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Improved large-scale synthesis of phenylisoserine and the taxol C-13 side chain

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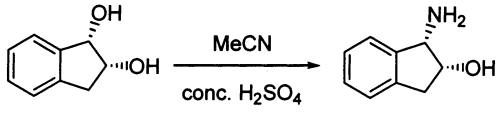
Abstract—Dihydrodihydroxycinnamic acids and their esters react with acetonitrile or benzonitrile in the presence of sulfuric acid to afford the corresponding *syn*-β-amino-α-hydroxypropionic acid derivatives. High yields and diastereoselectivity of this transformation allows preparation of various phenylisoserine derivatives on a practical scale.

The efficiency and high enantioselectivity of the Sharpless Asymmetric Dihydroxylation (AD) provides an excellent entry to various chiral building blocks.[1] Among those are *syn*-diols derived from cinnamate esters,[2] important intermediates en route to phenylisoserine and its analogs, notably, *N*-benzoylphenylisoserine, a C-13 side chain of taxol. Several approaches to the conversion of cinnamate diols to the corresponding *syn*-β-amino-α-hydroxy derivatives have been reported, all of them having a common strategy: the β-hydroxyl group is appropriately activated, then displaced with a halide which is finally substituted with azide or benzoylisothiocyanate.[3a,b] Thus, the *syn*-geometry of the resulting aminoalcohol is achieved through a double inversion at the β-carbon. We now report a simple one-step protocol for the preparation of various phenylisoserine derivatives from 2,3-dihydroxycinnamic acids or its esters which is based on the Ritter reaction.[4]

The Ritter reaction is a powerful yet rather underutilized synthetic tool, which allows one to convert alcohols to amines or their derivatives by treating the alcohol with a nitrile in the presence of a strong acid. Reportedly, the reaction proceeds though a carbocationic intermediate thus often scrambling the stereochemistry of the starting alcohol and limiting the synthetic value of the reaction.

However, certain factors can sometimes lead to high stereoselectivity levels in this transformation. For example, Buckland et al. developed a stereoselective process for converting *cis*-indanediol to *cis*-aminoindanol based on Ritter reaction[5] (Scheme 1). Vicinal diols react with nitriles in the presence of an acid through oxazoline intermediates;[6] in the indane case *cis*-aminoalcohol is the only possible isomer that can form due to a rigid *cis*-geometry of the two fused five-membered cycles. Acyclic diols, as in our case of dihydroxydihydrocinnamates, would not be expected to have such stringent stereocontrol.

In fact, when acetonitrile solutions of dihydroxy dihydrocinnamate esters (easily prepared by AD from commercially available cinnamates[3a]) or the corresponding acids were treated with concentrated sulfuric acid at −10°C, mixtures of diastereomeric aminoalcohols were isolated after aqueous HCl hydrolysis of the initially formed oxazolines[7] (Scheme 2). However, the levels of diastereoselectivity were surprisingly high: 20:1 to 11:1 (Table 1) in favor of the *syn* isomer. The major *syn* isomer was separated from the mixture by crystallization from isopropanol in 78–86% yield. The geometry of the product was confirmed by comparing the NMR data of aminoacid **3a** with those of the authentic samples of the corresponding *syn*- and *anti*-β-amino-α-hydroxyacid derivatives.[6] The geometry of other products was assigned by correlation of their spectroscopic data with that of **3a**.



Scheme 1.

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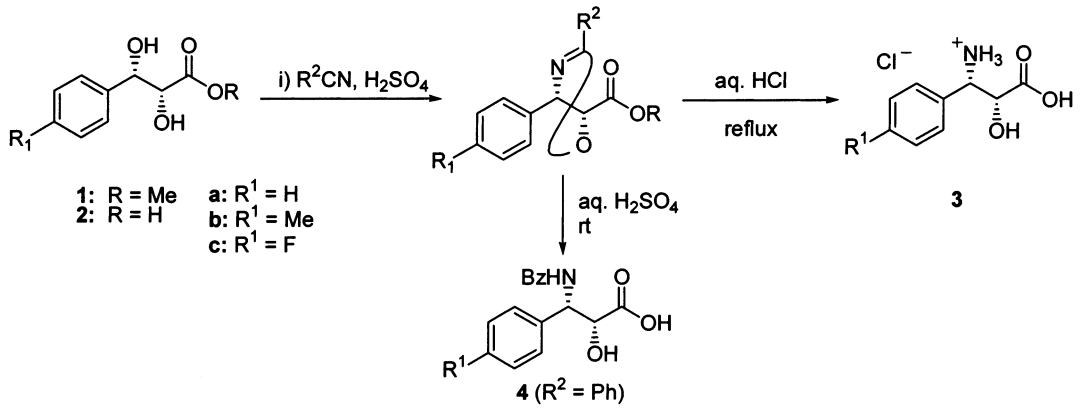

Scheme 2.

Table 1. Reaction of dihydroxycinnamic acids and esters with nitriles in the presence of sulfuric acid

Entry	R	R_1	Product	Diastereomer ratios	Yield (%)
1	Me	H	**3a**	18:1	86
2	H	H	**3a**	13:1	61
3	Me	Me	**3b**	15:1	82
4	H	Me	**3b**	14:1	77
5	Me	F	**3c**	11:1	81
6	H	F	**3c**	11:1	78
7	Me	H	**4a**	20:1	52
8	H	H	**4a**	20:1	59
9	Me	Me	**4b**	20:1	54
10	H	Me	**4b**	20:1	64

N-Benzoylphenylisoserines **4a** and **4b** were prepared in a similar fashion from either **1a** and **2a** or **1b** and **2b** and benzonitrile. The oxazoline intermediates were treated by dilute acid at room temperature to effect opening of the oxazoline and ester hydrolysis and to keep the amide bond intact.[9] The pure hydroxyamido acids crystallized from the reaction mixture and were purified by crystallization (Table 1, entries 7–10).[3a] In this case acids **2a**,**b** rather that esters **1a**,**b** proved to be beneficial due to simplified work-up.

To explain such a high level of stereocontrol in the reaction we have to assume that the benzylic carbocation generated from the alcohol in the presence of the acid is stabilized by the neighboring hydroxyl group, i.e. the *cis*-epoxide-like intermediate locks the stereochemistry at the benzylic position and then reacts with the nucleophilic nitrogen of the nitrile.

In conclusion, an efficient one-step protocol for preparation of both phenylisoserine derivatives and the corresponding taxol C-13 side chain has been demonstrated on a 0.2 mol scale. This method compliments the AD reaction and allows preparation of various phenylisoserine derivatives in enantio- and diastereoselective fashion.

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7. In a typical procedure, methyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate **1a** (39.2 g, 0.20 mol) was mixed with 100 mL of actonitrile and the mixture was cooled to −10°C in an ice/NH_4Cl bath. Concentrated sulfuric acid (20 mL)

was added dropwise and the resulting solution was allowed to warm to room temperature over a period of 2 h. The stirring was continued until no starting material was detected by GC analysis. At that point, the reaction mixture was treated with aqueous KOH to bring pH to 2. The intermediate oxazoline was extracted with ethyl acetate (3×70 mL), the solvent was evaporated and the oily residue was heated at reflux with 250 mL of 2 M hydrochloric acid for 2 h. Water was removed in vacuum yielding crude HCl salt of **3a**. Recrystallization from isopropanol afforded pure **3a**·HCl (36.9 g, 86%) as colorless crystals: mp (decomp.) 218–219°C (lit.[8] mp 222–224°C). Hydroxyaminoacids **3b** and **3c** were prepared according to the similar procedure.

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9. Literature suggests that acidic hydrolysis of the oxazoline leads to the equilibrium mixture of *N*- and *O*-benzoyl derivatives. In our case, only the former derivative had crystallized out of the acidic aqueous solution, while the latter remained dissolved. See: Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375 and references cited therein.