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Enantio- and Diastereoselective Syntheses of 3-Hydroxypiperidines through Iridium-Catalyzed Allylic Substitution

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Stereoselective syntheses of 3-hydroxypiperidines have been developed. Key intermediates are *N*-protected allylamines that are prepared by an enantioselective iridium-catalyzed allylic amination. A subsequent catch and release procedure that involves an epoxidation and base-mediated elimination yields δ-lactams that are suitably functionalized to prepare biologically active 3-hydroxypiperidines. In addition, applications of this method to the total syntheses of deoxymannojirimycin, D-*erythro*-sphingosine, and chiral building blocks of interest for medicinal chemistry are described.

Introduction

The 3-hydroxypiperidine unit is a chemically and biologically important structural motif that is found in natural products, particularly alkaloids[1] and azasugars.[2] It can also be found in a number of pharmaceutically relevant small molecules. Typical examples (see Figure 1) of 3-hydroxypiperidines and their derivatives are the neurokinin NK-1 receptor antagonist (+)-*L*-733.060,[3] prosopinine, which is a member of the *Cassia* and *Prosopis* families of alkaloids,[4] and the azasugar miglustat (Zavesca), a drug used for the treatment of Gauchers' disease.[5]

Given their interesting biological properties, the stereoselective syntheses of 3-hydroxypiperidines have been pursued with some intensity.[6] The preferred targets have been azasugars, which are mostly synthesized through carbohydrate-based routes.[7] For the large group of monohydroxypiperidines, a great variety of diastereoselective total syntheses have been developed. Chirality was mostly introduced by using a chiral pool approach or with the help of stoichiometric chiral auxiliaries.[6] Asymmetric catalysis has only been applied to a comparatively small number of syntheses.[8]

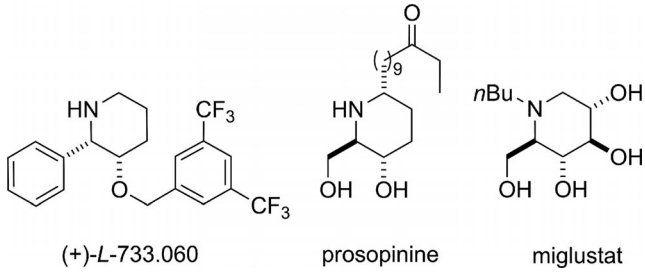
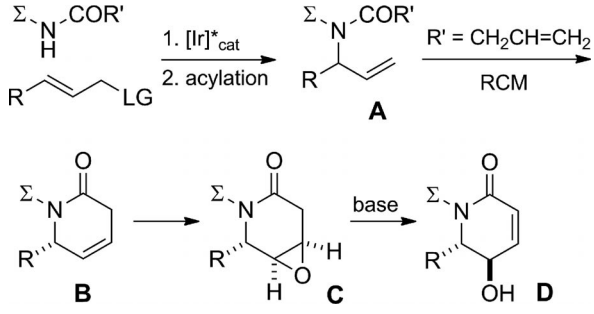


Figure 1. Examples of 3-hydroxypiperidines that are found among alkaloids and drugs.

In the course of our work on the stereoselective syntheses of piperidine and pyrrolidine alkaloids,[9] we have developed an enantio- and diastereoselective route to α,β-unsaturated hydroxylactams **D** and related cyclohexenones that is a combination of an iridium-catalyzed asymmetric allylic substitution reaction,[10] a ring-closing metathesis (RCM), and a catch and release methodology that involves an epox-



Scheme 1. Strategy for the enantio- and diastereoselective synthesis of 3-hydroxypiperidines (Σ = protecting group, LG = leaving group).

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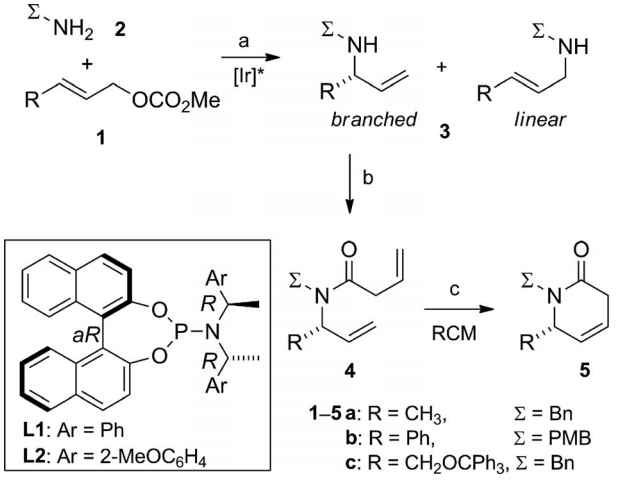
idation and elimination reaction (see Scheme 1).[11] Knight et al. have developed a route to compounds of type **B** that employs a Pd-catalyzed decarboxylative carbonylation of 5-vinyloxazolidin-2-ones, which are derived from amino acids, that is, an exchiral pool approach.[12] Independence of our approach from amino acids with their limited set of substituents R allows to widen the range of compounds of types **B**–**D**. A further variety of targets can be synthesized with this approach as will be shown below.

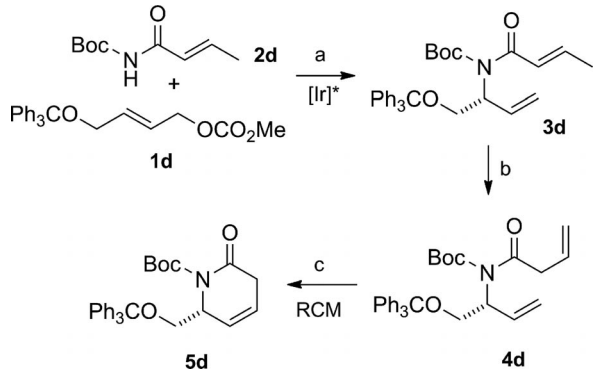
Results and Discussion

The lactams **5a**–**5d** (see Schemes 2 and 3) were synthesized by two different routes, that is, either by allylic amination[13] and a subsequent N-acylation to give **5a**–**5c** (see Scheme 2) or by allylic amination with an amide,[14] in this case with *N*,*N*-diacylamine **2d**,[15] followed by deprotonation/reprotonation to give **5d** (see Scheme 3). The direct amination with *N*-Boc-but-3-enamide (Boc = *tert*-butoxycarbonyl) could not be accomplished because of the competing isomerization of the double bond under basic conditions to give *N*-boc-but-2-enamide.



Scheme 2. *Reagents and conditions:* (a) $[Ir(COD)Cl]_2$ (2 mol-%, COD = 1,5-cyclooctadiene), **L1 or L2** (4 mol-%), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), tetrahydrofuran (THF), 45 °C; **3a**: **L2**, 89%, b/l, 93:7, 97%*ee*; **3b**: **L2**, 77%, b/l, 97:3, 98%*ee*; **3c**: **L1**, 70%, b/l, 81:19, 96%*ee*; (b) But-3-enoic acid, DMAP, CH_2Cl_2, DCC, 0 °C to room temp.; **4a**: 90%; **4b**: 95%; **4c**: 92%; (c) Grubbs I or II, CH_2Cl_2, reflux; **5a**: 93%; **5b**: 91%; **5c**: 100%.

The chiral phosphoramidite ligands **L1** and **L2**[13e] were used for the allylic amination reactions (see Scheme 2). The reactions of the amines [$BnNH_2$ or $PMBNH_2$ (PMB = *para*-methoxybenzyl)] with carbonates **1a**–**1c** proceeded with high enantio- and regioselectivity [**3a**: 89%, branched (b)/linear (l), 93:7, 97%*ee*; **3b**: 77%, b/l, 97:3, 98%*ee*; **3c**: 70%, b/l, 81:19, 96%*ee*], essentially as reported for **3a**,[16] **3b**,[13a] and **3c**.[13f] The amines were acylated by using Steglich's method with but-3-enoic acid, 4-(dimethylamino)pyridine (DMAP), and *N*,*N*′-dicyclohexylcarbodiimide (DCC) to give amides **4** in 90–95% yield. Finally, the ring closure of dienes **4a**–**4c** was carried out by employing a ring-closing metathesis in good to excellent yields.



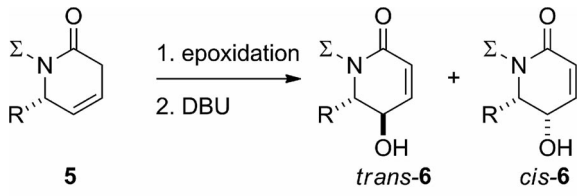
Scheme 3. *Reagents and conditions:* (a) $[Ir(COD)Cl]_2$, **L2**, TBD, THF, 45 °C, 87%, b/l, 93:7, 98%*ee*; (b) KHMDS, THF/DMPU, –78 °C, then dimethyl malonate, –78 °C, 85%; (c) Grubbs I, CH_2Cl_2, reflux, 73%.

Carbamate **3d** (see Scheme 3) was prepared in 87% yield (b/l, 93:7, 98%*ee*) by treating carbonate **1d** with pronucleophile **2d** under salt-free conditions as previously reported.[15] The shift of the double bond to the terminal position was accomplished in 85% yield by deprotonation at –78 °C with potassium hexamethyldisilazide (KHMDS) in THF followed by the addition of 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (DMPU) and dimethyl malonate as a proton source. A subsequent ring closure to give lactam **5d** was carried out through a ring-closing metathesis as described above for **5a**–**5c**.

With **5a**–**5d** available, we investigated the catch and release procedure to yield α,β-unsaturated hydroxylactam building blocks **6a**–**6d** (see Table 1). For the epoxidation, we used the reaction conditions that were reported by Knight et al. for their synthesis of D-mannolactam, that is, Oxone (2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in a mixture of a saturated aqueous $NaHCO_3$ solution and acetone at room temperature (see Table 1, Entry 1).[11c,17] In the case of **5** in which R = CH_2OTBS (TBS = *tert*-butyldimethylsilyl) and Σ = H, these authors obtained a *trans*/*cis* diastereoselectivity of 4.1:1 (see Table 1, Entry 1). The diastereoselectivities with the N-protected amides were generally high, even in case of **5a** with R = Me (see Table 1, Entry 3). With the sterically more demanding substituents (i.e., **5c** and **5d**, see Table 1, Entries 5 and 6), the *trans* isomer was produced almost exclusively.[18]

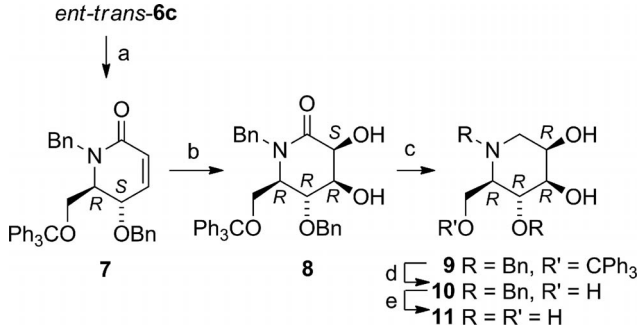
The synthesis of azasugar 1-deoxymannojirimycin (**11**) was carried out using chiral building block **6c** as the starting material (see Scheme 4). A similar synthesis was reported by Knight et al.[11c] The reaction of **6c** with NaH/benzyl bromide/NBu_4I gave **7** in excellent yield. Dihydroxylation under standard conditions (OsO_4 in *tert*-butanol with water and pyridine as additives) gave diastereomerically pure **8** in 74% yield. The reduction of **8** with $LiAlH_4$ furnished piperidine derivative **9** in 86% yield. The deprotection of **9** was effected by treatment with acetic acid followed by a catalytic hydrogenation reaction to give the azasugar 1-deoxymannojirimycin, which was isolated as its hydrochloride **11**·HCl in 47% yield from **8**.

Table 1. Epoxidation/elimination of lactams **5a**–**5d**.



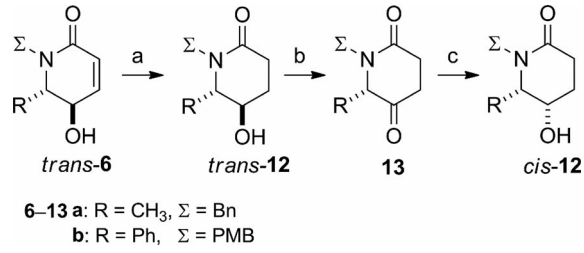
Entry	5	Conditions[a]	*trans*-**6**/*cis*-**6**[b]	% Yield[c]
1	**5**[d]	Oxone	4.1:1	90
2	**5a**	*m*-CPBA[e]	82:18	–[f]
3	**5a**	Oxone[g]	92:8	68
4	**5b**	Oxone	93:7	61
5	*ent*-**5c**	Oxone	>50:1[h]	85
6	**5d**	Oxone	>50:1[h]	90

[a] See GP4 in the Exp. Section. [b] Regioselectivity was determined by ^{1}H NMR analysis of the crude allylic alcohol or by isolation of the regioisomers. [c] Isolated yield of the mixture of both regioisomers. [d] Starting material is **5** with R = CH_2OTBS and Σ = H (see ref.[11c]). [e] *m*-CPBA = *meta*-chloroperoxybenzoic acid. [f] The yield was not determined. [g] Epoxidation was performed at 0 °C. [h] The *cis* isomer was not detected by ^{1}H NMR spectroscopy.



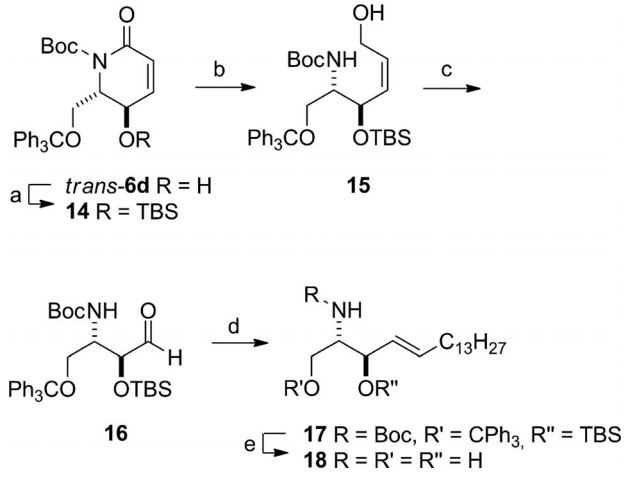
Scheme 4. *Reagents and conditions:* (a) NaH (2.5 equiv.), NBu_4I, $PhCH_2Br$, THF, 0 °C to room temp., 97%; (b) OsO_4, *N*-methylmorpholine-*N*-oxide (NMO), *t*BuOH/H_2O/pyridine, room temp., 74%; (c) $LiAlH_4$, Et_2O, room temp., 86%; (d) AcOH, reflux, 79%; (e) $Pd(OH)_2$/C, H_2, room temp., 69%.

To access *cis*-configured hydroxypiperidines, which are also encountered in pharmaceuticals and alkaloids (cf. Figure 1), the inversion of the relative configuration at C-3 of the *trans*-lactams **6** was studied and accomplished. Catalytic hydrogenation gave lactams **12** (see Scheme 5), which were oxidized by treatment with Dess–Martin periodinane (DMP) or under Swern conditions to give ketones **13a** and **13b**, respectively. The potential racemization was of concern at this stage, therefore, the *ee* values of the ketones were carefully determined by HPLC analysis. The values were determined to be 96.5 and 98% *ee*, respectively, which demonstrated that the degree of racemization was small. Reduction of ketones **13** with a large excess amount of $NaBH_4$[19] in methanol at room temp. furnished the *cis*-hydroxypiperidines *cis*-**12a** and *cis*-**12b** in >80% yield over the two steps with diastereoselectivities of 92:8 and >99:1, respectively. The lactam *cis*-**12b** has been used by Huang and co-workers in the synthesis of the neurokinin 1 antagonist (+)-L-733.060 (cf. Figure 1).[20]



Scheme 5. *Reagents and conditions:* (a) for *trans*-**12a**: Pd/C, H_2, EtOAc, room temp.; for *trans*-**12b**: Rh/C, H_2, EtOAc/MeOH, room temp.; (b) for **13a**: DMP, CH_2Cl_2, 0 °C, 99% (over 2 steps); for **13b**: $(COCl)_2$, dimethyl sulfoxide (DMSO), NEt_3, CH_2Cl_2, 84% (over 2 steps); (c) $NaBH_4$, MeOH, room temp., *cis*-**12a**: 81%; *cis*-**12b**: 97%.

Finally, the reductive ring-opening reaction of hydroxylactams *trans*-**6** appeared of interest. This was investigated with a derivative of *trans*-**6d** to access D-*erythro*-sphingosine (**18**, see Scheme 6).[21]



Scheme 6. *Reagents and conditions:* (a) *N*-methylimidazole, I_2, TBSCl, CH_2Cl_2, 0 °C to room temp., 2 h, 91%; (b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH/CH_2Cl_2/H_2O, –10 °C to –2 °C, 1 h, 88% (corr.) of **15**; (c) (i) O_3, MeOH/CH_2Cl_2, –78 °C, 5 min; (ii) Me_2S, –78 °C to room temp., 76%; (d) (i) 1-phenyl-5-tetradecylsulfonyl-1*H*-tetrazole, KHMDS, dimethoxyethane (DME), –56 °C, 1 h; (ii) **16** in DME, 3 h, 64% (*E*/*Z*, 88:12); (e) trifluoroacetic acid (TFA), CH_2Cl_2, room temp., 2 h, 40%.

Lactam *trans*-**6d** was treated with TBSCl/iodine[22] to give derivative **14** in 91% yield. The ring-opening reaction of *N*-acyl-δ-lactams is commonly accomplished by using $NaBH_4$.[23] The reductive ring-opening reaction of unsaturated lactam **14** required application under Luche conditions[24] to avoid reduction of the double bond. Initially, an *N*,*O*-acetal was formed as a byproduct, but its formation could be avoided by screening the reaction conditions. The optimized reaction involved using an excess amount of $CeCl_3$ and the reducing agent (1.5 equiv. of $CeCl_3$, 4 equiv. of $NaBH_4$) in combination with a reaction temperature slightly below 0 °C. Apparently, other rare earth metal salts,

for example, ErI_3, induced deprotection of the Boc group. The α,β-unsaturated hydroxylactam **15** was finally obtained in 88% yield (8% recovered starting material).

Treatment of allylic alcohol **15** with ozone gave aldehyde **16** (76% yield), which is a valuable building block for syntheses of azasugars. The alkenyl side chain of the sphingosine target was introduced by a Julia–Kocienski reaction,[25] which involved the reaction of a tetradecylsulfonyltetrazole[26] with KHMDS and then with aldehyde **16** to obtain protected sphingosine **17** in moderate yield (64%) with an *E*/*Z* selectivity of 88:12. Finally, deprotection gave (–)-D-*erythro*-sphingosine (**18**) in 9 linear steps and 5% overall yield. Analytical data were in full agreement with those reported.[27,28]

Conclusions

The combination of an iridium-catalyzed allylic amination, a ring-closing metathesis, and a catch and release procedure based on epoxidation/elimination reactions allows chiral 3-hydroxypiperidines to be prepared in a highly stereoselective way. This route was applied to the total syntheses of 1-deoxymannojirimycin and D-*erythro*-sphingosine.

Experimental Section

General Methods: The ^1H NMR spectroscopic data were recorded at room temp. in $CDCl_3$, unless otherwise reported, with a Bruker Avance 300 (300 MHz) or 500 (500 MHz) spectrometer. Chemical shifts are given in δ (ppm) relative to $CHCl_3$ (δ_H = 7.26 ppm) or TMS (δ_H = 0.00 ppm). For system of numbering the atoms, see the Supporting information. The ^{13}C NMR spectroscopic data were recorded at room temp. in $CDCl_3$, unless otherwise reported, with a Bruker Avance 300 (75 MHz) or 500 (125 MHz) spectrometer. Chemical shifts are given in δ (ppm) relative to $CDCl_3$ [δ_C = 77.16 ppm (central line of the triplet)]. The abbreviations are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad). The assignment of signals was confirmed by $^1H,^1H$-COSY, $^1H,^{13}C$-COSY, and DEPT spectroscopic data. Optical rotations were measured with a Perkin–Elmer 341 polarimeter in a thermostated cuvette (1 dm) and with a mercury lamp. HRMS were recorded with either a JEOL JMS-700 instrument (EI and FAB) or a Bruker ApexQe instrument (ESI). GC–MS chromatograms/spectra were recorded with the HP 5890 Series II Plus instrument that was coupled with the HP 5972 Mass Selective Detector. For a capillary column, the HP-1 cross-linked methyl silicone gum (25 m × 0.2 mm, 0.33 μm film thickness) was employed with helium as the carrier gas. All given retention times (t_R) refer to the default temperature program [isothermal 50 °C (1 min), heating rate of 20 °C/min (10 min), isothermal 250 °C (14 min), injector temperature: 250 °C]. Enantiomeric excess values were determined either by HPLC analysis with the HP 1090 or HP 1100 instrument or by GC with the HP 5890 instrument. For HPLC analysis, the employed Daicel columns were Chiralpak AD-H (250 × 4.6 mm, 5 μm) with guard cartridge AD-H (10 × 4 mm, 5 μm) and Chiralcel OD-H (250 × 4.6 mm, 5 μm) with guard cartridge OD-H (10 × 4 mm, 5 μm). For GC analysis, a permethyl-β-cyclodextrin column from Chrompack (WCOT fused silica, Cp-cyclodextrin-B-236-M-19, 25 m × 0.25 mm) was used. For preparative HPLC analysis, a Gilson-305 pump that was coupled with the Knauer UV detector 2600 and a silica gel column (ProntoSIL, 250 × 20 mm, 5 m silica, 15 mL/min, 45 bar) were used. The iridium-catalyzed allylic substitutions (GP1) are described in the Supporting Information. CCDC-947888 (for **5b**), -947889 (for *trans*-**6b**), and -947890 (for *cis*-**12b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for Acylation with 3-Butenoic Acid (GP2): A solution of 3-butenoic acid (1.2 equiv.), DMAP (20–30 mol-%), and amine **3** (1.0 equiv.) in CH_2Cl_2 (0.5–0.3 M with respect to **3**) at 0 °C was treated slowly with DCC (1.2 equiv.), and the resulting mixture was stirred at 0 °C (in case of **4b** and **4c** at room temp.) until there was complete conversion as monitored by TLC. The reaction mixture was diluted with ethyl acetate, and the suspension was filtered through a pad of Celite. Water was added, and the mixture was extracted with ethyl acetate and CH_2Cl_2. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude product was subjected to flash column chromatography on silica gel.

(–)-*N*-Benzyl-*N*-[(1*S*)-1-methylprop-2-en-1-yl]but-3-enamide (4a): GP2 was carried out using 3-butenoic acid (1.21 g, 14.0 mmol), DMAP (428 mg, 3.50 mmol), DCC (2.89 g, 14.0 mmol), and **3a** (1.88 g, 11.7 mmol) in CH_2Cl_2 (40 mL) for a reaction time of 3.5 h. TLC [petroleum ether/diethyl ether, 1:2; R_f = 0.22 (**3a**) and R_f = 0.40 (**4a**); $KMnO_4$]. The crude product was subjected to flash column chromatography on silica gel [petroleum ether/ethyl acetate, 4:1; R_f = 0.18 (**4a**)] to yield **4a** contaminated with 3% of the isomerized product (2.41 g combined yield, 90%) as a pale yellow oil. The latter was removed in the next step (metathesis). $[\alpha]_D^{20}$ = –82 (*c* = 1.01, $CHCl_3$); 97% *ee*. ^1H NMR (300 MHz, toluene, 90 °C): δ = 1.02 (d, *J* = 6.9 Hz, 3 H, CH_3), 2.93 (d, *J* = 6.2 Hz, 2 H, 2-H), 4.14 (d, *J* = 16.7 Hz, 1 H, $PhCH_aH_b$), 4.40 (d, *J* = 16.7 Hz, 1 H, $PhCH_aH_b$), 4.71–4.84 (m, 1 H, 1′-H), 4.84–5.00 (m, 4 H, 4-H and 3′-H), 5.69 (ddd, *J* = 16.3, 10.4, 5.2 Hz, 1 H, 2′-H), 6.00 (ddt, *J* = 16.9, 10.5, 6.4 Hz, 1 H, 3-H), 6.94–7.03 (m, 1 H, Ar), 7.03–7.12 (m, 4 H, Ar) ppm. ^{13}C NMR (75 MHz, toluene, 90 °C): δ = 17.90 (q, CH_3), 39.57 (t, C-2), 47.38 (t, $PhCH_2$), 53.83 (d, C-1′), 115.42 (t, C-3′), 116.78 (t, C-4), 127.26, 127.37, 128.83 (3 d, Ar), 133.31 (d, C-3), 139.62 (d, C-2′), 140.19 (s, Ar), 170.74 (s, C-1) ppm. GC–MS: t_R = 10.6 min. HRMS (EI+): calcd. for $C_{15}H_{19}NO^+$ $[M]^+$ 229.1467; found 229.1456.

(+)-*N*-(4-Methoxybenzyl)-*N*-[(1*R*)-1-phenylprop-2-en-1-yl]but-3-enamide (4b): GP2 was carried out using 3-butenoic acid (1.53 g, 17.7 mmol), DMAP (360 mg, 2.95 mmol), DCC (3.66 g, 17.7 mmol), and **3b** (3.74 g, 14.8 mmol, 98% *ee*) in CH_2Cl_2 (45 mL) for a reaction time of 30 min at 0 °C and 90 min at room temp. TLC [petroleum ether/ethyl acetate, 2:1; R_f = 0.28 (**3b**) and R_f = 0.39 (**4b**); $KMnO_4$]. The crude product was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, from 6:1 to 4:1) to give **4b** (4.51 g, 95%) as a colorless foam. $[\alpha]_D^{20}$ = +60.6 (*c* = 1.05, $CHCl_3$); 98% *ee*. ^1H NMR (300 MHz, [D$_8$]toluene, 80 °C): δ = 2.97 (d, *J* = 6.2 Hz, 2 H, 2-H), 3.34 (s, 3 H, OCH_3), 4.22 (d, *J* = 16.4 Hz, 1 H, 1′′-H_a), 4.39 (d, *J* = 16.4 Hz, 1 H, 1′′-H_b), 4.85–5.10 (m, 4 H, 4-H, 3′-H), 5.85–6.15 (m, 3 H, 3-H, 2′-H, 1′-H), 6.60 (d, *J* = 8.5 Hz, 2 H, 3′′′-H), 6.86 (d, *J* = 8.3 Hz, 2 H, 2′′′-H), 6.90–7.20 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, [D$_8$]-toluene, 80 °C): δ = 40.41 (t, C-2), 49.02 (d, C-1′′), 55.74 (q, OCH_3), 63.07 (d, C-1′), 115.20 (d, C-3′′′), 117.64, 118.92 (2d, C-3′, C-4), 128.44 (d, Ar), 129.27 (d, Ar), 129.49 (d, Ar), 129.52 (d, Ar), 132.19 (s, C-1′′′), 133.97, 137.35 (d, C-3, C-2′), 141.04 (s, Ph),

160.36 (s, C-4′′′), 171.88 (s, C-1) ppm. GC–MS: t_R = 16.72 min. HRMS (ESI+): calcd. for $C_{21}H_{24}NO_2^+$ [M + H]$^+$ 322.18063; found 322.18016.

(–)-*N*-Benzyl-*N*-{(1*S*)-1-[(trityloxy)methyl]prop-2-en-1-yl}but-3-enamide (*ent*-4c): GP2 was carried out using 3-butenoic acid (90%, 1.21 g, 12.7 mmol), DMAP (358 mg, 2.93 mmol), DCC (2.62 g, 12.07 mmol), and **3c** (4.10 g, 9.77 mmol) in CH_2Cl_2 (68 mL) for a reaction time of 25 min at 0 °C and 3 h at room temp. TLC [petroleum ether/ethyl acetate, 5:1; R_f = 0.37 (**3c**) and R_f = 0.36 (*ent*-**4c**); $KMnO_4$]. The crude product was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 7:1) to yield **4c** (4.36 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ = –32.2 (*c* = 1.38, $CHCl_3$); 94%*ee*. ^{1}H NMR (300 MHz, [D$_8$]toluene, 85 °C): δ = 3.05 (d, *J* = 4.5 Hz, 2 H, 2′-H), 3.32–3.54 (m, 2 H, 1′′-H), 4.35 (d, *J* = 16.6 Hz, 1 H, 1′′′-H$_a$), 4.46 (d, *J* = 16.7 Hz, 1 H, 1′′′-H$_b$), 4.79–5.08 (m, 5 H, 1-H, 3-H, and 4′-H), 5.67–5.91 (m, 1 H, 2-H), 5.98–6.17 (m, 1 H, 3′-H), 6.96–7.19 (m, 14 H, Ar), 7.38–7.47 (m, 6 H, Ar) ppm. ^{13}C NMR (75 MHz, [D$_8$]toluene, 85 °C): δ = 39.76 (t, C-2), 60.03 (d, C-1), 65.21 (t, C-1′′), 88.17 [s, C(Ph)$_3$], 117.03 (t, C-3), 117.10 (t, C-4′), 127.33, 127.54, 128.28, 128.84, 129.50 (5 d, Ar), 133.35 (d, C-3′), 135.87 (d, C-2), 139.80 (s, NCH_2Ph), 144.84 (s, Ar), 171.30 (s, C-1′) ppm. HRMS (ESI+): calcd. for $C_{34}H_{34}NO_2^+$ [M + H]$^+$ 488.2584; found 488.2584.

(+)-*tert*-Butyl But-3-enoyl{(1*R*)-1-[(trityloxy)methyl]prop-2-en-1-yl}carbamate (4d): Under argon, a solution of KHMDS (0.5 M in toluene, 19.50 mL, 9.75 mmol) was added over a period of 30 min through a syringe to a stirred, cooled (–78 °C) solution of carbamate **3d** (2.21 g, 4.44 mmol) in dry THF (15 mL). After stirring for an additional 20 min, DMPU (11 mL) was added over a period of 20 min. The resultant orange solution was stirred for 30 min and then treated with dimethyl malonate (2.09 mL, 17.76 mmol) by dropwise addition. For this step to be successful, it was crucial to maintain a temperature of –75 ± 5 °C. The mixture was warmed to room temp. within 4 h and then was treated with HCl (2 M solution, 10 mL) to give a clear solution. TLC [petroleum ether/ethyl acetate, 4:1; R_f = 0.41 (**3d**), R_f = 0.50 (**4d**), and R_f = 0.19 (dimethyl malonate); $KMnO_4$]. After evaporation of the solvent, the residue was dissolved in diethyl ether (200 mL), and the solution was washed with saturated $NaHCO_3$ solution (2 × 50 mL), water (2 × 50 mL), and brine (50 mL) and then dried with Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel (petroleum ether/diethyl ether, 10:1) to give **4d** (1.88 g, 85%) as a colorless foam. $[\alpha]_D^{20}$ = –36.6 (*c* = 1.01, $CHCl_3$); 98%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 [s, 9 H, C(CH$_3$)$_3$], 3.29–3.35 (m, 1 H, OCH$_a$H$_b$), 3.41 (dd, *J* = 8.4, 8.4 Hz, 1 H, OCH$_a$H$_b$), 3.60 (ddd, *J* = 17.2, 6.9, 1.4 Hz, 1 H, 2′-H$_a$), 3.68 (ddd, *J* = 17.6, 6.6, 1.1 Hz, 1 H, 2′-H$_b$), 5.08–5.18 (m, 4 H, 3-H and 4′-H), 5.57–5.64 (m, 1 H, 1-H), 5.84 (ddd, *J* = 17.1, 10.7, 6.1 Hz, 1 H, 2-H), 5.96–6.10 (m, 1 H, 3′-H), 7.19–7.42 (m, 15 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.97 [3 q, C(CH$_3$)$_3$], 43.29 (t, C-2′), 56.21 (d, C-1), 64.14 (t, C-1′′), 83.38 [s, C(CH$_3$)$_3$], 86.60 [s, C(Ph)$_3$], 117.41 (t, C-3 or C-4′), 118.11 (t, C-3 or C-4′), 127.09 (3 d, C-Ar), 127.90 (6 d, C-Ar), 128.90 (6 d, C-Ar), 131.85 (d, C-3′), 135.25 (d, C-2), 144.05 (3 s, C-Ar), 153.15 [s, COOC(CH$_3$)$_3$], 174.25 (s, C-1′) ppm. HRMS (ESI+): calcd. for $C_{32}H_{36}NO_4^+$ [M + H]$^+$ 498.2639; found 498.2646.

General Procedure for Ring-Closing Metathesis (GP3): In a dry Schlenk flask under argon, a solution of diene **4** (1.0 equiv.) and Grubbs II catalyst [1.0–6.0 mol-%; for the preparation of **5d**, Grubbs I catalyst (5 mol-%)] in dry CH_2Cl_2 (0.1–0.03 M) was heated at reflux until TLC indicated complete conversion. The mixture was concentrated in vacuo, and the residue was subjected to flash column chromatography on silica gel to yield lactam **5**.

(–)-(6*S*)-1-Benzyl-6-methyl-3,6-dihydropyridin-2(1*H*)-one (5a): GP3 was carried out using **4a** (2.10 g, 9.16 mmol), Grubbs II catalyst (77.8 mg, 91.6 μmol), and dry CH_2Cl_2 (300 mL) for a reaction time of 5 h. TLC [petroleum ether/diethyl ether, 1:1; R_f = 0.20 (**4a**) and R_f = 0.05 (**5a**); $KMnO_4$]. The mixture was concentrated in vacuo, and the residue was subjected to flash column chromatography on silica gel (petroleum ether/diethyl ether, 1:1) to yield **5a** (1.65 mg, 93%) as a pale brown oil. $[\alpha]_D^{20}$ = –54.9 (*c* = 1.19, $CHCl_3$), 96.5%*ee*; ref.[29a] $[\alpha]_D^{20}$ = –34.5 (*c* = 0.23, $CHCl_3$). HPLC analysis (Daicel Chiralpak OJ-H, *n*-hexane/isopropanol, 90:10, 0.5 mL/min): t_R = 22.7 [(–)-(*S*)-**5a**] and t_R = 27.1 min [(+)-(*R*)-**5a**]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.6 Hz, 3 H, CH_3), 3.03–3.07 (m, 2 H, 3-H), 3.81–3.94 (m, 1 H, 6-H), 4.05 (d, *J* = 15.2 Hz, 1 H, PhCH$_a$H$_b$), 5.43 (d, *J* = 15.2 Hz, 1 H, PhCH$_a$H$_b$), 5.64–5.78 (m, 2 H, 4-H and 5-H), 7.20–7.35 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.51 (q, CH_3), 32.18 (t, C-3), 46.53 (t, $PhCH_2$), 52.84 (d, C-6), 121.39 (d, C-4 or C-5), 127.78 (d, Ar), 127.87 (d, C-4 or C-5), 128.63 (d, Ar), 137.61 (s, Ar), 167.94 (s, C-2) ppm. GC–MS: t_R = 10.7 min. HRMS (EI+): calcd. for $C_{13}H_{15}NO^+$ [M]$^+$ 201.1154; found 201.1157.

(+)-(6*R*)-1-(4-Methoxybenzyl)-6-phenyl-3,6-dihydropyridin-2(1*H*)-one (5b): GP3 was carried out using **4b** (4.38 g, 13.6 mmol), Grubbs II catalyst (290 mg, 2.5 mol-%), and dry CH_2Cl_2 (450 mL) for a reaction time of 2 h. TLC [petroleum ether/ethyl acetate, 2:1; R_f = 0.37 (**4b**) and R_f = 0.14 (**5b**); $KMnO_4$]. The mixture was concentrated in vacuo, and the residue was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, from 2:1 to 1:1) to give **5b** (3.66 g, 91%) as colorless plates; m.p. 68–70 °C, which were suitable for X-ray crystal structure analysis. $[\alpha]_D^{20}$ = +98 (*c* = 0.88, $CHCl_3$); 98%*ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.08 (m, 1 H, 3-H$_a$), 3.13–3.24 (m, 1 H, 3-H$_b$), 3.26 (d, *J* = 14.8 Hz, 1 H, 1′-H$_a$), 3.72 (s, 3 H, OCH_3), 4.73 (m, 1 H, 6-H), 5.48 (d, *J* = 14.7 Hz, 1 H, 1′-H$_b$), 5.55–5.70 (m, 2 H, 4-H, 5-H), 6.77 (d, *J* = 8.7 Hz, 2 H, 3′′-H), 7.02–7.13 (m, 4 H, Ar), 7.20–7.34 (m, 3 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.25 (t, C-3), 45.74 (d, C-1′), 55.36 (q, OCH_3), 61.47 (d, C-6), 114.07 (d, C-3′′), 120.52 (d, C-4 or C-5), 126.50 (d, C-4 or C-5), 127.13 (d, C-Ar), 128.25 (d, C-Ar), 128.90 (s, C-1′′), 129.19 (d, C-Ar), 129.79 (d, C-Ar), 140.24 (s, C-Ph), 159.08 (s, C-4′′), 167.57 (s, C-2) ppm. GC–MS: t_R = 17.80 min. HRMS (ESI+): calcd. for $C_{19}H_{20}NO_2^+$ [M + H]$^+$ 294.14929; found 294.14886.

(+)-(*S*)-1-Benzyl-6-[(trityloxy)methyl]-3,6-dihydropyridin-2(1*H*)-one (*ent*-5c): GP3 was carried out using *ent*-**4c** (4.24 g, 8.70 mmol), Grubbs II catalyst (440 mg, 0.52 mmol), and dry CH_2Cl_2 (100 mL) for a reaction time of 19 h. TLC [petroleum ether/ethyl acetate, 5:1; R_f = 0.25 (*ent*-**4c**) and R_f = 0.08 (*ent*-**5c**); $KMnO_4$]. The solvent was evaporated in vacuo, and the residue was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to yield *ent*-**5c** (4.03 g, quantitative) as a colorless oil. $[\alpha]_D^{20}$ = +12.7 (*c* = 1.16, $CHCl_3$); 94%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.98–3.19 (m, 2 H, 3-H), 3.19–3.29 (m, 2 H, 1′-H), 3.72 (d, *J* = 15.3 Hz, 1 H, 1′′-H$_a$), 3.82–3.93 (m, 1 H, 6-H), 5.43 (d, *J* = 15.3 Hz, 1 H, 1′′-H$_b$), 5.67–5-79 (m, 1 H, 5-H), 5.91 (dt, *J* = 10.0, 3.2 Hz, 1 H, 4-H), 7.02–7.11 (m, 2 H, Ar), 7.15–7.35 (m, 12 H, Ar), 7.35–7.44 (m, 6 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.98 (t, C-3), 47.02 (t, C-1′′), 57.11 (d, C-6), 63.88 (t, C-1′), 87.22 [s, C(Ph)$_3$], 124.33 (d, C-4), 124.61 (d, C-5), 127.31, 127.34, 127.85, 128.01, 128.66, 128.77 (6 d, Ar), 137.05 (s, NCH_2Ph), 143.70 (s, Ar), 168.85 (s, C-2) ppm. HRMS (ESI+): calcd. for $C_{32}H_{30}NO_2^+$ [M + H]$^+$ 460.2271; found 460.2272.

(+)-*tert*-Butyl (6*R*)-2-Oxo-6-[(trityloxy)methyl]-3,6-dihydropyridine-1(2*H*)-carboxylate (5d): GP3 was carried out using **4d** (1.69 g,

3.39 mmol), Grubbs I catalyst (168 mg, 5 mol-%), and dry CH_2Cl_2 (137 mL) for a reaction time of 16 h. TLC [petroleum ether/ethyl acetate, 4:1; R_f = 0.51 (**4d**) and R_f = 0.24 (**5d**); $KMnO_4$]. The solvent was evaporated in vacuo, and the residue was subjected to flash column chromatography on silica gel (pentane/diethyl ether/diethylamine, 3:1:0.02) to yield **5d** (1.16 g, 73%) as a colorless foam. $[\alpha]_D^{20}$ = +103 (*c* = 1.09, $CHCl_3$); 98%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 3.04–3.27 (m, 3 H, 3-H and OCH_aH_b), 3.40 (dd, *J* = 9.2, 4.5 Hz, 1 H, OCH_aH_b), 4.79 (m, 1 H, 6-H), 5.80–5.91 (m, 2 H, 4-H and 5-H), 7.19–7.38 (m, 15 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.10 [3 q, $C(CH_3)_3$], 35.67 (t, C-3), 57.08 (d, C-6), 64.78 (t, C-1′), 83.23 [s, $C(CH_3)_3$], 87.21 [s, $C(Ph)_3$], 123.77 (d, C-4 or C-5), 124.79 (d, C-4 or C-5), 127.22 (3 d, C-Ar), 127.95 (6 d, C-Ar), 128.86 (6 d, C-Ar), 143.69 (3 s, C-Ar), 151.99 [s, $COOC(CH_3)_3$], 169.76 (s, C-2) ppm. HRMS (ESI+): calcd. for $C_{30}H_{31}NNaO_4^+$ $[M + Na]^+$ 492.2145; found 492.2143.

General Procedure for Epoxidation/Elimination (GP4): Oxone (5.0 equiv.) was added in a few portions to a suspension of lactam **5** (1.0 equiv.) and $NaHCO_3$ (15.0 equiv.) in acetone/H_2O (2:1, v/v; 2.1–9.2 mL per 100 mg of **5**). The mixture was stirred at room temp. (for the preparation of **6a** at 0 °C and afterwards at room temp.) until TLC indicated complete consumption of the starting material. The suspension was diluted with ethyl acetate, and the resulting solution was treated with aqueous $Na_2S_2O_5$ (10% in H_2O) as the mixture was vigorously stirred. The aqueous phase was separated and extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried with Na_2SO_4, and then concentrated in vacuo. A solution of the crude product and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.3–2.0 equiv.) in CH_2Cl_2 (1.9–5.6 mL per 100 mg of **5**) was stirred and heated at reflux (for the preparation of **6a** at room temp. followed by stirring and heating at reflux) until TLC indicated complete conversion. The workup was initiated by the addition of a saturated aqueous NH_4Cl solution or stirring for 1 h with Amberlite IR-120. The phases were separated, and the aqueous phase was extracted with ethyl acetate and washed with brine. The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel. Regioselectivity was determined by ^{1}H NMR analysis of the crude product or isolation of the regioisomers.

(–)-(5*R*,6*S*)-1-Benzyl-5-hydroxy-6-methyl-5,6-dihydropyridin-2(1*H*)-one (6a): GP4 was carried out using Oxone (15.03 g, 24.45 mmol), $NaHCO_3$ (6.16 g, 73.4 mmol), and **5a** (0.98 g, 4.89 mmol) in acetone/H_2O (2:1, v/v, 90 mL) for a reaction time of 3 h at 0 °C and 1 h at room temp. TLC [ethyl acetate; R_f = 0.36 (**5a**) and R_f = 0.21 (epoxide); $KMnO_4$]. After workup, the elimination reaction was carried out with the crude product, CH_2Cl_2 (50 mL), and DBU (1.49 g, 9.78 mmol), and the reaction mixture was stirred at room temp. for 11 h and then heated at reflux for 7 h. TLC [ethyl acetate; R_f = 0.22 (*trans*-**6a**) and R_f = 0.30 (*cis*-**6a**); $KMnO_4$]. Column chromatography on silica gel (diethyl ether) afforded *trans*-**6a** (670 mg, 63%) as colorless needles and *cis*-**6a** (56 mg, 5%) as colorless needles. Data for (5*R*,6*S*)-*trans*-**6a**: M.p. 68–69 °C. NMR spectroscopic data are in accordance with reported data.[29a] $[\alpha]_D^{20}$ = –156 (*c* = 0.49, $CHCl_3$), 96.5%*ee*; ref.[29a] $[\alpha]_D^{20}$ = –40.5 (*c* = 0.47, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.75 (d, *J* = 8.9 Hz, 1 H, OH), 3.60 (qdd, *J* = 6.9, 1.6, 1.6 Hz, 1 H, 6-H), 3.90 (ddd, *J* = 8.9, 5.7, 1.6 Hz, 1 H, 5-H), 4.02 (d, *J* = 14.8 Hz, 1 H, $PhCH_aH_b$), 5.26 (d, *J* = 14.8 Hz, 1 H, $PhCH_aH_b$), 6.14 (d, *J* = 9.7 Hz, 1 H, 3-H), 6.59 (ddd, *J* = 9.7, 5.7, 1.5 Hz, 1 H, 4-H), 7.22–7.39 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.02 (q, CH_3), 48.35 (t, $PhCH_2$), 58.24 (d, C-6), 66.48 (d, C-5), 127.60 (d, C-3), 128.29, 128.73 (2 d, Ar), 137.16 (s, Ar), 137.22 (d, C-4), 162.34 (s, C-2) ppm. GC–MS: t_R = 11.5 min (*trans*-**6a**). HRMS (EI+): calcd. for $C_{13}H_{15}NO_2^+$ $[M]^+$ 217.1103; found 217.1087. Data for (*S*,*S*)-*cis*-**6a**: M.p. 122–124 °C. NMR spectroscopic data are in accordance with reported data.[29b] $[\alpha]_D^{20}$ = +22.2 (*c* = 0.96, $CHCl_3$), 96.5%*ee*; ref.[29b] $[\alpha]_D^{20}$ = +21.8 (*c* = 0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.7 Hz, 3 H, CH_3), 3.42–3.54 (m, 1 H, 6-H), 3.84 (d, *J* = 15.1 Hz, 1 H, $PhCH_aH_b$), 4.62 (ddd, *J* = 6.3, 2.2, 2.2 Hz, 1 H, 5-H), 5.20 (d, *J* = 15.1 Hz, 1 H, $PhCH_aH_b$), 5.81 (dd, *J* = 10.0, 2.2 Hz, 1 H, 3-H), 6.34 (ddd, *J* = 10.0, 1.8, 1.8 Hz, 1 H, 4-H), 7.18–7.34 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.97 (q, CH_3), 47.39 (t, $PhCH_2$), 55.25 (d, C-6), 67.20 (d, C-5), 123.40 (d, C-3), 127.56, 127.82, 128.74 (3 d, Ar), 137.73 (s, Ar), 143.08 (d, C-4), 163.61 (s, C-2) ppm. GC–MS: t_R = 11.8 min (*cis*-**6a**).

(–)-(5*R*,6*S*)-5-Hydroxy-1-(4-methoxybenzyl)-6-phenyl-5,6-dihydropyridin-2(1*H*)-one (6b): GP4 was carried out using Oxone (31.45 g, 51.15 mmol), lactam **5b** (3.00 g, 10.22 mmol), and $NaHCO_3$ (12.87 g, 153.3 mmol) in acetone/H_2O (2:1, v/v, 132 mL) for a reaction time of 7 h. TLC [petroleum ether/ethyl acetate, 1:2; R_f = 0.22 (**5b**) and R_f = 0.30 (epoxide); $KMnO_4$] indicated incomplete conversion, and, therefore, Oxone (6.29 g, 10.30 mmol) and $NaHCO_3$ (2.57 g, 30.66 mmol) were added. After another 1 h, TLC indicated complete conversion. After workup, the elimination reaction was carried out with the crude product, DBU (2.02 g, 13.29 mmol), and CH_2Cl_2 (167 mL), and the reaction mixture was heated at reflux for 3 h. TLC [petroleum ether/ethyl acetate, 1:2; R_f (**6b**) = 0.22; $KMnO_4$]. Chromatography on silica gel (petroleum ether/ethyl acetate/dichloromethane, 1:2:1) afforded **6b** (1.922 g, 61%, *trans*-**6b**/*cis*-**6b**, 93:7) as a colorless foam. Separation of the diastereomers was accomplished by preparative HPLC (petroleum ether/ethyl acetate/dichloromethane, 5:5:4). Data for *trans*-**6b**: Colorless plates (1.640 g, 52%) that were suitable for X-ray crystal structure analysis; m.p. 108–109 °C. $[\alpha]_D^{20}$ = –13.8, (*c* = 0.99, $CHCl_3$); 98%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (br. s, 1 H, OH), 3.55 (d, *J* = 14.7 Hz, 1 H, 1′-H_a), 3.77 (s, 3 H, OCH_3), 4.16 (dd, *J* = 5.8, 5.8 Hz, 1 H, 5-H), 4.66 (s, 1 H, 6-H), 5.47 (d, *J* = 14.7 Hz, 1 H, 1′-H_b), 6.22 (d, *J* = 9.7 Hz, 1 H, 3-H), 6.47 (ddd, *J* = 9.7, 5.6, 1.0 Hz, 1 H, 4-H), 6.82 (d, *J* = 8.7 Hz, 2 H, 3′′-H), 7.09–7.19 (m, 4 H, Ar), 7.25–7.38 (m, 3 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.49 (t, C-1′), 55.38 (q, OCH_3), 65.90 (d, C-6), 68.07 (d, C-5), 114.20 (d, C-3′′), 126.87 (d, Ar), 128.00, 128.22 (2 d, C-3, C-4′′′), 128.72 (s, C-1′′), 129.04 (d, Ar), 129.82 (d, Ar), 136.59 (d, C-4), 136.79 (s, C-1′′′), 159.10 (s, C-4′′), 163.15 (s, C-2) ppm. HRMS (ESI+): calcd. for $C_{19}H_{20}NO_3^+$ $[M + H]^+$ 310.14398; found 310.14404. Data for *cis*-**6b**: Colorless oil (100 mg, 3%). $[\alpha]_D^{20}$ = +143, (*c* = 0.59, $CHCl_3$); 98%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (br. s, 1 H, OH), 3.37 (d, *J* = 14.7 Hz, 1 H, 1′-H_a), 3.80 (s, 3 H, OCH_3), 4.55 (dd, *J* = 7.7, 1.0 Hz, 1 H, 5-H), 4.86 (br. s, 1 H, 6-H), 5.45 (d, *J* = 14.7 Hz, 1 H, 1′-H_b), 6.02 (dd, *J* = 10.0, 2.6 Hz, 1 H, 3-H), 6.22 (dd, *J* = 10.0, 1.7 Hz, 1 H, 4-H), 6.84 (d, *J* = 8.7 Hz, 2 H, 3′′-H), 7.13 (d, *J* = 8.5 Hz, 2 H, 2′′-H), 7.18–7.24 (m, 2 H, 2′′′-H), 7.34–7.41 (m, 3 H, 3′′′-H, 4′′′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.12 (t, C-1′), 55.42 (q, OCH_3), 62.21 (d, C-5), 67.31 (d, C-6), 114.20 (d, C-3′′), 124.24 (d, C-3), 128.89 (d, C-3′′′), 128.93 (d, C-4′′′), 129.31 (s, C-1′′), 129.34 (d, C-2′′′), 129.74 (d, C-2′′), 133.37 (s, C-1′′′), 142.24 (s, C-4), 159.25 (s, C-4′′), 163.69 (s, C-2) ppm. HRMS (ESI+): calcd. for $C_{19}H_{20}NO_3^+$ $[M + H]^+$ 310.14377; found 310.14404.

(+)-(5*S*,6*R*)-1-Benzyl-5-hydroxy-6-[(trityloxy)methyl]-5,6-dihydropyridin-2(1*H*)-one (*ent*-*trans*-6c): GP4 was carried out with Oxone (6.89 g, 11.20 mmol), lactam *ent*-**5c** (1.03 g, 2.24 mmol), $NaHCO_3$ (2.82 g, 33.6 mmol), and acetone/water (2:1, v/v, 25 mL) for a reac-

tion time of 2 h at room temp. TLC [petroleum ether/ethyl actetate, 2:1; R_f = 0.26 (*ent*-**5c**) and R_f = 0.22 (epoxide); $KMnO_4$]. After workup, the elimination reaction was carried out with the crude product, CH_2Cl_2 (40 mL), and DBU (0.61 g, 4.03 mmol) for a reaction time of 7 h. TLC [petroleum ether/ethyl actetate; 2:1; R_f = 0.22 (epoxide) and R_f = 0.15 (*ent-trans*-**6c**); $KMnO_4$]. Chromatography on silica gel (petroleum ether/ethyl acetate, from 2:1 to 1:1) afforded *ent-trans*-**6c** (906 mg, 85%, single diastereoisomer) as a colorless foam. $[\alpha]_D^{20}$ = +38.4 (*c* = 1.07, $CHCl_3$); 94%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (d, *J* = 8.5 Hz, 1 H, OH), 2.90 (dd, *J* = 9.6, 8.8 Hz, 1 H, 1′-H_a), 3.16 (dd, *J* = 9.8, 4.9 Hz, 1 H, 1′-H_b), 3.50–3.62 (m, 1 H, 6-H), 3.80 (d, *J* = 14.8 Hz, 1 H, 1′′-H), 4.23 (dd, *J* = 6.2, 6.2 Hz, 1 H, 5-H), 5.02 (d, *J* = 14.8 Hz, 1 H, 1′′-H), 5.91 (d, *J* = 9.8 Hz, 1 H, 3-H), 6.37 (ddd, *J* = 9.7, 5.7, 1.3 Hz, 1 H, 4-H), 7.06–7.31 (m, 20 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.68 (t, C-1′′), 62.11 (t, C-1′), 62.21 (d, C-6), 62.83 (d, C-5), 87.57 [s, $C(Ph)_3$], 127.25 (d, C-3), 127.40, 127.71, 128.06, 128.34, 128.65, 128.79 (6 d, Ar), 136.99 (d, C-4), 137.11 (s, NCH_2Ph), 143.52 (s, Ar), 162.47 (s, C-2) ppm. HRMS (ESI+): calcd. for $C_{32}H_{30}NO_3^+$ $[M + H]^+$ 476.2220; found 476.2221.

(–)-*tert*-Butyl (2*S*,3*R*)-3-Hydroxy-6-oxo-2-[(trityloxy)methyl]-3,6-dihydropyridine-1(2*H*)-carboxylate (6d): GP4 was carried out with Oxone (3.70 g, 6.02 mmol), lactam **5d** (565 mg, 1.20 mmol), $NaHCO_3$ (1.52 g, 18.06 mmol), and acetone/water (2:1, v/v, 12 mL) for a reaction time of 4 h at room temp. TLC [petroleum ether/ethyl acetate, 3:1; R_f = 0.33 (**5d**) and R_f = 0.23 (epoxide); $KMnO_4$]. After workup, a yellowish foam (531 mg) was obtained. The elimination reaction was carried out by the addition of CH_2Cl_2 (11 mL) and DBU (0.33 g, 2.20 mmol) for a reaction time of 2 h. TLC [petroleum ether/ethyl actetate, 2:1; R_f = 0.36 (epoxide) and R_f = 0.18 (**6d**); $KMnO_4$]. Chromatography on silica gel (diethyl ether/diethylamine, 1:0.005) afforded **6d** (527 mg, 90%, single diastereomer) as a colorless foam. $[\alpha]_D^{20}$ = –30.3 (*c* = 1.32, $CHCl_3$); 98%*ee*. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 2.51 (br. s, 1 H, OH), 3.04 (dd, *J* = 9.2, 8.2 Hz, 1 H, OCH_aH_b), 3.31 (dd, *J* = 9.2, 4.8 Hz, 1 H, OCH_aH_b), 4.40 (dd, *J* = 5.9, 1.2 Hz, 1 H, 3-H), 4.64–4.68 (m, 1 H, 2-H), 5.90 (d, *J* = 9.6 Hz, 1 H, 5-H), 6.61 (ddd, *J* = 9.7, 5.8, 1.5 Hz, 1 H, 4-H), 7.24–7.39 (m, 15 H, Ar) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 28.27 [3 q, $C(CH_3)_3$], 61.51 (d, C-3), 63.27 (d, C-2), 63.74 (t, C-1′), 83.71 [s, $C(CH_3)_3$], 87.73 [s, $C(Ph)_3$], 127.74 (3 d, C-Ar), 128.14 (d, C-5), 128.47 (6 d, C-Ar), 129.08 (6 d, C-Ar), 139.59 (d, C-4), 144.08 (3 s, C-Ar), 152.40 [s, $COOC(CH_3)_3$], 162.45 (s, C-6) ppm. HRMS (ESI+): calcd. for $C_{30}H_{31}NNaO_5^+$ $[M + Na]^+$ 508.2094; found 508.2102.

(+)-(5*S*,6*R*)-1-Benzyl-5-(benzyloxy)-6-[(trityloxy)methyl]-5,6-dihydropyridin-2(1*H*)-one (7): Under argon, a solution of *ent-trans*-**6c** (1.00 g, 2.10 mmol) in dry THF (20 mL) was cooled to 0 °C. NaH (126 mg, 5.26 mmol) was added, and the mixture was stirred for 20 min and then warmed to room temp. Tetrabutylammonium iodide (155 mg, 0.42 mmol) and BnBr (1.26 g, 7.36 mmol) were added, and the mixture was gently heated at reflux. After 7 h, TLC [petroleum ether/ethyl acetate, 2:1; R_f = 0.09 (*ent-trans*-**6c**) and R_f = 0.31 (**7**); $KMnO_4$] indicated complete consumption of the starting material. The mixture was concentrated in vacuo, and the residue was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to give benzyl ether **7** (1.16 g, 97%) as light yellow foam. $[\alpha]_D^{20}$ = +58.1 (*c* = 1.13, $CHCl_3$); 94%*ee*. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.01 (dd, *J* = 9.4, 9.4 Hz, 1 H, 1′-H_a), 3.30 (dd, *J* = 9.9, 4.7 Hz, 1 H, 1′-H_b), 3.70 (dd, *J* = 8.8, 4.7 Hz, 1 H, 6-H), 3.75 (d, *J* = 15.2 Hz, 1 H, 1′′-H_a), 4.11 (d, *J* = 5.6 Hz, 1 H, 5-H), 4.29 (d, *J* = 11.8 Hz, 1 H, 1′′′-H_a), 4.35 (d, *J* = 11.8 Hz, 1 H, 1′′′-H_b), 5.29 (d, *J* = 15.1 Hz, 1 H, 1′′-H_b), 6.07 (d, *J* = 9.8 Hz, 1 H, 3-H), 6.37 (ddd, *J* = 9.6, 5.7, 0.9 Hz, 1 H, 4-H), 7.11–7.19 (m, 2 H, Ar), 7.20–7.39 (m, 23 H, Ar) ppm. ^{13}C NMR (125 Hz, $CDCl_3$): δ = 48.04 (t, C-1′′), 58.05 (d, C-6), 61.88 (t, C-1′), 68.69 (d, C-5), 70.24 (t, C-1′′′), 87.63 [s, $C(Ph)_3$], 127.41 (d, C-3), 127.45, 127.84, 127.91, 128.07, 128.18, 128.52, 128.63 (7 d, Ar), 134.56 (d, C-4), 137.06 (s, NCH_2Ph), 137.77 (s, OCH_2Ph), 143.56 (s, Ar), 162.46 (s, C-2) ppm. HRMS (ESI+): calcd. for $C_{39}H_{36}NO_3^+$ $[M + H]^+$ 566.2689; found 566.2688.

(+)-(3*S*,4*R*,5*R*,6*R*)-1-Benzyl-5-(benzyloxy)-3,4-dihydroxy-6-[(trityloxy)methyl]piperidin-2-one (8): A drop of water, four drops of pyridine, and osmium tetroxide (2.5% OsO_4 in *tert*-butanol, 1.8 mL) were added to a stirred solution of the dihydropyridinone **7** (540 mg, 0.955 mmol) and NMO (336 mg, 2.87 mmol) in *tert*-butanol (3 mL). The reaction mixture was stirred for 3.5 h at room temp., and aqueous saturated $Na_2S_2O_5$ (8 mL) and water (20 mL) were then added. The mixture was extracted with EtOAc (50 mL). TLC [ethyl acetate; R_f = 0.67 (**7**) and R_f = 0.58 (**8**); $KMnO_4$]. The organic phase was washed with a saturated NH_4Cl solution (20 mL) and then H_2O (2× 20 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to yield diol **8** (424 mg, 74%, single diastereomer) as a colorless foam. $[\alpha]_D^{20}$ = +2.5 (*c* = 1.20, $CHCl_3$); 94%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (br. s, 1 H, OH), 3.38 (dd, *J* = 9.7, 4.7 Hz, 1 H, 1′-H_a), 3.60 (dd, *J* = 16.8, 7.0 Hz, 1 H, 1′-H_b), 3.58–3.69 (m, 1 H, 6-H), 3.84 (br. s, 1 H, OH), 4.01 (dd, *J* = 3.4, 2.7 Hz, 1 H, 5-H), 4.09 (d, *J* = 15.5 Hz, 1 H, 1′′-H_a), 4.33 (dd, *J* = 3.6, 3.6 Hz, 1 H, 4-H), 4.41 (d, *J* = 3.7 Hz, 1 H, 3-H), 4.43 (d, *J* = 11.9 Hz, 1 H, 1′′′-H_a) 4.47 (d, *J* = 11.9 Hz, 1 H, 1′′′-H_b), 5.11 (d, *J* = 15.5 Hz, 1 H, 1′′-H_b), 6.94–7.05 (m, 2 H, Ar), 7.11–7.49 (m, 23 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.68 (t, C-1′′), 59.91 (d, C-6), 63.44 (t, C-1′), 68.12 (d, C-3), 68.94 (d, C-4), 71.62 (t, C-1′′′), 74.60 (d, C-5), 87.64 [s, $C(Ph)_3$], 127.32, 127.46, 127.75, 128.03, 128.59, 128.63, 128.74 (7 d, Ar), 136.76 (s, NCH_2Ph), 137.46 (s, OCH_2Ph), 143.73 (s, Ar), 171.25 (s, C-2) ppm. HRMS (ESI+): calcd. for $C_{39}H_{37}NNaO_5^+$ $[M + Na]^+$ 622.2564; found 622.2566.

(+)-(3*R*,4*R*,5*R*,6*R*)-1-Benzyl-5-(benzyloxy)-6-[(trityloxy)methyl]piperidine-3,4-diol (9): Under argon, a solution of **8** (230 mg, 0.384 mmol) in dry Et_2O (20 mL) was treated with $LiAlH_4$ (73.0 mg, 1.92 mmol). After 5 h [R_f of **8** and R_f of **9** were identical], the suspension was cooled to 0 °C and treated with 10% aqueous NaOH. The mixture was treated with EtOAc (40 mL), and the resulting mixture was filtered through a pad of Celite. Water (40 mL) was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3× 30 mL). The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to yield **9** (193 mg, 86%) as a colorless foam. $[\alpha]_D^{20}$ = +4.8 (*c* = 0.95, $CHCl_3$); 94%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.17 (dd, *J* = 12.3, 1.0 Hz, 1 H, 2-H_a), 2.52 (br. s, 2 H, 2 OH), 2.57 (ddd, *J* = 8.4, 4.2, 1.3 Hz, 1 H, 6-H), 2.89 (dd, *J* = 12.3, 4.2 Hz, 1 H, 2-H_b), 3.09 (d, *J* = 13.3 Hz, 1 H, 1′′-H_a), 3.27 (dd, *J* = 10.2, 4.5 Hz, 1 H, 1′-H_a), 3.57 (dd, *J* = 16.7, 8.2 Hz, 1 H, 5-H), 3.57–3.78 (m, 3 H, 4-H, 1′-H_b and 3-H), 4.11 (d, *J* = 13.0 Hz, 1 H, 1′′-H_b), 4.47 (d, *J* = 11.3 Hz, 1 H, 1′′′-H_a), 4.87 (d, *J* = 11.2 Hz, 1 H, 1′′′-H_b), 7.01–7.09 (m, 4 H, Ar), 7.09–7.32 (m, 15 H, Ar), 7.36–7.50 (m, 6 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.58 (t, C-2), 57.35 (t, C-1′′), 62.16 (t, C-1′), 65.65 (d, C-6), 68.20 (d, C-3), 74.19 (t, C-1′′′), 76.45 (d, C-4), 78.54 (d, C-5), 86.93 [s, $C(Ph)_3$], 127.19, 127.62, 127.95, 128.13, 128.42, 128.50, 128.91, 129.06 (8 d, Ar), 138.46 (s, NCH_2Ph), 138.75 (s, OCH_2Ph), 143.89 (s, Ar) ppm. HRMS (ESI+): calcd. for $C_{39}H_{40}NO_4^+$ $[M + H]^+$ 586.2951; found 586.2951.

(+)-(3*R*,4*R*,5*R*,6*R*)-1-Benzyl-5-(benzyloxy)-6-(hydroxymethyl)piperidine-3,4-diol (10): AcOH (80% in H_2O, 5 mL) was added to the protected piperidinediol **9** (75 mg, 0.128 mmol), and the resulting yellow mixture was stirred and heated at reflux for 6 h whereupon TLC [ethyl acetate; R_f = 0.63 (**9**) and R_f = 0.19 (**10**); $KMnO_4$] indicated full conversion. The mixture was diluted with H_2O (10 mL), and the resulting mixture was treated with solid $NaHCO_3$ until it became basic. Ethyl acetate (20 mL) was added to the resulting suspension, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3× 20 mL), and the organic layer was concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel (ethyl acetate) to yield **10** (34.7 mg, 79%) as a colorless foam. Analytical data were in accordance with data from the literature.[11c] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14–2.30 (m, 2 H, 2-H_a and 6-H), 2.53 (br. s, 3 H, 3 OH), 2.93 (dd, J = 12.6 Hz, J = 4.1 Hz, 1 H, 2-H_b), 3.31 (d, J = 13.5 Hz, 1 H, 1′′-H_a), 3.52 (dd, J = 8.7 Hz, J = 3.4 Hz, 1 H, 4-H), 3.71 (dd, J = 8.7 Hz, J = 8.7 Hz, 1 H, 5-H), 3.75–3.80 (m, 1 H, 3-H), 3.85 (dd, J = 12.2 Hz, J = 2.1 Hz, 1 H, 1′-H_a), 3.95 (dd, J = 12.1 Hz, J = 2.8 Hz, 1 H, 1′-H_b), 4.05 (d, J = 13.5 Hz, 1 H, 1′′-H_b), 4.68 (d, J = 11.2 Hz, 1 H, 1′′′-H_a), 4.84 (d, J = 11.2 Hz, 1 H, 1′′′-H_b), 7.13–7.35 (m, 10 H, Ar) ppm.

1-Deoxymannojirimycin Hydrochloride (11·HCl): $Pd(OH)_2$/C (20% Pd, 100 mg) was added to a stirred solution of piperidine **10** (40 mg, 0.116 mmol) in MeOH (1.5 mL), and the mixture was placed under a hydrogen atmosphere (1 bar). TLC [ethyl acetate; R_f = 0.19 (**10**)] indicated full conversion after 3 h. Then, concentrated HCl (1 mL) was added, and the mixture was stirred for an additional 10 min and diluted with MeOH (10 mL). The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the residue recrystallized from MeOH to give 1-deoxymannojirimycin hydrochloride (**11**·HCl, 16.0 mg, 69%) as colorless needles. Analytical data were in accordance with data from the literature.[11c] M.p. 190–192 °C; ref.[11c] m.p. 192–195 °C. ^{1}H NMR (600 MHz, D_2O): δ = 3.11–3.28 (m, 1 H, 5-H), 3.30 (d, J = 13.8 Hz, 1 H, 6-H_a), 3.47 (dd, J = 13.7, 1.9 Hz, 1 H, 6-H_b), 3.75 (dd, J = 9.6, 2.0 Hz, 1 H, 3-H), 3.82–3.98 (m, 2 H, 1-H_a, 4-H), 4.03 (dd, J = 12.5, 2.28 Hz, 1 H, 1-H_b), 4.24–4.36 (m, 1 H, 2-H) ppm. ^{13}C NMR (150 MHz, D_2O): δ = 47.59 (t, C-6), 58.11 (t, C-1′), 60.27 (d, C-2), 65.73, 65.94 (2 d, C-3 and C-4), 72.31 (d, C-5) ppm.

(+)-(6*S*)-1-Benzyl-6-methylpiperidine-2,5-dione (13a): A suspension of Pd/C (10% Pd, 30 wt.-%, 60 mg) and *trans*-**6a** (200 mg, 0.92 mmol) in ethyl acetate (9 mL) was vigorously stirred under a hydrogen atmosphere (1 atm). TLC [ethyl acetate; R_f = 0.22 (*trans*-**6a**), R_f = 0.30 (*cis*-**6a**), and R_f = 0.10 (*trans*-**12a**); $KMnO_4$] showed that the reaction was complete after 1 h. The suspension was filtered through a pad of Celite, and the solvent was removed in vacuo. The crude hydrogenation product was dissolved in CH_2Cl_2 (9 mL), and Dess–Martin periodinane (585 mg, 1.379 mmol) was added at 0 °C. After stirring for 1 h, TLC showed complete conversion [ethyl acetate; R_f = 0.36 (**13a**); $KMnO_4$]. Saturated aqueous $Na_2S_2O_3$ solution (4 mL) and saturated $NaHCO_3$ solution (8 mL) were added at 0 °C. After stirring for 10 min, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3× 15 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo at a temperature not exceeding 10 °C. The residue was subjected to flash chromatography on silica gel (diethyl ether) to yield **13a** (198 mg, 99%) as colorless needles; m.p. 63–64 °C. NMR spectroscopic data were in accordance with reported data for the racemic compound.[11c] $[\alpha]_D^{20}$ = +104 (c = 0.93, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, *n*-hexane/isopropanol, 90:10, 0.5 mL/min): t_R = 28.6 **[**(–)-(*R*)-**13a]** and t_R = 45.2 min [(+)-(*S*)-**13a**]; 96.5% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, J = 7.2 Hz, 3 H, CH_3), 2.63–2.87 (m, 4 H, 3-H and 4-H), 3.74 (q, J = 7.2 Hz, 1 H, 6-H), 4.04 (d, J = 14.9 Hz, 1 H, $PhCH_aH_b$), 5.25 (d, J = 14.9 Hz, 1 H, $PhCH_aH_b$), 7.20–7.37 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.58 (q, CH_3), 29.28, 35.51 (2 t, C-3 and C-4), 47.52 (t, $PhCH_2$), 60.73 (d, C-6), 127.95, 128.16, 128.97 (3 d, Ar), 136.52 (s, Ar), 169.55 (s, C-2), 207.10 (s, C-5) ppm. GC–MS: t_R = 11.1 min. HRMS (ESI+): calcd. for $C_{13}H_{16}NO_2^+$ $[M + H]^+$ 218.1176; found 218.1176.

(–)-(5*S*,6*S*)-1-Benzyl-5-hydroxy-6-methylpiperidin-2-one (*cis*-12a): $NaBH_4$ (121 mg, 3.22 mmol) was added to a solution of **13a** (70.2 mg, 0.32 mmol) in methanol (9 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and 45 min at room temperature whereupon TLC showed complete conversion [ethyl acetate; R_f = 0.36 (**13a**) and R_f = 0.12 (*cis*-**12a**); $KMnO_4$]. The reaction mixture was treated with a saturated NH_4Cl solution (1 mL), and the resulting mixture was concentrated in vacuo. The residue was diluted with water (3 mL), and the solution was extracted with CH_2Cl_2 (4× 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel (ethyl acetate) to yield *cis*-**12a** (67 mg, 95%, 92:8 mixture of diastereoisomers as determined by GC–MS) as a colorless amorphous solid. Pure *cis*-**12a** (57 mg, 81%) was obtained as colorless plates by preparative HPLC (petroleum ether/2-propanol, 70:30); m.p. 118–119 °C. NMR spectroscopic data were in accordance with published data for the racemic compound.[19] $[\alpha]_D^{20}$ = –114 (c = 1.11, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, *n*-hexane/isopropanol, 90:10, 0.5 mL/min): t_R = 30.2 [(+)-(*R*,*R*)-**12a**] and t_R = 31.9 min [(–)-(*S*,*S*)-**12a**]; 96% *ee*. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (d, J = 6.6 Hz, 3 H, CH_3), 1.80–1.88 (m, 1 H, 4-H_a), 1.90–2.00 (m, 1 H, 4-H_b), 2.40–2.50 (m, 1 H, 3-H_a), 2.57 (ddd, J = 18.3, 7.4, 3.8 Hz, 1 H, 3-H_b), 2.89 (br. s, 1 H, OH), 3.38–3.44 (m, 1 H, 6-H), 3.88–3.96 (m, 1 H, 5-H), 3.91 (d, J = 15.0 Hz, 1 H, $PhCH_aH_b$), 5.26 (d, J = 15.0 Hz, 1 H, $PhCH_aH_b$), 7.19 (d, J = 7.1 Hz, 2 H, Ar), 7.21–7.32 (m, 3 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.32 (q, CH_3), 24.90 (t, C-4), 29.12 (t, C-3), 47.83 (t, $PhCH_2$), 55.09 (d, C-6), 67.37 (d, C-5), 127.46, 127.86, 128.70 (3 d, Ar), 137.43 (s, Ar), 169.52 (s, C-2) ppm. GC–MS: t_R = 12.2 min. HRMS (EI+): calcd. for $C_{13}H_{17}NO_2^+$ $[M]^+$ 219.1259; found 219.1249.

(–)-(5*R*,6*S*)-5-Hydroxy-1-(4-methoxybenzyl)-6-phenylpiperidin-2-one (*trans*-12b): A suspension of Rh/C (10%, 69 mg) and *trans*-**6b** (690 mg, 2.23 mmol) in ethyl acetate (16 mL) and methanol (3 mL) was vigorously stirred for 5 h under hydrogen (1 atm). The suspension was filtered through a pad of Celite, and the solvent was removed in vacuo to yield **12b** (688 mg, 98%) as a colorless solid; m.p. 132–134 °C. $[\alpha]_D^{20}$ = –48.5 (c = 0.83, $CHCl_3$); 98% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65–1.80 (m, 1 H, 4-H_a), 1.81–1.98 (m, 1 H, 4-H_b), 2.40–2.60 (m, 1 H, 3-H_a), 2.77 (ddd, J = 17.9, 10.7, 7.0 Hz, 1 H, 3-H_b), 3.31 (d, J = 14.8 Hz, 1′-H_a), 3.76 (s, 3 H, OCH_3), 3.95–4.03 (m, 1 H, 5-H), 4.38 (d, J = 3.0 Hz, 1 H, 6-H), 5.55 (d, J = 14.8 Hz, 1 H, 1′-H_b), 6.80 (d, J = 8.6 Hz, 2 H, 3′′-H), 7.08 (d, J = 8.6 Hz, 2 H, 2′′-H), 7.16 (dd, J = 7.16, 1.4 Hz, 2 H, 2′′-H), 7.28–7.42 (m, 3 H, 3′′′-H, 4′′′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.38 (t, C-4), 27.41 (t, C-3), 47.12 (t, C-1′), 55.36 (q, OCH_3), 66.83 (d, C-6), 69.99 (d, C-5), 114.07 (d, C-3′′), 127.01 (d, C-2′′′), 128.16 (d, C-4′′′), 128.95 (s, C-1′′), 129.13 (d, C-3′′′), 129.54 (d, C-2′′), 138.75 (s, C-1′′′), 158.98 (s, C-4′′), 170.30 (s, C-2) ppm. GC–MS (T_{max} = 300 °C): t_R = 16.21 min. HRMS (ESI+): calcd. for $C_{19}H_{22}NO_3^+$ $[M + H]^+$ 312.15975; found 312.15942.

(+)-(6*S*)-1-(4-Methoxybenzyl)-6-phenylpiperidine-2,5-dione (13b): DMSO (146 μL, 2.056 mmol) was added to a solution of oxalyl

chloride (90 μL, 1.028 mmol) in CH_2Cl_2 (1.3 mL) at –78 °C. After stirring for 10 min at the same temperature, a solution of *trans*-**12b** (80 mg, 257 μmol) in CH_2Cl_2 (1.3 mL) was added dropwise, and the suspension was stirred for an additional 20 min. NEt_3 (570 μL, 4.112 mmol) was then added dropwise, and the stirring was continued at –78 °C for 30 min whereupon TLC indicated complete conversion [petroleum ether/ethyl acetate, 1:2; R_f = 0.45 (*trans*-**12b**) and R_f = 0.18 (**13b**); $KMnO_4$]. The solution was treated with a NaH_2PO_4/Na_2HPO_4 buffer solution (5 mL), and the resulting solution was warmed to ambient temperature and extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate/dichloromethane, 2:1:0.2) to yield **13b** (68.2 mg, 86%) as a colorless white solid; m.p. 119–121 °C. $[a]_D^{20}$ = +20.1 (*c* = 0.69, $CHCl_3$). HPLC (Daicel Chiracel ADH-II, *n*-hexane/*i*PrOH, 80:20, 0.5 mL/min): t_R = 23.53 [(–)-(*R*)-**13b**] and t_R = 26.93 min [(+)-(*S*)-**13b**]; 98%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.64–2.74 (m, 2 H, 3-H or 4-H), 2.74–2.86 (m, 2 H, 3-H or 4-H), 3.46 (d, *J* = 14.5 Hz, 1 H, 1′-H_a), 3.77 (s, 3 H, OCH_3), 4.74 (s, 1 H, 6-H), 5.54 (d, *J* = 14.5 Hz, 1 H, 1′-H_b), 6.81 (d, *J* = 8.7 Hz, 2 H, 3′′-H), 7.07 (d, *J* = 8.5 Hz, 2 H, 2′′-H), 7.21–7.27 (m, 2 H, 2′′′-H), 7.20–7.43 (m, 3 H, 3′′′-H, 4′′′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.40 (t, C-4), 35.09 (t, C-3), 47.28 (t, C-1′), 55.43 (q, OCH_3), 68.41 (d, C-6), 114.37 (d, C-3′′), 126.66 (d, C-2′′′), 127.99 (s, C-1′′), 128.78 (d, C-4′′′), 129.44 (d, C-3′′′), 129.97 (d, C-2′′), 134.22 (s, C-1′′′), 159.47 (s, C-4′′), 170.00 (s, C-2), 202.97 (s, C-5) ppm. HRMS (ESI+): calcd. for $C_{19}H_{20}NO_3^+$ $[M + H]^+$ 310.14413; found 310.14377.

(–)-(5*S*,6*S*)-5-Hydroxy-1-(4-methoxybenzyl)-6-phenyl-5,6-dihydropyridin-2(1*H*)-one (*cis*-12b): $NaBH_4$ (75.6 mg, 2 mmol) was added to a solution of **13b** (62 mg, 0.2 mmol) in methanol (4 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and 30 min at room temp. whereupon TLC [petroleum ether/ethyl acetate, 1:2; R_f = 0.19 (*cis*-**12b**); $KMnO_4$] indicated complete consumption of the starting material. Aqueous NH_4Cl solution (3 mL) was added, and the mixture was concentrated under reduced pressure. Water (2.5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo to give *cis*-**12** (66.4 mg, 97%) as a colorless solid, m.p. 171–173 °C; ref.[20] m.p. 172.5–173.5 °C. Analytical data are in accordance with reported data.[20] $[a]_D^{20}$ = –64.2 (*c* = 0.6, $CHCl_3$); 98%*ee*; ref.[20] $[a]_D^{20}$ = –63.39 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (br. s, 1 H, OH), 1.68–1.78 (m, 2 H, 4-H), 2.59 (ddd, *J* = 18.1, 8.6, 8.6 Hz, 1 H, 3-H_a), 2.77 (ddd, *J* = 18.3, 5.2, 5.2 Hz, 1 H, 3-H_b), 3.29 (d, *J* = 14.5 Hz, 1 H, 1′-H_a), 3.79 (s, 3 H, OCH_3), 4.03 (br. s, 1 H, 5-H), 4.48 (d, *J* = 5.3 Hz, 1 H, 6-H), 5.42 (d, *J* = 14.5 Hz, 1 H, 1′-H_b), 6.84 (d, *J* = 8.7 Hz, 2 H, 3′′-H), 7.06 (d, *J* = 8.6 Hz, 2 H, 2′′-H), 7.22 (dd, *J* = 7.6, 1.7 Hz, 2 H, 2′′′-H), 7.35–7.48 (m, 3 H, 3′′′-H, 4′′′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.62 (t, C-4), 29.63 (t, C-3), 47.46 (t, C-1′), 55.41 (q, OCH_3), 63.47 (d, C-6), 67.37 (d, C-5), 114.13 (d, C-3′′), 128.68 (d, C-4′′′), 128.74 (d, C-2′′′), 128.93 (d, C-3′′′), 129.02 (s, C-1′′), 129.85 (d, C-2′′), 135.45 (s, C-1′′′), 159.19 (s, C-4′′), 169.84 (s, C-2) ppm. GC–MS: t_R = 20.08 min. HRMS (ESI+): calcd. for $C_{19}H_{22}NO_3^+$ $[M + H]^+$ 312.15914; found 312.15942.

(–)-*tert*-Butyl (2*S*,3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-oxo-2-[(trityloxy)methyl]-3,6-dihydropyridine-1(2*H*)-carboxylate (14): *N*-Methylimidazole (0.25 mg, 3.03 mmol), iodine (0.51 mg, 2.02 mmol), and TBSCl (0.16 mg, 1.06 mmol) were consecutively added to a solution of *trans*-**6d** (491 mg, 1.01 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was allowed to reach room temp. and was stirred for 2 h whereupon TLC indicated full conversion [petroleum ether/ethyl acetate, 2:1; R_f = 0.18 (**6d**) and R_f = 0.56 (**14**); $KMnO_4$]. The solution was diluted with ethyl acetate (10 mL), and the resulting mixture was washed with saturated aqueous $Na_2S_2O_3$ solution (20 mL) until the organic layer was colorless. The aqueous layer was extracted with ethyl acetate (3× 25 mL), and the combined organic phases were washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, from 30:1 to 4:1) to yield **14** (551 mg, 91%) as a colorless foam. $[a]_D^{20}$ = –57 (*c* = 1.72, $CHCl_3$); 98%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.12, 0.17 (2 s, 6 H, OTBS), 0.90 (s, 9 H, OTBS), 1.49 [s, 9 H, $C(CH_3)_3$], 2.94 (dd, *J* = 9.2, 9.2 Hz, 1 H, OCH_aH_b), 3.35 (dd, *J* = 9.0, 4.9 Hz, 1 H, OCH_aH_b), 4.39 (dd, *J* = 5.9, 1.5 Hz, 1 H, 3-H), 4.66–4.71 (m, 1 H, 2-H), 5.84 (d, *J* = 9.5 Hz, 1 H, 5-H), 6.33 (ddd, *J* = 9.7, 5.7, 1.5 Hz, 1 H, 4-H), 7.21–7.44 (m, 15 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.56, –4.25 (2 q, OTBS), 18.19 (s, OTBS), 25.82 (3 q, OTBS), 28.10 [3 q, $C(CH_3)_3$], 61.05 (d, C-2), 62.81 (d C-3), 62.96 (t, C-1′), 83.05 [s, $C(CH_3)_3$], 87.29 [s, $C(Ph)_3$], 127.10 (d, C-5), 127.32 (3 d, C-Ar), 128.02 (6 d, C-Ar), 128.66 (6 d, C-Ar), 138.99 (d, C-4), 143.51 (3 s, C-Ar), 151.75 [s, $COOC(CH_3)_3$], 162.46 (s, C-6) ppm. HRMS (ESI+): calcd. for $C_{36}H_{45}NNaO_5Si^+$ $[M + Na]^+$ 622.29.59; found 622.2957.

(+)-(4*Z*)-2-[(*tert*-Butoxycarbonyl)amino]-3-*O*-[*tert*-butyl(dimethyl)-silyl]-2,4,5-trideoxy-1-*O*-trityl-D-*erythro*-hex-4-enitol (15): $CeCl_3 \cdot 7H_2O$ (58 mg, 0.16 mmol) was added portionwise to a cooled (–10 °C), stirred solution of lactam **14** (85 mg, 0.14 mmol) in $MeOH/H_2O/CH_2Cl_2$ (10:1:0.05, v/v, 6 mL). After stirring for 5 min, $NaBH_4$ (16 mg, 0.43 mmol) was added in one portion. Vigorous gas evolution took place. After this had ceased, the mixture was warmed to –2 °C and stirred precisely at this temperature for 1 h whereupon TLC indicated complete conversion [petroleum ether/ethyl acetate, 2:1; R_f = 0.56 (**14**) and R_f = 0.40 (**15**); $KMnO_4$]. The solution was neutralized to pH = 7 by the addition of HCl (1 N solution), and the resulting solution was extracted with ethyl acetate (3× 15 mL). The organic layers were washed with a saturated $NaHCO_3$ solution (5 mL) and brine (5 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 4:1) to yield **15** (68 mg, 80%) as a colorless foam and **14** (7 mg, corrected yield 88%). $[a]_D^{20}$ = +7.6 (*c* = 1.14, $CHCl_3$); 98%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.08, –0.04 (2 s, 6 H, OTBS), 0.75 (s, 9 H, OTBS), 1.44 [s, 9 H, $C(CH_3)_3$], 2.22 (br. s, 1 H, OH), 3.23–3.33 (m, 2 H, 1-H), 3.73 (br. s, 1 H, 2-H), 4.12–4.29 (m, 2 H, 6-H), 4.65–4.72 (m, 2 H, 3-H and NH), 5.45 (dd, *J* = 10.5, 9.1 Hz, 1 H, 4-H), 5.66 (ddd, *J* = 11.8, 6.2, 6.0 Hz, 1 H, 5-H), 7.21–7.44 (m, 15 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.93, –4.26 (2 q, OTBS), 18.10 (s, OTBS), 25.85 (3 q, OTBS), 28.58 [3 q, $C(CH_3)_3$], 56.31 (d, C-2), 58.99 (t, C-6), 62.13 (t, C-1), 69.42 (d, C-3), 79.65 [s, $C(CH_3)_3$], 86.99 [s, $C(Ph)_3$], 127.21 (3 d, C-Ar), 127.96 (6 d, C-Ar), 128.90 (6 d, C-Ar), 130.29 (d, C-5), 133.47 (d, C-4), 143.98 (3 s, C-Ar), 155.91 [s, $COOC(CH_3)_3$] ppm. HRMS (ESI+): calcd. for $C_{36}H_{49}NNaO_5Si^+$ $[M + Na]^+$ 626.3272; found 626.3271.

***tert*-Butyl ((1*S*,2*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-oxo-1-[(trityloxy)methyl]-propyl)carbamate (16):** A solution of **15** (45 mg, 0.075 mmol) and the indicator Sudan III in CH_2Cl_2/MeOH (1:1, v/v) was exposed to ozone at –78 °C for 5 min and then treated with dimethylsulfide (35 μL) at –78 °C. After stirring for 10 min, the solution was warmed to room temp. The crude product was purified by flash column chromatography [petroleum ether (PE)/diethyl ether (EE), 4:1; R_f = 0.32 (**15**) and R_f = 0.61 (**16**); $KMnO_4$] on silica gel (pentane/diethyl ether, 8:1) to give **16** (33 mg, 76%) as a colorless foam. $[a]_D^{20}$ = +21.5 (*c* = 1.22, $CHCl_3$). ^{1}H NMR

(300 MHz, $CDCl_3$): δ = –0.04 and 0.04 [2 s, 6 H, OSi*t*Bu-$(CH_3)_2$], 0.82 [s, 9 H, OSi*t*Bu$(CH_3)_2$], 1.41 [s, 9 H, C$(CH_3)_3$], 3.11–3.24 (m, 2 H, 1′-H), 4.14–4.32 (m, 2 H, 2-H and 1-H), 4.50 (d, *J* = 8.8 Hz, 1 H, NH), 7.20–7.42 (m, 15 H, Ar), 9.61 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) = –5.10 and –4.46 {2 q, OSi[C$(CH_3)_3$]$(CH_3)_2$}, 18.22 {s, OSi[C$(CH_3)_3$]$(CH_3)_2$}, 25.84 {3 q, OSi[C$(CH_3)_3$]$(CH_3)_2$}, 28.46 [3 q, C$(CH_3)_3$], 52.79 (d, C-1), 61.04 (t, C-1′), 78.22 (d, C-2), 79.99 [s, C$(CH_3)_3$], 87.82 [s, C$(Ph)_3$], 127.25 (3 d, C-Ar), 128.02 (6 d, C-Ar), 128.80 (6 d, C-Ar), 143.54 (3s, C-Ar), 155.00 (s, COO*t*Bu), 201.43 (d, CHO) ppm. HRMS (ESI+): calcd. for $C_{34}H_{45}NNaO_5Si^+$ [M + Na]$^+$ 598.2959; found 598.2955.

***tert*-Butyl ((1*S*,2*R*,3*E*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[(trityloxy)methyl]-heptadec-3-en-1-yl)carbamate (17):** A solution of KHMDS (0.5 M in toluene, 0.50 mL, 0.25 mmol) was added to a solution of 1-phenyl-5-tetradecylsulfonyl-1*H*-tetrazole (146 mg, 0.30 mmol) in dry DME (2.5 mL) under argon at –56 °C. The solution was stirred for 30 min as the color of the solution turned to yellow. A solution of aldehyde **16** (67 mg, 0.12 mmol) in DME (1.5 mL) was slowly added by cannula, and the mixture was stirred at –60 to –50 °C until TLC [PE/EE, 10:1; R_f = 0.35 (**16**) and R_f = 0.53 (**17**); $KMnO_4$] indicated full conversion of the aldehyde (4 h). Water was then added, and the mixture was warmed to room temp. After stirring for an additional 30 min, the mixture was extracted with Et_2O, and the organic layers were washed with water, dried, and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel (pentane/diethyl ether, 20:1) to give **17** (56 mg, 64%, *E*/*Z*, 88:12). The *Z*/*E* isomers were separated by preparative HPLC [pentane/diethyl ether, 25:1; t_R = 8.3 (*Z*-**17**) and t_R = 10.1 min (*E*-**17**)]. Data for (*E*)-**17**: Colorless oil. $[\alpha]_D^{20}$ = +0.5 (*c* = 2.70, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = –0.00 [s, 6 H, OSi*t*Bu$(CH_3)_2$], 0.82 [s, 9 H, OSi*t*Bu$(CH_3)_2$], 0.91 (pseudo-t, *J* = 6.7 Hz, 3 H, 17-H), 1.29 (s, 22 H, 6-H–16-H), 1.47 [s, 9 H, C$(CH_3)_3$], 1.93–1.97 (m, 2 H, 5-H), 3.22 (br. d, *J* = 4.8 Hz, 2 H, 1′-H), 3.80–3.87 (m, 1 H, 1-H), 4.32 (m, 1 H, 2-H), 4.59 (br. d, *J* = 8.5 Hz, 1 H, NH), 5.29 (dd, *J* = 15.4 Hz, *J* = 6.7 Hz, 1 H, 3-H), 5.60 (ddd, *J* = 15.6 Hz, *J* = 6.7 Hz, *J* = 6.7 Hz, 1 H, 4-H), 7.24–7.48 (m, 15 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.82 and –4.04 {2 q, OSi[C$(CH_3)_3$]$(CH_3)_2$}, 14.27 (q, C-17), 22.84 (t, C-16), 25.97 {3 q, OSi[C$(CH_3)_3$]$(CH_3)_2$}, 28.61 [3 q, C$(CH_3)_3$], 29.31–29.85 (m, C-6–C-15), 32.08 {s, OSi[C$(CH_3)_3$]$(CH_3)_2$}, 32.32 (t, C-5), 55.73 (d, C-1), 62.37 (t, C-1′), 73.94 (d, C-2), 79.01 [s, C$(CH_3)_3$], 86.75 [s, C$(Ph)_3$], 127.07 (3 d, C-Ar), 127.87 (6 d, C-Ar), 128.91 (6 d, C-Ar), 129.78 (d, C-3), 133.08 (d, C-4), 144.14 (3 s, C-Ar), 155.69 (s, COO*t*Bu) ppm. HRMS (ESI+): calcd. for $C_{48}H_{73}NNaO_4Si^+$ [M + Na]$^+$ 778.5201; found 778.5204. Data for (*Z*)-**17**: Colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = –0.07 and –0.05 [2s, 6 H, OSi*t*Bu$(CH_3)_2$], 0.75 [s, 9 H, OSi*t*Bu$(CH_3)_2$], 0.88 (pseudo-t, *J* = 6.5 Hz, 3 H, H-17), 1.26 (s, 22 H, 6-H–16-H), 1.44 [s, 9 H, C$(CH_3)_3$], 1.94–2.12 (m, 2 H, 5-H), 3.20–3.31 (br. d, 2 H, 1′-H), 3.68–3.78 (m, 1 H, 1-H), 4.58–4.69 (m, 2 H, 2-H and NH), 5.23 (dd, *J* = 11.0 Hz, *J* = 8.6 Hz, 1 H, 3-H), 5.37 (ddd, *J* = 11.4 Hz, *J* = 7.2 Hz, *J* = 7.2 Hz, 1 H, 4-H), 7.18–7.46 (m, 15 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.86 and –4.10 {2 q, OSi[C$(CH_3)_3$]$(CH_3)_2$}, 14.27 (q, C-17), 22.85 (t, C-16), 25.92 {3 q, OSi[C$(CH_3)_3$]$(CH_3)_2$}, 28.64 [3 q, C$(CH_3)_3$], 29.51–30.09 {m, C-6–C-15 and OSi[C$(CH_3)_3$]$(CH_3)_2$}, 32.08 (t, C-5), 55.82 (d, C-1), 62.35 (t, C-1′), 69.44 (d, C-2), 77.36 [s, C$(CH_3)_3$], 86.88 [s, C$(Ph)_3$], 127.10 (3 d, C-Ar), 127.88 (6 d, C-Ar), 128.96 (6 d, C-Ar), 130.64 (d, C-3), 131.88 (d, C-4), 144.13 (3 s, C-Ar), 155.63 (s, COO*t*Bu) ppm. HRMS (ESI+): calcd. for $C_{48}H_{73}NNaO_4Si^+$ [M + Na]$^+$ 778.5201; found 778.5204.

(2*S*,3*R*,4*E*)-2-Aminooctadec-4-ene-1,3-diol [(–)-D-*erythro*-Sphingosine, 18]: TFA (1 mL) was added to a solution of (*E*)-**17** (41 mg, 0.05 mmol) in CH_2Cl_2 (1 mL), and the resulting yellow solution was stirred at room temp. for 2 h. The solvent was removed under reduced pressure, and the residual ammonium salt was dissolved in MeOH and subjected to an ion-exchange column (Dowex 50Wx8, H^+ form) that was eluted with MeOH (20 mL), NH_3 (4 M in MeOH, 30 mL), and CH_2Cl_2/MeOH/NEt_3 (8:1:0.01, 40 mL) to give **18** (7 mg, 40%) as white plates. Analytical data were in accordance with the literature.[27] $[\alpha]_D^{20}$ = –2.4 (*c* = 0.90, $CHCl_3$); ref.[27] $[\alpha]_D^{20}$ = –1.6 (*c* = 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H, 18-H), 1.26 (s, 22 H, 7-H–17-H), 2.04–2.06 (m, 2 H, 6-H), 2.80–2.99 (2 br. s, 5 H, NH_2, 2 OH, and 2-H), 3.64–3.74 (m, 2 H, 1-H), 4.14 (br. s, 1 H, 3-H), 5.46 (dd, *J* = 14.8 Hz, *J* = 5.7 Hz, 1 H, 4-H), 5.77 (ddd, *J* = 15.1 Hz, *J* = 6.1 Hz, *J* = 6.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.27 (q, C-18), 22.85 (t, C-17), 29.33, 29.45, 29.52, 29.67, 29.80–29.86 (5 t), 32.08 (all t, C-7–C-16), 32.51 (t, C-6), 56.45 (d, C-2), 62.21 (t, C-1), 74.62 (d, C-3), 128.80 (d, C-4), 134.96 (d, C-5) ppm. HRMS (ESI+): calcd. for $C_{18}H_{38}NO_2^+$ [M + H]$^+$ 300.2897; found 300.2897.

Supporting Information (see footnote on the first page of this article): Additional synthetic route to **18**, general procedures for the Ir-catalyzed allylic substitution, HPLC data, and ^1H NMR spectra of all compounds.

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