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# Expeditious synthesis of 1-substituted taurines with diverse functionalized side-chains

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ABSTRACT

A radical addition reaction and subsequent performic acid oxidation were used for the synthesis of 1-substituted taurines with diverse functionalized side-chains from *N*-allylphthalimide and various xanthates. The current approach shows high yields and short synthetic route and reaction time. Moreover, the current method is a convenient and practical method for the synthesis of 1-substituted taurines with different functionalized side-chains.



## 1. Introduction

The good biological compatibility is a reason for the increasing interest in the preparation of amino acids. Among these compounds, 2-aminoethanesulfonic acid, known as taurine, and its derivatives have been found in many mammals, marine algaes, fishes, and shellfishes.[1,2] They are closely related to the many biological processes in living organisms. Taurine and its cyclic analogs have been reported to show different effects on ATP-dependent calcium ion uptake and protein phosphorylation in rat retina.[3] Taurine and substituted taurines are building blocks for synthesis of sulfonopeptides, important mimetics of naturally occurring peptides.[4]

Due to the importance, much attention has been devoted to the synthesis of substituted taurines.[4,5] 1-Substituted and 1,1-disubstituted taurines have been prepared via the Mitsunobu substitution from β-amino secondary and tertiary alcohols and oxidation with performic acid;[6] via a ring-opening with ammonia/amines from aliphatic thiiranes and oxidation with performic acid;[7] via the bisulfite ring-opening process from aromatic 2,2-disubstituted aziridines;[8] via the oxidation of 5-substituted thiazolidine-2-thiones;[9] and via the Michael addition from sulfur nucleophiles, such as sodium sulfite, potassium *O*-ethyl xanthate, and thiolacetic acid, and nitroolefins and subsequent (oxidation and) catalytic hydrogenation.[10]

Because important protein encoded amino acids possess various functionalized side-chains, 1-substituted taurines with different functionalized side-chains are significant sulfur analogs of naturally occurring amino acids and also a class of important natural products, such as cysteic acid, 3-amino-2-sulfopropoinic acid,[11] which is a well-known nontoxic, nonallergenic, and physiological compound, and was prepared from L-cysteine via the bromine oxidation,[12] hydrogen peroxide oxidation,[13] $I_2$–HCl oxidation,[14] or chlorine oxidation.[15] Its enantiomer was synthesized from the corresponding aziridine[5b] and thiazolidine-2-thione derivative as well.[9] Some 1-subsituted taurines with functionalized side-chains, such as alkoxy, aminoalkyl, and chloromethyl, have been prepared from the corresponding amino secondary alcohols[6b] or from the ring-opening of substituted thiiranes.[7c] Similarly, racemic and enantiopure 1-benzyloxymethyl and 1-hydroxymethyl taurines were synthesized from alkyloxymethylthiiranes via a ring-opening with dibenzylamine and further oxidation and deprotection.[7a] Boc-Arg($Cbz_2$)-ψ[$CH_2SO_2$]–$NH_2$, a 1-substituted taurinamide with a side chain containing a guanidine group, was prepared from the deprotected ornithine derivative.[16] Additionally, 5-hydroxy-2-aminopentane-1-sulfonic acid, a taurine derivative containing a hydroxypropyl side-chain, was afforded from the corresponding olefin via an amino-sulfonation process.[17] However, the side-chains of the synthesized 1-substituted taurines are limited. An efficient

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and versatile synthetic method for 1-substituted taurines with diverse functionalized side-chains is still scarce and in demand.

Thiazolidine-2-thiones[9] and *O*-ethyl *S*-2-nitroalkyl dithiocarbonates[10b] have been used as the key intermediates for the preparation of various substituted taurines. As the linear analogs of thiazolidine-2-thiones and analogs of *O*-ethyl *S*-2-nitroalkyl di-thiocarbonates, *S*-2-aminoalkyl *O*-ethyl dithiocarbonates can be considered as another class of useful precursors for the preparation of 1-substituted taurines with diverse functionalized side-chains. Various 2-*N*-phthalimidoalkylxanthates can be synthesized from *N*-allylphthalimide and different xanthates via a radical addition process according to Zard and co-workers' method (Fig. 1).[18] Herein, we describe an expeditious and versatile route for the preparation of *N*-protected 1-substituted taurines with diverse functionalized side-chains.

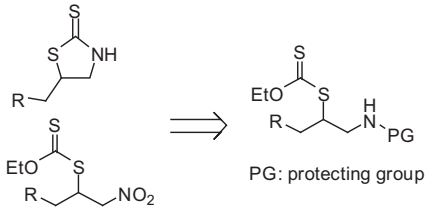
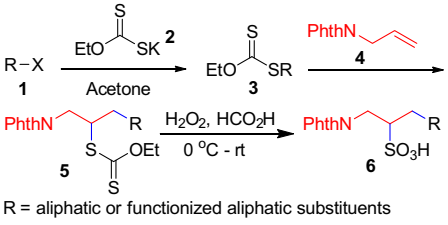



**Fig. 1.** Design on the synthesis of taurine precursors.

## 2. Results and discussion

In our studies, different xanthates **3** were prepared via the displacement of potassium *O*-ethyl xanthate **2** with various halo derivatives **1**. They reacted with *N*-allylphthalimide (**4**) to afford *S*-2-phthalimidoethyl xanthate derivatives **5**, which were oxidized to *N*-phthalimido-1-substituted taurine derivatives with performic acid (Scheme 1).



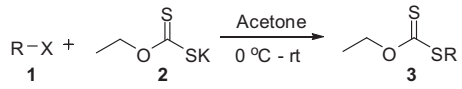

**Scheme 1.** Synthesis of 1-substituted taurine derivatives.

Various xanthates **3** were synthesized in high yields from potassium *O*-ethyl dithiocarbonate **2** and different haloalkane derivatives **1**. The results are listed in Table 1. *N*-Allylphthalimide (**4**) was prepared from allylamine in acetic acid and phthalic anhydride.

To prepare *S*-2-phthalimidoethyl xanthate derivatives **5**, we first selected the reaction of xanthate **3a** with *N*-allylphthalimide (**4**) as a model reaction with dilauroyl peroxide (DLP) as a radical initiator to optimize the reaction conditions. The results are presented in Table 2. No desired product **5a** was observed after 7 h under the total 21% loading of DLP (3 mol % DLP was added portionwise per hour) in 1,2-dichloroethane (DCE) at room temperature (Table 2, entry 1). However, the product **5a** was obtained in 8% yield at 50 °C (Table 2, entry 2), and the yield increased to 15% at 84 °C in refluxing DCE. The yield was improved to 35% by changing the ratio of **3a**:**4** to 2:1 (Table 2, entries 3 and 4). When the loading amount of DLP was increased from 3 to 5 mol % per hour, the yield was further improved remarkably from 35 to 88% (Table 2, entries 4 and 5). However, further increasing to 8 mol % DLP per hour resulted in a sudden decrease of the yield from 88 to 25% (Table 2, entry 6) possibly because DLP generated lauroyl radical, which further lossed $CO_2$ to yield dodecyl radical. The dodecyl radical combined to generate a linear alkane under a high concentration conditions. Thus, the optimal conditions are xanthate **3**: *N*-allylphthalimide (**4**) in a molar ratio of 2:1 with addition of DLP at 5 mol% per hour in refluxing DCE for 7 h (Table 2, entry 5).

A series of xanthates **5** was synthesized under the optimized conditions. The results are listed in Table 3. In most cases, *S*-2-

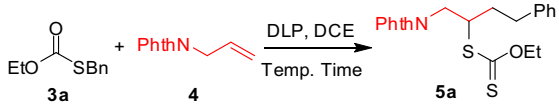
**Table 1**
Synthesis of various xanthates **3**




| Entry | R | 3 | Isolated yield (%) |
|---|---|---|---|
| 1 | Bn | **3a** | 82 |
| 2 | $AcCH_2$ | **3b** | 77 |
| 3 | $PhCOCH_2$ | **3c** | 83 |
| 4 | $PhthNCH_2$ | **3d** | 83 |
| 5 | $(EtO_2C)_2CH$ | **3e** | 72 |
| 6 | $MeO_2CCH_2$ | **3f** | 84 |
| 7 | $EtO_2CCH_2$ | **3g** | 88 |
| 8 | $C_4H_6O_2$[a] | **3h** | 61 |
| 9 | $NCCH_2$ | **3i** | 88 |
| 10 | Me | **3j** | 94 |
| 11 | *n*-Bu | **3k** | 91 |

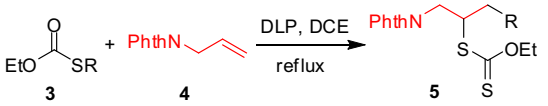
[a] 2-Oxotetrahydrofuran-3-yl.

**Table 2**
Optimization of reaction conditions in the preparation of dithiocarbonate **5a**




| Entry | 3a:4a | DLP (mol %/h) | Temp (°C) | Time (h) | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 | 1:1 | 3 | rt | 7 | 0 |
| 2 | 1:1 | 3 | 50 | 7 | 8 |
| 3 | 1:1 | 3 | 84 | 7 | 15 |
| 4 | 2:1 | 3 | 84 | 7 | 35 |
| 5 | 2:1 | 5 | 84 | 7 | 88 |
| 6 | 2:1 | 8 | 84 | 7 | 25 |

**Table 3**
Radical addition of xanthates **3** with olefin **4**



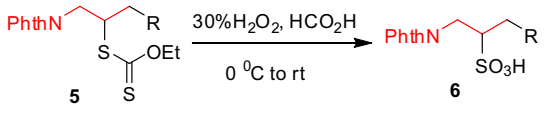

| Entry | 3 | R | 5 | Isolated yield (%) |
|---|---|---|---|---|
| 1 | **3a** | $BnCH_2$ | **5a** | 88 |
| 2 | **3b** | $AcCH_2$ | **5b** | 56 |
| 3 | **3b** | $AcCH_2$ | **5b** | 81[a] |
| 4 | **3c** | $PhCOCH_2$ | **5c** | 93 |
| 5 | **3d** | $PhthNCH_2$ | **5d** | 84 |
| 6 | **3e** | $(EtO_2C)_2CH$ | **5e** | 27 |
| 7 | **3e** | $(EtO_2C)_2CH$ | **5e** | 94[a] |
| 8 | **3f** | $MeO_2CCH_2$ | **5f** | 98 |
| 9 | **3g** | $EtO_2CCH_2$ | **5g** | 92 |
| 10 | **3h** | $C_4H_6O_2$[b] | **5h** | 94[c] |
| 11 | **3i** | $NCCH_2$ | **5i** | 79 |
| 12 | **3j** | Me | **5j** | 0 |
| 13 | **3k** | *n*-Bu | **5k** | 0 |

[a] Xanthate **3**:**4**=4:1.
[b] 2-Oxotetrahydrofuran-3-yl.
[c] Dr value is 1.1:1.0.

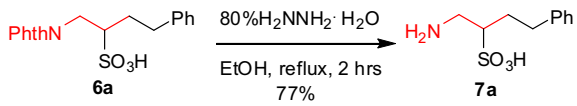
phthalimidoalkyl xanthates **5** were obtained in moderate to good yields. However, for *S*-alkyl *O*-ethyl dithiocarbonates **3j** and **3k**, no desired reaction occurred (Table 3, entries 12 and 13). According to Zard's proposed mechanism,[19] the carbon–sulfur single bond in xanthates **3** firstly underwent a homolytic cleavage to give two radicals (R• and ethoxythiocarbonylthio radical EtOCSS·) under the initiation of DLP. The formation and stability of the R• are the key factors for the reactions. When the radical carbon is attached with conjugative systems, such as phenyl (**3a**), acyl (keto) (**3b**,**c**), phthalimido (**3d**), esters (alkoxycarbonyl) (**3e**–**g**) and 2-oxotetrahydrofuran-3-yl (lacton-2-yl) (**3h**), and cyano (**3i**) groups, the radical R• groups are more stable and favorable formation due to the conjugative effect, leading to the corresponding *S*-2-phthalimidoalkyl xanthates **5** in higher yields (Table 3, entries 1–11). On the other hand, when *S*-substituents in xanthates **3** are simple aliphatic alkyl groups, neither **5j** nor **5k** was obtained because the corresponding radicals R• are highly unstable with higher energy, possibly difficult generation under the reaction conditions and favorable dimerization in the reaction system even if they generated (Table 3, entries 12 and 13). Additionally, the steric hindrance also affected the radical reactions. Compared with **5g** (Table 3, entry 9), the yield of **5e** decreased to 27% due to the bulky substituent of xanthate **3e** (Table 3, entry 6). However, the yield of **5e** was remarkably improved to 94% when the ratio of **3e**:**4** was increased to 4:1 (Table 3, entry 7).

In our previously reported method,[10b] 2-nitroalkyl xanthates were oxidized by performic acid to generate the corresponding 2-nitroalkanesulfonic acids, which were further converted to the corresponding substituted taurines under the catalytic hydrogenation. Referring to the previous oxidation conditions, *S*-2-phthalimidoalkyl xanthate **5a** was oxidized with performic acid for 12 h to afford the corresponding 4-phenyl-1-phthalimidobutane-2-sulfonic acid (**6a**) in 85% yield (Table 4, entry 1). It is well-known that the phthalimido group can be converted into the corresponding free amino group via acidic or basic hydrolysis or hydrazinolysis. Thus, the method can be used as a novel route to the preparation of *N*-phthoyl-protected or *N*-free 1-substituted taurines. Various substituted xanthates **5** were oxidized to the corresponding *N*-phthoyl-protected 1-substituted taurines **6** in moderate to good yields (Table 4). The *N*-protected taurines **6** can be used as building blocks for synthesis of sulfonopeptides. The *N*-protected taurine **6a** was selected as an example to remove the protecting group. It was refluxed in ethanol in the presence of 80% hydrazine hydrate to give rise to *N*-free taurine **7a** in a good yield (77%) (Scheme 2). Hydrazinolysis is a good choice for removal of the protecting group because it is very convenient for separation of substituted taurines from crystalline byproduct phthalhydrazide.

**Table 4**
Oxidation of aminoalkyl xanthates **5** to taurines **6**




| Entry | 5 | R | 6 | Isolated yield (%) |
|---|---|---|---|---|
| 1 | **5a** | $BnCH_2$ | **6a** | 85 |
| 2 | **5b** | $AcCH_2$ | **6b** | 92 |
| 3 | **5c** | $PhCOCH_2$ | **6c** | 54 |
| 4 | **5d** | $PhthNCH_2$ | **6d** | 90 |
| 5 | **5e** | $(EtO_2C)_2CH$ | **6e** | 87 |
| 6 | **5f** | $MeO_2CCH_2$ | **6f** | 77 |
| 7 | **5g** | $EtO_2CCH_2$ | **6g** | 78 |
| 8 | **5h** | $C_4H_6O_2$ | **6h** | 89 |
| 9 | **5i** | $NCCH_2$ | **6i** | 91 |

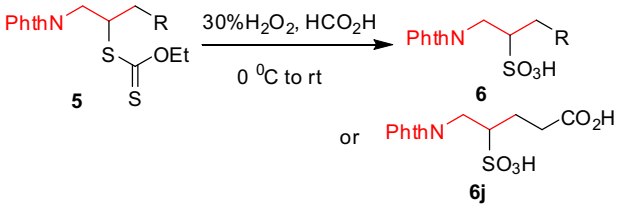



**Scheme 2.** Removal of the *N*-phthoyl protecting group via hydrazinolysis.

Besides *S*-2-phthalimidoalkyl xanthate **5a** with a phenylethyl substituent, side-chain functionalized substrates **5b**–**e** were also oxidized readily to the corresponding taurine derivatives **6b**–**e** in good yields (Table 4, entries 2–5). However, xanthates **5f**,**g** with esters and **5i** with cyano group in their side-chains produced 5-phthalimido-4-sulfonopentanoic acid (**6j**) under the same reaction conditions due to acidic hydrolysis of the esters or cyano groups. *S*-2-Phthalimidoalkyl xanthates **5f**–**i** gave rise to the corresponding 1-substituted taurines **6f**–**i** with the original side-chains when they were oxidized at room temperature with a controlled amount of water (hydrogen peroxide) in formic acid and were worked up at room temperature (Table 4, entries 6–9)(*vide post*).

It is well-known that ester and cyano groups are easily hydrolyzed to the corresponding carboxylic acids in a diluted acidic aqueous solution. Actually, only hydrolyzed product taurine **6j** was obtained when **5f** was oxidized with $H_2O_2$ (2 mL)/$HCO_2H$ (10 mL) for 1 mmol of substrate **5f** by referring to our previously reported method, that is, the solvent was removed under reduced pressure at 50–60 °C[6b,10b] (Table 5, entry 6). It demonstrates that the ester was hydrolyzed to the corresponding carboxylic acid during the oxidation process or workup. The oxidation mechanism of xanthates to sulfonic acids has been studied previously.[10b] We attempted to control the temperature and the amount of water in the performic acid oxidation to prepare the taurines with both original esters or cyano groups and the corresponding carboxylic acid group.

**Table 5**
Optional hydrolyzes during oxidation of **5** to taurines **6**[a]



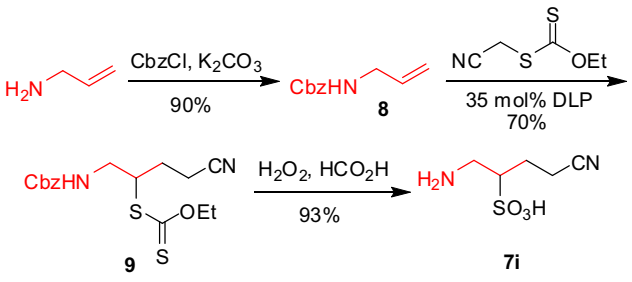

| Entry | 5[a] | Oxidation conditions | | 6 | Isolated yield (%) |
|---|---|---|---|---|---|
| | | $H_2O_2/HCO_2H$ (mL:mL) | Temp (°C) | | |
| 1 | **5f** | 0.5:10 | rt | **6f** | 75 |
| 2 | **5f** | 1:10 | rt | **6f**+**6j** (42:58) | 75 |
| 3 | **5f** | 2:10 | rt | **6f**+**6j** (37:63) | 77 |
| 4 | **5f** | 0.5:10 | 60 | **6f**+**6j** (16:84) | 76 |
| 5 | **5f** | 1:10 | 60 | **6f**+**6j** (12:88) | 77 |
| 6 | **5f** | 2:10 | 60 | **6j** | 69 |
| 7 | **6f** | 2[b]:10 | rt | **6j** | 98 |
| 8 | **6f** | 2[b]:10 | 60 | **6j** | 97 |
| 9 | **5e** | 0.5:10 | rt | **6e** | 79 |
| 10 | **5e** | 2:10 | 60 | **6e** | 80 |
| 11 | **5e** | 4:10 | 80 | **6e** | 87 |
| 12 | **5g** | 0.5:10 | rt | **6g** | 78 |
| 13 | **5g** | 2:10 | 60 | **6j** | 78 |
| 14 | **5h** | 0.5:10 | rt | **6h** | 81 |
| 15 | **5h** | 2:10 | 60 | **6h** | 89 |
| 16 | **5h** | 4:10 | 80 | **6h** | 88 |
| 17 | **5i** | 0.5:10 | rt | **6i** | 87 |
| 18 | **5i** | 2:10 | 60 | **6j** | 65 |

[a] All reactions were run in 1 mmol scale of xanthates **5**.
[b] 2 mL of water was added instead of 30% $H_2O_2$.

To control the hydrolysis, **5f** was selected as an example to investigate the oxidation conditions. The xanthate **5f** (1 mmol) was oxidized in formic acid (10 mL) with different amount of $H_2O_2$ at different temperature (Table 5, entries 1–6). The results illustrate that the xanthate **5f** was oxidized to taurine **6f** without the hydrolysis of the ester in its side-chain with 0.5 mL of $H_2O_2$ during the oxidation process for 1 day and workup at rt (Table 5, entry 1). However, it was hydrolyzed partly when $H_2O_2$ was increased to 1–2 mL, or the solvent was removed at 50–60 °C during workup (Table 5, entries 2–5). The ester group was completely hydrolyzed when 2 mL of $H_2O_2$ was added and the solvent was removed at 50–60 °C and the hydrolyzed product **6j** was obtained as sole product (Table 5, entry 6). To verify whether the hydrolysis is acidic hydrolysis or performic acid-catalyzed hydrolysis, taurine **6f** was stirred in a mixture of water (2 mL) and formic acid (10 mL) to afford taurine **6j** at both rt and 60 °C, indicating that the hydrolysis is acidic hydrolysis (Table 5, entries 7 and 8). To avoid the hydrolysis at higher temperature when removal of solvent, the reaction mixture was mixed with silica gel and allowed to evaporate to dry at room temperature during workup. Other xanthates **5g** and **5i** were converted to the corresponding taurines **6g** and **6i** or the corresponding carboxylic acid **6j**, respectively, in good yields under different oxidation conditions (0.5 mL of $H_2O_2$ at rt or 2 mL of $H_2O_2$ and removal of solvent at 50–60 °C) (Table 5, entries 12, 13, 17, and 18). To our surprise, xanthate **5e** with malonate in its side-chain cannot be hydrolyzed to the corresponding carboxylic acid under the oxidation (Table 5, entry 10), even with the more excessive amount of $H_2O_2$ (4 mL) at higher reaction temperature (at 80 °C) (Table 5, entry 11). Apparently, the malonate group is more stable than the other esters during the oxidation process possibly due to its steric hindrance. Additionally, **6h** also cannot be hydrolyzed, even after 1 day with addition of 4 mL of $H_2O_2$ at reflux temperature (Table 5, entries 14–16). The stability may be a consequence of the favorable formation of the five-membered ring γ-lactone. The results reveal that the use of excessive hydrogen peroxide and the increase of temperature have no significant effect on the hydrolysis of the side-chain malonate and γ-lactone groups in **5e** and **5h**.

Compared with previous method for the synthesis of taurine derivatives, the current method is a novel route for the preparation of 1-substituted taurines with ketone, ester, cyano, or carboxylic acid as functionalized side-chains. This process is quite practical and versatile for only two steps. In addition, the whole process is salt-free, which is beneficial for the purification of water soluble and strong polar taurine derivatives.

Having synthesized the desired functionalized and non-functionalized *N*-phthoyl-1-substituted taurines, the process was extended to the radical addition to other olefins. Benzyl *N*-allylcarbamate (**8**), generated from allylamine and benzyl chloroformate, reacted with xanthate **3i** to give rise to the corresponding *S*-2-Cbz-aminoalkyl xanthate **9** in 70% yield. Subsequent performic acid oxidation furnished the corresponding taurine derivative **7i** in 93% yield. The protecting group (Cbz) was removed, while the cyano group was remained during the oxidation process at room temperature (Scheme 3).




**Scheme 3.** Synthesis of 1-substituted taurine **9**.

## 3. Conclusion

In summary, we have developed a novel and practical protocol for the preparation of 1-substituted taurines with diverse functionalized side-chains from *N*-allylphthalimide and various xanthates with different functionalized groups via a radical addition process and subsequent performic acid oxidation. Compared with previous methods, the current approach shows higher overall yields and a short synthetic route. Additionally, the esters and cyano group in the side-chain can be hydrolyzed with diluted formic acid or at higher temperature. Controlling the amount of water in the reaction mixture and the reaction temperature can selectively realize the synthesis of 1-substituted taurines with different functionalized groups in their substituents.

## 4. Experimental section

### 4.1. General

Melting points were determined with a melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded at 400 MHz in $CDCl_3$ or $D_2O$ with TMS or DOH as the internal standards. $^{13}$C NMR spectra were recorded at 100.6 MHz in $CDCl_3$ or $D_2O$ (with $HCO_2H$ as an internal standard at 163.3 ppm). IR spectra were determined directly. HRMS spectra were recorded with an LC/MSD TOF mass spectrometer. TLC analysis was performed on glass pre-coated silica gel YT257-85 (10–40 μm) plate. Spots were visualized with UV light or iodine. Column chromatography was performed on silica gel zcx II (200–300 mesh) with silica gel (200–300 mesh) with petroleum ether and ethyl acetate as the eluent.

### 4.2. General procedure for synthesis of xanthates 3

To a solution of a haloalkane derivative **1** (25.0 mmol) in acetone (12 mL) precooled at 0 °C was added a solution of potassium *O*-ethyl dithiocarbonate **2** (4.00 g, 25.0 mmol) in acetone (25 mL) slowly under stirring at 0 °C. After the addition, the mixture was allowed to warm to rt under stirring. After acetone was evaporated, water (50 mL) was added to the residue and the mixture was extracted with $CHCl_3$ (3×50 mL). The combined organic phase was dried over $MgSO_4$. After removal of solvents with a rotary evaporator, the residue was purified on a silica gel column with petroleum ether and ethyl acetate (from 20:1 to 10:1, v/v) as eluent to afford the desired xanthate **3**. Their analytical data are identical to those reported previously (for details, see SD).

### 4.3. General procedure for synthesis of *O*-ethyl *S*-2-phthalimidoalkyl xanthates 5

A magnetically stirred solution of *N*-allylphthalimide **4** (1 equiv) and a xanthate **3** (2–4 equiv) in 1,2-dichloroethane (2–4 mL/mmol of *N*-allylphthalimide) was heated at reflux for 15 min. DLP (3–5 mol %) was added and additional DLP (5 mol %) was added per hour until complete consumption of **4**. The mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the desired product **5**.

*4.3.1. O-Ethyl S-3-phenyl-1-phthalimidomethylpropyl dithiocarbonate (**5a**).* Yellow oil, yield: 88%. $^1$H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 7.84 (dd, *J*=5.6, 3.0 Hz, 2H, ArH), 7.72 (dd, *J*=5.6, 3.0 Hz, 2H, ArH), 7.27–7.18 (m, 5H, ArH), 4.60 (dq, *J*=10.7, 7.2 Hz, 1H in $OCH_2$), 4.65 (dq, *J*=10.7, 7.2 Hz, 1H in $OCH_2$), 4.17 (dddd, *J*=8.6, 7.2, 7.1, 5.1 Hz, 1H, CHS), 4.01 (dd, *J*=14.0, 7.2 Hz, 1H in $CH_2N$), 3.96 (dd,

$J$=14.0, 7.1 Hz, 1H in $CH_2N$), 2.92 (ddd, $J$=13.8, 10.2, 5.1 Hz, 1H in $CH_2$), 2.74 (ddd, $J$=13.8, 10.4, 6.4 Hz, 1H in $CH_2$), 2.06 (dddd, $J$=14.3, 10.2, 6.4, 5.1 Hz, 1H in $CH_2$), 1.95 (dddd, $J$=14.3, 10.4, 8.6, 5.1 Hz, 1H in $CH_2$), 1.39 (t, $J$=7.2 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 212.5, 168.1, 140.9, 134.1, 131.8, 128.4, 128.3, 126.1, 123.4, 70.1, 48.9, 41.0, 33.5, 32.9, 14.1. IR ($\nu_{max}$, $cm^{-1}$) 3023.7, 2927.4, 1716.3, 1608.3, 1467.3, 1047.3, 722.1. HRMS (ESI) calcd for $C_{21}H_{21}NO_3S_2Na$ $m/z$: 422.0855 $[M+Na]^+$; found 422.0855.

*4.3.2. O-Ethyl S-4-oxo-1-phthalimidomethylpentyl dithiocarbonate (**5b**).* Yellow oil; yield: 81%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.85 (dd, $J$=5.4, 3.0 Hz, 2H, ArH), 7.73 (dd, $J$=5.4, 3.0 Hz, 2H, ArH), 4.59 (dq, $J$=10.7, 7.1 Hz, 2H, $CH_2$), 4.62 (dq, $J$=10.7, 7.1 Hz, 2H, $CH_2$), 4.14 (dddd, $J$=8.9, 7.6, 7.2, 5.1 Hz, 1H, CHS), 3.99 (dd, $J$=13.9, 7.6 Hz, 1H in $NCH_2$), 3.92 (dd, $J$=13.9, 7.2 Hz, 1H in $NCH_2$), 2.72 (ddd, $J$=18.0, 8.8, 5.7 Hz, 1H in $CH_2$), 2.64 (ddd, $J$=18.0, 8.6, 6.6 Hz, 1H in $CH_2$), 2.15 (s, 3H, $CH_3$), 2.09 (dddd, $J$=14.6, 8.9, 8.6, 5.7 Hz, 1H in $CH_2$), 1.84 (dddd, $J$=14.6, 8.8, 6.6, 5.1 Hz, 1H in $CH_2$), 1.40 (t, $J$=7.1 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 212.3, 207.1, 168.0, 134.1, 131.8, 123.4, 70.3, 48.8, 40.9, 40.3, 29.9, 25.1, 13.6. IR ($\nu_{max}$, $cm^{-1}$) 3010.1, 2930.3, 1774.0, 1715.7, 1607.5, 1469.8, 1045.7, 713.5. HRMS (ESI) calcd for $C_{17}H_{19}NO_4S_2Na$ $m/z$: 388.0648 $[M+Na]^+$; found 388.0560.

*4.3.3. O-Ethyl S-4-oxo-4-phenyl-1-phthalimidomethylbutyl dithiocarbonate (**5c**).*[20] Yellowish solids; mp: 93–97 °C; yield: 93%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.94 (d, $J$=7.6 Hz, 2H, $ArH_{ortho}$), 7.86 (dd, $J$=5.4, 3.1 Hz, 2H, ArH), 7.73 (dd, $J$=5.4, 3.1 Hz, 2H, ArH), 7.55 (dd, $J$=7.5, 7.5 Hz, 1H, $ArH_{para}$), 7.45 (dd, $J$=7.6, 7.5 Hz, 2H, $ArH_{meta}$), 4.58 (q, $J$=7.1 Hz, 2H, $CH_2O$), 4.26 (dddd, $J$=9.2, 7.5, 7.3, 4.6 Hz, 1H, SCH), 4.06 (dd, $J$=14.0, 7.5 Hz, 1H in $NCH_2$), 3.99 (dd, $J$=14.0, 7.3 Hz, 1H in $NCH_2$), 3.26 (ddd, $J$=17.6, 9.0, 5.4 Hz, 1H in $CH_2$), 3.18 (ddd, $J$=17.6, 8.3, 6.8 Hz, 1H in $CH_2$), 2.29 (dddd, $J$=14.6, 9.0, 6.8, 4.6 Hz, 1H in $CH_2$), 2.02 (dddd, $J$=14.6, 9.2, 8.3, 5.4 Hz, 1H in $CH_2$), 1.39 (t, $J$=7.1 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 212.3, 198.6, 168.0, 136.6, 134.1, 133.1, 131.8, 128.6, 128.0, 123.4, 70.3, 48.9, 41.1, 35.4, 25.7, 13.6. IR ($\nu_{max}$, $cm^{-1}$) 3028.1, 2933.8, 1773.6, 1613.9, 1467.3, 1047.2, 714.6.

*4.3.4. O-Ethyl S-3-phthalimido-1-phthalimidomethylpropyl dithiocarbonate (**5d**).* White solid, mp: 154–155 °C; yield: 84%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.84 (dd, $J$=5.2, 3.2 Hz, 2H, ArH), 7.83 (dd, $J$=5.2, 3.2 Hz, 2H, ArH), 7.73 (dd, $J$=5.2, 3.2 Hz, 2H, ArH), 7.73 (dd, $J$=5.2, 3.2 Hz, 2H, ArH), 4.59 (dq, $J$=10.8, 7.2 Hz, 1H in $OCH_2$), 4.56 (dq, $J$=10.8, 7.2 Hz, 1H in $OCH_2$), 4.15 (dddd, $J$=8.8, 7.0, 7.0, 6.7 Hz, 1H, CHS), 4.08 (dd, $J$=14.0, 7.0 Hz, 1H in $CH_2N$), 4.01 (dd, $J$=14.0, 6.7 Hz, 1H in $CH_2N$), 3.95 (ddd, $J$=13.9, 8.1, 6.5 Hz, 1H in $CH_2N$), 3.87 (ddd, $J$=13.9, 8.5, 6.0 Hz, 1H in $CH_2N$), 2.15 (dddd, $J$=14.6, 8.8, 8.1, 6.0 Hz, 1H in $CH_2$), 2.06 (dddd, $J$=14.6, 8.5, 7.0, 6.5 Hz, 1H in $CH_2$), 1.39 (t, $J$=7.2 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 212.1, 168.12, 168.10, 134.1, 133.9, 132.1, 131.8, 123.5, 123.3, 70.3, 47.1, 40.7, 35.6, 30.5, 13.6. IR ($\nu_{max}$, $cm^{-1}$) 3110.1, 2925.3, 1712.8, 1610.7, 1431.6, 1047.0, 719.7. HRMS (ESI) calcd for $C_{23}H_{20}N_2O_5S_2Na$. $m/z$: 491.0706 $[M+Na]^+$; found 491.0718.

*4.3.5. O-Ethyl S-4-ethoxy-3-ethoxycarbonyl-4-oxo-1-phthalimidomethylbutyl dithiocarbonate (**5e**).* Yellow oil; yield: 94%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.86 (dd, $J$=5.6, 3.0 Hz, 2H, ArH), 7.73 (dd, $J$=5.6, 3.0 Hz, 2H, ArH), 4.59 (q, $J$=7.1 Hz, 2H, $CH_2$), 4.20–4.17 (m, 5H, $SCH_2$ & SCH), 4.02 (dd, $J$=14.0, 6.9 Hz, 1H in $NCH_2$), 3.97 (dd, $J$=14.0, 7.4 Hz, 1H in $NCH_2$), 3.68 (dd, $J$=9.6, 4.8 Hz, 1H, CHCO), 2.43 (ddd, $J$=14.8, 9.6, 4.4 Hz, 1H in $CH_2$), 2.14 (ddd, $J$=14.8, 10.6, 4.8 Hz, 1H in $CH_2$), 1.42 (t, $J$=7.1 Hz, 3H, $CH_3$), 1.26 (t, $J$=7.1 Hz, 3H, $CH_3$), 1.25 (t, $J$=7.1 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 212.7, 168.8, 168.5, 167.9, 134.1, 131.8, 123.4, 70.4, 61.8, 61.7, 49.6, 47.5, 41.2, 30.5, 13.9 (2C overlaps), 13.6. IR ($\nu_{max}$, $cm^{-1}$) 2981.1, 2928.8, 1719.5, 1615.9, 1467.3, 1046.3, 715.9. HRMS (ESI) calcd for $C_{21}H_{26}NO_7S_2$ $m/z$: 468.1151 $[M+H]^+$; found 468.1119.

*4.3.6. O-Ethyl S-4-methoxy-4-oxo-1-phthalimidomethylbutyl dithiocarbonate (**5f**).*[21] Yellow oil; yield: 98%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.86 (dd, $J$=5.4, 3.1 Hz, 2H, ArH), 7.73 (dd, $J$=5.4, 3.1 Hz, 2H, ArH), 4.61 (dq, $J$=10.7, 7.1 Hz, 1H in $OCH_2$), 4.58 (dq, $J$=10.7, 7.1 Hz, 1H in $OCH_2$), 4.18 (dddd, $J$=9.4, 7.6, 7.2, 4.6 Hz, 1H, SCH), 4.01 (dd, $J$=14.0, 7.6 Hz, 1H in $NCH_2$), 3.94 (dd, $J$=14.0, 7.2 Hz, 1H in $NCH_2$), 3.66 (s, 3H, $OCH_3$), 2.60 (ddd, $J$=16.4, 9.1, 5.7 Hz, 1H in $CH_2$), 2.51 (ddd, $J$=16.4, 9.0, 6.8 Hz, 1H in $CH_2$), 2.15 (dddd, $J$=14.6, 9.1, 6.8, 4.6 Hz, 1H in $CH_2$), 1.93 (dddd, $J$=14.6, 9.4, 9.0, 5.7 Hz, 1H in $CH_2$), 1.42 (t, $J$=7.1 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 212.2, 172.9, 168.0, 134.1, 131.8, 123.4, 70.3, 51.7, 48.8, 40.9, 31.2, 26.8, 13.6. IR ($\nu_{max}$, $cm^{-1}$) 3049.3, 2965.2, 1773.6, 1613.9, 1467.3, 1047.2, 714.6.

*4.3.7. O-Ethyl S-4-ethoxy-4-oxo-1-phthalimidomethylbutyl dithiocarbonate (**5g**).* Yellow oil; yield: 92%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.87 (dd, $J$=5.5, 3.1 Hz, 2H, ArH), 7.73 (dd, $J$=5.5, 3.1 Hz, 2H, ArH), 4.61 (dq, $J$=10.8, 7.2 Hz, 1H in $CH_2O$), 4.58 (dq, $J$=10.8, 7.2 Hz, 1H in $CH_2O$), 4.20 (dddd, $J$=9.6, 7.6, 7.2, 4.6 Hz, 1H, SCH), 4.12 (q, $J$=7.2 Hz, 2H, $CH_2O$), 3.98 (dd, $J$=14.0, 7.6 Hz, 1H in $NCH_2$), 3.93 (dd, $J$=14.0, 7.2 Hz, 1H in $NCH_2$), 2.58 (ddd, $J$=16.0, 9.2, 5.6 Hz, 1H in $CH_2CO$), 2.49 (ddd, $J$=16.0, 9.0, 6.9 Hz, 1H in $CH_2CO$), 2.16 (dddd, $J$=14.5, 9.2, 6.9, 4.6 Hz, 1H in $CH_2$), 1.92 (dddd, $J$=14.5, 9.6, 9.0, 5.6 Hz, 1H in $CH_2$), 1.41 (t, $J$=7.2 Hz, 3H, $CH_3$), 1.24 (t, $J$=7.2 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 212.2, 172.5, 168.0, 134.1, 131.8, 123.4, 70.5, 60.6, 48.8, 40.9, 31.4, 26.8, 14.1, 13.6. IR ($\nu_{max}$, $cm^{-1}$) 3028.1, 2933.8, 1773.6, 1613.9, 1467.3, 1047.2, 714.6. HRMS (ESI) calcd for $C_{18}H_{22}NO_5S_2$ $m/z$: 396.0939 $[M+H]^+$; found 396.0916.

*4.3.8. O-Ethyl S-3-(2-oxotetrahydrofuran-3-yl)-1-phthalimidomethylethyl dithiocarbonate (**5h**).* Yellow oil; yield: 94%. Dr=1.1:1.0. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.86 (dd, $J$=5.4, 3.1 Hz, 2H, ArH), 7.74 (dd, $J$=5.4, 3.1 Hz, 2H, ArH), 4.66–4.54 (m, 2H, $OCH_2$), 4.40–3.94 (m, 5H, $OCH_2$, SCH, & $NCH_2$), 2.89 (dddd, $J$=11.3, 11.2, 8.7, 3.8 Hz, 1H, CHCO), 2.49 (dddd, $J$=12.3, 8.3, 6.3, 1.8 Hz, 1H in $CH_2CO$), 2.31 (ddd, $J$=14.8, 11.0, 3.8 Hz, 1H in $CH_2CS$), 1.98 (dddd, $J$=12.3, 11.3, 11.0, 8.7 Hz, 1H in $CH_2CO$), 1.83 (ddd, $J$=14.8, 11.2, 4.0 Hz, 1H in $CH_2CS$), 1.40 (t, $J$=7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (100.6 MHz, $CDCl_3$) ($\delta$, ppm) 212.1, 178.4, 168.0, 134.2, 131.7, 123.4, 70.6, 66.4, 48.2, 41.5, 37.3, 32.2, 29.2, 13.6. IR ($\nu_{max}$, $cm^{-1}$) 3049.3, 2965.2, 1773.6, 1613.9, 1467.3, 1047.2, 714.6. HRMS (ESI) calcd for $C_{18}H_{20}NO_5S_2$ $m/z$: 394.0783 $[M+H]^+$; found 394.0650.

*Its diastereoisomer.* $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.85 (dd, $J$=5.4, 3.1 Hz, 2H, ArH), 7.73 (dd, $J$=5.4, 3.1 Hz, 2H, ArH), 4.66–4.54 (m, 2H, $OCH_2$), 4.40–3.94 (m, 5H, $OCH_2$, SCH, & $NCH_2$), 2.83 (dddd, $J$=11.3, 8.8, 8.7, 5.8 Hz, 1H, CHCO), 2.61 (dddd, $J$=12.6, 8.4, 6.3, 1.9 Hz, 1H in $CH_2CO$), 2.33 (ddd, $J$=14.8, 6.5, 6.2 Hz, 1H in $CH_2CS$), 2.13 (dddd, $J$=12.6, 11.0, 11.0, 8.6 Hz, 1H in $CH_2CO$), 1.86 (ddd, $J$=14.8, 8.2, 8.0 Hz, 1H in $CH_2CS$), 1.40 (t, $J$=7.1 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 212.3, 178.3, 168.0, 134.1, 131.7, 123.5, 70.4, 66.5, 48.1, 40.2, 37.4, 33.0, 29.4, 13.6. HRMS (ESI) calcd for $C_{18}H_{20}NO_5S_2$ $m/z$: 394.0783 $[M+H]^+$; found 394.0650.

*4.3.9. O-Ethyl S-3-cyano-1-phthalimidomethylethyl dithiocarbonate (**5i**).* Yellow solid; mp: 96–99 °C; yield: 79%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.87 (dd, $J$=5.5, 3.1 Hz, 2H, ArH), 7.75 (dd, $J$=5.5, 3.1 Hz, 2H, ArH), 4.63 (q, $J$=7.1 Hz, 2H, $CH_2$), 4.24 (dddd, $J$=9.5, 7.1, 7.1, 4.8 Hz, 1H, CHS), 4.03 (dd, $J$=14.1, 7.1 Hz, 1H in $CH_2N$), 3.96 (dd, $J$=14.1, 7.1 Hz, 1H in $CH_2N$), 2.76 (ddd, $J$=16.9, 8.8, 5.6 Hz, 1H in $CH_2CN$), 2.56 (ddd, $J$=16.9, 8.8, 7.1 Hz, 1H in $CH_2CN$), 2.19 (dddd, $J$=14.6, 8.8, 7.1, 4.8 Hz, 1H in $CH_2$), 2.00 (dddd, $J$=14.6, 9.5, 8.8, 5.6 Hz, 1H in $CH_2$), 1.43 (t, $J$=7.1 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 211.0, 167.9, 134.3, 131.7, 123.6, 118.6, 70.7, 48.4,

40.4, 27.9, 14.9, 13.6. IR ($\nu_{max}$, $cm^{-1}$) 3009.4, 2927.4, 2244.8, 1715.6, 1613.9, 1467.2, 1045.5, 713.8. HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3S_2$ *m/z*: 349.0681 $[M+H]^+$; found 349.0650.

### 4.4. General procedure for synthesis of vicinal amino-alkanesulfonic acids 6

*Procedure A without hydrolysis of side-chains*: To a performic acid solution, prepared by mixing and stirring 30% $H_2O_2$ (0.5 mL) and 98% $HCO_2H$ (10 mL) at room temperature for 1 h and cooled in an ice bath, was added dropwise a solution of a dithiocarbonate derivative **5** (1 mmol) in 98% formic acid (2 mL), keeping the temperature at 0 °C. After the mixture was stirred at 0 °C for 2 h and at room temperature for 20 h, the resulting mixture was mixed with silica gel and allowed to evaporate to dry at room temperature. The residue was separated on a silica gel column with a mixture of chloroform and methanol in 20:1–10:1 (v/v), and methanol as eluents to give the pure product **6**.

*Procedure B with hydrolysis of side-chains in **5f,g,i***: To a performic acid solution, prepared by mixing and stirring 30% $H_2O_2$ (2 mL) and 98% $HCO_2H$ (10 mL) at room temperature for 1 h and cooled in an ice bath, was added dropwise a solution of a dithiocarbonate derivative **5** (1 mmol) in 98% formic acid (2 mL), the resulting mixture was stirred overnight at rt. After removal of solvent under reduce pressure at 50–60 °C and washing with chloroform, the residue was crystallized from methanol to afford pure product **6j**.

*4.4.1. 4-Phenyl-1-phthalimidobutane-2-sulfonic acid (**6a**).* Colorless oil; yield: 85%. $^1H$ NMR ($D_2O$, 400 MHz) ($\delta$, ppm) 7.44 (dd, *J*=5.2, 3.0 Hz, 2H, ArH), 7.35 (dd, *J*=5.2, 3.0 Hz, 2H, ArH), 6.64–6.50 (m, 5H, ArH), 3.58 (dd, *J*=14.1, 4.8 Hz, 1H in $NCH_2$), 3.39 (dd, *J*=14.1, 4.7 Hz, 1H in $NCH_2$), 2.81 (dddd, *J*=8.4, 4.8, 4.7, 4.7 Hz, 1H, SCH), 2.43 (ddd, *J*=13.9, 6.0, 6.0 Hz, 1H in $CH_2$), 2.28 (ddd, *J*=13.9, 9.3, 5.8 Hz, 1H in $CH_2$), 1.94 (dddd, *J*=14.9, 6.0, 6.0, 4.7 Hz, 1H in $CH_2$), 1.40 (dddd, *J*=14.9, 9.3, 8.4, 5.8 Hz, 1H in $CH_2$). $^{13}C$ NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 169.4, 140.8, 134.6, 130.7, 128.3, 125.8, 123.3, 56.0, 38.4, 32.8, 29.6. IR ($\nu_{max}$, $cm^{-1}$) 3344.4, 2347.3, 1704.8, 1219.3. HRMS (ESI) calcd for $C_{18}H_{18}NO_5S$ *m/z*: 360.0900 $[M+H]^+$; found 360.0874.

*4.4.2. 5-Oxo-1-phthalimidohexane-2-sulfonic acid (**6b**).* Colorless crystals, mp: 179–183 °C; yield: 92%. $^1H$ NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.58–7.56 (m, 4H, ArH), 3.83 (dd, *J*=14.4, 6.6 Hz, 1H in $NCH_2$) 3.60 (dd, *J*=14.4, 7.6 Hz, 1H in $NCH_2$), 3.01 (dddd, *J*=8.8, 7.6, 6.6, 6.4 Hz, 1H, CHS), 2.69–2.58 (m, 1H, SCH), 1.94 (s, 3H, $COCH_3$), 1.92 (m, 1H, $CH_2$, Overlapped with COMe), 1.78–1.72 (m, 1H in $CH_2$), 1.61 (m, 1H in $CH_2$). $^{13}C$ NMR ($D_2O$: HCOOH as the internal standard, 100 MHz) ($\delta$, ppm) 215.4, 170.7, 135.5, 131.8, 124.1, 57.1, 40.7, 38.6, 30.0, 22.5. IR ($\nu_{max}$, $cm^{-1}$) 3344.8, 2518.4, 1709.5, 1222.9. HRMS (ESI) calcd for $C_{14}H_{16}NO_6S$ *m/z*: 326.0698 $[M+H]^+$; found 326.0936.

*4.4.3. 5-Oxo-1-phthalimidopentane-2-sulfonic acid (**6c**).* Colorless crystals; mp 72–76 °C, yield: 54%. $^1H$ NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.54 (d, *J*=8.0 Hz, 2H, $ArH_{ortho}$), 7.62 (dd, *J*=5.4, 3.1 Hz, 2H, ArH), 7.56 (dd, *J*=5.4, 3.1 Hz, 2H, ArH), 7.20 (dd, *J*=7.6, 7.2 Hz, 1H, $ArH_{para}$), 7.06 (dd, *J*=8.0, 7.6 Hz, 2H, $ArH_{meta}$), 3.78 (dd, *J*=14.4, 5.2 Hz, 1H in $NCH_2$), 3.51 (dd, *J*=14.4, 8.8 Hz, 1H in $NCH_2$), 3.11–2.99 (m, 1H, SCH), 3.97 (ddd, *J*=15.2, 7.1, 7.1 Hz, 1H in $CH_2$), 2.89 (ddd, *J*=15.2, 7.2, 6.8 Hz, 1H in $CH_2$), 1.95 (dddd, *J*=13.6, 7.1, 7.1, 6.8 Hz, 1H in $CH_2$), 1.67 (dddd, *J*=13.6, 7.9, 7.2, 6.8 Hz, 1H in $CH_2$). $^{13}C$ NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 203.2, 169.6, 135.4, 134.7, 133.8, 130.7, 128.6, 127.8, 123.3, 56.4, 38.1, 35.7, 22.8. IR ($\nu_{max}$, $cm^{-1}$) 3028.1, 2933.8, 1773.6, 1613.9, 1467.3, 1047.2, 714.6. HRMS (ESI) calcd for $C_{19}H_{18}NO_6S$ *m/z*: 388.0849 $[M+H]^+$; found 388.0841.

*4.4.4. 1,4-Diphthalimidobutane-2-sulfonic acid (**6d**).* Colorless crystals, mp: 216–217 °C; yield: 90%. $^1H$ NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.28–7.23 (m, 4H, ArH), 7.10 (dd, *J*=5.1, 3.1 Hz, 2H, ArH), 6.95 (dd, *J*=5.1, 3.1 Hz, 2H, ArH), 3.52 (dd, *J*=13.8, 3.4 Hz, 1H in $NCH_2$), 3.42–3.33 (m, 2H, $NCH_2$), 3.20 (d, *J*=13.8 Hz, 1H in $NCH_2$), 2.83–2.74 (m, 1H, CHS), 1.92–1.87 (m, 1H in $CH_2$), 1.50–1.44 (m, 1H in $CH_2$). $^{13}C$ NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 169.9, 169.5, 135.1, 134.9, 130.2, 130.1, 123.2, 123.0, 55.4, 38.8, 37.2, 26.9. IR ($\nu_{max}$, $cm^{-1}$) 3529.1, 2383.1, 1712.1, 1, 1228.7. HRMS (ESI) calcd for $C_{20}H_{16}N_2NaO_7S$ *m/z*: 451.0576 $[M+Na]^+$; found 451.0535.

*4.4.5. Diethyl 3-phthalimido-2-sulfopropylmalonate (**6e**).* Colorless crystals, mp: 168–172 °C; yield: 87%. $^1H$ NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.67–7.62 (m, 4H, ArH), 4.02 (dq, *J*=10.8, 7.1 Hz, 1H in $CH_2O$), 3.98 (dq, *J*=10.8, 7.1 Hz, 1H in $CH_2O$), 3.94 (dd, *J*=14.2, 8.8 Hz, 1H in $NCH_2$), 3.91 (dq, *J*=10.8, 7.1 Hz, 1H in $CH_2O$), 3.89 (dq, *J*=10.8, 7.1 Hz, 1H in $CH_2O$), 3.78 (dd, *J*=9.4, 5.8 Hz, 1H, CH), 3.65 (dd, *J*=14.2, 8.8 Hz, 1H in $NCH_2$), 3.14–3.05 (m, 1H, CHS), 2.24 (ddd, *J*=14.3, 6.8, 5.8 Hz, 1H in $CH_2$), 1.95 (ddd, *J*=14.3, 9.4, 4.2 Hz, 1H in $CH_2$), 1.03 (t, *J*=7.1 Hz, 3H, $CH_3$), 0.94 (t, *J*=7.1 Hz, 3H, $CH_3$). $^{13}C$ NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 170.34, 170.29, 169.77, 169.72, 134.9, 130.9, 123.4, 62.89, 62.84, 55.0, 50.2, 38.3, 27.2, 13.13, 13.09. IR ($\nu_{max}$, $cm^{-1}$) 3401.6, 2939.9, 1772.7, 1712.7, 1439.4, 1402.7, 1224.3, 722.2. HRMS (ESI) calcd for $C_{18}H_{21}DNO_9S$ *m/z*: 429.1073 $[M+D]^+$; found 429.1052.

*4.4.6. Methyl 5-phthalimido-4-sulfopentanoate (**6f**).* Colorless crystals, mp: 109–112 °C; yield: 77%. $^1H$ NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.42–7.37 (m, 4H, ArH), 3.70 (dd, *J*=14.4, 6.0 Hz, 1H in $NCH_2$), 3.39 (dd, *J*=14.4, 8.0 Hz, 1H in $NCH_2$), 3.05 (s, 3H, $CH_3$), 2.94 (dddd, *J*=8.0, 7.2, 6.8, 6.0 Hz, 1H, SCH), 2.31 (t, *J*=7.2 Hz, 2H, $CH_2$), 1.73 (dddd, *J*=14.0, 7.2, 7.2, 6.8 Hz, 1H in $CH_2$), 1.54 (dddd, *J*=14.0, 7.2, 7.2, 6.8 Hz, 1H in $CH_2$). $^{13}C$ NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 176.9, 169.5, 134.7, 130.8, 123.2, 56.3, 48.8, 37.8, 30.8, 23.1. IR ($\nu_{max}$, $cm^{-1}$) 3441.2, 2923.8, 1770.8, 1710.0, 1401.8, 717.1. HRMS (ESI) calcd for $C_{14}H_{15}NO_7S$ *m/z*: 342.0642 $[M+H]^+$; found 342.0649.

*4.4.7. Ethyl 5-phthalimido-4-sulfopentanoate (**6g**).* Colorless crystals, mp: 189–193 °C; yield: 78%. $^1H$ NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.78–7.69 (m, 4H, ArH), 4.03–3.89 (m, 2H, $CH_2O$), 3.96 (dd, *J*=14.4, 7.3 Hz, 1H in $NCH_2$), 3.70 (dd, *J*=14.4, 7.5 Hz, 1H in $NCH_2$), 3.25–3.16 (m, 1H, CHS), 2.58 (ddd, *J*=16.9, 8.8, 7.1 Hz, 1H in $CH_2$), 2.50 (ddd, *J*=16.9, 7.1, 6.2 Hz, 1H in $CH_2$), 2.02 (dddd, *J*=14.1, 7.1, 7.1, 5.9 Hz, 1H in $CH_2$), 1.80 (dddd, *J*=14.1, 6.8, 6.8, 6.2 Hz, 1H in $CH_2$), 1.05 (t, *J*=7.0 Hz, 3H, $CH_3$). $^{13}C$ NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 175.5, 170.1, 134.8, 131.1, 123.4, 61.7, 56.3, 38.0, 31.3, 23.3, 13.2. IR ($\nu_{max}$, $cm^{-1}$) 3410.7, 2930.3, 1777.2, 1712.7, 1400.4, 1400.4, 1189.5, 717.1. HRMS (ESI) calcd for $C_{15}H_{18}NO_7S$ *m/z*: 356.0798 $[M+H]^+$; found 356.0787.

*4.4.8. 3-(2-Oxo-3-oxacyclopentyl)-1-phthalimidopropane-2-sulfonic acid (**6h**).* Colorless crystals, mp: 199–203 °C; yield: 89% (dr=1.1:1.0). $^1H$ NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.14–7.06 (m, 4H, ArH), 3.82–3.62 (m, 2H, $OCH_2$), 3.48 (dd, *J*=14.3, 5.1 Hz, 1H in $CH_2N$), 3.11 (dd, *J*=14.3, 6.6 Hz, 1H in $CH_2N$), 2.89–2.77 (m, 1H, CHS), 2.56 (dddd, *J*=10.0, 9.8, 9.6, 5.1 Hz, 1H, CHCO), 2.00–1.90 (m, 1H in $CH_2CO$), 1.73 (ddd, *J*=14.3, 8.3, 5.1 Hz, 1H in $CH_2CS$), 1.45–1.37 (m, 1H in $CH_2CO$), 1.36–1.27 (m, 1H in $CH_2CS$). $^{13}C$ NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 181.84, 169.10, 134.6, 130.62, 123.04, 67.74, 54.9, 38.3, 37.4, 28.7, 28.3.

*Its diastereoisomer*: $^1H$ NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.14–7.06 (m, 4H, ArH), 3.82–3.62 (m, 2H, $OCH_2$), 3.50 (dd, *J*=14.4, 5.8 Hz, 1H in $CH_2N$), 3.14 (dd, *J*=14.4, 8.0 Hz, 1H in $CH_2N$), 2.89–2.77 (m, 1H, CHS), 2.43 (dddd, *J*=10.8, 8.7, 8.1, 7.7 Hz, 1H, CHCO), 2.00–1.90 (m, 1H in $CH_2CO$), 1.47 (ddd, *J*=14.3, 8.0, 5.8 Hz, 1H in $CH_2CS$), 1.39–1.27 (m, 1H in $CH_2CO$), 1.09 (ddd, *J*=14.5, 9.9, 4.4 Hz, 1H in $CH_2CS$). $^{13}C$ NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 181.88, 169.12, 134.5, 130.65, 123.02, 67.67, 55.0, 37.6, 37.0, 28.8, 27.9. IR ($\nu_{max}$, $cm^{-1}$) 3429.8, 2914.2,

1767.5, 1711.6, 1434.5, 1170.5, 726.7. HRMS (ESI) calcd for $C_{15}H_{16}NO_7S$ *m/z*: 354.0642 $[M+H]^+$; found 354.0644.

*4.4.9. 4-Cyano-1-phthalimidobutane-3-sulfonic acid (**6i**).* Colorless crystals, mp: 187–190 °C; yield: 91%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.61–7.57 (m, 4H, ArH), 3.86 (dd, *J*=14.4, 6.8 Hz, 1H in $NCH_2$), 3.20 (dd, *J*=14.4, 7.5 Hz, 1H in $NCH_2$), 3.01 (dddd, *J*=8.0, 7.5, 6.8, 6.8 Hz, 1H, CHS), 2.33 (t, *J*=7.6 Hz, 2H, $CH_2$), 1.89 (dddd, *J*=14.4, 7.5, 7.1, 6.8 Hz, 1H in $CH_2$), 1.69 (dddd, *J*=14.4, 8.0, 7.5, 5.6 Hz, 1H in $CH_2$). $^{13}$C NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 177.0, 134.8, 131.1, 123.5, 120.9, 56.1, 37.8, 24.2, 14.8. IR ($\nu_{max}$, $cm^{-1}$) 3436.5, 2939.9, 2244.8 ($\nu_{CN}$), 1767.6, 1711.6, 1431.3, 1189.5, 716.9. HRMS (ESI) calcd for $C_{13}H_{12}NaN_2O_5S$ *m/z*: 331.0359 $[M+Na]^+$; found 331.0363.

*4.4.10. 5-Phthalimido-4-sulfopentanoic acid (**6j**).* Colorless crystals, mp: 228–231 °C; yield: 65%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.75–7.63 (m, 4H, ArH), 3.94 (dd, *J*=14.5, 6.8 Hz, 1H in $NCH_2$), 3.64 (dd, *J*=14.5, 7.5 Hz, 1H in $NCH_2$), 3.14 (dddd, *J*=7.5, 7.0, 6.8, 5.9 Hz, 1H, SCH), 2.41 (t, *J*=7.5 Hz, 2H, $CH_2$), 1.98 (dddd, *J*=14.0, 7.5, 7.5, 7.0 Hz, 1H in $CH_2$), 1.77 (dddd, *J*=14.0, 7.5, 7.5, 5.9 Hz, 1H in $CH_2$). $^{13}$C NMR ($D_2O$, 100 MHz) ($\delta$, ppm) 177.2, 169.9, 134.7, 131.0, 123.4, 56.4, 37.9, 30.9, 23.2. IR ($\nu_{max}$, $cm^{-1}$) 3218.8–2635.5 ($\nu_{OH}$), 1771.9, 1713.2, 1402.7, 1031.9, 720.9. HRMS (ESI) calcd for $C_{13}H_{13}NNaO_7S$ *m/z*: 350.0310 $[M+Na]^+$; found 350.0293.

### 4.5. Synthesis of 1-amino-4-phenylbutane-2-sulfonic acid (7a)

A solution of 1-phthalimido-4-phenylbutane-2-sulfonic acid (**6a**) (718 mg, 2 mmol) and 80% hydrazine hydrate (0.42 mL, 6 mmol) in ethanol (5 mL) was refluxed for 2 h. After cooling to room temperature the solution was diluted with dichloromethane (30 mL) to precipitate phthalhydrazide. After filtration and washing with dichloromethane and ethyl acetate. The combined filtrate was evaporated to dryness. The residue was crystallized from methanol to give 1-amino-4-phenylbutane-2-sulfonic acid (**7a**) as colorless crystals 353 mg, yield: 77%; mp>300 °C $^1$H NMR ($D_2O$, 400 MHz) ($\delta$, ppm) 7.19–7.05 (m, 5H, ArH) 3.19–3.15 (m, 1H in $NCH_2$), 3.11–3.05 (m, 1H in $NCH_2$), 2.89–2.83 (m, 1H, SCH), 2.66 (ddd, *J*=14.2, 7.1, 6.5 Hz, 1H in $CH_2$), 2.58 (ddd, *J*=14.2, 7.5, 7.1 Hz, 1H in $CH_2$), 2.02 (dddd, *J*=14.6, 7. 6, 6.9, 6.6 Hz, 1H in $CH_2$), 1.46 (dddd, *J*=14.6, 8.5, 7.5, 7.4 Hz, 1H in $CH_2$). $^1$H NMR (DMSO-$d_6$, 400 MHz) ($\delta$, ppm) 7.90–7.31 (m, 3H, $SO_3H$, $NH_2$), 7.30–7.12 (m, 5H, ArH), 3.15–3.03 (m, 1H in $CH_2N$), 3.02–2.90 (m, 1H in $CH_2N$), 2.83–2.73 (m, 1H, CHS), 2.72–2.55 (m, 2H, $CH_2$), 2.15–1.96 (m, 1H in $CH_2$), 1.71–1.54 (m, 1H in $CH_2$). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) ($\delta$, ppm) 141.6, 128.3, 128.2, 125.7, 55.0, 39.5, 32.1, 29.9. IR ($\nu_{max}$, $cm^{-1}$) 3247.3, 3012.5, 2728.5, 2549.1, 1563.9, 1494.2, 1081.4, 968.8. HRMS (ESI) calcd for $C_{10}H_{16}NO_3S$ *m/z*: 230.0845 $[M+H]^+$; found 230.0842.

### 4.6. Synthesis of benzyl *N*-allylcarbamate (8)[22]

A round-bottomed flask equipped with a magnetic stir bar was charged with allylamine (0.57 g, 10 mmol), 15 mL of water, potassium carbonate (0.35 g, 25 mmol), and 15 mL of ethyl acetate. The flask was cooled in an ice bath and 95% of benzyl chloroformate (1.79 g, 10.5 mmol) was added during 30 min by using a syringe pump. After stirring at room temperature for 2 h, the organic layer was separated and washed twice with 10 mL portions of 1 mol/L HCl, once with 10 mL of saturated aqueous NaCl. The combined organic phase was dried over $MgSO_4$. After removal of solvents with a rotary evaporator, the residue was purified by flash chromatography on silica gel to give the desired colorless oil **7**. Colorless oil; yield: 90%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.35–7.32 (m, 5H, ArH), 5.83 (ddt, *J*=17.1, 10.5, 5.3 Hz, 1H, CH=), 5.18 (dd, *J*=17.1, 1.4 Hz, 1H, $CH_{trans}$), 5.12 (dd, *J*=10.5, 1.4 Hz, 1H, $CH_{cis}$), 5.11 (s, 2H, $OCH_2$), 4.84 (br s, 1H, NH), 3.81 (t, *J*=7.6 Hz, 2H, $CH_2NH$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 156.2, 136.5, 134.4, 128.4, 128.0, 115.9, 66.7, 43.4.

### 4.7. Synthesis of benzyl 4-cyano-2-(ethoxycarbonothioylthio) butyl-carbamate (9)

Benzyl 4-cyano-2-(ethoxycarbonothioylthio)butylcarbamate (**9**) was obtained according to the general synthetic procedure of **5**. Yellow oil; yield: 70%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 7.38–7.32 (m, 5H, ArH), 5.13 (br s, NH), 5.10 (s, 2H, $OCH_2$), 4.64 (q, *J*=7.2 Hz, 2H, $OCH_2$), 3.94 (dddd, *J*=9.0, 7.7, 6.5, 5.7 Hz, 1H, SCH), 3.56 (ddd, *J*=14.4, 8.0, 6.2 Hz, 1H in $CH_2N$), 3.50 (ddd, *J*=14.4, 8.0, 6.2 Hz, 1H in $CH_2N$), 2.52 (ddd, *J*=16.8, 8.8, 7.6 Hz, 1H in $CH_2$), 2.48 (ddd, *J*=16.8, 8.8, 8.8 Hz, 1H in $CH_2$), 2.15 (dddd, *J*=14.0, 9.2, 8.8, 7.6 Hz, 1H in $CH_2$), 1.93 (dddd, *J*=14.0, 8.8, 8.8, 5.7 Hz, 1H, $CH_2$), 1.42 (t, *J*=7.1 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 211.8, 156.5, 136.1, 128.5, 128.2, 128.1, 118.7, 70.7, 67.1, 50.4, 43.7, 27.3, 14.9, 13.7. IR ($\upsilon_{max}$, $cm^{-1}$) 3348.1, 2932.1, 2244.8, 1721.2, 1519.7, 1231.4. HRMS (ESI) calcd for $C_{16}H_{21}N_2O_3S_2$ *m/z*: 353.0994 $[M+H]^+$; found 353.0960.

### 4.8. Synthesis of 1-amino-4-cyanobutane-2-sulfonic acid (7i)

1-Amino-4-cyanobutane-2-sulfonic acid (**7i**) was obtained according to the general synthetic procedure of **6** (Procedure A). Colorless crystals, mp: 221–223 °C; yield: 93%. $^1$H NMR ($CDCl_3$, 400 MHz) ($\delta$, ppm) 3.24 (d, *J*=6.3 Hz, 2H, $NCH_2$), 3.12 (dddd, *J*=6.9, 6.3, 6.3, 6.2 Hz, 1H, $SCH_2$), 2.69 (ddd, *J*=17.3, 7.6, 7.5 Hz, 1H in $CH_2CN$), 2.64 (ddd, *J*=17.3, 7.5, 6.6 Hz, 1H in $CH_2CN$), 2.11 (dddd, *J*=14.6, 7.6, 6.9, 6.6 Hz, 1H, $CH_2$), 1.89 (dddd, *J*=14.6, 7.6, 7.5, 6.2 Hz, 1H, $CH_2$). $^{13}$C NMR ($CDCl_3$, 100 MHz) ($\delta$, ppm) 120.5, 55.4, 39.4, 24.1, 14.5. IR ($\nu_{max}$, $cm^{-1}$) 3151.4, 3101.3, 2361.2 ($\nu_{CN}$), 1718.6, 1701.9, 1400.2, 1033.7. HRMS (ESI) calcd for$C_5H_{11}N_2O_3S$ *m/z*: 179.0485 $[M+H]^+$; found 179.0483.

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### Supplementary data

Analytical data of xanthates **3**, Copies of the $^1$H NMR and $^{13}$C NMR spectra of all key intermediates and final products. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.029. These data include MOL files and InChiKeys of the most important compounds described in this article.

### References and notes

1. Huxtable, R. J. *Physiol. Rev.* **1992**, *72*, 101–163.
2. Kalir, A. John Wiley & Sons: New York, 1991; Vol. 43, pp 767–787.
3. (a) Liebowitz, S. M.; Lombardini, J. B.; Salva, P. S. *Biochem. Pharmacol.* **1987**, *36*, 2109–2114; (b) Liebowitz, S. M.; Lombardini, J. B.; Allen, C. I. *Biochem. Pharmacol.* **1988**, *37*, 1303–1309; (c) Militante, J.; Lombardini, J. *Amino Acids* **1998**, *15*, 99–108.
4. Xu, J. X. *Chin. J. Org. Chem.* **2003**, *23*, 1–9.
5. (a) Zhang, W.; Wang, B. Y.; Chen, N.; Du, D. M.; Xu, J. X. *Synthesis* **2008**, 197–200; (b) Xu, J. X. *Tetrahedron: Asymmetry* **2002**, *13*, 1129–1134.
6. (a) Xu, J. X.; Xu, S. *Synthesis* **2004**, 276–282; (b) Xu, J. X.; Xu, S.; Zhang, Q. H. *Heteroat. Chem.* **2005**, *16*, 466–471.
7. (a) Huang, J. X.; Wang, F.; Du, D. M.; Xu, J. X. *Synthesis* **2005**, 2122–2128; (b) Huang, J. X.; Du, D. M.; Xu, J. X. *Synthesis* **2006**, 315–319; (c) Yu, H.; Cao, S. L.; Zhang, L. L.; Liu, G.; Xu, J. X. *Synthesis* **2009**, 2205–2209.
8. Chen, N.; Zhu, M.; Zhang, W.; Du, D. M.; Xu, J. X. *Amino Acids* **2009**, *37*, 309–313.
9. Chen, N.; Jia, W. Y.; Xu, J. X. *Eur. J. Org. Chem.* **2009**, 5841–5846.
10. (a) Gold, M.; Skebelsky, M.; Lang, G. *J. Org. Chem.* **1951**, *16*, 1500–1503; (b) Xu, C. X.; Xu, J. X. *Amino Acids* **2011**, 195–203; (c) Chen, N.; Xu, J. X. *Tetrahedron* **2012**, *68*, 2513–2522.

11. (a) Braghiroli, D.; Mussati, E.; Di Bella Monica, M. *Tetrahedron: Asymmetry* **1996**, *7*, 831–836; (b) Ong, J.; Kerr, D. I. B.; Abbenante, J.; Prager, R. H. *Eur. J. Pharmacol.* **1991**, *205*, 319–322.
12. Clarke, H. T. *Org. Synth.* **1955**, *Coll. Vol. 3*, 226.
13. Lipton, S. H.; Bodwell, C.; Coleman, A. H., Jr. *J. Agric. Food Chem.* **1977**, *25*, 624–628.
14. Lowe, O. G. *J. Org. Chem.* **1977**, *42*, 2524–2525.
15. Tao, F.; Luo, Y.; Wei, Q.; Zhang, G. *Amino Acids* **2004**, *27*, 149–151.
16. Lowik, D. W. P. M.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, 1219–1228.
17. Cordero, F. M.; Cacciarini, M.; Machetti, F.; De Sarlo, F. *Eur. J. Org. Chem.* **2002**, 1407–1411.
18. Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Tetrahedron* **2010**, *66*, 6656–6666.
19. Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201–236.
20. Boivin, J.; Pothier, J.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 3701–3704.
21. Verron, J.; Joerger, J. M.; Pucheault, M.; Vaultier, M. *Tetrahedron Lett.* **2007**, *48*, 4055–4058.
22. Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 3457–3465.