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Solid support synthesis of 15-membered macrocycles containing a serotonin unit

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Abstract—Efficient assembly of 15-membered macrocycles utilizing the S_NAr of fluorine in 3-fluoro-4-nitrobenzoic acid with the OH functionality of serotonin on solid support is reported. This flexible synthesis yields a set of title macrocycles with good purity (>90%).

1. Introduction

Efficient assembly of biaryl macrocycles continues to attract considerable attention due to a wide array of biological activities displayed by these compounds.[1] For example, K-13 is a noncompetitive inhibitor of angiotensin I converting enzyme.[2] Pierazinomycin, bouvardin, deoxybouvardin, and the RA class of bicyclic hexapeptide macrocycles possess anti-tumor and anti-bacterial activities.[3–5] Several biaryl macrocycles contain the indole ring as a structural unit. Chloropeptins I and II, as well as kistamycins A and B (complestatins), are peptide antibiotics isolated from the *Streptomyces* species WK-3419. They display a broad range of anti-bacterial activities including inhibition of *gp* 120-CD4 binding.[6–8]

We were interested in the versatile synthesis of 15-membered biaryl macrocycles containing the indole fragment.[9] In order to accomplish this goal, we decided to use the strategy based on the nucleophilic aromatic substitution (S_NAr) of fluoride in a properly substituted fluoronitroaromatic substrates with the phenolic oxygen of the 5-hydroxyindole derivatives.[10,11] The anticipated advantages of this approach include: (i) mild reaction conditions for the formation of the biaryl fragment, (ii) availability of the starting materials, (iii) possibility to introduce an additional point of diversity in the final macrocycles by reduction/acylation reactions of the nitro group, (iv) potential to assemble the desired 15-membered macrocycles on the solid phase.

Several solid support syntheses of medium-, and large-ring cyclic structures utilizing the S_NAr strategy have been reported.[9,12] In our approach, we decided to use serotonin **1**,[13] and 3-fluoro-4-nitrobenzoic acid **2**[14] as components for the final S_NAr coupling (Scheme 1). After experimenting with several solid support alternatives, we selected 4-[4-hydroxymethyl-3-methoxyphenoxy]butyric acid–benzhydrylamide (HMPB–BHA) resin (available from Advanced ChemTech) modified with acrylic ester for attachment of serotonine.[15]

2. Experimental procedure

2.1. Immobilization of serotonine on the HMPB–BHA-acrylate resin

A mixture of serotonin hydrochloride (2.12 g, 10 mmol), and Hunig's base (5 equiv, 6.45 g, 50 mmol) in 25 mL of DMF was added to 5 g of HMPB–BHA-acrylate resin.[16] The resulting slurry was shaken for 24 h at 60 °C. The resin was then washed with DMF, MeOH, and CH_2Cl_2. Loading of the acrylate resin at this stage was determined to be ca. 0.45 mmol/g (3% TFA in CH_2Cl_2, 10% of Et_3SiH as acid scavenger, 20 min). At this stage, we noticed that prolonged treatment of the resin with acid (>30 min) dramatically reduced the yield of the serotonine derivative and caused the extensive formation of high molecular weight products, presumably due to

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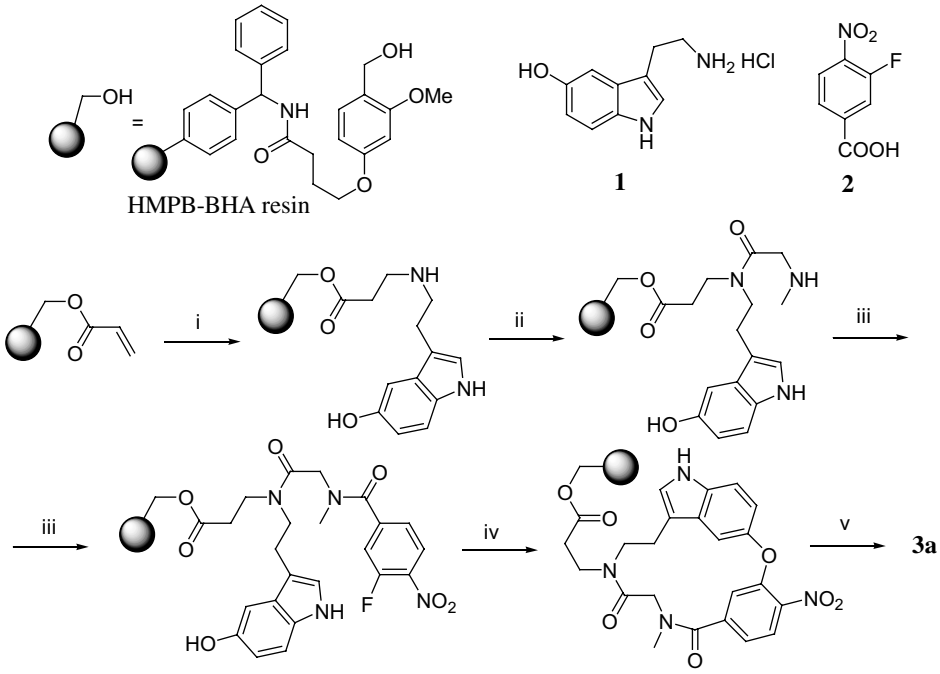


Scheme 1. Reagents and conditions: (i) **1**, Hunig's Base (5 equiv), DMF, 60 °C, 24 h (0.45 mmol/g loading); (ii) Fmoc-Sar-OH (**A**), HOAt, DIC, DMF, rt, 8 h; 20% piperidine/DMF; (iii) **2**, HOAt, DIC, DMF, rt, 8 h; (iv) 5% DBU/DMF, rt, 12 h; (v) 3% TFA, CH_2Cl_2, Et_3SiH, 20 min.

polymerization. Application of alternative reagent systems for cleavage (2–5% HCl/dioxane, 2–5% HCl/EtOAc, 1–2% TFA/AcOH, 1 M NaOH/MeOH) did not improve the outcome of the cleavage step.[17]

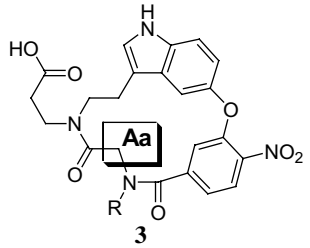
2.2. Attachment of the amino acid to the sarcosine resin

A mixture of Fmoc-protected sarcosine (**a**, 622 mg, 2 mmol), 1-hydroxy-7-azabenzotriazole (HOAt, 272 mg, 2 mmol), and 1,3-diisopropylcarbodiimide (DIC, 252 mg, 2 mmol) in 5 mL of DMF was added to the serotonin resin (250 mg).[18] The resulting slurry was shaken for 8 h washed with DMF, MeOH, and CH_2Cl_2. The resin containing the serotonin modified with sarcosine was deprotected using a 20% solution of piperidine in DMF (5 mL). Loading of the resin was determined based on Fmoc-cleavage to be 0.40 mmol/g. Other amino acids were attached to the serotonin resin using analogous conditions.

2.3. The synthesis of macrocycles 3a–i

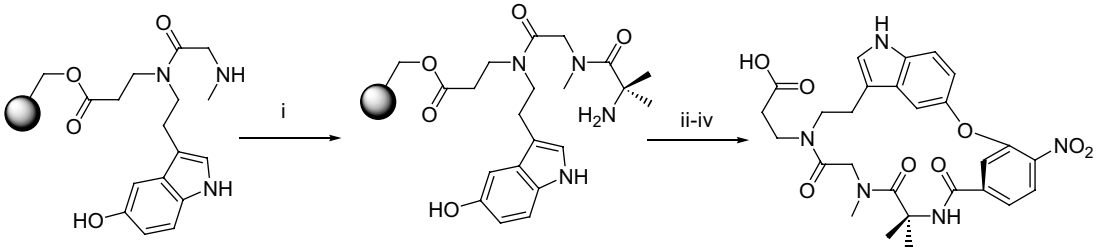
The resultant resin (250 mg) was then treated with 3-fluoro-4-nitrobenzoic acid **2** (370 mg, 2 mmol) using the same HOAt/DIC (2 mmol of each in 5 mL of DMF) strategy described above for the coupling of amino acids.[18] Loading of the resin was determined to be 0.25 mmol/g. The precursor was then successfully

Table 1. Yields and HPLC purity of 15-membered macrocycles based on serotonin **3**



	Aa = amino acid input								
	Sar **a**	L-Ala **b**	D-Ala **c**	L-Phe **d**	D-Phe **e**	L-Pro **f**	Aib[a] **g**	Ac3c[b] **h**	L-Phg **i**
Yield, %[c]	52	50	46	57	51	43	58	45	43
HPLC purity, %	92	91	92	94	92	90	95	93	93
Retention time, min[d]	3.90	4.13	4.14	5.46	5.48	5.65	4.56	4.74	5.02

[a] Aib = Aminoisobutyric acid.
[b] Ac3c = aminocyclopropanoic acid (*N*-Fmoc derivatives available from Advanced Chemtech).
[c] Yields refer to the analytically pure compounds obtained by preparative chromatography after trituration with EtOH/Et_2O (4:1).
[d] The analytical column employed was an Ultrasphere C18 cartridge 250 mm × 4.6 mm; the solvent system was MeCN/H_2O (start: 5/95 ratio; finish: 10/90 ratio; 8 min runs, 1% TFA added), flow rate: 1 mL/min.



Scheme 2. Reagents and conditions: (i) Fmoc-Aib-OH (**g**), HOAt, DIC, DMF, rt, 8 h; 20% piperidine/DMF; (ii) **2**, HOAt, DIC, DMF, rt, 8 h; (iii) 5% DBU/DMF, rt, 12 h; (iv) 3% TFA, CH_2Cl_2, Et_3SiH, 20 min.

cyclized using a 5% solution of DBU in DMF (10 mL) in 12 h. The resultant resin was subsequently cleaved with 10 mL of a 3% solution of TFA in CH_2Cl_2 containing 10% of Et_3SiH for 20 min. A set of nine macrocycles has been synthesized using this protocol (Table 1). The purity was determined by both ^1H NMR and LCMS analyses to be in the range of 90–95%. Interestingly, the nature of the amino acid affected neither the yield nor the purity of the final product as illustrated for both D-, and L-amino acids (entries **b**–**d**). Also, yields of the final products **3** were not significantly affected by the steric hindrance of the amino acid (entries **g**–**i**). The analytically pure samples were prepared by reverse-phase preparative chromatography.[19,20]

Nitro group of the aromatic ring was further reduced to the amino group with $SnCl_2{\cdot}2H_2O$ in DMF and subsequently modified by acylation with Ac_2O as described earlier.[9]

In addition, we found that the size of the macrocyclic ring containing serotonin unit could be further increased by introducing a second amino acid input. In a representative example, serotonin immobilized on the acrylate resin was modified with *N*-Fmoc sarcosine (**a**) using the HOAt/DIC protocol. Fmoc protection was removed with 20% piperidine in DMF followed by coupling of Fmoc-Aib-OH (**g**), deprotection, attachment of **2** and final macrocyclization to yield the desired 18-membered product **3ag** in a 47% isolated yield and 90% HPLC purity (Scheme 2).

In summary, an efficient assembly of 15-membered macrocycles utilizing the S_NAr of fluorine in 3-fluoro-4-nitrobenzoic acid with the OH of serotonin on solid support is reported. The procedure could be further expanded to the synthesis of the respective 18-membered rings containing serotonin unit. The flexibility of this synthesis, as well as the good purity (>90%) of the final products are the advantages of this synthesis.

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19. The major impurity detected in the reaction mixtures was β-alanine derivative of sarcosine (5–9%).
20. For preparative chromatography we used the Phenomenex Prodigy 5μ ODS(3) 100 A 21.2 mm × 250 mm column on Waters DeltaPrep4000 HPLC instrument. The solvent system was MeCN/H_2O (start: 20:80; finish 50:50 ratio; 10 min run; 0.1% of formic acid added) with a flow rate 20 mL/min. *Analytical data for* ***1a***: 15.1 mg yield (52%, based on 0.45 mmol/g loading), HPLC, t_R = 3.90 min, mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 2.25 (t, J = 8.4 Hz, 2H), 2.59 (t, J = 8.4 Hz, 2H), 2.89 (s, 3H), 3.28 (m, 2H), 3.56 (s, 2H), 3.64 (m, 2H), 6.72 (s, 1H), 6.82 (s, 1H), 7.08 (s, 1H), 7.22 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 10.8 (br s, 1H). ESI MS (M+1): 467; (M−1): 465; HR ESIMS, calculated for $C_{23}H_{22}N_4O_7$: 466.1489; found: 466.1482.