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Asymmetric synthesis of β-amino acids through application of chiral sulfoxide

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Abstract—This paper describes asymmetric synthesis of β-aminophenylpropionic acid through application of a homochiral sulfoxide auxiliary. High kinetically controlled ($3R,2S,R_S$)-diastereoselectivity (−60°C) is achieved during addition of the lithium enolate of *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate to substituted *N*-(benzylidene)toluene-4-sulfonamides **2a**–**2d**. The reductive cleavage of adduct **3a** with sodium amalgam yielded *tert*-butyl 3-(toluene-4-sulfonamido)-3-phenylpropionate **5a**, which was subjected to ester hydrolysis and subsequent detosylation with sodium in liquid ammonia to yield (*S*)-β-aminophenylpropionic acid in good yield and high 91% e.e.

1. Introduction

Peptides containing β-amino acids have recently attracted considerable interest due to their interesting structural and important pharmacological properties. In particular, most β-amino acids themselves exhibit powerful antibacterial properties and are key constituents of many naturally occurring peptides, terpenes, alkaloids, macrolide and β-lactam antibiotics.[1,2] Moreover, there has been a recent surge of research activity in the taxol related terpenoids containing the (2*R*,3*S*)-β-amino-α-hydroxyphenylpropionic acid side chain, which is known to be crucial to their anti-cancer activity.[3]

In view of the potential biological applications of β-amino acids, their synthesis in enantiomerically pure form is necessary and considerable effort has been expended to design stereocontrolled methods for their synthesis. However, only few reports describe satisfactory methods for the asymmetric synthesis of β-amino acids. They include the Michael addition of chiral amines to cinnamate esters,[4,5] the addition of methyl acetate lithium enolates to chiral sulfinimines,[6] the biocatalytic reduction of β-amino-α-keto-phenylpropionates[7] and the biocatalytic preparation of enantiomerically pure β-aryl-β-alanines via resolution of their racemic *N*-phenylacetyl derivatives by penicillin acylase (EC 3.5.1.11) from *Escherichia coli* ATCC 9631.[8]

Application of the chiral sulfoxide group as a chiral auxiliary provides unique synthetic benefits associated with its manifold reactivity. The use of chiral sulfoxide stabilized carbanions for asymmetric carbon–carbon bond formation via alkylation, or addition to carbonyl and activated C=C double bonds has been extensively studied over the past two decades.[9] In contrast, there are few reports on chiral sulfoxide anion addition to imines. One example of this type of reaction is the asymmetric synthesis of α-arylglycinols via the addition of lithium *p*-tolylsulfoxide to N-(PMP) arylaldimines, followed by 'non-oxidative' Pummerer rearrangement.[10] This led us to examine the condensation of *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate to various sulfonylimines. We report herein our efforts towards the synthesis of chiral β-amino-β-phenylpropionic acid derivatives.

2. Results and discussion

An elegant synthesis of β-amino acids has been achieved by the condensation of *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate with *N*-sulfonylimines at −60°C in the presence of LDA in THF. The requisite *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate **1** was synthesized by nucleophilic displacement of (*S*)-aryl-menthyl-sulfinate using Anderson's method.[11]

The sulfonylimines **2a**–**2d** were synthesized in good yields from direct condensation of aromatic aldehyde and *p*-toluene-sulfonamide in the presence of acidic amberlite IR-120 resin and 4 Å molecular sieve in

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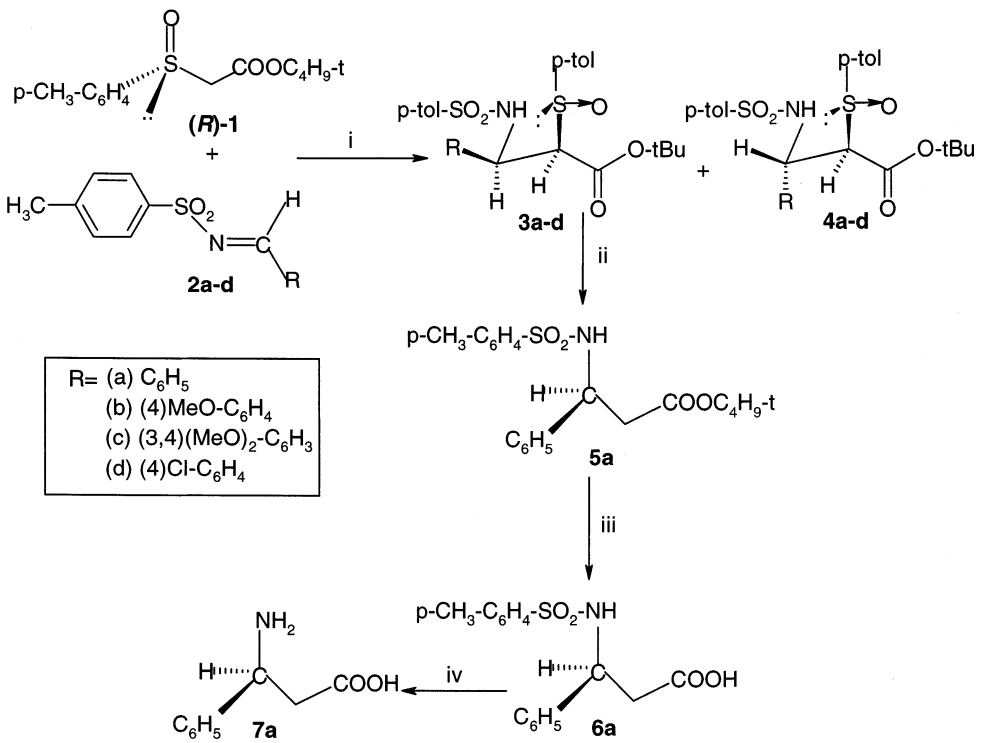
toluene at 120°C with azeotropic removal of water.[12] Addition of the lithium enolate of *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate (1.97 mmol scale) generated with 1.2 equivalents of LDA at −60°C to the imines **2a**–**2d** (2.16 mmol) in THF under kinetic conditions afforded the *syn* (3*R*,2*S*,R_S)-adducts **3a**–**3d**, with the minor *anti* (3*S*,2*S*,R_S)-diastereoisomer **4a**–**4d**. Total yields for the reaction ranged from 68 to 95% (Scheme 1).

The structure and stereochemistry of the adducts **3a**–**3d** were assigned based on ^{1}H NMR spectral data. The coupling constant (*J*) of the H_α and H_β protons of the adducts **3a**–**3d** ranges from 5.12 to 5.49 Hz, which indicated the *syn* stereochemistry of the (3*R*,2*S*,R_S)-configuration. The specific rotation $[\alpha]_D^{20}$ and ^{1}H NMR coupling constant values of the adducts **3a**–**3d** are given in Table 1. The diastereomeric excess (d.e.) of compounds **3a**–**3d** was evaluated by chiral HPLC (Chiracel® OD analytical column) with hexane/propan-2-ol (ratio 4:1) as the mobile phase.

To improve the yield of the *anti* diastereoisomer **4a** the reaction of *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate and the imine **2a** was repeated at −20°C. As expected, this reaction yielded **3a** and the *anti* diastereoisomer **4a** in a 7:3 ratio (82% combined yield). The latter compound was isolated by column chromatography over silica. The stereochemistry of compound **4a** was assigned by the ^{1}H NMR coupling constant of the H_α and H_β protons ($J_{\alpha,\beta}=10$ Hz).

Formation of the *syn* isomer, (3*R*,2*S*,R_S)-**3a**, as the major diastereoisomer can be rationalized by the Zimmerman–Traxler transition state model,[13,14] which involves attack of the stable lithium (*Z*)-enolate of *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate on the *Si* face of the *N*-sulfonylimine leading to a cyclic transition state wherein Li^+ chelation between sulfoxide and enolate oxygens and sulfonylimine nitrogen forms a six-membered chair conformation (Fig. 1a). Attack on the *Re* face of the *N*-sulfonylimine leads to the *anti* (3*S*,2*S*,R_S)-diastereoisomer (Fig. 1b). Here the 1,3-diaxial repulsions of R/*tert*-BuO and *p*-tol-SO/*p*-tol-SO_2 disfavor formation of the *anti* diastereoisomer.



Scheme 1. Synthesis of enantioselective (*S*)-β-amino-β-phenylpropionic acid from *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate and *N*-(benzylidine)toluene-4-sulfonamides **2a**–**2d**. Keys: (i) LDA, THF, −60°C; (ii) Na/Hg, Na_2HPO_4, 0°C to rt; (iii) KOH, ethanol, 60°C; (iv) Na/liq. NH_3, 3 h reflux.

Table 1. ^{1}H NMR coupling constants, yields and specific rotations of compounds **3a**–**3d**

S. No.	R	Yield (%)	D.e. (%)[a]	$[\alpha]_D^{20}$ (*c* 1.00, acetone)	δ H_α	δ H_β	$J_{\alpha,\beta}$ (Hz)
3a	C_6H_5	95	91.52	80.99	3.57	4.70	5.12
3b	4-MeO-C_6H_4	79	88.45	63.49	3.53	4.64	5.13
3c	3,4-di MeO-C_6H_3	68	92.72	96.49	3.56	4.71	5.49
3d	4-Cl-C_6H_4	81	88.78	120.99	3.51	4.65	5.13

[a] D.e. was measured by chiral HPLC (Chiracel® OD analytical column).

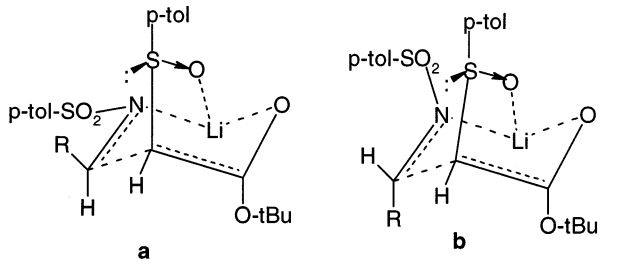


Figure 1. Chelated cyclic transition state for the formation of diastereoisomer **3a**–**3d** with configuration ($3R,2S,R_S$) and **4a**–**4d** with configuration ($3S,2S,R_S$).

Compound **3a** was subjected to reductive cleavage of the sulfoxide moiety by treatment with Na/Hg in dry methanol to give **5a** in 95% yield {$[\alpha]_D^{20}=-14.0$ ($c=1.0$, acetone)}. Basic hydrolysis of **5a** yielded acid **6a** which on subsequent detosylation with Na in liquid ammonia, followed by purification over ion exchange chromatography gave (*S*)-β-amino-β-phenylpropionic acid **7a** with an e.e. of 91% {$[\alpha]_D^{20}=-6.9$ (*c* 1.0, H_2O), lit.[15] $[\alpha]_D^{25}=-7.5\pm1$ (*c* 1.0, H_2O)}.

3. Conclusion

In summary, we have developed an efficient method for the enantioselective synthesis of β-amino-β-phenylpropionic acid. High kinetically controlled ($3R,2S,R_s$)-diastereoselectivity was observed during addition of the lithium enolate of *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate to substituted *N*-sulfonylimines **2a**–**2d**. The final compound **7a** was obtained with 91% e.e.

4. Experimental

4.1. General methods

All solvents were purified by standard procedures. IR spectra were run on a Perkin–Elmer model 681 spectrometer. ^{1}H NMR spectra were recorded on a Varian (300 MHz) spectrometer in $CDCl_3$ and D_2O with TMS as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field and coupling constants (J) are expressed in Hertz (Hz). Optical rotations were measured using a Jasco DIP-370 digital polarimeter. Microanalyses were performed using a Carlo Erba Model 1106 elemental analyzer. Melting points are uncorrected and were obtained on a capillary apparatus. Silica gel (100–200 mesh) used for column chromatography was activated by heating at 120°C for 4 h.

4.2. General procedure for the preparation of *N*-(benzylidene)toluene-4-sulfonamides 2a–2d

A solution of the aldehyde (17 mmol) in toluene (70 mL) was placed in a round bottomed flask equipped with a Dean Stark assembly. *p*-Toluenesulfonamide (3.25 g, 19 mmol), amberlite H^+ resin IR-120 (2 g) and powdered molecular sieves (4 Å, 2 g) were added to the reaction flask and the mixture was stirred at 120°C for 12 h, with azeotropic removal of water. After the reaction was complete (based upon the theoretical amount of water removal, and monitoring reaction by TLC), the mixture was allowed to cool at room temperature and filtered. The solvent was removed in vacuo and the product was purified by crystallization from *n*-hexane. Imines **2a**–**2d** are solids, recrystallized from ethyl acetate, hexane solvents. Quantitative yields were obtained.

4.3. General method for condensation of the lithium enolate of *tert*-butyl (+)-(*R*)-*p*-toluene sulfinylacetate with *N*-(benzylidene)toluene-4-sulfonamides

A solution of *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate (0.5 g, 1.97 mmol) in dry THF (2 mL) was added dropwise with stirring to a solution of LDA (2.36 mmol) in THF (10 mL) at −60°C. After 15 min, a solution of the *N*-(benzylidene)toluene-4-sulfonamide (2.16 mmol) **2a**–**2d** in THF (3 mL) was added to the reaction mixture and stirring was continued for a further 15 min. The reaction was quenched with saturated aqueous NH_4Cl, and the solvent was removed in vacuo. The residue was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent was evaporated in vacuo to give a white residue, which was further purified by column chromatography over silica gel (100–200 mesh). Elution with petroleum ether/ethyl acetate (7:3) yielded the adducts **3a**–**3d**, respectively.

4.3.1. Compound 3a. White solid, mp 172–174°C; $[\alpha]_D^{20}=+81.0$ (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (s, 6H), 1.60 (s, 3H), 2.31 (s, 3H), 2.43 (s, 3H), 3.57 (d, $J=5.12$ Hz, 1H), 4.70 (dd, $J=5.12$, 8.4 Hz, 1H), 6.62 (d, $J=8.4$ Hz, 1H), 6.89 (d, $J=8.05$ Hz, 2H), 7.15–7.02 (m, 5H), 7.36 (d, $J=8.40$ Hz, 2H), 7.46 (d, $J=8.05$ Hz, 2H), 7.58 (d, $J=8.05$ Hz, 2H). IR (KBr): 3230, 2934, 1736, 1710, 1341, 1163 cm^{-1}. Anal. calcd for $C_{27}H_{31}NO_5S_2$: C, 63.13; H, 6.08; N, 2.72. Found: C, 62.89; H, 6.04; N, 2.46%.

4.3.2. Compound 4a. White solid, mp 193–195°C; $[\alpha]_D^{20}=+121.0$ (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.08 (s, 9H), 2.34 (s, 3H), 2.46 (s, 3H), 3.89 (d, $J=10$ Hz, 1H), 4.98 (dd, $J=10$, 6 Hz, 1H), 6.44 (d, $J=6$ Hz, 1H), 7.03 (d, $J=8$ Hz, 2H), 7.07–7.13 (m, 5H), 7.34 (d, $J=8$ Hz, 2H), 7.42 (d, $J=8$ Hz, 2H), 7.53 (d, $J=8$ Hz, 2H). IR (KBr): 3236, 2934, 1716, 1611, 1347, 1150 cm^{-1}. Anal. calcd for $C_{27}H_{31}NO_5S_2$: C, 63.13; H, 6.08; N, 2.72. Found: C, 63.10; H, 6.06; N, 2.70%.

4.3.3. Compound 3b. White solid, mp 154–156°C; $[\alpha]_D^{20}=+63.50$ (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 9H), 2.32 (s, 3H), 2.44 (s, 3H), 3.53 (d, $J=5.12$ Hz, 1H), 3.71 (s, 3H), 4.63–4.66 (m, 1H), 6.48 (d, $J=8.79$ Hz, 1H), 6.81 (d, $J=8.42$ Hz, 2H), 7.06 (d, $J=8.05$ Hz, 2H), 7.35 (d, $J=7.68$ Hz, 2H), 7.46 (d, $J=8.05$ Hz, 2H), 7.58 (d, $J=8.42$ Hz, 2H). IR (KBr): 3361, 3262, 2933, 1723, 1618, 1308, 1163 cm^{-1}. Anal. calcd for $C_{28}H_{33}NO_6S_2$: C, 61.85; H, 6.12; N, 2.57. Found: C, 61.84; H, 6.14; N, 2.55%.

4.3.4. Compound 3c. White solid, mp 158–160°C; $[\alpha]_D^{20}=+96.50$ (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 9H), 2.31 (s, 3H), 2.44 (s, 3H), 3.56 (d, $J=5.49$ Hz, 1H), 3.6 (s, 3H), 3.8 (s, 3H), 4.7 (m, 1H), 6.35–6.48 (m, 3H), 6.59 (d, $J=8.24$ Hz, 1H), 7.04 (d, $J=8.05$ Hz, 2H), 7.36 (d, $J=8.05$ Hz, 2H), 7.44 (d, $J=8.24$ Hz, 2H), 7.60 (d, $J=8.24$ Hz, 2H). IR (KBr): 3247, 2927, 1729, 1611, 1341, 1268, 1156 cm^{-1}. Anal. calcd for $C_{29}H_{35}NO_7S_2$: C, 60.71; H, 6.14; N, 2.44. Found: C, 60.68; H, 6.12; N, 2.40%.

4.3.5. Compound 3d. White solid, mp 120–122°C; $[\alpha]_D^{20}=+121.0$ (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (s, 9H), 2.35 (s, 3H), 2.44 (s, 3H), 3.51 (d, $J=5.12$ Hz, 1H), 4.65 (m, 1H), 6.60 (d, $J=8.42$ Hz, 1H), 6.85 (d, $J=8.42$ Hz, 2H), 7.03–7.05 (m, 4H), 7.36 (d, $J=8.06$ Hz, 2H), 7.46 (d, $J=8.06$ Hz, 2H), 7.58 (d, $J=8.42$ Hz, 2H). IR (KBr): 3357, 3259, 2922, 1722, 1596, 1341, 1164 cm^{-1}. Anal. calcd for $C_{27}H_{30}NO_5S_2Cl$: C, 59.16; H, 5.51; N, 2.55. Found: C, 58.94; H, 5.48; N, 2.34%.

4.4. Preparation of *tert*-butyl 3-(4-toluenesulfonamido)-3-phenylpropanoate 5a

To a mixture of adduct **3a** (500 mg, 0.974 mmol) and anhydrous disodium hydrogen phosphate (550 mg, 3.89 mmol) in dry methanol (30 mL) at 0°C was added pulverized sodium amalgam (2 g). The solution was stirred for 20 min at 0°C and the mixture was allowed to warm to room temperature. Stirring was continued for another 0.5 h and the reaction mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by chromatography over silica gel (100–200 mesh), elution with ethyl acetate/petroleum ether (1:9), yielded *tert*-butyl 3-(4-tolenesulfonamido)-3-phenylpropanoate **5a** as a white crystalline solid (348 mg, 95%), mp 104–106°C; $[\alpha]_D^{20}=-14.0$ (*c* 1.00, acetone); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 9H), 2.36 (s, 3H), 2.62 (dd, $J=15.8$, 6.6 Hz, 1H, 1/2CH_2), 2.74 (dd, $J=15.7$, 6.2 Hz, 1H, 1/2CH_2), 4.68 (dd, $J=6.2$, 7.3 Hz, 1H), 5.84 (d, $J=7.3$ Hz, 1H), 7.06–7.19 (m, 7H), 7.58 (d, $J=8.42$ Hz, 2H). IR (KBr): 3256, 2920, 1729, 1670, 1295, 1156 cm^{-1}. Anal. calcd for $C_{20}H_{25}NO_4S$: C, 64.0; H, 6.7; N, 3.7. Found: C, 63.9; H, 6.8; N, 3.6%.

4.5. Preparation of (*S*)-β-amino-β-phenylpropionic acid 7a

A solution of **5a** (300 mg, 0.802 mmol) and potassium hydroxide (450 mg, 8.02 mmol) in ethanol/water (1:1, 15 mL) was heated at 60°C for 1 h. The ethanol was evaporated in vacuo and the pH of the residue was adjusted to 3 with concentrated hydrochloric acid and extracted with chloroform (2×50 mL). The organic layer was evaporated in vacuo to give acid **6a** (250 mg, 0.789 mmol). Compound **6a** was treated with sodium (200 mg, 8.7 mmol) in liquid ammonia (20 mL) at reflux for 3 h. The mixture was then evaporated to dryness and the residue was diluted with water (2 mL) and acidified to pH 6 with aqueous HCl (10%). The reaction mixture was extracted with ether (5×20 mL). The aqueous portion was evaporated to dryness in vacuo. The hydrochloride of β-amino-β-phenylpropionic acid was obtained contaminated with other inorganic impurities. The hydrochloride was dissolved in water and filtered through a column of strong acidic ion-exchange resin (5 g, amberlite IR-120, H^+ form) using first water (100 mL) and then 1N ammonia (200 mL) as eluents. Evaporation of the ammonia gave free amino acid **7a** (100 mg, 77%); mp 215–217°C [Lit.[16] for (*S*)-**7a**, mp 216°C], $[\alpha]_D^{20}=-6.9$ ($c=1.00$, H_2O). [Lit.[15] for (*S*)-**7a**, $[\alpha]_D^{25}=7.5\pm1$]; ^{1}H NMR (D_2O, 300 MHz): δ 2.88 (dd, *J* 16, 7 Hz, 1H, 1/2CH_2), 2.98 (dd, *J* 16, 8 Hz, 1H, 1/2CH_2), 4.69–4.85 (m, 1H), 7.48–7.61 (m, 5H). IR (KBr): 2612, 2205, 1625, 1580 cm^{-1}.

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