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Asymmetric induction in cyclohexadienones carrying α-D-glucopyranosyl moiety

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ABSTRACT

Cyclohexadienone derivatives possessing α-D-glucopyranosyl moiety were designed and synthesized using chemical oxidation or electrochemical oxidation with boron-doped diamond electrode in the final stage. In the chiral induction studies, catalytic hydrogenation provided high diastereoselectivity (dr ratio: > 9:1). Conformational analyses of the *C*-glucoside structures were performed by NOE experiments and force field calculations, and supported the observed regio-selectivity.

1. Introduction

Highly reactive cyclohexadienones have been synthesized by oxidation of appropriately functionalized phenol precursors, and utilized as synthetic intermediates of natural products and biologically important substances (Fig. 1). In a relatively early investigation, a plausible biomimetic synthesis of asatone, a component of *Asarum taitonense* H.,[1] was achieved through spontaneous dimerization of the cyclohexadienone (type **B**), which was produced by anodic oxidation of the corresponding phenol (**A**). Closely related synthesis of penicillone A[2a] and asatone[2b] was reported using a chemical oxidant [PhI(OAc)$_2$ (PIDA)].[2] Cationic cyclohexadienones (type **C**) have been generated by chemical[3] and electrochemical methods,[1b,4] and utilized as cationic dienes in Diels–Alder reactions, leading to bicyclic derivatives,[5] or as scaffolds for continuous cyclization reactions.[6]

We have synthesized another series of cyclohexadienones (type **D**) as intermediates of natural marine spiroisoxazoline products, such as aerothionins,[7] calafianin,[7] and fistularins.[8] The absolute configurations of several members were confirmed using optically active intermediates, which were obtained successfully in pure form by diastereomeric separation.[7] Acquisition of optically active cyclohexadienones has attracted a great deal of attention in connection with structural determination and biological activities. For this purpose, enantioselective oxidation of the corresponding phenols has been reported by substrate or reagent control methodologies. An example of the former was the oxidation of *O*-glycosyl catechol to the corresponding cyclohexadienone, which was automatically converted to the bicyclo [2.2.2]octanes.[9] The latter was reported by application of chiral hypervalent iodine oxidants.

In the present investigation, we examined the scope and limitation of the chiral induction onto cyclohexadienone substrates attached to sugars through *C*-glycosidic linkage (type **F**), which were synthesized from the precursor **E**. Although the above-mentioned *ortho*-dienones are prone to Diels–Alder-type dimerization, the *para* isomer is relatively stable and can be isolated.[1b,10] The relatively rigid conformation of the *C*-glycoside was expected to affect the stereochemical contribution of the sugar to the

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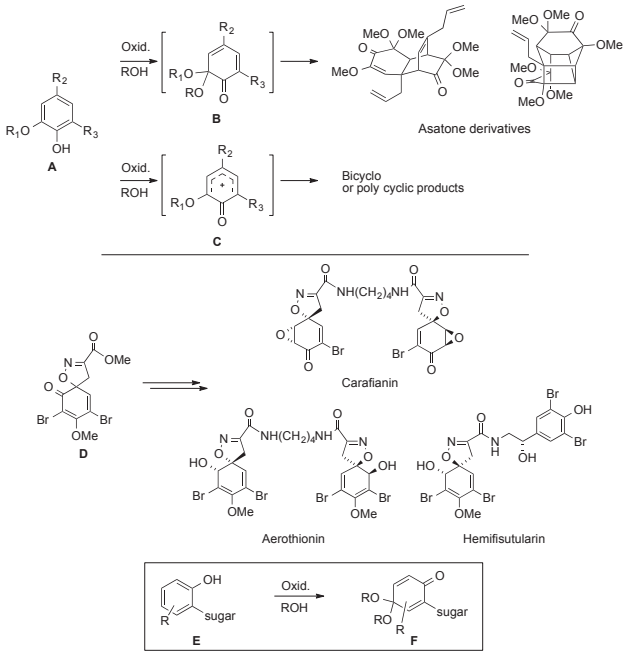


Fig. 1. 2,4- and 2,5-Cyclohexadienones in natural products.

regioselectivity in the cyclohexadienone moiety. In contrast to the *C*-glycosides, upon oxidation of catechol *O*-glycosides (type **A**, R_1 = sugar), the stability of the oxocarbenium ion will support nucleophilic attack of the carbon attached to the glycosyl moiety, producing the corresponding acetal (type **B**, R_1 = sugar).[2,6] From among several protocols for synthesis of **F** from **E**,[11] we employed the *O*– to *C*-glycosidic conversion to give the corresponding phenolic substrates, followed by oxidation to yield the desired cyclohexadienone bearing a glycosyl residue (type **F**, R' = sugar). Catalytic hydrogenation reactions of the optically active cyclohexadienone derivatives were determined.

2. Results and discussion

The required *C*-glycoside was synthesized according to the Schmidt protocol,[12] which involves coupling of the glycosyl imidates with phenol derivatives in the presence of TMSOTf to give the corresponding *O*-glycosides, along with the *C*-glycosides.[13] Among α-D-glucopyranosyl phenol substrates synthesized by coupling of the imidate **1** and phenols **2a**–**c** (Table 1), the 3-methoxy derivative **3a** was accompanied by the corresponding *C*-glycoside **4a** as a minor product (entry 1).

Substrates **2b** and **2c** with higher electron density of the aromatic ring, provided no *C*-glycosides (**4b** and **4c**, entries 2, 3). Further assessment of Lewis acids revealed that TMSOTf (entry 4; ratio of *O*-glycoside vs. *C*-glycoside = 46:31) and $HfCl_4$ (entry 5; 12:46) affected the desired conversion to afford *O* to *C* glycosyl migration (**3a** to **4a**) (Table 2).[14] The former case gave better material balance than the latter.

2.1. Oxidation of glycosides

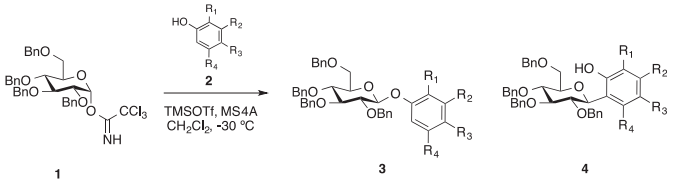
As conversion of phenols to dienone structures proceeded by a two-electron oxidation process, chemical oxidation of the product **4a** with PIDA in MeOH was examined. Smooth conversion by the plausible reaction process provided the desired dienone **5** in 77% yield (Scheme 1). In contrast, further attempts by anodic oxidation of **3b** provided no expected products. In our previous work, similar difficulties had been circumvented by protection of the phenols.[11] Thus, **4a** was methylated under standard reaction conditions to give the methylether **6** in 97% yield. The anodic oxidation of **6** was inspected under several reaction conditions. As outlined in Table 3, the desired reaction proceeded only when BDD electrode was used as anode (entry 3). In our previous study of electrolysis on BDD electrodes, we reported the generation of methoxyradicals on BDD electrodes better than the others and methoxyradicals mediated the anodic oxidation of dimethoxybenzene.[15] This observation suggested that the oxidative methoxylation and followed oxidation reactions would be mediated by methoxyradicals. In addition, in the flow cell system which manipulate methoxy radicals, **5** was provided in 49% yield along with the recovered educt **6** (entry 4).

2.2. Catalytic hydrogenation

During manipulation of the cyclohexadienone attached to the glycosyl moiety **5**, Pd/C-catalyzed hydrogenation was found to provide a diastereomeric mixture in 31% yield (**7a**/**7b** = 48:52), although partial deprotection of Bn groups caused low yields (entry 1 in Table 4). To improve the yield of the reaction, Bn protecting groups of the glycosyl moiety were replaced with other acyl groups, including Ac (**9**), Bz (**10**), and Boc (**11**), through **7** and **8** (Scheme 2). In the reaction entries using the synthetic acyl derivatives, the Bz derivative **10** gave the highest selectivity and yield (**13a** and **13b** in 75% and 8% yields, entry 3 in Table 4).

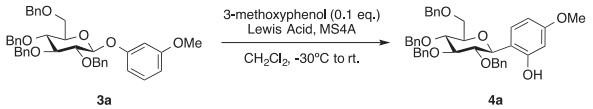
In the hydrogenation reactions of **10**, protic solvents facilitated the production of the aromatic compound **15** as main products (entries 3 and 5 in Table 5), while aprotic solvents suppressed generation of **15**. This is probably because protic solvent allows

Table 1
Synthesis of *O*– and C-glycosides.

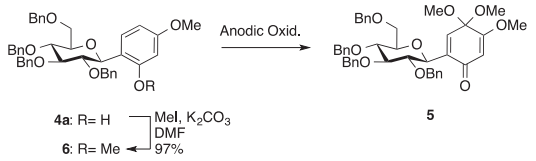


Entries	Phenol substrates 2	Yield (%)	
		O-Glycoside **3**	*C*-Glycoside **4**
1	**a**: $R_{1,3,4}$ = H, R_2 = OMe	73	16
2	**b**: $R_{3,4}$ = H, $R_{1,2}$ = OMe	90	0
3	**c**: R_1 = H, $R_{2,3,4}$ = OMe	80	0

Table 2
Synthesis of *C*-glycoside **4a** through *O*–*C* migration.



Entries	Lewis Acid	Yields (%)	
		O-Glycoside **3a**	*C*-Glycoside **4a**
1	$ZrCl_4$ (>10 eq.)	no reaction	
2	$Sc(OTf)_3$ (>10 eq.)	no reaction	
3	$Yb(OTf)_3$ (>10 eq.)	no reaction	
4	$HfCl_4$ (1 eq.)	12	46
5	TMSOTf (5 eq.)	46	31



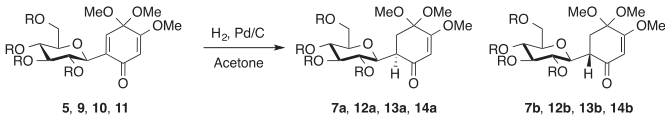
Scheme 1. Phenol oxidation into 2,5-cyclohexadienone.

Table 3
Anodic oxidation of *C*-glycoside **6**[a].

Entry	Anode	Flow rate (mL/min)	Yield (%)[d]	
			6	**5**
Batch[b]				
1	GC	–	80	–
2	Pt	–	75	–
3	BDD	–	28	26
Flow cell[c]				
4	BDD	0.005	34	49
5	BDD	0.01	11	37
6	BDD	0.003	0	44

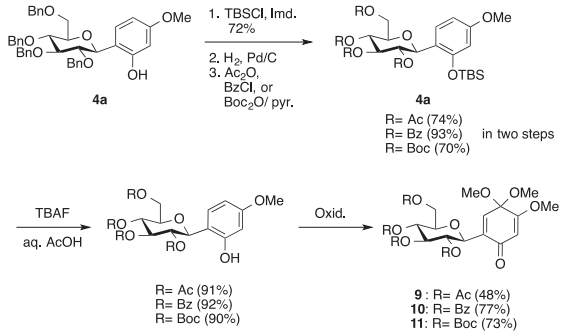
[a] 10 mM solution of **6** in 2% KOH MeOH solution was used.
[b] Pt wire cathode, current density 8.0 mA, 13 $Fmol^{-1}$.
[c] Pt plate cathode, current density 0.8 $mAcm^{-2}$, 10 $Fmol^{-1}$.
[d] Isolated yield.

Table 4
Hydrogenation of C-glycosides **5**, **9**–**11**[a].



Entries	Educts (R)	Yields (%)[b]		*dr* (**a**:**b**)
1	**5** (Bn)	**7a** (15)	**7b** (16)	42:58
2	**9** (Ac)	**12a** (49)	**12b** (14)	78:22
3	**10** (Bz)	**13a** (75)	**13b** (8)	90:10
4	**11** (Boc)	**14a** (30)	**14b** (11)	73:27

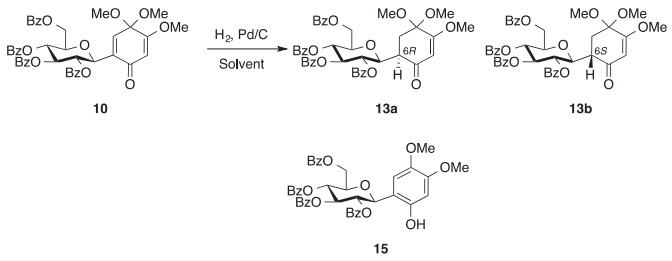
[a] Reaction conditions: cyclohexadienone in acetone (0.05 M), 5% Pd/C (10 mol%), H_2 atmosphere, room temperature.
[b] Isolated yield.



Scheme 2. Synthesis of **9**–**10**.

proton migration to generate the corresponding arylic system. The highest regioselectivity was achieved in acetone as solvent. Interestingly, the preferential **13a**-type diastereoselectivity was observed in all of the solvents we used. Structures of the products were confirmed by NOE experiments. In **13a**, C-8 proton with a *cis*-relationship to the C-7 proton was correlated with the C-2 proton of

Table 5
Effects of solvents on diastereoselective hydrogenation[a].



Entries	Solvent	Yields (%)[b]				dr ratio (**a**:**b**)
		10	**13a**	**13b**	**15**	
1	dioxane	2.3	59	7	n.d.	90:10
2	THF	7.5	65	6	n.d.	92:8
3	tBuOH	12.5	n.d.	n.d.	40	n.d.
4	acetone	2.1	75	8	1	90:10
5	EtOH	24.3	23	0.2	49	99:1
6	DMF	38	43	3	16	93:7
7	MeOH/EtOAc	n.d.	59	4	n.d.	93:7

[a] Reaction conditions: cyclohexadienone in acetone (0.05 M), 5% Pd/C (10 mol%), H_2 atmosphere, room temperature.
[b] Isolated yield.

the glycosyl moiety. Similarly, **13b** showed a correlation between C-8 carrying *trans*-relationship to C-7 and C-2 (Fig. 2). To support the NMR-based structural elucidation, lowest energy conformations of **12a** and **12b** were calculated by MOE (Molecular Operating Environment, ver. moe 2012.1001) using the Born solvation model with the dielectric constant of $CHCl_3$ (4.8). As indicated in Fig. 2, the configurations at C-7 in **12a** and **12b** were in good accordance with those obtained by the NOE measurement. The same C-7 configurations in **7a**,**b**, **13a**,**b**, and **14a**,**b** as **12a**,**b** were confirmed by chemical conversion of the protecting groups. Although the 6*R*

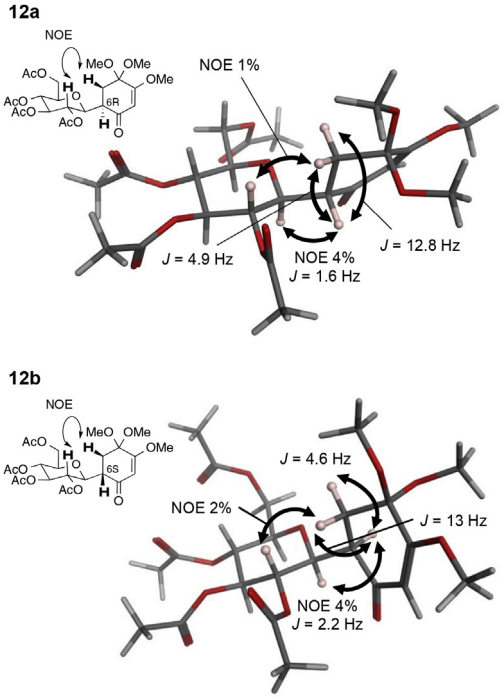


Fig. 2. Structures of **12a** and **12b** and NOE correlations.

configuration in the hydrogenated derivatives was dominantly produced in the acyl derivatives (**12**, **13**, and **14**), the benzyl derivative **7** showed the opposite stereoselectivity. To confirm the reaction prospect, theoretical calculations were carried out to estimate the opposite stereoselectivity. To confirm the reaction prospect, theoretical calculations were carried out to estimate the conformational abundance ratio in solution. Conformers of compounds **5**, **9**, **10**, and **11** were corrected with the following conditions. Stability of each conformers are within 2.75 kcal/mol from the global minimum, and each structures are at least 0.015 Å root mean square distance (RMSD) apart from each other. The diastereomer ratio predicted by the calculation agreed quite well with the experimental data (Table 6). This observation indicated that the theoretical calculation can reproduce the remarkable effect of the substrate conformations in solutions.

3. Conclusion

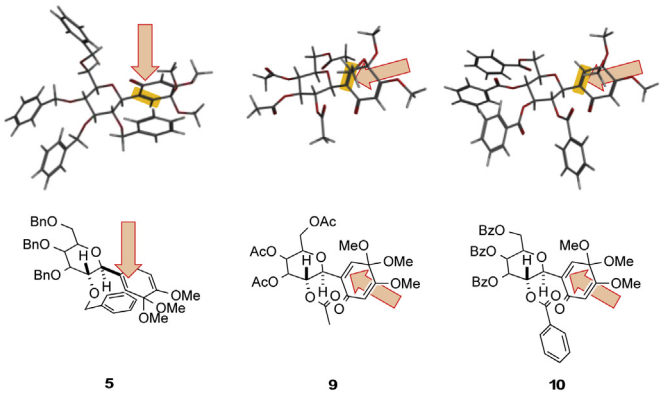
In conclusion, cyclohexadienone derivatives carrying the α-D-glucopyranosyl moiety were designed and synthesized using chemical or anodic oxidation in the final oxidative stage. In the chiral induction reactions, catalytic hydrogenation provided high diastereoselectivity, although low yields and stereoselectivity were observed in 1,2-nucleophilic addition reaction.[16,17] The conformations of the *C*-glucoside structures responsible for the selectivity were examined by NOE experiments and force field calculations.

4. Experimental section

4.1. General information

All reactions were carried out under an argon atmosphere unless otherwise noted. Dry THF, dry Et_2O and dry CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. Optical rotations were measured on a JASCO P-2200 digital polarimeter with a sodium (D line) lamp. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were obtained on JNM-α400, JNM-AL400 and JNM-ECX400 spectrometers in deuterated solvent. Deuteriochloroform was used as a solvent, unless otherwise stated. High-resolution mass spectra were obtained on Waters LCT Piemier XE (ESI). Preparative and analytical TLC were carried out on silica gel plate (Kieselgel 60 F254, E. Merck AG., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto silica 60 N (spherical, neutral, 105–210 μM) was used for column chromatography.

Table 6
Conformation of *C*-glycosides and comparison of selectivity.



5 9 10

Comp.	*dr* ratio (**a**:**b**)	
	Experimental	Calculated
5	42:58	11:89
9	78:22	90:10
10	90:10	92:8
11	73:27	64:36

4.1.1. (2R,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-(3-methoxyphenoxy)tetrahydro-2H-pyran (*3a*) and 5-methoxy-2-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-2-yl)phenol (*4a*)

To a stirring mixture of **1**[12] (200 mg, 0.29 mmol), 3-methoxyphenol (**2a**, 0.025 mL, 0.8 mmol), and MS4A (150 mg) in anhydrous CH_2Cl_2 (1 mL) was added TMSOTf (4 mL, 0.03 mmol) in CH_2Cl_2 (0.5 mL). After being stirred at −30 °C for 30 min, the reaction temperature was raised to room temperature. After 15 h, the reaction was quenched by the addition of sat. aq. $NaHCO_3$. The resulting mixture was filtered through a Celite pad. The filtrate was washed with sat. aq. $NaHCO_3$, and brine, dried (Na_2SO_4). After concentration *in vacuo*, the residue was purified by silica gel column chromatography ($CHCl_3$: hexane: EtOAc = 4/8/1) to afford **3a**[17] as a colorless oil (109 mg, 73%, ~1:1 mixture) and **4a**[12b] as a colorless oil (24.0 mg, 16%), respectively. **3a** (α-isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.08 (m, 20H), 7.16 (dd, *J* = 8.3, 8.3 Hz, 1H), 6.69 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.66 (dd, *J* = 2.5, 2.3 Hz, 1H), 6.58 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.46 (d, *J* = 3.6 Hz, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 4.88 (d, *J* = 11.2 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 12.1 Hz, 1H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 10.6 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.19 (dd, *J* = 9.2, 9. Hz, 1H), 3.87 (ddd, *J* = 10.3, 3.0, 2.0 Hz, 1H), 3.78 (dd, *J* = 10.3, 9.2 Hz, 1H), 3.75 (s, 3H), 3.72 49 (dd, *J* = 10.8, 2.5 Hz, 1H), 3.72 (dd, *J* = 9.2, 3.0 Hz, 1H), 3.57 (dd, *J* = 10.8, 2.0 Hz, 1H). **3a** (β-isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.08 (m, 20H), 7.16 (dd, *J* = 8.3, 8.3 Hz, 1H), 6.69 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.66 (dd, *J* = 2.5, 2.3 Hz, 1H), 6.58 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.00 (d, *J* = 3.6 Hz, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 4.88 (d, *J* = 11.2 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 12.1 Hz, 1H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 10.6 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.19 (dd, *J* = 9.2 Hz, 9.2 Hz, 1H), 3.87 (ddd, *J* = 10.3, 3.0, 2.0 Hz, 1H), 3.78 (dd, *J* = 10.3, 9.2 Hz, 1H), 3.72 (s, 3H), 3.72 (dd, *J* = 10.8, 2.5 Hz, 1H), 3.72 (dd, *J* = 9.2, 3.0 Hz, 1H), 3.57 (dd, *J* = 10.8, 2.0 Hz, 1H). **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.01–7.34 (m, 20H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 2.7 Hz, 1H), 6.47 (dd, *J* = 2.7, 8.4 Hz, 1H), 4.98–4.37 (m, 8H), 3.93–3.67 (m, 6H), 3.77 (s, 3H), 3.57 (d, *J* = 9.6 Hz, 1H).

4.1.2. (2R,3R,4S,5R)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-(2,3-dimethoxyphenoxy)tetrahy dro-2H-pyran (*3b*)

A mixture of **1** (50.0 mg, 0.0732 mmol), 2,3-dimethoxyphenol (**2b**, 18 μL, 0.138 mmol) and MS4A (100 mg) in anhydrous CH_2Cl_2 (0.5 mL) was treated with TMSOTf (10 μL, 0.0769 mmol) in CH_2Cl_2 (0.5 mL), essentially by the same procedure as the case of **3a** and **4a**, to afford **3b** as a colorless oil (44.6 mg, 90%, α/β ratio = 2:1). Chromatographic separation provided both of the glycosides in pure form. **3b** (β-isomer): $[\alpha]_D^{21}$ − 7.4 (*c* 1.0, $CHCl_3$); IR (film) 2863, 1086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 18H), 7.11 (dd, *J* = 7.3, 2.0 Hz, 2H), 6.88 (t, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 8.5, 1.2 Hz, 1H), 6.60 (dd, *J* = 8.5, 1.2 Hz, 1H), 5.49 (d, *J* = 3.4 Hz, 1H), 4.99 (d, *J* = 10.7 Hz, 1H), 4.84 (d, *J* = 10.7 Hz, 1H), 4.82 (d, *J* = 10.7 Hz, 1H), 4.73 (s, 2H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.46 (d, *J* = 10.7 Hz, 1H), 4.36 (d, *J* = 12.2 Hz, 1H), 4.18 (t, *J* = 9.3 Hz, 1H), 4.01 (dt, *J* = 10.2, 2.3 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.75–3.67 (m, 4H), 3.56 (dd, *J* = 10.7, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 150.9, 140.2, 138.9, 138.4, 138.3, 138.0, 128.52, 128.49, 128.47, 128.2, 128.1, 128.0, 127.93, 127.85, 127.8, 127.7, 123.6, 111.3, 107.1, 97.3, 81.9, 80.0, 77.6, 75.8, 75.2, 73.6, 73.1, 68.4, 61.3, 56.2. HRMS (ESI) calcd for $C_{42}H_{44}O_8Na$,

699.2934 (M+Na), found *m/z* 699.2936.**3b** (α-isomer): $[\alpha]_D^{22}$ +82.3 (*c* 1.0, $CHCl_3$); IR (film) 2937, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.17 (m, 20H), 6.95 (t, *J* = 8.4 Hz, 1H), 6.85 (dd, *J* = 8.4, 1.3 Hz, 1H), 6.66 (dd, *J* = 8.4, 1.3 Hz, 1H), 5.21 (d, *J* = 10.7 Hz, 1H), 4.99 (d, *J* = 11 Hz, 1H), 4.99 (d, *J* = 11 Hz, 1H), 4.86 (d, *J* = 10.7 Hz, 1H), 4.85 (d, *J* = 10 Hz, 1H), 4.83 (d, *J* = 10.7 Hz, 1H), 4.59 (d, *J* = 10 Hz, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.80–3.62 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 153.3, 151.6, 139.3, 138.7, 138.4, 138.2, 138.1, 128.6, 128.5, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7, 123.9, 110.1, 106.9, 102.5, 84.8, 81.9, 77.8, 75.9, 75.2, 74.9, 73.6, 69.0, 61.1, 56.2, 55.0. HRMS (ESI) calcd for $C_{42}H_{44}O_8Na$, 699.2934 (M+Na), found *m/z* 699.2910.

4.1.3. *(2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-2-((benzyloxy) methyl)-6-(3,4,5-trimethoxyphenoxy)tetrahydro-2H-pyran (**3c**).*[19]

A mixture of **1** (45.0 mg, 0.659 mmol), 3,4,5-trimethoxyphenol (**2c**, 13 mg, 0.0706 mmol), and MS4A (100 mg) in anhydrous CH_2Cl_2 (0.5 mL) was reacted with TMSOTf (10 μL, 0.0769 mmol) in CH_2Cl_2 (0.5 mL), essentially by the same procedure as the case of **3a** and **4a**, to afford **3c** (α-glycoside) as a colorless oil (37.0 mg, 80%, only α isomer). Chromatographic separation provided **3c**: ^1H NMR (500 MHz) δ 7.41–7.20 (m, 20H), 6.35 (s, 2H), 5.40 (d, *J* = 3.5 Hz, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 4.91–4.81 (m, 4H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 10.7, 1H), 4.46 (d, *J* = 10.8, 1H), 4.18 (t, *J* = 9.2 Hz, 1H), 3.92–3.88 (m, 1H), 3.79–3.76 (m, 10H), 3.75–3.70 (m, 4H), 3.59 (dd, *J* = 10.6, 2.0, 1H).

4.2. *Typical procedures for oxidation of C-glycosides*

4.2.1. *4,4,5-Trimethoxy-2-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)cyclohexa-2,5-dien-1-one (**5**) via chemical oxidation*

To a solution of **4a** (23.0 mg, 0.0356 mmol) in methanol (2.6 mL) was added $PhI(OAc)_2$ (34.5 mg, 0.107 mmol) at 0 °C. After being stirred at room tempertature for 2 h, the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$, and extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4), then concentrated *in vacuo*. The residue was purified by PTLC (hexane: EtOAc = 3/1) to afford **5** as a yellow oil (19.4 mg, 77%). $[\alpha]_D$[19] − 16.9 (*c* 1.00, $CHCl_3$); IR (film) 1677, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.12 (m, 20H), 6.76 (s, 1H), 5.66 (s, 1H), 4.87–4.88 (m, 2H), 4.85 (d, *J* = 10.8 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 9.6 Hz, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 3.81 (s, 3H, overlapped with 3H signals), 3.74–3.69 (m, 3H), 3.58–3.54 (m, 2H), 3.28 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 138.7, 138.4, 138.2, 138.0, 128.6, 128.5, 128.4, 128.1, 127.9, 127.9, 127.8, 127.7, 127.7, 104.2, 94.5, 86.9, 79.5, 78.5, 77.4, 75.7, 75.2, 75.2, 75.0, 73.5, 69.1, 56.3, 51.7, 51.5; HRMS (ESI) calcd for $C_{43}H_{47}O_9$, 707.3200 (M+H), found *m/z* 707.3222.

4.2.2. *(2R,3R,4R,5S,6S)-3,4,5-tris(benzyloxy)-2-((benzyloxy) methyl)-6-(2,4-dimethoxyphenyl)tetrahydro-2H-pyran (**6**)*

To a solution of **4a** (120 mg, 0.186 mmol) in DMF (2.0 mL) were added K_2CO_3 (31.0 mg, 0.224 mmol) and CH_3I (0.015 mL, 0.241 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction was quenched by sat. aq. NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, then dried (Na_2SO_4). The filtrate was concentrated *in vacuo*, and the residue was purified by PTLC to afford (2*R*,3*R*,4*R*,5*S*,6*S*)-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-6-(2,4-dimethoxyphenyl) tetrahydro-2*H*-pyran as a colorless oil (**6**, 79.4 mg, 97%)[18]: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.18 (m, 19H), 6.93 (d, *J* = 9.0 Hz, 1H, overlapped with 1H signal), 6.54 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.47 (d, *J* = 2.3 Hz, 1H), 4.97 (d, *J* = 11.5 Hz, 1H), 4.89 (d, *J* = 11.5 Hz, 2H), 4.75 (d, *J* = 9.3 Hz, 1H), 4.67 (d, *J* = 12.2 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.44 (d, *J* = 10.3 Hz, 1H), 3.96 (d, *J* = 10.3 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.82–3.72 (m, 5H), 3.60 (ddd, *J* = 9.9, 1.8, 0.9 Hz, 1H).

4.2.3. *4,4,5-Trimethoxy-2-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)cyclohexa-2,5-dien-1-one (**5**) via anodic oxidation*

A solution of **6** (20.0 mg, 0.0303 mmol) in MeOH (3 mL) containing KOH (47.0 mg) as a supporting salt was electrolyzed under constant current electrolysis conditions using BDD, platinum or glassy carbon as an anode and platinum wire or plate as a cathode. The reaction mixture was diluted with EtOAc and washed with H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by PTLC (hexane: EtOAc = 2/1, two times developped) to afford **5** as a yellow oil.

Synthesis of Ac (**9**), Bz (**10**), and Boc (**11**) protected C-glycosides.

4.2.4. *(2R,3R,4R,5S,6S)-2-(Acetoxymethyl)-6-(3,3,4-trimethoxy-6-oxocyclohexa-1,4-dien-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**9**)*

To a solution of **4a** (336 mg, 0.520 mmol) in CH_2Cl_2 (5 mL) were added TBSCl (235 mg, 1.56 mmol) and imidazole (106 mg, 1.56 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction was quenched by the addition of sat. aq. $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4). After concentration *in vacuo*, the residue was purified by silica gel column chromatography ($CHCl_3$: hexane: EtOAc = 4/1/1) to afford a siloxy ether (286 mg, 72%): $[\alpha]_D^{21}$ +20.8 (*c* 1.00, $CHCl_3$); IR (film) 2858, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.17 (m, 20H), 7.00 (d, *J* = 3.6 Hz, 1H), 6.55 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 4.94 (d, *J* = 11.1 Hz, 1H), 4.89 (d, *J* = 10.3 Hz, 1H), 4.87 (d, *J* = 11.1 Hz, 1H), 4.75 (br s, 1H), 4.65 (d, *J* = 12.5 Hz, 1H), 4.64 (d, *J* = 10.3 Hz, 1H), 4.53 (d, *J* = 12.5 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.06 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H, overlapped with 4H signals), 3.68–3.56 (m, 2H), 0.99 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 154.9, 138.9, 138.6, 138.5, 138.4, 128.53, 128.45, 128.42, 128.38, 128.2, 128.1, 127.9, 127.8, 127.60, 127.58, 127.3, 122.6, 106.5, 105.2, 87.2, 84.0, 79.6, 78.5, 77.5, 77.4, 77.2, 76.8, 75.7, 75.3, 74.4, 73.5, 69.3, 55.3, 25.9, 18.4, −4.2, −4.4. HRMS (ESI) calcd for $C_{47}H_{56}O_7NaSi$, 783.3693 (M+Na), found *m/z* 783.3677.

To a solution of the siloxy ether (130 mg, 0.171 mmol) in MeOH (2.5 mL) was added 5% Pd–C (10 mol %). After being stirred under H_2 atmosphere at room temperature for 2 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. To a solution of the resulting residue in pyridine (1.0 mL) was added Ac_2O (1.0 mL) at 0 °C. After 3 h, the reaction was quenched by sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4). The filtrate was concentrated *in vacuo*., and the residue was purified by silica gel column chromatography (hexane: EtOAc = 2/1) to afford an acetyl derivative as a colorless oil (71.9 mg, 74% yield): $[\alpha]_D^{23}$ − 2.2 (*c* 1.00, $CHCl_3$); IR (film) 1757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 1H), 6.52 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 5.35 (t, *J* = 9.5 Hz, 1H), 5.28 (t, *J* = 9.5 Hz, 1H), 5.20 (t, *J* = 9.5 Hz, 1H), 4.85 (d, *J* = 9.5 Hz, 1H), 4.24 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.09 (dd, *J* = 12.3, 2.1 Hz, 1H), 3.76 (ddd, *J* = 9.5, 4.7, 2.1 Hz, 1H), 3.75 (s, 3H), 2.051 (s, 3H), 2.047 (s, 3H), 2.01 (s, 3H), 1.79 (s, 3H), 1.04 (s, 9H), 0.27 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.6, 169.7, 169.3, 160.8, 155.1, 129.0, 118.9, 106.5, 105.4, 77.4, 76.3, 75.0, 71.5, 68.9, 62.6, 55.4, 25.9, 20.90, 20.86, 20.80, 20.6, 18.4, −4.0, −4.3. HRMS (ESI) calcd for $C_{27}H_{40}O_{11}NaSi$, 591.2238 (M+Na), found *m/z* 591.2222.

To a solution of the acetyl ester (291 mg, 0.512 mmol) in THF (10.3 mL) and H_2O (9.0 μL) were added AcOH (30 μL) and TBAF

(0.5 mL, 1 M solution in THF) at 0 °C. After 18 h, the reaction mixture was diluted with EtOAc, and washed with brine, dried (Na_2SO_4). The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane: EtOAc = 2/1) to afford a phenol as a colorless oil (211 mg, 91%).

To a solution of the phenol (211 mg, 0.465 mmol) in MeOH (5.0 mL) was added $PhI(OAc)_2$ (450 mg, 1.40 mmol) at 0 °C. After being stirred at room temperature for 1 h, the reaction was quenched by sat. aq. $Na_2S_2O_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous (Na_2SO_4). The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$: hexane: EtOAc = 4/4/1) to afford **9** as a yellow oil (115 mg, 48%): $[\alpha]_D^{22}$ − 40.5 (*c* 1.00, $CHCl_3$); IR (film) 1751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 0.6 Hz, 1H), 5.62 (s, 1H), 5.33 (t, *J* = 9.6 Hz, 1H), 5.14 (t, *J* = 9.6 Hz, 1H), 5.03 (t, *J* = 9.6 Hz, 1H), 4.68 (dd, *J* = 9.6, 0.6 Hz, 1H), 4.26 (dd, *J* = 12.3, 4.8 Hz, 1H), 4.11 (dd, *J* = 12.3, 2.4 Hz, 1H), 3.82 (s, 3H), 3.77 (ddd, *J* = 9.6, 4.8, 2.4 Hz, 1H), 3.32 (s, 3H), 3.31 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 170.8, 170.2, 169.8, 169.2, 138.97, 138.96, 138.2, 103.8, 94.5, 76.2, 74.2, 72.8, 71.8, 68.7, 62.3, 56.4, 51.73, 51.69, 20.9, 20.77, 20.76, 20.6. HRMS (ESI) calcd for $C_{23}H_{30}O_{13}Na$, 537.1584 (M+Na), found *m/z* 537.1560.

4.2.5. (2R,3R,4R,5S,6S)-2-((benzoyloxy)methyl)-6-(3,3,4-trimethoxy-6-oxocyclohexa-1,4-dien-1-yl)tetrahydro-2H-pyran-3,4,5-triyl tribenzoate (**10**)

A solution of the siloxy ether of **4a** (580 mg, 0.763 mmol) in MeOH (10 mL) was submitted to catalytic hydrogenation in the presence of 5% Pd−C (10 mol %). A crude product was benzoylated with BzCl (0.87 mL) in pyridine (7.4 mL) and $CHCl_3$ (1 mL) to afford a benzoyl ester as a colorless oil (598 mg, 93% yield): $[\alpha]_D^{21}$ +12.2 (*c* 1.00, $CHCl_3$); IR (film) 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.94 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.83 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.76 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.53−7.26 (m, 13H), 6.55 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 5.95 (t, *J* = 9.6 Hz, 1H), 5.81 (t, *J* = 9.6 Hz, 2H), 5.23 (d, *J* = 9.6 Hz, 1H), 4.61 (dd, *J* = 12.2, 2.9 Hz, 1H), 4.47 (dd, *J* = 12.2, 5.0 Hz, 1H), 4.21 (ddd, *J* = 9.6, 5.0, 2.9 Hz, 1H), 3.71 (s, 3H), 1.08 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 166.1, 165.5, 165.1, 160.7, 154.9, 133.5, 133.2, 133.1, 133.1, 130.0, 129.89, 129.85, 129.8, 129.4, 129.2, 129.1, 128.51, 128.47, 128.41, 128.38, 128.20, 119.2, 106.8, 105.4, 77.4, 76.8, 75.3, 72.6, 70.2, 63.8, 55.3, 26.0, 25.7, 18.5, 18.1, −3.4, −4.1. HRMS (ESI) calcd for $C_{47}H_{48}O_{11}SiNa$, 839.2864 (M+Na), found *m/z* 839.2873.

A solution of the ester (578 mg, 0.708 mmol) and TBAF (0.70 mL) in THF (14.1 mL), AcOH (41 μL), and H_2O (12 μL) was kept at room temperature for 12 h, to afford a phenol as colorless oil (456 mg, 92%).

Oxidation of the phenol (160 mg, 0.228 mmol) in MeOH (5.7 mL) with $PhI(OAc)_2$ (222 mg, 0.689 mmol) afford **10** as a yellow oil (134 mg, 77%): $[\alpha]_D^{21}$ − 20.6 (*c* 1.00, $CHCl_3$); IR (film) 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dt, *J* = 6.8, 1.5 Hz, 2H), 7.93 (dt, *J* = 6.9, 1.5 Hz, 2H), 7.83 (dt, *J* = 6.9, 1.5 Hz, 2H), 7.80 (dt, *J* = 7.0, 1.5 Hz, 2H), 7.57−7.24 (m, 12H), 6.88 (s, 1H), 6.00 (t, *J* = 9.8 Hz, 1H), 5.76 (t, *J* = 9.8 Hz, 1H), 5.58 (t, *J* = 9.8 Hz, 1H), 5.52 (s, 1H), 5.08 (d, *J* = 9.8 Hz, 1H), 4.64 (dd, *J* = 12.2, 3.1 Hz, 1H), 4.49 (dd, *J* = 12.2, 5.0 Hz, 1H), 4.23 (ddd, *J* = 9.8, 5.0, 3.1 Hz, 1H), 3.73 (s, 3H), 3.25 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 169.0, 166.3, 165.9, 165.43, 165.41, 139.1, 138.2, 133.6, 133.5, 133.3, 133.26, 130.0, 129.91, 129.88, 129.83, 129.75, 129.0, 128.93, 128.88, 128.57, 128.53, 128.50, 128.40, 103.9, 94.6, 76.7, 74.5, 73.2, 72.2, 69.9, 63.2, 56.3, 51.67, 51.66. HRMS (ESI) calcd for $C_{43}H_{38}O_{13}Na$, 785.2210 (M+Na), found *m/z* 785.2209.

4.2.6. (2R,3R,4R,5S,6S)-2-(((tert-butoxycarbonyl)oxy)methyl)-6-(3,3,4-trimethoxy-6-oxocyclohexa-1,4-dien-1-yl)tetrahydro-2H-pyran-3,4,5-triyl tri-tert-butyl tricarbonate (**11**)

A solution of the siloxy ether of **4a** (74 mg, 0.0973 mmol) in MeOH (1.5 mL) was submitted to catalytic hydrogenation in the presence of 5% Pd−C (10 mol %). A crude product was acylated with $(Boc)_2O$ (0.10 mL) and TEA (0.33 mL) in THF (2 mL) to afford a Boc ester as a colorless oil (54.5 mg, 70% yield): $[\alpha]_D^{21}$ +7.4 (*c* 1.00, $CHCl_3$); IR (film) 1759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 1H), 6.49 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 5.13 (t, *J* = 9.4 Hz, 1H), 5.06 (t, *J* = 9.4 Hz, 1H), 4.97 (t, *J* = 9.4 Hz, 1H), 4.83 (d, *J* = 9.4 Hz, 1H), 4.24 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.12 (dd, *J* = 12.0, 2.6 Hz, 1H), 3.79 (ddd, *J* = 9.4, 5.4, 2.6 Hz, 1H), 3.73 (s, 3H), 1.47 (s, 9H), 1.45 (s, 9H), 1.43 (s, 9H), 1.26 (s, 9H), 1.01 (s, 9H), 0.26 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 155.3, 153.3, 152.6, 152.2, 152.0, 149.4, 146.9, 106.1, 105.1, 85.3, 83.1, 82.6, 82.2, 77.8, 77.4, 77.2, 76.2, 73.8, 72.0, 65.2, 55.4, 27.86, 27.84, 27.78, 27.6, 26.0, 25.8, 21.2, 18.4, 14.3, −4.1, −4.3. HRMS (ESI) calcd for $C_{39}H_{64}O_{15}NaSi$, 823.3912 (M+Na), found *m/z* 823.3911.

A solution of the ester (10 mg, 0.0125 mmol) and TBAF (0.0125 mL) in THF (0.25 mL) was kept at room temperature for 4 h, to afford a phenol as colorless oil (7.7 mg, 90%): $[\alpha]_D^{23}$ − 16.0 (*c* 1.00, $CHCl_3$); IR (film) 3437, 1757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 6.36 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.12 (t, *J* = 9.6 Hz, 1H), 5.02 (t, *J* = 9.6 Hz, 2H), 4.50 (d, *J* = 9.6 Hz, 1H), 4.37 (dd, *J* = 12.2, 5.1 Hz, 1H), 4.18 (dd, *J* = 12.2, 2.5 Hz, 1H), 3.86 (ddd, *J* = 9.6, 5.1, 2.5 Hz, 1H), 3.73 (s, 3H), 1.47 (s, 9H), 1.45 (s, 9H), 1.44 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 156.9, 153.3, 152.6, 152.1, 151.3, 129.6, 112.7, 106.4, 103.0, 83.6, 82.9, 82.8, 80.7, 77.4, 76.6, 76.3, 73.3, 71.0, 64.3, 55.4, 28.6, 28.5, 28.4, 27.8, 27.7, 27.5. HRMS (ESI) calcd for $C_{33}H_{50}O_{15}Na$, 709.3047 (M+Na), found *m/z* 709.3025.

Oxidation of the phenol (7.50 mg, 0.0109 mmol) in MeOH (1 mL) with $PhI(OAc)_2$ (10 mg, 0.0311 mmol) afford **11** as a yellow oil (5.9 mg, 73%): $[\alpha]_D^{21}$ − 23.5 (*c* 1.00, $CHCl_3$); IR (film) 1759, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 1H), 5.61 (s, 1H), 5.10 (t, *J* = 9.6 Hz, 1H), 4.90 (t, *J* = 9.6 Hz, 1H), 4.85 (t, *J* = 9.6 Hz, 1H), 4.66 (d, *J* = 9.6 Hz, 1H), 4.27 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.13 (dd, *J* = 12.1, 2.4 Hz, 1H), 3.79 (ddd, *J* = 9.6, 5.4, 2.4 Hz, 1H), 3.78 (s, 3H), 3.298 (s, 3H), 3.296 (s, 3H), 1.46 (s, 18H), 1.44 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 168.7, 153.3, 152.4, 152.20, 152.16, 138.9, 138.0, 104.1, 94.6, 83.2, 82.74, 82.67, 82.5, 77.0, 76.2, 74.9, 72.1, 71.5, 65.0, 56.3, 51.8, 51.7, 27.9, 27.81, 27.77, 27.7. HRMS (ESI) calcd for $C_{35}H_{54}O_{17}Na$, 769.3259 (M+Na), found *m/z* 769.3251.

4.3. Typical procedure for hydrogenation of C-glycosides

To a solution of substrate (20 mg) in solvent (0.05 M) was added 5% Pd−C (10 mol %). After being stirred under H_2 atmosphere at room temperature for 2−9 h, the reaction mixture was filtered, and concentrated *in vacuo*. The resulting residue was purified by PTLC (hexane: EtOAc = 1/1−1/3, two times developed) to give the corresponding products.

4.3.1. (R) −3,4,4-Trimethoxy-6-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(methoxymethyl)tetrahydro-2H-pyran-2-yl) cyclohex-2-en-1-one (7a) and (S)-3,4,4-trimethoxy-6-((2S,3S,4R,5R,6R)-3,4,5-tris(benzyloxy)-6-(methoxymethyl) tetrahydro-2H-pyran-2-yl)cyclohex-2-en-1-one (7b)

7a: $[\alpha]_D^{24}$ − 56.5 (*c* 1.00, $CHCl_3$); IR (film) 1652, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.18 (m, 20H), 5.26 (s, 1H), 4.94 (d, *J* = 11.2 Hz, 1H), 4.91 (d, *J* = 10.5 Hz, 1H), 4.87 (d, *J* = 11.2 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 10.5 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.24 (t, *J* = 9.3 Hz, 1H), 3.69 (s, 3H), 3.69−3.65 (m, 2H), 3.59 (t, *J* = 9.3 Hz,

2H), 3.44 (ddd, J = 9.3, 4.8, 2.4 Hz, 1H), 3.36 (s, 3H), 3.27 (dd, J = 7.2, 2.4 Hz, 1H), 3.24 (s, 3H), 3.05 (ddd, J = 12.5, 4.8, 1.6 Hz, 1H), 2.36 (dd, J = 12.5, 4.8 Hz, 1H), 2.13 (t, J = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 172.0, 138.8, 138.63, 138.56, 138.3, 128.55, 128.45, 128.41, 128.2, 127.91, 127.89, 127.8, 127.7, 127.68, 127.64, 127.61, 104.5, 97.6, 87.9, 80.0, 79.0, 78.8, 77.4, 75.5, 75.2, 74.7, 73.5, 69.3, 56.1, 51.1, 49.0, 43.0, 34.4. HRMS (ESI) calcd for $C_{43}H_{48}O_9Na$, 731.3196 (M+Na), found m/z 731.3195.**7b**: $[\alpha]_D^{21}$ +4.7 (c 1.00, $CHCl_3$); IR (film) 1652, 1616 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.20 (m, 20H), 5.41 (s, 1H), 4.96 (d, J = 11.2 Hz, 1H), 4.91 (d, J = 11.2 Hz, 1H), 4.89 (d, J = 10.8 Hz, 1H), 4.82 (d, J = 10.8 Hz, 1H), 4.68 (d, J = 10.7 Hz, 1H), 4.64 (d, J = 10.7 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 4.25 (dd, J = 10.2, 1.2 Hz, 1H), 3.81–3.63 (m, 4H), 3.76 (s, 3H), 3.49–3.42 (m, 2H), 3.34 (s, 3H), 3.28 (s, 3H), 3.06 (ddd, J = 12.7, 4.6, 1.2 Hz, 1H), 2.29 (dd, J = 12.7, 4.6 Hz, 1H), 2.16 (dd, J = 12.7, 12.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 172.2, 138.8, 138.6, 138.4, 138.2, 128.6, 128.5, 128.40, 128.38, 128.0, 127.9, 127.84, 127.78, 127.72, 127.71, 127.58, 104.3, 97.8, 87.6, 79.2, 78.7, 77.9, 77.4, 76.0, 75.6, 75.1, 75.0, 73.4, 68.9, 56.2, 51.2, 48.9, 43.2, 30.9. HRMS (ESI) calcd for $C_{43}H_{48}O_9Na$, 731.3196 (M+Na), found m/z 731.3171.

4.3.2. (2R,3R,4R,5S,6S)-2-(Acetoxymethyl)-6-((R)-4,5,5-trimethoxy-2-oxocyclohex-3-en-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**12a**) and (2R,3R,4R,5S,6S)-2-(acetoxymethyl)-6-((S)-4,5,5-trimethoxy-2-oxocyclohex-3-en-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**12b**)

12a: $[\alpha]_D^{28}$ − 122.7 (c 1.00, $CHCl_3$); IR (film) 1752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (t, J = 9.4 Hz, 1H), 5.27 (s, 1H), 5.18 (t, J = 9.4 Hz, 1H), 5.04 (t, J = 9.4 Hz, 1H), 4.20 (dd, J = 9.4, 2.5 Hz, 1H), 4.15 (dd, J = 12.4, 5.3 Hz, 1H), 4.08 (dd, J = 12.4, 2.6 Hz, 1H), 3.73 (s, 3H), 3.68 (ddd, J = 9.8, 5.3, 2.6 Hz, 1H), 3.38 (s, 3H), 3.24 (s, 3H), 2.99 (ddd, J = 12.7, 4.7, 2.5 Hz, 1H), 2.43 (dd, J = 12.8, 4.7 Hz, 1H), 2.0 (dd, J = 12.8, 12.7 Hz, 1H), 2.06 (s, 3H), 2.00 (s, 3 H), 1.96 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 172.9, 170.8, 170.4, 169.7, 169.6, 103.2, 97.4, 76.5, 76.3, 74.8, 69.5, 68.7, 62.6, 56.3, 51.2, 49.1, 44.7, 32.1, 20.9, 20.8, 20.8. HRMS (ESI) calcd for $C_{23}H_{32}O_{13}Na$, 539.1741 (M+Na), found m/z 539.1754.**12b**: $[\alpha]_D^{21}$ − 9.6 (c 1.00, $CHCl_3$); IR (film) 1751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H), 5.23 (t, J = 9.9 Hz, 1H), 5.05 (t, J = 9.9 Hz, 1H), 5.04 (t, J = 9.9 Hz, 1H), 4.41 (dd, J = 10.2, 1.6 Hz, 1H), 4.20 (dd, J = 12.4, 4.5 Hz, 1H), 3.98 (dd, J = 12.4, 2.3 Hz, 1H), 3.76 (s, 3H), 3.68 (ddd, J = 10.0, 4.5, 2.3 Hz, 1H), 3.41 (s, 3H), 3.22 (s, 3H), 2.56 (ddd, J = 12.7, 4.8, 1.6 Hz, 1H), 2.47 (dd, J = 12.7, 4.8 Hz, 1H), 2.10 (dd, J = 12.7, 12.7 Hz, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 173.3, 170.8, 170.4, 169.8, 103.7, 97.5, 75.7, 75.1, 74.8, 68.6, 68.4, 62.0, 56.3, 51.1, 49.2, 42.9, 29.7, 20.9, 20.8, 20.8, 20.8, 20.7. HRMS (ESI) calcd for $C_{23}H_{32}O_{13}Na$, 539.1741 (M+Na), found m/z 539.1750.

4.3.3. (2R,3R,4R,5S,6S)-2-((benzoyloxy)methyl)-6-((R)-4,5,5-trimethoxy-2-oxocyclohex-3-en-1-yl)tetrahydro-2H-pyran-3,4,5-triyl tribenzoate (**13a**), (2R,3R,4R,5S,6S)-2-((benzoyloxy)methyl)-6-((S)-4,5,5-trimethoxy-2-oxocyclohex-3-en-1-yl)tetrahydro-2H-pyran-3,4,5-triyl tribenzoate (**13b**) and (2R,3R,4R,5S,6S)-2-((benzoyloxy)methyl)-6-(2-hydroxy-4,5-dimethoxyphenyl) tetrahydro-2H-pyran-3,4,5-triyl tribenzoate (**15**)

13a: $[\alpha]_D^{23}$ − 51.4 (c 1.00, $CHCl_3$); IR (film) 2947, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.3, 1.0 Hz, 2H), 7.90 (dd, J = 8.3, 1.0 Hz, 2H), 7.84 (dd, J = 8.3, 1.5 Hz, 2H), 7.79 (dd, J = 8.3, 1.5 Hz, 2H), 7.56–7.24 (m, 12H), 5.87 (t, J = 9.7 Hz, 1H), 5.75 (t, J = 9.7 Hz, 1H), 5.64 (t, J = 9.7 Hz, 1H), 4.98 (s, 1H), 4.68 (dd, J = 9.7, 2.2 Hz, 1H), 4.58 (dd, J = 12.0, 2.8 Hz, 1H), 4.42 (dd, J = 12.0, 5.6 Hz, 1H), 4.17 (ddd, J = 9.8, 5.6, 2.8 Hz, 1H), 3.47 (s, 3H), 3.36 (s, 3H), 3.19 (s, 3H), 3.13 (ddd, J = 12.5, 4.9, 2.4 Hz, 1H), 2.56 (dd, J = 12.5, 4.9 Hz, 1H), 2.10 (t, J = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 172.7, 166.3, 165.9, 165.4, 165.1, 133.5, 133.4, 133.2, 129.9, 129.83, 129.79, 129.77, 129.03, 128.96, 128.9, 128.63, 128.56, 128.48, 128.45, 128.4, 128.3, 103.3, 97.4, 76.7, 75.0, 70.0, 69.8, 63.6, 56.0, 51.1, 49.1, 45.0, 31.8. HRMS (ESI) calcd for $C_{43}H_{40}O_{13}Na$, 787.2367 (M+Na), found m/z 787.2347.**13b**: $[\alpha]_D^{22}$ +45.4 (c 1.00, $CHCl_3$); IR (film) 2942, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.3, 1.1 Hz, 2H), 7.93 (dd, J = 8.4, 1.2 Hz, 2H), 7.90 (dd, J = 8.2, 1.2 Hz, 2H), 7.80 (dd, J = 8.2, 1.2 Hz, 2H), 7.56–7.24 (m, 12H), 5.95 (t, J = 9.8 Hz, 1H), 5.63 (t, J = 9.8 Hz, 1H), 5.55 (t, J = 9.8 Hz, 1H), 5.32 (s, 1H), 4.79 (dd, J = 9.8, 1.1 Hz, 1H), 4.51 (dd, J = 12.1, 3.1 Hz, 1H), 4.39 (dd, J = 12.1, 4.9 Hz, 1H), 4.15 (ddd, J = 9.8, 4.9, 3.1 Hz, 1H), 3.70 (s, 3H), 3.41 (s, 3H), 3.15 (s, 3H), 2.67 (m, 2H), 2.22 (t, J = 13.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 173.3, 166.2, 165.9, 165.6, 165.4, 133.6, 133.5, 133.3, 133.1, 130.03, 129.97, 129.91, 129.89, 129.8, 129.1, 129.0, 128.6, 128.54, 128.46, 128.4, 103.7, 97.6, 77.5, 77.4, 77.2, 76.8, 76.1, 75.6, 75.0, 69.9, 69.1, 63.1, 56.2, 50.9, 49.4, 29.6. HRMS calcd for $C_{43}H_{40}O_{13}Na$, 787.2367 (M+Na), found m/z 787.2350.**15**: $[\alpha]_D^{24}$ − 48.7 (c 1.00, $CHCl_3$); IR (film) 3447, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.3, 1.3 Hz, 2H), 7.93 (dd, J = 8.4, 1.2 Hz, 2H), 7.83 (dd, J = 8.1, 1.3 Hz, 2H), 7.82 (dd, J = 8.3, 1.3 Hz, 2H), 7.61–7.25 (m, 12H), 6.92 (s, 1H), 6.48 (s, 1H), 6.46 (s, 1H), 6.04 (t, J = 9.8 Hz, 1H), 5.88 (t, J = 9.8 Hz, 1H), 5.83 (t, J = 9.8 Hz, 1H), 4.90 (d, J = 9.8 Hz, 1H), 4.66 (dd, J = 12.4, 2.7 Hz, 1H), 4.58 (dd, J = 12.4, 3.9 Hz, 1H), 4.32 (ddd, J = 9.8, 3.9, 2.7 Hz, 1H), 3.78 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.1, 165.2, 164.6, 150.5, 149.9, 142.3, 133.7, 133.5, 133.42, 133.40, 130.01, 129.95, 129.9, 129.8, 129.7, 129.5, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 111.6, 110.7, 102.3, 80.8, 76.9, 74.0, 71.6, 69.1, 62.6, 56.1, 55.9. HRMS (ESI) calcd for $C_{42}H_{37}O_{12}Na$, 733.2285 (M+Na), found m/z 733.2270.

4.3.4. (2R,3R,4R,5S,6S)-2-(((tert-butoxycarbonyl)oxy)methyl)-6-((R)-4,5,5-trimethoxy-2-oxocyclohex-3-en-1-yl)tetrahydro-2H-pyran-3,4,5-triyl tri-tert-butyl tricarbonate (**14a**) and (2R,3R,4R,5S,6S)-2-(((tert-butoxycarbonyl)oxy)methyl)-6-((S)-4,5,5-trimethoxy-2-oxocyclohex-3-en-1-yl)tetrahydro-2H-pyran-3,4,5-triyl tri-tert-butyl tricarbonate (**14b**)

14a: $[\alpha]_D^{21}$ − 61.7 (c 1.00, $CHCl_3$); IR (film) 1759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (s, 1H), 5.25 (t, J = 9.6 Hz, 1H), 4.98 (t, J = 9.6 Hz, 1H), 4.77 (t, J = 9.6 Hz, 1H), 4.20 (dd, J = 12.0, 6.5 Hz, 1H), 4.10 (dd, J = 12.0, 2.7 Hz, 1H), 4.03 (dd, J = 9.6, 2.2 Hz, 1H), 3.71 (s, 3H), 3.39 (s, 3H), 3.23 (s, 3H), 3.00 (ddd, J = 12.7, 4.7, 2.2 Hz, 1H), 2.40 (dd, J = 12.6, 4.7 Hz, 1H), 1.44 (dd, J = 12.6, 12.7 Hz, 1H), 1.47 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 172.2, 153.2, 152.5, 152.2, 152.1, 103.9, 97.5, 83.1, 82.7, 82.54, 82.52, 77.6, 77.0, 76.2, 72.4, 71.9, 65.5, 56.1, 51.1, 49.2, 44.0, 32.8, 27.9, 27.84, 27.78. HRMS calcd for $C_{35}H_{56}O_{17}Na$, 771.3415 (M+Na), found m/z 771.3397.**14b**: $[\alpha]_D^{23}$ +10.0 (c 1.00, $CHCl_3$); IR (film) 1759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.03 (t, J = 9.8 Hz, 1H), 4.83 (t, J = 9.8 Hz, 2H), 4.39 (dd, J = 9.8, 1.5 Hz, 1H), 4.23 (dd, J = 12.1, 4.2 Hz, 1H), 4.05 (dd, J = 12.1, 2.6 Hz, 1H), 3.74 (s, 3H), 3.67 (ddd, J = 9.8, 4.2, 2.6 Hz, 1H), 3.40 (s, 3H), 3.19 (s, 3H), 2.67 (ddd, J = 12.7, 4.5, 1.5 Hz, 1H), 2.56 (dd, J = 12.7, 4.5 Hz, 1H), 2.09 (t, J = 12.7 Hz, 1H), 1.455 (s, 9H), 1.448 (s, 18H), 1.445 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 173.0, 153.3, 152.6, 152.4, 152.1, 103.8, 97.6, 83.0, 82.5, 82.3, 75.8, 74.9, 71.5, 71.0, 64.5, 56.2, 50.9, 49.2, 42.9, 29.9, 27.90, 27.86, 27.8, 27.7. HRMS (ESI) calcd for $C_{35}H_{56}O_{17}Na$, 771.3415 (M+Na), found m/z 771.3433.

4.4. Computational studies

Theoretical calculations were carried out using MOE (Molecular Operating Environment, ver. moe 2012.1001) with force field (MMFF94x).[20] Low Mode MD (initial temperature = 400 K) implemented in MOE was used for the conformational search.

Solvent effects were included by Distance or Born approximations.

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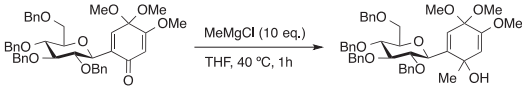
16. 

5 **Me adduct** (1:3 diastereo mixture)

1,2-Addition reaction of 5 with Grignard and alkyl lithium nucleophiles provided the corresponding adducts in low to moderate yields with low diastereoselectivities. Optimized result was obtained in the reaction with MeMgCl/THF 40 °C, which afforded the product in 56% yield with 1:3 diastereoselection. Contribution of reaction temperature indicated the steric hindrance of the substrate, which seemed to impede smooth attack of the reagent to the reactive point.
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