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Asymmetric Synthesis of Ring Functionalized *trans*-2,6-Disubstituted Piperidines from *N*-Sulfinyl δ-Amino β-Keto Phosphonates. Total Synthesis of (−)-Myrtine

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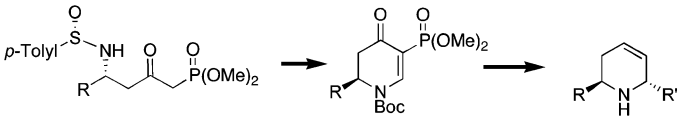

Sulfinimine-derived *N*-sulfinyl δ-amino β-ketophosphonates are transformed via the enaminones to the phosphoryl dihydropyridones that selectively give *trans*-2,6-disubstituted 1,2,5,6-tetrahydropyridines on organocuprate addition and dephosphorylation.

Introduction

The piperidine ring is a common motif found in natural products, drugs, and drug candidates.[1,2] Simple 2,6-disubstituted piperidines, isolated from fire ant venom, are reported to possess a broad range of activities (necrotic, insecticidal, antibacterial, antifungal, anti-HIV).[3] Polyhydroxylated piperidines (azasugars) are potent inhibitors of carbohydrate-processing enzymes, which suggests they will find utility in treating viral infections, cancer, diabetes, and tuberculosis.[4] Furthermore, piperidines serve as building blocks for the synthesis of more complex alkaloids, including the indolizidine and quinolizidine ring systems, which in themselves exhibit a broad range of biological activities.[5] Although *cis*-2,6-disubstituted piperidines are readily accessible, there are fewer methods for the synthesis of *trans*-2,6-disubstituted piperidines.[6,7] Unfortunately, most of these procedures lack generality, are racemic,[7c] or target specific syntheses.[7d−n] Few of these methods provide convenient access to enantiopure ring functionalized examples, with the majority of these being target-specific.[8] Among the more general methods for the synthesis of *trans*-2,6-disubstituted piperidines are the addition

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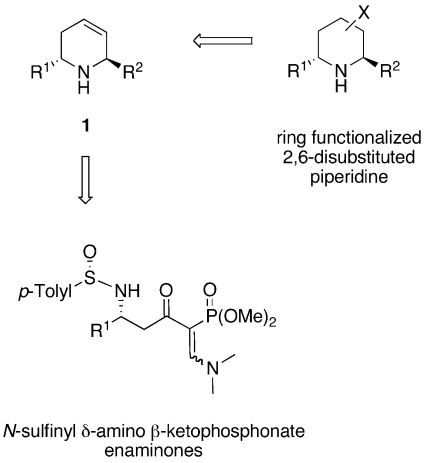
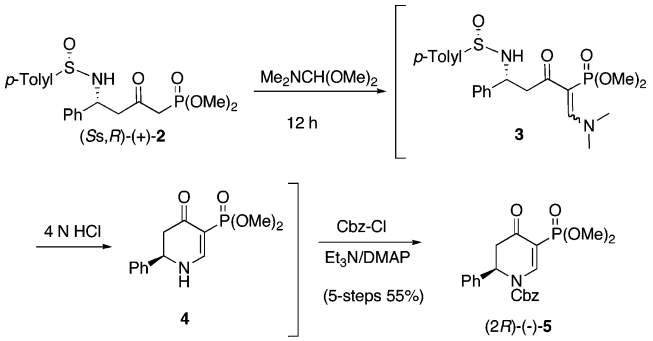
SCHEME 1



of silanes to chiral dihydropyridones,[9] the hydroxyl-directed reduction of 1,2-dehydropiperidines,[10] the diastereoselective addition of organometallic reagents to chiral piperidine epoxides,[11] and the synthesis of 2,4,6-trisubstituted piperidines via an azaelectrocyclization protocol.[12]

trans-2,6-Disubstituted 1,2,5,6-tetrahydropyridines **1** are potentially valuable chiral building blocks for asymmetric synthesis of polysubstituted piperidines because of the many methods available for functionalization of the ring carbon−carbon double bond (Scheme 1).[13] Overman et al. developed an iminiuim ion−vinylsilane cyclization process to produce **1** with excellent stereocontrol.[14] However, racemization via an aza-Cope process proved to be faster than cyclization. Panek and co-workers demonstrated that **1** could be prepared via cyclization of imines generated from α-allylsilane amino acids using Lewis acids.[15] Reaction of Grignard reagents with oxazolidine derivatives derived from chiral pyridinium salts is also reported to give **1**, in addition to the cis product.[16] Employing ring-closing metathesis of chiral aminodienes, the groups of Couty[8i] and Leberton[17] prepared **1** having a 2-hydroxymethyl group. We describe here a new method for the asymmetric synthesis of *trans*-2,6-disubstituted 1,2,5,6-tetrahydropyridines **1** from *N*-sulfinyl *δ*-amino *β*-ketophosphonate enaminones, a new sulfinimine-derived chiral building block (Scheme 1). The application of this new protocol to the asymmetric synthesis of the quinolizidine alkaloid (−)-myrtine is presented.

SCHEME 2



Results and Discussion

(S_S,*R*)-(+)-*N*-Sulfinyl *δ*-amino *β*-ketophosphonate **2** was prepared as previously described[18] and treated with 20 equiv of commercially available dimethylformamide dimethyl acetal at room temperature for 12 h.[19] Removal of the solvent gave the crude *N*-sulfinyl *δ*-amino *β*-ketophosphonate enaminone **3** (Scheme 2). The absorptions appearing in the proton NMR of **3** at *δ* 8.02 and 2.63 ppm are attributed to the vinyl and *N*,*N*-dimethyl protons, respectively, suggesting that a single isomer was formed of unknown stereochemistry. Because of the hydrolytic instability of **3**, it was treated with 4 N HCl in dioxane without purification to give **4**. Concentration and treatment of **4** with Cbz-Cl/DMAP gave 5-(dimethoxyphosphoryl) 2,3-dihydropyridone (2*R*)-(−)-**5** in 55% yield for the five-step single-flask reaction sequence (Scheme 2). As noted earlier for the related *δ*-amino *β*-ketoester enaminones,[19] the formation of **4** is consistent with an intramolecular Michael-type addition followed by retro-Michael elimination. The structure of (2*R*)-(−)-**5** is supported by the chemical shift of the vinyl proton at *δ* 8.81 ppm and the phosphonate methoxy groups at *δ* 3.71 ppm in the ^{1}H NMR. Comins and Ollinger prepared a related compound in racemic form via a nickel(II) cross-coupling reaction.[9d]

With dihydropyridone (−)-**5** in hand, Michael addition of various cuprates was next explored. The expectation was that trans addition would predominate based on earlier observations by Comins et al., where it was suggested that the C-2 phenyl and C-5 phosphonate groups sterically inhibit axial attack via the lower energy chair conformation leading to the cis product.[9d] The cuprates were prepared by addition of methylmagnesium chloride, *n*-propylmagnesium chloride, and phenylmagnesium chloride to CuI at −78 °C in THF.[20] The pale-white cuprate solutions were added via cannula to a −78 °C solution of (−)-**5** to give the dihydropyridones **6** and **7** as separable trans/cis mixtures (Scheme 3). The chemical shift of the proton absorption at *δ* 10−11 ppm exchanges with MeOD and suggests that they exist 80−95% in the enol form. We attribute the major absorption at ca. *δ* 25.5 ppm in the ^{31}P NMR spectra of **6a**−**c** to the enol forms. It was not possible to assign the stereochemistry of the major product to the trans isomer because of the complexity of the NMR spectra. However, the stereochemistry of the major product was assigned as trans by conversion into compounds of known absolute configuration as discussed below.

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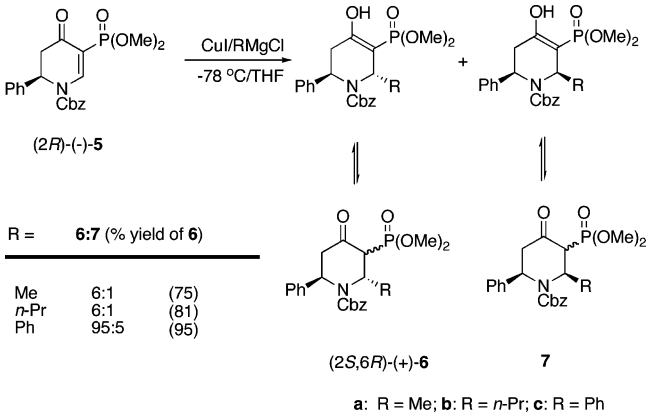
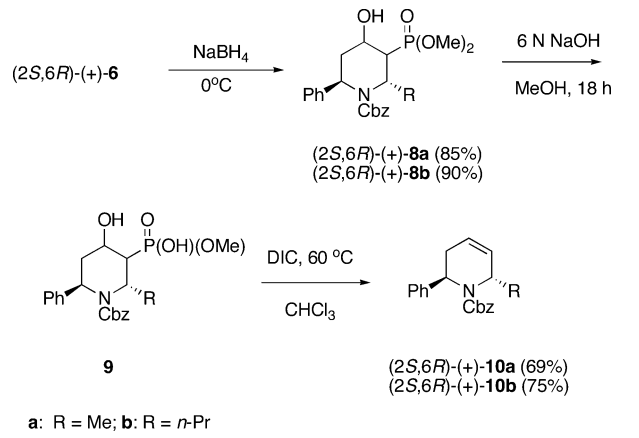
SCHEME 3



SCHEME 4

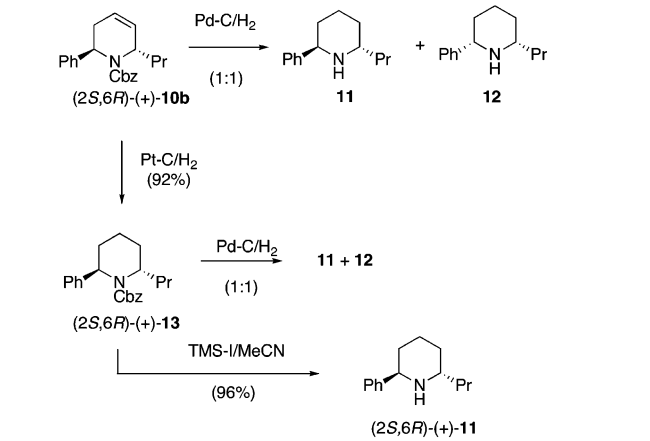


In order for the enols/ketophosphonates **6** to be useful building blocks, methods need to be devised for the efficient removal of the phosphonate group. However, attempted conversion of the C-3 phosphonate into an enone using HWE reaction with acetaldehyde and DBU/LiCl or NaH failed, resulting in recovery of the starting material. Selective removal of the phosphonate groups in β-ketophosphonates has been described by reduction of the sodium enolate with lithium aluminum hydride.[21] However, similar attempts to remove the C-3 phosphonate group in **6** resulted in decomposition.

Pagenkopf et al. reported a procedure for conversion of acyclic β-hydroxy phosphonates into alkenes involving hydrolysis of the phosphonate and treatment with diisopropylcarbodiimide (DIC).[22] Reduction of **6a,b** with $NaBH_4$ gave the alcohols **8a** and **8b** in 85% and 90% yields, respectively (Scheme 4). All attempts to reduce **6c** (R = Ph) failed. Hydrolysis of **8** to **9** was accomplished by reaction with 6 N NaOH/MeOH for 18 h. The crude acids **9** were not purified but heated with DIC for 8 h to give the corresponding tetrahydropyridines **10a** and **10b** in 69% and 75% yields for the two-step sequence (Scheme 4).

Hydrogenation of (2*S*,6*R*)-(+)-**10b** was initially performed with Pd−C/H_2 at 1 atm to reduce the double bond as well as to remove the Cbz group (Scheme 4). However, a 1:1 mixture of cis and trans isomers **11**/**12** resulted as determined by proton

SCHEME 5



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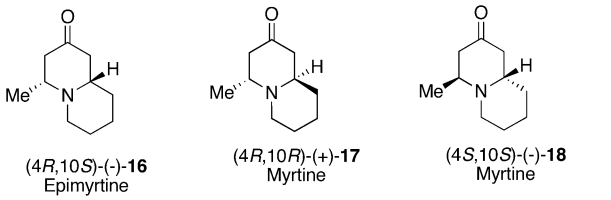

NMR. These results initially suggested that the double bond had migrated during the hydrogenation step. Selective hydrogenation of the carbon−carbon double bond in **10b** was accomplished using Pt−C/H_2, affording (+)-**13** in 92% yield. Interestingly, when the hydrogenolysis of (+)-**11** was carried out with Pd−C/H_2, a 1:1 mixture of **11** and **12** was obtained, suggesting that the source of the cis product **12** was isomerization at the C-2 phenyl group. The Cbz group was successfully removed without isomerization by treating (+)-**13** with TMS−I, affording *trans*-(+)-**11** in 96% yield (Scheme 5).[23] Similar results were obtained for **10a**, resulting in *trans*-(+)-**15** in 86% yield. Since both (+)-**11**[24] and (+)-**15**[25] are known compounds, this confirms that the major product for the addition of organocuprates to dihydropyridone (−)-**5** occurs trans to the C-2 phenyl group as predicted.

Asymmetric Synthesis of (−)-Myrtine. (−)-Epimyrtine (**16**) and (+)-myrtine (**17**) are naturally occurring quinolizidine alkaloids isolated from *Vaccinium myrtillus* (Scheme 6).[26] Whereas a number of racemic syntheses[27,28] of these compounds have been described, there are only three asymmetric synthesis of (−)-**16**.[29] Two asymmetric syntheses of (+)-myrtine have been reported. Comins and LaMunyon described a three-step synthesis of this material starting from a chiral 4-methoxy-3-

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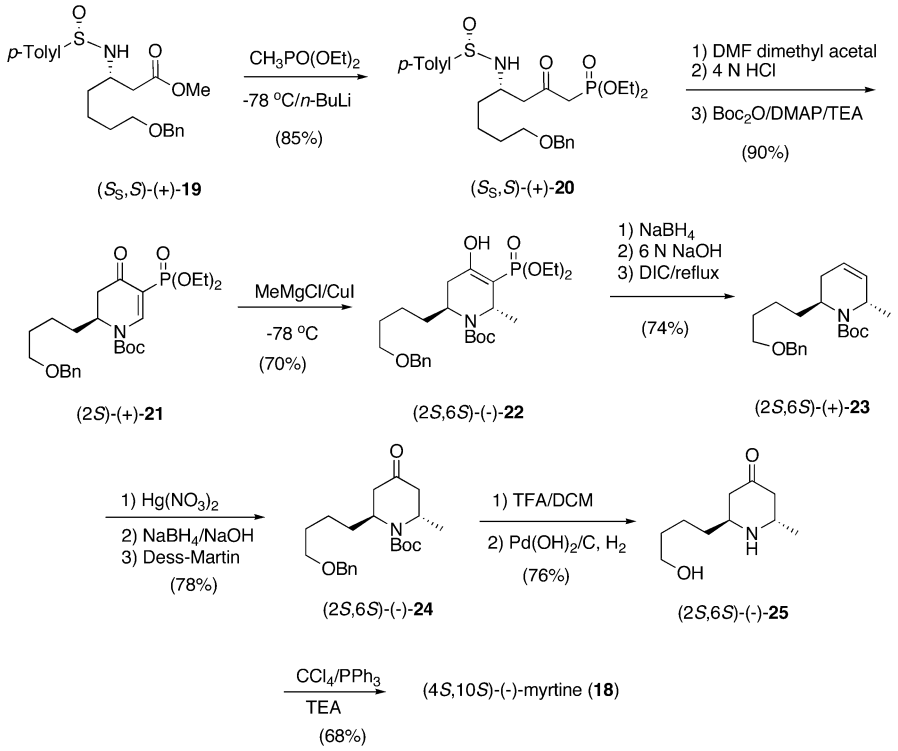
SCHEME 7



(triisopropylsilyl)pyridine.[9a] Gelas-Mialhe et al. employed (*S*)-2-(2-hydroxypropyl)allyltrimethylsilane and an intramolecular allylsilane *N*-acyliminium ion cyclization in their synthesis of (+)-**17**.[8e] However, this latter method also gave (−)-epimyrtine (**16**), resulting in poor selectivity.

We illustrate the utility of our new methodology for the asymmetric synthesis of *trans*-2,6-disubstituted 1,2,5,6-tetrahydropiperidines **1** with a total synthesis of (4*S*,10*S*)-(−)-myrtine (**18**), the unnatural myrtine isomer that has never been prepared. Our synthesis begins with *β*-amino ketoester (S_S,*S*)-(+)-**19** prepared earlier in our synthesis of (−)-**16** (Scheme 7).[29a] The ester was treated with diethyl lithiummethylphosphonate to give an 85% isolated yield of (S_S,*S*)-(+)-**20**. With DMF dimethyl acetal (+)-**20** gave the intermediate enaminone, which was not purified but treated with HCl-dioxane followed by trapping with $(Boc)_2O$ to give dihydropyridone (+)-**21** in 55−60%. We found that hydrolysis of the enaminone intermediate with aqueous HCl improved the yield to 90%. Reaction of (+)-**21** with the methyl cuprate at −78 °C afforded both the *trans*- and *cis*-piperidines in a ratio of 4:1 and an isolated yield of (2*S*,6*S*)-(−)-**22** of 70%. The lower selectivity for this reaction is presumably due to the fact that the straight-chain C-2 alkyl substituent is not as sterically demanding as a phenyl group. *trans*-Tetrahydropyridine (2*S*,6*S*)-(+)-**23** was prepared by reduction of (−)-**22** with $NaBH_4$, hydrolysis without purification with NaOH/MeOH, and treatment of the crude acid with DIC to give (+)-**23** in 74% yield for the three steps (Scheme 7).

The 4-oxy group was introduced by oxymercuration of (+)-**23** with $Hg(NO_3)_2/NaBH_4$/NaOH to give a mixture of alcohols that were not isolated but oxidized using the Dess−Martin periodinane, affording 4-oxo-*trans*-2,6-disubstituted piperidine (2*S*,6*S*)-(−)-**24** in 78% yield for the three steps (Scheme 7).[30] The *N*-Boc and benzyl protecting groups were sequentially removed with TFA and subsequent hydrogenolysis with $Pd(OH)_2-C/H_2$ gave 4-oxo-*trans*-2,6-disubstituted piperidine (2*S*,6*S*)-(−)-**25** in 76% overall yield for the two steps. Cyclization to form the quinolizidine ring was readily accomplished using $CCl_4/PPh_3/Et_3N$ to give (4*S*,10*S*)-(−)-myrtine (**18**) in 68% yield (Scheme 7). Our synthesis of (−)-**18** was accomplished in 14 steps (7 operations) with an overall yield of 17% from *β*-amino ester (+)-**19**. The alkaloid had spectral properties consistent with literature values.[8e,9a,27f]

In summary, new methodology for the asymmetric synthesis of 1,2,5,6-tetrahydropyridines, valuable chiral building blocks for the asymmetric synthesis of ring functionalized *trans*-2,6-disubstituted piperidines, has been devised. Highlights of the method include (1) the one-pot conversion of sulfinimine-derived *N*-sulfinyl *δ*-amino *β*-ketophosphonates to 3-phosphoryl dihydropyridones; (2) the stereoselective addition of organocuprates to dehydropyridones to give the *trans*-2,6-disubstituted piperidines; and (3) the one-pot dephosphorylation of the 3-phosphoryl piperidines to give the *trans*-1,2,5,6-tetrahydropyridine. The utility of this methodology was demonstrated in the synthesis of (−)-myrtine **18**.

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Experimental Section

(S_S,*R*)-(+)-Dimethyl-4-(4-methylphenylsulfinamido)-2-oxo-4-phenylbutylphosphonate (**2**)[18] and (S_S,*S*)-(+)-methyl 7-(benzyloxy)-3-(4-methylphenylsulfinamido)heptanoate (**19**)[29a] were prepared as previously described.

(*R*)-(−)-Benzyl 5-(Dimethoxyphosphoryl)-4-oxo-2-phenyl-3,4-dihydropyridine-1-carboxylate (5). In a 100-mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (S_S,*R*)-(+)-**2** (1.5 g, 3.66 mmol) in toluene (30 mL). To the solution was added DMF dimethyl acetal (5.2 mL, 36.6 mmol) by syringe at room temperature. The reaction mixture was stirred for 12 h and concentrated to give a yellow solid. To the yellow solid was added 4 N HCl (20 mL) solution, and the solution was stirred for 1 h. Then 6 N NaOH solution (12 mL) was added and neutralized to pH 7 with saturated $NaHCO_3$ solution. The solution was extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. To the residue were added THF (20 mL), Et_3N (1.53 mL, 11.0 mmol), DMAP (0.02 g), and benzyl chloroformate (1.03 mL, 7.3 mmol). The reaction mixture was stirred at room temperature for 3 h and quenched with saturated NH_4Cl (10 mL). The solution was extracted with EtOAc (3 × 40 mL), and the combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc) afforded 0.84 g (55%) of a colorless oil; $[\alpha]^{20}_D = -93.0$ (*c* 0.5, $CHCl_3$); IR (neat) 3185, 1867, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.81 (dd, J = 15.2, 1.2 Hz, 1 H), 7.38−7.28 (m, 8 H), 7.14 (m, 2 H), 5.77 (d, J = 7.2 Hz, 1 H), 5.28 (dd, J = 31.6, 12.0 Hz, 2 H), 3.71 (dd, J = 34.4, 11.6 Hz, 6 H), 3.16 (m, 1 H), 2.86 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 189.1, 152.7 (J = 18.9 Hz), 152.1, 137.5, 134.4, 129.2, 129.1, 128.9, 128.8, 128.6, 125.7, 105.7 (J = 194.4 Hz), 70.2, 56.7, 53.1 (J = 20.8, 6.2 Hz), 42.3 (J = 7.8 Hz); ^{31}P NMR ($CDCl_3$) δ 17.65; HRMS calcd for $C_{21}H_{23}NO_6P$ (M + H) 416.1263, found 416.1273.

(2*S*,6*R*)-(+)-Benzyl 3-(Dimethoxyphosphoryl)-4-hydroxy-6-phenyl-2-propyl-5,6-dihydropyridine-1-carboxylate (6b). Typical Procedure. In a 100-mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (−)-**5** (0.45 g, 1.08 mmol) in THF (20 mL), and the solution was cooled to −78 °C. In second 50-mL, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed CuI (0.825 g, 4.32 mmol) in THF (20 mL), the solution was cooled to −78 °C, and PrMgCl (2.2 mL, 2.0 M in THF, Aldrich) was added. The solution was stirred for 45 min at this temperature and was transferred via cannula via to the −78 °C solution of (−)-**9**. The reaction mixture was quenched after 0.5 h with saturated NH_4Cl (20 mL) and extracted with EtOAc (3 × 40 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc/hexane/acetic acid, 50:50:3) afforded 0.40 g (81%) of a light yellow oil; $[\alpha]^{20}_D$ +80.4 (*c* 0.8, $CHCl_3$); IR (neat) 3442, 1769, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.27 (broad, 1 H), 7.22−6.44 (m, 10 H), 5.05 (m, 1 H), 4.78 (m, 1 H), 4.67 (m, 2 H), 3.69 (m, 6 H), 2.87 (m, 1 H), 2.28 (d, J = 15.2 Hz, 1 H), 1.71 (m, 1 H), 1.42 (m, 1 H), 1.19 (m, 2 H), 0.69 (t, J = 7.2 Hz 3 H); ^{13}C NMR ($CDCl_3$) δ 201.6 (J = 42.4 Hz), 174.9, 169.6, 155.7, 143.2, 136.4, 129.1, 128.5, 128.3, 128.2, 127.8, 127.7, 127. 5, 127.4, 127.1, 126.2, 125.6, 125.3, 91.4 (J = 188.3 Hz), 67.3, 52.9, 52.4, 52.2, 38.8, 36.1 (J = 14.0 Hz), 18.9, 14.2; ^{31}P NMR ($CDCl_3$) δ 25.82, 22.01, 21.59; HRMS calcd for $C_{24}H_{31}NO_6P$ (M + H) 460.1889, found 460.1893.

(2*S*,6*R*)-(+)-Benzyl 3-(Dimethoxyphosphoryl)-4-hydroxy-2-methyl-6-phenyl-5,6-dihydropyridine-1-carboxylate (6a). Yield 50%; light yellow oil; $[\alpha]^{20}_D$ +78.8 (*c* 0.8, $CHCl_3$); IR (neat) 3423, 3310, 1745, 1698, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.6 (s, 1 H), 7.24−6.99 (m, 10 H), 5.30 (m, 1 H), 4.93 (m, 2 H), 4.72 (m, 1 H), 3.61 (m, 6 H), 3.03 (m, 1 H), 2.43 (d, 1 H), 1.35 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.0 (J = 6.8 Hz), 168.8, 155.0, 142.8, 136.5, 129.0, 128.3, 127.7, 127.1, 125.6, 125.2, 92.2 (J = 189.5 Hz), 67.6, 67.1, 55.4, 53.7, 53.2, 52.8, 52.3, 48.9, 48.1, 44.7, 35.9 (J = 14.1 Hz), 22.4, 20.8; ^{31}P NMR ($CDCl_3$) δ 25.46, 21.80; HRMS calcd for $C_{22}H_{26}NO_6PNa$ (M + Na) 454.1395, found 454.1400.

(2*S*,6*R*)-(+)-Benzyl 3-(Dimethoxyphosphoryl)-4-hydroxy-2,6-diphenyl-5,6-dihydropyridine-1-carboxylate (6c). Yield 91%; light yellow oil; $[\alpha]^{20}_D$ +139.4 (*c* 1.36, $CHCl_3$); IR (neat) 3430, 3298, 1730, 1683, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.95 (s, 1 H), 7.50−6.97 (m, 13 H), 6.73 (m, 2 H), 5.55 (m, 2 H), 4.93 (m, 1 H), 4.78 (m, 1 H), 3.62 (d, J = 11.2 Hz, 3 H), 3.27 (m, 1 H), 3.01 (d, J = 11.6 Hz, 3 H), 2.58 (d, J = 16.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 201.0 (J = 6.8 Hz), 169.2, 155.7, 143.0, 136.2, 128.7, 128.5, 127.8, 127.7, 127.4, 127.3, 125.7, 91.7 (J = 182.0 Hz), 67.5, 56.4 52.8, 51.9, 36.7; ^{31}P NMR ($CDCl_3$) δ 25.83; HRMS calcd for $C_{27}H_{28}NO_6PNa$ (M + Na) 516.1552, found 516.1562.

(2*S*,6*R*)-(+)-Benzyl 3-(Dimethoxyphosphoryl)-4-hydroxy-6-phenyl-2-propylpiperidine-1-carboxylate (8b). Typical Procedure. In a 25-mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**6b** (0.040 g, 0.087 mmol) in MeOH (10 mL). The solution was cooled to 0 °C, and $NaBH_4$ (0.02 g, 0.261 mmol) was slowly added. The reaction mixture was stirred for 0.5 h and quenched by addition of H_2O (10 mL). At this time the solution was extracted with DCM (3 × 20 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc) afforded 0.036 g (90%) of a colorless oil; $[\alpha]^{20}_D$ +47.5 (*c* 0.55, $CHCl_3$); IR (neat) 3490, 1690, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (m, 8 H), 7.01 (m, 2 H), 4.89 (m, 2 H), 4.66 (m, 1 H), 4.39 (m, 2 H), 3.77 (dd, J = 10.8, 2.8 Hz, 6 H), 2.41 (m, 2 H), 2.18 (m, 2 H), 1.72 (m, 2 H), 1.50 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.0, 141.9, 136.3, 128.1, 127.9, 127.6, 126.5, 126.0, 66.9, 65.2 (J = 5.4 Hz), 53.5 (J = 9.2 Hz), 53.0 (J = 6.8 Hz), 52.7 (J = 5.9 Hz), 41.8 (J = 137.3 Hz), 36.1 (J = 8.8 Hz), 34.7 (J = 6.2 Hz), 19.7, 13.7; ^{31}P NMR ($CDCl_3$) δ 32.15; HRMS calcd for $C_{24}H_{32}NO_6PNa$ (M + Na) 484.1865, found 484.1874.

(2*S*,6*R*)-(+)-Benzyl 3-(Dimethoxyphosphoryl)-4-hydroxy-2-methyl-6-phenylpiperidine-1-carboxylate (8a). Yield 85%; colorless oil; $[\alpha]^{20}_D$ +54.4 (*c* 0.23, $CHCl_3$); IR (neat) 3502, 3313, 1697, 1099 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29−6.98 (m, 10 H), 4.91 (m, 2 H), 4.63 (m, 2 H), 4.38 (m, 1 H), 3.78 (m, 6 H), 2.31 (m, 2 H), 2.12 (m, 1 H), 1.43 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.8, 142.4, 136.3, 128.3, 128.0, 127.8, 126.6, 125.8, 67.1, 65.0, 54.5, 53.0, 52.7, 49.1, 43.6 (J = 136.2 Hz), 37.3, 19.2; ^{31}P NMR ($CDCl_3$) δ 31.5, 29.2; HRMS calcd for $C_{22}H_{28}NO_6PNa$ (M + Na) 456.1552, found 456.1554.

(2*S*,6*R*)-(+)-Benzyl 2-propyl-6-phenyl-5,6-dihydropyridine-1-carboxylate (10b). Typical Procedure for Dephosphonylation. In a 25-mL, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and an argon inlet was placed (+)-**8b** (0.160 g, 0.348 mmol) in MeOH (5 mL). To the solution was added 6 N NaOH (5 mL), and the solution was stirred for 16 h and brought to pH < 2 by addition of 1 N HCl (25 mL). The reaction mixture was extracted with DCM (3 × 30 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in $CHCl_3$ (20 mL), and DIC (0.43 mL), 2.77 mmol) was added. The reaction mixture was heated at 60 °C in an oil bath for 8 h and concentrated. Flash chromatography (EtOAc/hexane, 10:90) afforded 0.88 g (75%) of a colorless oil; $[\alpha]^{20}_D$ +207.2 (*c* 0.9, $CHCl_3$); IR (neat) 3210, 2993, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24−7.11 (m, 8 H), 7.11−7.04 (m, 2 H), 6.01 (m, 1 H), 5.66 (m, 1 H), 5.24 (dd, J = 5.6, 1.6 Hz, 1 H), 4.97 (m, 2 H), 4.54 (m, 1 H), 2.72 (m, 1 H), 2.33 (m, 1 H), 1.86 (m, 1 H), 1.73 (m, 1 H), 1.37 (m, 2 H), 0.92 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.1, 145.2, 136.8, 130.6, 128.3, 128.1, 127.7, 126.5, 126.1, 123.0, 66.9, 55.2, 53.7, 37.9, 30.9, 19.0, 14.2; HRMS calcd for $C_{22}H_{25}NO_2Na$ (M + Na) 358.1783, found 358.1773.

(2*S*,6*R*)-(+)-Benzyl 2-methyl-6-phenyl-5,6-dihydropyridine-1-carboxylate (10a). Yield 69%; colorless oil; $[\alpha]^{20}_D$ +184.7 (*c* 0.55, $CHCl_3$); IR (neat) 3312, 2987, 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23−7.06 (m, 8 H), 7.02 (m, 2 H), 5.90 (m, 1 H), 5.56 (m, 1 H), 5.25 (m, 1 H), 4.95 (m, 2 H), 4.52 (m, 1 H), 2.72 (m, 1 H), 2.28 (m, 1 H), 1.34 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.0, 145.1, 136.9, 132.0, 128.4, 128.2, 127.7, 126.6, 126.1, 122.0, 67.0, 55.2, 49.4, 30.6, 21.4; HRMS calcd for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470, found 330.1477.

(2*S*,6*R*)-(+)-Benzyl 2-Propyl-6-phenylpiperidine-1-carboxylate (13). Typical Hydrogenation Procedure. In a 25-mL, single-necked round-bottom flask equipped with a magnetic stirring bar and rubber septum was placed (+)-**10b** (0.034 g, 0.1 mmol) and 5% Pt/C (0.015 g) in MeOH (10 mL). The solution was stirred under 1 atm of H_2 (balloon) for 0. 5 h, filtered, and concentrated. Flash chromatography (EtOAc/hexane, 10:90) afforded 0.031 g (92%) of a colorless oil; $[\alpha]^{20}_D$ +61.1 (*c* 0.36, $CHCl_3$); IR (neat) 3269, 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26−7.00 (m, 10 H), 5.07−4.95 (m, 3 H), 3.92 (m, 1 H), 2.06 (m, 2 H), 1.81−1.20 (m, 8 H), 0.84 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.5, 143.3, 137.0, 128.4, 128.3, 127.9, 127.8, 126.3, 125.9, 66.9, 55.1, 52.7, 36.9, 27.4, 23.7, 20.4, 14.6, 14.2; HRMS calcd for $C_{22}H_{27}NO_2Na$ (M + Na) 360.1940, found 360.1947.

(2*S*,6*R*)-(+)-Benzyl 2-Methyl-6-phenylpiperidine-1-carboxylate (14). Yield 91%; colorless oil; $[\alpha]^{20}_D$ +66.0 (*c* 0.22, $CHCl_3$); IR (neat) 3287, 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25−7.06 (m, 10 H), 5.04 (m, 2 H), 5.01 (m, 1 H), 4.17 (m, 1 H), 2.09 (m, 2 H), 1.73 (m, 1 H), 1.57 (m, 1 H), 1.40 (m, 2 H), 1.28 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.5, 143.6, 137.1, 128.4, 127.8, 126.3, 125.8, 66.9, 54.9, 48.1, 27.4, 26.7, 21.0, 14.1; HRMS calcd for $C_{15}H_{19}NO_2Na$ (M + Na) 332.1626, found 332.1633.

(2*S*,6*R*)-(+)-2-Propyl-6-phenylpiperidine (11). In a 25-mL, single-necked round-bottom flask equipped with a magnetic stirring bar and rubber septum was placed (+)-**13** (0.034 g, 0.1 mmol) in MeCN (10 mL). To the solution was added TMS−I (57.0 mL, 0.4 mmol), and the reaction mixture was stirred for 15 min, concentrated, and quenched with 1 N HCl (10 mL). The solution was extracted with ether (2 × 5 mL), and the aqueous phase was neutralized 3 N NaOH until a white precipitate was formed. At this time the solution was extracted with DCM (3 × 10 mL), and the combined DCM extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc) afforded 0.2 g (96%) of a colorless oil; $[\alpha]^{20}_D$ +28.1 (*c* 0.2, acetone); IR (neat) 3280, 3060, 1231, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 2 H), 7.32 (m, 2 H), 7.24 (m, 1 H), 3.96 (m, 1 H), 3.05 (m, 1 H), 2.01−1.21 (m, 11 H), 0.94 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.3, 128.5, 126.9, 54.4, 52.1, 34.8, 33.6, 29.8, 20.4, 19.9, 14.3; HRMS calcd for $C_{14}H_{22}N$ (M + H) 204.1752, found 204.1753.

(2*S*,6*R*)-(+)-2-Methyl-6-phenylpiperidine (15). Yield 95%; colorless oil; $[\alpha]^{20}_D$ +34.2 (*c* 0.3, $CHCl_3$) [lit.[25] +33.4 (*c* 1.25, $CHCl_3$)]; IR (neat) 3287, 3050, 1233, 1042 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 2 H), 7.32 (m, 2 H), 7.23 (m, 1 H), 4.05 (m, 1 H), 3.30 (m, 1 H), 1.72 (m, 6 H), 1.42 (m, 1 H), 1.22 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.3, 128.5, 126.9, 54.3, 47.5, 33.5, 31.5, 20.1, 20.0; HRMS calcd for $C_{12}H_{17}N$ (M) 175.1361, found 175.1358.

(S_S,*S*)-(+)-Diethyl 8-(Benzyloxy)-4-(4-methylphenylsulfinamido)-2-oxooctylphosphonate (20). In a 250-mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed diethyl methyl phosphonate (5.12 mL, 35.4 mmol) in THF (100 mL). The solution was cooled to −78 °C, and *n*-BuLi (2.5 M in hexane, 14.2 mL, 35.4 mmol) was slowly added via syringe. In a second 500-mL oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (+)-**19** (2.85 g, 7.07 mmol) in THF (120 mL) at −78 °C. The diethyl methyl phosphonate solution was transferred after 45 min to the −78 °C solution of (+)-**19**, and the reaction mixture was stirred for 2 h. At this time the reaction was quenched by addition of saturated NH_4Cl (30 mL), warmed to room temperature, and diluted with H_2O (10 mL). The solution was extracted with Et_2O (50 mL) and EtOAc (2 × 50 mL), and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc) gave a colorless oil, which was subjected to Kugelrohr vacuum distillation (60 °C under 2.5 mmHg) to remove the diethyl methylphosphonate, affording 3.15 g (85%) of a colorless oil; $[\alpha]^{20}_D$ +26.9 (*c* 3.3, $CHCl_3$); IR (neat) 3420, 3180, 1721, 1226 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (m, 2 H), 7.31−7.13 (m, 7 H), 4.51 (d, J = 9.2 Hz, 1 H), 4.43 (s, 2 H), 4.05 (m, 4 H), 3.61 (m, 1 H), 3.42 (t, J = 6.4 Hz, 2 H), 2.98 (d, J = 22.8 Hz, 2 H), 2.88 (q, J = 5.2, 3.2 Hz, 2 H), 2.33 (s, 3 H), 1.66−1.34 (m, 6 H), 1.25 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 201.1 (J = 6.1 Hz), 142.8, 141.5, 139.0, 129.8, 128.6, 127.9, 127.8, 125.8, 73.2, 70.4, 62.9 (J = 6.3 Hz), 52.7, 50.0, 43.4 (J = 125.2 Hz), 35.8, 29.6, 23.1, 21.6, 16.6 (J = 6.0 Hz); ^{31}P NMR ($CDCl_3$) δ 19.53; HRMS calcd for $C_{26}H_{39}NO_6PS$ (M + H) 524.2236, found 524.2239.

(*S*)-(+)-*tert*-Butyl 2-(4-(Benzyloxy)butyl)-5-(diethoxyphosphoryl)-4-oxo-3,4- dihydropyridine-1-carboxylate (21). In a 100-mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**20** (1.92 g, 3.66 mmol) in toluene (30 mL). To the solution was added DMF dimethyl acetal (5.2 mL, 36.6 mmol), and the reaction mixture was stirred for 12 h and concentrated to give a yellow solid. To the solid was added 4 N HCl (20 mL), the solution was stirred for 1 h, 6 N NaOH (12 mL) was added, and the solution was neutralized to pH >10 with saturated $NaHCO_3$ solution. The aqueous solution was extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in THF (20 mL), and TEA (1.53 mL, 11.0 mmol), DMAP (0.20 g), and benzyl chloroformate (1.03 mL, 7.3 mmol) were added. After 3 h of stirring, saturated NH_4Cl (10 mL) was added. The solution was extracted with EtOAc (3 × 40 mL), and the combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc) afforded 1.63 g (90%) of a colorless oil; $[\alpha]^{20}_D$ +31.2 (*c* 1.0, $CHCl_3$); IR (neat) 3211, 1731, 1654, 1256 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.49 (dd, J = 14.8, 1.2 Hz, 1 H), 7.36−7.24 (m, 5 H), 4.56 (m, 1 H), 4.47 (s, 2 H), 4.13 (m, 4 H), 3.42 (m, 2 H), 2.77 (m, 1 H), 2.48 (m, 1 H), 1.65−1.35 (m, 6 H), 1.53 (s, 9 H), 1.31 (q, J = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 190.5, 151.9 (J = 18.5 Hz), 150.7, 138.8, 126.7, 127.9, 127.8, 104.9 (J = 195.2 Hz), 85.3, 73.3, 70.2, 62.6, 40.2 (J = 8.9 Hz), 31.0, 29.7, 28.2, 22.8, 16.7; ^{31}P NMR ($CDCl_3$) δ 15.27; HRMS calcd for $C_{25}H_{39}NO_7P$ (M + H) 496.2464, found 496.2461.

(2*S*,6*S*)-(−)-*tert*-Butyl 6-(4-(Benzyloxy)butyl)-3-(diethoxyphosphoryl)-4-hydroxy-2-methyl-5,6-dihydropyridine-1-carboxylate (22). In a 100-mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**21** (0.496 g, 1.08 mmol) in THF (20 mL), and the solution was cooled to −78 °C. In a second 50-mL, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed CuI (0.83 g, 4.32 mmol) in THF (20 mL). The reaction mixture was cooled to −78 °C, and MeMgCl (1.4 mL, 3.0 M in THF, Aldrich) was added. The reaction mixture was stirred for 45 min and cannulated to the solution of (+)-**21**, and after 0.5 h saturated NH_4Cl (10 mL) was added. The solution was extracted with EtOAc (3 × 40 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc/hexane/acetic acid, 30:70:4) afforded 0.357 g (70%) of a light yellow oil; $[\alpha]^{20}_D$ −7.5 (*c* 0.8, $CHCl_3$); IR (neat) 3450, 1737, 1697, 1256, 1109 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.90 (s, 1 H), 7.31−7.18 (m, 5 H), 4.42 (s, 2 H), 4.41 (m, 1 H), 4.04 (m, 4 H), 3.90 (m, 1 H), 3.39 (m, 2 H), 2.60 (m, 1 H), 2.24 (m, 1 H), 1.55 (m, 3 H), 1.40 (s, 9 H), 1.30−1.17 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 202.7 (J = 6.4 Hz), 170.3, 154.6, 139.1, 128.7, 127.9, 127.8, 127.7, 92.9 (J = 187.0 Hz), 80.0, 73.3, 70.7, 62.4, 52.5, 47.5 (J = 14.2 Hz), 34.8, 32.3 (J

= 15.0 Hz), 30.0, 28.9, 23.8, 22.7, 16.5; ^{31}P NMR ($CDCl_3$) δ 24.84, 20.42, 20.32; HRMS calcd for $C_{26}H_{43}NO_7P$ (M + H) 512.2777, found 512.2803.

(2*S*,6*S*)-(+)-*tert*-Butyl 6-(4-(Benzyloxy)butyl)-2-methyl-5,6-dihydropyridine-1-carboxylate (23). In a 25-mL, oven-dried, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**22** (0.178 g, 0.348 mmol) in MeOH (10 mL). The solution was cooled to 0 °C, $NaBH_4$ (0.105 g, 1.39 mmol) was slowly added, and the reaction mixture was stirred for 0.5 h before addition of H_2O (10 mL). The solution was extracted with DCM (3 × 20 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give an oil. The oil, without further purification, was placed in a 25-mL, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and an argon inlet, and MeOH (5 mL) was added. To the solution was added 6 N NaOH (5 mL), and the mixture was stirred for 16 h. At this time the reaction mixture was brought to pH < 2 with 1 N HCl (25 mL), and the mixture was extracted with DCM (3 × 30 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. To the residue were added $CHCl_3$ (20 mL) and DIC (430 mL, 2.77 mmol), and the reaction mixture was refluxed at 60 °C for 8 h. Concentration and flash chromatography (EtOAc/hexane, 10:90) afforded 0.088 g (74%) of a colorless oil; $[\alpha]^{20}_D$ +55.0 (*c* 0.5, $CHCl_3$); IR (neat) 3310, 2210, 1700, 1231 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34−7.26 (m, 5 H), 5.72 (m, 2 H), 4.49 (s, 2 H), 4.13 (m, 1 H), 4.00 (m, 1 H), 3.45 (t, *J* = 6.8 Hz, 2 H), 2.26 (m, 1 H), 2.08 (m, 1 H), 1.60 (m, 2 H), 1.50 (m, 2 H), 1.47 (s, 9 H), 1.31 (m, 2 H), 1.27 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.1, 139.3, 132.2, 128.9, 128.1, 128.0, 122.7, 79.8, 73.4, 70.9, 52.1, 48.7, 33.9, 30.3, 29.1, 27.4, 24.3, 22.1; HRMS calcd for $C_{22}H_{33}NO_3Na$ (M + Na) 382.2358, found 382.2365.

(2*S*,6*S*)-(−)-*tert*-Butyl 2-(4-(Benzyloxy)butyl)-6-methyl-4-oxopiperidine-1-carboxylate (24). In a 10-mL round-bottom flask fitted with a magnetic stirring bar were placed mercuric nitrate (0.210 g, 0.612 mmol) in THF (0.5 mL) and H_2O (1.0 mL). In one portion was added (+)-**23** (0.200 g, 0.556 mmol) in THF (0.5 mL). The reaction mixture was stirred for 10 min at room temperature, and NaOH solution (6 M, 1 mL) was added, followed by $NaBH_4$ solution (0.5 M in 3 M NaOH, 1 mL). At this time, EtOAc (5 mL) and solid NaCl were added, the solid mercury was allowed to settle, and the organic phase was separated, dried ($MgSO_4$), and concentrated. The crude oil, without further purification, was placed in a 25-mL round-bottom flask equipped with a magnetic stirring bar, and DCM (5 mL) was added. Dess−Martin periodinane (0.3 M in DCM, 0.69 mL, 0.334 mmol) was added, the reaction mixture was stirred for 2 h, and saturated $Na_2S_2O_3$ (10 mL) solution was added. The solution was extracted with ether (3 × 10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc/hexane, 20:80) afforded 0.165 g (78%) of a colorless oil; $[\alpha]^{20}_D$ −85.0 (*c* 1.2, $CHCl_3$); IR (neat) 3320, 1789, 1720, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34−7.26 (m, 5 H), 4.47 (s, 2 H), 4.34 (m, 1 H), 4.15 (m, 1 H), 3.44 (t, *J* = 6.0 Hz, 2 H), 2.75 (m, 2 H), 2.53 (m, 1 H), 2.35 (m, 1 H), 1.75 (m, 2 H), 1.60 (m, 2 H), 1.48 (s, 9 H), 1.35 (m, 2 H), 1.25 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.2, 154.9, 138.9, 128.7, 127.9, 127.8, 80.3, 73.2, 70.4, 51.4, 46.9, 44.9, 41.6, 37.3, 29.9, 28.8, 23.8, 23.0; HRMS calcd for $C_{22}H_{33}NO_4Li$ (M + Li) 382.2570, found 382.2555.

(2*S*,6*S*)-(−)-2-(4-Hydroxybutyl)-6-methylpiperidin-4-one (25). In a 25-mL oven-dried round-bottom flask equipped with a magnetic stirring bar, rubber septum, and an argon inlet was placed (−)-**24** (0.075 g, 0.2 mmol) in DCM (5 mL). The solution was cooled to 0 °C, TFA (1.5 mL) was added, and the reaction mixture was stirred at room temperature for 45 min. At this time the solution was concentrated, and the salt was placed in a second 25-mL, one-necked round-bottom flask equipped with a magnetic stirring bar and rubber septum. To the solution were added $Pd(OH)_2$ (20 mg, 20% on carbon) and 2 drops of TFA in THF (5 mL), and the reaction mixture was stirred at room temperature for 3 h under an atmosphere of H_2. At this time saturated $NaHCO_3$ (5 mL) was added, the solution was extracted with EtOAc (3 × 10 mL), and the organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (MeOH/DCM, 10:90) afforded 0.029 g (85%) of a colorless oil; $[\alpha]^{20}_D$ −14.0 (*c* 0.3, $CHCl_3$); IR (neat) 3485, 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.65 (t, *J* = 6.8 Hz, 2 H), 3.46 (m, 1 H), 3.35 (m, 1 H), 2.51 (m, 2 H), 2.18 (m, 2 H), 2.00 (br, 2 H), 1.61−1.38 (m, 6 H), 1.17 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.7, 62.9, 53.0, 49.7, 48.2, 47.9, 34.6, 32.7, 22.6, 21.7; HRMS calcd for $C_{10}H_{20}NO_2$ (M + H) 186.1494, found 186.1493.

(4*S*,10*S*)-(−)-Myrtine (18). In a 25-mL, one-necked, round-bottomed flask fitted with magnetic stirring bar, rubber septum, and argon balloon were placed (−)-**25** (0.036 g, 0.19 mmol) in MeCN (3 mL). A solution of Et_3N (0.028 mL, 0.20 mmol) in CCl_4 (0.028 mL, 0.29 mmol) was added, and the solution was cooled to 0 °C. At this time triphenylphosphine (0.047 g, 0.18 mmol) was added, and the reaction mixture was stirred for 45 min, warmed to room temperature, and stirred for 20 h. To the reaction mixture was added saturated $NaHCO_3$ (5 mL), and the solution was extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc) gave 0.022 g (68%) of an oil; $[\alpha]^{20}_D$ −12.5 (*c* 0.4, $CHCl_3$) [lit.[26c] +11.3 (*c* 2.7, $CHCl_3$) and lit.[9a] +19.3 (*c* 1.85, $CHCl_3$)] for its enantiomer); IR (neat) 2801, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.40 (m, 1 H), 2.92−2.74 (m, 2 H), 2.65 (m, 1 H), 2.49 (t, *J* = 12.0, 3.6 Hz, 1 H), 2.32−2.15 (m, 3 H), 1.91−1.56 (m, 4 H), 1.48−1.17 (m, 2 H), 0.97 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.5, 57.2, 53.6, 51.5, 48.7, 48.0, 34.3, 25.9, 23.4, 11.2; HRMS calcd for $C_{10}H_{18}NO$ (M + H) 168.1389, found 168.1389.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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