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Synthesis and Structural Studies of Homooligomers of Geminally Disubstituted $\beta^{2,2}$-Amino Acids with Carbohydrate Side Chain

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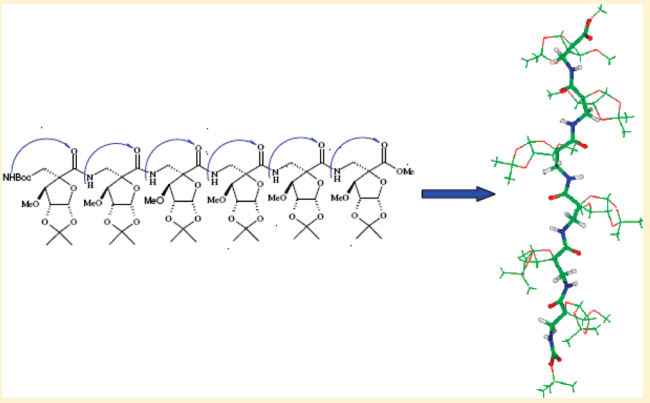
Supporting Information

ABSTRACT: A new class of geminally disubstituted C-linked carbo-$\beta^{2,2}$-amino acids ($\beta^{2,2}$-Caa) were prepared from D-glucose. The structures of homooligomeric di-, tetra-, and hexapeptides prepared from (*S*)-$\beta^{2,2}$-Caa were studied with NMR (in $CDCl_3$), CD, and Molecular Dynamics calculations. These $\beta^{2,2}$-peptides have shown the presence of stable 6-membered (6-mr) NH-(*i*)···CO(*i*) intra-residue H-bonded (C_6) strands. It was found that the strand structures realized in these systems were additionally stabilized by the electrostatic interaction arising due to the proximity of amide proton (NH(*i*)) to the oxygen of the preceding methoxy group (O(Me)(*i*−1)) at the C3 carbon of the carbohydrate ring. The new $\beta^{2,2}$-Caa residues with additional support to H-bonding considerably expand the domain of foldamers.



INTRODUCTION

The discovery of 14-helix[1,2] in short oligomers of β-peptides, derived from β-amino acids generated immense research interest. β-Peptides, which form a major class of foldamers,[3] show greater diversity in secondary structures compared to their natural counterparts.[4,5] The presence of one additional carbon atom in β-amino acids results in considerably enhanced scope for monomer design and conformational freedom. A variety of conformations have been generated in β-peptides using β^2-,β^3- and "like" and "unlike" β^2-,β^3-disubsituted β-amino acids. Though the oligomers of α,α-disubstituted α-amino acids[6] take well-defined structures and are known to display enzyme inhibitory activity,[7] very few reports are available on the peptides, using their β-counterparts, consisting of the geminally disubstituted $\beta^{2,2}$- and $\beta^{3,3}$-amino acids.[8] In one of the earliest studies, Drey et al.[9] reported the synthesis of short peptides consisting of β^2-hAib or β^3-hAib. However, no details on their structures were mentioned. Seebach et al.[10] noticed that the peptides from geminally disubstituted $\beta^{2,2}$- or $\beta^{3,3}$-amino acids do not adopt commonly found secondary structures observed in β-amino acid foldamers, probably because of their propensity to break the helix and sheets. Seebach et al.,[10a] from the X-ray studies on a tripeptide containing geminally disubstituted β-amino acid, 1-(aminomethyl)cyclo-hexanecarboxylic acid), revealed the presence of 10-memberd (10-mr) turns (C_{10}). In yet another study, they reported 8-mr turns (C_8)[11] in the peptides derived from 1-(amino-methyl)cyclopropanecarboxylic acid.[12] Taillefumier et al.[13] have recently studied oligomers of a spirocyclic disubstituted anomeric sugar $\beta^{3,3}$-amino acid,[14] wherein the hexamer showed preference for a double C_8 turn. All these studies point out that the secondary folds are stabilized through H-bonded interactions involving the neighboring residues.

Similar to ST turns[15] in serine/threonine, additional interactions[16] involving the side chain oxygen atom participation in H-bonding assist in the stabilization of novel structures in β-peptides. We surmised that $\beta^{2,2}$-amino acids, constrained through a cyclization into a spiro system, are likely to provide considerable rigidity in the side chain. Further, the rigidity may enhance the possibility of such interactions compared to our earlier β-amino acids, wherein the carbohydrates side chains[17] influence the folding propensity[18] in the derived peptides. We thus focused our attention to the *gem* disubstituted ($\beta^{2,2}$) β-amino acid with a carbohydrate side chain. The present report describes the first synthesis of a new class of C-linked carbo-$\beta^{2,2}$-amino acid ($\beta^{2,2}$-Caa) **1** from D-glucose, peptides **2**−**4** (Figure 1), and exploration of their folding propensities.

RESULTS AND DISCUSSIONS

$\beta^{2,2}$-Amino Acid Synthesis. The Boc-(*S*)-$\beta^{2,2}$-Caa-OMe (**1**) was prepared from known aldehyde **5**, derived from D-(+)-glucose (Scheme 1). Accordingly, reaction of **5** with 37% aq formaldehyde in the presence of 1 N NaOH in 1:1 ratio of THF:H_2O at room temperature for 16 h afforded the 1,3-diol **6** in 59% yield, following the procedure reported by Youssefyeh et al.[19] Selective protection of the diol **6** with TBDMS-Cl and imidazole at −20 °C for 1 h gave **7** (55%), **8** (7%), and **9** (35%), which were

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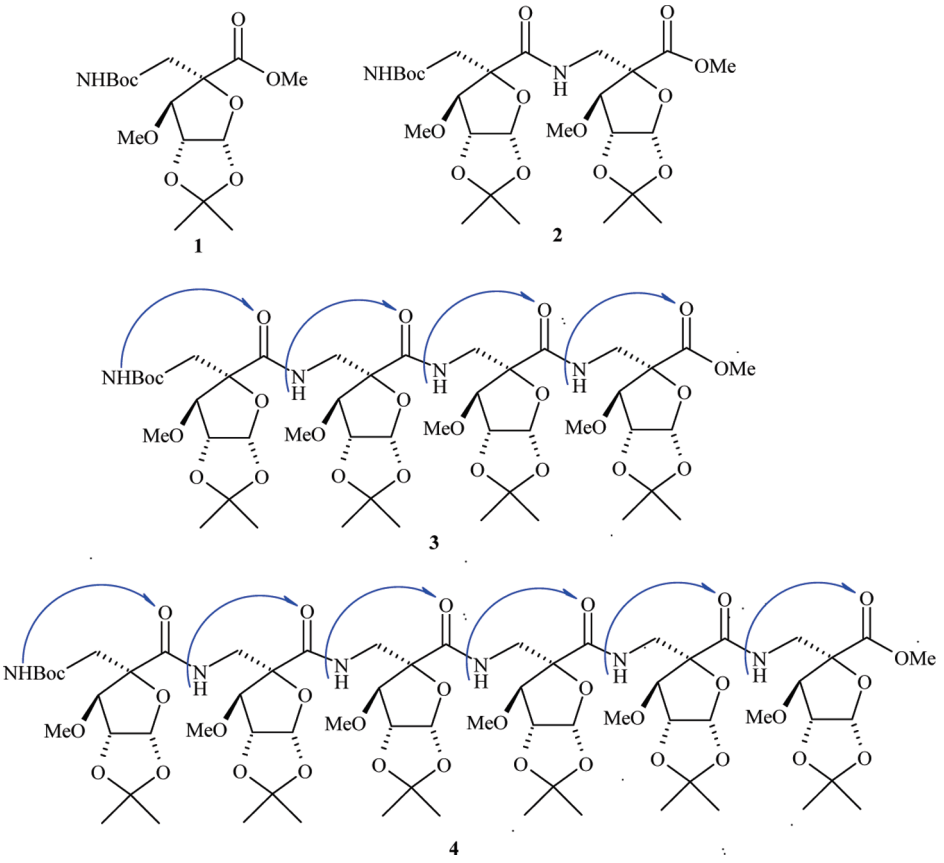
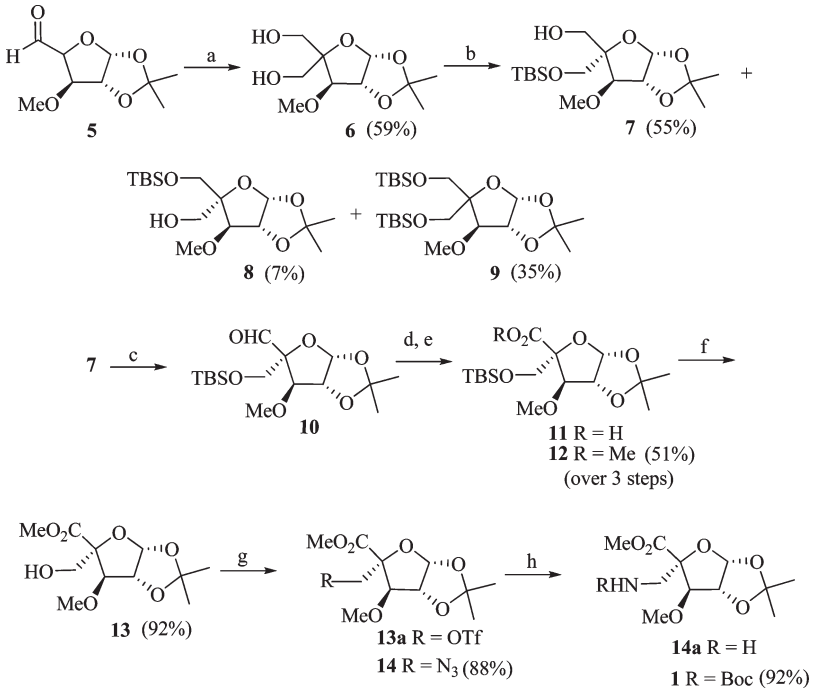


Figure 1. Structures of $\beta^{2,2}$-peptides **2** to **4** (arrows indicate the H-bonding pattern deduced from structural studies).

Scheme 1. Synthesis of $\beta^{2,2}$-Caa 1[a]



[a] Reagents and conditions: (a) 37% HCHO, THF, H_2O, 1 N NaOH, 0 °C to rt, 16 h; (b) TBS-Cl, imidazole, CH_2Cl_2, −20 °C, 1 h ; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (d) $NaClO_2$, 30% H_2O_2, ^{t}BuOH:H_2O (7:3), 0 °C to rt, 5 h; (e) CH_2N_2, ether, 0 °C to rt, 2 h; (f) TBAF, THF, 0 °C to rt, 3 h; (g) (i) Tf_2O, pyridine, CH_2Cl_2, 0 °C to rt, 30 min; (ii) NaN_3, DMF, 0 °C to rt, 3 h; (h) (i) 10% Pd/C−H_2, MeOH, rt, 4 h; (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C to rt, 5 h.

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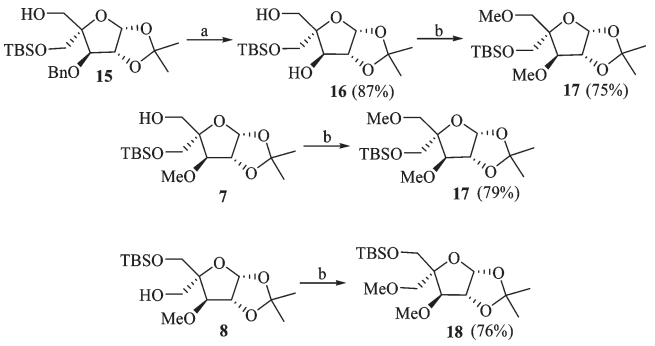
Scheme 2. Stereochemistry Correlation of 7 with 17[a]



[a] Reagents and conditions: (a) 10% Pd/C−H_2, EtOAc, 8 h; (b) NaH, MeI, THF, 0 °C to rt, 2 h.

separated by column chromatography. The major alcohol **7** on oxidation under Swern reaction conditions at −78 °C for 2 h furnished aldehyde **10**, which, on oxidation with $NaClO_2$ and H_2O_2 at 0 °C to room temperature for 5 h, afforded acid **11**. Reaction of acid **11** with CH_2N_2 generated in situ at 0 °C for 2 h afforded ester **12** in 51% yield (over 3 steps). Desilylation of the TBS group in **12** on treatment with TBAF in THF at 0 °C to room temperature for 3 h gave alcohol **13** (92%). Treatment of **13** with Tf_2O and pyridine in CH_2Cl_2 at −20 °C for 30 min gave triflate **13a**, which on subsequent treatment with NaN_3 in DMF at 0 °C to room temperature for 3 h furnished azide **14** (88%). Finally, azide **14** on reaction with 10% Pd/C−H_2 in MeOH at room temperature for 4 h afforded the amine **14a**, which on further reaction with $(Boc)_2O$ and Et_3N in CH_2Cl_2 at 0 °C to room temperature for 5 h furnished Boc-(*S*)-$\beta^{2,2}$-Caa-OMe (**1**) in 92% yield.

The stereochemistry at the spiro-carbon center in the diastereo isomers **7** and **8** was determined by correlation with known compound[19] (Scheme 2). Alcohol **15** (prepared by a known[19a] procedure) was subjected to debenzylation under hydrogenation conditions using 10% Pd/C−H_2 in EtOAC at room temperature for 8 h to give diol **16** (87%), which on further treatment with MeI in the presence of NaH in THF at 0 °C to room temperature for 2 h afforded the dimethyl ether **17** (75%). Similarly, **7** and **8** were subjected to methylation under the above reaction conditions to give **17** (79%) and **18** (76%), respectively. The comparable spectral analysis and optical rotation values for **17** prepared both from **16** and **7** unambiguously confirm the stereochemistry in alcohol **7**. Thus, it is imperative that alcohol **8** is the diastereo isomer of **7**.

***β*^{2,2}-Peptides Synthesis.** The peptides **2**−**4** were synthesized in solution phase[20] from the $\beta^{2,2}$-Caa **1** (Scheme 3). Accordingly, ester **1** was subjected to hydrolysis with aq 4 N NaOH at room temperature to afford the acid **19** (96%), while, on the other hand, **1** on exposure to CF_3COOH in CH_2Cl_2 for 2 h was converted into the corresponding amine salt **20**. Coupling of acid **19** with the amine salt **20** in the presence of EDCI, HOBt, and DIPEA in CH_2Cl_2 at room temperature for 5 h furnished the dipeptide **2** in 73% yield, $[\alpha]_D$ −156.0 (*c* 0.1, $CHCl_3$). Base (aq 4 N NaOH) hydrolysis of dipeptide **2** gave the acid **21**, while **2** was converted into the corresponding amine salt **22** on exposure to CF_3COOH in CH_2Cl_2 for 2 h. The thus derived acid **21** was then coupled (EDCI, HOBt, DIPEA) with amine **22** in CH_2Cl_2 for 5 h to furnish the tetrapeptide **3** in 66% yield, $[\alpha]_D$ −27.7 (*c* 0.3, $CHCl_3$). Reaction of **3** with NaOH in CH_3OH gave the corresponding acid **23** (91%), which on coupling with the salt **22** under the above reaction conditions afforded the hexapeptide **4** in 53% yield, $[\alpha]_D$ −215.1 (*c* 0.2, $CHCl_3$).

CONFORMATIONAL ANALYSIS

NMR studies were carried out on 8−10 mM solutions in $CDCl_3$. Resonance assignments were obtained from a combination of TOCSY, ROESY, HSQC, and HMBC experiments.[21] The results of the NMR studies in the dimer **2** substantiate the presence of H-bonding for both the amide protons and the underlying structure.[21] However, a definite structure could not be deduced from the data.

In the ^{1}H NMR spectrum of peptide **3**, two isomers were observed. The major isomer with a population of 93% was fully investigated to determine the structure. In **3**, all the amide protons, except Boc-amide proton, were found to have a chemical shift (δ) >7 ppm, suggesting their possible participation in H-bonding.[21] This was further supported from solvent titration studies (addition of up to 33% (v/v) of DMSO-d_6 to the $CDCl_3$ solution),[22] wherein the amide protons showed a very small chemical shift change ($\Delta\delta$NH) of <0.10 ppm (Figure 2). The couplings, $^3J_{NH\text{-}C\beta H}$, for the first three residues are quite distinctive, with one large (>8.0 Hz) and another rather small (<2.8 Hz) coupling, thus providing strong evidence for an antiperiplanar arrangement of NH and CβH, corresponding to a value of ∼±120° for the torsion angle ϕ (C(O)−N−Cβ−Cα). Due to the lack of protons at the Cβ, the information on torsion angle θ (N−Cβ−Cα−C(O)) had to be obtained through the NOE correlations only (Figure 3). The presence of several NH(i)/C3H(i) and CβH$_{(pro\text{-}R)}$(i)/C3H(i) NOE cross peaks along with the above value of ϕ provided adequate support for $\theta \approx -60°$. The Cβ protons with large $^3J_{NH\text{-}C\beta H}$ also had a strong NOE correlation with C3H proton in the sugar ring, permitting the assignments CβH$_{(pro\text{-}R)}$ and $\phi \approx -120°$. Additionally, NH(i)/C3H(i) and NH(i+1)/C1H(i) enabled the deduction that ψ (Cβ−Cα−C(O)−N) is constrained to ∼180°. Further, it was also noticed that the two couplings in the sugar ring, $^3J_{CH1\text{-}CH2} \approx$ 3.9 Hz and $^3J_{CH2-CH3} \approx 0$ Hz, are identical with those observed in C-linked-carbo-β-amino acids (β-Caa) and the peptides derived from them containing xylose side chains.[18a,18c,23] Therefore, it was concluded that the sugar pucker does not change on the formation of the spiro group, implying the dihedral angle C2H−C2−C3−C3H ≈ −90°.

The above findings were crucial, since NOE correlations were observed only within the same or neighboring residues, while the long- or medium-range NOE correlations were conspicuous by their absence. It was thus realized that the Molecular Dynamics (MD) calculations were not straightforward and these deductions about the backbone geometry were rather important and useful to provide the very important dihedral angle constraints during the simulations. Grierson et al.[15b] encountered similar difficulties in their studies, wherein, they found a stranded structure stabilized by a 5-mr inter-residue and a 6-mr intra-residue H-bond and hydrophobic interactions.

Restrained molecular dynamics (MD)[21,24] calculations for **3** were thus carried out by the simulated annealing method, using the distance constraints derived from the ROESY experiments and the backbone dihedral angle constraints $\phi = -120 \pm 20°$, $\theta = -60 \pm 20°$, and $\psi = 180 \pm 20°$ deduced above (these dihedral angle constraints were not applied for the last residue, in view of the limitations of the NMR data to fix some of them).[21] In fact, it was found that in the absence of any constraints in the sugar pucker, there were discrepancies in the derived structures. Therefore, in addition, the dihedral angle C2H−C2−C3−C3H was constrained between −70° and −110°.

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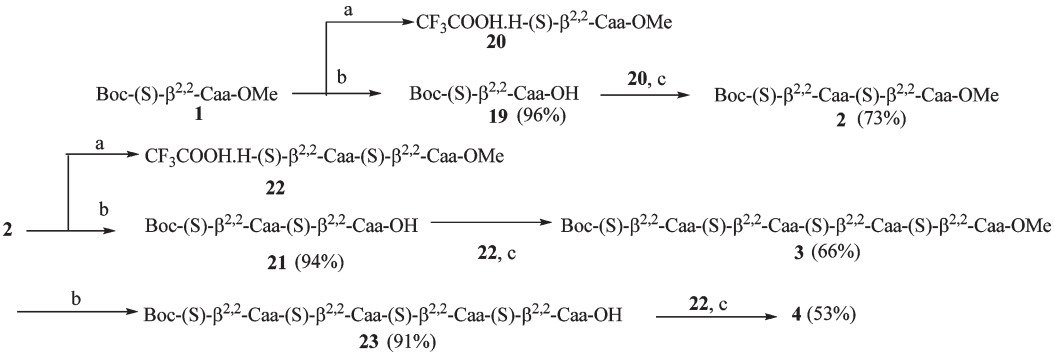
Scheme 3. Synthesis of Peptides 2−4[a]



[a] Reagents and conditions: (a) CF_3COOH, CH_2Cl_2, 0 °C to rt, 2 h; (b) aq 4 N NaOH, CH_3OH, 0 °C to rt, 1 h; (c) HOBt, EDCI, DIPEA, CH_2Cl_2, 0 °C to rt.

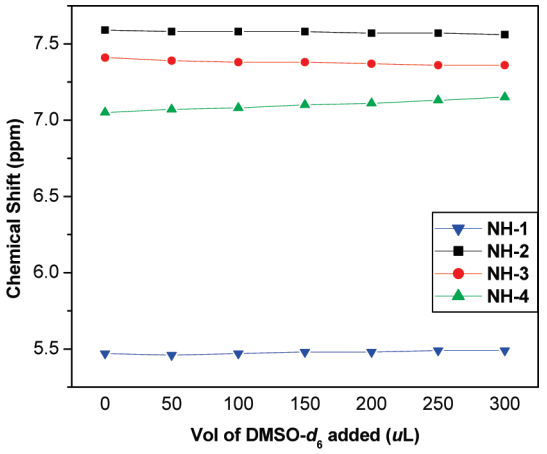


Figure 2. Solvent titration plots for peptides **3**, depicting the variation of chemical shift on sequential addition of DMSO-d_6 to 600 μL of $CDCl_3$ solution.

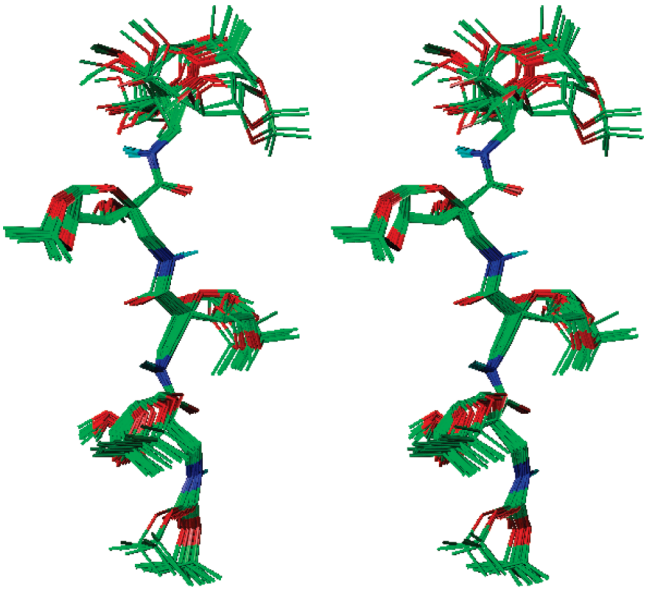


Figure 3. Stereoview of the superimposition of the 20 best structures for peptide **3** (for clarity, except for the amide hydrogen, other hydrogens are not displayed).

The 20 best structures (Figure 3) obtained have a backbone rmsd of 0.56 Å and a heavy atoms rmsd of 1.29 Å. No violations larger than 0.13 Å and 7° were observed. The average values of the dihedral angles for tetramer **3** are the following: $\phi = -116 \pm 3°$, $\theta = -65 \pm 2°$, and $\psi = -164 \pm 4°$. The structure interestingly is stabilized by 6-(mr) H-bonds between NH(i)···CO(i), wherein, the 6-mr H-bond NH---(O=)C has (N)H---O(C) = 2.50 Å and N−H---O(C) = 108°, which are weak and similar to those observed by Grierson et al.[15b]

The distance of amide proton with the preceding methoxy oxygen at the C3 in the sugar ring was found to be 2.63 Å, while the NH(i)---O(Me)($i-1$) angle was 103°. Interestingly, the distance of 2.63 Å recorded for **3** just falls short of the expected distance of <2.50 Å in the Insight II program for H-bonding. The resulting electrostatic interaction, though much smaller than expected for ideal H-bonds,[15b] might be making a small contribution toward the stabilization of the C_6 strand in **3**. Unlike the findings of Taillfumier et al.[13] on a double C_8 turn in their $\beta^{3,3}$-hexamer, the present study describes the extended C_6 strand in the $\beta^{2,2}$-peptides.[21]

The theoretical calculations by Wu et al.[25] seem to suggest that the C_6 structures are less favored in the β-hGly oligomers, while Hofmann et al.[26] predicted the 6-mr H-bonded pseudoring, resulting in a strand structure in oligomers of $\beta^{3,3}$-amino acid. Though self-stabilizing C_6 secondary structures in β-peptides, without the need of any additional interaction, are reported,[27−29] such an additionally stabilized C_6 strand, to the best of our knowledge, has only been described for the hexamer of phenylisoserine.[15b]

The hexamer **4** has shown populations for two isomers in the ratio of 84:16, wherein, the detailed study was carried out on the major isomer. The δNH as well as the $\Delta\delta$NH values provide compelling evidence for the involvement of all the amide protons in H-bonding.[21,22] Like **3**, except for the last residue, one large and another small value for $^3J_{NH\text{-}C\beta H}$ (either >8.0 Hz or <2.5 Hz) are consistent with an antiperiplanar arrangement of NH and CβH, corresponding to $\phi \approx \pm 120°$. The assignments of prochiral CβH were carried out as discussed for **3**. A series of NOE correlations (Figure 4), NH(i)/C3H(i), NH($i+1$)/C1H(i), and $C_\beta H_{(pro\text{-}R)}(i)$/C3H($i$), support the constrained values for $\theta \approx -60°$ and $\psi \approx 180°$.

The 20 best structures (Figure 5) obtained from restrained MD calculations have a backbone rmsd of 1.37 Å and a heavy atom rmsd of 1.44 Å. The average value of the backbone dihedral angles for hexamer are the following: $\phi = -117 \pm 3°$, $\theta = -68 \pm 2°$, and $\psi = -159 \pm 5°$.

Further, NMR experiments were performed in the $CDCl_3$ solution as a function of solute concentration (0.1 to 25 mM).

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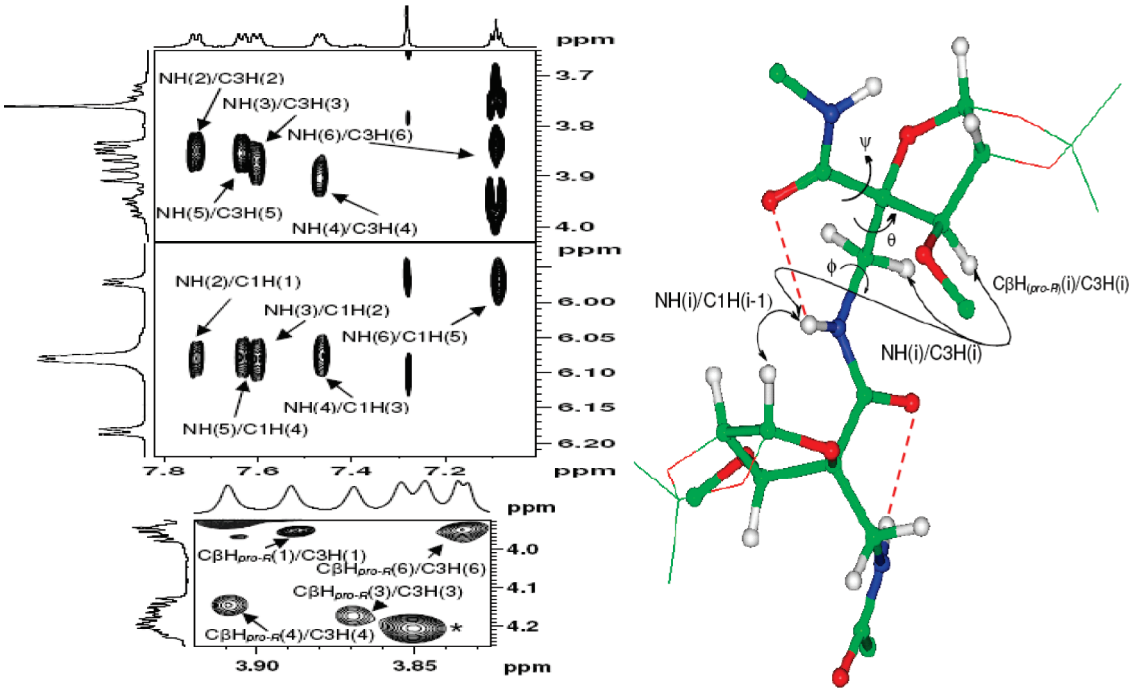

Figure 4. Characteristic nOes supporting backbone 6-mr H-bonding (C_6 strand) (dotted lines represent the intra-residue H-bonds). The asterisk (∗) identifies the overlap of two NOE correlations, $C_\beta H_{(pro\text{-}R)}(2)/C3H(2)$ and $C_\beta H_{(pro\text{-}R)}(5)/C3H(5)$.

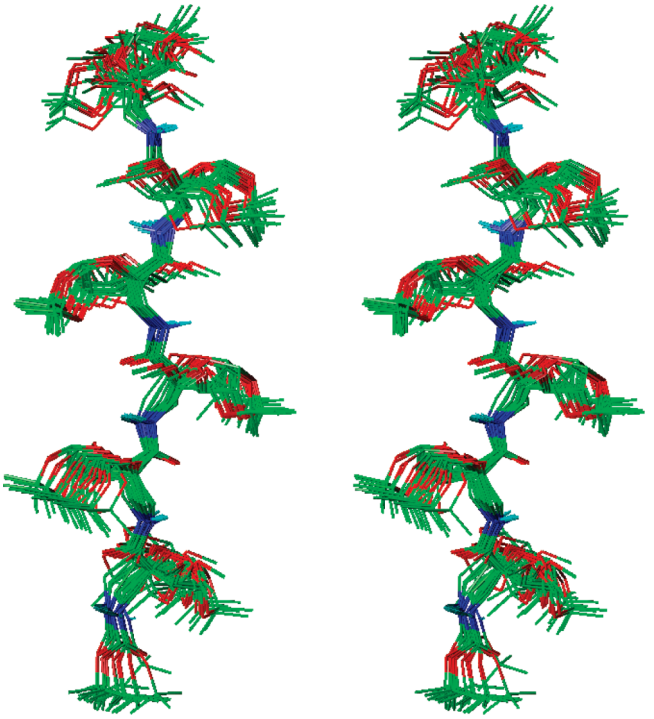

Figure 5. Stereoview of 20 best structures for peptide **4** (for clarity, except for the amide hydrogen, other hydrogens are not displayed).

These experiments[21] showed virtually the same ^{1}H spectra and thus ruled out the molecular aggregation. Additionally, NMR experiments were also performed in methanol (CD_3OD), as a function of time[21] to understand the behavior of **4** in polar solvents, and to explore the exchange of the labile amide protons. These studies revealed the presence of all the amide resonances in the spectrum even after 21 h. However, when the studies were extended for longer duration, it was noticed that four resonances were still present even after 117 h. These observations suggest that **4** retains similar structure even in methanol. These results were further supported by the CD studies,[21] wherein, 0.2 mM solution in methanol for both **3** and **4** showed a narrow and another broad shallow negative maxima at ∼192 nm and at 215 nm, respectively, along with a maxima for **4** at ∼195 nm, while, the molecular ellipticity $[\theta]$ values are zero at about 194 and 200 nm. Though the $[\theta]$ per residue are rather small, these findings suggest the presence of secondary structures for these oligomers.

CONCLUSIONS

In conclusion, the present work described the synthesis of new geminally disubstituted C-linked carbo $\beta^{2,2}$-amino acids ($\beta^{2,2}$-Caa) and peptides from $\beta^{2,2}$-Caa. The conformational studies on the homooligomers derived from (*S*)-$\beta^{2,2}$-Caa revealed the presence of a C_6-strand structure involving weak intra-residue H-bonding between the amide protons with the sequential carbonyls. In addition, these C_6 strands were found to be further stabilized by additional rather weak inter-residue electrostatic interactions involving the amide protons with the oxygen of the −OMe group at the C-3 position of the furanoside. The exploitation of such additional interactions, exemplified in these studies, would help in the design of diverse families of peptides, opening up the possibilities to generate novel structures. In addition, small changes such as stereochemistry or the ring size in the carbohydrate side chain might help in realizing β-peptides with diverse scaffolds with desired functions.

EXPERIMENTAL SECTION

NMR spectra (1D and 2D experiments) for peptides **2**−**4** were obtained at 300, 400, 500, and 600 MHz (^{1}H), and at 75 and 150 MHz (^{13}C).

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Chemical shifts are reported in δ scale with respect to internal TMS reference. Information on hydrogen bonding in $CDCl_3$ was obtained from solvent titration studies at 298 K by sequentially adding up to 300 μL of DMSO-d_6 in 600 μL of $CDCl_3$ solution of peptides. States-TPPI procedure was used to run various NMR experiments in the phase sensitive mode,[30] using standard programs in the library provided by the instrument manufacturer. The ROESY experiments were performed with mixing times of 100, 200, and 300 ms, using a continuous spin-locking field of about 2.5 kHz. The TOCSY experiments were performed with the spin locking field of about 10 kHz and a mixing time of 80 ms. The HSQC experiments were optimized for a $^1J_{C-H}$ value of 140 Hz, while for the HMBC experiments the optimization was done for four sets of the multiple bond $^1H-^{13}C$ couplings (3, 5, 8, and 10 Hz). The composite information was further used for the assignment of the resonances. The 2D data were processed with Gaussian apodization in both dimensions. With use of two spin approximations and a reference distance of 1.80 Å for the geminal proton at Cβ, the distance constraints were derived from the volume integrals of the cross peaks in the ROESY spectra.

The CD spectra were obtained in rectangular fused quartz cells of 0.2 cm path length at room temperature with a scan range of 190−260 nm and scanning speed of 50 nm/min, using peptide concentrations of 0.2 mM in MeOH. The binomial method was used for smoothing the spectra. The values are expressed in terms of $[\theta]$, the total molar ellipticity $(deg \cdot cm^2 \cdot dmol^{-1})$/residue.

The Insight-II(97.0)/Discover program was used for construction of the molecular model and for structural analysis of different obtained conformations, including molecular modeling calculations and energy minimization. The CVFF force field with default parameters was used throughout the calculations with the aid of a distance dependent dielectric constant with ε = 4.7 (dielectric constant of $CDCl_3$). The upper and lower bound of the distance constraints have been obtained by enhancing and reducing the derived distance by 10%. The complete set of 10 and 14 NOE distance constraints used for **3** and **4** respectively have been tabulated in the Supporting Information. The dihedral angle constraints used for both peptides **3** and **4** are listed in the Supporting Information. Backbone dihedral angles for the last residue were not constrained, as there was inadequate support from the NMR data. For the initiation of the dynamics the molecular model was built based on the inputs from the NMR experiments. The following general protocol was used for minimizing energy. Initial minimizations were done with steepest descent, followed by conjugate gradient methods for a maximum of 1000 iterations each or rms deviation of 0.001 kcal/mol, whichever was earlier. The molecules were initially equilibrated for 1 ps and subsequently subjected to a 2 ns simulated annealing protocol. Starting from 300 K, they were heated to 1500 K in four steps increasing the temperature by 300 K and simulating for 2.5 ps at each step, and then subsequently cooling back to 300 K in 4 steps decreasing the temperature by 300 K and again simulating for 2.5 ps. After this, a structure was saved and the above process was repeated 100 times. The 100 structures generated so were energy minimized with the above protocol and 20 of the best possible structures were superimposed for display.

((3a*R*,6*R*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro-[2,3-*d*][1,3]dioxole-5,5-diyl) dimethanol (6): Aqueous 37% formaldehyde (32 mL) and 1 N NaOH (96 mL) were added sequentially at 0 °C to a stirred solution of **5** (16.0 g, 79.20 mmol) in a mixture of water (80 mL) and THF (80 mL) at 0 °C and the reaction mixture was stirred at room temperature for 16 h. Solvent was evaporated under reduced pressure and the residue was extracted with EtOAc (3 × 200 mL). Combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and evaporated and the residue obtained was purified by column chromatography (60−120 mesh Silica gel, 40% ethyl acetate in petroleum ether) to give **6** (10.86 g, 59%) as a white solid: mp 67−69 °C; $[\alpha]^{20}_D$ −91.2 (*c* 0.3, $CHCl_3$); IR (KBr) 3294, 2986, 2940, 1462, 1381, 1219, 1077, 1025, 933, 857, 640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) δ 5.92 (d, 1H, *J* = 4.5 Hz, C1H), 4.62 (dd, 1H, *J* = 2.0, 4.5 Hz, C2H), 3.87 (d, 1H, *J* = 2.0 Hz, C3H), 3.66−3.55 (m, 4H, 2 × OCH_2), 3.49 (s, 3H, OMe), 2.28−2.15 (br, 2H, 2 × OH), 1.54 (s, 3H, Me), 1.33 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 113.1, 104.9, 89.8, 87.0, 85.3, 63.4, 63.3, 58.3, 27.3, 26.7; HRMS (ESI+) *m*/*z* calcd for $C_{10}H_{18}O_6$ (M^+ + Na) 257.1001, found 257.0996.

((3a*R*,5*S*,6*R*,6a*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-6-methoxy-2,2-di methyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methanol (7): To a solution of compound **6** (5.56 g, 23.76 mmol) in CH_2Cl_2 (84 mL) at −20 °C were added imidazole (4.85 g, 71.28 mmol) and TBDMS-Cl (3.58 g, 23.76 mmol) then the mixture was stirred for 1 h at −20 °C. The reaction mixture was allowed to reach room temperature and extracted with CH_2Cl_2 (3 × 60 mL). Combined organic layers were washed with water (40 mL) and brine (60 mL), and the residue was dried (Na_2SO_4), evaporated, and purified by column chromatography (60−120 mesh Silica gel) to afford, sequentially, **9** (3.84 g, 35%) as colorless syrup (eluted with 6% ethyl acetate in petroleum ether), **8** (0.61 g, 7%) as colorless syrup (eluted with 9% ethyl acetate in petroleum ether), and **7** (4.85 g, 55%) as colorless syrup (eluted with 10% ethyl acetate in petroleum ether). **7**: $[\alpha]^{20}_D$ −71.4 (*c* 0.3, $CHCl_3$); IR (neat) 3505, 2935, 2859, 1634, 1465, 1378, 1254, 1213, 1113, 842. 779, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 295 K) δ 5.99 (d, 1H, *J* = 4.2 Hz, C1H), 4.64 (dd, 1H, *J* = 1.3, 4.2 Hz, C2H), 3.95 (d, 1H, *J* = 1.3 Hz, C3H), 3.84 (dd, 1H, *J* = 3.8, 12.2 Hz, OCH), 3.72−3.68 (m, 2H, CH_2OTBS), 3.59 (dd, 1H, *J* = 9.5, 12.2 Hz, OCH′), 3.47 (s, 3H, OMe), 2.32 (dd, 1H, *J* = 3.8, 9.5 Hz, OH), 1.55 (s, 3H, Me), 1.35 (s, 3H, Me), 0.90 (s, 9H, 3 × Me), 0.07 (s, 6H, 2 × Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 112.9, 104.8, 89.3, 87.4, 85.9, 64.5, 64.1, 58.5, 27.4, 26.7, 25.8 (3C), 18.2, −5.5 (2C); HRMS (ESI+) *m*/*z* calcd for $C_{16}H_{32}O_6Si$ (M^+ + Na) 371.1865, found 371.1859.

((3a*R*,5*R*,6*R*,6a*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-6-methoxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methanol (8): $[\alpha]^{20}_D$ −53.5 (*c* 0.3, $CHCl_3$); IR (neat) 3451, 2930, 2857, 1739, 1637, 1463, 1378, 1252, 1087, 1028, 843, 776, 672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) δ 5.88 (d, 1H, *J* = 4.5 Hz, C1H), 4.61 (dd, 1H, *J* = 2.1, 4.5 Hz, C2H), 3.75 (d, 1H, *J* = 2.1 Hz, C3H), 3.65−3.57 (m, 4H, 2 × OCH_2), 3.43 (s, 3H, OMe), 1.53 (s, 3H, Me), 1.33 (s, 3H, Me), 0.91 (s, 9H, 3 × Me), 0.07 (s, 3H, Me), 0.06 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 112.9, 105.0, 89.6, 85.5, 85.4, 63.2, 63.1, 58.1, 27.3, 26.8, 25.8 (2C), 25.7, 18.2, −5.6, −5.7; HRMS (ESI+) *m*/*z* calcd for $C_{16}H_{32}O_6Si$ (M^+ + Na) 371.1865, found 371.1862.

((3a*R*,6*R*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro-[2,3-*d*][1,3]dioxole-5,5-diyl)bis(methylene)bis(oxy)bis(*tert*-butyldimethylsilane) (9): $[\alpha]^{20}_D$ −19.0 (*c* 0.2, $CHCl_3$); IR (neat) 3449, 2934, 2893, 2858, 1639, 1466, 1378, 1254, 1101, 1006, 839, 777, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 295 K) δ 5.90 (d, 1H, *J* = 4.6 Hz, C1H), 4.58 (dd, 1H, *J* = 2.2, 4.6 Hz, C2H), 3.78 (d, 1H, *J* = 2.2 Hz, C3H), 3.67 (d, 1H, *J* = 10.4 Hz, CHOTBS), 3.64 (d, 1H, *J* = 10.4 Hz, CHOTBS), 3.58 (d, 1H, *J* = 10.3 Hz, CHOTBS), 3.52 (d, 1H, *J* = 10.3 Hz, CHOTBS), 3.40 (s, 3H, OMe), 1.53 (s, 3H, Me), 1.34 (s, 3H, Me), 0.90 (s, 18H, 6 × Me), 0.07 (s, 3H, Me), 0.06 (s, 3H, Me), 0.05 (s, 6H, 2 × Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 112.8, 104.9, 89.5, 86.5, 86.3, 63.3, 63.2, 58.0, 27.7, 27.2, 25.9 (6C), 18.3, 18.2, −5.4, −5.5 (2C), −5.7; HRMS (ESI+) *m*/*z* calcd for $C_{22}H_{46}O_6Si_2$ (M^+ + Na) 485.2730, found 485.2733.

(3a*R*,5*S*,6*R*,6a*R*)-Methyl 5-((*tert*-butyldimethylsilyloxy)-methyl)-6-methoxy-2,2-dimethyltetrahydrofuro[2,3-*d*]-[1,3]dioxole-5-carboxylate (12): To a solution of oxalyl chloride (1.71 mL, 19.57 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added DMSO (2.78 mL, 39.14 mmol) dropwise then the mixture was stirred for 20 min. A solution of **7** (4.54 g, 13.05 mmol) in CH_2Cl_2 (15 mL) was added and the reaction was stirred for 2 h at −78 °C. Then Et_3N (10.89 mL, 78.28 mmol) was added and the mixture was stirred to room temperature, then diluted with

CH_2Cl_2 (80 mL) and washed with water (40 mL) and brine (40 mL), dried (Na_2SO_4), and evaporated to afford (3a*R*,5*S*,6*R*,6a*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-6-methoxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole-5-carbaldehyde (**10**) as a colorless syrup, which was immediately used for further reaction without purification.

To a solution of the above aldehyde **10** in *tert*-butanol:water (7:3, 22 mL) at 0 °C were added $NaClO_2$ (1.77 g, 19.55 mmol) and 30% aq H_2O_2 (7.4 mL, 65.15 mmol) and the solution was stirred at room temperature for 5 h. The reaction mixture was extracted with EtOAc (3 × 40 mL), dried (Na_2SO_4), and evaporated to afford crude carboxylic acid **11** as a light yellow syrup.

To the solution of acid **11** in ether (10 mL) at 0 °C was added a solution of CH_2N_2 in ether (100 mL) until the persistence of yellow color in the reaction mixture. After 2 h, ether was evaporated and the residue obtained was purified by column chromatography (60−120 mesh Silica gel, 10% ethyl acetate in petroleum ether) to afford **12** (2.5 g, 51%, over 3 steps) as a colorless syrup: $[\alpha]^{20}_D$ −37.2 (*c* 0.3, $CHCl_3$); IR (neat) 3452, 2933, 2857, 1744, 1632, 1464, 1378, 1253, 1098, 1021, 840, 779, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) δ 6.10 (d, 1H, *J* = 4.3 Hz, C1H), 4.60 (dd, 1H, *J* = 2.3, 4.3 Hz, C2H), 3.96 (m, 2H, CH_2OTBS), 3.90 (d, 1H, *J* = 2.3 Hz, C3H), 3.72 (s, 3H, COOMe), 3.42 (s, 3H, OMe), 1.55 (s, 3H, Me), 1.36 (s, 3H, Me), 0.90 (s, 9H, 3 × Me), 0.09 (s, 3H, Me), 0.07 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 170.3, 113.7, 106.2, 91.3, 85.7, 84.9, 64.2, 58.7, 52.0, 27.4, 27.0, 25.8 (3C), 18.4, −5.3, −5.4; HRMS (ESI+) *m*/*z* calcd for $C_{17}H_{32}O_7Si$ (M^+ + Na) 399.1815, found 399.1801.

(3a*R*,5*S*,6*R*,6a*R*)-Methyl 5-(hydroxymethyl)-6-methoxy-2,2-dimethyltetrahy drofuro[2,3-*d*][1,3]dioxole-5-carboxylate (13): To a solution of **12** (2.50 g, 6.65 mmol) in THF (8 mL) at 0 °C was added 1 M TBAF in THF (6.65 mL) then the reaction was stirred at room temperature for 4 h. THF was removed under reduced pressure and the residue obtained was purified by column chromatography (60−120 mesh Silica gel, 25% ethyl acetate in petroleum ether) to give **13** (1.61 g, 92%) as a colorless syrup: $[\alpha]^{20}_D$ −55.7 (*c* 0.35, $CHCl_3$); IR (neat) 3485, 2989, 2945, 1742, 1635, 1444, 1380, 1213, 1163, 1088, 1028, 863, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) δ 6.10 (d, 1H, *J* = 4.2 Hz, C1H), 4.60 (dd, 1H, *J* = 1.5, 4.2 Hz, C2H), 3.92−3.84 (m, 2H, OCH_2), 3.90 (d, 1H, *J* = 1.5 Hz, C3H), 3.76 (s, 3H, COOMe), 3.43 (s, 3H, OMe), 2.40 (br, 1H, OH), 1.53 (s, 3H, Me), 1.35 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 170.3, 113.8, 106.2, 91.6, 86.1, 84.2, 64.2, 58.7, 52.4, 27.0, 26.5; HRMS (ESI+) *m*/*z* calcd for $C_{11}H_{18}O_7$ (M^+ + Na) 285.0950, found 285.0955.

(3a*R*,5*S*,6*R*,6a*R*)-Methyl 5-(azidomethyl)-6-methoxy-2,2-dimethyltetrahydrofuro [2,3-*d*][1,3]dioxole-5-carboxylate (14): A solution of **13** (1.61 g, 6.15 mmol) and pyridine (1 mL, 12.3 mmol) in CH_2Cl_2 (14 mL) was treated with triflic anhydride (1.21 mL, 7.37 mmol) at −20 °C. After 30 min, the reaction mixture was diluted with CH_2Cl_2 (35 mL) and washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4), and evaporated to obtain triflate **13a** as a solid, which was immediately used for further reaction. To the solution of triflate **13a** in DMF (10 mL) at 0 °C was added NaN_3 (1.20 g, 18.43 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was treated with water (15 mL) and extracted with ether (2 × 20 mL). Organic layers were washed with brine (15 mL), dried (Na_2SO_4), evaporated, and the residue was purified by column chromatography (60−120 mesh Silica gel, 12% ethyl acetate in petroleum ether) to give **14** (1.55 g, 88%) as a white solid: mp 62−64 °C; $[\alpha]^{20}_D$ −164.1 (*c* 0.25, $CHCl_3$); IR (KBr) 3501, 3346, 2985, 2941, 2839, 2520, 2098, 1760, 1457, 1378, 1267, 1212, 1092, 1026, 969, 892, 743, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 295 K) δ 6.14 (d, 1H, *J* = 4.3 Hz, C1H), 4.61 (dd, 1H, *J* = 1.8, 4.3 Hz, C2H), 3.80 (d, 1H, *J* = 1.8 Hz, C3H), 3.76 (s, 3H, COOMe), 3.66 (m, 2H, CH_2N_3), 3.42 (s, 3H, OMe), 1.58 (s, 3H, Me), 1.37 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 169.7, 114.0, 106.5, 90.9, 86.9, 84.0, 58.8, 53.9, 52.6, 27.0, 26.6; HRMS (ESI+) *m*/*z* calcd for $C_{11}H_{17}N_3O_6$ (M^+ + Na) 310.1015, found 310.1005.

(3a*R*,5*S*,6*R*,6a*R*)-Methyl 5-((*tert*-butoxycarbonylamino)-methyl)-6-methoxy-2,2-di methyltetrahydrofuro[2,3-*d*]-[1,3]dioxole-5-carboxylate (1): To a solution of **14** (1.55 g, 5.40 mmol) in MeOH (2 mL) was added a catalytic amount of Pd−C (10%) and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 4 h. It was then filtered and washed with EtOAc (20 mL). The filtrate was evaporated under reduced pressure to furnish amine **14a**, which was immediately used for the next reaction without further purification.

To a stirred solution of the above amine **14a** and Et_3N (1.50 mL, 10.8 mmol) in CH_2Cl_2 (11 mL) was added $(Boc)_2O$ (1.48 mL, 6.48 mmol) at 0 °C. After 5 h, water (15 mL) was added and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with brine (15 mL), dried (Na_2SO_4), and evaporated and the crude residue obtained was purified by column chromatography (60−120 mesh Silica gel, 15% ethyl acetate in petroleum ether) to furnish **1** (1.79 g, 92%) as a colorless syrup: $[\alpha]^{20}_D$ −73.1 (*c* 0.55, $CHCl_3$); IR (neat) 3399, 2981, 2939, 1744, 1715, 1512, 1455, 1371, 1244, 1167, 1097, 1018, 989, 864, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) δ 6.08 (d, 1H, *J* = 4.3 Hz, C1H), 4.94 (t, 1H, *J* = 6.4 Hz, NH), 4.60 (dd, 1H, *J* = 1.9, 4.3 Hz, C2H), 3.79 (d, 1H, *J* = 1.9 Hz, C3H), 3.74 (s, 3H, COOMe), 3.64 (m, 2H, CβH), 3.42 (s, 3H, OMe), 1.55 (s, 3H, Me), 1.43 (s, 9H, Boc), 1.35 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 170.2, 155.7, 113.8, 106.1, 90.3, 86.9, 84.6, 79.4, 58.9, 52.4, 43.9, 28.3 (3C), 27.2, 26.7; HRMS (ESI+) *m*/*z* calcd for $C_{16}H_{27}NO_8$ (M^+ + Na) 384.1634, found 384.1625.

(3a*R*,5*S*,6*R*,6a*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-5-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*]-[1,3]dioxol-6-ol (16): Reaction of a solution of compound **15** (0.12 g, 0.28 mmol) in EtOAc (1 mL) with 10% Pd−C, as described for **14a**, gave **16** (0.09 g, 87%) as a white solid: mp 65−67 °C; $[\alpha]^{20}_D$ −22.6 (*c* 0.35, $CHCl_3$); IR (KBr) 3458, 3384, 2934, 2859, 1650, 1468, 1381, 1257, 1216, 1167, 1071, 1002, 849, 777, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) δ 5.90 (d, 1H, *J* = 3.9 Hz, C1H), 4.58 (d, 1H, *J* = 3.9 Hz, C2H), 4.40 (d, 1H, *J* = 3.5 Hz, C3H), 4.01−3.90 (m, 2H, OCH_2), 3.80−3.55 (m, 3H, OCH_2, OH), 2.81 (dd, 1H, *J* = 4.8, 8.2 Hz, OH), 1.50 (s, 3H, Me), 1.29 (s, 3H, Me), 0.91 (s, 9H, 3 × Me), 0.09 (s, 6H, 2 × Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 112.1, 105.4, 88.2, 87.5, 77.5, 67.1, 66.2, 26.7 (2C), 25.8 (3C), 18.1, −5.5 (2C); HRMS (ESI+) *m*/*z* calcd for $C_{15}H_{30}O_6Si$ (M^+ + Na) 357.1709, found 357.1703.

(*tert*-Butyl-((3a*R*,5*S*,6*R*,6a*R*)-6-methoxy-5-(methoxymethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methoxy)dimethylsilane (17) from 16: To an ice-cooled suspension of NaH (0.02 g, 0.72 mmol, 60% w/w dispersion in paraffin oil) in THF (1 mL) was added a solution of **16** (0.06 g, 0.18 mmol) in THF (1 mL) dropwise. After 15 min, MeI (0.03 mL, 0.43 mmol) was added at 0 °C and the reaction was stirred at room temperature for 2 h. The reaction mixture was then quenched with saturated aq NH_4Cl (3 mL) and extracted with EtOAc (10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), and evaporated. The crude residue obtained was purified by column chromatography (60−120 mesh Silica gel, 5% ethyl acetate in petroleum ether) to afford **17** (0.05 g, 75%) as a colorless syrup: $[\alpha]^{20}_D$ −34.2 (*c* 0.2, $CHCl_3$, 278 K); IR (neat) 2933, 2859, 1466, 1377, 1254, 1210, 1163, 1104, 1008, 841, 779, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K) δ 5.87 (d, 1H, *J* = 4.4 Hz, C1H), 4.55 (dd, 1H, *J* = 1.9, 4.4 Hz, C2H), 3.79 (d, 1H, *J* = 1.9 Hz, C3H), 3.71 (d, 1H, *J* = 9.9 Hz, OCH), 3.58 (d, 1H, *J* = 9.9 Hz, OCH′), 3.43−3.35 (m, 2H, CH_2OTBS), 3.41 (s, 3H, OMe), 3.35 (s, 3H, OMe), 1.52 (s, 3H, Me), 1.32 (s, 3H, Me), 0.91 (s, 9H, 3 × CH_3), 0.06 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 112.6, 105.1, 89.2, 86.7, 85.7, 71.9, 63.0, 59.5, 58.4, 27.3, 26.8, 25.8 (3C), 18.3, −5.4, −5.5; HRMS (ESI+) *m*/*z* calcd for $C_{17}H_{34}O_6Si$ (M^+ + Na) 385.2022, found 385.2026.

(*tert*-Butyl-((3a*R*,5*S*,6*R*,6a*R*)-6-methoxy-5-(methoxymethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methoxy)-dimethylsilane (17) from 7: To an ice cooled suspension of NaH (0.01 g, 0.57 mmol, 60% w/w dispersion in paraffin oil) in THF (1 mL) was added a solution of **7** (0.10 g, 0.29 mmol) in THF (1 mL) dropwise. After 15 min MeI (0.02 mL, 0.34 mmol) was added at 0 °C and stirred at room temperature for 2 h. It was worked up and purified as described for **17** (from **16**) to give **17** (0.08 g, 79%) as a colorless syrup, whose spectral data were identical with those of **17** prepared from **16**.

(*tert*-Butyl-((3a*R*,5*R*,6*R*,6a*R*)-6-methoxy-5-(methoxymethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methoxy)-dimethylsilane (18): To a cooled (0 °C) suspension of NaH (0.01 g, 0.46 mmol, 60% w/w dispersion in paraffin oil) in THF (1 mL) was added a solution of **8** (0.08 g, 0.23 mmol) in THF (1 mL) dropwise. After 15 min MeI (0.02 mL, 0.28) was added at 0 °C and the mixture was stirred at room temperature for 2 h. It was worked up and purified as described for **17** (from **16**) to give **18** (0.06 g, 76%) as a colorless syrup: $[\alpha]^{20}_{D}$ −15.0 (*c* 0.15, $CHCl_3$); IR (neat) 3448, 2931, 2857, 1637, 1464, 1377, 1252, 1162, 1104, 1020, 842, 777, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 295 K) δ 5.89 (d, 1H, *J* = 4.5 Hz, C1H), 4.57 (dd, 1H, *J* = 2.4, 4.5 Hz, C2H), 3.70 (d, 1H, *J* = 2.4 Hz, C3H), 3.65 (d, 1H, *J* = 10.3 Hz, OCH), 3.53 (d, 1H, *J* = 10.3 Hz, OCH′), 3.45−3.38 (m, 2H, CH_2OTBS), 3.41 (s, 3H, OMe), 3.37 (s, 3H, OMe), 1.52 (s, 3H, Me), 1.34 (s, 3H, Me), 0.90 (s, 9H, 3 × Me), 0.05 (s, 6H, 2 × Me); ^{13}C NMR (75 MHz, $CDCl_3$, 295 K) δ 113.1, 105.0, 88.8, 87.1, 86.2, 73.2, 63.2, 59.5, 58.1, 27.6, 27.4, 25.9 (3C), 18.3, −5.5, −5.6; HRMS (ESI+) *m*/*z* calcd for $C_{17}H_{34}O_6Si$ (M^+ + Na) 385.2022, found 385.2014.

Boc-(*S*)-$\beta^{2,2}$-Caa-(*S*)-$\beta^{2,2}$-Caa-OMe (2): A solution of ester **1** (0.50 g, 1.36 mmol) in MeOH (4 mL) was treated with aq 4 N NaOH solution (4 mL) at 0 °C to room temperature. After 1 h, MeOH was removed and adjusted to pH 2−3 with aq 1 N HCl solution at 0 °C and extracted with EtOAc (2 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated to give **19** (0.46 g, 96%) as a white solid, which was used for the next reaction without further purification.

A solution of **1** (0.48 g, 1.33 mmol) and CF_3COOH (0.5 mL) in CH_2Cl_2 (2 mL) was stirred at 0 °C to room temperature for 2 h. Solvent was evaporated under reduced pressure and the resulting salt **20** was dried under high vacuum and used as such for further reaction.

A solution of **19** (0.46 g, 1.33 mmol), HOBt (0.22 g, 1.59 mmol), and EDCI (0.31 g, 1.59 mmol) in dry CH_2Cl_2 (6 mL) was stirred at 0 °C for 15 min and treated with the above obtained salt **20** and DIPEA (0.34 mL, 1.99 mmol) under nitrogen atmosphere for 5 h. The reaction mixture was quenched with satd aq NH_4Cl (10 mL) at 0 °C and diluted with $CHCl_3$ (20 mL). It was sequentially washed with 1 N HCl (10 mL), water (10 mL), and aq NaCl solution (10 mL). The organic layer was dried (Na_2SO_4) and evaporated to give the residue, which was purified by column chromatography (60−120 mesh Silica gel, 50% ethyl acetate in petroleum ether) to afford **2** (0.57 g, 73%) as a white solid: mp 63−65 °C; $[\alpha]^{20}_{D}$ −156.0 (*c* 0.1 in $CHCl_3$); IR (KBr) ν 3434, 2928, 2853, 1717, 1682, 1521, 1376, 1244, 1165, 1117, 1017, 863 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.07 (t, 1H, *J* = 6.3 Hz, NH(2)), 6.18 (d, 1H, *J* = 4.0 Hz, C1H(2)), 5.98 (d, 1H, *J* = 3.9 Hz, C1H(1)), 5.15 (dd, 1H, *J* = 2.6, 8.1 Hz, NH(1)), 4.67 (d, 1H, *J* = 4.0 Hz, C2H(2)), 4.58 (d, 1H, *J* = 3.9 Hz, C2H(1)), 3.98 (dd, 1H, *J* = 8.1, 13.3 Hz, CβH(1)), 3.90 (dd, 1H, *J* = 6.3, 13.2 Hz, CβH(2)), 3.88 (s, 1H, C3H(1)), 3.83 (s, 1H, C3H(2)), 3.81 (dd, 1H, *J* = 6.3, 13.2 Hz, Cβ'H(2)), 3.76 (s, 3H, COOMe), 3.43 (dd, 1H, *J* = 2.6, 13.3 Hz, Cβ'H(1)), 3.42 (s, 3H, OMe), 3.41 (s, 3H, OMe), 1.61 (s, 3H, Me), 1.55 (s, 3H, Me), 1.43 (s, 9H, Boc), 1.38 (s, 3H, Me), 1.32 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.3, 169.3, 155.6, 114.2, 113.0, 106.1, 105.9, 91.6, 89.4, 86.6, 85.5, 85.4, 85.2, 82.7, 79.1, 59.1, 59.0, 58.6, 52.5, 44.1, 41.9, 29.7, 26.1, 26.0, 25.6, 25.4; HRMS (ESI+) *m*/*z* calcd for $C_{26}H_{42}N_2O_{13}$ (M^+ + Na) 613.2584, found 613.2578.

Boc-(*S*)-$\beta^{2,2}$-Caa-(*S*)-$\beta^{2,2}$-Caa-(*S*)-$\beta^{2,2}$-Caa-(*S*)-$\beta^{2,2}$-Caa-OMe (3): A solution of **2** (0.20 g, 0.34 mmol), as described for **19**, gave **21** (0.18 g, 94%) as a white solid, which was used for further reaction.

A solution of **2** (0.19 g, 0.31 mmol) and CF_3COOH (0.2 mL) in CH_2Cl_2 (1 mL) as described for **20** afforded the salt **22**, which was dried under high vacuum and used as such for further reaction.

A solution of **21** (0.18 g, 0.31 mmol), HOBt (0.05 g, 0.37 mmol), and EDCI (0.07 g, 0.37 mmol) in dry CH_2Cl_2 (4 mL) was stirred at 0 °C for 15 min and treated with the above obtained salt **22** and DIPEA (0.08 mL, 0.47 mmol) under nitrogen atmosphere for 5 h. Workup as described for **2** and purification by column chromatography (60−120 mesh Silica gel, 1.7% CH_3OH in $CHCl_3$) afforded **3** (0.22 g, 66%) as a white solid: mp 96−98 °C; $[\alpha]^{20}_{D}$ −27.7 (*c* 0.3 in $CHCl_3$); IR (KBr) ν 3427, 2932, 1682, 1522, 1379, 1251, 1109, 1021, 859 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.59 (dd, 1H, *J* = 1.8, 8.6 Hz, NH(2)), 7.40 (dd, 1H, *J* = 1.9, 8.0 Hz, NH(3)), 7.06 (t, 1H, *J* = 5.8 Hz, NH(4)), 6.18 (d, 1H, *J* = 3.9 Hz, C1H(4)), 6.07 (d, 1H, *J* = 3.9 Hz, C1H(1)), 6.06 (d, 1H, *J* = 3.9 Hz, C1H(2)), 5.98 (d, 1H, *J* = 3.9 Hz, C1H(3)), 5.47 (dd, 1H, *J* = 2.8, 8.5 Hz, NH(1)), 4.68 (d, 1H, *J* = 3.9 Hz, C2H(4)), 4.58 (d, 1H, *J* = 3.9 Hz, C2H(1)), 4.57 (d, 1H, *J* = 3.9 Hz, C2H(3)), 4.56 (d, 1H, *J* = 3.9 Hz, C2H(2)), 4.17 (dd, 1H, *J* = 8.6, 14.1 Hz, CβH(2)), 4.15 (dd, 1H, *J* = 8.0, 13.8 Hz, CβH(3)), 3.98 (dd, 1H, *J* = 5.8, 14.2 Hz, CβH(4)), 3.94 (dd, 1H, *J* = 8.5, 13.8 Hz, CβH(1)), 3.89 (s, 1H, C3H(1)), 3.88 (s, 1H, C3H(3)), 3.84 (s, 1H, C3H(2)), 3.83 (s, 1H, C3H(4)), 3.72 (dd, 1H, *J* = 5.8, 14.2 Hz, Cβ'H(4)), 3.70 (s, 3H, COOMe), 3.43 (dd, 1H, *J* = 2.8, 13.8 Hz, Cβ'H(1)), 3.42 (s, 6H, 2 × OMe), 3.40 (dd, 1H, *J* = 1.9, 13.8 Hz, Cβ'H(3)), 3.38 (s, 3H, OMe), 3.37 (s, 3H, OMe), 3.36 (dd, 1H, *J* = 1.8, 14.1 Hz, Cβ'H(2)), 1.63 (s, 3H, Me), 1.61 (s, 3H, Me), 1.60 (s, 3H, Me), 1.54 (s, 3H, Me), 1.43 (s, 9H, Boc), 1.37 (s, 3H, Me), 1.31 (s, 6H, 2 × Me), 1.29 (s, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$, 278 K) δ 170.2, 169.4, 169.2, 168.9, 155.7, 114.2, 113.0, 112.9, 112.7, 106.3, 106.2, 106.1, 105.9, 96.0, 91.3, 90.7, 90.6, 89.4, 89.3, 86.1, 85.5, 85.3, 85.1, 85.0, 83.0, 82.9, 82.4, 78.9, 59.1, 59.0, 58.8, 58.5, 52.6, 44.3, 42.5, 42.4, 41.5, 29.7, 27.3, 27.2, 26.9, 26.1, 25.9, 25.8, 25.7, 25.6; HRMS (ESI+) *m*/*z* calcd for $C_{46}H_{72}N_4O_{23}$ (M^+ + Na) 1071.4485, found 1071.4531.

Boc-(*S*)-$\beta^{2,2}$-Caa-(*S*)-$\beta^{2,2}$-Caa-(*S*)-$\beta^{2,2}$-Caa-(*S*)-$\beta^{2,2}$-Caa-(*S*)-$\beta^{2,2}$-Caa-(*S*)-$\beta^{2,2}$-Caa-OMe (4): A solution of **3** (0.12 g, 0.12 mmol), as described for **19** gave **23** (0.11 g, 91%) as a white solid. To a solution of **23** (0.10 g, 0.10 mmol), HOBt (0.02 g, 0.12 mmol) and EDCI (0.02 g, 0.12 mmol) in dry CH_2Cl_2 (3 mL) was added salt **22** [prepared from **2** (0.06 g, 0.10 mmol) and CF_3COOH (0.1 mL) in CH_2Cl_2 (1 mL)] and the reaction was stirred at room temperature for 5 h. Workup as described for **2** and purification by column chromatography (60−120 mesh Silica gel, 2.1% CH_3OH in $CHCl_3$) furnished **4** (0.08 g, 53%) as a white solid: mp 124−126 °C; $[\alpha]^{20}_{D}$ −215.1 (*c* 0.2, $CHCl_3$); IR (KBr) ν 3429, 2987, 2939, 2838, 1684, 1517, 1381, 1214, 1111, 1070, 1018, 855 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.73 (dd, 1H, *J* = 1.6, 8.8 Hz, NH(2)), 7.63 (dd, 1H, *J* = 1.3, 8.8 Hz, NH(5)), 7.60 (dd, 1H, *J* = 1.5, 8.6 Hz, NH(3)), 7.46 (dd, 1H, *J* = 2.1, 7.9 Hz, NH(4)), 7.09 (t, 1H, *J* = 6.1 Hz, NH(6)), 6.19 (d, 1H, *J* = 4.2 Hz, C1H(6)), 6.08 (m, 1H, C1H(1)), 6.08 (m, 1H, C1H(2)), 6.08 (m, 1H, C1H(3)), 6.08 (m, 1H, C1H(4)), 5.97 (d, 1H, *J* = 4.0 Hz, C1H(5)), 5.49 (dd, 1H, *J* = 2.1, 8.8, NH(1)), 4.67 (dd, 1H, *J* = 1.2, 4.2 Hz, C2H(6)), 4.58 (m, 1H, C2H(1)), 4.58 (m, 1H, C2H(2)), 4.58 (m, 1H, C2H(3)), 4.58 (m, 1H, C2H(5)), 4.57 (d, 1H, *J* = 3.9 Hz, C2H(4)), 4.22 (dd, 1H, *J* = 8.8, 13.9 Hz, CβH(5)), 4.21 (dd, 1H, *J* = 8.8, 13.7 Hz, CβH(2)), 4.19 (dd, 1H, *J* = 8.6, 13.8 Hz, CβH(3)), 4.15 (dd, 1H, *J* = 7.9, 13.7 Hz, CβH(4)), 3.97 (dd, 1H, *J* = 6.1, 13.8 Hz, CβH(6)), 3.95 (dd, 1H, *J* = 8.8, 13.9 Hz, CβH(1)), 3.91 (s, 1H, C3H(4)), 3.89 (s, 1H, C3H(1)), 3.87 (s, 1H, C3H(3)), 3.86 (s, 1H, C3H(2)), 3.85 (s, 1H, C3H(5)), 3.83 (d, 1H, *J* = 1.2 Hz, C3H(6)), 3.76 (s, 3H, COOMe), 3.74 (dd, 1H, *J* = 6.1, 13.8 Hz, Cβ'H(6)), 3.44 (dd, 1H, *J* = 2.3, 13.9 Hz, Cβ'H(1)), 3.42 (s, 3H, OMe), 3.41 (s, 3H, OMe), 3.39 (dd, 1H, *J* = 2.1, 13.7 Hz, Cβ'H(4)), 3.38 (s, 6H, 2 × OMe), 3.37 (s, 3H, OMe), 3.36 (dd, 1H, *J* = 1.3, 13.9 Hz, Cβ'H(5)),

3.36 (s, 3H, OMe), 3.35 (dd, 1H, J = 1.6, 13.7 Hz, Cβ'H(2)), 3.34 (dd, 1H, J = 1.5, 13.8 Hz, Cβ'H(3)), 1.62 (s, 6H, 2 × Me), 1.59 (s, 9H, 3 × Me), 1.54 (s, 3H, Me), 1.43 (s, 9H, Boc), 1.37 (s, 3H, Me), 1.30 (s, 6H, 2 × Me), 1.29 (s, 6H, 2 × Me), 1.28 (s, 3H, Me); ^{13}C NMR (150 MHz, $CDCl_3$, 278 K) δ 170.3, 169.7, 169.3, 169.2, 169.1, 168.9, 155.8, 114.3, 113.2, 113.0, 112.9, 112.8, 112.7, 106.4, 106.3, 106.2, 106.1, 105.9, 105.8, 91.4, 91.3 90.9, 90.8, 90.7, 89.4, 86.3, 85.6, 85.5, 85.4, 85.3, 85.2, 85.1, 83.3, 83.2, 83.1, 83.0, 82.6, 78.9, 59.2, 59.1, 59.0, 58.8, 58.6, 52.6, 44.5, 44.2, 42.8, 42.7, 41.7, 41.6, 29.7, 29.6, 29.5, 28.4, 28.3, 27.4, 27.3, 27.2, 27.0, 26.1, 26.0, 25.9, 25.8, 25.7, 25.6, 25.4; HRMS (ESI+) m/z calcd for $C_{66}H_{102}N_6O_{33}$ (M^+ + Na) 1529.6385, found 1529.6398.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra, solvent titration plots, and distance constraints used in MD calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) See the Supporting Information.

(22) Solvent titration studies were carried out by sequentially adding up to 300 μL of DMSO-d_6 to 600 μL of $CDCl_3$ solutions of the peptides.

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