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EFFICIENT PREPARATION OF MEDIUM RING OXYGEN HETEROCYCLES

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Abstract – We achieved efficient preparation of medium ring oxygen heterocycles (**1**), 1-benzoxepines and 1-benzoxocines, by applying intramolecular Claisen-type condensation in dialkyl carbonate with metal alcoholate. Furthermore, we accomplished the preparation of 2,3-dihydro-1-benzoxepin-4-carboxylate intermediate (**1e**) for orally active CCR5 antagonists by this method.

INTRODUCTION

Medium ring heterocycles were especially investigated in order to develop orally active CCR5 antagonists by Baba and Shiraishi *et al.*,[1] and 2,3-dihydro-1-benzoxepines (**Figure 1**) were chosen as a novel scaffold for small-molecule CCR5 antagonists.

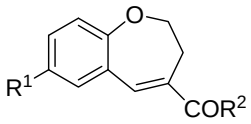
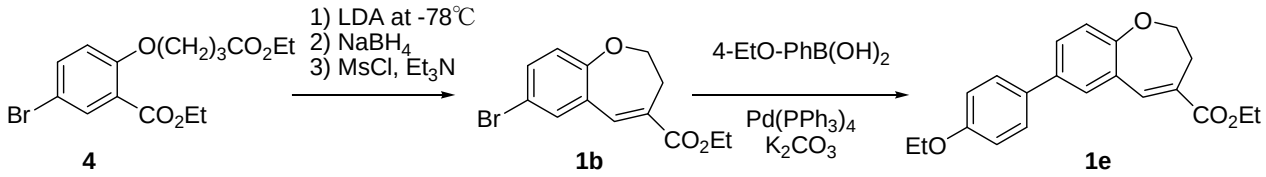


Figure 1

In their research,[1b] ethyl 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepine-4-carboxylate (**1e**) was synthesized by Dieckmann condensation of diester (**4**) followed by reduction, dehydration and Suzuki-Miyaura coupling reaction (**Scheme 1**). There were some drawbacks in this method for large-scale preparation; 1) it was inefficient since multi-steps were required and significant waste was produced, 2) hazardous waste was produced by reduction using $NaBH_4$, 3) chromatographic purification was required, 4) overall yield was low (27% in four steps). For toxicological and pharmacological evaluation, a practical preparation method for 4-substituted-2,3-dihydro-1-benzoxepines (**Figure 1**) was required.

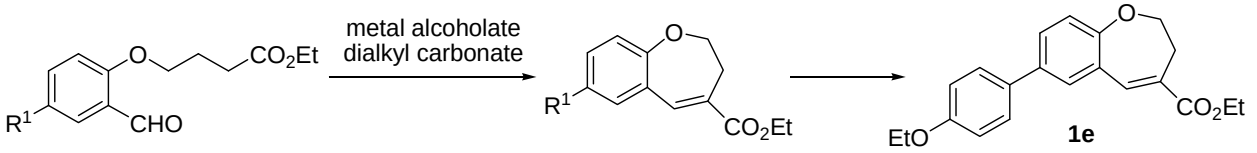


Scheme 1

We report the convenient synthesis of an important intermediate (**1e**) for orally active CCR5 antagonist and other medium ring oxygen heterocycles, 2,3-dihydro-1-benzoxepines and 2,3,4-trihydro-1-benzoxocine.

RESULTS AND DISCUSSION

There are a few reports on the synthesis of 2,3-dihydro-1-benzoxepines, for instance, ring-closing metathesis,[2] Wittig reaction,[3] and Dieckmann condensation;[4] however, they require multi-steps or they are too complicated to be applied for large-scale preparation. Recently, we developed practical syntheses of 2,3-dihydro-1-benzothiepines[5] and 7-10-membered ring nitrogen heterocycles[6] by the improved Claisen-type reaction conducted with metal alcoholate in dialkyl carbonate. This methodology was intended to be applied for the preparation of oxygen heterocyclic intermediate (**1e**) (**Scheme 2**).

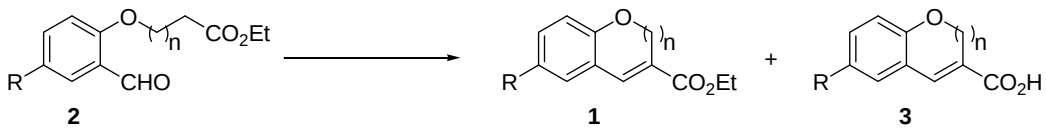


Scheme 2

For the model cyclization, *o*-formylphenoxybutyrate (**2a**) was prepared by alkylation of *o*-salicylaldehyde (**4**) with ethyl 4-bromobutyrate (**5**). First, a general method of Claisen reaction using KO^{t}Bu in THF was employed for the cyclization of **2a**, and it provided **1a** in only 17% yield together with the hydrolyzed acid (**3**) in 15% yield (**Table 1**, entry 1). On the other hand, the use of diethyl carbonate in this reaction afforded **1a** in 61% yield as expected (entry 2). Substituents on the aromatic ring also affected the yield significantly, that is, the yield of **1** increased when R was the electron-donating group (entry 4). Conversely, the yield of **1** decreased when R was the electron-withdrawing group (entry 3).

Moreover, this reaction condition was applied for the preparation of 1-benzoxocine. *o*-Formylphenoxypentanoate (**2d**) was prepared by alkylation of *o*-salicylaldehyde (**4**) with ethyl 4-bromovalerate. The cyclization of **2d** having a methoxy group proceeded to give 1-benzoxocine (**1d**) in 11% yield.[7] This method was considered to be useful in spite of low yield because there are only a few reports on the synthesis of 5-substituted-2,3,4-trihydro-1-benzoxocine,[8] to the best of our knowledge.

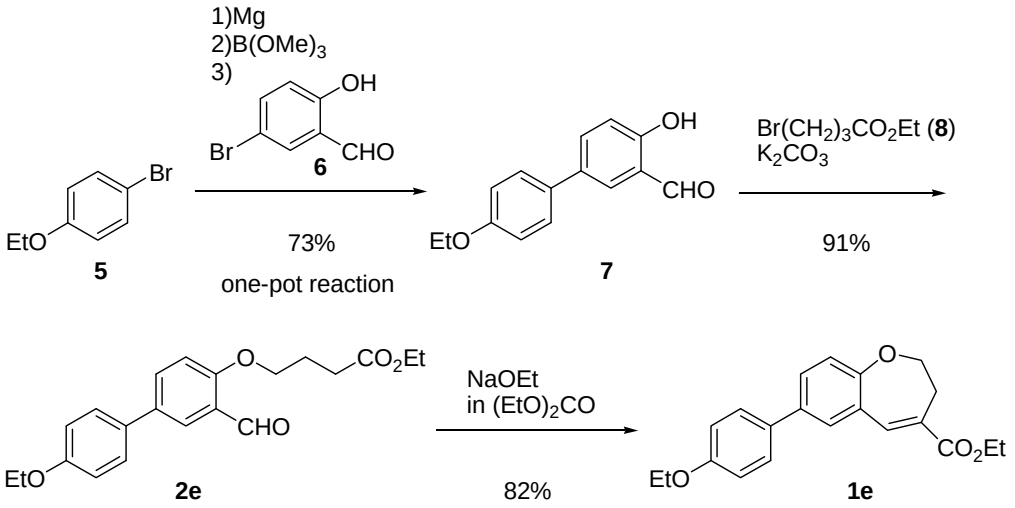
Table 1. Intramolecular Claisen-type reaction of **2**



	Conditions					Isolated yield (%)	
Entry	Base	Solv.	Temp.	**2**	n	Ester (**1**)	Acid (**3**)
1	KO^{t}Bu	THF	rt	**2a** R=H	2	**1a** (17)	**3** (15)
2	NaOEt[a]	$(EtO)_2CO$	rt	**2a** R=H	2	**1a** (61)	
3	NaOEt[a]	$(EtO)_2CO$	rt	**2b** R=4-Br	2	**1b** (34)	
4	NaOEt[a]	$(EtO)_2CO$	rt	**2c** R=4-MeO	2	**1c** (82)	
5	NaOEt[a]	$(EtO)_2CO$	rt	**2d** R=4-MeO	3	**1d** (11)	

[a]20% NaOEt in EtOH soln

On the basis of these results, we set up the synthesis of 2,3-dihydro-1-benzoxepine (**1e**) (**Scheme** 3). Since the intramolecular condensation of 4-bromo-2-formylphenoxybutyrate afforded a low yield (**Table 1**, entry 3), the cyclization of 4-aryl-2-formylphenoxybutyrate (**2e**) was performed.



Scheme 3

The first attempted method was Suzuki-Miyaura coupling of 5-bromosalicylaldehyde (**6**) with the arylborate reagent generated from 4-ethoxyphenylbromide (**5**). The boronation of Grignard reagent generated from **5** followed by the coupling reaction with **6** was conducted in one pot in order to avoid a tedious procedure to isolate the aryl borate reagent, and afforded 5-arylsalicylaldehyde (**7**) in 73% yield. The alkylation of **7** provided **2e** in 91% yield, and then the intramolecular condensation of **2e** proceeded smoothly to give **1e** in 82% yield.

In conclusion, we accomplished the practical and efficient preparation of medium ring oxygen heterocycles (**1**), 1-benzoxepines and 1-benzoxocines[8b], by Claisen-type condensation as a key reaction performed with metal alcoholate in dialkyl carbonate. According to this method, short-step (3 steps from **6**) and free of complex metal hydride reduction, the intermediate (**1e**) of orally active CCR5 antagonist was obtained in 54% overall yield, which is twice as high as the previous method.[9]

EXPERIMENTAL

General

Melting points were recorded on a Yanagimoto micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brüker DPX-300. ^{1}H NMR spectra are reported as follows: chemical shifts in ppm (δ) downfield from tetramethylsilane as an internal standard, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet), coupling constants spectra (Hz) and integration. ^{13}C NMR spectra recorded in ppm (δ) relative to the central line for $CDCl_3$ at 77 ppm and DMSO-d_6 at 39.7 ppm. Column chromatography was performed with a Wakogel C-200 (75-150mm). Elemental analyses and mass spectra were carried out by Takeda Analytical Research Laboratories Limited.

General procedure for the preparation of 2

Ethyl 4-bromobutanoate (**5**) (1.2 equiv.) was added to a suspension of 4-substituted-2-hydroxybenzaldehyde (5.0 g), K_2CO_3 (2 equiv.) in DMF (3 v/w), and stirred for 1h at 90 °C. The reaction mixture was cooled to rt and diluted with AcOEt. The mixture was neutralized with 1 M HCl. The organic layer was washed with brine, dried by Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (n-hexane-AcOEt = 4/1).

Ethyl 4-(2-formylphenoxy)butanoate (**2a**)

A colorless oil, yield 99%. MS (EI-MS): *m/z* 236 $(M)^+$. ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.27 (3H, t, *J* = 7.1 Hz), 2.14-2.23 (2H, m), 2.54 (2H, t, *J* = 7.1 Hz), 4.11-4.18 (4H, m), 6.96-7.04 (2H, m), 7.52 (1H, dt, *J* = 1.7, 7.1 Hz), 7.82 (1H, dd, *J* = 1.7, 7.1 Hz), 10.49 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.12, 24.37, 30.57, 60.51, 67.26, 112.39, 120.70, 124.85, 128.29, 135.89, 161.10, 172.90, 189.60. IR (neat): 1733, 1687, 1598, 1243 cm^{-1}.

Ethyl 4-(4-bromo-2-formylphenoxy)butanoate (**2b**)

A colorless oil, yield 98%. MS (EI-MS): *m/z* 314 $(M)^+$. ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.23 (3H, t, *J* = 7.1 Hz), 2.11-2.20 (2H, m), 2.50 (2H, t, *J* = 7.1 Hz), 4.08-4.16 (4H, m), 6.85 (1H, d, *J* = 8.9 Hz), 7.58 (1H, dd, *J* = 2.6, 8.9 Hz), 7.88 (1H, d, *J* = 2.6 Hz), 10.37 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.13, 24.25, 30.46, 60.58, 67.71, 113.48, 114.47, 126.09, 130.86, 138.21, 159.96, 172.76, 188.12. IR (neat):

1731, 1683, 1590, 1272 cm^{-1}.

Ethyl 4-(2-formyl-4-methoxyphenoxy)butanoate (**2c**)

A colorless oil, yield 99%. MS (EI-MS): *m/z* 266 $(M)^+$. ^1H NMR (300MHz, $CDCl_3$): δ = 1.23 (3H, t, *J* = 7.1 Hz), 2.09-2.18 (2H, m), 2.50 (2H, t, *J* = 7.1 Hz), 3.77 (3H, s), 4.05-4.15 (4H, m), 6.90 (1H, d, *J* = 9.1 Hz), 7.08 (1H, dd, *J* = 3.2, 9.1 Hz), 7.30 (1H, d, *J* = 3.2 Hz), 10.43 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.11, 24.48, 30.59, 55.70, 60.45, 67.92, 110.17, 114.28, 123.40, 125.07, 153.62, 155.89, 172.86, 189.28. IR (neat): 1731, 1683, 1496, 1218 cm^{-1}.

Ethyl 5-(2-formyl-4-methoxyphenoxy)pentanoate (**2d**)

A colorless oil, yield 99%. MS (EI-MS): *m/z* 280 $(M)^+$. ^1H NMR (300MHz, $CDCl_3$): δ = 1.21 (3H, t, *J* = 7.1 Hz), 1.80-1.87 (4H, m), 2.37 (2H, t, *J* = 7.1 Hz), 3.77 (3H, s), 4.01-4.14 (4H, m), 6.89 (1H, d, *J* = 9.1 Hz), 7.08 (1H, dd, *J* = 3.2, 9.1 Hz), 7.29 (1H, d, *J* = 3.2 Hz), 10.44 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.15, 21.55, 28.57, 33.77, 55.71, 60.29, 68.58, 110.12, 114.26, 123.43, 125.06, 153.55, 156.07, 173.17, 189.38. IR (neat): 1731, 1683, 1496, 1218 cm^{-1}.

General procedure for the preparation of 1

20% NaOEt (1.2 equiv.) in EtOH was added to a solution of **2** (2.4 g) in diethyl carbonate (20 v/w), and stirred for 1h at 90 °C. The reaction mixture was cooled to rt and diluted with AcOEt. The mixture was neutralized with 1 M HCl. The organic layer was washed with brine, dried by Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (n-hexane-AcOEt = 10/1).

Ethyl 2,3-dihydro-1-benzoxepine-4-carboxylate (**1a**)

A colorless oil, yield 61%. MS (EI-MS): *m/z* 218 $(M)^+$. ^1H NMR (300MHz, $CDCl_3$): δ = 1.36 (3H, t, *J* = 7.1 Hz), 2.97-3.00 (2H, m), 4.26-4.31 (4H, m), 6.96-7.04 (2H, m), 7.21-7.27 (1H, m), 7.32-7.35 (1H, m), 7.58 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.30, 33.20, 60.92, 68.65, 120.05, 122.21, 123.52, 130.53, 130.69, 135.27, 137.86, 160.44, 167.61. IR (neat): 1700, 1249 cm^{-1}.

Ethyl 7-bromo-2,3-dihydro-1-benzoxepine-4-carboxylate (**1b**)

A white powder, yield 34%. Mp 85-86 °C. ^1H NMR (300MHz, $CDCl_3$): δ = 1.34 (3H, t, *J* = 7.1 Hz), 2.92-2.97 (2H, m), 4.19-4.25 (4H, m), 6.82 (1H, d, *J* = 8.6 Hz), 7.28 (1H, dd, *J* = 2.4, 8.6 Hz), 7.42 (1H, d, *J* = 2.4 Hz), 7.43 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.27, 33.10, 61.09, 68.77, 114.25, 121.88, 125.41, 132.23, 132.99, 136.25, 137.01, 159.46, 167.15. IR (neat): 1704, 1418, 1305, 1259, 1228, 1211 cm^{-1}. Anal. Calcd for $C_{13}H_{13}O_3Br$: C, 52.55; H, 4.41; Br, 26.89. Found: C, 52.54; H, 4.19, Br, 27.06.

Ethyl 7-methoxy-2,3-dihydro-1-benzoxepine-4-carboxylate (**1c**)

A white powder, yield 82%. Mp 62-63 °C. ^1H NMR (300MHz, $CDCl_3$): δ = 1.32 (3H, t, *J* = 7.1 Hz), 2.92-2.95 (2H, m), 3.76 (3H, s), 4.17-4.28 (4H, m), 6.77-6.81 (2H, m), 6.87 (1H, dd, *J* = 1.6, 7.4 Hz), 7.49 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.29, 33.35, 55.65, 60.94, 68.71, 116.92, 118.38, 120.84,

124.11, 131.21, 137.54, 154.46, 154.63, 167.59. IR (neat): 1698, 1500, 1274, 1247, 1209 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.71; H, 6.76.

Ethyl 8-methoxy-2,3,4-trihydro-1-benzoxocine-5-carboxylate (**1d**)

A colorless oil, yield 11%. MS (EI-MS): *m/z* 262 $(M)^+$. ^1H NMR (300MHz, $CDCl_3$): δ = 1.44 (3H, t, *J* = 7.1 Hz), 1.82-1.88 (2H, m), 2.66-2.70 (2H, m), 3.86 (3H, s), 4.24-4.39 (4H, m), 6.77 (1H, d, *J* = 3.0 Hz), 6.92 (1H, dd, *J* = 3.0, 8.9 Hz), 7.02 (1H, d, *J* = 8.9 Hz), 7.70 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.27, 24.02, 24.73, 55.58, 60.82, 71.04, 115.16, 116.88, 122.80, 126.16, 131.50, 137.26, 151.65, 154.41, 167.67. IR (neat): 1704, 1496, 1243 cm^{-1}.

4'-Ethoxy-4-hydroxybiphenyl-3-carbaldehyde (**7**)

Under an atmosphere of argon, a solution of 4-ethoxybromobenzene (**6**) (4.0 g, 19.9 mmol) in THF (2.5 mL) was added dropwise to a suspension of magnesium (0.5 g, 20.4 mmol) in THF (14 mL), and the mixture was refluxed for 1h. After cooling to –10 °C, a solution of trimethoxyborane (2.1 g, 19.9 mmol) in THF (2.5 mL) was added dropwise to the reaction mixture and stirred for 1 h at –10 °C. $Pd(PPh_3)_4$ (115 mg, 0.1 mmol) was added to the resulting mixture at room temperature, and stirred for 30 min at rt. 4-Bromosalytylaldehyde (**4**) (2.0 g, 9.9 mmol), K_3PO_4 (11.1 g, 52.2 mmol) and purified water (15 mL) were added to the resulting mixture which was refluxed for 1 h. It was cooled to rt and 6 M HCl (20 mL) was added dropwise at 20-30 °C. The aqueous layer was extracted with toluene (20 mL), and the combined organic solution was washed with H_2O (10 mL) and 10% NaCl solution (10 mL x 3). Activated charcoal (0.4 g) was added to the organic solution, and stirred for 20 min at rt. The charcoal was filtered off and washed with toluene (5 mL). The filtrate and washing solution were concentrated *in vacuo*, and the residue was crystallized from IPE-Hexane (1:1) to give **7** (1.77 g, 73%) as a pale yellow powder. Mp 94-95 °C. ^1H NMR (300MHz, $CDCl_3$): δ = 1.43 (3H, t, *J* = 6.9 Hz), 4.06 (2H, q, *J* = 6.9 Hz), 6.98 (2H, dd, *J* = 2.0, 6.8 Hz), 7.04 (1H, d, *J* = 8.3 Hz), 7.46 (2H, dd, *J* = 2.0, 6.8 Hz), 7.69-7.74 (2H, m), 9.95 (1H, s), 10.95 (1H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.77, 63.49, 114.66, 114.89, 117.92, 120.63, 127.52, 131.19, 131.62, 132.98, 135.28, 158.51, 160.40, 196.62. IR (neat): 2981, 1660, 1473, 1276, 1245, 1182, 1118, 1047 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.61; H, 5.80.

Ethyl 7-((4'-ethoxy-3-formylbiphenyl-4-yl)oxy)butanoate (**2e**)

Ethyl 4-bromobutanoate (**5**) (0.89 g, 4.5 mol, 1.2 equiv.) was added to a suspension of **7** (1.0 g, 4.1 mmol), K_2CO_3 (1.14 g, 8.3 mmol, 2 equiv.) in DMF (5 v/w), and stirred for 14 h at rt and then for 3h at 50 °C. The reaction mixture was cooled to rt and diluted with AcOEt (30 mL). The mixture was neutralized with 1 M HCl. The organic layer was washed with brine, dried by Na_2SO_4 and concentrated *in vacuo*. The residue was crystallized from IPE to give **2e** (1.34 g, 91%) as a white powder. Mp 69-70 °C. ^1H NMR (300MHz, $CDCl_3$): δ = 1.26 (3H, t, *J* = 7.1 Hz), 1.43 (3H, t, *J* = 7.1 Hz), 2.18-2.25 (2H, m), 2.56 (2H, t, *J*

= 7.2 Hz), 4.04-4.20 (6H, m), 6.94 (2H, dd, *J* = 1.9, 6.7 Hz), 7.03 (1H, d, *J* = 8.7 Hz), 7.47 (2H, dd, *J* = 1.9, 6.7 Hz), 7.72 (2H, dd, *J* = 2.5, 8.7 Hz), 8.02 (1H, d, *J* = 2.5 Hz), 10.52 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.14, 14.77, 24.40, 30.57, 60.50, 63.45, 67.46, 112.87, 114.79, 124.88, 125.92, 127.60, 131.76, 133.55, 133.79, 158.46, 160.05, 172.84, 189.54. IR (neat): 2985, 2861, 1735, 1683, 1490, 1471, 1376, 1270, 1240, 1187 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.91; H, 7.08.

Ethyl 7-(4-ethoxy)-2,3-dihydro-1-benzoxepine-4-carboxylate (**1e**)

20% NaOEt (0.57 g, 1.7 mmol, 1.2 equiv.) in EtOH was added to a solution of **2e** (0.5 g, 1.4 mmol) in diethyl carbonate (5 mL, 20 v/w), and stirred for 1h at 50 °C. The reaction mixture was cooled to rt and diluted with AcOEt. The mixture was neutralized with 1 M HCl. The organic layer was washed with brine, dried by Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (n-hexane-AcOEt = 10/1). The filtrate and washing solution were concentrated *in vacuo* to give **1e** (0.39 g, 82%) as a white powder. Mp 128-129 °C. ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.37 (3H, t, *J* = 7.1 Hz), 1.44 (3H, t, *J* = 7.0 Hz), 2.99-3.02 (2H, m), 4.07 (2H, q, *J* = 7.0 Hz), 4.25-4.32 (4H, m), 6.96 (2H, dd, *J* = 2.0, 6.7 Hz), 7.03 (1H, d, *J* = 8.4 Hz), 7.4-7.51 (4H, m), 7.65 (1H, s). ^{13}C NMR (300MHz, $CDCl_3$): δ = 14.32, 14.81, 33.18, 60.94, 63.46, 68.74, 114.76, 120.44, 123.58, 127.67, 128.77, 130.94, 132.34, 133.24, 135.03, 137.96, 158.33, 159.38, 167.55. IR (neat): 2975, 1702, 1496, 1301, 1251, 1213 cm^{-1}. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.32; H, 6.46.

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7. In this reaction, multi and minor impurities were observed, and further investigation such as isolation and identification was not undertaken.
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9. This synthesis was also free of chromatography except for **1e**. The intermediate (**1e**) was isolated chromatographically since it was prepared in a small amount. We thought, however, **1e** could be crystallized without chromatographic purification because the cyclization proceeded well.