CH<sub>2</sub>N<sub>2</sub>, washing with H<sub>2</sub>O, and drying (Na<sub>2</sub>SO<sub>4</sub>) of the organic solvents prior to evaporation. The crude product was acetylated in 1:1 acetic anhydride-pyridine (5 °C, 8 h). Evaporation at 10<sup>4</sup> torr afforded 10 as a ca. 1:1 mixture of epimers (by GLC) which was distilled in the Kugelrohr at 80-90 °C (101 torr) to give 145 mg of 10 (80% yield).

The ca. 1:1 composition of the mixture 10 was determined by NMR, by using, as a reference, the spectra of the known<sup>9</sup> 8-exo-10 and of the endo-carbomethoxy epimer, which was obtained by chromatographic separation of the epimeric mixture 9 and by separate degradation of 8-endo-9.

8-endo-10: NMR (CCl<sub>4</sub>) 0.95 (3 H, d, J = 7), ca. 1.4-3.0 (5 H, m), 1.98 + 3.70 (2 s, each 3 H), ca. 3.2 + ca. 5.1 (2 m, each 1 H), ca. 5.3 (m, 2 H); IR (film) 1740, 1625, 1435, 1370, 1240, 900; MS 154 [M<sup>+</sup>(C<sub>13</sub>H<sub>18</sub>O<sub>4</sub>)-AcOH], 139, 119 (base peak), 95, 59, 43. Anal. Calcd for C<sub>13</sub>H<sub>18</sub>O<sub>4</sub>: C, 65.55; H, 7.56. Found: C, 65.81; H, 7.63.

Loganin Aglucon 6-Acetate (11). The highest yield was achieved when the hydroxylation of the epimeric mixture 10 (110 mg, 0.51 mmol) was carried out with a catalytic amount of OsO4 in combination with Nmethylmorpholine N-oxide in tert-butyl alcohol-tetrahydrofuran-H<sub>2</sub>O at room temperature.<sup>18</sup> Cleavage of the crude product with NaIO<sub>4</sub> in aqueous dioxane at 0 °C<sup>9c</sup> gave 66 mg 11 (60% yield),  $[\alpha]_D + 2^\circ$  (0.5).<sup>10</sup> The <sup>1</sup>H NMR and IR spectra were in agreement with the data given<sup>9c</sup> for  $(\pm)$ -11.

Registry No. (±)-1, 68908-13-4; (+)-1, 16196-15-9; (+)-2, 88195-48-6; (-)-2, 88106-35-8; (-)-3, 77551-15-6; (-)-4, 88195-49-7; (-)-5, 88195-50-0; (-)-6, 88106-36-9; (-)-7, 88106-37-0; (+)-8, 88106-38-1; 8-endo-9, 88106-39-2; 8-exo-9, 88106-40-5; 8-endo-10, 88195-51-1; 8exo-10, 88195-53-3; (+)-11, 88195-52-2; OC(CO<sub>2</sub>Et)<sub>2</sub>, 609-09-6; diethyl (R,R)-(+)-tartrate, 87-91-2.

# $\alpha$ -Amino Acids as Chiral Educts for Asymmetric Products. A General Synthesis of D- $\alpha$ -Amino Acids from L-Serine

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Abstract: A short and chirally efficient synthesis of four D- $\alpha$ -amino acids is described with L-serine as the chiral educt. The key C-C bond-forming reactions are the aminoacylations of organometallics with the lithium salt of N-(phenylsulfonyl)-L-serine (2) to give optically pure N-blocked  $\alpha$ -amino ketones. Reduction of the carbonyl group to carbinol or methylene followed by oxidation of the hydroxymethyl to carboxyl gives the N-blocked D-amino acids. The examples investigated (norleucine,  $\alpha$ -aminopimelic acid, DOPA, and allothreonine) demonstrate the broad applicability of the method.

The preparation of enantiomerically pure compounds is an increasingly important challenge in modern organic synthesis. To meet this challenge the synthetic chemist must rely on the "chiral pool" of organic substrates, either through their direct use or as inducing agents. While the natural L- $\alpha$ -amino acids are readily available, inexpensive members of this "chiral pool", the D- $\alpha$ -amino acids are in general rare and expensive materials. The most frequently described preparations of D-amino acids proceed either by resolution of a racemic mixture<sup>2-4</sup> or by asymmetric induction using a chiral auxiliary reagent.<sup>5,6</sup> These methods suffer from experimental unpredictability, the need for often expensive resolving agents or chiral auxiliary reagents, lack of complete diastereoselection, and tedious recovery or recycle processes.

Because the D-amino acids show great promise as precursors to biologically important compounds such as peptide analogues,<sup>7</sup>

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Scheme I



antibiotics,<sup>10,11</sup> and alkaloids,<sup>12</sup> we have developed a general Damino acid synthesis which consistently leads to optically pure materials and requires no resolving agents or chiral auxiliary reagents. Our synthesis proceeds from inexpensive L-serine and utilizes the aminoacylation of organolithium or Grignard reagents as the key carbon-carbon bond-forming step.<sup>13,14</sup> Four examples have been chosen to demonstrate the generality of the method. These are D-norleucine,<sup>15</sup> D- $\alpha$ -aminopimelic acid,<sup>16</sup> D-DOPA (D-

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3-(3,4-dihydroxyphenyl)alanine),<sup>17</sup> and D-allothreonine.<sup>18</sup> In each case optical purity has been established by HPLC analysis of diastereomeric derivatives of the D-amino acids.

#### **Results and Discussion**

Aminoacylations. It has been previously demonstrated that Grignard reagents and organolithium compounds can be aminoacylated with the lithium carboxylates of several N-protected  $\alpha$ -amino acids.<sup>13,14</sup> These reactions proceed with complete retention of configuration at the  $\alpha$ -chiral center when a suitable N-protecting group is used. Thus, optically pure  $\alpha$ -amino ketones may be obtained with little or no overaddition to tertiary alcohols.14 In the present work the dilithio salt of N-(phenylsulfonyl)-L-serine was shown to aminoacylate several organometallics affording the various  $\alpha$ -amino- $\beta$ -hydroxy ketones **3a-d** (Scheme I). Hydroxyl group protection was found to be unnecessary and presumably a trianion is formed prior to carbonyl addition. When Grignard reagents are used, 200 mol % of n-butyllithium is added first to neutralize the acidic protons in part since the lithium counter ion improves the outcome of these reactions<sup>14</sup> and to conserve the Grignard reagent. In general, a total of 600 mol % of organometallic reagents gave the best results.

Thus, ketones 3a and 3b were formed by treating N-(phenylsulfonyl)-L-serine (2) with 200 mol % of *n*-butyllithium followed by 400 mol % of the proper Grignard reagent. On the other hand, 3c and 3d were formed by treating 2 directly with 600 mol % of the proper lithium reagents. The lithium reagents were aminoacylated in about 2 h at room temperature or 0 °C in THF, whereas the Grignard reagnets required 20-40 h at room temperature. In the reaction of 2 with methyllithium to give 3d, the yield was consistently above 60% only if tetramethylethylenediamine was included. Otherwise the yield of 3d was inconsistent and sometimes as low as 25%. No such additives were required in the other three cases.

Ketone Reductions. Ketones 3a-c were reduced to the corresponding methylene compounds. For the alkyl ketones 3a and 3b this was best accomplished by a two-step process in which the thioketals 4a and 4b are first formed and subsequently desulfurized with Raney nickel to afford 5a and 5b, respectively. While these were successful and high yield reactions, we considered that dimethoxyphenyl ketone 3c might be reduced in a single step. Catalytic reduction proved to be rather troublesome, generally proceeding only to the alcohol stage, although deoxygenation to methylene derivative 5c did proceed in low yield when a mixture of acetic and perchloric acids was used as the solvent with 10% Pd on carbon as catalyst. Much better results were obtained by reducing the ketone with triethylsilane in trifluoroacetic acid.<sup>19</sup> In this way 5c was obtained in 81% yield.

Methyl ketone 3d was not reduced to the methylene stage. Rather, the diols 5d and 5e were prepared by stereoselective reductions. Sodium borohydride in ethanol gave the highest ratio of 5d to 5e (7:3). On the other hand, 5e could be prepared with very high selectivity (>99:1) by using L-selectride. All other reducing agents examined gave intermediate results. These reductions are shown in Scheme II.

Oxidations of Primary Alcohols to Acids. All the oxidations  $(5a-d \rightarrow 6a-d)$  were performed catalytically with O<sub>2</sub> and platinum.<sup>20,21</sup> Best results were obtained by using water as the solvent at 55-60 °C. Under these conditions, primary diol 5b is converted to diacid 6b. On the other hand, primary-secondary diol 5d is selectively oxidized at the primary hydroxyl affording the hydroxy acid 6d. At higher temperatures this selectivity is diminished. Furthermore, higher temperatures led to the formation of 3,4dimethoxybenzoic acid from 5c. The yields of these oxidations

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L-selectride 3d

1% 5d.

Scheme III



varied from about 55% for 6d to 73% for 6b, with some recovery of alcohol educt. Some chemical oxidations of 5c were also attempted<sup>22-24</sup> but these gave unsatisfactory results. While relatively large amounts of platinum are required for these catalytic oxidations, we routinely recovered >95% of the catalyst used.

Deblocking. The amino acids 7a-c were obtained from their blocked counterparts 6a-c by refluxing with 48% HBr containing phenol.<sup>25,26</sup> In the case of **6c**, demethylation and dephenylsulfonylation took place simultaneously affording D-DOPA (7c) directly. N-(phenylsulfonyl)-D-allothreonine (6c) was deprotected with sodium in liquid ammonia.<sup>27</sup> In each case the amino acids were isolated by ion-exchange chromatography and crystallized from a suitable solvent. These reactions are summarized in Scheme III.

Optical Purity. The optical purity of each amino acid was established as >99% (the limits of detection). This was done by diastereomer formation with N-(phenylsulfonyl)-L-prolyl chloride14

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or (+)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl chloride<sup>28</sup> and analysis by HPLC. Parallel reactions with the  $(\pm)$ -acylating reagnets allowed us to develop HPLC conditions with limits of detection at <1%.

**Conclusions.** Four optically pure D- $\alpha$ -amino acids have been efficiently synthesized from L-serine. The results indicate that the method should be widely applicable to aliphatic, aromatic, and further functionalized D-amino acids. At this point, the generality of the method appears to be limited only by the availability of the required organometallic reagnet for a given target, a relatively minor limitation in view of the rapidly expanding arsenal of such reagents.<sup>29</sup>  $\beta$ -Hydroxy-D- $\alpha$ -amino acids may also be formed with stereocontrol being exerted at the ketone reduction stage (as in  $3d \rightarrow 5d$  or 5e).

#### **Experimental Section**

General. Ether and THF were distilled from sodium/benzophenone immediately before use, and were transferred by syringe. Organometallic reactions were carried out under N2, reagents being transferred by syringe. Methyllithium was used as an ether solution and *n*-butyllithium (n-BuLi) was used as a hexane solution. Platinum oxide (used for preparing platinum oxidation catalyst) was prepared from ammonium chloroplatinate as described<sup>30,31</sup> using a platinum vessel. <sup>1</sup>H NMR spectra were recorded on a Varian EM 390 (90 MHz), UCB 200 (200 MHz), or UCB 250 (250 MHz) spectrometer in CDCl<sub>3</sub> unless otherwise noted, and are reported in ppm ( $\delta$  units) downfield of internal tetramethylsilane (Me4Si). Melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241 digital plolarimeter. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer.

N-(Phenylsulfonyl)-L-serine (2). L-Serine (33.82 g, 0.322 mol) was dissolved in  $H_2O$  (250 mL) and treated with  $Na_2CO_3$  (95 g, 0.9 mol), followed by phenylsulfonyl chloride (65 g, 0.37 mol). The mixture was vigorously stirred for 4 h, water was added to dissolve the precipitated sodium salt, the mixture was filtered, and the filtrate was acidified to pH 2 (concentrated HCl) and chilled to 4 °C. The product was collected and washed with water and ethanol: yield, 55.3 g, 70%; mp 222-224 °C dec (it.<sup>14</sup> mp 223-225 °C); <sup>1</sup>H NMR (Me<sub>2</sub>SO- $d_6$ )  $\delta$  3.56 (d, 2 H, J = 6 Hz), 3.83 (m, 1 H), 7.5–8.2 (m, 7 H);  $[\alpha]^{2}_{D}$  +9.25° (c 2, MeOH).

(S)-2-(N-(Phenylsulfonyl)amino)-1-hydroxy-3-hexanone (3a). N-(Phenylsulfonyl)-L-serine (2, 2.45 g, 10.0 mmol) in THF (100 mL) was treated with n-BuLi (13.3 mL, 20.0 mmol) at -78 °C, followed by npropylmagnesium bromide (40.0 mmol) in THF (40 mL). The mixture was warmed to room temperature and stirred for 40 h. It was then poured into 1 N HCl (130 mL) with ice cooling and extracted with three portions of ether. The extracts were washed with NaHCO<sub>3</sub> (saturated) and brine, dried, and evaporated. Crystallization of the residue from EtOAc/petroleum ether gave **3a** (2.1 g, 78%): mp 123-124 °C; <sup>1</sup>H NMR  $\delta$  0.74 (t, 3 H, J = 7 Hz), 1.44 (m, 2 H), 2.41 (m, 2 H), 3.87 (br s, 3 H), 5.95 (br s, 1 H), 7.52 (m, 3 H), 7.82 (m, 2 H), IR (nu)0) 3480, 3240, 1720 cm<sup>-1</sup>;  $[\alpha]^{20}_{D}$  +18.5° (c 3, MeOH). Anal. Calcd for  $C_{12}H_{17}NO_4S$ : C, 53.1; H, 6.3; N, 5.2. Found: C, 53.1; H, 6.3; N, 5.1. Also 15% of educt 2 was recovered by acidifying the bicarbonate

washings and extracting with EtOAc.

(S)-2-(N-(Phenylsulfonyl)amino)-3-oxo-1,7-dihydroxyheptane (3b) was prepared in the same manner as 3a, but using a Grignard reagent prepared from 1-bromo-4-((trimethylsilyl)oxy)butane<sup>32</sup> and Mg in THF. The reaction proceeded for 20 h and gave 12% of recovered 2 and 55% of 3b: mp 102-103 °C from EtOAc/petroleum ether; <sup>1</sup>H NMR (acetone- $d_6$ )  $\delta$  1.39 (m, 4 H), 2.56 (m, 2 H), 2.76 (s, 2 H), 3.25-4.15 (m, 5 H), 6.59 (d, 1 H), 7.60 (m, 3 H), 7.85 (m, 2 H); IR (nujol) 3530, 3235, 1712 cm<sup>-1</sup>;  $[\alpha]_{20}^{20}$  +6.7° (c 2, MeOH). Anal. Calcd for C<sub>13</sub>H<sub>19</sub>NO<sub>5</sub>S: C, 51.8; H, 6.4; N, 4.6. Found: C, 51.9; H, 6.4; N, 4.7.

 $(S) \cdot \alpha \cdot (N \cdot (Phenylsulfonyl) a mino) \cdot \beta \cdot hydroxy \cdot 3, 4 \cdot dimethoxy propio$ phenone (3c). A solution of 4-bromoveratrole (3.26 g, 15 mmol) in THF (20 mL) was cooled to -78 °C and treated with n-BuLi (9.74 mL, 14.7 mmol). After stirring this solution for 20 min, a suspension of 2 (0.60 g, 2.45 mmol in THF 40 mL) was added over 30 min. After a further 30 min at -78 °C, the mixture was warmed to room temperature and stirred for 2 h, and the product was isolated as above to provide 3c (0.74 g, 83%): mp 194-195 °C from acetone; <sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 3.82 (s, 3 H), 3.86 (s, 3 H), 3.8-4.2 (m, 3 H), 6.97 (d, 1 H, J = 9 H), 7.3-7.9 (m, 7 H); IR (nujol) 3484, 3279, 1689, 1605 cm<sup>-1</sup>;  $[\alpha]^{23}_{D}$  +22° (c 0.5, MeOH). Anal. Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>6</sub>S: C, 55.9; H, 5.2; N, 3.8. Found: C, 55.8; H, 5.3; N, 3.7.

(S)-3-(N-(Phenylsulfonyl)amino)-4-hydroxy-2-butanone (3d). N-(Phenylsulfonyl)-L-serine (4.56 g, 18.6 mmol) was suspended in THF (200 mL) and treated with tetramethylethylenediamine (16.8 mL, 112 mmol), the resulting solution was cooled to -78 °C, and MeLi (72 mL, 112 mmol) was added over 30 min. After being stirred 1 h at -78 °C, the solution was warmed to 0 °C, stirred for 2 h, poured into ice cold 2 M H<sub>3</sub>PO<sub>4</sub> (150 mL), and extracted three times with EtOAc. The extracts were washed with four small portions of saturated NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The residue was crystallized from EtOAc to give 3d (2.72 g, 60%): mp 157–158 °C; <sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 1.72 (s, 1 H), 2.12 (s, 3 H), 3.6-4.2 (m, 3 H), 7.6 (m, 3 H), 7.85 (m, 2 H);  $[\alpha]^{25}_{D}$  +23.8° (c 1, MeOH). Anal. Calcd for C<sub>10</sub>H<sub>13</sub>NO<sub>4</sub>S: C, 49.4; H, 5.4; N, 5.8. Found: C, 49.3; H, 5.4; N, 5.8.

(S)-2-(N-(Phenylsulfonyl)amino)-3,3-(ethylenedithio)-1-hexanol (4a). Ketone 3a (170 mg, 0.63 mmol) was stirred in ethanedithiol (0.45 mL) and BF3. Et2O (0.45 mL) for 20 h at room temperature then poured into ice cold saturated NaHCO<sub>3</sub> (15 mL). Extracting with  $CH_2Cl_2$  (3 × 10 mL) and drying (MgSO<sub>4</sub>) and evaporating the extracts left a residue which was chromatographed on silica gel (EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) to give 4a as an oil (197 mg, 91%): <sup>1</sup>H NMR  $\delta$  0.83 (t, 3 H, J = 7 Hz), 1.2-2.1 (m, 4 H), 2.49 (m, 1 H), 3.13 (m, 4 H), 3.66 (m, 3 H), 5.31 (d, 1 H, J = 10 Hz), 7.5 (m, 3 H), 7.85 (m, 2 H); IR (neat) 3600, 3300 cm<sup>-1</sup>;  $[\alpha]^{20}_{D}$  +4.8° (c 4, CH<sub>2</sub>Cl<sub>2</sub>). Anal. Calcd for C<sub>14</sub>H<sub>21</sub>NO<sub>3</sub>S<sub>3</sub>: C, 48.4; H, 6.1; N, 4.0. Found: C, 48.3; H, 6.1; N, 4.0.

(S)-2-(N-(Phenylsulfonyl)amino)-3,3-(ethylenedithio)-1,7-dihydroxyheptane (4b) was prepared from 3b in the same manner as 4a. The yield of 4b was 87%, as an oil: <sup>1</sup>H NMR δ 1.27-2.20 (m, 6 H), 2.87 (br s, 2 H), 3.17 (m, 4 H), 3.4-3.9 (m, 5 H), 5.60 (d, 1 H, J = 9 Hz),7.5 (m, 3 H), 7.9 (m, 2 H); IR (neat) 3330 cm<sup>-1</sup>;  $[\alpha]^{20}_{D}$  -19.2° (c 1, MeOH).

(R)-2-(N-(Phenylsulfonyl)amino)-1-hexanol (5a). A mixture of thioketal 4a (150 mg, 0.43 mmol) and W-2 Raney Ni (1.5 g) in EtOH (15 mL) was refluxed for 2 h, then filtered, and evaporated. The residue was chromatographed on silica gel (EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) to give 5a (92 mg, 83%) as an oil: <sup>1</sup>H NMR  $\delta$  0.70 (t, 3 H, J = 7 Hz), 0.9–1.6 (m, 6 H), 2.68 (br s, 1 H), 3.27 (m, 1 H), 3.50 (m, 2 H), 5.37 (d, 1 H, J = 9 Hz), 7.5 (m, 3 H), 7.9 (m, 2 H); IR (neat) 3470, 3280 cm<sup>-1</sup>;  $[\alpha]^{20}_{D}$  +24.7° (c 2, MeOH). Anal. Calcd for C<sub>12</sub>H<sub>19</sub>NO<sub>3</sub>S: C, 56.0; H, 7.4; N, 5.4. Found: C, 55.9; H, 7.4; N, 5.4.

(R)-2-(N-(Phenylsulfonyl)amino)-1,7-dihydroxyheptane (5b) was prepared from 5a in the same manner as above; chromatography was unnecessary. The yield of 5b was 83%: mp 81-82 °C from EtOAc; <sup>1</sup>H NMR (CDCl<sub>3</sub>/acetone- $d_6$ )  $\delta$  1.0–1.7 (m,  $\hat{8}$  H), 2.73 (s, 2 H), 3.10 (m, 1 H), 3.44 (m, 4 H), 5.91 (d, 1 H, J = 9 Hz), 7.49 (m, 3 H), 7.9 (m, 2 H); IR (nujol) 3480, 3125 cm<sup>-1</sup>;  $[\alpha]^{20}_{D}$  +19.7° (c 1, MeOH). Anal. Calcd for C13H21NO4S: C, 54.3; H, 7.4; N, 4.9. Found: C, 54.2; H, 7.2; N, 4.8.

(R)-2-(N-(Phenylsulfonyl)amino)-1-hydroxy-3-(3,4-dimethoxyphenyl)propane (5c). To a solution of aryl ketone 3c (100 mg, 0.27 mmol) in trifluoroacetic acid (624 mg, 5.4 mmol) was added triethylsilane (140 mg, 1.19 mmol) over 15 min, and the mixture was stirred at 45 °C for 24 h. After cooling, NaHCO<sub>3</sub> (saturated, 5 mL) was added, the mixture was extracted three times with EtOAc, and the extracts were dried and evaporated. The residue was chromatographed on silica gel (EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) to yield **5c** (75 mg, 81%): mp 120-121 °C from EtOAc/petroleum ether; <sup>1</sup>H NMR  $\delta$  2.65 (m, 2 H), 3.33-4.00 (m, 3 H), 3.66 (s, 3 H), 3.77 (s, 3 H), 5.28 (d, 1 H, J = 7 Hz), 6.06-6.66 (m, 4H), 7.2–7.5 (m, 3 H), 7.55–7.75 (m, 2 H); IR (nujol) 3448 cm<sup>-1</sup>;  $[\alpha]^{23}$ +130° (c 1, MeOH). Anal. Calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>5</sub>S: C, 58.1; H, 6.0; N, 4.0. Found: C, 57.9; H, 5.9; N, 3.9.

(2S,3R)-2-(N-(Phenylsulfonyl)amino)-1,3-dihydroxybutane (5d). Ketone 3d (2.65 g, 10.9 mmol) was suspended in EtOH (100 mL) at 0 °C, NaBH<sub>4</sub> (1.0 g, 26 mmol) was added, and the mixture was stirred at 0 °C for 1 h and then warmed to room temperature. A mixture of acetic acid and  $H_2O$  (1/1, 10 mL) was added dropwise, the solvent was evaporated, and the residue was dissolved in saturated NaHCO3 and extracted three times with CHCl<sub>3</sub>/i-PrOH (4/1). The extracts were dried (Na<sub>2</sub>-SO<sub>4</sub>) and evaporated to leave a 7/3 mixture of 5d and 5e (2.67 g, 100%), which was separated by medium-pressure reverse-phase (C<sub>18</sub>) chromatography ( $H_2O/CH_3CN, 95/5$ ). Crystallization from CHCl<sub>3</sub>/Et<sub>2</sub>O gave **5d** as needles: mp 69–70 °C; <sup>1</sup>H NMR  $\delta$  1.17 (d, 3 H, J = 6.4 Hz), 2.43 (s, 1 H), 3.06 (m, 1 H), 3.40 (m, 1 H), 3.65-3.90 (m, 3 H), 6.39 (d, 1 H, J = 7 Hz), 7.56 (m, 3 H), 7.91 (m, 2 H);  $[\alpha]^{25}_{D} - 1.6^{\circ}$  (c 1.6, MeOH). Anal. Calcd for C<sub>10</sub>H<sub>15</sub>NO<sub>4</sub>S: C, 49.0; H, 6.2; N, 5.7. Found: C, 48.9; H. 6.2; N. 5.7.

(25,35)-2-(N-(Phenylsulfonyl)amino)-1,3-dihydroxybutane (5e). Ketone 3d (182 mg, 0.75 mmol) was dissolved in THF (15 mL) and

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cooled to -78 °C. D-Selectride (1*M* in THF, 3 mL) was added and stirring was continued for 2 h at -78 °C. The reaction was quenched by adding HOAc/H<sub>2</sub>O (1/1, 5 mL). After warming to room temperature, the solvents were evaporated and the residue was dissolved in EtOH (10 mL) and treated with 1 N HCl (10 mL) with sitrring overnight at room temperature. The solvents were gain evaporated, and the residue was dissolved in H<sub>2</sub>O which was washed with petroleum ether twice and then extracted with CHCl<sub>3</sub>/*i*-PrOH (4/1) four times. The latter extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give 5e (164 mg, 90%): mp 115-116 °C from CHCl<sub>3</sub>; <sup>1</sup>H NMR (acetone-d<sub>6</sub>)  $\delta$  0.97 (d, 3 H, J = 7 Hz), 3.20 (m, 1 H), 3.45-3.85 (m, 2 H), 4.03 (m, 1 H), 6.03 (d, 1 H, J = 8 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H).

This material was identical with the minor component obtained from the  $NaBH_4$  reduction of 3d.

(*R*)-2-(*N*-(Phenylsulfonyl)amino)hexanoic Acid (6a). To PtO<sub>2</sub> (120 mg), reduced by shaking under H<sub>2</sub> (50 psi) for 15 min in H<sub>2</sub>O (15 mL), was added primary alcohol 5a (200 mg, 0.78 mol), and oxygen was passed through the mixture at 55 °C for 20 h. The mixture was filtered, NaHCO<sub>3</sub> was added to the filtrate until it was faintly alkaline, and the aqueous solution was washed with EtOAc and then acidified (6 N HCl) to pH 2. The acidic solution was extracted with EtOAc, and the extracts were dried and evaporated to give 6a (152 mg, 72%): mp 97–99 °C from CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane; <sup>1</sup>H NMR  $\delta$  0.83 (t, 3 H, J = 7 Hz), 1.22 (m, 4 H), 1.67 (m, 2 H), 3.93 (m, 1 H), 5.39 (d, 1 H, J = 10 Hz), 7.4–7.75 (m, 3 H), 7.8–8.0 (m, 2 H); IR (nujol) 3330, 1710 cm<sup>-1</sup>;  $(\alpha]^{20}_{D}$  –4.2° (*c* 0.6, MeOH). Anal. Calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>4</sub>S: C, 53.1; H, 6.3; N, 5.2. Found: C, 53.0; H, 6.3; N, 5.1.

(R)-2-(N-(Phenylsulfonyl)amino)-1,7-heptanedioic acid (6b) was prepared similarly to 6a using reduced PtO<sub>2</sub> (200 mg), H<sub>2</sub>O (30 mL), O<sub>2</sub>, and diol **5b** (300 mg, 1.04 mmol) at 60 °C for 48 h. The product was obtained as an oil and was not further purified (240 mg, 73%): <sup>1</sup>H NMR (acetone- $d_6$ )  $\delta$  1.1–1.9 (m, 6 H), 2.23 (t, 2 H, J = 7 Hz), 3.93 (m, 1 H), 6.7 (d, 1 H, J = 10 Hz), 7.4–7.7 (m, 3 H), 7.8–8.0 (m, 2 H).

(*R*)-2-(*N*-(Phenylsulfonyl)amino)-3-(3,4-dimethoxyphenyl)propionic Acid (6c). The oxidation of 5c was performed at 55 °C for 5.5 h to give 6c (55%) plus recovered educt (25%). Acid 6c had mp 173-174 °C from EtOAc/petroleum ether: <sup>1</sup>H NMR (acetone- $d_6$ )  $\delta$  2.93 (m, 2 H), 3.71 (s, 3 H), 3.77 (s, 3 H), 4.12 (m, 1 H), 6.70 (m, 3 H), 7.47 (m, 3 H), 7.67 (m, 2 H); IR (nujol) 3325, 1765 cm<sup>-1</sup>; [ $\alpha$ ]<sup>20</sup><sub>D</sub> +6.8° (c 1, MeOH). Anal. Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>6</sub>S: C, 55.9; H, 5.2; N, 3.8. Found: C, 55.7; H, 5.2; N, 3.7.

(2*R*,3*R*)-2-(*N*-(Phenylsulfonyl)amino)-3-hydroxybutanoic Aicd (6d). Diol 5d was oxidized for 24 h at 55 °C as above. The yield of pure, crystalline acid 6d was 55%: mp 175–177 °C from EtOAc/petroleum ether; <sup>1</sup>H NMR (5% Me<sub>2</sub>SO-*d*<sub>6</sub> in CDCl<sub>3</sub>)  $\delta$  1.17 (d, 3 H, *J* = 6.5 Hz), 3.83 (dd, 1 H, *J*<sub>1</sub> = 3.7 Hz, *J*<sub>2</sub> = 8.6 Hz), 4.01 (m, 1 H), 4.2–5.6 (s, 2 H), 6.29 (d, 1 H, *J* = 8.8 Hz), 7.5 (m, 3 H), 7.85 (m, 2 H), [ $\alpha$ ]<sup>23</sup><sub>D</sub>–16.8° (c 1.6, MeOH). Anal. Calcd for C<sub>10</sub>H<sub>13</sub>NO<sub>5</sub>S: C, 46.3; H, 5.1; N, 5.4.

These properties are identical with those of **6d** prepared from commercial D-allothreonine and phenylsulfonyl chloride under Schotten-Bauman conditions.

D-Norleucine (7a). A mixture of 6a (90 mg, 0.33 mmol), phenol (90 mg), and 48% HBr (1.2 mL) was refluxed for 30 min. After cooling the mixture, it was washed with EtOAc and evaporated to a residue which was purified by ion exchange chromatography on Dowex AG-1, X-8, 50–100 mesh, OH<sup>-</sup>. After loading the column and washing it with  $H_2O$ , the amino acid was eluted with 1 N HOAc in 80% yield (35 mg): mp

Table I			
	amino acid	acyl derivative <sup>a</sup>	HPLC conditions <sup>b</sup>
	7a	А	NP (EtOAc/isooctane, 18/32)
	7b	В	RP (H, O/MeOH, 50/50)
	7c	В	RP (H, O/MeOH, 50/50)
	7d	В	RP (H <sub>2</sub> O/CH <sub>3</sub> CN, 85/15)

<sup>a</sup> A is  $\alpha$ -Methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl, B is N-(phenylsulfonyl)prolyl. <sup>b</sup> NP is normal phase, RP is reversed phase.

299–301 °C dec (lit.<sup>15</sup> mp 301 °C dec);  $[\alpha]^{15}_{D}$  –20.1° (c 0.8, 6 N HCl) [lit.<sup>15</sup>  $[\alpha]^{20}_{D}$  –22.4° (c 4.7, 6 N HCl)].

D- $\alpha$ -Aminopimelic Acid (7b). Phenylsulfonyl derivative 6a was deblocked with HBr/phenol as above to give 7b in 66% yield: mp 218-220 °C from aqueous EtOH;  $[\alpha]^{20}_D - 20.5^\circ$  (c 1, 5 N HCl) [lit.<sup>16</sup>  $[\alpha]^{26}_D - 21.0$ (c, 1, 5 N HCl)]. Anal. Calcd for C<sub>7</sub>H<sub>13</sub>NO<sub>4</sub>: C, 48.0; H, 7.5; N, 8.0. Found: C, 47.85; H, 7.39; N, 7.83.

**D-Dopa** [D-3-(3,4-Dihydroxyphenyl)alanine, 7c] was prepared by deblocking 6c with HBr/phenol by refluxing for 1 h in 62% yield: mp 275-276 °C dec (lit.<sup>17</sup> mp 276-278 °C dec);  $[\alpha]^{20}_{D}$  +12.1° (c 1, 1 N HCl) [lit.<sup>17</sup>  $[\alpha]^{11}_{D}$  +13.0° (c 5, 1 N HCl)].

D-Allothreonine (7d). To 6d (150 mg, 0.58 mmol) dissolved in liquid NH<sub>3</sub> was added Na until a blue color persisted for 5 min, then NH<sub>4</sub>Cl was added to quench the blue color. After evaporating the NH<sub>3</sub>, the residue was purified by ion exchange as above and crystallized from H<sub>2</sub>O/ethanol: yield, 59 mg (86%); mp 268–270 °C (lit.<sup>18</sup> mp 272–273 °C dec);  $[\alpha]^{22}_{D}$  -8.8° (c 1, H<sub>2</sub>O) [lit.<sup>18</sup>  $[\alpha]^{25}_{D}$  -9.1° (c 3.9, H<sub>2</sub>O)].

**Determination of Optical Purities.** Each amino acid was converted to its methyl ester with methanolic HCl. The esters were then N-acylated with either N-(phenylsulfonyl)prolyl chloride<sup>14</sup> or  $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl chloride<sup>28</sup> When racemic N-acylating agents were used the resulting diastereomeric derivatives were shown to be separable by analytical HPLC. When optically pure N-acylating agents were used, HPLC showed that >99% of only one diastereomer was present (the limits of detection). Table I shows the specific acylated derivatives and HPLC conditions used in each case.

*N*-(Phenylsulfonyl)-L- or *N*-(Phenylsulfonyl)-D,L-proline. L- or D,L-proline (2.87 g, 25 mmol) was dissolved in 50 mL of 1 N NaOH (0.05 mol) and phenylsulfonyl chloride (4.41 g, 3.19 mL, 25 mmol) was added dropwise at room temperature. After being stirred for 5 h, the mixture was acidified with 2 N HCl to pH 2 and extracted with ether. The organic layer was dried (MgSO<sub>4</sub>) and evaporated to give 4.0 g (62%) of a white solid: mp 84-86 °C; <sup>1</sup>H NMR  $\delta$  1.9 (m, 2 H), 2.2 (m, 2 H), 3.4 (m, 2 H), 4.7 (t, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H). Anal. Calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>4</sub>S: C, 51.8; H, 5.1; N, 5.5. Found: C, 52.1; H, 5.2; N, 5.4.

*N*-(Phenylsulfonyl)-L- or *N*-(Phenylsulfonyl)-D,L-propyl Chloride. A solution of 1.27 g (5 mmol) of *N*-(phenylsulfonyl)-L- or *N*-(phenylsulfonyl)-D,L-proline in 10 mL of dry  $CH_2Cl_2$  with 1.0 mL (11 mmol) of oxalyl chloride and 2 drops of DMF was stirred for 1 h at room temperature. Volatile solvents were removed on the rotary evaporator and the residue was dissolved in benzene, washed with saturated NaH-CO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>), and evaporated to give 1.15 g (62%) of the acid chloride as a low melting solid: <sup>1</sup>H NMR  $\delta$  1.90 (m, 2 H), 2.20 (m, 2 H), 3.40 (m, 2 H), 4.70 (t, 1 H), 7.60 (m, 3 H), 7.9 (m, 2 H).

# Regiospecific Total Syntheses of $(\pm)$ -Aklavinone and $(\pm)$ - $\epsilon$ -Pyrromycinone from a Common Synthon

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Abstract: The preparation and use of the cyclohexenone 10 as a common intermediate for regiospecific total synthesis of both  $(\pm)$ -aklavinone (1a) and  $(\pm)$ - $\epsilon$ -pyrromycinone (2a) is described.

Aklavinone (1a) and pyrromycinone (2a) are the parent aglycons of two extensive families of glycosidically derived anthracycline antibiotics possessing significant anticancer activity.<sup>2,3</sup> Aklavin (1b), which has rhodosamine as the sugar residue, was