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Diastereoselective Synthesis of 2,3,6-Trisubstituted Piperidines

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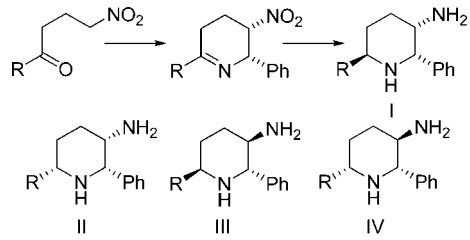

We report the diastereoselective and chromatography-free syntheses of four 2-phenyl-6-alkyl-3-aminopiperidines. Ring construction was accomplished through a nitro-Mannich reaction linking a nitroketone and phenylmethanimine, followed by a ring-closure condensation. Relative stereocontrol was achieved between C-2 and C-3 by kinetic protonation of a nitronate or by equilibration of the nitro group under thermodynamic control. Stereocontrol at C-6 was accomplished by utilizing a variety of imine reduction methods. The C-2/C-6-cis stereochemistry was established via triacetoxyborohydride iminium ion reduction, whereas the trans relationship was set either by triethylsilane/TFA acyliminium ion reduction or by Lewis acid catalyzed imine reduction with lithium aluminum hydride.

Introduction

In medicinal chemistry the elucidation of structure−activity relationships can be greatly facilitated through the use of rigid ligand scaffolds that project key substituents in a stereochemically defined way. In concert with the inherent binding interactions of the scaffold, the orientation of substituents and the efficiency of their interaction with individual binding pockets is partially dependent upon the geometry imparted by the skeletal framework. However, once the pharmacophore is understood, new scaffolds can be created to afford ligands of similar or enhanced affinity.[1−4] Whereas increased ligand potency is often the primary goal of such a study, secondary objectives such as adjustment of lipohilicity, solubility, and/or blockade of metabolic sites are equally important and ideally target regions of the molecule that will augment receptor binding.

Variably substituted piperidines are attractive scaffolds possessing well-characterized geometries dictated by predictable ring conformations. In addition to providing high stereochemical definition, extensive arrays of piperidine substitution patterns are possible in both chiral and achiral formats. Pfizer chemists exploited this rich piperidine chemistry years ago during work on NK-1 antagonists, exemplified by the phenylpiperidine CP-099994[5] and the rigidified piperidine, quinuclidine CP-96345[6] (Scheme 1). These structures possess a *cis*-2,3-piperidine scaffold and project a 2-aryl group equatorially and a 3-(2-methoxy)benzylamine group axially in defining the basic NK-1 pharmacophore. The piperidine ring, apart from the amino residue, does not appear to be an integral part of the pharmacophore but merely serves to present the necessary groups in the correct orientation for efficient receptor interaction.[7,8]

Insight into the NK-1 pharmacophore presented an opportunity to further explore the pharmacological characteristics of this class of piperidine derivative. Specifically, we were interested in improving the pharmacokinetic/pharmacodynamic

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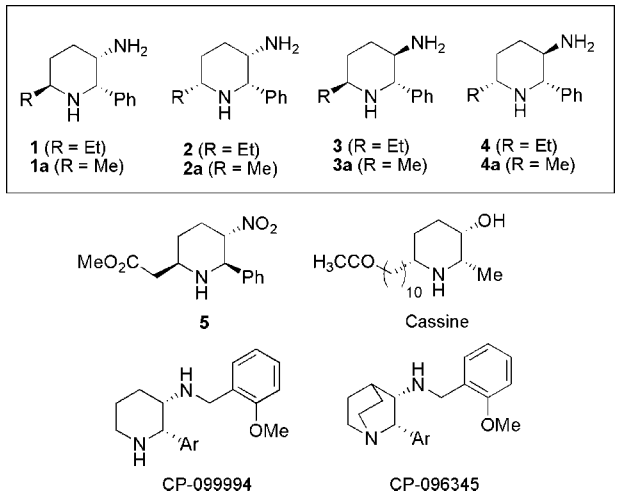
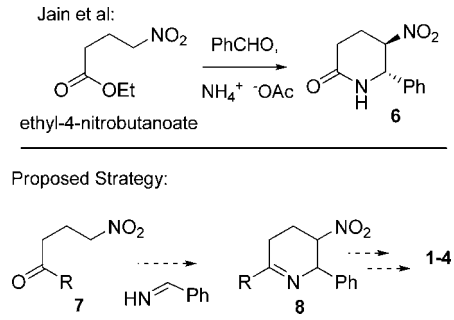
SCHEME 1



(PK/PD) profile by blocking sites of metabolism and by adjustment of log *P*. However, any modification to the core structure that added stereochemical complexity needed to be balanced by the simplicity of chemical construction for this approach to be viable. Our target choice coincided with SAR hypothesis around the influence of position C-6 of the piperidine ring. We therefore considered various known cyclization strategies (vide infra) which would be facilitated by ring closure onto the nitrogen atom at this site. Thus, trisubstituted piperidines of the type **1**−**4** (Scheme 1) became the primary targets of the campaign.

Compounds **1** and **2** possess the 2,3-cis stereochemistry present in CP-099994 and other potent NK-1 analogues from the piperidine class. However, SAR from other series demonstrated that the trans-orientation can provide good activity with the optimum choice of functionality. Ideally, we wanted a synthetic route that would provide each diastereomer **1**−**4** selectively, on large scale, and with minimal chromatography. A literature search uncovered several synthetic routes to 2,3,6-trisubstituted piperidines, primarily from the cassine class of alkaloids (Scheme 1).[9−14] However, these compounds lacked amino and phenyl substituents, and the synthetic routes were not readily amenable for eventual scale-up. A recent report by Compain et al. described the diastereoselective synthesis of 2,6-*cis*-piperidine derivatives through an iterative process involving Rh-catalyzed functionalization of C−H bonds.[15] Stereocontrol in the synthesis of 2,6-disubstituted piperidines has been studied, but its application to more complex piperidines has not been reported.[16−21] Aside from an early Pfizer report on a lengthy, nonselective route to the 6-methyl derivatives **1a** and **2a**,[22] and a more recent report from Takemoto et al.[23] on the asymmetric synthesis of the related compound **5**, the literature contained no account of a stereoselective route to each of the diastereomers **1**−**4**.[24]

SCHEME 2



We devised a selective route to the 2,3-cis targets **1** and **2** because this stereochemistry afforded greater receptor affinity for this class of antagonist. We anticipated that the 2,6-trans arrangement of alkyl and aromatic residues in **1** would likely pose the greatest challenge due to conformational and steric factors (vide infra) but expected that all four possible diastereomers would be accessible from a versatile strategy through careful choice of reaction conditions and functionality.

Previous work from our laboratories demonstrated that the nitro group would be an effective surrogate for the C-3 amine while affording a synthon to aid in ring construction and adjustment of C-3 stereochemistry.[25] Related chemistry precedent included a nitro-Mannich reaction reported by Jain[26] and Desai[5] to prepare early members of this series lacking the 6-substituent. According to this method, condensation of ethyl 4-nitrobutanoate with phenylmethanimine (obtained in situ via condensation of benzaldehyde and ammonium acetate; Scheme 2) afforded lactam **6** in good yield. We reasoned that an analogous sequence, substituting a ketone (i.e., **7**) for the ester, would provide an intermediate imine (**8**), which could then be reduced selectively via precedented methods to give either the common 2,6-cis or the more challenging 2,6-trans relationship present in **2** and **1**, respectively. Owing to the rich chemistry offered by the nitro group, we anticipated stereocontrol of the piperidine 3-position through selective epimerization and/or nitro group reduction sequences utilizing known methods (vide infra).[25] The cis and trans isomers of **8** would thus constitute key synthetic intermediates from which we hoped to selectively access each of the four trisubstituted piperidines **1**−**4**. Additionally, because the variable 6-alkyl group was to be incorporated in the first step of the synthesis, we needed a route that could be prosecuted efficiently.

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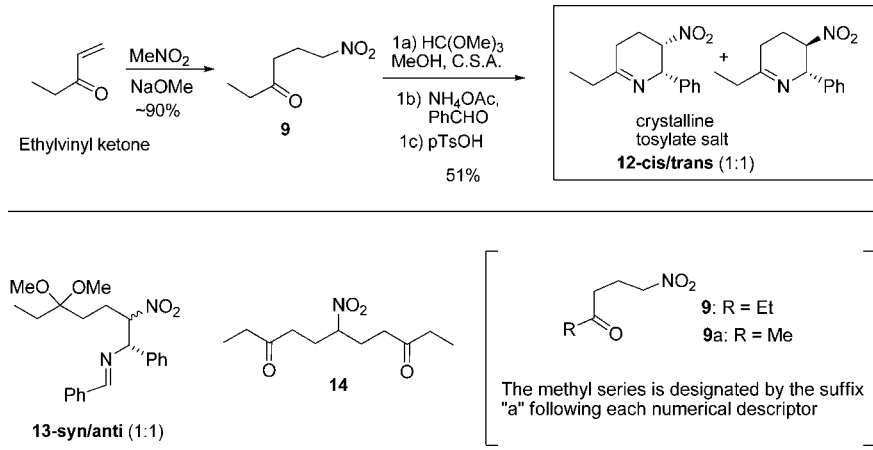
SCHEME 3



Results and Discussion[27]

We began with the synthesis of 6-nitro-3-hexanone **9** and its subsequent conversion into the key cyclic imine **12** (Scheme 3). Of several literature reports on the preparation of this ketone, we chose the original method of Shechter which included purification of the product by distillation.[28−30] The main drawback to this method was the formation of multiple-addition side products that were thermally unstable and which could decompose violently near the end of the distillation process. After some experimentation, we found that most of the byproduct could be eliminated by replacing ether with methanol as the solvent and by conducting the reaction at a low temperature. Under the new conditions, the desired product was afforded on a kilogram scale in >90% yield with only small amounts of undesired **14** detected (∼6%). Since this minor product did not affect future reactions in this sequence, the capricious distillation step could be eliminated.

The nitro-Mannich reaction of intermediate **9** en route to the formation of the cyclic imine **12** was the next step in the sequence. Unfortunately, the reaction of **9** with benzaldehyde and ammonium acetate in methanol afforded a complex mixture containing only small quantities (∼10%) of the desired product. All subsequent attempts to improve this yield by adjusting reagent stoichiometry and reaction temperature failed. We concluded from these studies that unrestrained secondary aldol or Mannich reactions were interfering with the desired process and that the products of these fast side reactions could not be funneled into the desired cyclic **12** via thermodynamic control. With the ketone functionality of **9** a likely participant in these side reactions, an easy remedy was anticipated via protection of the ketone as an acetal. In practice, the dimethyl acetal of **9** (not shown) underwent smooth reaction with 2 equiv of benzaldehyde in the presence of ammonium acetate to provide the acyclic benzylimine **13** in ∼60% crystallized yield as a 1:1 mixture of diastereomers (Scheme 3). Subsequent hydrolysis of the benzylidine and cyclization to yield crystalline **12-cis/trans** (1:1 cis/trans) was easily achieved by treatment with toluenesulfonic acid (hydrate) in ethyl acetate. Final process improvements, including an optional one-pot **9**−**12** conversion, afforded an efficient two-step procedure for the synthesis of the crystalline **12-cis/trans** (tosylate salt) from ethyl vinyl ketone as shown in Scheme 3.

With **12-cis/trans** in hand, we considered options for separation of the isomers. Due to a significantly higher polarity of the cis isomer, the two could be readily separated by silica gel chromatography after conversion into the free base imines. This provided pure material for stereochemical assignment through both NMR spectroscopy and X-ray crystallography of **12-trans** (tosylate). However, we were still interested in other options that would facilitate eventual scale-up. We expected that the **12-cis/trans** mixture could be equilibrated to the more stable trans isomer via base-catalyzed epimerization of the nitro group. This was indeed the case as simple treatment of the mixture with neat triethylamine gave a 6:1 trans/cis equilibrium ratio from which the pure isomer **12-trans** could be precipitated as the *p*-toluenesulfonate salt in 73% yield (Scheme 4).

Selective formation of **12-cis** posed a greater challenge, which we hoped to meet using the nitronate anion as a key intermediate. According to a recent report by Takemoto, protonation of the related 2-phenyl-3-nitropiperidine selectively afforded the kinetic cis product in a 95:5 ratio.[23] This has been explained by allylic strain arguments[31,32] that predict a pseudoaxial conformation of the adjacent phenyl group and a preferential axial approach of a quenching proton from the less hindered opposite face to produce the kinetic product. Alternative arguments have been postulated to explain the observed selectivity in this type of system.[33−38] Our early attempts centered around employment of a bulky proton donor,[25,39] but repeated attempts to effect this strategy with a variety of bases, acids, and solvents afforded only moderate improvements in the cis/trans ratio (up to 3:1 cis/trans). However, during these experiments we made the serendipitous discovery that the nitronate could be quenched directly onto a silica TLC plate to

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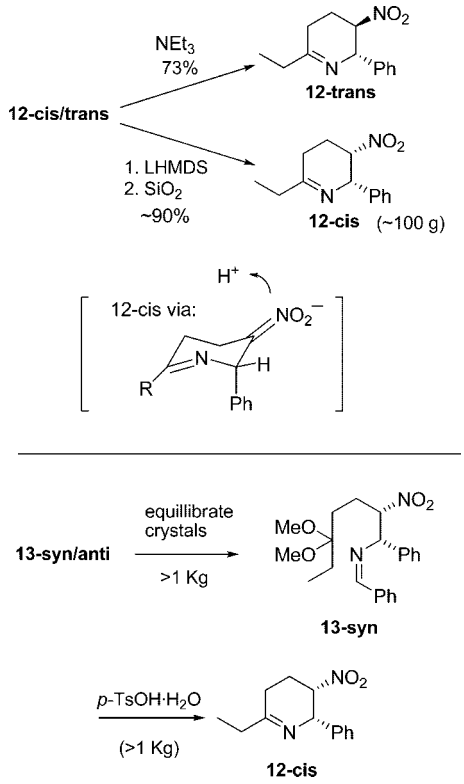
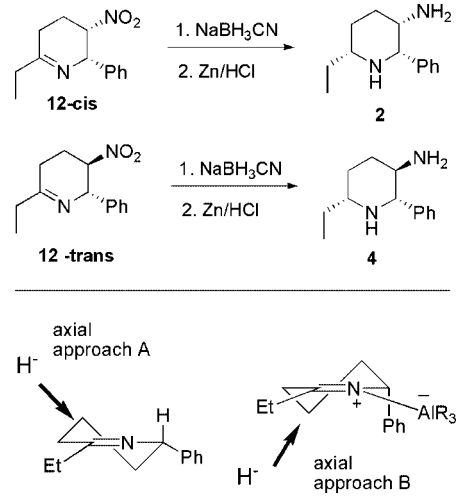
SCHEME 4



provide pure cis isomer as indicated by TLC cospot with authentic **12-cis**. In subsequent experiments, the direct quench of the nitronate into slurries of silica gel in THF afforded the cis isomer exclusively. The difficulty in obtaining a majority of the cis isomer under most conditions in our more functionalized system (relative to the Takemoto example) might be ascribed to the internal imine which adds ring strain and basic character that could elicit equilibration prior to isolation. We surmised that silica gel may circumvent equilibration in one of two ways: by mitigating the basicity of the imine, or by coordination of the nitronate to enhance C-protonation over nitronate (NO_2^-) protonation.

While this method was quite suitable for processing quantities up to 100 g, we were not satisfied that it would be amenable to large-scale synthesis due to technical difficulties associated with mixing voluminous slurries of silica gel. In the course of this work, we noted that product **13** (1:1 syn/anti) readily crystallized to afford the expected 1:1 mixture of syn and anti isomers. However, NMR experiments demonstrated that, in the presence of an equilibration catalyst (NH_4OAc), **13-syn** was favored thermodynamically over **13-anti** by a 2:1 ratio in methanolic solution. Further experimentation revealed that stirred slurries of **13-syn/anti** in methanolic NH_4OAc yielded syn-isomer crystals, free of detectable isomeric impurities, within 3 days (Scheme 4).[40,41] This thermodynamically driven crystallization process[42] ultimately provided us with the desired **13-syn** on kilogram scale. The subsequent cyclization of **13-syn** to form **12-cis** was accomplished via treatment with *p*-toluenesulfonic

SCHEME 5



acid hydrate in ethyl acetate as was done previously with the cis/trans **12** mixture. Thus, the selective and scaleable synthesis of each of the key intermediates **12-cis** and **12-trans** was achieved in approximately three easy steps from ethyl vinyl ketone.

The 2,6-*cis*-aminopiperidines **2** and **4** were accessed from **12-cis** and **12-trans**, respectively, as follows. Assuming an equatorial phenyl group orientation and Fürst−Plattner control (trans-diaxial addition) for the reduction of **12-cis** and **12-trans**, we expected that 2,6-cis stereochemistry would be available via simple borohydride reduction of the imine (axial approach A, Scheme 5).[43,44] This would be followed by nitro group reduction to complete the synthesis. In practice, this strategy worked well: imine reduction gave the expected stereochemical result and subsequent zinc/HCl reduction afforded the piperidines **2** and **4** from the respective precursors **12-cis** and **12-trans** in 58% and 96% yield, respectively, as crystalline ditosylate salts (Scheme 5). The low yield in the former case was due to a less efficient crystallization. Stereochemistry was initially assigned using established predictions of piperidine conformational preferences and experimentally determined ^1H NMR coupling constants and was later confirmed by analogy with the X-ray structure of **34** (Scheme 12).

The remaining two diastereomers **1** and **3**, possessing the trans arrangement of substituents at C2/C6, posed a greater challenge in requiring the opposite facial selectivity of reduction. With axial hydride approach heavily favored in this type of imine system, reversal of selectivity can be realized in some cases via a "chair flip" induced through complexation of the imine nitrogen atom with a bulky Lewis acid such as trimethylaluminum (Scheme 5).[44] As applied to the present system, $A_{1,2}$-strain between the nitrogen/Lewis acid complex and the α-phenyl substituent should favor the flipped chair form which places the phenyl in the pseudoaxial position. Axial hydride addition, this time from the same face as the phenyl group, would afford the "trans" ethyl product (see "axial approach B," Scheme 5).[44−46]

(40) Deuterium enrichment studies in methanol-d_4 revealed that equilibration occurrs by proton exchange at the nitro center rather than through reversal of the nitro-Mannich process.

(41) The stereochemistry of the syn isomer, including the trans-geometry of the benzylidine group, was determined by X-ray crystallography.

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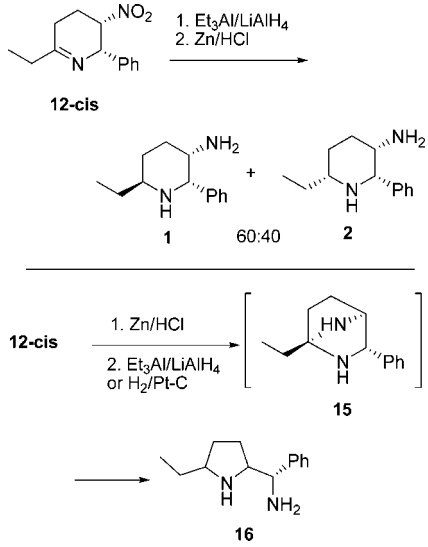
SCHEME 6

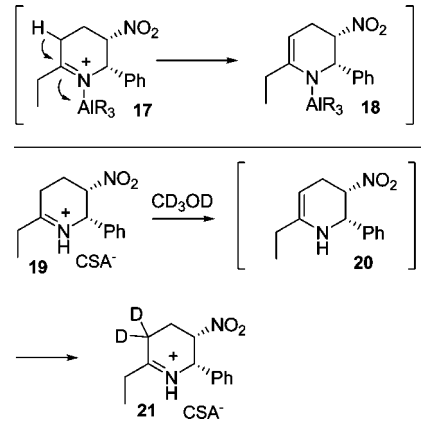


In practice, a THF solution of **12-cis** was pretreated with trimethylaluminum at −78 °C followed by addition of $LiAlH_4$ according to the method of Yamamoto. The nitro group was subsequently reduced with zinc/HCl prior to characterization of the products. Unfortunately, this method produced a disappointing ∼60:40 ratio of the products **1** and **2** (Scheme 6). On considering successful literature reports from less functionalized systems, we attributed this poor selectivity to interference of the nitro group with the action of the Lewis acid. In an effort to mitigate this effect, we reversed the order of the two-stage reduction sequence by attempting the zinc/HCl nitro-reduction first, followed by the Yamamoto reduction protocol. Under these conditions, we instead obtained a 1:1 stereoisomeric mixture of the undesired rearrangement product **16** formed via intermediate **15** (Scheme 6). A similar transformation was noted by Nicolaou et al. during the total synthesis of thiostrepton.[47]

The $AlR_3/LiAlH_4$ reduction was even less successful on scale-up and afforded significant recovery of starting material. NMR studies demonstrated that prolonged stirring of the imine **12-cis** with triethylaluminum prior to hydride addition affected deprotonation of the Lewis acid complex **17** to afford the unreactive species **18** (Scheme 7). The propensity for imine−enamine tautomerization was also observed upon dissolution of the camphorsulfonate imine salt **19** in CD_3OD. Rapid proton/deuterium exchange via the presumed intermediate **20** resulted in deuterium enrichment at C-5 to provide **21**.

An alternative plan to effect the transformation of **12-cis** into **1** hinged on removal of the problematic nitro group via the Nef reaction, with the resultant ketone functionality providing a route for introduction of the requisite 3-amino group later in the synthesis (Scheme 8).[5] However, this strategy was thwarted by the instability of **25**, which rapidly aromatized to yield the hydroxypyridine **26**. Fortunately, the Nef reaction conducted in dry methanol provided acetal products that averted aromatization. Thus, a solution of **12-cis/trans** in methanol and trimethylorthoformate was treated at −20 °C with sodium methoxide followed by quenching into sulfuric acid. The desired acetal **22** was isolated in 80% yield as a stable crystalline

SCHEME 7



camphorsulfonate salt (Scheme 8). This procedure worked equally well with the methyl series to provide **22a**.

Subsequent treatment of **22** with $AlMe_3$ and $LiAlH_4$ at −78 °C gave the 2,6-trans isomer **23** selectively (10:1) over the 2,6-cis isomer. On further experimentation, we found that the trans isomer could be obtained exclusively when the bulkier $AlEt_3$ was used in place of $AlMe_3$. For the methyl imine **22a**, reductions catalyzed by $AlMe_3$ provided a 4:1 trans/cis ratio, whereas reductions mediated by $AlEt_3$ again provided the trans isomer **23a** exclusively. In each case, the desired 2,6-*trans*-piperidine (**23** and **23a**) was obtained in high yield as a crystalline *p*-toluenesulfonate salt.

We then set about reintroduction of the C-3 nitrogen atom in the required 2,3-cis fashion and planned to accomplish this via precedented hydrogenation of the oxime **24** (Scheme 8).[5] Allylic strain imparted by the oxime group should favor an axial phenyl conformation and direct the approach of hydrogen to the opposite face (Scheme 9). This plan was immediately complicated by the instability of the oxime precursor, ketone **27**. Epimerization at C2 gave **28**, and air-oxidation gave the imine **29**. Fortunately, both of these side products could be avoided through a one-pot process involving acetal hydrolysis in the presence of hydroxylamine. Under these conditions, the ketone was trapped as the oxime prior to side reaction. In both the ethyl and methyl series, treatment of the crude product with *p*-TsOH provided the crystalline oximes (**24** and **24a**, respectively) in good yield as a 1:1 mixture of oxime isomers.

Hydrogenation of the methyl-series oxime **24a** with freshly prepared Raney nickel catalyst gave a 12:1 mixture of **1a** and **3a** (^{1}H NMR), from which isomer **1a** was obtained cleanly in 63% yield after a single crystallization. Unfortunately, this success with the methyl derivative did not carry over to the ethyl series. Under a variety of conditions, oxime **24** suffered poor facial selectivity in the hydrogenation. The origins of this effect remain unexplained but given the unsatisfactory outcome of several Raney nickel reduction attempts, we shifted focus to an alternative method under concurrent development.

As stated previously, we could not achieve acceptable 2,6-trans selectivity in reduction of **12-cis** via the Yamamoto precedent (Scheme 6). We believed this resulted from an inefficient complexation of the Lewis acid with the imine. To test this hypothesis, we replaced the transient Lewis acid complex with a covalently attached urethane group to enhance imine reactivity and control reduction selectivity. This methodology has been used to accomplish trans-selective reductions in less functionalized systems as reported independently by

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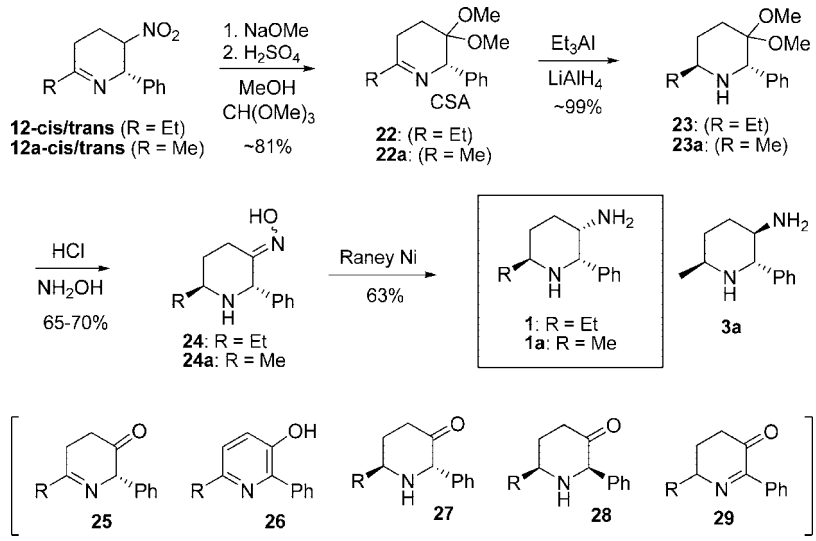
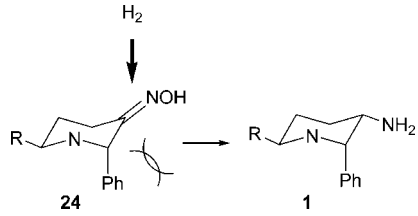
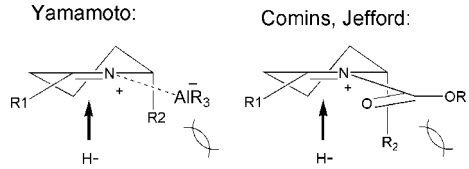
SCHEME 8



SCHEME 9



SCHEME 10

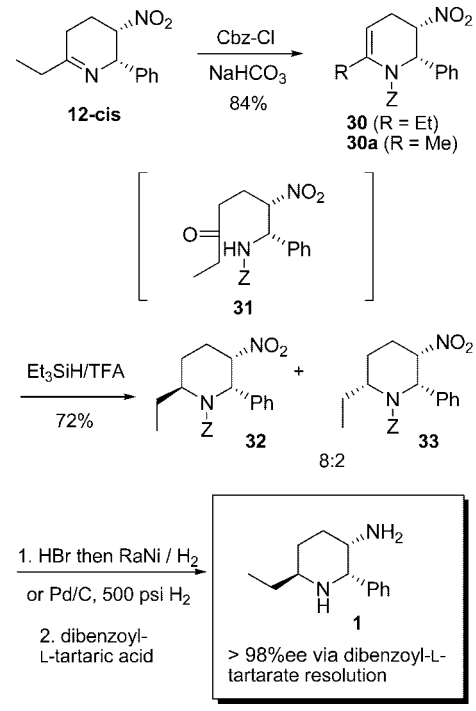


Comins and Jefford (Scheme 10).[48,49] According to these reports, the planar urethane C−N bond induced a conformational shift that placed the phenyl substituent in an axial position and, in addition, activated the imine toward stereocontrolled reduction.

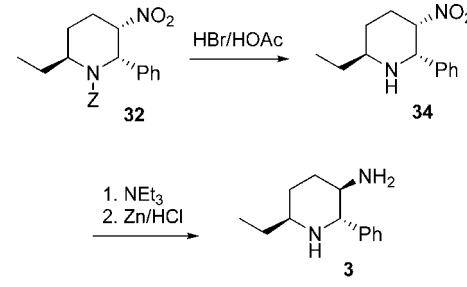
Thus, the nitroimine **12-cis** was converted into the crystalline enecarbamate **30** by treatment with benzylchloroformate and sodium bicarbonate in a methylene chloride/water mixture (Scheme 11). Efficient stirring was required for this two-phase reaction mixture to ensure a basic pH in the organic phase and to prevent formation of significant amounts of the acid-catalyzed hydrolysis product **31**. X-ray crystallography of the corresponding methyl isomer **30a** confirmed retention of the cis-configuration and verified a quasi-axial ring orientation of the phenyl group. Reduction of **30** with triethylsilane and trifluoroacetic acid provided an 80:20 trans/cis ratio of **32** and **33** from which the desired trans isomer was obtained cleanly via crystallization in 72% yield.

The 2,6-trans product **32** was converted into the desired 3-aminopiperidine **1** by either of two methods. According to the first method, the benzylchloroformate group was cleaved with HBr and the nitro group was reduced by hydrogenation over Raney nickel to yield the final product **1** in 77% yield. In the second method, hydrogenation of **32** over palladium at 500 psi provided **1** in a comparable yield in one pot. We were also gratified to find that chiral resolution of **1** was efficiently accomplished by crystallization as the dibenzoyl-L-tartarate salt to give the (2*S*,3*S*,6*S*)-enantiomer in >98% ee.[50] No attempt was made at chiral resolution of isomers **2**−**4**.

SCHEME 11



SCHEME 12



(48) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506–2512.
(49) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 2911–2914.

With efficient, selective routes to diastereomers **1**, **2**, and **4** in place, the remaining diastereomer **3** was prepared using similar chemistry as illustrated in Scheme 12. First, the carbamate group of the triethylsilane reduction product **32** was cleaved by treatment with HBr in acetic acid to provide the piperidine **34** in 85% yield as a crystalline HBr salt. Single-crystal X-ray analysis of **34** provided definitive confirmation of stereochemistry. Epimerization of **34** with triethylamine afforded a 4:1 thermodynamic ratio of isomers favoring the trans nitro epimer **35** (not shown), and subsequent zinc/HCl reduction of the nitro group afforded the remaining target piperidine **3** after workup to give a crystalline dibenzoyl-L-tartaric acid salt.

Conclusions

Each of the possible diastereomers of the racemic 2-phenyl-3-amino-6-ethylpiperidines (**1**−**4**) were prepared selectively in four to six steps from ethyl vinyl ketone in routes diverging from a common tetrahydropyridine intermediate (**12**). The methyl isomers, described in part, were prepared via similar chemistry starting from methyl vinyl ketone. The 2,3-trans and 2,3-cis stereochemical arrangements were established via thermodynamic epimerization processes conducted on the cyclic and acyclic intermediates **12** and **13**, respectively. The 2,6-cis and 2,6-trans arrangements were established through precedented iminium ion reductions. Compound stereochemistry was determined via ^{1}H NMR methods and confirmed by single-crystal X-ray analysis of intermediate **34**. With the exception of the starting nitroketone **9**, all products and intermediates are either crystalline, or form crystalline salts, such that each isomer (**1**−**4**) was prepared selectively without chromatography. An efficient chiral salt resolution was employed for the resolution of isomer **1** using dibenzoyl-L-tartaric acid. The 2,3-cis isomers **1** and **2** are of particular interest as precursors to potent neurokinin NK-1 antagonists.

Experimental Section

Active Raney Nickel Catalyst. To 7.0 g of nickel−aluminum alloy (50/50 wt. %) in 100 mL of water in a 1 L Erlenmeyer flask was added 14.0 g (350 mmol) of sodium hydroxide. The mixture was swirled by hand several times over 15−20 min. When foaming subsided, the mixture was cooled to rt and the solid was collected by filtration taking care to keep the filter cake moist. The filter cake was rinsed with 200 mL of water, and the active catalyst was carefully transferred to a vial and stored under 5 mL of water. Aliquots were transferred via pipet and weighed as thick aqueous slurries.

6-Nitrohexan-3-one (9). This compound was prepared through a modification of the literature procedure.[28] To ethyl vinyl ketone (90.1 g, 1280 mmol) in methanol (550 mL) was added nitromethane (550 mL) at −40 °C as a steady stream of 25% methanolic NaOMe (84 mL, 386 mmol). The resultant pale yellow slurry was allowed to warm to rt over 5 h and was stirred overnight. The mixture was quenched with satd NH_4Cl (300 mL) followed by water (250 mL) and brine (250 mL). The mixture was then extracted with CH_2Cl_2 (250 mL × 4). The extracts were treated with $MgSO_4$ and decolorizing carbon for 10 min, filtered, and concentrated to yield 154 g (92%) of a pale yellow liquid that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.43 (t, J = 6.6 Hz, 2H), 2.56 (t, J = 6.6 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H), 2.25 (m, 2H), 1.06 (t, J = 7.5 Hz, 3H).

***rel*-(1*S*,2*S*)- and *rel*-(1*S*,2*R*)-Benzylidene-(5,5-dimethoxy-2-nitro-1-phenylheptyl)amine (13-syn/anti).** To 6-nitrohexan-3-one (**9**) (66.4 g, 457 mmol) in methanol (90 mL) and trimethylorthoformate (90 mL) was added camphorsulfonic acid (5.70 g, 24.7 mmol). After 30 min, a solution of ammonium acetate (75.9 g, 986 mmol) in methanol (200 mL) was added followed by benzaldehyde (110 g, 1030 mmol). The solution was stirred for 7 h and then seeded to induce crystallization. The resultant slurry was stirred overnight, and the crystals were collected and rinsed with 300 mL of cold methanol to yield 100 g (53%) of an inseparable mixture of 1:1 *syn*- and *anti*-benzylidene-(5,5-dimethoxy-2-nitro-1-phenylheptyl)-amine as a white powder: mp 105−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.31 (s, 1H), 8.21 (s, 1H), 7.78 (m, 1H), 7.72 (m, 1H), 7.30−7.46 (m, 8H), 5.00−5.05 (m, 2H), 4.77 (d, J = 7.9 Hz, 1H), 4.66 (d, J = 10.0 Hz, 1H), 3.09 (s, 3H), 3.06 (s, 3H), 3.05 (s, 3H), 2.98 (s, 3H), 2.02 (m, 1H), 1.95−1.80 (comp, 2H), 1.50−1.61 (comp, 9H), 1.41 (q, J = 7.4 Hz, 2H), 0.75 (t, J = 7.4 Hz, 3H), 0.66 (t, J = 7.5 Hz, 3H); MS m/z (ion) 353 (M − OCH_3). Combustion analysis and IR data for the pure syn isomer is provided below.

***cis/trans*-6-Ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine *p*-Toluenesulfonate (12-cis/trans).** To a stirred solution of 1:1 *rel*-(1*S*,2*S*)- and *rel*-(1*S*,2*R*)-benzylidene-[(1,2-*syn*)-5,5-dimethoxy-2-nitro-1-phenylheptyl] amine (**13-syn/anti**) (100 g, 260 mmol) in ethyl acetate (300 mL) was added a solution of *p*-toluenesulfonic acid hydrate (*p*-TsOH·H_2O) (54.3 g, 286 mmol) and water (4.68 g, 260 mmol) in warm EtOAc (300 mL). The mixture was stirred at rt overnight, and the resultant precipitate was collected and rinsed with 250 mL of EtOAc followed by 250 mL of ether to yield 95 g (90%) of the title compounds as a 1:1 cis/trans mixture: MS m/z (ion) 233 (M + H). Analytical data for the individual pure isomers is provided below.

***trans*-6-Ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine *p*-Toluenesulfonate (12-trans).** A 1:1 mixture of *cis*/*trans*-6-ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine *p*-toluenesulfonate (**12-cis/trans**) (9.97 g, 24.7 mmol) was converted into the free base as follows: the white powder was stirred vigorously with satd $NaHCO_3$ (50 mL) for 10 min. The mixture was extracted with $CHCl_3$ (2 × 50 mL), and the extracts were dried via filtration through cotton and concentrated to give a colorless oil. The oil was dissolved in triethylamine (15 mL) and kept at rt for 4 h. The triethylamine was removed via rotary evaporator, and the residue was reconcentrated from $CHCl_3$ (2 × 30 mL) to remove residual triethylamine. The resultant oil comprised a 6:1 trans/cis mixture of isomers by ^{1}H NMR analysis. The oil was then stirred with EtOAc (80 mL) and treated with a solution of *p*-TsOH·H_2O (4.92 g, 25.9 mmol) in methanol (20 mL). After being stirred for 40 min, the resultant precipitate was collected, rinsed with EtOAc, and dried to give 7.28 g (73%) of the pure trans isomer according to ^{1}H NMR and TLC analysis: mp 169−170 °C; IR (DRIFTS) 2980, 2689, 1683, 1553, 1454, 1436, 1374, 1228, 1209, 1164, 1123, 1029, 1007 cm^{-1}. A sample was converted into the free base for NMR analysis: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.34−7.22 (comp, 3H), 7.14 (d, J = 7.0 Hz, 2H), 5.22 (d, J = 6.2 Hz, 1H), 4.49 (ddd, J = 8.3, 6.6, 3.7 Hz, 1H), 2.49 (m, 1H), 2.40−2.23 (comp, 4H), 2.13 (m, 1H), 1.47 (t, J = 7.5 Hz, 3H);^{13}C NMR (DMSO-d_6, δ): 195.0, 146.1, 138.5, 134.5, 130.3, 129.8, 128.8, 128.8, 126.2, 82.9, 60.0, 31.4, 27.9, 21.5, 21.0, 10.8; MS m/z (ion) 233 (M + H); HRMS calcd for $C_{13}H_{17}N_2O_2$ M + H 233.1284, obsd 233.1287. Anal. Calcd for $C_{13}H_{16}N_2O_2$·*p*-TsOH: C, 59.39; H, 5.98; N, 6.93. Found: C, 59.34; H, 6.06; N, 6.86.

***cis*-6-Ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine (12-cis).** To a 1:1 cis/trans-6-ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine *p*-toluenesulfonate (**12-cis/trans**) (250 mg, 1.07 mmol) in THF (5 mL) at −78 °C was added LiHMDS (1.07 mL of a 1 M solution in THF). The solution was stirred for 20 min and was then quenched directly into a well-stirred mixture of Baker silica gel (40 μM flash chromatography grade) (2.0 g) in THF (5 mL). The silica gel was removed via filtration, and the filtrate was concentrated under

(50) The absolute stereochemistry of the resolved piperidine was determined by conversion into the known NK-1 antagonist CP-728663 (D-lactate salt), for which we subsequently obtained an X-ray crystal structure. See ref 24.

vacuum to afford 230 mg (92%) of a red-orange oil consisting solely of the cis isomer. See below for characterization data on this compound.

***rel*-(1*S*,2*S*)-Benzylidene(5,5-dimethoxy-2-nitro-1-phenylheptyl)-amine (13-syn).** To a solution of 6-nitrohexan-3-one (**9**) (13.9 g, 95.7 mmol) in methanol (28 mL) and trimethylorthoformate (28 mL) was added camphorsulfonic acid (1.11 g, 4.78 mmol). After 30 min, a solution of ammonium acetate (36.9 g, 478 mmol) in methanol (120 mL) was added followed by benzaldehyde (19.5 mL, 191 mmol). A precipitate appeared within 6 h, and ^{1}H NMR analysis revealed a 1:1 mixture of *syn*/*anti*-benzylidene(5,5-dimethoxy-2-nitro-1-phenylheptyl)amine isomers. The remaining slurry was heated to 40 °C for 7 h: ^{1}H analysis of an aliquot revealed that the crystals were free of detectable isomeric impurities and that the solution consisted of a mixture of syn and anti isomers. The slurry was then gradually cooled to rt and stirred for 48 h. The slurry was finally cooled on ice for 1 h, and the crystals were collected via filtration to afford 24.3 g (66%) of the title compound as a white powder: mp 104 °C; IR (DRIFTS) 2967, 1635, 1552, 1452, 1079, 1060, 757, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.2 (s, 1H), 7.72 (dd, J = 1.7, 8.3 Hz, 2H), 7.45 (m, 1H), 7.35 (m, 8H), 5.03 (dt, J = 1.7, 10 Hz, 1H), 4.65 (d, J = 10 Hz, 1H), 3.04 (s, 3H), 2.98 (s, 3H), 1.85 (m, 1H) 1.5 − 1.6 (comp, 3H), 1.42 (q, J = 7.5 Hz, 2H), 0.65 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ) 163.5, 138.9, 136.0, 132.0, 129.5, 129.4, 129.0, 128.88, 128.87, 103.0, 93.6, 76.6, 47.7, 28.2, 25.6, 25.2, 8.2; MS *m*/*z* (ion) 353 (M − OCH_3). Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N: 7.29. Found: C, 68.73; H, 7.45; N, 7.25.

***rel*-(1*S*,2*S*)-Benzylidene(5,5-dimethoxy-2-nitro-1-phenylhexyl)-amine (13a-syn).** To a solution of 1-nitropentan-2-one (**9a**) (55.0 g 420 mmol) in MeOH (150 mL) and trimethyl orthoformate (180 mL) was added camphorsulfonic acid (2.45 g, 21 mmol). After 4 h, ammonium acetate (80.8 g, 1.05 mol) was added followed by benzaldehyde (91.2 g, 861 mmol). The mixture was stirred for 36 h and then was diluted with water (150 mL) followed by (carefully) satd $NaHCO_3$ (200 mL). The mixture was extracted with chloroform (2 × 200 mL), and the extracts were dried via filtration through cotton and concentrated. The resultant oil was dissolved in MeOH (400 mL) and diluted with water (40 mL). To the mixture was added ammonium acetate (32.3 g, 420 mmol), which caused an oil to precipitate. An additional volume of MeOH (135 mL) and water (15 mL) was added, and the mixture was stirred vigorously for 5 days. The resultant crystalline precipitate was collected via filtration, rinsed with a solution of 1:10 water/MeOH (150 mL), and dried under vacuum to provide 88.5 g (57%) of the title compound as a white powder: mp 71−72 °C; IR (DRIFTS) 2994, 1645, 1549, 1379, 1047, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.21 (s, 1H), 7.72 (dd, J = 1.6, 7.8 Hz, 2H), 7.30−7.48 (comp, 8H), 5.05 (ddd, J = 12, 12, 2.5 Hz, 1H), 4.66 (d, J = 9.5 Hz, 1H), 3.07 (s, 3H), 3.02 (s, 3H), 1.82−2.00 (m, 1H), 1.50−1.60 (comp, 3H), 1.09 (s, 3H); MS *m*/*z* (ion) 307 (M − OCH_3).

***cis*-6-Ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine *p*-Toluenesulfonate (12-cis).** To s*yn*-benzylidene[(1,2-*syn*)-5,5-dimethoxy-2-nitro-1-phenylheptyl]amine (**13-syn**) (1.00 g, 2.6 mmol) in EtOAc (3 mL) was added a solution of *p*-TsOH·H_2O (543 mg, 2.60 mmol) in EtOAc (3 mL). The solution was stirred at rt overnight. The resultant slurry was diluted with ether (3 mL), and the solids were collected via filtration to yield 1.02 g (97%) of the title compound as a white powder: mp 161−162 °C; IR (DRIFTS) 2924, 2676, 1679, 1551, 1221, 1160, 1031, 680, 564 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, δ)**:** 7.66 (d, J = 8.3 Hz, 2H), 7.43−7.45 (comp, 3H), 7.27−7.30 (m, 2H), 7.20 (d, J = 7.9 Hz, 2H), 5.59 (d, J = 5.3 Hz, 1H), 5.42 (app q, J = 5.8 Hz, 1H), 4.87 (br s, 1H), 3.32 (solvent-exchangeable, par obsc ddd, J = 2.1, 6.6, 21.5 Hz, 1H), 3.17 (solvent-exchangeable, dt, J = 6.6, 21.5 Hz, 1H), 2.88 (ddq, J = 1.7, 1.7, 7.5 Hz, 2H), 2.46 (m, 2H), 2.34 (s, 3H), 1.36 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ) 195.5, 146.1, 138.5, 132.5, 130.2, 129.5, 128.8, 128.5, 126.1, 81.8, 58.7, 31.4, 27.9, 21.4, 18.8, 11.0; MS *m*/*z* (ion) 233 (M − OTs); HRMS calcd for $C_{13}H_{17}N_2O_2$ M + H 233.1284, obsd 233.1288.

***cis*-6-Methyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine *p*-Toluenesulfonate (12a-cis).** To benzylidene[(1,2-*syn*)-5,5-dimethoxy-2-nitro-1-phenylhexyl]amine (**13a-cis**) (47.0 g, 127 mmol) in EtOAc (200 mL) was added a solution of *p*-TsOH·H_2O (26.5 g, 140 mmol) in EtOAc (100 mL). The solution was stirred overnight, and the resultant precipitate was collected via filtration and rinsed with EtOAc and Et_2O to provide 42.2 g (85%) of a white solid: mp 160−162 °C; IR (DRIFTS) 3046, 2968, 2696, 1695, 1557, 1228, 1217, 1165, 1122, 1030, 1006, 814, 681, 570 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 58.45; H, 5.68; N, 7.17. Found: C, 58.40; H, 5.50; N, 7.05. A sample was converted into the free base by partitioning between $CHCl_3$ and satd $NaHCO_3$: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.26−7.30 (comp, 3H), 7.08−7.10 (m, 2H), 2.27 (br d, J = 5.0 Hz, 1H), 4.91 (ddd, J = 3.7, 5.4, 9.1 Hz, 1H), 2.62 (dddd, J = 1.2, 6.6, 6.6, 19.1 Hz, 1H), 2.37 (dddd, J = 1.7, 7.5, 7.5, 18.7 Hz, 1H), 2.17−2.27 (m, 1H), 2.14 (s, 3H), 2.06−2.14 (m, 1H); MS *m*/*z* (ion) 219 (M + H); ^{13}C NMR (DMSO-d_6, δ) 191.9, 146.1, 138.4, 132.5, 130.3, 129.5, 128.8, 128.5, 126.1, 81.0, 58.6, 29.6, 24.9, 21.4, 18.9; HRMS calcd for $C_{12}H_{15}N_2O_2$ M + H 219.1128, obsd 219.1137.

***rel*-(2*S*,3*S*,6*R*)-6-Ethyl-2-phenylpiperidin-3-ylamine Hydrochloride (2).** To a slurry of *cis*-6-ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine *p*-toluenesulfonate (**12-cis**) (341 mg, 0.844 mmol) in THF (4 mL) was added a 1 M THF solution of sodium cyanoborohydride (1.69 mmol). The solution was stirred for 40 min and was then quenched carefully with 6 M HCl (10 mL). To the solution was added zinc powder (549 mg, 8.44 mmol), and the resultant mixture was stirred overnight. The resultant colorless solution was diluted with water (20 mL) and basified by the slow addition of a 1 M NaOH solution. The resultant cloudy mixture was stirred for 30 min and extracted three times with methylene chloride. The combined extracts were dried via filtration through cotton and concentrated. The resultant colorless oil was then dissolved in EtOAc (3 mL) and methanol (1 mL). To the stirred solution was added a solution of 12 N HCl (155 uL, 1.86 mmol) in methanol (1 mL). After being stirred for 15 min, the solution was diluted with EtOAc (5 mL), and a precipitate formed within a few minutes. The mixture was stirred for 2 days, and the resultant crystals were isolated via filtration to provide 135 mg (58%) of the title compound: mp 347 °C; IR (DRIFTS) 2942, 2048, 2009, 1613, 1571, 1548, 1528, 1460, 1432, 980, 751, 703 cm^{-1}; ^{1}H NMR (400 MHz, D_2O, δ) 7.35−7.45 (comp, 3H), 7.25 (d, J = 7.4 Hz, 2H), 4.83 (d, J = 3.5 Hz, 1H), 3.98 (ddd, J = 3.3, 3.3, 3.3 Hz, 1H), 3.29 (m, 1H), 2.02−2.20 (comp, 3H), 1.76 (m, 1H), 1.62 (m, 1H), 1.5 (m, 1H), 0.92 (br t, 3H); MS *m*/*z* (relative intensity, ion) 205 (100, M + H), 188 (M − NH_2, 86). Anal. Calcd for $C_{13}H_{20}N_2$·2HCl: C, 56.32; H, 8.00; N, 10.01. Found: C, 56.07; H, 8.10; N, 10.00.

***rel*-(2*S*,3*S*,6*R*)-6-Methyl-2-phenylpiperidin-3-ylamine Di(*p*-toluenesulfonate) (2a).** To *cis*-6-methyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine hydro-*p*-toluenesulfonate (**12a-cis**) (5.10 g, 12.5 mmol) in THF (60 mL) was added $NaBH(OAc)_3$ (5.3 g, 25 mmol). After 1 h, the mixture was cooled in an ice bath, and 6 M HCl (60 mL) was carefully added followed by zinc powder (4.5 g, 100 mmol). The ice bath was removed, and the solution was stirred overnight. The solution was then cooled in an ice bath and diluted with ice-cold 6 M NaOH (170 mL). After 10 min, the mixture was extracted with $CHCl_3$ (3 × 170 mL). The extracts were dried via filtration through cotton and concentrated to provide 2.5 g of an oil. ^{1}H NMR revealed the presence of the desired cis-isomer and ca. 4% of the 2,6-trans isomer. The material was dissolved in EtOAc (50 mL), and *p*-toluenesulfonic acid hydrate (4.75 g, 25 mmol) was added as a solution in methanol (10 mL). The mixture was stirred for 2.5 h, and the resultant precipitate was collected via filtration and rinsed with EtOAc to provide 6.1 g (91%) of the title compound as a single isomer according to ^{1}H NMR analysis: mp 241−242 °C. A sample was converted into the free base for analysis: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.20−7.38 (comp, 5H), 3.87 (d, J =

2.1 Hz, 1H), 2.90 (ddd, J = 3.3, 3.3, 3.3 Hz, 1H), 2.79 (m, 1H), 1.70−1.85 (comp, 2H), 1.25−1.60 (comp, 2H), 1.11 (d, J = 6.2 Hz, 3H); IR (DRIFTS) 2855, 2585, 1601, 1548, 1452, 1175, 1124, 1034, 1010, 683, 568 cm^{-1}; MS *m*/*z* (relative intensity, ion) 191; HRMS calcd for $C_{12}H_{19}N_2$ M + H 191.1542, obsd 191.1548. Anal. Calcd for $C_{12}H_{18}N_2 \cdot 2p$-TsOH: C, 58.4; H, 6.32; N, 5.24. Found: C, 58.34; H, 6.41; N, 5.17.

***rel*-(2*S*,3*R*,6*R*)-6-Ethyl-2-phenylpiperidin-3-ylamine Di(*p*-toluensulfonate) (4).** To a slurry of *trans*-6-ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine *p*-toluenesulfonate (**12-trans**) (6.00 g, 14.9 mmol) in THF (40 mL) was added a 1 M solution of sodium cyanoborohydride in THF (30 mmol, 30 mL). The mixture was stirred for 30 min, cooled in an ice bath, and carefully diluted with 6 M HCl (60 mL) added in portions over 20 min. Zinc powder (6.7 g, 149 mmol) was then added in two portions 5 min apart. The mixture was warmed to rt and stirred 4 h. The mixture was cooled in an ice bath and quenched via slow addition of ice-cold 3 M NaOH (140 mL). The resultant milk-white mixture was warmed to rt for 15 min and filtered through Celite to remove zinc salts. The filter cake was rinsed with water, and the combined filtrates were extracted twice with chloroform. The extracts were dried via filtration through cotton and concentrated to give a 3.02 g (99%) of a colorless oil. The oil was dissolved in EtOAc (50 mL) and MeOH (3 mL). To the stirred solution was added p-TsOH·H_2O as a solution in MeOH (10 mL). After the solution was stirred overnight, the resultant solid was collected via filtration, rinsed sequentially with EtOAc and ether, and dried to give 7.83 g (96%) of the title compound as a white powder: mp 311−312 °C; ^{1}H NMR (400 MHz, D_2O, δ) 7.48 (d, J = 8.3 Hz, 4H), 7.37 (comp, 5H), 7.16 (d, J = 7.9 Hz, 4H), 4.16 (d, J = 11.2 Hz, 1H), 3.72 (dt, J = 3.7, 11.6 Hz, 1H), 3.14 (m, 1 H), 2.27−2.10 (comp, 2H), 2.19 (s, 6H), 1.68 (dq, J = 3.7, 12.9 Hz, 1H), 1.60−1.40 (comp, 3H), 0.78 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ) 145.4, 139.0, 132.5, 130.1, 130.0, 129.8, 129.0, 126.1, 62.4, 59.5, 49.8, 28.2, 25.7, 21.5, 10.4. Anal. Calcd for $C_{13}H_{20}N_2 \cdot 2p$-TsOH: C, 59.1; H, 6.61; N, 5.11. Found: C, 59.02; H, 6.61; N, 5.11. A sample was converted into the free base via neutralization with satd $NaHCO_3$ and extraction with chloroform: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.41 (comp, 5H), 3.21 (d, J = 9.1 Hz, 1H), 2.75 (m, 1H), 2.54 (m, 1H), 2.02 (m, 1H), 1.76 (m, 1H), 1.46−1.22 (comp, 7H), 0.88 (t, J = 7.9 Hz, 3H); IR (DRIFTS) 2971, 2731, 1617, 1545, 1174, 1036, 1011, 684 cm^{-1}; MS *m*/*z* (relative intensity, ion) 205 (15, M + H), 188 (100, M − NH_2); HRMS calc'd for $C_{13}H_{21}N_2$ M + H 205.1699, obsd 205.1703.

6-Ethyl-3,3-dimethoxy-2-phenyl-2,3,4,5-tetrahydropyridine Camphorsulfonate (22). To a 1:1 mixture of *trans*- and *cis*-6-ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine *p*-toluenesulfonate (**12-cis/trans**) (18.8 g, 46.5 mmol) in methanol (150 mL) was added a 25 wt %/wt solution of NaOMe in methanol (30 mL). The solution was stirred at rt for 5 min and then was added rapidly dropwise to an ice-cold solution of H_2SO_4 (45.6 g, 465 mmol) in MeOH (200 mL). The mixture was warmed rt over ∼2 h and stirred overnight. The mixture was then concentrated under vacuum until a viscous cloudy oil resulted. The oil was poured carefully into a stirred solution of ice-cold aqueous Na_2CO_3 (41.8 g, 394 mmol) in water (400 mL). The mixture was then extracted with CH_2Cl_2 (3 × 200 mL), and the combined extracts were dried and concentrated. The resultant oil was dissolved in a 1:1 solution of ether/EtOAc (100 mL) and cooled in an ice bath. To the stirred solution was added camphorsulfonic acid (10.7 g, 46.5 mmol) as a solution in 1:1 ether/EtOAc (100 mL). The mixture was warmed to rt and stirred overnight. The precipitate was collected via filtration and rinsed with THF to supply 18.0 g (81%) of the title compound as a white powder: mp 156−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.40−7.03 (comp, 3H), 7.20−7.17 (comp, 2H), 5.55 (s, 1H), 3.4 (s, 3H), 3.20 (s, 3H), 3.11 (d, J = 14.6 Hz, 1H), 3.06−2.96 (comp, 3H), 2.65 (d, J = 14.6 Hz, 1H), 2.54 (ddd, J = 4.2 Hz, 12, 15, 1H), 2.38−2.22 (comp, 2H), 2.08−2.16 (m, 1H), 1.98 (t, J = 3.6 Hz, 1H), 1.73−1.94 (comp, 3H), 1.46 (par obsc m, 1H), 1.44 (t, J = 7.8 Hz, 3H), 1.19−1.28 (m, 1H), 1.01 (s, 3H), 0.74 (s, 3H); MS *m*/*z* (relative intensity, ion) 248 (98, M + H), 216 (100, M − OCH_3).

3,3-Dimethoxy-6-methyl-2-phenyl-2,3,4,5-tetrahydropyridine Camphorsulfonate (22a). To *trans*-6-methyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine (**12a-trans**) (30.5 g 74.8 mmol) in methanol (270 mL) at rt was added 49 mL of 25 wt %/wt NaOMe/MeOH solution. After 15 min, the resultant colorless solution was added rapidly dropwise over 45 min to an ice-cold solution of H_2SO_4 (73.3 g, 748 mmol) in MeOH (374 mL) containing trimethyl orthoformate (39.6 g, 374 mmol). The resultant blue-gray solution was allowed to warm to rt and was stirred overnight. The near-colorless solution was then concentrated via rotary evaporator to ca. half it is original volume and was poured into an ice-cold, stirred solution of Na_2CO_3 (67.4 g, 636 mmol) in water (700 mL). The mixture was then extracted with $CHCl_3$ (2 × 250 mL), dried via filtration through cotton, and concentrated. The resultant oil was dissolved in THF (40 mL) and cooled to ice-bath temperature. To the stirred solution was added camphorsulfonic acid (CSA) (17.3 g, 74.8 mmol) as a solution in THF (40 mL), followed by ether (80 mL). The mixture was warmed to rt and stirred for 3 h. The crystals were collected via filtration and rinsed with THF until colorless to yield 29.1 g (84%) of a white powder: mp 182.8−183.4 °C; IR (DRIFTS) 2958, 2701, 1739, 1686, 1166, 1036 cm^{-1}. A sample was converted into the free base for NMR analysis by partitioning between satd $NaHCO_3$ and $CDCl_3$: ^{1}H NMR (free base) (400 MHz, $CDCl_3$, δ) 7.18−7.31 (comp, 3H), 7.16 (d, J = 6.7 Hz, 2H), 5.00 (s, 1H), 3.28 (s, 3H), 3.14 (s, 3H), 2.48−2.44 (comp, 2H), 2.11 (s, 3H), 1.88 (ddd, J = 2.5, 3.7, 6.2 Hz, 1H), 1.65 (ddd, J = 7.8, 9.9, 13.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, δ) 216.6, 189.4, 133.6, 128.9, 128.7, 128.6, 99.9, 97.6, 61.1, 58.5, 48.9, 48.7, 47.9, 47.3, 43.0, 42.7, 31.5, 27.2, 24.6, 24.0, 21.28, 20.1, 19.9; MS *m*/*z* (relative intensity, ion) 202 (M − OCH_3); HRMS calcd for $C_{14}H_{20}NO_2$ M + H 234.1488, obsd 234.1492;. Anal. Calcd for $C_{14}H_{19}NO_2 \cdot$CSA: C, 61.91; H, 7.58; N, 3.01. Found: C, 61.80; H, 7.74; N, 3.00.

***trans*-6-Ethyl-3,3-dimethoxy-2-phenylpiperidine (23).** The imine salt 6-ethyl-3,3-dimethoxy-2-phenyl-2,3,4,5-tetrahydropyridine camphorsulfonate (**22**) (14.1 g, 29.4 mmol) was partitioned between satd $NaHCO_3$ (1 × 100 mL) and methylene chloride (2 × 100 mL). The combined organic extracts were dried via filtration through cotton and concentrated. The resultant oil was dissolved in 40 mL of THF and cooled to −78 °C. Triethylaluminum (31 mL of a 1 M solution in hexanes) was added, and the solution was stirred for 10 min. To the solution was then added via cannula over 10 min $LiAlH_4$ (35.3 mL of a 0.5 M solution in THF), with precooling along the side of the flask. After 90 min of stirring, the mixture was quenched carefully via dropwise addition of a 50% satd solution of sodium potassium tartrate (Rochelle's salt). When vigorous bubbling stopped, the mixture was diluted with additional 50% satd Rochelle's salt solution (100 mL) and stirred overnight. The mixture was then diluted with water (100 mL) and extracted once with ether (50 mL) and once with ethyl acetate (50 mL). The combined extracts were washed with brine, dried with $MgSO_4$, and cooled in an ice bath. A 1 M solution of HCl in methanol was added (32 mL), and the solution was concentrated to a thin oil under vacuum. With stirring, the oil was diluted with ether (150 mL), which initiated crystallization. The resultant slurry was stirred for 1 h, and the precipitate was collected via filtration to yield 6.15 g of the title compound as a white powder. A second crop obtained from ethyl acetate/methanol provided another 786 mg for a total combined yield of 6.94 g (83%): mp 135−136 °C; ^{1}H NMR (400 MHz, free base, $CDCl_3$, δ) 7.78 (d, J = 7.5 Hz, 2H), 7.25−7.40 (comp, 3H), 4.15 (s, 1H), 3.23 (s, 3H), 3.19 (s, 3H), 2.43 (m, 1H), 1.91−2.10 (comp, 2H), 1.68−1.74 (m, 1H), 1.29−1.50 (comp, 3H), 0.89 (t, J = 7.5 Hz, 3H). MS *m*/*z* (ion) 218 (M − OMe).

***trans*-3,3-Dimethoxy-6-methyl-2-phenylpiperidine Hydrochloride (23a).** 3,3-Dimethoxy-6-methyl-2-phenyl-2,3,4,5-tetrahydropyridine camphorsulfonate (**22a**) (10.0 g 21.5 mmol) was converted into the free base by partitioning between satd $NaHCO_3$ and CH_2Cl_2.

The organic portion was dried via passage through a cotton plug and concentrated to a colorless oil. The oil was dissolved in dry THF (25 mL) and cooled to −78 °C. Triethylaluminum (23.7 mmol, 23.7 mL of a 1.0 M solution in hexanes) was added rapidly dropwise. After the mixture was stirred for 10 min, $LiAlH_4$ (25.8 mmol of a 1.0 M solution in THF) was added over 15 min with precooling along the flask side. The solution was stirred for 70 min and quenched via dropwise addition of 100 mL of a 50% satd Rochelle's salt solution. The mixture was warmed to rt and stirred vigorously for 2.5 h. The mixture was then diluted with 50 mL each of water and brine and extracted sequentially with ether and ethyl acetate. The combined extracts were washed with brine, dried with magnesium sulfate, and filtered. The resultant colorless solution was cooled to 0 °C with stirring, and a solution of 1 M HCl in methanol (21.5 mL) was added. Cooling and stirring were continued for 2 h. The resultant slurry was reduced under vacuum to approximately half the original volume, and the precipitate was collected via filtration to provide a first crop of 3.33 g (57%). Two additional crops were obtained from ethyl acetate/ether to provide another 1.81 g (31%). The mother liquor was washed with satd $NaHCO_3$, dried, concentrated, and chromatographed to yield another 366 mg of free-base product. This was converted into the hydrochloride salt and crystallized as above to yield an additional 303 mg (5%) of the title compound for a total combined yield of 5.44 g (93%): mp 197.0−197.6 °C; IR (DRIFTS) 2956, 2704, 2540, 2473, 1574, 1437, 1416, 1336, 1142, 1111, 1068, 765, 704 cm^{-1}. Anal. Calcd for $C_{14}H_{22}NO_2Cl$: C, 61.87; H, 8.16; N, 5.15. Found: C, 61.60; H, 8.34; N, 5.05. A sample was converted into the free base for NMR analysis by partitioning between satd $NaHCO_3$ and $CDCl_3$: ^1H NMR (free base, 400 MHz, $CDCl_3$, δ) 7.67 (d, $J = 8$ Hz, 2H), 7.29 (app. t, $J = 8$ Hz, 2H), 7.24−7.21 (m, 1H), 4.06 (s, 1H), 3.18 (s, 3H), 3.10 (s, 3H), 2.62 (m, 1H), 2.02−1.85 (comp, 3H), 1.60 (m, 1H), 1.28 (m, 1H), 0.98 (d, $J = 6.6$ Hz, 3 H); MS *m/z* (ion) 204 (M − OMe).

***rel*-(2*S*,6*S*)-6-Ethyl-2-phenylpiperidin-3-one Oxime Hydrochloride (24).** A mixture of *trans*-6-ethyl-3,3-dimethoxy-2-phenylpiperidine **23** (1.00 g, 3.51 mmol) and hydroxylamine hydrochloride (968 mg, 14.3 mmol) was dissolved in an ice-cold solution of 4 M HCl (9 mL). The resultant solution was warmed to rt for 1 h, and the pH was then raised from to ∼2 by the addition of saturated sodium acetate to accelerate oxime formation. After being stirred for 30 min, the mixture was basified carefully with $NaHCO_3$, diluted with water, and extracted three times with CH_2Cl_2. The combined extracts were dried and concentrated. ^1H NMR analysis revealed the presence of the desired cis and trans oxime isomers in an approximate 1:1 ratio, along with ca. 7% of a single undesired epimer. The material was dissolved in ethyl acetate, and a solution of 12 M HCl (292 uL, 3.5 mmol) in MeOH (1 mL) was added. The mixture was stirred for 3 h, and the resultant precipitate was isolated via filtration to provide 455 mg (51%) of a mixture consisting of the desired cis/trans oximes and the undesired epimer in a ∼3:3:1 ratio, respectively: mp 187−188 °C. ^1H NMR resonances corresponding to the desired oxime hydrochlorides are as follows: IR (DRIFTS) 2940, 2639, 2471, 2436, 1583, 1556, 1461, 1439, 1373, 752, 697 cm^{-1}; ^1H NMR (400 MHz, D_2O, δ) 7.51 (d, $J = 8.3$ Hz, 4H), 7.34−7.36 (comp, 6H), 7.28 (m, 4H), 7.16 (d, $J = 8.3$ Hz, 4H), 5.95 (s, 1H), 5.16 (s, 1H), 3.53 (m, 1H), 3.37 (m, 1H), 2.99 (dt, $J = 16.6$, 4.9 Hz, 1H), 2.52−2.57 (comp, 2H), 2.39 (m, 1H), 2.19 (s, 6H), 1.90−2.01 (comp, 2H), 1.60 (m, 2H), 1.24 (d, $J = 6.2$ Hz,, 3H), 1.16 (d, $J = 6.2$ Hz, 3H); MS *m/z* (ion) 218 (M − HCl); HRMS calcd for $C_{13}H_{19}N_2O$ M + H 219.1491, obsd 219.1500. Anal. Calcd for $C_{13}H_{18}N_2O\cdot HCl$: C, 61.29; H, 7.52; N, 11.00. Found: C, 61.20; H, 7.70; N, 10.95.

***rel*-(2*S*,6*S*)-6-Methyl-2-phenylpiperidin-3-one Oxime *p*-Toluenesulfonate (24a).** To *trans*-3,3-dimethoxy-6-methyl-2-phenylpiperidine (**23a**) was added ice-cold 4 N HCl (60 mL) followed by hydroxylamine hydrochloride (5.80 g, 84 mmol). The solution was warmed to rt and stirred for 2.5 h. Ammonium acetate was added (28.4 g, 369 mmol) to raise the pH and accelerate oxime formation. The mixture was then diluted with water, basified carefully with satd $NaHCO_3$, and extracted with ethyl acetate (2 × 75 mL). The combined extracts were washed with brine. To the extract was then added, with stirring, *p*-toluenesulfonic acid hydrate (7.98 g, 42 mmol) as a solution in 15 mL of methanol. The mixture was stirred overnight, and the resultant precipitate was collected via filtration, rinsing with 1:1 ethyl acetate/ether, to provide 12.3 g (78%) of the title compound as a white powder: mp 186−187 °C; IR (DRIFTS) 3359, 3308, 2990, 2771, 2582, 1616, 1455, 1212, 1175, 1159, 1034, 1009, 703, 682, 571 cm^{-1}; ^1H NMR (400 MHz, D_2O, δ) (∼1:1 mixture of two geometrical oxime isomers) 7.51 (d, $J = 8.3$, 4H), 7.34−7.36 (comp, 6H), 7.28 (m, 4H), 7.16 (d, $J = 8.3$, 4H), 5.95 (s, 1H), 5.16 (s, 1 H), 3.53 (m, 1H), 3.37 (m, 1H), 2.99 (dt, $J = 16.6$, 4.9, 1H), 2.52−2.57 (comp, 2H), 2.39 (m, 1H), 2.19 (s, 6H), 1.90−2.01 (comp, 2H), 1.60 (m, 2H), 1.24 (d, $J = 6.2$, 3H), 1.16 (d, $J = 6.2$, 3H); MS *m/z* (ion) 205 (M − $pTsO^-$); HRMS calcd for $C_{12}H_{17}N_2O$ M + H 205.1335, obsd 205.1342. Anal. Calcd for $C_{12}H_{16}N_2O\cdot pTsOH$: C, 60.62; H, 6.43; N, 7.44. Found: C, 60.47; H, 6.32; N, 7.36.

***rel*-(2*S*,3*S*,6*S*)-6-Methyl-2-phenylpiperidin-3-ylamine (1a).** *rel*-(2*S*,6*S*)-6-Methyl-2-phenylpiperidin-3-one oxime *p*-toluenesulfonate (**24a**) (3.59 g, 9.56 mmol) was partitioned between satd $NaHCO_3$ and CH_2Cl_2. The organic phase was removed, and the aqueous phase was extracted with CH_2Cl_2. The combined organic portions were dried through cotton and concentrated, and the residue was dissolved in 2 mL of ethyl acetate. To freshly prepared Raney nickel catalyst (1.8 g of a thick aqueous slurry) in a Parr bottle were added EtOH (2.5 mL) and the oxime solution utilizing 2.5 mL of EtOH as a rinse. The mixture was hydrogenated at 45 psi for 8 h. The catalyst was carefully removed via filtration, and the filter cake was rinsed with 1:1 ethyl acetate/EtOH. To the filtrate was added 25 mL of 1 M HCl in methanol, and the solution was concentrated. The residue was dissolved in a warm solution of 1:1 MeOH/EtOH (70 mL), treated with decolorizing carbon for 15 min, and then filtered through Celite and concentrated to give an off-white solid. The solid was then dissolved in a minimal quantity of warm methanol, diluted with 50 mL of hot EtOAc, and stirred at rt for 4 h. The resultant precipitate was isolated via filtration rinsing with EtOAc to supply 1.57 g (63%) of a white powder. ^1H NMR revealed the presence of the title compound **1a** as well as ∼8% of the *rel*-(2*S*,3*R*,6*S*)-isomer **3a**: IR (DRIFTS) 2939, 2835, 2632, 2020, 1611, 1573, 1527, 1501, 1456, 1391, 754, 748, 703 cm^{-1}. A portion was converted into the free base for NMR analysis: ^1H NMR (400 MHz, $CDCl_3$, δ) 7.2−7.4 (comp, 5H), 4.25 (d, $J = 2.5$ Hz, 1H), 3.48−3.53 (m, 1H), 3.00−3.03 (m, 1H), 2.01−2.15 (m, 2H), 1.75−1.80 (m, 1H), 1.30−1.40 (m, 1H), 1.28 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (DMSO-d_6, δ) 133.2, 129.8, 129.6, 129.0, 54.0, 50.1, 22.9, 21.6, 15.3, 14.5; MS *m/z* (relative intensity, ion) 191 (76, M + H), 174 (100, M − NH_2); HRMS calcd for $C_{12}H_{19}N_2$ M + H 191.1542, obsd 191.1538. Anal. Calcd for $C_{12}H_{18}N_2\cdot 2HCl\cdot 0.25\ H_2O$: C, 53.84; H, 7.72; N, 10.46. Found: C, 53.88; H, 7.80; N, 10.55.

***cis*-Benzyl 6-Ethyl-3-nitro-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (30).** To a solution of *cis*-6-ethyl-3-nitro-2-phenyl-2,3,4,5-tetrahydropyridine (**12-cis**) (404 g, 1.00 mol) in methylene chloride (1.6 L) was added carefully satd $NaHCO_3$ (2.4 L). To the vigorously stirred mixture was added rapidly dropwise benzyl chloroformate (202 g, 1.18 mol). The mixture was heated to reflux with vigorous stirring for ∼2 h and was then cooled back to rt. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried via passage through a cotton plug and concentrated to an oil. The residue was diluted with ∼1.5 L of isopropyl ether and stirred in an ice bath for several hours to induce crystallization. The resultant solids were collected via filtration to yield 267 g (73%) of the title compound as a pale yellow powder: mp105−106 °C; ^1H NMR ($CDCl_3$, 400 MHz, δ) 7.4−7.1 (br m, 10H), 6.22 (d, $J = 5$ Hz, 1H), 5.25−5.05 (br m, 2H), 4.96 (br t, 1H), 4.90 (m, 1H), 2.8−2.5 (m, 4H), 1.0 (t, 3H); ^{13}C NMR (DMSO-d_6, δ) 153.8, 139.8, 136.6, 136.3, 129.3,

129.12, 129.08, 128.8, 128.6, 127.8, 107.3, 81.3, 68.3, 57.7, 28.0, 23.3, 13.1; MS *m/z* (ion) 367 (M + H); HRMS calcd for $C_{21}H_{23}N_2O_4$ M + H 367.1652, obsd 367.1648.

***rel*-(2*S*,3*S*,6*S*)-6-Ethyl-3-nitro-2-phenylpiperidine-1-carboxylic Acid Benzyl Ester (32).** To *cis*-benzyl-6-ethyl-3-nitro-2-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (**30**) in methylene chloride (1.8 L) at −30 °C was added triethylsilane (239 mL, 1.50 mol), and the solution was stirred for 10 min. Trifluoroacetic acid (130 mL, 3.00 mol) was added over 3 h, maintaining an internal temperature of −25 to −30 °C (Caution! After a brief latency period during the early part of the TFA addition, the reaction becomes exothermic.) The resultant clear yellow solution was stirred for an additional 5 h at −25 to −30 °C and was finally warmed to rt for 12 h. *n*-Butanol (880 mL) was added, and the methylene chloride was removed via distillation under reduced pressure. Ethanol (880 mL) and water (880 mL) were added, and the resultant suspension was stirred with cooling for several hours. The solids were collected via filtration, rinsed with 50% aqueous ethanol (100 mL), and dried under at flow of nitrogen to afford 265 g (72%) of a white solid: mp 78−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.08−7.32 (m, 10H), 5.99 (d, J = 5.1 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 5.04 (d, J = 12.4 Hz, 1H), 4.97−4.99 (m, 1H), 5.02 (dddd, J = 5.4, 6.8, 10.2 Hz, 1H), 1.44−2.25 (m, 6H), 0.93 (t, J = 7.5 Hz, 3H); MS *m/z* (ion) 369 (M + H).

***rel*-(2*S*,3*S*,6*S*)-6-Ethyl-3-nitro-2-phenylpiperidine Hydrobromide (34).** *rel*-(2*S*,3*S*,6*S*)-6-Ethyl-3-nitro-2-phenylpiperidine-1-carboxylic acid benzyl ester (**32**) (40 g, 108 mmol) was dissolved in 80 mL of 30% HBr in propionic acid at rt with efficient stirring. Rapid evolution of gas occurred, and the desired product precipitated after 3−5 min. Stirring was continued at rt for 16 h, at which point the off-white precipitate was collected, washed with ether, and dried in vacuo to afford 29.0 g (85%) of the title compound as a off-white powder: mp 219−220 °C; ^{1}H NMR (400 MHz, D_2O, δ) 7.30−7.19 (br m, 5 H), 5.22 (q, J = 4.1 Hz, 1H), 4.92 (d, J = 3.7 Hz, 1 H), 3.65 (br. m.), 2.4−2.3 (m, 1H), 2.28 − 2.17 (m, 1H), 2.9−1.98 (m, 1H), 1.85−1.75 (comp, 2H), 1.66−1.59 (m, 1H), 0.85 (t, 3H); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.48−7.43 (m, 5H), 5.27 (q, J = 8.3 Hz, 1H), 5.10 (d, J = 3.7 Hz, 1H), 3.71 (br. m, 1H), 2.61−2.51 (m, 1H), 2.32 (app dq, J = 3.6, 15.6 Hz, 1H), 2.23 (m, 1H), 2.10 (m, 1H), 1.99 (app dq, J = 3.6, 15.2 Hz, 1H), 1.81 (m, 1H), 1.07 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ) 133.2, 129.9, 129.4, 128.1, 83.5, 54.3, 53.1, 21.8, 21.3, 19.8, 10.8; IR (DRIFTS) 2967, 2898, 2755, 2726, 2686, 2624, 1547, 1434, 1406, 1374, 1257, 1130, 697 cm^{-1}; MS *m/z* (ion) 235 (M + H); HRMS calcd for $C_{13}H_{19}N_2O_2$ M + H 235.1441, obsd 235.1436. Anal. Calcd for $C_{13}H_{18}N_2O_2$·HBr: C, 49.54; H, 6.08; N, 8.89. Found: C, 49.48; H, 6.22; N, 8.80.

***rel*-(2*S*,3*S*,6*S*)-6-Ethyl-2-phenylpiperidin-3-ylamine (1).** Approximately 1.0 g of commercial Raney nickel was rinsed with deionized water until the supernatant registered neutral pH. The wet slurry was then added to a 259 mL Parr Bottle followed by a solution of *rel*-(2*S*,3*S*,6*S*)-6-ethyl-3-nitro-2-phenylpiperidine hydrobromide (**34**) (1.00 g, 3.18 mmol) in methanol (60 mL). The mixture was hydrogenated in a Parr shaker at ∼42 psi for 4 h and was then carefully filtered through Celite and concentrated under vacuum. The residue was partitioned twice between CH_2Cl_2 and 1 N NaOH. The combined organic portions were washed with brine, dried, and evaporated to afford 470 mg (72%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (br m, 5 H), 4.05 (d, 1H), 3.0 (br t, 1H), 2.90 (m, 1H), 1.98 (m, 1H), 1.75 (m, 2H), 1.6−1.4 (m, 3H), 0.80 (t, 3H). A sample was converted into the hydrochloride salt by treatment with an excess of HCl in methanol. The mixture was concentrated under vacuum and the residue was recrystallized from methanol/EtOAc: IR (DRIFTS) 2930, 2837, 1614, 1573, 1527, 1505, 1456 cm^{-1}; ^{1}H NMR (D_2O) δ 7.59−7.40 (comp, 5H), 4.89 (d, J = 5.8, 1H), 3.90 (ddd, J = 7.5, 13.9 Hz, 1H), 3.64−3.49 (m, 1H), 2.24 (m, 1H), 2.16 (m, 2H), 1.67−1.50 (comp, 3H), 0.88 (t, J = 7.5 Hz, 3H); MS *m/z* (ion) 205 (M + H); HRMS calcd for $C_{13}H_{21}N_2$ M + H 205.1699, obsd 205.1705.

Chiral Resolution of 1. A mixture of **1** (1.17 g, 5.7 mmol) and (−)-dibenzoyltartaric acid (2.05 g, 5.7 mmol) in 2-propanol (30 mL) and water (15 mL) was heated to reflux with stirring. The solution was allowed to cool to rt with stirring overnight. The resultant solid was collected via filtration, washed with 2:1 2-propanol/water (6 mL), and dried to yield (2*S*,3*S*,6*S*)-6-ethyl-2-phenylpiperidin-3-ylamine (**1**) (1.65 g, 49%) as a white solid in 96% ee as determined by chiral HPLC (chiralpak AD, 5% EtOH, 95% heptane, 0.2% Et_2NH): mp 163−164 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ) 7.87 (d, J = 7.2 Hz, 4H), 7.59 (t, J = 5.7 Hz, 2H), 7.43 (t, J = 8.0, 11.6 Hz, 4H), 7.42−7.20 (comp, 5H), 5.59 (s, 2H), 4.19 (d, J = 1.8 Hz, 1H), 3.25 (br m, 1H), 2.90 (br m, 1H), 1.90 (m, 1H), 1.75 (m, 2H), 1.54 (dq, J = 7.4, 2H), 1.25 (m, 1H), 0.73 (t, J = 7.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ) 169.2, 165.6, 138.8, 133.9, 130.5, 129.9, 129.3, 129.2, 128.4, 127.8, 73.8, 54.2, 53.7, 50.1, 23.5, 22.3, 20.4, 11.4; $[\alpha]^{22}_D$ +20.7 (*c* 4.5, CH_3OH).

***rel*-(2*S*,3*R*,6*S*)-6-Ethyl-3-nitro-2-phenylpiperidine Hydrochloride (35).** *rel*-(2*S*,3*S*,6*S*)-6-Ethyl-3-nitro-2-phenylpiperidine hydrobromide (**34**) (1.07 g, 3.40 mmol) was converted into the free base by partitioning between CH_2Cl_2 and satd $NaHCO_3$. The organic phase was dried through a plug of cotton and concentrated. The residual oil was dissolved in triethylamine (4 mL) for 6.5 h and concentrated. Residual triethylamine was removed via azeotropic evaporation with chloroform to yield a colorless oil consisting of the 2,3-trans epimer and starting material in a 40:1 ratio, respectively, by ^{1}H NMR analysis. The material was dissolved in ethyl acetate (8 mL) and treated with a slight excess of HCl (added as 935 uL of a 4 N solution in methanol). The slurry was stirred for 4 days, and the precipitate was collected via filtration to yield 656 mg (72%) of the title compound as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.4−7.2 (comp, 5 H), 4.63 (ddd, J = 4.1, 4.2, 8.7 Hz, 1H), 4.33 (d, J = 8.7 Hz, 1 H), 2.95−2.93 (m, 1H), 2.33−2.26 (m, 1H), 2.21−2.17 (m, 1H), 1.94−1.71 (comp, 2 H), 1.76−1.71 (m, 1 H), 1.62−1.55 (m, 1H), 0.92 (t, J = 7.5 Hz, 3 H); ^{1}H NMR (400 MHz, D_2O, δ) 7.40 − 7.31 (comp, 5 H), 5.25 (dt, J = 5.0, 10.4 Hz, 1H), 4.87 (d, J = 10.0 Hz, 1H), 3.46 (m, 1 H), 2.37 (comp, 2 H), 1.99−1.86 (comp, 4H), 1.75 (m, 1H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ) 132.9, 130.7, 129.9, 129.5, 85.5, 55.7, 55.0, 24.9, 22.0, 20.8, 11.1; MS *m/z* (ion) 235 (M + H); HRMS calcd for $C_{13}H_{19}N_2O_2$ M + H 235.1441, obsd 235.1451.

***rel*-(2*S*,3*R*,6*S*)-6-Ethyl-2-phenylpiperidin-3-ylamine Dihydrochloride (3).** To a slurry of *rel*-(2*S*,3*R*,6*S*)-6-ethyl-3-nitro-2-phenylpiperidine (**35**) (585 mg, 2.17 mmol) in water (5 mL) was added 6 M HCl (10 mL) followed by zinc powder (2.00 g, 30.8 mmol) added in three portions over 1 h. After being stirred overnight, the mixture was diluted with water (25 mL) and cooled in an ice bath. The solution was basified with ice-cold 6 N NaOH and stirred for 15 min. The resultant cloudy mixture was then filtered through Celite, and the filter cake was rinsed with copious water. The combined filtrate was extracted three times with chloroform, and the extracts were dried via filtration through cotton and concentrated. The resultant oil was dissolved in a solution of ethyl acetate (23 mL) and methanol (7 mL), and a solution of 12 M HCl (380 μL, 4.56 mmol) in methanol (1 mL) was added with stirring. The mixture was stirred for 2 days, and the precipitate was collected via filtration and rinsed with ethyl acetate to yield 575 mg (96%) of the title compound as a white powder: mp 298−300 °C; ^{1}H NMR (500 MHz, D_2O, δ) 7.41−7.34 (comp, 5H), 4.27 (d, J = 11.2 Hz, 1H), 3.72 (app. dt, J = 4.1, 11.6 Hz, 1H), 3.48 (m, 1H), 3.14 (s, amine protons), 2.09−1.79 (comp, 5H), 1.70 (M, 1H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, δ) 133.2, 130.1, 130.0, 129.7, 55.4, 55.0, 50.7, 23.0, 22.0, 20.5, 10.9; IR (DRIFTS) 3366, 2815, 2724, 2550, 2000, 1655, 1634, 1574, 1538, 1464, 1059, 1018, 700 cm^{-1}; MS *m/z* (relative intensity, ion) 205 (29, M + H), 188 (100, M − NH_2); HRMS calcd for $C_{13}H_{21}N_2$ M + H 205.1699, obsd 205.1698. Anal. Calcd for $C_{13}H_{22}N_2Cl_2$·0.75H_2O: C, 53.70; H, 8.15; N, 9.63. Found: C, 53.79; H, 8.34; N, 9.63.

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Supporting Information Available: ^{1}H NMR spectra and crystallographic information files including ORTEP diagrams. This material is available free of charge via the Internet at http://pubs.acs.org.

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