

Synthesis of a C_3 -Symmetric Furyl-Cyclopeptide Platform with Anion Recognition Properties

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A new furyl amino acid derivative was trimerized to give a linear peptide and finally was cyclized. The newly generated cyclopeptide was subjected to a conformational study in order to be considered as a C_3 -symmetric platform for the ratio-

nal design of complex receptors. Moreover, the recognition properties towards cyanide, acetate and chloride anions were studied.

Introduction

The development of synthetic receptors with specific recognition properties for anions is an important area in supramolecular chemistry that has attracted much attention over the last years.^[1] This interest is due to the important role exerted by various anions in biological systems,^[2] medicine and catalysis,^[3] industrial and environmental processes.^[1a,4] In particular, cyanide anion devotes special attention for its noxiousness that causes poisoning in biology and environment.^[5] Nevertheless, its use in various industrial areas is inevitable and is released into the environment as a toxic contaminant.^[6] Despite that a variety of synthetic receptors for anions has been reported, the great importance of cyanide ion has led to the development of an increasing number of synthetic receptors for cyanide.^[7] In general, the binding interactions of anions with their receptors are weak because anions are larger than isoelectronic cations, are pH-dependent and, due to their diverse geometries, require a higher degree of design for the receptors.^[1a] The usually weak nature of these interactions means that anion binding relies on multiple interactions to achieve strength and selectivity. It is known that amide groups with their intrinsic ability to form hydrogen bonds, play an important role in anion recognition, and especially amide-based macrocycles remain among the most popular designs for anion hosts.^[1a,1b,1j,8]

Heterocyclic amino acids are of interest because they are substructures of biologically active marine cyclopeptides.^[9] They are also important as building blocks for peptidomimetics with the purpose of drug discovery.^[10] Recently they

have been employed in the preparation of macrocyclic peptides (Figure 1, a) that have been used as rigid molecular platforms for the construction of receptors. Cyclopeptides based on imidazole,^[11] thiazole^[12] and oxazole^[12,13] have been reported for this purpose, some of them were used in the synthesis of larger receptors for the recognition of phloroglucinol.^[11a]

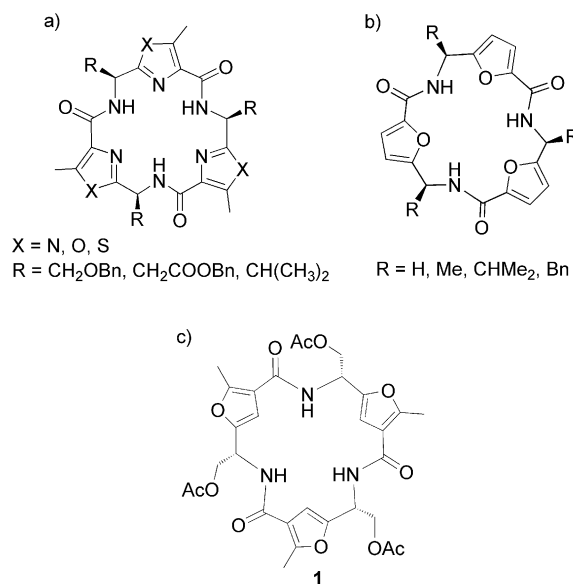


Figure 1. a) Heteroaromatic cyclopeptides as molecular platforms. b) Furyl cyclopeptides as anion binding receptors. c) New furyl cyclopeptide prepared.

Heteroaromatic cyclopeptides with restricted conformational degrees of freedom and multidentate H-bonding sites are good candidates in the anion recognition field. However, despite the potential of this type of cyclopeptides, their use as anion binding receptors has been scarce.^[14] Furyl cyclopeptides depicted in part b of Figure 1 were proven to

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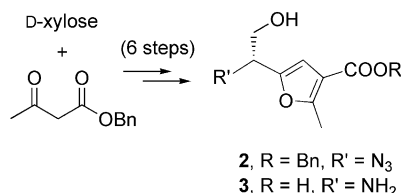
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be moderate anion receptors for acetate and halides. These are the only examples of C_3 -symmetric furyl cyclopeptides described in the literature.^[14a,14b]

As part of our continuing interest in the synthesis and applications of chiral furan amino acids,^[10c,15] we present herein the synthesis of the new furyl-based cyclic peptide **1** (Figure 1, c) from D-xylose as inexpensive starting material and source of chirality. Cyclopeptide **1** decorated with a number of precisely positioned binding units present obvious advantages for the production of anion receptors. It combines two interesting properties: it can be used as an anion binding receptor due to the multidentate H-bonding sites $[-(\text{CO})\text{NH}-, \text{Ar}-\text{H}]$ and also used as a molecular platform to generate C_3 -symmetric armed receptors by fixing the ligands to its contained pendant functionalities (CH_2OR). The conformational rigidity of the heteroaromatic cyclopeptide and the chirality of the furyl amino acids used in its construction, will guarantee the orientation of the receptor arms. This compound represents the first molecular platform based on furan amino acids. The selective recognition properties for cyclopeptide **1** towards different anions (acetate, cyanide and chloride) have been investigated by ^1H NMR and MS.

Results and Discussion

In a previous paper, we reported a new methodology for the stereoselective synthesis of α -furfurylamines from sugars, that was applied to the synthesis of different furyl-based amino acids.^[15c,15d] Among them, amino acid **3** and its azido ester precursor **2**, were efficiently obtained from D-xylose and benzyl acetoacetate (Scheme 1).

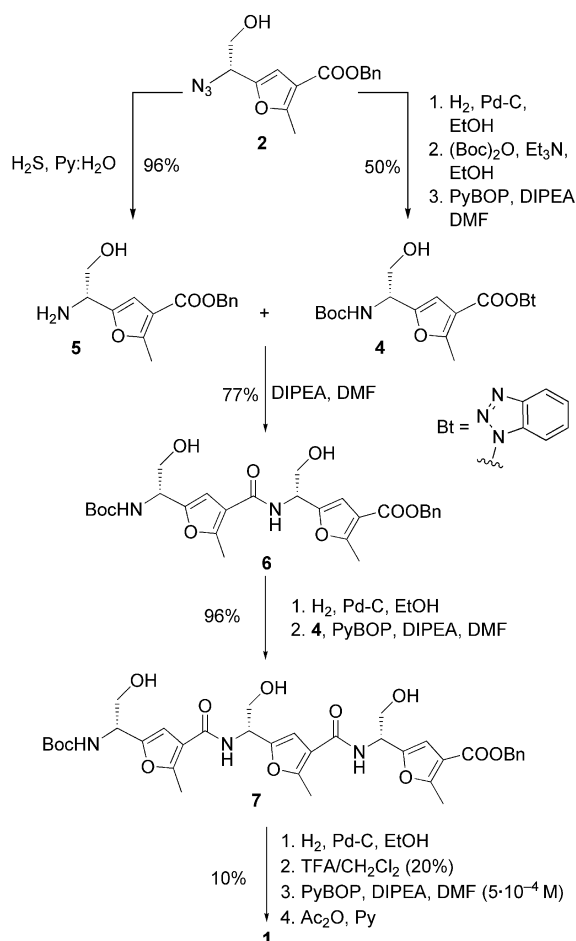


Scheme 1. Stereoselective synthesis of furyl-based amino acids.

With furyl amino acid **3** in hand, the synthesis of furyl cyclopeptide **1** was firstly attempted by one-pot cyclotrimerization under high dilution conditions (10^{-2} – 10^{-3} M), based on reported procedures,^[11–13] and using different coupling reagents, PyBOP (benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate) and FDPP (pentafluorophenyl diphenylphosphinate). Unfortunately, compound **1** was not detected.

We then decided to carry out the synthesis by cyclization of the linear tripeptide precursor. Hydrogenation of azido derivative **2** and subsequent Boc protection followed by reaction with PyBOP and DIPEA efficiently gave the hydroxybenzotriazole-activated Boc-amino acid **4** that was stable and could be purified by column chromatography (Scheme 2).^[16] Amino ester **5** was obtained by reduction of

the azide function in **2** using H_2S as reductive reagent. The solution phase peptide synthesis was carried out under standard conditions (head to tail strategy) to give dimer **6** in 78% yield. Hydrogenolysis of the benzyl ester and subsequent coupling with **4** gave linear tripeptide **7** in good overall yield. Hydrogenolysis and acidic treatment of **7** followed by cyclization under high dilution conditions and final acetylation afforded furyl cyclopeptide **1** in 10% overall yield (4 steps). Attempts to increase the yield of the cyclization step using FDPP and EDCI [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide] as coupling agents were unsuccessful. The lower yield in the cyclization step, comparing with other heteroaromatic-based cyclic peptide analogues^[11–13] (Figure 1, a), can be explained by the absence of internal hydrogen bonding interactions between the NH group and the oxygen of the furan ring in the intermediate unprotected acyclic peptide. These interactions could stabilize the adequate conformation of the tripeptide before the cyclization.



Scheme 2. Synthesis of furyl cyclopeptide **1**.

The NMR spectra of furyl cyclopeptide **1** in CD_3CN and CDCl_3 , showed a perfect C_3 symmetry. In the ^1H NMR spectrum, the NH signal appeared at $\delta = 6.04$ ppm with a coupling constant $^3J_{\text{NH,CH}}$ of 9.6 Hz in CDCl_3 . This chemical shift is lower than other δ values for NH signals (>6.7 ppm) of heteroaryl cyclopeptides where a network of

intramolecular $\text{NH} \rightarrow \text{X}$ (ring, $\text{X} = \text{N}$ in Figure 1, a and $\text{X} = \text{O}$ in Figure 1, b) H-bonds is possible.^[11–13,14b] Moreover, a strong NOE between H-4 and the $-\text{NH}-$ group was also observed. All these facts are in agreement with the proposed structure for compound **1**, where the oxygen atom is outside of the internal cavity. A structural analysis of compound **1** by molecular modeling using MacroModel^[17] and the MM2* force field^[18] was performed. The energy-minimized structure thus obtained showed H–N–C $_{\alpha}$ –H dihedral angles of the three amide linkages of 169° which are supported by a $^3J_{\text{NH,CH}}$ of 9.6 Hz.

The analysis showed that the furan moieties do not form a single plane but have a “bowl-like” structure^[19] with three pendant functionalities (CH_2OAc , Figure 2). The average distance between the three oxygens of the acetoxy groups (oxygen linked to methylene groups) in the minimized

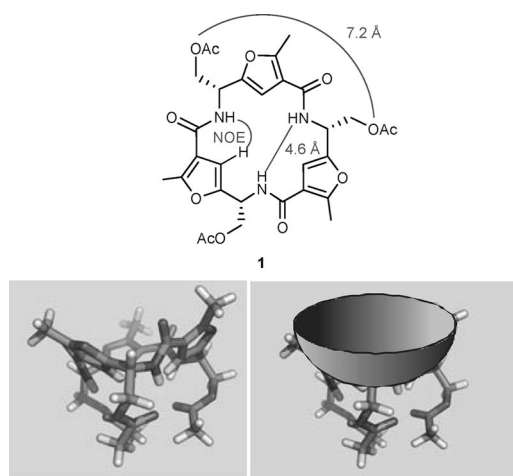


Figure 2. Structural analysis of cyclopeptide **1** by molecular modeling using MacroModel and the MM2* force field.

structure, as key pendant functionalities in the design of a possible receptor, is ca. 7.2 Å. In the internal cavity of the cyclopeptide the distance between $-\text{NH}-$ is ca. 4.6 Å. These parameters are very important in order to use this molecule as a platform for the rational design of complex receptors.

The ability of compound **1** to complex cyanide, acetate and chloride anions was determined by ^1H NMR titrations (see Supporting Information) in CD_3CN following the procedure described by Kelly and co-workers.^[20] The addition of anions (guest) in the form of tetrabutylammonium (TBA) salts to the solution of cyclopeptide **1** (host) caused significant downfield shifts of the amide NH and internal aromatic H-4 signals in the ^1H NMR spectra (see Figure 3 for cyanide), suggesting the formation of very tightly bound H-bonded complexes by anion nested inside the macrocyclic cavity. The initial chemical shifts of NH and H-4 protons of the host were 6.65 and 6.60 ppm, respectively. After addition of an excess of tetrabutylammonium cyanide (TBACN) ($[\text{G}]/[\text{H}] = 14$), the NH shifted to 8.33 ppm ($\Delta\delta_{\text{max}} = 1.68$ ppm); the H-4 shift was smaller ($\Delta\delta_{\text{max}} = 1.07$ ppm). With tetrabutylammonium acetate (TBAA) at the saturation point ($[\text{G}]/[\text{H}] = 6$), the NH amide and H-4 aromatic proton shifts ($\Delta\delta_{\text{max}}$) were 1.92 ppm and 1.08 ppm, respectively. In the case of tetrabutylammonium chloride (TBACl), the amide and aromatic proton shifts ($\Delta\delta_{\text{max}}$) were 1.04 ppm and 1.23 ppm, respectively, at the saturation point ($[\text{G}]/[\text{H}] = 4.5$). Typical titration curves are shown in Figure 4 (bottom). The stoichiometry of complexation of **1** with the corresponding TBA salt of the anion was determined using Job's method (Figure 4, top). The representation showed a maximum at ca. 0.5 mol fraction (X_{H}) in all the cases, confirming the formation of 1:1 complexes. These complexes could be detected by mass spectrometry (ESI). The molecular ions $[\text{M}]^-$ of the complexes **1**·AcO $^-$ (m/z 686.2) and **1**·Cl $^-$ (m/z 662.2) and $[\text{M} - \text{H}]^-$ of the complex **1**·CN $^-$ (m/z 652.2), are observed together with

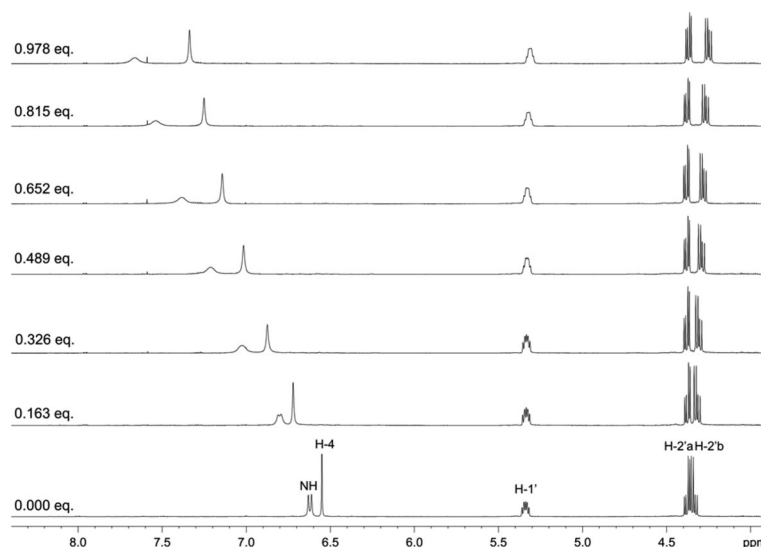


Figure 3. Plots of ^1H NMR (500 MHz) spectra of **1** on addition of TBACN using CD_3CN as solvent.

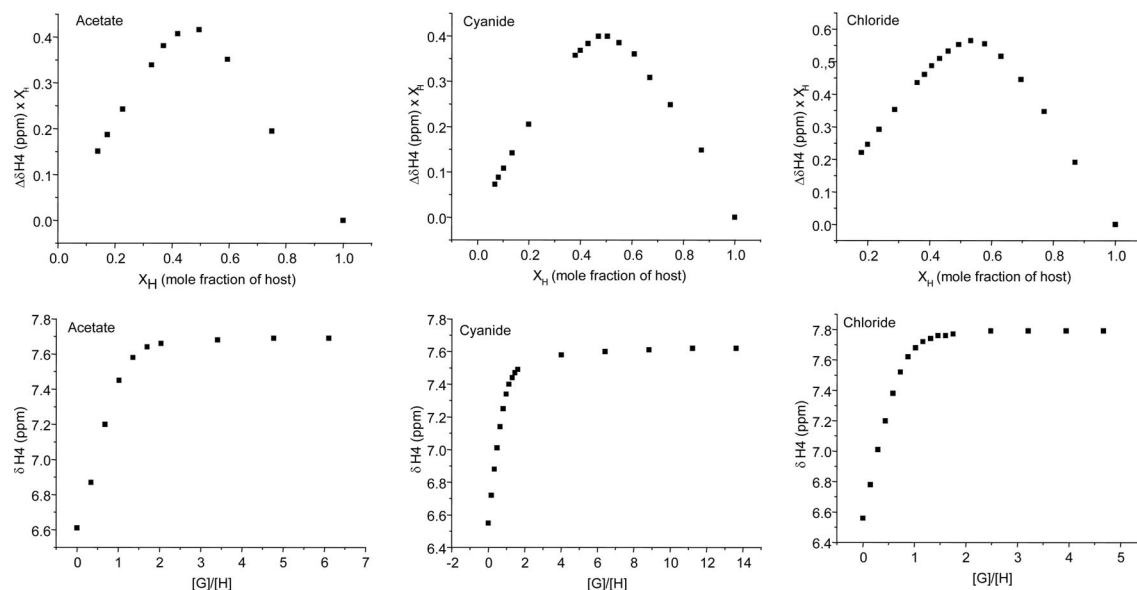


Figure 4. Job plots (top) and ^1H NMR titration plots (bottom) for the complexation of cyclopeptide **1** with tetrabutylammonium acetate, cyanide and chloride salts in CD_3CN solution.

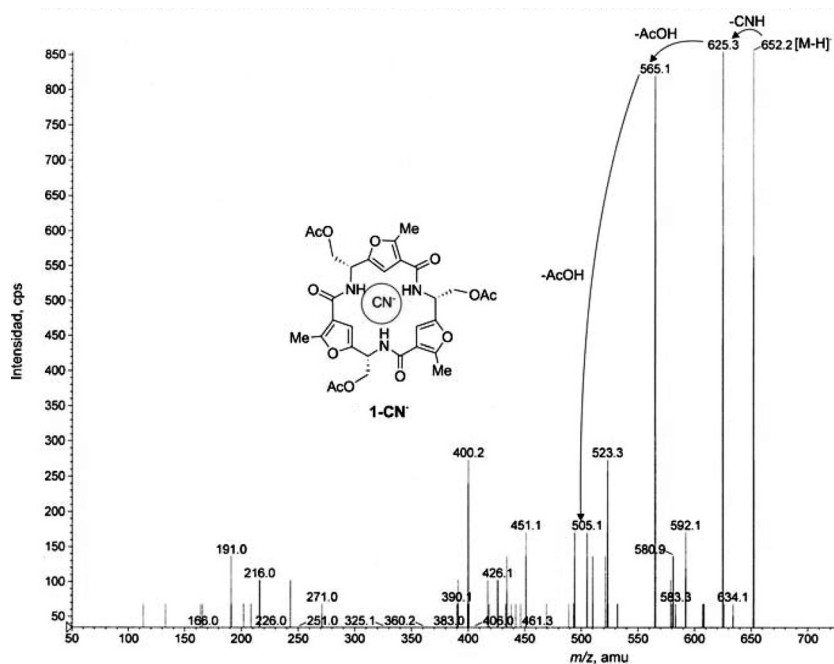


Figure 5. ESI spectra for the complexation of **1** with cyanide.

the corresponding fragmentation through consecutive loss of AcOH and CNH in the two first cases (see Figure 5 for cyanide complexation).

The association constants (K_a) were calculated as averaged values obtained from non-linear fitting of a 1:1 binding model^[21] to the graphic that represents the H-4 aromatic shift towards anion concentration. While K_a calculated for trigonal acetate was $1.0 \times 10^3 \text{ M}^{-1}$, binding with cylinder cyanide was slightly higher, $K_a = 1.6 \times 10^3 \text{ M}^{-1}$.

The best result was obtained with spheric chloride, $K_a = 1.6 \times 10^4 \text{ M}^{-1}$, which is in agreement with the geometry of the central cavity of **1**. It is worth noting the evidence that aromatic C–H groups within the anionophore cavity participate in bonding^[22] and lead to enhanced anion-binding affinity. The presence of an electron-withdrawing group, as the amide group, on the furan ring (Figure 6) strengthens this anion hydrogen bond as was recently reported by others for phenyl rings.^[23]

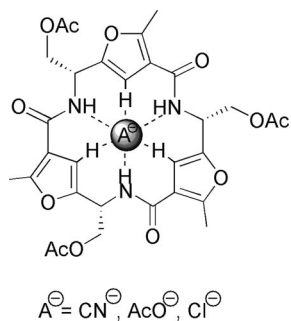


Figure 6. Aryl CH-anion hydrogen bonds in complexation of anions.

Conclusions

In summary, we have synthesized the first molecular platform derived from furan. This C_3 -symmetric furyl cyclopeptide has shown good recognition properties towards cyanide, acetate and chloride anions. This ability has been enhanced due to the formation of an unusual hydrogen bond between the furyl CH and the guest anion.

Experimental Section

Benzotriazol-1-yl 5-[(R)-1-N-(tert-Butoxycarbonylamino)-2-hydroxyethyl]-2-methylfuran-3-carboxylate (4): A solution of **2** (331 mg, 1.1 mmol) in MeOH (20 mL) was hydrogenated under atmospheric pressure for 3 h, using Pd/C (10%) as catalyst. Then, the solution was filtered through celite and the catalyst washed with MeOH. The filtered solution was concentrated in vacuo to give crude amino acid **3**. The resulting crude was dissolved in EtOH (8 mL) and (Boc)₂O (368 mg, 1.65 mmol) followed by Et₃N (233 μ L, 1.65 mmol) were added to the solution. The reaction mixture was stirred for 1 h. Then, the solvent was evaporated, the resulting crude was dissolved in DMF (8 mL) and PyBOP (435 mg, 0.81 mmol) and DIPEA (283 μ L, 1.65 mmol) were added. The reaction mixture was stirred for 1 h, then the solvent was evaporated, the resulting crude was dissolved in AcOEt and washed with saturated aqueous solution of NaHCO₃ and brine. The organic phase was dried (Na₂SO₄), filtered and the solvents were evaporated. The resulting crude was purified by column chromatography (AcOEt/petroleum ether, 1:1) to give **4** (218 mg, 50%) as a colourless oil. $[\alpha]_D^{23} = +39$ ($c = 1.36$ in CH₂Cl₂); $\bar{\nu}_{\text{max}} = 3397$ (OH), 2961, 1793 (CO), 1713 (CO), 1368, 1166, 960, 743; ¹H NMR (300 MHz, CD₃OD, 25 °C): $\delta = 1.47$ [s, 9 H, (CH₃)₃C], 2.67 (s, 3 H, CH₃), 3.80 (dd, 1 H, 2'-b-H), 3.85 (dd, $J_{2'a,2'b} = 11.2$ Hz, 1 H, 2'-a-H), 4.79 (t, $J_{1',2'a} = J_{1',2'b} = 6.0$ Hz, 1 H, 1'-H), 6.83 (s, 1 H, 4-H), 7.52 (m, 1 H, Ar-H), 7.66–7.64 (m, 2 H, Ar-H), 8.06 (br. dt, $J = 8.6$, $J = 0.8$ Hz, 1 H, Ar-H) ppm. ¹³C NMR (754 MHz, CD₃OD, 25 °C): $\delta = 164.7$ (COOBt), 161.0 (CO of Boc), 155.1 (C-2), 144.5 (C-5), 130.3, 126.5, 120.8, 109.9 (6 C, C-aromat.), 109.6 (C-3), 107.7 (C-4), 80.7 [(CH₃)₃C], 63.7 (C-2'), 52.0 (C-1'), 28.7 [(CH₃)₃C], 14.1 (CH₃) ppm. MS (CI): $m/z = 403.1628$ [[M + H]⁺. C₁₉H₂₃O₆N₄ requires 403.1618], 268 [(M – OBT)⁺, 26%].

Benzyl 5-[(R)-1-Amino-2-hydroxyethyl]-2-methylfuran-3-carboxylate (5): SH₂ was bubbled for 1 h through a solution of **2** (685 mg, 2.28 mmol) in pyridine/H₂O, 1:1 (40 mL), then the mixture was stirred overnight. The solvent was evaporated, the resulting crude was dissolved in MeOH and filtered through celite. The filtered

solution was concentrated to dryness and purified by column chromatography (dichloromethane/methanol, 10:1) to give **5** (600 mg, 96%) as a colourless oil. $[\alpha]_D^{23} = +13$ ($c = 1.38$, CH₂Cl₂); $\bar{\nu}_{\text{max}} = 3359$ (OH), 2922, 1712 (CO), 1422, 1226, 1071; ¹H NMR (300 MHz, CD₃OD, 25 °C): $\delta = 2.54$ (s, 3 H, CH₃), 3.66 (dd, $J_{2'b,1'} = 6.9$ Hz, 1 H, 2'-b-H), 3.77 (dd, $J_{2'a,2'b} = 10.9$, $J_{2'a,1'} = 5.2$ Hz, 1 H, 2'-a-H), 3.95 (m, 1 H, 1'-H), 5.26 (s, 2 H, CH₂Ph), 6.55 (s, 1-H, 4-H), 7.40–7.32 (m, 5 H, Ar-H) ppm. ¹³C NMR (75.4 MHz, CD₃OD, 25 °C): $\delta = 165.2$ (COOBn), 160.2 (C-2), 154.8 (C-5), 137.8, 129.6, 129.2, 129.2 (6 C, C-aromat.), 115.0 (C-3), 108.0 (C-4), 67.0 (CH₂Ph), 65.7 (C-2'), 52.3 (C-1'), 13.8 (CH₃) ppm. m/z (CI) 274.1075 [(M – H)⁺. C₁₅H₁₆O₄N requires 274.1079], 259 [(M – NH₂)⁺, 46%].

Benzyl 5-[(R)-1-[5-[(R)-1-(tert-Butoxycarbonylamino)-2-hydroxyethyl]-2-methyl-3-furamide]-1-deoxy-2-hydroxyethyl]-2-methylfuran-3-carboxylate (6): To a solution of compound **4** (290 mg, 0.72 mmol) in DMF (10 mL), a solution of **5** (198 mg, 0.72 mmol) in DMF (10 mL) and DIPEA (504 μ L, 2.88 mmol) was added. The reaction mixture was stirred for 3 h. Then, the solution was evaporated to dryness and the resulting crude was purified by column chromatography (dichloromethane/methanol, 25:1) to give **6** (300 mg, 77%) as a colourless oil. $[\alpha]_D^{23} = +67$ ($c = 0.46$ in CH₂Cl₂); $\bar{\nu}_{\text{max}} = 3348$ (OH), 2922, 1713 (CO), 1520, 1366, 1228, 1166, 1070, 776; ¹H NMR (300 MHz, CD₃OD, 25 °C): $\delta = 1.44$ [s, 9 H, (CH₃)₃C], 2.51 [s, 3 H, CH₃(A)], 2.53 [s, 3 H, CH₃(B)], 3.72 [dd, $J_{2'bB,1'B} = 6.5$ Hz, 1 H, 2'-b-H(B)], 3.78 [dd, $J_{2'aB,2'bB} = 11.3$, $J_{2'aB,1'B} = 5.9$ Hz, 1 H, 2'-a-H(B)], 3.84 [dd, $J_{2'bA,1'A} = 6.5$ Hz, 1 H, 2'-b-H(A)], 3.89 [dd, $J_{2'aA,2'bA} = 11.3$, $J_{2'aA,1'A} = 5.9$ Hz, 1 H, 2'-a-H(A)], 4.68 [m, 1 H, 1'-H(A)], 5.19 [m, 1 H, 1'-H(B)], 5.26 (s, 2 H, CH₂Ph), 6.55 [s, 1 H, 4-H(B)], 6.60 [s, 1 H, 4-H(A)], 7.42–7.31 (m, 5 H, Ar-H) ppm. ¹³C NMR (125.7 MHz, CD₃OD, 25 °C): $\delta = 166.1$ (CONH), 165.2 (COOBn), 160.3 (CO of Boc), 157.8 [2 C, C-2(A,B)], 152.7 [2 C, C-5(A, B)], 137.7, 129.6, 129.2, 129.2 (6 C, C-aromat.), 117.2 (C-3A), 115.0 (C-3B), 108.7 (C-4B), 106.9 (C-4A), 80.6 [(CH₃)₃C], 67.0 (CH₂Ph), 63.8 (C-2'A), 63.5 (C-2'B), 52.1 (C-1'A), 50.4 (C-1'B), 28.7 [(CH₃)₃C], 13.8 (CH₃A), 13.6 (CH₃B) ppm. m/z (FAB) 565.2151 [[M + Na]⁺. C₂₈H₃₄N₂O₉Na requires 565.2162].

Benzyl 5-[(R)-1'-[5-(R)-1'-(tert-Butoxycarbonylamino)-2'-hydroxyethyl]-2-methyl-3-furamide-(N→1')-5-[(R)-2'-hydroxyethyl]-2-methyl-3-furamide-(N→1')-2'-hydroxyethyl]-2-methylfuran-3-carboxylate (7): A solution of **6** (307 mg, 0.55 mmol) in EtOH (35 mL) was hydrogenated under atmospheric pressure for 2 h, using Pd/C (10%) as catalyst. Then, the solution was filtered through celite and the catalyst washed with EtOH. The filtered solution was concentrated in vacuo. The resulting residue was dissolved in DMF (15 mL) and a solution of **5** (151 mg, 0.55 mmol) in DMF (20 mL), DIPEA (385 μ L, 2.2 mmol) and PyBOP (322 mg, 0.61 mmol) were added. The reaction mixture was stirred for 3 h, then the solution was evaporated and purified by column chromatography (diethyl ether/acetone, 3:1) to give **7** (376 mg, 96%) as a white solid. $[\alpha]_D^{23} = +41$ ($c = 0.73$ in CH₂Cl₂); $\bar{\nu}_{\text{max}} = 3332$ (OH), 2928, 1697 (CO), 1642 (CO), 1581, 1523, 1367, 1229, 1166, 1070, 737; ¹H NMR (500 MHz, CD₃OD, 25 °C): $\delta = 1.41$ [s, 9 H, (CH₃)₃C]; 2.51 [s, 6 H, CH₃(A, B)], 2.53 [s, 3 H, CH₃(C)], 3.73 [dd, $J_{2'bA,1'A} = 6.3$ Hz, 1 H, 2'-b-H(A)]; 3.78 [dd, $J_{2'aA,2'bA} = 11.2$, $J_{2'aA,1'A} = 5.9$ Hz, 1 H, 2'-a-H(A)], 3.92–3.82 [m, 4 H, 2'-a-H(B, C), 2'-b-H(B, C)], 4.68 [m, 1 H, 1'-H(A)], 5.18 [t, $J_{1'A,2'A} = J_{1'B,2'B} = 6.0$ Hz, 2 H, 1'-H(B, C)], 5.25 (s, 2 H, CH₂Ph), 6.54 [s, 1 H, 4-H(A)], 6.60 [s, 1 H, 4-H(B)], 6.65 [s, 1 H, 4-H(C)], 7.41–7.31 (m, 5 H, Ar-H) ppm. ¹³C NMR (125.7 MHz, CD₃OD, 25 °C): $\delta = 166.1$ [2 C, CONH(A, B)], 165.2 (COOBn), 160.3 (CO of Boc), 157.9 (C-2C), 157.8 [2 C, C-2(A, B)], 152.7 [2 C, C-5(B, C)], 152.2 (C-5A),

137.7, 129.6, 129.2 (6 C, C-aromat.), 117.2 [2 C, C-3(A, B)], 115.3 (C-3C), 108.7 (C-4C), 107.2 (C-4B), 106.9 (C-4A), 80.6 [(CH₃)₃C], 67.0 (CH₂Ph), 63.9 (C-2'A), 63.5 [2 C, C-2'(B,C)], 52.1 (C-1'A), 50.6, 50.4 [C-1'(B,C)], 28.7 [(CH₃)₃C], 13.8 (CH₃C), 13.6 [2 C, CH₃(A,B)] ppm. *m/z* (FAB) 732.2736 [[M + Na]⁺. C₃₆H₄₃O₁₂N₃Na requires 732.2744].

Furyl Cyclopeptide 1: A solution of **7** (90 mg, 0.125 mmol) in EtOH (8 mL) was hydrogenated under atmospheric pressure for 2 h, using Pd/C (10%) as catalyst. Then the solution was filtered through celite and the catalyst washed with EtOH. The filtered solution was concentrated in vacuo. The resulting residue was dissolved in a solution of TFA (20%) in CH₂Cl₂ and the mixture was stirred for 20 min. Then the solution was evaporated to dryness, the resulting crude was dissolved in DMF (250 mL), PyBOP (100 mg, 0.19 mmol) and DIPEA (218 μL, 1.25 mmol) were added and the mixture was stirred for 19 d. Then, the mixture was evaporated to dryness and the resulting crude was acetylated (1 mL Ac₂O/1 mL pyridine) overnight. Then the solvent was evaporated, the residue was dissolved in dichloromethane and washed with HCl (1 M), saturated aqueous solution of NaHCO₃ and brine. The organic phase was dried (Na₂SO₄), filtered, and purified by column chromatography (diethyl ether/acetone, 6:1) to give **1** (8 mg, 10%) as a colourless oil; ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 2.10 (s, 9 H, CH₃CO), 2.51 (s, 9 H, CH₃), 3.37 (dd, *J*_{2'b,1'} = 4.3 Hz, 3 H, 2'b-H), 4.50 (dd, *J*_{2'a,2'b} = 11.5, *J*_{2'a,1'} = 6.2 Hz, 3 H, 2'a-H), 5.47–5.41 (m, 3 H, 1'-H), 6.04 (d, *J*_{NH,1'} = 9.6 Hz, 3 H, NH), 6.33 (s, 3 H, 4-H) ppm. ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 171.2 (3 C, CH₃CO), 163.5 (3 C, CONH), 157.5 (3 C, C-2), 151.8 (3 C, C-5), 116.8 (3 C, C-3), 106.3 (3 C, C-4), 64.7 (3 C, C-2'), 47.7 (3 C, C-1'), 21.0 (3 C, CH₃CO), 13.3 (3 C, CH₃) ppm. *m/z* (FAB) 650.1952 [[M + Na]⁺. C₃₀H₃₃O₁₂N₃Na requires 650.1962].

General Procedure for NMR Titrations: The titration of cyclic furyl-carbopeptoid receptor **1** with acetate, cyanide and chloride was carried out following the procedure described by Kelly and co-workers.^[20] A 0.0108 M solution of **1** in CD₃CN was prepared (3.4 mg, 0.5 mL) in a NMR tube. A 0.038 M solution of tetrabutylammonium cyanide (TBACN) in CD₃CN was prepared in a 2-mL volumetric flask under nitrogen. An initial NMR spectrum of the solution of **1** was taken, and the initial chemical shift of the NH proton and H-4 (aromatic) was determined to be 6.65 and 6.60 ppm, respectively (control studies indicated that in the absence of binding partner, the chemical shift of the NH proton was not concentration dependent). The solution of cyanide (guest) was then added, initially in 15-μL aliquots, and the chemical shifts of the NH and H-4 protons were recorded after each addition. After 1 equiv. of guest had been added, the concentration of the aliquot was increased to 0.56 M and several 15-μL aliquots were added until no further change in the chemical shift of the NH and H-4 protons was observed (8 equiv. approx.). The chemical shifts of the NH and H-4 protons at this saturation point were 8.33 and 7.72 ppm, respectively. The temperature of the NMR experiment was 23 °C. In the case of titration with acetate and chloride, the procedure was similar except that tetrabutylammonium acetate and chloride were used.

A graph was then plotted of chemical shift (NH or H-4) vs. [guest]/[host] (titration plot). The association constant (*K*_a) was obtained by non linear fitting using the equation below^[21] (for stoichiometry complex 1:1):

$$\delta = \delta_h - \left(\frac{\Delta\delta_{\max}}{2} \right) \left(b - \sqrt{b^2 - 4R} \right)$$

where

$$b = 1 + R + \frac{1}{(K_a[H_o])}; R = \frac{[H_o]}{[G_o]}; \Delta\delta_{\max} = \delta_h - \delta_c$$

δ is the chemical shift for NH or H-4 at each titration point, δ_h is the initial chemical shift for NH or H-4 (host only), δ_c is the chemical shift for NH or H-4 when the receptor is entirely bound, [H_o]/[G_o] is [host]/[guest] at each titration point (guest and host concentrations for each point take into account the changes in volume).

Supporting Information (see also the footnote on the first page of this article): ¹H and ¹³C NMR spectra for all new compounds, NMR plots for titration experiments and mass spectra for cyclopeptide–anion complexes.

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