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Parallel synthesis of cyclic sugar amino acid/amino acid hybrid molecules

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Abstract

The synthesis of a furanoid sugar amino acid and its application in a parallel robot-assisted construction of cyclic sugar amino acid/amino acid hybrids as new potential host molecules is described. A cursory structural analysis by NMR revealed that one of the resulting cyclic hybrids (i.e. **2b**) adopts a preferred conformation.

Keywords: sugar amino acid; host molecule; robot-assisted SPS; oxime linker.

An interesting and challenging subject in contemporary organic chemistry concerns the development of artificial receptors with enhanced solubility behaviour and complexation properties. In this respect, cyclodextrins (CDs) have been extensively studied due to their ability to include a variety of guest molecules in their hydrophobic cavities.[1] CDs selectively functionalized with different groups showed additional specific interactions between host and guest molecules.[2] For instance, CDs substituted with amino acids or peptides led inter alia to new molecular carriers, spectroscopically active inclusion complexes and enzyme mimetics.[3] Recently, Penadés and co-workers generated a novel type of hybrid receptor molecule with improved selectivity by combining the complexing properties of cyclodextrins with those of cyclophanes.[4] On the basis of this concept, a new class of receptor molecules endowed with structural elements of both cyclodextrins and cyclopeptides may be envisaged. This class of molecules can be attained by constructing cyclic arrangements comprising sugar amino acids (SAAs) and natural amino acids (AAs). An obvious advantage of this approach is that the amino and carboxylic acid functionalities in the SAA can be linked via amide bonds to either an AA or SAA following well-established peptide chemistry. The latter was demonstrated in the synthesis of linear oligosaccharide mimics in which the glycosidic linkages were replaced by amide bonds.[5] Fleet et

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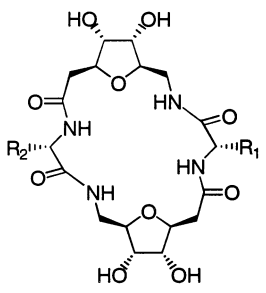
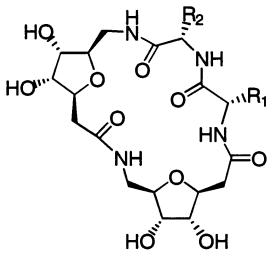
al. showed that oligomers solely composed of furanoid SAAs adopt a defined secondary structure.[6] Moreover, incorporation of an SAA at a specific location in peptide sequences led to a conformational restriction.[7]

In this paper we present a robot-assisted parallel solid phase synthesis of two types of tetrameric cyclic SAA/AA hybrids comprising a randomly chosen D-*allo*-furanoid SAA and hydrophobic AAs. In one of these, two SAAs are separated by one AA residue (i.e. glycine, alanine or phenylalanine) as in **1a**–**d**. In the other one, a dimeric SAA unit is connected to a dipeptide as in **2a**–**b**. In addition, evidence indicating that one of the cyclic hybrids (i.e. **2b**) adopts a preferred conformation will be presented.



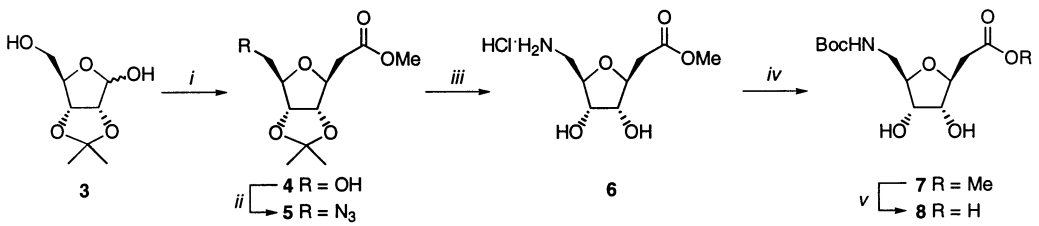
1a-d



2a-b

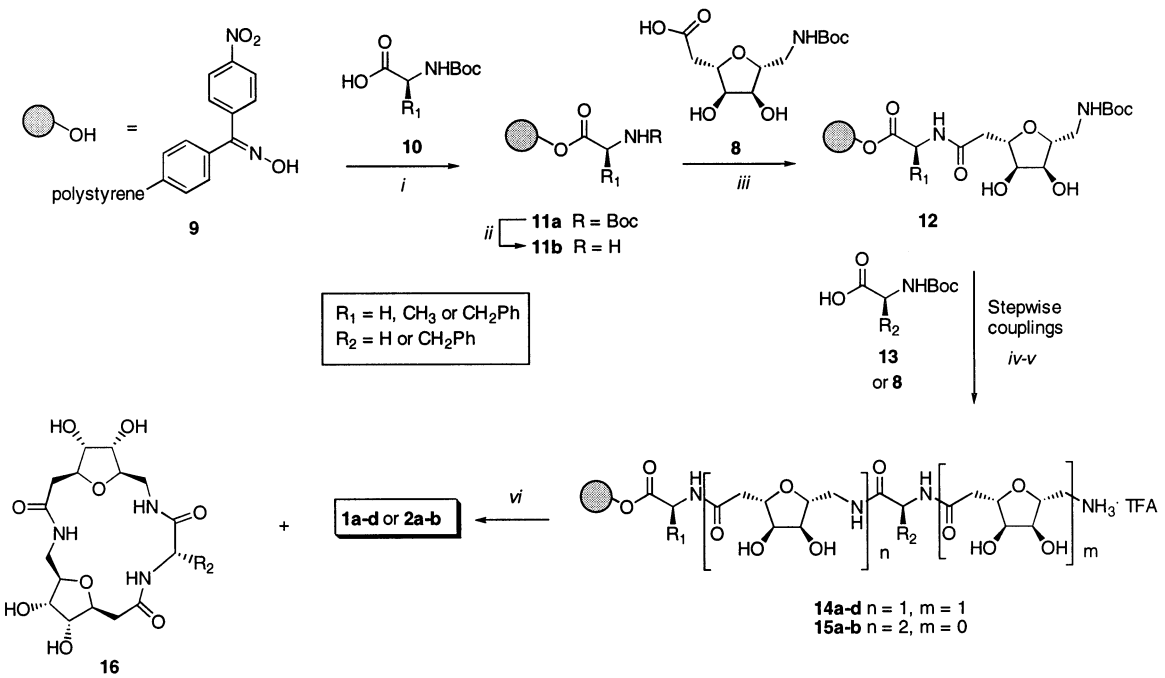
Compound	R_1	R_2
1a	H	H
1b	H	CH_2Ph
1c	CH_3	CH_2Ph
1d	CH_2Ph	CH_2Ph
2a	H	CH_2Ph
2b	CH_3	CH_2Ph

A crucial step in the synthesis of the target molecules **1**–**2** entails the cyclization of the linear precursors. It has been shown that on resin, cyclization of peptides with concomitant release from the solid support can be effected using a *p*-nitrobenzophenone oxime linker.[8] However, as the intrinsically base labile oxime linker is not compatible with Fmoc-chemistry, it is imperative to use a strategy based on Boc-protected building blocks. The preparation of the requisite *N*-Boc protected furanoid SAA unit **8**,[9] starting from 2,3-*O*-isopropylidene-D-ribose (**3**), is outlined in Scheme 1.



Scheme 1. Synthesis of furanoid SAA building block **8**. Reagents and conditions: (i) methyl(triphenylphosphoranylidene) acetate, CH_3CN (81%); (ii) (a) MsCl, pyridine (80%); (b) NaN_3, DMF, 75°C, 1 h (89%); (iii) H_2, Pd/C, HCl/EtOH; (iv) Boc_2O, $NaHCO_3$, Na_2CO_3, H_2O/dioxane (82%); (v) NaOH, H_2O, dioxane (89%)

Thus, reaction[10] of **3** with methyl(triphenylphosphoranylidene) acetate afforded β-*C*-furanoside **4** as the major product. Treatment of **4** with methanesulfonyl chloride in pyridine, followed by substitution of the intermediate mesylate with sodium azide provided compound **5**. Palladium-catalyzed hydrogenation of **5** in the presence of an equimolar amount of hydrochloric acid yielded the amine **6** as its hydrochloric salt. Treatment of **6** with di-*tert*-butyl dicarbonate under Schotten–Baumann conditions afforded the carbamate **7**, basic hydrolysis of which gave the free carboxylic acid **8** in an overall yield of 42%. The automated parallel synthesis of the cyclic compounds using a synthesis robot[11] is presented in Scheme 2. For example, in the case



Scheme 2. Parallel solid phase synthesis of the target cyclic hybrids **1a–d** and **2a–b**. Reagents and conditions: All coupling steps were carried out twice. (i) **10** (5 equiv.), DIC (5 equiv.), HOBT (5 equiv.), NMP/DCM; (ii) A; (iii) **8** (5 equiv.), B; (iv) (a) A; (b) **8** or **13** (5 equiv.), B; (v) (a) A; (b) **8** or **13** (5 equiv.), B; (c) A; (vi) DIPEA (2 equiv.), AcOH (2 equiv.), DMF. Boc-deprotection conditions A: 25% TFA, 1% TiPS, DCM. Coupling conditions B: BOP (5 equiv.), HOBT (5 equiv.), DIPEA (6.5 equiv.), NMP

of cyclic hybrid **1a**, the first amino acid **10** ($R_1 = H$) was anchored to the oxime resin **9** under the influence of diisopropylcarbodiimide (DIC) and hydroxybenzotriazole (HOBT). In order to ensure a high loading of the resin the condensation step was performed twice. Immobilized amino acid **11** was, after removal of the Boc-group with TFA (25% in DCM), coupled to SAA **8** in the presence of Castro's reagent (BOP) and diisopropylethylamine (DIPEA) to give dimer **12**. Stepwise extension of **12** (i.e. Boc-deprotection and subsequent coupling) with AA **13** ($R_2 = H$) and SAA building block **8**, followed by a final Boc-deprotection step, afforded the immobilized tetramer **14a** ($R_1 = H$, $R_2 = H$). In a similar fashion, the immobilized linear precursors **14b–d** and **15a–b** ($R_1 = H$, CH_3 or CH_2Ph, $R_2 = CH_2Ph$) were prepared by sequential elongation of **12** with the appropriate AAs and SAA **8**. Acid catalyzed cyclization of linear peptides **14a–d** and **15a–b** released the target compounds **1a–d** and **2a–b**, respectively, from the solid support. LCMS analysis of the crude cyclic products revealed, in all cases, the presence of a side product lacking the first amino acid (**10**).[12] The structure of one of the two possible trimeric side products, obtained in the synthesis of **1b–d** and **2a–b**, was in accordance with **16** ($R_2 = CH_2Ph$) as gauged by NMR.[13] Purification of the crude compounds by HPLC gave the target molecules **1–2** in a yield ranging from 10–30%. The homogeneity and identity of the cyclic tetramers was firmly established by NMR spectroscopy techniques (e.g. ^1H COSY, CH–COSY, TOCSY).[14] Conformational analysis of the cyclic hybrid **2b** by NMR in H_2O/D_2O (9/1) at pD 4 revealed a pronounced downfield shift (1 ppm) of the signal associated with the amide proton of alanine. The coupling constant ($J_{N\alpha} = 2$ Hz) of this amide proton with its neighbouring

α-proton is of the same order of magnitude as the coupling constants $J_{N\alpha}$ of a linear peptide having an α-helix structure.[15] Furthermore, a ROESY experiment showed the presence of several inter-residue cross peaks. Two of these cross peaks could be ascribed to the NOEs between the amide proton of phenylalanine and the amide protons of both alanine and the neighbouring SAA (see Fig. 1). These observations imply a preferred conformation for **2b**.

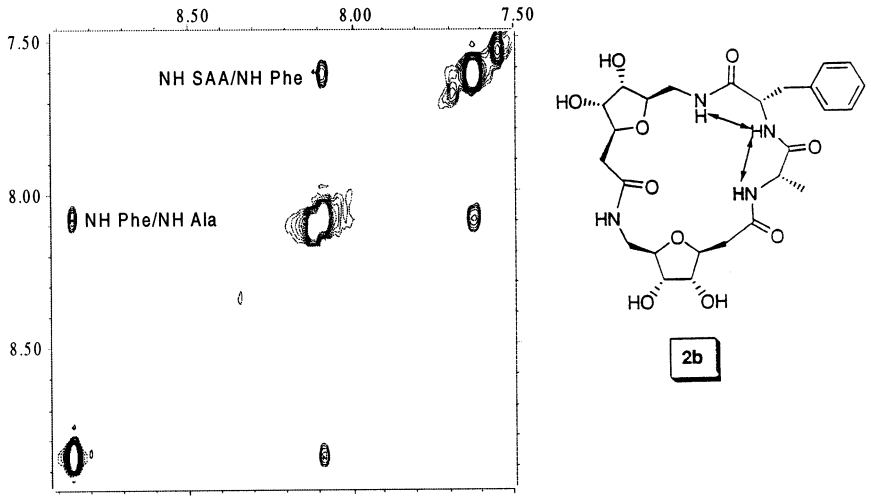


Figure 1. Part of the ROESY spectrum of **2b**

The results presented in this paper demonstrate that cyclic SAA/AA hybrid molecules are easily accessible via robot-assisted solid phase synthesis using an oxime resin. The preliminary structural evaluation of **2b**, containing an arbitrarily chosen furanoid SAA, indicates that this cyclic member adopts a defined structure. The results thus far obtained hold promise for a combinatorial approach towards potential receptor molecules based on a variety of pyranoid[16] and furanoid SAAs. The outcome of this study will be reported in due course.

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12. Later on it turned out that in most cases the formation of the side product could be prevented by using BOP/DIPEA as the condensation reagents in the anchoring step.
13. *Cyclo*[SAA–SAA–Phe] **16**: ^{1}H NMR (600 MHz, D_2O) δ 7.31 (t, $J=7.33$ Hz, 2H), 7.25 (t, $J=7.30$ Hz, 1H), 7.20 (d, $J=7.27$ Hz, 2H), 4.40 (dd, $J=6.98$ Hz, $J=8.57$ Hz, 1H), 4.10 (dd, $J=5.59$ Hz, $J=7.84$ Hz, 1H), 3.98 (m, 1H), 4.01 (dt, $J=2.5$ Hz, $J=11.4$ Hz, 1H), 3.91 (m, 1H), 3.94 (m, 1H), 3.88 (dd, $J=2.94$ Hz, $J=5.51$ Hz, 1H), 3.86 (m, 1H), 3.82 (dd, $J=3.64$ Hz, $J=6.94$ Hz, 1H), 3.69 (dd, $J=4.91$ Hz, $J=15.31$ Hz, 1H), 3.66 (dd, $J=2.40$ Hz, $J=1.96$ Hz, 1H), 3.46 (dd, $J=4.69$ Hz, $J=14.47$ Hz, 1H), 3.23 (dd, $J=2.80$ Hz, $J=14.47$ Hz, 1H), 3.09 (dd, $J=6.76$ Hz, $J=13.80$ Hz, 1H), 3.00 (dd, $J=8.88$ Hz, $J=13.70$ Hz, 1H), 2.90 (dd, $J=3.88$ Hz, $J=14.98$ Hz, 1H), 2.69 (dd, $J=4.91$ Hz, $J=15.31$ Hz, 1H), 2.46 (dd, $J=2.0$ Hz, $J=13.28$ Hz, 1H), 2.37 (dd, $J=4.90$ Hz, $J=15.32$ Hz, 1H), 2.25 (t, $J=11.60$ Hz, 1H).
14. All new compounds were obtained in an analytically pure form and characterized by NMR. A relevant example: *Cyclo*[Phe–SAA–SAA–Ala] **2b**: ^{1}H NMR (600 MHz, H_2O/D_2O 9/1) δ 8.85 (d, $J=2.4$ Hz, 1H), 8.11 (d, $J=7.3$ Hz, 1H), 8.08 (d, $J=7.8$ Hz, 1H), 7.62 (q, $J=7.6$ Hz, $J=4.1$, 1H), 4.62 (d, $J=8.9$ Hz, $J=13.9$, Hz, 1H), 4.21, (q, $J=4.6$ Hz, 1H), 4.06 (p, $J=6.2$ Hz, $J=2.9$ Hz, $J=3.4$ Hz, 1H), 4.03 (m, $J=2.7$ Hz, $J=3.3$ Hz, $J=2.9$ Hz, 1H), 4.04 (dd, $J=5.7$ Hz, $J=2.7$ Hz, 1H), 4.02 (dd, $J=6.1$ Hz, $J=4.6$ Hz, 1H), 3.94 (t, $J=2.51$ Hz, 1H), 3.84 (t, $J=6.1$ Hz, 1H), 3.79 (ddd, $J=14.7$, $J=2.9$ Hz, $J=8.6$, 1H), 3.64 (dd, $J=5.71$ Hz, $J=8.00$ Hz, 1H), 3.59 (ddd, $J=14.3$ Hz, $J=3.4$ Hz, $J=1.9$ Hz, 1H), 3.35 (ddd, $J=14.3$ Hz, $J=2.9$ Hz, $J=7.7$ Hz, 1H), 3.32 (dd, $J=4.97$ Hz, $J=14.1$ Hz, 1H), 3.25 (ddd, $J=14.7$ Hz, $J=3.27$ Hz, $J=4.2$ Hz, 1H), 2.99 (dd, $J=10.7$ Hz, $J=14.0$ Hz, 1H), 2.74 (dd $J=14.8$ Hz, $J=4.4$ Hz, 1H), 2.65 (dd, $J=14.8$ Hz, $J=4.2$ Hz, 1H), 2.53 (dd, $J=13.2$ Hz, $J=2.5$ Hz, 1H), 2.47 (dd, $J=13.2$ Hz, $J=10.7$ Hz, 1H), 1.12 (d, $J=7.2$ Hz, 3H).
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16. A closely related approach using a pyranoid SAA was recently presented as a poster at the *20th International Carbohydrate Symposium (Hamburg)* by Stockle, M.; Locardi, E.; Gruner, S.; Kessler, H.