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Short, Highly Efficient Syntheses of Protected 3-Azido- and 4-Azidoproline and Their Precursors

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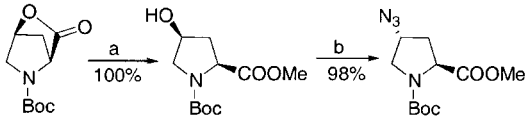
ABSTRACT



Conditions: a) NaN_3, MeOH; b) DPPA, DEAD, Ph_3P, THF

An improved synthesis of protected *cis*- and *trans*-3-azido-L-proline and *cis*- and *trans*-4-azido-L- and -D-proline is reported. These compounds have been synthesized from the corresponding hydroxyproline precursors using diphenylphosphoryl azide under Mitsunobu conditions. Short, highly efficient syntheses of these precursors are described, based on a new lactone-opening reaction and *p*-nitrobenzoate hydrolysis under very mild conditions.

Protected 4-aminoproline stereoisomers have been reported frequently during the past 10 years as part of biologically active compounds. These include matrix metalloproteinases inhibitors,[1] spermine analogues to study DNA triplex stability,[2] contrast agents for magnetic resonance imaging,[3] conformationally restricted amino acid analogues for protein−peptide interactions,[4] peptide nucleic acids (PNA),[5] receptor-adhesive modular protein (RAMP),[6] Calpain I inhibitors,[7] building blocks in a potential anti-Tat library,[8] and antifungal cyclic aminohexapeptides.[9] Another recent application is the study of photochemical energy conversion.[10]

A common method used for their syntheses, starting from the appropiate hydroxyproline stereoisomer, is via a sequence of protection, treatment with methanesulfonyl chloride (or tosyl chloride[5c]), displacement with sodium azide, and hydrogenation over Pd−C.[1] The fact that the hydroxyproline enantiomer precursor must be synthesized through several steps has been reported as an important limitation.[11] A nonstereoselective synthesis of 4-aminoproline has been reported by solid-phase synthesis.[12]

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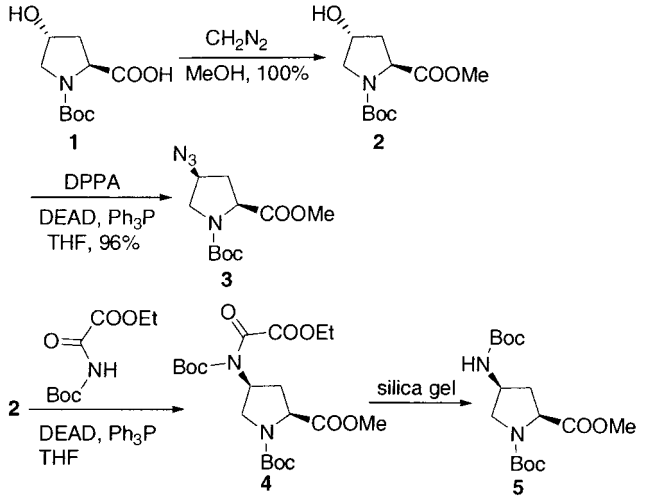
The four 3-aminoproline stereoisomers are less well-known than the 4-amino regioisomers. 3-Aminoproline has been described in pristinamycin IIB derivatives as antibacterials.[13] Recently, this β-amino acid has been used to obtain β-polypeptide foldamers.[14] The *cis*-3-amino-L-proline enantiomer is a naturally occurring amino acid described as part of some metabolites isolated from *Morchella esculenta*.[15] This enantiomer has been synthesized from *cis*-3-carboxy-L-proline via a Curtius rearrangement at the 3-carboxyl group.[16] Its synthesis has been described as a limitation for further development of aminohexapeptides with antifungal activity.[9]

Herein we report an improved synthesis of all 4-azidoproline stereoisomers from commercially available *N*-Boc-*trans*-4-hydroxy-L-proline and *cis*-4-hydroxy-D-proline. This synthetic pathway has been applied to the synthesis of *N*-Boc-*cis*- and -*trans*-3-azido-L-proline methyl esters as synthetically useful precursor intermediates. The reduction of protected azidoprolines to the corresponding aminoprolines has been reported.[5c]

Synthesis of 4-Azidoproline Stereoisomers. The synthesis of protected *N*-Boc-*cis*-4-azido-L-proline methyl ester **3**[17] is possible in one step using protected *trans*-4-hydroxyproline **2** under Mitsunobu conditions (Scheme 1). The use of

Scheme 1

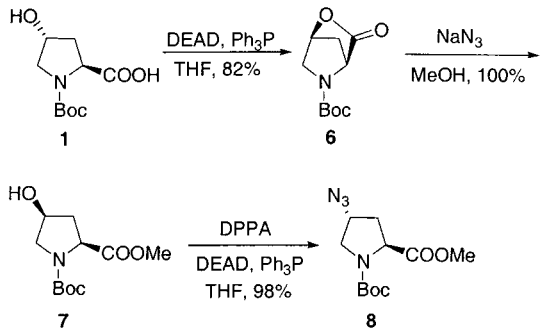


diphenylphosphoryl azide (DPPA) for the conversion of a hydroxyl group into an azido group with inversion of configuration has been described previously,[18] but it has not been applied to the synthesis of **3**.

N-Boc ethyl oxamate has recently been described as a new nitrogen nucleophile for use in Mitsunobu reactions.[19] Proline derivative **4** was obtained with this reagent (Scheme 1). However, **4** was obtained in only a 45−50% yield, even though different temperatures and reaction times were tried. Compound **4** proved to be unstable on silica gel or aluminum oxide, producing the di-Boc-protected compound **5**. This important limitation during the purification step of this compound prompted us to abandon this synthetic procedure.

The synthesis of *N*-Boc-*trans*-4-azido-L-proline methyl ester **8** was achieved from *N*-Boc-*cis*-4-hydroxyl-L-proline methyl ester **7** under conditions similar to those used to make **3**. This compound was obtained by conversion of commercially available **1** into lactone **6**[20] and subsequent highly efficient transesterification with methanol in the presence of sodium azide[21] (Scheme 2). This represents a very short

Scheme 2



stereochemically controlled synthesis of the protected compound **7** from **1** under mild conditions and in high overall yield. An attempt to obtain lactone **6** using tributylphosphine instead of triphenylphosphine gave only a 45% yield.

The use of sodium azide in the selective opening of lactone **6** represents a new application for this reagent. Remarkably, chiral β-hydroxyl carbonyl compounds are obtained by methanolysis of *p*-nitrobenzoic esters in the presence of sodium azide.[21]

N-Boc-*trans*-4-azido-D-proline methyl ester **10** was synthesized in high yield from protected *cis*-4-hydroxy-D-proline **9**[22] under the same conditions (Scheme 3).

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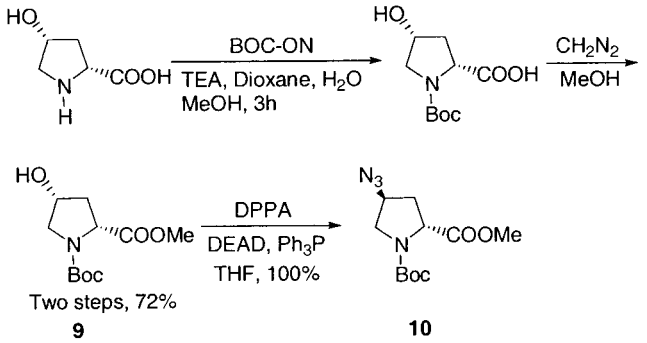
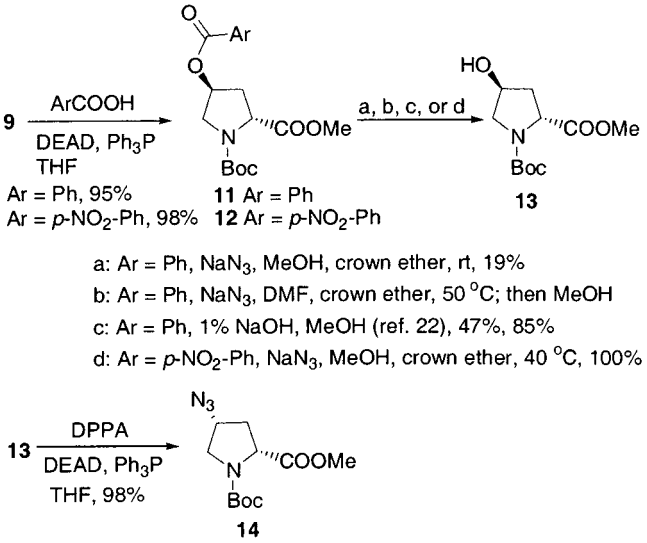
Scheme 3



Inversion of configuration of **9** using benzoic acid under Mitsunobu conditions afforded benzoate ester **11**[23] (Scheme 4). Different conditions for the selective cleavage of the

Scheme 4



benzoate ester were tried, but the yields were generally poor. Compound **13** was obtained by the reaction of 1% NaOH in methanol, although the yield was not reported.[23] In our hands the reaction proceeded in an 85% yield, but this result was not reproducible.

Benzoate **11** was cleaved with sodium azide in methanol at room temperature in a very low yield (19%). The use of DMF as solvent during the reaction to increase the nucleophilicity did not improve the yield.

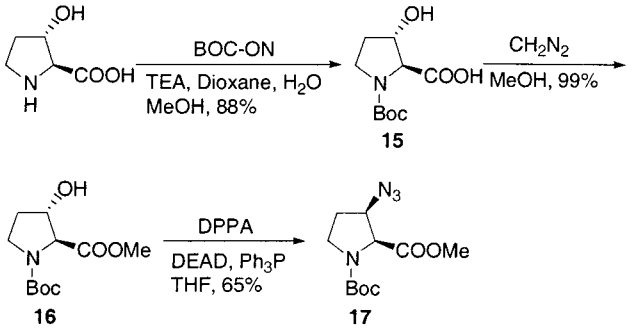
Therefore, *p*-nitrobenzoic acid was used under Mitsunobu conditions[24] to increase the reactivity of the benzoate derivative. Inversion of configuration proceeds in nearly the same yield as with benzoic acid, and the ester could be cleaved by treatment with sodium azide in methanol in a quantitative yield.[21] Compound **13** was obtained in two steps from **9** in a 98% overall yield (Scheme 4).

The final step in the synthesis of *N*-Boc-*cis*-4-azido-D-proline methyl ester **14** from **13** was accomplished in high yield under Mitsunobu conditions using diphenylphosphoryl azide (Scheme 4).

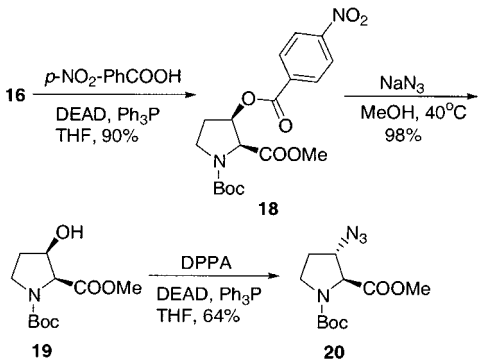
The methyl esters **3**, **8** **10**, and **14** were cleanly converted to the corresponding acids by using lithium hydroxide in THF/H_2O.

Synthesis of 3-Azidoproline Stereoisomers. The *N*-Boc-*cis*- and -*trans*-3-azido-L-proline methyl esters were synthesized from commercially available *trans*-3-hydroxy-L-proline (Schemes 5 and 6). Thus, the two-step protection of the

Scheme 5



Scheme 6



α-amino group and the carboxylic acid afforded, under the same conditions as above, protected *trans*-3-hydroxyproline **16**. Synthesis of protected *cis*-3-azidoproline **17** under Mitsunobu conditions was carried out in a 65% yield. This moderate yield is explained because of the steric hindrance in the 3-hydroxy isomer.

The synthesis of protected *trans*-3-azido-L-proline **20** was carried out under the conditions identical to those in Scheme 5 from protected *cis*-3-hydroxyproline **19** in 64% yield

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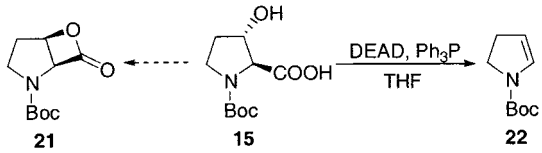
Scheme 7



(Scheme 6). Inversion of configuration of **16** under Mitsunobu conditions gave *p*-nitrobenzoate **18** in 90% isolated yield. Compound **18** was selectively hydrolyzed with sodium azide in methanol to afford **19** in an excellent yield.

cis-3-Hydroxy-L-proline has been reported previously as part of the natural products telomycin[25] and cyclothilidine,[26] and it is produced by certain strains of *Streptomyces* and *Bacillus*.[27] Several syntheses have been described to date.[28] The approach in Scheme 6 represents a short synthesis of protected amino acid **19** in high overall yield.

Lactone **21** (see Scheme 7) could be a synthetic precursor of protected *cis*-3-hydroxy-L-proline **19** under the same conditions used to open lactone **6** (see Scheme 2). Inversion of configuration to obtain lactone **21** from *N*-Boc-*trans*-3-hydroxyproline **15** resulted in a concerted dehydroxydecarboxylation yielding the known enecarbamate **22** (Scheme 7).[29] This reaction clearly depends on the presence of a free carboxylic acid to occur. A hydroxamate derivative of **15** has been reported to form the lactam with inversion of configuration in 86% yield.[30]

In summary, the protected 3-azido- and 4-azidoproline compounds **3**, **8**, **10**, **14**, **17**, and **20** have been synthesized in high overall yields. A new mild lactone opening has been devised.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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