Solid-Phase Synthesis of β-Sultams

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Solid-phase synthesis of β-sultams amenable for construction of sulfonyl β-lactam analogue combinatorial libraries is reported. Imine intermediates generated from polymer-immobilized amino acids and aldehydes are reacted with (chlorosulfonyl)acetates in the presence of pyridine to afford the solid-phase-tethered β-sultam products. The latter can be released from support by acidic cleavage (TFA) or photocleavage, depending on the nature of the linker employed (acid-labile or photolabile linkers). Immobilized 4-(9-fluorenyl)methoxycarbonyl β-sultams are further functionalized on supports to afford, upon cleavage, the respective carboxy and amido thiazetidine derivatives. The method can be employed in production of β-sultam libraries for identification of new antibacterial agents.

The ability of combinatorial technology to quickly provide large numbers of novel, low molecular weight, potential bioactive molecules is directly related to the limitations to which the chemist is constrained in performing solid phase organic synthesis. While conceptual validation of the promise of combinatorial methods to provide millions of compounds emerged in the form of simple oligomeric molecules such as peptides, realistic applications to drug discovery demands libraries of small-sized, nonpolymeric molecules.[1] Modern drug discovery has often involved the rational design of specific pharmacophores and scaffolds based on mechanistic and structural understanding of the biological target(s) of interest, rather than, for example, relying on screening large libraries of easily synthesizable scaffolds. Thus, to fully exploit the multitude of new genomically derived potential drug targets, a closer integration of actual targets with appropriate libraries based on specific pharmacophoric groups is desirable. It will likely become necessary to prepare libraries of novel pharmacophores and scaffolds whose solid-phase synthesis (SPS) may demand nonconventional chemistries, reagents, and reaction conditions.[2] It is therefore advantageous to explore the boundaries and limits of applying solid-phase synthesis to produce small, reactive molecules.

In this paper, we report the first SPS of a β-sultam (1,2-thiazetidine 1,1-dioxides) scaffold and describe a synthetic strategy that offers sufficient latitude for preparation of corresponding chemical libraries with broad structural diversity. β-Sultams have recently attracted attention due to their apparent structural analogy to the β-lactams.[3] Limited studies on β-sultams have previously indicated an increased chemical reactivity of such heterocycles as compared to β-lactams.[3b] The β-sultams however remain a rare heterocyclic class, whose functionalized derivatives are largely unknown.

We set out to develop a SPS of β-sultams based on the [2 + 2] cycloaddition of activated sulfenes with imines as the critical step.[3] While first examples of this transformation in solution were reported by Tsuge and Iwanami in 1970,[4] little progress has been made since then, and the majority of synthetic routes to β-sultams are based on stepwise strategies via cyclization of 2-aminoalkanesulfonic acid derivatives.[3a−c] Our synthetic strategy relies on the feasibility of efficient [2 + 2] cycloaddition of sensitive and reactive intermediates generated in situ, namely, imines and sulfenes, at low temperatures (−78 °C) on a solid support. As part of the efforts to arrive at the optimal set of reaction parameters and choice of appropriate sulfene precursors, we undertook a gel-phase ^{13}C NMR[5] study employing ^{13}C-labeled benzaldehyde to monitor the formation of a β-sultam heterocycle on a solid support. Thus, reaction of Sasrin resin[6] immobilized alanine **1** (R_1 = Me) with Ph^{13}CHO gave rise to the corresponding ^{13}C-labeled imine **2** (R_1 = Me, R_2 = Ph, $\delta(^{13}CH)$ = 160 ppm). Treatment of imine **2** with methyl (chlorosulfonyl)acetate as a reactive sulfene precursor and pyridine as a base in THF at −78 °C followed by gradual warm-up to rt resulted in an upfield shift of the ^{13}C-labeled methine group (δ = 52−53 ppm), indicating a clean conversion to the [2 + 2] cycloadduct.[7] Mild acidolytic cleavage (1−2% TFA) followed by conventional characterization of resulting product **4a** (Scheme 1, Table

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(1) For some reviews, see: (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−1251. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385−1401. (c) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res* **1996**, *29*, 9; 144−154. (d) Patel, D. V.; Gordon, E. M. *Drug Discovery Today* **1996**, *1*, 134−144.

(2) See, for example, a recent review on solid-phase organic reactions: Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527−4554.

(3) For reviews on β-sultams, see: (a) Timberlake, J. W.; Alder, E. S. In *Comprehensive Heterocyclic Chemistry*, Vol. I; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; p 449. (b) Chanet-Ray, J.; Vessiere, R. *Org. Prep. Proced. Int.* **1986**, *18*, 159−178. (c) Harris, P. A. In *Comprehensive Heterocyclic Chemistry II*, Vol. I; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science Inc.: Oxrford, 1996; p 1009. For a related solution-phase synthesis, see: (d) Szymonifka, M. J.; Heck, J. V. *Tetrahedron Lett.* **1989**, *30*, 2869−2872.

(4) Tsuge, O.; Iwanami, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3543.

(5) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588−7590.

(6) Polystyrene-based 2-methoxy-4-alkoxybenzyl alcohol resin: Mergler, M.; Tanner, R.; Gosteli, J.; Grogg, P. *Tetrahedron Lett.* **1988**, *29*, 4005−4008. The superacid labile Sasrin resin allows for cleavage of potentially acid-labile[3b] sultam products with dilute trifluoroacetic acid.

(7) While ^{13}C NMR data indicated a quantitative conversion of imines into β-sultams, subsequent ^1H NMR and HPLC analysis of cleaved products in most cases did reveal presence of impurities with exception of clean transformations with alanine. In part, this might be accounted for by a two-step cycloaddition mechanism of the β-sultam formation commencing from the sulfonylation of imines with a reactive sulfonyl halide to generate hydrolytically unstable sulfonyliminium intermediates (cf. ref 3d). The latter may cyclize into β-sultams (in presence of bases) or produce sulfonylated amino acids upon workup (as detected by ESI MS in a crude product of this reaction with benzylidenevaline-functionalized Sasrin resin). In all cases (see Scheme 1, Table 1), β-sultams were detected as principal products and separated by HPLC.

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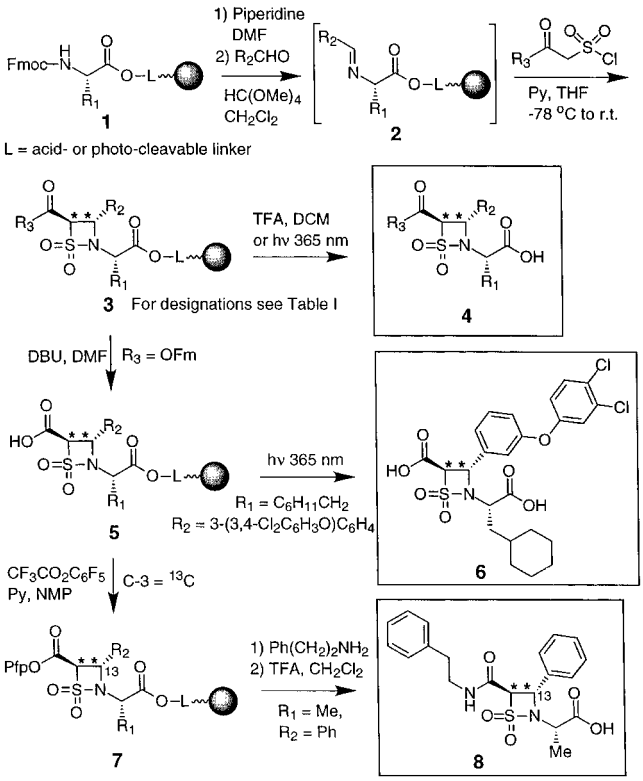
Scheme 1



1; 90% yield, 95% HPLC purity[8]) demonstrated the reliability of the entire synthetic sequence. Following this synthetic protocol, several β-sultam products **4** were obtained in good yield and purity (see Table 1, entries **4a**−**d**,**n**: 58−90% yield, 70−95% purity). While initial studies employed polystyrene-based Sasrin resin possessing the highly acid-labile alcohol linker,[6] the synthetic sequence, intermediates, and products are robust enough to tolerate other types of linkers and cleavage conditions. Thus, β-sultams were successfully synthesized using poly(ethylene glycol) (PEG) based TentaGel resin derivatized with an α-methyl-6-nitroveratryl alcohol based photolabile linker.[9] The final products **4** were released from polymeric support upon photolysis in 2-propanol at 365 nm.[10] In most cases, β-sultam products were isolated in satisfactory yield and purity (Table 1, compounds **4e**−**m**, **6**: 19−39% yield, 70−94% purity). The photocleavable linker methodology[11] integrates well with recently developed high throughput screening (HTS) strategies and whole cell lawn assays which call for direct, tiered release of compounds from polymeric beads onto live cells under nonacidic conditions.[12] In the cycloaddition step, formation of two *trans* diastereomers was usually observed,[13] which is in agreement with the results of solution synthesis of 4-methoxycarbonyl β-sultams by Szymonifka et al.[3d] The cycloaddition appears to be sensitive to steric hindrance, as evidenced by lower yields and purity observed in the reaction with sterically more demanding amino acids, such as aspartic acid *tert*-butyl ester (Table 1, compound **4m**, 19% yield, 58% purity).

Notably, the synthesis appears to tolerate further modifications in substitutions around the core thiazetidine ring. Thus, it has been possible to extend the scope of this transformation employing 9-fluorenylmethyl (chlorosulfonyl)acetate as a novel α-carboxy sulfene synthon.[14] The (9-fluorenyl)methoxycarbonyl group thus introduced into the immobilized β-sultam heterocycle **3** (Scheme 1, R_3 = OFm) could be smoothly deprotected with 0.5% DBU in DMF to afford the corresponding 4-carboxy derivatives **5**. This transformation opens up routes to new functionalized β-sultams via subsequent derivatization of the carboxylic acid moiety of immobilized 4-carboxy β-sultam **5**. As an example, we acylated phenethylamine with the resin-bound β-sultam **5** (R_1 = Me, R_2 = Ph) via its activated pentafluorophenyl ester **7** to produce the corresponding 4-phenethylcarbamoyl β-sultam **8** (37% overall yield, 79% purity).[15]

In summary, herein we report development of the first solid-phase synthesis of β-sultams based on low-temperature [2 + 2] cycloaddition of activated sulfenes with immobilized imines. The flexibility of the current method to efficiently introduce and further modify various substituents around the core thiazetidine nucleus is noteworthy. The current method is well suited for combinatorial library synthesis of a diverse collection of structurally novel β-sultams with potential for antibacterial activity. The results of synthesis and screening of β-sultam libraries for identification of new antibacterial agents will be reported soon.

Experimental Section

General. All reagents were of the best grade available (Aldrich, Sigma, Bachem Biosciences, and Rapp Polymere) and used without further purification. 1-^{13}C-Labeled benzaldehyde was from Cambridge Isotope Laboratories, Inc. Methyl and butyl (chlorosulfonyl)acetates were prepared according to ref 3d. Immobilization of N-Fmoc-protected amino acids on alcohol-functionalized solid supports was performed according to ref 16. Loading of amino acids on polymeric supports was determined by photometry after Fmoc deprotection with 20% piperidine in dimethylformamide.[17] All reactions with sulfonyl chlorides were carried out in dry glassware under a nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra (400 and 75 MHz, respectively) were recorded in $CDCl_3$ as solvent unless noted. HRMS were obtained using the FAB technique. Analytical HPLC was performed using a 5 μm C18 (4.6 mm × 150 mm) reverse phase column (gradient from 90% of the aqueous 0.1% TFA (eluent A)−10% of 0.1% TFA in MeCN (eluent B) to 20% eluent A−80% eluent B over 45 min, flow rate 1.5 mL/min; detection at 220 nm). Preparative HPLC was performed using a 5 μm C18 (10 mm × 250 mm) reverse phase column (gradient

(8) Detection at 220 nm. See Experimental Section for details of the HPLC analysis.

(9) Holmes, C. P. *J. Org. Chem.* **1997**, *62*, 2370.

(10) While DMSO has been originally recommended as solvent for photorelease from solid supports,[9] we observed overall cleaner results using 2-propanol that can be easily removed in vacuo prior to HPLC purifications.

(11) For a review of early works, see: Pillai, V. N. R. *Synthesis* **1980**, 1−26.

(12) (a) Oldenburg, K. R.; Vo, K. T.; Ruhland, B.; Schatz, P. J.; Yuan, Z. *J. Biomol. Screen.* **1996**, *1*, 123. (b) Schullek, J. R.; Butler, J. H.; Ni, Z.-J.; Chen, D.; Yuan, Z. *Anal. Biochem.* **1997**, in press.

(13) As evidenced by coupling constants of ca. 4.9−6.0 Hz between H-3 and H-4 protons in ^{1}H NMR spectra of the compounds thus obtained (cf. also refs 3c and 5d). Diastereomeric ratios for most products was in a range of 1:1 to 2.5:1 (see Supporting Information), with the exception of compounds obtained from L-tyrosine *tert*-butyl ester (Table 1, compound **4f**; isomeric ratio of 15:1) and L-serine *tert*-butyl ether (Table 1, compound **4h**; single diastereomer). The reaction with racemic DL-aminocaprylic acid was also diastereoselective, as only two *trans* diastereomers were obtained. Absolute stereochemistry of major and minor *trans* diastereomers is not known.

(14) Prepared from (chlorosulfonyl)acetyl chloride and (9-fluorenyl)-methyl alcohol (see Experimental Section).

(15) This stepwise transformation with the ^{13}C-3-labeled β-sultam has been monitored by gel-phase ^{13}C NMR (see Experimental Section).

(16) Green, J.; Bradley, K. *Tetrahedron* **1993**, *49*, 4141−4146.

(17) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404−3409.

Table 1. β-Sultam Derivatives Prepared on Solid Supports[a]

compd	R_1[b]	R_2	R_3	HPLC (%)[c]	yield (%)[d]
4a	Me	Ph(^{13}C)[e]	MeO	95	90
4b	$C_6H_{11}CH_2$	4-biphenylyl	MeO	95	68 (21)[f]
4c	$PhCH_2$	Ph	MeO	70	58
4d	$^tBuO_2C(CH_2)_2$	Ph(^{13}C)[e]	MeO	90	74
4e	Me	4-biphenylyl	MeO	94	39
4f	$^tBuOC_6H_4$	4-biphenylyl	MeO	71	26
4g	hexyl	4-biphenylyl	MeO	97	26
4h	$^tBuOCH_2$	4-biphenylyl	MeO	82	33
4i	$C_6H_{11}CH_2$	3-(3,4-$Cl_2C_6H_3O$)C_6H_4	MeO	79	20
4j	hexyl	3-(3,4-$Cl_2C_6H_3O$)C_6H_4	MeO	93	19
4k	$^iPrCH_2$	3-(3,4-$Cl_2C_6H_3O$)C_6H_4	MeO	79	20
4l	$C_6H_{11}CH_2$	3-(3,4-$Cl_2C_6H_3O$)C_6H_4	BuO	70	20
4m	$^tBuO_2CCH_2$	4-biphenylyl	MeO	58	19
4n	Me	Ph(^{13}C)[e]	FmO[g]	89	80
6	$C_6H_{11}CH_2$	3-(3,4-$Cl_2C_6H_3O$)C_6H_4	HO	80	24
8	Me	Ph(^{13}C)[e]	$Ph(CH_2)_2NH$	79	37

[a] Compounds of entries **4a**−**d**,**n** and **8** were made on Sasrin resin; all other products were obtained on TentaGel resin functionalized with the photolinker. [b] L-Amino acids were used in all cases with exceptions of DL-aminocaprylic acid (compounds **4g**,**j**) and D-leucine (**4k**). [c] Crude products. Detection at 220nm. [d] Based on the loading of starting *N*-Fmoc-protected resin. For two diastereomeric HPLC purified products (see Experimental Section for diastereomeric ratios of the products). [e] Made with $Ph^{13}CHO$. [f] Yield in parentheses correspond to that obtained using photolinker TentaGel resin. [g] FmO = (9-fluorenyl)methoxy group.

from 90% eluent A−10% of the eluent B to 20% of the eluent A−80% of the eluent B over 50 min, flow rate 4 mL/min).

General Procedure for Solid-Phase Preparation of β-Sultams 3 and 4. An appropriate N-Fmoc-protected amino acid resin **1** [100 mg, ca. 0.06 mmol for Sasrin support (method A) or 150 mg, ca. 0.03 mmol for TentaGel S NH_2 resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker (method B)] was deprotected with 20% piperidine in dimethylformamide for 30 min. The resin was filtered, washed liberally with dimethylformamide, MeOH, and CH_2Cl_2, and dried under vacuum. The deprotected resin was suspended in a solution of an appropriate aldehyde (1 mmol) in DCM (0.5 mL) and trimethyl orthoformate (0.5 mL) with catalytic AcOH (10 μL), and the mixture was agitated by gentle shaking for 5 h. The resulted imine resin was filtered, washed liberally with dimethylformamide, MeOH, and CH_2Cl_2, and dried under vacuum. Anhydrous pyridine (0.080 mL, 1.0 mmol) was added under an inert atmosphere to a suspension of the above imine in THF (2.0 mL) precooled to ca. −78 °C, followed by dropwise addition of an appropriate (chlorosulfonyl)acetate (0.86 mmol) in THF (0.4 mL). The mixture was stirred at −78 °C for 3 h and allowed to warm to rt over ca. 24 h. MeOH (ca. 5 mL) was added, and the resin **3** was filtered off, washed liberally with MeOH and CH_2Cl_2, and dried under vacuum. Photolinker-tethered compounds **4** were released by photolysis (365 nm, 12 h) in 2-propanol (2.0 mL), whereas Sasrin-supported sultams **4** were cleaved with 2% trifluoroacetic acid in CH_2Cl_2 (ca. 2 mL, rt, 20 min). In the latter case, MeCN (7 mL) and toluene (ca. 3 mL) were added (to prevent concentration of the labile products in trifluoroacetic acid), and the solvent was removed under vacuum. Products **4** were purified by preparative HPLC. From reactions where mixtures of two *trans*-β-sultam isomers were obtained, no further attempts to separate the individual compounds were made.

Sasrin resin ester of [3-^{13}C]-*trans*-2-[(*S*)-1-carboxyethyl]-4-(methoxycarbonyl)-3-phenyl-1,2-thiazetidine 1,1-dioxide (4a) (intermediate 3: R_1 = Me; R_2 = Ph; C-3 = ^{13}C) was prepared as described above (method A) from Fmoc-L-alanine immobilized on Sasrin resin (100 mg, 0.06 mmol) and ^{13}C-1-benzaldehyde (107 mg, 1.0 mmol) with methyl (chlorosulfonyl)acetate (148 mg, 0.86 mmol). Fast gel-phase ^{13}C NMR (C_6D_6) δ: 51.8 (3-C).

[3-^{13}C]-*trans*-2-[(*S*)-1-Carboxyethyl]-4-(methoxycarbonyl)-3-phenyl-1,2-thiazetidine 1,1-Dioxide (4a). Following method A, 100 mg (0.06 mmol) of Fmoc-L-alanine immobilized on Sasrin resin yielded 17.0 mg (90%) of the lyophilized product **4a** as a white solid (a 1.9:1 mixture of two *trans* diastereomers). ^{1}H NMR (major isomer) δ: 1.41 (d, *J* = 7.2 Hz, 3 H), 3.89 (s, 3 H), 4.16 (m, 1 H), 4.89 (m, 1 H), 5.19 (dd, *J* = 154.2 and 6.0 Hz, 1 H), 7.40 (m, 3 H), 7.55 (m, 2 H). ^{1}H NMR (minor isomer) δ: 1.55 (d, *J* = 7.2 Hz, 3 H), 3.90 (s, 3 H), 3.97 (m, 1 H), 4.89 (m, 1 H), 5.03 (dd, *J* = 154.9 and 5.7 Hz, 1 H), 7.40 (m, 3 H), 7.55 (m, 2 H). Fast ^{13}C NMR (major isomer) δ: 52.6 (3-C). Fast ^{13}C NMR (minor isomer) δ: 52.9 (3-C). HRMS: calcd for $C_{12}{}^{13}CH_{16}NO_6S$ 315.0732, found 315.0725 $(M + H)^+$.

***trans*-2-[(*S*)-2-Cyclohexyl-1-carboxyethyl]-4-(methoxycarbonyl)-3-(4-biphenylyl)-1,2-thiazetidine 1,1-Dioxide (4b).** Following method A, 115 mg (0.075 mmol) of the Fmoc-L-cyclohexylalanine immobilized on Sasrin resin yielded 24.0 mg (68%) of the lyophilized product **4b** as a white solid (a 1.07:1 mixture of two trans diastereomers). Alternatively, following method B, 150 mg (0.03 mmol) of the Fmoc-L-cyclohexylalanine immobilized on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker yielded 3.0 mg (21%) of the product. ^{1}H NMR (major isomer) δ: 0.65−1.95 (m, 13 H), 3.90 (s, 3 H), 4.17 (dd, *J* = 8.7 and 6.4 Hz, 1 H), 5.00 (d, *J* = 5.8 Hz, 1 H), 5.45 (d, *J* = 5.8 Hz, 1 H), 7.36−7.50 (m, 3 H), 7.55−7.68 (m, 6 H). ^{1}H NMR (minor isomer) δ: 0.65−1.95 (m, 13 H), 3.79 (dd, *J* = 9.2 and 5.9 Hz, 1 H), 3.91-(s, 3 H), 4.95 (d, *J* = 5.7 Hz, 1 H), 5.21 (d, *J* = 5.7 Hz, 1 H), 7.36−7.50 (m, 3 H), 7.55−7.68 (m, 6 H). HRMS: calcd for $C_{25}H_{30}NO_6S$ 472.1793, found 472.1792 $(M + H)^+$.

***trans*-2-[(*S*)-2-Phenyl-1-carboxyethyl]-4-(methoxycarbonyl)-3-phenyl-1,2-thiazetidine 1,1-Dioxide (4c).** Following method A, 100 mg (0.06 mmol) of the Fmoc-L-phenylalanine immobilized on Sasrin resin yielded 13.5 mg (58%) of the lyophilized product **4c** as a white solid (a 1.25:1 mixture of two *trans* diastereomers). ^{1}H NMR (major isomer) δ: 3.27 (m, 2 H), 3.84 (m, 1 H), 3.88 (s, 3 H), 4.78 (d, *J* = 6.0 Hz, 1 H), 5.18 (d, *J* = 6.0 Hz, 1 H), 7.10 (m, 2 H), 7.10−7.48 (m, 8 H). ^{1}H NMR (minor isomer) δ: 3.05 (m, 2 H), 3.88 (s, 3 H), 4.28 (m, 1 H), 4.89 (d, *J* = 6.1 Hz, 1 H), 5.11 (d, *J* = 6.1 Hz, 1 H), 7.10 (m, 2 H), 7.10−7.48 (m, 8 H). ^{13}C NMR (major isomer) δ: 35.9, 53.7, 60.0, 79.4, 126.8, 127.1, 128.5, 128.7, 129.2, 129.4, 134.9, 136.3, 162.3, 172.0. ^{13}C NMR (minor isomer) δ: 36.6, 52.7, 53.7, 59.7, 79.8, 127.1, 127.2, 127.3, 129.0, 129.3, 129.5, 135.2, 136.0, 162.2, 172.0. HRMS: calcd for $C_{19}H_{20}NO_6S$ 390.1011, found 390.1010 $(M + H)^+$.

Sasrin resin ester of [3-^{13}C]-*trans*-2-[(*S*)-2-(*tert*-Butoxycarbonyl)-1-carboxypropyl]-4-(methoxycarbonyl)-3-phenyl-1,2-thiazetidine 1,1-dioxide (4d) (intermediate 3: R_1 = $^tBuO_2C(CH_2)_2$; R_2 = Ph; C-3 = ^{13}C) was prepared as described above (method A) from Fmoc-L-glutamic acid acid γ-*tert*-butyl ester immobilized on Sasrin resin (100 mg, 0.06 mmol) and [1-^{13}C]benzaldehyde (107.0 mg, 1.0 mmol) with methyl (chlorosulfonyl)acetate (148 mg, 0.86 mmol). Fast gel-phase ^{13}C NMR (C_6D_6) δ: 51.7 and 52.4 (3-C).

[3-^{13}C]-*trans*-2-[(*S*)-2-(*tert*-Butoxycarbonyl)-1-carboxypropyl]-4-(methoxycarbonyl)-3-phenyl-1,2-thiazetidine 1,1-Dioxide (4d). Following method A, 100 mg (0.06 mmol) of Fmoc-L-glutamic acid γ-*tert*-butyl ester immobilized on Sasrin resin yielded 19.0 mg (74%) of the lyophilized product **4d** as a white solid (a 2.5:1 mixture of two *trans*

diastereomers). ^{1}H NMR (major isomer) δ: 1.36 (s, 9 H), 2.20 (m, 2 H), 2.48 (m, 2 H), 3.89 (s, 3 H), 3.90 (m, 1 H), 4.92 (m, 1 H), 5.14 (dd, J = 155.3 and 5.9 Hz, 1 H), 7.37−7.44 (m, 3 H), 7.52−7.60 (m, 2 H). ^{1}H NMR (minor isomer) δ: 1.40 (s, 9 H), 1.75 (m, 1 H), 1.97 (m, 1 H), 2.48 (m, 2 H), 3.88 (s, 3 H), 4.16 (m, 1 H), 4.92 (m, 1 H), 5.36 (dd, J = 155.3 and 5.8 Hz, 1 H), 7.37−7.44 (m, 3 H), 7.52−7.60 (m, 2 H). Fast ^{13}C NMR (major isomer) δ: 53.2 (3-C). Fast ^{13}C NMR (minor isomer) δ: 52.3 (3-C). HRMS: calcd for $C_{18}{}^{13}CH_{25}NNaO_8S$ 451.1232, found 451.1229 $(M + Na)^+$.

***trans*-2-[(*S*)-1-Carboxyethyl]-4-(methoxycarbonyl)-3-(4-biphenylyl)-1,2-thiazetidine 1,1-Dioxide (4e).** Following method B, 150 mg (0.03 mmol) of the Fmoc-L-alanine on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker yielded 4.5 mg (39%) of the lyophilized product **4e** as a white solid (a 1.27:1 mixture of two *trans* diastereomers). ^{1}H NMR (major isomer) δ: 1.42 (d, J = 7.1 Hz, 3 H), 3.89 (s, 3 H), 4.16 (q, J = 7.1 Hz, 1 H), 4.93 (d, J = 5.9 Hz, 1 H), 5.24 (d, J = 5.9 Hz, 1 H), 7.35−7.38 (m, 4 H), 7.55−7.65 (m, 5 H). ^{1}H NMR (minor isomer) δ: 1.56 (d, J = 7.3 Hz, 3 H), 3.91 (s, 3 H), 3.99 (q, J = 7.3 Hz, 1 H), 4.93 (d, J = 5.7 Hz, 1 H), 5.08 (d, J = 5.7 Hz, 1 H), 7.35−7.38 (m, 3 H), 7.55−7.65 (m, 6 H). HRMS: calcd for $C_{19}H_{20}NO_6S$ 390.1011, found 390.1012 $(M + H)^+$.

***trans*-2-[(*S*)-2-(4-*tert*-Butoxyphenyl)-1-carboxyethyl]-4-(methoxycarbonyl)-3-(4-biphenylyl)-1,2-thiazetidine 1,1-Dioxide (4f).** Following method B, 150 mg (0.03 mmol) of the Fmoc-L-tyrosine *tert*-butyl ether immobilized on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker yielded 4.2 mg (26%) of the lyophilized product **4f** as a white solid (a 15:1 mixture of two *trans* diastereomers). ^{1}H NMR (major isomer) δ: 1.37 (s, 9 H), 3.24 (m, 2 H), 3.84 (m, 1 H), 3.89 (s, 3 H), 4.84 (d, J = 6.0 Hz, 1 H), 5.22 (d, J = 6.0 Hz, 1 H, 3-H), 6.94 (d, J = 8.5 Hz, 2 H), 7.18 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 8.3 Hz, 2 H), 7.37 (m, 1 H), 7.42−7.50 (m, 4 H), 7.56 (dd, J = 8.3 and 1.5 Hz, 2 H). ^{1}H NMR (minor isomer was inseparable by preparative HPLC, partial spectrum from the mixture of two diastereomers is given below) δ: 1.33 (s, 9 H), 3.03 (m, 2 H), 4.28 (m, 1 H), 4.92 (d, J = 6.0 Hz, 1 H), 5.15 (d, J = 6.0 Hz, 1 H). HRMS: calcd for $C_{29}H_{32}NO_7S$ 538.1899, found 538.1894 $(M + H)^+$.

***trans*-2-[1-Carboxyheptyl]-4-(methoxycarbonyl)-3-(4-biphenylyl)-1,2-thiazetidine 1,1-Dioxide (4g).** Following method B, 150 mg (0.03 mmol) of the Fmoc-DL-aminocaprylic acid immobilized on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker yielded 3.6 mg (26% for two diastereomers in a ratio of ca. 1.2:1) of the lyophilized product **4g** as a white solid. Isomers were separated during HPLC purification. ^{1}H NMR (major isomer) δ: 0.83 (t, J = 7.0 Hz, 3 H), 1.05−1.36 (m, 6 H), 1.32−1.54 (m, 2 H), 1.83−2.02 (m, 2 H), 3.84 (dd, J = 7.3 and 5.9 Hz, 1 H), 3.90 (s, 3 H), 4.95 (d, J = 5.7 Hz, 1 H), 5.07 (d, J = 5.7 Hz, 1 H), 7.37 (m, 1 H), 7.47 (m, 2 H), 7.55−7.67 (m, 6 H). ^{1}H NMR (minor isomer) δ: 0.81 (t, J = 7.3 Hz, 3 H), 1.00−1.32 (m, 6 H), 1.32−1.54 (m, 2 H), 1.56 (m, 2 H), 1.71 (m, 2 H), 3.89 (s, 3 H), 4.04 (dd, J = 7.2 and 7.3 Hz, 1 H), 4.96 (d, J = 5.9 Hz), 5.36 (d, J = 5.9 Hz, 1 H), 7.38 (m, 1 H), 7.46 (m, 2 H), 7.57−7.60 (m, 2 H), 7.63 (m, 4 H). HRMS: calcd for $C_{24}H_{30}NO_6S$ 460.1793, found 460.1794 $(M + H)^+$.

***trans*-2-[(*S*)-2-*tert*-Butoxy-1-carboxyethyl]-4-(methoxycarbonyl)-3-(4-biphenylyl)-1,2-thiazetidine 1,1-Dioxide (4h).** Following method B, 150 mg (0.03 mmol) of the Fmoc-L-serine *tert*-butyl ester immobilized on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker yielded 4.6 mg (33%) of the lyophilized product as a white solid **4h** (a single *trans* diastereomer). ^{1}H NMR δ: 1.19 (s, 9 H), 3.84 (m, 2 H), 3.90 (s, 3 H), 3.94 (t, J = 4.1 Hz, 1 H), 4.92 (d, J = 5.9 Hz, 1 H), 5.16 (d, J = 5.9 Hz, 1 H), 7.40 (m, 1 H), 7.47 (m, 2 H), 7.55−7.65 (m, 6 H). HRMS: calcd for $C_{23}H_{28}NO_7S$ 462.1586, found 462.1584 $(M + H)^+$.

***trans*-2-[(*S*)-2-Cyclohexyl-1-carboxyethyl]-4-(methoxycarbonyl)-3-[3,4-dichlorophenoxy)phenyl]-1,2-thiazetidine 1,1-Dioxide (4i).** Following method B, 150 mg (0.03 mmol) of the Fmoc-L-cyclohexylalanine immoblized on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker yileded 3.3 mg (20% for two diastereomers in a ratio of ca. 1.2:1) of the lyophilized product **4i** as a white solid. Isomers were separated during HPLC purification. ^{1}H NMR (major isomer) δ: 0.75−1.00 (m, 2 H), 1.10−1.80 (m, 9 H), 1.88 (m, 2 H), 3.81 (dd, J = 8.2 and 6.4 Hz, 1 H), 3.91 (s, 3 H), 4.90 (d, J = 5.7 Hz, 1 H), 5.15 (d, J = 5.7 Hz, 1 H), 6.89 (dd, J = 8.8 and 2.7 Hz, 1 H), 7.01 (m, 1 H), 7.10 (d, J = 2.9 Hz, 1 H), 7.23 (m, 1 H), 7.34 (m, 1 H), 7.40−7.45 (m, 2 H). ^{1}H NMR (minor isomer) δ: 0.72−0.94 (m, 2 H), 1.08−1.7 (m, 11 H), 3.91 (s, 3 H), 4.18 (dd, J = 8.6 and 6.8 Hz, 1 H), 4.94 (d, J = 5.8 Hz, 1 H), 5.39 (d, J = 5.8 Hz, 1 H), 6.90 (m, 1 H), 7.01 (m, 1 H), 7.10 (d, J = 2.8 Hz, 1 H), 7.23 (m, 1 H), 7.34 (m, 1 H), 7.38−7.46 (m, 2 H). HRMS: calcd for $C_{25}H_{28}Cl_2NO_7S$ 556.0964, found 556.0963 $(M + H)^+$.

***trans*-2-[1-Carboxyheptyl]-4-(methoxycarbonyl)-3-[(3,4-dichlorophenoxy)phenyl]-1,2-thiazetidine 1,1-Dioxide (4j).** Following method B, 150 mg (0.03 mmol) of the Fmoc-DL-aminocaprylic acid immobilized on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker yielded 3.1 mg (19% for two diastereomers in a ratio of ca. 1.25:1) of the lyophilized product **4j** as a white solid. Isomers were separated during HPLC purification. ^{1}H NMR (major isomer) δ: 0.86 (t, J = 7.2 Hz, 3 H), 1.10−1.53 (m, 8 H), 1.83−2.00 (m, 2 H), 3.80 (dd, J = 7.4 and 5.9 Hz, 1 H), 3.90 (s, 3 H), 4.89 (d, J = 5.7 Hz, 1 H), 5.03 (d, J = 5.7 Hz, 1 H), 6.88 (m, 1 H), 7.02 (m, 1 H), 7.10 (d, J = 2.8 Hz, 1 H), 7.22 (m, 1 H), 7.34 (m, 1 H), 7.38−7.44 (m, 2 H). ^{1}H NMR (minor isomer) δ: 0.85 (t, J = 7.2 Hz, 3 H), 1.07−1.37 (m, 8 H), 1.56 (m, 1 H), 1.73 (m, 1 H), 3.89 (s, 3 H), 4.04 (dd, J = 7.3 and 7.2 Hz, 1 H), 4.90 (d, J = 5.8 Hz, 1 H), 5.30 (d, J = 5.8 Hz, 1 H), 6.86 (dd, J = 8.8 and 2.7 Hz, 1 H), 7.01 (m, 1 H), 7.07 (d, J = 2.8 Hz, 1 H), 7.26 (m, 1 H), 7.35−7.43 (m, 3 H). HRMS: calcd for $C_{24}H_{28}Cl_2NO_7S$ 544.0964, found 544.0964 $(M + H)^+$.

***trans*-2-[(*R*)-3-Methyl-1-carboxybutyl]-4-(methoxycarbonyl)-3-[(3,4-dichlorophenoxy)phenyl]-1,2-thiazetidine 1,1-Dioxide (4k).** Following method B, 150 mg (0.03 mmol) of the Fmoc-D-leucine immobilized on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker yielded 3.1 mg (20% for two diastereomers in a ratio of ca. 1:1) of the lyophilized product **4k** as a white solid. Isomers were separated during HPLC purification. ^{1}H NMR (major isomer) δ: 0.83 (d, J = 6.2 Hz, 3 H), 0.98 (d, J = 6.2 Hz, 3 H), 1.80−2.00 (m, 2 H), 3.78 (m, 1 H), 3.90 (s, 3 H), 4.90 (d, J = 5.8 Hz, 1 H), 5.16 (d, J = 5.8 Hz, 1 H), 6.89 (m, 1 H), 7.03 (m, 1 H), 7.10 (d, J = 2.9 Hz, 1 H), 7.23 (m, 1 H), 7.38 (m, 1 H), 7.40−7.47 (m, 2 H). ^{1}H NMR (minor isomer) δ: 0.72 (d, J = 6.2 Hz, 3 H), 0.99 (d, J = 6.2 Hz, 3 H), 1.38−1.60 (m, 2 H), 3.89 (s, 3 H), 4.12 (m, 1 H), 4.92 (d, J = 5.9 Hz, 1 H), 5.35 (d, J = 5.9 Hz, 1 H), 6.86 (dd, J = 8.8 and 2.7 Hz, 1 H), 7.00 (m, 1 H), 7.07 (d, J = 2.7 Hz, 1 H), 7.26 (m, 1 H), 7.35−7.43 (m, 3 H). HRMS: calcd for $C_{22}H_{24}Cl_2NO_7S$ 516.0651, found 516.0658 $(M + H)^+$.

***trans*-2-[(*S*)-2-Cyclohexyl-2-carboxyethyl]-4-(butoxycarbonyl)-3-[(3,4-dichlorophenoxy)phenyl]-1,2-thiazetidine 1,1-Dioxide (4l).** Following method B, 150 mg (0.03 mmol) of the Fmoc-L-cyclohexylalanine immobilized on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker yielded 3.6 mg (20% for two diastereomers in a ratio of ca. 1.2:1) of the lyophilized product **4l** as a white solid. Isomers were separated during HPLC purification. ^{1}H NMR (major isomer) δ: 0.65−1.00 (m, 2 H), 0.94 (t, J = 7.4 Hz, 3 H), 1.10−1.95 (m, 15 H), 3.70 (m, 1 H), 4.26 (m, 1 H), 4.31 (m, 1 H), 4.87 (d, J = 5.6 Hz, 1 H), 5.12 (d, J = 5.6 Hz, 1 H), 6.87 (dd, J = 8.8 and 2.8 Hz, 1 H), 7.00 (m, 1 H), 7.09 (d, J = 2.8 Hz, 1 H), 7.23 (m, J = 2.0 and 1.9 Hz, 1 H), 7.30−7.44 (m, 3 H). ^{1}H NMR (minor isomer) δ: 0.70−1.00 (m, 2 H), 0.94 (t, J = 7.4 Hz, 3 H), 1.05−1.75 (m, 15 H), 4.24 (dd, J = 7.7 and 7.3 Hz, 1 H), 4.25 (m, 1 H), 4.32 (m, 1 H), 4.90 (d, J = 5.8 Hz, 1 H), 5.34 (d, J = 5.8 Hz, 1 H), 6.86 (dd, J = 8.8 and 2.8 Hz, 1 H), 6.99 (m, 1 H), 7.07 (d, J = 2.8 Hz, 1 H), 7.26 (m, 1 H), 7.35−7.43 (m, 3 H). HRMS: calcd for $C_{28}H_{34}Cl_2NNO_7S$ 598.1433, found 598.1434 $(M + H)^+$.

***trans*-2-[(*S*)-2-(*tert*-Butoxycarbonyl)-1-carboxyethyl]-4-(methoxycarbonyl)-3-(4-biphenylyl)-1,2-thiazetidine 1,1-Dioxide (4m).** Following method B, 150 mg (0.03 mmol) of the Fmoc-L-aspartic acid *β*-*tert*-butyl ester immobilized on TentaGel resin functionalized with α-methyl-6-nitroveratryl

alcohol photolinker yielded 2.8 mg (19%) of the lyophilized product **4m** as a white solid (a 2.15:1 mixture of two *trans* diastereomers). ^{1}H NMR (major isomer) δ: 1.42 (s, 9 H), 2.80 (m, 2 H), 3.89 (s, 3 H), 4.44 (m, 1 H), 4.92 (d, J = 5.9 Hz, 1 H), 5.21 (d, J = 5.9 Hz, 1 H), 7.38 (m, 1 H), 7.47 (m, 2 H), 7.55−7.65 (m, 6 H). ^{1}H NMR (minor isomer) δ: 1.44 (s, 9 H), 2.96 (m, 2 H), 3.89 (s, 3 H), 4.23 (m, 1 H), 4.91 (d, J = 6.0 Hz, 1 H), 5.23 (d, J = 6.0 Hz, 1 H), 7.38 (m, 1 H), 7.47 (m, 2 H), 7.55−7.65 (m, 6 H). HRMS: calcd for $C_{24}H_{28}NO_8S$ 490.1535, found 490.1525 $(M + H)^+$.

(9-Fluorenyl)methyl (Chlorosulfonyl)acetate. (9-Fluorenyl)methyl alcohol (3.15 g, 16.1 mmol) in CH_2Cl_2 (55 mL) was added dropwise with stirring to (chlorosulfonyl)acetyl chloride (2.85 g, 16.1 mmol) in CH_2Cl_2 (30 mL) at −20 °C. The mixture was allowed to warm to rt over ca. 3 h and stirred at rt for another 2 h. Solvent was evaporated in vacuo. The resulting crude product was dissolved in CH_2Cl_2 (ca. 70 mL) and hexane (ca. 20 mL), and the solution was stirred with charcoal (3.0 g) for 1.5 h. Supernatant was filtered off and evaporated in vacuo to afford 4.00 g (74%) of the product as yellowish crystals, mp 78−80 °C. ^{1}H NMR δ: 4.27 (t, J = 6.5 Hz, 1 H), 4.60 (s, 2 H), 4.63 (d, J = 6.5 Hz), 7.34 (m, 2 H), 7.43 (m, 2 H), 7.62 (d, J = 7.5 Hz, 2 H), 7.77 (d, J = 7.5 Hz, 2 H). ^{13}C NMR δ: 46.9, 67.4, 69.4, 120.6, 125.3, 127.7, 128.5, 141.8, 143.2, 160.4.

Sasrin resin ester of [3-^{13}C]-*trans*-2-[(*S*)-1-Carboxyethyl]-4-[(9-fluorenyl)methoxycarbonyl]-3-phenyl-1,2-thiazetidine 1,1-Dioxide (4n) (intermediate 3: R_1 = Me; R_2 = Ph; R_3 = FmO; C-3 = ^{13}C) was prepared as described above (method A) from Fmoc-L-alanine immobilized on Sasrin resin (100 mg, 0.06 mmol) [1-^{13}C]benzaldehyde (107 mg, 1.0 mmol) with (9-fluorenyl)methyl (chlorosulfonyl)acetate (289 mg, 0.86 mmol). Fast gel-phase ^{13}C NMR (C_6D_6) δ: 53.4 (3-C).

[3-^{13}C]-*trans*-2-[(*S*)-1-Carboxyethyl]-4-[(9-fluorenyl)-methoxycarbonyl]-3-phenyl-1,2-thiazetidine 1,1-Dioxide (4n). Following method A, 100 mg (0.06 mmol) of the Fmoc-L-alanine immobilized on Sasrin resin yielded 22.9 mg (80%) of the lyophilized product **4n** as a white solid (a 2.3:1 mixture of two *trans* diastereomers inseparable by HPLC). ^{1}H NMR (notes *major* and *minor* refer to resonances of the major and minor diastereomers, respectively; the note is absent when signals of both isomers overlap) δ: 1.39 (d, J = 7.2 Hz, 3 H, *major*), 1.50 (d, J = 7.3 Hz, 3 H, *minor*), 3.92 (m, 1 H, *minor*), 4.11 (m, 1 H, *major*), 4.26−4.31 (m, 1 H), 4.43−4.52 (m, 1 H), 4.67−4.75 (m, 1 H), 4.89 (d, J = 155.6 and 5.9 Hz, 1 H, *minor*), 4.91−4.97 (m, 1 H), 5.09 (dd, J = 154.8 and 5.9 Hz, 1 H, *major*), 7.22−7.50 (m, 9 H), 7.55−7.67 (m, 2 H), 7.77 (d, J = 7.7 Hz, 2 H). Fast ^{13}C NMR δ: 52.5 (3-C, *major*), 53.0 (3-C, *minor*). HRMS: calcd for $C_{25}{}^{13}CH_{23}NO_6S$ 478.1280, found 478.1280 (M^+).

Sasrin resin ester of [3-^{13}C]-*trans*-2-[(*S*)-1-Carboxyethyl]-4-carboxy-3-phenyl-1,2-thiazetidine 1,1-Dioxide (intermediate 5: R_1 = Me; R_2 = Ph; C-3 = ^{13}C) was prepared by deprotection of the respective 4-Fm-ester resin **3** (100 mg, 0.06 mmol) by gentle shaking with 0.5% 1.8-diazabicyclo[5.4.0]undec-7-ene in dimethylformamide (2 mL) for 2 h at rt. The resulting product was washed liberally with dimethylformamide, MeOH, and CH_2Cl_2 and dried in vacuo. Fast gel-phase ^{13}C NMR (C_6D_6) δ: 55.1 (3-C, minor), 56.1 (3-C, major).

***trans*-2-[(*S*)-2-Cyclohexyl-1-carboxyethyl]-4-carboxy-3-[(3,4-dichlorophenoxy)phenyl]-1,2-thiazetidine 1,1-Dioxide (6).** Following method B, 150 mg (0.03 mmol) of the Fmoc-L-cyclohexylalanine immobilized on TentaGel resin functionalized with α-methyl-6-nitroveratryl alcohol photolinker was converted into the respective tethered β-sultam **3** [R_1 = $C_6H_{11}CH_2$, R_2 = 3-(3,4-$Cl_2C_6H_3O$)C_6H_4, R_3 = FmO]. The latter was deprotected with 0.5% 1.8-diazabicyclo[5.4.0]undec-7-ene in DMF (4 mL) for 2 h, washed liberally with MeOH and CH_2Cl_2, and dried in vacuo. Photocleavage of the resulting resin **5** [R_1 = $C_6H_{11}CH_2$, R_2 = 3-(3,4-$Cl_2C_6H_3O$)C_6H_4] according to method B followed by HPLC purification yielded a total of 4.1 mg (24% for two diastereomers in a ratio of ca. 1.75:1) of the lyophilized product **6** as a white solid. Isomers were separated during HPLC purification. ^{1}H NMR (major isomer) δ: 0.67−0.92 (m, 2 H), 1.01−1.24 (m, 5 H), 1.24−1.49 (m, 2 H), 1.54−1.74 (m, 4 H), 4.24 (dd, J = 9.2 and 5.9 Hz, 1 H), 5.01 (d, J = 5.2 Hz, 1 H), 5.51 (d, J = 5.2 Hz, 1 H), 6.88 (dd, J = 8.8 and 2.8 Hz, 1 H), 7.13 (m, 1 H), 7.09 (d, J = 2.8 Hz, 1 H), 7.29 (m, 1 H), 7.38−7.46 (m, 3 H). ^{1}H NMR (minor isomer) δ: 0.70−1.00 (m, 2 H), 1.03−1.78 (m, 9 H), 1.80−1.97 (m, 2 H, CH_2), 3.71 (m, 1 H), 4.89 (d, J = 4.9 Hz, 1 H), 5.19 (d, J = 4.9 Hz, 1 H), 6.86 (dd, J = 8.7 and 2.7 Hz, 1 H), 6.98 (m, 1 H), 7.08 (d, J = 2.7 Hz, 1 H), 7.24−7.43 (m, 4 H). HRMS: calcd for $C_{24}H_{25}Cl_2NNaO_7S$ 564.0626, found 564.0631 $(M + Na)^+$.

Sasrin Ester of *trans*-2-[(*S*)-1-Carboxyethyl]-4-(phenethylcarbamoyl)-3-phenyl-1,2-thiazetidine 1,1-Dioxide (8) (cf. 3: R_1 = Me; R_2 = Ph; R_3 = Ph(CH$_2$)$_2$NH; C-3 = ^{13}C). An appropriate resin (**3**, R_1 = Me; R_2 = Ph; R_3 = FmO; C-3 = ^{13}C; 100 mg, 0.06 mmol) was agitated with 0.5% 1.8-diazabicyclo[5.4.0]undec-7-ene in DMF (4 mL) for 2 h, washed liberally with MeOH and CH_2Cl_2, and dried. The resulting immobilized 4-carboxy β-sultam **5** (R_1 = Me; R_2 = Ph; C-3 = ^{13}C) was converted into 4-pentafluorophenyl ester by gentle shaking with pentaflurophenyl trifluoroacetate (0.25 mL, 1.45 mmol) and pyridine (0.25 mL) in *N*-methylpyrrolidine-2-one (0.35 mL). The activated ester was filtered and washed with *N*-methylpyrrolidine-2-one (5 × 1 mL). *N*-Methylpyrrolidine-2-one (1.5 mL) and phenethylamine (0.10 mL, 0.80 mmol) were added, and the mixture was agitated by gentle shaking for 1 h. The resulting Sasrin ester of **8** was filtered, washed liberally with dimethylformamide, MeOH, and CH_2Cl_2, and dried in vacuo. Fast gel-phase ^{13}C NMR (C_6D_6) δ: 53.1 (3-C).

***trans*-2-[(*S*)-1-Carboxyethyl]-4-(phenethylcarbamoyl)-3-phenyl-1,2-thiazetidine 1,1-Dioxide (8).** Following the general procedure, acidic cleavage of the corresponding Sasrin ester of **8** (100 mg, ca. 0.06 mmol) followed by HPLC purification yielded 9.0 mg (37%) of the lyophilized product as a white solid (a mixture of two *trans* diastereomers in a ratio of 1.4:1). ^{1}H NMR (10% CD_3OD in $CDCl_3$, major isomer) δ: 1.34 (d, J = 7.2 Hz, 3 H), 2.81 (t, J = 7.3 Hz, 2H), 3.40−3.50 (m, 1 H), 3.54−3.60 (m, 1 H), 4.02 (m, 1 H), 4.65 (m, 1 H), 5.11 (dd, J = 154.7 and 5.6 Hz, 1 H), 7.13−7.47 (m, 8 H), 7.43−7.50 (m, 2 H). ^{1}H NMR (10% CD_3OD in $CDCl_3$, minor isomer) δ: 1.39 (d, J = 7.3 Hz, 3 H), 2.81 (t, J = 7.3 Hz, 2H), 3.40−3.50 (m, 1 H), 3.54−3.60 (m, 1 H), 3.90 (m, 1 H), 4.65 (m, 1 H), 4.90 (dd, J = 154.0 and 5.7 Hz, 1 H), 7.13−7.47 (m, 8 H), 7.43−7.50 (m, 2 H). Fast ^{13}C NMR (10% CD_3OD in $CDCl_3$, major isomer) δ: 52.2 (3-C). Fast ^{13}C NMR (10% CD_3OD in $CDCl_3$, minor isomer) δ: 53.0 (3-C). HRMS: calcd for $C_{19}{}^{13}CH_{23}N_2O_5S$ 404.1361, found 404.1364 $(M + H)^+$.

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