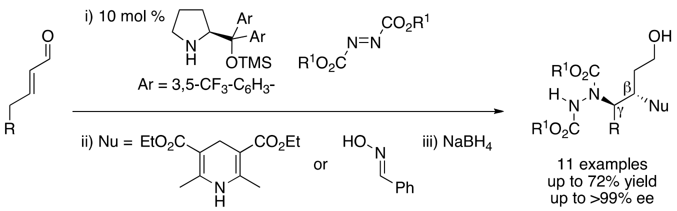
γ-Amino Alcohols via Organocascade Reactions Involving Dienamine Catalysis

Chandrakumar Appayee, Americo J. Fraboni, Stacey E. Brenner-Moyer*

Department of Chemistry, Brooklyn College and the City University of New York, 2900
Bedford Avenue, Brooklyn, New York 11210

SBrenner@brooklyn.cuny.edu

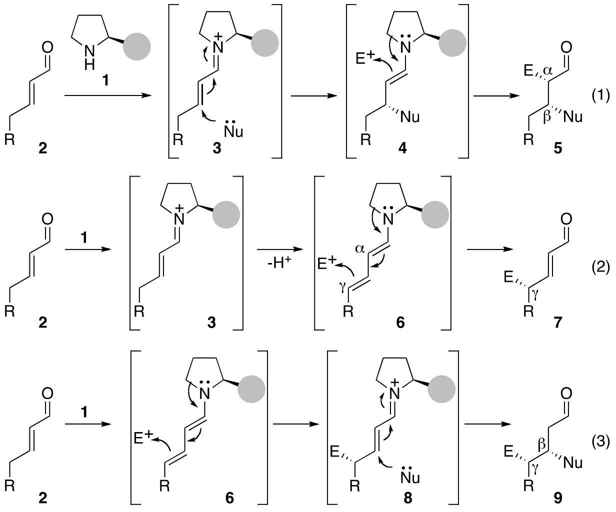


Abstract

Whereas cascade reactions catalyzed by secondary amines combine iminium- and/or enamine-catalyzed reactions, we introduce the feasibility of combining these modes of catalysis with dienamine-catalysis as a new general mechanism for cascade reactions. Enantioenriched β-functionalized-γ-amino alcohols were produced from simple achiral enals in one flask by combining dienamine-and iminium-catalyzed intermolecular reactions. Reaction products are precursors of γ-amino acids, δ-lactams, and pyrrolidines; one was employed in a synthesis of γ-amino acid (*S*)-vigabatrin, the bioactive enantiomer of Sabril©.

In recent years, organocascade reactions have been established as efficient green chemical methods for rapidly building molecular complexity.[1-4] Cascade reactions catalyzed by chiral secondary amines (**1**, Scheme 1) entail some combination of iminium- and/or enamine-catalysis. For example, in a typical cascade reaction catalyzed by **1**, an α,β-unsaturated aldehyde is sequentially functionalized at the β- and α-positions via iminium- and enamine-catalyzed reactions, respectively (equation 1).[1-2] While iminium- and enamine-catalysis are well-established modes of catalysis for chiral secondary amines, dienamine catalysis is a relatively underexplored mode of catalysis for these catalysts. Perhaps this is because dienamine intermediates of type **6** are prone to multiple reaction motifs, rendering deliberate manipulation of their reactivity challenging. For example, the olefin(s) in dienamines can react to generate formal [2+2] and [4+2] cycloaddition products.[5-12] Alternatively, both the α- and γ-carbons of dienamine **6** are nucleophilic, and either position can react with discrete electrophiles.[13-25] There are four examples of dienamine catalyzed reactions producing γ-functionalized-α,β-unsaturated carbonyl compounds (equation 2).[20,23-25] We suspected that γ-functionalized-α,β-unsaturated aldehydes of type **7** would be suitable substrates for subsequent iminium-catalyzed intermolecular reactions (equation 3). This straightforward but heretofore unexplored transformation is significant because, if successful, it would introduce the feasibility of organocascade reactions entailing some combination of iminium- and enamine-catalysis *with dienamine catalysis*. Organocascade reactions proceeding by these novel mechanisms would generate functionalized aldehyde products that are not directly accessible via current organocascade reactions. We report herein the first example of a cascade reaction combining dienamine- and iminium-catalyzed intermolecular reactions. This organocascade reaction directly produces γ-amino alcohols, which are valuable synthetic precursors of γ-amino acids and substituted δ-lactams and pyrrolidines. In fact, one cascade product was employed in a formal synthesis of non-natural γ-amino acid (*S*)-vigabatrin, the biologically active enantiomer of the racemic anticonvulsant drug marketed as Sabril©.[26]

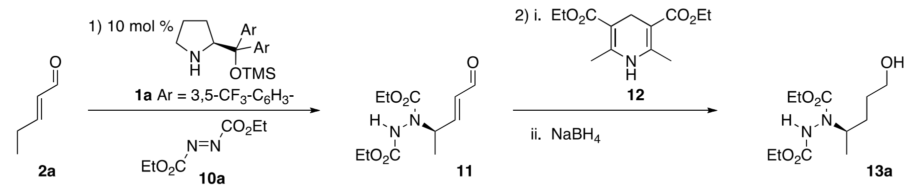
Scheme 1. Reactions catalyzed by chiral secondary amines.[a]



[a] Equation (1): organocascade reactions via iminium- and enamine-catalysis; equation (2): γ-functionalization via dienamine catalysis; equation (3): proposed organocascade reaction via dienamine- and iminium-catalysis.

Both steps of the proposed cascade reaction were initially optimized independently to identify a common set of reaction conditions that would be suitable for a one-pot cascade reaction (Table 1). Catalyst **1a** was found to be effective for both steps. Next, both steps were evaluated in the optimal solvents for the γ-amination (toluene) and conjugate reduction ($CHCl_3$) reactions (entries 1-4).[20,27] While the γ-amination proceeded in either solvent, the conjugate reduction was ineffective in toluene—the Hantzsch ester was insoluble in this solvent at low temperature and product decomposition was observed in this solvent at rt. Thus, $CHCl_3$ was identified as the optimal solvent for the cascade reaction. While a number of variables were examined in an effort to improve the yield of the first step,[28] the variable that was most impactful was reaction concentration (entries 3, 5-7). In our hands, more dilute reaction conditions led to higher yields in the ©-amination reaction. Interestingly, this is opposite the trend observed by Jørgensen (in toluene and CH_2Cl_2) for this reaction.[20] Ultimately optimal reaction conditions for the one-pot cascade reaction were identified,[28] which provided γ-amino alcohol **13a** in a single flask from **2a** in 63% yield and 92% ee (entry 8).[29]

Table 1. Cascade reaction development.[a]



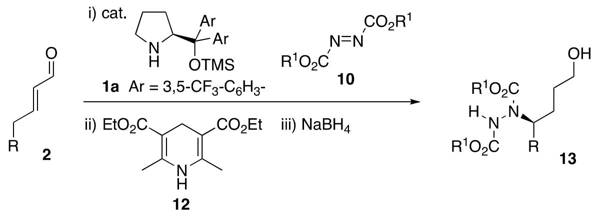
	step 1				step 2			
entry	solvent	conc.	yield **11** (%)[b]	ee **11** (%)[c]	solvent	*t* (°C)	yield **13a** (%)[d]	ee **13a** (%)[e]
1	toluene	2M	42	90				
2					toluene	-20	--	--
3	$CHCl_3$	2M	45	90				
4					$CHCl_3$	0[f]	98	90

5	$CHCl_3$	1M	54	nd			
6	$CHCl_3$	0.5M	63	nd			
7	$CHCl_3$	0.25M	72	nd			
8[g]	$CHCl_3$	0.25M			0	63	92

[a] Reaction conditions for step 1: **2a** (1.5 equiv), **10a**, **1a** (0.1 equiv), $PhCO_2H$ (0.1 equiv), solvent, rt. Reaction conditions for step 2: i) **11**, **12** (1.1 equiv), **1a** (0.1 equiv), $PhCO_2H$ (0.1 equiv), solvent (0.25M), temp. ii) $NaBH_4$ (4.5 equiv), MeOH, 0°C. [b] ^1H NMR yield using internal standard. [c] Determined by chiral phase HPLC of derivative of (corresponding) alcohol. [d] Isolated yield. [e] Determined by chiral phase HPLC of its corresponding 4-chlorobenzoyl derivative, **22a**. [f] Reaction time was 5 h. Longer reaction times led to product decomposition at this temperature. [g] Reaction conditions: i) **2a** (1.5 equiv), **10a**, **1a** (0.1 equiv), $PhCO_2H$ (0.2 equiv), solvent, rt; ii) **12** (1.5 equiv), **1a** (0.1 equiv), 0°C; iii) $NaBH_4$ (6 equiv), MeOH, 0°C.

With optimal reaction conditions for the one-pot cascade reaction in hand, a variety of other α,β-unsaturated aldehydes were examined in this transformation (Table 2). Enals with unbranched aliphatic R groups provided γ-amino alcohols in excellent yield (≥89% average yield per step) and ee (entries 1-3). Sterically demanding substituents at the δ-position of enals were tolerated in this transformation (entries 4-5), while bulky substitution at the γ-position (R = *i*Pr) was not (data not shown). A heteroatom at the δ-position of enals was also tolerated (entry 6). The use of dibenzyl azodicarboxylate (DBAD; R^1 = Bn) required that the second step of the cascade reaction be run at lower temperatures to prevent product decomposition, and resulted in lower yields and slightly lower ee's (entry 7 vs. entry 2). γ-Amino alcohol **13i** was generated in lower yield (72% average yield per step) and lower, but still good, ee (entry 8). Use of enals with related δ-substituents (R = CH_2OTBS and CH_2OMOM) gave similar results (data not shown). This is possibly due to the combination of the use of DBAD and the inductive effect of the electronegative oxygen at the ™-position of the enal, which reduces the nucleophilicity of the adjacent, γ-position of the dienamine in the first step of the cascade reaction. Nonetheless, the reaction with this substrate was readily scalable (entry 9). Finally, this transformation was also compatible with remote reactive functionality (entry 10).

Table 2. Substrate scope.[a]



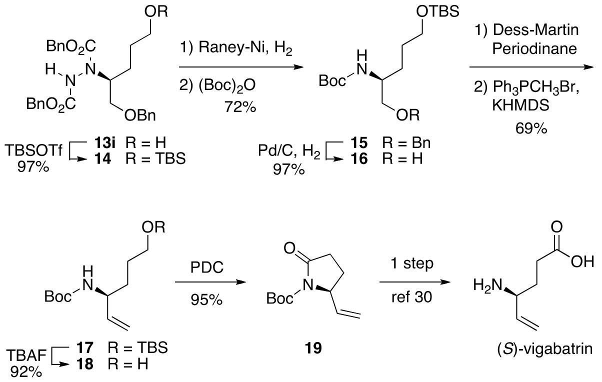
entry	**13**	R	R^1	yield **13** (%)[b]	ee **13** (%)[c]
1	**13b**	Et	Et	72	92
2	**13c**	*n*Pr	Et	70	93
3	**13d**	C_7H_{15}	Et	72	93
4	**13e**	*i*Bu	Et	57	92
5	**13f**	Bn	Et	49	94
6	**13g**	CH_2SCH_3	Et	45	93

7[d]	**13h**	*n*Pr	Bn	44	87
8[d]	**13i**	CH$_2$OBn	Bn	37	72
9[d-e]	**13i**	CH$_2$OBn	Bn	35	73
10[d]	**13j**	(CH$_2$)$_4$CN	Et	44	93

[a] Reaction conditions: i) **2** (0.375 mmol), **10** (0.25 mmol), **1a** (0.025 mmol), PhCO$_2$H (0.050 mmol), CHCl$_3$ (1 mL), rt, 16-48 h; ii) **12** (0.375 mmol), **1a** (0.025 mmol), 0°C, 20-48 h; iii) NaBH$_4$ (1.5 mmol), MeOH, 0°C. [b] Isolated yield. [c] Determined by chiral phase HPLC of alcohol or of its corresponding 4-chlorobenzoyl derivative, **22**. [d] Step ii of cascade run at -20°C. [e] Reaction run on 2.5 mmol (of **10**) scale.

Cascade product **13i** was elaborated to produce (*S*)-vigabatrin, the biologically active enantiomer of the racemic anticonvulsant drug Sabril© (Scheme 2). It was found that protection of the alcohol in **13i** was necessary for the tandem carbamate removal / N-N bond cleavage to proceed smoothly. Alcohol **13i** was therefore protected as a TBS ether (**14**). Tandem carbamate removal / N-N bond cleavage, followed by Boc protection of the resulting free amine produced **15**. Removal of the benzyl ether generated alcohol **16**, which underwent a two-step, oxidation / Wittig olefination protocol to furnish **17**. Deprotection of the TBS ether afforded alcohol **18**. Oxidation and in situ lactam formation produced **19**, a known penultimate intermediate in the total synthesis of (*S*)-vigabatrin.[30]

Scheme 2. Synthesis of (*S*)-vigabatrin from cascade product **13i**.

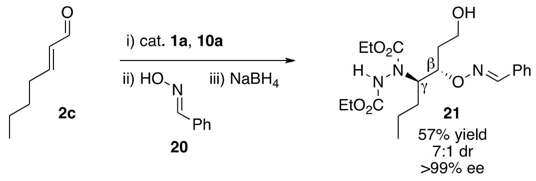


Comparison of the optical rotation of γ-lactam **19** to the literature value established the configuration of **19**, and of the corresponding stereocenter in cascade product **13i**. The configurations of all other cascade products were assigned by analogy.

Thus, this formal synthesis of (*S*)-vigabatrin started from a simple achiral 〈,®-unsaturated aldehyde, and utilized a cascade reaction combining dienamine- and iminium-catalysis both to install the γ-amino functionality and to establish the γ-stereocenter. Presumably, this strategy could be employed in the synthesis of other non-natural γ-amino acids (or substituted γ-lactams or pyrrolidines). Inherent in this strategy is the ability to access either enantiomer of a γ-amino acid from the same starting material simply by using the appropriate enantiomer of the catalyst in the cascade reaction.

Finally, this cascade reaction is amenable to the use of nucleophiles other than **12**, such as oxime **20** (Scheme 3).[31] This result is illustrative of the capacity of cascade reactions combining dienamine- and iminium catalysis to generate enantiopure ©,®-difunctionalized alcohol products.

Scheme 3. Cascade product with vicinal, γ,β-stereocenters.[a]



[a] Reaction conditions: i) **2c** (0.375 mmol), **10a** (0.25 mmol), **1a** (0.025 mmol), $PhCO_2H$ (0.025 mmol), toluene (0.125 mL), rt, 21 h; ii) **20** (1.125 mmol), **1a** (0.025 mmol), $PhCO_2H$ (0.025 mmol), 0°C, 21 h; iii) $NaBH_4$ (0.565 mmol), MeOH, 0°C.

In conclusion, we have developed the first cascade reaction combining dienamine- and iminium-catalyzed intermolecular reactions. This cascade reaction produces enantioenriched γ-amino alcohols, and was the key step in a formal synthesis of the γ-amino acid (*S*)-vigabatrin, the bioactive enantiomer of the anticonvulsant drug, Sabril©. Additionally, this cascade reaction was readily adapted to provide an enantiopure β-functionalized-γ-amino alcohol, thereby demonstrating that the combination of dienamine- and iminium-catalyzed reactions is a new, *general* mechanism for organocascade reactions. Organocascade reactions of this type furnish useful molecular scaffolds that cannot be accessed directly by existing organocascade reactions.

Experimental Section

General Information

NMR data were acquired on a 400 MHz NMR spectrometer, and use the abbreviations: s=singlet, d=doublet, t=triplet, m=multiplet, dd=doublet of doublets, ddd=doublet of doublets of doublets, brm=broad multiplet, brs=broad singlet. Ee's were determined using chiral phase HPLC with Chiralpak AD-H (0.46 x 25 cm) and Chiralpak AS-H (0.46 x 25 cm) columns. HRMS spectra were acquired using an MS spectrometer with Q-TOF mass analyzer. Flash chromatography was carried out with F60, 40-63 mm, 60 Å silica gel and EMD silica 60 F_{254} glass TLC plates. Solvents were dried and kept air-free in a solvent purification unit, and were evaporated using a standard rotovapor and high vacuum. All reactions were carried out in oven-dried glassware, under an Ar atmosphere. All enals were distilled freshly before use.

Preparation of catalyst (1a), enals (2e-g, i-j) and oxime (20)

Catalyst **1a**[32] was prepared from the corresponding diarylprolinol[33] using a known procedure. Enals **2e**[34], **2f**[35], **2g**[35], **2i**[36]and **2j**[37], and oxime **20**[38] were prepared using known procedures.

General procedure for dienamine-iminium cascade

To a mixture of catalyst **1a** (15 mg, 0.025 mmol) and benzoic acid (6 mg, 0.05 mmol) was added $CHCl_3$ (1 mL) and the mixture was stirred at rt. After 5 min enal **2** (0.375 mmol) was added. After 10 min **10** (0.25 mmol) was added and the reaction was stirred in the dark until complete consumption of **10** as observed by ^{1}H-NMR. The reaction was cooled to 0 °C, catalyst **1a** (15 mg, 0.025 mmol) was added followed by **12** (95 mg, 0.375 mmol), and the reaction was stirred at 0 °C until complete consumption of enal as observed by ^{1}H-NMR. The reaction was diluted with MeOH (2.5 mL), $NaBH_4$ (57 mg, 1.5 mmol) was added in portions, and was stirred at 0 °C for 30 min, and then quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over $MgSO_4$ and filtered. After removal of solvent under reduced pressure, the residue was purified by flash chromatography (EtOAc:petroleum ether) to yield γ-amino alcohol **13**.

(*R*)-Diethyl 1-(5-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (13a): Colorless oil (41 mg, 63%); $[\alpha]_D^{22}$ = –9.9 (*c*=0.55 in $CHCl_3$); IR (thin film, KBr): 3292, 2982, 2936, 1710, 1523, 1418,1379, 1236, 1058, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (brm, 1H), 4.21-4.09 (m, 5H), 3.67-3.60 (m, 2H), 1.88 (brs, 1H), 1.72-1.62 (m, 2H), 1.42-1.40 (m, 1H), 1.28-1.21 (m, 6H), 1.14 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.3, 62.6, 62.6, 62.2, 53.5, 30.3, 29.5, 18.4, 14.6, 14.5 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{11}H_{23}N_2O_5]$: 263.1607, found: 263.1603.

(*R*)-Diethyl 1-(6-hydroxyhexan-3-yl)hydrazine-1,2-dicarboxylate (13b): Colorless oil (50 mg, 72%); $[\alpha]_D^{23}$ = 4.5 (*c*=1.2 in $CHCl_3$); IR (thin film, KBr): 3284, 2979, 2935, 1693, 1525, 1416,1383, 1262, 1058, 937 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-6.67 (m, 1H), 4.15-3.87 (m, 5H), 3.61-3.53 (m, 2H), 2.53 (brs, 1H), 1.55-1.39 (m, 6H), 1.24-1.20 (m, 6H), 0.87 (brs, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6/157.4, 157.1/156.8, 62.6, 62.3, 62.0, 60.8/59.6, 29.5, 28.5, 25.8/25.7, 14.5, 14.4, 11.1 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{12}H_{25}N_2O_5]$: 277.1763, found: 277.1766.

(*R*)-Diethyl 1-(1-hydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (13c): Colorless oil (51 mg, 70%); $[\alpha]_D^{23}$ = 3.6 (*c*=1.0 in $CHCl_3$); IR (thin film, KBr): 3466, 3283, 2960, 2933, 1711, 1417, 1257, 1060, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (brm, 1H), 4.21-4.03 (m, 5H), 3.67-3.59 (m, 2H), 1.80-1.42 (m, 8H), 1.29-1.25 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5/157.1, 156.5, 62.4, 62.4, 62.1, 58.4/57.5, 34.9, 29.5, 28.7, 19.7, 14.5, 14.4, 13.9 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{13}H_{27}N_2O_5]$: 291.1920, found: 291.1920.

(*R*)-Diethyl 1-(1-hydroxyundecan-4-yl)hydrazine-1,2-dicarboxylate (13d): Colorless oil (62 mg, 72%); $[\alpha]_D^{23}$ = 3.8 (*c*=1.58 in $CHCl_3$); IR (thin film, KBr): 3453, 3277, 2926, 2856, 1757, 1712, 1416, 1260, 1062, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (brm, 1H), 4.18-3.99 (m, 5H), 3.66-3.57 (m, 2H), 1.99-1.24 (m, 16H), 1.28-1.24 (m, 6H), 0.86 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6/157.2, 157.1/156.7, 62.5, 62.2, 62.1, 58.9/57.9, 32.8, 31.9, 29.5, 29.4, 28.8, 26.6, 22.8, 14.6/14.5, 14.2 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{17}H_{35}N_2O_5]$: 347.2546, found: 347.2555.

(*S*)-Diethyl 1-(1-hydroxy-6-methylheptan-4-yl)hydrazine-1,2-dicarboxylate (13e): Colorless oil (43 mg, 57%); $[\alpha]_D^{23}$ = 1.9 (*c*=2.12 in $CHCl_3$); IR (thin film, KBr): 3465, 3284, 2957, 2870, 1756, 1711, 1417, 1259, 1062, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.39 (brm, 1H), 4.19-4.17 (m, 5H), 3.67-3.58 (m, 2H), 1.96-1.11 (m, 8H), 1.29-1.25 (m, 6H), 0.90-0.88 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.3/156.7, 62.8, 62.7, 62.5, 57.1/56.0, 42.3/42.0, 29.8/29.3, 25.4/25.2, 23.6, 22.5/22.2, 14.8 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{14}H_{29}N_2O_5]$: 305.2076, found: 305.2072.

(*S*)-Diethyl 1-(5-hydroxy-1-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate (13f): Colorless oil (41 mg, 49%); $[\alpha]_D^{23}$ = 14.4 (*c*=0.94 in $CHCl_3$); IR (thin film, KBr): 3285, 2981, 2929, 1712, 1414, 1291, 1233, 1063, 758, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.19 (m, 5H), 6.31 (brm, 1H), 4.58-4.07 (m, 5H), 3.67-3.58 (m, 2H), 2.85-2.79 (m, 2H), 2.05-1.51 (m, 4H), 1.30-1.18 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8/157.2, 156.7/156.4, 138.5, 128.9, 128.7, 126.7, 62.6, 62.4, 60.3, 39.6.1/39.3, 29.5, 28.3, 14.6 ppm; HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 39.6 min, minor enantiomer t_R = 33.5 min; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{17}H_{27}N_2O_5]$: 339.1920, found: 339.1920.

(*S*)-Diethyl 1-(5-hydroxy-1-(methylthio)pentan-2-yl)hydrazine-1,2-dicarboxylate (13g): Colorless oil (35 mg, 45%); $[\alpha]_D^{23}$ = 31.5 (*c*=1.07 in $CHCl_3$); IR (thin film, KBr): 3465, 3284, 2980, 2922, 2871, 1712, 1414, 1331, 1249, 1063, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.47 (brm, 1H), 4.39-4.16 (m, 5H), 3.68-3.60 (m, 2H), 2.58 (brs, 2H), 2.08 (s, 3H), 2.02 (brs, 1H), 1.83-1.52 (m, 3H), 1.27 (t, *J* = 7.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8/157.3, 156.9/156.8, 62.9, 62.7, 62.3, 57.3/55.8, 37.3/36.7, 29.6, 28.3, 15.5/15.2, 14.6 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{12}H_{25}N_2O_5S]$: 309.1484, found: 309.1492.

(*R*)-Dibenzyl 1-(1-hydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (13h): white solid (46 mg, 44%); mp 83-84 ºC; $[\alpha]_D^{24}$ = 4.4 (*c*=1.6 in $CHCl_3$); IR (thin film, KBr): 3280, 3033, 2958, 2872, 1711, 1455, 1413, 1258, 1216, 1050, 740, 697 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$): δ 7.31 (brs, 10H), 6.81 (brm, 1H), 5.68-4.65 (m, 4H), 4.23-4.05 (m, 1H), 3.57-3.34 (m, 2H), 2.10 (brs, 1H), 1.62-1.23 (m, 7H), 0.89-0.71 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3/157.0, 156.9/156.4, 136.2/136.0, 135.7, 128.6, 128.7, 128.6, 128.5, 128.3, 128.2, 127.8, 68.4/68.1, 67.9, 62.5, 59.0/57.9, 34.9, 29.5, 28.7, 19.7, 14.0 ppm; HPLC with an AD-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 23.0 min, minor enantiomer t_R = 28.3 min; HRMS (ESI): $[M+H]^+$ calcd. for [$C_{23}H_{31}N_2O_5$]: 415.2233, found: 415.2228.

(*S*)-Dibenzyl 1-(1-(benzyloxy)-5-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate (13i): Colorless oil (46 mg, 37%); $[\alpha]_D^{26}$ = 7.2 (*c*=1.7 in $CHCl_3$); IR (thin film, KBr): 3279, 3032, 2942, 2867, 1713, 1498, 1454, 1411, 1218, 1091, 739, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (brs, 15H), 6.53-6.24 (brm, 1H), 5.20-4.96 (m, 4H), 4.54-4.38 (m, 3H), 3.68-3.38 (m, 4H), 1.97-1.27 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.9, 138.0, 136.1, 135.7, 128.7, 128.6, 128.5, 128.2, 127.9, 127.8, 72.8, 69.6, 68.4/68.1, 67.9, 62.2, 58.4/56.9, 29.4, 24.7 ppm; HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 83.5 min, minor enantiomer t_R = 74.3 min; HRMS (ESI): $[M+H]^+$ calcd. for [$C_{28}H_{33}N_2O_6$]: 493.2339, found: 493.2328.

(*R*)-Diethyl 1-(8-cyano-1-hydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (13j): Colorless oil (36 mg, 44%); $[\alpha]_D^{23}$ = 8.9 (*c*=1.62 in $CHCl_3$); IR (thin film, KBr): 3473, 3285, 2934, 2869, 2246, 1752, 1708, 1417, 1260, 1233, 1058, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (brm, 1H), 4.19-4.00 (m, 5H), 3.65-3.58 (m, 2H), 2.33 (t, *J* = 6.6 Hz, 2H), 2.10 (brs, 1H), 1.91-1.24 (m, 10H), 1.26 (t, *J* = 7.0 Hz, 6H) ppm; ^{13}C NMR (100

MHz, $CDCl_3$) δ 157.6, 157.1/156.7, 119.9, 62.8, 62.6, 62.2, 58.6/57.4, 32.2/31.9, 29.3/28.8, 25.7, 25.3, 17.1, 14.6 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{15}H_{28}N_3O_5]$: 330.2029, found: 330.2030.

General procedure for preparation of esters 22a-e, **22g**, **22j**

To alcohol **13** (1 equiv) in CH_2Cl_2 (0.1 M) was added Et_3N (1.3 equiv) and 4-chlorobenzoyl chloride (1.3 equiv). After disappearance of alcohol by TLC, the solvent was removed under reduced pressure and the product was purified by flash chromatography (EtOAc:petroleum ether).

(*R*)-Diethyl 1-(5-((4-chlorobenzoyl)oxy)pentan-2-yl)hydrazine-1,2-dicarboxylate (22a): Colorless oil (62 mg, 78%); $[⟨]_D^{22}$ = –8.8 (*c*=1.02 in $CHCl_3$); IR (thin film, KBr): 3300, 2980, 2934, 1756, 1720, 1595, 1405, 1274, 1172, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): ™ 7.96 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.28 (brs, 1H), 4.31 (t, *J* = 6.4 Hz, 2H), 4.32-4.17 (m, 5H), 1.90-1.67 (m, 3H), 1.48 (brs, 1H), 1.28-1.23 (m, 6H), 1.60 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) ™ 165.9, 157.4, 156.1, 139.4, 131.1, 128.9, 128.8, 65.2, 62.5, 62.1, 53.4, 30.6, 25.8, 18.3, 14.6, 14.5 ppm; HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 28.7 min, minor enantiomer t_R = 38.9 min; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{18}H_{26}ClN_2O_6]$: 401.1479, found: 401.1477.

(*R*)-Diethyl 1-(6-((4-chlorobenzoyl)oxy)hexan-3-yl)hydrazine-1,2-dicarboxylate (22b): Colorless oil (42 mg, 84%); $[⟨]_D^{23}$ = –9.6 (*c*=0.7 in $CHCl_3$); IR (thin film, KBr):

3296, 2978, 2934, 1757, 1718, 1595, 1405, 1274, 1093, 1015, 928 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): ™ 7.97 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.13 (brs, 1H), 4.32 (t, *J* = 6.4 Hz, 2H), 4.19-3.97 (m, 5H), 1.99 (brs, 1H), 1.82 (brs, 1H), 1.53-1.41 (m, 4H), 1.29-1.21 (m, 6H), 0.90 (brs, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) ™ 165.9, 157.5/157.2, 156.8/156.7, 139.4, 131.1, 129.1, 128.8, 65.2, 62.5, 62.2, 60.3/59.4, 29.0/28.9, 25.9, 25.7/25.6, 14.7, 14.6, 11.2 ppm; HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 15.9 min, minor enantiomer t_R = 25.2 min; HRMS (ESI): $[M+H]^+$ calcd. for [$C_{19}H_{28}ClN_2O_6$]: 415.1636, found: 415.1638.

(*R*)-Diethyl 1-(1-((4-chlorobenzoyl)oxy)heptan-4-yl)hydrazine-1,2-dicarboxylate (22c): Colorless oil (82 mg, 91%); [⁆]$_D^{24}$ = –10.5 (*c*=1.4 in $CHCl_3$); IR (thin film, KBr): 3293, 2961, 2933, 1757, 1717, 1274, 1093, 1015, 851 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): ™ 7.96 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.25-6.18 (brm, 1H), 4.38-4.16 (m, 5H), 4.31 (t, *J* = 6.4 Hz, 2H), 1.99 (brs, 1H), 1.81-1.50 (m, 7H), 1.41-1.28 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) ™ 165.9, 157.4/157.1, 156.8/156.5, 139.4, 131.1, 129.0, 128.8, 65.2, 62.7/62.5, 62.2, 58.1/57.3, 34.9, 29.2, 25.9, 19.7, 14.6, 14.5, 14.0 ppm; HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 13.2 min, minor enantiomer t_R = 18.9 min; HRMS (ESI): $[M+H]^+$ calcd. for [$C_{20}H_{30}ClN_2O_6$]: 429.1792, found: 429.1788.

(*R*)-Diethyl 1-(1-((4-chlorobenzoyl)oxy)undecan-4-yl)hydrazine-1,2-dicarboxylate (22d): Colorless oil (33 mg, 49%); [⁆]$_D^{23}$ = –8.8 (*c*=1.0 in $CHCl_3$); IR (thin film, KBr):

3299, 2957, 2928, 2856, 1759, 1721, 1405, 1274, 1228, 1118, 1104, 1093, 761 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): ™ 7.97 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.13 (brm, 1H), 4.33-4.05 (m, 5H), 4.31 (t, *J* = 6.4 Hz, 2H), 2.00-1.25 (m, 16H), 1.29-1.25 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) ™ 165.9, 157.4/157.1, 156.8/156.5, 139.4, 131.1, 129.0, 128.8, 65.2, 62.5, 62.2, 58.4/57.7, 32.7, 32.0, 29.5, 29.4, 26.6/25.9, 22.8, 14.7, 14.2 ppm; HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t$_R$ = 8.5 min, minor enantiomer t$_R$ = 11.0 min; HRMS (ESI): [M+H]$^+$ calcd. for [$C_{24}H_{38}ClN_2O_6$]: 485.2418, found: 485.2409.

(*S*)-Diethyl 1-(1-((4-chlorobenzoyl)oxy)-6-methylheptan-4-yl)hydrazine-1,2-dicarboxylate (22e): Colorless oil (38 mg, 77%); $[\alpha]_D^{23}$ = –8.5 (*c*=2.06 in CHCl$_3$); IR (thin film, KBr): 3301, 2958, 2869, 1759, 1720, 1405, 1273, 1218, 1105, 1093, 761 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): ™ 7.97 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.20-6.13 (brm, 1H), 4.33-4.17 (m, 5H), 4.31 (t, *J* = 6.2 Hz, 2H), 1.99-0.74 (m, 7H), 1.28-1.27 (m, 6H), 0.90-0.88 (m, 6H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) ™ 165.9, 157.4/156.9, 156.8/156.4, 139.4, 131.1, 129.0, 128.8, 65.4/65.2, 62.7/62.5, 62.2/62.2, 56.4/55.6, 42.0/41.7, 29.5, 25.9, 25.2/25.0, 23.4, 22.3/22.0, 14.6 ppm; HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 0.5 mL/min; major enantiomer t$_R$ = 24.2 min, minor enantiomer t$_R$ = 30.0 min; HRMS (ESI): [M+H]$^+$ calcd. for [$C_{21}H_{32}ClN_2O_6$]: 443.1949, found: 443.1939.

(*S*)-Diethyl 1-(5-((4-chlorobenzoyl)oxy)-1-(methylthio)pentan-2-yl)hydrazine-1,2-dicarboxylate (22g): Colorless oil (35 mg, 79%); $[\alpha]_D^{23}$ = 7.9 (*c*=0.71 in CHCl$_3$); IR (thin film, KBr): 3299, 2980, 2922, 1755, 1719, 1404, 1275, 1121, 1092, 760 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): ™ 7.98 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.31 (brm, 1H), 4.35-4.18 (m, 5H), 4.33 (t, *J* = 6.0 Hz, 2H), 2.61 (brs, 2H), 2.09-1.60 (m, 7H), 1.29-1.25 (m, 6H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) ™ 165.9, 157.6, 156.8, 139.5, 131.1, 129.0, 128.8, 65.2/65.0, 63.0/62.7, 62.4, 56.8/55.5, 37.2/36.7, 28.7, 26.0, 15.5/15.2, 14.6 ppm; HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t$_R$ = 26.6 min, minor enantiomer t$_R$ = 41.5 min; HRMS (ESI): [M+H]$^+$ calcd. for [$C_{19}H_{28}ClN_2O_6S$]: 447.1357, found: 447.1347.

(*R*)-Diethyl 1-(1-((4-chlorobenzoyl)oxy)-8-cyanooctan-4-yl)hydrazine-1,2-dicarboxylate (22j): Purified by flash chromatography (5% Et$_2$O: CH$_2$Cl$_2$); Colorless oil (37 mg, 68%); $[\alpha]_D^{23}$ = –1.9 (*c*=1.42 in CHCl$_3$); IR (thin film, KBr): 3298, 2934, 2869, 2246, 1755, 1717, 1405, 1274, 1232, 1093, 761 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): ™ 7.96 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.40-6.25 (brm, 1H), 4.32-4.07 (m, 5H), 4.31 (t, *J* = 6.2 Hz, 2H), 2.33 (t, *J* = 6.6 Hz, 2H), 1.90-1.20 (m, 10H), 1.28-1.24 (m, 6H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) ™ 165.9, 157.5, 156.9/156.5, 139.5, 131.5, 131.1, 128.8, 119.8, 65.1/64.9, 62.9/62.6, 62.3, 58.2/57.1, 32.1/31.8, 29.2, 25.9, 25.6, 25.3, 17.2, 14.6 ppm; HPLC with an AS-H column (*n*-hexane: *i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t$_R$ = 47.6 min, minor enantiomer t$_R$ = 36.2 min; HRMS (ESI): [M+H]$^+$ calcd. for [$C_{22}H_{31}ClN_3O_6$]: 468.1901, found: 468.1891.

Preparation of (*S*)-dibenzyl 1-(1-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)hydrazine-1,2-dicarboxylate (14): To a solution of **13i** (227 mg, 0.46 mmol) in

CH_2Cl_2 (2.3 mL) was added 2,6-lutidine (110 mL, 0.92 mmol) and TBDMSOTf (160 mL, 0.69 mmol) at –78 °C. After 2h, MeOH (0.7mL) was added and the reaction was warmed to rt. Solvents were removed under vacuum and flash chromatography (25% Et_2O: petroleum ether) yielded **14** (270 mg, 97% yield) as a colorless oil.; $[\alpha]_D^{26}$ = 1.3 (c=0.7 in $CHCl_3$); IR (thin film, KBr): 3270, 2954, 2928, 2856, 1759, 1716, 1255, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 15H), 6.71-6.43 (m, 1H), 5.20-5.11 (m, 4H), 4.54-4.34 (m, 3H), 3.67-3.33 (m, 4H), 1.70-1.39 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 156.4, 138.1, 136.2, 135.9, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 72.9, 69.9, 68.4/68.0, 67.8, 67.6, 62.7, 58.2/56.6, 29.3, 26.1, 25.1, 18.5, –5.2 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{34}H_{47}N_2O_6Si]$: 607.3203, found: 607.3212.

Preparation of (*S*)-tert-butyl (1-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)carbamate (15): To a slurry of Raney-Nickel (~210 mg, pre-washed with MeOH) in MeOH (1 mL), was added AcOH (5 drops) and a solution of **14** (190 mg, 0.31 mmol) in MeOH (4 mL). The reaction was purged with a hydrogen filled balloon for 15 min and stirred under a slightly positive pressure of hydrogen (balloon) at rt for 16 h. The reaction was then filtered through a short pad of Celite and the Celite was washed with CH_2Cl_2. After solvents were removed, the crude product was diluted with CH_2Cl_2 and refiltered through a short pad of Celite. After removal of CH_2Cl_2 under vacuum, the crude product was subjected to Boc-protection.

To a solution of the above crude product (0.31 mmol) in THF (2.1 mL) was added $(Boc)_2O$ (170 mL, 0.74 mmol) and Et_3N (206 mL, 1.48 mmol). The reaction was stirred at rt for 16 h, then concentrated under vacuum to give a residue, which was purified by flash chromatography (25% Et_2O: petroleum ether) to yield **15** (94 mg, 72% yield for two steps) as a colorless oil.; $[\alpha]_D^{26}$ = –10.3 (*c*=0.55 in $CHCl_3$); IR (thin film, KBr): 3341, 2954, 2857, 1716, 1498, 1365, 1100, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 4.77 (brs, 1H), 4.54 (d, *J* = 12.0 Hz, 2H), 4.49 (d, *J* = 12.0 Hz, 2H), 3.74 (brs, 1H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.48-3.47 (m, 2H), 1.67-1.52 (m, 4H), 1.44 (s, 9H), 0.89 (s, 9H), 0.46 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 138.4, 128.5, 127.7, 127.6, 79.2, 73.3, 72.3, 63.1, 50.3, 29.4, 28.6, 26.1, 18.5, –5.2 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{23}H_{42}NO_4Si]$: 424.2883, found: 424.2877.

Preparation of (*S*)-tert-butyl (5-((tert-butyldimethylsilyl)oxy)-1-hydroxypentan-2-yl)carbamate (16): To a solution of **15** (17 mg, 0.040 mmol) in EtOAc (0.4 mL) was added $NaHCO_3$ (4 mg, 0.048 mmol) and 10% Pd/C (3.1 mg), and the reaction was stirred under a hydrogen atmosphere at rt for 16 h. The mixture was filtered through a short pad of Celite, and the Celite was washed with EtOAc. The solvent was removed under vacuum and the residue was purified by flash chromatography (50% EtOAc: petroleum ether) to give **16** (13 mg, 97% yield) as a colorless oil.; $[\alpha]_D^{24}$ = –6.0 (*c*=1.73 in $CHCl_3$); IR (thin film, KBr): 3349, 2954, 2885, 2858, 1690, 1516, 1391, 1366, 1254, 1174, 1100, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.92 (brs, 1H), 3.63-3.52 (m, 5H), 2.93 (brs, 1H), 1.58-1.47 (m, 4H), 1.41 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H) ppm; ^{13}C

NMR (100 MHz, $CDCl_3$) δ 156.8, 79.6, 66.1, 62.9, 52.8, 29.1, 28.5, 27.8, 26.1, 18.4, –5.2 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{16}H_{36}NO_4Si]$: 334.2414, found: 334.2429.

Preparation of (*S*)-tert-butyl (6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-yl)carbamate (17): $NaHCO_3$ (60 mg, 0.72 mmol) and Dess–Martin periodinane (152 mg, 0.36 mmol) were added to a solution of **16** (80 mg, 0.24 mmol) in CH_2Cl_2 (1.2 mL) at rt. After 30 min, the reaction was diluted with saturated aqueous $Na_2S_2O_3$ (0.5 mL), saturated aqueous $NaHCO_3$ (0.2 mL), and H_2O (0.3 mL). The resulting solution was stirred vigorously until clear, then was diluted further with saturated aqueous $Na_2S_2O_3$ (2 mL), saturated aqueous $NaHCO_3$ (2 mL), and H_2O (1 mL) and was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvents were removed under vacuum. The crude aldehyde was used directly in the Wittig reaction.

To a slurry of Ph_3PCH_3Br (154 mg, 0.43 mmol) in THF (0.8 mL) was added KHMDS (0.5 M in toluene, 0.8 mL, 0.41 mmol) and the resulting yellow suspension was stirred at rt for 2 h, then cooled to -78 °C. A solution of the above crude aldehyde (0.24 mmol) in THF (0.2 mL) was slowly added. After the reaction was stirred at -78 °C for 2 h, it was warmed to rt and stirred for another 14 h. Then the reaction was cooled to 0 °C and quenched with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and the solvents were removed under vacuum. The residue was purified by flash chromatography (5% EtOAc: petroleum ether) to give **17** (54 mg, 69% yield for two steps) as a colorless oil.; $[\alpha]_D^{25}$ = 5.6 (c=1.0 in $CHCl_3$); IR (thin film, KBr): 3341, 2955, 2930, 2857, 1705, 1517, 1366, 1252, 1174, 1100, 1005, 835, 776 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$): δ 5.74 (ddd, *J* = 16.4, 10.4, 5.6 Hz, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.62 (brs, 1H), 4.08 (brs, 1H), 3.61 (t, *J* = 5.6 Hz, 2H), 1.60-1.47 (m, 4H), 1.43 (s, 9H), 0.88 (s, 9H), 0.03 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 139.2, 114.4, 79.3, 62.8, 52.6, 31.5, 28.9, 28.5, 26.1, 18.4, –5.2 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{17}H_{36}NO_3Si]$: 330.2464, found: 330.2465.

Preparation of (*S*)-tert-butyl (6-hydroxyhex-1-en-3-yl)carbamate (18): To a solution of **17** (50 mg, 0.15 mmol) in THF (1 mL) was added TBAF (1M in THF, 0.45 mL, 0.45 mmol) at rt. After 3.5 h, the reaction was quenched with saturated aq. NH_4Cl (5 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were dried over $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, the residue was passed through a short pad of silica gel and washed with 7% EtOAc: petroleum ether (15 mL) and the eluent was discarded. Then the silica gel pad was washed with 50% EtOAc: petroleum ether (10 mL) and the solvents were removed under reduced pressure to yield **18** (32 mg, 98% yield) as a colorless oil.; $[\alpha]_D^{25}$ = 7.7 (*c*=1.4 in $CHCl_3$); IR (thin film, KBr): 3332, 2978, 2933, 2871, 1690, 1527, 1367, 1172, 1059, 993, 918 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (ddd, *J* = 16.4, 10.4, 5.6 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.63 (brs, 1H), 4.08 (brs, 1H), 3.63 (t, *J* = 5.6 Hz, 2H), 2.40 (brs, 1H), 1.62-1.46 (m, 4H), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 138.9, 114.7, 79.5, 62.4, 52.6, 31.6, 28.8, 28.5 ppm; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{11}H_{22}NO_3]$: 216.1600, found: 216.1610.

Preparation of (*S*)-tert-butyl 2-oxo-5-vinylpyrrolidine-1-carboxylate (19): To a solution of **18** (28 mg, 0.13 mmol) in DMF (2.3 mL) was added PDC (294 mg, 0.8 mmol), and the reaction was stirred at rt for 18 h. The reaction was diluted with H_2O (5 mL), extracted with EtOAc (3×15 mL), and the combined organic layers were dried with $MgSO_4$. The solution was filtered and the solvents were removed under reduced pressure. Crude product was purified by flash chromatography (50% EtOAc: petroleum ether) to give **19** (26 mg, 95% yield) as a colorless oil.; $[\alpha]_D^{25} = -25.0$ (c=0.9 in $CHCl_3$ for 72% *ee*); Lit.[39] $[\alpha]_D = -24.3$ (c=1.07 in $CHCl_3$ for 72% *ee*); IR (thin film, KBr): 2980, 2931, 1785, 1752, 1719, 1368, 1308, 1256, 1156, 922, 851, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.84 (ddd, J = 17.2, 10.4, 6.0 Hz, 1H), 5.18 (dd, J = 16.0, 0.8 Hz, 1H), 5.17 (dd, J = 11.2, 1.2 Hz, 1H), 4.65-4.61 (m, 1H), 2.61-2.51 (m, 1H), 2.45-2.37 (m, 1H), 2.26-2.16 (m, 1H), 1.83-1.77 (m, 1H), 1.49 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 149.9, 136.9, 115.4, 83.0, 59.7, 31.2, 28.1, 24.4 ppm; HRMS (ESI): $[M+Na]^+$ calcd. for $[C_{11}H_{17}NO_3Na]$: 234.1106, found: 234.1113. This data matches that in the literature.[39]

Preparation of diethyl 1-((3*S*,4*R*)-3-(((*Z*)-benzylideneamino)oxy)-1-hydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (21): To a mixture of catalyst **1a** (15 mg, 0.025 mmol) and benzoic acid (3 mg, 0.025 mmol) was added toluene (54 mL) and the mixture was stirred at rt. After 5 min enal **2b** (50 mL, 0.375 mmol) was added. After 10 min a solution of **10a** (40% in toluene, 114 mL, 0.25 mmol) was added and the reaction was stirred in the dark. After 21 h (complete consumption of **10a** observed by ^1H-NMR), the reaction was cooled to 0 °C and catalyst **1a** (15 mg, 0.025 mmol) and benzoic acid

(3 mg, 0.025 mmol) were added and the reaction was stirred for 5 min. Oxime **20** (122 mL, 1.125 mmol) was added and the reaction was stirred at 0 °C for 21 h (complete disappearance of enal peaks in ^{1}H-NMR). MeOH (0.75 mL) and $NaBH_4$ (21 mg, 0.565 mmol) were added simultaneously and the reaction was stirred for 15 min, then was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over $MgSO_4$ and filtered. After removal of solvent under reduced pressure, the residue was purified by flash chromatography (cold column, 20% Et_2O: CH_2Cl_2) to yield **21** (58 mg, 57% yield) as a colorless oil.; $[\alpha]_D^{24} = -2.8$ (c=0.8 in $CHCl_3$); IR (thin film, KBr): 3277, 2962, 2873, 1714, 1414, 1253, 1058, 947, 759, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.58-7.56 (m, 2H),7.38-7.36 (m, 3H), 6.46 (brs, 1H), 4.42-4.18 (m, 6H), 3.80-3.78 (m, 2H), 2.27-1.60 (m, 6H), 1.28-1.25 (m, 6H), 0.91 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5/157.0, 156.6/156.1, 149.0, 132.1, 130.1, 128.8, 127.2, 82.0/81.1, 62.9/62.7, 62.4, 60.9/60.0, 59.7, 34.6/34.5, 29.8/29.3, 19.6/19.4, 14.5, 14.4, 14.0/13.9 ppm; HPLC with an AD-H column (n-hexane: i-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 12.1 min, major enantiomer t_R = 14.4 min, minor diastereomer t_R = 18.3 min; HRMS (ESI): $[M+H]^+$ calcd. for $[C_{20}H_{32}N_3O_6]$: 410.2291, found: 410.2289.

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Supporting Information

Copies of ^{1}H, ^{13}C and HPLC spectra for compounds **13a-j**, **14**, **15**, **16**, **17**, **18**, **19**, **21**, **22a-e**, **22g** and **22j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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