7.4, 1 mM DTT, 2 mM EDTA, 5 μg/mL PS): [S240K(DnsG)] = 0.5 μM, [PDBu] = 0 to 0.8 μM. λ_{ex} = 330 nm.

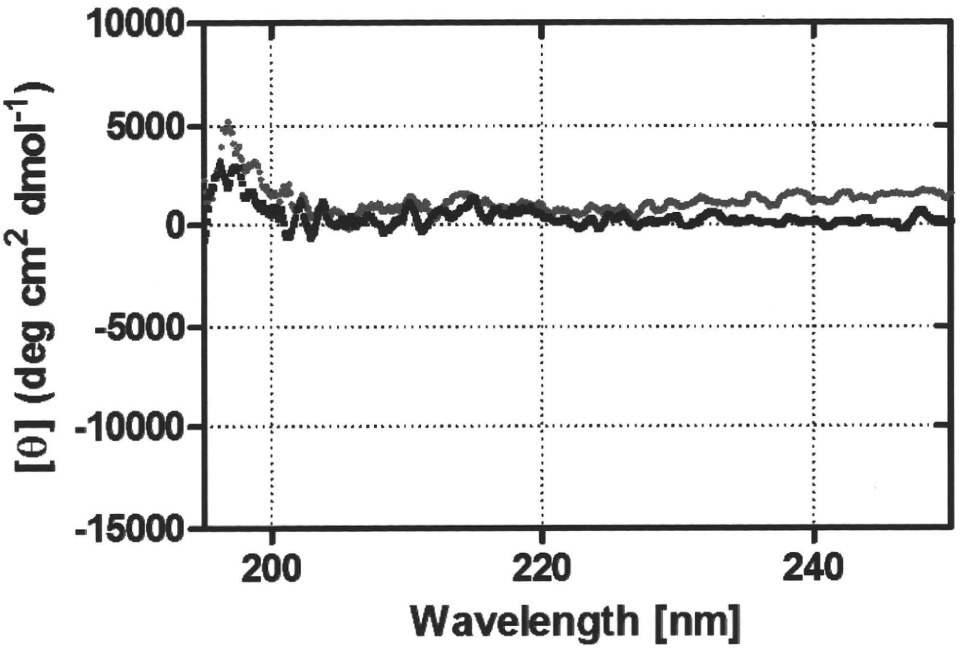


Figure S3. CD spectra of Y238K(DnsG)-δC1b(231-281) in the presence and absence of $ZnCl_2$. The buffer contains 50 mM Tris-HCl (pH 7.5) and 1 mM DTT. Spectra shown are as follows: blue dots, peptide (4.85 μM) only; black dots, peptide (4.85 μM) + 97 μM $ZnCl_2$ (20 eq).

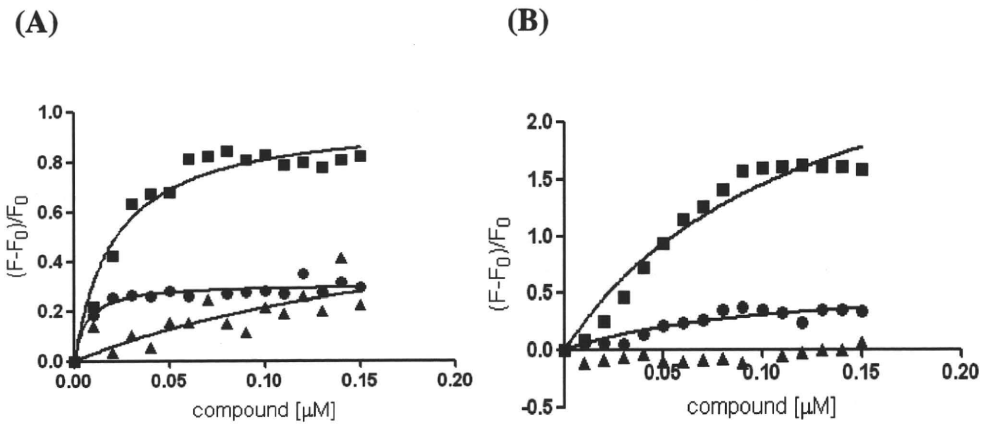


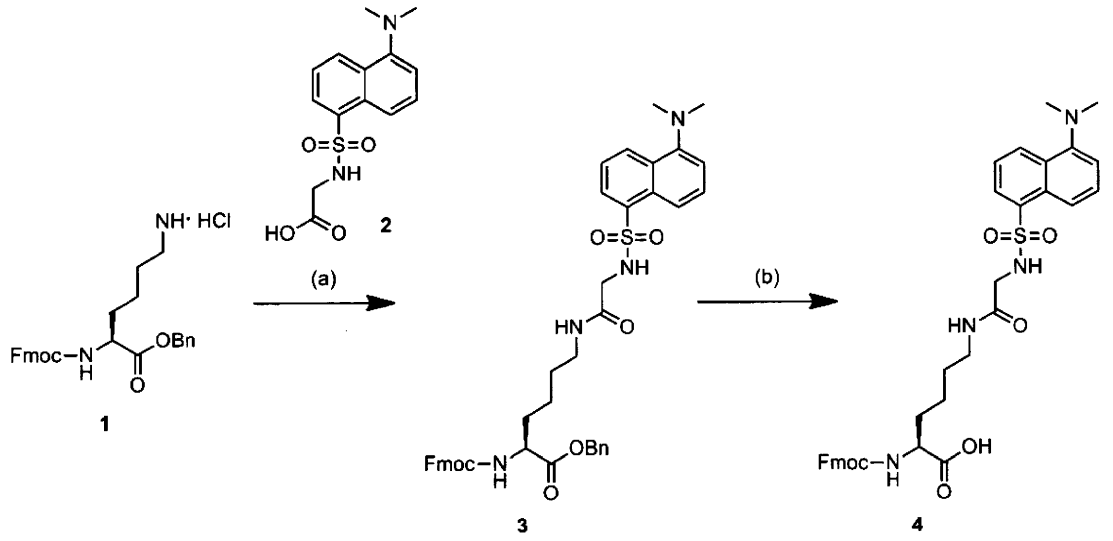
Figure S4. Fitting curves based on titration of ligands to the dansyl-labeled δC1b domains.

(A) S240K(DnsG), (B) T242K(DnsG). Fitting was performed using following formula.

$\Delta F = \Delta F_{max} \times ([compound] / (K_d + [compound]))$

Supporting Information Scheme

Scheme S1. Synthesis of the dansylated lysine (**4**).



Condition: (a) compound **2**, HOBt•H_2O, EDCI•HCl, *N*-methylmorpholine, dry CH_2Cl_2, 87%; (b) Pd/C, AcOH, CH_3OH, H_2, 88%.

Supporting Information Methods

(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-6-(2-(5-(dimethylamino)naphthalene-1-sulfonamido)acetamido)hexanoic acid (4):

Compounds **1** and **2** were synthesized based on the reported papers.[1, 2] **1** (990 mg, 2.0 mmol, 1.0 eq), **2** (678 mg, 2.2 mmol, 1.1 eq), and HOBt·H_2O (337 mg, 2.2 mmol, 1.1 eq) were dissolved in CH_2Cl_2 (5 mL) at 0°C and stirred for 10 min, and *N*-methylmorpholine (459 mL, 4.2 μmol, 2.1 eq) was then added dropwise to the mixture. After the addition of EDCI·HCl (422 mg, 2.2 mmol, 1.1 eq), the stirring was continued at 0 °C for 2 h and then

at room temperature for 2 h. After concentration of the reaction mixture under reduced pressure followed by extraction with EtOAc, the extract was purified by short column chromatography ($CHCl_3$-CH_3OH, 45:1) to yield compound **3** (1.3 mg, 1.7 mmol, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26-1.34 (m, 4H), 1.64-1.72 (m, 2H), 2.84 (s, 6H), 3.04-3.12 (m, 2H), 3.46-3.47 (m, 2H), 4.17-4.21 (m, 1H), 4.36-4.43 (m, 3H), 5.14-5.22 (m, 2H), 5.46-5.48 (m, 1H), 5.58-5.61 (m, 1H), 6.31-6.33 (m, 1H), 7.14-7.16 (m, 1H), 7.27-7.40 (m, 9H), 7.44-7.48 (m, 1H), 7.52-7.59 (3H), 7.74-7.76 (m, 2H), 8.19-8.25 (m, 2H), 8.52-8.54 (m, 1H) ; LRMS (ESI), *m/z* calcd for $C_{42}H_{45}N_4O_7S$ [M+H$^+$] 749.3, found 749.6.

Compound **3** was dissolved in AcOH (70 mL) and CH_3OH (15 mL), and then treated with Pd/C and H_2 for 2.5 h. After filtration of the mixture and concentration under reduced pressure, flash column chromatography with hexane-AcOEt (1:3) containing 0.1 % AcOH gave the title compound **4** (1.0 g, 1.5 mmol, 88% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.20-1.26 (br, 4H), 1.52-1.67 (m, 2H), 2.82 (s, 6H), 2.89 (br, 2H), 3.40-3.46 (m, 2H), 3.84-3.93 (m, 1H), 4.18-4.24 (m, 1H), 4.26-4.29 (m. 2H), 7.24-7.26 (m, 1H), 7.30-7.34 (m, 2H), 7.39-7.43 (m, 2H), 7.56-7.62 (m, 3H), 7.65-7.67 (m, 1H), 7.71-7.73 (m, 2H), 7.88-7.90 (m, 2H), 8.12-8.13 (m, 1H), 8.21-8.24 (m, 1H), 8.29-8.31 (m, 1H), 8.44-8.46 (m, 1H), 12.55 (m, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 22.9, 28.4, 30.3, 38.3, 45.0, 45.1, 46.6, 53.7, 65.6, 115.1, 119.2, 120.1, 123.5, 125.2, 127.0, 127.6, 127.9, 128.2, 129.1, 129.4, 135.8, 140.7, 143.8, 143.8, 151.3, 156.1, 167.3, 173.9; HRMS (FAB), *m/z* calcd for $C_{35}H_{39}N_4O_7S$ [M+H$^+$] 659.2534, found 659.2531.

Preparation of Fmoc-His(Trt)-Trt(2-Cl)-resin

2-Chlorotrityl chloride resin (1.4 mmol/g, 1.4 mmol) (Novabiochem) was treated with Fmoc-His(Trt)-OH (0.63 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (2.25 mmol) in

dry CH_2Cl_2 (10 mL) for 1 h. The resin was dried *in vacuo* after washing with dry CH_2Cl_2. The loading was determined by measuring UV absorption at 301 nm of the piperidine-treated Fmoc-His(Trt)-Trt(2-Cl)-resin (0.42 mmol/g).

Synthesis of Y238K(DnsG)-δC1b(231-281)

Y238K(DnsG)-δC1b(231-246) were manually elongated on an Fmoc-His(Trt)-Trt(2-Cl)-resin (0.40 mmol/g) by Fmoc-based SPPS as in the synthesis of δC1b(247-281). The following side-chain protecting groups were used; Boc for Lys, Pbf for Arg, OBu^t for Asp, Trt for Asn, Cys, and His, Bu^t for Ser, Thr, and Tyr. At the dansyl-labeled position, Fmoc-Lys(DnsGly)-OH was used. The resulting protected peptides were cleaved from the resin with trifluoroethanol (TFE)-AcOH-DCM (1:1:3, v/v) (2 h treatment), followed by thioesterification. Deprotection was performed as in the synthesis of δC1b(247-281). The product was then purified by RP-HPLC. Thioesterification was performed with ethyl mercaptopropionate (20 equiv), HOBt·H_2O (10 equiv), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI)·HCl (10 equiv) in DMF (1.5 mL) (0°C, overnight). DMF was removed by evaporation, and the crude products were washed with H_2O. Y238K(DnsG)-δC1b(231-246) (0.5 mg, 0.2 μmol) and the δC1b(247-281) (0.8 mg, 0.2 μmol) were dissolved in 500 μL of 100 mM phosphate buffer (pH 8.5) containing 6M guanidine hydrochloride (Gn·HCl) containing 2 mM EDTA and tris(2-carboxyethyl)phosphine hydrochloride (TCEP·HCl) (0.7 mg, 2.4 μmol). Thiophenol (15 μl, 3%) was then added to the mixture. The ligation reaction was performed at 37 °C under an N_2 atmosphere. Progress of the ligation reaction was monitored by RP-HPLC (gradient; 25-45% of acetonitrile/0.1% TFA against H_2O/0.1% TFA). The product was subjected to gel filtration with Sephadex G-10 and then purified by RP-HPLC.

Analysis of Inhibition of [^{3}H]PDBu Binding by Non-radioactive Ligands

Competition for [^{3}H]PDBu binding to the PKC δ isozyme by different compounds was assayed as described previously.[3] Two hundred and fifty μL of the assay mixture contains 50 mM Tris·HCl (pH 7.4), 1 mM ethylenebis(oxyethylenenitrilo)tetraacetic acid (EGTA), 0.1 mg/mL phosphatidylserine, 5 mg/mL bovine immunoglobulin G, 7 nM [^{3}H]PDBu and increasing concentrations of non-radioactive ligand. After addition of protein, binding was carried out at 18 °C for 10 min. Samples were then incubated on ice for 10 min. Two hundred μL of 35% polyethylene glycol in 50 mM Tris·HCl (pH 7.4) was added, and the samples were incubated on ice for an additional 10 min. The tubes were centrifuged at 4 °C (15,000 rpm, 15 min), and 100 μL aliquots of each supernatant were then transferred to scintillation vials for determination of the amount of the free [^{3}H]PDBu. After the remaining supernatant was aspirated off, the bottom of each centrifuge tube was cut off just above the pellet and transferred to a scintillation vial for the determination of the amount of the total bound [^{3}H]PDBu. To calculate K_i values, nonlinear least squares analysis was used.

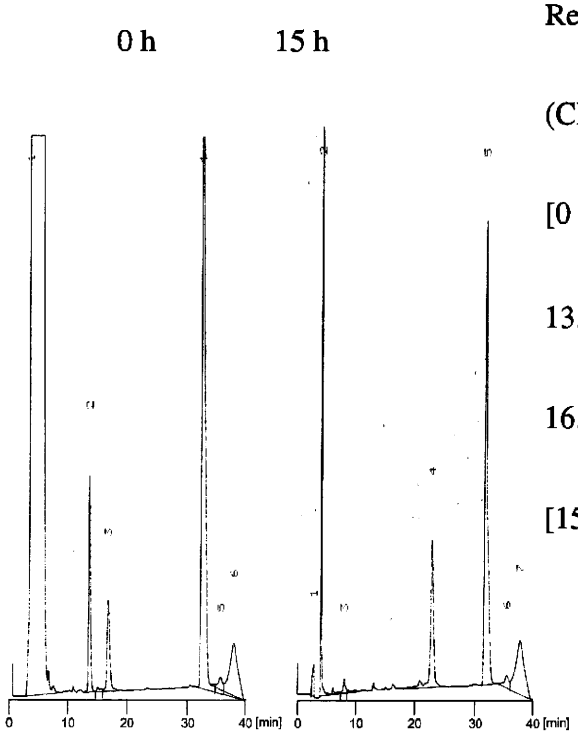
Table S1. Yields and ESI-TOF-MS data of peptide fragments.

peptide	yield (%)	found	calcd. $(M+H)^+$	molecular formula $(M+H)^+$
δC1b(247-281)	3.8	3828.3	3827.9	$C_{161}H_{268}N_{51}O_{45}S_6$
Y238K(DnsG)-δC1b(221-246)	20	3716.1	3716.7	$C_{166}H_{243}N_{44}O_{44}S_5$
S240K(DnsG)-δC1b(221-246)	21	3794.2	3792.7	$C_{172}H_{247}N_{44}O_{44}S_5$
T242K(DnsG)-δC1b(221-246)	16	3781.2	3778.7	$C_{171}H_{245}N_{44}O_{44}S_5$

Table S2. ESI-TOF-MS data of dansyl-labeled δC1b peptides.

peptide	found	calcd. $(M+H)^+$	molecular formula $(M+H)^+$
Y238K(DnsG)	7410.4	7409.5	$C_{322}H_{500}N_{95}O_{87}S_{10}$
S240K(DnsG)	7486.7	7485.5	$C_{328}H_{504}N_{95}O_{87}S_{10}$
T242K(DnsG)	7472.6	7471.5	$C_{327}H_{502}N_{95}O_{87}S_{10}$

(A) Y238K(DnsG)



Retention time

(CH_3CN 25-40%, 30 min)

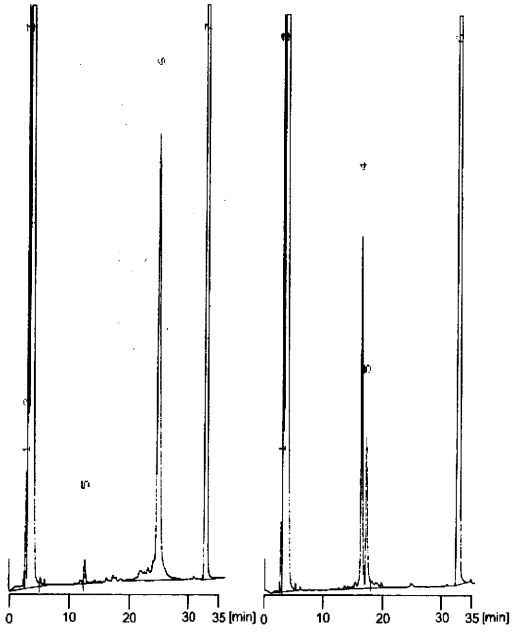
[0 h]

13.0 min: Y238K(DnsG)-δC1b(221-246)

16.3 min: δC1b(247-281)

[15 h]

(B) S240K(DnsG)



Retention time

(CH_3CN 25-45%, 30 min)

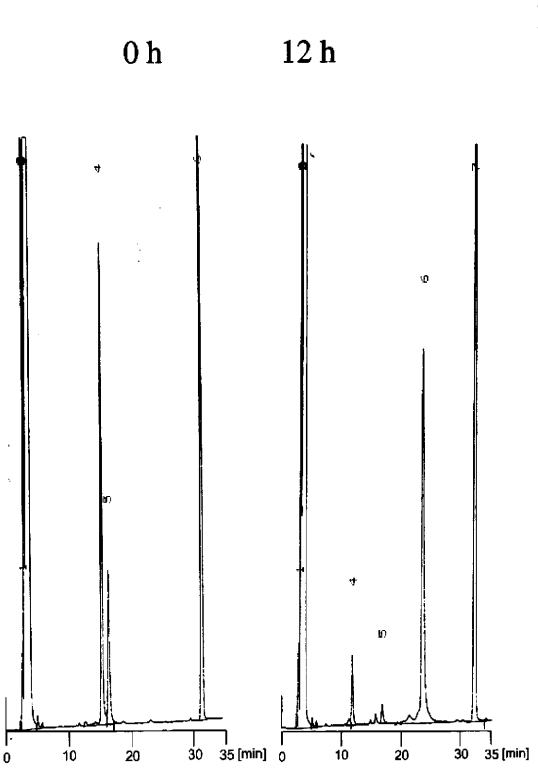
[0 h]

16.0 min: S240K(DnsG)-δC1b(221-246)

16.9 min: δC1b(247-281)

[17 h]

(**C**) T242K(DnsG)



Retention time

(CH_3CN 25-45, 30 min)

[0 h]

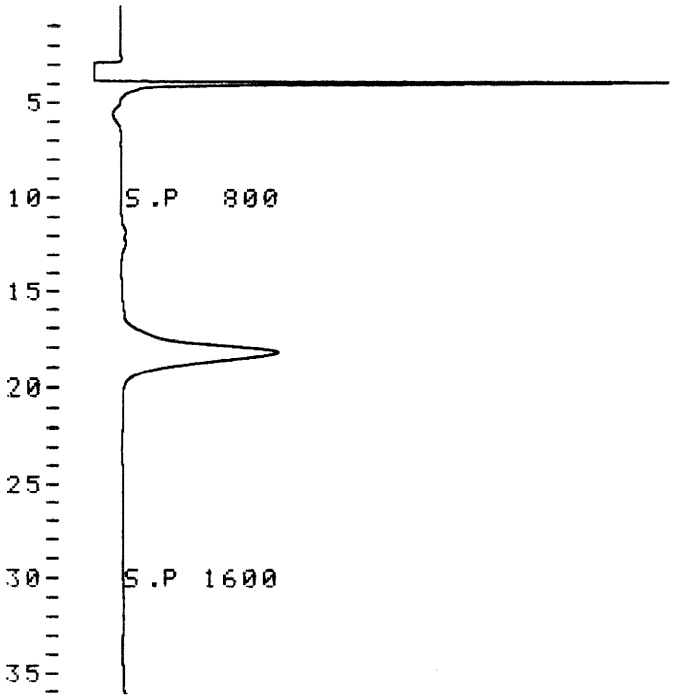
15.4 min: T242K(DnsG)-δC1b(221-246)

16.5 min: δC1b(247-281)

[12 h]

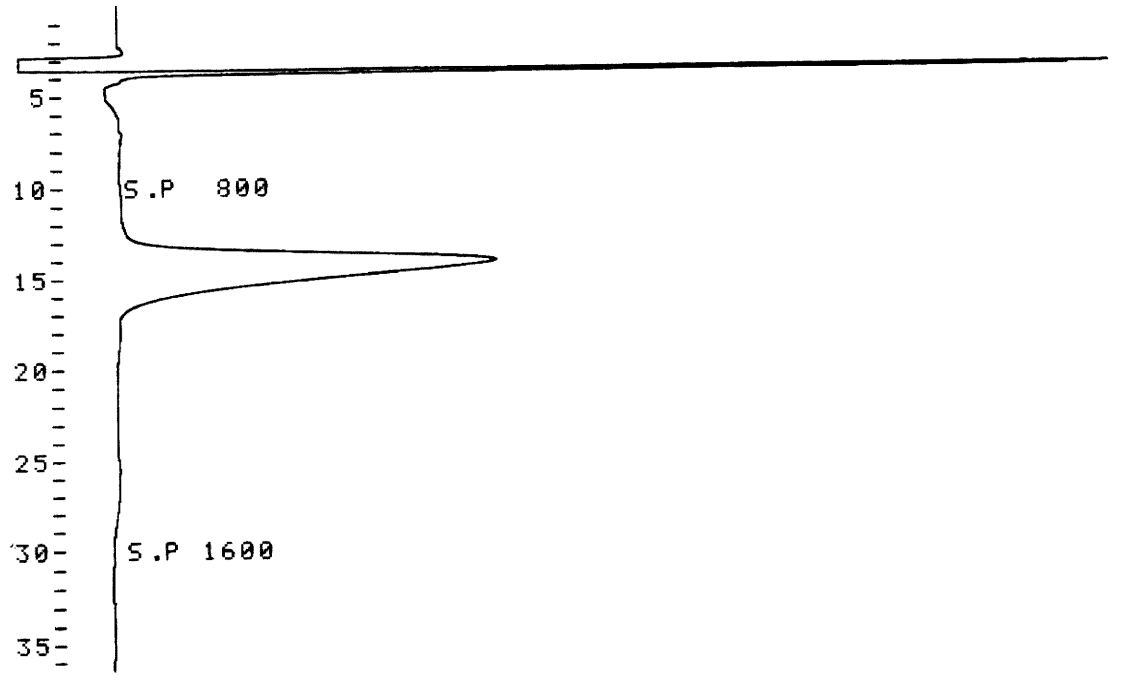
Figure S5. HPLC charts of NCL reactions: **(A)** Y238K(DnsG), **(B)** S240K(DnsG), and **(C)** T242K(DnsG).

(A) Y238K(DnsG)



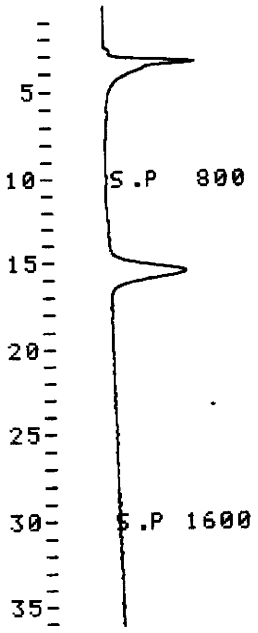
Retention time: 18.2 min with CH_3CN (33-38%, 30 min).

(B) S240K(DnsG)



Retention time: 14.0 min with CH_3CN (33%, isocratic).

(**C**) T242K(DnsG)

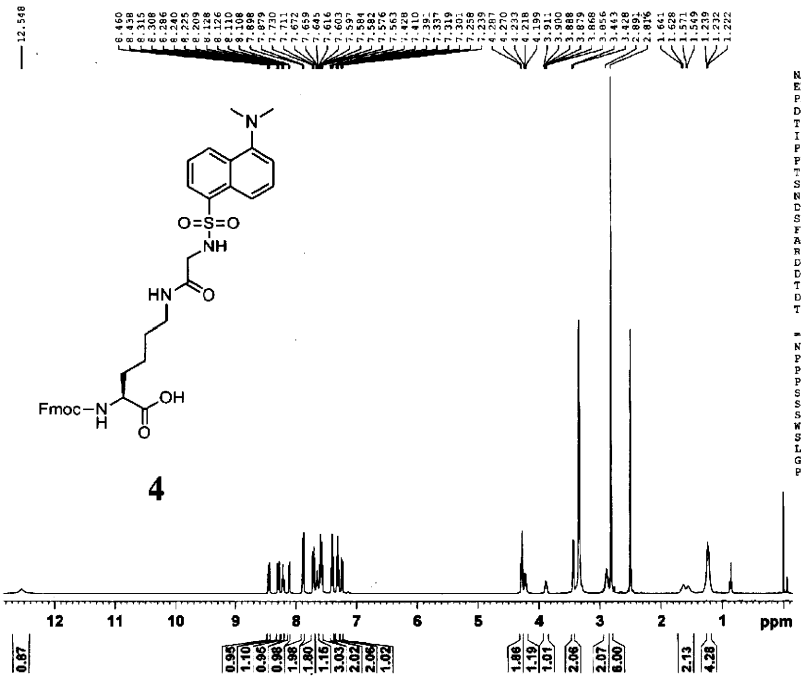


Retention time: 15.6 min with CH_3CN (33-42%, 30 min).

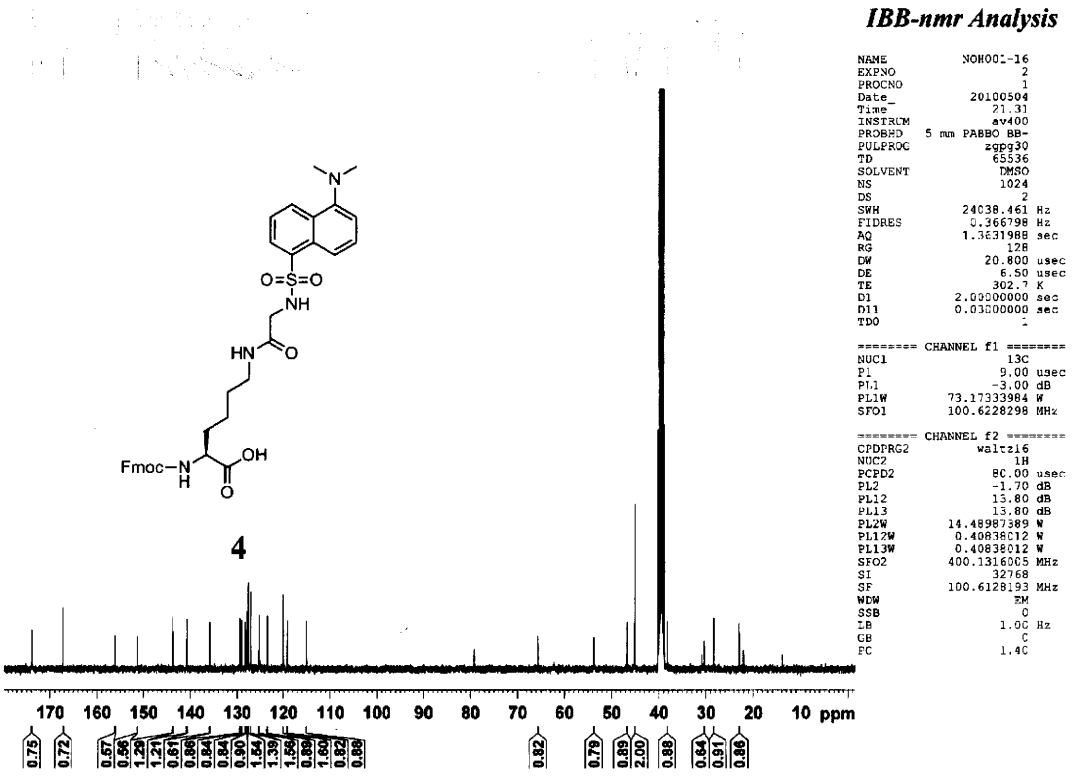
Figure S6. HPLC chart of purified dansyl-labeled δC1b domain analogs: (**A**) Y238K(DnsG), (**B**) S240K(DnsG), and (**C**) T242K(DnsG).

^{1}H-NMR and ^{13}C-NMR Charts of Compound 4.

^{1}H-NMR of compound **4** (DMSO-d_6, 400 MHz, 300 K)



^{13}C-NMR of compound **4** (DMSO-d_6, 100 MHz, 300 K)



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2. O. V. Larionov, A. de Meijere, *Org. Lett.* **2004**, *6*, 2153-2156.
3. N. E. Lewin, P. M. Blumberg, *Methods Mol. Biol.* **2003**, *233*, 129-156.

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α,α-DICHLOROISOXAZOLIDINONES FOR THE SYNTHESIS AND CHEMOSELECTIVE PEPTIDE LIGATION OF α-PEPTIDE α-KETOACIDS

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Abstract – In seeking to develop an iterative approach to the preparation of α-oligopeptides by the chemoselective amide-forming coupling of α-ketoacids and hydroxylamines, we have designed and synthesized novel enantiopure monomers. Key to our approach is the use of α,α-dichloroacids as masked α-ketoacids. The preparation of these monomers, their coupling with α-ketoacids, and the conversion of the α,α-dichloroacids to α-ketoacids is described. These studies provide a first step to a conceptually unique approach to peptide synthesis that does not require activating reagents or produce chemical byproducts.

This paper is dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.

INTRODUCTION

The chemical and biogenic synthesis of α-amino acids relies on the activation of the carboxylic acid moiety towards coupling with an amine nucleophile.[1] The success and prevalence of this paradigm has obscured the consideration of alternative approaches to iterative peptide couplings that could have advantages in chemical synthesis or a potential role in the prebiotic or exobiotic assembly of oligopeptide chains. In addressing this, we have sought to develop methods for amide bond formation that are chemically distinct from classical peptide synthesis and have recently identified the coupling of α-

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ketoacids and hydroxylamines as a novel, chemoselective, and water-compatible approach to amide and peptide bond formation.[2]

We have previously documented the application of the α-ketoacid–hydroxylamine ligation (KAHA ligation) to the iterative synthesis of β^3-oligopeptides.[3] These reactions proceed in water, do not require coupling reagents, and produce only CO_2 and MeOH as reaction byproducts (Figure 1). Provided that suitable enantiopure monomers for the preparation of α-oligopeptides could be identified, this chemistry could offer a novel and chemically orthogonal route to iterative peptide synthesis. Importantly, such an approach could obviate the problematic and wasteful coupling reagents typically employed in large excess during classical peptide synthesis.[4]

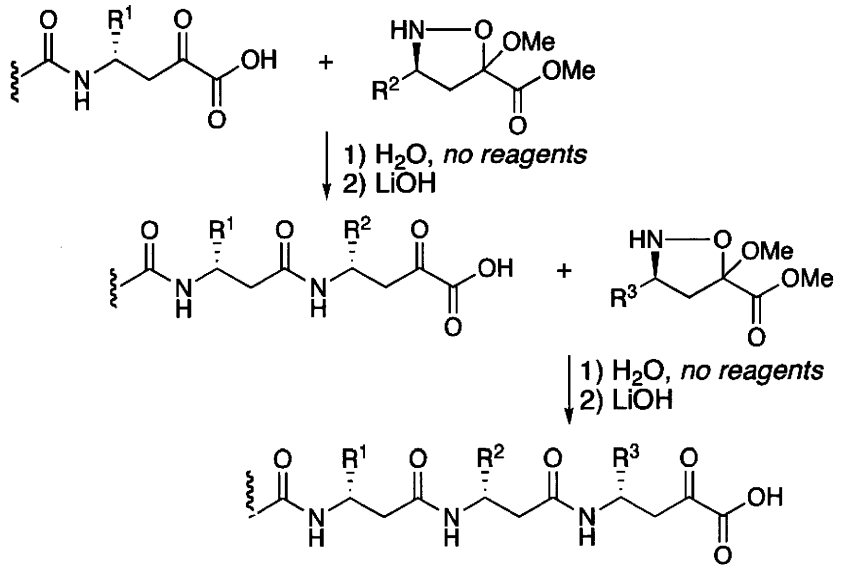


Figure 1. Iterative synthesis of β^3-oligopeptides by chemoselective amidation without reagents or byproducts.

The difficulty in extending our earlier work to the iterative synthesis of α-oligopeptides lies in the identification and synthesis of a suitable monomer class to serve as the building blocks for the amino acid residues. These monomers must 1) cleanly afford the peptides by decarboxylative condensations with α-ketoacids, 2) result in products that can be converted to the next α-ketoacids following the ligation, and 3) be amenable to preparation in enantiopure form on a multigram scale. Initially, we envisioned an extention of the isoxazolidine approach we applied towards the preparation of β-peptides, which would require α-ketolactone monomers **2**. However, such monomers are likely to be highly prone to epimerization, as such 5-membered ring heterocycles have a tendency to exist predominantly in the conjugated enol form.[5] After considering several alternatives, we elected to pursue the use of α,α-

dicholoroacids as masked α-ketoacid surrogates (Figure 2). In this article, we describe our preliminary investigations into the preparation of enantiomerically enriched α,α-dichloroisoxazolidinones and their use for the iterative synthesis of α-oligopeptides. These studies establish a synthetic entry into these monomers, their viability in the key amide-forming ligation reaction, and the conversion of the resulting α,α-dichloroacids into the corresponding α-ketoacids.

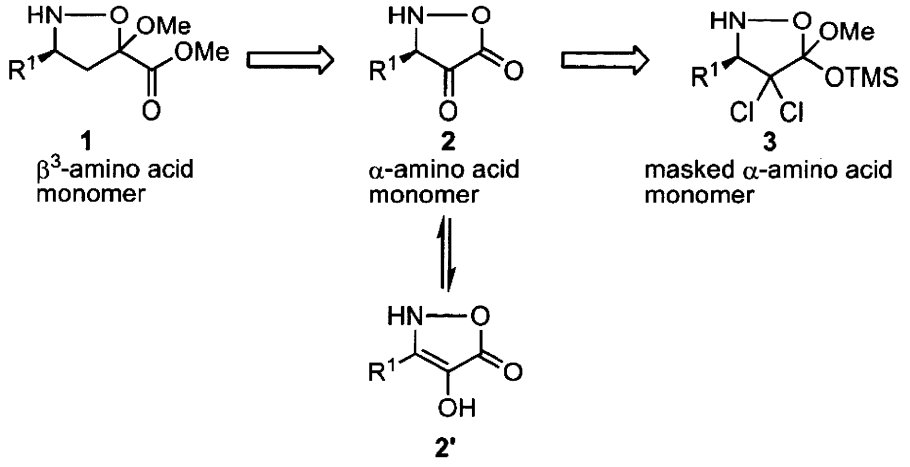
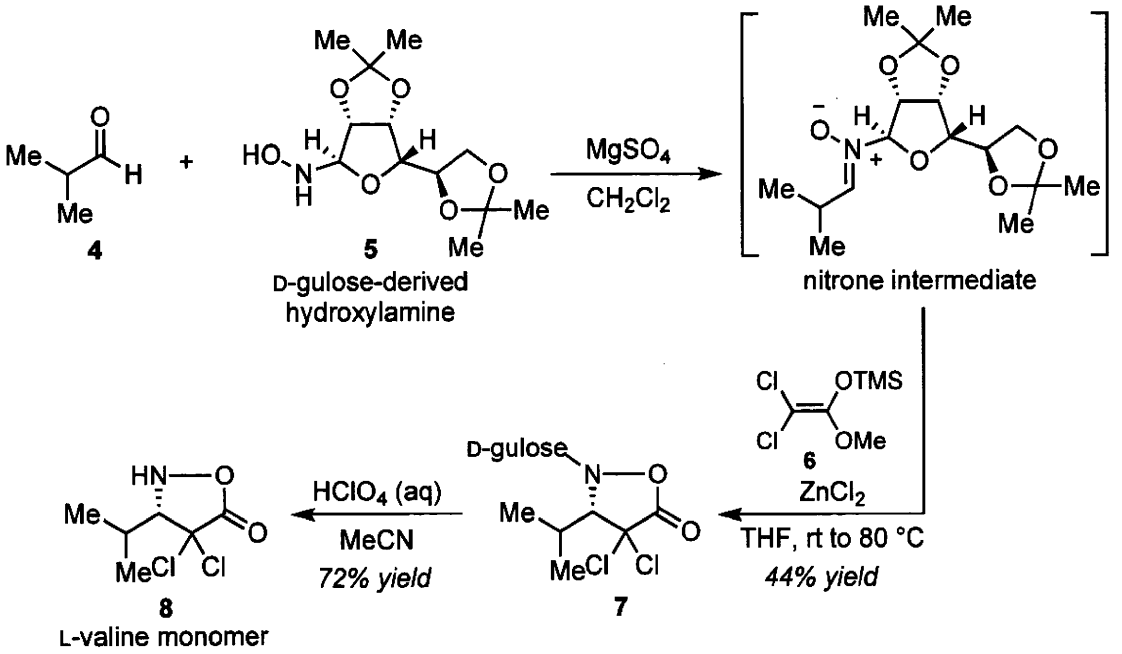


Figure 2. Design of monomers for iterative α-peptide synthesis.

RESULTS AND DISCUSSION

Our synthetic route to the enantiomerically enriched valine-derived dichloro monomer is illustrated in Scheme 1. After exploring several different cycloaddition routes, we selected a modification of Vasella's carbohydrate-derived nitrone as a viable synthesis of monomer **8**.[6] Simply heating a mixture of the nitrone, prepared from isobutyl aldehyde **4** and D-Gulose-derived hydroxylamine **5**,[78] with α,α-dichloroketene silyl acetal **6**[9] containing a stoichiometric amount of $ZnCl_2$ provided directly the α,α-dichloroisoxazolidin-5-ones **7** in 44% yield with high regio- and diastereoselectivity, rather than the expected α,α-dichloroisoxazolidine.[1011] Removal of the chiral auxiliary by perchloric acid-mediated hydrolysis provided L-α-Val monomer **8** in 72% yield. The enantiomer D-α-Val monomer **ent-8** was prepared from L-Gulose-derived hydroxylamine by a similar sequence.

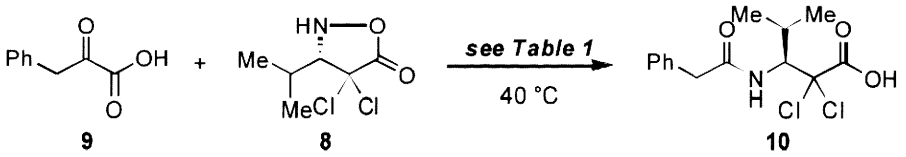


Scheme 1. Preparation of L-Valine-derived α,α-dichloroisoxazolidinone monomer.

Although the condensation of the nitrone and the silyl ketene acetal could also be applied to give isoxazolidinones corresponding to leucine, phenylalanine, and alanine-monomers, the removal of the chiral auxiliary proved problematic. We believe that this can be addressed with optimization, but have instead pressed on with our exploration of the chemistry of these heterocycles using the valine-derived monomers.

With α,α-dichloro-isoxazolidinone **8** in hand, the decarboxylative amide bond formation with phenylpyruvic acid (**9**) was examined (Table 1). Polar solvents such as DMF or DMSO are ideal solvents for the coupling of O-unsubstituted hydroxylamines.[2] On the other hand, non-polar or protic solvents including aqueous media are suitable for the coupling of isoxazolidine-based monomer.[3] We therefore began our studies with a screen of solvents for the amide-formation using phenylpyruvic acid (1.5 equiv) and 0.1 M monomer **8** at 40 °C for 12 h. Non-polar solvents such as CH_2Cl_2, toluene and THF were unproductive (entries 1-3). Polar solvents, including DMF and DMSO, gave the desired amides in low conversion along with significant amounts of unidentified products (entries 4 and 5), probably due to the decomposition of the starting material. A 1:1 mixture of ^{t}BuOH and water gave the desired amide **10** cleanly, albeit with low conversion (entry 6). Reaction with higher substrate concentration (0.2 M) gave **10** with improved conversion (entry 7), but further increases in concentration did not improve the outcome (entry 8). Additional optimization of these conditions revealed that MeOH or EtOH were superior cosolvents (entries 9–11). Alcohol solvents alone, however, did not afford amide products (entry 12).

Table 1. Conditions for amide-forming reactions of α-ketoacids and isoxazolidinone **8**.



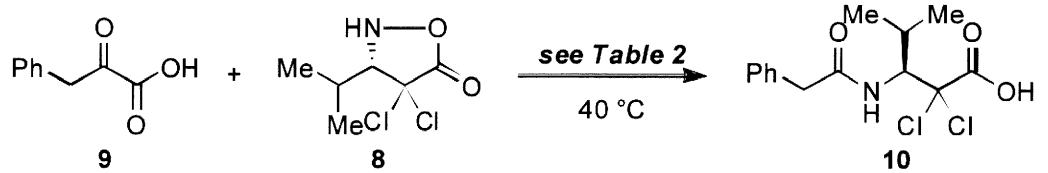
9 **8** **10**

entry	conditions [a]	coversion (%) [b]
1	CH_2Cl_2 (0.1 M)	nr
2	toluene (0.1 M)	nr
3	THF (0.1 M)	nr
4	DMF (0.1 M)	27 [c]
5	DMSO (0.1 M)	25 [c]
6	1:1 H_2O/^{t}BuOH (0.1 M)	12
7	1:1 H_2O/^{t}BuOH (0.2 M)	31
8	1:1 H_2O/^{t}BuOH (0.4 M)	26
9	1:1 H_2O/MeOH (0.2 M)	77
10	1:1 H_2O/EtOH (0.2 M)	75
11	1:1 H_2O/^{i}PrOH (0.2 M)	55
12	MeOH (0.2 M)	trace

[a] All reactions were carried out using Val monomer **8** and phenylpyruvic acid **9** (1.5 equiv) at 40 °C for 12 h. [b] determined by ^{1}H-NMR. [C] A significant amount of unidentified products was detected.

Having identified aqueous alcohol as the preferred solvent for amide-bond formation, we performed a second level optimization of the reaction pH (Table 2). The ligations occurred over a wide pH range, with slightly acidic oxalic acid buffers offering the best results.

Table 2. Optimization of pH for amide-forming ligations.



9 **8** **10**

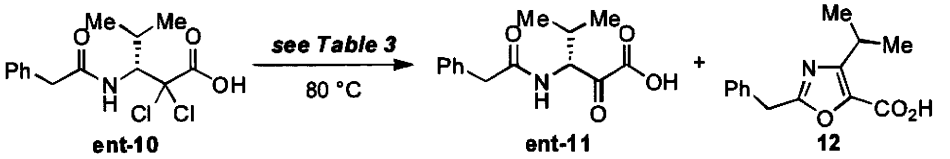
entry	conditions [a]	coversion (%) [b]
1	1:1 H_2O/MeOH	77
2	1:1 pH 3.4 Ac buffer/MeOH	74
3	1:1 pH 4.6 Ac buffer/MeOH	68
4	1:1 pH 5.3 Ac buffer/MeOH	77
5	1:1 pH 5.3 citric buffer/MeOH	66
6	1:1 pH 6.2 citric buffer/MeOH	78
7	1:1 pH 5.3 oxalic buffer/MeOH	80
8	1:1 pH 6.1 oxalic buffer/MeOH	90
9	1:1 pH 7.4 phosphate buffer/MeOH	22

[a] All reactions were carried out using Val monomer **8** and phenylpyruvic acid **9** (1.5 equiv) in 0.2 M solution at 40 °C for 12 h. [b] determined by ^{1}H-NMR.

The key underlying concept to the proposed iterative synthesis of α-oligopeptides is the use of the α,α-dicholoro carboxylic acid as a masked α-ketoacids. Although the conversions of dihaloacids and related compounds to α-ketoacids are rare, several encouraging examples were known[12] including a thorough study from a group at Bristol-Myers Squibb that implicated the formation of an α-lactone in the hydrolysis.[13] It was unclear, however, if any of these methods would be compatible with the proximal amide functionality and the epimerizable α-stereocenter.

Working from the BMS precedent for conversion of α,α-dichloroacids **10** to the α-ketoacids **11**, we began our investigations with base promoted hydrolysis (Table 3). Strong bases including LiOH (entry 1), K_3PO_4 (entry 2), and Na_2CO_3 (entry 3) afforded exclusively undesired oxazole **12**. Success was obtained with weaker bases (entries 4–8) and several conditions afforded the α-ketoacids as the major product. Although the oxazole byproduct could not be completely excluded, acceptable yields could be obtained with potassium bases including potassium oxalate at 80 °C (entry 8).

Table 3. Conditions for conversion of α,α-dichloroacid **10** to α-ketoacid **11**.

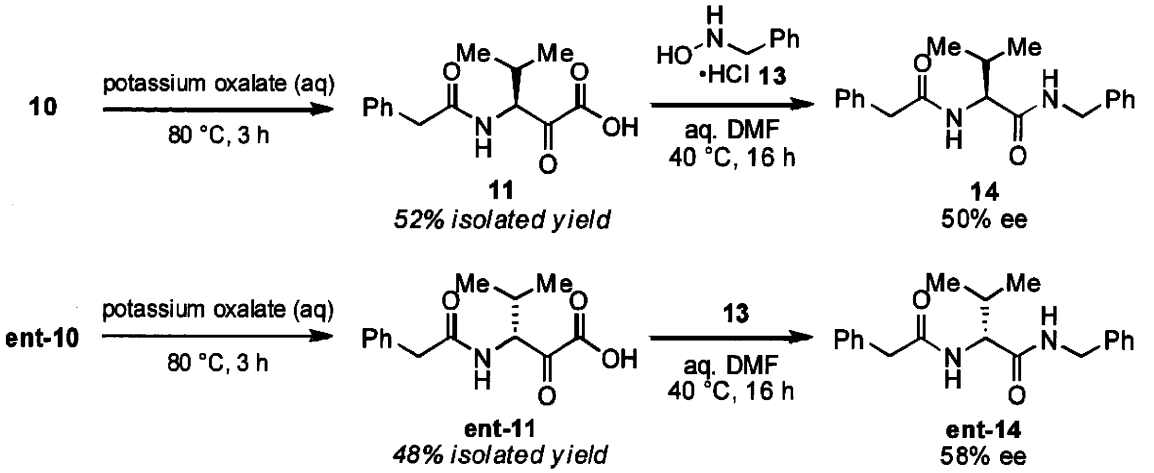


entry	condition [a] (1.0 M)	conv. to **11** (%) [b]	conv. to **12** (%) [b]
1	LiOH	nd	73
2	K_3PO4	nd	>90
3	Na_2CO_3	nd	40
4	AcONa	43	39
5	Na_2HPO_4	26	26
6	sodium citrate	44	33
7	K_2HPO_4	60	22
8	potassium oxalate	62	33

[a] All reactions were carried out using a,a-dichloroacid **10** in 1.0 M aqueous solution at 80 °C for 3 h. [b] determined by RP-HPLC.

At this juncture, we sought to address the critical questions of the stereochemical integrity of the α-stereocenter under the basic conditions necessary for the unmasking of the α-ketoacids. In our experience, which is consistent with the chemical literature,[14] α-ketoacids are configurationally stable in organic solvents and in the presence of aqueous acid, but are prone to racemization in the presence of base.[15] They are generally stable under the ligation conditions.

α,α-Dichloroacid **10** and its enantiomer **ent-10**, prepared from the L-gulose-derived chiral auxiliary, were each hydrolyzed with 1.0 M potassium oxalate at 80 °C for 3 h and the resulting α-ketoacids isolated in 48–52% yield by preparative HPLC (Scheme 2). We were not able to assay the enantiopurity of α-ketoacid **11** directly and therefore elected to perform a second ligation prior to analysis. Each enantiomer of valine-derived α-ketoacid **11** was subjected to ligation with benzylhydroxylamine **13** in aqueous DMF under unoptimized conditions and the resulting amides analyzed by SFC on a AD-H column. Unfortunately, this study revealed significant epimerization of the valine residue, presumably due to the basic conditions employed in the hydrolysis of the α,α-dichloroacid.



Scheme 2. Investigation of epimerization during hydrolysis of α,α-dichloroacid **10**.

In preliminary work, we have prepared dichloroisoxazoline monomers corresponding to other amino acid residues including L-leucine and L-phenylalanine and found that these examples are less prone to racemization during hydrolysis, suggesting that improvements to these protocols are possible. Further efforts to improve the hydrolysis conditions and the preparation of the monomers may provide an alternative route to the iterative synthesis of α-peptides that does not require coupling reagents or protecting groups and which operates under aqueous conditions

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EXPERIMENTAL

General Methods. All reactions utilizing air- or moisture-sensitive reagents were performed in dried