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Synthesis of Tofogliflozin as an SGLT2 Inhibitor via Construction of Dihydroisobenzofuran by Intramolecular [4 + 2] Cycloaddition

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Supporting Information

ABSTRACT: The synthesis of tofogliflozin (**1**), a sodium glucose cotransporter 2 (SGLT2) inhibitor, was achieved through the key steps of intramolecular [4 + 2] cycloaddition of dienone-yne intermediate, aerobic aromatization, and anomeric equilibration, thus enabling the construction of a dihydroisobenzofuran moiety of **1**. Subsequent hydrogenolysis followed by global deprotection afforded the desired compound **1**. The divergent synthesis of the anomer of **1** (**15**) is also described.

KEYWORDS: *tofogliflozin, [4 + 2] cycloaddition, dienone-yne, dihydroisobenzofuran*

INTRODUCTION

Tofogliflozin (**1**) is a spirocyclic *C*-arylglycoside which functions as a sodium glucose cotransporter 2 (SGLT2) inhibitor for the treatment of diabetes.[1] Several reports of the synthesis of **1** have recently appeared in the literature.[2] In all of these cases, halogen−metal exchange reactions were used to form a *C*-glycosidic bond between an aromatic ring and a sugar moiety, and construction of a dihydroisobenzofuran moiety in **1** was attained by cyclization under acidic conditions, while a diarylmethyl moiety was prepared in various ways.[2] All syntheses reported to date have used such halogen−metal exchange reactions to produce **1**. In contrast, we focused our attention on cycloaddition reactions to synthesize **1**. Recently, syntheses of spirocyclic *C*-arylglycosides by the [2 + 2 + 2] cycloaddition of three alkyne units have become well-known,[3] and transition metals such as Rh and Ru have been used as representative catalysts for the formation of a dihydroisobenzofuran moiety. Although the application of these cycloaddition reactions to **1** seems like a good method for constructing a dihydroisobenzofuran moiety, it requires control of the regioselectivity of alkyne addition. Furthermore, the removal of residual transition metal could also be troublesome in practical manufacturing. The [4 + 2] cycloaddition of dienone-yne compounds is another powerful tool for the formation of a dihydroisobenzofuran moiety. Intramolecular cycloaddition reactions of ether-tethered diene-yne compounds are known to afford Diels−Alder adducts and/or dihydroisobenzofuran as an aromatized product under thermal conditions.[4] Base-catalyzed cyclization of an ether-tethered diene-yne compound has also been reported.[5] While these examples demonstrate intramolecular reactions between a diene and yne moiety, little is known about cyclization where dienone compounds are used to form a dihydroisobenzofuran moiety.[6] Herein we describe the synthesis of **1** via [4 + 2] cyclization of a dienone-yne compound.

RESULTS AND DISCUSSION

We intended to construct a dihydroisobenzofuran moiety of **1** by the [4 + 2] cycloaddition of a diene-yne compound **3** followed by oxidation (Figure 1). To realize our intention, dienone was chosen as a diene component, because it can be readily prepared by transformation of alkynone compounds.[7] Hydrogenolysis of the carbonyl group of cyclized product **2** followed by deprotection would afford the desired product **1**. Thus, the precursor to [4 + 2] cyclization adduct, dienone-yne **3**, was planned to be prepared from dienylmethyl alcohol **4** and acetoxypyranose **5** (Figure 2).

Dienylmethyl alcohol **4** was prepared from commercially available 4-pentyn-1-ol (**6**) as shown in Scheme 1. Protection of the hydroxyl group of **6** was carried out by treatment with 2-methoxypropene and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) to give acetal **7**. The acylation of the terminal alkyne of **7** with *p*-ethylbenzoyl chloride by use of triethylamine, copper(I) iodide, and dichlorobis(triphenylphosphine)palladium(II) gave **8**.[7] Transformation of alkynone **8** to dienone by use of triphenylphosphine and phenol afforded dienone **9**;[8] however, a side product, which was deduced to be phenol adduct **10** by ^{1}H NMR and mass spectra, was produced in 6% yield. In order to suppress its formation, we turned to bulkier and less nucleophilic phenol. Thus, by using 2,6-dimethylphenol, we avoided the phenol adduct and obtained dienone **9** as a single geometric isomer of *E,E*-configuration as judged by the ^{1}H NMR coupling constants of each proton pair (J = 15.0 Hz, 15.5 Hz). Removal of triphenylphosphine, as a triphenylphosphine oxide, was attained by filtration after treatment with sodium hypochlorite. This workup process was efficient for large scale synthesis since it did not require column chromatography. Finally, deprotection afforded the desired dienylmethyl alcohol **4**. It is noted that these reactions were carried out by telescoping in a 76% yield over the four

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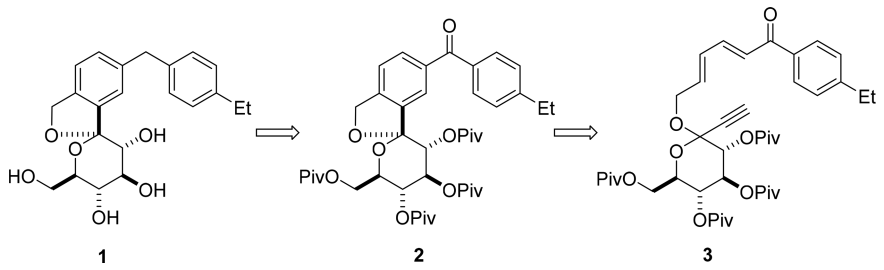


Figure 1. Retrosynthesis of tofogliflozin (**1**).

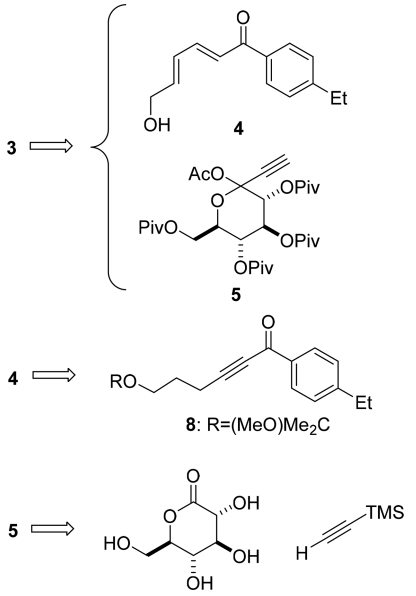


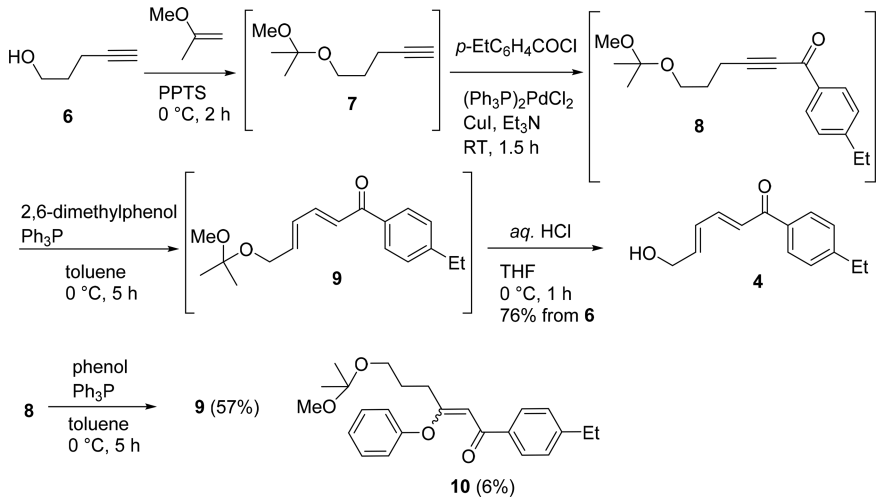
Figure 2. Retrosynthesis of dienone-yne **3**.

steps (calculated by ^{1}H NMR spectra with an internal standard), and the product **4** was sufficiently pure to be used without purification in the next step.

Acetoxypyranose **5** was prepared from commercially available gluconolactone (**11**) as shown in Scheme 2. First, hydroxyl groups of **11** were protected as pivaloyl esters to afford **12** because the bulky protecting group was expected to be stable in the next nucleophilic addition. Thus, this lactone was subjected to 1,2-addition by lithium trimethylsilylacetylide,[3a,c,9] and the resulting alkoxide was trapped by acetic anhydride. When toluene was used as a solvent, the conversion was moderate. We found that the reaction led to completion by adding tetramethylethylenediamine (TMEDA):[10] acetate **13** was afforded as a six-membered pyranose form with a 64% yield after recrystallization from heptane−toluene. The configuration of anomeric carbon was not determined at this stage. The influence of the reaction temperature and variation in mixing time was minimal (Table 1). Mixing time had little influence on the chemical yield of **13** before adding acetic anhydride (entries 1−3 in Table 1). When the reaction temperature was changed from −20 to 0 °C, almost the same yields were obtained (entry 1 vs 4 in Table 1). These results indicated that the initial alkoxide anion was stable under the reaction conditions. This stability would be favorable for scale-up because a longer addition time is often required to control the temperature increase in the large scale synthesis. Removal of the trimethylsilyl group of **13** by use of KF afforded **5** in 80% isolated yield.

With the desired dienylmethyl alcohol **4** and acetoxypyranose **5** in hand, we examined the reaction conditions of glycosylation (Table 2).[3a,11] The reaction with boron trifluoride etherate (BF_3·OEt_2) in acetonitrile at 0 °C proceeded smoothly and led to 97% conversion after 3 h affording diene-yne **3** as an anomeric mixture of **3-*α*** and **3-*β*** (entry 1 in Table 2), while the reaction without an acid at 0 °C did not afford the desired product. The ratio of the anomer was calculated from the integration of proton peaks of alkyne in ^{1}H NMR (^{1}H NMR: δ 2.58 for **3-*α***; δ 2.90 for **3-*β***). The stereochemistry of anomeric carbon was determined by

Scheme 1. Preparation of Dienylmethyl Alcohol 4



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Scheme 2. Preparation of Acetoxypyranose 5

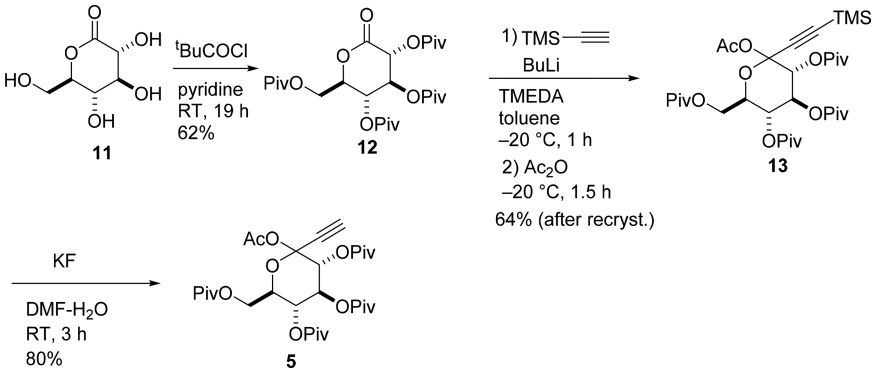
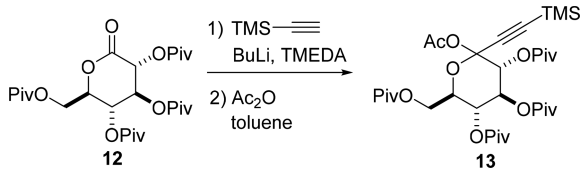


Table 1. 1,2-Addition of Trimethylsilylacetylene to Lactone 12 in the Presence of TMEDA[a]

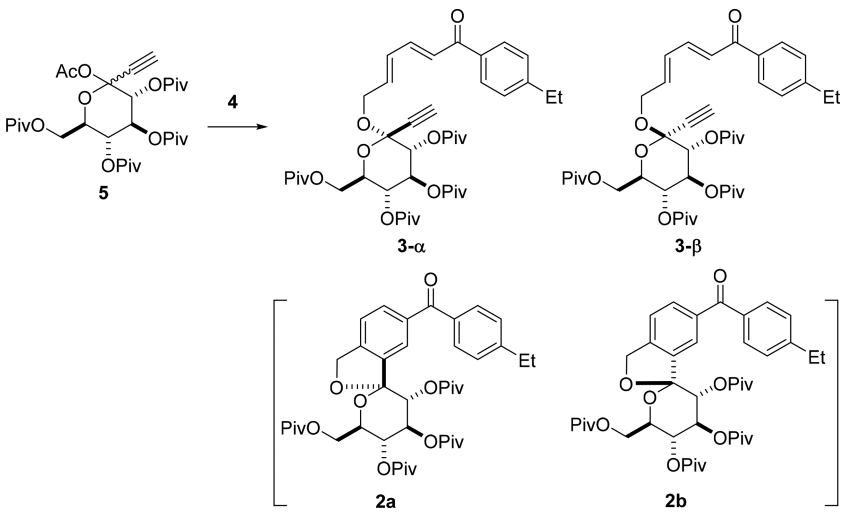


entry	temp (°C)	mixing time (h)[b]	yield[c] (%)
1	−20	0.5	80
2	−20	2	80
3	−20	4	79
4	0	0.5	83

[a]All reactions were carried out by use of BuLi (1.4 equiv), trimethylsilylacetylene (1.5 equiv), and TMEDA (1.5 equiv) in toluene. [b]Time before adding acetic anhydride. [c]Determined by ^{1}H NMR spectra with 1,3,5-trimethoxybenzene as an internal standard.

correlation with [4 + 2] cycloaddition products **2a** and **2b** in the next step (the reaction affording **2a** and **2b**: *vide infra*). When the reaction was carried out at 0 °C for a short time or at −20 °C in acetonitrile (entries 2 and 3 in Table 2), the conversion was low. The reaction in toluene also resulted in low conversion (entry 4 in Table 2). When trimethylsilyl triflate (TMSOTf) was used as an acid in acetonitrile, the anomer **3-*α*** increased in comparison to the reaction catalyzed by $BF_3{\cdot}OEt_2$, and [4 + 2] cycloaddition products **2** were newly produced, suggesting that TMSOTf promoted not only glycosylation but also cycloaddition (entry 5 in Table 2). Although the reaction with $BF_3{\cdot}OEt_2$ afforded only **3-*α*** and **3-*β*** as shown in entry 1, cycloaddition products **2a** and **2b** were partially observed during storage. Thus, the reaction mixture of **3-*α*** and **3-*β*** obtained by $BF_3{\cdot}OEt_2$ (entry 1 in Table 2) was then subjected to the next cycloaddition step without purification for the synthesis of **1**.

Table 2. Glycosylation of 5[a]



entry	solvent	acid	temp (°C)	reaction time (h)	conv[b] (%)	Ratio[c] **3-*α*/3-*β*/2a/2b**
1	MeCN	$BF_3{\cdot}OEt_2$	0	3	97	61:39:0:0
2	MeCN	$BF_3{\cdot}OEt_2$	0	0.17	40	59:41:0:0
3	MeCN	$BF_3{\cdot}OEt_2$	−20	3	19	52:48:0:0
4	toluene	$BF_3{\cdot}OEt_2$	0	3	63	54:46:0:0
5	MeCN	TMSOTf	0	3	97	59:22:18:1
6	toluene	TMSOTf	0	3	–[d]	–[d]

[a]All reactions were carried out by use of 1 equiv of **4** and 3 equiv of acid. [b]Ratio of products to staring material. [c]Determined by the integration of proton peak of terminal alkyne in ^{1}H NMR spectra. [d]Complex mixture.

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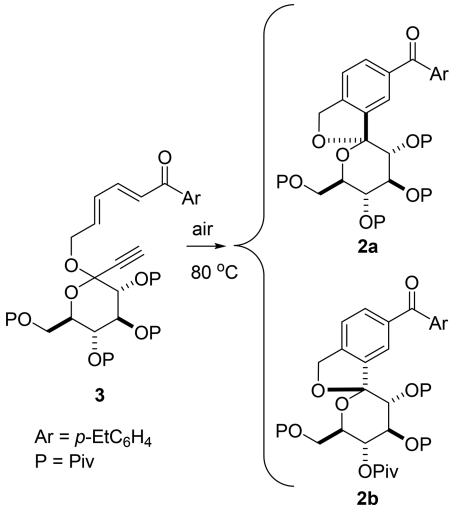
Results of the [4 + 2] cycloaddition of **3** and successive anomeric equilibration were summarized in Tables 3 and 4,

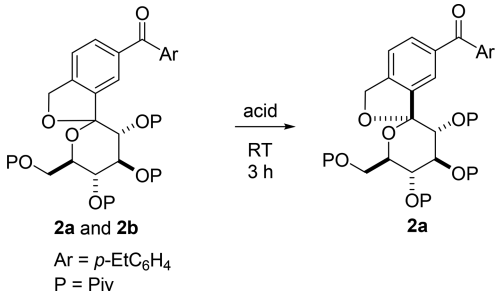
Table 3. Intramolecular [4 + 2] Cycloaddition[a]



entry	solvent	reaction time (h)	Ratio[b] 3/2a/2b
1	MeCN	1	3:60:37
2	MeCN	7	0:61:39
3	CPME	1	23:52:25
4	CPME	7	0:62:38
5	toluene	1	22:53:25
6	toluene	7	0:61:39

[a]All reactions were carried out at 80 °C under aerobic conditions. Starting material **3** (**3-α**:**3-β** = 61:39, calculated by ^{1}H NMR) was used; see entry 1 in Table 2. [b]Calculated by peak areas in LC/MS.

Table 4. Anomeric Equilibration of 2[a]



entry	solvent	Lewis acid	2a (%)[b]	2b (%)[b]
1	MeCN	BF_3·OEt_2	82	19
2	CPME	BF_3·OEt_2	51	31
3	toluene	BF_3·OEt_2	94	0
4	toluene	TfOH	93	0
5	toluene	$ZnCl_2$	52	36

[a]The reaction was carried out by use of acid (1 equiv) at room temperature for 3 h. A mixture of **2a** and **2b** (61:39) obtained from the [4 + 2] cycloaddition in toluene was used as starting material; see entry 6 in Table 3. [b]Determined by ^{1}H NMR spectra with 1,3,5-trimethoxybenzene as an internal standard.

respectively. The ratio of starting material **3** and cyclized products (**2a** and **2b**) was analyzed by LC/MS. As shown in Table 3, [4 + 2] cyclization of **3** proceeded smoothly in acetonitrile at 80 °C for 1 h under aerobic conditions, and air oxidation afforded aromatic compounds **2a** and **2b** as an anomeric mixture (entry 1 in Table 3). Ratio of **2a** and **2b** was almost the same as that of **3-α** and **3-β** used as a mixture of starting materials, suggesting that interconversion of isomers did not take place under neutral, thermally activated conditions. The reaction in CPME or toluene under the same conditions also gave **2a** and **2b**, but a considerable amount of starting material **3** remained (entries 3 and 5 in Table 3). These results demonstrated that acetonitrile accelerates cycloaddition−oxidation, although a long reaction time (7 h) led to completion in each solvent used (acetonitrile, CPME, or toluene: entries 2, 4, and 6 in Table 3). On the other hand, acetonitrile was found to be inefficient for the isomerization of **2b** to **2a** as shown in Table 4.[12] When the mixture of **2a** and **2b** (61:39) was treated with BF_3·OEt_2 in acetonitrile, the undesired **2b** remained at 19% yield after 3 h (entry 1 in Table 4). The reaction in CPME also did not lead to completion (entry 2 in Table 4). The complete conversion of **2b** to **2a** was accomplished by treatment with BF_3·OEt_2 in toluene at room temperature for 3 h to afford **2a** as a single stereoisomer in 94% yield (entry 3 in Table 4). Trifluoromethanesulfonic acid (TfOH) was also effective in toluene (entry 4 in Table 4). Zinc chloride did not work sufficiently—probably due to its low solubility in toluene (entry 5 in Table 4). These findings suggested that toluene was a suitable solvent for the cyclization−isomerization telescoping process.

Considering these results, the glycosylation of **5** in acetonitrile and successive [4 + 2] cyclization−isomerization in toluene were carried out by the telescoping process (Scheme 3). After recrystallization from methanol, **2a** was obtained in 52% isolated yield from **5**. The hydrogenolysis of **2a** was attained by use of $Pd(OH)_2$ under balloon pressure of hydrogen to give **14a** (68% isolated yield after crystallization from isopropanol−H_2O), the hydrolysis of which afforded the desired compound **1** in 60% isolated yield after recrystallization from acetone−H_2O.

Next, we focused our attention on the synthesis of the anomer of **1**, because having access to a stereoisomer of the final API would be valuable for validation of analytical methods. The [4 + 2] cyclization described above was able to form the spiro-ring under neutral conditions where both anomers **2a** and **2b** were afforded. Thus, we planned to separate the anomers after the [4 + 2] cyclization and synthesize the anomer of **1** as shown in Scheme 4. As expected, separation of **2b** from the mixture of **2a** and **2b** was feasible by column chromatography to afford **2b** in 20% yield from **5**. Hydrogenolysis of **2b** by use of $Pd(OH)_2$ proceeded smoothly to give **14b** in 55% isolated yield. Finally, hydrolysis of **14b** with lithium hydroxide afforded the anomer **15** in 76% isolated yield. The stereochemistry of **15** was confirmed by COSY and NOESY experiments (Figure 3). The doublet methine proton H_b of the tetrahydropyran moiety showed a correlation signal to the H_c proton in the COSY experiment. The H_a proton of aromatic ring was observed to have a correlation signal to the H_c proton and also showed a correlation signal to the H_d proton in the NOESY experiment.

CONCLUSION

The synthesis of tofogliflozin **1** was achieved by the [4 + 2] cyclization as a key reaction. It was found that the intramolecular [4 + 2] cycloaddition of a dienone-yne compound **3** under aerobic conditions successfully resulted in the construction of a dihydroisobenzofuran moiety of **1**. Thus, the desired compound **1** was synthesized in 12 total steps in 5% overall yield. Although there is room for

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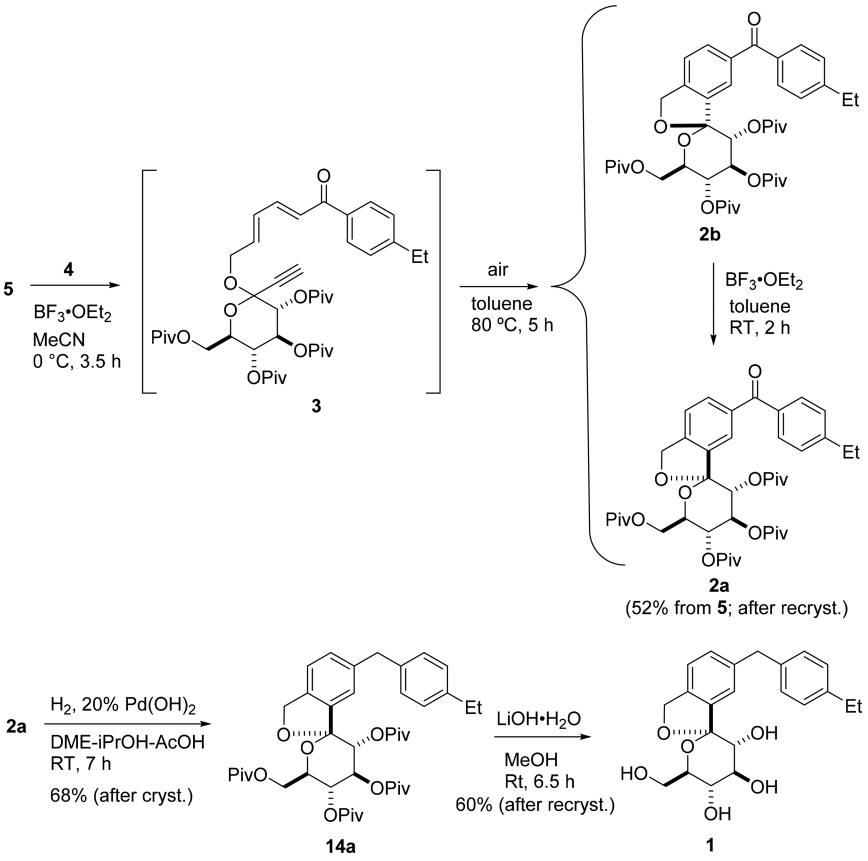
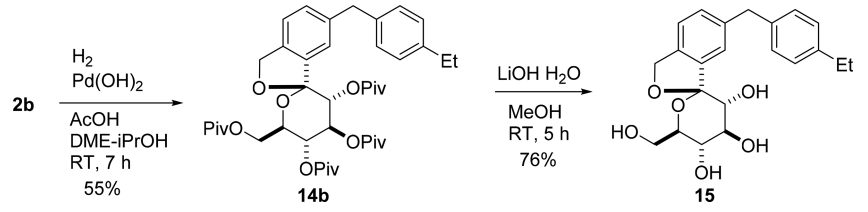
Scheme 3. Synthesis of 1 *via* Intramolecular [4 + 2] Cycloaddition



Scheme 4. Synthesis of the Anomer of 1



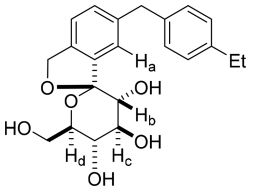


Figure 3. Structure of **15**.

improvement for the number of reaction steps and yield of each reaction in comparison with a previous method in the literature,[2a−e] the present study demonstrates a new methodology for the synthesis of **1**, which was performed under noncryogenic conditions to afford the desired product **1** with high diastereomeric purity without column chromatography purification. This synthetic method also allowed preparation of the anomer of **1**, which was of value in the validation of analytical methods for the final API.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Melting points were measured by differential scanning calorimetry (DSC) (Mettler Toledo). FTIR spectra were recorded on an FT/IR-480 plus (JASCO) spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a JNM-ECP 500 (JEOL) spectrophotometer with tetramethylsilane or the solvent resonance as an internal standard. COSY and NOESY experiments were performed with a JNM-ECZ500R (JEOL) spectrophotometer. Mass spectra were measured on an LC/MS [Ultimate3000 (LC)/Q-Exactive (MS) or Vanquish (LC)/Fusion Lumos (MS)] (Thermo Fisher) system. Specific rotation was measured on a AUTOPOL IV (Rudolph Research Analytical) digital polarimeter. Column chromatography was performed on silica gel. Routine LC/MS analysis was performed on ACQUITY UPLC H-Class with a QDa mass detector (Waters).

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*5-((2-Methoxypropan-2-yl)oxy)pent-1-yne (**7**).* To a mixture of 4-pentyn-1-ol (14.9 g, 177.3 mmol) and 2-methoxypropene (170 mL, 1.78 mol) was added pyridinium *p*-toluenesulfonate (8.9 mg, 0.036 mmol) at 0 °C, followed by stirring at 0 °C for 2 h. The resulting solution was used in the next step without workup. For the collection of analytical data, the reaction mixture was poured into aqueous $NaHCO_3$, and then the resulting mixture was extracted with *tert*-butyl methyl ether (MTBE). The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography (heptane−AcOEt) to afford **7** as a colorless oil. FTIR (cm^{-1}, neat) 3297, 2991, 2942, 2117, 1434, 1371, 1259, 1211, 1184, 1151, 1078, 1051. ^1H NMR (500 MHz, $CDCl_3$) δ 3.49 (t, J = 6.0 Hz, 2H), 3.20 (s, 3H), 2.30 (dt, J = 7.0, 2.0 Hz, 2H), 1.95 (t, J = 2.0 Hz, 1H), 1.77 (quin, J = 7.0 Hz, 2H), 1.34 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.8, 84.0, 68.4, 58.9, 48.4, 28.9, 24.4 (C × 2), 15.4. HRMS (ESI+) calcd for $C_9H_{16}O_2Na$ $[M + Na]^+$, 179.1043; found, 179.1043.

*1-(4-Ethylphenyl)-6-((2-methoxypropan-2-yl)oxy)hex-2-yn-1-one (**8**).* To the solution of **7** obtained above (starting from 14.9 g of 4-pentyn-1-ol) were added successively triethylamine (247.0 mL, 1.78 mol), copper(I) iodide (1.02 g, 5.34 mmol), and dichlorobis(triphenylphosphine)palladium-(II) (1.25 g, 1.78 mmol). To the resulting mixture *p*-ethylbenzoyl chloride (26.2 mL, 177.9 mmol) was added dropwise at room temperature, followed by stirring for 1.5 h. After addition of saturated $NaHCO_3$ at 0 °C, the resulting mixture was extracted with heptane. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product as an oil (52.7 g). This oil was used in the next step without purification. For the collection of analytical data, the oil was purified by column chromatography (0.1% Et_3N−toluene−AcOEt) to afford **8** as a colorless oil. FTIR (cm^{-1}, neat) 2937, 1641, 1604, 1571, 1459, 1415, 1371, 1309, 1265, 1211, 1178, 1151, 1078, 1051. ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 3.55 (t, J = 6.5 Hz, 2H), 3.21 (s, 3H), 2.72 (q, J = 7.5 Hz, 2H), 2.62 (t, J = 6.5 Hz, 2H), 1.92 (quin, J = 6.5 Hz, 2H), 1.36 (s, 6H), 1.26 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 151.1, 134.8, 129.8, 128.0, 99.9, 95.5, 79.8, 58.8, 48.5, 29.0, 28.3, 24.4 (C × 2), 16.3, 15.1. HRMS (ESI+) calcd for $C_{18}H_{24}O_3Na$ $[M + Na]^+$, 311.1618; found, 311.1617.

*(2E,4E)-1-(4-Ethylphenyl)-6-((2-methoxypropan-2-yl)oxy)-hexa-2,4-dien-1-one (**9**).* The oil **8** (52.7 g) obtained above was dissolved in toluene (465 mL). Next, a solution of 2,6-dimethylphenol (22.5 g, 184.2 mmol) and triphenylphosphine (24.2 g, 92.3 mmol) at 0 °C in toluene (110 mL) was added dropwise, followed by stirring for 5 h. After addition of aqueous NaOH (1M, 400 mL) at 0 °C, the resulting mixture was stirred at room temperature for 0.5 h. The layers were separated, and the organic layer was washed with water. To the resulting organic layer was added a solution of aqueous NaOCl at 0 °C, followed by stirring for 0.5 h. The layers were separated, and the organic layer was washed with water and saturated NaCl successively and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was taken up in heptane (400 mL) followed by stirring at 0 °C for 1 h. After filtration, to the filtrate was added heptane (400 mL), and the mixture was then washed with a solution composed of acetonitrile (350 mL), water (700 mL), and triethylamine (20 mL), and then washed with saturated NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product as an oil (46.9 g). This oil was used in the next step without purification. For analytical data, the oil was purified by column chromatography (0.1% Et_3N−toluene−AcOEt) to afford **9** as a colorless oil. FTIR (cm^{-1}, neat) 2989, 1662, 1631, 1589, 1457, 1413, 1378, 1332, 1257, 1332, 1257, 1211, 1182, 1149, 1101, 1064, 1027, 1006. ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2H), 7.43 (dd, J = 15.0, 11.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 15.0 Hz, 1H), 6.59−6.54 (m, 1H), 6.29 (dt, J = 15.5, 5.0 Hz, 1H), 4.12 (dd, J = 5.0, 2.0 Hz, 2H), 3.22 (s, 3H), 2.72 (q, J = 7.5 Hz, 2H), 1.40 (s, 6H), 1.27 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 149.8, 143.8, 140.7, 135.8, 129.0, 128.7, 128.2, 125.3, 100.4, 60.7, 48.7, 29.0, 24.5 (C × 2), 15.3. HRMS (APCI+) calcd for $C_{18}H_{25}O_3$ $[M + H]^+$, 289.1798; found, 289.1073.

*(2E,4E)-1-(4-Ethylphenyl)-6-hydroxyhexa-2,4-dien-1-one (**4**).* The oil **9** (46.9 g) obtained above was dissolved in THF (470 mL). To this solution was added aqueous HCl (0.25 M, 235 mL) at 0 °C, and then the resulting mixture was stirred for 1 h. After addition of saturated $NaHCO_3$ at 0 °C, the resulting mixture was extracted with AcOEt. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **4** as an amorphous solid (35.3 g, 84% purity; 76% yield from 4-pentyn-1-ol). The purity of the crude solid was assayed by ^1H NMR spectrum with 1,3,5-trimethoxybenzene as an internal standard. This amorphous solid **4** was used in the next step without purification. For the collection of analytical data, the amorphous solid was purified by column chromatography (heptane−AcOEt) to afford **4** as a pale yellow powder. Mp 62.6 °C. FTIR (cm^{-1}, neat) 3291, 2966, 1654, 1627, 1604, 1581, 1452, 1413, 1334, 1249, 1180, 1155, 1089, 1006. ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2H), 7.43 (dd, J = 15.0, 11.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 15.0 Hz, 1H), 6.60−6.54 (m, 1H), 6.34 (dt, J = 15.5, 5.0 Hz, 1H), 4.35−4.34 (m, 2H), 2.72 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 149.8, 143.4, 142.1, 135.7, 128.7, 128.5, 128.1, 125.6, 62.8, 29.0, 15.2. HRMS (ESI+) calcd for $C_{14}H_7O_2$ $[M + H]^+$, 217.1223; found, 217.1224.

*1-(4-Ethylphenyl)-6-((2-methoxypropan-2-yl)oxy)-3-phenoxyhex-2-en-1-one (**10**).* The reaction was carried out by the same method described above (preparation of **9**) except that phenol was used insted of 2,6-dimethylphenol. The crude product was purified by column chromatography (heptane−AcOEt) to afford **10** as a pale yellow oil (6% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 8.5 Hz, 2H), 7.46−7.42 (m, 2H), 7.28−7.25 (m, 1H: overlap with $CHCl_3$), 7.17 (d, J = 8.5 Hz, 2H), 7.09 (dd, J = 9.0, 1.0 Hz, 2H), 5.95 (s, 1H), 3.57 (t, J = 7.0 Hz, H), 3.22 (s, 3H), 3.12−3.09 (m, 2H), 2.64 (q, J = 7.5 Hz, 2H), 2.09−2.03 (m, 2H), 1.36 (s, 6H), 1.20 (t, J = 7.5 Hz, 3H). HRMS (APCI+) calcd for $C_{24}H_{30}O_4Na$ $[M + Na]^+$, 405.2036; found, 405.2051.

*(3R,4S,5R,6R)-2-Oxo-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (**12**).* To a solution of gluconolactone (50.5 g, 283.4 mmol) in pyridine (454 mL) was added pivaloyl chloride (350 mL, 2.84 mol) at −10 °C over 1.5 h, followed by stirring at room temperature for 19 h. The resulting mixture was poured into aqueous HCl (2 M, 500 mL), and the product was extracted with AcOEt and heptane. The organic layer was washed with aqueous HCl.

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After the phase separation, to the organic layer was added AcOEt, and the mixture was washed with water, saturated $NaHCO_3$, and aqueous NaCl, successively, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was recrystallized (heptane−toluene) to afford **12** (98.6 g) which contained residual pivalic acid. To remove the residual pivalic acid, the product was dissolved to toluene and washed with saturated $NaHCO_3$ and aqueous NaCl. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford **12** as colorless needles (90.1 g, 62%). Mp 161.6 °C. $[\alpha]^{20}_D$ +82.7 (*c* 1.07, CH_2Cl_2). FTIR (cm^{-1}, neat) 2971, 1774, 1735, 1479, 1278, 1130. ^1H NMR (500 MHz, $CDCl_3$) δ 5.65 (t, *J* = 9.0 Hz, 1H), 5.44 (t, *J* = 9.0 Hz, 1H), 5.02 (d, *J* = 9.0 Hz, 1H), 4.68−4.65 (m, 1H), 4.31−4.25 (m, 2H), 1.23 (s, 18H), 1.17 (s, 9H), 1.16 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 177.5, 176.8, 176.1, 164.8, 75.7, 70.9, 70.0, 65.3, 61.0, 38.9, 38.8, 38.71, 38.66, 27.1 (C × 3), 26.99 (C × 3), 26.95 (C × 3), 26.8 (C × 3). HRMS (ESI+) calcd for $C_{26}H_{46}O_{10}N$ $[M + NH_4]^+$, 532.3116; found, 532.3125.

*(3R,4S,5R,6R)-2-Acetoxy-6-((pivaloyloxy)methyl)-2-((trimethylsilyl)ethynyl)tetrahydro-2H-pyran-3,4,5-triyl Tris-(2,2-dimethylpropanoate) (**13**).* To a solution of trimethylsilylacetylene (36.3 mL, 262.6 mmol) and *N,N,N′N′*-teteramethylethylenediamine (39.7 mL, 263.1 mmol) in toluene (450 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 153 mL, 244.8 mmol) at −20 °C over 3 h,[13] which was followed by stirring at −20 °C for 1 h. The resulting mixture was added to a solution of lactone **12** (90.1 g, 175.1 mmol) in toluene (450 mL) at −20 °C over 20 min. After the mixture stirred for 1 h, acetic anhydride (49.7 mL, 525.8 mmol) was added at −20 °C. The mixture was stirred again at −20 °C for 1.5 h. The reaction was then quenched with saturated NH_4Cl. The resulting mixture was extracted with AcOEt. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was recrystallized from hexane to afford **13** as colorless needles (73.7 g, 64%). Mp 130.8 °C. $[\alpha]^{20}_D$ +97.5 (*c* 1.02, CH_2Cl_2). FTIR (cm^{-1}, neat) 2968, 1776, 1743, 1479, 1367, 1278, 1209, 1162, 1124, 1064, 1041. ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (t, *J* = 10.0 Hz, 1H), 5.23 (d, *J* = 10.0 Hz, 1H), 5.15 (t, *J* = 10.0 Hz, 1H), 4.25−4.21 (m, 2H), 4.10 (dd, *J* = 12.5, 5.0 Hz, 1H), 2.02 (s, 3H), 1.24 (s, 9H), 1.19 (s, 9H), 1.17 (s, 9H), 1.11 (s, 9H), 0.27 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 176.9, 176.5, 176.4, 166.4, 98.9, 95.3, 93.9, 72.3, 71.9, 71.0, 67.0, 61.4, 38.9, 38.74, 38.71 (C × 2), 27.12, 27.09, 27.0, 26.9, 21.4, −0.5. HRMS (ESI+) calcd for $C_{33}H_{58}O_{11}NSi$ $[M + NH_4]^+$, 672.3774; found, 672.3752.

*(3R,4S,5R,6R)-2-Acetoxy-2-ethynyl-6-((pivaloyloxy)-methyl)tetrahydro-2H-pyran-3,4,5-triyl Tris(2,2-dimethyl-propanoate) (**5**).* To a solution of **13** (73.7 g, 112.5 mmol) in DMF (1900 mL)−H_2O (120 mL) was added potassium fluoride (9.84 g, 168.7 mmol) at room temperature, followed by stirring at room temperature for 3 h. After addition of saturated $NaHCO_3$ at 0 °C, the resulting mixture was extracted with cyclopentyl methyl ether. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was crystallized from *tert*-butyl methyl ether to afford **5** as colorless needles (51.9 g, 80%). Mp 195.6 °C. $[\alpha]^{20}_D$ +69.7 (*c* 1.09, CH_2Cl_2). FTIR (cm^{-1}, neat) 3282, 2973, 2119, 1770, 1731, 1479, 1367, 1278, 1218, 1135, 1064, 1035. ^1H NMR (500 MHz, $CDCl_3$) δ 5.49 (t, *J* = 10.0 Hz, 1H), 5.26 (d, *J* = 10.0 Hz, 1H), 5.18 (t, *J* = 10.0 Hz, 1H), 4.25 (ddd, *J* = 10.0, 5.0, 1.5 Hz, 1H), 4.21 (dd, *J* = 12.5, 1.5 Hz, 1H), 4.14 (dd, *J* = 12.5, 5.0 Hz, 1H), 2.99 (s, 1H), 2.04 (s, 3H), 1.24 (s, 9H), 1.19 (s, 9H), 1.16 (s, 9H), 1.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 177.0, 176.5, 176.4, 166.5, 93.8, 80.1, 74.5, 72.3, 71.9, 70.8, 67.0, 61.3, 38.9, 38.76, 38.74, 38.73, 27.11 (C × 3), 27.08 (C × 3), 27.02 (C × 3), 26.9 (C × 3), 21.3. HRMS (ESI+) calcd for $C_{30}H_{50}O_{11}N$ $[M + NH_4]^+$, 600.3378; found, 600.3390.

*(2S,3R,4S,5R,6R)-2-(((2E,4E)-6-(4-Ethylphenyl)-6-oxohexa-2,4-dien-1-yl)oxy)-2-ethynyl-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl Tris(2,2-dimethylpropanoate) (**3-α**) and (2R,3R,4S,5R,6R)-2-(((2E,4E)-6-(4-Ethylphenyl)-6-oxohexa-2,4-dien-1-yl)oxy)-2-ethynyl-6-((pivaloyloxy)methyl)-tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethyl-propanoate) (**3-β**).* To a suspension of **5** (25.1 g, 43.0 mmol) and dienol **4** (84% purity; 11.2 g, 43.2 mmol) in acetonitrile (426 mL) was added boron trifluoride etherate (16.2 mL, 129.0 mmol) at 0 °C, followed by stirring at 0 °C for 3.5 h. After addition of saturated $NaHCO_3$ at 0 °C, the resulting mixture was extracted with AcOEt. The organic layer was washed with aqueous NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product containing **3** as an anomeric mixture consisting of **3-α** and **3-β** as an oil (39.0 g). The crude product was used for the next reaction without purification. ^1H NMR spectrum was measured immediately after workup. The ratio of **3-α** to **3-β** was calculated by the integration of the proton peak of the terminal alkyne in the ^1H NMR spectrum to be 61:39. **3-α**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 15.0, 11.0 Hz, 1H, olefin), 7.04 (d, *J* = 15.0 Hz, 1H, olefin), 6.68−6.62 (m, 1H, olefin), 6.30 (dt, *J* = 15.0, 5.0 Hz, 1H, olefin), 2.58 (s, 1H, alkyne). HRMS (ESI+) calcd for $C_{42}H_{59}O_{11}$ $[M + H]^+$, 739.4052; found, 739.4055. **3-β**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 15.5, 11.5 Hz, 1H, olefin), 6.96 (d, *J* = 15.0 Hz, 1H, olefin), 6.50−6.45 (m, 1H, olefin), 6.20 (dt, *J* = 15.0, 4.5 Hz, 1H, olefin), 2.90 (s, 1H, alkyne). HRMS (ESI+) calcd for $C_{42}H_{59}O_{11}$ $[M + H]^+$, 739.4052; found, 739.4053. Due to overlap (**3-α**, **3-β**, and slight amount of starting materials), other proton signals in the ^1H NMR spectrum were not assignable. For ^1H NMR spectrum of **3**: see Supporting Information.

*(1S,3′R,4′S,5′R,6′R)-6-(4-Ethylbenzoyl)-6′-((pivaloyloxy)-methyl)-3′,4′,5′,6′-tetrahydro-3H-spiro[isobenzofuran-1,2′-pyran]-3′,4′,5′-triyl Tris(2,2-dimethylpropanoate) (**2a**) and (1R,3′R,4′S,5′R,6′R)-6-(4-ethylbenzoyl)-6′-((pivaloyloxy)-methyl)-3′,4′,5′,6′-tetrahydro-3H-spiro[isobenzofuran-1,2′-pyran]-3′,4′,5′-triyl tris(2,2-dimethylpropanoate) (**2b**).* The crude product **3** (37.8 g out of 39.0 g) obtained above was dissolved in toluene (1130 mL) at room temperature. The mixture was warmed to 80 °C and stirred for 5 h under aerobic conditions. This reaction was carried out in a separable flask equipped with a Dimroth condenser under an air atmosphere.[14] The solvent was removed under reduced pressure to give **2a** and **2b** as an anomeric mixture (35.2 g). The ratio of **2a** and **2b** was determined by LC/MS to be 61:39 (column: Ascentis Express C18, 2.7 μm, 5.0 cm × 4.6 mm; 0.05% TFA−water with 0.05% TFA−MeCN, gradient operation; flow rate, 1.0 mL/min; **3-α**: *Rt* 11.5 min, *m/z* 761.4 $[M + Na]^+$; **3-β**: *Rt* 11.8 min, *m/z* 761.4 $[M + Na]^+$; **2a**: *Rt* 12.0 min, *m/z* 759.3 $[M + Na]^+$; **2b**: *Rt* 11.4 min, *m/z* 759.3 $[M + Na]^+$). This product was used for the next step without further purification. **2a**: *vide infra*. Analytical sample of **2b** was prepared by

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purification through column chromatography (toluene−AcOEt). **2b**: colorless oil. $[\alpha]^{20}_{D}$ +62.4 (*c* 1.17, CH_2Cl_2). FTIR (cm^{-1}, neat) 2969, 1741, 1660, 1608, 1479, 1461, 1280, 1132, 1033. ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (brs, 1H), 7.94 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.67 (t, *J* = 9.5 Hz, 1H), 5.51 (d, *J* = 9.5 Hz, 1H), 5.33 (t, *J* = 9.5 Hz, 1H), 5.32 (d, *J* = 14.0 Hz, 1H), 5.03 (d, *J* = 14.0 Hz, 1H), 4.19−4.02 (m, 3H), 2.75 (q, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.5 Hz, 3H), 1.14 (s, 9H), 1.12 (s, 9H), 1.07 (s, 9H), 0.88 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 178.0, 176.9, 176.5, 176.2, 149.9, 145.2, 137.4, 135.8, 134.5, 131.6, 130.5 (C × 2), 128.1(C × 2), 125.0, 121.7, 109.5, 72.1, 72.0, 71.4, 70.2, 68.0, 62.1, 38.7 (C × 2), 38.6, 38.5, 29.0, 27.13 (C × 3), 27.06 (C × 3), 27.0 (C × 3), 26.9 (C × 3), 15.1. HRMS (ESI+) calcd for $C_{42}H_{57}O_{11}$ $[M + H]^+$, 737.3895; found, 737.3903.

*(1S,3′R,4′S,5′R,6′R)-6-(4-Ethylbenzoyl)-6′-((pivaloyloxy)-methyl)-3′,4′,5′,6′-tetrahydro-3H-spiro[isobenzofuran-1,2′-pyran]-3′,4′,5′-triyl Tris(2,2-dimethylpropanoate) (**2a**).* The mixture of **2a** and **2b**, which was obtained by the above-described procedure (17.6 g out of 35.2 g), was dissolved in toluene (420 mL) at room temperature. To this solution was added boron trifluoride etherate (3.0 mL, 23.9 mmol) at 0 °C, followed by stirring at room temperature for 2 h. After addition of saturated $NaHCO_3$ at 0 °C, the resulting mixture was extracted with AcOEt. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was recrystallized from methanol to afford **2a** as a white powder (8.2 g, 52% from **5**). Mp 172.6 °C. $[\alpha]^{20}_{D}$ +34.5 (*c* 1.00, CH_2Cl_2). FTIR (cm^{-1}, neat) 2966, 1743, 1726, 1656, 1606, 1479, 1280, 1160, 1139, 1087, 1014. ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 5.73 (t, *J* = 10.0 Hz, 1H), 5.60 (d, *J* = 10.0 Hz, 1H), 5.34 (t, *J* = 10.0, Hz, 1H), 5.31 (d, *J* = 13.5 Hz, 1H), 5.25 (d, *J* = 13.5 Hz, 1H), 4.39 (ddd, *J* = 10.0, 4.0, 2.0 Hz, 1H), 4.15 (dd, *J* = 12.5, 2.0 Hz, 1H), 4.09 (dd, *J* = 12.5, 4.0 Hz, 1H), 2.76 (q, *J* = 7.5 Hz, 2H), 1.31 (t, *J* = 7.5 Hz, 3H), 1.18 (s, 9H), 1.17 (s, 9H), 1.12 (s, 9H), 0.82 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 178.0, 177.0, 176.5, 176.4, 149.7, 144.2, 138.1, 135.6, 134.5, 131.9, 130.5 (C × 2), 127.9 (C × 2), 124.9, 121.0, 108.9, 72.9, 70.85, 70.78, 70.5, 67.8, 61.6, 38.8, 38.71, 38.66, 38.5, 28.9, 27.2 (C × 3), 27.05 (C × 3), 27.03 (C × 3), 26.6 (C × 3), 15.1. HRMS (ESI+) calcd for $C_{42}H_{57}O_{11}$ $[M + H]^+$, 737.3895; found, 737.3901.

*(1S,3′R,4′S,5′R,6′R)-6-(4-Ethylbenzyl)-6′-((pivaloyloxy)-methyl)-3′,4′,5′,6′-tetrahydro-3H-spiro[isobenzofuran-1,2′-pyran]-3′,4′,5′-triyl Tris(2,2-dimethylpropanoate) (**14a**).* A solution of **2a** (8.02 g, 10.9 mmol) in DME (48 mL)−isopropanol (32 mL)−AcOH (160 μL) was hydrogenated over 20% $Pd(OH)_2$ on carbon (50% wet, 1.6 g) under H_2 at room temperature for 7 h. After filtration, the solvent was removed under reduced pressure. To the residue was added saturated $NaHCO_3$, and then the resulting mixture was extracted with AcOEt. The organic layer was washed with saturated NH_4Cl and saturated NaCl, successively, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was crystallized from isopropanol−H_2O to afford **14a** as a white powder (5.4 g, 68%). Mp 82.4 °C. $[\alpha]^{20}_{D}$ +33.0 (*c* 1.00, CH_2Cl_2). FTIR (cm^{-1}, neat) 2967, 1739, 1479, 1459, 1280, 1133, 1018. ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (brs, 1H), 7.17 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 5.70 (t, *J* = 10.0 Hz, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 5.37 (dd, *J* = 10.5, 10.0 Hz, 1H), 5.21 (d, *J* = 12.5 Hz, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 4.37 (ddd, *J* = 10.5, 4.0, 2.0 Hz, 1H), 4.16 (dd, *J* = 12.5, 2.0 Hz, 1H), 4.10 (dd, *J* = 12.5, 4.0 Hz, 1H), 3.93 (s, 2H), 2.60 (q, *J* = 8.0 Hz, 2H), 1.203 (s, 9H), 1.200 (t, *J* = 8.0 Hz, 3H), 1.17 (s, 9H), 1.11 (s, 9H), 0.71 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 177.0, 176.5, 176.4, 142.0, 141.5, 138.0, 137.9, 135.9, 130.9, 128.6 (C × 2), 127.9 (C × 2), 123.3, 120.6, 109.0, 73.0, 71.1, 70.9, 70.4, 67.9, 61.6, 41.4, 38.8, 38.72, 38.67, 38.5, 28.4, 27.2 (C × 3), 27.08 (C × 3), 27.06 (C × 3), 26.5 (C × 3), 15.6. HRMS (ESI+) calcd for $C_{42}H_{59}O_{10}$ $[M + H]^+$, 723.4103; found, 723.4109.

*(1S,3′R,4′S,5′S,6′R)-6-(4-Ethylbenzyl)-6′-(hydroxymethyl)-3′,4′,5′,6′-tetrahydro-3H-spiro[isobenzofuran-1,2′-pyran]-3′,4′,5′-triol (**1**).* To a solution of **14a** (5.19 g, 7.18 mmol) in methanol (36 mL) was added lithium hydroxide monohydrate (903.0 mg, 21.5 mmol) at room temperature, followed by stirring at room temperature for 6.5 h. The solvent was removed under reduced pressure. To the residue was added saturated NaCl, and then the resulting mixture was extracted with AcOEt. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was recrystallized from acetone−H_2O to afford **1** (1.75 g, 60% as monohydrate). Spectral data were identical to those described in the literature.[2b]

Synthesis of the Anomer of 1 (15). *(1R,3′R,4′S,5′R,6′R)-6-(4-Ethylbenzyl)-6′-((pivaloyloxy)methyl)-3′,4′,5′,6′-tetrahydro-3H-spiro[isobenzofuran-1,2′-pyran]-3′,4′,5′-triyl Tris-(2,2-dimethylpropanoate) (**14b**).* Hydrogenolysis of **2b** (2.98 g, 4.04 mmol), which was isolated from the mixture of **2a** and **2b** by silica gel column chromatography (toluene−AcOEt), was carried out in DME (18 mL)−isopropanol (12 mL)−AcOH (60 μL) over 20% $Pd(OH)_2$ on carbon (50% wet, 596 mg) under H_2 at room temperature for 7 h. After filtration, the solvent was removed under reduced pressure. To the residue was added saturated $NaHCO_3$, and then the resulting mixture was extracted with AcOEt. The organic layer was washed with saturated NH_4Cl and aqueous NaCl, successively, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (AcOEt−heptane) to give **14b** as a colorless oil (1.60 g, 55%). $[\alpha]^{20}_{D}$ +38.3 (*c* 1.07, CH_2Cl_2). FTIR (cm^{-1}, neat) 2968, 1739, 1479, 1460, 1278, 1133, 1031. ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (brs, 1H), 7.24−7.23 (m, 1H), 7.20−7.19 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 5.78 (t, *J* = 9.5 Hz, 1H), 5.48 (d, *J* = 9.5 Hz, 1H), 5.30 (t, *J* = 9.5 Hz, 1H), 5.21 (d, *J* = 12.5 Hz, 1H), 4.88 d, *J* = 12.5 Hz, 1H), 4.10 (dd, *J* = 12.0, 1.5 Hz, 1H), 4.08 (s, 2H), 4.03 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.97 (ddd, *J* = 9.5, 5.5, 1.5 Hz, 1H), 2.61 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.19 (s, 9H), 1.14 (s, 9H), 1.06 (s, 9H), 0.83 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 177.2, 176.6, 176.2, 142.1, 140.8, 139.0, 137.9, 136.0, 130.4, 128.6 (C × 2), 128.1 (C × 2), 123.7, 121.6, 109.8, 72.1, 72.0, 71.5, 69.8, 68.3, 62.0, 41.3, 38.8, 38.72, 38.67, 38.5, 28.4, 27.11 (C × 3), 27.07 (C × 3), 26.9 (C × 3), 26.6 (C × 3), 15.6. HRMS (ESI+) calcd for $C_{42}H_{59}O_{10}$ $[M + H]^+$, 723.4103; found, 723.4109.

*(1R,3′R,4′S,5′S,6′R)-6-(4-Ethylbenzyl)-6′-(hydroxymethyl)-3′,4′,5′,6′-tetrahydro-3H-spiro[isobenzofuran-1,2′-pyran]-3′,4′,5′-triol (**15**).* To a solution of **14b** (1.47 g, 2.03 mmol) in methanol (10 mL) was added lithium hydroxide monohydrate

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(255 mg, 6.08 mmol) at room temperature, followed by stirring at room temperature for 5 h. After addition of saturated NaCl, the resulting mixture was extracted with AcOEt. The organic layers were washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was crystallized from dichloromethane to afford **15** as colorless needles (594 mg, 76%). Mp 149.0 °C. $[\alpha]^{20}_D$ +20.0 (*c* 1.00, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 7.47 (brs, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.20 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.01 (d, *J* = 12.0 Hz, 1H), 4.05 (dd, *J* = 10.0, 9.0 Hz, 1H), 3.99 (s, 2H), 3.71 (dd, *J* = 12.0, 1.5 Hz, 1H), 3.71 (d, *J* = 10.0 Hz, 1H), 3.64−3.57 (m, 2H), 3.48 (t, *J* = 9.0 Hz, 1H), 2.58 (q, *J* = 7.5 Hz, 2H), 1.19 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 143.2, 141.8, 141.2, 139.7, 138.2, 131.0, 129.8, 128.9, 125.4, 122.6, 112.7, 76.6, 76.0, 75.6, 72.8, 72.0, 63.0, 42.3, 29.5, 16.3. HRMS (ESI+) calcd for $C_{22}H_{27}O_6$ $[M + H]^+$, 387.1802; found, 387.1800.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00400.

^{1}H and ^{13}C NMR spectra of key compounds, COSY and NOESY experiments, and LC/MS chart (PDF)

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Notes

The authors declare no competing financial interest.

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