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1,4-Dithiane-2,5-diol as an efficient synthon for a straightforward synthesis of functionalized tetrahydrothiophenes via sulfa-Michael/aldol-type reactions with electrophilic alkenes

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ABSTRACT

'One-pot' tandem reactions of commercially available 1,4-dithiane-2,5-diol (the dimer of mercaptoacetaldehyde) with electrophilic alkenes resulted in the facile formation of substituted tetrahydrothiophene derivatives. Thus, sulfa-Michael/Henry and sulfa-Michael/aldol sequences provided polysubstituted tetrahydrothiophenes using in situ generated nitroalkenes and α,β-unsaturated carbonyl compounds as the electrophilic partners of mercaptoacetaldehyde dimer, respectively.

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1. Introduction

The tetrahydrothiophene moiety is the core structural component of many natural products, bioactive compounds, and synthetic intermediates. Tetrahydrothiophene-based compounds include the essential coenzyme biotin **1**, a water-soluble vitamin involved in important biological functions,[1] the cholecystokinin type-B receptor antagonist tetronothiodin **2**,[2] the nucleoside **3** showing potent activity against human cytomegalovirus,[3] and glucosidase inhibitors, such as kotalanol **4**[4] and salacinol **5**[5] (Fig. 1).

Furthermore, tetrahydrothiophene derivatives have been used in a range of chemical transformations, including asymmetric hydrogenation,[6] catalytic asymmetric epoxidation,[7] and catalytic intramolecular cyclopropanation.[8] The synthetic usefulness and the wide range of biological activities give tetrahydrothiophenes a privileged role in organic chemistry. Accordingly, various approaches to these interesting scaffolds have been developed, the earliest and present most common ones being listed in our recent paper dealing with the synthesis of nitrohydroxylated tetrahydrothiophenes by 'one-pot' tandem sulfa-Michael/Henry reactions.[9]

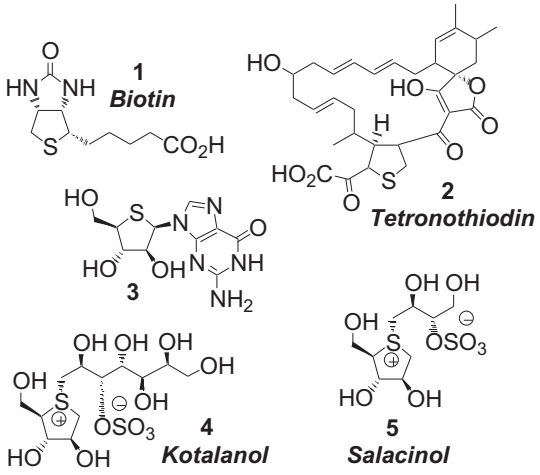

Fig. 1. Structure of bioactive tetrahydrothiophenes **1**–**5**.

2. Results and discussion

Our studies entailed the use of 1,4-dithiane-2,5-diol **6**, the mercaptoacetaldehyde dimer, as a convenient and efficient synthon incorporating a thiol group able to add to in situ generated

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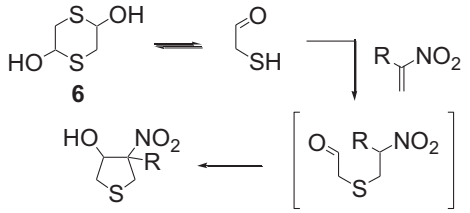
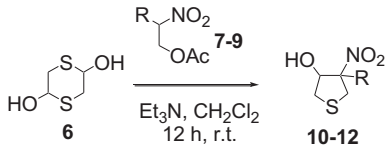
nitroalkenes. The derived nitroalkane adducts provided 4-nitro-tetrahydrothiophen-3-ol scaffolds through a subsequent intramolecular nitroaldol reaction (Scheme 1).



Scheme 1. General approach to the synthesis of 4-nitro-tetrahydrothiophen-3-ol derivatives via tandem reactions.

Thus, tandem sulfa-Michael/Henry sequences smoothly took place by reaction of 2-nitroethylacetates **7**–**9**, used as stable precursors for the corresponding nitroalkenes, with dimer **6** in dichloromethane containing triethylamine providing good yields of the expected 4-nitro-tetrahydrothiophen-3-ols **10**–**12** as 1.5:1 mixtures of diastereomers (Table 1).[9,10] The ratio was determined by integration of characteristic signals in their ^{1}H NMR spectra.

Table 1
Synthesis of tetrahydrothiophene compounds **10**–**12**

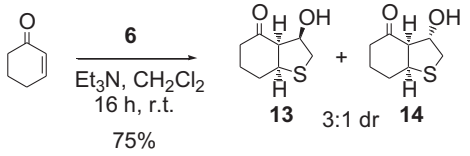


Nitroacetate	R	Product (dr)	Yield[a] (%)
7	H	**10** (1.5:1)	65
8	CH_2OH	**11** (1.5:1)	70
9	$(CH_2)_2OCH_2OMe$	**12** (1.5:1)	80

[a] Isolated yield after purification by column chromatography.

Quite surprisingly, the simple two-carbon atom unit incorporating a thiol group and an additional electrophilic functionality, such as the aldehydic group, has been only occasionally used in domino reactions with α,β-unsaturated carbonyl compounds.[11]

We envisioned the reaction of 1,4-dithiane-2,5-diol **6** with cyclohexenone as a straightforward route to the hexahydro-benzothiophen-4-one nucleus, the scaffold of a diterpenoid isolated from the seeds of Japanese Morning Glory (*Ipomoea violacea*),[12] which seems to regulate the activity of gibberellin A_3. Indeed, the reaction, performed in dichloromethane containing catalytic triethylamine (5 mol %), proceeded smoothly via a sulfa-Michael/aldol reaction sequence leading to the formation in good yield (75%) of a 3:1 mixture of the diastereomeric hexahydro-benzothiophen-4-ones **13** and **14**, easily separated by column chromatography (Scheme 2).



Scheme 2. Synthesis of tetrahydrothiophenes **13** and **14**.

The structure of the prevalent compound **13** has been unequivocally assigned through single-crystal X-ray analysis (Fig. 2).[13]

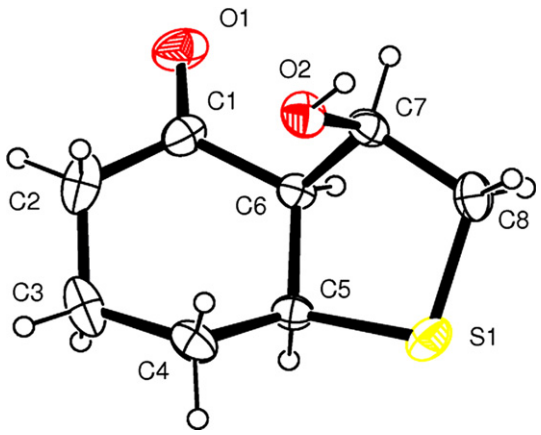
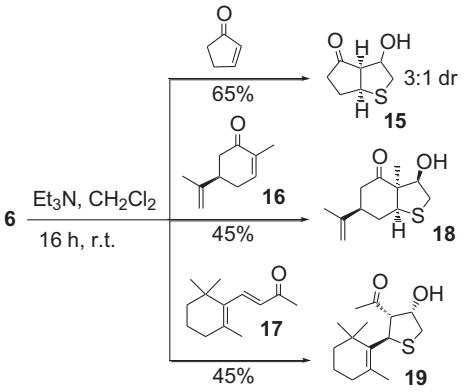


Fig. 2. ORTEP view of compound **13** displaying the thermal ellipsoids at 30% probability.

Analogously, use of different α,β-unsaturated ketones as partners of mercaptoacetaldehyde dimer in the tandem Michael-aldol reaction process resulted in the efficient preparation of monocyclic and bicyclic 3-hydroxythiophanes in good yields and high diastereoselectivity.

As shown in Scheme 3, treatment of **6** with cyclopentenone under the same conditions as above gave rise to an inseparable diastereomeric mixture of bicyclic derivatives **15** (3:1 ratio from ^{1}H NMR, 65% yield), while single stereoisomers **18** and **19** could be obtained in 45% yield through reaction of **6** with (*S*)-carvone **16** and β-ionone **17**, respectively.



Scheme 3. Synthesis of tetrahydrothiophenes **15**, **18**, and **19**.

The stereochemistry of compound **18** was tentatively assigned by NOE experiments, while X-ray crystallographic analysis allowed us to assign the structure of tetrahydrothiophene **19** (Fig. 3).[13]

In the context of our studies, we considered also dehydroalanine esters as counterparts of mercaptoacetaldehyde dimer in the tandem sulfa-Michael/aldol reaction process. These compounds have been largely utilized as Michael acceptors for conjugate addition reactions[14] even though typically considered poor electrophiles due to the electron-donating effects of the nitrogen lone pair. However, to the best of our knowledge, dehydroalanine esters have not been hitherto employed in tandem reaction processes. Therefore, we were intrigued to test the reactivity of differently *N*-

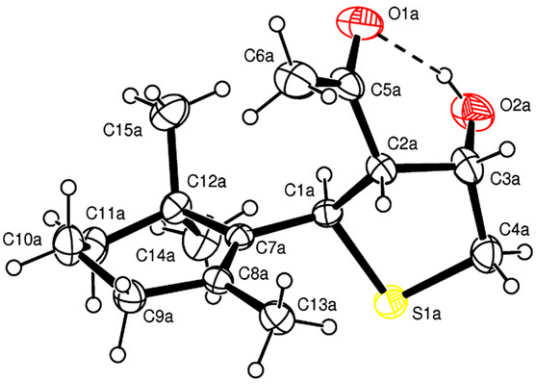
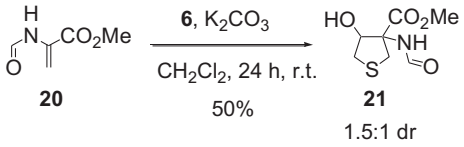


Fig. 3. ORTEP view of compound **19** displaying the thermal ellipsoids at 30% probability.

protected dehydroalanine esters in cascade reactions with a simple bifunctional reagent, such as mercaptoacetaldehyde dimer.

Thus, the reaction between **6** and methyl 2-formamidoacrylate **20**, in turn easily obtained from serine methyl ester hydrochloride and methyl formate as described in the literature,[15] performed in dichloromethane at room temperature in the presence of potassium carbonate gave the interesting 3,4-trisubstituted tetrahydrothiophene **21** in satisfactory yield (50%) as an inseparable 1.5:1 mixture of diastereomers (Scheme 4). The ratio was determined by integration of characteristic signals in their ^{1}H NMR spectra.



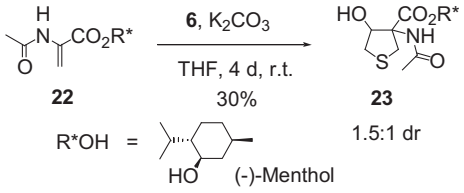
Scheme 4. Synthesis of tetrahydrothiophene **21**.

Unsuccessful attempts to induce asymmetry in this domino process using conventional organocatalysts (e.g., quinine and some derived thioureas, proline and (*S*)-diphenylprolinol TMS ether) led us to turn our attention to a chiral auxiliary-assisted approach using (−)-menthyl 2-acetamidoacrylate **22**, which could be conveniently obtained through a known two-step procedure.[16]

Menthyl esters have been conveniently applied in the copper-promoted 1,4-conjugate addition of phenylmagnesium bromide to chiral 2-acetamidoacrylates to produce *N*-acetylphenylalanine esters in high chemical yields and good diastereoselectivity.[17]

Based on these findings, we were confident that the domino reaction between mercaptoacetaldehyde dimer and (−)-menthyl 2-acetamidoacrylate **22** could be stereocontrolled by the bulky chiral auxiliary group.

Treatment of **22** with **6** in THF at room temperature in the presence of potassium carbonate provided tetrahydrothiophene **23** in disappointing low yield (30%) and diastereoselectivity (dr 1.5:1 from ^{1}H NMR) (Scheme 5). All attempts to improve the reaction outcome proved unsuccessful.



Scheme 5. Synthesis of tetrahydrothiophene **23**.

Notwithstanding, compound **23** could be considered a very interesting intermediate to accomplish a new synthetic approach to (−)-4-amino-2-thiabicyclo-[3.1.0]hexane-4,6-dicarboxylate **24**, or its *S*-oxidized variants **25** and **26** (Fig. 4), which have been shown to be highly potent and selective agonists of metabotropic glutamate receptors 2 (mGlu2) and 3 (mGlu3).[18]

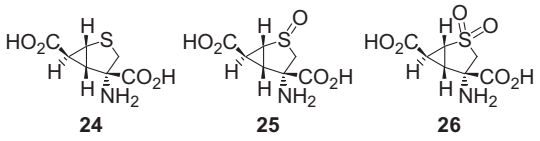
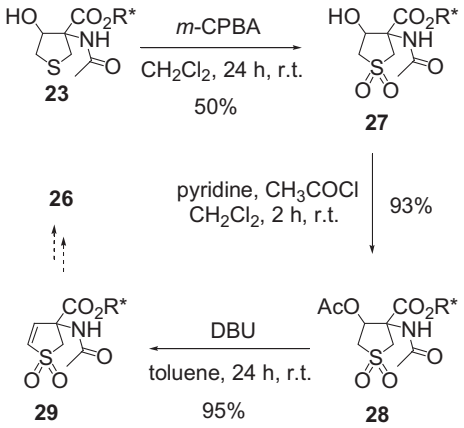


Fig. 4. Agonists of metabotropic glutamate receptors.

As shown in Scheme 6, tetrahydrothiophene **23** has been readily converted into the dihydrothiophene compound **29**, which represents an advanced intermediate toward **26**.



Scheme 6. Synthesis of compound **29**.

Thus, *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of **23** produced the intermediate sulfone **27** (50% yield), which took part in a subsequent acylation step providing the acetoxy derivative **28** in 93% yield. The latter has been eventually taken to the target compound **29** through a quantitative DBU-promoted elimination reaction.

3. Conclusion

In summary, we have developed highly efficient tandem reactions to form tetrahydrothiophene ring systems using the mercaptoacetaldehyde dimer as a common and convenient starting material. The diverse functional groups in the products obtained will permit further manipulation for synthesizing bioactive compounds.

4. Experimental

4.1. General methods

Melting points were determined on a Büchi-Tottoli apparatus.

IR spectra were recorded using a Perkin–Elmer FT-IR SPECTRUM 100 spectrophotometer equipped with ATR (diamond/ZnSe serial No. 14031), and only the more representative frequencies (cm^{-1}) are reported.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shifts (δ) are given in parts per million and coupling constants (J) in Hertz. Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Solvents were distilled prior to use and reactions were performed under nitrogen or argon atmosphere. Organic solutions were dried over anhydrous magnesium sulfate and evaporated

with a rotary evaporator. Chromatographic purifications were carried out using 70–230 mesh silica gel.

Nitroacetates **7** and **8** were prepared from commercially available 2-nitroethanol and acetyl chloride by adopting the same procedure used for the synthesis of the corresponding nitrobenzoates,[19] while nitroacetate **12** was obtained through already reported directions.[20]

4.2. General procedure for the preparation of compounds 10–12

A solution of nitroacetate (1.5 mmol) in CH_2Cl_2 (2 mL) was added to a stirred suspension of 1,4-dithiane-2,5-diol **6** (0.75 mmol) in CH_2Cl_2 (2 mL) containing triethylamine (1.65 mmol). The reaction mixture was stirred at room temperature for 12 h, then the solvent was evaporated. The residual oil was purified by flash chromatography (silica gel, EtOAc/cyclohexane 1:4).

*4.2.1. 4-Nitro-tetrahydrothiophen-3-ol (**10**).* Oil (0.14 g, 65%). Data for the major isomer: IR (neat) 3410, 1545 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.81 (dd, J=7.0, 14.0 Hz, 1H), 3.07 (dd, J=7.0, 14.0 Hz, 1H), 3.34 (dd, J=7.0, 14.0 Hz, 1H), 3.38 (dd, J=7.0, 14.0 Hz, 1H), 4.80 (q, J=7.0 Hz, 1H), 5.06 (q, J=7.0 Hz, 1H), 5.90 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.9, 37.3, 72.7, 93.9; $C_4H_7NO_3S$ (149.17): calcd C 32.21, H 4.73, N 9.39; found C 32.23, H 4.70, N 9.35. Selected data for the minor isomer: ^1H NMR (300 MHz, DMSO-d_6) δ 2.78 (dd, J=7.0, 14.0 Hz, 1H), 3.03 (dd, J=6.8, 13.6 Hz, 1H), 3.30 (dd, J=7.0, 13.0 Hz, 1H), 3.35 (dd, J=7.0, 13.0 Hz, 1H), 4.71–4.82 (m, 2H), 5.60 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.9, 37.2, 73.0, 94.0.

*4.2.2. 4-Hydroxymethyl-4-nitro-tetrahydrothiophen-3-ol (**11**).* Oil (0.19 g, 70%). Data for the major isomer: IR (neat) 3400, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.87 (dd, J=7.2, 14.6 Hz, 1H), 3.10 (d, J=8.2 Hz, 1H), 3.35 (dd, J=7.2, 14.6 Hz, 1H), 3.57 (d, J=8.2 Hz, 1H), 3.90 (d, J=14.0 Hz, 1H), 4.30 (d, J=14.0 Hz, 1H), 4.72 (br s, 1H), 5.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.3, 37.6, 60.5, 71.8, 94.7; $C_5H_9NO_4S$ (179.20): calcd C 33.51, H 5.06, N 7.82; found C 33.55, H 5.08, N 7.84. Selected data for the minor isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 3.10 (dd, J=4.0, 13.5 Hz, 1H), 3.15 (d, J=8.0 Hz, 1H), 3.20 (dd, J=6.8, 13.5 Hz, 1H), 3.61 (d, J=8.0 Hz, 1H), 3.80 (dd, J=15.0, 5.0 Hz, 1H), 3.95 (dd, J=4.5, 15.0 Hz, 1H), 4.18 (s, 2H), 5.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.8, 38.6, 72.0, 96.0.

*4.2.3. 4-(2-Methoxymethoxy-ethyl)-4-nitro-tetrahydrothiophen-3-ol (**12**).* Oil (0.28 g, 80%). Data for the major isomer: IR (neat) 3460, 1545 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 160 °C) δ 2.25 (t, J=6.0 Hz, 1H), 2.46 (t, J=6.0 Hz, 1H), 2.85 (dd, J=6.0, 15.0 Hz, 1H), 3.20 (d, J=14.0 Hz, 1H), 3.30 (dd, J=6.0, 15.0 Hz, 1H), 3.38 (s, 3H), 3.60 (m, 3H), 3.65 (d, J=14.0 Hz, 1H), 4.58 (s, 2H), 5.20 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.3, 36.4, 37.6, 55.5, 64.5, 71.3, 94.0, 97.3; $C_8H_{15}NO_5S$ (237.27): calcd C 40.50, H 6.37, N 5.90; found C 40.53, H 6.33, N 5.88. Selected data for the minor isomer: ^1H NMR (300 MHz, DMSO-d_6, 160 °C) δ 2.35 (t, J=6.0 Hz, 1H), 2.39 (t, J=6.0 Hz, 1H), 3.05 (dd, J=3.0, 15.0 Hz, 1H), 3.30 (dd, J=5.0, 15.0 Hz, 1H), 3.35 (s, 3H), 3.65 (m, 3H), 4.62 (s, 2H), 5.30 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2, 36.0, 55.7, 63.4, 76.0, 98.5.

4.3. General procedure for the preparation of compounds 13, 14, 15, 18, and 19

A suspension of dithiane **6** (1.30 mmol), enone (2.60 mmol), and triethylamine (0.13 mmol) in CH_2Cl_2 (8 mL) was stirred at room temperature for 16 h. After this time, the reaction mixture was concentrated under reduced pressure and the residue obtained was purified by column chromatography (silica gel, EtOAc/cyclohexane 1:4).

*4.3.1. 3-Hydroxy-hexahydro-benzo[b]thiophen-4-one (**13**).* White solid (0.25 g, 57%); mp 68–70 °C. IR (neat) 3500, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80–1.90 (m, 2H), 2.20–2.55 (m, 6H), 3.10 (m, 1H), 3.80 (m, 1H), 4.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 30.3, 38.1, 39.6, 47.0, 59.9, 76.9, 207.9; $C_8H_{12}O_2S$ (172.25): calcd C 55.78, H 7.02; found C 55.71, H 7.10.

*4.3.2. 3-Hydroxy-hexahydro-benzo[b]thiophen-4-one (**14**).* White solid (0.08 g, 18%); mp 78–79 °C. IR (neat) 3500, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80–1.90 (m, 2H), 1.95–2.60 (m, 6H), 2.87 (m, 1H), 3.20 (m, 1H), 4.20 (m, 1H), 5.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 28.2, 35.3, 42.1, 44.5, 56.0, 77.7, 214.5; $C_8H_{12}O_2S$ (172.25): calcd C 55.78, H 7.02; found C 55.71, H 7.10.

*4.3.3. 3-Hydroxy-hexahydro-cyclopenta[b]thiophen-4-one (**15**).* White solid (0.27 g, 65%). Data for the major isomer: IR (neat) 3600, 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10–2.40 (m, 4H), 2.70 (m, 1H), 2.85 (m, 1H), 3.15 (m, 1H), 3.90–4.10 (br s, 1H), 4.02 (m, 1H), 4.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 36.8, 38.1, 58.2, 58.3, 75.3, 218.1; $C_7H_{10}O_2S$ (158.22): calcd C 53.14, H 6.37; found C 53.20, H 6.28. Selected data for the minor isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.09–2.38 (m, 2H), 2.60 (m, 1H), 2.80 (m, 1H), 3.21 (m, 1H), 3.80–4.00 (br s, 1H), 4.30 (m, 1H), 4.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.5, 36.2, 39.7, 58.2, 58.4, 55.8, 75.4, 220.5.

*4.3.4. (3R,3aR,6S,7aS)-3-Hydroxy-6-isopropenyl-3a-methyl-hexahydro-benzo[b]thiophen-4-one (**18**).* Oil (0.26 g, 45%). IR (neat) 3300, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.63 (m, 1H), 1.66 (s, 3H), 2.00–2.40 (m, 4H), 2.82 (dd, J=12.0, 8.0 Hz, 1H), 3.09 (t, J=7.5 Hz, 1H), 3.23 (dd, J=12.0, 7.5 Hz, 1H), 4.61 (s, 1H), 4.72 (s, 1H), 4.84 (t, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 20.4, 36.3, 37.2, 42.7, 44.5, 49.7, 65.4, 74.5, 109.9, 149.3, 200.0; $C_{12}H_{18}O_2S$ (226.34): calcd C 63.68, H 8.02; found C 63.75, H 7.90.

*4.3.5. 1-[4-Hydroxy-2-(2,6,6-trimethyl-cyclohex-1-enyl)-tetrahydrothiophen-3-yl]-ethanone (**19**).* White solid (0.31 g, 45%). IR (neat) 3400, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.85 (s, 3H), 1.05 (s, 3H), 1.40–1.60 (m, 5H), 1.98 (s, 3H), 2.00 (m, 1H), 2.40 (s, 3H), 3.00 (d, J=9.0 Hz, 1H); 3.30 (m, 1H), 3.60 (dd, J=9.0, 5.0 Hz, 1H), 4.20 (s, 1H), 4.50 (d, J=10.0 Hz, 1H), 4.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 20.4, 29.0, 30.8, 34.4, 37.3, 38.3, 39.2, 51.2, 63.4, 79.7, 133.7, 135.0, 211.3; $C_{15}H_{24}O_2S$ (268.42): calcd C 67.12, H 9.01; found C 67.20; H 8.90.

4.4. Synthesis of compounds 21, and 27–29

*4.4.1. 3-Formylamino-4-hydroxy-tetrahydrothiophene-3-carboxylic acid, methyl ester (**21**).* Dithiane **6** (0.94 g, 6.20 mmol) and K_2CO_3 (1.71 g, 12.4 mmol) were added to a solution of acrylate **20** (1.60 g, 12.4 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature for 24 h, then filtered and evaporated. The residue obtained was purified by column chromatography (silica gel, EtOAc/cyclohexane 3:1) to furnish tetrahydrothiophene **21** (1.27 g, 50%) as an oil. Data for the major isomer: IR (neat) 3450, 1740, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.82–3.17 (m, 2H), 3.18 (d, J=10.7 Hz, 1H), 3.60 (d, J=10.7 Hz, 1H), 3.81 (s, 3H), 4.62 (t, J=7.1 Hz, 1H), 6.70 (br s, 1H), 8.23 (s, 1H); the ^{13}C NMR data have not been recorded as the compound slowly decomposes under the long accumulation times required to obtain the spectrum; $C_7H_{11}NO_4S$ (205.23): calcd C 40.97, H 5.40, N 6.82; found C 41.06, H 5.33, N 6.75. Selected data for the minor isomer: ^1H NMR (300 MHz, $CDCl_3$)

δ 2.75–3.01 (m, 3H), 3.50 (d, *J*=10.0 Hz, 1H), 3.75 (s, 3H), 4.80 (t, *J*=7.0 Hz, 1H), 6.40 (br s, 1H), 8.15 (s, 1H).

*4.4.2. 3-Acetylamino-4-hydroxy-tetrahydrothiophene-3-carboxylic acid, (−)-menthyl ester (**23**).* K_2CO_3 (0.22 g, 1.58 mmol) and a few drops of triethylamine were added to a stirred suspension of dithiane **6** (0.24 g, 1.58 mmol) and acrylate **22** (0.42 g, 1.58 mmol) in THF (4 mL). The reaction mixture was stirred at room temperature for 4 days, then filtered, and evaporated. The residue obtained was purified by column chromatography (silica gel, EtOAc/cyclohexane 1:1) to furnish tetrahydrothiophene **23** (0.16 g, 30%) as an oil. Data for the major isomer: IR (neat) 3500, 1660, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 6H), 0.95–2.20 (m, 9H), 2.05 (s, 3H), 2,85 (dd, *J*=7.0, 14.0 Hz, 1H), 3.05 (d, *J*=14.2 Hz, 1H), 3.15 (dd, *J*=6.8, 14.0 Hz, 1H), 3.55 (d, *J*=14.2 Hz, 1H), 4.58 (m, 1H), 4.75 (m, 1H), 6.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.6, 22.3, 23.1, 23.6, 28.1, 30.9, 34.1, 37.6, 38.4, 41.2, 47.1, 74.9, 76.4, 78.5, 169.9, 171.8; $C_{17}H_{29}NO_4S$ (343.48): calcd C 59.44, H 8.51, N 4.08; found C 59.50, H 8.47, N 4.00. Selected data for the minor isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=7.0 Hz, 6H), 0.95–1.95 (m, 9H), 2.04 (s, 3H), 2.80 (dd, *J*=14.0, 7.0 Hz, 1H), 3.10 (d, *J*=14.0 Hz, 1H), 3.20 (dd, *J*=7.0, 14.0 Hz, 1H), 3.60 (d, *J*=14.0 Hz, 1H), 4.80 (m, 1H), 6.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 20.0, 23.1, 24.2, 24.8, 27.9, 32.0, 35.0, 38.5, 39.6, 40.3, 46.1, 75.2, 77.1, 79.1, 170.0, 172.0.

*4.4.3. 3-Acetylamino-4-hydroxy-1,1-dioxo-tetrahydro-1λ⁶-thiophene-3-carboxylic acid, (−)-menthyl ester (**27**).* A solution of **23** (0.27 g, 0.80 mmol) in CH_2Cl_2 (10 mL) was treated with *m*-chloroperbenzoic acid (0.49 g, 2.00 mmol, 70%) and stirred at room temperature for 24 h. Aqueous saturated $NaHCO_3$ solution was added under stirring and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried, and evaporated under reduced pressure, yielding **27** (0.15 g, 50%) as an oil, which was sufficiently pure to be used in the next step without further purification. Data for the major isomer: IR (neat) 3450, 1660, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 6H), 0.95–2.20 (m, 9H), 2.05 (s, 3H), 3.35 (dd, *J*=6.5, 14.0 Hz, 1H), 3.45 (dd, *J*=6.5, 14.0 Hz, 1H), 3.65 (d, *J*=14.4 Hz, 1H), 4.15 (d, *J*=14.4 Hz, 1H), 4.58 (m, 1H), 4.75 (m, 1H), 6.90 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 20.7, 22.3, 23.1, 23.6, 28.1, 30.9, 34.1, 38.4, 47.1, 59.0, 59.8, 70.6, 73.5, 78.5, 169.7, 171.8; $C_{17}H_{29}NO_6S$ (375.48): calcd C 54.38, H 7.78, N 3.73; found C 54.35, H, 7.82, N 3.78. Selected data for the minor isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=7.0 Hz, 6H), 0.95–1.95 (m, 9H), 2.04 (s, 3H), 3.30 (dd, *J*=7.0, 14.0 Hz, 1H), 3.40 (dd *J*=7.0, 14.0 Hz, 1H), 3.70 (d, *J*=14.0 Hz, 1H), 4.20 (d, *J*=14.0 Hz, 1H), 4.70 (m, 1H), 4.80 (m, 1H), 6.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.6, 22.1, 23.2, 24.1, 28.9, 31.0, 35.2, 38.7, 47.6, 59.3, 60.1, 71.2, 77.6, 79.5, 170.1, 172.3.

*4.4.4. Synthesis of 4-acetoxy-3-acetylamino-1,1-dioxo-tetrahydro-1λ⁶-thiophene-3-carboxylic acid, (−)-menthyl ester (**28**).* Pyridine (0.16 mL, 2.00 mmol) and acetyl chloride (0.14 mL, 2.00 mmol) were added to a solution of compound **27** (0.15 g, 0.40 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h at room temperature, then water was added, the organic layer separated and sequentially washed with HCl 1 N and aqueous saturated $NaHCO_3$ solution. The organic extracts were dried and evaporated to give crude **28** (0.15 g, 93%) as an oil, which was used in the next step without further purification. Data for the major isomer: IR (neat) 1660, 1735, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 6H), 0.95–2.20 (m, 9H), 2.10 (s, 3H), 2.18 (s, 3H), 3.41 (dd, *J*=6.2, 14.0 Hz, 1H), 3.65 (dd, *J*=6.2, 14.0 Hz, 1H), 4.05 (d, *J*=16.0 Hz, 1H), 4.10 (d, *J*=16.0 Hz, 1H), 4.58 (m, 1H), 5.65 (m, 1H), 6.35 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5 (×2), 21.3, 22.3, 23.1, 23.6, 28.1, 30.9, 34.1, 38.4, 47.1, 56.9, 59.4, 72.8, 73.9, 78.5, 168.6, 171.2, 171.8; $C_{19}H_{31}NO_7S$ (417.52): calcd C 54.66, H 7.48, N 3.35; found: C 54.60, H 7.55, N 3.40. Selected data for the minor isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, *J*=7.0 Hz, 3H), 0.87 (d, *J*=7.0 Hz, 6H), 0.95–2.00 (m, 9H), 2.15 (s, 3H), 2.50 (s, 3H), 3.40 (dd, *J*=7.0, 14.0 Hz, 1H), 3.75 (dd *J*=7.0, 14.0 Hz, 1H), 4.00 (d, *J*=14.0 Hz, 1H), 4.15 (d, *J*=14.0 Hz, 1H), 4.80 (m, 1H), 5.60 (m, 1H), 6.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5 (×2), 21.8, 23.2, 23.8, 29.0, 31.0, 38.7, 38.9, 47.6, 59.5, 60.1, 71.2, 76.6, 79.5, 170.2, 173.0.

*4.4.5. Synthesis of 3-acetylamino-1,1-dioxo-2,3-dihydro-1H-1λ⁶-thiophene-3-carboxylic acid, (−)-menthyl ester (**29**).* Compound **28** (0.22 g, 0.53 mmol) was dissolved in toluene (8 mL) and treated with DBU (0.16 mL, 1.06 mmol). The reaction mixture was stirred at room temperature for 24 h and evaporated. The oily residue was dissolved in CH_2Cl_2 (10 mL) and sequentially washed with HCl 1 N and aqueous saturated $NaHCO_3$ solution. The organic extracts were dried and evaporated, and the crude product was purified by column chromatography (silica gel, EtOAc/cyclohexane 1:2) to give **29** (0.18 g, 95%) as an oil. IR (neat) 1660, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 6H), 0.95–2.02 (m, 9H), 2.03 (s, 3H), 3.50 (d, *J*=16.0 Hz, 1H), 3.95 (d, *J*=16.0 Hz, 1H), 4.75 (m, 1H), 6.80 (d, *J*=7.0 Hz, 1H), 7.45 (d, *J*=7.0 Hz, 1H), 9.20 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8, 21.9, 22.7, 23.0, 26.0, 31.4, 33.9, 40.0, 46.7, 56.8, 63.5, 78.3, 135.0, 137.0, 167.1, 170.0; $C_{17}H_{27}NO_5S$ (357.47): calcd C 57.12, H 7.61, N 3.92; found C 57.20, H 7.55, N 3.85.

4.5. X-ray structure determinations of compounds 13 and 19

X-ray diffraction data for compounds **13** and **19** were collected at room temperature, 295 K, on a Nonius Kappa CCD diffractometer with graphite monochromated Mo Kα radiation (λ=0.7107 Å). The structures were solved by direct methods (SIR97)[21] and refined (SHELXL-97)[22] by full matrix least squares with anisotropic non-hydrogen atoms. For compound **13** the hydrogen atoms were refined isotropically while for compound **19** the hydrogens were included on calculated positions, riding on their carrier atoms, except the O–H ones, which were refined isotropically.

Crystal data: **13**, $C_8H_{12}O_2S$; monoclinic, space group $P2_1/a$, *a*=11.5646(3), *b*=6.3291(2), *c*=12.5747(4) Å, β=114.702(1)°, *V*=836.16(4) $Å^3$, *Z*=4, D_c=1.368 g cm^{-3}. Intensity data collected with θ≤30°; 2393 independent reflections measured; 2070 observed [$I>2\sigma(I)$]. Final *R* index=0.0433 (observed reflections), *wR*=0.1138 (all reflections), *S*=1.023. CCDC N. 827486.

ORTEP[23] view of compound **13** is shown in Fig. 2. The molecules in the crystal are linked in chains by means of intermolecular O2–H···O1(1/2+*x*, −1/2−*y*, *z*) hydrogen bond with O2···O1 distance of 2.830(2) Å.

Compound **19**, $C_{15}H_{24}O_2S$; monoclinic, space group $P2_1/a$, *a*=15.0396(3), *b*=7.2266(1), *c*=28.0275(7) Å, β=104.504(1)°, *V*=2949.1(1) $Å^3$, *Z*=8, D_c=1.209 g cm^{-3}. Intensity data collected with θ≤26°; 5767 independent reflections measured; 3570 observed [$I>2\sigma(I)$]. Final *R* index=0.0483 (observed reflections), *wR*=0.1247 (all reflections), *S*=1.009. CCDC N. 827487.

The asymmetric unit contains two independent molecules. ORTEP[23] view of molecule A is shown in Fig. 3. Both molecules display an intramolecular O2–H···O1 hydrogen bond having O2···O1 distances of 2.737(3) and 2.750(3) Å, for molecules A and B, respectively.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.10.064.

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