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Synthesis of (*R*)-(+)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate, an analog of L-azatyrosine

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Abstract—A concise asymmetric synthesis of (*R*)-(+)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate **2**, a β-amino acid analog of L-azatyrosine **1** starting from the commercially available (−)-Andersen reagent (−)-**3** in good overall yield is described.
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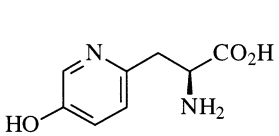
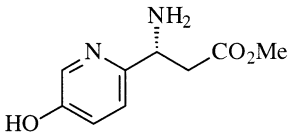
1. Introduction

L-Azatyrosine **1** is an antibiotic isolated from *Streptomyces chibanesis*[1] (Fig. 1), which attracted considerable attention recently due to its intriguing anti-tumor properties. It was shown that the pyridine-amino acid (+)-**1** restores normal phenotypic behavior to the transformed cells bearing oncogenic Ras genes[2,3] and more importantly it does not appear to affect the cells possessing normal Ras genes.[3] Additionally, the amino acid (+)-**1** has also been found to inhibit chemically induced tumor growth in mice harboring normal human c-Ha Ras genes.[4] Since the Ras proteins are important components of cellular signaling pathways and their mutated form plays a major role in cell proliferation/differentiation processes,[5] the pyridine-amino acid (+)-**1** has become an important compound in anti-cancer research.



(*S*)-(+)-**1**



(*R*)-(+)-**2**

Figure 1.

There is considerable interest in the identification of novel inhibitors of protein farnesyltransferase (FTase),[6] an enzyme which renders Ras inactive and blocks uncontrolled mitogenic signal pathway.[7] In this context, we were interested in the synthesis of a variety of analogs of L-azatyrosine **1**, particularly the non-proteinogenic β-amino acids. In this paper, we describe a concise asymmetric synthesis of (*R*)-(+)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate **2** starting from the commercially available Andersen reagent (−)-**3**.

2. Results and discussion

The basic strategy for this synthesis of (*R*)-(+)-**2** involves introduction of a β-amino acid group via addition of methyl acetate enolate to chiral sulfinamine (Scheme 1),[8] which can be prepared from the Andersen reagent (−)-**3**.[9] Our initial plan was to protect the phenolic group in (*R*)-(+)-**2** in the form of a methyl ether through the synthesis for cleavage in the final stages. Thus, the desired sulfinamine (*S*)-(+)-**6** was prepared from (−)-**3** by treatment with LiHMDS in THF,[10] followed by reaction with 5-methoxy-2-pyridinecarbaldehyde **4** in 57% yield after purification by silica gel column chromatography.

Addition of the sodium enolate of methyl acetate to the sulfinamine (*S*)-(+)-**6** in THF at −78°C proceeded smoothly, but analysis of crude product by ^{1}H NMR and HPLC indicated that the two sulfinamide

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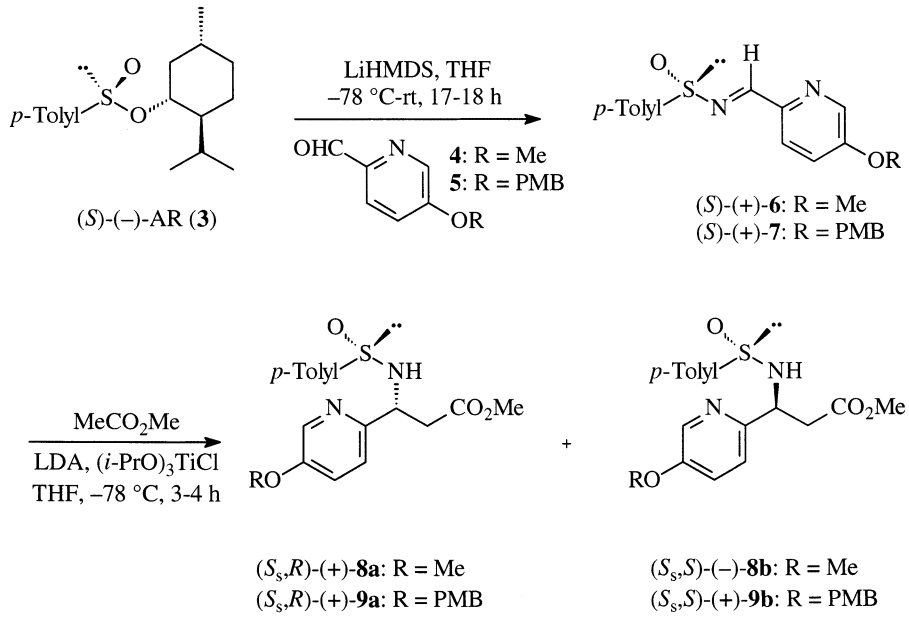
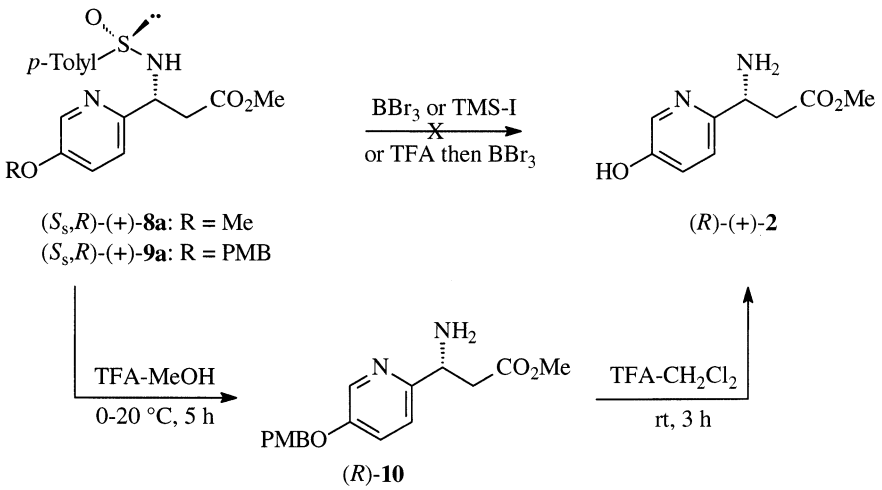


Scheme 1.

diastereomers (S_s,R)-**8a**/(S_s,S)-**8b** were present in a 52:48 ratio. Both diastereomers could be purified by preparative reversed-phase HPLC to afford (S_s,R)-(+)-**8a** in 33% and (S_s,R)-(–)-**8b** in 30% yield. It was found that addition of methyl acetate enolate to sulfinamine (*S*)-(+)-**6** under modified conditions[11] using 2.6 equivalents of chlorotitaniumtri-*iso*-propoxide in THF at –78°C improved the selectivity and afforded (S_s,R)-**8a**/(S_s,S)-**8b** in a 63:37 ratio.

With pure (S_s,R)-(+)-sulfinamide **8a** in hand, we proceeded to remove the *p*-toluenesulfinyl and methyl ether groups. Our attempts to cleave the methyl ether selectively or together with the *p*-toluenesulfinyl group in (S_s,R)-(+)-sulfinamide **8a**, using BBr_3 or TMS-I in a variety of solvents (e.g. CH_2Cl_2, MeCN, DMF) and temperatures (–78 to 50°C) were unsuccessful (Scheme 2). Under these conditions, the *p*-toluenesulfinyl group was cleaved but the methyl ether remained intact. Elimination of the amino group was observed in a reaction at higher temperature (50°C) to yield the α,β-unsaturated ester, as determined by ESI-MS analysis of the reaction mixture. These results prompted us to protect the phenol as its 4-methoxybenzyl (PMB) ether. The PMB group provides greater flexibility for cleavage and is removed cleanly by treatment with trifluoroacetic acid.[12]

Accordingly, 5-[(4-methoxybenzyl)oxy]-2-pyridinecarbaldehyde **5** was prepared from commercially available 5-hydroxy-2-methylpyridine in four steps and good overall yield. The sulfinamine (*S*)-(+)-**7** was then prepared (Scheme 1) from (–)-Andersen reagent (–)-**3** by treatment with LiHMDS in THF followed by reaction with aldehyde **5**. Addition of the enolate of methyl acetate to the sulfinamine (*S*)-(+)-**7** using chlorotitani-



Scheme 2.

umtri-*iso*-propoxide in THF at −78°C then afforded sulfinamides (S_s,*R*)-**9a**/(S_s,*S*)-**9b** in a 71:29 ratio, as determined by ^{1}H NMR and HPLC analysis of the crude product. The diastereomers were separated by preparative reversed-phase HPLC to afford the major sulfinamide isomer (S_s,*R*)-(+)-**9a** in 43% yield and the minor isomer (S_s,*R*)-(−)-**9b** in 20% yield. Treatment of (S_s,*R*)-(+)-**9a** with trifluoroacetic acid in MeOH, the conditions generally used for cleavage of sulfinyl groups, selectively cleaved the *p*-toluenesulfinyl group to afford the amine (*R*)-**10**. Subsequent treatment of the crude (*R*)-**10** with trifluoroacetic acid in CH_2Cl_2 cleaved the PMB ether. The crude product was purified by preparative reversed-phase HPLC. Lyophilization then afforded the desired β-amino ester (*R*)-(+)-(*R*)-(+)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate **2** in 76% yield. Cleavage of both *p*-toluenesulfinyl and PMB groups in (S_s,*R*)-(+)-**9a** was achieved in a single step by treatment with trifluoroacetic acid in CH_2Cl_2 at 0°C over 3 h, but the selective removal of the *p*-toluenesulfinyl group provides flexibility for derivatization of the amino group (*R*)-**10**. Finally, the enantiomeric purity of β-amino ester (*R*)-(+)-**2** was determined by converting it to the corresponding Mosher's amide by treatment with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid chloride and found to be >95% e.e.[13]

In summary, a concise asymmetric synthesis of (*R*)-(+)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate **2** was achieved starting from the readily available Andersen reagent (−)-**3** and utilizing sulfinimine chemistry.

3. Experimental

3.1. General methods and materials

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz) and the chemical shifts (δ) are reported in ppm relative to TMS. Electrospray ionization mass spectrometry (ESI-MS) was carried out on a Perkin–Elmer (Norwalk, CT) Sciex API 100 Benchtop system employing Turbo IonSpray ion source, and the HRMS were obtained on a Nermang 3010 MS-50, JEOL SX102-A. Thin layer chromatography was performed on pre-coated Whatman MK6F silica gel 60 Å plates (layer thickness: 250 μm) and visualized with UV light and/or using 0.2% ninhydrin in ethanol. Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). Anhydrous solvents were freshly distilled [THF from a purple solution of sodium and benzophenone, and CH_2Cl_2 from CaH_2] under nitrogen. All reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) or Sigma Chemical Co. (St. Louis, MO). All the solvents employed were of HPLC grade purchased from EM Science (Gibbstown, NJ). Analytical reversed-phase (RP) HPLC was performed using a Waters, Symmetry, RCM C18, 7.0 μm (8×100 mm) column. Preparative reversed-phase (RP) HPLC was performed using a Waters, Symmetry, RCM C18, 7.0 μm (40×100 mm) column. Optical rotations were measured on an Autopol III polarimeter from Rudolph Research, Flanders, NJ.

3.2. 5-Methoxy-2-pyridinecarbaldehyde 4

Aqueous sodium hydroxide (16.68 g, 0.417 mol, 4.0 equiv., dissolved in 50 mL of water), tetra-*n*-butylammonium bromide (2.01 g, 6.26 mmol, 0.06 equiv.) and dimethyl sulfate (10.84 mL, 0.114 mol, 1.1 equiv.) were added sequentially to 5-hydroxy-2-methylpyridine (11.37 g, 0.104 mmol) in CH_2Cl_2 (300 mL) at room temperature. The reaction mixture was stirred for 18 h and the resulting dark brown mixture was diluted with water (200 mL) and CH_2Cl_2 (200 mL). The organic layer was separated and washed with 25% aqueous NH_4OH (2×200 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The crude compound was purified by silica gel column chromatography (50–80% EtOAc in hexanes) to afford 5-methoxy-2-methylpyridine (2.77 g, 22%). R_f: 0.43 (60% EtOAc in hexanes); analytical RP HPLC: MeCN:0.1% aq trifluoroacetic acid/10:90, 2.0 mL/min at 225 nm, R_t: 2.29 min, >99%; ^{1}H NMR ($CDCl_3$): δ 8.19 (d, 1H, J=2.1 Hz), 7.13–7.05 (m, 2H), 3.83 (s, 3H), 2.49 (s, 3H); ESI-MS (m/z): 124 $(M)^+$.

m-Chloroperoxybenzoic acid (77% max, 8.5 g, 49.39 mmol, 1.5 equiv.) was added to a solution of 5-methoxy-2-methylpyridine (4.05 g, 32.93 mmol) in $CHCl_3$ (198 mL) at room temperature and the mixture stirred for 2.5 h. The reaction mixture was then quenched with aqueous Na_2SO_3 (6.22 g, 49.39 mmol, 1.5 equiv., in 35 mL of water) and stirred for 15 min. The mixture was diluted with $CHCl_3$ (150 mL), washed with water (75 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The resulting crude *N*-oxide (2.41 g, 17.2 mmol) in CH_2Cl_2 (86 mL) was cooled with an ice bath and trifluoroacetic anhydride (4.37 mL, 30.96 mmol, 1.8 equiv.) was added in two portions over a 5 min period. After stirring the mixture for 20 min, the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was stirred for 15 h and MeOH (33 mL) was added at room temperature. After 30 min, the mixture was concentrated on a rotary evaporator and the residue was purified by silica gel column chromatography (5% MeOH in EtOAc) to afford 2-hydroxymethyl-5-methoxypyridine as a colorless viscous oil (2.51 g). R_f: 0.10 (5% MeOH in EtOAc); analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid/5:95, 2.0 mL/min at 225 nm, R_t: 1.39 min, 87%; ^{1}H NMR ($CDCl_3$): δ 8.31 (d, 1H, J=2.7 Hz), 8.23 (br s, 1H), 7.66 (dd, 1H, J=9.0, 3.0 Hz), 7.56 (d, 1H, J=9.0 Hz), 4.87 (s, 3H), 3.97 (s, 3H); ESI-MS (m/z): 140 $(M+H)^+$, 162 $(M+Na)^+$.

MnO_2 (20.34 g, 0.234 mol, 13.0 equiv.) was added to the above prepared 2-hydroxymethyl-5-methoxypyridine (2.5 g, 17.99 mmol) in $CHCl_3$ (180 mL) at room temperature under nitrogen and the mixture was stirred for 18 h. The reaction mixture was then filtered through Celite powder and washed with $CHCl_3$

(25 mL). The filtrate was concentrated on a rotary evaporator and the residue was purified by silica gel column chromatography (45% EtOAc in hexanes) to afford 5-methoxy-2-pyridinecarboxaldehyde **4** as a colorless viscous oil (1.85 g, 75%), which solidified on standing at room temperature. R_f: 0.56 (50% EtOAc in hexanes); mp: 38–40°C; analytical RP HPLC: MeCN:0.1% aq trifluoroacetic acid/30:70, 2.0 mL/min at 225 nm, R_t: 2.44 min, >99%; ^{1}H NMR ($CDCl_3$): δ 10.00 (d, 1H, $J=0.6$ Hz), 8.44 (dd, 1H, $J=2.7$, 0.6 Hz), 7.97 (dd, 1H, $J=8.4$, 0.6 Hz), 7.31 (ddd, 1H, $J=8.7$, 2.7, 0.9 Hz), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 192.1, 159.0, 146.4, 138.5, 123.4, 120.0, 55.9; ESI-MS (m/z): 138 $(M+H)^+$; HRMS (FAB, m/z): calcd for $C_7H_8NO_2$, 138.0555 $(M+H)^+$, observed 138.0556.

3.3. 5-[(4-Methoxybenzyl)oxy]-2-pyridinecarbaldehyde 5

NaH (60% dispersion in mineral oil, 2.6 g, 65.0 mmol, 1.3 equiv.) was added to a 0°C cooled solution of 5-hydroxy-2-methylpyridine (5.45 g, 50.0 mmol) in anhydrous DMF (50 mL) in three portions under nitrogen over a period of 5 min. After stirring the mixture for 45 min, 4-methoxybenzyl chloride (8.1 mL, 60.0 mmol, 1.2 equiv.) was added via a syringe and the resultant mixture was stirred for an additional 3 h at 0°C. The reaction mixture was then quenched with MeOH (10 mL) at 0°C and diluted with EtOAc (500 mL). The mixture was washed with brine (4×100 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The crude product was purified by silica gel column chromatography (50% EtOAc in hexanes) to afford 5-[(4-methoxybenzyl)oxy]-2-methylpyridine as a colorless viscous oil (8.20 g, 72%). R_f: 0.35 (50% EtOAc in hexanes); analytical RP HPLC: MeCN:0.1% aq trifluoroacetic acid/25:75, 2.0 mL/min at 225 nm, R_t: 4.13 min, 99.3%; ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 1H, $J=2.7$ Hz), 7.38–7.32 (m, 2H), 7.15 (dd, 1H, $J=8.4$, 3.0 Hz), 7.05 (d, 1H, $J=8.7$ Hz), 5.00 (s, 2H), 3.82 (s, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.6, 152.9, 150.6, 137.1, 129.3, 128.4, 123.3, 122.5, 114.1, 70.3, 55.3, 23.4; ESI-MS (m/z): 230 $(M+H)^+$; HRMS (FAB, m/z): calcd for $C_{14}H_{16}NO_2$, 230.1181 $(M+H)^+$, observed 230.1189.

m-Chloroperoxybenzoic acid (77% max, 8.56 g, 49.78 mmol, 1.5 equiv.) was added to a solution of 5-[(4-methoxybenzyl)oxy]-2-methylpyridine (7.6 g, 33.19 mmol) in $CHCl_3$ (200 mL) at room temperature and the reaction mixture was stirred for 2 h. The mixture was then quenched with aqueous Na_2SO_3 (6.27 g, 49.78 mmol, 1.5 equiv., in 34 mL of water) and stirred for 15 min. The mixture was diluted with $CHCl_3$ (150 mL), washed with water (100 mL), 4% aqueous $NaHCO_3$ (2×80 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The resulting crude *N*-oxide (8.30 g, 33.19 mmol, white solid) was dissolved in CH_2Cl_2 (80 mL) and trifluoroacetic anhydride (9.37 mL, 66.38 mmol, 2.0 equiv.) was added at room temperature under nitrogen. After stirring the mixture for 17 h, MeOH (66 mL) was added at room temperature and stirred for an additional 15 min. The mixture was concentrated on a rotary evaporator, the residue was diluted with EtOAc (200 mL), washed with 10% aqueous $NaHCO_3$ (2×75 mL) and dried (Na_2SO_4). The solvent was removed on a rotary evaporator and the crude compound was purified by silica gel column chromatography (EtOAc to 5% MeOH in EtOAc) to afford 2-hydroxymethyl-5-[(4-methoxybenzyl)oxy]pyridine as a pale yellow solid (5.75 g). R_f: 0.51 (5% MeOH in EtOAc); mp: 94–96°C; analytical RP HPLC: MeCN:0.1% aq trifluoroacetic acid/15:85, 2.0 mL/min at 225 nm, R_t: 14.39 min, 98%; ^{1}H NMR ($CDCl_3$): δ 8.31 (d, 1H, $J=3.0$ Hz), 7.38–7.33 (m, 2H), 7.27 (dd, 1H, $J=7.8$, 2.7 Hz), 7.17 (dd, 1H, $J=8.7$, 0.6 Hz), 5.04 (s, 2H), 4.70 (s, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.7, 154.1, 151.3, 136.2, 129.3, 128.1, 122.9, 120.9, 114.1, 70.4, 64.0, 55.3; ESI-MS (m/z): 246 $(M+H)^+$; HRMS (FAB, m/z): calcd for $C_{14}H_{16}NO_3$, 246.1130 $(M+H)^+$, observed 246.1137.

MnO_2 (15.26 g, 175.6 mmol, 13.0 equiv.) was added to the above prepared 2-hydroxymethyl-5-[(4-methoxybenzyl)oxy]pyridine (3.31 g, 13.5 mmol) in $CHCl_3$ (135 mL) at room temperature under nitrogen and the mixture was stirred for 4.5 h. The reaction mixture was then filtered over Celite powder and washed with $CHCl_3$ (25 mL). The filtrate was concentrated on a rotary evaporator and the residue was purified by silica gel column chromatography (50–70% EtOAc in hexanes) to afford 5-[(4-methoxybenzyl)oxy]-2-pyridinecarbaldehyde **5** as a white solid (2.59 g, 79%). R_f: 0.63 (70% EtOAc in hexanes); mp: 73–75°C; analytical RP HPLC: MeCN:0.1% aq trifluoroacetic acid/70:30, 2.0 mL/min at 225 nm, R_t: 2.43 min, >99%; ^{1}H NMR ($CDCl_3$): δ 9.99 (d, 1H, $J=0.9$ Hz), 8.49 (d, 1H, $J=3.0$ Hz), 7.96 (d, 1H, $J=8.4$ Hz), 7.39–7.33 (m, 3H), 6.97–6.92 (m, 2H), 5.13 (s, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 192.0, 159.9, 158.2, 146.3, 139.0, 129.4, 127.1, 123.3, 121.0, 114.2, 70.5, 55.3; ESI-MS (m/z): 244 $(M+H)^+$; HRMS (FAB, m/z): calcd for $C_{14}H_{14}NO_3$, 244.0974 $(M+H)^+$, observed 244.0974.

3.4. (*S*)-(+)-*N*-[(1*E*)-(5-Methoxy-2-pyridinyl)-methylidene]-4-methylbenzenesulfinamide 6

In an oven dried 250 mL round bottom flask equipped with magnetic stir bar, nitrogen inlet and a rubber septum, (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate, Andersen's reagent (−)-**3** (3.45 g, 11.75 mmol, 1.0 equiv.) was dissolved in THF (40 mL). The mixture was cooled to −78°C (dry ice–acetone bath) and a solution of LiHMDS (1.0 M solution in THF, 15.27 mL, 15.27 mmol, 1.3 equiv.) was added dropwise via a syringe. After 15 min at −78°C, the cooling bath was removed and the mixture was allowed to warm to room temperature and stirring was continued for an additional 4 h. The reaction mixture was then cooled to −78°C, and a solution of 5-methoxy-2-pyridinecarboxaldehyde **4** (1.61 g, 11.75 mmol) in THF (20 mL) was added via a double ended needle. After stirring the mixture for 3 h, it was allowed to warm to room temperature and stirred for an additional 15 h. The reaction was cooled to −78°C and quenched with water (15 mL). The mixture was diluted with EtOAc (300 mL) and washed with water (25 mL), brine (50 mL), dried ($MgSO_4$) and the

solvent was removed on a rotary evaporator. The crude compound was purified by silica gel column chromatography (40–50% EtOAc in hexanes) to afford (*S*)-(+)-sulfinimine **6** as a pale yellow powder (1.82 g, 57%). Aldehyde **4** (0.257 g) was also recovered. R_f: 0.33 (40% EtOAc in hexanes); mp: 119–121°C; $[\alpha]_D^{23}$ +88.1 (*c* 0.99, $CHCl_3$); analytical RP HPLC: MeCN/H_2O/50:50, 2.0 mL/min at 225 nm, R_t: 5.26 min, 99.3%; ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 8.40 (d, 1H, J=2.4 Hz), 7.94 (d, 1H, J=8.7 Hz), 7.65 (d, 2H, J=8.1 Hz), 7.31 (d, 2H, J=8.1 Hz), 7.24 (dd, 1H, J=8.7, 3.0 Hz), 3.91 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.4, 157.5, 145.2, 141.8, 141.6, 138.4, 129.4, 125.1, 124.8, 120.2, 55.8, 21.4; ESI-MS (*m*/*z*): 275 $(M+H)^+$, 549 $(2\times M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{14}H_{15}N_2O_2S$, 275.0854 $(M+H)^+$, observed 275.0855.

3.5. (*S*)-(+)-*N*-((1*E*)-{5-[(4-Methoxybenzyl)oxy]-2-pyridinyl}methylidene)-4-methylbenzenesulfinamide 7

In an oven dried 250 mL round bottom flask equipped with magnetic stir bar, nitrogen inlet and a rubber septum, (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate Andersen reagent, (−)-**3** (2.83 g, 9.63 mmol, 1.0 equiv.) was dissolved in THF (30 mL). The mixture was cooled to −78°C (dry ice–acetone bath) and a solution of LiHMDS (1.0 M solution in THF, 12.52 mL, 12.52 mmol, 1.3 equiv.) was added dropwise via a syringe. After stirring the mixture for 15 min at −78°C, the cooling bath was removed and the mixture allowed to warm to room temperature and stirring was continued for an additional 4 h. The reaction mixture was then cooled to −78°C, and a solution of 5-[(4-methoxybenzyl)oxy]-2-pyridinecarbaldehyde **5** (2.34 g, 9.63 mmol, 1.0 equiv.) in THF (20 mL) was added via a double ended needle. After stirring the mixture for 3 h, it was allowed to warm to room temperature and stirred for an additional 13 h. The reaction was then cooled to −78°C and quenched with water (10 mL). The mixture was diluted with EtOAc (250 mL) and water (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with brine (2×75 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The crude compound was purified by silica gel column chromatography (30–40% EtOAc in hexanes) to afford (*S*)-(+)-sulfinimine **7** as a pale yellow powder (0.805 g, 22%). Aldehyde **5** (1.45 g) was recovered and the yield of (*S*)-(+)-**7** based on the recovered starting material **5b** was 58%. R_f: 0.56 (40% EtOAc in hexanes); mp: 114–116°C; $[\alpha]_D^{23}$ = +42.3 (*c* 0.97, $CHCl_3$); analytical RP HPLC: MeCN/H_2O/70:30, 2.0 mL/min at 225 nm, rt: 4.03 min, 97.1%; ^{1}H NMR ($CDCl_3$): δ 8.75 (s, 1H), 8.45 (d, 1H, J=2.4 Hz), 7.91 (d, 1H, J=8.4 Hz), 7.66–7.62 (m, 2H), 7.37–7.27 (m, 5H), 6.95–6.90 (m, 2H), 5.09 (s, 2H), 3.82 (s, 3H), 2.39 (s, 3H); ^{13}C ($CDCl_3$) δ 160.3, 159.9, 156.8, 145.2, 141.8, 141.6, 139.0, 129.9, 129.4, 127.3, 125.1, 124.8, 121.3, 114.2, 70.4, 55.3, 21.4; ESI-MS (*m*/*z*): 381 $(M+H)^+$, 761 $(2\times M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{21}H_{21}N_2O_3S$, 381.1273 $(M+H)^+$, observed 381.1280.

3.6. (S_s,*R*)-(+)-Methyl 3-(5-methoxy-2-pyridinyl)-3-{[(4-methylphenyl)sulfinyl]amino}propanoate 8a

In an oven dried 50 mL round bottom flask equipped with magnetic stir bar, nitrogen inlet and a rubber septum, THF (30 mL) and methyl acetate (0.357 mL, 4.5 mmol, 1.5 equiv.) were placed. The mixture was cooled to −78°C (dry ice–acetone bath) and a solution of NaHMDS (1.0 M in THF, 4.5 mL, 4.5 mmol, 1.5 equiv.) was added and the mixture was stirred for 40 min. To the resulting sodium enolate, a solution of (*S*)-(+)-*N*-[(1*E*)-(5-methoxy-2-pyridinyl)methylidene]-4-methylbenzenesulfinamide **6** (0.822 g, 3.0 mmol) in THF (20 mL) was added at −78°C via a double ended needle. The reaction mixture was stirred for 5 h, quenched with a sat. NH_4Cl solution (6 mL) at −78°C and the mixture was allowed to warm to room temperature. The mixture was diluted with EtOAc (300 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The crude product [diastereomeric ratio of (S_s,*R*)/(S_s,*S*)-methyl 3-(5-methoxy-2-pyridinyl)-3-{[(4-methylphenyl)-sulfinyl]amino}propanoate **8a** and **8b**: 52:48] was purified by silica gel column chromatography (50–80% EtOAc in hexanes) to afford 0.82 g of material, which was dissolved in MeCN–water (1:1 ratio, 40 mL) and separated by preparative reversed-phase HPLC (MeCN:H_2O/25:75, 45 mL/min at 225 nm). The compound was collected, concentrated on a rotary evaporator (bath temperature: 40°C) to about 150 mL volume and lyophilized to afford (S_s,*R*)-(+)-methyl 3-(5-methoxy-2-pyridinyl-3-{[(4-methylphenyl)-sulfinyl]amino}propanoate **8a** as a colorless viscous oil (0.347 g, 33%). R_f: 0.45 (80% EtOAc in hexanes); $[\alpha]_D^{23}$ = +235.8 (*c* 0.38, MeOH); analytical RP HPLC: MeCN:H_2O/30:70, 2.0 mL/min at 225 nm, R_t: 16.84 min, 97.8%; ^{1}H NMR ($CDCl_3$): δ 8.21 (d, 1H, J=2.4 Hz), 7.64–7.59 (m, 2H), 7.39–7.29 (m, 3H), 7.17 (dd, 1H, J=8.4, 3.0 Hz), 5.46 (d, 1H, J=8.7 Hz), 4.83–4.75 (m, 1H), 3.84 (s, 3H), 3.54 (s, 3H), 2.93–2.77 (m, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.5, 154.8, 152.0, 141.5, 141.4, 136.7, 129.6, 125.8, 122.6, 121.1, 55.6, 53.4, 51.6, 41.0, 21.4; ESI-MS (*m*/*z*): 349 $(M+H)^+$, 697 $(2\times M+H)^+$, 719 $(2\times M+Na)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{17}H_{21}N_2SO_4$, 349.1222 $(M+H)^+$, observed 349.1233.

The minor isomer (S_s,*S*)-(−)-methyl 3-(5-methoxy-2-pyridinyl)-3-{[(4-methylphenylsulfinyl]amino}propanoate **8b** was also obtained as a colorless viscous oil (0.315 g, 30%). R_f: 0.45 (80% EtOAc in hexanes); $[\alpha]_D^{23}$ = −15.6 (*c* 0.36, MeOH); analytical RP HPLC: MeCN:H_2O/30:70, 2.0 mL/min at 225 nm, R_t: 14.27 min, >99%; ^{1}H NMR ($CDCl_3$): δ 8.16 (dd, 1H, J= 3.0, 0.6 Hz), 7.58–7.53 (m, 2H), 7.28–7.23 (m, 2H), 7.16 (d, 1H, J=8.4 Hz), 7.09 (dd, 1H, J=8.7, 2.7 Hz), 5.39 (d, 1H, J=9.3 Hz), 4.84–4.76 (m, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.17–2.99 (m, 2H), 2.40 (s, 3H);

^{13}C NMR ($CDCl_3$): δ 171.8, 154.8, 151.6, 141.5, 141.3, 136.7, 129.5, 125.9, 122.2, 121.0, 55.6, 54.5, 51.7, 41.7, 21.3; ESI-MS (m/z): 349 $(M+H)^+$, 697 $(2\times M+H)^+$, 719 $(2\times M+Na)^+$; HRMS (FAB, m/z): calcd for $C_{17}H_{21}N_2SO_4$, 349.1222 $(M+H)^+$, observed 349.1213.

3.7. Preparation of (S_s,*R*)-(+)-methyl 3-(5-methoxy-2-pyridinyl)-3-{[(4-methylphenyl)sulfinyl]amino}propanoate using chlorotitaniumtri-*iso*-propoxide 8a

In an oven dried 50 mL round bottom flask equipped with magnetic stir bar, nitrogen inlet and a rubber septum, a mixture of lithium di-*iso*-propylamide mono(tetrahydrofuran) (1.5 M soln in cyclohexane, 1.67 mL, 2.5 mmol, 1.25 equiv.) and THF (5 mL) was cooled to −78°C (dry ice–acetone bath). Methyl acetate (0.190 mL, 2.4 mmol, 1.2 equiv.) was added and the mixture was stirred for 30 min. A solution of chlorotitaniumtri-*iso*-propoxide (1.23 mL, 5.2 mmol, 2.6 equiv.) in THF (3 mL) was added to the lithium enolate solution using a double ended needle at −78°C. The resulting dark lemon yellow solution was stirred for 45 min and a solution of (*S*)-(+)-sulfinimine **6** (0.548 g, 2.0 mmol) in THF (3 mL) was added via a double ended needle. The reaction mixture was stirred for an additional 3 h at −78°C, quenched with a sat. NH_4Cl solution (4 mL) at −78°C and the mixture was allowed to warm to room temperature. The mixture was diluted with EtOAc (150 mL) and water (150 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2×150 mL). The combined organic layers were washed with water (50 mL) brine (2×50 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The crude product [diastereomeric ratio of (S_s,*R*)/(S_s,*S*)-methyl 3-(5-methoxy-2-pyridinyl)-3-{[(4-methylphenyl)sulfinyl]amino}propanoate **8a** and **8b**: 63:37] was purified by silica gel column chromatography (50–80% EtOAc in hexanes) to afford a mixture of (S_s,*R*)/(S_s,*S*)-methyl 3-(5-methoxy-2-pyridinyl)-3-{[(4-methylphenyl)sulfinyl]amino}-propanoate **8a** and **8b** (0.616 g, 89%). R_f: 0.45 (80% EtOAc in hexanes); analytical RP HPLC: MeCN:H_2O/30:70, 2.0 mL/min at 225 nm, R_t: 16.84 min, 68% and 14.12 min, 32%.

3.8. (S_s,*R*)-(+)-Methyl 3-{5-[(4-methoxybenzyl)oxy]-2-pyridinyl}-3-{[(4-methylphenyl)sulfinyl]amino}propanoate 9a

In an oven dried 50 mL round bottom flask equipped with magnetic stir bar, nitrogen inlet and a rubber septum, a mixture of lithium di-*iso*-propylamide mono(tetrahydrofuran) (1.5 M soln in cyclohexane, 1.34 mL, 2.01 mmol, 1.25 equiv.) and THF (5 mL) was cooled to −78°C (dry ice–acetone bath). Methyl acetate (0.153 mL, 1.932 mmol, 1.2 equiv.) was added and the mixture was stirred for 35 min. A solution of chlorotitaniumtri-*iso*-propoxide (0.997 mL, 4.19 mmol, 2.6 equiv.) in THF (3 mL) was added to the lithium enolate solution at −78°C using a double ended needle. The resulting lemon yellow solution was stirred for 45 min and a solution of (*S*)-(+)-*N*-((1*E*)-{5-[(4-methoxybenzyl)oxy]-2-pyridinyl}methylidene)-4-methylbenzenesulfinamide **7** (0.610 g, 1.61 mmol) in THF (4 mL) was added via a double ended needle. The reaction mixture was stirred for an additional 3.5 h at −78°C, quenched with a sat. NH_4Cl solution (4 mL) at −78°C and the mixture was allowed to warm to room temperature. The mixture was diluted with EtOAc (200 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine (2×75 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The crude product [diastereomeric ratio of (S_s,*R*)/(S_s,*S*)-methyl 3-{5-[(4-methoxybenzyl)oxy]-2-pyridinyl}-3-{[(4-methylphenyl)-sulfinyl]amino}propanoate **9a** and **9b**: 71:29] was purified by silica gel column chromatography (40–70% EtOAc in hexanes) to afford a mixture of (S_s,*R*)/(S_s,*S*)-methyl 3-{5-[(4-methoxybenzyl)oxy]-2-pyridinyl}-3-{[(4-methylphenyl)sulfinyl]amino}propanoate **9a** and **9b**, (0.505 g), which was dissolved in MeCN–water (1:1 ratio, 25 mL) and separated by preparative reversed-phase HPLC (MeCN:H_2O/25:75, 45 mL/min at 225 nm). The compound was collected, concentrated on a rotary evaporator (bath temperature: 40°C) to about 150 mL volume and lyophilized to afford (S_s,*R*)-(+)-methyl 3-{5-[(4-methoxybenzyl)oxy]-2-pyridinyl}-3-{[(4-methylphenyl)sulfinyl]amino}propanoate **9a** as a colorless viscous oil (0.310 g, 43%). R_f: 0.29 (50% EtOAc in hexanes); $[\alpha]_D^{23}=+165.6$ (*c* 0.61, $CHCl_3$); analytical RP HPLC: MeCN:H_2O/45:55, 2.0 mL/min at 225 nm, R_t: 15.10 min, 99.3%; ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 1H, $J=2.4$ Hz), 7.64–7.59 (m, 2H), 7.39–7.29 (m, 5H), 7.22 (dd, 1H, $J=8.4$, 2.7 Hz), 6.96–6.90 (m, 2H), 5.46 (d, 1H, $J=8.7$ Hz), 5.01 (s, 2H), 4.82–4.75 (m, 1H), 3.82 (s, 3H), 3.54 (s, 3H), 2.93–2.77 (m, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.5, 159.7, 154.1, 152.1, 141.5, 141.4, 137.3, 129.6, 129.4, 128.1, 125.8, 122.6, 122.2, 114.1, 70.2, 55.3, 53.4, 51.6, 41.0, 21.4; ESI-MS (m/z): 455 $(M+H)^+$, 477 $(M+Na)^+$, 909 $(2\times M+H)^+$, 931 $(2\times M+Na)^+$; HRMS (FAB, m/z): calcd for $C_{24}H_{27}N_2SO_5$, 455.1641 $(M+H)^+$, observed 455.1645.

(S_s,*S*)-(+)-Methyl 3-{5-[(4-methoxybenzyl)oxy]-2-pyridinyl}-3-{[(4-methylphenyl)sulfinyl]amino}propanoate **9b** was isolated as a colorless viscous oil (0.157 g, 20%). R_f: 0.29 (50% EtOAc in hexanes); $[\alpha]_D^{23}=+4.3$ (*c* 0.3, $CHCl_3$); analytical RP HPLC: MeCN:H_2O/45:55, 2.0 mL/min at 225 nm, R_t: 13.01 min, >99%; ^{1}H NMR ($CDCl_3$): δ 8.22 (dd, 1H, $J=2.1$ Hz), 7.57–7.53 (m, 2H), 7.37–7.28 (m, 5H), 7.15 (d, 1H, $J=1.5$ Hz), 6.95–6.90 (m, 2H), 5.39 (d, 1H, $J=9.3$ Hz), 4.98 (s, 2H), 4.83–4.76 (m, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 3.16–2.99 (m, 2H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.8, 159.7, 154.1, 151.7, 141.5, 141.3, 137.4, 129.5, 129.3, 128.1, 125.9, 122.2, 122.1, 114.1, 70.2, 55.3, 54.6, 51.7, 41.7, 21.3; ESI-MS (m/z): 455 $(M+H)^+$, 477 $(M+Na)^+$, 909 $(2\times M+H)^+$, 931 $(2\times M+Na)^+$; HRMS (FAB, m/z): calcd for $C_{24}H_{27}N_2SO_5$, 455.1641 $(M+H)^+$, observed 455.1629.

3.9. (*R*)-(+)-Methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate 2

Trifluoroacetic acid (0.25 mL, 3.22 mmol, 5.0 equiv.) was added to a 0°C cooled solution of (S_s,*R*)-(+)-methyl 3-{5-[(4-methoxybenzyl)oxy]-2-pyridinyl}-3-{[(4-methylphenyl)sulfinyl]amino}propanoate **9a** (0.292 g, 0.643 mmol) and methanol (13 mL) under nitrogen and the mixture was stirred for 5 h. After completion of the reaction, as determined by TLC (60% EtOAc in hexanes), the solvent was removed on a rotary evaporator at <35°C bath temperature. The residue was dissolved in water (20 mL) and ether (20 mL). The aqueous layer was separated and the organic layer was extracted with water (15 mL). The combined aqueous layer was washed with ether (2×20 mL) and concentrated on a rotary evaporator. The residue was dried under vacuum (0.1 mmHg) over 15 h to afford PMB ether (*R*)-methyl 3-amino-3-{5-[(4-methoxybenzyl)oxy]-2-pyridinyl}propanoate **10** (0.271 g) along with small amounts of (*R*)-(+)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate **2**. Analytical RP HPLC: MeCN:0.1% aqueous trifluoroacetic acid/30:70, 2.0 mL/min at 225 nm, R_t: 4.13 min, 86%, (*R*)-**10** and 1.29 min, 14% (*R*)-(+)-**2**; ESI-MS (*m*/*z*): 377 $(M+H)^+$, 633 $(2\times M+H)^+$. The crude mixture of (*R*)-**10** and (*R*)-(+)-**2** was dissolved in CH_2Cl_2 (13 mL), and trifluoroacetic acid (0.99 mL, 12.86 mmol, 20.0 equiv.) was added at room temperature under nitrogen. The mixture was stirred for 3 h and the resulting violet solution was concentrated on a rotary evaporator. The colorless residue was dissolved in MeCN–0.1% aq TFA (8:2 ratio, 30 mL) and purified by preparative RP HPLC using MeCN:0.1% aqueous trifluoroacetic acid/15:85, 45 mL/min at 225 nm. Lyophilization of the product afforded of (*R*)-(+)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate **2** as its TFA salt (0.195 g, >95%). $[\alpha]_D^{23}=+3.4$ (*c* 0.62, MeOH); analytical RP HPLC: MeCN:0.1% aq TFA/5:95, 2.0 mL/min at 225 nm, R_t: 6.10 min, >99%; ^{1}H NMR (CD_3OD): δ 8.18 (d, 1H, $J=2.7$ Hz), 7.30 (d, 1H, $J=8.4$ Hz), 7.20 (dd, 1H, $J=8.4$, 3.3 Hz), 4.75–4.70 (m, 1H), 3.70 (s, 3H), 3.08–2.93 (m, 2H); ^{13}C NMR (CD_3OD): δ 171.8, 155.8, 146.2, 139.1, 124.4, 124.2, 52.7, 52.3, 38.7; ESI-MS (*m*/*z*): 197 $(M+H)^+$, 219 $(M+Na)^+$, 393 $(2\times M+H)^+$, 415 $(2\times M+Na)^+$; HRMS (FAB, *m*/*z*): calcd for $C_9H_{13}N_2O_3$, 197.0926 $(M+H)^+$, observed 197.0927.

3.10. Preparation of Mosher's amide of (*R*)-(+)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate 2

In an oven dried 10 mL round bottom flask equipped with magnetic stir bar, nitrogen inlet and a rubber septum, (*R*)-(+)-methyl 3-amino-3-(5-hydroxy-2-pyridinyl)propanoate **2** (0.031 g, 0.01 mmol) was dissolved in anhydrous CH_2Cl_2 (1.5 mL). Triethylamine (0.140 mL, 1.0 mmol, 10.0 equiv.) and (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (MTP-Cl, 0.018 mL, 0.1 mmol, 1.0 equiv.) were added sequentially at room temperature and the mixture was stirred for 2 h. The mixture was quenched with ice and stirred for an additional 10 min, then diluted with CH_2Cl_2 (50 mL) and water (15 mL). The organic layer was separated, dried ($MgSO_4$) and the solvent removed on a rotary evaporator with the bath temperature kept below 35°C. The crude product was purified by silica gel column chromatography (40–60% EtOAc in hexanes) to afford the Mosher's amide of (*R*)-(+)-β-amino ester **2** as a colorless gummy material (0.022 g 65%). R_f: 0.41 (60% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 1H, $J=8.1$ Hz), 8.08 (d, 1H, $J=2.7$ Hz), 7.57–7.41 (m, 5H), 7.15 (d, 1H, $J=8.4$ Hz), 6.97 (dd, 1H, $J=8.4$, 3.0 Hz), 5.47–5.40 (m, 1H), 3.58 (s, 3H), 3.36–3.35 (m, 3H), 3.04–2.83 (m, 2H); ^{19}F NMR ($CDCl_3$ and 2.0 μL of α,α,α-trifluorotoluene): δ −5.98 (s, CF_3); ESI-MS (*m*/*z*): 413 $(M+H)^+$, 825 $(2\times M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{19}H_{20}N_2O_5F_3$, 413.1324, observed 413.1327.

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