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Asymmetric Synthesis of an Important Precursor to 5'-Nor Carbocyclic Nucleosides

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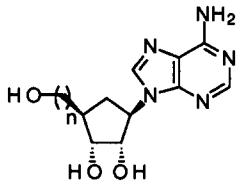
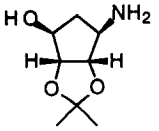
Abstract: An asymmetric hetero-Diels-Alder reaction involving an amino acid-derived acylnitroso dienophile was utilized to synthesize (1*S*, 4*R*)-4-[*N*-(*tert*-butoxycarbonyl)amino]-2-cyclopentene-1-ol (**4**). The amino acid chiral auxiliary was removed by the Edman degradation. This enantiomerically pure aminoalcohol is a key intermediate in the synthesis of 5'-nor carbocyclic nucleosides.

Research related to the design, synthesis and study of carbocyclic nucleosides has been extensive[1] and has led to the preparation of many biologically active carbocyclic nucleosides, including aristeromycin (**1a**).[2] An analog of **1a**, 5'-noraristeromycin (**1b**), in which the hydoxymethyl group has been replaced with a hydroxyl group, has also been synthesized and its strong antiviral properties have been evaluated.[3] With their potential for antiviral and anticancer activity, the need to synthesize new carbocyclic nucleoside analogs, especially 5'-nor analogs, is apparent. Known precursors to 5'-nor carbocyclic nucleosides include amine **2**,[3a,4] and allylic alcohol **3**.[5] Amine **2** has recently been synthesized in enantiomerically pure form from D-ribose.[6] We envisioned that aminoalcohol **4** would be a useful addition to this series as its chiral form can be produced with the olefin intact and thus serve as a versatile intermediate to dihydroxy, deoxy, dideoxy and related carbocyclic nucleoside derivatives. Also, aminocyclopentitols are important synthetic targets on their own as potential glycosidase inhibitors.[7]



1a, n=1, aristeromycin
1b, n=0, 5'-noraristeromycin



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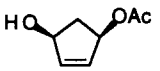

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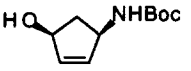

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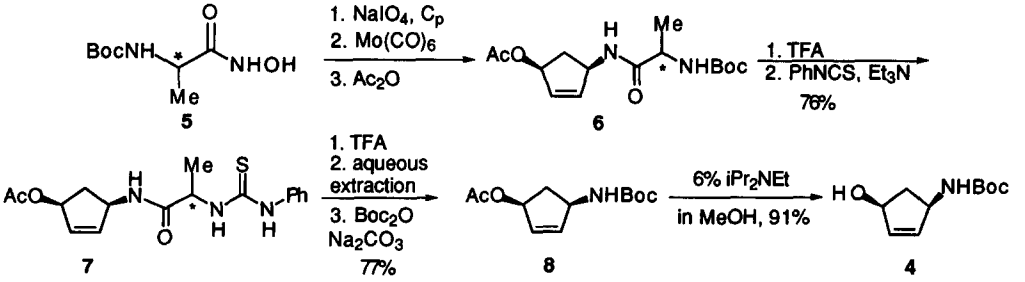
Recent studies of asymmetric hetero Diels-Alder reactions involving acylnitroso dienophiles[8] have been extended in our group by use of amino acid hydroxamates **5** as precursor to the acylnitroso component.[9] The products of the amino acid-based acylnitroso cycloaddition have been elaborated efficiently to yield compounds such as **6**.[10] Our route to the desired aminoalcohol **4** involved removal of the amino acid chiral auxiliary from **6**. This route adds versatility as the desired product can be obtained from either enantiomeric chiral auxiliary (amino acid) and the other diastereomeric cycloadduct formed can be used in alternative synthetic pathways.

After attempts to remove the amino acid chiral auxiliary with standard acidic or basic amide bond hydrolysis failed, the Edman degradation, a classical method for the removal of terminal amino acids in

peptides, was examined.[11] Thus, treatment of **6** with TFA, followed by phenylisothiocyanate led to thiourea **7**. Thiourea **7** was then treated with TFA again and, after extracting the resulting amine salt into an aqueous layer, reaction with Boc anhydride and base provided allylic acetate **8** (Scheme). Treatment of **8** with 6% Hünig's base in MeOH gave the target alcohol **4**. The transformation of **6** to **8** has been simplified by not isolating the corresponding thiourea (overall yield of 71%).

Scheme



In this letter we have described an asymmetric synthesis of an important precursor to 5'-nor carbocyclic nucleosides. With the Edman degradation being a simple, clean method to remove the chiral auxiliary, the versatility of the amino-acid derived acylnitroso dienophiles in synthesis has been greatly extended. The use of this methodology in the synthesis of novel 5'-nor carbocyclic nucleosides, and other biologically interesting products, will be published in due course.

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