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A Chemoenzymatic Approach to Chiral Phenylisoserinates using 4-Isopropyl-2-Oxazolin-5-one as Masked Umpoled Synthon for Hydroxycarbonyl Anion.

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Abstract: The aldol adduct between the anion of 4-isopropyl-2-oxazolin-5-one with racemic N-(tert-butoxycarbonyl)-phenylglycinal underwent concomitant isomerization and ring cleavage under mild basic conditions producing the racemic dipeptide N-Boc-phenylisoserine-valine methyl ester, which after acid hydrolysis followed by sequential esterification and N-benzoylation, gave a separable 1:4 *syn/anti* diasteroisomeric mixture of N-benzoyl-3-phenylisoserine methyl esters, the predominant *anti* racemate being resolved by lipase from *Pseudomonas fluorescens* (P) using vinyl acetate as the acyl donor leading to the corresponding chiral phenylisoserine derivatives.

Of all the rare hydroxy amino acids of biological relevance, often occurring in Nature as components of more complex molecules, none has received more attention than 3-phenylisoserine, as the essential role of the properly N-protected-(2R,3S)-3-phenylisoserine C-13 side chain in the antitumor activity of taxol became evident.[1]

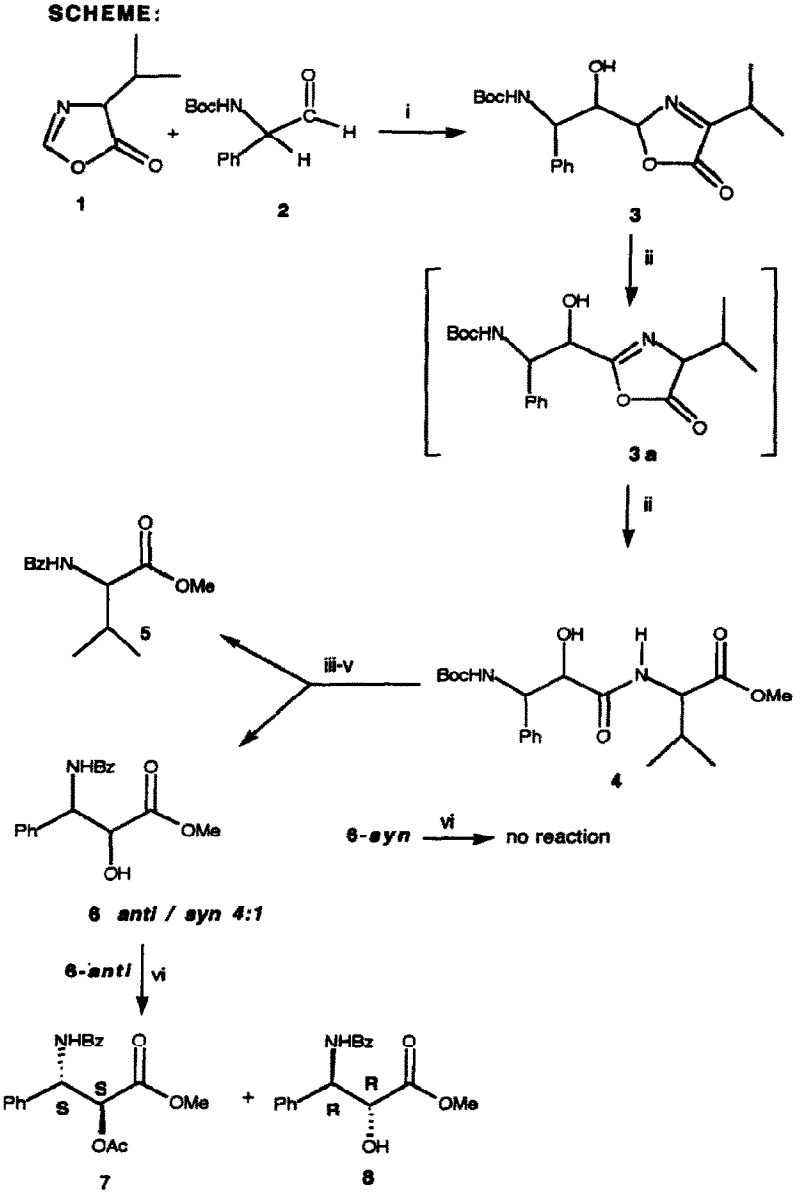
Therefore, the synthesis of chiral 3-phenylisoserine derivatives has become the target of intensive synthetic efforts, which are both of practical importance as well as useful tests for the development of new methodologies. Several methods have been so far reported for their preparation including: a) hydroxyamination of cinnamic acid derivatives;[2] b) β-lactam synthon methodology;[3] c) hetero-Diels-Alder reaction;[4] d) enolate addition to chiral sulfinimines;[5] d) aldol reaction.[6]

As a continuation of our studies centered on the use of heterocyclic compounds as latent functionalities,[7-9] we wish to report in this communication a new chemoenzymatic approach to the preparation of chiral 3-phenylisoserinate derivatives featuring the use of 4-isopropyl-2-oxazolin-5-one **1**[10] as a masked umpoled synthon for a carboxyl group.

We used the readily available racemic N-(tert-butoxycarbonyl)-phenylglycinal **2**[11] as the electrophilic counterpart for the anion of **1**, simply generated at room temperature by addition of a catalytic amount of triethylamine, in the key carbon-carbon bond forming reaction, producing the diastereomeric mixture **3**.§

The heterocyclic ring system of **3** smoothly underwent *via* the tautomer **3a** ring cleavage by treatment with methanolic triethylamine at room temperature for 36h to afford in moderate yield the diasteromeric mixture of the N-protected Boc-Phe-isoSer-Val-OMe dipeptide **4**.

SCHEME:



Reagents: i, Et_3N cat., CH_2Cl_2, rt, 2.5h; ii, Et_3N cat., MeOH; iii, 6N HCl, 110°C, 12h; iv, $SOCl_2$; MeOH; v, BzCl, Et_3N, DMAP; vi, *Pseudomonas fluorescens*(P), t-BuOMe, vinyl acetate, rt, 4 days.

Hydrolysis of the peptide bond was efficiently performed using the well-standardized classical protocol of peptide chemistry, involving heating in a sealed tube at 110°C for 12h in the presence of 6N HCl, to give rise to the expected mixture of two amino acids. The crude mixture was then successively treated with $SOCl_2$-MeOH to effect the transformation into the corresponding methyl esters, which were selectively N-benzoylated by action of benzoyl chloride/triethylamine system and eventually separed by column chromatography. This operation allowed to isolate, beside N-benzoylvaline by-product **5**, a 30% yield of a separable 4:1 mixture of racemic *anti*- and *syn* N-benzoyl-3-phenylisoserine derivatives **6**. Their exposure to lipase from *Pseudomonas fluorescens* (P) using vinyl acetate as the acyl donor[12,13] led us to discover that the minor *syn* racemate was not a substrate for this enzyme under our experimental conditions, while the predominant *anti* racemate could be resolved through the expected enzyme-mediated irreversible O-acetylation. Silica gel chromatography allowed to isolate (2S)-O-acetyl-N-benzoyl-(3S)-phenylisoserine methyl ester **7** as an homogeneous oil, $[\alpha]_D$ = +29 (c 1, MeOH) in essentially quantitative yield and high optical purity [§§] and the *anti*-(2R,3R)-N-benzoyl-3-phenylisoserine methyl ester **8**, m.p. 158°C, $[\alpha]_D$ = -9 (c 1, MeOH); lit.[2b] m.p.153°C, $[\alpha]_D$ = -9.6 (c 1, MeOH), already transformed[2b] into the unnatural (2S,3R) C-13 taxol side chain.

Interestingly, *anti* (2S,3S)-phenylisoserine derivatives can be directly utilized[14] in the esterification of Baccatin III, the known precursor for semisynthetic taxane derivatives.

In summary, the diastereoselective reaction of a rather uncommon umpoled synthon for a carboxyl group with a racemic aldehyde, coupled with enantioselective resolution of the derived racemates provides an alternative route to the preparation of α-hydroxy-β-amino acids.

It is interesting to underline that the anion of 4-isopropyl-2-oxazolin-5-one may serve both as umpoled formyl[9] as well as hydroxycarbonyl group, mild acid or basic treatment respectively being required for the regeneration of the two masked functions, the different oxidation state of the carbon originally attached to two heteroatoms in the heterocyclic precursor simply originating by the involvement of different tautomeric forms.

Further applications of this strategy to preparation of both taxol side chain analogues as well as bestatin congeners are actively in progress.

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§. All new compounds were fully characterized by spectroscopic (^{1}H and ^{13}C NMR, IR) techniques and gave satisfactory elemental analyses.

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§§. p-Toluenesulfonic acid-catalyzed methanolysis of the acetate **7** (MeOH, 12h, reflux) gave the corresponding *anti*-(2S,3S)-N-benzoyl-3-phenylisoserine methyl ester, m.p. 159°C, $[\alpha]_D = +8.5$ (c 1, MeOH).

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