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Synthesis of Boc-protected bicycloproline

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ABSTRACT

The synthesis of a highly constrained quaternary carbocyclic α-amino acid, (+)-*N*-Boc-bicycloproline, has been achieved starting from sodium cyclopentadienylide. Key steps include a rhodium-catalyzed nitrenoid C–H insertion to install the *tert*-alkylamine and a ring-closing metathesis reaction to form the pyrrolidine ring.

Structure-based peptidomimetic drug design has been aided by the development of synthetic methods toward various rigidified amino acids (Fig. 1). Cyclic residues and quaternary α-amino acids (or α,α-dialkylated amino acids) have garnered special interest due to their ability to restrict the ψ, φ, and ω torsional angles of the peptide backbone.[1] While proline is the only canonical proteinogenic amino acid harboring a cyclic constraint, various other cyclic and quaternary amino acids have been found in nature, often as components of biologically active peptides with well-defined secondary structures.[2] The conformational and biological properties of many of these residues have been the impetus for a number of synthetic studies.[2d,3]

In connection with our interest in α-amino acids that may have a profound influence on the amide backbone (cis–trans) rotameric equilibrium, we selected bicycloproline (octahydrocyclopenta[b]pyrrole-**6a**-carboxylic acid, **1**) as an initial target (Fig. 2). Recently, Trauner and co-workers reported a strategy toward bicycloproline starting from Meyer's lactam, providing a potential precursor to **1**.[4] Although the synthesis of racemic **1** and related structural motifs has been reported in the literature,[5] we describe herein the first synthesis of enantiopure N-protected bicycloproline from a readily available chiral progenitor.

The octahydrocyclopenta[*b*]pyrrole core of bicycloproline comprises a substituted cyclopentane ring fused to pyrrolidine. Assuming that the heterocyclic ring could be formed at a late stage, our strategy centered on the synthesis of a cyclopentane harboring a quaternary aminated carbon. We envisioned that the *tert*-alkylamino group could be installed via intramolecular C–H insertion of an oxycarbonylnitrene onto an appropriately substituted tertiary carbon.[6] In our search for a useful cyclopentanoid substrate, we settled on 2-benzyloxymethylcyclopent-3-enol for its pattern of substitution and its availability from cyclopentadiene in optically pure form.[7]

The synthesis of (2*R*,3*S*)-2-benzyloxymethylcyclopent-3-enol was carried out following the modification by Gellman and coworkers.[8] We prepared **2** in multi-gram batches over three steps[9] and introduced the primary carbamate with trichloroacetylisocyanate to give **3** in 85% yield (Scheme 1). We explored a number of different conditions for the ensuing C–H insertion using Rh(II) catalysts (DuBois conditions[6d]) as well as the Ag(I)-catalyzed conditions recently reported by He and Cui[6e]. In our hands, Ag(I) catalysis failed to give appreciable amounts of insertion products. In conjunction with various Rh(II) catalysts, different permutations of oxidant ($PhI(OAc)_2$, PhI=O), base (K_2CO_3, 2,6-lutidine, MgO), sol-

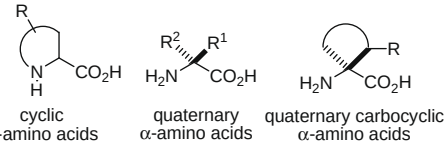

Figure 1. General structures of some constrained α-amino acids.

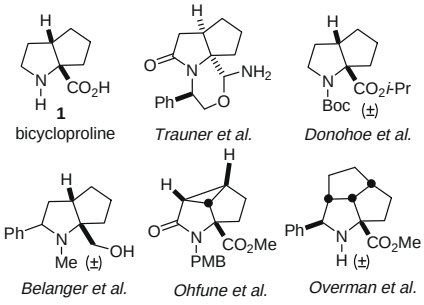

Figure 2. Bicycloproline and related structures.

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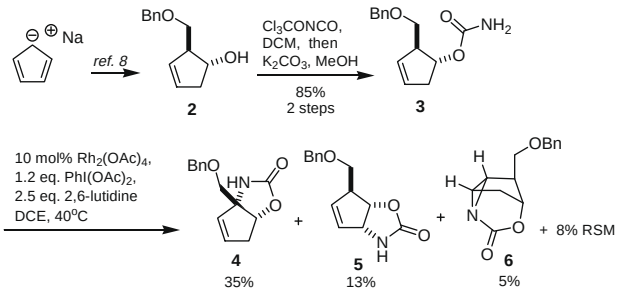
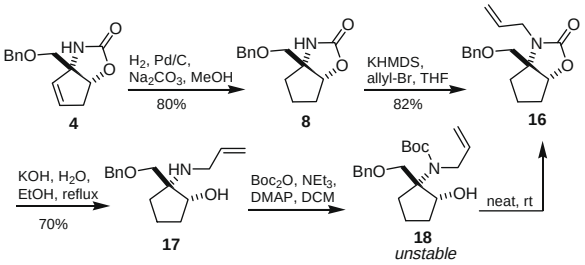


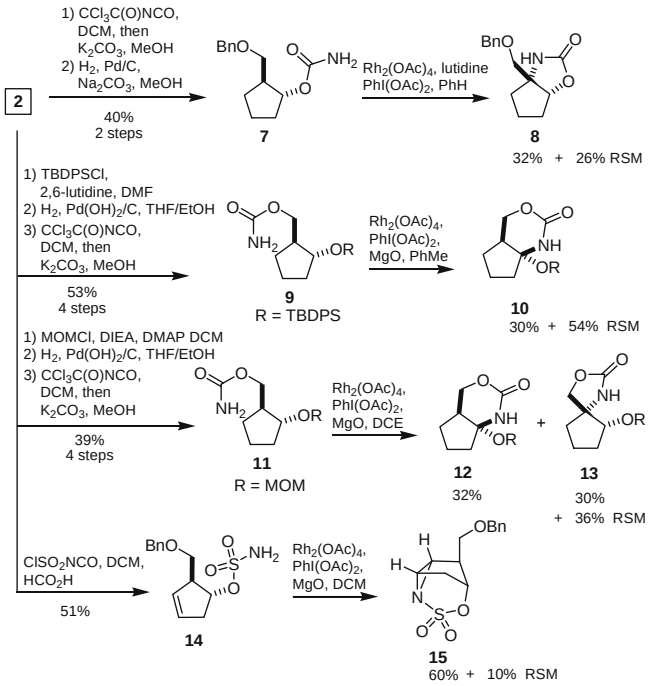
Scheme 1. Synthesis of **4** (RSM = recovered starting material).



Scheme 3. Synthesis of aminoalcohol **17**.

vent (toluene, DCM, 1,2-DCE, benzene), and temperature were investigated. Under optimized conditions, the desired product (**4**) was obtained in 35% yield after purification. In addition, we isolated 13% of the isomeric product **5**, as well as a small amount of aziride **6**. In nearly every case screened, we observed an approximately 2:1 ratio of tertiary:secondary C–H insertion products (**4**:**5**). These results are consistent with the enhanced reactivity exhibited by more substituted carbons toward *N*-acyloxynitrenoids.[6d,10]

In an effort to parse the factors contributing to reaction regioselectivity, we synthesized a variety of other substrates (Scheme 2). Reactions carried out with saturated substrate **7** under optimized conditions resulted in lower conversion and in 32% yield of the desired product, but no appreciable insertion at the secondary C–H bond. Substrates **9** and **11** were prepared in an attempt to compel insertion at the tertiary carbon center. Reaction of **9** under optimized conditions led to exclusive insertion at the *ethereal* carbon to give *N*-acyloxyaminal **10** as the only major product. This result was unexpected in light of the well-established preference for five-membered cyclic carbamate formation in related systems and is probably due to the blocking effect of the *O*-TBDPS group on the β-face of the cyclopentane ring. When the reaction was carried out with the less sterically demanding *O*-MOM derivative **11**, the six-membered *N*-acyloxyaminal (**12**) was similarly obtained as

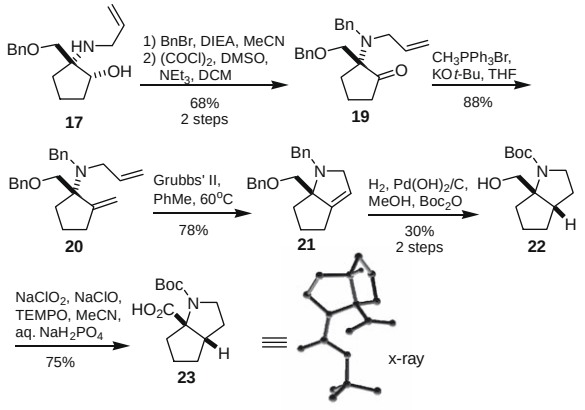


Scheme 2. Selectivity of C–H insertion in related substrates.

the major product along with desired spirocycle **13**. The appreciable formation of products **10** and **12** in these reactions suggests that ether substituents act as strong activators of the geminal C–H bonds. Reaction of sulfamate ester **14** under similar Rh(II)-catalyzed conditions gave 60% yield of tricyclic aziridine derivative **15**.

Although compounds **4**, **8**, and **13** represented useful intermediates for our synthesis, we opted to continue with cyclopentene **4** due to step economy and higher overall yields. Compound **4** was saturated by hydrogenation and the cyclic carbamate allylated with KHMDS and allyl bromide in 82% yield (Scheme 3). Alkaline hydrolysis of the carbamate gave **17** in good yield, but Boc-protection of the resulting amine met with difficulties, providing large amounts of **16** in addition to **18**. Presumably, Boc-protection is followed by rapid attack of the vicinal hydroxyl group to give the cyclic precursor. Moreover, we found compound **18** to be unstable toward subsequent oxidation conditions, and also unstable upon storage at room temperature (neat), resulting in recovery of additional **16**.

As an alternative to *N*-acyloxy protection, the secondary amine was benzylated under standard conditions and subjected to Swern oxidation to give ketone **19**. Wittig methylenation then provided diene **20** in 88% yield. In consideration of the free amine group in **20**, the subsequent RCM reaction required some optimization. We found that pyrroline formation occured smoothly in 78% yield using 7 mol % of Grubbs' 2nd generation catalyst (added in two portions) in toluene at 60 °C. Treatment of **21** with Perlman's catalyst and H_2 resulted in saturation and concomitant debenzylation. This was followed by Boc-protection of the crude aminoalcohol to afford **22**. Finally, oxidation using sodium chlorite, bleach, and catalytic TEMPO provided *N*-Boc-bicycloproline (**23**) in 75% yield. The ^{1}H NMR spectrum of **23** is consistent with that of the expected structure but is complicated by the presence of cis and trans carbamate rotamers. Compound **23** was recrystalized out of DCM/hexane for analysis by X-ray diffraction. The crystal structure we obtained confirmed the structure and relative stereochemistry of synthetic (+)-*N*-Boc-bicycloproline (Scheme 4).[11]



Scheme 4. Synthesis and X-ray structure of (+)-*N*-Boc-bicycloproline (**23**).

In summary, we have utilized (2*R*,3*S*)-2-benzyloxymethylcyclopent-3-enol as a practical starting material for the synthesis of bicycloproline. The key steps in our synthesis are a Rh(II)-catalyzed nitrenoid insertion reaction to provide the *tert*-alkylamine and a Grubbs' ring-closing metathesis to form the pyrrolidine ring. We are currently investigating the regioselectivity of C–H insertions in polyfunctional substrates for the synthesis of other complex amino acids. The incorporation of bicycloproline into host structures and its effects on peptide conformation will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, complete spectral data, copies of NMR spectra for new compounds, and X-ray and for **23**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.092.

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