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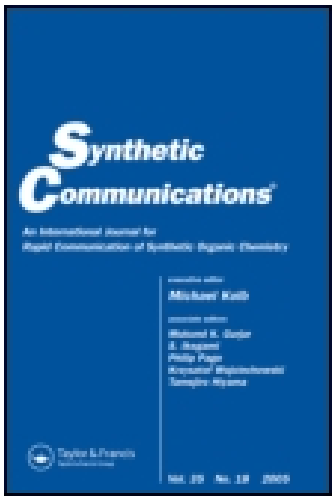

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SYNTHESIS OF HIGHLY FUNCTIONALIZED ARENE SYSTEMS. NOVEL SELECTIVITIES OF INTRA- AND INTERMOLECULAR FRIEDEL-CRAFTS REACTIONS

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SYNTHESIS OF HIGHLY FUNCTIONALIZED ARENE SYSTEMS. NOVEL SELECTIVITIES OF INTRA- AND INTERMOLECULAR FRIEDEL–CRAFTS REACTIONS

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ABSTRACT

The intermolecular Friedel–Crafts acylation of electron-rich aromatic rings can be difficult in the presence of easily ionized groups. During these studies directed toward the synthesis of colchicine, it was observed that the stability of the cation is key to controlling alternative competing processes.

Key Words: Friedel-Crafts reaction; Cyclization; Indane

During efforts directed toward the synthesis of colchicine and colchicine analogs,[1] it became necessary to synthesize a highly substituted diazoketone **1** as a precursor for a carbonyl ylide cycloaddition with the allylic

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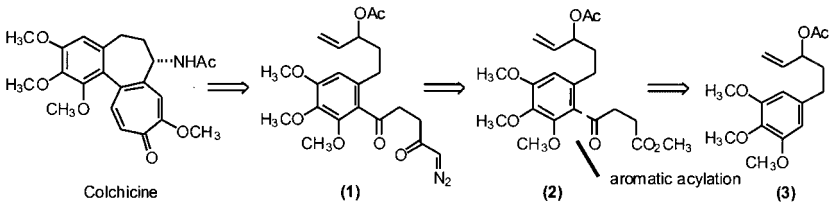
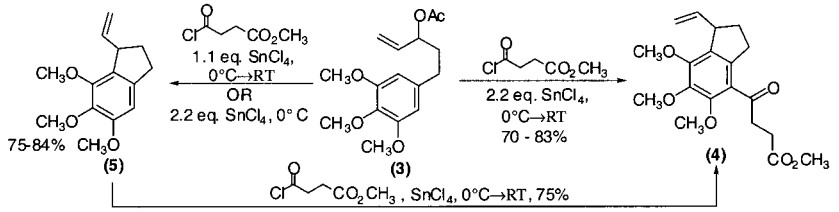


Scheme 1.



Scheme 2.

acetate functioning as a dipolarophile. Ketoester **2** was seen as a convenient precursor that could in turn be prepared directly from arene **3**. To accomplish this goal, it was anticipated that a Friedel–Crafts acylation[2] reaction could place the necessary functionality onto **3** under relatively mild conditions (Scheme 1).

The precursor allylic acetate **3** was synthesized from trimethoxyphenyl proprionic acid by standard methods[3] (see experimental section for details). Exposure of acetate **3** to an appropriate acid chloride[4] ($ClCOCH_2CH_2CO_2CH_3$) and $SnCl_4$ as a Lewis acid catalyst in either dichloromethane or nitromethane failed to generate the acylated product **2**. Surprisingly, a highly substituted indane **4** had been cleanly formed in very good yield (Scheme 2).

Indane **4** was envisioned to arise from an initial intramolecular capture of an allylic cation initiated through acetate ionization.[5] Subsequent intermolecular Friedel–Crafts acylation followed to prepare the hexasubstituted arene. In an attempt to prevent ionization, alternate protecting groups such as a pivalate ester or silyl ether were prepared, but found to be ineffective as well, resulting only in the quantitative recovery of the starting aromatic nucleus. Despite the electron rich nature of **3**, the aromatic may suffer from steric congestion at the unsubstituted phenyl position, exacerbated in part by the steric bulk of the alcohol protecting group. This possibility was supported by further studies regarding the reactivity of **3**.

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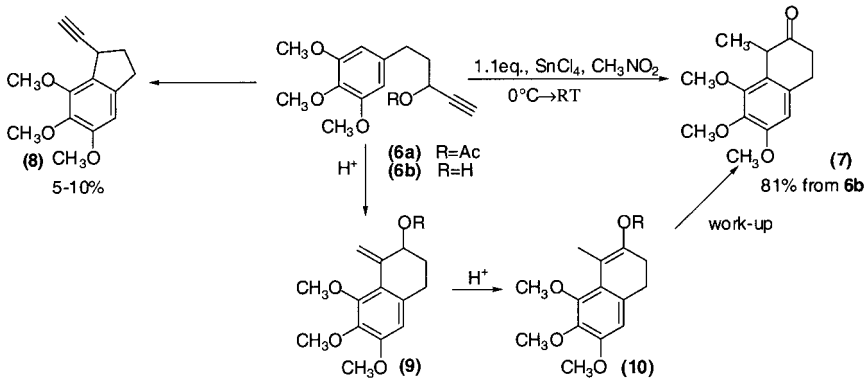

Scheme 3.

The conversion of **3** to **4** required the overall consumption of two equivalents of Lewis acid. Limiting the amount of Lewis acid available to 1 equivalent, in the presence of the acid chloride, produced only vinyl indane **5**.[6] Subsequent addition of a second equivalent of Lewis acid to the reaction mixture resulted in conversion of indane **5** to the acylated indane **4.** Moreover, if the reaction was quenched at 0°C, even in the presence of excess Lewis acid, indane **5** was produced exclusively, indicating that acylation can occur only after cyclization removes the steric constraint of the freely rotating side chain. The isolated indane **5** could also be converted to **4** upon re-exposure to the reaction conditions.

Concurrent with these studies, an alternative cycloaddition approach to colchicine that utilized an acetylenic dipolarophile was considered. Therefore, it was necessary to examine the behavior of the propargylic acetate[3] **6a** under the same cyclization conditions used previously (Scheme 3).

Propargylic acetate **6a** was expected from previous observations to cyclize to the alkynyl indane **8** upon exposure to a Lewis acid. In contrast to the prior results, treatment of acetate **6a** with tin tetrachloride produced a complex mixture of products. The recovered mixture was determined to be primarily tetralone **7** along with small quantities of indane **8** (conversion based on crude NMR and GC-MS data). The appearance of the tetralone was surprising and was surmised to be formed through an acid catalyzed cyclization of the internal carbon atom of the alkyne to initially produce an exo-methylene derivative **9**. Acid catalyzed isomerization to the endocyclic olefin would produce enol acetate **10**, that could further undergo hydrolysis to **7** upon aqueous work-up. The protic acid required for this process would

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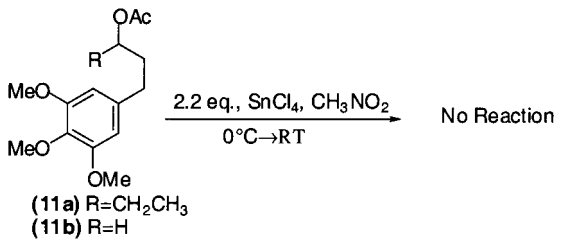
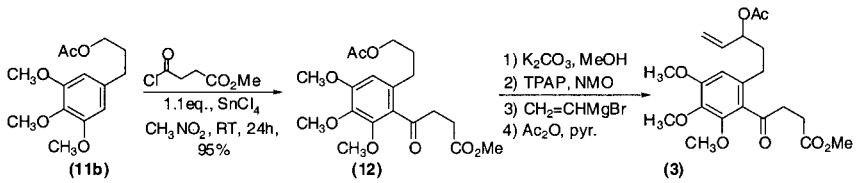


Scheme 4.



Scheme 5.

conceivably arise through the initial formation of indane **8**. Subjecting propargyl alcohol **6b** to the same conditions resulted in the clean production of tetralone **7** in 81% isolated yield. The more efficient synthesis of **7** would be due to the generation of HCl from initial reaction of tin tetrachloride with a free hydroxyl group.

It was presumed that the cyclization was facilitated by allylic stabilization of a carbocationic intermediate derived from **3** and that a less reactive acetate might survive the conditions needed for the acylation. To investigate this possibility, two additional acetates were prepared by the same synthetic route[3] and subjected to the cyclization conditions found to be effective in the prior indane forming reactions (Scheme 4).

Exposure of secondary acetate **11a** to Lewis acid conditions failed to produce any of the saturated indane. Similarly, primary acetate **11b** also failed to produce any product resulting from intramolecular cyclization, but instead a nearly quantitative yield of the starting material was recovered. *The stability of propylacetate **11b** towards Lewis acid afforded an opportunity to prepare the key synthetic intermediate **3** targeted for a synthesis of colchicine* (Scheme 5).

Gratifyingly, it was found that Friedel–Crafts acylation of primary acetate **11b** can be carried out (1.1 eq. $SnCl_4$, CH_2Cl_2, reflux 24 h, 95%) in excellent overall yield to prepare acetate **12**. The primary acetate is completely stable to the acylation conditions and even survives the more

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severe conditions needed to promote acylation. Conversion to arene **3** can be accomplished in four step reaction sequence starting with primary acetate **12**.[7]

This work represents the first step toward the synthesis of highly functionalized arenes that are to be utilized for tandem diazodecomposition reactions applied to the synthesis of colchicine analogs.

EXPERIMENTAL

General

^{1}H (250 MHz) and ^{13}C (62.5 MHz) NMR were recorded on a Bruker AC-250 NMR. GC-MS data was obtained on a Hewlett Packard 5890 Series II Gas Chromatograph with MSD detector. IR spectra were recorded using a Perkin-Elmer 1600 Series FT-IR. Dichloromethane and nitromethane were distilled from phosphorus pentoxide prior to use, all other compounds were used without further purification.

Synthesis of Acetates 3, 6a, 11a, 11b

3-(3,4,5-trimethoxyphenyl)propionic acid (5.0 g, 20.8 mmol) was added to 100 mL of dry THF and cooled to 0°C. A dropping funnel was attached and charged with borane–THF (31.2 mL, 31.2 mmol). The borane solution was added over a 15 min period and the resulting solution was allowed to warm to room temperature. The cloudy solution was allowed to stir for an additional 12 h at ambient temperature and then re-cooled to 0°C. The reaction was quenched by the addition of saturated NH_4Cl (100 mL) and allowed to stir for 30 min. The layers were separated and the organic layer extracted (3×20 mL) with ether. The layers were washed (NaCl), dried ($MgSO_4$), and concentrated to give a clear oil. The residue was purified by flash chromatography with ether/petroleum ether (5 : 1) as the eluent to give 4.66 g (98%) of 3-(3,4,5-trimethoxyphenyl) propanol as a clear oil. TLC $R_f = 0.49$ (ether/pet ether = 5 : 1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.33 (s, 2H) 3.76 (s, 6H), 3.73 (s, 3H), 3.59 (t, $J = 6.4$ Hz, 2H), 2.57 (t, $J = 7.5$ Hz, 2H), 1.91 (bs, 1H), 1.79 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.9, 137.6, 135.9, 105.2, 62, 60.7, 55.9, 34.1, 32.4; $IR_{(neat)}$ 3422, 3058, 2940, 1590, 1504, 1454, 1422; MS (70 eV) m/z (M^+) 226, 181, 151. Anal. calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.52; H, 8.04.

A flask containing a solution of pyridinium chlorochromate (1.11 g, 5.18 mmol) and 4 Å molecular sieves (2.22 g) in dry dichloromethane

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(50 mL) was cooled to 0°C, fitted with a pressure equalizing dropping funnel, then charged with a solution of 3-(3,4,5-trimethoxy phenyl) propanol (780 mg, 3.45 mmol) in dichloromethane (25 mL) and added over 15 min. The black solution was allowed to stir at room temperature until the reaction was judged complete by TLC (typically 3–4 h.). Celite was added and the resulting solution filtered through a 1 inch pad of celite. The dark solution was concentrated to one-half volume and an equal portion of toluene added. The solution was filtered through a 2 inch pad of silica gel and the pad washed with solvent (1 : 1 ether/toluene). The solution was concentrated to give an oily residue that was purified by flash column chromatography with hexane/ethyl acetate (1 : 1) to give 3-(3,4,5-trimethoxyphenyl) propanal (626 mg, 81%) as a light yellow oil. TLC $R_f = 0.26$ (hexane/ethyl acetate = 1 : 1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.75 (t, $J = 1.3$ Hz, 1H), 6.33 (s, 2H), 3.76 (s, 6H), 3.74 (s, 3H), 2.83 (dt, $J = 6.9$, 1.3 Hz, 2H), 2.69 (t, $J = 6.9$ Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 201.4, 153.2, 136.4, 105.2, 99.2, 60.7, 55.9, 45.3, 28.4; $IR_{(neat)}$ 3058, 2942, 2825, 2719, 1719, 1584, 1454, 1419; MS (70 eV) m/z (M^+)224, 196, 181, 151. Anal. calcd. for $C_{12}H_{15}O_4 \cdot 0.5\ H_2O$: C, 61.79; H, 7.34. Found: C, 62.17; H, 6.99.

General Procedure for Grignard Addition

To a solution of the aldehyde (200 mg, 0.89 mmol) in dry THF (10 mL) at 0°C was added the alkyl magnesium bromide (1.07 mmol) as a solution in THF. The ice bath was removed and the solution allowed to stir at room temperature for 6 h. At that time, $NH_4Cl_{(sat)}$ was added and the solution allowed to stir for 10 min, extracted (3 × 10 mL) with ether and the combined layers washed with $NaHCO_{3(sat)}$ then $NaCl_{(sat)}$, dried (Na_2SO_4) and concentrated in vacuo. The residue was subjected to flash column chromatography with ether/pet ether (5 : 1) as the eluent to give the alcohol as a colorless oil.

General Procedure for Acetate Formation

To a stirred solution of the alcohol (1.0 mmol) in dry dichloromethane (10 mL) was added DMAP (catalytic), pyridine (5.0 mmol) and acetic anhydride (5.0 mmol). The yellow solution was allowed to stir for 24 h, quenched by the addition of $NH_4Cl_{(sat)}$, extracted (3 × 5 mL) with dichloromethane and the combined organic layers are washed with $NaCl_{(sat)}$, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography with ether/pet ether (5 : 1) as the eluent to give the acetate as a clear oil.

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3-Acetoxy-5-(3,4,5-trimethoxyphenyl) pentene (3): Colorless oil (96% yield); TLC $R_f = 0.55$ (ether/pet ether = 5 : 1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.33 (s, 2H), 5.75 (ddd, $J = 6.2$, 10.6, 19.8 Hz, 1H), 5.23 (dd, $J = 1.3$, 19.8 Hz, 1H), 5.22 (q, $J = 6.2$ Hz, 1H), 5.03 (dd, $J = 1.3$, 10.6 Hz, 1H), 3.78 (s, 6H), 3.75 (s, 3H), 2.54 (m, 2H), 2.0 (s, 3H), 1.89 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 219.9, 170, 152.9, 136.5, 136.1,105.1, 73.9, 60.5, 55.8, 38.5, 31.6, 20.9; $IR_{(neat)}$ 3002, 2919, 1725, 1584, 1500; MS (70 eV) m/z (M^+)294, 181, 167, 151. Anal. calcd for $C_{16}H_{21}O_5 \cdot 0.5\ H_2O$: C, 65.07; H, 7.88. Found: C, 65.47; H, 7.75.

3-Acetoxy-5-(3,4,5-trimethoxyphenyl) pentyne (6a): Colorless oil (96% yield); TLC $R_f = 0.55$ (ether/pet ether = 5:1); 1H NMR (250 MHz, $CDCl_3$) δ 6.36 (s, 2H), 5.33 (dt, $J = 2.2$, 7.5 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 2.69 (t, $J = 7.5$ Hz, 2H), 2.49 (d, $J = 2.2$ Hz, 1H), 2.05 (s, 3H), 2.1 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.7, 153.1, 136.3, 136.1, 105.2, 80.8, 73.9, 63.1, 60.7, 55.9, 35.9, 31.4, 20.8; $IR_{(neat)}$ 2931, 2108, 1737, 1589, 1502, 1465; MS (70 eV) m/z (M^+)292, 250, 217, 201, 181, 167, 151, 43. Anal. calcd for $C_{16}H_{19}O_5 \cdot 0.5$ H2O: C, 65.51; H, 7.22. Found: C, 65.46; H, 7.41.

3-Acetoxy-5-(3,4,5-trimethoxyphenyl) pentane (11a): Colorless oil (91% yield) TLC $R_f = 0.17$ (ether/pet ether = 1 : 1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.38 (s, 2H), 4.88 (dt, $J = 5.8$, 6.5 Hz, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 2.55 (m, 2H),1.83 (m, 2H), 1.56 (d, $J = 7.6$ Hz, 2H), 0.89 (t, $J = 7.6$ Hz, 3H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.9, 153.1, 137.4, 136.2, 105.2, 74.9, 60.8, 56.1, 35.4, 32.3, 27.1, 21.2, 9.5; $IR_{(neat)}$ 3055, 2926, 1732, 1588, 1248; MS (70 eV) m/z (M^+)296, 236, 221, 207, 181, 151, 43. Anal. calcd for $C_{16}H_{21}O_4 \cdot 0.5\ H_2O$: C, 63.86; H, 8.80. Found: C, 63.63; H, 8.73.

1-Acetoxy-5-(3,4,5-trimethoxyphenyl) propane (11b): Colorless oil (96% yield from 3-(3,4,5-trimethoxyphenyl) propanol); TLC $R_f = 0.51$ (ether/pet ether = 5 : 1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.32 (s, 2H), 4.02 (t, $J = 6.6$ Hz, 2H), 3.75 (s, 6H), 3.73 (s, 3H), 2.55 (t, $J = 7.6$ Hz, 2H), 1.97 (s, 3H), 1.83 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171, 153, 136.9, 136.1, 105.2, 63.7, 60.7, 55.9, 32.5, 30.1, 20.8; $IR_{(neat)}$ 3064, 2937, 1737, 1591, 1509, 1462; MS (70 eV) m/z (M^+)268, 193, 181, 151, 43. Anal. calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.44; H, 7.45.

4-Oxo-4-(5,6,7-trimethoxy-1-vinyl-indan-4-yl)-butyric acid methyl ester (4): To allylic acetate **3** (80 mg, 0.27 mmol) in dry nitromethane (3 mL, 0°C) was added 3-carbomethoxypropionyl chloride (36 mL, 0.30 mmol, Aldrich Chemical) and tin tetrachloride (0.680 mL, 0.68 mmol, 1.0 M in dichloromethane). The mixture was allowed to stir at 0°C for 15 min, then at room temperature for an additional 30 min. Water (3 mL) was added, the solution was extracted with dichloromethane (3 × 3 mL), washed with $NaHCO_3$ and brine. The solution was dried (Na_2SO_4) and concentrated under reduced

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pressure. The residue was purified (flash column chromatography 1 : 1 ether : petroleum ether as eluent) to give **4** (66 mg, 70%) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.95(ddd, $J = 7.5$, 10, 17.2 Hz, 1H), 5.0 (dd, $J = 1.2$, 17.2 Hz, 1H), 4.9 (dd, $J = 1.2$, 10 Hz, 1H), 3.83–3.85 (m, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.70 (s, 3H), 3.20 (t, $J = 6.6$ Hz, 2H), 2.90 (t, $J = 6.6$ Hz), 2.15–2.3 (m, 8 lines, 2H), 1.96–1.84 (m, 8 lines, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 202.2, 173.4, 152.2, 153.4, 144.3, 141.2, 140.7, 133.9, 126.2, 113.4, 62, 61.9, 61.3, 51.3, 38.1, 33.4, 31.2, 28.5, 27.3; $IR_{(neat)}$ 2938, 1740, 1684, 1576, 1455, 1403, 1332; MS (70 eV) m/z 348(M^+), 261, 233, 115. Anal. calcd for $C_{19}H_{26}O_6$: C, 65.50; H, 6.94. Found: C, 65.73; H, 7.21.

6,7,8-Trimethoxy-1-methyl-3,4-dihydro-1H-naphthalen-2-one (7): To a solution of propargyl alcohol **11b** (70 mg, 0.28 mmol) in dry nitromethane (3 mL, 0°C) was added tin tetrachloride (420 mL, 0.42 mmol, 1.0 M in dichloromethane). The mixture was allowed to stir at 0°C for 30 min, water (3 mL) was added, the solution extracted (3 × 3 mL) with dichloromethane then washed with $NaHCO_3$(sat) and brine. The solution was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified (flash column chromatography 1 : 1 ether:petroleum ether as eluent) to give **7** (65 mg, 81%) as a colorless oil. ^{1}H NMR (C_6D_6) δ 6.23 (s, 1H), 3.89 (q, $J = 7.5$ Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.44 (s, 3H), 2.74 (ddd, $J = 15.1$, 12.2, 4.4 Hz, 1H), 2.53 (ddd, $J = 12.6$, 4.4, 3.5 Hz, 1H) 2.41 (ddd, $J = 12.2$, 6, 3.5 Hz, 1H), 2.16 (ddd, $J = 15.1$, 12.6, 6 Hz, 1H), 1.42 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 211.3, 152.7, 151.8, 141.7, 131.4, 125.5, 107.6, 60.7, 60.4, 55.7, 42.6, 38, 28.2, 19.5; $IR_{(neat)}$ 2936, 1712, 1602, 1501; MS (70 eV) m/z 250(M^+), 235, 207, 176. Anal. calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.37; H, 7.33.

4-[6-(3-Acetoxy-propyl)-2,3,4-trimethoxy-phenyl]-4-oxo-butyric acid methyl ester (12):. To a solution of acetate **11b** (900 mg, 2.35 mmol) in dry dichloromethane (20 mL, 0°C) was added 3-carbomethoxypropionyl chloride (451 mL, 3.69 mmol) and tin tetrachloride (5.04 mL, 1.0 M in dichloromethane, 5.04 mmol) dropwise. The mixture was heated at reflux for 24 h, water (20 mL) was added and the solution was extracted (3 × 10 mL) with dichloromethane then washed with $NaHCO_{3(sat)}$ and brine. The solution was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified (flash column chromatography 1 : 5 ether : petroleum ether as eluent) to give **12** (1.22 g, 95%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.43 (s, 1H), 3.99 (t, $J = 6.4$ Hz, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 3.02 (t, $J = 6.6$ Hz, 2H), 2.61 (t, $J = 6.6$ Hz, 2H), 2.45 (t, $J = 7.8$ Hz, 2H), 1.96 (s, 3H), 1.91–1.75 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.9, 172.9, 170.8, 154.1,

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150.5, 139.6, 134.3, 127.8, 108.5, 63.6, 61.4, 60.6, 55.8, 51.5, 39.5, 32.5, 32.3, 27.8, 20.6; $IR_{(neat)}$ 2940, 1733, 1732, 1701, 1541, 1442; MS (70 eV) m/z 382(M^+), 351, 294, 253, 235, 207, 115. Anal. calcd for $C_{19}H_{24}O_8$: C, 59.68; H, 6.85. Found: C, 59.47; H, 6.81.

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7. Acetate **12** can be converted to the allylic acetate **3** through the following sequence; (i) K_2CO_3 (5 eq.), MeOH–H_2O, RT, 30 min, 92% (ii) TPAP (5 mole %), NMO (1.6 eq.), molecular sieves, CH_2Cl_2, 81% (iii) $CH_2CHMgBr$, Et_2O, −78°C to RT, 8 h, 84% (iv) Ac_2O, pyridine, 95%.

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