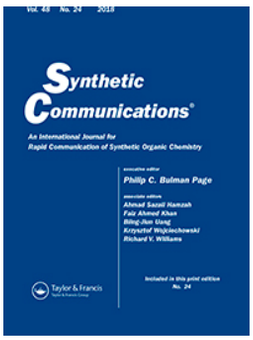

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Facile synthesis of 2,3-disubstituted benzofurans via DBU-promoted intramolecular annulation of *ortho* oxyether aroylformates

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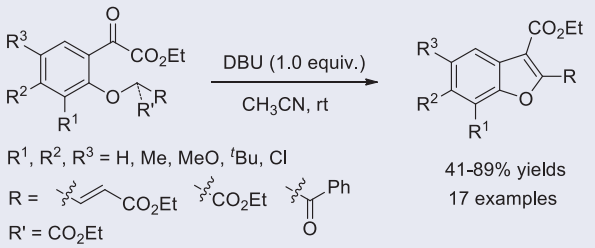
ABSTRACT

A facile synthesis of 2,3-disubstituted benzofurans from *ortho* oxyether aroylformates has been developed. Under the mediation of DBU, the intramolecular annulation of *ortho* oxyether aroylformates proceeds smoothly to provide the corresponding 2,3-disubstituted benzofurans in moderate to good yields under mild conditions. Furthermore, a one-pot two-step synthesis of 2,3-disubstituted benzofurans has also been demonstrated from readily available *ortho* hydroxy aroylformates.

GRAPHICAL ABSTRACT



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Annulation; benzofurans; DBU; intramolecular; ortho oxyether aroylformates

Introduction

The benzofurans are an important class of heterocycles frequently present in a wide range of naturally occurring molecules and pharmaceutically active compounds.[1–8] For example, natural products Daphnodorin A and B, which display a wide array of biological activities, contain the benzofuran nucleus.[2] Amiodarone, a marketed drug for the treatment of intractable cardiac arrhythmias, is also based on the benzofuran moiety.[3] The compound SKF-64346 bearing a benzofuran core has been identified as a potent inhibitor of β-amyloid aggregation and exhibits therapeutic potential toward

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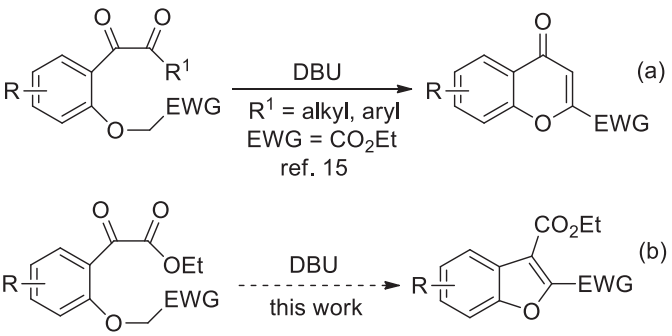
Alzheimer's disease.[4] Other molecules with a benzofuran moiety have also shown a variety of biological properties such as antimicrobial,[5] antitumor,[6] antiproliferative,[7] and MMP-13 inhibitory activities (Figure 1).[8] Furthermore, the benzofurans have also been demonstrated to be versatile building blocks for construction of complex molecules with biological interest.[9] The development of efficient synthetic methods to benzofurans has accordingly attracted extensive efforts from chemists due to their bioactivities and versatility. As a result, a number of synthetic methodologies have been established.[1,10] Among them, the transition-metal-catalyzed tandem reactions provide powerful approaches to benzofurans with specific structures.[1,11] However, the use of heavy metals and the requirement of harsh reaction conditions negatively influence their wide application. Efficient synthesis of benzofurans under metal-free and mild conditions is, therefore, attractive from an aspect of green and environmental benign chemistry, but by far it has only witnessed limited successes.[12] Additionally, different types of substitution patterns in benzofurans afford new opportunities for drug discovery and other applications. Thus, it remains in demand for exploration of new and efficient methodologies for structurally diverse benzofurans, particularly under metal-free and mild conditions.

Aroylformates are versatile building blocks in organic synthesis due to their functionality-enriched structural features. Under the influence of Lewis bases such as phosphines and amines, the aroylformates can serve as versatile coupling partners in *intermolecular* reactions. Our group and others recently have reported in a number of studies that the aroylformates could readily undergo annulation and insertion reactions with both electrophiles and nucleophiles under the mediation of phoshines through the well-known Kukhtin–Ramirez adducts.[13] Moreover, the amine-catalyzed annulation reactions involving aroylformates have also been well documented.[14] Although the aroylformates involved *intermolecular* reactions have been extensively explored, the corresponding *intramolecular* variants have been seldom touched. Notably, in 2013, a DBU-mediated intramolecular condensation of the analogous *ortho* diketo phenoxyethers was reported, affording 2,3-disubstituted γ-benzopyranones selectively (Scheme 1, eq. (a)).[15] Considering the bioactive prevalence and versatility of benzofurans, we envisioned that by introducing an oxyether group to the *ortho* position of the phenyl ring of the aroylformates would lead to a potential intramolecular aldol type condensation in the presence of a base such as DBU, thus resulting in the formation of 2,3-disubstituted benzofurans (Scheme 1, eq. (b)). Herein, we report a DBU-mediated intramolecular annulation of *ortho* oxyether aroylformates, affording 2,3-disubstituted benzofurans in

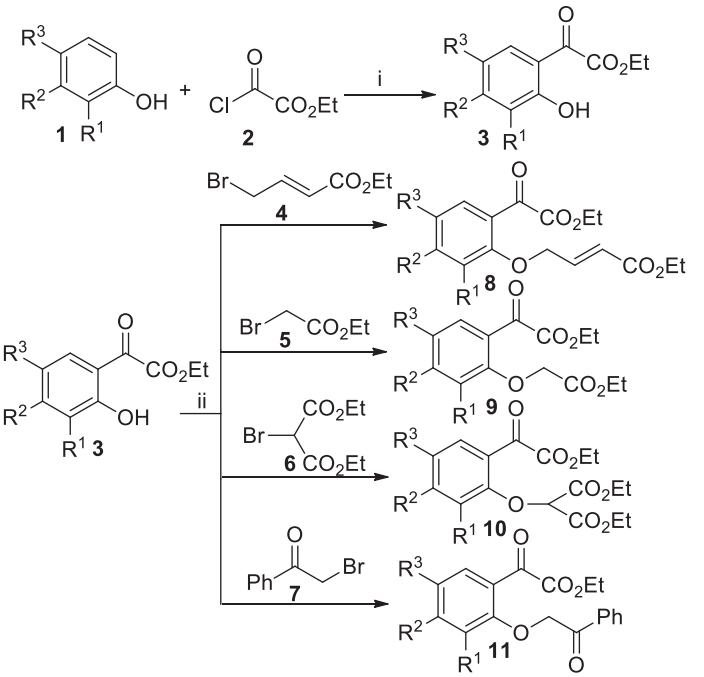


Scheme 1. Syntheses of benzopyranones and benzofurans via selective intramolecular cyclization.

moderate to good yields under metal-free and mild conditions. Furthermore, a one-pot two-step synthesis of 2,3-disubstituted benzofurans has also been demonstrated from readily available *ortho* hydroxyl aroylformates.

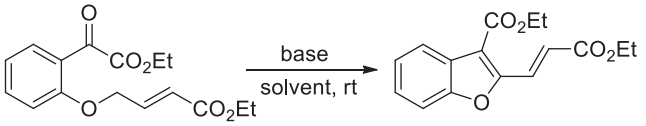
Results and discussion

We commenced our study with a two-step synthesis of *ortho* oxyether aroylformates **8**, **9**, **10**, and **11** (Scheme 2). The first step consists of a $TiCl_4$-mediated Friedel–Crafts acylation of substituted phenol **1** with oxaloyl chloride monoethyl ester **2**, which provided *ortho* hydroxy aroylformates **3** in generally high yields. Subsequent K_2CO_3-promoted nucleophilic substitution of **3** with bromides **4**, **5**, **6**, and **7** afforded the desired *ortho* oxyether aroylformates **8**, **9**, **10**, and **11**, respectively. We attempted the proposed annulation with the model substrate **8a**. In the presence of DBU (0.04 mmol), a reaction mixture of **8a** (0.2 mmol) in CH_2Cl_2 was stirred at room temperature for 24 h. To our delight, the expected 2,3-disubstituted benzofuran **12a** was exclusively afforded in 59% yield, without detection of the corresponding benzopyranone byproduct. A brief survey on the model reaction conditions was conducted in order to further improve the reaction efficiency (Table 1). Solvents screening indicated that CH_3CN was the optimal reaction medium, although other common solvents such as CH_2Cl_2, THF,



Scheme 2. Synthesis of *ortho* oxyether aroylformates **8**, **9**, **10**, and **11.**

Table 1. Survey on the model reaction conditions[a].



8a **12a**

Entry	Base	Solvent	Time (h)	Yield (%)[b]
1	DBU	CH_2Cl_2	24	59
2	DBU	THF	24	52
3	DBU	Toluene	24	9
4	DBU	DMF	22	47
5	DBU	CH_3CN	22	65
6	Et_3N	CH_3CN	24	trace
7	DABCO	CH_3CN	24	trace
8	K_2CO_3	CH_3CN	24	trace
9	Cs_2CO_3	CH_3CN	24	5
10	KOH	CH_3CN	24	9
11	DBU	CH_3CN	2	64[c]
12	DBU	CH_3CN	1	75[c,d]
13	DBU	CH_3CN	4	50[e]

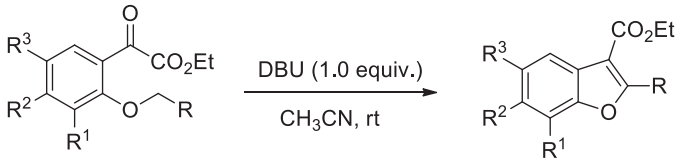
[a]Reaction conditions: substrate **8a** (0.2 mmol), base (0.04 mmol), solvent (2 mL), rt.
[b]Isolated yield.
[c]DBU (0.2 mmol) was used.
[d]CH_3CN (5.0 mL) was used.
[e]The reaction was conducted at 70 °C.

and DMF were accommodated as well (entries 1–4). The influence of base catalysts was also investigated. Replacement of DBU with other organic or inorganic bases all brought about inferior results (entries 6–10). Increasing the loading of DBU to stoichiometric amounts shortened the reaction time significantly while retaining the yield (entry 11). Using one equivalent of DBU in a diluted reaction mixture further improved the yield of **12a** (entry 12). A decrease in yield was observed when elevating the reaction temperature to 70 °C (entry 13).

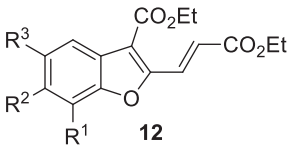
Employing the optimal reaction conditions listed in Table 1 entry 12, the generality of the intramolecular annulation was explored (Table 2). Substrates **8** with different substituents on the phenyl ring were first examined. Both electron-donating and electron-withdrawing groups on **8** were well tolerated, readily affording their corresponding products **12** in moderate to good yields. Notably, the steric properties and the location of the substituents on the phenyl ring of **8** have limited influence on their reactivity. Substrates **9** and **10**, derived from ethyl bromoacetate and diethyl bromomalonate respectively, were all capable of providing their corresponding benzofuran products **13** under refluxing acetonitrile. It is worth noting that both substrates **9** and **10** afford the same products under the reaction conditions. The annulation was also applicable to substrates **11** which were derived from 2-bromoacetophenone. Under the standard conditions, the annulation reactions of **11** uneventfully occurred to afford their corresponding benzofurans **14** in moderate to good yields.

The structures of substrates **8–11**, and products **12–14** were all fully characterized by ^{1}H, 13C NMR and HRMS-ESI/MALDI measurements. The annulation reaction proceeds smoothly by using a common organic base and provides a range of 2,3-disubstituted benzofurans in generally high yields in one single step under mild conditions,

Table 2. Synthesis of 2,3-disubstituted benzofurans[a].

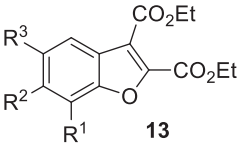


8 or **9** or **10** or **11** → **12** or **13** or **14**



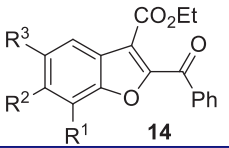
12

R^1, R^2, R^3 = H; **12a,** 1 h, 75%
R^1 = Me, R^2, R^3 = H; **12b,** 5 h, 72%
R^1, R^3 = H, R^2 = Me; **12c**, 2 h, 80%
R^1, R^2 = H, R^3 = Me; **12d**, 3 h, 68%
R^1, R^2 = H, R^3 = MeO; **12e**, 2 h, 66%
R^1, R^2 = H, R^3 = ^{t}Bu; **12f**, 5 h, 80%
R^1, R^3 = ^{t}Bu, R^2 = H; **12g**, 5 h, 75%
R^1, R^3 = H, R^2 = Cl; **12h**, 2 h, 43%



13

R^1, R^2, R^3 = H; **13a,** from **9a**, 2 h, 61%[b]
R^1 = Me, R^2, R^3 = H; **13b**, from **9b**, 3 h, 60%[b]
R^1, R^3 = H, R^2 = Me; **13c**, from **9c**, 5 h, 58%[b]; from **10c**, 5 h, 47%[b]
R^1, R^2 = H, R^3 = ^{t}Bu; **13f**, from **9f**, 5 h, 63%[b]; from **10f**, 5 h, 41%[b]



14

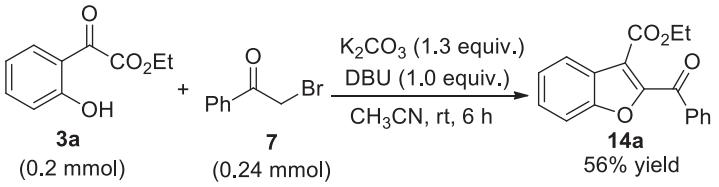
R^1, R^2, R^3 = H; **14a,** 3 h, 60%
R^1, R^3 = H, R^2 = Me; **14c**, 5 h, 89%
R^1, R^2 = H, R^3 = ^{t}Bu; **14f**, 5 h, 86%

[a]Reaction conditions: substrate **8** or **9** or **10** or **11** (0.2 mmol), DBU (0.2 mmol), CH_3CN (5.0 mL), rt. Isolated yield.
[b]Under reflux.

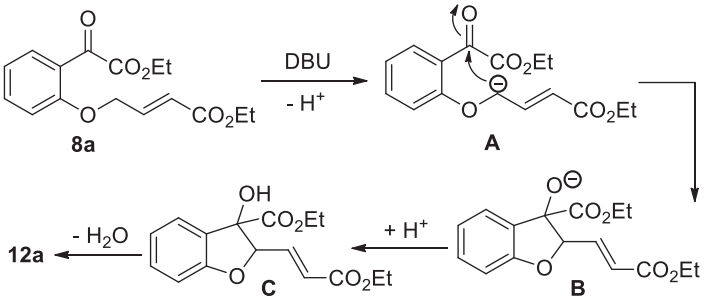
which therefore represents a metal-free and efficient protocol for these biologically important structural scaffolds.

To make our protocol more synthetically appealing, the feasibility of performing the reaction in one-pot was examined. As depicted in Scheme **3**, in the presence of both K_2CO_3 and DBU, a tandem substitution-intramolecular annulation of *ortho* hydroxy benzoylformate **3a** with 2-bromoacetophenone **7** smoothly proceeded, affording the benzofuran **14a** in 56% yield (for optimization of the reaction conditions, see Table S1 in Supplementary Information).[16] It thus demonstrated a green and step-economic protocol to 2,3-disubstituted benzofurans.

A proposed mechanism to account for the formation of benzofuran derivatives is exemplified in Scheme **4** based on the experimental results. The reaction is presumably initiated with the generation of carbanion intermediate **A** through deprotonation of *ortho* oxyether aroylformate such as **8a** by organic base DBU. Intermediate **A** then triggers an intramolecular aldol type reaction by addition of the carbanion to the carbonyl group, generating intermediate **B**, which undergoes protonation to afford intermediate **C**. Finally, **C** brings about the benzofuran product such as **12a** after dehydration. As for



Scheme 3. One-pot synthesis of benzofuran **14a.**



Scheme 4. A proposed mechanism for the formation of benzofuran.

the annulation of substrates **10**, elimination of monoethyl carbonate is envisioned in the final step to generate the products **13**.

Conclusions

In summary, we have developed a facile synthesis of 2,3-disubstituted benzofurans through DBU-mediated intramolecular annulation of *ortho* oxyether aroylformates. The annulation reaction proceeds smoothly under metal-free and mild conditions and affords a broad range of biologically important 2,3-disubstituted benzofurans in moderate to good yields. It represents a rare intramolecular reaction mode involving aroylformates. Furthermore, a one-pot two-step synthesis of benzofurans has also been developed from readily available *ortho* hydroxy aroylformates, enabling a green and step-economic synthesis of 2,3-disubstituted benzofurans. Future efforts in our laboratory will be directed toward the application of this methodology for the synthesis of bioactive compounds.

Experimental

Unless otherwise noted, all reactions were carried out under anhydrous conditions. All solvents were purified according to standard procedures. ^{1}H and 13C NMR spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. HRMS spectra were acquired in the ESI mode with the mass analyzer of TOF used. Column chromatography was performed on silica gel (200 $\sim$ 300 mesh) using a mixture of petroleum ether/ethyl acetate as eluant.

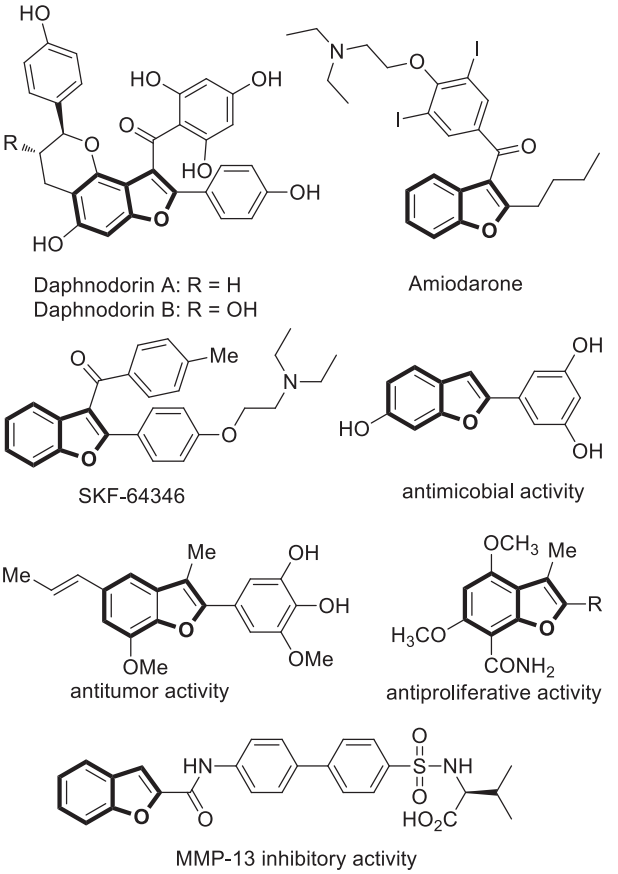


Figure 1. Representative natural products and bioactive compounds with a benzofuran core.

Typical procedure for synthesis of substrates 8, 9, 10, and 11

The substrates *ortho* oxylether aroylformates **8**, **9**, **10**, and **11** were synthesized according to reported procedures in two steps.[17]

To a solution of phenol (20 mmol) in CH_2Cl_2 (25 mL) at −15 °C was added $TiCl_4$ (22 mmol). After that ethyl chlorooxoacetate (22 mmol) was added slowly. The resulting mixture was stirred at −15 °C for 3–5 h for completion. The reaction was then diluted with CH_2Cl_2 (30 mL) and poured into previously cooled 1.0 M HCl (75 mL). The aqueous layer was separated and extracted with CH_2Cl_2. The organic layers were combined and washed with 1.0 M HCl and 20% NaCl aqueous solution, dried over $MgSO_4$, and filtered, and the filtrate was concentrated and purified by column chromatography on silica gel to afford compound **3**.

To a mixture of compound **3** (10 mmol) and bromides **4** or **5** or **6** or **7** (10.8 mmol) in DMF (4.0 mL) was added K_2CO_3 (13 mmol). The reaction mixture was stirred at rt until compound **3** was completely consumed. Water (50 mL) was added, and the mixture was extracted with ether (3 × 50 mL). The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel to afford compound **8**, **9**, **10**, and **11**, respectively.

(*E*)-Ethyl 4-(2-(2-ethoxy-2-oxoacetyl)phenoxy)but-2-enoate **8a**; 58% yield over two steps; a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.8, 1.7 Hz, 1H), 7.54–7.46 (m, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.95 (dt, J = 15.8, 4.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.07 (dt, J = 15.8, 1.9 Hz, 1H), 4.70 (dd, J = 4.4, 2.0 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 186.4, 165.6, 164.9, 158.5, 140.7, 136.1, 131.1, 123.3, 122.9, 121.9, 112.8, 67.5, 62.0, 60.7, 14.1, 13.9; HRMS–ESI $[M + H]^+$ Calcd for $C_{16}H_{19}O_6$ 307.1176, found 307.1187.

Typical procedure for DBU-mediated intramolecular annulation of substrates 8, 9, 10, and 11

To a 25 mL round bottom flask, substrate **8** or **9** or **10** or **11** (0.2 mmol), DBU (0.2 mmol), and acetonitrile (5 mL) were added. The resulting mixture was stirred at rt (for **8** and **11**) or under reflux (for **9** and **10**) until the substrate was completely consumed, as monitored by TLC. After removing the solvent, the residue was re-dissolved in CH_2Cl_2 (20 mL), washed with water and brine, dried with $MgSO_4$. Removal of CH_2Cl_2 gave the crude product, which was subjected to column chromatographic isolation on silica gel by gradient elution using petroleum ether/ethyl acetate (20:1 $\sim$ 10:1) to give the annulation product **12** or **13** or **14**.

(*E*)-Ethyl 2-(3-ethoxy-3-oxoprop-1-en-1-yl)benzofuran-3-carboxylate **12a**; prepared according to the typical procedure, **8a** (61 mg, 0.2 mmol) is employed to give **12a** (43 mg, 75%) as a white solid; mp: 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 16.0 Hz, 1H), 8.06 (ddd, J = 7.8, 1.3, 0.6 Hz, 1H), 7.52–7.45 (m, 1H), 7.37 (dtd, J = 15.0, 7.2, 1.2 Hz, 2H), 6.79 (d, J = 16.0 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 166.0, 163.2, 155.9, 154.4, 130.0, 127.0, 126.2, 124.6, 123.6, 122.9, 113.7, 111.3, 61.0, 60.9, 14.3, 14.2; HRMS–ESI $[M + H]^+$ Calcd for $C_{16}H_{17}O_5$ 289.1071, found 289.1080.

Typical procedure for one-pot synthesis of benzofuran 14a

K_2CO_3 (0.26 mmol) and DBU (0.2 mmol) were added to a solution of *ortho* hydroxyl phenylformate **3a** (0.2 mmol) and 2-bromoacetophenone **7** (0.24 mmol) in CH_3CN (5.0 mL). The resulting mixture was stirred at rt for 6 h for completion. The solvent was removed and the residue was dissolved in CH_2Cl_2 (10 mL). Water (10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (2 $\times$ 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated, and the crude mixture was subjected to column chromatographic isolation on silica gel by gradient elution using petroleum ether/ethyl acetate (20:1 $\sim$ 10:1) to give the annulation product **14a**.

Funding

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