Enantiodivergent Approach to D- and L-Secondary *N*-Hydroxy-α-amino Acids by Using *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde Nitrone as an Effective *N*-Hydroxyglycine Cation Equivalent

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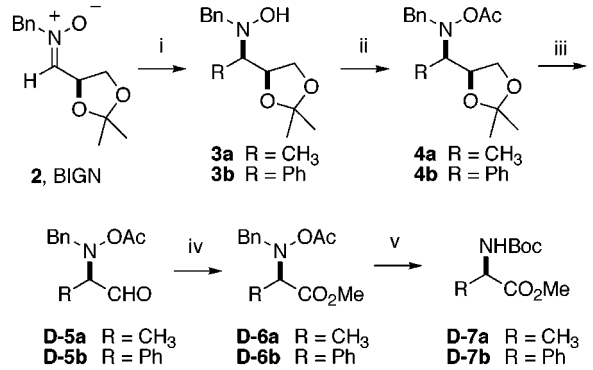
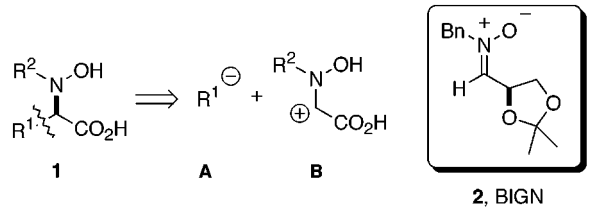
The development of efficient asymmetric syntheses of both natural and unnatural α-amino acids is one of the most important and challenging goals in organic synthesis. However, although there are numerous methods for the asymmetric synthesis of α-amino acids,[1] relatively few publications have appeared concerning the synthesis of the corresponding *N*-hydroxy-α-amino acids in optically pure form.[2] *N*-Hydroxy-α-amino acids are important compounds since they can be found in human and animal tumors and they are key intermediates in metabolic pathways.[3]

In connection with our general program aimed at the development of new nitrone-based methodologies for the preparation of nitrogenated compounds of biological interest,[4] we report herein a new and efficient general method for the asymmetric synthesis of secondary *N*-hydroxy-α-amino acids **1**. A retrosynthetic analysis leads to a carbanion synthon **A** and a *N*-hydroxy glycine cation synthon **B** by disconnection of the R−C bond. The nucleophilic addition of an organometallic compound, like a Grignard reagent, to the nitrone **2**, namely, *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (hereafter BIGN) should open a new enantiodivergent pathway to secondary *N*-hydroxy-α-amino acids **1**. According to this strategy, BIGN **2** can be considered as a convenient synthetic equivalent of the *N*-hydroxyglycine cation synthon. In addition, since *N*-hydroxy-α-amino acids are immediate precursors of the corresponding α-amino acids by reduction, BIGN (**2**) also constitutes a new equivalent of the glycine cation synthon.[5]

Scheme 1[a]



[a] Reagents and conditions: (i) $ZnBr_2$, Et_2O, rt, 5 min, then RMgBr, Et_2O, −60 °C, 6 h; (ii) Ac_2O, Py, rt, 1 h; (iii) H_5IO_6, Et_2O, rt, 4 h; (iv) $NaClO_2$, NaH_2PO_4, $CH_3CN{\cdot}H_2O$, 10 °C, 2 h, then Na_2SO_3, 10% HCl (aq), then CH_2N_2, Et_2O, 0 °C, 15 min; (v) H_2, $Pd(OH)_2$−C, MeOH−AcOEt, Boc_2O, 70 psi, 5 days.



The addition of Grignard reagents to BIGN (**2**) according to our previously established conditions[6] afforded the corresponding *syn*-hydroxylamines **3** (R = Me, ds = 91%; R = Ph, ds = 90%). It is worth mentioning that by carrying out the addition reaction 20 °C below (i.e., −60 °C) the temperature given in our previous paper[6] better results regarding both selectivity and chemical yield were obtained with similar reaction times. The relative *syn*-configuration of hydroxylamines **3** had been unambiguously ascertained as described.[6] After chromatographic purification, the obtained *syn*-hydroxylamines **3** were acetylated (Ac_2O, pyridine) to give compounds **4** in good overall yields (75% and 77% for R = Me and R = Ph, respectively). Oxidation of the dioxolane ring was achieved by employing periodic acid in dry diethyl ether, following the procedure given by Wu[7] (Scheme 1). Under that treatment, the *N*-acetoxy-α-amino aldehydes D-**5** were obtained, and they were used in the following step without further purification. Subsequent oxidation of aldehydes D-**5** with sodium chlorite according to the Dalcanale and Montanari procedure[8] followed by esterification with diazomethane afforded the secondary *N*-hydroxy-α-amino acid derivatives D-**6**. These compounds were further converted to the *N*-(*tert*-butoxycarbonyl)

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(4) For some recent examples see: (a) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero T. *J. Org. Chem.* **1996**, *61*, 9028−9032. (b) Merino, P.; Anoro, S.; Castillo, E.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1887−1890. (c) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5497−5507. (d) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron Lett.* **1997**, *38*, 1813−1816. (e) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2381−2401.

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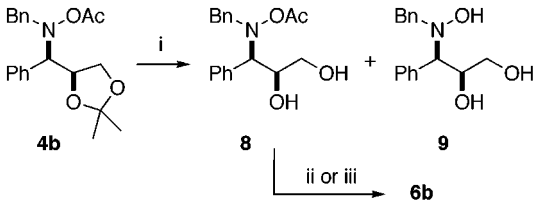
Scheme 2[a]



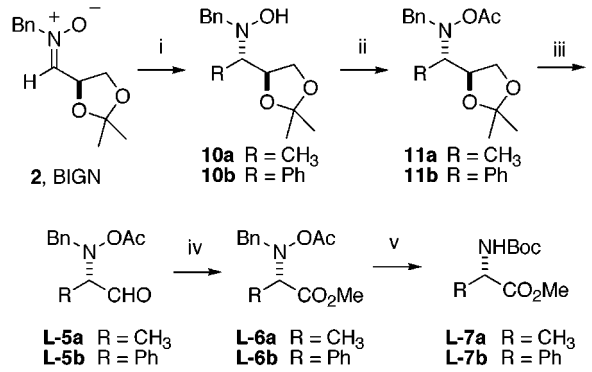
[a] Reagents and conditions: (i) *p*-TosOH, MeOH, 4 h, reflux; (ii) $NaIO_4$, CH_2Cl_2−$NaHCO_3$ (aq), rt, 2 h, then $NaClO_2$, NaH_2PO_4, $CH_3CN{\cdot}H_2O$, 10 °C, 2 h, then Na_2SO_3, 10%, HCl (aq); then CH_2N_2, Et_2O, 0 °C, 15 min; (iii) $NaIO_4$, $RuCl_3$, CH_3CN−$CCl_4{\cdot}H_2O$, rt, 15 min.

methyl ester forms of D-alanine D-**7a** and D-phenylglycine D-**7b** by catalytic hydrogenation (H_2, $Pd(OH)_2$−C) in the presence of an excess of di-*tert*-butyl dicarbonate.

The successful conversion of the diastereomerically pure hydroxylamines **4** to α-amino esters D-**7** in homochiral forms, as shown in Scheme 1, provided not only an additional confirmation of the absolute configuration of each product but also a basis for determining the enantiomeric purity of the obtained compound; the $[\alpha]_D$ value and melting point of D-**7a** were in excellent agreement with those found for an authentic sample.[9] Similarly, the physical and spectroscopic properties of D-**7b** were identical to those reported for its enantiomer, except for the sign of the optical rotation[10] (see the Experimental Section).

Since the dioxolane−carboxylic acid equivalence is a well-known subject and several examples can be found in the literature,[11] we also decided to study alternative elaborations of compounds **4** in order to improve the preparation of the targeted *N*-hydroxy-α-amino acid derivatives. As an example, deprotection of compounds **4b** to the corresponding diol **8** was achieved by using catalytic *p*-toluenesulfonic acid in refluxing methanol (Scheme 2); however, this cleavage appeared to be troublesome. This was mainly due to the partial deacetylation of the acetoxyamino group, gave **9** as a byproduct.[12] In addition, the poor solubility of the deprotected compounds in organic solvents made purification of **8** rather difficult. Nevertheless, diol **8** was oxidized in a two-step procedure consisting of (i) sodium periodate oxidation and (ii) treatment with sodium chlorite as described above. The obtained *N*-hydroxy-α-amino acid derivative was identical with the compound obtained by the oxidation of D-**4b**; however, it was obtained in an even lower overall yield (40%). Oxidation of diol **8** was also attempted in a one-pot procedure by using the system $NaIO_4$−$RuCl_3$. Surprisingly, with the conditions analogous to those reported by Sharpless,[13] only 15% of D-**6b** could be obtained from **8**, merely due to undesired ruthenium-mediated oxidation of the *N*-benzyl group. A similar situation had been reported by Pericas and co-workers,[11a] and in that case better results were obtained by changing the oxidation conditions to $NaIO_4$−$KMnO_4$ according to the Martin procedure.[14] Unfortunately, oxidation of **8** under these conditions also led to a poor yield of D-**6**. Thus, the first reaction sequence outlined in Scheme 1 remains as the most effective for the transformation of the dioxolane ring into a carboxylic acid derivative.

Scheme 3[a]



[a] Reagents and conditions: (i) Et_2AlCl, Et_2O, rt, 5 min, then RMgBr, Et_2O, −60 °C, 6 h; (ii) Ac_2O, Py, rt, 1 h; (iii) H_5IO_6, Et_2O, rt, 4 h; (iv) $NaClO_2$, NaH_2PO_4, $CH_3CN{\cdot}H_2O$, 10 °C, 2 h, then Na_2SO_3, 10% HCl (aq), then CH_2N_2, Et_2O, 0 °C, 15 min; (v) H_2, $Pd(OH)_2$−C, MeOH−AcOEt, Boc_2O, 70 psi, 5 days.

To demonstrate the enantiodivergency of our strategy, we also prepared the *anti*-hydroxylamines **10** according to our previously described protocol[6] for the *anti*-addition of Grignard reagents to **2** (Scheme 3). That protocol consists of precomplexing BIGN **2** with 1.0 equiv of Et_2-AlCl before carrying out the addition of the nucleophile. Also in this case, better results were obtained by carrying out the reaction at −60 °C (R = Me, ds = 82%; R = Ph, ds = 85%). Conversion of the *N*-acetoxy derivatives **11** into the *N*-hydroxy-α-amino acid derivatives was performed by the similar two-step sequence employed for the conversion of **4** to D-**6**, affording L-**6a** and L-**6b** in 61% and 65% overall yield, respectively. Catalytic hydrogenation of those compounds in the presence of di-*tert*-butyl dicarbonate furnished L-**7a** and L-**7b**. The physical and spectroscopic properties of L-**7a** were identical to those of an authentic sample.[9] Analogously, physical and spectroscopic properties of L-**7b** were coincident to those reported in the literature.[10]

In conclusion, a short and efficient route toward optically active *N*-acetoxy-α-amino acid derivatives has been developed. We have established a method for a preparation of a pair of enantiomers of *N*-hydroxy-α-amino acid derivatives starting with nitrone **2** as the only chiral source. The substituent on the nitrogen atom could be changed by starting from the corresponding *N*-substituted nitrone, which, in turn, could be prepared from D-glyceraldehyde and the appropriate *N*-substituted hydroxylamine[15] as described.[16] Deacetylation of the acetoxy moiety under standard conditions would yield free hydroxyamino derivatives. These considerations

(9) *N*-(*tert*-Butoxycarbonyl)-D-alanine methyl ester (cat. no. 41,464-6) and *N*-(*tert*-butoxycarbonyl)-L-alanine methyl ester (cat. no. 42,357-2) can be purchased from Aldrich.

(10) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181−186.

(11) See inter alia: (a) Medina, E.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1581−1586. (b) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585−587. (c) Poch, M.; Alcon, M.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1993**, *34*, 7781−7784.

(12) A variety of conditions were checked, including HCl (aq), AcOH (aq), and Dowex-50, and in all cases deacetylated **9** was found as a byproduct. Following the periodic acid hydrolysis/cleavage outlined in Scheme 1, only the expected aldehydes were found.

(13) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(14) Martin, T.; Rodriguez, C. M.; Martin, V. S. *J. Org. Chem.* **1996**, *61*, 6450−6453.

(15) The use of sugar-derived hydroxylamines would allow the introduction, on the nitrogen atom, of a group that could be removed without reducing the N−O bond. For an example see: Huber, R.; Vasella, A. *Helv. Chim. Acta* **1987**, *70*, 1461−1476.

show that the present method will be applicable to syntheses of other *N*-hydroxy-α-amino acid derivatives as a general method.

Experimental Section

General Methods. For general experimental information see ref 4e. Methyl- and phenylmagnesium bromide were used in diethyl ether from a 1.0 M commercial solution. *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (BIGN, **2**) was prepared as described.[16]

(2*S*,3*R*)-*N*-Benzyl-3-(hydroxyamino)-1,2-*O*-isopropylidene-1,2-butanediol (3a). To a well-stirred solution of nitrone **2** (0.94 g, 4 mmol) in diethyl ether (80 mL) was added anhydrous $ZnBr_2$ (0.9 g, 4 mmol) in one portion at room temperature, and the resulting mixture was stirred for 5 min. The mixture was then cooled to −60 °C and treated with methylmagnesium bromide (6 mmol, 6.0 mL of a 1.0 M solution in Et_2O). The mixture was stirred for 6 h at −60 °C and then treated with 1 N aqueous NaOH (25 mL). After additional stirring for 15 min at ambient temperature, the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and the solvent was evaporated in vacuo to give the crude product. The diastereoselectivity (ds = 91%) was established by ^{1}H NMR analysis. Purification by column chromatography on silica gel (70:30 hexane−diethyl ether) gave pure **3a** (0.754 g, 75%) as a sticky oil: $[\alpha]_D$ −19.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3H, J = 6.6 Hz), 1.33 (s, 3H), 1.34 (s, 3H), 2.91 (dq, 1H, J = 6.6, 7.0 Hz), 3.72 (dd, 1H, J = 7.5, 8.5 Hz), 3.80 (d, 1H, J = 13.2 Hz), 3.88 (dd, 1H, J = 5.8, 8.5 Hz), 3.92 (d, 1H, J = 13.2 Hz), 4.23 (ddd, 1H, J = 5.8, 7.0, 7.5 Hz), 6.10 (bs, 1H, ex. D_2O), 7.20−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.1, 25.6, 26.5, 60.9, 63.7, 66.7, 76.7, 108.8, 127.3, 128.3, 129.2, 137.7. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.04; H, 8.38; N, 5.61.

(2*S*,3*R*)-*N*-Benzyl-3-(hydroxyamino)-1,2-*O*-isopropylidene-3-phenyl-1,2-propanediol (3b). The nitrone **2** (0.94 g, 4 mmol) was treated as described above for the preparation of **3a** using phenylmagnesium bromide (6 mmol, 6.0 mL of a 1.0 M solution in Et_2O) as a Grignard reagent. ^{1}H NMR analysis of the crude product revealed a diastereoselectivity of 90%. Column chromatography (80:20 hexane−diethyl ether) of that crude product gave 0.965 g (77%) of **3b** as an oil: $[\alpha]_D$ −6.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.43 (s, 3H), 3.43 (dd, 1H, J = 6.6, 8.5 Hz), 3.66 (dd, 1H, J = 6.6, 8.5 Hz), 3.67 (d, 1H, J = 13.2 Hz), 3.73 (d, 1H, J = 8.8 Hz), 3.82 (d, 1H, J = 13.2 Hz), 4.79 (dt, 1H, J = 6.6, 8.8 Hz), 6.64 (bs, 1H, ex. D_2O), 7.21−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.8, 26.7, 61.5, 67.3, 72.4, 76.2, 109.8, 127.2, 127.7, 128.1, 128.7, 129.4, 129.8, 135.9, 137.5. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 73.02; H, 7.57; N, 4.40.

(2*S*,3*R*)-*N*-Benzyl-3-(acetoxyamino)-1,2-*O*-isopropylidene-1,2-butanediol (4a). A solution of hydroxylamine **3a** (0.70 g, 2.79 mmol) in CH_2Cl_2 (5 mL) at room temperature was treated sequentially with pyridine (5 mL) and acetic anhydride (5 mL). The resulting mixture was allowed to stir for 1 h, at which time it was diluted with CH_2Cl_2 (15 mL) and then poured into saturated aqueous $CuSO_4$ (25 mL). After the mixture was stirred vigorously for 5 min, the layers were separated and the organic layer was sequentially washed with saturated aqueous $CuSO_4$, water, and brine. The solution was dried ($MgSO_4$) and concentrated under reduced pressure to give a colorless oil that was subjected to purification by column chromatography on silica gel (80:20 hexane−diethyl ether) to give the acetylated product **4a** as a colorless oil (0.817 g, 100%): $[\alpha]_D$ +4.4 (*c* 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.11 (d, 3H, J = 6.7 Hz), 1.29 (s, 3H), 1.35 (s, 3H), 1.79 (s, 3H), 3.19 (dq, 1H, J = 5.7, 6.7 Hz), 3.79 (dd, 1H, J = 7.8, 8.1 Hz), 3.90 (dd, 1H, J = 6.4, 8.1 Hz), 4.00 (d, 1H, J = 13.3 Hz), 4.14 (d, 1H, J = 13.3 Hz), 4.24 (ddd, 1H, J = 5.7, 6.4, 7.8 Hz), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.5, 19.1, 25.1, 26.2, 60.1, 61.6, 65.8, 76.5, 108.6, 127.4, 128.1, 129.3, 136.1, 169.9. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.46; H, 8.11; N, 4.83.

(2*S*,3*R*)-*N*-Benzyl-3-(acetoxyamino)-1,2-*O*-isopropylidene-3-phenyl-1,2-propanediol (4b). The hydroxylamine **3b** (0.80 g, 2.55 mmol) was treated as described above for the preparation of **4a**. Column chromatography (80:20 hexane−diethyl ether) of the crude product gave 0.907 g (100%) of **4b** as a white solid: mp 76 °C; $[\alpha]_D$ −5.7 (c 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.34 (s, 3H), 1.76 (s, 3H), 3.34 (t, 1H, J = 8.5 Hz), 3.46 (dd, 1H, J = 6.2, 8.5 Hz), 3.92 (d, 1H, J = 13.4 Hz), 3.95 (d, 1H, J = 6.2 Hz), 3.97 (d, 1H, J = 13.4 Hz), 4.63 (dt, 1H, J = 6.2, 8.5 Hz), 7.20−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 19.4, 25.8, 26.7, 60.8, 67.5, 74.2, 77.8, 109.9, 127.4, 128.1, 128.6, 128.7, 128.9, 129.3, 130.4, 136.4, 170.2. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.04; H, 7.13; N, 3.88.

Methyl (2*R*)-*N*-Benzyl-2-(acetoxyamino)propanoate (D-6a). To a well-stirred suspension of periodic acid (0.912 g, 4.0 mmol) in dry diethyl ether was added compound **4a** (0.5 g, 1.7 mmol) at ambient temperature under argon atmosphere in one portion. Stirring was maintained for an additional 4 h, at which time the reaction mixture was filtered. The filtrate was evaporated under reduced pressure to give the crude aldehyde D-**5a** (^{1}H NMR ($CDCl_3$) δ 1.49 (d, 3H, J = 7.0 Hz), 1.89 (s, 3H), 3.74 (dq, 1H, J = 3.9, 7.0 Hz), 3.99 (d, 1H, J = 13.4 Hz), 4.14 (d, 1H, J = 13.4 Hz), 7.22−7.37 (m, 5H), 9.58 (d, 1H, J = 3.9 Hz)), which was dissolved in CH_3CN (5 mL). To the resulting mixture was added a solution of $NaClO_2$ (0.226 g, 2.6 mmol) in 5 mL of water dropwise. The resulting mixture was then treated with a solution of NaH_2PO_4 (50 mg, 0.417 mmol) in H_2O (2 mL) and 35% H_2O_2 (0.14 mL, 1.5 mmol), keeping the temperature of the mixture below 10 °C. After the mixture was stirred for 1 h, Na_2SO_3 (15 mg, 0.12 mmol) was added and the resulting mixture was acidified (pH = 2−3) with 10% aqueous HCl. The resulting mixture was partitioned between brine (30 mL) and dichloromethane (30 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give a residue that was taken up in diethyl ether (25 mL) and treated with a freshly distilled ethereal solution of diazomethane at 0 °C for 5 min. The solvent was removed under reduced pressure, and the residue was subjected to purification by column chromatography on silica gel (80:20 hexane−diethyl ether) to give the *N*-hydroxy-α-amino acid derivative D-**6a** as a colorless oil (0.265 g, 62%): $[\alpha]_D$ +10.9 (*c* 2.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 3H, J = 6.9 Hz), 1.88 (s, 3H), 3.77 (s, 3H), 3.83 (q, 1H, J = 6.9 Hz), 4.11 (d, 1H, J = 13.3 Hz), 4.21 (d, 1H, J = 13.3 Hz), 7.24−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.0, 51.8, 59.2, 62.8, 127.7, 128.2, 129.5, 135.5, 169.5, 171.4. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.13; H, 6.75; N, 5.50.

Methyl (2*R*)-*N*-Benzyl-2-(acetoxyamino)-2-phenylethanoate (D-6b). The compound **4b** (0.604 g, 1.7 mmol) was treated as described above for the preparation of crude D-**5b** (^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3H), 3.79 (d, 1H, J = 13.8 Hz), 4.11 (d, 1H, J = 13.8 Hz), 4.44 (d, 1H, J = 3.7 Hz), 7.24−7.6 (m, 10H), 9.63 (d, 1H, J = 3.7 Hz)). Further treatment of aldehyde D-**5b** as indicated above for the preparation of D-**6a** afforded, after column chromatography (80:20 hexane−diethyl ether), 0.320 g (60%) of pure D-**6b** as an oil: $[\alpha]_D$ −24.5 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3H), 3.65 (s, 3H), 3.79 (d, 1H, J = 13.5 Hz), 4.05 (d, 1H, J = 13.5 Hz), 4.70 (s, 1H), 7.20−7.42 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 19.4, 52.3, 59.9, 73.6, 127.9, 128.3, 128.6, 129.1, 129.2, 130.1, 133.8, 135.0, 168.8, 169.9. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.82; H, 6.08; N, 4.54.

***N*-(*tert*-Butoxycarbonyl)-D-alanine Methyl Ester (D-7a).** To a solution of D-**6a** (0.20 g, 0.80 mmol) in methanol (20 mL) were added Boc_2O (0.46 g, 2.1 mmol) and 20% palladium hydroxide on activated charcoal (Pearlman's catalyst) (30 mg). The resulting mixture was hydrogenated at 70 psi for 5 days (Parr hydrogenation apparatus). Filtration of the catalyst and evaporation of the solvent afforded a residue that was purified by column chromatography on silica gel (90:10 hexane−diethyl ether) to give 0.151 g (93%) of pure D-**7a** as a solid. The physical and spectroscopic data were identical to those of an authentic sample (Aldrich, cat. no. 41,464-6).

(16) (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3489−3496. (b) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537−2550.

***N*-(*tert*-Butoxycarbonyl)-D-phenylglycine Methyl Ester (D-7b).** The *N*-hydroxy-α-amino acid derivative D-**6b** (0.20 g, 0.638 mmol) was treated as described above for the preparation of D-**7a**. Column chromatography (80:20 hexane−diethyl ether) of the crude product gave 0.162 g (96%) of L-**7a** as a white solid: mp 112−114 °C; $[\alpha]_D$ −132.3 (*c* 1.1, $CHCl_3$) [lit. for enantiomer:[10] $[\alpha]_D$ +135.7 (*c* 0.8, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.73 (s, 3H), 5.34 (d, 1H, *J* = 7.3 Hz), 5.55 (d, 1H, *J* = 7.3 Hz), 7.30−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.3, 52.7, 57.5, 79.90, 127.2, 128.6, 129.1, 137.0, 154.8, 171.6. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.44; H, 7.10; N, 5.19.

(2*S*,3*R*)-*N*-Benzyl-3-(acetoxyamino)-3-phenyl-1,2-propanediol (8) and (2*S*,3*R*)-*N*-Benzyl-3-(hydroxyamino)-3-phenyl-1,2-propanediol (9). A solution of **4b** (0.2 g, 0.563 mmol) in MeOH (30 mL) was treated with *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol), and the resulting solution was refluxed for 4 h. After the solution was cooled to ambient temperature, the solvent was evaporated under reduced pressure and the residue was partitioned between saturated aqueous $NaHCO_3$ (30 mL) and EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. ^{1}H NMR analysis of this crude material revealed an 8:1 mixture of **8** and **9**, respectively. Attempts to purify of this material both by column chromatography and preparative TLC only afforded enriched mixtures of the products.

8: ^{1}H NMR ($CDCl_3$ + D_2O) (selected signals) δ 2.15 (s, 3H), 3.15 (dd, 1H, *J* = 4.3, 11.8 Hz), 3.48 (dd, 1H, *J* = 2.8, 11.8 Hz), 3.65 (s, 2H), 3.81 (d, 1H, *J* = 9.5 Hz), 4.20 (ddd, 1H, *J* = 2.8, 4.3, 9.5 Hz), 7.20−7.45 (m, 5H).

9: ^{1}H NMR ($CDCl_3$ + D_2O) (selected signals) δ 3.19 (dd, 1H, *J* = 3.7, 11.6 Hz), 3.56 (dd, 1H, *J* = 2.9, 11.6 Hz), 3.69 (s, 2H), 3.86 (d, 1H, *J* = 9.8 Hz), 4.26 (ddd, 1H, *J* = 2.9, 3.7, 9.8 Hz), 7.20−7.40 (m, 5H).

(2*S*,3*S*)-*N*-Benzyl-3-(hydroxyamino)-1,2-*O*-isopropylidene-1,2-butanediol (10a). The nitrone **2** (0.94 g, 4 mmol) was treated as described above for the preparation of **3a** using diethyl aluminum chloride (4 mmol, 4.0 mL of a 1.0 M solution in hexanes) as a Lewis acid. ^{1}H NMR analysis of the crude product revealed a diastereoselectivity of 82%. Column chromatography (70:30 hexane−diethyl ether) of that crude product gave 0.633 g (63%) of **10a** as a white solid: mp 84−86 °C; $[\alpha]_D$ −8.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 3H, *J* = 6.6 Hz), 1.34 (s, 3H), 1.39 (s, 3H), 2.84 (dq, 1H, *J* = 6.6, 7.3 Hz), 3.71 (d, 1H, *J* = 13.2 Hz), 3.86 (dd, 1H, *J* = 6.3, 8.4 Hz), 3.96 (d, 1H, *J* = 13.2 Hz), 4.08 (dd, 1H, *J* = 6.3, 8.4 Hz), 4.20 (dt, 1H, *J* = 6.3, 7.3 Hz), 5.60 (bs, 1H, ex. D_2O), 7.26−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.0, 25.4, 26.7, 61.0, 63.7, 66.7, 76.7, 108.8, 127.3, 128.3, 129.2, 137.7. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.85; H, 8.40; N, 5.77.

(2*S*,3*S*)-*N*-Benzyl-3-(hydroxyamino)-1,2-*O*-isopropylidene-3-phenyl-1,2-propanediol (10b). The nitrone **2** (0.94 g, 4 mmol) was treated as described above for the preparation of **3a** using diethyl aluminum chloride (4 mmol, 4.0 mL of a 1.0 M solution in hexanes) as a Lewis acid and phenylmagnesium bromide (6 mmol, 6.0 mL of a 1.0 M solution in Et_2O) as a Grignard reagent. ^{1}H NMR analysis of the crude product revealed a diastereoselectivity of 85%. Column chromatography (80:20 hexane−diethyl ether) of that crude product gave 0.852 g (68%) of **10b** as a white solid: mp 141−143 °C; $[\alpha]_D$ −17.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.29 (s, 3H), 3.52 (d, 1H, *J* = 13.4 Hz), 3.67 (d, 1H, *J* = 13.4 Hz), 3.70 (d, 1H, *J* = 6.7 Hz), 3.94 (dd, 1H, *J* = 6.7, 8.4 Hz), 4.15 (dd, 1H, *J* = 6.3, 8.4 Hz), 4.75 (dt, 1H, *J* = 6.3, 6.7 Hz), 4.86 (bs, 1H, ex. D_2O), 7.23−7.43 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 24.5, 26.5, 62.3, 68.3, 73.6, 76.4, 109.1, 127.3, 128.0, 128.2, 128.3, 129.3, 130.1, 136.3, 137.3. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.77; H, 7.60; N, 4.55.

(2*S*,3*R*)-*N*-Benzyl-3-(acetoxyamino)-1,2-*O*-isopropylidene-1,2-butanediol (11a). The hydroxylamine **10a** (0.70 g, 2.79 mmol) was treated as described above for the preparation of **4a**. Column chromatography (80:20 hexane−diethyl ether) of the crude product gave 0.816 g (100%) of **11b** as an oil: $[\alpha]_D$ −9.4 (*c* 1.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3H, *J* = 6.5 Hz), 1.30 (s, 3H), 1.34 (s, 3H), 1.81 (s, 3H), 2.96 (dq, 1H, *J* = 5.5, 6.5 Hz), 3.91 (d, 1H, *J* = 13.5 Hz), 3.92−3.99 (m, 2H), 4.08 (d, 1H, *J* = 13.5 hz), 4.09−4.15 (m, 1H), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.1, 19.2, 25.2, 26.7, 59.3, 63.0, 68.4, 77.4, 109.1, 127.6, 128.3, 129.1, 136.2, 169.4. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.46; H, 8.11; N, 4.83.

(2*S*,3*R*)-*N*-Benzyl-3-(acetoxyamino)-1,2-*O*-isopropylidene-3-phenyl-1,2-propanediol (11b). The hydroxylamine **10b** (0.80 g, 2.55 mmol) was treated as described above for the preparation of **4a**. Column chromatography (80:20 hexane−diethyl ether) of the crude product gave 0.904 g (100%) of **11b** as a white solid: mp 87−89 °C; $[\alpha]_D$ −37.9 (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3H), 1.24 (s, 3H), 1.85 (s, 3H), 3.71 (d, 1H, *J* = 13.3 Hz), 3.81 (d, 1H, *J* = 13.3 Hz), 3.84 (d, 1H, *J* = 8.1 Hz), 4.10 (dd, 1H, *J* = 6.8, 10.6 Hz), 4.16 (dd, 1H, *J* = 5.9, 10.6 Hz), 4.51 (ddd, 1H, *J* = 5.9, 6.8, 10.6 Hz), 7.22−7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 19.3, 25.2, 26.7, 60.4, 8.4, 72.1, 75.9, 109.3, 127.7, 128.2, 128.3, 128.4, 129.3, 130.4, 135.0, 135.9, 169.7. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.04; H, 7.13; N, 3.88.

Methyl (2*S*)-*N*-Benzyl-2-(acetoxyamino)propanoate (L-6a). Compound **11a** (0.5 g, 1.7 mmol) was treated as described above for the preparation of D-**6a**. Column chromatography (80:20 hexane−diethyl ether) of the residue gave 0.261 g (61%) of L-**6a** as an oil: $[\alpha]_D$ −10.1 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 3H, *J* = 6.9 Hz), 1.88 (s, 3H), 3.77 (s, 3H), 3.83 (q, 1H, *J* = 6.9 Hz), 4.11 (d, 1H, *J* = 13.3 Hz), 4.21 (d, 1H, *J* = 13.3 Hz), 7.24−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.0, 51.8, 59.2, 62.8, 127.7, 128.2, 129.5, 135.5, 169.5, 171.4. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.29; H, 6.92; N, 5.68.

Methyl (2*S*)-*N*-Benzyl-2-(acetoxyamino)-2-phenylethanoate (L-6b). Compound **11b** (0.604 g, 1.7 mmol) was treated as described above for the preparation of D-**6b**. Column chromatography (80:20 hexane−diethyl ether) of the residue gave 0.346 g (65%) of L-**6b** as an oil: $[\alpha]_D$ +24.5 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3H), 3.65 (s, 3H), 3.79 (d, 1H, *J* = 13.5 Hz), 4.05 (d, 1H, *J* = 13.5 Hz), 4.70 (s, 1H), 7.20−7.42 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 19.4, 52.3, 59.9, 73.6, 127.9, 128.3, 128.6, 129.1, 129.2, 130.1, 133.8, 135.0, 168.8, 169.9. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.02; H, 5.93; N, 4.60.

***N*-(*tert*-Butoxycarbonyl)-L-alanine Methyl Ester (L-7a).** The *N*-hydroxy-α-amino acid derivative L-**6a** (0.20 g, 0.80 mmol) was treated as described above for the preparation of D-**7a**. Column chromatography (90:10 hexane−diethyl ether) of the crude product gave 0.151 g (93%) of L-**7a** as a solid. The physical and spectroscopic data were identical to those of an authentic sample (Aldrich, cat. no. 42,357-2).

***N*-(*tert*-Butoxycarbonyl)-L-phenylglycine Methyl Ester (L-7b).** The *N*-hydroxy-α-amino acid derivative L-**6b** (0.20 g, 0.638 mmol) was treated as described above for the preparation of D-**7a**. Column chromatography (80:20 hexane−diethyl ether) of the crude product gave 0.159 g (94%) of L-**7a** as a white solid: mp 111−113 °C; $[\alpha]_D$ +133.1 (*c* 1.0, $CHCl_3$) [lit.[10] $[\alpha]_D$ +135.7 (*c* 0.8, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.73 (s, 3H), 5.34 (d, 1H, *J* = 7.3 Hz), 5.55 (d, 1H, *J* = 7.3 Hz), 7.30−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.3, 52.7, 57.5, 79.90, 127.2, 128.6, 129.1, 137.0, 154.8, 171.6. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.27; H, 7.15; N, 5.41.

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