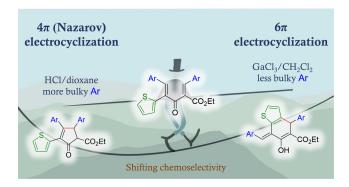
Divergent Reactivity of Triaryldivinyl Ketones: Competing 4π and Putative 6π Electrocyclization Pathways

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ABSTRACT: This work describes an acid-promoted cyclization of triaryldivinyl ketones containing a thiophene moiety in the α -position. Two cyclization pathways are accessible: one a 4π -Nazarov cyclization, the other we propose to proceed through a 6π electrocyclic mechanism. The relative proportion of products from these divergent pathways is affected by reaction conditions, and steric bulk in the substrate. We present experimental and computational evidence that using HCl in dioxane, the 4π -conrotatory electrocyclization is more favorable, whereas GaCl₃ in methylene chloride shifts the chemoselectivity toward a putative 6π -disrotatory electrocyclization. DFT calculations suggest that a complex interplay between kinetic and thermodynamic factors is implicated in the chemodivergent behavior.

INTRODUCTION

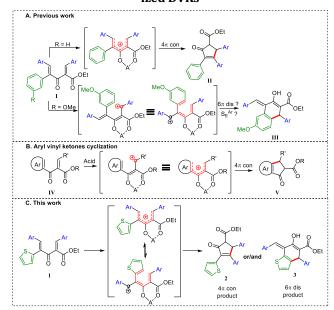
Divinyl ketone (DVK) reactants have played a critical role in the total synthesis of various carbocyclic natural compounds¹. These compounds have attracted the attention of chemists through their utility in the stereospecific Nazarov cyclization². One of the important challenges in this chemistry is the design of reactive, polarized DVKs, a strategy that makes the reaction more practical, efficient, and selective.³. Therefore, careful design and study of appropriately activated aryl-substituted DVKs should enable not only investigation of electronic and steric effects on reactivity, but also provide access to useful polyaromatic frameworks for medicinal and material chemistry⁴.

We have recently found that the cyclization of polarized triaryl DVKs I under acidic conditions proceeds *via* two competitive pathways (Scheme 1A).⁵ When DVK I bears an electron-deficient substituent, Nazarov cyclization product II is favored, whereas DVKs I with an electron-rich aro-

matic substituent generate dihydronaphthalenes III preferentially. While cyclopentenones II result from Nazarov reaction (4π -conrotatory electrocyclization), two mechanistic pathways are possible for this novel transformation resulting in dihydronaphthalenes. The first of them includes the Friedel-Crafts intramolecular electrophilic substitution, activated by the donor α -substituent (methoxy group), which provides chemoselectivity due to the stabilization of the arenium ion. The second pathway, that we propose, involves 6π -disrotatory electrocyclization of the enol form in a positively charged molecule. To the best of our knowledge, there have been only a few examples of 6π -electrocyclizations that proceed through an enol intermediate.⁶ A close example of an ambiguous mechanism is the cyclization of polarized arylvinyl ketones IV, which could be states as Nazarov cyclization or Friedel-Crafts alkylation (Scheme 1B).7 However, similar polarized aryl vinyl ketones were studied by Ishikawa, who proposed a 4π-electrocyclization mechanism.8

As demonstrated previously, the cyclization of triaryl DVKs I containing phenyl derivatives as α -substituents proceed with high chemoselectivity to afford II or III (Scheme 1A).

Scheme 1. Competing cyclization pathways of polarized DVKs



In contrast, thiophene derivatives ${\bf 1}$ led to the formation of a mixture of products ${\bf 2}$ and ${\bf 3}$ (Scheme 1C). Moreover, it was found that the ratio of these products varies depending on the nature of the reaction medium and β -substituent (vicinal to ester). This finding inspired us to seek further insight into the divergent reactivity observed. In this paper, we provide experimental and computational evidence that both products result from the electrocyclization processes of cationic intermediates.

RESULTS AND DISCUSSION

Experimentation began with treatment of ${\bf 1a}$ in HCl/CH_2Cl_2 ^{5a} led to the formation of a mixture of compounds ${\bf 2a}$ and ${\bf 3a}$ (1.2 : 1) in good yield (entry 2 in the Table 1). In a less polar solvent like HCl/dioxane, the main product is cyclopentenone ${\bf 2a}$ (3.5 : 1; entry 1), while in polar TFA, on the contrary, product ${\bf 3a}$ predominates (1 : 2.8; entry 3). The acid amount also contributes on the products ratio (from 0.4 : 1 to 1.4 : 1; entries 3-6), thus large amount led to product ${\bf 3a}$ due to increasing of the medium polarity.

The nature of the acid as a catalyst for this process is also critical. Strong Lewis acids such as TiCl₄ and AlCl₃ (entry 8, 12) provide the same product ratio as HCl (1.1 : 1) while mild Lewis acids (CuCl₂ and BF₃ · Et₂O) suppress the formation of dihydrobenzothiophene **3a** (from 1.6 : 1 to 3.1 : 1; entries 9-10). Results using a complex acid catalyst (aluminum chloride with pyridine) were similar to BF₃ · Et₂O, apart from an increase in side processes (1.9 : 1; entriy 13). The best chemoselectivity in favor of Nazarov product is achieved with BF₃ · Et₂O in dry dioxane (16 : 1; entry 11).

Comparison of Lewis acids from group IIIA, such as B, Al and Ga, suggests that an increase in atomic radius leads to an increase in the chemoselectivity of the product $\bf 3a$ (entry 10, 12, 14). Although, DVK $\bf 1a$ transforms into a mixture of products using GaCl $_3$ at room temperature, carrying out the reaction at -78 $^{\rm o}$ C in GaCl $_3$ /DCM leads to product $\bf 3a$ chemoselectivity chemoselectively and with good yield

(87%; entry 15). Finally, it was shown that lowering the temperature favors the formation of the benzothiophene product **3a** (entry 7),

Table 1. Optimization of the Reaction Parameters.

	Reaction Conditions ^a	NMR Yields ^b		Product
Entry		2a	3a	ratio 2a : 3a
1	HCl (1 equiv.)/dioxane	70	20	3.5 : 1
2	HCl (2 equiv.)/CH ₂ Cl ₂	53	45	1.2:1
3	TFA	22	61	1:2.8
4	TFA (2 equiv.)/CH ₂ Cl ₂	46	44	1:1
5	TFA (1 equiv.)/CH ₂ Cl ₂	53	38	1.4:1
6	TFA (0.2 equiv.)/CH ₂ Cl ₂	50	35	1.4:1
7	HCl (2 equiv.)/CH ₂ Cl ₂ (-78 °C)	30	68	1:2.3
8	$TiCl_4(2 equiv.)/CH_2Cl_2$	42	37	1.1:1
9	CuCl ₂ (2 equiv.)/CH ₂ Cl ₂	40	25	1.6:1
10	$BF_3 \cdot Et_2O$ (2 equiv.)/ CH_2Cl_2	37	12	3.1:1
11	BF ₃ · Et ₂ O (2 equiv.)/dioxane	64	4	16:1
12	AlCl ₃ (2 equiv.)/CH ₂ Cl ₂	42	36	1.1:1
13	AlCl ₃ · 4Pyr (2 equiv.)/CH ₂ Cl ₂	42	22	1.9:1
14	GaCl ₃ (2 equiv.)/CH ₂ Cl ₂	19	32	1:1.7
15	GaCl ₃ (2 equiv.)/CH ₂ Cl ₂ (-78 °C)	-	87	-:1
16	GaCl₃(2 equiv.)/dioxane	20	34	1:1.7

^aSubstrate **1a** (Ar = 4-methoxyphenyl) was subjected to the respective reaction conditions shown here. Unless otherwise stated, the reactions were performed at room temperature (rt). ^bYields and ratios were obtained from 1 H NMR spectra in the presence of CH₂Br₂ as the internal standard.

suggesting that this product forms under kinetic control.

In order to better understand the effects of different thienyl and β-aryl substituents on the chemoselectivity of the cyclization, a wide range of triaryldivinyl ketones **1a-n** was studied using the HCl/CH2Cl2 as the standardized conditions. In some cases, product dihydrobenzothiophenes 3 aromatized to benzothiophenes 3' (compounds 3'b, d-g, ii). The results obtained are summarized in Scheme 2. As can be seen, the elec-tronic effect of β -substituent on the ratio of products is negligible. In particular, substrate 1c, containing a 4-trifluoromethylphenyl residue as the substituent, gives a product ratio that is similar to the ratio that DVK **1a** (4-methoxyphenyl) or **1b** (isovanilin residue) produce. The fact that electron-withdrawing or donating groups didn't affect the rate of formation of dihydrobenzothiophene 3 supports our assumption that this transformation proceeds through electrocyclization rather than electrophilic substitution.

In contrast, the steric effect of β -substituent does impact the reaction behavior: compound **1f** cyclized *via* Nazarov reaction more selectively than compound **1a**, which has the same electronic character, but less steric bulk. To confirm the importance of the steric effect, different DVKs with bulky substituents (**1e**, **1g-i**) were also tested. The steric hindrance of the β -substituent is correlated to the product ratio: the

Scheme 2. Cyclizations of thienyl-substituted DVKs 1a-n a

3a-n 3'a-n 2 min, 85% 2a / 3a (1.2 : 1) 5 min, 54% 2b / 3'b (1.3 : 1) 2 min. 66% 2c / 3c (1.3 : 1) 5 min, 81% 27° / 3'f (2.5 : 1) 5 min, 77% 2g / 3'g (6.5 : 1) 3 min, 79% 2m / 3m (1 : 3.6)

^aYields correspond to the sum of the isolated yields of the separated isomers. Cases with significant chemoselectivity (> 4 : 1) are emphasized. ^bReaction was carried out in TiCl₄ (2 equiv.)/dichloromethane. ^cDecarboxylation was observed only in the case of **2**′*f*.

benzothiophene product is favored in substrates with a less bulky substituent (compounds **1m-n**), while the cyclopentenone (Nazarov cyclization) product is favored for substrates with a bulky substituent (compounds **1e**, **g-i**).

To demonstrate the impact of acid promoter on the reaction pathway, we exposed several substrates to HCl/dioxane (Table 2, conditions A) and GaCl₃/DCM (Table 2, conditions B). In these experiments, ratio of the product mixture could be reversed by reaction conditions, in some cases total suppression of the second product was observed (conditions A; entry 4 and conditions B; entry 7).

DFT calculations 9 were used to obtain insight into the mechanism of the conversion of the compound ${\bf 1a}$ into ${\bf 2a/3a}$. This case was chosen due to the balanced ratio of products in a large range of temperatures (Table 1, entry 2 and 7) that shows that both products ${\bf 2a/3a}$ are accessible. The results are summarized in Scheme 3. Following the protonation of ${\bf 1a}$, the molecule was found to exist as an

equilibrium mixture of two conformers, **1aH*** and **1'aH*** (other possible conformations

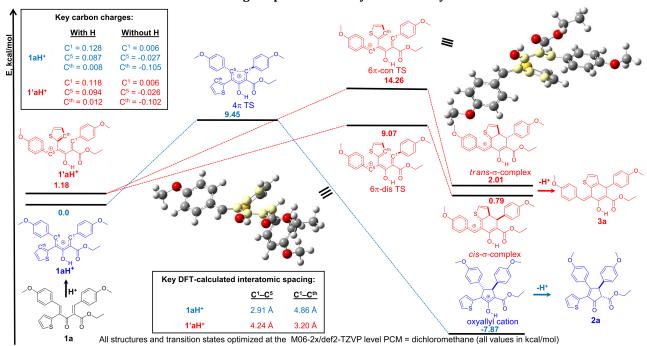
Table 2. Shifting the chemoselectivity by acid promoter^a

Table 2. Shifting the chemoselectivity by acid promoter ^a								
Entry	Product 2	Product 3/3'	Cond. Ab	Cond. B ^c				
1	O OET OM	MeO S OMe	90% 2a / 3a (3.5 : 1)	51% 2a / <i>3a</i> (1:1.7)				
2	O OEt CI	CI OEI	90% 2d / 3'd (5:1)	78% 2d / 3'd (1:1.9)				
3	Meo Meo	OMe OH OEt	91% 2'f / 3'f (8.1:1)	82% 2'f / 3'f (1:1.1)				
4	O OEt OM	OMe OH OEt	93% 2i	69% 2i / 3'i (2.3:1)				
5	O OEt	OH ODEI	86% 2k / 3k (2.1:1)	67% 2k / 3k (1:4.6)				
6	O OEt	MeO OEt OEt	87% 2l / 3l (1.1:1)	68% 2l / <i>3l</i> (1:7.5)				
7	OOELS	OH OEL	77% 2n / 3n (1:1.7)	65% 3n				

 $^{\alpha}$ Yields correspond to the sum of the NMR yields. $^{b}\overline{HCl}$ (1equiv.)/dioxane. $^{c}GaCl_{3}$ (2equiv.)/dichloromethane.

were shown to be less important, see Table S1 in the SI). Based on the key C1-C5 and C1-Cth interatomic distances, and the subsequent IRC calculations, it was discovered that 1aH+ leads to the formation of cyclopentenone 2a (pathway shown in blue), while 1'aH+ leads to the formation of benzothiophene 3a (pathway shown in red). A comparison of the two reaction pathways reveals several key observations: (i) low barriers for both pathways ($\Delta G^{\dagger}_{4\pi} = 9.45$ kcal/mol vs $\Delta G^{\ddagger_{6\pi}}$ = 9.07 kcal/mol) allow them to occur simultaneously within the full set of screened temperatures; (ii) formation of 3a occurs via a disrotatory transition state ($\Delta\Delta G^{\dagger}_{con/dis} = -5.19 \text{ kcal/mol}$), which is consistent with the Woodward-Hoffmann rules for the thermal 6π electrocyclizations; (iii) the product ratio 2a/3a (0.4:1) at -78 °C is consistent with the calculated $\Delta\Delta G^{\ddagger}_{4\pi/6\pi}$ = -0.38 kcal/mol, indicating that the reaction proceeds under kinetic control at low temperatures; (iv) the selectivity shifts in favor of 2a at higher temperatures, consistent with thermodynamic reaction control ($\Delta G_{4\pi} = -7.87 \text{ kcal/mol vs}$ $\Delta G_{6\pi}$ = +0.79 kcal/mol). Furthermore, difference between CM5 partial charges of reactive carbon atoms of 1aH+ and 1'aH+ (C1 and C5/th) is small, which is in line with an electrocyclic mechanism.10 It should be noted that all transition states were observed to be non-planar and had adopted helical conformations typical for electrocyclization reactions 11

Scheme 3. Energetic profile of divinyl ketone 1a cyclization.



In order to evaluate the impact of steric bulk and the importance of solvent polarity on chemoselectivity in cyclization of triaryl DVKs, we examined the cyclization of a reactant with a different α -substituent (Scheme 4). For this reason, substrate 4 was chosen, as our earlier studies^{5a} indicated thatsubstrates with a trimethoxyphenyl substituent in the α -position (compound **6**) cyclize to produce dihydronaphthalenes **7** (Scheme 4B). It occurred to us that cyclopentenones 5 could be important targets, given that they are isosteric structures with combretastatin A-4.5b Thus if we could selectively access the Nazarov cyclization pathway from DVK 4 (Scheme 4A), we could access potential candidates for photopharmacological research.4b

Scheme 4. Achieving chemoselectivity switch in cyclization of DVK 4.

To maximize the chemoselectivity for the 4π cyclization, 2,4,6-trimethoxyphenyl group was used as the bulky β -substituent. After the treatment with HCl in dioxane, substrate 4 produced the expected cyclopentenone 5 in a moderate yield (52%), offering evidence that chemoselectivity trends hold true across different triaryl DVK systems, and our methodology can be leveraged to synthesize attractive cyclopentenone targets.

CONCLUSION

In summary, the studies of the cyclization modes of thienyl-substituted triaryl DVKs have revealed chemodivergent behavior, which can be exploited to favor either a 4π or the 6π cationic electrocyclization pathway that we propose. Both products 2 and 3 are produced as readily separable mixtures using the Brønsted acid (HCl) in dichloromethane. Apart from this, the chemoselectivity could be shifted using different reaction conditions, either toward the 4π products 2 (using HCl in dioxane), or toward the 6π products 3 (using GaCl₃ in dichloromethane). The data also indicate that chemoselectivity is substratedependent, with the sterically more encumbered substrates showing a greater tendency for the 4π over 6π cyclization. Computational studies are consistent with experiments, showing that the 4π pathway is thermodynamically controlled, while the 6π pathway is kinetically controlled. Our work not only provides a useful strategy for the synthesis of biologically active CA-4 analogs, but also demonstrates the practical value of aryl DVKs in organic synthesis, which will expand the utility of the Nazarov reaction. Our future work will be focused on the extension of the developed methodology to different aryl DVK systems, and on gaining further insight into the divergent chemoselectivity of the $4\pi/6\pi$ electrocyclization pathways.

EXPERIMENTAL SECTION

Proton nuclear magnetic resonance spectra (¹H NMR) and carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded in deuterated solvents on a spectrometers working at 300 MHz for ¹H, 75 MHz for ¹³C. Both ¹H and ¹³C NMR reported in parts per million (ppm) at 293 K. Data are represented as follows: chemical shift, multiplicity (s, singlet; d, doublet; m, multiplet; br, broad; q, quartet), coupling constant in hertz (Hz). Melting points (m.p.) were recorded using an apparatus and not corrected. Mass spec-

tra were obtained on a mass spectrometer (70 eV) with direct sample injection into the ion source. High resolution mass spectra were obtained from a TOF mass spectrometer with an ESI source. All chemicals and anhydrous solvents were purchased from commercial sources and used without further purification. Silica column chromatography was performed using silica gel 60 (70–230 mesh); TLC analysis was conducted on silica gel 60 F254 plates. Petroleum ether boiling range: 40-70 °C. An oil bath was used for reactions requiring heating.

Divinylketone **1a-n** were prepared according previously reported method from corresponding ethyl 3-oxo-4-arylbutanoates and corresponding aldehydes, compounds **1a**, **3a** were described previously^{5a}. Hydrogen chloride was preparated *in situ* from NaCl and H₂SO₄.

General procedure for polarized divinylketones 1. To a solution of ethyl 3-oxo-4-(thiophen-2-yl)butanoate or ethyl 4-(2,5-dimethylthiophen-3-yl)-3-oxobutanoate (1.49 mmol) and corresponding aryl aldehyde (4.48 mmol) in benzene (6 ml) piperidine (0.3 ml, 0.03 mmol) and acetic acid (0.25 ml, 0.04 mmol) was added. The resulting mixture was refluxed in oil bath for 3 h with a Dean-Stark receiver. The solvent was removed in vacuum; the residue was dissolved in ethyl acetate (50 ml), washed with water (2 x 50 ml), dried over anhydrous MgSO₄ and evaporated in vacuum. The residue was purified by column chromatography eluting by petroleum ether / ethyl acetate.

(2Z,4Z)-ethyl 2-(4-methoxybenzylidene)-5-(4-methoxyphenyl)-3-oxo-4-(thiophen-2-yl)pent-4-enoate (1a)

Yield 0.327 g (49%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (3:1), darkbrown oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.74-7.78 (m, 2H), 7.42-7.45 (m, 3H), 7.05-7.10 (m, 3H), 6.83-6.87 (m, 3H), 6.73 (d, J = 8.6 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 195.9, 165.3, 161.3, 161.2, 144.8, 141.5, 135.9, 133.0, 132.1, 130.8, 129.4, 128.0, 127.4, 127.1, 126.7, 125.8, 114.3, 113.9, 61.3, 14.2.

(2Z,4Z)-ethyl 2-(3-hydroxy-4-methoxybenzylidene)-5-(3-hydroxy-4-methoxyphenyl)-3-oxo-4-(thiophen-2-yl)pent-4-enoate (1b)

Yield 0.314 g (44%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (2:1), brown oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.70 (s, 2H), 7.44 (dd, J = 5.1, 1.1 Hz, 1H), 7.09 (dd, J = 5.1, 3.5 Hz, 1H), 7.04-7.06 (m, 2H), 7.00-7.02 (m, 1H), 6.89 (dd, J = 3.5, 1.1 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 1.8 Hz, 1H), 6.71-6.72 (m, 1H), 6.64 (d, J = 1.8 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 195.9, 165.2, 148.6, 148.5, 145.6, 145.2, 145.0, 141.7, 135.6, 131.4, 129.9, 128.1, 127.6, 127.5, 127.2, 126.7, 125.0, 123.6, 116.6, 116.1, 110.7, 110.6, 110.2, 61.4, 55.9, 14.2. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₆H₂₄O₇SH: 481.1316; Found: 481.1314.

(2*Z*,4*Z*)-ethyl 3-oxo-4-(thiophen-2-yl)-2-(4-(trifluoromethyl)benzylidene)-5-(4-(trifluoromethyl)phenyl)pent-4-enoate (1c)

Yield 0.289 g (37%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (3:1), yel-

low oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.84 (s, 1H), 7.62-7.65 (m, 3H), 7.56 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.37 (dd, J = 5.0, 3.0 Hz, 1H), 7.16 (d, J = 8.3 Hz, 2H), 7.10 (dd, J = 3.0, 1.2 Hz, 1H), 6.74 (dd, J = 5.0, 1.2 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 195.1, 164.3, 140.9, 140.2, 137.7, 137.1, 136.5, 134.4, 133.6, 130.6, 130.0, 128.2, 126.4, 125.9, 125.8, 125.8, 125.7, 125.5, 125.3, 125.3, 125.2, 125.2, 62.0, 14.2. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C₂₆H₁₈F₆O₃SNa 547.0773; Found: 547.0773.

(2Z,4Z)-ethyl 2-(4-chlorobenzylidene)-5-(4-chlorophenyl)-3-oxo-4-(thiophen-2-yl)pent-4-enoate (1d)

Yield 0.288 g (43%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (3:1), orange-brown oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.76 (s, 1H), 7.68 (s, 1H), 7.43 (dd, J = 5.1, 1.1 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 7.01-7.07 (m, 3H), 6.82 (dd, J = 3.5, 1.1 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 195.1, 164.6, 143.2, 140.7, 136.6, 136.3, 134.6, 133.4, 132.4, 132.1 (2C), 131.6, 131.3 (2C), 130.1, 129.2 (2C), 128.8, 128.5 (2C), 127.7, 127.5, 61.8, 14.2. HRMS (ESI-TOF) m/z: [M+H]* Calcd for C₂₄H₁₈Cl₂O₃SH: 457.0426; Found: 457.0433.

(2Z,4Z)-ethyl 5-(3-methylthiophen-2-yl)-2-((3-methylthiophen-2-yl)methylene)-3-oxo-4-(thiophen-2-yl)pent-4-enoate (1e)

Yield 0.287 g (45%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (5:1), darkorange oil. ¹H NMR (300 MHz, CDCl₃): δ = 8.24 (s, 1H), 7.94 (s, 1H), 7.52 (d, J = 5.0 Hz, 1H), 7.37 (d, J = 5.0 Hz, 1H), 7.31 (d, J = 5.0 Hz, 1H), 7.10-7.15 (m, 1H), 6.94 (d, J = 3.4 Hz, 1H), 6.90 (d, J = 5.0 Hz, 1H), 6.85 (d, J = 5.0 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 194.6, 165.2, 145.2, 143.9, 136.3, 134.8, 132.7, 132.2, 132.0, 130.6, 130.4, 129.9, 129.8, 129.4, 128.8, 128.3, 128.0, 127.7, 61.4, 14.8, 14.4, 14.3. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C₂₂H₂₀O₃S₃Na: 451.0467; Found: 451.0466.

(2Z,4Z)-ethyl 2-(2-methoxybenzylidene)-5-(2-methoxyphenyl)-3-oxo-4-(thiophen-2-yl)pent-4-enoate (1f)

Yield 0.353 g (53%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (3:1), orange oil. $^1\mathrm{H}$ NMR (300 MHz, CDCl $_3$): δ = 8.20 (s, 1H), 8.02 (s, 1H), 7.39-7.43 (m, 1H), 7.33-7.37 (m, 1H), 7.20-7.29 (m, 2H), 6.96-7.01 (m, 1H), 6.79-6.93 (m, 5H), 6.67 (t, J = 7.7 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). $^{13}\mathrm{C}^{1}\mathrm{H}^{3}$ NMR (75 MHz, CDCl $_3$): δ = 195.5, 168.9, 165.4, 158.4, 157.5, 156.3, 139.4, 138.2, 131.6, 131.0, 130.5, 130.2, 129.3, 128.5, 127.4, 126.8, 126.3, 120.6, 120.4, 120.0, 110.8, 110.4, 61.3, 59.5, 55.3, 14.2. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C $_{26}\mathrm{H}_{24}\mathrm{O}_{5}\mathrm{SNa}$: 471.1237; Found: 471.1240.

(2Z,4Z)-ethyl 5-(2,5-dimethylthiophen-3-yl)-2-((2,5-dimethylthiophen-3-yl)methylene)-3-oxo-4-(thiophen-2-yl)pent-4-enoate (1g)

Yield 0.217 g (32%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (4:1), dark-

red oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.74 (s, 1H), 7.73 (s, 1H), 7.44 (dd, J = 5.1, 1.1 Hz, 1H), 7.09 (dd, J = 5.1, 3.5 Hz, 1H), 6.88 (dd, J = 3.5, 1.0 Hz, 1H), 6.69 (s, 1H), 5.86 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 2.22 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 196.1, 165.7, 144.6, 143.7, 137.0, 136.6, 135.9, 135.8, 133.4, 132.5, 131.0, 130.2, 128.4, 128.4, 127.1, 127.1, 125.0, 125.0, 61.3, 15.2, 15.1, 14.2, 13.6, 13.5. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₄H₂₄O₃S₃H: 457.0960; Found: 457.0953.

(2Z,4E)-ethyl 2-(2,4-dimethoxybenzylidene)-5-(2,4-dimethoxyphenyl)-4-(2,5-dimethylthiophen-3-yl)-3-oxopent-4-enoate (1h)

Yield 0.447 g (56%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (2:1), darkbrown oil. 1 H NMR (300 MHz, CDCl₃): δ = 8.19 (s, 1H), 8.05 (s, 1H), 7.41 (d, J = 8.6 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 6.34-6.40 (m, 3H), 6.24 (dd, J = 8.8, 2.4 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 2.44 (s, 3H), 1.92 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 197.3, 165.9, 162.7, 162.4, 159.9, 159.8, 138.9, 136.4, 136.1, 134.1, 132.8, 131.9, 131.4, 130.7, 129.6, 126.8, 117.0, 116.0, 105.0, 104.9, 98.2, 97.9, 61.0, 55.6, 55.6, 55.4, 55.3, 15.4, 14.2, 13.5. HRMS (ESI-TOF) m/z: [M+K] $^+$ Calcd for C₃₀H₃₂O₇SK: 575.1500; Found: 575.1500.

(2Z,4Z)-ethyl 2-(2,4-dimethoxybenzylidene)-5-(2,4-dimethoxyphenyl)-3-oxo-4-(thiophen-2-yl)pent-4-enoate (1i)

Yield 0.316 g (43%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (2:1), redorange oil. ¹H NMR (300 MHz, (CD₃)₂CO): δ = 8.10 (s, 1H), 8.07 (s, 1H), 7.53 (dd, J = 5.1, 1.1 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.07 (dd, J = 5.1, 3.5 Hz, 1H), 6.88 (dd, J = 3.5, 1.1 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.53-6.56 (m, 2H), 6.27 (dd, J = 8.8, 2.4 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 3.83-3.85 (m, 6H), 3.79 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H).¹³C{¹H} NMR (75 MHz, (CD₃)₂CO): δ = 195.2, 165.2, 163.3, 163.1, 160.4, 159.9, 138.6, 135.7, 131.1, 131.0, 130.6, 13.7, 129.6, 128.0, 127.0, 126.8, 115.7, 115.1, 106.1, 105.6, 105.4, 98.1, 97.8, 60.7, 55.4, 55.3, 55.0, 14.2. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₈H₂₈O₇SH: 509.1629; Found: 509.1621.

(2Z,4Z)-ethyl 2-benzylidene-3-oxo-5-phenyl-4-(thiophen-2-yl)pent-4-enoate (1j)

Yield 0.306 g (53%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (4:1), yellow-brown oil. H NMR (300 MHz, CDCl₃): δ = 7.86 (s, 1H), 7.77 (s, 1H), 7.46-7.49 (m, 1H), 7.41-7.45 (m, 1H), 7.36-7.40 (m, 3H), 7.32-7.34 (m, 1H), 7.19-7.25 (m, 3H), 7.10-7.14 (m, 2H), 7.04-7.09 (m, 1H), 6.86 (d, J = 3.4 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 195.6, 164.9, 135.1, 134.1, 133.3, 133.2, 130.9 (2C), 130.4, 130.1 (2C), 130.1, 129.8, 129.0, 128.9 (2C), 128.7, 128.7, 128.4 (2C), 127.4, 127.3, 61.6, 14.2. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₄H₂₀O₃SH: 389.1206; Found: 389.1192.

(2*Z*,4*E*)-ethyl 4-(2,5-dimethylthiophen-3-yl)-5-(3-methylthiophen-2-yl)-2-((3-methylthiophen-2-yl)methylene)-3-oxopent-4-enoate (1k)

Yield 0.299 g (44%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (3:1), darkbrown oil. ¹H NMR (300 MHz, CDCl₃): δ = 8.06 (s, 1H), 8.02 (s, 1H), 7.36 (d, J = 5.1 Hz, 1H), 7.31 (d, J = 5.1 Hz, 1H), 6.90 (d, J = 5.1 Hz, 1H), 6.83 (d, J = 5.1 Hz, 1H), 6.41 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.48 (s, 3H), 2.43 (s, 3H), 2.32 (s, 3H), 2.16 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 195.2, 165.5, 143.8, 143.7, 137.6, 137.5, 136.6, 135.3, 132.8, 132.3, 131.7, 130.5, 130.4, 130.3, 129.8, 129.8, 128.0, 125.9, 61.4, 15.4, 14.7, 14.5, 14.3, 13.5. HRMS (ESI-TOF) m/z: [M+K]⁺ Calcd for C₂₄H₂₄O₃S₃K 495.0519; Found: 495.0514.

(2Z,4E)-ethyl 4-(2,5-dimethylthiophen-3-yl)-2-(4-methoxybenzylidene)-5-(4-methoxyphenyl)-3-oxopent-4-enoate (1l)

Yield 0.454 g (64%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (3:1), brown oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.81 (s, 1H), 7.63 (s, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 6.40 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 2.47 (s, 3H), 2.00 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 13 C{¹H} NMR (75 MHz, CDCl₃): δ = 196.8, 165.5, 161.3, 161.0, 144.3, 141.2, 136.8, 134.4, 133.3, 132.5 (2C), 132.2 (2C), 131.3, 129.7, 127.4, 126.4, 126.0, 114.2 (2C), 114.0 (2C), 61.3, 55.3, 55.3, 15.4, 14.2, 13.5. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₈H₂₈O₅SH: 477.1730; Found: 477.1714.

(2Z,4Z)-ethyl 3-oxo-4,5-di(thiophen-2-yl)-2-(thiophen-2-ylmethylene)pent-4-enoate (1m)

Yield 0.232 g (39%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (4:1), orange crystals (m.p. = 68 °C). ¹H NMR (300 MHz, CDCl₃): δ = 8.11 (s, 1H), 7.88 (s, 1H), 7.54 (d, J = 5.0 Hz, 1H), 7.48 (d, J = 5.0 Hz, 1H), 7.41 (d, J = 5.0 Hz, 1H), 7.33 (d, J = 3.5 Hz, 1H), 7.28-7.30 (m, 1H), 7.14-7.16 (m, 1H), 7.06-7.09 (m, 1H), 6.99-7.02 (m, 1H), 6.96 (d, J = 3.3 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 194.3, 164.8, 138.4, 138.4, 136.5, 135.6, 134.4, 134.1, 133.7, 133.2, 131.3, 129.8, 129.1, 128.9, 128.3, 127.9, 127.8, 61.5, 14.2. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₀H₁₆O₃S₃H :401.0334; Found: 401.0331.

(2Z,4E)-ethyl 4-(2,5-dimethylthiophen-3-yl)-3-oxo-5-(thiophen-2-yl)-2-(thiophen-2-ylmethylene)pent-4-enoate (1n)

Yield 0.268 g (42%), purified by column chromatography by eluting with petroleum ether/ethyl acetate (3:1), brown oil. ^1H NMR (300 MHz, CDCl₃): δ = 7.98 (s, 1H), 7.93 (s, 1H), 7.48 (d, J = 5.0 Hz, 1H), 7.41 (d, J = 5.0 Hz, 1H), 7.36 (d, J = 3.5 Hz, 1H), 7.24 (d, J = 3.5 Hz, 1H), 7.07 (dd, J = 5.0, 3.5 Hz, 1H), 7.00 (dd, J = 5.0, 3.5 Hz, 1H), 6.42 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 2.17 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). $^{13}\text{C}^{1}\text{H}^{1}$ NMR (75 MHz, CDCl₃): δ = 194.9, 165.1, 138.7, 137.8, 137.4, 136.6, 136.5, 134.5, 134.1, 133.8, 132.9, 132.7, 131.3, 130.2, 128.9, 127.8, 127.0, 125.7, 61.5, 15.4, 14.2, 13.5. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for $\text{C}_{22}\text{H}_{20}\text{O}_{3}\text{S}_{3}\text{Na}$: 451.0467; Found: 451.0466.

General procedure for cycliczation of compounds 1. Anhydrous dichloromethane (4 ml) was saturated by dry hydrogen chloride for 1 minute (0.2M HCl solution in dichloromethane) then divinyl ketone 1 (0.4 mmol) was dis-

solved in solution of HCl/DCM. After the reaction was complete (TLC control), the reaction mixture was poured into water (50 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic phases were washed with water (50 ml), dried over anhydrous MgSO $_4$ and evaporated in vacuum. The residue was purified by column chromatography eluting by petroleum ether / ethyl acetate.

Cyclization of compound 1c. A solution of (2*Z*,4*Z*)-ethyl 3-oxo-4-(thiophen-2-yl)-2-(4-

(trifluoromethyl)benzylidene)-5-(4-

(trifluoromethyl)phenyl)pent-4-enoate (0.209 g, 0.4 mmol) in anhydrous dichloromethane (4 ml) was treated with SnCl₄ (0.046 ml, 0.4 mmol) and was stirred at room temperature. After the reaction was complete (TLC control), the mixture was poured into ice water (75 ml) and extracted with dichloromethane (2 × 30 ml); the combined organic layers were washed with 5% (w/w) NaHCO₃ solution (2×75 ml), water, then dried over anhydrous MgSO₄, and evaporated in vacuum. The residue was purified by column chromatography eluting by petroleum ether / ethyl acetate (8/1).

Ethyl 2,3-bis(4-methoxyphenyl)-5-oxo-4-(thiophen-2-yl)cyclopent-3-enecarboxylate (2a)

Yield 0.082 g (46%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), brown powder (m.p. = 72-73 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.31-7.34 (m, 2H), 7.21 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.00 (dd, J = 5.1, 3.7 Hz, 1H), 6.76-6.80 (m, 4H), 4.82 (d, J = 2.8 Hz, 1H), 4.23-4.34 (m, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.62 (d, J = 2.8 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H). 13 C{¹H} NMR (75 MHz, CDCl₃): δ = 198.6, 169.6, 168.3, 160.7, 158.7, 132.2, 132.0, 130.8, 130.2 (2C), 128.9 (2C), 128.4, 126.8, 126.8, 126.7, 114.4 (2C), 113.9 (2C), 62.2, 61.9, 55.2, 55.2, 51.2, 14.2. HRMS (ESI-TOF) m/z: [M+K]⁺ Calcd for C₂₆H₂₄O₅SK: 487.0976; Found: 487.0971.

Ethyl 2,3-bis(3-hydroxy-4-methoxyphenyl)-5-oxo-4-(thiophen-2-yl)cyclopent-3-enecarboxylate (2b)

Yield 0.057 g (30%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (5:1), dark-red powder (m.p. = 76-77 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.34 (d, J = 3.6 Hz, 1H), 7.31 (d, J = 4.7 Hz, 1H), 6.99 (dd, J = 4.7, 3.6 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H), 6.82 (dd, J = 8.4, 1.8 Hz, 1H), 6.73-6.74 (m, 1H), 6.69-6.71 (m, 2H), 6.63 (dd, J = 8.3, 1.6 Hz, 1H), 4.73(d, J = 2.6 Hz, 1H), 4.21-4.31 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.59 (d, J = 2.7 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 198.6, 176.3, 169.3, 168.3, 147.7, 145.9, 145.8, 145.4, 133.4, 131.8, 128.5, 127.6, 126.9, 126.6, 121.1, 119.5, 114.7, 113.8, 111.0, 110.4, 62.1, 61.9, 55.9, 55.8, 51.5, 14.2. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C₂₆H₂₄O₇SNa: 503.1135; Found: 503.1134.

Ethyl 2-oxo-3-(thiophen-2-yl)-4,5-bis(4-(trifluoromethyl)phenyl)cyclopent-3-enecarboxylate (2c)

Yield 0.079 g (38%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), paleyellow powder (m.p. = 89-90 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.74 (dd, J = 3.0, 1.2 Hz, 1H), 7.54 (d, J = 8.1 Hz, 4H), 7.35 (d, J = 8.1 Hz, 2H), 7.23-7.28 (m, 3H), 6.80 (dd, J =

5.1, 1.2 Hz, 1H), 5.02 (d, J = 3.0 Hz, 1H), 4.25-4.37 (m, 2H), 3.64 (d, J = 3.0 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl $_{3}$): δ = 198.4, 167.5, 165.7, 147.3, 147.0, 143.7, 143.7, 138.1, 134.7, 129.7, 128.9, 128.6, 128.2, 127.4, 127.3, 126.3, 126.3, 126.2, 126.2, 125.8, 125.7, 125.7, 125.6, 125.4, 62.3, 61.9, 51.1, 14.2. HRMS (ESI-TOF) m/z: [M+NH₄]⁺ Calcd for C₂₆H₁₈F₆O₃SNH₄: 542.1219; Found: 542.1211.

Ethyl 2,3-bis(4-chlorophenyl)-5-oxo-4-(thiophen-2-yl)cyclopent-3-enecarboxylate (2d)

Yield 0.093 g (55%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), graybrown powder (m.p. = 119-120 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.33-7.36 (m, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.99-7.02 (m, 1H), 4.82 (d, J = 2.9 Hz, 1H), 4.25-4.32 (m, 2H), 3.64 (d, J = 2.9 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H),. 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 197.9, 167.7, 166.8, 137.9, 135.8, 133.5, 132.9, 132.3, 130.9, 129.5 (2C), 129.3 (2C), 129.2 (2C), 129.1 (2C), 128.9, 127.6, 126.8, 62.2, 61.7, 51.5, 14.2. HRMS (ESI-TOF) m/z: [M+H]* Calcd for $C_{24}H_{18}$ Cl₂O₃SH: 457.0426; Found: 457.0411.

Ethyl 2,3-bis(3-methylthiophen-2-yl)-5-oxo-4-(thiophen-2-yl)cyclopent-3-enecarboxylate (2e)

Yield 0.101 g (59%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (10:1), darkbrown powder (m.p. = 82-83 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.48 (d, J = 3.5 Hz, 1H), 7.38 (d, J = 4.9 Hz, 1H), 7.34 (d, J = 5.0 Hz, 1H), 7.11 (d, J = 5.0 Hz, 1H), 7.00-7.03 (m, 1H), 6.83 (d, J = 5.0 Hz, 1H), 6.76 (d, J = 5.0 Hz, 1H), 5.06 (d, J = 2.7 Hz, 1H), 4.26-4.32 (m, 2H), 3.77 (d, J = 2.8 Hz, 1H), 2.19 (s, 3H), 1.90 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H). 13 C{¹H} NMR (75 MHz, CDCl₃): δ = 197.4, 167.8, 161.6, 138.3, 136.2, 136.1, 132.1, 131.6, 130.6, 130.2, 128.6, 128.3, 128.2, 127.7, 126.7, 123.6, 62.1, 61.9, 46.5, 15.2, 14.2, 13.8. HRMS (ESI-TOF) m/z: [M+K]+ Calcd for C₂₂H₂₀O₃S₃K: 467.0206; Found: 467.0206.

3,4-bis(2-methoxyphenyl)-2-(thiophen-2-yl)cyclopent-2-enone (2'f)

Yield 0.087 g (58%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), orange powder (m.p. = 65-66 °C). 1 H NMR (300 MHz, CDCl₃): δ = 7.37 (d, J = 3.7 Hz, 1H), 7.26-7.28 (m, 1H), 7.22 (d, J = 5.4 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 6.93-6.96 (m, 1H), 6.89-6.91 (m, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.83-6.78 (m, 2H), 6.74 (d, J = 8.2 Hz, 1H), 4.89-4.91 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.15 (dd, J = 18.8, 7.3 Hz, 1H), 2.78 (dd, J = 18.8, 2.4 Hz, 1H). 13 C 1 H} NMR (75 MHz, CDCl₃): δ = 206.4, 168.6, 157.4, 156.2, 133.5, 133.1, 132.5, 130.1, 129.1, 129.1, 128.0, 127.0, 126.3, 126.0, 125.1, 120.5, 120.4, 111.0, 110.6, 55.4, 55.3, 43.5, 43.1. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C₂₃H₂₀O₃SNa: 399.1025; Found: 399.1025.

Ethyl 2,3-bis(2,5-dimethylthiophen-3-yl)-5-oxo-4-(thiophen-2-yl)cyclopent-3-enecarboxylate (2g)

Yield 0.118 g (67%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (8:1), darkbrown powder (m.p. = 95-96 °C). 1 H NMR (300 MHz, CDCl₃): δ = 7.52 (d, J = 3.6 Hz, 1H), 7.28-7.29 (m, 1H), 6.98-7.01 (m, 1H), 6.29 (s, 1H), 6.18 (s, 1H), 4.62 (d, J = 2.5 Hz,

1H), 4.23-4.31 (m, 2H), 3.67 (d, J = 2.5 Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H), 1.99 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 198.7, 168.3, 166.4, 137.6, 136.5, 135.6, 134.0, 133.3, 132.1, 131.9, 131.2, 127.8, 127.0, 126.6, 124.1, 123.6, 62.0, 60.3, 46.0, 15.2, 15.2, 14.2, 13.8, 12.6. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₄H₂₄O₃S₃H: 457.0960; Found: 457.0958.

Ethyl 2,3-bis(2,4-dimethoxyphenyl)-4-(2,5-dimethylthiophen-3-yl)-5-oxocyclopent-3-enecarboxylate (2h)

Yield 0.111 g (52%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (4:1), brown powder (m.p. = 84-85 °C). ¹H NMR (300 MHz, CDCl₃): δ = 6.94 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.47 (s, 1H), 6.24-6.30 (m, 4H), 5.28 (d, J = 3.2 Hz, 1H), 4.18-4.33 (m, 2H), 3.71-3.73 (m, 6H), 3.65-3.67 (m, 4H), 3.61 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 200.2, 169.6, 161.7, 159.9, 158.4, 158.0, 135.2, 134.8, 130.9, 130.5, 130.4, 130.3, 128.9, 126.7, 121.0, 117.3, 104.5, 103.9, 98.4, 98.2, 61.2 (2C), 60.0, 55.2 (2C), 55.0, 55.0, 15.2, 14.3, 14.0. HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₃0H₃₂OγSH: 537.1942; Found: 537.1940.

Ethyl 2,3-bis(2,4-dimethoxyphenyl)-5-oxo-4-(thiophen-2-yl)cyclopent-3-enecarboxylate (2i)

Yield 0.164 g (81%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (5:1), brown powder (m.p. = 70-71 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.38 (d, J = 3.4 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 7.01 (d, J = 9.1 Hz, 1H), 6.93-6.96 (m, 2H), 6.36-6.38 (m, 2H), 6.28-6.30 (m, 2H), 5.11 (d, J = 3.4 Hz, 1H), 4.20-4.33 (m, 2H), 3.75-3.78 (m, 4H), 3.73 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). 13 C{¹H} NMR (75 MHz, CDCl₃): δ = 199.3, 169.2, 169.0, 162.0, 160.0, 158.4, 157.8, 133.2, 130.9, 130.5, 130.4, 127.3, 126.3, 125.9, 120.2, 116.9, 104.7, 103.9, 98.6, 98.4, 61.4, 60.4, 59.9, 55.3, 55.2, 55.2, 55.1, 14.3. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₈H₂₈O₇SH: 509.1629; Found: 509.1627.

Ethyl 2-oxo-4,5-diphenyl-3-(thiophen-2-yl)cyclopent-3-enecarboxylate (2j)

Yield 0.057 g (37%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (7:1), brown powder (m.p. = 61-62 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.37 (d, J = 3.6 Hz, 1H), 7.26-7.31 (m, 5H), 7.19-7.24 (m, 4H), 7.13-7.18 (m, 2H), 6.95-7.00 (m, 1H), 4.87 (d, J = 2.8 Hz, 1H), 4.24-4.36 (m, 2H), 3.74 (d, J = 2.8 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 198.7, 169.4, 168.1, 139.4, 135.0, 131.7, 131.5, 129.5, 129.0 (2C), 128.6 (2C), 128.5, 128.0 (4C), 127.5, 127.2, 126.6, 62.0, 61.9, 52.6, 14.2. HRMS (ESI-TOF) m/z: [M-H]+ Calcd for C₂₄H₂₀O₃SH: 387.1049; Found: 387.1048.

Ethyl 3-(2,5-dimethylthiophen-3-yl)-4,5-bis(3-methylthiophen-2-yl)-2-oxocyclopent-3-enecarboxylate (2k)

Yield 0.051 g (28%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), redbrown powder (m.p. = 81-82 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.30 (d, J = 5.1 Hz, 1H), 7.09 (d, J = 5.1 Hz, 1H), 6.78 (d, J = 5.1 Hz, 1H), 6.73 (d, J = 5.1 Hz, 1H), 6.52 (s, 1H), 5.15 (d, J = 2.5 Hz, 1H), 4.23-4.35 (m, 2H), 3.64 (d, J = 2.5 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H), 1.98 (s, 3H), 1.72 (s, 3H),

1.34 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl $_{3}$): δ = 198.3, 168.1, 163.8, 139.7, 137.3, 136.7, 136.1, 135.6, 134.6, 131.9, 130.9, 130.1, 128.5, 127.9, 126.4, 123.6, 61.9, 46.1, 15.5, 15.2, 14.3, 14.2, 14.2, 13.9. HRMS (ESI-TOF) m/z: [M+H] $^{+}$ Calcd for C $_{24}$ H $_{24}$ O $_{3}$ S $_{3}$ H: 457.0960; Found: 457.0970.

Ethyl 3-(2,5-dimethylthiophen-3-yl)-4,5-bis(4-methoxyphenyl)-2-oxocyclopent-3-enecarboxylate (21)

Yield 0.030 g (16%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (5:1), redbrown powder (m.p. = 56-57 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.25 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.51 (s, 1H), 4.96 (d, J = 2.4 Hz, 1H), 4.22-4.31 (m, 2H), 3.74-3.76 (m, 6H), 3.50 (d, J = 2.4 Hz, 1H), 2.42 (s, 3H), 2.03 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 199.5, 169.2, 168.6, 160.8, 158.6, 136.6, 135.3, 133.6, 133.5, 130.7 (2C), 128.5 (2C), 128.4, 126.6, 126.4, 114.5 (2C), 113.7 (2C), 62.4, 61.8, 55.2, 55.2, 49.7, 15.3, 14.2, 14.1. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C₂₈H₂₈O₅SNa: 499.1550; Found: 499.1554.

Ethyl 2-oxo-3,4,5-tri(thiophen-2-yl)cyclopent-3-enecarboxylate (2m)

Yield 0.027 g (17%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (9:1), darkbrown powder (m.p. = 59-60 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.53 (dd, J = 5.1, 1.1 Hz, 1H), 7.43 (dd, J = 5.0, 1.0 Hz, 1H), 7.36 (dd, J = 3.8, 1.0 Hz, 1H), 7.29 (dd, J = 3.6, 1.1 Hz, 1H), 7.23 (dd, J = 5.1, 1.0 Hz, 1H), 7.16 (dd, J = 5.1, 3.6 Hz, 1H), 7.00-7.02 (m, 1H), 6.95-6.98 (m, 2H), 5.25 (d, J = 2.5 Hz, 1H), 4.30 (q, J = 7.1 Hz, 1H), 3.72 (d, J = 2.5 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H). 13 C{¹H} NMR (75 MHz, CDCl₃): δ = 196.9, 167.7, 161.9, 144.3, 136.2, 132.1, 131.7, 130.9, 130.2, 129.3, 128.3, 127.4, 127.3, 127.2, 125.9, 125.2, 62.3, 62.2, 46.4, 14.2. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₀H₁₆O₃S₃H: 401.0334; Found: 401.0328.

Ethyl 3-(2,5-dimethylthiophen-3-yl)-2-oxo-4,5-di(thiophen-2-yl)cyclopent-3-enecarboxylate (2n)

Yield 0.018 g (11%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), brown powder (m.p. = 62-63 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.52 (br, 2H), 7.28-7.30 (m, 1H), 7.11 (d, J = 3.5 Hz, 1H), 7.03 (dd, J = 5.1, 3.5 Hz, 1H), 4.40 (d, J = 12.5 Hz, 1H), 4.10 (qd, J = 7.1, 2.5 Hz, 2H), 3.89 (d, J = 12.5 Hz, 1H), 2.29 (s, 3H), 1.66 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 193.1, 178.3, 168.6, 162.7, 158.8, 139.5, 128.9, 128.6, 128.5, 126.9, 126.5, 125.2, 124.8, 120.0, 119.2, 115.8, 61.7, 56.6, 48.2, 25.8, 18.4, 13.8. HRMS (ESITOF) m/z: [M+H]+ Calcd for C₂2H₂0O₃S₃H: 429.0647; Found: 429.0647.

(*Z*)-ethyl 6-hydroxy-7-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-4,7-dihydrobenzo[b]thiophene-5-carboxylate (3a)

Yield 0.069 g (39%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), yellow oil. H NMR (300 MHz, CDCl₃): δ = 12.95 (s, 1H), 7.63 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 5.2 Hz, 1H), 6.81 (d, J = 8.6 Hz, 2H), 6.64 (d, J = 5.2 Hz, 1H), 5.04 (s, 1H), 4.18 (q, J = 7.1 Hz,

2H), 3.88 (s, 3H), 3.78 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): $\delta = 172.5$, 164.2, 159.7, 158.0, 141.2, 136.5, 130.6 (2C), 129.8, 128.8 (2C), 128.7, 127.6, 126.2, 125.6, 125.1, 114.0 (2C), 113.7 (2C), 101.7, 60.8, 55.3, 55.2, 42.6, 14.0. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₆H₂₄O₅SH: 449.1398; Found: 449.1417.

Ethyl 6-hydroxy-7-(3-hydroxy-4-methoxybenzyl)-4-(3-hydroxy-4-methoxyphenyl)benzo[b]thiophene-5-carboxylate (3'b)

Yield 0.045 g (24%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (5:1), dark-orange powder (m.p. = 60-61 °C).¹H NMR (300 MHz, CDCl₃): δ = 11.03, 7.11 (d, J = 5.6 Hz, 1H), 7.02 (d, J = 1.7 Hz, 1H), 6.96 (d, J = 1.7 Hz, 1H), 6.87-6.93 (m, 3H), 6.78 (d, J = 8.2 Hz, 1H), 6.72 (dd, J = 8.2, 1.7 Hz, 1H), 5.68 (br, 1H), 5.56 (br, 1H), 4.23 (s, 2H), 4.00-4.06 (m, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 0.85 (t, J = 7.1 Hz, 3H).¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 171.7, 154.5, 145.9, 145.8, 145.4, 145.1, 138.0, 134.6, 133.1, 132.7, 125.2, 123.5, 121.0, 120.6, 120.4, 116.3, 115.5, 115.1, 111.2, 110.5, 110.0, 61.1, 56.2, 55.9, 34.1, 13.2. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂6H₂4OγSH: 481.1316; Found: 481.1305.

Ethyl 6-hydroxy-7-(4-(trifluoromethyl)benzyl)-4-(4-(trifluoromethyl)phenyl)benzo[b]thiophene-5-carboxylate (3'c)

Yield 0.061 g (28%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), yellow powder (m.p. = 94-95 °C).¹H NMR (300 MHz, CDCl₃): δ = 11.39 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.53-7.59 (m, 4H), 7.40 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 5.6 Hz, 2H), 6.74 (d, J = 5.6 Hz, 2H), 4.39 (s, 2H), 4.01 (q, J = 7.1 Hz, 2H), 0.73 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 171.1, 155.1, 146.3, 145.0, 143.2, 137.1, 131.7, 129.1, 129.0, 126.4, 125.3, 125.2, 124.8, 124.7, 124.7, 124.3, 120.8, 110.4, 105.9, 93.5, 91.3, 61.5, 34.7, 12.7. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C₂₆H₁₈F₆O₃SNa: 547.0773; Found: 547.0779.

Ethyl 7-(4-chlorobenzyl)-4-(4-chlorophenyl)-6-hydroxybenzo[b]thiophene-5-carboxylate (3'd)

Yield 0.064 g (35%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), pale-orange powder (m.p. = 90-91 °C).¹H NMR (300 MHz, CDCl₃): δ = 11.29 (s, 1H, OH), 7.43 (d, J = 8.3 Hz, 2H, Harom), 7.39 (d, J = 8.4 Hz, 2H, Harom), 7.25 (d, J = 8.4 Hz, 2H, Harom), 7.21 (d, J = 8.3 Hz, 2H, Harom), 7.16 (d, J = 5.6 Hz, 1H, Hthiophene), 6.80 (d, J = 5.6 Hz, 1H, Hthiophene), 4.29 (s, 2H, CH₂), 4.05 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 0.84 (t, J = 7.1 Hz, 3H, OCH₂CH₃). 13 C{ 14 H} NMR (75 MHz, CDCl₃): δ = 171.4, 154.9, 146.1, 139.7, 137.7, 137.2, 133.0, 132.9, 132.0, 130.2 (2C), 130.1 (2C), 128.4 (2C), 127.9 (2C), 124.8, 124.0, 121.0, 110.7, 61.4, 34.2, 13.0. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂4H18Cl₂O₃SH: 457.0426; Found: 457.0414.

Ethyl 6-hydroxy-4-(3-methylthiophen-2-yl)-7-((3-methylthiophen-2-yl)methyl)benzo[b]thiophene-5-carboxylate (3'e)

Yield 0.044 g (26%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (10:1), darkbrown powder (m.p. = 96-97 °C). 1 H NMR (300 MHz, CDCl₃): δ = 11.32 (s, 1H), 7.30 (d, J = 5.1 Hz, 1H), 7.18 (d, J = 5.6 Hz, 1H), 7.05 (d, J = 5.1 Hz, 1H), 6.94 (d, J = 5.1 Hz, 1H),

6.90 (d, J = 5.6 Hz, 1H), 6.83 (d, J = 5.1 Hz, 1H), 4.43 (s, 2H), 4.12 (qd, J = 7.1 Hz, 2.8 Hz, 2H), 2.40 (s, 3H), 1.98 (s, 3H), 0.96 (t, J = 7.1 Hz, 3H).¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 171.4, 155.0, 145.5, 135.5, 135.0, 134.5, 134.2, 129.7, 128.9, 128.1, 124.9, 124.5, 123.7, 122.1, 121.7, 112.5, 61.4, 27.3, 14.1, 14.1, 13.2. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₂H₂₀O₃S₃H: 429.0647; Found: 429.0631.

Ethyl 6-hydroxy-7-(2-methoxybenzyl)-4-(2-methoxyphenyl)benzo[b]thiophene-5-carboxylate (3'f)

Yield 0.040 g (23%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), palebrown powder (m.p. = 70-71 °C). ¹H NMR (300 MHz, CDCl₃): δ = 11.10, 7.36-7.42 (m, 1H), 7.17-7.24 (m, 2H), 7.02-7.10 (m, 3H), 6.98 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 7.4 Hz, 1H), 6.81 (d, J = 5.6 Hz, 1H), 4.40 (d, J = 16.0 Hz, 1H), 4.32 (d, J = 16.0 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 3.72 (s, 3H), 0.80 (t, J = 7.1 Hz, 3H).¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 171.6, 157.5, 156.5, 155.2, 146.7, 134.5, 132.9, 130.3, 130.2, 129.1, 128.5, 127.2, 127.1, 124.9, 123.6, 120.4, 120.2, 120.1, 111.6, 110.4, 110.1, 60.9, 55.5, 55.4, 28.4, 13.0. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₆H₂₄O₅SH: 449.1417; Found: 449.1409

Ethyl 4-(2,5-dimethylthiophen-3-yl)-7-((2,5-dimethylthiophen-3-yl)methyl)-6-hydroxybenzo[b]thiophene-5-carboxylate (3'g)

Yield 0.017 g (10%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (8:1), darkbrown oil. H NMR (300 MHz, CDCl₃): δ = 11.23 (s, 1H), 7.14 (d, J = 5.6 Hz, 1H), 6.88 (d, J = 5.6 Hz, 1H), 6.55 (s, 1H), 6.48 (s, 1H), 4.10-4.17 (m, 4H), 2.54 (s, 3H), 2.47 (s, 3H), 2.33 (s, 3H), 2.07 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 171.8, 154.9, 145.7, 136.9, 134.9, 134.7, 133.8, 133.3, 133.2, 131.6, 131.4, 127.4, 127.3, 125.1, 123.8, 120.8, 111.4, 61.2, 27.6, 15.2, 15.1, 14.1, 13.5, 13.2. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₄H₂₄O₃S₃H: 457.0960; Found: 457.0954.

(*E/Z*)-ethyl 7-(2,4-dimethoxybenzylidene)-4-(2,4-dimethoxyphenyl)-6-hydroxy-1,3-dimethyl-4,7-dihydrobenzo[c]thiophene-5-carboxylate (3h)

Yield 0.017 g (8%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (4:1), orange powder (m.p. = 145-148 °C) (mixture of E/Z isomers). H NMR (300 MHz, CDCl₃): δ = 12.81; 12.50 (s, 1H), 7.83; 7.56 (s, 1H), 7.42-7.47; 7.35-7.37 (m, 1H), 7.28-7.31; 6.86 (m, d, J = 8.4 Hz, 1H), 6.34-6.52 (m, 4H), 5.48; 5.45 (s, 1H), 4.14-4.20 (m, 2H), 3.86-3.90 (m, 6H), 3.83 (s, 3H), 3.76; 3.72 (s, 3H), 2.64; 2.35 (s, 3H), 1.85; 1.73 (s, 3H), 1.23-1.28 (m, 3H).¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 174.7, 172.7, 170.4, 169.2, 160.8, 160.1, 159.0, 158.0, 157.0, 137.1, 131.3, 131.1, 131.1, 129.7, 129.4, 129.3, 128.7, 128.6, 127.6, 127.5, 127.0, 126.4, 125.4, 123.8, 120.2, 119.7, 119.0, 118.2, 105.0, 104.7, 104.5, 104.1, 103.4, 101.4, 98.6, 98.3, 98.1, 98.0, 60.9, 60.5, 58.6, 55.5, 55.4, 55.2, 32.9, 32.0, 16.0, 14.1, 14.1, 13.9, 12.8, 12.7. HRMS (ESI-TOF) m/z: [M+K]+ Calcd for C₃₀H₃₂O₇SK: 575.1510: Found: 575.1500.

Ethyl 7-(2,4-dimethoxybenzyl)-4-(2,4-dimethoxyphenyl)-6-hydroxybenzo[b]thiophene-5-carboxylate (3'i)

Yield 0.016 g (8%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (5:1), beige powder (m.p. = 135-136 °C).¹H NMR (300 MHz, CDCl₃): δ = 10.99 (s, 1H), 7.06-7.09 (m, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 5.6 Hz, 1H), 6.56-6.59 (m, 2H), 6.51 (d, J = 2.3 Hz, 1H), 6.36 (dd, J = 8.4, 2.3 Hz, 1H), 4.29 (d, J = 15.8 Hz, 1H), 4.21 (d, J = 15.8 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.78 (s, 3H), 3.69 (s, 3H), 0.87 (t, J = 7.1 Hz, 3H).¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 171.8, 160.4, 159.3, 158.4, 157.5, 154.9, 146.5, 134.1, 133.3, 130.5, 129.4, 124.9, 123.5, 123.0, 120.3, 119.5, 112.0, 103.9, 103.7, 98.4, 98.3, 60.9, 55.5, 55.5, 55.4, 55.3, 27.9, 13.3. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for $C_{28}H_{28}O_7SNa$: 531.1448; Found: 531.1447.

Ethyl 7-benzyl-6-hydroxy-4-phenylbenzo[b]thiophene-5-carboxylate (3'j)

Yield 0.069 g (45%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (7:1), red oil. 1 H NMR (300 MHz, CDCl₃): δ = 11.20 (s, 1H), 7.42-7.50 (m, 4H), 7.23-7.31 (m, 6H), 7.13 (d, J = 5.4 Hz, 1H), 6.84 (d, J = 5.4 Hz, 1H), 4.37 (s, 2H), 4.01 (q, J = 6.9 Hz, 2H), 0.76 (t, J = 6.9 Hz, 3H), $.^{13}$ C{ 1 H} NMR (75 MHz, CDCl₃): δ = 171.7, 154.8, 146.1, 141.3, 139.4, 138.5, 133.0, 128.9 (2C), 128.7 (2C), 128.3 (2C), 127.7 (2C), 126.9, 126.2, 125.1, 123.7, 121.0, 110.9, 61.1, 34.9, 12.9. HRMS (ESI-TOF) m/z: [M+H] $^+$ Calcd for C₂₄H₂₀O₃SH: 389.1206; Found: 389.1205.

(*E*)-ethyl 6-hydroxy-1,3-dimethyl-4-(3-methylthiophen-2-yl)-7-((3-methylthiophen-2-yl)methylene)-4,7-dihydrobenzo[c]thiophene-5-carboxylate (3k)

Yield 0.067 g (37%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), yellow-orange powder (m.p. = 136-137 °C).¹H NMR (300 MHz, acetone-d6): δ = 12.87 (s, 1H), 7.48 (s, 1H), 7.39 (d, J = 5.1 Hz, 1H), 7.08 (d, J = 5.2 Hz, 1H), 6.94 (d, J = 5.1 Hz, 1H), 6.70 (d, J = 5.2 Hz, 1H), 5.44 (s, 1H), 4.23-4.35 (m, 2H), 2.49 (s, 3H), 2.33-2.34 (m, 6H), 1.94 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 172.1, 169.9, 142.4, 139.9, 136.8, 134.2, 133.3, 131.4, 129.6, 129.0, 128.9, 126.6, 126.1, 122.9, 122.4, 121.6, 102.2, 60.9, 33.8, 15.9, 14.9, 14.4, 14.3, 12.9. HRMS (ESI-TOF) m/z: [M+NH₄]⁺ Calcd for C₂₄H₂₄O₃S₃NH₄: 474.1226; Found: 474.1224.

(*E*)-ethyl 6-hydroxy-7-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-1,3-dimethyl-4,7-dihydrobenzo[c]thiophene-5-carboxylate (31)

Yield 0.106 g (56%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (5:1), palebrown powder (m.p. = 151-152 °C).¹H NMR (300 MHz, CDCl₃): δ = 12.81 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.40 (s, 1H), 7.27 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.96 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 2.35 (s, 3H), 1.81 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 172.3, 170.1, 159.2, 157.9, 136.8, 136.7, 131.7, 130.8, 130.4, 129.9, 128.6, 128.6 (2C), 128.5 (2C), 126.4, 114.0 (2C), 113.8 (2C), 101.7, 60.8, 55.3, 55.2, 39.9, 16.2, 14.3, 12.8. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂8H₂8O₅SH: 477.1730; Found: 477.1731.

(Z)-ethyl 6-hydroxy-4-(thiophen-2-yl)-7-(thiophen-2-ylmethylene)-4,7-dihydrobenzo[b]thiophene-5-carboxylate (3m)

Yield 0.099 g (62%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (9:1), redbrown oil.¹H NMR (300 MHz, CDCl₃): δ = 12.91 (s, 1H), 7.54 (s, 1H), 7.48 (d, J = 5.0 Hz, 1H), 7.34 (d, J = 3.3 Hz, 1H), 7.07-7.12 (m, 3H), 6.86-6.89 (m, 2H), 6.84 (d, J = 5.2 Hz, 1H), 5.44 (s, 1H), 4.21-4.32 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H).¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 172.2, 164.1, 148.2, 140.8, 137.8, 129.9, 128.7, 127.7, 127.5, 126.5, 126.4, 126.1, 124.0, 123.9, 123.6, 120.3, 101.7, 61.1, 37.8, 14.0. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂0H₁6O₃S₃H: 401.0334; Found: 401.0324.

(*E*)-ethyl 6-hydroxy-1,3-dimethyl-4-(thiophen-2-yl)-7-(thiophen-2-ylmethylene)-4,7-dihydrobenzo[c]thiophene-5-carboxylate (3n)

Yield 0.087 g (51%); purified by column chromatography by eluting with petroleum ether/ethyl acetate (6:1), yellow powder (m.p. = 130-131 °C). ¹H NMR (300 MHz, CDCl₃): δ = 12.70 (s, 1H), 7.40 (s, 1H), 7.31 (d, J = 4.9 Hz, 1H), 7.21 (d, J = 3.5 Hz, 1H), 7.05 (dd, J = 4.9, 1.4 Hz, 1H), 7.00-7.03 (m, 1H), 6.82-6.85 (m, 2H), 5.33 (s, 1H), 4.36 (qd, J = 7.1, 3.8 Hz, 2H), 2.40 (s, 3H), 2.04 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ¹³C{ ¹H} NMR (75 MHz, CDCl₃): δ = 171.9, 170.2, 148.1, 140.0, 135.7, 133.2, 130.7, 129.5, 129.2, 127.3, 127.1, 126.4, 126.4, 123.5, 122.1, 101.7, 61.0, 35.3, 16.3, 14.3, 12.7. HRMS (ESI-TOF) m/z: [M+H]* Calcd for C₂₂H₂₀O₃S₃H: 429.0647; Found: 429.0634.

General procedure for compound 4. To a solution of ethyl 3-oxo-4-(3,4,5-trimethoxyphenyl)butanoate (0.441 g, 1.49 mmol) and 2,4,6-trimethoxybenzaldehyde (0.878 g, 4.48 mmol) in benzene (10 ml) piperidine (5 drops) and acetic acid (6 drops) was added. The resulting mixture was refluxed for 3 h with a Dean-Stark receiver. The solvent was removed in vacuum,the residue was dissolved in ethyl acetate (50 ml),washed with water (2 x 50 ml), dried over anhydrous MgSO $_4$ and evaporated in vacuum. The residue was purified by column chromatography eluting by petrol. ester / ethyl acetate (2/1).

(2*Z*,4*E*)-ethyl 3-oxo-2-(2,4,6-trimethoxybenzylidene)-5-(2,4,6-trimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)pent-4-enoate (4)

Yield 0.442 g (44%), yellow powder (green after decomposition) (m.p. = 137-138 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.88 (s, 1H), 7.57 (s, 1H), 6.34 (s, 2H), 6.04 (s, 2H), 5.98 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.75 (s, 6H), 3.60 (s, 6H), 3.48 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ = 194.7, 167.1, 163.2, 162.0, 159.7 (2C), 158.7 (2C), 151.9 (2C), 140.8, 136.8, 135.3, 134.0, 133.1, 131.3, 107.0, 106.6 (2C), 105.7, 90.2 (2C), 90.0 (2C), 60.8, 55.9 (2C), 55.3 (2C), 55.3, 55.0, 55.0, 54.8 (2C), 14.1. HRMS (ESI-TOF) m/z: [M+Na]+ Calcd for C₃₅H₄₀O₁₂Na : 675.2412; Found: 675.2418.

General procedure for cyclization of compound 4. Hydrogen chloride dioxane solution (4M, 0.2 ml) was added to anhydrous dioxane (10 ml) was saturated by dry hydrogen chloride, then (2*Z*,4*E*)-ethyl 3-oxo-2-(2,4,6-trimethoxybenzylidene)-5-(2,4,6-trimethoxyphenyl)-4-(3,4,5-trimethoxyphenyl)pent-4-enoate (0.27 g, 0.4 mmol)

was dissolved in solution of HCl/dioxane. After the reaction was complete (TLC control), the reaction mixture was poured into water (50 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic phases were washed with water (50 ml), dried over anhydrous MgSO $_4$ and evaporated in vacuum. The residue was purified by column chromatography eluting by petrol. ester / ethyl acetate (1/1).

Ethyl 2-oxo-4,5-bis(2,4,6-trimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)cyclopent-3-enecarboxylate (5)

Yield 0.135 g (52%); yellow-brown powder (m.p. = 152-153 °C). ¹H NMR (300 MHz, CDCl₃): δ = 6.59 (s, 2H), 6.02 (d, J = 2.1 Hz, 1H), 5.99 (d, J = 2.1 Hz, 1H), 5.91 (d, J = 2.1 Hz, 1H), 5.78 (d, J = 2.0 Hz, 1H), 5.72 (d, J = 3.5 Hz, 1H), 4.18-4.32 (m, 2H), 3.92 (d, J = 3.5 Hz, 1H), 3.79-3.81 (m, 6H), 3.74 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.65-3.67 (m, 6H), 3.55 (s, 3H), 3.10 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). 13 C{ 1 H} NMR (75 MHz, CDCl₃): δ = 201.5, 170.8, 170.1, 169.9, 161.9, 160.0, 159.9, 159.1, 158.9, 157.9, 152.3 (2C), 137.1, 129.3, 107.8, 106.5, 105.5 (2C), 90.2, 90.2 (2C), 90.0 (2C), 61.0, 60.8, 58.9, 55.9, 55.8 (2C), 55.6, 55.2, 55.2, 54.8, 54.8, 41.3, 14.3. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₃₅H₄₀O₁₂H: 653.2593; Found: 653.2601.

Gram-Scale Experiment:

The synthesis of compound 1a.To a solution of ethyl 3-oxo-4-(thiophen-2-yl)butanoate (4.0 g, 18.87 mmol) and corresponding 4-methoxybenzaldehyde (6.8 ml, 56.60 mmol) in benzene (80 ml) piperidine (3.8 ml, 0.38 mmol) and acetic acid (3.2 ml, 0.50 mmol) was added. The resulting mixture was refluxed in oil bath for 3 h with a Dean-Stark receiver. After the reaction was complete (TLC control), the solvent was removed in vacuum, the residue was dissolved in ethyl acetate (150 ml), washed with water (2 x 200 ml), dried over anhydrous MgSO₄ and evaporated in vacuum. The residue was purified by column chromatography eluting by petroleum ether / ethyl acetate (3/1). Isolated yield of 1a is 52% (4.40 g).

The cycliczation of 1a. Anhydrous dichloromethane (100 ml) was saturated by dry hydrogen chloride for 15 minutes (0.2M HCl solution in dichloromethane) then (2Z,4Z)-ethyl 2-(4-methoxybenzylidene)-5-(4-methoxyphenyl)-3-oxo-4-(thiophen-2-yl)pent-4-enoate (1a) (4.40 g, 9.8 mmol) was dissolved in this solution. After the reaction was complete (TLC control), the reaction mixture was poured into water (500 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with water (500 ml), dried over anhydrous MgSO₄ and evaporated in vacuum. The residue was purified by column chromatography eluting by petroleum ether/ethyl acetate (6/1). The isolated yield of 2a is 50% (2.19 g) and of 3a is 43% (1.84 g).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, compound characterization data, HRMS, and NMR spectra, and xyz coordinates.

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