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A convenient stereoselective synthesis of β-lactams from β-hydroxy-α-thioalkylesters prepared from Michael/aldol tandem reaction or stereoselective addition of thiols to the Baylis–Hillman adducts

Akio Kamimura,[a,*] Rie Morita,[a] Kenji Matsuura,[a] Hiromasa Mitsudera[a] and Masashi Shirai[b]

[a]*Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, 2-16-1, Tokiwadai, Ube 755-8611, Japan*
[b]*Ube Laboratory, Ube Industries Ltd, Ube 755-8633, Japan*

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Abstract—A convenient stereoselective synthesis of β-lactams from thio-Michael/aldol tandem adduct is described. *syn*-Selective tandem reaction followed by amidation and intramolecular S_N2 reaction provided β-lactams in diastereomerically pure form. The tandem reaction with aliphatic aldehydes, on the other hand, afforded a mixture of diastereomers of corresponding tandem adducts in about 3:1 ratio so that the conversion to β-lactams afforded a diastereomeric mixture. As an alternative approach to prepare the tandem adducts, the stereoselective Michael addition of aliphatic thiols to Baylis–Hillman adduct was developed. The stereoselectivity was sensitive to the protective group at the hydroxyl group and TBS protection brought the most successful *syn*-selective formation of the tandem adducts. The procedure could be applied to the ketone derivatives of the Baylis–Hillman adduct but no selectivity was observed for the nitrile-Baylis–Hillman adducts. A similar conversion of the adduct provided desired β-lactams stereoselectively.

1. Introduction

Efficiency in synthesis is of interest in current organic chemistry. One of the solutions lies in the field of domino reactions, which is currently attracting many organic chemists and used in synthetic reports.[1] We have recently reported that Michael/aldol tandem reaction triggered by thiolate anion provides a useful method to prepare functionalized aldols which are regarded as potentially useful building blocks in organic synthesis.[2,3] The thio-functionality introduced here, in particular, is expected to work as a useful group for the further transformation.[4] During the course of our investigation, for example, we have applied to use the thio- or analogous groups to radical chemistry and successfully developed a new stereoselective construction of trisubstituted tetrahydrofurans[5] as well as a regioselective radical fragmentation reaction to give β,γ- or α,β-unsaturated esters.[6] We were then interested in the use of the thio-functionality as a leaving group. In this paper, we report a convenient and stereoselective procedure for the preparation of β-lactams through intramolecular S_N2 reaction of the Michael/aldol tandem adducts. Although the tandem reaction to aliphatic aldehydes proceeded in moderate to poor yields with less stereoselectivity, we developed an alternative method, stereoselective addition of thiol to the Baylis–Hillman adducts, which provided β-hydroxy-α-phenylthioalkylester in a highly *syn*-selective manner.[7,8] Diastereomerically pure β-lactam formation was readily achieved with this reaction. Full details of this reaction are also discussed here.

2. Results and discussion

2.1. *syn*-Selective preparation of β-lactams from tandem adducts

The Michael/aldol tandem adducts **1a**–**1c** were prepared in the method previously reported.[2] The adducts were obtained in solid form, and single recrystallization from hexane gave diastereomerically pure *syn*-**1a**–**1c**. Conversion to β-lactam **3** was performed in the four-step sequence illustrated in Scheme 1. The protection of hydroxyl group followed by deprotection of *tert*-butyl ester gave carboxylic acid, which then underwent condensation with amine to give lactam precursor **2**. Exposure of **2** into the intramolecular S_N2 reaction conditions resulted in the formation of desired β-lactam **3**.

Keywords: β-lactams; cascade reaction; stereoselection; Baylis–Hillman reaction; Michael addition.
* Corresponding author. Tel.: +81-836-85-9231; fax: +81-836-85-9201; e-mail: ak10@yamaguchi-u.ac.jp

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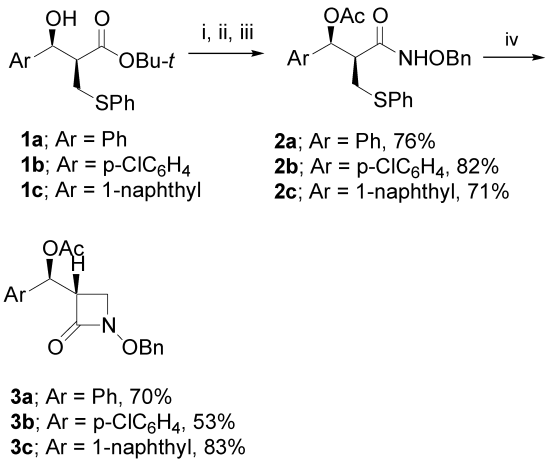
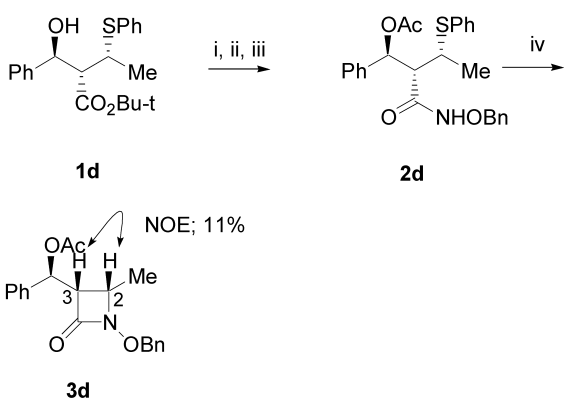


Scheme 1. *Reagents and conditions*. (i) Ac_2O, DMAP, pyridine, rt, 3 h. (ii) cat. TsOH, wet toluene, reflux, 2 h. (iii) NH_2OBn, EDCI, THF–H_2O, rt, 3 h. (iv) $AgClO_4$, MeI then K_2CO_3.

Although the procedure took four steps, the first three steps proceeded smoothly and the yields of the reaction were almost quantitative. All of the reaction gave only single diastereomer of each product. This result suggests that no epimerization have taken place during the transformation. Conventional TFA method for the deprotection of *tert*-butyl ester caused partial epimerization as well as slow reaction rate. We modified the reaction conditions and found that the deprotection in hot wet-benzene in the presence of TsOH completed in short hours to form carboxylic acid in nearly quantitative yield with complete prevention of epimerization. The intramolecular S_N2 reaction of **2** was performed according to a method reported by Naito et al.[9] Treatment of **2** with MeI in the presence of $AgClO_4$ sufficiently converted the phenylthio group to the sulfonium group, which was then kicked out by the amide nitrogen under basic conditions to give β-lactam **3** in good yields. Compounds **3** contained only single diastereomer so that no epimerization during the conversion had occurred.

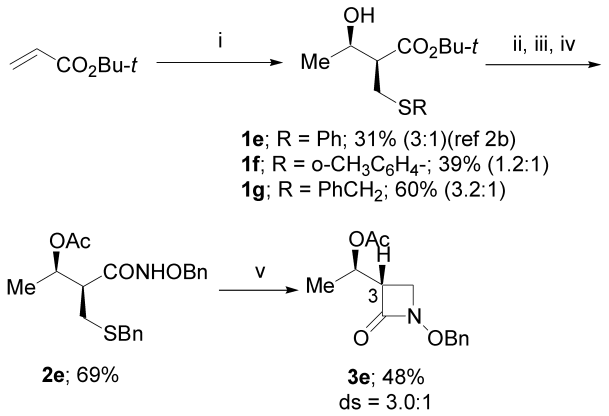
We next examined the conversion of the tandem adduct from crotonate ester that contained three contiguous stereogenic centers. The tandem reaction with lithium thiolate afforded a diastereomeric mixture of the adduct and single recrystallization from hexane gave diastereomerically pure **1d**.[10] Treatment of **1d** with the procedure



Scheme 2. *Reagents and conditions*. (i) Ac_2O, DMAP, pyridine, rt, 3 h (95%). (ii) Cat. TsOH, wet benzene, reflux, 3 h (76%). (iii) NH_2OBn, EDCI, THF–H_2O, rt, 3 h (85%). (iv) $AgClO_4$, MeI then K_2CO_3 (63%).

illustrated in Scheme 2 gave single diastereomer of disubstituted 2-azetidinone **3d** in good yield.

To determine the configuration between C2 and C3 in **3d**, an NOE experiment was performed. 11% Of signal enhancement, observed when H2 was irradiated, clearly indicated that configuration between C2 and C3 was *cis*. This is consistent with the configuration of **1d** that was converted to β-lactam **3d** through S_N2 inversion (Scheme 3).



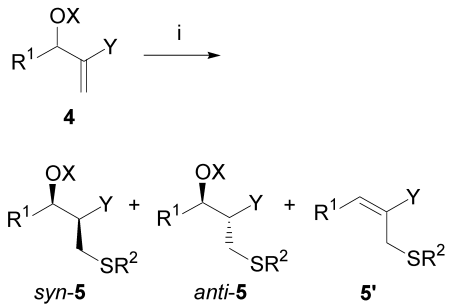
Scheme 3. *Reagents and conditions*. (i) RSLi, CH_3CHO, CH_2Cl_2, −50 °C. (ii) Ac_2O, DMAP, pyridine, rt, 3 h. (iii) cat. TsOH, wet benzene, reflux, 3 h. (iv) NH_2OBn, EDCI, THF–H_2O, rt, 3 h. (v) $AgClO_4$, MeI then K_2CO_3.

Although the present conversion consisted of the four-step reaction, all of steps could be carried out within a short term and β-lactams were isolated in a diastereomerically pure form. Thus, the present method provides a new convenient and stereoselective preparation of β-lactams. Due to the limitation of the tandem reaction, however, only aromatic side chain at C3 position was effectively introduced with this method.[2b] To introduce aliphatic side chain there, an aliphatic aldehyde should be used in the tandem reaction, but the reaction does not always takes place with satisfactory level of stereoselectivity or yield. Exposure of acetaldehyde into the tandem reaction conditions, for example, gave of the tandem adduct **1e** in only 31% yield.[2b] Change of thiolate somewhat improved the yield and the selectivity but both of them remained in the moderate levels. Conversion of **1g**, which was isolated as a diastereomeric mixture in about 3:1 ratio, to β-lactam was achieved in good yield but the obtained lactam **3e** contained the two diastereomers and the ratio was about 3:1, which was reflected by the ratio of the starting material **1g**. Hence, high stereoselectivity in the preparation of **1** must be achieved to prepare diastereomerically pure β-lactam **3** in the present method. Our tandem methodology, however, has never been improved regardless our extensive efforts. So we next examined an alternative preparation of **1**.

2.2. *syn*-Selective Michael addition to Baylis–Hillman adducts

The Baylis–Hillman reaction is recognized as a powerful tool for the preparation of β-hydroxy-α-methylene carbonyl compounds.[11] Although the reaction involves several drawbacks such as slow reaction rate, it is undoubtedly a potentially useful method because it can be performed in large scale under air atmosphere without care of dry

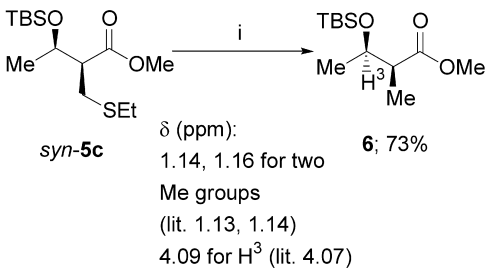
conditions. Conjugate addition to Baylis–Hillman adducts generates intermediate enolates which, if the elimination of hydroxide or alkoxide can be suppressed,[12] potentially provides a concise synthesis of substituted aldol adducts.[8,13] So we were interested in the Michael addition of thiol to the Baylis–Hillman adducts because that will afford the same type of products as the tandem reaction does. As we expected, exposure of the Baylis–Hillman adduct **4** to thiol under the basic conditions resulted in the smooth addition reaction to give **5** in good yields (Scheme 4). The results are summarized in Table 1.



Scheme 4. *Reagents and conditions.* (i) RSH, RSLi, THF.

Successful addition mainly depended on a sort of protection of the hydroxyl group. Addition of thiophenol to Baylis–Hillman acetate **4a**, for example, produced not desired adduct **5a** but S_N2' product **5′** quantitatively (entry 1). Use of TBS ether, less good leaving group than acetate, as well as catalytic amounts of PhSLi prevented the undesirable S_N2' process and resulted in the successful formation of **5b** in 91% yield (entry 2). The diastereomeric ratio of **5b** was about 2:1 so that we tried to find suitable conditions to improve the stereoselectivity. Use of ethanethiol instead of thiophenol brought a good selectivity; *syn*-**5c** was obtained in 97:3 ratio (entry 3). It should be remarked that the present *syn*-selective preparation was accomplished even in the reaction carried out at room temperature in wet-THF (entry 4). The use of free-OH **4** afforded a mixture of diastereomers in about 2:1 (entry 5). Other TBS ethers of Baylis–Hillman adducts **4** from acrylate ester also underwent the stereoselective addition and good *syn*-selectivity was achieved (entries 6–9). The procedure was useful for the selective addition to the ketone-Baylis–Hillman adduct (entry 10), while the selectivity was completely lost in the reaction of nitrile-Baylis–Hillman adduct (entry 11).

To determine the stereochemistry of **5**, conversion to **6** was attempted (Scheme 5). The ethylthio group in *syn*-**5c** was readily desulfurized by treatment with Raney-Ni (W2) to give simple aldol **6** isolated in 73% yield. Comparison of ^{1}H NMR unambiguously revealed **5** and **6** contained *syn*-configuration.[14]



Scheme 5. *Reagents and conditions.* (i) Raney Ni(W2), EtOH, rt, 4 h.

The origin of the stereoselectivity is rationalized in the following way that is illustrated in Scheme 6. The reaction begins with the nucleophilic attack of thiolate at the β-carbon of the Baylis–Hillman adduct **4**. The resultant enolate intermediate takes two possible conformation **A** and **B**, in which conformation **A** is supposed to be much favorable than **B** because of the steric interaction between R^1 and R^2. The top face of the enolate is effectively shielded by the bulky TBSO group so that the protonation to **A** likely occurs from the bottom face of the enolate, giving *syn*-adduct **5** in a selective manner. The present preference of the enolate is agreeable with the previous reported experimental results as well as theoretical calculation.[15] The free hydroxyl group (X=H) does not hold sufficient shielding effect to prevent the protonation from the top face of the intermediate **A** and the present *syn*-selectivity is lowered.[16] For the reaction with nitrile-Baylis–Hillman adduct, difference between conformation **A** and **B** becomes small due to the straight structure of the nitrile group and the present *syn*-selectivity is lost.

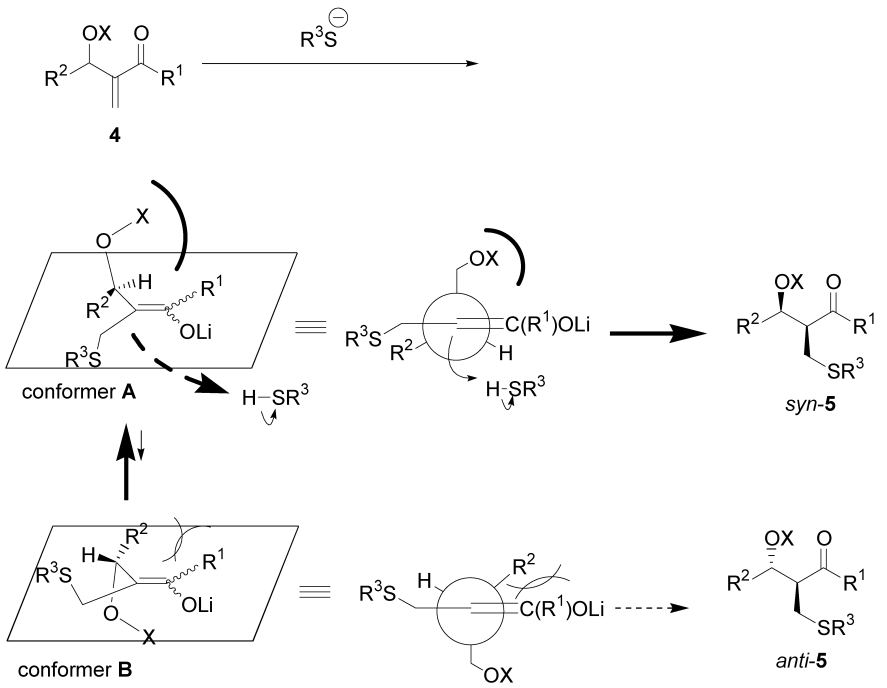
2.3. Conversion to β-lactam 2e

As we had diastereomeric pure **5e** in hand, conversion to β-lactam **3e** was attempted (Scheme 7). Change of the protective group of *syn*-**5e** to acetyl group was accomplished

Table 1. Michael addition of thiols to Baylis–Hillman adducts **4**

Entry	Y	R^1	R^2	X	Temperature (°C)	**5**; Yield (%)[a]	*syn*/*anti*[b]
1	CO_2Me	Me	Ph	Ac	−50	**5a**; 0[c]	–
2	CO_2Me	Me	Ph	TBS	−50	**5b**; 91	63/37
3	CO_2Me	Me	Et	TBS	−50	**5c**; 94	97/3
4	CO_2Me	Me	Et	TBS	rt	**5c**; 91	92/8
5	CO_2Me	Me	Et	H	−50	**5d**; 90	70/30
5	CO_2Bu-*t*	Me	Et	TBS	−50	**5e**; 83	92/8
7	CO_2Me	Et	Et	TBS	−50	**5f**; 78	94/6
8	CO_2Me	*i*-Pr	Et	TBS	−50	**5g**; 79	92/8
9	CO_2Me	*p*-Cl−C_6H_4−	Et	TBS	−50	**5h**; 95	99/1
10	COMe	Me	Et	TBS	−50	**5i**; 60	90/10
11	CN	Me	Et	TBS	−50	**5j**; 85	54/46

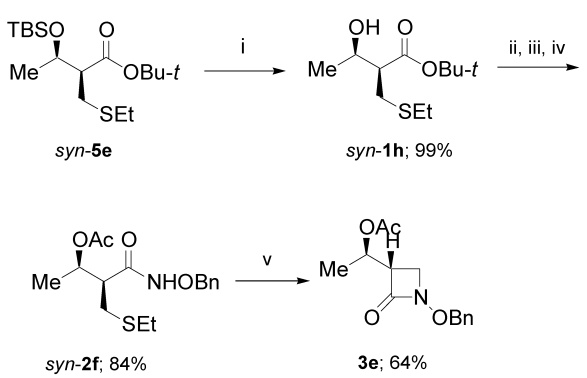
[a] Isolated yield.
[b] Determined by HPLC analyses.
[c] Et_3N was used as a base. S_N2' product was formed quantitatively.



Scheme 6.

in quantitatively. Subsequent acidic hydrolysis gave free-carboxylic acid, which was then converted amide *syn*-**2f** in 84% yield. The intramolecular S_N2 reaction through the sulfonium salt afforded β-lactam **3e** in diastereomerically pure form. Again no significant epimerization during the transformation was observed.

Due to the wide applicability and stereoselectivity of the tandem reaction, the present procedure will provide a useful stereoselective preparation of β-lactams. The Baylis–Hillman reaction followed by stereoselective addition of thiol serves as a good alternative when the tandem procedure does not work well. The present preparation of β-lactams can be carried out with easy manipulation as well as effective prevention of the epimerization problems. Thus, it will provide a useful and practical preparation of β-lactams. Further application of this methodology is now under way in our laboratory.



Scheme 7. *Reagents and conditions*. (i) TBAF, THF, rt. (ii) Ac_2O, DMAP, pyridine, rt, 3 h. (iii) Cat. TsOH, wet benzene, reflux, 3 h. (iv) NH_2OBn, EDCl, THF–H_2O, rt, 3 h. (v) $AgClO_4$, MeI then K_2CO_3.

3. Experimental

3.1. General

All ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on JEOL EX-270 (270 MHz for ^1H and 67.5 MHz for ^{13}C) spectrometer. All the reactions in this paper were performed under nitrogen atmosphere unless otherwise mentioned. Solvents used in the reaction described here were dried over appropriate drying agents (K for THF, Na for ether and toluene, and CaH_2 for all other solvents) and distilled under nitrogen before use. Aldehydes were purified by distillation. High resolution mass spectra (HRMS) were measured at Advanced Instrumentation Centre, Ehime University, Matsuyama, Japan.

3.1.1. Preparation of *tert*-butyl 3-hydroxy-2-(2-methylphenylthio)methylbutyrate 1f and *tert*-butyl 2-benzylthiomethyl-3-hydroxybutyrate 1g. These compounds were prepared in the similar procedure to our previous report.[2b] Physical data are listed below.

syn-**1f** (*Major isomer*). ^1H NMR δ 1.24 (d, 3H, J=6.4 Hz), 1.49 (s, 9H), 2.38 (s, 3H), 2.54 (ddd, 1H, J=4.6, 6.3, 7.9 Hz), 3.11–3.27 (m, 2H), 4.00–4.10 (m, 1H), 7.10–7.36 (m, 4H). ^{13}C NMR δ 20.2, 27.9, 32.3, 52.2, 67.7, 81.7, 125.9, 126.0, 126.3, 128.7, 130.0, 137.9, 172.7. HRMS (FAB) calcd for (M+) $C_{16}H_{24}O_3S$: 296.1445, found 296.1446.

anti-**1f** (*Minor isomer*). ^1H NMR δ 1.22 (d, 3H, J=6.2 Hz), 1.48 (s, 9H), 2.38 (s, 3H), 2.71–2.74 (m, 1H), 3.11–3.27 (m, 2H), 4.00–4.10 (m, 1H), 7.10–7.36 (m, 4H). ^{13}C NMR δ 20.7, 21.1, 31.4, 53.2, 68.0, 81.4, 126.1, 128.7, 130.0, 130.1, 134.8, 135.0, 172.4.

syn-**1g** (*Major isomer*). ^{1}H NMR δ 1.15 (d, 3H, J=6.4 Hz), 1.47 (s, 9H), 2.46–2.53 (m, 1H), 2.62–2.78 (m, 2H), 3.72 (s, 2H), 3.93–4.00 (m, 1H), 7.24–7.32 (m, 5H). ^{13}C NMR δ 20.5, 27.8, 29.2, 36.2, 53.1, 67.9, 81.3, 126.8, 128.3, 128.7, 137.9, 172.6. Anal. calcd for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16, found C, 64.26; H, 8.29.

anti-**1g** (*minor isomer*). ^{1}H NMR δ 1.20 (d, 3H, J=6.6 Hz), 1.47 (s, 9H), 2.46–2.53 (m, 1H), 2.62–2.78 (m, 2H), 3.72 (s, 2H), 3.93–4.00 (m, 1H), 7.24–7.32 (m, 5H). ^{13}C NMR δ 21.1, 27.8, 30.1, 36.2, 52.4, 67.5, 81.8, 126.8, 128.3, 128.7, 137.8, 172.9.

3.1.2. Preparation of *tert*-butyl 3-hydroxy-2-(2-ethylthio)methylbutyrate 1h. To a solution of *syn*-**5e** (1.735 g, 5.0 mmol) in THF (20 mL) was added TBAF (1 M in THF, 6 mL, 6 mmol) at room temperature and the reaction mixture was allowed to stir for 1 h. Solvent was removed in vacuo and the residue was subjected to flash chromatography (silica gel/hexane–ethyl acetate 20:1 then 5:1 v/v) to give free alcohol *syn*-**1h** in 99% yield (1.158 g, 4.94 mmol). ^{1}H NMR δ 1.22 (d, 3H, J=6.3 Hz), 1.26 (t, 3H, J=7.2 Hz), 1.48 (s, 9H), 1.59 (s, 1H), 2.57 (q, 2H, J=7.3 Hz), 2.52–2.60 (m, 1H), 2.78 (dd, 1H, J=5.9, 13.2 Hz), 2.84 (dd, 1H, J=8.6, 13.2 Hz), 4.04 (quint, 1H, J=6.3 Hz). ^{13}C NMR δ 14.3, 20.7, 25.8, 27.7, 29.6, 53.9, 67.9, 172.5. HRMS (FAB) calcd for (M+) $C_{11}H_{22}O_3S$: 234.1290, found 234.1294.

3.1.3. Preparation of 3-acetoxy-*N*-benzyloxy-3-phenyl-2-phenylthiomethylpropionamide 2a. General procedure. To a solution of **1a** (3.4469 g, 10 mmol) and DMAP (0.1220 g, 1.0 mmol) in pyridine (10 mL), acetic anhydride (2.8 mL, 30 mmol) was added at room temperature and the reaction mixture was allowed to stir for 3 h. The reaction mixture was poured into ice-water (10 mL) and extracted with ether (3×30 mL). The organic phase was washed successively with HCl aq. (1 M, 30 mL), water (30 mL), sat. $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL), then dried over Na_2SO_4. After filtration, solvent was removed in vacuo and the crude product was purified through flash chromatography (silica gel/hexane–ethyl acetate 10:1 v/v) to give acetate of **1a** in 98% yield (3.7719 g). Mp 44°C. ^{1}H NMR δ 1.25 (s, 9H), 2.08 (s, 3H), 3.02 (ddd, 1H, J=4.7, 7.6, 11.9 Hz), 3.19 (m, 2H), 5.98 (d, 1H, J=7.6 Hz), 7.14–7.35 (m, 10H). ^{13}C NMR δ 20.1, 27.0, 31.4, 51.9, 75.0, 80.5, 125.6, 126.5, 127.7, 128.4, 128.7, 135.2, 137.1, 168.5, 169.1. To toluene solution (20 mL) of acetate of **1a** (1.5433 g, 4 mmol) were added *p*-TsOH (0.0761 g, 0.4 mmol) and water (2 drops, about 0.1 g), and the resulting solution was heated to the refluxing temperature for 2 h. The solution was washed with water (5 mL) and dried over Na_2SO_4. Filtration and concentration of the solution gave corresponding carboxylic acid as a white solid in 97% yield (1.3226 g), which was used for the next step without further purification. Mp 74°C. ^{1}H NMR δ 2.09 (s, 3H), 3.09 (ddd, 1H, J=4.0, 6.3, 13.6 Hz), 3.12–3.22 (m, 2H), 6.12 (d, 1H, J=5.9 Hz), 7.14–7.36 (m, 10H), 10.8 (br, 1H). ^{13}C NMR δ 20.7, 30.8, 51.5, 74.8, 126.3, 126.4, 128.3, 128.4, 128.9, 129.6, 134.7, 137.0, 169.9, 176.0. pH of a solution of carboxylic acid (0.9930 g, 3.0 mmol) and $NH_2OBnHCl$ (1.2855 g, 8.0 mmol) in THF–water (9:1 v/v, 30 mL) was controlled to 4.5 by adding $NaHCO_3$ solution. Aqueous solution of EDCI (1.9183 g, 10 mmol in 27 mL of water) was added to the solution and the resulting mixture was allowed to stir for 6 h at room temperature. Acidified to pH 2 by adding HCl aq., the solution was concentrated in vacuo to remove THF. The resulting aqueous solution was extracted with EtOAc (3×30 mL). The organic phase was combined and dried over Na_2SO_4. After filtration and concentration, crude product was purified through flash chromatography (silica gel/hexane–ethyl acetate 20:1 then 5:1 v/v) to give **2a** in 96% yield (1.2508 g). White solid. Mp 128°C. ^{1}H NMR δ 2.10 (s, 3H), 3.52–2.54 (m, 1H), 3.28–3.31 (m, 2H), 4.48 (d, 1H, J=11.5 Hz), 4.71 (d, 1H, J=10.9 Hz), 5.97 (d, 1H, J=9.2 Hz), 7.18–7.41 (m, 15H), 7.70 (s, 1H). ^{13}C NMR δ 20.9, 31.7, 50.2, 75.7, 78.0, 126.1, 126.8, 126.9, 128.3, 128.5, 128.6, 128.7, 129.0, 129.1, 135.0, 135.3, 137.7, 167.7, 169.6. Anal. calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22, found C, 68.77; H, 5.96; N, 3.21.

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

3.1.4. 3-Acetoxy-*N*-benzyloxy-3-(4-chlorophenyl)-2-phenylthiomethylpropionamide 2b. Mp 104°C. ^{1}H NMR δ 2.07 (s, 3H), 2.48–2.56 (m, 1H), 3.24–3.29 (m, 2H), 4.51 (d, 1H, J=11.6 Hz), 4.72 (d, 1H, J=11.9 Hz), 5.92 (d, 1H, J=9.2 Hz), 7.02–7.38 (m, 14H), 7.98 (s, 1H). ^{13}C NMR δ 20.3, 31.7, 49.0, 74.5, 74.9, 125.7, 127.8, 128.0, 128.2, 128.4, 128.5, 128.6, 133.7, 134.7, 135.3, 135.8, 167.1, 169.3. Anal. calcd for $C_{25}H_{24}ClNO_4S$: C, 63.89; H, 5.15; N, 2.98, found C, 63.55; H, 5.25; N, 3.01.

3.1.5. 3-Acetoxy-*N*-benzyloxy-3-(1-naphthyl)-2-phenylthiomethylpropionamide 2c. Mp 145°C. ^{1}H NMR δ 2.13 (s, 3H), 2.87 (m, 1H), 3.36–3.40 (m, 2H), 4.16 (d, 1H, J=11.6 Hz), 4.52 (d, 1H, J=11.2 Hz), 6.71 (d, 1H, J=8.3 Hz), 6.99–8.05 (m, 18H). ^{13}C NMR δ 21.0, 31.5, 49.3, 73.7, 78.0, 123.3, 125.0, 125.1, 125.3, 125.9, 126.2, 126.6, 128.4, 128.5, 128.7, 128.9, 129.1, 129.3, 130.1, 133.6, 133.9, 134.9, 135.0, 167.8, 169.6. Anal. calcd for $C_{29}H_{27}NO_4S$: C, 71.73; H, 5.60; N, 2.88, found C, 71.50 H, 5.54; N, 2.90.

3.1.6. 2-(1-Acetoxyphenylmethyl)-*N*-benzyloxy-3-(1-naphthyl)-3-phenylthiobutyramide 2d. Mp 56°C. ^{1}H NMR δ 1.47 (d, 3H, J=7.3 Hz), 1.85 (s, 3H), 2.71 (dd, 1H, J=4.6, 10.6 Hz), 3.58–3.62 (m, 1H), 4.38 (d, 1H, J=11.2 Hz), 4.65 (d, 1H, J=11.2 Hz), 6.26 (d, 1H, J=10.2 Hz), 7.21–7.43 (m, 15H), 7.75 (s, 1H). ^{13}C NMR δ 21.1, 21.9, 45.0, 54.2, 75.8, 78.4, 127.2, 128.4, 128.6, 128.7, 128.9, 129.4, 131.7, 135.3, 137.9, 140.0, 167.3, 170.3. MS (FAB) m/z 450 [(M+H)$^+$, 20%].

3.1.7. 3-Acetoxy-*N*-benzyloxy-2-benzylthiomethylbutyramide 2e. Oil. ^{1}H NMR δ 1.15 (d, 3H for major isomer, J=6.3 Hz), 1.22 (d, 3H for minor isomer, J=7.2 Hz), 1.86 (s, 3H for major isomer), 1.96 (s, 3H for minor isomer), 2.42–2.52 (m, 2H), 2.68 (d, 1H for major isomer, J=11.9 Hz), 2.73 (d, 1H for minor isomer, J=12.9 Hz), 3.62 (d, 1H, J=13.9 Hz), 3.68 (d, 1H, J=13.5 Hz), 4.91 (s, 2H), 4.91–5.00 (m, 1H), 7.20–7.40 (m, 10H), 9.88 (br, 1H for minor isomer), 10.1 (br, 1H for major isomer). ^{13}C NMR δ for major isomer 17.3, 20.7, 29.2, 35.7, 48.2, 53.3, 70.5, 77.8, 126.5, 128.0, 128.1, 128.5, 128.6, 128.8, 135.0, 137.6,

168.5, 169.8, for minor isomer 16.9, 20.7, 28.3, 35.8, 48.2, 53.3, 70.2, 77.8, 126.6, 128.0, 128.1, 128.5, 128.6, 128.8, 135.0, 137.5, 168.6, 169.6.

3.1.8. 3-Acetoxy-*N*-benzyloxy-2-ethylthiomethylbutyramide 2f. Oil. ^{1}H NMR δ 1.21 (d, 3H), 1.23 (t, 3H, J=6.9 Hz), 1.99 (s, 3H), 2.30–2.35 (m, 1H), 2.53 (q, 2H, J=7.3 Hz), 2.66 (dd, 1H, J=4.9, 13.2 Hz), 2.84 (dd, 1H, J=10.2, 13.2 Hz), 4.94 (s, 2H), 5.06 (quint, 1H, J=6.3 Hz), 7.36–7.42 (m, 5H), 8.27 (br, 1H). ^{13}C NMR δ 14.6, 17.1, 21.1, 26.8, 30.0, 49.6, 70.7, 78.3, 128.6, 128.8, 129.3, 135.2, 169.1, 170.0. Anal. calcd for $C_{16}H_{23}NO_4S$: C, 59.05; H, 7.12; N, 4.30, found C, 58.81; H, 7.16; N, 4.39.

3.1.9. Preparation of 3-(acetoxyphenylmethyl)-*N*-benzyloxy-2-azetidinone 3a. General procedure. To a solution of amide **2a** (0.4368 g, 1.0 mmol) in CH_3CN (12 mL) were added MeI (0.6 mL, 10 mmol) and $AgClO_4$ (1.0978 g, 4.8 mmol) and the reaction mixture was allowed to stir for 4 h at room temperature in dark. Precipitate was removed by filtration and the filtrate was concentrated in vacuo. The residue was solved in acetone (20 mL) and K_2CO_3 (1.1841 g, 8.5 mmol) was added. The reaction mixture was allowed to heat to the refluxing temperature for 6 h. Precipitate was filtered and the filtrate was concentrate in vacuo. Water was added to the residue and the aqueous mixture was extracted with CH_2Cl_2 (3×30 mL). Combined organic phase was dried over Na_2SO_4. After filtration and evaporation, crude mixture was purified through flash chromatography (hexane–ethyl acetate, 3:1 then 2:1 v/v) to give β-lactam **3a** as oil in 70% yield (0.2237 g). ^{1}H NMR δ 2.06 (s, 3H,), 3.26–3.29 (m, 2H), 3.35 (td, 1H, J=2.9, 4.9 Hz), 4.80 (d, 1H, J=13.2 Hz), 4.88 (d, 1H, J=13.2 Hz), 6.00 (d, 1H, J=4.9 Hz), 7.24–7.37 (m, 10H). ^{13}C NMR δ 20.7, 47.3, 49.8, 71.6, 77.6, 126.1, 128.3, 128.4, 128.5, 128.7, 128.8, 134.8, 137.2, 162.7, 169.3. HRMS (FAB) calcd for (M+) $C_{19}H_{19}NO_4$: 325.1314, found 325.1322.

Other β-lactams **3** were prepared in a similar procedure.

3.1.10. 3-[Acetoxy(4-chlorophenyl)methyl]-*N*-benzyloxy-2-azetidinone 3b. Oil. ^{1}H NMR δ 2.08 (s, 3H), 3.19 (s, 1H), 3.27–3.32 (m, 2H), 4.84 (d, 1H, J=11.5 Hz), 4.89 (d, 1H, J=11.5 Hz), 5.91 (d, 1H, J=5.2 Hz), 7.18–7.34 (m, 9H). ^{13}C NMR δ 20.6, 47.4, 49.5, 71.2, 77.8, 127.6, 128.4, 128.6, 128.7, 134.1, 134.7, 135.6, 162.4, 169.2. Anal. calcd for $C_{19}H_{18}ClNO_4$: C, 63.42; H, 5.04; N, 3.89, found C, 63.11; H, 5.14; N, 3.80.

3.1.11. 3-[Acetoxy(1-naphthyl)methyl]-*N*-benzyloxy-2-azetidinone 3c. Oil. ^{1}H NMR δ 2.13 (s, 3H), 3.14 (t, 1H, J=5.1 Hz), 3.37 (dd, 1H, J=2.6, 4.6 Hz), 3.55 (m, 1H), 4.83 (d, 1H, J=11.6 Hz), 4.91 (d, 1H, J=11.6 Hz), 6.87 (d, 1H, J=4.3 Hz), 7.26–8.01 (m, 12H). ^{13}C NMR δ 20.5, 46.8, 49.1, 67.4, 77.5, 121.9, 122.8, 124.9, 125.3, 125.6, 126.4, 127.9, 128.0, 128.2, 128.5, 128.6, 128.7, 129.4, 133.1, 133.3, 134.7, 162.7, 168.9. HRMS (FAB) calcd for (M+) $C_{23}H_{21}NO_4$: 375.1471, found 375.1471.

3.1.12. 3-[Acetoxyphenylmethyl]-*N*-benzyloxy-4-methyl-2-azetidinone 3d. Mp 57°C. ^{1}H NMR δ 1.09 (d, 3H, J=6.3 Hz), 2.02 (s, 3H), 3.45 (dd, 1H, J=5.3, 10.2 Hz), 3.80 (dq, 1H, J=5.6, 6.3 Hz), 4.90 (d, 1H, J=11.4 Hz), 4.97 (d, 1H, J=11.4 Hz), 5.91 (d, 1H, J=10.2 Hz), 7.27–7.38 (m, 10H). ^{13}C NMR δ 13.3, 20.7, 52.3, 57.1, 71.5, 78.1, 126.6, 128.2, 128.3, 128.4, 128.8, 129.1, 135.1, 137.6, 162.6, 169.1. Anal. calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13, found C, 70.62; H, 6.47; N, 4.02.

3.1.13. 3-(1-Acetoxyethyl)-*N*-benzyloxy-2-azetidinone 3e. Oil. ^{1}H NMR δ1.30 (d, 3H, J=6.3 Hz), 2.00 (s, 3H), 3.02 (ddd, 1H, J=2.3, 5.3, 7.6 Hz), 3.17 (dd, 1H, J=2.3, 5.0 Hz), 3.33 (t, 1H, J=5.3 Hz), 4.95 (s, 2H), 5.05 (quint, 1H, J=7.0 Hz), 7.35–7.42 (m, 5H). ^{13}C NMR δ 18.4, 21.0, 48.6, 49.9, 68.2, 77.8, 128.6, 128.9, 129.0, 134.9, 163.0, 169.9. Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32, found C, 63.87; H, 6.63; N, 5.07.

3.1.14. Preparation of methyl 3-(*tert*-butyldimethysilyloxy)-2-ethylthiomethylbutyrate 5c. To a solution of EtSH (0.32 mL, 4.32 mmol) in THF (15 mL) was added BuLi (1.6 M, 0.25 mL, 0.40 mmol) at −50°C. Methyl 2-[1-(*tert*-butyldimethylsilyloxy)ethyl]acrylate (0.923 g, 3.78 mmol) was added to the solution at −50°C, and the resulting reaction mixture was allowed to stir at the same temperature for 15 h. HCl aq. (1 M, 40 mL) was added to the mixture and the organic phase was separated. The water phase was extracted with EtOAc (3×70 mL) and the combined organic phase was dried over Na_2SO_4. After filtration, the organic solvent was removed in vacuo and the residue was purified through flash chromatography (hexane then hexane–ether 30:1 v/v) to give adduct **5c** in 94% yield (1.08 g, 3.54 mmol) as an oil. ^{1}H NMR δ 0.06 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.16 (d, 3H, J=6.3 Hz), 1.24 (t, 3H, J=7.2 Hz), 2.53 (q, 2H, J=7.2 Hz), 2.62 (ddd, 1H, J=3.5, 6.9, 10.2 Hz), 2.71 (dd, 1H, J=10.6, 12.5 Hz), 2.86 (dd, 1H, J=3.6, 12.5 Hz), 3.71 (s, 3H), 3.98 (quint, 1H, J=6.3 Hz). ^{13}C NMR δ −4.8, −4.1, 14.8, 18.1, 22.2, 25.9, 26.3, 30.2, 51.8, 55.0, 69.4, 173.7. Anal. calcd for $C_{14}H_{30}O_3SSi$: C, 54.85; H, 9.86, found C, 54.58; H, 9.89.

Other **5** were prepared in a similar manner.

3.1.15. *tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-phenylthiomethylbutyrate 5b. *Major isomer*. Oil. ^{1}H NMR δ0.00 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 1.15 (d, 3H, J=6.3 Hz), 2.72 (dd, 1H, J=6.6, 12.9 Hz), 3.11–3.15 (m, 2H), 3.68 (s, 3H), 4.11 (quint, 1H, J=6.0 Hz), 7.15–7.38 (m, 5H). ^{13}C NMR δ −4.7, −4.5, 17.7, 20.6, 25.5, 31.1, 51.4, 53.6, 68.6, 126.2, 128.8, 129.7, 135.5, 172.6.

Minor isomer. Oil. ^{1}H NMR δ 0.01 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.15 (d, 3H, J=6.3 Hz), 2.65 (ddd, 1H, J=3.0, 6.9, 10.5 Hz), 3.13 (dd, 1H, J=10.4, 13.5 Hz), 3.30 (dd, 1H, J=3.6, 13.5 Hz), 3.65 (s, 3H), 4.02 (quint, 1H, J=6.0 Hz), 7.15–7.38 (m, 5H). ^{13}C NMR δ −4.7, −4.5, 17.7, 21.8, 25.6, 32.0, 51.4, 54.1, 69.0, 126.0, 128.7, 129.4, 135.7, 173.0.

3.1.16. *tert*-Butyl 2-ethylthiomethyl-3-hydroxybutyrate 5d. Oil. ^{1}H NMR δ 1.21–1.49 (m, 6H), 2.41 (br, 1H), 2.55 (q, 2H, J=7.3 Hz), 2.63–2.73 (m, 1H), 2.84–2.87 (m, 2H), 3.75 (s, 3H), 4.02–4.13 (m, 2H). ^{13}C NMR δ 14.2, 20.5, 25.8, 29.4, 51.4, 53.1, 67.7, 173.6. HRMS (FAB) calcd for (M+H) $C_8H_{16}O_3S$: 192.0898, found 192.0896.

3.1.17. *tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-ethylthiomethylbutyrate 5e. Oil. ^{1}H NMR δ 0.06 (s, 6H), 0.88 (s, 9H), 1.17 (d, 3H, J=5.9 Hz), 1.24 (t, 3H, J=7.4 Hz), 1.46 (s, 9H), 2.53 (q, 2H, J=7.5 Hz), 2.46–2.56 (m, 1H), 2.64 (dd, 1H, J=10.8, 12.7 Hz), 2.86 (dd, 1H, J=3.8, 12.7 Hz), 3.87 (quint, 1H, J=6.8 Hz). ^{13}C NMR δ −4.92, −4.30, 14.6, 17.8, 21.9, 25.7, 25.8, 28.0, 30.8, 55.5, 69.5, 80.7, 172.3. Anal. calcd for $C_{17}H_{36}O_3SSi$: C, 58.57; H, 10.41, found C, 58.37; H, 10.76.

3.1.18. Methyl 3-(*tert*-butyldimethylsilyloxy)-2-ethylthiomethylpentanoate 5f. Oil. ^{1}H NMR δ 0.04 (s, 6H), 0.88 (s, 9H), 0.92 (t, 3H, J=6.2 Hz), 1.25 (t, 3H, J=7.2 Hz), 1.43–1.61 (m, 2H), 2.53 (q, 2H, J=7.2 Hz), 2.74–2.83 (m, 3H), 3.70 (s, 3H), 3.87 (q, 1H, J=5.6 Hz). ^{13}C NMR δ −4.76, −4.33, 8.7, 14.6, 18.0, 25.8, 26.3, 27.7, 29.8, 51.5, 51.6, 73.8, 173.7. Anal. calcd for $C_{15}H_{32}O_3SSi$: C, 56.20; H, 10.06, found C, 56.00; H, 10.21.

3.1.19. Methyl 3-(*tert*-butyldimethylsilyloxy)-2-ethylthiomethyl-4-methylpentanoate 5g. Oil. ^{1}H NMR δ 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (d, 3H, J=7.0 Hz), 0.90 (s, 9H), 0.93 (d, 3H, J=6.9 Hz), 1.24 (t, 3H, J=7.3 Hz), 1.61–1.70 (m, 1H), 2.53 (q, 2H, J=7.2 Hz), 2.69 (d, 1H, J=10.9 Hz), 2.74–2.81 (m, 1H), 2.88 (d, J=9.6 Hz), 3.70 (s, 3H), 3.70–3.74 (m, 1H). ^{13}C NMR δ −3.83, −3.65, 15.0, 17.3, 18.5, 19.5, 26.3, 26.4, 30.9, 33.6, 50.7, 51.8, 77.8, 174.3. Anal. calcd for $C_{16}H_{34}O_3SSi$: C, 57.43; H, 10.24, found C, 57.62; H, 10.50.

3.1.20. Methyl 3-(*tert*-butyldimethylsilyloxy)-3-(4-chlorophenyl)-2-ethylthiomethyl-propionate 5h. Oil. ^{1}H NMR δ 0.00 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 1.17 (t, 3H, J=7.2 Hz), 2.44 (q, 2H, J=6.3 Hz), 2.81–2.91 (m, 3H), 3.51 (s, 3H), 4.80 (d, 1H, J=6.0 Hz), 7.24 (d, 2H, J=9.6 Hz), 7.26 (d, 2H, J=10.0 Hz). ^{13}C NMR δ 4.7, 14.4, 17.9, 25.6, 25.9, 29.4, 51.5, 56.2, 75.1, 127.6, 128.2, 133.4, 140.8, 172.4. Anal. calcd for $C_{19}H_{31}O_3SSi$: C, 56.62; H, 7.75, found C, 56.51; H, 7.85.

3.1.21. 4-(*tert*-Butyldimethylsilyloxy)-3-ethylthiomethyl-2-pentanone 5i. Oil. ^{1}H NMR δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.09 (d, 3H, J=6.3 Hz), 1.23 (t, 3H, J=7.4 Hz), 2.26 (s, 3H), 2.52 (q, 2H, J=7.4 Hz), 2.68 (dd, 1H, J=7.0, 13.2 Hz), 2.73 (dd, 1H, J=8.3, 13.0 Hz), 2.87 (td, 1H, J=6.3, 7.9 Hz), 3.99 (quint, 1H, J=6.2 Hz). ^{13}C NMR δ −4.60, 14.5, 17.8, 20.7, 25.6, 26.4, 29.8, 32.8, 59.8, 69.1, 210.1. Anal. calcd for $C_{14}H_{30}O_2SSi$: C, 57.88; H, 10.41, found C, 57.90; H, 10.56.

3.1.22. 3-(*tert*-Butyldimethylsilyloxy)-2-ethylthiomethylbutyronitrile 5j. Oil. HRMS (FAB) calcd for (M+H) $C_7H_{14}NOS$: 160.0796, found 160.0794 for **5j-A** isomer. ^{1}H NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 1.28 (t, 3H, J=7.3 Hz), 1.33 (d, 3H, J=5.6 Hz), 2.66 (q, 2H, J=7.3 Hz), 2.73–2.83 (m, 3H), 4.05 (m, 1H). ^{13}C NMR δ −4.7, −4.1, 14.9, 18.1, 21.6, 25.7, 26.9, 30.1, 42.3, 67.9, 120.1.

For **5j-B** *isomer*. ^{1}H NMR δ 0.09 (s, 3H), 0.16 (s, 3H), 0.90 (s, 9H), 1.28 (t, 3H, J=7.6 Hz), 1.32 (d, 3H, J=6.3 Hz), 2.61 (q, 2H, J=7.4 Hz), 2.68–2.72 (m, 1H), 2.79–2.82 (m, 2H), 4.11 (dq, 1H, J=3.3, 6.3 Hz). ^{13}C NMR δ −4.7, −4.0, 14.9, 18.2, 22.2, 26.0, 26.7, 30.7, 42.0, 66.9, 119.5.

3.1.23. Desulfurization of 5c. To a solution of **5c** (1.085 g, 3.54 mmol) in ethanol (20 mL) was added Raney-Ni W2 (about 15 g) at room temperature and the reaction mixture was allowed to stir for 2 h. Nickel was filtered and the filtrate was concentrated in vacuo. The residue was solved in CH_2Cl_2 and dried over Na_2SO_4. Filtration and concentration gave **6**[13] in 73% yield (0.6318 g, 2.57 mmol). ^{1}H NMR δ 0.03 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.14 (d, 3H, J=6.3 Hz), 1.16 (d, 3H, J=6.9 Hz), 2.42 (dq, 1H, J=6.8, 7.0 Hz), 3.67 (s, H), 4.09 (quint, 1H, J=6.1 Hz). ^{13}C NMR δ −4.89, −4.17, 12.0, 18.1, 22.1, 25.9, 47.6, 51.5, 46.7, 175.5.

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16. A referee of the paper pointed out that intermediate enolate should be isolated and used for further examination to perform detailed discussion. However, it has been impossible so far to isolate any intermediates despite our efforts. See Ref. 2b,e.