JOC Article

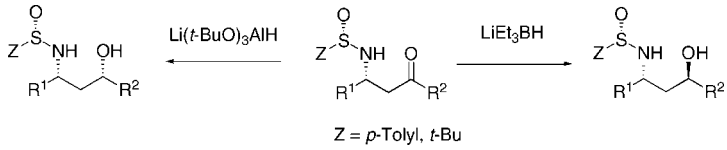
Asymmetric Synthesis of Acyclic 1,3-Amino Alcohols by Reduction of *N*-Sulfinyl *β*-Amino Ketones. Formal Synthesis of (−)-Pinidinol and (+)- Epipinidinol†

Franklin A. Davis,* Paul M. Gaspari, Brad M. Nolt, and Peng Xu

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19096

fdavis@temple.edu

Received July 25, 2008



Stereoselective reduction of acyclic *N*-sulfinyl *β*-amino ketones with ($LiEt_3BH$) and $Li(t\text{-}BuO)_3AlH$, respectively, gave *anti*- and *syn*-1,3-amino alcohols with excellent selectivity. A formal asymmetric synthesis of the hydroxy piperidine alkaloids (−)-pinidinol and (+)-epipinidinol from a common *N*-sulfinyl *β*-amino ketone ketal precursor was developed. The pinidinol piperidine ring was formed via a novel acid-catalyzed cascade reaction of a *N*-sulfinylamino silyl protected alcohol ketal.

Acyclic 1,3-amino alcohols are key structural components of numerous medicinal compounds as diverse as HIV protease inhibitors,[1] *μ*-opioid receptor agonists,[2] and the potent antibiotic negamycin.[3] This functionality has also been utilized in selective serotonin reuptake inhibitor antidepressants[4] and in the study of mutagenic deoxyguanosine oligonucleotides.[5] Many natural products such as the sedum alkaloids,[6] paliclavine,[7] and the Micronesian marine sponge toxin dysiherbaine[8] contain the 1,3-amino alcohol moiety. Additionally, 1,3-amino alcohols are useful chiral building blocks in asymmetric synthesis functioning as chiral ligands and auxiliaries.[9]

Several racemic syntheses of 1,3-amino alcohols have been described and include reductions of *β*-amino ketones,[10] reductions of *β*-hydroxy imines and oximes,[11] and the addition of organometallic reagents to *β*-amino aldehydes and ketones.[12] Despite the prevalence and importance of 1,3-amino alcohols, there are few general methods for their asymmetric synthesis, and many of these are target specific.[13,14] Undoubtedly, this is due to the lack of sources of enantiomerically pure precursors. Ellman and co-workers reported that the reduction of enantiopure sulfinimine-derived *β*-hydroxyl *N*-sulfinyl imines affords *syn*- and *anti*-1,3-amino alcohols in high diastereomeric ratio.[15]

† This paper is dedicated to the memory of Albert I. Meyers, a friend and outstanding scientist, whose pioneering contributions to the art of asymmetric synthesis continue to inspire.

(1) (a) Kempf, D. J.; Marsh, K. C.; Denissen, J. F.; McDonald, E.; Vasavanonda, S.; Flentge, C. A.; Green, B. E.; Fino, L.; Park, C. H.; Kong, X.-P.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H. L.; Robins, T.; Stewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard, J. M.; Norbeck, D. W. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2484. (b) Haight, A. R.; Stuk, T. L.; Allen, M. S.; Bhagavatula, L.; Fitzgerald, M.; Hannick, S. M.; Kerdesky, F. A. J.; Menzia, J. A.; Parekh, S. I.; Robbins, T. A.; Scarpetti, D.; Tien, J.-H. J. *Org. Process Res. Dev.* **1999**, *3*, 94. (c) Sham, H. L.; Zhao, C.; Li, L.; Betebenner, D. A.; Saldivar, A.; Vasavanonda, S.; Kempf, D. J.; Plattner, J. J.; Norbeck, D. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3101.

(2) Shi, Z.; Harrison, B. A.; Verdine, G. L. *Org. Lett.* **2003**, *5*, 633.

(3) (a) Kondo, S.; Shibahara, S.; Takahashi, S.; Maeda, K.; Umezawa, H.; Ohno, M. *J. Am. Chem. Soc.* **1971**, *93*, 6305. (b) Raju, B.; Mortell, K.; Anandan, S.; O'Dowd, H.; Gao, H.; Gomez, M.; Hackbarth, C.; Wu, C.; Wang, W.; Yuan, Z.; White, R.; Trias, J.; Patel, D. V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2413.

(4) (a) Carlier, P. R.; Lo, M. M.-C.; Lo, P. C -K.; Richelson, E.; Tatsumi, M.; Reynolds, I. J.; Sharma, T. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 487–492.

(5) Nechev, L. V.; Kozedov, I.; Harris, C. M.; Harris, T. M. *Chem. Res. Toxicol.* **2001**, *14*, 1506.

(6) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957.

(7) Kozikowski, A. P.; Chen, Y.-Y. *J. Org. Chem.* **1981**, *46*, 5248.

(8) Sakai, R.; Kamiya, H.; Murata, M.; Shimamoto, K. *J. Am. Chem. Soc.* **1997**, *119*, 4112.

(9) For a review on the use of 1,3-amino alcohols in asymmetric synthesis, see: (a) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.

(10) (a) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1985**, *50*, 4052. (b) Pilli, R. A.; Russowsky, D.; Dias, L. C. J. *Chem. Soc. Perkin Trans. 1* **1990**, 1213. (c) Barluenga, J.; Aguilar, E.; Fustero, S.; Olano, B.; Viado, A. *J. Org. Chem.* **1992**, *57*, 1219, and references cited therein. (d) Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, *4*, 3131.

(11) (a) Narasaka, K.; Ukaji, Y.; Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 525. (b) Williams, D. R.; Osterhout, M. H. *J. Am. Chem. Soc.* **1992**, *114*, 8750. (c) Veenstra, S. J.; Kinderman, S. S. *Synlett* **2001**, 1109.

(12) Toujas, J.-L.; Toupet, L.; Vaultier, M. *Tetrahedron* **2000**, *56*, 2665.

(13) For a review see: Tramontini, M. *Synthesis* **1982**, 605.

(14) Reduction of enantiopure *β*-amino ketones: (a) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623. (b) Davis, F. A.; Prasad, K. R.; Nolt, B. M.; Wu, Y. *Org. Lett.* **2003**, *5*, 923. (c) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855. (d) Kennedy, A.; Nelson, A.; Perry, A. *Synlett* **2004**, 967. (e) Huguenot, F.; Brigaud, T. *J. Org. Chem.* **2006**, *71*, 2159.

(15) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518.

10.1021/jo801653c CCC: $40.75 © 2008 American Chemical Society
Published on Web 11/06/2008

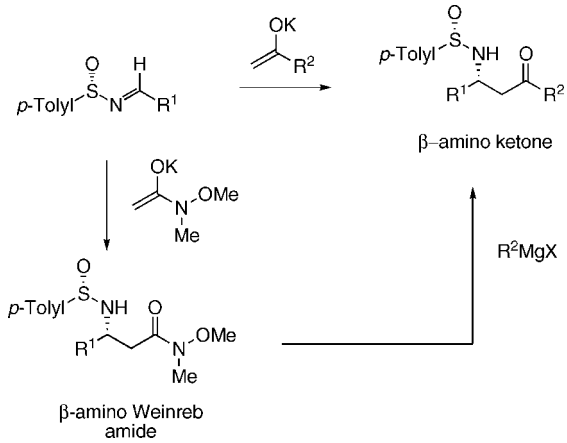


FIGURE 1. Asymmetric synthesis of β-amino ketones.

However, because the β-hydroxyl *N*-sulfinyl imines are prepared by aza-enolate addition to aldehydes this procedure may be limited.[15,16]

Studies of β-amino ketone reductions suggest that they offer the best potential for devising a general method for the asymmetric synthesis of acyclic *syn*- and *anti*-1,3-amino alcohols from a common precursor.[14] The reason why this method has not found general utility is that diverse enantiopure β-amino ketones were lacking. Acyclic enantiopure β-amino ketones are now readily available by the addition of methyl ketone enolates to sulfinimines (*N*-sulfinyl imines)[17,18] or by adding Grignard reagents to sulfinimine-derived β-amino Weinreb amides (Figure 1).[14a,b,19,20] *N*-Sulfinyl β-amino Weinreb amides, a new sulfinimine-derived chiral building block,[21,22] are prepared by the addition of Weinreb amide enolates to sulfinimines or by the reaction of lithium *N*,*O*-dimethylhydroxylamine with *N*-sulfinyl β-amino esters.[19,20] We describe here a general procedure for the asymmetric synthesis of acyclic *syn*- and *anti*-1,3-amino alcohols via the stereoselective reduction of *N*-sulfinyl β-amino ketones.

Synthesis of β-Amino Ketones *N*-(*p*-Toluenesulfinyl) Weinreb amides (S_S,3*S*)-(+)-**2a**, (S_S,3*S*)-(+)-**2b**, and (S_S,3*R*)-(+)-**2c** were prepared in 66%, 77%, and 65% yields, respectively, by addition of the corresponding sulfinimines (*S*)-(+)-**1a**−**c** to the preformed potassium enolate of *N*-methoxy-*N*-methylacetamide at −78 °C (Scheme 1). While single isomers were isolated for (+)-**2a** (R = Me) and (+)-**2b** (R = *n*-C_5H_{11}), Weinreb amide (+)-**2c** (R = Ph) was obtained as a 85:15 mixture.[19] As previously reported, *N*-(2-methylpropanesulfinyl) Weinreb amide (S_S,3*R*)-(+)-**4** was prepared by the reaction of LiN(OMe)Me with β-amino ester (S_S,3*R*)-(−)-**3** because the reaction of the Weinreb amide enolate with the sulfinimine resulted in a 52:48 mixture of diastereoisomers (Scheme 1).[19]

SCHEME 1

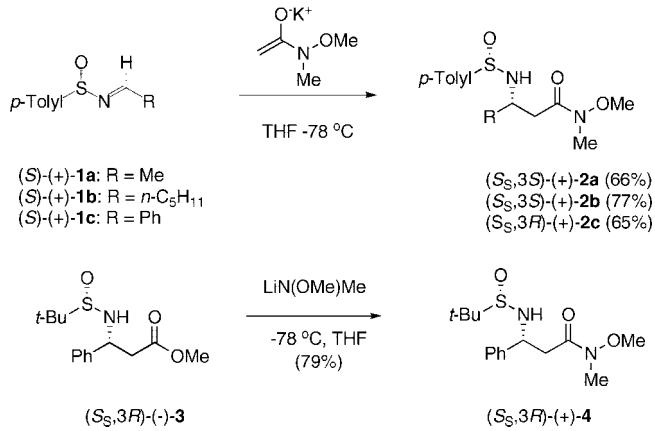


TABLE 1. Synthesis of β-Amino Ketones by Reaction of β-Amino Weinreb Amides with Grignard Reagents at −78 to 0 °C in THF

entry	Weinreb amide (R =)	Grignard reagent[a]	β-amino ketone (% isolated yield)
1	(+)-**2a** (R = Me)	PhMgBr	(+)-**5** (79)
2	(+)-**2b** (R = *n*-C_5H_{11})	MeMgBr	(+)-**6** (77)
3	(+)-**2c** (R = Ph)	MeMgBr	(+)-**7** (92)[b]
4	(+)-**2c** (R = Ph)	PhMgBr	(+)-**8** (84)[b]
5	(+)-**4** (R = Ph)	PhMgBr	(+)-**9** (83)
6	(+)-**4** (R = Ph)	MeMgBr	(+)-**10** (81%)[b]

[a] Five equivalents of Grignard reagents used. [b] Reference 19.

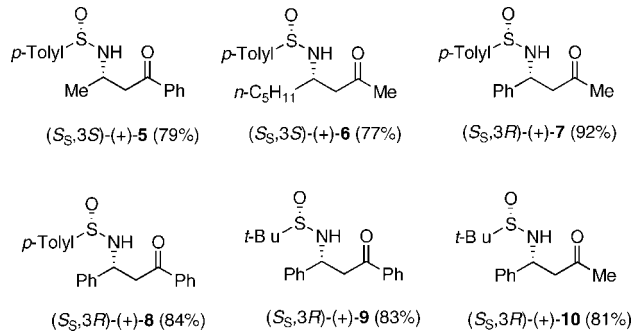
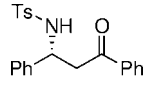


FIGURE 2. Reaction of *N*-sulfinyl Weinreb amides with Grignard reagents.

Treatment of *N*-sulfinyl β-amino Weinreb amides **2a**−**c** with 5 equiv of phenyl- or methylmagnesium bromide at −78 to 0 °C gave the corresponding β-amino ketones. The yields are good to excellent and are summarized in Table 1 and Figure 2.

Oxidation of (+)-**8** with *m*-CPBA produced (*R*)-(+)-*N*-(*p*-toluenesulfonyl)-3-amino-1,3-diphenylpropan-1-one (**11**) in 96% isolated yield.



(S_S,3*R*)-(+)-**11**

Reduction of *N*-Sulfinyl β-Amino Ketones. Pilli and coworkers suggested that the *anti*-selectivity observed in the reduction of *N*-aryl β-amino ketones with Superhydride ($LiEt_3BH$) resulted from external delivery of hydride to a *N*-coordinate boron−amine species.[10b] With $Zn(BH_4)_2$, the *syn*-

(16) Lanter, J. C.; Chen, H.; Zhang, X.; Sui, Z. *Org. Lett.* **2005**, *7*, 5905.
(17) Davis, F. A.; Yang, B. *Org. Lett.* **2003**, *5*, 5011.
(18) For recent reviews on the chemistry of sulfinimines, see: (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (b) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica. Acta* **2005**, *38*, 93. (c) Zhou, P.; Chem, B.-C.; Davis, F. A. *Tetrahedron* **2004,** *60*, 8003. (d) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
(19) Davis, F. A.; Nolt, M. B.; Wu, Y.; Prasad, K. R.; Li, D.; Yang, B.; Bowen, K.; Lee, S. H.; Eardley, J. H. *J. Org. Chem.* **2005**, *70*, 2184.
(20) Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413.
(21) For a review on S−N chemistry, which includes sulfinimines and sulfinimine-derived chiral building blocks, see: Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.
(22) For recent reviews on sulfinimine-derived chiral building blocks, see: (a) Davis, F. A.; Chao, B.; Andemichael, Y. W.; Mohanty, P. K.; Fang, T.; Burns, D. M.; Rao, A.; Szewczyk, J. M. *Heteroatom Chem.* **2002**, *13*, 486. (b) Davis, F. A.; Yang, B.; Deng, J.; Zhang, J. *ARKIVOC* **2006**, 120.

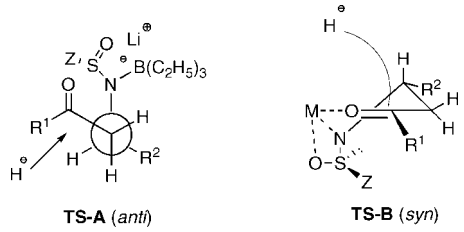
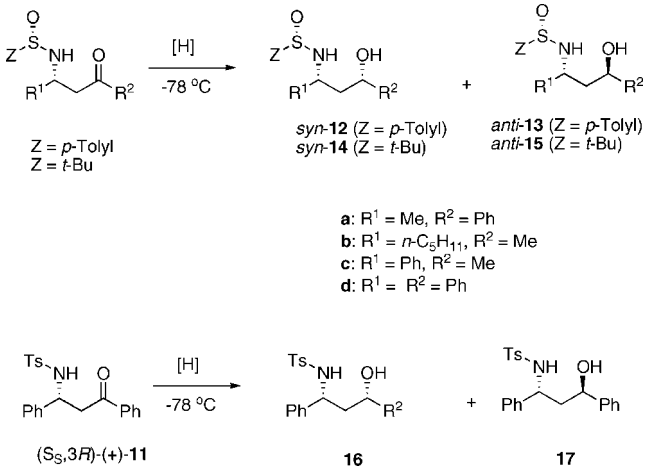


FIGURE 3. Transition-state structures for reduction of β-amino ketones.

SCHEME 2



selectivity arose via external attack of hydride on a cyclic chelated amino carbonyl species. Similar cyclic chelated intermediates have been proposed to explain the *syn*-selectivity obtained in the reductions of δ-hydroxy-β-ketoesters,[24] β-hydroxy oximes,[11a] β-hydroxy imines,[11c] and β-hydroxy *N*-sulfinyl imines.[15] Reduction of several *N*-sulfinyl β-amino ketones with $LiEt_3BH$ is reported to give *anti*-*N*-sulfinyl 1,3-amino alcohols,[14b,24] and with $Zn(BH_4)$ or $Li(t\text{-}BuO)_3AlH$ these amino ketones afforded the *syn* products.[14a,b] Although likely to be more complicated because of the presence of the *N*-sulfinyl group, transition-state structures **TS-A** and **TS-B** can be evoked to explain *anti*/*syn*-selectivity for metal hydride reductions of *N*-sulfinyl β-amino ketones (Figure 3).

Reduction of *N*-(*p*-toluenesulfinyl)-β-amino ketones (+)-**5**, (+)-**6**, (+)-**7**, and (+)-**8** with ($LiEt_3BH$) at −78 °C in CH_2Cl_2 in all cases gave the *anti*-1,3-amino alcohol **13** as the major isomer and is consistent with **TS-A** (Scheme 2, Table 2). When either R^1 or R^2 in the ketone is phenyl, a single diastereoisomer was obtained (Table 2, entries 1, 7, and 15). When both R^1 and R^2 are small alkyl groups as in (+)-**6** ($R^1 = n\text{-}C_5H_{11}$ and R^2 = Me) the *syn*/*anti* ratio was reduced to 20:80 affording the major diastereoisomer (+)-**13b** in 72% isolated yield (Table 2, entry 4). If the nitrogen substituent is a bulky *N*-(2-methylpropanesulfinyl) or *N*-tosyl group as in (+)-**9**, (+)-**10**, and (+)-**11**, lower selectivity was observed where the *syn*/*anti* ratios were 29:71, 30:70, and 1:9, respectively (Table 2, entries 26, 28, and 30). This may reflect the difficulty of $LiEt_3BH$ to efficiently coordinate with the nitrogen atom in these compounds resulting in hydride addition to both *Re* and *Si* faces of the carbonyl.

It was more difficult to achieve high syn-selectivity in reductions of *p*-tolyl *N*-sulfinyl β-amino ketones. The best *syn*-selectivity was observed with lithium tri-*tert*-butoxyaluminum hydride [$Li(t\text{-}BuO)_3AlH$]. Regardless of whether R^1 or R^2 in the *N*-sulfinyl β-amino ketone is a large or small group, the *syn*/*anti* selectivity was approximately 4:1 (Table 2, entries 3, 5, 9, and 16). Lithium aluminum hydride (LAH) also gave good *syn*-selectivity when R^1 in (+)-**8** was phenyl (82:18) but lower *syn*-selectivity when R^1 in (+)-**5** was Me (65:35) (Table 2, entries 21 and 2). Consistent with the cyclic chelated transition state **TS-B** (Figure 3), poorer coordinating solvents such as Et_2O, CH_2Cl_2, and PhMe resulted in improved selectivity as compared to THF (Table 2: compare entries 9−11 with entry 8). Addition of LiCl had little effect on the selectivity (Table 1: compare entries 6, 12, and 17 with 5, 9, and 16). The *syn* reduction selectivity for (+)-**9** ($R^1 = R^2$ = Ph) and (+)-**10** (R^1 Ph, R^2 = Me) having the *N*-*tert*-butanesulfinyl group was much better (Table 1, entries 27 and 29) where single isomers were obtained. This may reflect steric shielding of the bottom face of the carbonyl group by the large *t*-Bu group as in **TS-B** (Figure 3). Other reducing reagents such as DIBAL-H and $LiBH_4$ gave inferior results (Table 2, entries 14, 20, and 23). Interestingly, $Zn(BH_4)_2$, expected to give good *syn*-selectivity, resulted in modest *anti*-selectivity for reduction of (+)-**8** (R^1, R^2 = Ph) (Table 2, entries 19 and 24). Here the zinc ion may be coordinating with the polar sulfinyl group rather than the amino carbonyl groups. Modest *anti*-selectivity and poor *syn*-selectivity were observed for the reduction of (+)-**11** having the *N*-Ts group (Table 2, entries 30 and 31). In the latter case, this may reflect the difficulty in forming the cyclic transition state due to steric and electronic factors.

The stereochemical configurations of the *syn*- and *anti*-1,3-amino alcohols were assigned analogously to the earlier studies where $LiEt_3BH$ and $Li(t\text{-}BuO)_3AlH$ preferentially gave the *anti*- and *syn*-1,3-amino alcohols, respectively. Furthermore, as reported earlier, the C-2(OH) carbon chemical shifts of the *anti*-1,3-amino alcohols appear at higher field (lower δ values) as compared to the *syn*-alcohols.[25] The ^{13}C NMR spectra chemical shifts for C-2(OH) for *anti*-**13** and **15** appeared at δ 63−65 ppm and for *syn*-**12** and **14** at δ 67−71 ppm. In the single example where reduction of an *N*-sulfinyl-1,3-difuryl-β-amino ketone with $LiEt_3BH$ was reported to give the *syn*-1,3-amino alcohol, we believe that the configurational assignment was incorrect.[14d] Here, the reported chemical shifts for the C-OH carbons in the *syn*- and *anti*-amino alcohols appeared at δ 64.4 ppm and δ 66.4 ppm, respectively. This is just the opposite of what has been observed in all other examples.

Asymmetric Synthesis of (−)-Pinidinol and (+)-Epipindinol. (−)-Pinidinol (**18**), an alkaloid found in North American conifers of the Pinaceae family, belongs to the *Sedum* and *Lobelia* species: 2-substituted and 2,6-disubstituted piperidines with a $-CH_2CH(OH)R$ side chain (Scheme 3).[5,26] Pinidinol (**18**) exhibits antifeedent properties against the Eastern spruce budworms.[27] Other members of this class of alkaloids exhibit a broad range of biological activities that include memory-enhancing, antibiotic, anesthetic, and anti-Alzheimer properties.[5] Only four asymmetric syntheses of (−)-**18** have been described,[28] three of which are multistep, low overall yield procedures.[28a,b,d] Three of these syntheses use nonchiral amine starting materials,[28a,c,d] and none of them employ β-amino

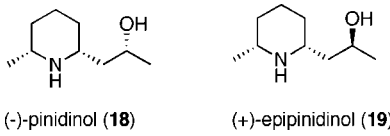
(23) Evans, D. A.; Chapman, K. T.; Carreria, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(24) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chem. Acta* **1986**, *69*, 803.
(25) Jager, V.; Buss, V. *Liebgs Ann. Chem.* **1980**, 110.
(26) Strunz, G. M.; Findlay, J. A. *Pyridine and Piperidine Alkaloids, The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p 89.
(27) Schneider, M. J.; Montali, J. A.; Hazen, D.; Stanton, C. E. *J. Nat. Prod.* **1991**, *54*, 905.

TABLE 2. Reduction of β-Amino Ketones at −78 °C

entry	β-amino ketone Z, R^1, R^2	reducing agent (equiv)	solvent	product *syn*/*anti* (dr)[a]	% yield[b]
1	(+)-**5**, *p*-tolyl, Me, Ph	$LiEt_3BH$ (5)	CH_2Cl_2	**12a**:**13a** (1:99)	73
2		LAH (3)	Et_2O	**12a**:**13a** (65:35)	70[c]
3		Li(*t*-BuO)$_3$AlH (3)	Et_2O	**12a**:**13a** (9:1)	61
4	(+)-**6**, *p*-tolyl, *n*-C_5H_{11}, Me	$LiEt_3BH$ (5)	CH_2Cl_2	**12b**:**13b** (20:80)	72
5		Li(*t*-BuO)$_3$AlH (3)	Et_2O	**12b**:**13b** (81:19)	76
6		Li(*t*-BuO)$_3$AlH (3), LiCl (10)	Et_2O	**12b**:**13b** (88:12)	61
7	(+)-**7**, *p*-tolyl, Ph, Me	$LiEt_3BH$ (5)	CH_2Cl_2	**12c**:**13c** (1:99)	87
8		Li(*t*-BuO)$_3$AlH (3)	THF	**12c**:**13c** (66:34)	76[c]
9			Et_2O	**12c**:**13c** (91:9)	70
10			CH_2Cl_2	**12c**:**13c** (91:9)	73
11			PhMe	**12c**:**13c** (89:11)	62
12		Li(*t*-BuO)$_3$AlH (3), LiCl (10)	Et_2O	**12c**:**13c** (91:9)	70
13		LAH (3)	Et_2O	**12c**:**13c** (65:35)	50[c]
15	(+)-**8**, *p*-tolyl, Ph, Ph	$LiEt_3BH$ (5)	CH_2Cl_2	**12d**:**13d** (1:99)	90
16		Li(*t*-BuO)$_3$AlH (3)	Et_2O	**12d**:**13d** (85:15)	68
17		Li(*t*-BuO)$_3$AlH (3), LiCl (10)	Et_2O	**12d**:**13d** (89:11)	71
18		$NaBH_4$ (7)	MeOH	**12d**:**13d** (55:45)	
19		$Zn(BH_4)_2$ (5)	THF[d]	**12d**:**13d** (32:68)	48[b]
20		DIBAL-H (5)	THF	**12d**:**13d** (23:77)	52[c]
21		LAH (3)	Et_2O	**12d**:**13d** (82:18)	70[c]
22		LAH (3)	THF	**12d**:**13d** (69:31)	63[c]
23		$LiBH_4/InCl_3$	Et_2O	**12d**:**13d** (69:31)	68[c]
24		$Zn(BH_4)_2$ (5)	Et_2O[d]	**12d**:**13d** (17:83)	86
25		Catecholborane (5)	THF[d]	decomposition	
26	(+)-**9**, *t*-Bu, Ph, Ph	$LiEt_3BH$ (5)	CH_2Cl_2	**14d**:**15d** (29:71)	90[c]
27		Li(*t*-BuO)$_3$AlH (3), LiCl (10)	Et_2O	**14d**:**15d** (1:99)	90
28	(+)-**10**, *t*-Bu, Ph, Me	$LiEt_3BH$ (5)	CH_2Cl_2	**14d**:**15d** (30:70)	93
29		Li(*t*-BuO)$_3$AlH (3), LiCl (10)	Et_2O	**14d**:**15d** (1:99)	90
30	(+)-**11**, Ts, Ph, Ph	$LiEt_3BH$ (5)	CH_2Cl_2	**16**:**17** (1:9)	47
31		Li(*t*-BuO)$_3$AlH (3)	Et_2O	**16**:**17** (55:45)	72[c]
32	(−)-**25**	$LiEt_3BH$	CH_2Cl_2	**27**:**26** (1:99)	90
33		Li(*t*-BuO)$_3$AlH (3)	Et_2O	**27**:**26** (54:46)	87[c]
34		Li(*t*-BuO)$_3$AlH (3), LiCl (10)	Et_2O	**27**:**26** (90:10)	72

[a] Determined by ^{1}H NMR on the crude reaction mixture. [b] Isolated yield of major diastereoisomer unless otherwise noted. [c] Combined yields of both diastereoisomers. [d] Reduction carried out at 0 °C.

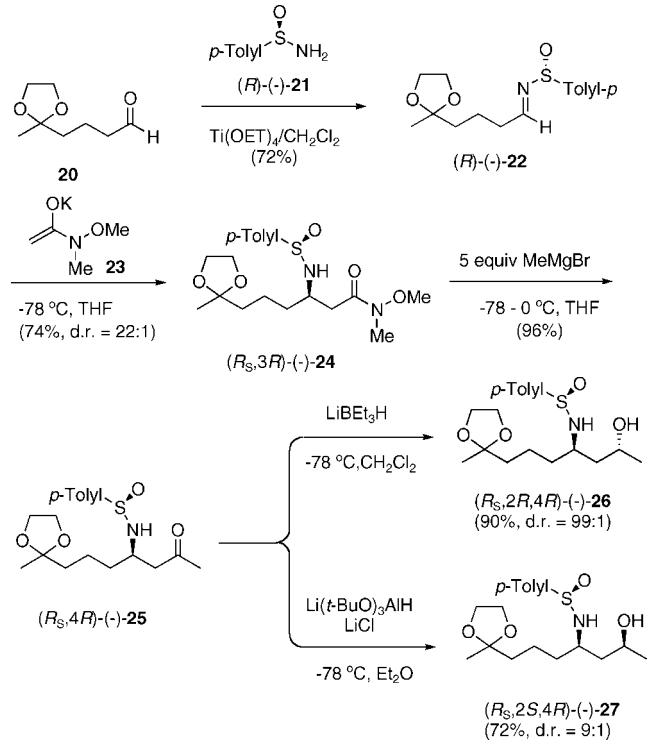
SCHEME 3



ketones as intermediates.[28] The advantage of using a β-amino ketone as an intermediate in the synthesis of (−)-**18** is that (+)-epipinidinol (**19**) would also be available, from a common precursor, via stereoselective reduction. Furthermore, it will be possible to test the feasibility of using a tandem or cascade cyclization reaction to form the piperidine ring from an *N*-sulfinyl 1,3-amino alcohol ketal.

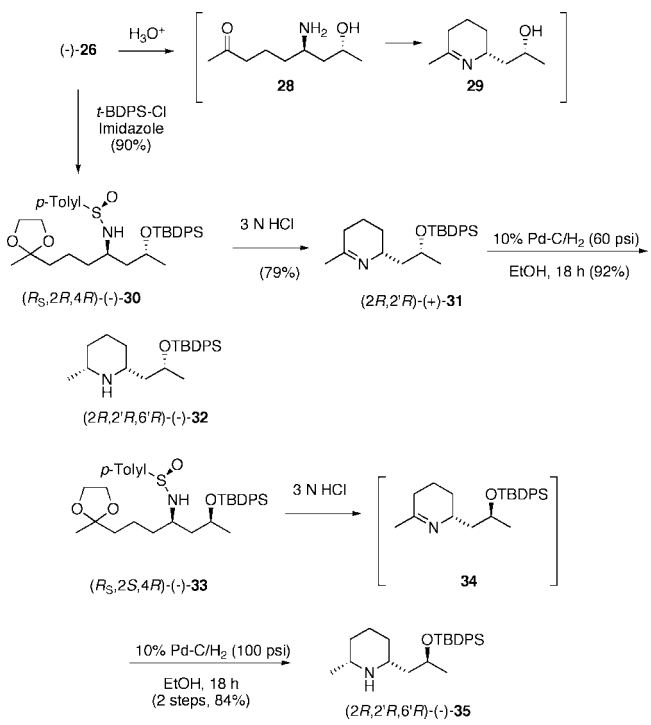
Our synthesis begins with masked oxo-sulfinimine (*R*)-(−)-**22** prepared in 72% yield from aldehyde **20** and (*R*)-(−)-*p*-toluenesulfinamide (**21**) (Scheme 4). Addition of (−)-**22** to the preformed potassium Weinreb amide enolate **23** gives the *N*-sulfinyl β-amino Weinreb amide (R_S,3*R*)-(−)-**24** with a dr of 22:1 and isolation of the major isomer in 74% yield. Next, the reaction of (−)-**24** with 5 equiv of methylmagnesium bromide afforded the desired β-amino ketone ketal (R_S,4*R*)-(−)-**25** in 96% isolated yield (Scheme 4). Reduction of (−)-**25** with $LiBEt_3H$, as expected, gave (R_S,2*R*,4*R*)-(−)-**26** as a single isomer having the *anti*-orientation of the amino and hydroxyl groups (Table 2, entry 32). This assignment is based on our previous results, its conversion into (−)-pinidinol (**18**), and the fact the C-OH ^{13}C NMR chemical shift appears at δ 63.7 ppm. With Li(*t*-BuO)$_3$AlH the *syn*/*anti*-1,3-amino alcohol ratio was a disappointing 54:46 (Table 2, entry 33). However, with 10 equiv

SCHEME 4



of LiCl the *syn*/*anti* ratio improved to 90:10 resulting in the isolation of the (R_S,2*S*,4*R*)-(−)-**27** in 72% yield (Table 2, entry

SCHEME 5



34). We speculate that the presence of LiCl promotes formation of the cyclic transition state **TS-B** (Figure 3). The C-OH ^{13}C NMR chemical shifts in (−)-**27** appears at 67.6 ppm and provides further validation for this method of assigning relative stereochemistry for acyclic 1,3-amino alcohols.

The feasibility of a single-flask, three-step cascade reaction of an amino alcohol ketal to produce the piperidine heterocycle was next explored. Acid-catalyzed hydrolysis of (−)-**26** is expected to remove the *N*-sulfinyl auxiliary, unmasked the oxo group to give **28** which cyclizes to imine **29** (Scheme 5). Hydrogenation would give (−)-pinidinol (**18**). However, hydrolysis with 3 N HCl in THF at 0 °C resulted in decomposition.

Considering that the problem may be the free hydroxyl group in (−)-**26**, it was protected as the *tert*-butyldiphenylsilyl ether to give (R_S,2*R*,4*R*)-(−)-**30**, which on reaction with 3 N HCl in THF afforded imine (2*R*,2′*R*)-(+)-**31** in 79% yield (Scheme 5). However, hydrogenation with 10% Pd/C at 1 atm of H_2 resulted in no reaction. Increasing the pressure of H_2 to 60 psi gave a 92% isolated yield of the TBDMS-protected pinidinol (−)-**32**. Similar methodology gave the TBDMS-protected epipinidinol (−)-**35**, but the hydrogenation pressure needed to be increased to 100 psi for any reaction to occur. Molander and co-workers had earlier prepared (−)-**32** and (−)-**35** using a lanthanocene-catalyzed intramolecular hydroamination reaction.[28c] This completes our formal synthesis of (−)-pinidinol (**18**) and (+)-epipinidinol (**19**) from a common *N*-sulfinyl β-amino ketone ketal (−)-**25**.

In summary, general methodology for the efficient asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols via the reduction of enantiopure *N*-sulfinyl-β-amino ketones using $LiEt_3BH$ and Li(*t*-BuO)$_3$AlH, respectively has been devised. These reagents gave good to excellent *syn*- and *anti*-selectivity for reduction of *N*-(*p*-toluenesulfinyl) β-amino ketones. For reduction of *N*-(2-methylpropanesulfinyl) β-amino ketones, $LiEt_3BH$ resulted in poor *anti*-selectivity but exhibited excellent *syn*-selectivity with Li(*t*-BuO)$_3$AlH. This new methodology was highlighted in a concise formal asymmetric synthesis of (−)-pinidinol (**18**) and (+)-epipinidinol (**19**) in six steps and 42−36% overall yield from a masked oxo sulfinimine. This procedure employed a novel acid-catalyzed cascade reaction of a *N*-sulfinylamino silyl protected alcohol ketal to prepare the pinidinol piperidine ring.

Experimental Section

Sulfinimines (*S*)-(+)-*N*-(acetylidene)-*p*-toluenesulfinamide (**1a**) and (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**1c**) were prepared as previously described.[29] (S_S,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*-3-phenylpropionamide (**2c**) and (S_S,3*R*)-(+)-*N*-(2-methylpropanesulfinyl)-3-amino-*N*-methoxy-*N*-methyl-3-phenylpropionamide (**4**) were prepared as previously described.[19] β-Amino ketones (S_S,3*R*)-(+)-*N*-(*p*-toluenesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-one (**7**),[19] (S_S,3*R*)-(+)-*N*-(*p*-toluenesulfinyl)-3-amino-1,3-diphenylpropan-1-one (**8**),[14b] and (S_S,3*R*)-(+)-*N*-(2-methylpropanesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-one (**10**)[19] were prepared as previously described.

Typical Procedure for the Preparation of Sulfinimines.[19] (*S*)-(+)-*N*-(Hexylidene)-*p*-toluenesulfinamide (1b). In a 250 mL, flame-dried, single-necked, round-bottomed flask equipped with a magnetic stirring bar and rubber septum were placed (*S*)-(+)-*p*-toluenesulfinamide[19] (1.55 g, 10 mmol) and *n*-hexanal (1.23 mL, 10 mmol) in CH_2Cl_2 (62 mL) at 0 °C. To the mixture was added Ti(OEt)$_4$ (0.114 g, 50 mmol) at 0 °C, and the solution was stirred for 4 h at rt. At this time, the reaction was quenched with H_2O (10 mL) and filtered through a Celite pad, and the Celite was washed with CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phases were combined, dried ($MgSO_4$), and concentrated. Chromatography (hexanes/EtOAc, 92:8) gave 1.9 g (80%) of a slightly yellow oil: $[\alpha]^{25}_D$ +328.6 (*c* 0.982, $CHCl_3$); IR, 1597, 1458, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.31 (4 overlapping H), 1.61 (m, 2H), 2.41 (s, 3H), 2.49 (m, 2H), 7.30 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 8.23 (t, J = 4.8 Hz, 1H); δ 14.1, 21.7, 22.6, 25.4, 31.6, 36.1, 124.9, 130.1, 141.9, 142.3, 167.6; HRMS calcd for $C_{13}H_{20}NOS$ (M + H) 238.1272, found 238.1265.

(*R*)-(−)-*N*-[5,5-(Ethylenedioxy)hexanylidene]-*p*-toluenesulfinamide (22). This sulfinimine was prepared from (*R*)-(−)-*p*-toluenesulfinamide[19] and 5,5-(ethylenedioxy)hexanal.[30] Flash chromatography (hexanes/EtOAc 8:2) provided 1.06 g (83%) of a colorless oil: $[\alpha]^{20}_D$ −279.7 (*c* 0.52, $CHCl_3$); IR (CH_2Cl_2) 3051, 1635, 1214 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.66 (m, 4 overlapping H), 2.41 (s, 3H), 2.50 (m, 2 overlapping H), 3.92 (m, 4H), 7.32 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 7.8 Hz, 2H), 8.23 (t, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2, 21.7, 24.1, 36.2, 38.7, 65.0, 124.9, 130.1, 142.0, 167.2; HRMS calcd for $C_{15}H_{22}NO_3S$ (M + H) 296.4051, found 296.4029.

(S_S,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methylpropionamide (2a). Typical Procedure. In a two-neck, oven-dried, 100 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed *N*-methoxy-*N*-methylacetamide (0.16 mL, 1.5 mmol) in THF (20 mL). The solution was cooled to −78 °C, KHMDS (1.5 mmol, 3 mL of 0.5 M solution in toluene) was added, and the reaction mixture was stirred at this temperature for 1 h. A solution of (*S*)-(+)-**1a** (0.25 g, 1.0 mmol) in THF (10 mL) was added, and the solution was stirred at this temperature for 2.5 h. At this time, the reaction

(28) (a) Gebauer, J.; Rost, D.; Blechert, S. *Heterocycles* **2006**, *68*, 2129. (b) Fréville, S.; Delbecq, P.; Thuy, V. M.; Petit, H.; Célérier, J. P.; Lhommet, G. *Tetrahedron Lett.* **2001**, *42*, 4609. (c) Molander, G. A.; Dowdy, E. D.; Pack, S. K. *J. Org. Chem.* **2001**, *66*, 4344. (d) Takahata, H.; Yotsui, Y.; Momose, T. *Tetrahedron* **1998**, *54*, 13505.

(29) (a) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. *J. Org. Chem.* **1997**, *62*, 2555. (b) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.

(30) Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759.

mixture was quenched with satd NH_4Cl (5 mL), slowly warmed to rt, and diluted with H_2O (10 mL). The solution was extracted with Et_2O (2 × 30 mL), and the organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexanes/EtOAc 1:9) yielded 0.19 g (66%) of a clear oil: $[\alpha]^{25}_D$ +154.8 (*c* 2.73, $CHCl_3$); IR (neat) 3482, 3220, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (d, *J* = 6.6 Hz, 3H), 2.42 (s, 3H), 2.67 (d, *J* = 5.5 Hz, 2H), 3.16 (s, 3 H), 3.66 (s, 3H), 3.85 (m, 1H), 5.06 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.61 (q, *J* = 4.9, 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.7, 32.2, 33.2, 39.7, 40.3, 47.9, 61.6, 126.1, 126.4, 129.9, 141.5, 142.6, 172.5; HRMS calcd for $C_{13}H_{21}O_3N_2SNa$ (M + Na) 307.1092, found 307.1090.

(S_S,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methyloctanamide (2b). Flash chromatography (hexanes:/EtOAc, 2:3) gave 1.1 g (77%) of a clear oil: $[\alpha]^{25}_D$ +105.7 (*c* 1.07, $CHCl_3$); IR (thin film) 3019, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J* = 6.8 Hz, 3H), 1.4−1.8 (8 overlapping H), 2.41 (s, 3H), 2.78 (m, 2H), 3.16 (s, 3H), 3.67 (s, 3H overlapped with 1H), 4.92 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 21.7, 22.9, 26.3, 31.9, 36.1, 37.9, 53.6, 61.6, 125.9, 129.8, 141.4, 143.3, 173.5; HRMS calcd for $C_{17}H_{29}N_2O_3S$ (M + H) 341.1899, found 341.1912.

(R_S,3*R*)-(−)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methyl-7,7-(ethylenedioxy)octamide (24). Chromatography (hexanes/EtOAc, 2:3) gave 0.619 g (74%) of a pale yellow oil: $[\alpha]^{25}_D$ −44.5 (*c* 0.951, $CHCl_3$); IR (neat) 3101, 1652, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.63 (m, 6H), 2.38 (s, 3H), 2.76 (m, 2H), 3.13 (s, 3H), 3.64 (s, 3H), 3.68 (m, 1H), 3.92 (m, 4H), 4.94 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.5, 24.0, 32.1, 36.0, 37.8, 38.9, 53.4, 61.5, 64.9,110.2, 125.8, 129.7, 141.3, 143.0, 172.5; HRMS calcd for $C_{19}H_{31}N_2O_5S$ (M + H) 399.1954, found 399.1947.

(S_S,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-phenyl-3-methylpropan-1-one (5). Typical Procedure. In an oven-dried, single-neck, 50-mL round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet was placed (S_S,*R*)-(+)-**2a** (0.284 g, 1.0 mmol) in THF (20 mL) under an argon atmosphere. The solution was cooled to −78 °C, PhMgBr (5.0 mmol, 5.0 mL of 1.0 M solution in THF) was added via syringe, and the reaction mixture was warmed to rt. After being stirred for 1 h, the solution was cooled to −78 °C, quenched with satd NH_4Cl (6 mL), and warmed to rt. The solution was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexanes/EtOAc 1:1) gave 0.2567 g (79%) of a clear oil: $[\alpha]^{25}_D$ +75.1 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3197, 1675, 1568 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (d, *J* = 6.6 Hz, 3H), 2.33 (s, 3H), 3.09 (dq, *J* = 5.4 Hz, *J* = 16.8 Hz, 1H), 3.89−3.95 (m, 1H), 4.62 (d, *J* = 7.8 Hz, 1H), 7.34 (m, 7H), 7.77 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.7, 22.5, 22.9, 46.7, 47.7, 125.8, 128.5, 129.0, 129.9, 133.8, 137.1, 141.6, 142.4, 198; HRMS calcd for $C_{17}H_{19}NO_2SNa$ (M + Na) 324.1034, found 324.1030.

(S_S,4*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-aminononan-2-one (6). Chromatography (hexanes/EtOAc, 7:3) gave 74% of a clear oil: $[\alpha]^{20}_D$ +101.6 (*c* 1.36, $CHCl_3$); IR (CH_2Cl_2) 3053, 1712, 1265, 1063 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.27−1.71 (8 overlapping H), 2.11 (s, 3H), 2.42 (s, 3H), 2.77 (d, *J* = 5.2 Hz, 2H), 3.66 (m, 1H), 4.42 (d, *J* = 9.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.3, 21.6, 22.8, 26.2, 31.1, 31.8, 36.1, 49.5, 52.9, 125.8, 129.8, 141.5, 143.0, 207.8; HRMS calcd for $C_{16}H_{26}N_1O_2S_1$ (M + H) 296.1684, found 296.1682.

(S_S,3*R*)-(+)-*N*-(2-Methylpropanesulfinyl)-3-amino-1,3-diphenylpropan-1-one (9). In a single-neck, oven-dried, 50-mL round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet were placed THF (10 mL) and KHMDS (1.8 mmol, 3.6 mL of a 0.5 M solution in THF) under argon atmosphere. The solution was cooled to −78 °C, acetophenone (0.21 mL, 1.8 mmol) was added via syringe, and the solution was stirred for 1 h. A cooled −78 °C solution of (*S*)-(−)-*N*-(benzylidene-2-methylpropane)sulfinamide[31] (0.209 g, 1.0 mmol) in THF (10 mL) was added dropwise via cannula to the enolate solution followed by THF (5 mL) to rinse the flask. The reaction mixture was stirred at −78 °C for 2 h and cautiously quenched with satd NH_4Cl (4 mL). The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 15 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Chromatography (30:70, hexanes/EtOAc) gave 0.273 g (83%) of a clear oil which solidified on standing: mp 68−70 °C; $[\alpha]^{25}_D$ +123.6 (*c* 0.25, $CHCl_3$); IR (neat) 3270, 3202, 1629; ^1H NMR ($CDCl_3$) δ 1.22 (s, 9H), 3.47 (dd, *J* = 8.0 Hz, *J* = 17.2 Hz, 1H), 3.59 (dd, *J* = 17.2 Hz, *J* = 4.0 Hz, 1H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.96 (m, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H), 7.35 (m, 7H), 7.55 (m, 1H), 7.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.0, 46.3, 55.7, 55.9, 127.9, 128.3, 128.5, 129.0, 134.0, 136.9, 141.4, 198.9; HRMS calcd for $C_{19}H_{23}NO_2SNa$ (M + Na) 352.1347, found 352.1348.

(*R*)-(+)-*N*-(*p*-Toluenesulfonyl)-3-amino-1,3-diphenylpropan-1-one (11). In a single-neck, 25-mL round-bottom flask equipped with magnetic stirring bar, rubber septum, and argon inlet were placed (S_S,3*R*)-(+)-**8** (0.363 g, 1.0 mmol) and CH_2Cl_2 (15 mL) under an argon atmosphere. The solution was cooled to 0 °C, *m*-CPBA (0.6 g, 3.5 mmol, 77%) was added, and the solution was stirred at this temperature for 3.5 h. At this time, $NaHCO_3$ (1 N aqueous solution) was added to the reaction mixture until pH 8 was reached. The solution was extracted with EtOAc (2 × 10 mL), and the organic phases were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexanes/EtOAc 1:1) gave 0.364 g (96%) of a clear oil: $[\alpha]^{20}D$ +18.3 (*c* 1.0, $CHCl_3$) [lit.[31] $[\alpha]^{25}D$ −22.0 (*c* 1.0, $CHCl_3$) for the *S*-isomer]; IR (neat) 3050, 1629, 1410, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.45 (dd, *J* = 6.0 Hz, *J* = 17.2 Hz, 1H), 3.59 (dd, *J* = 6.0 Hz, *J* = 17.2 Hz, 1H), 4.87 (dd, *J* = 6.4 Hz, *J* = 12.8 Hz, 1H), 5.81 (d, *J* = 6.4 Hz, 1H), 7.16 (m, 7H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.54 (t, 1H), 7.61 (d, *J* = 8 Hz, 2H), 7.80 (dd, *J* = 0.8 Hz, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 45.1, 54.8, 127.1, 127.6, 128.0, 128.4, 128.9, 129.0, 129.8, 133.9, 136.7, 137.6, 140.3, 143.6, 198.1.

(R_S,4*R*)-(−)-*N*-(*p*-Toluenesulfinyl)-4-amino-8,8-(ethylenedioxy)-nonan-2-one (25). In a flame-dried, 100-mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (−)-**24** (0.472 g, 1.18 mmol) in THF (38 mL). The solution was cooled to −78 °C, and methylmagnesium bromide (5.9 mmol, 1.97 mL of a 3.0 M solution in Et_2O) was added. The reaction mixture was warmed to 0 °C, stirred for 30 min, and quenched with satd aqueous NH_4Cl (3 mL). At this time, H_2O (5 mL) was added, the aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic phases were combined, dried ($MgSO_4$), and concentrated. Chromatography (hexanes/EtOAc, 2:3) gave 0.401 g (96%) of a clear oil: $[\alpha]^{25}_D$ −78.1 (*c* 0.547, $CHCl_3$); IR (thin film) 3210, 1712, 1063 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.4−1.7 (m, 6H), 2.10, (s, 3H), 2.40 (s, 3H), 2.77 (d, *J* = 4.8 Hz, 2H), 3.67 (m, 1H), 3.94 (m, 4H), 4.39 (d, *J* = 9.6 Hz, 1H with overlapping 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.4, 23.9, 30.9, 35.9, 38.7, 49.3, 52.6, 64.8, 110.0, 125.6, 129.6, 141.4, 142.7, 207.5; HRMS calcd for $C_{18}H_{28}NO_4S$ (M + H) 354.1739, found 354.1737.

(S_S,1*R*,3*R*)-(+)-3-(*p*-Toluenesulfinylamino)-1,3-diphenylpropan-1-ol (13d). Typical Procedure for the Reduction of β-Amino Ketones with $LiEt_3BH$ To Give *anti*-1,3-Amino Alcohols. In a single-neck, oven-dried, 25-mL round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet was placed (S_S,3*R*)-(+)-**8** (0.036 g, 0.1 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere. The solution was cooled to −78 °C, and $LiEt_3BH$ (0.5 mmol, 0.5 mL of 1.0 M solution in THF) was added via syringe. After being stirred at −78 °C for 2 h, the reaction mixture was cautiously quenched with satd NH_4Cl (1 mL) and warmed to rt. The solution

(31) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *64*, 1278.

was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (petroleum ether/EtOAc 1:1) gave 0.033 g (90%) of a white solid: mp 123−126 °C; $[\alpha]^{20}_D$ +130.8 (*c* 1.0, $CHCl_3$); IR (thin film) 3260, 3030, 1262 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (dq, *J* = 4.4 Hz, *J* = 4.8 Hz, *J* = 7.2 Hz, *J* = 18.8 Hz, m, 1H), 2.16−2.23 (dq, *J* = 4.4 Hz, *J* = 4.8 Hz, *J* = 7.2 Hz, *J* = 18.8 Hz, m, 1H), 2.32 (s, 1H), 3.06 (d, *J* = 4.0 Hz, 1H), 4.68−4.73 (m, 2H), 4.76 (d, *J* = 6.4 Hz, 1H), 7.15 (m, 1H), 7.22 (m, 7H), 7.29 (d, *J* = 4.0 Hz, m, 4H), 7.50 (d, *J* = 8.0 Hz, m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.7, 47.4, 56.5, 70.9, 125.9, 126.2, 127.2, 127.85, 127.90, 128.9, 129.1, 130.0, 141.9, 142.6, 143.0, 144.2. Anal. Calcd for $C_{22}H_{23}NO_2S$: C, 72.30; H, 6.34; N, 3.83. Found: C, 72.46; H, 6.82; N, 3.89.

(S_S,1*S*,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-phenyl-3-methylpropan-1-ol (13a). Chromatography (petroleum ether/EtOAc, 1:1) provided 73% of a clear oil: $[\alpha]^{25}_D$ +88.4 (*c* 2.6, $CHCl_3$); IR (neat) 3322, 2963, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, *J* = 6.5 Hz, 3H), 1.80 (m, 1H), 1.89−1.95 (m, 1H), 2.42 (s, 3H), 2.97 (d, *J* = 4.5 Hz, 1H), 3.53 (m, 1H), 4.35 (d, *J* = 7.5 Hz, 1H), 7.29 (m, 7H), 7.61 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 24.0, 47.3, 48.7, 126.0, 127.7, 128.8, 129.9, 141.8, 142.4, 144.9; HRMS calcd for $C_{17}H_{21}NO_2SNa$ (M + Na) 326.1191, found 326.1188.

(S_S,2*S*,4*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-aminononan-2-ol (13b). Chromatography (hexanes/EtOAc, 6:4) gave 72% of a clear oil: $[\alpha]^{25}_D$ +89.6 (*c* 0.341 $CHCl_3$); IR (CH_2Cl_2) 3054, 1422, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ (major diastereomer) 0.89 (m, 7 overlapping H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.31−1.78 (m, 6 overlapping H), 2.42 (s, 3H), 3.23 (m, 1H), 3.62 (m, 1H), 3.98−4.03 (m, 2 overlapping H), 4.48 (br s, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 21.7, 23.0, 23.9, 26.1, 32.0, 37.8, 45.1, 54.1, 63.9, 125.7, 129.9, 141.9, 142.7; HRMS calcd for $C_{16}H_{28}NO_2S$ (M + H) 298.4650, found 298.4632.

(S_S,1*S*,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol (13c). Chromatography (petroleum ether/EtOAc, 1:1) provided 84% of a clear oil: $[\alpha]^{25}_D$ +65.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3339, 3214, 1263 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, *J* = 6.3 Hz, 3H), 1.73 (m, 1H), 1.88 (m, 1H), 2.34 (s, 3H), 2.86 (d, *J* = 4.4 Hz, 1H), 4.65 (d, *J* = 6.3 Hz, 1H), 4.74 (m, 1H), 4.88 (br, 1H), 7.25 (m, 7H), 7.53 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 23.8, 45.7, 55.7, 64.7, 126.5, 127.5, 127.7, 128.8, 129.7, 137.9, 141.1, 143.5; HRMS calcd for $C_{17}H_{21}NO_2S$ (M + H) 304.1371, found 304.1368.

(S_S,1*R*,3*R*)-*N*-(2-Methylpropanesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol (15c). Mixture of inseparable *syn*/*anti* (30:70) isomers: ^1H NMR ($CDCl_3$) δ 1.22 (s, 9H), 1.29 (d, *J* = 8.8 Hz, 3H), 1.92 (t, *J* = 6.4 Hz, 2H), 3.54 (d, *J* = 6.4 Hz, 1H), 4.01 (m, *J* = 6.4 Hz, *J* = 14.0 Hz, 1H), 4.61 (d, *J* = 7.0 Hz, 1H), 4.73 (dt, *J* = 6.8 Hz, *J* = 8.0 Hz, *J* = 16.0 Hz, 1H), 7.23−7.28 (m, 1H), 7.30−7.35 (m, 4H).

(S_S,1*R*,3*R*)-(+)-*N*-(2-Methylpropanesulfinyl)-3-amino-1,3-diphenylpropan-1-ol (15d). Chromatography ($CHCl_3$ satd NH_3) gave 51% of the major diastereomer as a white solid: mp 156−160 °C; $[\alpha]_D$ +84.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3233, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 9H), 2.17 (m, 1H), 2.29 (m, 1H), 3.33 (br, 1H), 4.37 (d, *J* = 5.2 Hz, 1H), 4.66 (dt, *J* = 4.4 Hz, *J* = 8.2 Hz), 4.85 (q, *J* = 4.0 Hz, *J* = 8.8 Hz, 1H), 7.26 (m, 5H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.0, 47.2, 56.1, 57.2, 71.5, 126.2, 127.1, 127.7, 128.0, 128.90, 128.92, 143.1, 144.1. Anal. Calcd for $C_{19}H_{25}NO_2S$: C, 68.85; H, 7.60; N, 4.23. Found: C, 68.94; H, 7.68; N, 3.99.

(1*R*,3*R*)-(+)-*N*-(*p*-Toluenesulfonyl)-3-amino-1,3-diphenylpropan-1-ol (17). Chromatography (petroleum ether/EtOAc, 1:1) provided 58% of a colorless oil: IR (thin film) 3600, 3300, 1400, 1250 cm^{-1}; $[\alpha]^{20}_D$ +110.6 (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.03 (m, 2H), 2.37 (s, 3H), 2.54 (br, 1H), 4.61 (dt, *J* = 4.4 Hz, *J* = 8.0 Hz, 1H), 4.82 (t, *J* = 5.6 Hz, 1H), 5.66 (d, *J* = 8.0 Hz, 1H), 7.03 (m, 2H), 7.16 (m, 2H), 7.25 (m, 6H), 7.33 (m, 2H), 7.63 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 45.7, 55.4, 70.9, 125.7, 126.3, 127.2, 127.4, 127.8, 128.57, 128.60, 129.5, 137.7, 140.5, 143.2, 143.7. A satisfactory HRMS could not be obtained because of decomposition in the instrument.

(R_S,2*R*,4*R*)-(−)-*N*-(*p*-Toluenesulfinyl)-4-amino-8,8-(ethylenedioxy)nonan-2-ol (26). In a flame-dried, 100-mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (−)-**25** (0.120 g, 0.34 mmol) in CH_2Cl_2 (34 mL). The solution was cooled to −78 °C, $LiBHEt_3$ (2.04 mmol, 2.04 mL of a 1.0 M solution in THF) was added dropwise, and the solution was stirred at this temperature for 2.5 h. At this time, the reaction mixture was quenched by addition of satd aqueous NH_4Cl (2 mL) and H_2O (2 mL). The phases were separated, and the aqueous phase was saturated with NaCl and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (hexanes/EtOAc, 2:3) gave 0.102 g (85%) of a clear oil: $[\alpha]^{25}_D$ −132.6 (*c* 0.941, $CHCl_3$); IR (thin film) 3416, 3240, 1375, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (d, *J* = 6.3 Hz, 3H), 1.33 (s, 3H), 1.57 (m, 8H), 2.40 (s, 3H), 3.23 (d, *J* = 5.4 Hz, 1H), 3.61 (m, 1H), 3.95 (m, 4H), 4.05 (d, *J* = 8.7 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.5, 23.8, 24.0, 37.7, 39.0, 44.9, 53.7, 63.7, 64.8, 110.2, 125.6, 129.8, 141.7, 142.6; HRMS calcd for $C_{18}H_{30}NO_4S$ (M + H) 356.1895, found 356.1898.

(S_S,1*R*,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol (12c). Typical Procedure for the Reduction of β-Amino Ketones with Li(*t*-Bu)$_3$AlH and LiCl in Et_2O To Give *syn*-1,3-Amino Alcohols. In a flame-dried, 50-mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (+)-**7** (0.054 g, 0.179 mmol) and LiCl (0.076 g, 1.8 mmol) in Et_2O (9 mL). The reaction mixture was sonicated for 5−10 min and cooled to −78 °C, and Li(*t*-BuO)$_3$AlH (0.895 mmol, 0.895 mL of a 1.0 M solution in THF) was added dropwise. The solution was stirred at this temperature for 2 h and quenched with satd aqueous NH_4Cl (0.5 mL) and H_2O (0.5 mL). The organic phases were separated; the aqueous phase was washed with EtOAc (2 × 1 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (hexanes/EtOAc, 40:60) gave 0.040 g (70%) of a clear oil: $[\alpha]^{20}_D$ +16.6 (*c* 0.295, $CHCl_3$); IR (thin film) 3054, 1422, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (d, *J* = 6 Hz, 3H), 1.85 (m, 2H), 2.40 (s, 3H), 3.45 (d, *J* = 4.8 Hz, 1H), 4.01 (m, 1H), 4.74 (m, 1H), 5.51 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8 Hz, 2H), 7.35 (m, 5 overlapping H), 7.54 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.7. 25.0, 47.5, 58.8, 125.6, 127.5, 128.0, 129.1, 129.9, 141.7, 143.1, 143.2; HRMS calcd for $C_{17}H_{21}NO_2SNa$ (M + H) 326.1200, found 326.1199.

(S_S,1*R*,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-3-methyl-1-phenylpropan-1-ol (12a). Chromatography (petroleum ether/EtOAc, 1:1) provided 0.014 g (61%) of a clear oil: $[\alpha]^{25}_D$ +76.5 (*c* 4.5, $CHCl_3$); IR (neat) 3309, 3223, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, *J* = 6.5 Hz, 3H), 1.74 (m, 1H), 1.88 (m, 1H), 2.41 (s, 3H), 3.71 (m, 1H), 3.84 (d, *J* = 3.5 Hz, 1H), 4.79 (m, 1H), 5.03 (d, *J* = 4.5 Hz, 1H), 7.26 (m, 9H), 7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.9, 24.2, 47.7, 48.9, 50.8, 71.2, 74.2, 126.2, 127.9, 128.1, 129.1, 130.2, 145.3; HRMS calcd for $C_{17}H_{21}NO_2SNa$ (M + Na) 326.1191, found 326.1195.

(S_S,2*S*,4*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-aminononan-2-ol (12b). Chromatography (hexanes/EtOAc, 6:4) gave 61% of a clear oil: IR (CH_2Cl_2) 3054, 1422, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, *J* = 10.4 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.45 (m, 10H), 2.41 (s, 3H), 3.53 (m, 1H), 3.60 (br d, *J* = 2.8 Hz, 1H), 4.04 (m, 1H), 4.30 (d, *J* = 6.8 Hz, 1H), 7.29 (d, *J* = 8 Hz, 2H), 7.59 (d, *J* = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 21.7, 22.9, 24.7, 25.5, 32.0, 38.1, 45.5, 56.4, 67.6, 125.6, 129.9, 141.8, 142.8; HRMS calcd for $C_{16}H_{27}NO_2S$ (M + H) 298.1762, found 297.1831.

(S_S,1*S*,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1,3-diphenylpropan-1-ol (12d). Chromatography (hexanes/EtOAc, 65:35) gave 74% of a white solid: mp 46−47 °C; $[\alpha]^{20}_D$ +12.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3268, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (m, 1H), 2.14 (m, 1H), 2.33 (s, 3H), 3.27 (d, *J* = 2.8 Hz, 1H), 4.79 (dt, *J* = 2.8 Hz,

(32) Zhao, C.-H.; Liu, Li.; Wang, D.; Chen, Y.-J. *Eur. J. Org. Chem.* **2006**, 2977.

J = 9.2 Hz, 2H), 5.45 (d, J = 2.4 Hz, 1H), 7.16 (m, 2H), 7.23 (m, 6H), 7.30 (t, J = 8 Hz, 2H), 7.37 (t, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 47.7, 58.7, 125.7, 125.9, 127.7, 128.0, 128.1, 128.9, 129.0, 129.9, 141.7, 142.8, 144.9; HRMS calcd for $C_{22}H_{23}NO_2SNa$ (M + Na) 388.1347, found 388.1345.

(S_S,1S,3R)-(+)-*N*-(2-Methylpropanesulinyl)-3-amino-1,3-diphenyl-1-ol (14d). Chromatography (hexane/EtOAc, 3:1) gave 90% of white solid: mp 158−162 °C; $[\alpha]^{25}_D$ +66.3 (c 0.3, $CHCl_3$); IR (neat) 3231, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9H), 1.98 (dq, J = 2.4 Hz, J = 3.2 Hz, J = 14.4 Hz, 1H), 2.19 (dt, J = 4.4 Hz, J = 10.4 Hz, J = 14.4 Hz, 1H), 4.02 (br, 1H), 4.74 (m, 1H), 5.00 d, J = 10.4 Hz, 1H), 5.44 (s, 1H), 7.26 (m, 2H), 7.35 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 23.1, 46.3, 55.7, 56.0, 127.9, 128.3, 128.5, 129.0, 134.0, 136.9, 141.4, 198.9; HRMS calcd for $C_{19}H_{25}NO_2SNa$ (M + Na) 354.1504, found 354.1517.

(S_S,1S,3R)-(+)-*N*-(2-Methylpropanesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol (14c). Chromatography (EtOAc/hexanes 2:1) gave 90% of a white solid: mp 145−6 °C; $[\alpha]^{20}_D$ +181.9 (c 0.8, $CHCl_3$); IR (neat) 3100, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 9H), 1.23 (s, 3H), 1.70 (m, 1H), 1.83 (m, 1H), 2.06 (br, 1H), 4.09 (m, 1H), 4.30 (m, 1H), 4.52 (d, J = 9.6 Hz, 1H), 5.55 (s, 1H), 7.16 (m, 1H), 7.23 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 23.1, 25.2, 47.1, 55.8, 59.2, 68.8, 127.5, 127.83, 137.84, 143.6; HRMS calcd for $C_{14}H_{23}NSO_2$ (M + H) 270.1538, found 270.1521.

(R_S,2S,4R)-(−)-*N*-(*p*-Toluenesulfinyl)-4-amino-8,8-(ethylenedioxy)nonan-2-ol (27). In a flame-dried, 50-mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (−)-**25** (0.093 g, 0.262 mmol) and LiCl (0.111 g, 2.62 mmol) in Et_2O (10 mL). The solution was sonicated for 5−10 min and cooled to −78 °C. Li(t-BuO)$_3$AlH (0.95 mL, 0.895 mmol of a 1.0 M solution in THF) was added dropwise, and the reaction mixture was stirred at −78 °C for 2 h. At this time, the reaction was quenched by addition of satd aqueous NH_4Cl (0.5 mL) and H_2O (0.5 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 1 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (hexanes/EtOAc, 40:60) gave 0.049 g (90%) of a clear oil: $[\alpha]^{25}_D$ −43.1 (c 0.237, $CHCl_3$); IR (thin film) 3053, 1421, 1263 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 2H, J = 6.4 Hz), 1.34 (s. 3H), 1.510−1.712 (9 overlapping H), 2.40 (s, 3H), 3.55 (m, 1H), 3.70 (m, 1H), 3.96 (m, 4H), 4.05 (m, 1H), 4.39 (d, 1H, 6.8 Hz), 7.27 (d, 2H, J = 8.8 Hz), 7.59 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.4, 21.7, 24.1, 24.7, 38.2, 39.2, 45.5, 56.3, 65.0, 67.6, 110.3, 125.6, 129.9, 141.8, 142.7; HRMS calcd for $C_{18}H_{30}NO_4S$ (M + H) 356.1896, found 356.1906.

(R_s,2R,4R)-(−)-*N*-(*p*-Toluenesulfinyl)-2-(*tert*-butyldiphenylsilyloxy)-4-amino-7-(2-methyl-1,3-dioxolan-2-yl)heptane (30). In a flame-dried 5-mL vial, equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (−)-**26** (0.030 g, 0.084 mmol) and imidazole (0.014 g, 0.21 mmol) in CH_2Cl_2 (1 mL). To the solution was added TBDPSCl (0.025 g, 0.092 mmol) in CH_2Cl_2 (0.5 mL), and the reaction was stirred for 8 h and quenched by addition of H_2O (0.5 mL). The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 0.5 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (hexanes/EtOAc, 4:1) gave 0.047 g (90%) of a clear oil: $[\alpha]^{25}_D$ −62.8 (c 1.15, $CHCl_3$); IR (CH_2Cl_2) 3050, 1415, 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 9H), 1.07 (d, J = 6.4 Hz, 3H), 1.33 (s, 3H), 1.68 (m, 8H), 2.37 (s, 3H), 3.64 (m, 1H), 3.92 (m, 4H), 4.04 (m, 1H), 4.94 (d, J = 4.40 Hz, 1H), 7.44 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 19.2, 20.3, 21.6, 22.8, 24.1, 27.1, 30.0, 36.1, 39.3, 43.7, 51.9, 65.0, 68.6, 110.3, 125.9, 127.8, 127.9, 129.7, 129.9, 130.0, 133.9, 134.4, 136.2, 141.2, 143.2; HRMS calcd for $C_{34}H_{47}NO_4SSi$ (M + H) 594.3073, found 594.3093.

(R_s,2S,4R)-(−)-*N*-(*p*-Toluenesulfinyl)-2-(*tert*-butyldiphenylsilyloxy)-4-amino-7-(2-methyl-1,3-dioxolan-2-yl)heptane (33). Chromatography (hexanes/EtOAc, 4:1) gave 85% of a clear oil: $[\alpha]^{20}_D$ −46.8 (c 1.03, $CHCl_3$); IR (CH_2Cl_2) 3054, 1421, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 6.0 Hz, 3H), 1.02 (s, 9H), 1.31 (s, 3H), 1.51 (8 overlapping H), 2.39 (s, 3H), 3.23 (m, 1H), 3.49 (d, J = 8.0 Hz, 1H), 3.78 (m, 1H), 3.93 (m, 4H), 7.20 (d, J = 8.4 Hz, 2H), 7.38 (8 overlapping H), 7.68 (4 overlapping H); ^{13}C NMR ($CDCl_3$) δ 19.5, 20.3, 21.6, 23.5, 24.1, 27.3, 37.4, 39.2, 46.1, 52.5, 65.0, 67.4, 110.3, 126.0, 127.8, 128.0, 129.7, 129.9, 130.0, 134.9, 136.3, 141.3, 142.5; HRMS calcd for $C_{34}H_{47}NO_4SiSNa$ (M + Na) 616.2893, found 616.2907.

(2R,2′R)-(+)-2′,3′,4′,5′-Tetrahydro-6′-methylpyridinyl-2-(*tert*-butyldiphenylsilyloxy)propane (31). In a 50-mL, round-bottom flask equipped with magnetic stirring bar and rubber septum was placed (−)-**27** (0.244 g, 0.41 mmol) in THF (19 mL). The solution was cooled to 0 °C, 3 N HCl (1.8 mL) was added, and the reaction mixture was stirred for 3 h at this temperature. The solution was neutralized to pH 7.0 by dropwise addition of satd aqueous $NaHCO_3$. The phases were separated, the aqueous phase was extracted with Et_2O (3 × 2 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography (3% MeOH/CH_2Cl_2) gave 0.128 g (79%) of a clear oil: $[\alpha]^{25}_D$ +12.1 (c 1.14, $CHCl_3$); IR (thin film) 3070, 3048, 1660, 1427, 1374 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.12 (d, J = 6 Hz, 3H), 1.41−1.61 (m, 5 overlapping H), 1.76 (m, 1H), 1.88 (d, J = 1.6 Hz, 3 H), 2.00 (m, 2H), 3.24 (br m, 1H), 4.14 (m, 1H), 7.39 (m, 5H), 7.72 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.0, 19.6, 24.0, 27.4, 27.9, 30.3, 48.1, 55.1, 67.9, 127.7, 129.7, 135.0, 135.4, 136.3, 167.1; HRMS calcd for $C_{25}H_{35}NOSi$ (M + H) 394.2566, found 394.2555.

(2R,2′R,6′R)-(−)-1-(6′-Methylpiperidin-2′-yl)-2-(*tert*-butyldiphenylsilyloxy)propane (32). In a 2-dram vial equipped with a loose fitting lid were placed (−)-**31** (0.040 g, 0.1 mmol) and 10% Pd/C (0.001 g) in MeOH (2 mL). The vial was placed in a Parr bomb and pressurized with H_2 (60 psi), and the solution was stirred for 8 h. The bomb was depressurized, the reaction mixture was filtered through Celite, and the Celite washed with MeOH (1 mL). The filtrate was concentrated to give 0.036 g (92%) of a clear oil: $[\alpha]^{20}_D$ −1.5 (c 0.735 $CHCl_3$) [lit.[28c] $[\alpha]^{27}_D$ −1.4 (c 0.55, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.3 Hz, 3H), 0.99 (m, 1H), 1.07 (m, 12H), 1.28 (m, 1H), 1.51 (m, 5H), 1.70 (m, 2H), 2.46 (m, 1H), 2.73 (m, 1H), 3.95 (m, 1H), 7.37 (m, 6H), 7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.9, 23.2, 24.6, 25.4, 27.7, 33.1, 34.3, 47.1, 53.1, 54.2, 67.5, 128.1, 128.3, 130.2, 130.3, 134.7, 135.3, 136.5, 136.6. Spectral properties were consistent with literature values.[28c]

(2S,2′R,6′R)-(−)-1-(6′-Methylpiperidin-2′-yl)-2-(*tert*-butyldiphenylsilyloxy)propane (35). The same procedure used for the synthesis of (−)-**32** was employed for the preparation of (−)-**35** except that the cyclic imine **34** was hydrogenated without purification due to its instability. After hydrogenation at 100 psi of H_2 in MeOH for 18 h a clear, viscous oil (84%) was obtained: $[\alpha]^{20}_D$ −6.5 (c 0.499, $CHCl_3$) [lit.[28c] $[\alpha]^{27}_D$ −6.5 (c 0.51, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 1.06 (14 overlapping H), 1.25 (m, 2 overlapping H), 1.42 (d, J = 6.4 Hz, 3H), 1.64 (m, 4 overlapping H), 2.24 (m, 1H), 2.94 (m, 1H), 3.15 (m, 1H), 3.86 (m, 1H), 7.40 (m, 6 overlapping H), 7.67 (m, 4 overlapping H); ^{13}C NMR ($CDCl_3$) δ 19.4, 19.7, 23.0, 24.4, 27.2, 27.6, 30.9, 42.6, 54.5, 56.0, 66.6, 127.7, 128.0, 129.9, 130.0, 133.7, 134.1, 136.0, 136.1. Spectral properties were consistent literature values.[28c]

Acknowledgment. This work was supported by a grant from the National Institutes of General Medical Sciences (GM 57870).

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801653C