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# Sulfinyl moiety as an internal nucleophile. Part 6: Stereospecific synthesis of 3-amino-2-hydroxy-4-phenylbutanoate☆

Sadagopan Raghavan* and M. Abdul Rasheed

*Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

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**Abstract**—A novel and stereospecific synthesis of (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoate (AHPBA) is disclosed. The key step includes regio- and stereospecific functionalization of an alkene by the pendant sulfinyl group. 

## 1. Introduction

β-Amino-α-hydroxy acid derivatives are important because many of them occur in diverse natural and synthetic compounds possessing significant biological activity; for example in taxol **1**,[1] bestatin **2**,[2] microginin **3**,[3] HIV protease inhibitors,[4] and renin inhibitors[5] (Fig. 1).

Not surprisingly, a great deal of attention has been devoted towards their efficient synthesis. The methods include acid hydrolysis of cyanohydrins[6] derived from α-amino aldehydes, iodocyclocarbamation,[7] β-lactam ring opening,[8] aldol condensation of chiral enolates,[9] stereoselective reduction,[10] epoxidation,[11] conjugate addition of amines[12] and use of sugar derivatives as starting materials.[13] Bestatin, a dipeptide, isolated from *Streptomyces olivoreticuli* contains a non-proteinogenic (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid (AHPBA) residue. It is an aminopeptidase inhibitor that exhibits immunostimulatory as well as cytotoxic activity. Several synthetic routes to bestatin have been reported.[14] Many of the reported methods are non-stereoselective and are of limited practical utility because of their complexity, demand for unusual reagents and synthetic intermediates. We have been interested in the stereo- and regioselective functionalization of olefins using the sulfinyl moiety as an internal nucleophile.[15] We disclose herein an efficient, stereospecific synthesis of (2*R*,3*S*)-3-amino-2-hydroxy-4-phenyl butanoic acid derivative exploiting this methodology.

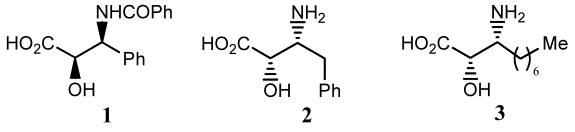


**Figure 1.**

## 2. Results and discussion

The synthesis of AHPBA commenced from the β-hydroxy sulfoxide **6** obtained by diastereoselective reduction (>95% d.e)[16] of β-keto sulfoxide **5**.[17] Treatment of the allyl alcohol **6** with NBS in toluene in the presence of water afforded the bromodiol **8**.[15c] Subjecting the bromodiol **8** to 2,2-dimethoxy propane in the presence of cat. amounts of CSA yielded the acetonide **9**, the $^{13}C$ spectrum of which revealed resonances at $\delta$ 19.4, 29.5 for the methyl groups and at $\delta$ 100.7 for the quaternary carbon of the acetonide proving unambiguously the 1,3-*syn* disposition[18] of the hydroxy groups in **8**. The proton attached to the carbon bearing the bromine atom in **8** appeared as a triplet with $J=10.26$ Hz indicating an *anti* disposition of bromine relative to the hydroxy groups. The regio- and stereoselectivity of the reaction can be rationalized by invoking the intermediate sulfoxonium salt **7** arising from the 6-*endo* nucleophilic attack of the sulfinyl moiety onto the olefin, π complexed to the bromonium ion, and its subsequent hydrolysis by attack of water at sulfur. The benzylic carbon being better able to stabilize a partial positive charge leads to the observed 6-*endo* opening product (Scheme 1).

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* Corresponding author. E-mail: purush101@yahoo.com

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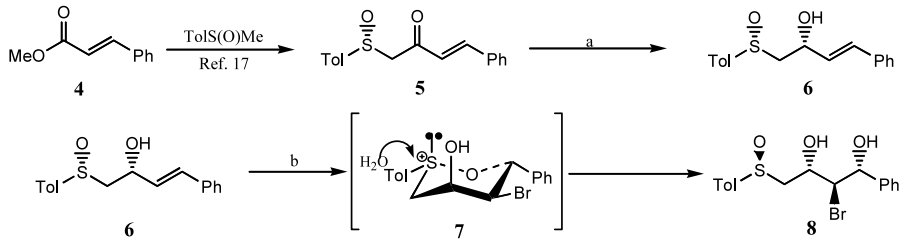
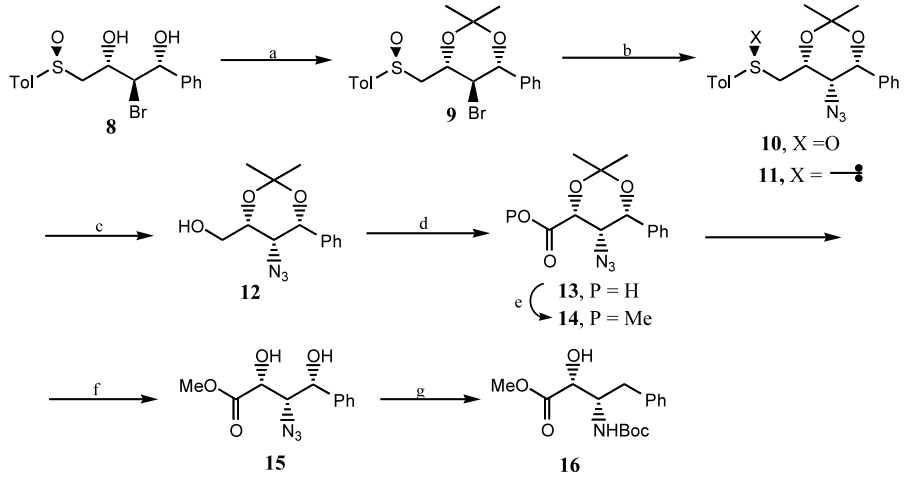


**Scheme 1.** *Reaction conditions*: (a) DIBAL, $ZnCl_2$, THF, −78°C 1 h, 80%; (b) NBS, $H_2O$, toluene, rt, 30 min 80%.



**Scheme 2.** *Reaction conditions*: (a) 2,2-DMP, cat. CSA, acetone, rt, 1 h, 90%; (b) $NaN_3$, DMSO, 100°C, 8 h, 75%; (c) TFAA, $Et_3N$, $CH_3CN$, 0°C, 10 min then aq. $NaHCO_3$, $NaBH_4$, 30 min, 85%; (d) PDC, DMF, rt, 16 h; (e) $CH_2N_2$, ether 70% for two steps; (f) cat. CSA, MeOH, rt, 2 h, 85%; (g) $Pd(OH)_2/C$, $H_2$, $(Boc)_2O$, MeOH, rt, 12 h, 80%.

The amino group was introduced by nucleophilic displacement of bromine by treatment of **9** with $NaN_3$ in DMSO. In addition to the expected azido acetonide **10**, another minor, less polar product, characterized as the sulfide **11** was also isolated. Treatment of **10** with TFAA in acetonitrile in the presence of $Et_3N$ afforded the Pummerer intermediate,[19] which without isolation was treated in the same vessel with aq. saturated $NaHCO_3$ and $NaBH_4$ to yield the alcohol **12** (Scheme 2).

Oxidation of **12** proceeded without incident with PDC in DMF[20] to afford the acid **13** which was characterized as its methyl ester **14**. The ester **14** was elaborated to AHPBA as depicted in Scheme 2. Thus, deprotection of the acetonide group by treatment with cat. amounts of CSA in methanol afforded the diol **15** which upon treatment with $Pd(OH)_2/C$ in the presence of $(Boc)_2O$ in methanol under an atmosphere of hydrogen yielded β-amino acid derivative **16**.

In summary, we have disclosed a stereospecific synthesis of (2*R*,3*S*)-AHPBA ester utilizing the sulfinyl moiety as an internal nucleophile to stereo- and regioselectively functionalize an olefin in the key step of the reaction sequence. It is pertinent to note that starting from (*S*)-tolyl methyl sulfoxide[21] and following an identical reaction sequence as detailed above, the (2*S*,3*R*)-AHPBA, constituent of bestatin can be prepared.

## 3. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. $^1H$ NMR spectra were recorded on Gemini-200 and Brucker 300 spectrophotometers in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan Matt 1200 mass spectrometer. Optical rotations were measured on a Jasco Dip 360 digital polarimeter. Column chromatography was performed on silica gel (Merck, 100–200 mesh).

### 3.1. ($S_S$)-1-(4-Methylphenylsulfinyl)-4-phenyl-(2*R*,3*E*)-3-buten-2-ol, 6

To a solution of β-ketosulfoxide **5** (1.78 g, 6.25 mmol) in THF (62 mL) was added the solution of anhydrous $ZnCl_2$ (6.9 mL, 6.9 mmol, 1 M/THF) and stirred at rt for 1 h. The reaction mixture was then cooled to −78°C and DIBAL-H (2 M/toluene, 3.46 mL 6.92 mmol) was added dropwise. After 1 h at −78°C the reaction was quenched by adding methanol (30 mL) and allowed to attain ambient temperature. The solvent was then evaporated and the residue diluted with water and extracted with ethyl acetate. The organic layer was washed successively with 5% aq. NaOH, water, brine, dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography using 30% EtOAc/pet. ether as the eluent

to afford **6** (1.43 g, 5 mmol) in 80% yield. White solid. Mp 95–97°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.55 (d, $J=8.2$ Hz, 2H), 7.40–7.20 (m, 7H), 6.70 (d, $J=16.5$ Hz, 1H), 6.15 (dd, $J=16.5$, 5.9 Hz, 1H), 5.0 (m, 1H), 3.90 (bs, 1H) 3.06 (dd, $J=12.9$, 8.2 Hz, 1H), 2.90 (dd, $J=12.9$, 2.4 Hz, 1H), 2.45 (s, 3H). MS (FAB) 287 ($M^+$+H). $[\alpha]_D$ +112.6 (*c* 0.6, $CHCl_3$).

### 3.2. 2-Bromo-($S_s$)-4-(4-methylphenylsulfinyl)-1-phenyl-(1*R*,2*R*,3*S*)-butane-1,3-diol, 8

To a solution of β-hydroxy sulfoxide **6** (1.43 g, 5.0 mmol) in toluene (20 mL) at rt was added water (153 μl, 8.5 mmol), *N*-bromosuccinimide (1.07g, 6 mmol) and stirred for 30 min. The reaction mixture was taken into ethyl acetate (50 mL) and washed successively with 10% aq. $NaHCO_3$, water and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography using 50% EtOAc/pet. ether as the eluent to afford **8** (1.53 g, 4 mmol) in 80% yield. White solid. Mp 123–125°C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50 (d, $J=8.2$ Hz, 2H), 7.32 (d, $J=8.2$ Hz, 2H), 7.28 (bs, 5H), 5.0 (bs, 1H), 4.94 (d, $J=8.0$ Hz, 1H), 4.40 (m, 1H), 4.25 (t, $J=8.0$ Hz, 1H), 3.90 (bs, 1H), 3.27 (dd, $J=13.4$, 10.7 Hz, 1H), 3.18 (dd, $J=13.4$, 2.7 Hz, 1H), 2.45 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 141.9, 140.4, 138.6, 130.2, 128.3, 126.9, 124.1, 74.2, 68.6, 61.8, 59.3, 21.4. MS (FAB) 383 ($M^+$+H), 365, 307, 154. $[\alpha]_D$ −124.9 (*c* 1.47, $CHCl_3$).

### 3.3. 5-Bromo-2,2-dimethyl-($S_s$)-4-(4-methylphenylsulfinylmethyl)-6-phenyl-(4*S*,5*R*,6*R*)-1,3-dioxane, 9

To a solution of the bromodiol **8** (1.43 g, 3.74 mmol) in acetone (7.5 mL) was added 2,2-dimethoxypropane (7.5 mL) and catalytic amounts of CSA and the mixture stirred at rt for 1 h. $Et_3N$, enough to neutralize CSA, was added and the volatiles were removed under reduced pressure. The residue was purified by column chromatography using 30% EtOAc/pet. ether as the eluent to afford **9** (1.43 g, 3.38 mmol) in 90% yield. Gummy liquid. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J=8.0$ Hz, 2H), 7.36 (m, 7H), 4.90 (d, $J=10.26$ Hz, 1H), 4.67 (td, $J=10.26$, 2.2 Hz, 1H), 3.62 (t, $J=10.26$ Hz, 1H), 3.36 (dd, $J=13.18$, 2.2 Hz, 1H), 2.76 (dd, $J=13.18$, 10.25 Hz, 1H), 2.45 (s, 3H), 1.76 (s, 3H), 1.57 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 141.6, 141.3, 138.1, 130.0, 128.3, 127.8, 124.0, 123.7, 100.7, 77.4, 69.3, 62.4, 52.4, 29.5, 21.4, 19.4. MS (FAB) 423 ($M^+$+H), 365, 285. $[\alpha]_D$ −127.5 (*c* 1.04, $CHCl_3$).

### 3.4. 5-Azido-2,2-dimethyl-($S_s$)-4-(4-methylphenylsulfinylmethyl)-6-phenyl-(4*R*,5*S*,6*R*)-1,3-dioxane, 10

To a solution of the bromo acetonide **9** (1.38 g, 3.25 mmol) in dimethyl sulfoxide (6.5 mL) was added sodium azide (0.85 g, 13 mmol) and the reaction mixture heated at 100°C for 8 h. The reaction mixture was cooled to rt, diluted with ether (60 mL) and washed successively with water, brine, dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure to afford a residue which was purified by column chromatography using 30% EtOAc/pet. ether as the eluent to afford initially the azido sulfide **11** (0.12 g, 0.33 mmol) in 10% yield and azido sulfoxide **10** (0.94 g, 2.43 mmol) in 75% yield. Viscous oil. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.50 (d, $J=8.2$ Hz, 2H), 7.31 (m, 7H), 5.24 (d, $J=1.5$ Hz, 1H), 4.83 (dd, $J=9.66$, 2.23 Hz, 1H), 3.0 (dd, $J=13.38$, 9.66 Hz, 1H), 2.80 (dd, $J=13.38$, 2.23 Hz, 1H), 2.75 (d, $J=1.5$, Hz, 1H), 2.39 (s, 3H), 1.67 (s, 3H), 1.62 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 141.7, 140.9, 137.9, 130.1, 128.5, 127.4, 125.5, 123.7, 100.9, 74.5, 67.3, 61.8, 60.4, 28.5, 21.3, 19.1. MS (FAB) 386 ($M^+$+H), 328, 139. $[\alpha]_D$ −131.75 (*c* 0.99, $CHCl_3$).

### 3.5. 5-Azido-2,2-dimethyl-6-phenyl-(4*R*,5*S*,6*R*)-1,3-dioxan-4-ylmethanol, 12

To a solution of the azido acetonide **10** (0.76 g, 1.98 mmol) in acetonitrile (10 mL) cooled at 0°C was added triethylamine (0.83 mL, 5.94 mmol) followed by trifluoroacetic anhydride (0.83 mL, 5.94 mmol) and stirred for 10 min. A solution of $NaHCO_3$ (1.67 g 19.8 mmol) in water (10 mL) was added at 0°C followed by solid $NaBH_4$ (0.15 g, 3.96 mmol) and the reaction mixture stirred for another 30 min. The reaction mixture was then extracted into ethyl acetate (40 mL) and washed successively with water, brine and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to afford a residue which was purified by column chromatography using 30% EtOAc/pet. ether as the eluent to afford **12** (0.44 g, 1.68 mmol) in 85% yield. Viscous oil. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.38 (m, 5H), 5.18 (d, $J=2.23$ Hz, 1H), 4.30 (m, 1H), 3.85 (dd, $J=11.15$, 6.69 Hz, 1H), 3.72 (dd, $J=11.15$, 5.2 Hz, 1H), 2.94 (d, $J=2.23$ Hz, 1H), 2.20 (bs, 1H), 1.60 (s, 6H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 138.2, 128.5, 127.9, 125.6, 100.4, 74.5, 73.5, 63.2, 57.9, 28.6, 19.1. MS (FAB) 264 ($M^+$+H), 246, 154. $[\alpha]_D$ −147.0 (*c* 1.0, $CHCl_3$).

### 3.6. Methyl 5-azido-2,2-dimethyl-6-phenyl-(4*R*,5*S*,6*R*)-1,3-dioxane-4-carboxylate, 14

To a solution of alcohol **12** (0.34 g, 1.29 mmol) in DMF (2.6 mL) at rt was added pyridinium dichromate (1.94 g, 5.18 mmol) and let stir for 16 h. The reaction mixture was then extracted into ethyl acetate (30 mL) and washed with water (2×10 mL). The organic layer was washed with 10% aq. $NaHCO_3$ (3×15 mL). The bicarbonate layer was acidified to pH 2 with 5N HCl and extracted with ethylacetate (3×15 mL). The combined organic layers were washed successively with water (10 mL) and brine. To this ethyl acetate layer was added cold (0°C) ethereal $CH_2N_2$, generated in situ from nitrosomethyl urea (0.28 g, 2.59 mmol) in ether (10 mL) and 50% aq. KOH (4 mL) at 0°C, and stirred at rt for 10 min. The solvent was removed under reduced pressure to afford a residue which was purified by column chromatography using 30% EtOAc/pet. ether as the eluent to afford **14** (0.26 g, 0.9 mmol) in 70% overall yield for two steps. White crystalline solid. Mp 143–145°C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40 (m, 5H), 5.23 (s, 1H), 4.83 (d, $J=2.3$ Hz, 1H), 3.83 (s, 3H), 3.34 (d, $J=2.3$ Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.6, 137.5, 128.6,

128.2, 125.6, 100.8, 74.0, 72.6, 58.5, 52.7, 28.6, 18.6. MS (FAB) 292 ($M^+$+H), 264, 234. $[\alpha]_D$ −94.95 (*c* 1.0, $CHCl_3$).

### 3.7. Methyl 3-azido-2,4-dihydroxy-4-phenyl-(2*R*,3*S*,4*R*)-butanoate, 15

To the solution of the azido ester **14** (0.2 g, 0.73 mmol) in methanol (1.5 mL) was added catalytic amounts of CSA and the mixture stirred at rt for 2 h. $Et_3N$ was added to neutralize CSA and methanol removed under reduced pressure. The residue was purified by column chromatography using 40% EtOAc/pet. ether as the eluent to yield **15** (0.155 g, 0.62 mmol) in 85% yield. White solid. Mp 154–156°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.40 (m, 5H), 5.02 (d, $J$=9.8 Hz, 1H), 3.83 (bs, 1H), 3.82 (s, 3H), 3.78 (d, $J$=9.8 Hz, 1H), 3.02 (bs, 1H), 2.6 (bs, 1H). MS (FAB) 252 ($M^+$+H), 234, 154. $[\alpha]_D$ −115.2 (*c* 1.0, $CHCl_3$).

### 3.8. Methyl 3-*N*-*t*-butyloxycarbonylamino-2-hydroxy-4-phenyl-(2*R*,3*S*)-butanoate, 16

To the solution of the diol ester **15** (50 mg, 0.2 mmol) in methanol (0.8 mL) was added $Pd(OH)_2$ (10 mg, 20% by weight) and $(Boc)_2O$ (48 mg, 0.22 mmol) and stirred under hydrogen atmosphere for 12 h. The catalyst was filtered through a small pad of Celite and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography using 30% EtOAc/pet. ether as the eluent to yield **16** (50 mg, 0.16 mmol) in 80% yield. White solid. Mp 96–97°C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.30 (m, 5H), 4.70 (d, $J$=10.4 Hz, 1H), 4.20 (m, 1H), 4.0 (bs, 1H), 3.70 (s, 3H), 3.0 (d, $J$=4.5 Hz, 1H), 2.90 (m, 2H), 1.40 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 174.0, 155.2, 137.5, 129.4, 128.6, 126.6, 79.6, 70.2, 54.2, 52.8, 38.2, 28.2. MS (FAB) 310 ($M^+$+H), 254, 210. $[\alpha]_D$ −73.4 (*c* 0.25, $CHCl_3$).

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