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Acetoxy Lactonization of Alkenyl Acetic Acids Promoted by Ammonium Persulfate and Trifluoromethanesulfonic Acid in Acetic Acid

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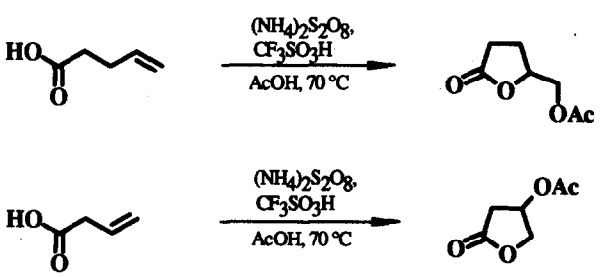
Abstract: The reactions of substituted 4-pentenoic and 3-butenoic acids with ammonium persulfate in acetic acid, in the presence of trifluoromethanesulfonic acid, gave the products of acetoxy lactonization in good yield.

The lactonization of unsaturated acids,[1-9] as well as of unsaturated nitriles,[10,11] is an interesting and familiar process in organic synthesis which can be promoted by several electrophilic reagents. For these ring closure reactions iodine (III) reagents can also be employed. Thus, with the use of PhI(OH)OTos and PhI(OH)OPO(OPh)2, tosyloxy[7] and phosphoryloxy[12] lactones can be obtained. Moreover, we have recently reported that alkenoic acids and nitriles can be easily converted into the corresponding acetoxy lactones using the commercially available iodobenzene diacetate.[13]

We now describe a very efficient new procedure which allows the acetoxy lactonization of alkenoic acids in a much more simple way. This method is exemplified in Scheme 1.

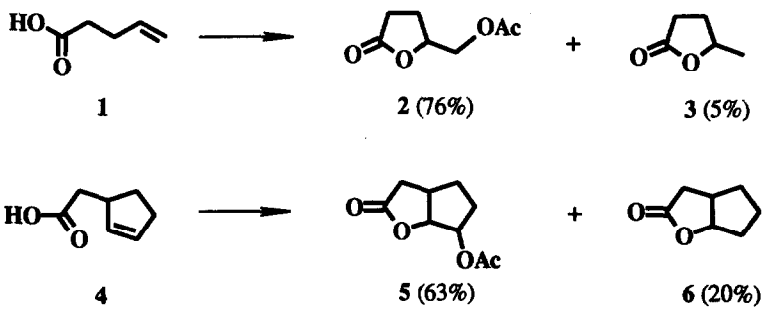
Scheme 1



This new procedure consists in the reactions of substituted 4-pentenoic and 3-butenoic acids with an excess of ammonium persulfate in acetic acid at 70 °C for 0.5-1.5 h, in the presence of trifluoromethanesulfonic acid. Similar results can be obtained using sulfuric acid. The reaction proceeds also with catalytic amounts of trifluoromethanesulfonic acid; in this case, however, longer reaction times are required (*ca.* 5 h). No reaction occurs in the absence of the strong acid.

The reactions of 4-pentenoic acid, **1**, and of 2-cyclopenteneacetic acid, **4**, (Scheme 2) afforded the corresponding γ-lactones **2** and **5** in good yield. Products **3** and **6**, deriving from the hydro lactonization of **1** and **4**, were also present.[11]

Scheme 2



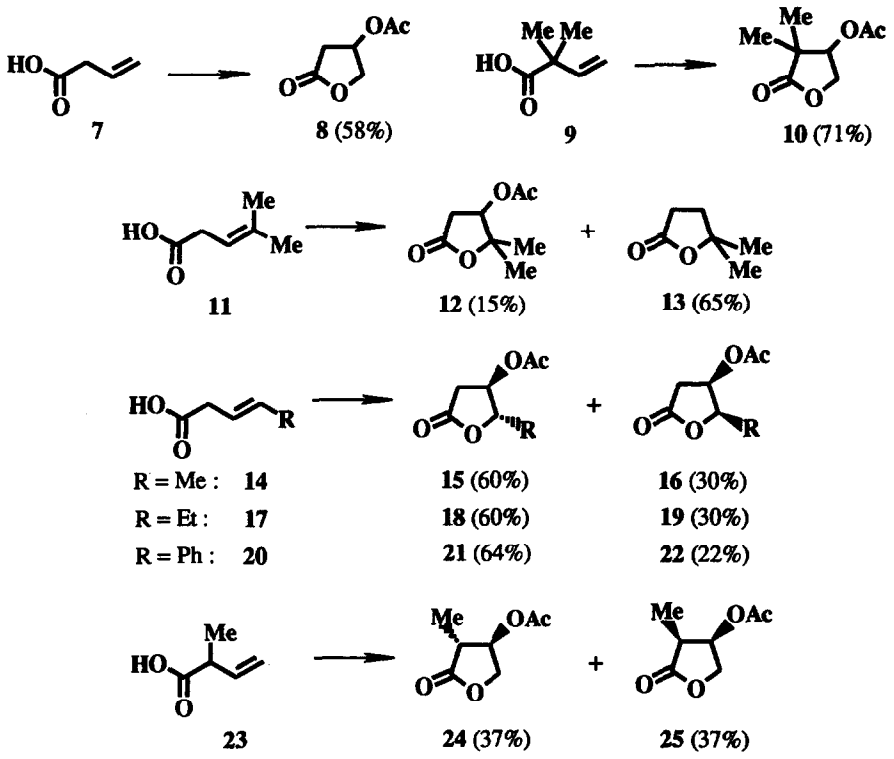
When the same reaction was carried out with 3-pentenoic acid and with its 2- and/or 4- derivatives the products obtained were the 4-acetoxy γ-lactones. The results of these experiments are summarized in Scheme 3 and in Scheme 4.

From 3-butenoic acid, **7**, and from 2,2-dimethyl-3-butenoic acid, **9**, the lactones **8** and **10** were isolated as the sole reaction products. In the case of the 4-methyl-3-pentenoic acid, **11**, on the contrary, the major reaction product was the dihydro-5,5-dimethyl-2(3H)-furanone, **13**, the acetoxy lactone **12** being formed only in 15% yield.

The reactions carried out on the 4-substituted 3-butenoic acids, **14**, **17** and **20**, demonstrated that this acetoxy lactonization is not a stereospecific process, a mixture of two stereoisomers being obtained in every case. These could be separated by column chromatography and their structures could be assigned on the basis of the different values of the vicinal coupling constants of the protons in the 4 and 5 positions. In agreement with literature data, the *Jcis* was in every case greater than the *Jtrans*.[14] Moreover, compound **19** was already described in the literature.[15] In every case the *trans* isomers were preferentially formed, the *trans/cis* ratios **15/16**, **18/19** and **21/22** being 2/1, 2/1 and 3/1, respectively.

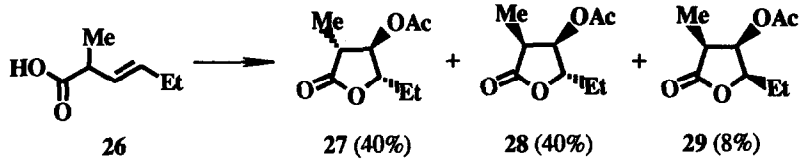
Similarly, the reaction of 2-methyl-3-butenoic acid, **23**, afforded a 1:1 mixture of the two possible stereoisomers, **24** and **25**. The stereochemistry of these two isomers was determined in a previous work also on the basis of the results of differential NOE experiments.[13]

Scheme 3



As expected, the reaction mixture deriving from 2-methyl-3-hexenoic acid, **26**, was more complex (Scheme 4). All the four possible stereoisomers could be detected by GC-MS, in a ratio of 1:1:0.2:0.2. However, only the three isomers indicated in Scheme 4 could be separated by column chromatography. The structures proposed for compounds **27**, **28** and **29** were again assigned on the basis of proton NMR data[16] and of differential NOE experiments.

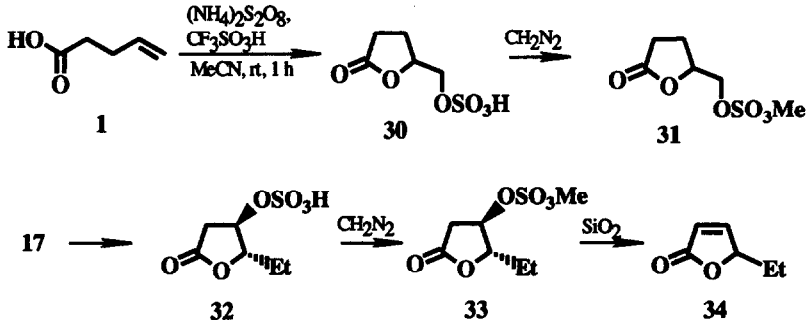
Scheme 4



In order to have some indications about the course of these reactions an experiment was carried out at room temperature starting from 4-pentenoic acid, **1**, and using acetonitrile as solvent. No products could be detected after the usual work up, the reaction mixture being completely soluble in water.

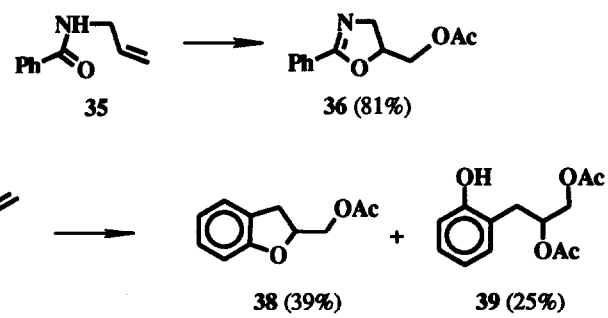
However, when acetic acid was added, the acetoxy lactone **2** could be obtained in good yield. Thus an intermediate is present in the reaction mixture which is completely soluble in water and which suffers substitution by acetic acid. This could possibly be the sulfate **30** indicated in Scheme 5. A further experiment was then carried out, under the same conditions, and the reaction mixture was treated with an excess of diazomethane. The reaction product which could be isolated and purified by column chromatography presented spectroscopic properties in agreement with the structure of the methyl sulfate **31**.

Scheme 5



Similar results were obtained when the same experiments were carried out with 3-hexenoic acid **17** (Scheme 5). The reaction mixture, which is proposed to contain the intermediate **32**, after treatment with diazomethane gave **33**. In this case, however, the methyl sulfate could not be obtained in a pure form since on attempted purification by column chromatography on silica gel it was almost completely converted into the butenolide **34**. NMR analysis of the crude reaction mixture showed that **33** was present as a single stereoisomer. From the results of these experiments it seems justified to assume that the sulfates **30** and **32** are formed as intermediates also in the case of the reactions carried out in acetic acid. At present, however, how these compounds can originate from the unsaturated acids and ammonium persulfate, in the presence of a strong acid, is still unclear.

Scheme 6



Some experiments were also carried out using alkenes containing other internal nucleophiles. Scheme 6 summarizes the results obtained with allyl benzamide, **35**, and with *o*-allyl phenol, **37**. In the first case the product of acetoxy etherification, **36**, was formed in good yield. In the case of the phenol, the expected product, **38**, was formed in 39% yield together with the diacetoxy derivative **39** (25%).

Thus, the very simple and efficient method of acetoxy lactonization of alkenoic acids described in this paper presents several advantages over the other previously described procedures and it can find useful applications in organic synthesis. Moreover, as indicated by the two examples described in Scheme 6, it can also be applied to other types of unsaturated compounds.

EXPERIMENTAL

GLC analyses and MS spectra were carried out with an HP 5890 gaschromatograph (dimethyl silicone column, 12.5 m) equipped with an HP 5971 Mass Selective Detector. Proton and carbon-13 NMR spectra were recorded at 200 and 50.32 MHz, respectively, on a Bruker AC 200 instrument; $CDCl_3$ was used as solvent and TMS as standard. IR spectra were recorded on a Perkin Elmer 1320 spectrophotometer. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer. Compounds **1**, **4**, **7**, **17**, **20**, and **37** were commercially available and were used without further purification. The acids **11** and **14** were obtained from the corresponding nitriles.[13]

Compounds **23**[17] and **35**[8] were prepared as described. Compounds **9**[18] and **26**[19] were prepared according to the following method. The acids **7** and **17** were deprotonated by treatment with lithium diisopropylamide (in THF, at -78 °C for 2 h). MeI was added at -78 °C and the resulting mixture was stirred and left to gradually reach room temperature (12 h).

All these compounds were fully characterized by MS, ^1H, and ^{13}C-NMR spectroscopy.

Preparation of Lactones. General Procedure. A mixture of the alkenyl acetic acid (10 mmol), ammonium persulfate (30 mmol), and trifluoromethanesulfonic acid (30 mmol) in acetic acid (15 mL) was stirred at 70 °C for 0.5 - 1.5 h. The progress of the reaction was monitored by GLC and TLC. The cooled mixture was poured on water and extracted with chloroform. The organic layer was washed with 10 % $NaHCO_3$, dried and evaporated. The reaction products were isolated in pure form after column chromatography on silica gel using a mixture of light petroleum and ether (80:20) or chloroform as eluant. Reaction yields are reported in the Schemes. Compounds **2**,[13] **3**,[11] **6**,[20] **8**,[13] **12**,[13] **13**,[21] **15**,[13] **16**,[13] **19**,[13] **24**,[13] **25**,[13] and **34**[13] have already been described in the literature. Physical and spectral data of the other reaction products are reported below.

8-Acetoxy-2-oxabicyclo[3.3.0]octan-3-one (5): oil; ^1H NMR δ 5.25 - 5.15 (m, 1 H), 4.8 (d, 1 H, J = 6.9 Hz), 3.2 - 2.95 (m, 1 H), 2.85 (dd, 1 H, J = 10.2 and 18.3 Hz), 2.3 (dd, 1 H, J = 3.0 and 18.3 Hz), 2.3 - 1.5 (m, 4 H), 2.05 (s, 3 H); ^{13}C NMR δ 176.1, 169.4, 87.3, 78.1, 36.2, 34.9, 30.6, 29.1, 20.6; MS *m/z* (relative intensity) 141(14), 124 (69), 97 (23), 82 (13), 67 (15), 55 (14), 43 (100). Anal. Calcd for $C_9H_{12}O_4$: C, 58.70; H, 6.57. Found: C, 58.57; H, 6.63.

Dihydro-4-acetoxy-3,3-dimethyl-2(3H)-furanone (10): oil; ^{1}H NMR δ 5.17 (dd, 1 H, J = 1.8 and 4.6 Hz), 4.55 (dd, 1 H, J = 4.6 and 11.0 Hz), 4.18 (dd, 1 H, J = 1.8 and 11.0 Hz), 2.12 (s, 3 H), 1.3 (s, 3 H), 1.2 (s, 3 H); ^{13}C NMR δ 179.3, 169.5, 76.2, 69.3, 41.9, 22.4, 20.1, 17.4; MS *m/z* (relative intensity) 129 (11), 86 (22), 72 (13), 71 (23), 70 (24), 68 (16), 43 (100). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 55.94; H, 7.12.

(4RS, 5SR)-Dihydro-4-acetoxy-5-ethyl-2-(3H)-furanone (18): oil; ^{1}H NMR δ 5.14 (dt, 1 H, J = 2.1 and 7.0 Hz), 4.44 (ddd, 1 H, J = 1.7, 5.9 and 7.6 Hz), 2.96 (dd, 1 H, J = 7.0 and 18.6 Hz), 2.57 (dd, 1 H, J = 2.1 and 18.6 Hz), 2.15 (s, 3 H), 1.9 - 1.6 (m, 2 H), 1.1 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 173.7, 169.8, 86.1, 72.6, 34.0, 25.8, 20.4, 8.9; MS *m/z* (relative intensity) 143 (3), 112 (10), 101 (22), 86 (18), 83 (40), 43 (100). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 55.73; H, 6.91.

(4RS, 5SR)-Dihydro-4-acetoxy-5-phenyl-2(3H)-furanone (21): oil; ^{1}H NMR δ 7.4 (br s, 5 H), 5.6 (br s, 1 H), 6.28 (dt, 1 H, J = 1.5 and 6.3 Hz), 2.89 (dd, 1 H, J = 6.3 and 18.3 Hz), 2.58 (dd, 1 H, J = 1.5 and 18.3 Hz), 2.2 (s, 3 H); ^{13}C NMR δ 174.0, 170.2, 136.0, 128.8, 128.6, 124.7, 85.0, 75.8, 32.9, 20.7; MS *m/z* (relative intensity) 160 (63), 149 (4), 131 (4), 107 (42), 105 (22), 77 (12), 71 (8), 43 (100). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.58; H, 5.34.

(4RS, 5RS)-Dihydro-4-acetoxy-5-phenyl-2(3H)-furanone (22): oil; ^{1}H NMR δ 7.45 - 7.25 (m, 5 H), 5.78 (ddd, 1 H, J = 1.4, 4.3 and 6.0 Hz), 5.65 (d, 1 H, J = 4.3 Hz), 3.05 (dd, 1 H, J = 6.0 and 18.1 Hz), 2.75 (dd, 1 H, J = 1.4 and 18.1 Hz), 1.7 (s, 3 H); ^{13}C NMR δ 173.9, 169.2, 133.2, 128.7, 128.2, 126.5, 83.8, 70.9, 36.2, 20.2; MS *m/z* (relative intensity) 220 (3), 177 (4), 160 (37), 149 (20), 107 (80), 77 (13), 71 (12), 43 (100). Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.37; H, 5.57.

(3RS, 4RS, 5SR)-Dihydro-4-acetoxy-5-ethyl-3-methyl-2(3H)-furanone (27): oil; ^{1}H NMR δ 4.9 (dd, 1 H, J = 5.2 and 6.1 Hz), 4.21 (ddd, 1 H, J = 5.1, 5.2 and 7.7 Hz), 2.7 (dq, 1 H, J = 6.1 and 7.5 Hz), 2.1 (s, 3 H), 1.9 - 1.6 (m, 2 H), 1.37 (d, 3 H, J = 7.5 Hz), 1.03 (t, 3 H, J = 7.3 Hz); ^{13}C NMR δ 176.1, 170.1, 83.2, 78.4, 41.8, 26.6, 20.6, 13.9, 9.2; MS *m/z* (relative intensity) 157 (2), 126 (5), 100 (44), 97 (21), 58 (14), 57 (7), 43 (100). Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.58. Found: C, 57.94; H, 7.63.

(3SR, 4RS, 5SR)-Dihydro-4-acetoxy-5-ethyl-3-methyl-2-(3H)-furanone (28): oil; ^{1}H NMR δ 5.2 (dd, 1 H, J = 1.0 and 6.4 Hz), 4.28 (ddd, 1 H, J = 1.0, 6.4 and 7.7 Hz), 2.88 (dq, 1 H, J = 6.4 and 7.3 Hz), 2.1 (s, 3 H), 1.8 - 1.6 (m, 2 H), 1.21 (d, 3 H, J = 7.3 Hz), 1.05 (t, 3 H, J = 7.4 Hz); ^{13}C NMR δ 176.8, 169.9, 84.9, 74.6, 36.9, 25.6, 20.5, 9.4, 8.3; MS *m/z* (relative intensity) 157 (3), 126 (6), 100 (44), 97 (17), 85 (5), 69 (8), 58 (11), 57 (8), 43 (100). Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.58. Found: C, 58.18; H, 7.67.

(3SR, 4RS, 5RS)-Dihydro-4-acetoxy-5-ethyl-3-methyl-2-(3H)-furanone (29): oil; ^{1}H NMR δ 5.62 (dd, 1 H, J = 3.4 and 5.3 Hz), 4.34 (ddd, 1 H, J = 3.4, 5.8 and 8.0 Hz), 2.83 (dq, 1 H, J = 5.4 and 7.2 Hz), 2.15 (s, 3 H), 1.95 - 1.5 (m, 2 H), 1.18 (d, 3 H, J = 7.2 Hz), 1.03 (t, 3 H, J = 7.4 Hz); ^{13}C NMR δ 176.6, 169.0,

82.4, 72.6, 40.5, 21.9, 20.2, 9.7, 8.3; MS *m/z* (relative intensity) 157 (1), 100 (60), 97 (6), 85 (6), 72 (12), 58 (15), 57 (10), 43 (100). Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.58. Found: C, 58.10; H, 7.49.

Dihydro-5-(methoxysulfonyloxymethyl)-2-(3H)-furanone (31): oil; ^{1}H NMR δ 4.85 - 4.70 (m, 1 H), 4.45 (dd, 1 H, J = 2.8 and 11.3 Hz), 4.28 (dd, 1 H, J = 4.8 and 11.3 Hz), 4.0 (s, 3 H), 2.70 - 2.55 (m, 2 H), 2.55 - 2.30 (m, 1 H), 2.25 - 2.05 (m, 1 H); ^{13}C NMR δ 175.5, 76.1, 72.5, 59.2, 27.9, 23.4; IR 1420 and 1210 cm^{-1}; MS *m/z* (relative intensity) 125 (3), 95 (10), 85 (100), 57 (10). Anal. Calcd for $C_6H_{10}O_6S$: C, 34.29; H, 4.80. Found: C, 34.16; H, 4.83.

(4RS, 5SR)-Dihydro-4-(methoxysulfonyloxy)-5-ethyl-2-(3H)-furanone (33): oil; ^{1}H NMR δ 5.04 (ddd, 1 H, J = 1.7, 2.3 and 6.5 Hz), 4.65 (dt, 1 H, J = 1.7 and 6.9 Hz), 4.05 (s, 3 H), 3.02 (dd, 1 H, J = 6.5 and 18.9 Hz), 2.85 (dd, 1 H, J = 2.3 and 18.9 Hz), 1.76 (quintet, 2 H, J = 7.2 Hz), 1.06 (t, 3 H, J = 7.2 Hz); IR 1400 and 1205 cm^{-1}; MS *m/z* (relative intensity) 112 (12), 95 (21), 83 (100), 71 (8), 57 (28), 55 (16), 43 (11).

4,5-Dihydro-2-phenyl-5-(acetoxymethyl)-oxazole (36): oil; ^{1}H NMR δ 7.9 - 7.8 (m, 2 H), 7.45 - 7.25 (m, 3 H), 4.9 - 4.7 (m, 1 H), 4.23 (dd, 1 H, J = 3.5 and 12.1 Hz), 4.1 (dd, 1 H, J = 5.8 and 12.1 Hz), 4.06 (dd, 1 H, J = 9.1 and 14.9 Hz), 3.73 (dd, 1 H, J = 7.4 and 14.9 Hz), 2.0 (s, 3 H); ^{13}C NMR δ 170.6, 163.9, 131.4, 128.3, 128.2, 77.0, 65.1, 56.9, 20.6; MS *m/z* (relative intensity) 219 (12), 177 (19), 159 (28), 146 (48), 130 (76), 118 (20), 117 (50), 105 (100), 91 (46), 77 (43), 51 (14), 43 (40). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.98; N, 6.39. Found: C, 65.83; H, 6.04; N, 6.28.

2-(Acetoxymethyl)-2,3-dihydrobenzofuran (38): oil; ^{1}H NMR δ 7.2 - 7.05 (m, 2 H), 6.9 - 6.75 (m, 2 H), 5.1 - 4.9 (m, 1 H), 4.34 (dd, 1 H, J = 3.7 and 11.9 Hz), 4.2 (dd, 1 H, J = 7.0 and 11.9 Hz), 3.3 (dd, 1 H, J = 9.5 and 15.7 Hz), 2.97 (dd, 1 H, J = 7.5 and 15.7 Hz), 2.1 (s, 3 H); ^{13}C NMR δ 170.7, 159.2, 128.1, 125.7, 124.8, 120.6, 109.5, 79.9, 65.8, 32.0, 20.7; MS *m/z* (relative intensity) 192 (12), 132 (51), 131 (100), 119 (23), 91 (38), 43 (40). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.61; H, 6.34.

2-[1-(2,3-Diacetoxy)propyl]phenol (39): oil; ^{1}H NMR δ 7.2 - 6.65 (m, 5 H), 5.15 - 5.0 (m, 1 H), 4.25 (dd, 1 H, J = 3.0 and 12.1 Hz), 4.15 (dd, 1 H, J = 6.4 and 12.1 Hz), 2.96 (dd, 1 H, J = 5.2 and 14.1 Hz), 2.85 (dd, 1 H, J = 7.7 and 14.1 Hz), 2.1 (s, 3 H), 2.05 (s, 3 H); MS *m/z* (relative intensity) 252 (1), 192 (5), 132 (73), 131 (83), 108 (15), 107 (32), 77 (12), 43 (100). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.04; H, 6.46.

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