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Morita-Baylis-Hillman Route to Dimethyl 2,3-Dihydrobenzo[*b*]oxepine-2,4-dicarboxylates and Methyl 2-(2-Carbomethoxybenzo[*b*]furan-3-yl)propanoates from Salicylaldehydes

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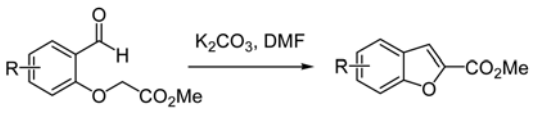
A new synthetic method for dimethyl 2,3-dihydrobenzo[*b*]oxepine-2,4-dicarboxylates and methyl 2-(2-carbomethoxybenzo[*b*]furan-3-yl)propanoates by an intramolecular conjugate displacement reaction or an S_N2 reaction of acetates of Morita-Baylis-Hillman adducts of methyl (2-formylphenoxy)acetates has been described.

Key Words : Morita-Baylis-Hillman, S_N2-S_N2' Reaction, 2,3-Dihydrobenzo[*b*]oxepines, Benzo[*b*]furans, Methyl (2-formylphenoxy)acetates.

Introduction

Medium-sized oxacycles, 1-benzoxepine[1] and 2-benzoxepine[2] are important structural units present in numerous biologically active molecules.[3] Especially 2,3-dihydro-1-benzoxepines were investigated in order to develop orally active CCR5 antagonists as a novel scaffold.[4] The several synthetic methods towards 2,3-dihydro-1-benzoxepines include ring-closing metathesis (RCM) of bis-olefins,[5] RCM of titanium-carbene complexes of diphenyl thioacetals having a carbon-carbon double bond,[6] Wittig reaction of carboethoxycyclopropyltriphenylphosphonium fluoroborate with salicylaldehyde,[7] Dieckmann condensation of diester of salicylic acid,[8] Claisen-type condensation of *o*-formylphenoxybutyrate,[9] palladium-catalyzed [5+2] annulations from 2-aroylmethoxyboronic acid and alkyne,[10] and palladium-catalyzed intramolecular carboesterification of 3-(2-allyloxyphenyl)propiolic acid.[11]

Also, benzofuran-2-carboxylates, benzofuran-3-yl-acetates and their derivatives display interesting physiological activities and have found potential therapeutic applications.[12] In addition, these were used to develop organic nonlinear optical cyan dyes for electro-optic devices.[13] The substituted benzofuran-2-carboxylates were prepared by the reaction of the appropriate salicylaldehyde with alkyl haloacetate in anhydrous dimethylformamide (DMF) at 130 °C in the presence of potassium carbonate[14] (Equation 1). Benzofuran-3-yl-acetic acid derivatives were prepared by an base-assisted ring-opening and ring-closing process of 4-chloromethyl-2*H*-chromen-2-ones, which were readily obtained from the reaction of ethyl 4-chloroacetoacetate with phenols in acidic conditions.[15]

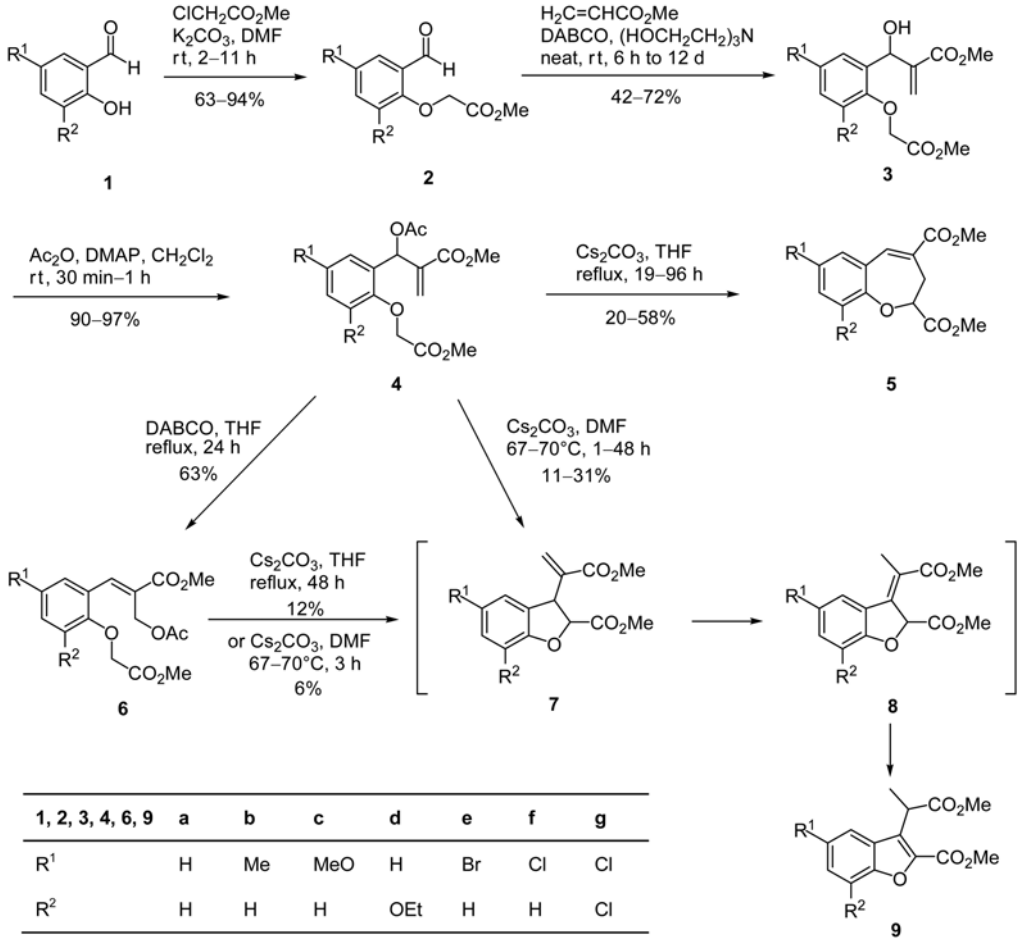


(1)

The Morita-Baylis-Hillman (MBH) reaction[16] has attracted attention of organic chemists in recent years. This reaction provides synthetically useful multifunctional molecules which have been employed in various heterocycles syntheses. Among them MBH adducts of salicylaldehydes or *O*-benzyl-protected salicylaldehydes with acrylic acid esters or cycloalkenones were successfully used for the syntheses of 3-substituted coumarins,[17] tetrahydroxanthenones,[18] and 2-oxo-2,3-dihydrobenzo[*b*]oxepines.[19] During the continuing efforts for the development of MBH chemistry,[20] we envisioned that we could synthesize the 2,3-dihydrobenzo[*b*]-oxepines **5** and benzo[*b*]furan derivatives **9** from the acetates of MBH adducts of methyl (2-formylphenoxy)acetates **2** *via* an intramolecular conjugate displacement (ICD) reaction[21] or S_N2 mechanism, respectively, as shown in Scheme 1.

Results and Discussion

The required key starting material methyl (2-formylphenoxy)acetates **2** were prepared by the reaction of salicylaldehydes **1** with methyl chloroacetate in the presence of anhydrous K_2CO_3 in DMF at room temperature in 63-94% yields following the earlier procedure.[22] The MBH reaction of **2** with methyl acrylate, 1,4-diazabicyclo[2,2,2]octane (DABCO), and triethanolamine without solvent at room temperature produced the MBH adducts **3** in 42-72% yields. The acetylation of **3** with acetic anhydride in the presence of *N,N*-dimethylaminopyridine (DMAP) in dichloromethane at room temperature gave MBH acetates **4** in 90-97% yields. With the substrate **4a** we examined the ICD reaction under the basic conditions (Table 1). When we first tried to cyclize **4a** to **5a**, we used LDA in THF, but obtained a complex mixture (Entry 1). Next we then used NaH in DMSO at room temperature. This experiment gave the desired product dimethyl 2,3-dihydrobenzo[*b*]oxepine-2,4-dicarboxylate (**5a**) in very low yield (8%) along with the rearranged product methyl 2-acetoxymethyl-3-[2-(carbomethoxymeth-



1, 2, 3, 4, 6, 9	a	b	c	d	e	f	g
R^1	H	Me	MeO	H	Br	Cl	Cl
R^2	H	H	H	OEt	H	H	Cl

Scheme 1

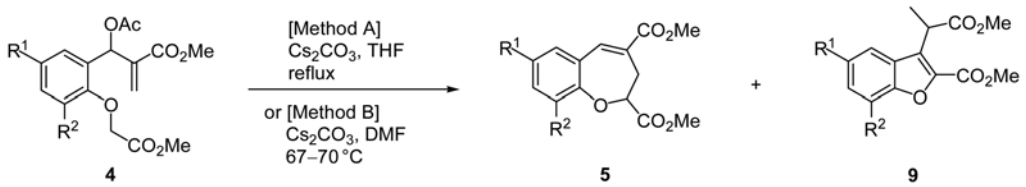
yloxy)phenyl]propenoate (**6a**) (26%) (Entry 2). Sodium hydride-THF system was also unsuccessful at reflux temperature, only starting acetate **4a** was recovered. Accordingly, we then tried a weaker base and selected Cs_2CO_3 in THF. Compound **4a** did not react at room temperature, but at reflux temperature the reaction occurred to give the expected product **5a** in 50% yield (Entry 5). We also explored K_2CO_3-THF and Cs_2CO_3-CH_3CN systems at reflux temperature. No reaction occurred in K_2CO_3-THF system (Entry 6) and the only rearranged product **6a** was obtained in 34% yield in Cs_2CO_3-CH_3CN system (Entry 7). Next we examined Cs_2CO_3 in aprotic polar solvents such as DMF, DMAc, and DMSO at 67-70 °C (Entries 8-10). In these reactions, **5a** was not produced. Instead an unexpected benzofuran **9a** was isolated in 31%, 10%, and 8% yields, respectively. As shown in Table 1, the yields are generally low, Cs_2CO_3 in THF and Cs_2CO_3 in DMF turned out to be preferred conditions giving 2,3-dihydrobenzo[*b*]oxepine **5a** and benzo[*b*]furan **9a**, respectively. With this result in hand, the reactions of other MBH acetates **4b-g** were carried out with Cs_2CO_3 in THF and Cs_2CO_3 in DMF, and the results are summarized in Table 2. The MBH acetates bearing electron-donating or electron-withdrawing groups are proceeded equally well and gave only the dihydrobenzo[*b*]oxepines **5b-f** in 20-58% yields under the Cs_2CO_3-THF system (Table 2, entries 1-6). The MBH acetate **4d** derived from 3-ethoxy-substituted salicylaldehyde **1d** required a longer reaction time (96 h) and gave a lower yield (20%) of the product than those with 5-methoxy-substituted one **4c** (54%) (Table 2, entries 3 and 4). Interestingly, the 3,5-dichloro-substituted MBH acetate **4g** gave only the benzo[*b*]furan **9g** in very low yield (21%) under the same reaction condition (Entry 7). It seems that the

Table 1. Reaction of **4a** under various basic conditions[a]

Entry	Base	Solvent	Temp (°C)	Time (h)	Product (% yield)[b]
1	LDA	THF	-78 to -10	4	decomp.
2	NaH	DMSO	rt	24	**5a** (8) **6a** (26)
3	NaH	THF	reflux	48	n.r.[c]
4	Cs_2CO_3	THF	rt	24	n.r.
5	Cs_2CO_3	THF	reflux	26	**5a** (50)
6	K_2CO_3	THF	reflux	24	n.r.
7	Cs_2CO_3	CH_3CN	reflux	3	**6a** (34)
8	Cs_2CO_3	DMF	67-70	3	**9a** (31)
9	Cs_2CO_3	DMAc	67-70	17	**9a** (10)
10	Cs_2CO_3	DMSO	67-70	4	**9a** (8)

[a]Reaction conditions: **4a** (1 mmol), base (2.2 mmol), solvent (5 mL). [b]Isolated yields based on **4a**. [c]n.r = no reaction.

Table 2. Synthesis of dimethyl 2,3-dihydrobenzo[*b*]oxepine-2,4-dicarboxylates **5** and methyl (2-carbomethoxybenzo[*b*]furan-3-yl)propanoates **9** from MBH acetates **4**[a]



4 **5** **9**

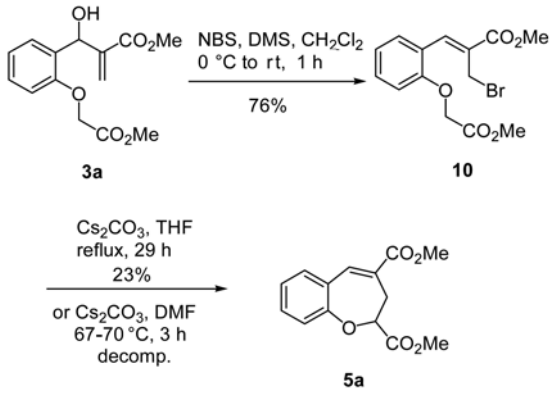
Entry	Acetate	R^1	R^2	Method	Time (h)	Product (% yield)[b]	
						5	**9**
1	**4a**	H	H	A	26	**5a** (50)	n.d.[c]
				B	3	n.d.	**9a** (31)
2	**4b**	Me	H	A	24	**5b** (58)	n.d.
				B	1	n.d.	**9b** (25)
3	**4c**	MeO	H	A	23	**5c** (54)	n.d.
				B	10	n.d.	**9c** (21)
4	**4d**	H	OEt	A	96	**5d** (20)	n.d.
				B	48	n.d.	**9d** (11)
5	**4e**	Br	H	A	24	**5e** (43)	n.d.
				B	3	n.d.	**9e** (21)
6	**4f**	Cl	H	A	22	**5f** (53)	n.d.
				B	5	n.d.	**9f** (23)
7	**4g**	Cl	Cl	A	19	n.d.	**9g** (21)
				B	3	n.d.	**9g** (24)

[a]Conditions: **4** (1 mmol), Cs_2CO_3 (2.2 mmol), THF or DMF (5 mL). [b]Isolated yields based on **4**. [c]n.d. = not detected.

substituent group of 3-position plays an important role in governing the reactivity of the substrates by the stereo-electronic factors.

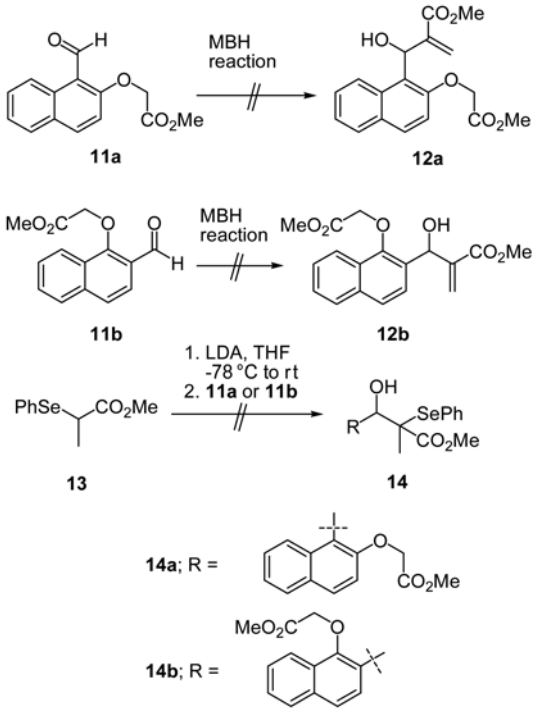
When we applied Cs_2CO_3 in DMF to MBH acetates **4b-g**, benzofurans **9b-g** were obtained in relatively poor yields (11-25%) along with a considerable amount of the de-composed materials. No dihydrobenzo[*b*]oxepines **5b-g** were produced. The formation of **5** could be explained by an S_N2' reaction in a 7-*endo-trig* mode. The formation of **9** could be regarded as an S_N2 reaction in a *5-exo-tet* mode to form **7** followed by aromatization through sequential proton migration.[23] The different ring closure mode in THF and DMF solvents is uncertain.

We also examined the rearranged MBH allyl acetate **6a** as a substrate, which was readily prepared from the MBH acetate **4a** with DABCO in refluxing THF,[24] by the present protocol. On cyclization of **6a** with Cs_2CO_3 in THF at reflux temperature for 48 hours, and with Cs_2CO_3 in DMF at 67-70 °C for 3 hours, the only benzofuran **9a** was produced in poor yields (12% and 6%), respectively, presumably *via* 5-*exo-trig* mode. Most of the starting material **6a** was decomposed (Scheme 1). In order to increase the yield, we also investi-gated the reaction of MBH allyl bromide **10**, which was readily obtained from the MBH adduct **3a** with *N*-bromo-succinimide/dimethyl sulfide (NBS/DMS).[25] On cyclization of **10** with Cs_2CO_3 in THF at reflux temperature for 29 hours, **5a** was produced in 23% yield. Under the influence of Cs_2CO_3 in DMF at 67-70 °C for 3 hours, the starting material was decomposed completely (Scheme 2). The use of some other basic conditions such as NaH/DMF, NaH/DMSO, *t*-BuOK/THF, LDA/THF, and DBU/CH_3CN were also ineffective.

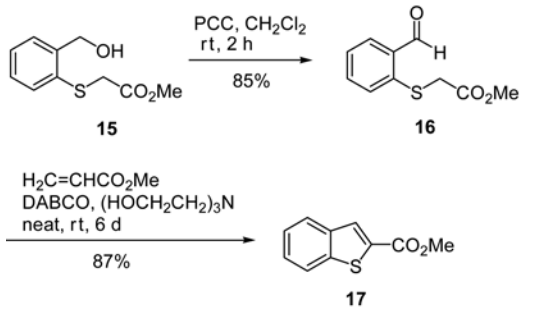


Scheme 2

With the intent to introduce more diversity in the products employing this strategy, we carried out the MBH reaction of methyl (1-formyl-2-naphthalenyloxy)acetate (**11a**)[26] and methyl (2-formyl-1-naphthalenyloxy)acetate (**11b**) with methyl acrylate. Unfortunately the MBH adducts **12a** and **12b** were not produced under typical reaction conditions such as DABCO, DMAP or DBU in THF, DMF, and MeOH solvent systems. We also attempted to make the MBH alcohols *via* selenium-based route.[21] Thus, methyl 2-phenyl-selanylpropanoate (**13**)[27] was deprotonated with LDA in THF, and a THF solution of the aldehyde **11a** or **11b** was added to the resulting carbanion. However, the alcohols **14a** or **14b** were not produced at all (Scheme 3).



Scheme 3



Scheme 4

Finally, we examined the MBH reaction of thiosalicylaldehyde derivative, methyl (2-formylthiophenoxy)acetate (**16**) under typical condition, which was readily obtainable from PCC oxidation of methyl (2-hydroxymethylthiophenoxy)acetate (**15**).[28] But, the MBH reaction did not occur, instead an intramolecular condensation proceeded slowly under the reaction conditions to give the methyl benzo[*b*]-thiophene-2-carboxylate (**17**)[29] in 87% yield (Scheme 4).

Conclusion

A new method for the synthesis of dimethyl 2,3-dihydrobenzo[*b*]oxepine-2,4-dicarboxylates and methyl 2-(2-carbomethoxybenzo[*b*]furan-3-yl)propanoates by an intramolecular conjugate displacement reaction of acetates of Morita-Baylis-Hillman adducts of methyl (2-formylphenoxy)-acetates has been developed. The synthetic yields are generally low, dihydrobenzo[*b*]oxepines were produced in Cs_2CO_3-THF system and benzo[*b*]furans were given in Cs_2CO_3-DMF system, respectively.

Experimental Section

Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical TLC was carried out on Merck silica gel 60 F_{254} TLC plates. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were obtained using a Thermo Electron Corporation Flash EA 1112 instrument. Low resolution mass spectra were recorded on a ThermoQuest Polaris Q mass spectrometer operating at 70 eV. IR spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Varian 300 spectrometer in $CDCl_3$. All chemical shifts are reported in ppm relative to TMS. The coupling constants (*J*) are expressed in Hz.

The known methyl (2-formylphenoxy)acetate (**2a**),[22] methyl (2-formyl-4-methylphenoxy)acetate (**2b**),[30] methyl (4-bromo-2-formylphenoxy)acetate (**2e**),[22] methyl (4-chloro-2-formylphenoxy)acetate (**2f**),[31] methyl (1-formyl-2-naphthalenyloxy)acetate (**11a**),[26] methyl (2-formyl-1-naphthalenyloxy)acetate (**11b**),[26] and methyl (2-hydroxymethylthiophenoxy)acetate (**15**)[28] were prepared according to the literature procedures. Petroleum ether (PE) used refers to the fraction boiling in the range 30-60 °C.

Methyl (2-Formylphenoxy)acetates 2; General Procedure. A mixture of salicylaldehyde **1** (20 mmol), methyl chloroacetate (2.39 g, 22 mmol), and K_2CO_3 (4.14 g, 30 mmol) in anhydrous DMF (20 mL) was stirred at rt for 2-11 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with Et_2O (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (5:1) to produce **2** as a solid. The physical and spectral data of **2** prepared by this general method are listed as follows.

Methyl (2-Formyl-4-methoxyphenoxy)acetate (2c): Reaction time: 11 h; yield: 94%; white solid; mp 70-71 °C (Et_2O-PE); IR (KBr): 1764, 1685, 1617, 1494 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 6H, 2 × OCH_3), 4.73 (s, 2H, CH_2), 6.85 (d, *J* = 9.1 Hz, 1H, aromatic), 7.11 (dd, *J* = 9.1 and 3.2 Hz, 1H, aromatic), 7.35 (d, *J* = 3.5 Hz, 1H, aromatic), 10.53 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.3, 55.8, 66.4, 110.5, 114.7, 123.2, 125.9, 154.5, 154.7, 168.9, 189.4; Ms *m/z* 224 (65, [M$^+$]), 165 (70), 151 (100), 150 (99), 136 (28), 135 (48), 123 (57); Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.69; H, 5.52.

Methyl (2-Ethoxy-6-formylphenoxy)acetate (2d): Reaction time: 2 h; yield: 92%; white solid; mp 80-81 °C (Et_2O-PE); IR (KBr): 1758, 1687, 1585, 1473 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (t, *J* = 7.0 Hz, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.10 (q, *J* = 7.0 Hz, 2H, CH_2), 4.87 (s, 2H, CH_2), 7.11-7.13 (m, 2H, aromatic), 7.40-7.45 (m, 1H, aromatic), 10.62 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 52.0, 64.6, 69.4, 118.8, 119.0, 124.3, 129.8, 150.1, 151.0, 169.8, 190.7; Ms *m/z* 238 (100, [M$^+$]), 179 (28), 165 (18), 149 (17); Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.34; H, 5.79.

Methyl (2,4-Dichloro-6-formylphenoxy)acetate (2g): Reaction time: 2 h; yield: 63%; white solid; mp 115-116 °C (Et_2O-PE); IR (KBr): 1753, 1692, 1439 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 3H, OCH_3), 4.84 (s, 2H, CH_2), 7.61 (d, *J* = 2.6 Hz, 1H, aromatic), 7.75 (d, *J* = 2.6 Hz, 1H, aromatic), 10.52 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.6, 70.1, 127.0, 128.7, 131.3, 132.1, 135.8, 155.3, 168.9, 188.4; Ms *m/z* 264 (7), 262 (18, [M^+]), 232 (20), 230 (31), 205 (67), 203 (100), 191 (65), 190 (62), 189 (78), 188 (24); Anal. Calcd for $C_{10}H_8Cl_2O_4$: C, 45.66; H, 3.07. Found: C, 45.31; H, 3.35.

Morita-Baylis-Hillman Adducts 3; General Procedure. A mixture of **2** (10 mmol), methyl acrylate (2.70 mL, 30 mmol), DABCO (1.12 g, 10 mmol), and triethanolamine (1.19 g, 8 mmol) was stirred at rt for 6 h to 12 d. The reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (2:1) to produce **3**. The physical and spectral data of **3** prepared by this general method are listed as follows.

Methyl 3-[2-(Carbomethoxymethyloxy)]phenyl-3-hydroxy-2-methylenepropanoate (3a): Reaction time: 6 d; yield: 48%; colorless oil; IR (CH_2Cl_2): 3485, 1759, 1741, 1722, 1631, 1490, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.05 (br s, 1H, OH), 4.70 (s, 2H, CH_2), 5.94 (s, 1H, CH), 5.98 (s, 1H, CH), 6.38 (s, 1H, CH), 6.77-6.80 (m, 1H, aromatic), 6.98-7.03 (m, 1H, aromatic), 7.21-7.27 (m, 1H, aromatic), 7.34-7.37 (m, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.6, 52.1, 65.2, 68.0, 111.8, 121.8, 125.6, 128.1, 128.7, 130.3, 140.9, 154.9, 166.6, 169.5; Ms *m/z* 248 (8), 230 (54), 220 (41), 202 (41), 193 (63), 165 (40), 147 (100), 135 (66); Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.73; H, 5.58.

Methyl 3-[2-(Carbomethoxymethyloxy)-5-methyl]-phenyl-3-hydroxy-2-methylenepropanoate (3b): Reaction time: 12 d; yield: 44%; white solid; mp 49-50 °C (Et_2O-PE); IR (KBr): 3483, 1760, 1741, 1721, 1631, 1499, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.05 (d, *J* = 5.9 Hz, 1H, OH), 4.67 (s, 2H, CH_2), 5.93 (d, *J* = 5.6 Hz, 1H, CH), 5.98 (s, 1H, CH), 6.38 (s, 1H, CH), 6.69 (d, *J* = 8.5 Hz, 1H, aromatic), 7.03 (d, *J* = 8.2 Hz, 1H, aromatic), 7.13 (s, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 51.8, 52.3, 65.7, 68.3, 112.0, 125.8, 128.9, 129.2, 130.2, 131.5, 141.0, 153.1, 166.8, 169.8; Ms *m/z* 294 (1, [M^+]), 262 (6), 244 (44), 234 (17), 216 (49), 207 (81), 205 (73), 179 (47), 161 (100), 149 (58). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.08; H, 5.84.

Methyl 3-[2-(Carbomethoxymethyloxy)-5-methoxy]-phenyl-3-hydroxy-2-methylenepropanoate (3c): Reaction time: 6 d; yield: 43%; colorless oil; IR (CH_2Cl_2): 3491, 1760, 1744, 1721, 1631, 1497, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.13 (d, *J* = 5.9 Hz, 1H, OH), 4.65 (s, 2H, CH_2), 5.94 (d, *J* = 5.6 Hz, 1H, CH), 5.97 (s, 1H, CH), 6.38 (s, 1H, CH), 6.74-6.75 (m, 2H, aromatic), 6.91-6.92 (m, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.8, 52.3, 55.6, 66.3, 68.0, 113.5, 113.6, 113.9, 125.9, 131.9, 140.9, 149.3, 154.6, 166.7, 170.0; Ms *m/z* 310 (21, [M^+]), 292 (9), 278 (12), 260 (18), 250 (12), 233 (12), 221 (47), 219 (38), 205 (23), 195 (25), 187 (27), 177 (100); Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85. Found: C, 58.31; H, 5.92.

Methyl 3-[(2-Carbomethoxymethyloxy)-3-ethoxy]-phenyl-3-hydroxy-2-methylenepropanoate (3d): Reaction time: 8 d; yield: 42%; white solid; mp 62-63 °C (Et_2O-PE); IR (KBr): 3476, 1763, 1743, 1723, 1632, 1473, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, *J* = 7.0 Hz, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.05 (q, *J* = 7.0 Hz, 2H, CH_2), 4.24 (d, *J* = 5.6 Hz, 1H, OH), 4.74 and 4.90 (AB quartet, *J* = 16.7 Hz, 2H, CH_2), 6.04 (s, 1H, CH), 6.06 (d, *J* = 5.6 Hz, 1H, CH), 6.38 (s, 1H, CH), 6.82-6.91 (m, 2H, aromatic), 6.98-7.03 (m, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 51.8, 52.1, 64.2, 67.5, 69.0, 112.9, 119.7, 124.1, 125.3, 134.9, 141.5, 144.9, 150.6, 166.6, 171.2; Ms *m/z* 306 (2), 292 (5), 281 (5), 278 (9), 274 (15), 262 (10), 235 (100), 191 (76), 179 (17); Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 58.93; H, 6.08.

Methyl 3-[5-Bromo-2-(carbomethoxymethyloxy)]phenyl-3-hydroxy-2-methylenepropanoate (3e): Reaction time: 6 h; yield: 49%; white solid; mp 71-72 °C (Et_2O-PE); IR (KBr): 3480, 1759, 1742, 1720, 1630, 1484, 1437 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.98 (d, *J* = 5.9 Hz, 1H, OH), 4.68 (s, 2H, CH_2), 5.92 (d, *J* = 5.9 Hz, 1H, CH), 5.96 (s, 1H, CH), 6.40 (s, 1H, CH), 6.67 (d, *J* = 8.5 Hz, 1H, aromatic), 7.34 (dd, *J* = 8.5 and 2.6 Hz, 1H, aromatic), 7.49 (d, *J* = 2.6 Hz, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.0, 52.5, 65.6, 67.6, 113.7, 114.7, 126.6, 131.1, 131.6, 132.9, 140.2, 154.1, 166.6, 169.3; Ms *m/z* 343 (5), 341 (4), 328 (9), 326 (8), 310 (31), 308 (31), 282 (31), 280 (30), 271 (51), 227 (100), 225 (74), 213 (42), 201 (27), 199 (26), 157 (13), 155 (12); Anal. Calcd for $C_{14}H_{15}BrO_6$: C, 46.82; H, 4.21. Found: C, 46.65; H, 4.32.

Methyl 3-[2-(Carbomethoxymethyloxy)-5-chloro)]-phenyl-3-hydroxy-2-methylenepropanoate (3f): Reaction time: 8 h; yield: 64%; yellow oil; IR (CH_2Cl_2): 3472, 1756, 1741, 1720, 1632, 1486, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.01 (br s, 1H, OH), 4.68 (s, 2H, CH_2), 5.92 (s, 1H, CH), 5.96 (s, 1H, CH), 6.40 (s, 1H, CH), 6.72 (d, *J* = 8.8 Hz, 1H, aromatic), 7.20 (dd, *J* = 8.8 and 2.6 Hz, 1H, aromatic), 7.35 (d, *J* = 2.6 Hz, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9, 52.4, 65.7, 67.6, 113.3, 126.5, 127.2, 128.3, 128.6, 132.5, 140.3, 153.6, 166.6, 169.3; Ms *m/z* 316 (1), 314 (2, [M^+]), 264 (17), 254 (22), 236 (12), 225 (33), 209 (17), 199 (26), 195 (21), 183 (33), 181 (100), 171 (29), 169 (82), 167 (22), 165 (40), 157 (20), 155 (58); Anal. Calcd for $C_{14}H_{15}ClO_6$: C, 53.43; H, 4.80. Found: C, 53.19; H, 4.95.

Methyl 3-[2-(Carbomethoxymethyloxy)-3,5-dichloro)]-phenyl-3-hydroxy-2-methylenepropanoate (3g): Reaction time: 13 h; yield: 72%; yellow oil; IR (CH_2Cl_2): 3478, 1769, 1712, 1631, 1459, 1437 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.01 (d, *J* = 5.3

Hz, 1H, OH), 4.76 and 4.83 (AB quartet, J = 16.1 Hz, 2H, CH_2), 6.08 (d, J = 5.3 Hz, 1H, CH), 6.09 (s, 1H, CH), 6.44 (s, 1H, CH), 7.21 (d, J = 2.6 Hz, 1H, aromatic), 7.30 (d, J = 2.6 Hz, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9, 52.3, 66.4, 69.5, 126.3, 126.7, 127.3, 129.7, 130.1, 138.4, 140.5, 150.7, 166.1, 169.9; Ms *m/z* 318 (9), 316 (14), 300 (15), 298 (24), 273 (10), 272 (16), 271 (12), 270 (20), 262 (14), 261 (46), 260 (22), 259 (66), 217 (50), 215 (100), 203 (31), 199 (31), 189 (43), 188 (26); Anal. Calcd for $C_{14}H_{14}Cl_2O_6$: C, 48.16; H, 4.04. Found: C, 47.89; H, 3.82.

Morita-Baylis-Hillman Acetates 4; General Procedure. Ac_2O (1.53 g, 15 mmol) was added to a stirred solution of the MBH adduct **3** (10 mmol) and DMAP (0.34 g, 3 mmol) in CH_2Cl_2 (20 mL) at rt After stirring at the same temperature for 30 min-1 h, the reaction mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The mixture was chromatographed on silica gel eluting with hexane-EtOAc (2:1) to produce **4**. The physical and spectral data of **4** prepared by this general method are listed as follows.

Methyl 3-Acetoxy-3-[2-(carbomethoxymethyloxy)]-phenyl-2-methylenepropanoate (4a): Reaction time: 1 h; yield: 90%; colorless oil; IR (CH_2Cl_2): 1743, 1729, 1635, 1493, 1438, 1232 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.67 (s, 2H, CH_2), 5.72 (s, 1H, CH), 6.43 (s, 1H, CH), 6.77 (d, J = 7.9 Hz, 1H, aromatic), 6.97-7.02 (m, 1H, aromatic), 7.10 (s, 1H, CH), 7.24-7.32 (m, 2H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 52.0, 52.1, 65.6, 68.1, 111.8, 121.6, 126.8, 127.5, 128.1, 129.5, 138.7, 155.2, 165.7, 169.1, 169.4; Ms *m/z* 304 (5), 279 (50), 248 (23), 247 (100), 231 (19), 220 (10), 219 (16), 215 (10), 194 (17), 187 (26), 165 (21); Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.39; H, 5.48.

Methyl 3-Acetoxy-3-[2-(carbomethoxymethyloxy)-5-methyl]phenyl-2-methylenepropanoate (4b): Reaction time: 1 h; yield: 93%; white solid; mp 53-54 °C (Et_2O-PE); IR (KBr): 1743, 1726, 1635, 1501, 1437, 1231 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.65 (s, 2H, CH_2), 5.73 (s, 1H, CH), 6.43 (s, 1H, CH), 6.67 (d, J = 7.9 Hz, 1H, aromatic), 7.04-7.07 (m, 2H, aromatic), 7.07 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 21.0, 51.9, 52.1, 65.9, 68.1, 112.0, 126.4, 127.2, 128.6, 129.9, 131.0, 138.8, 153.2, 165.7, 169.3, 169.4; Ms *m/z* 336 (2, [M$^+$]), 293 (56), 277 (11), 262 (29), 261 (100), 245 (20), 207 (25), 201 (56), 179 (25); Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99. Found: C, 60.49; H, 5.70.

Methyl 3-Acetoxy-3-[2-(carbomethoxymethyloxy)-5-methoxy]phenyl-2-methylenepropanoate (4c): Reaction time: 1 h; yield: 92%; colorless oil; IR (CH_2Cl_2): 1743, 1726, 1634, 1499, 1436, 1229 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.62 (s, 2H, CH_2), 5.71 (s, 1H, CH), 6.43 (s, 1H, CH), 6.76-6.78 (m, 2H, aromatic), 6.86-6.87 (m, 1H, aromatic), 7.06 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 52.0, 52.1, 55.6, 66.7, 68.0, 113.5, 113.7, 114.3, 127.6, 128.3, 138.6, 149.5, 154.4, 165.6, 169.3, 169.4; Ms *m/z* 352 (40, [M$^+$]), 309 (20), 278 (39), 277 (100), 261 (29), 249 (28), 233 (41), 223 (68), 219 (40), 205 (44), 195 (51), 177 (54), 161 (89); Anal. Calcd for $C_{17}H_{20}O_8$: C, 57.95; H, 5.72. Found: C, 57.76; H, 5.59.

Methyl 3-Acetoxy-3-[2-(carbomethoxymethyloxy)-3-ethoxy]phenyl-2-methylenepropanoate (4d): Reaction time: 1 h; yield: 92%; white solid; mp 75-76 °C (Et_2O-PE); IR (KBr): 1743, 1726, 1635, 1473, 1438, 1227 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J = 7.0 Hz, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.04 (q, J = 7.0 Hz, 2H, CH_2), 4.68 and 4.74 (AB quartet, 15.8 Hz, 2H, CH_2), 5.70 (s, 1H, CH), 6.40 (s, 1H, CH), 6.85-6.88 (m, 2H, aromatic), 7.00-7.06 (m, 1H, aromatic), 7.12 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 21.0, 51.9, 52.0, 64.2, 68.3, 69.7, 113.2, 119.5, 124.2, 127.1, 131.2, 139.0, 145.4, 151.1, 165.5, 169.4, 170.0; Ms *m/z* 366 (7, [M$^+$]), 323 (12), 292 (36), 291 (100), 231 (35), 191 (20); Anal. Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 58.78; H, 6.26.

Methyl 3-Acetoxy-3-[5-bromo-2-(carbomethoxymethyloxy)]phenyl-2-methylenepropanoate (4e): Reaction time: 30 min; yield: 97%; white solid; mp 64-65 °C (Et_2O-PE); IR (KBr): 1745, 1726, 1635, 1487, 1437, 1220 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.66 (s, 2H, CH_2), 5.74 (s, 1H, CH), 6.45 (s, 1H, CH), 6.65 (d, J = 8.5 Hz, 1H, aromatic), 7.04 (s, 1H, CH), 7.35-7.40 (m, 2H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 52.0, 52.2, 65.7, 67.4, 113.6, 114.1, 127.9, 129.1, 130.9, 132.2, 138.1, 154.2, 165.4, 168.6, 169.3; Ms *m/z* 402 (1), 400 (1, [M$^+$]), 384 (9), 382 (9), 359 (43), 357 (43), 327 (100), 326 (87); Anal. Calcd for $C_{16}H_{17}BrO_7$: C, 47.90; H, 4.27. Found: C, 47.72; H, 4.15.

Methyl 3-Acetoxy-3-[2-(carbomethoxymethyloxy)-5-chloro]phenyl-2-methylenepropanoate (4f): Reaction time: 1 h; yield: 95%; white solid; mp 68-70 °C (Et_2O-PE); IR (KBr): 1745, 1727, 1634, 1488, 1438, 1220 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.66 (s, 2H, CH_2), 5.74 (s, 1H, CH), 6.45 (s, 1H, CH), 6.70 (d, J = 8.5 Hz, 1H, aromatic), 7.04 (s, 1H, CH), 7.22 (dd, J = 8.8 and 2.6 Hz, 1H, aromatic), 7.27 (d, J = 2.6 Hz, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 52.0, 52.2, 65.8, 67.6, 113.2, 126.8, 127.9, 128.1, 128.8, 129.2, 138.2, 153.8, 165.4, 168.7, 169.3; Ms *m/z* 358 (2), 356 (6, [M$^+$]), 315 (19), 313 (53), 283 (38), 281 (100), 267 (10), 265 (20), 255 (8), 253 (20), 227 (71); Anal. Calcd for $C_{16}H_{17}ClO_7$: C, 53.87; H, 4.80. Found: C, 53.59; H, 4.62.

Methyl 3-Acetoxy-3-[2-(carbomethoxymethyloxy)-3,5-dichloro]phenyl-2-methylenepropanoate (4g): Reaction time: 30 min; yield: 96%; white solid; mp 71-72 °C (Et_2O-PE); IR (KBr): 1748, 1727, 1635, 1460, 1436, 1216 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.75 (s, 2H, CH_2), 5.78 (s, 1H, CH), 6.46 (s, 1H, CH), 7.03 (s, 1H, CH), 7.19 (d, J = 2.6 Hz, 1H, aromatic), 7.36 (d, J = 2.6 Hz, 1H, aromatic); ^{13}C NMR

(75 MHz, $CDCl_3$): δ 20.9, 52.1, 52.2, 67.7, 69.7, 127.0, 127.6, 128.5, 130.2, 130.4, 134.5, 138.0, 151.0, 165.0, 168.6, 169.2; Ms *m/z* 392 (2), 390 (3, [M^+]), 349 (34), 347 (49), 317 (71), 315 (100), 287 (42), 263 (19), 261 (44), 259 (49), 245 (28), 243 (45), 235 (35), 233 (54), 201 (50), 199 (69); Anal. Calcd for $C_{16}H_{16}Cl_2O_7$: C, 49.12; H, 4.12. Found: C, 48.95; H, 4.39.

Dimethyl 2,3-Dihydrobenzo[*b*]oxepine-2,4-dicarboxylates 5; General Procedure. A mixture of MBH acetate **4** (1 mmol) and Cs_2CO_3 (0.72 g, 2.2 mmol) in THF (5 mL) was stirred at reflux temperature for 22-96 h. After cooling to rt, the precipitate was filtered, and washed with THF (20 mL). The organic phases were concentrated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (4:1) to give **5** as a solid. The physical and spectral data of **5** prepared by this general method are listed as follows.

Dimethyl 2,3-Dihydrobenzo[*b*]oxepine-2,4-dicarboxylate (5a): Reaction time: 26 h; yield: 50%; white solid; mp 66-67 °C (Et_2O-PE); IR (KBr): 1757, 1708, 1635, 1487, 1436, 1261 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.08 (ddd, *J* = 18.5, 9.7, and 2.1 Hz, 1H, CH_2), 3.34 (dd, *J* = 18.5 and 1.8 Hz, 1H, CH_2), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.59 (dd, *J* = 9.7 and 1.8 Hz, 1H, CH), 7.05-7.13 (m, 2H, aromatic), 7.27-7.34 (m, 2H, aromatic), 7.63 (d, *J* = 2.1 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.2, 52.3, 52.6, 77.1, 120.6, 123.2, 123.5, 128.1, 131.1, 134.9, 138.1, 158.2, 167.6, 170.4; Ms *m/z* 262 (8, [M^+]), 230 (34), 203 (36), 173 (42), 171 (100), 143 (14), 115 (26); Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 64.01; H, 5.20.

Dimethyl 7-Methyl-2,3-dihydrobenzo[*b*]oxepine-2,4-dicarboxylate (5b): Reaction time: 24 h; yield: 58%; white solid; mp 89-91 °C (Et_2O-PE); IR (KBr): 1758, 1707, 1633, 1496, 1436, 1263, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 3.06 (ddd, *J* = 18.5, 9.7 and 2.1 Hz, 1H, CH_2), 3.32 (dd, *J* = 18.5 and 1.5 Hz, 1H, CH_2), 3.82 (s, 6H, 2 × OCH_3), 4.55 (dd, *J* = 9.7 and 1.5 Hz, 1H, CH), 6.83-7.11 (m, 3H, aromatic), 7.59 (d, *J* = 2.1 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 35.2, 52.3, 52.5, 77.1, 120.4, 123.2, 128.0, 131.8, 132.5, 135.1, 138.2, 156.1, 167.6, 170.5; Ms *m/z* 276 (8, [M^+]), 244 (14), 217 (15), 185 (100), 157 (12), 129 (12); Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.07; H, 5.72.

Dimethyl 7-Methoxy-2,3-dihydrobenzo[*b*]oxepine-2,4-dicarboxylate (5c): Reaction time: 23 h; yield: 54%; white solid; mp 96-97 °C (Et_2O-PE); IR (KBr): 1758, 1708, 1634, 1498, 1436, 1258, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.05 (ddd, *J* = 18.5, 10.0 and 2.1 Hz, 1H, CH_2), 3.31 (dd, *J* = 18.5 and 1.8 Hz, 1H, CH_2), 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.53 (dd, *J* = 10.0 and 1.8 Hz, 1H, CH), 6.80-6.87 (m, 2H, aromatic), 7.05 (d, *J* = 8.5 Hz, 1H, aromatic), 7.57 (d, *J* = 2.1 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.2, 52.3, 52.5, 55.7, 77.5, 117.2, 118.1, 121.6, 124.3, 128.7, 137.8, 152.3, 155.1, 167.6, 170.5; Ms *m/z* 292 (42, [M^+]), 260 (6), 233 (25), 219 (18), 201 (100), 174 (36); Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.35; H, 5.39.

Dimethyl 9-Ethoxy-2,3-dihydrobenzo[*b*]oxepine-2,4-dicarboxylate (5d): Reaction time: 96 h; yield: 20%; white solid; mp 103-106 °C (Et_2O-PE); IR (KBr): 1736, 1708, 1635, 1463, 1436, 1255, 1205 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (t, *J* = 7.0 Hz, 3H, CH_3), 3.15 (ddd, *J* = 18.8, 9.7 and 2.1 Hz, 1H, CH_2), 3.35 (dd, *J* = 18.8 and 1.8 Hz, 1H, CH_2), 3.83 (s, 6H, 2 × OCH_3), 4.10 (q, *J* = 7.0 Hz, 2H, CH_2), 4.63 (dd, *J* = 9.7 and 2.1 Hz, 1H, CH), 6.90-7.02 (m, 3H, aromatic), 7.61 (d, *J* = 1.8 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9, 35.2, 52.3, 52.6, 65.3, 77.7, 115.8, 122.9, 124.7, 126.6, 128.4, 138.1, 148.5, 150.1, 167.6, 170.2; Ms *m/z* 307 (10), 306 (54, [M^+]), 247 (56), 246 (42), 217 (38), 215 (80), 205 (14), 203 (22), 201 (54), 189 (29), 188 (22), 187 (100); Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.57; H, 5.76.

Dimethyl 7-Bromo-2,3-dihydrobenzo[*b*]oxepine-2,4-dicarboxylate (5e): Reaction time: 24 h; yield: 43%; white solid; mp 110-111 °C (Et_2O-PE); IR (KBr): 1759, 1709, 1637, 1479, 1436, 1259, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.10 (ddd, *J* = 18.5, 9.4, and 2.1 Hz, 1H, CH_2), 3.32 (dd, *J* = 18.5 and 1.8 Hz, 1H, CH_2), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.58 (dd, *J* = 9.4 and 1.8 Hz, 1H, CH), 7.01 (d, *J* = 8.8 Hz, 1H, aromatic), 7.37 (dd, *J* = 8.8 and 2.6 Hz, 1H, aromatic), 7.45 (d, *J* = 2.6 Hz, 1H, aromatic), 7.52 (d, *J* = 1.8 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.0, 52.4, 52.7, 77.1, 115.4, 122.5, 125.4, 129.7, 133.6, 136.5, 136.7, 157.1, 167.1, 170.0; Ms *m/z* 342 (20), 340 (20, [M^+]), 310 (37), 308 (37), 283 (24), 281 (15), 253 (55), 251 (100), 250 (54), 249 (72), 224 (17), 222 (18); Anal. Calcd for $C_{14}H_{13}BrO_5$: C, 49.29; H, 3.84. Found: C, 49.37; H, 3.95.

Dimethyl 7-Chloro-2,3-dihydrobenzo[*b*]oxepine-2,4-dicarboxylate (5f): Reaction time: 22 h; yield: 53%; white solid; mp 104-106 °C (Et_2O-PE); IR (KBr): 1757, 1711, 1637, 1482, 1436, 1258, 1225, 1196 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.09 (ddd, *J* = 18.5, 9.7, and 2.1 Hz, 1H, CH_2), 3.32 (dd, *J* = 18.5 and 1.8 Hz, 1H, CH_2), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.58 (dd, *J* = 9.7 and 2.1 Hz, 1H, CH), 7.06 (d, *J* = 8.5 Hz, 1H, aromatic), 7.23 (dd, *J* = 8.8 and 2.6 Hz, 1H, aromatic), 7.30 (d, *J* = 2.6 Hz, 1H, aromatic), 7.52 (d, *J* = 1.8 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.0, 52.4, 52.6, 77.2, 122.1, 124.9, 128.1, 129.7, 130.7, 133.7, 136.6, 156.6, 167.2, 170.0; Ms *m/z* 298 (5), 296 (14, [M^+]), 266 (2), 264 (6), 239 (8), 237 (25), 207 (33), 205 (100), 180 (7), 178 (19), 149 (18), 115 (37); Anal. Calcd for $C_{14}H_{13}ClO_5$: C, 56.67; H, 4.42. Found: C, 56.42; H, 4.27.

Methyl 2-[(2-Carbomethoxybenzo[*b*]furan)-3-yl]propanoates 9; General Procedure. A mixture of MBH acetate **4** (1 mmol) and Cs_2CO_3 (0.72 g, 2.2 mmol) in DMF (5 mL) was stirred at 67-70 °C for 1-48 h. After cooling to rt, the mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (4:1) to give **9** as a solid. The physical and spectral data of **9** prepared by this general method are listed as follows.

Methyl 2-[(2-Carbomethoxybenzo[*b*]furan)-3-yl]pro-

panoate (9a): Reaction time: 3 h; yield: 31%; white solid; mp 41-43 °C (Et_2O-PE); IR (KBr): 1737, 1718, 1595, 1436, 1303 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.62 (d, J = 7.3 Hz, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.92 (q, J = 7.3 Hz, 1H, CH), 7.27-7.32 (m, 1H, aromatic), 7.43-7.49 (m, 1H, aromatic), 7.57 (dd, J = 7.6 and 0.9 Hz, 1H, aromatic), 7.69 (dd, J = 7.9 and 0.9 Hz, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 35.7, 52.2, 52.3, 112.4, 122.0, 123.5, 126.4, 127.9, 128.4, 140.2, 154.5, 160.4, 173.5; Ms *m/z* 262 (5, [M^+]), 230 (100), 204 (38), 202 (34), 187 (14), 172 (34), 171 (70); Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.81; H, 5.12.

Methyl 2-[(2-Carbomethoxy-5-methylbenzo[*b*]furan)-3-yl]propanoate (9b): Reaction time: 1 h; yield: 25%; white solid; mp 106-108 °C (Et_2O-PE); IR (KBr): 1737, 1716, 1587, 1436, 1304 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.61 (d, J = 7.3 Hz, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.89 (q, J = 7.3 Hz, 1H, CH), 7.25-7.28 (m, 1H, aromatic), 7.43-7.46 (m, 2H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 21.4, 35.6, 52.2, 52.3, 111.9, 121.4, 126.5, 128.2, 129.5, 133.2, 140.3, 153.0, 160.5, 173.6; Ms *m/z* 276 (8, [M^+]), 245 (14), 244 (93), 218 (42), 216 (50), 201 (19), 187 (42), 185 (100); Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.98; H, 5.96.

Methyl 2-[(2-Carbomethoxy-5-methoxybenzo[*b*]-furan)-3-yl]propanoate (9c): Reaction time: 10 h; yield: 21%; white solid; mp 83-84 °C (Et_2O-PE); IR (KBr): 1736, 1716, 1584, 1480, 1435, 1237 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.61 (d, J = 7.3 Hz, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.89 (q, J = 7.3 Hz, 1H, CH), 7.05-7.09 (m, 2H, aromatic), 7.44-7.47 (m, 2H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 35.6, 52.1, 52.2, 55.8, 102.9, 113.0, 117.8, 126.8, 128.2, 140.9, 149.6, 156.2, 160.3, 173.5; Ms *m/z* 292 (25, [M^+]), 260 (39), 233 (25), 232 (27), 217 (14), 201 (100); Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.43; H, 5.36.

Methyl 2-[(2-Carbomethoxy-7-ethoxybenzo[*b*]furan)-3-yl]propanoate (9d): Reaction time: 48 h; yield: 11%; colorless oil; IR (KBr): 1737, 1718, 1589, 1438, 1316 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (t, J = 7.0 Hz, 3H, CH_3), 1.60 (d, J = 7.3 Hz, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.27 (q, J = 7.0 Hz, 2H, CH_2), 4.90 (q, J = 7.3 Hz, 1H, CH), 6.90-6.93 (m, 1H, aromatic), 7.15-7.24 (m, 2H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 16.7, 35.7, 52.1, 52.2, 64.5, 110.0, 113.4, 124.2, 128.1, 128.7, 140.4, 144.4, 145.3, 160.4, 173.6; Ms *m/z* 306 (49, [M^+]), 274 (100), 248 (48), 246 (58), 218 (70), 215 (66), 187 (67); Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.57; H, 5.79.

Methyl 2-[(5-Bromo-2-carbomethoxybenzo[*b*]furan)-3-yl]propanoate (9e): Reaction time: 2 h; yield: 21%; yellow solid; mp 141-142 °C (Et_2O-PE); IR (KBr): 1736, 1718, 1595, 1435, 1301 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.61 (d, J = 7.3 Hz, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.87 (q, J = 7.3 Hz, 1H, CH), 7.44 (d, J = 8.8 Hz, 1H, aromatic), 7.55 (dd, J = 8.8 and 2.1 Hz, 1H, aromatic), 7.84 (d, J = 2.1 Hz, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 35.6, 52.4, 52.5, 113.9, 116.7, 124.7, 127.6, 128.3, 131.0, 141.3, 153.2, 160.0, 173.2; Ms *m/z* 342 (4), 340 (4, [M^+]), 310 (92), 308 (91), 282 (29), 280 (28), 251 (100), 249 (74); Anal. Calcd for $C_{14}H_{13}BrO_5$: C, 49.29; H, 3.84. Found: C, 49.12; H, 3.70.

Methyl 2-[(2-Carbomethoxy-5-chlorobenzo[*b*]furan)-3-yl]propanoate (9f): Reaction time: 5 h; yield: 23%; white solid; mp 123-125 °C (Et_2O-PE); IR (KBr): 1737, 1720, 1595, 1435, 1302 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.61 (d, J = 7.3 Hz, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.88 (q, J = 7.3 Hz, 1H, CH), 7.41 (d, J = 8.8 Hz, 1H, aromatic), 7.49 (d, J = 8.8 Hz, 1H, aromatic), 7.68 (s, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 35.6, 52.3, 52.4, 113.5, 121.6, 127.7, 128.3 (2 peaks), 129.3, 141.5, 152.8, 160.1, 173.2; Ms *m/z* 298 (4), 296 (12, [M^+]), 266 (15), 264 (46), 237 (28), 236 (18), 205 (100), 149 (17), 115 (26); Anal. Calcd for $C_{14}H_{13}ClO_5$: C, 56.67; H, 4.42. Found: C, 56.49; H, 4.28.

Methyl 2-[(2-Carbomethoxy-5,7-dichlorobenzo[*b*]-furan)-3-yl]propanoate (9g).

Method A: A mixture of **4g** (0.39 g, 1 mmol) and Cs_2CO_3 (0.72 g, 2.2 mmol) in THF (5 mL) was stirred at reflux temperature for 19 h. After cooling to rt, the precipitate was filtered, and washed with THF (20 mL). The organic phases were concentrated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (4:1) to give **9g** (70 mg, 21%) as a white solid, which was recrystallized from Et_2O-PE; mp 147-149 °C; IR (KBr): 1740, 1711, 1597, 1435, 1308 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.60 (d, J = 7.3 Hz, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.89 (q, J = 7.3 Hz, 1H, CH), 7.47 (d, J = 1.9 Hz, 1H, aromatic), 7.59 (d, J = 1.9 Hz, 1H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 35.7, 52.5, 52.6, 118.6, 120.3, 127.9, 128.2, 128.7, 129.5, 142.3, 149.0, 159.8, 173.0; Ms *m/z* 332 (2), 330 (4, [M^+]), 300 (53), 298 (81), 273 (21), 272 (33), 271 (35), 270 (38), 243 (23), 242 (19), 241 (100), 240 (25), 239 (84); Anal. Calcd for $C_{14}H_{12}Cl_2O_5$: C, 50.78; H, 3.65. Found: C, 50.62; H, 3.57.

Method B: A mixture of MBH acetate **4g** (0.39 g, 1 mmol) and Cs_2CO_3 (0.72 g, 2.2 mmol) in DMF (5 mL) was stirred at 67-70 °C for 3 h. After cooling to rt, the mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (4:1) to give **9g** (79 mg, 24%) as a solid. The physical and spectral data of **9g** was the same as described above.

(*E*)-Methyl 2-Acetoxymethyl-3-[2-(carbomethoxy-methyloxy)phenyl]propenoate (6a): A mixture of **4a** (0.32 g, 1 mmol) and DABCO (0.12 g, 1.1 mmol) in THF (5 mL) was stirred at reflux temperature for 24 h. The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (3:1) to give **6a** (0.20 g, 63%) as a yellow oil;

IR (CH_2Cl_2): 1759, 1739, 1717, 1634, 1487, 1436, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.09 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.71 (s, 2H, CH_2), 4.91 (s, 2H, CH_2), 6.77-6.79 (m, 1H, aromatic), 7.01-7.04 (m, 1H, aromatic), 7.26-7.36 (m, 2H, aromatic), 8.21 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 52.2, 52.3, 59.8, 65.5, 111.6, 121.7, 124.0, 127.0, 130.3, 131.0, 141.1, 156.0, 167.2, 169.0, 170.7; Ms *m/z* 322 (1, [M^+]), 290 (19), 279 (16), 248 (63), 247 (100), 231 (19), 219 (28), 189 (82), 175 (55); Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.45; H, 5.41.

Synthesis of Benzo[*b*]furan 9a from 6a.

Method A: A mixture of **6a** (0.32 g, 1 mmol) and Cs_2CO_3 (0.72 g, 2.2 mmol) in THF (5 mL) was stirred at reflux temperature for 48 h. After cooling to rt, the precipitate was filtered, and washed with THF (20 mL). The organic phases were concentrated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (4:1) to give **9a** (31 mg, 12%) as a solid. The physical and spectral data of **9a** was the same as described in the preparation of **9a** from MBH acetate **4a**.

Method B: A mixture of **6a** (0.32 g, 1 mmol) and Cs_2CO_3 (0.72 g, 2.2 mmol) in DMF (5 mL) was stirred at 67-70 °C for 3 h. After cooling to rt, the mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (4:1) to give **9a** (16 mg, 6%) as a solid. The physical and spectral data of **9a** was the same as described in the preparation of **9a** from MBH acetate **4a**.

(*Z*)-Methyl 2-Bromomethyl-3-[2-(carbomethoxymethyloxy)phenyl]propenoate (10): A mixture of NBS (0.98 g, 5.5 mmol) and DMS (0.56 mL, 7.5 mmol) in CH_2Cl_2 (10 mL) was added MBH adduct **3a** (1.40 g, 5 mmol) at 0 °C. After stirring for 1 h at rt, the reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (3:1) to afford **10** (1.31 g, 76%) as a white solid, which was recrystallized from Et_2O-PE; mp 69-72 °C; IR (KBr): 1759, 1715, 1624, 1599, 1485, 1278, 1207 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.37 (s, 2H, CH_2), 4.71 (s, 2H, CH_2), 6.77-6.80 (m, 1H, aromatic), 7.09-7.14 (m, 1H, aromatic), 7.34-7.39 (m, 1H, aromatic), 7.70-7.78 (m, 1H, aromatic), 8.08 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.3, 52.3, 52.4, 65.5, 111.7, 121.9, 124.0, 129.0, 129.8, 131.0, 138.5, 156.2, 166.6, 169.0; Ms *m/z* 344 (1), 342 (1, [M^+]), 313 (1), 311 (1), 263 (35), 231 (72), 203 (100), 173 (65), 143 (46), 131 (73), 115 (84); Anal. Calcd for $C_{14}H_{15}BrO_5$: C, 49.00; H, 4.41. Found: C, 48.74; H, 4.36.

Synthesis of Dihydrobenzo[*b*]oxepine 5a from 10: A mixture of MBH allyl bromide **10** (0.34 g, 1 mmol) and Cs_2CO_3 (0.72 g, 2.2 mmol) in THF (5 mL) was stirred at reflux temperature for 29 h. After cooling to rt, the precipitate was filtered, and washed with THF (20 mL). The organic phases were concentrated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (4:1) to give **5a** (60 mg, 23%) as a solid. The physical and spectral data of **5a** was the same as described in the preparation of **5a** from MBH acetate **4a**.

Methyl (2-Formylthiophenoxy)acetate (16): To a suspension of PCC (1.62 g, 7.5 mmol) and celite (2.00 g) in CH_2Cl_2 (20 mL) was added dropwise a solution of alcohol **15** (1.06 g, 5 mmol) in CH_2Cl_2 (10 mL) at rt After stirring for 2 h, the precipitate was filtered, and washed with THF (20 mL). The organic phases were concentrated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (3:1) to give **16** (0.89 g, 85%) as a white solid, which was recrystallized from Et_2O-PE; mp 56-58 °C; IR (KBr): 2864, 2743, 1736, 1692, 1676, 1588, 1560, 1462, 1435 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 2H, CH_2), 3.73 (s, 3H, OCH_3), 7.35-7.41 (m, 1H, aromatic), 7.48-7.59 (m, 2H, aromatic), 7.85-7.88 (m, 1H, aromatic), 10.4 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.5, 52.7, 126.3, 128.7, 132.7, 134.1, 134.2, 139.7, 169.6, 191.6; Ms *m/z* 210 (100, [M^+]), 192 (60), 178 (64), 161 (75), 150 (73), 137 (51); Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79. Found: C, 57.08; H, 4.65.

Methyl Benzo[*b*]thiophene-2-carboxylate (17): A mixture of **16** (0.63 g, 3 mmol), methyl acrylate (0.81 mL, 9 mmol), DABCO (0.34 g, 3 mmol), and triethanolamine (0.36 g, 2.4 mmol) was stirred at rt for 6 d. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane-EtOAc (3:1) to produce **17** (0.50 g, 87%) as a white solid, which was recrystallized from Et_2O-PE; mp 69-71 °C (Lit.[27] mp 72-73 °C); IR (KBr): 1725, 1521, 1290, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.95 (s, 3H, OCH_3), 7.38-7.48 (m, 2H, aromatic), 7.85-7.89 (m, 2H, aromatic), 8.06 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.5, 122.7, 124.9, 125.5, 126.9, 130.6, 133.3, 138.6, 142.2, 163.2; Ms *m/z* 192 (98, [M^+]), 161 (100), 133 (21), 89 (24).

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