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Synthesis of 2,2-Disubstituted Pyrrolidine-4-carboxylic Acid Derivatives and Their Incorporation into β-Peptide Oligomers

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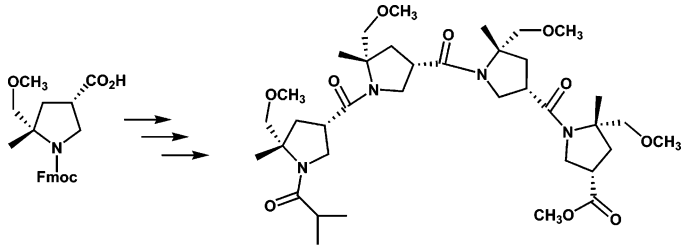

We have recently shown that members of a new class of β-peptides, containing 2,2-disubstituted pyrrolidine-4-carboxylic acid residues, display discrete conformational preferences despite the impossibility of internal hydrogen bonding (Huck et al. *J. Am. Chem. Soc.* **2003**, *125*, 9035). Here we describe the synthesis of a variety of 2,2-disubstituted pyrrolidine-4-carboxylic derivatives that bear a diverse set of side chains and protecting groups suitable for oligomer synthesis. In addition, we discuss coupling methods for construction of oligomers in solution and on solid phase. Non-hydrogen bonded foldamers such as those generated from 2,2-disubstituted pyrrolidine-4-carboxylic acids may be useful in biomedical applications because the low intrinsic polarity of their backbones may promote bioavailability.

Introduction

Complex molecular-level operations required for biological function, such as catalysis and signal transduction, are governed by biopolymers. Proteins, the key biopolymers in most such processes, are generated from a relatively small set (ca. 20) of simple α-amino acid building blocks. Proteins achieve the structural complexity required for complex activity via folding. Nucleic acids, too, can achieve a high level of operational complexity by adopting diverse secondary and tertiary structures. The substantial difference between the α-amino acid residues that comprise proteins and the nucleotide residues that comprise nucleic acids suggests that the propensity to fold, rather than any specific composition, provides the foundation for sophisticated molecular function. The rapidly expanding study of nonnatural "foldamers", oligomers that adopt specific folding patterns, emerges from these considerations.[1−3]

Oligo-β-amino acids ("β-peptides") represent a major feature in the current landscape of foldamer research. β-Peptides displaying all three types of regular secondary structure found among proteins, helix, sheet, and reverse turn, have been characterized via high-resolution structural methods,[4] and progress toward the development of β-peptide tertiary structure has been described.[5,6] In addition, β-peptides have been shown to display a number of interesting activities,[7] at least some of which depend on the adoption of specific conformations.

The interesting functions reported for various β-peptides, and the fundamental challenge of elucidating the relationship between β-amino acid substitution pattern and oligo-β-amino acid folding behavior, provide motivation for a continuing search for new β-peptide secondary structures. Recently, we reported the first high-resolution

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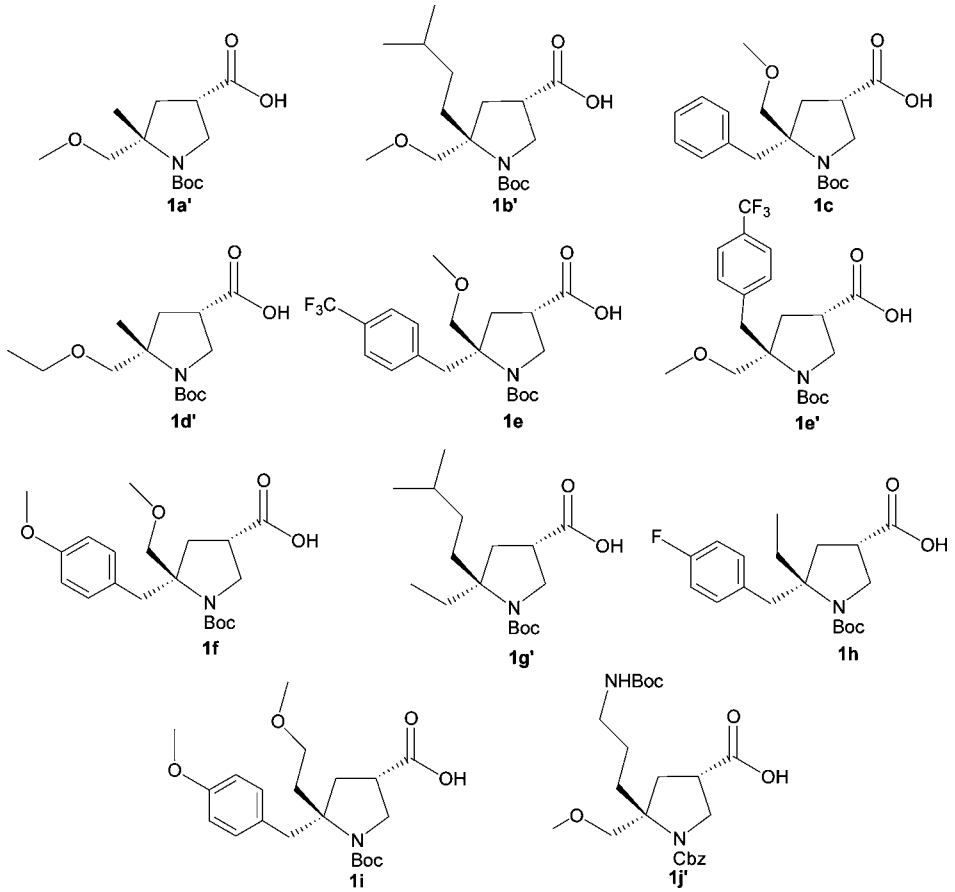

FIGURE 1. 2,2-DPCA building blocks prepared in this study.

structural evidence of folding by β-peptides that cannot form internal hydrogen bonds because all backbone linkages are tertiary amide groups.[8] This development is important at a fundamental level because internal hydrogen bonding is prevalent among the most common secondary structures found in proteins (α-helix, 3_{10}-helix, β-sheet) and in β-peptides. The network of noncovalent interactions that specifies the shape for internally hydrogen bonded structures must differ from the network that controls folding when backbone hydrogen bonding is precluded. The identification of tertiary amide foldamers is potentially important at a practical level because the backbone in this case is intrinsically less polar than a secondary amide backbone, which might ultimately lead to favorable properties in biomedical contexts.

Here we describe the synthesis of a variety of 2,2-disubstituted pyrrolidine-4-carboxylic acids (2,2-DPCAs; Figure 1) and the construction of short β-peptides from one of these β-imino acid building blocks. Placement of a quaternary center adjacent to the ring nitrogen proved to be necessary to limit the configuration of the interresidue tertiary amide linkages in 2,2-DPCA oligomers.[8] The presence of multiple backbone rotamers ((*E*)- and (*Z*)-amide configurations at some or all positions) has been detected by NMR for other tertiary amide-based oligomers, including those comprised of unsubstituted PCA residues[9] or 2-monosubstituted PCA residues,[8] and *N*-alkylglycine oligomers ("peptoids").[10] This local conformational heterogeneity ensures that oligomer secondary structure is heterogeneous as well. (In contrast, proline oligomers and oligomers of modified proline-like residues do not display tertiary amide rotamers;[11] the rotamer problem can also be eliminated by use of alkene isosteres for the tertiary amide linkage.[12]) Achieving conformational control via introduction of the quaternary center in 2,2-DPCA residues carries the additional benefit of providing two sites of side chain attachment, which should facilitate our long-term goal of generating foldamers with useful functions. Access to 2,2-DPCA building blocks carrying a range of side chain functional groups

(7) Selected examples of β-peptides with biological function: (a) Werder, M.; Hauser, H.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1774. (b) Hamuro, Y.; Schneider, J. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **1999**, *121*, 12200. (c) Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565. (d) Gademann, K.; Kimmerlin, T.; Hoyer, D.; Seebach, D. *J. Med. Chem.* **2001**, *44*, 2461. (e) Liu, D.; DeGrado, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 7553. (f) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 7324. (g) Raguse, T. L.; Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 12774. (h) Gelman, M. A.; Richter, S.; Cao, H.; Umezawa, N.; Gellman, S. H.; Rana, T. M. *Org. Lett.* **2003**, *5*, 3563.

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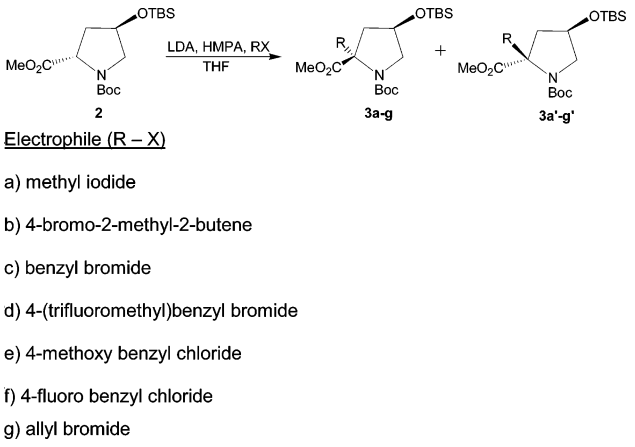


FIGURE 2. Introduction of the first side chain.

has already proven to be useful from the perspective of characterization, enabling the preparation of oligomers with sufficient ^{1}H NMR dispersion to allow high-resolution structural analysis.[8]

Results and Discussion

The synthesis of 2,2-DPCA residues begins with TBS-protected 4-hydroxy-proline methyl ester, **2** (Figure 2). The initial synthetic steps follow established precedents.[13,14] One side chain is introduced via alkylation of the ester enolate derived from **2**, and the second side chain is then generated from the ester group itself. Each ester enolate alkylation, performed with any of a variety of alkyl, benzyl, and allyl halides, provided a pair of products epimeric at the quaternary center, which is consistent with a previous report.[13] The diastereomers could be separated chromatographically either at this step or at a subsequent step; thus, each alkylating agent shown in Figure 2 can lead to at least two functionalized monomers for subsequent β-peptide synthesis. The diastereomeric ratio of the alkylation product depends on the nature of the electrophile. As noted in the original report,[13] benzyl halides afford a higher proportion of the less polar methyl ester **3a**−**g**, whereas alkyl and allyl halides yield a majority of the more polar methyl ester **3a′**−**g′**. The prime (′) designation introduced here, which originates from the polarity of the alkylation products, indicates the configuration at what will become the quaternary center of the 2,2-DPCA units. The prime/no prime distinction is retained in the designation of subsequent synthetic products.

Stereochemical assignment of the epimeric products was accomplished by following a literature procedure[14] in three cases (**3a**−**c**/**3a′**−**c′**). For example, diastereomers **3a** and **3a′** were separated from one another chromatographically. Then, as shown in Scheme 1, pure isomer **3a** was desilyated with tetrabutylammonium fluoride, and the ester was hydrolyzed with sodium hydroxide to provide **4a**. Lactonization conditions led to formation of **5a**. Similar sequences were carried out with resolved stereoisomers from mixtures **3b/3b′** and **3c/3c′**. In each case, one of the two diastereomers formed a lactone, and the other did not. The lactone-forming diastereomer was assigned as having the carboxyl and hydroxyl groups cis. In each case, the less polar constituent of the initial alkylation product mixture (polarity judged to be inversely related to elution order upon silica chromatography) led ultimately to lactone formation, and these less polar epimers were assigned structures **3a**−**c**. This behavior matches previous reports on such systems,[13,14] as does our observation that benzylic halides favor formation of the less polar epimer, while alkyl and allylic halides favor the more polar epimer. Stereochemical assignments for pairs **3d/3d′**, **3e/3e′**, **3f/3f′**, and **3g/3g′** were made by analogy on the basis of their relative chromatographic mobilities.

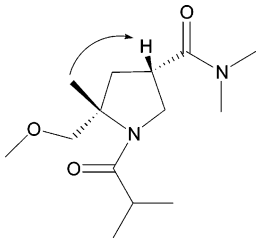
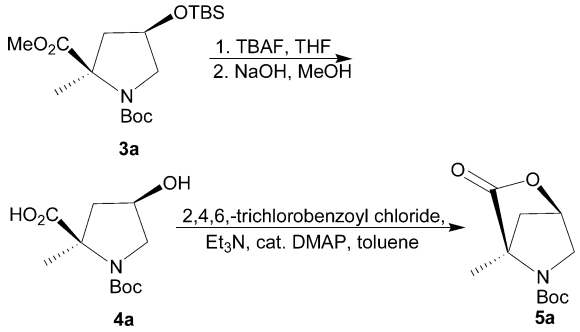


FIGURE 3. Key NOE of **6a′** that helps confirm substituent stereochemistry.

SCHEME 1. Conversion of 3a into Lactone 5a



Our stereochemical assignment was supported by NMR analysis of diamide **6a′** (Figure 3), which was produced as described below from **3a′**.[8] A nuclear Overhauser effect (NOE) was observed between the proton at the 4-position of the ring and the methyl group at the 2-position, which suggests that the 4-proton and 2-methyl group are cis on the ring. In addition, no NOE was detected between the 4-proton and the methylene protons from the ether substituent at the 2-position, suggesting a trans relationship. Further support for our stereochemical assignments was obtained from the crystal structure of a 2,2-DPCA dimer in which both residues were derived from **3c**.[8]

After the quaternary center had been generated via alkylation, a series of additional steps produced the 2,2-DPCA building blocks shown in Figure 1. The principal synthetic route we used is illustrated in Scheme 2, which shows conversion of **3a′** to **1a′** and further reactions to generate **6a′**. Sodium borohydride reduction of the methyl ester afforded primary alcohol **7a′** (Scheme 2). Two subsequent synthetic approaches were explored, silver oxide-promoted alkylation (Scheme 2) and a Swern

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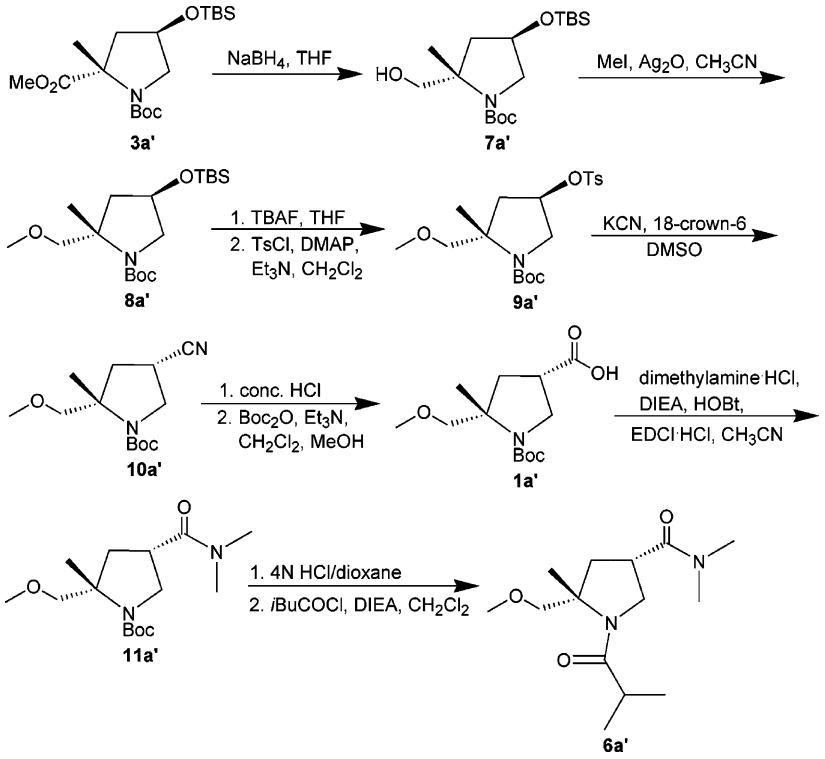
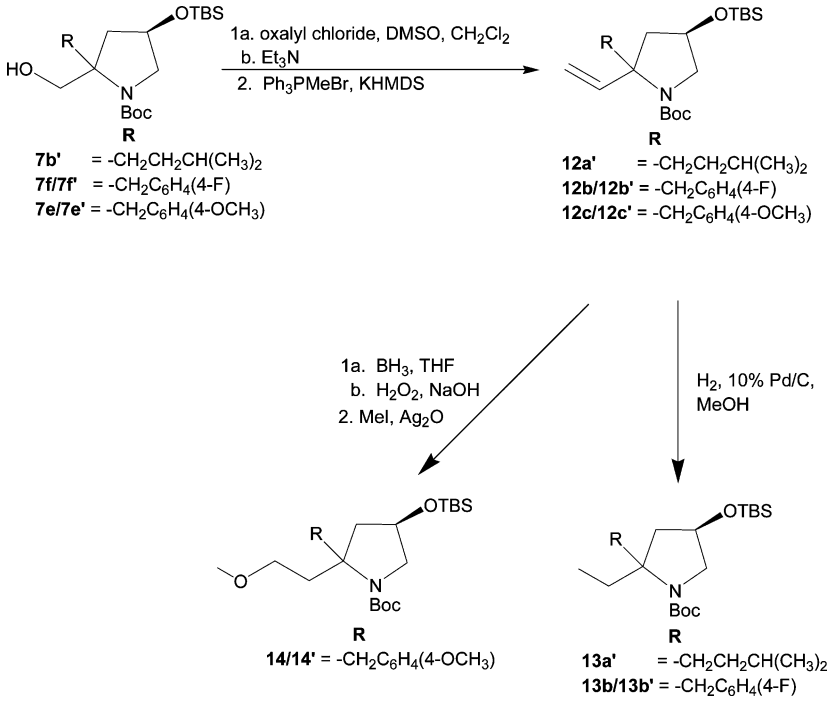
SCHEME 2. Conversion of Alkylation Product 3a′ to 2,2-DPCA Building Block 1a′ and Diamide Derivative 6a′



SCHEME 3. Alternative Manipulation of the Hydroxylmethyl Appendage



oxidation/Wittig sequence (Scheme 3; discussed below). Silver oxide-promoted alkylation of the primary alcohol group was performed with methyl iodide to generate **8a′** from **7a′** or with other alkyl and benzyl halides to provide analogues. This approach has two limitations. First, moderate yields (<60%) were obtained when a bulky electrophile was used. Second, benzylic ethers are labile under the highly acidic conditions employed for the subsequent nitrile hydrolysis.

With the substituents at the quaternary center established, the final synthetic steps were identical for each 2,2-DPCA building block, involving replacement of the

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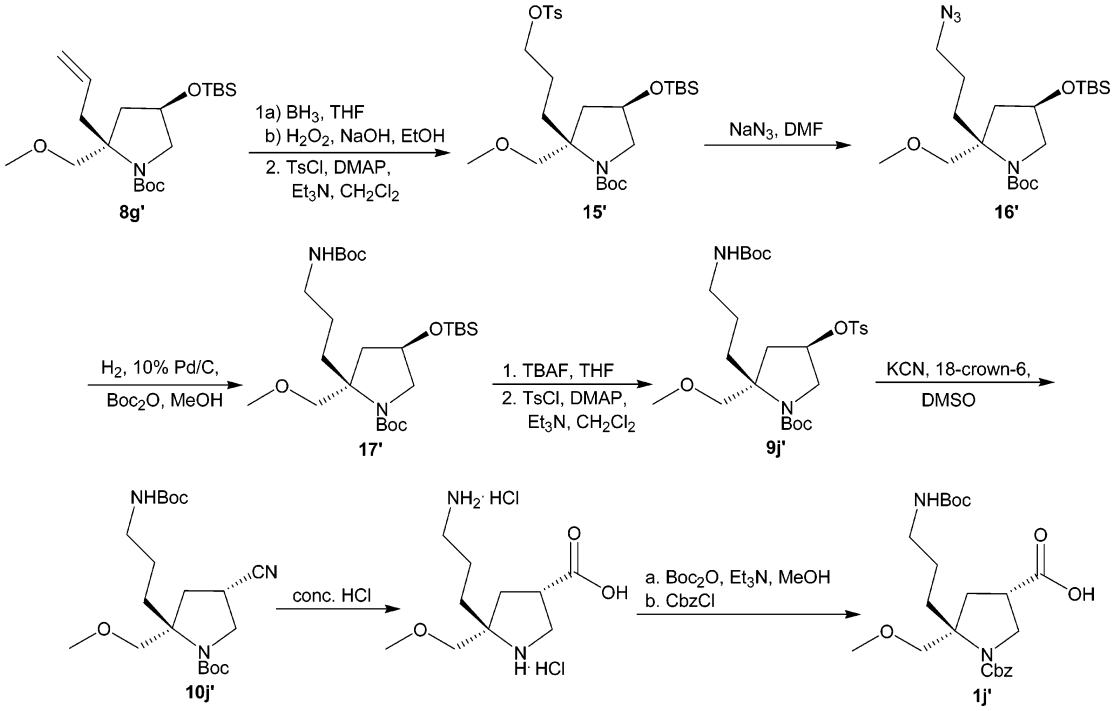
SCHEME 4. Synthesis of 2,2-DPCA Monomer 1j′



OTBS group with a carboxylic acid group, with inversion (Scheme 2). This portion of the route follows a previous synthesis of the parent β-imino acid, pyrrolidine-3-carboxylic acid.[15] For the case shown in Scheme 2, silyl ether deprotection followed by treatement with tosyl chloride yielded **9a′**. Potassium cyanide displacement generated nitrile **10a′**. Acidic hydrolysis of the nitrile group yielded the corresponding carboxylic acid, with concomitant cleavage of the *tert*-butyl carbamate protection group. The Boc group was replaced to afford the 2,2-DPCA building block **1a′**. Beginning with the commercially available 4-hydroxy-proline, we were able to prepare multigram quantities of this monomer and others shown in Figure 1 in about a week.

Each 2,2-DPCA monomer was converted to a diamide derivative, for example, **6a′** in Scheme 2, so that we could determine whether the quaternary center enforced a single tertiary amide rotamer for the group involving the ring nitrogen. ^{1}H and ^{13}C NMR analysis revealed that each diamide in this series displays a single detectable rotameric state in solution.

The potential limitations associated with hydroxyl group alkylation led us to pursue an alternative protocol for elaborating the second side chain, a Swern oxidation followed immediately by a Wittig reaction to give an alkene (Scheme 3). Although this reaction sequence was examined with only the ylide derived from methyl triphenylphosphonium bromide, it should be possible to use other ylides as well. Terminal alkenes **12a′**, **12b/12b′**, and **12c/12c′** (isomer separation was not carried out at this stage in the latter two cases) were modified in two ways. Hydrogenation afforded an ethyl side chain (**13a′** and **13b/13b′**). Alternatively, hydroboration/oxidation delivered primary alcohols that were then O-methylated to provide **14/14′**. The Swern/Wittig protocol appears to be more general than hydroxyl alkylation for introduction of diverse side chains into 2,2-DPCA monomers.

The side chains in 2,2-DPCA building blocks **1a′**−**1i** in Figure 1 are relatively nonpolar. We sought an analogue with a side chain that could be ionized, e.g., via protonation, for the long-term goal of generating water-soluble 2,2-DPCA oligomers. Synthesis of a 2,2-DPCA monomer bearing a protected amino group on a side chain began by alkylating the ester enolate of **2** with allyl bromide. Separation of the diastereomers and conversion of the carboxyl group to a methoxymethyl group generated intermediate **8g′**. As shown in Scheme 4, the terminal alkene substituent was subjected to a hydroboration/oxidation sequence to afford a primary alcohol, and the hydroxyl group was converted to the azide (**16′**) by way of a tosylate intermediate (**15′**). A one-pot procedure for azide hydrogenation followed by Boc protection delivered **17′**. The carboxylic acid group was then generated at the 4-position in the usual way (see Scheme 2). Both Boc protecting groups were removed during nitrile hydrolysis. The two amino groups of the resulting diamino acid were sequentially reprotected in

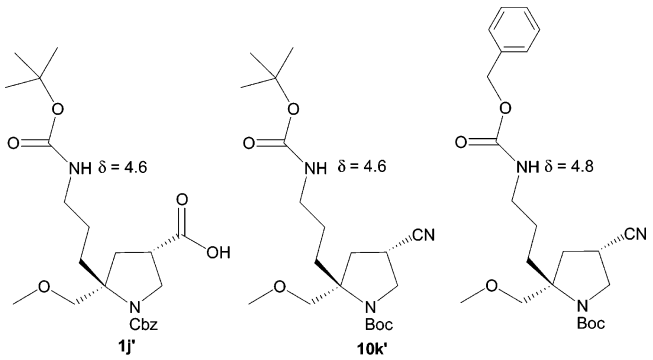


FIGURE 4. Location of the carbamate proton in **1j′**. Chemical shifts measured in $CDCl_3$ at a solute concentration of 10 mM.

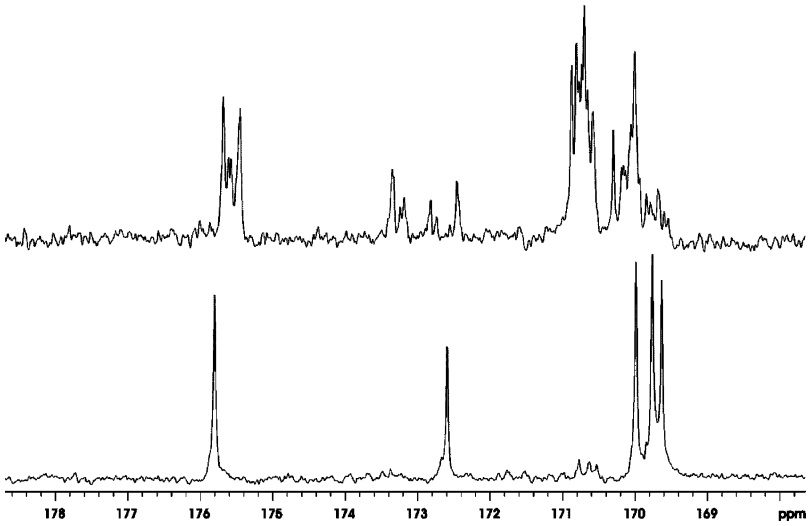


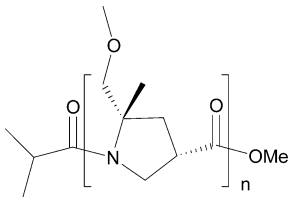
FIGURE 5. Carbonyl region ^{13}C NMR comparison of 2,2-DPCA tetramer **20** (lower) and the analogous unsubstituted PCA tetramer (upper) in $CDCl_3$ (25 °C).

a two-step process, the primary amine with a Boc group and the secondary amine with a Cbz group.

NMR data for **1j′** and related compounds suggest that the Boc and Cbz groups were introduced at the desired positions (side chain and ring amino groups, respectively). The NMR measurements were obtained for 10 mM samples in $CDCl_3$ (Figure 4); little or no intermolecular hydrogen bonding is expected under these conditions. Both **1j′** and nitrile precursor **10k′** display a carbamate proton resonance at 4.6 ppm. The Cbz-protected analogue of **10k′** was prepared as a reference compound, and in this case the carbamate proton appears at 4.8 ppm. This modest downfield shift relative to Boc-protected **10k′** suggests that the protecting group placement shown for **1j′** is correct.

The availability of 2,2-DPCA monomers led us to explore the synthesis of oligomers in solution. *t*-Boc-protected monomer **1a′** was coupled to the N-deprotected methyl ester derived from **1a′** through the use of BopCl[16] to yield a dimer. Higher oligomers (trimer through hexamer) were prepared analogously. These oligomers were obtained with quite high purity, according to reverse-phase HPLC of the crude products. We had been concerned that the proximity of the quaternary center to the secondary amino group might hinder the amide bond-forming step; however, synthetic yields in the 2,2-DPCA series were comparable to yields obtained for the synthesis of unsubstituted PCA oligomers.[17] Prior to NMR analysis of the oligomers, we removed the N-terminal Boc group, to avoid the presence of multiple tertiary carbamate rotamers. Thus, 2,2-DPCA oligomers were N-deprotected and an N-terminal isobutyryl amide group was introduced, generating **18**−**22**.

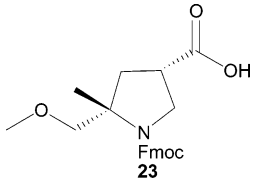
^{13}C NMR comparison of 2,2-DPCA tetramer **20** and the analogous tetramer containing unsubstituted PCA residues (Figure 5) suggests that disubstitution adjacent to the ring nitrogen limits rotational isomerism of the tertiary amide groups, as intended. The PCA tetramer displays a large number of signals in the carbonyl region



18 = n = 2
19 = n = 3
20 = n = 4
21 = n = 5
22 = n = 6

of the ^{13}C NMR spectrum, which is consistent with the expectation that each of the four tertiary amide units occurs in both *E* and *Z* conformations, which interchange slowly on the NMR time scale. In contrast, 2,2-DPCA tetramer **20** displays only five major ^{13}C resonances in this region, presumably arising from the five carbonyl carbon atoms in a single rotameric form of this molecule (or possibly from rapid rotation about the amide C−N bonds).

Our long-term goal is to screen libraries of 2,2-DPCA heterooligomers for specific biological activities. Solid-phase synthesis is generally preferred relative to solution-phase methods for the preparation of libraries. We undertook the solid-phase synthesis of a homotetramer derived from **1a′** in order to explore this approach.



23

Fmoc-protected monomer **23** was prepared from **1a′** and coupled to a modified TentaGel Rink amide resin with PyBrOP (a standard coupling agent for the solid-phase synthesis with hindered secondary amines[18]). The

(16) Tung, R. D.; Rich, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 4342.
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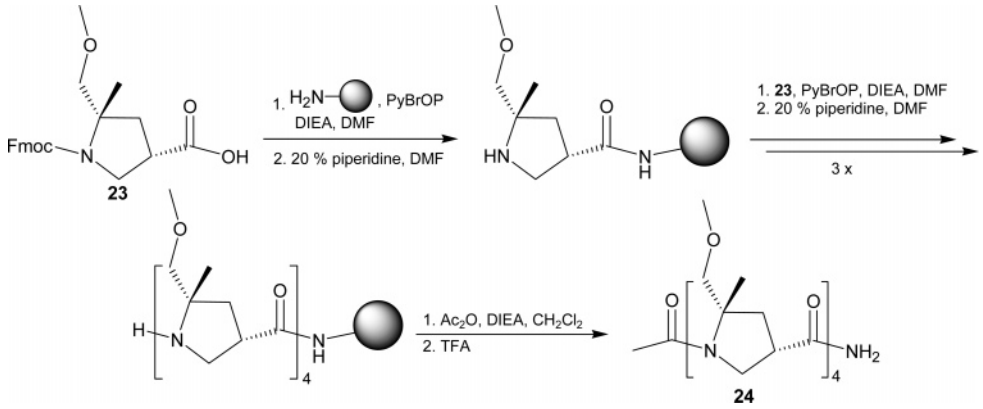
SCHEME 5. Solid-Phase 2,2-DPCA Tetramer Synthesis



protecting group was then removed, and the first coupling was carried out with preactivated **23** (Scheme 5). The coupling and deprotection sequence was repeated two more times, followed by acylation of the N-terminus. Tetramer **24** was then cleaved from the resin with TFA. Workup of the cleavage reaction afforded the crude 2,2-DPCA tetramer in quantitative yield; reverse-phase HPLC analysis revealed that this material was 80% pure on the basis of UV absorbance. The high yield and purity of tetramer **24** led us to undertake synthesis of the analogous hexamer and octamer. These β-peptides were also synthesized in high yields (on the basis of crude product mass) with moderate levels of purity (hexamer **25**: 90% yield, 65% purity; octamer **26**: 84% yield, 50% purity). The only side products from each of these syntheses were truncated β-peptides. It is possible that these byproducts could be minimized by longer coupling times or by double coupling. Even without such improvements, solid-phase synthesis of these β-peptides is much more efficient than solution-phase synthesis. For example, the hexamer was prepared in 3 days via manual solid-phase synthesis, but solution-phase synthesis required two weeks.

Conclusion

We have developed an efficient synthetic route for the synthesis of a diverse set of 2,2-DPCA monomers. In addition, we have shown that such β-imino acids can be coupled efficiently to generate oligomers, both in solution and via solid-phase methods. These synthetic achievements lay the groundwork for investigation of biological applications of 2,2-DPCA β-peptides. Such oligomers are attractive because of their ability to adopt predictable secondary structure despite the lack of intramolecular hydrogen bonding.

Experimental Section

General Procedures. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterated solvents on 300 MHz or 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interepreted or easily visualized are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on 300 MHz or 500 MHz spectrometers. Chemical shifts are reported in ppm (δ) relative to the central line of the $CDCl_3$ triplet (δ 77.0). Mass spectra (MS) were obtained using electrospray ionization. Benzene was distilled from Na/benzophenone. Hexanes were distilled at atmospheric pressure. Triethylamine (Et_3N) was distilled from CaH_2. Dichloromethane (CH_2Cl_2) was distilled from CaH_2. THF was distilled from sodium/benzophenone. All reagents and solvents were purchased from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was carried out on TLC plates pre-coated with silica gel 60 (250 μM layer thickness). Visualization was accomplished using either a UV lamp or potassium permanganate stain. Column chromatography was performed on silica gel 60 (230-400 mesh). Solvent mixtures used for TLC and column chromatography are reported in v/v ratios.

Compound 2. Di-*tert*-butyl dicarbonate (52.4 g, 0.24 mol) was dissolved in dioxane (120 mL) and added to a stirred solution of *trans*-4-hydroxy-L-proline (26.2 g, 0.2 mol) in 2 M NaOH (120 mL, 0.24 mol). The resulting solution was stirred for 2 h at room temperature. Dioxane was removed via rotary evaporation. The resulting solution was washed with ether, acidified to pH 2 with 1 M aqueous HCl, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The residue was dissolved in benzene/methanol (440 mL, 10/1, v/v). (Trimethylsilyl)diazomethane (100 mL, 0.2 mol, 2.0 M solution in hexanes) was added dropwise, and the resulting solution was stirred for 1 h at room temperature. The reaction was quenched with acetic acid until a clear color persisted, and the solution was then concentrated. The residue was dissolved in DMF (200 mL). Imidazole (68.1 g, 1.0 mol) and TBDMS−Cl (90.4 g, 0.6 mol) were added, and the resulting solution was stirred overnight at room temperature. The DMF was removed via rotary evaporation under vacuum. The resulting residue was dissolved in EtOAc and washed with 1 M HCl. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purifed by SiO_2 column chromatography eluting with hexane/EtOAc (4/1, v/v) (TLC R_f = 0.28) to afford 54.5 g (76% overall yield) of **2** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.37−4.28 (m, 1H), 4.27−4.21 (t, 7.7 Hz, 1H), 3.64 (s, 3H), 3.56−3.46 (dt, 11.0 Hz, 4.8 Hz, 1H), 3.35−3.20 (m, 1H), 2.14−2.03 (m, 1H), 1.98 − 1.87 (m, 1H), 1.41−1.30 (m, 9H), 0.79 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 173.6, 173.4, 154.5, 153.7, 79.9, 77.4, 77.0, 76.6, 70.3, 69.6, 57.9, 57.5, 54.8, 54.4, 52.0, 51.8, 39.7, 38.8, 28.3, 28.1, 25.6, 17.8, −3.2, −5.0; ESI-MS *m/z* (M + Na) calcd for $C_{17}H_{32}NO_5SiNa$ 382.5, obsd 382.1.

Compounds 3a and 3a′. Diisopropylamine (1.52 equiv) was dissolved in THF (220 mL) and cooled to 0 °C. ^{n}BuLi (2.5 M solution in hexanes, 1.50 equiv) was added dropwise. After the addition, the solution was stirred for 10 min at 0 °C and then cooled to −20 °C. HMPA (3.00 equiv) was added dropwise, and the solution was stirred for 10 min at −20 °C. Methyl ester **2** (7.9 g, 0.022 mol) was dissolved in THF (220 mL) and added to the stirred solution via cannula. The resulting solution was

stirred for 1 h while warming to 0 °C and then cooled to −78 °C. Methyl iodide (1.50 equiv) was added dropwise, and the reaction mixture was allowed to stir for 4 h. The reaction was quenched with saturated aqueous NH_4Cl, diluted with H_2O, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The crude product (7.96 g, mixture of diastereomers) was separated by column chromatography eluting with hexane/EtOAc (8/1; v/v) to afford 1.62 g (20% yield) of **3a** (R_f = 0.42) and 6.34 g (77% yield) of **3a′** (R_f = 0.34) as colorless oils. Characterization of **3a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.33−4.22 (m, 1H), 3.68−3.55 (m, 4H), 3.31−3.18 (m, 1H), 2.17−1.90 (m, 2H), 1.50−1.43 (m, 3H), 1.38−1.28 (m, 9H), 0.78 (s, 9H), −0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 175.0, 174.9, 153.3, 79.8, 79.4, 69.8, 69.1, 64.9, 64.6, 55.9, 55.8, 51.9, 48.1, 47.2, 28.3, 28.2, 25.6, 23.3, 22.5, 17.8; ESI-MS *m/z* (M + Na) calcd for $C_{18}H_{35}NO_5SiNa$ 396.5, obsd 396.2. Characterization of **3a′**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.35−4.25 (m, 1H), 3.68−3.52 (m, 4H), 3.37−3.20 (m, 1H), 2.26−2.12 (m, 1H), 1.83−1.74 (m, 1H), 1.60−1.54 (m, 3H), 1.38−1.28 (m, 9H), 0.78 (s, 9H), −0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 175.0, 174.9, 153.8, 153.3, 79.8, 79.4, 69.8, 69.1, 64.9, 64.6, 55.9, 55.8, 51.9, 48.1, 47.2, 28.8, 28.2, 28.1, 26.0, 25.6, 23.3, 22.5, 17.8; electrospray ionization-MS *m/z* (M + Na) calcd for $C_{18}H_{35}NO_5SiNa$ 396.5, obsd 396.2.

Compound 4a. Methyl ester **3a** (78 mg, 0.21 mmol) was dissolved in THF (2.1 mL). TBAF (0.23 mL, 0.23 mmol, 1.0 M solution in THF) was added, and the solution was stirred 5 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and the THF was removed via rotary evaporation. The resulting solution was diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated.

The resulting residue was dissolved in MeOH (1 mL). To this solution was added aqueous NaOH (1.05 mL, 2.1 mmol, 2.0 M solution in H_2O). The reaction solution was stirred overnight at room temperature, washed with ether, acidified with 1 M aqueous HCl, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to afford 41 mg (80% yield) of **4a** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 6.95−6.30 (bs, 1H), 4.52−4.27 (m, 1H), 3.91−3.39 (m, 2H), 2.63−2.38 (m, 1H), 2.15−1.92 (m, 1H), 1.71−1.35 (m, 12H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 177.3, 177.0, 155.5, 154.0, 81.6, 77.6, 69.3, 65.0, 64.1, 56.4, 55.3, 47.6, 47.4, 46.5, 28.4, 28.2, 23.8, 22.8; ESI-MS *m/z* (M + Na) calcd for $C_{11}H_{18}NO_5Na$ 244.3, obsd 244.1.

Compound 5a. Compound **4a** (0.041 g, 0.17 mmol) was dissolved in toluene (1.7 mL). DMAP (0.002 g, 0.017 mmol) and Et_3N (0.12 mL, 0.84 mmol) were added, followed by a solution of 2,4,6-trichlorobenzoyl chloride (0.13 mL, 0.84 mmol) in toluene (3.4 mL). The reaction was stirred overnight at reflux. The solution was cooled to room temperature and washed with 1 M aqueous HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purifed by column chromatography eluting with hexane/EtOAc (2/1, v/v) to afford 0.021 g (50% yield) of **5a** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.91 (s, 1H), 3.64−2.97 (m, 2H), 2.14−2.02 (m, 2H), 1.80 (s, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.4, 128.2, 81.4, 75.0, 64.0, 53.1, 53.0, 46.4, 42.0, 28.3, 24.7, 14.0; ESI-MS *m/z* (M + Na) calcd for $C_{11}H_{17}NO_4Na$ 250.3, obsd 250.1.

Compound 7a′. $NaBH_4$ (3.3 g, 0.085 mol) was added to a stirred solution of **3a′** (6.3 g, 0.017 mol) in THF (17 mL) and stirred overnight at reflux. The reaction was quenched by dropwise addition of MeOH (17 mL) and concentrated. The resulting residue was dissolved in EtOAc and washed with H_2O. The organic layer was dried with $MgSO_4$ and concentrated. The crude product was purifed by SiO_2 column chromatography eluting with hexane/EtOAc (5/1; v/v) (TLC R_f = 0.15) to afford 4.74 g (81% yield) of **7a′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.00−4.80 (bs, 1H), 4.27−4.14 (m, 1H), 3.55−3.27 (m, 4H), 1.78−1.58 (m, 2H), 1.46−1.30 (m, 12H), 0.78 (s, 9H), −0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 155.5, 79.8, 70.2, 69.0, 68.2, 67.6, 64.7, 63.7, 57.3, 57.0, 46.1, 45.9, 28.4, 25.6, 22.7, 20.7, 17.8; ESI-MS *m/z* (M + Na) calcd for $C_{17}H_{35}NO_4SiNa$ 368.5, obsed 368.2.

Compound 8a′. Methyl iodide (8.7 mL, 0.14 mol) and silver oxide (9.7 g, 0.042 mol) were added to a stirred solution of **7a′** (4.7 g, 0.014 mol) in CH_3CN (14 mL). The reaction mixture was stirred overnight at reflux, filtered through Celite, and concentrated. The crude product was purified by SiO_2 column chromatography eluting with hexane/EtOAc (9/1; v/v) (TLC R_f = 0.33) to afford 3.61 g (73% yield) of **8a′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.27−4.17 (m, 1H), 3.76−3.39 (m, 2H), 3.36−3.14 (m, 5H), 2.28−2.15 (m, 1H), 1.68−1.54 (m, 1H), 1.48−1.28 (m, 12H), 0.77 (s, 9H), −0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 154.6, 153.9, 119.6, 79.7, 79.0, 77.9, 77.6, 69.2, 68.6, 63.2, 62.5, 59.4, 57.1, 47.2, 46.2, 28.9, 26.1, 23.9, 22.9, 18.3; ESI-MS *m/z* (M + Na) calcd for $C_{18}H_{37}NO_4SiNa$ 382.5, obsd 382.2.

Compound 9a′. TBAF (11 mL, 0.011 mol, 1 M solution in THF) was added to a solution of **8a′** (3.61 g, 0.01 mol) in THF (50 mL) and stirred 6 h at room temperature. The reaction was quenched with saturated NH_4Cl and diluted with H_2O, and the THF was removed via rotary evaporation. The aqueous solution was washed with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. DMAP (1.83 g, 0.015 mol) and triethylamine (4.18 mL, 0.03 mol) were added, followed by TsCl (2.86 g, 0.015 mol). The solution was stirred overnight at room temperature and washed with 1 M HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by SiO_2 column chromatography eluting with hexane/EtOAc (5/1; v/v) (TLC R_f = 0.14) to afford 3.0 g (77% yield) of **9a′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82−7.75 (m, 2H), 7.40−7.33 (m, 2H), 5.00−4.92 (m, 1H), 3.90−3.50 (m, 3H), 3.35−3.11 (m, 4H), 2.52−2.33 (m, 4H), 2.05−1.80 (m, 1H), 1.50−1.32 (m, 12H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 153.7, 153.0, 144.8, 133.9, 133.7, 129.8, 127.6, 79.8, 79.2, 78.5, 77.7, 76.6, 75.4, 62.6, 61.9, 58.9, 54.0, 53.9, 43.7, 42.4, 28.4, 28.3, 23.2, 22.2, 21.5; ESI-MS *m/z* (M + Na) calcd for $C_{19}H_{29}NO_6SNa$ 422.6, obsd 422.1.

Compound 10a′. NOTE: Extreme Caution Must Be Used When Handling KCN. 18-Crown-6 (3.05 g, 11.55 mmol) and finely ground KCN (0.75 g, 11.55 mol) were added to a stirred solution of **9a′** (3.0 g, 7.70 mmol) in DMSO (7.7 mL). The reaction mixture was stirred for 8 h at 80 °C. After the reaction solution had cooled, H_2O (1.0 M) was added and the resulting solution was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by SiO_2 column chromatography eluting with hexane/EtOAc (5/1; v/v) (TLC R_f = 0.25) to afford 0.93 g (47% yield) of **10a′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.96−3.58 (m, 2H), 3.57−3.18 (m, 5H), 3.04−2.92 (m, 1H), 2.62−2.44 (m, 1H), 2.10−1.95 (m, 1H), 1.50−1.37 (m, 9H), 1.36−1.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 152.6, 119.6, 80.2, 79.6, 76.0, 74.8, 62.7, 62.0, 58.8, 51.0, 41.0, 39.8, 28.2, 24.5, 24.1, 22.7, 21.7; ESI-MS *m/z* (M + Na) calcd for $C_{13}H_{22}N_2O_3Na$ 277.3, obsd 277.1.

Compound 1a′. Compound **10a′** (0.92 g, 3.6 mmol) was dissolved in concentrated aqueous HCl (18 mL) and stirred at 60 °C for 6 h. The solution was then concentrated via rotary evaporation and placed on the vacuum line. The residue was dissolved in a CH_2Cl_2/MeOH solution (18 mL, 10/1, v/v). Triethylamine (3.0 mL, 22.0 mmol) and di-*tert*-butyl dicarbonate (0.83 g, 3.8 mmol) were added, and the solution was stirred at reflux overnight. The solution was concentrated via rotary evaporation. The residue was dissolved in saturated aqueous $NaHCO_3$ solution, washed with ether, and acidified to pH 2 with 0.5 M aqueous $KHSO_4$. The aqueous solution was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and concentrated to afford 0.71 g (71% yield) of **1a′** as

a colorless oil with no further purfication: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.7−10.2 (bs, 1H), 3.80−3.20 (m, 7H), 3.15−2.90 (m, 1H), 2.55−2.40 (m, 1H), 2.05−1.80 (m, 1H), 1.52−1.40 (m, 9H), 1.40−1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 178.3, 80.0, 79.3, 75.9, 63.2, 59.0, 50.2, 40.9, 40.8, 40.7, 39.7, 39.1, 28.5, 22.7, 21.7; ESI-MS *m/z* (M − H) calcd for $C_{13}H_{22}NO_5$ 272.3, obsd 272.1.

Compound 11a′. Compound **1a′** (0.2 g, 0.73 mmol) was dissolved in CH_3CN (7.3 mL) and cooled to 0 °C. Dimethylamine hydrochloride (0.077 g, 0.95 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI*HCl) (0.195 g, 1.02 mmol), 1-hydroxybenzotriazole hydrate (HOBt) (0.137 g, 1.02 mmol), and *N*,*N*-diisopropylethylamine (DIEA) (0.38 mL, 2.19 mmol) were added, and the solution was stirred 24 h at room temperature. The solution was concentrated via rotary evaporation. The residue was dissolved in EtOAc and washed with 1 M HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by SiO_2 column chromatography eluting with hexane/EtOAc (1/2; v/v) (TLC R_f = 0.23) to afford 0.20 g (90% yield) of **11a′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 3.87−3.37 (m, 4H), 3.32 (s, 3H), 3.18−2.91 (m, 7H), 2.57−2.24 (m, 1H), 2.86−2.76 (m, 1H), 1.47−1.36 (m, 9H), 1.34−1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 171.7, 153.4, 79.6, 79.0, 62.9, 62.1, 59.1, 50.9, 50.7, 41.3, 40.4, 37.4, 37.2, 37.0, 35.7, 35.6, 28.5, 22.9, 21.8; ESI-MS *m/z* (M + Na) calcd for $C_{15}H_{28}N_2O_4Na$ 323.4, obsd 323.2.

Compound 6a′. Compound **11a′** (0.20 g, 0.66 mmol) was dissolved in 4 N HCl/dioxane (2.1 mL) and stirred 2 h at room temperature. The solution was concentrated under a stream of nitrogen, and the residue was placed on the vacuum line. The residue was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. DIEA (0.66 mL, 3.78 mmol) and isobutyryl chloride (0.13 mL, 1.26 mmol) were added, and the solution was stirred at room temperature for 24 h. The reaction solution was washed with 1 M aqueous HCl and brine, and the organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by SiO_2 column chromatography eluting with EtOAc (TLC R_f = 0.26) to afford 0.052 g (34% yield) of **6a′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.92−3.66 (m, 4H), 3.36−3.17 (m, 4H), 3.12 (s, 3H), 2.97 (s, 3H), 2.66−2.52 (m, 1H), 2.39−2.28 (dd, 12.1 Hz, 1H), 1.86 (dd, 12.1 Hz, 6.6 Hz, 1H), 1.42 (s, 3H), 1.09 (dd, 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 175.7, 171.2, 76.1, 64.9, 58.9, 51.0, 40.1, 37.9, 36.9, 35.6, 33.0, 21.4, 18.9, 18.7; ESI-MS *m/z* (M + Na) calcd for $C_{14}H_{26}N_2O_3Na$ 293.4, obsd 293.2.

Compound 7b′. The ester enolate alkylation was performed with **2** (8.04 g, 0.022 mol) and 4-bromo-2-methyl-2-butene as the alkylating agent using a protocol similar to that used to prepare compounds **3a/3a′**. The crude product was purifed by column chromatography eluting with hexane/EtOAc (10/1, v/v) (TLC R_f = 0.40, 0.44) to afford 7.64 g (80% yield) of diastereomer mixture **3b/3b′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of diastereomers and rotamers δ 5.14−4.94 (m, 1H), 4.42−4.23 (m, 1H), 3.92−3.72 (m, 0.6H), 3.65 (s, 3H), 3.32−3.15 (m, 0.4H), 3.04−2.86 (m, 1H), 2.76−2.51 (m, 2H), 2.15−1.88 (m, 2H), 1.72−1.55 (m, 6H), 1.42−1.32 (m, 9H), 0.85−0.78 (m, 9H), 0.05 to −0.05 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of diastereomers and rotamers δ 174.8, 153.7, 153.4, 148.8, 135.4, 135.1, 119.2, 119.0, 118.9, 118.6, 118.5, 80.2, 80.1, 79.6, 79.5, 68.7, 68.4, 68.0, 67.9, 67.6, 67.3, 66.9, 55.3, 55.0, 54.6, 52.2, 52.1, 45.5, 44.3, 43.3, 33.6, 33.4, 32.5, 32.2, 28.3, 28.2, 26.1, 25.7, 25.6, 18.2, 18.1, 18.0, 17.9, −5.1; ESI-MS *m/z* (M + Na) calcd for $C_{22}H_{41}NO_5SiNa$ 450.7, obsd 450.2.

The alkyation product (7.6 g, 0.018 mol) was dissolved in MeOH (36 mL) and transferred to a hydrogenation apparatus. Palladium (10%) on carbon (1.0 g) was added, and the reaction mixture was charged with H_2 (45 psi) and shaken overnight. The mixture was filtered through Celite and concentrated. The resulting intermediate was allowed to react with $NaBH_4$ using a protocol similar to that used to prepare compound **7a′** from **3a′**. The crude product (4.93 g, mixture of diastereomers) was separated by column chromatography eluting with hexane/EtOAc (8/1; v/v) to afford 3.65 g (57% yield) of **7b′** (TLC R_f = 0.19) as a colorless oil and 1.28 g (20% yield) of the diastereomer **7b** (epimer at the quaternary center) (TLC R_f = 0.36) as a colorless oil. Characterization of **7b′**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.12−5.06 (dd, 1H), 4.27−4.16 (m, 1H), 3.96−3.27 (m, 4H), 2.28−1.72 (m, 3H), 1.65−1.33 (m, 11H), 1.28−1.14 (m, 1H), 1.11−0.81 (m, 16H), 0.12−0.01 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 155.6, 79.9, 69.3, 68.7, 68.6, 68.1, 67.6, 66.5, 58.2, 57.2, 45.3, 44.0, 33.4, 33.0, 31.9, 31.1, 28.5, 28.3, 25.7, 22.8, 22.7, 22.6, 18.0, −4.8, −4.9, −5.1; ESI-MS *m/z* (M + Na) calcd for $C_{21}H_{43}NO_4SiNa$ 424.6, obsd 424.2. Characterization of **7b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.04−4.98 (dd, 1H), 4.25−4.17 (m, 1H), 3.65−3.47 (m, 3H), 3.72−3.65 (dd, 1H), 2.02−1.83 (m, 3H), 1.65−1.30 (m, 12H), 0.92−0.82 (m, 16H), 0.06−0.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 155.8, 80.1, 69.1, 68.7, 67.9, 56.9, 42.4, 33.3, 30.3, 28.6, 28.5, 25.8, 22.8, 22.7, 18.0, −4.8, −4.9; ESI-MS *m/z* (M + Na) calcd for $C_{21}H_{43}NO_4SiNa$ 424.6, obsd 424.2.

Compound 12a′. A solution of DMSO (1.2 mL) in CH_2Cl_2 (12.5 mL) was added to a stirred solution of oxalyl chloride (0.72 mL) in CH_2Cl_2 (12.5 mL) at −78 °C and stirred for 10 min. **7b′** (2.0 g, 0.005 mol) in CH_2Cl_2 (2.5 mL) was added via cannula and stirred 20 min at −78 °C. The reaction was quenched with Et_3N and stirred for 20 min at room temperature. The reaction solution was diluted with H_2O and then extracted with ether. The organic extracts were washed with 0.5 M $KHSO_4$ and brine. The resulting organic solution was dried with $MgSO_4$ and concentrated to give the desired aldehyde. This material was carried on without purification or characterization.

KHMDS (16.8 mL, 8.3 mmol, 0.5 M solution in toluene) was added to a stirred solution of triphenylmethyl phosphonium bromide (3.12 g, 8.7 mmol) in THF (77 mL) for 1 h. To this solution was added the crude aldehyde (0.005 mol) in THF (15 mL). The reaction solution was stirred 2 h at room temperature. The reaction was quenched with MeOH and a solution of potassium sodium tartrate/H_2O (100 mL, 1/1, v/v). The resulting solution was extracted with ether. The organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purifed by column chromatography eluting with hexane/EtOAc (20/1; v/v) (TLC R_f = 0.29) to afford 1.15 g (58% yield) of **12a′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 6.06−5.82 (m, 1H), 5.00−4.84 (m, 2H), 4.19 (p, 1H), 3.84−3.58 (m, 1H), 3.13−3.01 (m, 1H), 2.08−1.70 (m, 2H), 1.68−1.38 (m, 11H), 1.28−0.95 (m, 2H), 0.92−0.80 (m, 16H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 142.8, 111.1, 110.9, 79.5, 78.6, 67.6, 67.0, 66.3, 65.6, 55.3, 55.1, 45.0, 43.8, 35.5, 34.7, 33.1, 32.6, 28.5, 28.3, 25.8, 22.8, 22.7, 18.1, −4.8; ESI-MS *m/z* (M + Na) calcd for $C_{22}H_{43}NO_3SiNa$ 420.7, obsd 420.3.

Compound 7g′. The ester enolate alklyation was performed with **2** (10.3 g, 0.029 mol) and allyl bromide using a protocol similar to that used to prepare compound **3a/3a′**. The crude product was purifed by column chromatography eluting with hexane/EtOAc (12/1, v/v) (TLC R_f = 0.28) to afford 8.3 g (72% yield) of diastereomeric mixture **3g/3g′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of diastereomers and rotamers δ 5.91−5.59 (m, 1H), 5.16−5.05 (m, 2H), 4.42−4.23 (m, 1H), 3.91−3.52 (m, 4H), 3.38−2.46 (m, 3H), 2.22−1.97 (m, 2H), 1.46−1.34 (m, 9H), 0.88−0.74 (m, 9H), 0.07−0.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of diastereomers and rotamers δ 174.6, 153.6, 153.3, 133.6, 133.5, 133.3, 133.2, 119.2, 119.0, 118.9, 80.3, 80.2, 79.8, 79.7, 68.5, 68.4, 68.1, 67.8, 66.8, 66.4, 55.6, 55.2, 54.8, 52.2, 52.1, 45.5, 44.2, 43.2, 40.0, 39.7, 38.9, 38.3, 28.3, 18.0, 17.9, −4.8, −4.9, −5.0; ESI-MS *m/z* (M + Na) calcd for $C_{20}H_{37}NO_5SiNa$ 422.6, obsd 422.2.

Diastereomeric mixture **3g/3g′** (8.3 g, 0.021 mol) was allowed to react with $NaBH_4$ via a protocol similar to that used to prepare compound **7a′**. The crude product (4.8 g, mixture

of diastereomers) was purified by column chromatography eluting with hexane/EtOAc (8/1; v/v) (TLC $R_f = 0.23$) to afford 1.5 g (20% yield) of **7g** ($R_f = 0.34$) and 3.3 g (44% yield) of **7g′** ($R_f = 0.14$) as colorless oils. Characterization of **7g**: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 5.75−5.52 (m, 1H), 5.13−5.01 (m, 2H), 4.26−4.18 (m, 1H), 4.00−3.23 (m, 4H), 2.78−2.61 (m, 1H), 2.45−2.06 (m, 2H), 1.50−1.39 (m, 9H), 0.87 (s, 9H), 0.10−0.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 133.7, 118.8, 80.1, 69.4, 68.4, 67.8, 67.2, 58.0, 57.1, 43.4, 39.8, 37.7, 28.4, 25.7, 18.0, −4.8, −4.9; ESI-MS *m/z* (M + Na) calcd for $C_{19}H_{37}NO_4SiNa$ 394.6, obsd 394.1. Characterization of **7g′**: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 5.88−5.62 (m, 1H), 5.17−5.03 (m, 2H), 4.35−4.15 (m, 1H), 3.88−3.19 (m, 3H), 4.02−3.37 (m, 2H), 2.02−1.50 (m, 2H), 1.50−1.39 (m, 9H), 0.90−0.80 (m, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 155.9, 134.3, 118.7, 118.6, 80.3, 68.8, 68.7, 67.4, 57.2, 41.8, 36.9, 28.4, 25.8, 18.0, −4.8, −4.9; ESI-MS *m/z* (M + Na) calcd for $C_{19}H_{37}NO_4SiNa$ 394.6, obsd 394.1.

Compound 8g′. Compound **8g′** was prepared from **7g′** (3.3 g, 9.0 mmol) alkylating with methyl iodide using a protocol similar to that used to prepare compound **8a′**. The crude product was purified by column chromatography eluting with hexane/EtOAc (10/1; v/v) (TLC $R_f = 0.40$) to afford 2.46 g (71% yield) of **8g′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 5.78−5.62 (m, 1H), 5.12−5.01 (m, 2H), 4.31 (m, 1H), 3.85−3.53 (m, 2H), 3.31−2.98 (m, 4H), 2.82−2.57 (m, 1H), 2.47−2.28 (m, 1H), 2.17−2.06 (m, 1H), 1.95−1.78 (m, 1H), 1.48−1.37 (m, 9H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 133.7, 133.6, 118.5, 78.9, 75.7, 68.2, 59.2, 56.2, 43.1, 42.0, 38.9, 28.6, 28.5, 25.8, 18.1, −4.7, −4.8; ESI-MS *m/z* (M + Na) calcd for $C_{20}H_{39}NO_4SiNa$ 408.6, obsd 408.3.

Compound 15′. BH_3 (12.8 mL, 12.8 mmol, 1 M solution in THF) was added to a stirred solution of **8g′** (2.4 g, 6.4 mmol) in THF (13 mL) at 0 °C. The solution was stirred for 45 min, and the reaction was quenched with a solution of aqueous NaOH (16 mL, 22.0 mmol, 2 M solution in H_2O), H_2O_2 (3.3 mL, 22.0 mmol, 30% solution in H_2O), and EtOH (13 mL). The organic solvents were removed via rotary evaporation. The resulting solution was diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The resulting intermediate was dissolved in CH_2Cl_2 and cooled to 0 °C. DMAP (1.17 g, 9.6 mmol), Et_3N (2.7 mL, 19.2 mmol), and TsCl (1.83 g, 9.6 mmol) were added, and the solution was stirred overnight at room temperature. The reaction solution was washed with 1 M aqueous HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography eluting with hexane/EtOAc (4/1; v/v) (TLC $R_f = 0.29$) to afford 1.77 g (50% yield) of **15′** as a colorless oil.

Compound 16′. NaN_3 (0.83 g, 12.8 mmol) was added to a stirred solution of **15′** (1.7 g, 3.2 mmol) in DMF (6.4 mL) at 80 °C. The reaction mixture was stirred for 8 h, diluted with H_2O, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography eluting with hexane/EtOAc (3/1; v/v) (TLC $R_f = 0.78$) to afford 1.01 g (74% yield) of **16′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 4.36−4.25 (m, 1H), 3.77−3.50 (m, 2H), 3.30−3.02 (m, 7H), 2.27−2.13 (m, 1H), 2.10−1.38 (m, 14H), 0.87 (m, 9H), 0.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 153.4, 79.8, 79.1, 68.1, 67.5, 65.4, 64.7, 59.3, 59.2, 56.5, 52.0, 51.8, 44.0, 42.8, 32.8, 31.6, 28.6, 28.5, 25.8, 23.4, 18.0, 14.1, −4.8, −4.9; ESI-MS *m/z* (M + Na) calcd for $C_{20}H_{40}N_4O_4SiNa$ 451.6, obsd 451.3.

Compound 17′. Compound **16′** (1.0 g, 2.3 mmol) was dissolved in MeOH (10 mL) and transferred to a hydrogenation apparatus. Boc_2O (1.0 g, 4.6 mmol) and 10% Pd/C (0.15 g) were added; the mixture was charged with H_2 (45 psi), and the reaction solution was shaken overnight. The reaction mixture was filtered through Celite and concentrated. The crude product was purified by column chromatography eluting with hexane/EtOAc (1/1; v/v) (TLC $R_f = 0.79$) to afford 0.79 g (69% yield) of **17′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 4.72−4.38 (bd, 1H), 4.31 (m, 1H), 3.75−3.49 (m, 2H), 3.27 (s, 3H), 3.23−2.98 (m, 4H), 2.23−1.65 (m, 2H), 1.65−1.30 (m, 21H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 118.0, 79.1, 68.0, 67.4, 65.6, 64.8, 59.3, 59.2, 56.3, 43.4, 42.7, 40.6, 32.6, 31.4, 28.6, 28.5, 28.4, 28.2, 25.8, 24.2, 18.0, 14.1, −4.7, −4.8; ESI-MS *m/z* (M + Na) calcd for $C_{25}H_{50}N_2O_6SiNa$ 525.7, obsd 525.3.

Compound 9j′. Compound **9j′** was prepared from **17′** (0.79 g, 1.5 mmol) using a protocol similar to that used to prepare compound **9a′**. The crude product was purified by column chromatography eluting with hexane/EtOAc (3/1; v/v) (TLC $R_f = 0.28$) to afford 0.62 g (76% yield) of **9j′** as a colorless oil: ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 155.9, 153.2, 144.9, 133.7, 129.9, 127.8, 79.6, 65.6, 64.9, 59.1, 59.0, 53.9, 53.7, 41.1, 40.5, 39.6, 32.3, 31.2, 28.5, 28.4, 28.3, 24.1, 23.8, 21.6; ESI-MS *m/z* (M + Na) calcd for $C_{26}H_{42}N_2O_8SNa$ 565.6, obsd 565.3.

Compound 10j′. Compound **10j′** was prepared from **9j′** (0.62 g, 1.10 mmol) using a protocol similar to that used to prepare compound **10a′**. The crude product was purified by column chromatography eluting with hexane/EtOAc (2/1; v/v) (TLC $R_f = 0.23$) to afford 0.31 g (71% yield) of **10j′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65−4.45 (m, 1H), 3.82−3.45 (m, 3H), 3.42−3.26 (m, 4H), 3.12−2.99 (m, 3H), 2.91 (m, 1H), 2.56−1.40 (m, 1H), 2.17−1.74 (m, 2H), 1.60−1.25 (m, 22H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 155.9, 120.1, 80.1, 75.0, 65.7, 59.1, 59.0, 51.6, 40.6, 40.5, 37.0, 31.7, 28.6, 28.4, 28.2, 25.1, 24.5, 24.4; ESI-MS *m/z* (M + Na) calcd for $C_{20}H_{35}N_3O_5Na$ 420.5, obsd 420.3.

Compound 1j′. Compound **10j′** (0.3 g, 0.78 mmol) was dissolved in concentrated HCl and stirred for 6 h at 60 °C. The reaction solution was concentrated via rotary evaporation and then placed on the vacuum line. The resulting intermediate was dissolved in a CH_2Cl_2/MeOH solution (2.2 mL, 10/1, v/v). Di-*tert*-butyl dicarbonate (0.16 g, 0.74 mmol) and DIEA (0.8 mL, 4.68 mmol) were added, and the reaction solution was stirred overnight at room temperature. Benzyl chloroformate (0.11 mL, 0.78 mmol) was added, and the reaction solution was stirred overnight at room temperature. The reaction solution was concentrated via rotary evaporation. The resulting intermediate was dissolved in EtOAc and washed with 1 M HCl and brine. The organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by SiO_2 column chromatography eluting with hexane/EtOAc/acetic acid (1/1/0.1; v/v/v) (TLC $R_f = 0.37$) to afford 0.18 g (52% yield) of **1j′** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 7.37−7.25 (m, 5H), 5.17−5.05 (m, 2H), 4.62−4.38 (m, 1H), 3.88−3.44 (m, 3H), 3.39−2.88 (m, 6H), 2.53−2.38 (m, 1H), 2.17−1.25 (m, 13H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) mixture of rotamers δ 153.7, 136.9, 128.4, 128.2, 127.8, 127.6, 75.4, 66.4, 66.3, 59.0, 50.2, 40.2, 36.5, 31.7, 28.4, 24.5; ESI-MS *m/z* (M + Na) calcd for $C_{23}H_{35}N_2O_7$ 473.5, obsd 473.2.

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Supporting Information Available: Synthetic procedures available for **4b**, **5b**, **1b′**, **6b′**, **8b′**−**11b′**, **1c**, **4c**, **6c**, **10c**, **11c**, **1d′**, **6d′**, **8d′**−**11d′**, **1e**, **6e**, **9e**, **11e**, **1e′**, **6e′**, **9e′**−**11e′**, **1f**, **6f**, **10f**, **11f**, **1g′**, **6g′**, **9g′**−**11g′**, **1h**, **6h**, **9h**−**11h**, **1i**, **6i**, **10i**, **11i**, and **18**−**26** and ^{1}H NMR and ^{13}C NMR spectra of compounds **2**, **4a**, **1a′**, **3a′**, **6a′**−**11a′**, **4b**, **5b**, **1b′**, **6b′**−**11b′**, **1c**, **5c**, **6c**, **10c**, **11c**, **6d′**, **8d′**, **1e**, **6e**, **9**−**11e**, **1e′**, **6e′**, **9e′**−**11e′**, **1f**, **6f**, **10f**, **11f**, **1g′**, **6g′**−**11g′**, **1h**, **6h**, **9h**, **10h**, **6i**, **10i**, **11i**, **1j′**, **9j′**, **15′**, **16′**, and **17′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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