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On the regioselectivity for the Michael addition of thiols to unsymmetrical fumaric derivatives

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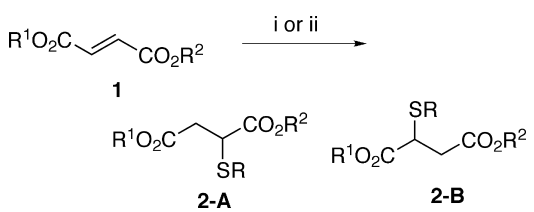
Abstract—The regiochemistry of the Michael addition of thiols to unsymmetrical fumaric derivatives was investigated. Conjugate addition of thiols to unsymmetrical fumaric diester was well controlled by the presence of lithium cation and one of the two possible regioisomers was prepared in a highly selective manner. Fumaric ester amides underwent the regioselective Michael addition that was controlled by the presence or absence of the base; either of the regioisomers was prepared as an almost diastereomerically pure form. The present control of the regiochemistry can be explained by the factors of change of active site for the addition by the coordination or non-coordination of proton or lithium cation to the carbonyls. To clarify the origin of the regioselectivity, the relative rates of the conjugate addition of thiol to acrylate derivatives were measured under competitive conditions. Ethyl acrylate reacted with thiol faster than *tert*-butyl acrylate and the rate difference was enhanced by the presence of lithium cation. In the presence of base, ethyl acrylate gave the adducts much faster than acrylamide, while under non-basic conditions acrylamide showed higher reactivity than the ester. This regioselectivity was also observed in the Michael/aldol reaction and multi-substituted γ-butyrolactones were prepared in a stereoselective manner. The thio groups introduced here served as a leaving group and a convenient stereoselective synthesis of β-, γ- and δ-lactams was developed.

1. Introduction

Efficient control of selectivity during chemical transformation has been of interest in organic chemistry. The Michael addition is regarded as a useful reaction in organic synthesis.[1] Fumaric esters are used as an active C4 building block due to the presence of two carboxylic groups that enhance the reactivity of the carbon–carbon double bond toward the Michael addition or other reactions. If the two carboxylic groups are differently derivatized, however, they incur a problem of regioselectivity. This may have been recognized as a difficult problem to solve because their steric and/or electronic differences, that should play a key role for the control of regiochemistry, are very subtle and provides insufficient control in a practical synthesis. As a result, this simple but inherent problem has remained unsolved so far. To the best of our knowledge, there has been only one report on this issue, in which a mixture of the two regioisomers was formed in poor regioselectivity.[2] Otherwise, conjugate adducts have been prepared in a different way that involves several steps.[3] In the previous paper, we reported that the Michael addition of thiols to unsymmetrical fumaric esters or amide esters was effectively controlled and either of the regioisomers could be prepared with good to high selectivity.[4] In this paper we will describe full details of the reaction as well as some investigation on its mechanistic aspect. A synthetic application that provides a useful method for the stereoselective preparation of β-, γ- and δ-lactams is also performed.



Scheme 1. *Reagents and conditions*: (i) RSH, base (0.1 equiv.), −50°C. (ii) $PhSSiMe_3$, TBAF (1 equiv.), −50°C.

Keywords: Michael addition; thiols; regioselectivity; lactams; radical cyclization.

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Table 1. Regioselective Michael addition of thiols to unsymmetric fumaric esters

Entry	R^1	R^2	R	Time (h)	Conditions	**2**; Yield (%)[a]	**A/B**[b]
1	Me	Et	Ph	1.5	Et_3N/C_2H_5CN	**2a**; 91 (7)	60/40
2	Me	Et	Ph	1.5	BuLi/THF	**2a**; 96 (3)	60/40
3	Me	Et	Ph	1.5	$BuLi/CH_2Cl_2$	**2a**; 99 (0)	59/41
4	Et	*t*Bu	Ph	4.5	Et_3N/C_2H_5CN	**2b**; 77 (2)	92/8
5	Et	*t*Bu	Ph	2.5	Bu_4NF/CH_2Cl_2[c]	**2b**; 12 (–)[d]	91/9
6	Et	*t*Bu	Ph	12	BuLi/THF	**2b**; 75 (0)	92/8
7	Et	*t*Bu	Ph	2	BuLi/DME	**2b**; 82 (0)	92/8
8	Et	*t*Bu	Ph	12	$BuLi/CH_2Cl_2$	**2b**; 84 (0)	97/3
9	Et	*t*Bu	Ph	24	BuLi/toluene	**2b**;42 (42)	94/6
10	Et	*t*Bu	*o*-MeC_6H_4–	2.5	$BuLi/CH_2Cl_2$	**2c**; 92 (0)	98/2
11	Et	*t*Bu	*p*-MeC_6H_4–	12	$BuLi/CH_2Cl_2$	**2d**; 87 (0)	96/4
12	Et	*t*Bu	Et	12	$BuLi/CH_2Cl_2$	**2e**; 75 (0)	89/11
13	Et	*t*Bu	$HOCH_2CH_2$–	1.5	$BuLi/CH_2Cl_2$	**2f**; 86 (0)	86/14
14	Et	*t*Bu	*o*-$MeOC_6H_4$–	42	$BuLi/CH_2Cl_2$	**2g**; 0 (100)	–

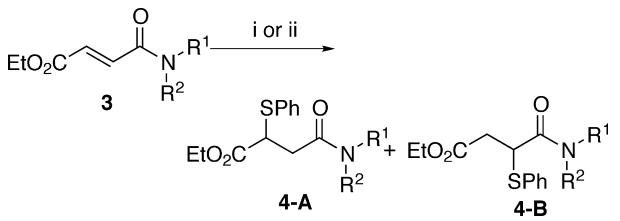
[a] Isolated yield. Recovery of the starting fumaric ester is in parentheses.
[b] Determined by ^1H NMR analyses.
[c] $PhSSiMe_3$ was used instead of PhSH.
[d] Not determined.

2. Results and discussion

2.1. Regioselective Michael addition to unsymmetrical fumaric diesters and amide esters

The Michael addition of thiophenol to unsymmetrical fumaric diester **1** was examined (Scheme 1). The results are summarized in Table 1.

Ethyl methyl fumarate underwent the Michael addition with thiophenol to give the adduct **2a** in 91% yield (entry 1). The product, as we expected, contained the two regioisomers, **2a**-**A** and **2a**-**B**, in about 1:1 ratio so that the addition occurred in non-selective manner. The use of lithium thiolate as a base promoted the reaction smoothly, but the observed selectivity was in a similar level (entries 2 and 3). To improve the regioselectivity, we examined the use of ethyl *tert*-butyl fumarate. The conventional basic Michael addition conditions brought the adduct **2b** in about 92/8 selectivity, in which **2b**-**A** was formed predominantly (entry 4). Other conditions such as PhSLi/PhSH and $PhSSiMe_3$/TBAF did not change the product ratio very much (entries 4–7). The **A** selectivity rose to 97/3 when CH_2Cl_2 was employed as the reaction solvent (entry 8). Toluene also worked as a useful solvent to achieve the high **2b**-**A** selectivity but the reaction rate decreased and the yield of **2b** was reduced to 42% (entry 9). Hence, we examined other thiols for the Michael addition under the best reaction conditions, $PhSLi/PhSH/CH_2Cl_2$.[5] *o*-Thiocresol underwent the highest selectivity 98/2 in the formation **2c** (entry 10).[6] Aliphatic thiol gave **2e** and **2f** in a less regioselective manner (entries 12 and 13). *o*-Methoxythiophenol was quite inert under these reaction conditions and no adduct was formed (entry 14).



Scheme 2. *Reagents and conditions*: (i) PhSH, Et_3N, C_2H_5CN. (ii) PhSH.

The present procedure achieved the interesting high regioselectivity in the Michael addition to unsymmetrical fumaric diesters in which regioisomers **2**-**A** were formed predominantly. We were next interested in the regiocontrol

Table 2. Regioselective conjugate addition of thiols to fumaric amide ester **3**

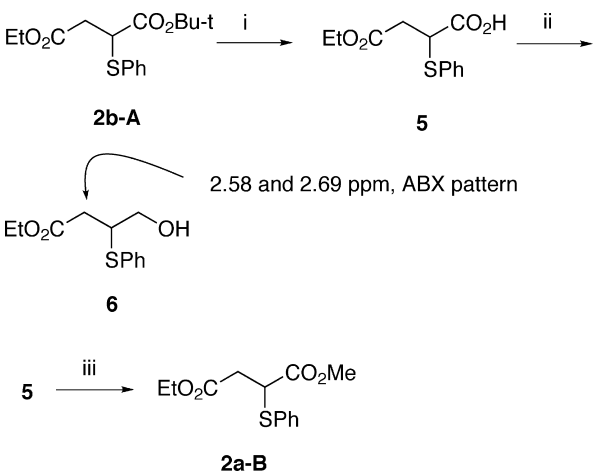
Entry	R^1	R^2	Conditions[a]	**4**	Yield (%)[b]	**A/B**[c]
1	$-(CH_2)_4-$		X	**4a**	88	10/90
2	$-(CH_2)_4-$		Y	**4a**	89	>99/1
3	$-(CH_2)_5-$		X	**4b**	87	7/93
4	$-(CH_2)_5-$		Y	**4b**	80	>98/2
5	Bn	Bn	X	**4c**	46	13/87
6	Bn	Bn	Y	**4c**	91	>98/2
7	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	X	**4d**	61	16/84
8	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	Y	**4d**	88	>98/2
9	Bn	H	X	**4e**	77	2/98
10	Bn	H	Y	**4e**	20	83/17[d]
11	OBn	H	X	**4f**	93	55/45
12	OBn	H	Y	**4f**	70	82/18

[a] X: Et_3N (0.1 equiv.), C_2H_5CN, room temperature, 6 h; Y: no solvent, room temperature, 48 h.
[b] Isolated yield.
[c] Determined by HPLC or NMR analyses.
[d] Before chromatographic purification. See Ref. 4.

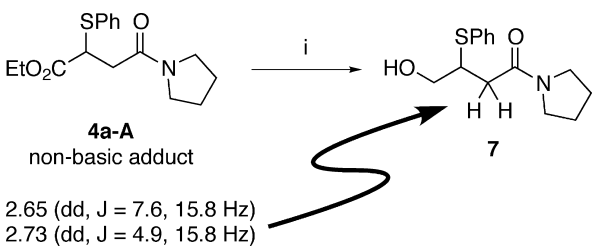
of the Michael addition with fumaric amide ester **3** (Scheme 2). The results are summarized in Table 2.

The presence of catalytic amount of Et_3N prompted the smooth Michael addition of **3a** to form the adduct **4a** in 88% yield (entry 1). Obtained **4a** consisted of two regioisomers but regioisomer **4a-B** predominated. Regioisomeric ratio was found to be 10/90 so that the addition proceeded in a good level of regioselectivity. To change or improve the regioselectivity, we tried various reaction conditions. To our surprise, the reaction occurred without an aid of base, although the reaction time took 24 h until completion. The product contained almost a single isomer that was found to be **4a-A**, the minor regioisomer obtained from the base-catalyzed conditions (entry 2). Thus, the switching of the orientation of the addition was now achieved by simple choice of the reaction conditions. The use of other fumaric amide ester also showed the same regiochemical behavior; the base-catalyzed reaction gave **4-B** selectively, while non-basic conditions brought **4-A** predominantly (entries 3–8). The use of secondary amide ester also underwent smooth formation of regioisomer **B** under the basic conditions, but the formation of **A** under the non-basic conditions occurred sluggishly (entries 9 and 10). The non-basic addition to benzyloxyamide **3f** took place smoothly to give **4f-A** in good yield, but the basic treatment of **3f** afforded a mixture of **4f-A** and **4f-B**.

Structural elucidation was carried out by chemical transformation of the adducts (Schemes 3 and 4). The adduct **2b-A**, for example, was treated with TFA to give monocarboxylic acid **5**, which was then reduced to terminal



Scheme 3. *Reagents and conditions*: (i) TFA, thioanisole, room temperature, 98%. (ii) BH_3·THF, THF, −10°C to room temperature, 48%. (iii) MeI, DBU, toluene, room temperature, 74%.



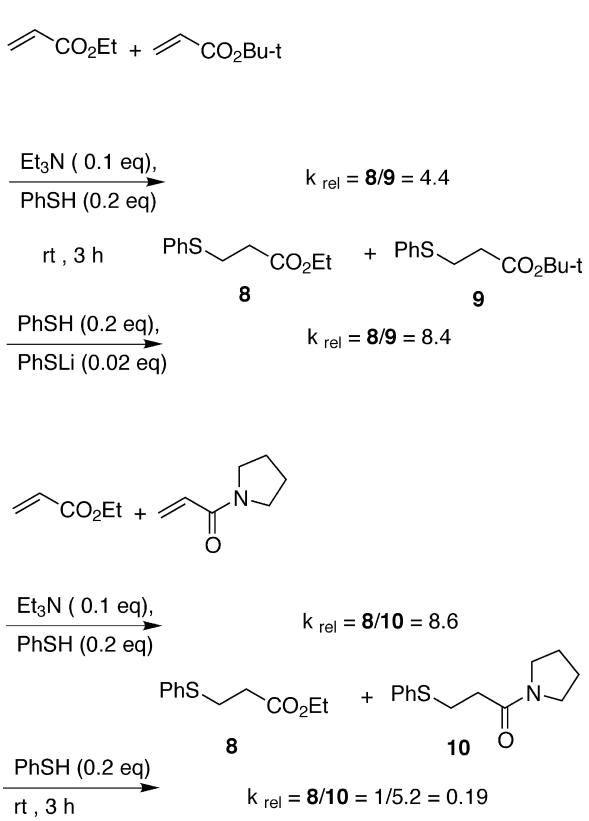
Scheme 4. *Reagents and conditions*: (i) $LiBH_4$, THF, 0°C, 25 h, 49%.

alcohol **6** in a moderate yield.[7] ^1H NMR indicated that the α-protons at the ester groups in **6** appeared in ABX pattern at 2.58 and 2.69 ppm which clearly supported the structure of **6** shown in Scheme 3. Treatment of **5** with MeI in the presence of DBU smoothly gave methyl ethyl ester, which was identical to **2a-B**.[8]

Structure determination of the amide esters **4** was performed in a similar manner. Treatment of **4a-A** with $LiBH_4$ achieved ester-selective reduction to give primary alcohol **7** in 49% yield. ^1H NMR showed α-protons of the amide group in **7** appeared at 2.65 and 2.73 ppm in ABX pattern so that the structure of **7** was determined as Scheme 4 shows. These results indicated the phenylthio group in **4a-A** was located in β-carbon to the amide group. Interestingly, between regioisomers **4-A** and **4-B** there were apparent difference in ^1H NMR patterns that was very helpful for the structural determination for other **4**; in **4-B** series, ABX around 2–3 ppm always appeared separately with wider gaps, i.e. the pair of signals was apart from each other, while the corresponding gaps for **4-A** series were narrower. Additionally, in the series of regioisomer **4-A**, the terminal methyl group in the ethyl ester always appeared in up-field than that in the regioisomer **4-B**, although the reason remained unclear. With help from these observations, we determined all of the structures of **2** and **4**.

2.2. Mechanistic investigation with competitive reaction

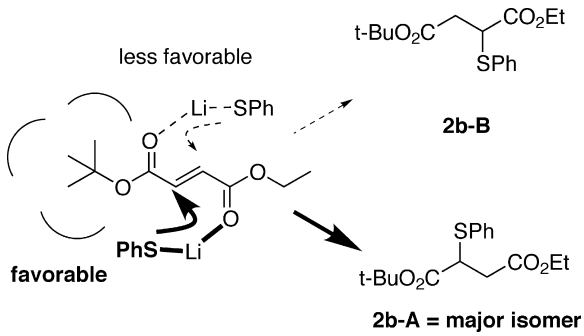
The interesting results mentioned above fascinated us to investigate the origin of the regioselectivity. First of all, we examined the relative rates of the Michael addition of thiols under various conditions (Scheme 5).



Scheme 5.

The relative rate was measured with a competitive reaction. The reaction was performed with a 1:1 mixture of the ethyl and *tert*-butyl acrylates in the presence of 0.2 equiv. of thiophenol and we measured the product ratio determined by HPLC. The presence of Et_3N gave a mixture of adducts **8** and **9** with the ratio in 4.4/1, whereas the ratio of **8/9** was enhanced to 8.4/1 in the reaction catalyzed by PhSLi/PhSH. Thus, ethyl acrylate is much reactive than *tert*-butyl acrylate and the difference of the reactivity reached about twice as much when the reaction performed in the presence of lithium thiolate. These results suggest that the ethyl ester is the much stronger activation group than the *tert*-butyl ester. Thus, the ethyl ester side plays a key role in the determination of the regiochemistry of the Michael addition.

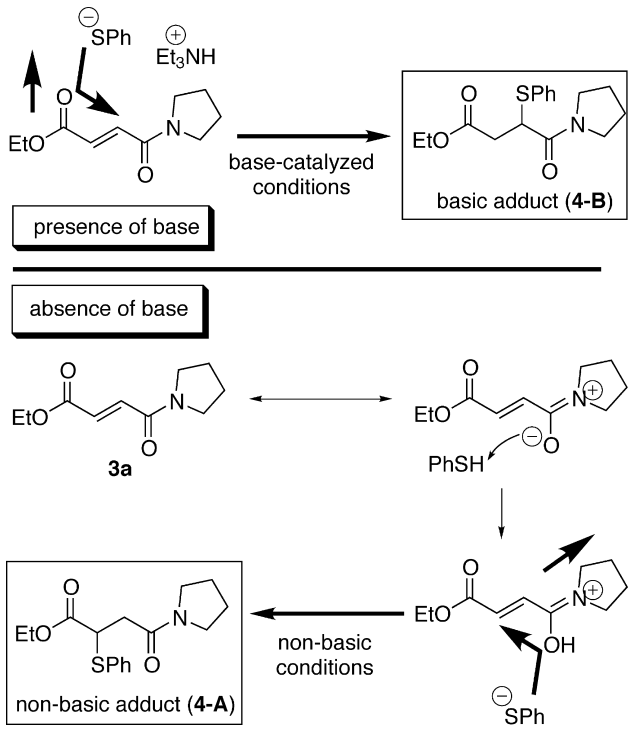
The base-catalyzed Michael addition of thiol to a mixture of acrylic ester and acrylamide smoothly proceeded to give **8** predominantly. The ratio of **8/10** reached 8.6 that showed acrylate was much reactive than acrylamide under basic conditions. Non-basic reaction furnished the totally different results. The mixture gave **10** as the main product and the ratio between **8** and **10** became 0.19. Thus, the orientation of the base-catalyzed Michael addition is governed by the ester group, while the amide group acts as a main activating group in the Michael addition without base.



Scheme 6.

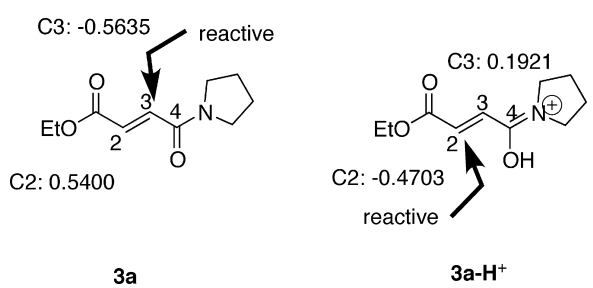
On the basis of these results, we assumed the reaction mechanism as shown in Schemes 6 and 7. The regioselectivity of the fumaric esters **1** is explained by the reactivity of difference between ethyl ester and *tert*-butyl ester; **2b**-**A** is mainly formed because the ethyl ester acts as much reactive group than *tert*-butyl ester group. The selectivity should be enhanced by the presence of lithium cation in CH_2Cl_2 which is expected to act as a Lewis acid.[9] Lithium thiolate in CH_2Cl_2 should prefer to coordinate with one of the ester carbonyl groups and activate it. Due to steric hindrance coming from *tert*-butyl group, coordination occurs more easily to the ethyl ester group, which is activated and encouraged nucleophilic attack of thiolate from its β-carbon to give **2b**-**A** selectively.

As the competitive reaction indicates, under basic Michael addition conditions, the ester group in the amide ester **3** works as much stronger activating group than the amide so thiolate anion attacks from the β-carbon of the ester group preferentially (Scheme 7, upper). Absence of base, on the other hand, causes the reaction rate to decrease. This is probably because less amount of thiolate anion is generated.



Scheme 7.

The amide carbonyl, on the other hand, acts as a Lewis base which coordinates to the acidic proton in thiophenol.[10] This activates the amide carbonyl group toward the nucleophilic addition due to contribution of the iminium form through equilibrium. The protonated amide group now becomes a much stronger activating group than the ester.[11] The addition takes place from the β-carbon of the amide selectively to give **4**-**A** as a sole product. In the secondary amide, however, sufficient formation of the iminium cation should be prevented due to releasing NH-proton from the iminium intermediates and the reaction rate under non-basic conditions decreased. To confirm these hypotheses, we executed the PM-3 level semi-empirical calculation for **3a** and **3a**-$\mathbf{H}^+$ (Scheme 8). In the optimized structure of **3a**, the coefficients of LUMO at C2 and C3 were 0.5400 and −0.5635, respectively, which indicated that C3, β-carbon of the ester, is the reactive carbon under basic conditions. When the amide carbonyl was protonated, the coefficients were calculated to be −0.4703 for C2 and 0.1921 for C3, in which C2, β-carbon of the amide, becomes much reactive toward the nucleophilic attack. These calculation results also support the observed regioselectivity for **3**.

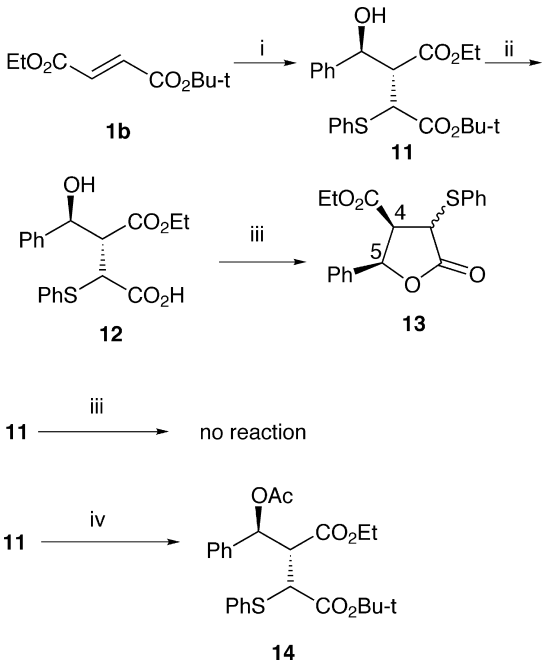


Scheme 8.

2.3. Application of the regioselective addition to the construction of heterocycles

The adducts of the present regioselective Michael addition were regarded as potentially useful intermediates in organic synthesis, because the sulfur group introduced in this reaction was expected to work as a leaving group or an activating group in the further molecular construction. So we examined several reactions for the adducts.

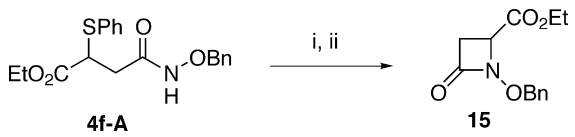
Application of the present procedure to the Michael/aldol tandem reaction was examined (Scheme 9).[12] A mixture of lithium thiolate, benzaldehyde and unsymmetrical fumarate **1b** gave a tandem adduct **11** in 83% yield. The adduct **11** contained four diastereomers which were all stereoisomers, no regioisomer of **11** was found in the crude mixture. Treatment of **11** with PPTS resulted in total recovery of the starting material, which was in contrast to the smooth formation of lactone **13** from the tandem adduct from diethyl fumarate. The lactonization from **11** smoothly occurred once the *tert*-butyl group was removed under acidic conditions. Thus, the regioselectivity of the Michael process was again achieved in a high level.



Scheme 9. *Reagents and conditions*: (i) PhSLi, PhCHO, CH_2Cl_2, −50°C, 15 h, 83%. (ii) TFA, thioanisole, room temperature. (iii) PPTS, toluene, 110°C, 89% from **11** (4,5-*cis*/4,5-*trans*=86/14). (iv) Ac_2O, DMAP, pyridine, room temperature, 2 h, 80% (dr=89:11).

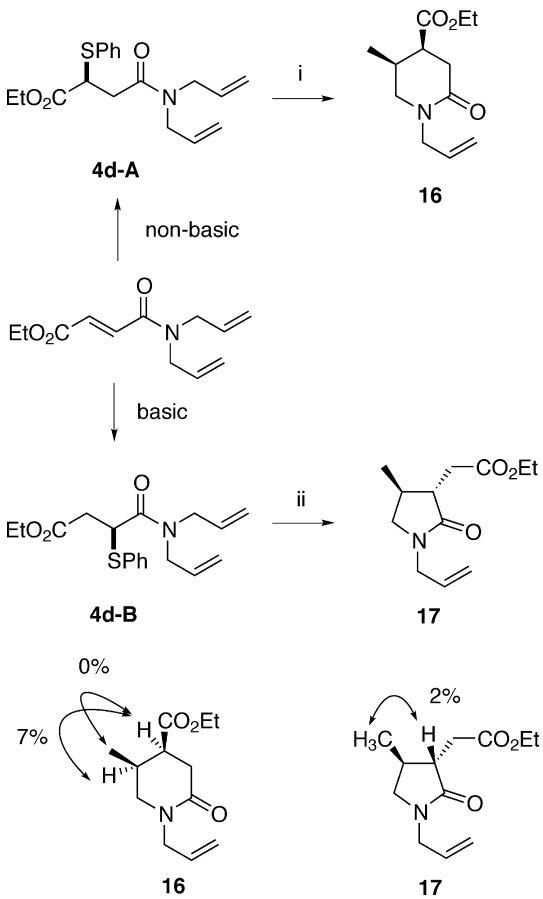
The ratio of the four diastereomers of **11** was determined after their conversion to acetate **14**, in which aldol ratio was found to be *anti*/*syn*=89/11. The ratio was close to the diastereomeric ratio of lactone **13**, 14/86.

Conversion to β-lactam was readily achieved from the adduct from *N*-benzyloxyamides (Scheme 10). Treatment of **3f-A** with MeI in the presence of $AgClO_4$ resulted in the smooth formation of sulfonium ion intermediate.[13] Subsequent exposure to K_2CO_3 provided β-lactam in **15** in 70% yield.[14]



Scheme 10. *Reagents and conditions*: (i) MeI, $AgClO_4$, MeCN, room temperature. (ii) K_2CO_3, acetone, reflux, 4 h 70%.

The use of the sulfur group as a radical precursor was examined (Scheme 11).[15] Treatment of **4d-B** with Bu_3SnH induced in the 5-*exo-trig* mode radical cyclization and 2-pyrrolidone **17** was obtained in 69% yield. No simply reduced product was observed. The diastereomeric ratio of **17** was about 5:1, in which *trans*-**17** was found to be the major isomer on the basis of NOE experiments. Compound **4d-A**, on the other hand, underwent the radical cyclization under slow-addition conditions, giving **16** in 68% yield.[16] The slow-addition of Bu_3SnH and AIBN was essential for the efficient 6-*exo-trig* mode radical cyclization, otherwise simple desulfurization dominated. To our surprise, **16** contained in a single isomer and the NOE experiment indicated the stereochemistry in **16** was *cis*.[17] No 7-*endo* cyclized product was observed.[18] Thus, this procedure realized stereoselective formation of 2-pyrrolidone **17** and 2-piperidone **16** from the same starting material **3d** in a two-step procedure. Thus, this procedure will provide a useful method for the preparation of these heterocyclic compounds.



Scheme 11. *Reagents and conditions*: (i) Bu_3SnH, AIBN, tolune, 110°C slow addition (2 h), 68% (dr >98:2). (ii) Bu_3SnH, AIBN, tolune, 110°C, 69% (dr=5:1).

In conclusion, we have demonstrated a simple solution of the control of Michael addition of thiols to unsymmetrical fumaric derivatives. This control is very efficient and desired regioisomers were prepared with high diastereomeric purity. The adduct serves as a useful intermediate for efficient heterocyclic construction in regio- and stereoselective manner. Further the use of the reaction is now underway in our laboratory.

3. Experimental

3.1. General

All reactions were carried out under nitrogen atmosphere. Purification of products were performed through flash chromatography (silica gel/hexane or hexane–ether) if necessary. Commercially available compounds except for benzaldehyde were used without further purification. Benzaldehyde was distilled under reduced pressure; it was stored under nitrogen and used within a month after the distillation. *tert*-Butyl ethyl fumarate, methyl ethyl fumarate, and fumaric amide ester derivatives were prepared from commercially available monoethyl fumaric ester. All reaction solvents were dried over appropriate drying agents and distilled before use. ^{1}H and ^{13}C NMR spectra were recorded at 270 or 400 MHz and 67.5 or 100 MHz, respectively. High resolution mass spectra (HRMS) were measured at Advanced Instrumentation Centre, Ehime University, Matsuyama, Japan.

3.1.1. Preparation of 2-*o*-tolylthiosuccinic acid 1-*tert*-butyl ester 4-ethyl ester (2c-A). General procedure. Under nitrogen atmosphere, BuLi in hexane (1.6 M, 0.0625 mL, 0.1 mmol) was added to a solution of *o*-thiocresol (128.7 mg, 1.04 mmol) in dry CH_2Cl_2 (10 mL, distilled over CaH_2) at 0°C. The resulting solution was cooled to −50°C and *tert*-butyl ethyl fumarate **1b** (193.7 mg, 0.967 mmol) was added. The reaction mixture was allowed to stir at the same temperature for 4 h. The reaction was quenched with addition of aqueous HCl (1 M, 30 mL) and the organic layer was separated. The water phase was extracted with EtOAc (3×30 mL) and the combined organic phase was dried over Na_2SO_4. After filtration and evaporation, the crude product was purified through flash chromatography (silica gel/hexane then hexane–ether) to give **2c-A** as oil in 92% yield (289.5 mg). Minor isomer **2c-B** could not be isolated. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.17 (t, 3H, J=7.3 Hz), 1.27 (s, 9H), 2.39 (s, 3H), 2.61 (dd, 1H, J=5.3, 16.9 Hz), 2.89 (dd, 1H, J=9.9, 16.8 Hz), 3.87 (dd, 1H, J=5.6, 10.2 Hz), 4.06 (q, 2H, J=7.2 Hz), 7.07–7.15 (m, 2H), 7.45–7.47 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 20.7, 27.5, 51.7, 36.4, 45.8, 61.0, 81.4, 126.2, 126.5, 127.1, 128.2, 128.4, 130.1, 131.9, 134.1, 140.8, 170.0, 170.4. Anal. calcd for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46. Found: C, 62.43; H, 7.68.

Other compound **2** were prepared in a similar manner.

3.1.2. 2-Phenylthiosuccinic acid 1-ethyl ester 4-methyl ester (2a-A). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20 (t, 3H, J=7.1 Hz), 2.73 (dd, 1H, J=6.6, 17.2 Hz), 2.96 (dd, 1H, J=9.6, 16.7 Hz), 3.68 (s, 3H), 4.01 (dd, 1H, J=6.6, 9.6 Hz), 4.14 (q, 2H, J=7.2 Hz), 7.22–7.51 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.6, 36.0, 45.3, 51.5, 61.0, 128.3, 128.7, 131.6, 133.7, 170.2, 170.6. Anal. calcd for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.01. Found: C, 57.87; H, 6.00.

3.1.3. 2-Phenylthiosuccinic acid 4-ethyl ester 1-methyl ester (2a-B). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23 (t, 3H, J=7.3 Hz), 2.73 (dd, 1H, J=5.6, 16.8 Hz), 2.95 (dd, 1H, J=9.9, 16.8 Hz), 3.70 (s, 3H), 4.02 (dd, 1H, J=5.6, 9.9 Hz), 4.13 (q, 2H, J=7.3 Hz), 7.32–7.52 (m, 5H). ^{13}C NMR δ (67.5 MHz, $CDCl_3$) 13.9, 36.5, 45.5, 52.2, 60.7, 128.5, 128.9, 131.5, 133.9, 170.2, 171.3. Anal. calcd for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.01. Found: C, 57.99; H, 6.00.

3.1.4. 2-Phenylthiosuccinic acid 1-*tert*-butyl ester 4-ethyl ester (2b-A). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.33 (t, 3H, J=7.1 Hz), 1.46 (s, 9H), 2.77 (dd, 1H, J=5.6, 16.8 Hz), 2.99 (dd, 1H, J=9.9, 17.2 Hz), 4.02 (dd, 1H, J=5.6, 9.9 Hz), 4.23 (q, 2H, J=7.3 Hz), 7.36–7.49 (m, 3H), 7.58–7.62 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 27.6, 36.4, 46.3, 60.7, 81.5, 128.2, 128.7, 128.9, 133.6, 169.9, 170.4. Anal. calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14. Found: C, 61.61; H, 7.32.

3.1.5. 2-*p*-Tolylthiosuccinic acid 1-*tert*-butyl ester 4-ethyl ester (2d-A). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.21 (t, 3H, J=6.8 Hz), 1.40 (s, 9H), 2.34 (s, 3H), 2.65 (dd, 1H, J=5.6, 16.8 Hz), 2.85 (dd, 1H, J=9.9, 16.7 Hz), 3.85 (dd, 1H, J=5.6, 9.9 Hz), 4.13 (q, 2H, J=6.9 Hz), 7.13 (d, 2H, J=7.9 Hz), 7.38 (d, 2H, J=8.1 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.1, 21.1, 27.7, 36.5, 46.5, 60.8, 81.5, 128.3, 129.6, 134.4, 138.7, 170.1, 170.7. Anal. calcd for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46. Found: C, 62.39; H, 7.51.

3.1.6. 2-Ethylthiosuccinic acid 1-*tert*-butyl ester 4-ethyl ester (2e-A). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (t, 3H, J=7.2 Hz), 1.28 (t, 3H, J=7.5 Hz), 1.48 (s, 9H), 2.61 (dd, 1H, J=5.5, 16.8 Hz), 2.70 (qd, 2H, J=7.4, 12.6 Hz), 2.92 (dd, 1H, J=10.0, 16.8 Hz), 3.57 (dd, 1H, J=5.6, 10.0 Hz), 4.15 (q, 2H, J=7.2 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.1, 14.4, 25.5, 27.8, 36.5, 42.2, 60.7, 81.4, 170.7, 170.8. Anal. calcd for $C_{12}H_{22}O_4S$: C, 54.93; H, 8.45. Found: C, 54.82; H, 8.63.

3.1.7. 2-(2-Hydroxyethylthio)succinic acid 1-*tert*-butyl ester 4-ethyl ester (2f-A). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (t, 3H, J=7.1 Hz), 1.48 (s, 9H), 2.64 (dd, 1H, J=6.9, 16.9 Hz), 2.79–3.01 (m, 4H), 3.64 (dd, 1H, J=7.2, 8.5 Hz), 3.81 (t, 2H, J=5.4 Hz), 4.17 (q, 2H, J=7.1 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 27.7, 35.0, 36.5, 42.3, 60.9, 61.0, 81.8, 170.7, 170.8. Anal. calcd for $C_{12}H_{22}O_5S$: C, 51.78; H, 7.97. Found: C, 51.39; H, 8.04.

3.1.8. Michael addition to amide ester 3 under basic conditions. Preparation of ethyl 4-oxo-3-phenylthio-4-(1-pyrrolidinyl)butyrate (4a-B). General procedure. To a solution of PhSH (550.9 mg, 5.0 mmol) and **3a** (986.3 mg, 5.0 mmol) in C_2H_5CN (10 mL) was added Et_3N (50.6 mg, 0.5 mmol) at room temperature and the reaction mixture was allowed to stand for 6 h. dil HCl (10 mL) was added to the reaction mixture and the resulting biphasic solution was extracted with EtOAc (3×30 mL). Combined organic phase was dried over Na_2SO_4. After filtration and evaporation of

solvent, crude product was purified through flash chromatography (hexane–ethyl acetate 1:2 v/v) to give **4a-B** in 88% yield (1.3487 g). Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23 (t, 3H, J=7.2 Hz), 1.80–1.90 (m, 4H), 2.65 (dd, 1H, J=5.7, 17.1 Hz), 3.19 (dd, 1H, J=10.0, 17.2 Hz), 3.37–3.55 (m, 4H), 4.05–4.14 (m, 3H), 7.30–7.51 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 24.2, 25.9, 36.7, 44.7, 46.1, 46.3, 60.7, 128.6, 128.9, 129.2, 134.3, 167.9, 171.5. Anal. calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56. Found: C, 62.51; H, 6.78; N, 4.47.

3.1.9. Michael addition to amide ester 3 under non-basic conditions. Preparation of ethyl 4-oxo-2-phenylthio-4-(1-pyrrolidinyl)butyrate (4a-A). General procedure. A mixture of PhSH (991.6 mg, 9.0 mmol) and **3a** (1.188 g, 6.0 mmol) was allowed to stand at room temperature for 48 h. The mixture was directly subjected to flash chromatography (hexane–ethyl acetate 1:2 v/v) to give **4a-A** in 89% yield (1.6431 g). Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, 3H, J=7.0 Hz), 1.84 (m, 2H, J=7.0 Hz), 1.92 (m, 2H, J=7.3 Hz), 2.65 (dd, 1H, J=4.8, 16.3 Hz), 2.95 (dd, 1H, J=10.1, 16.3 Hz), 3.33–3.46 (m, 4H), 4.11 (q, 2H, J=6.8 Hz), 4.20 (dd, 1H, J=4.2, 10.2 Hz), 7.15–7.52 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.9, 24.2, 25.9, 36.8, 45.6, 45.7, 46.3, 61.2, 128.1, 128.8, 132.6, 133.3, 168.1, 171.9. Anal. calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56. Found: C, 62.58; H, 6.83; N, 4.56.

Other adducts **4** were prepared in a similar manner.

3.1.10. Ethyl 4-oxo-2-phenylthio-4-(1-piperidinyl)butyrate (4b-A). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, 3H, J=7.0 Hz), 1.51–1.63 (m, 6H), 2.70 (dd, 1H, J=4.3, 16.2 Hz), 3.02 (dd, 1H, J=10.3, 16.2 Hz), 3.36–3.37 (m, 2H), 3.49–3.51 (m, 2H), 4.07–4.18 (m, 3H), 7.30–7.54 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.6, 24.0, 25.1, 25.9, 35.2, 42.4, 45.8, 46.0, 60.7, 127.9, 128.6, 132.4, 133.0, 167.4, 171.6. Anal. calcd for $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36. Found: C, 63.23; H, 7.24; N, 4.28.

3.1.11. Ethyl 4-oxo-3-phenylthio-4-(1-piperidinyl)butyrate (4b-B). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23 (t, 3H, J=6.9 Hz), 1.51–1.62 (m, 6H), 2.67 (dd, 1H, J=4.9, 16.8 Hz), 3.15 (dd, 1H, J=9.9, 16.8 Hz), 3.47–3.63 (m, 4H), 4.10 (dq, 2H, J=3.7, 7.3 Hz), 4.30 (dd, 1H, J=4.9, 9.9 Hz), 7.31–7.49 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.9, 24.2, 25.3, 26.0, 37.0, 42.0, 43.2, 46.9, 60.4, 128.4, 128.8, 131.4, 133.9, 167.5, 171.2. Anal. calcd for $C_{17}H_{23}NO_3S$: C, 63.52; H, 7.21; N, 4.36. Found: C, 63.24; H, 7.32; N, 4.11.

3.1.12. *N*,*N*-Dibenzyl-2-phenylthiosuccinamic acid ethyl ester (4c-A). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19 (t, 3H, J=7.3 Hz), 2.80 (dd, 1H, J=4.6, 16.5 Hz), 3.15 (dd, 1H, J=10.5, 16.5 Hz), 4.15 (dq, 2H, J=1.8, 7.3 Hz), 4.27 (dd, 1H, J=4.8, 10.5 Hz), 4.41 (s, 2H), 4.52 (d, 1H, J=14.9 Hz), 4.61 (d, 1H, J=14.6 Hz), 4.14–4.48 (m, 15H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.7, 35.7, 46.0, 48.2, 49.7, 61.2, 126.4, 127.3, 127.6, 128.0, 128.1, 128.4, 128.7, 128.8, 132.3, 134.1, 135.7, 136.6, 170.4, 171.6. Anal. calcd for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28; N, 3.23. Found: C, 71.74; H, 6.47; N, 3.16.

3.1.13. *N*,*N*-Dibenzyl-3-phenylthiosuccinamic acid ethyl ester (4c-B). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.22, (t, 3H, J=7.3 Hz), 2.70 (dd, 1H, J=4.6, 16.9 Hz), 3.24 (dd, 1H, J=10.2, 17.2 Hz), 4.12 (q, 2H, J=6.9 Hz), 4.27 (dd, 1H, J=4.5, 10.2 Hz), 4.43 (d, 2H, J=16.7 Hz), 4.93 (d, 1H, J=17.1 Hz), 5.01 (d, 1H, J=15.8 Hz), 7.20–7.51 (m, 15H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.1, 37.7, 42.9, 48.3, 50.2, 60.7, 127.1, 127.3, 127.4, 127.6, 128.4, 128.5, 128.6, 128.8, 129.0, 129.1, 134.1, 136.9, 169.9, 171.3. Anal. calcd for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28; N, 3.23. Found: C, 71.76; H, 6.27; N, 3.27.

3.1.14. *N*,*N*-Diallyl-2-phenylthiosuccinamic acid ethyl ester (4d-A). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, 3H, J=7.3 Hz), 2.71 (dd, 1H, J=4.6, 16.1 Hz), 3.03 (dd, 1H, J=10.2, 16.5 Hz), 3.84 (s, 2H), 3.95 (d, 2H, J=5.5 Hz), 4.10 (dq, 2H, J=3.6, 7.3 Hz), 4.17 (dd, 1H, J=4.3, 10.2 Hz), 5.07–5.22 (m, 4H), 5.64–5.82 (m, 2H), 7.28–7.51 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.7, 35.3, 45.8, 47.8, 48.9, 60.9. 116.7, 117.1, 128.0, 128.7, 132.0, 132.4, 132.7, 133.2, 169.5, 171.5. Anal. calcd for $C_{18}H_{23}NO_3S$: C, 64.84; H, 6.95; N, 4.20. Found: C, 64.67; H, 6.98; N, 4.00.

3.1.15. *N*,*N*-Diallyl-3-phenylthiosuccinamic acid ethyl ester (4d-B). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.22 (t, 3H, J=7.3 Hz), 2.67 (dd, 1H, J=4.6, 16.2 Hz), 3.15 (dd, 1H, J=9.9, 16.4 Hz), 3.70 (dd, 1H, J=6.3, 15.2 Hz), 3.88 (dd, 1H, J=5.3, 17.6 Hz), 4.09 (q, 2H, J=7.3 Hz), 4.18 (dd, 1H, J=4.6, 9.9 Hz), 4.22–4.35 (m, 2H), 5.14 (dd, 1H, J=1.4, 17.5 Hz), 5.17 (dd, 1H, J=1.3, 9.9 Hz), 5.24 (dd, 1H, J=1.3, 10.9 Hz), 5.26 (dd, 1H, J=1.3, 17.7 Hz), 5.66–5.92 (m, 2H), 7.31–7.47 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.9, 37.3, 42.5, 48.0, 49.3, 60.5, 117.1, 117.2, 128.6, 128.9, 132.7, 132.8, 134.0, 169.2, 171.2. Anal. calcd for $C_{18}H_{23}NO_3S$: C, 64.84; H, 6.95; N, 4.20. Found: C, 64.84; H, 6.95; N, 4.13.

3.1.16. *N*-Benzyl-3-phenylthiosuccinamic acid ethyl ester (4e-B). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (t, 3H, J=7.1 Hz), 2.78 (dd, 1H, J=6.6, 16.8 Hz), 3.13 (dd, 1H, J=7.3, 16.8 Hz), 4.04 (t, 1H, J=6.9 Hz), 4.16 (q, 2H, J=7.2 Hz), 4.54 (dd, 2H, J=3.6, 5.6 Hz), 6.75 (br, 1H), 7.18–7.39 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.9, 36.5, 43.6, 47.6, 60.7, 127.2, 127.5, 128.0, 128.4, 129.1, 132.4, 132.5, 137.7, 169.7, 170.9. Anal. calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.23; H, 6.17; N, 4.28.

3.1.17. *N*-Benzyloxy-2-phenylthiosuccinamic acid ethyl ester (4f-A). Oil. ^{1}H NMR (270 MHz, DMSO-d6) δ 1.07 (t, 3H, J=7.3 Hz), 2.45 (dd, 1H, J=6.4, 15.5 Hz), 2.58 (dd, 1H, J=8.6, 15.5 Hz), 3.97–4.08 (m, 3H), 4.76 (s, 2H), 7.35–7.47 (m, 10H), 11.2 (br, 1H). ^{13}C NMR (67.5 MHz, DMSO-d6) δ 13.9, 34.3, 45.5, 60.8, 77.0, 128.4, 128.5, 128.9, 129.2, 132.0, 133.2, 135.9, 166.2, 170.7. Anal. calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.10; H, 6.07; N, 3.72.

3.1.18. Preparation of 2-phenylthiosuccinic acid 4-ethyl ester (5). 2b-A (0.2723 g, 0.8772 mmol) and thioanisole (0.1 g) were added to trifluoroacetic acid (0.2 mL) and the reaction mixture was allowed to stand for 1 h. Trifluoroacetic acid and thioanisole were removed in vacuo and **5** was obtained in 98% yield (0.219 g, 0.862 mmol). Oil. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 1.25 (t, 3H, J=7.1 Hz), 2.75 (dd, 1H, J=5.8, 17.0 Hz), 2.92 (dd, 1H, J=9.4, 17.0 Hz), 4.01 (dd, 1H, J=5.9, 9.6 Hz), 4.16 (q, 2H, J=7.3 Hz), 7.26–7.53 (m, 5H), 10.68 (br, 1H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.4, 36.4, 36.9, 61.9, 129.2, 129.5, 131.5, 134.6, 171.4, 177.3. HRMS (FAB) calcd for (M+) $C_{12}H_{14}O_4S$: 254.0613, found 254.0620.

3.1.19. Preparation of ethyl 4-hydroxy-3-phenylthiobutyrate (6). To a solution of **5** (0.2333 g, 0.9174 mmol) in THF (10 mL) was added BH_3·THF (1 M, 1.02 mL, 1.02 mmol) dropwise at −10°C and the reaction mixture was allowed to stir at room temperature for 3.5 h. Aqueous AcOH (50%, 5 mL) and THF were removed in vacuo. $NaHCO_3$ aq (50 mL) was added to the residue and the resulting mixture was extracted with EtOAc (3×30 mL). The organic phase was combined and dried over Na_2SO_4. Chromatographic purification of crude product gave **6** in 48% yield (0.105 g, 0.4365 mmol). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (t, 3H, J=7.3 Hz), 2.40 (br, 1H), 2.58 (dd, 1H, J=6.9, 16.2 Hz), 2.69 (dd, 1H, J=6.8, 16.2 Hz), 3.58–3.67 (m, 3H), 4.16 (q, 2H, J=7.1 Hz), 7.27–7.36 (m, 3H), 7.45–7.50 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 36.6, 47.3, 60.7, 63.6, 127.7, 128.9, 132.5, 133.0, 171.4. HRMS (FAB) calcd for (M+H) $C_{12}H_{16}O_3S$: 241.0899, found 241.0900.

3.1.20. Preparation of 2-phenylthiosuccinic acid 4-ethyl ester 1-methyl ester (2a-B). To a solution of **6** (0.2463 g, 0.9685 mmol) in toluene (5 mL) was added DBU (0.1937 g, 1.27 mmol) and MeI (0.4798 g, 3.38 mmol) at room temperature. The reaction mixture was allowed to stir for 20 h. Precipitate was filtered and the filtrate was concentrated in vacuo. The residue was diluted with CH_2Cl_2 and the solution was washed with dil HCl and sat. $NaHCO_3$. Obtained crude product was purified through chromatography to give **2a**-**B** in 74% yield (0.1911 g, 0.712 mmol).

3.1.21. Preparation of 4-hydroxy-3-phenylthio-1-(1-pyrrolidinyl)butan-1-one (7). To a solution of **4a**-**A** (307.4 mg, 1.0 mmol) in THF (10 mL) was added $LiBH_4$ (2 M in THF, 1.0 mL) at 0°C and the reaction mixture was allowed to stir at 0°C for 25 h. Water (10 mL) was added and THF was removed in vacuo. The resulting aqueous mixture was extracted with CH_2Cl_2 (3×30 mL). The organic phase was combined and dried over Na_2SO_4. Chromatographic purification (hexane–ethyl acetate 4:1 v/v) of crude product gave **7** in 49% yield (130.0 mg, 0.49 mmol). Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.83–2.00 (m, 4H), 2.65 (dd, 1H, J=7.6, 15.8 Hz), 2.73 (dd, 1H, J=4.9, 15.8 Hz), 3.38 (q, 2H, J=6.8 Hz), 3.48 (q, 2H, J=6.9 Hz), 3.42–3.54 (br, 1H), 3.65–3.71 (m, 1H), 3.76–3.85 (m, 2H), 7.27-7.48 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 24.2, 25.9, 37.4, 45.8, 46.6, 46.7, 64.6, 127.2, 128.9, 132.0, 133.7, 169.5. HRMS (FAB) calcd for (M+H) $C_{14}H_{20}NO_2S$: 266.1215, found 266.1214.

3.1.22. Preparation of *tert*-butyl 3-phenylthiopropionate (9). A mixture of PhSH (110.1 mg, 1.0 mmol), *tert*-butyl acrylate (128.2 mg, 1.0 mmol) and Et_3N (13.9 μL, 0.1 mmol) in C_2H_5CN (5 mL) was allowed to stand at room temperature for 24 h. dil HCl (1 M, 20 mL) was added to the reaction mixture and the resulting biphasic mixture was extracted with EtOAc (3×30 mL). The organic phase was combined and dried over Na_2SO_4. Crude product was purified through flash chromatography (hexane–ethyl acetate 5:1) to give **9** in 90% yield (214.9 mg). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.55 (t, 2H, J=7.3 Hz), 3.14 (t, 2H, J=7.3 Hz), 7.21–7.52 (m, 5H).

Compounds **8** and **10** were prepared in a similar manner.

3.1.23. Ethyl 3-phenylthiopropionate (8). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, 3H, J=7.3 Hz), 2.62 (t, 2H, J=7.2 Hz), 3.16 (t, 2H, J=7.3 Hz), 4.14 (q, 2H, J=6.9 Hz), 7.20–7.52 (m, 5H).

3.1.24. 3-Phenylthio-1-(1-pyrrolidinyl)-1-propanone (10). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.78–1.93 (m, 4H), 2.59 (t, 2H, J=7.6 Hz), 3.23–3.35 (m, 4H), 3.45 (t, 2H, J=6.8 Hz), 7.17–7.52 (m, 5H).

3.1.25. Preparation of 2-(hydroxyphenylmethyl)-3-phenylthiosuccinic acid 4-*tert*-butyl ester 1-ethyl ester (11). BuLi (1.6 M, 4.1 mL, 6.5 mmol) was added to a solution of PhSH (0.628 g, 5.5 mmol) in CH_2Cl_2 (10 mL) at −50°C. Then benzaldehyde (0.6369 g, 6.0 mmol) and fumarate **1b** (0.9984 g, 5.0 mmol) were added. The reaction mixture was allowed to stir for 15 h at −50°C. dil HCl (1 M, 20 mL) was added to the reaction mixture and the resulting biphasic mixture was extracted with EtOAc (3×30 mL). The organic phase was combined and dried over Na_2SO_4. Crude product was purified through flash chromatography (hexane–ethyl acetate 5:1) to give **11** in 83% yield (1.7193 g, 4.3 mmol). Anal. calcd for $C_{23}H_{28}O_5S$: C, 66.32; H, 6.78. Found: C, 66.40; H, 6.55. Careful chromatographic treatment separated the two major isomers of **11**, **11**-**A** and **11**-**B**.

Compound **11**-**A**. Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, 3H, J=6.9 Hz), 1.37 (s, 9H), 3.09 (ddd, 1H, J=1.0, 3.6, 10.6 Hz), 3.06–3.12 (br, 1H), 3.91 (q, 2H, J=6.9 Hz), 4.10 (d, 1H, J=10.6 Hz), 5.53 (dd, 1H, J=3.3, 7.3 Hz), 7.24–7.34 (m, 8H), 7.52–7.56 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.9, 28.0, 51.2, 53.8, 61.2, 71.5, 82.2, 125.6, 126.5, 127.8, 128.5, 129.3, 133.3, 133.5, 141.8, 170.3, 172.4.

Compound **11**-**B**. Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02 (t, 3H, J=7.4 Hz), 1.40 (s, 9H), 3.35 (dd, 1H, J=1.0, 3.6, 10.6 Hz), 3.63–3.73 (br, 1H), 4.02 (q, 2H, J=7.3 Hz), 4.03 (d, 1H, J=9.6 Hz), 5.00 (br, 1H), 7.25–7.61 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.0, 27.9, 51.2, 54.2, 61.2, 72.6, 82.3, 125.4, 125.8, 128.4, 128.9, 129.0, 129.6, 133.4, 141.5, 169.6, 172.2.

3.1.26. Preparation of 3-ethoxycarbonyl-5-oxo-2-phenyl-4-phenylthiotetrahydrofuran (13). A solution of **11** (0.4429 g, 1.06 mmol) and thioanisole (0.1 g) in trifluoroacetic acid (0.2 mL) was allowed to stand at room temperature for 1 h. Trifluoroacetic acid and thioanisole were removed in vacuo. The residue was solved in toluene (10 mL) in the presence of PPTS (0.1 g) and the resulting solution was heated under refluxing conditions for 1 h. Solvent was removed in vacuo and the residue was subjected to flash chromatography (hexane–ethyl acetate 5:1) to give **13** in 89% yield (0.3255 g). The ratio of he four isomers was **A**–**B**–**C**–**D**=59:27:9:5. Anal. calcd for

$C_{19}H_{18}O_4S$: C, 66.65; H, 5.30. Found: C, 66.66; H, 5.30. Further chromatographic separation gave two major isomers **13-A** and **13-B**, both of which contain 4,5-*cis*-configuration, in pure form. Configuration of **13-B** was determined X-ray crystallographic analysis.[19]

Compound **13-A**. Mp 108°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=7.1 Hz), 3.84–3.91 (m, 3H), 4.29 (d, 1H, J=7.3 Hz), 5.60 (d, 1H, J=5.7 Hz), 7.30–7.38 (m, 8H), 7.56–7.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 52.5, 54.4, 61.3, 78.9, 125.2, 128.5, 128.7, 129.4, 132.8, 134.0, 134.4, 167.5, 172.5.

Compound **13-B**. Mp 117–118°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, 3H, J=7.2 Hz), 3.62–3.67 (m, 2H), 3.76 (qd, 1H, J=7.2, 10.8 Hz), 4.35 (d, 1H, J=5.6 Hz), 5.55 (d, 1H, J=8.0 Hz) 7.18–7.20 (m, 2H), 7.30–7.33 (m, 3H), 7.36–7.39 (m, 3H), 7.61–7.64 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 47.4, 53.6, 61.5, 79.4, 125.6, 128.5, 129.0, 129.4, 129.5, 130.6, 134.4, 134.8, 168.3, 173.1.

3.1.27. Preparation of 2-(acetoxyphenylmethyl)-3-phenylthiosuccinic acid 4-*tert*-butyl ester 1-ethyl ester (14). Acetic anhydride (0.5 mL, 0.55 mmol) was added to a solution of **11** (0.205 g, 0.493 mmol) in pyridine (10 mL). DMAP (0.1 g) was added and the resulting solution was allowed to stand at room temperature for 2 h. The reaction mixture was poured into ice–water (10 mL) and extracted with MTBE (3×30 mL). The organic phase was combined and dried over Na_2SO_4. Crude product was purified through flash chromatography (hexane–ethyl acetate 10:1 then 3:1) to give **14** in 80% yield (0.1799 g). The ratio of the four isomers was **A**–**B**–**C**–**D**=66:23:6:5. HRMS (FAB) calcd for (M+H) $C_{25}H_{31}O_6S$: 459.1841, found 459.1844.

Compound **14-A**. Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.01 (t, 3H, J=7.3 Hz), 1.41 (s, 9H), 2.00 (s, 3H), 3.15 (dd, 1H, J=4.3, 10.6 Hz), 3.89 (d, 1H, J=10.6 Hz), 3.91 (q, 1H, J=7.3 Hz), 3.98 (q, 1H, J=7.3 Hz), 6.55 (d, 1H, J=4.3 Hz), 7.18–7.34 (m, 8H), 7.50–7.53 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.7, 20.7, 27.7, 50.9, 52.9, 60.7, 72.6, 82.0, 125.8, 127.9, 128.3, 129.0, 133.4, 138.4, 169.4, 169.8, 170.0.

Compound **14-B**. Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11 (t, 3H, J=7.3 Hz), 1.34 (s, 9H), 2.08 (s, 3H), 3.41 (dd, 1H, J=6.6, 9.5 Hz), 3.71 (d, 1H, J=9.2 Hz), 3.87–4.13 (m, 2H), 6.11 (d, 1H, J=6.3 Hz), 7.12–7.56 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.8, 20.7, 27.8, 51.0, 52.6, 60.8, 72.7, 82.2, 125.8, 127.9, 128.1, 128.3, 128.4, 133.1, 137.4, 168.9, 169.3, 169.4.

3.1.28. Preparation of 2-ethoxycarbonyl-1-benzyloxy-2-azetidinone (15).[14] To a solution of **4f-A** (359.4 mg, 1.0 mmol) and MeI (1.419 g, 10 mmol) in CH_3CN (12 mL) was added $AgClO_4$ (1.037 g, 5.0 mmol) at room temperature and the resulting mixture was allowed to stir for 17 h. Precipitate was filtered and solvent of the filtrate was removed in vacuo. The residue was solved in acetone (20 mL) and the solution was added to a mixture of K_2CO_3 (1.244 g, 9.0 mmol) in acetone (20 mL) at room temperature. The resulting mixture was heated at refluxing temperature for 4 h. The reaction mixture was filtered and water (30 mL) was added to the filtrate. Acetone was removed in vacuo and the residue was extracted CH_2Cl_2 (3×30 mL). The organic phase was combined and dried over Na_2SO_4. After filtration and evaporation of solvent, crude product was purified through flash chromatography (hexane–ethyl acetate 4:1 v/v) to give **15** in 70% yield (173.2 mg). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.3 Hz), 2.76 (dd, 1H, J=2.8, 13.5 Hz), 2.93 (dd, 1H, J=6.0, 13.8 Hz), 4.10 (dd, 1H, J=2.6, 5.9 Hz), 4.22 (q, 2H, J=6.9 Hz), 5.01 (d, 1H, J=11.2 Hz), 5.08 (d, 1H, J=11.2 Hz), 7.36–7.42 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.9, 37.1, 56.8, 61.8, 78.5, 128.5, 128.8, 128.9, 134.9, 163.6, 169.1. HRMS (FAB) calcd for (M+H) $C_{13}H_{16}NO_4$: 250.1079, found 250.1086.

3.1.29. Preparation of 1-allyl-4-ethoxycarbonyl-5-methyl-2-oxopiperidine (16). To a solution of **4d-A** (333.5 mg, 1.0 mmol) in toluene (30 mL) at 110°C was added a solution of Bu_3SnH (436.6 mg, (1.5 mmol) and AIBN (34.0 mg, 0.2 mmol) in toluene (20 mL) over 2 h. The reaction mixture was heated for additional 4 h. Toluene was removed in vacuo and the residue was subjected to flash chromatography (hexane–ethyl acetate 5:1 then 1:1 v/v) to give **16** in 68% yield (155.5 mg). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.03 (d, 3H, J=6.9 Hz), 1.27 (t, 3H, J=7.3 Hz), 2.37–2.45 (m, 1H), 2.54 (dd, 1H, J=6.6, 17.8 Hz), 2.69 (dd, 1H, J=6.9, 17.8 Hz), 2.88 (dt, 1H, J=3.9, 6.9 Hz), 3.10 (dd, 1H, J=6.6, 12.2 Hz), 3.31 (dd, 1H, J=4.6, 12.2 Hz), 3.86 (dd, 1H, J=6.8, 14.9 Hz), 4.13 (dd, 1H, J=6.0, 14.9 Hz), 4.17 (q, 2H, J=6.9 Hz), 5.17 (d, 1H, J=11.2 Hz), 5.18 (d, 1H, J=15.7 Hz), 5.68–5.82 (m, 1H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.1, 14.4, 29.5, 31.7, 42.4, 49.2, 51.7, 60.6, 117.4, 132.4, 167.6, 172.3. HRMS (FAB) calcd for (M+H) $C_{12}H_{20}NO_3$: 226.1443, found 226.1445.

3.1.30. Preparation of ethyl 1-allyl-4-methyl-2-oxo-pyrrolidin-3-acetate (17). A solution of **4d-B** (333.5 mg, 1.0 mmol), Bu_3SnH (436.6 mg (1.5 mmol) and AIBN (36.5 mg, 0.2 mmol) in toluene (10 mL) was heated at 110°C for 2 h. Toluene was removed in vacuo and the residue was subjected to flash chromatography (hexane–ethyl acetate 5:1 then 1:1 v/v) to give **17** in 69% yield (155.1 mg). Oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.14 (d, 3H, J=6.6 Hz), 1.27 (t, 3H, J=7.0 Hz), 2.12–2.23 (m, 1H), 2.46 (d, 1H, J=11.5 Hz), 2.47 (m, 1H), 2.79 (d, 1H, J=11.5 Hz), 2.90 (dd, 1H, J=8.2, 9.5 Hz), 3.39 (dd, 1H, J=7.9, 9.5 Hz), 3.85 (dd, 1H, J=7.6, 15.2 Hz), 3.92 (dd, 1H, J=7.2, 15.2 Hz), 4.16 (q, 2H, J=6.9 Hz), 5.18 (dd, 1H, J=1.3, 12.5 Hz), 5.19 (dd, J=1.3, 17.5 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.1, 18.0, 33.5, 34.5, 45.2, 46.3, 52.2, 60.5, 117.8, 132.3, 172.0, 174.6. Anal. calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.17; H, 8.59; N, 6.14.

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