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N-(9-(9-Phenylfluorenyl))homoserine-Derived Cyclic Sulfamidates: Novel Chiral Educts for the Synthesis of Enantiopure γ-Substituted α-Amino Acids

Mohamed Atfani, Lan Wei, and William D. Lubell*

Département de chimie, Université de Montréal, C. P. 6128, Succursale Centre-ville,
Montréal, Québec, Canada H3C 3J7

lubell@chimie.umontreal.ca

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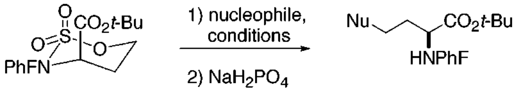
ABSTRACT



nucleophile: NaN_3, RNH_2, RR'NH, $ArNH_2$, KSCN, NaSAr, NaOAr

(4*S*)-*tert*-Butyl 2,2-dioxo-3-PhF-1,2,3-oxathiazainane-4-carboxylate reacted effectively with nitrogen, sulfur, and oxygen nucleophiles to provide enantiopure (>97% ee) γ-substituted α-amino acids.

α-Amino acids possessing remote electrophilic centers have served as important precursors for the synthesis of amino acid analogues and natural products.[1−5] Although a variety of ω-halogeno α-amino propanoates,[2a,b] butanoates,[2b−h] and pentanoates[2h−j] have been effectively synthesized and employed in intermolecular reactions with various nucleophiles, their utility has been compromised by side reactions involving eliminations,[2a] as well as intramolecular attack of amine and α-carbanion groups to form cyclic products.[2f,j] In the case of serine-derived electrophiles, the problem of intramolecular amine alkylation and aziridine formation has been alleviated by the employment of serine-derived cyclic sulfamidates[1,3] and β-lactones,[4] which have served as alanine β-cation equivalents for the synthesis of a variety of amino acid analogues. Employing *N*-(PhF)serine-derived sulfamidate **1**, we observed that weakly basic (conjugate acid $pK_a \leq 7$) nucleophiles reacted in nucleophilic displacements to provide enantiopure (>97% ee) β-substituted alanines; however, enolates of 1,3-dicarbonyl compounds added to sulfamidate **1** by a mechanism featuring β-elimination to provide a dehydroalanine intermediate that underwent subsequent Michael addition and afforded racemized product (PhF = 9-(9-phenylfluorenyl), Figure 1).[1]

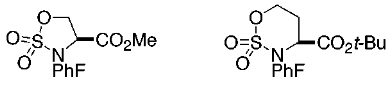


Figure 1. *N*-(PhF)serine and *N*-(PhF)homoserine cyclic sulfamidates **1** and **2**.

Seeking to expand the utility of amino-acid-derived cyclic sulfamidates, we have now investigated the related six-

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[1] (a) Wei, L.; Lubell, W. D. *Org. Lett.* **2000**, *2*, 2595 and refs 9−19 therein. (b) Wei, L.; Lubell, W. D. *Can. J. Chem.* **2001**, *79*, 94 and refs 1−3 therein.

[2] Representative examples include (a) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833. (b) Jackson, R. F. W.; Wishart, N.; Wythes, M. J. *Synlett* **1993**, 219. (c) Jost, K.; Rudinger, J. *Collect. Czech. Chem. Commun.* **1967**, *32*, 2485. (d) Ciapetti, P.; Soccolini, F.; Taddei, M. *Tetrahedron* **1997**, *53*, 1167. (e) Barton, D. H. R.; Crich, D.; Hervé, Y.; Poitier, P.; Thierry, J. *Tetrahedron* **1985**, *41*, 4347. (f) Strazewski, P.; Tamm, C. *Synthesis* **1987**, 298. (g) Hoffmann, M. G.; Zeis, H. J. *Tetrahedron Lett.* **1992**, *33*, 2669. (h) Barton, D. H. R.; Hervé, Y.; Poitier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479. (i) Maurer, P. J.; Miller, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 3096. (j) Olsen, R. K.; Ramasamy, K.; Emery, T. *J. Org. Chem.* **1984**, *49*, 3527.

[3] Baldwin, J. E.; Spivey, A. C.; Schofield, C. J. *Tetrahedron: Asymmetry* **1990**, *1*, 881.

[4] Pansare, S. V.; Huyer, G.; Arnold, L. D.; Vederas, J. C. *Org. Synth.* **1992**, *70*, 1.

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membered cyclic sulfamidate **2** derived from homoserine. Although numerous examples of five-membered cyclic sulfamidates have been presented in the literature,[1,3] few reports have been made of the synthesis and reactivity of their six-membered counterparts.[6,7] In the synthesis of *N*-methyl-D-aspartate receptor antagonists, nucleophilic ring opening of sulfamidate **3** was reported to proceed with tetrabutylammonium fluoride at 70 °C to furnish both the displacement product dibenzo[*a*,*d*]cycloalkenimine **4** and vinyl elimination product **5** (Figure 2).[6b] To the best of our knowledge, no example of a homoserine-derived cyclic sulfamidate had been reported prior to our study. In light of the importance of γ-substituted amino acids, such as γ-amino butyric acid (GABA), as well as the interesting reactivity observed with serine-derived sulfamidate **1**, we have now explored the synthesis and reactivity of *N*-(PhF)homoserine-derived sulfamidate **2**. Our preliminary findings have demonstrated that sulfamidate **2** reacts effectively with nitrogen, sulfur, and oxygen nucleophiles to provide enantiopure γ-substituted α-amino acids.

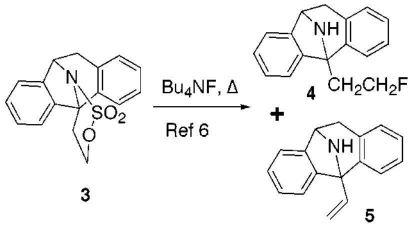
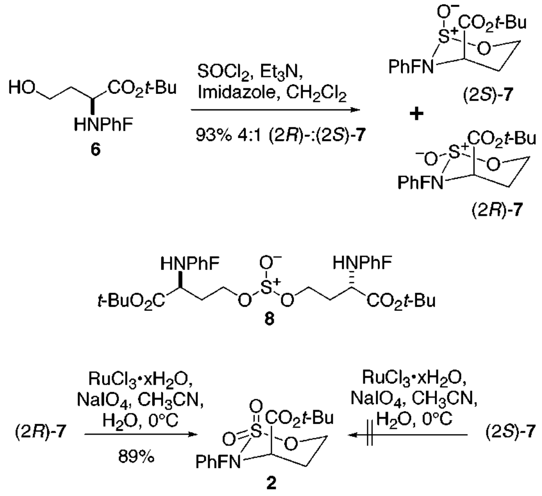


Figure 2. Ring opening of six-membered sulfamidate **3**.[6]

Scheme 1



(4*S*)-*tert*-Butyl 2,2-dioxo-3-PhF-1,2,3-oxathiazainane-4-carboxylate (**2**) was synthesized from *tert*-butyl *N*-(PhF)-homoserine **6**,[5] by using similar protocols as those reported for the preparation of its five-membered counterpart (Scheme 1).[1,8] Initially, amino alcohol **6** was treated with thionyl chloride, triethylamine, and imidazole in dichloromethane to furnish a 4:1 mixture of 2*R*:2*S*-sulfamidite diastereomers **7**.[8] When imidazole was omitted from the reaction mixture, the major isolated product was symmetrical sulfite **8**.[9] Diastereomers **7** were separated by chromatography on silica gel using an eluant of 0−20% EtOAc in hexane. Oxidation of the major (2*R*,4*S*)-sulfamidite **7** with catalytic ruthenium trichloride and sodium periodate in acetonitrile and water at 0 °C afforded sulfamidate **2** in 89% yield.[10] On the other hand, treatment of the minor (2*S*,4*S*)-sulfamidite **7** under the same conditions gave no oxidation product **2** and the starting material was recovered unchanged.

The configurational assignments for sulfamidites **7** were made on the basis of their proton NMR spectra with comparison to sulfamidate **2**. Sulfamidites **7** and sulfamidate **2** were expected to adopt a chair conformation, which has been shown by NMR studies to be the preferred conformation of the related six-membered cyclic sulfates (Figure 3).[11] Small coupling constants between the C-4 and C-5 protons suggested that **2** and **7** adopt conformations with the *tert*-butyl ester sitting axial, as has been previously observed for related *N*-(PhF)pipecolate *tert*-butyl esters.[12] In the proton spectrum of **2**, the anisotropy of the sulfamidate caused the signals for the axial *tert*-butyl ester singlet (1.66 ppm), the C-6 β-proton (4.88 ppm), and the PhF resonances (7.2−8.11

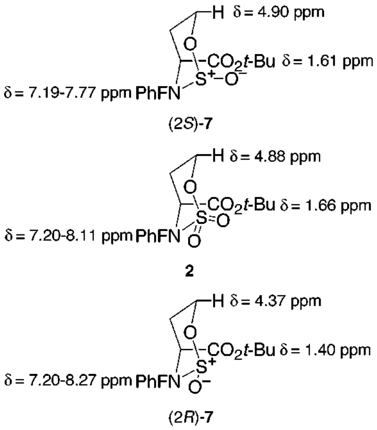


Figure 3. Influence of S−O bond anisotropy on chemical shift in sulfamidate **2** and sulfamidites **7**.

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[5] Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 7463 and ref 16 therein.

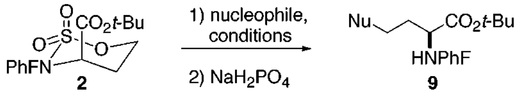
[6] (a) Lyle, T. A.; Magill, C. A.; Pitzenberger, S. M. *J. Am. Chem. Soc.* **1987**, *109*, 7890. (b) Thompson, W. J.; Anderson, P. S.; Britcher, S. F.; Lyle, T. A.; Thies, J. E.; Magill, C. A.; Varga, S. L.; Schwering, J. E.; Lyle, P. A.; Christy, M. E.; Evans, B. E.; Colton, C. D.; Holloway, M. K.; Springer, J. P.; Hirshfield, J. M.; Ball, R. G.; Amato, J. S.; Larsen, R. D.; Wong, E. H. F.; Kemp, J. A.; Tricklebank, M. D.; Singh, L.; Oles, R.; Priestly, T.; Marshall, G. R.; Knight, A. R.; Middlemiss, D. N.; Woodruff, G. N.; Iversen, L. L. *J. Med. Chem.* **1990**, *33*, 789.

[7] (a) Lowe, G.; Reed, M. A. *Tetrahedron: Asymmetry* **1990**, *1*, 885. (b) Meunier, N.; Veith, U.; Jäger, V. *Chem. Commun.* **1996**, 331. (c) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.

ppm) all to be shifted downfield.[13] In the spectrum of (2*S*)-**7**, the presence of the axial sulfoxide oxygen caused a similar downfield shift of its *tert*-butyl ester singlet (1.61 ppm) and C-6 β-proton (4.9 ppm). In the spectrum of (2*R*)-**7**, only the PhF resonances (7.20−8.27 ppm) were shifted further downfield by the presence of the equatorial sulfoxide oxygen, and the signals for the *tert*-butyl ester singlet (1.40 ppm) and C-6 β-proton (4.37 ppm) remained upfield. These assignments also correlated with the fact that only the (2*R*)-sulfamidite (2*R*)-**7** was oxidized to sulfamidate **2**, because in sulfamidite (2*S*)-**7**, the S^+-O^- group sits in an axial position and access of the oxidant to the sulfur was blocked by the PhF group.

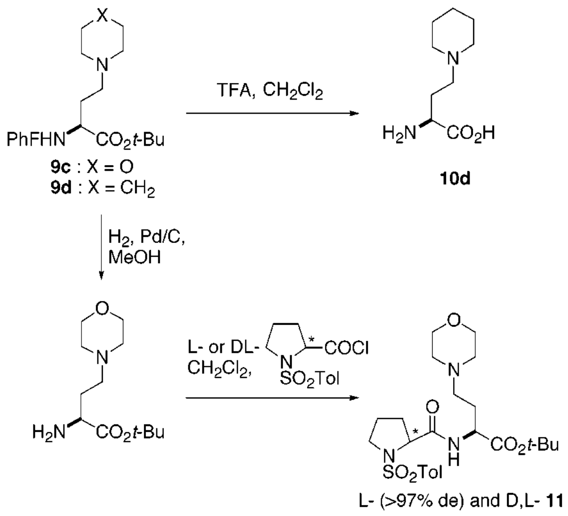
Ring opening of sulfamidate **2** was examined using nitrogen, sulfur, and oxygen nucleophiles (Table 1). In our initial procedure, sulfamidate **2** (100 mol %), the nucleophile (2−300 mol %), and sodium hydride (2−300 mol %) were heated in DMF at 60 °C for 24−48 h, when complete consumption of starting material ($R_f = 0.3$ in 1:3 EtOAc/hexanes) was observed by TLC. Sodium azide and potassium thiocyanate were used without additional NaH. The solution was then cooled, poured into a 1 M NaH_2PO_4 solution, and agitated to hydrolyze the sulfamic acid intermediate. The desired γ-substituted α-*N*-(PhF)amino esters **9** were isolated after extraction with EtOAc and column chromatography on silica gel. Amine nucleophiles were later found to be sufficiently reactive in the absence of NaH and provided clean products after heating with **2** in acetonitrile at 70 °C for 30 h. Phenolate and thiophenolate ions both reacted with sulfamidate **2** to provide, respectively, *O*-phenylhomoserine **9i** and *S*-phenylhomocysteine **9h**. The related *O*-alkylhomoserine and *S*-alkylhomocysteine analogues could not be isolated from treatment of **2** with methoxide and benzylthiolate ions in preliminary experiments; instead, cursory analyses of the reaction mixtures indicated decomposition of sulfamidate **2**.

Table 1. Nucleophilic Opening of Sulfamidate **2**



entry	nucleophile	conditions	**9** (%)	$[\alpha]^{20}_D$
a	NaN_3	DMF, 60°, 24 h	83	−211°
b	imidazole	NaH, DMF, 60°, 24 h	50	−165°
	imidazole	DMF, 60°, 24 h	56	−165°
	imidazole	CH_3CN, 75°, 30 h	65	−165°
c	morpholine	NaH, DMF, 60°, 24 h	85	−217°
	morpholine	CH_3CN, 75°, 30 h	95	−217°
d	piperidine	DMF, 60°, 24 h	80	−130°
	piperidine	CH_3CN, 75°, 30 h	90	−130°
e	$PhNH_2$	CH_3CN, 75°, 30 h	85	−146°
f	*i*-$BuNH_2$	CH_3CN, 75°, 30 h	91	−176°
g	KSCN	CH_3CN, 75°, 30 h	68	−210°
h	PhSH	NaH, DMF, 60°, 24 h	56	−310°
	PhSH	CH_3CN, 75°, 30 h	0	
i	PhOH	NaH, DMF, 60°, 60 h	56	−178°

Scheme 2



Deprotection of γ-substituted α-*N*-(PhF)amino esters **9** was demonstrated by treating piperidinyl analogue **9d** with TFA in dichloromethane for 18 h (Scheme 2). The trifluoroacetate salt was obtained in acceptable purity by evaporation of the volatiles, digestion of the residue into water, filtration of the insoluble hydrocarbon, and evaporation of the aqueous phase. Amino acid **10d** was later isolated in zwiterionic form after ion exchange chromatography.

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(8) A 0.05 M solution of *N*-(PhF)homoserine **6** (2 g, 4.7 mmol, prepared according to ref 5) in dichloromethane was treated in the same manner as described for the synthesis of serine-derived cyclic sulfamidites in ref 1. Chromatography on silica gel with a gradient of 0−10% EtOAc in hexane furnished 1.6 g (71%) of (2*R*,4*S*)-*tert*-butyl 2-oxo-3-PhF-1,2,3-oxathiazainane-4-carboxylate (2*R*)-**7** and 0.5 g (23%) of (2*S*)-**7**. First to elute was (2*S*)-**7**: $R_f = 0.36$ (30% EtOAc in hexanes); mp 166−167 °C; $[\alpha]^{20}_D$ 212° (*c* 0.34, $CHCl_3$); ^1H NMR δ 1.26 (m, 1 H), 1.61 (s, 9 H), 1.78 (m, 1 H), 3.16 (dd, 1 H, *J* = 2.5, 5.4), 3.53 (m, 1 H), 4.90 (m, 1 H), 7.19−7.77 (m, 13 H); ^{13}C NMR δ 22.6, 27.9, 49.3, 54.6, 76.6, 81.7, 169.9; HRMS calcd for $C_{27}H_{27}O_4NNaS$ (M + Na) 484.1559, found 484.1560. Second to elute was (2*R*)-**7**: $R_f = 0.27$ (20% EtOAc in hexanes); mp 172−173 °C; $[\alpha]^{20}_D$ 132° (*c* 0.33, $CHCl_3$); ^1H NMR δ 1.40 (s, 9 H), 2.18 (m, 1 H), 2.69 (m, 1 H), 3.31 (dd, 1 H, *J* = 3.4, 4.3), 3.94 (ddd, 1 H, *J* = 9.7, 10.9, 16.4), 4.37 (m, 1 H), 7.20−8.27 (m, 13 H); ^{13}C NMR δ 26.6, 27.8, 54.3, 57.0, 76.8, 81.3, 170.6; HRMS calcd for $C_{27}H_{27}O_4NNaS$ (M + Na) 484.1559, found 484.1541.

(9) HRMS calcd for $C_{54}H_{57}O_7N_2S$ (MH^+) 877.3887, found 877.3853. Dimerization product **8** was best prevented under dilute conditions (0.05 M) using excess imidazole (400 mol %).

(10) The same protocol described in ref 1 for the oxidation of serine-derived sulfamidite to sulfamidate **1** was employed to convert (2*R*)-**7** (500 mg) to **2**. *N*-(PhF)homoserine-derived cyclic sulfamidate **2** (468 mg, 89%) crystalized upon evaporation of the combined dried organic extractions: mp 188−188.5 °C; $[\alpha]^{20}_D$ 268° (*c* 0.37, CHCl3); ^1H NMR δ 1.10 (m, 1 H), 1.66 (s, 9 H), 1.74 (m, 1 H), 3.85 (br d, 1 H, *J* = 5.3), 4.15 (m, 1 H), 4.88 (m, 1 H), 7.20−8.11 (m, 13 H); ^{13}C NMR δ 22.4, 28.0, 58.3, 70.7, 78.6, 82.6, 168.3; HRMS calcd for $C_{27}H_{27}O_5NNaS$ (M + Na) 500.1508, found 500.1489.

(11) (a) Reviewed in: Lohray, B. B. *Synthesis* **1992**, 1035. (b) Wood, G.; McIntosh, J. M.; Miskow, M *Tetrahedron Lett.* **1970**, 4895.

(12) (a) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239. (b) Swarbrick, M. E.; Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1999**, *64*, 1993. (c) Swarbrick, M. E.; Lubell, W. D. *Chirality* **2000**, *12*, 366.

(13) Deyrup, J. A.; Moyer, C. L. *J. Org. Chem.* **1969**, *34*, 175.

The enantiomeric purity of morpholine adduct **9c**, prepared from conditions in the presence of NaH, was examined after its conversion to L- and D,L-*N*-(toluenesulfonyl)prolylamides **11** (Scheme 2). Hydrogenolytic cleavage of the PhF group was performed at 10 atm of H_2 with palladium-on-carbon as catalyst in MeOH for 72 h. Subsequently, the amine product was acylated with L- and D,L-*N*-(toluenesulfonyl)-prolyl chloride and Et_3N in CH_2Cl_2 for 1 h. After aqueous washes and evaporation of the organic phase, the 400 MHz ^1H NMR spectra of amides L- and D,L-**11** were measured. In the spectrum of D,L-**11**, diastereomeric *tert*-butyl ester signals were observed at 1.48 and 1.57 ppm in C_6D_6 in a ~1:1 ratio. Measurement of the *tert*-butyl ester signals for material prepared with L-proline under the same conditions demonstrated amide L-**11** to be of >97% diastereomeric purity. Hence, γ-substituted α-*N*-(PhF)amino esters **9** and their deprotection products **10** all are presumed to be of >97% enantiomeric purity.

In conclusion, we have developed a novel configurationally stable chiral educt for the synthesis of enantiopure (>97% ee) γ-substituted α-amino acids. Homoserine-derived cyclic sulfamidate **2** was readily synthesized from inexpensive aspartic acid and was shown to react effectively with nitrogen, sulfur, and oxygen nucleophiles. In light of the utility and limitations of contemporary α-amino acid analogues that possess remote electrophilic centers, sulfamidate **2** represents a practical alternative for the synthesis of novel amino acids and natural products.

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Supporting Information Available: Descriptions of experimental procedures and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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