Title

Regio- and Diastereoselective Synthesis of Highly Substituted, Oxygenated Piperidines from Tetrahydropyridines

Journal

The Journal of Organic Chemistry, 80(13)

ISSN

0022-3263

Authors

Chen, Shuming
Mercado, Brandon Q
Bergman, Robert G
et al.

Publication Date

2015-07-02

DOI

10.1021/acs.joc.5b00816

Peer reviewed

HHS Public Access

Author manuscript

J Org Chem. Author manuscript; available in PMC 2016 July 02.

Published in final edited form as:

J Org Chem. 2015 July 2; 80(13): 6660–6668. doi:10.1021/acs.joc.5b00816.

Regio- and Diastereoselective Synthesis of Highly Substituted, Oxygenated Piperidines from Tetrahydropyridines

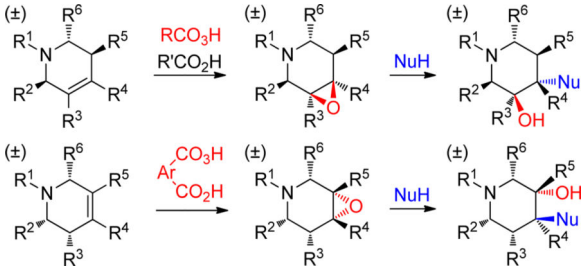
Shuming Chen[†], **Brandon Q. Mercado**[†], **Robert G. Bergman**[‡], and **Jonathan A. Ellman**[*,†]

[†] Department of Chemistry, Yale University, 225 Prospect St., New Haven, CT 06520 (USA)

[‡] Department of Chemistry, University of California, Berkeley Berkeley, CA 94720-1416 (USA) and Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, CA 94720 (USA)

Abstract

Diastereoselective epoxidation and regioselective ring-opening methods were developed for the synthesis of densely substituted, oxygenated piperidines from two classes of tetrahydropyridines with distinct stereochemical displays of functionalities. A new and practical *in situ* prepared epoxidation reagent was developed for the diastereoselective epoxidation of one class of sterically hindered tetrahydropyridines. The novel bifunctional epoxidation reagent, 2-carboperoxy-3,4,5,6-tetrafluorobenzoic acid, was designed to incorporate highly reactive percarboxy acid and pendant carboxylic acid groups, which through hydrogen bonding to the amino group successfully overrode steric effects and directed epoxidation to occur at the more hindered face of the tetrahydropyridine. Nucleophilic ring-opening of the epoxides with water, alcohols and HF proceeded with high regioselectivity, affording piperidinol products with adjacent tetrasubstituted carbons.



Introduction

Piperidine rings are ubiquitous in natural products and pharmaceuticals that play pivotal roles in the treatment of disease.[1–3] For this reason, various methods have been developed to prepare piperidines, although few methods enable the efficient preparation of densely substituted derivatives with high levels of regio- and stereocontrol.[4–5]

[*]jonathan.ellman@yale.edu.

Supporting Information

^{1}H, ^{13}C and ^{19}F NMR spectra of new compounds, and X-ray structures of **4a**, **4g**, **5a**, **5c**, **6a**, **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

We previously disclosed high-yielding and diastereoselective one-pot syntheses of densely substituted tetrahydropyridines **2** and **3** from simple imine and alkyne precursors (Scheme 1a). These tetrahydropyridines, which have different alkene regiochemistries and stereochemical displays, are obtained by a Rh(I)-catalyzed C–H alkenylation/electrocyclization cascade to give a common 1,2-dihydropyridine intermediate **1** followed by divergent kinetic or thermodynamic protonation and reduction sequences.[6–7]

While this convergent tetrahydropyridine synthesis approach provides rapid access to tetrahydropyridines, the preparation of piperidines requires further elaboration of the alkene functionality. Stereoselective epoxidation of the alkenes in **2** and **3** would arguably be the most powerful and versatile transformation because subsequent nucleophilic ring opening would enable the introduction of diverse functionalities within a drug relevant piperidinol framework.

Epoxidation of alkene substrates that contain basic amino functionalities faces the intrinsic chemoselectivity challenge of undesired electrophilic oxidation at nitrogen. To avoid *N*-oxide formation, acids have been added to protonate and thereby protect the amino group.[8-9] The resulting ammonium group is also capable of hydrogen bonding to the peracid to achieve high levels of stereoselectivity through directed epoxidation.

We report here our exploration of diastereoselective epoxidation of **2** and **3**. We find that tetrahydropyridines **2** obtained from a thermodynamic protonation/reduction sequence undergo highly diastereoselective epoxidation of the alkene via protonation and hydrogen bond directed epoxidation (Scheme 1b). However, for tetrahydropyridines **3**, which have a different stereochemical display of substituents about the 6-membered ring, this approach resulted in poor epoxidation stereoselectivity. To address this problem, we have developed a new and practical *in situ* prepared ammonium-directed epoxidation reagent that bears a highly reactive peracid functionality covalently tethered to a carboxylic acid group. Successful highly diastereoselective epoxidation of **3** is achieved by hydrogen bonding of the carboxylic acid group to the amino group, thereby enforcing high face selectivity for epoxidation. This new amino-directed epoxidation reagent should be useful for the oxidation of other alkene substrate classes that contain amino functionalities. Moreover, we demonstrate that nucleophiles react with epoxides **4** and **5** with high regioselectivity to provide densely substituted piperidinol products **6** and **7**, respectively, with each bearing adjacent tetrasubstituted carbons.

Results and Discussion

Stereoselective epoxidation of tetrahydropyridines 2

After evaluating different conditions that previously had been reported for amino-directed epoxidation, we elected to use trichloroacetic acid in excess, conditions initially introduced by Davies.[9] Protonation of tetrahydropyridine **2a** followed by treatment with *m*-chloroperbenzoic acid furnished epoxide **4a** in high yield, with excellent diastereoselectivity, and without any *N*-oxide byproduct (Scheme 2). Consistent with previously reported models for ammonium-directed epoxidation, we speculate that the excellent observed diastereoselectivity results from a transition state in which the

ammonium proton directs face selectivity by hydrogen bonding to the peroxy acid group oxygens.[10] The depicted structure of protonated **2a** corresponds to that observed in the x-ray crystal structure of the 2,4,6-trinitrobenzenesulfonate salt of **2a**.[7b]

We next explored epoxidation of tetrahydropyridines **2** with a wide range of substitution patterns (*vide infra*). While the Davies conditions effected complete conversion to the epoxide products for a fair range of tetrahydropyridines with good to excellent diastereoselectivity, we observed unacceptably slow rates of conversion for some derivatives. We therefore sought an alternative epoxidation protocol with an oxidant that is more reactive than *m*-chloroperbenzoic acid. Trifluoroperacetic acid was chosen due to its high reactivity.[8a,d] Mixing trifluoroacetic anhydride (TFAA) with hydrogen peroxide enabled the *in situ* preparation of trifluoroperacetic acid with concomitant generation of equimolar trifluoroacetic acid to protect the piperidine nitrogen by protonation. Indeed, model substrate **2a** underwent epoxidation cleanly and with high diastereoselectivity (>95:5) at room temperature when treated with pre-mixed TFAA and hydrogen peroxide.

A wide range of tetrahydropyridines **2** derived from the thermodynamic protonation/ reduction sequence (Scheme 1) can be successfully converted to epoxides in good to excellent yields and with high diastereoselectivities (Table 1). Different *N*-substitution patterns were well tolerated (**4a**–**4d**). For substrates with deactivating groups (**4f**, **4j**) or sterically hindered substitution patterns (**4h**), TFAA and hydrogen peroxide effected full conversion to the epoxide products in a diastereoselective manner. The relative configuration of the major diastereoisomer was determined unambiguously for epoxides **4a** and **4g** by X-ray crystallographic analysis and assigned by analogy to the rest of the products shown.

Development of a new class of peracids for directed epoxidation

Tetrahydropyridines **3** display all three substituents R^2, R^3 and R^6 on the same side of the heterocycle, which contrasts with tetrahydropyridines **2** with the R^2 and R^5 substituents displayed on the same face and the R^6 substituent on the opposite face of the heterocycle (Scheme 1a). As a result of the different stereochemical display of functionality, the epoxidation conditions that were successful for tetrahydropyridines **2** were ineffective for tetrahydropyridines **3**. For example, epoxidation of **3a** using the mCPBA/Cl_3CCO_2H conditions proceeded more slowly than for **2a** (see Table 1) with only 77% conversion after 3.5 h and resulted in very poor 51:49 diastereoselectivity. Epoxidation of **3a** with the TFAA and hydrogen peroxide protocol also proceeded with very low diastereoselectivity (Table 2, entry 1). We therefore designed a different hydrogen bonding motif for directly relating face-selectivity of protonation to epoxidation diastereoselectivity. We envisioned that cleaving cyclic or bicyclic anhydrides with hydrogen peroxide would generate a percarboxy acid group tethered to a carboxylic acid group capable of hydrogen bonding to the ammonium proton, thereby controlling the face selectivity of the epoxidation (Scheme 3). In this model, the depicted structure of protonated **3a** corresponds to that observed in the x-ray crystal structure of the 2,4,6-trinitrobenzenesulfonate salt of **3a**.[7a]

According to this design principle we evaluated a range of cyclic and bicyclic anhydrides (Table 2). Succinic and glutaric anhydrides gave poor conversion (entries 3 and 4), while phthalic anhydride resulted in good conversion but without significant improvement in diastereoselectivity (entry 5). The commercially available and highly electron-deficient tetrafluorophthalic anhydride afforded 2-carboperoxy-3,4,5,6-tetrafluorobenzoic acid upon cleavage with hydrogen peroxide, whose structure features a more electrophilic peracid group tethered to a more acidic and strongly hydrogen bonding carboxylic acid group. This novel epoxidation reagent brought about high conversion in almost all solvents evaluated (entries 6–10). Moreover, a significant increase in diastereoselectivity was observed in ethereal solvents, particularly THF, which gave >95:5 *dr* (Table 2, entry 10). The slightly less electron-deficient tetrachlorophthalic anhydride required higher temperatures to bring about satisfactory conversion and resulted in lower diastereoselectivity (Table 2, entries 11–12). It is noteworthy that TFAA, which upon treatment with hydrogen peroxide also generates a highly electrophilic peracid and acidic carboxylic acid, was completely unreactive when THF was used as the solvent (entry 2). This result indicates that appropriate tethering of the peracid to the acid functionality is crucial for successful epoxidation. X-ray crystallographic analysis of protonated **5a** was performed to rigorously establish relative stereochemistry with the carboxysubstituted peracid enabling introduction of the epoxide oxygen on the significantly more sterically hindered face of the molecule (Table 2).

Scope for stereoselective epoxidation of 3

Encouraged by the high diastereoselectivity achieved in the epoxidation of **3a**, we next applied this novel epoxidation protocol to other tetrahydropyridines **3** obtained via a kinetic protonation/reduction sequence (Scheme 1a). High diastereoselectivities were observed for tetrahydropyridines with differing degrees of substitution around the ring (**5a**–**5c**) as well as branched alkyl substitution on the nitrogen (**5d**). Even the sterically hindered bicyclic epoxide **5e** was obtained with good diastereoselectivity (Table 3). The relative configuration of the major diastereoisomer was established by X-ray crystallography for epoxides **5a** and **5c** and assigned by analogy for the other products.

It is also noteworthy that the new epoxidation protocol was similarly effective for epoxidation of tetrahydropyridines **2** as demonstrated for **2a** (79% yield, >95:5 dr). Furthermore, for the epoxidation of tetrahyropyridine **2k**, the tetrafluorophthalic anhydride protocol resulted in a good yield and reasonable diastereoselectivity to give stereoisomer **4k** (Table 1), whereas the use of TFAA led to the formation of multiple side products.

Regioselective opening of epoxides 4 and 5

Epoxides **4** and **5** are versatile intermediates for the preparation of a variety of functionalized piperidine products via ring opening transformations. For epoxide **4**, the addition of fluoride, alcohol, and water under acidic conditions occurred with high regioselectivity to give highly substituted piperidinols **6** with adjacent tetrasubstituted carbons (Table 4). Specifically, addition of an OH group to give **6a** was achieved by heating in saturated aqueous sodium bisulfate,[11] a methoxy group was installed to give **6b** by heating in neat anhydrous methanol with benzenesulfonic acid, and fluorohydrins **6c** and **6d** were obtained by treatment with ethereal fluoroboric acid at room temperature.[12] The

relative configuration and regiochemistry of the piperidinol products **6a** and **6b** were established by X-ray analysis. The observed high regioselectivity likely results from nucleophilic attack at the site distal from the deactivating protonated nitrogen of the piperidine ring.[13]

For epoxide **5c,** water, methanol and HF all cleanly added with high regio- and diastereoselectivity to give **7a**, **7b**, and **7c**, respectively. However, attempts to open more heavily substituted epoxides **5** derived from tetrahydropyridines **3**, led to complex mixtures, presumably due to elimination and other side reactions.

Conclusions

Highly diastereoselective epoxidation of tetrahydropyridines **2** and **3** have been demonstrated. Diastereoselective epoxidation of **2** was achieved by known methods of amino group protonation followed by epoxidation with a peracid. The diastereoselective epoxidation of **3** required the development of 2-carboperoxy-3,4,5,6-tetrafluorobenzoic acid, a new bifunctional epoxidation reagent that is prepared *in situ* from commercial materials, with the percarboxy acid group covalently tethered to the carboxylic acid functionality to enforce ammonium-directed epoxidation. A variety of nucleophiles were added to the epoxides **4** and **5** to provide piperidinols **6** and **7** with adjacent tetrasubstituted carbon stereocenters. Employing the methods reported here, high levels of substitution, functionalization, and stereocontrol can easily be achieved for the epoxide intermediates and the piperidinol products, with both compounds possessing valuable pharmaceutical potential.[1,2,14]

Experimental

General Methods

Chromatography was performed on preparative thin-layer chromatography plates (1 mm SiO_2, 20 × 20 cm). Molecular sieves were activated by heating to 280 °C *in vacuo* (*ca.* 0.1 Torr) for 6–12 h. For air-sensitive experiments, glassware was dried at 150 °C for at least 12 h and allowed to cool under an inert atmosphere. Experiments were set up inside a glovebox under a nitrogen atmosphere with oxygen and moisture levels not exceeding 1 ppm. Solvents for air-sensitive reactions were dried by passing through activated alumina, degassed and stored over 3 Å molecular sieves in a glovebox. Solvents of ACS reagent grade were used for work-up and purification. Alkynes were distilled under a nitrogen atmosphere or *in vacuo* and stored in a glovebox prior to use. Liquid amines were purified according to procedures described in literature[16] and stored in a glovebox prior to use. $[RhCl(coe)_2]_2$ was stored inside an N_2-filled inert atmosphere glovebox at −25 °C. The ligand, Me_2N-C_6H_4-PEt_2, was synthesized according to a previously published procedure[7a] and stored inside an N_2-filled inert atmosphere glovebox at −25 °C. Stock solutions of the rhodium catalyst were made by dissolving $[RhCl(coe)_2]_2$ (50.0 mg, 69.7 μmol) and Me_2N-C_6H_4-PEt_2 (30.0 mg, 143 μmol) in anhydrous PhMe until a total volume of 3.0 mL is reached. Stock solutions were used immediately and showed no difference in catalytic activity after being stored for months in a −25 °C freezer inside a N_2-filled glovebox. Methyl 4-methylpent-2-ynoate was prepared according to a literature procedure.[17] All

imines except (*E*)-1-cyclohexyl-*N*-((*E*)-3-methylpent-3-en-2-ylidene)methanamine were prepared according to literature procedures.[6,7a] With the exception of the tetrahydropyridines for which the preparations are described below, all tetrahydropyridines were prepared according to literature procedures.[6,7b]

NMR characterization was performed on 400, 500, or 600 MHz instruments. Data are reported in the following format: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, etc.), coupling constant *J* in Hz, integration, and interpretation. All spectra were referenced against residual solvent peaks (^{1}H: residual $CHCl_3$ = 7.25 ppm, 13C: $CDCl_3$ = 77.0 ppm). For final products, d1 relaxation times of 15 seconds were used to record ^{1}H NMR spectra for accurate integration and quantitative determination of regio- and diastereoselectivities. IR spectra were obtained using FT-IR instruments in CH_2Cl_2. Liquid chromatography-mass spectrometry (LC-MS) spectra were measured on an instrument equipped with dual atmospheric pressure chemical ionization (API)/eletrospray ionization (ESI) and a photodiode array detector. High resolution mass spectra (ESI HRMS) were obtained on a time-of-flight (TOF) mass spectrometer.

(*E*)-1-cyclohexyl-N-((*E*)-3-methylpent-3-en-2-ylidene)methanamine (8)

A 20-mL scintillation vial equipped with a stir bar was charged with 3-methylpent-3-en-2-one (363 mg, 3.70 mmol), cyclohexanemethylamine (423 mg, 3.74 mmol), dry THF (4 mL) and titanium (IV) ethoxide (4.0 mL, 18 mmol). The vial was capped and heated to 50 °C for 2 h and then allowed to cool to rt. *N*,*N*,*N*′*N*′-tetrakis(2-hydroxyethyl)ethylenediamine (EDTE) (4.5 mL, 25 mmol) was added, and the mixture was heated to 55 °C for 15 min until a clear yellow solution was observed. The mixture was cooled to rt and poured into a separatory funnel containing NH_4OH (20 mL) and brine (10 mL). The aqueous phase was extracted with EtOAc (30 mL), and the organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was filtered through basic Al_2O_3 (*ca.* 3 cm in a Pasteur pipet, eluting with pentane), and the filtrate was concentrated *in vacuo* to give the desired imine (>98% *E* isomer) as a slightly yellowish oil (480 mg, 2.48 mmol, 67%), which was stored at −25 °C under an N_2 atmosphere in a glovebox. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09–6.01 (m, 1 H), 3.15 (d, *J* = 6.7, 2 H), 1.90 (br s, 3 H), 1.84 (br s, 3 H), 1.82–1.58 (m, 7 H), 1.75 (d, *J* = 6.9, 3 H), 1.32–1.16 (m, 2 H), 1.00–0.87 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.4, 139.4, 126.6, 58.6, 39.6, 31.6, 26.8, 26.2, 14.4, 13.9, 12.8. IR (cm^{-1}): 3026, 2933, 2857, 1619, 1494, 1452, 1276, 1049, 731, 697. LC-MS: Exact mass calculated for $[C_{13}H_{23}N + H]^+$: 194.1909 *m/z*; found: 194.1920 *m/z*.

General Procedure for the Synthesis of Tetrahydropyridines 2d, 2k and 2i from Imines and Alkynes

Inside a glovebox, the appropriate α,β-unsaturated imine (0.53 mmol), Rh stock solution (200 μL, 1.8 mol %) and 3-hexyne (138 μL, 1.21 mmol, 2.30 equiv) was combined in a 4-mL vial and transferred to a J. Young NMR tube equipped with a C_6D_6 capillary for locking and shimming. The vial was washed with PhMe (3 × 10 drops), and the washings were transferred to the J. Young tube. More PhMe was added until a total volume of 0.6–0.7 mL was reached. The J. Young tube was capped and placed in an 80 °C oil bath inside a fume

hood for 3 h, at which point ^{1}H NMR indicated complete consumption of the imine. Inside a glovebox, a solution of diphenyl phosphate (320 mg, 1.28 mmol, 2.42 equiv) in anhydrous THF (0.3 mL) was added to the J. Young tube. The J. Young tube was capped and placed in a 50 °C oil bath for 1 h, at which point ^{1}H NMR indicated full conversion into the C5-protonated iminium ion.

Inside a glovebox, a 20-mL scintillation vial equipped with a stir bar and a pierceable cap was charged with $Na(AcO)_3BH$ (425 mg, 2.01 mmol, 3.80 equiv) and anhydrous THF (3 mL). The vial was capped and placed under a N_2 atmosphere at 0 °C inside a fume hood. While stirring vigorously, the contents of the J. Young tube were added dropwise to the vial *via* a syringe and needle. The J. Young tube was subsequently washed with anhydrous THF (2 × 0.4 mL), and the washings were transferred dropwise to the vial *via* the same syringe and needle. The reaction mixture was stirred at 0 °C for a further 2 h and then allowed to warm to rt over 2 h.

The reaction was quenched with dH_2O (2 mL) and basified with 1 M NaOH until a pH of *ca*. 9 was reached. The aqueous phase was extracted with hexanes/EtOAc/Et_3N (200:25:3, 3 × 10 mL). The combined organic layers were filtered through SiO_2 (2.5 cm in a Pasteur pipet, deactivated with hexanes/EtOAc/Et_3N (200:25:3)). The filtrate was concentrated under reduced pressure, and the crude product was purified by preparative TLC (SiO_2, eluent hexanes/EtOAc/Et_3N (200:25:3)) to afford tetrahydropyridines **2** and **3**.

(2R,3S,6R)/(2S,3R,6S)-1-(cyclohexylmethyl)-2,3-diethyl-4,5,6-trimethyl-1,2,3,6-tetrahydropyridine (2d)—Employing the General Procedure using **8** (102 mg), **2d** was obtained as a colorless oil (98.1 mg, 67%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.65 (dd, *J* = 12.2, 6.0, 1 H), 2.54–2.48 (m, 1 H), 2.31 (dd, *J* = 13.2, 5.4, 1 H), 2.15 (dd, *J* = 13.2, 9.0, 1 H), 1.93–1.86 (m, 1 H), 1.75–1.33 (m, 9 H), 1.61 (br s, 3 H), 1.51 (br s, 3 H), 1.31–1.05 (m, 4 H), 1.01 (d, *J* = 6.3, 3 H), 0.90–0.72 (m, 2 H), 0.86 (dd, *J* = 7.3, 7.1, 3 H), 0.79 (dd, *J* = 7.5, 7.5, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 128.7, 126.9, 57.5, 57.0, 56.6, 45.5, 37.0, 32.1, 31.9, 27.1, 26.5, 26.3, 24.5, 19.8, 18.7, 17.0, 16.3, 12.5, 12.4. IR (cm^{-1}): 2956, 2930, 2853, 1451, 1376, 1338, 1307, 1260, 1198, 1181, 1155, 1113, 1094, 1072, 1051, 891, 842. LC-MS: Exact mass calculated for $[C_{19}H_{35}N + H]^+$: 278.2848 *m/z*; found: 278.2865 *m/z*.

(1R,3R,4S)/(1S,3S,4R)-2-benzyl-3,4-diethyl-1-methyl-2,3,4,5,6,7-hexahydro-1H-cyclopenta[c]pyridine (2i)—Employing the General Procedure using (*E*)-*N*-(1-(cyclopent-1-en-1-yl)ethylidene)-1-phenylmethanamine (78.2 mg), **2i** was obtained as a yellowish oil (69.4 mg, 62%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.39 (m, 2 H), 7.35–7.28 (m, 2 H), 7.26–7.20 (m, 1 H), 3.76 (d, *J* = 14.4, 1 H), 3.62 (d, *J* = 14.4, 1 H), 3.06 (dd, J = 12.8, 7.2, 1 H), 2.55–2.45 (m, 2 H), 2.43–2.34 (m, 1 H), 2.22–2.11 (m, 2 H), 1.92–1.80 (m, 3 H), 1.65–1.47 (m, 3 H), 1.37–1.26 (m, 1 H), 1.15 (d, *J* = 6.6, 3 H), 0.86 (dd, *J* = 7.4, 7.5, 3 H), 0.72 (dd, *J* = 7.5, 7.5, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 141.9, 136.9, 135.8, 128.3, 129.0, 126.2, 57.1, 53.1, 52.5, 40.0, 35.0, 33.6, 24.0, 22.5, 19.0, 18.1, 12.0, 11.4. IR (cm^{-1}): 2963, 2931, 2853, 1494, 1452, 1373, 1199, 1063, 1028, 967, 919, 756. 728, 697. LC-MS: Exact mass calculated for $[C_{20}H_{29}N + H]^+$: 284.2378 *m/z*; found: 284.2380 *m/z*.

(2R,3S,6R)/(2S,3R,6S)-1-benzyl-2,3-diethyl-6-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (2k)—Employing the General Procedure using (*E*)-1-phenyl-*N*-((*E*)-4-phenylbut-3-en-2-ylidene)methanamine (120 mg), **2k** was obtained as a yellowish oil (117 mg, 72%, *dr* = 94:6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.33 (m, 4 H), 7.33–7.27 (m, 4 H), 7.24–7.19 (m, 2 H), 5.76–5.74 (m, 1 H) 3.95 (d, *J* = 14.0, 1 H), 3.72 (d, *J* = 14.0, 1 H), 3.31–3.25 (m, 1 H), 2.56–2.51 (m, 1 H), 2.35–2.30 (m, 1 H), 1.78–1.69 (m, 1 H), 1.67–1.58 (m, 1 H), 1.41–1.26 (m, 2 H), 1.24 (d, *J* = 6.5, 3 H), 0.83 (dd, *J* = 7.4, 7.6, 3 H), 0.54 (dd, *J* = 7.4, 7.6, 3 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 141.6, 141.1, 137.9, 128.8, 128.6, 128.3, 128.0, 126.7, 126.5, 125.8, 57.0, 53.7, 52.3, 41.8, 25.4, 21.1, 16.0, 12.5, 12.1. IR (cm^{-1}): 2963, 2931, 2871, 1494, 1453, 1374, 1067, 1029, 762, 724, 699, 642. LC-MS: Exact mass calculated for $[C_{23}H_{29}N + H]^{+}$: 320.2378 *m/z*; found: 320.2382 *m/z*.

(2S,3S,6R)/(2R,3R,6S)-1-benzyl-5,6-diethyl-2,3,4-trimethyl-1,2,3,6-tetrahydropyridine (3b)—Inside a glovebox, (*E*)-N-((*E*)-2-methylbut-2-en-1-ylidene)-1-phenylmethanamine (82.2 mg, 0.473 mmol), Rh stock solution (150 μL, 1.5 mol %) and 3-hexyne (118 μL, 1.04 mmol, 2.20 equiv) were combined in a 4-mL vial and transferred to a J. Young NMR tube equipped with a C_6D_6 capillary for locking and shimming. The vial was washed with PhMe (3 × 10 drops), and the washings were transferred to the J. Young tube. More PhMe was added until a total volume of 0.6–0.7 mL was reached. The J. Young tube was capped and placed in an 80 °C oil bath inside a fume hood for 2 h, at which point 1H NMR indicated complete consumption of the imine. Inside a glovebox, a 20-mL scintillation vial equipped with a stir bar and a pierceable cap was charged with $Na(AcO)_3BH$ (369 mg, 1.74 mmol, 3.68 equiv). The vial was capped and placed under a N_2 atmosphere at 0 °C inside a fume hood, and EtOH (3 mL) was added dropwise with stirring. The contents of the J. Young tube were transferred dropwise to the vial via a syringe and needle. The J. Young tube was subsequently washed with anhydrous THF (2 × 0.4 mL), and the washings were transferred dropwise to the vial via the same syringe and needle. AcOH (1.5 mL) was added dropwise over 3 min, and the reaction mixture was stirred at 0 °C for a further 2 h and then allowed to warm to rt over 2 h. The reaction was quenched with deionized water (2 mL) and basified with 1 M NaOH until a pH of *ca*. 9 was reached. The aqueous phase was extracted with hexanes/EtOAc/Et_3N (200:25:3, 3 × 10 mL). The combined organic layers were filtered through SiO_2 (2.5 cm in a Pasteur pipet, deactivated with hexanes/EtOAc/Et_3N (200:25:3)). The filtrate was concentrated under reduced pressure, and the crude product was purified by preparative TLC (SiO_2, eluent hexanes/EtOAc/Et_3N (200:25:3)) to afford **3b** as a yellowish oil (90.3 mg, 74%, *dr* = 88:12). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.35 (m, 2 H), 7.33–7.28 (m, 2 H), 7.25–7.21 (m, 1 H), 3.75 (d, *J* = 13.5, 1 H), 3.54 (d, *J* = 13.5, 1 H), 2.68–2.63 (m, 1 H), 2.64 (dd, *J* = 13.0, 8.2, 1 H), 2.58–2.53 (m, 1 H), 2.20–2.05 (m, 2 H), 1.82–1.74 (m, 1 H), 1.67 (br s, 3 H), 1.64–1.56 (m, 1 H), 1.52–1.41 (m, 1 H), 0.95 (dd, *J* = 7.4, 7.6, 3 H), 0.95 (d, *J* = 6.9, 3 H), 0.90 (dd, *J* = 7.3, 7.3, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.7, 133.4, 129.2, 128.8, 128.0, 126.5, 62.3, 58.2, 52.2, 30.5, 24.5, 23.4, 17.5, 16.0, 13.1, 11.0. IR (cm^{-1}): 3026, 2958, 2929, 2870, 1494, 1452, 1364, 1271, 1119, 1073, 1041, 1028, 996, 733, 699. LC-MS: Exact mass calculated for $[C_{18}H_{27}N + H]^{+}$: 258.2222 *m/z*; found: 258.2238 *m/z*.

General Procedure A for Preparation of Epoxides from Tetrahydropyridines 2 with *m*CPBA

A solution of the appropriate tetrahydropyridine **2** (0.4 mmol) in EtOAc (1 mL) was combined with a solution of CCl_3COOH (2 mmol) in EtOAc (1 mL) in an 8 mL vial, and the resulting mixture was stirred at room temperature for 5 min. A solution of *m*CPBA (0.9 mmol) in EtOAc (2 mL) was subsequently added, and the mixture was stirred for 2 h at room temperature. The reaction was quenched with sat. aq. Na_2SO_3 (1 mL). Sat. aq. $NaHCO_3$ was added until a pH of *ca.* 9 was reached. The mixture was extracted with hexanes/EtOAc/Et_3N (200:25:3) (3 × 5 mL), and the combined organic layers were filtered through silica gel (2.5 cm in a Pasteur pipet, deactivated with hexanes/EtOAc/Et_3N (200:25:3)). The filtrate was concentrated under reduced pressure, and the crude product was purified by preparative TLC (SiO_2, eluent hexanes/EtOAc/Et_3N (200:25:3)) to afford epoxide **4**.

General Procedure B for Preparation of Epoxides from Tetrahydropyridines 2 with TFAA and H_2O_2

At 0 °C, H_2O_2 (30% w/w in H_2O, 1.0 mmol) was added dropwise to a solution of trifluoroacetic anhydride (1.2 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at 0 °C for 15 min. A solution of tetrahydropyridine **2** (0.21 mmol) in CH_2Cl_2 (1 mL) was then added, the ice-water bath was removed, and the mixture was allowed to warm to room temperature over 5 h. The reaction was quenched with sat. aq. Na_2SO_3 (2 mL). Sat. aq. $NaHCO_3$ was added until a pH of *ca.* 9 was reached. The mixture was extracted with hexanes/EtOAc/Et_3N (200:25:3) (3 × 5 mL), and the combined organic layers were filtered through silica gel (2.5 cm in a Pasteur pipet, deactivated with hexanes/EtOAc/Et_3N (200:25:3)). The filtrate was concentrated under reduced pressure, and the crude product was purified by preparative TLC (SiO_2, eluent hexanes/EtOAc/Et_3N (200:25:3)) to afford epoxide **4**.

General Procedure C for Preparation of Epoxides from Tetrahydropyridines 3 and 2k with Tetrafluorophthalic Anhydride and H_2O_2

At 0 °C, H_2O_2 (30% w/w in H_2O, 1.1 mmol) was added dropwise to a solution of tetrafluorophthalic anhydride (1.3 mmol) in THF (2 mL), and the mixture was stirred for 15 min. A solution of tetrahydropyridine **3** (0.22 mmol) in THF (1 mL) was then added, the ice-water bath was removed, and the mixture was allowed to warm to room temperature over 5 h. The reaction was quenched with sat. aq. Na_2SO_3 (1 mL). Sat. aq. $NaHCO_3$ was added until a pH of *ca.* 9 was reached. The mixture was extracted with hexanes/EtOAc/Et_3N (200:25:3) (3 × 5 mL), and the combined organic layers were filtered through silica gel (2.5 cm in a Pasteur pipet, deactivated with hexanes/EtOAc/Et_3N (200:25:3)). The filtrate was concentrated under reduced pressure, and the crude product was purified by preparative TLC (SiO_2, eluent hexanes/EtOAc/Et_3N (200:25:3)) to afford epoxide **5** or **4k**.

Epoxide 4a—Employing General Procedure A using tetrahydropyridine **2a** (108 mg), **4a** was obtained as a colorless oil (106 mg, 93%, *dr* >20:1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.30 (m, 2 H), 7.30–7.25 (m, 2 H), 7.22–7.18 (m, 1 H), 3.60 (d, *J* = 14.2, 1 H), 3.50 (d, *J* = 14.2, 1 H), 2.67 (dd, *J* = 6.4, 6.4, 1 H), 2.26–2.19 (m, 1 H), 1.70–1.48 (m, 2 H), 1.48–

1.37 (m, 2 H), 1.33 (br s, 3 H), 1.30–1.20 (overlapping m, 1 H and br s, 3 H), 1.16 (d, *J* = 6.4, 3 H), 0.85 (dd, *J* = 7.4, 7.4, 3 H), 0.80 (dd, *J* = 7.5, 7.4, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 141.0, 128.3, 128.0, 126.5, 63.9, 62.7, 55.8, 54.5, 52.5, 41.2, 21.3, 21.1, 18.7, 18.6, 14.9, 12.3, 11.7. IR (cm^{-1}): 2960, 2930, 2873, 2805, 1494, 1453, 1379, 1149, 1140, 1112, 1078, 1061, 1037, 1027, 897, 869, 855, 834, 805. LC-MS: Exact mass calculated for $[C_{19}H_{29}NO + H]^+$: 288.2327 *m/z*; found: 288.2354 *m/z*.

Epoxide 4b—Employing General Procedure A using tetrahydropyridine **2b** (74.5 mg), **4b** was obtained as a yellowish oil (59.6 mg, 76%, *dr* = 84:16). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24–7.19 (m, 2 H), 6.88–6.83 (m, 2 H), 6.75–6.70 (m, 1 H), 4.01–3.97 (m, 1 H), 3.73–3.65 (m, 1 H), 2.14–2.07 (m, 1 H), 2.05–1.96 (m, 1 H), 1.89–1.79 (m, 1 H), 1.73–1.64 (m, 1 H), 1.49–1.40 (m, 1 H), 1.32 (br s, 3 H), 1.13 (d, *J* = 7.1, 3 H), 1.09 (d, *J* = 7.1, 3 H), 1.04 (dd, *J* = 7.6, 7.0, 3 H), 1.01 (dd, *J* = 7.4, 7.6, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 149.6, 129.1, 117.6, 115.9, 68.5, 64.8, 55.9, 52.2, 37.1, 26.7, 25.4, 16.7, 15.3, 13.1, 12.9, 10.3. IR (cm^{-1}): 2964, 2927, 2874, 1596, 1499, 1458, 1377, 1306, 1280, 1118, 1071, 1039, 990, 974, 890, 861, 812. LC-MS: Exact mass calculated for $[C_{18}H_{27}NO + H]^+$: 274.2171 *m/z*; found: 274.2163 *m/z*.

Epoxide 4c—Employing General Procedure A using tetrahydropyridine **2c** (120 mg), **4c** was obtained as a yellowish oil (117 mg, 92%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.99 (dd, *J* = 12.8, 6.5, 1 H), 2.63–2.56 (m, 1 H), 2.38–2.33 (m, 1 H), 1.79–1.69 (m, 3 H), 1.64–1.50 (m, 4 H), 1.48–1.28 (m, 5 H), 1.26 (s, 3 H), 1.26–1.21 (m, 1 H), 1.23 (s, 3 H), 1.09 (d, *J* = 6.4, 3 H), 0.93 (dd, *J* = 7.4, 7.6, 3 H), 0.84 (dd, *J* = 7.4, 7.4, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 64.2, 63.6, 55.1, 54.2, 50.3, 42.4, 33.3, 31.1, 26.9, 26.8, 26.4, 23.1, 21.7, 21.5, 17.6, 14.8, 12.5, 11.7. IR (cm^{-1}): 2963, 2928, 1493, 1449, 1373, 1261, 1201, 1192, 1118, 1078, 1027, 892, 599. LC-MS: Exact mass calculated for $[C_{18}H_{33}NO + H]^+$: 280.2640 *m/z*; found: 280.2675 *m/z*.

Epoxide 4d—Employing General Procedure A using tetrahydropyridine **2d** (84.1 mg), **4d** was obtained as a colorless oil (72.1 mg, 92%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64 (dd, *J* = 12.6, 6.2, 1 H), 2.18–2.14 (m, 1 H), 2.13–2.04 (m, 2 H), 1.80–1.58 (m, 6 H), 1.51–1.38 (m, 3 H), 1.28 (s, 3 H), 1.20 (s, 3 H), 1.27–1.08 (m, 5 H), 1.06 (d, *J* = 6.4, 3 H), 0.93 (dd, *J* = 7.4, 7.2, 3 H), 0.84 (dd, *J* = 7.4, 7.4, 3 H), 0.79–0.67 (m, 2 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 63.3, 63.0, 58.3, 56.2, 55.0, 41.3, 37.6, 31.8, 31.8, 27.0, 26.3, 26.3, 21.9, 21.6, 18.4, 18.2, 15.2, 12.6, 12.1. IR (cm^{-1}): 2958, 2922, 2873, 2851, 1449, 1379, 1163, 1137, 1113, 1082, 1059, 891, 870, 856. LC-MS: Exact mass calculated for $[C_{19}H_{35}NO + H]^+$: 294.2797 *m/z*; found: 294.2791 *m/z*.

Epoxide 4e—Employing General Procedure A using tetrahydropyridine **2e** (56.9 mg), **4e** was obtained as a yellowish oil (49.9 mg, 83%, *dr* = 94:6). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.35 (m, 2 H), 7.30–7.26 (m, 2 H), 7.21–7.17 (m, 1 H), 3.99 (d, *J* = 15.4, 1 H), 3.72 (d, *J* = 15.4, 1 H), 3.12–2.99 (m, 1 H), 2.21 (d, *J* = 5.4, 1 H), 1.93–1.86 (m, 1 H), 1.38 (br s, 3 H), 1.21 (d, *J* = 6.9, 3 H), 1.18 (s, 3 H), 1.11 (d, *J* = 6.8, 3 H), 0.99 (s, 9 H). The $^{13}C\{^{1}H\}$ NMR for epoxide **4e**was not informative due to slow rotation at room temperature on the ^{13}C NMR timescale. IR (cm^{-1}): 2958, 2929, 2873, 1494, 1453, 1367, 1171, 1149, 1124,

1061, 1028, 990, 971, 905, 861. LC-MS: Exact mass calculated for $[C_{20}H_{31}NO + H]^+$: 302.2484 *m/z*; found: 302.2479 *m/z*.

Epoxide 4f—Employing General Procedure B using tetrahydropyridine **2f** (66.3 mg), **4f** was obtained as a yellowish oil (48.8 mg, 70%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.28 (m, 4 H), 7.25–7.21 (m, 1 H), 3.85 (d, *J* = 14.6, 1 H), 3.74 (s, 3 H, ester CH_3), 3.25 (d, *J* = 14.6, 1 H), 2.85 (d, *J* = 1.2, 1 H), 2.84–2.83 (m, 1 H), 2.75 (dd, *J* = 13.7, 6.9, 1 H), 1.83–1.74 (m, 1 H), 1.40 (s, 3 H), 1.20 (br s, 3 H), 1.12 (d, *J* = 6.8, 3 H), 1.02 (d, *J* = 6.8, 3 H), 0.89 (d, *J* = 6.6, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 173.6, 140.1, 128.3, 127.8, 126.8, 62.1, 61.4, 56.4, 54.3, 51.8, 51.7, 46.9, 29.8, 21.2, 20.4, 20.1, 17.6, 13.9. IR (cm^{-1}): 2951, 1739, 1494, 1453, 1434, 1381, 1367, 1249, 1189, 1139, 1101, 1062, 1026, 973, 948, 920, 851. LC-MS: Exact mass calculated for $[C_{20}H_{29}NO_3 + H]^+$: 332.2226 *m/z*; found: 332.2210 *m/z*.

Epoxide 4g—Employing General Procedure A using tetrahydropyridine **2g** (63.8 mg), **4g** was obtained as a yellowish oil (53.5 mg, 79%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.25 (m, 4 H), 7.23–7.18 (m, 1 H), 3.63 (d, *J* = 13.5, 1 H), 3.59 (d, *J* = 13.5, 1 H), 2.83 (d, *J* = 13.3, 1 H), 2.57 (d, *J* = 13.3, 1 H), 2.16–2.11 (m, 1 H), 1.74–1.56 (m, 2 H), 1.55–1.44 (m, 1 H), 1.40–1.35 (m, 1 H), 1.32 (s, 3 H), 1.24 (s, 3 H), 1.12–1.01 (m, 1 H), 0.81 (dd, *J* = 7.3, 7.4, 3 H), 0.81 (dd, *J* = 7.5, 7.4, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 139.5, 128.6, 128.1, 126.7, 61.8, 60.2, 58.4, 58.2, 51.9, 42.7, 21.9, 21.7, 17.6, 17.4, 12.5, 11.6. IR (cm^{-1}): 2957, 2930, 2870, 1494, 1452, 1364, 1280, 1120, 1074, 1041, 1028, 996, 732. LC-MS: Exact mass calculated for $[C_{18}H_{27}NO + H]^+$: 274.2171 *m/z*; found: 274.2175 *m/z*.

Epoxide 4h—Employing General Procedure B using tetrahydropyridine **2h** (95.7 mg), **4h** was obtained as a yellowish oil (90.8 mg, 90%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.30 (m, 2 H), 7.30–7.24 (m, 2 H), 7.22–7.17 (m, 1 H), 3.63 (d, *J* = 14.3, 1 H), 3.49 (d, *J* = 14.3, 1 H), 2.70 (dd, *J* = 12.8, 6.4, 1 H), 2.29–2.23 (m, 1 H), 2.11–2.04 (m, 1 H), 1.90–1.82 (m, 1 H), 1.67–1.37 (m, 8 H), 1.37–1.20 (m, 3 H), 1.11 (d, *J* = 6.4, 3 H), 0.86 (dd, *J* = 7.4, 7.4, 3 H), 0.78 (dd, *J* = 7.5, 7.2, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 141.1, 128.6, 128.0, 126.4, 63.8, 62.4, 55.8, 55.1, 52.3, 41.4, 31.9, 29.7, 21.1, 20.8, 20.4, 18.8, 14.5, 12.0, 11.8. IR (cm^{-1}): 2958, 2932, 2873, 1494, 1453, 1374, 1178, 1159, 1103, 1068, 1027, 956, 880, 869, 849, 832, 815. LC-MS: Exact mass calculated for $[C_{21}H_{31}NO + H]^+$: 314.2484 *m/z*; found: 314.2451 *m/z*.

Epoxide 4i—Employing General Procedure B using tetrahydropyridine **2i** (72.0 mg), **4i** was obtained as a yellowish oil (63.9 mg, 84%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.32 (m, 2 H), 7.31–7.26 (m, 2 H), 7.23–7.18 (m, 1 H), 3.57 (d, *J* = 14.3, 1 H), 3.53 (d, *J* = 14.3, 1 H), 2.92 (dd, *J* = 13.1, 6.6, 1 H), 2.31–2.25 (m, 1 H), 2.17–2.12 (m, 1 H), 2.01–1.94 (m, 1 H), 1.74–1.25 (m, 9 H), 1.17 (d, *J* = 6.5, 3 H), 0.90 (dd, *J* = 7.2, 7.4, 3 H), 0.89 (dd, *J* = 7.0, 7.4, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 141.2, 128.2, 128.1, 126.5, 69.5, 68.3, 56.7, 51.8, 51.7, 38.4, 33.0, 31.0, 22.5, 19.9, 19.3, 15.8, 12.1, 11.9. IR (cm^{-1}): 2959, 2931, 2873, 1454, 1368, 1175, 1130, 1106, 1074, 1027, 972, 922, 890, 840. LC-MS: Exact mass calculated for $[C_{20}H_{29}NO + H]^+$: 300.2327 *m/z*; found: 300.2338 *m/z*.

Epoxide 4j—Employing General Procedure B using tetrahydropyridine **2j** (89.4 mg), **4j** was obtained as a yellowish oil (80.6 mg, 86%, *dr* = 91:9). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.18 (m, 10 H), 3.74 (m, 2 H), 2.82 (dd, *J* = 13.0, 6.6, 1 H), 2.59–2.51 (m, 1 H), 2.06–2.00 (m, 1 H), 1.65–1.50 (m, 3 H), 1.42–1.32 (m, 1 H), 1.22 (d, *J* = 6.5, 3 H), 1.01 (dd, *J* = 7.3, 7.3, 3 H), 0.86 (s, 3 H), 0.66 (dd, *J* = 7.6, 7.6, 3 H). The ^{13}C{^{1}H} NMR for epoxide **4j** was not informative due to slow rotation at room temperature on the ^{13}C NMR timescale. IR (cm^{-1}): 3060, 3026, 2961, 2931, 2874, 1658, 1603, 1494, 1446, 1375, 1200, 1155, 1122, 1090, 1069, 1051, 1027, 988, 956, 920, 898, 883, 840. LC-MS: Exact mass calculated for $[C_{24}H_{31}NO + H]^{+}$: 350.2484 *m/z*; found: 350.2478 *m/z*.

Epoxide 4k—Employing General Procedure C using tetrahydropyridine **2k** (52.5 mg), **4k** was obtained as a yellowish oil (30.3 mg, 55%, *dr* = 86:14). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.12 (m, 10 H), 3.79 (d, *J* = 14.4, 1 H), 3.58 (d, *J* = 14.4, 1 H), 3.06–3.00 (m, 1 H), 2.86–2.83 (m, 1 H), 2.42–2.33 (m, 1 H), 2.16–2.11 (m, 1 H), 1.74–1.59 (m, 2 H), 1.59–1.45 (m, 2 H), 1.45–1.35 (m, 1 H), 1.26 (d, *J* = 6.5, 3 H), 0.97 (dd, *J* = 7.3, 7.6, 3 H), 0.63 (dd, *J* = 7.5, 7.5, 3 H). The ^{13}C{^{1}H} NMR for epoxide **4k** was not informative due to slow rotation at room temperature on the ^{13}C NMR timescale. IR (cm^{-1}): 3027, 2962, 2932, 2872, 1659, 1604, 1494, 1375, 1200, 1155, 1122, 1090, 1068, 1052, 1027, 988, 898. LC-MS: Exact mass calculated for $[C_{23}H_{29}NO + H]^{+}$: 336.2327 *m/z*; found: 336.2346 *m/z*.

Epoxide 5a—Employing General Procedure C using tetrahydropyridine **3a** (70.7 mg), **5a** was obtained as a colorless oil (56.2 mg, 75%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.34 (m, 2 H), 7.31–7.27 (m, 2 H), 7.24–7.20 (m, 1 H), 3.73 (d, *J* = 13.9, 1 H), 3.66 (d, *J* = 13.9, 1 H), 2.76–2.69 (m, 1 H), 2.65 (dd, *J* = 8.6, 4.9, 1 H), 2.17–2.11 (m, 1 H), 1.83–1.74 (m, 1 H), 1.76–1.66 (m, 1 H), 1.61–1.52 (m, 1 H), 1.36–1.30 (m, 1 H), 1.34 (br s, 3 H), 1.13 (d, *J* = 7.4, 3 H), 1.00 (d, *J* = 7.1, 3 H), 0.99 (dd, *J* = 7.6, 7.6, 3 H), 0.88 (dd, *J* = 7.5, 7.5, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.9, 128.6, 128.0, 126.7, 67.9, 64.6, 59.8, 59.2, 56.6, 32.6, 26.4, 23.7, 16.9, 16.4, 12.8, 12.5, 10.1. IR (cm^{-1}): 2961, 2931, 2874, 1726, 1461, 1379, 1271, 1122, 1071, 1041, 1027, 957, 895, 874, 842. LC-MS: Exact mass calculated for $[C_{19}H_{29}NO + H]^{+}$: 288.2327 *m/z*; found: 288.2303 *m/z*.

Epoxide 5b—Employing General Procedure C using tetrahydropyridine **3b** (55.2 mg), **5b** was obtained as a yellowish oil (49.3 mg, 84%, *dr* = 93:7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.33 (m, 2 H), 7.33–7.26 (m, 2 H), 7.26–7.19 (m, 1 H), 3.68 (d, *J* = 13.5, 1 H), 3.56 (d, *J* = 13.5, 1 H), 2.53–2.48 (m, 1 H), 2.42 (dd, *J* = 14.0, 11.4, 1 H), 2.35–2.29 (m, 1 H), 2.07–1.99 (m, 1 H), 1.72–1.63 (m, 1 H), 1.61–1.51 (m, 1 H), 1.46–1.39 (m, 1 H), 1.39–1.30 (m, 1 H), 1.37 (s, 3 H), 0.98 (dd, *J* = 7.6, 7.6, 3 H), 0.88 (d, *J* = 6.7, 3 H), 0.85 (dd, *J* = 7.6, 7.4, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.2, 129.3, 128.5, 127.3, 67.3, 63.7, 58.8, 58.6, 48.6, 28.7, 27.1, 21.1, 16.6, 13.8, 12.3, 10.2. IR (cm^{-1}): 2963, 2931, 2872, 1493, 1453, 1374, 1281, 1121, 1073, 1028, 761, 725, 643. LC-MS: Exact mass calculated for $[C_{18}H_{27}NO + H]^{+}$: 274.2171 *m/z*; found: 274.2167 *m/z*.

Epoxide 5c—Employing General Procedure C using tetrahydropyridine **3c** (45.9 mg), **5c** was obtained as a yellowish oil (34.2 mg, 70%, *dr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.34 (m, 2 H), 7.32–7.28 (m, 2 H), 7.26–7.21 (m, 1 H), 3.67 (d, *J* = 13.4, 1 H), 3.56 (d,

J = 13.4, 1 H), 2.89–2.82 (m, 1 H), 2.52–2.47 (m, 1 H), 2.43–2.38 (m, 1 H), 2.03–1.94 (m, 1 H), 1.72–1.64 (m, 1 H), 1.64–1.54 (m, 1 H), 1.53–1.47 (m, 1 H), 1.47–1.35 (m, 2 H), 1.40 (br s, 3 H), 0.99 (dd, *J* = 7.6, 7.6, 3 H), 0.86 (dd, *J* = 7.4, 7.4, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 140.0, 128.9, 128.0, 126.9, 66.1, 60.5, 58.6, 57.6, 40.3, 26.3, 26.0, 20.8, 19.2, 11.9, 9.9. IR (cm^{-1}): 2962, 2930, 2874, 2805, 1454, 1376, 1138, 1109, 1082, 1074, 1058, 1009, 976, 902, 882, 856, 833. LC-MS: Exact mass calculated for $[C_{17}H_{25}NO + H]^+$: 260.2014 *m/z*; found: 260.1970 *m/z*.

Epoxide 5d—Employing General Procedure C using tetrahydropyridine **3d** (58.0 mg), **5d** was obtained as a yellowish oil (40.0 mg, 65% with respect to the tetrahydropyridine, *dr* = 86:14). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.91–2.78 (m, 2 H), 2.38–2.27 (m, 1 H), 1.99–1.64 (m, 6 H), 1.63–1.49 (m, 3 H), 1.42–1.10 (m, 6 H), 1.27 (s, 3 H), 1.07 (d, *J* = 7.4, 3 H), 0.99 (dd, *J* = 7.9, 7.4, 3 H), 0.97 (d, *J* = 7.1, 3 H), 0.96 (dd, *J* = 7.4, 7.5, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 68.9, 64.9, 64.9, 57.6, 51.3, 36.2, 32.9, 32.8, 26.9, 26.5, 26.4, 26.2, 25.1, 18.2, 16.5, 14.1, 11.9, 10.6. IR (cm^{-1}): 2962, 2930, 1494, 1461, 1451, 1375, 1261, 1199, 1150, 1115, 1078, 1027, 944, 892, 696. LC-MS: Exact mass calculated for $[C_{18}H_{34}NO + H]^+$: 280.2640 *m/z*; found: 280.2666 *m/z*.

Epoxide 5e—Employing General Procedure C using tetrahydropyridine **3e** (51.7 mg), **5e** was obtained as a yellowish oil (39.2 mg, 72% with respect to the tetrahydropyridine, *dr* = 88:12). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.14 (m, 5 H), 3.74 (d, *J* = 13.6, 1 H), 3.64 (d, *J* = 13.6, 1 H), 2.76–2.69 (m, 1 H), 2.64–2.60 (m, 1 H), 2.11–2.06 (m, 1 H), 1.90–1.31 (m, 12 H), 1.16 (d, *J* = 7.3, 3 H), 0.96 (dd, *J* = 7.6, 7.6, 3 H), 0.86 (dd, *J* = 7.3, 7.4, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 140.7, 128.8, 128.0, 126.8, 67.8, 65.7, 60.5, 58.8, 55.4, 35.2, 30.2, 27.7, 26.4, 25.9, 24.3, 23.5, 17.0, 12.4, 10.1. IR (cm^{-1}): 2956, 2933, 2872, 1494, 1454, 1372, 1199, 1179, 1061, 1027, 943, 884, 869, 849, 832, 815. LC-MS: Exact mass calculated for $[C_{21}H_{31}NO + H]^+$: 314.2484 *m/z*; found: 314.2460 *m/z*.

General Procedure for Water Opening of Epoxide 4 and 5

In a 4 mL vial equipped with a stir bar, a solution of epoxide **4** or **5** (0.2 mmol) in CH_2Cl_2 (0.2 mL) was added to sat. aq. $NaHSO_4$ (2 mL). The vial was capped and heated to 70 °C for 12 h with stirring. The reaction mixture was allowed to cool to room temperature, and sat. aq. $NaHCO_3$ added until a pH of *ca.* 9 was reached. The resultant mixture was extracted with hexanes/EtOAc/Et_3N (200:25:3 v:v:v) (3 × 5 mL) and the combined organic layers were filtered through silica gel (2.5 cm in a Pasteur pipet, deactivated with hexanes/EtOAc/Et_3N (200:25:3)). The filtrate was concentrated under reduced pressure, and the crude product was purified by preparative TLC (SiO_2, eluent hexanes/EtOAc/Et_3N (200:25:3)) to afford product **6** or **7**.

Product 6a—Employing the General Procedure using epoxide **4a** (51.5 mg), **6a** was obtained as an off-white solid (mp 110–112 °C, 36.2 mg, 66%, *rr* = 94:6). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.25 (m, 4 H), 7.24–7.19 (m, 1 H), 3.99 (d, *J* = 13.1, 1 H), 3.51 (d, *J* = 13.1, 1 H), 3.35 (dd, *J* = 13.6, 6.8, 1 H), 3.35 (br s, 1 H), 2.27 (dd, *J* = 10.8, 2.6, 1 H), 2.12–2.01 (m, 1 H), 1.71–1.60 (m, 1 H), 1.57–1.48 (m, 1 H), 1.27 (br s, 3 H), 1.19–1.17 (m, 1 H), 1.12–1.09 (m, 1 H), 1.07 (br s, 3 H), 1.04 (d, *J* = 6.8, 3 H), 0.74 (dd, *J* = 7.4, 7.4, 3 H), 0.52

(dd, *J* = 8.2, 7.4, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 140.7, 128.6, 128.2, 126.8, 76.7, 74.1, 59.6, 53.3, 53.3, 49.2, 25.4, 24.3, 18.2, 17.2, 14.4, 12.6, 11.4. IR (cm^{-1}): 3435, 2967, 2873, 1453, 1382, 1279, 1190, 1175, 1106, 1081, 1028, 997, 956, 921, 900, 837. LC-MS: Exact mass calculated for $[C_{19}H_{31}NO_2 + H]^+$: 306.2433 *m/z*; found: 306.2435 *m/z*.

Product 7a—Employing the General Procedure using epoxide **5c** (48.4 mg), **7a** was obtained as a colorless oil (39.9 mg, 77%, *rr* = 92:8). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.28 (m, 4 H), 7.26–7.22 (m, 1 H), 4.14 (d, *J* = 13.2, 1 H), 3.37 (br s, 1 H), 3.07 (d, *J* = 13.2, 1 H), 2.68 (dd, *J* = 3.7, 3.7, 1 H), 3.58–3.52 (m, 1 H), 2.30–2.22 (m, 1 H), 1.97–1.71 (m, 4 H), 1.68– 1.57 (m, 2 H), 1.32–1.27 (br s, 1 H), 1.24 (br s, 3 H), 1.09 (dd, *J* = 7.5, 7.6, 3 H), 1.03 (dd, *J* = 7.8, 7.9, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 140.0, 128.5, 128.3, 126.9, 75.6, 74.4, 63.9, 57.4, 47.5, 36.4, 25.9, 24.9, 20.3, 12.3, 9.6. IR (cm^{-1}): 3472, 2965, 2939, 2879, 2825, 1495, 1452, 1386, 1366, 1306, 1268, 1169, 1106, 1084, 1044, 1028, 1007, 922, 867, 840, 828, 809. LC-MS: Exact mass calculated for $[C_{17}H_{27}NO_2 + H]^+$: 278.2120 *m/z*; found: 278.2101 *m/z*.

General Procedure for Methoxide Opening of Epoxide 4 and 5

In an oven-dried 4 mL vial equipped with a stir bar, epoxide **4** or **5** (0.2 mmol) and anhydrous benzenesulfonic acid (0.4 mmol) was dissolved in anhydrous MeOH (1.5 mL, stored over 3 Å molecular sieves for 2 days). The vial was capped, sealed with Parafilm and heated to 80 °C for 7 h with stirring. The reaction mixture was allowed to cool to room temperature, and the volatiles were removed under a stream of N_2. Sat. aq. $NaHCO_3$ was then added until a pH of *ca.* 9 was reached. The resultant mixture was extracted with hexanes/EtOAc/Et_3N (200:25:3 v:v:v) (3 × 5 mL) and the combined organic layers were filtered through silica gel (2.5 cm in a Pasteur pipet, deactivated with hexanes/EtOAc/Et_3N (200:25:3)). The filtrate was concentrated under reduced pressure, and the crude product was purified by preparative TLC (SiO_2, eluent hexanes/EtOAc/Et_3N (200:25:3)) to afford product **6** or **7**.

Product 6b—Employing the General Procedure using epoxide **4a** (49.2 mg), **6b** was obtained as a yellowish solid (mp 80–82 °C, 29.6 mg, 54%, *rr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.24 (overlapping m, 4 H), 7.23–7.19 (m, 1 H), 3.97 (d, *J* = 13.1, 1 H), 3.57 (br s, 1 H), 3.48 (d, *J* = 13.1, 1 H), 3.34 (dd, *J* = 13.7, 7.0, 1 H), 3.08 (s, 3 H), 2.17 (dd, *J* = 11.0, 2.0, 1 H), 1.93–1.83 (m, 1 H), 1.68–1.59 (m, 1 H), 1.42–1.33 (m, 2 H), 1.19 (br s, 3 H), 1.20–1.12 (m, 1 H), 1.01 (d, *J* = 6.9, 3 H), 1.00 (br s, 3 H), 0.74 (dd, *J* = 7.4, 7.5, 3 H), 0.51 (dd, *J* = 7.3, 7.4, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 140.9, 128.6, 128.2, 126.7, 80.4, 74.6, 59.8, 53.3, 53.1, 48.4, 40.1, 23.8, 19.0, 18.2, 16.5, 14.4, 12.8, 11.8. IR (cm^{-1}): 3435, 2958, 2874, 2828, 1495, 1454, 1381, 1365, 1288, 1267, 1185, 1147, 1129, 1092, 1046, 1028, 997, 920, 896, 854. LC-MS: Exact mass calculated for $[C_{20}H_{33}NO_2 + H]^+$: 320.2590 *m/z*; found: 320.2570 *m/z*.

Product 7b—Employing the General Procedure using epoxide **5c** (43.3 mg), **7b** was obtained as a yellowish oil (31.1 mg, 54%, *rr* = 94:6). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.28 (m, 4 H), 7.26–7.20 (m, 1 H), 4.16 (d, *J* = 13.1, 1 H), 3.52 (br s, 1 H), 3.11 (s, 3 H), 3.00 (d, *J* = 13.1, 1 H), 2.72 (dd, *J* = 3.6, 3.6, 1 H), 2.47–2.40 (m, 1 H), 2.14–2.04 (m, 1 H),

1.96–1.86 (m, 1 H), 1.74 (dd, *J* = 15.7, 7.8, 2 H), 1.64–1.51 (m, 3 H), 1.13 (br s, 3 H), 1.09 (dd, *J* = 7.6, 7.7, 3 H), 0.99 (dd, *J* = 7.7, 7.9, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 140.3, 128.5, 128.3, 126.8, 78.5, 75.6, 63.6, 57.4, 48.1, 47.6, 28.8, 26.1, 20.6, 18.4, 12.3, 9.7. IR (cm^{-1}): 2967, 2940, 2879, 2825, 1452, 1387, 1366, 1306, 1242, 1176, 1160, 1121, 1095, 1066, 1028, 1007, 967, 909, 889, 867, 839, 828. LC-MS: Exact mass calculated for $[C_{18}H_{29}NO_2 + H]^+$: 292.2277 *m/z*; found: 292.2231 *m/z*.

General Procedure for Fluoride Opening of Epoxide 4 and 5

In a 4 mL vial equipped with a stir bar, $HBF_4{\cdot}Et_2O$ ("51–57% in Et_2O", *ca.* 0.4 mmol) was added to a solution of epoxide **4** or **5** (0.2 mmol) in CH_2Cl_2 (1 mL). The vial was capped, and the mixture was stirred at room temperature for 10 min. Sat. aq. $NaHCO_3$ was then added until a pH of *ca.* 9 was reached. The resultant mixture was extracted with hexanes/EtOAc/Et_3N (200:25:3 v:v:v) (3 × 5 mL), and the combined organic layers were filtered through silica gel (2.5 cm in a Pasteur pipet, deactivated with hexanes/EtOAc/Et_3N (200:25:3)). The filtrate was concentrated under reduced pressure, and the crude product was purified by preparative TLC (SiO_2, eluent hexanes/EtOAc/Et_3N (200:25:3)) to afford product **6** or **7**.

Product 6c—Employing the General Procedure using epoxide **4a** (63.5 mg), **6c** was obtained as an orange oil (50.7 mg, 75%, *rr* >20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.24 (m, 4 H), 7.24–7.20 (m, 1 H), 3.99 (d, *J* = 13.1, 1 H), 3.51 (d, *J* = 13.1, 1 H), 3.33–3.24 (overlapping br s and m, 2 H), 2.26 (dd, *J* = 11.1, 2.5, 1 H), 1.89–1.78 (m, 1 H), 1.68–1.59 (m, 1 H), 1.51–1.38 (m, 2 H), 1.38 (d, *J* = 23.5, 3 H), 1.20–1.14 (m, 1 H), 1.10 (d, *J* = 2.0, 3 H), 1.07 (d, *J* = 6.8, 3 H), 0.73 (dd, *J* = 7.4, 7.4, 3 H), 0.54 (dd, *J* = 7.2, 7.3, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 140.5, 128.6, 128.3, 126.9, 99.8 (d, *J* = 170.8), 72.9 (d, *J* = 26.2), 59.0 (d, *J* = 1.8), 53.5, 53.3, 47.0 (d, *J* = 18.8), 23.6 (d, *J* = 11.5), 21.7 (d, *J* = 24.3), 17.8, 16.8 (d, *J* = 6.9), 14.1, 12.7, 11.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ –139.7. IR (cm^{-1}): 3451, 3027, 2965, 2881, 2825, 1495, 1452, 1388, 1371, 1308, 1242, 1168, 1122, 1091, 1064, 1044, 1028, 1013, 930, 898, 867, 841, 804. LC-MS: Exact mass calculated for $[C_{19}H_{30}FNO + H]^+$: 308.2390 *m/z*; found: 308.2361 *m/z*.

Product 6d—Employing the General Procedure using epoxide **4c** (42.0 mg), **6d** was obtained as an orange oil (33.8 mg, 75%, *rr* >20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.47–3.41 (m, 1 H), 3.18 (br s, 1 H), 2.75–2.66 (m, 1 H), 2.58–2.52 (m, 1 H), 2.20–2.09 (m, 1 H), 1.86–1.56 (m, 7 H), 1.55–1.29 (m, 10H), 1.29–1.06 (m, 6 H), 1.04 (s, 3 H), 1.02 (d, *J* = 6.9, 3 H), 0.91 (dd, *J* = 7.3, 7.2, 3 H), 0.84 (dd, *J* = 7.4, 7.5, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 100.7 (d, *J* = 171.1), 72.4 (d, *J* = 26.8), 56.9, 56.5 (d, *J* = 2.1), 52.0, 48.0 (d, *J* = 18.2), 34.2, 33.3, 27.1, 26.6, 26.2, 24.3 (d, *J* = 7.8), 23.8 (d, *J* = 11.2), 21.9 (d, *J* = 24.7), 17.2, 14.5, 11.9, 11.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ –139.3. IR (cm^{-1}): 2928, 2854, 1451, 1383, 1132, 1091, 1058, 995, 923, 900, 892, 871, 803. LC-MS: Exact mass calculated for $[C_{18}H_{34}FNO + H]^+$: 300.2703 *m/z*; found: 300.2705 *m/z*.

Product 7c—Employing the General Procedure using epoxide **5c** (42.5 mg), **7c** was obtained as an orange oil (36.6 mg, 80%, *rr* = 94:6). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.28 (m, 4 H), 7.28–7.22 (m, 1 H, *para* H of Bn), 4.17 (d, *J* = 13.2, 1 H), 3.62 (br s, 1 H),

3.04 (d, *J* = 13.2, 1 H), 2.70 (dd, *J* = 7.8, 3.8, 1 H), 2.59–2.53 (m, 1 H), 2.26–2.19 (m, 1 H), 2.01–1.62 (m, 5 H), 1.52–1.44 (m, 1 H), 1.35 (d, *J* = 21.8, 3 H), 1.11 (dd, *J* = 7.6, 7.5, 3 H), 0.99 (ddd, *J* = 7.8, 7.8, 3.3, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 139.8, 128.5, 128.4, 127.0, 97.2 (d, *J* = 175.2), 74.5 (d, *J* = 22.4), 62.9, 57.1, 47.6, 34.2 (d, *J* = 21.4), 26.1 (d, *J* = 1.2), 21.5 (d, *J* = 23.5), 20.1, 11.4, 8.6 (d, *J* = 7.6). ^{19}F NMR (376 MHz, $CDCl_3$): δ –156.9. IR (cm^{-1}): 3451, 2965, 2881, 2825, 1495, 1452, 1388, 1371, 1308, 1242, 1168, 1122, 1091, 1064, 1044, 1028, 1013, 951, 930, 898, 867, 841, 804. LC-MS: Exact mass calculated for $[C_{17}H_{26}FNO + H]^+$: 280.2077 *m/z*; found: 280.2083 *m/z*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the NIH Grant GM069559 (to J.A.E.). R.G.B. acknowledges funding from the Office of Basic Energy Sciences, Chemical Sciences Division, U.S. DOE, under Contract DE-AC02-05CH11231. We are grateful to Prof. Scott Miller for helpful discussions.

References

1. Analysis of the prevalence of piperidines in drugs: Roughley SD, Jordan AM. J. Med. Chem. 2011; 54:3451. [PubMed: 21504168]
2. For perspectives on the importance of saturated, nonplanar heterocycles in drug disocvery, see: Lovering F, Bikker J, Humblet C. J. Med. Chem. 2009; 52:6752. [PubMed: 19827778] ; Walters WP, Green J, Weiss JR, Murcko MA. J. Med. Chem. 2011; 54:6405. [PubMed: 21755928] Ritchie TJ, Macdonald SJF. Drug. Discov. Today. 2009; 14:1011. [PubMed: 19729075]
3. General reviews on piperidines: Michael JP. Nat. Prod. Rep. 2008; 25:139–165. [PubMed: 18250900] ; Buffat MGP. Tetrahedron. 2004; 60:1701.; Mitchinson A, Nadin A. J. Chem. Soc. Perkin Trans. 1. 2000:2862.; Laschat S, Dickner T. Synthesis. 2000:1781.
4. Reviews on 1,2-dihydropyridines: Bull JA, Mousseau JJ, Pelletier G, Charette AB. Chem. Rev. 2012; 112:2642. [PubMed: 22352938] Silva EMP, Varandas PAMM, Silva AMS. Synthesis. 2013; 45:3053. For reviews on tetrahydropyridines, see Mateeva NN, Winfield LL, Redda KK. Curr. Med. Chem. 2005; 12:551. [PubMed: 15777212] Felpin FX, Lebreton J. Curr. Org. Synth. 2004; 1:83.
5. For select recent examples of stereoselective syntheses of multi-substituted piperidines, see: Tait MB, Butterworth S, Clayden J. Org. Lett. 2015; 17:1236. [PubMed: 25692395] Ballete R, Perez M, Proto S, Amat M, Bosch J. Angew. Chem. Int. Ed. 2014; 53:6202. Pelletier GG, Constantineau-Forget L, Charette AB. Chem. Commun. 2014; 50:6883. Pardo DG, Cossy J. Chem. Eur. J. 2014; 20:4516. [PubMed: 24644130] Mizoguchi H, Oikawa H, Oguri H. Nature Chem. 2014; 6:57. [PubMed: 24345948] Jäkel M, Qu J, Schnitzer T, Helmchen G. Chem. Eur. J. 2013; 19:16746. [PubMed: 24151151] Martin TJ, Rovis T. Angew. Chem. Int. Ed. 2013; 52:5368. Potowski M, Bauer JO, Strohmann C, Antonchick AP, Waldmann H. Angew. Chem. Int. Ed. 2012; 51:9512. Brizgys GJ, Jung HH, Floreancig PE. Chem. Sci. 2012; 3:438. Chen F, Tan CK, Yeung Y-Y. J. Am. Chem. Soc. 2013; 135:1232. [PubMed: 23312005] Lemonnier G, Charette AB. J. Org. Chem. 2012; 77:5832. [PubMed: 22676407] Yang DX, Micalizio GC. J. Am. Chem. Soc. 2012; 134:15237. [PubMed: 22957796]
6. Colby DA, Bergman RG, Ellman JA. J. Am. Chem. Soc. 2008; 130:3645. [PubMed: 18302381]
7. a Duttwyler S, Lu C, Rheingold AL, Bergman RG, Ellman JA. J. Am. Chem. Soc. 2012; 134:4064. [PubMed: 22356093] b Duttwyler S, Chen S, Takase MK, Wiberg KB, Bergman RG, Ellman JA. Science. 2013; 339:678. [PubMed: 23393259] c Ischay MA, Takase MK, Bergman RG, Ellman JA. J. Am. Chem. Soc. 2013; 135:2478. [PubMed: 23398467] d Duttwyler S, Chen S, Lu C, Mercado BQ, Bergman RG, Ellman JA. Angew. Chem. Int. Ed. 2014; 53:3877.

8. For olefinic oxidation of allylic and homoallylic amines under acidic conditions, see: Quick J, Khandelwal Y, Meltzer PC, Weinberg JS. J. Org. Chem. 1983; 48:5199. Asensio G, Mello R, Boix-Bernardini C, Gonzalez-Nunez ME, Castellano G. J. Org. Chem. 1995; 60:3692. Asensio G, Boix-Bernardini C, Andreu C, Gonzalez-Nunez ME, Mello R, Edwards JO, Castellano G. J. Org. Chem. 1999; 64:4705. [PubMed: 11674543] Gil L, Compere D, Guilloteau-Bertin B, Chiaroni A, Marazano C. Synthesis. 2000; 14:2117. Edwards AS, Wybrow RAJ, Johnstone C, Adams H, Harrity JPA. Chem. Commun. 2002:1542. Aggarwal VK, Fang GY. Chem. Commun. 2005:3448. Grishina GV, Borisenko AA, Veselov IS, Petrenko AM. Russ. J. Org. Chem. 2005; 41:272.

9. a Aciro C, Claridge TDW, Davies SG, Roberts PM, Russell AJ, Thomson JE. Org. Biomol. Chem. 2008; 6:3751. [PubMed: 18843405] b Aciro C, Davies SG, Roberts PM, Russell AJ, Smith AD, Thomson JE. Org. Biomol. Chem. 2008; 6:3762. [PubMed: 18843406] c Bond CW, Cresswell AJ, Davies SG, Kurosawa W, Lee JA, Fletcher AM, Roberts PM, Russell AJ, Smith AD, Thomson JE. J. Org. Chem. 2009; 74:6735. [PubMed: 19642691] d Davies SG, Fletcher AM, Kurosawa W, Lee JA, Poce G, Roberts PM, Thomson JE, Williamson DM. J. Org. Chem. 2010; 75:7745. [PubMed: 20954691] e Bagal SK, Davies SG, Fletcher AM, Lee JA, Roberts PM, Scott PM, Thomson JE. Tetrahedron Lett. 2011; 52:2216.f Brennan MB, Claridge TDW, Compton RG, Davies SG, Fletcher AM, Henstridge MC, Hewings DS, Kurosawa W, Lee JA, Roberts PM, Schoonen AK, Thomson JE. J. Org. Chem. 2012; 77:7241. [PubMed: 22827448] g Davies SG, Fletcher AM, Thomson JE. Org. Biomol. Chem. 2014; 12:4544. [PubMed: 24854106] h Brennan MB, Davies SG, Fletcher AM, Lee JA, Roberts PM, Russell AJ, Thomson JE. Aust. J. Chem. 2015; 68:610.

10. For kinetic studies on ammonium-directed stereoselective oxidations of olefins, see 8c and 9f.

11. Cavdar H, Saracoglu N. Tetrahedron. 2009; 65:985.

12. Cresswell AJ, Davies SG, Lee JAM, Morris J, Roberts PM, Thomson JE. J. Org. Chem. 2011; 76:4617. [PubMed: 21495698]

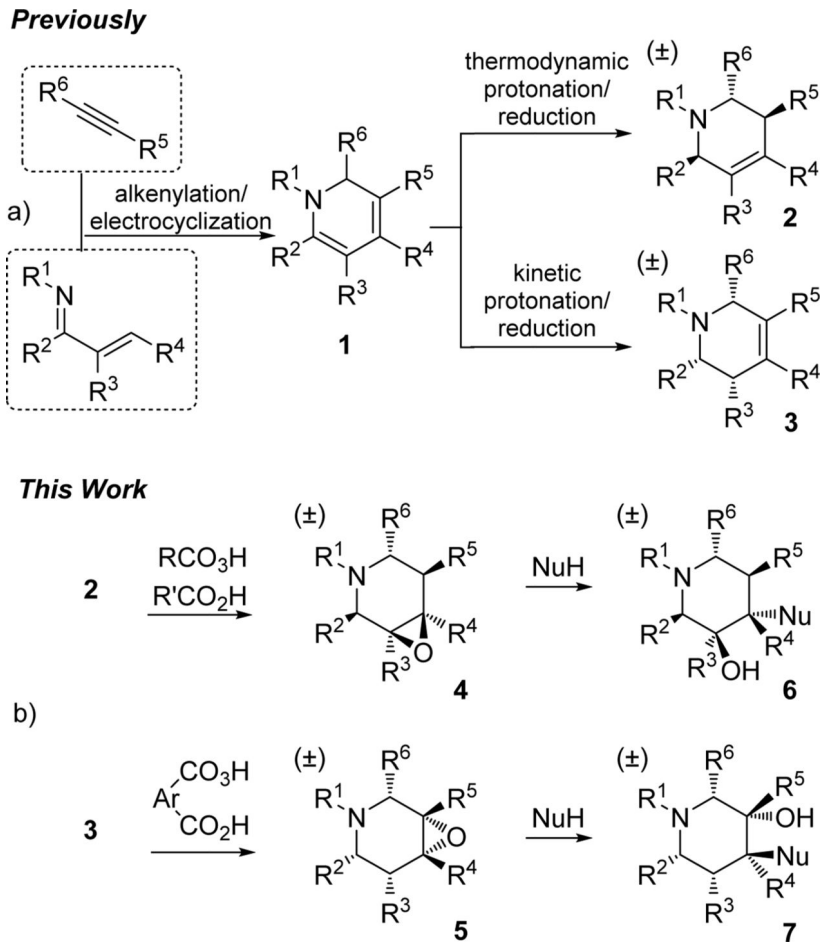
13. a Parker RE, Isaacs NS. Chem. Rev. 1959; 59:737.b Addy JK, Parker RE. J. Chem. Soc. 1963:915.c Rao AS, Paknikar SK, Kirtane JG. Tetrahedron. 1983; 39:2323.d Pocker Y, Ronald BP, Anderson KW. J. Am. Chem. Soc. 1988; 110:6492.

14. For detailed information (structure, bioactivity, published studies, ongoing clinical trials, applications and usage) of epoxide-containing drugs and drug candidates, enter the following names into PubChem (http://pubchem.ncbi.nlm.nih.gov/): spiriva (CID 5487426), scopoderm (CID 5184), kyprolis (CID 11556711), inspra (CID 443872), ixempra (CID 6445540), fumagillin (CID 6917655).

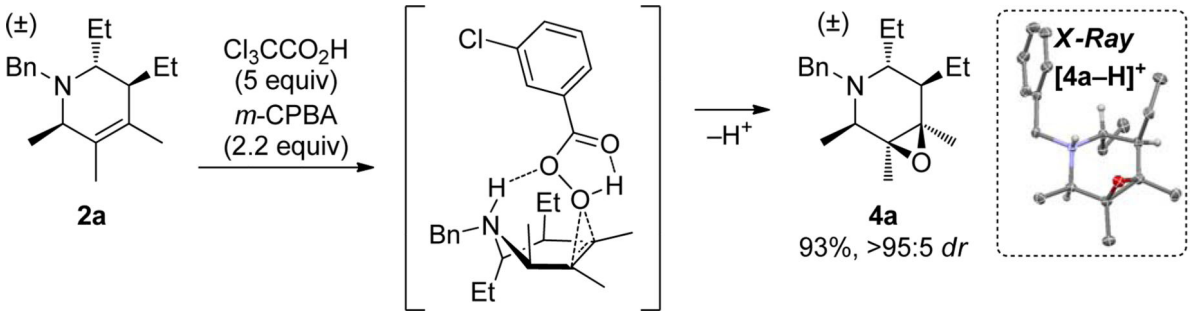
15. Synthetic details, characterization, and molecular structures obtained by X-ray structural analysis of compounds are described in the Supporting Information under CCDC Nos: 1000666 (**4a**), 1000667 (**4g**), 1000668 (**5a**), 1000669 (**5c**), 1000670 (**6a**), and 1000671 (**6b**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

16. Armarego, WLF.; Chai, CLL. Purification of Laboratory Chemicals. 5th ed.. Butterworth-Heinemann; Boston: 2003.

17. Hamper BC, Kurtzweil ML, Beck JP. J. Org. Chem. 1992; 57:5680.

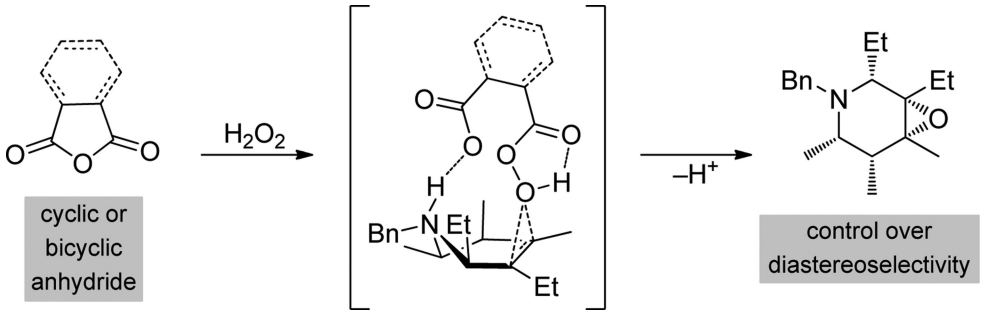


Scheme 1.
Previously disclosed tetrahydropyridine synthesis and comparison with this work.



Scheme 2.

Diastereoselective epoxidation of tetrahydropyridine **2a**. X-ray crystal structure shown with 50% displacement ellipsoids (anion and non-ring hydrogen atoms omitted for clarity).

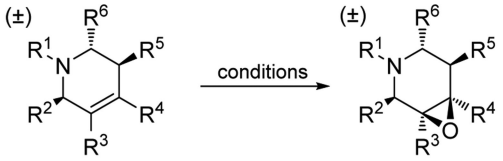


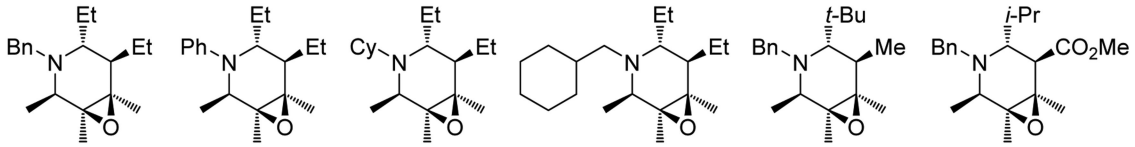
Scheme 3.

Controlling face selectivity in epoxidation of tetrahydropyridines derived from kinetic protonation/reduction sequence by tethering.

Table 1

Epoxidation of tetrahydropyridines **2**.[a,b]





4a, 93%
>95:5 *dr*

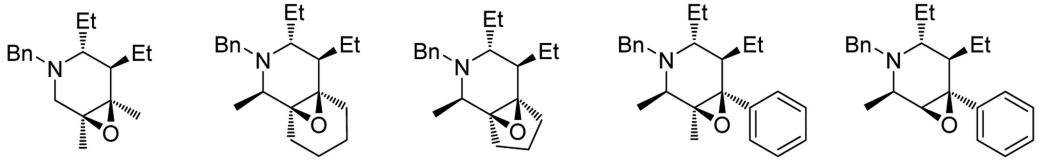
4b, 76%
84:16 *dr*

4c, 92%
>95:5 *dr*

4d, 81%
>95:5 *dr*

4e, 83%
94:6 *dr*

4f, 70%[c]
>95:5 *dr*



4g, 79%
>95:5 *dr*

4h, 90%[c]
>95:5 *dr*

4i, 84%
>95:5 *dr*

4j, 86%[c]
91:9 *dr*

4k, 55%[d]
86:14 *dr*

[c] Epoxidation was accomplished by treating with TFAA (6.0 equiv) and H_2O_2 (30% w/w in H_2O, 5.0 equiv) pre-mixed in THF at 0 °C.

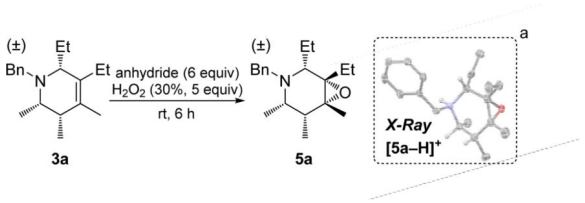
[d] The reported results were obtained by epoxidation with tetrafluorophthalic anhydride and H_2O_2 (*vide infra*). Epoxidation with TFAA and H_2O_2 resulted in a complex mixture of products.

[a] Diastereoselectivities were determined by ^1H and ^{13}C NMR analysis. Isolated yields were determined by mass balance after purification by chromatography.

[b] Products **4a–4e, 4g,** and **4i** were obtained by subjecting the corresponding tetrahydropyridines to Cl_3CCO_2H (5.0 equiv) followed by epoxidation with *m*-CPBA (2.2-3.0 equiv).

Table 2

Optimization of epoxidation conditions for tetrahydropyridines **3.**



Entry	Anhydride	Solvent	Conversion[b]	*dr* [c]
1	trifluoroacetic	CH_2Cl_2	100%	56:44
2	trifluoroacetic	THF	No reaction	-
3	succinic	CH_2Cl_2	15%	58:42
4	glutaric	CH_2Cl_2	27%	69:31
5	phthalic	CH_2O_2	95%	69:31
6	tetrafluorophthalic	CH_2Cl_2	100%	42:58
7	tetrafluorophthalic	EtOAc	100%	76:24
8	tetrafluorophthalic	PhMe	100%	52:48
9	tetrafluorophthalic	Et_2O	100%	85:15
10	tetrafluorophthalic	THF	100%	>95:5
11	tetrachlorophthalic	THF	32%	89:11
12	tetrachlorophthalic[d]	THF	74%	80:20

[a] X-ray crystal structure shown with 30% displacement ellipsoids (anion and hydrogen atoms omitted for clarity except for those on the ring).

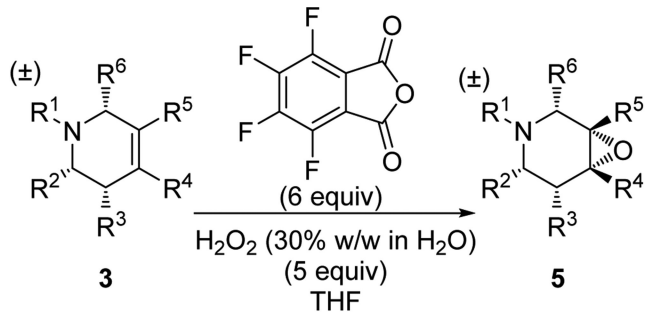
[b] Conversion was determined by the ratio of product versus starting material by ^{1}H NMR analysis.

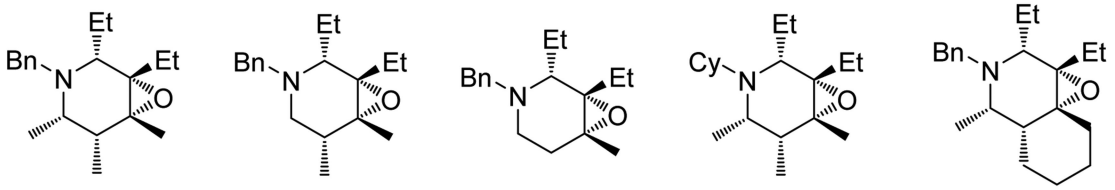
[c] Diastereoselectivity determined by ^{1}H NMR analysis.

[d] Reaction run at reflux.

Table 3

Epoxidation of tetrahydropyridines **3**.[a]





5a, 75%
>95:5 *dr*

5b, 84%
>93:7 *dr*

5c, 70%
>95:5 *dr*

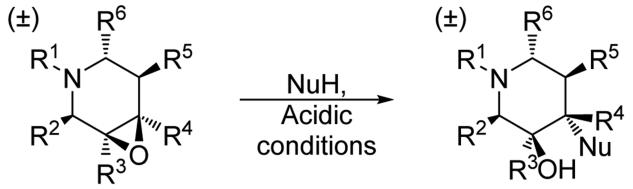
5d, 65%
86:14 *dr*

5e, 72%
88:12 *dr*

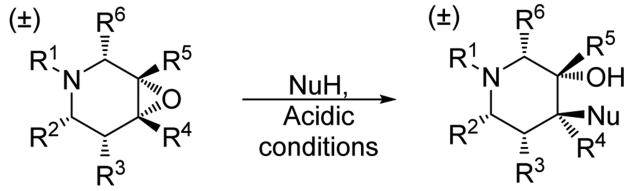
[a]Isolated yields were determined by mass balance after purification by chromatography. Diastereoselectivities were determined by ^{1}H and ^{13}C NMR analysis. Relative configuration rigorously assigned for **5a** and **5c** by X-ray structural analysis.

Table 4

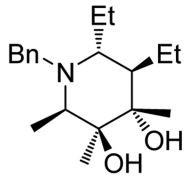
Nucleophilic opening of epoxides **4** and **5**.[a]



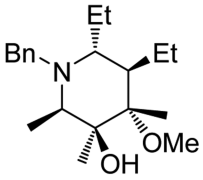
4 **6**



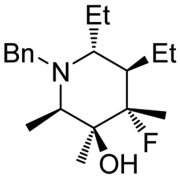
5 **7**



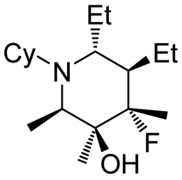
6a, 66%[b]
94:6 *rr*



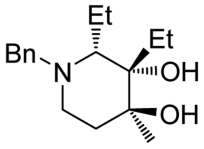
6b, 54%[c]
>95:5 *rr*



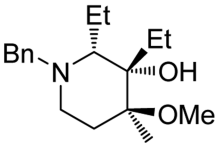
6c, 75%[d]
>95:5 *rr*



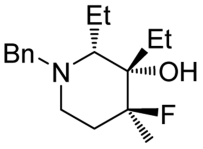
6d, 75%[d]
>95:5 *rr*



7a, 77%[b]
92:8 *rr*



7b, 64%[c]
94:6 *rr*



7c, 80%[d]
94:6 *rr*

[b] H_2O addition was achieved by heating at 70 °C in a CH_2Cl_2/sat. aq. $NaHSO_4$ mixture.

[c] MeOH addition was performed at 80 °C in anhydrous MeOH with dry $PhSO_3H$ (2 equiv).

[d] HF addition was accomplished by treating with $HBF_4{\cdot}Et_2O$ (2 equiv) at rt.

[a] Isolated yields were determined by mass balance after purification by chromatography. Regioselectivities were determined by X-ray structural analysis for **6a** and **6b**, and for the remaining derivatives by ^1H, ^{13}C, and ^{19}F NMR analysis where applicable.