Scope and limitations in the use of *N*-(PhF)serine-derived cyclic sulfamidates for amino acid synthesis

Lan Wei and William D. Lubell

Abstract: Ring-opening of *N*-(PhF)serine-derived cyclic sulfamidate **17** was achieved with different nucleophiles (β-keto esters, β-keto ketones, dimethyl malonate, nitroethane, sodium azide, imidazole, and potassium thiocyanate) to prepare a variety of amino acid analogs. Two different pathways for ring opening of **17** were elucidated: direct nucleophilic displacement, as well as β-elimination followed by Michael addition. Furthermore, β-keto ester and β-keto ketone products **18k**, **18m**, and **18i** were converted to prolines and pyrazole amino acids.

Key words: glutamate, amino acid, cyclic sulfamidate, proline.

Résumé : L'ouverture des sulfamidates cycliques dérivés de la serine a été explorée avec différents nucléophiles (β-céto esters, 1,3-dicétones, diméthyle de malonate, nitroéthane, azidure de sodium, imidazole et thiocyanate de potassium) pour préparer une variété d'analogues d'acides aminés. Deux voies différentes ont été proposées pour l'ouverture du cycle à cinq membres du sulfamidate **17**: le déplacement nucléophile et l'élimination β suivie de l'addition de Michael. De plus, les β-céto ester **18k**, **18m** et 1,3-dicétone **18i** ont été respectivement convertis en prolines et en acides aminés pyrazoyle.

Mots clés : glutamate, acide aminé, sulfamidate cyclique, proline.

Introduction

Serine-derived cyclic sulfamidates have served in syntheses of a series of amino acid analogs (Fig. 1) (1–3). For example, β-substituted alanines **1**–**11** have been prepared by ring opening of sulfamidate with oxygen, nitrogen, sulfur, and fluorine nucleophiles (1–3). Aspartate analogs **12** and **13** have also been prepared by nucleophilic opening of sulfamidate with a cyanide ion (1, 3). Moreover, γ-acyl pyroglutamate **14** was furnished on treatment of sulfamidate with diethyl malonate (1). These examples demonstrate that serine-derived cyclic sulfamidates are versatile chiral building blocks with complementary reactivity to related β-alanine cation equivalents such as serine-derived β-lactones (4, 5) and aziridines (6, 7).

Interested in harnessing its power to construct peptide mimics and glutamate receptor ligands, we have explored the reactivity of cyclic-sulfamidate **17** derived from *N*-(PhF)serine methyl ester (Scheme 1), because of the proven effectiveness of the PhF protecting group for preserving configurational integrity during manipulations of α-amino carbonyl compounds (PhF = 9-(9-phenylfluorenyl)) (8, 9). Sulfamidate **17** reacted with a series of heteroatomic as well as carbon nucleophiles to provide the desired amino acid analogs; however, careful examination of the configurational integrity of these products revealed that racemization occurred during reactions of **17** with carbon nucleophiles (10). Although enantiopure serine has often been employed as starting material, to the best of our knowledge, the enantiomeric purity of the products from ring opening of its cyclic sulfamidates had been previously reported in only two examples (2). Pyrazole **7** and piperidine **8** were checked for racemization after conversion to diastereomeric amides using, respectively, (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride and (–)-menthyl chloroformate. A comparison of the diastereomeric amides with material prepared from racemic serine using proton nuclear magnetic resonance (^{1}H NMR) spectroscopy led the authors to conclude that "no apparent racemization occurred in the course of both the ring opening and the hydrolysis" reactions involved in the preparation of **7** and **8**. This claim contrasted with our discovery of racemization in the reactions of sulfamidate **17** with carbon nucleophiles and provoked a detailed investigation of the enantiomeric purity of the various products from nucleophilic ring opening of sulfamidate **17**.

In reactions with different nucleophiles, sulfamidate **17** was found to undergo additions via two different mechanisms. In the case of weakly basic (conjugate acid $pK_a \leq 7$) nucleophiles, direct nucleophilic displacement occurred to provide enantiopure (>97% ee) β-substituted alanines. On the other hand, carbon nucleophiles, such as the enolates of 1,3-dicarbonyl compounds, added to sulfamidate **17** by a mechanism featuring β-elimination to provide a

Received June 30, 2000. Published on the NRC Research Press Web site on January 24, 2001.

L. Wei and W.D. Lubell.[1] Département de chimie, Université de Montréal, C.P. 6128, Succursale Centre Ville, Montréal, QC H3C 3J7, Canada.

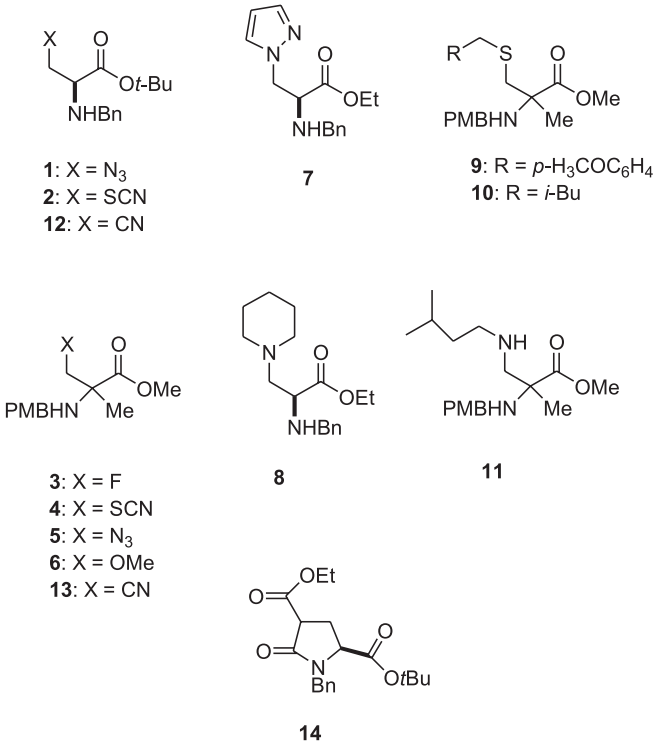
[1]Author to whom correspondence may be addressed. Telephone: (514) 343-7339. Fax: (514) 343-7586. e-mail: Lubell@chimie.umontreal.ca

 DOI: 10.1139/cjc-79-1-94

Table 1. ^{1}H NMR signal assignments of sulfamidites (2*R*)- and (2*S*)-**16**, and sulfamidate **17**.

Position	(2*R*)-**16**	(2*S*)-**16**	**17**
	δ_H [int. mult, *J* (Hz)]	δ_H [int. mult, *J* (Hz)]	δ_H [int. mult, *J* (Hz)]
4	3.51 (1H, dd, 1.4, 7.1)	3.37 (1H, t, 7.9)	3.64 (1H, dd, 4.0, 8.1)
5β	4.41 (1H, dd, 1.4, 9.4)	4.32 (1H, t, 7.9)	4.38 (1H, dd, 4.0, 8.7)
5α	4.75 (1H, dd, 7.1, 9.4)	4.95 (1H, t, 7.9)	4.02 (1H, dd, 8.1, 8.7)
MeO	3.42 (3H, s)	3.57 (3H, s)	3.69 (3H, s)
PhF	7.17–8.17 (13H, m)	7.19–7.77 (13H, m)	7.19–8.22 (13H, m)

Fig. 1. Representative amino acids prepared by ring-opening of serine-derived cyclic sulfamidates.



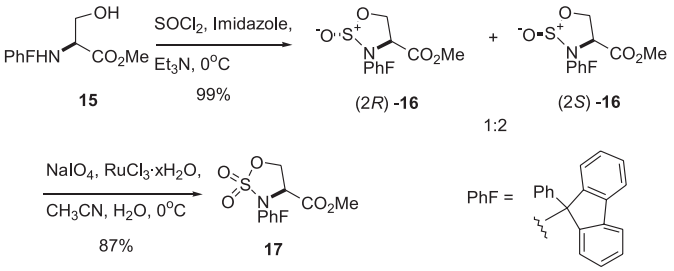
dehydroalanine intermediate that underwent subsequent Michael addition and afforded racemic product. In addition, several nucleophiles were found that caused β-elimination, yet failed to react with the dehydroalanine intermediate in a conjugate addition. This spectrum of reactivity and the utility of the addition products have been evaluated to better define the scope and limitations of *N*-(PhF)serine-derived sulfamidate **17** as a chiral educt for amino acid synthesis.

Results and discussion

Synthesis of cyclic sulfamidate 17

Sulfamidate derivatives of β-amino alcohols permit protection of the nitrogen moiety and conversion of the hydroxyl group into a leaving group. The most direct approach for their construction has been the reaction of the respective β-amino alcohol with sulfuryl chloride; however, this process has usually led to the corresponding aziridines, presumably due to ring closure of the corresponding -OSO_2Cl intermediate (11–13). Because of the difficulties encountered when using sulfuryl chloride, most cyclic sulfamidates have been prepared by oxidation of the corresponding sulfamidites (1–3, 11–22). Following this protocol, (4*S*)-methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**17**) was synthesized initially by treating *N*-(PhF)serine methyl ester **15** (23) with thionyl chloride, triethylamine, and imidazole in dichloromethane to furnish quantitatively a 1:2 mixture of diastereoisomeric sulfamidites **16** (Scheme 1). Cyclic sulfamidate **17** was then prepared by subsequent oxidation of sulfamidites **16** with sodium periodate and catalytic ruthenium trichloride in acetonitrile and water at 0°C.

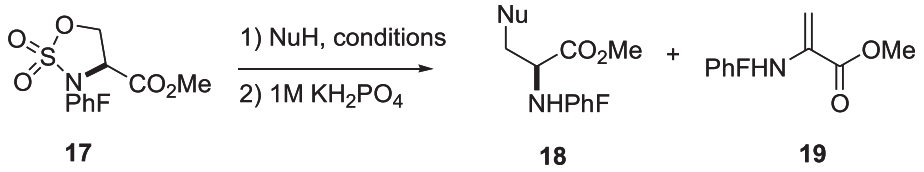
Scheme 1. Synthesis of cyclic sulfamidate **17**.



Diastereoisomers (2*R*)-**16** and (2*S*)-**16** could be separated by chromatography and independently converted into five-membered sulfamidate **17**. The assignment of the configuration at sulfur for the diastereoisomers (2*R*)-**16** and (2*S*)-**16** was initially attempted by comparisons of their ^{1}H NMR spectra with that of their oxidation product sulfamidate **17** (Table 1), as well as with spectral data for other cyclic sulfamidites (24). Comparing the spectra of **16** and **17**, we concluded that the (2*R*)-sulfamidite ((2*R*)-**16**), would exhibit similar steric as well as anisotropic effects as sulfamidate **17** (25, 26). For example, in the spectra of (2*R*)-**16** and **17**, the C-4 proton appeared as a doublet of doublets as the result of steric interactions between the exocyclic oxygen atom on sulfur and the PhF group, which twisted the five-membered ring such that significantly different dihedral angles existed between the C-4 and C-5 protons. In contrast, the C-4 proton in (2*S*)-**16** appeared as a triplet indicative of a conformation with similar dihedral angles between the C-4 proton and each of the C-5 protons. The magnetic anisotropy of the S—O bond (26) shifted downfield the resonances of proximal PhF protons as well as the C-4 proton in the spectra of (2*R*)-**16** and **17** relative to the respective signals in the spectrum of (2*S*)-**16**.

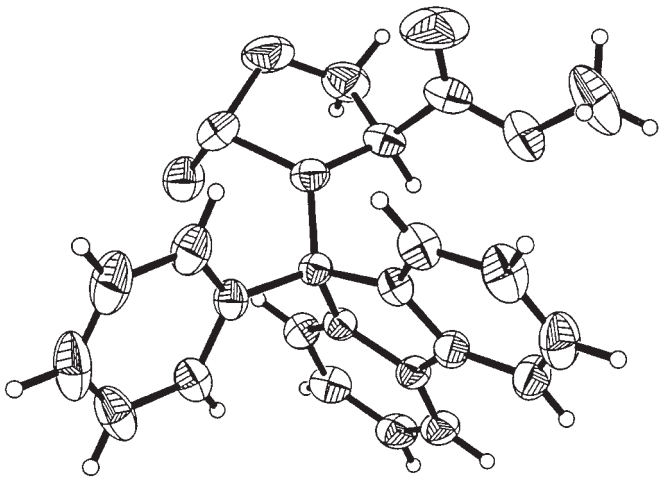
The configurational assignments for **16**, which were made based on the ^{1}H NMR chemical shift and coupling constant

Scheme 2. Ring opening of cyclic sulfamidate **17**.



17 **18** **19**

Fig. 2. ORTEP view of (2*R*,4*S*)-methyl 2-oxo-3-(PhF)-1,2,3-oxathiazolidine-4-carboxylate ((2*R*)-**16**).[2]



values, were confirmed by X-ray crystallographic analysis of (2*R*)-**16** (Fig. 2). Single-crystal X-ray analysis showed that the dihedral angle between the C-4 proton and the C-5α proton was 25.4°, and the dihedral angle between the C-4 proton and the C-5β proton was 82.6°. The crystal structure of (2*R*)-**16** exhibits a conformation in which the α-proton and the α-acid carbonyl are nearly coplanar (159.5°). Since α-deprotonation from the coplanar geometry is stereoelectronically less favoured than from an orthogonal geometry, this arrangement has been suggested to contribute to the configurational stability of PhF amino carbonyl compounds (27, 28).

Ring opening of five-membered cyclic sulfamidate 17

With cyclic sulfamidate **17** in hand, we next examined nucleophilic ring opening using different nucleophiles (Scheme 2, Table 2). Cyclic sulfamidate **17** reacted with heteroatomic nucleophiles to provide products from both nucleophilic displacement at C-5 and proton abstraction at C-4. For example, KSCN, NaN_3, and imidazole, all opened regioselectively the sulfamidate ring to afford, respectively, thioether **18d**, azide **18e**, and imidazole **18f**. Other nucleophiles, such as TBAF, MeONa, diethyl amine, and piperidine, gave mainly dehydroalanine **19** and recovered starting material as observed by NMR spectral analysis of the crude product after aqueous work-up.

Ring opening of sulfamidate **17** was also examined using *C*-nucleophiles including β-keto esters, β-keto ketones, dimethyl malonate, and nitroethane. Treatment of sulfamidate **17** with a premixed solution containing 400 mol% of either β-keto ester, β-keto ketone, or dimethyl malonate and 220 mol% of sodium hydride in DME, followed by heating at 60°C caused ring opening to form the polar sulfamic acid intermediate. Hydrolysis of the reaction mixture with 1 M KH_2PO_4 furnished the desired amino acid derivatives **18i**–**o** after chromatography (Table 2). Since β-keto ester **18k** and β-keto ketone **18i** were difficult to separate from methyl acetoacetate and 2,4-pentanedione, respectively, the crude material was used without purification in the next step towards the preparation of heterocyclic amino acids. Nitroethane reacted with **17** using similar conditions to provide γ-nitro-α-amino pentanoate **18o** in 52% yield as a 10:1 mixture of diastereomers.

β-Keto esters **18k** and **18m** were next converted, respectively, to 5-methylproline **23** and δ-keto α-amino ester **20m**, an intermediate in the synthesis of 5-*tert*-butylproline (29) (Scheme 3). Their respective δ-oxo-α-*N*-(PhF)amino acids were first obtained from hydrolysis and decarboxylation of β-keto esters **18k** and **18m** with sodium hydroxide in ethanol heated at a reflux. Esterification with iodomethane and potassium carbonate in acetonitrile provided methyl 5-oxo-2-[*N*-(PhF)amino]hexanoate (**20k**) and methyl 6,6-dimethyl-5-oxo-2-[*N*-(PhF)amino]heptanoate (**20m**) in 71% and 52% overall yields, respectively, from **17**. Hydrogenation of δ-oxoheptanoate with palladium-on-carbon and di-*tert*-butyl dicarbonate in methanol proceeded by cleavage of the PhF protection, *N*-acylation, imine formation, and hydrogenation of the imine intermediate on the face opposite the methyl ester to furnish *N*-(BOC)-5-methylproline methyl ester (**21**) as the *cis*-diastereomer. Hydrolysis of methyl ester *cis*-**21** with potassium trimethylsilanolate in Et_2O furnished *cis*-*N*-(BOC)-5-methylproline (*cis*-**22**) in 96% yield. In addition, removal of the BOC protecting group with trifluoroacetic acid in dichloromethane provided *cis*-5-methylproline **23** (30, 31).

The utility of β-keto ketone **18i** was illustrated by its conversion to pyrazole amino acid **26** (Scheme 3). Methyl 2-[*N*-(PhF)amino]-3-(3,5-dimethyl-2*H*-pyrazol-4-yl)propanoate (**24**) was initially prepared by treatment of β-keto ketone **18i** with

[2] The structure of (2*R*)-**16** was solved at l'Université de Montréal X-ray facility using direct methods (SHELXS 96) and refined with SHELXL 96: $C_{23}H_{19}NO_4S$, Mr = 405.452, orthorhombic, colourless crystal, space group $P2_12_12_1$, unit cell dimensions (Å) a = 9.5587(2), b = 9.7736(2), c = 21.0498(4), volume of unit cell (Å^3) 1966.53(7), Z = 4, R_1 = 0.0659 for $F^2 > 2\sigma(F^2)$, wR_2 = 0.1613 for all data; GOF = 1.048. The author has deposited the atomic coordinates for the structure of (2*R*)-**16** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (Fax: 44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary material may be purchased from the Depository of Unpublished Data Document Delivery, CISTI, National Research Council Canada, Ottawa, ON, K1A OS2, Canada. For information on ordering electronically (http://www.nrc.ca/cisti/irm/unpub_e.shtml).

Table 2. Treatment of cyclic sulfamidate **17** with nucleophiles.

Entry	Nucleophilic source	Base	Solvent	Time (h)	Temp (°C)	**18**[a] (% yield)	$[\alpha]_D^{20}$	**19**[c] (% yield)
a	TBAF		DME	18	rt	—		40
b	Et_2NH		DME	18	rt	—		<10
	Et_2NH		MeCN	48	rt	—		50
	Et_2NH		DMF	18	rt	—		100
c	piperidine		MeCN	48	rt	—		30
d	KSCN		DME	48	rt	64	–287°	—
	KSCN		DMF	36	rt	72	–287°	—
e	NaN_3		DME	72	rt	50	–294°	—
	NaN_3		MeCN	72	rt	82	–294°	—
	NaN_3		DMF	1	rt	90	–294°	—
f	imidazole		DME	18	80	85	–241°	—
g	$CH_3(CH_2)_2SH$		DMF	36	rt	—		—
	$CH_3(CH_2)_2SH$	NaH	DMF	36	rt	—		10
h	MeONa		DME	0.5	rt	—		100
i	$MeCOCH_2COMe$	NaH	DME	18	60	66[b]		[d]
j	$PhCOCH_2COMe$	NaH	DME	18	60	45		—
k	$MeCOCH_2CO_2Me$	K_2CO_3	DMF	72	rt	—		100
	$MeCOCH_2CO_2Me$	K_2CO_3	THF	72	rt	30[b]		[d]
	$MeCOCH_2CO_2Me$	Cs_2CO_3	THF	90	rt	—		100
	$MeCOCH_2CO_2Me$	K_3PO_4	DME	18	rt	43[b]		[d]
	$MeCOCH_2CO_2Me$	NaH	THF	6	60	51[b]		—
	$MeCOCH_2CO_2Me$	NaH	DME	4	60	67[b]		—
	$MeCOCH_2CO_2Me$	NaH	DME	18	60	86[b]		—
l	$EtCOCH_2CO_2Et$	NaH	DME	18	60	82		—
m	*t*-$BuCOCH_2CO_2Et$	NaH	DME	18	60	63		—
n	$MeCO_2CH_2CO_2Me$	NaH	DME	18	60	65[b]	–4.3°	—
o	$CH_3CH_2NO_2$	NaH	DME	18	60	52		—

[a]Isolated yield.
[b]Calculated yield from an isolated mixture of **18** and β-dicarbonyl starting material.
[c]Determined by ^{1}H NMR spectroscopy.
[d]Observed by TLC.

Scheme 3. Synthesis of 5-alkylproline **23** and amino-3-(3,5-dimethyl-1*H*-pyrazol-4-yl) propionic acid **26**.

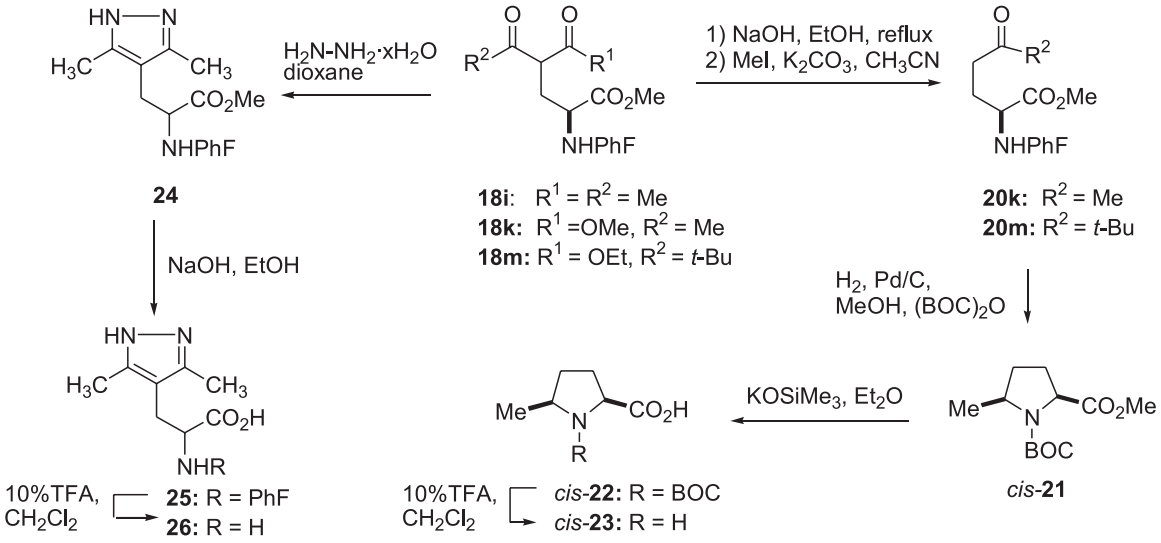
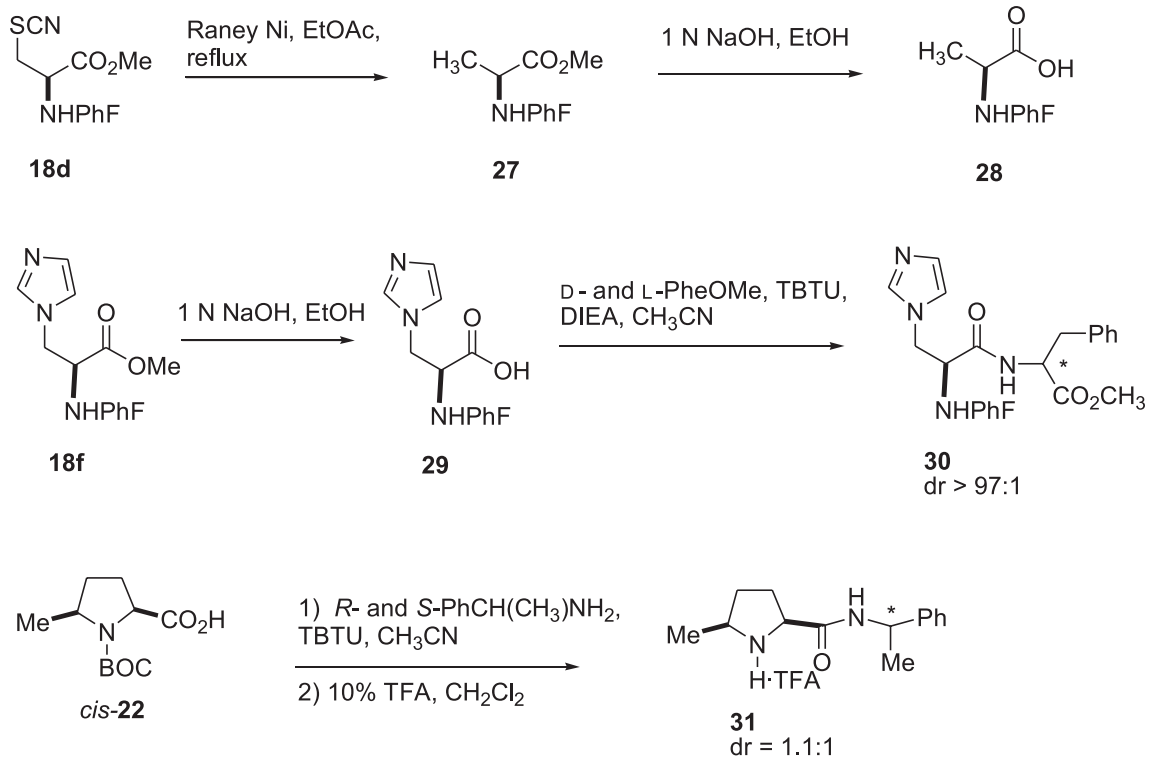


Fig. 3. Evaluation of enantiomeric purity of amino acids **28**, **29**, and *cis*-**22**.



hydrazine hydrate. Hydrolysis of methyl ester **24** with 1 N NaOH in EtOH then furnished 2-[*N*-(PhF)amino]-3-(3,5-dimethyl-1*H*-pyrazol-4-yl)propionic acid (**25**) as a solid after chromatography. Removal of the PhF group was cleanly accomplished by heating **25** with trifluoroacetic acid in dichloromethane at a reflux for 18 h and furnished **26** in 88% yield.

Enantiomeric purity

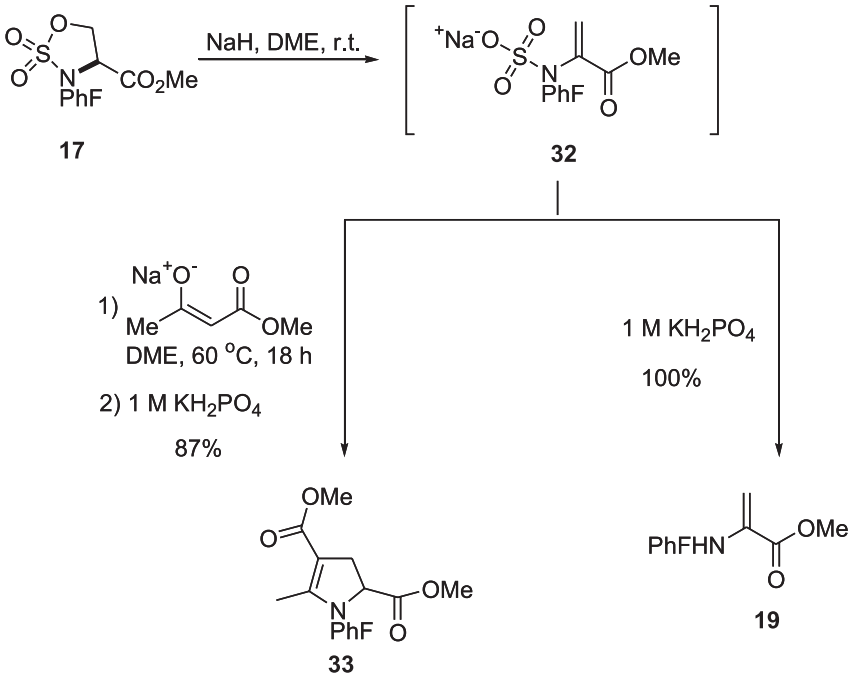
Enantiomeric purity was evaluated for two products by conversion to diastereomeric derivatives and analysis of the isomeric signals in their ^{1}H NMR spectra. In the case of (2*S*)-*N*-PhF-*S*-cyanocysteine methyl ester (**18d**), conversion to *N*-PhF-L-alanine (**28**) and comparison of its specific rotation with the literature value was used to estimate purity. Cleavage of the S—C bond with Raney nickel in EtOAc at reflux for 6 h gave *N*-PhF-L-alanine methyl ester (**27**). Hydrolysis of *N*-PhF-L-alanine methyl ester (**27**) with 1 N NaOH in ethanol for 1 h gave *N*-PhF-L-alanine (**28**) in 74% overall yield from **18d** (Fig. 3). The specific rotation of *N*-PhF-L-alanine (**28**) and comparison with its literature value (9) ($[\alpha]_D^{20}$ 150° (*c* 0.2, $CHCl_3$), lit. (9) $[[\alpha]_D^{20}$ 163° (*c* 1, $CHCl_3$)) demonstrated that the material from sulfamidate opening was significantly enriched with one enantiomer.

The enantiomeric purity of (2*S*)-methyl 3-(1-imidazol)-2-[*N*-(PhF)amino]propionate (**18f**) was determined after conversion to diastereomeric amides **30**, and subsequent spectral analysis. (2*S*)-3-(1-Imidazol)-2-[*N*-(PhF)amino]propionic acid (**29**) was first synthesized by ester hydrolysis in 86% yield using 1 N NaOH in EtOH. Acid **29** was coupled to L- and D-phenylalanine methyl ester in MeCN with TBTU and DIEA, respectively, at room temperature. Measurement of the methyl ester singlets at 3.71 and 3.76 ppm in $CDCl_3$ by 400 MHz ^{1}H NMR spectroscopy demonstrated **30** to be of >97% diastereomeric excess. Hence, (2*S*)-methyl 3-(1-imidazol)-2-[*N*-(PhF)amino]propionate (**18f**) is presumed to be of >97% enantiomeric purity. We consider, therefore, that no racemization occurred during nucleophilic substitution on cyclic sulfamidate **17** with imidazole nor with potassium thiocyanate nor with azide ion as nucleophiles.

The enantiomeric purity of *cis*-*N*-(BOC)-5-methylproline (*cis*-**22**) was studied after conversion to diastereomeric α-methylbenzylamides **31** by coupling, respectively, to *R*- and *S*-α-methylbenzylamine in MeCN with TBTU followed by removal of the BOC group with 10% TFA in CH_2Cl_2 (Fig. 3). In the ^{1}H NMR spectra of α-methylbenzylamides **31**, the diastereomeric methyl doublets were resolved and came at 1.50 and 1.49 ppm, as well as at 1.46 and 1.42 ppm. Integration of these doublets indicated that **31** was of only 10% diastereomeric excess.

In contrast to the amino acid syntheses using less basic nucleophiles, racemization had evidently occurred during the preparation of *cis*-*N*-(BOC)-5-methylproline **22**. The source of the loss of configurational integrity was narrowed down to the ring opening step after measurement of the specific rotation of δ-keto α-amino ester **20m**, which showed a considerable drop in optical purity ($[\alpha]_D^{20}$ –1.2° (*c* 0.8, $CHCl_3$), lit. (29) $[\alpha]_D^{20}$ –137.7° (*c* 1, MeOH)). Because hydrolysis and decarboxylation of β-keto ester **18m**, prepared from a route featuring acylation of *N*-(PhF)glutamate γ-methyl ester (32), produced enantiopure **20m** ($[\alpha]_D^{20}$ –139° (*c* 0.8, MeOH)), we considered that racemization occurred prior to or during the nucleophilic addition to cyclic sulfamidate **17** and not at the hydrolysis and decarboxylation steps.

Scheme 4. Michael addition of methyl acetoacetate enolate to dehydroalanine sulfamic acid **33**.



Low specific rotation values were also recorded for δ-keto α-amino ester **20k** ($[\alpha]_D^{20}$ –4.8° (*c* 0.15, $CHCl_3$)), pyrazole amino acid **25** ($[\alpha]_D^{20}$ –9.5° (*c* 0.2, MeOH)), and malonate **18i** ($[\alpha]_D^{20}$–4.3° (*c* 0.1, $CHCl_3$)). Because of the characteristically high specific rotations of *N*-(PhF)-α-amino carboxylates (9, 23, 27–29, 32, 33), racemization may be inferred to have occurred in these cases.

Dehydroalanine **19** was formed on ring opening of cyclic sulfamidate **17** by β-elimination induced with a variety of nucleophiles (Table 2). Postulating that the presumed dehydroalanine intermediate **32** could serve as a Michael acceptor for the formation of racemic β-keto ester, we treated sulfamidate **17** with 200 mol% of sodium hydride in DME to induce elimination (Scheme 4). A premixed solution of methyl acetoacetate (300 mol%) and NaH (400 mol%) in DME was then added to the reaction mixture which was heated at 60°C for 18 h. Hydrolysis of the polar sulfamic acid intermediate with 1 M KH_2PO_4 furnished (5*RS*)-methyl *N*-PhF-2-methyl-3-(methyloxy)carbonyl-Δ^2-pyrroline (**33**) in 87% yield. Previously, pyrroline **33** was encountered in the direct ring opening of sulfamidate **17** with the preformed enolate of methyl acetoacetate when the hot reaction mixture was quenched with 1 M KH_2PO_4. Its formation can be avoided by cooling the reaction mixture to room temperature prior to hydrolysis of the sulfamic acid; however, we elected to form pyrroline **33** in the present sequence because it was easier to characterize. Formation of **33** demonstrated that dehydroalanine **19** could serve as a prochiral intermediate for the formation of racemized amino acid product. To verify if sulfamidate racemized prior to ring opening, aliquots were taken at different time intervals from the reaction mixture containing **17** and the preformed enolate of methyl acetoacetate in DME at 60°C. No loss of configurational integrity of sulfamidate **17** was detected after 1 and 2 h of reaction as ascertained by measurement of its specific rotation after isolation by chromatography. Hence, α-deprotonation triggers β-elimination prior to reprotonation and racemization of **17**.

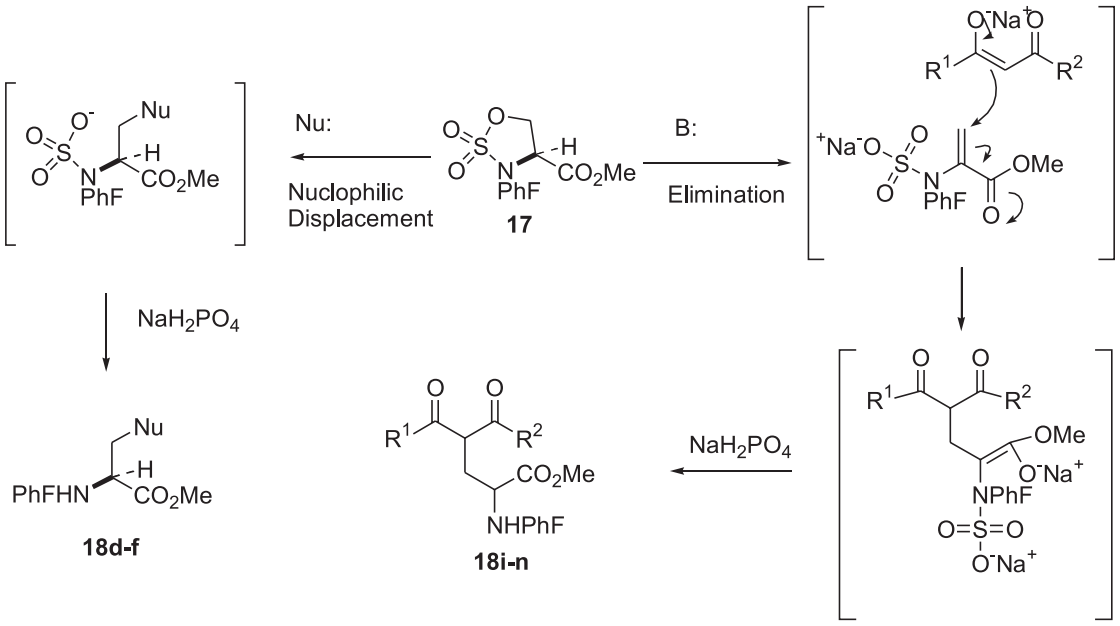
A mechanism that may explain the cause of racemization involves the nucleophile acting as base and removing the α-proton to trigger ring opening with elimination. A second nucleophile may then attack **32** to furnish β-keto ester by a Michael addition (Scheme 5). On the other hand, because (2*S*)-methyl 4-(1-imidazol)-2-[*N*-(PhF)amino]propionate (**18f**) was shown to be of >97% enantiomeric purity, ring opening of cyclic sulfamidate **17** with less basic nucleophiles should involve only nucleophilic displacement.

The formation of *N*-(PhF)dehydroalanine **19** by β-elimination on sulfamidate **17** is remarkable in light of a previous report in which the PhF group was found to completely suppress elimination during Mitsunobu reactions on the alcohol of *N*-(PhF)serine methyl ester **15** (34). The related β-*N*-(PhF)enamino ester has previously been reported; however, removal of the α-proton was not required for its formation via base induced rearrangement of dimethyl *N*-(PhF)-3,4-didehydroglutamate (33). In the X-ray crystal structure of cyclic sulfamidite **16**, the α-proton and β-hydroxyl group from serine are constrained in a nearly coplanar geometry within the five-membered ring. Most likely, sulfamidate **17** adopts a similar geometry that can favour orbital overlap facilitating β-elimination. Finally, pyroglutamate **14** should also be considered to be of suspect enantiomeric purity, because dehydoalanine product was encountered in its synthesis using sulfamidate derived from *N*-(Bn)serine *tert*-butyl ester (1).

Conclusion

Five-membered cyclic sulfamidate **17** was synthesized from serine in good yield. Ring opening of five-membered cyclic sulfamidate was achieved using a variety of nucleophiles

Scheme 5. Proposed mechanisms for the ring opening of sulfamidate **17.**



including β-keto esters, β-keto ketones, dimethyl malonate, nitroethane, sodium azide, imidazole, and potassium thiocyanate. A careful analysis of the enantiomeric purity of the products from ring opening of five-member cyclic sulfamidate **17** was performed using optical measurements as well as conversion of particular products to diastereomeric derivatives that were analyzed by NMR spectroscopy. Direct nucleophilic displacement and β-elimination followed by Michael addition were both found to be favoured mechanisms for the additions of different nucleophiles to **23**, which formed enantiopure and racemic amino acid product, respectively. Verification of product enantiomeric purity is thus essential when using serine-derived cyclic sulfamidates as chiral educts for amino acid synthesis.

Supporting information available: ^{1}H and ^{13}C NMR spectra for key compounds.[2]

Experimental section

General

Unless otherwise noted, all reactions were run under nitrogen atmosphere and distilled solvents were transferred by syringe. Tetrahydrofuran (THF) and ether were distilled from sodium–benzophenone immediately before use; 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and CH_2Cl_2 were distilled from CaH_2; Et_3N was distilled from BaO. Final reaction mixture solutions were dried over Na_2SO_4. Chromatography was on 230–400 mesh silica gel; thin layer chromatography (TLC) on aluminum-backed silica plates. Melting points are uncorrected. Mass spectral data, HRMS (EI and FAB), were obtained by the Université de Montréal Mass Spectroscopy facility. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane ($(CH_3)_4Si$). Coupling constants are given in Hz. Chemical shifts for aromatic PhF carbons are not reported.

*(2*R*,4*S*)-Methyl 2-oxo-3-(PhF)-1,2,3-oxathiazolidine-4-carboxylate ((2*R*)-**16**) and (2*S*,4*S*)-methyl 2-oxo-3-(PhF)-1,2,3-oxathiazolidine-4-carboxylate ((2*S*)-**16**)*

A solution of *N*-PhF-L-serine methyl ester ((*S*)-**15**, 3.57 g, 10 mmol, prepared according to ref. 23) in 150 mL of dichloromethane was cooled to 0°C, treated with imidazole (2.7 g, 40 mmol) followed by triethylamine (2.8 mL, 20 mmol), stirred for 10 min, then treated with thionyl chloride (0.8 mL, 11 mmol). After stirring an additional 45 min, water (100 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL) and the combined organic fractions were washed with water (2 × 50 mL), dried, filtered, and evaporated. The residue was normally used without purification in the next reaction. Purification of the residue by chromatography on silica gel with an eluant of 20–30% EtOAc in hexane provided 4 g (99%) of a 1:2 mixture of diastereomers ((2*R*)-**16** and (2*S*)-**16**). First to elute was (2*R*)-**16**: mp 83–84°C. $[\alpha]_D^{20}$ 121° (*c* 0.14, $CHCl_3$). TLC: R_f = 0.54 (30% EtOAc in hexanes). ^{1}H NMR δ: 3.42 (s, 3H), 3.51 (dd, 1H, *J* = 1.4, 7.1), 4.41 (dd, 1H, *J* = 1.4, 9.4), 4.75 (dd, 1H, *J* = 7.1, 9.4), 7.17–8.17 (m, 13H). ^{13}C NMR δ: 52.1, 59.0, 72.2, 75.2, 171.4. HRMS calcd. for $C_{23}H_{20}O_4NS$ (MH^+): 406.1113; found: 406.1130. Next to elute was (2*S*)-**16**: mp 71–72°C. $[\alpha]_D^{20}$ 243° (*c* 0.38, $CHCl_3$). TLC: R_f = 0.37 (30% EtOAc in hexanes). ^{1}H NMR δ: 3.37 (t, 1H, *J* = 7.9), 3.57 (s, 3H), 4.32 (t, 1H, *J* = 7.9), 4.95 (t, 1H, *J* = 7.9), 7.19–7.77 (m, 13H). ^{13}C NMR δ: 52.5, 61.3, 73.5, 76.2, 170.3. HRMS calcd. for $C_{23}H_{19}O_4NS$ (M^+): 405.1035; found: 405.1046.

*(4S)-Methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**17**)*

A solution of 2-oxo-1,2,3-oxathiazolidine **16** (1.25 g, 3.1 mmol) in 100 mL of acetonitrile was cooled to 0°C, treated with ruthenium(III) chloride monohydrate (10 mg) followed by sodium periodate (1.28 g, 6 mmol), stirred 10 min, and quenched with water (100 mL). After stirring for 4 h, the reaction mixture was diluted with ether

(100 mL) and the phases were separated. The aqueous phase was extracted with ether (3 × 60 mL). The combined organic fractions were washed with saturated aqueous sodium bicarbonate (100 mL) and brine (50 mL), dried, filtered, and evaporated to a residue that was purified by chromatography on silica gel with an eluant of 10–20% EtOAc in hexane. Evaporation of the collected fractions provided 1.14 g (87%) of **17**: mp 155–156°C. $[\alpha]_D^{20}$ 244° (*c* 0.1, $CHCl_3$). ^{1}H NMR δ: 3.64 (dd, 1H, *J* = 4.0, 8.2), 3.69 (s, 3H), 4.02 (dd, 1H, *J* = 8.2, 8.7), 4.38 (dd, 1H, *J* = 4.0, 8.7), 7.19–8.22 (m, 13H). ^{13}C NMR δ: 52.9, 58.8, 66.8, 77.9, 169.2. HRMS calcd. for $C_{23}H_{19}O_5NS$ (M^+): 421.0984; found: 421.0997.

*(2*S*)-*N*-*PhF*-*S*-cyanocysteine methyl ester (**18d**)*

A solution of (4*S*)-methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**17**, 48 mg, 0.12 mmol) in 5 mL of DMF was treated with potassium thiocynate 35 mg (0.36 mmol), stirred at room temperature for 36 h, poured into 1 M KH_2PO_4 (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried, filtered, and evaporated to a residue that was chromatographed on silica gel eluting with a gradient of 15–20% EtOAc in hexane. Concentration of the collected fractions provided 34.8 mg (72%) of **18d**: mp 149–150°C. $[\alpha]_D^{20}$ –287° (*c* 0.4, $CHCl_3$). ^{1}H NMR δ: 2.88 (dd, 1H, *J* = 4.7, 12.6,), 3.02 (dd, 1H, *J* = 4.7, 5.8), 3.13 (dd, 1H, *J* = 5.8, 12.6), 3.44 (brs, 1H), 3.48 (s, 3H), 7.23–7.75 (m, 13H). ^{13}C NMR δ: 39.5, 52.6, 54.9, 72.8, 112.8, 172.6. HRMS calcd. for $C_{24}H_{21}O_2SN_2$ (MH^+): 401.1324; found: 401.1339.

*(2*S*)-*N*-*(PhF)-3-azido-alanine methyl ester (**18e**)*

A solution of (4*S*)-methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**17**, 49 mg, 0.12 mmol) in 5 mL of DMF was treated with sodium azide (24 mg, 0.37 mmol), stirred at room temperature for 1 h, poured into 1 M KH_2PO_4 (20 mL), and extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with brine (10 mL), dried, filtered, and evaporated to a residue that was chromatographed on silica gel eluting with a gradient of 10–20% EtOAc in hexane. Concentration of the collected fractions provided 40.3 mg (90%) of **18e** as a thick clear oil. $[\alpha]_D^{20}$ –294° (*c* 0.12, $CHCl_3$). ^{1}H NMR δ: 2.85 (dd, 1H, *J* = 4.7, 5.3), 3.07 (dd, 1H, *J* = 4.7, 12.3), 3.18 (dd, 1H, *J* = 5.3, 12.3), 3.42 (s, 3H), 7.21–7.73 (m, 13H). ^{13}C NMR δ: 52.2, 54.5, 56.4, 73.0, 173.6. HRMS calcd. for $C_{23}H_{21}O_2N_4$ (MH^+): 385.1664; found: 385.1677.

*(2*S*)-Methyl 3-(1-imidazol)-2-[*N*-(PhF)amino]propionate (**18f**)*

A solution of (4*S*)-methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**17**, 100 mg, 0.24 mmol) in 15 mL of DME was treated with imidazole (49 mg, 0.72 mmol), heated at 80°C for 18 h, poured into 1 M KH_2PO_4 (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried, filtered, and evaporated to a residue that was chromatographed on silica gel eluting with a gradient of 5–10% MeOH in EtOAc. Concentration of the collected fractions provided 83.2 mg (85%) of **18f**: mp 146–147°C. $[\alpha]_D^{20}$ –241° (*c* 0.1, $CHCl_3$). MS (*m*/*z*): 410.2 (M + 1), 307.1, 289.1, 257.1, 241.1, 154.1. ^{1}H NMR δ: 2.85 (m, 1H), 3.16 (brs, 1H), 3.35 (s, 3H), 3.83 (dd, 1H, *J* = 4.9, 14.0), 3.94 (dd, 1H, *J* = 6.7, 14.0), 7.01–7.72 (m, 16H). ^{13}C NMR δ: 50.8, 52.3, 56.7, 72.9, 119.7, 128.4, 137.5, 173.4.

General procedure for ring opening of cyclic sulfamidate 17 with β-keto esters, β-keto ketones, and dimethyl malonate

A solution of sodium hydride (prewashed with hexane, 60 wt% in oil, 85 mg, 2.1 mmol) in DME (15 mL) was treated with the respective β-keto ester, β-keto ketone, or dimethyl malonate (3.6 mmol), stirred for 10 min, treated with (4*S*)-methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**17**, 380 mg, 0.9 mmol), heated at 60°C for 18 h, cooled to room temperature, and poured into 1 M NaH_2PO_4 (50 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (2 × 30 mL), dried, filtered, and evaporated to a residue.

*Methyl 5-oxo-4-(methylcarbonyl)-2-[*N*-(PhF)amino]hexanoate (**18i**)*

Methyl 5-oxo-4-(methylcarbonyl)-2-[*N*-(PhF)amino]hexanoate (**18i**) was prepared from 2,4-pentanedione and used directly in next step. HRMS calcd. for $C_{28}H_{28}O_4N$ (MH^+): 442.2018; found: 442.2033.

*Methyl 5-oxo-4-(phenylcarbonyl)-2-[*N*-(PhF)amino]hexanoate (**18j**)*

Methyl 5-oxo-4-(phenylcarbonyl)-2-[*N*-(PhF)amino]hexanoate (**18j**) was prepared from 1-benzoyl acetone and isolated by chromatography on silica gel eluting with a gradient of 10–20% EtOAc in hexane as a 1.1:1 mixture of diastereomers in 45% yield. ^{1}H NMR δ: 2.00 (s, 3H), 2.07 (m, 4H), 2.17 (s, 3H), 2.58 (m, 2H), 3.26 (s, 3H), 3.28 (s, 3H), 4.78 (t, 1H, *J* = 6.0), 4.83 (dd, 1H, *J* = 4.8, 7.4), 6.70–8.26 (m, 36H). ^{13}C NMR δ: 28.0, 28.7, 33.0, 33.2, 51.69, 51.73, 53.8, 54.5, 59.1, 59.3, 72.7, 72.8, 176.0 (2C), 195.0, 196.1, 202.9, 203.6. HRMS calcd. for $C_{33}H_{30}O_4N$ (MH^+): 504.2175; found: 504.2153.

*Methyl 5-oxo-4-(methyloxycarbonyl)-2-[*N*-(PhF)amino]hexanoate (**18k**)*

Methyl 5-oxo-4-(methyloxycarbonyl)-2-[*N*-(PhF)amino]hexanoate (**18k**) was prepared from methyl acetoacetate and used directly in next step. HRMS calcd. for $C_{28}H_{28}O_5N$ (MH^+): 458.1968; found: 458.1982.

*Methyl 5-oxo-4-(ethyloxycarbonyl)-2-[*N*-(PhF)amino]heptanoate (**18l**)*

Methyl 5-oxo-4-(ethyloxycarbonyl)-2-[*N*-(PhF)amino]heptanoate (**18l**) was prepared from ethyl propionylacetate and isolated as an inseparable 1.1:1 mixture of diastereomers by chromatography on silica gel eluting with a gradient of 10–20% EtOAc in hexane in 82% yield. ^{1}H NMR δ: 0.98 (t, 3H, *J* = 7.2), 1.11 (t, 3H, *J* = 7.2), 1.19 (t, 3H, *J* = 7.2), 1.28 (t, 3H, *J* = 7.2), 1.91–1.99 (m, 4H), 2.32–2.39 (m, 2H), 2.52–2.68 (m, 4H), 3.24 (s, 3H), 3.25 (s, 3H), 3.67 (t, 1H, *J* = 6.4), 3.89–4.10 (m, 3H), 4.23 (dd, 2H, *J* = 7.2, 14.1), 7.14–7.70 (m, 26H). ^{13}C NMR δ: 7.35, 7.59, 13.8, 13.9, 32.5, 32.7, 35.1, 35.3, 51.3, 51.6, 53.6, 54.1, 54.9, 55.6, 61.1, 61.4, 72.6, 72.7, 169.0, 169.7, 175.9, 176.0, 204.6, 205.5. HRMS calcd. for $C_{30}H_{31}O_5NNa$ (M^+ + Na): 508.2100; found: 508.2116.

*Methyl 6,6-dimethyl-5-oxo-4-(ethyloxycarbonyl)-2-[*N*-(PhF)amino]heptanoate (**18m**)*

Methyl 6,6-dimethyl-5-oxo-4-(ethyloxycarbonyl)-2-[*N*-(PhF)amino]heptanoate (**18m**) was prepared from ethyl pivaloylacetate and isolated as an 1:1 mixture of diastereomers by chromatography on silica gel eluting with a gradient of 10–20% EtOAc in hexane in 63% yield. ^{1}H NMR δ: 1.10 (s, 9H), 1.13 (t, 3H, *J* = 7.1), 1.27 (t, 3H, *J* = 7.1), 1.31 (s, 9H), 1.48 (m, 1H), 1.58 (m, 1H), 2.03 (m, 1H), 2.33 (m, 1H), 2.60 (m, 2H), 3.26 (s, 6H), 3.81–3.98 (m, 3H), 4.24 (q, 2H, *J* = 7.1), 4.45 (dd, 1H, *J* = 2.4, 10.4), 7.14–7.71 (m, 26H). ^{13}C NMR δ: 13.7, 14.0, 26.0, 26.2, 33.5, 34.4, 45.3, 45.6, 47.9, 49.8, 51.5, 51.7, 53.6, 54.6, 60.8, 61.2, 72.6, 72.8, 168.9, 169.5, 175.4, 176.5, 209.9, 210.5. HRMS calcd. for $C_{32}H_{35}O_5NNa$ (M^+ + Na): 536.2413; found: 536.2392.

*4-(Methyloxycarbonyl)-2-[*N*-(PhF)]glutamate dimethyl ester (**18n**)*

4-(Methyloxycarbonyl)-2-[*N*-(PhF)]glutamate dimethyl ester (**18n**) was prepared from dimethyl malonate and isolated as a 1:1 mixture of diastereomers by chromatography on silica gel eluting with a gradient of 10–20% EtOAc in hexane in 65% yield. ^{1}H NMR δ: 2.03 (m, 2H), 2.61 (dd, 1H, *J* = 4.7, 8.9), 3.20 (s, 3H), 3.36 (s, 3H), 3.57 (s, 3H), 3.73 (m, 1H), 7.11–7.67 (m, 13H). ^{13}C NMR δ: 33.3, 48.3, 51.5, 52.3, 52.5, 53.7, 72.6, 166.8, 169.0, 169.8. HRMS calcd. for $C_{28}H_{27}O_6NNa$ (M^+ + Na): 496.1736; found: 496.1728.

*Methyl 4-nitro-2-[*N*-(PhF)amino]pentanoate (**18o**)*

A solution of sodium hydride (prewashed with hexane, 60 wt% in oil, 40 mg, 1 mmol) in DME (12 mL) was treated with nitroethane (0.2 mL, 2.8 mmol), stirred at 60°C for 3 h, treated with (4*S*)-methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**17**, 100 mg, 0.24 mmol), heated at 60°C for 36 h, cooled to room temperature, and poured into 1 M NaH_2PO_4 (30 mL). The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic phases were washed with brine (2 × 30 mL), dried, filtered, and evaporated. Purification of the residue by chromatography on silica gel with an eluant of 0–20% EtOAc in hexane provided 52 mg (52%) of a 10:1 mixture of diastereomers **18o**. The spectra data for the major isomer was as follows. ^{1}H NMR δ: 1.51 (d, 3H, *J* = 6.9), 1.73 (ddd, 1H, *J* = 3.4, 9.4, 14.8), 2.16 (ddd, 1H, *J* = 4.2, 9.1, 14.8), 2.64 (dd, 1H, *J* = 3.4, 9.1), 3.25 (s, 3H), 4.92 (m, 1H), 7.15–7.71 (m, 13H). ^{13}C NMR δ: 20.3, 39.1, 51.8, 52.6, 72.6, 79.4, 175.6. HRMS calcd. for $C_{25}H_{25}O_4N_2$ (MH^+): 417.1814; found: 417.1826.

*Methyl 5-oxo-2-[*N*-(PhF)amino]hexanoate (**20k**)*

Crude methyl 5-oxo-4-(methyloxycarbonyl)-2-[*N*-(PhF)amino]hexanoate (**18k**) was dissolved in EtOH (10 mL), treated with 1 N NaOH (10 mL), and heated at a reflux for 5 h. The mixture was cooled to room temperature and adjusted to pH 5 using 10% HCl. The solution was extracted with EtOAc (3 × 30 mL) and the combined organic phases were washed with brine (30 mL), dried, filtered, and evaporated to a residue that was dissolved in acetonitrile (20 mL), treated with K_2CO_3 (300 mg, 2.2 mmol) and iodomethane (0.3 mL, 4.8 mmol), and stirred at room temperature for 18 h. Brine (50 mL) was added to the reaction mixture, which was extracted with EtOAc (3 × 30 mL). The organic phases were combined, washed with 0.65 M sodium thiosulfate (50 mL) and brine (50 mL), dried, filtered, and evaporated to a residue that was purified by chromatography on silica gel using a gradient of 10–20% EtOAc in hexane. Evaporation of the collected fractions gave 259 mg (71% overall from **17**) of **20k**. ^{1}H NMR δ: 1.71 (m, 2H), 2.11 (s, 3H), 2.45–2.61 (m, 3H), 3.29 (s, 3H), 7.18–7.73 (m, 13H). ^{13}C NMR δ: 28.6, 29.8, 39.6, 51.5, 54.6, 72.8, 176.3, 207.8. HRMS calcd. for $C_{26}H_{26}O_3N$ (MH^+): 400.1913; found: 400.1905.

cis-N-*(BOC)-5-methylproline methyl ester (*cis-***21***)*

A solution of methyl 5-oxo-2-[*N*-(PhF)amino]hexanoate (**20k**, 400 mg, 1 mmol) and di-*tert*-butyldicarbonate (670 mg, 3 mmol) in MeOH (50 mL) was placed into a hydrogenation vessel and treated with palladium-on-carbon (10 wt%, 65 mg). The vessel was filled, vented and filled three times with hydrogen, and the mixture was stirred under 4 atm of hydrogen for 48 h. The mixture was filtered on Celite™ and washed with MeOH (50 mL). The combined organic phase was evaporated to a residue that was purified by chromatography on silica gel using a gradient of 10–15% EtOAc in hexane. Evaporation of the collected fractions gave 225 mg (92%) of *cis*-**21** as an oil. ^{1}H NMR δ (showed a mixture of carbamate isomers): 1.24 (d, 6H, *J* = 6.2), 1.38 (s, 9H), 1.42 (s, 9H), 1.58 (m, 2H), 1.97 (m, 4H), 2.14 (m, 2H), 3.68 (s, 6H), 3.86 (m, 1H), 3.98 (m, 1H), 4.16 (m, 1H), 4.27 (m, 1H). ^{13}C NMR δ (showed a mixture of carbamate isomers): 19.7, 20.5, 28.3, 28.7, 31.6, 32.4, 51.9, 53.9, 59.7, 60.0, 79.5, 158.2, 159.0, 173.0, 173.9. HRMS calcd. for $C_{12}H_{22}O_4N$ (MH^+): 244.1549; found: 244.1556.

cis-N-*(BOC)-5-methylproline (*cis-***22***)*

Methyl ester **21** (110 mg, 0.45 mmol) was dissolved in 10 mL of Et_2O, treated with $KOSi(Me)_3$ (70 mg, 0.55 mmol) and stirred for 18 h at room temperature. The reaction mixture was extracted with water (5 × 20 mL), and the aqueous phases were combined, acidified with acetic acid to pH 2, saturated with NaCl, and extracted with EtOAc (3 × 30 mL). The organic phases were combined, dried, filtered, and evaporated to give 99.4 mg (0.43 mmol, 96%) of *cis*-**22**. ^{1}H NMR (CD_3OD) δ (showed a mixture of carbamate isomers): 1.27 (d, 3H, *J* = 6.2), 1.42 (brs, 9H), 1.65 (m, 1H), 2.02 (m, 2H), 2.23 (m, 1H), 3.96 (m, 1H), 4.18 (m, 1H). ^{13}C NMR (CD_3OD) δ (showed a mixture of carbamate isomers): 20.1, 20.9, 28.6, 28.8, 29.3, 29.8, 32.7, 33.4, 49.6, 49.8, 55.4, 55.7, 61.2, 61.5, 81.2, 81.3, 155.4, 155.8, 176.6, 176.8. HRMS calcd. for $C_{11}H_{20}O_4N$ (MH^+): 230.1392; found: 230.1385.

Enantiomeric purity of cis-N-*(BOC)-5-methylproline (*cis-***22***)*

A room-temperature solution of *cis-N*-(BOC)-5-methylproline (*cis*-**22**, 20 mg, 0.09 mmol) and either (*R*) or (*S*)-α-methylbenzylamine (28 μL, 0.22 mmol) in 1 mL of acetonitrile was treated with benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (30 mg, 0.09 mmol) and stirred for 2 h when TLC showed complete disappearance of the starting acid. Brine (2 mL) was added to the reaction mixture, which was then extracted with EtOAc (2 ×

3 mL). The combined organic phase was extracted with 2 N HCl (2 × 2 mL) and $NaHCO_3$ (2 × 2 mL), washed with H_2O (2 × 2 mL) and brine, dried, filtered, and evaporated to a residue that was dissolved in CH_2Cl_2 (5 mL), treated with 0.5 mL TFA, and stirred at room temperature for 1 h. The solution was concentrated, dried, and directly examined by ^{1}H NMR spectroscopy. When (*S*)- and (*R*)-α-methylbenzylamine of 99% diastereomeric purity were used, respectively, the same mixture of diastereomers were obtained. Examination of the methyl doublets at 1.50, 1.49, 1.46, and 1.42 ppm in the ^{1}H NMR spectra in $CDCl_3$ demonstrated **31** to be of 1.1:1 mixture of diastereomers. Hence, *cis*-**22** is presumed to be of 10% enantiomeric excess.

5-Methylproline N′-α-*methyl-benzylamide trifloroacetate (**31**)*

^{1}H NMR (CD_3OD) δ: 1.42 (d, 3H, *J* = 6.6), 1.46 (d, 3H, *J* = 6.6), 1.49 (d, 3H, *J* = 7.0), 1.50 (d, 3H, *J* = 7.0), 1.60 (m, 1H), 1.73 (m, 1H), 2.04 (m, 1H), 2.19 (m, 3H), 2.42 (m, 2H), 3.74 (m, 2H), 4.31 (m, 2H), 5.04 (m, 2H), 7.22–7.37 (m, 10H).

*Methyl [*N*-(PhF)amino]-3-(3,5-dimethyl-2*H*-pyrazol-4-yl)propanoate (**24**)*

Crude methyl 5-oxo-4-(methylcarbonyl)-2-[*N*-(PhF)amino]hexanoate (**18i**) was dissolved in dioxane (10 mL), treated with hydrazine hydrate (60 μL, 1.7 mmol), stirred for 1.5 h, and poured into 1 M NaH_2PO_4 (30 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phase was washed with brine (2 × 30 mL), dried, filtered, and evaporated. The residue was normally used without purification in the next reaction. Purification of the residue by chromatography on silica gel with an eluant of 20–30% EtOAc in hexane provided 169 mg (43% overall from **17**) of **24**. ^{1}H NMR δ: 1.99 (s, 6H), 2.50 (m, 2H), 2.58 (m, 1H), 3.22 (s, 3H), 6.73–7.69 (m, 13H). ^{13}C NMR δ: 10.5, 28.8, 51.4, 56.0, 72.9, 111.1, 142.8, 176.6. HRMS calcd. for $C_{28}H_{28}O_2N_3$ (MH^+): 438.2181; found: 438.2189.

*2-*N*-(PhF)Amino-3-(3,5-dimethyl-1*H*-pyrazol-4-yl)propionic acid (**25**)*

Crude methyl [*N*-(PhF)amino]-3-(3,5-dimethyl-2*H*-pyrazol-4-yl)propanoate (**24**) was dissolved in EtOH (5 mL), treated with 1 N NaOH (5 mL), heated at 60°C for 3 h, cooled to room temperature, and then poured into 1 M NaH_2PO_4 (50 mL). The mixture was extracted with EtOAc (2 × 30 mL). The combined organic phases were extracted with 1 N NaOH (2 × 30 mL), the aqueous phase was combined, acidified with citric acid to pH 2, and extracted with EtOAc (2 × 30 mL). The organic phases were combined, dried, filtered, and evaporated to a residue that was purified by chromatography on silica gel with a gradient of 10–20% MeOH in EtOAc as eluant. Evaporation of the collected fractions gave 143 mg (37% over all from **17**) of **25**. ^{1}H NMR (CD_3OD) δ: 1.95 (s, 6H), 2.50–2.54 (m, 3H), 6.61–7.72 (m, 13H). ^{13}C NMR (CD_3OD) δ: 10.5, 29.9, 57.7, 74.3, 112.6, 144.1, 179.1. HRMS calcd. for $C_{27}H_{26}N_3O_2$ (MH^+): 424.2025; found: 424.2043.

*Amino-3-(3,5-dimethyl-1*H*-pyrazol-4-yl)propionic acid (**26**)*

2-[*N*-(PhF)Amino]-3-(3,5-dimethyl-1*H*-pyrazol-4-yl)propionic acid (**25**, 143 mg, 0.34 mmol) was dissolved in 10 mL of CH_2Cl_2, treated with 2 mL of CF_3CO_2H, and heated at a reflux for 18 h. The volatiles were evaporated, and the residue was treated with 10 mL of H_2O and filtered. The aqueous solution was washed with hexanes (2 × 20 mL), and then evaporated to a solid 55 mg (88%) of **26**. ^{1}H NMR (CD_3OD) δ: 2.39 (s, 6H), 3.07 (dd, 1H, *J* = 7.2, 15.3), 3.19 (dd, 1H, *J* = 7.2, 15.3), 4.13 (t, 1H, *J* = 7.2). ^{13}C NMR (CD_3OD) δ: 9.7, 24.6, 53.4, 113.2, 146.1, 170.9. HRMS calcd. for $C_8H_{14}N_3O_2$ (MH^+): 184.1086; found: 184.1090.

*(2*S*)-*N*-PhF-Alanine methyl ester (**27**)*

(2*S*)-*N*-(PhF)-*S*-Cyanocysteine methyl ester (**18d**, 35 mg, 0.09 mmol) was dissolved in EtOAc (10 mL) and treated with Raney nickel (50% slurry in water, ≈ 200 mg). The mixture was heated at a reflux for 6 h, cooled to room temperature, and filtered through Celite™ to remove the catalyst. The filtrate was concentrated. The residue was used without purification in the next reaction. ^{1}H NMR δ: 1.14 (d, 3H, *J* = 7.0), 2.79 (dd, 1H, *J* = 7.0, 14.1), 3.31 (s, 3H), 7.17–7.73 (m, 13H).

*(2*S*)-*N*-PhF-Alanine (**28**)*

Crude (2*S*)-*N*-PhF-alanine methyl ester (**27**) was dissolved in ethanol (5 mL), treated with 1 N NaOH (5 mL), and heated at 75°C for 1 h. The mixture was cooled to room temperature, poured into 1 M KH_2PO_4 (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (2 × 10 mL), dried, filtered, and evaporated to a residue. Purification of the residue by chromatography on silica gel with an eluant of 60–70% EtOAc in hexane provided 22 mg (74% overall from **18d**) of **28**. $[\alpha]_D^{20}$ 150° (*c* 0.2, $CHCl_3$), lit. (9) $[\alpha]_D^{20}$ 163° (*c* 1, $CHCl_3$). ^{1}H NMR δ: 1.13 (d, 3H, *J* = 7.2), 2.71 (q, 1H, *J* = 7.2), 7.18–7.75 (m, 13H). ^{13}C NMR δ: 19.7, 52.2, 73.0, 175.9.

*(2*S*)-3-(1-Imidazol)-2-[*N*-(PhF)amino]propionic acid (**29**)*

Ester hydrolysis was performed on **18f** (83 mg, 0.2 mmol) using the same conditions described for the preparation of **28** and provided 69 mg (86%) of **29**: mp 156–157°C. $[\alpha]_D^{20}$ –149° (*c* 0.42, $CHCl_3$). ^{1}H NMR δ: 2.97 (t, 1H, *J* = 4.1), 3.94 (dd, 1H, *J* = 4.1, 13.6), 4.23 (dd, 1H, *J* = 4.1, 13.6), 7.18–7.70 (m, 15H), 8.86 (brs, 1H). ^{13}C NMR δ: 52.7, 56.4, 73.2, 119.4, 122.1, 135.6, 172.7. HRMS calcd. for $C_{25}H_{21}O_2N_3$ (M^+): 395.1634; found: 395.1644.

*Enantiomeric purity of (2*S*)-3-(1-imidazol)-2-[*N*-(PhF)amino]propionic acid (**29**)*

A solution of **29** (10 mg, 0.025 mmol) in acetonitrile (1 mL) was treated with D- or L- phenylalanine methyl ester hydrochloride (11 mg, 0.05 mmol), TBTU (16 mg, 0.05 mmol), and diisopropylethylamine (35 μL, 0.20 mmol) at room temperature. After stirring for 1 h, the solution was diluted with ethyl acetate (5 mL), washed with water (2 × 5 mL) and brine (5 mL), dried, and concentrated in vacuo to a crude oil, which was directly examined by ^{1}H NMR spectroscopy. The limits of detection were determined by measuring the diastereomeric methyl ester singlets at 3.71 and 3.76 ppm in $CDCl_3$ in the 400 MHz ^{1}H NMR spectra. Purification by chromatography using a gradient of 5–10%

methanol in EtOAc as eluant gave dipeptides having the following spectra.

*(2*S*)-3-(1-Imidazol)-2-[*N*-(PhF)amino]propionyl-*D*-phenylalanine methyl ester (2′*R*) (**30**)*

^{1}H NMR δ: 2.73 (m, 1H), 2.97 (dd, 1H, *J* = 8.1, 14.1), 3.16 (dd, 1H, *J* = 5.3, 14.1), 3.49 (dd, 1H, *J* = 4.1, 14.6), 3.76 (s, 3H), 4.09 (m, 1H), 4.49 (m, 1H), 7.01–7.68 (m, 21H).

*(2*S*)-3-(1-Imidazol)-2-[*N*-(PhF)amino]propionyl-*L*-phenylalanine methyl ester (2′*S*) (**30**)*

^{1}H NMR δ: 2.80 (m, 1H), 2.88 (dd, 1H, *J* = 6.0, 13.7), 3.11 (dd, 1H, *J* = 5.3, 13.7), 3.56 (dd, 1H, *J* = 4.3, 13.9), 3.71 (s, 3H), 4.21 (m, 1H), 4.73 (m, 1H), 6.80–7.72 (m, 21H).

*Methyl 1-*N*-PhF-2-methyl-3-[(methyloxy)carbonyl]-*Δ^2*-pyrroline (**33**)*

A solution of (4*S*)-methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**17**, 60 mg, 0.14 mmol) in 8 mL of DME was treated with NaH (40 mg, 1 mmol), stirred at room temperature for 30 min. A 0.5 mL aliquot was taken, poured into 1 M KH_2PO_4, and extracted with EtOAc (2 × 10 mL). The combined organic fractions were concentrated, dried on vacuum, and examined directly by ^{1}H NMR spectroscopy, which showed complete conversion to dehydroalanine **19**. ^{1}H NMR δ: 3.76 (s, 3H), 4.63 (brs, 1H), 5.62 (brs, 1H), 7.20–7.74 (m, 13H)). In a separate flask, a solution of methyl acetoacetate (50 μL, 0.46 mmol) in 3 mL of DME was treated with NaH (25 mg, 0.6 mmol) and stirred at room temperature for 1 h. The enolate solution was then added to the remaining solution of dehydroalanine, stirred at a reflux for 18h, poured into 40 mL of 1 M KH_2PO_4, and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (2 × 30 mL), dried, filtered, and evaporated to a residue that was chromatographed on silica gel eluting with a gradient of 10–15% EtOAc in hexane. Concentrated of the collected fractions provided 49.6 mg (87%) of **33**. ^{1}H NMR δ: 2.08 (s, 3H), 2.48 (dd, 1H, *J* = 6.8, 12.8), 2.82 (t, 1H, *J* = 12.8), 3.47 (dd, 1H, *J* = 6.8, 12.8), 3.48 (s, 3H), 3.61 (s, 3H), 7.12–7.77 (m, 13H). ^{13}C NMR δ: 13.4, 33.8, 50.8, 52.2, 61.9, 103.5, 161.9, 166.7, 174.7, 174.8. HRMS calcd. for $C_{28}H_{26}O_4N$ (MH^+): 440.1862; found: 440.1870.

Acknowledgment

This research was supported in part by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Ministère de l'Éducation du Québec. The crystal structure analysis of compound (2*R*)-**16** was performed by Francine Bélanger-Gariépy at l'Université de Montréal X-ray crystallography facility.

References

1. J.E. Baldwin, A.C. Spivey, and C.J. Schofield. Tetrahedron: Asymmetry, **1**, 881 (1990).
2. B.M. Kim and S.M. So. Tetrahedron Lett. **39**, 5381 (1998).
3. L.T. Boulton, H.T. Stock, J. Raphy, and D.C. Horwell. J. Chem. Soc. Perkin Trans. 1, 1421 (1999).
4. S.V. Pansare and J.C. Vederas. J. Org. Chem. **54**, 2311 (1989), and refs. 2*a–d* cited within.
5. S.V. Pansare, G. Huyer, L.D. Arnold, and J.C. Vederas. Org. Synth. **70**, 1 (1992).
6. L. Dubois, A. Mehta, E. Tourette, and R.H. Dodd. J. Org. Chem. **59**, 434 (1994), and refs. 1–13 cited within.
7. B. Hofmann, P. Dauban, J.P. Biron, P. Potier, and R.H. Dodd. Heterocycles, **46**, 473 (1997).
8. B.D. Christie and H. Rapoport. J. Org. Chem. **50**, 1239 (1985).
9. W.D. Lubell and H. Rapoport. J. Am. Chem. Soc. **109**, 236 (1987).
10. L. Wei and W.D. Lubell. Org. Lett. **2**, 2595 (2000).
11. D. Alker, K.J. Doyle, L.M. Harwood, and A. McGregor. Tetrahedron: Asymmetry, **1**, 877 (1990).
12. M. Pilkington and J.D. Wallis. J. Chem. Soc. Chem. Commun. 1857 (1993).
13. H.S.H. Gautun, T. Bergan, and P.H.J. Carlsen. Acta Chim. Scand. **53**, 446 (1999).
14. G.J. White and M.E. Garst. J. Org. Chem. **56**, 3178 (1991).
15. H.S.H. Gautun and P.H.J. Carlsen. Tetrahedron: Asymmetry, **6**, 1667 (1995).
16. (*a*) B. Aguilera, A. Fernandez-Mayoralas, and C. Jaramillo. Tetrahedron, **53**, 5863 (1997); (*b*) B. Aguilera and A. Fernandez-Mayoralas. J. Org. Chem. **63**, 270 (1998).
17. K.K. Andersen and M. Kociolek. J. Org. Chem. **60**, 2003 (1995).
18. M.E. Van Dort, Y.W. Jung, P.S. Sherman, M.R. Kilbourn, and D.M. Wieland. J. Med. Chem. **38**, 810 (1995).
19. M. Okuda and K. Tomioka. Tetrahedron Lett. **35**, 4585 (1994).
20. D. Ok, M.H. Fisher, M.J. Wyvratt, and P.T. Meinke. Tetrahedron Lett. **40**, 3831 (1999).
21. B. Aguilera and A. Fernandez-Mayoralas. Chem. Commun. 127 (1996).
22. T.A. Lyle, C.A. Mafill, and S.M. Pizenberger. J. Am. Chem. Soc. **109**, 7890 (1987).
23. W.D. Lubell and H. Rapoport. J. Org. Chem. **54**, 3824 (1989).
24. G. Lowe and M.A. Reed. Tetrahedron: Asymmetry, **1**, 885 (1990).
25. B.B. Lohray. Synthesis, 1035 (1992).
26. J.A. Deyrup and C.L. Moyer. J. Org. Chem. **34**, 175 (1969).
27. M. Atfani and W.D. Lubell. J. Org. Chem. **60**, 3184 (1995).
28. J.M. Huphrey, R.J. Bridges, J.A. Hart, and A.R. Chamberlin. J. Org. Chem. **59**, 2467 (1994).
29. E. Beausoleil, B. L'Archevêque, L. Bélec, M. Atfani, and W.D. Lubell. J. Org. Chem. **61**, 9447 (1996).
30. H. Li, T. Sakamoto, and Y. Kikugawa. Tetrahedron Lett. **38**, 6677 (1997).
31. T.L. Ho, B. Gopalan, J.J. Nestor Jr. J. Org. Chem. **51,** 2405 (1986).
32. H.H. Ibrahim and W.D. Lubell. J. Org. Chem. **58**, 6438 (1993).
33. M.M. Paz and J. Sardina. J. Org. Chem. **58**, 6990 (1993).
34. R.J. Cherney and L. Wang. J. Org. Chem. **61**, 2544 (1996).