Facile Synthesis of 4-Substituted 3-*Exo*-methylenechroman Derivatives *via* Radical Cyclization Starting from Salicylaldehydes

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Synthesis of 4-substituted 3-*exo*-methylenechroman derivatives was carried out by the *n*-Bu_3SnH-mediated vinyl radical cyclization as the key step starting from various salicylaldehydes.

Key Words : *Exo*-methylenechroman, Radical cyclization, Salicylaldehydes

Introduction

The family of 1-benzopyran subunits such as chromans,[1] 2*H*-chromenes,[2] and 4*H*-chromenes[2] represents an important family of oxygen-containing natural products and showed many interesting biological activities.[1,2] Thus, many synthetic procedures for these compounds have been reported.[1-3] However, the synthesis of *exo*-methylenechromans, the regioisomeric form of chromenes (Figure 1), has not been reported much even though this type of compounds would also show interesting biological activities.[3] Very recently, Roy and Jana reported the novel synthesis of *exo*-methylenechromans by radical-promoted cyclization using Cp_2TiCl.[3a]

Results and Discussion

During the studies on the radical cyclization with modified Baylis-Hillman adducts having triple bond,[4] we presumed that *exo*-methylenechroman derivatives could be synthesized by using vinyl radical cyclization protocol as shown in Scheme 1.[4-6] However, literature survey showed that such examination was never tried to our surprise. As shown in Scheme 1, the starting material **2a** was prepared straightforwardly from salicylaldehyde (**1a**) by the Wittig reaction with carbethoxymethylene triphenylphosphorane and the following propargylation (K_2CO_3, propargyl bromide, DMF) in good yield. Radical cyclization of **2a** was carried out by following the typical radical cyclization procedure[4-6] with *n*-Bu_3SnH in the presence of AIBN (cat) in benzene followed by destannylation with aq HCl in ether to give the desired *exo*-methylenechroman derivative **3a** in 85% isolated yield. The reaction mechanism was also shown in Scheme 1.

As shown in Table 1, we prepared other *exo*-methylenechroman derivatives **3b-e** according to the above general procedure in high yields from **2b-e**. When we subjected **2f** under the radical cyclization conditions, *exo*-methylenechroman derivative **3f** was obtained in 46% yield *via* the 6-*exo-trig* mode. In addition, in the reaction mixture we isolated seven-membered ring compound **4** in 40% as a *syn*/*anti* (1:1) mixture, which was formed *via* 7-*endo-trig* mode (entry 6). The results might be attributed to the increased

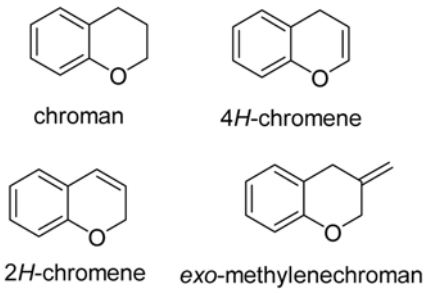
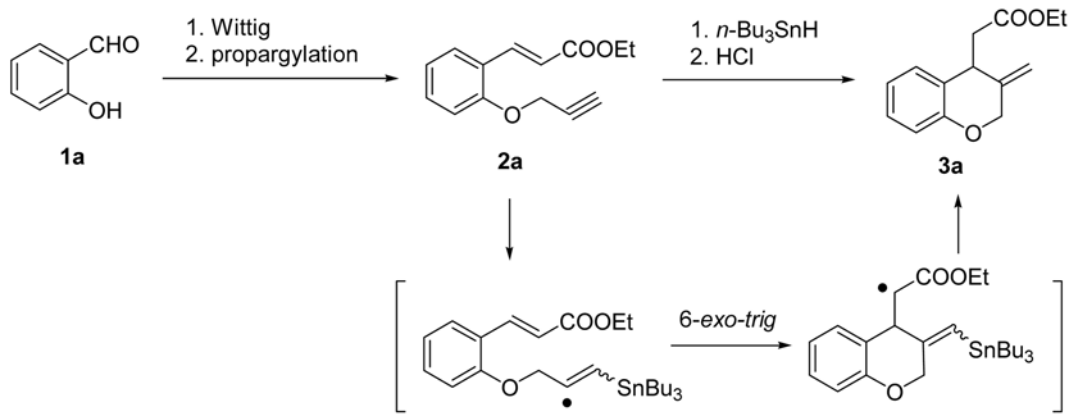
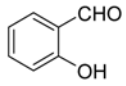
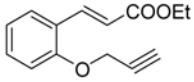
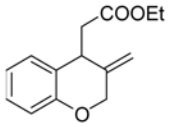
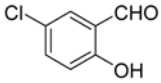
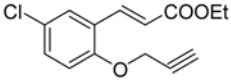
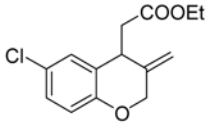
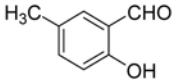
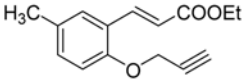
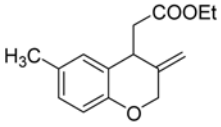
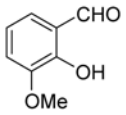
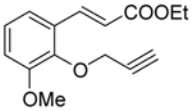
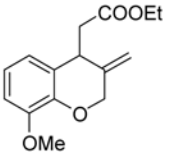
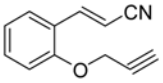
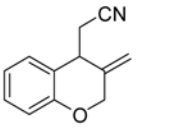
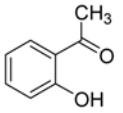
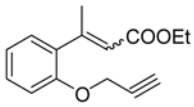
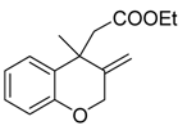
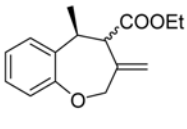


Figure 1



Scheme 1

Table 1. Synthesis of 4-substituted 3-methylenechromans

Entry	Starting Material	Intermediate (%)[a]	Product (%)[b]
1	 **1a**	 **2a** (90/86)	 **3a** (85)
2	 **1b**	 **2b** (89/83)	 **3b** (89)
3	 **1c**	 **2c** (82/86)	 **3c** (91)
4	 **1d**	 **2d** (92/84)	 **3d** (82)
5	**1a**	 **2e** (34/91)[c]	 **3e** (80)
6	 **1e**	 **2f** (63/65)	 **3f** (46)  **4** (40) *syn/anti* = 1:1

[a]Conditions: (i) **1a-e** (1.0 equiv), Ph_3P=CH-COOEt (1.1 equiv), benzene, reflux, 1 h, (ii) DMF, K_2CO_3 (1.1 equiv), propargyl bromide (1.1 equiv), rt, 3-5 h. The first yield in parenthesis refer to Wittig step and the second one to propargylation. [b]Conditions: (i) *n*-Bu_3SnH (1.1 equiv), AlBN (cat), benzene, reflux, 1 h, (ii) HCl, ether, 0 °C to rt, 30 min. [c]Conditions: (i) CH_3CN, KOH (1.1 equiv), reflux, 20 h (34%), (ii) propargylation (91%).

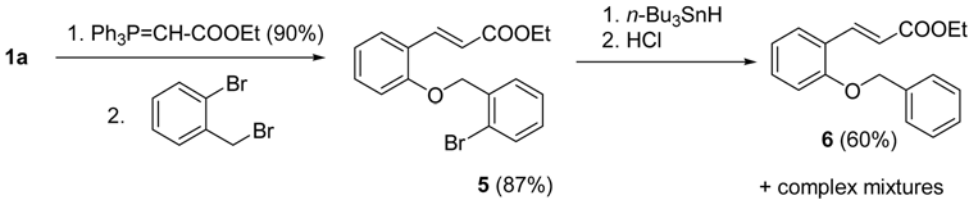
steric crowdedness around the β-position of the α,β-unsaturated ester moiety of **2f**.

It is interesting to note that the reaction of **5** under the same conditions gave the reduction compound **6** (60%) as the major product (Scheme 2). We could not isolate the corresponding 7-membered cyclized compound. Radical cyclization of aryl radical in a 7-*exo-trig* mode was not effective in this case. As a next trial, we prepared **7** from **1a** by the successive propargylation and Knoevenagel condensation with malononitrile. However, the radical cyclization of **7** was ineffective and we obtained simple reduction compounds **8** and **9** in 38% and 42%, respectively (Scheme 3).[7] Finally the *exo*-methylene moiety of **3a** could be readily isomerized into the *endo* form of compound **10**, 2*H*-chromene skeleton in Figure 1, by DBU treatment in high yield (Scheme 4).

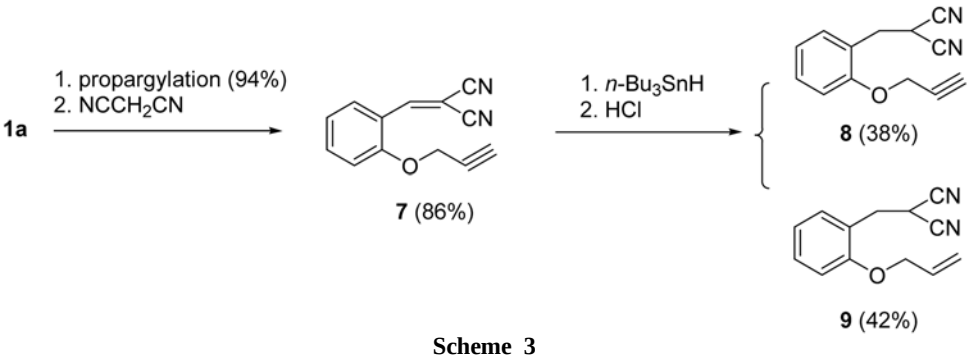
In summary, we developed a facile and practical method for the synthesis of 4-substituted 3-*exo*-methylenechroman derivatives by the *n*-Bu_3SnH-mediated vinyl radical cyclization as the key step starting from various salicylaldehydes.

Experimental Section

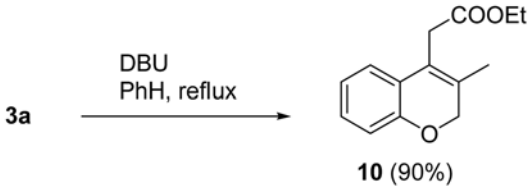
General procedure. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The signal positions are reported in ppm relative to TMS (δ scale) used as an internal standard. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). The elemental analyses were carried out at Korea Research Institute of Chemical Technology, Daejeon, Korea. All reagents were purchased from commercial sources and used without further treatment. The



Scheme 2



Scheme 3



Scheme 4

separations were carried out by flash column chromatography over silica gel (230-400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure.

Synthesis of starting materials 2a-f, 5 and 7. The synthesis of starting materials, **2a-d**, **2f**, and **5**, was carried out by Wittig reaction (Ph_3P=CHCOOEt, benzene, reflux) of the corresponding salicyladehydes and the following propargylation with propargyl bromide (K_2CO_3/DMF, rt) or benzylation with 2-bromobenzyl bromide (K_2CO_3/DMF, rt). Other starting materials, **2e** and **7**, were prepared by sequential propargylation of salicyladehyde followed by Knoevenagel condensation reaction with CH_3CN (KOH, reflux)[8] or with malononitrile (Ph_3P, benzene, reflux).[9]

Compound 2a: colorless oil; 86%; IR (neat) 3294, 2981, 2121, 1714, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ1.25 (t, *J* = 7.2 Hz, 3H), 2.45 (t, *J* = 2.4 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.68 (d, *J* = 2.4 Hz, 2H), 6.40 (d, *J* = 16.2 Hz, 1H), 6.89-7.46 (m, 4H), 7.90 (d, *J* = 16.2 Hz, 1H).

Compound 2b: colorless oil; 83%; IR (neat) 3298, 2981, 2123, 1710, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ1.25 (t, *J* = 7.5 Hz, 3H), 2.47 (t, *J* = 2.5 Hz, 1H), 4.18 (q, *J* = 7.5 Hz, 2H), 4.68 (d, *J* = 2.5 Hz, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 7.21 (dd, *J* = 9.0 and 2.5 Hz, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.82 (d, *J* = 16.0 Hz, 1H).

Compound 2c: colorless oil; 86%; IR (neat) 3294, 2981, 2121, 1709, 1631 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ1.25 (t, *J* = 7.0 Hz, 3H), 2.22 (s, 3H), 2.43 (t, *J* = 2.5 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 4.66 (d, *J* = 2.5 Hz, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 7.25 (s, 1H), 7.88 (d, *J* = 16.0 Hz, 1H).

Compound 2d: colorless oil; 84%; IR (neat) 3292, 2979, 2121, 1712, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ1.26 (t, *J* = 7.5 Hz, 3H), 2.38 (t, *J* = 2.5 Hz, 1H), 3.79 (s, 3H), 4.18 (q, *J* = 7.5 Hz, 2H), 4.69 (d, *J* = 2.5 Hz, 2H), 6.38 (d, *J* = 16.0 Hz, 1H), 6.89-7.46 (m, 3H), 8.04 (d, *J* = 16.0 Hz, 1H).

Compound 2e: colorless oil; 91%; IR (neat) 3236, 2212, 1608, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ2.57 (t, *J* = 2.4 Hz, 1H), 4.77 (d, *J* = 2.4 Hz, 2H), 6.06 (d, *J* = 16.8 Hz, 1H), 7.00-7.06 (m, 2H), 7.37-7.43 (m, 2H), 7.66 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ56.22, 76.32, 77.66, 97.37, 112.73, 118.82, 121.77, 123.11, 128.79, 132.14, 146.04, 156.02.

Compound 2f: colorless oil; 65%; IR (neat) 3292, 2981, 2121, 1712, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ1.23 (t, *J* = 7.2 Hz, 3H), 2.27 (d, *J* = 1.5 Hz, 3H), 2.42 (t, *J* = 2.4 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.64 (d, *J* = 2.4 Hz, 2H), 5.81 (q, *J* = 1.5 Hz, 1H), 6.88-7.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ14.32, 19.94, 56.03, 59.73, 75.63, 78.39, 112.77, 119.50, 121.55, 129.03, 129.26, 133.79, 154.23, 156.15, 166.70.

Compound 5: colorless oil; 87%; IR (neat) 3070, 2979, 1712, 1631, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ1.34 (t, *J* = 7.2 Hz, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 5.22 (s, 2H), 6.53 (d, *J* = 16.2 Hz, 1H), 6.91-7.60 (m, 8H), 8.14 (d, *J* = 16.2 Hz, 1H).

Compound 7: colorless oil; 86%; IR (neat) 3282, 2227, 2121, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ2.60 (t, *J* = 2.4 Hz, 1H), 4.84 (d, *J* = 2.4 Hz, 2H), 7.02-7.16 (m, 2H), 7.57-7.63 (m, 1H), 8.19-8.22 (m, 1H), 8.30 (s, 1H).

Typical procedure for the radical cyclization of 2a to

3a. A stirred mixture of **2a** (230 mg, 1.0 mmol), *n*-Bu_3SnH (320 mg, 1.1 mmol), AIBN (cat) in benzene (3 mL) was heated to reflux for 1 h. After cooling to rt the reaction mixture was poured into ether, and a few drops of *c*-HCl was added and stirred vigorously for 30 min. After usual aqueous workup procedure and column chromatographic purification process (hexanes/EtOAc, 7:3) we obtained **3a** as colorless oil, 198 mg (85%). The spectroscopic data of the prepared compounds **3a-f**, **4**, **6** and **8-10** are as follows.

Compound 3a: colorless oil; 85%; IR (neat) 2979, 1732, 1581, 1489 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, *J* = 7.0 Hz, 3H), 2.57 (dd, *J* = 15.0 and 10.0 Hz, 1H), 2.71 (dd, *J* = 15.0 and 5.0 Hz, 1H), 3.85 (dd, *J* = 10.0 and 5.0 Hz, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 4.39 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 5.04 (s, 1H), 5.09 (s, 1H), 7.00-7.16 (m, 2H), 7.41-7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.17, 38.87, 43.10, 60.46, 67.45, 113.57, 116.91, 120.87, 124.63, 127.91, 128.67, 140.69, 154.07, 171.18, FAB Mass 233 (M^++1). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.28; H, 6.98. The structure of compound **3a** was confirmed by HMBC and HSQC experiments as *exo*-methylenechromane skeleton.

Compound 3b: colorless oil; 89%; IR (neat) 2981, 1732, 1483 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.20 (t, *J* = 7.0 Hz, 3H), 2.58 (dd, *J* = 15.0 and 10.0 Hz, 1H), 2.70 (dd, *J* = 15.0 and 5.0 Hz, 1H), 3.82 (dd, *J* = 10.0 and 5.0 Hz, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 4.41 (d, *J* = 12.5 Hz, 1H), 4.54 (d, *J* = 12.5 Hz, 1H), 5.08 (s, 1H), 5.12 (s, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.99-7.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.23, 38.81, 42.94, 60.71, 67.71, 114.22, 118.37, 125.62, 126.25, 128.03, 128.33, 139.91, 152.79, 170.94; FAB Mass 267 (M^++1). Anal. Calcd for $C_{14}H_{15}ClO_3$: C, 63.04; H, 5.67. Found: C, 62.86; H, 5.84.

Compound 3c: colorless oil; 91%; IR (neat) 2981, 1732, 1498 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (t, *J* = 7.5 Hz, 3H), 2.16 (s, 3H), 2.56 (dd, *J* = 15.0 and 10.0 Hz, 1H), 2.70 (dd, *J* = 15.0 and 5.0 Hz, 1H), 3.80 (dd, *J* = 10.0 and 5.0 Hz, 1H), 4.05 (q, *J* = 7.5 Hz, 2H), 4.36 (d, *J* = 12.5 Hz, 1H), 4.51 (d, *J* = 12.5 Hz, 1H), 5.03 (s, 1H), 5.07 (s, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 6.82-6.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.18, 20.41, 38.91, 43.17, 60.43, 67.45, 113.43, 116.63, 124.32, 128.60, 128.92, 130.06, 140.98, 151.87, 171.25. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.10; H, 7.18.

Compound 3d: colorless oil; 82%; IR (neat) 2958, 1732, 1585, 1485 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (t, *J* = 7.5 Hz, 3H), 2.58 (dd, *J* = 14. 5 and 10.0 Hz, 1H), 2.72 (dd, *J* = 14.5 and 5.0 Hz, 1H), 3.76 (s, 3H), 3.86 (dd, *J* = 10.0 and 5.0 Hz, 1H), 4.08 (q, *J* = 7.5 Hz, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 5.07 (s, 1H), 5.10 (s, 1H), 6.65 (d, *J* = 7.5 Hz, 2H), 6.77 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.51, 39.16, 43.44, 56.10, 60.82, 68.13, 109.87, 114.12, 120.74, 120.87, 125.67, 140.64, 143.81, 148.73, 171.50. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.46; H, 7.02.

Compound 3e: colorless oil; 80%; IR (neat) 2924, 2248, 1489 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.72 (dd, *J* = 16.8 and 9.0 Hz, 1H), 2.84 (d, *J* = 16.8 and 5.4 Hz, 1H), 3.71 (dd, *J* = 9.0 and 5.4 Hz, 1H), 4.54 (d, *J* = 12.6 Hz, 1H), 4.64 (d, *J* = 12.6 Hz, 1H), 5.33 (s, 1H), 5.38 (s, 1H), 6.86-6.97 (m, 2H), 7.12-7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.21, 38.66, 67.29, 115.55, 117.44, 117.68, 121.40, 122.23, 128.67, 128.90, 138.81, 154.28; FAB Mass 186 (M^++1). Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.69; H, 6.11; N, 7.48.

Compound 3f: colorless oil; 46%; IR (neat) 2979, 1730, 1579, 1489 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, *J* = 7.2 Hz, 3H), 1.59 (s, 3H), 2.79 (d, *J* = 14.4 Hz, 1H), 2.89 (d, *J* = 14.4 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 5.13 (s, 1H), 5.19 (s, 1H), 6.82-7.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.05, 27.44, 39.13, 47.26, 60.16, 69.35, 111.67, 117.16, 121.13, 126.33, 127.61, 129.91, 146.10, 154.38, 170.31; FAB Mass 247 (M^++1). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.09; H, 7.21.

Compound 4 (*syn*/*anti* = 1:1): colorless oil; 40%; IR (neat) 2964, 1732, 1487 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, *J* = 6.9 Hz, 3H), 1.17 (t, *J* = 6.9 Hz, 3H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.51 (d, *J* = 7.2 Hz, 3H), 3.35-3.36 (m, 4H), 3.97-4.12 (m, 4H), 4.43-4.65 (m, 4H), 5.05 (s, 1H), 5.06 (s, 1H), 5.17 (s, 1H), 5.18 (s, 1H), 6.93-7.20 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.48, 18.84, 26.82, 27.82, 37.93, 39.59, 54.60, 56.08, 60.35, 60.68, 75.01, 76.00, 116.80, 119.78, 121.18, 121.63, 123.94, 123.98, 127.81, 127.98, 128.00, 129.45, 135.72, 136.11, 141.76, 143.37, 157.81, 159.15, 171.72, 172.38. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.29; H, 7.55.

Compound 6: colorless oil; 60%; IR (neat) 1711, 1631, 1489, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, *J* = 7.2 Hz, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 5.16 (s, 2H), 6.53 (d, *J* = 16.2 Hz, 1H), 6.92-7.54 (m, 9H), 8.08 (d, *J* = 16.2 Hz, 1H). We could not obtain the cyclized compound even under very dilute conditions in the reaction of compound **5**.

Compound 8: colorless oil; 38%; IR (neat) 3292, 2922, 2256, 2123, 1604, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.55 (t, *J* = 2.4 Hz, 1H), 3.32 (d, *J* = 7.5 Hz, 2H), 4.17 (t, *J* = 7.5 Hz, 1H), 4.76 (d, *J* = 2.4 Hz, 2H), 7.00-7.06 (m, 2H), 7.26-7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.56, 32.78, 56.01, 76.29, 77.78, 112.15, 112.56, 121.92, 122.08, 130.23, 131.61, 155.20.

Compound 9: colorless oil; 42%; IR (neat) 2958, 2924, 2256, 1603, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.32 (d, *J* = 7.5 Hz, 2H), 4.18 (t, *J* = 7.5 Hz, 1H), 4.58 (t, *J* = 1.5 Hz, 1H), 4.60 (t, *J* = 1.5 Hz, 1H), 5.30-5.43 (m, 2H), 5.99-6.10 (m, 1H), 6.88-6.99 (m, 2H), 7.23-7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.35, 32.80, 68.77, 111.71, 112.59, 118.04, 121.15, 121.42, 130.15, 131.32, 132.51, 156.15.

Compound 10: colorless oil; 90%; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.84 (s, 3H), 3.46 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.65 (s, 2H), 6.77-7.17 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.14, 16.02, 33.11, 60.88, 69.43, 115.61, 121.13, 121.30, 122.99, 123.82, 128.02, 129.53, 153.27, 171.01.

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