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Solvent-controlled diastereodivergent cascade synthesis of trisubstituted tetrahydrothiophenes utilizing polystyrene-supported amine

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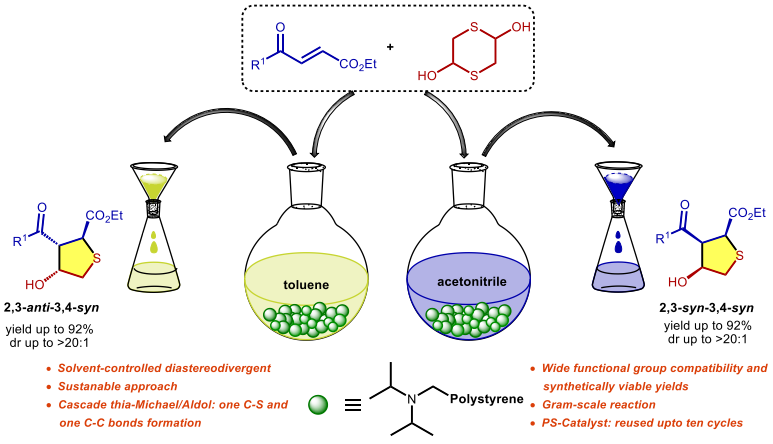
Abstract

An efficient and solvent–controlled diastereodivergent thia-Michael/aldol cascade synthesis of tetrahydrothiophenes (THTs) has been developed. The cascade reaction is catalyzed by polystyrene-supported amine to afford trisubstituted tetrahydrothiophene derivatives in excellent yields and diastereoselectivities. A broad range of substrate tolerance is examined under two different solvents to access a library of diastereomeric THTs. Moreover, the polymer-supported amines can be recovered and reused for the cascade reaction.



Keywords: Solvent-controlled, diastereodivergent, polymer-supported amines, Thia-Michael/aldol, cascade, tetrahydrothiophene

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Introduction

Sulfur-containing compound always holds a significant position in research due to their medicinal and biological importance.[1] Among the numerous groups of organic sulfur compounds, tetrahydrothiophene (THT) is one of the most prevalent scaffolds in various natural and bioactive chemicals with a wide range of biological activities.[2-7] For examples; biotin, a water-soluble B vitamin **A**, which plays an essential role in many biological processes; a potent-glucosidase inhibitor salacinol **B** and kotalanol **C**, isolated from several *Salacia* species; a highly efficient and specific A3 adenosine receptor antagonist 4′-thioadenosine derivative **D**; 4′-thiocytidine nucleoside **E** is shown to have activity against HSV-1 and HSV-2; (*R*)-tetrahydrothiophene-3-ol **F** is an essential intermediate to the synthesis of potent antibacterial sulopenem **G** and other penem-based antibiotics; and tetronothiodin **H** is a cholecystokinin type-B receptor antagonist. Furthermore, many synthetic THT derivatives have chiral ligand-like properties and were crucial intermediates in the synthesis of many natural compounds.[8-12] Adsorption of THT on gold has also been recognized as a crucial technique for producing self-assembled monolayers (SAMs), which are useful for controlling the physical and chemical characteristics of surfaces for various technological applications.[13] Over the past few decades, much effort has been made to synthesize THT derivatives due to their synthetic utilities and potent biological activities.[14,15]

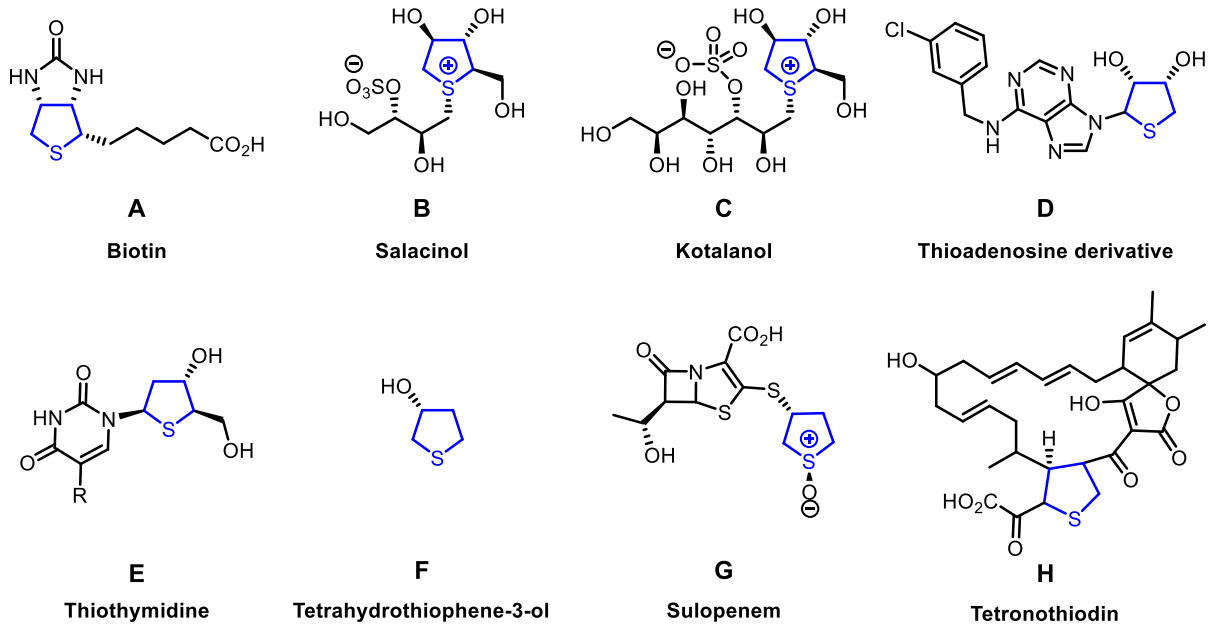

Figure 1: Selective bioactive compounds having tetrahydrothiophene core.

Several methods have been accomplished to reduce the tedious workup and purification processes during organic synthesis.[16] Despite overwhelming advancement, the development of efficient and sustainable methodologies still continues as a challenging and an attractive field of research. The utilization of solid-supported catalysts is one of the most fascinating ways to overcome waste generation and time-consuming purification. Besides, they have several advantages in both academic research and the industrial production of interesting organic compounds.[17-19] The solid supports can be either organic or inorganic, e.g., polystyrene resins, polyethylene glycol, silica, alumina, etc.[20,21] Several methods have been reported on the utilization of polystyrene-supported amines as a catalyst in organic synthesis.[22-24]

One of the significant focuses of current organic synthesis is the control of stereoselectivity. It is highly desirable to devise a synthetic method to produce all stereoisomers of an important molecule.[25-30] The

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effective approach for accessing various stereoisomers of a specific product using the same set of raw materials can be executed by stereodivergent catalysis, which can enable exact control of the relative configuration and/or absolute configuration by altering the reaction conditions.[31,32] Standard methods for achieving stereodivergent catalysis include the use of various central metals, chiral catalysts, additives, ligands, or synergistic catalytic systems.[25-38] It is widely thought to be challenging to reverse the naturally favoured diastereoselectivity by merely changing the reaction solvents, and studies on altering the selectivity by switching the reaction solvents are very elusive.[39-46]

Recently, we have reported a cascade thia-Michael/aldol to construct THTs catalyzed by DABCO.[47] Herein, we disclose the cascade thia-Michael/aldol approach utilizing polystyrene-supported amine as efficient catalyst, wherein, altering the solvent allows to access different diastereomers of trisubstituted tetrahydrothiophenes.

Results and Discussion

Our recent findings on the synthesis of trisubstituted THTs indicated that DABCO was an appropriate catalyst for the thia-Michael/aldol reaction.[47] We move towards the solid-supported catalyst to make the methodologies more sustainable, eco-friendly and to reduce the purification time. We initiate our investigation with the 5 mol % of polystyrene-supported 1,4-diazabicyclo[2.2.2]octane (PS-DABCO) **(I)** as a catalyst for the cascade reaction of β-keto ester **1a** and 1,4-dithiane-2,5-diol **2** in toluene at room temperature. The reaction was not fully completed after 48 h and the diastereoselectivity was quite low (Table 1, entry 1). Next, the reaction was performed with higher catalyst loadings and 20 mol % of PS-DABCO was found to be efficient enough to afford a synthetically viable yield and moderate dr (Table 1, entry 3). Pleasingly, the dr was enhanced by performing the reaction at 0 °C. However, the lowering reaction temperature had a detrimental effect on yield (Table 1, entry 5).

Further, we have explored several polymer-supported catalysts. The reaction was much faster in polystyrene-supported 4-(dimethylamino)pyridine (PS-DMAP) **(II)** than PS-DABCO **(I)** (Table 1, entry 6). Gratifyingly, diisopropylaminomethyl-polystyrene **(III)** afforded the desired product **3a** in excellent yield and diastereoselectivity (Table 1, entry 7). When the reaction was carried out with diethylaminomethyl-polystyrene **(IV)**, an almost similar yield was observed (Table 1, entry 8). In the presence of stronger base like bicyclic nitrogen-containing catalyst polystyrene-supported 1,8-diazabicyclo[5.4.0]undec-7-ene (PS-DBU) **(V)**, the reactants consumed much faster. However, diastereoselectivity was very poor (Table 1, entry 9). Diisopropylaminomethyl-polystyrene **(III)** was used as an organocatalyst for further optimization of reaction condition. Several solvents were tested. In general, non-polar solvents yielded **3a** as the major diastereomer. Toluene was the best-suited solvent among others to provide **3a** in high yield and dr (Table 1, entry 7). Surprisingly, it was found that the presence of ethanol as a solvent led to the different diastereoisomer **4a** as a major isomer (Table 1, entry 16). Serendipitously, complete switching of diastereoisomer was observed in the presence of acetonitrile as a reaction solvent. After seeing the reversal of diastereoselectivity, we again investigate all polymer-supported catalysts in the presence of acetonitrile solvent. Diisopropylaminomethyl-polystyrene was indeed found to be efficient for forming both diastereoisomers in the presence of different solvent systems (Table 1, entry 17).

Having the optimized reaction conditions, we explored the substrate generality for solvent-controlled diastereodivergent synthesis of trisubstituted tetrahydrothiophenes. Firstly, substrate scope under the condition A (in the presence of toluene as a solvent, Table 2) was investigated leading to 2,3-*anti*-3,4-*syn* isomer (**3**).

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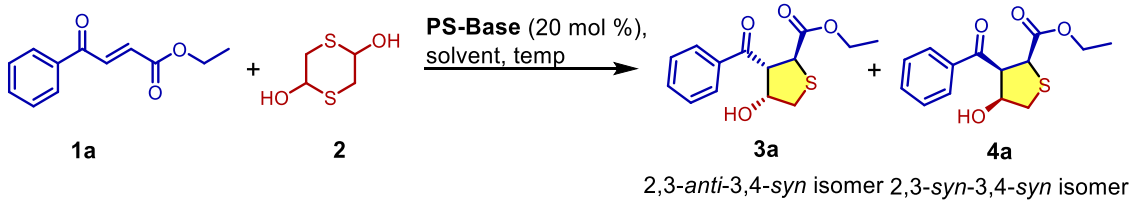
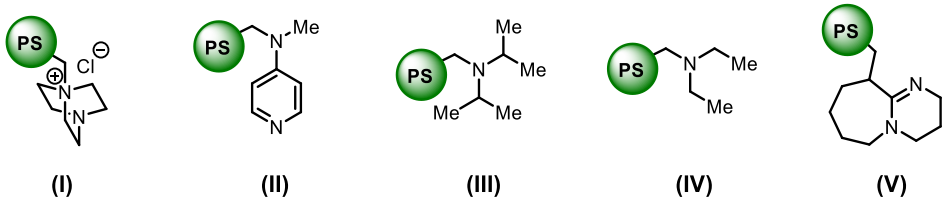
Table 1. Initial optimization of cascade thia-Michael/aldol reaction[a]





entry	PS-Base	temp. (°C)	solvent	time (h)	dr [b] (3a:4a)	yield (%)[c]
1	I (5 mol %)	rt	toluene	48	10:1	35
2	I (10 mol%)	rt	toluene	48	10:1	52
3	I (20 mol %)	rt	toluene	48	10:1	91
4	I (20 mol %)	20	toluene	48	18:1	87
5	I (20 mol %)	0	toluene	48	>20:1	82
6	II (20 mol %)	0	toluene	26	12:1	89
7	III (20 mol %)	0	toluene	36	>20:1	92
8	IV (20 mol %)	0	toluene	20	10:1	85
9	V (20 mol %)	0	toluene	16	1:1	90
10	III (20 mol %)	0	EtOAc	20	8:1	87
11	III (20 mol %)	0	THF	28	12:1	85
12	III (20 mol %)	0	hexane	48	20:1	65
13	III (20 mol %)	0	CH_2Cl_2	18	7:1	82
14	III (20 mol %)	0	$(CH_2Cl)_2$	18	7:1	87
15	III (20 mol %)	0	*m*-xylene	48	>20:1	89
16	III (20 mol %)	0	EtOH	16	1:9	84
17	III (20 mol %)	0	CH_3CN	8	1:>20	91
18	I (20 mol %)	0	CH_3CN	14	1:16	84
19	II (20 mol %)	0	CH_3CN	12	1:6	90
20	IV (20 mol %)	0	CH_3CN	7	1:8	87
21	V (20 mol %)	0	CH_3CN	5	1:4	88

[a]Reaction conditions: **1a** (81.7 mg, 0.4 mmol), **2** (33.5 mg, 0.22 mmol), PS-Cat. **(I-V)**, toluene (0.5 mL), unless specified. [b]Diastereomeric ratio for all entries was determined by ^{1}H NMR analysis of crude reaction mixture. [c]Isolated yield.

β–Ketoesters bearing *para*-halos (F, Cl, Br) on aryl led to the formation of desired products (**3a-d**) in excellent yield and diastereoselectivity. Both electron-withdrawing (cyano- and nitro-) and donating groups (*tert*-butyl- and methoxy-) on the *para*-position of the phenyl ring were well tolerated under the optimized reaction

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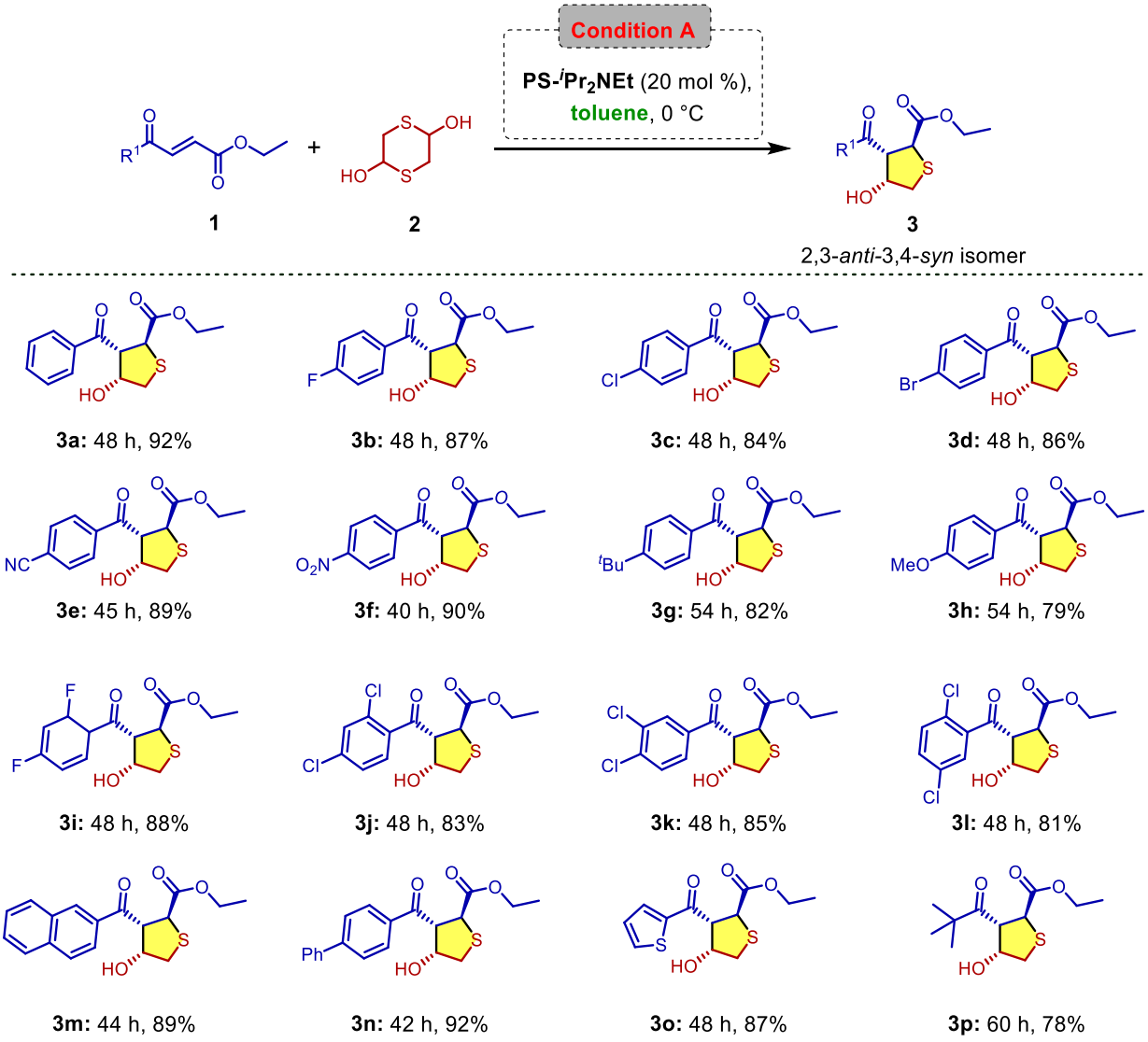
conditions, affording the tetrahydrothiophene products (**3e-h**). Excellent yield and dr were obtained with dihalo-substitution on several positions of the phenyl ring of unsaturated ketoesters (**1i-l**).

In addition, sterically and electronically distinct R^1 groups such as 2-naphthyl, biphenyl, 2-thiophenyl, and *tert*-butyl groups were also amenable, which yielded the desired products (**3m-p**) in high yields and stereoselectivities. The relative stereochemistry of product **3a** was assigned as 2,3-*anti*-3,4-*syn* by comparison of spectral data with previous report.[47]

Table 2 Substrate scope of the cascade thia-Michael/aldol reaction for the synthesis of 2,3-*anti*-3,4-*syn* isomer[a]



[a]Reaction conditions: **1** (0.4 mmol), **2** (33.5 mg, 0.22 mmol), Diisopropylamniomethyl-polystyrene **(III)** (29.1 mg 0.08 mmol, 2.75 mmol/g), toluene (0.5 mL), unless specified. The diastereomeric ratio (**3:4**) for all entries was determined to be >20:1 by ^{1}H NMR analysis of the crude reaction mixture. The stereochemistry shown for THTs are relative only.

Next, we examined the substrate scope under the optimized condition B (acetonitrile as a solvent, Table 3) leading to 2,3-*syn*-3,4-*syn* isomer (**4**). Initially, we varied the substitution on aryl ring of **1**. Both *p*-chloro (**1c**) and *p*-methoxy (**1h**) substitution on phenyl ring of α,β-unsaturated β-ketoesters led to expected diastereoisomer in excess with excellent yields and diastereomeric ratio. Methylene dioxide (**1q**) and dichloro-

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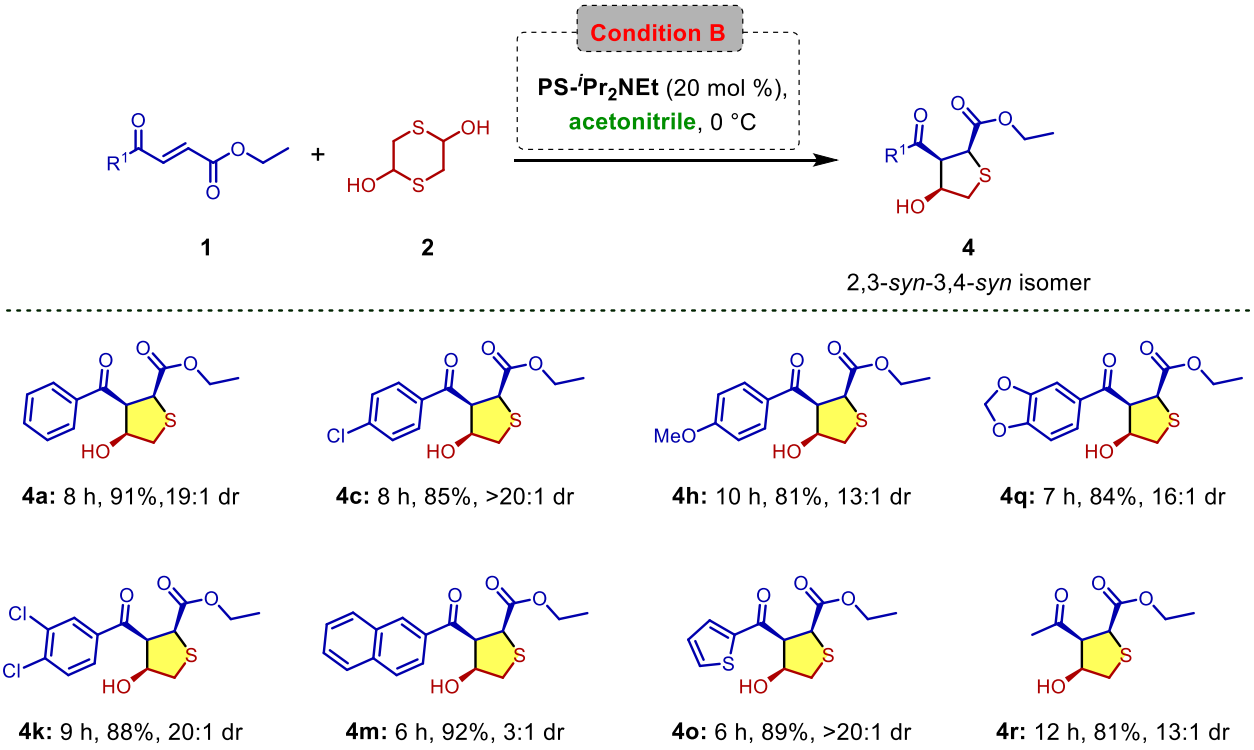
substituted phenyl (**1k**) were also found to smoothly undergo the cascade reaction providing the corresponding THTs in good yields and dr. Slightly lower diastereoselectivity (3:1) was observed in case of 2-naphthyl substituted Michael acceptor (**1m**).

Table 3 Substrate scope of the cascade thia-Michael/aldol reaction for the synthesis of 2,3-*syn*-3,4-*syn* isomer[a]



[a]Reaction conditions: **1** (0.4 mmol), **2** (33.5 mg, 0.22 mmol), Diisopropylamniomethyl-polystyrene **(III)** (29.1 mg 0.08 mmol, 2.75 mmol/g), acetonitrile (0.5 mL), unless specified. The diastereomeric ratio (**4:3**) for all entries was determined by ^{1}H NMR analysis of the crude reaction mixture. Relative stereochemistry was assigned by NOESY experiment. The stereochemistry shown for THTs are relative only.

Noteworthy, heteroaryl substituted, namely 2-thiophenyl, tetrahydrothiophene (**4o**) was prepared efficiently. Next, aliphatic Michael acceptor (R^1 = Me) was used. Although, the reaction was relatively slow, the desired THT (**4r**) was isolated in 81% yield with 13:1 dr. Gram-scale reactions were carried out to demonstrate the synthetic potential of the developed solvent-controlled diastereodivergent methodology. The cascade thia-Michael/aldol reactions at the gram scale under both conditions proceeded efficiently to afford desired diastereoisomers in excellent yield and selectivity.

Further, the supported catalyst was recovered and recycled up to 10 cycles under both optimized conditions (Scheme 1). Notably, after each cycle, the isolated yield decreased slightly. However, diastereoselectivity remained unaffected. In addition, the hydroxyl group of trisubstituted tetrahydrothiophenes **3a** and **4a** was transformed into hydrogen sulfate (**5a** and **6a**) group by treating with pyridine•SO_3 (Scheme 2).

The plausible mechanism of polystyrene-supported amine catalyzed thia-Michael/aldol reaction was shown in Figure 2. 1,4-Dithiane-2,5-diol would exist in equilibrium with its monomer, 2-mercaptoacetaldehyde in solution. The tert-nitrogen of polymer-supported catalyst activates mercaptoacetaldehyde by deprotonation. The sulfur centric activated nucleophile undergoes thia-Michael addition to generate an intermediate (**IM-1**). The intermediate further proceed for an intramolecular aldol reaction to afford trisubstituted tetrahydrothiophenes (**3** and/or **4**).

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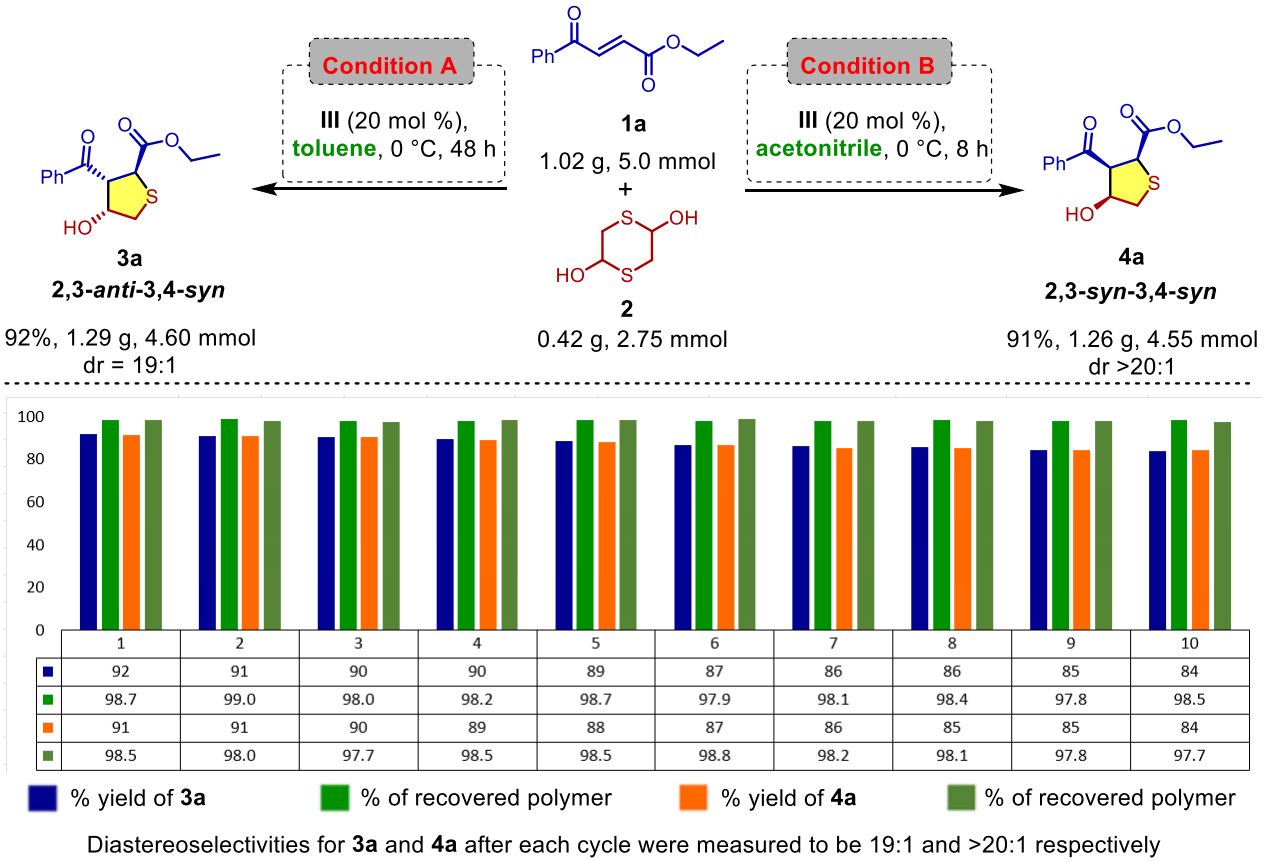
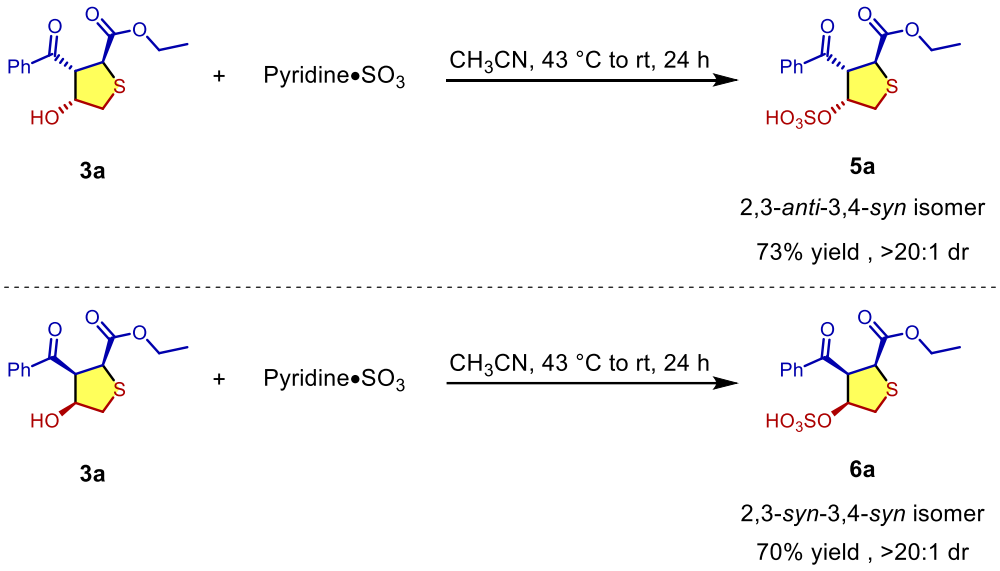


	1	2	3	4	5	6	7	8	9	10
■	92	91	90	90	89	87	86	86	85	84
■	98.7	99.0	98.0	98.2	98.7	97.9	98.1	98.4	97.8	98.5
■	91	91	90	89	88	87	86	85	85	84
■	98.5	98.0	97.7	98.5	98.5	98.8	98.2	98.1	97.8	97.7

Diastereoselectivities for **3a** and **4a** after each cycle were measured to be 19:1 and >20:1 respectively

Scheme 1. Gram-scale reaction and recycling of polymer



Scheme 2. Synthetic transformations of trisubstituted tetrahydrothiophenes

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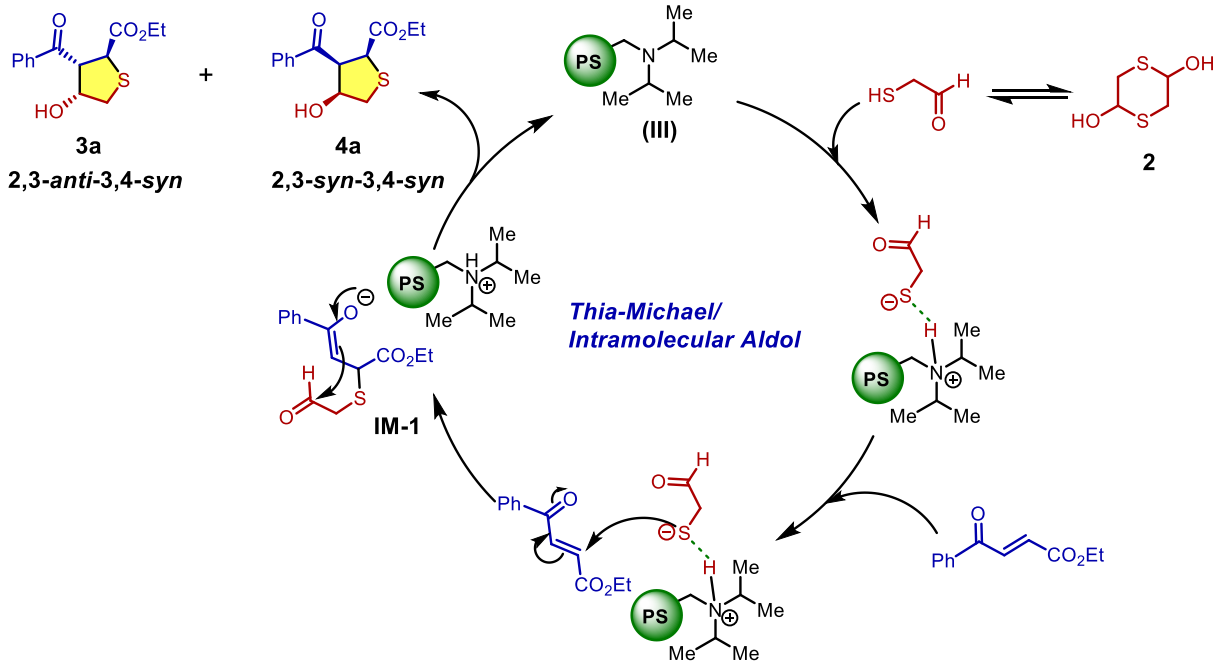

Figure 2: Proposed catalytic cycle of cascade thia-Michael/aldol reaction.

Conclusions

In summary, we have successfully established a diastereodivergent synthesis of trisubstituted tetrahydrothiophenes via thia-Michael/aldol reaction of 1,4-dithiane-2,5-diol to activated olefins. The diastereo-switch was achieved by altering solvents in the presence of a solid-supported amine catalyst giving excellent yield and dr. In addition, the synthetic utilities of the developed method were examined by gram scale reaction and by recycling of supported catalyst for the synthesis of both diastereoisomers. Also, the hydroxyl group of products THT was transformed into THT-hydrogen sulfate derivatives.

Experimental Section

General. Unless otherwise noted, all reactions were carried out in closed vial. ^{1}H NMR spectra were recorded on a 500 MHz or 400 MHz spectrometers (125 MHz or 100 MHz for 13C NMR). The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. TLC was performed with silica gel GF_{254} precoated on aluminium plates and spots were visualized with UV. Flash column chromatography was performed on silica gel. HPLC analysis was performed on an HPLC instrument equipped with a UV-Vis detector. IR spectra were recorded on an FT-IR spectrometer and only major peaks were reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained by the ESI-TOF method. Optical rotations were measured on a commercial automatic polarimeter and reported as follows: $[\alpha]_{25}^{D}$ (c = g/100 mL, solvent). Melting points were recorded on a digital melting point apparatus. α,β-Unsaturated ketone **1** derivatives.[24] All the other chemicals, reagents, catalysts **II-V,** and solvents were purchased from commercial sources and used as received unless specified. 4-(Dimethylamino)pyridine, polymer-bound extent of labelling: ~3.0 mmol/g DMAP loading, matrix crosslinked with 2% DVB purchased from Sigma Aldrich. Diisopropylamine, polymer-bound - 100-200 mesh, extent of labelling: 2.0-3.5 mmol/g loading, 1% cross-linked with divinylbenzene purchased from Sigma Aldrich. Diethylaminomethyl-polystyrene extent of labelling: ~3.2 mmol/g loading, 200 - 400 MESH purchased from Sigma Aldrich. 1,8-

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Diazabicyclo[5.4.0]undec-7-ene, polymer-bound, 100-200 mesh, extent of labelling: 1.5-2.5 mmol/g loading, 1 % cross-linked with divinylbenzene purchased from Sigma Aldrich. Chloromethyl Polystyrene Resin cross-linked with 1% DVB (100-200mesh) (2.0-3.0mmol/g) purchased from TCI chemicals. Diastereoisomeric ratio mentioned in the manuscript table 2, 3, and 4 is calculated by crude reaction mixture. Diastereoisomeric ratio mentioned on the proton NMR spectra is calculated after purification of products.

Synthesis of DABCO (PS-DABCO) catalyst I. Merrifield resin (2.5 mmol, 1 g; 2.5 mmol/g Cl-content) was added slowly to the solution of DABCO (12.5 mmol, 1.35 g) in dry THF under an inert atmosphere. The progress of the reaction was monitored by TLC. After the complete consumption of DABCO, the solid was filtered and washed with acetone to afford the PS-DABCO catalyst. [Elemental analysis of **III** (%) = C 73.69, H 8.41, N 4.67; *f* = 1.67 mmol/g]

Synthesis of trisubstituted tetrahydrothiophenes (3a–p) (Condition A). Dithiane-2,5-diol (0.22 mmol, 33.5 mg) and diisopropylaminomethyl-polystyrene **III** (20 mol%, 0.08 mmol, 29.1 mg) were added to the solution of (*E*)-4-oxo-4- aryl/alkylbut-2-enoate **1** (0.4 mmol) in dry toluene (0.5 mL). The mixture was stirred at 0 °C and the reaction was monitored by TLC. After the reaction was completed, the desired product was purified by column chromatography on silica gel (hexane/ethyl acetate = 5: 1).

Synthesis of tri-substituted tetrahydrothiophenes (4a–h) (Condition B). Dithiane-2,5-diol (0.22 mmol, 33.5 mg) and diisopropylaminomethyl-polystyrene **III** (20 mol%, 0.08 mmol, 29.1 mg) were added to the solution of (*E*)-4-oxo-4- aryl/alkylbut-2-enoate **1** (0.4 mmol) in dry acetonitrile (0.5 mL). The mixture was stirred at 0 °C and the reaction was monitored by TLC. After the reaction was completed, the desired product was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1).

Gram-scale reaction. 1,4-Dithiane-2,5-diol (2.75 mmol, 0.42 g) and diisopropylaminomethyl-polystyrene **III** (20 mol%, 1.0 mmol, 0.364 g) were added in the solution of (*E*)-4-oxo-4-phenylbut-2-enoate **1a** (5.0 mmol, 1.02 g) in dry toluene/acetonitrile (10 mL). The mixture was stirred at 0 °C and the reaction was monitored by TLC. After the reaction was completed, the desired product was purified by column chromatography on silica gel (hexane/ethyl acetate = 5 : 1).

Synthetic transformation. Trisubstituted tetrahydrothiophene (0.4 mmol, 112.1 mg) **3a** was dissolved in acetonitrile (2 ml) and stirred at 43 °C. Pyridine-sulphur trioxide complex (0.6 mmol, 95.5 mg) was added to the reaction mixture. Once all solid was dissolved, the reaction was transferred to room temperature and stirred for 24 h. Completion of the reaction was monitored by thin-layer chromatography. After completing the reaction, desired product **5a** was purified by column chromatography on silica gel (hexane/ethyl acetate = 5 : 1).

Ethyl-3-benzoyl-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3a).** White solid, Yield 92%, (103.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.99 (m, 2H), 7.63 – 7.60 (m, 1H), 7.52 – 7.48 (m, 2H), 4.92 – 4.89 (m, 1H), 4.65 (d, *J* 8.6 Hz, 1H), 4.47 (dd, *J* 8.6, 3.5 Hz, 1H), 4.16 – 4.12 (m, 2H), 3.40 (dd, *J* 11.6, 3.2 Hz, 1H), 3.05 (dd, *J* 11.6, 1.7 Hz, 1H), 2.90 (d, *J* 6.7 Hz, 1H), 1.22 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.02, 172.36, 136.65, 134.06, 129.01, 128.69, 77.33, 62.09, 57.21, 46.65, 41.53, 14.12; IR (KBr): ν 3474, 3062, 2982, 2936, 1729, 1681, 1597, 1580, 1448, 1376, 1272, 1187, 1076, 881, 762 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{17}O_4S$ $[M+H]^+$: 281.0843, found : 281.0844; mp 110–112 °C.

Ethyl-3-(4-fluorobenzoyl)-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3b).** White solid, Yield 87% (103.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 8.04 (m, 2H), 7.17 (t, *J* 8.5 Hz, 2H), 4.89 – 4.88 (m, 1H), 4.64 (d, *J* 8.6 Hz, 1H), 4.43 (dd, *J* 8.5, 3.5 Hz, 1H), 4.19 – 4.11 (m, 2H), 3.39 (dd, *J* 11.7, 3.2 Hz, 1H), 3.06 (d, *J* 11.6 Hz, 1H), 2.91 (d, *J* 6.7 Hz, 1H), 1.23 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.44, 172.32, 166.38 (d, J_{C-F} = 2.55

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Hz), 133.11 (d, J_{C-F} = 3.75 Hz), 131.48 (d, J_{C-F} = 10 Hz), 116.21 (d, J_{C-F} = 22.5 Hz), 77.32, 62.14, 57.02, 46.70, 41.55, 14.13; IR (KBr): ν 3523, 3066, 2962, 2926, 2856, 1721, 1674, 1602, 1478, 1416 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{16}FO_4S$ $[M+H]^+$: 299.0748, found : 299.0751; mp 84-86 °C.

Ethyl-3-(4-chlorobenzoyl)-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3c).** White solid, Yield 84% (105.8 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* 8.5 Hz, 2H), 7.48 (d, *J* 8.5 Hz, 2H), 4.89 (s, 1H), 4.64 (d, *J* 8.4 Hz, 1H), 4.42 (dd, *J* 8.4, 3.6 Hz, 1H), 4.20 – 4.12 (m, 2H), 3.39 (dd, *J* 11.7, 3.2 Hz, 1H), 3.06 (d, *J* 11.7 Hz, 1H), 2.81 (d, *J* 6.9 Hz, 1H), 1.24 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.78, 172.30, 140.66, 135.04, 130.12, 129.38, 77.33, 62.18, 57.19, 46.58, 41.60, 14.15; IR (KBr): ν 3518, 3035, 2989, 2921, 2847, 1742, 1668, 1601 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{16}ClO_4S$ $[M+H]^+$: 315.0452, found : 315.0454; MP 77-79 °C.

Ethyl-3-(4-bromobenzoyl)-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3d).** White solid, Yield 86% (123.6 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.99 (m, 2H), 7.63 – 7.60 (m, 1H), 7.52 – 7.48 (m, 2H), 4.92 – 4.89 (m, 1H), 4.65 (d, *J* 8.6 Hz, 1H), 4.47 (dd, *J* 8.6, 3.5 Hz, 1H), 4.16 – 4.12 (m, 2H), 3.40 (dd, *J* 11.6, 3.2 Hz, 1H), 3.05 (dd, *J* 11.6, 1.7 Hz, 1H), 2.90 (d, *J* 6.7 Hz, 1H), 1.22 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.02, 172.36, 136.65, 134.06, 129.01, 128.69, 77.33, 62.09, 57.21, 46.65, 41.53, 14.12; IR (KBr): ν 3474, 3062, 2982, 2936, 1729, 1681, 1597, 1580, 1448, 1376, 1272, 1187, 1076, 881, 762 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{17}O_4S$ $[M+H]^+$: 281.0843, found : 281.0844; mp 110-112 °C.

Ethyl-3-(4-cyanobenzoyl)-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3e).** Yelllow solid, Yield 89% (108.7 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* 8.3 Hz, 2H), 7.80 (d, *J* 8.3 Hz, 2H), 4.96 – 4.82 (m, 1H), 4.67 (d, *J* 8.1 Hz, 1H), 4.46 (dd, *J* 8.1, 3.7 Hz, 1H), 4.26 – 4.10 (m, 2H), 3.40 (dd, *J* 11.8, 3.2 Hz, 1H), 3.03 (d, *J* 11.8 Hz, 1H), 2.62 (d, *J* 7.7 Hz, 1H), 1.26 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.31, 172.23, 139.95, 132.83, 128.98, 117.86, 117.08, 77.34, 62.30, 58.10, 46.00, 41.70, 14.10; IR (KBr): ν 3474, 3019, 2984, 2962, 2936, 2905, 2047, 1731, 1657, 1601, 1514, 1453 cm^{-1}; HRMS (ES+) calc. for $C_{15}H_{14}NO_4S$ $[M-H]^-$: 304.0649, found : 304.0640; mp 69-71 °C.

Ethyl-4-hydroxy-3-(4-nitrobenzoyl)tetrahydrothiophene-2-carboxylate[47] **(3f).** Yellow solid, Yield 90% (117.1 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* 8.8 Hz, 2H), 8.15 (d, *J* 8.8 Hz, 2H), 4.92 – 4.90 (m, 1H), 4.69 (d, *J* 8.0 Hz, 1H), 4.49 (dd, *J* 8.0, 3.8 Hz, 1H), 4.23 – 4.13 (m, 2H), 3.42 (dd, *J* 11.8, 3.3 Hz, 1H), 3.04 (dd, *J* 11.8, 1.4 Hz, 1H), 2.56 (d, *J* 8.0 Hz, 1H), 1.27 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.08, 172.23, 150.71, 141.50, 129.58, 124.19, 77.27, 62.33, 58.46, 45.92, 41.70, 14.16; IR (KBr): ν 3358, 2988, 2928, 2848, 1735, 1682, 1601, 1520, 1353 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{15}NO_6SNa$ $[M+Na]^+$: 348.0512, found : 348.0516; mp 67-69 °C.

Ethyl-3-(4-(*tert*-butyl)benzoyl)-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3g).** White solid, Yield 82 % (110.4 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* 7.8 Hz, 2H), 7.51 (d, *J* 7.7 Hz, 2H), 4.89 (s, 1H), 4.63 (d, *J* 8.5 Hz, 1H), 4.45 (d, *J* 8.5 Hz, 1H), 4.17 – 4.10 (m, 2H), 3.39 (d, *J* 11.5 Hz, 1H), 3.06 (d, *J* 11.5 Hz, 1H), 1.34 (s, 9H), 1.21 (t, *J* 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.88, 172.37, 158.10, 134.01, 128.77, 126.00, 77.39, 62.03, 56.83, 46.98, 41.48, 35.37, 31.17, 14.11; IR (KBr): ν 3360, 3100, 3063, 2964, 2927, 2876, 1731, 1669, 1606, 1566, 1467, 1408 cm^{-1}; HRMS (ES+) calc. for $C_{18}H_{24}O_4SNa$ $[M+Na]^+$: 359.1288, found : 359.1268; mp 123-125 °C.

Ethyl-4-hydroxy-3-(4-methoxybenzoyl)tetrahydrothiophene-2-carboxylate[47] **(3h).** Off-white solid, Yield 79% (98.1 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* 8.9 Hz, 2H), 6.97 (d, *J* 8.9 Hz, 2H), 4.86 (d, *J* 3.5 Hz, 1H), 4.60 (d, *J* 8.9 Hz, 1H), 4.40 (dd, *J* 8.9, 3.4 Hz, 1H), 4.18 – 4.09 (m, 2H), 3.89 (s, 3H), 3.37 (dd, *J* 11.5, 3.3 Hz, 1H), 3.22 (d, *J* 5.6 Hz, 1H), 3.08 (dd, *J* 11.5, 1.1 Hz, 1H), 1.21 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.05, 172.37, 164.53, 131.31, 129.55, 114.23, 77.41, 62.03, 56.04, 55.74, 47.39, 41.47, 14.13; IR (KBr): ν 3478, 2982, 2941, 2848, 1728, 1661, 1594, 1319 cm^{-1}; HRMS (ES+) calc. for $C_{15}H_{19}O_5S$ $[M+H]^+$: 311.0948, found : 311.0959; mp 77-79 °C.

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Ethyl-4-acetoxy-3-(2,4-difluorobenzoyl)tetrahydrothiophene-2-carboxylate[47] **(3i).** White solid, Yield 88% (112.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 1H), 7.02 – 6.97 (m, 1H), 6.93 – 6.88 (m, 1H), 4.95 (s, 1H), 4.68 (dd, *J* 8.4, 1.0 Hz, 1H), 4.36 (dd, *J* 8.4, 3.6 Hz, 1H), 4.23 – 4.12 (m, 2H), 3.40 (dd, *J* 11.7, 3.2 Hz, 1H), 2.99 (dd, *J* 11.7, 1.6 Hz, 1H), 2.07 (s, 1H), 1.26 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.49, 193.46, 172.18, 167.25, 167.15, 165.20, 165.09, 163.34, 163.24, 161.30, 161.20, 133.31, 133.27, 133.22, 133.19, 122.10, 122.07, 122.00, 121.97, 112.88, 112.86, 112.71, 112.69, 105.22, 105.01, 105.00, 104.79, 76.28, 76.26, 62.37, 62.32, 62.06, 45.37, 41.33, 14.12; IR (KBr): ν 3485, 2988, 2933, 2850, 1711, 1684, 1610, 1500, 1430 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{14}F_2O_4SNa$ $[M+Na]^+$:339.0473, found : 339.0479; mp 70-72 °C.

Ethyl-4-acetoxy-3-(2,4-dichlorobenzoyl)tetrahydrothiophene-2-carboxylate[47] **(3j).** White solid, Yield 83% (115.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* 8.3 Hz, 1H), 7.46 (d, *J* 1.9 Hz, 1H), 7.34 (dd, *J* 8.3, 2.0 Hz, 1H), 4.81 – 4.79 (m, 1H), 4.58 (d, *J* 8.4 Hz, 1H), 4.42 (dd, *J* 8.4, 3.6 Hz, 1H), 4.23 – 4.15 (m, 2H), 3.33 (dd, *J* 11.8, 3.2 Hz, 1H), 2.96 (dd, *J* 11.8, 1.4 Hz, 1H), 2.53 (d, *J* 8.0 Hz, 1H), 1.28 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.65, 172.15, 137.80, 137.19, 131.79, 130.48, 130.39, 127.66, 76.42, 62.44, 62.20, 44.94, 41.32, 14.18; IR (KBr): ν 3497, 3084, 2980, 2932, 1728, 1698, 1582, 1546, 1467 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{15}Cl_2O_4S$ $[M+H]^+$: 349.0063, found : 349.0067; mp 89-91 °C.

Ethyl-3-(3,4-dichlorobenzoyl)-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3k).** White solid, Yield 85% (118.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* 1.7 Hz, 1H), 7.83 (dd, *J* 8.4, 1.7 Hz, 1H), 7.59 (d, *J* 8.4 Hz, 1H), 4.89 (s, 1H), 4.65 (d, *J* 8.2 Hz, 1H), 4.39 (dd, *J* 8.2, 3.7 Hz, 1H), 4.21 – 4.13 (m, 2H), 3.40 (dd, *J* 11.7, 3.2 Hz, 1H), 3.04 (d, *J* 11.7 Hz, 1H), 2.69 (d, *J* 7.3 Hz, 1H), 1.24 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.47, 172.23, 138.67, 136.30, 133.83, 131.12, 130.60, 127.62, 77.27, 62.26, 57.58, 46.27, 41.65, 14.16; IR (KBr): ν 3504, 3102, 2981, 2928, 1714, 1674, 1580, 1467 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{15}Cl_2O_4S$ $[M+H]^+$: 349.0063, found : 349.0067; mp 89-91 °C.

Ethyl-3-(2,5-dichlorobenzoyl)-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3l).** White solid, Yield 81% (113.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.37 – 7.35 (m, 2H), 4.82 (s, 1H), 4.58 (d, *J* 7.7 Hz, 1H), 4.42 – 4.40 (m, 1H), 4.21 – 4.18 (m, 2H), 3.34 (d, *J* 11.5 Hz, 1H), 2.96 (d, *J* 11.7 Hz, 1H), 2.19 (s, 1H), 1.28 – 1.27 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.29, 172.08, 140.18, 133.46, 132.01, 131.72, 129.07, 128.90, 76.34, 62.62, 62.20, 44.86, 41.33, 14.19; IR (KBr): ν 3485, 3055, 2993, 2910, 1731, 1700, 1462, 1384 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{14}Cl_2O_4SNa$ $[M+Na]^+$: 370.9882, found : 370.9859; mp 93-95 °C.

Ethyl-3-(2-naphthoyl)-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3m).** White solid, Yield 89% (117.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.05 – 7.99 (m, 4H), 7.65 – 7.57 (m, 2H), 4.97 (s, 1H), 4.70 – 4.65 (m, 2H), 4.19 – 4.12 (m, 2H), 3.45 (d, *J* 11.4 Hz, 1H), 3.09 (d, *J* 11.6 Hz, 1H), 2.99 (d, *J* 6.1 Hz, 1H), 1.21 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.10, 172.44, 136.10, 134.04, 132.61, 130.78, 129.91, 129.16, 128.99, 127.97, 127.21, 124.07, 77.53, 62.11, 57.10, 46.93, 41.59, 14.13; IR (KBr): ν 3663, 3341, 2959, 2927, 2854, 1732, 1672, 1506, 1468 cm^{-1}; HRMS (ES+) calc. for $C_{18}H_{19}O_4S$ $[M+H]^+$: 331.0999, found : 331.1007; mp 100-102 °C.

Ethyl-3-([1,1'-biphenyl]-4-carbonyl)-4-hydroxytetrahydrothiophene-2-carboxylate[47] **(3n).** White solid, Yield 92% (131.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* 8.3 Hz, 2H), 7.72 (d, *J* 8.3 Hz, 2H), 7.63 (d, *J* 7.5 Hz, 2H), 7.48 (t, *J* 7.5 Hz, 2H), 7.42 (t, *J* 7.3 Hz, 1H), 4.94 (s, 1H), 4.68 (d, *J* 8.6 Hz, 1H), 4.51 (dd, *J* 8.6, 3.5 Hz, 1H), 4.18 – 4.14 (m, 2H), 3.42 (dd, *J* 11.6, 3.2 Hz, 1H), 3.13 – 3.03 (m, 1H), 2.95 (d, *J* 6.5 Hz, 1H), 1.24 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.75, 172.38, 146.87, 139.77, 135.32, 129.37, 129.18, 128.62, 127.66, 127.46, 62.12, 57.05, 46.89, 41.57, 14.15 (one peak merged with $CDCl_3$); IR (KBr): ν 3471, 3062, 2974, 2921, 2854, 1714, 1668, 1601, 1373 cm^{-1}; HRMS (ES+) calc. for $C_{20}H_{20}O_4SNa$ $[M+Na]^+$: 379.0975, found : 379.0989; MP 135-137 °C.

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Ethyl-4-hydroxy-3-(thiophene-3-carbonyl)tetrahydrothiophene-2-carboxylate[47] **(3o).** White solid, Yield 87% (99.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.74 – 7.67 (m, 1H), 7.17 (s, 1H), 4.94 (s, 1H), 4.60 (d, *J* 8.7 Hz, 1H), 4.25 (d, *J* 8.7 Hz, 1H), 4.15 – 4.11 (m, 2H), 3.37 (d, *J* 11.5 Hz, 1H), 3.07 (d, *J* 11.5 Hz, 1H), 2.67 (s, 1H), 1.21 (t, *J* 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.83, 172.23, 152.43, 147.38, 119.20, 112.99, 77.31, 62.06, 57.78, 46.09, 41.60, 14.14; IR (KBr): ν 3334, 3096, 2955, 2921, 2850, 1728, 1651, 1522, 1410, 1309 cm^{-1}; HRMS (ES+) calc. for $C_{12}H_{14}O_4S_2Na$ $[M+Na]^+$: 309.0226, found : 309.0198; MP 64-66 °C.

Ethyl-4-hydroxy-3-pivaloyltetrahydrothiophene-2-carboxylate[47] **(3p).** White solid, Yield 78% (81.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (t, *J* 3.2 Hz, 1H), 4.41 (d, *J* 8.8 Hz, 1H), 4.20 – 4.10 (m, 2H), 3.99 – 3.96 (m, 1H), 3.31 – 3.24 (m, 1H), 3.04 (dd, *J* 11.6, 3.0 Hz, 1H), 1.27 – 1.23 (m, 3H), 1.20 (s, 3H), 1.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.22, 172.21, 77.33, 61.99, 56.07, 48.41, 45.21, 42.11, 26.19, 14.17; IR (KBr): ν 3655, 3363, 3131, 2968, 2859, 1739, 1698, 1472 cm^{-1}; HRMS (ES+) calc. for $C_{12}H_{20}O_4SK$ $[M+K]^+$: 299.0714, found : 299.0936; mp 99-101 °C.

Ethyl-3-benzoyl-4-hydroxytetrahydrothiophene-2-carboxylate (4a). Liquid, Yield 91% (102.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* 8.3, 1.1 Hz, 2H), 7.60 – 7.57 (m, 1H), 7.46 (dd, *J* 10.7, 4.9 Hz, 2H), 4.81 – 4.77 (m, 1H), 4.48 (t, *J* 4.3 Hz, 1H), 4.34 (d, *J* 4.4 Hz, 1H), 4.23 – 4.13 (m, 2H), 3.90 (d, *J* 8.5 Hz, 1H), 3.10 (dd, *J* 11.2, 4.7 Hz, 1H), 3.04 (dd, *J* 11.3, 4.5 Hz, 1H), 1.23 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$,) δ 197.24, 174.21, 135.68, 134.00, 128.99, 128.96, 79.04, 62.51, 58.86, 47.65, 40.28, 14.06; IR (KBr): ν 3477, 3065, 3011, 2922, 1738, 1688, 1597, 1577, 1443, 1384, 1268, 1205 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{17}O_4S$ $[M+H]^+$: 281.0843, found : 281.0842.

Ethyl-3-(4-chlorobenzoyl)-4-hydroxytetrahydrothiophene-2-carboxylate (4c). Liquid, Yield 85% (107.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.47 – 7.42 (m, 2H), 4.76 – 4.73 (m, 1H), 4.44 – 4.39 (m, 1H), 4.36 – 4.28 (m, 1H), 4.22 – 4.12 (m, 2H), 3.74 (d, *J* 8.3 Hz, 1H), 3.13 – 3.02 (m, 2H), 1.24 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.47, 173.78, 140.60, 134.13, 130.38, 129.28, 78.99, 62.53, 58.48, 47.42, 39.92, 14.05; IR (KBr): ν 3520, 3040, 2995, 2929, 2852, 1752, 1673, 1610 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{16}ClO_4S$ $[M+H]^+$: 315.0452, found : 315.0456.

Ethyl-4-hydroxy-3-(4-methoxybenzoyl)tetrahydrothiophene-2-carboxylate (4h). Liquid, Yield 81% (100.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* 9.0 Hz, 2H), 6.91 (d, *J* 8.9 Hz, 2H), 4.73 (dd, *J* 8.0, 4.6 Hz, 1H), 4.41 (t, *J* 4.6 Hz, 1H), 4.31 (d, *J* 4.7 Hz, 1H), 4.19 – 4.10 (m, 2H), 3.90 (d, *J* 8.2 Hz, 1H), 3.84 (s, 3H), 3.08 (dd, *J* 11.1, 4.8 Hz, 1H), 3.02 (dd, *J* 11.1, 4.8 Hz, 1H), 1.21 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.91, 174.00, 164.18, 131.33, 128.75, 114.05, 79.15, 62.32, 58.07, 55.61, 47.52, 39.88, 14.01; IR (KBr): ν 3460, 2975, 2921, 2853, 1739, 1655, 1609, 1312 cm^{-1}; HRMS (ES+) calc. for $C_{15}H_{19}O_5S$ $[M+H]^+$: 311.0948, found : 311.0961.

Ethyl 3-(benzo[d][1,3]dioxole-5-carbonyl)-4-hydroxytetrahydrothiophene-2-carboxylate (4q). Liquid, Yield 84% (108.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* 8.2, 1.7 Hz, 1H), 7.47 (d, *J* 1.7 Hz, 1H), 6.87 (d, *J* 8.2 Hz, 1H), 6.06 (s, 2H), 4.77 (q, *J* 4.3 Hz, 1H), 4.38 (t, *J* 4.1 Hz, 1H), 4.33 (d, *J* 4.3 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.13 (dd, *J* 11.2, 4.6 Hz, 1H), 3.06 (dd, *J* 11.2, 4.3 Hz, 1H), 1.26 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.26, 174.24, 152.66, 148.59, 130.51, 125.68, 108.55, 108.24, 102.22, 79.30, 62.52, 58.59, 47.76, 40.28, 14.11; IR (KBr): ν 3667, 3312, 2980, 2909, 2880, 1759, 1770, 1668, 1561, 1475 cm^{-1}; HRMS (ES+) calc. for $C_{15}H_{17}O_6S$ $[M+H]^+$: 325.0740, found : 325.0743.

Ethyl-3-(3,4-dichlorobenzoyl)-4-hydroxytetrahydrothiophene-2-carboxylate (4k). Liquid, Yield 88% (122.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* 2.1 Hz, 1H), 7.86 (dd, *J* 8.4, 2.1 Hz, 1H), 7.56 (d, *J* 8.4 Hz, 1H), 4.76 – 4.70 (m, 1H), 4.37 (t, *J* 4.9 Hz, 1H), 4.31 (d, *J* 5.1 Hz, 1H), 4.22 – 4.15 (m, 2H), 3.59 (d, *J* 6.7 Hz, 1H), 3.13 – 3.04 (m, 2H), 1.25 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.79, 173.48, 138.73, 135.45, 133.76, 131.05,

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130.89, 127.98, 78.90, 62.62, 58.44, 47.32, 39.78, 14.08; IR (KBr): ν 3505, 3107, 2991, 2938, 1754, 1681, 1580, 1476 cm^{-1}; HRMS (ES+) calc. for $C_{14}H_{15}Cl_2O_4S$ $[M+H]^+$: 349.0063, found : 349.0068.

Ethyl-3-(2-naphthoyl)-4-hydroxytetrahydrothiophene-2-carboxylate (4m). Liquid, Yield 92% (121.6 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* 1.1 Hz, 1H), 8.04 (dd, *J* 8.7, 1.8 Hz, 1H), 7.98 (d, *J* 7.9 Hz, 1H), 7.92 – 7.86 (m, 3H), 7.64 – 7.54 (m, 3H), 4.88 (d, *J* 3.9 Hz, 1H), 4.68 – 4.65 (m, 1H), 4.43 (d, *J* 4.2 Hz, 1H), 4.24 – 4.14 (m, 2H), 3.92 – 3.72 (m, 1H), 3.16 (dd, *J* 11.2, 4.7 Hz, 1H), 3.13 – 3.08 (m, 1H), 1.25 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.18, 174.31, 135.97, 133.00, 132.55, 131.12, 129.95, 129.13, 128.91, 127.89, 127.16, 124.16, 79.22, 62.54, 58.88, 47.74, 40.31, 14.09; IR (KBr): ν 3675, 3345, 2963, 2935, 2850, 1728, 1678, 1509, 1461 cm^{-1}; HRMS (ES+) calc. for $C_{18}H_{19}O_4S$ $[M+H]^+$: 331.0999, found : 331.1004.

Ethyl-4-hydroxy-3-(thiophene-3-carbonyl)tetrahydrothiophene-2-carboxylate (4o). Liquid, Yield 89% (101.9 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* 3.8, 1.0 Hz, 1H), 7.70 (dd, *J* 5.0, 0.9 Hz, 1H), 7.14 (dd, *J* 4.9, 4.0 Hz, 1H), 4.80 – 4.74 (m, 1H), 4.32 – 4.25 (m, 2H), 4.20 – 4.12 (m, 2H), 3.68 (d, *J* 7.8 Hz, 1H), 3.14 (dd, *J* 11.0, 5.0 Hz, 1H), 3.06 (dd, *J* 11.1, 5.6 Hz, 1H), 1.23 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.47, 173.46, 143.43, 135.54, 133.94, 128.66, 79.11, 62.40, 59.29, 47.26, 39.62, 14.03; IR (KBr): ν 3340, 3080, 2965, 2923, 2859, 1755, 1699, 1509, 1413, 1315 cm^{-1}; HRMS (ES+) calc. for $C_{12}H_{15}O_4S_2$ $[M+H]^+$: 287.0406, found : 287.0408.

Ethyl-3-acetyl-4-hydroxytetrahydrothiophene-2-carboxylate (4r). Liquid, Yield 81% (70.7 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 – 4.56 (m, 1H), 4.21 – 4.13 (m, 3H), 3.68 (d, *J* 7.5 Hz, 1H), 3.56 (t, *J* 6.0 Hz, 1H), 3.02 – 2.97 (m, 2H), 2.28 (s, 3H), 1.27 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.96, 173.44, 77.53, 62.77, 62.41, 45.65, 39.02, 30.18, 14.08; IR (KBr): ν 3355, 3278, 2951, 2921, 2856, 1743, 1711, 1355 cm^{-1}, HRMS (ES+) calc. for $C_9H_{15}O_4S$ $[M+H]^+$: 219.0686, found : 219.0689.

Ethyl-3-benzoyl-4-(sulfoxy)tetrahydrothiophene-2-carboxylate (5a). White solid, Yield 73% (105.2 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.93 (m, 2H), 7.62 (t, *J* 7.4 Hz, 1H), 7.52 – 7.49 (m, 2H), 4.91 (d, *J* 1.2 Hz, 1H), 4.65 (d, *J* 8.6 Hz, 1H), 4.48 (dd, *J* 8.6, 3.5 Hz, 1H), 4.17 – 4.12 (m, 2H), 3.40 (dd, *J* 11.6, 3.3 Hz, 1H), 3.06 (dd, *J* 11.6, 1.4 Hz, 1H), 1.22 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.08, 172.36, 136.70, 134.07, 129.03, 128.71, 77.34, 62.09, 57.19, 46.71, 41.54, 14.13; IR (KBr): ν 3540, 3310, 3060, 2985, 2936, 1729, 1681, 1597, 1580, 1448, 1376, 1187 cm^{-1}, HRMS (ES+) calc. for $C_9H_{15}O_4S$ $[M+H]^+$: 361.0410 , found : 361.0398; mp 78-81 °C.

Ethyl-3-benzoyl-4-(sulfoxy)tetrahydrothiophene-2-carboxylate (6a). White solid, Yield 70% (105.2 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* 7.4 Hz, 2H), 7.61 (t, *J* 7.4 Hz, 1H), 7.51 – 7.48 (m, 2H), 4.82 – 4.80 (m, 1H), 4.49 (t, *J* 3.8 Hz, 1H), 4.37 (d, *J* 4.0 Hz, 1H), 4.23 – 4.15 (m, 2H), 3.13 (dd, *J* 11.3, 4.6 Hz, 1H), 3.07 (dd, *J* 11.3, 4.0 Hz, 1H), 1.26 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.13, 174.32, 135.65, 134.03, 129.02, 128.97, 79.08, 62.55, 58.97, 47.69, 40.42, 14.08; IR (KBr): ν 3540, 3310, 3060, 2985, 2936, 1729, 1681, 1597, 1580, 1448, 1376, 1187 cm^{-1}, HRMS (ES+) calc. for $C_9H_{15}O_4S$ $[M+H]^+$: 361.0410 , found : 361.0411; mp 78-81 °C.

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Supplementary Material

Copies of ^1H and ^{13}C NMR of all compounds are available in the Supplementary Materials.

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