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A biocatalytic/reductive etherification approach to substituted piperidinyl ethers

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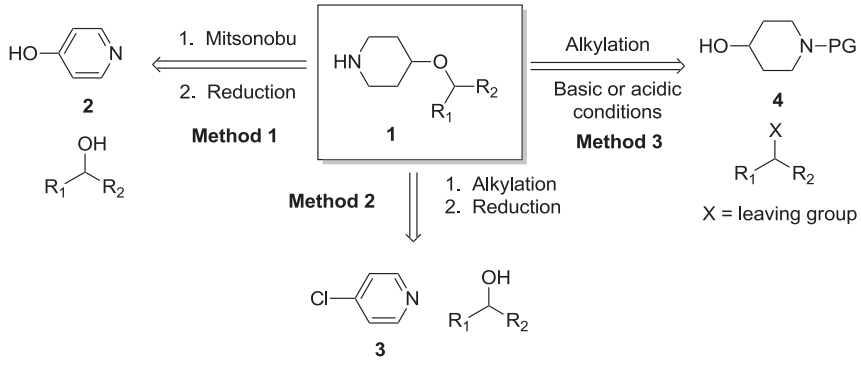
ABSTRACT

A synthetically useful protocol has been developed for the preparation of highly functionalized piperidinyl ethers. Biocatalytic reduction of cyclhexanones **7**, **10**, and **14** allows for the preparation of both *cis*- and *trans* diastereomers with an extremely high degree of stereochemical control. Reductive etherification of the corresponding trimethylsilylethers with 1-(benzyloxycarbonyl)-4-piperidinone **17** in the presence of triethylsilane and catalytic TMSO-Tf provides the desired piperidinyl ethers in good to excellent yields. Finally hygrogenolysis of the nitrogen protecting group leads to piperidinyl ethers in near quantitative yields. Application of the methodology to a range of piperidinyl ethers, including the core scaffolds of diphenylpyraline and ebastine, is also described.

1. Introduction

Piperidinyl ethers of subclass **1** have emerged in recent years as a central pharmacophore in a range of molecules possessing a diverse array of biological activity (Scheme 1).[1] There are several methods for the construction of **1** that have been developed, each offering certain advantages. For example, reaction of 4-hydroxypyridine with various secondary alcohols under standard Mitsunobu reaction conditions followed by reduction of the pyridine ring allows for a two-step preparation of compound **1** (Method 1).[2] Method 2, which has been less employed, involves alkylation of 4-chloropyridine **3** and subsequent reduction of the pyridine ring.[3] The major disadvantage of Methods 1 and 2 is the necessary reduction of the pyridine ring. Direct hydrogenation of the pyridine ring often requires forcing conditions including high pressures of hydrogen and prolonged reaction times. Partial reduction of the ring with $NaBH_4$ followed hydrogenation has served as an alternative approach, but requires an additional synthetic



Scheme 1.

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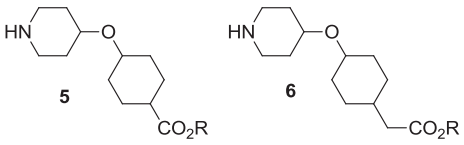
step. The third method for the preparation of compound **1** involves alkylation of 4-hydroxypiperidines with either secondary halides under basic conditions (S_N2)[4] or secondary alcohols under acidic conditions[5] when either R_1 or R_2 is an aromatic group (S_N1). Limitations of Method 3 include the potential for elimination of the secondary halide under both basic and acidic conditions and the lack of ability to set the stereogenic center under acidic conditions when $R_1 \neq R_2$.

Recently we required gram quantities of piperidinyl ethers **5** and **6** in order to further support an on-going program (Scheme 2). Initial milligram quantities of these intriguing intermediates were prepared employing Method 1 as outlined in Scheme 1. The initial Mitsunobu reaction provided a 1:1 mixture of *cis*/*trans* diastereomers due to the fact that the commercially available cyclohexanols employed were also obtained as a mixture of isomers. Separation of the Mitsunobu products by conventional chromatography was unsuccessful and required purification by supercritical fluid chromatography (SFC). Finally, hydrogenation of the pyridine ring system of both compounds **5** and **6** required extremely long reaction times (up to 5 days) and proceeded in low yield (<50%) for each of the individual diastereomers. In order to address these problems, it was envisioned that control of the *cis*/*trans* diastereomers about the cyclohexane ring and elimination of the challenging pyridine ring reduction would allow for the preparation of diastereomerically pure products **5** and **6**. In this paper, we disclose a highly efficient method for the preparation of diastereomerically pure cyclohexanols followed by reductive etherification leading to a general and improved route for the construction of piperidinyl ethers of type **1**.



Scheme 2.

2. Results and discussion

2.1. Biocatalytic reduction of cyclohexanones

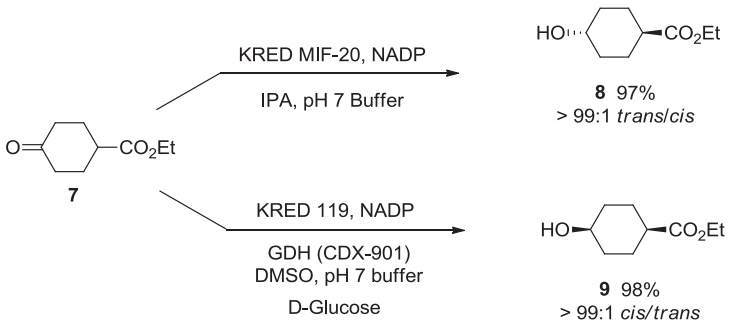
Of known enzymatic reductive reactions, the reduction of ketones to chiral alcohols is perhaps the most evolved. These enzymes are typically known as ketoreductases (KRED) and use NADPH cofactor, regenerated in situ, as the hydride donor for the reduction. The evolution of a large number of enzymes with broad substrate scope has led to the ability of rapid screening of conditions to effect the desired reduction with a high degree of stereocontrol. With a wealth of in-house experience,[6] we choose to first examine the diastereoselective reduction of commercially available ketone **7** (Scheme 3). Screening the reduction of ketone **7** resulted in multiple 'hits'; however there were two KREDs that gave exclusively either the *trans* or *cis* diastereomer as determined by gas chromatography (GC). In all cases, either a co-substrate isopropanol (IPA) system, or a co-enzyme GDH/glucose system was used to recycle the NADPH cofactor. For example, reduction of **7** with KRED MIF-20[7] in IPA/pH 7 buffer resulted in clean conversion to cyclohexanol **8**, which after workup was obtained in 97% isolated yield and in>99:1 *trans*/*cis* diastereoselectivity. On the other hand, reduction of ketone **7** with KRED 119 in the presence of GDH (CDX-901) and D-glucose afforded the *cis* isomer **9** in 98% isolated yield and >99:1 *cis*/*trans* diastereoselectivity. The products from these reductions were of sufficient purity that chromatographic purification was not required.

In order to access the diastereomers of piperidinyl ethers **6**, the screening process was repeated with ketone **11**. Since this ketone was not commercially available, it was synthesized in high yield from phenol **10**. Hydrogenation of phenol **10** over Rh/Al_2O_3 at 45 psi hydrogen gave alcohols **12** and **13** as a mixture of diastereomers in 99% yield. Oxidation of **6** was accomplished with bleach in AcOH and furnished ketone **11** in 97% overall yield for the two-steps. Optimal conditions that were identified for the biocatalytic reduction of ketone **11** involved the use of KRED 142, GDH (CDX-901), and D-glucose and provided exclusively *trans*-cyclohexanol **12** in 90% yield and in a 93:7 ratio of *trans*/*cis* diastereomers. While it was believed that further screening and enzyme optimization was possible to achieve complete diastereoselectivity, these initial conditions were deemed acceptable for our down-stream chemistry, and no additional effort was invested in optimization. Reduction of ketone **11** with KRED P3D1 in IPA/pH 7 buffer in the presence of D-glucose afforded *cis*-cyclohexanol **13** in 97% yield and in >99:1 *cis*/*trans* diastereomers. Crude cyclohexanols **12** and **13** were pure enough for use in subsequent chemistry without the need for chromatography (Scheme 4).

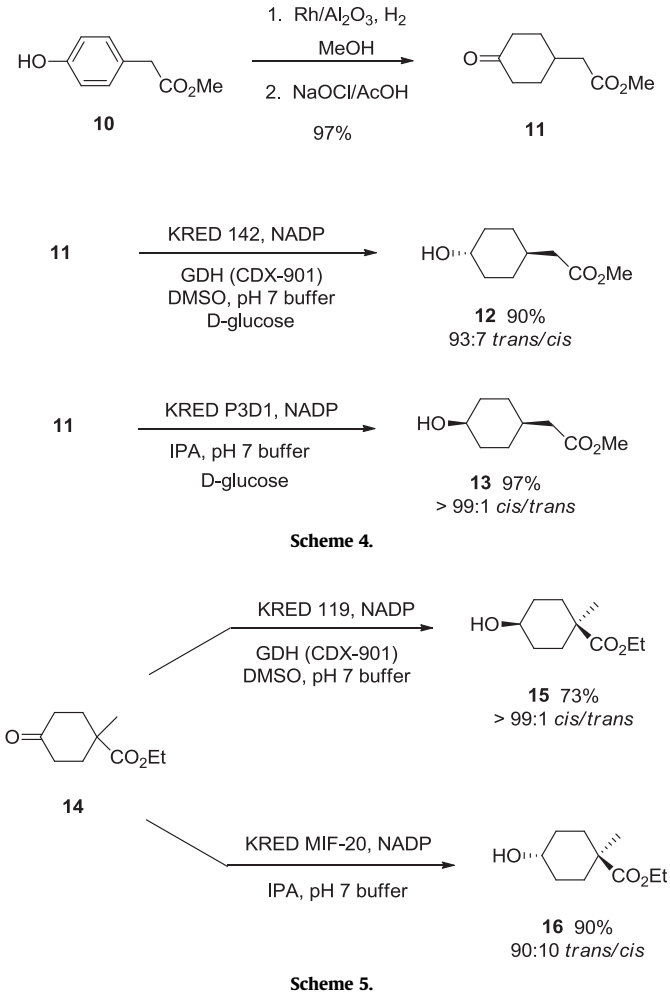
Finally, we were also interested in the reduction of the known ketone **14**[8] (Scheme 5). Screening the reduction of ketone **14** resulted in a number of enzymes that provided clean conversion to the *cis* diastereomer **15**. Optimal conditions involved reaction of ketone **14** with KRED 119 in the presence of GDH (CDX-901) and glucose and provided **15** in an unoptimized 73% yield and in >99:1 *cis*/*trans* selectivity. Access to diastereomer **16** proved difficult and, despite extensive screening, KRED MIF-20 provided a 90:10 ratio of diastereomers that was achieved in 90% yield. Although diastereoselectivity improvement of KRED MIF-20 was available via directed evolution, we choose not to pursue this option at this stage of development.

2.2. Reductive etherification

The reductive etherification of carbonyl compounds and alkoxytrimethylsilanes in the presence of triethylsilane is typically promoted by Lewis acids, such as $Cu(OTf)_2$,[9] $FeCl_3$,[10] TMSO-Tf,[11] trityl perchlorate,[12] TMSI,[13] and tris(pentafluorophenyl)borane,[14] and



Scheme 3.



Scheme 4.

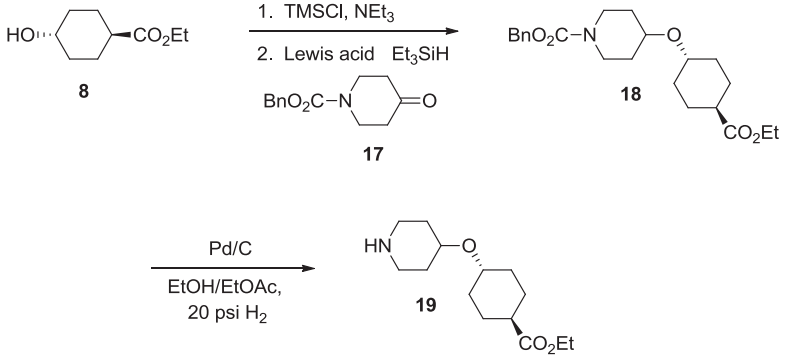
Scheme 5.

Brønsted acids, such as $BiBr_3$.[15,16] Although these conditions have been successfully employed with relatively simple carbonyl compounds and alkoxytrimethylsilanes, application to nitrogen-containing hetereocycles and more advanced silylethers has been limited to a few reported examples.[17] With a useful method for the preparation of diastereomerically pure cyclohexanols in hand, we next set out to examine reductive etherification conditions with CBz-protected piperidinone **17** (Scheme 6). Generation of the silyl ether of alcohol **8** involved reaction with TMS-Cl in THF in the presence of NEt_3[18] at 0 °C for 30 min. The resulting ammonium salts were filtered and the crude silyl ether concentrated and used directly in the reductive etherification reaction. Screening the reductive etherification with a number of Lewis acids afforded the desired product **18** in modest yields (Table 1). In all cases, competitive reduction of ketone **17** to the corresponding piperdinol was observed as the major by product of these reactions. The best conditions involved addition of 0.5 equiv of TMSO-Tf to a cold (−60 °C) mixture of ketone **17**, the silyl ether of cyclohexanol **8** (1 equiv), and Et_3SiH (1.1 equiv) in CH_2Cl_2 followed by warming to room temperature. Under these conditions, the desired product **18** was obtained in 81% isolated yield after chromatography on silica gel. It should also be noted that there was no detectable isomerization about either the C–O bond on the cyclohexyl ring or the center adjacent to the ester center. Finally, hydrogenolysis of ether **18** with Pd/C in a mixture of EtOH/EtOAc furnished ether **19** in 90% yield.

Table 1
Lewis acid promoted reductive etherification of **8** and **17**

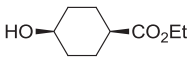
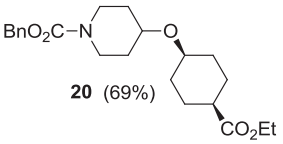
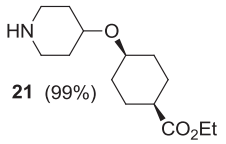
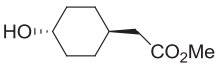
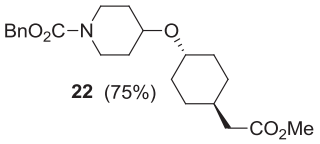
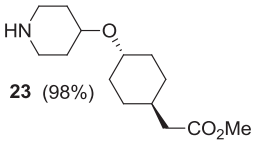
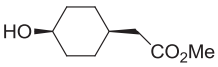
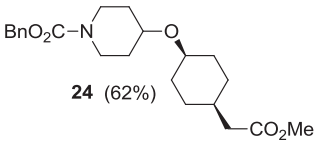
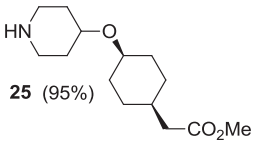
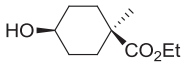
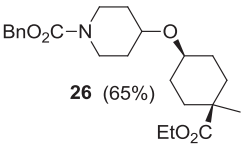
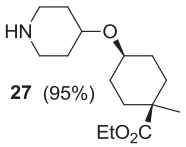
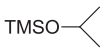
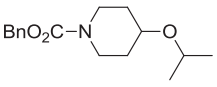
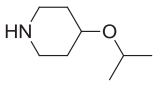
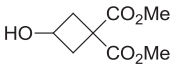
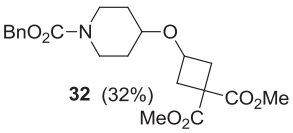
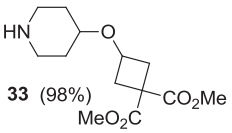
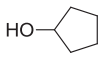
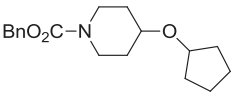
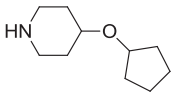
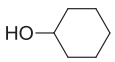
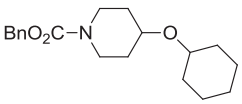
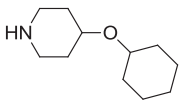
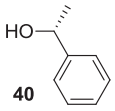
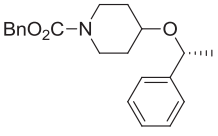
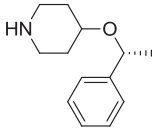
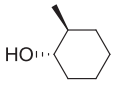
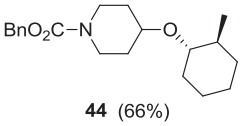
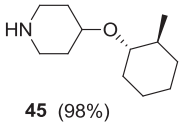
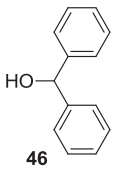
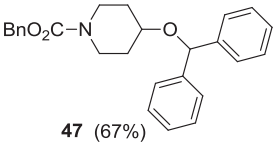
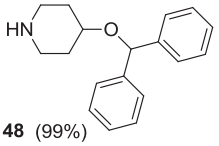
Entry	Lewis acid	Solvent	Temp	Yield of **18**
1	$Cu(OTf)_2$	CH_2Cl_2	rt	54%
2	$BiBr_3$	MeCN	rt	43%
3	$FeCl_3$	MeCN	rt	56%
4	$FeCl_3$	$MeNO_2$	rt	61%
5	TMSO-Tf	CH_2Cl_2	0 °C to rt	63%
6	TMSO-Tf	CH_2Cl_2	−60 °C to rt	81%

The sequence outlined in Scheme 6 proved to be general as highlighted in Table 2. Reductive etherification between ketone **17** and alcohols **9**, **12**, **13**, and **15** allowed for the diastereoselective synthesis of the desired piperidinyl ethers **21**, **23**, **25**, and **27** in good to excellent yield for the two-step protocol. Only when cyclobutyl alcohol **31** was employed did the yield of the reductive etherification product dramatically drop (entry 6). The reductive etherification reaction was not particularly susceptible to steric constraints about the silyl ether and compounds **41** and **44** (entries 9 and 10) were obtained as single enantiomers/diastereomers in good yields. While the reductive etherification products generally required purification by silica gel chromatography to remove impurities, such as the reduced starting material **17**, the products from the subsequent hydrogenolysis did not require chromatographic purification. Finally, the core scaffold of diphenylpyraline and ebastine, a class of marketed compounds shown to have antiallergic activity (entry 11, compound **48**), was prepared in 66% yield over the two-steps.[19] The advantage of the present methodology in the preparation of this subclass of piperidinyl ethers is the ability to start with a single enantiomer of any diarylmethanol derivative of type **46** allowing straight forward access to chiral piperidinyl ethers.[20]



Scheme 6.

Table 2
Preparation of substituted piperidinyl ethers

Entry	Alcohol	Reductive etherification product (% yield)	Hydrogenolysis product (% yield)
1	 **9**	 **20** (69%)	 **21** (99%)
2	 **12**	 **22** (75%)	 **23** (98%)
3	 **13**	 **24** (62%)	 **25** (95%)
4	 **15**	 **26** (65%)	 **27** (95%)
5	 **28**	 **29** (61%)	 **30** (99%)
6	 **31**	 **32** (32%)	 **33** (98%)
7	 **34**	 **35** (58%)	 **36** (99%)
8	 **37**	 **38** (68%)	 **39** (99%)
9	 **40**	 **41** (71%)	 **42** (98%)
10	 **43**	 **44** (66%)	 **45** (98%)
11	 **46**	 **47** (67%)	 **48** (99%)

3. Conclusions

In conclusion, we have demonstrated a highly efficient and diastereoselective biocatalytic reduction of cyclohexanones **7**, **11**, and **14**. Reductive cyclization employing TMSO-Tf and Et_3SiH proved to be an effective method for preparation of a range of functionalized piperidinyl ethers in good to excellent yields following removal of the CBz-protecting group via hydrogenolysis. In the case of piperidinyl ethers **5** and **6**, the synthetic protocol required just three synthetic steps and only one chromatographic purification. From commercially available achiral and chiral alcohols, the method allowed for the two-step preparation of the desired piperidinyl ethers.

4. Experimental section

4.1. General

Commercial grade reagents and solvents were used without further purification. ^1H NMR and ^{13}C NMR spectra were measured with a 400 MHz spectrometer. ^1H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). Purifications were carried out by flash column chromatography on a Teledyne Isco CombiFlash R_f using a gradient elution of 0–100% EtOAc/hexanes unless otherwise specified.

*4.1.1. Preparation of trans ethyl 4-hydroxycyclohexanecarboxylate (**8**).* To a solution of 1.43 L of water was added 9.70 g (71.2 mmol) of KH_2PO_4 and 12.4 g (71.2 mmol) of K_2HPO_4. To the resulting solution was added 5.71 g of MIF-20 and 1.43 g of NADP to give a pH of 7.0. To the mixture was added 256.8 g (1.51 mol) of ketone **7** in 1.43 L of 2-propanol. The pH of the mixture was controlled at 7.0 by the addition of 1 M HCl during the course of the reaction, and the mixture was stirred at 30 °C for 20 h. The reaction mixture was then extracted with MTBE (1.5 L). The aqueous layer was back extracted with a 3:1 mixture of MTBE/2-propanol (2×600 mL). The organic layer was concentrated under reduced pressure and re-dissolved in 1.5 L of MTBE. The organic layer was washed with brine (2×300 mL), dried over $MgSO_4$, and concentrated under reduced pressure to provide 268 g (97%) of **8** as a colorless solid and in >99:1 *trans*/*cis* diastereoselectivity. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19–1.34 (m, 5H), 1.51 (m, 2H), 1.67 (br s, 1H), 2.20 (m, 4H), 2.23 (m, 1H), 4.12 (q, 2H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 27.1, 34.4, 42.3, 60.2, 69.6, 176.7. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.51; H, 9.12.

*4.1.2. Preparation of cis ethyl 4-hydroxycyclohexanecarboxylate (**9**).* To a solution of 1.67 g of KRED 119, 1.67 g of NAPD, and 1.67 g of GDH (CDX-901), and 106 g (588.0 mmol) of D-glucose in 1.5 L of 0.1 M pH 7 phosphate buffer was added 45.6 g (268 mmol) of ketone **7** in 137 mL of DMSO. The pH of the reaction mixture was monitored and adjusted as needed with 5 N NaOH to maintain a constant pH of 7. The reaction mixture was stirred for 20 h at room temperature. The reaction mixture was diluted with 200 mL of a 1:1 mixture of EtOH/MTBE and the layers separated. The aqueous layer was back extracted with MTBE (3×500 mL). The combined organic extracts were washed with brine (2×250 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give 45.2 g (98%) of **9** as a colorless solid and in >99:1 *cis*/*trans* diastereoselectivity. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3H, J=7.2 Hz), 1.49 (br s, 1H), 1.71 (m, 6H), 1.98 (m, 2H), 2.39 (m, 1H), 3.90 (m, 1H), 4.14 (q, 2H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 23.7, 32.0, 41.3, 60.2, 66.8, 175.4. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.84; H, 9.53.

*4.1.3. Preparation of methyl 2-(4-oxocyclohexyl)acetate (**11**).* To a solution of 100.0 g (602 mmol) of **10** in 1 L of MeOH was added 10.0 g (244 mmol) of Rh/Al_2O_3. The resulting mixture was degassed via vacuum/hydrogen purges (3×) and hydrogenated at 22 °C and 45 psi hydrogen for 20 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to provide 103 g (99%) of the corresponding cyclohexanols **12** and **13** as a mixture of diastereomers that were used in the next step without further purification.

To a cooled (~10 °C) solution of 100.3 g (582.0 mmol) of the above alcohol in 361 mL of AcOH was added drop wise 954 mL of a 5% solution of NaOCl while maintaining the internal temperature <25 °C. After the addition was complete, the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with 500 mL of brine and 1 L of EtOAc and the layers were separated. The aqueous layer was back extracted with EtOAc (3×500 mL). The combined organic extracts were washed with 500 mL of 20% K_2CO_3 and then with 500 mL of satd $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give 97.0 g (98%) of **11**, which was sufficiently pure for use in the next step.

*4.1.4. Preparation of trans methyl 4-hydroxycyclohexylacetate (**12**).* To a mixture of 5.0 g of KRED 142, 2.2 g of NADP, 402 g of D-glucose, and 5.0 g of GDH (CDX-901) in 1.8 L of pH 7 phosphate buffer was added drop wise 95.0 g (558 mmol) of ketone **11** over 5 h while maintaining the internal pH at 7 by the addition of 8 N NaOH. After 4 h, the pH was adjusted to 2 by the addition of phosphoric acid. To the mixture was added 50 g of Celite and the slurry was stirred for 20 min and filtered. To the filtrate was added 800 mL of EtOAc and the layers were separated. The aqueous layer was back extracted with EtOAc (2×800 mL). The combined organic extracts were washed with 1 L of water, 200 mL of 5% $NaHCO_3$, 200 mL of 0.5% phosphoric acid, and 200 mL of brine. The solvent was removed under reduced pressure to provide 93.2 g (97%) of **12** as a colorless oil, which was sufficiently pure for use in the next reaction: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (m, 2H), 1.29 (m, 2H), 1.61 (br s, 1H), 1.70–1.81 (m, 3H), 1.99 (m, 2H), 2.20 (d, 2H, J=6.8 Hz), 3.55 (m, 1H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.9, 33.8, 35.1, 41.0, 51.4, 70.4, 173.4. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36.

*4.1.5. Preparation of cis methyl 4-hydroxycyclohexylacetate (**13**).* To a mixture of 1.80 g of KRED P3D1 and 200 mg of NADP in 140 mL of 1.0 M pH 7 phosphate buffer was added 10.0 g (58.8 mmol) of ketone **11** in 60 mL of 2-propanol. The resulting mixture was stirred at 30 °C for 20 h. The reaction mixture was then diluted with 60 mL of MTBE and the layers separated. The aqueous layer was back extracted with 150 mL of a 2:1 mixture of MTBE/2-propanol (2×). The organic layer was washed with water (2×100 mL) and then brine (100 mL) and dried over Na_2SO_4. Concentration of the organic layer afforded 9.8 g (97%) of **13** as a colorless oil that was sufficiently pure for use in the next reaction without the need for further purification: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39–1.63 (m, 7H), 1.74 (m, 2H), 1.86 (m, 1H), 2.26 (d, 2H, J=7.2 Hz), 3.67 (s, 3H), 3.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.7, 32.0, 33.4, 40.7, 51.4, 66.2, 173.5. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.96; H, 9.41.

*4.1.6. Preparation of ethyl 4-hydroxy-1-methylcyclohexane carboxylate (**15**).* To a solution of 0.17 g of KRED, 0.17 g of NADP,

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and 0.17 g of GDH (CDX-901), and 10.8 g (59.7 mmol) of D-glucose in 160 mL of a 0.1 M pH 7 phosphate buffer was added 5.00 g (27.1 mmol) of ketone **14** in 10 mL of DMSO. The pH of the reaction mixture was monitored and adjusted as needed with 5 N NaOH to maintain a constant pH of 7. After 1 h, the reaction was diluted with 150 mL of MTBE and the layers were separated. The aqueous layer was back extracted with 150 mL of MTBE. The combined extracts were washed with 50 mL of water and then with 50 mL of brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 3.67 g (73%) of **15** as an oil, which was sufficiently pure for use without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 3H), 1.16–1.38 (m, 7H), 1.66 (br s, 1H), 1.84 (m, 2H), 2.22 (m, 2H), 3.59 (m, 1H), 4.15 (q, 2H, J=7.0 Hz)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 25.8, 27.0, 30.6, 32.6, 33.6, 42.6, 60.3, 69.8, 176.9. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.92; H, 9.66.

4.2. General procedure A: preparation of 4-piperidinyl ethers. Preparation of *trans* benzyl-4-(4-(ethoxycarbonyl)cyclohexyl) oxy)piperidine-1-carboxylate (18)

To a solution of 10.0 g (58.1 mmol) of alcohol **8** in 150 mL of anhydrous THF was added 8.90 mL (63.9 mmoL, 1.1 equiv) of NEt_3 and the mixture was cooled in an ice bath to give an internal temperature of <5 °C. To the solution was added drop wise 7.79 mL (61.0 mmol, 1.05 equiv) of TMS-Cl. The resulting slurry was stirred at the same temperature for 30 min, diluted with 100 mL of hexane, and filtered to remove the insoluble salts. The filtrate was concentrated under reduced pressure. The resulting crude TMS-ether was re-dissolved in 150 mL of CH_2Cl_2 and cooled in a dry ice/acetone bath to an internal temperature of <−60 °C. To the cooled solution was added sequentially 13.0 g (58.1 mmol, 1 equiv) of 1-(benzyloxycarbonyl)-4-piperidinone **17**, 10.2 mL (63.9 mmol, 1.1 equiv) of triethylsilane, and 5.25 mL (29.0 mmol, 0.5 equiv) of TMS-OTf. The reaction mixture was allowed to slowly warm to 0 °C and stirred for 30 min. The reaction mixture was diluted with 125 mL of EtOAc and 100 mL of 1 M H_3PO_4 and the layers separated. The organic layer was washed with 100 mL of brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 18.3 g (81%) of **18** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3H, J=7.1 Hz), 1.28 (m, 2H), 1.49 (m, 4H), 1.80 (m, 2H), 2.00 (m, 4H), 2.25 (m, 1H), 3.19 (m, 2H), 3.35 (m, 1H), 3.62 (m, 1H), 3.84 (m, 2H), 4.13 (q, 2H, J=7.2 Hz), 5.14 (s, 2H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 27.2, 31.8, 32.0, 41.5, 42.4, 60.2, 67.0, 71.5, 74.3, 127.8, 127.9, 128.5, 136.9, 155.3, 175.6. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.54; H, 7.95; N, 3.55.

4.3. General procedure B: preparation of 4-piperidinyl ethers. Preparation of *trans* ethyl 4-(piperidin-4-yloxy)cyclohexanecarboxylate (19)

To a solution of 1.90 g (4.88 mmol) of **18** in 25 mL of a 1:1 mixture of EtOAc/EtOH was carefully added 150 mg of 10% Pd/C. The mixture was hydrogenated at 20 psi H_2 for 8–20 h or until TLC indicated that all SM had been consumed. The slurry was filtered through a pad of cellulose eluting with EtOAc. The solvent was removed under reduced to provide 1.12 g (90%) of **19** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3H, J=7.1 Hz), 1.32 (m, 2H), 1.86–2.13 (m, 8H), 2.23 (m, 1H), 3.15 (m, 2H), 3.38 (m, 3H), 3.78 (m, 1H), 4.13 (q, 2H, J=2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 27.0, 28.2, 31.8, 40.2, 42.2, 60.3, 67.0, 74.7. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.76; H, 9.84; N, 5.44.

*4.3.1. Preparation of cis benzyl-4-(4-(ethoxycarbonyl)cyclohexyl)oxy) piperidine-1-carboxylate (**20**).* According to general procedure A, treatment of 0.96 g (5.57 mmol) of alcohol **9** with 0.75 mL (5.85 mmol) in the presence of 1.17 mL (6.69 mmol) of NEt_3 followed by reaction with 1.30 g (5.57 mmol) of **17** in the presence of 0.98 mL (6.13 mmol) of triethylsilane and 0.40 mL (2.23 mmol) of TMS-OTf afforded 1.50 g (69%) of **20** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3H, J=7.1 Hz), 1.55 (m, 3H), 1.68 (m, 3H), 1.77 (m, 4H), 1.92 (m, 2H), 2.32 (m, 1H), 3.28 (m, 2H), 3.57 (m, 2H), 3.76 (m, 2H), 4.13 (q, 2H, J=7.1 Hz), 5.13 (s, 2H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 24.0, 30.0, 31.6, 41.3, 41.7, 60.1, 67.0, 70.7, 70.8, 127.8, 127.9, 128.5, 136.9, 155.3, 175.4. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 68.01; H, 8.22; N, 3.66.

*4.3.2. Preparation of cis ethyl 4-(piperidin-4-yloxy)cyclohexanecarboxylate (**21**).* According to general procedure B, hydrogenolysis of 1.35 g (3.47 mmol) of **20** provided 0.90 g (99%) of **21** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, 3H, J=7.1 Hz), 1.53 (m, 2H), 1.70 (m, 4H), 1.88 (m, 4H), 2.09 (m, 2H), 2.33 (m, 1H), 3.19 (m, 2H), 3.33 (m, 2H), 3.58 (m, 1H), 3.24 (m, 1H), 4.12 (q, 2H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 23.8, 27.8, 29.6, 40.4, 41.6, 60.2, 66.7, 71.0. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.89; H, 9.88; N, 5.42.

*4.3.3. Preparation of trans benzyl 4-(4-(2-methoxy-2-oxoethyl)cyclohexyl)oxy)piperidine-1-carboxylate (**22**).* According to general procedure A, treatment of 5.15 g (29.9 mmol) of alcohol **12** with 3.82 mL (29.9 mmol) TMS-Cl in the presence of 5.42 mL (38.9 mmol) of NEt_3 followed by reaction with 6.98 g (29.9 mmol) of **17** in the presence of 5.25 mL (32.9 mmol) of triethylsilane and 2.70 mL (14.98 mmol) of TMS-OTf afforded 8.74 g (75%) of **22** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (m, 2H), 1.07 (m, 2H), 1.29 (m, 2H), 1.51 (m, 2H), 1.78 (m, 4H), 1.96 (m, 2H), 2.20 (d, 2H, J=6.8 Hz), 3.18 (m, 2H), 3.28 (m, 1H), 3.57 (m, 1H), 3.68 (s, 3H), 3.85 (m, 2H), 5.13 (s, 2H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.1, 31.9, 32.6, 34.1, 41.1, 41.5, 51.4, 67.0, 71.4, 75.1, 127.9, 127.9, 128.5, 136.9, 155.3, 173.2. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 68.01; H, 8.31; N, 3.71.

*4.3.4. Preparation of trans methyl 2-(4-(piperidin-4-yloxy)cyclohexyl)acetate (**23**).* According to general procedure B, hydrogenolysis of 3.00 g (7.70 mmol) of **22** gave 1.92 g (98%) of **23** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (m, 2H), 1.29 (m, 2H), 1.63–1.83 (m, 8H), 1.93 (m, 4H), 2.06 (m, 2H), 2.21 (d, 2H, J=6.8 Hz), 3.18–34 (m, 5H), 3.68 (s, 3H), 3.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 30.9, 32.4, 33.9, 40.0, 41.0, 51.4, 66.5, 75.5, 173.2. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.83; H, 9.88; N, 5.51.

*4.3.5. Preparation of cis benzyl 4-(4-(2-methoxy-2-oxoethyl)cyclohexyl)oxy)piperidine-1-carboxylate (**24**).* According to general procedure A, treatment of 0.74 g (4.29 mmol) of alcohol **13** with 0.58 mL (4.50 mmol) TMS-Cl in the presence of 0.90 mL (5.14 mmol) of DIPEA followed by reaction with 1.00 g (4.29 mmol) of **17** in the presence of 0.74 mL (4.72 mmol) of triethylsilane and 0.31 mL (1.75 mmol) of TMS-OTf afforded 1.03 g (62%) of **24** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39–1.55 (m, 8H), 1.77 (m, 5H), 1.83 (m, 1H), 2.24 (d, 2H, J=7.2 Hz), 3.27 (m, 2H), 3.51 (m, 1H), 3.62 (m, 1H), 3.68 (s, 3H), 3.79 (m, 2H), 5.14 (s, 2H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2, 30.0, 31.6, 33.7, 41.0, 41.4, 51.3, 67.0, 70.5, 70.7, 127.8, 127.9, 128.4, 136.9, 155.3, 173.5. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.67; H, 7.93; N, 3.48.

*4.3.6. Preparation of cis methyl 2-(4-(piperidin-4-yloxy)cyclohexyl) acetate (**25**).* According to general procedure B, hydrogenolysis of

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0.72 g (1.85 mmol) of **24** afforded 0.45 g (95%) of **25** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28–1.46 (m, 6H), 1.70 (m, 2H), 1.82 (m, 3H), 2.06 (m, 2H), 2.17 (d, 2H, J=7.2 Hz), 3.14 (m, 2H), 3.27 (m, 2H), 3.53 (m, 1H), 3.61 (s, 3H), 3.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1, 27.7, 29.8, 33.7, 39.9, 41.0, 51.3, 66.3, 70.9, 173.4. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.67; H, 9.81; N, 5.45.

*4.3.7. Preparation of Benzyl 4-((4-(ethoxylcarbonyl)-4-methylcyclohexyl)oxy)pipereidine-1-carboxylate (**26**).* According to general procedure A, treatment of 1.12 g (6.00 mmol) of alcohol **15** with 0.81 mL (6.85 mmol) of TMS-Cl in the presence of 1.26 mL (7.20 mmol) of DIPEA followed by reaction with 1.40 g (6.00 mmol) of **17** in the presence of 1.05 mL (6.60 mmol) of triethylsilane and 0.43 mL (0.53 mmol) of TMS-OTf afforded 1.57 g (65%) of **26** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 3H), 1.64 (m, 2H), 1.24 (t, 3H, J=7.0 Hz), 1.34 (m, 2H), 1.53 (br m, 2H), 1.83 (m, 4H), 2.23 (m, 2H), 3.19 (m, 2H), 3.34 (m, 1H), 3.59 (m, 1H), 3.82 (m, 2H), 4.14 (q, 2H, J=7.0 Hz), 5.13 (s, 2H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 27.0, 30.2, 31.8, 33.7, 41.9, 42.8, 60.3, 67.0, 71.3, 74.4, 127.8, 127.9, 128.5, 155.3, 176.8. Anal. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.29; H, 8.15; N, 3.44.

*4.3.8. Preparation of ethyl 1-methyl-4-(piperidin-4-yloxy)cyclohexanecarboxylate (**27**).* According to general procedure B, hydrogenolysis of 0.51 g (1.26 mmol) of **26** gave 0.33 g (97%) of **27** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15–1.56 (m, 12H), 1.91 (m, 4H), 2.02 (br s, 1H), 2.34 (m, 2H), 2.62 (m, 2H), 3.24 (m, 2H), 3.45 (m, 1H), 3.51 (m, 1H), 4,26 (q, 2H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 27.4, 30.6, 34.1, 43.1, 44.8, 60.5, 73.0, 4.5, 177.0. Anal. Calcd for C, 66.88; H, 10.10; N, 5.20. Found: C, 67.02; H, 9.95; N, 5.03.

*4.3.9. Preparation of benzyl 4-isopropoxypiperidine-1-carboxylate (**29**).* According to general procedure A, treatment of 0.76 mL (4.29 mmol) of commercially available isopropoxytrimethylsilane **28** with 1.00 g (4.29 mmol) of **17** in the presence of 0.75 mL (4.72 mmol) of triethylsilane and 0.31 mL (1.72 mmol) of TMS-OTf afforded 725 mg (61%) of **29** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, 1H, J=6.12 Hz), 1.52 (br m, 2H), 1.79 (br m, 2H), 3.23 (m, 2H), 3.56 (m, 1H), 3.71 (m, 1H), 3.86 (m, 2H), 5.14 (s, 2H), 7.29–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8, 31.8, 41.5, 67.0, 68.2, 71.3, 127.8, 127.9, 128.5, 136.9, 155.3. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.09; H, 8.28; N, 4.97.

*4.3.10. Preparation of 4-isopropoxypiperidine (**30**).* According to general procedure B, hydrogenolysis of 0.64 g (2.31 mmol) of **29** gave 0.33 g (99%) of **30** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (d, 6H), 1.89 (m, 2H), 2.06 (m, 2H), 3.18 (m, 2H), 3.32 (m, 2H), 3.67 (sep, J=6.0 Hz), 3.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 27.8, 40.0, 66.4, 69.0. Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.87; H, 12.03; N, 9.81.

*4.3.11. Preparation of diethyl 3-((benzyloxy)carbonyl)piperidin-4-yl) oxy)cyclobutane-1,1-dicarboxylate (**32**).* According to general procedure A, treatment of 0.927 g (4.29 mmol) of alcohol **31**[21] with 0.58 mL (4.50 mmol) in the presence of 0.78 mL (5.58 mmol) of NEt_3 followed by reaction with 1.00 g (4.29 mmol) of **17** in the presence of 0.75 mL (4.72 mmol) of triethylsilane and 0.31 mL (1.72 mmol) of TMS-OTf afforded 600 mg (32%) of **32** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (m, 6H), 1.50 (br m, 2H), 1.78 (br m, 2H), 2.48 (m, 2H), 2.81 (m, 2H), 3.18 (m, 2H), 3.49 (m, 1H), 3.82 (m, 2H), 4.10 (m, 1H), 4.22 (m, 4H), 5.12 (s, 2H), 7.32–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 31.4, 38.6, 39.2, 40.2, 41.3, 46.2, 61.6, 66.2, 67.1, 73.2, 127.9, 128.0, 128.5, 155.2, 170.9, 171.8. Anal. Calcd for $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23. Found: C, 63.69; H, 7.11; N, 3.18.

*4.3.12. Preparation of diethyl 3-(piperidin-4-yloxy)cyclobutane-1,1-dicarboxylate (**33**).* According to general procedure B, hydrogenolysis of 0.50 g (1.15 mmol) of **32** afforded 0.34 g (98%) of **33** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (m, 6H), 1.43 (m, 2H), 1.84 (m, 2H), 2.18 (br m, 2H), 2.47 (m, 2H), 2.55 (m, 2H), 2.77 (m, 2H), 3.06 (m, 2H), 3.34 (m, 1H), 4.18 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 33.3, 38.7, 39.3, 40.3, 44.3, 61.4, 61.6, 65.9, 74.5, 170.3, 171.5. Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.99; H, 8.33; N, 4.58.

*4.3.13. Preparation of benzyl 4-cyclopentyloxypiperidine-1-carboxylate (**35**).* According to general procedure A, treatment of 0.39 mL (4.29 mmol) of cyclopentanol **31** with 0.58 mL (4.50 mmol) of TMS-Cl in the presence of 0.82 mL (4.72 mmol) of diisopropylethylamine followed by reaction with 1.00 g (429 mmol) of **17** in the presence of 0.75 mL (4.72 mmol) of triethylsilane and 0.31 mL (1.72 mmol) of TMS-OTf gave 760 mg (58%) of **35** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47–1.64 (m, 6H), 1.67–1.79 (m, 6H), 3.19 (m, 2H), 3.49 (m, 1H), 3.84 (m, 2H), 4.03 (m, 1H), 5.13 (s, 2H), 7.33 (m, 5H)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5, 31.6, 32.9, 41.6, 67.0, 72.2, 78.4, 127.8, 127.9, 128.5, 136.9, 155.3. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 70.98; H, 8.11; N, 4.59.

*4.3.14. Preparation of 4-(cyclopentyloxy)piperidine (**36**).* According to general procedure B, hydrogenolysis of 1.12 g (3.69 mmol) of **35** furnished 0.62 g (99%) of **36** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 01.32–1.56 (m, 6H), 1.67 (m, 4H), 1.85 (m, 2H), 2.57 (m, 3H), 3.05 (m, 2H), 3.33 (m, 1H), 3.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 32.9, 33.4, 44.5, 73.3, 78.1. Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.10; H, 11.36; N, 8.22.

*4.3.15. Preparation of benzyl 4-cyclohexyloxypiperidine-1-carboxylate (**38**).* According to general procedure A, treatment of 0.45 mL (4.29 mmol) of cyclohexanol **37** with 0.58 mL (4.50 mmol) of TMS-Cl in the presence of 0.82 mL (4.72 mmol) of diisopropylethylamine followed by reaction with 1.00 g (4.29 mmol) of **17** in the presence of 0.75 mL (4.72 mmol) of triethylsilane and 0.31 mL (1.72 mmol) of TMS-OTf gave 920 mg (68%) of **38** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17–1.34 (m, 5H), 1.53 (m, 3H), 1.73–1.88 (m, 6H), 3.17 (m, H), 3.32 (m, 1H), 3.60 (m, 1H), 3.83 (m, 2H), 5.14 (m, 2H), 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 25.8, 31.9, 33.1, 41.6, 67.0, 71.1, 74.7, 127.8, 127.9, 128.5, 137.0, 155.3. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.90; H, 5.60; N, 4.39.

*4.3.16. Preparation of 4-(cyclohexyloxy)piperidine (**39**).* According to general procedure B, hydrogenolysis of 0.90 g (2.84 mmol) of **38** gave 0.52 g (99%) of **39**[22] as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.1.23 (m, 5H), 1.49 (m, 1H), 1.68–1.87 (m, 6H), 2.06 (m, 2H), 3.13 (m, 2H), 3.28 (m, 3H), 3.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 25.6, 27.9, 32.7, 40.0, 66.3, 74.9. Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08, H, 11.55; N, 7.64. Found: C, 71.90; H, 11.49; N, 7.66.

*4.3.17. Preparation of (R)-benzyl 4-(1-phenylethoxy)piperidine-1-carboxylate (**41**).* According to general procedure A, treatment of 0.57 mL (4.72 mmol) of alcohol **40** with 0.63 mL (4.95 mmol) of TMS-Cl in the presence of 0.85 mL (6.13 mmol) of NEt_3 followed by reaction with 1.10 g (4.72 mmol) of **17** in the presence of 0.83 mL (5.19 mmol) of triethylsilane and 0.34 mL (1.90 mmol) of TMS-OTf afforded 1.14 g (71%) of **41** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (d, 3H, J=6.5 Hz), 1.49–1.67 (m, 3H), 1.85 (m, 1H),

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3.13 (m, 2H), 3.42 (m, 1H), 3.84 (m, 2H), 4.59 (q, 1H, J=6.5 Hz), 5.14 (s, 2H), 7.36 (m, 10H)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 30.4, 32.1, 41.3, 41.5, 67.0, 71.5, 74.7, 126.1, 127.4, 127.8, 127.9, 128.4, 128.5, 137.0, 144.4, 155.3. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.17; H, 7.34; N, 4.01.

*4.3.18. Preparation of (R)-4-(1-phenylethoxy)piperidine (**42**).* According to general procedure B, hydrogenolysis of 0.46 g (1.36 mmol) of **41** gave 0.27 g (98%) of **42** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.1.41 (d, 3H, J=6.5 Hz), 1.47 (m, 1H), 1.65 (m, 1H), 1.99 (m, 3H), 2.53 (m, 2H), 3.08 (m, 2H), 3.31 (m, 1H), 4.61 (q, 1H), 7.25–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 32.4, 34.0, 44.3, 44.5, 72.7, 74.2, 126.0, 127.2, 128.3, 144.7. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.98; H, 9.26; H, 6.82.

*4.3.19. Preparation of benzyl 4-(((1S, 2S)-2-methylcyclohexyl)oxy) piperidine-1-carboxylate (**44**).* According to general procedure A, treatment of 0.53 mL (4.29 mmol) of alcohol **43** with 0.58 mL (4.50 mmol) of TMS-Cl in the presence of 0.82 mL (4.72 mmol) of diisopropylethylamine followed by reaction with 1.00 g (4.29 mmol) of **17** in the presence of 0.75 mL (4.72 mmol) of triethylsilane and 0.31 mL (1.72 mmol) of TMS-OTf gave 935 mg (66%) of **44** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (m, 4H), 1.19 (m, 3H), 1.41 (m, 1H), 1.57 (m, 3H), 1.73 (m, 4H), 1.98 (m, 1H), 2.84 (m, 1H), 3.23 (m, 2H), 3.54 (m, 1H), 3.85 (m, 2H), 5.14 (s, 2H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 25.2, 25.6, 30.9, 32.6, 34.1, 38.6, 41.5, 67.0, 72.1, 81.7, 127.8, 127.9, 128.5, 136.9, 155.3. Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.21; H, 8.74; N, 4.18.

*4.3.20. Preparation of 4-(((1S,2S)-2-methylcyclohexyl)oxy)piperidine (**45**).* According to general procedure B, hydrogenolysis of 0.72 g (2.17 mmol) of **44** afforded 0.42 g (98%) of **45** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (m, 4H), 1.10 (m, 3H), 1.39 (m, 3H), 1.55 (m, 1H), 1.71 (m, 2H), 1.88 (m, 4H), 2.56 (m, 2H), 2.79 (m, 1H), 3.04 (m, 2H), 3.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 25.2, 25.6, 32.8, 33.1, 34.1, 34.8, 44.6, 44.7, 73.8, 81.4. Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.74; N, 7.10. Found: C, 73.18; H, 11.79; N, 7.14.

*4.3.21. Preparation of benzyl 4-(benzhydryloxy)piperidine-1-carboxylate (**47**).* According to general procedure A, treatment of 0.89 g (4.80 mmol) of alcohol **46** with 0.64 mL (5.04 mmol) of TMS-Cl in the presence of 0.92 mL (5.28 mmol) of diisopropylethylamine followed by reaction with 1.12 g (4.80 mmol) of **17** in the presence of 0.84 mL (5.28 mmol) of triethylsilane and 0.53 mL (2.40 mmol) of TMS-OTf furnished 1.30 g (67%) of **47** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (br m, 2H), 1.83 (br m, 2H), 3.29 (m, 2H), 3.65 (m, 1H), 3.83 (m, 2H), 5.15 (s, 2H), 5.54 (s, 1H), 7.25–7.40 (m, 15H)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.0, 41.23, 67.0, 71.6, 80.4, 127.0, 127.5, 127.8, 128.0, 128.4, 128.5, 136.9, 142.6, 155.3. Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.69; H, 6.63; H, 3.39.

*4.3.22. Preparation of 4-(benzhydryloxy)piperidine (**48**).* According to general procedure B, hydrogenolysis of 0.80 g (1.99 mmol) of **47** gave 0.53 g (99%) of **48** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.1.54 (m, 2H), 1,58 (br s, 1H), 1.94 (m, 2H), 2.56 (m, 2H), 3.14 (m, 2H), 3.53 (m, 1H), 5.57 (s, 1H), 7.24–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.0, 44.3, 73.0, 80.0, 127.1, 127.3, 128.3, 142.9. Anal. Calcd for $C_{18}H_{21}NO\cdot H_2O$: C, 75.76; H, 8.12; N, 4.91. Found: C, 76.92; H, 8.18; N, 4.94.

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