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Proline-Catalyzed Asymmetric Synthesis of *syn*- and *anti*-1,3-Diamines

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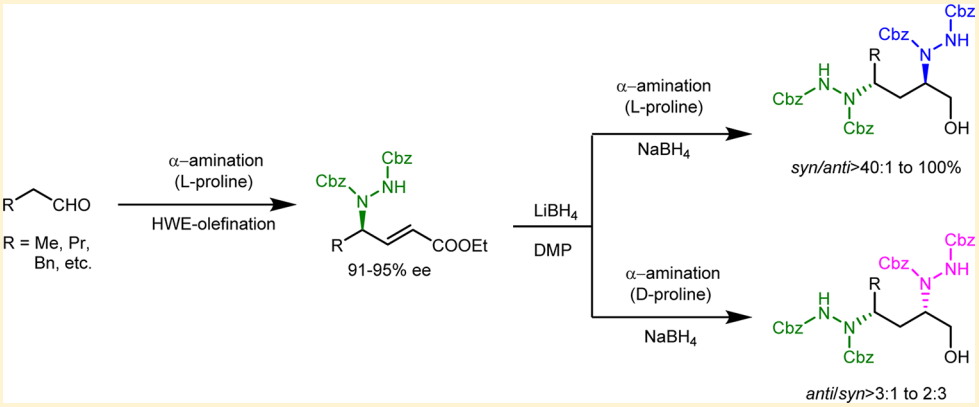
Supporting Information



ABSTRACT: A general organocatalytic strategy for asymmetric synthesis of both *syn*/*anti*-1,3-diamines has been developed. The strategy employs proline-catalyzed sequential α-amination and Horner−Wadsworth−Emmons (HWE) olefination of aldehydes as the key step where *syn*-1,3-diamine was obtained as the most favorable product.

INTRODUCTION

The 1,3-diamine functionality with *syn*- or *anti*-configuration are ubiquitous structural features in a wide range of natural products and various bioactive compounds,[1] viz., marine alkaloids batzelladines,[2] α-adrenoreceptor blockers manzacidin,[3] antibiotic glycocinnamoylspermidines,[4] or HIV-1 protease inhibitors, such as A-74704.[5] Additionally, 1,3-diamines have also been used as ligands for asymmetric catalysis and chiral core of numerous synthetic reagents.[6]

Increasingly, synthetic organic chemists are merging discrete organic reactions in one-pot (referred to by various names, viz., domino reactions, sequential addition reactions, one-pot multicomponent reactions, multicatalysis)[7] to generate complex organic molecules from simple starting material in order to increase efficiencies and reduce the environmental impact in terms of reduction in byproducts.[8]

Recently we and others have developed one-pot sequential addition reaction sequence to synthesize γ-hydroxy esters,[9a,10a] γ-amino-α,β-unsaturated ester[10b] from proline-catalyzed α-amination,[11a−d] α-aminoxylation[11e,f] of aldehydes. We have further used these reactions in a iterative or sequential manner to develop synthetic protocols for *syn*/*anti*-1,3-polyols[9a,b] and *syn*/*anti*-1,3-amino alcohols[9c] in good to useful level of stereoinduction. Herein we wish to report the method for the syntheses of *syn*- and *anti*-1,3-diamines. In case of both 1,3-polyols and 1,3-aminoalcohol, we were able to get good selectivity for *anti* isomer as compared to *syn* isomer, wherein steric factors interfere in the catalyst control to give lower level of selectivity. Given the importance of 1,3-diamines, it would be worthwhile to develop short reaction sequence for enantioselective and diastereoselective synthesis of 1,3-diamines.

Despite the biological and pharmacological importance of 1,3-diamine, only few methods are reported in literature for their stereoselective synthesis.[12,13] The most widely used strategy for their synthesis includes reduction of diimines,[13b] pyrazolidines,[13c,d] pyrimidines,[13e] azides,[13f] quaternary immonium salts generated in situ by aminoalkylation of enamines[13g] or β-amino imines.[13i] Recently Trost et al. have reported sequential process, which involves an asymmetric allylic amination and subsequent formation and opening of amino aziridines,[13h] while Menche et al. have reported stereodivergent cyclization of urea-type substrates by intramolecular allylic substitution.[13j] However, these methods involve specially modified starting materials such as pyrimidines, diimines, and amino imines being catalyzed by toxic metal catalysts like $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $Rh_2(esp)_2$, etc.

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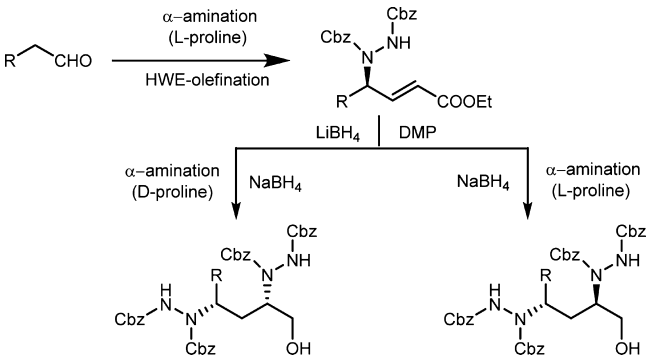
RESULTS AND DISCUSSION

As a part of our ongoing research program aimed at developing new organocatalytic protocols and their subsequent application to asymmetric synthesis of biologically active natural products,[9] we envisioned that the proline-catalyzed α-amination[11a,b] could provide an easy access to 1,3-diamines in stereocontrolled manner. However, it would be interesting to see the catalyst as well as substrate role in determining the ratio of *syn*/*anti*-1,3-diamine, since in this case we have bulky protected amine in place of relatively smaller OTBS group as used in the previous two cases. Our synthetic strategy for 1,3-diamines is illustrated in Scheme 1.

Scheme 1. General Synthetic Strategy for 1,3-Diamines



Toward the synthesis of 1,3-diamine, we first proceed with the synthesis of various protected γ-amino esters. Thus, commercially available aldehydes **1a**−**f** were subjected to sequential α-amination using commercially available dibenzylazodicarboxylate (DBAD) as the nitrogen source, L-proline as catalyst, and subsequent Horner−Wadsworth−Emmons (HWE) olefination using triethylphosphonoacetate to furnish the γ-amino-α,β-unsaturated esters **2a**−**f** in good yields (80−87%) and excellent enantioselectivities (91−95%) and *E*/*Z* ratio 98:2 (Table 1).

With protected γ-amino-α,β-unsaturated esters **2a**−**f** in hand, our next target was selective reduction of double bond in presence of Cbz group. For this purpose, ester **2a** was subjected to hydrogenation conditions using different catalyst such as Pd/C, PtO_2, Pt, Lindlar's catalyst, etc., but the formation of reduced product **3** could not be observed (Scheme 2).

The unsaturated ester **2a** was subjected to Mg/MeOH condition,[14] but interestingly we could obtain **4** as the only product. Extension of conjugation may be the possible cause for the formation of **4**, as the same reaction when repeated with acyclic substrate **2c** did not afford the product **5**; instead, the starting material was recovered back (Scheme 2).

We resorted next to reduce the ester group. For this purpose, ester **2a** was treated with $LiBH_4$ in THF, but to our surprise, the double bond also got reduced with concomitant reduction of the ester group to give alcohol **6a**. As shown in the Table 2, probably the reaction proceeds first via reduction of double bond followed by reduction of ester group. To assess the generality of this procedure for reduction of ester group as well as double bond, various γ-amino-α,β-unsaturated esters **2a**−**f** were subjected to reduction conditions using $LiBH_4$, and similar results were obtained in all the cases (Table 2).

With substantial amount of various hydrazine alcohols **6a**−**f** in hand, our next aim was to introduce another amine functionality stereoselectively at the 3-position. As depicted in Scheme 3, the DMP oxidation of alcohol **6a** furnished the corresponding aldehyde, which was subsequently subjected to α-amination using dibenzylazodicarboxylate (DBAD) and L-proline as a catalyst to furnish α-aminoaldehyde, which on further reduction with $NaBH_4$ afforded the *syn*-1,3-diamine **7a** in 68% yield and 99.9:0.1 diastereomeric ratio.[15] Surprisingly, when the same sequence of reaction was repeated using D-proline as a catalyst, we got *anti*-1,3-diamine **8a** in 64% yield and 3:1 diastereomeric ratio. The major *anti*-1,3-diamine diastereomer was easily separated by flash silica gel column chromatography. By analyzing the diastereomeric ratio of both *syn* as well as *anti* product, we concluded that not only the catalyst but also the existing stereochemistry of the substrate play a major role in asymmetric induction of new chiral center and favor the formation of *syn* product. To further prove this hypothesis, we repeated the same sequence of reaction using DL-proline as a catalyst and got diastereomeric ratio 4:1 in favor of *syn* isomer. Overall these results are in contrast with those observed in the case of *syn*/*anti*-1,3-diol[9a] and *syn*/*anti*-1,3-amino alcohols,[9b] where the asymmetric induction for the *anti*-isomer was found to be higher as compared to the *syn*-isomer. However, a detailed literature survey revealed the observed selectivity for the N−N−Cbz group,[10b,16] as reported by Sudalai et al. for the synthesis of *syn*-aminodiol.

The reaction sequence shows a wide substrate scope and is compatible to different functionalities such as alkyl, substituted alkyl, aryl, and substituted aryl groups. Excellent diastereomeric ratio (dr ∼98:2 to ∼100) and good yields (62−68%) were obtained for all the substrates in case of *syn* product, whereas moderate to low diastereomeric ratio (dr 3:1 to 2:3) and good yields (60−64%) were obtained for all the substrates in case of *anti* product (Scheme 3).

In order to demonstrate the synthetic utility of this protocol, we have accomplished a short synthesis of both diastereomers of *N*-protected N^2,N^4-dimethylpentane-2,4-diamine **13** and **14**. The chiral diamine ligand forms a complex with Pt, which interacts stereospecifically with DNA and even with mononucleotides and acts as antitumor.[17] As illustrated in Scheme 4, the diastereomerically pure *syn*-diamine **7e** was subjected to synthetic manipulation in order to achieve the synthesis of target compound **13**.

Toward this end, the free alcohol of protected *syn*-diamine **7e** was tosylated followed by treatment with $LiAlH_4$ to furnish compound **9**. The N−N bond of compound **9** was cleaved with Raney Ni under hydrogenation conditions, and free amine was protected as its Boc derivative **11**. Methylation of Boc derivative gave the target compound **13**. Same set of reactions were repeated with 1,3-*anti*-diamine **8e** to obtain the other diastereomer **14**.

In conclusion, a new, efficient, and organocatalytic strategy has been developed for the stereocontrolled synthesis of both *syn*- and *anti*-1,3-diamine using sequential α-amination and HWE olefination reaction of an aldehyde as key step. Interestingly, the *syn*-isomer was obtained as the most favorable product. The synthetic application of this protocol was demonstrated by the asymmetric synthesis of both the diastereomers of *N*-protected N^2,N^4-dimethylpentane-2,4-diamine.

EXPERIMENTAL SECTION

General Information. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Anhydrous

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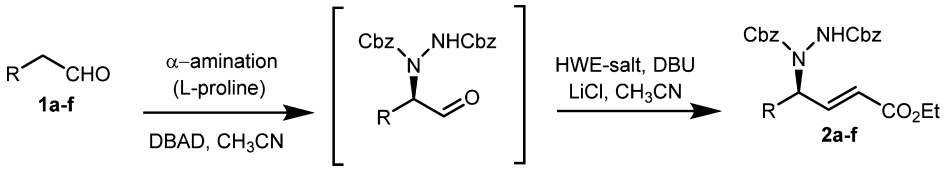
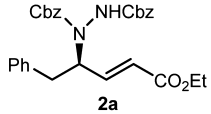
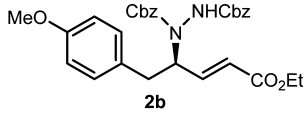
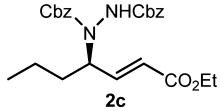
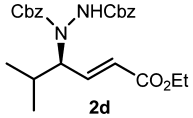
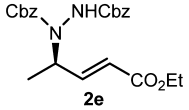
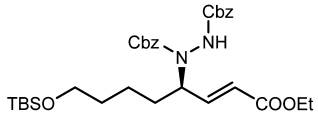
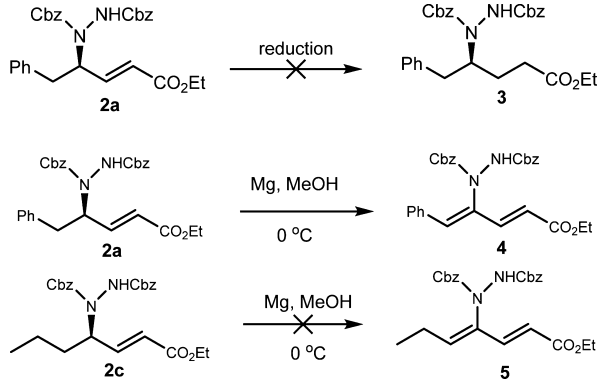
Table 1. Synthesis of γ-Amino-α,β-unsaturated Esters



Entry	R (1a-f)	Hydrazino Ester 2	Yield(%)	ee[a](%)
1	Bn	 2a	87	95
2	*p*-MeOC$_6$H$_4$CH$_2$	 2b	84	91
3	Pr	 2c	84	94
4	*i*-Pr	 2d	83	92
5	CH$_3$	 2e	80	93
6	(CH$_2$)$_3$CH$_2$OTBS	 2f	78	91

[a]ee was determined by HPLC analysis.

Scheme 2. Attempted Reduction of Double Bond by Hydrogenation Conditions



solvents were used for reactions. Solvents used for chromatography were distilled at respective boiling points using known procedures. Commercially available starting materials and reagents were used.

The IR spectra were recorded on FT-IR spectrometer. ^{1}H NMR spectra were recorded using deuterated solvent. Chemical shifts are reported in ppm. Proton coupling constants (J) are reported as absolute values in Hz and multiplicity (br, broadened; s, singlet; d, douplet; t, triplet; m, multiplet). ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. All HPLC analyses used to determine enantiomeric purity were calibrated with sample of the racemate.

The physical and spectroscopic data of compounds **2a**−**e** and **2f** are in accord with those described in literature.[10b,9d]

(*R*,*E*)-Dibenzyl 1-(5-ethoxy-5-oxo-1-phenylpent-3-en-2-yl)-hydrazine-1,2-dicarboxylate (2a). $[\alpha]_D^{25}$ +8.44 (*c* 1.0, $CHCl_3$) {Lit[10b] {$[\alpha]_D^{25}$ +8.5 (*c* 1.0, $CHCl_3$)}. HPLC: Chiralcel OD-H (250 × 4.6 mm) (2-propanol:petroleum ether = 3:97, flow rate 1.0 mL/min (λ = 254 nm). Retention time (min): 67.692 (major) and 75.817 (minor). The racemic standard was prepared in the same way using DL-proline as a catalyst. ee 95%

(*R*,*E*)-Dibenzyl 1-(5-ethoxy-1-(4-methoxyphenyl)-5-oxopent-3-en-2-yl)hydrazine-1,2-dicarboxylate (2b). $[\alpha]_D^{25}$ +4.12 (*c* 1.0, $CHCl_3$) {Lit[10b] {$[\alpha]_D^{25}$ +4.0 (*c* 1.0, $CHCl_3$)}. HPLC: Kromasil 5−Amycoat (250 × 4.6 mm) (2-propanol:petroleum ether = 10:90, flow rate 0.7 mL/min (λ = 254 nm). Retention time (min): 57.192 (major) and 63.683 (minor). The racemic standard was prepared in the same way using DL-proline as a catalyst. ee 91%

(*R*,*E*)-Dibenzyl 1-(1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (2c). $[\alpha]_D^{25}$ +8.14 (*c* 1.0, $CHCl_3$) {Lit[10b] {$[\alpha]_D^{25}$ +8.0 (*c* 1.0, $CHCl_3$)}. HPLC: Kromasil 5−Amycoat (250 × 4.6 mm) (2-propanol:petroleum ether = 10:90, flow rate 0.5 mL/min (λ = 254 nm). Retention time (min): 26.100 (major) and 36.575 (minor). The racemic standard was prepared in the same way using DL-proline as a catalyst. ee 94%

(*R*,*E*)-Dibenzyl 1-(6-ethoxy-2-methyl-6-oxohex-4-en-3-yl)-hydrazine-1,2-dicarboxylate (2d). ($[\alpha]_D^{25}$ +1.90 (*c* 1.0, $CHCl_3$) {Lit[10b] {$[\alpha]_D^{25}$ +2.0 (*c* 1.0, $CHCl_3$)}. HPLC: Kromasil 5−Amycoat

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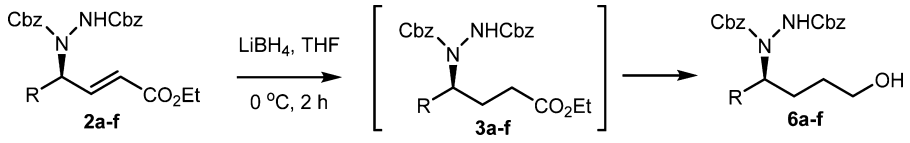
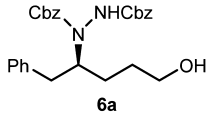
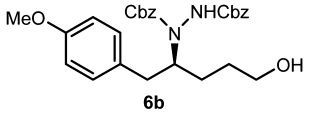
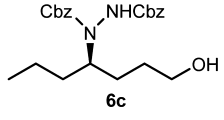
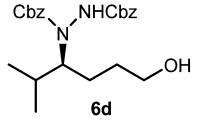
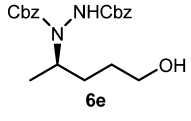
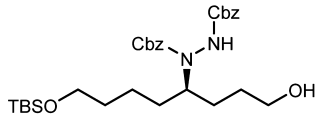
Table 2. Reduction of Ester Group



Entry	R (2a-f)	Hydrazino Alcohol 6	Yield (%)
1	Bn	 **6a**	92
2	*p*-$MeOC_6H_4CH_2$	 **6b**	92
3	Pr	 **6c**	89
4	*i*-Pr	 **6d**	88
5	CH_3	 **6e**	89
6	$(CH_2)_3CH_2OTBS$	 **6f**	90

(250 × 4.6 mm) (2-propanol:petroleum ether = 10:90, flow rate 0.7 mL/min (λ = 254 nm). Retention time (min): 19.250 (major) and 28.650 (minor). The racemic standard was prepared in the same way using DL-proline as a catalyst. ee 92%

(*R*,*E*)-Dibenzyl 1-(5-ethoxy-5-oxopent-3-en-2-yl)hydrazine-1,2-dicarboxylate (2e). $[\alpha]_D^{25}$ +5.09 (*c* 1.0, $CHCl_3$) {Lit[10b] {$[\alpha]_D^{25}$ +5.0 (*c* 1.0, $CHCl_3$)}. HPLC: Chiralcel OD-H (250 × 4.6 mm) (2-propanol: *n*-hexane = 6:94, flow rate 1.0 mL/min (λ = 254 nm). Retention time (min): 27.042 (minor) and 34.208 (major). The racemic standard was prepared in the same way using DL-proline as a catalyst. ee 93%

Dibenzyl (*R*,*E*)-1-(8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (2f). $[\alpha]_D^{25}$ +2.69 (*c* 1.0, $CHCl_3$) {Lit[9d] {$[\alpha]_D^{25}$ +2.67 (*c* 1.0, $CHCl_3$)}. HPLC: Kromasil 5−Amycoat (250 × 4.6 mm) (2-propanol:petroleum ether = 10:90, flow rate 0.5 mL/min (λ = 230 nm). Retention time (min): 13.300 (major) and 16.225 (minor). The racemic standard was prepared in the same way using DL-proline as a catalyst. ee 91%

Dibenzyl 1-((1*Z*,3*E*)-5-ethoxy-5-oxo-1-phenylpenta-1,3-dien-2-yl)hydrazine-1,2-dicarboxylate 4. To a solution of activated Mg (0.02 g, 0.8 mmol) under argon in dry MeOH (5 mL) was added ethyl ester **2a** (0.1 g, 0.2 mmol). The reaction mixture was stirred for 3 h at 10 °C in an ice bath. The reaction mixture was poured into 10 mL of ice-cooled 1 N HCl solution. The reaction mixture was then treated with 1 N ammonium hydroxide solution to adjust pH to 8 and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product. Silica gel column chromatography (petroleum ether:ethyl acetate = 9:1) of the crude product gave dibenzyl 1-((1*Z*,3*E*)-5-ethoxy-5-oxo-1-phenylpenta-1,3-dien-2-yl)hydrazine-1,2-dicarboxylate **4** as a colorless solid (0.08 g, 80%): mp 88 °C; IR ($CHCl_3$, cm^{-1}) ν_{max} 3294, 3030, 1715, 1497, 1218; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.14−5.24 (m, 4H), 6.07 (d, *J* = 15.8 Hz, 1H), 7.25−7.36 (m, 17H), 7.61 (d, *J* = 15.5 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 60.6, 6.9, 68.5, 120.8, 127.7, 128.2, 128.4, 128.5, 128.9, 129.7, 134.1, 135.3, 135.5, 136.2, 137.1, 138.6, 155.3, 156.1, 166.7 ppm; MS (ESI) *m*/*z* 523.18 (M + Na)$^+$; HRMS (ESI) *m*/*z* $[M + H]^+$ Calcd for $C_{29}H_{29}N_2O_6$ 501.2020, found 501.2019; $[M + NH_4]^+$ Calcd for $C_{29}H_{32}N_3O_6$ 518.2286, found 518.2287.

(*S*)-Dibenzyl 1-(5-hydroxy-1-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (6a). To a solution of ethyl ester **2a** (0.1 g, 0.2 mmol) in THF (2 mL), was added $LiBH_4$ (0.01 g, 0.6 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h. It was then quenched with aqueous ammonium chloride solution (1 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product. Silica gel column chromatography (petroleum ether:ethyl acetate = 7:3) of the crude product gave **6a** as a colorless solid (0.09 g, 92%): mp 97 °C; $[\alpha]_D^{25}$ +13.08 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3446, 3285, 2927, 1709, 1454, 1221, 1057; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45−1.58 (m, 2H), 1.71−1.76 (m, 2H), 2.72−2.86 (m, 2H), 3.26 (brs, 1H),

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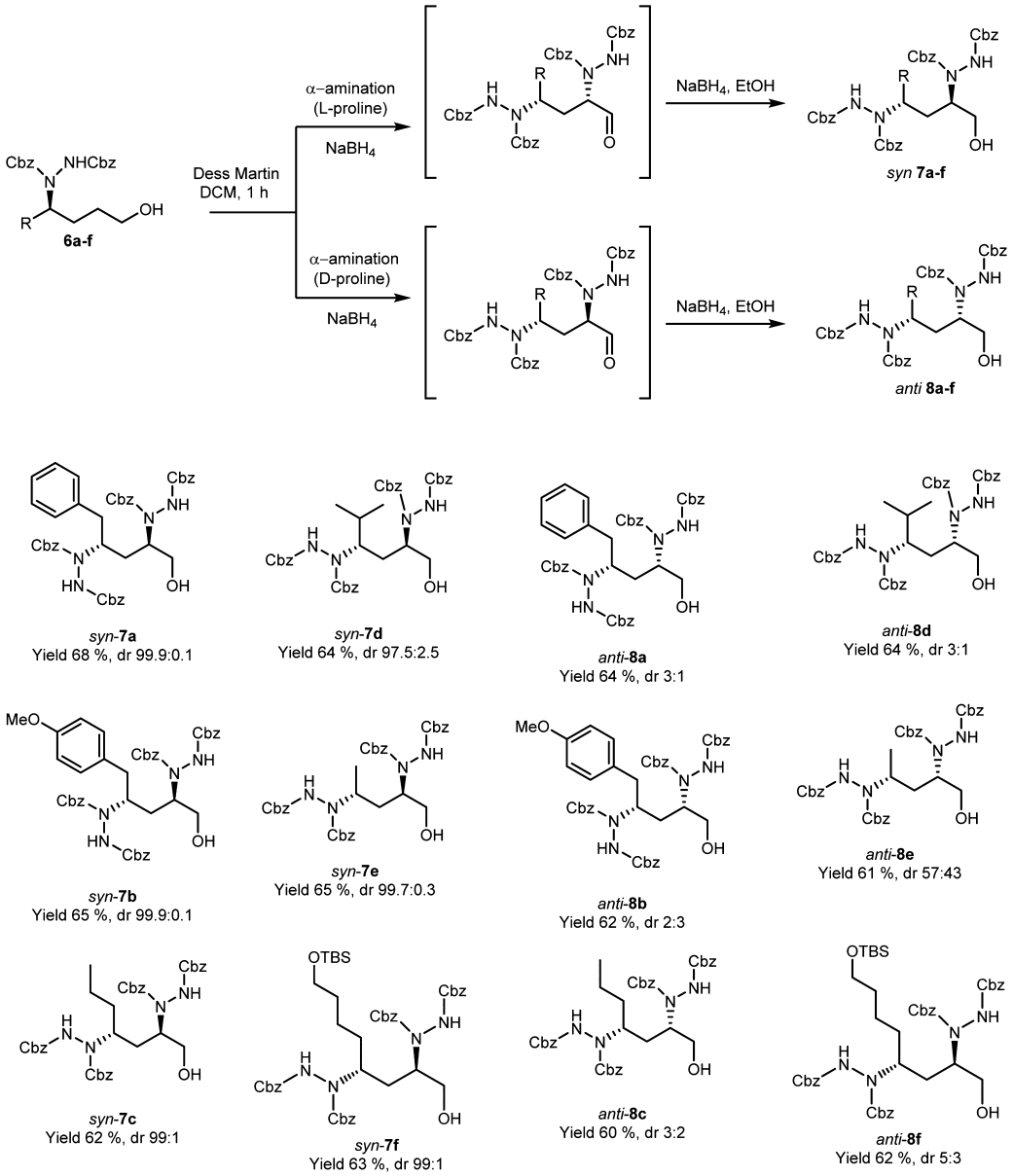
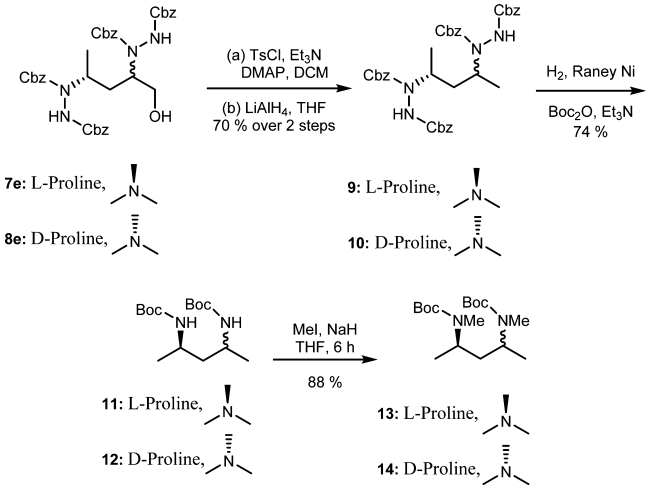
Scheme 3. Synthesis of *syn*/*anti*-1,3-Diamine



Scheme 4. Synthesis of N^2,N^4-Dimethylpentane-2,4-diamine



3.49–3.73 (m, 2H), 4.37–4.63 (m, 1H), 5.05–5.18 (m, 4H), 6.34 (s, 1H), 7.12–7.22 (m, 5H), 7.29–7.44 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.5, 28.9, 38.8, 60.3, 61.7, 67.3, 67.8, 126.0, 127.1, 127.8, 128.2, 128.6, 136.3, 135.7, 138.2, 155.8, 156.7 ppm; MS (ESI) m/z 485.19 $(M + Na)^+$; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{27}H_{31}O_5N_2$ 463.2227, found 463.2226; $[M + Na]^+$ Calcd for $C_{27}H_{30}N_2O_5Na$ 485.2044, found 485.2044

(*S*)-Dibenzyl 1-(5-hydroxy-1-(4-methoxyphenyl)pentan-2-yl)hydrazine-1,2-dicarboxylate (6b). Colorless solid (0.085 g, 92%): mp 120 °C; $[\alpha]_D^{25}$ +20.08 (*c* 0.75, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3420, 2925, 1711, 1456, 1127; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39–1.54 (m, 2H), 1.69–1.93 (m, 2H), 2.62–2.84 (m, 2H), 3.48–3.73 (m, 2H), 3.76 (s, 3H), 4.29–4.62 (m, 1H), 5.00–5.18 (m, 4H), 6.25 (brs, 1H), 6.78 (d, J = 8.5 Hz, 2H), 6.98–7.16 (m, 3H), 7.27–7.42 (m, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 29.4, 38.1, 55.1, 60.5, 62.2, 67.8, 68.2, 113.9, 127.4, 127.9, 128.2, 128.4, 128.5, 129.6, 129.8, 130.1, 135.4, 135.7, 135.9, 155.9, 156.9, 158.1 ppm; MS (ESI) m/z 515.21 $(M + Na)^+$; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{28}H_{33}N_2O_6$ 493.2333, found 493.2335; $[M + Na]^+$ Calcd for $C_{28}H_{32}N_2O_6Na$ 515.2153, found 515.2155

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(*R*)-Dibenzyl 1-(1-hydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (6c). Colorless solid (0.081 g, 89%): mp 95 °C; $[\alpha]_D^{25}$ +4.14 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3461, 3274, 2961, 1711, 1692, 1457, 1042; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (m, 3H), 1.10−1.56 (m, 8H), 3.30−3.61 (m, 2H), 4.06−4.23 (m, 1H), 5.04−5.24 (m, 4H), 6.47 (brs, 1H), 7.26−7.43 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 19.6, 28.6, 29.3, 34.7, 57.8, 62.3, 67.8, 68.2, 127.6, 127.8, 128.0, 128.2, 128.4, 128.5, 135.5, 135.8, 135.9, 156.3, 156.9 ppm; MS (ESI) *m*/*z* 437.12 (M + Na)$^+$; HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{23}H_{31}N_2O_5$ 415.2227, found 415.2224; [M + Na]$^+$ Calcd for $C_{23}H_{30}N_2O_5Na$ 437.2047, found 437.2042.

(*S*)-Dibenzyl 1-(6-hydroxy-2-methylhexan-3-yl)hydrazine-1,2-dicarboxylate (6d). Colorless solid (0.080 g, 88%): mp 97 °C; $[\alpha]_D^{25}$ +0.96 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3284, 2960, 1711, 1657, 1410, 1049; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83−0.97 (m, 6H), 1.52−1.80 (m, 5H), 3.26−3.69 (m, 2H), 3.87−4.12 (m, 1H), 5.10−5.19 (m, 4H), 6.49 (brs, 1H), 7.26−7.35 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 20.2, 25.2, 29.4, 30.4, 62.1, 64.1, 67.6, 68.2, 127.5, 127.7, 127.9, 128.1, 128.4, 135.5, 135.8, 135.9, 156.5, 157.2 ppm; MS (ESI) *m*/*z* 437.12 (M + Na)$^+$; HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{23}H_{31}N_2O_5$ 415.2227, found 415.2224; [M + Na]$^+$ Calcd for $C_{23}H_{30}N_2O_5Na$ 437.2047, found 437.2042.

(*R*)-Dibenzyl 1-(5-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (6e). Colorless solid (0.081 g, 89%): mp 81 °C; $[\alpha]_D^{25}$ −2.75 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3292, 2941, 1711, 1658, 1455, 1221; ^1H NMR (200 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.5 Hz, 3H), 1.37−1.50 (m, 2H), 1.63−1.73 (m, 2H), 3.51−3.73 (m, 2H), 4.21−4.44 (m, 1H), 5.08−5.21 (m, 4H), 6.49 (brs, 1H), 7.27−7.36 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.9, 29.1, 29.9, 53.5, 62.0, 67.5, 67.8, 127.6, 127.9, 128.2, 128.4, 135.6, 135.8, 155.8, 156.9 ppm; MS (ESI) *m*/*z* 409.14 (M + Na)$^+$; HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{21}H_{27}N_2O_5$ 387.1914, found 387.1913; [M + Na]$^+$ Calcd for $C_{21}H_{26}N_2O_5Na$ 409.1734, found 409.1732.

(*R*)-Dibenzyl 1-(8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (6f). Waxy solid (0.084 g, 90%): $[\alpha]_D^{25}$ +11.51 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3294, 295, 1705, 1658, 1224; ^1H NMR (200 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.16−1.73 (m, 10H), 2.48 (brs, 1H), 3.27−3.55 (m, 4H), 3.90−4.26 (m, 1H), 4.85−5.20 (m, 4H), 7.11−7.42 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.5, 18.1, 21.9, 22.2, 25.7, 28.4, 28.9, 32.1, 57.9, 61.8, 62.6, 67.3, 67.5, 127.3, 127.8, 127.9, 128.2, 135.5, 135.9, 156.2, 156.7 ppm; MS (ESI) *m*/*z* 581.24 (M + Na)$^+$; HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{30}H_{47}N_2O_6Si$ 559.3198, found 559.3189; [M + Na]$^+$ Calcd for $C_{30}H_{46}N_2O_6NaSi$ 581.3017, found 581.3010.

1,1′-((2*R*,4*R*)-Tetrabenzyl 1-hydroxy-5-phenylpentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (7a). To a solution of alcohol **6a** (0.1g, 0.216 mmol) in DCM (2 mL) was added DMP (0.137g, 3.25 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 h. It was then quenched with a 1:1 mixture of (10%) aqueous $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (0.065 g, 0.216 mmol) and L-proline (0.003 g, 10 mol %) in CH_3CN (2 mL) at 0 °C was added the above aldehyde (0.1 g, 0.216 mmol), and the mixture was stirred for 4 h at 0 °C and further for 1 h at 10 °C. Then the reaction mixture was cooled to 0 °C, treated with ethanol 1 mL and $NaBH_4$ (0.02 g), and stirred for 5 min at 0 °C. It was then quenched with aqueous ammonium chloride solution (3 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product. Silica gel column chromatography (petroleum ether:ethyl acetate = 70:30) of the crude product gave 1,1′-((2*R*,4*R*)- tetrabenzyl 1-hydroxy-5-phenylpentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) **7a** as a waxy solid (0.112 g, yield 68%): $[\alpha]_D^{25}$ +37.41 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3292, 2925, 1718, 1455, 1219, 1060; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41−1.70 (m, 1H), 1.75−2.12 (m, 1H), 2.72−3.14 (m, 2H), 3.39−3.61 (m, 2H), 3.66−3.93 (m, 1H), 4.23−4.52 (m, 1H), 4.85−5.35 (m, 8H), 6.19−6.33 (m, 1H), 7.12−7.44 (m, 25H), 7.94−8.16 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6, 37.7, 57.9, 61.7, 61.8, 67.9, 68.2, 68.4, 68.6, 126.6, 127.2, 127.5, 127.8, 128.0, 128.4, 128., 128.7, 135.1, 135.5, 156.7, 156.8, 158.6, 159.0 ppm; MS (ESI) *m*/*z* 783.33 (M + Na)$^+$, 799.30 (M + K)$^+$; HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{43}H_{45}N_4O_9$ 761.3181, found 761.3182.

Diastereomeric ratio was determined by HPLC analysis; 99.9:0.1 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.4 mL/min. IPA:petroleum ether = 6:4; t_R for (*anti*)-isomer = 25.800 min and t_R for (*syn*)-isomer = 19.667 min.

Using the same procedure as described for synthesis of **7a**, compounds **7b**−**7f** were prepared.

1,1′-((2*R*,4*R*)-Tetrabenzyl 1-hydroxy-5-(4-methoxyphenyl)-pentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (7b). Waxy solid (0.104 g, 65%): $[\alpha]_D^{25}$ +12.08 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3294, 2927, 1718, 1512, 1455, 1247, 1059; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45−1.74 (m, 2H), 2.61−2.88 (m, 2H), 3.33−3.70 (m, 3H), 3.77 (s, 3H), 4.15−4.69 (m, 2H), 4.88−5.37 (m, 8H), 6.21−6.49 (m, 1H), 6.73−6.82 (m, 2H), 7.00−7.09 (m, 2H), 7.19−7.48 (m, 20H), 8.03−8.21 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6, 38.1, 55.0, 60.3, 61.6, 62.2, 67.6, 67.9, 68.2, 68.5, 113.9, 114.0, 127.1, 127.4, 127.9, 128.2, 128.3, 128.5, 129.5, 129.6, 129.9, 135.1, 135.4, 135.7, 135.9, 155.9, 156.4, 156.8, 157.3, 158.1 ppm; MS (ESI) *m*/*z* 813.37 (M + Na)$^+$; HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{44}H_{47}N_4O_{10}$ 791.3287, found 791.3288; [M + Na]$^+$ Calcd for $C_{44}H_{46}N_4O_{10}Na$ 813.3106, found 813.3095.

Diastereomeric ratio was determined by HPLC analysis; 99.9:0.1 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 37.550 min and t_R for (*syn*)-isomer = 29.225 min.

1,1′-((2*R*,4*R*)-Tetrabenzyl 1-hydroxyheptane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (7c). Waxy solid (0.107 g, 62%): $[\alpha]_D^{25}$ −5.32 (*c* 1.85, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3293, 2925, 1714, 1498, 1456, 1259, 1049; ^1H NMR (200 MHz, $CDCl_3$) δ 0.72−0.88 (m, 3H), 1.26−1.34 (m, 3H), 1.48−1.80 (m, 3H), 3.40−3.72 (m, 2H), 3.88−4.02 (m, 1H), 4.21−4.54 (m, 2H), 4.83−5.33 (m, 8H), 6.64−6.96 (m, 1H), 7.22−7.48 (m, 20H), 7.56−7.83 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 19.5, 31.6, 34.7, 57.7, 61.6, 62.0, 67.5, 67.8, 68.1, 68.4, 127.2, 127.4, 127.7, 127.9, 128.1, 128.3, 128.4, 129.8, 132.9, 135.4, 135.5, 135.8, 156.2, 156.5, 156.7, 156.9 ppm; MS (ESI) *m*/*z* 735.34 (M + Na)$^+$; HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{39}H_{45}N_4O_9$ 713.3181, found 713.3182; [M + Na]$^+$ Calcd for $C_{39}H_{44}N_4O_9Na$ 735.3001, found 735.2983.

Diastereomeric ratio was determined by HPLC analysis; 99:1 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 22.283 min and t_R for (*syn*)-isomer = 14.792 min.

1,1′-((2*R*,4*S*)-Tetrabenzyl 1-hydroxy-5-methylhexane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (7d). Waxy solid (0.110 g, 64%): $[\alpha]_D^{25}$ −8.29 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3280, 2960, 1715, 1498, 1456, 1260, 1051; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83−0.94 (m, 6H), 1.55−1.84 (m, 3H), 3.42−3.66 (m, 2H), 3.75−4.16 (m, 3H), 5.08−5.14 (m, 8H), 5.65−5.78 (m, 1H), 6.72−6.91 (m, 1H), 7.26−7.39 (m, 20H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 19.7, 29.4, 30.4, 61.4, 62.5, 64.2, 67.6, 67.9, 68.3, 127.2, 127.5, 127.7, 127.9, 128.0, 128.3, 128.4, 129.9, 130.7, 131.9, 135.5, 135.8, 156.5, 156.7, 157.2 ppm; MS (ESI) *m*/*z* 735.34 (M + Na)$^+$; HRMS (ESI) *m*/*z* [M + H]$^+$ Calcd for $C_{39}H_{45}N_4O_9$ 713.3181, found 713.3182; [M + Na]$^+$ Calcd for $C_{39}H_{44}N_4O_9Na$ 735.3001, found 735.2983.

Diastereomeric ratio was determined by HPLC analysis; 97.5:2.5 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 25.542 min and t_R for (*syn*)-isomer = 17.342 min.

1,1′-((2*R*,4*R*)-Tetrabenzyl 1-hydroxypentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (7e). Waxy solid (0.115 g, 65%): $[\alpha]_D^{25}$ −10.17 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3290, 2936, 1712, 1498, 1455, 1223, 1050; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08−1.23 (m, 3H), 1.28−1.53 (m, 2H), 3.30−3.66 (m, 3H), 4.02−4.47 (m,

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2H), 4.91−5.53 (m, 8H), 6.84−6.98 (m, 1H), 7.19−7.41 (m, 20H), 7.64−7.75 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 29.6, 61.8, 61.9, 62.3, 67.7, 67.9, 68.1, 68.5, 127.4, 127.7, 127.8, 127.9, 128.1, 128.4, 128.5, 135.3, 135.5, 156.4, 156.6, 156.7, 156.8 ppm; MS (ESI) m/z 707.40 (M + Na)$^+$; HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{37}H_{41}N_4O_9$ 685.2868, found 685.2869; [M + Na]$^+$ Calcd for $C_{37}H_{40}N_4O_9Na$ 707.2687, found 707.2675.

Diastereomeric ratio was determined by HPLC analysis; 99.7:0.3 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 26.558 min and t_R for (*syn*)-isomer = 22.017 min.

1,1′-((2*R*,4*R*)-Tetrabenzyl 8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (7f). Waxy solid (0.117 g, 63%): $[\alpha]_D^{25}$ +4.45 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3295, 2932, 1712, 1496, 1261, 1051; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.93 (s, 9H), 1.31−1.89 (m, 8H), 3.46−3.73 (m, 4H), 3.83−4.61 (m, 3H), 4.83−5.39 (m, 8H), 6.88−6.99 (m, 1H), 7.12−7.34 (m, 20H), 7.91−8.28 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, 18.2, 22.6, 25.8, 29.5, 31.8, 61.6, 61.9, 62.7, 67.9, 68.1, 68.4, 127.2, 127.7, 127.9, 128.2, 128.4, 131.3, 132.4, 135.4, 141.3, 156.3, 156.7, 156.8 ppm; MS (ESI) m/z 879.24 (M + Na)$^+$; HRMS (ESI) m/z [M + Na]$^+$ Calcd for $C_{46}H_{60}N_4O_{10}NaSi$ 879.3971, found 879.3964.

Diastereomeric ratio was determined by HPLC analysis; 99:1 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 27.542 min and t_R for (*syn*)-isomer = 23.642 min.

Using the same procedure as described for the synthesis of **7a** and using D-proline as a catalyst in α-amination step, compounds **8a−8f** were prepared.

1,1′-((2*S*,4*R*)-Tetrabenzyl 1-hydroxy-5-phenylpentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (8a). Waxy solid (0.105 g, 64%): $[\alpha]_D^{25}$ +2.74 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3292,, 2925, 1718, 1455, 1219, 1060; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43−1.82 (m, 2H), 2.49−2.99 (m, 2H), 3.11−3.71 (m, 2H), 4.18−4.73 (m, 2H), 4.88−5.18 (m, 8H), 6.42−6.57 (m, 1H), 7.32 (m, 25H), 7.92−8.21 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.1, 38.9, 52.6, 60.4, 61.9, 67.3, 67.5, 67.7, 67.9, 127.2, 127.7, 127.9, 128.3, 128.7, 128.8, 129.7, 132.8, 134.9, 135.4, 135.8, 138.2, 155.8, 156.3, 156.7, 157.2 ppm; MS (ESI) m/z 783.33 (M + Na)$^+$; HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{43}H_{45}N_4O_9$ 761.3181, found 761.3182.

Diastereomeric ratio was determined by HPLC analysis; 3:1 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.4 mL/min. IPA:petroleum ether = 6:4; t_R for (*anti*)-isomer = 22.825 min and t_R for (*syn*)-isomer = 20.317 min.

1,1′-((2*S*,4*R*)-Tetrabenzyl 1-hydroxy-5-(4-methoxyphenyl)-pentane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (8b). Waxy solid (0.100 g, 62%): $[\alpha]_D^{25}$ +13.24 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3294, 2927, 1718, 1512, 1455, 1247, 1059; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30−1.49 (m, 2H), 2.46−2.71 (m, 2H), 3.40−3.61 (m, 3H), 3.66 (s, 3H), 3.90−4.58 (m, 2H), 4.67−5.17 (m, 8H), 6.27−6.43 (m, 1H), 6.69 (d, J = 7.8 Hz, 2H), 6.95 (d, J = 7.8 Hz, 2H), 7.02−7.23 (m, 20H), 7.45−7.73 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6, 38.1, 55.1, 60.4, 62.2, 62.3, 67.8, 67.9, 68.2, 113.9, 127.5, 127.9, 128.2, 128.4, 128.5, 129.4, 129.6, 129.8, 129.9, 135.2, 135.4, 135.7, 135.9, 155.9, 156.5, 156.8, 157.4, 158.1 ppm; MS (ESI) m/z 813.37 (M + Na)$^+$; HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{44}H_{47}N_4O_{10}$ 791.3287, found 791.3288; [M + Na]$^+$ Calcd for $C_{44}H_{46}N_4O_{10}Na$ 813.3106, found 813.3095.

Diastereomeric ratio was determined by HPLC analysis; 2:3 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 37.185 min and t_R for (*syn*)-isomer = 31.017 min.

1,1′-((2*S*,4*R*)-Tetrabenzyl 1-hydroxyheptane-2,4-diyl)bis-(hydrazine-1,2-dicarboxylate) (8c). Waxy solid (0.103 g, 60%): $[\alpha]_D^{25}$ −2.27 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3293, 2925, 1714, 1498, 1456, 1259, 1049; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86−0.89 (m, 3H), 1.11−1.27 (m, 2H), 1.30−1.38 (m, 2H), 1.53−1.64 (m, 2H), 3.42−3.76 (m, 3H), 3.90−4.39 (m, 2H), 4.86−5.30 (m, 8H), 6.70 (m, 1H), 7.18−7.42 (m, 20H), 7.58−7.79 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.6, 29.7, 34.8, 57.7, 58.8, 62.3, 67.8, 67.9, 68.1, 68.3, 126.9, 127.6, 127.7, 128.0, 128.2, 128.5, 135.5, 135.8, 135.9, 156.3, 156.6, 156.9, 157.2 ppm; MS (ESI) m/z 735.34 (M + Na)$^+$; HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{39}H_{45}N_4O_9$ 713.3181, found 713.3182; [M + Na]$^+$ Calcd for $C_{39}H_{44}N_4O_9Na$ 735.3001, found 735.2983.

Diastereomeric ratio was determined by HPLC analysis; 3:2 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 22.533 min and t_R for (*syn*)-isomer = 15.575 min.

1,1′-((2*S*,4*S*)-Tetrabenzyl 1-hydroxy-5-methylhexane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (8d). Waxy solid (0.110 g, 64%): $[\alpha]_D^{25}$ −10.14 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3280, 2960, 1715, 1498, 1456, 1260, 1051; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83−0.95 (m, 6H), 1.47−1.84 (m, 3H), 3.34−3.93 (m, 4H), 4.05−4.24 (m, 1H), 4.77−5.28 (m, 8H), 5.65−5.78 (m, 1H), 6.77−7.03 (m, 1H), 7.25−7.39 (m, 20H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 19.9, 29.4, 30.4, 62.3, 62.6, 64.2, 67.7, 67.8, 68.0, 68.3, 127.3, 127.5, 127.6, 127.7, 127.9, 128.1, 128.3, 128.4, 128.5, 129.9, 135.4, 135.8, 156.4, 156.7, 156.9, 157.2 ppm; MS (ESI) m/z 735.34 (M + Na)$^+$; HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{39}H_{45}N_4O_9$ 713.3181, found 713.3182; [M + Na]$^+$ Calcd for $C_{39}H_{44}N_4O_9Na$ 735.3001, found 735.2983.

Diastereomeric ratio was determined by HPLC analysis; 3:1 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 24.817 min and t_R for (*syn*)-isomer = 17.308 min.

1,1′-((2*S*,4*R*)-Tetrabenzyl 1-hydroxypentane-2,4-diyl)bis-(hydrazine-1,2-dicarboxylate) (8e). Waxy solid (0.108 g, 61%): $[\alpha]_D^{25}$ −3.08 (*c* 2.6, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3290, 2936, 1712, 1498, 1455, 1223, 1050; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (d, J = 6.4 Hz, 3H), 1.28−1.48 (m, 2H), 3.03−3.22 (s, 1H), 3.36−3.57 (m, 2H), 4.02−4.41 (m, 2H), 4.75−5.29 (m, 4H), 6.79−7.03 (m, 1H), 7.12−7.46 (m, 20H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 30.0, 53.5, 54.5, 62.2, 67.6, 67.8, 68.1, 127.3, 127.6, 128.0, 128.2, 135.6, 135.8, 155.7, 155.8, 156.6, 156.8 ppm; MS (ESI) m/z 707.40 (M + Na)$^+$; HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{37}H_{41}N_4O_9$ 685.2868, found 685.2869; [M + Na]$^+$ Calcd for $C_{37}H_{40}N_4O_9Na$ 707.2687, found 707.2675.

Diastereomeric ratio was determined by HPLC analysis; 57:43 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 26.092 min and t_R for (*syn*)-isomer = 21.625 min.

1,1′-((2*S*,4*R*)-Tetrabenzyl 8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctane-2,4-diyl)bis(hydrazine-1,2-dicarboxylate) (8f). Waxy solid (0.115 g, 62%): $[\alpha]_D^{25}$ −5.59 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3295, 2932, 1712, 1496, 1261, 1051; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.26−1.32 (m, 3H), 1.38−1.67 (m, 5H), 2.51 (brs, 1H), 3.40−4.27 (m, 6H), 4.79−5.34 (m, 8H), 6.79−6.97 (m, 1H), 7.27 (m, 20H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, 18.3, 22.2, 25.9, 29.6, 32.3, 62.2, 62.4, 62.7, 67.7, 67.9, 68.1, 127.5, 128.1, 128.2, 128.4, 128.5, 135.5, 135.7, 156.3, 156.5, 156.8 ppm; MS (ESI) m/z 879.24 (M + Na)$^+$; HRMS (ESI) m/z [M + Na]$^+$ Calcd for $C_{46}H_{60}N_4O_{10}NaSi$ 879.3971, found 879.3964.

Diastereomeric ratio was determined by HPLC analysis; 5:3 dr. UV detector: Shimadzu Class-VP V6.12 SP5. Column: Kromasil 5−AmyCoat. Flow rate: 0.5 mL/min. IPA:petroleum ether = 3:7; t_R for (*anti*)-isomer = 26.200 min and t_R for (*syn*)-isomer = 21.050 min.

Di-*tert*-butyl ((2*R*,4*S*)-pentane-2,4-diyl)dicarbamate 11. The solution of 1,1′-((2*R*,4*R*)-tetrabenzyl 1-hydroxypentane-2,4-diyl)bis-(hydrazine-1,2-dicarboxylate **7e** (0.5g, 0.73 mmol) in DCM was treated with triethylamine (0.148g, 1.46 mmol), and TsCl (0.21g, 1.1 mmol) was added at 0 °C followed by addition of catalytic DMAP. The reaction mixture was stirred at rt for 2 h. After completion of reaction, the reaction mixture was quenched with addition of water and extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude tosyl compound. This crude tosyl compound was then treated with $LiAlH_4$ (0.03g, 0.8 mmol) in THF for 1 h. The reaction was quenched by addition of

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saturated Na_2SO_4 solution. The mixture was filtered with pad of Celite and washed with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude diamine product **9**, which was directly used in the next step without further purification.

The solution of crude diamine product **9** in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel (0.8 g, excess) under H_2 (80 psi) atmosphere for 24 h. The reaction mixture was then filtered over Celite and concentrated to give crude free diamine, which was further treated with triethylamine (0.3g, 2.92 mmol), $(Boc)_2O$ (0.65 mL, 2.92 mmol) in dry DCM (2 mL) for 2 h. Ice pieces were added to the reaction mixture, and organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give crude *N*-boc derivative. Silica gel column chromatography (petroleum ether:ethyl acetate = 85:15) of the crude product gave **11** as a waxy solid (0.121 g, 51%): IR ($CHCl_3$, cm^{-1}) ν_{max} 3363, 2976, 1690, 1523, 1170; ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 (d, J = 6.4 Hz, 6H), 1.43 (s, 18H), 1.67 (m, 2H), 3.62−3.76 (m, 2H), 4.38−4.59 (brs, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1, 28.4, 29.7, 44.1, 79.1, 155.3 ppm; MS (ESI) m/z 325.15 $(M + Na)^+$; HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{15}H_{30}N_2O_4Na$ 325.2096, found 325.2098.

Di-*tert*-butyl ((2*R*,4*R*)-pentane-2,4-diyl)dicarbamate (12). Waxy solid (0.121 g, 51%): $[\alpha]_D^{25}$ +5.92 (c 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3363, 2976, 1690, 1523, 1170; ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (d, J = 6.7 Hz, 6H), 1.44 (s, 18H), 1.53−1.55 (m, 2H), 3.62−3.76 (m, 2H), 4.41−4.52 (brs, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0, 28.4, 29.6, 43.9, 79.0, 156.2 ppm; MS (ESI) m/z 325.15 $(M + Na)^+$; HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{15}H_{30}N_2O_4Na$ 325.2096, found 325.2098.

Di-*tert*-butyl ((2*R*,4*S*)-pentane-2,4-diyl)bis-(methylcarbamate) (13). To a stirred solution of **11** (0.03 g, 0.116 mmol) in dry toluene (3 mL) was added NaH (0.010 g, 0.464 mmol), CH_3I (0.1 mL, 1.55 mmol), and the reaction mixture was heated at 85 °C for 5 h. The reaction mixture was then diluted with EtOH (5 mL) and H_2O (2 mL), and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether:ethyl acetate = 85:15) of the crude product gave **13** as a colorless liquid (0.029 g, 88%): IR ($CHCl_3$, cm^{-1}) ν_{max} 3445, 2926, 1695, 1456, 1158; ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (d, J = 6.7 Hz, 6H), 1.46 (s, 18H), 1.54−1.69 (m, 2H), 2.70 (s, 6H), 3.87−4.26 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 28.5, 29.3, 31.9, 47.2, 79.1, 155.5 ppm; MS (ESI) m/z 353.21 $(M + Na)^+$; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{17}H_{35}N_2O_4$ 331.2591, found 331.2591; $[M + Na]^+$ Calcd for $C_{17}H_{34}N_2O_4Na$ 353.2411, found 353.2409.

Di-*tert*-butyl ((2*R*,4*R*)-pentane-2,4-diyl)bis-(methylcarbamate) (14). Colorless liquid (0.029 g, 88%): $[\alpha]_D^{25}$ +2.10 (c 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3445, 2926, 1695, 1456, 1158; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (d, J = 6.8 Hz, 6H), 1.46 (s, 18H), 1.61−1.66 (m, 2H), 2.68 (s, 3H), 2.71 (s, 3H), 3.88−4.07 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 28.5, 29.7, 31.9, 49.5, 79.0, 79.4, 155.4, 155.6 ppm; MS (ESI) m/z 353.21 $(M + Na)^+$; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{17}H_{35}N_2O_4$ 331.2591, found 331.2591; $[M + Na]^+$ Calcd for $C_{17}H_{34}N_2O_4Na$ 353.2411, found 353.2409.

***N,N′*-((2*R*,4*S*)-Pentane-2,4-diyl)bis(4-methylbenzenesulfonamide) 15.** The solution of crude diamine product **9** in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel (0.8 g, excess) under H_2 (80 psi) atmosphere for 24 h. The reaction mixture was then filtered over Celite and concentrated to give crude free diamine, which was further treated with triethylamine (0.3 g, 2.92 mmol), TsCl (0.555 g, 2.92 mmol) in dry DCM (2 mL) for 2 h. Ice pieces were added to the reaction mixture, and organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give crude *N*-boc derivative. Silica gel column chromatography (petroleum ether:ethyl acetate = 80:20) of the crude product gave *N,N′*-((2*R*,4*R*)-pentane-2,4-diyl)bis(4-methylbenzenesulfonamide) **15** as a crystalline solid (0.148 g, 50%): mp 115 °C; IR ($CHCl_3$, cm^{-1}) ν_{max} 3275, 2928, 1328, 1161; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (d, J = 6.5 Hz, 6H), 1.39−1.50 (m, 1H), 1.69−1.79 (m, 1H), 2.42 (s, 6H), 3.21−3.47 (m, 2H), 4.46 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.4 Hz, 4H), 7.74 (d, J = 8.4 Hz, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4, 21.5, 45.7, 47.2, 127.0, 129.7, 137.9, 143.3 ppm; MS (ESI) m/z 433.04 $(M + Na)^+$; HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{19}H_{26}N_2O_4S_2Na$ 433.1226, found 433.1224.

***N,N′*-((2*R*,4*R*)-Pentane-2,4-diyl)bis(4-methylbenzenesulfonamide) (16).** Crystalline solid (0.148 g, 50%): mp 113 °C; $[\alpha]_D^{25}$ +0.15 (c 0.75, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3275, 2928, 1328, 1161; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (d, J = 6.7 Hz, 6H), 1.59−1.63 (m, 2H), 2.44 (s, 6H), 3.43−3.57 (m, 2H), 4.61 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 8.3 Hz, 4H), 7.78 (d, J = 8.3 Hz, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.8, 21.5, 44.6, 47.4, 127.0, 129.7, 138.3, 143.3 ppm; MS (ESI) m/z 433.04 $(M + Na)^+$; HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{19}H_{26}N_2O_4S_2Na$ 433.1226, found 433.1224.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed spectral data (^1H and ^{13}C) for new compounds, X-ray crystal structure, and the CIF files of **15** and **16**, as well as HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Dr. Vijay Nair in recognition of his seminal contributions to so many aspects of organic chemistry.

■ REFERENCES

(1) For examples of bioactive 1,3-amines of natural or synthetic origin, see: (a) Jahn, T.; König, G. M.; Wright, A. D. *Tetrahedron Lett.* **1997**, *38*, 3883. (b) When, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950. (c) Kammermeier, T.; Wiegrebe, W. *Arch. Pharm.* **1995**, *328*, 409. (d) Vickery, K.; Bonin, A. M.; Fenton, R. R.; O'Mara, S.; Russell, P. J.; Webster, L. K.; Hambley, T. W. *J. Med. Chem.* **1993**, *36*, 3663.

(2) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512.

(3) (a) Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574. (b) Jahn, T.; Konig, G. M.; Wright, A. D.; Worheide, G.; Reitner, J. *Tetrahedron Lett.* **1997**, *38*, 3883.

(4) Ganem, B. *Acc. Chem. Res.* **1982**, *15*, 290.

(5) Erickson, J.; Neidhart, D. J.; VanDrie, J.; Kempf, D. J.; Wang, X. C.; Norbeck, D. W.; Plattner, J. J.; Rittenhouse, J. W.; Turon, M.; Wideburg, N.; Kohlbrenner, W. E.; Simmer, R.; Helfrich, R.; Paul, D. A.; Knigge, M. *Science* **1990**, *249*, 527.

(6) (a) Ozaki, S.; Mimura, H.; Yasuhara, N.; Masui, M.; Yamagata, Y.; Tomita, K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 353. (b) Pini, D.; Mastantuono, A.; Uccello-Baretta, G.; Iuliano, A.; Salvatori, P. *Tetrahedron* **1993**, *49*, 9613. (c) Yang, Z. H.; Wang, L. X.; Zhou, Z.

H.; Zhou, Q. L.; Tang, C. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1579. (d) Hems, W. P.; Groarke, M.; Gerosa, A. Z.; Grasa, G. A. *Acc. Chem. Res.* **2007**, *40*, 1340.

(7) (a) Bui, T.; Barbas III, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951. For reviews on organocatalytic tandem reactions, see: (b) Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res.* **2004**, *37*, 580. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (d) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (e) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477. (f) Lu, M.; Zhu, D.; Lu, Y.; Hou, Y.; Tan, B.; Zhong, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187.

(8) (a) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) For a review on proline-catalyzed asymmetric reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573. (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (e) List, B. *Chem. Commun.* **2006**, 819. (f) For α-functionalization reviews, see: Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (g) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.

(9) (a) Kondekar, N. B.; Kumar, P. *Org. Lett.* **2009**, *11*, 2611. (b) Dwivedi, N.; Kumar, P. *Acc. Chem. Res.* **2013**, *46*, 289. (c) Jha, V.; Kondekar, N. B.; Kumar, P. *Org. Lett.* **2010**, *12*, 2762. (d) Kauloorkar, S. V.; Jha, V.; Kumar, P. *RSC Adv.* **2013**, *3*, 18288.

(10) (a) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637. (b) Kotkar, S. P.; Chavan, V. B.; Sudalai, A. *Org. Lett.* **2007**, *9*, 1001.

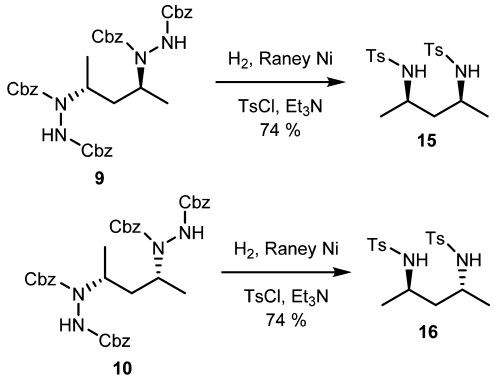
(11) (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (b) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A. *Angew.Chem., Int. Ed.* **2002**, *41*, 1790. (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448. (e) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (f) Chua, P. J.; Tan, B.; Zhong, G. *Green Chem.* **2009**, *11*, 543.

(12) For a recent review on chiral amine synthesis, see: Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753.

(13) (a) Merla, B.; Risch, N. *Synthesis* **2002**, 1365. (b) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1983**, *48*, 2255. (c) Alexakis, A.; Lensen, N.; Tranchier, J.-L.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 4563. (d) Denmark, S. E.; Kim, J.-H. *Synthesis* **1992**, 229. (e) Barluenga, J.; Tomas, M.; Kouznetsov, V.; Pardon, J.; Rubio, E. *Synlett* **1991**, 821. (f) Enders, D.; Jegelka, U.; Dücker, B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 423. (g) Merla, B.; Arend, M.; Risch, N. *Synlett* **1997**, 177. (h) Trost, B. M.; Malhotra, S.; Olson, D. E.; Maruniak, A.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 4190. (i) Zhao, C. H.; Wangand, L. L.; Chen, Y. J. *Eur. J. Org. Chem.* **2006**, 2977. (j) Morgen, M.; Bretzke, S.; Li, P.; Menche, D. *Org. Lett.* **2010**, *12*, 4494.

(14) (a) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409. (b) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599.

(15) Diastereoselectivity was determined using chiral HPLC (see Supporting Information). Relative stereochemistry of both *syn*- and *anti*-compound was determined by X-ray analysis of di-*N*-tosyl compound **15** and **16** derived from *syn*-**7e** and *anti*-**8e**, as shown below.



9 **15**

10 **16**

(16) Reetz, M. T.; Strack, T. J.; Mutulis, F.; Goddard, R. *Tetrahedron Lett.* **1996**, *37*, 9293.

(17) Cerasino, L.; Williams, K. M.; Intini, F. P.; Cini, R.; Marzilli, L. G.; Natile, G. *Inorg. Chem.* **1997**, *36*, 6070.

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