Efficient Preparation of Alkoxymethyl Carbonates by Using Potassium Carbonate, Chloromethyl Alkyl Ethers, and Alcohols

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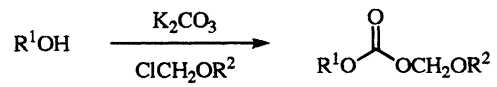
A synthesis of new "alkoxymethyl carbonate" is presented starting with alcohol. In the presence of potassium carbonate, primary alcohols react with chloromethyl alkyl ethers in *N*,*N*-dimethylformamide under mild conditions to give the corresponding alkoxymethyl carbonates in good yields without giving the alkoxymethyl ethers. The yield of alkoxymethyl carbonate is seriously effected by reaction solvent and the present method is not applicable for tertiary alcohol. Methoxymethyl carbonate can be removed readily under mild basic or acidic conditions, and undergoes selective alkoxide interchange of methoxymethoxide group under basic conditions.

The common carbonate groups are used as protecting group for alcohols and phenols,[1] prodrug systems of drug,[2] or such useful chemical materials as synthetic tools for glycosylation.[3] Carbonates are generated by phosgene,[4] metal alkoxide,[5] DBU-CO_2,[6] or other methods,[7] and the existing available carbonate groups have several characteristic, for example, these are stable for the acidic conditions. Our interest in the chemistry of new type carbonate "alkoxymethyl carbonate" as shown in Scheme 1 has prompted us to synthesize alkoxymethyl carbonate and to study its chemistry. Unfortunately, the general methods could not afford the desired alkoxymethyl carbonate. Although the alkoxymethyl carbonates may be prepared by several different routes, no general synthetic methodology has been developed. Consequently, we set out to investigate a synthesis of alkoxymethyl carbonate.

In this paper, we would like to describe one-step synthesis of alkoxymethyl carbonate by using alcohol, chloromethyl alkyl ethers, and potassium carbonate. The reaction is smoothly carried out in the presence of a large amount of potassium carbonate to afford the corresponding carbonates in good to excellent yields.

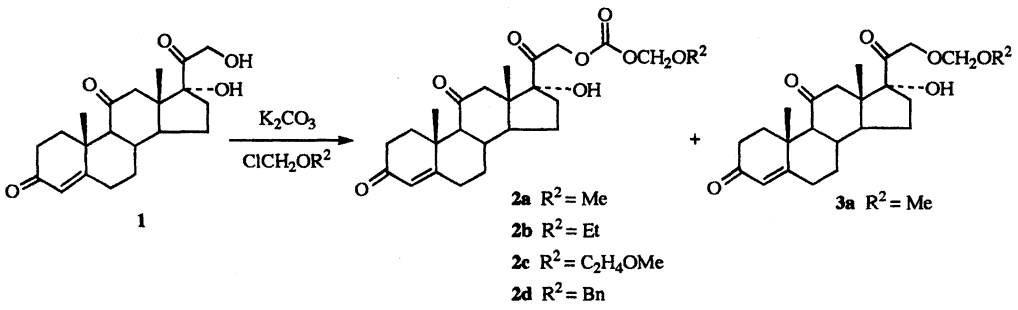
Results and Discussion

Recently, an unusual unique carbonate formation in saccharide synthesis has been reported.[8] Brumes et al. reported that geraniol reacted with 2,3,4,2′,3′,4′-hexa-*O*-acetyl-α-rutinosyl chloride in pyridine in the presence of silver carbonate for 8 d at room temperature to give geranyloxy carbonyl-β-rutinose derivative in 13% yield. Based on the result, the new possibility was considered that metal carbonate such as Na_2CO_3 or K_2CO_3 could serve as the C_1 sourse of the alkoxymethyl carbonate, according to Scheme 1.



Scheme 1.

In the first place, 17α,21-dihydroxypregn-4-ene-3,11,20-trione (cortisone) **1**, which has many functional groups, as an alcohol was tried by using several solvents together with chloromethyl methyl ether and potassium carbonate (see Scheme 2). To a stirred solution of **1**, in several solvents at 20 °C, under an argon atmosphere, was added potassium carbonate (5.0 equiv), followed by chloromethyl methyl ether (5.0 equiv) at −20—0 °C. This mixture was stirred at −20—0 °C for 3.5—6.0 h. To this mixture was added cooled acetone at −20 °C, with subsequent filtration through Celite. The filtrate was poured into water and extracted with benzene. The organic extracts were washed with cooled water and sat. NaCl solution, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed using ethyl acetate and *n*-hexane in a silica gel column to give **2a**. The best yield was obtained when the reaction was carried out in *N*,*N*-dimethylformamide (DMF) as shown in Table 1. The carbonate structure **2a** was supported by ^{1}H NMR ($CDCl_3$, δ=5.25, OCH_2O), ^{13}C NMR ($CDCl_3$, δ=154.16, *C*=O), IR (1745 cm^{-1}), and MS data. In the case of acetone or dichloromethane as the solvent, however, **2a** could not be obtained in good yields (see Entries 5 and 6). Furthermore, in the case of using 1.0 or 2.5 equiv each of chloromethyl methyl ether and potassium carbonate in DMF, **2a** was obtained in poor yields due to recovery of **1** (see Entries 1 and 2). In the present method, di(meth-



Scheme 2.

Table 1. Reaction of Cortisone (**1**) with Chloromethyl Methyl Ether

Entry	Solvent	M_2CO_3	Temp	Time	Product and yield[d]/%		Recovered **1**[d]/%
		equiv	°C	h	**2a**	**3a**	
1[a]	*N*,*N*-Dimethylformamide	K_2CO_3 (1.0)	−20	3.5	27	5	55
2[b]	*N*,*N*-Dimethylformamide	K_2CO_3 (2.5)	−20	24	40	8	39
3[c]	*N*,*N*-Dimethylformamide	K_2CO_3 (5.0)	−20	3.5	95	4	0
4[c]	*N*,*N*-Dimethylformamide	Na_2CO_3 (5.0)	0	11	21	67	7
5[c]	Acetone	K_2CO_3 (5.0)	−10	6.0	23	0	23
6[c]	Dichloromethane	K_2CO_3 (5.0)	20	5.0	0	6	59

a) The reaction was carried out with 1.0 equiv of $ClCH_2OMe$. b) The reaction was carried out with 2.5 equiv of $ClCH_2OMe$. c) The reaction was carried out with 5.0 equiv of $ClCH_2OMe$. d) Isolated yield after purification by silica gel column chromatography.

oxymethyl)carbonate is produced as a by-product, so that excess chloromethyl methyl ether and potassium carbonate are needed. In this connection, it is of interest that the substitution of Na_2CO_3 in DMF for K_2CO_3 gave methoxymethyl ether **3a** in a 67% yield as the main product (see Entry 4).

The structures of chloromethyl alkyl ethers used here are shown in Table 2. Cortisone (**1**) as an alcohol was dissolved in DMF and stirred with 5.0 equiv each of chloromethyl alkyl ether and potassium carbonate under an argon atmosphere. In every case, alkoxymethyl carbonates were produced in 69—95% yields without incident (see Entries 1—4). The presence of additional functionality in the examples cited did not appear to interfere with the reaction process. Tertiary alcohol, in which the contribution of the steric hindrance is large, and ketones were unaffected.

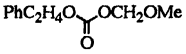
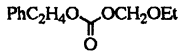
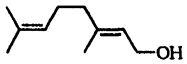
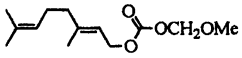
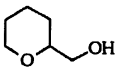
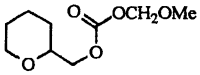
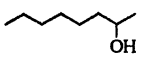
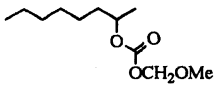
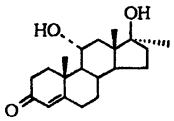
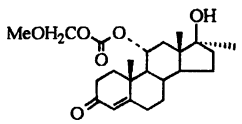
Several examples for the present carbonate formation from other primary alcohols are demonstrated in Entries 5—8. For example, if tetrahydropyran-2-methanol (**8**) and chloromethyl methyl ether are used, the desired carbonate **9** was obtained in a 66% yield without trouble. For a secondary alcohol, the present carbonate formation took place with recovery of alcohol (see Entries 9 and 10). For example, the reaction of 2-octanol (**10**) with chloromethyl methyl ether afforded the methoxymethyl carbonate (**11**) in a 28% yield and **10** was recovered in a 68% yield. In the case of 11α-hydroxy-17α-methylteststerone (**12**), methoxymethyl carbonate (**13**) and **12** were obtained in 37 and 35% yield, respectively.

Removal of the alkoxymethyl carbonate could be accomplished via reaction with K_2CO_3 in a mixture of CH_3OH and H_2O.[1] We have found that reasonable rates are observed in the mixture of CH_3OH and H_2O at 20 °C (see Table 3). Standard extractive workup, followed by silica gel column chromatography, gave the desired alcohols. For example, deprotection of **2a** gave **1** in a 76% yield.

Subsequently it was found that substitution of anhydrous C_2H_5ONa in C_2H_5OH for aqueous K_2CO_3, in the case of **5a**, gave 2-(ethoxycarbonyloxy)ethylbenzene (**14**) with a little amount of **4** for initial 4 h from the start of reaction, and then, at last, **14** was cleaved into **4** in a 95% overall yield (see Scheme 3 and Fig. 1). In the case of 2-(methoxycarbonyloxy)ethylbenzene (**16**), cleavage reaction under identical condition gave **14** and **4** at the ratio 1 to 1 for initial 4 h from the start of a reaction. This phenomenon is characteristic to methoxymethyl carbonate, which may be used successfully, it may be due to the elimination effect of metal chelate by oxygen atoms of methoxymethyl carbonate. Therefore, when deprotection of **5a** was carried out in a 93% yield via reaction with K_2CO_3 in the mixture of CH_3OH and H_2O, **4** was obtained not directly from **5a**, but by way of compound **15** or **16**.

In next stage, we attempted the removal of methoxymethyl carbonate using acid. Removal of the methoxymethyl carbonates could be accomplished via reaction with such acid as trifluoroacetic acid (TFA) in CH_3OH at 20 °C as well without giving methyl carbonates (see Scheme 3 and Table 4). For example, **4** was obtained

Table 2. Conversion of Alcohol into Alkoxymethyl Carbonate[a)]

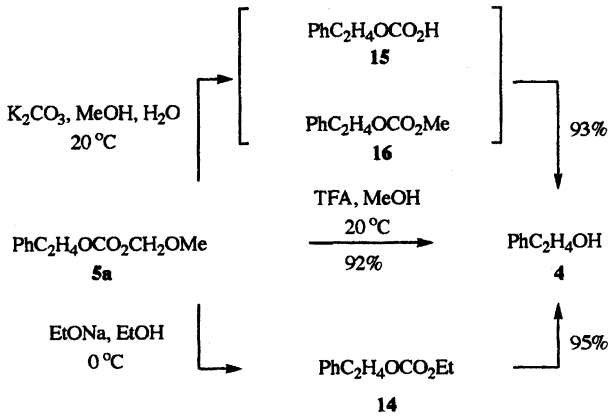
Entry	Alcohol	$ClCH_2OR^2$	Time/h	Product	Yield[b)]/%
1	Cortisone (**1**)	$ClCH_2OMe$	3.5	**2a**	95
2	**1**	$ClCH_2OEt$	3.5	**2b**	86
3	**1**	$ClCH_2OC_2H_4OMe$	6.0	**2c**	69
4	**1**	$ClCH_2OBn$	5.0	**2d**	85
5	PhC_2H_4OH (**4**)	$ClCH_2OMe$	6.0	 **5a**	56
6	**4**	$ClCH_2OEt$	6.0	 **5b**	51
7	 **6**	$ClCH_2OMe$	6.0	 **7**	56
8	 **8**	$ClCH_2OMe$	1.5	 **9**	66
9	 **10**	$ClCH_2OMe$	6.0	 **11**	28
10	 **12**	$ClCH_2OMe$	6.0	 **13**	37

a) With 5.0 equiv each of $ClCH_2OR^2$ and potassium carbonate in *N*,*N*-dimethylformamide at −20 °C. b) Isolated yield after purification by silica gel chromatography.

Table 3. Removal of Alkoxymethyl Carbonates via Reaction with K_2CO_3[a)]

Entry	Alkoxymethyl carbonate	Product	Yield/%[b)]
1	**2a**	**1**	76
2	**2b**	**1**	77
3	**2c**	**1**	80
4	**2d**	**1**	70
5	**5a**	**4**	93
6	**5b**	**4**	95
7	**7**	**6**	93
8	**9**	**8**	90
9[c)]	**11**	**10**	91
10[c)]	**13**	**12**	19

a) With 1.0 equiv of K_2CO_3 in MeOH–H_2O for 30 min at 20 °C. b) Isolated yield after purification by silica gel column chromatography. c) This reaction was carried out for 1 d at 20 °C.



Scheme 3.

in a 92% yield from **5a**. Under identical conditions, **16** or methoxymethyl ether of phenethyl alcohol is stable so that the goal of designing an carbonate which has unprecedented properties as a carbonate has been attained. It is of interest that the methoxymethyl carbonates are stable to methanolic acetic acid at 20 °C. The half-life of **5a** in CH_3OH containing TFA (1.0 equiv) at 20 °C is 3.5 h and that in CH_3OH containing acetic acid (1.0 equiv) at 20 °C is 60 h. Consequently, other acid-sensitive protecting groups can be removed selectively. In this connection, it should be noted that the removal of methoxymethyl carbonate of compound **13** could be carried out in a 88% yield by using TFA in CH_3OH (see Table 4. Entry 10), though such removal could not be carried out in a good yield by using K_2CO_3 (see Table 3. Entry 10).

Results of this nature show several advantages as a hydroxyl protecting group or useful chemical materials which should make it valuable in planning synthetic strategy. These include: (1) its ready availability; (2)

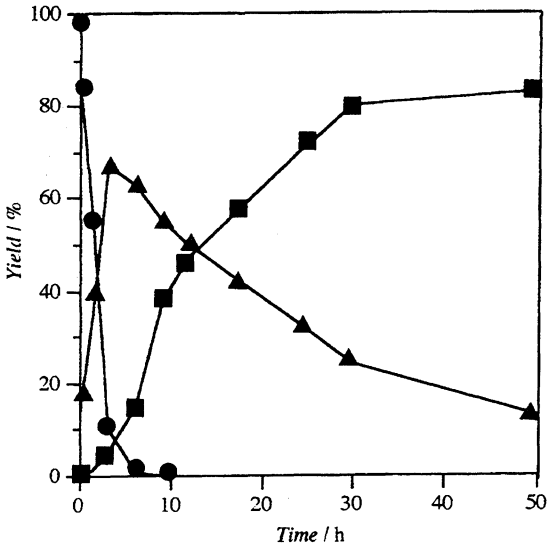


Fig. 1. Plots of product yields of the cleavage reaction of **5a** with EtONa in EtOH at 4 °C vs. time of the reaction. ●(**5a**), ▲(**14**), ■(**4**).

Table 4. Removal of Alkoxymethyl Carbonates via Reaction with TFA[a)]

Entry	Alkoxymethyl carbonate	Product	Yield[b)]/%
1	**2a**	**1**	79
2	**2b**	**1**	80
3	**2c**	**1**	83
4	**2d**	**1**	75
5	**5a**	**4**	92
6	**5b**	**4**	90
7	**7**	**6**	89
8	**9**	**8**	85
9	**11**	**10**	93
10	**13**	**12**	88

a) With 1.0 equiv of TFA in MeOH for 30 h at 20 °C.
b) Isolated yield after purification by silica gel column chromatography.

its lack of introduction of a new chiral center; (3) the selective cleavage under mild, protic conditions with TFA or K_2CO_3; (4) the efficient and mild protection and removal in the presence of some other functionality; (5) selective alkoxide interchange of methoxymethoxide group under basic conditions.

Experimental

All melting point data were measured with a Yanagimoto Seisakusho apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Hitachi R-90H spectrometer. Chemical shifts (δ) are given in ppm from internal Me_4Si, and coupling constants (J) in Hz. IR spectra were taken by a Shimadzu IR-470 infrared spectrometer. UV spectra were obtained on a Shimadzu UV-3100PC spectrometer. Mass spectra were measured by a Hitachi M-80B instrument.

All chemicals not otherwise mentioned were purchased from Nacalai Tesque, or Tokyo Kasei Organic Chemicals (chemical pure grade) and used as received. DMF was treated with molecular sieves 4A. Dichloromethane was distilled from calcium hydride under argon atmosphere.

21-*O*-(Methoxymethoxycarbonyl)cortisone (2a). Chloromethyl methyl ether (0.21 cm^3, 2.8 mmol) was added to 17α,21-dihydroxypregn-4-ene-3,11,20-trione (cortisone) **1** (0.20 g, 0.56 mmol) and potassium carbonate (0.39 g, 2.8 mmol) suspended in DMF (4.0 cm^3) at −20 °C under an argon atmosphere, and mixture was stirred for 3.5 h at −20 °C. To this mixture was added cooled acetone (8 cm^3) at −20 °C, with subsequent filtration through Celite. The filtrate was poured into water (20 cm^3) and extracted with benzene three times (3×20 cm^3). The organic extracts were washed with water (20 cm^3) and sat. NaCl solution (20 cm^3), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed using ethyl acetate and hexane in a silica gel column to give colorless prisms (**2a**; 0.24 g, 95%): Mp 170—171 °C (from ethyl acetate); UV λ_{max} (MeOH) nm (ε) 238 (13700); IR (KBr) 3500, 2970, 2930, 1745 (C=O), 1715 (C=O), 1690 (C=O), 1660 (C=O),1610, 1430, 1350, 1280, 1220 and 1165 cm^{-1}; ^{1}H NMR (90 MHz; $CDCl_3$) δ=0.69 (3H, s, C*H*$_3$), 1.38 (3H, s, C*H*$_3$), 1.1—3.0 (18 H, m), 3.50 (3H, s, C*H*$_3$), 4.70 (1H, d, J=18 Hz, O=CC*H*$_2$OC=O), 5.13 (1H, d, J=18 Hz, O=CC*H*$_2$OC=O), 5.25 (2H, s, OC*H*$_2$O) and 5.70 (1H, s, C*H*); ^{13}C NMR ($CDCl_3$) δ=15.34, 17.20, 23.17, 32.26, 33.63, 34.67, 34.88, 36.44, 38.20, 49.73, 49.85, 51.25, 57.69, 62.41, 70.34, 88.63, 93.82, 124.22, 154.16 (*C*=O), 169.25, 200.01, 204.04, and 208.86; SIMS m/z 449 (M+1$^+$). Found: C, 64.30; H, 7.18%. Calcd for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19%.

21-*O*-(Ethoxymethoxycarbonyl)cortisone (2b). Compound **2b** was prepared from **1** and chloromethyl ethyl ether in a 86% yield as colorless needles: Mp 104—106 °C (from ethyl acetate–hexane); UV λ_{max} (MeOH) nm (ε) 238 (17000); IR (KBr) 3480, 3270, 2940, 1760 (C=O), 1730 (C=O), 1710 (C=O), 1640 (C=O), 1630 (C=O), 1270 and 1250 cm^{-1}; ^{1}H NMR (90 MHz; $CDCl_3$) δ=0.69 (3H, s, C*H*$_3$), 1.25 (3H, t, J=7.0 Hz, CH$_2$C*H*$_3$), 1.40 (3H, s, C*H*$_3$), 1.0—3.0 (18H, m), 3.74 (2H, q, J=7.0 Hz, OC*H*$_2$CH$_3$), 4.70 (1H, d, J=18 Hz, O=CC*H*$_2$OC=O), 5.15 (1H, d, J=18 Hz, O=CC*H*$_2$OC=O), 5.31 (2H, s, OC*H*$_2$O) and 5.70 (1H, s, C*H*); ^{13}C NMR ($CDCl_3$) δ=15.00, 15.37, 17.26, 23.20, 32.26, 33.69, 34.73, 34.97, 36.47, 38.23, 49.82, 49.88, 51.25, 62.47, 66.22, 70.18, 88.69, 92.68, 124.37, 154.25 (O*C*=O), 168.88, 199.83, 203.92, and 208.73; SIMS m/z 463 (M+1$^+$). Found: C, 65.33; H, 7.60%. Calcd for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41%.

21-*O*-(Methoxyethyoxymethoxycarbonyl)cortisone (2c). Compound **2c** was prepared from **1** and 2-methoxyethoxymethyl chloride in a 69% yield as colorless prisms: Mp 95—98 °C (from ethyl acetate–hexane); UV λ_{max} (MeOH) nm (ε) 237 (20600); IR (KBr) 3400, 3200, 2950, 1755 (C=O), 1730 (C=O), 1695 (C=O), 1655 (C=O) and 1265 cm^{-1}; ^{1}H NMR (90 MHz; $CDCl_3$) δ=0.66 (3H, s, C*H*$_3$), 1.39 (3H, s, C*H*$_3$), 1.0—3.1 (18H, m), 3.37 (3H, s, OC*H*$_3$), 3.4—4.0 (4H, m, OC*H*$_2$C*H*$_2$O), 4.70 (1H, d, J=18 Hz, O=CC*H*$_2$OC=O), 5.13 (1H, d, J=18 Hz, O=CC*H*$_2$OC=O), 5.33 (2H, s, OC*H*$_2$O), 5.70 (1H, s, C*H*), and 7.2—7.4 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ=15.40, 17.26, 23.23, 32.29, 33.69, 34.73, 34.97, 35.06, 35.15, 36.47, 38.23, 49.79, 51.28, 58.94, 62.47, 69.85, 70.25, 71.35, 88.66, 92.87, 124.37, 154.13 (*C*=O), 168.85, 199.80, 203.82, and 208.67; SIMS m/z 493 (M+1$^+$). Found: C, 63.45; H, 7.32%. Calcd for $C_{26}H_{36}O_9$:

C, 63.40; H, 7.37%.

21-*O*-(Benzyloxymethoxycarbonyl)cortisone (2d). Compound **2d** was prepared from **1** and chloromethyl benzyl ether in a 85% yield as colorless prisms: Mp 150—151 °C (from ethyl acetate–hexane); UV λ_{max} (MeOH) nm (ε) 238 (12800); IR (KBr) 3500, 2930, 1765 (C=O), 1720 (C=O), 1695 (C=O), 1670 (C=O), 1610, 1458, 1410, 1390, 1350, 1260, 1190, 1170, 1140, and 1110 cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$) δ=0.64 (3H, s, CH_3), 1.0—3.1 (18H, m), 1.36 (3H, s, CH_3), 4.73 (1H, d, J=18 Hz, O=CCH_2OC=O), 4.71 (2H, s, OCH_2Ph), 5.12 (1H, d, J=18 Hz, O=CCH_2OC=O), 5.33 (2H, s, OCH_2O),5.68 (1H, s, CH), and 7.2—7.4 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ=15.34, 17.23, 23.14, 32.26, 33.66, 34.67, 34.88, 34.94, 36.40, 38.20, 49.75, 49.88, 51.23, 62.41, 70.34, 71.71, 88.66, 91.59, 124.31, 127.90, 127.97, 128.36, 136.32, 154.19 (OC=O), 169.04, 199.89, 203.95, and 208.73; SIMS m/z 525 (M+1$^+$). Found: C, 68.84; H, 7.08%. Calcd for $C_{30}H_{50}O_4$: C, 68.68; H, 6.92%.

2-(Methoxymethoxycarbonyloxy)ethylbenzene (5a). Compound **5a** was prepared from phenethyl alcohol (**4**) and chloromethyl methyl ether in a 56% yield as colorless oil: UV λ_{max} (MeOH) nm (ε) 252 (150), 258 (180), and 264 (140); IR (neat) 2950, 1750 (C=O), 1460, 1410, 1380, 1250, 1210, 1160, and 1100 cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$) δ=2.92 (2H, t, J=8.0 Hz, PhCH_2CH$_2$), 3.45 (2H, s, OCH_3), 4.35 (2H, t, J=8.0 Hz, PhCH$_2$CH_2), 5.20 (2H, s, OCH_2O), and 7.25 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) δ=34.80, (PhCH$_2$CH$_2$), 57.24 (OCH$_3$), 68.04 (PhCH$_2$CH$_2$), 93.04 (OCH$_2$O), 126.33 (*Ph*), 128.19 (*Ph*), 128.56 (*Ph*), 136.88 (*Ph*), and 154.14 (*C*=O); SIMS m/z 211 (M+1$^+$). Found: C, 63.05; H, 7.10%. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71%.

2-(Ethoxymethoxycarbonyloxy)ethylbenzene (5b). Compound **5b** was prepared from **4** and chloromethyl ethyl ether in a 51% yield as colorless oil: UV λ_{max} (MeOH) nm (ε) 253 (140), 258 (180), and 264 (130); IR (neat) 2950, 1750 (C=O), 1490, 1450, 1410, 1380, 1250, 1150, and 1130 cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$) δ=1.22 (3H, t, J=8.0 Hz, CH_3), 2.98 (2H, t, J=8.0 Hz, PhCH_2CH$_2$), 3.70 (2H, q, J=8.0 Hz, OCH_2CH$_3$), 4.35 (2H, t, J=8.0 Hz, PhCH$_2$CH_2), 5.26 (2H, s, OCH_2O), and 7.25 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ=14.86, (*C*H$_3$), 34.92 (PhCH$_2$CH$_2$), 65.81 (OCH$_2$CH$_3$), 68.07 (PhCH$_2$CH$_2$), 91.88 (OCH$_2$O), 126.39 (*Ph*), 128.28 (*Ph*), 128.65 (*Ph*), 136.94 (*Ph*), and 154.26 (*C*=O); SIMS m/z 225 (M+1$^+$). Found: C, 64.32; H, 7.40%. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%.

***trans*-1-(Methoxymethoxycarbonyloxy)-3,7-dimethyl-2,6-octadiene (7).** Compound **7** was prepared from geraniol (**6**) and chloromethyl methyl ether in a 56% yield as colorless oil: IR (neat) 2900, 1740 (C=O), 1450, 1250, and 1160 cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$) δ=1.57 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.9—2.2 (4H, m), 3.46 (3H, s, OCH_3), 4.64 (2H, d, J=7.5 Hz, CHCH_2OC=O), 5.05 (1H, m, (CH$_3$)$_2$CHCH$_2$), 5.21 (2H, s, OCH_2OCH$_3$), and 5.35 (1H, t, J=7.5 Hz, CHCH$_2$OC=O); ^{13}C NMR ($CDCl_3$) δ=16.46, 17.59, 25.55, 26.25, 39.48, 57.47, 64.64, 93.18, 117.54, 123.54, 131.59, 143.12, and 154.46 (*C*=O); SIMS m/z 243 (M+1$^+$). Found: C, 64.92; H, 9.53%. Calcd for $C_{13}H_{22}O_4$: C, 64.43; H, 9.15%.

Tetrahydro-2-(methoxymethoxycarbonyloxymethyl)-2*H*-pyran (9). Compound **9** was prepared from tetrahydropyran-2-methanol (**8**) and chloromethyl methyl ether in a 66% yield as colorless oil: IR (neat) 2930, 2830, 1740 (C=O), 1440, 1410, 1260, 1205, 1160, 1090, 1070, and 1040 cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$) δ=1.0—2.0 (6H, m), 3.47 (3H, s, CH_3), 3.2—4.3 (5H, m), 5.22 (2H, s, OCH_2OCH$_3$); ^{13}C NMR ($CDCl_3$) δ=22.64, 25.44, 27.39, 57.24, 67.91, 70.32, 74.74, 93.07, (OCH$_2$OCH$_3$), and 154.14 (OC=O); SIMS m/z 205 (M+1$^+$). Found: C, 53.41; H, 8.33%. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90%.

2-(Methoxymethoxycarbonyloxy)octane (11). Compound **11** was prepared from 2-octanol (**10**) and chloromethyl methyl ether in a 28% yield as colorless oil: IR (neat) 2930, 2850, 1750 (C=O), 1450, 1405, 1380, 1260, 1170, and 1040 cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$) δ=0.7—1.8 (16H, m), 3.50 (3H, s, OCH_3), 4.80 (1H, m, CHOC=O), and 5.23 (2H, s, O=COCH_2OCH$_3$); ^{13}C NMR ($CDCl_3$) δ=13.95, 19.74, 22.48, 25.17, 29.01, 31.63, 35.78, 57.43, 75.51, 92.95, and 154.05 (*C*=O); SIMS m/z 219 (M+1$^+$). Found: C, 61.01; H, 10.65%. Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16%.

11α-*O*-(Methoxymethoxycarbonyl)-17α-methylteststerone (13). Compound **13** was prepared from 11α-hydroxy-17α-methylteststerone (**12**) and chloromethyl methyl ether in a 37% yield as colorless needles: Mp 173—174 °C (from ethyl acetate–hexane); UV λ_{max} (MeOH) nm (ε) 240 (3160); IR (KBr) 3500, 2970, 2930, 1740 (C=O), 1670 (C=O), 1270, and 1160 cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$) δ=0.97 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.32 (3H, s,CH_3), 1.0—2.5 (17H, m), 3.48 (3H, s, OCH_3), 5.15 (1H, m, CHOC=O), 5.23 (2H, s, OCH_2OCH$_3$), and 5.75 (1H, s, CH); ^{13}C NMR ($CDCl_3$) δ=14.62, 18.34, 23.15, 25.87, 31.27, 33.37, 34.01, 36.27, 36.60, 38.67, 38.80, 39.74, 45.75, 49.07, 55.63, 57.49, 75.96, 80.66, 93.16, 124.72, 153.41 (OC=O), 169.23, and 198.99; SIMS m/z 407 (M+1$^+$). Found: C, 67.88; H, 8.49%. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43%.

Procedure for Measuring the product Yields of the Cleavage of Carbonates under Basic or Acidic Conditions vs. Time of the Reaction. A JASCO GULLIVER intelligent HPLC system with three-dimensional UV-vis detector (MD-910) was employed for analyzing the cleavage reaction of carbonates. A cosmosil 5C$_{18}$-MS column (4.6 mm×150 mm, Nacalai Tesque, Japan), with a precolumn (4.6 mm×10 mm, Nomura Chemicals Co.) was used for the analysis. Elution condition were solvent, MeOH–H$_2$O (60 : 40); flow rate, 0.8 $cm^3\,min^{-1}$. Xylene or toluene was used as internal standard.

To the mixture of compound **5a** (0.057 g, 0.27 mmol), xylene (0.032 cm^3) as an internal standard, and EtOH (1.7 cm^3) was added 1.0 mol dm^{-3} solution of EtONa in EtOH (0.026 cm^3, 0.027 mmol) at 4 °C. The rate of cleavage of **5a** was measured under this condition using HPLC with a three-dimensional UV-vis detector. Cleavage of 2-(methoxycarbonyloxy)ethylbenzene under identical basic conditions was measureed by the same method as that used for **5a**.

To the mixture of compound **5a** (0.058 g, 0.27 mmol), toluene (0.028 cm^3) as an internal standard, and MeOH (3.0 cm^3) was added 1 mol dm^{-3} sodolution of trifluoroacetic acid (TFA) in MeOH (0.27 cm^3, 0.27 mmol) at 20 °C. The rate of cleavage of **5a** was measured under this condition using HPLC with a three-dimensional UV-vis detector. Cleavage of 2-(methoxycarbonyloxy)ethylbenzene or methoxymethyl ether of phenethyl alcohol under identical acidic condition was measured by the same method as that used for **5a**.

General Procedure for the Removal of Alkoxymethyl Carbonate under Basic Condition. A carbonate (1 mmol), 1 mol dm^{-3} aqueous K_2CO_3 (1 mmol), and the mixture of CH_3OH (10 cm^3) and H_2O (2.0 cm^3) were stirred at 20 °C until no carbonate is detected with TLC. The mixture was poured into water (50 cm^3) and extracted with CH_2Cl_2 three times (3×20 cm^3). The organic extracts were dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed using ethyl acetate and *n*-hexane in a silica gel column to give alcohol.

General Procedure for the Removal of Alkoxymethyl Carbonate under Acidic Condition. A carbonate (1 mmol), 1 mol dm^{-3} solution of TFA in CH_3OH (1 mmol), and CH_3OH (10 cm^3) were stirred at 20 °C until no carbonate is detected with TLC. The mixture was poured into water (50 cm^3) and extracted with CH_2Cl_2 three times (3×20 cm^3). The orgaic extracts was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed using ethyl acetate and *n*-hexane in a silica gel column to give alcohol.

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