

Asymmetric synthesis of *N*-tosyl amino acids from *N*-sulfinyl α -amino-1,3-dithioketals

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This paper is dedicated to Cynthia A. Maryanoff and Bruce E. Maryanoff to honor their outstanding contributions to science and service to the profession

Abstract

Hydrolysis of diastereomerically pure *N*-sulfinyl α -amino-1,3-dithianes with 1,3-dibromo-5,5-dimethylhydantoin gives *N*-tosyl α -amino aldehydes which when subjected to a Pinnick-type oxidation gave *N*-tosyl α -amino acids without epimerization.

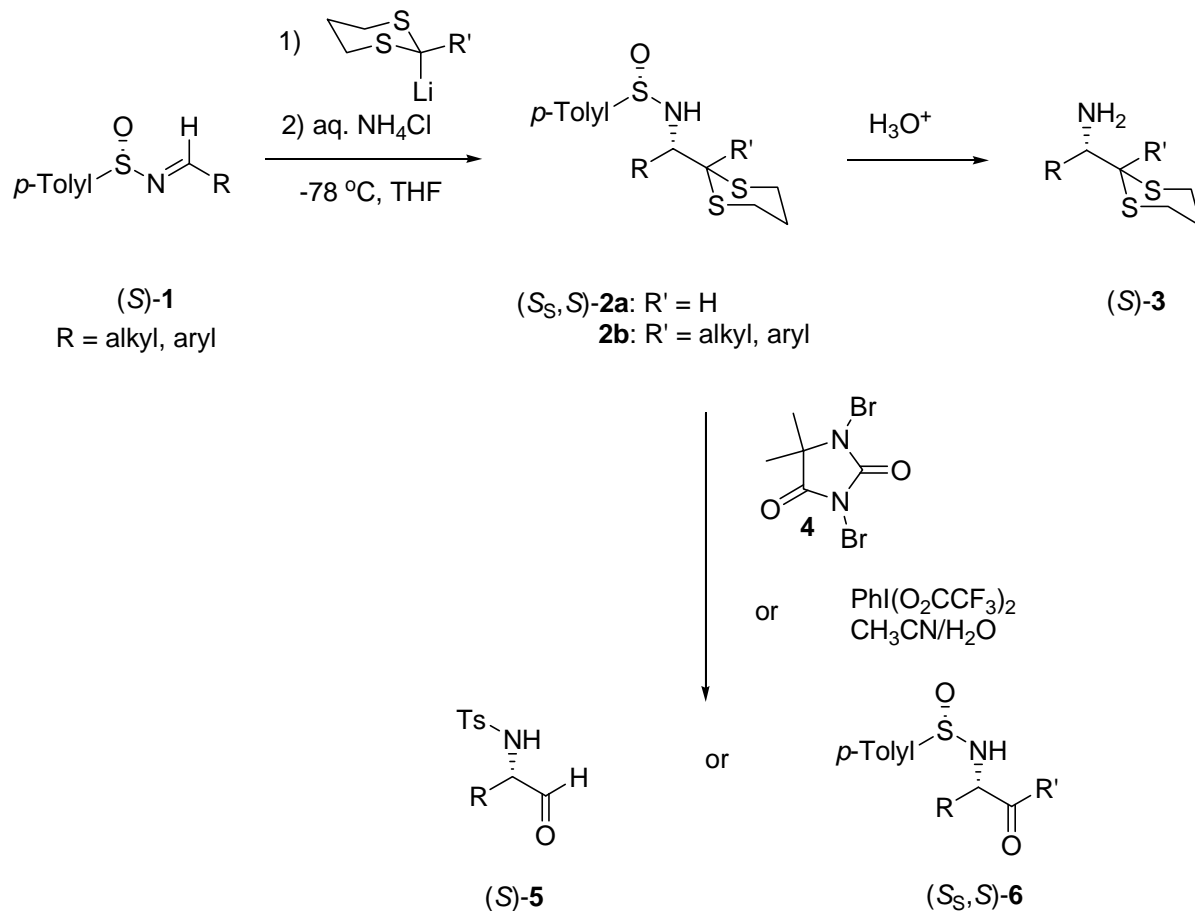
Keywords: Sulfinimine (*N*-sulfinyl imine); asymmetric synthesis; *N*-tosyl α -amino acids; *N*-sulfinyl α -amino-1,3-dithioketals.

Introduction

α -Amino aldehydes and ketones are valuable chiral building blocks widely used in asymmetric synthesis.^{1,2} They have been employed in the enantioselective synthesis of α -amino alcohols, 1,2-diamines, allylic amines, heterocycles, and natural products. Most often α -amino aldehydes and ketones are prepared from *N*-protected α -amino acids and are limited by the availability of the starting material.¹ Because these α -amino carbonyl compounds are notoriously unstable, their formation and subsequent transformations require a suitable *N*-protecting group for stabilization to inhibit racemization and self-condensation.^{1,2,3}

N-Sulfinyl α -amino-1,3-dithioketals **2** ($R' = \text{alkyl aryl, H}$), prepared by the addition of 2-lithio-1,3-dithianes to enantiopure sulfinimines (*N*-sulfinyl imines) **1**, are new sulfinimine-derived chiral building blocks for the asymmetric synthesis of α -amino aldehydes **5** and ketones **6** (Scheme 1).⁴⁻⁷ Removal of the thioketal group in **2b** was selectively accomplished using the Stork reagent $\text{PhI}(\text{O}_2\text{CCF}_3)_2$, affording the *N*-sulfinyl α -amino ketone (*S,S,S*)-**6** without epimerization.⁴ Similar treatment of **2a** resulted in decomposition, but with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, **4**) it gave the *N*-tosyl α -amino aldehyde (*S*)-**5**, again without epimerization.⁵ The fact that acid hydrolysis of **2** gives the free amine **3** while leaving the carbonyl group protected offers unique opportunities for functional group manipulation.⁴ These

new chiral building blocks have been employed in asymmetric syntheses of hydroxyprolines^{4,6} such as (-)-3-hydroxy-3-methylproline,⁴ 1,2-amino alcohols,⁵ allylamines,⁵ the 2,3-disubstituted piperidine (L-733,060),⁶ and the amino ketone (-)-cathinone.⁷

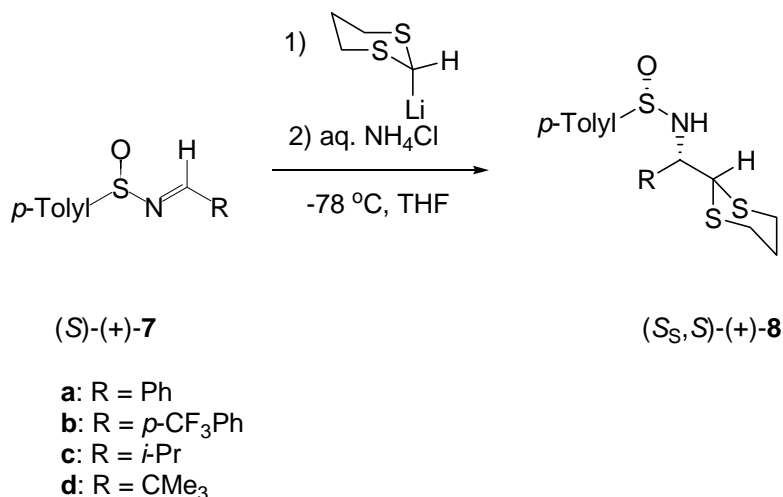


Scheme 1. Synthesis of α -amino- aldehydes and ketones.

Although the synthesis of α -amino acids from α -amino aldehydes has occasionally been described, this method has received little attention.^{1,2,8} Undoubtedly the reason for this is that α -amino aldehydes are usually prepared from α -amino acids. However, a procedure to prepare α -amino acids from α -amino- 1,3-dithianes would have considerable merit because of the structural diversity of available sulfonamide-derived α -amino-1,3-dithianes.⁹ We describe here a simple method for the asymmetric synthesis of *N*-tosyl α -amino acids from *N*-tosyl α -amino aldehydes **5** using a Pinnick-type oxidation.

Results and Discussion

The addition of 1.5 equivalents of a preformed solution of 2-lithio-1,3-dithiane at $-78\text{ }^{\circ}\text{C}$ to (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide **7a**, (*S*)-(+)-*N*-(*p*-(trifluoromethyl-benzylidene)-*p*-toluenesulfinamide **7b**, (*S*)-(+)-*N*-(isobutylidene)-*p*-toluenesulfinamide **7c**, or (*S*)-(+)-(2,2-dimethylpropylidene)-*p*-toluenesulfinamide **7d**, readily gave the corresponding *N*-sulfinyl α -amino-1,3-dithianes (*S*_S,*S*)-(+)-**8a** and (*S*_S,*S*)-(+)-**8b**, (*S*_S,*S*)-(+)-**8c**, and (*S*_S,*S*)-(+)-**8d** (Scheme 2).⁹ The diastereoselectivities, determined by ¹H-NMR on the crude reaction mixtures, were good to excellent (72-96% de) and the yields of the major diastereoisomers, isolated by flash chromatography, were good (Table 1). It is interesting to note that the highest de's were found for addition of the 2-lithio-1,3-dithiane to the bulky *tert*-butyl sulfinimine (*S*)-(+)-**7d** and lowest for the smaller *iso*-propyl sulfinimine (*S*)-(+)-**7c** (Table 1, compare entries 3 and 4).



Scheme 2. Synthesis of *N*-sulfinyl α -amino-1,3-dithianes.

Table 1. Synthesis of *N*-sulfinyl α -amino-1,3-dithianes (*S*_S,*S*)-(+)-**8**

Entry	Sulfinimine 7 (R =)	% <i>de</i> ^a	(+)- 8 , % yield ^b
1	7a (R = Ph)	82	73
2	7b (R = <i>p</i> -CF ₃ Ph)	80	75
3	7c (R = <i>i</i> -Pr)	72	70
4	7d (R = CMe ₃)	96	72

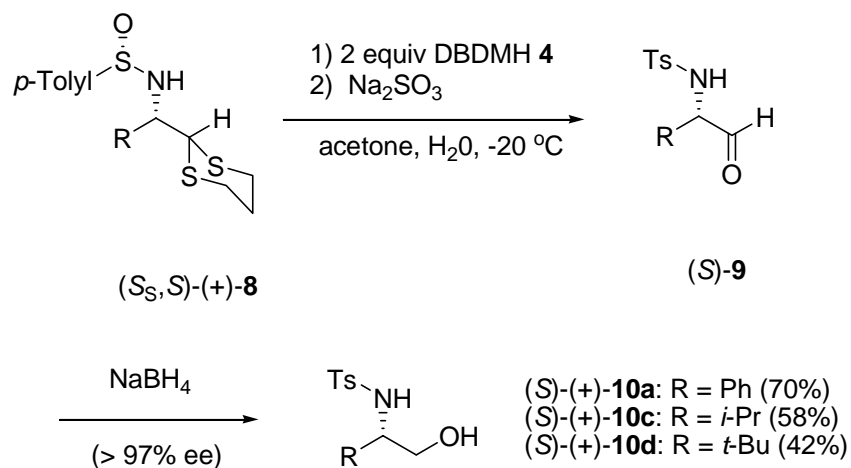
^a Determined by ¹H- NMR on the crude reaction mixture.

^b Isolated yield of pure major diastereoisomer.

The *N*-sulfinyl α -amino-1,3-dithianes **8** were hydrolyzed by treatment with 2 equivalents of DBDMH **4** in 80% acetone at $-20\text{ }^{\circ}\text{C}$. The solution quickly turned red and then faded to yellow-

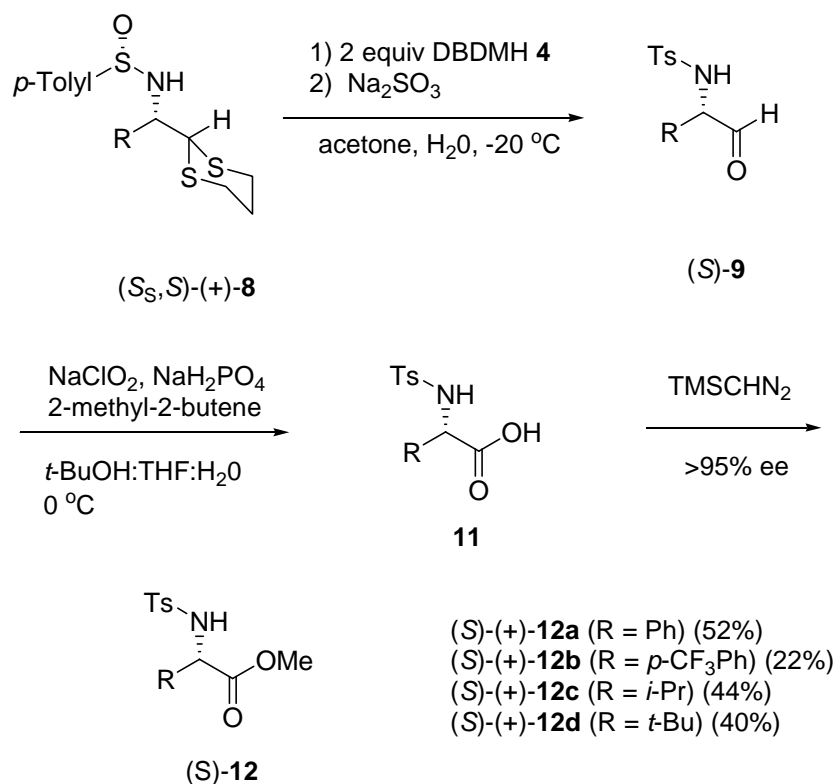
orange after a few minutes. The reaction was quenched after about 10 min by addition of aqueous sodium sulfite to afford the crude *N*-tosyl aldehydes (*S*)-**9** as colorless oils. Since the aldehydes were unstable to chromatographic purification they were used in crude form for the next reactions.

The enantiomeric purity of the crude *N*-tosyl amino aldehydes **9** were determined by reduction with 5 equiv. of NaBH₄ to give the known 1,2-amino alcohols (*S*)-(+)-**10**, which were transformed into their Mosher esters (Scheme 3). The enantiomeric purity of amino alcohol (*S*)-(+)-**10a** is estimated to be >97% *ee* based on its Mosher ester and by comparison its specific rotation to a literature value for this amino alcohol.¹⁰ Therefore the enantiomeric purity of the corresponding α -amino aldehyde **9a**, must be at least 97% *ee*. Similar results were found for **9c** and **9d**. These results confirm earlier studies that demonstrated that the *N*-tosyl group is an excellent protecting group for inhibiting base catalyzed epimerization in α -amino aldehydes, because it stabilizes anions at nitrogen.⁷



Scheme 3. Reduction of *N*-tosyl α -amino aldehydes.

A Pinnick-type oxidation was used to oxidize the crude aldehydes (*S*)-**9** to the corresponding *N*-tosyl amine acids, which were isolated as their methyl esters **12** (Scheme 4).¹¹ The crude *N*-tosylamino aldehydes **9** were converted into the amino acids **11** under standard conditions, *i.e.* NaClO₂, NaH₂PO₄ and 2-methyl-2-butene in THF: *t*-BuOH: H₂O at 0 °C. The crude amino acids were treated with (trimethylsilyl)diazomethane solution to give the amino acid methyl esters **12** in good yield for the four-step sequence (Scheme 4). The enantiomeric purities of the amino-acid methyl esters were excellent, as determined by comparison with literature values and conversion of the acids into the diastereomeric amides with (*R*)-(+)- α -methylbenzylamine – and the other diastereomeric amide was not detected by ¹H-NMR.



Scheme 4. Synthesis of *N*-tosyl α -amino acids.

Conclusions

Hydrolysis of *N*-sulfinyl α -amino-1,3-thianes **8** with 1,3-dibromo-5,5-dimethylhydantoin **4** affords *N*-tosyl α -amino aldehydes **9** which were oxidized to *N*-tosyl α -amino acids **11** which were isolated as their methyl esters **12**. The overall yield for the four-step sequence, **8** to **12** is very good, and epimerization was not detected. This protocol represents a valuable new method for the asymmetric synthesis of structurally diverse α -amino acids because of the great structural diversity of available sulfinimines.⁹ Furthermore, Rapoport has demonstrated the utility of *N*-arylsulfonyl protecting groups in many transformations of amino acids, including modifications of the carboxyl group to give α -amino ketones.¹⁴ Removal of the *N*-tosyl group is easily effected without epimerization, *via* reduction with sodium naphthalide or cleavage with HBr in HOAc.¹⁵ In our studies we have found that Na/NH₃ (liq.) is particularly effective for removal of the *N*-*p*-toluenesulfonyl protecting group.⁴

Experimental Section

General. Chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless otherwise noted. ^1H - and ^{13}C - NMR spectra were recorded at 400 and 100 MHz, respectively. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. The sulfinimines **7a**,¹² **7b**,¹³ **7c**,¹² and **7d**¹² were prepared as previously described. RT denotes room temperature.

General procedure for addition of 2-lithio-1,3-dithiane to sulfinimines (*S,S,S*)-(+)-*N*-(*p*-toluenesulfinyl)-2-phenylaminomethyl-1,3-dithiane **8a**

In a 50 mL, oven dried, two-neck, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and an argon- filled balloon was placed 1,3-dithiane (0.37 g, 3.08 mmol, Aldrich) in THF (20 mL). The solution was cooled to $-20\text{ }^\circ\text{C}$ and *n*-BuLi (1.64 mL, 4.11 mmol, 2.5 *M* in hexane) was added slowly. After 1.5 h, the resulting solution was cooled to $-78\text{ }^\circ\text{C}$ and added *via* cannula to a $-78\text{ }^\circ\text{C}$ solution of sulfinimine (+)-**7a** (0.5 g, 2.05 mmol) in THF (20 mL). The reaction was stirred for 20 min. and quenched at $-78\text{ }^\circ\text{C}$ by addition of sat. NH_4Cl solution (3 mL). To the reaction mixture was added EtOAc (25 mL), the aqueous phase was washed with EtOAc (2 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc/hexane, 2:8) afforded 0.545 g (73%) of a white crystalline solid, mp $172\text{--}174\text{ }^\circ\text{C}$ (dec.); $[\alpha]_{\text{D}}^{20} +69.8$ (*c* 1.0, CHCl_3); IR (KBr) 3260, 3040, 2941, 1418 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.40 (d, *J* = 8.0 Hz, 2 H), 7.07 (m, 7 H), 5.05 (d, *J* = 5.5 Hz, 1 H), 4.65 (t, *J* = 6.5 Hz, 1 H), 4.25 (d, *J* = 6.5 Hz, 1 H), 2.80-2.76 (m, 2 H), 2.72 (m, 2 H), 2.23 (s, 3 H), 2.11 (m, 1 H), 1.92-1.83 (m, 1 H); ^{13}C NMR (CDCl_3) δ 141.1, 140.2, 129.5, 129.0, 128.4, 127.7, 125.9, 125.3, 58.0, 53.6, 29.5, 28.4, 25.6, 21.6. HRMS Calcd for $\text{C}_{18}\text{H}_{21}\text{NOS}_3\text{Na}$ (*M* + *Na*) 386.0682. Found 386.0685.

(*S,S,S*)-(+)-*N*-(*p*-Toluenesulfinyl)-2-(4-trifluoromethylphenylaminomethyl)-1,3-dithiane **8b**.

Flash chromatography using EtOAc/hexane (3:7) gave 75% of a white solid, mp $139\text{--}140\text{ }^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} +70.4$ (*c* 0.33, CHCl_3) IR (KBr) 3207, 2931, 1429, 1037 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.02 (m, 1 H), 2.14 (m, 1 H), 2.31 (s, 3 H), 2.82 (m, 2 H), 3.02 (m, 2 H), 4.22 (d, *J* = 7.2 Hz, 1 H), 4.90 (m, 1 H), 5.52 (d, *J* = 3.9 Hz, 1 H), 7.02 (d, *J* = 8.1 Hz, 2 H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.39 (m, 4 H); ^{13}C NMR (CDCl_3) δ 21.1, 25.3, 28.2, 28.6, 31.9, 52.0, 54.6, 89.6, 124.7, 125.9, 128.4, 128.9, 139.5, 141.4, 143.7. HRMS Calcd for $\text{C}_{19}\text{H}_{21}\text{F}_3\text{NOS}_3$ (*M* + *H*) 432.0737. Found 432.0747.

(*S,S,S*)-(+)-*N*-(*p*-Toluenesulfinyl)-2-(1-amino-2-methylpropyl)-1,3-dithiane **8c**.

Flash chromatography with EtOAc/hexane (3:7) gave 70% of a white solid, mp $94\text{--}96\text{ }^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} +51.8$ (*c* 1.1, CHCl_3); IR (KBr) 3207, 2931, 1429, 1037 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.83 (d, *J* = 7.5 Hz, 2 H), 7.30 (d, *J* = 7.5 Hz, 2 H), 4.38 (d, *J* = 4.5 Hz, 1 H), 4.13 (d, *J* = 9.5 Hz, 1 H), 3.43-3.33 (m, 1 H), 2.97-2.83 (m, 4 H), 2.24 (s, 3 H), 2.17-2.10 (m, 1 H), 2.07-2.00 (m, 1 H), 1.94-1.84 (m, 1 H), 0.99 (d, *J* = 3.0 Hz, 3 H), 0.98 (d, *J* = 2.5 Hz, 3 H); ^{13}C NMR (CDCl_3) δ 142.8, 141.2, 129.3,

126.2, 64.9, 54.4, 30.7, 30.4, 30.2, 26.2, 21.3, 20.5, 18.5. Anal. Calcd for C₁₅H₂₃NOS₃: C, 54.67; H, 7.03; N, 4.25. Found: C, 54.65; H, 7.06; N, 4.29%.

(S_S,S)-(+)-N-(*p*-Tolunesulfinyl)-2-(1-amino-2,2-dimethylpropyl)-1,3-dithiane 8d. Flash chromatography with EtOAc/hexane (3:7) gave 72% of a colorless oil, [α]_D²⁰ +15.4 (*c* 1.91, CHCl₃); IR (KBr) 3219, 3040, 2955, 2899, 1473 cm⁻¹; ¹H NMR (CDCl₃) δ 7.91 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 4.49 (s, 1 H), 4.20 (d, *J* = 9.3, 1 H), 3.29 (d, *J* = 9.3 Hz, 1 H), 2.88 (m, 4 H), 2.36 (s, 3 H), 1.92 (m, 2 H), 1.03 (s, 9 H); ¹³C NMR (CDCl₃) δ 143.8, 141.6, 129.7, 126.8, 70.4, 53.8, 36.1, 32.3, 31.1, 28.1, 26.3, 21.7. HRMS Calcd for C₁₆H₂₅NOS₃ (M + H) 344.1176. Found 344.1181.

General procedure for hydrolysis of α -amino 1,3-dithianes to *N*-tosyl α -amino aldehydes using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, 4)

In a 50 mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed (+)-**8a** (0.5 g, 1.377 mmol) in acetone (20 mL) at 25 °C, and this solution was added with stirring to a solution of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, **4**) (0.787 g, 2.754 mmol) in 80% acetone (14 mL) at -20 °C. The solution quickly became red, but soon faded to yellow-orange, and was stirred for 10 min. The solution was then shaken with a mixture of saturated aq. sodium sulfite (10 mL) and 1:1 hexane-dichloromethane (10 mL). The organic phase was washed with aqueous sodium bicarbonate (12 mL), water (12 mL), then brine (12 mL), dried (Na₂SO₄), and concentrated to give a colorless oil that was used directly in the next step.

General procedure for the reduction of α -amino aldehydes using NaBH₄. (S)-(+)-N-(2-hydroxy-1-phenyl-ethyl)-4-methyl-benzenesulfonamide 10a

In a 25-mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon, was placed the crude aldehyde **9a** (0.08 g, 0.276 mmol) in EtOH (15 mL). The solution was cooled to 0 °C and NaBH₄ (0.125 g, 3.321 mmol) was added. After 10 min, the reaction mixture was quenched by addition of saturated aqueous NH₄Cl solution (10 mL) at 0 °C and diluted with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL), and the combined organic phases were washed with brine (15 mL), and dried (Na₂SO₄). Flash chromatography (EtOAc/hexane, 3.5:6.5) afforded 0.0560 g (70%) of **10a** as a white solid, mp 105-106 °C [lit.¹⁰ mp 106 °C]; [α]_D²⁰ +79.2 (*c*, 1.0, CHCl₃), [lit.¹⁶ [α]_D²⁵ +81.5 (*c*, 1.0, CHCl₃); IR (KBr) 3543, 3315, 1322, 1173 cm⁻¹; ¹H NMR (CDCl₃) δ 7.42 (d, *J* = 5.1 Hz, 2 H), 7.12-6.92 (m, 7 H), 5.16 (d, *J* = 7.2 Hz, 1 H), 4.14 (q, *J* = 7.2, 5.6 Hz, 1 H), 3.58 (d, *J* = 5.6 Hz, 2 H), 2.24 (s, 3 H), 1.61 (bs, 1 H, OH); ¹³C-NMR (CDCl₃) δ 141.9, 136.3, 135.9, 128.0, 127.1, 126.3, 125.8, 125.5, 64.8, 58.4, 20.0. Anal. Calcd for C₁₅H₁₇NO₃S: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.76; H, 5.91; N, 4.83%.

(S)-(+)-N-(1-Hydroxymethyl-2-methylpropyl)-4-methylbenzenesulfonamide 10c. Flash chromatography with EtOAc/hexane (4:6) gave 0.0450 g (58%) of a white solid, mp 89-90 °C [lit.¹⁶ mp 88-89 °C]; [α]_D²⁰ +30.7 (*c* 0.5, CHCl₃), [lit.¹⁶ [α]_D²⁵ +29.4 (*c*, 0.837, CHCl₃); IR (KBr) 3531, 3302, 2972, 1162 cm⁻¹; ¹H-NMR (CDCl₃) δ 7.82 (d, *J* = 4.5 Hz, 2 H), 7.38 (d, *J* = 4.5 Hz,

2 H), 4.81 (d, $J = 5.8$ Hz, 1 H), 3.60-3.62 (m, 2 H), 3.08 (m, 1 H), 2.49 (s, 3 H), 1.82-1.92 (m, 1 H), 0.83 (d, $J = 3.0$ Hz, 3 H), 0.80 (d, $J = 3.0$ Hz, 3 H); ^{13}C NMR (CDCl_3) δ 143.5, 137.5, 129.7, 127.2, 63.1, 60.9, 29.4, 29.6, 21.5, 19.1, 18.4; Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_3\text{S}$: C, 56.00; H, 7.44; N, 5.44. Found: C, 55.94; H, 7.47; N, 5.45%.

(S)-(+)-N-(1-Hydroxymethyl-2,2-dimethylpropyl)-4-methylbenzene-sulfonamide 10d. Flash chromatography with EtOAc/hexane (3:7) gave 0.032 g (42%) of a light yellow solid, mp 111-112 °C; $[\alpha]_{\text{D}}^{20} +10.3$ (c 1.45, CHCl_3); IR (KBr) 3471, 3292, 2958, 2924, 1325, 1154 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.85 (d, $J = 6.0$ Hz, 2 H), 7.37 (d, $J = 6.0$ Hz, 2 H), 4.96 (d, $J = 6.0$ Hz, 1 H), 3.67 (m, 2 H), 3.07 (m, 1 H), 2.49 (s, 3 H), 2.01 (s, 1 H), 0.86 (s, 9 H); ^{13}C NMR (CDCl_3) δ 143.9, 138.0, 130.0, 127.7, 64.4, 62.7, 34.4, 27.3, 21.9. Anal. Calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_3\text{S}$: C, 57.54; H, 7.80; N, 5.16. Found: C, 57.52; H, 7.82; N, 5.19%.

General procedure for the formation of amino acids. (S)-(+)-Methyl-2-(*p*-toluenesulfonyl)amino-2-phenyl acetate 12a

In a 50-mL, oven-dried, single-necked, round-bottomed flask equipped with a magnetic stirring bar and a glass stopper was placed the crude aldehyde **9a** (0.225 g, 0.778 mmol) in THF: *t*-BuOH (1:1, 15 mL). The solution was cooled to 0 °C and 2-methyl-2-butene (0.824 mL, 7.778 mmol), NaClO_2 (0.14 g, 1.557 mmol) and $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (0.186 g, 1.557 mmol) in 5 mL H_2O were added. The reaction mixture was warmed to RT and stirred for 12 h. The solution was then concentrated, 1 *N* HCl (8 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed with brine (15 mL), then dried (Na_2SO_4), and concentrated. The crude residue was dissolved in methanol (8 mL) and benzene (8 mL) and TMS- CHN_2 (0.778 mL, 1.557 mmol, 2.0 *M* in hexane) at RT. The mixture was stirred for 4h at this temperature, then concentrated. Flash chromatography (EtOAc/hexane, 3.5:6.5) afforded 0.137 g (52%) of **12a** as a white solid, mp 132 °C [lit.¹⁷ mp 131-133 °C]; $[\alpha]_{\text{D}}^{20} +101.6$ (c , 0.52, CHCl_3), [lit.¹⁷ $[\alpha]_{\text{D}}^{25} +102.0$ (c , 1.12, CHCl_3); IR (KBr) 3255, 1742 1084 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.64 (d, $J = 7.8$ Hz, 2 H), 7.38-7.21 (m, 7 H), 5.72 (d, $J = 7.8$ Hz, 1 H), 5.13 (d, $J = 7.8$ Hz, 1 H), 3.61 (s, 3 H), 2.42 (s, 3 H); ^{13}C NMR (CDCl_3) δ 172.1, 143.3, 136.4, 135.1, 130.1, 129.7, 128.8, 128.5, 127.1, 59.6, 53.2, 21.2. HRMS Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{SNa}$ ($\text{M} + \text{Na}$) 342.0775. Found 342.0773.

(S)-(+)-Methyl-2-(*p*-toluenesulfonyl)-amino-2-(4-trifluoromethyl-phenyl)-acetate 12b. Flash chromatography (EtOAc/hexane, 3.5:6.5) afforded 22% of a light yellow oil, $[\alpha]_{\text{D}}^{20} +31.3$ (c , 0.24, CHCl_3); IR (KBr) 3281, 1746, 1436, cm^{-1} ; ^1H NMR (CDCl_3) δ 7.63 (d, $J = 8.1$ Hz, 2 H), 7.56 (d, $J = 8.4$ Hz, 2 H), 7.4 (d, $J = 8.4$ Hz, 2 H), 7.24 (d, $J = 8.1$ Hz, 2 H), 5.87 (d, $J = 6.9$ Hz, 1 H), 5.2 (d, $J = 6.9$ Hz, 1 H), 3.7 (s, 3 H), 2.45 (s, 3 H); ^{13}C NMR (CDCl_3) δ 167.0, 147.9, 143.9, 136.7, 129.6, 128.3, 127.8, 127.2, 125.7, 114.6, 59.0, 53.4, 21.5. HRMS Calcd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{NO}_4\text{SNa}$ ($\text{M} + \text{Na}$) 410.0649. Found 410.0647.

(S)-(+)-Methyl-2-(*p*-toluenesulfonyl)-amino-2-isopropylacetate 12c. Flash chromatography EtOAc/hexane (4:6) gave 44% of a white solid, mp 78 °C [lit.¹⁷ mp 77-78 °C]; $[\alpha]_{\text{D}}^{20} +15.2$ (c , 0.91, CHCl_3), [lit.¹⁷ $[\alpha]_{\text{D}}^{25} +15.6$ (c , 0.89, CHCl_3); IR (KBr) 3247, 1723, 1092 cm^{-1} ; ^1H NMR

(CDCl₃) δ 7.65 (d, J = 8.0 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 2 H), 4.98 (d, J = 8.4 Hz, 1 H), 3.69 (d, J = 8.4 Hz, 1 H), 3.39 (s, 3 H), 2.38 (s, 3 H), 2.02-1.93 (m, 1 H), 0.94 (d, J = 6.7 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H); ¹³C NMR (CDCl₃) δ 171.0, 142.9, 136.8, 129.8, 126.1, 61.2, 52.1, 32.1, 21.8, 19.4, 18.6. Anal. Calcd for C₁₃H₁₉NO₄S: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.69; H, 6.88; N, 4.89%.

(S)-(+)-Methyl-3,3-dimethyl-2-(*p*-toluenesulfonyl)-amino-butyrates 12d. Flash chromatography EtOAc/hexane (4:6) gave 40% of a white solid, mp 108-110 °C; $[\alpha]_D^{20}$ +42.1 (c, 0.7, CHCl₃); IR (KBr) 3250, 1732, 1449, 1088 cm⁻¹; ¹H NMR (CDCl₃) δ 7.69 (d, J = 8.0 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H), 5.08 (d, J = 12 Hz, 1 H), 3.57 (d, J = 12 Hz, 1 H), 3.33 (s, 3 H), 2.41 (s, 3 H), 0.94 (m, 9 H); ¹³C NMR (CDCl₃) δ 171.1, 144.1, 136.8, 129.9, 127.8, 64.6, 52.1, 34.9, 26.6, 21.9. Anal. Calcd for C₁₄H₂₁NO₄S: C, 56.16; H, 7.07; N, 4.68. Found: C, 56.14; H, 7.12; N, 4.71%.

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