New Synthetic Methods for Seven- and Eight-Membered Cyclic Ethers Based on the Ring-Expansion Reactions of Hydroxy or Lithioxy Methoxyallenylisochroman Derivatives

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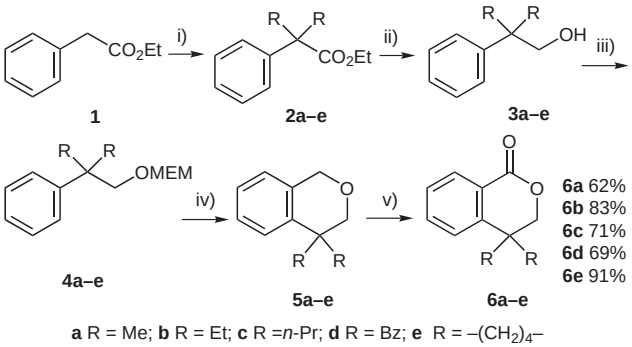
Abstract: The Pd(0)-catalyzed ring-expansion reactions of hydroxy methoxyallenyl-4,4-dialkylisochroman derivatives in the presence of P(*o*-tolyl)$_3$ proceeded smoothly via hydropalladation to give 3-benzoxepan-1-one derivatives in high yields. Treatment of isochroman-1-one derivatives with lithio methoxyallene followed by quenching the reaction with water furnished 3-benzoxocan-6-one derivatives in good yields.

Key words: allenes, cyclic ether, palladium, hydropalladation, ring expansion

Oxygen-containing medium-sized heterocycles are important structural units commonly found within the framework of a variety of natural and synthetic biologically active compounds.[1] Specifically, six- to nine-membered cyclic ethers often appear in marine natural products such as brevetoxin and ciguatoxin.[2,3] Hence, many efficient synthetic methods have been reported for cyclic ethers.[4] In a series of studies on cyclization, ring-expansion, and cascade reactions utilizing allenylic molecular structure characteristics, recent efforts in our laboratory have focused on base-mediated and Pd(0)-catalyzed ring-expansion reactions of various hydroxy allenyl cyclic compounds.[5] In the previous ring-expansion reactions of the cyclic ethers reported by our group, we carried out the synthesis of six- or seven-membered cyclic ethers from five-membered cyclic ethers (5→6 and 5→7) have been performed.[5d,f] Here, we describe Pd(0)-catalyzed one-atom ring-expansion reactions (6→7) of hydroxy methoxyallenylisochroman derivatives toward 3-benzoxepan-1-one derivatives via hydropalladation, as well as two-atom ring-expansion reactions (6→8) of lithioxy methoxyallenylisochroman derivatives.

The 4,4-dialkyl-isochroman-1-one derivatives **6a**–**e** were readily accessible from ethyl phenylacetate (**1**) through the reaction pathway represented in Scheme 1. Namely, dialkylation of **1** with five types of alkyl halides in the presence of NaH in THF followed by the reduction of the resulting α,α-dialkyl esters **2a**–**e** with $LiAlH_4$ gave the corresponding alcohols **3a**–**e**.[6] After protection of the hydroxy group of **3a**–**e** with the MEM group, the products **4a**–**e** were subjected to cyclization with $TiCl_4$ in CH_2Cl_2 to give 4,4-dialkylisochromans **5a**–**e**.[7] Oxidation of **5a**–**e** with $KMnO_4$ and $CuSO_4{\cdot}5H_2O$ in CH_2Cl_2 afforded the corresponding δ-lactones **6a**–**e** in 62–91% overall yields from compound **1**.[8]



Scheme 1 *Reagents and conditions*: i) NaH (3.0 mol equiv), R-X (3.0 mol equiv), THF, r.t.; ii) $LiAlH_4$ (1.3 mol equiv), THF, reflux; iii) MEMCl (1.2 mol equiv), DIPEA (1.2 mol equiv), CH_2Cl_2, r.t.; iv) $TiCl_4$ (1.19 mol equiv), CH_2Cl_2, 0 °C; v) $KMnO_4$ (7.96 mol equiv), $CuSO_4{\cdot}5H_2O$ (5.04 mol equiv), CH_2Cl_2, r.t.

Hydroxy methoxyallenyl-4,4-dialkylisochroman derivatives **7a**–**c**, precursors for the ring-expansion reaction, were obtained in 69–98% yields by treatment of **6a**–**c** with 1.2 mol equivalents of lithio methoxyallene[9] in THF at –30 °C for 1 hour, as shown in Scheme 2.[10] However, similar treatment of **6d**,**e** with lithio methoxyallene resulted in the decomposition of the starting compound. The structures of **7a**–**c** were determined by their characteristic spectroscopic data [^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42–3.48 (s, 3 H, OMe), 3.42–3.50 (s, 1 H, OH), 5.60–5.52 (d, 1 H, *J* = 8.3 Hz, allene H), and 5.55–5.66 (d, 1 H, *J* = 8.3 Hz, allene H). IR (KBr or neat): 3420–3470 (OH), 1956–1957 (allenyl) cm^{-1}; high resolution MS (M^+)].[10]

The desirable ring-expansion (6→7) reactions commenced with the Pd(0)-promoted conditions which we first used successfully for the conversion of five-membered phthalans to six-membered isochromanones via hydropalladation.[5f] Namely, the compounds **7a**–**c** were refluxed with 5 mol% of $Pd(PPh_3)_4$ and 10 mol% of P(*o*-tolyl)$_3$ in THF for 3–12 hours. The desired one-atom ring-expansion reactions proceeded smoothly to afford 3-benz-

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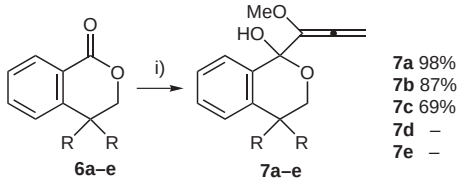


a R = Me; **b** R = Et; **c** R =*n*-Pr; **d** R = Bz; **e** R = –$(CH_2)_4$–

Scheme 2 *Reagents and conditions*: i) methoxyallene (2.0 mol equiv), *n*-BuLi (1.2 mol equiv), THF, –30 °C.

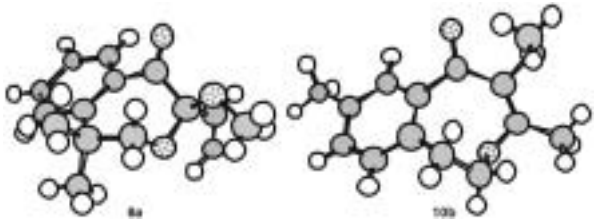
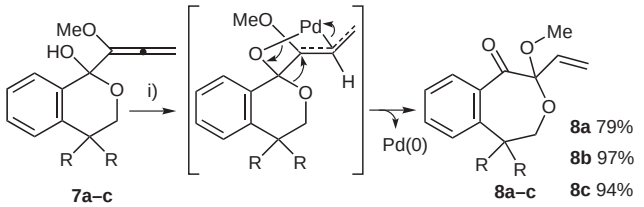


Figure 1 Computer-generated drawing from the X-ray coordinates of **8a** and **10b**.

oxepan-1-one derivatives **8a**–**c** in 79–97% yields, as shown in Scheme 3.[11] The structures of **8a**–**c** were explicitly determined by their characteristic spectroscopic data [^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.34–3.36 (s, 3 H, OMe), 5.35–5.37 (dd, 1 H, *J* = 1.5–1.6, 10.3–10.5 Hz, olefin H), 5.48–5.53 (dd, *J* = 1.5–1.6, 17.3 Hz, olefin H), and 5.61–5.65 (dd, 1 H, *J* = 10.3–10.5, 17.2–17.3 Hz, olefin H). IR (KBr or neat): 1700–1711 (ketone) cm^{-1}; high resolution MS (M^+)] and elemental analyses,[11] or by X-ray crystallographic analysis of **8a**, as shown in Figure 1.[12] Thus, we have achieved the first facile ring-expansion reaction of six-membered cyclic ethers to seven-membered cyclic ethers via hydropalladation.

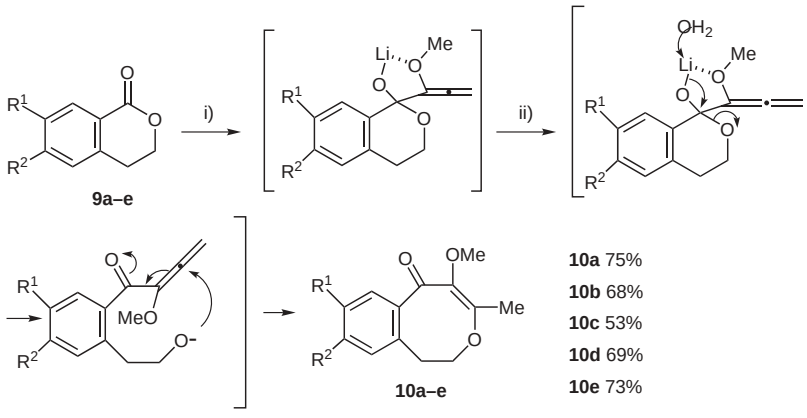


a R = Me; **b** R = Et; **c** R =*n*-Pr

Scheme 3 *Reagents and conditions*: i) $Pd(PPh_3)_4$ (5 mol%), P(*o*-tolyl)$_3$ (10 mol%), THF, reflux.

Subsequently, we undertook the development of a general method for the ring-expansion reaction involving the conversion of six-membered cyclic ethers into eight-membered cyclic ethers based on nucleophillic methoxyallenylation to the δ-lactone carbonyl followed by the water-quenched ring-opening of lithioxy methoxyallenylisochromans and then endo-mode cyclization, as shown in Scheme 4.[5d] Isochroman-1-one derivatives **9a**–**e**[8,7c,13] were allowed to react with 1.2 mol equivalents of lithio methoxyallene at –30 °C in THF for 0.5–1.0 hours, and then each reaction was quenched by the addition of water to furnish the corresponding 3-benzoxocan-6-one derivatives **10a**–**e** in 53–75% yields.[14] The structures of **10a**–**e** were determined by their characteristic spectroscopic data [^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.11–2.12 (s, 3 H, CMe), 2.92–2.98 (t, 2 H, *J* = 5.6–5.9 Hz, C1-H), 3.72–3.73 (s, 3 H, OMe), 3.99–4.03 (t, 2 H, *J* = 5.6–5.9 Hz, C2-H). IR (KBr or neat): 1613–1620 (α,β-unsaturated ketone) cm^{-1}; high resolution MS (M^+)] and elemental analyses,[14] or by X-ray crystallographic analysis of **10b**, as shown in Figure 1.[15]

Although we had previously encountered one example of such a ring-expansion reaction (5→7) in the reaction of a non-substituted phthalide with lithio methoxyallene,[5d] we have now established a new general synthetic method for the eight-membered cyclic ethers.



a $R^1 = R^2 = H$; **b** R^1 = Me, R^2 = H; **c** R^1 = H, R^2 = Me; **d** R^1 = OMe, R^2 = H; **e** $R^1 = R^2$ = OMe

Scheme 4 *Reagents and conditions*: i) methoxyallene (2.0 mol equiv), *n*-BuLi (1.2 mol equiv), THF, –30 °C; ii) H_2O.

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(10) **Typical Experimental Procedure for the Synthesis of Hydroxy Methoxyallenyl-4,4-dialkylisochromans 7a–c:** A solution of methoxyallene (280.4 mg, 4.0 mmol) in dry THF (4.0 mL) was treated with 1.58 M *n*-BuLi in *n*-hexane (1.52 mL, 2.4 mmol) under an argon atmosphere at –30 °C. The solution was stirred for 30 min, and then the solution was added to a THF (2.0 mL) solution of 4,4-dimethylisochroman-1-one (**6a**; 352.4 mg, 2.0 mmol) at –30 °C. After being stirred at –30 °C for 1 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to afford a crude product, which was purified by column chromatography on silica gel with *n*-hexane–EtOAc (3:1) to give 1-hydroxy-1-methoxyallenyl-4,4-dimethylisochroman (**7a**; 483.2 mg, 98%) as a pale yellow oil.
Compound **7a**: pale yellow oil. IR (neat): 3428, 1956 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3 H), 1.33 (s, 3 H), 3.42 (s, 1 H), 3.47 (s, 3 H), 3.61 (d, *J* = 11.0 Hz, 1 H), 4.04 (d, *J* = 11.0 Hz, 1 H), 5.60 (d, *J* = 8.3 Hz, 1 H), 5.66 (d, *J* = 8.3 Hz, 1 H), 7.17–7.36 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.5, 28.2, 33.4, 56.8, 70.8, 94.3, 96.1, 124.4, 125.7, 127.4, 128.5, 133.7, 137.2, 144.1, 197.1. HRMS-EI calcd for $C_{15}H_{18}O_3$: MW 246.1256. Found: *m/z* = 246.1254 (M^+). Compound **7b**: pale yellow oil. IR (neat): 3470, 1956 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.77 (t, *J* = 7.7 Hz, 3 H), 0.81 (t, *J* = 7.7 Hz, 3 H), 1.62–1.82 (m, 4 H), 3.48 (s, 3 H), 3.50 (s, 1 H), 3.76 (d, *J* = 11.2 Hz, 1 H), 4.11 (d, *J* = 11.2 Hz, 1 H), 5.52 (d, *J* = 8.3 Hz, 1 H), 5.55 (d, *J* = 8.3 Hz, 1 H), 7.16–7.31 (m, 3 H), 7.36–7.39 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.6, 8.7, 28.5, 31.3, 39.4, 56.9, 66.5, 94.0, 96.3, 125.5, 125.6, 127.6, 128.0, 135.2, 136.7, 141.2, 197.4. HRMS-EI calcd for $C_{17}H_{22}O_3$: MW 274.1569. Found: *m/z* = 274.1569 (M^+). Compound **7c**: white powder. IR (KBr): 3420, 1957 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.3 Hz, 3 H), 0.86 (t, *J* = 7.3 Hz, 3 H), 1.06–1.29 (m, 4 H), 1.59–1.73 (m, 4 H), 3.48 (s, 3 H), 3.49 (s, 1 H), 3.76 (d, *J* = 11.5 Hz, 1 H), 4.10 (d, *J* = 11.5 Hz, 1 H), 5.52 (d, *J* = 8.3 Hz, 1 H), 5.55 (d, *J* = 8.3 Hz, 1 H), 7.15–7.30 (m, 3 H), 7.35–7.37 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 15.0, 17.3, 17.4, 39.2, 39.4, 41.7, 57.0, 67.4, 94.1, 96.3, 125.4, 125.5, 127.6, 128.0, 134.7, 136.6, 141.9, 197.3. HRMS-EI calcd for $C_{19}H_{26}O_3$: MW 302.1882. Found: *m/z* = 302.1888 (M^+).

(11) **Typical Procedure for the Ring-Expansion Reaction of Hydroxy Methoxyallenyl-4,4-dialkylisochromans 7a–c:** A mixture of 1-hydroxy-1-methoxyallenyl-4,4-dimethylisochroman (**7a**; 173.1 mg, 0.703 mmol), $Pd(PPh_3)_4$ (40.6 mg, 5.0 mol%), P(*o*-tolyl)$_3$ (21.4 mg, 10.0 mol%) in THF (7.0 mL) was refluxed under an argon atmosphere for 3 h. The reaction mixture was evaporated in vacuo to afford a solid residue, which was purified by column chromatography on silica gel with *n*-hexane–EtOAc (3:1) to give 5,5-dimethyl-2-methoxy-2-vinyl-3-benzoxepan-1-one (**8a**; 137.4 mg, 79%) as colorless prisms.
Compound **8a**: colorless prisms; mp 78.5–79.5 °C (*n*-hexane–EtOAc). IR (KBr): 1711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3 H), 1.60 (s, 3 H), 3.36 (s, 3 H), 3.69 (d, *J* = 13.2 Hz, 1 H), 4.03 (d, *J* = 13.2 Hz, 1 H), 5.37 (dd, *J* = 1.6, 10.3 Hz, 1 H), 5.53 (dd, *J* = 1.6, 17.3 Hz, 1 H), 5.65 (dd, *J* = 10.3, 17.3 Hz, 1 H), 7.21–7.25 (m, 1 H), 7.41–7.50 (m, 3 H). HRMS-EI calcd for $C_{15}H_{18}O_3$: MW 246.1256. Found: *m/z* = 246.1258 (M^+). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.03; H, 7.38. Compound **8b**: colorless oil. IR (neat): 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.46 (t, *J* = 7.5 Hz, 3 H), 1.07 (t, *J* = 7.5 Hz, 3 H) 1.44–1.58 (m, 2 H), 1.76–1.89 (m, 1 H), 2.13–2.23 (m, 1 H), 3.35 (s, 3 H), 3.86 (d, *J* = 13.7 Hz, 1 H), 4.10 (d, *J* = 13.7 Hz, 1 H), 5.35 (dd, *J* = 1.5, 10.5 Hz, 1 H), 5.48 (dd, *J* = 1.5, 17.3 Hz, 1 H), 5.62 (dd, *J* = 10.5, 17.3 Hz, 1 H), 7.22–7.26 (m, 1 H), 7.24 (d, *J* = 7.8 Hz, 1 H), 7.42 (dd, *J* = 1.5, 7.7 Hz, 1 H), 7.46–7.50 (m, 1 H). HRMS-EI calcd for $C_{17}H_{22}O_3$: MW 274.1569. Found: *m/z* = 274.1558 (M^+). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.17; H, 8.08. Compound **8c**: colorless oil. IR (neat): 1701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.54–0.73 (m, 4 H), 0.92–1.04 (m, 4

H), 1.33–1.50 (m, 3 H), 1.63–1.78 (m, 3 H), 3.34 (s, 3 H), 3.87 (d, *J* = 13.7 Hz, 1 H), 4.11 (d, *J* = 13.7 Hz, 1 H), 5.35 (dd, *J* = 1.5, 10.5 Hz, 1 H), 5.48 (dd, *J* = 1.5, 17.3 Hz, 1 H), 5.61 (dd, *J* = 10.5, 17.3 Hz, 1 H), 7.21–7.24 (m, 1 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 7.40 (dd, *J* = 1.5, 7.8 Hz, 1 H), 7.46–7.50 (m, 1 H). HRMS-EI calcd for $C_{19}H_{26}O_3$: MW 302.1882. Found: *m/z* = 302.1888 (M^+). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.21; H, 8.71.

(12) X-ray data for **8a**: $C_{15}H_{18}O_3$, MW = 246.31, colorless block, orthorhombic, space group Aba2 (#41), *a* = 22.4114 Å, *b* = 7.929(2) Å, *c* = 14.737 (4) Å, *V* = 2618 (1) Å^3, *Z* = 8, *R* = 0.181, *Rw* = 0.181. The structure factors are available from the author upon request.

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(14) **Typical Experimental Procedure for the Ring-Expansion Reaction of Isochroman-1-ones 9a–e:** A solution of methoxyallene (140.2 mg, 2.0 mmol) in dry THF (2.0 mL) was treated with 1.58 M *n*-BuLi in *n*-hexane (0.76 mL, 1.2 mmol) under an argon atmosphere at –30 °C with stirring for 30 min. Then the solution was added to a THF (1.0 mL) solution of 7-methoxy-isochroman-1-one (**9d**; 178.2 mg, 1.0 mmol) at –30 °C. After being stirred at –30 °C for 1 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to afford a crude product, which was purified by column chromatography on silica gel with *n*-hexane–EtOAc (3:1) to give 5,8-dimethoxy-4-methyl-1,2-dihydro-3-benzoxocin-6-one (**10d**; 166.6 mg, 69%) as colorless plates.
Compound **10a**: colorless oil. IR (neat): 1619, 1596 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3 H), 2.98 (t, *J* = 5.7 Hz, 2 H), 3.73 (s, 3 H), 4.02 (t, *J* = 5.7 Hz, 2 H), 7.16 (d, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 1 H). HRMS-EI calcd for $C_{13}H_{14}O_3$: MW 218.0943. Found: *m/z* = 218.0957 (M^+). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.32; H, 6.43. Compound **10b**: colorless needles; mp 72.5–73.5 °C ($CHCl_3$–*n*-hexane–Et_2O). IR (KBr): 1620, 1601 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3 H), 2.36 (s, 3 H), 2.94 (t, *J* = 5.9 Hz, 2 H), 3.72 (s, 3 H), 4.00 (t, *J* = 5.9 Hz, 2 H), 7.05 (d, *J* = 7.8 Hz, 1 H), 7.23–7.26 (m, 1 H), 7.56 (d, *J* = 0.7 Hz, 1 H). HRMS-EI calcd for $C_{14}H_{16}O_3$: MW 232.1100. Found: *m/z* = 232.1104 (M^+). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.13; H, 6.96. Compound **10c**: colorless prisms; mp 56.0–56.5 °C (*n*-hexane–Et_2O). IR (KBr): 1617, 1608 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3 H), 2.37 (s, 3 H), 2.95 (t, *J* = 5.7 Hz, 2 H), 3.72 (s, 3 H), 4.01 (t, *J* = 5.7 Hz, 2 H), 6.97 (s, 1 H), 7.15 (d, *J* = 8.1 Hz, 1 H), 7.69 (d, *J* = 8.1 Hz, 1 H); HRMS-EI calcd for $C_{14}H_{16}O_3$: MW 232.1100. Found: *m/z* = 232.1092 (M^+). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.17; H, 6.98. Compound **10d**: colorless plates; mp 81.0 °C (*n*-hexane–EtOAc). IR (KBr): 1613, 1600 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3 H), 2.92 (t, *J* = 5.6 Hz, 2 H), 3.72 (s, 3 H), 3.83 (s, 3 H), 3.99 (t, *J* = 5.6 Hz, 2 H), 7.00 (dd, *J* = 2.0, 8.3 Hz, 1 H), 7.07 (d, *J* = 8.3 Hz, 1 H), 7.30 (d, *J* = 2.0 Hz, 1 H). HRMS-EI calcd for $C_{14}H_{16}O_4$: MW 248.1049. Found: *m/z* = 248.1049 (M^+). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.76; H, 6.52. Compound **10e**: colorless needless; mp 147.0–147.5 °C (*n*-hexane–EtOAc); IR (KBr) 1617, 1596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.11 (s, 3 H), 2.97 (t, *J* = 5.7 Hz, 2 H), 3.72 (s, 3 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 4.03 (t, *J* = 5.7 Hz, 2 H), 6.62 (s, 1 H), 7.44 (s, 1 H). HRMS-EI calcd for $C_{15}H_{18}O_5$ MW 278.1154, found *m/z* 278.1172 (M^+). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.47; H, 6.52. Found: C, 64.74; H, 6.58.

(15) X-ray data for **10b**: $C_{14}H_{16}O_3$, MW = 232.28, colorless needle, monoclinic, space group $P2_1/c$ (#14), *a* = 10.223(3) Å, *b* = 8.743(2) Å, *c* = 14.193(3) Å, *V* = 1237.9(5) Å^3, *β* = 102.64(1)°, *Z* = 4, *R* = 0.087, *Rw* = 0.131. The structure factors are available from the author upon request.