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Total Synthesis of (−)-4-Hydroxyzinowol

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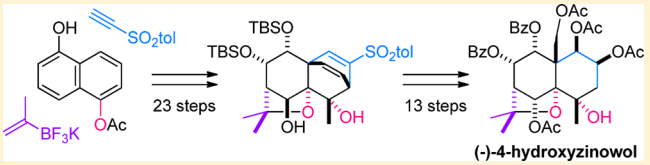
Supporting Information

ABSTRACT: (−)-4-Hydroxyzinowol (**1**) is a potent inhibitor of P-glycoprotein, which has been implicated in multi-drug resistance in the treatment of cancer. The highly oxygenated structure of **1** comprises a *trans*-decalin (AB-ring) and a tetrahydrofuran (C-ring) and possesses six acyloxy, one hydroxy, and one alkoxy groups. The challenge of synthesizing **1** is particularly heightened by the nine consecutive stereogenic centers on the 10-carbon decalin skeleton. The total synthesis of this extremely complex structure was achieved in 36 steps from 5-acetoxynaphthalen-1-ol by the judicious application of powerful chemo- and stereoselective reactions. The rhodium-catalyzed asymmetric 1,4-addition of the isopropenyl group set the C7-stereocenter, and the remaining three *cis*-oriented hydroxy groups (C6, 8, and 9) of the B-ring were stereoselectively constructed in a stepwise fashion. The C5-tetra-substituted and C10-quaternary carbons at the juncture of the AB-ring were then introduced by oxidative dearomatization and Diels−Alder reaction, respectively. After acid-promoted formation of the C-ring ether, the C1-, 2-, 4- and 6-oxygen-based functional groups were stereoselectively installed to deliver the fully functionalized tricycle. Finally, the polyhydroxylated structure was converted to the polyacylated target molecule **1** via regioselective acetylation and benzoylation.



INTRODUCTION

Many cancers fail to respond to chemotherapy due to acquired multi-drug resistance (MDR).[1] One major form of resistance to chemotherapy has been correlated with the presence of molecular pumps that actively transport anticancer drugs out of the cell. The most prevalent of the MDR transporters is P-glycoprotein (P-gp), a member of the adenosine triphosphate (ATP)-binding cassette superfamily.[2] As MDR is a major barrier to successful chemotherapy, development of selective inhibitors for P-gp is of high clinical relevance.

Jiménez, Gamarro, and co-workers isolated and determined the structure of a series of natural products with P-gp inhibitory activity from the South American medical plant *Zinowiewia costaricensis*. One of the most potent compounds, (−)-4-hydroxyzinowol (Figure 1, **1**), blocked P-gp-mediated transport of daunorubicin, a clinically used anticancer drug, at low micromolar concentrations.[3,4] Thus, **1** is considered as a lead compound for further development of specific inhibitors for the treatment of MDR malignancy.

Compound **1** belongs to the dihydro-*β*-agarofuran sesquiterpene family that incorporates a *trans*-decalin (the AB-ring) and a tetrahydrofuran (the C-ring).[5] To date, over 400 structurally different dihydro-*β*-agarofurans have been identified from plant sources and have attracted a great deal of interest due to their various biological functions such as anti-inflammatory (orbiculin I),[6] antiviral (triptofordin C-2),[7] and antitumor promoting (triptofordin F-2) activities.[8] These diverse yet selective biological activities of agarofurans are affected not only by the number and stereogenicities of the oxygen-based functional groups but also by the various acyl groups attached to the oxygens. For instance, a comprehensive structure−activity relationship study of 76 agarofurans by

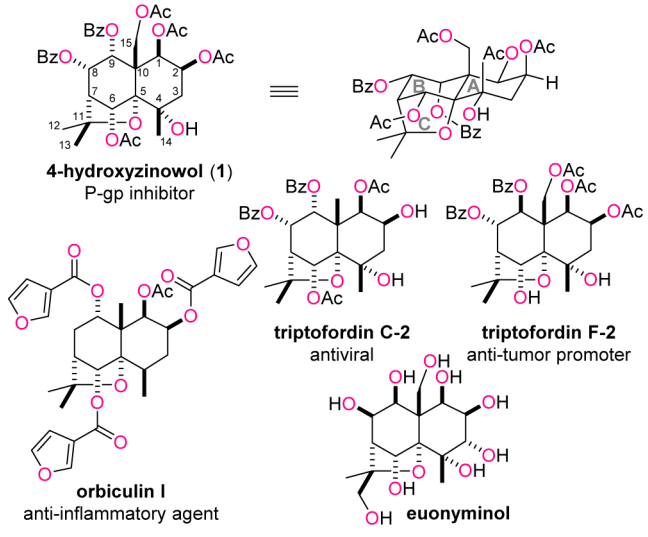


Figure 1. Structures of highly oxygenated dihydro-*β*-agarofuran sesquiterpenes.

Jiménez and Gamarro disclosed that the presence of at least two aromatic ester moieties (e.g., the two Bz groups of **1**) are necessary for high inhibitory activity toward P-gp.[3b]

Motivated by the complex architectures and promising biological activities of these compounds, a number of synthetic laboratories have been engaged in the chemical construction of dihydro-*β*-agarofuran sesquiterpenes.[9] However, despite overall

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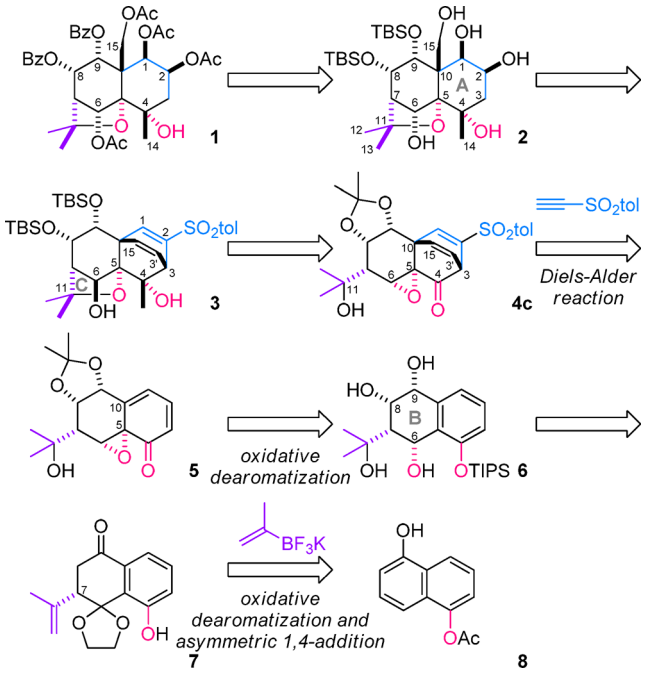
progress, the total synthesis of only one highly oxygenated agarofuran has been reported: (±)-euonyminol, which is the core structure of various polyacylated agarofurans, was synthesized by the White group.[10] Here we describe the first asymmetric total synthesis of (−)-4-hydroxyzinowol (**1**), a potent P-gp inhibitor. The entire structure of **1** was assembled in 36 steps from 5-acetoxynaphthalen-1-ol by constructing nine consecutive stereocenters (C1, 2, 4, 5, 6, 7, 8, 9, and 10) and attaching two Bz and four Ac groups.[11]

RESULTS AND DISCUSSION

Synthetic Plan. The retrosynthesis of target molecule **1** is illustrated in Scheme 1. To prepare for site-selective

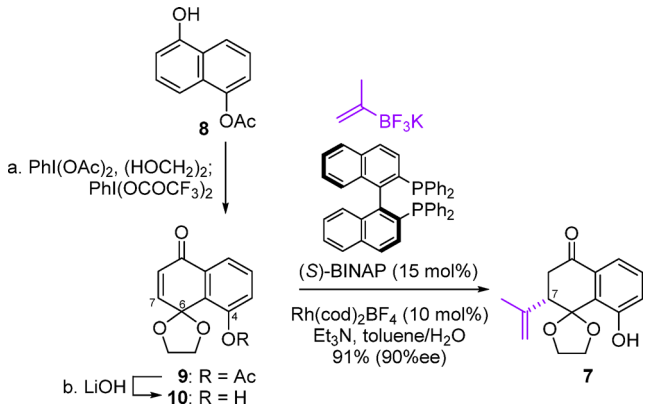
Scheme 1. Synthetic Plan for 4-Hydroxyzinowol (1)



benzoylation and acetylation at the last stage of synthesis, we retrosynthetically designed the bis-TBS-protected intermediate **2**, in which the C8- and 9-secondary hydroxy groups are differentiated from their C1, 2, 6, and 15 counterparts. The *trans*-decalin structure of **2** presents a formidable synthetic challenge because the six tri-substituted (C1, 2, 6, 7, 8, 9), two tetra-substituted (C4, 5), and one quaternary (C10) stereocenters are concentrated on this 10-carbon framework. We envisioned constructing this heavily substituted decalin **2** from the naphthalene derivative **8**. In the synthetic direction, oxidative dearomatization of **8** and subsequent asymmetric introduction of the isopropenyl group would set the C7-stereocenter of **7**. After establishment of the C6-, 8-, and 9-configurations of **6**, a second oxidative dearomatization was planned to install the C5-tetra-substituted carbon of **5**. The diene part of **5** in turn would undergo Diels−Alder reaction with a dienophile to construct the C10-quaternary carbon of **4c**.[12] Ring opening of the epoxide at C6, ring closure of the C-ring at C11, and introduction of the tetra-substituted carbon at C4 would convert **4c** into tetracycle **3**. Finally, oxidative cleavage of the cyclohexadiene, C2-desulfonylation, C3′-decarboxylation, and C1,2-dihydroxylation from **3** was to lead to the requisite **2**. In this plan, the series of highly chemo-, stereo-, and enantioselective reactions needed to be realized within the rather compact matrices of the intermediates. In fact, the proper selection and orchestration of such reactions were the most critical issues for the successful total synthesis of **1**.

Synthesis of the AB-Ring Structure. Before asymmetric introduction of the isopropenyl group at C7, 5-acetoxynaphthalen-1-ol **8**[13] needed to be oxidatively dearomatized (Scheme 2). A reagent combination of $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$

Scheme 2. Asymmetric 1,4-Addition of the Isopropenyl Group[a]



[a]Reagents and conditions: (a) $PhI(OAc)_2$, CH_3CN, $(CH_2OH)_2$, 0 °C; $PhI(OCOCF_3)_2$, 70%; (b) LiOH, THF, H_2O, 61%.

converted **8** into the naphthoquinone monoketal **9** in a mixture of CH_3CN and ethylene glycol.[14] The acetyl group of **9** was then removed by saponification to produce **10**. When **10** was treated with 2-propenyl trifluoroborate in the presence of catalytic $Rh(cod)_2BF_4$ (10 mol %), (*S*)-BINAP (15 mol %) and stoichiometric Et_3N,[15,16] the asymmetric 1,4-addition proceeded smoothly, providing **7** in 91% yield and 90% ee.[17]

Next, the three hydroxy groups at C6, 8, and 11 were constructed (Scheme 3). After protection of the C4-alcohol of **7** as the MOM ether of **11**, the C11-oxygen functional group was introduced as the epoxide using *m*-CPBA, leading to **12**. Stereoselective C8-oxidation was then explored. As expected, C8-hydroxylation of ketone **12** proceeded selectively from the β-face under typical conditions (e.g., TMS enol ether formation and subsequent *m*-CPBA oxidation) due to the presence of the bulky α-oriented C7-substituent. Given this stereochemical bias, an in situ inversion process was investigated to attain the requisite α-selectivity. Accordingly, **12** was treated with $PhI(OAc)_2$ and *t*-BuOK in MeOH[18] to afford the desired C8-alcohol **13** as the sole stereoisomer. In this Moriarty procedure, the C8-position of **12** was first iodinated from the less-hindered β-face with $PhI(OAc)_2$ to **A**, and then the iodide group was intramolecularly displaced by the alkoxide in S_N2 fashion to form epoxide **C**. Subsequent methanolysis of the reactive epoxy acetal of **C** provided **13**.

Having established the C8-stereochemistry, the C11-tertiary alcohol was generated from the C11-epoxide of **13** by the action of $LiAlH_4$, leading to **14**. Anhydrous HCl in THF then induced intramolecular acetal formation at C9 to afford **15**, recrystallization of which produced enantiopure **15**. After acid hydrolysis of the C6-acetal and the MOM group, the C6-ketone of tricycle **16** was stereoselectively reduced with $NaBH_4$ from the convex face to give the C6-alcohol of **17**. The NOE correlation between H6 and H8 and the coupling constant

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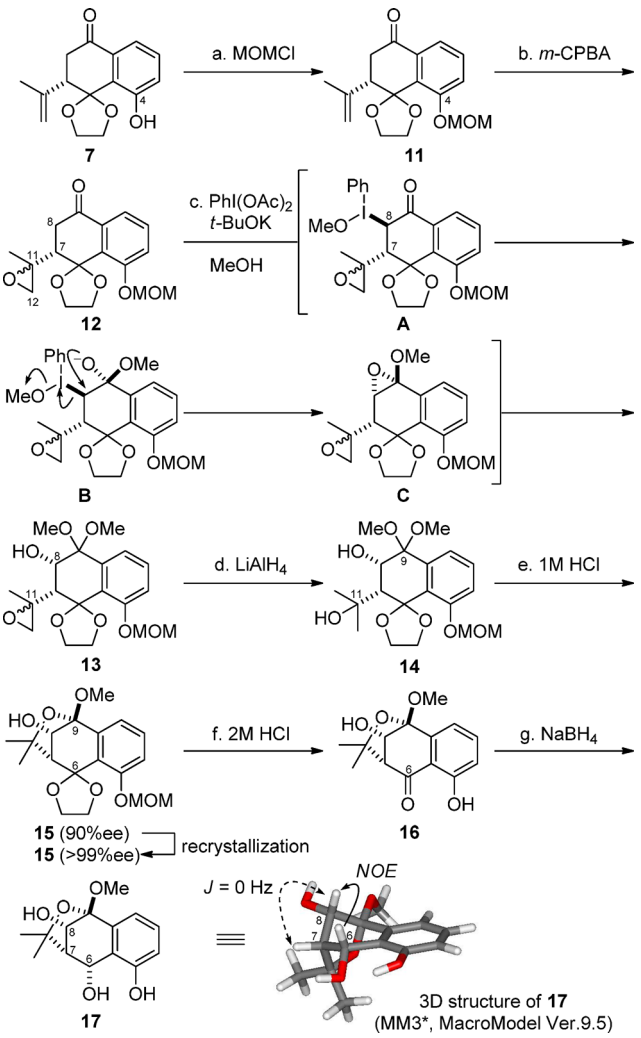
Scheme 3. Introduction of the C6-, 8-, and 11-Hydroxy Groups[a]

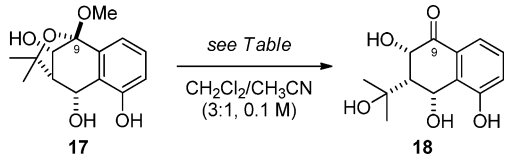


[a]Reagents and conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 99%; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (c) $PhI(OAc)_2$, *t*-BuOK, MeOH, −15 °C, 69% (2 steps, dr = 3:1); (d) $LiAlH_4$, Et_2O; (e) 1 M HCl (anhydrous), THF, 0 °C; recrystallization, 58% (2 steps); (f) 2 M HCl, THF, H_2O, 35 °C, 100%; (g) $NaBH_4$, CH_2Cl_2, MeOH, 0 °C, 92%.

between H7 and H8 (J = 0 Hz) confirmed the α-orientations of the C6-, 7-, and 8-substituents of **17**.

To construct the C9-hydroxy group of **1** through reduction, the temporarily protected C9-ketone needed to be liberated (Table 1). However, the cyclic acetal of **17** was found to be unusually stable under various acidic conditions. A strong Brønsted acid (H_2SO_4) in THF/H_2O hydrolyzed **17** to provide tetrahydroxylated ketone **18** in only low yield due to concomitant decomposition of **18** (entry 1). Extensive screening of Lewis acids revealed that stoichiometric $Sc(OTf)_3$ converted acetal **17** to ketone **18** in high yield (entry 2). Whereas the lower loading of $Sc(OTf)_3$ decreased the yield of **18** (entry 3), the combination of a catalytic amount of $Sc(OTf)_3$ and a stoichiometric amount of $Zn(OTf)_2$ enabled the formation of **18** in higher yield (64−97%, entry 4). The addition of 100 mol % of H_2O improved reproducibility, leading to **18** in 97% yield (entry 5). $Zn(OTf)_2$ alone did not induce the conversion of **17** to **18** (entry 6), and LiOTf/

Table 1. Hydrolysis of the Cyclic Acetal of 17



17 18

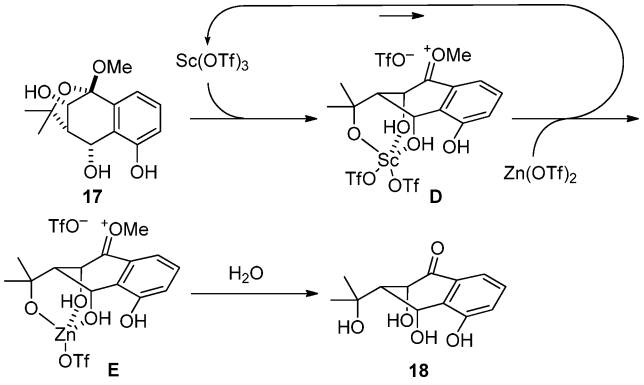
entry	acid (mol %)	additive (mol %)	yield (%)
1[a]	H_2SO_4 (excess)	none	14
2	$Sc(OTf)_3$ (110)	none	78
3	$Sc(OTf)_3$ (10)	none	52[b]
4	$Sc(OTf)_3$ (5)	$Zn(OTf)_2$ (120)	64−97
5	$Sc(OTf)_3$ (5)	$Zn(OTf)_2$ (120) H_2O (100)	97
6	$Zn(OTf)_2$ (120)	none	0[c]
7	$Sc(OTf)_3$ (5)	LiOTf (120)	76

[a]Reaction was performed in a mixture of THF/H_2O/H_2SO_4 (v/v/v = 15/5/1, 50 mM) at 45 °C. [b]**17** was recovered in 28%. [c]**17** was recovered in 98%.

$Sc(OTf)_3$ was less effective than $Zn(OTf)_2$/$Sc(OTf)_3$ in increasing the yield (entry 7). These data together suggested that multivalent $Zn(OTf)_2$ functioned as the assisting reagent for acetal cleavage.

A mechanism for this hydrolysis is proposed in Scheme 4. Strongly Lewis acidic $Sc(OTf)_3$ initially cleaves the acetal of **17**

Scheme 4. Proposed Mechanism for the Hydrolysis of the Acetal of 17



to afford Sc^{3+}-complex **D**, which is stabilized by the three chelating hydroxy groups. $Sc(OTf)_3$ in **D** is exchanged with the multivalent and more concentrated $Zn(OTf)_2$, regenerating the $Sc(OTf)_3$ catalyst.[19,20] Finally, the in situ hydrolysis of Zn^{2+}-complex **E** led to formation of **18**. In this proposed mechanism, the acid-labile **18** is mainly exposed to the weakly acidic $Zn(OTf)_2$, preventing its facile decomposition.

Reduction of the thus formed C9-ketone realized the construction of the four stereocenters of the B-ring (Scheme 5). After chemoselective protection of the C4-phenolic hydroxy group of tetraol **18** as the TIPS ether, the C9-ketone of **19** was reduced with $NaBH_4$ from the less hindered face, stereoselectively affording **6** (dr = 18:1). The NOE correlation between H7 and H9 confirmed the correct C9-stereochemistry of **6**.

The stage was now set to introduce the angular C5-stereogenic center through a second oxidative dearomatization. Before doing so, regioselective acetonide formation of the C8,9-diol in the presence of the C6,11-diol and subsequent TIPS

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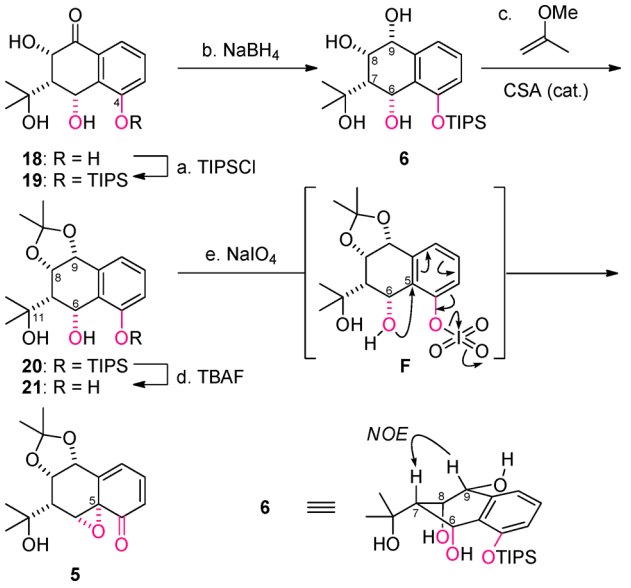
Scheme 5. Introduction of the C9- and C5-Stereocenters[a]



[a]Reagents and conditions: (a) TIPSCl, imidazole, DMF, 81%; (b) $NaBH_4$, EtOH, −78 °C, 98% (dr = 18:1); (c) camphorsulfonic acid (CSA), 2-methoxypropene, DMF, 79%; (d) tetra-*n*-butylammonium fluoride (TBAF), THF; (e) $NaIO_4$, MeOH, H_2O, 97% (2 steps).

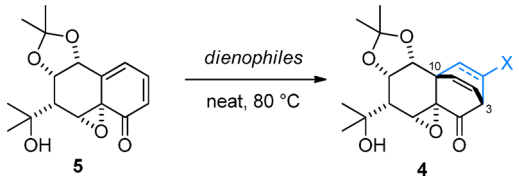
removal transformed tetraol **6** to triol **21**. Dearomatization of the phenol was then realized by submitting **21** to $NaIO_4$[21] in aqueous methanol. Nucleophilic attack of the proximal C6-hydroxy group of **21** on C5 occurred through intermediate **F**, leading to C5-epoxide **5** in excellent yield.[22]

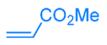
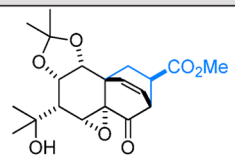
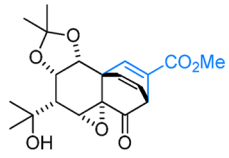
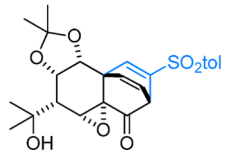
The diene fragment embedded in intermediate **5** was next utilized for the Diels–Alder reaction to install the C10-quaternary center (Table 2).[23] Reaction of various dienophiles with **5**[24] showed that methyl acrylate (entry 1), methyl propiolate (entry 2) and ethynyl *p*-tolyl sulfone (entry 3) provided excellent yields and stereoselectivities. When diene **5** was heated to 80 °C with neat methyl acrylate or methyl propiolate, the Diels–Alder adduct **4a** or **4b** was obtained in high yield as a single isomer. Alternatively, the reaction between **5** and 5 equiv of ethynyl *p*-tolyl sulfone[25] took place at 80 °C in toluene, providing the tricyclic structure **4c** with simultaneous introduction of the C10-stereocenter. Since the *p*-tolyl sulfone moiety could easily detach from the molecule, we selected **4c** as the intermediate for the total synthesis (vide infra).

The remarkably selective outcome of the Diels–Alder reactions could be rationalized by the intrinsic three-dimensional structures of **5** (Scheme 6). The J_{H6H7} and J_{H6H8} values indicate that the B-ring of both diene **5** and adduct **4c** adopts a similar twist-boat conformation, presumably due to the presence of the sterically encumbered moiety at C7. In this conformation, the β-face of **5** is sterically shielded. Thus, the approach of the dienophile from the α-face of **5**, with the bulky *p*-tolyl sulfonyl group outside the fused ring, becomes most favored, resulting in highly regio- and stereoselective formation of **4c**. The structure of **4c** was unambiguously established by the observed NOE between H7 and H15.

Total Synthesis of 4-Hydroxyzinowol. The entire AB-ring skeleton **4c** was efficiently assembled at this stage. The remaining tasks in the total synthesis of **1** from **4c** were construction of the C-ring, removal of the extra carbon (C3′), and generation of the four hydroxy groups (C1, 2, 4, 15) and

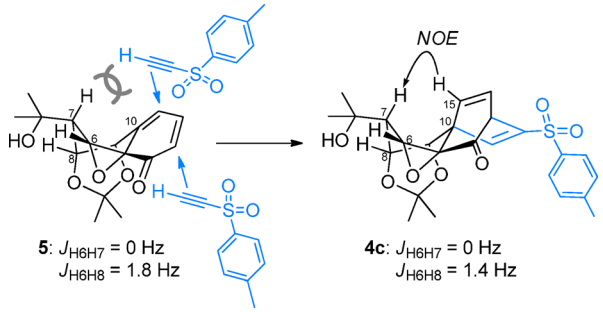
Table 2. Introduction of the C10-Quaternary Carbon by Diels–Alder Reaction



entry	dienophile	product and yield
1		 **4a**: 79%
2		 **4b**: 81%
3[a]		 **4c**: 70%

[a]Reaction was performed using 5 equiv of ethynyl *p*-tolyl sulfone in toluene (0.1 M) at 80 °C.

Scheme 6. Rationale for the Stereoselective Diels–Alder Reaction



methyl group (C14). Because of the densely functionalized structures of the intermediates, the judicious arrangement of multiple functional group manipulations were crucial for development of the route to **1**.

The tetrahydrofuran C-ring had to be formed by epoxide opening and etherification. A model study was first performed to optimize the procedure using **4b** as the substrate (Scheme 7). After deprotection of the 1,2-diol of **4b** with $Ce(OTf)_3$,[26] regioselective nucleophilic opening of the epoxide of **22b** proceeded by the action of CsOAc or CsOBz in DMF to afford acetylated **23ba** or benzoylated **23bb**.[27] The subsequent C-ring cyclization necessitated acid-promoted etherification from the two tertiary alcohols at C5 and C11. Interestingly, while treatment of **23ba** with *p*-tolSO_3H in benzene at 50 °C generated olefin **24ba** with concomitant loss of the Ac group, the acid-promoted etherification occurred from **23bb** to give **24bb**. The distinct outcomes from **23ba** and **23bb** were

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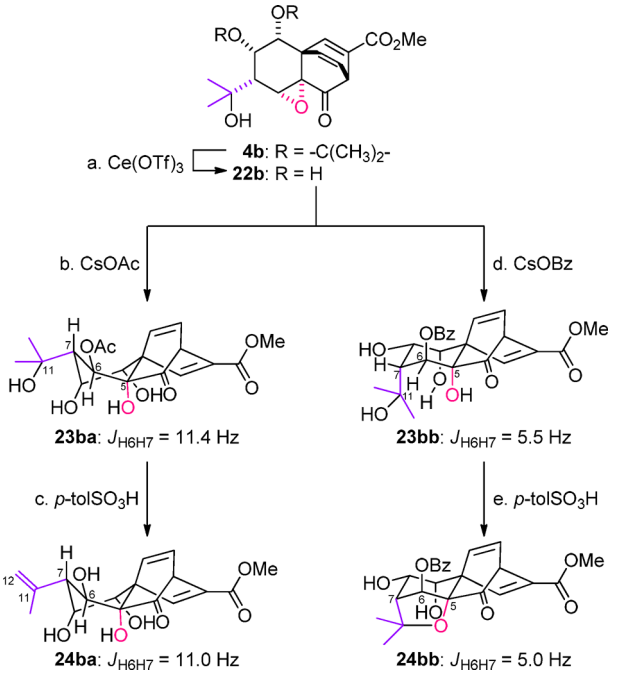
Scheme 7. Model Study for C-Ring Formation[a]



[a]Reagents and conditions: (a) $Ce(OTf)_3$, CH_3CN, H_2O, 70 °C; (b) CsOAc, DMF, 45 °C, 29% (2 steps); (c) *p*-$tolSO_3H$, benzene, 50 °C, 44%; (d) CsOBz, DMF, 50 °C; (e) *p*-$tolSO_3H$, toluene, 50 °C, 25% (3 steps).

attributable to their conformational preferences induced by the Ac and Bz groups, respectively. The large H6−H7 coupling constant (J = 11.4 Hz) of **23ba** indicates the twist-boat B-ring, in which the C11-hydroxy group points away from the C5-hydroxy group. Cyclization is thus disfavored, and the alternative C11-olefination gives unwanted **24ba**. On the other hand, judging from the H6−H7 coupling constant (J = 5.5 Hz), the B-ring of the benzoylated **23bb** adopts the chair form with axially oriented C6- and 7-substituents, probably because the equatorial orientations of these 1,2-vicinal groups suffer from larger gauche interactions.[28] Consequently, the C5- and 11-hydroxy groups are preorganized for the requisite etherification, resulting in successful formation of the C-ring.

Having clarified the critical role of the acyl protective group on C-ring formation, **4c** was submitted to the optimized procedure (Scheme 8). TFA-mediated acetonide removal of **4c** and subsequent regioselective epoxide opening of **22c** furnished the benzoylated intermediate **23c**. Treatment of **23c** with *p*-$tolSO_3H$ induced C-ring cyclization to provide **24c**. The C8,9-hydroxy groups of the obtained **24c** were capped as the TBS ethers, and the C6-hydroxy group was liberated from **25** under basic conditions, giving rise to **26**.

The C14-methyl group was then stereoselectively installed. When MeMgBr was allowed to react with the Bz-protected **25** in Et_2O, no product was observed. The proximal functional groups appeared to kinetically block the C4-ketone of **25**. In contrast, the C4-ketone of the deprotected **26** accepted the nucleophile under the same conditions, resulting in formation of the adduct **3** as a single stereoisomer. The distinct reactivity and excellent stereoselectivity in the conversion of **26** to **3** could arise from the intramolecular transfer of the methyl group from the magnesium ate complex **26′** (Scheme 9).[29] The requisite orientation of the C14-methyl group of **3** was determined by an NOE experiment.

A carefully tuned five-step sequence from **3** achieved C3′-decarboxylation and C2-desulfonylation (Scheme 8). Ozonolysis of diene **3** resulted in reaction with the more electron-rich C3′-olefin in the presence of the sulfone-substituted C2-olefin. Subsequent reductive workup provided **27** with the C15-hemiacetal and C3′-aldehyde. $NaClO_2$-mediated oxidation selectively converted the C3′-aldehyde of **27** to the carboxylic acid of **28**.[30] The C2-sulfonyl group, which functioned as the reactivity-controlling element for both the Diels−Alder reaction (**5** → **4c**) and ozonolysis (**3** → **27**), was then reductively removed with Na/Hg in buffered CH_2Cl_2 to produce **29**.[31] The extra C3′-carbon of **29** was in turn eliminated as CO_2 through the intermediacy of Barton ester **30**. After condensation of carboxylic acid **29** with 1-hydroxypyridine-2(1*H*)-thione **G**,[32] treatment of **30** with AIBN and Ph_3SnH generated the resultant allyl radical **H** that abstracted hydrogen at the more accessible C3-position over the C1-position, yielding product **31** without olefin transposition.

The next focus was the synthesis of compound **2** from **31**, which possessed the suitably differentiated seven hydroxy groups of 4-hydroxyzinowol (**1**). The C15-hemiacetal of **31** was reductively opened using $LiBH_4$ in refluxing THF to produce **32**, which bore the primary, secondary, and tertiary alcohols. The C6-secondary alcohol of **32** was then chemoselectively oxidized in the presence of the C15-primary alcohol by utilizing Trost's conditions [$(NH_4)_6Mo_7O_{24}$ and H_2O_2],[33] leading to **33** via C6-hemiacetal formation.[34] The C1-olefin was dihydroxylated with OsO_4 to introduce the C1- and 2-hydroxy groups of **34** in a completely stereoselective fashion. As shown in Scheme 9, the C9-TBS-ether is likely to impede the approach of OsO_4 from the α-face, resulting in β-face addition of the OsO_4. The NOE correlation of the product **34** confirmed the correct stereochemistry of the newly introduced diol and supported the close proximity of the α-face of the A-ring and the C9-TBS group. Finally, the C6-hemiacetal **34** was stereoselectively transformed to the C6,15-diol **2** by using $LiBH_4$ in refluxing 1,2-dichloroethane. Thus, inversion of the C6-stereochemistry through oxidation (**32** → **33**)/reduction (**34** → **2**) completed the construction of the nine consecutive stereocenters of the target molecule **1**.

Regioselective acetylation of the four hydroxy groups (C1, 2, 6, 15) and benzoylation of the two hydroxy groups (C8, 9) were necessary for the total synthesis of **1**. Extensive reactivity mapping revealed that the C1-hydroxy group was the most resistant to acetylation among the five hydroxy groups of **2**. Specifically, only one primary at C15 and two secondary hydroxy groups at C2 and 6 of **2** were acetylated using Ac_2O and DMAP in a mixed solvent of CH_2Cl_2 and Et_3N, affording **35**. Subjection of **2** to more forcing conditions [e.g., Ac_2O, $Sc(OTf)_3$, MeCN][35] resulted only in acetylation of tertiary C4-OH in addition to C2-, 6- and 15-OH. As the low reactivity of C1-OH would be affected by the surrounding bulky C15-OAc and C9-OTBS, the TBS groups of **35** were removed with TBAF prior to the acetylation of C1-OH, producing tetraol **36**. When **36** was treated with Bz_2O, Et_3N, and DMAP in CH_2Cl_2, the C8- and 9-secondary alcohols were regioselectively benzoylated to provide diol **37**.[36] Lastly, acetylation of the remaining C1-OH of **37** under the same conditions as the first acetylation proceeded without touching C4-OH, delivering (−)-4-hydroxyzinowol (**1**). All of the analytical data of

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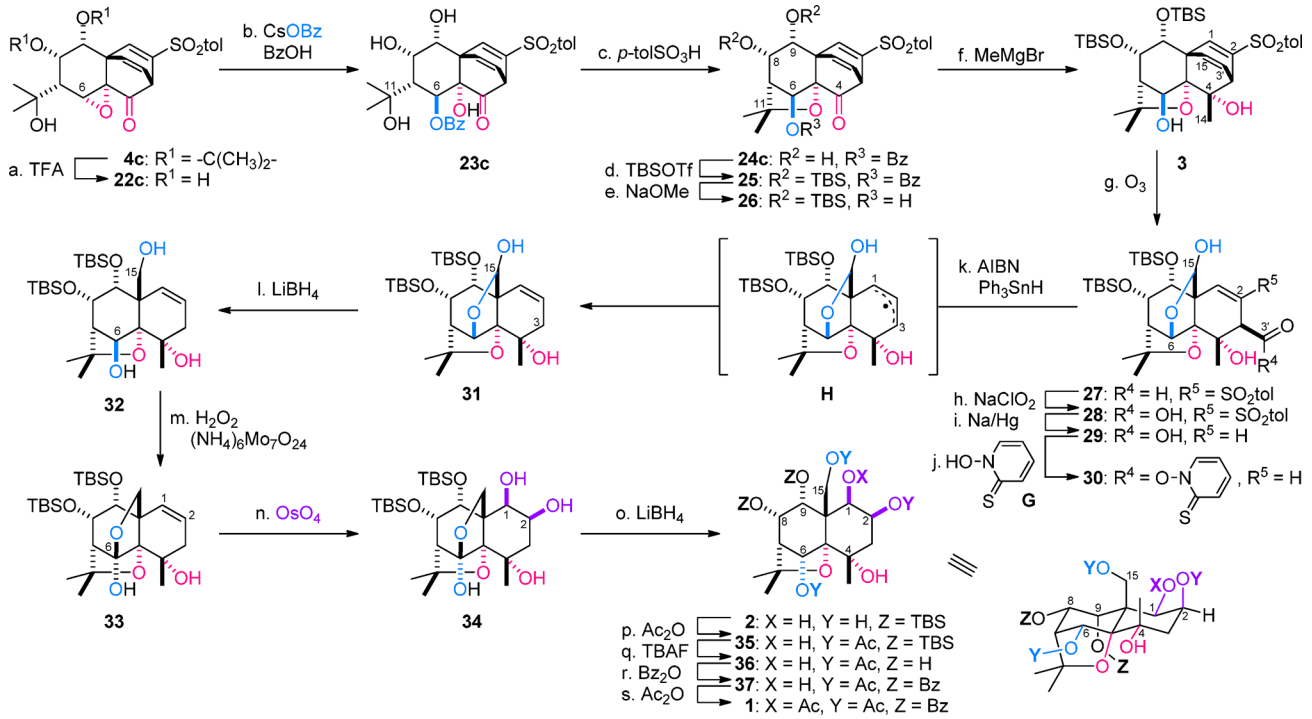
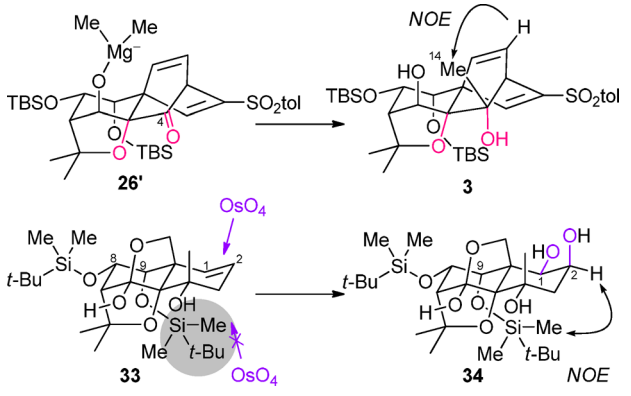
Scheme 8. Total Synthesis of 4-Hydroxyzinowol (1)[a]



[a]Reagents and conditions: (a) TFA, CH_3CN, H_2O, 50 °C, 60%; (b) CsOBz, BzOH, DMF; (c) *p*-tolSO_3H, toluene, 50 °C, 59% (2 steps); (d) TBSOTf, 2,6-lutidine, CH_3CN; (e) NaOMe, MeOH, 0 °C; (f) MeMgBr, Et_2O, −40 °C, 79% (3 steps); (g) O_3, CH_2Cl_2, −78 °C; SMe_2; evaporation; (h) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, *t*-BuOH, H_2O, 2-methyl-2-butene, 0 °C, 52% (2 steps); (i) Na/Hg, CH_2Cl_2, pH 7 buffer; (j) 1-hydroxypyridine-2(1*H*)-thione **G**, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI·HCl), CH_2Cl_2; (k) 2,2′-azobis-(isobutyronitrile) (AIBN), Ph_3SnH, benzene, 80 °C; (l) $LiBH_4$, THF, reflux, 32% (4 steps); (m) H_2O_2, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, K_2CO_3, tetra-*n*-butylammonium chloride, THF, 50 °C; (n) OsO_4, pyridine, 1,4-dioxane, H_2O; $NaHSO_3$, EtOAc, 43% (2 steps); (o) $LiBH_4$, 1,2-dichloroethane, reflux, 36% (brsm, 42%); (p) Ac_2O, Et_3N, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2; (q) TBAF, THF, 56% (2 steps); (r) Bz_2O, Et_3N, CH_2Cl_2; DMAP, 51%; (s) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 86%.

Scheme 9. Rationale for the Observed Stereoselective C14-Methylation and Dihydroxylation



synthetic **1** (^{1}H- and ^{13}C NMR, IR and $[\alpha]_D$) were identical with those of **1** from the natural source.

CONCLUSION

The asymmetric total synthesis of 4-hydroxyzinowol (**1**), a highly oxygenated dihydro-*β*-agarofuran, was accomplished in 36 steps from 5-acetoxynaphthalen-1-ol **8**. After rhodium-catalyzed asymmetric 1,4-addition of the isopropenyl group at C7, stereoselective introduction of the eight stereocenters on the decalin framework was realized by controlling the three-dimensional structures of the intermediates and selecting the appropriate conditions for each reaction. These include (i) C8-hydroxylation from the hindered face; (ii) reduction of the C6- and C9-ketones; (iii) C5-epoxidation by oxidative dearomatization and subsequent formation of the C5-ether; (iv) construction of the C10-quaternary center through Diels–Alder reaction; (v) hydroxy-directed addition of the methyl group at C4; (vi) C1,2-dihydroxylation; and (vii) introduction of the C6-stereochemistry through an oxidation/reduction sequence. The highly optimized acetylation and benzoylation of **2** furnished the targeted structure **1**. In addition to the series of selective transformations, application of the combination of $Sc(OTf)_3$ and $Zn(OTf)_2$ for the hydrolysis of the stable acetal and use of ethynyl *p*-tolyl sulfone as the reactive acetylene equivalent for the Diels–Alder reaction should have wider applications beyond this synthesis. The synthetic route to **1** developed here will accelerate the structure–activity relationship study for identification of effective inhibitors of P-glycoprotein for reversing multi-drug resistance in cancer chemotherapy.

EXPERIMENTAL SECTION

General Methods. All reactions sensitive to air or moisture were carried out under argon atmosphere under anhydrous conditions, unless otherwise noted. THF, CH_2Cl_2, toluene, DMF, and Et_2O were purified by a Glass Contour solvent dispensing system. All other reagents were used as supplied. Analytical thin-layer chromatography (TLC) was performed using precoated TLC glass plates (silica gel 60 F254, 0.25 mm). Flash chromatography was performed using silica gel (spherical, neutral, 40–50 μm, or granular, neutral, 32–53 μm).

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Melting points are reported uncorrected. Optical rotations were measured using the sodium D line. A 0.7 mL cell, which was filled with a solution of the weighed sample prepared in a 2.00 mL volumetric flask, was used for the measurement of optical rotations. The indicated temperatures refer to those of the polarimeter's cavity. Infrared (IR) spectra were recorded as a thin film on a NaCl disk using a FT/IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on 400 or 500 MHz, and 100 or 125 MHz spectrometers, respectively. Chemical shifts were reported in ppm on the δ scale relative to $CHCl_3$ (δ = 7.26 for ^{1}H NMR), $CDCl_3$ (δ = 77.0 for ^{13}C NMR), CD_2HOD (δ = 3.31 for ^{1}H NMR), CD_3OD (δ = 49.0 for ^{13}C NMR), C_6D_6 (δ = 128.0 for ^{13}C NMR), and $(CD_3)_2CO$ (δ = 29.84 for ^{13}C NMR) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broaden peak. The numbering of compounds corresponds to that of the natural product. High resolution mass spectra were measured on ESI-TOF or MALDI-TOF mass spectrometers.

4-Oxo-4*H*-spiro[naphthalene-1,2′-[1,3]dioxolan]-8-yl Acetate 9. $PhI(OAc)_2$ (21.5 g, 66.7 mmol) was added to a solution of 5-acetoxynaphthalene-1-ol **8** (11.0 g, 54.4 mmol) in a mixture of CH_3CN (140 mL) and ethylene glycol (540 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and then $PhI(OCOCF_3)_2$ (29.0 g, 67.4 mmol) was added. After the mixture was stirred at 0 °C for 2.5 h, saturated aqueous $NaHCO_3$ (200 mL) was slowly added. The resultant solution was extracted with CH_2Cl_2 (150 mL × 2), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The red residue was washed with a mixture of EtOH and hexane (2/1, 50 mL and 1/1, 30 mL) to afford pure **9** (9.96 g, 38.3 mmol) in 70% yield: brown powder; mp 198 °C; IR (neat) ν 2957, 2901, 1759, 1673, 1633, 1603, 1579, 1466, 1389, 1297, 1206, 1100, 1044, 970 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (3H, s, $COCH_3$), 4.31−4.34 (2H, m, $OCH_AH_BCH_AH_BO$), 4.36−4.38 (2H, m, $OCH_AH_BCH_AH_BO$), 6.33 (1H, d, J = 10.9 Hz, H8), 6.77 (1H, d, J = 10.9 Hz, H7), 7.31 (1H, dd, J = 8.0, 1.2 Hz, H3), 7.54 (1H, dd, J = 8.0, 8.0 Hz, H2), 8.02 (1H, dd, J = 8.0, 1.2 Hz, H1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 63.7, 65.9, 100.1, 124.7, 127.1, 129.3, 130.3, 130.4, 132.7, 142.5, 148.9, 168.7, 183.1; HRMS (ESI) calcd for $C_{14}H_{12}O_5Na$ 283.0577 [M + Na]$^+$, found 283.0582.

8-Hydroxy-4*H*-spiro[naphthalene-1,2′-[1,3]dioxolan]-4-one 10. $LiOH·H_2O$ (9.62 g, 229 mmol) was added to a solution of **9** (33.2 g, 128 mmol) in a mixture of THF (400 mL) and H_2O (100 mL) at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 5 h. Then saturated aqueous NH_4Cl (250 mL) was added. The resultant solution was extracted with CH_2Cl_2 (250 mL × 3) and EtOAc (1 L), and the combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (300 g, hexane/CH_2Cl_2 1/1 to CH_2Cl_2/EtOAc 15/1) to afford **10** (17.1 g, 78.4 mmol) in 61% yield: red powder; mp 141 °C; IR (neat) ν 3173, 2968, 2905, 1666, 1631, 1584, 1469, 1307, 1290, 1104, 1044, 972, 949 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35−4.40 (2H, m, $OCH_AH_BCH_AH_BO$), 4.40−4.45 (2H, m, $OCH_AH_BCH_AH_BO$), 6.36 (1H, d, J = 10.3 Hz, H8), 6.87 (1H, d, J = 10.3 Hz, H7), 7.15 (1H, dd, J = 8.0, 1.2 Hz, H3), 7.39 (1H, s, O*H*), 7.42 (1H, dd, J = 8.0, 8.0 Hz, H2), 7.68 (1H, dd, J = 8.0, 1.2 Hz, H1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.9, 102.5, 119.4, 121.4, 122.7, 128.7, 131.1, 132.2, 139.8, 155.8, 183.6; HRMS (ESI) calcd for $C_{12}H_{10}O_4Na$ 241.0471 [M + Na]$^+$, found 241.0476.

(*S*)-8-Hydroxy-2-(prop-1-en-2-yl)-2,3-dihydro-4*H*-spiro-[naphthalene-1,2′-[1,3]dioxolan]-4-one 7. Et_3N, H_2O, and toluene were degassed by freeze−thaw procedure (× 3). Et_3N (21 mL, 150 mmol) was added to a suspension of **10** (8.58 g, 39.4 mmol), potassium 2-propenyl trifluoroborate (9.31 g, 62.9 mmol), $Rh(cod)_2BF_4$ (1.49 g, 3.67 mmol), and (*S*)-BINAP (3.67 g, 5.90 mmol) in a mixture of toluene (160 mL) and H_2O (40 mL) at room temperature. The resultant solution was stirred at room temperature for 19 h, and then saturated aqueous NH_4Cl (150 mL) was added. The resultant solution was extracted with EtOAc (100 mL × 3), and the combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (150 g, hexane/EtOAc 5/1 to 2/1) to afford **7** (9.34 g, 35.9 mmol) in 91% yield. The enantiopurity of **7** was determined to be 90% ee from the ^{1}H NMR analysis of the corresponding MTPA-ester. ^{1}H−^{1}H COSY and HMQC spectra were utilized for the peak assignments: pale yellow oil; $[\alpha]^{21}_D$ −14.7 (*c* 1.89, $CHCl_3$); IR (neat) ν 3325, 2971, 2906, 1687, 1604, 1581, 1458, 1284, 1159, 1088, 1044, 914 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (3H, s, H13), 2.94 (1H, dd, J = 17.8, 5.5 Hz, H8a), 3.01 (1H, dd, J = 17.8, 7.3 Hz, H8b), 3.19 (1H, dd, J = 7.3, 5.5 Hz, H7), 4.12−4.30 (4H, m, OCH_2CH_2O), 4.84 (1H, s, H12a), 4.99 (1H, s, H12b), 7.10 (1H, dd, J = 8.2, 1.4 Hz, H3), 7.33 (1H, dd, J = 8.2, 7.8 Hz, H2), 7.58 (1H, dd, J = 7.8, 1.4 Hz, H1), 8.97 (1H, s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 40.8, 49.1, 65.2, 65.5, 111.3, 116.0, 119.3, 123.5, 123.7, 130.5, 133.7, 142.4, 155.2, 196.4; HRMS (ESI) calcd for $C_{15}H_{16}O_4Na$ 283.0941 [M + Na]$^+$, found 283.0929.

(*R*)-MTPA-ester I. (*S*)-MTPA-Cl (16 μL, 86 μmol) and DMAP (13 mg, 0.11 mmol) were successively added to a solution of **7** (11 mg, 42 μmol) in CH_2Cl_2 (830 μL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h, and then (*S*)-MTPA-Cl (16 μL, 83 μmol) and DMAP (13 mg, 0.11 mmol) were added. The reaction mixture was stirred at room temperature for 2.5 h, and then the (*S*)-MTPA-Cl (23 μL, 0.12 mmol) and DMAP (20 mg, 0.16 mmol) were added again. After the reaction mixture was stirred at room temperature for further 2 h, saturated aqueous $NaHCO_3$ (3 mL) was added. The resultant solution was extracted with CH_2Cl_2 (2 mL × 5), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of silica gel (1 g, hexane/EtOAc 20/1 to 2/1) to afford crude (*R*)-MTPA-ester **I** (23 mg), which was used for the ^{1}H NMR analysis without further purification. The diastereomeric ratio was determined to be 18.7:1 by comparing the ^{1}H NMR spectra of **I** and the diastereomeric mixture that was synthesized from racemic **7**[11a] and (*S*)-MTPA-Cl: pale yellow oil; ^{1}H−^{1}H COSY spectrum was utilized for the peak assignments; ^{1}H NMR (500 MHz, C_6D_6, 323 K) δ 1.62 (3H, s, H12), 2.71 (1H, dd, J = 17.0, 5.0 Hz, H8a), 2.77 (1H, dd, J = 10.1, 5.0 Hz, H7), 3.06 (1H, dd, J = 17.0, 10.1 Hz, H8b), 3.18 (1H, dt, J = 7.3, 7.3 Hz, $OCH_AH_BCH_AH_BO$), 3.34−3.44 (2H, m, $OCH_AH_BCH_AH_BO$), 3.49 (3H, s, OCH_3), 3.62 (1H, dt, J = 7.3, 7.3 Hz, $OCH_AH_BCH_AH_BO$), 4.76 (1H, s, H13a), 4.80 (1H, s, H13b), 6.90−6.97 (2H, m, aromatic), 7.09−7.13 (3H, m, aromatic), 7.77 (2H, d, J = 7.3 Hz, H2 and 3), 8.10 (1H, d, J = 7.3 Hz, H1); HRMS (ESI) calcd for $C_{25}H_{23}F_3O_6Na$ 499.1339 [M + Na]$^+$, found 499.1346.

MOM-ether 11. MOMCl (12.5 mL, 164 mmol) was added to a solution of **7** (9.34 g, 35.9 mmol) and *i*-Pr_2NEt (37.5 mL, 215 mmol) in CH_2Cl_2 (70 mL) at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 11 h. Then saturated aqueous NH_4Cl (70 mL) and H_2O (50 mL) were successively added. The resultant solution was extracted with CH_2Cl_2 (100 mL × 3), and the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by filtration through a pad of silica gel (50 g, hexane/EtOAc 2/1) to afford MOM-ether **11** (10.8 g, 35.5 mmol) in 99% yield: pale yellow oil; $[\alpha]^{23}_D$ −12.7 (*c* 1.61, $CHCl_3$); IR (neat) ν 2966, 2897, 1692, 1580, 1467, 1261, 1206, 1153, 1127, 1081, 1051, 1003 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (3H, s, H12), 2.76 (1H, d, J = 13.7 Hz, H8a), 3.08 (1H, dd, J = 13.3, 0.9 Hz, H8b), 3.06 (1H, dd, J = 11.9, 0.9 Hz, H7), 3.13 (1H, dd, J = 13.3, 11.9 Hz, H8b), 3.51 (3H, s, OCH_2OCH_3), 4.10−4.33 (4H, m, OCH_2CH_2O), 4.93 (1H, s, H13a), 5.03 (1H, m, H13b), 5.21 (1H, d, J = 6.9 Hz, $OCH_AH_BOCH_3$), 5.24 (1H, d, J = 6.9 Hz, $OCH_AH_BOCH_3$), 7.37−7.40 (2H, m, H2 and 3), 7.68−7.70 (1H, m, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 41.5, 50.8, 56.2, 67.0, 67.4, 95.0, 109.5, 116.0, 120.2, 121.3, 129.8, 131.7, 133.9, 143.0, 154.9, 197.4; HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ 327.1203 [M + Na]$^+$, found 327.1209.

Alcohol 13. *m*-CPBA (11.3 g, 75% purity, 49.1 mmol) was added to a suspension of MOM-ether **11** (8.27g, 27.2 mmol) and $NaHCO_3$ (8.20 g, 97.6 mmol) in CH_2Cl_2 (270 mL) at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 3 h. After the mixture was cooled to 0 °C, H_2O (150 mL) and saturated aqueous $Na_2S_2O_3$ (200 mL) were successively added. The resultant

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solution was extracted with CH_2Cl_2 (200 mL × 5), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of silica gel (15 g, hexane/EtOAc 2/1 to 1/1) to afford the crude epoxide **12** (9.99 g, a 3.0:1 diastereomeric mixture at the C11 position), which was used in the next reaction without further purification. $^1H-^1H$ COSY spectrum was utilized for the peak assignments: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H × 3/4, s, H12), 1.28 (3H × 1/4, s, H12), 2.14 (1H × 3/4, dd, J = 10.0, 5.2 Hz, H7), 2.37 (1H × 1/4, dd, J = 6.9, 5.2 Hz, H7), 2.52 (1H × 1/4, d, J = 4.6 Hz, H13a), 2.57 (1H × 1/4, d, J = 4.6 Hz, H13b), 2.74 (1H × 3/4, d, J = 5.2 Hz, H13a), 2.79 (1H × 1/4, dd, J = 16.6, 5.2 Hz, H8a), 2.89 (1H × 3/4, d, J = 5.2 Hz, H13b), 2.97 (1H × 3/4, dd, J = 16.6, 5.2 Hz, H8a), 2.99–3.02 (1H × 1/4, m, H8b), 3.05 (1H × 3/4, dd, J = 16.6, 10.0 Hz, H8b), 3.52 (3H, s, OCH_2OCH_3), 4.04–4.40 (4H, m, OCH_2CH_2O), 5.22 (1H × 3/4, J = 6.9 Hz, $OCH_AH_BOCH_3$), 5.23 (1H × 1/4, d, J = 6.9 Hz, $OCH_AH_BOCH_3$), 5.25 (1H, d J = 6.9 Hz, $OCH_AH_BOCH_3$), 7.37–7.42 (2H, m, H2 and 3), 7.69–7.74 (1H, m, H1); ^{13}C NMR (100 MHz, CD_3Cl) δ 19.1, 21.8, 38.3, 38.9, 49.9, 51.5, 52.3, 55.9, 56.11, 56.18, 56.24, 56.8, 66.1, 66.3, 66.70, 66.71, 95.0, 95.1, 107.7, 108.0, 120.0, 120.4, 121.6, 121.7, 130.0, 131.0, 134.0, 134.3, 154.8, 154.9, 196.0, 196.2.

t-BuOK (14.0 g, 125 mmol) and $PhI(OAc)_2$ (15.1 g, 46.9 mmol) were successively added to a solution of the above crude epoxide **12** in MeOH (105 mL) at −30 °C. The reaction mixture was warmed to −15 °C and was stirred for 48 h. Then saturated aqueous NH_4Cl (300 mL) was added. The resultant solution was extracted with EtOAc (200 mL × 4), and the combined organic layers were washed with brine (400 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (270 g, hexane/EtOAc 3/1 to 2/1 to 3/2 to 1/1) to afford alcohol **13** (7.15 g, 18.7 mmol, a 3.0:1 diastereomeric mixture at the C11 position) in 69% yield over 2 steps. $^1H-^1H$ COSY spectrum was utilized for the peak assignments: pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (3H × 1/4, s, H12), 1.63 (3H × 3/4, s, H12), 2.44 (1H × 3/4, d, J = 1.4 Hz, H7), 2.44 (1H × 1/4, d, J = 5.2 Hz, O*H*), 2.53 (1H × 3/4, d, J = 5.9 Hz, O*H*), 2.65 (1H × 1/4, d, J = 5.2 Hz, H13a), 2.75 (1H × 3/4, d, J = 5.5 Hz, H13a), 2.86 (1H × 1/4, s, H7), 3.02 (1H, d, J = 5.5 Hz, H13b), 3.06 (3H, s, OCH_3), 3.43 (3H × 1/4, s, OCH_3), 3.45 (3H × 3/4, s, OCH_3), 3.49 (3H, s, OCH_3), 4.10–4.15 (1H, m, $OCH_AH_BCH_AH_BO$), 4.22–4.29 (1H, m, $OCH_AH_BCH_AH_BO$), 4.33–4.39 (1H × 1/4, m, H8), 4.33–4.44 (2H, m, $OCH_AH_BCH_AH_BO$), 4.49 (1H, × 3/4, dd, J = 5.9, 1.4 Hz, H8), 5.18 (1H × 1/4, d, J = 7.5 Hz, $OCH_AH_BCOCH_3$), 5.19 (1H × 3/4, d, J = 6.9 Hz, $OCH_AH_BCOCH_3$), 5.23 (1H × 3/4, d, J = 6.9 Hz, $OCH_AH_BCOCH_3$), 5.25 (1H × 1/4, d, J = 7.5 Hz, $OCH_AH_BCOCH_3$), 7.15–7.18 (1H, m, H3), 7.29 (1H × 1/4, dd, J = 8.0, 8.0 Hz, H2), 7.30 (1H, 1H × 3/4, dd, J = 8.0, 8.0 Hz, H2), 7.37 (1H × 1/4, d, J = 8.0 Hz, H1), 7.38 (1H × 3/4, d, J = 8.0 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 23.1, 47.8, 47.8, 49.1, 49.1, 52.4, 55.5, 55.6, 55.7, 55.9, 66.2, 66.7, 68.0, 68.1, 68.5, 68.9, 94.5, 98.0, 99.6, 108.6, 114.8, 115.4, 115.5, 121.5, 126.5, 128.5, 128.6, 134.1, 134.4, 155.2 (some of ^{13}C peaks of the minor isomer were not observed); HRMS (ESI) calcd for $C_{19}H_{26}O_8Na$ 405.1520 $[M + Na]^+$, found 405.1522.

Ketal 15. $LiAlH_4$ (2.15 g, 56.7 mmol) was slowly added to a solution of alcohol **13** (7.12 g, 18.6 mmol, a 3:1 diastereomeric mixture at the C11 position) in Et_2O (180 mL) at −30 °C. The reaction mixture was warmed to room temperature and was stirred for 2 h. After the mixture was cooled to 0 °C, MeOH (20 mL) was slowly added. Then EtOAc (200 mL), H_2O (200 mL), and saturated aqueous Rochelle's salt (200 mL) were successively added. The resultant solution was stirred at room temperature for 1 h and was extracted with EtOAc (150 mL × 4). The combined organic layers were washed with brine (400 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude **14**, which was used in the next reaction without further purification.

One molar HCl solution in EtOAc (9 mL) was added to a solution of the above crude **14** in THF (180 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, and then saturated aqueous $NaHCO_3$ (100 mL) and H_2O (150 mL) were successively added. The resultant solution was extracted with EtOAc (100 mL × 4), and the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (220 g, hexane/EtOAc 1/1) to afford ketal **15** (4.57 g, 13.0 mmol). Recystallization of obtained **15** from hexane/EtOAc gave rise to enantiopure **15** (3.76 g, 10.7 mmol) in 58% yield over 2 steps. The enantiopurity of **15** was determined to be >99% ee by the ^1H NMR analysis of the corresponding MTPA-ester: white needles; mp 147–149 °C; $[\alpha]^{26}_D$ −43 (c 0.86, $CHCl_3$); IR (neat) ν 3464, 2954, 2899, 1583, 1471, 1261, 1153, 1092, 1059, 969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (3H, s, H12), 1.53 (3H, s, H13), 2.50 (1H, d, J = 5.2 Hz, O*H*), 2.52 (1H, s, H7), 3.47 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 4.07 (1H, ddd, J = 14.3, 7.5, 6.9 Hz, $OCH_AH_BCH_2O$), 4.15 (1H, m, $OCH_AH_BCH_2O$), 4.25 (1H, m, $OCH_2CH_AH_BO$), 4.31 (1H, ddd, J = 14.3, 7.5, 6.9 Hz, $OCH_2CH_AH_BO$), 4.46 (1H, br s, H8), 5.15 (1H, d, J = 6.3 Hz, $OCH_AH_BOCH_3$), 5.23 (1H, d, J = 6.3 Hz, $OCH_AH_BOCH_3$), 7.10 (1H, d, J = 8.6 Hz, H1 or 3), 7.17 (1H, d, J = 7.5 Hz, H1 or 3), 7.35 (1H, dd, J = 8.6, 7.5 Hz, H2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 31.3, 53.4, 56.1, 59.4, 65.5, 66.0, 74.8, 80.0, 94.3, 105.9, 110.6, 115.8, 116.8, 124.9, 130.6, 139.8, 155.4; HRMS (MALDI) calcd for $C_{18}H_{24}O_7Na$ 375.1414 $[M + Na]^+$, found 375.1413.

(*R*)-MTPA-ester J. (*S*)-MTPA-Cl (6.5 μL, 34 μmol) and DMAP (5.6 mg, 46 μmol) were successively added to a solution of ketal **15** (4.0 mg, 11 μmol) in CH_2Cl_2 (570 μL) at room temperature. The reaction mixture was stirred at room temperature for 3 h, and then H_2O (3 mL) was added. The resultant solution was extracted with CH_2Cl_2 (2 mL × 3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of silica gel (1 g, hexane/EtOAc 1/1) to afford crude (*R*)-MTPA-ester **J** (6.2 mg), which was used for the ^1H NMR analysis without further purification. (*R*)-MTPA-ester **J** was determined to be diastereomerically pure by comparing the ^1H NMR spectra of **J** and the (*S*)-MTPA-ester that was synthesized from **15** and (*R*)-MTPA-Cl: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, s, H12), 1.39 (3H, s, H13), 2.54 (1H, s, H7), 3.24 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 4.09–4.20 (2H, m, $OCH_AH_BCH_AH_BO$), 4.29–4.37 (2H, m, $OCH_AH_BCH_AH_BO$), 5.22 (2H, s, OCH_2OCH_3), 5.70 (1H, s, H8), 7.09 (1H, dd, J = 8.2, 0.9 Hz, H3), 7.16 (1H, dd, J = 8.2, 0.9 Hz, H1), 7.34 (1H, dd, J = 8.2, 8.2 Hz, H2), 7.41–7.44 (3H, m, aromatic), 7.60–7.62 (2H, m, aromatic); HRMS (ESI) calcd for $C_{28}H_{31}F_3O_9Na$ 591.1812 $[M + Na]^+$, found 591.1807.

Ketone 16. Two molar HCl in H_2O (27 mL) was added to a solution of ketal **15** (3.76 g, 10.7 mmol) in THF (80 mL) at room temperature. The reaction mixture was warmed to 35 °C and was stirred for 17 h. After the mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ (150 mL) was slowly added. The resultant solution was extracted with EtOAc (100 mL × 3), and the combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (120 g, hexane/EtOAc 2/1) to afford ketone **16** (2.82 g, 10.7 mmol) in 100% yield: pale yellow oil; $[\alpha]^{23}_D$ −101 (c 1.00, $CHCl_3$); IR (neat) ν 3444, 2978, 2950, 2844, 1649, 1619, 1458, 1336, 1245, 1214, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, s, H12), 1.69 (3H, s, H13), 2.76 (1H, d, J = 3.7 Hz, O*H*), 3.21 (1H, s, H7), 3.77 (3H, s, OCH_3), 4.20 (1H, d, J = 3.7 Hz, H8), 6.95 (1H, d, J = 8.2, 1.4 Hz, H3), 7.11 (1H, d, J = 7.8, 1.4 Hz, H1), 7.51 (1H, d, J = 8.2, 7.8 Hz, H2), 11.70 (1H, s, Ar*OH*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 29.6, 54.3, 65.6, 77.7, 81.3, 107.1, 113.9, 115.7, 118.0, 136.8, 145.4, 162.3, 203.1; HRMS (MALDI) calcd for $C_{14}H_{16}O_5Na$ 287.0890 $[M + Na]^+$, found 287.0880.

Alcohol 17. $NaBH_4$ (1.21 g, 32.0 mmol) was added to a solution of ketone **16** (2.83 g, 10.7 mmol) in a mixture of CH_2Cl_2 (50 mL) and MeOH (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and then 1 M HCl (200 mL) was slowly added. The resultant solution was extracted with EtOAc (50 mL × 9), and the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane/EtOAc 1/2) to afford alcohol **17** (2.62 g, 9.84 mmol) in 92% yield: colorless crystal; mp 223 °C; $[\alpha]^{23}_D$ −87 (c 0.86, MeOH); IR (neat) ν 3443, 3318, 2964, 2920,

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2851, 1583, 1463, 1241, 1084 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.19 (3H, s, H12), 1.53 (3H, s, H13), 2.57 (1H, d, J = 3.7 Hz, H7), 3.56 (3H, s, OCH_3), 4.07 (1H, s, H8), 5.38 (1H, d, J = 3.7 Hz, H6), 6.76 (1H, dd, J = 8.2, 1.4 Hz, H3), 6.94 (1H, dd, J = 7.8, 1.4 Hz, H1), 7.16 (1H, dd, J = 8.2, 7.8 Hz Hz, H2); ^{13}C NMR (100 MHz, CD_3OD) δ 28.4, 31.6, 53.7, 57.7, 73.7, 76.8, 83.2, 107.8, 115.5, 117.2, 123.2, 129.9, 140.6, 157.4; HRMS (MALDI) calcd for $C_{14}H_{18}O_5Na$ 289.1046 $[M + Na]^+$, found 289.1047.

Ketone 18. $Sc(OTf)_3$ (9.8 mg, 20 μmol) was added to a suspension of **17** (109 mg, 0.409 mmol), $Zn(OTf)_2$ (178 mg, 0.489 mmol), and H_2O (7.4 μL, 0.41 mmol) in a mixture of CH_2Cl_2 (3 mL) and CH_3CN (1 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h, and then saturated aqueous Rochelle's salt (5 mL) was added. The resultant solution was extracted with EtOAc (3 mL × 4), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane/EtOAc 1/2) to afford ketone **18** (100 mg, 0.396 mmol) in 97% yield. Because of its unstability, **18** was used in the next reaction immediately. HMQC and HMBC spectra were utilized for the peak assignments: colorless oil; ^1H NMR (500 MHz, CD_3OD) δ 1.50 (3H, s, H12), 1.54 (3H, s, H13), 2.01 (1H, dd, J = 2.9, 1.7 Hz, H7), 4.59 (1H, dd, J = 1.7, 1.7 Hz, H8), 5.57 (1H, dd, J = 2.9, 1.7 Hz, H6), 7.11 (1H, dd, J = 8.0, 1.2 Hz, H3), 7.30 (1H, dd, J = 8.0, 8.0 Hz, H2), 7.48 (1H, dd, J = 8.0, 1.2 Hz, H1); HRMS (ESI) calcd for $C_{13}H_{16}O_5Na$ 275.0890 $[M + Na]^+$, found 275.0901.

TIPS-ether 19. TIPSCl (90 μL, 0.42 mmol) was added to a solution of ketone **18** (100 mg, 0.397 mmol) and imidazole (88 mg, 1.3 mmol) in DMF (2.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 10 h, and then saturated aqueous NH_4Cl (10 mL) was added. The resultant solution was extracted with Et_2O (5 mL × 3), and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane/EtOAc 15/1 to 9/1) to afford TIPS-ether **19** (131 mg, 0.321 mmol) in 81% yield: colorless crystal; mp 121 °C; $[\alpha]^{17}_D$ −65 (c 1.0, $CDCl_3$); IR (neat) ν 3430, 2945, 2867, 1696, 1588, 1469, 1301, 1277, 1155, 1048, 987 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (9H, d, J = 7.8 Hz, CH_3CHCH_3 of TIPS × 3), 1.15 (9H, d, J = 7.8 Hz, $CH_3CHCH_3$of TIPS × 3), 1.37 (3H, septet, J = 7.8 Hz, $CH(CH_3)_2$ of TIPS × 3), 1.51 (3H, s, H12), 1.57 (3H, s, H13), 1.89 (1H, dd, J = 3.2, 3.2 Hz, H7), 3.68 (1H, d, J = 4.1 Hz, OH), 3.74 (1H, s, OH), 4.36 (1H, d, J = 4.1 Hz, OH), 4.73 (1H, m, H8), 5.78 (1H, m, H6), 7.11 (1H, d, J = 8.2 Hz, H3), 7.34 (1H, dd, J = 8.2, 7.8 Hz, H2), 7.65 (1H, dd, J = 7.8 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 17.96, 17.98, 28.4, 28.6, 47.3, 63.6, 72.7, 74.8, 120.3, 123.9, 129.8, 131.0, 133.3, 153.7, 195.9; HRMS (ESI) calcd for $C_{22}H_{36}O_5SiNa$ 431.2224 [M + Na], found 431.2235.

Conversion of Ketal 17 to TIPS-ether 19 without Purification of Ketone 18. According to the above synthetic procedure, the crude tetraol **18** was synthesized from ketal **17** (1.85 g, 6.95 mmol) by using $Sc(OTf)_3$ (173 mg, 0.352 mmol), $Zn(OTf)_2$ (3.03 g, 8.32 mmol), and H_2O (150 μL, 8.33 mmol) in a mixture of CH_2Cl_2 (54 mL) and CH_3CN (18 mL). The crude was immediately used in the next reaction without purification.

According to the above synthetic procedure, TIPS-ether **19** (2.51 g, 6.14 mmol) was synthesized from the crude ketone **18** in 88% yield over 2 steps by using imidazole (1.91 g, 28.0 mmol) and TIPSCl (3.0 mL, 14 mmol) in DMF (70 mL). The crude was purified by flash column chromatography on silica gel (25 g, hexane/EtOAc 3/1).

Tetraol 6. $NaBH_4$ (930 mg, 24.6 mmol) was added to a solution of **19** (3.33 g, 8.15 mmol) in EtOH (85 mL) at −90 °C. The reaction mixture was warmed to −78 °C and was stirred for 3 h. Then saturated aqueous NH_4Cl (150 mL) was added. After the mixture was warmed to room temperature, saturated aqueous Rochelle's salt (150 mL) was added. The resultant solution was stirred at room temperature for 12 h. The solution was extracted with EtOAc (150 mL × 4), and the combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (60 g, hexane/EtOAc 1/1 to 1/2) to afford tetraol **6** (3.29 g, 8.01 mmol, a 18:1 diastereomeric mixture at the C9 position) in 98% yield: colorless oil; $[\alpha]^{24}_D$ −30 (c 0.78, $CDCl_3$); IR (neat) ν 3390, 2945, 2867, 1585, 1467, 1280, 1158, 1067, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (9H, d, J = 7.8 Hz, CH_3CHCH_3 of TIPS × 3), 1.15 (9H, d, J = 7.8 Hz, CH_3CHCH_3 of TIPS × 3), 1.36 (3H, septet, J = 7.8 Hz, $CH(CH_3)_2$ of TIPS × 3), 1.47 (3H, s, H12), 1.58 (3H, s, H13) 1.58−1.61 (1H, m, H7), 2.97 (1H, d, J = 11.4 Hz, OH), 3.32 (1H, br s, OH), 3.79 (1H, br s, OH), 3.95 (1H, br s, OH), 4.51 (1H, dd, J = 11.4, 3.7 Hz, H9), 4.70 (1H, br d, J = 3.7 Hz, H8), 5.53 (1H, d, J = 4.1 Hz, H6), 6.79 (1H, d, J = 8.2 Hz, H3), 7.25 (1H, dd, J = 8.2, 7.8 Hz, H2), 7.35 (1H, d, J = 7.8 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 18.00, 18.03, 28.3, 28.7, 46.9, 65.1, 68.7, 71.4, 74.2, 116.8, 120.3, 126.9, 129.4, 138.1, 153.4; HRMS (ESI) calcd for $C_{22}H_{38}O_5SiNa$ 433.2381 $[M + Na]^+$, found 433.2393.

Acetonide 20. CSA (57 mg, 0.25 mmol) was added to a solution of tetraol **6** (3.29 g, 8.01 mmol, a 18:1 diastereomeric mixture at the C9 position) and 2-methoxypropene (1.2 mL, 13 mmol) in DMF (80 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then 2-methoxypropene (0.38 mL, 4.0 mmol) was added. The reaction mixture was stirred at room temperature for further 30 min, and then saturated aqueous $NaHCO_3$ (50 mL) was added. The resultant solution was diluted with H_2O (150 mL) and extracted with EtOAc (50 mL × 4). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (50 g, hexane/EtOAc 6/1 to 3/1 to 1/2 to 0/1) to afford acetonide **20** (2.84 g, 6.30 mmol) in 79% yield. ^1H−^1H COSY, HMQC and HMBC spectra were utilized for the peak assignments: colorless oil; $[\alpha]^{24}_D$ +3.30 (c 1.27, $CHCl_3$); IR (neat) ν 3520, 2944, 2868, 1587, 1463, 1278, 1230, 1058, 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (9H, d, J = 7.8 Hz, CH_3CHCH_3 of TIPS × 3), 1.14 (9H, d, J = 7.8 Hz, CH_3CHCH_3 of TIPS × 3), 1.29 (3H, s, CH_3), 1.33 (3H, septet, J = 7.8 Hz, $CH(CH_3)_2$ of TIPS × 3) 1.45 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.67 (1H, dd, J = 2.8, 2.8 Hz, H7), 4.96 (1H, ddd, J = 5.6, 2.8, 1.8 Hz, H8), 5.17(1H, d, J = 5.6 Hz, H9), 5.54 (1H, m, H6), 6.81 (1H, d, J = 8.2 Hz, H3), 7.02 (1H, d, J = 7.8 Hz, H1), 7.20 (1H, dd, J = 8.2, 7.8 Hz, H2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 17.99, 18.03, 25.8, 27.5, 29.0, 29.3, 47.8, 63.2, 73.0, 73.9, 76.4, 109.8, 118.2, 122.0, 129.0, 129.2, 135.5, 153.7; HRMS (ESI) calcd for $C_{25}H_{42}O_5SiNa$ 473.2694 $[M + Na]^+$, found 473.2693.

Epoxide 5. n-Bu_4NF (8.0 mL, 1.0 M in THF, 8.0 mmol) was added to a solution of acetonide **20** (2.95 g, 6.55 mmol) in THF (60 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min, and then saturated aqueous NH_4Cl (150 mL) and H_2O (50 mL) were successively added. The resultant solution was extracted with EtOAc (80 mL × 4), and the combined organic layers were washed with saturated aqueous NH_4Cl (50 mL × 3) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude **21**, which was used in the next reaction without further purification.

$NaIO_4$ (7.02 g, 32.8 mmol) was added to a suspension of the above crude **21** in a mixture of MeOH (90 mL) and H_2O (30 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h, and then H_2O (200 mL) was added. The resultant solution was extracted with $CHCl_3$ (100 mL × 4), and the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by recrystallization from hexane/$CHCl_3$ to afford epoxide **5** (1.85 g, 6.33 mmol) in 97% yield over 2 steps: white solid; mp 180−181 °C; $[\alpha]^{24}_D$ +490 (c 0.80, $CHCl_3$); IR (neat) ν 3448, 2969, 2918, 1659, 1630, 1366, 1209, 1142, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.99 (1H, d, J = 3.7 Hz, H7), 3.06 (1H, br s, OH), 3.87 (1H, d, J = 1.8 Hz, H6), 4.73−4.79 (2H, m, H8 and 9), 6.27 (1H, d, J = 10.5 Hz, H3), 6.60 (1H, d, J = 5.4 Hz, H1), 7.18 (1H, dd, J = 10.5, 5.4 Hz, H2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 26.0, 28.5, 29.0, 46.0, 59.4, 71.5, 72.4, 75.2, 75.3, 110.4, 127.16, 127.25, 140.7, 145.0, 194.6; HRMS (ESI) calcd for $C_{16}H_{20}O_5Na$ $[M + Na]^+$ 315.1203, found 315.1209.

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Cycloadduct 4a. A mixture of **5** (9.7 mg, 33 μmol) and methyl acrylate (1.5 mL) was heated to 80 °C and was stirred for 12 h. After being cooled to room temperature, the mixture was concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 1/1 to 1/2) to afford cycloadduct **4a** (9.8 mg, 26 μmol) in 79% yield. ^{1}H−^{1}H COSY spectrum was utilized for the peak assignments: white solid; mp 215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.45 (3H, s, 3H, s, CH_3), 1.50 (3H, s, 3H, s, CH_3), 1.78 (1H, d, *J* = 4.6 Hz, H7), 2.06 (1H, dd, *J* = 14.2, 4.1 Hz, H1a), 2.64 (1H, dd, *J* = 14.2, 10.5 Hz, H1b), 3.12−3.18 (1H, m, O*H*), 3.16 (1H, ddd, *J* = 10.5, 4.1, 2.3 Hz, H2), 3.42 (1H, d, *J* = 1.4 Hz, H6), 3.70 (3H, s, $COOCH_3$), 3.76 (1H, ddd, *J* = 5.5, 2.3, 2.3 Hz, H3), 4.39 (1H, d, *J* = 8.2 Hz, H9), 4.73 (1H, ddd, *J* = 8.2, 4.6, 1.4 Hz, H8), 6.24 (1H, dd, *J* = 8.2, 5.5 Hz, H3′), 6.28 (1H, dd, *J* = 8.5, 2.3 Hz, H15); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 26.1, 27.9, 28.4, 28.8, 40.5, 42.2, 43.6, 50.6, 52.5, 58.0, 60.2, 72.3, 72.4, 76.7, 108.9, 128.1, 136.8, 172.8, 204.8. HRMS (ESI) calcd for $C_{20}H_{26}NaO_7$ $[M + Na]^+$ 401.1571, found 401.1573.

Cycloadduct 4b. According to the synthetic procedure of **4a**, cycloadduct **4b** (289 mg, 0.768 mmol) was synthesized from **5** (279 mg, 0.954 mmol) and methyl propiolate (9.0 mL) in 81% yield. The residue was purified by flash column chromatography on silica gel (15 g, hexane/EtOAc 1/0 to 2/1 to 1/1 to 1/2 to 0/1) to afford impure cycloadduct **4b**. The impure material was further purified by flash column chromatography on silica gel (15 g, hexane/EtOAc 1/0 to 2/1 to 1/1 to 1/2 to 0/1). ^{1}H−^{1}H COSY, HMQC, and HMBC spectra were utilized for the peak assignments: pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.79 (1H, d, *J* = 4.1 Hz, H7), 3.06 (1H, s, O*H*), 3.44 (1H, d, *J* = 1.4 Hz, H6), 3.81 (3H, s, $COOCH_3$), 4.69 (1H, d, *J* = 8.2 Hz, H9), 4.78−4.82 (2H, m, H3 and 8), 6.32 (1H, dd, *J* = 7.3, 1.8 Hz, H15), 6.69 (1H, dd, *J* = 7.3, 6.0 Hz, H3′), 7.84 (1H, d, *J* = 2.3 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 26.1, 28.4, 28.8, 43.3, 49.1, 52.2, 54.2, 56.0, 57.0, 72.0, 72.4, 74.2, 109.3, 133.2, 134.3, 135.0, 146.2, 163.7, 196.1; HRMS (ESI) calcd for $C_{20}H_{24}NaO_7$ $[M + Na]^+$ 399.1414, found 399.1414.

Cycloadduct 4c. A mixture of **5** (1.85 g, 6.33 mmol) and ethynyl *p*-tolyl sulfone (5.0 g, 28 mmol) in toluene (60 mL) was heated to 80 °C and was stirred for 20 h. After being cooled to room temperature, the mixture was concentrated. The resultant residue was purified by flash column chromatography on silica gel (60 g, hexane/EtOAc 2/1 to 1/1 to 1/2) to afford cycloadduct **4c** (2.09 g, 4.42 mmol) in 70% yield. ^{1}H−^{1}H COSY, HMQC, and HMBC spectra were utilized for the peak assignments: pale yellow solid; mp 232−234 °C; $[\alpha]^{24}_D$ +9.0 (*c* 1.2, $CHCl_3$); IR (neat) ν 3531, 2980, 2935, 1743, 1319, 1212, 1155, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.76 (1H, d, *J* = 4.1 Hz, H7), 2.43 (3H, s, ArCH_3), 3.36 (1H, d, *J* = 1.4 Hz, H6), 4.39 (1H, ddd, *J* = 6.0, 2.3, 1.8 Hz, H3), 4.67 (1H, d, *J* = 8.2 Hz, H9), 4.77 (1H, ddd, *J* = 8.2, 4.1, 1.4 Hz, H8), 6.34 (1H, dd, *J* = 7.3, 1.8 Hz, H15), 6.63 (1H, dd, *J* = 7.3, 6.0 Hz, H3′), 7.34 (2H, d, *J* = 7.8 Hz, aromatic), 7.74 (2H, d, *J* = 7.8 Hz, aromatic), 7.87 (1H, d, *J* = 2.3 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 23.4, 26.1, 28.4, 28.7, 43.3, 49.5, 54.1, 55.7, 57.0, 71.9, 72.4, 74.1, 109.6, 127.9, 130.2, 132.2, 135.5, 135.8, 143.6, 144.5, 145.1, 194.3; HRMS (ESI) calcd for $C_{25}H_{28}O_7SNa$ $[M + Na]^+$ 495.1448, found 495.1434.

Acetate 23ba. $Ce(OTf)_3$ (49 mg, 83 μmol) was added to a solution of cycloadduct **4b** (6.2 mg, 16 μmol) in a mixture of CH_3CN (540 μL) and H_2O (270 μL) at room temperature. The reaction mixture was heated to 70 °C and was stirred for 14 h. After the mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ (5 mL) was added. The resultant mixture was extracted with EtOAc (2 mL × 8), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of silica gel (1 g, EtOAc/*i*-PrOH 1/0 to 5/1) to afford crude triol **22b**, which was used in the next reaction without further purification.

CsOAc (16 mg, 83 μmol) was added to a solution of the above crude **22b** in DMF (550 μL) at room temperature. The reaction mixture was heated to 45 °C and was stirred for 18 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (5 mL) was added. The resultant mixture was extracted with EtOAc (2 mL × 8), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, EtOAc/*i*-PrOH 1/0 to 5/1) to afford acetate **23ba** (1.8 mg, 4.6 μmol) in 29% yield over 2 steps: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, s, H12), 1.41 (3H, s, H13), 2.08 (3H, s, CH_3 of Ac), 2.43 (1H, dd, *J* = 11.4, 2.7 Hz, H7), 2.88 (1H, br, O*H*), 3.81 (3H, s, OCH_3), 4.29 (1H, d, *J* = 3.6 Hz, H9), 4.62 (1H, m, Hz, H8), 4.66 (1H, d, *J* = 6.4 Hz, H3), 5.14 (1H, d, *J* = 11.4 Hz, H6), 6.48−6.55 (2H, m, H3′and 15), 7.93 (1H, s, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 29.8, 30.8, 46.2, 52.3, 54.0, 56.5, 68.5, 69.3, 71.4, 72.8, 73.5, 129.4, 133.7, 137.6, 144.4, 163.9, 170.6, 201.0; HRMS (ESI) calcd for $C_{19}H_{24}O_9Na$ $[M + Na]^+$ 419.1313, found 419.1316.

Compound 24ba. *p*-tol$SO_3H·H_2O$ (5.1 mg, 27 μmol) was added to a solution of **23ba** (2.3 mg, 5.9 μmol) in benzene (550 μL) at room temperature. The reaction mixture was heated to 50 °C and was stirred for 2.5 h. After the mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ (3 mL) was added. The resultant mixture was extracted with EtOAc (2 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc) to afford **24ba** (1.0 mg, 2.6 μmol) in 44% yield. ^{1}H−^{1}H COSY spectrum was utilized for the peak assignments: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (3H, br s, H12), 2.25 (1H, d, *J* = 0.9 Hz, O*H*), 2.69 (1H, dd, *J* = 11.0, 2.8 Hz, H7), 2.76 (1H, d, *J* = 9.6 Hz, O*H*), 3.20 (1H, d, *J* = 1.4 Hz, O*H*), 3.28 (1H, s, O*H*), 3.80 (3H, s, OCH_3), 3.81 (1H, dd, *J* = 11.0, 1.4 Hz, H6), 4.18 (1H, m, H3), 4.40 (1H, dd, *J* = 9.6, 4.1 Hz, H9), 4.69 (1H, m, H8), 4.96 (1H, m, H13a), 5.20 (1H, dd, *J* = 1.8, 1.4 Hz, H13b), 6.58 (2H, d, *J* = 3.7 Hz, H3′ and 15), 7.86 (1H, d, *J* = 1.8 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 48.6, 52.3, 53.8, 55.6, 68.5, 68.7, 70.7, 70.8, 114.1, 128.3, 134.3, 137.0, 141.7, 146.1, 163.7, 204.4; HRMS (ESI) calcd for $C_{17}H_{20}O_7Na$ $[M + Na]^+$ 359.1101, found 359.1107.

Compound 24bb. $Ce(OTf)_3$ (510 mg, 0.869 mmol) was added to a solution of cycloadduct **4b** (97 mg, 0.26 mmol) in a mixture of CH_3CN (2 mL) and H_2O (1 mL) at room temperature. The reaction mixture was heated to 70 °C and was stirred for 12 h. After the mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ (10 mL) was added. The resultant mixture was extracted with EtOAc (10 mL × 8), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of silica gel (5 g, hexane/EtOAc 1/2 to 0/1) to afford crude triol **22b**, which was used in the next reaction without further purification.

CsOBz (117 mg, 0.461 mmol) was added to a solution of the above crude **22b** in DMF (1.5 mL) at room temperature. The reaction mixture was heated to 50 °C and was stirred for 14 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (10 mL) was added. The resultant mixture was extracted with EtOAc (5 mL × 6), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of silica gel (2 g, hexane/EtOAc 1/2 to 0/1) to afford crude tetraol **23bb**, which was used in the next reaction without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, s, H12), 1.50 (3H, s, H13), 2.04 (1H, dd, *J* = 5.5, 3.2 Hz, H7), 3.74 (3H, s, OCH_3), 4.45 (1H, d, *J* = 4.1 Hz, H9), 4.54 (1H, ddd, *J* = 6.4, 2.3, 1.4 Hz, H3), 4.75 (1H, m, H8), 4.78 (1H, br s, O*H*), 5.96 (1H, d, *J* = 5.5 Hz, H6), 6.32 (1H, dd, *J* = 6.4, 1.4 Hz, H15), 6.44 (1H, br, O*H*), 6.56 (1H, dd, *J* = 6.4, 6.4 Hz, H3′), 7.40 (2H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.54 (1H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.88 (2H, d, *J* = 7.8 Hz, aromatic), 7.94 (1H, d, *J* = 2.3 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 30.5, 51.2, 52.1, 53.9, 55.9, 68.8, 70.3, 72.0, 72.1, 72.6, 128.4, 129.5, 129.7, 130.0, 133.1, 133.3, 138.1, 146.1, 164.3, 164.7, 197.8; HRMS (ESI) calcd for $C_{24}H_{26}O_9Na$ $[M + Na]^+$ 481.1469, found 481.1459.

p-tol$SO_3H·H_2O$ (56 mg, 0.29 mmol) was added to a solution of the above crude tetraol **23bb** in toluene (2.5 mL) at room temperature. The reaction mixture was heated to 50 °C and was stirred for 2.5 h. After the mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ (10 mL) was added. The resultant mixture was extracted

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with EtOAc (5 mL × 4), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 2/1 to 1/1 to 1/2) to afford **24bb** (29 mg, 65 μmol) in 25% yield over 3 steps. $^1H-^1H$ COSY, HMQC, and HMBC spectra were utilized for the peak assignments: white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (3H, s, H12), 1.67 (3H, s, H13), 2.71 (1H, br s, O*H*), 2.74 (1H, dd, *J* = 5.0, 4.6 Hz, H7), 3.05 (1H, br d, *J* = 5.0 Hz, O*H*), 3.77 (3H, s, OCH_3), 4.59 (1H, dd, *J* = 6.4, 4.6 Hz, H9), 4.66 (1H, ddd, *J* = 6.0, 1.8, 1.8 Hz, H3), 4.80 (1H, m, H8), 5.65 (1H, d, *J* = 5.0 Hz, H6), 6.05 (1H, dd, *J* = 7.3, 1.8 Hz, H15), 6.12 (1H, dd, *J* = 7.3, 6.0 Hz, H3′), 7.48 (2H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.62 (1H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.95 (2H, d, *J* = 7.8 Hz, aromatic), 7.96 (1H, d, *J* = 1.8 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 31.1, 51.3, 52.1, 53.1, 57.0, 68.4, 70.2, 74.5, 75.4, 81.7, 126.3, 128.8, 129.1, 129.6, 133.4, 133.7, 136.3, 145.7, 164.1, 164.5, 194.7; HRMS (ESI) calcd. for $C_{24}H_{24}O_8Na$ $[M + Na]^+$ 463.1363, found 463.1362.

Triol 22c. A solution of cycloadduct **4c** (1.25 g, 2.65 mmol) in a mixture of CH_3CN (27 mL), TFA (14 mL), and H_2O (14 mL) was heated to 50 °C and was stirred for 13 h. After being cooled to 0 °C, the mixture was neutralized with aqueous saturated $NaHCO_3$ (200 mL). The resultant solution was extracted with EtOAc (50 mL × 4), and the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc 1/3 to 0/1) to afford impure triol **22c**. The impure material was further purified by flash column chromatography on silica gel (30 g, hexane/EtOAc 1/3 to 0/1) to afford triol **22c** (685 mg, 1.58 mmol) in 60% yield. $^1H-^1H$ COSY spectrum was utilized for the peak assignments: brown amorphous; $[\alpha]^{24}_D$ −52 (*c* 0.83, $CHCl_3$); IR (neat) ν 3479, 1746, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, s, H12), 1.46 (3H, s, H13), 2.02 (1H, d, *J* = 3.7 Hz, H7), 2.41 (3H, s, ArCH_3), 2.74 (1H, br s, O*H*), 3.31 (1H, d, *J* = 11.0 Hz, O*H*), 3.85 (2H, m, H6 and O*H*), 4.16 (1H, m, H9), 4.23 (1H, m, H8), 4.41 (1H, ddd, *J* = 6.4, 1.8, 1.4 Hz, H3), 6.40 (1H, dd, *J* = 6.9, 1.4 Hz, H15), 6.61 (1H, dd, *J* = 6.9, 6.4 Hz, H3′), 7.32 (2H, d, *J* = 8.2 Hz, aromatic), 7.72 (2H, d, *J* = 8.2 Hz, aromatic), 7.89 (1H, d, *J* = 1.8 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 28.7, 29.1, 45.6, 50.5, 53.7, 56.3, 59.8, 69.9, 72.5, 72.9, 127.9, 130.2, 130.9, 135.2, 140.8, 143.0, 143.5, 145.2, 191.7; HRMS (ESI) calcd for $C_{22}H_{24}O_7SNa$ $[M + Na]^+$ 455.1135, found 455.1119.

Compound 24c. CsOBz (532 mg, 2.09 mmol) was added to a solution of triol **22c** (302 mg, 0.698 mmol) and BzOH (256 mg, 2.10 mmol) in DMF (7 mL) at room temperature. The reaction mixture was stirred at room temperature for 48 h, and then H_2O (35 mL) was added. The resultant solution was extracted with Et_2O (15 mL × 9), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane/EtOAc 1/2) to afford impure benzoate **23c**, which was used in the next reaction without further purification. $^1H-^1H$ COSY spectrum was utilized for the peak assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, s, H12), 1.49 (3H, s, H13), 2.00 (1H, dd, *J* = 6.0, 2.3 Hz, H7), 2.38 (3H, s, ArCH_3), 4.14 (1H, m, H3), 4.51 (1H, d, *J* = 4.1 Hz, H9), 4.78 (1H, br s, H8), 5.92 (1H, d, *J* = 6.0 Hz, H6), 6.21 (1H, br s, O*H*), 6.36 (1H, d, *J* = 7.3 Hz, H15), 6.49 (1H, dd, *J* = 7.3, 6.4 Hz, H3′), 7.28 (2H, d, *J* = 8.7 Hz, aromatic), 7.37 (2H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.52 (1H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.72 (2H, d, *J* = 8.7 Hz, aromatic), 7.82 (2H, d, *J* = 7.8 Hz, aromatic), 7.97 (1H, d, *J* = 1.8 Hz, H1); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 21.5, 30.6, 31.2, 52.8, 54.7, 57.8, 69.7, 69.8, 72.4, 73.1, 73.6, 128.6, 129.35, 129.43, 130.3, 130.8, 130.9, 133.9, 137.6, 140.3, 142.8, 145.4, 145.8, 165.1, 195.5; HRMS (ESI) calcd for $C_{29}H_{30}O_9SNa$ $[M + Na]^+$ 577.1503, found 577.1511.

p-tol$SO_3H{\cdot}H_2O$ (321 mg, 1.69 mmol) was added to a solution of the above crude benzoate **23c** in toluene (40 mL) at room temperature. The reaction mixture was heated to 50 °C and was stirred for 16 h. After the mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ (20 mL) and H_2O (50 mL) were successively added. The resultant solution was extracted with EtOAc (30 mL × 3), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane/EtOAc 1/1) to afford **24c** (222 mg, 0.414 mmol) in 59% yield over 2 steps. $^1H-^1H$ COSY, HMQC, and HMBC spectra were utilized for the peak assignments: white solid; mp 223 °C; $[\alpha]^{23}_D$ +59 (*c* 1.2, $CHCl_3$); IR (neat) ν 3490, 2978, 2951, 1739, 1717, 1268, 1254, 1119, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, s, H12), 1.65 (3H, s, H13), 2.41 (3H, s, ArCH_3), 2.69 (1H, dd, *J* = 5.0, 4.1 Hz, H7), 3.23 (1H, d, *J* = 7.8 Hz, O*H*), 4.00 (1H, *J* = 5.0 Hz, O*H*), 4.15 (1H, ddd, *J* = 6.9, 1.8, 1.4 Hz, H3), 4.65 (1H,dd, *J* = 6.9, 5.0 Hz, H9), 4.78 (1H, m, H8), 5.53 (1H, d, *J* = 5.0 Hz, H6), 5.95 (1H, dd, *J* = 6.9, 6.9 Hz, H3′), 6.07 (1H, dd, *J* = 6.9, 1.4 Hz, H15), 7.28 (2H, d, *J* = 7.8 Hz, aromatic), 7.43 (2H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.57 (1H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.70 (2H, d, *J* = 7.8 Hz, aromatic) 7.89 (2H, d, *J* = 7.8 Hz, aromatic), 8.01 (1H, d, *J* = 1.8 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 26.0, 31.1, 51.0, 52.9, 57.7, 67.8, 69.3, 74.4, 75.1, 81.9, 124.6, 127.9, 128.8, 128.9, 129.6, 129.9, 133.7, 135.4, 137.4, 140.7, 144.8, 145.8, 164.6, 193.1; HRMS (ESI) calcd for $C_{29}H_{28}O_8SNa$ $[M + Na]^+$ 559.1397, found 559.1374.

Compound 3. TBSOTf (860 μL, 3.7 mmol) was added to a solution of **24c** (502 mg, 0.936 mmol) and 2,6-lutidine (650 μL, 5.6 mmol) in CH_3CN (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 3.5 h. After the mixture was cooled to 0 °C, H_2O (20 mL) was added. The resultant solution was extracted with EtOAc (10 mL × 3), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated to afford the crude bis-TBS ether **25**, which was used in the next reaction without further purification.

NaOMe (640 μL, 25 wt % in MeOH, 3.0 mmol) was added to a solution of the above crude **25** in MeOH (28 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, and then saturated aqueous NH_4Cl (10 mL) was added. The resultant solution was extracted with EtOAc (10 mL × 3), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of silica gel (10 g, hexane/EtOAc 1/1) to afford impure ketone **26** (578 mg), which was used in the next reaction without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ −0.01 (3H, s, CH_3 of TBS), 0.135 (3H, s, CH_3 of TBS), 0.137 (3H, s, CH_3 of TBS), 0.16 (3H, s, CH_3 of TBS), 0.95 (9H, s, *t*-Bu of TBS), 0.99 (9H, s, *t*-Bu of TBS), 1.19 (3H, s, H12), 1.63 (3H, s, H13), 2.30 (1H, dd, *J* = 5.0, 3.2 Hz, H7), 2.40 (3H, s, ArCH_3), 4.21 (1H, ddd, *J* = 6.4, 1.8, 1.4 Hz, H3), 4.38 (1H, d, *J* = 6.9 Hz, H9), 4.49 (1H, d, *J* = 5.0 Hz, H6), 4.80 (1H, dd, *J* = 6.9, 3.2 Hz, H8), 6.07 (1H, dd, *J* = 7.3, 6.4 Hz, H3′), 6.27 (1H, dd, *J* = 7.3, 1.4 Hz, H15), 7.27 (2H, d, *J* = 7.3 Hz, aromatic), 7.70 (2H, d, *J* = 7.3 Hz, aromatic), 7.83 (1H, d, *J* = 1.8 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.2, −4.1, −4.0, −3.2, 18.3, 18.4, 21.6, 26.0, 26.2, 26.3, 31.1, 52.7, 53.2, 58.5, 68.2, 72.4, 73.2, 77.6, 81.6, 123.0, 127.9, 129.7, 136.3, 139.4, 139.7, 144.3, 146.6, 195.6; HRMS (ESI) calcd for $C_{34}H_{52}O_7SSi_2Na$ $[M + Na]^+$ 683.2864, found 683.2853.

MeMgBr (2.5 mL, 3 M in Et_2O, 7.5 mmol) was added over 5 min to a stirred suspension of the above crude ketone **26** in Et_2O (15 mL) at −50 °C. After the suspension became clear, the reaction mixture was warmed to −40 °C and stirred for 1.5 h. Then saturated aqueous NH_4Cl (10 mL) was added. The resultant solution was diluted with H_2O (10 mL) and was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane/EtOAc 1/1) to afford **3** (499 mg, 0.737 mmol) in 79% yield over 3 steps. HMBC spectrum was utilized for the peak assignments: colorless oil; $[\alpha]^{23}_D$ −47 (*c* 1.1, $CHCl_3$); IR (neat) ν 3476, 2953, 2930, 2858, 1146, 1107, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.04 (3H, s, CH_3 of TBS), 0.126 (3H, s, CH_3 of TBS), 0.134 (3H, s, CH_3 of TBS), 0.15 (3H, s, CH_3 of TBS), 0.95 (9H, s, *t*-Bu of TBS), 1.01 (9H, s, *t*-Bu of TBS), 1.13 (3H, s, H12), 1.23 (3H, s, H14), 1.65 (3H, s, H13), 2.30 (1H, dd, *J* = 5.0, 3.6 Hz, H7), 2.39 (3H, s, ArCH_3), 3.75 (1H, ddd, *J* = 6.4, 2.3, 1.4 Hz, H3), 4.37 (1H, d, *J* = 6.8 Hz, H9), 4.48 (1H, d, *J* = 5.0 Hz, H6), 4.85 (1H, dd, *J* = 6.8, 3.6 Hz, H8), 5.91 (1H, dd, *J* = 7.3, 1.4 Hz, H15), 6.03 (1H, dd, *J* = 7.3, 6.4 Hz, H3′), 7.26 (2H, d, *J* = 8.2 Hz,

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aromatic), 7.71 (2H, d, J = 8.2 Hz, aromatic), 7.77 (1H, d, J = 2.3 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.3, −4.1, −4.0, −3.2, 18.3, 18.4, 21.6, 26.07, 26.11, 26.3, 26.5, 31.1, 51.9, 53.7, 59.8, 68.1, 72.1, 72.7, 75.6, 80.6, 86.5, 128.1, 129.4, 130.9, 136.5, 137.5, 143.6, 144.8, 145.3; HRMS (ESI) calcd for $C_{35}H_{56}O_7SSi_2Na$ $[M + Na]^+$ 699.3177, found 699.3158.

Carboxylic Acid 28. Ozone was bubbled through a suspension of **3** (499 mg, 0.737 mmol) in CH_2Cl_2 (15 mL) at −78 °C until the solution color turned to purple. Then oxygen gas was bubbled into the reaction mixture for 5 min. After Me_2S (ca. 3 mL) was added, the mixture was warmed to room temperature, stirred for 5 min, and then concentrated. The remaining solvents were removed under an Ar stream for 5 min to afford the crude aldehyde **27**, which was used in the next reaction without further purification.

$NaClO_2$ (1.33 g, 14.7 mmol) was added to a solution of the above crude aldehyde **27** in a mixture of *t*-BuOH (3.5 mL) and 2-methyl-2-butene (7 mL) at 0 °C. Then a cooled solution of $NaH_2PO_4{\cdot}2H_2O$ (4.65 g, 29.8 mmol) in H_2O (7 mL) at 0 °C was added over 5 min. The reaction mixture was stirred at 0 °C for 16 h, and then H_2O (15 mL) was added. The resultant solution was extracted with Et_2O (10 mL × 5), and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane/EtOAc 3/1 to 2/1 to 1/2) to afford carboxylic acid **28** (280 mg, 0.386 mmol, a 4:1 diastereomeric mixture at the C15 position) in 52% over 2 steps: white amorphous; ^{1}H NMR (400 MHz, $CDCl_3$); δ 0.14 (3H × 1/5, s, CH_3 of TBS), 0.15 (3H, s, CH_3 of TBS), 0.156 (3H × 4/5, s, CH_3 of TBS), 0.162 (3H, s, CH_3 of TBS), 0.25 (3H, s, CH_3 of TBS), 0.95 (9H, s, *t*-Bu of TBS), 0.97 (9H, s, *t*-Bu of TBS), 1.13 (3H × 4/5, s, CH_3), 1.23 (3H × 4/5, s, CH_3), 1.26 (3H × 1/5, s, CH_3), 1.67 (3H × 1/5, s, CH_3), 1.72 (3H × 4/5, s, CH_3), 2.31 (1H × 4/5, dd, J = 5.5, 4.6 Hz, H7), 2.38 (3H × 1/5, s, ArCH_3), 2.40 (3H × 4/5, s, ArCH_3), 3.88 (1H × 1/5, d, J = 2.8 Hz, H3), 3.89 (1H × 4/5, d, J = 2.8 Hz, H3), 4.29 (1H × 1/5, d, J = 5.0 Hz, H9), 4.33 (1H × 1/5, dd, J = 5.0 Hz, H8), 4.75 (1H × 4/5, d, J = 5.5 Hz, H9), 4.84 (1H × 4/5, d, J = 5.5 Hz, H6), 4.88 (1H × 4/5, dd, J = 5.5, 4.6 Hz, H8), 5.03 (1H × 1/5, d, J = 5.0 Hz, H6), 5.24 (1H × 1/5, s, H15), 5.32 (1H × 4/5, s, H15), 7.01 (1H × 1/5, d, J = 3.2 Hz, H1), 7.05 (1H × 4/5, d, J = 2.8 Hz, H1), 7.23 (2H × 1/5, d, J = 8.2 Hz, aromatic), 7.28 (2H × 4/5, d, J = 8.2 Hz, aromatic), 7.70 (1H × 4/5, d, J = 8.2 Hz, aromatic), 7.75 (1H × 1/5, d, J = 8.2 Hz, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.22, −5.15, −4.7, −4.6, −3.4, −3.3, −2.0, 14.2, 18.0, 18.4, 18.7, 18.8, 21.1, 21.7, 26.4, 26.5, 26.6, 26.9, 29.7, 29.9, 51.6, 53.9, 54.1, 57.1, 60.5, 70.4, 72.5, 72.7, 73.3, 80.2, 85.6, 89.1, 101.5, 126.8, 127.4, 128.3, 129.2, 129.4, 138.5, 140.6, 140.7, 143.5, 173.8 (Some of ^{13}C peaks of the minor isomer were not observed); HRMS (ESI) calcd for $C_{35}H_{55}O_{10}SSi_2Na_2$ $[M - H + 2Na]^+$ 769.2844, found 769.2830.

Triol 32. Na/Hg (446 mg, 10 wt % Na, 1.94 mmol for Na) was added to a solution of carboxylic acid **28** (70 mg, 97 μmol) in a mixture of CH_2Cl_2 (2 mL) and pH 7 phosphate buffer (4 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h, and then Na/Hg (368 mg, 10 wt % Na, 1.60 mmol for Na) was added. The reaction mixture was stirred for 40 min, and then Na/Hg (550 mg, 10 wt % Na, 2.39 mmol for Na) was added again. The reaction mixture was stirred for further 70 min. While the reaction was being performed, pH 7 phosphate buffer was continuously added to keep the pH of the aqueous layer of reaction mixture below 9 (approximately 20 mL of buffer was added). Then saturated aqueous NH_4Cl (15 mL) was added. The mixture was filtered through a pad of cotton with EtOAc. The filtrate was extracted with EtOAc (10 mL × 3), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of silica gel (5 g, hexane/EtOAc 1/1) to afford impure **29**, which was used in the next reaction without further purification. ^{1}H−^{1}H COSY spectrum was utilized for the peak assignments: ^{1}H NMR (400 MHz, $CDCl_3$) *major isomer* δ 0.051 (3H, s, CH_3 of TBS), 0.11 (3H, s, CH_3 of TBS), 0.12 (3H, s, CH_3 of TBS), 0.13 (3H, s, CH_3 of TBS), 0.83 (9H, s, *t*-Bu of TBS), 0.94 (9H, s, *t*-Bu of TBS), 1.27 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.68 (3H, s, CH_3), 2.28 (1H, dd, J = 5.5, 4.1 Hz, H7), 3.38 (1H, m, H3), 4.52 (1H, d, J = 5.0 Hz, H9), 4.80 (1H, dd, J = 5.0, 4.1 Hz, H8), 4.84 (1H, d, J = 5.5 Hz, H6), 5.28 (1H, s, H15), 5.50 (1H, dd, J = 10.5, 2.8 Hz, H2), 6.11 (1H, dd, J = 10.5, 1.8 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ −4.9, −4.8, −3.5, −2.4, 17.6, 18.4, 18.6, 26.4, 26.5, 26.6, 30.2, 49.6, 53.9, 56.0, 70.3, 71.8, 72.4, 79.6, 85.5, 89.4, 102.6, 127.3, 172.7; HRMS (ESI) calcd for $C_{28}H_{49}O_8Si_2Na_2$ $[M - H + 2Na]^+$ 615.2756, found 615.2751.

A flask charged with the above crude **29**, 1-hydroxypyridine-2(1*H*)-thione **G** (30 mg, 0.24 mmol), and CH_2Cl_2 (1.4 mL) was wrapped with aluminum foil. Then EDCI·HCl (45 mg, 0.23 mmol) was added to the solution. After being stirred at room temperature for 30 min, the reaction mixture was concentrated to afford the crude Barton ester **30**, which was used in the next reaction without purification.

AIBN (1.4 mg, 8.6 μmol) was added to the above crude residue. Then a solution of Ph_3SnH (270 mg, 0.769 mmol) in benzene (1.4 mL), which was degassed by freeze−thaw procedure (× 3), was added to the mixture. After the aluminum foil was removed, the reaction mixture was heated to 80 °C and was stirred under room light for 1.5 h. After the mixture was cooled to room temperature, H_2O (5 mL) was added. The resultant solution was extracted with CH_2Cl_2 (3 mL × 3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of short column, which was consecutively packed with silica gel 10 g and 10% (w/w) KF contained silica gel 2 g, with eluents (CH_2Cl_2 to hexane/EtOAc 10/1 to 5/1) to afford impure **31**, which was used in the next reaction without further purification. ^{1}H−^{1}H COSY, HMQC, and HMBC spectra were utilized for the peak assignments: ^{1}H NMR (400 MHz, $CDCl_3$) *major isomer* δ 0.06 (3H, s, CH_3 of TBS), 0.11 (3H, s, CH_3 of TBS), 0.12 (3H, s, CH_3 of TBS), 0.13 (3H, s, CH_3 of TBS), 0.86 (9H, s, *t*-Bu of TBS), 0.95 (9H, s, *t*-Bu of TBS), 1.23 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.65 (3H, s, CH_3), 2.01 (1H, dd, J = 17.4, 6.4 Hz, H3a), 2.23 (1H, dd, J = 5.5, 3.7 Hz, H7), 2.29 (1H, br d, J = 17.4 Hz, H3b), 2.99 (1H, d, J = 0.9 Hz, OH), 3.21 (1H, d, J = 4.1 Hz, OH), 4.47 (1H, d, J = 5.0 Hz, H9), 4.78 (1H, dd, J = 5.0, 3.7 Hz, H8), 4.84 (1H, d, J = 5.5 Hz, H6), 5.31 (1H, d, J = 4.1 Hz, H15), 5.36 (1H, dd, J = 10.1, 3.2 Hz, H1), 5.73 (1H, ddd, J = 10.1, 6.4, 1.8 Hz, H2); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ −4.9, −4.7, −3.5, −2.3, 18.5, 18.6, 21.9, 26.47, 26.51, 26.7, 30.2, 38.3, 53.9, 55.6, 68.9, 70.7, 72.6, 79.9, 84.4, 89.2, 103.0, 126.0, 128.6; HRMS (ESI) calcd for $C_{27}H_{50}O_6Si_2Na$ $[M + Na]^+$ 549.3038, found 549.3047.

$LiBH_4$ (125 μL, 2 M in THF, 0.250 mmol) was added to a solution of the above crude **31** in THF (1.2 mL) at room temperature. The reaction mixture was heated to reflux temperature and was stirred for 18 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (5 mL) and H_2O (5 mL) were successively added. The resultant solution was extracted with EtOAc (5 mL × 3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 4/1 to 3/1 to 2/1) to afford triol **32** (16 mg, 31 μmol) in 32% yield over 4 steps: colorless oil; $[\alpha]^{21}_D$ +6.9 (c 0.80, $CHCl_3$); IR (neat) ν 3304, 2953, 2929, 2857, 1472, 1254, 1104, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.128 (3H, s, CH_3 of TBS), 0.134 (9H, s, CH_3 of TBS × 3), 0.90 (9H, s, *t*-Bu of TBS), 0.94 (9H, s, *t*-Bu of TBS), 1.30 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.67 (3H, s, CH_3), 2.10 (1H, dd, J = 4.6, 2.8 Hz, H7), 2.12 (1H, dd, J = 17.8, 4.6 Hz, H3a), 2.27 (1H, br d, J = 17.8 Hz, H3b), 3.31 (1H, d, J = 12.4 Hz, H15a), 3.84 (1H, d, J = 12.4 Hz, H15b), 4.28 (1H, d, J = 6.0 Hz, H9), 4.60 (1H, dd, J = 6.0, 2.8 Hz, H8), 5.13 (1H, d, J = 4.6 Hz, H6), 5.38 (1H, dd, J = 10.5, 1.0 Hz, H1), 5.48 (1H, ddd, J = 10.5, 4.6, 2.3 Hz, H2); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.6, −3.0, −2.2, 18.6, 18.8, 24.0, 26.5, 26.7, 26.8, 31.3, 41.6, 54.3, 54.7, 66.4, 69.9, 70.8, 70.9, 75.0, 78.4, 85.2, 123.0, 129.9; HRMS (ESI) calcd for $C_{27}H_{52}O_6Si_2Na$ $[M + Na]^+$ 551.3195, found 551.3194.

Hemiacetal 34. H_2O_2 (105 μL, 30 wt % in H_2O, 0.926 mmol) was added to a solution of triol **32** (27 mg, 51 μmol), *n*-Bu_4NCl (69 mg, 0.25 mmol), K_2CO_3 (6.5 mg, 47 μmol), and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (67 mg, 54 μmol) in THF (1.0 mL) at room temperature. The reaction mixture was heated to 50 °C and was stirred for 19 h. H_2O_2 (105 μL, 30 wt % in H_2O, 0.926 mmol) was added to the mixture, and then the reaction mixture was stirred at 50 °C for 24 h. H_2O_2 (105 μL, 1.03 mmol) was added again, and the mixture was stirred for further 9

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h. After the mixture was cooled to room temperature, saturated aqueous $Na_2S_2O_3$ (5 mL) and Et_2O (5 mL) were successively added. The resultant solution was extracted with Et_2O (5 mL × 3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane/EtOAc 4/1 to 2/1) to afford the crude **33**, which was used in the next reaction without further purification. ^{1}H−^{1}H COSY spectrum was utilized for the peak assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, C*H*$_3$ of TBS), 0.12 (3H, s, C*H*$_3$ of TBS), 0.14 (3H, s, C*H*$_3$ of TBS), 0.15 (3H, s, C*H*$_3$ of TBS), 0.87 (9H, s, *t*-Bu of TBS), 0.95 (9H, s, *t*-Bu of TBS), 1.53 (3H, s, C*H*$_3$), 1.57 (3H, s, C*H*$_3$), 1.70 (3H, s, C*H*$_3$), 1.97 (1H, dd, *J* = 16.6, 6.9 Hz, H3a), 2.12 (1H, d, *J* = 3.5 Hz, H7), 2.38 (1H, br d, *J* = 16.6 Hz, H3b), 3.27 (1H, br s, O*H*), 3.47 (1H, d, *J* = 9.2 Hz, H15a), 3.89 (1H, d, *J* = 5.2 Hz, H9), 3.93 (1H, d, *J* = 9.2 Hz, H15b), 4.50 (1H, dd, *J* = 5.2, 3.5 Hz, H8), 4.74 (1H, br s, O*H*), 5.24 (1H, dd, *J* = 10.3, 3.5 Hz, H1), 5.72 (1H, ddd, *J* = 10.3, 6.9, 2.3 Hz, H2); HRMS (ESI) calcd for $C_{27}H_{50}O_6Si_2Na$ $[M + Na]^+$ 549.3038, found 549.3041.

OsO_4 (350 μL, 0.16 M in H_2O, 56 μmol) was added to a solution of the above crude **33** in a mixture of pyridine (200 μL), H_2O (200 μL), and 1,4-dioxane (400 μL). The reaction mixture was stirred at room temperature for 3 h, and then saturated aqueous $NaHSO_3$ (4 mL) was added. The resultant solution was diluted with EtOAc (4 mL). After being vigorously stirred at room temperature for 53 h, the solution was extracted with EtOAc (5 mL × 4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane/EtOAc 1/1 to 1/2) to afford hemiacetal **34** (13 mg, 22 μmol) in 43% yield over 2 steps. ^{1}H−^{1}H COSY, HMQC, and HMBC spectra were utilized for the peak assignments: colorless oil; $[\alpha]^{21}_D$ −1.8 (*c* 0.40, $CHCl_3$); IR (neat) ν 3443, 2955, 2929, 2857, 1257, 1092, 1000 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.151 (3H, s, C*H*$_3$ of TBS), 0.154 (3H, s, C*H*$_3$ of TBS), 0.16 (3H, s, C*H*$_3$ of TBS), 0.20 (3H, s, C*H*$_3$ of TBS), 0.91 (9H, s, *t*-Bu of TBS), 0.95 (9H, s, *t*-Bu of TBS), 1.51 (3H, s, C*H*$_3$), 1.69 (3H, s, C*H*$_3$), 1.81 (1H, dd, *J* = 14.7, 3.2 Hz, H3a) 1.85 (3H, s, C*H*$_3$), 1.96 (1H, dd, *J* = 14.7, 4.1 Hz, H3b), 1.95−2.01 (1H, br s, O*H*), 2.12 (1H, d, *J* = 3.6 Hz, H7), 2.19−2.21 (1H, br s, O*H*), 3.45 (1H, d, *J* = 10.1 Hz, H15a), 3.54 (1H, s, O*H*), 3.79 (1H, d, *J* = 4.1 Hz, O*H*), 4.06 (1H, d, *J* = 5.5 Hz, H9), 4.20 (1H, m, H2), 4.36 (1H, dd, *J* = 6.4, 5.5 Hz, H1), 4.49 (1H, dd, *J* = 5.5, 3.6 Hz, H8), 4.50 (1H, d, *J* = 10.1 Hz, H15b); ^{13}C NMR (100 MHz, C_6D_6) δ −5.5, −4.4, −3.0, −1.5, 19.0, 19.3, 25.4, 26.7, 27.2, 28.2, 31.6, 44.6, 56.5, 60.3, 66.1, 69.2, 69.5, 72.4, 72.8, 77.6, 86.0, 88.5, 113.0; HRMS (ESI) calcd for $C_{27}H_{52}O_8Si_2Na$ $[M + Na]^+$ 583.3093, found 583.3107.

Pentaol 2. $LiBH_4$ (140 μL, 2 M in THF, 0.28 mmol) was added to a solution of hemiacetal **34** (7.9 mg, 14 μmol) in 1,2-dichloroethane (5 mL) at room temperature. The reaction mixture was heated to reflux temperature and was stirred for 28 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (3 mL) and H_2O (3 mL) were successively added. The resultant solution was extracted with EtOAc (5 mL × 4), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford the borate ester of **2**. For the methanolysis of the borate ester and the azeotropic removal of trimethyl borate, the residue was dissolved in MeOH (5−10 mL), and the resultant solution was concentrated at 60 °C. The procedure was repeated 8 times. Then the resultant residue was purified by flash column chromatography on silica gel (1 g, $CHCl_3$/acetone 3/1) and preparative TLC (CH_2Cl_2/acetone 3/1) to afford pentaol **2** (2.8 mg, 5.0 μmol) and **34** (1.2 mg, 2.1 μmol) in 36% and 15% yields, respectively. The yield of **2** was calculated to be 42% based on the recovered **34**. ^{1}H−^{1}H COSY spectrum was utilized for the peak assignments: colorless oil; $[\alpha]^{20}_D$ −9.2 (*c* 0.21, $CHCl_3$); IR (neat) ν 3394, 2954, 2928, 2856, 1472, 1253, 1137, 1071, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (3H, s, C*H*$_3$ of TBS), 0.16 (3H, s, C*H*$_3$ of TBS), 0.17 (3H, s, C*H*$_3$ of TBS), 0.22 (3H, s, C*H*$_3$ of TBS), 0.93 (9H, s, *t*-Bu of TBS), 0.95 (9H, s, *t*-Bu of TBS), 1.50 (3H, s, C*H*$_3$), 1.73 (3H, s, C*H*$_3$), 1.75 (3H, s, C*H*$_3$), 1.90 (1H, dd, *J* = 14.2, 3.6 Hz, H3a), 2.05 (1H, dd, *J* = 14.2, 2.8 Hz, H3b), 2.31 (1H, d, *J* = 2.3 Hz, H7), 3.56 (1H, d, *J* = 11.9 Hz, H15a), 4.11 (1H, dd, *J* = 5.5, 2.3 Hz, H8), 4.14 (1H, m, H6), 4.19 (1H, ddd *J* = 4.1, 3.6, 2.8 Hz, H2), 4.43 (1H, d, *J* = 5.5 Hz, H9), 4.53 (1H, d, *J* = 4.1 Hz, H1), 4.62 (1H, d, *J* = 11.9 Hz, H15b), 5.12 (1H, br s, O*H*); ^{13}C NMR (125 MHz, C_6D_6) δ −5.6, −4.5, −2.7, −0.3, 19.1, 19.7, 25.4, 26.9, 27.6, 28.1, 31.2, 43.5, 53.5, 58.5, 66.9, 70.6, 71.6, 73.0, 74.1, 74.2, 78.5, 84.7, 91.4; HRMS (ESI) calcd for $C_{27}H_{54}O_8Si_2Na$ $[M + Na]^+$ 585.3249, found 585.3270.

Tetraol 36. DMAP (1.0 mg, 8.1 μmol) was added to a solution of pentaol **2** (4.1 mg, 7.3 μmol) in a mixture of Et_3N (150 μL), Ac_2O (75 μL), and CH_2Cl_2 (750 μL) at room temperature. The reaction mixture was stirred at room temperature for 9 h, and then aqueous NH_4Cl (5 mL) was added. The resultant solution was extracted with EtOAc (3 mL × 5), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a pad of silica gel (1 g, hexane/EtOAc 1/1) to afford impure triacetate **35**, which was used in the next reaction without further purification.

n-Bu_4NF (24 μL, 1 M in THF, 24 μmol) was added to a solution of the above crude triacetate **35** in THF (620 μL) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and then aqueous NH_4Cl (3 mL) was added. The resultant solution was extracted with EtOAc (3 mL × 4), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 1/3) to afford tetraol **36** (1.9 mg, 4.1 μmol) in 56% yield over 2 steps. ^{1}H−^{1}H COSY spectrum was utilized for the peak assignments: colorless oil; $[\alpha]^{23}_D$ −16 (*c* 0.095, $CHCl_3$); IR (neat) ν 3480, 2926, 1739, 1367, 1240, 1148, 1097, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, s, C*H*$_3$), 1.51 (3H, s, C*H*$_3$), 1.73 (3H, s, C*H*$_3$), 2.00−2.01 (2H, m, H3), 2.10 (3H, s, C*H*$_3$ of Ac), 2.170 (3H, s, C*H*$_3$ of Ac), 2.172 (3H, s, C*H*$_3$ of Ac), 2.44 (1H, d, *J* = 3.7 Hz, H7), 2.89 (1H, br s, O*H*), 3.30 (1H, br s, O*H*), 4.10 (1H, br d, *J* = 6.4 Hz, H9), 4.33−4.36 (1H, m, H8), 4.35 (1H, d, *J* = 12.8 Hz, H15a), 4.67 (1H, d, *J* = 3.6 Hz, H1), 4.74 (1H, d, *J* = 12.8 Hz, H15b), 5.30 (1H, td, *J* = 3.6, 3.2 Hz, H2), 5.81 (1H, s, H6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.3, 21.5, 25.0, 26.3, 30.3, 42.5, 54.0, 55.7, 65.2, 69.70, 69.73, 70.4, 71.7, 72.5, 76.5, 84.0, 90.7, 170.0, 170.5, 172.1; HRMS (ESI) calcd for $C_{21}H_{32}O_{11}Na$ $[M + Na]^+$ 483.1837, found 483.1816.

Diol 37. Bz_2O (4.7 mg, 21 μmol) was added to a solution of tetraol **36** (1.9 mg, 4.1 μmol) in a mixture of Et_3N (410 μL) and CH_2Cl_2 (410 μL) at room temperature. The reaction mixture was stirred at room temperature for 7.5 h, and then Bz_2O (4.2 mg, 19 μmol) was added. After the reaction mixture was stirred for 15 h, DMAP (1.3 mg, 11 μmol) was added. The reaction mixture was stirred at room temperature for further 29 h, and then pH 7 phosphate buffer (5 mL) was added. The resultant solution was extracted with CH_2Cl_2 (3 mL × 3), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (4 mL × 3), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative TLC (hexane/EtOAc 1/2) to afford diol **37** (1.4 mg, 2.1 μmol) in 51% yield: colorless oil; $[\alpha]^{22}_D$ −20 (*c* 0.07, $CHCl_3$); IR (neat) ν 3515, 2919, 2849, 1733, 1235, 1097, 1044 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (3H, s, C*H*$_3$), 1.60 (3H, s, C*H*$_3$), 1.85 (3H, s, C*H*$_3$), 2.04 (1H, dd, *J* = 14.9, 2.9 Hz, H3a), 2.12−2.14 (1H, m, H3b), 2.13 (3H, s, C*H*$_3$ of Ac), 2.14 (3H, s, C*H*$_3$ of Ac), 2.36 (3H, s, C*H*$_3$ of Ac), 2.62 (1H, d, *J* = 3.5 Hz, H7), 2.90 (1H, s, O*H*), 4.48 (1H, d, *J* = 13.1 Hz, H15a), 4.70 (1H, d, *J* = 2.9 Hz, H1), 4.77 (1H, d, *J* = 13.1 Hz, H15b), 5.29 (1H, ddd, *J* = 2.9, 2.9, 2.9 Hz, H2), 5.80 (1H, d, *J* = 6.3 Hz, H9), 6.05 (1H, dd, *J* = 6.3, 3.5 Hz, H8), 6.14 (1H, s, H6), 7.27 (2H, dd, *J* = 7.5, 7.5 Hz, aromatic), 7.45−7.49 (3H, m, aromatic), 7.61 (1H, m, aromatic), 7.78 (2H, dd, *J* = 8.1, 1.4 Hz aromatic), 8.00 (2H, d, *J* = 8.1 Hz, aromatic) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.3, 21.4, 25.1, 26.6, 30.0, 42.1, 53.8, 55.2, 64.1, 68.4, 68.8, 69.7, 70.8, 72.0, 76.2, 84.7, 91.0, 128.3, 128.6, 129.4, 129.6, 129.7, 130.0, 133.1, 133.3, 164.9, 165.1, 169.8, 170.7, 171.7; HRMS (ESI) calcd for $C_{35}H_{40}NaO_{13}$ $[M + Na]^+$ 691.2361, found 691.2343.

4-Hydroxyzinowol (1). DMAP (0.5 mg, 4.1 μmol) was added to a solution of triol **37** (1.4 mg, 2.1 μmol) in a mixture of Et_3N (85 μL), Ac_2O (42 μL), and CH_2Cl_2 (420 μL) at room temperature. The reaction mixture was stirred at room temperature for 17 h, and then pH 7 phosphate buffer (5 mL) was added. The resultant solution was extracted with CH_2Cl_2 (3 mL × 3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was

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purified by preparative TLC (hexane/EtOAc 1/1) to afford 4-hydroxyzinowol **1** (1.3 mg, 1.8 μmol) in 86% yield: colorless oil; $[\alpha]^{21}_{D}$ −11 (*c* 0.065, $CHCl_3$); IR (neat) ν 3550, 2923, 2850, 1747, 1368, 1280, 1229, 1093, 1045, 757, 709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52 (3H, s, H14), 1.60 (3H, s, H12), 1.62 (3H, s, CH_3 of Ac), 1.80 (3H, s, H13), 2.03 (1H, dd, *J* = 15.5, 3.4 Hz, H3a), 2.12 (3H, s, CH_3 of Ac), 2.14 (3H, s, CH_3 of Ac), 2.20 (1H, dd, *J* = 15.5, 3.4 Hz, H3b), 2.41 (3H, s, CH_3 of Ac), 2.59 (1H, d, *J* = 4.0 Hz, H7), 2.88 (1H, s, OH), 4.48 (1H, d, *J* = 13.2 Hz, H15a), 4.90 (1H, d, *J* = 13.2 Hz, H15b), 5.52 (1H, ddd, *J* = 3.4, 3.4, 3.4 Hz, H2), 5.65 (1H, d, *J* = 3.4 Hz, H1), 5.77 (1H, d, *J* = 6.9 Hz, H9), 6.06 (1H, dd, *J* = 6.9, 4.0 Hz, H8), 6.19 (1H, s, H6), 7.22 (2H, dd, *J* = 7.5, 7.5 Hz, aromatic), 7.42 (2H, dd, *J* = 7.5, 7.5 Hz, aromatic), 7.47 (1H, dd, *J* = 7.5, 7.5 Hz, aromatic), 7.59 (1H, dd, *J* = 7.5, 7.5 Hz, aromatic), 7.70 (2H, d, *J* = 7.5 Hz, aromatic), 7.89 (2H, d, *J* = 7.5 Hz, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 21.1, 21.3, 21.4, 25.0, 26.6, 30.0, 42.0, 53.8, 54.0, 64.6, 68.0, 68.1, 69.8, 70.1, 70.6, 76.0, 84.9, 91.0, 128.26, 128.31, 128.8, 129.2, 129.5, 130.3, 133.2, 133.6, 164.9, 165.4, 169.2, 169.6, 169.9, 170.6; HRMS (ESI) calcd for $C_{37}H_{42}O_{14}Na$ $[M + Na]^+$ 733.2467, found 733.2485.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for all isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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