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Graphical Abstract

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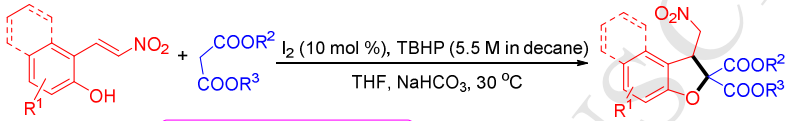
Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China



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Formal [4 + 1] Cycloaddition Strategy for the Synthesis of Dihydrobenzofurans *via* Michael Addition of 2-(2-nitrovinyl)-phenols and Malonate Esters (C1 Synthon) and Subsequent Iodine-catalyzed Oxidative Annulation

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ABSTRACT

A novel [4 + 1] cycloaddition protocol for the synthesis of dihydrobenzo(naphtho)furan skeletons from readily available 2-(2-nitrovinyl)-phen(naphth)ols and malonate esters *via* a tandem Michael addition/iodine-catalyzed oxidative annulation has been developed. This method provides a new and facile application of malonate esters as 1,1-nucleophilic/electrophilic type C1 synthons without a pre-functionalization step and the plausible reaction mechanism is proposed.

1. Introduction

Five-membered heterocycles such as dihydrobenzofuran represent pivotal structural motifs found in a large number of biologically active molecules, drugs, and materials (Figure 1).[1] Thus, the development of novel and highly efficient methodologies for their synthesis has attracted continuous attention from synthetic chemists. As known, cycloaddition reactions such as [3 + 2] are powerful and well-studied tools for the construction of five-membered rings.[2] Comparatively, the less-studied [4 + 1] annulations providing alternative and versatile approaches to obtain these compounds are attracting more and more attentions owing to their distinct synthetic advantages.[3] According to the literatures, carbon monoxide, fischer carbenes, nucleophilic carbenes, isocyanides, diazo reagents and sulfur/phosphine ylides are widely used as one-carbon(C1) synthons in the [4 + 1] annulations.[4] Based on these C1 synthons, a variety of highly efficient methodologies toward five-membered heterocycles have been reported. However, there are rare methodologies being developed based on a new C1 synthon for it is a rather challenging work. Thus, the novel [4 + 1] annulation to construct five-membered heterocycles relied on new C1 synthons or strategies is worth to explore.

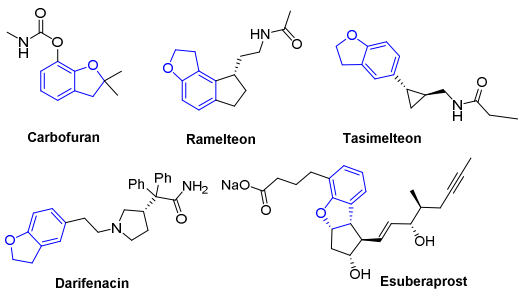
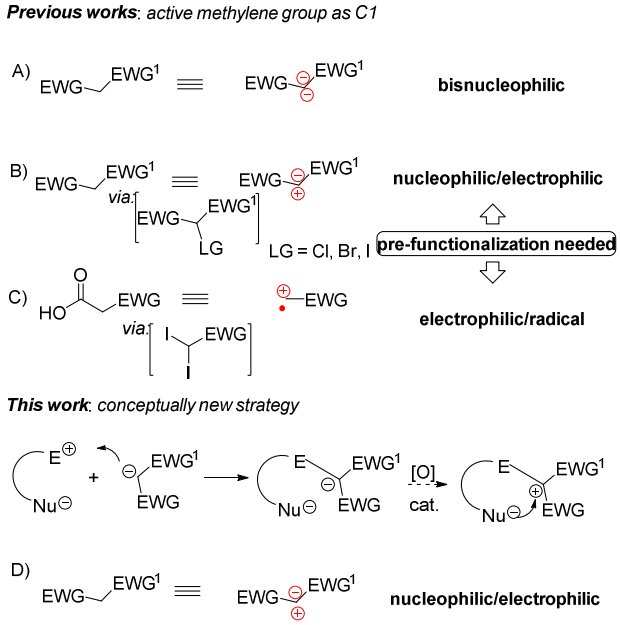


Figure 1. Pharmaceutical compounds containing 2,3-dihydrobenzofuran rings

Differing from the aforementioned C1 synthons, the compounds with active methylene group such as 1,3-dicarbonyl compounds also can be used as C1 synthons for that they can be easily transformed into carbon dianion under basic conditions (scheme 1A).[5] Therefore, they are commonly used as 1,1-bisnucleophilic type C1 synthons in the [4 + 1] annulations, while the aforementioned nucleophilic carbenes, isocyanides, diazo reagents and sulfur/phosphine ylides are used as 1,1-nucleophilic/electrophilic type ones owing to their special structures or characters such as with leaving groups. In 2011, Xie *et al*[6] and co-workers reported a noval cycloaddition to construct dihydrobenzofuran using *α*-halo-1,3-dicarbonyl compound as C1 synthon to react with salicylic aldehyde derivatives (scheme 1B). Recently, Lei *et al*[7] reported a novel N-iodosuccinimide-mediated decarboxylative [4 + 1] oxidative annulation between 2-vinylpyridine derivatives and malonate monoesters to construct indolizine derivatives by utilizing malonate monoesters as a C1 synthons, in which the in situ formed 2,2-diiodoacetate was the active intermediate, which reacted with 2-vinylpyridine derivatives through an electro-philic/radical reaction path way (scheme 1C). With the sustaining interests in heterocycle synthesis, we have reported the novel iodine-catalyzed [3 + 2] annulations of allenes with 1,3-dicarbonyl compounds or enamines for synthesis of polysubstituted furans and pyrroles, in which the *a*-carbon anion with potential nucleophilic reactivity of the intermediate could be inverted into electrophilic site under oxidative conditions.[8] With this information in mind, we envisioned that the compounds with active methylene group would find new application for they can first be used as nucleophile in the reaction and then converted into electrophile under oxidative conditions without a necessary

prefunctionalization step. This strategy would endow these traditional 1,1-bisnucleophiles the new reactivity as 1,1-nucleophilic/electrophilic type C1 synthons which are equal to diazo reagents, α-halo carbonyl compounds and sulfur/phosphine ylides (scheme 1D).

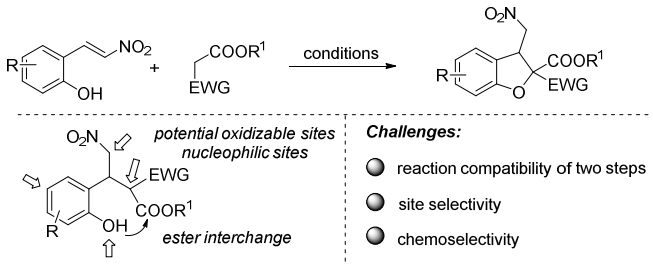
Scheme 1. The reaction modes of active methylene groups as C1 synthons



2. Results and discussion

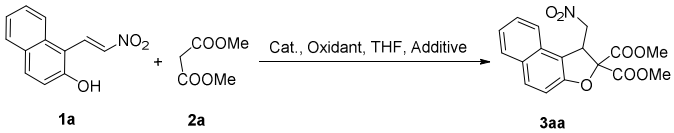
The reaction of nitroalkenes based on salicylaldehydes and malonate esters was designed to test our hypothesis. It was envisaged that malonate esters would first react with nitroalkenes to form the Michael adducts, which could be further oxidized under oxidative conditions and captured by phenolic hydroxyl to construct dihydrobenzofurans (scheme 2). The possible side reactions such as the oxidation of phenol and *a*-carbon of nitroalkane, intramolecular ester interchange of phenolic hydroxyl with ester along with some intermolecular reactions would unambiguously increase the difficulty of the designed [4 + 1] reaction, not to mention the compatibility of Michael addition reaction and the crucial oxidative step.[9] Herein, we report the first iodine-catalyzed formal [4 + 1] oxidative annulation of malonate esters and readily available 2-(2-nitrovinyl)-naphthols or 2-(2-nitrovinyl)-phenols for the synthesis of dihydrobenzo(naphtho)furans with the new reactivity of active methylenes as 1,1-nucleophilic/electrophilic type C1 synthons.

Scheme 2. Initial design and its challenges



After initial screening of the reaction conditions, 2-(2-nitrovinyl)-naphthol **1a** and methyl malonate **2a** were chosen as the substrates and $NaHCO_3$ was chosen as base for the further optimization of the formal [4 + 1] oxidative annulation (see the Supplementary Material for the details, Table 1). When KI (20 mol %) was used as the catalyst and TBHP (70 wt % in H_2O) as oxidant in 1,4-dioxane, the desired dihydronaphthofurans **3aa** was obtained in 47% yield (Table 1, entry 1). The examination of catalysts revealed that NIS (20 mol %) gave a better result and the yield of **3aa** was increased to 60% after prolonging the reaction time to 36 h (Table 1, entry 2), while I_2 (20 mol %) afforded the nearly same result (Table 1, entry 3). Other catalyst like NaBr could not trigger this reaction (Table 1, entry 4). The further screening of catalysts proved that when the same molar quantity of iodide was employed, the reaction that employing I_2 as catalyst would perform better and the improvement of the catalyst loading could deteriorate the desired reaction (Table 1, entries 5-6). Some other oxidants (such as DTBP and H_2O_2) failed to improve the yield of **3aa** (Table 1, entries 7 and 8). Surprisingly, the result was dramatically increased to 82% when using TBHP (5.5 M in decane) as oxidant (Table 1, entry 9). This encouraging result implied that the water in oxidant might deteriorate the reaction. To our surprised, the use of dried THF as solvent did not improve the yield (Table 1, entry 10). Further experiments showed that 90% of **3aa** would be obtained by increasing the amount of methyl malonate **2a** to 1.8 equiv (Table 1, entry 11) and 71% of **3aa** could still be got after reducing the catalyst loading to 5 mol % (Table 1, entry 12). Control experiments exhibited that both $NaHCO_3$ and catalyst are necessary for this transformation (Table 1, entry 13 and 15). Our initial screening of the reaction conditions showed that the stronger base such as K_2CO_3 was not suitable for this reaction for which would unambiguously lead to intramolecular ester interchange side reaction (see the Supplementary Material for the details, Table 1). When replacing $NaHCO_3$ with K_2CO_3, a considerable drop in yield is observed unsurprisingly (Table 1, entry 14), but the reaction time was shorten to 2 h.

Table 1. The optimization of reaction conditions for the formal [4 + 1] annulation[a]



entry	cat.	oxidant	equiv of **2a**	yield(%)[b]
1	KI (20 mol %)	TBHP[c]	1.2	47
2	NIS (20 mol %)	TBHP[c]	1.2	60
3	I_2 (20 mol %)	TBHP[c]	1.2	58
4	NaBr (20 mol %)	TBHP[c]	1.2	nr
5	I_2 (10 mol %)	TBHP[c]	1.2	67
6	NIS (10 mol %)	TBHP[c]	1.2	64
7	I_2 (10 mol %)	DTBP	1.2	trace
8	I_2 (10 mol %)	H_2O_2	1.2	43
9	I_2 (10 mol %)	TBHP[d]	1.2	82
10[e]	I_2 (10 mol %)	TBHP[d]	1.8	64
11	**I_2** (10 mol %)	**TBHP[d]**	**1.8**	**90**

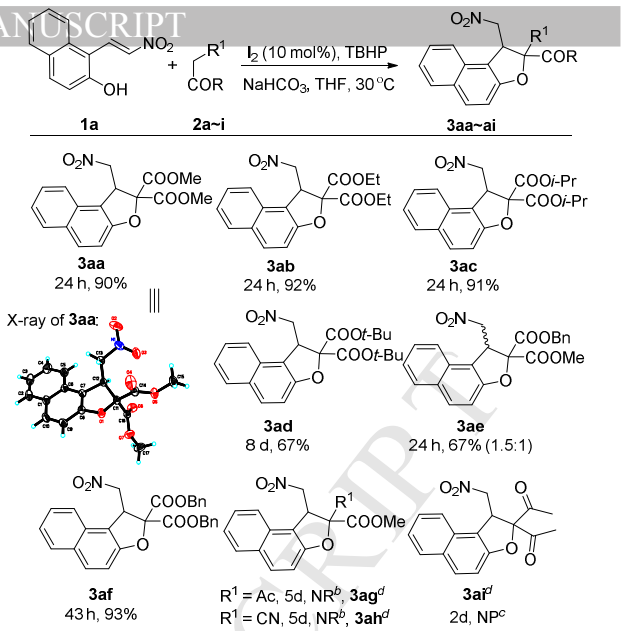
12	I_2 (5 mol %)	TBHP[d]	1.8	71
13[f]	I_2 (10 mol %)	TBHP[d]	1.8	trace
14[g]	I_2 (10 mol %)	TBHP[d]	1.8	64
15	none	TBHP[d]	1.8	np

[a]Standard conditions: **1a** (0.2 mmol), I_2 (10 mol %), TBHP (5.5 M in decane) (2 equiv), $NaHCO_3$ (1 equiv), THF (1.5 mL), 30 °C, and 24 h. [b]Isolated yield. [c]TBHP (70 wt.% in H_2O) was used. [d]TBHP (5.5 M in decane) was used. [e]dry THF was used. [f]no $NaHCO_3$. [g]K_2CO_3 was used instead of $NaHCO_3$. DTBP = di-*tert*-butyl peroxide. nr = no reaction. np = no product.

Under the optimal conditions, the substrate scope of this synthetic protocol was evaluated. Various malonate esters were suitable reaction partners for **1a** to afford corresponding dihydronaphthofurans (Table 2). Methyl, ethyl and isopropyl malonates reacted smoothly with **1a** to deliver dihydronaphthofurans **3aa-ac** in excellent yields. When *tert*-butyl malonate was used, product **3ad** was obtained in 67% yield after 8 days presumably owing to the steric hindrance. Furthermore, changing one of the methyl group in **2a** to benzyl afforded **3ae** in 67% yield (dr = 1.5/1), while the reaction of benzyl malonate **2f** with **1a** gave **3af** in 93% yield after prolonging reaction time to 43 h. Unfortunately, further extending the substrate scope of malonate esters to ethyl acetoacetate, methyl cyanoacetate and acetoacetone was proved to be unsuitable for the reaction under the current conditions, even employing K_2CO_3 as base or adding Takemoto catalyst.

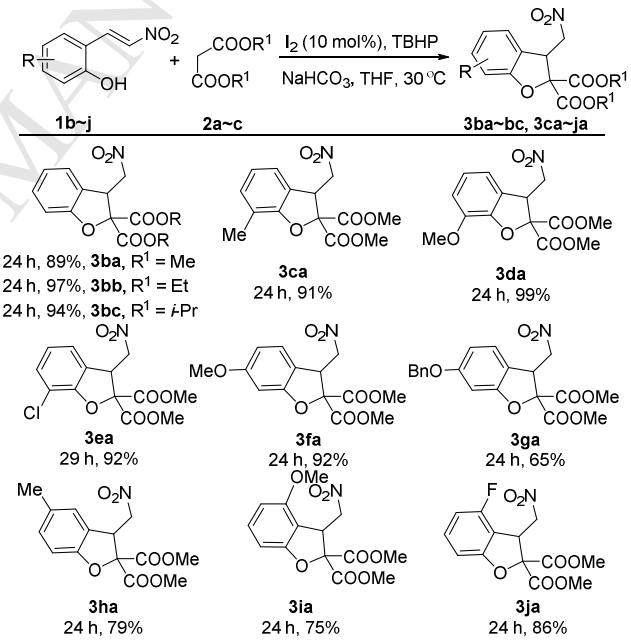
After testing the limitation of malonate esters, we moved forward to examine substitution patterns for various 2-(2-nitrovinyl)-phenols (Table 3). As indicated in table 3, 2-(2-nitrovinyl)-phenols **1b** reacted smoothly with the methyl, ethyl and isopropyl malonates in good to excellent yields to afford dihydrobenzofurans **3ba-bc**. Also, various substituted 2-(2-nitrovinyl)-phenols **1c-j** were found suitable for this transformation, delivering the desired products **3ca-ja** in 65-99% yields. These results revealed that the reactions were insignificantly affected by positions or electronic properties of the substituents. However, it should be noted that the reaction of 6-Cl substituted 2-(2-nitrovinyl)-phenols **1e** with methyl malonate **2a** needed longer time to complete the transformation, which implied that the nucleophilic property of the phenolic hydroxyl might influence this transformation.

Table 2. Synthesis of dihydronaphthofurans from 2-(2-nitrovinyl)-naphthol **1a** with various malonate esters[a]



[a]Standard conditions: **1a** (0.2 mmol), **2a** (0.36 mmol), I_2 (10 mol %), TBHP (5.5 M in decane) (2 equiv), $NaHCO_3$ (1 equiv), THF (1.5 mL), 30 °C. [b]NR = no reaction. [c]NP = no product. [d]Takemoto catalyst was used.

Table 3. Synthesis of dihydrobenzofurans from malonate esters with various 2-(2-nitrovinyl)-phenols[a]

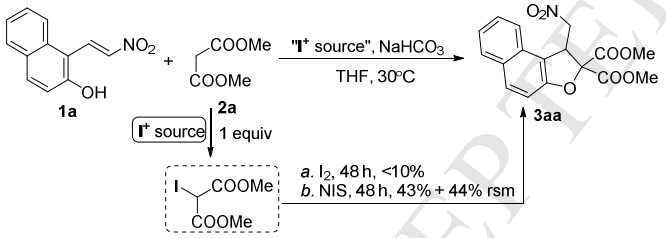


[a]Standard conditions: **1a** (0.2 mmol), **2a** (0.36 mmol), I_2 (10 mol %), TBHP (5.5 M in decane) (2 equiv), $NaHCO_3$ (1 equiv), THF (1.5 mL).

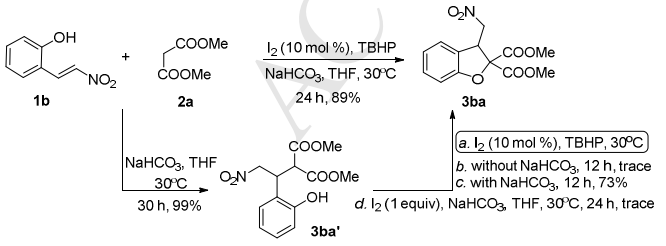
As mentioned above, the dihydrobenzo(naphtho)furan ring systems represent the privileged skeletons prevalent in an increasing number of biologically active natural products and pharmaceuticals. To date, a great deal of research efforts have been devoted to the development of new methods for the synthesis of these ring systems.[10] In spite of the significant achievements, most methods used for the preparation of these ring systems still need a necessary pre-functionalization step to prepare the substrates or rely on some special substrates.[11] This method here provided a new perspective for solving the problem.

To gain insight into the reaction pathway, several control experiments were conducted. As is known, 1,3-dicarbonyl compounds can react with molecular iodine (I_2) or N-iodosuccinimide (NIS) under basic conditions to form *a*-monoiodinated 1,3-dicarbonyl compounds, in which I_2 and NIS act as I^+ sources.[12] As indicated in scheme 3, 1 equivalent of I_2 or NIS was used without additional oxidant to promote the reaction. Obviously, the desired product could also be obtained, but only in less than 10% and 43% yield respectively with a rather low conversion after prolonging reaction time to 48 h. These results revealed that iodinated 1,3-dicarbonyl compounds may be included in this reaction, but they are not the real active intermediates and I_2 is not the active catalyst. At the beginning of the reaction conditions screening, Michael product was obtained when using TBAI as catalyst (see the Supporting Information for the details, Table 1), which indicated the Michael adduct could be the key intermediate of this transformation. Thus, the Michael adduct of 2-(2-nitrovinyl)-phenols **1b** and methyl malonate **2a** was obtained to test the hypothesis. As shown in scheme 4, the intermediate **3ba'** was transformed into product **3ba** in 73% yield after 12 h under standard conditions, while only trace amount of product **3ba** was obtained without $NaHCO_3$. These results proved that the Michael adducts are indeed the intermediate and base is necessary in both steps of Michael addition and oxidative annulation in this reaction. Moreover, the intermediate **3ba'** could not be further converted into **3ba** with 1 equivalent of I_2 and $NaHCO_3$, which further confirmed that I_2 is not the active species. Moreover, the addition of TEMPO did not retard the desired reaction under standard conditions, which indicated that the oxidative annulation might not proceed through a radical pathway (scheme 5).

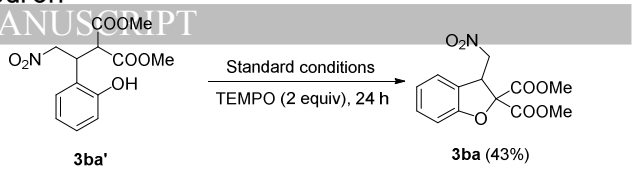
Scheme 3. The reaction of 2-(2-nitrovinyl)-phenols **1a** with *a*-monoiodinated methyl malonate



Scheme 4. Investigation of the reaction intermediate

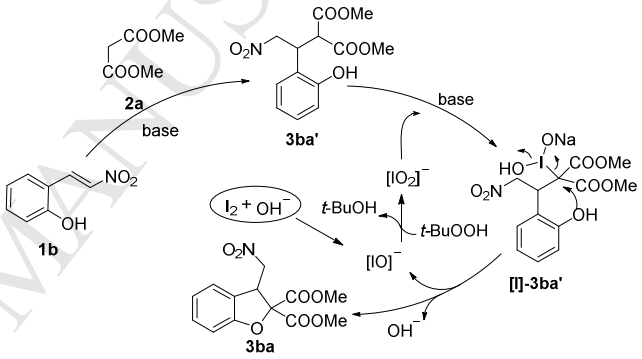


Scheme 5. Transformation of reaction intermediate with radical scavenger



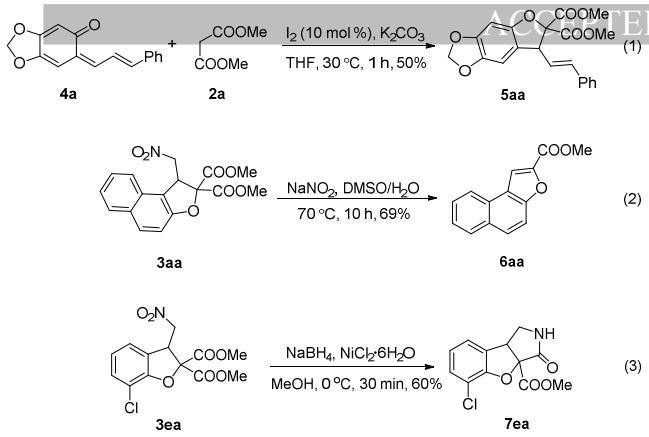
According to Ishihara and co-workers' pioneered work and our previous reports, the potential actual oxidant species, $[IO_2]^-$, could be generated by oxidation of I_2 with TBHP under basic conditions.[13] Thus, a tentative mechanism is proposed in scheme 6 based on the results of control experiments described above and other related work. As depicted in scheme 6, I_2 could be transformed into hypoiodite $[IO]^-$ under basic conditions initially, then, which is further oxidized by TBHP to form the iodite $[IO_2]^-$. The Michael adduct formed by the reaction of malonate ester **2a** and nitroalkene **1b** could possibly react with the in situ formed reactive species $[IO_2]^-$ to give the intermediate [I]-**3ba'**, which could be captured by intramolecular phenolic hydroxyl to construct dihydrobenzofuran and releasing hypoiodite species $[IO]^-$ for the next catalytic cycle.

Scheme 6. Tentative Mechanism



Finally, to demonstrate the further applications of this strategy for the application of malonate esters as 1,1-nucleophilic/electrophilic type C1 synthons, the reaction of ortho-quinone methides (*o*-QMs) **4a** and malonate ester **2a** was examined. As a result, the reaction was performed smoothly to deliver desired product **5aa** in 50% yield with K_2CO_3 as base (scheme 7, eq 1). An intending to convert the primary nitro derivative **3aa** to acid[14] gave methyl naphtho[2,1-b]furan-2-carboxylate **6aa** in 69% yield (scheme 7, eq 2), which provided a novel approach to obtain this useful skeleton. The naphtho[2.1-b]furan skeleton is proved to have analgesic activity.[15] Moreover, we can also obtain a new kind of tricyclic skeleton **7ea** *via* simple reduction and cyclization (scheme 7, eq 3).[16]

Scheme 7. Further applications



3. Conclusion

In conclusion, a novel [4 + 1] strategy by employing malonate esters as 1,1-nucleophilic/electrophilic type C1 synthons through a tandem Michael addition/iodine-catalyzed oxidative annulation has been developed. This method provides a facile synthetic protocol for the construction of dihydrobenzo(naphtho)furan ring systems from readily available 2-(2-nitrovinyl)-phen(naphth)ols and malonate esters in good to excellent yields (up to 99%) under mild conditions. Notably, this tactic can also be applied to the reaction of *o*-QMs and malonate esters. Further explorations of this strategy are ongoing in our laboratory and will be reported in due course.

4. Experimental section

4.1 General

Melting points were obtained in open capillary tubes using SGW X-4 micro melting point apparatus which were uncorrected. ^{1}H NMR spectrum were recorded on a Bruker DPX 400 MHz spectrometer in $CDCl_3$. Chemical shifts were reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The spectra are interpreted as: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, coupling constant(s) J are reported in Hz and relative integrations are reported. ^{13}C NMR (100 MHz) spectrum were recorded on a Bruker DPX 400 MHz spectrometer in $CDCl_3$. Chemical shifts were reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Mass spectra were recorded on TOF mass spectrometer. TLC (thin-layer chromatography) was performed using commercially prepared 100−400 mesh silica gel plates, and visualization was effected at 254 or 365 nm.

4.2 General procedure

2-(2-nitrovinyl)-phenol or 2-(2-nitrovinyl)-naphthol **1**, base, Cat., and 1.5 mL solvent were added to an oven-dried tube, successively. Then malonate ester or related compound **2** and oxidant were added. The reaction mixture was then stirred in air until the reaction was nearly completed, as determined by TLC. Once **1** consumed, the reaction mixture was cooled to ambient temperature. The resulting mixture was concentrated in vacuo and directly purified by column chromatography (petroleum ether/ethyl acetate= 7:1~5:1) on silica gel to give the desired products **3**.

*4.2.1. Dimethyl 1-(nitromethyl)naphtho[2,1-b]furan-2,2(1H)-dicarboxylate (**3aa**)*

A yellow solid (62 mg, 90% yield), Mp: 145-147 °C. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.63-7.53 (m, 1H), 7.46-7.37 (m, 1H), 7.26 (d, *J* = 8.9 Hz, 1H), 5.49 (t, *J* = 5.9 Hz, 2H), 4.78 (d, *J* = 5.9 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-d) δ 167.7, 165.9, 155.3, 132.1, 130.6, 129.7, 129.1, 128.4, 124.5, 121.4, 114.4, 112.3, 91.1, 73.0, 54.2, 53.8, 46.1. **HRMS** (EI-TOF): calcd for, $C_{17}H_{15}NO_7$ $[M]^+$:345.0849; found, 345.0848.

*4.2.2. Diethyl 1-(nitromethyl)naphtho[2,1-b]furan-2,2(1H)-dicarboxylate (**3ab**)*

A yellow solid (69 mg, 92% yield), Mp: 103-105 °C. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.60-7.56 (m, 1H), 7.43-7.39 (m, 1H), 7.26 (d, *J* = 8.9 Hz, 1H), 5.51 (dd, *J* = 8.0, 3.8 Hz, 1H), 4.83-4.74 (m, 2H), 4.43-4.18 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-d) δ 167.1, 165.5, 155.4, 131.9, 130.6, 129.6, 129.2, 128.3, 124.4, 121.4, 114.6, 112.3, 91.2, 73.1, 63.5, 63.3, 45.7, 14.0, 13.9. **HRMS** (EI-TOF): calcd for, $C_{19}H_{19}NO_7$ $[M]^+$, 373.1162; found, 373.1164.

*4.2.3. Diisopropyl 1-(nitromethyl)naphtho[2,1-b]furan-2,2(1H)-dicarboxylate (**3ac**)*

A yellow solid (73 mg, 91% yield), Mp: 145-147 °C. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.86 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.59-7.55 (m, 1H), 7.42-7.38 (m, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 5.49 (dd, *J* = 9.1, 2.7 Hz, 1H), 5.18-5.04 (m, 2H), 4.85 (dd, *J* = 15.3, 9.2 Hz, 1H), 4.74 (dd, *J* = 15.2, 2.7 Hz, 1H), 1.34 (d, *J* = 6.3 Hz, 3H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-d) δ 166.7, 165.1, 155.5, 131.9, 130.5, 129.6, 129.2, 128.3, 124.3, 121.4, 114.7, 112.3, 91.2, 72.9, 72.1, 71.2, 45.3, 21.7, 21.6, 21.5, 21.3. **HRMS** (EI-TOF): calcd for, $C_{21}H_{23}NO_7$ $[M]^+$, 401.1475; found, 401.1476.

*4.2.4. Ditertbutyl 1-(nitromethyl)naphtho[2,1-b]furan-2,2(1H)-dicarboxylate (**3ad**)*

A yellow solid (58 mg, 67% yield), Mp: 137-139 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.56-7.52 (m, 1H), 7.40-7.36 (m, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 5.51 (dd, *J* = 8.3, 2.8 Hz, 1H), 4.80 (dd, *J* = 15.7, 8.4 Hz, 1H), 4.72 (dd, *J* = 15.7, 2.9 Hz, 1 H), 1.54 (s, 9H), 1.47 (s, 9H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 165.8, 164.6, 155.5, 131.7, 130.5, 129.6, 129.2, 128.1, 124.2, 121.4, 115.1, 112.3, 92.0, 85.7, 84.0, 73.4, 44.7, 27.9 (3C), 27.8 (3C). **HRMS** (EI-TOF): calcd for, $C_{23}H_{27}NO_7$ $[M]^+$, 429.1788; found, 429.1783.

*4.2.5. 2-benzyl 2-methyl 1-(nitromethyl)naphtho[2,1-b]furan-2,2(1H)-dicarboxylate (**3ae**)*

A yellow oil (57 mg, 67% yield) (dr = 1.5:1). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.87-7.84 (m, 1.67H) (overlapping), 7.82-7.79 (m, 1.67H) (overlapping), 7.70 (d, *J* = 8.3 Hz, 1.67H) (overlapping), 7.56 (t, *J* = 7.6 Hz, 1.67H) (overlapping), 7.43-7.23 (m, 11.69H) (overlapping), 5.51-5.47 (m, 1.67H) (overlapping), 5.42 (d, *J* = 12.1 Hz, 0.67H) (minor), 5.28 (d, *J* = 12.3 Hz, 1H) (major), 5.18 (d, *J* = 12.3 Hz, 1H) (major), 5.13 (d, *J* = 12.1 Hz, 0.67H) (minor), 4.82-4.72 (m, 3.34H) (overlapping), 3.76 (s, 3H) (major), 3.70 (s, 2H) (minor). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 167.4(minor), 166.8(major), 165.6(major), 165.1(minor), 155.3(major), 155.3(minor), 134.7, 134.2, 131.98, 131.95, 130.5, 130.5, 129.5, 129.04, 129.02, 128.8, 128.7, 128.57, 128.56, 128.56, 128.5, 128.3, 128.3, 127.9, 127.9, 124.4, 124.4, 121.3, 114.37, 114.36, 112.24, 112.20, 91.1(major), 91.0, 72.95, 72.89(major), 68.7, 68.5(major), 53.9, 53.5(major),

45.9(major), 45.8. **HRMS** (EI-TOF): calcd for, $C_{23}H_{19}NO_7$ $[M]^+$, 421.1162; found, 421.1165.

*4.2.6. Dibenzyl 1-(nitromethyl)naphtho[2,1-b]furan-2,2(1H)-dicarboxylate (**3af**)*

A yellow solid (92 mg, 93% yield), Mp: 118-120 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.58-7.54 (m, 1H), 7.43-7.39 (m, 1H), 7.34-7.27 (m, 6H), 7.25-7.21 (m, 3H), 7.16-7.13 (m, 2H), 5.50 (dd, *J* = 8.7, 3.1 Hz, 1H), 5.31 (d, *J* = 12.1 Hz, 1H), 5.16 (d, *J* = 12.3 Hz, 1H), 5.10 (dd, *J* = 12.2, 3.6 Hz, 2H), 4.85-4.70 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.9, 165.1, 155.4, 134.5, 134.0, 132.0, 130.5, 129.5, 129.1, 128.8, 128.7 (4C), 128.5 (2C), 128.5, 128.3, 128.0 (2C), 124.4, 121.4, 114.4, 112.3, 91.1, 72.9, 68.8, 68.6, 45.9. **HRMS** (EI-TOF): calcd for, $C_{29}H_{23}NO_7$ $[M]^+$, 497.1475; found, 497.1477.

*4.2.7. Dimethyl 3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3ba**)*

A yellow solid (53 mg, 89% yield), Mp: 85-87 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.27 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.01-6.98 (m, 2H), 5.04 (t, *J* = 6.7 Hz, 1H), 4.80 (dd, *J* = 14.2, 6.8 Hz, 1H), 4.64 (dd, *J* = 14.2, 6.7 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 167.3, 166.3, 157.4, 130.5, 124.4, 123.3, 122.9, 110.9, 89.8, 74.9, 54.2, 53.8, 45.8. **HRMS** (EI-TOF): calcd for, $C_{13}H_{13}NO_7$ $[M]^+$, 295.0692; found, 295.0693.

*4.2.8. Diethyl 3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3bb**)*

A yellow solid (63 mg, 97% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.28-7.24 (m, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.01-6.96 (m, 2H), 5.04 (t, *J* = 6.8 Hz, 1H), 4.81 (dd, *J* = 14.1, 6.8 Hz, 1H), 4.63 (dd, *J* = 14.1, 6.9 Hz, 1H), 4.39-4.21 (m, 4H), 1.31 (td, *J* = 7.2, 3.0 Hz, 6H).

*4.2.9. Diisopropyl 3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3bc**)*

A yellow solid (66 mg, 94% yield); Mp: 82-84 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.27-7.23 (m, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.00-6.95 (m, 2H), 5.19-5.09 (m, 2H), 5.01 (t, *J* = 6.9 Hz, 1H), 4.83 (dd, *J* = 14.1, 6.6 Hz, 1H), 4.63 (dd, *J* = 14.1, 7.2 Hz, 1H), 1.32-1.28 (m, 12H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.1, 165.2, 157.5, 130.2, 124.2, 123.7, 122.6, 110.7, 89.8, 74.9, 71.7, 71.3, 45.3, 21.5, 21.45, 21.40, 21.38. **HRMS** (EI-TOF): calcd for, $C_{17}H_{21}NO_7$ $[M]^+$, 351.1318; found, 351.1314.

*4.2.10. Dimethyl 7-methyl-3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3ca**)*

A yellow oil (57 mg, 91% yield); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.07 (d, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 5.03 (t, *J* = 6.8 Hz, 1H), 4.79 (dd, *J* = 14.2, 7.1 Hz, 1H), 4.61 (dd, *J* = 14.2, 6.6 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.29 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 167.5, 166.5, 155.9, 131.7, 122.8, 122.6, 121.6, 121.3, 89.6, 74.9, 54.1, 53.7, 46.2, 15.2. **HRMS** (EI-TOF): calcd for, $C_{14}H_{15}NO_7$ $[M]^+$, 309.0849; found, 309.0851.

*4.2.11. Dimethyl 7-methoxy-3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3da**)*

A yellow solid (66 mg, 99% yield), Mp: 132-134 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.95 (t, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 5.06 (t, *J* = 6.8 Hz, 1H), 4.82 (dd, *J* = 14.3, 6.9 Hz, 1H), 4.64 (dd, *J* = 14.3, 6.7 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 167.3, 166.2, 145.9, 144.9, 124.4, 123.8, 115.9, 113.3, 90.1, 74.8, 56.2, 54.2, 53.8, 46.4. **HRMS** (EI-TOF): calcd for, $C_{14}H_{15}NO_8$ $[M]^+$, 325.0798; found, 325.0799.

*4.2.12. Dimethyl 7-chloro-3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3ea**)*

A white solid (67 mg, 92% yield), Mp: 150-152 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 8.0 Hz, 1H), 7.04-7.01 (m, 1H), 6.94 (t, *J* = 7.8 Hz, 1H), 5.09 (t, *J* = 6.7 Hz, 1H), 4.83 (dd, *J* = 14.3, 6.5 Hz, 1H), 4.66 (dd, *J* = 14.3, 7.0 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 166.8 165.9, 153.7, 130.9, 125.2, 123.9, 122.6, 116.5, 90.0, 74.6, 54.4, 53.9, 46.4. **HRMS** (EI-TOF): calcd for, $C_{13}H_{12}Cl^{35}NO_7$ $[M]^+$, 329.0302; found, 329.0303.

*4.2.13. Dimethyl 6-methoxy-3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3fa**)*

A yellow solid (60 mg, 92% yield), Mp: 140-142 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.01 (d, *J* = 8.3 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.95 (t, *J* = 6.8 Hz, 1H), 4.76 (dd, *J* = 13.9, 6.7 Hz, 1H), 4.58 (dd, *J* = 14.0, 6.9 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.77 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 167.3, 166.2, 162.0, 158.7, 124.7, 114.9, 108.9, 97.2, 90.5, 75.2, 55.7, 54.2, 53.8, 45.4. **HRMS** (EI-TOF): calcd for, $C_{14}H_{15}NO_8$ $[M]^+$, 325.0798; found, 325.0795.

*4.2.14. Dimethyl 6-(benzyloxy)-3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3ga**)*

A yellow solid (52 mg, 65% yield), Mp: 122-124 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.42-7.33 (m, 5H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 6.60 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.02 (s, 2H), 4.95 (t, *J* = 6.8 Hz, 1H), 4.76 (dd, *J* = 14.0, 6.7 Hz, 1H), 4.57 (dd, *J* = 14.0, 6.9 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 167.3, 166.2, 161.2, 158.7, 136.5, 128.8 (2C), 128.3, 127.6 (2C), 124.7, 115.3, 109.8, 98.2, 90.5, 75.2, 70.5, 54.2, 53.8, 45.4. **HRMS** (EI-TOF): calcd for, $C_{20}H_{19}NO_8$ $[M]^+$, 401.1111; found, 401.1108.

*4.2.15. Dimethyl 5-methyl-3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3ha**)*

A yellow solid (49 mg, 79% yield), Mp: 60-62 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.08-7.03 (m, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.99 (t, *J* = 6.8 Hz, 1H), 4.79 (dd, *J* = 14.2, 6.7 Hz, 1H), 4.62 (dd, *J* = 14.2, 6.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 167.4, 166.4, 155.3, 132.6, 130.9, 124.7, 123.3, 110.5, 89.9, 74.9, 54.1, 53.7, 45.9, 20.9. **HRMS** (EI-TOF): calcd for, $C_{14}H_{15}NO_7$ $[M]^+$, 309.0849; found, 309.0850.

*4.2.16. Dimethyl 4-methoxy-3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3ia**)*

A yellow solid (49 mg, 75% yield), Mp: 79-81 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.23-7.19 (m, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 5.11 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.98 (dd, *J* = 14.9, 3.3 Hz, 1H), 4.75 (dd, *J* = 14.9, 8.4 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.83 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 167.5, 166.3, 158.4, 156.3, 131.6, 109.5, 104.8, 103.7, 89.9, 72.1, 55.7, 54.1, 53.6, 45.1. **HRMS** (EI-TOF): calcd for, $C_{14}H_{15}NO_8$ $[M]^+$, 325.0798; found, 325.0799.

*4.2.17. Dimethyl 4-fluoro-3-(nitromethyl)benzofuran-2,2(3H)-dicarboxylate (**3ja**)*

A yellow solid (54 mg, 86% yield), Mp: 100-102 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.28-7.22 (m, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.71 (t, *J* = 8.7 Hz, 1H), 5.19 (dd, *J* = 7.8, 3.6 Hz, 1H), 4.95 (dd, *J* = 15.0, 3.7 Hz, 1H), 4.82 (dd, *J* = 15.0, 7.8 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 166.9, 165.9, 159.2 (d, *J* = 7.6 Hz), 158.8 (d, *J* = 249.4 Hz), 157.6, 132.0 (d, *J* = 8.7 Hz), 109.8 (d, *J* = 19.7 Hz), 109.8 (d, *J* = 19.7 Hz), 106.9, 90.1, 72.5, 54.3, 53.8, 44.6. **HRMS** (EI-TOF): calcd for, $C_{14}H_{12}FNO_7$ $[M]^+$, 313.0598; found, 313.0596.

*4.2.18. Dimethyl 2-(1-(2-hydroxyphenyl)-2-nitroethyl)malonate (**3ba'**)*

A yellow oil (59 mg, 99% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.16-7.06 (m, 1H), 6.83 (td, *J* = 7.6, 0.9 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.65 (s, 1H), 5.08 (dd, *J* = 13.1, 8.9 Hz, 1H), 4.92 (dd, *J* = 13.1, 4.8 Hz, 1H), 4.41-4.35 (m, 1H), 4.29 (d, *J* = 10.1 Hz, 1H), 3.78 (s, 3H), 3.54 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 168.5, 168.3, 154.1, 130.7, 129.8, 121.9, 120.9, 116.4, 76.1, 53.2, 53.0, 52.8, 40.4.

*4.2.19. Dimethyl(E)-7-styryl-[1,3]dioxolo[4,5-f]benzofuran-6,6(7H)-dicarboxylate (**5aa**)*

A colorless oil (19 mg, 50% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.37 – 7.21 (m, 5H), 6.63 (d, J = 15.8 Hz, 1H), 6.60 – 6.54 (m, 2H), 6.06 (dd, J = 15.8, 9.0 Hz, 1H), 5.95 – 5.87 (m, 2H), 4.93 (d, J = 9.0 Hz, 1H), 3.87 (s, 3H), 3.69 (s, 3H).

*4.2.20. Methyl naphtho[2,1-b]furan-2-carboxylate (**6aa**)*

A yellow solid (31 mg, 69% yield). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 8.03 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 9.1 Hz, 1H), 7.70 (d, *J* = 9.1 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 4.02 (s, 3H).

*4.2.21. Methyl5-chloro-3-oxo-1,2,3,8b-tetrahydro-3aH-benzofuro[2,3-c]pyrrole-3a-carboxylate (**7ea**)*

A white soild (25 mg, 60% yield), Mp: 210-212 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.21 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.09 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 4.44 – 4.39 (m, 1H), 4.03 (dd, *J* = 10.2, 7.4 Hz, 1H), 3.87 (s, 3H), 3.60 – 3.53 (m, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 170.6, 167.4, 154.2, 130.2, 128.5, 123.4, 122.5, 116.3, 90.3, 53.5, 47.2, 47.0. **HRMS** (EI-TOF): calcd for, $C_{12}H_{10}ClNO_4$ $[M]^+$, 267.0298; found, 267.0296.

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Supplementary Material

Supplementary data related to this article can be found at http://