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Solid Support Synthesis of 14-Membered Macrocycles Containing 4-Hydroxyproline Structural Unit *via* SNAr Methodology.

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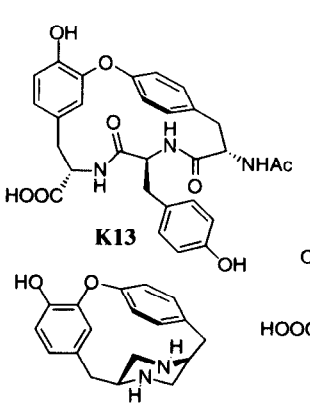
Summary: We describe an efficient solid-phase synthesis of 14-membered macrocycles derived from 4-hydroxyproline and 3-fluoro-4-nitrobenzoic acid. The procedure is based on the aromatic nucleophilic displacement of fluoride with the OH function. The targeted macrocycles are obtained in good yields, and are 90-95% pure. The diversity elements in the synthesis are: amine immobilized on solid support and amino acids.

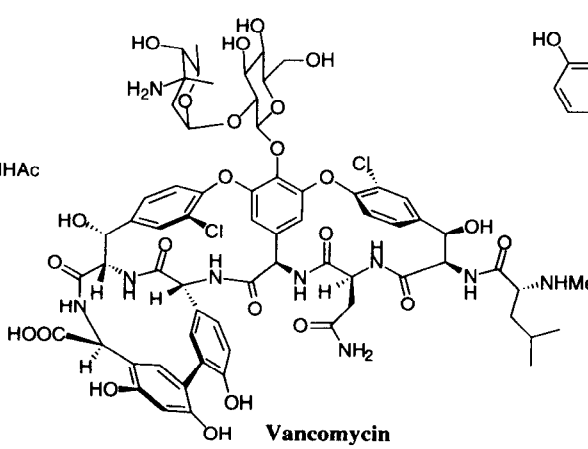
Key words: macrocycles; supported reagents/reactions; solid-phase synthesis

The aryl ether moiety is a common structural motif of macrocyclic natural products representing a broad array of biological activity.[1] For example, a nonsymmetrical biaryl ether functionality is found within the vancomycin family of antibiotics.[2,3] Other examples of compounds containing this unit include: i) K-13, a non competetive inhibitor of angiotensin I converting enzyme,[4] ii) macrocyclic 17-membered tripeptides of the OF4949 family,[4] iii) piperazinomycin, and related 14-membered macrocycles, namely bouvardin, deoxybouvardin, and the RA class of bicyclic hexapeptide macrocycles, possessing pronounced antitumor activity.[5] Several strategies have been designed to address the numerous challenges in the synthesis of these compounds.[6-12] Macrocycles containing an alkoxy aryl bridge or alkylthio aryl bridge within the main ring are less prevalent in natural products.[13] Recent literature reports describe the synthesis of macrocycles containing the Ar-O-Alk motif, for example serine-based macrocycles representing β-turn mimetics.[13]

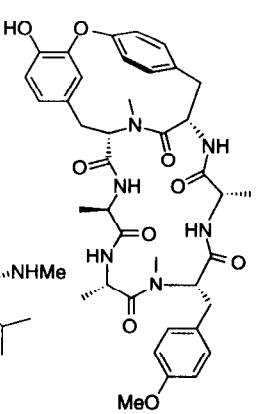


K13

Piperazinomycin



Vancomycin



Deoxybouvardin

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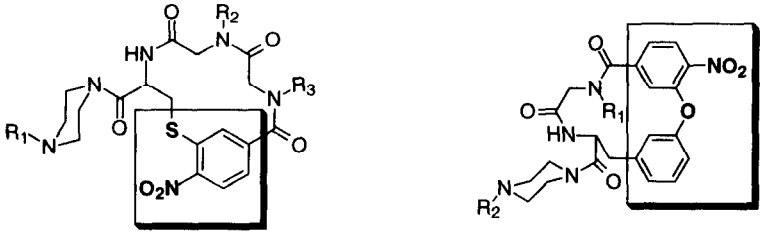
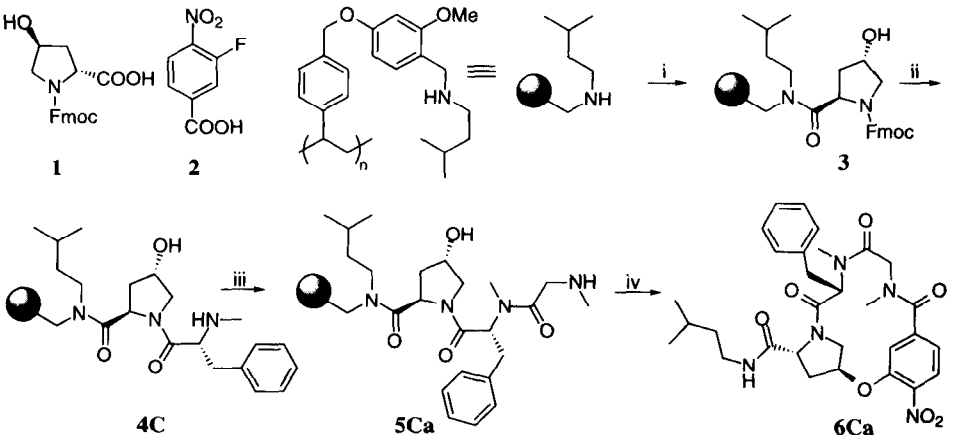
One of the strategies commonly used to prepare macrocycles containing the aryl ether structural unit is based on the nucleophilic aromatic substitution (S_NAr) of fluoride in various fluoronitroaromatic substrates with the oxygen of tyrosine derivatives or serine to install the aryl ether bridge in the desired macrocycles.[14] Several factors make this strategy particulary attractive for the parallel assembly of macrocycles. These are: i) exceptionally mild coupling conditions, ii) the ready availability of starting materials, and iii) the possibility to expand the diversity of substituents in the final macrocycles *via* postmodification reactions of the nitro group.

As a part of our combinatorial chemistry effort,[15] we reported the successful syntheses of 14-membered macrocycles containing either an aryl thioether moiety, or a nonsymmetrical biaryl ether.[16]



In this paper we describe the efficient synthesis of 14-membered macrocycles containing 4-hydroxyproline. In our approach we decided to use the commercially available *N*-Fmoc 4-hydroxy proline **1** and 3-fluoro-4-nitrobenzoic acid **2**[17] as components for the final S_NAr coupling. To further expand the size, and to introduce an additional diversity element into the library of the targeted 14-membered macrocycles, we selected the previously reported AMEBA (**A**cid sensitive **ME**thoxy **B**enz**A**ldehyde polystyrene) resin, which can be easily derivatized with amines.[18] The coupling sequence involving the attachment of two amino acids introduced additional diversity to the desired library (Scheme 1).

Scheme 1.

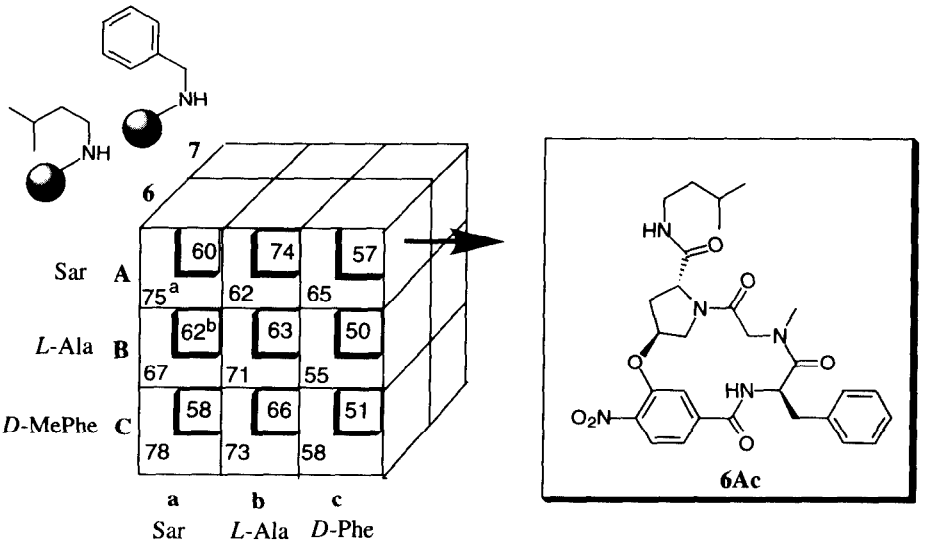


Reagents and Conditions: i) **1**, DCC, DMF/CH_2Cl_2 (1:1), RT, 24 h (0.35 mmol/g loading); ii) 20% piperidine/ DMF; Fmoc-*D*-MePhe-OH (**C**), HOAt, DIC, DMF, RT, 3 h; 20% piperidine/DMF; iii) Fmoc-Sar-OH (**a**), HOAt, DIC, DMF, RT, 8 h; 20% piperidine/DMF; iv) **2**, HOAt, DIC, DMF, RT, 8 h; 5% DBU/DMF, RT, 24 h; 15% TFA in CH_2Cl_2, 45 min, 78% overall yield from **3**.

In the initial experiment we coupled **1** to the AMEBA resin modified with isoamylamine using the standard DCC protocol[16] (loading was determined by standard Fmoc cleavage with 20% piperidine in DMF to be 0.35 mmol/g). *N*-Fmoc-Me*D*-Phe was coupled to the resulting immobilized 4-hydroxyproline **3** *via* the previously reported procedure,[19] and the resulting resin was treated with 20% piperidine in DMF to remove the Fmoc moiety. Fmoc-protected sarcosine was successfully coupled to resin **4**, followed by deprotection of the Fmoc-amine to afford **5**. Successful coupling of **2** to the resulting resin **5** was achieved using the HOAt/DIC strategy.[20] The resin was treated with a 5% solution of DBU in DMF for 24 h at room temperature, and cleaved with 15% TFA in DCM to afford the desired macrocycle **6Ca** in a 78% overall yield.

A set of 18 macrocycles (Scheme 2) was synthesized using the reaction conditions described above (Scheme 1). Neither the nature of the AMEBA resin bound amine nor that of the amino acid inputs affected the yield or purity of the final products **6** and **7**. For example, macrocycles containing combinations of *L-/L-*, *L-/D-*, or *D-/D* amino acids as ring components were synthesized successfully. The average yields of the targeted macrocycles ranged from 55% to 78%. The purities of **6** and **7** were determined by both ^{1}H NMR and HPLC analyses to be 85-95%. The minor impurity (*ca.* 5-7%) in several instances was identified to be 4-hydroxyproline.

Scheme 2. Library of 14-membered macrocycles.



[a] Isolated yields of macrocycles cleaved from resin **6**.

[b] Isolated yields of macrocycles isolated from resin **7**.

Analytically pure macrocycles were obtained by circular chromatography on silica gel using a CH_2Cl_2/MeOH (97:3) system as the eluent. The synthetic procedure can be easily scaled up on solid support to generate gram quantities of the targeted macrocycles. Selected ^{1}H NMR data for compounds **6** and **7** are summarized in Table 1.

Table 1. Analytical data for compounds **6** and **7**.[a]

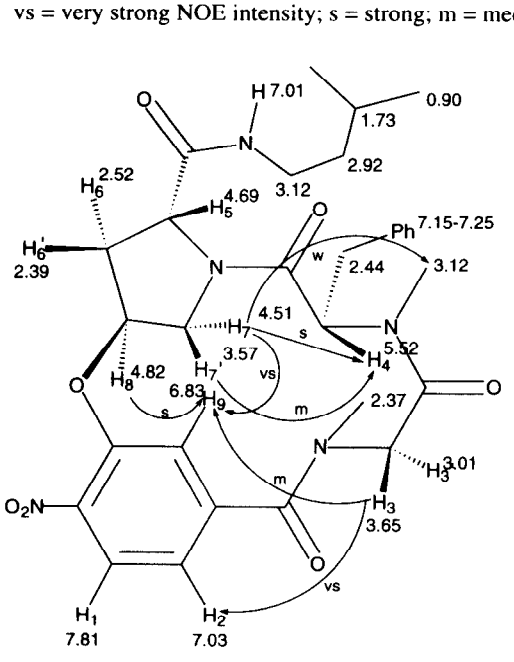
Compound	Chemical shift, ppm												
	H_1	H_2	H_3	H_3'	H_4	H_4'	H_5	H_6	H_6'	H_7	H_7'	H_8	H_9
6Aa	7.93	7.12	3.47	2.98	5.34	4.91	4.68	2.48	2.38	4.52	3.61	4.79	6.76
6Ab	7.84	7.11	2.67	n/a	5.22	4.95	4.74	2.53	2.35	4.38	3.60	4.87	6.85
6Ac	7.94	7.10	n/a	2.97	5.25	4.88	4.72	2.56	2.44	4.53	3.45	4.77	6.88
6Ba	7.90	7.06	3.49	2.85	n/a	5.28	4.47	2.42	2.41	4.44	3.62	4.76	6.73
6Bb	7.80	7.03	2.99	n/a	n/a	5.32	4.77	2.56	2.42	4.56	3.68	4.71	6.84
6Bc	7.98	7.19	n/a	3.06	n/a	5.38	4.79	2.61	2.44	4.64	3.55	4.72	6.91
6Ca	7.81	7.03	3.65	3.01	5.52	n/a	4.69	2.52	2.39	4.51	3.57	4.82	6.83
6Cb	7.80	7.08	2.89	n/a	5.46	n/a	4.75	2.57	2.44	4.63	3.58	4.86	6.89
6Cc	8.01	7.21	n/a	3.02	5.54	n/a	4.78	2.45	2.39	4.60	3.58	4.76	6.92
7Aa	7.99	7.11	3.44	2.97	5.37	4.93	4.72	2.49	2.37	4.53	3.64	4.73	6.71
7Ab	7.81	7.15	2.63	n/a	5.23	4.97	4.73	2.51	2.38	4.35	3.63	4.82	6.82
7Ac	7.79	7.12	n/a	2.94	5.31	4.83	4.72	2.52	2.46	4.55	3.49	4.74	6.87
7Ba	7.82	7.06	3.45	2.86	n/a	5.27	4.42	2.44	2.42	4.43	3.60	4.77	6.76
7Ba	7.83	7.08	3.02	n/a	n/a	5.33	4.76	2.57	2.44	4.59	3.63	4.75	6.87
7Bc	8.03	7.16	n/a	3.08	n/a	5.41	4.78	2.66	2.46	4.70	3.56	4.76	6.90
7Ca	7.84	7.09	3.66	3.04	5.51	n/a	4.54	2.54	2.36	4.53	3.53	4.80	6.84
7Cb	7.75	7.13	2.88	n/a	5.43	n/a	4.70	2.57	2.50	4.65	3.55	4.85	6.87
7Cc	8.07	7.16	n/a	3.03	5.57	n/a	4.81	2.49	2.34	4.61	3.57	4.72	6.91

[a] For the proton numbering system see Figure 1.

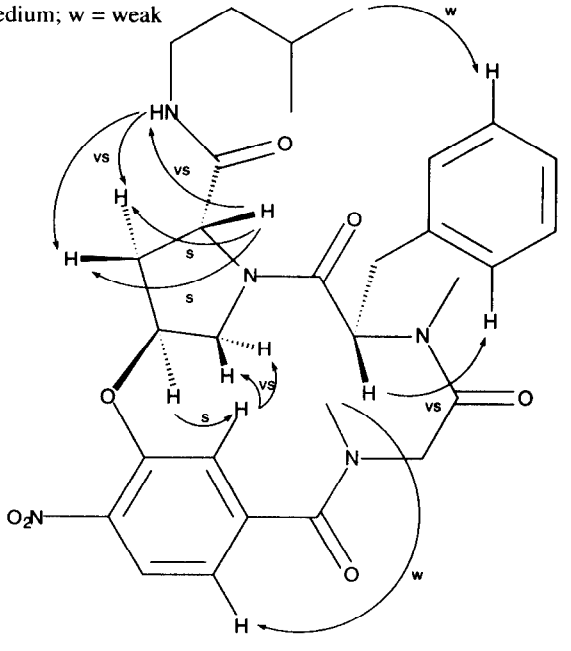
COSY, TOCSY and NOESY experiments were performed to assign the proton resonances and to confirm the bond connectivity of the macrocyclic ring. 4-Hydroxyproline, and nitroaromatic ring spin systems were readily identified by COSY and TOCSY experiments. Protons of both the pyrrolidine ring, as well as the nitroaromatic ring in the synthesized 14-membered macrocycles exhibit individual chemical shifts and strong COSY/NOE connectivities. The transannular NOEs, and the long-range NOEs observed are shown in Figure 1.

Figure 1. Chemical shifts, transannular NOEs, and long-range NOEs of **6Ca**

vs = very strong NOE intensity; s = strong; m = medium; w = weak



Chemical shifts and NOEs across the ring



Long-range NOEs

In summary, we described an efficient route to 14-membered macrocycles derived from 4-hydroxyproline and 3-fluoro-4-nitrobenzoic acid. The procedure is based on the aromatic nucleophilic displacement of fluoride by the OH function of 4-hydroxyproline. The target macrocycles are obtained in good yields, and are 85-95% pure. The diversity elements in the synthesis are: amine immobilized on solid support and both *L*- and *D*-amino acids as components of the 14-membered macrocyclic ring.

Experimental Part.

General Methods. All reactions were carried out in Alltech® vessels (100 mg of resin per reaction vessel). Concentration of solutions after workup was performed by reduced pressure rotary evaporation. ^1H NMR spectra were obtained on a Bruker 500 instrument with $CDCl_3$ as the solvent. MS analysis (ES and CI modes)

were performed on a Perkin Elmer API 165 instrument. HPLC analyses were performed on a Beckman Gold Analytic 126 apparatus with a diode array detector model 168 at the wavelengths of 220 nm and 254 nm. The column employed was an Ultrasphere C18 cartridge 250mm x 4.6 mm. Solvent system was MeCN/H_2O (.1% TFA added), with a flow rate of 1 mL/min.

General Procedure for the Preparation of 4-Hydroxyproline on AMEBA Resin. In the standard resin preparation protocol, *N*-Fmoc protected 4-hydroxyproline (8.06 g, 20 mmol) was treated with DCC (2.06 g, 10 mmol) in 50 mL of dry CH_2Cl_2. The resulting mixture was stirred for 2 h, and filtered. 50 mL of dry DMF were added, and the AMEBA resin immobilized with amine[18] (10 g, 0.45mmol/g loading as determined by coupling of 4-nitrobenzoylchloride followed by cleavage of the resultant amide with 20% TFA/DCM) was introduced. The resulting slurry was stirred at room temperature for 24 h, filtered, washed with DMF, MeOH, CH_2Cl_2, and dried *in vacuo* to afford the desired resin **3** (0.35 mmol/g loading as determined by Fmoc group cleavage). The resin was then treated with 100 mL of 20% solution of piperidine in DMF for 30 min, washed with DMF, MeOH, and CH_2Cl_2, and dried *in vacuo* to afford the immobilized deprotected 4-hydroxyproline.

General Procedure for the Preparation of Modified 4-Hydroxyproline Resins 4 and 5. This procedure was run in parallel using the following reaction conditions: a mixture of amino acid (20 mmol), DIC (22 mmol), and HOAt (22 mmol) in 100 mL of dry DMF was added to the deprotected 4-hydroxyproline resin (10 g). The resulting slurry was stirred for 3 h, filtered, washed with DMF, CH_2Cl_2, and treated with a 20% solution of piperidine in DMF at room temperature for 20 min, filtered, washed with DMF, MeOH, and CH_2Cl_2, and dried *in vacuo* to afford the desired modified 4-hydroxyproline resin **4**. Repetition of this procedure allowed the attachment of a second amino acid to afford resin **5**.

General Procedure for the Preparation of Modified 4-Hydroxyproline 6. This procedure was run in parallel using the following reaction conditions: 2 mL of a mixture of 3-fluoro-4-nitrobenzoic acid (1.85g, 10 mmol), HOAt (1.36 g, 10 mmol), and DIC (1.26 g, 10 mmol) (clear solution in 100 mL of DMF) was added to the modified 4-hydroxyproline resin **5** (100 mg, 0.3 mmol/g loading). The resulting slurry was stirred for 8 h, filtered, washed with DMF, MeOH, CH_2Cl_2, and treated with 100 mL of a 5% solution of DBU in DMF at room temperature for 24 h. The resin was filtered, washed with DMF, MeOH, and CH_2Cl_2, dried *in vacuo*, and cleaved with 15% TFA in CH_2Cl_2 for 45 min. The resulting solution was collected, triturated with ether, and dried to afford the desired macrocycles **6** in a 85-95% purity determined by HPLC, LC MS, and ^1H NMR. Analytically pure materials were obtained by chromatography of crude materials on Silicagel (Chromatotron), eluent system CH_2Cl_2/MeOH, 97:3. All compounds were completely characterized by ^1H NMR, HPLC, ESI MS, HR MS, and elemental analyses.

Selected experimental data.

Melting points of compounds **6** and **7** were higher than 280°C.

(6Aa): 11.0 mg (75%); HPLC t_R = 6.01; ^1H NMR ($CDCl_3$): δ 0.86 (d, J = 8.0 Hz, 6H), 1.74 (m, 1H), 2.42 (s, 3H), 2.38 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.48 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.96 (m, 2H),

2.98 (s, 1H), 3.11-3.13 (m, 5H), 3.47 (s, 1H), 3.61 (d, J= 7.0 Hz, 1H), 4.52 (d,J = 3.0 Hz, 1H), 4.68 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.79 (m, 1H), 4.91 (s, 1H), 5.34 (s, 1H), 6.76 (s, 1H), 7.06 (br s, exch D_2O, 1H), 7.12 (d, J= 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H); ESI MS for $C_{23}H_{31}N_5O_7$: *m/z* 490 (M + H^+), 488 (M - H^+). Elemental analysis, Calcd. for $C_{23}H_{31}N_5O_7$: C, 56.43; H, 6.38; Found: C, 56.22; H, 6.11.

(6Ab): 9.1 mg (62%); HPLC t_R = 6.19; ^1H NMR ($CDCl_3$): δ 0.91 (d, J = 8.0 Hz, 6H), 1.70 (m, 1H), 2.35 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.53 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.76 (m, 1H), 2.92 (m, 2H), 3.12-3.14 (m, 5H), 3.60 (d, J= 7.0 Hz, 1H), 4.38 (d,J = 3.0 Hz, 1H), 4.74 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.87 (m, 1H), 4.95 (s, 1H), 5.22 (s, 1H), 6.85 (s, 1H), 7.08 (br s, exch D_2O, 1H), 7.11 (d, J= 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.02 (br s, exch D_2O, 1H); ESI MS for $C_{23}H_{31}N_5O_7$: *m/z* 490 (M + H^+), 488 (M-H^+). Elemental analysis, Calcd. for $C_{23}H_{31}N_5O_7$: C, 56.43; H, 6.38; Found: C, 56.19; H, 6.09.

(6Ac): 11.0 mg (65%); HPLC t_R = 6.26; ^1H NMR ($CDCl_3$): δ 0.94 (d, J = 8.0 Hz, 6H), 1.73 (m, 1H), 2.44 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.47 (m, 2H), 2.56 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.91 (m, 2H), 2.97 (m, 1H), 3.10-3.13 (m, 5H), 3.45 (d, J= 7.0 Hz, 1H), 4.53 (d,J = 3.0 Hz, 1H), 4.72 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.77 (m, 1H), 4.88 (s, 1H), 5.25 (s, 1H), 6.88 (s, 1H), 7.01 (br s, exch D_2O, 1H), 7.10 (d, J= 8.0 Hz, 1H), 7.14-7.26 (m, 5H), 7.94 (d, J = 8.0 Hz, 1H), 8.06 (br s, exch D_2O, 1H); ESI MS for $C_{29}H_{35}N_5O_7$: *m/z* 566 (M + H^+), 564 (M - H^+). Elemental analysis, Calcd. for $C_{29}H_{35}N_5O_7$: C, 61.58; H, 6.24; Found: C, 61.41; H, 6.12.

(6Ba): 9.8 mg (67%); HPLC t_R = 6.14; ^1H NMR ($CDCl_3$): δ 0.87 (d, J = 8.0 Hz, 6H), 1.71 (m, 1H), 2.30 (s, 3H), 2.41 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.42 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.85 (s, 1H), 2.92 (m, 2H), 3.08-3.12 (m, 5H), 3.49 (s, 1H), 3.62 (d, J= 7.0 Hz, 1H), 4.44 (d,J = 3.0 Hz, 1H), 4.47 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.76 (m, 1H), 5.28 (m, 1H), 6.73 (s, 1H), 7.02 (br s, exch D_2O, 1H), 7.06 (d, J= 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 8.11 (br s, exch D_2O, 1H); ESI MS for $C_{23}H_{31}N_5O_7$: *m/z* 490 (M + H^+), 488 (M - H^+). Elemental analysis, Calcd. for $C_{23}H_{31}N_5O_7$: C, 56.43; H, 6.38; Found: C, 56.27; H, 6.19.

(6Bb): 10.4 mg (71%); HPLC t_R = 6.58; ^1H NMR ($CDCl_3$): δ 0.93 (d, J = 8.0 Hz, 6H), 1.74 (m, 1H), 2.42 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.56 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.97 (m, 2H), 3.06 (m, 1H), 3.03 (m, 3H), 3.12 (m, 2H), 3.27 (m, 3H), 3.68 (d, J= 7.0 Hz, 1H), 4.56 (d,J = 3.0 Hz, 1H), 4.71 (m, 1H), 4.77 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 5.32 (m, 1H), 6.84 (s, 1H), 6.98 (br s, exch D_2O, 1H), 7.03 (d, J= 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 8.04-8.08 (br s, exch D_2O, 2H); ESI MS for $C_{23}H_{31}N_5O_7$: *m/z* 490 (M + H^+), 488 (M - H^+). Elemental analysis, Calcd. for $C_{23}H_{31}N_5O_7$: C, 56.43; H, 6.38; Found: C, 56.20; H, 6.09.

(6Bc): 9.3 mg (55%); HPLC t_R = 6.84; ^1H NMR ($CDCl_3$): δ 0.87 (d, J = 8.0 Hz, 6H), 1.69 (m, 1H), 2.44 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.50 (m, 2H), 2.61 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.93 (m, 2H), 3.06 (m, 1H), 3.13 (m, 2H), 3.28 (m, 3H), 3.55 (d, J= 7.0 Hz, 1H), 4.64 (d,J = 3.0 Hz, 1H), 4.72 (m, 1H), 4.79 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 5.38 (m, 1H), 6.91 (s, 1H), 7.06 (br s, exch D_2O, 1H), 7.19 (d, J= 8.0 Hz, 1H), 7.13-7.20 (m, 5H), 7.98 (d, J = 8.0 Hz, 1H), 8.02-8.06 (br s, exch D_2O, 2H) ; ESI MS for $C_{29}H_{35}N_5O_7$: *m/z* 566 (M + H^+), 564 (M - H^+). Elemental analysis, Calcd. for $C_{29}H_{35}N_5O_7$: C, 61.58; H, 6.24; Found: C, 61.31; H, 6.10.

(6Ca): Yield: 13.5 mg (78%); HPLC t_R = 6.67; ^1H NMR ($CDCl_3$): δ 0.90 (d, J = 8.0 Hz, 6H), 1.73 (m, 1H), 2.37 (s, 3H), 2.39 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.44 (m, 2H), 2.52 (dd, J_1 = 7.0 Hz, J_2 = 3.0

Hz, 1H), 2.92 (m, 2H), 3.01 (s, 1H), 3.12 (m, 5H), 3.57 (d, J = 7.0 Hz, 1H), 3.65 (s, 1H), 4.51 (d,J = 3.0 Hz, 1H), 4.69 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.82 (m, 1H), 5.52 (m, 1H), 6.83 (s, 1H), 7.01 (br s, exch D_2O, 1H), 7.03 (d, J = 8.0 Hz, 1H), 7.15-7.25 (m, 5H), 7.81 (d, J = 8.0 Hz, 1H); ESI MS for $C_{30}H_{37}N_5O_7$: *m/z* 580 ($M + H^+$), 578 ($M - H^+$). Elemental analysis, Calcd. for $C_{30}H_{37}N_5O_7$: C, 62.16; H, 6.43; Found: C, 62.01; H, 6.28.

(6Cb): 12.7 mg (73%); HPLC t_R = 6.83; ^1H NMR ($CDCl_3$): δ 0.95 (d, J = 8.0 Hz, 6H), 1.72 (m, 1H), 2.31 (s, 3H), 2.44 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.50 (m, 2H), 2.57 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.89 (m, 1H), 2.95 (m, 2H), 3.11 (m, 2H), 3.35 (m, 3H), 3.58 (d, J = 7.0 Hz, 1H), 4.63 (d,J = 3.0 Hz, 1H), 4.75 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.86 (m, 1H), 5.46 (m, 1H), 6.89 (s, 1H), 7.05 (br s, exch D_2O, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.13-7.25 (m, 5H), 7.80 (d, J = 8.0 Hz, 1H); 8.04 (br s, exch D_2O, 1H); ESI MS for $C_{30}H_{37}N_5O_7$: *m/z* 580 ($M + H^+$), 578 ($M - H^+$). Elemental analysis, Calcd. for $C_{30}H_{37}N_5O_7$: C, 62.16; H, 6.43; Found: C, 61.97; H, 6.30.

(6Cc): 11.4 mg (58%); HPLC t_R = 7.15; ^1H NMR ($CDCl_3$): δ 0.93 (d, J = 8.0 Hz, 6H), 1.71 (m, 1H), 2.35 (s, 3H), 2.39 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.47 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.52 (m, 2H), 2.61 (m, 2H), 3.02 (m, 1H), 2.93 (m, 2H), 3.14 (m, 2H), 3.58 (d, J = 7.0 Hz, 1H), 4.60 (d,J = 3.0 Hz, 1H), 4.78 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.76 (m, 1H), 5.54 (m, 1H), 6.92 (s, 1H), 7.01 (br s, exch D_2O, 1H), 7.08-7.22 (m, 10 H), 7.21 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H); 8.06 (br s, exch D_2O, 1H); ESI MS for $C_{36}H_{41}N_5O_7$: *m/z* 656 ($M + H^+$), 654 ($M - H^+$). Elemental analysis, Calcd. for $C_{36}H_{41}N_5O_7$: C, 65.94; H, 6.30; Found: C, 65.66; H, 6.21.

(7Aa): 9.2 mg (60%); HPLC t_R = 6.29; ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.37 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.49 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.52 (m, 2H), 2.97 (s, 1H), 3.18 (s, 3H), 3.44 (s, 1H), 3.64 (d, J = 7.0 Hz, 1H), 4.53 (d,J = 3.0 Hz, 1H), 4.72 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.73 (m, 1H), 4.93 (s, 1H), 5.37 (s, 1H), 6.71 (s, 1H), 7.02 (br s, exch D_2O, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.13-7.25 (m, 5H), 7.99 (d, J = 8.0 Hz, 1H); ESI MS for $C_{25}H_{27}N_5O_7$: *m/z* 510 ($M + H^+$), 508 ($M - H^+$). Elemental analysis, Calcd. for $C_{25}H_{27}N_5O_7$: C, 58.93; H, 5.34; Found: C, 58.71; H, 5.22.

(7Ab): 11.2 mg (74%); HPLC t_R = 6.43; ^1H NMR ($CDCl_3$): δ 2.29 (s, 3H), 2.38 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.51 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.63 (m, 1H), 3.08 (s, 2H), 3.45 (m, 3H), 3.63 (d, J = 7.0 Hz, 1H), 4.35 (d,J = 3.0 Hz, 1H), 4.73 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.82 (m, 1H), 4.97 (s, 1H), 5.23 (s, 1H), 6.82 (s, 1H), 7.10 (br s, exch D_2O, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.16-7.26 (m, 5H), 7.81 (d, J = 8.0 Hz, 1H), 8.04 (br s, exch D_2O, 1H); ESI MS for $C_{25}H_{27}N_5O_7$: *m/z* 510 ($M + H^+$), 508 ($M - H^+$). Elemental analysis, Calcd. for $C_{25}H_{27}N_5O_7$: C, 58.93; H, 5.34; Found: C, 58.66; H, 5.19.

(7Ac): 9.9 mg (57%); HPLC t_R = 6.71; ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H), 2.46 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.49 (m, 2H), 2.52 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.56 (s, 2H), 2.94 (m, 1H), 3.49 (d, J = 7.0 Hz, 1H), 4.55 (d,J = 3.0 Hz, 1H), 4.72 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.74 (m, 1H), 4.83 (s, 1H), 5.31 (s, 1H), 6.87 (s, 1H), 7.06 (br s, exch D_2O, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.12-7.36 (m, 10H), 7.79 (d, J = 8.0 Hz, 1H), 8.02 (br s, exch D_2O, 1H); ESI MS for $C_{31}H_{31}N_5O_7$: *m/z* 586 ($M + H^+$), 584 ($M - H^+$). Elemental analysis, Calcd. for $C_{31}H_{31}N_5O_7$: C, 63.58; H, 5.34; Found: C, 63.32; H, 5.21.

(7Ba): 9.5 mg (62%); HPLC t_R = 6.32; ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.42 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.44 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.52 (s, 2H), 2.86 (s, 1H), 3.38 (m, 3H), 3.45 (s, 1H), 3.60 (d, J = 7.0 Hz, 1H), 4.43 (d,J = 3.0 Hz, 1H), 4.42 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.77 (m, 1H),

5.27 (m, 1H), 6.76 (s, 1H), 7.01 (br s, exch D_2O, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.15-7.26 (m, 5H), 7.82 (d, J = 8.0 Hz, 1H), 8.07 (br s, exch D_2O, 1H); ESI MS for $C_{25}H_{27}N_5O_7$: *m/z* 510 ($M + H^+$), 508 ($M- H^+$). Elemental analysis, Calcd. for $C_{25}H_{27}N_5O_7$: C, 58.93; H, 5.34; Found: C, 58.69; H, 5.18.

(7Bb): 9.6 mg (63%); HPLC t_R = 6.84; ^1H NMR ($CDCl_3$): δ 2.44 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.57 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.59 (s, 2H), 3.09 (m, 1H), 3.13 (m, 3H), 3.31 (m, 3H), 3.63 (d, J = 7.0 Hz, 1H), 4.59 (d,J = 3.0 Hz, 1H), 4.75 (m, 1H), 4.76 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 5.33 (m, 1H), 6.87 (s, 1H), 7.03 (br s, exch D_2O, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.11-7.24 (m, 5H), 7.83 (d, J = 8.0 Hz, 1H), 8.01-8.06 (br s, exch D_2O, 2H); ESI MS for $C_{25}H_{27}N_5O_7$: *m/z* 510 ($M + H^+$), 508 ($M- H^+$). Elemental analysis, Calcd. for $C_{25}H_{27}N_5O_7$: C, 58.93; H, 5.34; Found: C, 58.65; H, 5.16.

(7Bc): 8.8 mg (50%); HPLC t_R = 7.07; ^1H NMR ($CDCl_3$): δ 2.46 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.50 (m, 2H), 2.56 (s, 2H), 2.66 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 3.08 (m, 1H), 3.34 (m, 3H), 3.56 (d, J = 7.0 Hz, 1H), 4.70 (d,J = 3.0 Hz, 1H), 4.76 (m, 1H), 4.78 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 5.41 (m, 1H), 6.90 (s, 1H), 7.01 (br s, exch D_2O, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.12-7.30 (m, 10H), 8.03 (d, J = 8.0 Hz, 1H), 8.01-8.08 (br s, exch D_2O, 2H); ESI MS for $C_{31}H_{31}N_5O_7$: *m/z* 586 ($M + H^+$), 584 ($M- H^+$). Elemental analysis, Calcd. for $C_{31}H_{31}N_5O_7$: C, 63.58; H, 5.34; Found: C, 63.37; H, 5.26.

(7Ca): 10.4 mg (58%); HPLC t_R = 6.93; ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H), 2.36 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.48 (m, 2H), 2.54 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.62 (s, 2H), 3.04 (s, 1H), 3.10 (m, 3H), 3.53 (d, J = 7.0 Hz, 1H), 3.66 (s, 1H), 4.53 (d,J = 3.0 Hz, 1H), 4.54 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.80 (m, 1H), 5.51 (m, 1H), 6.84 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.11 (br s, exch D_2O, 1H), 7.12-7.25 (m, 10H), 7.84 (d, J = 8.0 Hz, 1H); ESI MS for $C_{32}H_{33}N_5O_7$: *m/z* 600 ($M + H^+$), 598 ($M- H^+$). Elemental analysis, Calcd. for $C_{32}H_{33}N_5O_7$: C, 64.10; H, 5.55; Found: C, 63.71; H, 5.42.

(7Cb): 11.9 mg (66%); HPLC t_R = 7.16; ^1H NMR ($CDCl_3$): δ 2.50 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.54 (m, 2H), 2.57 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.61 (s, 2H), 2.88 (m, 1H), 3.11 (m, 3H), 3.42 (m, 3H), 3.55 (d, J = 7.0 Hz, 1H), 4.65 (d,J = 3.0 Hz, 1H), 4.70 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 4.85 (m, 1H), 5.43 (m, 1H), 6.87 (s, 1H), 7.02 (br s, exch D_2O, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.12-7.28 (m, 10H), 7.75 (d, J = 8.0 Hz, 1H); 8.01 (br s, exch D_2O, 1H); ESI MS for $C_{32}H_{33}N_5O_7$: *m/z* 600 ($M + H^+$), 598 ($M- H^+$). Elemental analysis, Calcd. for $C_{32}H_{33}N_5O_7$: C, 64.10; H, 5.55; Found: C, 63.82; H, 5.44.

(7Cc): 10.3 mg (51%); HPLC t_R = 7.46; ^1H NMR ($CDCl_3$): δ 2.34 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 2.49 (dd, J_1 = 7.0 Hz, J_2 = 3.0 Hz, 1H), 2.52 (m, 2H), 2.55 (s, 2H), 2.61 (m, 2H), 3.02 (m, 1H), 3.18 (s, 3H), 3.57 (d, J = 7.0 Hz, 1H), 4.61 (d,J = 3.0 Hz, 1H), 4.72 (m, 1H), 4.81 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 5.57 (m, 1H), 6.91 (s, 1H), 7.09 (br s, exch D_2O, 1H), 7.08-7.28 (m, 15 H), 7.16 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H); 8.08 (br s, exch D_2O, 1H); ESI MS for $C_{38}H_{37}N_5O_7$: *m/z* 676 ($M + H^+$), 674 ($M- H^+$). Elemental analysis, Calcd. for $C_{38}H_{37}N_5O_7$: C, 67.54; H, 5.52; Found: C, 67.26; H, 5.38.

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[@]This paper is dedicated with love to my daughter Alexandra on the occasion of her 2nd Birthday.

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