Tetrahedron Letters 52 (2011) 5051–5054

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Asymmetric synthesis of monocyclic β-lactams from L-cysteine using photochemistry

Xiao Lu [a], Timothy E. Long [a,b,*]

[a] Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Athens, GA 30602, USA
[b] Center for Drug Discovery, University of Georgia, Athens, GA 30602, USA

ARTICLE INFO

Article history:
Received 5 July 2011
Revised 18 July 2011
Accepted 20 July 2011
Available online 27 July 2011

Keywords:
Photo-oxidation
Pummerer rearrangement
β-Lactams
Thiazolidines
Hydroxamates

ABSTRACT

An asymmetric method to synthesize *cis*-configured β-lactams using photochemistry has been developed. Aerobic photo-oxidation of L-cysteine-derived thiazolidine hydroxamate esters afforded C-3 hydroxylated products which when cyclized and deprotected gave the corresponding *N*-protio monocyclic β-lactams.

Published by Elsevier Ltd.

1. Introduction

For over 60 years, β-lactam antibacterials have been mainstays as first-line treatments for infection due to their therapeutic efficacy and inherent safety profile. Penicillins (e.g., ampicillin), cephalosporins (e.g., cephalexin), and carbapenems (e.g., meropenem) comprise the vast majority of β-lactams in clinical use today (Fig. 1) and like many mechanistic classes of drugs, their biological activity is predicated by the stereochemistry. As acylating agents of bacterial cell wall transpeptidases, each family member functions as a suicide substrate by mimicking the D-configured peptides in peptidoglycan. To date, a limited number of asymmetric methods to synthesize a β-lactam nucleus with a proper configuration for antibacterial activity have been reported. The most commonly employed is Miller's biomimetic approach utilizing hydroxamate esters of L-serine and L-threonine.[1] The efficiency of this method aided the development of aztreonam,[2] a monobactam (Fig. 1) used in the treatment of life-threatening Gram-negative infections such as chronic pneumonia by *Pseudomonas aeruginosa* in cystic fibrosis patients.

Prior to 1980, L-cysteine was the amino acid of choice to prepare synthetic penicillins,[3] cephalosporins,[4] and nocardicins.[5] Each respective β-lactam nucleus was constructed from *N*-protected 2,2-dimethylthiazolidines (e.g., **1**, Scheme 1) and the ensuing functionalizations at the C-3 methylene were accomplished with either

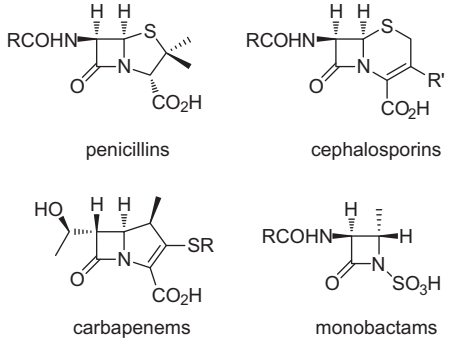


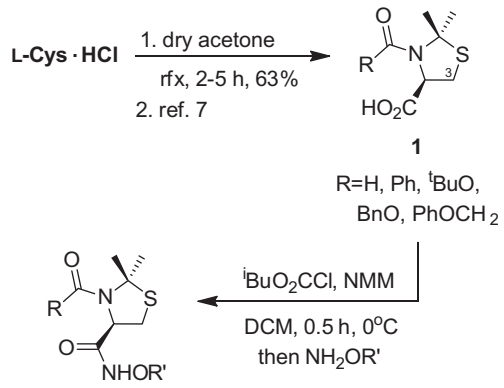
Figure 1. Families of β-lactam antibacterials used in therapy.

DMAD,[4] NBS,[3c] or benzoyl peroxide.[3a,b,5] The stereospecific reactions generated predominately trans products that enabled subsequent cyclization to *cis*-configured β-lactams via intramolecular S_N2 substitution at the amide nitrogen.

An alternative approach we envisioned that could be used to generate chiral β-lactams is to install a hydroxyl group at the C-3 methylene of L-cysteine-derived thiazolidines by aerobic photo-oxidation (Scheme 2). The Pummerer-type rearrangement (i.e., lacks use of an acid/anhydride activator) described previously by Ando[6] offers a facile route to access an array of highly functionalizable *cis*-configured β-lactams when merged with the cyclization strategy by Miller. Herein, this Letter details the first asymmetric

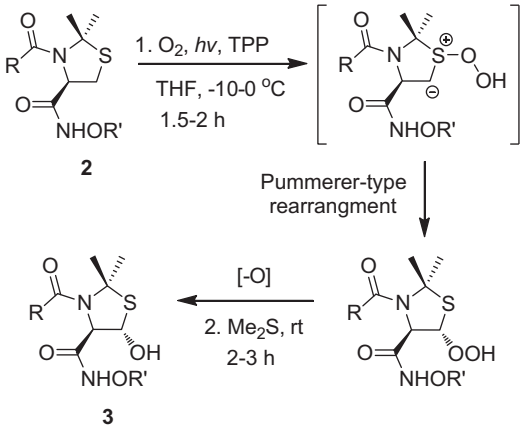
* Corresponding author. Tel.: +1 706 542 8597; fax: +1 706 542 5358.
E-mail address: tlong@rx.uga.edu (T.E. Long).

0040-4039/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2011.07.085



2a R=Ph, R'=Me, 80%
2b R=Ph, R'=Bn, 68%
2c R=H, R'=Bn, 48%
2d R=Ph, R'=CH_2CO_2Bn, 67%
2e R=^{t}BuO, R'=CH_2CO_2Bn, 58%
2f R=BnO, R'=CH_2CO_2Bn, 53%
2g R=$PhOCH_2$, R'=$CH_2CO_2{}^t$Bu, 60%

Scheme 1. Synthesis of thiazolidine hydroxamate esters **2**.



Scheme 2. Photo-oxidation of thiazolidine hydroxamate esters **2**.

synthesis of *N*-protio monocyclic β-lactams from L-cysteine that is facilitated by the aerobic photo-oxidation of thiazolidine hydroxamate esters.

2. Results and discussion

The hydroxamate esters (i.e., **2**) screened in the photo-oxidation reactions were prepared from L-cysteine via *N*-protected 2,2-dimethylthiazolidine-4-carboxylates **1** (Scheme 1). Following previously described methods,[7] L-cysteine was first converted to the corresponding 2,2-dimethylthiazolidine HCl salt under acetone reflux. Various carbonyl protecting groups were then attached to the ring nitrogen to afford acid **1**. Conversion to hydroxamate esters **2a–g** was next achieved by the *N*-acylation of different alkoxyamines[8] via the isobutyl anhydride of acid **1**. In comparison, when the HOBt and NHS esters of acid **1** were used, multiple products of similar polarities resulted that led to purified yields of less than 30%.

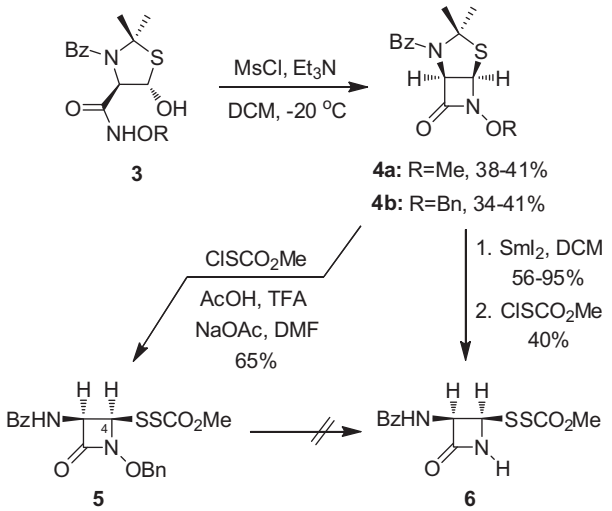
The photo-oxidation of thiazolidines **2** (Scheme 2) was next examined using singlet O_2 generated from triplet O_2 via a 500 W halogen lamp in the presence of a photosensitizer, tetraphenylporphyrin (TPP).[9] Various hydroxamate esters (Table 1) that would be

Table 1
Isolated yields of photo-oxidation products **3a–h**

Entry	R	R′	Solvent	Product	Yield (%)
1	Ph	Me	THF	**3a**	80
2	Ph	Bn	THF	**3b**	68–73
3	H	Bn	THF	**3c**	48
4	H	Bn	PhH	**3c**	37
5	H	Bn	MeCN	**3c**	35
6	Ph	CH_2CO_2Bn	THF	**3d**	67–84
7	^{t}BuO	CH_2CO_2Bn	THF	**3e**	58–73
8	BnO	CH_2CO_2Bn	THF	**3f**	53
9	$PhOCH_2$	$CH_2CO_2{}^t$Bu	THF	**3g**	60–68
10	$PhOCH_2$	Ac	THF	**3h**	44

useful in the synthesis of cephalosporins,[4] monobactams,[2] and penems[10] (entries 1–5), oxamazins[11] (entries 6–9), and monosulfactams[12] (entry 10) were evaluated in the reaction. The photo-oxidations were monitored by TLC, however, the hydroperoxide intermediates were often indiscernible on the plates. This issue was resolved by co-spotting with Me_2S which converted the hydroperoxide to thiohemiacetal **3** on the TLC plate and allowing the chemically stable product to be readily detected at a lower R_f value. The reaction scales ranged from 0.4 to 2.0 g with a slight to moderate decrease in the resulting yields (entries 2, 6–8) when over 1.0 g of hydroxamate ester **2** was used. In many instances, the yields after purification were ⩾60%, with the highest consistently observed for thiazolidines bearing an *N*-benzoyl protecting group.

The photo-oxidation products were next cyclized to the fused thiazolidine β-lactam **4** (Scheme 3) using Miller's strategy which capitalizes on the acidity of hydroxamate esters. Unlike standard amides ($pK_a \geqslant 20$) that require a strong base for lactam ring formation,[3–5] hydroxamate ester anions ($pK_a \leqslant 10$) can be readily generated with mild tertiary amines to effect the cyclization. When the method was applied to the synthesis of bicyclic lactams **4a** and **b**, the reaction was easily accomplished when MsCl and Et_3N were combined with the hydroxamate ester **3** in DCM and left overnight in a −20 °C freezer.[13] Alternatively at 0 °C, cyclization to *O*-methyl lactam **4a** was complete in less than 10 min while several hours were required for the more sterically hindered *O*-benzyl analog **4b**. Regardless of the time and temperature, both reactions resulted in yields of about 40%. This moderately low outcome was attributed to the decomposition of the constrained lactams during isolation as only trace impurities were observed in the ^{1}H NMR spectra of the crude reaction mixtures before silica gel chromatography.



Scheme 3. Synthesis of monocyclic β-lactams from thiohemiacetal **3b**.

The conversion to monocyclic β-lactams was subsequently examined by screening methods to cleave the thiazolidine with mineral acids and mercury salts. In most instances, lactam **4b** was unreactive or the azetidinone ring could not tolerate the conditions applied. Attention was then turned to the use of methoxycarbonylsulfenyl (Scm) chloride which has served as a deprotecting reagent of the thiazolidine rings in cysteine-containing peptides.[14] Under the standard conditions with AcOH as the solvent/catalyst, DMF to solubilize the peptide, water to promote the hydrolysis, and NaOAc as a Cl^- scavenger, the cleavage was found to be slow and incomplete after 18 h. The problem was resolved by supplementing the reaction with a stronger acid catalyst (i.e., TFA) and the monocyclic β-lactam **5** was obtained as a triturable white solid in 65% yield (Scheme 3).[15]

In the final stage of the reaction sequence to produce *N*-protio monocyclic β-lactams, cleavage of the benzyloxy group was attempted using a range of reducing agents (e.g., LAH, $NaBH_4$, Zn dust, and SmI_2); however, the N-1/C-4 bond of lactam **5** proved to be too labile in the reactions. With this impasse, it was realized that removal of the alkoxy group before conversion to the monocyclic ring would be required for entry to *N*-protio β-lactams. Thus, SmI_2-mediated scission of the N–O bond[16] followed by cleavage of the thiazolidine successfully afforded the *N*-protio monocyclic β-lactam **6**[17] (Scheme 3) possessing the *cis*-configured azetidinone nucleus of penicillins and cephalosporins.

3. Conclusion

In summary, a new method to synthesize monocyclic β-lactams from L-cysteine has been achieved with the use of photochemistry. The aerobic photo-oxidations were scalable to at least 2 g and a diversity of hydroxamate esters could be employed in the reactions. Subsequent cyclizations to bicyclic β-lactams were found to be clean and facile, though the stability of the constrained rings likely had an adverse effect on the isolated yields. Evidence for this was observed during our efforts to deprotect lactam **4** which frequently resulted in the regeneration of the hydroxamate ester. Removal of the *N*-alkoxy group prior to thiazolidine ring cleavage successfully afforded the *N*-protio monocyclic β-lactam capable of further elaboration into biologically active antibacterials.

Acknowledgments

The authors thank the American Foundation for Pharmaceutical Education for its generous financial support of this research. Special thanks are also given to the UGA College of Pharmacy and Department of Pharmaceutical and Biomedical Sciences.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.085.

References and notes

1. (a) Mattingly, P. G.; Kerwin, J. F.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983–3985; (b) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026–7032; (c) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410–415; (d) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 1557–1564; (e) Miller, M. J.; Biswas, A.; Krook, M. A. *Tetrahedron* **1983**, *39*, 2571–2575; (f) Krook, M. A.; Miller, M. J. *J. Org. Chem.* **1985**, *50*, 1126–1128.
2. (a) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopapadakou, N. H.; Koster, W. M.; Liu, W. C.; Parker, W. L.; Principe, P. A.; Rathnum, M. L.; Slusarchyk, W. A.; Trejo, W. H.; Wells, J. S. *Nature (London)* **1981**, *291*, 489–491; (b) Floyd, D. M.; Fritz, A. W.; Plusces, J.; Weaver, E. R.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 5160–5167; (c) Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176–178; (d) Cimarusti, C. M.; Applegate, H. E.; Chang, H. W.; Floyd, D. M.; Koster, W. H.; Slusarchyk, W. A.; Young, M. G. *J. Org. Chem.* **1982**, *47*, 179–180.
3. (a) Baldwin, J. E.; Christie, M. A.; Haber, S. B.; Kuse, I. K. *J. Am. Chem. Soc.* **1976**, *98*, 3045–3047; (b) Baldwin, J. E.; Au, A.; Christie, M. A.; Haber, S. B.; Hessan, H. *J. Am. Chem. Soc.* **1975**, *97*, 5957–5958; (c) Nakatsuka, S.; Tanino, H.; Kishi, Y. *J. Am. Chem. Soc.* **1975**, *97*, 5008–5010.
4. (a) Woodward, R. B. *Science* **1966**, *153*, 487–493; (b) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, J.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852–853.
5. Koppel, G. A.; McShane, L.; Jose, F.; Cooper, R. D. G. *J. Am. Chem. Soc.* **1978**, *100*, 3933–3935.
6. (a) Takata, T.; Hoshino, K.; Takeuchi, E.; Tamura, Y.; Ando, W. *Tetrahedron Lett.* **1984**, *25*, 4767–4770; (b) Takata, T.; Tamura, Y.; Ando, W. *Tetrahedron* **1985**, *41*, 2133–2137; (c) Takata, T.; Ishibashi, K.; Ando, W. *Tetrahedron Lett.* **1985**, *26*, 4609–4612; (d) Takata, T.; Huang, L.; Ando, W. *Chem. Lett.* **1985**, 1705–1708; (e) Takata, T.; Ando, W. *Tetrahedron Lett.* **1986**, *27*, 1591–1594; (f) Takata, T.; Ando, W. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1275–1276.
7. (a) Iwakawa, M.; Pinto, B. M.; Szarek, W. A. *Can. J. Chem.* **1978**, *56*, 329–335; (b) Sheehan, J. C.; Yang, D. H. *J. Am. Chem. Soc.* **1958**, *80*, 1158–1164; (c) Suaifan, G. A. R.; Mahon, M. F.; Arafat, T.; Threadgill, M. D. *Tetrahedron* **2006**, *62*, 11245–11266.
8. (a) Shepherd, A.; Miller, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2519–2525; (b) Shin, I.; Park, K. *Org. Lett.* **2002**, *4*, 869–872.
9. *Photo-oxidation of thiazolidines* **2**; *general procedure*: To a 500 mL jacketed beaker equipped with a circulating −10 to 0 °C bath was added tetraphenylporphyrin (17 mg, 28 μmol) and hydroxamate ester **2** (2.8 mmol) in dry THF (55 mL). A 500 W halogen lamp was illuminated ca. 1 inch above the beaker for 1.5 h while a stream of purified oxygen was bubbled into the solution. Methyl sulfide (520 μL, 7.0 mmol) was next added and the solution was left at rt until conversion to the thiohemiacetal was complete (2–3 h). The solvent was then evaporated and the oil was purified by silica gel chromatography using a 10–70% gradient of EtOAc in hexanes to afford the product.
(4*R*,5*S*)-3-Benzoyl-*N*-(benzyloxy)-5-hydroxy-2,2-dimethylthiazolidine-4-carboxamide (**3b**): Yield: 68–73%; pale solid, mp: 64–66 °C; TLC (SiO_2) R_f 0.28 (1:1 hexanes/EtOAc); $[\alpha]_D^{28}$: −58 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 11.20 (s, 1H), 7.46–7.28 (m, 10H), 6.64 (d, 1H, *J* = 3.0 Hz), 5.27 (d, 1H, *J* = 3.0 Hz), 4.72 and 4.62 (ABq, 2H, $\Delta\nu$ = 40.5 Hz, *J* = 11.0 Hz), 4.52 (s, 1H), 2.08–1.93 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.4, 165.4, 142.3, 139.4, 136.1, 129.5, 129.4, 128.9, 128.8, 128.7, 125.9, 78.9, 77.0, 75.2, 73.7, 32.3, 28.5.
10. Pfaendler, H. R.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6306–6310.
11. (a) Woulfe, S. R.; Miller, M. J. *Tetrahedron Lett.* **1984**, *25*, 3293–3296; (b) Woulfe, S. R.; Miller, M. J. *J. Med. Chem.* **1985**, *28*, 1447–1453; (c) Boyd, D. B.; Eigenbrot, C.; Indelicato, J. M.; Miller, M. J.; Pasini, C. E.; Woulfe, S. R. *J. Med. Chem.* **1987**, *30*, 528–536.
12. (a) Gordon, E. M.; Ondetti, M. A.; Pluscec, J.; Cimarusti, C. M.; Bonner, D. P.; Sykes, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 6053–6060; (b) Agenoa, G.; Banfia, L.; Casciob, G.; Guanti, G.; Manghisib, E.; Riva, R.; Roccaa, V. *Tetrahedron* **1995**, *51*, 8121–8134.
13. *Cyclization of thiohemiacetals* **3**; *general procedure*: Thiohemiacetal **3** (2.0 mmol), mesyl chloride (318 μL, 4.0 mmol) and Et_3N (1.14 mL, 8.2 mmol) were combined in 16 mL of DCM at 0 °C. The flask was capped and placed overnight in a −20 °C freezer. The brown solution was then transferred to a separatory funnel with 10 mL of DCM, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography using a 6–50% gradient afforded the bicyclic β-lactam product.
(1*R*,5*R*)-2-Benzoyl-6-(benzyloxy)-3,3-dimethyl-4-thia-2,6-diazabicyclo[3.2.0]-heptan-7-one (**4b**): Yield: 34–41%; white solid, mp: 104–106 °C; TLC (SiO_2) R_f 0.26 (4:1 hexanes/EtOAc); $[\alpha]_D^{28}$: −122 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.56 (m, 2H), 7.46–7.39 (m, 8H), 5.27 (d, 1H, *J* = 5.0 Hz), 5.17 (d, 1H, *J* = 5.0 Hz), 5.09 and 5.03 (ABq, 2H, $\Delta\nu$ = 40.5 Hz, *J* = 11.0 Hz), 2.05 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 162.6, 136.9. 134.0, 130.0, 129.2, 129.0, 128.8, 128.6, 126.8, 78.5, 76.8, 72.2, 69.3, 31.4, 29.9.
14. (a) Kemp, D. S.; Carey, Robert I. *J. Org. Chem.* **1989**, *54*, 3640–3646; (b) Yang, H.; Sheng, X. C.; Harrington, E. M.; Ackermann, K.; Garcia, A. M.; Lewis, M. D. *J. Org. Chem.* **1999**, *64*, 242–251.
15. *Thiazolidine ring cleavage of β-lactam* **4b**: Methoxycarbonylsulfenyl chloride (57 μL, 0.69 mmol) was added dropwise into an ice-chilled solution of β-lactam (169 mg, 0.46 mmol) and NaOAc (76 mg, 0.92 mmol) in a 12:2:1 solution of AcOH/DMF/TFA (2.25 mL). The solution was stirred at 0 °C for 1.5 h, and then added with distilled water. The yellow solution was then transferred to a separatory funnel with 10 mL of EtOAc, washed three times with distilled water. The organic layer was then dried over $MgSO_4$, filtered, and concentrated giving a yellow solid which was triturated in a 4:1 solution of hexanes/EtOAc to afford the monocyclic β-lactam product (125 mg, 0.29 mmol).
SS-((2*R*,3*R*)-3-Benzamido-1-(benzyloxy)-4-oxoazetidin-2-yl) *O*-methyl carbon-(dithioperoxoate) (**5**): Yield: 65%; white solid, mp: 139–141 °C; TLC (SiO_2) R_f 0.12 (2:1 hexanes/EtOAc); $[\alpha]_D^{28}$: −16 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, 2H, *J* = 7.5 Hz), 7.69 (1H, d, *J* = 7.0 Hz), 7.54–7.43 (m, 7H), 7.30 (s, 1H), 5.43 (m, 1H), 5.15 (s, 2H), 4.99 (d, 1H, *J* = 4.5 Hz), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 167.8, 161.7, 134.1, 132.9, 132.2, 129.5, 129.4, 128.8, 128.6, 127.5.
16. Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755–11772.
17. *Conversion to N-protio monocyclic β-lactam* **6**: To a stirring solution of β-lactam **4b** (48 mg, 0.13 mmol) in dry DCM (1 mL) under Ar was added SmI_2 in THF (4.6 mL, 0.32 mmol). After 15 min, the reaction was quenched with 5% $Na_2S_2O_3$ (1 mL) and 5% $NaHCO_3$ (5 mL). The product was extracted with DCM, dried over

$MgSO_4$, filtered, and evaporated. Purification by silica gel chromatography using an 8–66% EtOAc in hexanes gradient afforded the *N*-protio bicyclic β-lactam as a colorless oil. Methoxycarbonylsulfenyl chloride (12 μL, 0.145 mmol) was next added dropwise to an ice-chilled solution of the β-lactam (25.5 mg, 0.096 mmol) and NaOAc (15.8 mg, 0.192 mmol) in a 12:2:1 mixture of AcOH/DMF/TFA (1 mL). The ice bath was removed and the solution was stirred at rt for 15 min. Distilled water (2 mL) was then added and the cloudy solution was transferred to a separatory funnel. The product was extracted with EtOAc, washed with distilled water, dried over $MgSO_4$, filtered, and evaporated. Purification by silica gel chromatography using an 8–66% EtOAc in hexanes gradient afforded the monocyclic β-lactam product (12 mg, 0.04 mmol).

SS-((2*R*,3*R*)-3-Benzamido-4-oxoazetidin-2-yl) *O*-methyl carbon-(dithioperoxoate) (**6**): Yield: 40%; white solid, mp: 161–163 °C; TLC (SiO_2) R_f 0.18 (1:1 hexanes/EtOAc); $[\alpha]_D^{22}$: −16 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.90 (d, 2H, *J* = 7.5 Hz), 7.57 (d, 1H, *J* = 7.5 Hz), 7.49 (t, 2H, *J* = 7.5 Hz), 5.49 (d, 1H, *J* = 4.5 Hz), 5.16 (d, 1H, *J* = 4.5 Hz), 3.87 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.8, 170.7, 168.8, 134.8, 133.4, 129.8, 128.8, 69.8, 63.2, 56.6.