

Reaction of α,β -dihydroxydihydrocinnamic esters with acetonitrile: a new approach to β -amino- α -hydroxydihydrocinnamic acids

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Dedicated to academician Michael G. Voronkov on the occasion of his 80th birthday

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Abstract

Diols and their derivatives, readily available from cinnamate esters by the Sharpless asymmetric dihydroxylation (AD) reaction, react with acetonitrile in the presence of an acid affording the corresponding β -amino- α -hydroxyacid derivatives. In combination with the AD reaction, this method provides an efficient entry to various phenylisoserine derivatives on multigram scale.

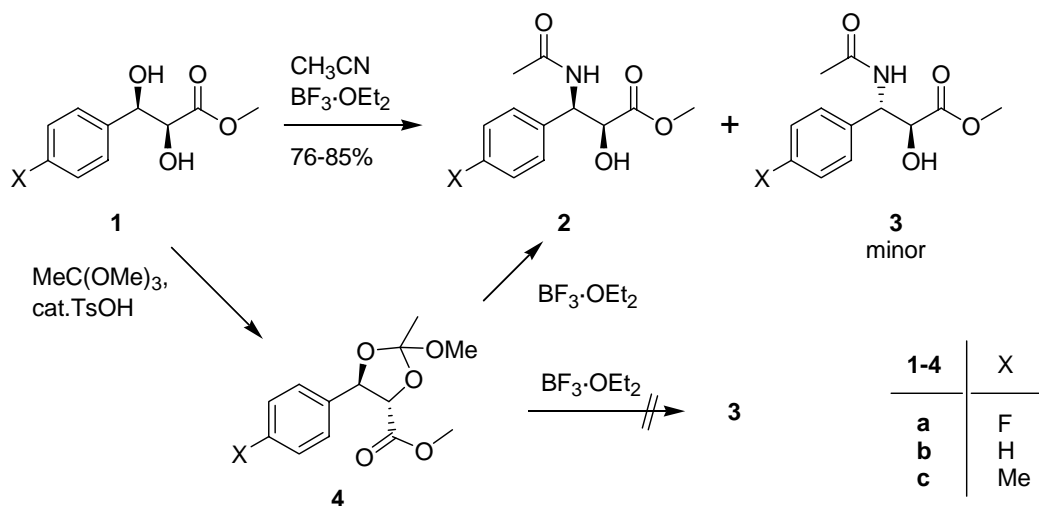
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Introduction

β -Amino- α -hydroxy acids and more specifically, phenylisoserine derivatives have recently become an important synthetic target.¹⁻³ There are three general approaches to these compounds: i) direct Sharpless asymmetric aminohydroxylation (AA) of cinnamic acid esters;^{1a-d} ii) asymmetric carbon-carbon bond formation;^{2a-d} iii) using other chiral sources, e.g. 2,3-dihydroxyesters readily available from Sharpless asymmetric dihydroxylation (AD)^{3a,b} or aminoacids.^{3c,d} Among these approaches, the synthesis of phenylisoserine from 2,3-dihydroxydihydrocinnamic esters generally proceeds with highest regio- and enantioselectivity. The desired *syn* geometry is achieved through double inversion at the β -carbon. This transformation requires the activation of the β -hydroxy group followed by the displacement with halide and subsequent reaction with azide or benzoyl isothiocyanate. We now report a simple one-step protocol based on the Ritter reaction⁴ for the preparation of various phenylisoserine derivatives from 2,3-dihydroxy-2,3-dihydrocinnamates **1**.

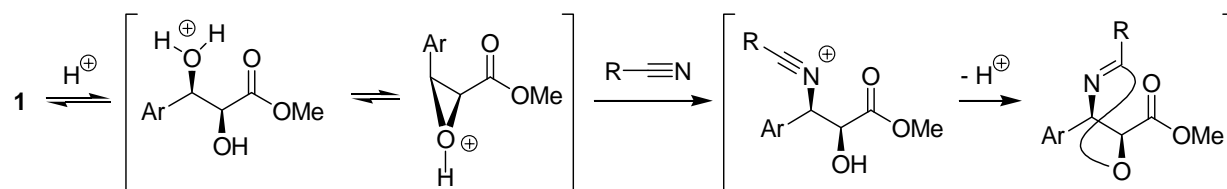
Results and Discussion

In a typical procedure (Method A), neat $\text{BF}_3 \cdot \text{OEt}_2$ was added dropwise to a stirred solution of (2*S*,3*R*)-dihydroxydihydrocinnamic ester **1** in acetonitrile at 0 °C (Scheme 1). The reaction mixture was stirred at 0 °C for 4–24 hours. The product was isolated as a mixture of diastereomers: (2*R*,3*S*)-**2** and (2*S*,3*S*)-**3** in 76–85% combined yield (Table 1). Based on the characteristic $^3J_{2,3} = 8.4\text{--}8.6\text{ Hz}$ ^{3a,5} the major product was assigned to the *syn* diastereomer **2**. We found the highest product ratio (8:1) for the *p*-methyl derivatives **2c/3c**, it was only 6:1 for the *p*-fluoro derivatives **2a/3a**. It is worth noting that the reaction time required for completion of the reaction greatly varied from 4 h to 24 h for *p*-methyl and the *p*-fluoro derivative, respectively. This may suggest the development of a positive charge at the β -carbon. The high degree of diastereoselectivity of the transformation suggests participation of the neighboring hydroxyl in the stabilization of this charge, i. e. it seems reasonable to assume the *cis*-disubstituted epoxide as the intermediate (see the proposed mechanism in Scheme 2).⁶



Scheme 1

Figure 1 shows how various acids (both protic and Lewis acids) affect the rate of conversion of **1c** into **2c** + **3c**. The reactions of diol **1c** with acetonitrile in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, AlCl_3 or TfOH were monitored by GC. The mixture of diastereomer **2c** and **3c** was observed in all reactions with approximately the same ratios. Since the reaction with $\text{BF}_3 \cdot \text{OEt}_2$ was the fastest and proceeded to completion, this Lewis acid was generally chosen for these transformations. We found that a higher reaction temperature generally accelerates the reaction but affects the ratio of diastereomers **2c** and **3c**; at 50 °C the diastereomer ratio was 3:1.



Scheme 2

Table 1. Conversion of diols **1** into the diastereomer mixtures of aminoalcohols **2** and **3**

1	X	Method	Reaction time [h]	Ratio 2:3	Yield 2+3 (%)
1a	F	A	24	6:1	78
1a	F	B	2	10:1	82
1b	H	A	18	6:1	76
1b	H	B	4	7:1	74
1c	Me	A	4	8:1	85
1c	Me	B	24	5:1	69

We attempted to prepare diastereomer **3** by the reaction of acetonitrile with the cyclic orthoacetate **4**, formed in situ from diol **1** (Method B), a method known to give the substitution of oxygen at the benzylic position with inversion of configuration.^{3a,7} Contrary to our expectations, we obtained not only **2** as the major diastereomer, but also the influence of *para* substituents on the rate of the transformation reversed. In fact, the reaction of **1a** (with *p*-fluoro substituent) went to completion within 2 h, while the *p*-methyl derivative required over 24 h.

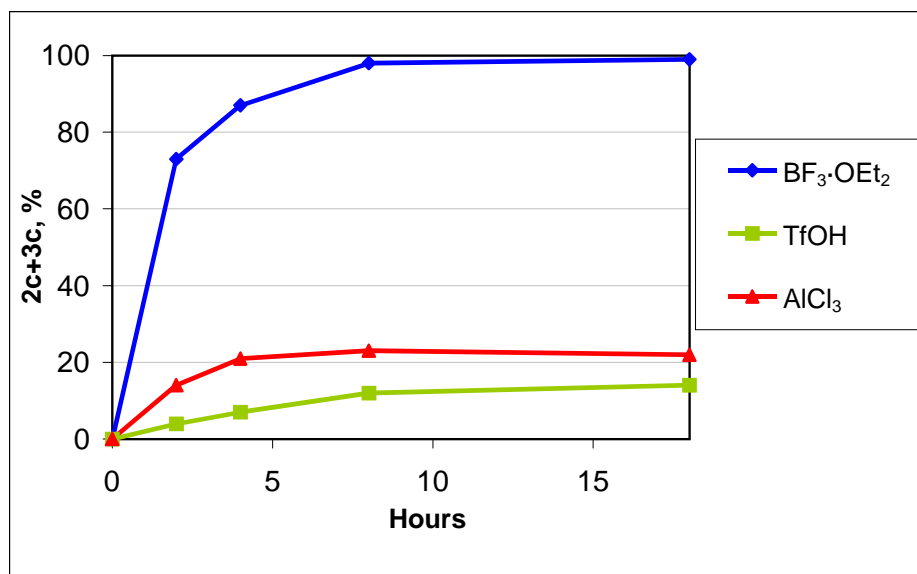
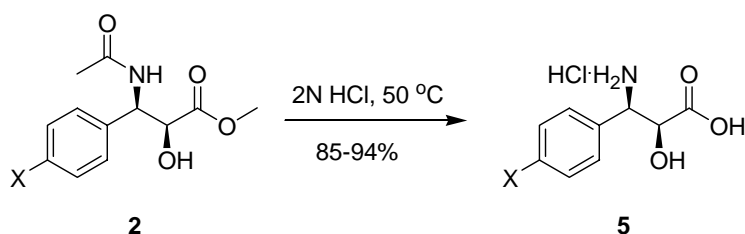


Figure 1

The major diastereomers **2** were separated by flash chromatography on silica gel and were subsequently subjected to hydrolysis with 2N HCl at 50 °C for 6 h. The desired products **5** were isolated upon concentration of the reaction mixtures as white powders in 85–94% yield (Scheme 3). Based on the fact that both ^1H and ^{13}C NMR spectra of amino acid **5b** were identical to that of the commercial (2*S*,3*R*)-3-phenylisoserine hydrochloride, it was assigned the same *syn* geometry. Since in our opinion inversion of both stereocenters is not likely and the starting diol had 2*S*,3*R* geometry, the specific stereochemistry of the product was also assigned as 2*S*,3*R*. Furthermore, chiral HPLC (CHIRALPAK WH00CE) trace of **5b** indicated that the retention time of the major peak was identical to that of the commercial (2*S*,3*R*)-3-phenylisoserine. The geometry of **5a** and **5c** was tentatively assigned based on comparison of their NMR spectra with that of **5b**.



Scheme 3

In conclusion, six phenylisoserine derivatives were prepared on multigram scale. This approach provides straightforward entry to various phenylisoserines in stereoselective fashion and practical yields.

Experimental Section

General Procedures. NMR experiments were conducted with a Bruker ARX300 NMR spectrometer at 75 MHz for ^{13}C and 300 MHz for ^1H spectra. Samples were dissolved in CDCl_3 or DMSO-d_6 with the internal reference being TMS ($\delta_{\text{H}} = 0.00$ ppm) for ^1H spectra, and the solvent peak ($\delta_{\text{C}} = 77.0$ ppm and $\delta_{\text{C}} = 39.5$ ppm, respectively) for ^{13}C spectra. Methyl (2*R*,3*S*)-3-(4-fluorophenyl)-2,3-dihydroxypropanoate (**1a**), methyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropanoate (**1b**), methyl (2*R*,3*S*)-2,3-dihydroxy-3-(4-methylphenyl)propanoate (**1c**) were prepared from the corresponding commercially available cinnamic esters using $\text{K}_2\text{OsO}_2(\text{OH})_4$ and (DHQD)₂-PHAL.^{3a} (2*S*,3*R*)-3-Phenylisoserine was purchased from Chirogen, Inc. All other chemicals were obtained from commercial sources and were used without further purification. Reactions were carried out in an atmosphere of dry nitrogen with magnetic stirring, and were monitored by GC (HP6850 series GC system with an FID detector and HP-1 0.32 mm x 30 m column) and/or LCMS (HP1100 series LCMS system equipped with a Polaris C18-A 5u PN2000-030x046 column, APCI ionization mode).

Methyl (2*S*,3*R*)-3-(acetylamino)-3-aryl-2-hydroxypropanoates (2). Method A: Neat BF₃·OEt₂ (31.68 mL, 0.25 mol) was added dropwise to a stirred mixture of diol **1** (0.05 mol) and acetonitrile (30 mL) at 0 °C. The resulting solution was stirred at 0 °C for 24 h. The reaction mixture was treated with saturated aq. NaHCO₃ (50 mL), the organic phase was separated, dried over MgSO₄ and concentrated in vacuum to give the desired product as a mixture of diastereomers **2** and **3**. The major isomer **2** was separated by flash chromatography on silica gel using hexane/ethyl acetate (4:1) as the eluent.

Method B: Diol **1** (10 mmol) was mixed with trimethyl orthoacetate (25 mL), and after addition of a catalytic amount of *p*-toluenesulfonic acid the resulting mixture was stirred at room temperature for 5 h. The mixture was concentrated under reduced pressure and diluted with dichloromethane (25 mL). To this solution BF₃·OEt₂ (2.53 mL, 20 mmol) was added dropwise at 0 °C, and the mixture was stirred at this temperature for 2–24 h and then treated with saturated aq. NaHCO₃ (50 mL). The organic phase was separated, dried over MgSO₄ and concentrated in vacuum to give the desired product as a mixture of diastereomers **2** and **3**.

Methyl (2*S*,3*R*)-3-(acetylamino)-3-(4-fluorophenyl)-2-hydroxypropanoate (2a). Off-white microcrystals (Method B; 82%), mp 151–152 °C. ¹H NMR (300 MHz; CDCl₃): δ 1.92 (s, 3H), 3.71 (s, 3H), 4.31 (d, *J* = 8.6 Hz, 1H), 4.62 (br s, 1H), 5.38 (d, *J* = 8.6 Hz, 1H), 7.03–7.21 (m, 2H), 7.37–7.46 (m, 3H); ¹³C NMR (75 MHz; CDCl₃): δ 23.3, 52.7, 54.8, 73.9, 115.9 (d, *J* = 42.8 Hz), 129.8, 135.5, 162.4 (d, *J* = 244.5 Hz), 170.0, 173.4. LC/MS: *m/z* 255.3 (M+1). Anal. Calcd for C₁₂H₁₄FNO₄ (255.25): C, 56.47; H, 5.53. Found: C, 56.09; H, 5.44.

Methyl (2*S*,3*R*)-3-(acetylamino)-2-hydroxy-3-phenylpropanoate (2b). Colorless solid (Method A; 76%), mp 145–146 °C (lit.^{3a} mp 148–149 °C). ¹H NMR (300 MHz; CDCl₃): δ 2.02 (s, 3H), 3.69 (s, 3H), 4.59 (d, 1H, *J* = 8.6 Hz), 5.11 (d, 1H, *J* = 8.6 Hz), 7.35–7.43 (m, 5H); ¹³C NMR (75 MHz; CDCl₃): δ 22.3, 52.4, 69.1, 77.9, 126.9, 127.9, 128.7, 138.8, 169.2, 172.4. LC/MS: *m/z* 238.1 (M+1).

Methyl (2*S*,3*R*)-3-(acetylamino)-2-hydroxy-3-(4-methylphenyl)propanoate (2c). White needles (Method A; 85%), mp 174–175 °C. ¹H NMR (300 MHz; CDCl₃): δ 2.11 (s, 3H), 2.37 (s, 3H), 3.73 (s, 3H), 4.67 (d, *J* = 8.4 Hz, 1H), 5.09 (d, *J* = 8.4 Hz, 1H), 7.32–7.39 (m, 4H); ¹³C NMR (75 MHz; CDCl₃): δ 13.8, 21.1, 52.7, 73.0, 83.1, 125.7, 129.5, 136.2, 137.6, 164.8, 170.2; LC/MS: *m/z* 252.1 (M+1). Anal. Calcd for C₁₃H₁₇NO₄ (251.28): C, 62.14; H, 6.82; N, 5.57. Found: C, 61.91; H, 6.85; N, 5.42.

(2*S*,3*R*)-3-Amino-3-aryl-2-hydroxypropionic acid hydrochlorides (5). General procedure

The appropriate methyl (2*S*,3*R*)-3-(acetylamino)-3-aryl-2-hydroxypropanoate (**2**) (0.02 mol) was stirred with 2*N* HCl (25 mL) at 50 °C for 6 h. The reaction mixture was concentrated to yield the desired product **5** as a white solid.

(2*S*,3*R*)-3-Amino-3-(4-fluorophenyl)-2-hydroxypropanoic acid hydrochloride (5a). White solid (94%), mp (decomp.) 255–258 °C (lit.⁸ mp 259–260 °C). ¹H NMR (300 MHz; DMSO-*d*₆): δ 4.32 (br s, 2H), 7.31–7.58 (m, 2H), 7.63–7.72 (m, 2H), 8.64 (br s, 2H); ¹³C NMR (75 MHz;

DMSO-*d*₆): δ 56.9, 73.1, 116.2 (d, $J = 42.6$ Hz), 131.7, 163.0 (d, $J = 243.8$ Hz), 170.0, 173.4. LC/MS: m/z 200.2 (M+1).

(2*S*,3*R*)-2-hydroxy-3-amino-3-phenylpropionic acid hydrochloride (5b). White solid (87%), mp (decomp.) 218–219 °C (lit.¹⁰ mp 222–224 °C). ¹H NMR (300 MHz; DMSO-*d*₆): δ 3.49 (br s, 2H), 4.22 (br s, 2H), 7.50–7.61 (m, 5H), 8.67 (br s, 2H); ¹³C NMR (75 MHz; DMSO-*d*₆): δ 56.9, 72.6, 128.6, 128.9, 129.3, 131.8, 172.1. LC/MS: m/z (M+1) 182.1.

(2*S*,3*R*)-2-hydroxy-3-amino-3-(4-methyl)-phenylpropionic acid hydrochloride (5c).⁹ Off-white powder (85%), mp (decomp.) 234–235 °C. ¹H NMR (300 MHz; DMSO-*d*₆): δ 2.21 (s, 3H), 3.27 (br s, 2H), 4.29 (br s, 2H), 7.14 (m, 2H), 7.30 (m, 2H), 8.55 (br s, 2H); ¹³C NMR (75 MHz; DMSO-*d*₆): δ 21.1, 56.7, 72.6, 128.5, 129.4, 138.7, 172.1. LC/MS: m/z (M+1) 196.2. Anal. Calcd for C₁₀H₁₄ClNO₃ (231.68): N, 6.05. Found: N, 5.77.

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