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Report

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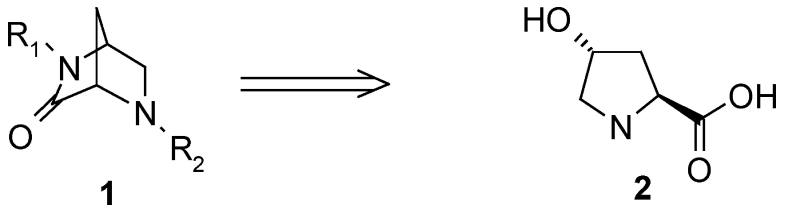

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Polymer-Supported Synthesis of Bicyclic γ-Lactams

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Recent advances in combinatorial chemistry have dramatically improved the efficiency of library synthesis. Modern high-throughput chemistry employing solid phase, solution phase, and appropriate combinations of both expedites lead discovery and lead optimization. Screening well-designed small-molecule libraries utilizing drug-relevant building blocks and biologically privileged scaffolds can provide better coverage of biological target information and druglike chemically accessible spaces and, therefore, enhance the chances of lead discovery.

Bicyclic γ-lactams are potential analogues of the β-lactams and competitive inhibitors of β-lactamases;[1−3] however, only small numbers of compounds in this class and limited substitution patterns have been described so far.[4] We report herein an efficient methodology for the synthesis of a library of bicyclic γ-lactams based on 2,5-diazabicylco[2.2.1]heptan-3-one skeleton (Figure 1). A range of bicyclic γ-lactams with various N substituents were successfully synthesized on solid phase using *trans*-4-hydroxy-L-proline as starting material.

The normal Mitsunobu reaction involves the S_N2 displacement of an activated hydroxyl group by an acidic functionality such as a carboxylic acid or phenol.[5] A few examples have been reported in which fewer acidic nucleophiles, such as amides, can perform the displacement intramolecularly in solution phase.[5,6] We envisioned that this approach could provide a convenient route to construct the bicyclic γ-lactams on solid support. Cleavage via Hofmann elimination using a range of reactive alkyl halide will bring another point of diversity to the library design.

The synthesis started from commercially available *N*-benzyloxycarbonyl(Cbz)-4-hydroxy-*trans*-L-proline, which was treated with *O*-*tert*-butyl *N*,*N*-diisopropylisourea[7] to give the corresponding *tert*-butyl ester. Hydrogenolysis over Pd/C removed the Cbz group, and the obtained secondary amine was immobilized onto REM resin (Polymer Labs, 1.6 mmol/g) via Michael addition (Scheme 1).[8] Loading was monitored by FT-IR and not quantitated.

The *tert*-butyl group was removed under standard acidic conditions using 10% triethylsilane as a cation scavenger. Among a few coupling reagents tested to make the proline amides with aniline, 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) was found to be the reagent of choice, since it allows formation of the mixed anhydride in the presence of a hydroxyl.[9] Each step was monitored by LC/MS on a very small amount of crude product released from a few beads by treatment with aqueous sodium hydroxide in THF/MeOH. The intramolecular cyclization under Mitsunobu conditions turned out to be problematic. The undesired diethyl azodicarboxylate (DEAD) adduct which arose from S_N2 displacement of the activated hydroxy group by the hydrazine anion generated under Mitsunobu conditions was isolated as a major product. Various reagents ((*n*-Bu_3)P, DIAD) and ratios between phosphine and azodicarboxylate were tested to minimize the formation of the side product. We found that the combination of triphenyl phosphine and DEAD (2/1) produced the best result, and only a very small amount of DEAD adduct was formed (<10%). Next, the polymer-bound tertiary amine was quaternized with a range of active alkyl halides, followed by Hofmann elimination promoted by 20% DIEA in DCM to give the crude product. The DIEA*HX salt was removed by aqueous workup (Scheme 2, Table 1).

Although the scope of the approach described above is limited to anilines, a complementary synthetic route was designed for the aliphatic hydroxyl proline amides to be cyclized into bicyclic γ-lactams. The hydroxy group was successfully converted to the azido group with inverted configuration under Mitsunobu conditions using DPPA as a source of azide anion. The azido group was reduced to amine with triphenylphosphine. The revealed primary amine was then reductively alkylated with an aldehyde to give a secondary amine. Although dialkylation often occurs and is of major concern, over 95% monoalkylation was achieved using IRORI MiniKans as the resin carrier, with over 50 aldehydes in most cases, under conditions reported by

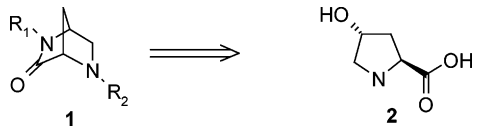

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Figure 1.

Table 1. Bicyclic γ-Lactam **9** Synthesized

entry	X	R2	purity % (crude by ELSD)	yield % (after HPLC)
1[10]	H	−Me	91	31
2	H	−Bn	90	26
3	*p*-F	−All	88	20
4	*p*-OMe	−Me	75	22
5	*p*-F	−Me	78	24

Table 2. Bicyclic γ-Lactam **13** Prepared

entry	R	R2	purity % (crude by ELSD)	yield % (after HPLC)
1[12]	Ph	−Me	72	69
2	*p*-OMe-Ph	−Me	96	37
3	2-thiophene	−Me	88	24
4	*p*-F-Ph	−Me	95	43
5	*p*-Me-Ph	−Me	97	32
6	Ph	−Bn	100	40
7	Ph	−All	96	46

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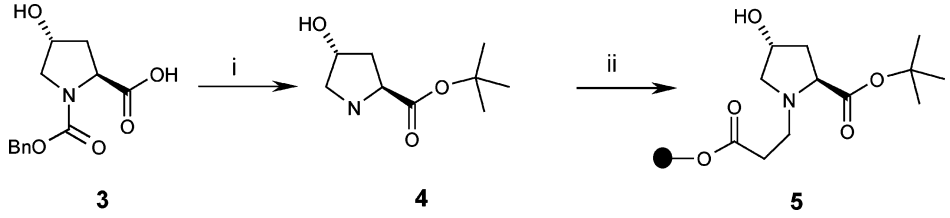
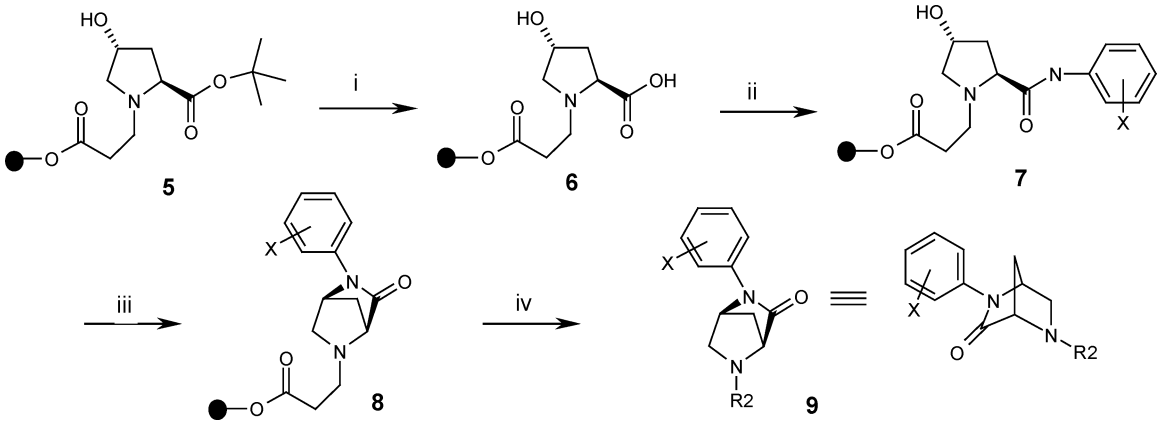
Scheme 1. Immobilization of Hydroxyproline onto REM Resin[a]



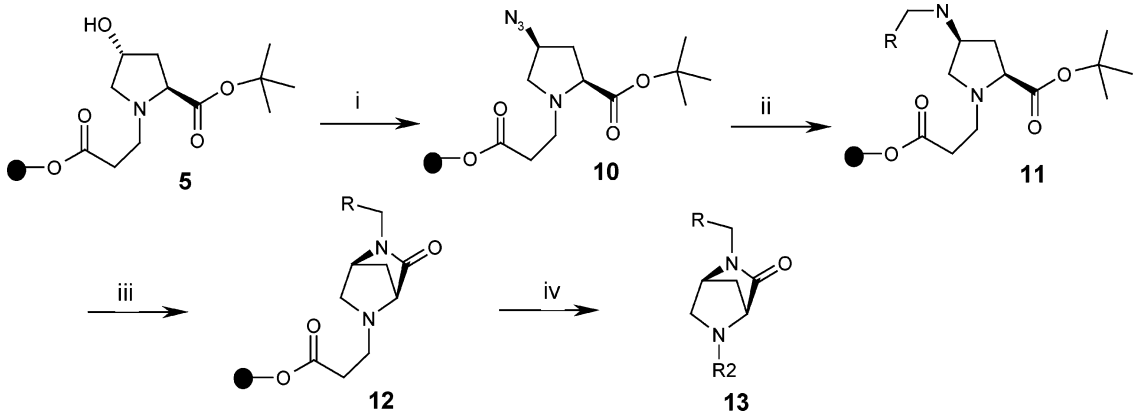
[a] Regents and conditions: (i) (a) *O-tert*-butyl *N,N*-diisopropylisourea, THF; (b) Pd/C, H_2, MeOH. (ii) REM resin, DMF.

Scheme 2. Synthesis of Bicyclic γ-Lactam Library **9**[a]



[a] Reagents and conditions: (i) TFA, TESH, DCM. (ii) anilines, EEDQ, DCM. (iii) PPh_3, DEAD, THF, 0 °C−r.t. (iv) (a) R_2X, DMF, 24 h; (b) DIEA/DCM (20%).

Scheme 3. Synthesis of Bicyclic γ-Lactam Library **13**[a]



[a] Reagents and conditions: (i) DPPA, PPh_3, DEAD, THF. (ii) (a) PPh_3, H_2O, THF, 60 °C; (b) RCHO, TMOF, 1 h, then $NaCNBH_3$, HOAc, MeOH. (iii) (a) TFA/DCM, TESH; (b) HATU, DMF. (iv) (a) R_2X, DMF; (b) DIEA/DCM (20%).

Campbell et al.[11] and modified in this report by prolonging the reaction time to 2 h. It is worthwhile to note that overalkylation was found in virtually every reaction that preformed on loose resin. The difference in selectivity could be attributed to the different reaction dynamics. It is commonly observed that reaction in an IRORI MiniKan is relatively slower in comparison with the reaction on loose resin. After removal of the *tert*-butyl group, the cyclization was carried out utilizing HATU as a coupling reagent. To our surprise, other coupling reagents attempted, such as PyBOP or HBTU, gave an unidentified side product in addition to the desired product. Standard quaternization and Hofmann elimination protocol were followed to produce the bicyclic γ-lactam library (Scheme 3, Table 2).

In conclusion, we have developed a facile method of synthesizing diverse bicyclic γ-lactams on solid phase. We are currently evaluating the biological activity of those compounds, and the results will be reported in due course.

Supporting Information Available. ^{1}H NMR and MS data for all samples listed in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Analytical data (Table 1, entry 1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.68−7.15 (m, 5H), 4.53 (br s, 1H), 3.75 (br s, 1H), 3.46 (dd, 1H, J = 9.6, 1.7), 2.47 (s, 3H), 2.34 (dd, 1H, J = 9.6, 1.7), 2.11−2.04 (m, 1H), 2.02−1.95 (m, 1H). MS: m/z = 203 $[M + H]^+$.
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(12) Analytical data for entry 1 in Table 2. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.42−7.30 (m, 5H), 4.45 (AB q, J = 12), 4.33 (s, 1H), 4.21 (s, 1H), 3.48 (d, 1H, J = 9), 3.08 (br s, 1H), 2.79 (s, 3H), 2.26 (d, 1H, J = 9), 2.05 (d, 1H, J = 9). MS: m/z = 215 $[M + H]^+$.

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