, 132.0, 128.6, 127.9, 126.5, 124.4, 115.9, 113.5, 109.2, 96.4, 70.3, 62.1, 55.2; HRMS (EI^+) calcd for $C_{22}H_{20}O_5$ $[M]^+$ 364.1311, found 364.1314.

6-(Benzyloxy)-3-formyl-2,4′-dimethoxy-[1,1′-biphenyl]-4-yl Trifluoromethanesulfonate (18). To a stirred solution of **17** (50.5 mg, 0.139 mmol) in *N*,*N*-dimethylformamide (1.3 mL) were added *N*-phenylbis(trifluoromethanesulfonimide) (54.5 mg, 0.152 mmol) and potassium carbonate (21.0 mg, 0.152 mmol) at −17 °C, and the mixture was stirred at −17 °C → rt for 6.5 h, poured into ice–water, and then extracted with ether. The combined organic layers were washed with water (2×) and brine and concentrated to give a white

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J. Org. Chem. XXXX, XXX, XXX–XXX

solid, which was treated with dichloromethane−ether to afford **18** (61.4 mg, 86%) as white needles. The mother liquid was chromatographed on silica gel (*n*-hexane−ethyl acetate = 10:1 → 4:1) to give additional **18** (5.4 mg, 8%) as white needles: mp 163−164 °C (*n*-hexane−ethyl acetate); IR (ZnSe) 3027, 2954, 1692, 1595, 1427, 1189, 1122, 1028, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.28 (1H, s), 7.37−7.22 (7H, m), 7.00 (2H, d, J = 8.9 Hz), 6.67 (1H, s), 5.11 (2H, s), 3.88 (3H, s), 3.44 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.5, 162.9, 161.5, 159.4, 147.7, 135.1, 131.6, 128.7, 128.3, 126.6, 125.2, 122.9, 118.7 (q, J_{CF} = 321.4 Hz), 116.5, 113.7, 103.6, 71.1, 62.5, 55.3; HRMS (EI$^+$) calcd for $C_{23}H_{19}F_3O_7S$ $[M]^+$ 496.0804, found 496.0798.

(5-Chlorobenzo[*d*][1,3]dioxol-4-yl)boronic Acid (20). To a stirred solution of lithium diisopropylamide (LDA) prepared from diisopropylamine (0.77 mL, 5.5 mmol) and *n*-butyllithium (1.6 M in *n*-hexane, 3.43 mL, 5.50 mmol) in tetrahydrofuran (15 mL) was added dropwise a solution of **19** (0.79 g, 5.0 mmol) in tetrahydrofuran (0.6 mL) at −78 °C. After 15 min, triisopropylborate (1.44 mL, 6.25 mL) was added, and the mixture was stirred at −78 °C for 10 min and then gradually warmed to 0 °C over 2 h with stirring. After addition of cold 1 M HCl, the resulting mixture was stirred vigorously for 15 min and then extracted with ethyl acetate. The combined organic layers were washed successively with water and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 4:1 → 2:1 → 1:1) to give **20** (526 mg, 52%) as an amorphous solid: IR (ZnSe) 3325, 2900, 1630, 1430, 1230, 1038, 947, 794 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (1H, d, J = 8.3 Hz), 6.83 (1H, d, J = 8.3 Hz), 6.08 (2H, s), 5.95 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 145.7, 130.2, 123.3, 111.3, 101.7; HRMS (EI$^+$) calcd for $C_7H_6ClO_4B$ $[M]^+$ 200.0048, found 200.0039.

6-(Benzyloxy)-4-(5-chlorobenzo[*d*][1,3]dioxol-4-yl)-2,4′-dimethoxy-[1,1′-biphenyl]-3-carbaldehyde (21). To a stirred mixture of **18** (15 mg, 30 μmol), **20** (8.0 mg, 39 μmol), and potassium phosphate (9.0 mg, 45 μmol) in dioxane (0.5 mL) was added tetrakis(triphenylphosphine)palladium (1.7 mg, 1.4 μmol), and the mixture was stirred at 75 °C for 6.5 h, cooled, and concentrated. The residue was purified by preparative TLC (*n*-hexane−ethyl acetate = 4:1, and then benzene−ether = 30:1, two developments) to give **21** (3.7 mg, 24%) as a foam: IR (ZnSe) 2925, 2853, 1685, 1547, 1438, 1238, 1102, 932, 800, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.21 (1H, s), 7.45 (2H, d, J = 8.8 Hz), 7.31−7.22 (5H, m), 6.99 (2H, d, J = 8.8 Hz), 6.95 (1H, d, J = 8.3 Hz), 6.78 (1H, d, J = 8.3 Hz), 6.74 (1H, s), 5.95 (1H, d, J = 1.5 Hz), 5.94 (1H, d, J = 1.5 Hz), 5.12 (2H, s), 3.88 (3H, s), 3.46 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 162.3, 160.4, 158.9, 146.1, 146.0, 136.0, 135.5, 131.8, 128.5, 127.8, 126.6, 125.15, 125.11, 124.2, 122.0, 121.9, 121.1, 113.4, 111.7, 108.3, 101.8, 70.4, 62.1, 55.2; HRMS (EI$^+$) calcd for $C_{29}H_{23}ClO_6$ $[M]^+$ 502.1183, found 502.1183.

3-Bromo-6-chloro-2-methoxyphenol (24) and 3-Bromo-4-chloro-2-methoxyphenol (25). To a stirred solution of **22** (200 mg, 0.985 mmol) and (*R*)-[1,1′-binaphthalene]-2,2′-diylbis(diphenylphosphine sulfide) (**23**) (68 mg, 99 μmol) in dichloromethane (1 mL) was added *N*-chlorosuccinimide (132 mg, 0.989 mmol) by portions, and the mixture was stirred at rt in the dark for 14 h and then directly poured into a column of silica gel (*n*-hexane). Elution with *n*-hexane−ethyl acetate (1:0 → 20:1 → 10:1) gave **24** (10.7 mg, 5%) and **25** (158 mg, 67%).

24: syrup; IR (ZnSe) 3382, 2952, 1455, 1415, 1201, 1142, 996, 786 cm^{-1}; ^1H NMR (500 MHz,$CDCl_3$) δ 7.03 (1H, d, J = 8.8 Hz), 6.99 (1H, d, J = 8.8 Hz), 5.91 (1H, s), 3.93 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 145.3, 125.8, 124.1, 119.9, 114.8, 61.1; HRMS (EI$^+$) calcd for $C_7H_6BrClO_2$ $[M]^+$ 235.9240, found 235.9243.

25: syrup; IR (ZnSe) 3408, 2940, 1576, 1466, 994, 896, 839, 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (1H, d, J = 8.8 Hz), 6.89 (1H, d, J = 8.8 Hz), 5.68 (1H, brs), 3.91 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 145.6, 126.05, 125.99, 117.1, 115.3, 61.1; HRMS (EI$^+$) calcd for $C_7H_6BrClO_2$ $[M]^+$ 235.9240, found 235.9236.

2-Bromo-1-chloro-3-methoxy-4-(methoxymethoxy)benzene (26). To a stirred solution of **25** (168 mg, 0.707 mmol) and *N*,*N*-diisopropylethylamine (0.22 mL, 1.3 mmol) in dichloromethane (1.5 mL) was added dropwise methoxymethyl chloride (70 μL, 0.92 mmol) at 0 °C, and then the mixture was stirred at 0 °C → rt for 1.2 h. After being quenched with addition of saturated aqueous $NaHCO_3$, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ether = 8:1) to give **26** (180 mg, 90%) as a syrup: IR (ZnSe) 2930, 1468, 1156, 1082, 992, 877 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (1H, d, J = 9.1 Hz), 7.06 (1H, d, J = 9.1 Hz), 5.20 (2H, s), 3.88 (3H, s), 3.51 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 148.8, 128.1, 125.1, 119.0, 116.4, 95.5, 60.7, 56.4; HRMS (EI$^+$) calcd for $C_9H_{10}BrClO_3$ $[M]^+$ 279.9502, found 279.9496.

2-(6-Chloro-2-methoxy-3-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (28). To a stirred solution of **26** (377 mg, 1.34 mmol) in tetrahydrofuran (4.7 mL) was added dropwise a 1.1 M solution of *n*-butyllithium (1.28 mL, 1.41 mmol) in hexane at −78 °C. After 5 min, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**27**) (0.38 mL, 1.9 mmol) was added, and the mixture was stirred at −78 °C for 1 h and then gradually warmed to 0 °C over 1 h with stirring. After addition of water, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine and concentrated. The residue was chromatographed on silica gel (dichloromethane−ether = 200:1 → 0:1) to give **28** (229 mg, 52%) as a syrup: IR (ZnSe) 2976, 1459, 1319, 1254, 1157, 1143, 998 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (1H, d, J = 8.8 Hz), 6.98 (1H, d, J = 8.8 Hz), 5.16 (2H, s), 3.85 (3H, s), 3.48 (3H, s), 1.40 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 148.2, 129.6, 124.7, 119.0, 95.3, 84.6, 61.5, 56.2, 24.7; HRMS (EI$^+$) calcd for $C_{15}H_{22}ClO_5B$ $[M]^+$ 328.1249, found 328.1252.

5′-(Benzyloxy)-6-chloro-2,3′,4″-trimethoxy-3-(methoxymethoxy)-[1,1′:4′,1″-terphenyl]-2′-carbaldehyde (29). To a stirred mixture of **18** (185 mg, 0.372 mmol), **28** (147 mg, 0.447 mmol), and potassium phosphate (119 mg, 0.561 mmol) in dioxane (3.5 mL) was added tetrakis(triphenylphosphine)palladium (34 mg, 29 μmol), and the mixture was stirred at 75 °C for 10 h, cooled, diluted with water, and then extracted with ethyl acetate. The combined organic layers were washed successively with water and brine and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 10:1 → 8:1 → 6:1) to give **29** (169 mg, 82%) as a foam: IR (ZnSe) 2934, 2833, 1685, 1547, 1463, 1364, 1244, 1114, 1002, 805, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.20 (1H, s), 7.49 (2H, d, J = 8.8 Hz), 7.31−7.21 (5H, m), 7.16 (1H, d, J = 8.8 Hz), 7.14 (1H, d, J = 8.8 Hz), 7.01 (2H, d, J = 8.8 Hz), 6.65 (1H, s), 5.26 (1H, d, J = 6.6 Hz), 5.23 (1H, d, J = 6.6 Hz), 5.12 (1H, d, J = 11.3 Hz), 5.08 (1H, d, J = 11.3 Hz), 3.88 (3H, s), 3.56 (3H, s), 3.55 (3H, s), 3.48 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 162.1, 160.3, 158.9, 149.1, 147.9, 138.4, 136.1, 134.1, 131.9, 128.4, 127.7, 126.5, 125.8, 124.6, 124.4, 122.0, 116.8, 113.3, 111.5, 95.4, 70.3, 62.1, 60.7, 56.3, 55.2; HRMS (FD$^+$) calcd for $C_{31}H_{29}ClO_7$ $[M]^+$ 548.1602, found 548.1605.

8-(Benzyloxy)-1,6-dimethoxy-2-(methoxymethoxy)-7-(4-methoxyphenyl)dibenzo[*b*,*d*]furan (30). To a stirred suspension of **29** (43 mg, 78 μmol) and $NaHCO_3$ (33 mg, 0.39 mmol) in dichloromethane (1.2 mL) was added dropwise a solution of *m*CPBA (70−75% assay; 100 mg, ca. 400 μmol) in dichloromethane (1.5 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. After being quenched with saturated aqueous $Na_2S_2O_3$, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed successively with saturated aqueous $NaHCO_3$, water, and brine, dried, and concentrated to give a solid (47.7 mg) which was dissolved in pyridine (2.5 mL). Cu_2O (56.2 mg, 0.393 mmol) was added, and the mixture was heated under reflux with stirring for 5 h, cooled, and then filtered through a pad of Celite. The filtrate was concentrated to give a solid, which was chromatographed on silica gel (*n*-hexane−ethyl acetate = 5:1 → 4:1) to give **30** (21.4 mg, 54%) as an amorphous solid: IR (ZnSe) 2933, 1497, 1427, 1245, 1070, 1050, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43−7.41 (3H, m), 7.31−7.22 (7H, m), 7.00 (2H, brd, J = 8.8 Hz), 5.25 (2H, s), 5.08 (2H, s), 4.01 (3H, s), 3.95 (3H, s), 3.88 (3H, s), 3.59 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 152.9, 152.8, 145.15, 145.10, 143.4, 142.9, 137.4, 132.1, 128.4, 127.5, 126.9, 126.2, 123.6, 123.5, 118.8, 118.1, 113.3, 107.0, 101.9,

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J. Org. Chem. XXXX, XXX, XXX−XXX

96.9, 71.6, 61.0, 60.8, 56.4, 55.2; HRMS (EI$^+$) calcd for $C_{30}H_{28}O_7$ [M]$^+$ 500.1835, found 500.1835.

8-(Benzyloxy)-1,6-dimethoxy-2-hydroxy-7-(4-methoxyphenyl)dibenzo[*b*,*d*]furan (7). Treatment of **30** (40.4 mg, 80.7 μmol) in dichloromethane (1.5 mL) with a 10% HCl solution in methanol (1.5 mL) at rt for 1 h gave, after evaporation, a solid, which was diluted with ethyl acetate; washed successively with saturated aqueous $NaHCO_3$, water, and brine; and concentrated. The residue was chromatographed on silica gel (*n*-hexane−ethyl acetate = 4:1) to give **7** (36.8 mg, quant.) as an amorphous solid: IR (ZnSe) 3390, 2925, 1428, 1245, 1070, 1029, 803, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (2H, brd, *J* = 8.8 Hz), 7.31−7.28 (6H, m), 7.24 (1H, brd, *J* = 8.8 Hz), 7.07 (1H, brd, *J* = 8.8 Hz), 7.01 (2H, d, *J* = 8.8 Hz), 5.46 (1H, s), 5.08 (2H, s), 3.96 (3H, s), 3.91 (3H, s), 3.89 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 152.8, 151.5, 144.1, 143.6, 143.1, 140.4, 137.4, 132.0, 128.4, 127.6, 126.9, 126.1, 123.8, 122.6, 117.7, 115.0, 113.3, 107.9, 101.9, 71.8, 61.2, 60.8, 55.2; HRMS (EI$^+$) calcd for $C_{28}H_{24}O_6$ [M]$^+$ 456.1573, found 456.1579.

Kehokorin B (2). To a stirred solution of **7** (4.5 mg, 10 μmol) in methanol (0.3 mL) was added 10% palladium on carbon (1.0 mg). The mixture was stirred vigorously under a hydrogen atmosphere at rt for 5 h, filtered through a pad of Celite, and then concentrated. The residue was chromatographed on silica gel (benzene−ethyl acetate = 20:1) to give **2** (3.4 mg, 94%) as an amorphous solid: IR (ZnSe) 3513, 3392, 2939, 2832, 1498, 1427, 1248, 1164, 1056, 953 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.39 (1H, s), 7.36 (2H, brd, *J* = 8.8 Hz), 7.19 (1H, d, *J* = 8.8 Hz), 7.06 (1H, d, *J* = 8.8 Hz), 6.98 (2H, brd, *J* = 8.8 Hz), 4.02 (3H, s), 3.90 (3H, s), 3.84 (3H, s); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.8, 152.0, 151.9, 145.9, 143.7, 143.2, 142.5, 133.0, 127.1, 124.5, 121.9, 119.0, 117.3, 114.1, 107.6, 103.2, 60.9, 60.7, 55.5; HRMS (EI$^+$) calcd for $C_{21}H_{18}O_6$ [M]$^+$ 366.1103, found 366.1114.

Glycoside 32. To a stirred suspension of **7** (36.8 mg, 80.6 μmol), **31** (109 mg, 0.176 mmol), and MS4A (130 mg) in dichloromethane (4.0 mL) was added trimethylsilyl trifluoromethanesulfonate (0.01 mL, 0.06 μmol) at −20 °C. After 30 min, more trimethylsilyl trifluoromethanesulfonate (0.01 mL, 0.06 μmol) was added and stirring was continued for additional 15 min. Triethylamine (0.11 mL, 0.79 mmol) was added, and the mixture was stirred at −10 °C for 15 min and then concentrated. The residue was passed through a short column of silica gel (*n*-hexane−ethyl acetate = 8:1 → 4:1) to give a solid (88.7 mg) which was dissolved in methanol−dichloromethane (2:1, 1.5 mL). A 1.0 M solution of sodium methoxide in methanol (0.02 mL) was added at rt, and the mixture was stirred at rt for 1 h, made neutral with Dowex 50W X-8 (H$^+$) resin, and filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel (chloroform−methanol = 100:1 → 50:1 → 20:1) to give **32** (42.4 mg, 87%) as an amorphous solid: $[\alpha]_D^{25}$ −49 (*c* 0.41, $CHCl_3$); IR (ZnSe) 3406, 2973, 2912, 1236, 1087, 878 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (2H, brd, *J* = 8.8 Hz), 7.31 (1H, s), 7.25−7.14 (7H, m), 6.97 (2H, brd, *J* = 8.8 Hz), 5.56 (1H, brs), 4.98 (2H, s), 4.39 (1H, brs), 4.20 (1H, brd, *J* = 7.8 Hz), 4.04 (1H, m), 3.93 (3H, s), 3.89 (3H, s), 3.86 (3H, s), 3.76 (1H, m), 1.39 (3H, d, *J* = 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 153.0, 152.9, 144.8, 144.2, 143.4, 142.9, 137.3, 132.0, 128.3, 127.5, 126.9, 126.0, 123.8, 123.1, 119.0, 117.7, 113.3, 107.2, 101.7, 100.3, 73.2, 71.8, 71.5, 71.2, 69.3, 61.1, 60.7, 55.2, 17.6; HRMS (FD$^+$) calcd for $C_{34}H_{34}O_{10}$ [M]$^+$ 602.2152, found 602.2125.

Kehokorin A (1). According to the method described for the preparation of **2** from **7**, compound **32** (12 mg, 20 μmol) was hydrogenated over 10% palladium on carbon (2.0 mg) in methanol−ethyl acetate (5:2, 0.7 mL) for 7 h and upon purification by chromatography on silica gel (dichloromethane−methanol =100:1 → 50:1 → 10:1) gave **1** (9.4 mg, 92%) as an amorphous solid: $[\alpha]_D^{25}$ −54 (*c* 0.31, methanol); lit.[13a] $[\alpha]_D^{25}$ −49 (*c* 0.50, methanol); IR (ZnSe) 3406, 2919, 1236, 1088, 884, 830 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.00 (1H, brs), 7.42 (1H, s), 7.37 (1H, d, *J* = 8.8 Hz), 7.36 (2H, d, *J* = 8.8 Hz), 7.29 (1H, d, *J* = 8.8 Hz), 6.98 (2H, d, *J* = 8.8 Hz), 5.47 (1H, s), 4.19 (1H, brs), 4.07 (3H, s), 3.94 (1H, brdd, *J* = 9.3, 2.5 Hz), 3.91 (3H, s), 3.89 (1H, m), 3.84 (3H, s), 3.53 (1H, t, *J* = 9.3 Hz), 1.23 (3H, d, *J* = 6.1 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.8, 153.7, 152.3, 146.2, 145.6, 143.7, 143.2, 133.0, 127.0, 124.5, 122.2, 119.4, 119.3, 114.1, 107.5, 103.3, 101.9, 73.6, 72.5, 71.9, 70.5, 61.3, 60.8, 55.5, 18.1; HRMS (FD$^+$) calcd for $C_{27}H_{28}O_{10}$ [M]$^+$ 512.1683, found 512.1693.

5,5′-Bis(benzyloxy)-2-chloro-3′,4″-dimethoxy-[1,1′:4′,1″-terphenyl]-2′-carbaldehyde (34). To a stirred mixture of **18** (15 mg, 30 μmol), **33** (9.5 mg, 36 μmol), and cesium carbonate (20 mg, 61 μmol) in dioxane (0.5 mL) was added $PdCl_2$(dppf) (1.8 mg, 2.4 μmol), and the mixture was stirred at 100 °C for 10 h, cooled, and then concentrated. The residue was directly chromatographed on silica gel (*n*-hexane−ethyl acetate = 8:1 → 4:1 → 0:1) to give **34** (16.4 mg, 96%) as a foam: IR (ZnSe) 3061, 3031, 2933, 2833, 1685, 1547, 1452, 1243, 1166, 1011, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ10.12 (1H, s), 7.47−7.22 (8H, m), 7.00 (2H, brd, *J* = 8.5 Hz), 6.96 (1H, dd, *J* = 8.8, 3.2 Hz), 6.87 (1H, d, *J* = 3.2 Hz), 6.66 (1H, s), 5.10, 5.08 (2H, each d, *J* = 12.2 Hz), 5.04 (2H, s), 3.88 (3H, s), 3.48 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 161.6, 160.3, 158.9, 157.2, 142.6, 139.7, 136.4, 136.0, 131.9, 130.0, 128.6, 128.5, 128.1, 127.8, 127.6, 126.6, 124.8, 124.4, 124.3, 121.8, 116.8, 115.6, 113.4, 111.1, 70.4, 70.3, 62.0, 55.2; HRMS (FD$^+$) calcd for $C_{35}H_{29}ClO_5$ [M]$^+$ 564.1704, found 564.1741.

2,8-Bis(benzyloxy)-4-methoxy-3-(4-methoxyphenyl)-dibenzo[*b*,*d*]furan (35). As described for the preparation of **30** from **29**, treatment of **34** (42.7 mg, 75.6 μmol) with *m*CPBA (70−75% assay; 37 mg, ca. 0.15 mmol) in dichloromethane (0.66 mL) afforded the corresponding formate (44.1 mg), which was treated with Cu_2O (54.0 mg, 378 μmol) in pyridine (2.7 mL) at 110 °C for 4 h. The usual workup followed by chromatography on silica gel (benzene−ethyl acetate = 50:0 → 20:1) gave **35** (16.5 mg, 42%) as an amorphous solid: IR (ZnSe) 3066, 3031, 2942, 2834, 1601, 1430, 1246, 1182, 1151, 1027, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.24 (14H, m), 7.21 (1H, s), 7.12 (1H, dd, *J* = 8.8, 2.5 Hz), 6.99 (2H, d, *J* = 8.6 Hz), 5.17 (2H, s), 5.07 (2H, s), 3.98 (3H, s), 3.88 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 154.9, 152.8, 151.5, 143.9, 143.2, 137.3, 137.0, 132.1, 128.6, 128.4, 128.0, 127.6, 127.5, 126.8, 126.2, 124.9, 124.7, 123.7, 116.0, 113.2, 112.3, 104.9, 99.3, 71.5, 71.0, 60.8, 55.2; HRMS (EI$^+$) calcd for $C_{34}H_{28}O_5$ [M]$^+$ 516.1937, found 516.1943.

Kehokorin C (3). According to the method described for the preparation of **2** from **7**, compound **35** (14.3 mg, 27.7 μmol) was hydrogenated over 10% palladium on carbon (4.0 mg) in tetrahydrofuran (1.0 mL) for 23 h and upon purification by preparative TLC (benzene−ethyl acetate = 10:1, three developments) gave **3** (7.6 mg, 81%) as an amorphous solid: IR (ZnSe) 3533, 3370, 2930, 2850, 1173, 1147, 1047, 796 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (1H, d, *J* = 8.8 Hz), 7.36 (2H, brd, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 2.4 Hz), 7.17 (1H, s), 7.07 (2H, brd, *J* = 8.8 Hz), 6.96 (1H, dd, *J* = 8.8, 2.4 Hz), 4.92 (1H, s), 4.76 (1H, brs), 4.01 (3H, s), 3.89 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 151.5, 151.2, 149.3, 142.9, 142.5, 131.9, 125.5, 125.1, 124.2, 119.9, 115.5, 114.8, 112.2, 106.2, 99.8, 60.8, 55.3; HRMS (EI$^+$) calcd for $C_{20}H_{16}O_5$ [M]$^+$ 336.0998, found 336.1004.

4,6-Bis(benzyloxy)-3-phenyl-2-methoxybenzaldehyde (37). According to the procedure described for the preparation of **16**, a mixture of **15** (50.0 mg, 0.117 mmol) and **36** (20.0 mg, 0.164 mmol) in THF−water (12:1, 2.0 mL) was treated with palladium acetate (1.3 mg, 5.7 μmol) in the presence of potassium phosphate (75 mg, 0.35 mmol) and XPhos (8.5 mg, 18 μmol) at 65 °C for 10 h. The usual workup followed by chromatography on silica gel (benzene−ethyl acetate = 100:1 → 50:1) gave **37** (44.5 mg, 89%) as an amorphous solid: IR (ZnSe) 2931, 2856, 1672, 1579, 1173, 1096, 1009, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.44 (1H, s), 7.46−7.40 (8H, m), 7.37−7.28 (5H, m), 7.19 (2H, brd, *J* = 8.1 Hz), 6.40 (1H, s), 5.14 (2H, s), 5.04 (2H, s), 3.43 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.0, 161.83, 161.75, 161.7, 136.0, 132.5, 130.9, 128.7, 128.55, 128.47, 128.12, 128.06, 127.9, 127.8, 127.2, 127.0, 126.4, 118.7, 113.2, 94.5, 70.8, 70.3, 61.9; HRMS (EI$^+$) calcd for $C_{28}H_{24}O_4$ [M]$^+$ 424.1675, found 424.1665.

6-(Benzyloxy)-4-hydroxy-2-methoxy-[1,1′-biphenyl]-3-carbaldehyde (38). According to the procedure described for the

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J. Org. Chem. XXXX, XXX, XXX−XXX

preparation of **17**, compound **37** (338 mg, 0.796 mmol) was treated with magnesium bromide ethyl etherate (268 mg, 1.04 mmol) in benzene−ether (7:1, 16 mL) at 80 °C for 3 h. The usual workup followed by chromatography on silica gel (*n*-hexane−ethyl acetate = 1:0 → 15:1) gave **38** (235 mg, 88%) as a crystalline solid: mp 120−121 °C (*n*-hexane−ether); IR (ZnSe) 3024, 2939, 2867, 1603, 1362, 1265, 1172, 1052, 1004, 943, 811, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.28 (1H, s), 10.11 (1H, s), 7.44−7.26 (8H, m), 7.21 (2H, brd, J = 8.1 Hz), 6.33 (1H, s), 5.10 (2H, s), 3.40 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 164.6, 164.3, 162.0, 135.8, 132.4, 131.0, 128.5, 128.0, 127.9, 127.3, 126.5, 116.4, 109.2, 96.5, 70.3, 62.3; HRMS (EI^+) calcd for $C_{21}H_{18}O_4$ $[M]^+$ 334.1205, found 334.1195.

6-(Benzyloxy)-3-formyl-2-methoxy-[1,1′-biphenyl]-4-yl Trifluoromethanesulfonate (39). According to the procedure described for the preparation of **18**, compound **38** (181 mg, 0.541 mmol) was treated with *N*-phenylbis(trifluoromethanesulfonimide) (213 mg, 0.596 mmol) and potassium carbonate (82 mg, 0.60 mmol) at −20 °C for 3.5 h. The usual workup followed by chromatography on silica gel (dichloromethane−ether = 1:0 → 15:1) gave **39** (253 mg, quant.) as a crystalline solid: mp 146−148 °C (*n*-hexane−ethyl acetate); IR (ZnSe) 3061, 2947, 2897, 1692, 1595, 1427, 1200, 1117, 1036, 987, 843, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.29 (1H, s), 7.50−7.43 (5H, m), 7.36−7.29 (3H, m), 7.23 (2H, brd, J = 7.8 Hz), 6.70 (1H, s), 5.12 (2H, s), 3.44 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.5, 162.9, 161.4, 148.0, 135.0, 131.0, 130.3, 128.7, 128.4, 128.3, 128.2, 128.1, 126.5, 125.5, 118.6 (q, J_{CF} = 320.5 Hz), 116.4, 103.5, 71.0, 62.7; HRMS (EI^+) calcd for $C_{22}H_{17}F_3O_6S$ $[M]^+$ 466.0698, found 466.0689.

5,5′-Bis(benzyloxy)-2-chloro-3′-methoxy-[1,1′:4′,1″-terphenyl]-2′-carbaldehyde (41). According to the procedure described for the preparation of **34**, a mixture of **39** (50.0 mg, 0.107 mmol) and **33** (37.0 mg, 0.139 mmol) in dioxane (1.6 mL) was treated with $PdCl_2$(dppf) (6.3 mg, 8.6 μmol) in the presence of cesium carbonate (70 mg, 0.21 mmol) at 95 °C for 4 h. The usual workup followed by chromatography on silica gel (*n*-hexane−ethyl acetate = 100:0 → 20:1 → 10:1) gave **41** (50.7 mg, 88%) as a crystalline solid: mp 134−135 °C (*n*-hexane−ethyl acetate); IR (ZnSe) 3031, 2939, 1684, 1546, 1371, 1266, 1145, 1013, 733 cm^{-1}; H NMR (500 MHz, $CDCl_3$) δ 10.13 (1H, s), 7.52 (2H, brd, J = 8.6 Hz), 7.48−7.34 (9H, m), 7.32−7.25 (3H, m), 7.20 (2H, brd, J = 8.3 Hz), 6.97 (1H, dd, J = 8.8, 3.2 Hz), 6.89 (1H, d, J = 3.2 Hz), 6.67 (1H, s), 5.11, 5.08 (2H, each d, J = 12.5 Hz), 5.05 (2H, s), 3.49 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 161.5, 160.1, 157.3, 143.0, 139.7, 136.4, 136.0, 132.3, 130.7, 130.0, 128.6, 128.5, 128.1, 127.9, 127.8, 127.56, 127.52, 126.5, 125.2, 124.4, 121.7, 116.8, 115.6, 111.1, 70.3, 62.2; HRMS (FD^+) calcd for $C_{34}H_{27}ClO_4$ $[M]^+$ 534.1598, found 534.1566.

2,8-Bis(benzyloxy)-4-methoxy-3-phenyldibenzo[*b*,*d*]furan (43). According to the procedure described for the preparation of **30**, treatment of **41** (36.7 mg, 68.6 μmol) with *m*CPBA (70−75% assay; 84 mg, ca. 0.34 mmol) in the presence of $NaHCO_3$ (29 mg, 0.34 mmol) in dichloromethane (2.7 mL) afforded the corresponding formate (31.9 mg), which was treated with Cu_2O (40.5 mg, 283 μmol) in pyridine (1.7 mL) at 110 °C for 4 h. The usual workup followed by chromatography on silica gel (benzene−ethyl acetate = 100:1) gave **43** (14.2 mg, 50%) as an amorphous solid: IR (ZnSe) 2926, 2851, 1602, 1478, 1448, 1424, 1264, 1182, 1150, 1016, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52−7.37 (12H, m), 7.32−7.21 (6H, m), 7.13 (1H, dd, J = 8.9, 2.5 Hz), 5.18 (2H, s), 5.07 (2H, s), 3.99 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 152.7, 151.5, 143.8, 143.1, 137.2, 137.0, 134.1, 131.0, 128.6, 128.3, 128.0, 127.7, 127.6, 127.5, 127.1, 126.7, 125.0, 124.9, 124.0, 116.1, 112.4, 104.9, 99.2, 71.5, 71.0, 60.8; HRMS (EI^+) calcd for $C_{33}H_{26}O_4$ $[M]^+$ 486.1831, found 486.1852.

Kehokorin D (4). According to the method described for the preparation of **2**, compound **43** (10.1 mg, 20.8 μmol) was hydrogenated over 10% palladium on carbon (2.8 mg) in tetrahydrofuran (0.6 mL) for 19 h, and purification by preparative TLC (*n*-hexane−ethyl acetate = 1:1, two developments) gave **4** (5.0 mg, 79%) as an amorphous solid: IR (ZnSe) 3386, 2942, 1609, 1479, 1426, 1180, 1146, 1051, 799, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (2H, brt, J = 7.8 Hz), 7.47−7.41 (4H, m), 7.31 (1H, d, J = 2.7 Hz), 7.18 (1H, s), 6.96 (1H, dd, J = 8.8, 2.7 Hz), 4.91 (1H, s), 4.88 (1H, s), 4.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 151.3, 149.1, 142.8, 142.4, 132.5, 130.7, 129.3, 128.4, 125.8, 125.0, 120.2, 115.6, 112.2, 106.2, 100.1, 60.8; HRMS (EI^+) calcd for $C_{19}H_{14}O_4$ $[M]^+$ 306.0892, found 306.0880.

5′-Benzyloxy-2-chloro-5,3′-dimethoxy-[1,1′:4′,1″-terphenyl]-2′-carbaldehyde (42). According to the procedure described for the preparation of **34**, a mixture of **39** (50.0 mg, 0.107 mmol) and **40** (26.0 mg, 0.139 mmol) in dioxane (1.6 mL) was treated with $PdCl_2$(dppf) (6.3 mg, 8.6 μmol) in the presence of cesium carbonate (70 mg, 0.21 mmol) at 95 °C for 10 h. The usual workup followed by chromatography on silica gel (*n*-hexane−ethyl acetate = 15:1 → 8:1) gave **42** (36.5 mg, 74%) as a crystalline solid: mp 136−138 °C (*n*-hexane−ether); IR (ZnSe) 3029, 2935, 1684, 1542, 1366, 1137, 1020, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.12 (1H, s), 7.52 (2H, brd, J = 8.0 Hz), 7.47 (2H, brt, J = 7.9 Hz), 7.40 (1H, m), 7.36 (1H, d, J = 8.8 Hz), 7.32−7.25 (3H, m), 7.20 (2H, brd, J = 8.0 Hz), 6.89 (1H, dd, J = 8.8, 2.9 Hz), 6.79 (1H, d, J = 2.9 Hz), 6.69 (1H, s), 5.13, 5.09 (2H, each d, J = 12.0 Hz), 3.81 (3H, s), 3.49 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 161.4, 160.1, 158.0, 143.1, 139.6, 136.0, 132.3, 130.7, 129.9, 128.4, 128.0, 127.8, 127.5, 126.5, 125.2, 124.1, 121.7, 115.9, 114.7, 111.1, 70.3, 62.2, 55.5; HRMS (FD^+) calcd for $C_{28}H_{23}ClO_4$ $[M]^+$ 458.1285, found 458.1289.

2-Benzyloxy-4,8-dimethoxy-3-phenyldibenzo[*b*,*d*]furan (44). According to the procedure described for the preparation of **30**, treatment of **42** (33.9 mg, 73.9 μmol) with *m*CPBA (70−75% assay; 90 mg, ca. 0.37 mmol) in the presence of $NaHCO_3$ (31.0 mg, 369 μmol) in dichloromethane (2.7 mL) afforded the corresponding formate (38.2 mg), which was treated with Cu_2O (53.0 mg, 369 μmol) in pyridine (2.0 mL) at 110 °C for 5 h. The usual workup followed by chromatography on silica gel (*n*-hexane−ethyl acetate−dichloromethane = 20:2:1) gave **44** (16.8 mg, 55%) as an amorphous solid: IR (ZnSe) 2934, 2831, 1602, 1480, 1422, 1265, 1183, 1149, 1064, 1027, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50−7.45 (5H, m), 7.40−7.37 (1H, m), 7.37 (1H, d, J = 2.7 Hz), 7.32−7.22 (6H, m), 7.06 (1H, dd, J = 9.1, 2.7 Hz), 5.08 (2H, s), 4.00 (3H, s), 3.93 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 152.7, 151.3, 143.8, 143.1, 137.2, 134.1, 130.9, 128.3, 127.7, 127.5, 127.0, 126.7, 125.0, 124.9, 123.9, 115.3, 112.3, 103.3, 99.2, 71.5, 60.8, 56.0; HRMS (EI^+) calcd for $C_{27}H_{22}O_4$ $[M]^+$ 410.1518, found 410.1512.

Kehokorin E (5). According to the method described for the preparation of **2**, compound **44** (11.6 mg, 28.3 μmol) was hydrogenated over 10% palladium on carbon (3.0 mg) in tetrahydrofuran (0.7 mL) for 16 h, and purification by chromatography on silica gel (*n*-hexane−ethyl acetate = 5:1) gave **5** (7.6 mg, 84%) as an amorphous solid: IR (ZnSe) 3419, 2936, 2831, 1586, 1481, 1422, 1267, 1188, 1146, 1026, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (2H, brt, J = 7.5 Hz), 7.47−7.44 (4H, m), 7.35 (1H, d, J = 2.7 Hz), 7.21 (1H, s), 7.05 (1H, dd, J = 9.0, 2.7 Hz), 4.90 (1H, brs), 4.03 (3H, s), 3.92 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 151.4, 149.1, 142.7, 142.3, 132.5, 130.7 129.3, 128.4, 126.1, 124.7, 120.0, 115.5, 112.2, 103.6, 99.9, 60.8, 56.0; HRMS (EI^+) calcd for $C_{20}H_{16}O_4$ $[M]^+$ 320.1049, found 320.1045.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00147.

NMR spectra of **1**−**5**, **7**, **14**−**18**, **20**, **21**, **24**−**26**, **28**−**30**, **32**, **34**, **35**, **37**−**39**, and **41**−**44** and 2D NMR spectra of **14** (PDF)

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J. Org. Chem. XXXX, XXX, XXX−XXX

Notes

The authors declare no competing financial interest.

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