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Conformationally Assisted Lactamizations for the Synthesis of Symmetrical and Unsymmetrical Bis-2,5-diketopiperazines

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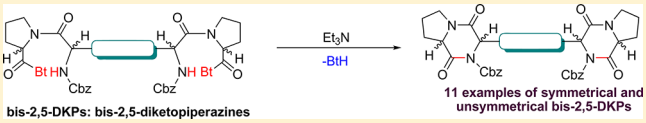
Supporting Information

ABSTRACT: Open-chain *N*-Cbz-protected-peptidoyl benzotriazolides are converted by a novel lactamization strategy using proline as a turn introducer into both symmetrical (**5a−c** and **11a−c**) and unsymmetrical (**19a−e**) bis-2,5-diketopiperazines (bis-2,5-DKPs), previously recognized as difficult targets.



INTRODUCTION

2,5-Diketopiperazines (2,5-DKPs) occur in numerous natural products, often as such, but also embedded in larger, more complex molecular architectures in a variety of natural products from fungi, bacteria, the plant kingdom, and mammals.[1−3] 2,5-DPKs have the ability to bind to a wide range of receptors, together with several characteristics attractive in scaffolds for drug discovery.[4] DKPs are small, conformationally constrained heterocyclic molecules stable to proteolysis. Diversity can be introduced at up to six positions and stereochemistry controlled at up to four positions.[1,5,6] Recent advances in solid-phase methodology have increased their availability for combinatorial drug discovery.[5,7]

In sharp contrast to numerous studies dedicated to the synthesis and biological properties of DKPs, relatively few bis-DKPs have been reported.[1,8,9] They have, however, shown considerable biological activity: (i) (+)-WIN 64821, from *Aspergillus flavus* cultures is a potent competitive P antagonist with submicromolar potency for both the human neurokinin 1 and the cholecystokinin B receptors;[10] (ii) dimeric diketopiperazine (−)-ditryptophenaline alkaloids and (−)-N1-(2-phenylethylene)ditryptophenaline inhibit the former receptor;[11] (iii) (+)-11,11′-dideoxyverticillin A is a tyrosine kinase inhibitor with potent antitumor activity;[11] (iv, v) naturally occurring bis-DPKs chaetocin and chetomin are inhibitors of HIF-1α-p300/CBP interaction, although the inhibition mechanism remains unclear[12] (comparative analysis has shown that bis-DKPs impact highly on the expression level of hypoxia-inducible genes and have more genome-wide effects than DPKs);[13] (vi) X-ray crystallographic studies show that xylylene-linked bis-2,5-DKPs obtained by direct C3 alkylation of the *N*-substituted 2,5-DKP cores via carbanion chemistry can adopt open and closed conformations, which enable them to serve as building blocks for metallo-supramolecular assemblies, metal−organic polygons, and other metal−organic materials.[14]

Head-to-tail condensation between the *N*- and *C*-termini of the corresponding linear peptides represents the most straightforward synthesis for bis-2,5-DKPs.[15,16] However, head-to-tail condensation may require harsh conditions which cause partial epimerization, other side reactions, and low yields. Dimeric DKPs can also be obtained by radical dimerization[8,17,18] or direct modification of the *N*-alkylated DKP core via carbanion chemistry,[13,14] but these procedures are challenging because multiple protection and deprotection steps limit the methodology to specific peptide sequences.

As a part of our research program dedicated to the development of innovative and efficient cyclization procedures,[19−21] we now report novel and versatile strategies for the synthesis, from peptidoyl benzotriazolides containing proline as a turn introducer, of both symmetrical and unsymmetrical bis-2,5-DKPs by triethylamine-promoted lactamization (Figure 1). Proline has high tendency to induce reverse turns in polypeptides because it can accommodate both the *cis* and the *trans* conformers of a tertiary Xaa-Pro amide bond (where Xaa represents any l-α-amino-acid).[22] It has therefore been utilized to introduce reverse turns to achieve short end-to-end distance in peptide chains.[23]

RESULTS AND DISCUSSION

Synthesis of Symmetrical Bis-DPKs. Dimeric DKP **5a** was synthesized in four steps (Scheme 1): (i) N^a,N^a-bis-Cbz-L-cystine (**1a**) was converted to benzotriazolide **2a** in 86% yield; (ii) reaction of l-Cbz-L-cystinyl benzotriazole **2a** with D-proline, according to our previously reported procedure,[24−26] was

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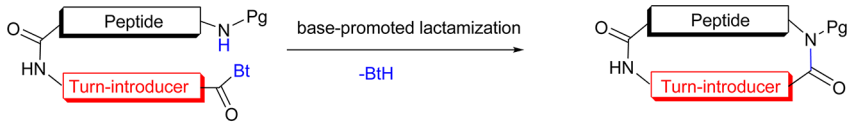
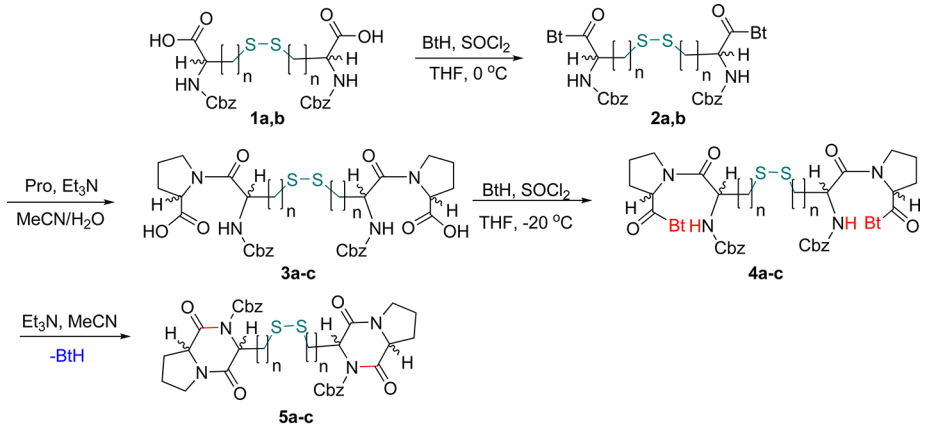


BtH: benzotriazole; Turn-introducer: proline; Pg: protecting group

Figure 1. Ring construction strategy to form DKPs.

Scheme 1. Cyclization of Bis-Cbz-dipeptidoyl Benzotriazoles 4a−c



For n and yields refer to table 1, entries 1-3

complete within 3 h at 20 °C and produced dipeptide dimer bis-Cbz-L-Cys-D-Pro-OH **3a**; (iii) the reaction of **3a** with BtS(O)Bt, generated *in situ* at −20 °C in dry THF, led without epimerization to the Cbz *N*-protected dipeptidoyl benzotriazolides **4a** (82%); (iv) cyclization of **4a** formed bis-(Cbz-L-Cys-D-Pro) **5a** (Scheme 1, Table 1).

Optimum preparative conditions, coreagents, and solvents for cyclization of **4a** were examined: little reaction was observed when compound **4a** was treated under microwave irradiation in acetonitrile without additive for 3 h, and conversion reached just 10% after 18 h under reflux in acetonitrile. Addition of triethylamine (2.2 equiv), however, gave the desired novel cyclic bis-(Cbz-L-Cys-D-Pro) **5a** in 76% yield (Scheme 1, Table 1). The presence of water (MeCN/H_2O, 9: 1) in the reaction mixture caused minimal (<5%) hydrolysis of **4a**. No epimerization of **5a** was detected by HPLC. Thus, HPLC analysis [chirobiotic T column (250 mm × 4.6 mm), detection at 254 nm, flow rate 5 mL min^{-1}, MeOH] showed a single peak, retention time 12.0 min on **5a** (see Supporting Information), which confirmed the absence of diastereomers in the lactamization product bis-2,5-DKP **5a**. To study further racemization-free evidence during Bt-mediated lactamization, dimeric 2,5-DKP bis-(Cbz-L-Cys-D,L-Pro) **5b** was synthesized (Scheme 1, Table 1). HPLC analysis [chirobiotic T column (250 mm −4.6 mm), detection at 230 nm, flow rate 0.25 mL/min, MeOH] on **5a** (single peak, retention time 19.0 min) and **5b** (two equal peaks, retention times 18.9 and 20.6 min) which suggest that product **5a** should be enantiomerically pure (see Supporting Information). Compounds **5a**,**b** were characterized by ^1H and ^{13}C NMR and HRMS (Table 1).

A similar protocol was used to synthesize bis-2,5-DPK **5c** bis-(Cbz-D,L-Homo-Cys-D-Pro) (83%) by cyclization of its precursor **4c** (Scheme 1, Table 1). Compound **5c** was purified by semipreparative HPLC and fully characterized by ^1H and ^{13}C NMR spectroscopy, HRESI-MS, and analytical HPLC. ^{13}C NMR spectra indicated formation of desired lactamization product **5c** (appearance of two more upfield amide carbon signals), and was corroborated by ^1H NMR data. Dimeric Cbz-*N*-protected dipetidoyl benzotriazolide **4c** has one typical carbamate and four benzotriazolide proton signals with chemical shifts ranging from δ 7.43 to 8.34 ppm. In sharp contrast, the ^1H NMR of bis-2,5-DKP **5c** showed these peaks were absent, which confirmed cyclization of the Cbz-protected *N*-terminus with the *C*-terminus (Scheme 1).

2D NMR Studies of Dimeric DKP 5a (bis-(Cbz-L-Cys-D-Pro). 2D NMR spectra were recorded at 500 MHz for ^1H and 125 MHz for ^{13}C equipped with a three-channel, 5-mm, indirect detection probe, with *z*-axis gradients. The chemical shifts for ^1H and ^{13}C were referenced to the residual solvent signal on the TMS scale. ^1H and ^{13}C chemical shifts were assigned based on the $^1H-^1H$, one-bond and long-range $^1H-^{13}C$ couplings, seen in the gDQCOSY, gHMQC, and gHMBC spectra. The methylene protons in **5a** were not stereochemically assigned. Compound **5a** was fully assigned based on different 2D NMR experiments (Figure 2). The most important correlations that confirm the successful cyclization were seen in the $^1H-^{13}C$ gHMBC experiment. The gHMBC (see the Supporting Information for more details) experiment shows that the methine proton of Cbz-*N*-protected L-cystein at 5.04 ppm has a three-bond correlation with the carbonyl group of the D-proline fragment at 167.7 ppm. This correlation confirms the cyclic structure of **5a**. There was no significant correlation between methine protons 5.04 ppm and 4.39 ppm in NOE experiment which suggests that the compound exists exclusively in the *trans*-form (important correlations are indicated with a single headed arrow in Figure 2).

Turn-Introducer Effect of Proline on Cyclization To Form Bis-DKPs. A prerequisite for facile cyclization is to bring the Cbz-protected amino group into close proximity to the BtH activated carbonyl group. In order to evaluate the role of proline in cyclization, we analyzed the spatial distances between relevant reaction centers *b*(N−C) in disulfides Cbz-Cys-Pro-Bt **4a** and Cbz-Cys-Leu-Bt **4d**. Computational analysis used previously were employed[27−30] for long-range acyl migration

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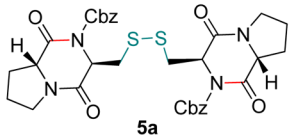
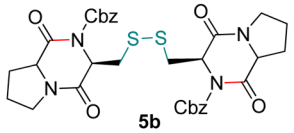
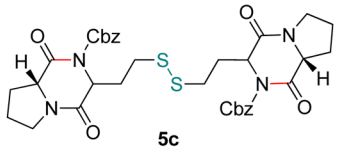
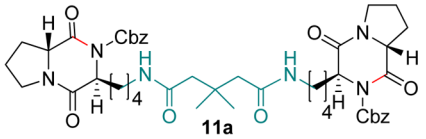
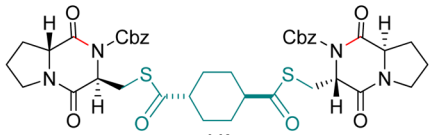
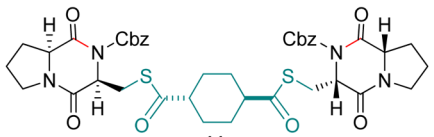
Table 1. ***En Route*** **to Symmetrical Bis-DKPs**

Entry	Time (h)	HMRS ($M+Na^+$) Calcd.	HMRS ($M+Na^+$) Found	Product	Yield (%)
1	48	689.1710	689.1731	 **5a**	76
2	50	689.1710	689.1724	 **5b**	78
3	58	717.2023	717.2034	 **5c**	83
4	78	865.4107	865.4125	 **11a**	91
5	82	827.2391	827.2371	 **11b**	85
6	84	827.2391	827.2398	 **11c**	81

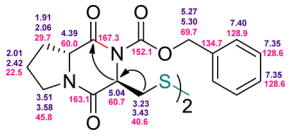


Figure 2. ^{1}H and ^{13}C chemical shift assignments of **5a**.

reactions including a full conformational search followed by scoring the conformers based on energies and spatial distances between relevant centers *b*(N−C). To justify the spatial distance *b*(N−C), quantum chemical calculations were carried out at DFT level of theory[31,32] and/SV(P),[33] def2-SV(P)[34] basis sets using TURBOMOLE V5.9,[35,36] a development of the University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989−2007, TURBOMOLE GmbH, since 2007; available from http://www.turbomole.com.

The relevant energies and *b*(N−C) calculated for the different preorganized structures were considered to prioritize the conformers. Thus, the conformation with the shortest geometrical distance between reaction centers *b*(N−C) affords the preorganized structure through which cyclization was expected to occur.

A full conformational search considering both rotatable bonds and the phenyl ring of the two related structures **4a,d** (Table 2) was implemented using the MMX force field, in PCModel v. 9.3 software.[37] The resultant conformers were ranked in ascending order of *b*(N−C), and the best preorganized structures, with the smallest *b*(N−C) values, are shown in Figure 3. In addition, the spatial calculated distances *b*(N−C), energies and heat of formation for the two structures are shown in Table 2.

We investigated the effect of the turn-introducer proline moiety in **4a** against **4d** (leucine) in Figure 3 and Table 2. The

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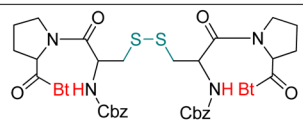
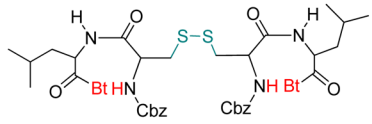
Table 2. Geometrical Distances between (b(N−C)) in the Preorganized Structures

Compound	Structure	Energy (kcal/mol)	b(N-C) (Å)	HF (kcal/mol)
4a–Proline		-101.85	2.55 – 2.75	-120.3
4d–Leucine		-59.69	4.34 – 4.79	-70.4

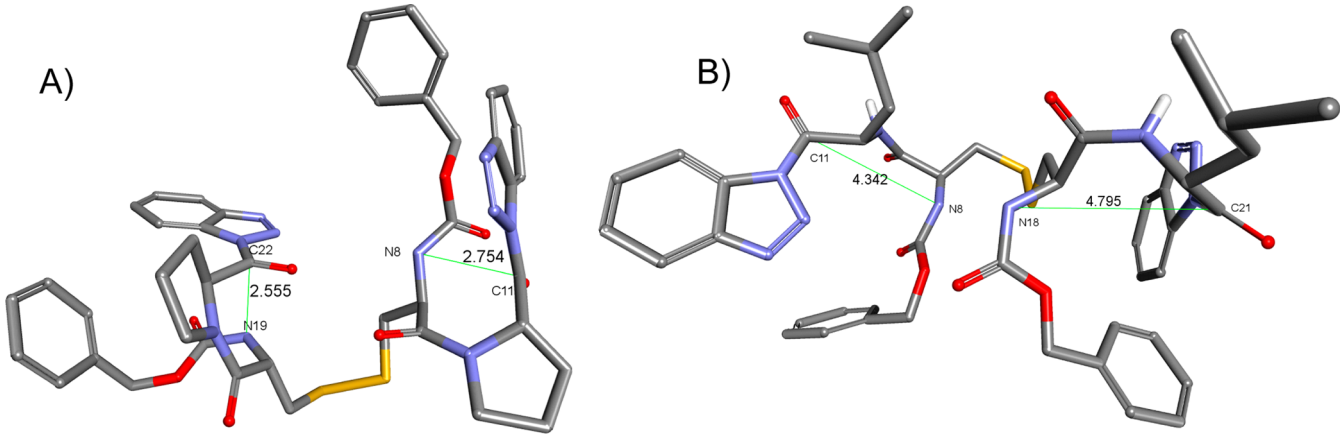
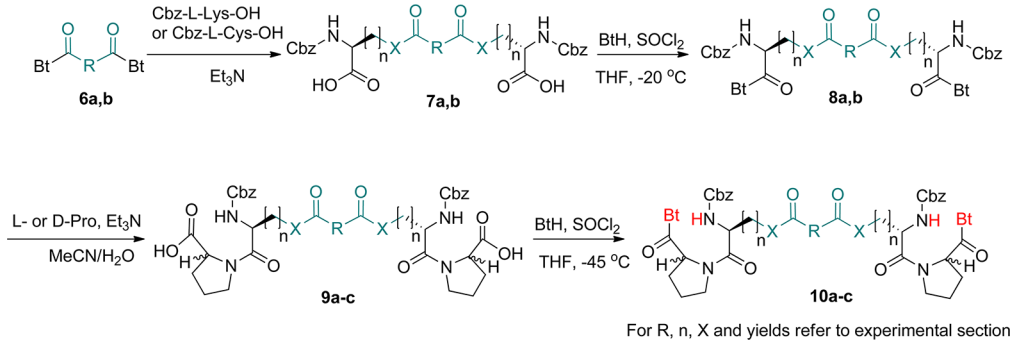


Figure 3. (A) Representation of **4a** with proline. (B) Representation of **4d** with leucine.

Scheme 2. Synthesis of Bis-benzotriazoles 10a−c



conformational analysis shows that the presence of proline in the peptide chain brings the terminal protected amine and Bt−activated carbonyl closer by 1.79−2.04 Å compared to the system with leucine. In addition, the energy level of **4d** lies significantly higher than the energy level of **4a**. These results indicate that a reverse turn effect furnished by proline favors intramolecular cyclization. Conformational analysis and quantum chemical calculations showed that the spatial distance between the terminal Cbz-protected amine and the CO group b(N−C) is a central factor in controlling cyclization rate and product yields.

Further Development of Bt Auxiliary Method for Synthesis of Symmetrical Bis-2,5-DPKs. To broaden the utility of our method, we applied the procedure to the cyclization of open chain peptidoyl benzotriazolides **10a−c** for the synthesis of symmetrical dimeric DPKs **11a−c** (Table 1, entries 4−6) with aliphatic "mimetic" linkers (Scheme 2, Table 1). Bis-DKP derivative ICRF-159 with an aliphatic linker between the DKP units showed unique preclinical properties: chelation with divalent cations, potential amelioration of anthracycline cardiac toxicity and possible antimetastatic effects.[38−40] Dicarboxylic acids: 3,3-dimethylglutaric and *trans*-1,4-cyclohexanedicarboxylic acids were chosen as linker-precusors for the DKPs units. To study the lactamization reaction to form symmetrical bis-DKPs **11a−c**, the starting materials **10a−c** were obtained in a six-step procedure starting from commercially available bis-benzotriazolides **6a,b**. The symmetrical *N*-Cbz-protected tripeptide derivatives **7a,b** were prepared in yields of 72−78% by coupling bis-benzotriazolides **6a,b** with N^{α}-Cbz-L-lysine, or *N*-Cbz-L-cysteine. Compounds **7a,b** were then converted into *N*-(Cbz-α-aminoacyl)-benzotriazoles **8a,b** (78−83%) which were subsequently

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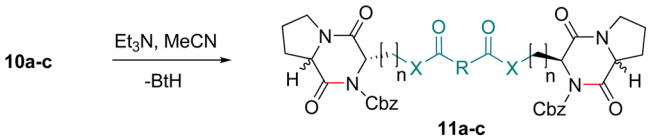
coupled with D-proline or L-proline to afford the side-chain linked tetrapeptides **9a,c**. Treatment of *N*-Cbz-tetrapeptides **9a–c** with 8 equiv of BtH and 2 equiv of thionyl chloride in tetrahydrofuran at −45 °C for 6 h gave *N*-protected *α*-tetrapeptidoyl benzotriazolides **10a–c** in yields of 68–88% (Scheme 2).

Cyclization of bis-benzotriazolides **10a–c** was carried out in dry acetonitrile in the presence of 3.5 equiv of triethylamine. The lactamization mixture was stirred at room temperature until TLC revealed complete reaction. Open chain *N*-Cbz-protected-peptidoyl benzotriazolides **10a–c** were converted into symmetrical bis-2,5-DKPs **11a–c** in yields of 91%, 85%, and 81% correspondingly by our cyclization strategy (Scheme 3, Table 1 entries 4–6).

Scheme 3. Synthesis of Aliphatic "Mimetic" Linked Bis-2,5-DKPs 11a–c



For R, n, X and yields refer to table 1, entries 4-6

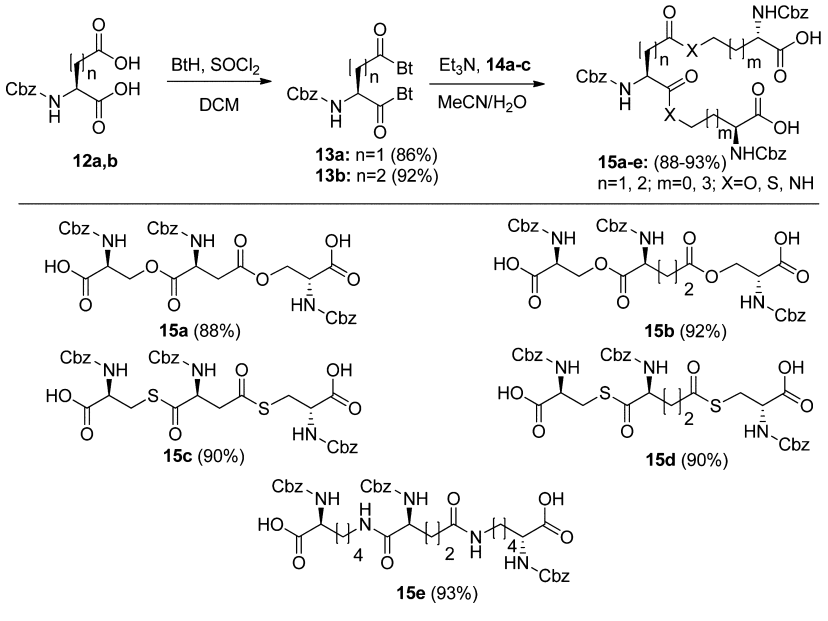
Synthesis of Unsymmetrical Bis-2,5-DKPs. Literature examples of unsymmetrical bis-DPKs include compounds endowed with antagonist and anticancer activity.[1,41,42] We therefore targeted bis-DKPs with unsymmetrical linkers to broaden the scope of our methodology. Our strategy included three key transformations: (i) preparation of unsymmetrical linkers (**15a–e**) derived from amino dicarboxylic acids (**12a,b**) to provide functional groups in one of the amino acid constituents of the DKPs (Scheme 4); (ii) coupling of linkers (**15a–e**) at both *C*-termini with a turn-introducer proline unit as a second amino acid that forms a DPK unit forming intermediates (**17a–e**) (Scheme 5); (iii) lactamization of (**17a–e**) to form the designed bis-2,5-DKPs (**19a–e**). Cbz *N*-protected L-aspartic and L-glutamic acids were chosen as linker-precursors. Scheme 4 shows coupling reactions with side chain functional groups in the linkers. Cbz-L-Asp-OH (**12a**) and Cbz-L-Glu-OH (**12b**) were each converted into *N*-(Cbz-*α*-amino-acyl)-benzotriazolides **13a,b** (86% and 92% respectively). Coupling of these benzotriazole derivatives **13a,b** with functional groups of the side chains in Cbz-*N*-protected-*α*-aminoacids **14a–c** in the presence of diisopropylethylamine (for **15a,b**) or triethylamine (for **15c–e**) gave **15a–e** (88–93%) (Scheme 4).

Peptides **15a–e** were converted into the corresponding benzotriazolides **16a–e** (68–78%, Scheme 5). Coupling **16a–e** with Cbz-protected L-proline or D-proline in acetonitrile–water (3:1) in the presence of triethylamine provided peptides **17a–e**, which were subsequently treated with *in situ* generated BtS(O)Bt to afford the peptide benzotriazolides **18a–e** in 62–72% yields. Cyclization of **18a–e** occurred under conditions similar to those used for the cyclization of **4a–c** and gave the desired bis-2,5-DPKs **19a–e** in yields of 72–88% (Scheme 5, Table 3). Samples **19a–e** (Table 3) showed the advantage of our base-assisted lactamization of open chain *N*-Cbz-protected peptidoyl benzotriazolides for synthesis of DKPs derivatives since direct lactamization of *N*-protected dipetides to form DKPs using peptide coupling reagents often requires harsh conditions,[1,43,44] and the deprotection/cyclization strategy can lead to extended procedures and lower yields.[1,45]

CONCLUSION

In summary, we have developed novel, straightforward, and versatile Bt-mediated cyclization for the synthesis of bis-2,5-DKPs with both symmetrical and unsymmetrical linkers. The methodology was utilized to ring-close a series of peptidoyl benzotriazolides yielding a small library of bis-DKPs with novel features, which could not be prepared efficiently using previously reported methods. The approach described herein should provide a convenient entry to the design and synthesis of a variety of bis-DKPs with potential utility in drug discovery, biological catalysis, and material chemistry. Our Bt-assisted cyclization offers the following advantages: (i) lactamization at room temperature; (ii) formation of bis-2,5-DKPs in good

Scheme 4. Preparation of 15a–e



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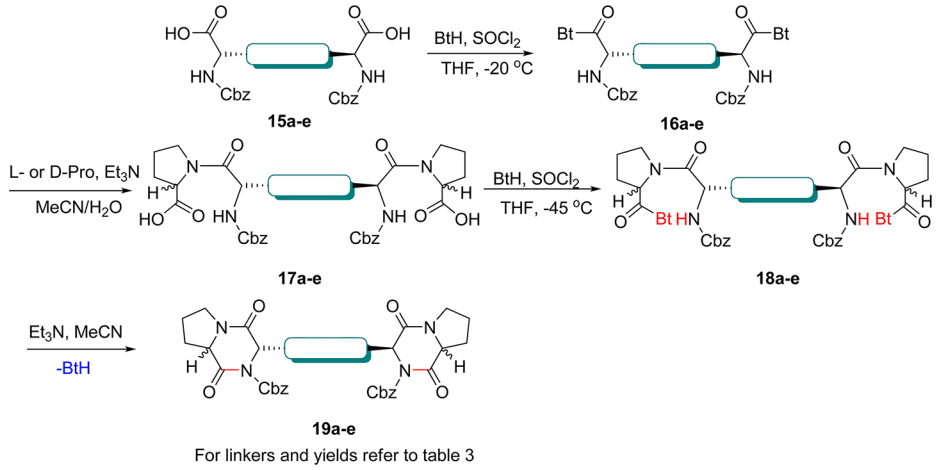
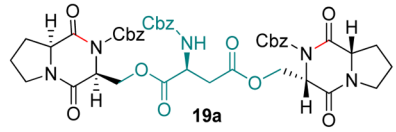
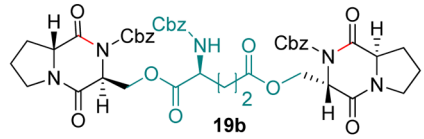
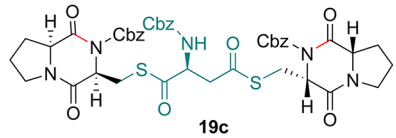
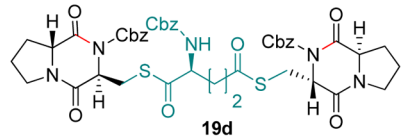
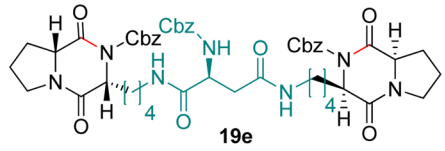
Scheme 5. Synthesis of Bis-DKPs 19a−e with Unsymmetrical Linkers



For linkers and yields refer to table 3

Table 3. *En Route* to Unsymmetrical Bis-DKPs 19a−e

Entry	Time (h)	HMRS (M+Na$^+$) Calcd.	HMRS (M+Na$^+$) Found	Product	Yield (%)
1	48	890.2855	890.2828	 19a	72
3	52	904.3012	904.3021	 19b	88
2	54	922.2398	922.2382	 19c	76
4	48	936.2555	936.2562	 19d	86
5	52	972.4114	972.4115	 19e	88

yields with no detectable racemization; (iii) the use of commercially available and inexpensive reagents, and (iv) easy purification. Given that there are an increasing number of studies involving the synthesis of symmetrical and unsymmetrical DKPs to evaluate their biological activities, we believe

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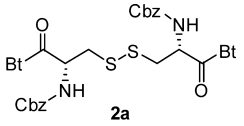
this new approach represents a significant development in the field.

EXPERIMENTAL SECTION

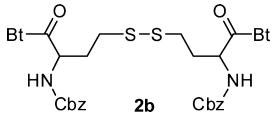
Melting points were determined on a capillary point apparatus equipped with a digital thermometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6, acetone-d_6, or CD_3OD using a 300 or 500 MHz spectrometer (with TMS as an internal standard). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublets, ddd = doublet of doublets of doublets, and dt = doublet of triplets. 3,3-DMG refers to 3,3 dimethyl glutarate, and *trans*-1,4-CHD refers to *trans*-cyclohexane-1,4-dicarboxylate. HPLC–MS analyses were performed on a reverse phase gradient using 0.2% acetic acid in H_2O/methanol as mobile phases; wavelength =254 nm; mass spectrometry was done with electrospray ionization (ESI), matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) or atmospheric-pressure chemical ionization (APCI). Ether refers to diethyl ether.

General Procedure for the Preparation of Bis-Benzotriazolides 2a,b. A stirred solution of 1*H*-benzotriazole (BtH) (8 equiv) in dry tetrahydrofuran (THF) (10 mL/1 g) was treated at 20 °C with thionyl chloride ($SOCl_2$) (2 equiv). After 20 min, a solution of (Cbz-L-Cys-OH)$_2$ (for **2a**) or (Cbz-D,L-Homo-Cys-OH)$_2$ (for **2b**) (1 equiv) in dry THF (10 mL/1 g) was added dropwise, and the resulting solution was then stirred for 2 h at 20 °C. Upon completion, the mixture was filtered, and THF was removed under reduced pressure. The residue was dissolved by dichloromethane (CH_2Cl_2 50 mL/1 g of **1a,b**) and washed successively with HCl (4 N, 2 × 1 mL/1 mL CH_2Cl_2), aq Na_2CO_3 (10%, 2 × 1 mL/1 mL CH_2Cl_2), and brine (1 mL/1 mL). The organic layer was dried over magnesium sulfate ($MgSO_4$), filtered, and evaporated to give the crude product. The solid was recrystallized from CH_2Cl_2/hexanes to yield bis-benzotriazolides **2a,b**.



2a

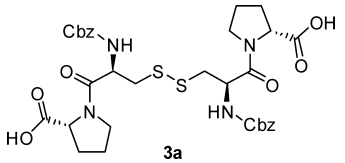
*(Cbz-L-Cys-Bt)$_2$ (**2a**).* White microcrystals, 3.82 g, 5.38 mmol, 86% yield. Mp: 105–108 °C.[46] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.20–3.37 (m, 2H), 3.38–3.50 (m, 2H), 5.11 (br s, 4H), 5.91 (d, J = 7.2 Hz, 2H), 5.97–6.07 (m, 2H), 7.26–7.38 (m, 10H), 7.51 (t, J = 7.3 Hz, 2H), 7.65 (t, J = 7.2 Hz, 2H), 8.05 (d, J = 8.2 Hz, 2H), 8.19 (d, J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 41.0, 54.3, 67.7, 114.5, 120.6, 126.9, 128.4, 128.7, 131.2, 136.1, 146.2, 155.9, 169.4. Anal. Calcd for $C_{34}H_{30}N_8O_6S_2$: C, 57.45; H, 4.25; N, 15.76. Found: C, 57.66; H, 4.09; N, 15.40.



2b

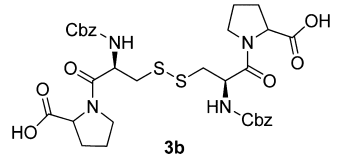
*(Cbz-D,L-Homo-Cys-Bt)$_2$ (**2b**).* White microcrystals, 1.86 g, 2.5 mmol, 68% yield; mp 98–104 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.21–2.32 (m, 2H), 2.48–2.62 (m, 2H), 2.85–2.96 (m, 4H), 5.15 (br s, 4H), 5.87–5.95 (m, 2H), 6.00–6.13 (m, 2H), 7.16 (br s, 2H), 7.28–7.42 (m, 8H), 7.50–7.57 (m, 2H), 7.66–7.70 (m, 2H), 8.09–8.15 (m, 2H), 8.26 (t, J = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.1, 34.7, 54.2, 67.6, 114.5, 120.6, 126.8, 128.5, 128.7, 131.1, 131.3, 136.1, 146.2, 156.3, 171.3. HRMS (ESI): calcd for $C_{36}H_{34}N_8O_6S_2Na$ [M + Na]$^+$ 761.1935, found 761.1949.

General Procedure for the Preparation of Disulfide Dipeptides 3a–c. Disulfide dipeptide benzotriazolides **2a,b** (1 equiv) were each suspended in acetonitrile/water (3:1) (25 mL/1 g), and a solution of D-proline or D,L-proline (2 equiv) in water (10 mL/1 g of proline) containing triethylamine (2–2.2 equiv) was added slowly. The mixtures were stirred at 20 °C for 15 h until TLC revealed consumption of the starting materials. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed with 4 N HCl (3 × 1.5 mL/1 mL of ethyl acetate) and brine (1 mL/1 mL of ethyl acetate). Recrystallization from ethyl acetate/hexanes yielded disulfide dipeptides **3a–c**.



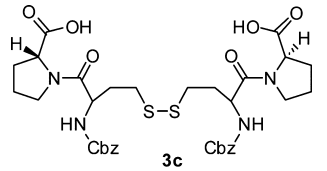
3a

*(Cbz-L-Cys-D-Pro-OH)$_2$ (**3a**).* White microcrystals, 2.22 g, 3.17 mmol, 75% yield. Mp: 78–80 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.78–1.96 (m, 6H), 2.08–2.18 (m, 2H), 2.85 (dd, J = 13.9, 9.9 Hz, 2H), 3.02 (dd, J = 13.7, 3.9 Hz, 2H), 3.56–3.68 (m, 4H), 4.24 (dd, J = 8.8, 3.8 Hz, 2H), 4.48–4.62 (m, 2H), 5.03 (br s, 4H), 7.28–7.51 (m, 10H), 7.78 (d, J = 8.2 Hz, 2H), 12.37 (br s, 2H). ^{13}C NMR (CD_3OD, 75 MHz): δ 26.0, 30.2, 40.7, 53.6, 60.7, 68.0, 129.0, 129.1, 129.6, 138.2, 158.6, 171.5, 175.3. HRMS (ESI): calcd for $C_{32}H_{37}N_4O_{10}S_2$ [M − H]$^-$ 701.1945, found 701.1959.



3b

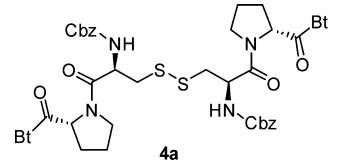
*(Cbz-L-Cys-D,L-Pro-OH)$_2$ (**3b**).* White microcrystals, 1.54 g, 2.20 mmol, 78% yield. Mp: 68–72 °C. ^{1}H and ^{13}C NMR were identical to those for **3a**.



3c

*(Cbz-D,L-Homo-Cys-D-Pro-OH)$_2$ (**3c**).* Sticky gel, 0.77 g, 1.05 mmol, 78% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.80–2.00 (m. 8H), 2.02–2.24 (m, 4H), 2.62–2.82 (m, 4H), 3.64 (br s, 4H), 4.144.27 (m, 2H), 5.01 (t, J = 3.4 Hz, 2H), 5.04 (br s, 4H), 7.24–7.40 (m, 10H), 7.81 (d, J = 8.3 Hz, 2H). ^{13}C NMR (CD_3OD, 75 MHz): δ 26.0, 30.2, 32.2, 35.6, 53.0, 54.1, 67.8, 127.2, 128.9, 129.1, 129.5, 138.1, 158.7, 174.2. HRMS (ESI): calcd for $C_{34}H_{41}N_4O_{10}S_2$ [M − H]$^-$ 729.2259, found 729.2268.

General Procedure for the Preparation of Disulfide Dipeptidoyl Benzotriazolides 4a–c. A stirred solution of BtH (8 equiv) in dry tetrahydrofuran (THF) (15 mL/1 g) was treated at −20 °C with $SOCl_2$ (1 equiv). After 20 min, a solution of **3a–c** (1 equiv) in dry THF (15 mL/1 g **3a–c**) was added dropwise, and the resulting solutions were then stirred for 1.5 h at −20 °C. The ice bath was then removed, and the reaction mixture was stirred for an additional 1.5 h at room temperature. The mixture was filtered, and THF was removed under reduced pressure. The residue was dissolved CH_2Cl_2 (100 mL/1 g **3a–c**) and washed successively with HCl (4 N, 2 × 0.7 mL/1 mL of CH_2Cl_2), Na_2CO_3 10 wt % in water (2 × 1 mL/1 mL of CH_2Cl_2), and brine (1 × 30 mL). The organic layer was dried over magnesium sulfate, filtered, and evaporated. The crude product was then recrystallized from CH_2Cl_2/hexanes to yield disulfide dipeptidoyl benzotriazolides **4a–c**.



4a

*(Cbz-L-Cys-D-Pro-Bt)$_2$ (**4a**).* White microcrystals, 1.58 g, 1.75 mmol, 82% yield. Mp: 119–124 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.02–2.26 (m, 6H), 2.38–2.47 (m, 2H), 2.89 (dd, J = 13.7, 8.8 Hz, 2H), 3.14 (dd, J = 13.7, 5.1 Hz, 2H), 3.74–3.95 (m, 4H), 4.72–4.82

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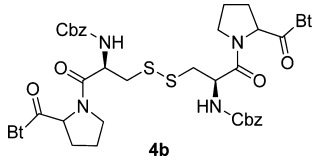
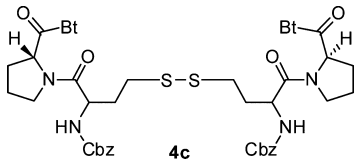
(m, 2H), 5.09 (br s, 4H), 5.68−5.78 (m, 2H), 7.28−7.42 (m, 10H), 7.64 (dt, J = 8.3, 1.2 Hz, 2H), 7.81 (dt, J = 8.3, 1.1 Hz, 2H), 7.84 (d, J = 8.6 Hz, 2H), 8.22 (d, J = 8.3 Hz, 2H), 8.29 (d, J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.2, 29.9, 41.2, 48.0, 52.1, 60.0, 67.3, 114.7, 120.4, 126.6, 128.2, 128.3, 128.7, 130.7, 131.3, 136.3, 146.2, 155.9, 169.0, 170.3. HRMS (ESI): calcd for $C_{44}H_{44}N_{10}O_8S_2Na$ $[M + Na]^+$ 927.2677, found 927.2681.



4b

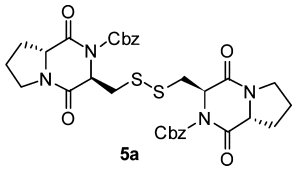
(Cbz-L-Cys-D,L-Pro-Bt)$_2$ ***(4b)***. White microcrystals, 1.09 g, 1.21 mmol, 85% yield. Mp: 111−114 °C. ^{1}H and ^{13}C NMR were identical to those of **4a**.



4c

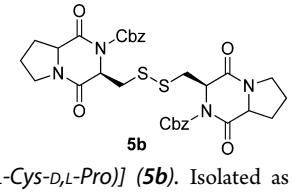
(Cbz-D,L-Homo-Cys-D-Pro-Bt)$_2$ ***(4c)***. White microcrystals, 5.32 g, 5.7 mmol 91% yield. Mp: 83−84 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.78−2.00 (m, 4H), 2.01−2.26 (m, 8H), 2.66−2.86 (m, 4H), 3.49−4.29 (m, 4H), 4.34−4.74 (m, 2H), 5.03 (br s, 4H), 5.21−5.32 (m, 1H), 5.60−5.80 (m, 1H), 7.24−7.46 (m, 12H), 7.56−7.84 (m, 4H), 8.14−8.24 (m, 2H), 8.26−8.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.2, 25.5, 29.9, 32.4, 34.1, 47.9, 51.5, 59.9, 67.2, 114.6, 120.4, 126.4, 126.6, 128.3, 128.7, 128.9, 130.8, 136.3, 146.1, 156.3, 170.2. HRMS (ESI): calcd for $C_{46}H_{48}N_{10}O_8S_2Na$ $[M + Na]^+$ 955.2990, found 955.2996.

General Procedure for the Cyclization of Disulfide Dipeptidoyl Benzotriazolides 4a−c to Form Symmetrical Bis-DKPs 5a−c. A solution of disulfide dipeptidoyl bentrotriazolides **4a−c** (1 equiv) and triethylamine (2.2 equiv) in dry acetonitrile (15 mL/1 g) was stirred at room temperature until the TLC revealed completion of the reaction. The mixture was then concentrated under vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 4 N HCl (3 × 1 mL/1 mL of ethyl acetate) and Na_2CO_3 10 wt % in water (3 × 1 mL/1 mL of ethyl acetate), and purified by column chromatography (hexanes/ethyl acetate gradient) to give the corresponding symmetrical bis-DKPs **5a−c**.



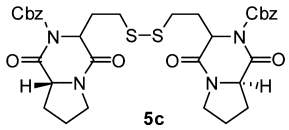
5a

Bis[cyclo-(Cbz-L-Cys-D-Pro)] ***(5a)***. White microcrystals, 0.51 g, 0.76 mmol, 76% yield. Mp: 116−120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.86−1.94 (m, 2H), 1.97−2.11 (m, 4H), 2.38−2.46 (m, 2H), 3.23 (d, J = 6.1 Hz, 2H), 3.42−3.63 (m, 6H), 4.39 (dd, J = 9.1, 6.9 Hz, 2H), 5.04 (dd, J = 5.8, 5.8 Hz, 2H), 5.27 (d, J = 7.5 Hz, 2H), 5.31 (d, J = 7.5 Hz, 2H), 7.31−7.41 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.5, 29.7, 40.6, 45.8, 60.0, 60.7, 69.7, 128.6, 128.9, 134.7, 152.1, 163.1, 167.3. HRMS (ESI): calcd for $C_{32}H_{34}N_4O_8S_2Na$ $[M + Na]^+$ 689.1710, found 689.1731.



5b

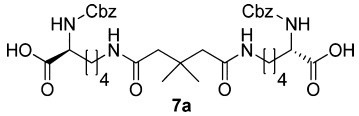
Bis[cyclo-(Cbz-L-Cys-D,L-Pro)] ***(5b)***. Isolated as mixture of diastereomers. White microcrystals, 0.43 g, 0.65 mmol, 78% yield. Mp: 96−101 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.90−2.14 (m, 6H), 2.34−2.42 (m, 1H), 3.12 (dd, J = 8.7, 3.6 Hz, 2H), 3.18 (dd, J = 8.7, 4.5 Hz, 2H), 3.44−3.58 (m, 4H), 4.54−4.60 (m, 2H), 5.005.06 (m, 2H), 5.26−5.36 (m, 4H), 7.24−7.48 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): 22.9, 29.4, 31.8, 31.8, 34.2, 45.8, 59.7, 60.5, 69.7, 128.4, 128.6, 128.8, 128.9, 134.8, 152.3, 152.4, 164.7, 167.5. HRMS (ESI): calcd for $C_{32}H_{34}N_4O_8S_2Na$ $[M + Na]^+$ 689.1710, found 689.1724.



5c

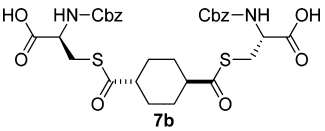
Bis[cyclo-(Cbz-D,L-Homo-Cys-D-Pro)] ***(5c)***. White microcrystals, 0.29 g, 0.42 mmol 83% yield. Mp: 85−86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.86−2.24 (m, 10H), 2.35−2.48 (m, 2H), 2.64−2.78 (m, 4H), 3.48−3.59 (m, 4H), 4.26 (t, J = 7.6 Hz, 2H), 4.85 (t, J = 7.7 Hz, 2H), 5.29 (br s, 4H), 7.26−7.44 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1, 29.6, 32.0, 34.4, 46.0, 59.9, 60.7, 69.8, 128.8, 129.0, 129.1, 135.0, 152.5, 164.9, 167.7. HRMS (ESI): calcd for $C_{34}H_{38}N_4O_8S_2Na$ $[M + Na]^+$ 717.2023, found 717.2034.

General Procedure for the *S*- and *N*-Acylations of 6a,b for Preparation of Compounds 7a,b. Bis-benzotriazolides **6a,b** (1 equiv) were each suspended in acetonitrile/water (3:1) (20 mL/1 g) (for *S*-and *N*-acylations), and a solution of Cbz-L-Cys-OH (2−2.1 equiv) or Cbz-L-Lys-OH (2−2.1 equiv) in water (10 mL/1 g) containing triethylamine (2.2 equiv) was added slowly. The mixtures were stirred at 20 °C for 16−72 h until the TLC revealed consumption of the starting materials. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (30 mL/1 g of **6a,b**). The organic layer was washed with 4 N HCl (3 × 1 mL/1 mL of ethyl acetate) and evaporated, and the products were recrystallized from ethyl acetate/hexanes to yield **7a,b**.



7a

3,3-DMG-(Cbz-L-Lys-OH)$_2$ ***(7a)***. Sticky gel, 5.36 g, 7.83 mmol, 72% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.08 (s, 6H), 1.36−1.61 (m, 8H), 1.64−1.75 (m, 2H), 1.80−1.92 (m, 2H), 2.25 (s, 2H), 2.35 (s, 2H), 3.18 (t, J = 6.8 Hz, 2H), 3.26 (t, J = 6.8 Hz, 2H), 4.09−4.17 (m, 2H), 5.09 (s, 4H), 7.27−7.38 (m, 10H). ^{13}C NMR (CD_3OD, 75 MHz): δ 24.4, 28.7, 30.0, 32.5, 34.1, 40.2, 47.0, 55.3, 67.7, 128.9, 129.1, 129.6, 138.2, 158.7, 174.4, 176.0. HRMS (ESI): calcd for $C_{35}H_{47}N_4O_{10}$ $[M - H]^-$ 683.3287, found 683.3293.

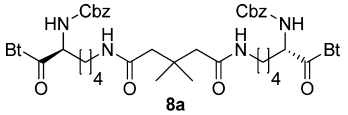


7b

trans-1,4-CHD-(Cbz-L-Cys-OH)$_2$ ***(7b)***. Sticky gel, 1.51 g, 2.33 mmol, 78% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.52−1.75 (m, 4H), 1.78−2.06 (m, 4H), 2.40−2.68 (m, 2H), 3.13 (dd, J = 13.7, 8.9 Hz, 2H), 3.50 (dd, J = 13.8, 4.5 Hz, 2H), 4.36 (dd, J = 8.6 Hz, 4.4 Hz, 2H), 5.18−5.01 (m, 4H), 7.21−7.41 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2, 30.6, 49.3, 53.7, 67.4, 128.3, 128.3, 128.7, 136.1, 156.2, 173.8, 201.6. Compound **7b** was characterized by ^{1}H and ^{13}C NMR.

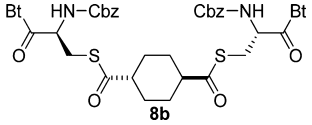
General Procedure for the Preparation of Bis-benzotriazolides 8a,b. A stirred solution of BtH (8 equiv) in dry THF (10 mL/1 g) was treated at 20 °C by $SOCl_2$ (2 equiv). After 20 min, a solution of **7a,b** (1 equiv) in dry THF (15 mL/1 g) was added dropwise at −20 °C, and each resulting solution was stirred for 2 h at −20 °C. The ice bath was removed, and each reaction mixture was stirred for an additional 2 h at room temperature. The mixtures were filtered, and THF was removed under reduced pressure. Each residue was dissolved in ethyl acetate (50 mL/1 g of **7a,b**) and washed successively with HCl (4 N, 2 × 1.5 mL/1 mL of ethyl acetate), Na_2CO_3 10 wt % in water (2 × 1.5 mL/1 mL of ethyl acetate), and brine (1 × 1 mL/1 mL of ethyl acetate). The organic layers were dried over sodium sulfate, filtered, evaporated, and recrystallized from CH_2Cl_2/hexane to give the corresponding bis-benzotriazolides **7a,b**.

dx.doi.org/10.1021/jo401235k | J. Org. Chem. 2013, 78, 8510−8523



8a

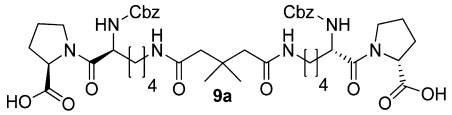
*3,3-DMG-(Cbz-L-Lys-Bt)$_2$ (**8a**).* Sticky gel, 1.01 g, 1.14 mmol, 78% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.12 (s, 6H), 1.34−1.50 (m, 8H), 1.79−1.96 (m, 4H), 2.25 (s, 4H), 2.92−3.06 (m, 4H), 5.03 (br s, 4H), 5.28−5.52 (m, 2H), 7.28−7.38 (m, 10H), 7.53−7.66 (m, 2H), 7.74−7.81 (m, 2H), 7.85−7.92 (m, 2H), 8.16−8.29 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.5, 28.5, 29.1, 29.8, 30.9, 32.6, 34.1, 44.4, 69.4, 114.6, 120.1, 125.9, 126.3, 127.7, 128.5, 130.5, 131.1, 138.9, 146.1, 156.5, 170.9, 172.4. HRMS (ESI): calcd for $C_{47}H_{54}N_{10}O_8Na$ [M + Na]$^+$ 909.4018, found 909.4038.



8b

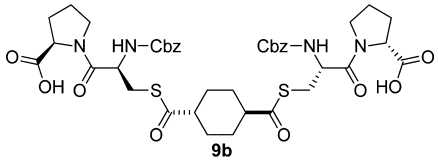
*trans-1,4-CHD-(Cbz-L-Cys-Bt)$_2$ (**8b**).* Sticky gel, 0.70 g, 0.83 mmol, 83% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38−1.83 (m, 8H), 2.42−2.58 (m, 2H), 3.51 (dd, J = 14.6, 4.7 Hz, 2H), 3.76 (dd, J = 14.6, 5.3 Hz, 2H), 5.08−5.17 (m, 4H), 5.87−6.20 (m, 4H), 7.20−7.42 (m, 10H), 7.51 (t, J = 7.8 Hz, 2H), 7.64 (t, J = 7.8 Hz, 2H), 8.11−8.24 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7, 26.2, 31.3, 49.1, 54.2, 67.4, 114.3, 120.4, 126.6, 128.2, 128.2, 128.5, 130.9, 131.0, 146.1, 155.6, 168.8, 200.9. HRMS (ESI): calcd for $C_{42}H_{40}N_8O_8S_2Na$ [M + Na]$^+$ 871.2303, found 871.2322.

General Procedure for the Coupling of 8a,b with Proline to Prepare Compounds 9a−c. Bis-benzotriazolides **8a,b** (1 equiv) were each suspended in acetonitrile/water (3:1) (15 mL/1 g), and a solution of D- or L-proline (2−2.1 equiv) in water (10 mL/1 g) containing triethylamine (2−2.2 equiv) was added slowly. The mixtures were stirred at 20 °C for up to 16 h until the TLC revealed consumption of the starting materials. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (30 mL/1 g of **8a,b**). The organic layer was washed with 4 N HCl (3 × 1 mL/1 mL of ethyl acetate) and Na_2CO_3 10 wt % in water (3 × 1 mL/1 mL of ethyl acetate), and purified by column chromatography (ethyl acetate/hexanes gradient) to yield compounds **9a−c**.



9a

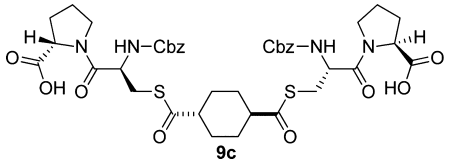
*3,3-DMG-(Cbz-L-Lys-D-Pro-OH)$_2$ (**9a**).* Sticky gel, 1.67 g, 1.89 mmol, 84% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.03 (s, 6H), 1.28−1.40 (m, 4H), 1.45−1.59 (m, 4H), 1.60−1.77 (m, 4H), 1.78−2.12 (m, 5H), 2.13−2.31 (m, 3H), 2.52 (s, 4H), 3.14−3.25 (m, 1H), 3.41−3.55 (m, 1H), 3.58−3.69 (m, 1H), 3.68−3.77 (m, 4H), 3.80−3.87 (m, 1H), 4.00−4.22 (m, 2H), 4.31−4.53 (m, 2H), 5.03−5.15 (m, 4H),7.28−7.37 (m, 10H). ^{13}C NMR (CD_3OD, 75 MHz): δ 24.0, 24.4, 25.8, 27.8, 28.5, 30.1, 32.2, 40.0, 47.0, 54.0, 55.3, 60.8, 67.8, 127.2, 128.9, 129.5, 140.1, 158.2, 174.2, 175.4, 176.0. HRMS (ESI): calcd for $C_{45}H_{61}N_6O_{12}$ [M − H]$^-$ 877.4342, found 877.4361.



9b

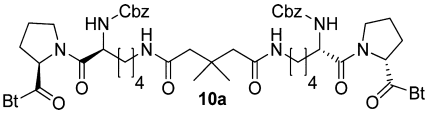
*trans-1,4-CHD-(Cbz-L-Cys-D-Pro-OH)$_2$ (**9b**).* Sticky gel, 0.99 g, 1.18 mmol, 80% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.30−1.99 (m, 14H), 2.01−2.23 (m, 2H), 2.58−2.74 (m, 2H), 2.91 (dd, J = 13.3, 9.3 Hz, 2H) 3.18 (dd, J = 13.7, 5.0 Hz, 2H), 3.51−3.72 (m, 4H), 4.19 (dd, J = 9.1, 3.7 Hz, 2H), 4.41−4.54 (m, 1H), 4.95−5.12 (m, 5H), 7.23−7.42 (m, 10H), 7.60−7.76 (m, 2H), 12.45 (br s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.0, 25.4, 28.4, 29.8, 46.2, 48.2, 51.2, 58.4, 65.2, 127.2, 127.4, 127.9, 136.6, 155.4, 156.6, 167.7, 171.4, 172.6, 200.6, 201.2. Compound **9b** was characterized by ^{1}H and ^{13}C NMR.

*trans-1,4-CHD-(Cbz-L-Cys-L-Pro-OH)$_2$ (**9c**).* Sticky gel, 0.93 g, 1.11 mmol, 75% yield. ^{1}H and ^{13}C NMR were identical to **9b**.



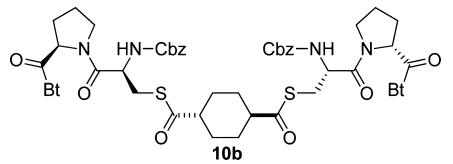
9c

General Procedure for the Preparation of Cyclization Precursors 10a−c. A stirred solution of BtH (8 equiv) in dry THF (10 mL/1 g) was treated at 0 °C with $SOCl_2$ (2 equiv). After 20 min, the reaction mixture was cooled to −45 °C in acetone/dry ice bath and a solution of **9a−c** (1 equiv) in dry THF (15 mL/1 g) was added dropwise. The resulting solution was stirred for 6 h at −45.0 °C, after which THF was removed under reduced pressure. The residue was dissolved by ethyl acetate (20 mL/1 g of **9a−c**) and washed with brine (2 × 1.5 mL/1 mL), HCl (4 N, 2 × 1 mL/1 mL ethyl acetate), and Na_2CO_3 10 wt % in water (2 × 1 mL/1 mL ethyl acetate). The organic layer was dried over sodium sulfate, filtered, and evaporated. The residue was recrystallized with CH_2Cl_2/hexane to yield compounds **10a−c**.



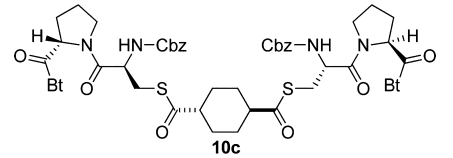
10a

*3,3-DMG-(Cbz-L-Lys-D-Pro-Bt)$_2$ (**10a**).* Sticky gel, 1.67 g, 1.55 mmol, 68% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.07 (br s, 6H), 1.14−1.31 (m, 6H), 1.33−1.87 (m, 10H), 2.10−2.31 (m, 4H), 2.50 (br s, 4H), 3.26 (br s, 2H), 3.52−3.58 (m, 1H), 3.68−3.85 (m, 4H), 3.90−4.08 (m, 1H), 4.56−4.70 (m, 2H), 5.03−5.18 (m, 4H), 5.51−5.67 (m, 2H), 5.68−5.82 (m, 2H), 5.88−5.98 (m, 2H), 7.27−7.42 (m, 10H), 7.52 (t, J = 7.2 Hz, 2H), 7.66 (t, J = 7.7 Hz, 2H), 8.13 (d, J = 8.1 Hz, 2H), 8.27 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.3, 25.2, 27.9, 28.9, 29.3, 29.8, 32.3, 39.0, 46.6, 47.7, 52.5, 59.8, 67.1, 114.7, 120.4, 126.5, 128.1, 128.7, 130.7, 131.4, 136.6, 146.2, 156.0, 170.3, 170.7, 172.2. HRMS (ESI): calcd for $C_{57}H_{68}N_{12}O_{10}Na$ [M + Na]$^+$ 1103.5074, found 1103.5096.



10b

*trans-1,4-CHD-(Cbz-L-Cys-D-Pro-Bt)$_2$ (**10b**).* Sticky gel, 0.72 g, 0.85 mmol, 85% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.79−1.52 (m, 5H), 2.05−2.78 (m, 5H), 2.06−2.31 (m, 6H), 2.47−2.71 (m, 2H), 3.30 (dd, J = 14.1, 4.2 Hz, 2H), 3.38 (dd, J = 13.5, 6.6 Hz, 2H), 3.64−4.09 (m, 4H), 4.84−4.80 (m, 2H), 5.03−5.18 (m, 4H), 5.70 (dd, J = 14.2 Hz, 8.0 Hz, 2H), 5.84 (dd, J = 8.4 Hz, 3.9 Hz, 2H), 7.26−7.42 (m, 10H), 7.46−7.56 (m, 2H), 7.59−7.69 (m, 2H), 8.12 (d, J = 8.4 Hz, 2H), 8.25 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.1, 26.1, 29.7, 31.2, 47.6, 49.3, 51.8, 59.8, 66.9, 114.5, 120.2, 126.4, 127.9, 128.0, 128.5, 130.5, 131.2, 136.4, 146.0, 155.8, 168.4, 170.0, 201.6. HRMS (ESI): calcd for $C_{52}H_{54}N_{10}O_{10}S_2Na$ [M + Na]$^+$ 1065.3358, found 1065.3372.



10c

*trans-1,4-CHD-(Cbz-L-Cys-L-Pro-Bt)$_2$ (**10c**).* Sticky gel, 0.78 g, 0.92 mmol, 88% yield. ^{1}H and ^{13}C NMR were identical to those of **10b**.

General Procedure for the Cyclization of Precursor 10a−c To Form Symmetrical DKPs 11a−c. A solution of **10a−c** (1 equiv) and triethylamine (2−2.2 equiv) in dry acetonitrile (100 mL) was stirred for 48−84 h until TLC revealed cyclization was complete. Each mixture was concentrated under vacuum, and the residue was

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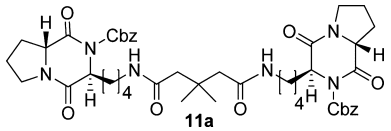
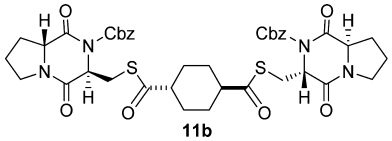
dissolved in ethyl acetate (20 mL/1 g of **11a−c**). The organic layer was washed with 4 N HCl (3 × 1 mL/1 mL ethyl acetate) and Na_2CO_3 10 wt % in water (3 × 1 mL/1 mL ethyl acetate) and purified by column chromatography (CH_2Cl_2/hexanes gradient) to give the corresponding symmetrical bis-DKPs **11a−c**.



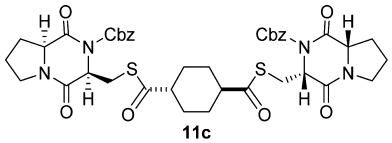
11a

*3,3-DMG-cyclo-(Cbz-L-Lys-D-Pro)$_2$ (**11a**).* Sticky gel, 0.35 g, 0.42 mmol, 91% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 0.98 (br s, 6H), 1.22−1.34 (m, 8H), 1.42−1.63 (m, 6H), 1.78−2.00 (m, 4H), 2.13−2.24 (m, 1H), 2.28−2.37 (m, 1H), 2.47 (br s, 4H), 3.07−3.19 (m, 1H), 3.37−3.52 (m, 2H), 3.54−3.61 (m, 1H), 3.62−3.73 (m, 3H), 3.73−3.83 (m, 1H), 4.02−4.38 (m, 2H), 4.40−4.82 (m, 2H), 4.99−5.27 (m, 4H), 7.21−7.36 (m, 8H), 7.37−7.44 (m, 2H) . ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.8, 24.8, 27.8, 29.4, 29.9, 31.4, 38.6, 46.5, 52.5, 59.6, 61.5, 67.1, 69.9, 128.1, 128.7, 129.0, 134.9, 156.1, 165.3, 167.9, 172.3. HRMS (ESI): calcd $C_{45}H_{58}N_6O_{10}Na$ [M + Na]$^+$ 865.4107, found 865.4125.



11b

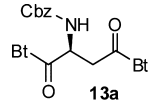
*trans-1,4-CHD-[cyclo-(Cbz-L-Cys-D-Pro)]$_2$ (**11b**).* Sticky gel, 0.85 g, 1.05 mmol, 85% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.49−1.67 (m, 3H), 1.74−2.12 (m, 12H), 2.34−2.46 (m, 2H), 2.50−2.58 (m, 1H), 3.34−3.59 (m, 8H), 4.66 (dd, J = 8.0, 8.0 Hz, 2H), 4.95 (dd, J = 7.1, 7.1 Hz, 2H), 5.22−5.36 (m, 4H), 7.22−7.45 (m, 10H). ^{13}C NMR (CD_3OD, 75 MHz): δ 23.5, 27.2, 27.4, 30.3, 46.9, 50.0, 61.3, 61.7, 70.4, 129.6, 129.7, 129.8, 136.7, 153.6, 165.4, 169.0, 202.3. HRMS (ESI): calcd for $C_{40}H_{44}N_4O_{10}S_2Na$ [M + Na]$^+$ 827.2391, found 827.2371.



11c

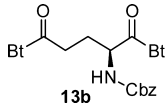
*trans-1,4-CHD-[cyclo-(Cbz-L-Cys-L-Pro)]$_2$ (**11c**).* Sticky gel, 0.61 g, 0.75 mmol, 81% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.82−2.20 (m, 12H), 2.42−2.65 (m, 6H), 3.32−3.43 (m, 2H), 3.46−3.63 (m, 6H), 4.56 (dd, J = 5.7, 4.2 Hz, 2H), 4.98 (t, J = 4.4 Hz, 2H), 5.27−5.36 (m, 4H), 7.28−7.46 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): 22.7, 26.1, 26.3, 29.2, 29.4, 45.8, 59.9, 60.4, 69.6, 128.6, 128.7, 128.8, 134.8, 152.2, 163.3, 167.2, 200.7. HRMS (ESI): calcd for $C_{40}H_{44}N_4O_{10}S_2Na$ [M + Na]$^+$ 827.2391, found 827.2398.

Preparation of Compounds 13a,b. The compounds were prepared according to the method for preparation of **2a,b**.



13a

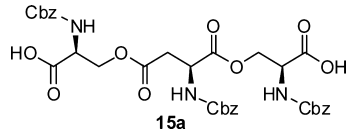
*Cbz-L-Asp-(Bt)-Bt (**13a**).* White microcrystals, 1.51 g, 3.22 mmol, 86% yield. Mp: 140−143 °C.[47] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.35−4.54 (m, 2H), 5.13 (br s, 2H), 6.08−6.13 (m, 1H), 6.19−6.26 (m, 1H), 7.26−7.36 (m, 5H), 7.46−7.71 (m, 4H), 8.07−8.19 (m, 3H), 8.26 (d, J = 8.5 Hz, 1H).



13b

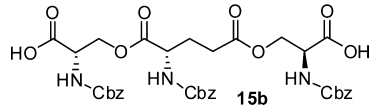
*Cbz-L-Glu-(Bt)-Bt (**13b**).* White microcrystals, 6.33 g, 13.09 mmol, 92% yield. Mp: 150−152 °C.[47] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.47−2.61 (m, 1H), 2.73−2.87 (m, 1H), 3.72 (t, J = 7.1 Hz, 2H), 5.10 (br s, 2H), 5.80−6.04 (m, 2H), 7.20−7.38 (m, 5H), 7.45−7.71 (m, 4H), 8.07−8.26 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.5, 31.9, 54.3, 67.7, 114.5, 120.4, 120.7, 126.5, 126.9, 128.4, 128.7, 130.7, 131.1, 131.2, 136.0, 146.3, 156.1, 171.1, 171.3. Anal. Calcd for $C_{25}H_{21}N_7O_4$: C, 62.11; H, 4.38; N, 20.28. Found: C, 62.15; H, 4.26; N, 20.56.

Synthesis of Compounds 15a−e. Compounds **15a−e** were prepared by *O*-acylation (for **15a,b**) of **13a,b** by Cbz-L-Ser-OH (2−2.1 equiv) in acetonitrile (10 mL/1 g) containing diisopropylamine (DIPEA) (6.5 equiv) or *S*-acylation (for **15c,d**) of **13a,b** by Cbz-L-Cys-OH (2−2.1 equiv) in water (10 mL/1 g) containing triethylamine (2.2 equiv) or *N*-acylation (for **15e**) of of 13a by Cbz-L-Lys-OH (2−2.1 equiv) in water (10 mL/1 g) containing triethylamine (2.2 equiv) according to the method for preparation of **7a,b**.



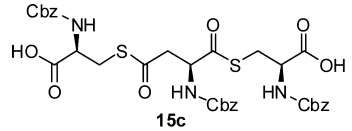
15a

*Cbz-L-Asp-(Cbz-L-Ser-OH)-Cbz-L-Ser-OH (**15a**).* Sticky gel, 5.32 g, 7.50 mmol, 88% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.79 (dd, J = 16.9, 7.0 Hz, 1H), 2.87 (dd, J = 16.9, 7.0 Hz, 1H), 3.79 (ddd, J = 18.0, 11.4, 4.5 Hz, 1H), 4.26−4.42 (m, 2H), 4.45−4.63 (m, 4H), 5.07 (br s, 6H), 7.26−7.40 (m, 15H). ^{13}C NMR (CD_3OD, 75 MHz): δ 37.2, 51.9, 54.6, 57.8, 63.2, 65.6, 66.0, 68.0, 68.1, 127.2, 128.9, 129.1, 129.3, 129.5, 137.9, 138.0, 158.4, 158.5, 171.7, 172.0, 172.4, 172.6. Anal. Calcd for $C_{34}H_{35}N_3O_{14}$: C, 57.54; H, 4.97; N, 5.92. Found: C, 57.37; H, 5.02; N, 5.96.



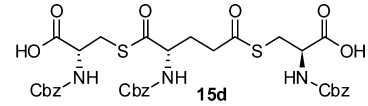
15b

*Cbz-L-Glu-(Cbz-L-Ser-OH)-Cbz-L-Ser-OH (**15b**).* Sticky gel, 5.51 g, 7.62 mmol, 92% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.93−2.04 (m, 1H), 2.21−2.40 (m, 2H), 2.42−2.47 (m, 1H), 3.66 (d, J = 4.8 Hz, 1H), 4.00−4.12 (m, 1H), 4.20 (dd, J = 10.5, 6.9 Hz, 1H), 4.31−4.42 (m, 2H), 4.48 (dd, J = 10.8, 4.5 Hz, 1H), 4.70 (dd, J = 9.8, 2.6 Hz, 1H), 4.99−5.07 (m, 4H), 5.15−5.26 (m, 2H), 7.24−7.46 (m, 15H), 7.62−7.80 (m, 2H), 7.91 (br s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.9, 30.6, 52.7, 56.6, 58.3, 61.3, 64.0, 65.4, 65.7, 67.3, 127.5, 127.7, 128.1, 128.3, 135.4, 136.8, 150.5, 156.0, 170.5, 170.9, 172.0, 172.8. HRMS (ESI): calcd for $C_{35}H_{36}N_3O_{14}$ [M − H]$^-$ 722.2192, found 722.2181.



15c

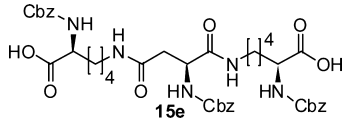
*Cbz-L-Asp-(Cbz-L-Cys-OH)-Cbz-L-Cys-OH (**15c**).* Sticky gel, 1.38 g, 1.86 mmol, 90% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.84−3.19 (m, 6H), 4.02−4.19 (m, 2H), 4.42−4.68 (m, 1H), 5.03 (br s, 4H), 5.07 (br s, 2H), 7.22−7.41 (m, 15H), 7.75 (d, J = 9.0 Hz, 2H), 8.18 (t, J = 9.0 Hz, 1H). ^{13}C NMR (CD_3OD, 75 MHz): δ 27.1, 31.8, 45.9, 54.9, 59.2, 67.9, 128.9, 129.1, 129.6, 138.2, 158.5, 165.0, 173.4, 196.7. HRMS (ESI): calcd for $C_{34}H_{34}N_3O_{12}S_2$ [M − H]$^-$ 740.1578, found 740.1594.



15d

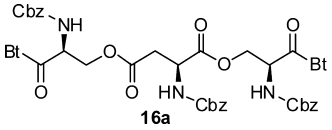
*Cbz-L-Glu-(Cbz-L-Cys-OH)-Cbz-L-Cys-OH (**15d**).* Sticky gel, 9.65 g, 12.78 mmol, 90% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.94−2.08 (m, 1H), 2.14−2.49 (m, 2H), 2.50−2.71 (m, 1H), 3.05−3.38 (m, 3H), 3.43−3.58 (m, 1H), 4.47−4.80 (m, 3H), 4.99−5.26 (m, 6H), 5.56 (d, J = 9.0 Hz, 1H), 5.87 (d, J = 9.0 Hz, 1H), 7.23−7.40 (m, 14H), 7.53 (br s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.5, 30.8, 53.3, 65.3, 67.5, 68.8, 128.3, 128.4, 128.7, 134.8, 136.0, 150.8, 156.2, 173.1, 173.7, 198.3. HRMS (ESI): calcd for $C_{35}H_{36}N_3O_{12}S_2$ [M − H]$^-$ 754.1735, found 754.1716.

dx.doi.org/10.1021/jo401235k | J. Org. Chem. 2013, 78, 8510−8523

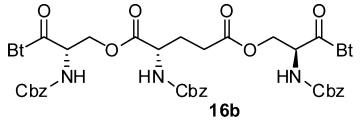

15e

Cbz-L-Asp-(Cbz-L-Lys-OH)-Cbz-L-Lys-OH (***15e***). Sticky gel, 6.27g, 7.92 mmol, 93% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.37−1.45 (m, 5H), 1.57−1.72 (m, 5H), 1.80−1.90 (m, 2H), 2.64 (dd, J = 5.7, 5.7 Hz, 1H), 2.67 (dd, J = 5.6, 5.6 Hz, 1H), 3.00 (dd, J = 10.7, 5.6 Hz, 1H), 3.52 (t, J = 3.9 Hz, 3H), 4.111−4.15 (m, 2H), 4.32−4.39 (m, 1H), 5.06 (s, 2H), 5.08 (s, 4H), 7.25−7.31 (m, 3H), 7.32−7.38 (m, 12H). ^{13}C NMR (CD_3OD, 75 MHz): δ 23.8, 27.9, 29.7, 32.1, 36.1, 39.4, 51.1, 51.2, 55.1, 67.6, 67.9, 68.0, 128.7, 128.9, 129.1, 129.4, 137.8, 138.1, 158.1, 158.6, 175.8, 176.9, 178.3. Anal. Calcd for $C_{40}H_{49}N_5O_{12}$: C, 60.67; H, 6.24; N, 8.84. Found: C, 60.61; H, 6.27; N, 9.11.

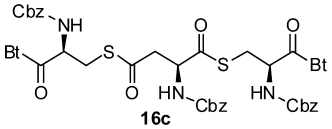
Preparation of Compounds 16a−e. The compounds were prepared according to the method for preparation of **8a,b**.


16a

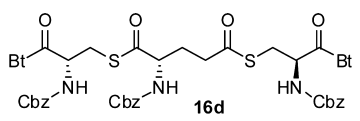
Cbz-L-Asp-(Cbz-L-Ser-Bt)-Cbz-L-Ser-Bt (***16a***). White microcrystals, 1.86 g, 2.5 mmol, 68%. Mp: 80−83 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.76 (dd, J = 17.0, 4.4 Hz, 1H), 2.87 (dd, J = 17.4, 4.5 Hz, 1H), 4.50−4.59 (m, 2H), 4.65−4.73 (m, 1H), 4.77−4.96 (m, 2H), 5.02−5.17 (m, 6H), 5.79−5.90 (m, 1H), 5.94−6.60 (m, 2H), 6.24 (t, J = 10.2 Hz, 2H), 7.20−7.37 (m, 15H), 7.43−7.59 (m, 4H), 8.05−8.14 (m, 4H). ^{13}C NMR (DMSO−d_6, 75 MHz): δ 35.5, 50.1, 53.6, 63.1, 63.6, 65.7, 66.11, 113.9, 120.22, 126.8, 127.7, 127.9, 128.4, 130.6, 130.9, 131.2, 136.5, 136.6, 136.8, 145.3, 155.7, 156.1, 168.4, 168.5, 169.5, 170.3. HRMS (ESI): calcd for $C_{46}H_{41}N_9O_{12}Na$ [M + Na]$^+$ 934.2767, found 934.2756.


16b

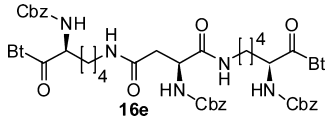
Cbz-L-Glu-(Cbz-L-Ser-Bt)-Cbz-L-Ser-Bt (***16b***). White microcrystals, 1.86 g, 2.5 mmol, 68% yield. Mp: 71−75 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.97−2.13 (m, 1H), 2.22−2.37 (m, 1H), 2.39−2.66 (m, 2H), 4.44 (dd, J = 12.3, 5.1 Hz, 1H), 4.66 (dd, J = 9.3, 2.9 Hz, 1H), 4.68 (dd, J = 9.3, 2.3 Hz, 1H), 4.78−4.86 (m, 2H), 5.04−5.20 (m, 4H), 5.21−5.34 (m, 2H), 5.81 (d, J = 7.5 Hz, 1H), 5.94−6.08 (m, 2H), 6.09−6.19 (m, 1H), 6.39−6.52 (m, 1H), 7.28−7.42 (m, 15H), 7.48−7.60 (m, 2H), 7.61−7.70 (m, 2H), 8.09−8.32 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 21.9, 31.2, 54.9, 58.8, 59.0, 65.3, 67.8, 69.0, 114.4, 115.1, 120.7, 126.3, 127.1, 128.4, 128.5, 128.7, 131.1, 131.3, 135.0, 136.0, 138.7, 146.2, 151.5, 156.1, 168.0, 170.8, 172.7, 173.6. HRMS (ESI): calcd for $C_{47}H_{43}N_9O_{12}Na$ [M + Na]$^+$ 948.2923, found 948.2938.


16c

Cbz-L-Asp-(Cbz-L-Cys-Bt)-Cbz-L-Cys-Bt (***16c***). Sticky gel, 0.99 g, 1.05 mmol, 78% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.25−3.71 (m, 4H), 3.76−4.00 (m, 2H), 4.50−4.96 (m, 1H), 5.15 (br s, 6H), 5.40−5.80 (m, 2H), 5.80−6.20 (m, 3H), 7.24−7.40 (m, 15H), 7.42−7.59 (m, 3H), 7.60−7.78 (m, 1H), 7.85−8.28 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.6, 36.7, 45.2, 53.4, 54.2, 57.4, 67.9, 115.1, 120.6, 126.3, 126.9, 128.3, 128.8, 131.2, 136.0, 138.8, 146.2, 155.9, 168.9, 196.6. HRMS (ESI): calcd for $C_{46}H_{41}N_9O_{10}S_2Na$ [M + Na]$^+$ 966.2310, found 966.2304.

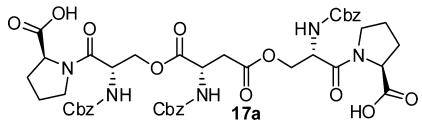

16d

Cbz-L-Glu-(Cbz-L-Cys-Bt)-Cbz-L-Cys-Bt (***16d***). Sticky gel, 0.93 g, 0.97 mmol, 68% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.92−2.04 (m, 1H), 2.28−2.50 (m, 1H), 2.51−2.81 (m, 2H), 3.47−3.70 (m, 4H), 4.18−4.46 (m, 1H), 5.075.17 (m, 5H), 5.195.29 (m, 1H), 5.88−5.99 (m, 2H), 7.27−7.40 (m, 15H), 7.57−7.69 (m, 2H), 7.71−7.85 (m, 2H), 8.15−8.22 (m, 2H), 8.23−8.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.6, 27.5, 30.7, 31.6, 39.3, 54.0, 60.0, 65.1, 67.5, 68.7, 114.3, 114.4, 120.4, 120.5, 125.9, 126.7, 126.9, 128.2, 128.6, 131.0, 136.0, 146.0, 155.8, 168.6, 168.9, 197.9, 198.5. HRMS (ESI): calcd for $C_{47}H_{43}N_9O_{10}S_2Na$ [M + Na]$^+$ 980.2466, found 980.2482.

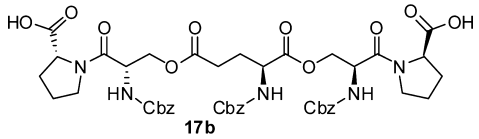

16e

Cbz-L-Asp-(Cbz-L-Lys-Bt)-Cbz-L-Lys-Bt (***16e***). Sticky gel, 1.86 g, 1.87 mmol 74% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.44−1.71 (m, 7H), 1.72−1.83 (m, 1H), 1.85−1.98 (m, 2H), 2.05−2.16 (m, 2H), 2.70−2.88 (m, 1H), 2.99−3.06 (m, 2H), 3.51−3.62 (m, 3H), 4.21−4.32 (m, 1H), 5.04−5.13 (m, 7H), 5.64−5.77 (m, 3H), 5.79−5.85 (m, 1H), 6.00 (br s, 1H), 7.10 (br s, 1H), 7.26−7.38 (m, 15H), 7.52 (t, J = 4.7 Hz, 2H), 7.66 (t, J = 4.4 Hz, 2H), 8.12 (d, J = 5.1 Hz, 2H), 8.25 (d, J = 4.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.3, 26.6, 32.1, 35.6, 38.3, 50.1, 54.5, 67.2, 114.4, 120.3, 126.5, 128.1, 128.2, 128.3, 128.5, 130.8, 131.1, 135.8, 136.1, 145.9, 156.0, 156.3, 171.7, 174.6, 176.1. HRMS (ESI): calcd for $C_{52}H_{55}N_{11}O_{10}Na$ [M + Na]$^+$ 1016.4026, found 1016.4033.

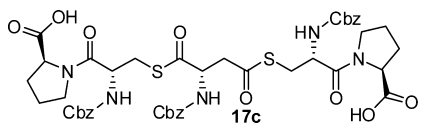
Preparation of Compounds 17a−e. The compounds were prepared according to the method for preparation of **9a−c**.


17a

Cbz-L-Asp-(Cbz-L-Ser-L-Pro-OH)-Cbz-L-Ser-L-Pro-OH (***17a***). White microcrystals, 3.69 g, 4.08 mmol, 92% yield; sticky gel. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.62−1.94 (m, 6H), 1.98−2.20 (m, 2H), 2.72 (dd, J = 16.5, 8.0 Hz, 1H), 2.84 (dd, J = 16.8, 4.7 Hz, 1H), 3.56−3.66 (m, 3H), 3.93−4.05 (m, 2H), 4.22−4.27 (m, 2H), 4.30−4.37 (m, 2H), 4.44−4.53 (m, 2H), 4.57−4.65 (m, 2H), 4.93−5.06 (m, 6H), 7.24−7.37 (m, 15H), 7.71 (d, J = 8.3 Hz, 1H), 7.80 (t, J = 7.6 Hz, 2H). ^{13}C NMR (CD_3OD, 75 MHz): δ 25.8, 30.1, 37.1, 51.8, 53.1, 60.6, 64.9, 65.2, 68.0, 115.7, 127.2, 128.7, 128.9, 129.1, 129.5, 138.0, 140.0, 158.3, 169.8, 171.8, 172.2, 175.2. HRMS (ESI): calcd for $C_{44}H_{48}N_5O_{16}$ [M − H]$^-$ 902.3091, found 902.3099.


17b

Cbz-L-Glu-(Cbz-L-Ser-D-Pro-OH)-Cbz-L-Ser-D-Pro-OH (***17b***). Sticky gel, 0.81 g, 0.89 mmol, 82% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.78−2.10 (m, 6H), 2.10−2.32 (m, 3H), 2.34−2.46 (m, 2H), 2.48−2.62 (m, 1H), 3.41−3.78 (m, 1H), 3.57−3.75 (m, 2H), 4.03−4.18 (m, 1H), 4.18−4.46 (m, 3H), 4.48−4.60 (m, 1H), 4.62−4.73 (m, 2H), 4.76−4.89 (m, 1H), 5.04−5.11 (m, 4H), 5.12−5.30 (m, 2H), 7.23−7.38 (m, 15H). ^{13}C NMR (CD_3OD, 75 MHz): δ 22.8, 26.2, 30.7, 32.3, 53.1, 60.7, 61.1, 66.0, 68.4, 69.8, 116.1, 127.6, 129.4, 129.5, 129.7, 130.0, 130.1, 137.1, 138.5, 140.5, 152.6, 158.6, 169.7, 173.0, 175.7, 176.4. HRMS (ESI): calcd for $C_{45}H_{50}N_5O_{16}$ [M − H]$^-$ 916.3247, found 916.3266.


17c

Cbz-L-Asp-(Cbz-L-Cys-L-Pro-OH)-Cbz-L-Cys-L-Pro-OH (***17c***). Sticky gel, 0.89 g, 0.95 mmol, 86% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.50−2.02 (m, 5H), 2.02−2.35 (m, 2H), 2.62−3.20 (m, 7H), 3.48−

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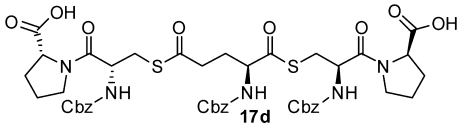
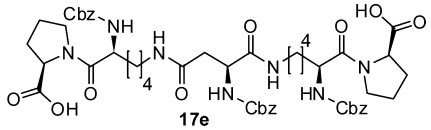
3.73 (m, 3H), 3.95−4.14 (m, 1H), 4.14−4.29 (m, 2H), 4.39−4.74 (m, 2H), 4.93−5.18 (m, 7H), 7.25−7.42 (m, 15H), 7.73 (d, J = 8.1 Hz, 2H), 7.80−8.21 (m, 1H). ^{13}C NMR (CD_3OD, 300 MHz): δ 25.8, 30.4, 31.9, 45.9, 53.2, 54.9, 59.2, 60.8, 68.0, 128.9, 129.1, 129.6, 138.2, 158.2, 158.5, 170.6, 173.5, 175.4, 196.7. HRMS (ESI): calcd for $C_{44}H_{48}N_5O_{14}S_2$ $[M - H]^-$ 934.2634, found 934.2649.



17d

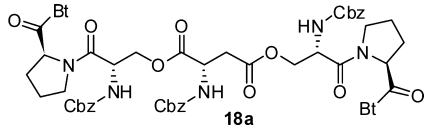
Cbz-L-Glu-(Cbz-L-Cys-D-Pro-OH)-Cbz-L-Cys-D-Pro-OH (***17d***). Sticky gel, 0.81 g, 0.89 mmol, 82% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.75−2.06 (m, 8H), 2.12−2.31 (m, 3H), 2.32−2.74 (m, 3H), 2.99−3.18 (m, 2H), 3.31−3.62 (m, 2H), 3.63−3.78 (m, 2H), 4.24−4.48 (m, 3H), 4.54−4.74 (m, 1H), 5.02−5.12 (m, 5H), 5.13−5.26 (m, 2H), 7.23−7.48 (m, 15H). ^{13}C NMR (CD_3OD, 75 MHz): δ 23.4, 25.8, 30.4, 31.7, 32.1, 40.7, 48.0, 52.8, 53.4, 60.8, 61.7 66.8, 68.0, 69.5, 128.9, 129.2, 129.3 129.4, 129.6, 136.6, 138.2, 152.1, 158.3, 158.4, 170.4, 170.7, 175.4, 176.1, 200.4. HRMS (ESI): calcd for $C_{45}H_{50}N_5O_{14}S_2$ $[M - H]^-$ 948.2790, found 948.2772.



17e

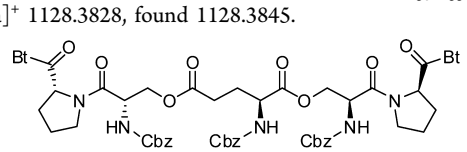
Cbz-L-Asp-(Cbz-L-Lys-D-Pro-OH)-Cbz-L-Lys-D-Pro-OH (***17e***). Sticky gel, 0.77 g, 1.53 mmol, 76% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.22−1.52 (m, 6H), 1.53−1.80 (m, 7H), 1.82−1.94 (m, 2H), 1.95−2.08 (m, 3H), 2.16−2.32 (m, 2H), 2.63 (dd, J = 5.9, 5.9 Hz, 1H), 2.66 (dd, J = 5.7, 5.7 Hz, 1H), 3.00 (dd, J = 10.8, 5.4 Hz, 1H), 3.08−3.19 (m, 1H), 3.46−3.55 (m, 4H), 3.56−3.67 (m, 1H), 3.78−3.85 (m, 1H), 4.32−4.42 (m, 3H), 4.43−4.48 (m, 1H), 5.05−5.10 (m, 7H), 7.27−7.40 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 22.8, 24.7, 26.9, 28.8, 31.6, 35.6, 28.4, 47.3, 50.0, 52.2, 53.6, 59.5, 66.9, 67.2, 76.8, 77.3, 77.7, 136.0, 136.3, 156.2, 156.5, 171.5, 174.0, 175.0, 176.5. HRMS (ESI): calcd for $C_{50}H_{62}N_7O_{14}$ $[M - H]^-$ 984.4349, found 984.4362.

Preparation of Compounds 18a−e. The compounds were prepared according to the method for preparation of **10a−c**.



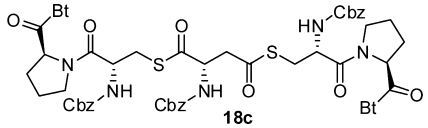
18a

Cbz-L-Asp-(Cbz-L-Ser-L-Pro-Bt)-Cbz-L-Ser-L-Pro-Bt (***18a***). Sticky gel, 0.44 g, 0.40 mmol, 72% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.64−1.98 (m, 2H), 1.98−2.30 (m, 6H), 2.68−2.96 (m, 2H), 3.72−3.90 (m, 3H), 3.95−4.17 (m, 2H), 4.28−4.58, (m, 4H), 4.64−4.80 (m, 2H), 5.02 (br s, 6H), 5.68−5.84 (m, 2H), 7.24−7.42 (m, 15H), 7.56−7.68 (m, 3H), 7.68−7.85 (m, 4H), 8.08−8.30 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.3, 29.8, 36.7, 47.9, 50.9, 51.8, 60.1, 67.3, 114.5, 120.3, 126.5, 127.7, 128.2, 128.6, 130.8, 131.2, 136.3, 146.0, 156.2, 167.6, 169.9, 170.4. HRMS (ESI): calcd for $C_{56}H_{55}N_{11}O_{14}Na$ $[M + Na]^+$ 1128.3828, found 1128.3845.



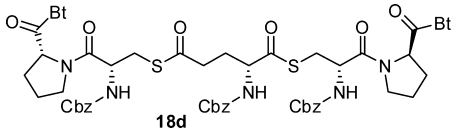
18b

Cbz-L-Glu-(Cbz-L-Ser-D-Pro-Bt)-Cbz-L-Ser-D-Pro-Bt (***18b***). White microcrystals, 1.24 g, 1.11 mmol 68% yield. Mp: 85−89 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.88−2.10 (m, 6H), 2.14−2.23 (m, 2H), 2.28−2.48 (m, 2H), 2.48−2.76 (m, 2H), 3.45−3.68 (m, 3H), 3.82−3.94 (m, 1H), 4.19−4.42 (m, 3H), 4.48−4.66 (m, 3H), 4.92−5.08 (m, 2H), 5.12−5.17 (m, 1H), 5.20−5.35 (m, 4H), 5.74 (d, J = 8.2 Hz, 2H), 5.86−5.93 (m, 3H), 7.28−7.40 (m, 15H), 7.50−7.56 (m, 2H), 7.64−7.70 (m, 2H), 8.13−8.16 (m, 2H), 8.2−8.27 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.9, 22.3, 25.2, 29.6, 29.9, 31.2, 45.8, 52.1, 58.8, 59.8, 60.1, 64.8, 67.4, 68.7, 67.0, 69.9, 114.6, 115.2, 120.5, 125.9, 126.7, 128.2, 128.3, 128.5, 128.7, 128.9, 130.8, 134.6, 135.0, 136.3, 146.2, 151.3, 152.2, 156.0, 162.2, 167.3, 170.6, 172.9. HRMS (ESI): calcd for $C_{57}H_{57}N_{11}O_{14}Na$ $[M + Na]^+$ 1142.3979, found 1142.3995.



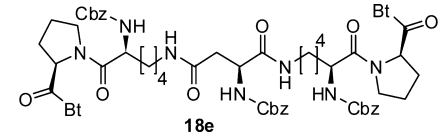
18c

Cbz-L-Asp-(Cbz-L-Cys-L-Pro-Bt)-Cbz-L-Cys-L-Pro-Bt (***18c***). Sticky gel, 1.60 g, 1.40 mmol, 67% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.89−2.32 (m, 8H), 2.40−2.72 (m, 2H), 2.78−3.45 (m, 4H), 3.48−3.82 (m, 3H), 3.82−4.08 (m, 2H), 4.34−4.94 (m, 2H), 4.95−5.28 (m, 6H), 5.46−5.78 (m, 1H), 5.78−5.98 (m, 2H), 5.98−6.12 (m, 1H), 6.18−6.50 (m, 1H), 7.15−7.44 (m, 15H), 7.50−7.62 (m, 2H), 7.62−7.74 (m, 2H), 8.08−8.20 (m, 2H), 8.20−8.32 (m, 2H). ^{13}C NMR (CDCl3, 75 MHz): δ 24.9, 28.6, 29.6, 31.3, 40.6, 44.7, 47.6, 51.5, 51.9, 57.4, 59.5, 59.8, 67.1, 67.3, 114.3, 114.8, 120.1, 120.2, 125.7, 126.3, 126.5, 127.9, 130.5, 130.9, 131.0, 135.9, 136.1, 138.5, 145.8, 155.9, 168.7, 169.7, 195.9, 199.5. HRMS (ESI): calcd for $C_{56}H_{55}N_{11}O_{12}S_2Na$ $[M + Na]^+$ 1160.3365, found 1160.3355.



18d

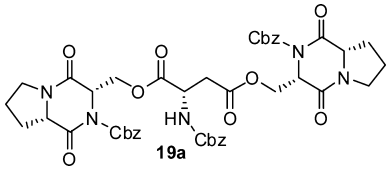
Cbz-L-Glu-(Cbz-L-Cys-D-Pro-Bt)-Cbz-L-Cys-D-Pro-Bt (***18d***). White microcrystals, 1.50 g, 1.3 mmol 62% yield. Mp: 93−98 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.80−2.09 (m, 1H), 2.10−2.34 (m, 6H), 2.362.78 (m, 5H), 3.10−3.40 (m, 3H), 3.40−3.65 (m, 2H), 3.88−4.44 (m, 3H), 4.77 (dd, J = 9.5, 2.3 Hz, 1H), 4.78−4.94 (m, 1H), 4.98−5.16 (m, 5H), 5.20−5.38 (m, 2H), 5.73 (d, J = 9 Hz, 2H), 5.76−5.88 (m, 3H), 7.33−7.45 (m, 15H), 7.46−7.55 (m, 2H), 7.60−7.68 (m, 2H), 8.00−8.15 (m, 2H), 8.20−8.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.6, 25.2, 29.9, 31.0, 31.7, 47.7, 51.3, 60.0, 60.3, 65.3, 67.2, 68.7, 114.6, 120.4, 125.8, 126.6, 128.3, 128.7, 130.8, 131.3, 135.1, 136.3, 146.1, 151.1, 155.9, 168.0, 170.1, 173.2, 199.0. HRMS (ESI): calcd for $C_{57}H_{57}N_{11}O_{12}S_2Na$ $[M + Na]^+$ 1174.3522, found 1174.3541.



18e

Cbz-L-Asp-(Cbz-L-Lys-D-Pro-Bt)-Cbz-L-Lys-D-Pro-Bt (***18e***). Sticky gel, 0.83 g, 0.70 mmol, 69% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28−1.42 (m, 5H), 1.56−1.64 (m, 5H), 1.64−1.84 (m, 5H), 2.12−2.26 (m, 5H), 2.50−2.66 (m, 2H), 3.03 (dd, J = 10.8, 5.4 Hz, 2H), 3.50−3.66 (m, 3H), 3.68−3.74 (m, 2H), 3.92−3.98 (m, 1H), 4.36−4.48 (m, 2H), 4.55−4.61 (m, 1H), 5.03−5.13 (m, 7H), 5.60−5.68 (m, 2H), 5.92 (dd, J = 5.4, 2.1 Hz, 2H), 5.98 (d, J = 3.0 Hz, 1H), 7.27−7.36 (m, 17H), 7.48−7.54 (m, 2H), 7.65 (t, J = 4.4 Hz, 2H), 8.11−8.14 (m, 2H), 8.22−8.27 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 21.9, 25.1, 26.9, 29.7, 32.4, 35.9, 38.5, 47.6, 50.1, 52.1, 59.7, 67.0, 67.4, 114.7, 120.4, 126.6, 127.9, 128.1, 128.2, 128.3, 128.4, 128.7, 130.7, 131.3, 136.4, 146.1, 156.2, 156.3, 170.3, 170.7, 174.7, 176.1. HRMS (ESI): calcd for $C_{62}H_{69}N_{13}O_{12}Na$ $[M + Na]^+$ 1210.5081, found 1210.5099.

Preparation of Unsymmetrical bis-DKPs 19a−e. The compounds were prepared according to the method for preparation of **11a−c**.

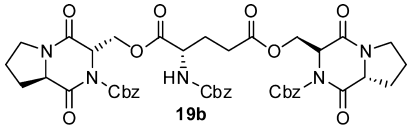


19a

Cbz-L-Asp-[cyclo-(Cbz-L-Ser-L-Pro)]-cyclo-(Cbz-L-Ser-L-Pro) (***19a***). Sticky gel, 0.56 g, 0.65 mmol, 72% yield. ^{1}H NMR (DMSO-d_6, 300

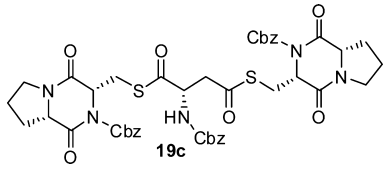
dx.doi.org/10.1021/jo401235k | J. Org. Chem. 2013, 78, 8510−8523

MHz): δ 1.69−1.98 (m, 6H), 2.02−2.24 (m, 2H), 2.54−2.78 (m, 2H), 3.54−3.62 (m, 4H), 3.68−4.06 (m, 2H), 4.23−4.80 (m, 6H), 4.82−4.92 (m, 1H), 4.94−5.06 (m, 4H), 5.20−5.29 (m, 2H), 7.24−7.43 (m, 15H), 7.68−7.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.4, 22.8, 29.6, 31.8, 36.1, 45.8, 50.3, 60.0, 64.0, 65.2, 66.0, 67.3, 67.5, 69.8, 128.3, 128.5, 128.7, 128.8, 134.6, 136.0, 152.2, 156.0, 162.5, 167.3, 170.3. HRMS (ESI): calcd for $C_{44}H_{45}N_5O_{14}Na$ [M + Na]$^+$ 890.2855, found 890.2828.



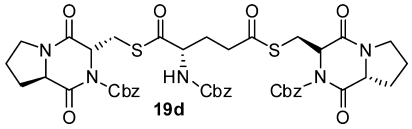
19b

Cbz-L-Glu-[cyclo-(Cbz-L-Ser-D-Pro)]-cyclo-(Cbz-L-Ser-D-Pro) ***(19b)***. White microcrystals, 178.4 mg, 0.20 mmol, 88% yield. Mp: 70−72 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.91−2.10 (m, 6H), 2.26−2.45 (m, 4H), 2.46−2.60 (m, 2H), 3.41−3.62 (m, 4H), 4.364.44 (m, 2H), 4.49 (dd, J = 12.0, 4.5 Hz, 2H), 4.57 (dd, J = 11.7, 4.2 Hz, 2H), 4.73 (dd, J = 9.5, 2.9 Hz, 1H),5.01 (t, J = 4.2 Hz, 2H), 5.13−5.30 (m, 2H), 5.31 (br s, 4H), 7.28−7.39 (m, 12H), 7.43−7.47 (m, 3H). ^{13}C NMR (CD_3OD, 75 MHz): δ 22.6, 23.2, 26.7, 27.1, 30.4, 32.0, 44.4, 46.9, 60.3, 61.1, 61.6, 66.1, 68.0, 69.6, 70.5, 129.0, 129.2, 129.5, 129.6, 129.7, 136.6, 136.7, 152.5, 153.5, 164.2, 168.9, 172.3, 175.6. HRMS (ESI): calcd for $C_{45}H_{47}N_5O_{14}Na$ [M + Na]$^+$ 904.3012, found 904.3021.



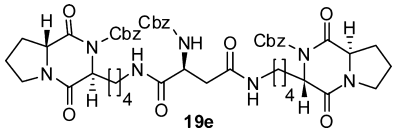
19c

Cbz-L-Asp-[cyclo-(Cbz-L-Ser-L-Pro)]-cyclo-(Cbz-L-Ser-L-Pro) ***(19c)***. Sticky gel, 0.69 g, 0.76 mmol, 76% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.72−2.04 (m, 8H), 2.18−2.24 (m, 2H), 3.21−3.30 (m, 2H), 3.38−3.42 (m, 6H), 4.60 (dd, J = 9.8, 5.6 Hz, 2H), 4.76−4.83 (m, 1H), 4.91 (t, J = 4.4 Hz, 1H), 4.98−5.12 (m, 3H), 5.20−5.34 (m, 4H), 7.22−7.51 (m, 16H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 22.2, 28.6, 29.4, 37.9, 45.3, 59.0, 59.5, 65.6, 66.0, 68.4, 127.7, 127.9, 128.2, 135.2, 136.6, 136.9, 151.7, 151.9, 155.8, 162.3, 162.4, 166.9, 167.3, 199.6, 199.9. HRMS (ESI): calcd for $C_{44}H_{45}N_5O_{12}S_2Na$ [M + Na]$^+$ 922.2398, found 922.2382.



19d

Cbz-L-Glu-[cyclo-(Cbz-L-Cys-D-Pro)]-cyclo-(Cbz-L-Cys-D-Pro) ***(19d)***. Sticky gel, 0.17 g, 0.19 mmol, 86% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.88−2.37 (m, 9H), 2.38−2.52 (m, 3H), 2.53−2.67 (m, 1H), 3.29 (dd, J = 14.1, 5.8 Hz, 2H), 3.24−3.43 (m, 3H), 3.46−3.66 (m, 4H), 4.50 (dd, J = 9.3, 7.2 Hz, 2H), 4.78 (dd, J = 9.0, 2.4 Hz, 1H), 4.93 (dd, J = 8.7, 5.7 Hz, 1H), 5.04−5.16 (m, 1H), 5.18−5.37 (m, 6H), 7.25−7.45 (m, 16H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.5, 22.6, 28.9, 29.4, 30.9, 45.7, 59.7, 60.3, 65.1, 68.7, 69.8, 128.3, 128.4, 128.5, 128.7, 128.9, 134.6, 135.0, 152.2, 162.7, 167.2, 172.9, 197.7. HRMS (ESI): calcd for $C_{45}H_{47}N_5O_{12}S_2Na$ [M + Na]$^+$ 936.2555, found 936.2562.



19e

Cbz-L-Asp-[cyclo-(Cbz-L-Lys-D-Pro)]-cyclo-(Cbz-L-Lys-D-Pro) ***(19e)***. Sticky gel, 0.24 g, 0.26 mmol, 88% yield. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.34−1.44 (m, 4H), 1.49−1.68 (m, 3H), 1.77−1.89 (m, 2H), 1.90−2.01 (m, 5H), 2.03−2.12 (m, 2H), 2.33−3.39 (m, 2H), 2.62 (dd, J = 5.0, 5.0 Hz, 1H), 2.66 (dd, J = 5.0, 5.0 Hz, 1H), 2.95−3.03 (m, 2H), 3.43−3.53 (m, 6H), 4.33−4.40 (m, 2H), 4.47−4.54 (m, 1H), 4.68−4.75 (m, 2H), 5.08 (br s, 4H), 5.26−5.32 (m, 2H), 7.25−7.38 (m, 13H), 7.42−7.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.9, 22.6, 22.7, 26.3, 29.2, 30.4, 36.1, 38.1, 45.8, 50.0, 59.4, 60.8, 67.4, 69.4, 128.3, 128.5, 128.7, 128.8, 134.8, 136.1, 152.1, 156.3, 165.1, 167.6, 174.9, 176.5. HRMS (MALDI-TOF): calcd for $C_{50}H_{59}N_7O_{12}Na$ [M + Na]$^+$ 972.4114, found 972.4115.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C spectra of all novel compounds listed in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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