# A Diastereoselective Intramolecular Hydroamination Approach to the Syntheses of (+)-, (±)-, and (−)-Pinidinol

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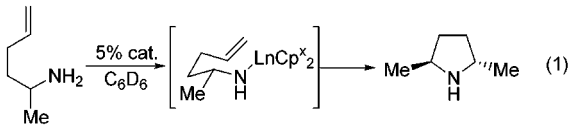
*Received March 1, 2001*

A diastereoselective, lanthanocene-catalyzed, intramolecular hydroamination reaction was applied to the preparation of 2,6-disubstituted piperidines. Various metal/ligand arrays in the catalysts were examined using a model substrate to allow optimization of the diastereoselectivity. It was determined that the relationship between metal size and ligand bulk plays an integral role in the transformation. The complex $Cp^*_2NdCH(TMS)_2$ converted 2-substituted 8-nonen-4-amines to 2,6-disubsituted piperidines with greater than 100:1 selectivity for the formation of the cis isomer. A short synthesis of pinidinol, an alkaloid isolated from various pine and spruce species, was then carried out to exploit this stereoselective reaction.

## Introduction

The formation of polysubstituted heterocycles is an important endeavor in synthetic organic chemistry, and approaches to many naturally occurring and biologically important molecules would benefit by the development of diastereoselective ring-forming reactions. A highly selective preparation of 2,5-disubstituted pyrrolidines employing the intramolecular hydroamination of substituted aminopentenes was reported by Marks and coworkers (eq 1).[1] In a thorough study, they elucidated the



(1)

effects of catalyst structure and reaction conditions on the diastereoselectivity of the intramolecular reaction. The major diastereomer obtained (trans) in the olefin insertion process was rationalized by considering a chairlike transition structure that minimized steric interactions during the cyclization.

Left unanswered was the stereochemistry of the process exhibited during the formation of disubstituted piperidines under similar reaction conditions. A simple, one methylene extension of the chairlike model proposed above predicts the formation of *cis*-2,6-disubstituted piperidines (Figure 1). However, the well-known differences between five- and six-membered rings would most likely require tuning of the steric and electronic environments about the catalyst to achieve useful selectivity. Consequently, the current study was undertaken to determine these optimal conditions and to apply it to the synthesis of a natural product.

A simple alkaloid bearing this structural feature is (−)-pinidinol (**1**) (eq 2).[2] Isolated from a variety of spruce

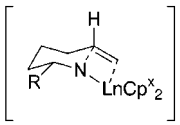
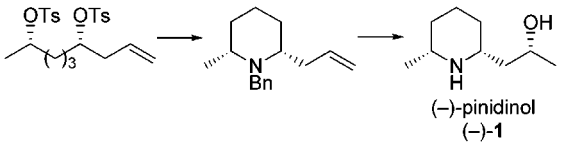


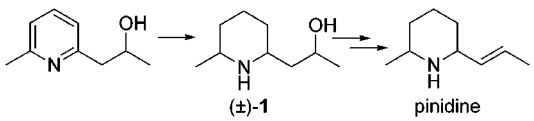

**Figure 1.** Proposed transition structure for the formation of 2,6-disubstituted piperidines via the intramolecular hydroamination reaction.



(2)

(*Picea*) species, pinidinol is also absorbed by parasitic plants feeding on the roots of these trees. Although specific biological activity information is lacking, a crude alkaloid extract containing **1** has shown moderate to high antifeedant activity against Eastern spruce budworms.

Pinidinol was recently synthesized by the double alkylation of benzylamine with an appropriately functionalized ditosylate (eq 2).[2c] The stereocenters in the molecule were established using asymmetric dihydroxylation reactions. Prior to its isolation from a natural source, **1** was prepared in racemic fashion as an intermediate in the synthesis of pinidine by the reduction of a 2,6-disubstituted pyridine (eq 3).[2d] The former synthesis



(3)

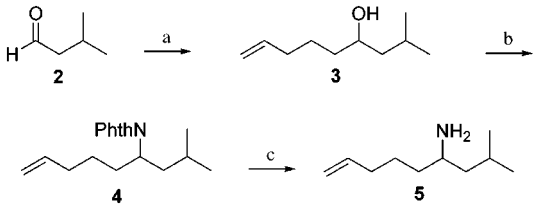
was 11 steps with a low overall yield (1.25%). Although not targeted at the preparation of **1**, the latter synthesis

(1) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.

(2) (a) Schneider, M. J.; Montali, J. A.; Hazen, D.; Stanton, C. E. *J. Nat. Prod.* **1991**, *54*, 905. (b) Schneider, M. J.; Stermitz, F. R. *Phytochemistry* **1990**, *29*, 1811. (c) Takahata, H.; Yotsui, Y.; Momose, T. *Tetrahedron* **1998**, *54*, 13505. (d) Leete, E.; Carver, R. A. *J. Org. Chem.* **1975**, *40*, 2151.

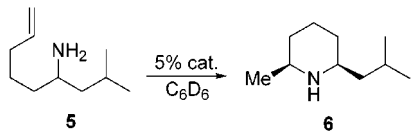
10.1021/jo015603n CCC: $20.00 
Published on Web 05/16/2001

**Scheme 1**[a]




[a] Key: (a) 4-Pentenylmagnesium bromide, 83%. (b) Phthalimide, $Ph_3P$, DEAD, 56%. (c) Aqueous $MeNH_2$, THF, 55%.

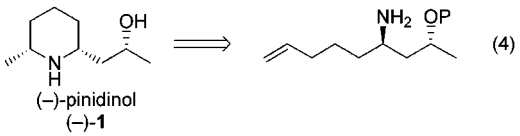
**Table 1. Fine Tuning of the Catalyst**




| entry | catalyst | time (h) | temp (°C) | ratio |
|---|---|---|---|---|
| 1 | $Me_2SiCpCp''YCH(TMS)_2$ | ~12 | rt | 7:1 |
| 2 | $[Cp^{TMS}{}_2YMe]_2$ | 48 | rt | 10:1 |
| 3 | $Cp^*{}_2YMe{\cdot}THF$ | 48 | 80 | 17:1 |
| 4 | $Cp^*{}_2NdCH(TMS)_2$ | ~12 | rt | 115:1 |

generated an inseparable mixture of enantiomers and diastereomers in the reduction step.

A straightforward retrosynthesis based on the intramolecular hydroamination reaction (eq 4) provides an interesting approach to this synthetic target and a means to probe the stereochemical preferences of the key transformation.

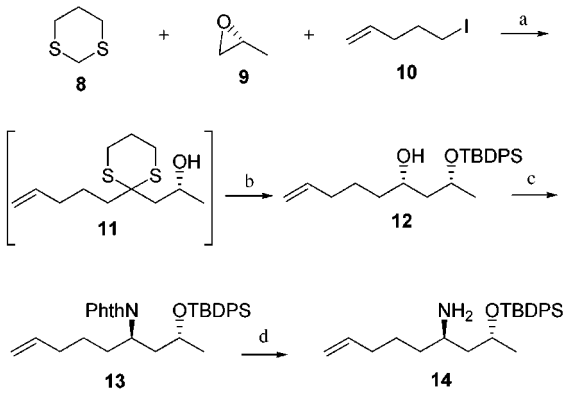



## Results and Discussion

A model system that mimics the steric demands of pinidinol was prepared to allow easy optimization of the cyclization conditions and to provide a rapid assessment of the stereochemical preference of the reaction (Scheme 1). The carbon framework of the model substrate was constructed by the addition of pentenylmagnesium bromide to isobutyraldehyde (**2**).[3] The primary amine was installed by Mitsunobu inversion with phthalimide[4] followed by deprotection with methylamine.[5]

A series of catalysts were surveyed in this hydroamination reaction, with improved diastereoselectivity achieved by modifying the structure of the catalyst (Table 1). Although varying reaction conditions were required, all catalysts used were active in the cyclization, and gas chromatography (GC) analysis indicated complete consumption of starting material and clean conversion to product. The least selective catalyst proved to be the bridged and lightly substituted yttrium complex described in entry 1 ($Cp'' = C_5Me_4$).[6] By using a catalyst with slightly bulkier ligands (entry 2),[7] a modest improvement in the diastereoselectivity was observed. A much bulkier ligand array ($Cp^* = C_5Me_5$)[8] provided another gain, although heating was required to push the reaction to completion in a synthetically useful time (entry 3). As the heating could have eroded the selectivity imparted by the hindered ligands, a complex based on a metal with a larger ionic radius (entry 4)[9] was used with the hope that the reaction would proceed under milder conditions. This combination of very hindered Cp* ligands and a large lanthanide metal (Nd) provided a satisfactory level of diastereoselectivity. The identity of the major isomer was confirmed by conversion of this material to the corresponding picrate salt (**7**) and X-ray diffraction analysis of the resulting crystalline solid. As expected, the major isomer was found to be cis. This result can be rationalized from the proposed chairlike transition structure (Figure 1) where both the isopropyl and the incipient methyl group occupy equatorial orientations in the developing six-membered ring.

**Scheme 2**[a]

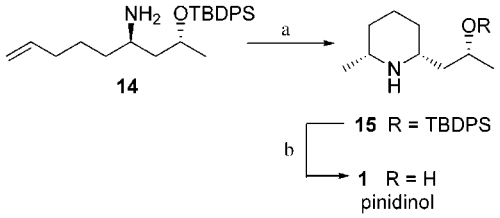



[a] Key (racemic yields): (a) *n*-BuLi. (b) (i) TBDPSCl, imidazole, DMAP; (ii) $HgCl_2$; (iii) $NaBH_4$, 3.7:1, 74% (65%). (c) Phthalimide, $Ph_3P$, DEAD, 78% (45%). (d) $NaBH_4$ then HOAc, 72% (45%).

With reaction conditions established for the preparation of cis-2,6-disubstituted piperidines, an enantioselective route to (−)-pinidinol was devised utilizing appropriately functionalized cyclization substrates (Scheme 2). To assess the enantiomeric purity of the final target, an approach was utilized that allowed the synthesis of the enantiomerically pure product as well as the racemate. The synthetic scheme began with a lynchpin reaction,[10] coupling the dithiane **8** to the epoxide **9** and iodopentene **10** in a single pot. The 5-iodo-1-pentene (**10**) was synthesized from the commercially available 5-bromo-1-pentene via a Finkelstein reaction.[11] Without purification, **11** was converted to **12** by protecting the alcohol with *tert*-butyldiphenylsilyl chloride, removing the dithiane with $HgCl_2$,[12] and stereoselectively reducing the siloxy ketone with $NaBH_4$. A 3.7:1 ratio of chromatographically separable diastereomers was obtained, with the major isomer being syn. A Mitsunobu reaction,[4] followed by a $NaBH_4$ reduction,[13] was then used to generate the substrate **14** for cyclization.

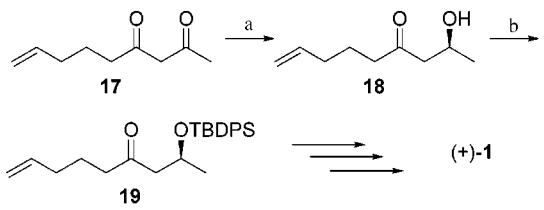
(3) Hwa, J. C. H.; Sims, H. *Organic Syntheses*; Wiley and Sons: New York, 1973; Collect. Vol. V, p 608.
(4) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961.
(5) Wolfe, S.; Hasan, S. K. *Can. J. Chem.* **1970**, *48*, 3572.
(6) Molander, G. A.; Dowdy, E. D.; Noll, B. C. *Organometallics* **1998**, *17*, 3754.
(7) Schumann, H.; Keitsch, M. R.; Demtschuk, J.; Molander, G. A. *J. Organomet. Chem.* **1999**, *582*, 70.
(8) den Haan, K. H.; de Boer, J. L.; Teuben, J. H.; Smeets, W. J.; Spek, A. L. *J. Organomet. Chem.* **1987**, *327*, 31.
(9) Jeske, G.; Lauke, H.; Mauermann, H.; Swepston, P. N.; Schumann, H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 8091.
(10) Bracher, F.; Schulte, B. *Org. Prep. Proced. Int.* **1995**, *27*, 682.
(11) Kuwajima, I.; Hirokazu, U. *Organic Syntheses*; Wiley and Sons: New York, 1993; Collect. Vol. VIII, p 486.
(12) Corey, E. J.; Crouse, D. *J. Org. Chem.* **1968**, *33*, 298.
(13) Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093.

**Scheme 3**[a]




[a] Key (racemic yields): (a) 9% $Cp^*_2NdCH(TMS)_2$, rt, 90% (89%). (b) (i) KOH in MeOH then HCl; (ii) KOH, 66% (36%).

**Scheme 4**[a]




[a] Key: (a) Baker's yeast, 50%, 96% ee. (b) TBDPSCl, imidazole, DMAP, 84%.

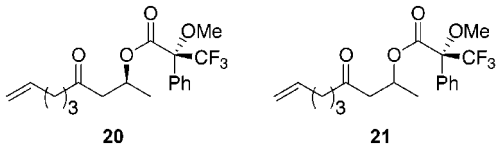
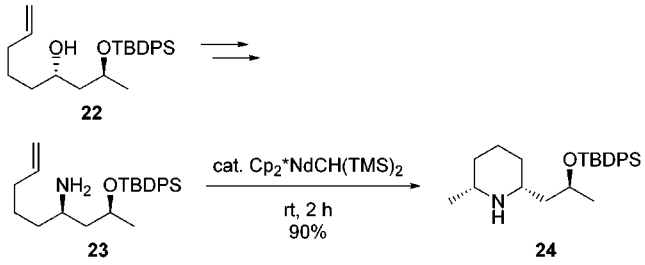



**Figure 2.** Mosher's esters formed from alcohol **18**.

The cyclization of **14** proceeded smoothly, providing piperidine **15** with good diastereoselectivity (>100:1) and with good yield after silica gel chromatography (Scheme 3). The protecting group was removed by boiling in methanol with KOH.[14] Purification of (−)-**1** and (±)-**1** was achieved by generating the crystalline HCl salts **16**. The spectra of the material obtained matched those reported in the literature for (−)- and (±)-pinidinol.[2] Chiral GC using the racemate as a standard confirmed the enantiomeric purity of the natural product as being 99.9+% ee.

An enantioselective synthesis of (+)-pinidinol was carried out by another route. The synthesis began with the known diketone **17** (Scheme 4), itself prepared by the alkylation of the dianion of 2,4-pentanedione.[15] Enantioselective introduction of the hydroxyl group was achieved by a selective baker's yeast reduction of the desired ketone.[16] The enantioselectivity of the reaction was established by conversion of the material to the corresponding Mosher's ester **20** (Figure 2).[17] As **18** contained small amounts of isomeric impurities resulting in similar $^1$H NMR resonances, an authentic sample of (±)-**18** was prepared.[18] Formation of Mosher's ester from the racemic alcohol gave **21**, and NMR analysis allowed the identification of the appropriate peaks in the NMR spectrum of **20**, revealing the enantiomeric excess of the material to be 96%.

**Scheme 5**




Conversion of **19** to (+)-**1** was accomplished using the general procedures outlined in Schemes 2 and 3, without the isolation of the HCl salt, in 38.5% overall yield. The spectra of the product obtained matched that of the natural material, with the optical rotation being similar in magnitude but opposite in sign, thus confirming the synthesis of (+)-pinidinol.

The role of the siloxy stereocenter on the diastereoselectivity of the hydroamination was explored in greater detail by converting **23** to piperidine **24** (Scheme 5). The synthesis of **23** was achieved by using the above-mentioned procedures from the alcohol **22**. The alcohol was isolated as the minor isomer in the reduction of **19**. The hydroamination proceeded with greater than 100:1 selectivity for the 1,3-cis isomer, indicating little or no dependence of the diastereoselectivity on the size or stereochemistry of additional stereocenters in the pendant group.

## Conclusions

The stereoselectivity exhibited during the construction of 2,6-disubstituted piperidines from substituted aminohexenes using the intramolecular hydroamination reaction was determined and optimized. A steric model that minimizes the interactions between the 2,6 substituents of the incipient ring, with only the amine stereocenter determining the outcome, can be used to rationalize the observed (cis) product. The variability of the lanthanide metallocene scaffold provided a means to maximize the diastereoselectivity of the reaction. The high diastereoselectivity achieved upon tuning was then used for the enantioselective synthesis of (+)- and (−)-pinidinol as well as (±)-pinidinol. A brief and efficient synthetic scheme was used for the substrate synthesis with the absolute stereochemistry introduced by the readily available, enantiomerically pure, propylene oxide and by a highly enantioselective baker's yeast reduction. Cyclization using the optimized catalyst followed by deprotection yielded (−)-**1** in 10 steps in 19% yield, (+)-**1** in 7 steps from the known diketone **17** in 16% yield, and (±)-**1** in 10 steps in 3.3% yield (unoptimized).

## Experimental Section

**Reagents.** $Et_2O$, tetrahydrofuran (THF), and $C_6D_6$ were distilled from sodium benzophenone ketyl. $C_6D_6$ was degassed prior to use. $Cp^*_2NdCH(TMS)_2$ was prepared by a literature procedure[9] and handled in a nitrogen-filled glovebox. All other reagents were used as received. GC conditions: 60 °C for 5 min, 10 °C/min ramp, max temp = 250 °C; HP Ultra 2, cross-linked 5% phenylmethyl silicone, 25 m × 0.32 mm.

**(2*R*,2′*R*,6′*R*)-1-(6′-Methylpiperidin-2′-yl)-2-*tert*-butyldiphenylsilyloxypropane [(−)-15]. General Procedure for Intramolecular Hydroamination.** In a nitrogen-filled glovebox, a vial was charged with 10 mg (17 μmol) of

(14) Malik, A. A.; Cormier, R. J.; Sharts, C. M. *Org. Prep. Proced. Int.* **1986**, *18*, 345.
(15) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(16) (a) Bolte, J.; Gourcy, J. G.; Veschambre, H. *Tetrahedron Lett.* **1986**, *27*, 565. (b) Fauve, A.; Veschambre, H. *J. Org. Chem.* **1988**, *53*, 5215. (c) Dauphin, G.; Fauve, A.; Veschambre, H. *J. Org. Chem.* **1989**, *54*, 2238.
(17) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969,** *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(18) Bernardi, R.; Ghiringhelli, D. *J. Org. Chem.* **1987**, *52*, 5021.

$Cp^*_2NdCH(TMS)_2$ and 100 mg of $C_6D_6$. A solution of (+)-**14** was prepared by dissolving 73 mg (180 $\mu$mol) in 200 mg of $C_6D_6$. The amine solution was charged to the green catalyst solution followed by a 200-mg $C_6D_6$ rinse. The brown/green solution was allowed to stand overnight at rt. The vial was removed from the glovebox and charged with 2 mL of hexanes. The catalyst solution was allowed to oxidize for ca. 1 h. The yellow/brown slurry was then filtered through 2 g of flash silica gel. The product was eluted with 2 mL of hexanes followed by 10 mL of 10% EtOAc/hexanes. The combined fractions were concentrated to give 63.6 mg of a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.70−7.64 (m, 4H), 7.42−7.33 (m, 6H), 3.99−3.90 (m, 1H), 2.79−2.66 (m, 1H), 2.52−2.40 (m, 1H), 1.75−1.65 (m, 2H), 1.64−1.38 (m, 5H), 1.30−1.27 (m, 1H), 1.10−1.04 (m, 12H), 1.00−0.97 (m, 1H), 0.96−0.94 (d, $J$ = 6.3 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 136.14, 136.07, 134.90, 134.22, 129.84, 129.72, 127.82, 127.65, 66.94, 53.32, 52.40, 46.98, 34.28, 32.91, 27.26, 25.11, 24.17, 23.11, 19.46. IR (neat): 3344.0, 3070.6, 1589.7 cm$^{-1}$. HRMS: $(M + H)^+$ calcd for $C_{25}H_{38}NOSi$, 396.2644; found, 396.2732. LRMS $m/z$ : ($EI^+$) 437 (5), 393 (5), 396 (100). $[\alpha]^{27}_D$ −1.4 ($c$ 0.55, $CHCl_3$).

**(2*R*,2′*R*,6′*R*)-1-(6′-Methylpiperidinium-2′-yl)-2-hydroxypropane, HCl Salt [(−)-16]. General Procedure for the HCl Salt Formation of Pinidinol.** A 10-mL round-bottom flask equipped with a nitrogen line, reflux condenser, and magnetic stirrer was charged with 58.1 mg (150 $\mu$mol) of (−)-**15**, 1.5 mL of MeOH, and 347 mg of KOH. The mixture was heated to reflux and stirred overnight, ca. 9 h. The solution was cooled to rt and charged with 1 mL of water and 2 mL of $CH_2Cl_2$. The mixture was separated, and the aqueous layer was extracted with 5 × 2 mL of $CH_2Cl_2$. The combined organic layers were dried over $K_2CO_3$. The solvents were removed under vacuum and replaced with 0.5 mL of MeOH and 2 mL of ether. The solution was cooled to 0 °C and charged with 25 $\mu$L of concentrated HCl (300 $\mu$mol). The solution was stirred for ca. 30 min at 0 °C. The product was crystallized with the addition of 15 mL of ether. The slurry was stirred for ca. 2 h before collecting 21 mg of white, birefringent, needlelike solids (73%). mp 218−220 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 9.15−8.55 (s, 2H), 4.80−4.45 (s, 1H), 4.35−4.20 (m, 1H), 3.38−3.23 (m, 1H), 3.23−3.02 (m, 1H), 2.20−2.08 (m, 1H), 2.00−1.71 (m, 6H), 1.70−1.60 (s, 1H), 1.59−1.47 (m, 4H), 1.39−1.15 (d, $J$ = 6.3 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 62.81, 55.28, 54.19, 41.27, 30.30, 28.60, 23.19, 22.91, 19.69. IR (solid): 3396 (s), 2845, 2530, 2458 cm$^{-1}$. HRMS: (M + H, $CI^+$) calcd for $C_9H_{20}NO$, 158.1545; found, 158.1549. LRMS $m/z$ : ($EI^+$) 159 (10), 158 (100), 140 (10). $[\alpha]^{26}_D$ −22.4 ($c$ 0.29, $CHCl_3$).

**(−)-Pinidinol [(−)-1]. General Procedure for the Free-Base Formation of Pinidinol.** A 10-mL round-bottom flask equipped with a nitrogen line and magnetic stirrer was charged with 9.9 mg (63 $\mu$mol) of (−)-**16**, 1 mL of MeOH, and 100 mg of KOH. The mixture was stirred for 30 min. The solution was charged with 1 mL of water and 2 mL of $CH_2Cl_2$. The mixture was separated, and the aqueous layer was washed with 4 × 2 mL of $CH_2Cl_2$. The combined organic layers were dried over $K_2CO_3$, and the solvents were removed under vacuum, resulting in the isolation of 7.1 mg of white, needlelike solids (88.8%). mp 70−72 °C, literature[2c] 70.5−72 °C. The spectral data matched that given in the literature. $[\alpha]^{27}_D$ −14.2 ($c$ 0.55, $CDCl_3$), literature[2c] $[\alpha]^{26}_D$ −15.0 ($c$ 0.55, $CHCl_3$). 99.9+% ee by chiral GC: 80 °C for 2 min, 0.1 °C/min ramp, 220 °C max temp, Supelco $\beta$-dex 120, 15 m × 0.25 mm. Retention times (min): (−)-**1**: 36.46, (+)-**1**: 35.33.

**(2*S*,2′*S*,6′*S*)-1-(6′-Methylpiperidin-2′-yl)-2-*tert*-butyldiphenylsilyloxypropane [(+)-15].** Prepared from (−)-**14** according to the general procedure for intramolecular hydroamination given above. After the reaction was complete, the mixture was added directly to a silica gel column. The product was eluted using a 74/25/1 mixture of hexanes/EtOAc/$Et_3N$. The title compound was obtained as a viscous oil in 90% yield. The NMR was similar to that of (−)-**15**. $[\alpha]^{20}_D$ +0.7 ($c$ 0.55, $CHCl_3$).

**(+)-Pinidinol [(+)-1].** A MeOH solution of (+)-**15** (0.063 g, 0.159 mmol) was treated with an excess of KOH (∼2 g). The mixture obtained was heated to reflux overnight. After being cooled, the mixture was poured onto $H_2O$ and made acidic with concentrated HCl. The aqueous layer was washed with $Et_2O$ before it was made basic with solid NaOH. The aqueous layer was extracted four times with $CH_2Cl_2$. The combined organic phase was dried over $K_2CO_3$ and concentrated after filtration. The title compound (0.023 g, 0.146 mmol, 92%) was obtained as a white solid. mp 68−69 °C, literature[2c] 70.5−72 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 4.13−4.07 (m, 1H), 2.94−2.90 (m, 1H), 2.60−2.54 (m, 1H), 1.80−1.74 (m, 1H), 1.61−1.41 (m, 5H), 1.39−1.30 (m, 2H), 1.14 (d, $J$ = 6.4 Hz, 3H), 1.01 (d, $J$ = 6.4 Hz, 3H), 0.99−0.96 (m, 1H), 0.93−0.81 (m, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 65.10, 55.04, 52.55, 43.76, 33.85, 30.28, 24.68, 23.68, 23.14. IR (neat): ∼3200 (br) cm$^{-1}$. HRMS: $(M + H)^+$ calcd for $C_9H_{19}NO$, 157.1467; found, 157.1475. LRMS $m/z$ : ($EI^+$) 157 (5), 142 (25), 112 (6), 98 (100). $[\alpha]^{26}_D$ +11.7 ($c$ 0.535, $CHCl_3$), literature[2c] $[\alpha]^{26}_D$ −15.0 ($c$ 0.55, $CHCl_3$) for (−)-**1**.

**(2*S*,2′*R*,6′*R*)-1-(6′-Methylpiperidin-2′-yl)-2-*tert*-butyldiphenylsilyloxypropane (24).** Prepared from **23** according to the general procedure for intramolecular hydroamination given above. After the reaction was complete, the mixture was added directly to a silica gel column. The product was eluted using a 74/25/1 mixture of hexanes/EtOAc/$Et_3N$. The title compound was obtained as a viscous oil in 90% yield. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.69−7.66 (m, 4H), 7.42−7.33 (m, 6H), 3.97−3.91 (m, 1H), 2.66−2.60 (m, 1H), 2.54−2.48 (m, 1H), 1.75−1.58 (m, 3H), 1.52−1.49 (m, 1H), 1.42−1.35 (m, 2H), 1.27−1.18 (m, 2H), 1.03 (s, 9H), 1.00 (d, $J$ = 6.2 Hz, 3H), 0.97 (d, $J$ = 6.4 Hz, 3H), 0.95−0.84 (m, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 135.92, 135.83, 134.75, 134.19, 129.54, 129.43, 127.54, 127.39, 68.54, 54.88, 52.35, 47.42, 34.22, 32.44, 27.02, 24.84, 24.48, 22.94, 19.26. IR (neat): 3349.3, 3071.0, 1589.8 cm$^{-1}$. HRMS: $(M + H)^+$ calcd for $C_{25}H_{36}NOSi$, 394.2566; found, 394.2551. LRMS $m/z$ : ($EI^+$) 394 (2), 338 (50), 199 (15), 98 (100). $[\alpha]^{20}_D$ −6.5 ($c$ 0.505, $CHCl_3$).

**Acknowledgment.** We thank Dr. Bruce Noll for the X-ray structure determination of **7**. We gratefully acknowledge the National Institutes of Health (Grant GM48580), Merck & Co., and NATO for their generous support of this research. E.D.D. thanks Smith Kline-Beecham for their support in the form of a graduate fellowship administered by the Organic Division of the American Chemical Society. S.K.P. thanks the Process R&D group of Bristol-Myers Squibb for their generous financial support and study leave.

**Supporting Information Available:** Experimental procedures for all compounds not described within the text. HRMS, LRMS, $^1$H and, $^{13}$C NMR spectra of representative compounds. X-ray data for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015603N