JOC The Journal of Organic Chemistry

Article

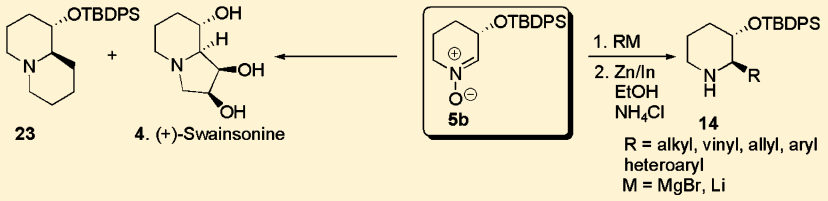
pubs.acs.org/joc

A Divergent Approach to 3-Piperidinols: A Concise Syntheses of (+)-Swainsonine and Access to the 1-Substituted Quinolizidine Skeleton

Glenn Archibald,[||] Chih-Pei Lin,[§] Peter Boyd, David Barker,* and Vittorio Caprio*,[‡]

School of Chemical Sciences, University of Auckland, 23 Symonds Street, Auckland, New Zealand

Supporting Information



ABSTRACT: Nucleophilic addition of Grignard reagents and organolithium species to a 3-silyloxy-3,4,5,6-tetrahydropyridine *N*-oxide provides *trans*-2,3-disubstituted *N*-hydroxypiperidines exclusively. The application of this methodology to the preparation of a diversity of useful *trans*-2-substituted-3-hydroxypiperidines, a concise synthesis of (+)-swainsonine, and an enantiopure 1-substituted quinolizidine of utility in target-directed synthesis is reported.

INTRODUCTION

Flexible and stereoselective syntheses of diversely functionalized piperidines are of much value in synthetic and medicinal chemistry. Methods for the construction of *trans*-2-substituted-3-hydroxypiperidines are of particular importance,[1] as this substructure is found in a range of bioactive alkaloids (Figure 1). These include the antimalarial (+)-febrifugine **1**,[2] a range of

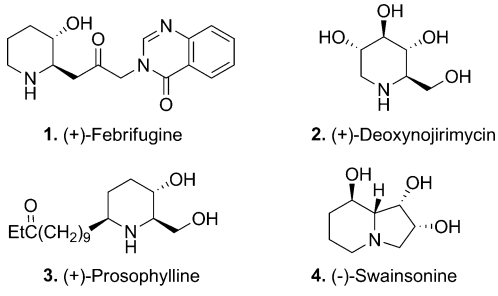


Figure 1. Naturally occurring *trans*-2-substituted-3-hydroxypiperidines.

iminocyclitols, including the α-glucosidase inhibitor deoxynojirimycin **2**,[3] and *Prosopis* alkaloids, including prosophylline **3**, which displays antibiotic and anesthetic properties.[4] This motif is also embedded within the bicyclic structure of hydroxylated indolizidines such as the α-mannosidase inhibitor (−)-swainsonine (−)-**4**.[5] The widespread occurrence of the 3-hydroxypiperidine substructure has led to the recent designation of this fragment as a privileged scaffold in drug discovery.[1d]

We reasoned that as the nitrone functional group is known to undergo cycloaddition with a wide range of alkenes and alkynes,[6] nucleophilic addition with an array of organometallic species,[7] and, most recently, samarium iodide-mediated additions of electrophiles,[8] access to a single, suitably substituted cyclic nitrone such as **5**, which maps onto the 2-hydroxy-3-substituted piperidine substructure, would enable the parallel, enantioselective synthesis of the core structures of all targets **1**−**4** and associated compound libraries. The use of nitrones to access the 2-substituted 3-hydroxy piperidine motif has received scant attention however. There are few examples of diastereoselective nucleophilic additions to either simple or highly substituted six-membered ring nitrones.[9] There are a number of reports covering the substrate-controlled stereoselective 1,3-dipolar cycloadditions of functionalized tetrahydropyridine *N*-oxides,[10] but these are mainly focused on the conversion of 6-substituted derivatives to *trans*-2,6-disubstituted piperidines. The only two reports of nitrones related to **5** are restricted to describing the in situ generation and trapping of these species in the presence of allyl alcohol.[10l,m] In contrast, O-protected derivatives of pyrroline *N*-oxide **6** have been studied in some detail. These species undergo highly stereoselective dipolar cycloadditions to alkenes and nucleophilic additions with Grignard reagents and have shown much utility in the synthesis of 2,3-disubstituted pyrrolidine alkaloids (Figure 2).[11]

Recently, we have shown that nitrone (*S*)-**5a** may be efficiently accessed from L-glutamic acid and is sufficiently stable for purification and storage. However, our studies revealed that the stereoselectivity of 1,3-dipolar cycloadditions onto **5a**, while in favor of the trans-adducts did not match the levels obtained with nitrone **6**.[12] We also briefly studied the addition of Grignard reagents to nitrone **5a**. In this instance, stereoselectivity was highly in favor of the trans-2,3-

Received: June 14, 2012
Published: August 14, 2012

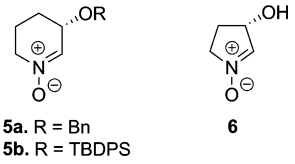


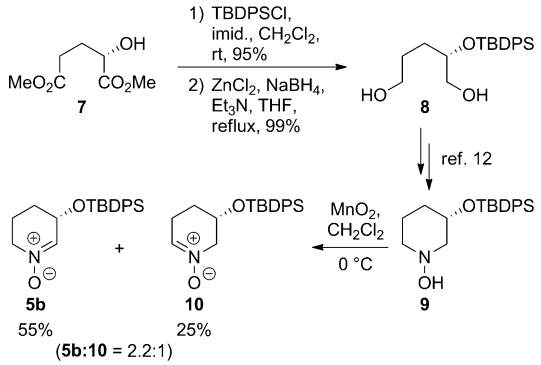
Figure 2. Structures of tetrahydropyridine *N*-oxides **5a**/**b** and pyrroline *N*-oxide **6**.

disubstituted isomer and equivalent to results observed with nitrone **6**. Unfortunately, isolated yields of products were consistently low. We attributed product loss to complications arising from competing deprotonation at the benzylic position by the organometallic nucleophile and/or loss of the potentially hydrophilic hydroxypiperidine products to aqueous media during the workup procedure. We envisaged that both problems could be alleviated by the use of the more lipophilic and robust TBDPS moiety as O-protecting group, and we now report a method for the efficient and highly stereoselective synthesis of a diversity of *trans*-2-substituted-3-hydroxypiperidines based on the addition of Grignard and organolithium reagents to *O*-silyl-protected nitrone **5b**.

RESULTS AND DISCUSSION

Preparation of Nitrone 5b. Our strategy toward nitrone **5b** is a slight modification of a route previously developed toward *O*-benzyl nitrone **5a**[12] and centers on regioselective oxidation of the corresponding *N*-hydroxypiperidine, prepared by cyclization of a suitably protected triol (Scheme 1). The

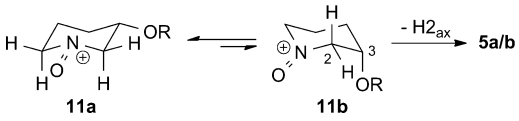
Scheme 1. Synthesis of Nitrone 5b



sequence commences with O-protection of the secondary alcohol in L-glutamate-derived hydroxy diester **7** followed by reduction to triol **8**. Reduction of **7** using lithium aluminum hydride resulted in silyl deprotection while the use of lithium borohydride/MeOH[13] and calcium borohydride[14] led to extensive migration of the silyl group. The desired reduction product **8** was obtained using DIBAL-H in THF at −78 °C provided that the workup procedure was maintained at −20 °C to avoid silyl deprotection. Finally, we found that reduction could be achieved most conveniently, in near quantitative yield, using in situ-prepared zinc borohydride under the conditions developed by Yamakawa et al.[15] The position of the *O*-TBDPS group in **8** was unambiguously determined by single crystal X-ray analysis. Compound **8** was then converted to *N*-hydroxypiperidine **9** using the strategy previously developed en route to the *O*-benzyl-protected derivative.[12] Oxidation of **9** was initially attempted using HgO[16] and TPAP/NMO,[17] but these reagents gave low yields. However, freshly prepared manganese dioxide[18] proved to be a reliable, repeatable method and provided a separable, regioisomeric mixture of nitrones **5b** and **10**, in a combined 80% yield, in a moderate 2.2:1 ratio in favor of the desired regioisomer **5b**.

The regioselectivity of the oxidation is lower than the 6:1 ratio observed during the conversion of the 3-benzyloxy-substituted *N*-hydroxypiperidine to nitrone **5a**.[12] It has been established, by Cicchi and co-workers, that high regioselectivity observed in the oxidation of *N*-hydroxypyrrolidines to nitrones **6** arises from selective activation and subsequent loss of the C2 proton antiperiplanar to the adjacent C−O bond in a nitrosonium intermediate.[19] Although no such relationship exists in the predicted major conformer of nitrosonium **11a** a similar explanation for regiocontrol can apply in our case if we apply the Curtin−Hammett principle[20] and consider that the most rapid proton loss is that of H-2 axial of the relatively inaccessible conformer **11b** (Scheme 2).

Scheme 2

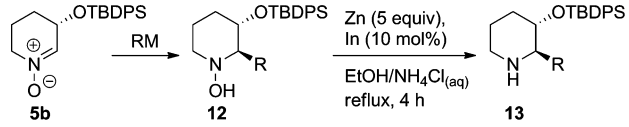


The lower levels of regiocontrol observed in the synthesis of **5b** compared to **5a** may then be attributed to the much diminished populations of **11b**, and/or perhaps to higher levels of steric hindrance to proton removal, in moving from a 3-benzyloxy to a more bulky *O*-TBDPS moiety. Nitrone **5b** is stable to purification and storage at 0 °C for up to 4 days. We attribute this stability to the presence of the protected hydroxyl group sterically blocking the dimerization observed with more simple nitrones such as 2,3,4,5-tetrahydropyridine *N*-oxide.[21]

Addition of Organometallic Reagents to Nitrone 5b. We next examined the reactivity of **5b** with a range of Grignard and organolithium reagents and reduction of the resulting adducts. The results of this study are summarized in Table 1. Optimum conditions for the addition of Grignard species involved adding a solution of the nucleophile to nitrone in THF at 0 °C while the organolithium reagents were added at −78 °C. Addition of a range of primary and secondary alkyl, allyl, vinyl, alkynyl, aryl, and heteroaryl organometallic species proceeded in good to excellent yield. Even *tert*-butyllithium also undergoes addition, albeit in lower yield (Table 1, entry 12). The lower yields arising from addition of alkyllithiums (Table 1, entries 10−12) in comparison to the Grignard counterparts (Table 1, entries 1−3) may be partly attributed to the greater basicity of the former, leading to the competing formation of hydroxyenamines. The only addition that proved problematic was that of a 3-pyridyl moiety (entry 9). The addition of lithiothiophene and lithiofuran (entries 15 and 16) proceeded smoothly; however, addition of 3-lithiopyridine, prepared in diethyl ether, or toluene following the method of Cai et al.,[22] provided none of the desired product. The best results were obtained by addition of a THF solution of (3-pyridyl)magnesium chloride, prepared from isopropylmagnesium chloride and 3-bromopyridine, using conditions developed by Trecourt et al.[23] While the addition with allylmagnesium bromide (entry 5, Table 1) proceeds with 86:14 trans:cis ratio, in all other cases the trans-isomer is the only product isolated. Reduction of the *N*-hydroxy group of **12**, using zinc in the presence of catalytic indium,[24] proceeded

dx.doi.org/10.1021/jo3011914 | J. Org. Chem. 2012, 77, 7968−7980

Table 1. Addition of Nucleophiles to Nitrone 5b and Reduction of the Resulting Hydroxylamines 12a−o



5b 12 13

Entry	RM[a]	Yield 12a-o (%)[b,c]	Yield 13a-o (%)[b]	Product 13[c,d]	Entry	RM[a]	Yield 12 (%)[b,c]	Yield 13 (%)[b]	Product 13[c,d]
1	Me−MgBr	81	81	13a	9	MgCl	62	71	13i
2	MgBr	81	84	13b	10	Me−Li	64	81	13a
3	MgCl	73	82	13c	11	Li	50	73	13j
4	Ph MgCl	92	99	13d	12	Li	31	93	13k
5	MgBr	70	91	13e	13	TMS Li	81	70	13l
6	MgBr	85	79	13f	14	MeO Li	69	92	13m
7	Ph−MgCl	80	76	13g	15	O Li	72	94	13n
8	MeO MeO MgBr	73	97	13h	16	S Li	85	81	13o

[a]Addition carried out at 0 °C in THF (M = MgBr/MgCl) or at −78 °C using 1.5 equiv of RM (M = Li); see Experimental Section for details. [b]Isolated, chromatographically pure products. [c]Relative stereochemistry determined by 2D-NOESY studies performed on piperidines **13a−o**. The trans-product was obtained exclusively in all cases except entry 5 (dr = 86:14). [d]All reductions preformed using 5 equiv of Zn/10 mol % In, EtOH/NH_4Cl except entry **13** (1.2 equiv of In, EtOH/1% HCl)

smoothly to afford the corresponding piperidine in all cases except entry 13 where rapid, clean conversion only occurred using stoichiometric quantities of In and 1% aqueous HCl in place of ammonium chloride. The stereochemistry of addition was determined by analysis of the 2D-NOESY spectra obtained for reduction products **13a−o** (Figure 3). Strong correlations

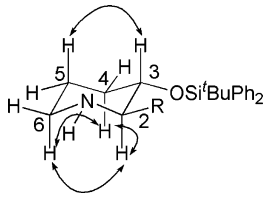


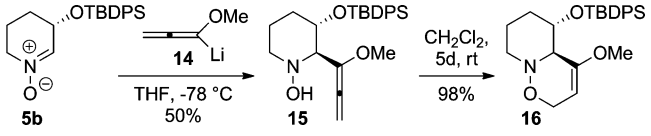
Figure 3. Selected NOE observed in adducts **13a−o**.

were observed between the axial protons on either face of the piperidine ring: H2/H4/H6 and H3/H5 indicating a trans-diaxial substitution pattern across C2/C3. Unfortunately, stereochemical analysis of adducts **12a−o**, and hence determination of accurate levels of diastereoselectivity of addition by analysis of crude mixtures **12**, could not be performed owing to the considerable line broadening observed in the ^{1}H NMR spectra of these *N*-hydroxylamines.

Recently, Reissig and co-workers have reported the highly diastereoselective addition of lithiated methoxyallene **14** to chiral five-membered cyclic nitrones of type **6**.[25] The resulting adducts rearrange to 1,2-oxazines which have shown utility in the synthesis of furan and pyran derivatives,[26] amino alcohols,[25,27] and pyrrolidines.[27] We were also able to effect the stereoselective addition of **14** to nitrone **5b**. The resulting allenyl adduct **15** was isolable but unstable, undergoing rearrangement to oxazine **16** on prolonged stirring (Scheme 3).

We postulate that the trans-stereoselectivity observed in the above additions can be rationalized by application of the model depicted in Figure 4.[28] In this model reaction occurs, preferentially, with a nitrone conformer bearing an axially

Scheme 3. Synthesis of *trans*-Oxazine 16



5b 15 16

dx.doi.org/10.1021/jo3011914 | J. Org. Chem. 2012, 77, 7968−7980

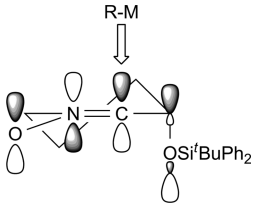


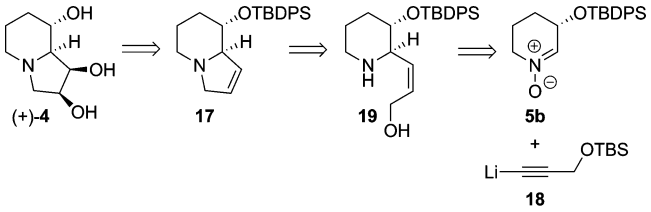
Figure 4. Proposed origin of stereocontrol in addition of organometallic reagents to **5b**.

disposed C−O bond, for maximum π^*(nitrone)−σ^*(C−O) overlap. Nucleophilic addition to the least hindered face gives rise to the selectivity observed.

The significance of a number of members of the small library of *trans*-2,3-disubstituted piperidines detailed above further underlines the potential of our methodology. For instance, differentially N/O-protected derivatives of piperidines **13a**, **13e**, **13f**, and **13g** have been used as key intermediates en route to *Prosopis* alkaloids,[29] febrifugine **1**,[30] swainsonine **4**,[31] and a range of Substance P antagonists,[29] respectively.

Total Synthesis of (+)-Swainsonine. With the scope of nitrone **5b** established, we became interested in the use of this compound in the targeted synthesis of more complex molecules. This was initially illustrated by the development of a novel, concise, enantioselective route to (+)-swainsonine (+)-**4**.[32] While naturally occurring (−)-swainsonine is a potent inhibitor of α-mannosidase,[5] the (+)-enantiomer has been shown to inhibit the action of rhamnosidase[32b] and thus has potential as an anti-tuberculosis agent. Our synthetic route centers on the construction of hexahydroindolizines such as **17**, which have been previously shown to undergo highly diastereoselective dihydroxylation to give the core of swainsonine (Scheme 4).[33,31b] Inspired by our successful

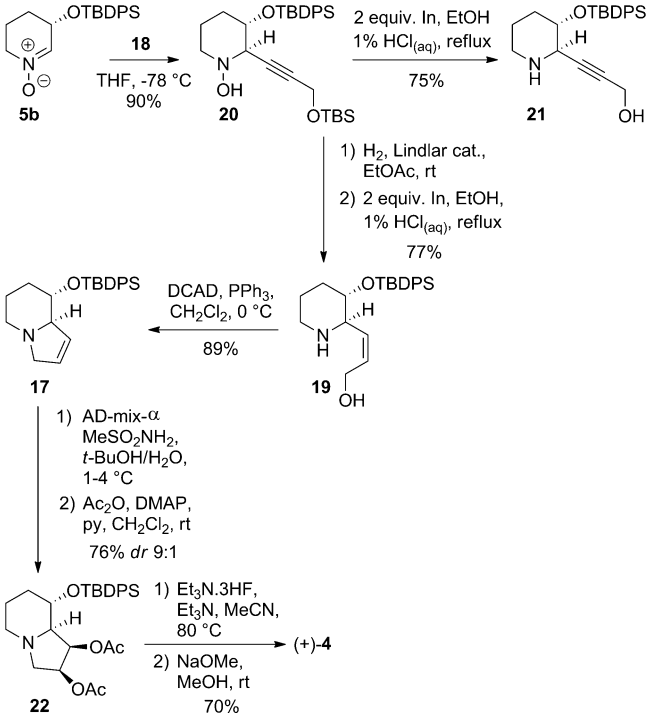
Scheme 4. Retrosynthesis of (+)-Swainsonine



addition of trimethylsilylacetylide to **5b** (Table 1, entry 13), we based our strategy toward **17** on the reaction of **5b** with the lithium acetylide **18** followed by Lindlar reduction to *cis*-alkene **19** and cyclization.

Our approach to (+)-swainsonine proceeded largely as planned (Scheme 5). Thus, addition of the lithium acetylide **18** onto nitrone **5b** gave trans-diastereoisomer **20** as the sole product in high yield. The stereochemistry of addition was determined by analysis of the 2D-NOESY spectrum of **20** which exhibited key correlations identical to those depicted in Figure 3. In a fashion similar to the reduction of **12l**, reductive cleavage of the N−O bond of **20** proceeded sluggishly using catalytic In/Zn in the presence of aqueous NH_4Cl and resulted in partial deprotection of the *O*-TBS group. However, rapid, clean reduction, with concomitant total cleavage of the primary silyl ether, occurred using stoichiometric In in 1% HCl/EtOH to furnish propargylpiperidine **21**. All attempts at partial reduction of the alkyne moiety of **21** by Lindlar catalysis resulted in significant overreduction and/or isomerization of

Scheme 5. Synthesis of (+)-Swainsonine



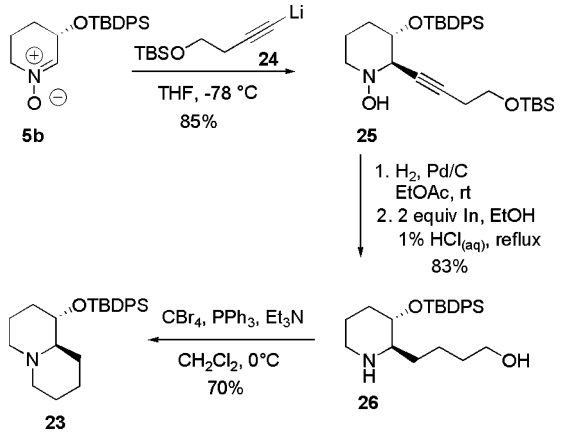
the resulting *cis*-alkene. This may be partially attributable to adherence of the unprotected amine moiety to the catalysts.[34] Unfortunately, this problem was only partially alleviated by the use of catalyst poisons including ethylenediamine, quinoline, and 3,6-dithiaoctane-1,8-diol. We reasoned that reversal of reduction steps would alleviate this problem owing to reduced catalyst binding of the hydroxylamine moiety.[35] Indeed, Lindlar hydrogenation of alkyne **20** followed by N−O bond reduction, with accompanying deprotection, proceeded smoothly to afford the *cis*-alkene **19** in good overall yield. The structure and stereochemistry of **19** was further established by single crystal X-ray analysis. Key bicycle **17** was then accessed by cyclization of **19** under Mitsunobu conditions using DCAD (dicyclohexylcarbodiimide). Dihydroxylation of **17**, using AD-mix-α, followed by acetylation of the resulting mixture of diols gave a separable 9:1 diastereomeric mixture of diacetates in favor of **22**.[33d] Finally, global deprotection of **22** yielded (+)-swainsonine [mp 143−144 °C, $[\alpha]_D$ +79.9 (*c* 0.37, MeOH); lit.[32a] mp 143−145 °C, $[\alpha]_D$ +83.3 (*c* 0.5, MeOH)].

Synthesis of Quinolizidines. We next became interested in modifying the general strategy described in Scheme 4 to prepare enantiopure quinolizidine skeleta. In particular, we focused on the synthesis of quinolizidine **23**. O-Deprotected **23** provides access, via short synthetic sequences to the 1-substituted quinolizidine alkaloids epiquinamide,[36,37] (−)-lupinine,[38,39] and (−)-lusitanine.[40] We envisioned that compound **23** could be accessed via addition of the homologue of **18**, lithium acetylide **24**, to nitrone **5b**. In practice, the addition of **24** to **5b** furnished the trans-adduct **25** as sole product in 85% yield (Scheme 6).

Hydrogenation of **25** to the alkane, followed by N−O bond cleavage, with simultaneous removal of the TBS moiety using indium in 1% HCl/EtOH gave (2-hydroxybutyl)piperidine **26**. In contrast to compound **19**, piperidine **26** failed to cyclize under Mitsunobu conditions using either DEAD or DCAD.

dx.doi.org/10.1021/jo3011914 | *J. Org. Chem.* 2012, 77, 7968−7980

Scheme 6. Synthesis of Quinolizidine 23



However use of Appel conditions provided rapid conversion to quinolizidine **23** in 70% yield.

CONCLUSION

We have shown that 3-hydroxytetrahydropyridine *N*-oxide **5b** undergoes highly diastereoselective nucleophilic addition with a wide range of Grignard reagents and organolithium species. Furthermore, we have demonstrated that this methodology enables the efficient generation of libraries of *trans*-2-substituted-3-hydroxypiperidines of synthetic/therapeutic value. Additionally, the utility of synthon **5b** in the enantioselective synthesis of specific targets, with multiple stereocenters, has been established by the development of a concise synthetic route to (+)-swainsonine **4** and O-protected hydroxyquinolizidine **23**.

EXPERIMENTAL SECTION

All reactions sensitive to air or moisture were performed under a nitrogen atmosphere using oven-dried glassware in dry, freshly distilled solvents, unless otherwise noted. Flash column chromatography was performed using normal phase or reverse phase (C18) silica gel. Thin layer chromatography was performed on silica gel plates. Melting points are uncorrected. IR spectra were recorded using an FT-IR ATR spectrometer. NMR spectra were recorded using a 300 or 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to TMS (^{1}H δ 0.00), $CDCl_3$ (^{1}H δ 7.26, ^{13}C δ 77.00), CD_3OD (^{1}H δ 3.31, ^{13}C δ 49.00) or DMSO-d_6 (^{1}H δ 2.50, ^{13}C δ 39.52). ^{1}H NMR values are reported as chemical shifts δ, relative integral, multiplicity (s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dt, doublet of triplets; t, triplet; td, triplet of doublets; m, multiplet; br, broad peak), coupling constant (J) and assignment. Coupling constants were taken directly from the spectra. Assignments were made with the aid of DEPT, COSY, HSQC, HMBC, and NOESY experiments. High-resolution mass spectroscopy (HRMS) was carried out by either electron impact (EI+), chemical ionization (CI), electrospray ionization (ESI), or fast atom bombardment (FAB) on a MicroTOF-Q mass spectrometer. Optical rotations were measured using a polarimeter at the sodium-D line (589 nm). ^{1}H and ^{13}C NMR spectra for all new compounds are reported in Supporting Information.

(2*S*)-2-(*tert*-Butyldiphenylsilyloxy)pentane-1,5-diol (8). *tert*-Butyldiphenylsilyl chloride (11.4 mL, 41.6 mmol) was added to a solution of diester **7** (6.98 g, 39.6 mmol) and imidazole (4.0 g, 59.4 mmol) in CH_2Cl_2 (70 mL) at 0 °C. The mixture was warmed to rt and stirred for 3 h. Saturated aqueous NH_4Cl (50 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash column chromatography, eluting with EtOAc/hexanes (gradient 1:49 to 1:1), gave the silyloxy diester (15.6 g, 95%) as a colorless oil. $[\alpha]_D^{20}$ −29.0 (*c* 1.09, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2952, 2932, 2858, 1737, 1427, 1256, 1110; δ_H (400 MHz; $CDCl_3$) 1.09 (9H, s, Si^{t}Bu), 1.98−2.13 (2H, m, H-3), 2.33−2.44 (1H, m, CH_a,H$_b$-4), 2.44−2.56 (1H, m, CH$_a$,H_b-4), 3.45 (3H, s, 1-OMe), 3.64 (3H, s, 5-OMe), 4.29 (1H, t, J = 5.4 Hz, H-2), 7.33−7.46 (6H, m, H-Ar), 7.60−7.68 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.3 (C, Si^{t}Bu), 26.8 (CH_3, Si^{t}Bu), 28.9 (CH_2, C-4), 29.9 (CH_2, C-3), 51.4 (CH_3, 1-OMe), 51.5 (CH_3, 5-OMe), 71.4 (CH, C-2), 127.5 (CH, C-Ar), 127.6 (CH, C-Ar), 129.7 (CH, C-Ar), 129.8 (CH, C-Ar), 132.9 (C, C-Ar), 133.0 (C, C-Ar), 135.7 (CH, C-Ar), 135.9 (CH, C-Ar), 172.8 (C=O, C-1), 173.3 (C=O, C-5); HRMS (CI, NH_3) $C_{23}H_{34}NO_5Si$ [MNH_4^+] calcd 432.2206, obsd 432.2202.

A solution of the silyloxy diester prepared above (11.2 g, 27.0 mmol) in THF (60 mL) was added slowly to a stirred suspension of $ZnCl_2$ (8.10 g, 59.4 mmol) and $NaBH_4$ (4.50 g, 119 mmol) in THF (40 mL) at 0 °C. Et_3N (8.24 mL, 59.4 mmol) was added and the mixture stirred at 0 °C for 10 min. The reaction mixture was warmed to 80 °C, stirred for a further 4 h, and then cooled to 0 °C. $CHCl_3$ (100 mL) was added to the suspension, the mixture was stirred for 10 min, and then saturated aqueous NH_4Cl (100 mL) was added dropwise. The aqueous phase was extracted with $CHCl_3$ (4 × 250 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography, using EtOAc/hexanes (gradient 1:3 to 1:1), to give the title compound (9.46 g, 98%) as a white solid. Recrystallization from Et_2O/hexanes (1:1) afforded colorless needles. mp 75−77 °C; $[\alpha]_D^{20}$ +19.3 (*c* 1.18, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3289, 2957, 2927, 2876, 2876, 1584, 1428, 1108, 1080, 1018, 991; δ_H (300 MHz; $CDCl_3$) 1.07 (9H, s, Si^{t}Bu), 1.35−1.67 (4H, m, H-3, H-4), 2.54 (2H, br s, 2 × O*H*), 3.32−3.55 (4H, m, H-5, H-1), 3.74−3.84 (1H, m, H-2), 7.31−7.46 (6H, m, H-Ar), 7.63−7.73 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.2 (C, Si^{t}Bu), 27.0 (CH_3, Si^{t}Bu), 27.7 (CH_2, C-4), 29.6 (CH_2, C-3), 62.4 (CH_2, C-5), 65.4 (CH_2, C-1), 73.4 (CH, C-2), 127.6 (CH, C-Ar), 127.6 (CH, C-Ar), 129.7 (CH, C-Ar), 133.7 (C, C-Ar), 133.9 (C, C-Ar), 135.6 (CH, C-Ar), 135.7 (CH, C-Ar); HRMS (CI, NH_3) $C_{21}H_{31}O_3Si$ [MH^+] calcd 359.2042, obsd 359.2038.

(3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-*N*-hydroxypiperidine (9). *p*-Toluenesulfonyl chloride (5.49 g, 28.8 mmol) was added portionwise to a solution of diol **8** (3.44 g, 9.60 mmol) in CH_2Cl_2 (80 mL) at 0 °C and the mixture stirred for 30 min. A solution of Et_3N (4.0 mL, 29.0 mmol) and DMAP (0.24 g, 1.92 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the mixture warmed to rt and stirred overnight. Brine (80 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with EtOAc/hexanes (gradient 1:19 to 3:17), to give the ditosylate (6.20 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ −8.5 (*c* 2.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2931, 2857, 1598, 1427, 1358, 1174; δ_H (400 MHz; $CDCl_3$) 0.98 (9H, s, Si^{t}Bu), 1.37−1.47 (2H, m, H-3), 1.47−1.57 (2H, m, H-4), 2.44 (6H, s, Ar-Me), 3.72−3.86 (5H, m, H-1, H-2, H-5), 7.24−7.36 (8H, m, H-Ar), 7.38−7.45 (2H, m, H-Ar), 7.49−7.56 (4H, m, H-Ar), 7.59−7.64 (2H, m, H-Ar), 7.70−7.74 (2H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.2 (C, Si^{t}Bu), 21.6 (CH_3, Ar-Me), 23.8 (CH_2, C-4), 26.8 (CH_3, Si^{t}Bu), 29.5 (CH_2, C-3), 69.7 (CH, C-2), 70.1, 71.4 (CH_2, C-3, C-5), 127.6 (CH, C-Ar), 127.7 (CH, C-Ar), 127.7 (CH, C-Ar), 127.8 (CH, C-Ar), 127.8 (CH, C-Ar), 129.8 (CH, C-Ar), 129.8 (CH, C-Ar), 129.8 (CH, C-Ar), 129.9 (CH, C-Ar), 132.6 (CH, C-Ar), 133.0 (CH, C-Ar), 133.0 (C, C-Ar), 133.0 (C, C-Ar), 135.7 (CH, C-Ar), 135.7 (CH, C-Ar), 144.7 (C, C-Ar), 144.8 (C, C-Ar); HRMS (FAB+) $C_{35}H_{43}O_7S_2Si$ [MH^+] calcd 667.2220, obsd 667.2222.

NH_2OH·HCl (5.44 g, 78.3 mmol) was added to a solution of the ditosylate prepared above (11.6 g, 17.4 mmol) in Et_3N (100 mL) at room temperature. The reaction mixture was stirred under reflux for 4 h and then cooled to room temperature. Et_2O (100 mL) was added and the suspension stirred for 1 h and filtered through Celite. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure.

dx.doi.org/10.1021/jo3011914 | *J. Org. Chem.* 2012, 77, 7968−7980

The residue was purified by flash column chromatography, eluting with MeOH/CH_2Cl_2 (gradient 1:99 to 1:19), to give the title compound (4.46 g, 73%) as a colorless oil. $[\alpha]_D^{20}$ −24.2 (*c* 2.34, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3177, 3070, 2930, 2855, 1427, 1103; δ_H (300 MHz; DMSO-d_6, 393 K) 1.07 (9H, s, Si^{t}Bu), 1.18−1.48 (2H, m, CH_a,H$_b$-4, CH_a,H$_b$-5), 1.59−1.77 (2H, m, CH$_a$,H_b-4, CH$_a$,H_b-5), 2.35−2.50 (2H, m, CH_a,H$_b$-2, CH_a,H$_b$-6), 2.80−2.91 (1H, m, CH$_a$,H_b-6), 3.02−3.14 (1H, m, CH$_a$,H_b-2), 3.87−4.00 (1H, m, 3-H), 7.36−7.59 (6H, m, H−Ar), 7.60−7.71 (4H, m, H-Ar); δ_C (75 MHz; DMSO-d_6, 393 K) 18.0 (C, Si^{t}Bu), 20.0 (CH_2, C-4), 26.1 (CH_3, Si^{t}Bu), 31.9 (CH_2, C-5), 56.9 (CH_2, C-6), 64.8 (CH_2, C-2), 67.9 (CH, C-3), 126.8 (CH, C-Ar), 128.8 (CH, C-Ar), 133.6 (C, C-Ar), 134.4 (CH, C-Ar); HRMS (CI, NH_3) $C_{21}H_{30}NO_2Si$ [MH$^+$] calcd 356.2046, obsd 356.2049.

(3*S*)-3-*tert*-Butyldiphenylsilyloxy-3,4,5,6-tetrahydropyridine *N*-Oxide (5b) and (5*S*)-5-*tert*-Butyldiphenylsilyloxy-3,4,5,6-tetrahydropyridine *N*-Oxide (10). Activated MnO_2 (1.43 g, 16.5 mmol) was added portionwise to a solution of hydroxylamine **9** (2.34 g, 6.58 mmol) in CH_2Cl_2 (50 mL) at 0 °C and the reaction mixture stirred for 2 h. The resulting suspension was filtered through a pad of $MgSO_4$/Celite and the filtrate concentrated under reduced pressure, at a water bath temperature below 20 °C. The residue was purified by flash column chromatography, eluting with MeOH/CH_2Cl_2 (gradient 0:100 to 1:19), to give the title compounds **5b** (1.29 g, 55%) and **10** (0.59 g, 25%) as colorless oils. Data for **5b**: R_f (5% MeOH/CH_2Cl_2) 0.10; $[\alpha]_D^{20}$ −113.8 (*c* 2.53, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 2931, 2858, 1590, 1427, 1105, 1081; δ_H (400 MHz; $CDCl_3$) 1.07 (9H, s, Si^{t}Bu), 1.69−1.85 (3H, m, H-4, CH_a,H$_b$-5), 2.11−2.23 (1H, m, CH$_a$,H_b-5), 3.59−3.71 (1H, m, CH_a,H$_b$-6), 3.72−3.85 (1H, m, CH$_a$,H_b-6), 4.34−4.42 (1H, m, H-3), 6.93−6.97 (1H, m, H-2), 7.35−7.49 (6H, m, H-Ar), 7.61−7.69 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 18.9 (CH_2, C-5), 19.0 (C, Si^{t}Bu), 26.7 (CH_3, Si^{t}Bu), 27.6 (CH_2, C-4), 58.4 (CH_2, C-6), 65.4 (CH, C-3), 127.8 (CH, C-Ar), 127.9 (CH, C-Ar), 130.0 (CH, C-Ar), 130.1 (CH, C-Ar), 132.8 (C, C-Ar), 133.0 (C, C-Ar), 135.5 (CH, C-Ar), 135.6 (CH, C-Ar), 137.4 (CH, C-2); HRMS (ESI) $C_{21}H_{28}NO_2Si$ [MH$^+$] calcd 354.1884, obsd 354.1884. Data for **10**: R_f (5% MeOH/CH_2Cl_2) 0.17; $[\alpha]_D^{20}$ −9.8 (*c* 2.43, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 2931, 2857, 1623, 1427, 1104; δ_H (400 MHz; $CDCl_3$) 1.07 (9H, s, Si^{t}Bu), 1.56−1.67 (1H, m, CH_a,H$_b$-4), 1.67−1.78 (1H, m, CH$_a$,H_b-4), 2.25−2.37 (1H, m, CH_a,H$_b$-3), 2.63−2.77 (1H, m, CH$_a$,H_b-3), 3.66−3.80 (2H, m, H-6), 4.18−4.25 (1H, m, H-5), 7.16−7.22 (1H, m, H-2), 7.33−7.49 (6H, m, H-Ar), 7.60−7.68 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 19.1 (C, Si^{t}Bu), 21.6 (CH_2, C-3), 25.0 (CH_2, C-4), 26.8 (CH_3, Si^{t}Bu), 64.0 (CH_2, C-6), 65.5 (CH, C-5), 127.8 (CH, C-Ar), 127.9 (CH, C-Ar), 130.0 (CH, C-Ar), 130.1 (CH, C-Ar), 132.8 (C, C-Ar), 133.1 (C, C-Ar), 135.6 (CH, C-Ar), 135.9 (CH, C-2); HRMS (ESI) $C_{21}H_{28}NO_2Si$ [MH$^+$] calcd 354.1884, obsd 354.1883.

General Procedure A: Synthesis of 2-Substituted-3-silyloxy-1-hydroxypiperidines Using Grignard Reagents. The Grignard reagent was added dropwise to a solution of nitrone **5b** in THF (10 mL) at 0 °C and the mixture stirred at this temperature for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with the specified solvent to give the *trans*-2,3-disubstituted-piperidin-1-ol.

General Procedure B: Synthesis of 2-Substituted-3-silyloxy-1-hydroxypiperidines Using Organolithium Reagents. A solution of nitrone **5b** in THF (3 mL) was added dropwise to a solution of the organolithium in THF (7 mL) at −78 °C and the mixture stirred at this temperature for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with the specified solvent to give the *trans*-2,3-disubstituted-piperidin-1-ol.

General Procedure C: Reduction of *N*-Hydroxypiperidines. Zinc powder (5 equiv) and indium powder (10 mol %) were added to a solution of hydroxylamine in EtOH/saturated aqueous NH_4Cl (2:1, 4.5 mL). The suspension was stirred under reflux for 4 h, cooled to rt, and filtered through a pad of Celite. The filtrate was concentrated, and saturated aqueous Na_2CO_3 (15 mL) was added. The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with MeOH/CH_2Cl_2 (gradient 1:99 to 9:91), to give the *trans*-2,3-disubstituted-piperidine.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpiperidine (13a). Following general procedure A, reaction of methylmagnesium bromide (3.0 M in Et_2O, 0.17 mL, 0.50 mmol) and nitrone **5b** (0.12 g, 0.33 mmol) followed by purification of the residue by column chromatography, using EtOAc/hexanes (1:4), gave the 2-methylpiperidin-1-ol **12a** (0.10 g, 81%) as a yellow oil. Following general procedure C, reduction of 2-methylpiperidin-1-ol **12a** (0.20 g, 0.53 mmol) gave the title compound (0.15 g, 81%) as a yellow oil. $[\alpha]_D^{20}$ +26.0 (*c* 2.16, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 3048, 2930, 2856, 1427, 1105, 1085; δ_H (300 MHz; $CDCl_3$) 1.05 (9H, s, Si^{t}Bu), 1.13 (3H, d, *J* = 6.3 Hz, H-1′), 1.16−1.42 (2H, m, CH_a,H$_b$-4, CH_a,H$_b$-5), 1.47−1.57 (1H, m, CH$_a$,H_b-5), 1.70−1.81 (1H, m, CH$_a$,H_b-4), 1.97 (1H, br s, N*H*), 2.52 (1H, td, *J* = 11.6, 3.1 Hz, CH_a,H$_b$-6), 2.59 (1H, dq, *J* = 8.4, 6.3 Hz, H-2), 2.78−2.89 (1H, m, CH$_a$,H_b-6), 3.25 (1H, ddd, *J* = 9.9, 8.4, 4.1 Hz, H-3), 7.29−7.45 (6H, m, H-Ar), 7.64−7.74 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.3 (C, Si^{t}Bu), 19.4 (CH_2, C-1′), 25.7 (CH_2, C-5), 27.0 (CH_3, Si^{t}Bu), 34.1 (CH_2, C-4), 45.7 (CH_2, C-6), 58.6 (CH, C-2), 75.7 (CH, C-3), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.3 (CH, C-Ar), 129.5 (CH, C-Ar), 133.9 (C, C-Ar), 134.8 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (EI+) $C_{22}H_{31}NOSi$ [M$^+$] calcd 353.2175, obsd 353.2171.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-ethylpiperidine (13b). Following general procedure A, reaction of ethylmagnesium bromide (3.0 M in Et_2O, 0.29 mL, 0.87 mmol) and nitrone **5b** (0.21 g, 0.58 mmol) followed by purification of the residue by column chromatography, using EtOAc/hexanes (1:4), gave the 2-ethylpiperidin-1-ol **12b** (0.18 g, 81%) as a yellow oil. Following general procedure C, reduction of 2-ethylpiperidin-1-ol **12b** (0.15 g, 0.39 mmol) gave the title compound (0.12 g, 84%) as a yellow oil. $[\alpha]_D^{20}$ +30.4 (*c* 2.40, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3070, 2932, 2857, 1427, 1105, 1075; δ_H (400 MHz; $CDCl_3$) 0.86 (3H, t, *J* = 7.5 Hz, H-1′), 1.05 (9H, s, Si^{t}Bu), 1.14−1.41 (3H, m, CH_a,H$_b$-2′, CH_a,H$_b$-4, CH_a,H$_b$-5), 1.47−1.57 (1H, m, CH$_a$,H_b-5), 1.69−1.79 (1H, m, CH$_a$,H_b-4), 1.88−2.04 (2H, m, N*H*, CH$_a$,H_b-2′), 2.41 (1H, td, *J* = 8.3, 3.3 Hz, H-2), 2.51 (1H, td, *J* = 11.2, 3.0 Hz, CH_a,H$_b$-6), 2.83−2.92 (1H, m, CH$_a$,H_b-6), 3.34 (1H, ddd, *J* = 9.6, 8.3, 4.1 Hz, H-3), 7.31−7.44 (6H, m, H-Ar), 7.64−7.72 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 10.0 (CH_3, C-1′), 19.4 (C, Si^{t}Bu), 24.7 (CH_2, C-2′), 25.4 (CH_2, C-5), 27.0 (CH_3, Si^{t}Bu), 34.0 (CH_2, C-4), 45.7 (CH_2, C-6), 64.2 (CH, C-2), 73.6 (CH, C-3), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 133.9 (C, C-Ar), 134.9 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (ESI) $C_{23}H_{34}NOSi$ [MH$^+$] calcd 368.2404, obsd 368.2411.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-isopropylpiperidine (13c). Following general procedure A, reaction of isopropylmagnesium chloride (2.0 M in THF, 0.44 mL, 0.87 mmol) and nitrone **5b** (0.21 g, 0.58 mmol) followed by purification of the residue by column chromatography, using MeOH/CH_2Cl_2 (0.5:99.5), gave the 2-isopropylpiperidin-1-ol **12c** (0.17 g, 73%) as a colorless oil. Following general procedure C, reduction of 2-isopropylpiperidin-1-ol **12c** (0.097 g, 0.24 mmol) gave the title compound (0.076 g, 82%) as a yellow oil. $[\alpha]_D^{20}$ +24.9 (*c* 1.36, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 2932, 2857, 1472, 1428, 1105, 1079; δ_H (300 MHz; $CDCl_3$) 0.67 (3H, d, *J* = 6.8 Hz, ^{i}Pr), 0.94 (3H, d, *J* = 6.8 Hz, ^{i}Pr), 1.04 (9H, s, Si^{t}Bu), 1.09−1.28 (1H, m, CH_a,H$_b$-5), 1.37 (1H, tdd, *J* = 12.2, 9.8, 4.0 Hz, CH_a,H$_b$-4), 1.45−1.57 (1H, m, CH$_a$,H_b-5), 1.71−1.83 (1H, m, CH$_a$,H_b-4), 2.29−2.43 (2H, m, H-2, H-1′), 2.48 (1H, td, *J* = 11.6, 3.0 Hz, CH_a,H$_b$-6), 2.84−2.94 (1H, m, CH$_a$,H_b-6), 3.44 (1H, ddd, *J* = 9.7, 8.3, 4.2 Hz, H-3), 7.31−7.46 (6H, m, H-Ar), 7.64−7.74 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 15.3 (CH_3, ^{i}Pr), 19.3 (C, Si^{t}Bu), 20.5 (CH_3, ^{i}Pr), 25.5 (CH_2, C-5), 26.0 (CH, C-1′), 27.0 (CH_3, Si^{t}Bu), 34.3 (CH_2, C-4), 45.9 (CH_2, C-6), 67.9 (CH, C-2), 71.3 (CH, C-3), 127.3 (CH, C-Ar),

dx.doi.org/10.1021/jo3011914 | *J. Org. Chem.* 2012, 77, 7968−7980

127.6 (CH, C-Ar), 129.4 (CH, C-Ar), 129.6 (CH, C-Ar), 133.8 (C, C-Ar), 135.1 (C, C-Ar), 135.9 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (ESI) $C_{24}H_{36}NOSi$ [MH^+] calcd 382.2572, obsd 382.2561.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-benzylpiperidine (13d). Following general procedure A, reaction of benzylmagnesium chloride (2.0 M in THF, 0.45 mL, 0.89 mmol) and nitrone **5b** (0.21 g, 0.59 mmol) followed by purification of the residue column chromatography using $MeOH/CH_2Cl_2$ (0.5:99.5), gave the 2-benzylpiperidin-1-ol **12d** (0.24 g, 92%) as a colorless oil. Following general procedure C, reduction of 2-benzylpiperidin-1-ol **12d** (0.13 g, 0.31 mmol) gave the title compound (0.13 g, 99%) as a colorless oil. $[\alpha]_D^{20}$ +6.8 (*c* 1.34, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3070, 3027, 2932, 2857, 1453, 1427, 1104, 1084; δ_H (300 MHz; $CDCl_3$) 1.09 (9H, s, Si^{t}Bu), 1.19−1.41 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.44−1.54 (1H, m, CH$_a$,H_b-5), 1.61 (1H, br s, N*H*), 1.79−1.89 (1H, m, CH$_a$,H_b-4), 2.18 (1H, dd, *J* = 10.5, 13.3 Hz, CH_a,H_bPh), 2.34 (1H, td, *J* = 11.5, 2.8 Hz, CH_a,H_b-6), 2.66 (1H, ddd, *J* = 2.6, 8.5 10.5 Hz, H-2), 2.70−2.79 (1H, m, CH$_a$,H_b-6), 3.45 (1H, ddd, *J* = 9.9, 8.5, 4.3 Hz, H-3), 3.51 (1H, dd, *J* = 13.4, 2.6 Hz, CH$_a$,H_bPh), 7.16−7.33 (5H, m, CH$_2$*Ph*), 7.33−7.46 (6H, m, H-Ar), 7.68−7.78 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.4 (C, Si^{t}Bu), 25.1 (CH_2, C-5), 27.1 (CH_3, Si^{t}Bu), 34.6 (CH_2, C-4), 39.2 (CH_2, CH_2Ph), 46.0 (CH_2, C-6), 64.9 (CH, C-2), 74.4 (CH, C-3), 126.2 (CH, C-Ph), 127.4 (CH, C-Ar), 127.6 (CH, C-Ar), 128.5 (CH, C-Ph), 129.3 (CH, C-Ph), 129.5 (CH, C-Ar), 129.6 (CH, C-Ar), 133.9 (C, C-Ar), 134.8 (C, C-Ar), 135.9 (CH, C-Ar), 136.0 (CH, C-Ar), 139.6 (C, C-Ph); HRMS (ESI) $C_{28}H_{36}NOSi$ [MH^+] calcd 430.2561, obsd 430.2571.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-allylpiperidine (*trans*-13e) and (2*S*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-allylpiperidine (*cis*-13e). Following general procedure A, reaction of allylmagnesium chloride (1.0 M in Et_2O, 1.13 mL, 1.13 mmol) and nitrone **5b** (0.27 g, 0.75 mmol) followed by purification of the residue by column chromatography, using $MeOH/CH_2Cl_2$ (0.5:99.5), gave the *trans*-2-allylpiperidin-1-ol *trans*-**12e** (0.21 g, 70%) and *cis*-2-allylpiperidin-1-ol *cis*-**12e** (0.032 g, 11%) as a colorless oils. Following general procedure C, reduction of the first eluted compound, *trans*-2-allylpiperidin-1-ol *trans*-**12e** (0.11 g, 0.28 mmol) gave *trans*-**13e** (0.095 g, 91%) as a yellow oil. $[\alpha]_D^{20}$ +11.1 (*c* 1.88, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3072, 2932, 2857, 1428, 1105, 1083; δ_H (400 MHz; $CDCl_3$) 1.05 (9H, s, Si^{t}Bu), 1.15−1.41 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.45−1.54 (1H, m, CH$_a$,H_b-5), 1.66−1.82 (2H, m, N*H*, CH$_a$,H_b-4), 1.82−1.93 (1H, m, CH_a,H_b-3′), 2.42−2.53 (2H, m, H-2, CH_a,H_b-6), 2.77−2.89 (2H, m, CH$_a$,H_b-6, CH$_a$,H_b-3′), 3.34 (1H, ddd, *J* = 9.9, 8.6, 4.2 Hz, H-3), 5.02−5.12 (2H, m, H-1′), 5.71 (1H, dddd, *J* = 16.9, 10.2, 8.8, 5.7 Hz, H-2′), 7.32−7.44 (6H, m, H-Ar), 7.65−7.73 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 19.4 (C, Si^{t}Bu), 25.4 (CH_2, C-5), 27.0 (CH_3, Si^{t}Bu), 34.5 (CH_2, C-4), 37.1 (CH_2, C-3′), 45.9 (CH_2, C-6), 62.1 (CH, C-2), 73.9 (CH, C-3), 117.7 (CH_2, C-1′), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.4 (CH, C-Ar), 129.6 (CH, C-Ar), 133.8 (C, C-Ar), 134.8 (C, C-Ar), 135.8 (CH, C-2′), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (EI+) $C_{24}H_{33}NOSi$ [M^+] calcd 379.2331, obsd 379.2323.

Following general procedure C, reduction of the second eluted compound, *cis*-2-allylpiperidin-1-ol *cis*-**12e** (0.027 g, 0.068 mmol) gave *cis*-**13e** (0.021 g, 81%) as an opaque oil. $[\alpha]_D^{20}$ −13.1 (*c* 0.20, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3072, 2931, 2856, 1427, 1104; δ_H (300 MHz; $CDCl_3$) 1.11 (9H, s, Si^{t}Bu), 1.27−1.46 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.65−1.78 (1H, m, CH$_a$,H_b-4), 1.79−1.97 (1H, m, CH$_a$,H_b-5), 2.14−2.40 (2H, m, H-3′), 2.56−2.70 (2H, m, H-2, CH_a,H_b-6), 2.86 (1H, br s, N*H*), 3.05−3.18 (1H, m, CH$_a$,H_b-6), 3.79−3.86 (1H, m, H-3), 4.89−5.01 (2H, m, H-1′), 5.55−5.71 (1H, m, H-2′), 7.32−7.48 (6H, m, H-Ar), 7.65−7.74 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.5 (C, Si^{t}Bu), 21.1 (CH_2, C-5), 27.2 (CH_3, Si^{t}Bu), 31.0 (CH_2, C-4), 35.3 (CH_2, C-3′), 44.9 (CH_2, C-6), 60.1 (CH, C-2), 68.7 (CH, C-3), 117.0 (CH_2, C-1′), 127.5 (CH, C-Ar), 127.6 (CH, C-Ar), 129.7 (CH, C-Ar), 129.7 (CH, C-Ar), 133.7 (C, C-Ar), 134.2 (C, C-Ar), 135.5 (CH, C-2′), 136.0 (CH, C-Ar), 136.1 (CH, C-Ar); HRMS (ESI) $C_{24}H_{34}NOSi$ [MH^+] calcd 380.2404, obsd 380.2395.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-vinylpiperidine (13f). Following general procedure A, reaction of vinylmagnesium bromide (1.0 M in THF, 0.93 mL, 0.93 mmol) and nitrone **5b** (0.22 g, 0.62 mmol) followed by purification of the residue by column chromatography, using EtOAc/hexanes (1:9), gave the 2-vinylpiperidin-1-ol **12f** (0.20 g, 85%) as a colorless oil. Following general procedure C, reduction of 2-vinylpiperidin-1-ol **12f** (0.11 g, 0.30 mmol) gave the title compound (0.085 g, 79%) as a colorless oil. $[\alpha]_D^{20}$ +12.5 (*c* 1.10, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3072, 2932, 2857, 1427, 1104; δ_H (300 MHz; $CDCl_3$) 1.03 (9H, m, Si^{t}Bu), 1.16−1.45 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.47−1.59 (1H, m, CH$_a$,H_b-5), 1.70−1.85 (2H, m, CH$_a$,H_b-4, N*H*), 2.55 (1H, td, *J* = 11.5, 2.9 Hz, CH_a,H_b-6), 2.83−2.93 (1H, m, CH$_a$,H_b-6), 2.99−3.08 (1H, m, H-2), 3.44 (1H, ddd, *J* = 9.7, 8.4, 4.1 Hz, H-3), 5.05−5.25 (2H, m, H-1′), 5.82−5.96 (1H, m, H-2′), 7.29−7.45 (6H, m, H-Ar), 7.63−7.72 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.4 (C, Si^{t}Bu), 25.1 (CH_2, C-5), 27.0 (CH_3, Si^{t}Bu), 34.1 (CH_2, C-4), 45.4 (CH_2, C-6), 66.0 (CH, C-2), 73.7 (CH, C-3), 116.2 (CH_2, C-1′), 127.3 (CH, C-Ar), 127.4 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 133.9 (C, C-Ar), 134.9 (C, C-Ar), 135.9 (CH, C-Ar), 136.0 (CH, C-Ar), 139.4 (CH, C-2′); HRMS (ESI) $C_{23}H_{32}NOSi$ [MH^+] calcd 366.2248, obsd 366.2255.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-phenylpiperidine (13g). Following general procedure A, reaction of phenylmagnesium chloride (2.0 M in THF, 0.42 mL, 0.86 mmol) and nitrone **5b** (0.10 g, 0.28 mmol) followed by purification of the residue by column chromatography, using $MeOH/CH_2Cl_2$ (0.5:99.5), gave the 2-phenylpiperidin-1-ol **12g** (0.098 g, 80%) as a colorless oil. Following general procedure C, reduction of 2-phenylpiperidin-1-ol **12g** (0.11 g 0.26 mmol) gave the title compound (0.080 g, 76%) as a colorless oil. $[\alpha]_D^{20}$ −15.2 (*c* 1.60, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3070, 2931, 2855, 1427, 1103; δ_H (400 MHz; $CDCl_3$) 0.75 (9H, s, Si^{t}Bu), 1.28−1.48 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.48−1.57 (1H, m, CH$_a$,H_b-5), 1.68−1.79 (1H, m, CH$_a$,H_b-4), 1.80 (1H, br s, N*H*), 2.59−2.69 (1H, m, CH_a,H_b-6), 2.90−2.98 (1H, m, CH$_a$,H_b-6), 3.49 (1H, d, *J* = 8.7 Hz, H-2), 3.62−3.70 (1H, m, H-3), 7.18−7.42 (13H, m, H-Ar), 7.55−7.61 (2H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 19.0 (C, Si^{t}Bu), 25.3 (CH_2, C-5), 26.6 (CH_3, Si^{t}Bu), 35.1 (CH_2, C-4), 46.8 (CH_2, C-6), 69.6 (CH, C-2), 74.5 (CH, C-3), 127.2 (CH, C-Ar), 127.4 (CH, C-Ar), 128.1 (CH, C-Ar), 128.6 (CH, C-Ar), 129.3 (CH, C-Ar), 129.3 (CH, C-Ar), 133.5 (C, C-Ar), 135.2 (C, C-Ar), 135.9 (CH, C-Ar), 142.6 (C, C-Ar); HRMS (EI+) $C_{27}H_{33}NOSi$ [M^+] calcd 415.2331, obsd 415.2324.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(3′,4′-dimethoxyphenyl)piperidine (13h). Following general procedure A, reaction of 3,4-dimethoxyphenylmagnesium bromide (0.5 M in THF, 1.9 mL, 0.96 mmol) and nitrone **5b** (0.11 g, 0.32 mmol) followed by purification of the residue by column chromatography, using EtOAc/hexanes (5:95), gave the 2-(3,4-dimethoxyphenyl)piperidin-1-ol **12h** (0.12 g, 73%) as a colorless oil. Following general procedure C, reduction of 2-(3′,4′-dimethoxyphenyl)piperidin-1-ol **12h** (0.11 g, 0.23 mmol) gave the title compound (0.10 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ −17.4 (*c* 2.08, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3017, 2933, 2856, 1591, 1516, 1463, 1262, 1104; δ_H (300 MHz; $CDCl_3$) 0.80 (9H, s, Si^{t}Bu), 1.30−1.48 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.48−1.57 (1H, m, CH$_a$,H_b-5), 1.74−1.84 (1H, m, CH$_a$,H_b-4), 1.91 (1H, br s, N*H*), 2.64 (1H, td, *J* = 11.4, 2.6 Hz, CH_a,H_b-6), 2.89−2.99 (1H, m, CH$_a$,H_b-6), 3.43 (1H, d, *J* = 8.7 Hz, H-2), 3.56−3.67 (1H, m, H-3), 3.78 (3H, s, 3′-OMe), 3.87 (3H, s, 4′-OMe), 6.76 (1H, d, *J* = 8.2 Hz, H-5′), 6.84 (1H, d, *J* = 1.9 Hz, H-2′), 6.86 (1H, dd, *J* = 8.2, 1.9 Hz, H-6′), 7.17−7.27 (4H, m, H-Ar), 7.27−7.42 (4H, m, H-Ar), 7.53−7.69 (2H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 18.9 (C, Si^{t}Bu), 25.1 (CH_2, C-5), 26.6 (CH_3, Si^{t}Bu), 35.1 (CH_2, C-4), 46.7 (CH_2, C-6), 55.7 (CH_3, C-3′), 55.9 (CH_3, C-4′), 69.3 (CH, C-2), 74.5 (CH, C-3), 110.8 (CH, C-5′), 111.1 (CH, C-2′), 121.0 (CH, C-6′), 127.1 (CH, C-Ar), 127.1 (CH, C-Ar), 129.2 (CH, C-Ar), 133.4 (C, C-Ar), 135.0 (C, C-Ar), 135.3 (C, C-1′), 135.8 (CH, C-Ar), 135.8 (CH, C-Ar), 148.3 (C, C-4′), 148.8 (C, C-3′); HRMS (ESI) $C_{29}H_{38}NO_3Si$ [MH^+] calcd 476.2615, obsd 476.2604.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(3′-pyridyl)-piperidine (13i). Following general procedure A, reaction of (3-pyridyl)magnesium chloride, prepared by reaction of 3-bromopyridine (0.11 mL, 0.67 mmol) and isopropylmagnesium chloride (2.0 M in THF, 0.31 mL, 0.62 mmol), with nitrone **5b** (0.15 g, 0.42 mmol) followed by purification of the residue by column chromatography

dx.doi.org/10.1021/jo3011914 | *J. Org. Chem.* 2012, 77, 7968−7980

using MeOH/CH_2Cl_2 (1:99), gave the 2-(3′-pyridyl)piperidin-1-ol **12i** (0.11 g, 62%) as a colorless oil. Following general procedure C, reduction of 2-(3′-pyridyl)piperidin-1-ol **12i** (0.11 g, 0.58 mmol) gave the title compound (0.077 g, 71%) as a colorless oil. $[\alpha]_D^{20}$ −16.5 (*c* 1.54, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 2932, 2857, 1590, 1577, 1426, 1103; δ_H (300 MHz; $CDCl_3$) 0.76 (9H, s, Si^{t}Bu), 1.24−1.61 (3H, m, CH_a,H_b-4, H-5), 1.70−2.00 (2H, m, CH$_a$,H_b-4, N*H*), 2.65 (1H, td *J* = 11.5, 2.6 Hz, CH_a,H_b-6), 2.90−3.00 (1H, m, CH$_a$,H_b-6), 3.53 (1H, d, *J* = 8.7 Hz, H-2), 3.57−3.68 (1H, m, H-3), 7.16 (1H, dd, *J* = 4.7, 7.7 Hz, H-5′), 7.20−7.30 (4H, m, H-Ar), 7.30−7.45 (4H, m, H-Ar), 7.52−7.63 (3H, m, H-Ar, H-4′), 8.50 (1H, dd, *J* = 1.4, 4.7 Hz, H-6′), 8.60 (1H, d, *J* = 1.6 Hz, H-2′); δ_C (75 MHz; $CDCl_3$) 18.9 (C, Si^{t}Bu), 25.1 (CH_2, C-5), 26.5 (CH_3, Si^{t}Bu), 34.9 (CH_2, C-4), 46.6 (CH_2, C-6), 67.0 (CH, C-2), 74.4 (CH, C-3), 123.2 (CH, C-5′), 127.2 (CH, C-Ar), 127.4 (CH, C-Ar), 129.4 (CH, C-Ar), 129.4 (CH, C-Ar), 133.0 (C, C-Ar), 134.7 (C, C-Ar), 135.5 (CH, C-4′), 135.7 (CH, C-Ar), 135.8 (CH, C-Ar), 138.0 (C, C-3′), 148.8 (CH, C-6′), 150.3 (CH, C-2′); HRMS (ESI) $C_{26}H_{33}N_2OSi$ [MH^+] calcd 417.2357, obsd 417.2366.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-butylpiperidin-1-ol (12a). Following general procedure B, reaction of nitrone **5b** (0.30 g, 0.83 mmol) and MeLi (1.6 M in Et_2O, 0.78 mL, 1.25 mmol) followed by purification of the residue by column chromatography using EtOAc/hexanes (1:4) as eluent gave the 2-methylpiperidin-1-ol **12a** (0.20 g, 64%) as a colorless oil.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-butylpiperidine (13j). Following general procedure B, reaction of nitrone **5b** (0.10 g, 0.28 mmol) and *n*-BuLi (1.6 M in hexanes, 0.27 mL, 0.42 mmol) followed by purification of the residue by column chromatography, using EtOAc/hexanes (1:9), gave the 2-butylpiperidin-1-ol **12j** (0.070 g, 50%) as a colorless oil. Following general procedure C, reduction of 2-butylpiperidin-1-ol **12j** (0.068 g, 0.17 mmol) gave the title compound (0.048 g, 73%) as a colorless oil. $[\alpha]_D^{20}$ +22.5 (*c* 0.84, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 2931, 2857, 1428, 1105, 1082; δ_H (300 MHz; $CDCl_3$) 0.86 (3H, t, *J* = 6.9 Hz, 1′-H), 1.05 (9H, s, Si^{t}Bu), 1.13−1.44 (7H, m, CH_a,H_b-4, CH_a,H_b-5, 2′-H, 3′-H, CH_a,H_b-4′), 1.49−1.60 (1H, m, CH$_a$,H_b-5), 1.70−1.81 (1H, m, CH$_a$,H_b-4), 1.83−1.98 (1H, m, CH$_a$,H_b-4′), 2.32 (1H, m, N*H*), 2.42−2.58 (2H, m, H-2, CH_a,H_b-6), 2.82−2.93 (1H, m, CH$_a$,H_b-6), 3.34 (1H, ddd, *J* = 9.6, 8.2, 4.1 Hz, H-3), 7.30−7.45 (6H, m, H-Ar), 7.63−7.73 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 14.0 (CH_3, C-1′), 19.4 (C, Si^{t}Bu), 22.8 (CH_2, C-2′), 25.2 (CH_2, C-5), 27.1 (CH_3, Si^{t}Bu), 27.8 (CH_2, C-3′), 31.6 (CH_2, C-4′), 33.9 (CH_2, C-4), 45.5 (CH_2, C-6), 62.8 (CH, C-2), 73.7 (CH, C-3), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 133.9 (C, C-Ar), 134.9 (C, C-Ar), 135.9 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (ESI) $C_{25}H_{38}NOSi$ [MH^+] calcd 396.2717, obsd 396.2719.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-*tert*-butylpiperidine (13k). Following general procedure B, reaction of nitrone **5b** (0.26 g, 0.74 mmol) and *tert*-BuLi (1.7 M in pentane, 0.65 mL, 1.10 mmol) followed by purification of the residue by column chromatography, using EtOAc/hexanes (1:9), gave the *tert*-butylpiperidin-1-ol **12k** (0.099 g, 31%) as a colorless oil. Following general procedure C, reduction of *tert*-butylpiperidin-1-ol **12k** (0.082 g, 0.20 mmol) gave the title compound (0.073 g, 93%) as a colorless oil. $[\alpha]_D^{20}$ +46.0 (*c* 1.18, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 2933, 2858, 1474, 1428, 1105, 1075; δ_H (300 MHz; $CDCl_3$) 0.96−1.18 (19H, m, CH_a,H_b-5, Si^{t}Bu, C^{t}Bu), 1.24−1.45 (2H, m, CH_a,H_b-4, CH$_a$,H_b-5), 1.57−1.70 (1H, m, CH$_a$,H_b-4), 1.87 (1H, br s, N*H*), 2.33 (1H, d, *J* = 7.8 Hz, H-2), 2.47 (1H, td, *J* = 11.6, 3.0 Hz, CH_a,H_b-6), 2.82−2.93 (1H, m, CH$_a$,H_b-6), 3.67 (1H, ddd, *J* = 9.4, 7.7, 3.7 Hz, H-3), 7.31−7.46 (6H, m, H-Ar), 7.70−7.82 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$); 19.3 (C, Si^{t}Bu), 24.9 (CH_2, C-5), 27.0 (CH_3, Si^{t}Bu), 28.1 (CH_3, ^{t}Bu), 33.8 (C, ^{t}Bu), 35.0 (CH_2, C-4), 46.3 (CH_2, C-6), 70.7 (CH, C-2), 74.0 (CH, C-3), 127.2 (CH, C-Ar), 127.6 (CH, C-Ar), 129.2 (CH, C-Ar), 129.6 (CH, C-Ar), 133.7 (C, C-Ar), 135.5 (C, C-Ar), 135.7 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (ESI) $C_{25}H_{38}NOSi$ [MH^+] calcd 396.2717, obsd 396.2717.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(trimethylsilylethynyl)piperidine (13l). Following general procedure B, reaction of nitrone **5b** (0.22 g, 0.62 mmol) with (trimethylsilylethynyl)lithium, prepared by reaction of *n*-BuLi (1.6 M in hexanes, 0.48 mL, 0.77 mmol) and ethynyltrimethylsilane (0.091 g, 0.93 mmol), followed by purification of the residue by column chromatography, using EtOAc/hexanes (gradient 1:39 to 1:4), gave the 2-(trimethylsilylethynyl)-piperidin-1-ol **12l** (0.22 g, 80%) as a colorless oil. Indium powder (0.070 g, 0.61 mmol) was added to a solution of 2-(trimethylsilylethynyl)piperidin-1-ol **12l** (0.18 g, 0.31 mmol) in EtOH (3 mL) and the suspension heated to 80 °C. Aqueous HCl (2 M, 0.045 mL) was added and the suspension heated to 100 °C and stirred for 2 h. The reaction was concentrated under reduced pressure and the residue dissolved in EtOAc (20 mL). The pH was adjusted to 10 by the dropwise addition of an aqueous solution of 2 M NaOH. The mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with brine (20 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with EtOAc/hexanes (3:17), to give the title compound (0.093 g, 70%) as a colorless oil. $[\alpha]_D^{20}$ −5.3 (*c* 1.66, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 3051, 2932, 2857, 2175, 1590, 1428, 1249, 1105, 840; δ_H (400 MHz; $CDCl_3$) 0.12 (9H, s, $SiMe_3$), 1.09 (9H, s, Si^{t}Bu), 1.18−1.38 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.53−1.63 (1H, m, CH$_a$,H_b-5), 1.71−1.81 (1H, m, CH$_a$,H_b-4), 1.81 (1H, br s, N*H*), 2.55 (1H, ddd, *J* = 12.3, 9.1, 3.2 Hz, CH_a,H_b-6), 2.86−2.95 (1H, m, CH$_a$,H_b-6), 3.45 (1H, d, *J* = 7.0 Hz, H-2), 3.71 (1H, ddd, *J* = 8.0, 7.2, 3.5 Hz, H-3), 7.32−7.45 (6H, m, H-Ar), 7.68−7.78 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) −0.1 (CH_3, $SiMe_3$), 19.4 (C, Si^{t}Bu), 24.0 (CH_2, C-5), 27.0 (CH_3, Si^{t}Bu), 32.4 (CH_2, C-4), 44.3 (CH_2, C-6), 55.4 (CH, C-2), 72.1 (CH, C-3), 88.1 (C, C-2′), 106.1 (C, C-1′), 127.4 (CH, C-Ar), 127.5 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 133.6 (C, C-Ar), 134.6 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (ESI) $C_{26}H_{38}NOSi_2$ [MH^+] calcd 436.2486, obsd 436.2491.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(4′-methoxyphenyl)-piperidine (13m). Following general procedure B, reaction of nitrone **5b** (0.26 g 0.74 mmol) and (4 methoxyphenyl)lithium, prepared from *n*-BuLi (1.6 M in hexanes, 0.69 mL, 1.11 mmol) and 4-bromoanisole (0.23 g, 1.26 mmol), followed by purification of the residue by column chromatography, using MeOH/CH_2Cl_2 (0.5:99.5), gave the 2-(4′-methoxyphenyl)piperidin-1-ol **12m** (0.22 g, 69%) as a colorless oil. Following general procedure C, reduction of 2-(4′-methoxyphenyl)-piperidin-1-ol **12m** (0.13 g, 0.27 mmol) gave the title compound (0.11 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ −37.0 (*c* 1.76, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 2932, 2856, 1612, 1512, 1427, 1249, 1239, 1104; δ_H (400 MHz; $CDCl_3$) 0.79 (9H, s, Si^{t}Bu), 1.27−1.47 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.48−1.56 (1H, m, CH$_a$,H_b-5), 1.70−1.84 (2H, m, CH$_a$,H_b-4, N*H*), 2.57−2.67 (1H, m, CH_a,H_b-6), 2.89−2.96 (1H, m, CH$_a$,H_b-6), 3.44 (1H, d, *J* = 8.7 Hz, H-2), 3.57−3.65 (1H, m, H-3), 3.80 (3H, s, OMe), 6.79−6.85 (2H, m, H-3′, H-5′), 7.17−7.26 (6H, m, H-Ar, H-2′, H-6′), 7.28−7.41 (4H, m, H-Ar), 7.54−7.61 (2H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 18.9 (C, Si^{t}Bu), 25.3 (CH_2, C-5), 26.7 (CH_3, Si^{t}Bu), 35.1 (CH_2, C-4), 46.8 (CH_2, C-6), 55.3 (CH_3, OMe), 68.9 (CH, C-2), 74.6 (CH, C-3), 113.5 (CH, C-3′, C-5′), 127.2 (CH, C-Ar), 127.2 (CH, C-Ar), 129.2 (CH, C-Ar), 129.3 (CH, C-Ar), 129.4 (CH, C-2′, C-6′), 133.5 (C, C-Ar), 135.0 (C, C-1′), 135.2 (C, C-Ar), 135.9 (CH, C-Ar), 135.9 (CH, C-Ar), 159.0 (C, C-4′); HRMS (ESI) $C_{28}H_{36}NO_2Si$ [MH^+] calcd 446.2510, obsd 446.2522.

(2*S*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(2′-furanyl)-piperidine (13n). Following general procedure B, reaction of nitrone **5b** (0.20 g, 0.56 mmol) and 2-lithiofuran, prepared by reaction of *n*-BuLi (1.6 M in hexanes, 0.53 mL, 0.84 mmol) and furan (0.065 g, 0.96 mmol), followed by purification of the residue by column chromatography, using EtOAc/hexanes (1:9), gave the 2-(2′-furanyl)-piperidin-1-ol **12n** (0.17 g, 72%) as a yellow oil. Following general procedure C, reduction of 2-(2′-furanyl)piperidin-1-ol **12n** (0.10 g, 0.24 mmol) gave the title compound (0.091 g, 94%) as a yellow oil. $[\alpha]_D^{20}$ +4.5 (*c* 1.82, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 2930, 2856, 1590, 1427, 1104; δ_H (300 MHz; $CDCl_3$) 0.88 (9H, m, Si^{t}Bu), 1.22−1.49 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.49−1.60 (1H, m, CH$_a$,H_b-5), 1.70−1.83 (2H, m, CH$_a$,H_b-4, N*H*), 2.59 (1H, td, *J* = 11.5, 2.9 Hz, CH_a,H_b-

dx.doi.org/10.1021/jo3011914 | *J. Org. Chem.* 2012, 77, 7968−7980

6), 2.87−2.96 (1H, m, CH_aH_b-6), 3.67 (1H, d, J = 8.6 Hz, H-2), 3.85 (1H, ddd, J = 9.7, 8.6, 4.2 Hz, H-3), 6.19 (1H, dd, J = 3.2, 0.8 Hz, H-3′), 6.28 (1H, dd, J = 3.2, 1.9 Hz, H-4′), 7.24−7.48 (9H, m, H-Ar, H-5′), 7.59−7.66 (2H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.0 (C, Si^{t}Bu), 25.1 (CH_2, C-5), 26.7 (CH_3, Si^{t}Bu), 34.5 (CH_2, C-4), 46.0 (CH_2, C-6), 61.8 (CH, C-2), 72.4 (CH, C-3), 107.3 (CH, C-3′), 110.0 (CH, C-4′), 127.2 (CH, C-Ar), 127.3 (CH, C-Ar), 129.3 (CH, C-Ar), 129.3 (CH, C-Ar), 133.5 (C, C-Ar), 134.9 (C, C-Ar), 135.8 (CH, C-Ar), 135.8 (CH, C-Ar), 141.2 (CH, C-5′), 155.1 (C, C-2′); HRMS (ESI) $C_{25}H_{32}NO_2Si$ [MH^+] calcd 406.2197, obsd 406.2192.

(2*S*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(2′-thienyl)-piperidine (13o). Following general procedure B, reaction of nitrone **5b** (0.22 g, 0.62 mmol) with 2-lithiothiophene, prepared by reaction of *n*-BuLi (1.6 M in hexanes, 0.58 mL, 0.93 mmol) and thiophene (0.089 g, 1.06 mmol), followed by purification of the residue by column chromatography, using EtOAc/hexanes (1:9), gave 2-(2′-thienyl)-piperidin-1-ol **12o** (0.23 g, 85%) as a colorless oil. Following general procedure C, reduction of 2-(2′-thienyl)piperidin-1-ol **12o** (0.12 g, 0.26 mmol) gave the title compound (0.090 g, 81%) as a yellow oil. $[\alpha]_D^{20}$ +2.7 (*c* 1.32, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3338, 3072, 3048, 2934, 2856, 1590, 1428, 1106; δ_H (300 MHz; $CDCl_3$) 0.85 (9H, s, Si^{t}Bu), 1.24−1.43 (2H, m, CH_aH_b-4, CH_aH_b-5), 1.43−1.55 (1H, m, CH_aH_b-5), 1.65−1.75 (1H, m, CH_aH_b-4), 1.87 (1H, br s, N*H*), 2.56−2.68 (1H, m, CH_aH_b-6), 2.87−2.97 (1H, m, CH_aH_b-6), 3.57−3.67 (1H, m, H-3), 3.84 (1H, d, J = 8.3 Hz, H-2), 6.93 (1H, dd, J = 5.0, 3.4 Hz, H-4′), 7.00−7.04 (1H, m, H-3′), 7.16−7.20 (1H, m, H-5′), 7.20−7.28 (2H, m, H-Ar), 7.28−7.43 (6H, m, H-Ar), 7.58−7.67 (2H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.0 (C, Si^{t}Bu), 24.8 (CH_2, C-5), 26.7 (CH_3, Si^{t}Bu), 34.6 (CH_2, C-4), 46.4 (CH_2, C-5), 64.3 (CH, C-2), 75.4 (CH, C-3), 123.9 (CH, C-5′), 125.5 (CH, C-3′), 126.1 (CH, C-4′), 127.3 (CH, C-Ar), 127.3 (CH, C-Ar), 129.3 (CH, C-Ar), 129.3 (CH, C-Ar), 133.4 (C, C-Ar), 135.0 (C, C-Ar), 135.7 (CH, C-Ar), 135.8 (CH, C-Ar), 146.3 (C, C-2′); HRMS (ESI) $C_{25}H_{32}NOSSi$ [MH^+] calcd 422.1968, obsd 422.1977.

(4a*S*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)-4-methoxy-2,4a,5,6,7,8-hexahydropyrido[1,2-*b*][1,2]oxazine (16). Following general procedure B, reaction of nitrone **5b** (0.055 g, 0.17 mmol) with lithiated methoxyallene, prepared by reaction of *n*-BuLi (1.6 M in hexanes, 0.15 mL, 0.23 mmol) and methoxyallene (0.018 g, 0.26 mmol), followed by purification of the residue by column chromatography, using EtOAc/hexanes (1:4), gave the 2-(1′-methoxypropa-1,2-dien-1-yl)piperidin-1-ol **15** (0.036 g, 50%) as a colorless oil. A solution of 2-(1′-methoxypropa-1,2-dien-1-yl)-piperidin-1-ol **15** (0.033 g, 0.078 mmol) in CH_2Cl_2 (1.5 mL) was stirred at rt for 5 d. The solvent was removed under reduced pressure and the residue purified by flash column chromatography, eluting with EtOAc/hexanes (1:9), to give the title compound (0.031 g, 95%) as a colorless oil. $[\alpha]_D^{20}$ +36.1 (*c* 0.62, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3072, 2931, 2866, 1669, 1428, 1105; δ_H (400 MHz; $CDCl_3$) 0.99−1.11 (9H, m, Si^{t}Bu), 1.23−1.40 (2H, m, CH_aH_b-6, CH_aH_b-7), 1.57−1.80 (2H, m, CH_aH_b-6, CH_aH_b-7), 2.69−2.88 (1H, m, CH_aH_b-8), 3.07−3.21 (1H, m, H-4a), 3.22−3.49 (4H, m, OMe, CH_aH_b-8), 4.13−4.58 (3H, m, H-2, H-5), 4.53 (1H, t, J = 2.5 Hz, H-3), 7.29−7.44 (6H, m, H-Ar), 7.65−7.73 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 19.3 (C, Si^{t}Bu), 20.0 (CH_2, C-7), 26.8 (CH_3, Si^{t}Bu), 33.7 (CH_2, C-6), 53.1 (CH_2, C-8), 54.0 (CH_3, OMe), 65.9 (CH, C-4a), 66.7 (CH_2, C-2), 70.7 (CH, C-5), 91.0 (CH, C-3), 127.3 (CH, C-Ar), 127.3 (CH, C-Ar), 129.3 (CH, C-Ar), 129.3 (CH, C-Ar), 134.3 (C, C-Ar), 135.2 (C, C-Ar), 135.9 (CH, C-Ar), 156.2 (C, C-4); HRMS (ESI) $C_{25}H_{34}NO_3Si$ [MH^+] calcd 424.2302, obsd 424.2315.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)piperidin-1-ol (20). A solution of *n*-BuLi (1.5 M in hexanes, 1.98 mL, 2.97 mmol) was added dropwise to a solution of 3-(*tert*-butyldimethylsilyloxy)prop-1-yne (0.61 g, 3.56 mmol) in THF (8 mL) at −78 °C. The solution was stirred for 15 min and then warmed to 0 °C and stirred for an additional 30 min. A solution of nitrone **5b** (0.84 g, 2.38 mmol) in THF (18 mL) was added at −78 °C and the mixture warmed to 0 °C and stirred for a further 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with EtOAc/hexanes (1:19), to give the title compound (1.12 g, 90%) as a colorless oil. $[\alpha]_D^{20}$ −23.0 (*c* 2.04, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3222, 3073, 2930, 2857, 1471, 1253, 1427, 1104; δ_H (300 MHz; DMSO-d_6, 373 K) 0.07 (6H, s, $SiMe_2$), 0.88 (9H, s, Si^{t}Bu), 1.07 (9H, s, Si^{t}Bu), 1.24−1.46 (2H, m, CH_aH_b-5, CH_aH_b-4), 1.56−1.82 (2H, m, CH_aH_b-5, CH_aH_b-4), 2.57−2.69 (1H, m, CH_aH_b-6), 2.85−2.99 (1H, m, CH_aH_b-6), 3.53−3.62 (1H, m, H-2), 3.91−4.01 (1H, m, H-3), 4.20−4.27 (2H, m, H-3′), 7.35−7.49 (6H, m, H-Ar), 7.49−7.59 (1H, m, NO*H*), 7.61−7.76 (4H, m, H-Ar); δ_C (75 MHz; DMSO-d_6, 373 K) −5.9 (CH_3, $SiMe_2$), 17.2 (C, Si^{t}Bu), 18.3 (C, Si^{t}Bu), 19.5 (CH_2, C-5), 25.1 (CH_3, Si^{t}Bu), 26.3 (CH_3, Si^{t}Bu), 29.2 (CH_2, C-4), 50.8 (CH_2, C-3′), 54.2 (CH_2, C-6), 63.9 (CH, C-2), 71.7 (CH, C-3), 82.3 (C, C-2′), 83.2 (C, C-1′), 126.9 (CH, C-Ar), 126.9 (CH, C-Ar), 128.9 (CH, C-Ar), 129.0 (CH, C-Ar), 133.2 (C, C-Ar), 133.4 (C, C-Ar), 134.7 (CH, C-Ar), 134.7 (CH, C-Ar); HRMS (ESI) $C_{30}H_{46}NO_3Si_2$ [MH^+] calcd 524.3011, obsd 524.3012.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(3-hydroxyprop-1-ynyl)piperidine (21). Indium powder (0.44 g, 3.80 mmol) was added to a solution of hydroxylamine **20** (0.99 g, 1.90 mmol) in EtOH (22 mL) and the suspension heated to 80 °C. Aqueous HCl (1 M, 3.4 mL) was added and the suspension heated to 100 °C and stirred for 2 h. The reaction mixture was cooled to rt and the pH adjusted to 10 by the dropwise addition of an aqueous solution of 2 M NaOH. The mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with a solution of saturated brine (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with MeOH/CH_2Cl_2 (gradient 5:95 to 9:91), to give the title compound (0.64 g, 85%) as a yellow oil. $[\alpha]_D^{20}$ −0.4 (*c* 1.08, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3285, 3071, 2932, 2856, 1428, 1105; δ_H (300 MHz; $CDCl_3$) 1.08 (9H, s, Si^{t}Bu), 1.18−1.34 (1H, m, CH_aH_b-5), 1.34−1.49 (1H, m, CH_aH_b-4), 1.58−1.74 (1H, m, CH_aH_b-5), 1.78−1.91 (1H, m, CH_aH_b-4), 2.52−2.64 (1H, m, CH_aH_b-6), 2.84−3.00 (3H, m, CH_aH_b-6, N*H*, O*H*), 3.45−3.52 (1H, m, H-2), 3.61−3.70 (1H, m, H-3), 4.04 (2H, d, J = 1.5 Hz, H-1), 7.31−7.41 (6H, m, H-Ar), 7.63−7.73 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.3 (C, Si^{t}Bu), 23.4 (CH_2, C-5′), 26.9 (CH_3, Si^{t}Bu), 31.4 (CH_2, C-4′), 43.6 (CH_2, C-6′), 50.4 (CH_2, C-1), 54.1 (CH, C-2′), 71.5 (CH, C-3′), 83.6, (C, C-2), 84.2 (C, C-3), 127.4 (CH, C-Ar), 127.5 (CH, C-Ar), 129.6 (CH, C-Ar), 129.6 (CH, C-Ar), 133.8 (C, C-Ar), 133.9 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (EI) $C_{24}H_{31}NO_2Si$ [M^+] calcd 393.2124, obsd 393.2119.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-((*Z*)-3-hydroxyprop-1-enyl)piperidine (19). Lindlar catalyst (0.095 g) was added portionwise to a solution of hydroxylamine **20** (0.38 g, 0.75 mmol) in EtOAc (10 mL). The mixture was stirred under a hydrogen atmosphere for 1.25 h, filtered through Celite, and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with EtOAc/hexanes (gradient 1:19 to 3:17), to give the alkene (0.34 g, 90%) as a colorless oil. $[\alpha]_D^{20}$ −38.8 (*c* 0.60, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3228, 2928, 2856, 1427, 1090; δ_H (300 MHz; DMSO-d_6, 373 K) 0.06 (6H, s, $SiMe_2$), 0.91 (9H, s, Si^{t}Bu), 1.03 (9H, s, Si^{t}Bu), 1.15−1.36 (2H, m, CH_aH_b-4, CH_aH_b-5), 1.39−1.64 (2H, m, CH_aH_b-5, CH_aH_b-4), 2.36−2.49 (1H, m, CH_aH_b-6), 2.95−3.06 (1H, m, CH_aH_b-6), 3.08−3.19 (1H, m, H-2), 3.55−3.68 (1H, m, H-3), 4.23−4.44 (2H, m, H-3′), 5.25−5.37 (1H, m, H-1′), 5.53−5.65 (1H, m, H-2′), 7.10−7.20 (1H, m, NO*H*), 7.34−7.49 (6H, m, H-Ar), 7.60−7.71 (4H, m, H-Ar); δ_C (75 MHz; DMSO-d_6, 373 K) −5.9 (CH_3, $SiMe_2$), −5.8 (CH_3, $SiMe_2$), 17.2 (C, Si^{t}Bu), 18.2 (C, Si^{t}Bu), 19.8 (CH_2, C-5), 25.2 (CH_3, Si^{t}Bu), 26.3 (CH_3, Si^{t}Bu), 32.1 (CH_2, C-4), 56.3 (CH_2, C-6), 59.5 (CH_2, C-3′), 70.1 (CH, C-2), 72.1 (CH, C-3), 126.7 (CH, C-Ar), 126.8 (CH, C-Ar), 128.8 (CH, C-Ar), 128.9 (CH, C-Ar), 129.1 (CH, C-1′), 132.7 (CH, C-2′), 133.2 (C, C-Ar), 134.0 (C, C-Ar), 134.7 (CH, C-Ar), 134.8 (CH, C-Ar); HRMS (ESI) $C_{30}H_{48}NO_3Si_2$ [MH^+] calcd 526.3167, obsd 526.3163.

dx.doi.org/10.1021/jo3011914 | *J. Org. Chem.* 2012, 77, 7968−7980

Indium powder (0.43 g, 3.70 mmol) was added to a solution of the alkene prepared above (0.97 g, 1.85 mmol) in EtOH (22 mL) and the suspension heated to 80 °C. Aqueous HCl (1 M, 3.4 mL) was added and the suspension heated to 100 °C and stirred for 2 h. The reaction mixture was cooled to rt and the pH adjusted to 10 by the dropwise addition of an aqueous solution of 2 M NaOH. The mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with brine (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with MeOH/CH_2Cl_2 (gradient 3:97 to 9:91), to give the title compound (0.63 g, 86%) as a white solid. Recrystallization from Et_2O/hexanes (1:1) gave white needles. mp 123.1−124.5 °C; $[\alpha]_D^{20}$ −19.7 (*c* 1.33, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3261, 3072, 3048, 2946, 2930, 2905, 2873, 1590, 1427, 1106, 1092; δ_H (300 MHz; $CDCl_3$) 1.04 (9H, s, Si^{t}Bu), 1.14−1.31 (1H, m, CH_a,H$_b$-5), 1.36−1.51 (1H, m, CH_a,H$_b$-4), 1.57−1.70 (1H, m, CH$_a$,H_b-5), 1.70−1.82 (1H, m, CH$_a$,H_b-4), 2.59 (1H, ddd, *J* = 12.8, 9.8, 3.2 Hz, CH_a,H$_b$-6), 2.83 (1H, dt, *J* = 12.8, 4.3 Hz, CH$_a$,H_b-6), 3.40−3.57 (2H, m, H-2, H-3), 3.74 (2H, br s, N*H*, O*H*), 4.08 (1H, ddt, *J* = 14.6, 5.1, 1.2 Hz, CH_a,H$_b$-1′), 4.23 (1H, ddd, *J* = 14.6, 5.9, 1.2 Hz, CH$_a$,H_b-1′), 5.46 (1H, ddt, *J* = 11.5, 6.3, 1.2 Hz, H-3′), 5.74−5.85 (1H, m, H-2′), 7.31−7.46 (6H, m, H-Ar), 7.63−7.72 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.3 (C, Si^{t}Bu), 24.5 (CH_2, C-5), 27.0 (CH_3, Si^{t}Bu), 32.3 (CH_2, C-4), 43.8 (CH_2, C-6), 59.1 (CH, C-2), 59.6 (CH_2, C-1′), 72.9 (CH, C-3), 127.4 (CH, C-Ar), 127.6 (CH, C-Ar), 129.6 (CH, C-Ar), 129.7 (CH, C-Ar), 131.4 (CH, C-3′), 133.5 (CH, C-2′), 133.6 (C, C-Ar), 134.4 (C, C-Ar), 135.8 (CH, C-Ar), 135.8 (CH, C-Ar); HRMS (EI+) $C_{24}H_{33}NO_2Si$ [M$^+$] calcd 395.2281, obsd 395.2288.

(8*S*,8a*R*)-8-(*tert*-Butyldiphenylsilyloxy)-3,5,6,7,8,8a-hexahydroindolizine (17). A solution of di-*p*-chlorobenzyl azodicarboxylate (DCAD) (0.34 g, 0.93 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of amino alcohol **19** (0.30 g, 0.75 mmol) and PPh_3 (0.24 g, 0.93 mmol) in CH_2Cl_2 (20 mL) over a period of 10 min at 0 °C. The solution was stirred for 1 h at 0 °C and then filtered through a short pad of Celite and concentrated under reduced pressure. The residue was purified by column chromatography on basic alumina, eluting with EtOAc/hexanes (gradient 0:100 to 3:97), to give the title compound (0.25 g, 89%) as an opaque oil. $[\alpha]_D^{20}$ +72.7 (*c* 0.48, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3071, 2932, 2856, 1427, 1110, 1082; δ_H (300 MHz; $CDCl_3$) 1.06 (9H, s, Si^{t}Bu), 1.20−1.57 (3H, m, CH_a,H$_b$-7, H-6), 1.72−1.83 (1H, m, CH$_a$,H_b-7), 2.36 (1H, td, *J* = 11.2, 3.2 Hz, CH_a,H$_b$-5), 2.79−2.89 (1H, m, CH$_a$,H_b-5), 2.97−3.07 (1H, m, H-8a), 3.14−3.25 (1H, m, CH_a,H$_b$-3), 3.50−3.66 (2H, m, CH$_a$,H_b-3, H-8), 5.76−5.84 (1H, m, H-1), 6.02−6.10 (1H, m, H-2), 7.29−7.44 (6H, m, H-Ar), 7.64−7.72 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.3 (C, Si^{t}Bu), 24.3 (CH_2, C-6), 27.0 (CH_3, Si^{t}Bu), 34.2 (CH_2, C-7), 48.8 (CH_2, C-5), 57.8 (CH_2, C-3), 72.9 (CH, C-8), 74.0 (CH, C-8a), 127.4 (CH, C-Ar), 127.5 (CH, C-Ar), 128.4 (CH, C-1), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 131.6 (CH, C-2), 134.1 (C, C-Ar), 134.6 (C, C-Ar), 135.8 (CH, C-Ar), 135.8 (CH, C-Ar); HRMS (EI+) $C_{24}H_{31}NOSi$ [M$^+$] calcd 377.2175, obsd 377.2175.

(1*R*,2*S*,8*S*,8a*R*)-8-(*tert*-Butyldiphenylsilyloxy)octahydroindolizine-1,2-diyl Diacetate (22) and (1*S*,2*R*,8*S*,8a*R*)-8-(*tert*-Butyldiphenylsilyloxy)octahydroindolizine-1,2-diyl Diacetate. A solution of alkene **17** (0.25 g, 0.67 mmol) in *t*-BuOH (2.5 mL) was added to a solution of AD-mix-α (1.75 g) and $MeSO_2NH_2$ (0.076 g, 0.80 mmol) in *t*-BuOH/H_2O (1:2, 7.5 mL) at 0 °C. The suspension was stirred vigorously at 1−4 °C for 4 d. Saturated aqueous Na_2SO_3 (15 mL) was added and the mixture stirred for a further 2 h. The reaction mixture was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was passed through a short pad of silica gel eluting with MeOH/$CHCl_3$ (9:91), to give a crude mixture of diols. DMAP (8 mg, 0.066 mmol), pyridine (0.32 mL, 3.98 mmol), and Ac_2O (0.25 mL, 2.65 mmol) were added to a solution of the crude diols in CH_2Cl_2 (16 mL) at rt and the mixture stirred overnight. MeOH (5 mL) was added and the mixture concentrated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and washed with a 10% $CuSO_{4(aq)}$ (15 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with EtOAc/hexanes (gradient 1:9 to 3:7), to give the title compound **22** (0.23 g, 68%) and the (1*S*,2*R*,8*S*,8a*R*)-isomer (0.025 g, 7.6%) as colorless oils. Data for **22**: R_f (25% EtOAc/hexanes) 0.14; $[\alpha]_D^{20}$ +63.4 (*c* 0.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2933, 2856, 1743, 1428, 1371, 1243, 1223, 1079; δ_H (300 MHz; $CDCl_3$) 1.01 (9H, s, Si^{t}Bu), 1.14−1.55 (3H, m, 6-H, CH_a,H$_b$-7), 1.70−1.90 (5H, m, CH_a,H$_b$-5, CH$_a$,H_b-7, OAc), 1.98 (3H, s, OAc), 2.15 (1H, dd, *J* = 8.8, 4.1 Hz, 8a-H), 2.56 (1H, dd, *J* = 11.2, 7.7 Hz, CH_a,H$_b$-3), 2.86−2.96 (1H, m, CH$_a$,H_b-5), 2.98 (1H, dd, *J* = 11.2, 1.9 Hz, CH$_a$,H_b-3), 3.96 (1H, ddd, *J* = 10.5, 8.8, 4.6 Hz, 8-H), 5.33−5.42 (1H, m, 2-H), 5.51 (1H, dd, *J* = 6.4, 4.1 Hz, 1-H), 7.30−7.46 (6H, m, H-Ar), 7.57−7.68 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.0 (C, Si^{t}Bu), 20.5 (CH_3, OAc), 20.7 (CH_3, OAc), 23.3 (CH_2, C-6), 26.8 (CH_3, Si^{t}Bu), 33.9 (CH_2, C-7), 52.1 (CH_2, C-5), 60.1 (CH_2, C-2), 68.5 (CH, C-8), 69.4 (CH, C-2), 71.7 (CH, C-1), 71.9 (CH, C-8a), 127.4 (CH, C-Ar), 127.7 (CH, C-Ar), 129.6 (CH, C-Ar), 129.7 (CH, C-Ar), 133.7 (C, C-Ar), 134.6 (C, C-Ar), 135.7 (CH, C-Ar), 135.8 (CH, C-Ar), 170.0 (C═O, 2-OAc), 170.3 (C═O, 1-OAc); HRMS (ESI) $C_{28}H_{38}NO_5Si$ [MH$^+$] calcd 496.2514, obsd 496.2512. Data for (1*S*,2*R*,8*S*,8a*R*)-isomer: R_f (25% EtOAc/hexanes) 0.34; $[\alpha]_D^{20}$ −54.8 (*c* 1.46, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2934, 2858, 1743, 1427, 1371, 1243, 1223, 1104; δ_H (300 MHz; $CDCl_3$) 1.02 (9H, s, Si^{t}Bu), 1.17−1.37 (2H, m, CH_a,H$_b$-6, CH_a,H$_b$-7), 1.41−1.52 (1H, m, CH$_a$,H_b-6), 1.63−1.74 (1H, m, CH$_a$,H_b-7), 1.95−2.08 (7H, m, CH_a,H$_b$-5, 2 × OAc), 2.22 (1H, dd, *J* = 9.3, 6.9 Hz, CH_a,H$_b$-3), 2.34−2.43 (1H, m, 8a-H), 2.74−2.84 (1H, m, CH$_a$,H_b-5), 3.45 (1H, dd, *J* = 9.4, 6.9 Hz, CH$_a$,H_b-3), 3.57−3.68 (1H, m, 8-H), 4.92 (1H, t, *J* = 7.4 Hz, 1-H), 5.17 (1H, dt, *J* = 7.4, 6.9 Hz, 2-H), 7.32−7.46 (6H, m, H-Ar), 7.64−7.72 (4H, m, H-Ar); δ_C (75 MHz; $CDCl_3$) 19.2 (C, Si^{t}Bu), 20.6 (CH_3, OAc), 20.7 (CH_3, OAc), 23.7 (CH_2, C-6), 26.8 (CH_3, Si^{t}Bu), 34.3 (CH_2, C-7), 51.2 (CH_2, C-5), 58.3 (CH_2, C-3), 68.0 (CH, C-2), 71.2 (CH, C-8a), 73.6 (CH, C-8), 74.7 (CH, C-1), 127.4 (CH, C-Ar), 127.7 (CH, C-Ar), 129.5 (CH, C-Ar), 129.7 (CH, C-Ar), 133.4 (C, C-Ar), 134.7 (C, C-Ar), 135.7 (CH, C-Ar), 135.8 (CH, C-Ar), 169.6 (C═O, OAc), 170.0 (C═O, OAc); HRMS (ESI) $C_{28}H_{38}NO_5Si$ [MH$^+$] calcd 496.2514, obsd 496.2521.

(1*R*,2*S*,8*S*,8a*S*)-Octahydroindolizine-1,2,8-triol. (+)-Swainsonine (+)-(4). A solution of indolizidine **22** (0.40 g, 0.81 mmol), Et_3N (1.57 mL, 11.3 mmol), and triethylamine trihydrofluoride (1.32 mL, 8.07 mmol) in MeCN (25 mL) was stirred at 80 °C for 5 d. The reaction was cooled to rt and saturated aqueous $NaHCO_3$ (50 mL) added. The aqueous phase was extracted with EtOAc (3 × 80 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with MeOH/CH_2Cl_2 (gradient 1:99 to 3:97), to give the diacetate (0.182 g, 88%) as a tan solid. Recrystallization from Et_2O/hexanes (1:1) yielded colorless needles. mp 126−128 °C; $[\alpha]_D^{20}$ −58.8 (*c* 1.04, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3338, 2961, 2809, 1727, 1417, 1371, 1217, 1032; δ_H (300 MHz; $CDCl_3$) 1.23 (1H, tdd, *J* = 12.5, 11.0, 5.3 Hz, CH_a,H$_b$-7), 1.54−1.77 (2H, m, C-6), 1.84−1.98 (2H, m, H-8a, CH_a,H$_b$-5), 2.02−2.14 (4H, m, 2-OAc, CH$_a$,H_b-7), 2.17 (3H, s, 1-OAc), 2.60 (1H, dd, *J* = 11.0, 8.2 Hz, CH_a,H$_b$-3), 2.97−3.07 (1H, m, CH$_a$,H_b-5), 3.09 (1H, br s, O*H*), 3.20 (1H, dd, *J* = 11.0, 2.3 Hz, CH$_a$,H_b-3), 3.49 (1H, ddd, *J* = 10.8, 8.9, 4.7 Hz, H-8), 5.16 (1H, ddd, *J* = 8.2, 6.3, 2.3 Hz, H-2), 5.47 (1H, dd, *J* = 6.3, 3.6 Hz, H-1); δ_C (75 MHz; $CDCl_3$) 20.5 (CH_3, 2-OAc), 20.6 (CH_3, 1-OAc), 23.2 (CH_2, C-6), 31.5 (CH_2, C-7), 51.8 (CH_2, C-5), 58.5 (CH_2, C-3), 65.9 (CH, C-8), 70.6 (CH, C-2), 71.8 (CH, C-1), 72.7 (CH, C-8a), 170.3 (C═O, 2-OAc), 171.9 (C═O, 1-OAc); HRMS (ESI) $C_{12}H_{20}NO_5$ [MH$^+$] calcd 258.1336, obsd 258.1333.

A solution of NaOMe (1 M, 0.14 mL, 0.14 mmol) was added dropwise to a solution of the diacetate prepared above (0.073 g, 0.28 mmol) in MeOH (10 mL) at rt and the mixture stirred for 1 h. The solution was concentrated under reduced pressure and the residue purified by reverse phase chromatography (C-18), eluting with milli-Q water to give the title compound (0.039 g, 80%) as a white solid. mp 143−144 °C (lit.[32a] 143−145 °C); $[\alpha]_D^{20}$ +79.9 (*c* 0.37, MeOH);

dx.doi.org/10.1021/jo3011914 | J. Org. Chem. 2012, 77, 7968−7980

[lit.[32a] $[\alpha]_D^{24}$ +83.3 (*c* 0.50, MeOH)]; ν_{max}(neat)/cm^{-1} 3364, 2941, 2800, 1316, 1072, 1023; δ_H (400 MHz; CD_3OD) 1.20 (1H, tdd, *J* = 12.7, 11.2, 4.9 Hz, CH_a,H_b-7), 1.52−1.73 (2H, m, H-6), 1.70 (1H, dd, *J* = 9.2, 3.3 Hz, H-8a), 1.87 (1H, td, *J* = 11.6, 3.1 Hz, CH_a,H_b-5), 1.98−2.06 (1H, m, CH$_a$,H_b-7), 2.41 (1H, dd, *J* = 10.4, 6.8 Hz, CH_a,H_b-3), 2.88−2.95 (2H, m, CH$_a$,H_b-3, CH$_a$,H_b-5), 3.79 (1H, ddd, *J* = 11.0, 9.2, 4.7 Hz, H-8), 4.18−4.25 (2H, m, H-1, H-2); δ_C (100 MHz; CD_3OD) 24.5 (CH_2, C-6), 34.1 (CH_2, C-7), 53.1 (CH_2, C-5), 63.1 (CH_2, C-3), 67.0 (CH, C-8), 69.8 (CH, C-2), 70.7 (CH, C-1), 75.2 (CH, C-8a); HRMS (ESI) $C_8H_{16}NO_3$ [MH$^+$] calcd 174.1125, obsd 174.1120.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(4-(*tert*-butyldimethylsilyloxy)but-1-ynyl)piperidin-1-ol (25). A solution of *n*-BuLi (1.6 M in hexanes, 0.39 mL, 0.63 mmol) was added dropwise to a solution of 4-(*tert*-butyldimethylsilyloxy)but-1-yne (0.14 g, 0.76 mmol) in THF (7 mL) at −78 °C. The solution was stirred for 15 min and then warmed to 0 °C and stirred for an additional 30 min. A solution of nitrone **5b** (0.18 g, 0.50 mmol) in THF (3 mL) was added at −78 °C and the mixture warmed to 0 °C and stirred for a further 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with EtOAc/hexanes (gradient 1:19 to 1:9), to give the title compound (0.23 g, 85%) as a colorless oil. $[\alpha]_D^{20}$ −21.0 (*c* 1.06, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3205, 3072, 2952, 2929, 2856, 1471, 1427, 1102; δ_H (400 MHz; DMSO-d_6, 393 K) 0.03 (6H, s, $SiMe_2$), 0.86 (9H, s, Si^{t}Bu), 1.06 (9H, s, Si^{t}Bu), 1.22−1.42 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.59−1.77 (2H, m, CH$_a$,H_b-4, CH$_a$,H_b-5), 2.28 (2H, td, *J* = 7.1, 1.9 Hz, H-2′), 2.52−2.63 (1H, m, CH_a,H_b-6), 2.89−2.97 (1H, m, CH$_a$,H_b-6), 3.47 (1H, br s, H-2), 3.60 (2H, t, *J* = 7.1 Hz, H-1′), 3.87−3.96 (1H, m, H-3), 7.37−7.48 (6H, m, H-Ar), 7.54 (1H, br s, NO*H*), 7.63−7.74 (4H, m, H-Ar); δ_C (100 MHz; DMSO-d_6, 393 K) −5.9 (CH_3, $SiMe_2$), 17.3 (C, Si^{t}Bu), 18.4 (C, Si^{t}Bu), 19.6 (CH_2, C-5), 22.3 (CH_2, C-2′), 25.2 (CH_3, Si^{t}Bu), 26.3 (CH_3, Si^{t}Bu), 29.5 (CH_2, C-4), 54.3 (CH_2, C-6), 61.1 (CH_2, C-1′), 64.4 (CH, C-2), 71.9 (CH, C-3), 78.8 (C, C-2′), 81.5 (C, C-3′), 127.0 (CH, C-Ar), 127.0 (CH, C-Ar), 129.0 (CH, C-Ar), 129.1 (CH, C-Ar), 133.3 (C, C-Ar), 133.5 (C, C-Ar), 134.8 (CH, C-Ar), 134.8 (CH, C-Ar); HRMS (ESI) $C_{31}H_{48}NO_3Si_2$ [MH$^+$] calcd 538.3167, obsd 538.3160.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(4-hydroxybutyl)-piperidine (26). Pd/C (96 mg) was added portionwise to a solution of alkyne **25** (0.64 g, 1.19 mmol) in MeOH (15 mL) and the mixture stirred under an atmosphere of hydrogen for 12 h. The reaction mixture was filtered through Celite and the filtrate concentrated under reduced pressure to give a yellow oil. The residue was purified by flash column chromatography, eluting with EtOAc/hexanes (gradient 1:19 to 1:9), giving the alkane (0.58 g, 90%) as a colorless oil. Indium powder (0.22 g, 1.93 mmol) was added to a solution of the above prepared alkane (0.53 g, 0.97 mmol) in EtOH (22 mL) and the suspension heated to 80 °C. Aqueous HCl (2 M, 3 mL) was added and the suspension heated to 100 °C and stirred for 2 h. The reaction mixture was cooled to rt and the pH adjusted to 10 by the dropwise addition of an aqueous solution of 2 M NaOH. The mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with brine (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with MeOH/CH_2Cl_2 (gradient 1:19 to 1:17), to give the title compound (0.36 g, 91%) as a yellow oil. $[\alpha]_D^{20}$ +21.2 (*c* 0.92, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3252, 3071 2930, 2857, 1427, 1104, 1074; δ_H (400 MHz; $CDCl_3$) 1.05 (9H, s, Si^{t}Bu), 1.12−1.61 (8H, m, H-3′, H-5, H-2′, CH_a,H_b-4′, CH_a,H_b-4), 1.72−1.82 (1H, m, CH$_a$,H_b-4), 1.84−1.96 (1H, m, CH$_a$,H_b-4′), 2.44−2.55 (2H, m, H-2, CH_a,H_b-6), 2.80−2.91 (1H, m, CH$_a$,H_b-6), 2.96 (2H, m, N*H*, O*H*), 3.26−3.35 (1H, m, H-3), 3.46−3.59 (2H, m, H-1′), 7.32−7.45 (6H, m, H-Ar), 7.63−7.73 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 19.3 (C, Si^{t}Bu), 21.5 (CH_2, C-2′), 25.1 (CH_2, C-5), 26.9 (CH_3, Si^{t}Bu), 31.3 (CH_2, C-1′), 32.4 (CH_2, C-3′), 33.6 (CH_2, C-4), 45.1 (CH_2, C-6), 61.9 (CH_2, C-4′), 62.2 (CH, C-2), 73.5 (CH, C-3), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 133.6 (C, C-Ar), 134.5 (C, C-Ar), 135.8 (CH, C-Ar), 135.8 (CH, C-Ar); HRMS (ESI) $C_{25}H_{38}NO_2Si$ [MH$^+$] calcd 412.2666, obsd 412.2663.

(1*S*,9a*S*)-1-(*tert*-Butyldiphenylsilyloxy)octahydro-1*H*-quinolizine (23). CBr_4 (0.092 g, 0.29 mmol) and PPh_3 (0.080 g, 0.37 mmol) were added portionwise to a solution of amino alcohol **26** (0.10 g, 0.25 mmol) in CH_2Cl_2 (4 mL) at 0 °C and the mixture stirred for 30 min. Et_3N (0.10 mL, 0.74 mmol) was added and the mixture stirred for 1 h at 0 °C and then a further 6 h at rt. Water (5 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with EtOAc/hexanes (gradient 1:9 to 1:1), to give the title compound (0.068 g, 70%) as a yellow oil. $[\alpha]_D^{20}$ +25.4 (*c* 1.40, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2931, 2856, 1427, 1110, 1084; δ_H (400 MHz; $CDCl_3$) 0.93−1.09 (10H, m, CH_a,H_b-9, Si^{t}Bu), 1.17−1.33 (2H, m, CH_a,H_b-2, CH_a,H_b-8), 1.33−1.49 (2H, m, H-3), 1.49−1.63 (2H, m, H-7), 1.66−1.73 (1H, m, CH$_a$,H_b-2), 1.73−1.82 (2H, m, H-9a, CH$_a$,H_b-8), 1.95 (1H, td, *J* = 11.6, 3.2 Hz, CH_a,H_b-4), 2.02 (1H, td, *J* = 11.8, 3.3 Hz, CH_a,H_b-6), 2.28−2.37 (1H, m, CH$_a$,H_b-9), 2.58−2.66 (1H, m, CH$_a$,H_b-4), 2.75−2.84 (1H, m, CH$_a$,H_b-6), 3.38−3.47 (1H, m, H-1), 7.30−7.43 (6H, m, H-Ar), 7.65−7.72 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 19.4 (C, Si^{t}Bu), 23.1 (CH_2, C-3), 24.2 (CH_2, C-8), 25.6 (CH_2, C-7), 27.0 (CH_3, Si^{t}Bu), 29.1 (CH_2, C-9), 34.3 (CH_2, C-2), 55.8 (CH_2, C-4), 56.2 (CH_2, C-6), 68.9 (CH, C-9a), 74.6 (CH, C-1), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.3 (CH, C-Ar), 129.5 (CH, C-Ar), 133.7 (C, C-Ar), 134.9 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (ESI) $C_{25}H_{36}NOSi$ [MH$^+$] calcd 394.2561, obsd 394.2564.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

CIF and ORTEP diagrams of compounds **8** and **19**; ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: v.caprio@mmu.ac.uk; d.barker@auckland.ac.nz

Present Addresses

[∥]Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470, Müllheim-an-der-Ruhr, Germany.

[§]School of Chemistry, Centre for Green Chemistry, Monash University, PO Box 23, Clayton, Victoria 3800, Australia.

[‡]School of Science and the Environment, Manchester Metropolitan University, All Saints Campus, Oxford Road, Manchester, M15 6BH, UK.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to The University of Auckland Staff Research Fund and Doctoral Scholarship Scheme for funding of this work.

■ REFERENCES

(1) For recent reviews covering the synthesis of 2-substituted-3-hydroxypiperidines, see: (a) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (b) Winchester, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645. (c) Davis, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 652. (d) Wijdeven, M. A.; Willemsen, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2010**, 2831.

(2) (a) Koepfli, J. B.; Mead, J. F.; Brockman, J. A. *J. Am. Chem. Soc.* **1947**, *69*, 1837. (b) Koepfli, J. B.; Mead, J. F.; Brockman, J. A. *J. Am. Chem. Soc.* **1949**, *71*, 1048.

(3) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 495. (b) Yagi, M.; Kouno, T.; Aoyagi, Y.; Murai, H. *J. Agric. Chem. Soc. Jpn.* **1976**, *50*, 571. *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, I.; Martin, O. R., Eds.; Wiley-VCH: Chichester, 2007.
(4) (a) Ratle, G.; Monseur, X.; Das, B. C.; Yassi, J.; Khuong-Huu, Q.; Goutarel, R. *Bull. Soc. Chem. Fr.* **1966**, *9*, 2945. (b) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Gouratel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425.
(5) (a) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055. (b) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29.
(6) For recent reviews covering cycloadditions to nitrones, see: (a) Frederickson, M. *Tetrahedron* **1997**, *53*, 403. (b) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905. (c) de March, P.; Figueredo, M.; Font, J. *Heterocycles* **1999**, *50*, 1213. (d) Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419. (e) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 585. (f) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (g) Kanemasa, S. *Heterocycles* **2010**, *82*, 87. (h) Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2010**, 3363.
(7) For reviews covering nucleophilic additions to nitrones, see: (a) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759. (b) Lombardo, M.; Trombini, C. *Curr. Org. Chem.* **2002**, *6*, 695.
(8) (a) Masson, G.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1772. (b) Riber, D.; Skrydstrup, T. *Org. Lett.* **2003**, *5*, 229. (c) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2265. (d) Masson, G.; Zeghida, W.; Cividino, P.; Py, S.; Vallée, Y. *Synlett* **2003**, 1527. (e) Johannesen, S. A.; Albu, S.; Hazell, R. G.; Skrydstrup, T. *Chem. Commun.* **2004**, 1962. (f) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 3953. (g) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459. (h) Masson, G.; Philouze, C.; Py, S. *Org. Biomol. Chem.* **2005**, *3*, 2067. (i) Cividino, P.; Py, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2007**, *72*, 485. (j) Desvergnes, S.; Desvergnes, V.; Martin, O. R.; Itoh, K.; Liu, H.-W.; Py, S. *Bioorg. Med. Chem.* **2007**, *15*, 6443. (k) Burchak, O. N.; Philouze, C.; Chavant, P. Y.; Py, S. *Org. Lett.* **2008**, *10*, 3021. (l) Rehák, J.; Fišera, L.; Podolan, G.; Kožíšek, J.; Perašínová, L. *Synlett* **2008**, 1260. (m) Burchak, O. N.; Py, S. *Tetrahedron* **2009**, *65*, 7333. (n) Wu, S.-F.; Zheng, X.; Ruan, Y.-P.; Huang, P.-Q. *Org. Biomol. Chem.* **2009**, *7*, 2967. (o) Wu, S.-F.; Ruan, Y.-P.; Zheng, X.; Huang, P.-Q. *Tetrahedron* **2010**, *66*, 1653. (p) Burchak, O. N.; Masson, G.; Py, S. *Synlett* **2010**, 1623.
(9) (a) Gössinger, E. *Monatsh. Chem.* **1982**, *113*, 495. (b) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Durif, A.; Averbuch, M.-T.; Pierre, J.-L. *Tetrahedron Lett.* **1998**, *39*, 2565. (c) Peer, A.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 1044. (d) Berge, J. M.; Copley, R. C. B.; Eggleston, D. S.; Hamprecht, D. W.; Jarvest, R. L.; Mensah, L. M.; O'Hanlon, P. J.; Pope, A. *Bioog. Med. Chem. Lett.* **2000**, *10*, 1811. (e) Eriksson, C.; Sjödin, K.; Schlyter, F.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2006**, *17*, 1074. (f) Chan, T.-H.; Chang, Y.-F.; Hsu, J.-J.; Cheng, W.-C. *Eur. J. Org. Chem.* **2010**, 5555.
(10) (a) Gössinger, E. *Tetrahedron Lett.* **1980**, *21*, 2229. (b) Gössinger, E. *Monatsh. Chem.* **1981**, *112*, 1017. (c) Lathbury, D.; Gallagher, T. *Tetrahedron Lett.* **1985**, *26*, 6249. (d) Tufariello, J. J.; Puglis, J. M. *Tetrahedron Lett.* **1986**, *27*, 1489. (e) Adams, D. R.; Carruthers, W.; Williams, M. J.; Crowley, P. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1507. (f) Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J. *J. Chem. Soc. Chem. Commun.* **1992**, 1537. (g) Herczegh, P.; Kovács, I.; Szilágyi, L.; Varga, T.; Dinya, Z.; Sztaricskai, F. *Tetrahedron Lett.* **1993**, *34*, 1211. (h) van den Broek, L. A. G. M. *Tetrahedron* **1996**, *52*, 4467. (i) Chackalamannil, S.; Wang, Y. *Tetrahedron* **1997**, *53*, 11203. (j) Chackalamannil, S.; Davies, R. J.; Wang, Y.; Asberom, T.; Doller, D.; Wong, J.; Leone, D.; McPhail, A. T. *J. Org. Chem.* **1999**, *64*, 1932. (k) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (l) Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2001**, *3*, 953. (m) Kikuchi, H.; Tasaka, H.; Hirai, S.; Takaya, Y.; Iwabuchi, Y.; Ooi, H.; Hatakeyama, S.; Kim, H.-S.; Wataya, N Y.; Oshima, Y. *J. Med. Chem.* **2002**, *45*, 2563. (n) Brandi, A.; Cicchi, S.; Paschetta, V.; Gomez Pardo, D.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 9357. (o) Alsbaiee, A.; Ali, S. A. *Tetrahedron* **2008**, *64*, 6635. (p) Moosa, B. A.; Ali, S. A. *Tetrahedron* **2009**, *65*, 8231.
(11) For the most recent reviews covering the reactions of chiral pyrroline *N*-oxides, see: (a) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.
(12) Ashoorzadeh, A.; Archibald, G.; Caprio, V. *Tetrahedron* **2009**, *65*, 4671.
(13) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000.
(14) Ikunaka, M.; Matsumoto, J.; Fujima, Y.; Hirayama, Y. *Org. Process Res. Dev.* **2002**, *6*, 49.
(15) Yamakawa, T.; Masaki, M.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2730.
(16) Ali, S. A. *Tetrahedron Lett.* **1993**, *34*, 5325.
(17) Goti, A.; De Sarlo, F.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6571.
(18) Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **2001**, *42*, 6503.
(19) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743.
(20) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
(21) Thesing, J.; Mayer, H. *Chem. Ber.* **1956**, *89*, 2159.
(22) Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 4285.
(23) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349.
(24) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773.
(25) Pulz, R.; Cicchi, S.; Brandi, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, 1153.
(26) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Synlett* **2002**, 817.
(27) (a) Pulz, R.; Watanabe, T.; Schade, W.; Reissig, H.-U. *Synlett* **2000**, 983. (b) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353.
(28) (a) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353. (b) Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S.; Goti, A. *Eur. J. Org. Chem.* **2004**, 776.
(29) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001.
(30) (a) Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193. (b) Huang, P.-Q.; Wei, B.-G.; Ruan, Y.-P. *Synlett* **2003**, 1663. (c) Emmanuvel, L.; Kamble, D. A.; Sudalai, A. *Tetrahedron: Asymmetry* **2009**, *20*, 84.
(31) (a) Déchamps, I.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2007**, *63*, 9082. (b) Bates, R. W.; Dewy, M. R. *Org. Lett.* **2009**, *11*, 3706.
(32) For synthetic routes to (+)-swainsonine, see: (a) Oishi, T.; Iwakuma, T.; Hirama, M.; Itô, S. *Synlett* **1995**, 404. (b) Davis, B.; Bell, A. A.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Jones, M. G.; Smith, C.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8565. (c) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609. (d) Guo, H.; O'Doherty, G. A. *Tetrahedron* **2008**, *64*, 304. (e) Håkansson, A. E.; van Ameijde, J.; Horne, G.; Nash, R. J.; Wormald, M. R.; Kato, A.; Besra, G. S.; Gurcha, S.; Fleet, G. W. J. *Tetrahedron Lett.* **2008**, *49*, 179. (f) Alam, M. A.; Kumar, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2008**, 4972. (g) Chen, M.-J.; Tsai, Y.-M. *Tetrahedron* **2011**, *67*, 1564. (h) Chooprayoon, S.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Org. Biomol. Chem.* **2011**, *9*, 531.
(33) (a) Mukai, C.; Sugimoto, Y.-i.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281. (b) de Vicente, J.; Arrayás, R. G.; Cañada, J.; Carretero, J. C. *Synlett* **2000**, 53. (c) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325. (d) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774. (e) Ceccon, J.; Greene, A. E.; Poisson, J. F. *Org. Lett.* **2006**, *8*, 4739. (f) Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J. H.; Kang, S. H. *Chem.—Eur. J.* **2008**, *14*, 1023.
(34) For example, see: (a) Campos, K. R.; Cai, D.; Journet, M.; Kowal, J. J.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 3634. (b) Campos, K. R.; Journet, M.; Cai, D.; Kowal, J. J.; Lee, S.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2003**, *68*, 2338.
(35) For a previous example, see: Xu, Q.; Rozners, E. *Org. Lett.* **2005**, *7*, 2821.

(36) Fitch, R. W.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345.
(37) For synthetic routes to epiquinamide, see: (a) Wijdeven, M. A.; Botman, P. N. M.; Wijtmans, R.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2005**, *7*, 4005. (b) Kanakubo, A.; Gray, D.; Innocent, N.; Wonnacott, S.; Gallagher, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4648. (c) Suyama, T. L.; Gerwick, W. H. *Org. Lett.* **2006**, *8*, 4541. (d) Huang, P.-Q.; Guo, Z.-Q.; Ruan, Y.-P. *Org. Lett.* **2006**, *8*, 1435. (e) Tong, S. T.; Barker, D. *Tetrahedron Lett.* **2006**, *47*, 5017. (f) Voituriez, A.; Ferreira, F.; Pérez-Luna, A.; Chemla, F. *Org. Lett.* **2007**, *9*, 4705. (g) Wijdeven, M. A.; Wijtmans, R.; van den Berg, R. J. F.; Noorduin, W.; Schoemaker, H. E.; Sonke, T.; van Delft, F. L.; Blaauw, R. H.; Fitch, R. W.; Spande, T. F.; Daly, J. W.; Rutjes, F. P. J. T. *Org. Lett.* **2008**, *10*, 4001. (h) Airiau, E.; Spangenberg, T.; Girard, N.; Breit, B.; Mann, A. *Org. Lett.* **2010**, *12*, 528. (i) Chandrasekhar, S.; Parida, B. B.; Rambabu, C. *Tetrahedron Lett.* **2009**, *50*, 3294. (j) Fitch, R. W.; Saturgeon, G. D.; Patel, S. R.; Spande, T. F.; Garraffo, H. M.; Daly, J. W.; Blaauw, R. H. *J. Nat. Prod.* **2009**, *72*, 243. (k) Ghosh, S.; Shashidhar, J. *Tetrahedron Lett.* **2009**, *50*, 1177. (l) Srivastava, A. K.; Das, S. K.; Panda, G. *Tetrahedron* **2009**, *65*, 5322. (m) Tuan, L. A.; Pyeon, H.; Kim, G. *Tetrahedron Lett.* **2010**, *51*, 157. (n) Santos, L. S.; Mirabal-Gallardo, Y.; Shankaraiah, N.; Simirgiotis, M. J. *Synthesis* **2011**, 51.
(38) Couch, J. F. *J. Am. Chem. Soc.* **1934**, *56*, 2434.
(39) For synthetic routes to lupinine, see: (a) Leonard, N. J.; Conrow, K.; Fulmer, R. W. *J. Org. Chem.* **1957**, *22*, 1445. (b) Goldberg, S. I.; Ragade, I. *J. Org. Chem.* **1967**, *32*, 1046. (c) Okita, M.; Wakamatsu, T.; Ban, Y. *Heterocycles* **1983**, *20*, 401. (d) Takahata, H.; Yamabe, K.; Suzuki, T.; Yamazaki, T. *Chem. Pharm. Bull.* **1986**, *34*, 4523. (e) Haddad, M.; Célérier, J.-P.; Lhommet, G. *Heterocycles* **1987**, *26*, 2335. (f) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325. (g) Morley, C.; Knight, D. W.; Share, A. C. *Tetrahedron: Asymmetry* **1990**, *1*, 147. (h) Hua, D. H.; Miao, S. W.; Bravo, A. A.; Takemoto, D. J. *Synthesis* **1991**, 970. (i) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215. (j) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732. (k) Wanner, M. J.; Koomen, G.-J. *J. Org. Chem.* **1996**, *61*, 5581. (l) Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349. (m) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368. (n) Agami, C.; Dechoux, L.; Hebbe, S.; Ménard, C. *Tetrahedron* **2004**, *60*, 5433. (o) Ma, S.; Ni, B. *Chem.—Eur. J.* **2004**, *10*, 3286. (p) Chang, M.-Y.; Tai, H.-M.; Lin, C.-H.; Chang, N.-C. *Heterocycles* **2005**, *65*, 395. (q) Pohmakotr, M.; Seubsai, A.; Numeechai, P.; Tuchinda, P. *Synthesis* **2008**, 1733.
(40) Saito, K.; Yoshino, T.; Tsai, S.; Ohmiya, S.; Kubo, H.; Otomasu, H.; Murakoshi, I. *Chem. Pharm. Bull.* **1987**, *35*, 1308.