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Highly Regioselective Cleavages and Iodinations of Cyclic Ethers Utilizing SmI_2

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Abstract: Various functionalized cyclic ethers such as oxiranes, oxetanes, and tetrahydrofurans have been prepared, and the regiochemistry of their ring opening with samarium diiodide and acyl chloride or anhydride has been investigated. Alkyl-substituted oxetane **5** and tetrahydrofurans **1** and **2** show almost no regioselectivity. However, high regioselectivities from the branched cyclic ethers (**3**, **8**, **9**, and **10**) containing ethereal or hydroxyl moieties have been observed. This is probably the result of the bidentate chelated species between samarium and oxygen.

The cleavage of ethers is a versatile reaction in organic synthesis, particularly in degradation or transformation of natural products and polyfunctional molecules. Transformations of cyclic ethers to haloesters[1] are effective methods for producing difunctional synthetic intermediates and are also important for the removal of ethereal protecting groups.[2] Since the protection of a hydroxyl group as an acetate is frequently employed in the total synthesis of complex natural products such as carbohydrates and macrolide antibiotics, a number of ether-cleavage reactions have been developed.

Lewis acids such as $ZnCl_2$,[3] $FeCl_3$,[4] $Mo(CO)_6$,[5] $MoCl_5$,[6] $PdCl_2(PPh_3)_2$,[7] $CoCl_2$,[8] NaI,[9] lanthanide salts,[10] Zn,[11] graphite,[12] and Al complexes[13] have been used for cleavages of ethers. A variety of other different reagents have been utilized for the cleavage of ethers but are not always satisfactory for complex molecules containing sensitive functionalities, and frequently long reaction times are required, or for the lack of regioselectivity in the cleavage of nonsymmetrical cyclic systems.[14]

Nucleophilic acylations of esters,[15] ketones, or aldehydes[16] with SmI_2 have been demonstrated. Ring opening of THF with samarium(III) triiodide−acid chloride[17] and ring opening of cyclic ethers with samarium(II) diiodide−BF_3·Et_2O−benzene−HMPA[18] have been reported. On the basis of our previous works on the reactivity of SmI_2,[19] we have found that small-membered ring ethers can be cleaved with SmI_2 and acyl chloride or anhydride in tetrahydropyran as a solvent to afford iodinated esters in a regioselective manner. Herein, we describe a facile acylative cleavage of functionalized cyclic ethers utilizing SmI_2 and acylating reagents. The cleavage reactions were investigated focusing on whether the regioselectivity depends on the ring size and the functional groups already attached (Scheme 1).

A variety of functionalized epoxides, oxetanes, and tetrahydrofuran derivatives were prepared. α-Substituted tetrahydrofurans **1**−**3** are commercially available. The oxetanes were prepared by the reaction of dimethyloxosulfonium methylide with epoxides or with carbonyl compounds.[20] The epoxides **8**−**10** were prepared by *m*-CPBA oxidations of the corresponding olefin compounds.

Tetrahydrofuran reacted with acyl chlorides or acetic anhydride in the presence of 2 equiv of SmI_2 to afford the corresponding iodinated esters in excellent yields (entries 1−4). In the absence of acyl chloride, the reaction did not proceed: for instance, THF and oxetane **6** were inert toward SmI_2 in the absence of acyl chloride, and the starting substrates were recovered quantitatively. Tetrahydrofuran **2** substituted with a methyl group at the α-position (entry 6) or oxetane **5** substituted with a phenyl group at the γ-position (entry 9) gave almost no regioselectivity (1:1 (entry 6) or 5:4 (entry 9) in Table 1, respectively). However, in contrast to the poor regioselectivity from 2-methyltetrahydrofuran **2**, the tetrahydrofurfuryl alcohol **3** resulted in extremely high regioselectivity (>99:1, 70%, entry 7). The branched oxetane **6** containing a benzyl ether moiety at the β-position also

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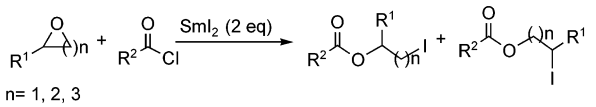
SCHEME 1



n= 1, 2, 3

R^1: Alkyl, Aryl, Hydroxyl or Ethereal moiety

gave regiospecific ring opening (~100:0, entry 10). Thus, the high regioselectivity appears to arise from the intervention of a five-membered ring bidentate chelated intermediate **A**, which might be formed by the strong electrophilicity of samarium for the oxygen attached at β-position (Scheme 2 and Figure 1). The oxetane **7** substituted with a benzyloxy group at the γ-position gave relatively lower selectivity (4:1, entry 11) than that (~100:0) obtained from β-substituted **6** (entry 10). To compare the substituent effect of benzyl group in **7**, a bulky *tert*-butyldimethylsilyloxy (TBDMS) moiety was introduced instead of benzyl. In this case, the regioselectivity decreased (**a**:**b** = 2:1) probably due to a steric hindrance of bulky TBDMS moiety in **A′**. The selective cleavage may be influenced by the ring size of intermediates: high selectivity presumably arises from the five-membered chelated ring **A**, but a lower selectivity (4:1) may be caused by the six-membered chelated ring intermediate **A′** (Figure 2). The extremely high regioselective cleavage (entries 7 and 10) is probably due to the formation of a five-membered ring intermediate **A** that arose due to the oxophilicity of samarium. All the monosubstituted oxiranes **8**−**10** yielded only one regioisomer in excellent yields (entries 12−14) obtained by an attack of iodide on the less substituted carbon atom of the highly strained epoxide ring.

Although the precise mechanism of the acylative cleavage is not clear, the reaction is presumably initiated by formation of acyl radical **11** and then acylsamarium species **12**. The use of 1 equiv of SmI_2 gave a low yield (45%) of cleaved iodide product, but 2 equiv of SmI_2 resulted in high yield (92%, entry 1), which might be required for forming acyl radical **11** and then acylsamarium **12**. Acylsamarium **12** interacts with cyclic ethers to form an intermediate **A** or **B** depending on the branched cyclic ethers being substituted at α-, β-, or γ-positions. A strong electrophilicity of samarium toward two oxygens may form **A** giving the corresponding iodide products with extremely high regioselectivity by "**a**" attack. Simple interaction between samarium and an oxygen of cyclic ethers having no substituent (substituted with alkyl groups) forms **B**, which provided both "**a**" and "**b**" routes without giving high selectivity. Thus, the high regioselectivity observed might arise from the complexation of acylsamarium with cyclic ethers substituted with a hydroxyl or ethereal moiety, where oxygen plays an important role.

In summary, we have developed cleavage reactions of cyclic ethers by the use of SmI_2 based on chelation control to obtain functionalized acylated iodide compounds with both high regioselectivity and high chemical yields.

Experimental Section

General. All reactions were performed in oven-dried glassware under argon using anhydrous solvents. THF was dried and freshly distilled over sodium/benzophenone, and CH_2Cl_2 was freshly distilled over CaH_2. Reactions were monitored by thin-layer chromatography (TLC) analysis. NMR spectra were measured in $CDCl_3$/TMS at 300 or 400 MHz (^{1}H) and 100 MHz (^{13}C). ^{1}H NMR coupling constants are given in hertz. For column chromatography, silica gel (230−400 mesh) was employed. Flash column chromatography on silica gel (2 cm × 25 cm; solvent = Et_2O/*n*-hexane) was normally used for purification of the reaction mixtures. Samarium diiodide was freshly prepared by the reaction of diiodomethane with samarium metal powder (1.2 equiv) in THP under argon with vigorous stirring for 2 h. The epoxides were commercially available or prepared by epoxidation of the corresponding olefins.

Typical Procedure for the Synthesis of Oxetanes (4). A mixture of KOBu-*t* (1.12 g, 10 mmol) and trimethyloxosulfonium iodide (2.2 g, 10 mmol) in dry *t*-BuOH (13 mL) was stirred magnetically at 50 °C for 1 h. A solution of styrene oxide (0.6 g, 5 mmol) in dry *t*-BuOH (10 mL) was then added dropwise and stirred for 3 days. The solvent was carefully evaporated under reduced pressure, and water (30 mL) was added to the residual suspension. The mixture was extracted with *n*-hexane, dried over anhydrous $MgSO_4$, and concentrated to give the crude product **4**, which was purified by column chromatography to afford **4** as a colorless oil (0.47 g, 3.5 mmol, 70%).

2-(3-Methylhexa-3,5-dienyl)-oxetane (5). The same procedure described for compound **4** was carried out to give **5** as a colorless oil (60%): ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.83 (m, 1H), 4.68 (m, 1H), 4.52 (m, 1H), 2.64 (m, 3H), 2.35 (m, 1H), 2.15 (m, 1H), 1.98 (m, 1H); ^{13}C NMR δ 141.5, 128.5, 128.3, 125.7, 81.9, 68.1, 39.5, 30.3, 27.4; HREIMS [M^+] calcd for $C_{11}H_{14}O$, 162.1044; found, 162.1049.

2-Benzyloxymethyl-oxetane (6). The same procedure described for compound **4** was carried out to give **6** as a colorless oil (65%): ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 4.96 (m, 1H), 4.63 (m, 4H), 3.66 (m, 2H), 2.63 (m, 2H); ^{13}C NMR δ 137.7, 128.3, 127.6, 127.5, 81.2, 73.49, 73.44, 68.9, 23.8; HREIMS [M^+] calcd for $C_{11}H_{14}O_2$, 178.09938; found, 178.0991.

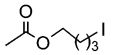
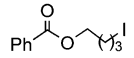
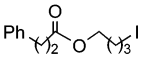
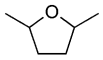
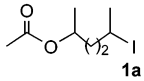
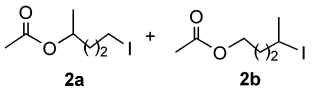
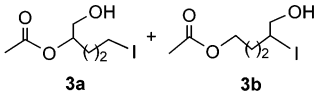
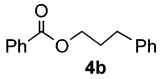
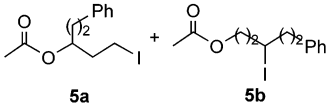
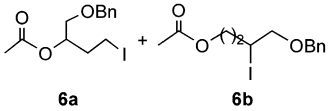
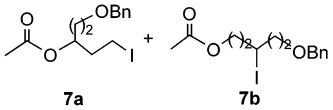
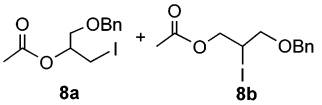
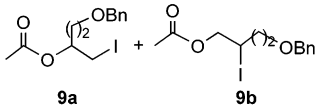
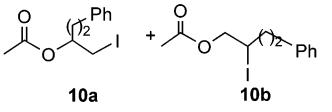
2-(2-Benzyloxyethyl)-oxetane (7). The same procedure described for compound **4** was carried out to give **7** as a colorless oil (63%): ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 4.98 (m, 1H), 4.64 (m, 1H), 4.52 (m, 1H), 4.46 (s, 2H), 3.52 (m, 2H), 2.65 (m, 1H), 2.41 (m, 1H), 2.09 (m, 2H); ^{13}C NMR δ 138.3, 128.3, 127.5, 127.4, 80.2, 73.0, 68.3, 65.9, 38.0, 27.5; HREIMS [M^+] calcd for $C_{12}H_{16}O_2$, 192.11503; found, 192.1151.

Typical Reaction for Cleavages of Cyclic Ethers (1a). To a solution of SmI_2 (1.0 mmol) in THP (10 mL) were added cyclic ether **1** (55 mg, 0.55 mmol) and acetyl chloride (39 mg, 0.5 mmol) in one portion. The mixture was stirred for 1 h under argon at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The reaction mixture was diluted with Et_2O (5 mL), and the organic layer was washed with water. The aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give the crude product, which was purified by column chromatography (2 cm × 25 cm; eluent = 1:1 Et_2O/*n*-hexane) to afford **1a** as a yellow oil (117 mg, 87%): ^{1}H NMR ($CDCl_3$) δ 4.9 (m, 1H), 4.14 (m, 1H), 2.0 (s, 3H), 1.89 (d, J = 6.4, 3H), 1.7 (m, 4H), 1.47 (d, J = 6.3, 3H); ^{13}C NMR δ 170.7, 70.2, 69.7, 38.7, 38.3, 36.1, 35.8, 29.4, 28.8, 21.3, 20.0; HREIMS [M^+] calcd for $C_8H_{15}IO_2$, 270.0116; found, 270.0124.

Acetic Acid 4-Iodo-1-methylbutyl Ester (2a). The ratio of **2a** and **2b** was determined by ^{1}H NMR analysis of the mixture of **2a** and **2b**. The **2a** and **2b** were separated by column chromatography (2 cm × 30 cm; eluent = 1:20 ethyl acetate/*n*-hexane). **2a**: yellow oil (42%); ^{1}H NMR ($CDCl_3$) δ 4.91 (m, 1H), 3.15 (t, J = 6.8, 2H), 1.99 (s, 3H), 1.88−1.55 (m, 4H), 1.21 (d, J = 6.3, 3H); ^{13}C NMR δ 170.5, 69.7, 36.6, 29.3, 21.2, 19.9, 6.1; HREIMS [M^+] calcd for $C_7H_{13}IO_2$, 255.9960; found, 255.9968. **2b**: yellow oil (42%); ^{1}H NMR ($CDCl_3$) δ 4.12 (m, 1H), 4.05 (t, J = 6.1, 2H), 2.02 (s, 3H), 1.92 (d, J = 6.9, 3H), 1.88−1.55 (m, 4H); ^{13}C NMR δ 171.0, 63.4, 39.1, 29.0, 28.95, 28.90, 20.9; HREIMS [M^+] calcd for $C_7H_{13}IO_2$, 255.9960; found, 255.9960.

Acetic Acid 1-Hydroxymethyl-4-iodo-butyl Ester (3a). The same procedure described for compound **1a** was carried out

TABLE 1. Acylative Cleavage of Cyclic Ethers Using SmI_2

Entry	Ethers	Acyl Chlorides	Products	Ratio of Isomers[b]	Yield (%)[a]
1	THF	AcCl			92
2	THF	Ac_2O			71
3	THF	BzCl			91
4	THF	Hydro-cinnamoyl chloride			93
5	 **1**	AcCl	 **1a**		87
6	 **2**	AcCl	 **2a** **2b**	**2a**:**2b** = 1:1	84
7	 **3**	AcCl	 **3a** **3b**	**3a**:**3b** = >99:1	70
8	 **4**	BzCl	 **4b**		89[c]
9	 **5**	AcCl	 **5a** **5b**	**5a**:**5b** = 5:4	82
10	 **6**	AcCl	 **6a** **6b**	**6a**:**6b** = 100:0[c]	81
11	 **7**	AcCl	 **7a** **7b**	**7a**:**7b** = 4:1	83
12	 **8**	AcCl	 **8a** **8b**	**8a**:**8b** = 100:0[c]	91
13	 **9**	AcCl	 **9a** **9b**	**9a**:**9b** = 100:0[c]	92
14	 **10**	AcCl	 **10a** **10b**	**10a**:**10b** = 100:0[c]	91

[a] Isolated yield after column chromatography. Products were fully characterized by ^{1}H NMR, ^{13}C NMR, and HR mass spectrometry. [b] Determined by ^{1}H NMR spectroscopy (see Experimental Section). [c] Only one isomer was detected and isolated.

to give **3a** (70%) as the major product. **3a**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 5.07 (m, 1H), 4.22 (dd, J = 11.9, 3.5, 1H), 4.04 (dd, J = 11.9, 6.3, 1H), 3.16 (t, J = 6.7, 2H), 2.05 (s, 3H), 1.82−1.65 (m, 4H); ^{13}C NMR δ 170.7, 70.3, 64.8, 31.6, 28.9, 21.0, 20.7, 5.6; HREIMS [M^+] calcd for $C_7H_{13}IO_3$, 271.9909; found, 271.9892.

Benzoic Acid 3-Phenylpropyl Ester (4b). The same procedure described for compound **1a** was carried out to give deiodinated product **4b** (89%) as the sole product. **4b**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.0−7.1 (m, 10H), 4.35 (t, J = 6.5, 2H), 2.8 (t, J = 7.6, 2H), 2.1 (m, 2H); ^{13}C NMR δ 166, 141, 132, 130, 129, 128.5, 128.4, 128.3, 126, 64.2, 32, 30; HREIMS [M^+] calcd for $C_{16}H_{16}IO_2$, 240.1150; found, 240.1150.

Acetic Acid 3-Iodo-1-phenethylpropyl Esters (5a and 5b). The reaction gave a mixture of **5a** and **5b** whose ratio (**5a**:**5b** = 5:4) was determined by ^{1}H NMR, and the compounds were separated by column chromatography (2 cm × 25 cm; eluent = 1:2 Et_2O/*n*-hexane) to give **5a** (46%) and **5b** (36%). **5a**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H), 4.95 (m, 1H), 3.12 (m, 2H), 2.61 (m, 2H), 2.15 (m, 2H), 2.04 (s, 3H), 1.83 (m, 2H); ^{13}C NMR δ 170.6, 141.1, 128.4, 128.2, 126.0, 73.8, 38.5, 35.3, 31.5, 21.0, −0.25; HREIMS [M^+] calcd for $C_{13}H_{17}IO_2$, 332.0273; found, 332.0242. **5b**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H), 4.27 (m, 1H), 4.11 (m, 2H), 2.88 (m, 1H), 2. 71 (m, 1H), 2.19−2.02 (m, 4H), 1.99 (s, 3H); ^{13}C NMR δ 170.8, 140.4, 128.4, 128.2, 126.0,

SCHEME 2

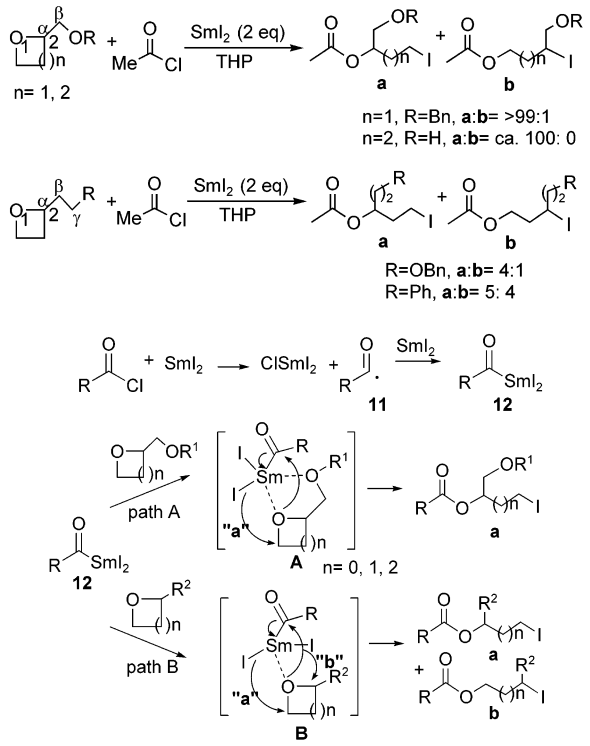
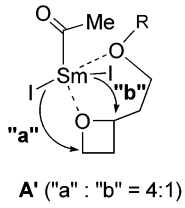


FIGURE 1. Proposed mechanism of acylative cleavage of cyclic ethers with SmI_2.



A' ("a" : "b" = 4:1)

FIGURE 2.

63.9, 42.1, 39.1, 35.4, 32.6, 20.8; HREIMS [M^+] calcd for $C_{13}H_{17}IO_2$, 332.0273; found, 332.0207.

Acetic Acid 1-Benzyloxymethyl-3-iodo-propyl Esters (6a and 6b). The same procedure described for compound **1a** was carried out to give **6a** as the sole product (81%). Compound **6b** could not be detected by ^{1}H NMR. **6a**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 5.05 (m, 1H), 4.53 (d, J = 11.8, 1H), 4.49 (d, J = 12.1, 1H), 3.52 (d, J = 4.6, 2H), 3.11 (m, 2H), 2.20 (m, 2H), 2.05 (s, 3H); ^{13}C NMR δ 170.4, 137.7, 128.4, 127.7, 127.6, 73.2, 72.7, 70.1, 35.0, 21.0, 0.037; HREIMS [M^+] calcd for $C_{10}H_{17}IO_3$, 348.0222; found, 348.0221.

Acetic Acid 1-(2-Benzyloxyethyl)-3-iodo-propyl Esters (7a and 7b). The reaction gave a mixture of **7a** and **7b** whose ratio (**7a**:**7b** = 4:1) was determined by ^{1}H NMR spectroscopy, and the compounds were separated by column chromatography (2 cm × 25 cm; eluent = 1:2 Et_2O/*n*-hexan) to give **7a** (67%) and **7b** (16%). **7a**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 5.04 (m, 1H), 4.45 (s, 2H), 3.47 (m, 2H), 3.09 (m, 2H), 2.11 (m, 2H), 2.00 (s, 3H), 1.89 (m, 2H); ^{13}C NMR δ 170.5, 138.1, 128.3, 127.7, 127.6, 73.1, 72.1, 66.3, 38.7, 33.8, 21.0, −0.255; HREIMS [M^+] calcd for $C_{14}H_{19}IO_3$, 362.0378; found, 362.0396. **7b**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 4.50 (s, 2H), 4.48−4.16 (m, 3H), 3.62 (m, 2H), 2.12−2.01 (m, 4H), 2.03 (s, 3H); ^{13}C NMR δ 170.8, 138.1, 128.3, 127.7, 127.6, 73.2, 69.4, 64.1, 40.5, 39.2, 29.9, 20.8; HREIMS [M^+] calcd for $C_{14}H_{19}IO_3$, 362.0378; found, 362.0356.

Acetic Acid 1-Benzyloxymethyl-2-iodo-ethyl Ester (8a). The same procedure described for compound **1a** was carried out to give **8a** (91%) as the sole product. Conpound **8b** could not be detected by ^{1}H NMR. **8a**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 4. 90 (m, 1H), 4.54 (q, J = 3.4, 2H), 3.67 (dd, J = 10.3, 4.9, 1H), 3.56 (dd, J = 10.3, 5.1, 1H), 3.43 (dd, J = 10.4, 5.6, 1H), 3.33 (dd, J = 10.4, 5.6, 1H), 2.07 (s, 3H); ^{13}C NMR δ 170.01, 137.55, 128.41, 127.82, 127.68, 73.39, 71.30, 70.02, 20.96, 3.92; HREIMS [M^+] calcd for $C_{12}H_{15}IO_3$, 334.0065; found, 334.0059.

Acetic Acid 3-Benzyloxy-1-iodomethylpropyl Ester (9a). The same procedure described for compound **1a** was carried out to give **9a** (92%) as the sole product. Isomeric **9b** could not be detected by ^{1}H NMR. **9a**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5H), 4. 84 (m, 1H), 4.46 (q, J = 4.3, 2H), 3.48 (m, 2H), 3.44 (dd, J = 10.6, 4.7, 1H), 3.27 (dd, J = 10.7, 5.0, 1H), 2.02 (s, 3H), 1.96 (m, 2H); ^{13}C NMR δ 170.15, 137.99, 128.35, 127.64, 127.62, 73.02, 69.87, 65.79, 34.39, 20.98, 8.83; HREIMS [M^+] calcd for $C_{13}H_{17}IO_3$, 348.022; found, 348.023.

Acetic Acid 1-Iodomethyl-3-phenylpropyl Ester (10a). The same procedure described for compound **1a** was carried out to give **10a** (91%) as the sole product. Isomeric **10b** could not be detected by ^{1}H NMR. **10a**: yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 5H), 4. 71 (m, 1H), 3.36 (dd, J = 10.8, 5.2, 1H), 3.26 (dd, J = 10.7, 5.2, 1H), 2.63 (m, 2H), 2. 07 (s, 3H), 1.99 (m, 2H); ^{13}C NMR δ 170.32, 140.73, 128.50, 128.28, 126.16, 71.72, 35.77, 31.39, 21.04, 8.14; HREIMS [M^+] calcd for $C_{12}H_{15}IO_2$, 318.0116; found, 318.0110.

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Supporting Information Available: Experimental details and spectral data of ^{1}H NMR, ^{13}C NMR, and HREIMS for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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