Sulfinimine-Mediated Asymmetric Synthesis of (*R*)-(4-Methoxy-3,5-dihydroxyphenyl)glycine: The Central Amino Acid of Vancomycin and Related Agents

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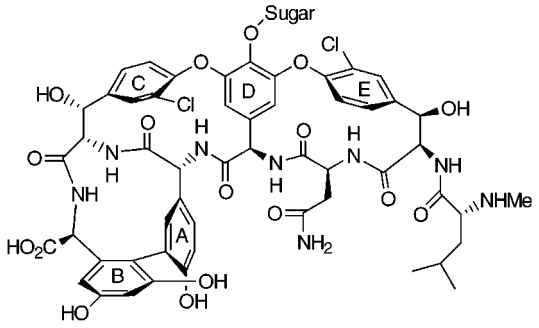
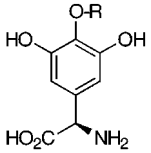
The sulfinimine asymmetric Strecker synthesis, the addition of ethyl aluminum cyano alkoxide, "EtAl(OR)CN", to sulfinimine **10**, has been applied to a concise highly efficient four-step enantioselective synthesis of (*R*)-(4-methoxy-3,5-dihydroxyphenyl)glycine (**3**) and its derivatives in >97% ee. These epimerization-sensitive arylglycines are precursors of the key central amino acid of vancomycin and related glycopeptide antibiotics.

Vancomycin (**1**) is the prototypical member of the large class of clinically important glycopeptide antibiotics which include teicoplanin, ristocetin, actaplanin (A4696), and A33512b.[1] Vancomycin is the drug of choice, and increasingly of last resort, for treatment of infections by methicillin-resistant *Staphylococcus aureus* and other Gram-positive organisms. Its unique structure and the emergence of vancomycin-resistant microbes have made it an important synthetic target, but despite efforts by many groups, the total synthesis of vancomycin (**1**) has not yet been achieved.[1]



1, Vancomycin

The centrally located (*R*)-(3,4,5-trihydroxyphenyl)glycine (**2**) of vancomycin is of paramount importance due to the 3,5-biaryl ether linkages which define the vancomycin skeleton, as well as the 4-*O*-glycosyl bond linking it to the sugar L-vancosamine. In addition, this amino acid has been shown to be essential for vancomycin's activity through formation of its "binding pocket" for cell wall complexation. A number of synthetic strategies require this epimerization-sensitive central amino acid and its derivatives such as (*R*)-(4-methoxy-3,5-dihydroxyphenyl)glycine (**3**) for construction of the **C**-O-**D**-O-**E** biaryl ether segments. These methods include Boger's Ullmann macrocyclization approach,[2] Pearson's organometallic methodology,[3] and Zhu's S_NAr macrocyclization



2: R = H
3: R = Me

technology.[4] Boger, using Sharpless asymmetric dihydroxylation, prepared the N-Boc derivative of **3** in 12−13 steps and 94% ee.[2c] Zhu employed a Strecker type synthesis with (*S*)-phenylglycinol as the chiral auxiliary which required 13−14 steps and separation of diastereoisomers and afforded the N-Troc derivative of **3** in 80% ee.[4b] A somewhat more efficient 8−15-step asymmetric synthesis of derivatives of **3** has recently been reported by Zhu[5] and by Pearson[6] using Evans' asymmetric azidation methodology.

Recently we reported a new and practical asymmetric Strecker synthesis of α-amino acids involving the highly diastereoselective addition of ethyl aluminum cyano alkoxide ["EtAl(OR)CN"] to nonracemic sulfinimines (thiooxime *S*-oxides **4**) (Scheme 1).[7] Importantly, the sulfinyl group in the α-amino nitrile **5** is hydrolyzed under exceedingly mild conditions such that epimerization of the amino acid **6** was not detected. Sulfinimines **4** are prepared in "one pot" from commercially available reagents.[8] They are chiral imine building blocks which have recently been employed in the asymmetric synthesis of amines,[9,10] β-amino acids,[9,11,12] β-aminophosphonic acids,[12e] the taxol C-13 side chain[11] and its fluorinated

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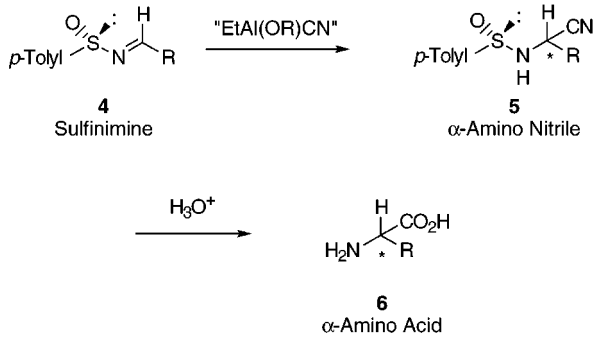
Scheme 1



analogue,[12f] 2-arylpyrrolines,[13] *N*-sulfinyl *cis*-aziridine 2-carboxylic acids,[14] *β*-hydroxy α-amino acids,[14e] and 2*H*-azirine carboxylate esters.[14d,g] In this paper we describe the application of the sulfinimine Strecker methodology in a concise, highly efficient four-step synthesis of (*R*)-**3** and its derivatives **13** in >95% ee and 40% overall yield.

Results and Discussion

The aldehydes **8**, required for the preparation of the sulfinimines **10**, have previously been prepared from **7** in two steps by reduction and selective oxidation.[2c,4b,15] We found that controlled reduction of **7** with diisobutylaluminum hydride (DIBAL-H) at −78 °C affords these materials in a single step in 78−89% yield (Scheme 2). However, careful monitoring of the reaction mixture is necessary to avoid over-reduction since the reduction is complete within 15−20 min. The sulfinimines (*R*)-**10** were prepared as previously descibed,[8] in "one-pot", by treating (1*S*,2*R*,5*S*)-(+)-menthyl *(R)-p*-toluenesulfinate (**9**, Andersen reagent) with lithium (bistrimethylsilyl)-amide (LiHMDS) followed by addition of the aldehyde **8**. After purification by crystallization or flash chromatography, the isolated yields were 73−81%. The new sulfinimines exhibit characteristic absorption at *δ* 8.51−8.64 ppm for the imino proton.

Our previously established protocol for the sulfinimine Strecker synthesis involves addition of the sulfinimine to ethyl aluminum cyano isopropoxide ["EtAl(O-*i*-Pr)-CN"], prepared by treating 1.5 equiv of commercially available diethylaluminum cyanide (Et_2AlCN) with 1.0 equiv of isopropyl alcohol.[7] The de's were significantly

Scheme 2

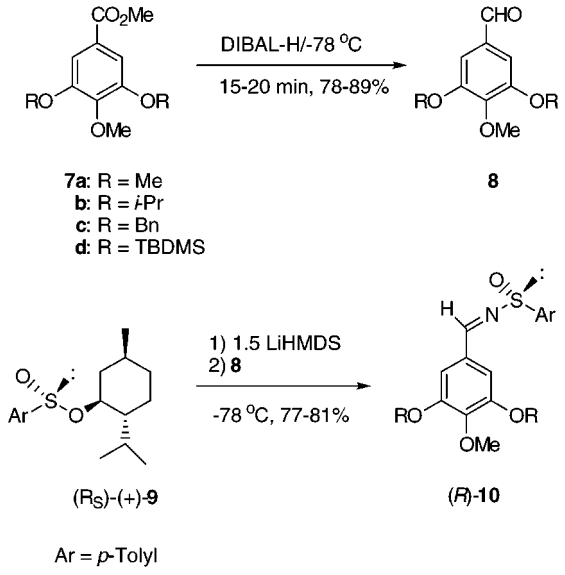


Table 1. Addition of Diethylaluminum Cyanide to Sulfinimines 10 in THF at − 78 °C

entry	sulfinimine	Et_2AlCN/ *i*-PrOH[a]	time (h)	% yield[b] **11** [(*R*S,*R*):(*R*S,*S*)]
1	**10a** (R = Me)	1.5/1.0	4.5	74 [98:2]
2	**10b** (R = *i*-Pr)	1.5/1.0	5.0	75 (96:4)
3	**10c** (R = Bn)	1.5/0	24	no reaction
4		1.5/1.0	24	no reaction
5		2.5/1.0	24	46 [89:11]
6		2.5/2.5	24	39 [88:12]
7		5.0/0.0	24	66 [76:24]
8		5.0/3.3	24	73 [90:10]
9		5.0/4.0	24	72 [86:14]
10		5.0/5.0	24	75 [87:13]
11	**10d** (R = TBDMS)	1.5/1.0	24	no reaction
12		5.0/5.0	24	no reaction

[a] 1.0 equiv of the sulfinimine **10** was added. [b] Isolated.

better with this reagent system than with Et_2AlCN alone; e.g. 82−92% vs 36−42.[7] The excess of Et_2AlCN over isopropyl alcohol is necessary because it improves the rates of CN addition. The addition of diethylaluminum cyanide to sulfinimines (*R*)-**10** is summarized in Table 1 (Scheme 3).

With the standard protocol addition of EtAl(O-*i*-Pr)-CN to the 3,4,5-trimethoxy and 3,5-diisopropoxy-4-methoxy sulfinimines **10a** and **10b** afforded the corresponding α-amino nitriles **11a** and **11b** in good yield and excellent diastereoselectivity (92−96% de) (Table 1, entries 1 and 2). Crystallization affords these materials in diastereomerically pure form. By contrast, there was no reaction with the 3,5-bis(benzoyloxy)-4-methoxy sulfinimine **10c** using the standard protocol (Table 1, entries 3 and 4). It was not until a large excess of EtAl(O-*i*-Pr)CN was added that addition was detected (Table 1, entries 4−10). Optimum results were obtained with 5.0 equiv of Et_2-AlCN and 3.3 equiv of *i*-PrOH for 24 h, affording **11c** in 80% de and 73% yield (Table 1, entry 8). The possibility that the longer reaction times caused some racemization of the product was eliminated by subjecting diastereomerically pure (*R*)-**11** (>97% de), obtained by crystallization, to the reaction conditions. No epimerization was detected after 24 h. Attempts to add EtAl(O-*i*-Pr)CN to the 3,5-bis-*tert*-(butyldimethylsilyloxy)-4-methoxy sulfinimine **10d** failed, and starting material was recovered (Table 1, entry 11 and 12).

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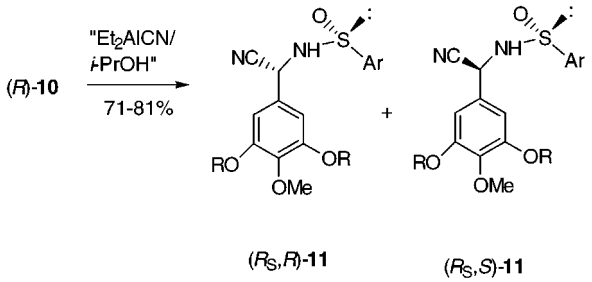
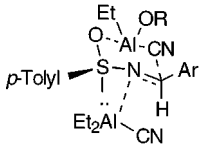
Scheme 3



In all cases the major α-amino nitrile **11** diastereoisomer obtained had the (*R*)-configuration, consistent with our original hypothesis that EtAl(O-*i*-Pr)CN coordinates to the sulfinyl oxygen in **10** with intramolecular delivery of CN to the *Si*-face; e.g. **TS-1**. It was also suggested



TS-1

that chelation of a second aluminum Lewis acid species to the imino nitrogen is necessary activation for addition to occur. Thus it is quite curious that EtAl(O-*i*-Pr)CN readily adds to sulfinimines **10a** and **10b**, is slow for **10c**, and fails completely with **10d**. The mildly electron withdrawing *meta*-alkoxy groups (*m*-MeO, $\sigma = 0.12$)[16] could deactivate the C−N bond in **10c** and **10d** to such an extent that the Lewis acid does not chelate. However, this hypotheses fails to explain the rapid rates of addition for **10a** and **10b**. Furthermore, all attempts to discern any electronic difference between **8a**−**d** and **10a**−**d** by ^{1}H or ^{13}C NMR or UV spectroscopy failed. Another possibility is that the bulky benzyl and *t*-butyldimethylsilyl groups in **10c** and **10d** inhibit association of EtAl(O-*i*-Pr)CN with the sulfinyl oxygen or the imino nitrogen atoms. However, inspection of models (Dreiding) and molecular modeling provided no clear answers in this regard.

We next turned our attention to the critical step of removing the *N*-sulfinyl auxiliary and hydrolyzing the nitrile in **11a**−**c** without epimerization of the sensitive trihydroxyphenylglycine **13** (Scheme 3). Hydrolysis was readily accomplished by heating the amino nitrile in 3−6 N HCl and isolating the amino acids by passing the aqueous solution through a DOWEX-50 ion exchange column. The enantiomeric purity was determined by comparison with literature values and by conversion to the Mosher amides. These results are summarized in Table 2.

Table 2. Hydrolysis Diastereomerically Pure α-Amino Nitriles (R_S,*R*)-11 to (*R*)-α-Amino Acids at 100 °C

entry	α-amino nitriles (R_S,*R*)-**11**	conditions	α-amino acid	% yield	% ee[a]
1	**11a** (R = Me)	3.0 N HCl, 3 h	**13a** (R = Me)	74	>95
2		6.0 N HCl, 3 h	**13a** (R = Me)	78	>95
3	**11b** (R = *i*-Pr)	3.0 N HCl, 3 h	**13b** (R = *i*-Pr)	76	>95
4		6.0 N HCl, 3 h	**3** (R = H)	74	>95
5	**11c** (R = Bn)	3.0 N HCl, 2 h	**3** (R = H)	76	>97
6		6.0 N HCl, 2 h	**3** (R = H)	46	81
7		6.0 N HCl, 4.5 h	decomposition		

[a] The ee's were determined by conversion of the amino acids to the Mosher amides and examining the ^{19}F NMR spectra.

As indicated in Table 2, hydrolysis of the amino nitriles **11** occurs efficiently, without epimerization, on heating in 3.0 N HCl. Importantly, these conditions resulted in hydrolysis of **11b** without removal of the isopropyl groups, affording (*R*)-[3,5-bis(isopropoxy)-4-methoxyphenyl]glycine (**13b**) in 76% isolated yield (Table 2, entry 3). In contrast the isopropyl groups in **11b** was removed with 6 N HCl, affording (*R*)-**3** in 74% yield (Table 2: entry 4). Moreover, hydrolysis of **11c** with 3 N HCl resulted in debenzylation to give (*R*)-(4-methoxy-3,5-dihydroxyphenyl)glycine (**3**) in 76% yield and >97% ee (Table 2, entries 3 and 5). With 6.0 N HCl racemization and decomposition of product (*R*)-**3** resulted (Table 2, entries 6 and 7). Conversion of (*R*)-(−)-**3** into the N-Boc **12** was readily accomplished in 74% yield by treatment with di-*tert*-butyl dicarbonate according to the method of Boger.[2c]

In summary, the sulfinimine asymmetric Strecker synthesis affords the epimerization-sensitive (*R*)-(−)-(4-methoxy-3,5-dihydroxyphenyl)glycine (**3**) in four steps in 40% overall yield from readily available starting materials. This represents the most efficient synthesis of this key central vancomycin amino acid to date.

Experimental Section

General Procedure. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). Analytical and preparative thin-layer chromatography was performed on precoated silica gel plates (250 and 1000 μm) purchased from Analtech Inc. TLC plates were visualized with UV in an iodine chamber or with phosphomolybdic acid, unless noted otherwise. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. THF was freshly distilled under nitrogen from a purple solution of sodium and benzophenone. Elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

3,4,5-Trimethoxylbenzaldehyde (**8a**) and 1.0 M Et_2AlCN were dissolved in toluene. (1*S*,2*R*,5*S*)-(+)-menthyl-(*R*)-*p*-toluenesulfinate (**9**) can be purchased from Aldrich or prepared on a large scale according to the Posner/Solladie procedure.[17] Methyl 3,5-bis(benzyloxy)-4-methoxybenzoate (**7c**)[2c] and methyl 3,5-bis(*tert*-butyldimethylsilyloxy)-4-methoxybenzoate (**7d**)[15] were prepared as previously described.

Methyl-3,5-diisopropoxy-4-methoxybenzoate (7b). In a 100 mL single-neck round-bottom flask equipped with a magnetic stir bar, rubber septum, and argon-filled balloon was placed methyl 3,5-dihydroxy-4-methoxybenzoate[15] (1.7 g, 8.57

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mmol), in anhydrous DMF (25 mL). Anhydrous K_2CO_3 (4.46 g, 32.3 mmol) and 2-bromopropane (2.74 g, 22.3 mmol) were added to the solution, and the reaction mixture was refluxed for 3 h. At this time the solution was diluted with H_2O (25 mL), the aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to give a yellow oil. Flash chromatography (EtOAc:hexane 1.5:8.5) afforded 1.99 g (82%) of **7b** as an oil. IR (neat) 2977, 2829, 1721, 1221 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (s, 2H), 4.51 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 1.28 (d, 12H, 6.5 Hz); ^{13}C NMR δ 167.3, 152.1, 145.9, 125.4, 111.1, 72.2, 61.0, 52.6, 22.7. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.80; H, 7.83.

Standard Procedure for the Reduction of Esters to Aldehydes Using DIBAL-H. In a 250 mL single-neck round-bottom flask equipped with a magnetic stir bar, rubber septum, and argon-filled balloon was placed the appropriate ester **7** (4.7 mmol) in dry toluene (40 mL). The mixture was cooled to −78 °C and stirred, and 1.0 M DIBALH in hexane (10.5 mL, 10.5 mmol) was added dropwise via syringe over 15 min. The reaction mixture was carefully monitored by TLC and quenched after 15−20 min at −78 °C by addition of 1 N HCl (10 mL). The solution was diluted with H_2O (25 mL), extracted with EtOAc (3 × 50 mL), dried (Na_2SO_4), and concentrated to give the aldehydes **8b**−**d**, which were purified by chromatography or crystallization.

3,5-Diisopropoxy-4-methoxybenzaldehyde (8b): yield 82% (flash chromatography 15% EtOAc/hexane); mp 72−73 °C (lit.[19] mp 74 °C); IR (KBr) 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.73 (s, 1H), 7.02 (s, 2H), 4.53 (m, 2H), 3.82 (s, 3H), 1.29 (d, 12H, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 191.6, 152.7, 147.0, 132.2, 110.5, 72.1, 60.9, 22.5. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.63; H, 8.00. Found: C, 66.62; H, 7.97.

3,5-Bis(benzyloxy)-4-methoxybenzaldehyde (8c): yield 89%; mp 87 °C (lit.[2c] mp 85.5−87.5 °C).

3,5-Bis(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde (8d): yield 78%; mp 75−76 °C (lit.[15] mp 74−75 °C).

Standard Procedure for the Asymmetric Synthesis of Sulfinimines.[8] In a 250 mL single-neck round-bottom flask equipped with a magnetic stir bar, rubber septum, and an argon balloon was dissolved (1*S*,2*R*,5*S*)-(+)-menthyl-(*R*)-*p*-toluenesulfinate (1.11 g, 3.78 mmol) in THF (35 mL) and cooled to −78 °C. Via syringe, 1.0 M LiHMDS in THF (5.3 mL, 5.3 mmol) was added dropwise to the solution which was brought to room temperature and stirred for 2 h. At this time the reaction mixture was cooled to 0 °C, the appropriate aldehyde **8** (3.0 mmol) added, and the solution cooled to −78 °C and monitored by TLC for the disappearance of the aldehyde (2−24 h). At this time the solution was quenched with aqueous NH_4Cl (4 mL) and diluted with EtOAc (50 mL) and H_2O (25 mL) and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated to give the crude sulfinimines **10** which were purified by flash chromatography (EtOAc:*n*-hexane, 2:8) or crystallization.

(*R*)-(−)-*N*-(3,4,5-Trimethoxybenzylidene)-*p*-toluenesulfinamide (10a): yield 76% (crystallization from ether); mp 93 °C; $[\alpha]^{25}_D$ −24.3 (*c* 0.8, $CHCl_3$); IR (KBr) 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.64 (s, 1H), 7.62 (d, 2H, J = 8.1 Hz), 7.31 (d, 2H, J = 8.1 Hz), 7.09 (s, 2H), 3.89 (s, 9H), 2.40 (s,3H); ^{13}C NMR ($CDCl_3$) δ 160.1, 153.4, 141.9, 141.8, 141.7, 129.8, 129.1, 124.7, 106.6, 60.9, 56.1, 21.4. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.75; N, 4.19. Found: C, 61.19; H, 5.73; N, 4.14.

(*R*)-(+)-*N*-[3,5-Diisopropoxy-4-methoxybenzylidene]-*p*-toluenesulfinamide (10b): yield 80% (flash chromatography 20% EtOAc/hexane); mp 123−125 °C; $[\alpha]^{25}_D$ +7.2 (*c* 0.8, $CHCl_3$); IR (KBr) 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (s, 1H), 7.60 (d, 2H, J = 8.5 Hz), 7.28 (d, 2H, J = 8.5 Hz), 7.05 (s, 2H), 4.54 (m, 2H), 3.84 (s, 3H), 2.36 (s, 3H), 1.33 (d, 12H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 161.0, 152.7, 145.7, 142.6, 142.3, 130.4, 129.6, 125.5, 111.0, 72.4, 61.2, 22.7, 22.0; IR (KBr) 1570 cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.72; H, 6.92; N, 3.51.

(*R*)-(+)-*N*-[3,5-Bis(benzyloxy)-4-methoxybenzylidene]-*p*-toluenesulfinamide (10c): yield 81% (crystallization 20% EtOAc/hexane); mp 97−98 °C; $[\alpha]^{25}_D$ +6.7 (*c* 0.75, $CHCl_3$); IR (KBr) 1573 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.56 (s,1H), 7.61 (d, 2H, J = 8.5 Hz), 7.45 (d, 2H, J = 8.5 Hz), 7.40−7.31 (m, 10H), 7.15 (s, 2H), 5.18 (s, 4H), 3.95 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.7, 153.4, 144.0, 142.5, 142.4, 137.2, 130.2, 129.7, 129.3, 128.7, 128.0, 125.5, 109.7, 71.8, 61.7, 22.1. Anal. Calcd for $C_{29}H_{27}NO_4S$: C, 71.73; H, 5.60; N, 2.88. Found: C, 71.70; H, 5.59; N, 2.81.

(*R*)-(+)-*N*-(3,5-Bis(*t*-butyldimethylsilyloxy)-4-methoxybenzylidene)-*p*-toluenesulfinamide (10d): yield 73% (flash chromatography 20% EtOAc/hexane); mp 123−124 °C; $[\alpha]^{25}_D$ +8.14 (*c* 0.8, $CHCl_3$); IR (neat) 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.51 (s, 1H), 7.59 (d, 2H, J = 8.1 Hz), 7.27 (d, 2H, J = 8.1 Hz), 6.98 (s, 2H), 3.73 (s, 3H), 2.36 (s, 3H), 0.97 (s, 18H), 0.14 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 160.7, 150.8, 147.8, 142.7, 142.2, 130.4, 129.8, 125.5, 116.5, 60.7, 26.3, 22.0, 18.9, −3.9. Anal. Calcd for $C_{27}H_{43}NO_4SSi_2$: C, 60.76; H, 8.13; N, 2.63. Found: C, 60.74; H, 8.15; N, 2.60.

Standard Procedure for the Synthesis of the α-Aminonitriles. In a 25 mL two-neck round-bottom flask equipped with a magnetic stir bar, rubber septa, and an argon balloon was placed the appropriate sulfinimine **10** (1.2 mmol) in THF (7 mL). The solution was cooled to −78 °C. In a separate 25 mL single-neck round-bottom flask equipped with a magnetic stir bar, rubber septum, and argon balloon were placed THF (6 mL), Et_2AlCN (1.8 mL, 1.8 mmol, 1.0 M in toluene), and anhydrous *i*-PrOH (0.1 mL). The solution was stirred for 15 min at room temperature and added via cannula to the sulfinimine at −78 °C. After 15 min, the reaction mixture was brought to room temperature, stirred, and monitoring by TLC for the disappearance of the sulfinimine (4−24 h). The reaction mixture was cooled to −78 °C and quenched by addition of aqueous $NaHCO_3$ (1.0 mL). The suspension was diluted with EtOAc (20 mL), filtered through Celite, and diluted with H_2O (25 mL) and the aqueous phase extracted with EtOAc (2 × 25 mL). The combined organic phases were washed with brine (35 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude amino nitriles **11** which were purified by chromatography or crystallization.

(*R*)-(−)-[*N*-(*R*)-*p*-Tolylsulfinyl]-2-amino-2-(3,4,5-trimethoxy)phenylacetonitrile (11a): yield 77%, de 96% (crystallization from ether); mp 166 °C; $[\alpha]^{25}_D$-184.5 (*c* 0.7, $CHCl_3$); IR (KBr) 2217, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (d, 2H, J = 8.5 Hz), 7.45 (d, 2H, J = 8.5 Hz), 6.80 (s, 2H), 5.28 (s, 1H), 3.92 (s, 6H), 3.87 (s, 3H), 2.50 (s, 3H); ^{13}C NMR δ 153.6, 142.5, 138.8, 138.1, 130.0, 129.0, 126.2, 117.5, 104.7, 60.7, 56.1, 43.8, 21.4. Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.60; N, 7.76. Found: C, 60.01; H, 5.58; N, 7.69.

(*R*)-(−)-[*N*-(*R*)-*p*-Tolylsulfinyl]-2-amino-2-(3,5-diisopropoxy-4-methoxy)phenylacetonitrile (11b): yield 77%, de 92% (flash chromatography 15% EtOAc/hexane); mp 154−156 °C; $[\alpha]^{25}_D$ −79.1 (*c* 1.6, $CHCl_3$); IR (neat) 2198, 1571 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (d, 2H, J = 8.4 Hz), 7.30 (d, 2H, J = 8.4 Hz), 6.49 (s, 2H), 5.05 (d, 1H, J = 7.8 Hz), 4.76 (d, 1H, J = 7.8 Hz), 4.43 (m, 2H), 3.74 (s, 3H), 2.38 (s, 3H), 1.30 (d, 12H, 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 152.9, 144.2, 130.5, 130.3, 128.8, 127.1, 126.4, 118.8, 108.8, 72.5, 61.1, 47.1, 22.8, 22.0. Anal. Calcd for $C_{22}H_{28}N_2O_4S$: C, 63.44; H, 6.78; N, 6.73. Found: C, 63.41; H, 6.72; N, 6.62.

(*R*)-(−)-[*N*-(*R*)-*p*-Tolylsulfinyl]-2-amino-2-[3,5-bis(benzyloxy)-4-methoxy]phenylacetonitrile (11c): yield 66% (flash chromatography 40% CH_2Cl_2/hexane); mp 155 (dec) °C; IR (KBr) 2282 cm^{-1}; $[\alpha]^{25}_D$ −134.1 (*c* 1.1, $CHCl_3$); ^1H NMR δ 7.62 (d, 2H, J = 8.1 HZ), 7.44−7.28 (m, 12H), 6.79 (s, 2H), 5.14 (d, 1H, J = 6.0 Hz), 5.10 (s, 4H), 4.58 (d, 1H, J = 6.0 Hz), 3.84 (s, 3H), 2.42 (s, 3H); ^{13}C NMR δ 154.4, 144.0, 141.4, 140.4, 137.9, 131.5, 130.1, 129.5, 129.0, 128.5, 127.6, 118.9, 108.7, 72.5, 62.4, 45.3, 22.9. Anal. Calcd for $C_{30}H_{28}N_2O_4S$: C, 70.28; H, 5.51; N, 5.46. Found: C, 70.21; H, 5.48; N,5.36.

(*S*)-(−)-[*N*-(*R*)-*p*-Tolylsulfinyl]-2-amino-2-(3,5-bis(benzyloxy)-4-methoxy)phenylacetonitrile (11c): yield 7%; mp

(18) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723.
(19) Personal communication from Professor Jieping Zhu.

147−149 °C; $[\alpha]^{25}_D$ −41.2 (*c* 0.9, $CHCl_3$); IR (KBr) 2251 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 7.53 (d, 2H, J = 8.1 Hz), 7.41−7.25 (m, 12H), 6.58 (s, 2H), 5.05 (s, 4H), 5.01 (d, 1H, J = 7.8 HZ), 4.66 (d, 1H, J = 7.8 HZ), 3.82 (s, 3H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.7, 142.3, 140.0, 139.6, 136.4, 129.8, 128.5, 128.2, 128.0, 127.3, 125.7, 117.8, 106.8, 71.0, 60.8, 46.3, 21.3. Anal. Calcd for $C_{30}H_{28}N_2O_4S$: C, 70.28; H, 5.51; N, 5.46. Found C, 70.25; H, 5.49; N, 5.40.

Standard Procedure for Hydrolysis of the α-Aminonitriles to Amino Acids. In a 25 mL single-neck round-bottom flask equipped with a magnetic stir bar and a water condenser were placed the appropriate α-aminonitrile **11** (0.7 mmol) and 3−6 N HCl (12 mL). The solution was refluxed and monitored by TLC for the absence of **11** (2−4.5 h). The reaction mixture was cooled to room temperature and extracted with ether (3 × 15 mL), and the aqueous layer was passed through a 6−8 g DOWEX 50 ion exchange column eluting with 1.4 N NH_4OH to give the amino acids on concentration.

Determination of α-Amino Acid Enantiomeric Purity by Conversion to the Mosher Amide. The enantiomeric purity of the amino acids were determined according to the method of Williams[18] by converting **3**, **13a,** and **13b** to their Mosher (MTPA) amides and examining the ^{19}F NMR spectra.

***(R)*-(−)-(3,4,5-Trimethoxyphenyl)glycine (13a):** yield 78%, ee >95%; mp 270 (dec) °C; $[\alpha]^{25}_D$ −119.7 (*c* 0.8, H_2O); IR (KBr) 3490 (br), 2975, 2815, 2604, 1601, 1510, 1310 cm^{-1}; ^{1}H NMR (D_2O + CD_3OD) δ 6.75 (s, 2H), 4.08 (s, 1H), 3.83 (s, 6H), 3.75 (s,3H); ^{13}C NMR (D_2O) δ 177.4, 148.2, 132.2, 129.3, 109.4, 65.7, 56.9, 56.1. Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.28; N, 5.80. Found: C, 54.75; H, 6.25; N 5.71.

***(R)*-(−)-(3,5-Diisopropoxy-4-methoxyphenyl)glycine (13b):** yield 71%, ee >97%; $[\alpha]^{25}_D$ −95.0 (*c* 0.9, $CHCl_3$) [lit.[19] $[\alpha]^{25}_D$ −92.0 (*c* 1.5, $CHCl_3$)]; IR (KBr) 3515 (br), 3042, 2831, 1972, 1695, 1536, 1325 cm^{-1}; ^{1}H NMR (D_2O + CD_3OD) δ 6.45 (s, 2H), 4.75 (m, 2H), 4.53 (s, 1H), 3.80 (s, 3H), 1.94 (d, 12 H, J = 4 0.5 Hz); ^{13}C NMR (D_2O+CD_3OD) δ 179.5, 142.0, 132.7, 131.3, 110.8, 73.2, 61.3, 58.7, 22.4. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.55; H, 7.80; N, 4.66.

***(R)*-(−)-(3,5-Dihydroxy-4-methoxyphenyl)glycine (3):** yield 76%, ee >97%; $[\alpha]^{25}_D$ −97.1 (*c* 0.9, H_2O) IR (KBr) 3590 (br), 2988, 1995, 1577 cm^{-1}; ^{1}H NMR (D_2O + CD_3OD) δ 6.45 (s, 2H), 4.50 (s, 1H), 3.67 (s, 3H); ^{13}C NMR (D_2O) δ 173.8, 150.9, 136.7, 131.3, 108.4, 61.2, 58.6. Anal. Calcd for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57. Found: C, 50.62; H, 5.17; N, 6.55.

***(R)*-(−)-N-[(*tert*-Butyloxy)carbonyl]-(3,5-dihydroxy-4-methoxyphenyl)glycine (12)**. This amino acid was prepared according to the procedure of Boger[2c] by treating (−)-**3** in aqueous THF with $NaHCO_3$ and di-*tert*-butyl dicarbonate, affording (−)-**12** in 74% yield; $[\alpha]^{25}_D$ −91.0 (*c* 1.1, MeOH) [lit.[2c] $[\alpha]^{25}_D$ −89 (*c* 0.8, MeOH)]. Its spectral properties were identical to literature values.[2c]

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