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CRYSTAL STRUCTURE ANALYSIS AND REACTIVITY OF *N*-ALKYL- AND *N*-ACYLDIOXATHIAZINANES

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*Dedicated to Professor Ryoji Noyori, a tremendous mentor and pioneering spirit, on the occasion of his 70th birthday.

Abstract – Cyclic sulfamidates have served as reactive electrophiles for the synthesis of various products, including alkaloids, substituted amines, amino acids and lactams. *N*-Acyl dioxathiazinanes exhibit enhanced reactivity relative to their unsubstituted and *N*-alkyl counterparts, and were previously suggested to be more reactive due to carbamoylation of the –NH moiety generating an electron withdrawing effect. Probing this enhanced reactivity by the synthesis and structural analysis of *N*-Boc- and *N*-PhF-dioxathiazinanes using NMR spectroscopy, X-ray diffraction, and DFT calculations, we now describe a unique, reactive twisted conformation in *N*-acyl dioxathiazinanes.

INTRODUCTION

Cyclic sulfamidates[1] have served as reactive electrophiles for the synthesis of various products, including alkaloids,[2] substituted amines,[3] amino acids and lactams.[4-7] *N*-Acyl dioxathiazinanes exhibit enhanced reactivity relative to their unsubstituted and *N*-alkyl counterparts. For example, *N*-Cbz-dioxathiazinanes[8] were suggested to be more reactive due to carbamoylation of the amine moiety generating an electron withdrawing effect.[9] Greater reactivity was similarly observed for *N*-Fmoc-dioxathiazinanes relative to *N*-PhF-dioxathiazinanes [PhF = 9-(9-phenylfluorenyl)] in the synthesis of GHRP-6 analogues.[10] We have probed this enhanced reactivity by the synthesis and structural analysis of *N*-Boc- and *N*-PhF-dioxathiazinanes **1** and **2** (Figure 1) using NMR spectroscopy, X-ray diffraction, and DFT calculations.

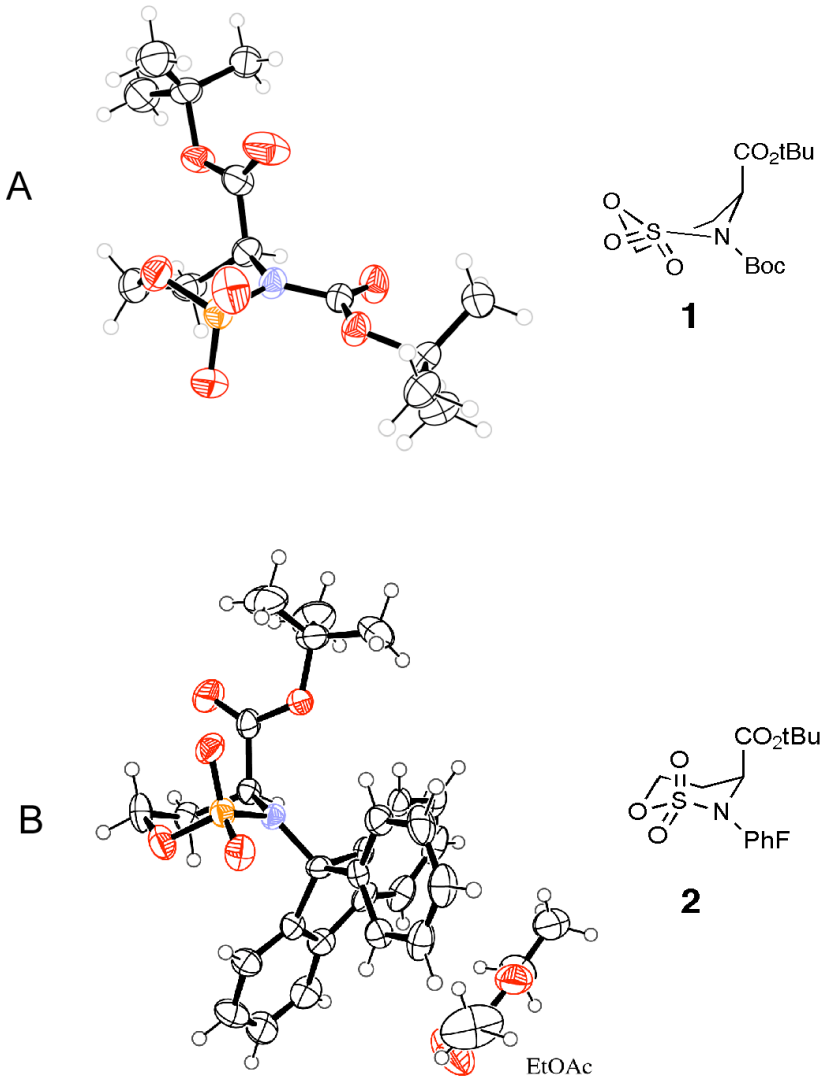
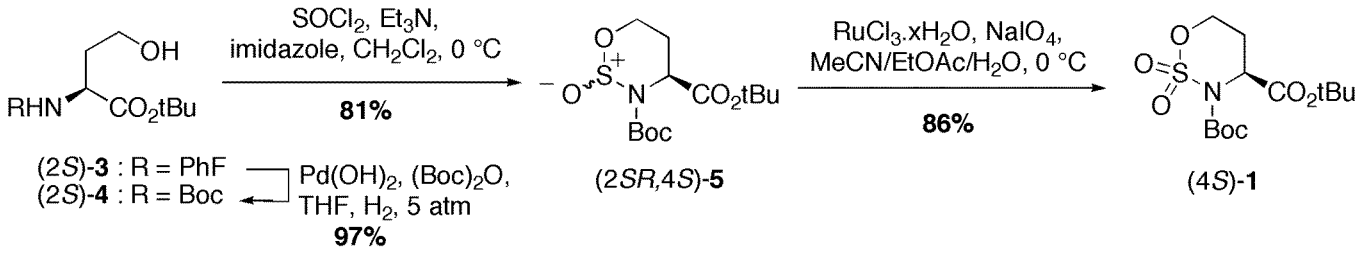


Figure 1. ORTEP images of crystal structures of (A) *N*-Boc-dioxathiazinane **1** and (B) *N*-PhF-dioxathiazinane **2**.

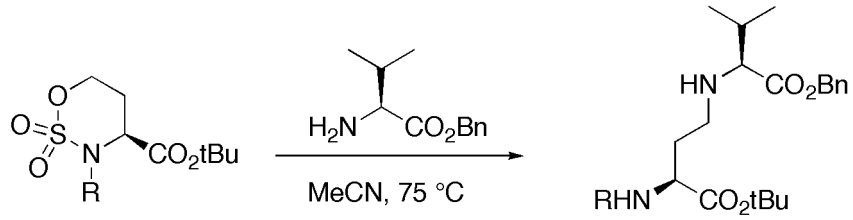
RESULTS AND DISCUSSION

N-PhF-dioxathiazinane **2** was prepared as previously described by treatment of (2*S*)-*tert*-butyl 2-[*N*-PhF-amino]-4-hydroxybutanoate (**3**) with thionyl chloride, triethylamine, and imidazole in dichloromethane to furnish a 4:1 mixture of 2*R*:2*S*-sulfamidite diastereomers, which was oxidized with catalytic ruthenium trichloride and sodium periodate in acetonitrile and water at 0 °C to afford sulfamidate **2**.[5b] *N*-Boc-Dioxathiazinane **1** was similarly synthesized starting by hydrogenation of *N*-PhF-homoserine **3** in the presence of $(Boc)_2O$ in THF using $Pd(OH)_2$ as catalyst to provide the corresponding *N*-Boc-homoserine **4**.[7,10] Sulfamidate **1** was then prepared in the same way as **2** by treatment with thionyl chloride to furnish the corresponding sulfamidite **5** as a mixture of diastereomers, that was oxidized with ruthenium trichloride (Scheme 1).



Scheme 1.

Ring opening of *N*-Boc- and *N*-PhF-dioxathiazinanes **1** and **2**[11] with valine benzyl ester in acetonitrile at 75°C (Scheme 2) demonstrated the superior reactivity of *N*-acyldioxathiazinane **1** which was converted completely to the *N*-alkyl valine adduct **6** after 3 h in 95 % isolated yield.



(4*S*)-**1** : R = Boc
(4*S*)-**2** : R = PhF

(2*S*,3'*S*)-**6** : R = Boc
(2*S*,3'*S*)-**7** : R = PhF

Scheme 2.

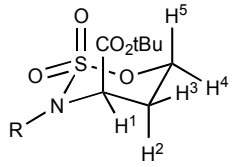
After 28 h, *N*-PhF-dioxathiazinane **2** provided 72% isolated yield of the corresponding secondary amine under the same conditions (Table 1). Repeating the reaction in chloroform as a less polar solvent doubled the time of reaction for **1** and dramatically slowed the reaction of **2**.

Table 1. Reactivity of **1** and **2** with Val-OBn at 75°C.

Compound	Solvent	% conv. / % yield	Time (h)
1	MeCN	99 / 95	3
1	$CHCl_3$	99 / 60	5
2	MeCN	99 / 72	28
2	$CHCl_3$	20 / 20	73

A chairlike conformation was shown to be, respectively, not adopted and adopted by *N*-Boc- and *N*-PhF-dioxathiazines **1** and **2** in their NMR spectra in $CDCl_3$ and CD_3CN. Dihedral angles were calculated for each ring proton employing the Karplus equation[12] and were close to a twisted boat conformation for **1** in $CDCl_3$ (Table 2), yet unresolved in CD_3CN due to coalescence of the signals for H4 and H5. In both solvents, a chair-like conformation was observed for *N*-PhF-dioxathiazinane **2,** similar to that previously observed for related *N*-PhF-pipecolate esters.[5b, 13]

Table 2. Comparison of dihedral angles of **1** and **2** as calculated from observed NMR coupling constants and observed in their respective X-ray structures.



Dihedral	NMR ($CDCl_3$) **1**	NMR (CD_3CN) **1**	X-ray **1**	NMR ($CDCl_3$) **2**	NMR (CD_3CN) **2**	X-ray **2**
H^1-H^2	(J = 2.7) ± 54°	(J = 3.1) ± 51°	57.7°	(J = 5.5) ± 34°	(J = 5.6) ± 34°	48.7°
H^1-H^3	(J = 5.5) ± 34°	(J = 5.5) ± 34°	-60.7°	± 90°	(J = 1.6) ± 62°	-68.9°
H^2-H^4	(J = 5.4) ± 35°	—	-22.4°	(J = 5.5) ± 34°	(J = 5.5) ± 34°	-55.8°
H^2-H^5	(J = 2.8) ± 125°	—	-140.5°	(J = 13.4) ± 180°	(J = 13.3) ± 180°	-174.8°
H^3-H^4	(J = 10.5)	—	96.2°	± 90°	(J = 1.5) ± 62°	61.8°
H^3-H^5	(J = 6.8) ± 24°	—	-22.0°	(J = 2.0) ± 59°	(J = 2.3) ± 57°	-57.2°

Orthorhombic crystals of *N*-Boc- and *N*-PhF-dioxathiazinanes **1** and **2** were grown from mixtures of EtOAc and hexane, and were analyzed by X-ray diffraction.[14, 15] The resulting crystal structures represent the first examples of 6-membered cyclic sulfamidates bearing a nitrogen ring substituent.[16] In the crystals of **1** and **2** (Figure 1), twisted boat and chair conformations were observed, respectively, having dihedral angles in close agreement to values calculated using coupling constants measured by NMR spectroscopy in chloroform (Table 2). The X-ray structure of **1** had similarities with twisted boat conformations previously observed in crystal structures of an *N*-acyl thiazine[17] and an *N*-acyl piperidine.[18] A theoretical study was carried out to evaluate the differences in stability between the chair and twisted boat conformations for **1** and **2.** Optimized chair and twisted boat geometries were calculated for both **1** and **2** in Gaussian 98[19] using hybrid density functional theory (B3LYP)[20] and the 6-311G(d,p) basis set. Solvated (IPCM)[21] single point energy calculations in chloroform (ε=4.9), acetonitrile (ε=36.64) and water (ε=78.39) were also performed on all four optimized geometries, as well as frequency calculations on both conformations of **1**. For *N*-Boc-dioxathiazinane **1** in vacuum, the optimized chair conformer was 0.2 kcal/mol more stable than the twisted boat conformer found in the crystal structure (Table 3). This relationship was reversed in solvated calculations, with the observed twisted boat conformation found to be 2.17, 2.97, and 3.09 kcal/mol more stable than the chair conformer in chloroform, acetonitrile, and water, respectively.

Table 3. DFT Calculated Energies:

molecule	Conformer	SCF (unsolv) *hartrees*	ΔSCF *hartrees*	ΔSCF *kcal/mol*†
1	twisted boat	-1489.03532030		
1	chair	-1489.03565708	-0.00036780	-0.211332
2	twisted boat	-1874.52063835		
2	chair	-1874.53288117	-0.01224282	-7.682486

molecule	Conformer	Solvent (IPCM)	$SCRF_{solv}$ *hartrees*	ΔSCF-$SCRF_{solv}$ *hartrees*	ΔSCF-$SCRF_{solv}$ *kcal/mol*†
1	twisted boat	$CHCl_3$	-1489.05679549	-0.02147519	-13.47589
1	twisted boat	CH_3CN	-1489.06597644	-0.03065614	-19.23702
1	twisted boat	H_2O	-1489.06697872	-0.03165842	-19.86595
1	chair	$CHCl_3$	-1489.05333035	-0.01801005	-11.30148
1	chair	CH_3CN	-1489.06124854	-0.02592824	-16.27022
1	chair	H_2O	-1489.06205914	-0.02640206	-16.56754
2	twisted boat	$CHCl_3$	-1874.53758226	-0.01694931	-10.63585
2	twisted boat	CH_3CN	-1874.54731243	-0.02667408	-16.73823
2	twisted boat	H_2O	-1874.54825477	-0.02761642	-17.32956
2	chair	$CHCl_3$	-1874.54287438	-0.00999321	-6.270834
2	chair	CH_3CN	-1874.54846169	-0.01558052	-9.776924
2	chair	H_2O	-1874.54906819	-0.01618702	-10.15750

molecule	Comparison	Solvent (IPCM)	Δ$SCRF_{solv}$ *hartrees*	Δ$SCRF_{solv}$ *kcal/mol*†
1	twisted boat over chair	$CHCl_3$	-0.00346514	-2.17441
1	twisted boat over chair	CH_3CN	-0.00472790	-2.96680
1	twisted boat over chair	H_2O	-0.00491958	-3.08708
2	chair over twisted boat	$CHCl_3$	-0.00549212	-3.44636
2	chair over twisted boat	CH_3CN	-0.00114926	-0.72117
2	chair over twisted boat	H_2O	-0.00081342	-0.51042

† Using the conversion that 1 hartree = 627.5095 kcal/mol.

Neglible differences were observed between thermodynamic free energies (Table 4) determined from frequency calculations between the twisted boat and chair conformers for **1**, suggesting that a difference in solvation is the primary factor favoring the less stable twisted boat conformation. For *N*-PhF-dioxathiazinane **2** in vacuum, the chair conformer was respectively 7.68 kcal/mol more stable than the corresponding twisted boat conformer. As was observed with **1**, the twisted boat conformer of **2** was preferentially stabilized by solvation over the chair conformer; however, the chair conformer of **2** was still 0.72 kcal/mol more stable than the twisted boat conformer in acetonitrile.

Table 4. Thermodynamic Properties from Frequency Calculations:

molecule	Conformation	SCF *hartrees*	E (Thermal) *kcal/mol*	CV *cal/mol•K*	S (vibr.) *cal/mol•K*	S (total) *cal/mol•K*
1	twisted boat	-1489.03532030	246.079	91.038	90.315	168.281
1	chair	-1489.03565708	246.062	90.886	87.758	165.658

The first crystal structures of *N*-substituted dioxathiazinanes, along with solution NMR data and DFT calculations, provide potential insights into the significant enhancement of reactivity previously observed for *N*-acyl substituted dioxathiazinanes. Rate enhancement of nucleophilic displacements in polar aprotic solvents has been typically attributed to reduced solvation of the nucleophile and improved solvation of the transition state;[22] however, this does not completely explain the greater reactivity of the *N*-acyl sulfamidate. Although a simple inductive electron withdrawing effect of the *N*-substituent may explain the enhanced reactivity of *N*-acyl dioxathiazinanes, the increased reactivity of *N*-acyl over *N*-alkyl substituted dioxathiazinanes may also arise from a preference for the twisted boat conformation. The origin of this preference could be caused by a difference in the energy of solvation of the more polar Boc group, or a partial change in hybridization of the N atom, and subsequent flattening of the ring resulting from an *N*-acyl substituent. The ground state crystal structures may not reflect the transition states during the attack of the nucleophile; however, the concept that the twisted boat conformation may serve as a more reactive transition state relative to the chair conformation is intriguing. In such a case, solvation stabilization and a lower energy of activation of the twisted boat conformer may account for the increased reactivity of *N*-acyl dioxathiazinanes to nucleophilic ring opening. In light of the increasing application of cyclic sulfamidates in organic synthesis,[1] the present study may prove useful for guiding the effective employment of these interesting electrophiles.

EXPERIMENTAL

Unless otherwise noted, all reactions were run under nitrogen atmosphere and distilled solvents were transferred by syringe. Triethylamine (Et_3N) and DIEA were distilled first from ninhydrin then from CaH_2. Dichloromethane (CH_2Cl_2), MeCN, DMF, Et_2O and THF, were all obtained from a Solvent Filtration System (GlassContour™). Final reaction mixture solutions were dried over Na_2SO_4. Chromatography was on 230-400 mesh silica gel; TLC on aluminum-backed silica plates. Melting points are uncorrected. Specific rotations are reported as follows: $[\alpha]^{25}_D$, concentration (*c* in g/100 mL), and solvent. Mass spectral data, HRMS (ESI and FAB), were obtained by the Université de Montréal Mass Spectrometry Facility. ^{1}H NMR (300/400 MHz) and ^{13}C NMR (75/100 MHz) spectra were recorded in $CDCl_3$ or CD_3CN. Chemical shifts are reported in ppm (units) downfield from internal tetramethylsilane ($(CH_3)_4Si$), residual $CHCl_3$ (δ 7.27 and 77.2), residual MeOH (δ 3.31 and 49.0) or residual DMSO (δ 2.50 and 39.5).

Coupling constants are given in Hz. Chemical shifts for aromatic carbons are not reported for compounds possessing PhF groups.

(2*S*)-*tert*-Butyl 2-[*N*-Boc-amino]-4-hydroxybutanoate (**4**):

A stirred solution of (2*S*)-*tert*-butyl 2-[*N*-PhF-amino]-4-hydroxybutanoate **3** (2.33 g, 5.6 mmol prepared according to ref. 23) and $(Boc)_2O$ (1.96 g, 9.0 mmol) in THF (20 mL) was placed into a hydrogenation vessel and treated with $Pd(OH)_2$ (678 mg). The vessel was filled, vented and filled three times with hydrogen and the mixture was stirred under 5 atm of hydrogen for 48 h. The catalyst was filtered on Celite™, washed with THF (3 x 10 mL) and MeOH (3 × 10 mL) and the filtrate and washings were combined, dried, filtered and evaporated to a residue that was purified by chromatography on silica gel with 30% EtOAc in hexanes as eluant. Evaporation of the collecting fractions gave (2*S*)-*tert*-butyl-2-[*N*-Boc-amino]-4-hydroxybutanoate **4** (1.5 g, 97%) as an oil. Characterization matched previous reports in the literature. [24-26]

(2*R*,4*S*)- and (2*S*,4*S*)-*t*-Butyl 2-Oxo-3-Boc-1,2,3-oxathiazinane-4-carboxylate (**5**):

A solution of (2*S*)-*tert*-butyl 2-[*N*-Boc-amino]-4-hydroxybutanoate **4** (904.1 mg, 3.28 mmol) in 74 mL of CH_2Cl_2 was cooled to 0°C, treated with imidazole (1.35 g, 19.7 mmol) followed by triethylamine (0.92 mL, 6.57 mmol), stirred for 10 min, treated with thionyl chloride (0.264 mL, 3.61 mmol), and stirred for 2 h, when complete consumption of starting material (R_f = 0.34 in 30% EtOAc in hexanes) was observed by TLC. The solution was diluted with 40 mL of water. The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fraction was washed with water (2 × 20 mL), dried, filtered and evaporated to a residue that was purified by chromatography on silica gel with 10% EtOAc in hexanes as eluant to provide 855.7 mg (81%) of a mixture of (2*R*,4*S*)- and (2*S*,4*S*)-sulfamidites (2*R*,4*S*)- and (2*S*,4*S*)-**5** as a white solid: first to elute (104.3 mg); R_f = 0.18 (10% EtOAc / hexanes); mp 64.6-65.4 °C; $[\alpha]^{25}_D$ +63.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.45 (s, 9H), 1.50 (s, 9H), 2.18 (m, 1H), 2.36 (d, 1H, *J* = 13.4), 3.83 (dd, 1H, *J* = 2.6, 11.6), 4.68 (br s, 1H), 4.82 (t, 1H, *J* = 11.6); ^{13}C NMR δ 23.7, 27.6, 27.9, 48.9, 54.6, 82.4, 83.4 151.6, 168.6; HRMS calcd for $C_{13}H_{23}NO_6NaS$ $(M + Na)^+$ 344.1138, found 344.1141; second to elute (751.4 mg) R_f = 0.23 (10% EtOAc / Hexanes); mp 88-89 ºC; $[\alpha]^{25}_D$ −50.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.45 (s, 9H), 1.50 (s, 9H), 2.60 (m, 2H), 4.03 (dt, 1H, *J* = 8.5, 10.8), 4.51 (m, 1H), 4.61 (br s, 1H); ^{13}C NMR δ 24.7, 27.7, 27.9, 51.5, 56.5, 82.4, 83.5, 151.1, 168.8; HRMS calcd for $C_{13}H_{23}NO_6NaS$ $(M + Na)^+$ 344.1138, found 344.1137.

(4*S*)-*t*-Butyl 2,2-Dioxo-3-Boc-1,2,3-oxathiazinane-4-carboxylate ((4*S*)-**1**) :

A mixed solution of (2*R*,4*S*)- and (2*S*,4*S*)-sulfamidites **5** (711.7 mg, 2.21 mmol) in 61 mL of MeCN and 7

mL of EtOAc was cooled to 0°C and treated with ruthenium (III) chloride monohydrate (7.4 mg, 0.035 mmol) followed by sodium periodate (920 mg, 4.3 mmol). After stirring for 15 min, the reaction mixture was treated with 70 mL of water, stirred for an additional 5 h at 0°C and diluted with 100 mL of Et_2O. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (2 × 15 mL) and brine (15 mL), dried, filtered and evaporated to a residue that was purified by chromatography on silica gel with 30% EtOAc in hexanes as eluant to provide 640.4 mg (86%) of *N*-Boc-sulfamidate (4*S*)-**1** as a white solid : R_f = 0.45 (30% EtOAc / Hexanes); mp 128-129 °C; $[\alpha]^{25}_D$ –43.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.54 (s, 9H), 2.36 (dddd, 1H, *J* = 5.5, 6.8, 10.5, 14.2), 2.59 (ddt, 1H, *J* = 2.8, 5.4, 14.2), 4.60 (ddd, 1H, *J* = 2.8, 6.9, 11.1), 4.68 (dt, 1H, *J* = 5.4, 11.1), 5.05 (dd, 1H, *J* = 2.6, 5.5); ^{1}H NMR (CD_3CN) δ 1.49 (s, 9H), 1.53 (s, 9H), 2.43 (dddd, 1H, *J* = 5.6, 7.3, 9.8, 20.3), 2.55 (ddt, 1H, *J* = 3.4, 5.1, 14.7), 4.66 (multiplet, 2H), 5.08 (dd, 1H, *J* = 2.87, 5.5); ^{13}C NMR ($CDCl_3$) δ 24.3, 27.5, 27.8, 57.3, 70.3, 83.4, 85.1, 150.2, 167.3; HRMS calcd for $C_{13}H_{23}NO_7NaS$ $(M + Na)^+$ 360.1087, found 360.1083.

(4*S*)-*t*-Butyl 2,2-Dioxo-3-PhF-1,2,3-oxathiazinane-4-carboxylate ((4*S*)-**2**) : prepared according to literature procedures [5b].

^{1}H NMR ($CDCl_3$) δ 1.11 (ddt, 1H, *J* = 5.5, 13.4, 14.4), 1.68 (s, 9H), 1.75 (dd, 1H, *J* = 1.6, 14.4), 3.87 (d, 1H, *J* = 5.4), 4.16 (dd, 1H, *J* = 5.4, 11.4), 4.89 (ddd, 1H, *J* = 2.4, 11.3, 13.5), 7.20-8.11 (m, 13H); ^{1}H NMR (CD_3CN) δ 1.04 (dd, 1H, *J* = 5.6, 13.1, 14.4), 1.82 (s, 9H), 1.71 (ddt, 1H, *J* = 1.78, 2.2, 14.4), 3.94 (dt, 1H, *J* = 1.44, 5.56), 4.21 (ddt, 1H, *J* = 1.3, 5.4, 11.35), 4.77 (ddd, 1H, *J* = 2.43, 11.45, 13.4), 7.23-8.12 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 22.4, 28.0, 58.3, 70.7, 78.6, 82.6, 168.3.

(2*S*, 3'*S*)-Benzyl *N*-[3'-*t*-Butyloxycarbonyl-3'-[*N*-Boc-amino]propyl]valinate (**6**) :

The *p*-toluenesulfonic acid salt of valine benzyl ester was dissolved in water, saturated with K_2CO_3 and extracted several times with $CHCl_3$. The combined organic phases were dried, filtered and evaporated to afford the free amine which was employed in the ring opening step without further purification. A solution of sulfamidate (4*S*)-**1** (50 mg, 0.148 mmol) in MeCN (1.14 mL) was treated with valine benzyl ester (92.1 mg, 0.445 mmol), heated at 75°C for 3 h, until complete consumption of starting material (R_f = 0.42 in 20% EtOAc in hexanes) was observed by TLC, cooled to rt, poured into 1M KH_2PO_4 (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (2 × 10 mL), dried, filtered and evaporated to a residue that was chromatographed on silica gel with 30% EtOAc in hexanes as eluant to afford 65.3 mg (95%) of (2*S*,3'*S*)-**6** as a thick clear oil : R_f = 0.31 (20% EtOAc in hexanes); ^{1}H NMR δ 0.92 (d, 6H, *J* = 7.3), 1.42 (s, 9H), 1.44 (s, 9H), 1.71 (m, 2H), 1.90 (m, 2H), 2.43 (quin, 1H, *J* = 6.1), 2.78 (quin, 1H, *J* = 6.3), 3.01 (d, 1H, *J* = 6.1), 4.20 (m, 1H), 5.14 (s, 2H), 5.85 (d, 1H,

J = 7.2), 7.34 (m, 5H); ^{13}C NMR δ 18.2, 19.1, 27.7, 27.9, 31.2, 44.5, 52.9, 66.1, 66.8, 79.1, 81.2, 128.0, 128.2, 135.4, 155.2, 171.6, 174.5; HRMS calcd for $C_{25}H_{41}N_2O_6$ (M+H) 465.2960, found 465.2963.

(2*S*, 3'*S*)-Benzyl *N*-[3'-*t*-Butyloxycarbonyl-3'-[*N*-PhF-amino]propyl]valinate (**7**) :
In a similar manner, a solution of (4*S*)-*t*-butyl 2,2-dioxo-3-PhF-1,2,3-oxathiazinane-4-carboxylate((4*S*)-**2**) (50 mg, 0.105 mmol) in MeCN (0.8 mL) was treated with valine benzyl ester (65 mg, 0.314 mmol), heated at 75 °C for 28 h, until complete consumption of starting material (R_f = 0.67 in 30% EtOAc in hexanes) was observed by TLC. Purification of the residue with 10% EtOAc in $CHCl_3$ as eluant provided 45.6 mg (72%) of (2*S*,3'*S*)-**7** as a thick clear oil: R_f = 0.64 (10% EtOAc in $CHCl_3$); ^{1}H NMR δ 0.84 (d, 3H, *J* = 3.6), 0.86 (d, 3H, *J* = 3.6), 1.19 (s, 9H), 1.54 (m, 2H), 1.88 (m, 1H), 2.55 (m, 1H), 2.66 (m, 2H), 2.98 (d, 1H, *J* = 5.7), 5.18 (d, 2H, *J* = 1.5), 7.31 (m, 18H), 7.68 (t, 2H, *J* = 6.9); ^{13}C NMR δ 18.3, 18.8, 27.5, 31.2, 44.4, 53.8, 65.9, 66.7, 72.7, 80.1, 175.1; HRMS calcd for $C_{39}H_{45}N_2O_4$ (MH^+) 605.3374, found 605.376.

DFT Calculations
DFT calculations were carried out using the multiprocessor version of Gaussian 98 (revision A.9) [19] on a cluster of personal computers running the Linux operating system (kernel 2.4.18). The X-ray structures of both **1** and **2** were used as the initial input structures. Models were built in Gaussview in the twisted boat or chair configurations, with either the *N*-Boc or *N*-PhF protecting groups. Geometry optimizations, frequency calculations, and population analysis were all carried out using the B3LYP method [20] with the 6-311G(d,p) basis set. Solvation energies (SCRF) were calculated using the Isodensity Polarized Continuum Model (IPCM) with chloroform (ε=4.9), acetonitrile (ε=36.64) and water (ε=78.39). Images of crystal structures and DFT structures were made using ORTEP-3 for Windows, version 1.08.

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15. The structure of sulfamidate (4*S*)-**2** was resolved using the direct method (SHELXS97) and refined with SHELXL97 : $C_{27}H_{27}NO_5S$ $0.5(C_4H_8O_2)$; M_r = 521.61; orthorhombic; colorless crystal; space group $P2_12_12_1$; lattice parameters: a = 8.8569(4) Å, b = 14.6054(6) Å, c = 20.4276(8) Å, V = 2642.49(19) Å^3 Z = 4; R_1 = 0.073 for I>2 sigma (I), wR_2 = 0.1998 for all data; GOF = 1.015.
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