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Solid Phase Synthesis of Azabicyclo[4.3.0]nonen-8-one Amino Acid Derivatives via Intramolecular Pauson-Khand Cyclization

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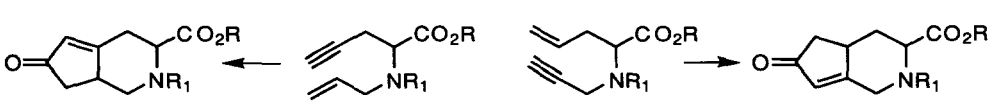
Abstract: A solid phase synthetic strategy leading to the rapid, stereocontrolled construction of highly functionalized fused bicyclic amino acid derivatives has been developed. The key step involves a unique application of the intramolecular Pauson-Khand cyclization.

The generation and screening of libraries of small organic compounds is currently of intense interest in the pharmaceutical industry.[1] Solid phase synthesis techniques have been the primary method for the rapid and efficient preparation of these large numbers of compounds. As a result, the adaptation of well-established solution-phase organic reactions to a solid supported format has emerged as an important tool in drug discovery. The development of reactions which result in the efficient formation of carbon-carbon bonds on solid phase is of particular importance. Recent reports have demonstrated the utility of palladium coupling reactions[2] and enolate anion chemistry[3] for this transformation. Described herein are the solution and solid phase preparation of a series of fused bicyclic amino acid derivatives via a novel application of the intramolecular Pauson-Khand reaction.[4]

The intramolecular Pauson-Khand cyclization has become one of the most powerful methods for the preparation of bicyclo[3.3.0]oct-1-en-3-ones, which are valuable intermediates in the preparation of di- and triquinane natural products.[4] However, the use of this methodology in the construction of bicyclo[4.3.0]non-1-en-3-ones has seen little investigation.[5] The preparation of heterocyclic ring systems by incorporation of heteroatoms within the alkyne-olefin tether has been more extensively studied.[6] An efficient entry into the unexplored azabicyclo[4.3.0]nonen-8-one ring system via Pauson-Khand cyclization of an appropriately substituted amino acid is shown in Scheme 1. Either of the desired regioisomeric cyclopentenone derivatives could be obtained depending on the allyl or propargyl glycine chosen as starting material. Another objective was an extension of this methodology to the solid phase,[7] which would allow the preparation of a diverse array of unnatural amino acid derivatives as potential drug candidates from the functionality embedded within this novel bicyclic template.

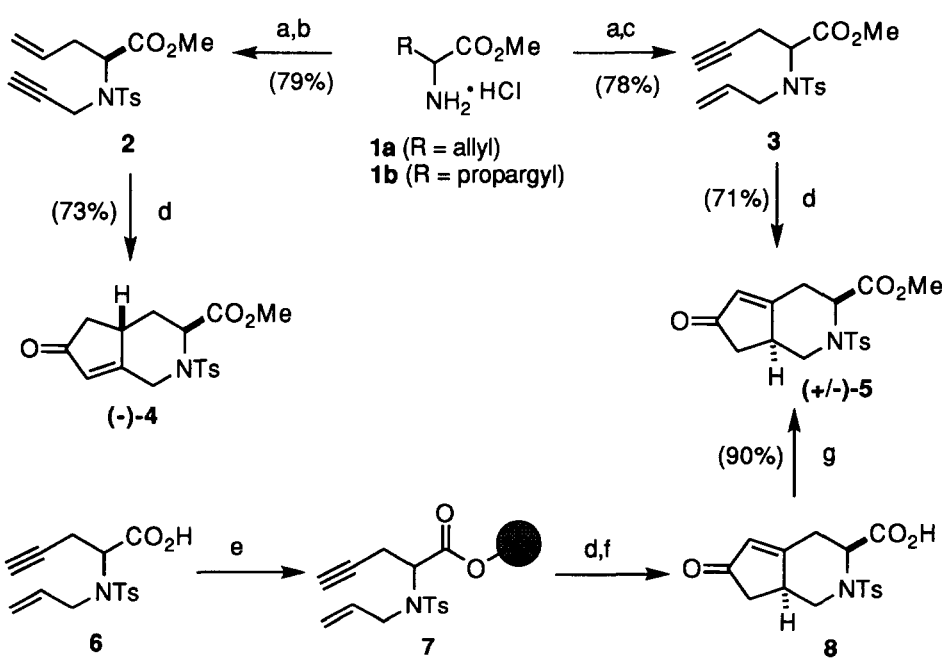
Scheme 1



The viability of this approach was quickly established in solution. As shown in Scheme 2, sulfonylation of the hydrochloride salt of either (S)-allyl or racemic propargyl glycine methyl ester **1a,b** provided the intermediate tosylamides.[8] N-alkylation with propargyl bromide or allyl bromide in the presence of cesium carbonate in DMF provided the cyclization precursors **2** and **3**, respectively. Treatment of these intermediates with $Co_2(CO)_8$ (1.1 eq.) for two hours at room temperature resulted in complete conversion to the cobalt complex as observed by thin-layer chromatography. Addition of excess N-methylmorpholine-N-oxide[5b] at 0°C (two portions over two hours) followed by filtration and flash chromatography provided the cyclopentenone derivatives **4** as a single enantiomer ($[\alpha]_D$=-167) and **5** as a single diastereomer in good yields. The absolute stereochemical assignment of **4** was confirmed by an X-ray crystal structure determination. The relative stereochemistry of **5** was assigned by ^1H NMR analysis which was indicative of an axial carbomethoxy substituent.

Initial solid phase studies began with hydrolysis (LiOH, THF/H_2O) of **3** to provide acid **6**, which was loaded onto commercial Wang resin via the mixed anhydride[9] as as shown in Scheme 2. Subjection of this resin to the cobalt-mediated cyclization conditions afforded **5** in excellent yield after cleavage, esterification, and flash chromatography. In addition to improved yields, the workup and isolation of the product is greatly simplified by the solid phase method.[10]

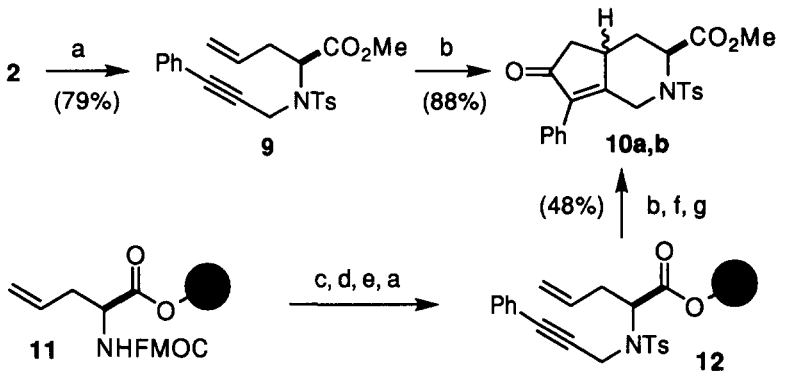
Scheme 2



a) TsCl, Et_3N, CH_2Cl_2 ; b) propargyl bromide, Cs_2CO_3, DMF ; c) allyl bromide, Cs_2CO_3, DMF ; d) $Co_2(CO)_8$, NMO, CH_2Cl_2 ; e) 2,6-dichlorobenzoyl chloride, pyridine, Wang resin ; f) TFA/CH_2Cl_2 (1:1) ; g) CH_2N_2, Et_2O

Further diversification can be incorporated into the sequence as illustrated in Scheme 3. Palladium catalyzed coupling of iodobenzene and **2** proceeded smoothly at room temperature to provide the substituted alkyne derivative **9**.[11,2d] Cobalt-mediated cyclization then gave the bicyclic enones **10a,b** as a 5:1 mixture of diastereomers in excellent yield. The major diastereomer (S),(S)-**10a** ($[\alpha]_D$=-80) could be obtained by chromatography and the absolute stereochemistry was assigned by analogy with **4**. Finally, the full synthetic sequence was efficiently carried out entirely on solid phase. Deprotection of allyl glycine **11** (on Wang resin) followed by tosylation, alkylation with propargyl bromide, and coupling with iodobenzene provided resin-bound intermediate **12**. Cyclization, followed by cleavage, esterification, and flash chromatography again afforded **10a,b** as a similar mixture of diastereomers, in an overall yield of 48% for the seven step sequence based on an initial loading of **11** of 0.57 mmol/g.

Scheme 3



a) $(PPh_3)_2PdCl_2$, CuI, iodobenzene, Et_3N, CH_2Cl_2; b) $Co_2(CO)_8$, NMO, CH_2Cl_2 ; c) 20% piperidine, CH_2Cl_2 ; d) TsCl, Et_3N, CH_2Cl_2 ; e) propargyl bromide, Cs_2CO_3, DMF ; f) TFA/CH_2Cl_2 (1:1) ; g) CH_2N_2, Et_2O

In conclusion, we have demonstrated that a novel application of the intramolecular Pauson-Khand reaction proceeds efficiently and with a high level of asymmetric induction in solution or solid phase to provide functionalized bicyclic amino acid derivatives. Further elaboration of these intermediates in the generation of libraries as well as examination of other variations of this process are ongoing.

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8. All new compounds reported herein exhibited satisfactory ^{1}H NMR, IR, MS, and combustion analyses. ^{1}H NMR (400 MHz, $CDCl_3$) data: **4:** δ 7.66 (d, J=8Hz, 2H), 7.30 (d, J=8Hz, 2H), 5.98 (s, 1H), 4.88 (br dd, J=5 and 2Hz, 1H)), 4.76 (d, J=14Hz, 1H), 4.20 (d, J=14Hz, 1H), 3.61 (s, 3H), 2.76 (m, 1H), 2.58 (dd, J=19 and 6Hz, 1H), 2.48 (ddd, J=13, 5, and 2Hz, 1H), 2.43 (s, 3H), 1.95 (dd, J=19 and 3Hz, 1H), 1.58 (ddd, J=13,13,and 5Hz, 1H); **5**: δ 7.71 (d, J=8Hz, 2H), 7.31 (d, J=8Hz, 2H), 5.97 (s, 1H), 5.11 (d, J=7Hz, 1H), 4.18 (br dd, J=11 and 5Hz, 1H), 3.54 (s, 3H), 3.26 (d, J=14Hz, 1H), 2.91 (m, 2H), 2.79 (dd, J=14 and 7Hz, 1H), 2.51 (dd, J=19 and 6Hz, 1H), 2.43 (s, 3H), 1.91 (dd, J=19 and 2Hz, 1H); **10a:** δ 7.52 (d, J=8Hz, 2H), 7.43 (m, 3H), 7.20 (m, 4H), 4.97 (br d, J=4Hz, 1H), 4.92 (d, J=15Hz, 1H), 4.30 (d, J=15Hz, 1H), 3.68 (s, 3H), 2.86 (m, 1H), 2.75 (dd, J=19 and 7Hz, 1H), 2.55 (ddd, J=13, 5, and 2Hz, 1H), 2.42 (s, 3H), 2.07 (dd, J=19 and 3Hz, 1H), 1.60 (ddd, J=13, 13, and 6Hz, 1H).
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10. A typical procedure for the solid phase preparation of **5:** To a suspension of the resin **7** (0.53g, 0.34 mmol, 0.64 mmol/g) in CH_2Cl_2 (10mL) in a peptide shaker flask was added $Co_2(CO)_8$ (0.17g, 0.51 mmol). The suspension was shaken under N_2 for 2 hr. with periodic venting. The solvent was filtered off and the resin was washed with CH_2Cl_2 (3x10ml). The resin was suspended in CH_2Cl_2 (10mL) and N-methylmorpholine-N-oxide (0.13g, 1.11 mmol) was added. The mixture was shaken under N_2 with periodic venting for 1 hr, and a second portion of NMO (0.13g) was added. After shaking another 1 hr, the solvent was filtered off, and the resin was washed with CH_2Cl_2 (3x10mL), $HOAc/CH_2Cl_2$ (1:3, 3x10mL), and CH_2Cl_2 (3x10mL). The resin was then shaken with TFA/CH_2Cl_2 (1:1, 15mL) for 1 hr, filtered, and washed with CH_2Cl_2 (3x10mL). The combined filtrates were concentrated, taken up in CH_2Cl_2 and reconcentrated (2x), and dried in vacuo to give 0.11g of **8** as a tan solid. Esterification with CH_2N_2 afforded **5**.
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