Synthesis and Conformational Studies of Peptidomimetics Containing Furanoid Sugar Amino Acids and a Sugar Diacid

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Furanoid sugar amino acids (**1**) were synthesized and used as dipeptide isosteres to induce interesting turn structures in small linear peptides. They belong to a new variety of designed hybrid structures that carry both amino and carboxyl groups on rigid furanose sugar rings. Four such molecules, 6-amino-2,5-anhydro-6-deoxy-D-gluconic acid (**3**, Gaa) and its mannonic (**4**, Maa), idonic (**5**, Iaa), and a 3,4-dideoxyidonic (**6**, ddIaa) congeners were synthesized. The synthesis followed a novel reaction path in which an intramolecular 5-*exo* S_N2 opening of the hexose-derived terminal aziridine ring in **2** by the γ-benzyloxy oxygen with concomitant debenzylation occurred during pyridinium dichromate oxidation of the primary δ-hydroxyl group to carboxyl function, leading to the formation of furanoid sugar amino acid frameworks in a single step. Incorporation of these furanoid sugar amino acids into Leu-enkephalin replacing its Gly-Gly portion gave analogues **8**−**11**. Detailed structural analysis of these molecules by circular dichroism (CD) and various NMR techniques in combination with constrained molecular dynamics (MD) simulations revealed that two of these analogues, **8a** and **10a**, have folded conformations composed of an unusual nine-membered pseudo β-turn-like structure with a strong intramolecular H-bond between LeuNH → sugarC3-OH. This, in turn, brings the two aromatic rings of Tyr and Phe in close proximity, a prerequisite for biological activities of opioid peptides. The analgesic activities of **8a**,**b** determined by mouse hot-plate and tail-clip methods were similar to that of Leu-enkephalin methyl ester. The syn disposition of the β-hydroxycarboxyl motif on the sugar rings appears to be the driving force to nucleate the observed turn structures in some of these molecules (**8** and **10**). Repetition of the motif on both sides of a furanose ring resulted in a novel molecular design of sugar diacid, 2,5-anhydro-D-idaric acid (**7**, Idac). Bidirectional elongation of the diacid moieties of **7** with identical peptide strands led to the formation of a C_2-symmetric reverse-turn mimetic **12** which displayed a very ordered structure consisting of identical intramolecular H-bonds at two ends between LeuNH → sugar-OH, the same as in **8** and **10**.

Introduction

Despite an exponential growth in the number of reports on the development of constrained non-peptide scaffolds as peptidomimetics,[1] very few peptide-based drugs have been developed,[2] necessitating an overhaul in the existing design principles. Newer concepts are emerging where the fundamental building blocks used by nature, such as amino acids, sugars, and nucleosides, are amalgamated to produce nature-like, and yet unnatural, de novo structural entities with multifunctional groups anchored on a single ensemble.[3] One such hybrid design is represented by a class of compounds called sugar amino acids (Saa).[4] These are carbohydrate molecules bearing both amino and carboxyl functional groups on the regular

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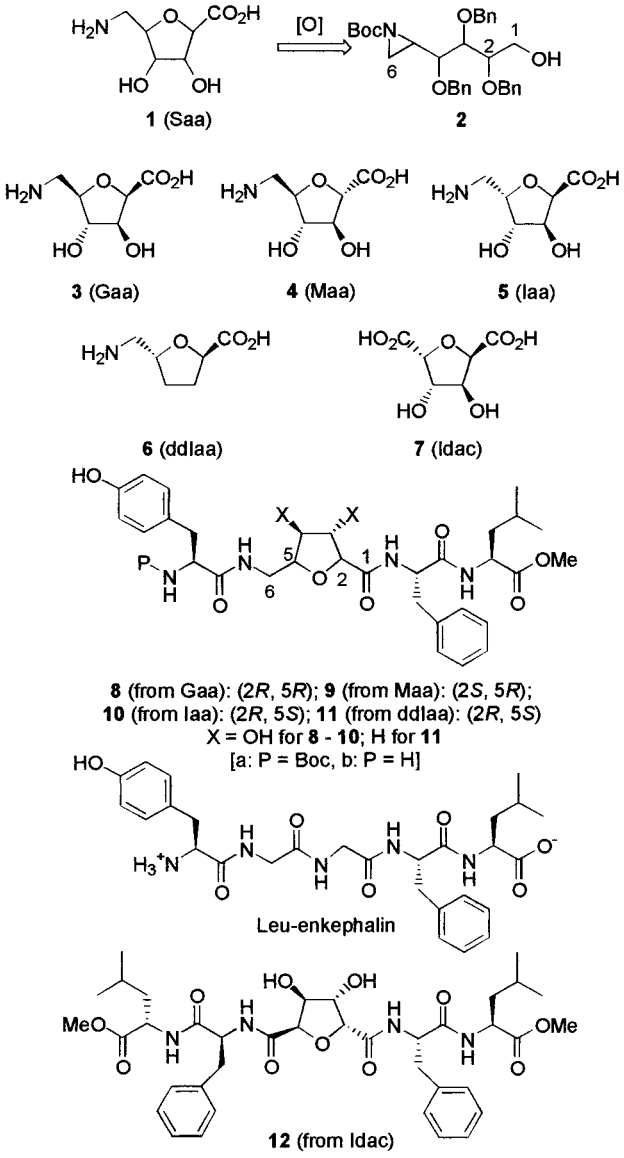
sugar framework. The rigid furan or pyran rings of these molecules make them ideal candidates as non-peptide scaffolds in peptidomimetics where they can be easily incorporated by using their carboxyl and amino termini. Sugar amino acids exist in nature in the form of neuraminic and muramic acids as cell wall components[5] and also in some natural products.[6] In recent years they have been used as novel monomeric entities in the developments of sequenceamers and foldamers[3g,i,4c−h,k] and as dipeptide isosteres in peptidomimetics.[4a,i−j,m] The diversity of sugar molecules can be exploited to create a combinatorial library of sugar amino acid based molecular frameworks predisposed to fold into architecturally beautiful, ordered structures which may also have interesting properties. The protected/unprotected hydroxyl groups of sugar rings can also influence the hydrophobic/hydrophilic nature of such molecular assemblies.

Recently, we have communicated the synthesis of furanoid sugar amino acids **1** from the hexose-derived substrate **2**, involving an unusual intramolecular 5-*exo* opening of the terminal aziridine ring of **2** by the γ-benzyloxy oxygen with concomitant debenzylation during pyridinium dichromate (PDC) oxidation of the primary δ-hydroxyl group.[4i] Complete stereocontrol was achieved in this electrophile-activated S_N2 opening of the aziridine ring under remarkably mild conditions. The method was followed to synthesize 6-amino-2,5-anhydro-6-deoxy-D-gluconic acid (**3**, Gaa) and its mannonic congener (**4**, Maa).[7]

The rigid frameworks of these furanoid sugar amino acids prompted us to use them as dipeptide isosteres in peptidomimetic studies. These molecules with constrained backbone angles, ω_i and φ_{i+1}, were expected to induce folded conformations in linear peptides. To verify this, it was decided to incorporate them into Leu-enkephalin, chosen as a representative example of a short peptide, replacing its Gly-Gly spacer segment that is known to be flexible and amenable to different conformations depending on the binding environment.[8] Structure−activity relationship studies have revealed that in enkephalins the C-terminal "address" segment stabilizes specific bioactive conformations of the N-terminal "message" segment, Tyr-Gly-Gly-Phe, in which the two pharmacophoric residues, Tyr and Phe, come close to each other.[8a,9] This happens when enkephalins interact with lipid bilayer membranes in which opioid receptors are located, and it is this membrane-bound conformation that is suggested to be essential for biological activity.[10] Many potent δ-receptor-selective opioid antagonists, based on the N-terminal message domain of the enkephalins, contain at least two aromatic residues in close proximity having approximate parallel orientation of the aromatic rings.[11]



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To determine whether furanoid sugar amino acids can bring the aromatic pharmacophoric residues into close proximity or not, these templates were inserted into Leu-enkephalin in its Gly-Gly segment giving peptidomimetic analogues **8** and **9**. One of these analogues, Boc-Tyr-Gaa-Phe-Leu-OMe (**8a**) showed a nine-membered β-turn-like ring structure involving H-bonding between LeuNH → sugarC3-OH determined by CD and detailed structural studies by NMR.[4i] This structure has a very strong resemblance to the conformation of the natural peptide bound to the cell surface δ-receptor. The analgesic activities of **8a**,**b** were found to be similar to that of Leu-enkephalin by mouse hot-plate and tail-clip tests. The Maa-containing analogues showed less activity.

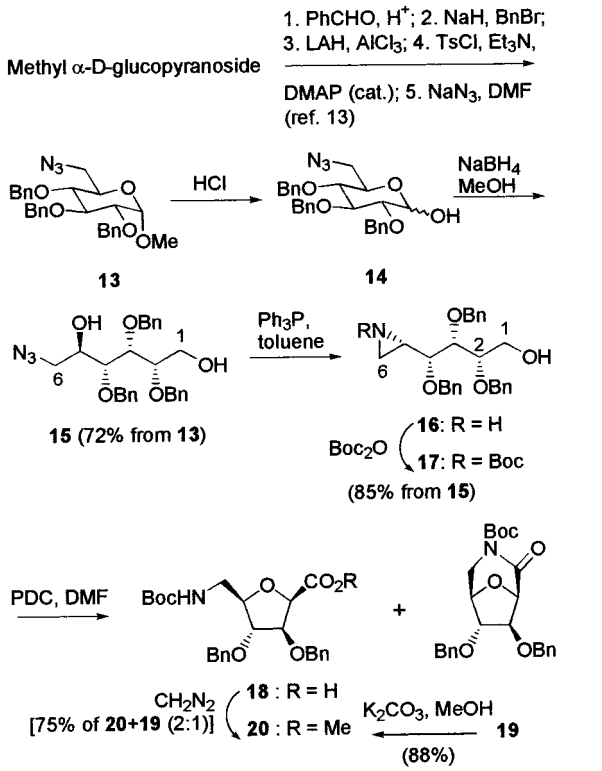
In this paper, we present the details of the above-mentioned syntheses as well as structural and biological studies. This paper also includes the synthesis of two new furanoid sugar amino acids, 6-amino-2,5-anhydro-6-deoxy-D-idonic acid (**5**, Iaa) and its 3,4-dideoxy congener **6** (ddIaa) and their incorporation in Leu-enkephalin giving peptidomimetics **10a** and **11a**. Structural studies revealed that the Iaa-containing peptidomimetic **10a** exhibited similar, but somewhat less prominent, turn structure as it was seen in **8a**, whereas dideoxy sugar amino acid **7** did not induce any significant turn in **11a**. Compounds **10a** and **11a** showed reduced analgesic activities. Careful investigations of the 3-D structures of these enkephalin analogues **8**−**11** eventually led to the identification of a *cis*-β-hydroxycarboxyl moiety anchored on a five-membered ring as the essential structural motif whose presence in some of these analogues was responsible for their folded conformations. Designing a logical structural exploitation of this motif, a novel C_2-symmetric reverse-turn molecular scaffold of a sugar diacid, 2,5-anhydro-D-idaric acid (**7**, Idac), was synthesized for the first time. Attachment of identical peptide strands to the carboxyl groups of **7** resulted in the formation of a C_2-symmetric reverse-turn mimetic **12**. The two *cis*-β-hydroxycarboxyl moieties appropriately anchored on two sides of the scaffold were expected to nucleate identical β-turn-like structures at both ends involving intramolecular H-bonding, as observed earlier, between amideNH → sugar-OH. The conformational studies of the peptidomimetics **8**−**12** were carried out by circular dichroism (CD) spectra and various NMR techniques in combination with distance geometry calculations that was subsequently used in constrained molecular dynamic (MD) simulations to derive energy-minimized structures. The aim of our present study is to project furanoid sugar amino acids and sugar diacids as novel class of rigid structural templates capable of instilling defined secondary structures in small linear peptides.

Results

Syntheses of Sugar Amino Acids. On the basis of the known susceptibility of linear molecules having S_N2 active sites to undergo spontaneous ring-closure, induced by heteroatom at the γ-position to produce thermodynamically favorable five-membered cyclic product,[12] we envisaged that a terminal aziridine ring could be opened regio- and stereoselectively by a γ-hydroxy group, to build the tetrahydrofuran ring of our targeted sugar amino acids. The hexose-derived aziridinyl compound **2** was chosen as an ideally functionalized intermediate where oxidation of the primary C1-hydroxyl group and the aziridine ring opening by C2-oxygen would lead to the formation of carboxyl and amino termini, respectively, anchored on the resulting tetrahydrofuran framework. It was also conceived that a double inversion at C5 position, first during the aziridine ring formation and second during its opening, would ensure the synthesis of any sugar amino acid using its corresponding hexose as the starting material, e.g., glucose for Gaa (**3**), mannose for Maa (**4**), etc.

The actual synthesis is depicted in Scheme 1. The starting material for Gaa (**3**) was methyl 6-deoxy-6-azido-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**13**) which was prepared from methyl α-D-glucopyranoside in five simple steps according to the reported procedure.[13] Acid hydrolysis of the methyl pyranoside **13** was followed by opening of the ring by borohydride reduction to furnish the intermediate diol **15** in 72% yield. Treatment of **15** with triphenylphosphine in refluxing toluene led to the formation of the aziridinyl compound **16**, which was protected in situ with Boc_2O to give the target intermediate **17** in 85% yield. The aziridine formation followed an S_N2 mechanism executing the first inversion at C5 position.

Scheme 1. Synthesis of Methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-gluconate (20)



The stage was now set to try out the crucial cyclization step. Our initial plan was to oxidize first the primary hydroxyl group, followed by deprotection of benzyl groups by hydrogenation before the cycloetherification could be carried out. Accordingly, the Boc-protected aziridinyl intermediate **17** was treated with an excess of PDC (5

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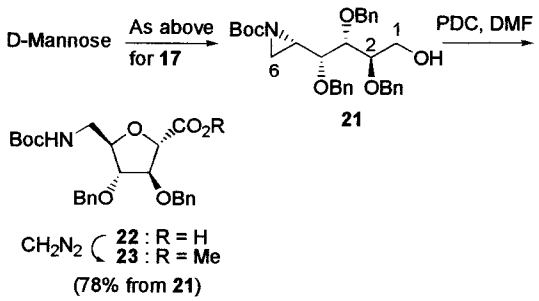
molar equivalents) in DMF as solvent, leading to the formation of two products, **18** and **19**. After workup, the crude mixture was treated with diazomethane in ether. Chromatographic purification at this stage gave two compounds, unchanged **19**, as shown by TLC, and **20**, presumably the ester of **18**, in ca. 1:2 ratio, with a combined yield of about 75%. The ^{1}H NMR spectrum of major product **20** in $CDCl_3$ showed, besides other peaks, one signal at δ 5.3 characteristic of a Boc-protected-NH and the loss of one benzyl group. Careful analysis of all the spectroscopic data for the minor product established its structure as **19**. Treatment of **19** with anhydrous K_2CO_3 in MeOH converted it to **20**, increasing its overall yield to 72% from **17**. It is noteworthy that the crucial cyclization reaction took place concomitantly during the oxidation step under remarkably mild conditions involving the intramolecular 5-*exo* S_N2 opening of the aziridine ring by γ-oxygen as planned previously with simultaneous loss of its benzyl protective group. Smooth transformation of the linear molecule **17** into the cyclic sugar amino acid **18** in one step under mild oxidative conditions is the essence of our methodology.

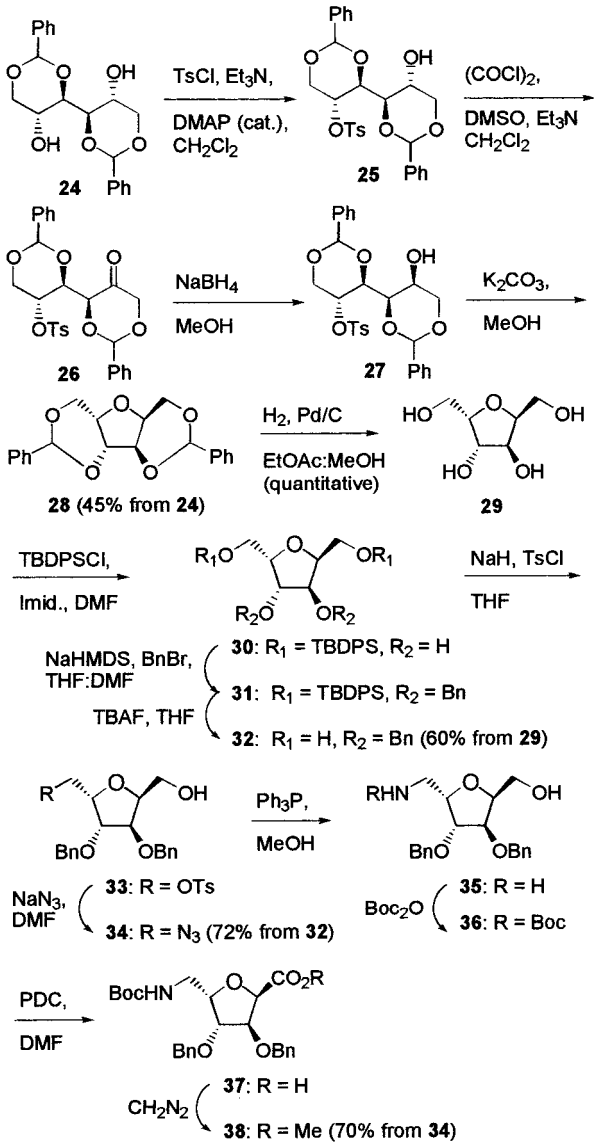
Similar oxidative rearrangement of **21** (Scheme 2), prepared from D-mannose following the same route as outlined for **17**, furnished the expected mannonate **23** as the only product in 78% yield. In this case, the "2,5-trans" geometry in the furanoid framework prevented the formation of "**19**-type" bicyclic product.

Scheme 2. Synthesis of Methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-mannonate (23)



Because of the high cost of D-idose, an alternate route was followed for the synthesis of Iaa, i.e., 6-amino-2,5-anhydro-6-deoxy-D-idonic acid (**5**) where D-mannitol was used as the starting material. Scheme 3 outlines the synthesis. Monotosylation of 1,3:4,6-di-*O*-benzylidene-D-mannitol (**24**) gave **25** which was followed by Swern oxidation of the remaining hydroxyl group leading to a keto intermediate **26**. Excellent diastereoselectivity was achieved in the reduction of **26** by sodium borohydride to get the D-glucitol derivative **27** as the major product in ca. 6:1 ratio. The mixture itself was subjected to a base-catalyzed intramolecular ring-closure reaction in which only the D-glucitol derivative **27** underwent cycloetherification with S_N2 type inversion at the tosylate center giving the desired D-iditol framework **28**, in 45% overall yield in four steps starting from **24**. The minor D-mannitol derivative failed to cyclize due to structural constraints, making it easier to purify **28** by chromatography. Removal of the benzylidene protections by hydrogenation gave quantitative yield of the known[14] tetrol **29**, the spectroscopic data of which were in all aspects identical with reported values. Routine functional group manipulations transformed **29** into the 2,5-anhydro-3,4-

Scheme 3. Synthesis of Methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-idonate (38)



di-*O*-benzyl-D-iditol (**32**) in three steps in 60% overall yield. One of the primary hydroxyls of **32** was tosylated and then treated with NaN_3 to give the azido derivative **34**, in 72% yield from **32**. Reduction of the azido group converted it to the amine **35** that was protected in situ with Boc_2O to get the intermediate **36**. Finally, PDC oxidation of the remaining hydroxyl of **36**, followed by treatment with CH_2N_2 resulted in the formation of the protected Iaa **38**, in 70% yield from **34**.

For the synthesis of the 3,4-dideoxy congener **6** of Iaa (Scheme 4), the starting material chosen was **28** of Scheme 3. Opening of the benzylidene rings of **28** gave selectively primary *O*-benzylated diol **39** as the major product in 60% yield. Treatment of **39** with Ph_3P/I_2/imidazole led to the formation of an olefin intermediate **40** in 62% yield that was hydrogenated to get the 2,5-anhydro-3,4-dideoxy-1,6-diol framework **41**, prepared earlier by resolution methods.[15] Conversion of **41** to the

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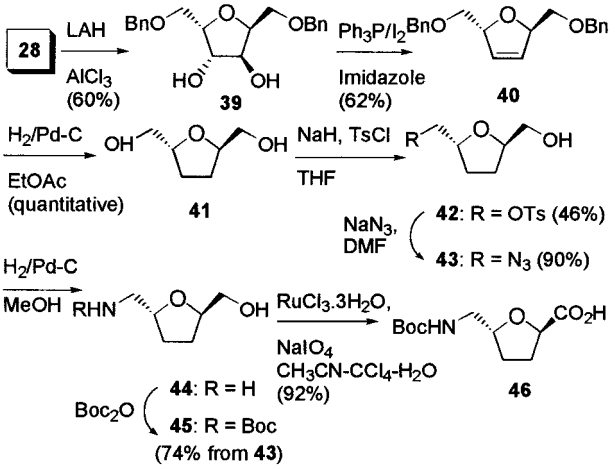
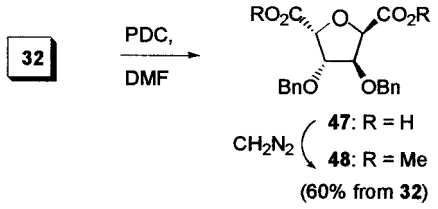
Scheme 4. Synthesis of *N*-Boc-6-amino-2,5-anhydro-3,4,6-trideoxy-D-idonic Acid (46)



N-Boc-protected ddIaa **46** followed the same route described above for the synthesis of **38** from **32**. Monotosylation of **41** gave **42**, in 46% yield from **40**, from which the azido compound **43** was made (90% yield). Transformation of **43** to the Boc-protected amine **45** was carried out in two steps (yield 74%): hydrogenation and in-situ Boc-protection. Finally, **45** was oxidized using $RuCl_3 \cdot 3H_2O/NaIO_4$ to get the dideoxy sugar amino acid **46**, in 92% yield, which was used directly in the subsequent peptide coupling step.

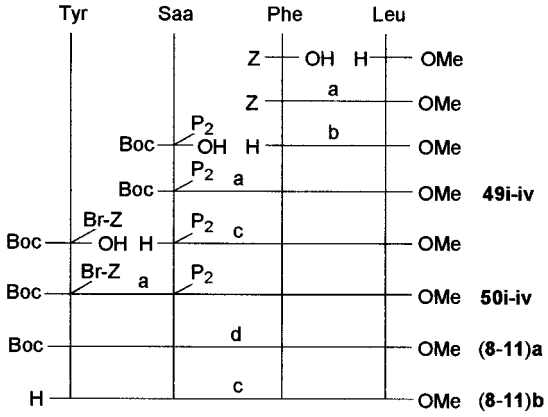
The 2,5-anhydro-3,4-di-*O*-benzyl-D-iditol (**32**) of Scheme 3 served as the starting material for the synthesis of Idac **7**. Oxidation of **32** with an excess of PDC in DMF gave the diacid **47** (Scheme 5) which was treated with CH_2N_2 in ether, for easy purification, to get the dimethyl ester of 2,5-anhydro-3,4-di-*O*-benzyl-D-idaric acid (**48**) in 60% yield (from **32**).

Scheme 5. Synthesis of 2,5-anhydro-3,4-di-*O*-benzyl-D-idaric Acid Dimethyl Ester (48)



Synthesis of the Peptidomimetics. All the peptidomimetic molecules were synthesized by standard solution methods using 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) as coupling agents and amine-free dry DMF and/or dry CH_2Cl_2 as solvent. The protocol followed for the synthesis of the enkephalin analogues **8**−**11** is depicted in Scheme 6. Reaction of Boc-Gaa(Bn_2)-OH (**18**), prepared from the ester **20** by simple saponification, with H_2N-Phe-Leu-OMe gave the protected peptide Boc-Gaa(Bn_2)-Phe-Leu-OMe (**49i**), which was deprotected at the N-terminus with trifluoroacetic acid (TFA) in dichloromethane and subsequently coupled with Boc-Tyr(Br-Z)-OH to give Boc-Tyr(Br-Z)-Gaa(Bn_2)-Phe-Leu-OMe (**50i**).

Scheme 6. Synthesis of Enkephalin Analogues 8−11



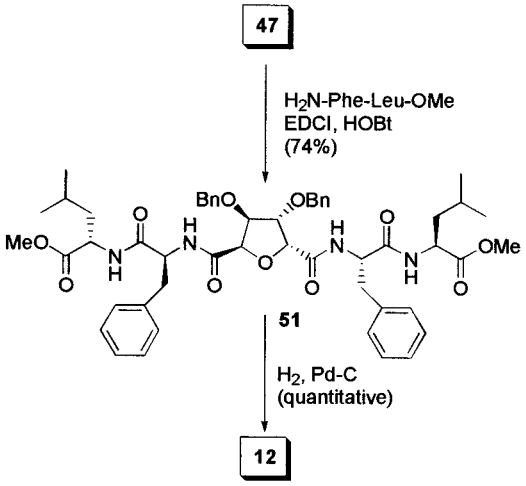
Saa = i) Gaa (**3**), ii) Maa (**4**), iii) Iaa (**5**), or iv) ddIaa (**6**)
P = Bn for **3** - **5**; no side chain for **6**

a = EDCI/HOBt; b = H_2, Pd/C; c = TFA/CH_2Cl_2; d = H_2, $Pd(OH)_2$/C

Finally, hydrogenation using $H_2/Pd(OH)_2$−C in EtOAc yielded the side-chain deprotected compound Boc-Tyr-Gaa-Phe-Leu-OMe (**8a**). A similar reaction sequence starting with Boc-protected sugar amino acids **22**, **37**, and **46** led to the formation of their corresponding enkephalin analogues, **9a**, **10a**, and **11a**, respectively.

For the synthesis of the reverse-turn mimetic **12** (Scheme 7), the dibenzyl derivative of idaric acid (**47**), prepared from the diester **48** by saponification, was reacted with an excess of H_2N-Phe-Leu-OMe under the coupling conditions described in Scheme 6 to get the coupled product **51** in 74% yield. Hydrogenation of **51** gave a quantitative yield of the target molecule **12**.

Scheme 7. Synthesis of Reverse-turn Mimetic 12



Conformational Analysis. Circular Dichroism Studies. The conformational analysis of the peptidomimetics **8**−**12** were carried out by studying their circular dichroism (CD) spectra in trifluoroethanol (TFE). The CD spectrum of **8a** having a "2,5-cis" geometry in the sugar amino acid exhibits a strong positive band at 216 nm (Figure 1) characteristic of a type II β-turn.[16] The corresponding deprotected peptide H_2N-Tyr-Gaa-Phe-

(15) (a) Naemura, K.; Fukuda, R.; Takahashi, N.; Konishi, M.; Hirose, Y.; Tobe, Y. *Tetrahedron Asymmetry* **1993**, *4*, 911−918. (b) Naemura, K.; Ebashi, I.; Matsuda, A. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3057−3058. (c) Nakazaki, M.; Naemura, K.; Makimura, M.; Matsuda, A.; Kawano, T.; Ohta, Y. *J. Org. Chem.* **1982**, *47*, 2429−2435.

(16) Woody, R. W. In *The Peptides: Analysis, Synthesis, Biology*; Udenfriend, S. J., Meienhofer, J., Hruby, V. J., Eds.; Academic Press: New York, 1985; Vol. 7, pp 15−114.

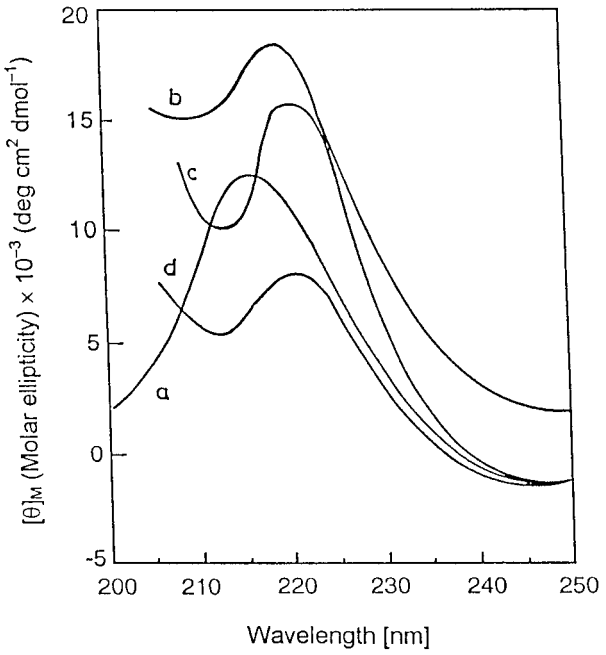


Figure 1. CD spectra (in TFE) of **8a** (a), **8b** (b), **9a** (c), and **9b** (d).

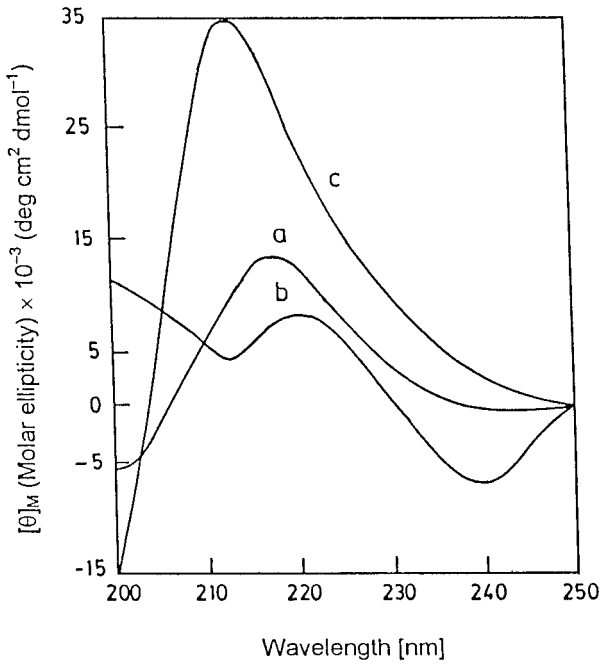


Figure 2. CD spectra (in TFE) of **10a** (a), **11a** (b), and **12** (c).

Leu-OMe (**8b**) also shows a positive band although of reduced ellipticity at ~217 nm. The spectra of the Maa-containing analogues, both protected (**9a**) and deprotected H_2N-Tyr-Maa-Phe-Leu-OMe (**9b**), indicate a lower tendency to form turn structures. The CD spectra of **10a**, **11a**, and **12** are shown in Figure 2. While **10a** shows a positive band at ~218 nm, the spectrum of **11a** indicates the absence of any prominent structure. Of all the substrates studied here, the most ordered structure is observed in the CD spectrum of the reverse turn mimetic **12** with a very strong positive band of high ellipticity at ~212 nm, indicating the presence of a very predominant β-turn structure in the molecule.

Conformational Analysis. NMR Studies. The NMR spectra of the peptides described here are quite well resolved, and most of the spectral parameters could be obtained and are reported in the Tables 1−6. The cross-peak intensities in the NOESY and ROESY spectra were used for obtaining the restraints in the MD calculations. The cross-peak intensities were semiqualitatively characterized as strong, medium, weak, and very weak, corresponding to internuclear distances in the range of 2.0−2.7 Å, 2.0−3.3 Å, 2.0−4.0 Å, and 2.0−5.0 Å, respectively. The temperature coefficient of amide proton chemical shift ($\Delta\delta/\Delta T$) is a measure of their involvement in the hydrogen bonding. Most of the amide protons, leaving apart the LeuNH in some of the peptides, showed a large magnitude of temperature coefficients.

The $^3J_{HN\alpha H}$ are large (>8 Hz) for Phe and Tyr residues, whereas for Leu residues they are between 7 and 8 Hz. This corresponds to a value of φ in the vicinity of −120°. The existence of a complete set of sequential CαH-NH NOE connectivities, wherever possible, implies propensity of structures with large population of conformers in the β-region of the $\varphi-\psi$ space (φ = −180° to −60° and ψ = 60° to 180°). However, observation of weak NH−NH

Table 1. ^{1}H Chemical Shifts (δ) in ppm, Coupling Constants (J) in Hz, and Temperature Coefficients ($\Delta\delta/\Delta T$, in ppb/K) of the Amide Protons of 8a (500 MHz, DMSO-d_6)

protons	Tyr	Phe	Leu
NH	6.89 (d) $J_{NH-\alpha H}$ = 8.7	8.41 (d) $J_{NH-\alpha H}$ = 9.3	7.93 (d) $J_{NH-\alpha H}$ = 7.3
CαH	4.04 (ddd)	4.60 (ddd)	4.24 (ddd)
Cβ*H*(*pro-S*)	2.82 (dd) $J_{\alpha-\beta(pro-S)}$ = 4.4	3.36 (dd) $J_{\alpha-\beta(pro-S)}$ = 3.1	1.43 (ddd) $J_{\alpha-\beta(pro-S)}$ = 4.6
Cβ*H*(*pro-R*)	2.64 (dd) $J_{\alpha-\beta(pro-R)}$ = 10, $J_{\beta(pro-S)-\beta(pro-R)}$ = 13.7	3.06 (dd) $J_{\alpha-\beta(pro-R)}$ = 10.4, $J_{\beta(pro-S)-\beta(pro-R)}$ = 14	1.51 (ddd) $J_{\alpha-\beta(pro-R)}$ =11.4, $J_{\beta(pro-S)-\beta(pro-R)}$ = 13.6
Cγ*H*			1.73 (m) $J_{\beta(pro-S)-\gamma}$ = 9.6, $J_{\beta(pro-R)-\gamma}$ = 4.6
Cδ*H*	7.01 (d)		0.81 (d, C*H*$_3$(*pro-R*)), 0.77 (d, C*H*$_3$(*pro-S*)) $J_{\gamma-\delta(pro-S)}$, $J_{\gamma-\delta(pro-R)}$ = 6.5
Cε*H*	6.61 (d) $J_{\delta-\epsilon}$ = 8.4		
others	9.15 (s, O*H*), 1.29 (s, Boc)	7.14−7.22 (m, Ar*H*)	3.6 (s, CO_2CH_3)
$-\Delta\delta/\Delta T$ (ppb/K) for NH	7.6	5.0	1.3

Gaa: 8.21 (t, N*H*, $J_{NH-6,6'}$ = 3.5), 5.97 (d, O*H*(3), J_{H3-OH} = 3.8), 5.34 (d, O*H*(4), J_{H4-OH} = 3.5), 4.26 (d, *H*2), 4.05 (d, *H*3, J_{2-3} = 3.8), 3.76 −3.84 (*H*6$_{pro-R}$,*H*5, *H*4), 2.92 (*H*6$_{pro-S}$, $J_{6-6'}$ = 11.4); $-\Delta\delta/\Delta T$ (ppb/K) for NH = 4.2

Table 2. ^{1}H Chemical Shifts (δ) in ppm, Coupling Constants (J) in Hz, and Temperature Coefficients ($\Delta\delta/\Delta T$, in ppb/K) of the Amide Protons of 9a (500 MHz, DMSO-d_6)

protons	Tyr	Phe	Leu
NH	6.74 (d) $J_{NH-\alpha H} = 8.7$	7.58 (d) $J_{NH-\alpha H} = 8.6$	8.41 (d) $J_{NH-\alpha H} = 7.7$
CαH	4.08 (ddd)	4.54 (ddd)	4.30 (ddd)
CβH(*pro-S*)	2.82 (dd) $J_{\alpha-\beta(pro-S)} = 3.8$	2.93 (dd) $J_{\alpha-\beta(pro-S)} = 5.4$	1.49 (ddd) $J_{\alpha-\beta(pro-S)} = 5.3$
CβH(*pro-R*)	2.60 (dd) $J_{\alpha-\beta(pro-R)} = 10.5$, $J_{\beta(pro-S)-\beta(pro-R)} = 13.8$	2.96 (dd) $J_{\alpha-\beta(pro-R)} = 7.8$, $J_{\beta(pro-S)-\beta(pro-R)} = 13.7$	1.56 (ddd) $J_{\alpha-\beta(pro-R)} = 9.5$, $J_{\beta(pro-S)-\beta(pro-R)} = 13.7$
CγH			1.59 (m) $J_{\beta(pro-S)-\gamma} = 8.9$, $J_{\beta(pro-R)-\gamma} = 4.9$
CδH	7.02 (d)		0.88 (d, CH_3(*pro-R*)), 0.82 (d, CH_3(*pro-S*)) $J_{\gamma-\delta(pro-S)}$, $J_{\gamma-\delta(pro-R)} = 6.5$
CϵH	6.60 (d) $J_{\delta-\epsilon} = 8.4$		
Others	9.12 (s, O*H*), 1.30 (s, Boc)	7.15−7.24 (m, Ar*H*)	3.6 (s, CO_2CH_3)
$-\Delta\delta/\Delta T$ (ppb/K) for NH	6.1	2.5	4.2

Maa: 8.01 (dd, N*H*, $J_{NH-6,6'} = 5.1, 7.1$), 5.55 (d, O*H*(4), $J_{H4-OH} = 3.5$), 5.25 (d, O*H*(3), $J_{H3-OH} = 3.5$), 4.08 (d, *H*2, $J_{2-3} = 2.9$), 3.96 (t, *H*3), 3.84 (*H*5, $J_{4-5} = 3.7$), 3.72 (dd, *H*4, $J_{3-4} = 2.9$), 3.25−3.31 ($H6_{pro-S}$, $H6_{pro-R}$, $J_{6-6'} = 13.7$), $-\Delta\delta/\Delta T$ (ppb/K) for NH = 5.2

Table 3. ^{1}H Chemical Shifts (δ) in ppm, Coupling Constants (J) in Hz, and Temperature Coefficients ($\Delta\delta/\Delta T$, in ppb/K) of the Amide Protons of 10a (400 MHz, DMSO-d_6)

protons	Tyr	Phe	Leu
NH	6.84 (d) $J_{NH-\alpha H} = 8.4$	7.72 (d) $J_{NH-\alpha H} = 9.0$	8.02 (d) $J_{NH-\alpha H} = 7.2$
CαH	4.06 (ddd)	4.60 (ddd)	4.17 (ddd)
CβH(*pro-S*)	2.80 (dd) $J_{\alpha-\beta(pro-S)} = 4.1$	3.16 (dd) $J_{\alpha-\beta(pro-S)} = 4.2$	1.43 (ddd) $J_{\alpha-\beta(pro-S)} = 5.4$
CβH(*pro-R*)	2.61 (dd) $J_{\alpha-\beta(pro-R)} = 10.5$, $J_{\beta(pro-S)-\beta(pro-R)} = 13.8$	2.88 (dd) $J_{\alpha-\beta(pro-R)} = 9.2$, $J_{\beta(pro-S)-\beta(pro-R)} = 14.1$	1.49 (ddd) $J_{\alpha-\beta(pro-R)} = 9.7$, $J_{\beta(pro-S)-\beta(pro-R)} = 13.6$
CγH			1.58 (m) $J_{\beta(pro-S)-\gamma} = 8.8$, $J_{\beta(pro-R)-\gamma} = 5.1$
CδH	7.02 (d)		0.84 (d, CH_3(*pro-R*)), 0.81 (d, CH_3(*pro-S*)) $J_{\gamma-\delta(pro-S)}$, $J_{\gamma-\delta(pro-R)} = 6.4$
CϵH	6.63 (d) $J_{\delta-\epsilon} = 8.4$		
others	9.14 (s, O*H*), 1.29 (s, Boc)	7.14−7.23 (m, Ar*H*)	3.60 (s, CO_2CH_3)
$-\Delta\delta/\Delta T$ (ppb/K) for NH	6.3	4.9	2.0

Iaa: 7.95 (t, N*H*, $J_{NH-6,6'} = 5.5$), 5.71 (d, O*H*(3), $J_{H3-OH} = 4.1$), 5.26 (d, O*H*(4), $J_{H4-OH} = 3.6$), 4.27 (d, *H*2, $J_{2-3} = 3.7$), 4.11 (dd, *H*3), 4.11 (*H*5, $J_{4-5} = 2.7$), 3.84 (dd, *H*4, $J_{3-4} = 1.2$), 3.24, 3.30 ($H6_{pro-S}$, $H6_{pro-R}$, $J_{6-6'} = 11.4$); $-\Delta\delta/\Delta T$ (ppb/K) for NH = 4.4

ROESY cross-peaks between Tyr-Saa and Phe-Leu is consistent with some, but significant, populations of the molecules with φ and ψ values in the α-region of the $\varphi-\psi$ space ($\varphi = -120°$ to $-10°$ and $\psi = -120°$ to 20°). The populations of side-chain conformations about Cα−Cβ (χ_1) for all the peptides are shown in Table 7. There is a clear-cut dominance of g^- rotamers, while the populations of g^+ rotamers is invariably small. These general comments serve as a prelude to the following detail individual discussion on the structures and conformations of all the peptides **8-11a**, **51**, and **12**.

Conformational Analysis of 8a. The side-chains of Tyr, Phe, and Leu of **8a** are quite rigid and show larger than 70% rotamer population of g^- about χ_1. The rigidity of the Leu side-chain is also observed between Cβ−Cγ (χ_2) bond, with about 68% population of rotamers having anti relationship between βH(*pro-S*) and γH. The cross-peak in the ROESY spectrum between the LeuCαH-LeuδCH_3(*pro-S*) provide additional evidence of the rigidity of the Leu side-chain. The predominance of the g^- rotamers about Cα−Cβ is further supported by much stronger ROESY cross-peaks between NH-CβH(*pro-R*) than between NH-CβH(*pro-S*).

The small J_{2-3} of 3.8 Hz and ROESY cross-peak between GaaC2-H and C5-H support an envelope ($C_{2'}$-*exo* or $C_{3'}$-*endo*) conformer for the sugar ring. The presence of cross-peaks between LeuCβH(*pro-R*)-GaaC3-OH, LeuδCH_3(*pro-R*)-GaaC3-OH, LeuCγH-GaaC6-H(*pro-R*), LeuδCH_3(*pro-R*)-GaaC6-H(*pro-R*) show that Leu and Gaa ring come close to each other resulting in the propensity of a single major conformation of Leu. This conformation is further stabilized by a unique H-bonding between LeuNH → GaaC3-OH leading to a nine-membered β-turn-like ring structure. The sugar-hydroxyl can also possibly act as H-bond donor to Leu carbonyl or solvent molecules. There is a downfield shift of sugarC3-hydroxyl proton by 0.44 ppm compared to its chemical shift in the ^{1}H NMR spectrum of Boc-Gaa-OMe in DMSO-d_6 (10 mM), whereas the C4-OH signal did not show any appreciable shift. Amino acids with hydroxyl groups in their side-chains

Table 4. ^{1}H Chemical Shifts (δ) in ppm, Coupling Constants (J) in Hz, and Temperature Coefficients ($\Delta\delta/\Delta T$, in ppb/K) of the Amide Protons of 11a (400 MHz, DMSO-d_6)

protons	Tyr	Phe	Leu
NH	6.81 (d) $J_{NH-\alpha H} = 8.6$	7.69 (d) $J_{NH-\alpha H} = 8.8$	8.40 (d) $J_{NH-\alpha H} = 7.8$
CαH	4.03 (ddd)	4.56 (ddd)	4.28 (ddd)
CβH(*pro-S*)	2.76 (dd) $J_{\alpha-\beta(pro-S)} = 4.4$	3.02 (dd) $J_{\alpha-\beta(pro-S)} = 4.6$	1.50−1.52 (m) $J_{\alpha-\beta(pro-S)} = 5.2$
CβH(*pro-R*)	2.59 (dd) $J_{\alpha-\beta(pro-R)} = 10.1$, $J_{\beta(pro-S)-\beta(pro-R)} = 13.7$	2.84 (dd) $J_{\alpha-\beta(pro-R)} = 9.6$, $J_{\beta(pro-S)-\beta(pro-R)} = 13.9$	1.50−1.52 (m) $J_{\alpha-\beta(pro-R)} = 9.5$
CγH			1.50−1.52 (m)
CδH	7.02 (d)		0.89 (d, CH_3(*pro-R*)), 0.83 (d, CH_3(*pro-S*)) $J_{\gamma-\delta(pro-S)}$, $J_{\gamma-\delta(pro-R)} = 6.5$
CϵH	6.62 (d) $J_{\delta-\epsilon} = 8.4$		
others	9.14 (s, O*H*), 1.29 (s, Boc)	7.14−7.24 (m, Ar*H*)	3.6 (s, CO_2CH_3)
$-\Delta\delta/\Delta T$ (ppb/K) for NH	6.4	3.7	4.6

ddIaa: 7.90 (t, N*H*, $J_{NH-6,6'} = 5.8$), 4.23 (dd, *H*2, $J = 7.8, 5.3$), 4.08 (m, *H*5), 3.23 (ddd, $H6_{pro-S}$, $J = 13.8, 5.8, 4.4$), 3.06 (ddd, $H6_{pro-R}$, $J = 13.8, 5.8, 4.4$), 2.01−1.5 (m, *H*3, *H*4); $-\Delta\delta/\Delta T$ (ppb/K) for NH = 4.8

Table 5. ^{1}H Chemical Shifts (δ) in ppm, Coupling Constants (J) in Hz, and Temperature Coefficients ($\Delta\delta/\Delta T$, in ppb/K) of the Amide Protons of 51 (400 MHz, DMSO-d_6)

protons	Phe	Leu
NH	7.80 (d, $J_{NH-\alpha H} = 8.5$)	8.35 (d, $J_{NH-\alpha H} = 7.6$)
CαH	4.64 (ddd)	4.26 (q)
CβH(*pro-S*)	3.04 (dd, $J_{\alpha-\beta(pro-S)} = 4.6$)	1.47 (m, $J_{\alpha-\beta(pro-S)} = 7.6$)
CβH(*pro-R*)	2.86 (dd, $J_{\alpha-\beta(pro-R)} = 8.7$), $J_{\beta(pro-S)-\beta(pro-R)} = 13.8$)	1.47 (m, $J_{\alpha-\beta(pro-R)} = 7.6$)
CγH		1.56 (m)
CδH		0.84 (d, CH_3(*pro-R*)), 0.77 (d, CH_3(*pro-S*)) $J_{\gamma-\delta(pro-S)}$, $J_{\gamma-\delta(pro-R)} = 6.6$
others	7.12−7.26 (m, Ar*H*)	3.58 (s, CO_2CH_3)
$-\Delta\delta/\Delta T$ (ppb/K) for NH	3.7	3.9

Idac(Bn_2): 7.16−7.11 (m, Ph), 4.54 (d, *H*2, *H*5, $J_{2-3} = 3.5$), 4.17 (d, *H*3, *H*4), 4.34 and 4.28 (ABq, $J = 12.5$, PhCH_2O-)

Table 6. ^{1}H Chemical Shifts (δ) in ppm, Coupling Constants (J) in Hz, and Temperature Coefficients ($\Delta\delta/\Delta T$, in ppb/K) of the Amide Protons of 12 (400 MHz, DMSO-d_6)

protons	Phe	Leu
NH	8.03 (d, $J_{NH-\alpha H} = 9.2$)	7.93 (d, $J_{NH-\alpha H} = 7.2$)
CαH	4.61 (ddd)	4.17 (ddd)
CβH(*pro-S*)	3.21 (dd, $J_{\alpha-\beta(pro-S)} = 3.6$)	1.43 (ddd, $J_{\alpha-\beta(pro-S)} = 5.1$)
CβH(*pro-R*)	2.91 (dd, $J_{\alpha-\beta(pro-R)} = 10.4$), $J_{\beta(pro-S)-\beta(pro-R)} = 14.3$	1.49 (ddd, $J_{\alpha-\beta(pro-R)} = 10.2$), $J_{\beta(pro-S)-\beta(pro-R)} = 13.7$)
CγH		1.64 (m, $J_{\beta(pro-S)-\gamma} = 9.0$, $J_{\beta(pro-R)-\gamma} = 5.1$)
CδH		0.86 (d, CH_3(*pro-R*)), 0.81 (d, CH_3(*pro-S*)) $J_{\gamma-\delta(pro-S)}$, $J_{\gamma-\delta(pro-R)} = 6.7$
Others	7.17−7.27 (m, Ar*H*)	3.59 (s, CO_2CH_3)
$-\Delta\delta/\Delta T$ (ppb/K) for NH	6.3	1.2

Idac: 5.99 (d, O*H*(3), O*H*(4), $J_{H-OH} = 3.7$), 4.50 (d, *H*2, *H*5, $J_{2-3} = 3.2$), 4.13 (d, *H*3, *H*4).

Table 7. Populations of Various Rotamers about Cα−Cβ Bond (χ_1) in Peptides 8−11a, 51, and 12

	Tyr			Phe			Leu		
peptides	g^-	g^+	t	g^-	g^+	t	g^-	g^+	t
8a	0.72	0.08	0.20	0.82	0.10	0.08	0.76	0.04	0.20
9a	0.77	0.07	0.16	0.51	0.17	0.32	0.67	0.05	0.28
10a	0.77	0.07	0.16	0.64	0.16	0.20	0.69	0.03	0.28
11a	0.73	0.08	0.19	0.68	0.10	0.22	0.67	0.06	0.27
51				0.59	0.17	0.24	0.49	0.02	0.49
12				0.76	0.11	0.13	0.74	0.01	0.25

(serine, threonine) serve as acceptors only ~30% of the time.[17] Moreover, a H-bond between main-chainNH → side-chainOH leading to this type of turn structure is also very rare, mainly because of the free rotation about χ_1 in these amino acids. In sugar amino acids, unlike in serine and threonine, the hydroxyls are conformationally restricted, forcing one of them to participate in the formation of an unusual secondary structure. This pseudo β-turn is probably responsible for the strong positive band at 216 nm in the CD spectrum of the molecule (Figure 1). Another long-range ROESY cross-peak between Tyrβ-protons and Phe aromatic protons suggests their close proximity.

Several long-range restraints, derived from the ROESY experiments, were used in the MD calculations. These MD simulations resulted in four families of structures based on the RMS deviations of the nonhydrogen atoms, and the average structures from each of these families (I−IV) are shown in Figure 3, while the superimpositions

(17) (a) McDonald, I. K.; Thornton, J. M. *J. Mol. Biol.* **1994**, *238*, 777−793. (b) Burley, S. K.; Petsko, G. A. *Adv. Protein Chem.* **1988**, *39*, 125−189.

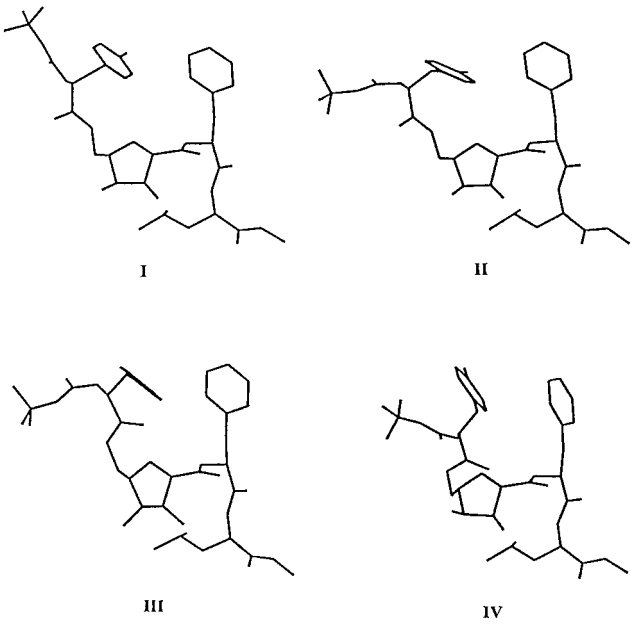


Figure 3. The average structures (I−IV) of the four families from the 100 structures sampled during 100 ps MD simulations of **8a**.

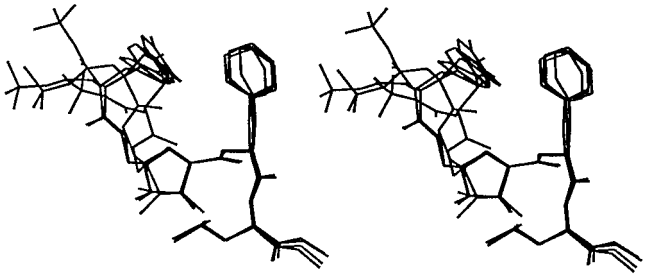


Figure 4. Stereoview of the superimposed average structures of the four families from the 100 structures sampled during 100 ps MD simulations of **8a**.

of I−IV are presented in Figure 4. These structures differ in their sugar puckers, φ(Tyr), ψ(Tyr), and φ(Gaa). Tyrosine being the terminal residue, variation in φ(Tyr) and ψ(Tyr) is not unexpected. Interestingly, the ψ(Tyr) and φ(Gaa) variations are coupled and two of the four average structures show amide plane flip. The ψ(Tyr) and φ(Gaa) of both I and II are around −80° and 85°, respectively, while the same for both III and IV are around 105° and −92°, respectively. Thus, the flip of the amide bond takes place through a 180° change of sequential ψ and φ dihedral angles. Such flips are responsible for changes in conformations of proteins through switch in turn structures.[18]

The four families show variations in the sugar pucker as well. The values of pseudorotation phase angle (P) and maximum angle of pucker (ν_{max}) are (109°, 26°), (113°, 23°), (17°, 32°), and (162°, 31°). These values of P refer to approximate sugar puckers of $C_{2'}$-*exo*, $C_{2'}$-*exo*, $C_{4'}$-*endo*, and $C_{3'}$-*endo*. The broadening of the spectral lines from the Gaa residue seems to support the observations from MD calculations that show the existence of the conformational equilibrium between several structural families involving the sugar moiety.

The values of φ(Tyr), φ(Phe), and φ(Leu) are around −100°, consistent with the observed $^3J_{HNC\alpha H}$. A close look at the superimposed structures shows that the peptide follows a turn-like structure stabilized by aromatic−aromatic as well as hydrophobic interaction between the Leu side-chain and the Gaa sugar ring. This structure has very strong resemblance with the conformation of enkephalins in the presence of SDS micelles[10] which is also stabilized by hydrophobic aromatic−aromatic interaction and corresponds to one of the two theoretical binding conformations[19] that enkephalin may adopt while interacting with cell membranes in which opioid receptors are located. We find that such a structure is preintroduced in **8a** making it a potential ligand for the δ-receptor which require folded conformations with close proximity (<10 Å) of the two aromatic rings having nearly parallel orientation.[20]

Conformational Analysis of 9a. In the Maa-containing peptide **9a**, the large magnitude of $\Delta\delta/\Delta T$ for LeuNH (−4.2 ppb/K) indicates the absence of any intramolecular H-bonding. PheNH on the other hand, with a medium $\Delta\delta/\Delta T$ of −2.5 ppb/K, is probably involved in a weak intramolecular H-bond. The side-chain of Leu, however, shows that it exists predominantly in a single conformation, g^- about Cα−Cβ having a population of 67%. The population profile of Leu side-chain in **9a** is very similar to that in **8a**, with slight reduction in the population of predominant rotamers about Cα−Cβ and Cβ−Cγ. Though Tyr shows a large population of g^- rotamer, the same for Phe is much smaller in **9a** than in other peptides. On the other hand, the population of t rotamer for Phe is quite significant in **9a** (32%).

All the ^3Js in the sugar ring of Maa in **9a** have very small values (J_{2-3}, J_{3-4} = 2.9 Hz; J_{4-5} = 3.7 Hz). These couplings are consistent with a twisted sugar ring conformation, $^4{}_3T$ with $P \approx 180°$. The Maa sugar ring leads to a conformation of the molecule where the two aromatic rings do not come close to each other, a prerequisite for imparting activity to the molecule.

Conformational Analysis of 10a. The small magnitude of $\Delta\delta/\Delta T$ for LeuNH (−2.0 ppb/K) in **10a** indicates its involvement in an intramolecular H-bonding, though it is believed to be somewhat weaker than that in the Gaa-containing peptide **8a** where the temperature coefficient for LeuNH was −1.3 ppb/K. The cross-peaks in the ROESY spectrum between LeuCγH-IaaC3-H, LeuCγH-IaaC3-OH, LeuCδH(*pro-R*)-IaaC3-OH, and a downfield shift of about 0.21 ppm of the IaaC3-OH compared to its chemical shift in the ^{1}H NMR spectrum of Boc-Iaa-OMe in DMSO-d_6 (10 mM), imply the presence of LeuNH → IaaC3-O(H) H-bond. The side-chains of Tyr, Phe, and Leu take predominantly g^- conformation about χ_1. While Tyr has a larger population of g^- rotamers, Phe has a smaller percentage of it compared to their counterparts in **8a**. Similarly, the predominance of a single conformer about Cβ−Cγ is not as prominent as in **8a**.

MD calculations show five families of structures (Figure 5) arising mainly due to variations in the terminal and side chain conformations. The only notable variation in the backbone conformation is around φ(Tyr) and φ-(Iaa) (it is a pseudo φ angle). Sugar pucker for all the

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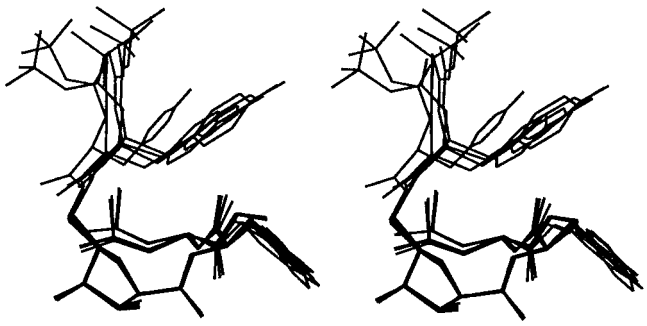

Figure 5. Stereoview of the superimposed average structures of the five families from the 100 structures sampled during 100 ps MD simulations of **10a**.

families has P of about 225°, corresponding to $C_{5'}$-*endo* and an unusually large ν_{max} of about 47°. The average value of φ for all the residues is between −95° to −118°, in conformity with large $^3J_{HNC\alpha H}$ observed experimentally. The structures also reveal that the aromatic rings in **10a** are orthogonal and pointing away from each other.

Conformational Analysis of 11a. As discussed already, the Gaa and Iaa containing peptides, **8a** and **10a**, respectively, due to the syn disposition of SaaC3-OH and Phe-Leu amide chain, have an unusual nine-membered β-turn-like structure stabilized by LeuNH → SaaC3-O(H) H-bond. Such a turn structure is expected to be absent in the dideoxy congener of these peptides, due to the absence of the H-bond accepting OH group. The observation of large magnitudes of $\Delta\delta/\Delta T$ for all amide protons in **11a** supports the above presumption. There is a similar predominance of g^- conformer about the Cα−Cβ bond for Tyr, Phe, and Leu residues. Due to spectral overlap, it was not possible to get information on sugar pucker and rotamer preferences about Cβ−Cγ in the Leu side-chain.

Conformational Analysis of 51. To further substantiate the participation of LeuNH → SaaC3-O(H) H-bond in the unusual β-turn-like structure, the protected Idac containing peptide **51** was investigated in detail by NMR spectroscopy. A large value of $\Delta\delta/\Delta T$ for LeuNH is consistent with the absence of the said H-bond. This can be attributed to the presence of a bulky protective group on C3-oxygen that also effects the rigidity of the Leu side-chain. The Leu side-chain in **51** shows the existence of equal population (about 50%) of g^- and t rotamers about Cα−Cβ, whereas for Phe, despite the dominance of g^- rotamers, other rotamers have sizable populations.

Conformational Analysis of 12. The turn structure observed in some of the above peptides where sugar amino acids have "*cis*-β-hydroxycarboxyl" moiety, was manifested in more ordered form in Idac-bearing reverse turn mimetic **12**. The anticipated nucleation of β-turn-like structures at both ends of this C_2-symmetric assembly involving identical intramolecular H-bonding, as observed earlier in **8a** and **10a**, between LeuNH → sugarC3(C4)-O(H) was realized as expected. A very small $\Delta\delta/\Delta T$ for LeuNH (−1.2 ppb/K) and a very low-field shift of 5.99 ppm of IdacC3(C4)-OH support the formation of a strong intramolecular LeuNH → IdacC3(C4)-O(H) H-bond. The side-chains of Phe and Leu point to the existence of large population of a single conformation. The 2-fold symmetry of the molecule was also evident in its ^{13}C NMR spectrum which showed peaks for only half of the molecule.

The MD calculations show the presence of seven families of conformations (Figure 6), largely differing due to different orientations of terminal groups. The sugar pucker has a twist conformation with P = 180° and maximum puckering amplitude of about 35°. The average values of φ from MD simulations are consistent with the observed $^3J_{HNC\alpha H}$.

Table 8. Analgesic Activity Assay by Hot Plate Method

		analgesic activity	
peptides	ED_{50} (μmol/animal)	peak (min)	relative (Leu-enk Me ester = 1)
8a	1.14	90	1.18
8b	1.48	30	0.91
9a	2.51	60	0.54
9b	2.22	90	0.61
10a	2.80	90	0.48
11a	2.49	90	0.54
12	2.70	90	0.50
Leu-enk Me ester	1.35	60	1.00

Table 9. Analgesic Activity Assay by Tail Clip Method

		analgesic activity	
peptides	ED_{50} (μmol/animal)	duration (min)	relative (Leu-enk Me ester = 1)
8a	1.17	90	1.76
8b	1.33	90	1.55
9b	2.45	120	0.84
Leu-enk Me ester	2.06	90	1.00

Biological Assays. The analgesic activities of the enkephalin analogues[21] **8**−**11** and **12** were tested in vivo by mouse hot-plate[22] and tail-clip[23] assays following intraperitoneal (ip) administration of the test substrates and compared to that of Leu-enkephalin methyl ester. The results of the assays are summarized in Tables 8 and 9, respectively. In the hot-plate test (Table 8) compounds **8a**,**b** showed activities (ED_{50} = 1.14 and 1.48 μmol/animal, respectively), similar to that of Leu-enkephalin methyl ester (ED_{50} = 1.35 μmol/animal). The same trend was observed when analgesic activities were

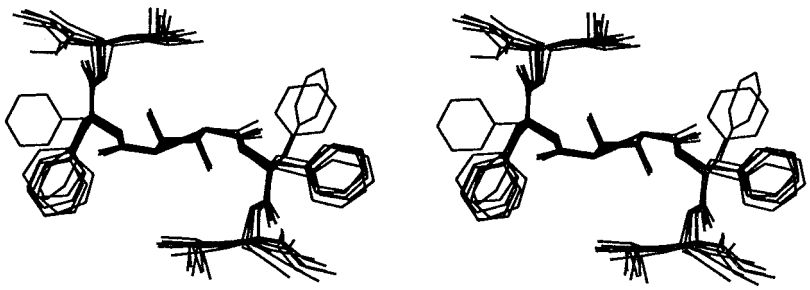

Figure 6. Stereoview of the superimposed average structures of the seven families from the 100 structures sampled during 100 ps MD simulations of **12**.

Table 10. Comparison of the ^{1}H Chemical Shifts (δ, in ppm) in DMSO-d_6 (7−10 mM) of the OH Groups in Various Sugar Amino Acids and the Corresponding Peptides[a]

	Gaa in		Maa in		Iaa in		Idac in	
protons	**8a**	**A**	**9a**	**B**	**10a**	**C**	**12**	**D**
OH(3)	5.97	5.53	5.25	5.17	5.71	5.50	5.99	5.72
OH(4)	5.34	5.27	5.55	5.61	5.26	5.12	5.99	5.72

[a] **A** = Boc-Gaa-OMe; **B** = Boc-Maa-OMe; **C** = Boc-Iaa-OMe; **D** = MeO-Idac-OMe.

tested by the tail-clip method (Table 9). Compounds **9a**,**b**, **10a**, **11a**, and **12** showed lower actvities than Leu-enkephalin methyl ester.

Discussion

The spectroscopic data strongly support the proposed turn structures in **8a**, **10a**, and **12**. The *cis*-β-hydroxycarboxyl moieties present on the sugar rings of these molecules engage their LeuNH residues in intramolecular H-bonds with sugar-OH which is somewhat weaker in **10a** than in **8a** and **12**. It is noteworthy to mention here that in these peptides, the chemical shifts of LeuNH show about 0.4 ppm downfield shift in substrates where intramolecular H-bonds are absent (**9a**, **11a**, and **51**). This indicates that in the absence of intramolecular H-bond, the LeuNH is solvent exposed and participates in stronger H-bonds with DMSO. At the same time, the sugarC3-OH protons show substantial downfield shifts (Table 10) in some of these peptides (0.44 ppm for **8a**, 0.21 ppm for **10a**, and 0.27 ppm for **12**), where the OH oxygen acts as H-bond acceptor resulting in the decreased electron density on the proton.[24] The changes in the sugarC4-OH proton chemical shifts are less pronounced.

The two aromatic rings in **8a** come close enough to each other resulting in its biological activity. This is in conformity with earlier observations that in enkephalins the C-terminal address segment stabilizes the bioactive conformation of the N-terminal message segment in which the two aromatic rings remain in close proximity with nearly parallel orientation.[10] While the higher temperature coefficient of LeuNH and the absence of any significant ROESY cross-peaks between the aromatic rings in **10a**, resulting in their divergent disposition as revealed by MD simulations, can possibly explain its reduced activity, the inability of **9a** and **11a** to exhibit any detectable folded conformation makes them biologically less active. The reverse turn mimetic **12**, despite showing a highly ordered structure, also exhibits reduced analgesic activity possibly for lacking the essential pharmacophoric framework.

The small HO−C3−C2−C1(O) dihedral angles on sugar rings in **8a**, **10a**, and **12** with average values of 26°, 16°, and 41°, respectively, explains the failure to exhibit any significant turn structure by the biologically inactive pyranoid sugar amino acid-containing enkephalin analogues reported earlier,[4j,4m] where the HO−C3−C2−C1(O) dihedral angle of ~60° (e,e relationship in a chair conformation) was probably unable to bring LeuNH and C3-OH close enough to initiate any H-bond formation. It can be stated here that the strength of the H-bond depends largely on the nature of the sugar amino acids and their ring size. The intramolecular H-bond inducing the *cis*-β-hydroxycarboxyl structural motif appropriately anchored on five-membered sugar rings described herein is considered as the key element to bestow folded conformations in linear peptides and may find applications in designing useful compounds.

Conclusions

An interesting rearrangement observed in a hexose-derived acyclic aziridinyl compound, involving an intramolecular 5-*exo* S_N2 opening of the terminal aziridine ring by γ-benzyloxy oxygen with concomitant debenzylation under remarkably mild conditions, led to the development of a new class of molecular scaffolds with a 2,5-anhydro sugar framework. The various functional groups on each of these designed scaffolds, specially their amino and carboxyl termini, besides serving as facile adapters for solid-phase synthetic methods, may provide opportunities to create libraries of multifaceted molecules that can emulate structural diversities of natural products and their properties. The nonproteinogenic properties of sugar amino acids will make compounds physiologically more stable. They will find wide ranging applications in peptidomimetics, especially in designing bioactive conformations of small peptides and in creating de novo molecular entities with architecturally beautiful structures and useful properties.

Experimental Section

General Procedures. All reactions were carried out in oven- or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2, 7% ethanolic phosphomolybdic acid−heat, and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% concentrated H_2SO_4)−heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

IR spectra were recorded as neat liquids or KBr pellets. Mass spectra were obtained under electron impact (EI) and liquid secondary ion mass spectrometric (LSIMS) techniques, respectively. For LSIMS, *m*-nitrobenzyl alcohol was used as a matrix. Melting points are uncorrected.

The CD spectra were recorded in quartz cells of 1 mm path length at 25 °C using peptide concentrations of 0.2 mM in TFE.

Analgesic Activity Assay. (a) Effect of enkephalin and its analogues on mechanically induced pain (heat; hot plate method) in mice: Albino Swiss mice weighing between 20 and 22 g were subjected to the hot plate test. The test substances dissolved/suspended in physiological solution (0.1 mL/mg) were administered in varying doses (0.5, 1.0, 2.0 mg/animal) by intraperitoneal (ip) route with a 24 gauge needle using 10 animals for each group ($N = 10$). The hot plate (Socrel, model DS-37, Italy) was adjusted to the temperature of 55.0 ± 0.1 °C. The individual reaction time (licking of paws) was recorded before administering the test substances. The cut-off point of reaction was about 12 s to avoid the thermal injury to the paw. Analgesic response was calculated as the percent increase in reaction time before and after administration of test substances measured at intervals of 30, 60, 90, and 120 min taking 95% confidence limit. An initial gap of 30 min was given after

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each administration before starting the measurements. The ED_{50} values were calculated using the probit analysis and compared to that of Leu-enkephalin methyl ester. The results are summarized in Table 8.

(b) Effect of enkephalin and its analogues on the mechanically induced pain (Tail clip method) in mice: Albino Swiss mice weighing between 20 and 22 g were used for the experiment. The pain was induced by applying an artery clip to the base of the mouse tail. The animals which responded by biting the clip or attempting to remove the clip within 2−3 s were selected a day prior to experiment. The test substances dissolved in physiological solution (0.1 mL/mg) were administered in varying doses (0.5, 1.0, 2.0 mg/animal) by i.p. route with 24 gauge needle using 10 animals for each group (N = 10). Measurements were made after 30 min at intervals of 30, 60, 90, 120 min. The analgesic activity was expressed as a percent of mice not showing the biting response or attempt to remove the clip. The confidence limit was 95% and the cut-off time was about 6−8 s to avoid mechanical injury to the mice. The ED_{50} values were calculated using the probit analysis and compared to that of Leu-enkephalin methyl ester. The results are summarized in Table 9.

NMR Spectroscopy. NMR spectra were recorded on 200, 400, and 500 MHz spectrometers at room temperature of ∼21 °C (unless otherwise mentioned) with 7−10 mM solutions in appropriate solvents using tetramethylsilane as internal standard or the solvent signals as secondary standards, and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded with complete proton decoupling. The assignments were carried out with the help of two-dimensional double quantum filtered correlation spectroscopy (DQF COSY) and total correlation spectroscopy (TOCSY).[25] For some cases the nuclear Overhauser effect spectroscopy (NOESY) or rotating frame nuclear Overhauser effect spectroscopy (ROESY) experiments,[25] which provide the information on the proximity of protons, were additionally used to confirm the assignments made. All the experiments were carried out in the phase-sensitive mode using the procedure of States et al.[26] The spectra were acquired with 2 × 256 or 2 × 192 free induction decays (FID) containing 8−32 transients with relaxation delays of 1.5 to 2.0 s. The NOESY and ROESY experiments were performed with mixing time of 0.1 to −0.5 s. For ROESY experiments a spin locking field of about 2 kHz and pulsed field locking with 30° pulses were used. The TOCSY experiments were performed with the spin locking fields of about 10 kHz and a mixing time of 0.08 s. The two-dimensional data were processed with Gaussian apodization in both the dimensions. The chemical shifts, coupling constants and temperature coefficients ($\Delta\delta/\Delta T$) of amide proton chemical shifts are given in Tables 1−6. To obtain the temperature coefficients of NH-chemical shifts, the spectra were recorded between room temperature and 70 °C.

Molecular Dynamics. All molecular mechanics/dynamics calculations were carried out using Insight II (97.0)/Discover program on a Silicon Graphics Octane workstation. The cvff force field with default parameters was used throughout the simulations. In the calculations, the peptides were soaked with three shells of DMSO solvent molecules with the radii of 18, 7, and 10 Å, respectively. The first shell solvent molecules were allowed to move freely along with the peptides, while in the second shell, they were tethered with respect to the hydrogen atoms. In the third shell, all atoms of the solvent molecules were fixed. Minimizations were done first with steepest decent, followed by conjugate gradient methods for a maximum of 1000 iterations each or RMS deviation of 0.01 kcal/mol, whichever was earlier. The energy-minimized structures were then subjected to MD simulations. A number of interatomic distance and torsional angle constraints[27] obtained from NMR data were used as restraints in the minimization as well as MD runs. For MD runs, a temperature of 300 K was used. The assemblies of molecules soaked in solvents were initially equilibrated for 10 ps and subsequently subjected to a 100 ps dynamics with a step size of 1 fs, sampling the trajectory at equal intervals of 1 ps. The samples were minimized using above-mentioned energy minimization protocol and analyzed for similarities in their structures by comparing the RMS deviations between each possible pair of structures. The RMS deviations were plotted in a 100 × 100 matrix with the *x*- and *y*-axes representing the structure numbers. The plot revealed a number of areas of clusters along the diagonal, indicating that several families of distinct structures were visited during the simulation period. The average structures from various families were compared and superimposed as shown in Figures 4−6.

6-Deoxy-6-azido-2,3,4-tri-(*O*-benzyl)-D-glucitol (15). To a solution of **13** (9 g, 18.4 mmol) in glacial acetic acid (60 mL) was added dilute HCl (2 M, 14 mL), and the reaction mixture was heated with stirring for 8 h at 80−85 °C. It was then cooled to room temperature, diluted with EtOAc, washed sequentially with water, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 5−20% EtOAc in petroleum ether eluant) gave unreacted **13** (3.6 g) and the desired lactol **14** (4.32 g, 83%) as a syrupy liquid which was used without characterization in the next step. To a solution of the lactol **14** (4.32 g, 9.09 mmol) in dry MeOH (25 mL) was added $NaBH_4$ (3.4 g, 90 mmol) portionwise at 0 °C. The reaction mixture was slowly brought to room temperature and stirred under nitrogen atmosphere for 6 h. It was then cooled to 0 °C and quenched by slow addition of saturated NH_4Cl solution. The aqueous solution was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 10−25% EtOAc in petroleum ether eluant) afforded pure diol **15** (3.76 g, 87%) as a syrupy liquid. R_f = 0.4 (silica, 25% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 35.9 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3450, 2100, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.45−7.2 (m, 15 H, Ar*H*), 4.65 (s, 4 H, PhC*H*$_2$O-), 4.51 (s, 2 H, PhC*H*$_2$O-). 3.95 (m, 1 H, C5-*H*), 3.78 (br s, 2 H, C*H*$_2$OH), 3.74−3.55 (m, 2 H, C3-*H*, C4-*H*), 3.44 (dd, J = 12.6, 3 Hz, 1 H, C6-*H*), 3.35 (m, 1 H, C2-*H*), 3.25 (dd, J = 12.6, 5 Hz, 1 H, C6-*H*′); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 137.69, 137.3, 137.25, 128.45, 128.14, 128.06, 127.94, 78.89, 78.73, 76.75, 74.11, 73.44, 73.10, 71.42, 61.60, 53.52; MS (LSIMS): *m*/*z* (%): 478 [M$^+$], 450 [M$^+$ − N$_2$]. HRMS (LSIMS): calcd for $C_{27}H_{31}N_3O_5$ [M$^+$]: 478.2342, found: 478.2355.

(2*S*)-*N*-Boc-2-[(1*R*,2*S*,3*S*)-1,2,3-tribenzyloxy-4-hydroxybut-1-yl]aziridine (17). To a solution of **15** (3.5 g, 7.32 mmol) in dry toluene (30 mL) was added Ph_3P (3.84 g, 14.64 mmol) at room temperature. The reaction mixture was refluxed under nitrogen atmosphere for 24 h. After cooling to room temperature, Boc_2O (3.19 g, 14.64 mmol) was added to it followed by stirring for an additional 6 h. It was then diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 10−30% EtOAc in petroleum ether eluant) gave pure Boc-protected aziridine **17** (3.32 g, 85%) as a syrupy liquid. R_f = 0.45 (silica, 30% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −52.1 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3450, 1720, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.4−7.05 (m, 15 H, Ar*H*), 4.98−4.57 (three ABq, 6 H, PhC*H*$_2$O-), 3.84 (dt, J = 4.0, 2.5 Hz, 1 H, C2-*H*), 3.68 (ddd, J = 12.8, 6.4, 2.5 Hz, 1 H, C1-*H*), 3.62 (t, J = 4.0 Hz, 1 H, C3-*H*), 3.43 (ddd, J = 12.8, 6.4, 4.0 Hz, 1 H, C1-*H*′), 3.21 (dd, J = 6.8, 4.0 Hz, 1 H, C4-*H*), 2.52 (ddd, J = 6.8, 6.8, 3.7 Hz, 1 H, C5-*H*), 2.16 (t, J = 6.4 Hz, 1 H, CH$_2$O*H*), 1.93 (d, J = 6.8 Hz, 1 H, C6-*H*), 1.78 (d, J = 3.7 Hz, 1 H, C6-*H*′), 1.44 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 161.98, 138.26, 137.93, 137.83, 128.54, 128.34, 128.25, 127.87, 127.72, 127.65, 81.41, 80.00, 79.41,

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78.61, 74.55, 72.77, 71.59, 61.31, 38.77, 27.87, 27.19; MS (LSIMS): *m/z* (%): 534 [$M^+ + H$], 434 [$M^+ + H - 100$]; HRMS (LSIMS): calcd for $C_{32}H_{40}NO_6$ [$M^+ + H$]: 534.2855, found: 534.2842.

Methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-gluconate (20). To a solution of **17** (3 g, 5.63 mmol) in dry DMF (10 mL) was added PDC (10.59 g, 28.15 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. It was then diluted with EtOAc, washed with saturated $CuSO_4$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was dissolved in ether (30 mL), and an ethereal solution of diazomethane was added dropwise at 0 °C till the esterification was complete as shown by TLC. The reaction mixture was then concentrated in vacuo and chromatographed (SiO_2, 5−25% EtOAc in petroleum ether eluant) to get pure ester **20** (1.35 g) and the bicyclic product **19** (0.6 g). A solution of **19** (0.6 g, 1.36 mmol) in dry MeOH (5 mL) was treated with anhydrous K_2CO_3 (0.188 g, 1.36 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at the same temperature. It was then diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 5−25% EtOAc in petroleum ether eluant) afforded the ester **20** (0.54 g), as a syrupy liquid, leading to an overall yield of 72% from **17**. Data for **19**: $R_f = 0.6$ (silica gel, 30% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −18.4 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 1780, 1725, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.4−7.28 (m, 10 H, Ar*H*), 4.77 and 4.45 (ABq, 2 H, PhCH_2O-), 4.76 (d, $J = 5$ Hz, 1 H, C2-*H*), 4.5 (ABq, 2 H, PhCH_2O-), 4.44 (d, $J = 5$ Hz, 1 H, C3-*H*), 4.3 (dd, $J = 5.3$, 2.2 Hz, 1 H, C5-*H*), 4.04 (d, $J = 2.2$ Hz, 1 H, C4-*H*), 3.83 (dd, $J = 12.8$, 5.3 Hz, 1 H, C6-*H*), 3.55 (d, $J = 12.8$ Hz, 1 H, C6-*H′*), 1.54 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.2, 152, 137.1, 136.9, 128.5, 128.4, 128.1, 128, 127.8, 86.8, 86.3, 83.6, 79.6, 77.8, 72.9, 71.7, 48.9, 28; MS (LSIMS): *m/z* (%): 439 (10) [M^+], 384 (100) [$M^+ + H - CH_2{=}C(CH_3)_2$]; HRMS (LSIMS): calcd For $C_{21}H_{22}NO_6$ [$M^+ + H - CH_2{=}C(CH_3)_2$]: 384.1447, found: 384.1462. Data for **20**: $R_f = 0.4$ (silica gel, 30% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 9.4 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 1765, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.4−7.2 (m, 10 H, aromatic), 5.3 (m, 1 H, N*H*Boc), 4.68 (d, $J = 5$ Hz, 1 H, C2-*H*), 4.48 (ABq, 4 H, PhCH_2O-), 4.22 (dd, $J = 5$, 2 Hz, 1 H, C3-*H*), 4.13 (m, 1 H, C5-*H*), 3.88 (dd, $J = 3$, 2 Hz, 1 H, C4-*H*), 3.72 (s, 3 H, CO_2CH_3), 3.4 (m, 2 H, C6-*H*), 1.42 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.6, 156.1, 137.3, 137.1, 128.5, 128.4, 128, 127.8, 127.7, 83.6, 83.2, 82.7, 80, 79.1, 72.4, 72.1, 52, 42.2, 28.4; MS (LSIMS): *m/z* (%): 494 (25) [M^+ + Na], 472 (20) [$M^+ + H$], 372 (100) [$M^+ + H - 100$]. HRMS (LSIMS): calcd for $C_{26}H_{34}NO_7$ [$M^+ + H$]: 472.2335, found: 472.2363.

(2*S*)-*N*-Boc-2-[(1*R*,2*S*,3*R*)-1,2,3-tribenzyloxy-4-hydroxybut-1-yl]aziridine (21). It was synthesized following the same method as described above for the synthesis of **17**. Data for **21**: $R_f = 0.5$ (silica gel, 30% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −78.4 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3430, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.4−7.1 (m, 15 H, Ar*H*), 4.9, 4.7, and 4.3 (three ABq, 6 H, PhCH_2O-), 3.9−3.55 (m, 4 H, C1-H_2, C2-*H*, C3-*H*), 3.15 (dd, $J = 8.4$, 2.3 Hz, 1 H, C4-*H*), 2.55 (ddd, $J = 8.4$, 6.8, 3.7 Hz, 1 H, C5-*H*), 2.05 (broad t, 1 H, CH_2OH), 1.85 (d, $J = 6.8$ Hz, 1 H, C6-*H*), 1.7 (d, $J = 3.7$ Hz, 1 H, C6-*H′*), 1.44 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.3, 137.95, 137.87, 128.56, 128.36, 128.21, 127.92, 127.73, 127.54, 81.49, 79.26, 78.81, 74.10, 72.03, 71.14, 60.24, 39.54, 27.9, 27.13; MS (LSIMS): *m/z* (%): 534 (5) [$M^+ + H$], 434 (30) [$M^+ + H - 100$]; HRMS (LSIMS): calcd for $C_{32}H_{40}NO_6$ [$M^+ + H$]: 534.2855, found: 534.2847.

Methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-mannonate (23). Following the same method as described above for the conversion of **17** to **20**, the mannonate congener **23** was prepared from **21** in 78% yield by PDC oxidation. Data for **23**: $R_f = 0.45$ (silica gel, 30% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 14.3 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 1770, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.4−7.2 (m, 10 H, Ar*H*), 5.0 (m, 1 H, N*H*), 4.6 and 4.47 (two ABq, 4 H, PhCH_2O-), 4.65 (s, 1 H, C2-*H*), 4.33 (s, 1 H, C3-*H*), 4.3 (m, 1 H, C5-*H*), 3.88 (d, $J = 1.8$ Hz, 1 H, C4-*H*), 3.72 (s, 3 H, CO_2CH_3), 3.48 and 3.38 (two m, 2 H, C6-H_2), 1.42 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169, 156.1, 138.25, 128.37, 127.88, 127.68, 82.68, 78.65, 75.91, 75.41, 72.68, 71.68, 71.28, 66.93, 41.62, 28.4; MS (LSIMS): *m/z* (%): 494 (16) [M^+ + Na], 472 (10) [$M^+ + H$], 372 (100) [$M^+ + H - 100$].

1,3:4,6-Di-*O*-benzylidene-2-*O*-tosyl-D-mannitol (25). To a solution of **24** (15 g, 41.89 mmol) and Et_3N (6.37 mL, 46.07 mmol) in CH_2Cl_2:DMF (4:1, 150 mL) was added TsCl (8.83 g, 46.07 mmol) under nitrogen atmosphere, and the reaction mixture was stirred at room temperature for 5 h. It was then diluted with EtOAc, washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 20−35% EtOAc in petroleum ether eluant) afforded the monotosylate **25** (17.19 g, 80%) as a white solid. $R_f = 0.5$ (silica gel, 40% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −23.2 (*c* 1, $CHCl_3$); IR (KBr): ν_{max} 3500, 1600, 1350, 1175, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.76 and 7.12 (two d, $J = 8.5$ Hz, 4 H, tosyl), 7.5−7.3 (m, 10 H, Ar*H*), 5.52 (s, 1 H, benzylideneC*H*), 5.0 (s, 1 H, benzylideneC*H*), 4.85 (dt, $J = 11.2$, 5.6 Hz, 1 H, C2-*H*), 4.42 (dd, $J = 11.2$ and 5.6 Hz, 1 H, C1-*H*), 4.3−4.0 (m, 3 H, C6-*H*, C4-*H*, C5-*H*), 3.85 (t, $J = 11.2$ Hz, 1 H, C1-*H′*), 3.65 (dd, $J = 11.2$, 2 Hz, 1 H, C4-*H*), 3.54 (t, $J = 11.2$ Hz, 1 H, C6-*H′*), 2.25 (s, 3 H, tosyl-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 145.38, 137.36, 136.82, 132.61, 129.99, 129.16, 128.75, 128.19, 127.98, 127.87, 126.18, 126.08, 101.31, 100.48, 77.3, 75.03, 71.05, 68.55, 67.29, 59.71, 21.47; MS (LSIMS): *m/z* (%): 513 (100) [$M^+ + H$]; HRMS (LSIMS): calcd for $C_{27}H_{29}O_8S$ [$M^+ + H$]: 513.1583, found: 513.1589.

The Keto Compound 26. A solution of oxalyl chloride (4.09 mL, 46.7 mmol) in dry CH_2Cl_2 (140 mL), cooled to −78 °C, was treated with DMSO (6.64 mL, 93.5 mmol). After 5 min, the alcohol **25** (16 g, 31.25 mmol) dissolved in CH_2Cl_2 (40 mL) was added to the reaction mixture at the same temperature. After stirring for 1 h at −78 °C, the reaction mixture was treated with Et_3N (19.41 mL, 140.35 mmol), slowly warmed to 0 °C, and stirred at this temperature for 15 min. It was then poured into a cold saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 20% EtOAc in petroleum ether eluant) afforded the ketone **26** (14.34 g, 90%) as a white solid. $R_f = 0.4$ (silica gel, 30% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −60.2 (*c* 1, $CHCl_3$); IR (KBr): ν_{max} 1740, 1600, 1365, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.75 and 7.15 (two d, $J = 8.5$ Hz, 4 H, tosyl), 7.5−7.2 (m, 10 H, Ar*H*), 5.58 (s, 1 H, benzylideneC*H*), 5.48 (s, 1 H, benzylideneC*H*), 4.82 (dt, $J = 11.2$, 5.6 Hz, 1 H, C2-*H*), 4.5 (s, 1 H, C4-*H*), 4.45−4.3 (m, 2 H, C1-*H*, C3-*H*), 4.35 (ABq, *2* H, C6-*H*, C6-*H′*), 3.7 (t, $J = 11.2$ Hz, 1 H, C1-*H′*), 2.3 (s, 3 H, tosyl-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 203.6, 145.44, 136.78, 136.46, 132.52, 129.98, 129.23, 129.12, 128.23, 128.15, 127.94, 126.21, 126.05, 101.24, 98.57, 78.8, 76.99, 72.03, 68.43, 67.03, 21.53; MS (LSIMS): *m/z* (%): 511 (100) [$M^+ + H$]; HRMS (LSIMS): calcd for $C_{27}H_{27}O_8S$ [$M^+ + H$]: 511.1426, found: 511.1436.

D-Glucitol Intermediate 27. To a solution of **26** (12 g, 23.52 mmol) in dry MeOH (120 mL) was added $NaBH_4$ (4.437 g, 117.25 mmol) portionwise at 0 °C. The reaction mixture was stirred at the same temperature for 1 h. It was then quenched by careful addition of cold saturated aqueous NH_4Cl solution. After removal of MeOH under reduced pressure, the aqueous solution was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. ^1H NMR of the crude residue indicated it as a mixture of **25** and **27** (ca. 1:6 ratio). The mixture was used as such in the next step.

1,3:4,6-Di-*O*-benzylidene-2,5-anhydro-D-iditol (28). The residue from the previous step (11 g, 21.56 mmol), dissolved in dry MeOH (125 mL), was treated at 0 °C with anhydrous K_2CO_3 (5.926 g, 42.88 mmol). The reaction mixture was stirred under nitrogen atmosphere at room temperature for 12 h. It was then cooled to 0 °C and quenched by slow addtion of a cold saturated aqueous NH_4Cl solution. After removal of MeOH under reduced pressure, the aqueous solution was extracted with EtOAc. The combined organic extracts were

washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 8−12% EtOAc in petroleum ether eluant) afforded the cyclic product **28** (5 g, 62% from **26**) as a white solid. $R_f = 0.5$ (silica gel, 20% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 21.5 (*c* 1.02, $CHCl_3$); IR (KBr): ν_{max} 1425, 1390, 1150, 1100, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.5−7.3 (m, 10 H, Ar*H*), 5.45 (s, 2 H, benzylideneC*H*), 4.5 (m, 2 H, C_2-*H*, C_5-*H*), 4.45 (d, $J = 17.6$ Hz, 2 H, C_6-*H*), 4.32 (br s, 2 H, C_3-*H*, C_4-*H*), 4.08 (dd, $J = 17.6$, 1 Hz, 2 H, C_6-*H′*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 137.94, 128.95, 128.11, 126.22, 98.97, 96.22, 79.86, 73.56, 68.08; MS (LSIMS): *m*/*z* (%): 341 (100) [$M^+ + H$]; HRMS (LSIMS): calcd for $C_{20}H_{20}O_5$ [M^+]: 340.1310, found: 340.1293.

2,5-Anhydro-D-iditol (29). To a solution of **28** (5 g, 14.7 mmol) in MeOH:EtOAc (1:1, 40 mL) was added 10% Pd on C (1 g). It was hydrogenated under atmospheric pressure using a H_2 balloon. The reaction mixture was then filtered through a short pad of Celite, and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated in vacuo. The residue was azeotroped with dry toluene to afford pure **29** in quantitative yield, which was used directly in the next step without further purification.

2,5-Anhydro-1,6-di-*O*-(*tert*-butyldiphenylsilyl)-D-iditol (30). The tetrol **29** from the previous step (2.41 g, 14.7 mmol), dissolved in dry DMF (50 mL), was treated at 0 °C under nitrogen atmosphere sequentially with imidazole (2 g, 29.4 mmol) and TBDPSCl (7.52 mL, 29.4 mmol). After stirring for 12 h at room temperature, the reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 10−20% EtOAc in petroleum ether eluant) afforded the product **30** (8.47 g, 90%) as a syrupy liquid. $R_f = 0.45$ (silica gel, 30% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −10.6 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3375, 1425, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.75−7.3 (m, 20 H, Ar*H*), 4.34 (t, $J = 3.6$ Hz, 2 H, C3-*H*, C4-*H*), 4.22 (dd, $J = 3.6$, 3.2 Hz, 2 H, C2-*H*, C5-*H*), 4.03 (d, $J = 3.6$ Hz, 4 H, C1-H_2, C6-H_2), 3.8 (d, $J = 3.2$ Hz, 2 H, O*H*), 1.02 (s, 18 H, *tert*-butyl); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 135.66, 135.51, 132.71, 132.4, 129.97, 129.91, 127.86, 79.69, 79.12, 63.67, 26.75, 19.1; MS (LSIMS): *m*/*z* (%): 663 (30) [$M^+ + Na$].

2,5-Anhydro-3,4-di-*O*-benzyl-1,6-di-*O*-(*tert*-butyldiphenylsilyl)-D-iditol (31). To a solution of **30** (7.5 g, 11.71 mmol) in THF−DMF (2:1, 30 mL) was added benzyl bromide (3.5 mL, 29.27 mmol). The reaction mixture was cooled to 0 °C and treated by dropwise addition with a solution of NaHMDS in THF (2 M, 14.63 mL, 29.27 mmol). After stirring for 15 min at 0 °C, it was quenched by careful addition of a cold saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 1−2% EtOAc in petroleum ether eluant) afforded the product **31** (6.73 g, 70%) as a syrupy liquid. $R_f = 0.45$ (silica gel, 6% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 3.96 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} 3062, 1475, 1425 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.65 (d, $J = 7$ Hz, 8 H, Ar*H*), 7.4−7.2 (m, 22 H, Ar*H*), 4.56 (s, 4 H, PhCH_2O-), 4.25 (m, 2 H, C2-*H*, C5-*H*), 4.22 (d, $J = 3.6$ Hz, 2 H, C3-*H*, C4-*H*), 3.92 (dd, $J = 10.5$, 7 Hz, 2 H, C1-*H*, C6-*H*), 3.8 (dd, $J = 10.5$, 5.6 Hz, 2 H, C1-*H′*, C6-*H′*), 1.05 (s, 18 H, *tert*-butyl); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.21, 135.58, 133.73, 133.5, 129.53, 128.37, 127.6, 81.75, 80.35, 72.6, 61.88, 26.89, 19.2; MS (LSIMS): *m*/*z* (%): 843 (10) [$M^+ + Na$].

2,5-Anhydro-3,4-di-*O*-benzyl-D-iditol (32). A solution of **31** (5 g, 6.09 mmol) in THF (30 mL) was treated at 0 °C with TBAF (1 M in THF, 15.2 mL, 15.2 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched with saturated NH_4Cl solution, and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 60−80% EtOAc in petroleum ether eluant) afforded the product **32** (2.0 g, 95%) as a syrupy liquid. $R_f = 0.5$ (silica gel, EtOAc); $[\alpha]^{20}_D$ 33.2 (*c* 1.61, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.35−7.15 (m, 10 H, Ar*H*), 4.46 (ABq, 4 H, PhCH_2O-), 4.2 (m, 2 H, C_2-*H*, C_5-*H*), 4.05 (d, $J = 4.5$ Hz, 2 H, C_3-*H*, C_4-*H*), 3.78 and 3.68 (two dd, $J = 11.5$, 4.5 Hz, 4 H, C_1-H_2, C_6-H_2), 3.8 (d, $J = 3.2$ Hz, 2 H, O*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 197.3, 128.45, 128, 127.56, 82.52, 79.9, 72.22, 61.54; MS (LSIMS): *m*/*z* (%): 345 (95) [$M^+ + H$], 367 (100) [$M^+ + Na$]; HRMS (LSIMS): calcd for $C_{20}H_{25}O_5$ [$M^+ + H$]: 345.1702, found: 345.1738.

2,5-Anhydro-3,4-di-*O*-benzyl-6-*O*-tosyl-D-iditol (33). To a solution of **32** (1.8 g, 5.23 mmol) in dry THF (20 mL) under nitrogen atmosphere at 0 °C was added NaH (60% dispersion, 209 mg, 5.24 mmol) portionwise. After stirring for 15 min at the same temperature, TsCl (1 g, 5.23 mmol) was added to it and stirring continued for 1 h. It was quenched with saturated NH_4Cl solution, extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 20−30% EtOAc in petroleum ether eluant) gave the desired monotosylated compound **33** (2.08 g, 80%) as a syrupy liquid, which was used directly in the next step.

2,5-Anhydro-6-azido-6-deoxy-3,4-di-*O*-benzyl-D-iditol (34). To a solution of **33** (1.8 g, 3.6 mmol) in dry DMF (10 mL) was added NaN_3 (468 mg, 7.2 mmol), and the reaction mixture was heated with stirring at 80 °C for 3 h. After cooling to room temperature, it was diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 16−18% EtOAc in petroleum ether eluant) gave the azide **34** (1.1 g, 90%) as a syrupy liquid. $R_f = 0.5$ (silica gel, 30% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 27.2 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3450, 2300, 1485 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.45−7.2 (m, 10 H, Ar*H*), 4.55 and 4.5 (two ABq, 4 H, PhCH_2O-), 4.25 (m, 2 H, C2-*H*, C5-*H*), 4.05 (m, 2 H, C3-*H*, C4-*H*), 3.8 (m, 2 H, C1-H_2), 3.52 and 3.45 (two dd, $J = 11.5$, 4.5 Hz, 2 H, C6-H_2), 2 (broad, 1 H, O*H*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 137.34, 137.23, 128.63, 128.54, 128.36, 128.17, 128.08, 127.76, 127.67, 82.32, 81.67, 79.96, 78.62, 72.46, 72.34, 61.65, 50.1; MS (LSIMS): *m*/*z* (%): 392 (20) [$M^+ + Na$].

***N*-Boc-6-Amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-iditol (36).** To a solution of **34** (1 g, 2.71 mmol) in MeOH (20 mL) was added Ph_3P (1.42 g, 5.42 mmol), and the reaction mixture was stirred for 12 h at room temperature. This was followed by the addtion of Boc_2O (1.24 mL, 5.42 mmol) to the reaction and stirring continued for an additional 1 h. It was then diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 25−30% EtOAc in petroleum ether eluant) gave pure Boc-protected amino alcohol **36** (1.08 g, 90%) as a syrupy liquid. $R_f = 0.3$ (silica gel, 40% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 30.6 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3400, 1700, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.4−7.2 (m, 10 H, Ar*H*), 4.8 (m, 1 H, N*H*Boc), 4.6 and 4.3 (m, 4 H, PhCH_2O-), 4.2 (m, 2 H, C2-*H*, C5-*H*), 4.05 (m, 2 H, C3-*H*, C4-*H*), 3.75 (m, 2 H, C1-H_2), 3.5 and 3.2 (two m, 2 H, C6-H_2), 2.03 (broad, 1 H, O*H*), 1.45 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 156.01, 137.38, 137.27, 128.57, 128.25, 128.1, 128.04, 127.67, 82.61, 82.03, 79.61, 79.14, 78.85, 72.31, 72.23, 61.65, 40.47, 28.36; MS (LSIMS): *m*/*z* (%): 344 (100) [$M^+ + H - 100$], 444 (15) [$M^+ + H$], 466 (20) [$M^+ + Na$]; HRMS (LSIMS): calcd for $C_{25}H_{34}NO_6$ [$M^+ + H$]: 444.2386, found: 444.2376.

Methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-idonate (38). To a solution of **36** (0.9 g, 2.03 mmol) in dry DMF (10 mL) was added PDC (3.81 g, 10.15 mmol) at 0 °C. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 12 h. It was then worked up in the same way as described above for the preparation of **20** to get the idonate **38** (0.7 g, 78%). $R_f = 0.4$ (silica gel, 25% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 10.1 (*c* 1.25, $CHCl_3$); IR (neat): ν_{max} 1762, 1712, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.45−7.22 (m, 10 H, Ar*H*), 4.85 (m, 1 H, N*H*Boc), 4.8 (d, $J = 4.5$ Hz, 1 H, C2-*H*), 4.5 (s, 2 H, PhCH_2O-), 4.48 (ABq, 2 H, PhCH_2O-), 4.4 (m, 1 H, C5-*H*), 4.28 (m, 1 H, C3-*H*), 3.97 (m, 1 H, C4-*H*), 3.78 (s, 3 H, CO_2CH_3), 3.55 and 3.32 (two m, 2 H, C6-H_2), 1.45 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.98, 155.91, 137.17, 128.6, 128.46, 128.34, 128.13, 128.04, 127.78, 82.69, 81.34, 80.54, 79.7, 72.76, 72.23, 51.87, 40.28, 28.37; MS (LSIMS): *m*/*z* (%): 372 (60) [$M^+ + H - 100$], 472

(6) [M^+ + H], 494 (14) [M^+ + Na]; HRMS (LSIMS): calcd for $C_{26}H_{34}NO_7$ [M^+ + H]: 472.2335, found: 472.2327.

2,5-Anhydro-1,6-di-*O*-benzyl-D-iditol (39). To a solution of compound **28** (4 g, 11.76 mmol) in CH_2Cl_2:Et_2O (1:1, 30 mL) was added LAH (2.67 g, 70.56 mmol) at 0 °C under nitrogen atmosphere. Then the reaction mixture was heated to 40 °C and $AlCl_3$ (6.27 g, 47.04 mmol) dissolved in ether (15 mL) was added to the reaction mixture at the same temperature. After stirring for 1 h at 40 °C, the reaction mixture was cooled to 0 °C and quenched with a saturated aqueous solution of Na_2SO_4. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 20% EtOAc in petroleum ether eluant) afforded the diol **39** (2.42 g, 60%) as a white solid. R_f = 0.5 (silica gel, 60% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −2.9 (*c* 1, $CHCl_3$); IR (KBr): ν_{max} 3425, 1500, 1430, 1100, 750 cm^{-1}; ^1H NMR ($CDCl_3$, D_2O exchanged, 200 MHz): δ 7.4−7.25 (m, 10 H, Ar*H*), 4.65 and 4.58 (ABq, 4 H, PhCH_2O-), 4.32 (q, *J* = 4 Hz, 2 H, C2-*H*, C5-*H*), 4.25 (d, *J* = 4 Hz, 2 H, C3-*H*, C4-*H*), 3.88 (d, *J* = 4 Hz, 4 H, C1-H_2, C6-H_2); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 137.37, 128.44, 127.86, 127.73, 79.0, 78.39, 73.88, 69.17; MS (LSIMS): *m*/*z* (%): 367 (20) [M^+ + Na]; MS (EI): *m*/*z* (%): 253 (90) [M^+ − Bn]; HRMS (LSIMS): calcd for $C_{20}H_{25}O_5$ [M^+ + H]: 345.1702, found: 345.1700.

Dihydrofuran Intermediate 40. A mixture of compoumd **39** (2.3 g, 6.68 mmol), triphenylphosphine (7 g, 26.72 mmol), and imidazole (1.81 g, 26.72 mmol) were refluxed in toluene (150 mL) with stirring. Iodine (5.08 g, 20.04 mmol) was added in small portions. The white, finely dispersed complex initially formed was transformed into a clear yellow solution that darkened as iodine was liberated. At the bottom of the reaction vessel, a dark tarry complex was formed from which the product was gradually dissolved. After 3 h, the reaction mixture was cooled and iodine (1.695 g, 6.68 mmol) was added, followed by aqueous sodium hydroxide (2.40 g, 60.12 mmol in 45 mL H_2O). The mixture was stirred until virtually all of the tarry red deposits were dissolved. The mixture was transferred to a separating funnel. The aqueous layer was separated, and the organic layer was washed successively with water, saturated aqueous sodium thiosulfate, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 1.5−2% EtOAc in petroleum ether eluant) afforded **40** (1.3 g, 62%). R_f = 0.5 (silica gel, 4% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 183.4 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 2850, 1462, 1350, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.4−7.25 (m, 10 H, Ar*H*), 5.9 (s, 2 H, C3-*H*, C4-*H*), 5.03 (m, 2 H, C2-*H*, C5-*H*), 4.6 and 4.5 (ABq, 4 H, PhCH_2O-), 3.55 (dd, *J* = 11.5, 5.6 Hz, 2 H, C1-*H*, C6-*H*), 3.48 (dd, *J* = 11.5, 4.5 Hz, 2 H, C_1-*H*′, C_6-*H*′); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.27, 128.84, 128.28, 127.58, 127.51, 85.46, 73.41, 72.75; MS (LSIMS): *m*/*z* (%): 333 (40) [M^+ + Na], 309 (10) [M^+ − H]; HRMS (LSIMS): calcd for $C_{20}H_{21}O_3$ [M^+ − H]: 309.1491, found: 309.1505.

2,5-Anhydro-3,4-dideoxy-D-iditol (41). To a solution of **40** (1.2 g, 3.87 mmol) in EtOAc (12 mL) was added 10% Pd on C (200 mg). It was hydrogenated for 1 h under atmospheric pressure using a H_2 balloon. The reaction mixture was then filtered through a short pad of Celite, and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated in vacuo. The residue was azeotroped with dry toluene to afford **41**, which was used directly in the next step without further purification.

2,5-Anhydro-3,4-dideoxy-6-*O*-tosyl-D-iditol (42). The diol **41** from the previous step (0.5 g, 3.78 mmol), dissolved in dry THF (10 mL), was treated at 0 °C under nitrogen atmosphere with NaH (60% suspension, 0.151 g, 3.78 mmol). After 15 min, TsCl (0.72 g, 3.78 mmol) was added to the reaction mixture and stirred for 1 h at 0 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 36−40% EtOAc in petroleum ether eluant), afforded the monotosylated product **42** (0.5 g, 46%) as a colorless liquid. R_f = 0.4 (silica gel, 50% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −12.6 (*c* 1.24, $CHCl_3$); IR (neat): ν_{max} 3450, 1600, 1487, 1350, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, D_2O exchanged, 200 MHz): δ 7.8 and 7.35 (two d, *J* = 9.5 Hz, 4 H, Ar*H*), 4.18 (m, 1 H, C2-*H*), 4.1−3.9 (m, 3 H, C6-H_2, C5-*H*), 3.62 (dd, *J* = 11.6, 4 Hz, 1 H, C1-*H*), 3.4 (dd, *J* = 11.6, 5.6 Hz, 1 H, C1-*H*′), 2.47 (s, 3 H, ArCH_3), 2.15−1.6 (m, 4 H, C3-H_2, C4-H_2); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 144.8, 132.85, 129.75, 127.83, 80.04, 76.22, 71.51, 64.46, 28.07, 26.0, 21.51; MS (LSIMS): *m*/*z* (%): 133 (24) [M^+ + H − Ts].

2,5-Anhydro-3,4,6-trideoxy-6-azido-D-iditol (43). To a solution of **42** (0.4 g, 1.39 mmol) in dry DMF (5 mL) was added NaN_3 (0.271 g, 4.18 mmol), and the reaction mixture was heated with stirring for 3 h at 70−80 °C. It was then brought to room temperature, diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 25−30% EtOAc in petroleum ether eluant) gave the desired azido compound **43** (0.2 g, 90%) as a colorless liquid. R_f = 0.45 (silica gel, 50% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −50.85 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 4.3−4.1 (m, 2 H, C2-*H*, C5-*H*), 3.7 (dd, *J* = 11.5, 3.5 Hz, 1 H, C1-*H*), 3.5 (dd, *J* = 11.5, 5.5 Hz, 1 H, C1-*H*′), 3.38 (dd, *J* = 11.5, 3.5 Hz, 1 H, C6-*H*), 3.22 (dd, *J* = 11.5, 5.5 Hz, 1 H, C6-*H*′), 2.15−1.7 (m, 4 H, C3-H_2, C4-H_2); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 79.98, 78.28, 64.68, 54.58, 29.19, 27.41; MS (EI): *m*/*z* (%): 101 (50) [M^+ − CH_2N_3], 57 (100) [CH_3N_3].

***N*-Boc-6-amino-2,5-anhydro-3,4,6-trideoxy-D-iditol (45).** To a solution of **43** (0.17 g, 1.08 mmol) in MeOH (4 mL) was added 10% Pd on C (20 mg). It was hydrogenated under atmospheric pressure using H_2 balloon. After 1 h, Boc_2O (0.5 mL, 2.165 mmol) was added to the reaction mixture and stirred for 5 h. The reaction mixture was then filtered through a short pad of Celite, and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated in vacuo. Purification by column chromatography (SiO_2, 50−60% EtOAc in petroleum ether eluant) afforded **45** (0.16 g, 74%). R_f = 0.35 (silica gel, 80% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −16.9 (*c* 0.3, $CHCl_3$); IR (neat): ν_{max} 3350, 1700, 1525 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.9 (m, 1 H, N*H*Boc), 4.15−4.0 (m, 2 H, C2-*H*, C5-*H*), 3.62 (dd, *J* = 11.5, 3.5 Hz, 1 H, C1-*H*), 3.45 (dd, *J* = 11.5, 5.5 Hz, 1 H, C1-*H*′), 3.35 and 3.1 (m, 2 H, C6-H_2), 2.1−1.6 (m, 4 H, C3-H_2, C4-H_2), 1.45 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.13, 79.65, 79.21, 78.42, 64.82, 44.34, 28.92, 28.34, 27.4; MS (LSIMS): *m*/*z* (%): 254 (12) [M^+ + Na], 232 (20) [M^+ + H].

***N*-Boc-6-amino-2,5-anhydro-3,4,6-trideoxy-D-idonic Acid (46).** A mixture of $NaIO_4$ (0.256 g, 1.2 mmol) and $RuCl_3 \cdot 3H_2O$ (1.5 mg, 0.006 mmol) in CH_3CN:CCl_4:H_2O (1:1:1.5, 4.5 mL) was stirred at room temperature for 0.5 h and then added into an CH_3CN solution of the alcohol **45** at 0 °C. After stirring for 0.5 h, an additional amount of $NaIO_4$ was added to the reaction mixture. After 10 min, it was diluted with EtOAc, washed with saturated aqueous NH_4Cl, brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was azeotroped with dry toluene to afford pure acid **46** in quantitative yield, which was used directly in the next step without further purification.

2,5-Anhydro-3,4-di-*O*-benzyl-D-idaric Acid Dimethyl Ester (48). To a solution of **32** (0.4 g, 1 mmol) in dry DMF (6 mL) were added PDC (3.76 g, 10 mmol) and 4 Å mol sieves (3.76 g) at 0 °C. The reaction mixture was stirred at room temperature for 12 h under nitrogen atmosphere. After cooling to 0 °C, an ethereal solution of CH_2N_2 was added to it until all the acids were converted into the diester. It was then diluted with EtOAc and filtered through a short pad of Celite, and the filter cake was washed with EtOAc. The filtrate and washings were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 20−25% EtOAc in petroleum ether eluant) gave pure idaric acid diester **48** (0.24 g, 60%) as a syrupy liquid. R_f = 0.5 (silica gel, 45% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 11.2 (*c* 0.9, $CHCl_3$); IR (neat): ν_{max} 1762, 1737, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.4−7.15 (m, 10 H, Ar*H*), 4.95 (d, *J* = 4.5 Hz, 2 H, C2-*H*, C5-*H*), 4.48 (ABq, 4 H, PhCH_2O-), 4.24 (d, *J* = 4.5 Hz, 2 H, C3-*H*, C4-*H*), 3.74 (s, 6 H, CO_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.1, 136.9, 128.47, 128.1, 127.76, 82.1, 80.79, 72.74, 52; MS (LSIMS): *m*/*z* (%): 399 (20) [M^+ − H], 423 (34) [M^+ +

Na]; HRMS (LSIMS): calcd for $C_{22}H_{24}O_7$ [M^+]: 400.1522, found: 400.1504.

Boc-Gaa(Bn$_2$)-Phe-Leu-OMe (49i). A solution of Cbz-Phe-Leu-OMe (0.4 g, 0.93 mmol) in MeOH:1 N HCl (4:1, 5 mL) was hydrogenated under atmospheric pressure using Pd on C (10%, 0.2 g) for 0.5 h. The reaction mixture was then filtered through a short pad of Celite, and the filter cake was washed with EtOAc. The combined filtrate and washings were concentrated in vacuo to get the hydrochloride of the deprotected amine.

Saponification of **20** (0.4 g, 0.85 mmol) was carried out in THF:MeOH:H_2O (3:1:1, 5 mL) at 0 °C using LiOH·H_2O (0.107 g, 2.55 mmol). After 1 h, the reaction mixture was acidified by adding 1 N HCl till pH 2. It was then diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in dry CH_2Cl_2 (3 mL), cooled to 0 °C, and treated sequentially with HOBt (0.114 g, 0.85 mmol) and EDCI (0.164 g, 0.85 mmol). After 0.25 h, the hydrochloride of the amine, HCl·H_2N-Phe-Leu-OMe, prepared above and dissolved in dry DMF (2 mL), was added to the reaction mixture followed by the addition of DIPEA (0.3 mL, 1.72 mmol). After stirring for 6 h at room temperature, the reaction mixture was diluted with EtOAc, washed with saturated NH_4-Cl and brine, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 10−40% EtOAc in petroleum ether eluant) gave pure tripeptide **49i** (0.41 g, 66%) as a white solid. R_f = 0.5 (silica, 40% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 7.4 (*c* 1, $CHCl_3$); mp 32−33 °C; IR (KBr): ν_{max} 1760, 1665, 1625, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.52 (d, *J* = 9.4 Hz, 1 H, PheN*H*), 7.4−7.05 (m, 15 H, Ar*H*), 6.6 (d, *J* = 8.5 Hz, 1 H, LeuN*H*), 4.8 (m, 2 H, Gaa-N*H*, PheCα*H*), 4.55 and 4.2 (two ABq, 4 H, PhCH_2O), 4.52 (d, *J* = 5 Hz, 1 H, GaaC2-*H*), 4.5 (m, 1 H, LeuCα*H*), 4.22 (dd, *J* = 5, 2 Hz, 1 H, GaaC3-*H*), 4.13 (m, 1 H, GaaC5-*H*), 4.0 (m, 1 H, GaaC4-*H*), 3.6 (s, 3 H, CO_2CH_3), 3.4−3.1 (m, 2 H, GaaC6-*H*), 3.15 (d, *J* = 7.4 Hz, 2 H, PheCβH_2), 1.8−1.3 (m, 3 H, LeuCβH_2, Cγ*H*), 1.45 (s, 9 H, Boc), 0.84 and 0.8 (two d, *J* = 6.5 Hz, 6 H, Leu-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.68, 170.66, 168.38, 156.32, 137.14, 136.97, 129.45, 128.59, 128.50, 128.13, 127.96, 127.53, 126.85, 85.68, 83.44, 82.54, 81.93, 79.70, 72.86, 71.53, 53.43, 52.05, 50.87, 43.41, 41.23, 37.63, 28.49, 24.64, 22.69, 21.86; MS (LSIMS): *m*/*z* (%): 754 (10) [M^+ + Na], 732 (50) [M^+ + H], 632 (100) [M^+ + H − 100]. HRMS (LSIMS): calcd for $C_{41}H_{54}N_3O_9$ [M^+ + H]: 732.3860, found: 732.3876.

Boc-Maa(Bn$_2$)-Phe-Leu-OMe (49ii). R_f = 0.5 (silica, 40% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 1.3 (*c* 1, $CHCl_3$); mp 118−120 °C; IR (KBr): ν_{max} 1750, 1710, 1650, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.4−7.05 (m, 16 H, Ar*H*, PheN*H*), 6.23 (d, *J* = 8.2 Hz, 1 H, LeuN*H*), 4.84 (t, *J* = 5.6 Hz, 1 H, MaaN*H*), 4.62 (ABq, 2 H, PhCH_2O-), 4.6−4.5 (m, 2 H, PheCα*H*, MaaC2-*H*), 4.35 (m, 3 H, PhCH_2O-, MaaC3-*H*), 4.0 (m, LeuCα*H*), 3.77 (m, 1 H, MaaC4-*H*), 3.7 (s, 3 H, CO_2CH_3), 3.45−3.15 (m, 2 H, MaaC6-H_2), 3.0 (dd, *J* = 13.7, 5.9 Hz, 1 H, PheCβH), 2.75 (dd, *J* = 13.7, 7.2 Hz, 1 H, PheC$\beta H'$), 1.7−1.4 (m, LeuCβH_2, Cγ*H*), 1.46 (s, 9 H, Boc), 0.91 and 0.88 (two d, *J* = 6.5 Hz, 6 H, Leu-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.74, 170.43, 170.15, 155.85, 137.26, 137.06, 136.19, 129.4, 128.56, 128.46, 128.41, 127.96, 127.89, 126.95, 85.34, 83.9, 83.32, 79.44, 71.97, 71.64, 53.73, 52.18, 50.89, 42.32, 41.41, 37.48, 28.38, 24.71, 22.64, 21.94; MS (LSIMS): *m*/*z* (%): 754 (10) [M^+ + Na], 732 (40) [M^+ + H]; HRMS (LSIMS): calcd for $C_{41}H_{53}N_3O_9$ [M^+]: 731.3782, found: 731.3771.

Boc-Iaa(Bn$_2$)-Phe-Leu-OMe (49iii). R_f = 0.5 (silica, 40% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 13.3 (*c* 0.9, $CHCl_3$); IR (KBr): ν_{max} 1750, 1725, 1675, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.4−7.05 (m, 15 H, Ar*H*), 7.0 (d, *J* = 9.1 Hz, 1 H, PheN*H*), 6.45 (d, *J* = 8.2 Hz, 1 H, LeuN*H*), 4.84 (dd, *J* = 9.1, 6.8 Hz, 1 H, IaaN*H*), 4.68 and 4.48 (ABq, 2 H, PhCH_2O-), 4.6 (d, *J* = 4.5 Hz, 1 H, IaaC2-*H*), 4.6−4.4 (m, 2 H, IaaC5-*H*, PheCα*H*), 4.35 and 4.05 (ABq, 2 H, PhCH_2O-), 4.28 (d, *J* = 4.5 Hz, 1H, IaaC3-*H*), 4.18 (m, 1 H, LeuCα*H*), 3.72 (d, *J* = 4.5 Hz, 1 H, IaaC4-*H*), 3.64 (s, 3 H, CO_2CH_3), 3.5−3.15 (m, 3 H, PheCβH, IaaC6-H_2), 3.05 (dd, *J* = 13.7, 6.8 Hz, 1 H, PheC$\beta H'$), 1.7 (m, 1 H, LeuCγ*H*), 1.5 (s, 9 H, Boc), 1.5−1.15 (m, 2 H, LeuCβH_2), 0.91 (d, *J* = 6.5 Hz, 6 H, Leu-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.52, 170.21, 168.78, 155.82, 137.15, 136.94, 136.28, 129.52, 128.54, 128.06, 127.65, 127, 81.5, 80.79, 79.39, 73.14, 71.01, 53, 52.01, 50.93, 40.93, 40.09, 37.3, 28.38, 24.77, 22.58, 21.82; MS (LSIMS): *m*/*z* (%): 754 (20) [M^+ + Na], 732 (24) [M^+ + H]; HRMS (LSIMS): calcd for $C_{41}H_{54}N_3O_9$ [M^+ + H]: 732.3860, found: 732.3868.

Boc-ddIaa-Phe-Leu-OMe (49iv). R_f = 0.5 (silica, 40% EtOAc in petroleum ether); IR (neat): ν_{max} 1750, 1710, 1660, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.3−7.15 (m, 5 H, Ar*H*), 7.06 (d, *J* = 7.9 Hz, 1 H, PheN*H*), 6.18 (d, *J* = 7.9 Hz, 1 H, LeuN*H*), 4.71 (br t, *J* = 6 Hz, 1 H, ddIaaN*H*), 4.53 (q, *J* = 7.9 Hz, 1 H, PheCα*H*), 4.43 (m, 1 H, LeuCα*H*), 4.29 (t, *J* = 7.9 Hz, 1 H, ddIaaCα*H*), 4.03 (m, 1 H, ddIaaC5-*H*), 3.62 (s, 3 H, CO_2CH_3), 3.32−3.0 (m, 4 H, PheCβH_2, ddIaaC6-H_2), 2.3−2.2, 1.97−1.83 and 1.62−1.38 (m, 7 H, LeuCβH_2, LeuCγ*H*, ddIaaC3-H_2, ddIaaC4-H_2), 1.4 (s, 9 H, Boc), 0.81 (d, *J* = 6.0 Hz, 6 H, Leu-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.07, 172.7, 170.3, 156, 136.42, 129.24, 128.68, 127.1, 79.9, 78.5, 53.93, 52.26, 50.93, 44.14, 41.37, 37.63, 30.08, 29.7, 28.4, 28.23, 24.8, 22.68, 21.9; MS (LSIMS): *m*/*z* (%): 542 (60) [M^+ + Na], 520 (80) [M^+ + H].

Boc-Tyr(Br-Z)-Gaa(Bn$_2$)-Phe-Leu-OMe (50i). To a solution of **49i** (0.4 g, 0.55 mmol) in dry CH_2Cl_2 (4 mL) was added trifluoroacetic acid (2 mL) at 0 °C and stirred under nitrogen for 0.5 h. The reaction mixture was then concentrated in vacuo. In another round-bottom flask, Boc-Tyr(Br-Z)-OH (0.298 g, 0.6 mmol), dissolved in dry CH_2Cl_2 (4 mL), was sequentially treated with HOBt (0.082 g, 0.6 mmol) and EDCI (0.116 g, 0.6 mmol) at 0 °C. After 0.25 h, TFA·H_2N-Gaa(Bn$_2$)-Phe-Leu-OMe, prepared above and dissolved in dry DMF (2 mL), was added to the reaction mixture, followed by the addition of DIPEA (0.21 mL. 1.2 mmol). After stirring for 6 h at room temperature, the reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 10−50% EtOAc in petroleum ether eluant) gave pure tetrapeptide **50i** (0.39 g, 64%) as a white solid. R_f = 0.45 (silica, 40% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 23.0 (*c* 1, $CHCl_3$); mp 54−55 °C; IR (KBr): ν_{max} 1765, 1715, 1650, 1500 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.31 (t, *J* = 5.6 Hz, 1 H, GaaN*H*), 8.23 (d, *J* = 7.5 Hz, 1 H, LeuN*H*), 7.9 (d, *J* = 8.5 Hz, 1 H, PheN*H*), 7.69 (dd, *J* = 7.6, 1 Hz, 1 H, Br-Z-*H*3), 7.55 (dd, *J* = 7.6, 1.6 Hz, 1 H, Br-Z-*H*6), 7.45 (dt, *J* = 7.6, 1 Hz, 1 H, Br-Z-*H*5), 7.35 (dt, *J* = 7.6, 1.6 Hz, 1 H, Br-Z-*H*4), 7.32−7.12 (m, 19 H, aromatic), 7.01 (d, *J* = 8.6 Hz, 1 H, TyrN*H*), 5.3 (s, 2 H, Br-Z−CH_2O-), 4.7 (dt, *J* = 8.5, 4.6 Hz, 1 H, PheCα*H*), 4.45 (ABq, 2 H, PhCH_2O-), 4.43 (s, 2 H, PhCH_2O-), 4.35 (d, *J* = 4.2 Hz, 1 H, GaaC2-*H*), 4.27 (q, *J* = 7.5 Hz, 1 H, LeuCα*H*), 4.14 (m, 1 H, TyrCα*H*), 4.12 (d, *J* = 4.2 Hz, 1 H, GaaC3-*H*), 4.01 (m, 1 H, GaaC4-*H*), 3.94 (m, 1 H, GaaC5-*H*), 3.55 (s, 3 H, CO_2CH_3), 3.4 and 3.3 (m, 2 H, GaaC6-H_2), 3.12 (dd, *J* = 14.1, 4.6 Hz, 1 H, PheCβH), 2.98−2.92 (m, 2 H, TyrCβH, PheC$\beta H'$), 2.74 (dd, *J* = 13.8, 10.5 Hz, 1 H, TyrC$\beta H'$), 1.59 (m, 1 H, LeuCγ*H*), 1.46 (m, 2 H, LeuCβH_2), 1.27 (s, 9 H, Boc), 0.81 and 0.75 (two d, *J* = 6.4 Hz, 6 H, Leu-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.59, 172.15, 170.91, 168.38, 155.7, 153.34, 150.01, 137.08, 136.79, 132.93, 130.46, 130.13, 130.01, 129.32, 128.56, 128.48, 128.37, 128.21, 128.12, 127.93, 127.60, 127.48, 126.92, 120.95, 84.08, 82.52, 81.24, 80.14, 73.0, 71.47, 69.54, 53.74, 52.10, 51.05, 42.25, 41.19, 38.35, 38.21, 28.19, 24.67, 22.64, 22.04; MS (LSIMS): *m*/*z* (%): 1109 (20) [M^+(^{81}Br) + H], 1107 (18) [M^+(^{79}Br) + H], 1009 (60) [M^+(^{81}Br) + H − 100], 1007 (54) [M^+(^{79}Br) + H − 100].

Boc-Tyr(Br-Z)-Maa(Bn$_2$)-Phe-Leu-OMe (50ii). R_f = 0.45 (silica, 40% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 5.4 (*c* 1, $CHCl_3$); mp 59−60 °C; IR (KBr): ν_{max} 1770, 1650, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.51 (d, *J* = 7.6 Hz, 1 H, LeuN*H*), 8.25 (t, *J* = 5.6 Hz, 1 H, MaaN*H*), 7.69 (dd, *J* = 7.7, 1 Hz, 1 H, Br-Z-*H*3), 7.64 (d, *J* = 8.5 Hz, 1 H, PheN*H*), 7.55 (dd, *J* = 7.7, 1.2 Hz, 1 H, Br-Z-*H*6), 7.45 (dt, *J* = 7.7, 1 Hz, 1 H, Br-Z-*H*5), 7.35 (dt, *J* = 7.7, 1.2 Hz, 1 H, Br-Z-*H*4), 7.32−7.07 (m, 19 H, aromatic), 6.96 (d, *J* = 8.5 Hz, 1 H, TyrN*H*), 5.3 (s, 2 H, Br-Z−CH_2O-), 4.7 (ddd, *J* = 8.5, 8, 5 Hz, 1 H, PheCα*H*), 4.51 (ABq, 2 H, PhCH_2O-), 4.41 (ABq, 2 H, PhCH_2O-), 4.39 (s, 1 H, MaaC2-*H*), 4.27 (m, 1 H, LeuCα*H*), 4.2 (m, 1 H, TyrCα*H*), 4.13

(s, 1 H, MaaC3-*H*), 3.94 (m, 2 H, MaaC4-*H*, MaaC5-*H*), 3.61 (s, 3 H, CO_2CH_3), 3.4 and 3.3 (two, m, 2 H, MaaC6-H_2), 2.98−2.82 (m, 4 H, TyrCβH_2, PheCβH_2), 1.59−1.46 (m, 3 H, LeuCβH_2, CγH), 1.22 (s, 9 H, Boc), 0.87 and 0.84 (two d, J = 6.4 Hz, 6 H, Leu-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.96, 171.77, 170.9, 170.63, 155.9, 153.35, 149.89, 137.22, 137.1, 136.7, 135.11, 134.25, 132.9, 130.42, 130.11, 130.04, 129.4, 128.45, 128.38, 127.88, 127.60, 126.78, 123.43, 120.82, 85.53, 83.6, 83.38, 83.31, 79.98, 71.98, 71.51, 69.52, 54.25, 52.18, 51.0, 41.27, 38.6, 37.94, 29.64, 28.27, 24.7, 22.57, 22.02; MS (LSIMS): *m*/*z* (%): 1108 (54) [M^+(^{79}Br) + H_2], 1110 (52) [M^+(^{81}Br) + H_2], 1130 (82) [M^+(^{79}Br) + H + Na], 1132 (100) [M^+(^{81}Br) + H + Na].

Boc-Tyr(Br-Z)-Iaa(Bn$_2$)-Phe-Leu-OMe (50iii). R_f = 0.35 (silica, 50% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 16.2 (*c* 1, $CHCl_3$); IR (KBr): ν_{max} 1700, 1662, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.6 (dd, J = 7.7, 1 Hz, 1 H, Br-Z-*H*3), 7.5 (dd, J = 7.7, 1.2 Hz, 1 H, Br-Z-*H*6), 7.37−7.07 (m, 22 H, aromatic, PheN*H*), 6.33 (d, J = 7.8 Hz, 1 H, LeuN*H*), 6.1 (t, J = 5.8 Hz, 1 H, IaaN*H*), 5.36 (s, 2 H, Br-Z−CH_2O-), 4.9 (m, 1 H, TyrN*H*), 4.79 (dt, J = 8.7, 6.5 Hz, 1 H, PheCαH), 4.66 and 4.48 (two d, ABq, 2 H, PhCH_2O-), 4.55 (d, J = 3.8 Hz, 1 H, IaaC2-*H*), 4.44 (m, 1 H, IaaC5−H), 4.36 and 4.05 (two d, ABq, 2 H, PhCH_2O-), 4.28 (d, J = 3.8 Hz, 1 H, IaaC3-*H*), 4.2 (m, 1 H, LeuCαH), 4.16 (m, 1 H, TyrCαH), 3.72 (d, J = 3.8 Hz, 1 H, IaaC4-*H*), 3.63 (s, 3 H, CO_2CH_3), 3.52 and 3.38 (two m, 2 H, IaaC6-H_2), 3.2 and 3.14 (two dd, J = 13.8, 6.4 Hz, 2 H, PheCβH_2), 3.01 and 2.94 (two dd, J = 14, 6.7 Hz, 2 H, TyrCβH_2), 1.5−1.2 (m, 3 H, LeuCβH_2, CγH), 1.4 (s, 9 H, Boc), 0.8 (d, J = 6.5 Hz, 6 H, Leu-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.55, 171.13, 170.19, 168.71, 155.19, 153.31, 150.02, 137.23, 136.91, 136.46, 134.57, 132.91, 130.26, 130.13, 130.03, 129.41, 128.66, 128.57, 128.28, 128.08, 127.96, 127.89, 127.6, 126.95, 123.41, 121, 81.73, 81.55, 81.29, 80.16, 79.41, 73.08, 71.98, 69.56, 53.52, 52.06, 50.94, 41.06, 38.59, 37.72, 37.64, 28.25, 24.75, 22.55, 21.92; MS (LSIMS): *m*/*z* (%): 1007 (30) [M^+(^{79}Br) + H − 100], 1009 (32) [M^+(^{81}Br) + H − 100]; HRMS (LSIMS): calcd for $C_{53}H_{60}{}^{79}BrN_4O_{11}$ [M^+(^{79}Br) + H − $C_5H_8O_2$]: 1007.3442, found: 1007.3457; calcd for $C_{53}H_{60}{}^{81}BrN_4O_{11}$ [M^+(^{81}Br) + H − $C_5H_8O_2$]: 1009.3421, found: 1009.3430.

Boc-Tyr(Br-Z)-ddIaa-Phe-Leu-OMe (50iv). R_f = 0.5 (silica, 70% EtOAc in petroleum ether); $[\alpha]^{20}_D$−29.5 (*c* 1.1, $CHCl_3$); IR (KBr): ν_{max} 1765, 1750, 1650, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (dd, J = 7.7, 1 Hz, 1 H, Br-Z-*H*3), 7.5 (dd, J = 7.7, 1.2 Hz, 1 H, Br-Z-*H*6), 7.36 (dt, J = 7.7, 1.2 Hz, 1 H, Br-Z-*H*5), 7.35−7.07 (m, 11 H, Ar*H*, PheN*H*), 6.2 (d, J = 7.8 Hz, 1 H, LeuN*H*), 6.18 (m, 1 H, ddIaaN*H*), 5.38 (s, 2 H, Br-Z−CH_2O-), 5.05 (d, J = 8.5 Hz, 1 H, TyrN*H*), 4.79 (q, J = 7.5 Hz, 1 H, PheCαH), 4.5 (m, 1 H, ddIaaC2-*H*), 4.4−4.25 (m, 2 H, ddIaaC5-*H*, LeuCαH), 4.0 (m, 1 H, TyrCαH), 3.7 (s, 3 H, CO_2CH_3), 3.32 (t, J = 7 Hz, 2 H, ddIaaC6-H_2), 3.12 and 3.08 (two d, J = 7.5 Hz, 4 H, PheCβH_2, TyrCβH_2), 2.5−1.4 (m, 7 H, ddIaaC3-H_2, ddIaaC4-H_2, LeuCβH_2, CγH), 1.42 (s, 9 H, Boc), 0.88 (d, J = 6.5 Hz, 6 H, Leu-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.9, 172.7, 171.42, 170.4, 155.4, 153.3, 150.0, 136.4, 134.7, 134.2, 132.9, 130.3, 130.1, 130.0, 129.2, 128.5, 127.5, 126.9, 123.4, 121.0, 80.3, 79.0, 78.3, 69.5, 56.0, 54.0, 52.1, 50.8, 42.4, 41.1, 37.8, 29.7, 28.2, 24.7, 22.6, 21.8; MS (LSIMS): *m*/*z* (%): 795 (34) [M^+(^{79}Br) + H − 100], 797 (33) [M^+(^{81}Br) + H − 100], 917 (5) [M^+(^{79}Br) + Na], 919 (5) [M^+(^{81}Br) + Na], 1027 (96) [M^+(^{79}Br) + Cs], 1029 (100) [M^+(^{81}Br) + Cs].

Boc-Tyr-Gaa-Phe-Leu-OMe (8a). To a solution of **50i** (o.3 g, 0.27 mmol) in EtOAc (4 mL), $Pd(OH)_2$ on C (10%, 0.03 g) was added and the mixture was hydrogenated under atmospheric pressure using a H_2-filled balloon for 4 h. It was then filtered through a short pad of Celite and the filter cake was washed with EtOAc. The combined filtrate and washings were concentrated in vacuo to get **8a** (0.181 g, 94%) as a white solid. R_f = 0.4 (silica, EtOAc); $[\alpha]^{20}_D$ −4.8 (*c* 0.5, MeOH); mp 159−160 °C; IR (KBr): ν_{max} 3325, 1725, 1655, 1510 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): see Table 1; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 173, 172.66, 170.97, 169.34, 155.77, 155.23, 138.74, 130.12, 128.97, 128.24, 128.13, 126.17, 114.87, 87.72, 82.52, 78.06, 77.92, 77.84, 56.42, 53.01, 51.94, 50.55, 41.64, 37, 36.19, 28.24, 23.79, 22.83, 21.16; MS (LSIMS): *m*/*z* (%): 737 (34) [M^+ + Na], 715 (36) [M^+ + H], 615 (100) [M^+ + H − 100]; HRMS (LSIMS) calcd for $C_{36}H_{51}N_4O_{11}$ [M^+ + H]: 715.3554, found: 715.3557.

Boc-Tyr-Maa-Phe-Leu-OMe (9a). R_f = 0.35 (silica gel, EtOAc); $[\alpha]^{20}_D$ 91.2 (*c* 1, MeOH); mp 119−120 °C; IR (KBr): ν_{max} 3360, 1740, 1660, 1525 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): see Table 2; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 172.81, 172.13, 170.7, 170.32, 155.74, 155.26, 137.2, 130.17, 129.58, 128.33, 128.08, 126.38, 114.82, 84.37, 80.28, 78.15, 77.94, 56.0, 52.93, 51.95, 50.3, 40.83, 39.79, 37.54, 37.15, 28.21, 24.19, 22.79, 21.36; MS (LSIMS): *m*/*z* (%): 715 (28) [M^+ + H], 615 (100) [M^+ + H − 100]; HRMS (LSIMS) calcd for $C_{36}H_{51}N_4O_{11}$ [M^+ + H]: 715.3554, found: 715.3523.

Boc-Tyr-Iaa-Phe-Leu-OMe (10a). R_f = 0.4 (silica gel, EtOAc); $[\alpha]^{20}_D$ −13.5 (*c* 1.63, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): see Table 3; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.84, 172.92, 171.0, 170.78, 155.5, 155.48, 135.83, 130.36, 129.23, 128.71, 127.37, 127.2, 115.7, 81.67, 80.34, 77.5, 75.93, 56.31, 53.24, 52.39, 51.08, 40.28, 37.8, 37.7, 37.0, 28.28, 24.65, 22.62, 21.64; MS (LSIMS): *m*/*z* (%): 715 (18) [M^+ + H], 615 (100) [M^+ + H − 100]; HRMS (LSIMS) calcd for $C_{36}H_{51}N_4O_{11}$ [M^+ + H]: 715.3554, found: 715.3553.

Boc-Tyr-ddIaa-Phe-Leu-OMe (11a). R_f = 0.4 (silica gel, 80% EtOAc in petroleum ether); $[\alpha]^{20}_D$ −3.4 (*c* 1, $CHCl_3$); IR (KBr): ν_{max} 3400, 1650, 1525 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): see Table 4; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.57, 172.51, 171.24, 171.12, 155.98, 155.25, 135.0, 130.27, 129.34, 128.58, 127.76, 127.1, 115.62, 80.04, 79.4, 78.15, 53.88, 52.34, 51.1, 42.96, 41.07, 38.77, 38.37, 29.77, 28.31, 24.75, 22.6, 21.83; MS (LSIMS): *m*/*z* (%): 583 (100) [M^+ + H − 100], 683 (48) [M^+ + H], 705 (30) [M^+ + Na], 815 (14) [M^+ + Cs]; HRMS (LSIMS): calcd for $C_{36}H_{51}N_4O_9$ [M^+ + H]: 683.3656, found: 683.3655.

MeO-Leu-Phe-Idac(Bn$_2$)-Phe-Leu-OMe (51). The dibenzyl derivative of idaric acid (**47**), prepared from the diester **48** (100 mg, 0.25 mmol) by saponification, was reacted with H_2N-Phe-Leu-OMe obtained from Cbz-Phe-Leu-OMe (276 mg, 0.645 mmol) under the same coupling conditions described above for the synthesis of **49i** to get the reverse turn mimetic **51** (170 mg, 74%). R_f = 0.4 (silica, 50% EtOAc in petroleum ether); $[\alpha]^{20}_D$ 3.8 (*c* 1, $CHCl_3$); IR (KBr): ν_{max} 1750, 1650, 1512 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): see Table 5; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.44, 169.95, 167.61, 136.7, 136.25, 129.37, 128.62, 128.48, 128.03, 127.64, 127.1, 82.77, 81.4, 72.76, 53.47, 52.1, 50.94, 41.03, 37.87, 24.73, 22.49, 21.91; MS (LSIMS): *m*/*z* (%): 921 (100) [M^+ + H], 943 (50) [M^+ + Na]; HRMS (LSIMS): calcd for $C_{52}H_{64}N_4O_{11}Na$ [M^+ + Na]: 943.4469, found: 943.4442.

MeO-Leu-Phe-Idac-Phe-Leu-OMe (12). The intermediate **51** (120 mg, 0.112 mmol) was hydrogenated in the usual way using Pd−C/H_2-balloon to get a quantitative yield of compound **12** (100 mg). R_f = 0.5 (silica, EtOAc); $[\alpha]^{20}_D$ 21.2 (*c* 1, $CHCl_3$); IR (KBr): ν_{max} 3375, 1725, 1662, 1512 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): see Table 6; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 174.1, 170.04, 168.91, 135.84, 129.09, 128.7, 127.3, 83.33, 77.63, 53.16, 52.33, 50.77, 40.87, 36.86, 24.6, 22.62, 21.64; MS (LSIMS): *m*/*z* (%): 741 (90) [M^+ + H], 763 (40) [M^+ + Na]; HRMS (LSIMS): calcd for $C_{38}H_{53}N_4O_{11}$ [M^+ + H]: 741.3711, found: 741.3725.

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Supporting Information Available: ^{1}H, ^{13}C, TOCSY, ROESY, ^{1}H VT NMR and mass (LSIMS) spectra of **8**−**11a**, **51**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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