

1 β -Methylcarbapenem intermediates via the thiolysis of a Meldrum's precursor

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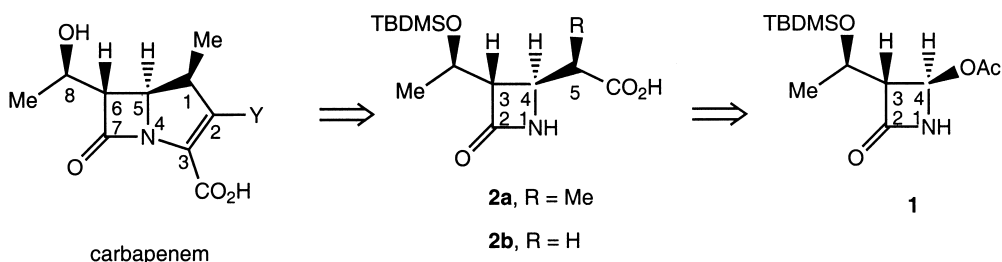
Abstract—5-{3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-oxo-azetidin-2-yl}-2,2,5-trimethyl-[1,3]dioxane-4,6-dione (**3**) has been submitted to nucleophilic attack with various nucleophiles. Meldrum's moiety transesterification, C4-substitution, β -lactam ring opening and Meldrum's moiety decarboxylation were observed. Reaction of **3** with ethanethiol and dimethylaminopyridine in ethanol quantitatively furnished ethyl 2-{3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-4-oxo-azetidin-2-yl}-thiopropionate as the 1:1 mixture of β (**7a**) and α (**8a**) diastereoisomers. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Carbapenem antibiotics bearing 1 β -methyl substituent possess remarkable chemical and metabolic stability; they are potent drugs against a variety of pathogens, including multiple drug resistant bacteria. Therefore, the search for efficient synthesis of these carbapenems has summoned up considerable works.¹ The main strategies make use of acetoxy-azetidinone **1**² as the chiral starting material allowing stereocontrolled substitution at C4 (Scheme 1). Introduction of the methyl-substituted two-carbon chain of **2a** results from enolate addition,³ vinylation followed by hydrogenation,⁴ or allylation followed by ozonolysis.⁵ Other methods are based on methylation of **2b**, also obtained from **1**.⁶ In all cases the stereochemical control of the C5 chiral center appears to be a difficult task, and

requires expensive (chiral) reagents and/or (chiral) catalysts, difficult to handle on the industrial scale.

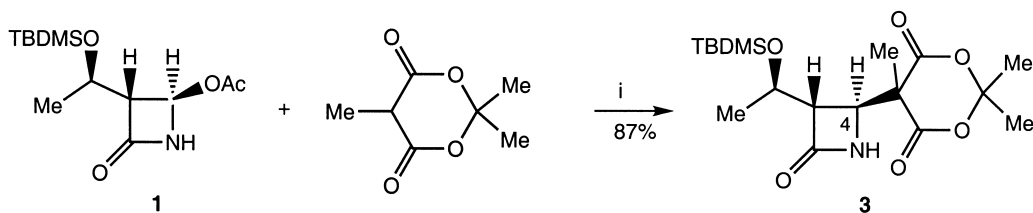
An alternative interesting approach, disclosed independently by the Takasago's^{7,8} and Merck's^{9–12} scientists, is based on the diastereoselective decarboxylation of malonic precursors. The 2-methyl-malonate residue was introduced by reacting **1** with 2-methyl-malonate diesters in the presence of sodium hydride,⁸ or with 2-methyl Meldrum's acid (2,2,5-trimethyl-1,3-dioxan-4,6-dione) in the presence of triethylamine⁹ (Scheme 2). In both cases, the azetidinone N1 position was further protected with a *t*-butyldimethylsilyl group before the cleavage of the ester functions by using standard methods; the resulting malonic diacid was then decarboxylated in refluxing ethyl acetate with formic acid as the catalyst. In a last step, the *N*-protecting group was removed (five-step process from **1**).



Scheme 1.

Keywords: azetidinones; carbapenems; decarboxylation.

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Scheme 2. (i) Et₃N (excess), EtOAc, reflux, 4 h.

Table 1.

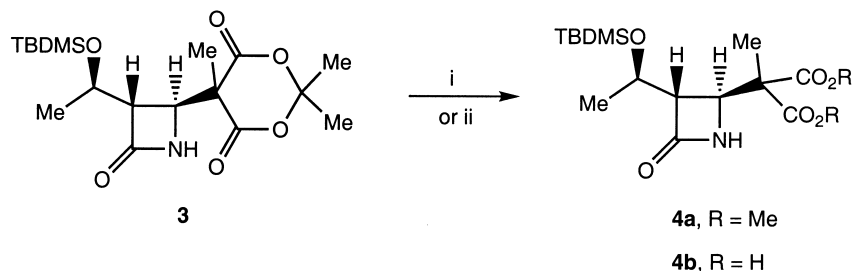
Entry	Conditions	Results
1	1 M HCl aq., CH ₂ Cl ₂ , 20–80°C, 24 h	No reaction
2	1 M HCl aq., CH ₂ Cl ₂ , Triton X-100, 50°C, 12 h	No reaction
3	HOAc–H ₂ (10:1), 70°C, 5 h	β-Lactam opening
4	EtOH, 60°C, 72 h	No reaction
5	2 M NaOH aq., MeOH, 50°C, 1 h	4a (87%)
6	1 M MeOLi aq., THF, 20°C, 1 h	β-Lactam opening
7	EtONa (2 equiv.), EtOH–THF (1:1), 60°C, 17 h	No reaction
8	MeONa (1.5 equiv.), MeOH–THF (1:1), 60°C, 17 h	No reaction
9	PhONa (2 equiv.), THF, 20°C, 3 h	5a (96%)
10	LiOH (2 equiv.), THF–H ₂ (5:1), 20°C, 2 h	4b (50%)+ 3

The authors mentioned that in the absence of a bulky *N*-protecting group (Si*t*BuMe₂), the major product resulted from azetidinone ring opening. Moreover, the high diastereoselectivity ($\beta/\alpha > 90:10$) of the enol intermediate reprotonation was explained by particular conformational effects due to the presence of this bulky substituent.^{10,11}

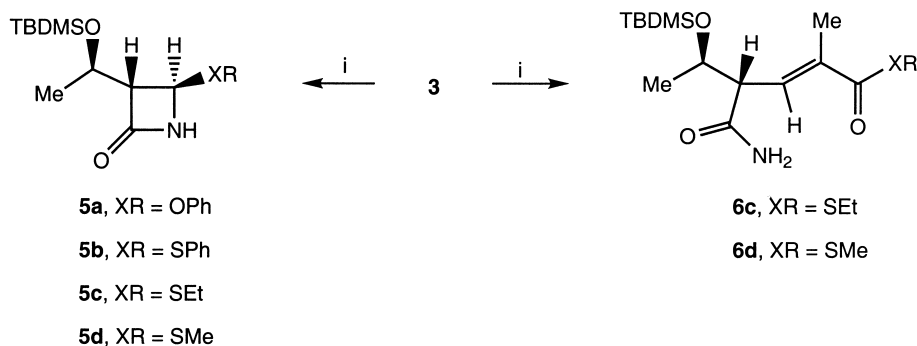
We recently revisited the decarboxylation process of Meldrum's derivative **3** with in mind the following questions: is it possible, (i) to avoid the *N*-protection and deprotection steps and, (ii) to perform the decarboxylative decomposition of the 2,2-dimethyl-1,3-dioxan-4,6-dione ring in a one-step reaction^{13–15} (two-step process from **1**)?

2. Results and discussion

The precursor **3** was obtained in 87% yield by substitution of acetoxy-azetidinone **1** with 2-methyl Meldrum's acid in the presence of a large excess of triethylamine⁹ (Scheme 2). Without protecting the N1 position, we systematically examined different classical conditions of ester hydrolysis or transesterification, as summarized in Table 1. No reaction was observed in biphasic acidic media (entries 1 and 2), and β-lactam opening occurred in homogeneous acidic medium (entry 3). Transesterification in ethanol (entry 4) required a basic catalyst (entry 5). Thus, dimethyl malonate derivative **4a** (Scheme 3) was recovered when refluxing **3** in methanol and aqueous sodium hydroxide; the same compound could be obtained by reaction of acetoxy-azetidinone **1** with sodium salt of dimethyl 2-methylmalonate.⁷



Scheme 3. (i) MeOH, NaOH aq., 50°C, 1 h; (ii) LiOH, THF–H₂O, 50°C, 1 h.



Scheme 4. (i) RXNa, THF, 20°C or reflux, in the presence of 18-crown-6 or not (Table 2).

Table 2.

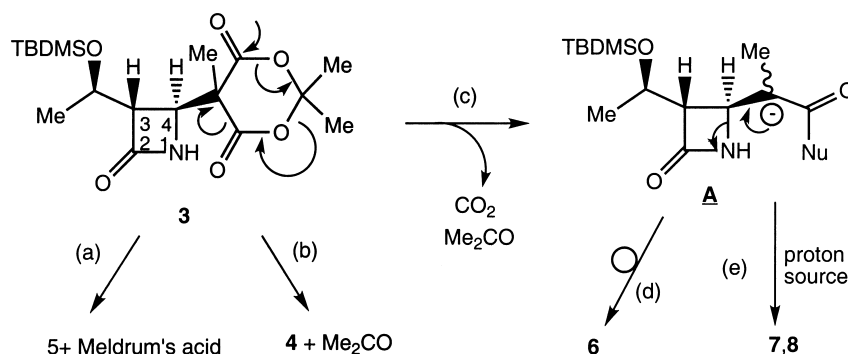
Entry	Conditions	Results
1	HSNa (1.5 equiv.), THF–H ₂ O (1:1), 65°C, 17 h	β-Lactam opening
2	PhSNa (2 equiv.), CH ₃ CN, 80°C, 24 h	β-Lactam opening
3	PhSNa (2 equiv.), DMF, 20°C, 24 h	β-Lactam opening
4	PhSNa (2 equiv.), THF, 20°C, 24 h	5b (95%)
5	EtSNa (2 equiv.), CH ₃ CN, 80°C, 24 h	β-Lactam opening
6	EtSNa (2 equiv.), THF, 20°C, 24 h	5c (92%)
7	EtSNa (2 equiv.), 18-crown-6, THF, 20°C, 24 h	5c + 6c (88%; 9:1)
8	EtSNa (2 equiv.), 18-crown-6, THF–H ₂ O, 60°C, 12 h	6c (95%)
9	MeSNa (1.5 equiv.), 18-crown-6, THF–H ₂ O, 60°C, 12 h	5d ²² + 6d (87%; 0.4:1)
10	MeSNa (1.5 equiv.), 18-crown-6, THF–H ₂ O, 20°C, 24 h	6d (97%)

Treatment of **3** with alkoxides gave various results, from the absence of transformation to the β-lactam destruction, depending on the experimental conditions (entries 6–8). With sodium phenoxide, nucleophilic attack at C4 resulted in quantitative formation of 4-phenoxy-azetidinone **5a**¹⁶ (entry 9, Scheme 4). Lastly, basic hydrolysis with lithium hydroxide in aqueous THF at room temperature, followed by smooth acidification, furnished the malonic diacid **4b**⁹ (Scheme 3). Thus, in this first set of experiments, the Meldrum's moiety decomposition in a one-step reaction according to route (c) of Scheme 5, was never observed; only products resulting from routes (a) and (b) were obtained. Therefore, we next decided to examine non-classical conditions of transesterification using sulphur-nucleophiles as reagents; such reactions are scarcely described in the field of Meldrum's acid chemistry.^{17,18}

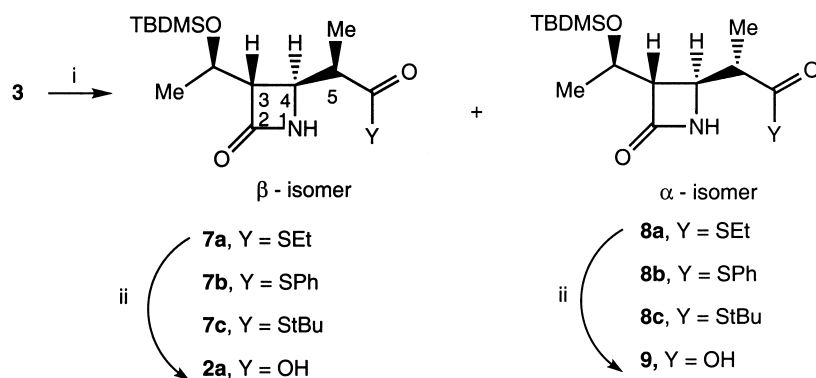
Sodium hydrosulfide and sodiumthiophenoxide in polar solvents destroyed the β-lactam ring (Table 2, entries 1–3); in THF, at room temperature, sodium thiophenoxide substituted quantitatively the Meldrum's moiety of compound **3** to furnish thiophenoxy-azetidinone **5b**^{19–21} (Scheme 4, Table 2, entry 4). Similarly, sodium thioethoxide reacted with **3** to give **5c**⁵ (entry 6); in the presence of crown-ether, some open-product **6c** was formed together with **5c** (entry 7, Scheme 4). But, in refluxing moist THF, with crown-ether, open-product **6c** was quantitatively obtained (entry 8). This compound is characterized in ¹H NMR by a singlet at 1.90 δ (Me–C=C) and a doublet at 6.93 δ (H–C=C); in the ¹³C NMR spectrum, two olefinic carbons (133.7 and 139.6 δ) and two carbonyl carbons (172.6 and 193.7 δ) are visible. Such a competition between routes (a) and (c)+(d), as illustrated in Scheme 5, was also

observed by treatment of **3** with sodium thiomethoxide (entries 9 and 10). The spectroscopic features of **6d** were similar to those of **6c**. Products resulting from the cleavage of the β-lactam N1–C4 bond have been already mentioned in the previous works devoted to the decarboxylation strategy, but under acidic conditions.^{9,12} The quantitative formation of **6**, most probably from the carbanion intermediate **A** (Scheme 5), demonstrated, at this stage, the feasibility of a clean 'one-step decomposition' of the Meldrum's substituent of **3**, initiated by a sulphur-nucleophile. We speculated that in the presence of a proton source, the enolate anion **A** could be quenched, without cleavage of the azetidinone ring. Accordingly, a last series of experiments was realized using thiols as soft nucleophiles.

Treatment of **3** in refluxing ethanethiol used as solvent and reagent, slowly produced a mixture of the desired thioesters **7a**²³ and **8a**, but in which the 'wrong' α-isomer **8a** was largely the major compound (Scheme 6, Table 3, entry 1). Addition of an organic base, such as triethylamine (entry 2), 1,4-diazabicyclo[2.2.2]octane (entry 3), diisopropylamine (entry 4), or *N*-dimethylaminopyridine (DMAP) (entry 5), accelerated the reaction, and slightly increased the ratio of the β-isomer **7a**, the required precursor of 1β-methyl-carbapenems. Addition of ethanol as co-solvent (entry 6) improved the β/α isomers ratio. Finally, the best conditions involved the use of a mixture of ethanethiol and ethanol as protic nucleophilic medium, and the addition of DMAP as soft base (entry 8); a 50:50 mixture of stereoisomers was obtained. This result could not be improved by using *iso*-propanol or *tertio*-butanol as co-solvents (entries 7, 9 and 10). Thiophenol appeared to be less reactive than ethanethiol (entries 11 and 12), with a less favorable β/α isomers



Scheme 5. (a) Nucleophilic attack on C4 and elimination of the Meldrum's substituent; (b) transesterification or saponification of the Meldrum's substituent; (c) nucleophilic attack on Meldrum's carbonyl, elimination of acetone and decarboxylation; (d) cleavage of the N1–C4 bond; (e) protonation of the enolate **A**.



Scheme 6. (i) RSH, base, solvent, heating (Table 3); (ii) NaOH–H₂O, then HCl.

ratio (entry 13); a 40:60 mixture of compounds **7b**^{24–27} and **8b** was obtained (Scheme 6). *tertio*-Butanethiol was also less reactive (entries 14 and 16), but gave a stereoselectivity similar to that of ethanethiol (entry 15); stereoisomers **7c**²⁸ and **8c**²⁵ were formed in equimolar ratio (Scheme 6). Thus, the 'one-step' nucleophilic decomposition of the Meldrum's moiety was not particularly influenced by steric effects, considering the thiol reagent (EtSH, PhSH, *t*BuSH) and the alcohol co-solvent (EtOH, *i*PrOH, *t*BuOH). The role of the organic base was further investigated, but without success: stronger bases, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene), led to the β -lactam ring opening; chiral bases derived from alkaloids^{29,30} did not improve the β/α stereoselectivity.

The thioesters **7a–c** and **8a–c**, obtained in one-step from the Meldrum's precursor (**3**), were characterized by NMR spectroscopy: H5 proton gave a signal at 2.8–2.7 and 2.7–2.6 δ in the β and α series, respectively; the β -lactamic protons, H3 and H4, were visible around 3 and 3.9 δ in the β series, and around 2.8 and 3.7 δ in the α series. Saponification of **7a** and **8a** as usual furnished the corre-

sponding acids **2a** and **9** (Scheme 6), already described in the previous literature.^{6,31}

3. Conclusion

This work pointed out the various possibilities of nucleophilic attack on β -lactam **3** (Scheme 5) substituted with a Meldrum's acid moiety. The competition between the possible mechanisms appeared hardly manageable. However, significant differences were observed between O- and S-nucleophiles. Charged oxygen-species in aprotic solvent mainly attacked the C2 (MeOLi; β -lactam ring destruction), or the C4 positions (PhONa; substitution of the Meldrum's group), while, in protic medium, the malonic carbonyls reacted to give hydrolysis (LiOH–H₂O) or transesterification products (NaOH–MeOH) without concomitant extrusion of CO₂. Charged sulphur-species attacked either the C4 position, or the Meldrum's part. In this last case, decarboxylation occurred, followed by the cleavage of the β -lactam C4–N1 bond. Finally, neutral sulphur-species in protic medium furnished exclusively the thioesters derived from attack on one malonic carbonyl, followed by extrusion

Table 3.

Entry	Conditions					Yield		
	Thiol ^a	Solvent (ratio)	Base ^b	<i>T</i> (°C)	Time (h)	%	Compound	β/α^c
1	EtSH	–	–	40	17	40 ^d	7a/8a	7:93
2	EtSH	–	Et ₃ N	40	6	99	7a/8a	19:81
3	EtSH	–	DABCO	40	6	96	7a/8a	22:78
4	EtSH	–	DIPEA	40	6	95	7a/8a	24:76
5	EtSH	–	DMAP	40	5	86 ^d	7a/8a	33:67
6	EtSH	EtOH (1:4)	–	65	24	97	7a/8a	48:52
7	EtSH	<i>i</i> PrOH (1:1)	–	65	17	0 ^d	–	–
8	EtSH	EtOH (1:2)	DMAP	65	6	98 ^d	7a/8a	50:50
9	EtSH	<i>i</i> PrOH (1:2)	DMAP	65	17	97	7a/8a	38:62
10	EtSH	<i>t</i> BuOH (1:2)	DMAP	65	17	38 ^d	7a/8a	42:58
11	PhSH	–	–	80	24	0 ^d	–	–
12	PhSH	EtOH (1:1)	–	80	24	0 ^d	–	–
13	PhSH	EtOH (1:1)	DMAP	80	17	97	7b/8b	40:60
14	<i>t</i> BuSH	EtOH (1:2)	DMAP	65	17	70 ^{d,c}	7c/8c	36:64
15	<i>t</i> BuSH	<i>i</i> PrOH (1:2)	DMAP	65	17	50 ^d	7c/8c	50:50
16	<i>t</i> BuSH	<i>t</i> BuOH (1:2)	DMAP	65	17	0 ^d	–	–

^a Large excess.

^b One equivalent.

^c ¹H NMR analysis of the crude mixtures.

^d Starting material recovered.

^e 20% of **6** (β -lactam opening product).

of acetone and CO₂, without cleavage of the β-lactam ring. Thus, these simple experimental conditions allowed the preparation of carbapenem precursors in two steps from acetoxy-azetidinone **1**. The control of the C5 chiral center remains to be optimized: actually our best results give a 1:1 ratio of β and α diastereoisomers which could be separated after hydrolysis, by selective crystallization.^{6,31} We are now examining the possibility of enantioselective protonation^{32,33} of enolate intermediates (**A**, Scheme 5) derived from **7**, **8**.

4. Experimental

4.1. General

The melting points were determined with an electrothermal microscope and are uncorrected. The specific rotations (± 0.2) were determined on a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). The IR spectra were taken with a Bio-Rad FTS 135 instrument, and calibrated with polystyrene (1601 cm⁻¹). The ¹H and ¹³C NMR spectra were recorded on Varian Gemini 200–300 (at 200–300 MHz for proton and 50–75 MHz for carbon), or Bruker AM-500 spectrometers (at 500 MHz for proton and 125 MHz for carbon); the chemical shifts are reported in ppm downfield from tetramethylsilane (internal standard). The mass spectra were obtained on a Finnigan-MAT TSQ-70 instrument at 70 eV (chemical ionization mode). The microanalyses were performed at the Christopher Ingold Laboratories of the University College London.

Thin-layer chromatography was carried out on silica gel 60 plates F254 (Merck, 0.2 mm thick); visualization was effected with UV light, or phosphomolybdic acid. Column-chromatography (under medium pressure) was carried out with Merck silica gel 60 of 230–240 mesh ASTM.

4.1.1. 5-{3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-oxoazetidin-2-yl}-2,2,5-trimethyl-[1,3]dioxane-4,6-dione (3**).** To a solution of (*3R,4R*)-4-acetoxy-3-[(*5R*)-1'-*tert*-butyldimethylsilyloxy]ethyl]-azetidin-2-one **1** (1 g, 3.48 mmol) in ethyl acetate (100 mL) were added 2,2,5-trimethyl-1,3-dioxane-4,6-dione (826 mg, 5.22 mmol) and triethylamine (12 mL). The mixture was refluxed for 4 h, then diluted with ethyl acetate and washed with brine. After drying over MgSO₄ and concentration, the solid residue was purified by flash column-chromatography on silica gel (elution with 30% EtOAc/hexane) to give **3** (1.17 g, 87% yield) as white crystals. Mp 87–88°C; [Found: C, 55.82; H, 8.20; N, 3.54. C₁₈H₃₁NO₆Si requires C, 56.08; H, 8.10; N, 3.63%]; *R*_f (30% EtOAc/hexane) 0.26; [α]_D²⁰ = +0.042 (*c* 0.53, CH₂Cl₂); ν_{\max} (KBr) 3200, 1768, 1742 cm⁻¹; δ_{H} (200 MHz, CDCl₃) 6.20 (1H, br s, *NH*), 4.15 (1H, m, Me-CH(OTBDMS)-), 4.09 (d, 1H, *J*=2 Hz, H-2), 3.48 (m, 1H, H-3), 1.72 (s, 3H, one of the *CMe*₂), 1.68 (s, 3H, one of the *CMe*₂), 1.56 (s, 3H, *Me*), 1.12 (d, 3H, *J*=6.3 Hz, Me-CH(OTBDMS)-), 0.79 (s, 9H, Si-*Bu*), 0.01 (s, 6H, Si-*Me*); δ_{C} (50 MHz, CDCl₃) 168.8, 168.4, 167.7, 105.4, 64.7, 61.2, 55.6, 50.9, 29.9, 28.2, 25.7, 22.7, 18.6, 17.8, -4.4, -5.0; *m/z* (CI) 386.5 (MH⁺, 22), 370.5 (40), 328.5 (100), 285.3 (64%).

4.1.2. 2-{3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-oxoazetidin-2-yl}-2-methyl-malonic acid, dimethyl ester (4a**).** To a solution of **3** (100 mg, 0.259 mmol) in methanol (2 mL) and water (0.5 mL) was added 2 M NaOH (0.26 mL, 0.52 mmol, 2 equiv.). The mixture was stirred at 50°C for 1 h, then diluted with CH₂Cl₂ and washed with brine. The organic phase was dried (MgSO₄) and concentrated to furnish **4a** (85 mg, 87% yield) which could be purified by flash column-chromatography on silica gel (elution with 30% EtOAc/hexane): mp 122.4–122.6°C (white solid); [Found: C, 54.82; H, 8.48; N, 3.73. C₁₇H₃₁NO₆Si requires C, 54.67; H, 8.37; N, 3.75%]; *R*_f (30% EtOAc/hexane) 0.33; δ_{H} (200 MHz, CDCl₃) 6.11 (br s, 1H, *NH*), 4.18 (m, 1H, Me-CH(OTBDMS)-), 4.13 (d, 1H, *J*=2.1 Hz, H-2), 3.72 (s, 6H, -*OMe*), 2.97 (m, 1H, H-3), 1.44 (s, 3H, *Me*), 1.08 (d, 3H, *J*=6.3 Hz, Me-CH(OTBDMS)-), 0.84 (s, 9H, Si-*Bu*), 0.03 (s, 6H, Si-*Me*); δ_{C} (50 MHz, CDCl₃) 170.9, 167.7, 64.6, 60.3, 59.9, 55.7, 52.8, 52.5, 25.7, 22.3, 20.9, 16.5, 14.1, -4.4, -5.0; *m/z* (CI) 374 (MH⁺, 44), 358 (23), 316 (16), 231 (12), 199 (17), 89 (100%).

4.1.3. 2-{3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-oxoazetidin-2-yl}-2-methyl-malonic acid (4b**).** To a solution of **3** (100 mg, 0.259 mmol) in THF (5 mL) and water (1 mL) was added LiOH (22 mg, 0.54 mmol, 2 equiv.). The mixture was stirred at 20°C for 2 h, then concentrated under vacuum. The residue was dissolved in water and extracted with ether. The aqueous phase was acidified with 1N HCl (to reach pH 2) and extracted with ethyl acetate (3×). Drying over MgSO₄ and concentration gave the known malonic derivative **4b**⁹ (45 mg, 50% yield); *R*_f (AcOEt) 0.22; δ_{H} (200 MHz, CD₃OD) 4.15 (m, 2H, H-2 and Me-CH(OTBDMS)-), 2.97 (m, 1H, H-3), 1.35 (s, 3H, *Me*), 1.10 (d, 3H, *J*=6.4 Hz, Me-CH(OTBDMS)-), 0.83 (s, 9H, Si-*Bu*), 0.02 (s, 3H, one of the Si-*Me*), 0.01 (s, 3H, one of the Si-*Me*); δ_{C} (50 MHz, CD₃OD) 174.2, 173.8, 171.6, 65.9, 60.4, 56.7, 53.6, 30.7, 26.3, 22.6, 18.8, 16.8, -4.1, -4.8.

4.1.4. (3*R*,4*R*)-4-Phenylthioxy-3-[(5*R*)-1'-*tert*-butyldimethylsilyloxy]ethyl]-azetidin-2-one (5a**).** To a solution of **3** (100 mg, 0.259 mmol) in THF (10 mL) was added sodium phenoxide (60 mg, 2 equiv.). The mixture was stirred at 20°C for 2 h, then concentrated under vacuum. Addition of ethyl acetate, washing with brine, drying and concentration gave known **5a**¹⁶ (80 mg, 96% yield); δ_{H} (300 MHz, CDCl₃) 7.34 (t, 2H, *J*=8 Hz, Ph), 7.07 (t, 1H, *J*=8 Hz, Ph), 6.93 (d, 2H, *J*=8 Hz, Ph), 6.46 (br s, 1H, *NH*), 5.72 (s, 1H, H-2), 4.25 (dq, 1H, *J*=3 and 7 Hz, Me-CH(OTBDMS)-), 3.33 (d, 1H, *J*=3 Hz, H-3), 1.29 (d, 3H, *J*=7 Hz, Me-CH(OTBDMS)-), 0.89 (s, 9H, Si-*Bu*), 0.07 (s, 3H, one of the Si-*Me*), 0.06 (s, 3H, one of the Si-*Me*).

4.1.5. (3*R*,4*R*)-4-Phenylthioxy-3-[(5*R*)-1'-*tert*-butyldimethylsilyloxy]ethyl]-azetidin-2-one (5b**).** A mixture of **3** (100 mg, 0.259 mmol) and sodium thiophenoxide (68 mg, 2 equiv.) in THF (10 mL) was stirred overnight at 20°C, then worked-up as above, to furnish known **5b**¹⁹ (83 mg, 95% yield); δ_{H} (200 MHz, CDCl₃) 7.48 (m, 2H, Ph), 7.34 (m, 3H, Ph), 6.29 (br s, 1H, *NH*), 5.06 (d, 1H, *J*=2.4 Hz, H-2), 4.15 (m, 1H, Me-CH(OTBDMS)-), 3.02 (m, 1H, H-3), 1.23 (d, 3H, *J*=6.6 Hz, Me-CH(OTBDMS)-), 0.86 (s, 9H, Si-*Bu*), 0.06 (s, 3H, one of the Si-*Me*), 0.05

(s, 3H, one of the Si–Me); δ_C (50 MHz, $CDCl_3$) 167.7, 134.4, 132.5, 130.0, 129.3, 66.2, 65.2, 56.9, 26.4, 22.9, 18.6, –3.6, –4.4.

4.1.6. (3R,4R)-4-Ethylthioxy-3-[(5R)-1'-(tert-butyl-dimethylsilyloxy)ethyl]-azetid-2-one (5c). A mixture of **3** (100 mg, 0.259 mmol) and sodium ethanethiolate (42 mg, 2 equiv.) in THF (10 mL) was stirred for 24 h at 20°C, then worked-up as above, to furnish known **5c**⁵ (69 mg, 92% yield); δ_H (200 MHz, $CDCl_3$) 6.0 (br s, 1H, NH), 4.85 (d, 1H, $J=2.5$ Hz, H-2), 4.27 (m, 1H, Me–CH(OTBDMS)–), 3.15 (m, 1H, H-3), 2.66 (q, 2H, $J=7.5$ Hz, –SCH₂CH₃), 1.30 (t, 3H, $J=7.5$ Hz, –SCH₂CH₃), 1.25 (d, 3H, $J=6.9$ Hz, Me–CH(OTBDMS)–), 0.88 (s, 9H, Si–Bu), 0.07 (s, 6H, Si–Me).

4.1.7. 5-(tert-Butyldimethylsilyloxy)-4-carbamoyl-2-methyl-hex-2-enethioic acid, ethyl ester (6c). To a solution of **3** (100 mg, 0.259 mmol) in THF (5 mL) and water (60 μ L), were added sodium ethanethiolate (32 mg, 1.5 equiv.) and 18-crown-6 (38 mg, 0.55 equiv.). The mixture was refluxed overnight, then diluted with ethyl acetate and washed with brine. The organic layer was dried (MgSO₄), concentrated under vacuum, and purified by flash column-chromatography on silica gel (elution with 30% AcOEt/hexane) to give **6c** (85 mg, 93%) as a white solid; mp 86.2–87°C; [Found: C, 55.82; H, 9.28; N, 3.79. C₁₆H₃₁NO₃SSi requires C, 55.61; H, 9.04; N, 3.79%]; R_f (30% AcOEt/hexane) 0.64; $[\alpha]_D^{20} = +0.68$ ($c=2.19$, CH₂Cl₂); ν_{max} (KBr) 3429, 1691, 1646 cm^{–1}; δ_H (300 MHz, $CDCl_3$) 6.93 (d, 1H, $J=7.6$ Hz, H–C=), 6.12 (br s, 1H, one of the NH), 5.30 (br s, 1H, one of the NH), 4.22 (m, 1H, Me–CH(OTBDMS)–), 3.30 (dd, 1H, $J=5$ and 7.6 Hz, H-3), 2.91 (q, 2H, $J=7.3$ Hz, –SCH₂CH₃), 1.90 (s, 3H, Me–C=), 1.26 (t, 3H, $J=7.3$ Hz, –SCH₂CH₃), 1.16 (d, 3H, $J=6.0$ Hz, Me–CH(OTBDMS)–), 0.88 (s, 9H, Si–Bu), 0.09 (s, 3H, one of the Si–Me), 0.08 (s, 3H, one of the Si–Me); δ_C ($CDCl_3$, 75 MHz) 193.7, 172.6, 139.6, 133.7, 69.3, 53.4, 25.7, 23.4, 21.2, 17.9, 14.6, 13.0, –4.5, –4.9; m/z (CI) 346.3 (MH⁺, 6), 302.2 (8), 240.2 (100), 159.1 (17), 126.1 (13), 103.1 (13%).

4.1.8. 5-(tert-Butyldimethylsilyloxy)-4-carbamoyl-2-methyl-hex-2-enethioic acid, methyl ester (6d). **6d** was prepared as **6c**, from **3** (100 mg, 0.259 mmol), sodium methanethiolate (27 mg, 1.5 equiv.), 18-crown-6 (27 mg, 0.4 equiv.), acetonitrile (5 mL) and water (60 μ L), stirred at 20°C for 24 h. Work-up as usual and chromatography (elution with 30% EtOAc/hexane) furnished a white solid (84 mg, 97% yield); mp 95.4–96.5°C; [Found: C, 54.90; H, 9.01; N, 4.17. C₁₅H₂₉NO₃SSi requires C, 54.34; H 8.82; N, 4.22%]; R_f (30% EtOAc/hexane) 0.62; $[\alpha]_D^{20} = +0.96$ ($c=2.61$, CH₂Cl₂); ν_{max} (KBr) 3421, 1691, 1652 cm^{–1}; δ_H ($CDCl_3$, 300 MHz) 6.91 (dd, 1H, $J=1.8$ and 9.6 Hz, H–C=), 6.12 (br s, 1H, one of the NH), 5.87 (br s, 1H, one of the NH), 4.23 (m, 1H, Me–CH(OTBDMS)–), 3.27 (dd, 1H, $J=3.6$ Hz and 9.6 Hz, H-3), 2.33 (s, 3H, –SMe), 1.91 (d, 3H, $J=1.8$ Hz, Me–C=), 1.17 (d, 3H, $J=6.3$ Hz, Me–CH(OTBDMS)–), 0.87 (s, 9H, Si–Bu), 0.08 (s, 3H, one of the Si–Me), 0.07 (s, 3H, one of the Si–Me); δ_C ($CDCl_3$, 75 MHz) 194.4, 173.0, 139.7, 134.0, 69.4, 53.5, 25.9, 21.4, 18.0, 13.3, 11.9, –4.3, –4.8; m/z (CI) 332 (MH⁺, 100), 316.1 (31), 274.0 (23), 240.0 (16), 88.9 (60%).

4.1.9. 2-{3-[1-(tert-Butyldimethylsilyloxy)ethyl]-4-oxo-azetid-2-yl}-thiopropionic acid, ethyl esters (7a) and (8a). A solution of **3** (100 mg, 0.259 mmol) and ethanethiol (1 mL) in ethanol (4 mL) was heated at 60°C for 24 h, then diluted with ethyl acetate (7 mL) and washed successively with 0.5 M HCl and brine (2 \times). Drying over MgSO₄, concentration and flash chromatography on silica gel (elution with 30% EtOAc/hexane) gave a 1:1 mixture of **7a** (β -isomer) and **8a** (α -isomer) as a white solid (87 mg, 97% yield); mp 113.7–114.9°C; [Found: C, 55.68; H, 9.33; N, 3.82. C₁₆H₃₁NO₃SSi requires C, 55.61; H, 9.04; N, 4.05%]; R_f (30% EtOAc/hexane) 0.74; ν_{max} (KBr) 3116, 3093, 1763, 1717, 1680 cm^{–1}; δ_H (500 MHz, $CDCl_3$) (α -isomer **8a**) 5.95 (br s, 1H, NH), 4.17 (dq, 1H, $J=5.3$ and 6.0 Hz, Me–CH(OTBDMS)–), 3.73 (dd, 1H, $J=2.1$ and 9.8 Hz, H-2), 2.90 (m, 2H, –SCH₂CH₃), 2.78 (dd, 1H, $J=2.1$ and 5.3 Hz, H-3), 2.72 (qd, 1H, $J=7.0$ and 9.8 Hz, –CH(Me)–COSEt), 1.26 (t, 3H, $J=7.2$ Hz, –SCH₂CH₃), 1.26 (d, 3H, $J=7.6$ Hz, Me), 1.23 (d, 3H, $J=6.0$ Hz, Me–CH(OTBDMS)–), 0.87 (s, 9H, Si–Bu), 0.08 (s, 3H, one of the Si–Me), 0.07 (s, 3H, one of the Si–Me)—(β -isomer **7a**) 5.86 (br s, 1H, NH), 4.17 (dq, 1H, $J=4.3$ and 6.0 Hz, Me–CH(OTBDMS)–), 3.87 (dd, 1H, $J=2.1$ and 5.9 Hz, H-2), 2.99 (dd, 1H, $J=2.1$ and 4.3 Hz, H-3), 2.90 (m, 2H, –SCH₂CH₃), 2.84 (qd, 1H, $J=7.0$ and 5.9 Hz, –CH(Me)–COSEt), 1.26 (t, 3H, $J=7.2$ Hz, –SCH₂CH₃), 1.26 (d, 3H, $J=7.0$ Hz, Me), 1.14 (d, 3H, $J=6.0$ Hz, Me–CH(OTBDMS)–), 0.87 (s, 9H, Si–Bu), 0.08 (s, 3H, Si–Me), 0.07 (s, 3H, Si–Me); δ_C (125 MHz, $CDCl_3$) (α -isomer **8a**) 201.7, 167.5, 65.3, 63.6, 53.1, 52.7, 23.2, 22.7, 17.8, 15.1, 14.5, –4.4, –4.9—(β -isomer **7a**) 202.3, 169.1, 64.9, 61.9, 51.8, 51.1, 25.7, 22.8, 22.2, 17.8, 15.1, 13.1, –4.4, –4.9; m/z (CI) 346.5 (MH⁺, 100), 330.0 (52), 288.0 (40), 170.9 (40), 145.9 (69%).

4.1.10. 2-{3-[1-(tert-Butyldimethylsilyloxy)ethyl]-4-oxo-azetid-2-yl}-thiopropionic acid, phenyl esters (7b) and (8b). A solution of **3** (100 mg, 0.259 mmol), thiophenol (2 mL) and dimethylaminopyridine (30 mg) in ethanol (2 mL) was heated at 80°C for 17 h, then diluted with ethyl acetate and worked-up as above to give a 1:1.5 mixture of **7b** (β -isomer) and **8b** (α -isomer) as a white solid (100 mg, 98% yield) mp 89–89.5°C; [Found: C, 60.30; H, 8.23; N, 3.13. C₂₀H₃₁NO₃SSi·0.3H₂O requires C, 60.15; H 7.94; N 3.50]; R_f (30% EtOAc/hexane) 0.71; δ_H (300 MHz, $CDCl_3$) (α -isomer **8b**) 7.35–7.44 (m, 5H, Ph), 6.07 (br s, 1H, NH), 4.20 (m, 1H, Me–CH(OTBDMS)–), 3.78 (dd, 1H, $J=2.1$ Hz and 9.6 Hz, H-2), 2.80–2.93 (m, 2H, –CH(Me)–COSPh and H-3), 1.36 (d, 3H, $J=7.8$ Hz, Me), 1.24 (d, 3H, $J=6.3$ Hz, Me–CH(OTBDMS)–), 0.86 (s, 9H, Si–Bu), 0.08 (s, 3H, one of the Si–Me), 0.07 (s, 3H, one of the Si–Me)—(α -isomer **7b**) 7.35–7.44 (m, 5H, Ph), 5.98 (br s, 1H, NH), 4.20 (m, 1H, Me–CH(OTBDMS)–), 3.94 (dd, 1H, $J=2.1$ Hz and 5.4 Hz, H-2), 2.90–3.05 (m, 2H, –CH(Me)–COSPh and H-3), 1.32 (d, 3H, $J=6.9$ Hz, Me), 1.18 (d, 3H, $J=6.3$ Hz, Me–CH(OTBDMS)–), 0.87 (s, 9H, Si–Bu), 0.08 (s, 3H, one of the Si–Me), 0.07 (s, 3H, one of the Si–Me); δ_C (75 MHz, $CDCl_3$) (α and β isomers) 200.1, 167.7, 134.5, 134.3, 129.7, 129.3, 65.0 and 65.4, 62.0 and 63.7, 52.8 and 53.1, 50.8 and 51.7, 25.7, 22.5 and 22.9, 17.9, 13.2 and 15.3, –5.1 and –4.8; m/z (CI) 394.3 (MH⁺, 100), 378.3 (54), 346.3 (67), 336.2 (45), 330.2 (34), 288.2 (26), 219.1 (38), 111.1 (31%).

4.1.11. 2-{3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-oxo-azetidin-2-yl}-thiopropionic acid, *tert*-butyl esters (7c**) and (**8c**).** A solution of **3** (100 mg, 0.259 mmol), *tert*-butanethiol (1 mL) and dimethylaminopyridine (30 mg) in *iso*-propanol (2 mL) was heated at 65°C for 17 h, then diluted with ethyl acetate and worked-up as above to give a 1:1:2 mixture of **7c** (β -isomer), **8c** (α -isomer), and **3** (starting material) as a white gummy solid (quantitative yield). The ^1H NMR data of **7c** and **8c** were identical to those previously reported by *endo*.²⁸

4.1.12. (3*S*,4*S*)-3-[(1'*R*)-1'-*tert*-Butyldimethylsilyloxy-ethyl]-4-[1'-carboxyethyl]-azetidin-2-ones (2a**) and (**9**).** A 1:7 mixture of **7a** and **8a** (56 mg, 0.16 mmol) in methanol (1.7 mL) and water (0.5 mL) was treated with 2.5 M NaOH (0.2 mL) and stirred at 20°C for 2 days. The mixture was diluted with water (10 mL) and extracted with ether. The aqueous phase was acidified with cc HCl and extracted with ethyl acetate (2 \times). The organic phase was washed with brine, dried (MgSO_4) and concentrated to afford a 1:3 mixture of the known acids **2a**^{6,31} and **9**^{6,28} as a white solid (45 mg, 94% yield): δ_{H} (300 MHz, CDCl_3) **2a**: 6.18 (br s, 1H, *NH*), 4.20 (m, 1H, $\text{Me}-\text{CH}(\text{OTBDMS})-$), 3.95 (dd, 1H, $J=2$ and 5 Hz, H-2), 3.03 (dd, 1H, $J=2$ and 4.5 Hz, H-3), 2.76 (m, 1H, $-\text{CH}(\text{Me})-\text{COOH}$), 1.28 (d, 3H, $J=7.5$ Hz, *Me*), 1.19 (d, 3H, $J=7$ Hz, $\text{Me}-\text{CH}(\text{OTBDMS})-$), 0.89 (s, 9H, *Si-Bu*), 0.10 (s, 3H, one of the *Si-Me*), 0.09 (s, 3H, one of the *Si-Me*); **9**: 6.47 (br s, 1H, *NH*), 4.20 (m, 1H, $\text{Me}-\text{CH}(\text{OTBDMS})-$), 3.70 (dd, 1H, $J=2$ and 9.9 Hz, H-2), 2.79 (dd, 1H, $J=2$ and 6 Hz, H-3), 2.57 (m, 1H, $-\text{CH}(\text{Me})-\text{COOH}$), 1.27 (d, 3H, $J=7$ Hz, *Me*), 1.24 (d, 3H, $J=6$ Hz, $\text{Me}-\text{CH}(\text{OTBDMS})-$), 0.87 (s, 9H, *Si-Bu*), 0.08 (s, 3H, one of the *Si-Me*), 0.07 (s, 3H, one of the *Si-Me*).

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