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Via Ester Enolate Claisen Rearrangements To a Variety of Non-Proteinogenic Amino Acids

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Abstract

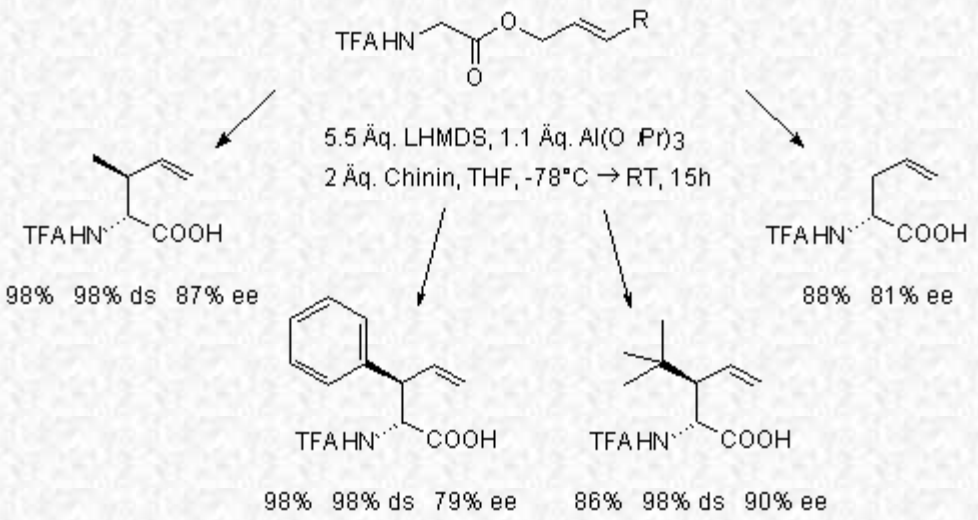
Allylic esters of TFA-protected amino acids undergo asymmetric Claisen rearrangements in the presence of cinchona alkaloids, giving rise to g,d-unsaturated amino acids in a highly stereoselective fashion. The products are useful precursors for the short and efficient synthesis of more complex compounds such as substituted 4-hydroxyprolines, 4-hydroxyornithines and iminosugars.

Introduction

The synthesis of g,d-unsaturated amino acids has received more attention in recent years, since some of this compounds,[1] which also occur in nature, showed distinct antibiotic activity and could be used as enzyme inhibitors.[2] Herein, the synthesis of 3-substituted *cis* 4-hydroxyprolines, 4-hydroxyornithine and one iminosugar has been described to show the versatility of g,d-unsaturated amino acids, which are accessible by asymmetric ester enolate Claisen rearrangements.

Rearrangements as key step

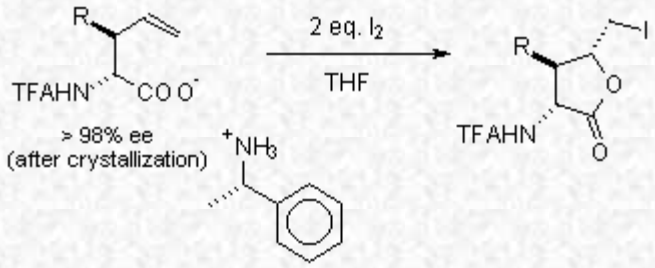
The chelate controlled ester enolate Claisen rearrangement of achiral TFA-protected glycine allyl esters leads to the respective g,d-unsaturated amino acids in good yields and selectivities.[3]



With Al(O*i*Pr)$_3$, lithiumhexamethyldisilazide, quinine and its pseudoenantiomeric quinidine, respectively, both enantiomeres of 2-aminopentenoic acid derivates are available in very good yields, diastereoselectivities > 98 % and enantiomeric excesses of up to 90 %. This method is suitable for a great variety even of sterically highly demanding substrates.[4] The purity of the crude rearrangement products can be increased by enzymatic techniques[5] or by single crystallization of the acid with (*S*)-phenylethyl amine (PEA) in ether.

Iodolactones as useful precursors

Iodolactonization of the optically pure rearrangement products allows the generation of a further stereogenic center in excellent yields and good diastereoselectivities.[6]

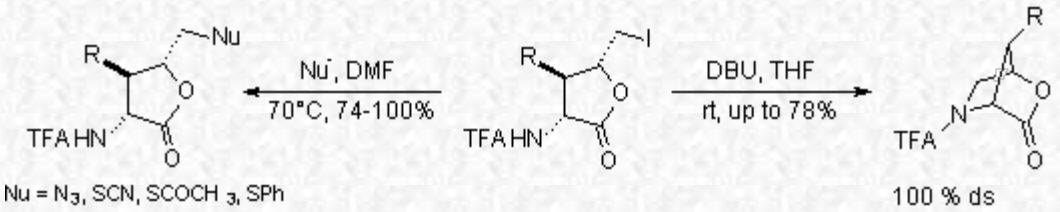


R	Yield	ds (%)
H	88	91
Me	quant.	90*
iso-Propyl	97	85
Phenyl	99	82

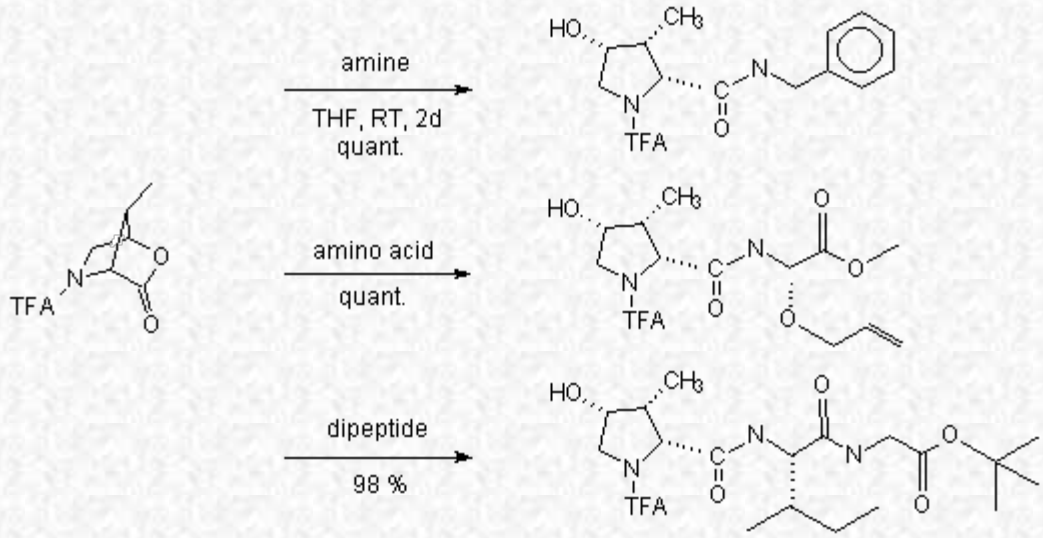
* in the presence of 1.1 eq. Mg-salt

Depending on the reaction conditions used, the iodolactones can undergo *inter*- and *intramolecular*

substitution. In the latter case only the *syn* product can cyclize and therefore enantiomerically and diastereomerically pure lactones are obtained.

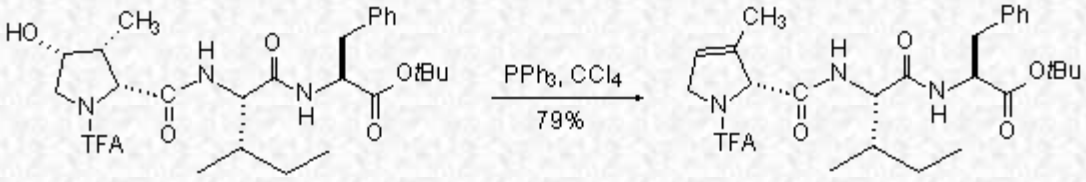


3-Substituted 4-hydroxyprolines

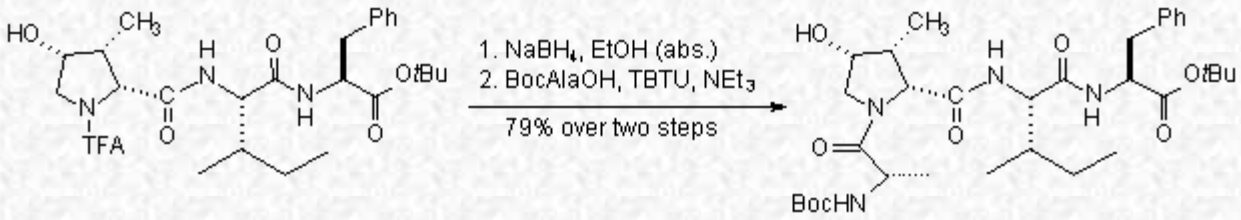


After intramolecular ring closure the potential of the strained bicyclic lactones can be utilized in the synthesis of amides and peptides by opening with amines, amino acids and dipeptides.[6]

Under Appel-conditions[7] not the epimeric chloride but the corresponding 3,4-dehydroproline was obtained, a type of amino acid, that usually has to be synthesized *via* a multi-step procedure.[8]

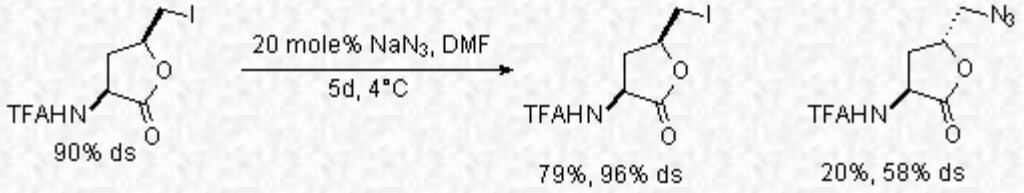


After reductive cleavage of the TFA-protecting group further coupling at the *N*-terminal position becomes possible.

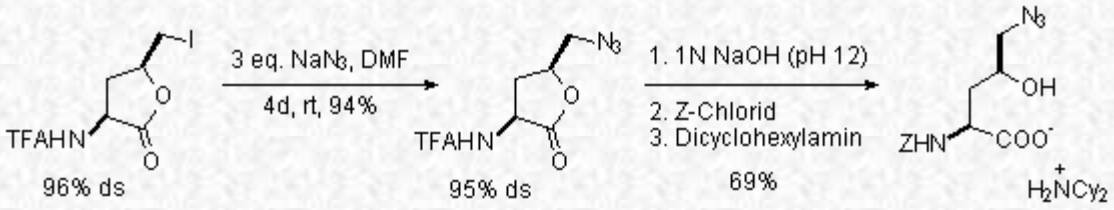


4-Hydroxyornithine

Before the iodolactones can be substituted *intermolecularly* the optical purity has to be increased. In contrast to the racemic iodolactones, which were obtained as crystalline solids, the enantiomerically pure compounds were colorless oils and the diastereomeres could not be separated by flash chromatography. Fortunately we found an effect of kinetic resolution by substituting with sodium azide. Because the reaction of the minor *anti*-diastereomer was favored, we transformed it with a small amount of nucleophile into the corresponding azide. After separation the *syn*-iodolactones, whose purity is now > 96 % ds, was stirred with an excess of sodium azide.

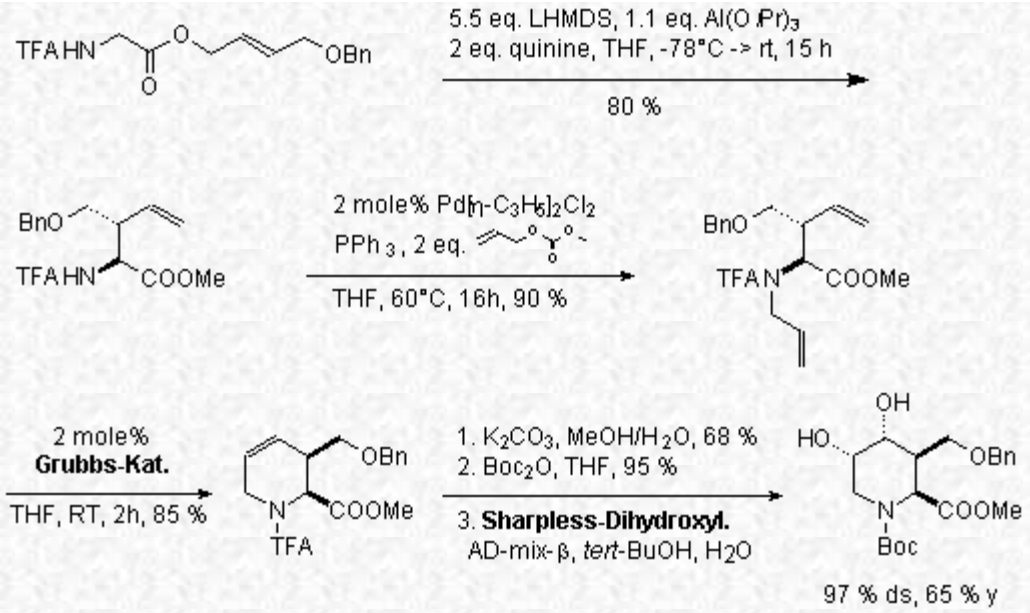


The resulting azide could be seen as totally protected hydroxyornithine, an amino acid that also occurs in nature. By saponification with sodium hydroxide at pH 12 and changing the base-labile protecting group TFA for benzyloxycarbonyl, the desired amino acid was obtained as dicyclohexylamine salt with 69 % yield. In a further step, hydrogenization leads to 4-hydroxyornithine.



Polyhydroxylated pipecoline acid derivative

In addition other classes of substances are also accessible from the rearrange-ment products in just a few steps. When a benzyloxy-methylated TFA-allyl ester was subjected to the Claisen rearrangement and methylated with diazomethane, the resulting product could be *N*-allylated by a very mild palladium-mediated reaction, which was developed in our group.[9] The diene obtained underwent a ring closing metathesis in the presence of 2 mole % Grubbs-alkylidene catalyst[10] at rt. Subsequent Sharpless dihydroxylation[11] using AD-mix-bÒ provided the corresponding polyalcohol in excellent diastereoselectivities (> 97 % ds).



Conclusion

In conclusion we have shown that the asymmetric ester enolate Claisen rearrangement is a highly efficient tool for the synthesis of a variety of potentially bioactive amino acids with *de novo* generation of all stereogenic centers.

Acknowledgement

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