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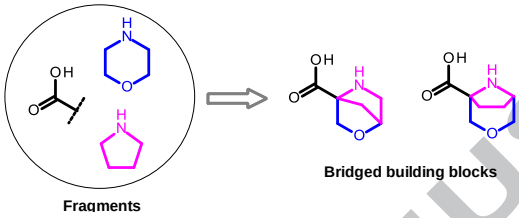

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Synthesis of Novel and Conformationally Constrained Bridged Amino Acids as Compact Modules for Drug Discovery

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ABSTRACT

As novel scaffolds with rigid inherent three-dimensional conformation, the bridged amino acid building blocks containing both morpholine and pyrrolidine motifs, 2-oxa-5-azabicyclo[2.2.1]heptane-4-carboxylic acid **1** and 3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid **2**, were first synthesized as compact modules for future applications in the optimization of physicochemical and pharmacokinetic properties of drug candidates in drug discovery.

There has been increasing awareness of drug-like properties in the medicinal chemistry community since Lipinski's seminal paper on "rule of five".[1] As key determining factors for quality of small-molecule drug candidates, physicochemical properties[2] have important impact on compound's performance in humans related to ADMET (absorption, distribution, metabolism, excretion and toxicity) characteristics and target engagement.[3] Optimization of physicochemical and pharmacokinetic properties of drug candidates should occur early and could be as important as that of target affinity and selectivity. A number of computational approaches[4] for compound property prediction are utilized to guide compound selection and optimization. Nevertheless, the optimization process of small molecular entities remains a considerable challenge. One way to address this issue is to develop building block libraries which cover a broad range of scaffolds with distinct properties and can be readily incorporated into drug candidates to modulate compound profiles. The recent identification of novel and diversified building blocks,[5] such as spirocyclic and oxetane containing modules,[6] opens up new chemical space and offers multiple options for medicinal chemists to manipulate physicochemical and pharmacokinetic properties and eventually improve quality of small-molecule drug candidates.

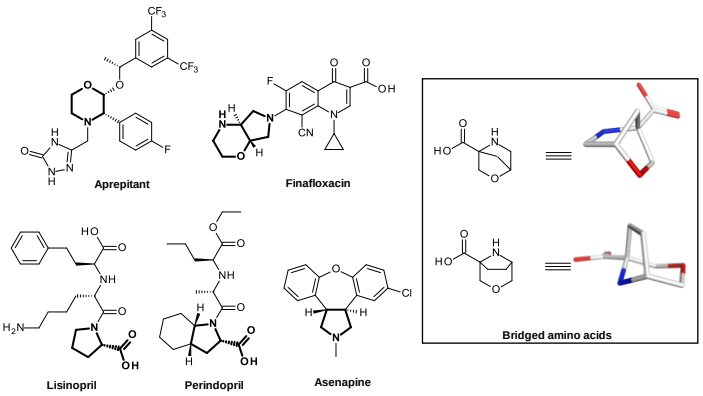

Figure 1. Parmaceuticals containing aliphatic heterocycles, bridged amino acids of interest and their calculated lowest energy conformations[9]

Morpholine and pyrrolidine, as very popular scaffolds in medicinal chemistry, are widely applied in marketed drugs (**Figure 1**).[7] And their carboxylic acid[8] substituted derivatives, as in the case of Lisinopril and Perindopril in Figure **1**, are also widely used in the drug discovery. To modulate conformational constraint of those fragments, we are particularly interested in a series of bridged amino acids such as compounds **1** and **2** (**Figure 1**). Conformational analysis shows that the [2.2.1]-bridging pattern in compound **1** locks morpholine in a boat-like conformation, while [3.2.1]-bridging pattern in

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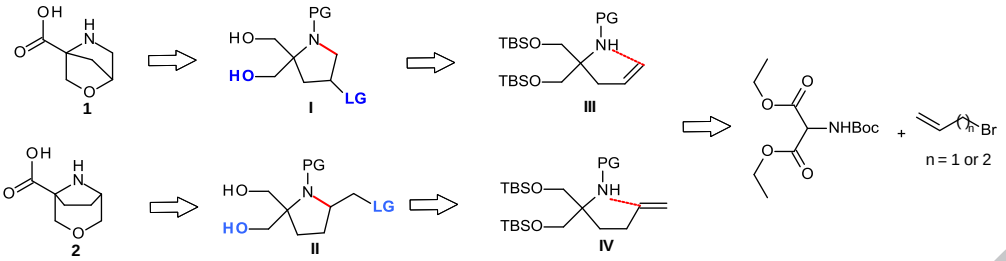
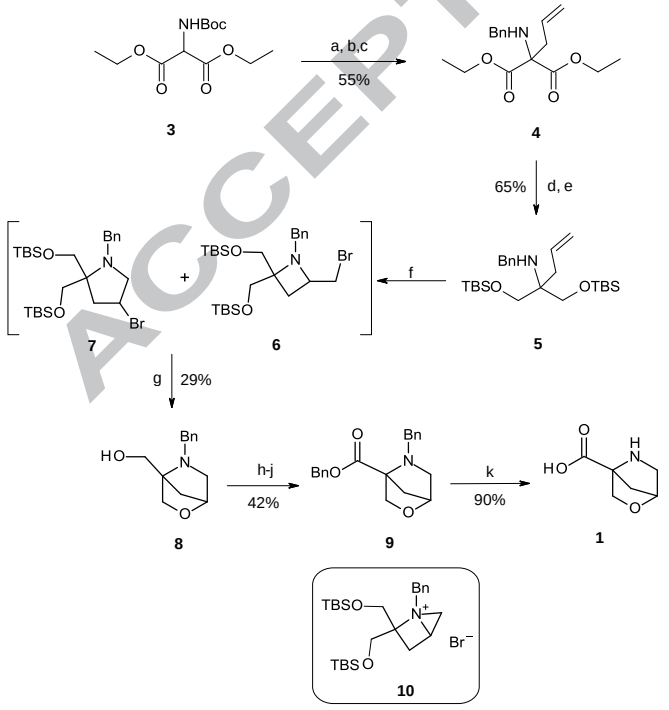


Figure 2. Retrosynthetic analysis of bridged amino acids **1** and **2**

compound **2** adopts a chair-like conformation (**Figure 1**).[9] In addition, the inherent out-of-plane three dimensionality of the bridged scaffold may have advantages over traditional flat (hetero)aromatic ring systems.[10] Moreover, the conformation restriction of the bridged systems may help reduce entropy penalty upon binding to a target protein. So it is very worthwhile to develop an efficient synthesis of those conformational restricted motifs and explore their impact to physicochemical and pharmacokinetic properties, which to the best of our knowledge, are not reported in the public domain. Herein we report the first synthesis of the two novel bridged *α*-amino acids with distinct rigid conformations, 2-oxa-5-azabicyclo[2.2.1]heptane-4-carboxylic acid **1** and 3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid **2**.

The retrosynthetic analysis of the bridged bicyclic scaffolds **1** and **2** is illustrated in **Figure 2**. In general, similar synthetic approaches were adopted for both building blocks. The morpholine ring formation could be achieved via an intramolecular S_N2 reaction. The key intermediates **I** and **II** were synthesized by a halogen-mediated ring cyclization of intermediates **III** and **IV**, respectively. The latter two, in turn, can be prepared in a few steps from commercially available *N*-Boc-aminomalonate and alkenyl bromides.

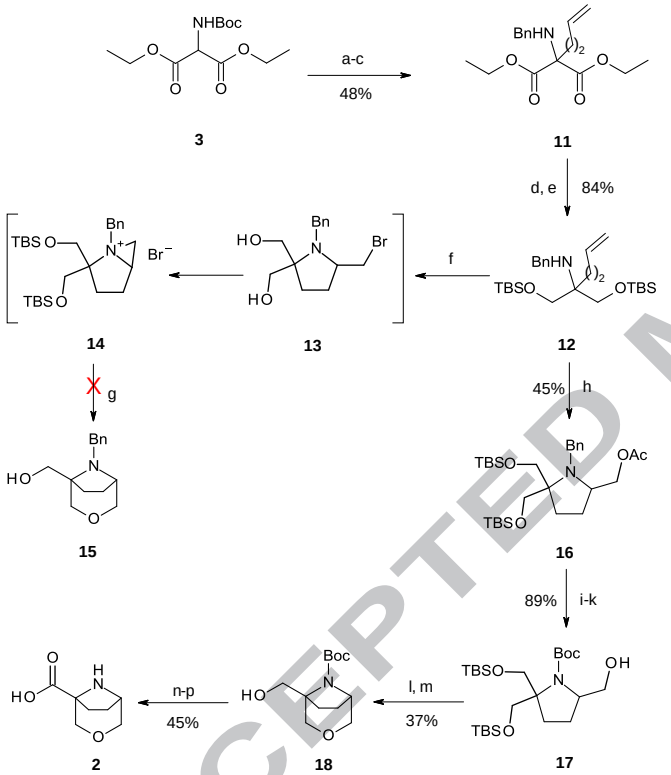


Scheme 1. Preparation of compound **1**. Reagents and conditions: (a) NaH, allybromide, THF, 80 °C; (b) TFA, CH_2Cl_2; (c) benzyl bromide, K_2CO_3, CH_3CN; (d) $LiAlH_4$, THF; (e) TBSCl, Et_3N, CH_2Cl_2; (f) NBS, CH_3CN, rt, 15min; (g) TBAF, THF, 80 °C, overnight; (h) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt; (i) $NaClO_2$, $NaH_2PO_3{\cdot}2H_2O$, cyclohexane, *t*-BuOH/H_2O; (j) BnBr, K_2CO_3, DMF, 60 °C; (k) Pd/C, H_2, MeOH.

The synthesis of compound **1** commenced with the allylation of diethyl 2-(*N*-(*tert*-butoxycarbonyl)amino)malonate **3** with allyl bromide (**Scheme 1**),[11] which was followed by *N*-Boc-deprotection and benzylation to afford compound **4** with modest yield over three steps. The ethyl esters of compound **4** were reduced with $LiAlH_4$ to yield diol, which was further protected with *tert*-butyldimethylsilyl (TBS) group to afford compound **5**. The subsequent halogen-mediated cyclization of homoallyl amine **5** was investigated with NBS in acetonitrile at room temperature. The reaction proceeded very fast, and presumably both 4-*exo* azetidine **6** and 5-*endo* pyrrolidine **7** could be formed according to the literature report.[12] However, we were unable to characterize those potential products due to decomposition of the crude mixture during silica gel chromatography. Therefore, the crude mixture was directly used in the next step and treated with TBAF at elevated temperature. As expected, the TBS deprotection and morpholine ring formation took place in one-pot to afford the desired bridged scaffold **8** as the only isolated product. Here we assumed intermediate **6** could be converted to intermediate **7** via an unstable and reactive aziridinium bromide **10**, and **7** was the actual precursor for compound **8**.[13] The free primary hydroxyl group in compound **8** was further transformed to carboxylic acid in moderate yield by Swern oxidation[14] and successive Pinnick-Lindgren oxidation[15]. To facilitate the purification, the carboxylic acid was masked as a less polar and easily handled benzyl ester to provide compound **9**. Global deprotection under catalytic hydrogenation condition furnished the final building block 2-oxa-5-azabicyclo[2.2.1]heptane-4-carboxylic acid **1**.

Next we investigated the synthesis for building block **2** (**Scheme 2**). Olefin **12** with one more CH_2 unit was successfully prepared according to similar procedures as the synthesis of compound **5**. Treatment of **12** with NBS led to complete consumption of the starting material as monitored by TLC. Interestingly, a mass corresponding to aziridinium **14** was detected by LC/MS. However, the following one-pot deprotection and morpholine ring formation in the presence of TBAF was very sluggish and only trace amount of the desired product **15** was observed by LC/MS. We speculated that the bromide **13** was unstable as the basic nitrogen could readily attack the neighboring bromine-bearing carbon to form a [3.1.0] bicyclic aziridinium bromide **14**. Unfortunately, upon treatment with TBAF at high temperature, the presumed aziridinium **14** was decomposed to give a complex mixture. In contrast, bromide **7** was relatively stable and probably had low propensity to form a much more constrained [2.1.0] bicyclic aziridinium salt **10** under the same condition (**Scheme 1**). To address this problem, we envisioned to trap the potential aziridinium species **14** with an

external nucleophile, and then diminish the nucleophilicity of the nitrogen by switching *N*-benzyl protecting group to unreactive *N*-carbamate before the intramolecular etherification. Thus compound **12** was treated with I_2 in the presence of $NaHCO_3$ and then NaOAc at elevated temperature. To our delight, compound **16** was obtained in 45% isolated yield presumably via regioselective opening of the aziridine ring at the less hindered position by acetate.[16] Further *N*-Bn and *O*-Ac deprotection reactions were followed by *N*-Boc protection to give alcohol **17** in 89% yield. The free hydroxyl group of **17** was converted to *O*-Ts leaving group, and the following one-pot TBS-deprotection and morpholine ring formation proceeded uneventfully in the presence of TBAF at 60 °C with moderate yield. Again the free alcohol of compound **18** was oxidized to carboxylic acid via Dess-Martin oxidation[17] and then Pinnick-Lindgren oxidation[15]. The final *N*-Boc deprotection furnished compact module 3-oxa-8-azabicyclo[3.2.1]octane-5-carboxylic acid **2** with 45% yield over 3 steps.



Scheme 2. Preparation of compound **2**. Reagents and conditions: (a) NaH, 4-bromo-1-butene, THF, 80 °C; (b) TFA, CH_2Cl_2; (c) benzyl bromide, K_2CO_3, CH_3CN; (d) $LiAlH_4$, THF; (e) TBSCl, imidazole, CH_2Cl_2; (f) NBS, CH_3CN, rt; (g) TBAF, THF, 60 °C; (h) I_2, $NaHCO_3$, CH_3CN, then NaOAc, 60 °C; (i) Pd/C, H_2, EtOH; (j) K_2CO_3, MeOH; (k) Boc_2O, toluene, 90 °C; (l) TsCl, DMAP, CH_2Cl_2; (m) TBAF, THF, 60 °C; (n) Dess-Martin periodinane, CH_2Cl_2; (o) $NaClO_2$, $NaH_2PO_3{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O; (p) HCl in dioxane.

In summary, the first synthesis of two novel bridged amino acid derivatives **1** and **2** was achieved. The synthetic strategy here featured a halogen-mediated ring closure to construct the pyrrolidine ring first, and then an intramolecular etherification reaction to afford the morpholine ring. The synthetic methods discussed herein are highly reproducible and the final amino acids **1** and **2** or their protected intermediates[18] may have wide applications. Considering their distinct 3D-shape, these modules may be considered as conformationally constrained amino acids, a very useful class of building blocks in peptidomimetics[19]. In addition, these structures contain both embedded morpholine and pyrrolidine thus serving as novel replacement of either motif in medicinal chemistry. The unique conformations and their potential impacts on biological activity upon incorporation into small molecule drug candidates will add further value into both scaffolds. In the future design and synthesis, the location of the carboxyl group could be tuned and placed to β- or γ- position of the nitrogen which would provide further opportunities to modulate basicity of the nitrogen and control the relative orientation of substituents on both nitrogen and carboxyl group. The application of these two building blocks in drug discovery is ongoing, and their impacts on physicochemical properties as well as pharmacokinetics will be evaluated and disclosed in due course.

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