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# Transformation of Methylene Acetals to Bromoformates with a Combination of Trimethyl(phenylthio)silane and *N*-Bromosuccinimide

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ABSTRACT: A novel transformation reaction of methylene acetals, using a combination of trimethyl(phenylthio)silane (PhSTMS) and *N*-bromosuccinimide (NBS) under mild reaction conditions, is described. Various methylene acetals were converted to their corresponding bromoformates in good to high yields. Under the given conditions, the reaction proceeded via a radical pathway. Further transformation of bromoformates to their corresponding epoxides was achieved by treatment with NaOMe.

Protective groups are essential in organic syntheses and numerous such groups have been developed.<sup>1</sup> Methylene acetal is one among the most popular protective group for diols and is stable under basic to medium acidic conditions.<sup>1</sup> This stability, however, can make deprotection difficult, often requiring strongly acidic conditions.<sup>1,2</sup> We have developed novel deprotection methods for various acetal-type protective groups, including methylene acetal.<sup>3</sup> A combination of silyl triflate and pyridines will react with acetals to form the corresponding pyridinium salts, which are easily hydrolyzed to give the deprotected products. This method is applicable to the deprotection of methylene acetals and amenable to further transformation into various types

of protected diols (Scheme 1-a).<sup>3f,g</sup>

# Scheme 1. Our studies of methylene acetals



Note that the protection of diols as methylene acetals also requires harsh reaction conditions, such as strongly acidic or basic conditions.<sup>1</sup> To address this limitation, we developed a novel method to protect diols as methylene acetals using PhSCH<sub>2</sub>OMe and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in the presence of di-*tert*-butylhydroxytoluene (BHT)<sup>4</sup> (Scheme 1-b). During the course of that study, we found that protection of simple aliphatic diols as methylene acetals, using our method and without BHT, afforded poor yields of the corresponding methylene acetal and fair amounts of bromoformate and bromohydrin, which were generated from methylene acetal under the same reaction conditions (Scheme 1-c).

As described above, methylene acetal is generally considered a robust protective group. We were therefore surprised to observe cleavage of the methylene acetal under such mild reaction conditions, prompting further study. And also, halohydrin and vicinal haloester like bromohydrin and bromoformate are not only seen in partial structure of bioactive compounds<sup>5</sup> but also used as useful synthetic intermediate.<sup>6</sup> In addition, conversion of methylene acetal to bromoformate will offer new synthetic strategy using diols, which makes easy to keep the protection of reactive structure such as bromo and ester group during synthetic process then reveals reactive structure at late stage. Therefore, the develop of new conversion method from methylene acetal to bromoformate and related structure is useful.

First, the effects of various solvents were investigated.  $CH_3CN$  proved to be a good choice of solvent, giving bromoformate (2) and a small amount of bromohydrin (3) for a total yield of 92% (Table 1, Entry 1). In contrast,  $CH_2Cl_2$  gave 2 and 3 in a combined yield of 68%. Other solvents gave the cleaved products in low

yields (see Table S1). We next examined the effects of a variety of sulfur-containing compounds using CH<sub>3</sub>CN as the solvent (Table 1, Entries 2 to 7). When the reaction was conducted in the absence of PhSCH<sub>2</sub>OMe, no cleaved products were obtained (Table 1, Entry 2). This indicated that a sulfur-containing compound was essential for the reaction progress. Diphenyl disulfide was effective for the transformation of methylene acetal and the bromoformate was obtained in 73% yield, while the use of diphenyl sulfide resulted in low yields (Table 1, Entries 3 and 4). Me<sub>2</sub>S<sup>+</sup>Br Br,<sup>7</sup> a bromine equivalent, gave bromoformate and bromohydrin but in low yields (Table 1, Entry 5). Finally, we examined thiophenol and trimethyl(phenylthio)silane (PhSTMS), with PhSTMS giving the highest yields (84%) for this reaction (Table 1, Entries 6 and 7). The use of *N*-bromosuccinimide (NBS) afforded better yields (92%) than the use of DBDMH (84%) (Table 1, Entry 8 vs. Entry 7). Regarding the molar equivalence of reagents, decreasing the amount of NBS from 3.0 to 1.5 equivalents caused a reduction in yield (Table 1, Entry 10) and 2.0 and 1.0 equivalents (Entry 11) was effective, resulting in 89% and 91% yields, respectively. The use of 0.5 equivalents of PhSTMS and 2.0 equivalents of NBS as optimized reaction conditions.

4	9 9 1a	ent ( N, rt (Hg	0 H Br + 2a	O⊢ ∽∽ 3a	l ∕∕ <sup>Br</sup>
Entry	Reagent		Time	Yield	d (%)
			(h)	2a <sup>a</sup>	3a
1	PhSCH <sub>2</sub> OMe	DBDMH	3	59	33
	(1.5)	(1.5)			
2	-	DBDMH	1	-	-
		(1.5)			
3	PhSPh	DBDMH	24	24	-
	(1.5)	(1.5)			
4	PhSSPh	DBDMH	1.5	73	-
	(1.5)	(1.5)			
5	Me₂S⁺Br Br		24	30 <sup>b</sup>	14 <sup>a</sup>
	(1.5)				
6	PhSH	DBDMH	1.5	68	-
	(1.5)	(1.5)			
7	PhSTMS	DBDMH	1.5	84	-
	(1.5)	(1.5)			
8	PhSTMS	NBS	1	92	-
	(1.5)	(3.0)			
9	PhSTMS	NBS	7.5	44	-

## Table 1. Effect of Reagent

	(1.5)	(1.5)			
10	PhSTMS (1.2)	NBS	1.5	89	-
		(2.4)			
11	PhSTMS (1.0)	NBS	1.5	91	
		(2.0)			
12	PhSTMS (0.5)	NBS	2	61	-
		(2.0)			

a) Inseparable byproducts were included.

The optimized reaction yielding compound (**2a**) also resulted in a small amount of byproduct (Table 1), which was identified as follows. Under optimized conditions, the substrate having a benzoyl group (**1b**) yielded the bromoformate (**2b**). A small amount of byproduct (**2'b**) (9%) was also produced and separated from **2b** (68%). The <sup>1</sup>H NMR spectrum of **2'b** was very similar to that of the compound produced alongside **2a**. Thus, the byproduct listed in Table 1 was identified as regioisomer (**2'b**) (See Scheme 2).

A variety of substrates were amenable to this transformation reaction giving bromoformates (2), most of which included regioisomers (2'). Isolation of these regioisomers was difficult and their relative quantities were estimated from <sup>1</sup>H NMR spectra (Scheme 2). The result of Entry 1 of Table 1 is included in Scheme 2. Substrates bearing ester, ether and halogen functionalities underwent transformation via their methylene acetal,<sup>8</sup> to give their corresponding bromoformates in good to high yields with a regioisomer ratio of roughly 10:1. Substrates bearing aromatic rings yielded two isomers in high yield, while the substrate with an aromatic ring connected directly to the methylene acetal group (1g) afforded only one regioisomer, (2'g), in moderate yields. The methylene acetals of internal diols (1h and 1i) also reacted with PhSTMS and NBS to give their corresponding bromoformates. In the case of 1h, the ratio of regioisomer (2'h) increased slightly compared to that of compounds 1a to 1f because the steric hindrance of the methyl group affected the degree of selectivity. The reaction of methylene acetal derived from tertiary alcohol (1) was examined and the corresponding bromoformate was obtained, but the product was contaminated with some inseparable byproducts after purifications, and the starting material was remained even increasing the amounts of reagents under the reflux conditions. The acetaldehyde acetal (1k) was also reacted under the conditions to give the corresponding bromoacetate in 79% yield. The same reaction with the methylene acetal of 1,3-diol (11) proceeded slowly at room temperature. Increasing the amounts of both reagents and proceeding under reflux conditions improved the yield of products to 80% with 1:1 selectivity of regioisomers. Conversely, the reaction with 1m proceeded only marginally, even under reflux conditions. The reaction of the methylene acetal derived from 1,4-diol (1n)

proceeded but unidentified product was obtained.

Scheme 2. Scope of Substrate



The ratio of **2** and **2'** was determined by <sup>1</sup>H NMR, which indicated in the parenthesis. a) Inseparable byproduct was detected in the reaction. b) 1.5 Equiv of PhSTMS and 3.0 equiv of NBS were used under reflux conditions. c) The yield could not determined.

This reaction was suppressed by the addition of BHT (a radical scavenger). Therefore, the reaction likely proceeds via a radical pathway. A similar reaction employing benzylidene acetal was reported as a Hanessian-Hüllar reaction, which features a radical mechanism.<sup>9</sup> Generation of a radical on the methylene carbon of methylene acetal has also been reported.<sup>10</sup> A plausible reaction mechanism for the cleavage of methylene acetal under our optimized conditions is illustrated in Scheme 3. First, the hydrogen on the acetal carbon is extracted by a bromine radical to generate the radical intermediate **A**. The bromine radical then reacts with **A** to afford intermediate **B**. An oxonium ion **C** was generated by the elimination of bromide ion from **B**, followed by an attack of bromide ion on the carbon adjacent to the oxygen atom, yielding bromoformates (**2** and **2**<sup>\*</sup>). While the bromide ion can attack both carbon atoms adjacent to oxygen (routes *a* and *b*), the less hindered carbon is preferred, resulting in a 10:1 ratio of regioisomer. In the case of **1h**, the methyl group affects the approach of bromide ion to the carbon, leading to a decrease in the ratio of **2h** to **2'h** (ca. 7:3).

In the reaction with 1g, benzyl cation was generated from oxonium ion C and subsequently attacked by

bromide ion to form  $2^{\circ}g$  exclusively. The reason for the necessity of a sulfur compound is not clear, but we speculate the generation of PhSBr<sup>11</sup> as a reactive intermediate from the reaction of PhSTMS and NBS. The reaction using PhSSPh or PhSH instead of PhSTMS afforded the corresponding bromoformate in good yields but the reaction using PhSPh resulted in poor yield since PhSPh could not generate PhSBr by the reaction with NBS. PhSBr could generate the bromine radical by the homolysis, which might promote the reaction. Or the disproportionation of PhSBr was occurred and Br<sub>2</sub> could be generated in situ and cause the conversion reaction to bromoformate. But the reaction with Br<sub>2</sub> instead of PhSTMS and NBS led to the significant decrease of the yield of bromoformate, therefore, we presumed that PhSBr is the real reactive intermediate.

## Scheme 3. Plausible Reaction Mechanism



We next investigated the further transformation of bromoformate to epoxide (Scheme 4). Bromoformates obtained from the transformation reaction were treated with 2.4 equivalents of NaOMe, affording the corresponding epoxide in good to high yields within 5 min. The epoxides were generated as a single product although, with the exception of compound (2i), the precursor bromoformates were a mixture of 2 and regioisomer (2'). The bromoformates bearing benzoyl groups (2b/2'b) proceeded without significant hydrolysis of the benzoyl group to give the epoxide (4b) in 80% yield. Benzyloxy and aromatic groups were tolerated under the reaction conditions to give the corresponding epoxides (4d and 4f), respectively. Bromoformate (2i), derived from an internal methylene acetal, was also converted to its epoxide (4i) in high yields. We also attempted the reaction of the bromoformate derived from the methylene acetal of 1,3-diol (1l) but the corresponding oxetane was not obtained.

## Scheme 4. Conversion of Bromoformates to Epoxides



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In addition, a one-pot conversion of methylene acetal to epoxide was achieved by the successive addition of  $CH_3OH$  and 4.4 equiv of NaOMe after the generation of bromoformate (Scheme 5).

Scheme 5. One-pot Conversion of Methylene Acetal to Epoxide



In conclusion, we developed a novel reaction for the transformation of methylene acetals to bromoformates using PhSTMS and NBS under mild reaction conditions. This is the first report detailing the cleavage of methylene acetals, via a radical mechanism, by a combination of sulfur-containing compound and NBS. A variety of functional groups, including esters, benzyl ethers and halogens, were tolerated under the optimized reaction conditions. Further transformation of bromoformate to epoxide was achieved by the stepwise addition of NaOMe in a one-pot procedure.

#### **Experimental Section**

## **General Information**

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a 400-MHz spectrometer in CDCl<sub>3</sub> with tetramethylsilane as an internal standard. Data are reported as follows: chemical shift in ppm ( $\delta$ ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet), coupling constant (Hz) and integration. HRMS was measured in ESI and FAB modes, and the mass analyzer of the HRMS was orbitrap for ESI and double-focusing for FAB. Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without further purification. Each regioisomer exhibited similar R<sub>f</sub> values on thin-layer chromatography (TLC) plates run with various solvents. Some could not be separated from the primary reaction product and remained as a mixture. In mixed samples, the ratio of regioisomer was determined by <sup>1</sup>H NMR; pure data were obtained for those regioisomers that could be isolated.

# General procedure for the cleavage of methylene acetal with PhSTMS and NBS (Scheme 2)

Typical procedure from 1a to 2a and 2'a: To a solution of methylene acetal 1a (30 mg, 0.14 mmol) in CH<sub>3</sub>CN (0.7 mL) were added PhSTMS (27.0 ml, 0.14 mmol) and NBS (49.8 mg, 0.28 mmol), successively. The resulting solution was stirred at room temperature using CaCl<sub>2</sub> tube connected with a flask under open air. After completion of the reaction (monitored by TLC), saturated aqueous NaHCO<sub>3</sub> and saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> were added and the mixture was extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (n-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 2/1) to give 2a and 2'a (37.4 mg, 0.13 mmol, 91%, obtained as a 92:8 mixture).

## 1-Bromododecan-2-yl formate (2a)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.11 (s, 1H), 5.17-5.15 (m, 1H), 3.55-3.44 (m, 2H), 1.74-1.69 (m, 2H), 1.32-1.26 (m, 16H), 0.88 (t, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.3, 72.4, 33.7, 32.5, 31.9, 29.54, 29.47, 29.4, 29.3, 29.2, 24.9, 22.7, 14.1; HRMS (FAB) calcd for C<sub>13</sub>H<sub>24</sub>O<sub>2</sub><sup>79</sup>Br [M-H]<sup>+</sup> 291.0960, found 291.0933.

# 2-Bromododecyl formate (2'a)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.11 (s, 1H), 4.45-4.36 (m, 2H), 4.16-4.10 (m, 1H), 1.93-1.75 (m, 2H), 1.46-1.27 (m, 16H), 0.88 (t, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.3, 67.2, 51.0, 35.1, 31.9, 29.54, 29.51, 29.4, 29.3, 28.9, 27.1, 22.7, 14.1; HRMS (FAB) calcd for C<sub>13</sub>H<sub>24</sub>O<sub>2</sub><sup>79</sup>Br [M-H]<sup>+</sup> 291.0960, found 291.0959.

Bromoformates **2b** and **2'b** (47.6 mg, 0.12 mmol, 85%) were obtained as 89:11 mixture from **1b** (44.9 mg, 0.14 mmol) after purification by silica gel column chromatography with *n*-hexane/CHCl<sub>3</sub> = 2/1 as an eluent.

## 11-Bromo-10-formyloxyundecyl benzoate (2b)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.11 (s, 1H), 8.05 (d, J = 7.6 Hz, 2H), 7.58-7.54 (m, 1H), 7.46-7.42 (m, 2H), 5.16-5.11 (m, 1H), 4.32 (t, J = 6.8 Hz, 2H), 3.55-3.43 (m, 2H), 1.80-1.71 (m, 4H), 1.47-1.26 (m, 12H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 166.7, 160.3, 132.8, 130.5, 129.5, 128.3, 72.3, 65.1, 33.7, 32.4, 29.31, 29.26, 29.17, 29.15, 28.7, 26.0, 24.9; HRMS (FAB) calcd for C<sub>19</sub>H<sub>28</sub>O<sub>4</sub><sup>79</sup>Br [M+H]<sup>+</sup> 399.1171, found 399.1160.

## 10-Bromo-11-formyloxyundecyl benzoate (2'b)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.11 (s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.58-7.54 (m, 1H), 7.46-7.43 (m, 2H), 4.45-4.36 (m, 2H), 4.32 (t, J = 6.6 Hz, 2H), 4.16-4.09 (m, 1H), 1.92-1.74 (m, 4H), 1.45-1.26 (m, 12H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 166.7, 160.3, 132.8, 130.5, 129.5, 128.3, 67.2, 65.1, 50.9, 35.1, 29.4, 29.3, 29.2, 28.9, 28.7, 27.1, 26.0; HRMS (ESI) calcd for C<sub>19</sub>H<sub>27</sub>O<sub>4</sub><sup>79</sup>BrNa [M+Na]<sup>+</sup>421.0990, found 421.0988.

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Bromoformates **2c** and **2'c** (117 mg, 0.35 mmol, 88%) were obtained as 89:11 mixture from **1c** (100 mg, 0.39 mmol) after purification by silica gel column chromatography with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/1 to 1/2 as an eluent.

## 11-Bromo-10-formyloxyundecyl acetate (2c)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.12 (s, 1H), 5.17-5.11 (m, 1H), 4.05 (t, *J* = 6.8 Hz, 2H), 3.55-3.44 (m, 2H), 2.05 (s, 3H), 1.74-1.69 (m, 2H), 1.65-1.29 (m, 14H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 171.2, 160.3, 72.3, 64.6, 33.6, 32.4, 29.3, 29.2, 29.1, 28.5, 25.8, 24.9, 21.0; HRMS (FAB) calcd for C<sub>14</sub>H<sub>26</sub>O<sub>4</sub><sup>79</sup>Br [M+H]<sup>+</sup> 337.1015, found 337.1029.

## 10-Bromo-11-formyloxyundecyl acetate (2'c)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.11 (s, 1H), 4.45-4.36 (m, 2H), 4.16-4.10 (m, 1H), 4.05 (t, *J* = 6.8 Hz, 2H), 2.05 (s, 3H), 1.93-1.75 (m, 2H), 1.64-1.25 (m, 14H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 171.3, 160.3, 67.2, 64.6, 50.9, 35.1, 29.33, 29.26, 29.15, 28.9, 28.6, 27.1, 25.9, 21.0; HRMS (FAB) calcd for C<sub>14</sub>H<sub>26</sub>O<sub>4</sub><sup>81</sup>Br [M+H]<sup>+</sup> 339.0994, found 339.0979.

Bromoformates **2d** and **2'd** (41.5 mg, 0.11 mmol, 77%) were obtained as 95:5 mixture from **1d** (42.9 mg, 0.14 mmol) after purification by silica gel column chromatography with *n*-hexane/CHCl<sub>3</sub> = 3/1 as an eluent.

## 11-Benzyloxy-1-bromoundecan-2-yl formate (2d)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.11 (s, 1H), 7.35-7.27 (m, 5H), 5.16-5.10 (m, 1H), 4.50 (s, 2H), 3.54-3.43 (m, 4H), 1.74-1.69 (m, 2H), 1.64-1.57 (m, 2H), 1.37-1.28 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.3, 138.7, 128.3, 127.6, 127.4, 72.8, 72.4, 70.5, 33.6, 32.4, 29.7, 29.4, 29.3, 29.2, 26.1, 24.9; HRMS (FAB) calcd for C<sub>19</sub>H<sub>30</sub>O<sub>3</sub><sup>81</sup>Br [M+H]<sup>+</sup> 387.1358, found 387.1369.

## 11-Benzyloxy-2-bromoundecyl formate (2'd)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.10 (s, 1H), 7.35-7.28 (m, 5H), 4.50 (s, 2H), 4.45-4.36 (m, 2H), 4.16-4.09 (m, 1H), 3.46 (t, J = 6.6 Hz, 2H), 1.92-1.75 (m, 2H), 1.65-1.29 (m, 14H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.3, 138.7, 128.3, 127.6, 127.5, 72.9, 70.5, 67.2, 50.9, 35.1, 29.7, 29.42, 29.39, 29.28, 28.9, 27.1, 26.2; HRMS (FAB) calcd for C<sub>19</sub>H<sub>30</sub>O<sub>3</sub><sup>81</sup>Br [M+H]<sup>+</sup> 387.1358, found 387.1339.

Bromoformates **2e** and **2'e** (35.5 mg, 0.11 mmol, 81%) were obtained as 88:12 mixture from **1e** (32.9 mg, 0.14 mmol) after purification by silica gel column chromatography with *n*-hexane/EtOAc = 30/1 as an eluent.

1-Bromo-11-chloroundecan-2-yl formate (2e)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.12 (s, 1H), 5.16-5.11 (m, 1H), 3.55-3.44 (m, 4H), 1.80-1.71 (m, 4H), 1.44-1.29 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.3, 77.2, 72.3, 45.1, 33.6, 32.6, 32.4, 29.24, 29.22, 29.1, 28.8, 26.8, 24.9; HRMS (FAB) calcd for C<sub>12</sub>H<sub>23</sub>O<sub>2</sub><sup>37</sup>Cl<sup>81</sup>Br [M+H]<sup>+</sup> 317.0520, found 317.0532.

## 2-Bromo-11-chloroundecyl formate (2'e)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.11 (s, 1H), 4.45-4.36 (m, 2H), 4.16–4.10 (m, 1H), 3.54 (t, *J* = 6.6 Hz, 2H), 1.93-1.23 (m, 16H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.3, 77.2, 67.2, 50.9, 45.2, 35.0, 32.6, 29.3, 29.2, 28.84, 28.80, 27.1, 26.8; HRMS (FAB) calcd for C<sub>12</sub>H<sub>21</sub>O<sub>2</sub><sup>37</sup>Cl<sup>81</sup>Br [M-H]<sup>+</sup> 315.0363, found 315.0389.

Bromoformates **2f** and **2'f** (39.2 mg, 0.15 mmol, 85%) were obtained as 91:9 mixture from **1f** (32.0 mg, 0.18 mmol) after purification by silica gel column chromatography with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 4/1 to 1/1 as an eluent.

## 1-Bromo-4-phenylbutan-2-yl formate (2f)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.13 (s, 1H), 7.32-7.17 (m, 5H), 5.18-5.12 (m, 1H), 3.56-3.45 (m, 2H), 2.75-2.60 (m, 2H), 2.13-2.01 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.2, 140.4, 128.6, 128.3, 126.3, 71.7, 34.1, 33.5, 31.2; HRMS (FAB) calcd for C<sub>11</sub>H<sub>14</sub>O<sub>2</sub><sup>81</sup>Br [M+H]<sup>+</sup> 259.0157, found 259.0150.

## 2-Bromo-4-phenylbutyl formate (2'f)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 8.09 (s, 1H), 7.33-7.20 (m, 5H), 4.47-4.36 (m, 2H), 4.10-4.04 (m, 1H), 2.97-2.73 (m, 2H), 2.22-2.09 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 160.2, 140.2, 128.6, 128.5, 126.4, 67.1, 50.0, 36.7, 33.2; HRMS (ESI) calcd for C<sub>11</sub>H<sub>13</sub>O<sub>2</sub><sup>81</sup>Br [M]<sup>+</sup> 258.0078, found 258.0060.

Bromoformate **2'g** (26.9 mg, 0.12 mmol, 58%) was obtained as a single isomer from **1g** (30.0 mg, 0.20 mmol) after purification by silica gel column chromatography with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 5/1 as an eluent.

# 2-Bromo-2-phenylethyl formate (2'g)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.03 (s, 1H), 7.44-7.32 (m, 5H), 5.13 (t, *J* = 7.2 Hz, 1H), 4.73-4.60 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.0, 137.7, 129.2, 128.9, 127.8, 66.7, 49.1; HRMS (FAB) calcd for C<sub>9</sub>H<sub>8</sub>O<sub>2</sub><sup>79</sup>Br [M-H]<sup>+</sup> 226.9708, found 226.9692.

Bromoformates **2h** and **2'h** (38.3 mg, 0.13 mmol, 93%) were obtained as 73:27 mixture from **1h** (30.0 mg, 0.14 mmol) after purification by silica gel column chromatography with *n*-hexane/ $CH_2Cl_2 = 6/1$  as an eluent.

2-Bromododecan-3-yl formate (2h) and 3-Bromododecan-2-yl formate (2'h) (inseparable mixture)

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Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.16 (s, 0.3H), 8.09 (s, 0.7H), 5.22-5.17 (m, 0.7H), 5.06-5.02 (m, 0.3H), 4.23-4.17 (m, 0.3H), 4.02-3.97 (m, 0.7H), 1.84-1.55 (m, 4H), 1.40-1.27 (m, 15H), 0.88 (t, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.4, 160.1, 75.8, 71.8, 57.6, 49.8, 34.5, 31.8, 29.5, 29.42, 29.36, 29.2, 28.9, 27.5, 25.2, 22.6, 22.0, 17.7, 14.1.

Bromoformate **2i** (40.0 mg, 0.10 mmol, 82%) was obtained as a single isomer from **1i** (40.0 mg, 0.12 mmol) after purification by silica gel column chromatography with *n*-hexane/ $CH_2Cl_2 = 10/1$  as an eluent.

#### 11-Bromoicosan-10-yl formate (2i)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.15 (s, 1H), 5.12-5.08 (m, 1H), 4.06–4.02 (m, 1H), 1.82-1.26 (m, 32H), 0.88 (t, *J* = 6.6 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.4, 74.9, 57.0, 35.0, 32.1, 31.8, 29.46, 29.45, 29.39, 29.37, 29.25, 28.9, 27.6, 25.2, 22.7, 14.1; HRMS (FAB) calcd for C<sub>21</sub>H<sub>41</sub>O<sub>2</sub><sup>79</sup>Br [M-H]<sup>+</sup> 403.2212, found 403.2220.

Bromoformate **2k** (56.6 mg, 0.22 mmol, 79%) was obtained as a single isomer from **1k** (49.8 mg, 0.28 mmol) after purification by silica gel column chromatography with *n*-hexane to n-hexane/EtOAc = 20/1 as an eluent and preparative TLC with n-hexane/EtOAc = 10/1 as developing solvent.

# 1-Bromo-3-phenylpropan-2-yl acetate (2k)<sup>12</sup>

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.33-7.23 (m, 5H), 5.21-5.15 (m, 1H), 3.50 (dd, *J* = 10.8 Hz, 4.8Hz, 1H), 3.37 (dd, 11.6 Hz, 4.8Hz, 2H), 3.07 (s, 3H).

Bromoformates **21** and **2'1** (39.1 mg, 0.14 mmol, 80%) were obtained as 56:44 mixture from **11** (34.6 mg, 0.18 mmol) after purification by silica gel column chromatography with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 20/1 to 2/1 as an eluent.

## 1-Bromo-5-phenylpentan-3-yl formate (21)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.12 (s, 1H), 7.31-7.16 (m, 5H), 5.23-5.17 (m, 1H), 3.44-3.33 (m, 2H), 2.73-2.59 (m, 2H), 2.28-2.10 (m, 2H), 2.03-1.87 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.6, 140.8, 128.5, 128.2, 126.2, 72.1, 37.2, 35.6, 31.4, 28.2; HRMS (FAB) calcd for C<sub>12</sub>H<sub>16</sub>O<sub>2</sub><sup>81</sup>Br [M+H]<sup>+</sup> 273.0313, found 273.0313.

## 3-Bromo-5-phenylpentyl formate (2'l)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 8.03 (s, 1H), 7.32-7.20 (m, 5H), 4.44-4.29 (m, 2H), 4.09-4.02 (m, 1H), 2.96-2.74 (m, 2H), 2.26-2.08 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 160.8, 140.5, 128.54, 128.50, 126.2, 61.9,

52.3, 40.8, 37.7, 33.6; HRMS (FAB) calcd for  $C_{12}H_{16}O_2^{-79}Br [M+H]^+ 271.0334$ , found 271.0320.

Bromoformate **2'm** (4.7 mg, 0.019 mmol, 11%) was obtained as a single isomer from **1m** (30.0 mg, 0.18 mmol) after purification by silica gel column chromatography with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 3/1 as an eluent.

## 3-Bromo-3-phenylpropyl formate (2'm)

Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.06 (s, 1H), 7.42-7.28 (m, 5H), 5.09 (dd, J = 8.8, 6.0Hz, 1H), 4.36-4.23 (m, 2H), 2.65-2.42 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 160.6, 141.1, 128.9, 128.7, 127.2, 61.8, 50.7, 38.5; HRMS (FAB) calcd for C<sub>10</sub>H<sub>11</sub>O<sub>2</sub><sup>79</sup>BrNa [M+Na]<sup>+</sup> 264.9840, found 264.9825.

# **1-Bromododecan-2-ol (3a)**<sup>13</sup>

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.81-3.75 (m, 1H), 3.57-3.53 (m, 1H), 3.41-3.37 (m, 1H), 2.10 (d, J = 5.2 Hz, 1H), 1.57-1.26 (m, 18H), 0.88 (t, J = 6.8 Hz, 3H).

## General procedure for the formation of epoxide 4 from bromoformates (Scheme 4)

**Typical procedure from 2a and 2'a to 4a:** NaOMe (36.2 mg, 0.67 mmol) was added to a solution of bromoformate **2a** and **2'a** (82 mg, 0.28 mmol) in CH<sub>3</sub>OH (1.4 mL) and the resulting solution was stirred until completion of the reaction (monitored by TLC). Saturated NH<sub>4</sub>Cl was then added and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated *in vacuo*, and the residues were purified by column chromatography on silica gel (n-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 3/1) to give **4a** (47.7 mg, 0.26 mmol, 93%).

# 2-Decyloxirane (4a)<sup>14</sup>

Colorless oil ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 2.93-2.88 (m, 1H), 2.75 (t, *J* = 4.6 Hz, 1H), 2.46 (dd, *J* = 4.8, 2.8 Hz, 1H), 1.55-1.26 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H).

#### 9-(Oxiran-2-yl)nonyl benzoate (4b)

Epoxide **4b** (23.2 mg, 0.080 mmol, 80%) was obtained from **2b** and **2'b** mixture (39.9 mg, 0.10 mmol) as yellow oil after purification by silica gel column chromatography with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/1 as an eluent; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.04 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 4.32 (t, *J* = 6.6 Hz, 2H), 2.93-2.88 (m, 1H), 2.75 (t, *J* = 4.4 Hz, 1H), 2.46 (dd, *J* = 5.0, 2.6 Hz, 1H), 1.80-1.73 (m, 2H), 1.57-1.26 (m, 14H);

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<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 166.7, 132.8, 130.5, 129.5, 128.3, 65.1, 52.4, 47.1, 32.5, 29.44, 29.38, 29.2, 28.7, 26.0, 25.9; HRMS (FAB) calcd for C<sub>18</sub>H<sub>27</sub>O<sub>3</sub> [M+H]<sup>+</sup>291.1960, found 291.1943.

# 2-(9-Benzyloxynonyl)oxirane (4d)<sup>15</sup>

Epoxide **4d** (15.1 mg, 0.055 mmol, 82%) was obtained from **2d** and **2'd** mixture (25.7 mg, 0.067 mmol) as yellow oil after purification by silica gel column chromatography with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 1/1 to 4/5 as an eluent; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.37-7.25 (m, 5H), 4.50 (s, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 2.93-2.88 (m, 2H), 2.75 (t, *J* = 4.6 Hz, 1H), 2.46 (dd, *J* = 5.0, 2.6 Hz, 1H), 1.65-1.26 (m, 16H).

## 2-Phenethyloxirane (4f)<sup>16</sup>

Epoxide 4d (35.9 mg, 0.24 mmol, 87%) was obtained from 2f and 2'f mixture (72.0 mg, 0.28 mmol) as yellow oil after purification by silica gel column chromatography with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 2/1 as an eluent; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.29 (t, J = 7.1 Hz, 2H), 7.22-7.18 (m, 3H), 2.98-2.93 (m, 1H), 2.87-2.72 (m, 3H), 2.48 (dd, J = 4.8, 2.8 Hz, 1H), 1.92-1.80 (m, 2H).

#### 2,3-Dinonyloxirane (4i)

Epoxide **4i** (35.2 mg, 0.12 mmol, 99%) was obtained from **2i** (50.6 mg, 0.12 mmol) as yellow solid after purification by silica gel column chromatography with *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> = 3/1 as an eluent; m.p. 37-38 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.92-2.89 (m, 2H), 1.58-1.27 (m, 32H), 0.88 (t, J = 6.4 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 57.3, 31.9, 29.56, 29.51, 29.3, 27.8, 26.6, 22.7, 14.1; HRMS (FAB) calcd for C<sub>20</sub>H<sub>41</sub>O [M+H]<sup>+</sup> 297.3158, found 297.3168.

## General procedure for the one-pot conversion of methylene acetal 1a to epoxide 4a (Scheme 5)

To a solution of methylene acetal **1a** (60 mg, 0.28 mmol) in CH<sub>3</sub>CN (1.4 mL) were added PhSTMS (54.0 ml, 0.28 mmol) and NBS (99.7 mg, 0.56 mmol), successively. The resulting solution was stirred at room temperature. After completion of the reaction (monitored by TLC), CH<sub>3</sub>OH (1.4 mL) and NaOMe (66.4 mg, 1.23 mmol) were added to the solution and the resulting mixture was stirred for 5 min. Saturated aqueous NaHCO<sub>3</sub> and saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> were then added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated *in vacuo*. The residue was purified by column

chromatography on silica gel (n-hexane/ $CH_2Cl_2 = 3/1$ ) to give 4a (44.1 mg, 0.24 mmol, 86%).

## ASSOCIATED CONTENT

#### **Supporting information**

The Supporting Information is available free of charge on the ACS Publication website at DOI:

<sup>1</sup>H and <sup>13</sup>C NMR spectra.

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## Notes

The authors declare no competing financial interest.

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