EtOAc/petroleum ether) = 0.30; ^{1}H NMR δ 7.30–7.70 (m, 10 H), 5.32 (m, J = 7.0 Hz, 2 H), 4.99–5.25 (dd, J = 5.7, 15.1 Hz, 2 H), 4.22 (m, 1 H), 3.90 (m, J = 6.0 Hz, 1 H), 3.65 (s, 3 H), 2.84 (m, J = 9.3 Hz, 1 H), 2.20–2.28 (m, 5 H), 2.00 (m, 3 H), 1.86 (m, 1 H), 1.62 (m, 4 H), 1.13–1.42 (m, 6 H), 1.05 (s, 9 H), 0.87 (t, 3 H); ^{13}C NMR δ 217.8, 174.4, 137.7, 136.8, 136.7, 136.0, 134.0, 133.7, 131.0, 130.7, 130.2, 128.1, 127.9, 126.2, 73.9, 72.3, 51.7, 51.6, 50.6, 45.5, 37.3, 33.6, 31.9, 27.1, 27.0, 25.1, 24.9, 23.2, 22.8, 19.3, 14.2; MS precise mass calcd for $C_{37}H_{52}SiO_5$ (M^+ – *tert*-butyl, C_4H_9) 547.2880, found 547.2921.

(+)-8-*epi*-Prostaglandin E_2 Methyl Ester (31) and (–)-Prostaglandin E_2 Methyl Ester (1b). A 77:23 mixture of allylic alcohols **30a** and **30b** (33 mg, 0.055 mmol) in CH_3CN (0.5 mL) was cooled to 0 °C. Pyridine (.030 mL) was added followed by 52% aqueous HF (0.05 mL). After 2 h, an additional 0.025 mL of HF was added. After an additional 6 h, the reaction mixture was poured into $CHCl_3$ (10 mL) and washed once with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed to give recovered starting **30a** and **30b** (3.4 mg), 8.5 mg (47% yield) of (+)-8-*epi*-PGE_2 methyl ester **31**, and 2.1 mg (12% yield) of (–)-PGE_2 methyl ester **1b**, R_f (4:1 hexane/EtOAc) = 0.14, identical with material prepared from PGE_2. (+)-8-*epi*-PGE_2 methyl ester **31**: R_f (20% acetone/CH_2Cl_2) = 0.22; ^{1}H NMR δ 5.63–5.73 (dd, J = 6.0, 15.3 Hz, 1 H), 5.27–5.41 (m, 3 H), 4.38 (m, 1 H), 4.10 (m, 1 H), 3.67 (s, 3 H), 2.96 (m, 1 H), 2.75 (m, 1 H), 2.51–2.62 (dd, J = 5.9, 19.4 Hz, 1 H), 2.22–2.60 (m, 5 H), 1.82–2.10 (m, 4 H), 1.40–1.75 (m, 4 H), 1.18–1.40 (m, 6 H), 0.88 (t, 3 H); ^{13}C NMR δ 216.2, 174.4, 137.1, 130.3, 127.8, 126.4, 72.5, 72.4, 53.3, 51.6, 50.8, 45.0, 37.5, 33.6, 31.9, 26.9, 25.3, 24.9, 22.8, 19.3, 14.2; $[\alpha]_D$ = +40.95 (c 0.00075, MeOH).

(–)-Prostaglandin E_2 Methyl Ester (1b). The pure C-8 epimer **31** (5 mg, 0.014 mmol) was dissolved in MeOH (0.15 mL) containing potassium acetate (2 mg). The reaction was monitored by TLC. A slow replacement of the upper R_f C-8 epimer **31** by the lower R_f (–)-PGE_2 **1b** was observed. After 8 h, the reaction mixture was diluted with ethyl acetate and washed once with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed to give **1b** (3.8 mg, 76% from **31**): R_f (4:1 hexane/EtOAc) = 0.14; ^{1}H NMR δ 5.57–5.65 (dd, J = 6.4, 12.1 Hz, 2 H), 5.30–5.38 (m, J = 6.0 Hz, 2 H), 4.09 (m, 2 H), 3.66 (s, 3 H), 2.69–2.79 (dd, J = 7.5, 18.0 Hz, 1 H), 2.21–2.45 (m, 6 H), 1.93–2.20 (m, 5 H), 1.45–1.76 (m, 4 H), 1.20–1.42 (m, 6 H), 0.89 (t, 3 H); ^{13}C NMR missing two carbonyls δ 137.4, 131.1, 130.6, 126.7, 72.9, 72.4, 54.7, 53.5, 51.7, 46.4, 37.6, 31.9, 26.8, 25.5, 25.3, 24.9, 22.8, 14.2; $[\alpha]_D$ = –59.87° (c 0.00155, MeOH) (lit. $[\alpha]_D$ –70.4° (c 1.04)).[3b]

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Supplementary Material Available: ^{1}H and ^{13}C spectra for compounds **5**, **7**, **8**, **10–12**, **14**, **22–24**, **26**, **27**, **29**, **30a**, **31**, and **1b** (59 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Chromium–Carbene-Mediated Synthesis of 4-Oxo β-Lactams (Malonimides) and Malonic Acid Derivatives

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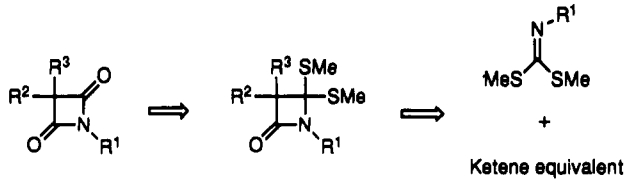
The photochemical reaction of chromium carbene (Fischer) complexes and readily available iminodithiocarbonates forms 4,4-bis(methylthio) β-lactams in good to excellent yields, and upon *N*-bromosuccinimide oxidation, these afford 4-oxo β-lactams (malonimides). Basic hydrolysis of the latter compounds yields malonic acid derivatives that are not otherwise easily accessible.

Recent efforts in β-lactam synthesis are focused not only on preparing novel, more active antibiotic drugs[1] but also on the use of these compounds as intermediates in organic synthesis[2a] (the β-lactam synthon method[2b]). Therefore, functionalized 2-azetidinones that, upon manipulation, would afford either suitable precursors for biologically active drugs or novel, unavailable compounds are always desirable. Among the growing number of monocyclic 2-azetidinones being reported, the synthesis and utility of 4-oxo β-lactams (malonimides) have been scarcely investigated. This is because they can be regarded as imides and not as true β-lactams. Nevertheless, they are very attractive compounds even in the β-lactam field, since the additional oxo group placed at the C-4 of the 2-azetidinone ring is suitable for functionalization either in inter- or intramolecular fashion, leading to interesting compounds. Furthermore, ring opening would lead to functionalized malonic acid derivatives that are potentially interesting compounds. In addition, it has been proven that malonimides are, by themselves, highly active as hypnotic-inducing drugs.[3]

Scheme I



(1) See, for example: (a) Dürckheimer, W.; Blumbach, J.; Latrell, R.; Sheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Recent Progress In the Chemical Synthesis of Antibiotics*, Lucas, G., Ohno, M., Eds.; Springer-Verlag: Berlin-Heidelberg, 1990. (c) Hungerbühler, E.; Biollaz, M.; Ernest, I.; Kalvoda, J.; Lang, M.; Schneider, P.; Sedelmeier, G. In *New Aspects of Organic Chemistry I*; Yoshida, Z., Shiba, T., Ohshiro, Y., Eds.; VCH: Tokyo, 1989; p 419.

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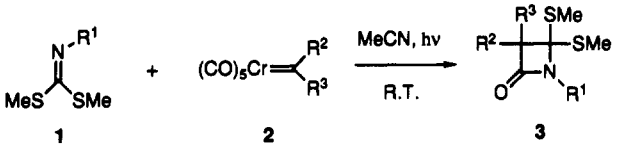
0022-3263/92/1957-0447$03.00/0

Table I. 4,4-Bis(methylthio) β-Lactams 3



1 2 3

R^1	R^2	R^3	yield[a] (%)
1a *p*-$MeOC_6H_4$	**2a** OMe	Me	**3a**, 85
	2b OMe	Ph	**3b**, 30
	2c OMe	cyclopropyl	**3c**, 86
	2d OCH_2Ph	Me	**3d**, 98
	2e OPr^i	Me	**3e**, 85
	2f $N(CH_2Ph)_2$	H	**3f**, 40
1b Ph	**2g** OMe	Me	**3g**, 80
1c 2-Me-3-ClC_6H_3	**2h** OMe	Me	**3h**, 85
1d CH_2Ph	**2i** OMe	Me	**3i**, 74
	2j $N(CH_2Ph)_2$	H	**3j**, 50
1e allyl	**2k** OMe	Me	**3k**, 65

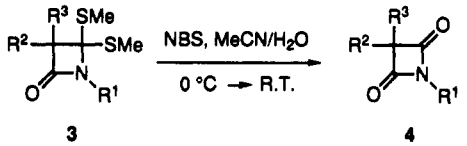
[a] In pure, isolated compound with correct analytical data.

Since the original report by Staüdinger[4] on the synthesis of 1,3,3-triphenylazetidine-2,4-dione by reaction of diphenylketene and phenylisocyanide, malonimides have been mainly prepared by $SOCl_2$-induced cyclization of suitable malonic acid monoamides[3,5] or photoinduced ring contraction of succinimides.[6] More recently, Alper[7] has reported the synthesis of some malonimides by carbonylation of α-lactams promoted by cobalt or rhodium carbonyl complexes. Often, these methods involve either sluggish reactions and low yields[3,5] or are constrained to 3-alkyl- or 3-aryl-substituted malonimides.[6,7] A straightforward entry into the azetidine-2,4-dione system would involve the use of β-lactams bearing a masked carbonyl group (for example, a thioketal functionality) at C-4 of the azetidin-2-one ring, as precursors. This masked carbonyl would lead to the desired compounds upon elaboration. Therefore, we focused our attention on 4,4-bis(methylthio)-2-azetidinones, **3**, which in turn are available from the easily prepared iminodithiocarbonates as suitable precursors for malonimides (Scheme I).

Iminodithiocarbonates **1** are known to react with ketenes or ketene precursors to give compounds **3**. However, these reactions seem to occur in acceptable yields only when aryloxyketenes[9,10] are used, while phthalimido-[9] and azidoketenes[11] give only moderate yields of β-lactam. Therefore, a more efficient and versatile access to compounds **3** was sought.

The photochemical reaction of chromium carbene (Fischer) complexes and imines[12] (the so-called Hegedus' reaction[13]) is among the most efficient and versatile ketene equivalent–imine routes to the β-lactam system described to date. Both alkoxy-[12] and aminochromium[14]– carbene

Table II. 4-Oxo β-Lactams (Malonimides) 4



3 4

	R^1	R^2	R^3	yield[a] (%)
4a	*p*-$MeOC_6H_4$	OMe	Me	83
4b	*p*-$MeOC_6H_4$	OMe	Ph	80
4c	*p*-$MeOC_6H_4$	OMe	cyclopropyl	75
4d	*p*-$MeOC_6H_4$	OMe	$PhCH_2O$	60
4e	Ph	OMe	Me	70
4f	$PhCH_2$	OMe	Me	75

[a] Reported yields are for isolated, purified materials with correct analytical data.

complexes react smoothly with a wide variety of C=N bonds to form β-lactams under mild reaction conditions and, often, in good to excellent yields. Thus, chromium–carbene complexes **2** were chosen as the ketene equivalent in our approach to compounds **3**. These complexes react nicely with a variety of iminodithiocarbonates **1** to give the desired β-lactams **3**. The results of these reaction are summarized in Table I. The reaction tolerates alkoxy, phenoxy, and amino groups on the ketene moiety (from the chromium–carbene complex) and aryl, alkyl, and even double bonds on the imine moiety (from the iminodithiocarbonate). In all cases, β-lactams **3** were formed as the sole reaction products, being in some cases contaminated by starting iminodithiocarbonate which was easily removed by flash chromatography to yield pure compounds **3** in fair to excellent yields. Analytical and spectroscopic data for compounds **3** are in good accordance with their β-lactam nature. Although olefinic double bonds are known to react with alkoxychromium–carbene complexes to form cyclobutanones[15] under analogous conditions to those used to obtain compounds **3**, compound **1e**, bearing an allyl substituent at the C=N nitrogen, yields exclusively β-lactam **3k** as determined by high-field ^1H NMR analysis of the crude reaction mixture. Obviously, the more nucleophilic imino nitrogen should be responsible for the observed *site* selectivity.

The wide variety of differently substituted chromium–carbene complexes coupled with the good yields obtained in the synthesis of compounds **3** makes this approach competitive and complementary to previously reported methods of synthesis of the above compounds. In addition, novel β-lactams **3** having alkoxy and amino groups at C-3 of the β-lactam ring, which are easily made from the corresponding chromium carbenes, were previously unknown.

Once an efficient entry into compounds **3** was available, unmasking of the oxo functionality on C-4 to yield the target malonimides was addressed. It has been previously reported[10] that 4,4-bis(methylthio) β-lactams with a phenoxy substituent at the 3-position fail to form the corresponding 4-oxo β-lactams under a number of experimental conditions, including cyanuric chloride and fluoride,[16] $HgO/HgCl_2$,[17] and $HgCl_2/CdCO_3$,[18] open-chain

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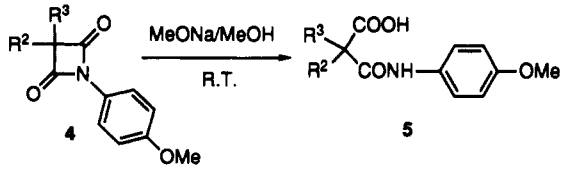
Table III. Malonic Acid Monoamides 5



	R^2	R^3	yield[a] (%)
5a	OMe	Me	90
5b	OMe	Ph	85
5c	OMe	cyclopropyl	95
5d	OCH_2Ph	Me	91

[a] In pure, isolated product with correct analytical data.

material being recovered in some cases. On the other hand, some compounds **3** having aryl groups at N-1 and C-3 of the β-lactam ring have been oxidized to the corresponding malonimides by using $KMnO_4$ in strong acid (sulfuric acid) medium.[9] These reported conditions seem to be somewhat drastic if useful synthetic groups would be attached to the β-lactam ring. Therefore, milder conditions to achieve the desired oxidation were needed.

Much to our delight, Corey's *N*-bromosuccinimide (NBS) oxidative hydrolysis of dithioketals[19] when applied to compounds **3** gave desired malonimides in mild reaction conditions. Compounds **4** were obtained essentially as the sole reaction products, in good to excellent yields (Table II). Neither open-chain compounds nor starting material was isolated. The malonimide nature of compounds **4** was established by spectroscopic and analytical methods. IR and ^{13}C NMR spectra are especially significant. Thus, IR spectra of compounds **4** show two characteristic absorptions between 1870–1860 (soft) and 1740–1730 cm^{-1} (strong) assignable to the CO–N–CO functionality. ^{13}C NMR spectra show a significative resonance between 169.0–171.0 ppm assignable to C-2 and C-4 of the symmetric four-membered ring.

Again, a variety of groups attached to C-3 and N-1 of the malonimide ring are compatible with reaction conditions (see Table II). These include alkoxy, alkyl, cyclopropyl and aryl groups. However, compound **3f** having an amino group at position 3 of the β-lactam ring fails to give the expected malonimide; intractable reaction mixtures with considerable loss of material were obtained instead. The reason for this anomalous behavior of the amino substituent is not clear to date.

As an example of the potential of compounds **4** as intermediates in preparation of novel, not easily available compounds, their hydrolysis to malonic acid derivatives was investigated. Treatment of compounds **4** with sodium methoxide in anhydrous methanol afforded after a few minutes malonic acid monoamides **5** (Table III) in essentially quantitative yield. Although these monoamides could be hydrolized to the corresponding acid, the former are usually crystalline compounds, soluble in standard solvents, and can be easily purified and handled. Some related malonic acid amides have been prepared, for example, by hydrolysis of cyanacetic acid ethyl ester[3] and by hydrolysis of some alkyl- or aryl-substituted malonimides.[8] However, compounds listed in Table III are, to the best of our knowledge, novel, previously unreported[20] alkoxy-substituted malonic acid derivatives that would be difficult to prepare by conventional deprotonation of malonic acid diester.

In conclusion, a two-step, easy, and efficient synthesis of novel azetidine-2,4-diones has been developed. The key to this approach is the high-yielding photochemical reaction of chromium–carbene (Fischer) complexes and iminodithiocarbonates to afford β-lactams **3**, which upon NBS oxidation afford novel malonimides **4**. Hydrolysis of these malonimides **4** gives novel malonic acid derivatives in quantitative yield. Efforts leading to development of other synthetic applications, both of compounds **3** and **4**, are currently under way in our laboratories.

Experimental Section

General Procedure. Melting points were taken on a Büchi 510 apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-300 instrument at 300 and 75.43 MHz, respectively. NMR spectra were registered in $CDCl_3$, and chemical shifts are given in ppm relative to TMS (^1H, 0 ppm) or $CDCl_3$ (^{13}C, 66.90 ppm). IR spectra were recorded on a Perkin-Elmer 781 grating spectrophotometer. Elemental analyses were preformed by the UCM Microanalysis Service (Facultad de Farmacia, UCM, Madrid).

For purification of crude reaction mixtures flash chromatography was applied in all cases. Merck silica gel (230–400 mesh) was used as the stationary phase.

The following chemicals were prepared according to literature procedures: pentacarbonyl(methoxymethylcarbene)chromium(0),[21] pentacarbonyl(methoxycyclopropylcarbene)chromium(0),[22] pentacarbonyl(methoxyphenylcarbene)chromium(0),[21] pentacarbonyl[(benzyloxy)methylcarbene]chromium(0),[23] pentacarbonyl[(isopropyloxy)methylcarbene]chromium(0),[23] and pentacarbonyl[(*N*,*N*-dibenzylamino)methylene]chromium(0).[24] N-aliphatic iminodithiocarbonates were prepared by using phase-transfer catalysis modification[26] of the previously reported method[25] which was used for N-aryl-substituted iminodithiocarbonates.

General Procedure for Preparation of 4,4-Bis(methylthio) β-Lactams 3. The carbene (1.1 mmol) was placed in a Pyrex test tube which was sealed with a rubber septum, evacuated, and purged with argon (three times). Degassed acetonitrile (30 mL) and iminodithiocarbene (0.9 mmol) in 5 mL of degassed acetonitrile were added via syringe. The resulting solution was irradiated (450-W medium-pressure mercury lamp, Pyrex well and Pyrex filter) until the reaction was complete. The solvent was removed under vacuo. The brown residue was dissolved in ethyl acetate, filtered through a short path of Celite, diluted with a volume of hexane, and air oxidized under direct sun light (10–12 h were usually required for complete oxidation). Filtration through Celite of the dark brown precipitate and solvent removal gave almost pure compound **3** slightly contaminated with small amounts of starting iminodithiocarbonate. Analytically pure compounds **3** were isolated by using flash chromatography (hexane–ethyl acetate mixtures).

2-Methoxy-1-(*p*-methoxyphenyl)-3-methyl-4,4-bis(methylthio)-2-azetidinone (3a): reaction time 18 h; colorless oil; yield 85%; ^1H NMR δ 1.77 (s, 3 H, CH_3), 2.18 (s, 3 H, SCH_3), 2.23 (s, 3 H, SCH_3), 3.64 (s, 3 H, OCH_3), 3.80 (s, 3 H, $ArOCH_3$), 6.89 (d, 2 H, J = 9.3 Hz, Ar), 7.70 (d, 2 H, J = 9.3 Hz, Ar); ^{13}C NMR δ 165.2 (CO), 157.7, 128.5, 122.5, 114.3, 94.4 (C-4), 85.6 (C-3), 55.5 ($ArOCH_3$), 54.0 (OCH_3), 15.3 (CH_3), 14.9 (SCH_3), 14.8 (SCH_3); IR (Cl_3CD) ν 1750 (CO), 1610, 1585, 1510, 1380, 1300, 1250, 1215, 1150, 1045 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NS_2O_3$: C, 53.65; H, 6.11; N, 4.47; S, 20.46. Found: C, 53.84; H, 6.14; N, 4.54; S, 20.32.

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3-Methoxy-1-(*p*-methoxyphenyl)-4,4-bis(methylthio)-3-phenyl-2-azetidinone (3b): reaction time 46 h; colorless oil; yield 30%; ^{1}H NMR δ 1.85 (s, 3 H, SCH_3), 2.29 (s, 3 H, SCH_3), 3.48 (s, 3 H, OCH_3), 3.80 (s, 3 H, $ArOCH_3$), 6.90 (d, 2 H, J = 8.7 Hz, Ar), 7.41 (m, 4 H, Ph), 7.60 (m, 1 H, Ph), 7.83 (d, 2 H, J = 8.7 Hz, Ar); ^{13}C NMR δ 164.1 (CO), 158.0, 133.2, 129.3, 128.6, 122.4, 114.3, 97.0 (C-4), 86.6 (C-3), 55.4 ($ArOCH_3$), 55.1 (OCH_3), 15.4 (SCH_3), 14.0 (SCH_3); IR ($CDCl_3$) ν 1750 (CO), 1605, 1585, 1510, 1370, 1295, 1250, 1210, 1200, 1115 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NS_2O_3$: C, 60.77; H, 5.64; N, 3.73; S, 17.08. Found: C, 60.96; H, 5.43; N, 3.76; S, 16.85.

3-Cyclopropyl-3-methoxy-1-(*p*-methoxyphenyl)-4,4-bis(methylthio)-2-azetidinone (3c): reaction time 20 h; colorless oil; yield 86%; ^{1}H NMR δ 0.69 (m, 1 H, cyclopropyl), 0.78 (m, 2 H, cyclopropyl), 0.97 (m, 1 H, cyclopropyl), 1.47 (m, 1 H, cyclopropyl), 2.18 (s, 3 H, SCH_3), 2.25 (s, 3 H, SCH_3), 3.75 (s, 3 H, OCH_3), 3.80 (s, 3 H, $ArOCH_3$), 6.89 (d, 2 H, J = 9.0 Hz, Ar), 7.65 (d, 2 H, J = 9.0 Hz, Ar); ^{13}C NMR δ 163.2 (CO), 157.8, 128.3, 122.9, 114.3, 97.2 (C-4), 86.2 (C-3), 55.4 ($ArOCH_3$), 54.5 (OCH_3), 15.0 (SCH_3), 14.9 (SCH_3), 10.9, 4.8, 2.6 (cyclopropyl); IR ($CHCl_3$) ν 1750 (CO), 1605, 1580, 1510, 1460, 1440, 1370, 1295, 1250, 1210, 1125, 1035 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NS_2O_3$: C, 56.61; H, 6.24; N, 4.13; S, 18.89. Found: C, 56.83; H, 5.98; N, 3.97; S, 19.07.

3-(Benzyloxy)-1-(*p*-methoxyphenyl)-3-methyl-4,4-bis(methylthio)-2-azetidinone (3d): reaction time 23 h; colorless oil; yield 98%; ^{1}H NMR δ 1.85 (s, 3 H, CH_3), 2.10 (s, 3 H, SCH_3), 2.23 (s, 3 H, SCH_3), 3.79 (s, 3 H, $ArOCH_3$), 4.89 (d, 1 H, J = 10.8 Hz, CH_2), 4.95 (d, 1 H, J = 10.8 Hz, CH_2), 6.89 (d, 2 H, J = 9.3 Hz, Ar), 7.20–7.50 (m, 5 H, Ph), 7.70 (d, 2 H, J = 9.3 Hz, Ar); ^{13}C NMR δ 165.2 (CO), 157.8, 137.6, 128.3, 127.7, 122.8, 114.3, 94.3 (C-4), 68.6 (CH_2), 62.2 (C-3), 55.4 ($ArOCH_3$), 16.6 (SCH_3), 14.9 (SCH_3); IR ($CDCl_3$) ν 1750 (CO), 1605, 1585, 1510, 1440, 1375, 1300, 1250, 1215, 1150, 1040 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NS_2O_3$: C, 61.67; H, 5.95; N, 3.60; S, 16.46. Found: C, 61.91; H, 6.17; N, 3.65; S, 19.32.

1-(*p*-Methoxyphenyl)-3-methyl-4,4-bis(methylthio)-3-(isopropyloxy)-2-azetidinone (3e): reaction time 23 h; colorless oil; yield 85%; ^{1}H NMR δ 1.28 (d, 3 H, J = 6.0 Hz, $(CH_3)_2CH$)) 1.31 (d, 3 H, J = 6.0 Hz, $(CH_3)_2CH$), 1.73 (s, 3 H, CH_3), 2.13 (s, 3 H, SCH_3), 2.16 (s, 3 H, SCH_3), 2.79 (s, 3 H, $ArOCH_3$), 4.28 (q, 1 H, J = 6.0 Hz, $CH(CH_3)_2$), 6.87 (d, 2 H, J = 9.0 Hz, Ar), 7.63 (d, 2 H, J = 9.0 Hz, Ar); ^{13}C NMR δ 166.3 (CO), 157.9, 128.3, 123.4, 114.3, 94.3 (C-4), 87.3 (C-3), 70.6 ($CH(CH_3)_2$), 24.2 ($CH(CH_3)_2$), 23.9 ($CH(CH_3)_2$), 15.1 (2 × SCH_3), 18.5 (CH_3); IR ($CDCl_3$) ν 1750 (CO), 1505, 1585, 1510, 1460, 1440, 1380, 1300, 1250, 1215, 1150, 1105, 1030 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NS_2O_3$: C, 56.28; H, 6.79; N, 4.10; S, 18.78. Found: C, 56.63; H, 6.91; N, 4.28; S, 18.52.

3-(*N*,*N*-Dibenzylamino)-1-(*p*-methoxyphenyl)-4,4-bis(methylthio)-2-azetidinone (3f): reaction time 42 h; colorless oil; yield 40%; ^{1}H NMR δ 1.77 (s, 3 H, SCH_3), 2.32 (s, 3 H, SCH_3), 2.78 (s, 3 H, $ArOCH_3$), 4.02 (d, 2 H, J = 14.1 Hz, CH_2), 4.14 (d, 2 H, J = 14.1 Hz, CH_2), 4.56 (s, 1 H, H-3), 6.88 (d, 2 H, J = 9.0 Hz, Ar), 7.20–7.47 (m, 10 H, 2 × Ph), 7.67 (d, 2 H, J = 9.0 Hz, Ar); ^{13}C NMR δ 164.4 (CO), 157.2, 138.1, 129.2, 128.3, 127.3, 122.6, 114.3, 82.1 (C-4), 78.3 (C-3), 55.8 (CH_2), 55.4 ($ArOCH_3$), 14.3 (SCH_3), 13.1 (SCH_3); IR ($CHCl_3$) ν 1745 (CO), 1605, 1580, 1510, 1450, 1440, 1375, 1295, 1245, 1210, 1035 cm^{-1}. Anal. Calcd for $C_{26}H_{28}N_2S_2O_2$: C, 67.21; H, 6.07; N, 6.03; S, 13.80. Found: C, 67.54; H, 6.24; N, 6.18; S, 13.56.

3-Methoxy-3-methyl-4,4-bis(methylthio)-1-phenyl-2-azetidinone (3g): reaction time 22.5 h; colorless oil; yield 80%; ^{1}H NMR δ 1.77 (s, 3 H, CH_3), 2.19 (s, 3 H, SCH_3), 2.26 (s, 3 H, SCH_3), 3.63 (s, 3 H, OCH_3), 7.20 (t, 1 H, Ph), 7.36 (t, 2 H, Ph), 7.84 (d, 2 H, Ph); ^{13}C NMR δ 165.4 (CO), 135.7, 129.0, 125.7, 120.0, 94.3 (C-4), 88.5 (C-3), 53.6 (OCH_3), 15.3 (CH_3), 15.0 (SCH_3), 14.9 (SCH_3); IR ($CDCl_3$) ν 1765 (CO), 1595, 1490, 1430, 1370, 1360, 1210, 1150, 1045 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NS_2O_2$: C, 55.10; H, 6.05; N, 4.94; S, 22.62. Found: C, 55.04; H, 6.23; N, 5.19; S, 22.87.

1-(3-Chloro-2-methylphenyl)-3-methoxy-3-methyl-4,4-bis(methylthio)-2-azetidinone (3h): reaction time: 24 h; colorless oil; yield 85%; ^{1}H NMR δ 1.79 (s, 3 H, CH_3), 2.02 (s, 3 H, SCH_3), 2.09 (s, 3 H, SCH_3), 2.42 (s, 3 H, $ArCH_3$), 3.67 (s, 3 H, OCH_3), 7.12 (t, 1 H, J = 7.9 Hz, Ar), 7.37 (d, 2 H, J = 7.9 Hz, Ar); ^{13}C NMR δ 165.4 (CO), 135.6, 135.4, 133.7, 129.9, 126.8, 125.6, 94.1 (C-4), 89.4 (C-3), 54.9 (OCH_3), 16.1 (2 × CH_3), 14.6 (SCH_3), 14.4 (SCH_3); IR ($CDCl_3$) ν 1780 (CO); 1590, 1485, 1400, 1380, 1225, 1180, 1070 cm^{-1}. Anal. Calcd for $C_{14}H_{18}NS_2O_2Cl$: C, 50.67; H, 5.47; N, 4.22; S, 19.32; Cl, 10.68. Found: C, 50.33; H, 5.68; N, 4.46; S, 19.64, Cl, 10.35.

1-Benzyl-3-methoxy-3-methyl-4,4-bis(methylthio)-2-azetidinone (3i): reaction time 17.5 h; colorless oil; yield 74%; ^{1}H NMR δ 1.69 (s, 3 H, CH_3), 2.01 (s, 3 H, SCH_3), 2.08 (s, 3 H, SCH_3), 3.50 (s, 3 H, OCH_3), 4.33 (d, 1 H, J = 15.6 Hz, CH_2), 4.49 (d, 1 H, J = 15.6 Hz, CH_2), 7.32–7.34 (m, 5 H, Ph); ^{13}C NMR δ 167.2 (CO), 135.7, 128.5, 127.8, 127.6, 94.9 (C-4), 86.2 (C-3), 54.2 (OCH_3), 43.2 (CH_2), 15.5 (CH_3), 14.5 (SCH_3), 14.3 (SCH_3); IR ($CDCl_3$) ν 1760 (CO), 1495, 1450, 1430, 1380, 1215, 1145, 1045. Anal. Calcd for $C_{14}H_{19}NS_2O_2$: C, 56.54; H, 6.44; N, 4.71; S, 21.56. Found: C, 56.35; H, 6.78; N, 4.79; S, 21.91.

1-Benzyl-3-(*N*,*N*-dibenzylamino)-4,4-bis(methylthio)-2-azetidinone (3j): reaction time 25 h; colorless oil; yield 50%; ^{1}H NMR δ 1.58 (s, 3 H, SCH_3), 2.02 (s, 3 H, SCH_3), 3.84 (d, 2 H, J = 12.8 Hz, $N(CH_2)Ph$), 4.11 (d, 2 H, J = 12.8 Hz, $N(CH_2Ph)$), 4.20 (d, 1 H, J = 15.7 Hz, CH_2Ph), 4.40 (s, 1 H, H-3), 4.58 (d, 1 H, J = 15.7 Hz, CH_2Ph), 7.21–7.44 (m, 15 H, 3 × Ph); ^{13}C NMR δ 166.4 (CO), 138.2, 136.0, 128.9, 128.4, 127.7, 127.5, 126.1, 82.1 (C-4), 79.8 (C-3), 56.0 ($N(CH_2Ph)$, 43.7 (CH_2Ph), 13.2 (SCH_3), 12.8 (SCH_3); IR ($CDCl_3$) ν 1770 (CO), 1510, 1470, 1400, 1370, 1110 cm^{-1}. Anal. Calcd for $C_{26}H_{28}N_2S_2O$: C, 69.61; H, 6.29; N, 6.24; S, 14.29. Found: C, 69.36; H, 6.53; N, 6.18; S, 14.54.

1-Allyl-3-methoxy-3-methyl-4,4-bis(methylthio)-2-azetidinone (3k): reaction time 18 h; colorless oil; yield 65%; ^{1}H NMR δ 1.66 (s, 3 H, CH_3), 2.16 (s, 3 H, SCH_3), 2.23 (s, 3 H, SCH_3), 3.57 (s, 3 H, OCH_3), 3.77 (dq, 2 H, J_1 = 5.7 Hz, J_2 = 6.0 Hz; J_3 = 16.2 Hz; CH_2), 5.13 (d, 1 H, J = 10.2 Hz, H_2C=), 5.25 (d, 1 H, J = 17.1 Hz, H_2C=), 5.82 (m, 1 H, J_1 = 6.0 Hz, J_2 = 5.7 Hz, J_3 = 10.2 Hz, J_4 = 17.1 Hz, CH=); ^{13}C NMR δ 166.8 (CO), 131.8 (CH=), 118.0 (H_2C=), 94.7 (C-4), 85.8 (C-3), 54.1 (OCH_3), 42.1 (CH_2), 15.23 (CH_3), 14.6 (SCH_3), 14.5 (SCH_3); IR ($CDCl_3$) ν 1760 (CO), 1640 (CH=CH_2), 1430, 1385, 1220, 1145, 1045 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NS_2O_2$: C, 48.55; H, 6.93; N, 5.66; S, 25.92. Found: C, 48.57; H, 6.72; N, 5.83; S, 25.64.

General Procedure for Synthesis of Azetidine-2,4-diones 4. Compound **3** in MeCN (8 mL) was added dropwise via syringe, under argon, to a cold solution (−5 °C, ice–salt bath) of *N*-bromosuccinimide (NBS) in MeCN/H_2O (80:20, 30 mL). The deep yellow solution was allowed to reach room temperature and stirred for 5–10 min. Then, saturated aqueous Na_2SO_3 was added until complete decoloration occurred, and the resulting mixture was extracted with hexane/Cl_2CH_2 (1:1; 3 × 20 mL). The collected organic layers were washed with 1 M $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of solvent led to crude compounds **4** which were purified by flash chromatography (hexane/EtOAc mixtures) to yield pure azetidine-2,4-diones.

3-Methoxy-1-(*p*-methoxyphenyl)-3-methylazetidine-2,4-dione (4a). From 0.2 g (0.64 mmol) of **3a** and NBS (1.12 g, 6.3 mmol) was obtained 0.13 g (83%) of compound **4a** after chromatography as a colorless solid: mp 76–77 °C (EtOH); ^{1}H NMR δ 1.62 (s, 3 H, CH_3), 3.50 (s, 3 H, OCH_3), 3.90 (s, 3 H, $ArOCH_3$), 6.92 (d, 2 H, J = 9.0 Hz, Ar), 7.80 (d, 2 H, J = 9.0 Hz, Ar); ^{13}C NMR δ 171.2 (2 × CO), 158.4, 126.8, 120.8, 114.4, 95.1 (C-3), 55.8 ($ArOCH_3$), 54.7 (OCH_3), 16.5 (CH_3); IR (Cl_3CD) ν 1860, 1740 (CONCO), 1610, 1590, 1410, 1460, 1440, 1390, 1300, 1250, 1210, 1170, 1120, 1050, 1030 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.54; H, 5.79; N, 5.92.

3-Methoxy-1-(*p*-methoxyphenyl)-3-phenylazetidine-2,4-dione (4b). From 0.05 g (0.14 mmol) of compound **3b** and NBS (0.25 g, 14 mmol) was obtained 0.033 g (80%) of compound **4b** after chromatography as a colorless oil: ^{1}H NMR δ 3.59 (s, 3 H, OCH_3), 3.82 (s, 3 H, $ArOCH_3$), 6.93 (d, 2 H, J = 10.0 Hz, Ar), 7.42–7.67 (m, 5 H, Ph), 7.83 (d, 2 H, J = 10.0 Hz, Ar); ^{13}C NMR δ 168.8 (2 × CO), 158.6, 130.4, 129.0, 128.6, 126.9, 114.4, 99.8 (C-3), 55.5 ($ArOCH_3$), 55.0 (OCH_3); IR (Cl_3CD) ν 1850, 1740 (CONCO), 1510, 1460, 1380, 1250, 1115 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.79; H, 4.85; N, 4.98.

3-Cyclopropyl-3-methoxy-1-(*p*-methoxyphenyl)azetidine-2,4-dione (4c). From 0.27 g (0.8 mmol) of **3c** and NBS (1.14 g, 6.4 mmol) was obtained 0.15 g (75%) of compound **4c** after chromatography as a colorless oil: ^{1}H NMR δ 0.57–0.65 (m, 4 H, cyclopropyl), 1.26–1.33 (m, 1 H, cyclopropyl), 3.47 (s, 3 H, OCH_3), 3.72 (s, 3 H, $ArOCH_3$), 6.84 (d, 2 H, J = 9.0 Hz, Ar), 7.69 (d, 2

H, J = 9.0 Hz, Ar); ^{13}C NMR δ 169.7 (2 × CO), 158.5, 126.6, 120.7, 114.2, 98.5 (C-3), 55.4 ($ArOCH_3$), 54.7 (OCH_3), 11.9, 1.8 (cyclopropyl); IR (Cl_3CD) ν 1870, 1859, 1735 (CONCO), 1610, 1590, 1465, 1440, 1390, 1250, 1120, 1050 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.66; H, 5.43; N, 5.21.

3-(Benzyloxy)-1-(*p*-methoxyphenyl)-3-methylazetidine-2,4-dione (4d). From 0.19 g (0.5 mmol) of **3d** and NBS (0.72 g, 4.0 mmol) was obtained 95 mg (60%) of compound **4d** afer chromatography as a colorless solid: mp 75–76 °C (EtOH); ^{1}H NMR δ 1.68 (s, 3 H, CH_3), 3.79 (s, 3 H, $ArOCH_3$), 4.68 (s, 2 H, CH_2), 6.91 (d, 2 H, J = 9.3 Hz, Ar), 7.29–7.32 (m, 5 H, Ph), 7.76 (d, 2 H, J = 9.3 Hz, Ar); ^{13}C NMR δ 171.2 (2 × CO), 158.5, 136.1, 128.4, 128.1, 120.9, 114.4, 94.5 (C-3), 69.7 (CH_2), 55.4 ($ArOCH_3$), 17.1 (CH_3); IR ($CDCl_3$) ν 1855, 1735 (CONCO), 1605, 1585, 1510, 1460, 1440, 1385, 1300, 1250, 1210, 1160, 1120 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.43; H, 5.51; N, 4.50. Found: C, 69.28; H, 5.79; N, 4.23.

3-Methoxy-3-methyl-1-phenylazetidine-2,4-dione (4e). From 0.17 g (0.6 mmol) of compound **3g** and NBS (0.85 g, 4.8 mmol) was obtained 87 mg (70%) of compound **4e** after chromatography as a colorless oil: ^{1}H NMR δ 1.64 (s, 3 H, CH_3), 3.52 (s, 3 H, OCH_3), 7.30 (m, 1 H, Ph), 7.42 (m, 2 H, Ph), 7.87 (d, 2 H, Ph); ^{13}C NMR δ 171.2 (2 × CO), 133.7, 129.3, 127.5, 119.3, 95.2 (C-3), 54.8 (OCH_3), 16.6 (CH_3); IR ($CDCl_3$) ν 1860, 1640 (CONCO), 1685, 1595, 1495, 1455, 1380, 1370, 1210, 1115, 1100, 1080, 1060, 1030 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.42; H, 5.55; N, 7.12.

1-(Benzyloxy)-3-methoxy-3-methylazetidine-2,4-dione (4f). From 0.2 g (0.67 mmol) of **3i** and NBS (1.07 g, 6.0 mmol) was obtained 110 mg (75%) of compound **4f** after chromatography as a colorless oil: ^{1}H NMR δ 1.49 (s, 3 H, CH_3), 3.36 (s, 3 H, OCH_3), 4.49 (s, 2 H, CH_2), 7.32 (broad s, 5 H, Ph); ^{13}C NMR δ 173.3 (2 × CO), 134.2, 128.9, 128.3, 128.0, 94.6 (C-3), 54.5 (OCH_3), 43.0 (CH_2), 16.0 (CH_3); IR ($CDCl_3$) ν 1870, 1730 (CONCO), 1600, 1585, 1495, 1450, 1430, 1385, 1345, 1280, 1210, 1175 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.05; H, 5.76; N, 6.54.

General Procedure for Synthesis of Malonic Acid Monoamides 5. Sodium methoxide (4 mmol per mmol of compound 4) was added in one portion as solid onto a solution of compound **4** in anhydrous methanol at room temperature. The resulting solution was stirred for 30–45 min until complete reaction. Then, the solvent was removed under vacuo, and the colorless residue was dissolved in water (10 mL). Upon acidification (5% HCl) the aqueous solution was extracted (Cl_2CH_2, 3 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent yielded pure compound **5**.

Malonic Acid Monoamide 5a. From 0.05 g (0.22 mmol) of **4a** and $NaOCH_3$ (0.05 g, 0.88 mmol) was obtained 0.049 g (90%) of **5a** as a colorless, crystalline solid: mp 68–70 °C (EtOH–H_2O); ^{1}H NMR δ 1.74 (s, 3 H, CH_3), 3.50 (s, 3 H, OCH_3), 3.78 (s, 3 H, $ArOCH_3$), 6.11 (broad, 1 H, COOH), 6.87 (d, 2 H, J = 9.0 Hz, Ar), 7.46 (d, 2 H, J = 9.0 Hz, Ar), 8.63 (broad, 1 H, NH); ^{13}C NMR δ 171.0 (COOH), 168.8 (CONHAr), 157.2, 129.4, 122.0, 114.3, 81.5 (–C–), 55.5 ($ArOCH_3$), 53.7 (OCH_3), 12.5 (CH_3); IR ($CDCl_3$) ν 3700–2400 (broad, max. 3380, 2840), 1740 (COOH), 1680 (CONH), 1530, 1510, 1460, 1210, 1150, 1120 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.66; H, 5.86; N, 5.58.

Malonic Acid Monoamide 5b. From 0.02 g (0.07 mmol) of **4b** and $NaOCH_3$ (0.015 g, 0.27 mmol) was obtained 0.019 g (85%) of **5b** as a pale yellow oil: ^{1}H NMR δ 3.49 (s, 3 H, OCH_3), 3.74 (s, 3 H, $ArOCH_3$), 6.84 (d, 2 H, Ar), 7.33–7.40 (m, 7 H, Ar + Ph), 8.45 (b, s, NH); ^{13}C NMR δ 171.2 (COOH), 170.6 (CONH), 157.3, 136.8, 129.7, 129.1, 126.4, 122.8, 114.5, 99.5 (–C–), 55.8 ($ArOCH_3$), 55.2 (OCH_3); IR ($CDCl_3$) ν 3700–2200 (broad, max. 3400, 3320), 1760, 1700 (COOH), 1640 (CONH), 1610, 1520, 1460, 1425, 1310, 1260, 1230, 1190, 1120 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.98; H, 5.68; N, 4.17.

Malonic Acid Monoamide 5c. From 0.13 g (0.5 mmol) of **4c** and $NaOCH_3$ (0.12 g, 2.3 mmol) was obtained 0.133 g (95%) of **5c** as a colorless oil: ^{1}H NMR δ 0.61–0.64 (m, 2 H), 0.74–0.78 (m, 2 H), 1.39–1.44 (m, 1 H, cyclopropyl), 3.56 (s, 3 H, OCH_3), 3.79 (s, 3 H, $ArOCH_3$), 6.89 (d, 2 H, J = 9.0 Hz, Ar), 7.43 (d, 2 H, J = 9.0 Hz, Ar), 8.65 (broad, 1 H, NH); ^{13}C NMR δ 171.3 (COOH), 168.7 (CONH), 157.5, 128.4, 122.3, 114.2, 82.3 (–C–), 55.3 ($ArOCH_3$), 54.8 (OCH_3), 19.2, 2.5, 2.2 (cyclopropyl); IR ($CDCl_3$) ν 3600–2500 (broad, max 3380, 2920, 2840), 1760, 1730 (COOH), 1690, 1630 (CONH), 1540, 1515, 1450, 1410, 1250, 1150 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.44; H, 6.38; N, 5.39.

Malonic Acid Monoamide 5d. From 0.07 g (0.22 mmol) of **4d** and $NaOCH_3$ (0.06 g, 1 mmol) was obtained 0.066 g (91%) of **5d** as a colorless, crystalline solid: mp dec before melting above 142 °C (EtOH/H_2O); ^{1}H NMR δ 1.85 (s, 3 H, CH_3), 3.77 (s, 3 H, $ArOCH_3$), 4.59 (d, 1 H, J = 10.5 Hz, CH_2), 4.82 (d, 1 H, J = 10.5 Hz, CH_2), 6.85 (d, 2 H, J = 9.0 Hz, Ar), 7.34–7.42 (m, 7 H, Ar + Ph), 8.58 (s, 1 H, NH), 9.91 (broad, 1 H, COOH); ^{13}C NMR δ 171.0 (COOH), 170.1 (CONH), 157.3, 136.8, 129.2, 128.9, 128.3, 128.0, 122.0, 114.3, 81.3 (–C–), 69.3 (CH_2), 55.3 ($ArOCH_3$), 12.5 (CH_3); IR ($CDCl_3$) ν 3600–2200 (broad, max 3380, 3300, 2840, 2700), 1760 (COOH), 1625 (CONH), 1530, 1510, 1440, 1410, 1300, 1250, 1180, 1160, 1110, 1090 cm^{-1}. Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.75; H, 5.45; N, 4.13.

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