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The Solid Phase Synthesis of Trisubstituted 1,4-Diazabicyclo[4.3.0]nonan-2-one Scaffolds: On Bead Monitoring of Heterocycle Forming Reactions Using ^{15}N NMR

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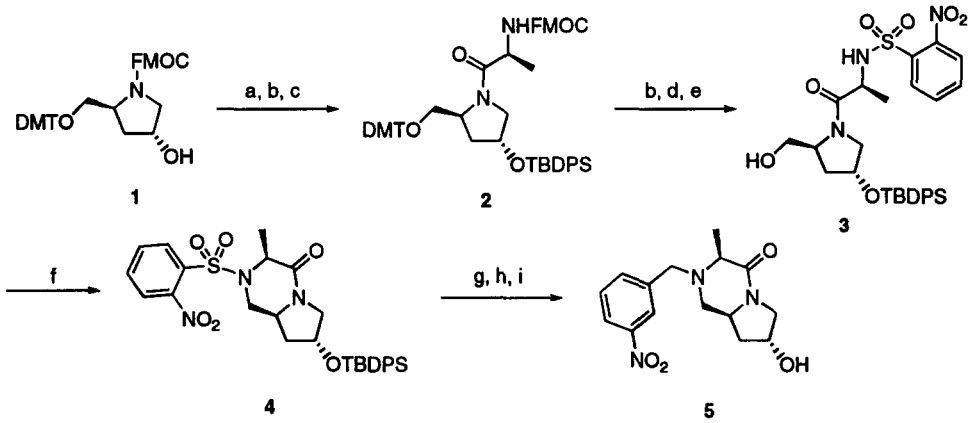
Abstract: Several representative 3,4,8-trisubstituted 1,4-diazabicyclo[3.4.0]nonan-2-ones have been prepared employing solid phase methodologies. Elaboration of a 4-hydroxyproline derivative with an ^{15}N-amino acid derivative allowed convenient monitoring of the reaction sequence on solid support by gel-phase ^{15}N NMR. An intramolecular Mitsunobu cyclization provided the desired heterocycle, which could be further functionalized at the 4-position. This synthetic method is facile, general, and suitable for the construction of large libraries of compounds for biological assays.

In order to increase the diversity of new structures readily available for biological assays, we have undertaken studies to prepare a series of non-structure based molecules[1] amenable to assembly *via* combinatorial methods.[2] A particularly appealing strategy for accomplishing this goal involves the construction of a heterocyclic system using amino acids as key building blocks, since they are readily available from commercial suppliers, and bear functionality having a high degree of diversity. This approach was used by both the Ellman[3] and Parke-Davis[4] groups in their early work on the synthesis of small molecule combinatorial libraries in a exploration of known pharmacophores, and has more recently been applied to the synthesis of cyclic ureas,[5] as well as novel heterocyclic structures.[6] We envisioned a similar strategy, using amino acid derivatives as building blocks for the construction of the 1,4-diazabicyclo[3.4.0]nonan-2-one ring system employing solid phase methodologies. Although the piperazinedione derivatives of this ring system have been more extensively investigated, derivatives unsubstituted at the 5-postion are unknown. A recent report in the literature[7] describes the synthesis of a related fused piperazinone ring system by the intramolecular displacement of a mesyl group with an amine, however the yields were modest, and required forcing conditions. Since we are interested in the automated synthesis of a large number of compounds *via* solid phase methodologies for biological screening, we required facile reactions throughout the synthetic pathway in order to obtain acceptable yields and purities of the final products. These considerations led us to consider an intramolecular Mitsunobu reaction using the 2-nitrobenzenesulfonamide group[8] as an easily removable activating group for effecting synthesis of the ring system.

As a model system, the protected *trans*-4-hydroxyproline derivative **1**[9] (Scheme 1) was silylated, deprotected at nitrogen, then coupled to FMOC-Ala-OH to provide **2**. The protecting group on the amino acid was then exchanged for the 2-nitobenzenesulfonyl group, and the DMT protection removed. Treatment of the resulting derivative **3** under Mitsunobu conditions effected a clean cyclization to the desired compound **4**, providing a 99% yield of isolated product. The sulfonamide was then removed, the unsubstituted nitrogen functionalized by alkylation with 3-nitrobenzyl bromide, and the material desilylated to give **5**.

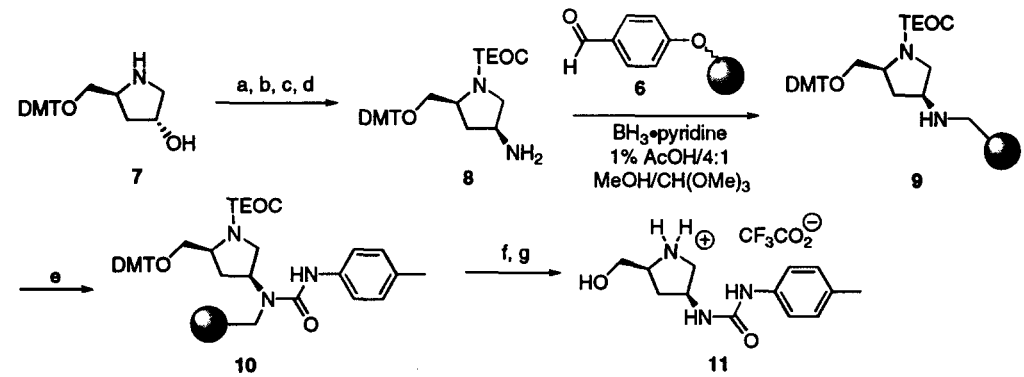
The methodology was next adapted to the solid phase in order to facilitate synthesis of related structures on our automated high throughput parallel array synthesizer.[10] A suitable attachment point to the support would be the free



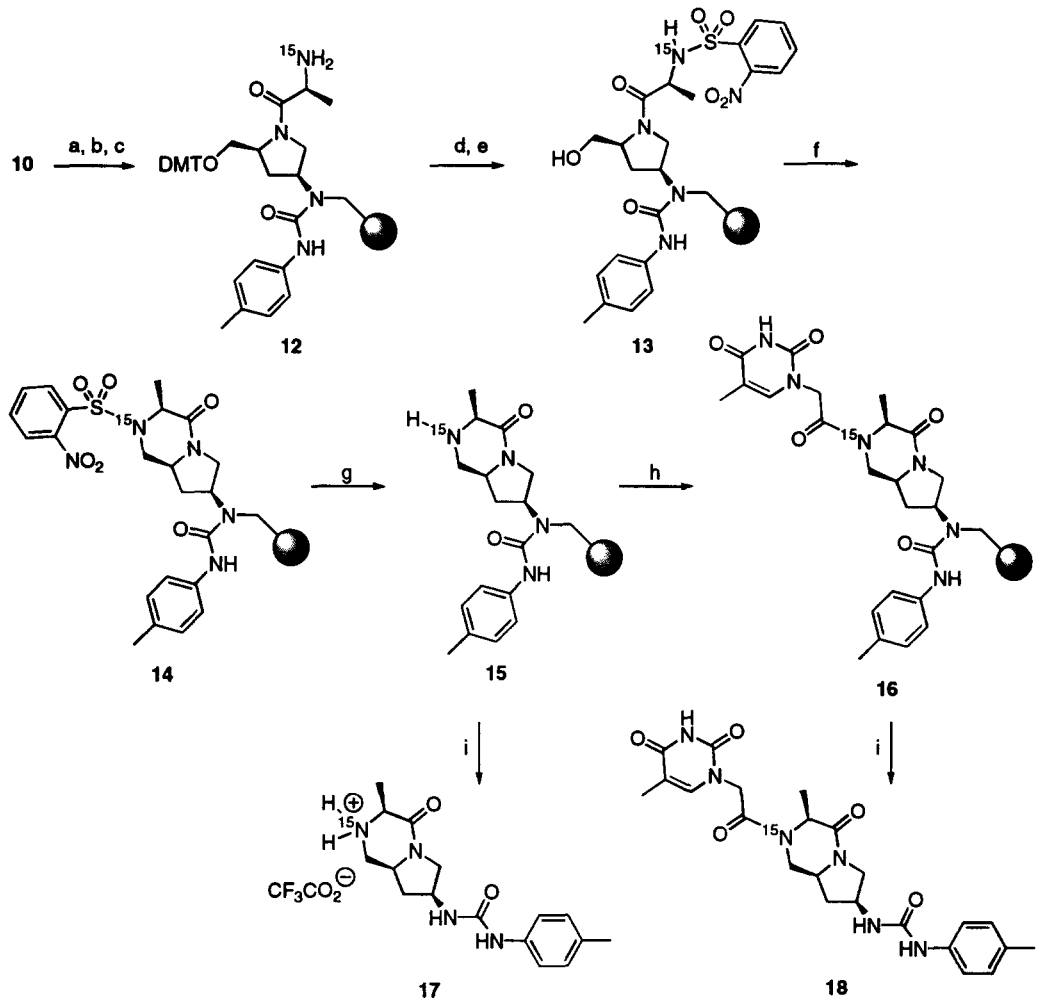
Scheme 1. a) TBDPSCl/imidazole/DMF; b) 10% piperidine/DMF; c) FMOC-L-Ala-OH/HATU/DIPEA/ DCM; d) 2-nitrobenzene-sulfonyl chloride/DIPEA/DCM; e) 1 eq. AcCl/DCM/MeOH; f) DEAD/Ph_3P/THF; g) PhSH/K_2CO_3/DMF; h) 3-nitrobenzylbromide/ Et_3N/DMF/THF; i) TBAF/THF

hydroxyl group of **1**, however this would result in the 8-hydroxy group being present in all libraries prepared, and therefore limit the diversity achieved. To overcome this problem, we investigated the possibility of attaching a linker at an amino group on the 8-position of the final product, which would allow for functionalization at this position during the synthetic pathway.[11] The necessary support **6** was prepared from 4-hydroxybenzaldehyde and the acid stabile ArgoGel™-OH resin[12] *via* modified Mitsunobu conditions,[13] and the structure verified by gel-phase ^{13}C NMR.[14] The hydroxyprolinol derived scaffold was elaborated to an amine derivative by protecting **7**[9] as the 2-trimethylsilylethoxycarbonyl (Teoc)[15] derivative (Scheme 2), followed by mesylation, azide displacement, and reduction[16] to provide amine **8** in high yield. This material was then loaded onto support *via* a BH_3•pyridine[17] mediated reductive amination, affording a quantitative yield of **9**.[18] The secondary amine of **9** was functionalized with an isocyanate to give urea **10**, which could be cleanly cleaved from the support by treatment with TFA to provide **11** in quantitative yield and >90% purity.[18]

In order to follow the progress of subsequent reactions without detaching material from the support, isotopically enriched ^{15}N-Alanine was used as the amino acid, which allowed convenient monitoring of the success of transformations by gel phase ^{15}N NMR. This technique provided a convenient label for following the progress of the reaction sequence, as the amino-acid derived nitrogen is involved in the key ring forming reactions, and therefore exhibits significant differences in chemical shift. Furthermore, the sensitivity obtained was sufficient to gauge the



Scheme 2. a) Teoc-NHS; b) MsCl/CH_2Cl_2/pyridine; c) NaN_3/DMF/80 °C; d) $SnCl_2$/PhSH/Et_3N/MeCN e) 4 eq. *p*-tolyl isocyanate/ DMF; f) $CHCl_2CO_2H/CH_2Cl_2$; g) CF_3CO_2H/5% Et_3SiH



Scheme 3. a) 1 M TBAF/THF; b) ^{15}N-FMOC-Ala-OH/HATU/DIPEA/CH_2Cl_2; c) piperidine/DMF; d) 2-nitrobenzenesulfonyl chloride/DIPEA/CH_2Cl_2; e) $CHCl_2CO_2H/CH_2Cl_2$; f) 3 eq. Ph_3P-sulfonamide betaine (ref. 13)/5% DMF/ CH_2Cl_2; g) 0.5 M $HSCH_2CO_2H$/1 M DBU/DMF; h) 5 eq. thymine-1-acetic acid/HATU/DIPEA/ CH_2Cl_2; i) CF_3CO_2H/5% Et_3SiH

success or failure of reactions, as by-products were evident by the presence of multiple peaks when inappropriate reaction conditions were chosen.

After the Teoc protection of **10** (Scheme 3) was removed, the product was functionalized with ^{15}N-FMOC-Ala-OH, and then deprotected to provide **12**, which showed a single resonance at δ -350.6 ppm in the ^{15}N NMR spectrum (referenced to formamide in DMSO-d_6). Introduction of the 2-nitrobenzene sulfonamide group, followed by removal of the DMT and gave **13** (^{15}N NMR δ -275.5 ppm, doublet, J=79 Hz). Reaction under modified Mitsunobu conditions[13] effected a clean cyclization to **14** (^{15}N NMR δ -283.4 ppm, singlet), which was deprotected with mercaptoacetic acid/DBU to provide **15** (^{15}N NMR δ -344.5 ppm). Functionalization of the unsubstituted nitrogen provided **16** (^{15}N NMR δ -261.6 ppm), and cleavage of **15** and **16** gave the corresponding non-resin bound compounds **17** and **18**. The yield of **18** (by mass) over the 12 steps from the commercially available support was 64%, with an estimated purity of 80% (by ^{1}H NMR), representing a true yield of ~50%, and an average chemical yield of 95%. This yield would most likely be unattainable with a traditional solution synthesis, and illustrates that reasonably long synthetic pathways are

feasible for the synthesis of small molecule combinatorial libraries on solid support.

In conclusion, a synthetic pathway has been developed which provides functionalized piperazin-2-one ring systems in excellent yields. For demonstrative purposes, representative combinatorial library structures based upon a 3,4,8-trisubstituted 1,4-diazabicyclo[3.4.0]nonan-2-one scaffold have been prepared employing solid phase methodologies. This framework provides three variable positions for the introduction of diverse functionality, two *via* common electrophilic reagents, and one derived from commercially available FMOC-amino acids. The starting materials for the synthesis (*trans*-4-hydroxyproline and α-amino acids) determine the chirality of the final product, which eliminates stereochemical ambiguities. While a five-membered starting framework has been used to prepare a 6:5 fused ring system in this study, it should be noted that other functionalized heterocycles could presumably be prepared *via* this methodology. In particular, 6:6 fused systems would be accessible from azasugars such as the 1-deoxynojirimycin analogs.[19] We have adapted this methodology to high throughput mode on an automated parallel array synthesizer, and are currently pursuing this strategy for the synthesis of large combinatorial libraries based upon this scaffold for screening in biological assays.

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