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(Diacetoxyiodo)benzene-Mediated Reaction of Ethynylcarbinols: Entry to α,α′-Diacetoxy Ketones and Glycerol Derivatives

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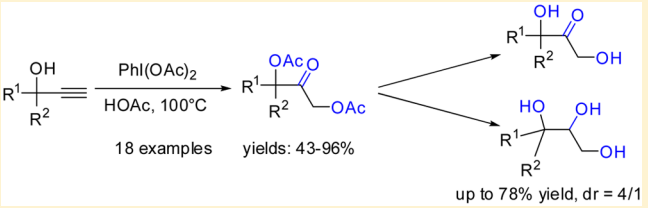
Supporting Information

ABSTRACT: Efficient access to α,α′-diacetoxy ketones has been developed from ethynylcarbinols and $PhI(OAc)_2$. A plausible mechanism for this was proposed on the basis of experimental studies. The usefulness of α,α′-diacetoxy ketone products has been documented, and glycerol derivatives can be easily synthesized in good yields via a one-pot reaction.



Among the most useful intermediates and key building blocks in organic synthesis have been α,α′-diacetoxy ketone compounds. They are easily transferred into acetoxy α-ketols,[1] α,α′-dihydroxy ketones,[2] or glycerol derivatives,[3] which are common structural motifs in natural products and biologically active compounds such as fluocinonide,[4] pirarubicin,[5] betamethasone,[6] and disaccharides[7] (Figure 1). The

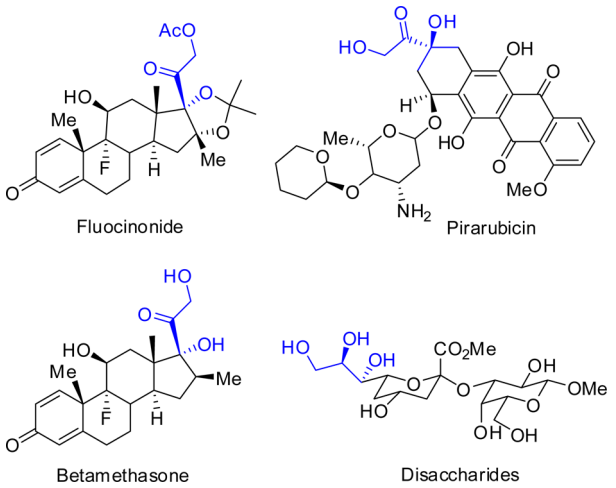
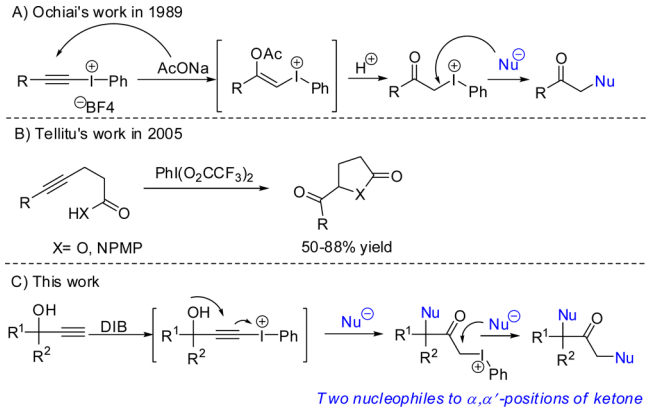


Figure 1. Selected examples for α,α′-dihydroxy ketones or related natural products.

methods for synthesizing α,α′-diacetoxy ketone from ketone starting material have been studied, most of which proceeded through an acetoxy acetone as a key intermediate and a sequence of bromination followed by acetolysis.[8] It has also been prepared by different routes involving the lead tetraacetate oxidation of an enamide intermediate.[9] Although such a method gives a satisfactory overall yield, it requires many steps and the use of toxic mercuric oxide or lead tetraacetate and thus suffers from environmental problems. Therefore, a simple and efficient conversion method for preparing α,α′-diacetoxy ketones would be an important step in organic synthesis and medicinal chemistry. Meanwhile, much attention has been paid to hypervalent iodine(III) reagents in recent years due to their interesting activity, ready availability, and ease of handling.[10,11] In 1989, Ochiai and co-workers documented that α-acetoxy ketones can be synthesized by conjugate addition of acyloxy groups to alkynylphenyliodonium under both basic and acidic conditions (Scheme 1A).[12] Phenyliodine

Scheme 1. Oxidation of Alkynes by Hypervalent Iodine(III) Compounds



bistrifluoroacetate (PIFA)-promoted intramolecular electrophilic cyclization of alkynyl amides or alkynyl carboxylic acids, leading to the formation of pyrrolidinone and lactone skeletons, has been developed by Tellitu and co-workers in 2005 (Scheme 1B).[13] In these reactions, the attack of the alkynyliodonium salt intermediate by the nucleophiles was the key step.[14] When ethynylcarbinols were used as substrates, we

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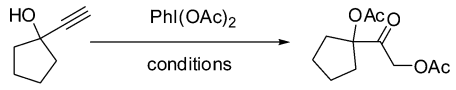
reasoned that the OH group might go through an intramolecular Michael-type addition to the alkynyliodonium salt intermediate following attack by other nucleophiles, which would introduce two nucleophiles into two α-positions of the carbonyl (Scheme 1C). Herein, we report our results for this new transformation in the preparation of α,α'-diacetoxy ketones from ethynylcarbinols with $PhI(OAc)_2$.

Initially, 1-ethynylcyclopentanol **1a** was treated with $PhI(OAc)_2$ in toluene at 80 °C under an air atmosphere. α,α'-Diacetoxy ketone **2a** was isolated in 28% yield, accompanied by the recovery of some starting material (Table 1, entry 1). The

Table 1. Optimizations for the Reaction of 1-Ethynylcyclopentanol 1a with $PhI(OAc)_2$[a]



1a 2a

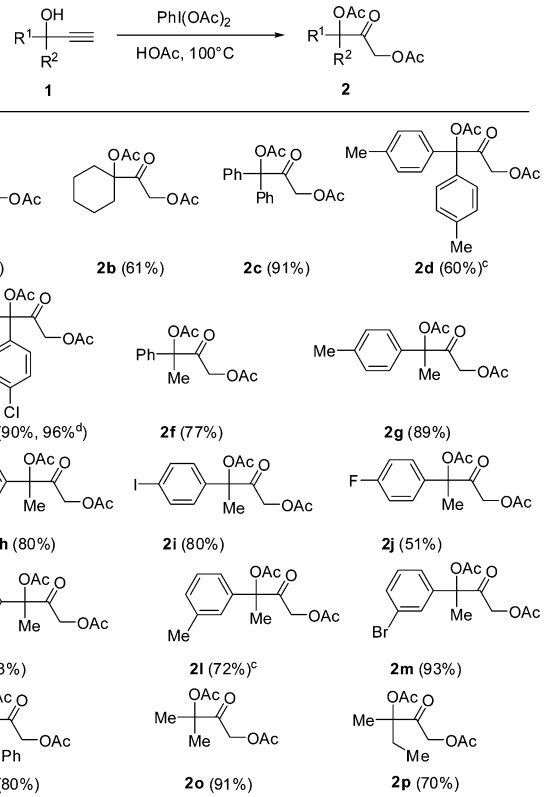
entry	oxidants	solvent	T (°C)	**2a** (%)[b]
1	$PhI(OAc)_2$	toluene	80	26
2	$PhI(OAc)_2$	MeCN	80	30
3	$PhI(OAc)_2$	DMSO	80	15
4	$PhI(OAc)_2$	DMF	80	11
5	$PhI(OAc)_2$	CF_3CH_2OH	80	21
6	$PhI(OAc)_2$	THF	80	16
7	$PhI(OAc)_2$	DCE	80	39
8[c]	$PhI(OAc)_2$	DCE	80	51
9	$PhI(OAc)_2$	HOAc	80	61
10	$PhI(OAc)_2$	HOAc	100	68
11	$PhI(OAc)_2$	HOAc	60	59
12	$PhI(OAc)_2$	HOAc	rt	<5
13[d]	$PhI(OAc)_2$	HOAc	100	71
14[e]	$PhI(OAc)_2$	HOAc	100	75
15[f]	$PhI(OAc)_2$	HOAc	100	74
16[g]		HOAc	100	0

[a]Reaction conditions: 1-ethynylcyclopentanol **1a** (0.5 mmol), $PhI(OAc)_2$ (0.6 mmol), solvent (1.5 mL), 24 h. [b]Isolated yield. [c]HOAc (5.0 equiv) was added. [d]$PhI(OAc)_2$ (2.0 equiv). [e]$PhI(OAc)_2$ (3.0 equiv). [f]$PhI(OAc)_2$ (4.0 equiv). [g]Only starting material was recovered.

influence of the solvent on the reaction was then evaluated. Performing the reaction in DCE (1, 2-dichloroethane) afforded **2a** in 39% yield (Table 1, entry 7), whereas the yield dropped sharply when MeCN, DMSO, DMF, CF_3CH_2OH, or THF was used as solvent (Table 1, entries 2–6). Product **2a** increased to 51% yield when 5.0 equiv of HOAc was added to DCE (Table 1, entry 8). To our delight, when HOAc was used as the solvent, the yield of product **2a** was improved to 68% due to HOAc playing roles as both nucleophile and solvent (Table 1, entry 9). Studies of the effect of temperature showed that product **2a** was obtained in higher yield at 100 °C, whereas no reaction occurred and the substrate was recovered for reactions at room temperature (Table 1, entries 9–12). The amount of $PhI(OAc)_2$ used also greatly impacted the yield of α,α'-diacetoxy ketone **2a**. Using 3.0 equiv of $PhI(OAc)_2$ proved to be optimal for the transformation (Table 1, entries 10 and 13–15). No desired product was observed in the absence of $PhI(OAc)_2$ after 24 h (Table 1, entry 16).

To examine the scope of present protocols, a variety of ethynylcarbinols **1** were subjected to the standard conditions. The results are summarized in Table 2. Treatment of cyclic ethynylcarbinols **1a** and **1b** with $PhI(OAc)_2$ provided

Table 2. Substrate Scope for the Preparation of α,α'-Diacetoxy Ketone by the Reaction of Ethynylcarbinols 1 with $PhI(OAc)_2$[a,b]



[a]Reaction conditions: ethynylcarbinols **1** (0.5 mmol), $PhI(OAc)_2$ (3.0–4.0 equiv), HOAc (1.5 mL), 24 h. [b]Isolated yields. [c]Run at 60 °C. [d]$PhI(OAc)_2$ (3.75 equiv).

corresponding α,α'-diacetoxy ketones **2a** and **2b** in good yields. The reaction ran smoothly to furnish the desired products in high yields when both R^1 and R^2 were aromatic-substituted ethynylcarbinols (Table 2, **2c–2e**). The reaction was also tolerated with ethynylcarbinols in which R^1 is an aromatic group and R^2 is an aliphatic group (Table 2, **2f–2n**). Having an electron-donating group at the 4-position of the phenyl group gave higher yields, whereas an electron-withdrawing group gave lower yields (Table 2, **2j** vs **2h–2k**). The presence of *meta*-substituted groups on the phenyl ring also afforded the desired products in high yields (Table 2, **2l** and **2m**). It is noted that when using a substrate with a methyl group substituted on the aryl ring the reaction must run at 60 °C to provide higher yields (Table 2, **2d** and **2l**). When R^1 and R^2 were acyclic aliphatic groups, the desired products were obtained in high yields (Table 2, **2o** and **2p**). We were pleased to observe that aryl groups with chlorine, bromide, and iodine were tolerated under the reaction conditions because these substituents further enhance the potential synthetic utility of these functionalized products (Table 2, **2e**, **2h**, **2i**, and **2m**).

To understand the mechanism better, the reaction was carried out with 1,1-diphenyl ethanol **3** under the standard conditions; no desired acetate product **4** was observed, affording only benzophenone and acetophenone in 46 and 32% yields, respectively (Scheme 2-1). This result revealed that the OH group of ethynylcarbinol could not be converted to the acetate intermediate first and that the alkynyl acetate was oxidized by $PhI(OAc)_2$ to form product **2**. When compound **5**

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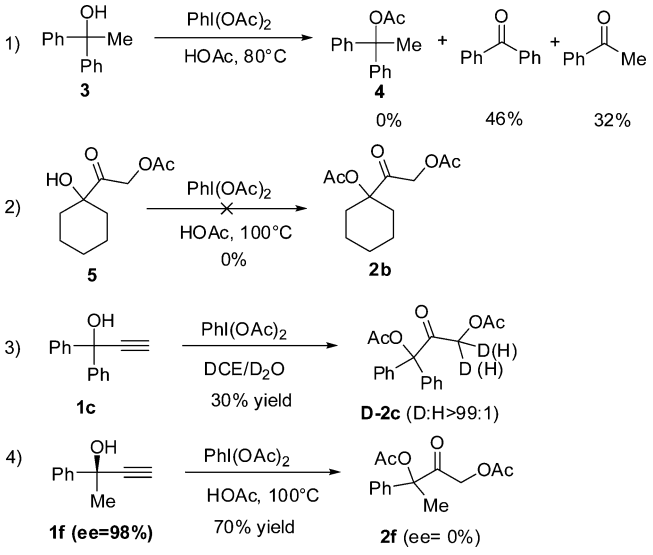
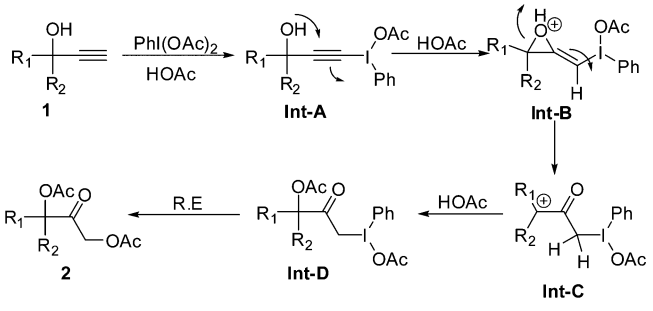
Scheme 2. Mechanism Studies



was used in the presence or absence of $PhI(OAc)_2$ at 100 °C for 24 h, no α,α'-diacetoxy ketone **2b** was observed, with only starting material recovered (Scheme 2-2). This demonstrated that α,α'-diacetoxyketone **2** might not be obtained directly from compound **5**. When substrate **1c** was used in DCE/D_2O (3:1) instead of HOAc (Scheme 2-3), desired product **D-2c** was obtained in 30% yield with a D/H ratio of 99:1 at the α-position of the carbonyl group. When chiral ethynylcarbinol **1f** was subjected to the reaction conditions, only racemic product **2f** was afforded in 70% yield (Scheme 2-4).

On the basis of the literature[12,14d] and our observations, a plausible mechanism is proposed in Scheme 3. The terminal

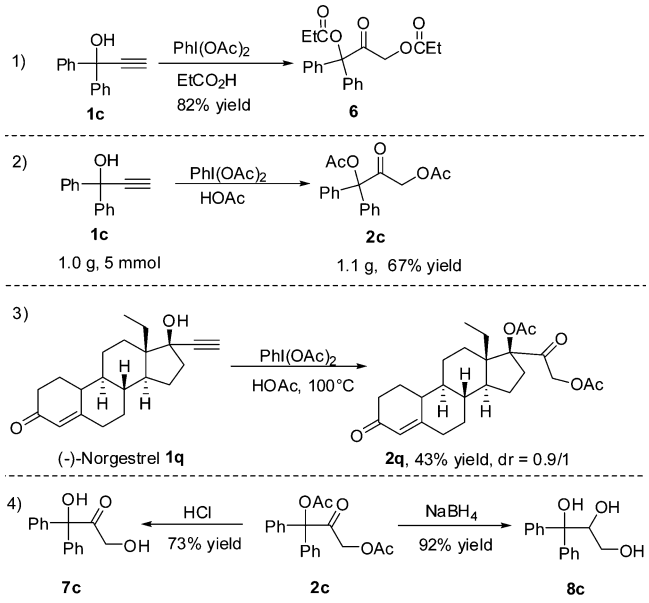
Scheme 3. A Plausible Mechanism for the Formation of Product 2



alkyne could be oxidized to form the alkynyliodonium salt (**Int-A**) by $PhI(OAc)_2$ first; then, a Michael-type addition of the *ortho*-OH group to the alkynyliodonium salt in **Int-A** provides **Int-B**. A carbocation in **Int-C** could be obtained from the epoxide in **Int-B** in the presence of HOAc. Then, **Int-C** can be trapped by ^-OAc to form **Int-D**. Reductive elimination or substitution of the phenyliodonium salt provides α,α'-diacetoxy ketone **2**.

The potential value of α,α'-diacetoxy ketones in organic synthesis and their possible reaction mechanism inspired us to investigate the possibility of using other trapping reagents and exploring their synthetic utility. When 1,1-diphenyl ethynylcarbinol **1c** was treated with $EtCO_2H$ as the solvent in the presence of $PhI(OAc)_2$, desired products **6** was obtained in 82% yield (Scheme 4-1). To demonstrate the synthetic utility

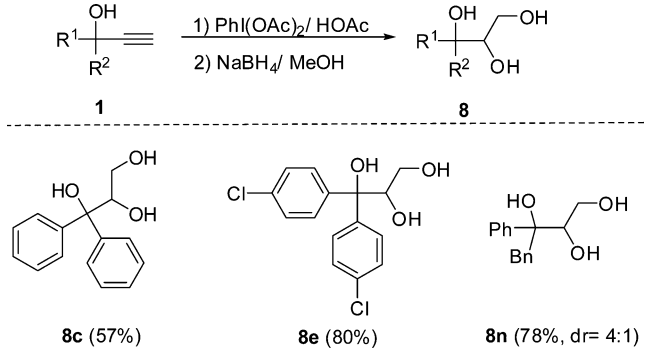
Scheme 4. Usefulness of α,α'-Diacetoxy Ketones



of this direct oxidative process on a gram scale, 1,1-diphenyl ethynylcarbinol **1c** was used as substrate at 5 mmol (1.0 g). To our delight, α,α'-diacetoxy ketone **2c** was isolated in 67% yield (Scheme 4-2). When commercial (−)-Norgestrel **1q** was subjected to the reaction, desired product **2q** was obtained in 43% yield with a 0.9:1 diastereoisomeric ratio, which is one of the most important steroids (Scheme 4-3). When α,α'-diacetoxy ketone **2c** was treated with diluted HCl in MeOH, α,α'-dihydroxylketone **7c** was obtained in 73% yield. Interestingly, the glycerol product **8c** was isolated in 92% yield by reduction of **2c** with excess $NaBH_4$ (Scheme 4-4).

Because glycerine product **8c** was obtained easily by reduction of $NaBH_4$, we anticipated that we could obtain glycerine product **8** from ethynylcarbinol **1** by a one-pot reaction (Scheme 5). To our delight, an efficient process was observed for the transformation in good yields by two steps with no formal purification of the intermediates; this approach required only the removal of HOAc prior to reduction. It is worth noting that when ethynylcarbinol **1n** was subjected to

Scheme 5. Synthesis of Glycerol Derivatives by a One-Pot Reaction[a]



[a]Reaction conditions: (1) ethynylcarbinol **1** (0.5 mmol), $PhI(OAc)_2$ (3.0−4.0 equiv), HOAc (1.5 mL), 24 h; (2) $NaBH_4$ (22 equiv), MeOH (3 mL).

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the same procedure the desired product **8n** was obtained in 78% yield with a 4:1 diastereoisomeric ratio value.

In summary, we have shown that α,α′-diacetoxy ketones can be synthesized in good to excellent yields from ethynylcarbinols in one step through oxidation by $PhI(OAc)_2$. Studies of the mechanism revealed that the OH group might attack the hypervalent iodinium salts to form a carbocation intermediate under HOAc. The glycerol derivatives were easily synthesized from ethynylcarbinols by a one-pot reaction. This new method provides a facile entry into the study of the reactivity of α,α′-dihydroxyketone or glycerol products.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an atmosphere of air. Commercially available reagents were used without further purification. ^1H and ^{13}C NMR spectra were recorded at 500 MHz in $CDCl_3$. ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$. IR spectra were recorded on a FT-IR spectrometer, and only major peaks are reported in cm^{-1}. HRMS were measured in EI or ESI mode, and the mass analyzer of the HRMS was TOF. Flash column chromatography was performed on silica gel (200−300 mesh). Alkynols **1o**, **1p**, and **1q** were purchased from Aldrich. **1a**−**1n**,[15] **3**,[16] and **5**[17] were prepared according to literature methods, and their spectral data matched literature values.

General Procedure for the Synthesis of α,α′-Diacetoxyketone 2 from Ethynylcarbinol 1 with $PhI(OAc)_2$. In a Teflon-sealed reaction flask, ethynylcarbinol **1** (0.5 mmol) and $PhI(OAc)_2$ (1.5 mmol, 3.0 equiv) were dissolved in HOAc (1.5 mL) under air, and the reaction vessel was sealed with a Teflon cap. The reaction mixture was stirred at 100 °C until substrate **1** disappeared (monitored by TLC). At this time, the reaction was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (1 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, and filtered. The solvent was then removed under vacuum. The crude product mixture was purified by flash chromatography on silica gel (1:20−1:5; ethyl acetate/petroleum ether) to give product **2**.

2a,[8a] 85.5 mg, yield: 75%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 4.77 (s, 2H), 2.29−2.24 (m, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 1.95−1.92 (m, 2H), 1.79−1.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.8, 171.0, 170.3, 92.7, 65.1, 36.1, 24.8, 21.0, 20.4; IR (KBr): 2960, 2877, 1738, 1432, 1373, 1236, 1177, 799 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{11}H_{16}O_5Na$ (M + Na)$^+$: calcd, 251.0895; found, 251.0887.

2b,[8a] 73.8 mg, yield: 61%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 4.83 (s, 2H), 2.15 (s, 3H), 2.13 (s, 3H), 1.74−1.65 (m, 5H), 1.54−1.52 (m, 2H), 1.33−1.26 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.0, 170.5, 170.3, 84.3, 64.3, 31.1, 24.9, 21.1, 21.0, 20.4; IR (KBr): 2940, 2864, 1737, 1449, 1373, 1271, 1137, 710 cm^{-1}; HRMS (EI) *m*/*z* for $C_{12}H_{18}O_5Na$ (M + Na)$^+$: calcd, 265.1052; found, 265.1042.

2c, 148.3 mg, yield: 91%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.0 Hz, 4H), 7.35−7.33 (m, 6H), 4.88 (s, 2H), 2.21 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.6, 170.0, 169.8, 138.3, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.6, 89.0, 64.8, 21.4, 20.4; IR (KBr): 3062, 3031, 2942, 2850, 1748, 1595, 1446, 1372, 1231, 755, 701 cm^{-1}; HRMS (EI) *m*/*z* for $C_{19}H_{18}O_5Na$ (M + Na)$^+$: calcd, 349.1052; found, 349.1047.

2d, 106.2 mg, yield: 60%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.5 Hz, 4H), 7.15 (d, *J* = 8.5 Hz, 4H), 4.87 (s, 2H), 2.34 (s, 6H), 2.19 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.7, 170.1, 169.9, 138.3, 135.5, 128.9, 128.8, 128.4, 128.2, 128.1, 128.0, 89.1, 64.8, 21.5, 21.1, 21.0, 20.4; IR (KBr): 3029, 2925, 2872, 1747, 1413, 1371, 1231, 1013, 813, 766 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{21}H_{22}O_5Na$ (M + Na)$^+$: calcd, 377.1365; found, 377.1377.

2e, 177.3 mg, yield: 90%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.5 Hz, 4H), 7.33 (d, *J* = 8.5 Hz, 4H), 4.84 (s, 2H), 2.21 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.1, 169.9, 169.7, 136.5, 134.9, 129.6, 129.5, 129.0, 128.9, 128.8, 128.5, 87.9, 64.5, 21.4, 20.3; IR (KBr) 3010, 2953, 1741, 1592, 1489, 1368, 1231, 819 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{19}H_{16}O_5Cl_2Na$ (M + Na)$^+$: calcd, 417.0272; found, 417.0286.

2f, 101.6 mg, yield: 77%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44−7.42 (m, 4H), 7.39−7.35 (m, 1H), 4.80 (d, *J* = 16.5 Hz, 1H), 4.72 (d, *J* = 16.5 Hz, 1H), 2.27 (s, 3H), 2.08 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.9, 170.1, 170.0, 137.9, 128.9, 128.5, 124.7, 86.4, 64.3, 23.2, 21.3, 20.4; IR (KBr) 3062, 2940, 2866, 1743, 1599, 1447, 1373, 1229, 762, 701 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{14}H_{16}O_5Na$ (M + Na)$^+$: calcd, 287.0895; found, 287.0911.

2g, 123.7 mg, yield: 89%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.79 (d, *J* = 17.0 Hz, 1H), 4.72 (d, *J* = 17.0 Hz, 1H), 2.35 (s, 3H), 2.26 (s, 3H), 2.09 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.0, 170.0, 169.9, 138.3, 135.0, 129.5, 124.6, 86.3, 64.2, 23.1, 21.3, 21.0, 20.3; IR (KBr): 3062, 2940, 2866, 1743, 1599, 1447, 1373, 762, 701 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{15}H_{18}O_5Na$ (M + Na)$^+$: calcd, 301.1052; found, 301.1050.

2h, 136.8 mg, yield: 80%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.78 (d, *J* = 16.5 Hz, 1H), 4.72 (d, *J* = 16.5 Hz, 1H), 2.26 (s, 3H), 2.10 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.7, 170.0, 169.8, 137.1, 132.0, 126.5, 122.8, 86.0, 64.3, 23.3, 21.3, 20.4; IR (KBr): 3003, 2942, 2872, 1743, 1412, 1372, 1229, 1020, 817 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{14}H_{15}O_5BrNa$ (M + Na)$^+$: calcd, 365.0001; found, 364.9994.

2i, 155.9 mg, yield: 80%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.77 (d, *J* = 16.5 Hz, 1H), 4.71 (d, *J* = 16.5 Hz, 1H), 2.25 (s, 3H), 2.08 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.7, 169.9, 169.8, 138.0, 137.8, 126.7, 94.5, 86.1, 64.3, 23.2, 21.3, 20.3; IR (KBr): 3001, 2940, 1743, 1585, 1484, 1373, 1228, 823 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{14}H_{15}O_5INa$ (M + Na)$^+$: calcd, 412.9862; found, 412.9848.

2j, 71.9 mg, yield: 51%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 4.77 (d, *J* = 16.5 Hz, 1H), 4.73 (d, *J* = 16.5 Hz, 1H), 2.25 (s, 3H), 2.09 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.9, 170.0, 169.9, 163.5 (d, *J* = 246.4 Hz), 133.8, 126.8 (d, *J* = 9.0 Hz), 115.8 (d, *J* = 21.7 Hz), 85.9, 64.3, 23.2, 21.2, 20.3; IR (KBr): 3005, 2944, 1744, 1510, 1373, 1223, 1015, 833 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{14}H_{15}O_5FNa$ (M + Na)$^+$: calcd, 305.0801; found, 305.0801.

2k, 112.8 mg, yield: 68%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 4.80 (d, *J* = 16.5 Hz, 1H), 4.72 (d, *J* = 16.5 Hz, 1H), 2.27 (s, 3H), 2.08 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.6, 170.0, 169.8, 142.0, 130.8 (q, *J* = 32.7 Hz), 125.9 (q, *J* = 2.6 Hz), 125.3, 124.9 (q, *J* = 270.7 Hz), 86.0, 64.4, 23.4, 21.2, 20.2; IR (KBr): 3004, 2947, 1745, 1412, 1374, 1328, 1103, 844, 799 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{15}H_{15}O_5F_3Na$ (M + Na)$^+$: calcd, 355.0769; found, 355.0757.

2l, 100.0 mg, yield: 72%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29 (s, 1H), 7.23−7.23 (m, 2H), 7.16 (d, *J* = 7.0 Hz, 1H), 4.80 (d, *J* = 16.5 Hz, 1H), 4.70 (d, *J* = 16.5 Hz, 1H), 2.38 (s, 3H), 2.27 (s, 3H), 2.09 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.0, 170.1, 170.0, 138.6, 137.8, 128.2, 128.7, 125.3, 121.7, 86.4, 64.3, 23.2, 21.5, 21.4, 20.4; IR (KBr): 3001, 2942, 2855, 1743, 1414, 1373, 1233, 1029, 706 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{15}H_{18}O_5Na$ (M + Na)$^+$: calcd, 301.1052; found, 301.1063.

2m, 159.0 mg, yield: 93%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.31−7.25 (m, 2H), 4.78 (d, *J* = 16.5 Hz, 1H), 4.71 (d, *J* = 16.5 Hz, 1H), 2.28 (s, 3H), 2.09 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.6, 170.0, 169.9, 140.2, 131.6, 130.4, 127.8, 123.5, 123.1, 85.7, 64.4, 23.4, 21.3, 20.4; IR (KBr): 3077, 3005, 2941, 1744, 1415, 1373, 1227, 1026, 697 cm^{-1}; HRMS (ESI) *m*/*z* for $C_{14}H_{15}O_5BrNa$ (M + Na)$^+$: calcd, 365.0000; found, 364.9985.

2n, 136.0 mg, yield: 80%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38−7.32 (m, 3H), 7.29 (d, *J* = 6.5 Hz, 2H), 7.17−7.09 (m, 3H), 6.63 (d, *J* = 7.5 Hz, 2H), 4.69 (d, *J* = 17.0 Hz, 1H), 4.65 (d, *J* = 17.0 Hz, 1H), 3.93 (d, *J* = 14.5 Hz, 1H), 3.59 (d, *J* = 14.5 Hz, 1H), 2.21 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1,

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170.1, 169.9, 135.8, 134.5, 130.1, 128.7, 128.5, 127.9, 126.8, 125.4, 88.6, 64.6, 40.7, 21.2, 20.4; IR (KBr): 3033, 2940, 1744, 1495, 1375, 1226, 1059, 754, 702 cm^{-1}; HRMS (ESI) *m/z* for $C_{20}H_{20}O_5Na$ $(M + Na)^+$: calcd, 363.1208; found, 363.1202.

2o,[18] 91.9 mg, yield: 91%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 4.86 (s, 2H), 2.16 (s, 3H), 2.09 (s, 3H), 1.55 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.8, 170.4, 170.2, 82.8, 64.3, 23.6, 21.1, 20.4.

2p, 75.6 mg, yield: 70%. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 4.91 (d, J = 16.5 Hz, 1H), 4.83 (d, J = 16.5 Hz, 1H), 2.16 (s, 3H), 2.09 (s, 3H), 2.00−1.94 (m, 1H), 1.92−1.86 (m, 1H), 1.55 (s, 3H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.0, 170.3, 170.2, 85.9, 85.0, 29.8, 21.1, 20.4, 20.1, 7.3; IR (KBr): 2983, 2946, 2888, 1741, 1423, 1374, 1239, 1048, 943 cm^{-1}; HRMS (ESI) *m/z* for $C_{10}H_{16}O_5Na$ $(M + Na)^+$: calcd, 239.0895; found, 239.0892.

2q, 67.0 mg, yield: 43%. Colorless oil; *one isomer:* ^1H NMR (500 MHz, $CDCl_3$): δ 5.82 (s, 1H), 5.26 (d, J = 18.0 Hz, 1H), 4.91 (d, J = 18.0 Hz, 1H), 2.50−2.46 (m, 2H), 2.25−2.20 (m, 2H), 2.17 (s, 3H), 2.16 (s, 3H), 2.08−2.05 (m, 3H), 1.86−1.81 (m, 2H), 1.69−1.66 (m, 5H), 1.53−1.46 (m, 5H), 1.13 (t, J = 7.0 Hz, 3H), 1.04−0.97 (m, 2H), 0.82−0.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.7, 199.9, 171.3, 170.6, 166.0, 124.8, 97.0, 67.9, 49.5, 49.1, 48.1, 42.3, 40.4, 36.5, 35.4, 34.0, 30.6, 29.2, 26.5, 26.1, 23.7, 21.2, 20.6, 20.3, 9.6; *another isomer:* ^1H NMR (500 MHz, $CDCl_3$): δ 5.82 (s, 1H), 4.90 (d, J = 17.0 Hz, 1H), 4.69 (d, J = 17.0 Hz, 1H), 2.85−2.79 (m, 1H), 2.38−2.36 (m, 3H), 2.17 (s, 3H), 2.16 (s, 3H), 2.08−2.05 (m, 3H), 1.86−1.81 (m, 2H), 1.69−1.66 (m, 5H), 1.53−1.46 (m, 5H), 1.13 (t, J = 7.0 Hz, 3H), 1.04−0.97 (m, 2H), 0.82−0.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.5, 199.8, 171.3, 170.3, 166.3, 124.7, 92.3, 66.7, 49.5, 48.3, 47.7, 42.4, 40.6, 37.2, 35.3, 34.0, 30.5, 28.6, 26.5, 26.3, 23.5, 21.1, 20.6, 20.3, 9.6; IR (KBr): 3271, 2940, 2876, 1736, 1667, 1449, 1371, 1234, 1049, 888 cm^{-1}; HRMS (ESI) *m/z* for $C_{25}H_{35}O_6$ $(M+H)^+$: calcd, 431.2433; found, 431.2425.

Synthesis for Product 6. In a Teflon-sealed reaction flask, ethynylcarbinol **1c** (104 mg, 0.5 mmol) and $PhI(OAc)_2$ (483 mg, 1.5 mmol) were dissolved in $EtCO_2H$ (1.5 mL) under air. The reaction mixture was stirred at 100 °C until substrate **1c** disappeared (monitored by TLC). At this time, the reaction was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (1 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, and filtered. The solvent was then removed under vacuum, and the crude product mixture was purified by flash chromatography on silica gel (1:20−1:5; ethyl acetate/petroleum ether) to give product **6** as a colorless oil: 145.2 mg, yield: 82%. ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 7.0 Hz, 4H), 7.36−7.32 (m, 6H), 4.88 (s, 2H), 2.53 (q, J = 7.5 Hz, 2H), 2.42 (q, J = 7.5 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H), 1.15 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.7, 173.5, 173.1, 138.5, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.6, 88.8, 64.6, 28.1, 27.1, 8.99, 8.85; IR (KBr): 3062, 3029, 2984, 2944, 2884, 1745, 1449, 1368, 1173, 1081, 753, 700 cm^{-1}; HRMS (ESI) *m/z* for $C_{21}H_{22}O_5Na$ $(M + Na)^+$: calcd, 377.1365; found, 377.1378.

Hydrolysis of 2c with HCl (Synthesis of Product 7c). In a round bottom flask, **2c** (163 mg, 0.5 mmol) was dissolved in MeOH (5.0 mL), and HCl (1.0 mL, 36%) was added. The reaction mixture was stirred at room temperature until substrate **2c** disappeared (monitored by TLC). At this time, the reaction was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (1 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, and filtered. The solvent was then removed under vacuum, and the crude product mixture was purified by flash chromatography on silica gel (1:20−1:1; ethyl acetate/petroleum ether) to give product **7c** as a colorless oil: 88 mg, 73% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38−7.36 (m, 6H), 7.34−7.28 (m, 4H), 4.53 (s, 2H), 3.67 (s, 1H), 2.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.4, 141.3, 128.6, 128.5, 127.5, 84.6, 66.2; IR (KBr): 3422, 3060, 3030, 2924, 2858, 1719, 1600, 1448, 1061, 745, 700 cm^{-1}; HRMS (EI) *m/z* for $C_{15}H_{14}O_3Na$ $(M + Na)^+$: calcd, 265.0841; found, 265.0843.

Synthesis of Glycerol Derivatives from Ethynylcarbinol 1 by a One-Pot Reaction. In a Teflon-sealed reaction flask, ethynylcarbinol **1** (0.5 mmol) and $PhI(OAc)_2$ (483 mg, 1.5 mmol) were dissolved in HOAc (1.5 mL) under air. The reaction mixture was stirred at 100 °C until substrate **1** disappeared (monitored by TLC). At this time, the reaction was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (1 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, and filtered. The solvent was then removed under vacuum and used in next step directly.

In a round bottom flask, the above crude products **2** were dissolved in MeOH (3 mL), and $NaBH_4$ (418 mg, 11 mmol) was added under air. The reaction mixture was stirred at room temperature for 4 h. At this time, the reaction was diluted with H_2O (10 mL), MeOH was removed, and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over Na_2SO_4, and filtered. The solvent was then removed under vacuum, and the crude product mixture was purified by flash chromatography on silica gel (1:20−1:1; ethyl acetate/petroleum ether) to give product **8**.

8c, 69.5 mg, 57% yield. Colorless oil; ^1H NMR (500 MHz, MeOD): δ 7.60 (d, J = 7.5 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.31−7.26 (m, 4H), 7.20−7.16 (m, 2H), 4.62−4.60 (m, 1H), 3.55−3.49 (m, 2H), 3.32 (s, 1H) (the two −OH resonances were not observed in MeOD); ^{13}C NMR (125 MHz, MeOD): δ 145.7, 145.1, 127.6, 127.4, 126.5, 126.3, 126.2, 125.6, 79.2, 75.2, 63.0; IR (KBr): 3541, 3479, 3324, 3060, 2995, 2941, 1494, 1177, 752, 699 cm^{-1}; HRMS (ESI) *m/z* for $C_{15}H_{16}O_3Na$ $(M + Na)^+$: calcd, 267.0997; found, 267.0991.

8e, 124.8 mg, 80% yield. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J = 8.5 Hz, 2H), 7.35−7.24 (m, 6H), 4.58−4.56 (m, 1H), 3.84 (s, 1H), 3.67 (dd, J = 11.5 Hz, 6.0 Hz, 1H), 3.57 (dd, J = 11.0 Hz, 3.0 Hz, 1H), 3.00 (s, 1H) (one −OH resonance was not observed in $CDCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 141.8, 133.4, 133.2, 128.6, 128.5, 127.8, 126.7, 79.2, 73.5, 62.9; IR (KBr): 3324, 2925, 2851, 1756, 1490, 1404, 1092, 814, 788 cm^{-1}; HRMS (EI) *m/z* for $C_{15}H_{14}O_3Cl_2Na$ $(M + Na)^+$: calcd, 335.0218; found, 335.0206.

8n, 100.6 mg, 78% yield, dr = 4:1. Colorless oil; *major isomer*: ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, J = 7.5 Hz, 2H), 7.32−7.31 (m, 2H), 7.29−7.22 (m, 2H), 7.15−7.12 (m, 2H), 6.83−6.82 (m, 2H), 3.99−3.98 (m, 1H), 3.85−3.84 (m, 1H), 3.74−3.73 (m, 1H), 3.39 (d, J = 13.5 Hz, 1H), 3.27 (d, J = 13.5 Hz, 1H), 2.86 (s, 2H) (one −OH resonance was not observed in $CDCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.5, 135.5, 130.7, 128.2, 127.2, 126.7, 126.0, 125.4, 78.2, 76.0, 62.9, 44.2; *minor isomer*: ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 7.5 Hz, 2H), 7.35−7.31 (m, 2H), 7.30−7.26 (m, 2H), 7.22−7.12 (m, 2H), 7.01−7.00 (m, 2H), 3.91−3.90 (m, 1H), 3.83−3.82 (m, 1H), 3.77−3.75 (m, 1H), 3.34 (d, J = 13.5 Hz, 1H), 3.20 (d, J = 13.5 Hz, 1H), 2.71 (s, 2H) (one −OH resonance was not observed in $CDCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 135.5, 130.6, 128.1, 127.1, 126.8, 126.0, 125.4, 79.4, 75.1, 63.2, 45.5; IR (KBr): 3382, 3030, 2925, 2854, 1495, 1450, 1191, 1060, 702 cm^{-1}; HRMS (EI) *m/z* for $C_{16}H_{18}O_3Na$ $(M + Na)^+$: calcd, 281.1154; found, 281.1152.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of compounds **2a−2q**, **5**, **6**, **7c**, **8c**, **8e**, and **8n**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00740.

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The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Prof. Xue-Long Hou, Shanghai Institute of Organic Chemistry, on the occasion of his 60th birthday.

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