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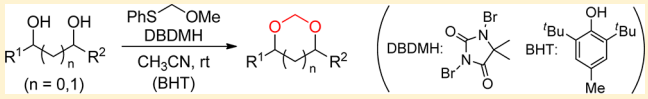
Methylene Acetal Formation from 1,2- and 1,3-Diols Using an *O,S*-Acetal, 1,3-Dibromo-5,5-dimethylhydantoin, and BHT

Tomohiro Maegawa, Yasuyuki Koutani, Kazuki Otake, and Hiromichi Fujioka*

Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan

Supporting Information

ABSTRACT: A mild and efficient method for formation of methylene acetals from 1,2- and 1,3-diols using methoxymethylphenylsulfide, 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), and dibutylhydroxytoluene (BHT) is described. The use of BHT in this process suppresses side reactions and enables high-yielding formation of methylene acetals of various diols, including carbohydrate-type substrates.



Protection of diols is a fundamental reaction in organic synthesis. Among the protection groups that have been developed to date for this purpose,[1] those that involve acetal/ketal-type moieties are preferred. For example, the acetonide moiety is commonly utilized for diol protection owing to its stability under strongly basic and neutral conditions and its ready cleavability using weak acids. The benzylidene acetal group is also used for protection of diols because its deprotection can be promoted by using conditions similar to those employed for acetonides as well as by employing simple hydrogenolysis.

Although it is known to be robust under a wide range of conditions, including those that are strongly basic and moderately acidic, the methylene acetal group has not been used often for diol protection. The main reason for this lies in the fact that formation of methylene acetals is generally conducted under strongly acidic or basic conditions and removal of this group typically requires harsh conditions. Therefore, the development of mild and facile methylene acetal protection and deprotection protocols is highly desirable. As part of an investigation aimed at this goal, we recently developed a novel, mild method for deprotection of methylene acetals.[2] Specifically, we observed that use of a combination of TMSOTf (or TESOTf) and 2,2′-bipyridyl effectively converts methylene acetals to the corresponding 2,2′-bipyridilium salts, which then are transformed to various types of diol derivatives, including free diols, by treatment with H_2O or CH_3OH. Various functional groups, even those that are acid-labile, remain unreactive under the deprotection conditions.

In contrast, procedures for forming methylene acetals have not been fully developed, and some of those described thus far suffer from low efficiencies. The existing methods for methylene acetal generation rely on either acid-catalyzed acetalization or CH_2Br_2-promoted Williamson ether synthesis reactions.[3] Other methods developed for producing methylene acetals utilize DMSO/$POCl_3$ or $SOCl_2$,[4] DMSO/*N*-bromosuccinimide (NBS),[5] DMSO/Br_2,[6] DMSO/TMSCl(/Et_3N),[7,8] TMSOTf/2,6-lutidine/ $(CH_3O)_2CH_2$,[9] 1,1-thiocarbonyldiimidazole/triphenyltin hydride/AIBN,[10] or DMSO/MeOTCT.[11] Some of these procedures have been applied in natural product synthesis,[7b,8,9] and one, the Guiso method (DMSO/$POCl_3$ or $SOCl_2$),[4] is both mild and high-yielding and, consequently, is applicable to carbohydrate substrates. However, in general the yields of most processes producing methylene acetals from corresponding diols are only moderate and their substrate scopes have not been fully explored.

In continuing studies in this area, we investigated a new procedure for forming methylene acetals. Methods for the direct conversion of thioacetals (*S,S*-acetal) and *O,S*-acetals to acetals (*O,O*-acetal) under oxidative conditions have been described in the context of new carbonyl protection protocols.[12] We hypothesized that the methylene unit transfer strategy employed in these processes could be applied to reactions between thioacetals or *O,S*-acetals and diols. Our plan was to employ a combination of simple 1,3-dithianes or *O,S*-acetals as methylene sources and halonium reagents as oxidants in processes that convert diols to methylene acetals. In a study designed to test the feasibility of this strategy, we first investigated suitable methylene sources in reactions of diol **1a** that utilize 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the oxidant (Table 1, entries 1−4). The results showed that 1,3-dithiane does not participate in this reaction (entry 1) but that *O,S*-acetals serve as methylene sources in reactions that generate methylene acetal **2a**. In these processes, the commercially available methoxymethylphenylsulfide was found to be the best methylene donor (entry 2). In addition, we observed that only a trace amount of a methylene acetal is produced when 2-methoxymethylthiopyridine[13] is used for this purpose (entry 4).

Next, a study was conducted to explore several halonium oxidants for the methylene acetal forming reaction of diol **1a** promoted by methoxymethylphenylsulfide (Table 1, entries 5−10). The observations demonstrated that all halonium sources promote this reaction but with different rates. For example, the reaction using *N*-chlorosuccinimide (NCS) requires 24 h for completion, but the yield of the process is high (89%) (entry 5). *N*-Iodosuccinimide (NIS) was observed to be the most reactive oxidant (20 min for completion), but the yield of the reaction is

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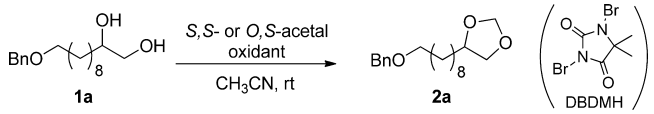
Table 1. Methylene Acetal 2b Formation by Reactions of Diol 1a with *S,S*- or *O,S*-Acetals and Oxidants[a]



entry	*S,S* or *O,S*-acetal	oxidant	reagent equivalent[b]	time	yield (%)[c]
1	1,3-dithiane	DBDMH	1.5	5 h	0
2	PhS OMe	DBDMH	1.5	0.5 h	93
3	$C_{10}H_{21}S$ OMe	DBDMH	1.5	1 h	< 75[d]
4	2-PyS OMe	DBDMH	1.5	1 h	trace
5	PhS OMe	NCS	1.2	24 h	88
6	PhS OMe	NIS	1.2	20 min	82
7	PhS OMe	NBS	1.2	1 h	89
8	PhS OMe	DBDMH	1.2	1 h	89
9	PhS OMe	NBS	1.5	1 h	85
10	PhS OMe	DBDMH	1.5	30 min	93

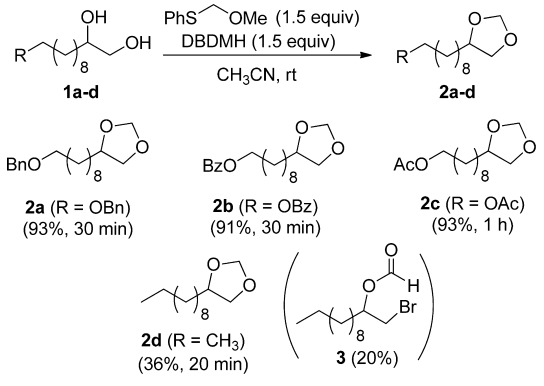
[a]Reactions were carried out using the same amounts of the *S,S*- or *O,S*-acetal and oxidants (1.5 or 1.2 equiv) at rt in CH_3CN. [b]Equivalent of DBDMH is based on the molecule, not on the bromine atom. [c]Isolated yields. [d]Reaction afforded an inseparable mixture of products.

slightly lower (entry 6). Processes promoted by both NBS and DBDMH take place reasonably fast and in high yields (entries 7 and 8), and in contrast to NBS, increasing the amount of DBDMH lowers the reaction time and increases the yield (entries 9 and 10). The findings suggested that DBDMH is an ideal oxidant to be employed in further studies of the methylene acetal forming reaction.

The scope of the new protection methodology was probed utilizing diols containing functional groups other than a benzyl ether, including a benzoate and acetate ester (**1b** and **1c**). In both cases, reactions take place smoothly to afford the corresponding methylene acetals **2b** and **2c** in high yields (Scheme 1). However, reaction of the nonfunctionalized diol **2d** occurs with low efficiency (36%), and the bromoformate **3** is also generated (20%) as a byproduct.

A plausible mechanism for the methylene acetal forming reaction is shown in Scheme 2. In the pathway, oxidation at the sulfur center in $PhSCH_2OCH_3$ by a bromonium ion activates loss

Scheme 1. Methylene Acetal Formation of Diols Promoted by $PhSCH_2OCH_3$ and DBDMH[a]



[a]Equivalent of DBDMH is based on the molecule, not on the bromine atom.

of the phenylthio moiety to form an oxonium ion that reacts with the diol to form a mono-MOM ether intermediate **4**. Cyclization of the mono-MOM monoalcohol **4** then generates the methylene acetal. In fact, we observed that a regioisomeric mixture of mono-MOM protected diols **4** reacts to form a single methylene acetal in quantitative yield under the reaction conditions.[14] Evidence supporting the proposed formation of bromoformate **3** through secondary, Hanessian–Hullar-type bromination reaction[15] of initial formed methylene acetal came from the finding that methylene acetal **2d** reacts to form **3** and the bromoalcohol hydrolysis product under the conditions employed.

On the basis of the thought that the initial step of the Hanessian–Hullar-type reaction is a radical process,[16] we speculated that the presence of the radical scavenger dibutylhydroxytoluene (BHT) in the reaction mixture would inhibit the undesirable side reaction and lead to improved product yields. Indeed, reactions of a variety of diols **1d–l** (Table 2) carried out using 1.5 equiv of $PhSCH_2OCH_3$, 1.5 equiv of DBDMH, and 1.5 equiv of BHT at rt in CH_3CN were found to generate the respective methylene acetals in high yields. Notably, the styrene-derived diol **1h** as well as internal 1,2-diols containing sterically crowded *sec*- and *tert*-hydroxy groups (**1i** and **1j**) are transformed to the corresponding methylene acetals under these conditions (entries 5–7). The method is also applicable to protection of the 1,3-diol **1k**, whose reaction affords a 1,3-dioxane in 85% yield (entry 8). Moreover, triol **1l** is also converted to the methylene acetal **2l**, leaving the terminal hydroxyl group intact (60%) (entry 9).

Finally, we have shown that the protection strategy is also applicable to the sugar substrate **5**, which reacts to produce the corresponding methylene acetal **6** in 85% yield. Importantly, the use of conventional methods, such as those employing acid and base conditions, are not as effective for promoting methylene acetal generation with this substrate (Scheme 3).

In summary, the study described above has led to the development of a novel, mild method, which uses a combination

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Scheme 2. Plausible Mechanism for the Methylene Acetal and Bromoformate Forming Reactions

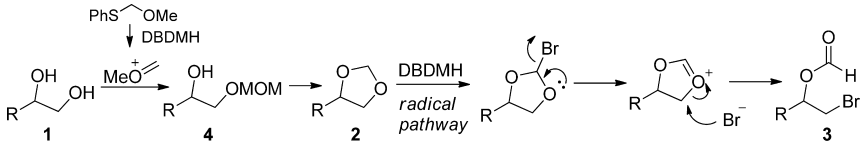
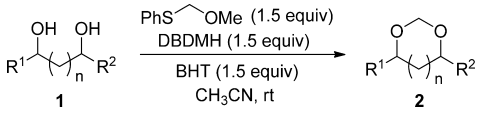
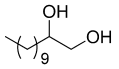
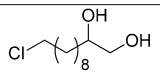
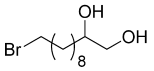
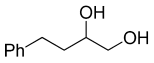
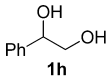
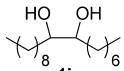
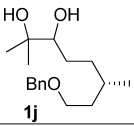
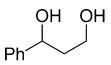
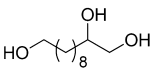


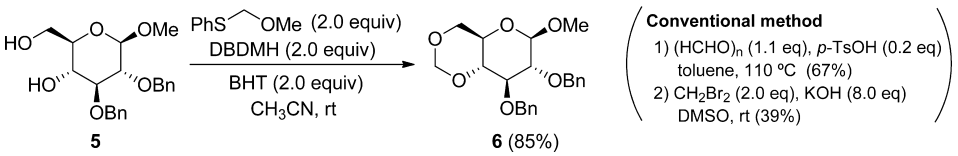
Table 2. Substrate Scope for the Methylene Acetal Forming Reaction Promoted by $PhSCH_2OCH_3$, DBDMH, and BHT[a]



entry	substrate	time	yield (%)[b]
1	 **1d**	20 min	98 (**2d**)
2	 **1e**	50 min	94 (**2e**)
3	 **1f**	1 h	92 (**2f**)
4	 **1g**	30 min	quant (**2g**)
5	 **1h**	15 min	93 (**2h**)
6[c]	 **1i**	30 min	84 (**2i**)
7[c]	 **1j**	30 min	76 (**2j**)
8	 **1k**	1 h	85 (**2k**)
9	 **1l**	45 min	60 (**2l**)

[a]Reactions were carried out using 1.5 equiv of $PhSCH_2OCH_3$, 1.5 equiv of DBDMH, and 1.5 equiv of BHT at rt in CH_3CN. Equivalent of DBDMH is based on the molecule, not on the bromine atom. [b]Isolated yields. [c]2 equiv of each reagent was used.

Scheme 3. Methylene Acetal Formation of Sugar-Type Substrate[a]



[a]Equivalent of DBDMH is based on the molecule, not on the bromine atom.

of $PhSCH_2OCH_3$, DBDMH, and BHT, for converting 1,2- and 1,3-diols to methylene acetals. Noteworthy features of the new method, associated with high yields, short reaction times, and functional group tolerance, should make the methylene acetal procedure a useful method for diol protection.

EXPERIMENTAL SECTION

General Consideration. Infrared spectra (IR) were recorded using a diffuse reflectance measurement of samples dispersed in KBr powder. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t =

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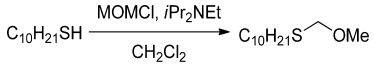
triplet, q = quartet, m = multiplet, brs = broad singlet), coupling constant (Hz), and integration. Mass spectra were obtained with ionization voltages of 70 eV using quadrupole mass spectrometer. Column chromatography and TLC were carried out on Merck Silica gel 60 (230−400 mesh), Kanto kagaku Silica gel 60N (40−50 μm, spherical, neutral), and Merck silica gel F_{254} plates (0.25 mm), respectively. The commercially available reagents were used without further purification. The equivalent of DBDMH indicates whole molecules, not the bromine atom in DBDMH. Compound **1d**, **9**, **2k**, and *n*-decylthiol are commercially available, and compounds **1a**,[2a] **1b**,[2a] **1c**,[17] **1f**,[18] **1g**,[2a] **1h**,[19] **1j**,[20] **1k**,[2a] **1l**,[2a] **5**,[21] **2a**,[2a] **2b**,[2a] **2d**,[22] **2g**,[2a] **2h**,[23] **2l**,[2a] and **7**[24] are known compounds.

General Procedure for Methylene Acetal 2a Formation by Reactions of Diol 1a with *S,S*- or *O,S*-Acetals and Oxidants (Table 1). An oxidant (1.5 or 1.2 equiv) was added to a solution of diol **1a** (1.0 equiv) and *S,S*- or *O,S*-acetal (1.5 or 1.2 equiv) in CH_3CN (0.2 M) at room temperature under N_2. After **1a** was consumed (checking by TLC), 10% aqueous KOH (2 mL) was added to the reaction mixture, and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes → hexanes/AcOEt = 15/1) affording methylene acetal **2a**.

11-(Benzyloxy)undecane-1,2-diol (1a).[2a] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22−1.46 (m, 14H), 1.59−1.64 (m, 2H), 1.72 (brs, 2H), 3.38−3.46 (m, 3H), 3.61−3.66 (m, 2H), 4.48 (s, 2H), 7.24−7.33 (m, 5H).

4-[9-(Benzyloxy)nonyl]-1,3-dioxolane (2a).[2a] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29−1.61 (m, 16H), 3.41−3.48 (m, 3H), 3.95−3.98 (m, 2H), 4.50 (s, 2H), 4.87 (s, 1H), 5.02 (s, 1H), 7.26−7.35 (m, 5H).

Synthesis of Decyl(methoxymethyl)sulfane.



Chloromethyl methyl ether (2 mL, 26.3 mmol) was added to the solution of *n*-decylthiol (2 mL, 9.6 mmol) and *N*-ethyldiisopropylamine (4 mL, 23.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C under N_2. After the starting material was consumed (48 h) (monitored by TLC), the reaction mixture was concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 5/1) affording decyl(methoxymethyl)sulfane as colorless oil (1.65 g, 79%); IR (KBr) 2853, 1971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.7 Hz, 3H), 1.18−1.41 (m, 14H), 1.53−1.61 (m, 2H), 2.57 (t, J = 7.4 Hz, 2H), 3.33 (s, 3H), 4.61 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 28.9, 29.2, 29.3, 29.51, 29.53, 29.9, 30.9, 31.9, 55.6, 75.4; HRMS (EI) calcd for $C_{12}H_{26}OS$ (M^+) 218.1704, found 218.1715.

General Procedure for the Methylene Acetal Formation of Diols Promoted by $PhSCH_2OCH_3$ and DBDMH (Scheme 1). DBDMH (1.5 equiv) was added to a solution of diol **1** (1.0 equiv) and methoxymethyl phenyl sulfide (1.5 equiv) in CH_3CN (0.2 M) at room temperature under N_2. After the substrate **1** was consumed (monitored by TLC), saturated aqueous $NaHCO_3$ (2 mL) was added to the reaction mixture, and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2) affording methylene acetal.

2a: According to the general procedure, the treatment of diol **1a** (63.0 mg, 0.213 mmol) with DBDMH (92.0 mg, 0.320 mmol) and methoxymethyl phenyl sulfide (47.0 μL, 0.320 mmol) for 0.5 h afforded **2a** (60.4 mg, 93%). Eluent, hexanes → hexanes/AcOEt (15/1).

2b: According to the general procedure, the treatment of diol **1b** (60.0 mg, 0.195 mmol) with DBDMH (83.2 mg, 0.292 mmol) and methoxymethyl phenyl sulfide (43.0 μL, 0.292 mmol) for 0.5 h afforded **2b** (56.7 mg, 91%). Eluent, hexanes → hexanes/AcOEt (15/1).

10,11-Dihydroxyundecyl Benzoate (1b).[2a] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29−1.42 (m, 14H), 1.71−1.78 (m, 2H), 1.82 (brs, 1H), 1.97 (brs, 1H), 3.39−3.44 (m, 1H), 3.62−3.70 (m, 2H), 4.29 (t, J = 6.9 Hz, 2H), 7.40−7.44 (m, 2H), 7.51−7.56 (m, 1H), 8.01−8.04 (m, 2H).

9-[1,3-Dioxolan-4-yl]nonyl benzoate (2b).[2a] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23−1.78 (m, 16H), 3.35−3.42 (m, 1H), 3.91−3.97 (m, 2H), 4.29 (t, J = 6.5 Hz, 2H), 4.83 (s, 1H), 4.99 (s, 1H), 7.38−7.43 (m, 2H), 7.50−7.55 (m, 1H), 8.00−8.03 (m, 2H).

2c: According to the general procedure, the treatment of diol **1c** (69.7 mg, 0.282 mmol) with DBDMH (123.0 mg, 0.430 mmol) and methoxymethyl phenyl sulfide (63.0 μL, 0.430 mmol) for 1 h afforded **2c** (68.0 mg, 93%). Eluent, hexanes → hexanes/AcOEt (10/1).

10,11-Dihydroxyundecyl Acetate (1c).[17] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22−1.46 (m, 14H), 1.56−1.63 (m, 2H), 2.03 (s, 3H), 3.40−3.44 (m, 1H), 3.63−3.70 (m, 2H), 4.03 (t, J = 6.9 Hz, 2H).

9-[1,3-Dioxolan-4-yl]nonyl Acetate (2c). Colorless oil; IR (KBr) 2932, 2253, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.64 (m, 16H), 2.01 (s, 3H), 3.38 (t, J = 10.1 Hz, 1H), 3.92−3.96 (m, 2H), 4.01 (t, J = 6.9 Hz, 2H), 4.83 (s, 1H), 4.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 25.77, 25.83, 28.5, 29.2, 29.34, 29.37, 29.48, 33.0, 64.6, 69.6, 76.2, 94.7, 171.2; HRMS (FAB) calcd for $C_{14}H_{27}O_4$ (M^+ + H) 259.1909, found 259.1911.

2d: According to the general procedure, the treatment of diol **1d** (106.6 mg, 0.527 mmol) with DBDMH (226.0 mg, 0.791 mmol) and methoxymethyl phenyl sulfide (116.0 μL, 0.791 mmol) for 20 min afforded **2d** (40.2 mg, 36%) and **3** (30.1 mg, 20%). Eluent, hexanes → hexanes-Et_2O (100/1 → 50/1).

4-Decyl-1,3-dioxolane (2d).[22] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 6.7 Hz, 3H), 1.15−1.65 (m, 18H), 3.36−3.42 (m, 1H), 3.90−3.99 (m, 2H), 4.84 (s, 1H), 4.99 (s, 1H).

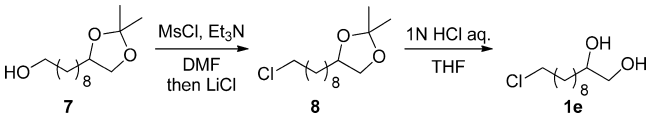
1-Bromododecan-2-yl formate (3). Yellow oil; IR (KBr) 2926, 2255, 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 0.85 (t, J = 6.6 Hz, 3H), 1.20−1.33 (m, 16H), 1.66−1.72 (m, 2H), 3.41−3.52 (m, 2H), 5.10−5.23 (m, 1H), 8.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 24.9, 29.22, 29.29, 29.37, 29.47, 29.54, 31.9, 32.5, 33.7, 72.4, 160.3 ; HRMS (FAB) calcd for $C_{13}H_{25}BrNaO_2$ (M^+ + Na) 315.0936, found 315.0907.

General Procedure for the Methylene Acetal Forming Reaction Promoted by $PhSCH_2OCH_3$, DBDMH, and BHT (Table 2). DBDMH (1.5 equiv) was added to a solution of diol **1** (1.0 equiv), BHT (1.5 equiv), and methoxymethyl phenyl sulfide (1.5 equiv) in CH_3CN (0.2 M) at room temperature under N_2. After **1** was consumed (monitored by TLC), 10% aqueous KOH (2 mL) was added to the reaction mixture ,and the mixture was extracted with Et_2O (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2) affording methylene acetal **2**.

Entry 1: According to the general procedure, the treatment of diol **1d** (101.1 mg, 0.500 mmol) with DBDMH (214.4 mg, 0.750 mmol), BHT (165.3 mg, 0.750 mmol) and methoxymethyl phenyl sulfide (110.0 μL, 0.750 mmol) for 20 min afforded **2d** (105.0 mg, 98%). Eluent, hexanes → hexanes/Et_2O (50/1).

Entry 2: According to the general procedure, the treatment of diol **1e** (83.0 mg, 0.372 mmol) with DBDMH (160.0 mg, 0.558 mmol), BHT (123.0 mg, 0.558 mmol) and methoxymethyl phenyl sulfide (82.0 μL, 0.558 mmol) for 50 min afforded **2e** (82.0 mg, 94%). Eluent, hexanes → hexanes/Et_2O (15/1).

Synthesis of 1e.



4-(9-Chlorononyl)-2,2-dimethyl-1,3-dioxolane (8). MsCl (0.2 mL, 2.2 mmol) was added to the solution of **7**[24] (514.0 mg, 2.1 mmol) and triethylamine (0.4 mL, 2.2 mmol) in DMF (5 mL) at 0 °C under N_2, and the reaction mixture was stirred at room temperature. After **7** was consumed (42 h) (monitored by TLC), LiCl (350.0 mg, 8.2 mmol) was added to the reaction mixture at room temperature under N_2, and the resulting solution was stirred at the same temperature for 8 h. Then H_2O was added to the reaction mixture, and the solution was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 10/1)

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affording **8** as colorless oil (347 mg, 63%); IR (KBr) 2930, 2251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27−1.79 (m, 22H), 3.45−3.53 (m, 3H), 3.98−4.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 26.8, 27.0, 28.8, 29.3, 29.4, 29.6, 32.6, 33.6, 45.2, 69.5, 76.1, 108.6; HRMS (FAB) calcd for $C_{14}H_{28}ClO_2$ (M^+ + H) 263.1778, found 263.1785.

11-Chloroundecane-1,2-diol (1e). A solution of **8** (236.0 mg, 0.898 mmol) in 1 N HCl aq (1 mL) and THF (1 mL) was stirred at room temperature. After **8** was consumed (90 h) (monitored by TLC), saturated aqueous $NaHCO_3$ was added to the reaction mixture, and the resulting solution was extracted with AcOEt (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 1/1) affording **1e** as white solid (181.9 mg, 91%); mp 49 °C; IR (KBr) 3342, 2930, 2251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21−1.50 (m, 14H), 1.69−1.80 (m, 2H), 2.40 (brs, 2H), 3.38−3.42 (m, 1H), 3.49−3.52 (m, 2H), 3.61−3.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 26.8, 28.8, 29.3, 29.4, 29.6, 32.6, 33.1, 45.2, 66.8, 72.3; HRMS (FAB) calcd for $C_{11}H_{24}ClO_2$ (M^+ + H) 223.1465, found 223.1481.

4-[9-Chlorononyl]-1,3-dioxolane (2e). Brown oil; IR (KBr) 2930, 2253, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22−1.78 (m, 16H), 3.39 (t, J = 11.6 Hz, 1H), 3.50 (t, J = 6.9 Hz, 2H), 3.94−3.96 (m, 2H), 4.84 (s, 1H), 4.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 26.8, 28.8, 29.3, 29.4, 29.5, 32.6, 33.0, 45.2, 69.6, 76.3, 94.8. Anal. Calcd for $C_{12}H_{23}ClO_2$: C, 61.39; H, 9.87; Cl, 15.10. Found: C, 61.52; H, 9.92; Cl, 15.05.

Entry 3: According to the general procedure, the treatment of diol **1f** (64.2 mg, 0.241 mmol) with DBDMH (103.4 mg, 0.362 mmol), BHT (79.7 mg, 0.362 mmol), and methoxymethyl phenyl sulfide (47.0 μL, 0.362 mmol) for 1 h afforded **2f** (61.8 mg, 92%). Eluent, hexanes → hexanes/Et_2O (50/1).

11-Bromoundecane-1,2-diol (1f).[18] White solid; IR (KBr) 3325, 2928, 2251, 1794 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28−1.42 (m, 14H), 1.79−1.87 (m, 3H), 1.95 (d, J = 4.6 Hz, 1H), 3.37−3.44 (m, 3H), 3.62−3.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 28.1, 28.7, 29.3, 29.4, 29.5, 32.8, 33.1, 34.1, 66.8, 72.3.

4-(9-Bromononyl)-1,3-dioxolane (2f). Yellow oil; IR (KBr) 2930, 2251, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24−1.42 (m, 14H), 1.78−1.85 (m, 2H), 3.36−3.39 (m, 3H), 3.92−3.95 (m, 2H), 4.83 (s, 1H), 4.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 28.1, 28.7, 29.26, 29.34, 29.5, 32.8, 32.9, 34.0, 69.6, 76.2, 94.7; HRMS (FAB) calcd for $C_{12}H_{24}BrO_2$ (M^+ + H) 279.0960, found 279.0942.

Entry 4: According to the general procedure, the treatment of diol **1g** (86.0 mg, 0.516 mmol) with DBDMH (221.3 mg, 0.774 mmol), BHT (170.5 mg, 0.774 mmol) and methoxymethyl phenyl sulfide (114.0 μL, 0.774 mmol) for 30 min afforded **2g** (99.5 mg, quant.). Eluent, hexanes → hexanes/Et_2O (50/1).

4-Phenylbutane-1,2-diol (1g).[2a] White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 1.74−1.84 (m, 2H), 2.21 (t, J = 5.5 Hz, 1H), 2.41 (d, J = 4.1 Hz, 1H), 2.69−2.88 (m, 2H), 3.46−3.52 (m, 1H), 3.66−3.78 (m, 2H), 7.20−7.33 (m, 5H).

4-Phenethyl-1,3-dioxolane (2g).[2a] Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.81−1.90 (m, 1H), 1.95−2.04 (m, 1H), 2.67−2.87 (m, 2H), 3.47 (t, J = 7.2 Hz, 1H), 3.95−4.07 (m, 2H), 4.90 (s, 1H), 5.07 (s, 1H), 7.21−7.34 (m, 5H).

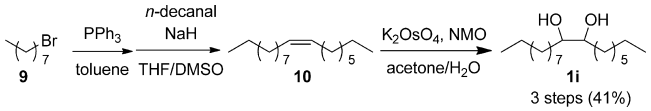
Entry 5: According to the general procedure, the treatment of diol **1h** (207.0 mg, 1.498 mmol) with DBDMH (648.7 mg, 2.269 mmol), BHT (496.0 mg, 2.247 mmol) and methoxymethyl phenyl sulfide (330.0 μL, 2.247 mmol) for 15 min afforded **2h** (209.7 mg, 93%). Eluent, hexanes → hexanes/Et_2O (50/1).

1-Phenylethane-1,2-diol (1h).[19] White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (dd, J = 7.3, 4.6 Hz, 1H), 2.49 (d, J = 3.2 Hz, 1H), 3.63−3.79 (m, 2H), 4.80−4.84 (m, 1H), 7.27−7.37 (m, 5H).

4-Phenyl-1,3-dioxolane (2h).[23] Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (t, J = 7.6 Hz, 1H), 4.17 (t, J = 7.3 Hz, 1H), 4.91 (t, J = 6.6 Hz, 1H), 5.01 (s, 1H), 5.19 (s, 1H), 7.16−7.31 (m, 5H).

Entry 6: According to the general procedure, the treatment of diol **1i** (95.0 mg, 0.322 mmol) with DBDMH (189.9 mg, 0.644 mmol), BHT (146.3 mg, 0.644 mmol) and methoxymethyl phenyl sulfide (98.0 μL, 0.644 mmol) for 30 min afforded **2i** (83.5 mg, 84%). Eluent, hexanes → hexanes/Et_2O (150/1 → 100/1).

Synthesis of Octadecane-8,9-diol (1i).



Triphenylphosphine (7.6 g, 29 mmol) was added to the solution of **9** (5 mL, 29 mmol) in toluene (29 mL) at room temperature under N_2, and the resulting solution was stirred at 110 °C. After **9** was consumed (48 h) (monitored by TLC), the mixture was concentrated in vacuo to afford the crude phosphonium bromide.

NaH (1.2 g, 29 mmol) was added to the solution of the crude phosphonium bromide in THF (63 mL) and DMSO (10 mL) at 0 °C under N_2, and the mixture was stirred at room temperature for 1 h. Then *n*-decanal (18 mL, 96 mmol) was added to the reaction mixture at 0 °C, and the solution was stirred at room temperature. After the phosphonium salt was consumed (4 h) (monitored by TLC), saturated aqueous NH_4Cl was added to the reaction mixture, and the solution was extracted with hexanes (50 mL × 1). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was roughly purified by flash column chromatography (SiO_2, hexanes) affording crude **10**.

A catalytic amount of K_2OsO_4 was added to the solution of the crude **10** and *N*-methylmorpholine-*N*-oxide (44.6 mmol) in acetone (11 mL) and H_2O (3 mL) at room temperature. After **10** was consumed (56 h) (monitored by TLC), saturated aqueous $Na_2S_2O_3$ was added to the reaction mixture, and the resulting solution was extracted with AcOEt (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt (10/1) → AcOEt) affording **1i** as yellow solid (2.93 g, 3 steps 41%); mp 114 °C; IR (KBr) 3584, 3154, 2928, 2253, 1790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.5 Hz, 6H), 1.12−1.46 (m, 28H), 1.67 (brs, 2H), 3.58 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.09, 14.11, 22.6, 22.7, 26.0, 29.2, 29.3, 29.56, 29.58, 29.62, 29.66, 31.2, 31.8, 31.9, 74.7; HRMS (EI) calcd for $C_{18}H_{38}O_2$ (M^+) 286.2872, found 286.2862.

4-Heptyl-5-nonyl-1,3-dioxolane (2i). Yellow oil; IR (KBr) 2926, 2253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 6.8 Hz, 6H), 1.25−1.56 (m, 28H), 3.87−3.90 (m, 2H), 4.79 (s, 1H), 5.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 22.7, 26.4, 29.1, 29.2, 29.3, 29.4, 29.54, 29.56, 29.62, 29.7, 31.8, 31.9, 78.2, 93.7; HRMS (FAB) calcd for $C_{19}H_{38}LiO_2$ (M^+ + Li) 305.3032, found 305.3039.

Entry 7: According to the general procedure, the treatment of diol **1j** (65.1 mg, 0.232 mmol) with DBDMH (132.7 mg, 0.464 mmol), BHT (104.2 mg, 0.472 mmol), and methoxymethyl phenyl sulfide (68.0 μL, 0.464 mmol) for 20 min afforded **2j** (51.6 mg, 76%). Eluent, hexanes → hexanes/AcOEt (10/1).

(6*S*)-8-(Benzyloxy)-2,6-dimethyloctane-2,3-diol (1j).[20] Orange oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89−0.92 (m, 3H), 1.14−1.47 (m, 13H), 2.12 (brs, 2H), 3.29−3.34 (m, 1H), 3.51−3.53 (m, 2H), 4.50 (s, 2H), 7.26−7.35 (m, 5H).

5-[(*S*)-5-Benzyloxy-3-methylpentyl]-4,4-dimethyl-1,3-dioxolane (2j). Yellow oil; IR (KBr) 3154, 2930, 2253, 1790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.4 Hz, 3H), 1.02−1.62 (m, 13H), 3.31−3.36 (m, 1H), 3.39−3.49 (m, 2H), 4.42 (s, 2H), 4.81 (s, 1H), 4.96 (s, 1H), 7.18−7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 19.5, 21.20, 21.23, 24.82, 24.85, 26.86, 26.88, 29.9, 30.0, 34.1, 34.2, 36.5, 36.6, 68.4, 68.5, 72.86, 72.88, 79.3, 84.4, 84.5, 92.6, 127.4, 127.5, 127.6, 128.3, 138.5; HRMS (EI) calcd for $C_{18}H_{28}O_3$ (M^+) 292.2039, found 292.2030.

Entry 8: According to the general procedure, the treatment of diol **1k** (93.2 mg, 0.612 mmol) with DBDMH (262.5 mg, 0.918 mmol), BHT (202.3 mg, 0.918 mmol), and methoxymethyl phenyl sulfide (135.0 μL, 0.918 mmol) for 1 h afforded **2k** (85.1 mg, 85%). Eluent, hexanes → hexanes/Et_2O (50/1).

1-Phenylpropane-1,3-diol (1k).[2a] White solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87−1.98 (m, 2H), 3.81 (t, J = 5.3 Hz, 2H), 4.91 (dd, J = 8.6, 4.1 Hz, 1H), 7.19- 7.39 (m, 5H).

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4-Phenyl-1,3-dioxane (2k). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60−1.66 (m, 1H), 1.97−2.08 (m, 1H), 3.80 (dt, J = 11.8, 2.4 Hz, 1H), 4.12 (dd, J = 11.4, 4.6 Hz, 1H), 4.57 (dd, J = 11.2, 2.5 Hz, 1H), 4.81 (d, J = 6.4 Hz, 1H), 5.14 (d, J = 6.4 Hz, 1H), 7.17−7.31 (m, 5H), commercially available.

Entry 9: According to the general procedure, the treatment of diol **1l** (64.7 mg, 0.316 mmol) with DBDMH (137.2 mg, 0.474 mmol), BHT (105.8 mg, 0.474 mmol) and methoxymethyl phenyl sulfide (70.0 μL, 0.474 mmol) for 45 min afforded **2l** (40.9 mg, 60%). Eluent, hexanes → hexanes/AcOEt (5/1 → 2/1).

Undecane-1,2,11-triol (1l).[2a] White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27−1.55 (m, 16H), 1.82 (brs, 1H), 1.97 (brs, 1H), 3.39−3.45 (m, 1H), 3.59−3.70 (m, 4H).

9-(1,3-Dioxolan-4-yl)nonan-1-ol (2l).[2a] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.59 (m, 16H), 3.34−3.41 (m, 1H), 3.59 (t, J = 6.5 Hz, 2H), 3.91−3.96 (m, 2H), 4.82 (s, 1H), 4.97 (s, 1H).

General Procedure for Methylene Acetal Formation of Sugar-Type Substrate (Scheme 3). According to the general procedure, the treatment of diol **5** (50.8 mg, 0.136 mmol) with DBDMH (77.8 mg, 0.272 mmol), BHT (60.0 mg, 0.272 mmol), and methoxymethyl phenyl sulfide (40.0 μL, 0.272 mmol) for 20 min afforded **6** (44.7 mg, 85%). Eluent, hexanes → hexanes/AcOEt (10/1).

(2*R*,3*R*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-2-(hydroxymethyl)-6-methoxytetrahydro-2*H*-pyran-3-ol (5).[21] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (brs, 1H), 2.23 (brs, 1H), 3.29−3.53 (m, 4H), 3.56 (s, 3H), 3.70−3.80 (m, 1H), 3.83−3.92 (m, 1H), 4.35 (d, J = 7.2 Hz, 1H), 4.67 (t, J = 11.5 Hz, 2H), 4.93 (dd, J = 13.2, 11.2 Hz, 2H), 7.24−7.36 (m, 10H).

(4a*R*,6*R*,7*R*,8*S*,8a*R*)-7,8-Bis(benzyloxy)-6-methoxyhexahydropyrano[3,2-*d*][1,3]dioxine (6). Yellow oil; IR (KBr) 2870, 2251, 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22−3.26 (m, 1H), 3.30−3.35 (m, 2H), 3.43 (t, J = 10.1 Hz, 1H), 3.49 (s, 3H), 3.59 (t, J = 8.9 Hz, 1H), 4.15 (dd, J = 10.5, 5.0 Hz, 1H), 4.32 (d, J = 7.8 Hz, 1H), 4.55 (d, J = 6.4 Hz, 1H), 4.65 (d, J = 10.8 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.78 (d, J = 10.8 Hz, 1H), 4.79 (d, J = 11.6 Hz, 1H), 5.00 (d, J = 6.0 Hz, 1H), 7.18−7.28 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.4, 66.1, 68.5, 75.0, 75.2, 80.8, 81.3, 82.1, 93.6, 105.1, 127.6, 127.7, 127.9, 128.0, 128.27, 128.32, 138.3, 138.4; HRMS (EI) calcd for $C_{22}H_{26}O_6$ (M^+) 386.1729, found 386.1725.

Procedure for the Synthesis of 6 under Acidic Conditions. *p*-Toluenesulfonic acid (4.0 mg, 0.02 mmol) was added to the solution of diol **5** (38.6 mg, 0.103 mmol) and paraformaldehyde (3.4 mg, 0.113 mmol) in toluene (3.4 mL) at room temperature under N_2, and the reaction mixture was stirred at 110 °C. After **5** was consumed (monitored by TLC), saturatedrated aqueous $NaHCO_3$ (4 mL) was added to the reaction mixture, and the mixture was extracted with AcOEt (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 5/1) affording **6** (26.6 mg, 67%).

Procedure for the Synthesis of 6 under Basic Conditions. KOH (48 mg, 0.848 mmol) and dibromomethane (15.0 μL, 0.212 mmol) were added to the solution of diol **5** (39.6 mg, 0.106 mmol) in DMSO (0.22 mL) at room temperature under N_2, and the reaction mixture was stirred at the same temperature for 8 h. Then H_2O was added to the reaction mixture and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, hexanes/AcOEt = 5/1) affording **6** (15.9 mg, 39%).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: fujioka@phs.osaka-u.ac.jp.

Notes

The authors declare no competing financial interest.

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