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Solid Support Synthesis of 14-Membered Macrocycles Containing the Thioether Bridge *via* S_NAr Methodology

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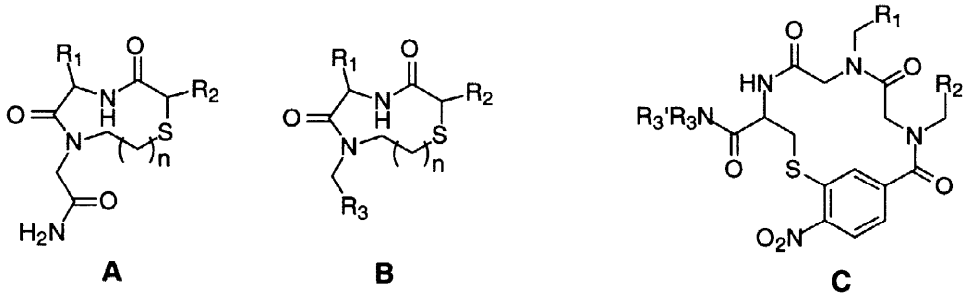
Abstract: An efficient assembly of 14-membered macrocycles utilizing the S_NAr of fluorine in 3-fluoro-4-nitrobenzoic acid with the SH of cysteine on solid support is reported. The flexibility of this synthesis, as well as the excellent purity (>90%) of the final products, are the distinctive characteristics of the resulting library.

Application of combinatorial chemistry as both a lead generation, and a lead optimization tool for drug research and development is well documented.[1] Numerous solid-phase, and solution-pahse techniques have been developed to generate a diverse array of compounds based upon a wide range of reaction types, and scaffolds.[2] In our continuing effort toward identifying new reaction templates to investigate by solid support methods,[3] we were interested in the versatile synthesis of macrocycles containing the thioether bridge. These substrates are well represented in nature,[4] recently attracting attention as β-turn mimetics.[5] Solid-support approaches to a diverse array of 9-, and 10-membered sulfur macrocycles **A**, and **B** have been reported.[5] The key macrocyclization step in this strategy was the nucleophilic displacement of Br with sulfur of the cysteine moiety.



A **B** **C**

The procedure developed by Zhu and others[6] for the synthesis of various cyclic substrates containing the biaryl ether bridge[7] represents an alternative route to the desired sulfur macrocycles. The nucleophilic aromatic substitution (S_NAr) of fluoride in various fluoronitroaromatic substrates with the phenolic oxygen of the tyrosine derivatives[8] allows the efficient macrocyclization to occur. Exceptionally mild coupling conditions, ready availability of starting materials, as well as the possibility to expand the diversity of substituents in the final macrocycles *via* post-modification reactions of the nitro group make this strategy amenable to solid phase.[9] In our approach, we decided to adopt a similar strategy for the synthesis of sulfur containing macrocycles **C**, and use Mmt-protected cysteine **1**, and 3-fluoro-4-nitrobenzoic acid **2**[10] 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 desired 14-membered macrocycles, we selected the previously reported acrylate resin[11] modified with piperazine as a solid support for the synthesis. Subsequent alkylation to quaternize the trisubstituted amine followed by base induced Hofmann elimination were reported to yield the product in good yield and excellent purity.[11] Furthermore, the coupling sequence involving bromoacetic acid followed by the nucleophilic displacement of Br with primary amines would introduce an additional dimension to the desired library.

In the initial experiment, we coupled **1** to the acrylate resin modified with piperazine (Scheme 1) using the standard DCC protocol (the loading was determined by standard Fmoc cleavage with 20% piperidine in DMF to be 0.35 mmol/g). Bromoacetic acid was coupled to the resulting immobilized *S*-Mmt cysteine **3** *via* the previously reported procedure,[12] and the resulting resin was treated with a 0.5 M solution of amine in DMF to afford the resin **4**. The procedure was repeated again to afford the resin **5**, followed by coupling of **2** using the HOAt/DIC strategy.[13] The resulting resin was treated with a 5% solution of DBU in DMF for 24 h, alkylated, and treated with a 0.5M solution of Et_3N in DCM to afford the target macrocycles **6** (Scheme 1).[10] The progress of this

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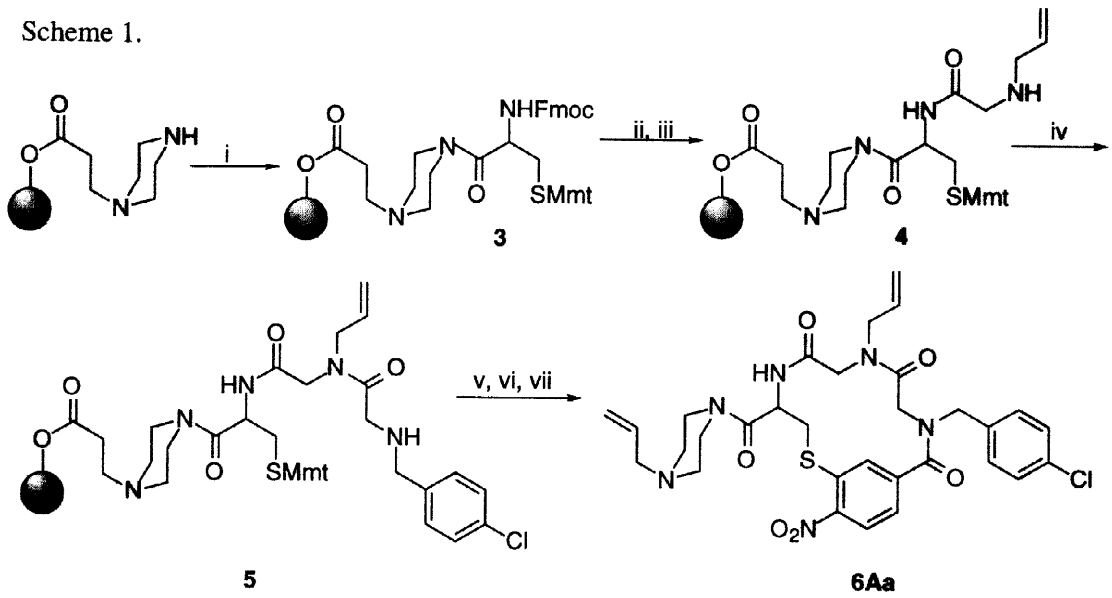
Scheme 1.

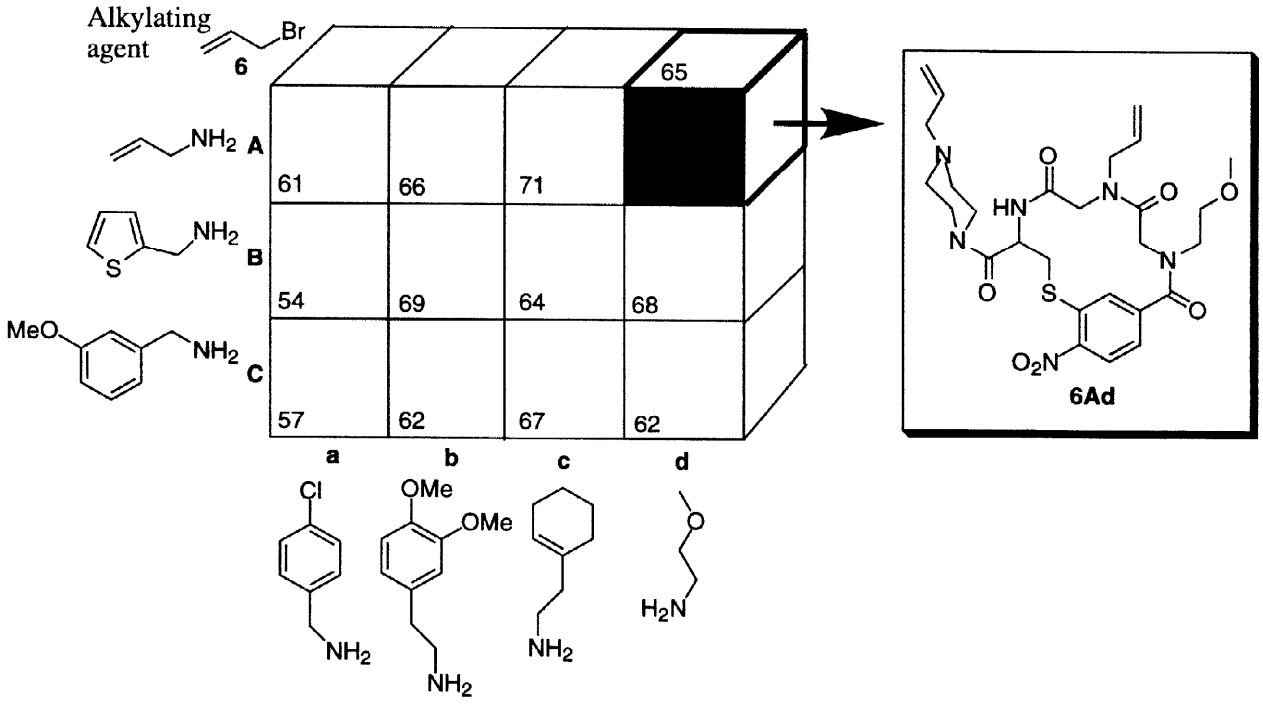


Reagents and Conditions: i) **1**, DCC, DMF/CH_2Cl_2 (1:1), RT, 24 h. (0.3 mmol/g loading); ii) 20% piperidine/DMF; $BrCH_2COOH$, DIC, DMF, RT, 3 h.; iii) CH_2=$CHCH_2NH_2$ (**A**), DMF, RT, 12 h.; iv) $BrCH_2COOH$, DIC, DMF, RT, 3 h *p*-$C_6H_4CH_2NH_2$ (**a**), DMF, RT, 12 h. ; v) **2**, HOAt, DIC, DMF, RT, 8 h.; vi) 3% TFA/DCM, 45 min., RT; vii) 5% DBU DMF, RT, 24 h.; CH_2=$CHCH_2Br$, DMF, 24 h., RT; Et_3N/DCM, RT, 12 h., RT.

macrocyclization step was monitored by ^{19}F NMR.[9] Macrocyclization was not observed with the K_2CO_3/18-crown-6 system or with *N*-methylmorpholine in DMF.[9] Tetramethylguanidine, and TBAF afforded the desired product in a lower yield and inferior purity. We found that 14-membered macrocycles were the smallest representatives of this class of macrocycles. Attempts to prepare smaller rings by coupling **2** on to the resin **4** followed by the standard DBU-promoted cyclization and Hofmann elimination afforded only a complex mixture.

The elaboration of the reaction conditions allowed us to synthesize a library of 12 members (Scheme 2).

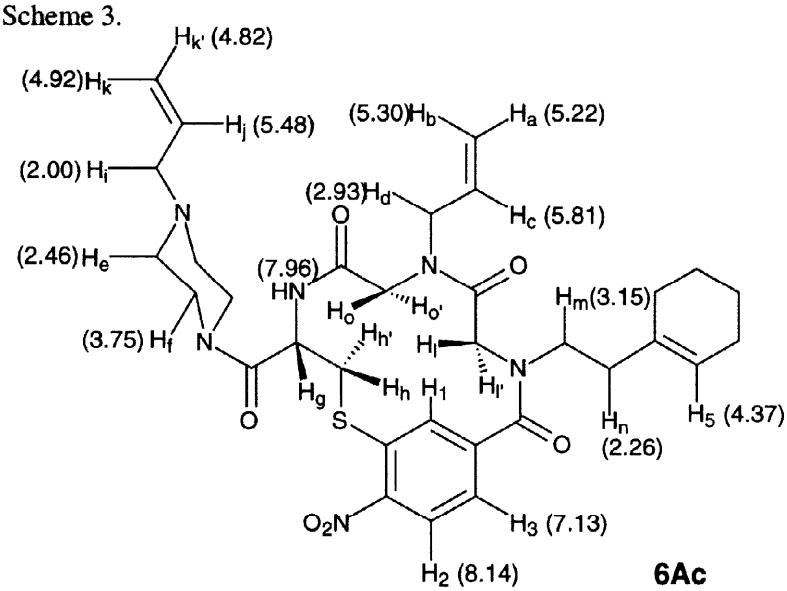
Scheme 2.



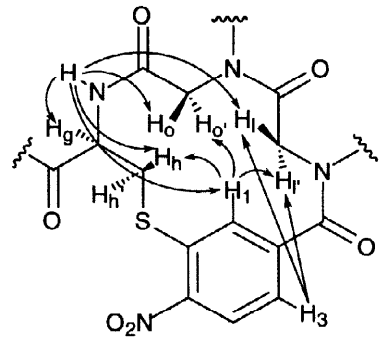
Neither the nature of the alkylating agent, nor the primary amines used for the bromine displacement in bromoacetic acid affected the yield, or purity of the final products **6**. The average yield of the target macrocycles ranged from 54% to 74%. The purity was determined by both ^{1}H NMR, and HPLC analyses to be greater than 90%. An additional 5-10% of product was isolated after the resin was resubjected to the alkylating agent for 48 h followed by Hofmann elimination of the target product with Et_3N. Interestingly, when 3-fluoro-4-nitrobenzoic acid (**2**) was substituted with its regioisomers, namely, 2-fluoro-5-nitro-, and 4-fluoro-3-nitrobenzoic acids, the yields of the macrocyclization products did not exceed 25-30% by HPLC analysis. In these two instances, the reaction mixtures after Hofmann elimination were complex.

COSY, TOCSY and NOESY experiments were performed to assign the proton resonances and confirm the bond connectivity of the macrocycle ring (Scheme 3). The characteristic allylic, cysteine, and aromatic ring spin systems were readily identified by COSY, and TOCSY experiments. The two protons of each of the two

Scheme 3.



6Ac



NOE

Compound	Chemical shifts of the macrocyclic ring protons, ppm							
	H_h'	H_h	H_l'	H_l	H_o'	H_o	H_g	H_1
6Aa	3.19	3.29	3.84	3.95	3.16	4.86	5.16	7.33
6Ab	3.27	3.35	3.86	3.97	3.05	4.82	5.19	7.36
6Ac	3.21	3.38	3.78	3.91	3.11	4.83	5.14	7.37
6Ad	3.19	3.26	3.83	3.85	3.13	4.79	5.09	7.27
6Ba	3.13	3.31	3.88	3.90	3.17	4.85	5.18	7.39
6Bb	3.27	3.32	3.82	3.93	3.14	4.79	5.13	7.39
6Bc	3.23	3.35	3.72	3.84	3.14	4.91	5.12	7.35
6Bd	3.24	3.31	3.80	3.93	3.14	4.82	5.11	7.32
6Ca	3.18	3.22	3.77	3.97	3.05	4.83	5.10	7.35
6Cb	3.25	3.36	3.83	3.94	3.07	4.80	5.21	7.33
6Cc	3.26	3.31	3.85	3.98	3.13	4.82	5.22	7.41
6Cd	3.28	3.35	3.85	3.92	3.17	4.93	5.20	7.33

methylene groups on the 14 membered ring exhibited individual chemical shifts, and strong COSY/NOE connectivities. The key NOEs between the protons across the ring were observed as shown. Chemical shifts for the protons in the macrocyclic core are summarized in the table of Scheme 3.

In summary, we have described a protocol for the efficient assembly of 14-membered macrocycles utilizing S_NAr of fluorine in 3-fluoro-4-nitrobenzoic acid with the SH of cysteine on solid support. Flexibility of this synthesis, as well as the excellent purity of the final products are the distinctive characteristic of the resulting library.

Experimental Section.

Materials. All solid phase reactions were carried out at room temperature. Reagents were purchased from Aldrich and Acros and used without further purification. Wang resin (loading 0.6 mmol/g) was purchased from Novabiochem and washed with DMF, MeOH, CH_2Cl_2, and MeCN prior to use.

General Methods. All reactions were carried out in Alltech® vessels (250 mg of resin per reaction vessel). Concentration of solutions after work-up was performed by reduced pressure rotary evaporation. ^1H NMR spectra were obtained on a Bruker DRX 500 instrument with $CDCl_3$ as the solvent. The TOCSY and NOESY spectra were obtained with mixing times of 80 msec., and 600 msec. respectively. MS analysis (ES, and CI modes) was performed on a Perkin Elmer API 165 instrument. HPLC analysis was 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 Preparation of Mmt-protected Cysteine on acrylate resin 3. In a standard resin preparation protocol, *N*-Fmoc, and *S*-Mmt protected cysteine (12.3 g, 20 mM) was treated with DCC (2.06 g, 10 mM) in 50 mL of dry dichloroethane. The resulting mixture was stirred for 2 hrs., and filtered. 50 mL of dry DMF was added, and the acrylate resin modified with piperazine (10 g, 0.45mmol/g loading as determined by coupling of 4-nitrobenzoylchloride followed by cleavage of the resultant amide with allylamine) 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 the Fmoc group cleavage). The resulting resin was treated with 100 mL of a 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 *S*-Mmt protected cysteine **3**.

General Procedure for Preparation of Modified *S*-Mmt Cysteine 5. This procedure was run using following reaction conditions: mixture of bromoacetic acid (2.78g, 20 mM) and DIC (2.77 g, 22 mM) in 100 mL of dry DMF was added to *S*-Mmt resin **3** (10 g). The resulting slurry was stirred for 3 hrs., filtered, washed with DMF, CH_2Cl_2, and treated with a 0.5 M solution of amine in DMF at room temperature for 12 h., filtered, washed with DMF, MeOH, and CH_2Cl_2, and dried *in vacuo* to afford the desired modified *S*-Mmt cysteine resin **4**. This procedure was repeated once again to afford resin **5**.

General Procedure for Preparation of Macrocycles 6. This procedure was run using following reaction conditions: 2 mL of a mixture of 3-fluoro-4-nitrobenzoic acid (1.85g, 10 mM), HOAt (1.36 g, 10 mM), and DIC (1.26 g, 10 mM) (clear solution in 100 mL of DMF) was added to resin **5** (250 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 5% solution of DBU in DMF at room temperature for 24 hrs, filtered, washed with DMF, treated with alkylating agent (0.5 M solution in DMF) for 24 h., washed with DMF, MeOH, CH_2Cl_2, treated with 0.5 M solution of Et_3N in DCM for 12 hrs, and filtered. The filtrate was collected, dried *in vacuo*, triturated with ether, and dried to afford the desired macrocycles **6**.

Selected Analytical Data:

(6Aa): 30.0 mg (61%); HPLC t_R = 6.26; ^1H NMR: δ 2.02 (m, 2H), 2.52 (m, 4H), 2.95 (m, 2H), 3.16 (m, 1H), 3.19 (m, 1H), 3.29 (m, 1H), 3.61 (m, 2H), 3.79 (m, 4H), 3.84 (m, 1H), 3.95 (m, 1H), 4.86 (d, *J* =

4.5Hz, 1H), 4.92 (m, 1H), 4.96 (d, J = 8.5Hz, 1H), 5.16 (m, 1H), 5.28 (d, J =4.5Hz, 1H), 5.34 (d, J =8.5Hz, 1H), 5.73 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 5.86 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 7.13 (d, J = 8.0Hz, 1H), 7.24 (d, J = 8.0Hz, 2H), 7.33 (s, 1H), 7.43 (d, J = 8.0Hz, 2H), 7.94 (m, exch D_2O, 1H), 8.11 (d, J = 8.0Hz, 1H); ESI MS *m/z* 656 ($M + H^+$), 654 ($M - H^+$).

(6Ab): 34.4 mg (66%); HPLC t_R = 6.37; ^1H NMR: δ 2.08 (m, 2H), 2.43 (m, 4H), 2.90 (m, 2H), 3.05 (m, 1H), 3.27 (m, 1H), 3.35 (m, 1H), 3.52 (m, 2H), 3.66-3.68 (m, 6H), 3.78 (m, 2H), 3.83 (m, 4H), 3.86 (m, 1H), 3.97 (m, 1H), 4.71 (d, J = 4.5Hz, 1H), 4.82 (m, 1H), 4.88 (d, J = 8.5Hz, 1H), 5.19 (m, 1H), 5.23 (d, J =4.5Hz, 1H), 5.36 (d, J =8.5Hz, 1H), 5.84 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 5.92 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 6.68 (s, 1H), 6.82-6.85 (m, 2H), 7.12 (d, J = 8.0Hz, 1H), 7.36 (s, 1H), 7.86 (m, exch D_2O, 1H), 8.05 (d, J = 8.0Hz, 1H); ESI MS *m/z* 695 ($M + H^+$), 693 ($M - H^+$).

(6Ac): 34.0 mg (71%); HPLC t_R = 6.31; ^1H NMR: δ 1.86-2.24 (m, 8H), 2.26 (m, 2H), 2.46 (m, 4H), 2.93 (m, 2H), 3.11 (m, 3H), 3.15 (m, 2H), 3.21 (m, 1H), 3.38 (m, 1H), 3.75 (m, 4H), 3.78 (m, 1H), 3.91 (m, 1H), 4.37 (m, 1H), 4.82 (d, J = 4.5Hz, 1H), 4.83 (m, 1H), 4.92 (d, J = 8.5Hz, 1H), 5.14 (m, 1H), 5.22 (d, J =4.5Hz, 1H), 5.30 (d, J =8.5Hz, 1H), 5.48 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 5.81 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 7.13 (d, J = 8.0Hz, 1H), 7.37 (s, 1H), 7.96 (m, exch D_2O, 1H), 8.14 (d, J = 8.0Hz, 1H); ESI MS *m/z* 639 ($M + H^+$), 637 ($M - H^+$).

(6Ad): 28.7 mg (65%); HPLC t_R = 6.02; ^1H NMR: δ 2.06 (m, 2H), 2.44 (m, 4H), 2.98 (m, 2H), 3.13 (m, 1H), 3.19 (m, 1H), 3.26 (m, 1H), 3.54 (m, 2H), 3.67 (s, 3H), 3.78 (m, 2H), 3.81 (m, 4H), 3.83 (m, 1H), 3.85 (m, 1H), 4.75 (d, J = 4.5Hz, 1H), 4.79 (m, 1H), 4.81 (d, J = 8.5Hz, 1H), 5.09 (m, 1H), 5.16 (d, J =4.5Hz, 1H), 5.24 (d, J =8.5Hz, 1H), 5.80 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 5.84 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 7.10 (d, J = 8.0Hz, 1H), 7.27 (s, 1H), 7.83 (m, exch D_2O, 1H), 8.11 (d, J = 8.0Hz, 1H); ESI MS *m/z* 589 ($M + H^+$), 587 ($M - H^+$).

(6Bb): 38.8 mg (69%); HPLC t_R = 6.42; ^1H NMR: δ 2.03 (m, 2H), 2.34 (m, 4H), 3.14 (m, 1H), 3.27 (m, 1H), 3.32 (m, 1H), 3.39 (m, 2H), 3.54 (m, 2H), 3.69-3.71 (m, 6H), 3.75 (m, 2H), 3.81 (m, 4H), 3.82 (m, 1H), 3.93 (m, 1H), 4.76 (d, J = 4.5Hz, 1H), 4.84 (m, 1H), 4.88 (d, J = 8.5Hz, 1H), 5.13 (m, 1H), 5.81 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 6.71 (s, 1H), 6.73 (d, J = 8.0Hz, 1H), 7.04-7.21 (m, 5H), 7.39 (s, 1H), 7.83 (m, exch D_2O, 1H), 8.12 (d, J = 8.0Hz, 1H); ESI MS *m/z* 751 ($M + H^+$), 749 ($M-H^+$).

(6Ca): 31.4 mg (57%); HPLC t_R = 6.83; ^1H NMR: δ 1.96 (m, 2H), 2.45 (m, 4H), 3.05 (m, 1H), 3.18 (m, 1H), 3.22 (m, 1H), 3.47 (m, 2H), 3.59 (s, 3H), 3.69 (m, 2H), 3.74 (m, 4H), 3.77 (m, 1H), 3.97 (m, 1H), 4.73 (d, J = 4.5Hz, 1H), 4.83 (m, 1H), 4.86 (d, J = 8.5Hz, 1H), 5.10 (m, 1H), 5.75 (dd, J_1 = 4.5Hz, J_2 = 8.5Hz, 1H), 6.82 (s, 1H), 6.93-7.16 (m, 4H), 7.29 (d, J = 8.0Hz, 2H), 7.35 (s, 1H), 7.44 (d, J = 8.0Hz, 2H), 7.81 (m, exch D_2O, 1H), 8.11 (d, J = 8.0Hz, 1H); ESI MS *m/z* 735 ($M + H^+$), 733 ($M - H^+$).

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†This paper is dedicated to my beloved wife Natalie and daughter Alexandra.

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