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**COMMUNICATION**

# Conformationally rigid aromatic amino acids as potential building blocks for abiotic foldamers†

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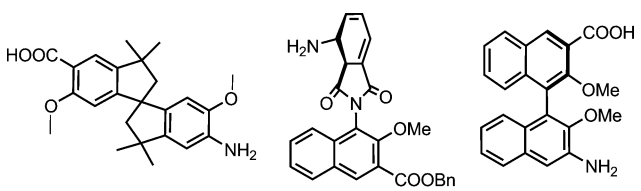
**This communication describes the development of conformationally constrained unnatural aromatic amino acids, constructed on rigid backbone wherein the carboxyl and amino groups project in two dimensions (planes) on the aromatic framework. Such a feature offers the possibility of design and development of conformationally ordered synthetic oligomers with intriguing structural architectures distinct from those classically observed. Furthermore, such amino acids will have the potential to extend the conformational space available for foldamer design with diverse backbone conformation and structural architectures.**

The conformation of biomolecules such as peptides and proteins are determined by their sequence of monomeric units and the torsional constraints of individual residues.[1] Alteration of the sequence of amino acid residues and the torsional parameters of the individual units have been shown to have a marked influence on the overall conformation and structural architecture (shape) of biopolymers. Indeed, extensive efforts have been made in the past to generate structural and conformational diversity in peptides and their analogs by the use of modified amino acid residues. Of particular interest is the emergence of homologous amino acids, such as α, β, δ, ω *etc.* in generating conformational diversity in oligomers.[2] Hectic activity in this area later culminated into the emergence of a new area of interest called foldamers; a class of conformationally ordered synthetic oligomers stabilized by non-covalent interactions.[3] In the last decade, considerable work has been contributed to the research area of foldamers to attain novel molecular architectures with wide range of applications.[4] The foldamer approach has been extensively utilized for generating diverse sets of structures which are able to mimic secondary structure elements like turns, helices, and β-pleated sheets.[5] The driving force for these efforts has been the possibility of achieving suitable templates for the design of biologically active molecules that compete for a variety of protein–protein[6] and protein–membrane interactions,[7] respectively. These synthetic oligomers may provide excellent starting points for the elaboration of peptide mimics that could be designed only with difficulties on the basis of small-molecule scaffolds.[8]

Although there are innumerable unnatural amino acids reported in the literature,[9–11] aromatic amino acids with two dimensional orientations of amino and carboxylic groups appended on conformationally rigid framework suitable for foldamer generation have not yet been explored. Positioning of the amino and carboxyl chain propagating groups on a rigid aromatic framework can be expected to show a marked influence on the overall shape of the oligomers containing such building blocks. Furthermore, such a strategy could furnish synthetic oligomers with dazzling structural architectures, distinctly different from those classically observed.[12]

Towards this end, we synthesized three novel unnatural aromatic amino acids **1–3** in their racemic form wherein the amino and carboxyl groups (chain propagating groups) are appended on conformationally rigid two-dimensional aromatic frameworks. Whereas the chain propagating groups are arranged on a heavily rigid spirobiindane framework in **1** having the aryl rings arranged in an anti-periplanar fashion (projected in two dimensions), the amino and carboxyl groups are displayed in two dimensions (planes) in **2** wherein anti-periplanar arrangement of the aryl rings is caused due to their restricted rotation; a notable feature already reported for conformationally restricted aryl amides.[13] The case of the BINOL-derived amino acid **3** is also similar to **2**, involving restricted rotation of the aryl rings forcing the chain propagating groups to be displayed in two dimensions (planes).




**1** **2** **3**

The synthesis of the aromatic amino acids **1–3** were accomplished according to Schemes 1–3. The spirobiindane based amino acid **1** was synthesized as follows (Scheme 1). Spirobiindane bis-ether **5**, obtained in quantitative yield by the exhaustive methylation of the known spirobiindanol **4**,[12b,14] was subjected to

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† Electronic supplementary information (ESI) available: General experimental procedures, $^{1}H$, $^{13}C$, DEPT-135 NMR spectra and ESI mass spectra of all new compounds are included. CCDC reference numbers 679298 and 773238. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00593b

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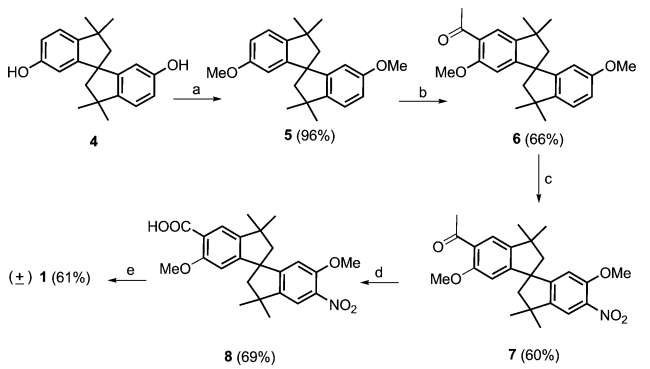
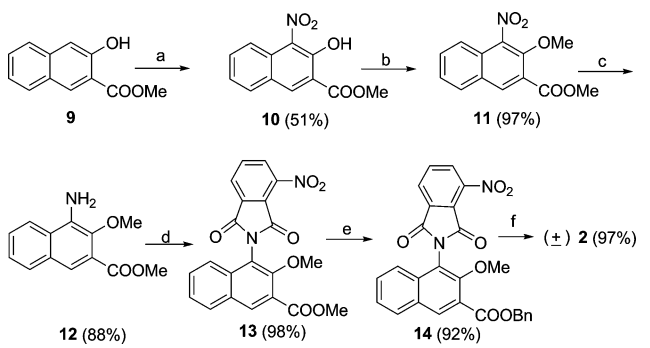



**Scheme 1** (a) Dimethyl sulfate, $K_2CO_3$, acetone, reflux, 8 h; (b) $CH_3COCl$, $SnCl_4$, DCM, –10 °C, 1.5 h; (c) conc. $HNO_3$, $H_2SO_4$ (cat.), acetic acid, rt, 2 min.; (d) 4% NaOCl, 50% NaOH, dioxane, 70 °C, 12 h; (e) ammonium formate, Pd–C, methanol, reflux, 6 h.

Friedel–Crafts acylation–haloform reaction sequence to introduce the carboxyl group on the aromatic framework. This procedure for the installation of the carboxyl group on the aryl rings *ortho* to alkoxy groups was preferred over a possible metal-directed (*O*-lithiation)-one-step carboxylation procedure, due to the anticipated difficulties associated with the latter procedure, particularly when working on a larger scale. The nitro derivative **7**, obtained by the careful nitration of **6**, was subjected to haloform reaction to afford the nitro acid **8**, which after catalytic nitro reduction readily furnished the novel amino acid **1** in an overall yield of 16% starting from **4** (Scheme 1).

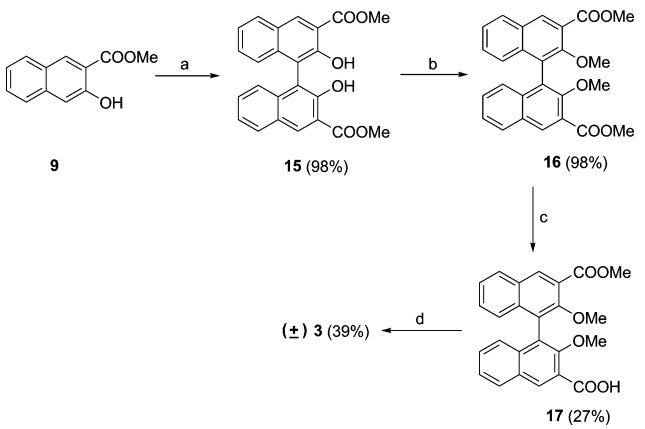
Starting from 3-hydroxy-2-naphthoic acid methyl ester **9**, the phthalimide based constrained amino acid **2** was obtained in six steps (Scheme 2). The methyl ester **9** was first subjected to careful nitration using conc. $HNO_3$ in DCM at 0 °C to furnish **10**, which was *O*-methylated subsequently to yield **11**. The amine **12**, obtained after reduction of **11** with $H_2$/Pd–C, was subjected to phthalimide protection with 3-nitrophthalic acid furnishing **13**, which could be crystallized. The corresponding benzyl ester **14** was prepared by *trans*-esterification of **13** in benzyl alcohol containing titanium tetraisopropoxide. This was followed by the selective reduction of $NO_2$ group with $NaBH_4/CoCl_2$[15] furnishing the benzyl ester of the constrained amino acid **2** in good overall yield (38% starting from **9**).




**Scheme 2** (a) Conc. $HNO_3$, DCM, rt, 15 min; (b) acetone, $K_2CO_3$, dimethyl sulfate, rt, 12 h; (c) $H_2$, Pd–C, AcOEt, rt, 6 h; (d) nitrophthalic acid, 140 °C, 30 min.; (e) BnOH, Ti(*i*-Pro)$_4$, 90 °C, 6 h; (f) $NaBH_4$, $CoCl_2$, MeOH, 10 min.

The idea of swapping the methyl ester with benzyl was owing to the anticipated difficulties in selective saponification of methyl ester in presence of phthalimide functionality, during oligomer synthesis using segment doubling strategy; a common strategy used for foldamer synthesis.

1,1′-Bi-2-naphthol-based constrained aromatic amino acid **3**, was synthesized starting from 3-hydroxy-2-naphthoic acid methyl ester **9** in overall four steps (Scheme 3). The racemic BINOL ester **15**, obtained by the oxidative coupling of methyl-3-hydroxy-naphthalene-2-carboxylate **9** using CuCl(OH).TMEDA[16] as catalyst, was subjected to *O*-methylation to afford the corresponding bis-ether derivative **16**. Partial hydrolysis of the ester group followed by Curtius rearrangement furnished **3** in an over all 10% yield starting from **9**.




**Scheme 3** (a) CuCl(OH).TMEDA, $O_2$, MeOH, reflux, 72 h; (b) dimethyl sulfate, $K_2CO_3$, acetone, reflux, 5 h; (c) LiOH (1.3 eq.), $H_2O$–THF, 0 °C (1 h), then 12 h, rt; (d) i. $(COCl)_2$, DCM, DMF (cat.), 0 °C, then rt, 3 h, ii. $NaN_3$, acetone, $H_2O$, 0 °C, 15 min.; iii. $C_6H_6$, reflux, 1 h; iv. 10% KOH, reflux, 1 h. *Note*: the isolated yield of **17** based on the recovered starting material, the bis-ester **16**, is 52%.

In order to get insight into the structural architecture of these novel amino acids, crystal structure studies were undertaken. Extensive efforts to grow crystals of the conformationally restricted aromatic amino acid building blocks culminated in the formation of crystals of **1** and **13**. Single crystal X-ray diffraction studies[17] of spirobiindane-based amino acid **1** and the phthalimide based amino acid precursor **13** of **2** revealed that the aryl rings projecting the amino and carboxy groups assume anti-periplanar conformation, as anticipated. In the spirobiindane based unnatural aromatic amino acid **1**, the amine and acid groups are oriented in such a way that they lie in two different planes, reversing the growth of the backbone by about 80° (Fig. 1a, b).

In the case of **13**, the single crystal X-ray diffraction studies substantiate that the aryl rings bearing nitro and carboxylic groups orient at about 90° (Fig. 1c, d) to each other and this conformational rigidity results from the restricted rotation of the aryl rings caused by steric effect.[18] Though the 1,1′-bi(2-naphthol)-based unnatural aromatic amino acid derivatives could not be crystallized despite our best efforts, it is clear from the observed atropisomerism of bi-napthol compounds[19] that in molecule **3** the naphthyl rings bearing carboxylic group and amino group adopt anti-periplanar conformations as observed in **1** and **13**, because of restricted rotation of the naphthyl rings.

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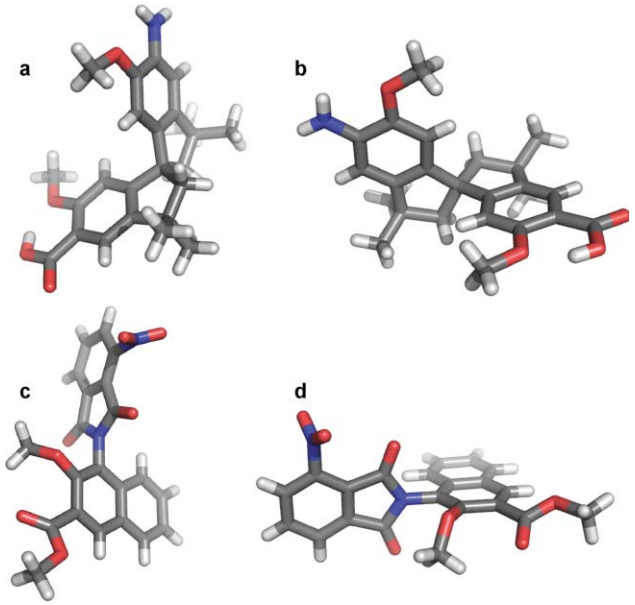


**Fig. 1** Crystal structure of **1** (a, b) and **13** (c, d) with different views exhibiting the two-dimensional orientation of the amino and carboxylic chain propagating groups appended on the aromatic rigid frameworks.

Inspection of the UV-visible spectra of the compounds **1**, **3**, and **13** showed λmax (nm) at around 240.

Summarizing our results, we have developed three novel conformationally rigid aromatic amino acids, wherein the chain propagating amino and carboxyl groups, embedded on the aryl rings, are projected in an anti-periplanar arrangement (two-dimensional arrangement). Oligomers containing such building blocks are expected to have overwhelming 'conformational ordering', facilitating ease of characterization.[20] Structural investigations of **1** and **13** by single-crystal X-ray studies provide clear evidence for their two-dimensional orientation of the chain propagating groups. The strategy disclosed herein for the construction of conformationally restricted aromatic amino acids[21] would be useful for the construction of oligomers displaying novel molecular architectures with unique conformations, distinct from those classically observed.

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17 The X-ray diffraction data of **1** and **13** were collected on a SMART APEX CCD single crystal X-ray diffractometer. The crystal structures were solved by direct method using SHELXS-97 and the refinement was performed by full matrix least squares of $F^2$ using SHELXL-97. Crystallographic data of **1** and **13** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC- 679298, and 773238, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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