Diamine Synthesis: Exploring the Regioselectivity of Ring Opening of Aziridinium Ions

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Chiral 1,2-diamines continue to attract synthetic interest as they are prevalent in pharmaceuticals and in nature, and they are also utilized as chiral ligands in asymmetric synthesis.[1] Because of their abundance and usefulness, there is a need to develop regio- and stereocontrolled syntheses of 1,2-diamines. One general approach that has attracted recent attention is the reaction of an amine with an aziridinium ion,[2−7] a reaction that we have been interested in for some time now.[8]

Some trends are emerging from previous studies on the ring opening of aziridinium ions. For example, terminal aziridinium ions **1**−**4** are preferentially attacked by amines at the least hindered position with good to excellent levels of regiocontrol (Figure 1).[3−5] These reactions are mainly controlled by steric effects, although the strongly electron-withdrawing CF_3 group also has an important role in the opening of aziridinium ion **3**. In contrast, when the aziridinium ion has a benzylic position as in **5**−**7** (R = Ph), virtually exclusive ring opening by amines at this position is the norm.[6−8] As Gmeiner and co-workers have recently demonstrated,[9] the regioselectivity of aziridinium ion ring opening is also nucleophile dependent: opening of aziridinium ion **7** (R = Bn) occurs at the least hindered position with cyanide[9] (in an analogous fashion to aziridinium ions **1**−**4**) but at the more hindered position with chloride or bromide.[9,10]

Set against this background, we have systematically varied R (Me, Bn, ^{i}Pr, Ph) in aziridinium ions **7** and have uncovered the effect on the regioselectivity of ring opening of **7** with methylamine. Furthermore, using a novel deuterium substitution approach, we have confirmed that aziridinium ions are intermediates in the conversion of *N*,*N*-dialkylamino alcohols into 1,2-diamines.

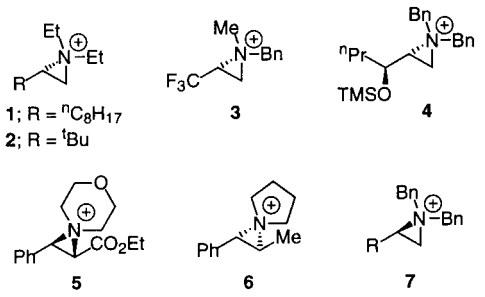
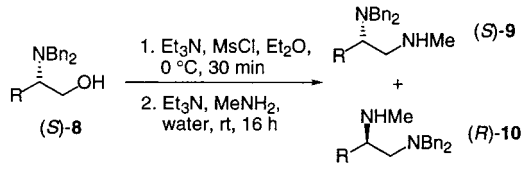


Figure 1. Aziridinium Ions

Scheme 1



We were especially interested in studying the regioselectivity in the conversion of *N*,*N*-dialkylamino alcohols into 1,2-diamines using our previously reported diamine-forming reaction conditions.[8] Thus, four dibenzylamino alcohols (*S*)-**8a**−**d** (R = Me, Bn, ^{i}Pr, Ph, respectively) were prepared by standard dibenzylation[8a] of the parent amino alcohols and subjected to mesylation in diethyl ether followed by reaction with aqueous methylamine. We expected these reactions to generate mixtures of regioisomeric diamines (*S*)-**9a**−**d** and (*R*)-**10a**−**d** via formation of aziridinium ions **7** (Scheme 1). Before we could determine the regioselective outcome of these diamine-forming reactions, we needed to synthesize each regioisomer independently for subsequent comparison of ^{1}H and ^{13}C NMR spectroscopic data. As described in the Experimental Section, diamines (*S*)-**9** were prepared by Swern oxidation of amino alcohol (*S*)-**8** followed by reductive amination with methylamine; diamines (*S*)-**10** were prepared via a known[11] two-step route from *N*-Cbz-protected amino acids [(i) isobutyl chloroformate-mediated coupling of dibenzylamine with *N*-Cbz-protected phenylalanine and then (ii) $LiAlH_4$ reduction (NHCbz → NHMe with concomitant amide reduction)].

The results of the diamine-forming reactions (Scheme 1) are presented in Table 1. High crude yields (78−96%) of mixtures of diamines (*S*)-**9** and (*R*)-**10** were obtained and for R = alkyl (entries 1−3) preferential attack at the least hindered end of the proposed aziridinium ion intermediate occurred. Under identical conditions, essentially exclusive attack at the benzylic position was observed starting from **8d** (R = Ph; entry 4). The sterically less demanding methyl group in **8a** (R = Me) resulted in a lowering of the regioselectivity, and a 70:30 ratio of (*S*)-**9a** and (*R*)-**10a** was obtained in this case (entry 1). The results we obtained with amino alcohol **8b** and methylamine show essentially the same level of regioselectivity as that in Gmeiner's work with the same amino alcohol and cyanide as the nucleophile.[9]

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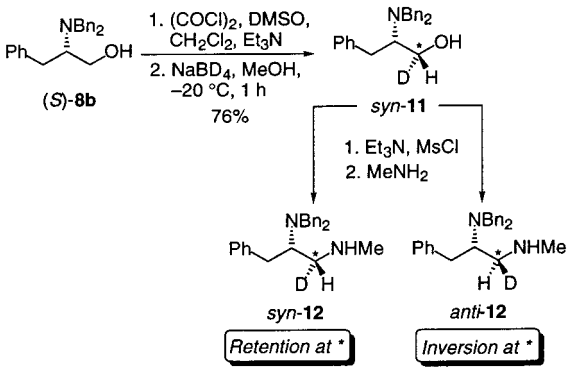
Table 1. Study of Regioselectivity of Diamine Synthesis

entry[a]	starting material	R	% yield[b]	(*S*)-**9**:(*R*)-**10**[c]
1	**8a**	Me	96 (78)	70:30
2	**8b**	Bn	94 (70)	94:6
3	**8c**	^{i}Pr	81 (62)	93:7
4	**8d**	Ph	78 (−)	2:98

[a] Reaction conditions described in Scheme 1. [b] Yield of crude product mixture (yield in brackets refers to the yield after purification by flash chromatography). [c] Ratio of regioisomeric diamines (*S*)-**9** and (*R*)-**10** in the crude product mixtures determined by ^{1}H NMR spectroscopy. These ratios of diamines were virtually identical after purification by flash chromatography.

Scheme 2

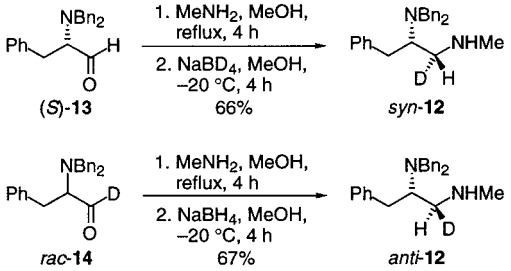


The results in Scheme 1 and Table 1 indicate that amino alcohols **8a**−**c** are converted preferentially into diamines (*S*)-**9a**−**c** upon mesylation and reaction with methylamine. Such a regioselectivity could, in principle, have been obtained by direct S_N2 substitution of the mesylate from the hydroxyl group in the starting amino alcohols **8a**−**c** without the need of invoking an aziridinium ion **7**. Obviously, the preparation of (*R*)-**10d** from amino alcohol (*S*)-**8d** must have proceeded via an aziridinium ion to account for the dibenzylamino group migration. To investigate whether the preparation of diamines (*S*)-**9a**−**c** also proceeds via an aziridinium ion, we have investigated the chemistry outlined in Scheme 2.

The dibenzylamino group, originally introduced and further exploited by Reetz, is a well-known and widely used stereocontrolling element in synthesis.[12] We proposed to use the dibenzylamino group to control the stereochemistry of deuterium incorporation and then to use stereochemical information to follow the mechanism of our diamine synthesis. If we could prepare amino alcohol *syn*-**11**, then we could investigate whether subsequent diamine formation occurred with retention or inversion of stereochemistry at C* (see Scheme 2): conversion of *syn*-**11** into diamine *syn*-**12** would indicate stereochemical retention via an aziridinium ion, whereas transformation of *syn*-**11** into diamine *anti*-**12** would occur via direct S_N2 substitution. A mixture of the two mechanisms would lead to the formation of both diamines *syn*- and *anti*-**12**. Crucial to the success of our proposed approach was the stereocontrolled synthesis of each of *syn*-**11**, *syn*-**12**, and *anti*-**12**.

Amino alcohol *syn*-**11** was prepared in 76% yield by Swern oxidation of amino alcohol (*S*)-**8b** and subsequent reduction with sodium borodeuteride at −20 °C (Scheme 2).[13] A single diastereoisomer (by ^{1}H and ^{13}C NMR spectroscopy) of deuterated amino alcohol **11** was obtained from this reduction, and we assigned it as syn assuming Felkin−Anh attack and on the basis of precedent.[12,13] The stereocontrolled synthesis of each of the diamines *syn*- and *anti*-**12** is shown in Scheme 3.

Scheme 3



Aldehyde (*S*)-**13** was converted into an imine by reaction with methylamine, and then reduction with sodium borodeuteride (MeOH, −20 °C) under Felkin−Anh control gave diamine *syn*-**12** in 66% yield after chromatography. Stereocontrolled additions of sodium borohydride and other nucleophiles to similar imines have previously been described by Reetz and co-workers.[14] Reversing the order of incorporation of hydrogen and deuterium gave diamine *anti*-**12**. Thus, reductive amination of deuterated aldehyde *rac*-**14** (obtained by lithium aluminum deuteride reduction of the corresponding methyl ester followed by Swern oxidation) using methylamine and sodium borohydride gave a 67% yield of diamine *anti*-**12**, which had different ^{1}H NMR spectroscopic data than *syn*-**12**.

Finally, reaction of amino alcohol *syn*-**11** under the diamine-forming conditions generated a 96% crude yield of a 94:6 regioisomeric diamine mixture. Examination of the ^{1}H NMR spectrum of the crude product indicated that the major regioisomer was composed of an 85:15 mixture of diamine *syn*-**12** and diamine *anti*-**12**. This result indicates that, under these reaction conditions, 15% of the substitution reaction proceeds via direct S_N2 displacement and 85% proceeds via the aziridinium ion intermediate (Scheme 2). Thus, it appears that some direct S_N2 substitution should be factored into the observed regioselectivites reported in entries 1−3 of Table 1 as only about 85% of the reaction proceeds via an aziridinium ion.

In summary, from a mechanistic viewpoint, we have established the intermediacy of aziridinium ions in the conversion of *N*,*N*-dialkylamino alcohols into 1,2-diamines and we have further investigated the regioselectivity of ring opening of aziridinium ions. However, our results indicate that only around 85% of the reaction proceeds via the aziridinium ion. Furthermore, synthetically, we have reported regioselective syntheses of chiral 1,2-diamines (*S*)-**9b**, (*S*)-**9c**, and (*R*)-**10d** and two routes (see Schemes 2 and 3) for the stereocontrolled synthesis of deuterated diamines *syn*- and *anti*-**12**.

Experimental Section

General Methods. Distilled water was used. THF and Et_2O were dried over sodium-benzophenone and distilled before use. CH_2Cl_2 was dried over calcium hydride and distilled before use.

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Petrol refers to the fraction of petroleum ether boiling in the range of 40−60 °C and was redistilled before use. All nonaqueous reactions were carried out under oxygen-free nitrogen using oven-dried glassware. Flash column chromatography was carried out using ICN Biomedicals GmbH 33−63 silica (60 Å) or Fisher Matrex silica 60. Thin-layer chromatography was carried out on commercially available Merck 5554 aluminum-backed silica plates.

Proton (270 MHz) and carbon (67.9 MHz) NMR spectra were recorded on a 270 MHz spectrometer using an internal deuterium lock. All samples were recorded as solutions in deuterated chloroform, and chemical shifts are quoted in parts per million downfield of tetramethylsilane. Coupling constant (*J*) values are given in Hertz. Carbon NMR spectra were recorded with broad band proton decoupling.

Melting points were measured on a digital melting point apparatus. Infrared spectra were recorded on an FT IR spectrometer as solutions in chloroform. Chemical ionization and high-resolution mass spectra were recorded on an Autospec spectrometer. Optical rotations were recorded on a polarimeter (using the sodium D line; 589 nm) at 20 °C, and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Representative Procedures for Synthesis of Regioisomeric Diamines 9 and 10 (2*S*)-*N*^{2},*N*^{2}-Dibenzyl-*N*^{1}-methyl-3-phenyl-1,2-propanediamine (9b). DMSO (0.16 mL, 2.4 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.12 mL, 1.4 mmol) in CH_2Cl_2 (4 mL) at −78 °C under N_2. After 5 min, a solution of amino alcohol (*S*)-**8b** (400 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After an additional 10 min, Et_3N (0.72 mL, 4.8 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature over 1 h before water (2 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (1 × 15 mL). The combined organic extracts were washed with 5% $NaHCO_{3(aq)}$ (30 mL), water (30 mL), and brine (30 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude aldehyde (*S*)-**13** as a viscous yellow-green oil. To the aldehyde (*S*)-**13** in MeOH (5 mL) was added $MeNH_2$ (2 M in MeOH, 0.48 mL, 2.4 mmol) at room temperature under N_2. The mixture was heated at reflux for 4 h and then cooled to −20 °C, and $NaBH_4$ (46 mg, 1.2 mmol) was added. After 4 h at −20 °C, 2 M $HCl_{(aq)}$ was added dropwise until effervescence ceased. Then, water (5 mL) and KOH pellets were added until pH > 9 and Et_2O (20 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with $CHCl_3$−MeOH (10:1) as the eluent gave diamine (*S*)-**9b** (211 mg, 53%) as a colorless oil: R_f (10:1 $CHCl_3$−MeOH) 0.2; $[\alpha]_D$ +27.0 (*c* 0.95, EtOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.34−7.07 (m, 15H), 3.86 (d, 2H, J = 13.5), 3.52 (d, 2H, J = 13.5), 3.16−3.01 (m, 2H), 2.68 (dd, 1H, J = 10, 12), 2.49−2.34 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 139.9, 129.1, 128.8, 128.4, 127.1, 126.0, 58.9, 53.7, 51.7, 35.9, 33.1.

(2*S*)-*N*^{1},*N*^{1}-Dibenzyl-*N*^{2}-methyl-3-phenyl-1,2-propanediamine (10b). 4-Methylmorpholine (0.11 mL, 1.0 mmol) was added dropwise to a stirred solution of *N*-Cbz-protected phenylalanine (300 mg, 1.0 mmol) and isobutyl chloroformate (0.13 mL, 1.0 mmol) in THF (2 mL) at −15 °C under N_2. After 5 min, a solution of Bn_2NH (0.19 mL, 1.0 mmol) in THF (1 mL) was added. After 1 h at −15 °C, the solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (20 mL) and water (30 mL). The layers were separated, and the organic layer was washed with 1 M $HCl_{(aq)}$ (2 × 30 mL), water (20 mL), 5% $NaHCO_{3(aq)}$ (2 × 30 mL), water (20 mL), and brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol−EtOAc (2:1) as the eluent gave the dibenzylamide (1.63 g, 91%) as a gummy colorless oil: R_f (2:1 petrol−EtOAc) 0.6; $[\alpha]_D$ −9.4 (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) 3427, 1716, 1641 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35−7.33 (m, 20H), 5.74 (d, 1H, J = 8.5), 5.06 (s, 2H), 5.00−4.92 (m, 1H), 4.76 (d, 1H, J = 14.5), 4.30 (d, 1H, J = 16.5), 4.22 (d, 1H, J = 14.5), 4.17 (d, 1H, J = 16.5), 3.10−2.95 (m, 2H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 172.0, 155.5, 136.4, 136.3, 127.8, 127.7, 127.5, 126.8, 66.7, 52.2, 49.6, 48.3, 39.9; MS (CI, NH_3) *m*/*z* 479 (M + H)$^+$, 100; HRMS (CI, NH_3) *m*/*z* calcd for $C_{31}H_{31}N_2O_3$ (M + H)$^+$ 479.2335, found 479.2337.

A solution of the dibenzylamide (200 mg, 0.4 mmol) in THF (1 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (71 mg, 1.7 mmol) in THF (2 mL) at room temperature under N_2. The mixture was heated at reflux for 16 h and then coooled to room temperature, and EtOAc was added until effervescence ceased. Water (0.5 mL) and then 4 M $NaOH_{(aq)}$ (0.5 mL) were added. After 5 min, water (1 mL) was added, and after an additional 15 min, the precipitate was removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with $CHCl_3$−MeOH−NH_3 (10:1:0.1) as the eluent gave diamine (*S*)-**10b** (141 mg, 68%) as a colorless oil: R_f (10:1:0.1 $CHCl_3$−MeOH−NH_3) 0.5; $[\alpha]_D$ +44.8 (*c* 1.05, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.31−7.06 (m, 15H), 3.59 (d, 2H, J = 13.5), 3.41 (d, 2H, J = 13.5), 2.71−2.60 (m, 2H), 2.50−2.30 (m, 3H), 2.27 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 139.3, 139.0, 129.2, 128.9, 128.6, 128.2, 127.1, 126.0, 59.4, 58.9, 57.5, 38.8, 34.1.

General Procedure for Diamine Formation from Amino Alcohols. MsCl (2.1 mmol) was added dropwise to a stirred solution of amino alcohol (1.8 mmol) and Et_3N (2.8 mmol) in Et_2O (10 mL) at 0 °C under N_2. A white precipitate formed. After 30 min, Et_3N (3.5 mmol) was added and the mixture was allowed to warm to room temperature. Then, $MeNH_{2(aq)}$ (40%; 30.0 mmol) was added and the two-phase mixture was stirred vigorously for 16 h at room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with 5% $NaHCO_{3(aq)}$ (30 mL) and water (30 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product. The ratio of regioisomers (see Table 1) was determined from the ^{1}H NMR spectrum of the crude product.

(2*S*)-*N*^{2},*N*^{2}-Dibenzyl-*N*^{1}-methyl-1,2-propanediamine (9a) and (2*R*)-*N*^{1},*N*^{1}-Dibenzyl-*N*^{2}-methyl-1,2-propanediamine (10a). Using the general procedure for diamine synthesis, we obtained the crude product (201 mg, 96%), which contained a 70:30 mixture of diamines (*S*)-**9a** and (*R*)-**10a** (by ^{1}H NMR spectroscopy), from amino alcohol (*S*)-**8a** (200 mg, 0.8 mmol). Purification by flash column chromatography on silica with $CHCl_3$−MeOH−NH_3 (200:10:1) as the eluent gave an 80:20 mixture of diamines (*S*)-**9a** and (*R*)-**10a** (163 mg, 78%) as an orange oil: R_f (200:10:1 $CHCl_3$−MeOH−NH_3) 0.2. Diagnostic signals for (*S*)-**9a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.74 (d, 2H, J = 13.5), 3.35 (d, 2H, J = 13.5), 2.19 (s, 3H), 0.99 (d, 3H, J = 6.5); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 139.7, 58.1, 52.4, 50.8, 34.8, 9.6. Diagnostic signals for (*R*)-**10a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.67 (d, 2H, J = 13.5), 3.43 (d, 2H, J = 13.5), 2.25 (s, 3H), 0.91 (d, 3H, J = 6.5); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 138.2, 59.6, 53.8, 51.4, 32.6, 16.5.

(2*S*)-*N*^{2},*N*^{2}-Dibenzyl-*N*^{1}-methyl-3-phenyl-1,2-propanediamine (9b) and (2*R*)-*N*^{1},*N*^{1}-Dibenzyl-*N*^{2}-methyl-3-phenyl-1,2-propanediamine (10b). Using the general procedure for diamine synthesis, we obtained the crude product (981 mg, 94%), which contained a 94:6 mixture of diamines (*S*)-**9b** and (*R*)-**10b** (by ^{1}H NMR spectroscopy), from amino alcohol (*S*)-**8b** (1.0 g, 3.0 mmol). Purification by flash column chromatography on silica with $CHCl_3$−MeOH (10:1) as the eluent gave a 95:5 mixture of diamines (*S*)-**9b** and (*R*)-**10b** (127 mg, 70%) as a colorless oil: R_f (10:1 $CHCl_3$−MeOH) 0.2; IR ($CDCl_3$) 3319, 1602 cm^{-1}; MS (CI, NH_3) *m*/*z* 345 (M + H)$^+$, 100; HRMS (CI, NH_3) *m*/*z* calcd for $C_{24}H_{29}N_2$ (M + H)$^+$ 345.2331, found 345.2330.

(2*S*)-*N*^{2},*N*^{2}-Dibenzyl-*N*^{1}-3-dimethyl-1,2-butanediamine (9c) and (2*R*)-*N*^{1},*N*^{1}-Dibenzyl-*N*^{2}-3-dimethyl-1,2-butanediamine (10c). Using the general procedure for diamine synthesis, we obtained the crude product (422 mg, 81%), which contained a 93:7 mixture of diamines (*S*)-**9c** and (*R*)-**10c** (by ^{1}H NMR spectroscopy), from amino alcohol (*S*)-**8c** (500 mg, 1.8 mmol). Purification by flash column chromatography on silica with $CHCl_3$−MeOH (10:1) as the eluent gave a 94:6 mixture of diamines (*S*)-**9c** and (*R*)-**10c** (327 mg, 62%) as an orange oil: R_f (10:1 $CHCl_3$−MeOH) 0.2; IR ($CDCl_3$) 3317, 1602, 1494, 1454, 1196 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.44−7.19 (m, 10H), 3.80 (d, 2H, J = 13.5), 3.78 (d, 2H, J = 13.5), 2.68−2.52 (m, 3H), 2.25 (s, 3H), 2.07 (dsept (appearing as an octet), 1H, J = 6.5, 6.5), 1.78 (br s, 1H), 1.04 (d, 3H, J = 6.5), 0.93 (d, 3H, J = 6.5); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 140.4, 128.8, 128.2, 126.8, 62.5,

54.5, 49.8, 36.1, 27.7, 22.3, 20.1; MS (CI, NH_3) *m*/*z* 297 (M + H)$^+$, 100; HRMS (CI, NH_3) *m*/*z* calcd for $C_{20}H_{29}N_2$ (M + H)$^+$ 297.2331, found 297.2328. Diagnostic signals for (*R*)-**10c**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.44 (d, 2H, J = 13.5), 2.28 (s, 3H), 0.0.82 (d, 3H, J = 6.5).

Synthesis of Amino Alcohol *syn*-11. DMSO (0.21 mL, 3.0 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.16 mL, 1.8 mmol) in CH_2Cl_2 (10 mL) at −78 °C under N_2. After 5 min, a solution of amino alcohol (*S*)-**8b** (500 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After an additional 10 min, Et_3N (0.84 mL, 6.0 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature over 1 h before water (2 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (1 × 15 mL). The combined organic extracts were washed with 5% $NaHCO_{3(aq)}$ (30 mL), water (30 mL), and brine (30 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude aldehyde (*S*)-**13** (500 mg, 100%) as a viscous yellow-green oil. To the aldehyde (*S*)-**13** (50 mg, 0.15 mmol) in MeOH (5 mL) at −20 °C under N_2 was added $NaBD_4$ (7 mg, 0.2 mmol). After 1 h at −20 °C and 3 h at room temperature, water was added dropwise until effervescence ceased and Et_2O (20 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol−Et_2O (1:1) as the eluent gave amino alcohol *syn*-**11** (38 mg, 76%) as a white solid: mp 62−63 °C; R_f (1:1 petrol−Et_2O) 0.4; $[\alpha]_D$ +39.6 (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) 3440 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35−7.08 (m, 15H), 3.92 (d, 2H, J = 13.0), 3.48 (d, 2H, J = 13.0), 3.31 (d, 1H, J = 4.0), 3.15−3.01 (m, 3H), 2.47−2.39 (m, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 139.2, 139.1, 129.0, 128.5, 127.3, 126.2, 60.8, 59.9 (1:1:1 triplet, J = 21), 53.2, 31.7; MS (CI, NH_3) *m*/*z* 333 (M + H)$^+$, 100; HRMS (CI, NH_3) *m*/*z* calcd for $C_{23}H_{25}DNO$ (M + H)$^+$ 333.2077, found 333.2068.

Synthesis of Aldehyde *rac*-14. A solution of methyl 2-(dibenzylamino)-3-phenylpropanoate (580 mg, 1.6 mmol) in THF (2 mL) was added dropwise to a stirred suspension of $LiAlD_4$ (136 mg, 3.2 mmol) in THF (3 mL) at 0 °C under N_2. After 40 min, water was added dropwise until effervescence ceased. Then, Et_2O (20 mL) was added and the layers were separated. The aqueous layer was washed with water (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol−Et_2O (1:1) as the eluent gave bis deuterated amino alcohol (438 mg, 81%) as a white solid: mp 92−94 °C; R_f (1:1 petrol−Et_2O) 0.3; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36−7.09 (m, 15H), 3.92 (d, 2H, J = 13.0), 3.48 (d, 2H, J = 13.0), 3.31 (d, 1H, J = 4.0), 3.15−3.03 (m, 2H), 2.98 (s, 1H), 2.48−2.37 (m, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 139.2, 139.1, 129.0, 128.8, 128.5, 127.3, 126.2, 60.7, 59.9 (quintet, J = 20.5, appearing as a triplet), 53.2, 31.7; MS (CI, NH_3) *m*/*z* 334 (M + H)$^+$, 100; HRMS (CI, NH_3) *m*/*z* calcd for $C_{23}H_{24}D_2NO$ (M + H)$^+$ 334.2140, found 334.2145.

DMSO (0.08 mL, 1.05 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.06 mL, 0.6 mmol) in CH_2Cl_2 (5 mL) at −78 °C under N_2. After 5 min, a solution of the amino alcohol (175 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After an additional 10 min, Et_3N (0.03 mL, 2.1 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature over 1 h before water (2 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (1 × 15 mL). The combined organic extracts were washed with 5% $NaHCO_{3(aq)}$ (30 mL), water (30 mL), and brine (30 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product aldehyde (*S*)-**13** (500 mg, 100%) as a viscous yellow-green oil. Purification by flash column chromatography on silica with petrol−Et_2O (1:1) as the eluent gave deuterated aldehyde *rac*-**14** (54 mg, 31%) as a yellow oil: R_f (1:1 petrol−Et_2O) 0.5; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.29−7.12 (m, 15H), 3.80 (d, 2H, J = 13.5), 3.60 (d, 2H, J = 13.5), 3.55 (d, 1H, J = 6.0, 7.5), 3.13 (dd, 1H, J = 7.5, 14.0), 2.92 (dd, 1H, J = 6.0, 14.0); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 201.8 (1:1:1 triplet, J = 26), 139.1, 138.8, 129.4, 128.7, 128.6, 128.4, 127.3, 126.2, 68.3, 54.8, 30.0; MS (CI, NH_3) *m*/*z* 331 (M + H)$^+$, 100; HRMS (CI, NH_3) *m*/*z* calcd for $C_{23}H_{23}DNO$ (M + H)$^+$ 331.1921, found 331.1919.

Synthesis of Diamine *syn*-12. To the aldehyde (*S*)-**13** (50 mg, 0.15 mmol) in MeOH (5 mL) was added $MeNH_2$ (2 M in MeOH, 0.08 mL, 0.02 mmol) at room temperature under N_2. The mixture was heated at reflux for 4 h and then cooled to −20 °C, and $NaBD_4$ (7 mg, 0.2 mmol) was added. After 4 h at −20 °C, 2 M $HCl_{(aq)}$ was added dropwise until effervescence ceased. Then, water (5 mL) and KOH pellets were added until pH > 9 and Et_2O (20 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2−MeOH−NH_3 (10:1:0.1) as the eluent gave diamine *syn*-**12** (33 mg, 66%) as an orange oil: R_f (10:1:0.1 CH_2Cl_2−MeOH−NH_3) 0.2; $[\alpha]_D$ +31.0 (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) 3320 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35−7.08 (m, 15H), 3.86 (d, 2H, J = 13.5), 3.52 (d, 2H, J = 13.5), 3.16−3.05 (m, 2H), 2.49−2.35 (m, 3H), 2.08 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 139.9, 139.8, 129.1, 128.8, 128.1, 128.0, 127.0, 126.0, 58.75, 53.65, 51.05 (1:1:1 triplet, J = 21), 35.66, 33.02; MS (CI, NH_3) *m*/*z* 346 (M + H)$^+$, 100; HRMS (CI, NH_3) *m*/*z* calcd for $C_{24}H_{28}DN_2$ (M + H)$^+$ 346.2394, found 346.2393.

Synthesis of Diamine *anti*-12. To the aldehyde *rac*-**14** (50 mg, 0.15 mmol) in MeOH (5 mL) was added $MeNH_2$ (2 M in MeOH, 0.08 mL, 0.02 mmol) at room temperature under N_2. The mixture was heated at reflux for 4 h and then cooled to −20 °C, and $NaBH_4$ (7 mg, 0.2 mmol) was added. After 4 h at −20 °C, 2 M $HCl_{(aq)}$ was added dropwise until effervescence ceased. Then, water (5 mL) and KOH pellets were added until pH > 9 and Et_2O (20 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2−MeOH−NH_3 (10:1:0.1) as the eluent gave diamine *anti*-**12** (35 mg, 67%) as an orange oil: R_f (10:1:0.1 CH_2Cl_2−MeOH−NH_3) 0.2; IR ($CDCl_3$) 3322 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35−7.08 (m, 15H), 3.86 (d, 2H, J = 13.5), 3.52 (d, 2H, J = 13.5), 3.16−3.02 (m, 2H), 2.69−2.63 (m, 1H), 2.48−2.39 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 140.0, 139.9, 129.1, 128.8, 128.4, 128.3, 127.0, 125.9, 58.75, 53.65, 51.11 (1:1:1 triplet, J = 20), 35.74, 33.04.

Synthesis of Diamine *syn*-12 from Amino Alcohol *syn*-11. MsCl (0.07 mL, 0.9 mmol) was added dropwise to a stirred solution of amino alcohol *syn*-**11** (248 mg, 0.75 mmol) and Et_3N (0.17 mL, 1.2 mmol) in Et_2O (15 mL) at 0 °C under N_2. A white precipitate formed. After 30 min, Et_3N (0.21 mL, 1.5 mmol) was added and the mixture was allowed to warm to room temperature. Then, $MeNH_{2(aq)}$ (40%; 1.09 mL, 12.7 mmol) was added and the two-phase mixture was stirred vigorously for 16 h at room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with 5% $NaHCO_{3(aq)}$ (30 mL) and water (30 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product (247 mg, 96%), which contained a 94:6 mixture of regioisomeric diamines (by ^{1}H NMR spectroscopy). The major regioisomer contained an 85:15 mixture of diamine *syn*-**11** and diamine *anti*-**12** (by ^{1}H NMR spectroscopy).

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Supporting Information Available: ^{1}H NMR spectra of compounds (*S*)-**9b**, (*S*)-**10b**, *syn*-**11**, *rac*-**14**, *syn*-**12**, and *anti*-**12** as well as the crude mixtures of compounds (*S*)-**9a** and (*R*)-**10a**, (*S*)-**9b** and (*R*)-**10b**, and (*S*)-**9c** and (*R*)-**10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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