# Enzymatic Route to Chiral, Nonracemic *cis*-2,6- and *cis,cis*-2,4,6-Substituted Piperidines. Synthesis of (+)-Dihydropinidine and Dendrobate Alkaloid (+)-241D

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Piperidine-based compounds are an important class of natural alkaloids found in plants, insects, and amphibians. A general asymmetric synthesis of 2-alkyl-6-methylpiperidines is presented via the enzymatic desymmetrization of *meso cis*-2,6- and *cis,cis*-2,4,6-substituted piperidines with *Aspergillus niger* lipase (ANL). The enzymatic reaction proceeds in excellent chemical yield and high enantiotopic selectivity (ee ≥ 98%). The general method is used to effect the synthesis of (+)-dihydropinidine−HCl as well as the first asymmetric synthesis of dendrobate alkaloid (+)-241D.

Piperidine compounds constitute an important class of naturally occurring alkaloids found in plants and insects.[1] In addition, a handful of monocyclic, piperidine-based alkaloids as well as numerous bicyclic ones have been identified in dendrobate frogs.[2] What is remarkable about these alkaloids is the preponderance of 2,6-disubstitution, many times in the cis configuration, on the piperidine ring. Pinidine (**1**) is a well-known *cis*-piperidine compound found in several species of the family Pinaceae.[3] An often associated compound, dihydropinidine (**2**) has recently been isolated from the Mexican bean beetle, *Epilachna varivestis*, as a minor constituent.[4] Many *cis*-2,6-piperidine alkaloids **3** have been found in the venom of fire ants of the genus *Solenopsis*.[5] The four monocyclic piperidines isolated from the skins of poison-dart, dendrobate frogs all contain 2,6-disubstitution. The most well-known of these, *cis,cis*-2-*n*-nonyl-6-methyl-4-hydroxypiperidine 241D (**4**), has recently been synthesized in its racemic form.[6] Among the many bicyclic alkaloids containing a piperidine ring, the indolizidine, monomorine I (**5**), and decahydroquinoline *cis*-195A (**6**) are representative[2c,7] (Figure 1).

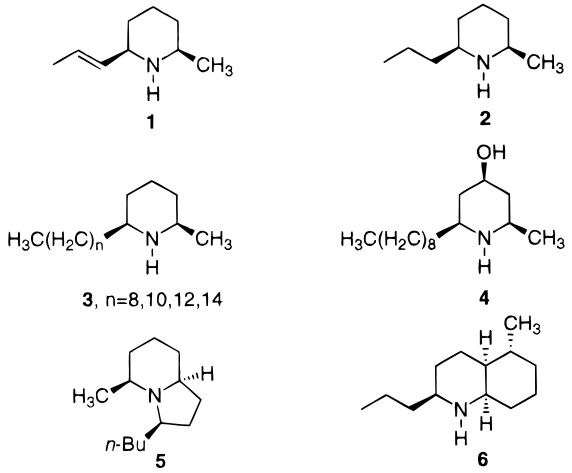


**Figure 1.**

The interest in these compounds is well displayed by the wealth of published material detailing their sources, biological activities, and syntheses. Pinidine has been shown to be a powerful teratogen.[3] Numerous studies have outlined the wide range of activities (necrotoxic, hemolytic, phytotoxic, insecticidal, antibacterial, and antifungal) that the 2-alkyl-6-methylpiperidines of fire ant venom possess.[1b] Racemic piperidine 241D (**4**) has been found to block the action of acetylcholine by a noncompetitive blockade of the nicotinic receptor-channel complex as well as blocking the binding of [$^3$H]perhydrohistrionicotoxin.[8] The bicyclic indolizidines and decahydroquinolines show extensive physiological activities.[2c,7]

These alkaloids have been the object of intensive synthetic efforts resulting in a variety of racemic and asymmetric syntheses.[1b,6,7,9] We report here the first total, asymmetric synthesis of (+)-241D (**4**). Building on previous work,[10] the enzymatic desymmetrization of *meso cis*-2,6-disubstituted piperidines with *Aspergillus niger* lipase (ANL) was extended to *meso cis,cis*-2,4,6-trisubstituted piperidines, thus opening the way to the synthesis of enantiopure (+)-piperidine 241D ((+)-**4**). In addition, the synthesis of (+)-dihydropinidine hydrochloride ((+)-**2**−HCl) by the same chemoenzymatic method displays the generality of this technique.

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

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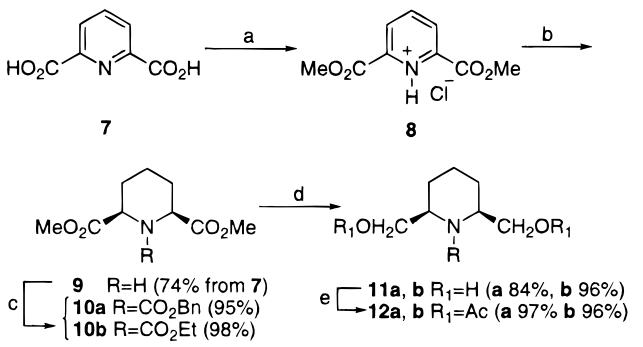
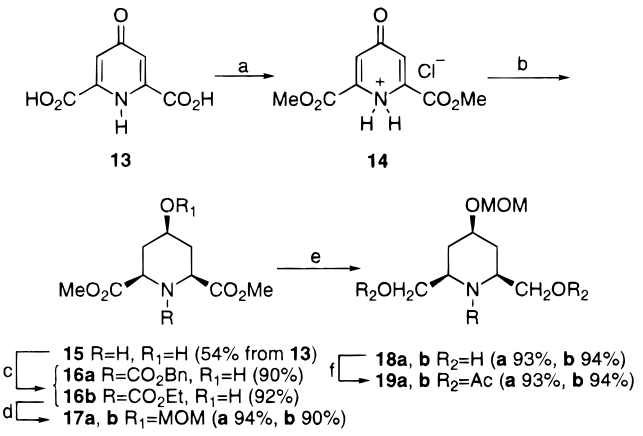
**Scheme 1**[a]




[a] Reaction conditions: (a) MeOH, 2,2-dimethoxypropane, 12 N HCl; (b) (i) $H_2$, (ii) $K_2CO_3$; (c) $BnO_2CCl$ or $EtO_2CCl$; (d) $LiBH_4$; (e) $Ac_2O$.

**Scheme 2**[a]




[a] Reaction conditions: (a) MeOH, 2,2-dimethoxypropane, 12 N HCl; (b) (i) $H_2$, (ii) $K_2CO_3$; (c) $BnO_2CCl$ or $EtO_2CCl$; (d) MOM−Cl; (e) $LiBH_4$; (f) $Ac_2O$.

## Results and Discussion

**Substrate Preparation.** In a previous paper, we outlined a simple and rapid method for the preparation of meso *cis*-2,6-piperidines.[10] Unfortunately, we have since discovered that this method leads to a mixture of cis:trans isomers (~8:1) which are inseparable by standard chromatographic techniques. This forced the development of a different route to the required meso piperidines. Though this new method is longer by one step, the overall yield of the substrates is significantly higher than for the former preparation.

Esterification of pyridine-2,6-dicarboxylic acid (**7**) in absolute MeOH, 2,2-dimethoxypropane and 12 N HCl gave the diester hydrochloride **8** (Scheme 1). The crude pyridine salt was hydrogenated in $H_2O$ over palladium on carbon, and after filtration of the catalyst, the free piperidine **9** was generated by the addition of solid $K_2CO_3$. This amino diester was recrystallized in hexane before further use to ensure the complete absence of any contamination by the trans isomer. Protection of the amine with the appropriate carboalkoxy chloride yielded **10**, which was reduced with $LiBH_4$ to give the diol **11**. Acetylation with acetic anhydride afforded the diacetate **12**.

The synthesis of the *meso cis*,*cis*-2,4,6-piperidine substrates followed a route similar to that of the 2,6-piperidines (Scheme 2). Esterification of chelidamic acid (**13**) under the same conditions as for **7** produced the diester **14**. Hydrogenation of the crude amine hydrochloride in $H_2O$ over rhodium on alumina[11] followed by liberation of the amine with $K_2CO_3$ gave the amino alcohol **15** which was recrystallized before further use to ensure cis,cis purity. The yield of **15** was moderate (54% from **13**) because of losses due to hydrogenolysis of the C−O bond at position 4, but no attempt was made to improve the yield, since Dreiding's study reported that the above hydrogenation conditions were the best possible.[11] Protection of the amine with the appropriate carboalkoxy chloride gave **16**, and protection of the alcohol as the MOM ether yielded the diester **17**. Reduction of this diester with $LiBH_4$ gave the diol **18** which was acetylated to afford the diacetate **19**.

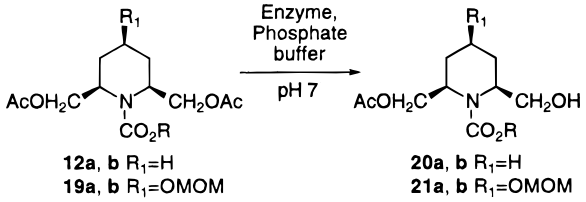
**Enzymatic Desymmetrization.** Initially, a wide range of lipases and proteases were screened for activity with the *meso cis*-piperidine substrates. All tested enzymes in a variety of aqueous reaction conditions showed no or very little hydrolytic activity in the presence of diesters **10** and **17**. The enzymatic acetylation of diols **11** and **18** in organic solvent was more successful, but poor yields of monoacetate and competitive conversion to diacetate rendered this technique of little value. However, the reverse reaction, enzymatic hydrolysis of the diacetates **12** and **19**, gave good to excellent results in terms of both chemical yield and enantioselectivity (Table 1). Three enzymes consistently hydrolyzed the four acetates. Pig liver esterase (PLE) hydrolyzed the acetates relatively quickly, but the chemical yields of monoacetates **20** and **21** were negligible to poor. Hydrolysis in the presence of wheat germ lipase (WGL) provided monoacetates of good enantiomeric purity (71−93%) but only moderate chemical yield (30−58%). *Aspergillus niger* lipase (ANL) in the presence of 7% $CH_3CN$ gave very high enantiomeric excess values (ee ≥ 98%) and good to excellent chemical yields (76−92%).

The first set of experiments with ANL were conducted in pure phosphate buffer at pH 7. However, within 18−24 h the growth of a bacillus in the medium (observed by microscopic analysis) made the reaction difficult to monitor and necessitated the addition of more enzyme to complete the reaction. It was found that by adding 7% $CH_3CN$ to the reaction, the growth of the bacillus (probably a spore contaminant in the bought enzyme) was suppressed. This had the effect of slowing the reaction, but both chemical yield and enantioselectivity were improved. The enantiopurities of all the monoacetates were determined by formation of Mosher's ester and analysis of the diastereomeric composition with $^{19}F$ NMR.

**Absolute Configuration.** Since the absolute configuration of the monoacetate **20a** produced by the action of ANL on **12a** is known,[10] the absolute configuration of **20b** from ANL hydrolysis was not difficult to ascertain. The *N*-carbobenzoxy monoacetate **20a** was mesylated under standard conditions to give the unstable acetate **22a** (Scheme 3). Addition of 0.5 N NaOH to a solution of **22a** in THF and MeOH hydrolyzed the acetate and provoked concomitant, intramolecular attack on the carbonyl of the carbamate by the newly formed hydroxy group to form the oxazolidinone **23** in 73% yield. The moderate yield of **23** was due to an interesting secondary reaction. The alcohol was found to also attack the methylene carbon of the 2-substituent, thereby displacing the mesylate to give a *meso N*-carbobenzoxy bicyclic ether in 20% yield. This sequence of reactions was repeated

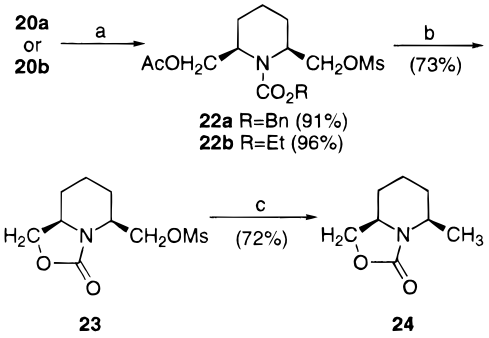
(11) Dreiding, A. S.; Hermann, K. *Helv. Chim. Acta* **1976**, *59*, 626.

**Table 1. Enzymatic Desymmetrization of Diacetates 12 and 19**



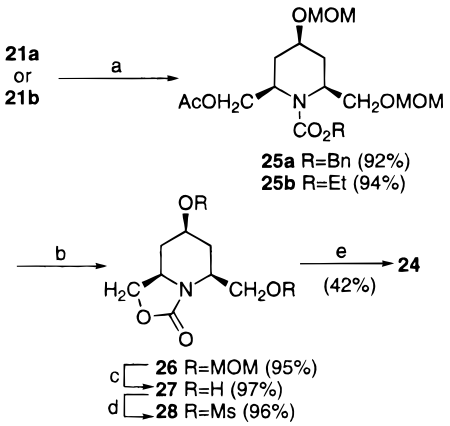

| | time (h) (1 equiv, hydrolysis) | | | | yield (% monoOAc) | | | | sign of optical rotation, % ee (Mosher ester) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **12** | | **19** | | **20** | | **21** | | **20** | | **21** | |
| enzyme | **a** R = Bn | **b** R = Et | **a** R = Bn | **b** R = Et | **a** R = Bn | **b** R = Et | **a** R = Bn | **b** R = Et | **a** R = Bn | **b** R = Et | **a** R = Bn | **b** R = Et |
| PLE | 1.5 | 3 | 2 | 16 | <5 | 38 | 19 | 46 | | (+) 25 | (−) 83 | (−) 77 |
| WGL | 40 | 9 | 31 | 24 | 43 | 58 | 30 | 55 | (+) 81 | (−) 71 | (−) 93 | (−) 89 |
| ANL | 50 | 24 | 46 | 39 | 73 | 85 | 71 | 74 | (+) 95 | (−) 92 | (−) 91 | (−) 92 |
| ANL (7% $CH_3CN$) | 108 | 72 | 102 | 95 | 82 | 92 | 76 | 82 | (+) ≥98 | (−) ≥98 | (−) ≥98 | (−) ≥98 |

**Scheme 3**[a]




[a] Reaction conditions: (a) Ms-Cl; (b) 0.5 N NaOH; (c) $NaBH_4$.

**Scheme 4**[a]




[a] Reaction conditions: (a) MOM−Cl; (b) 0.5 N NaOH; (c) MeOH, 12 N HCl; (d) Ms−Cl; (e) $NaBH_4$.

for the *N*-carbethoxy monoacetate **20b**, obtained from ANL hydrolysis, to yield **23** which was identical to **23** (from **20a**) in all respects including the same sign for their optical rotations. Therefore, the monoacetate **20b** was found to have the same absolute configuration as **20a**, 2(*R*)-(acetoxymethyl)-6(*S*)-(hydroxymethyl).

The absolute configurations of the monoacetates **21a,b** were more difficult to determine, because of the absence of *cis,cis*-2,4,6-piperidines of known configuration. However, it was realized that if the relative positions of the acetate and alcohol could be discovered then the absolute configuration of the compound would be known, since the 4-substituent is cis.[11] Thus, the reduction of the methoxy methyloxy group to hydrogen was deemed necessary in order to relate the reduced compound to a known *cis*-2,6-piperidine. After much effort directed toward reducing the −OMOM group without affecting the rest of the molecule, it was decided to follow the cyclization tendencies of these *N*-carboalkoxy monoacetates.

The hydroxy group of monoacetate **21a** was protected with methyl chloromethyl ether to give **25a**, which was hydrolyzed and cyclized to afford **26** (Scheme 4). Regeneration of the two MOM-protected alcohols gave **27**, which was reacted with methanesulfonyl chloride to yield the dimesylate **28**. Reduction of **28** with $NaBH_4$ in DMSO at 120 °C gave the desired oxazolidinone **24**. This compound was found to be identical in all respects to the product obtained by the $NaBH_4$ reduction of monomesylate **23** in DMSO at 80 °C (Scheme 3). Therefore, the absolute configuration of **21a** from ANL hydrolysis was determined to be 2(*R*)-(acetoxymethyl)-4(*S*)-[(methoxymethyl)oxy]-6(*S*)-(hydroxymethyl). The absolute configuration of **21b** was found to be the same by synthesizing **25b** and then **26** and relating its optical rotation to that of **26** (from **21a**).

**Synthesis of Piperidine Alkaloids (+)-2-HCl and (+)-4.** In order to demonstrate the utility of the enzymatic desymmetrization of *meso* piperidines, the synthesis of natural piperidine alkaloids was begun using monoacetates **20** and **21**. Initially, much experimentation was conducted in the hope of either reducing the 6-(hydroxymethyl) group to 6-methyl and transforming the acetoxy group to a long-chain alkyl or the opposite sequence of hydroxymethyl to long-chain alkyl and acetoxymethyl to methyl. However, it was found that most such efforts led to cyclization and the formation of oxazolidinones. Two cases in point are demonstrative: Any basic, protic solvent system will effect cyclization to the oxazolidinone of a *N*-carbalkoxy 2- or 6-(hydroxy(or acetoxy-)methyl) piperidine.[12] Also, any *N*-carbalkoxypiperidine with a 2- or 6-substituent in the form of $-CH_2R$, where R is a leaving group, is inherently unstable. This is due to carbamate carbonyl attack on the aforementioned $CH_2$ to give a resonance-stabilized oxonium ion which will degrade to the oxazolidinone on addition of any relatively acid substance (e.g., $H_2O$). Alternatively, Momose *et al.*[13] reported the reduction of a *N*-carbomethoxy-2-(hydroxymethyl)piperidine to 2-methylpiperidine by Swern oxidation of the alcohol to give the aldehyde which was transformed to a dithiane and then

(12) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.
(13) Momose, T.; Toyooka, N.; Hirai, Y. *Chem. Lett.* **1990**, 1319.

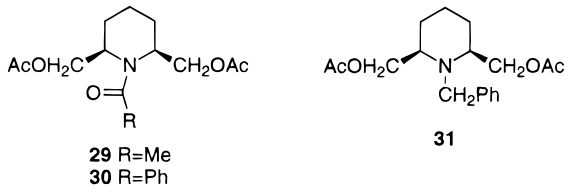
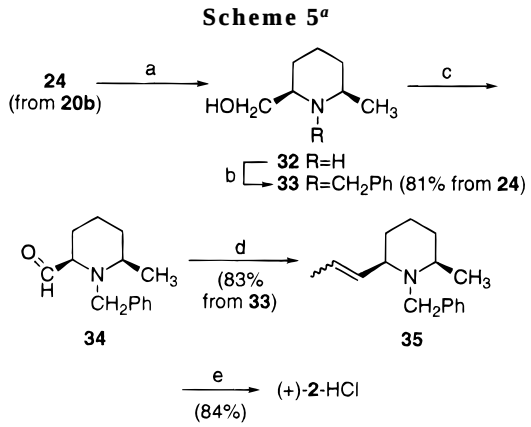



**Figure 2.**

**Scheme 5**[a]




[a] Reaction conditions: (a) 1 N KOH; (b) $PhCH_2Br$; (c) Swern; (d) Wittig; (e) $H_2$.

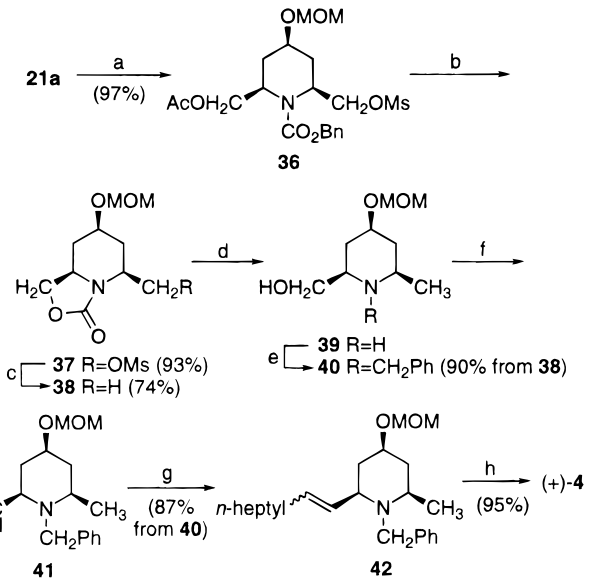
desulfurized with Raney nickel. Unfortunately, our attempts to repeat this synthetic sequence with **20b** met with limited success.

As a result of these problems, a brief study was undertaken of the effect other N-protecting groups on the enzymatic desymmetrization of *cis*-2,6-piperidines.

Substrates **29**, **30** and **31** (Figure 2) were prepared following standard procedures and subjected to enzymatic hydrolysis with ANL in phosphate buffer/7% $CH_3CN$. Activity was observed with all three substrates, but the results were disappointing. The chemical yields of the monoacetates were moderate (47%−62%), and more seriously, the best ee was only 22%. Thus, returning to the monoacetates **20** and **21**, the syntheses of (+)-dihydropinidine hydrochloride and (+)-241D were pursued via the oxazolidinone.

From the monoacetate **20b**, (+)-**2**−HCl was obtained in eight steps. The *N*-carbethoxy monoacetate **20b** was chosen for this synthesis over the *N*-carbobenzoxy analog **20a** because of the higher overall yield of **20b** from **7** (61% versus 47% for **20a**) and the need for only two flash-chromatographic columns during the synthetic sequence **7** to **20b**. Thus, **20b** was transformed to **24** in three steps as already described earlier. The oxazolidinone ring of **24** was opened by the action of 1 N KOH in MeOH at reflux to give the amino alcohol **32** which was transformed without purification to the *N*-benzylamino alcohol **33** (Scheme 5). In order to verify that no racemization had occured from **20b** to **33**, the Mosher esters of enantiopure **33** and racemic **33** were prepared and compared using $^1H$ NMR. (The $CH_2$ group α to the ester showed excellent diastereotopicity.) The ee of enantiopure **33** was found to be ≥98%. Swern oxidation of **33** gave the highly unstable aldehyde **34**, which, after workup, was immediately added to the already prepared ethyl Wittig ylide to afford the olefin **35** in a mixture of cis:trans isomers (∼9:1). No special effort was made to completely isolate the two isomers, since the next step was the hydrogenation of the olefin and removal of the *N*-benzyl group using Pearlman's catalyst in acidic EtOH

**Scheme 6**[a]




[a] Reaction conditions: (a) Ms−Cl; (b) 0.5 N NaOH; (c) $NaBH_4$; (d) 1 N KOH; (e) $PhCH_2Br$; (f) Swern; (g) Wittig; (h) (i) $H_2$, (ii) $K_2CO_3$.

to yield (+)-**2**−HCl quantitatively from **35**. An analytical sample of (+)-**2**−HCl was prepared by recrystallization from absolute EtOH/EtOAc, and its spectral data ($^1H$ and $^{13}C$ NMR) were found to be identical to literature values [$[\alpha]^{25}_D = +13.3$ (*c* 1.14, EtOH) (lit.[14] $[\alpha]^{25}_D = +12.8$ (*c* 1.07, EtOH))]. Thus, enantiopure (+)-dihydropinidine−HCl was synthesized from pyridine-2,6-dicarboxylic acid (**7**) in 14 steps with an overall yield of 21%.

The synthesis of (+)-**4** from the monoacetate **21a** was completed in eight steps via a similar synthetic pathway (Scheme 6). Methanesulfonyl chloride was reacted with monoacetate **21a** to give mesylate **36**. Because of its instability, **36** was immediately cyclized to the oxazolidinone **37**. This reaction proceeded in high yield without the formation of the meso ether analogous to those observed during the reactions of **22a** and **22b**. Steric hindrance by the *cis*-4-methoxy methyl ether was evoked to explain this effect. The mesylate **37** was reduced by nucleophilic substitution with $NaBH_4$ in DMSO at 80 °C to yield the oxazolidinone **38** which was opened by 1 N KOH in refluxing MeOH to afford the amino alcohol **39**. This was followed by benzylation of crude **39** to give the alcohol **40**. In order to verify the enantiopurity of **40**, the Mosher esters of enantiopure **40** and racemic **40** were prepared and compared using $^1H$ NMR. (Once again, the $CH_2$ group α to the ester showed excellent diastereotopicity.) The ee of enantiopure **40** was found to be ≥98%. Swern oxidation of **40** gave the highly unstable aldehyde **41**, which was added to the *n*-octyl Wittig ylide immediately after workup, and olefin **42** was obtained as a mixture of cis:trans isomers (∼10:1) in 87% yield from **40**. The final synthetic step was accomplished by hydrogenation of olefin **42** in acidic EtOH with Pearlman's catalyst. This reaction removed both O- and N-protecting groups as well as hydrogenating the double bond in near-quantitative yield to afford (+)-**4**−HCl. Recrystallization from absolute EtOH/EtOAc gave a pure analytical sample of (+)-**4**−HCl as white needles [$[\alpha]^{25}_D = +15.8$ (*c* 1.30, EtOH)]. Liberation of the amine with $Na_2CO_3$ yielded

(14) Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569.

(+)-**4** which was recrystallized from EtOAc. The spectral data for (+)-**4** ($^1$H NMR and mass spectrum) were found to be identical to the literature,[2a] but our value for the optical rotation of (+)-**4** [$[\alpha]^{25}_D = +6.5$ (*c* 2.0, MeOH)] was much lower than the literature value [lit.[2a] $[\alpha]^{25}_D = +39$ (*c* 0.2, MeOH)]. This can be attributed to the fact that Edwards *et al.* measured their optical rotation with less than 1 mg of column-purified product,[2a] whereas we used 40 mg of recrystallized (+)-**4**. Therefore, enantiopure piperidine alkaloid (+)-241D was synthesized from chelidamic acid **13** in an overall yield of 14%.

Two naturally-occurring piperidine alkaloids have been asymmetrically synthesized from nonracemic, commercially available compounds. One of these alkaloids, (+)-241D [(+)-**4**], has been synthesized in enantiopure form for the first time. The key reaction step, the enzymatic desymmetrization of *meso* piperidines, has opened the way to a general synthesis of any *cis*-2,6-dialkyl- or *cis*-2,6-dialkyl-*cis*-4-hydroxypiperidine. The synthesis of other monocyclic and bicyclic piperidine-based alkaloids via this enzymatic step is currently in progress.

## Experimental Section

**General.** Type I lipase from wheat germ (WGL) and esterase from porcine liver (PLE) were purchased from Sigma Chemical Co. Lipase from *Aspergillus niger* (ANL) was obtained from Fluka Chemical Corp. (catalogue no. 62301). All enzymes were used without further purification. All enzymatic hydrolytic desymmetrizations were carried out in phosphate buffer at pH 7 prepared by mixing 50 mL of 0.1 M potassium dihydrogen phosphate, 29.1 mL of 0.1 M sodium hydroxide (NaOH), and 20.9 mL of distilled water. The enzymatic reactions were followed by measurement of the pH with a glass electrode and titration with 0.1 M NaOH to maintain the pH at 7.

All extractions were done with undistilled, reagent grade solvents and dried with $MgSO_4$. Evaporations were performed with a rotary evaporator. Column purifications were conducted by flash chromatography (FC) on silica gel 60 (230−400 mesh), and the FC solvents, petroleum ether 35−60 (PE) and ethyl acetate (EtOAc), were distilled before use. Anhydrous solvents were distilled under nitrogen:THF and benzene from sodium wire/benzophenone and $CH_2Cl_2$ and $CH_3CN$ from $CaH_2$. Anhydrous DMSO was distilled under vacuum from $CaH_2$ and stored over 4 Å molecular sieves. Diisopropylethylamine (DiPEA), $Et_3N$, and pyridine were distilled from KOH and stored over KOH in brown bottles.

Proton (300 and 400 MHz), $^{13}$C (75.47 and 100.61 MHz), and $^{19}$F (282.41 MHz) magnetic resonance experiments were performed in $CDCl_3$ or $CD_3OD$.

**2,6-Bis(methoxycarbonyl)pyridine Hydrochloride (8).** To a suspension of 2,6-pyridinedicarboxylic acid (**7**, 19.9 g, 119.08 mmol) in 400 mL of absolute MeOH was added 160 mL of 2,2-dimethoxypropane (1.301 mol) and 15 mL of concentrated HCl (180 mmol HCl). The mixture was refluxed for 4 h under a $CaCl_2$ drying tube. Following reflux, the temperature was allowed to go to rt, and the reaction was stirred overnight. After evaporation of the solvents and the addition of anhydrous ether (100 mL), the insoluble hydrochloride was filtered to give 23.25 g of crude **8**. The crude product could be used "as is" for the next step. An analytical sample of the free pyridine of **8** was obtained as follows: 150 mg of crude **8** was suspended in 50 mL of $CH_2Cl_2$/20 mL of 5% $NaHCO_3$ solution and stirred for 10 min. The free pyridine was extracted three times with $CH_2Cl_2$, and the $CH_2Cl_2$ was dried and evaporated. FC was performed using 25% EtOAc/75% PE to 50% EtOAc/50% PE to yield 122 mg of the free pyridine of **8** which was recrystallized from hexane to give 98 mg of pure **8** as the free pyridine: mp 120.5−121.0 °C; IR (KBr) $\upsilon$ 3420, 3055, 2960, 1735 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.22 (d, $J$ = 7.81 Hz, 2H), 7.96 (t, $J$ = 7.81 Hz, 1H), 3.93 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.0, 148.2, 138.3, 128.0, 53.1. Anal. Calcd for $C_9H_9NO_4$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.49; H, 4.66; N, 7.19.

***cis*-2,6-Bis(methoxycarbonyl)piperidine (9).** To a suspension of crude **8** (23.08 g, 99.64 mmol) in freshly degassed $H_2O$ (125 mL) was added 460 mg of 10% Pd/C. Hydrogenation was performed at 45 psi for 15 h at rt. After filtration of the mixture through a pad of Celite, $Na_2CO_3$ (15.8 g, 149.5 mmol) and 300 mL of EtOAc were added, and the mixture was stirred at 0 °C for 10 min. Saturation of the $H_2O$ with NaCl was followed by three extractions with EtOAc which on drying and evaporation yielded 19.2 g of crude **9**. Recrystallization of **9** from hexane to eliminate any trace of contamination by the trans isomer gave 17.8 g (74% from **7**) of pure *cis*-**9**: mp 91.5−92.5 °C; IR (KBr) $\upsilon$ 3338, 3010, 2978−2800, 1760 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.55 (s, 6H), 3.21 (dd, $J_1$ = 11.3 Hz, $J_2$ = 2.56 Hz, 2H), 2.25 (br s, 1H), 1.86−1.77 (m, 3H), 1.40−1.15 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 172.5, 58.0, 51.6, 28.3, 23.8. Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.82; H, 7.67; N, 7.01.

**General Procedure for N-Protection of Amino Diester 9.** Dry THF (100 mL) was freshly distilled into a round-bottomed flask containing 40 mmol of **9**, and a dry $N_2$ atmosphere was established. After the solution was cooled to 0 °C, 1.3 equiv of DiPEA followed by 1.2 equiv of the appropriate carboalkoxy chloride were added. The ice bath was immediately removed, and the reaction was stirred for 4 h at rt. The mixture was then poured into 200 mL of ether/50 mL of 3 N HCl and extracted two times with ether. The solvents were dried and evaporated.

***N*-Carbobenzoxy-*cis*-2,6-bis(methoxycarbonyl)piperidine (10a).** Purification of the crude product by FC (10% EtOAc/90% PE to 25% EtOAc/75% PE) gave a 95% yield of **10a** as an oil: IR (neat) $\upsilon$ 3080−3020, 2942−2840, 1735, 1700 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.37−7.29 (m, 5H), 5.20 (br d, 2H), 4.90 (br s, 2H), 3.67 (s, 6H), 2.16 (br d, 2H), 1.85−1.54 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.5, 155.9, 136.2, 128.3, 127.9, 127.7, 67.8, 52.4, 52.1, 25.6, 16.5.

***N*-Carbethoxy-*cis*-2,6-bis(methoxycarbonyl)piperidine (10b).** Purification of the crude product by crystallization from pentane provided a 98% yield of **10b** as white cubes: mp 47.5−48.5 °C; IR (KBr) $\upsilon$ 2960−2825, 1745, 1705 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.92−4.75 (br d, 2H), 4.17 (br s, 2H), 3.65 (s, 6H), 2.17−2.10 (m, 2H), 1.77−1.50 (m, 4H), 1.23 (t, $J$ = 7.15 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.8, 156.2, 62.1, 52.2, 51.9, 25.6, 16.5, 14.5. Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 53.12; H, 7.14; N, 5.34.

**General Procedure for Reduction of Carbamate Diesters 10 and 17.** To a 0 °C solution of **10** or **17** (30−40 mmol) in 200 mL of anhydrous THF under a $N_2$ atmosphere was added 4 equiv of $LIBH_4$. The ice bath was immediately removed, and the reaction was stirred for 5 h. On completion of the reaction, the solution was poured into a stirred mixture of 300 mL of EtOAc/100 mL of 5% $NaHCO_3$/solid $NaHCO_3$ (attention: violent foaming) and stirred vigorously for 5 min. After saturation of the aqueous phase with NaCl, the mixture was extracted four times with EtOAc and the organic solvents were dried.

***N*-Carbobenzoxy-*cis*-2,6-bis(hydroxymethyl)piperidine (11a).** FC beginning with 50% EtOAc/50% PE and progressing to pure EtOAc gave the diol **11a** in 84% yield. An analytical sample was prepared by crystallization from ether to give **11a** as white plates: mp 85.0−86.5 °C; IR (KBr) $\upsilon$ 3400, 3060−3040, 2980−2835, 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.36−7.30 (m, 5H), 5.16 (s, 2H), 4.50−4.42 (m, 2H), 3.62 (d, $J$ = 7.98 Hz, 4H), 3.43 (s, 2H), 1.63−1.45 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.2, 136.7, 128.5, 127.9, 127.7, 67.5, 64.5, 51.2, 24.5, 15.1. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.57; H, 7.69; N, 5.01.

***N*-Carbethoxy-*cis*-2,6-bis(hydroxymethyl)piperidine (11b).** FC of the crude diol with 75% EtOAc/25% PE to pure EtOAc afforded **11b** in 96% yield as a viscous oil: IR (neat) $\upsilon$ 3410, 2945−2880, 1665 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.44−4.37 (m, 2H), 4.13 (q, $J$ = 7.11, 2H), 3.64−3.59 (m, 4H), 3.50 (br s, 2H), 1.65−1.40 (m, 6H), 1.24 (t, $J$ = 7.11 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.6, 64.6, 61.8, 51.0, 24.5, 15.1, 14.6.

***N*-Carbobenzoxy-*cis,cis*-2,6-bis(hydroxymethyl)-4-[(methyloxy)methoxy]piperidine (18a).** FC of the crude diol with pure EtOAc afforded **18a** in 93% yield as a viscous oil: IR (neat) $\upsilon$ 3425, 3070−3040, 2950−2830, 1687 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.29−7.24 (m, 5H), 5.18 (s, 2H), 4.63 (s, 2H), 4.57−4.45 (m, 2H), 3.95−3.84 (m, 3H), 3.80−3.72 (m, 2H), 3.37 (s, 3H), 2.91 (br s, 2H), 1.93−1.71 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.2, 136.3, 128.2, 127.7, 127.5, 94.7, 69.0, 67.3, 64.9, 55.2, 51.3, 29.0; MS (CI, $NH_3$) *m*/*z* 340 ($MH^+$).

***N*-Carbethoxy-*cis,cis*-2,6-bis(hydroxymethyl)-4-[(methyloxy)methoxy]piperidine (18b).** FC of the crude diol with 1% MeOH/99% EtOAc gave **18b** in 94% yield as a viscous oil: IR (neat) $\upsilon$ 3400, 2970−2815, 1665 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.61 (s, 2H), 4.47−4.36 (m, 2H), 4.13 (q, $J$ = 6.74 Hz, 2H), 3.90−3.69 (m, 5H), 3.34 (s, 3H), 3.28 (br s, 2H), 1.95−1.77 (m, 4H), 1.24 (t, $J$ = 6.74 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.9, 95.0, 69.1, 65.4, 61.7, 55.4, 51.0, 29.1, 14.4.

**General Procedure for Acetylation of Diols 11 and 18.** A solution of **11** or **18** (30 mmol) in 10 equiv of anhydrous pyridine was acetylated by the addition of 0.05 equiv of DMAP as catalyst and 4 equiv of $Ac_2O$. The solution was heated with stirring to about 100 °C with a heat gun and left to cool for 30 min. The solvents were evaporated to near dryness, and 200 mL of ether and 50 mL of 3 N HCl were added. After transfer to a separatory funnel, the ether portion was removed, and the aqueous phase was extracted two more times with ether. The combined ether fractions were dried and evaporated. In the case of diol **18**, a minimum of 1 N HCl was used for the neutralization of the remaining pyridine, and the combined ether fractions were washed with 5% $NaHCO_3$ solution before drying and evaporating.

***N*-Carbobenzoxy-*cis*-2,6-bis(acetoxymethyl)piperidine (12a).** FC was performed using 10% EtOAc/90% PE to 20% EtOAc/80% PE to give the diOAc **12a** in 97% yield as a viscous oil: IR (neat) $\upsilon$ 3082−3026, 2943−2860, 1740, 1695 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.40−7.25 (m, 5H), 5.15 (s, 2H), 4.51 (br s, 2H), 4.21 (dd, $J_1$ = 10.79 Hz, $J_2$ = 7.91 Hz, 2H), 3.94 (dd, $J_1$ = 10.79 Hz, $J_2$ = 6.48 Hz, 2H), 1.97 (s, 6H), 1.81−1.50 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.4, 155.9, 136.3, 128.3, 127.8, 127.7, 67.1, 64.2, 48.1, 24.7, 20.5, 14.4; HRMS (CI, $NH_3$) calcd for $C_{19}H_{25}NO_6$ ($M^+$ + H) 364.1760, found 364.1753 ± 0.0011.

***N*-Carbethoxy-*cis*-2,6-bis(acetoxymethyl)piperidine (12b).** Crystallization of the crude diOAc from hexane afforded **12b** in 96% yield as white cubes: mp 60.5−62.0 °C; IR (KBr) $\upsilon$ 2960−2880, 1747, 1695 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.40 (br s, 2H), 4.15 (dd, $J_1$ = 10.80 Hz, $J_2$ = 8.26 Hz, 2H), 4.08 (q, $J$ = 7.00 Hz, 2H), 3.85 (dd, $J_1$ = 10.80 Hz, $J_2$ = 6.36 Hz, 2H), 2.00 (s, 6H), 1.72−1.65 (m, 2H), 1.59−1.44 (m, 4H), 1.21 (t, $J$ = 7.00 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.5, 156.2, 64.3, 61.6, 48.0, 24.7, 20.8, 14.5; HRMS (CI, $NH_3$) calcd for $C_{14}H_{23}NO_6$ ($M^+$ + H) 302.1603, found 302.1601 ± 0.0009. Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.98; H, 7.85; N, 4.71.

***N*-Carbobenzoxy-*cis,cis*-2,6-bis(acetoxymethyl)-4-[(methyloxy)methoxy]piperidine (19a).** FC was done beginning with 10% EtOAc/90% PE to 25% EtOAc/75% PE to give the diOAc (**19a**) in 93% yield as a viscous oil: IR (neat) $\upsilon$ 3085−3030, 2950−2820, 1745, 1700 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.38−7.28 (m, 5H), 5.12 (s, 2H), 4.66−4.51 (m, 2H), 4.58 (s, 2H), 4.31 (dd, $J_1$ = 10.92 Hz, $J_2$ = 7.02 Hz, 2H), 4.15 (dd, $J_1$ = 10.92 Hz, $J_2$ = 7.85 Hz, 2H), 3.94 (m, 1H), 3.31 (s, 3H), 2.03−1.73 (m, 4H), 1.90 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.4, 156.0, 136.4, 128.3, 127.9, 127.9, 94.5, 67.9, 67.3, 66.0, 55.3, 47.6, 29.1, 20.6; HRMS (CI, $NH_3$) calcd for $C_{21}H_{29}NO_8$ ($M^+$ + H) 424.1971, found 424.1974 ± 0.0012.

***N*-Carbethoxy-*cis,cis*-2,6-bis(acetoxymethyl)-4-[(methyloxy)methoxy]piperidine (19b).** FC was performed using 20% EtOAc/80% PE to 40% EtOAc/60% PE to give the diOAc (**19b**) in 94% yield as a viscous oil: IR (neat) $\upsilon$ 2980−2805, 1737, 1690 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.55 (s, 2H), 4.52−4.46 (m, 2H), 4.28 (dd, $J_1$ = 10.76 Hz, $J_2$ = 7.30, 2H), 4.09 (dd, $J_1$ = 10.76 Hz, $J_2$ = 7.71 Hz, 2H), 4.07 (q, $J$ = 7.13 Hz, 2H), 3.90 (m, 1H), 3.28 (s, 3H), 1.98 (s, 6H), 1.91−1.72 (m, 4H), 1.20 (t, $J$ = 7.13 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.4, 156.1, 94.4, 67.9, 66.0, 61.5, 55.3, 47.3, 28.9, 20.7, 14.4; HRMS (CI, $NH_3$) calcd for $C_{16}H_{27}NO_8$ ($M^+$ + H) 362.1815, found 362.1807 ± 0.0011.

**Chelidamic Acid Dimethyl Ester Hydrochloride (14).** The title compound was synthesized by following the same protocol as that for **8**, except the starting material was chelidamic acid (**13**, 12.37 g, 61.50 mmol). In this way, 14.62 g of crude **14** was obtained which could be used "as is" for the next step. An analytical sample of the free amine of **14** was obtained as follows: 141 mg of crude **14** was suspended in 50 mL of $CH_2Cl_2$/10 mL of 5% $Na_2CO_3$ solution and stirred for 10 min. The free amine was extracted three times with $CH_2Cl_2$, and the extract was dried and evaporated. FC was done with 50% EtOAc/50% PE progressing to 75% EtOAc/25% PE to give 108 mg of the free amine of **14**, which was recrystallized from EtOAc: mp 169.5−170.5 °C; IR (KBr) $\upsilon$ 3220, 2960, 2700, 2455, 1725, 1680, 1600, 1575 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 10.15 (br s, 1H), 7.49 (s, 2H), 3.97 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.5, 163.3, 142.8, 118.5, 53.6. Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.21; H, 4.20; N, 6.58.

***cis,cis*-2,6-Bis(methoxycarbonyl)-4-hydroxypiperidine (15).** The same procedure was employed for the synthesis of **15** as that used for **9**, except Rh on alumina powder-Degussa type (479 mg) was the catalyst for this hydrogenation. Also, considering the high solubility of **15** in $H_2O$, five extractions with EtOAc were performed. Thus, 14.45 g of crude **14** gave 10.47 g of a white solid on evaporation of the dried EtOAc fractions. All of this white solid was ground up and suspended in 100 mL of hexane, and the mixture was refluxed for 30 min. After hot filtration through a Buchner funnel, the filtrate was evaporated to give 3.09 g (25% from **13**) of crude **9**. The hexane-insoluble solid was taken up in a minimum of $CHCl_3$ and precipitated with hexane to give 7.347 g (54% from **13**) of pure *cis,cis*-**15**. An analytical sample of **15** was obtained by recrystallization from EtOAc: mp 139.0−140.0 °C; IR (KBr) $\upsilon$ 3300, 3150, 2960−2760, 1735 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.75 (m, 1H), 3.73 (s, 6H), 3.38 (dd, $J_1$ = 11.85 Hz, $J_2$ = 2.40 Hz, 2H), 2.36−2.27 (m, 4H), 1.32 (ddd, $J_1 \sim J_2 \sim J_3$ = 11.9 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 172.2, 68.3, 56.4, 52.3, 37.8. Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.79; H, 7.07; N, 6.47.

**General Procedure for N-Protection of Amino Alcohol 15.** To a mixture of 20 mmol of **15** and 2 equiv of $NaHCO_3$ in 100 mL of $CH_2Cl_2$/20 mL of $H_2O$ at rt was added 1.5 equiv of the appropriate carboalkoxy chloride, and the reaction was stirred vigorously for 4 h. Brine was added, and the mixture was extracted four times with $CH_2Cl_2$.

***N*-Carbobenzoxy-*cis,cis*-2,6-bis(methoxycarbonyl)-4-hydroxypiperidine (16a).** After the $CH_2Cl_2$ fractions were dried and evaporated, FC was performed with 25% EtOAc/75% PE to 40% EtOAc/60% PE to give the carbamate **16a** in 90% yield. An analytical sample of **16a** was prepared by crystallization from ether: mp 71.5−72.5 °C; IR (KBr) $\upsilon$ 3468, 3082−3015, 2951−2865, 1730, 1695 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.38−7.30 (m, 5H), 5.20 (s, 2H), 4.99 (br s, 2H), 4.11 (m, 1H), 3.80 (d, $J$ = 3.18 Hz, 1H), 3.72 (s, 6H), 2.50−2.39 (m, 2H), 1.89−1.76 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.2, 155.4, 135.9, 128.2, 127.8, 127.6, 67.8, 61.3, 52.3, 50.1, 31.6. Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.24; H, 6.00; N, 3.87.

***N*-Carbethoxy-*cis,cis*-2,6-bis(methoxycarbonyl)-4-hydroxypiperidine (16b).** After the $CH_2Cl_2$ fractions were dried and evaporated, FC was performed with 40% EtOAc/60% PE to 60% EtOAc/40% PE to give the carbamate **16b** as a viscous oil in 92% yield: IR (neat) $\upsilon$ 3458, 2980−2840, 1740, 1700 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.02−4.88 (br s, 2H), 4.21 (br s, 2H), 4.12 (m, 1H), 3.84 (d, $J$ = 3.59 Hz, 1H), 3.74 (s, 6H), 2.47−2.38 (m, 2H), 1.86−1.78 (m, 2H), 1.26 (t, $J$ = 7.12 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.9, 155.9, 62.4, 61.6, 52.6, 50.0, 31.8, 14.5.

**General Procedure for O-Protection of Alcohols 16 and 21.** To a solution of **16** or **21** (20 mmol) and 3.5 equiv of DiPEA in 50 mL of anhydrous $CH_2Cl_2$ at 0 °C under $N_2$ was added 3 equiv of MOM-Cl dropwise with stirring. After 30 min, the ice bath was removed, and the reaction was stirred for 15 h. The reaction mixture was then poured into 200 mL of EtOAc/50 g of ice/50 mL of 3 N HCl with stirring at 0 °C,

and the aqueous phase was extracted three times with EtOAc. The combined EtOAc fractions were washed with 5% $NaHCO_3$ solution, dried with $MgSO_4$, and then evaporated.

***N*-Carbobenzoxy-*cis*,*cis*-2,6-bis(methoxycarbonyl)-4-[(methyloxy)methoxy]piperidine (17a).** FC beginning with 15% EtOAc/85% PE and finishing with 30% EtOAc/70% PE afforded **17a** in 94% yield as a colorless oil: IR (neat) $\upsilon$ 3080−3020, 2980−2810, 1760, 1735, 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.31−7.22 (m, 5H), 5.12 (s, 2H), 4.71 (br s, 2H), 4.49 (s, 2H), 3.87 (m, 1H), 3.61 (s, 6H), 3.24 (s, 3H), 2.41−2.30 (m, 2H), 1.98−1.86 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 171.3, 155.6, 135.9, 128.1, 127.8, 127.6, 93.8, 67.5, 65.8, 54.9, 51.7, 51.3, 29.5; MS (CI, $NH_3$) $m/z$ 396 ($MH^+$).

***N*-Carbethoxy-*cis*,*cis*-2,6-bis(methoxycarbonyl)-4-[(methyloxy)methoxy]piperidine (17b).** FC beginning with 30% EtOAc/70% PE and finishing with 50% EtOAc/50% PE gave **17b** as a colorless oil in 90% yield: IR (neat) $\upsilon$ 2980−2810, 1735, 1695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.68 (br s, 2H), 4.50 (s, 2H), 4.12 (q, $J$ = 7.08 Hz, 2H), 3.87 (m, 1H), 3.65 (s,6H), 3.25 (s, 3H), 2.37−2.29 (m, 2H), 1.98−1.90 (m, 2H), 1.18 (t, $J$ = 7.08 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 171.8, 156.1, 94.0, 66.1, 62.2, 55.2, 52.0, 51.5, 29.9, 14.5.

***N*-Carbobenzoxy-*cis*,*cis*-2(*R*)-(acetoxymethyl)-4(*S*)-[(methyloxy)methoxy]-6(*S*)-[[(methyloxy)methoxy]methyl]piperidine (25a).** FC was done with 25% EtOAc/75% PE to afford **25a** in 92% yield as a colorless oil: $[\alpha]^{25}_D$ = −6.2 (*c* 4.4, $CHCl_3$); IR (neat) $\upsilon$ 3100−3040, 2950−2825, 1745, 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40−7.29 (m, 5H), 5.16 (AB system, 2H), 4.66−4.55 (m, 5H), 4.46 (br s, 1H), 4.30 (dd, $J_1$ = 10.38 Hz, $J_2$ = 7.11 Hz, 1H), 4.12 (dd, $J_1$ = 10.38 Hz, $J_2$ = 7.65 Hz, 1H), 3.96 (m, 1H), 3.76 (dd, $J_1 \sim J_2$ = 9.1 Hz, 1H), 3.62 (dd, $J_1$ = 9.14 Hz, $J_2$ = 5.45 Hz, 1H), 3.36 (s, 3H), 3.33 (s, 3H), 2.08 (m, 1H), 1.96 (s, 3H), 1.98−1.77 (m, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.7, 156.0, 136.7, 128.5, 128.1, 128.0, 96.5, 94.5, 69.9, 68.1, 67.4, 66.5, 55.4, 55.3, 49.0, 47.8, 29.4, 28.7, 20.8.

***N*-Carbethoxy-*cis*,*cis*-2(*R*)-(acetoxymethyl)-4(*S*)-[(methyloxy)methoxy]-6(*S*)-[[(methyloxy)methoxy]methyl]piperidine (25b).** FC with 35% EtOAc/65% PE gave **25b** in 94% yield as a colorless oil: $[\alpha]^{25}_D$ = −9.9 (*c* 2.2, $CHCl_3$); IR (neat) $\upsilon$ 2980−2820, 1740, 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.62−4.55 (m, 4H), 4.48 (m, 1H), 4.36 (m, 1H), 4.25 (dd, $J_1$ = 10.76 Hz, $J_2$ = 7.31 Hz, 1H), 4.16−4.03 (m, 3H), 3.92 (m, 1H), 3.62 (dd, $J_1 \sim J_2$ = 9.4 Hz, 1H), 3.54 (dd, $J_1$ = 9.41 Hz, $J_2$ = 4.45 Hz, 1H), 3.33 (s, 3H), 3.30 (s, 3H), 2.03 (m, 1H), 1.99 (s, 3H), 1.86−1.70 (m, 3H), 1.22 (t, $J$ = 6.92 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.7, 156.2, 96.4, 94.3, 69.8, 68.1, 66.4, 61.6, 55.4, 55.2, 48.6, 47.5, 29.2, 28.5, 20.9, 14.6; MS (CI, $CH_4$) $m/z$ 364 ($MH^+$).

**General Procedure for Enzymatic Hydrolysis of Diacetates 12 and 19.** The diOAc (1.0−1.5 mmol) was suspended in 30 mL of phosphate buffer at pH 7.0. To this mixture was added the appropriate enzyme (100 $\mu$L of PLE suspension, 50 mg of WGL, or 60 mg of ANL), and the reaction was stirred at 350 rpm at rt. When 7% $CH_3CN$ was used with ANL, the diOAc was first dissolved in 2.0 mL of $CH_3CN$, and then 28.0 mL of phosphate buffer at pH 7.0 was added with stirring. Once 1 equiv of the diOAc was hydrolyzed, the aqueous mixture was saturated with NaCl and extracted three times with EtOAc. The combined EtOAc fractions were dried and evaporated. The monoacetate, diol, and any remaining diOAc were separated by FC beginning with 20% EtOAc/80% PE and finishing with pure EtOAc. (See Table 1 for the various yields and enantiomeric purities of monoacetates **20** and **21** with each enzyme.)

***N*-Carbobenzoxy-*cis*-2(*R*)-(acetoxymethyl)-6(*S*)-(hydroxymethyl)piperidine (20a).** When ANL in 7% $CH_3CN$/93% phosphate buffer was used, pure **20a** was isolated in 82% yield as a colorless oil with an ee ≥98% as measured by $^{19}F$ NMR of Mosher's ester made from **20a**: $[\alpha]^{25}_D$ = +5.2 (*c* 3.8, $CHCl_3$); IR (neat) $\upsilon$ 3450, 3020−3080, 2860−2930, 1745, 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.27−7.37 (m, 5H), 5.13 (AB system, 2H), 4.49 (m, 1H), 4.35 (m, 1H), 4.14 (dd, $J_1$ = 10.77 Hz, $J_2$ = 7.82 Hz, 1H), 3.98 (dd, $J_1$ = 10.77 Hz, $J_2$ = 7.01 Hz, 1H), 3.59 (d, $J$ = 7.39 Hz, 2H), 2.39 (br s, 1H), 1.94 (s, 3H), 1.44-1.81 (m, 6H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.7, 157.0, 136.6, 128.5, 128.1, 127.9, 67.5, 51.9, 48.6, 25.0, 24.6, 20.7, 14.7; HRMS (CI, $NH_3$) calcd for $C_{17}H_{23}NO_5$ ($M^+$ + H) 322.1654, found 322.1651 ± 0.0009.

***N*-Carbethoxy-*cis*-2(*R*)-(acetoxymethyl)-6(*S*)-(hydroxymethyl)piperidine (20b).** When ANL in 7% $CH_3CN$/93% phosphate buffer was used, the monoacetate **20b** was isolated in 92% yield as a colorless oil with an ee ≥98% as measured by $^{19}F$ NMR of Mosher's ester made from **20b**: $[\alpha]^{25}_D$ = −6.1 (*c* 2.6, $CHCl_3$); IR (neat) $\upsilon$ 3460, 2950−2880, 1745, 1692 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.45 (m, 1H), 4.34 (m, 1H), 4.17−4.11 (m, 3H), 3.97 (dd, $J_1$ = 10.92 Hz, $J_2$ = 6.88 Hz, 1H), 3.58 (d, $J$ = 7.42 Hz, 2H), 2.35 (br s, 1H), 2.03 (s, 3H), 1.82−1.44 (m, 6H), 1.25 (t, $J$ = 7.15 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.7, 157.4, 64.8, 64.5, 61.7, 51.6, 48.4, 24.9, 24.6, 20.8, 14.8, 14.6; HRMS (CI, $NH_3$) calcd for $C_{12}H_{21}NO_5$ ($M^+$ + H) 260.1498, found 260.1496 ± 0.0008.

***N*-Carbobenzoxy-*cis*,*cis*-2(*R*)-(acetoxymethyl)-4(*S*)-[(methyloxy)methoxy]-6(*S*)-(hydroxymethyl)piperidine (21a).** After the reaction with ANL in 7% $CH_3CN$/93% phosphate buffer, the monoacetate **21a** was isolated in 76% yield as a colorless oil with an ee ≥98% as measured by $^{19}F$ NMR of Mosher's ester made from **21a**: $[\alpha]^{25}_D$ = −2.0 (*c* 3.2, $CHCl_3$); IR (neat) $\upsilon$ 3450, 3080−3020, 2940−2820, 1735, 1687 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.35−7.29 (m, 5H), 5.18 (AB system, 2H), 4.67−4.58 (m, 3H), 4.45 (m, 1H), 4.28 (AB system, 2H), 3.94 (m, 1H), 3.82 (m, 1H), 3.77 (m, 1H), 3.39 (s, 3H), 2.70 (br s, 1H), 2.02−1.81 (m, 4H), 1.92 (s, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.8, 156.9, 136.5, 128.6, 128.1, 128.0, 95.1, 68.7, 67.6, 66.6, 65.8, 55.6, 51.4, 48.1, 29.6, 29.0, 20.8; HRMS (CI, $NH_3$) calcd for $C_{19}H_{27}NO_7$ ($M^+$ + H) 382.1866, found 382.1875 ± 0.0011.

***N*-Carbethoxy-*cis*,*cis*-2(*R*)-(acetoxymethyl)-4(*S*)-[(methyloxy)methoxy]-6(*S*)-(hydroxymethyl)piperidine (21b).** After the reaction with ANL in 7% $CH_3CN$/93% phosphate buffer, the monoacetate **21b** was isolated in 82% yield as a colorless oil with an ee ≥98% as measured by $^{19}F$ NMR of Mosher's ester made from **21b**: $[\alpha]^{25}_D$ = −15.2 (*c* 2.0, $CHCl_3$); IR (neat) $\upsilon$ 3450, 2975−2820, 1735, 1685 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.59 (AB system, 2H), 4.50 (m, 1H), 4.34 (m, 1H), 4.23−4.18 (m, 2H), 4.16−4.05 (m, 2H), 3.87 (m, 1H), 3.79−3.64 (m, 2H), 3.32 (s, 3H), 2.81 (br s, 1H), 1.99 (s, 3H), 1.97−1.78 (m, 4H), 1.21 (t, $J$ = 7.56 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.6, 156.9, 94.8, 68.5, 66.3, 65.6, 61.6, 55.3, 51.0, 47.7, 29.3, 28.8, 20.7, 14.4; HRMS (CI, $NH_3$) calcd for $C_{14}H_{25}NO_7$ ($M^+$ + H) 320.1709, found 320.1712 ± 0.0009.

**General Procedure for Mesylation of Monoacetates 20 and 21 and Diol 27.** To a stirred solution of 1 mmol of monoacetate **20** or **21** (obtained from ANL hydrolysis in 7% $CH_3CN$/93% phosphate buffer) or 1 mmol of diol **27** and 2 equiv of $Et_3N$ in 6 mL of anhydrous THF under dry $N_2$ at −10 °C was added dropwise 1.5 equiv of methanesulfonyl chloride (4 equiv of $Et_3N$ and 3 equiv of $MeSO_2Cl$ for **27**). The mixture was stirred for 4 h between −5 and −10 °C and then poured into 40 mL of EtOAc/20 g of ice/10 mL of 3 N $H_2SO_4$ and stirred for 5 min. (For the monoacetate **21a**, 5% $NaHCO_3$ solution was substituted for 3 N $H_2SO_4$ in the workup.) The aqueous phase was extracted three times with EtOAc, and the organic fractions were dried and evaporated. (Mesylates **22** and **36** are relatively unstable, and so they were made as needed and then converted to the subsequent product.)

***N*-Carbobenzoxy-*cis*-2(*S*)-[[(methylsulfonyl)oxy]methyl]-6(*R*)-(acetoxymethyl)piperidine (22a).** FC was performed with 20% EtOAc/80% PE progressing quickly to 40% EtOAc/60% PE to give **22a** in 91% yield as a colorless oil: $[\alpha]^{25}_D$ = −11.3 (*c* 1.5, $CHCl_3$); IR (neat) $\upsilon$ 3100- 3020, 2940−2850, 1735, 1685 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40−7.35 (m, 5H), 5.15 (AB system, 2H), 4.48 (br s, 2H), 4.23−4.08 (m, 3H), 3.90 (dd, $J_1$ = 11.19 Hz, $J_2$ = 6.91 Hz, 1H), 2.96 (s, 3H), 1.98 (s, 3H), 1.88 (m, 1H), 1.79−1.54 (m, 5H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.4, 155.7, 136.0, 128.4, 128.0, 127.9, 68.2, 67.3, 64.4, 48.5, 48.1, 37.1, 24.6, 24.1, 20.5, 14.2.

***N*-Carbethoxy-*cis*-2(*S*)-[[(methylsulfonyl)oxy]methyl]-6(*R*)-(acetoxymethyl)piperidine (22b).** FC beginning with 25% EtOAc/75% PE and progressing quickly to 50% EtOAc/50% PE afforded **22b** in 96% yield as a colorless oil: $[\alpha]^{25}_D$ = −15.7 (*c* 2.8, $CHCl_3$); IR (neat) $\upsilon$ 3030, 2960−2870, 1740, 1695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.42 (br s, 2H), 4.21−4.05 (m, 5H),

3.86 (dd, $J_1$ = 11.00 Hz, $J_2$ = 6.58 Hz, 1H), 3.03 (s, 3H), 2.03 (s, 3H), 1.87 (m, 1H), 1.75−1.52 (m, 5H), 1.25 (t, $J$ = 7.12 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.5, 156.0, 68.3, 64.5, 61.8, 48.4, 47.9, 37.3, 24.6, 24.1, 20.7, 14.4, 14.2.

***N*-Carbobenzoxy-*cis*,*cis*-2(*S*)-[[(methylsulfonyl)oxy]-methyl]-4(*R*)-[(methyloxy)methoxy]-6(*R*)-(acetoxymethyl)piperidine (36).** FC was begun with 25% EtOAc/75% PE and went quickly to 50% EtOAc/50% PE to give **36** in 97% yield as a colorless oil: $[\alpha]^{25}_D$ = −13.7 (*c* 2.2, $CHCl_3$); IR (neat) $\upsilon$ 3090−3020, 2960−2820, 1740, 1695 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.39−7.27 (m, 5H), 5.15 (AB system, 2H), 4.62−4.56 (m, 4H), 4.46 (dd, $J_1 \sim J_2$ = 9.1 Hz, 1H), 4.26 (dd, $J_1$ = 10.33 Hz, $J_2$ = 5.89 Hz, 2H), 4.14 (dd, $J_1$ = 10.33 Hz, $J_2$ = 7.50 Hz, 1H), 4.01 (m, 1H), 3.35 (s, 3H), 2.93 (s, 3H), 2.05 (br d, $J$ = 14. 9 Hz, 1H), 1.95 (br d, 1H), 1.93 (s, 3H), 1.84−1.75 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.5, 155.8, 136.1, 128.4, 128.1, 128.0, 94.5, 70.3, 67.6, 67.4, 66.1, 55.5, 47.8, 47.4, 37.1, 28.7, 28.2, 20.6.

***cis*,*cis*-1,2(*R*)-(1-Oxooxazolidino)-4(*S*)-[(methylsulfonyl)oxy]-6(*S*)-[[(methylsulfonyl)oxy]methyl]piperidine (28).** FC was performed beginning with 50% EtOAc/50% PE and progressing to 75% EtOAc/25% PE to afford the dimesylate **28** in 96% yield as a viscous oil: $[\alpha]^{25}_D$ = −13.5 (*c* 4.5, $CHCl_3$); IR (neat) $\upsilon$ 3030, 2980−2870, 1750 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.88−4.81 (m, 3H), 4.43 (dd, $J_1$ = 8.54 Hz, $J_2$ = 7.53 Hz, 1H), 3.98 (dd, $J_1$ = 8.54 Hz, $J_2$ = 6.12 Hz, 1H), 3.78 (m, 1H), 3.58 (m, 1H), 3.09 (s, 3H), 3.07 (s, 3H), 2.38 (m, 1H), 2.28 (m,1H), 1.82 (ddd, $J_1 \sim J_2 \sim J_3$ = 11.9 Hz, 1H), 1.70 (ddd, $J_1 \sim J_2 \sim J_3$ = 11.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.0, 75.1, 67.7, 67.1, 54.7, 52.2, 39.0, 37.4, 36.0, 34.1; MS (CI, $CH_4$) *m*/*z* 344 ($MH^+$).

**General Procedure for Hydrolysis and Cyclization of Acetates 22, 25, and 36.** A quantity of acetate (15 mmol) was dissolved in 100 mL of THF and 40 mL of MeOH at rt. To this solution was added 40 mL (20 mmol) of 0.5 N NaOH, and the mixture was stirred for 1 h. After the addition of solid $NaHCO_3$ to saturate the aqueous phase and separate it from the organic solvents, the mixture was extracted three times with EtOAc. The combined organic fractions were then dried and evaporated.

***cis*-1,2(*R*)-(1-Oxooxazolidino)-6(*S*)-[[(methylsulfonyl)-oxy]methyl]piperidine (23).** (This mesylate, whether from **22a** or **22b**, was identical in all respects.) FC was performed beginning with 10% EtOAc/90% PE and finishing with 60% EtOAc/40% PE to give **23** in 73% yield. (The secondary product, the *meso* ether mentioned in the text, was isolated in 20% yield.) An analytical sample of mesylate **23** was obtained by crystallization from EtOAc: mp 59.0−60.0 °C; **23** (from **22a**), $[\alpha]^{25}_D$ = −26.7 (*c* 2.2, $CHCl_3$); **23** (from **22b**), $[\alpha]^{25}_D$ = −26.4 (*c* 1.8, $CHCl_3$); IR (KBr) $\upsilon$ 3030, 2950−2870, 1745 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.79 (d, $J$ = 5.20 Hz, 2H), 4.35 (dd, $J_1 \sim J_2$ = 8.3 Hz, 1H), 3.85 (dd, $J_1$ = 8.30 Hz, $J_2$ = 6.94 Hz, 1H), 3.61 (m, 1H), 3.41 (m, 1H), 3.04 (s, 3H), 1.98 (m, 1H), 1.83−1.75 (m, 2H), 1.60−1.32 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.5, 68.8, 67.9, 56.9, 54.7, 37.2, 29.2, 27.6, 22.7. Anal. Calcd for $C_9H_{15}NO_5S$: C, 43.36; H, 6.06; N, 5.62. Found: C, 43.36; H, 6.25; N, 5.55.

***cis*,*cis*-1,2(*R*)-(1-Oxooxazolidino)-4(*S*)-[(methyloxy)-methoxy]-6(*S*)-[[(methyloxy)methoxy]methyl]piperidine (26).** (This oxazolidinone, whether from **25a** or **25b**, was identical in all respects.) FC was done beginning with 25% EtOAc/75% PE and progressing to 50% EtOAc/50% PE to afford **26** as a colorless oil in 95% yield: **26** (from **25a**), $[\alpha]^{25}_D$ = −13 (*c* 3.2, $CHCl_3$); **26** (from **25b**), $[\alpha]^{25}_D$ = −13 (*c* 3.2, $CHCl_3$); IR (neat) $\upsilon$ 2960−2790, 1755 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.70−4.64 (m, 4H), 4.34(dd, $J_1$ = 8.31 Hz, $J_2$ = 7.70 Hz, 1H), 4.25 (dd, $J_1$ = 10.26 Hz, $J_2$ = 5.54 Hz, 1H), 4.04 (dd, $J_1$ = 10.26 Hz, $J_2$ = 6.36 Hz, 1H), 3.91 (dd, $J_1$ = 8.31 Hz, $J_2$ = 6.05 Hz, 1H), 3.75−3.61 (m, 2H), 3.37 (s, 3H), 3.36 (s, 3H), 3.32 (m, 1H), 2.14 (m,2H), 1.46 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.1, 96.9, 94.8, 72.6, 67.1, 66.9, 55.5, 55.4, 53.9, 36.3, 35.1; MS (CI, $CH_4$) *m*/*z* 276 ($MH^+$).

***cis*,*cis*-1,2(*R*)-(1-Oxooxazolidino)-4(*S*)-[(methyloxy)-methoxy]-6(*S*)-[[(methylsulfonyl)oxy]methyl]piperidine (37).** The pure mesylate **37** was recovered in 93% yield as a viscous oil after FC beginning with 50% EtOAc/50% PE and ending with 66% EtOAc/34% PE: $[\alpha]^{25}_D$ = −7.6 (*c* 1.4, $CHCl_3$); IR (neat) $\upsilon$ 3020, 2960−2780, 1745 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.79 (2 dd's, AB system, 2H), 4.65 (AB system, 2H), 4.37 (dd, $J_1 \sim J_2$ = 8.3 Hz, 1H), 3.92 (dd, $J_1$ = 8.30 Hz, $J_2$ = 6.31 Hz, 1H), 3.78−3.63 (m, 2H), 3.46 (m, 1H), 3.35 (s, 3H), 3.06 (s, 3H), 2.20−2.07 (m, 2H), 1.54 (ddd, $J_1 \sim J_2 \sim J_3$ = 11.5 Hz, 1H), 1.43 (ddd, $J_1 \sim J_2 \sim J_3$ = 11.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.1, 94.8, 72.0, 68.1, 67.2, 55.4, 55.0, 52.4, 37.1, 35.9, 34.1; MS (CI, $CH_4$) *m*/*z* 310 ($MH^+$).

***cis*,*cis*-1,2(*R*)-(1-Oxooxazolidino)-4(*S*)-hydroxy-6(*S*)-(hydroxymethyl)piperidine (27).** To a solution of **26** (183 mg, 0.665 mmol) in 7 mL of absolute MeOH at rt was added 3 drops of 12 N HCl. The stirred solution was heated to 60 °C for 4 h and then cooled to rt. Solid $NaHCO_3$ (200 mg) was added, and the MeOH was evaporated. The nonvolatile components were dissolved in EtOAc, and the EtOAc was dried. FC was begun with pure EtOAc and finished with 5% MeOH/95% EtOAc to yield 121 mg (97%) of the diol **27** as a viscous oil: $[\alpha]^{25}_D$ = −3.4 (*c* 4.8, $CHCl_3$); IR (neat) $\upsilon$ 3390, 2960−2860, 1725 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.65 (dd, $J_1$ = 8.25 Hz, $J_2$ = 6.74 Hz, 1H), 4.47 (dd, $J_1 \sim J_2$ = 8.5 Hz, 1H), 3.98 (dd, $J_1$ = 8.49 Hz, $J_2$ = 7.30 Hz, 1H), 3.94−3.72 (m, 4H), 3.25 (m, 1H), 3.05 (br s, 1H), 2.24 (br d, $J$ = 12.01 Hz, 1H), 1.99 (br d, $J$ = 12.63 Hz, 1H), 1.55−1.40 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.4, 68.0, 67.2, 63.1, 56.6, 55.4, 39.0, 36.9; MS (CI, $CH_4$) *m*/*z* 188 ($MH^+$).

**General Procedure for Reduction of Mesylates 23, 28, and 37.** To a stirred solution of the mesylate (10 mmol) in 30 mL of anhydrous DMSO under $N_2$ at rt was added 4 equiv of $NaBH_4$, and the temperature was increased to 80−90 °C with an oil bath (120 °C for the dimesylate **28**). After being stirred for 8 h, the solution was cooled by replacing the oil bath with a rt $H_2O$ bath, and 5 mL of $H_2O$ was carefully added with stirring. After 5 min, the mixture was carefully poured into a stirred 1 L flask of 300 mL of ether/100 mL of 5% $NaHCO_3$ solution and again stirred for 5 min. The aqueous phase was extracted four times with ether, and the combined ether fractions were dried and evaporated.

***cis*-1,2(*R*)-(1-Oxooxazolidino)-6(*S*)-methylpiperidine (24).** (This oxazolidinone, whether from mesylate **23** or dimesylate **28**, was identical in all respects.) FC was done beginning with 10% EtOAc/90% PE and progressing to 25% EtOAc/75% PE to give **24** in 72% yield (from **23**) or 42% yield (from **28**). An analytical sample was crystallized from diisopropyl ether: mp 41.0−42.5 °C; **24** (from **23**), $[\alpha]^{25}_D$ = −58.8 (*c* 2.4, $CHCl_3$); **24** (from **28**), $[\alpha]^{25}_D$ = −57.2 (*c* 1.3, $CHCl_3$); IR (KBr) $\upsilon$ 2980−2860, 1750 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.31 (dd, $J_1 \sim J_2$ = 8.3 Hz, 1H), 3.76 (dd, $J_1 \sim J_2$ = 8.3 Hz, 1H), 3.53 (m, 1H), 3.18 (m, 1H), 1.92−1.79 (m, 2H), 1.71−1.63 (m, 1H), 1.58 (d, $J$ = 6.72 Hz, 3H), 1.50−1.21 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.6, 67.2, 57.1, 51.8, 34.0, 29.5, 23.0, 18.7. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.66; H, 8.62; N, 9.06.

***cis*,*cis*-1,2(*R*)-(1-Oxooxazolidino)-4(*S*)-[(methyloxy)-methoxy]-6(*S*)-methylpiperidine (38).** FC of the reaction residue with 25% EtOAc/75% PE to 50% EtOAc/50% PE afforded **38** in 74% yield. An analytical sample was prepared by crystallization from diisopropyl ether: mp 44.0−45.5 °C; $[\alpha]^{25}_D$ = −35.3 (*c* 1.2, $CHCl_3$); IR (KBr) $\upsilon$ 2940−2780, 1745 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.65 (s, 2H), 4.30 (dd, $J_1 \sim J_2$ = 8.0 Hz, 1H), 3.82 (dd, $J_1 \sim J_2$ = 8.0 Hz, 1H), 3.71−3.55 (m, 2H), 3.34 (s, 3H), 3.24 (m, 1H), 2.15 (br d, $J$ = 12.06 Hz, 1H), 1.99 (br d, $J$ = 12.84 Hz, 1H), 1.60 (d, $J$ = 6.59 Hz, 3H), 1.35 (ddd, $J_1 \sim J_2 \sim J_3$ = 11.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.3, 94.6, 72.4, 66.5, 55.4, 55.2, 49.6, 40.5, 36.1, 18.3. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.84; H, 7.62; N, 6.50.

**General Procedure for Hydrolysis of Oxazolidinones 24 (from 20b) and 38.** A solution of the oxazolidinone (6 mmol) in 50 mL of absolute MeOH was mixed with 30 mL (30 mmol) of 1 N KOH and refluxed for 40 h. The reaction was then cooled to rt, and the MeOH was evaporated. After partition between 80 mL of $CH_2Cl_2$ and 20 mL of brine, the aqueous phase was extracted three times with $CH_2Cl_2$, and the combined $CH_2Cl_2$ fractions were dried and evaporated to give the crude, crystalline amino alcohol in quantitative yield. In both cases, the crude product was sufficiently pure to proceed to the next synthetic step without purification.

***cis*-2(*R*)-(Hydroxymethyl)-6(*R*)-methylpiperidine (32).** (Attention: This amino alcohol (**32**) sublimes very readily.) An analytical sample of amino alcohol **32** was obtained by recrystallization from diisopropyl ether: mp 93.0−94.0 °C; $[\alpha]^{25}_D$ = −22.4 (*c* 1.02, $CHCl_3$); IR (KBr) *v* 3245, 3110, 2950−2600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) *δ* 4.11 (br s, 2H), 3.55 (dd, $J_1$ = 10.98 Hz, $J_2$ = 3.64 Hz, 1H), 3.40 (dd, $J_1$ = 10.98 Hz, $J_2$ = 8.10 Hz, 1H), 2.74−2.60 (m, 2H), 1.75 (m, 1H), 1.59 (m, 1H), 1.50 (m, 1H), 1.32 (m, 1H), 1.19−1.04 (m, 2H), 1.08 (d, $J$ = 6.18 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) *δ* 65.4, 58.3, 52.1, 33.5, 27.3, 23.9, 22.2. Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.11; H, 12.08; N, 10.80.

***cis,cis*-2(*R*)-(Hydroxymethyl)-4(*S*)-[(methyloxy)-methoxy]-6(*S*)-methylpiperidine (39).** An analytical sample of amino alcohol **39** was prepared by recrystallization from EtOAc: mp 88.5−89.5 °C; $[\alpha]^{25}_D$ = −16.9 (*c* 1.05, $CHCl_3$); IR (KBr) *v* 3250, 3120, 2960−2600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) *δ* 4.63 (br s, 2H), 3.64−3.53 (m, 2H), 3.42 (dd, $J_1$ = 11.04 Hz, $J_2$ = 7.49 Hz, 1H), 3.33 (s, 3H), 2.78−2.65 (m, 2H), 1.96 (br d, $J$ = 12.22 Hz, 1H), 1.87 (br d, $J$ = 11.82 Hz, 1H), 1.10 (d, $J$ = 5.52 Hz, 3H), 1.13−1.00 (m, 2H); $^{13}C$ NMR ($CDCl_3$) *δ* 94.4, 73.9, 65.8, 56.0, 55.1, 49.8, 40.8, 34.6, 22.2. Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.40 Found: C, 57.05; H, 10.30; N, 7.35.

**General Procedure for N-Benzylation of Amino Alcohols 32 and 39.** The crude amino alcohol (5 mmol) and 1.5 equiv of DiPEA were dissolved in 10 mL of anhydrous $CH_3CN$, and 1.2 equiv of BnBr was added to the solution which was then refluxed for 3 h under a $CaCl_2$ drying tube. After being cooled to rt, the reaction mixture was poured into 50 mL of $CH_2Cl_2$/10 mL of 1N NaOH and stirred for 10 min. The aqueous phase was extracted three times with $CH_2Cl_2$, and the combined organic fractions were dried and evaporated.

***N*-Benzyl-*cis*-2(*R*)-(hydroxymethyl)-6(*S*)-methylpiperidine (33).** FC was performed beginning with 10% EtOAc/90% PE (to eliminate any trace of **24**) and then progressing quickly to 50% EtOAc/50% PE to give **33** as a colorless oil in 81% yield (from **24**): $[\alpha]^{25}_D$ = −27.1 (*c* 1.4, $CHCl_3$); IR (neat) *v* 3360, 3080−3020, 2960−2780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) *δ* 7.40−7.21 (m, 5H), 3.69 (AB system, 2H), 3.65 (dd, $J_1$ = 11.24 Hz, $J_2$ = 4.06 Hz, 1H), 3.32 (dd, $J_1$ = 11.24 Hz, $J_2$ = 3.87 Hz, 1H), 2.71−2.57 (m, 2H), 2.32 (br s, 1H), 1.90−1.54 (m, 4H), 1.44−1.25 (m, 2H), 1.18 (d, $J$ = 6.33 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) *δ* 141.1, 128.3, 127.4, 126.5, 63.6, 63.2, 56.7, 53.8, 32.8, 27.2, 22.9, 22.1; MS (CI, $NH_3$) *m*/*z* 220 ($MH^+$).

***N*-Benzyl-*cis,cis*-2(*R*)-(hydroxymethyl)-4(*S*)-[(methyloxy)methoxy]-6(*S*)-methylpiperidine (40).** FC was done with 25% EtOAc/75% PE and progressing to 50% EtOAc/50% PE to afford **40** as a colorless oil in 90% yield (from **38**): $[\alpha]^{25}_D$ = −22.8 (*c* 2.0, $CHCl_3$); IR (neat) *v* 3440, 3090−3020, 2970−2790 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) *δ* 7.39−7.20 (m, 5H), 4.68 (s, 2H), 3.73 (AB system, 2H), 3.65−3.54 (m, 2H), 3.36 (s, 3H), 3.34 (m, 1H), 2.76−2.62 (m, 2H), 1.95−1.82 (m, 3H), 1.64 (ddd, $J_1 \sim J_2 \sim J_3$ = 11.8 Hz, 1H), 1.35 (ddd, $J_1 \sim J_2 \sim J_3$ = 11.8 Hz, 1H), 1.20 (d, $J$ = 6.15 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) *δ* 141.1, 128.4, 127.3, 126.7, 94.4, 73.1, 63.7, 62.3, 55.6, 55.1, 51.9, 39.4, 33.6, 21.9; HRMS (CI, $NH_3$) calcd for $C_{16}H_{25}NO_3$ ($M^+$ + H) 280.1913, found 280.1917 ± 0.0008.

**General Procedure for Swern Oxidation of Alcohols 33 and 40.** To a stirred solution of 2 equiv of oxalyl chloride in 12 mL of anhydrous $CH_2Cl_2$ at −78 °C under $N_2$ was added 3 equiv of anhydrous DMSO in 4 mL of anhydrous $CH_2Cl_2$ dropwise and the mixture allowed to react for 5 min at −78 °C. The alcohol (4 mmol) in 4 mL of anhydrous $CH_2Cl_2$ was added, and the reaction mixture was stirred for 1 h at −78 °C. On addition of 4 equiv of anhydrous $Et_3N$, the dry ice/acetone bath was removed, and the reaction temperature was left to go to rt. The reaction was diluted with 20 mL of $CH_2Cl_2$ and then poured into 50 mL of $CH_2Cl_2$/20 mL of 10% $NH_4OH$ solution. The aqueous phase was extracted twice with $CH_2Cl_2$, and the combined $CH_2Cl_2$ fractions were dried and evaporated. The residue was dissolved in ether and filtered through a $MgSO_4$ pad and the ether evaporated. The crude aldehyde (**34** or **41**) was used immediately in the next step of the synthesis (Wittig reaction). All attempts to purify or analyze the aldehyde resulted in its degradation.

***N*-Benzyl-*cis*-2(*R*)-(1-propenyl)-6(*S*)-methylpiperidine (35).** Anhydrous benzene (30 mL) and 628 mg (5.60 mmol) of *t*-BuOK were mixed at rt under $N_2$, and 2.23 g (6.00 mmol) of $Ph_3P(Et)(Br)$ was added to the mixture. After the mixture was stirred for 1.5 h, the crude aldehyde **34** (4.00 mmol, assuming 100% yield from Swern oxidation of **33**) was added with 15 mL of anhydrous benzene to the reaction mixture, and it was refluxed for 1 h. The reaction mixture was then partitioned between 100 mL of EtOAc/50 mL of 10% $Na_2S_2O_3$ solution, and the aqueous phase was extracted two times with EtOAc. The organic fractions were dried and evaporated, and the residue was dissolved in 50 mL of PE and filtered. FC beginning with pure PE and progressing to 3% EtOAc/97% PE was performed to yield 761 mg (83% from **33**) of **35** (cis:trans 9:1) as a colorless oil: $[\alpha]^{25}_D$ (cis) = −5.9 (*c* 1.7, $CHCl_3$); IR (neat) *v* (cis) 3080−3020, 2965−2780, 2580, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (cis) *δ* 7.36−7.18 (m, 5H), 5.58−5.41 (m, 2H), 4.02 (d, $J$ = 15.81 Hz, 1H), 3.65 (d, $J$ = 15.81 Hz, 1H), 3.17 (m, 1H), 2.41 (m, 1H), 1.68−1.54 (m, 3H), 1.63 (d, $J$ = 5.37 Hz, 3H), 1.45−1.28 (m, 3H), 1.07 (d, $J$ = 5.99 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) (cis) *δ* 140.9, 135.8, 128.6, 127.8, 126.2, 123.7, 59.2, 57.2, 55.2, 35.6, 33.3, 24.2, 22.5, 13.4; HRMS (EI, 70 eV) calcd for $C_{16}H_{23}N$ ($M^+$) 229.1830, found 229.1835 ± 0.0006.

***N*-Benzyl-*cis,cis*-2(*R*)-(1-nonenyl)-4(*S*)-[(methyloxy)-methoxy]-6(*S*)-methylpiperidine (42).** This olefin was prepared according to the procedure for **35**, except $Ph_3P$(*n*-octyl)(Br) was used as the Wittig reagent. [Triphenyl-*n*-octylphosphonium bromide was prepared by reacting $Ph_3P$ with n-octylBr in refluxing anhydrous benzene overnight. No precipitate was observed so the benzene was evaporated, and the resulting viscous oil was triturated repeatedly with anhydrous ether to remove the slight excess of *n*-octylBr. The crude $Ph_3P$(*n*-octyl)(Br) was dried under vacuum over $P_2O_5$ and used "as is".] Thus, the crude aldehyde (**41**, 4.00 mmol, assuming 100% yield from Swern oxidation of **40**) was reacted to afford, after FC beginning with pure PE and progressing to 5% EtOAc/95% PE, 1.31 g (87% from **40**) of **42** (cis:trans 10:1) as a colorless oil: $[\alpha]^{25}_D$ (cis) = 9.40 (*c* 1.50, $CHCl_3$); IR (neat) *v* (cis) 3080−1010, 2980−2740, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (cis) *δ* 7.34−7.18 (m, 5H), 5.40 (m, 2H), 4.65 (s, 2H), 4.01 (d, $J$ = 15.79 Hz, 1H), 3.58 (d, $J$ = 15.79 Hz, 1H), 3.54 (m, 1H), 3.37 (s, 3H), 3.22 (m, 1H), 2.47 (m, 1H), 2.10−2.01 (m, 2H), 1.98−1.83 (m, 2H), 1.50−1.26 (m, 12H), 1.06 (d, $J$ = 5.69 Hz, 3H), 0.90 (t, $J$ = 6.32 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) (cis) *δ* 140.8, 133.4, 130.5, 128.1, 127.7, 126.1, 94.3, 72.8, 57.9, 55.5, 55.0, 54.5, 41.5, 39.5, 31.7, 29.4, 29.3, 29.1, 27.8, 22.5, 22.3, 14.0; HRMS (EI, 70 eV) calcd for $C_{24}H_{39}NO_2$ ($M^+$) 373.2981, found 373.2979 ± 0.0011.

**(+)-2(*R*),6(*S*)-Dihydropinidine Hydrochloride [(+)-2−HCl].** A quantity of olefin (**35**, 646 mg, 2.816 mmol) and 3.0 mL (9.0 mmol HCl) of 3 N HCl were dissolved in 15 mL of freshly, degassed absolute EtOH. Pearlman's catalyst ($Pd(OH)_2$ on carbon, 94 mg) was suspended in the solution, and the mixture was hydrogenated at 40 psi at 40 °C for 15 h. After filtration of the mixture through a pad of Celite, the EtOH and $H_2O$ were evaporated. Toluene (50 mL) was added and evaporated to dryness in order to remove any trace of $H_2O$. The crude (+)-**2**−HCl (pure by $^1H$ and $^{13}C$ NMR) was obtained in near-quantitative yield (496 mg). Recrystallization from absolute EtOH/EtOAc gave 422 mg (84% from **35**) of (+)-**2**-HCl as white needles: mp 242.0−243.0 °C (lit.[9e] mp 245.0−246.2 °C); $[\alpha]^{25}_D$ = +13.3 (*c* 1.14, EtOH) (lit.[14] $[\alpha]^{25}_D$ = +12.8 (*c* 1.07, EtOH)); IR (KBr) *v* 3180, 2960−2370, 2075, 1600, 1585 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) *δ* 9.41 (br s, 1H), 9.03 (br s, 1H), 3.06 (m, 1H), 2.89 (m, 1H), 2.16−2.05 (m, 1H), 1.95−1.23 (m, 9H), 1.55 (d, $J$ = 6.50 Hz, 3H), 0.88 (t, $J$ = 7.32 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) *δ* 58.1, 54.3, 35.0, 30.4, 27.2, 22.7, 19.3, 18.6, 13.6.

**(+)-*cis,cis*-2(*R*)-*n*-Nonyl-4(*S*)-hydroxy-6(*S*)-methylpiperidine Hydrochloride [(+)-241D−HCl] [(+)-4−HCl].** The synthesis of (+)-**4**−HCl was conducted in the same manner as that for (+)-**2**−HCl. The acidic hydrogenation conditions successfully removed both the *N*-benzyl group and the methoxymethyl ether as well as reduced the olefin. Thus, 330 mg (0.883 mmol) of **42** was converted to crude (+)-**4**−HCl (243 mg) in near-quantitative yield. An analytical sample was

obtained by recrystallization from absolute EtOH/EtOAc to afford (+)-**4**−HCl as white needles: mp 228 °C dec; $[\alpha]^{25}_D$ = +15.8 (*c* 1.30, EtOH); IR (KBr) *υ* 3320, 2960−2640, 2485, 2440, 2100 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) *δ* 3.82 (m, 1H), 3.27 (m, 1H), 3.16 (m, 1H), 2.23 (m, 1H), 2.14 (m, 1H), 1.76 (m, 1H), 1.61 (m, 1H), 1.47−1.28 (m, 16 H), 1.39 (d, *J* = 7.30 Hz, 3H), 0.90 (t, *J* = 6.44 Hz, 3H); $^{13}C$ NMR ($CD_3OD$) *δ* 68.9, 59.3, 55.3, 43.0, 40.5, 36.8, 35.4, 33.0, 32.9, 32.8, 28.6, 26.1, 21.6, 16.9.

**(+)-*cis*,*cis*-2(*R*)-*n*-Nonyl-4(*S*)-hydroxy-6(*S*)-methylpiperidine [(+)-241D] [(+)-4].** The free piperidine ((+)-**4**) was prepared by dissolving 134 mg (0.482 mmol) of crude (+)-**4**−HCl in 10 mL of $H_2O$ and adding 102 mg (0.962 mmol) of $Na_2CO_3$. Extraction of the precipitated amino alcohol with EtOAc (2 × 30 mL) was followed by drying and evaporation of the solvent to give 111 mg (95%) of crude (+)-**4**. Recrystallization from EtOAc afforded 96 mg of pure (+)-**4** as white flakes: mp 108.0−109.0 °C; $[\alpha]^{25}_D$ = +6.5 (*c* 2.0, MeOH) (lit.[2a] $[\alpha]^{25}_D$ = +39 (*c* 0.2, MeOH)); IR (KBr) *υ* 3250, 3145, 2945−2550 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) *δ* 3.63 (m, 1H), 2.66 (m, 1H), 2.53 (m, 1H), 2.00−1.89 (m, 2H), 1.58 (br s, 2H), 1.42−1.21 (m, 16H), 1.11 (d, *J* = 6.09 Hz, 3H), 1.07−0.90 (m, 2H), 0.88 (t, *J* = 6.57 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) *δ* 69.2, 54.7, 50.0, 43.8, 41.7, 36.7, 31.7, 29.6, 29.4, 29.2, 25.9, 22.5, 22.3, 13.9; HRMS (EI, 70 eV) calcd for $C_{15}H_{31}NO$ ($M^+$) 241.2406, found 241.2395 ± 0.0007.

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**Supporting Information Available:** Spectrometric information ($^1H$ or $^{13}C$ NMR) for new compounds (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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