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Solid Support Synthesis of 14-Membered Macrocycles *via* SNAr Methodology on Acrylate Resin.

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Abstract: Efficient assembly of 14-membered macrocycles utilizing SNAr of fluorine in 3-fluoro-4-nitrobenzoic acid with the OH of 3-hydroxytyrosine on the 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.

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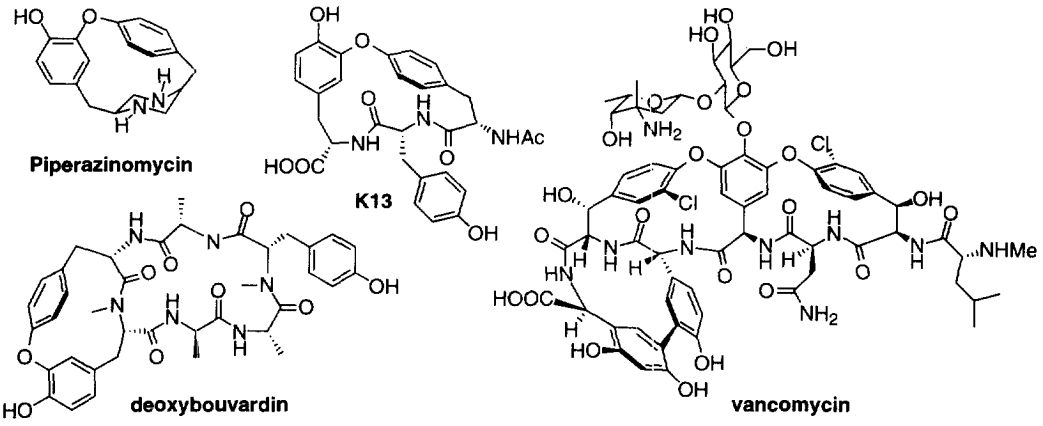
Macrocycles containing a nonsymmetrical biaryl ether moiety are well represented in nature.[1] These architecturally complex substrates exhibit a wide range of biological activity. For example K-13 is a non competitive inhibitor of angiotensin I converting enzyme.[2] It contains the characteristic isodityrosine moiety, also common for the related macrocyclic 17-membered tripeptides of the OF4949 family.[2] Piperazinomycin possesses the 14-membered biaryl motif found in the related 14-membered macrocycles, namely bouvardin, deoxybouvardin, and the RA class of bicyclic hexapeptide macrocycles. Several of these agents have been reported to possess antitumor activity.[3] Vancomycin is a polycyclic glycopeptide antibiotic which is effective against gram-positive microorganisms including *staphylococcus aureus*.[4] Teicoplanin is yet another representative of this family of macrocycles.[5] Biaryl macrocycles continue to attract interest due to their pronounced biological activity, as well as the synthetic challenges they pose.[6]



Two main strategies have been developed for the assembly of the macrocyclic biaryl core. They are: i) macrolactamization of the preformed biaryl ether,[7] and ii) traditional peptide synthesis followed by biaryl ether formation as a key step. The conventional macrolactamization techniques were performed with only marginal success. In these cases, the reported yields of the target macrocycles were usually low.[7] The second strategy involves coupling of the two aromatic units incorporated into the peptide *via* a variety of methods. Studies conducted by numerous research teams including those of Yamamura,[8] Evans,[9] Boger,[10] Zhu and Beugelmans,[11] Rao,[12] Rich,[13] and Nicolaou[14] have shown that a wide array of coupling conditions, and a diverse number of possible components lead to the biaryl ether. Of these strategies, the approach developed by Zhu and others[11] deserves special attention. It is based on the nucleophilic aromatic substitution (S_NAr) of fluoride in various fluoronitroaromatic substrates with the phenolic oxygen of the tyrosine derivatives to install the biaryl ether bridge

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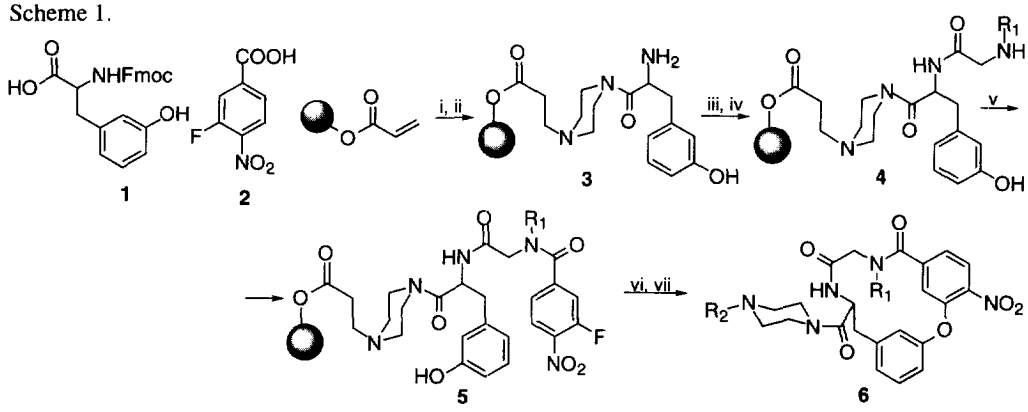
in the desired macrocycles.[15] The exceptionally mild coupling conditions, the ready availability of starting materials, as well as the possibility to of expanding the diversity of the substituents in the final macrocycles *via* postmodification reactions of the nitro group make this strategy amenable for solid phase assembly of 14-membered macrocycles.

In our continuing effort toward the identification of new reaction templates to investigate by solid support methods,[16] we were interested in the versatile synthesis of 14-membered macrocycles containing the biaryl ether bridge. Several solid support syntheses of similar structures have been reported by Burgess.[17] In our approach, we decided to use the easily available 3-hydroxytyrosine **1**[18], and 3-fluoro-4-nitrobenzoic acid **2**[19] 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 acrylate resin.[20] The resin was further modified with piperazine, and used as the 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.[20] Furthermore, the coupling sequence involving bromoacetic acid followed by the nucleophilic displacement of Br with primary amines would introduce an additional dimension in the desired library (Scheme 1).

Scheme 1.



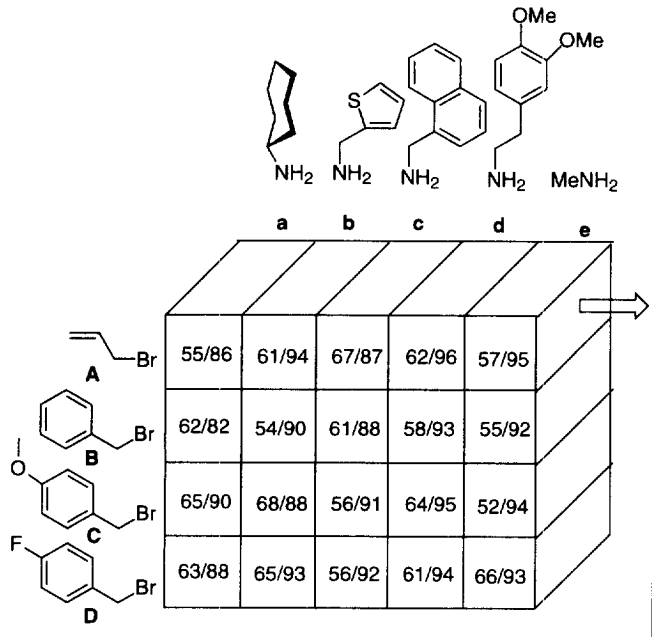
Reagents and Conditions: i) piperazine, DMF, 80°C, 24 h.; ii) **1**, DCC, DMF/CH_2Cl_2 (1:1), RT, 24 h. (0.3 mmol/g loading); 20% piperidine/DMF; iii) $BrCH_2COOH$, DIC, DMF, RT, 3 h.; iv) $R_1CH_2NH_2$, DMF, RT, 12 h.; v) **2**, HOAt, DIC, DMF, RT, 8 h.; vi) 5% DBU/DMF, RT, 24 h.; vii) R_2CH_2Br, DMF, RT, 12 h.; Et_3N, DCM, RT, 4 h

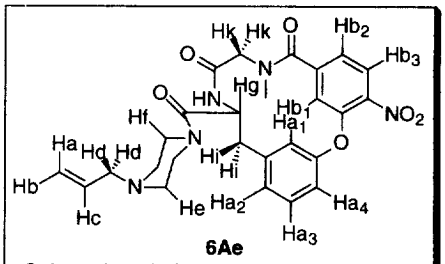
In the initial experiment, we coupled **1** to the acrylate resin modified with piperazine using a standard DCC protocol (loading was determined by standard Fmoc cleavage with 20% piperidine in DMF to be 0.35 mmol/g). Notably *protection of the OH function was not required in the following steps!* Bromoacetic acid was coupled onto the resulting immobilized 3-hydroxytyrosine **3** *via* the previously reported procedure.[21] The resulting resin was treated with a 0.5 M solution of amine in DMF to afford resin **4**. Resin **4** was coupled with **2** using the HOAt/DIC strategy[22] to afford resin **5**. Resin **5** was treated with a 5% solution of DBU in DMF for 24 h., alkylated, and treated with a 0.5 M solution of Et_3N in DCM to afford targeted macrocycles **6**.[10] The progress of this macrocyclization step was monitored by ^{19}F NMR.[17] Macrocyclization was not observed with the K_2CO_3/18-crown-6 system in DMF.[10,17] The elaboration of the reaction conditions allowed us to synthesize a library of 20 members (Table 1). Neither the nature of the alkylating agent, nor the nature of the primary amines used for the bromine displacement in bromoacetic acid affected the yield, or purity of the final product **6**. The average yield of the targeted macrocycles ranged from 54% to 68%. The purity was determined by both ^1H NMR, and HPLC analysis to be greater than 90%. An additional 10-15% of product was isolated when the resin was resubjected to the alkylating agent for 48 h., and treated with Et_3N to eliminate **6**.

General Procedure for Preparation of 3-Hydroxytyrosine on acrylate resin 3. In the standard resin preparation protocol, N-Fmoc protected 3-hydroxytyrosine (8.06 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 h., filtered, 50 mL of dry DMF were added, and the acrylate resin modified with piperazine (10 g, 0.45mmol/g loading as determined by coupling

Table 1. Yield and purities of macrocycles **6**.





6Ae

Selected analytical data: yield 21.7 mg (57%); HPLC t_R = 7.18, purity 95%; ^{1}H NMR (CDCl3): δ 2.47 (m, 4H, H_f), 2.51 (m, 4H, H_e), 2.97 (m, 2H, H_i), 2.99 (s, 3H, NMe), 3.07 (m, 2H, H_d), 3.69 (m, 2H, H_k), 5.02 (m, 1H, H_g), 5.22 (s, 1H, H_b), 5.25 (m, 1H, H_a), 5.87 (m, 1H, H_c), 6.65 (s, 1H, NH), 6.76 (s, 1H, H_{a1}), 6.80 (s, 1H, H_{b1}), 7.15 (d, J = 7.5 Hz, 1H, H_{a2}), 7.17 (d, J = 7.5 Hz, 1H, H_{a4}), 7.25 (d, J = 9.0 Hz, 1H, H_{b2}), 7.47 (t, J = 7.5 Hz, 1H, H_{a3}), 7.99 (d, J = 9.0 Hz, 1H, H_{b3}); ESI MS m/z 508 (M + H+), 506 (M- H+). HRMS: M+1 calcd. for $C_{26}H_{29}N_5O_6$: 508.2189; found: 508.2194.

of 4-nitrobenzoylchloride followed by treatment with allylamine and cleavage of the resultant amide with Et_3N) was introduced. The slurry was stirred at room temperature for 24 h., filtered, washed with DMF, MeOH, CH_2Cl_2, and dried *in vacuo* to afford resin **3** (0.35 mmol/g loading as determined by 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 deprotected 3-hydroxytyrosine **3**.

General Procedure for the Preparation of Modified 3-Hydroxytyrosine 4. This procedure was run using the following reaction conditions: a mixture of bromoacetic acid (2.78g, 20 mM) and DIC (2.77 g, 22 mM) in 100 mL of dry DMF was added to the deprotected 3-hydroxytyrosine resin **3** (10 g), the resulting slurry was stirred for 3 h., filtered, washed with DMF, CH_2Cl_2, and treated with 0.5 M solution of the 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 3-hydroxytyrosine **4**.

General Procedure for Preparation of Resin 5. This procedure was run using the 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 the modified 3-hydroxytyrosine resin (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 a 5% solution of DBU in DMF at room temperature for 24 h. The resin was then filtered, washed with DMF, treated with alkylating agent (0.5 M solution in DMF) for 12 h., washed with DMF, MeOH, CH_2Cl_2, treated with a 0.5 M solution of Et_3N in DCM, and filtered. The filtrate was collected, dried *in vacuo*, triturated with ether, and dried to afford the targeted macrocycles **6**. All compounds were completely characterized by ^{1}H NMR, including NOESY and COSY experiments, HPLC, and ESI MS.

In summary, we have described a protocol for the efficient assembly of 14-membered macrocycles *via* S_NAr of fluorine in 3-fluoro-4-nitrobenzoic acid with the OH of 3-hydroxytyrosine on solid support. The

flexibility of this synthesis, as well as the excellent purity of the final products, are the distinctive characteristics of the resulting library.

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†This paper is dedicated to Professor Ronald G. Harvey on the occasion of his 70th birthday.

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