JOC Article

Enantioselective Synthesis of Primary 1-(Aryl)alkylamines by Nucleophilic 1,2-Addition of Organolithium Reagents to Hydroxyoxime Ethers and Application to Asymmetric Synthesis of G-Protein-Coupled Receptor Ligands

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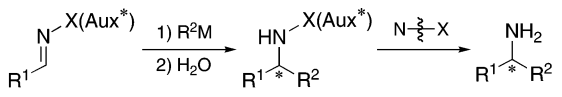
(*E*)-Arylaldehyde oxime ethers bearing a (1*S*)-2-hydroxy-1-phenylethyl or (2*R*)-1-hydroxy-2-phenylethyl group as a chiral auxiliary, both derived from a single precursor, methyl (*R*)-mandelate, underwent nucleophilic addition with organolithium reagents via six-membered chelates to give the diastereomerically enriched (*R*)- and (*S*)-adducts, respectively, which, after chiral auxiliary removal by reductive N−O bond cleavage, led to the corresponding (*R*)- and (*S*)-1-(aryl)ethylamines. This organolithium addition protocol using methyllithium was applied in an enantiodivergent fashion to the preparation of both enantiomers of 1-(2-hydroxyphenyl)ethylamine, which has been previously used as an efficient chiral auxiliary for the synthesis of natural products in this laboratory. The synthetic utility of this methodology involving diastereoselective methyl addition was demonstrated by further application to the asymmetric synthesis of a new type of calcium receptor agonist (calcimimetics), (*R*)-(+)-NPS R-568 and its thio analogue. Furthermore, diastereoselective vinylation was accomplished by application of the hydroxy oxime ether-based protocol using vinyllithium, which allowed the development of the enantioselective synthesis of the NK-1 receptor antagonists, (+)-CP-99,994 and (+)-CP-122,721.

Introduction

Optically active primary amines bearing a stereogenic center at the α-position play a crucial role as characteristic structural features in bioactive natural products and pharmaceutically important compounds and also could serve as chiral building blocks and chiral auxiliaries in asymmetric synthesis.[1] In this regard, the development of new and efficient methods for the asymmetric preparation of enantiopure primary amines and their derivatives is of paramount importance in synthetic as well as in practical organic chemistry. One very widely used method for the preparation of such compounds is nucleophilic addition of organometallic reagents to the C=N bond of imines bearing a chiral auxiliary bound by an N−C, N−N, N−O, or N−S bond to the imine nitrogen atom (eq 1).[1]



(1)

X = C, N, O, S; Aux* = chiral auxiliary

However, the scope of this methodology has been limited because of the poor electrophilicity of the azomethine carbon compared to the carbonyl carbon. Moreover, a general problem often encountered in this methodology is the harsh conditions sometimes required for cleavage of the chiral auxiliary, which is not compatible with a wide range of functional groups. In the chiral auxiliary-based asymmetric synthesis, the use of oxime ethers as substrates for the addition reaction of organometallic reagents is an attractive approach to primary amines since the cleavage of N−O bond could be readily performed by using a wide range of methods.[2] However, despite numerous studies of imine addition, there have been only limited examples of this approach reported[3] due to the low electrophilicity of the azomethine carbon in oxime ethers in comparison to the corresponding imine carbon and the ease of α-deprotonation giving rise to a variety of products. To overcome these problems associated with the poor electrophilicity, activation of oxime ethers by a Lewis acid such as boron trifluoride etherate is required,[3] thereby precluding the use of the substrates that possess acid-sensitive functional groups.

(1) For recent reviews, see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (c) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651−673.

(2) Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 8, pp 381−402.

(3) (a) Ukaji, Y.; Kume, K.; Watai, T.; Fujisawa, T. *Chem. Lett.* **1991**, 173−176. (b) Rodriques, K. E.; Basha, A.; Summers, J. B.; Brooks, D. W. *Tetrahedron Lett.* **1988**, *29*, 3455−3458. (c) Brown, D. S.; Gallagher, P. T.; Lightfoot, A. P.; Moody, C. J.; Slawin, A. M. Z.; Swann, E. *Tetrahedron* **1995**, *51*, 11473-11488. (d) Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *Synlett* **1997**, 659−660. (e) Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *J. Org. Chem.* **1997**, *62*, 746−748. (f) Gallagher, P. T.; Hunt, J. C. A.; Lightfoot, A. P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2633−2637.

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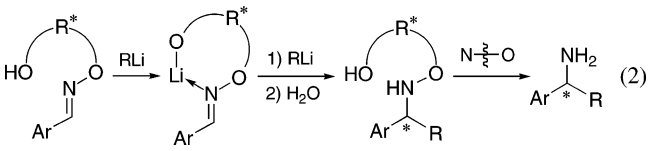
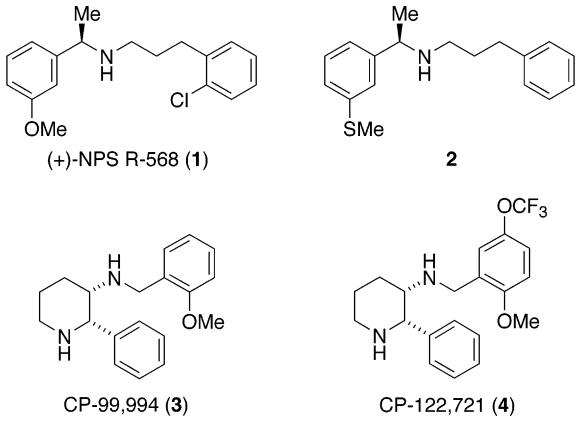
In this paper, we disclose a diastereoselective organolithium addition to oxime ethers bearing at the imine nitrogen a chiral auxiliary with a hydroxy moiety that could serve both to activate the C=N bond and to rigidify the transition state through intramolecular lithium chelation leading to optically active primary 1-(aryl)alkylamines (eq 2).



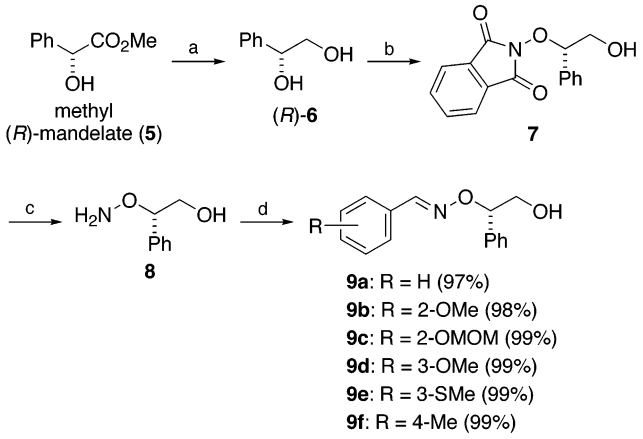
In addition, the synthetic utility of this hydroxyoxime ether-based methodology has been demonstrated[4] by the enantioselective synthesis of G-protein-coupled receptor ligands containing a new class of parathyroid cell calcium receptor agonists, (+)-(*R*)-NPS R-568 (**1**)[5] and its thio analogue (**2**),[6] and potent neurokinin-1 (NK-1) receptor antagonists, (+)-(2*S*,3*S*)-CP-99,994 (**3**)[7,8] and (+)-(2*S*,3*S*)-CP-122,721 (**4**).[9]



Results and Discussion

Diastereoselective Addition of Organolithium Reagents to Hydroxyoxime Ethers. The chiral auxiliary, (*R*)-1-phenyl-1,2-ethanediol [(*R*)-**6**], used in this synthesis was available on a multigram scale by $NaBH_4$ reduction of methyl (*R*)-mandelate (**5**) in 97% yield. Mitsunobu reaction of (*R*)-**6** with *N*-hydroxyphthalimide occurred regioselectively at C1 of (*R*)-**6** due to its benzylic nature, affording the 1-phenyl alkoxyphthalimide **7** with clean inversion of the stereochemistry.[10] The free 2-phenyl aminooxy ethanol **8**, generated from **7** under standard conditions with hydrazine hydrate, was condensed with the aryl aldehydes in refluxing toluene in the presence of a trace amount of TsOH to produce the 1-phenyl hydroxyoxime ethers **9a**−**f** as the (*E*)-isomers in excellent yields within 15−20 min (Scheme 1).[11] The (*E*)- (anti) geometry for the oxime double bond was unambiguously confirmed by X-ray analysis of one of the oxime ethers **9f**, which formed good single crystals (see Supporting Information).

SCHEME 1[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 97%; (b) *N*-hydroxyphthalimide, Ph_3P, DEAD, 81%; (c) $(NH_2)_2 \cdot H_2O$, EtOH, 99%; (d) ArCHO, toluene, TsOH, reflux.

Similarly, the 1-*O*-MOM-protected (*R*)-1-phenyl-1,2-ethanediol **10**, prepared from the (*R*)-mandelate **5** via MOM protection and $LiAlH_4$ reduction, was converted to the 1-phenyl aminooxy ethanol **12** by the Mitsunobu reaction with *N*-hydroxyphthalimide followed by removal of the MOM and the phthaloyl groups (Scheme 2). In a manner similar to that used to prepare the 2-phenyl hydroxyoxime ethers **9a**−**f**, 2-phenyl (*E*)-hydroxyoxime ethers **13a**−**e** were obtained in excellent yields by condensation of **12** with the aryl aldehydes.

With the 1-phenyl hydroxyoxime ethers **9a**−**f** in hand, diastereoselective addition with organolithium reagents was investigated. Thus, after treatment of a THF solution of **9a** with 1 equiv of MeLi (1.14 M solution in diethyl ether) at 0 °C for 5 min, another 1.5 equiv of MeLi was added, and the mixture was stirred at 0 °C for 25 min; however, during the reaction, extensive decomposition was observed without formation of the desired methyl adduct as seen from Table 1 (entry 1). On the other hand, when **9a** was subjected to the above reaction conditions, but using diethyl ether instead of THF as the solvent, the methyl adducts (*R*,*S*)-**14** and (*S*,*S*)-**14** were obtained in 64% total yield in a 9.8:1 ratio (entry 2) in favor of the (1′*R*)-isomer (*R*,*S*)-**14**, along with some decomposition of

(4) For preliminary reports of a part of this work, see: (a) Yamazaki, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 5029−5032. (b) Yamazaki, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2002**, *43*, 7979−7982.

(5) For the synthesis of (+)-(*R*)-NPS R-568 (**1**), see: (a) Barmore, R. M.; Logan, S. R.; Van Wagenen, B. C. *Tetrahedron Lett.* **1998**, *39*, 3451−3454. (b) Hansen, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2033−2034.

(6) Nemeth, E. F.; Van Wagenen, B. C.; Balandrin, M. F.; Delmar, E. G.; Moe, S. T. U.S. Patent 6001884, 1999; *Chem. Abstr.* **2000**, *132*, 35523.

(7) For the asymmetric synthesis of (+)-CP-99,994, see: (a) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911−4913. (b) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071−5072. (c) Tsuritani, N.; Yamada, K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276−277.

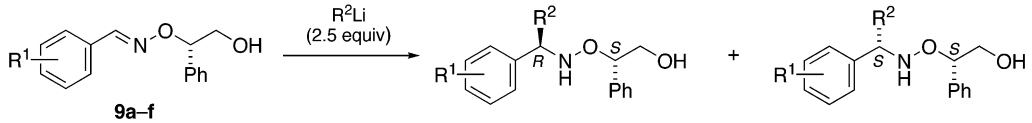
(8) For the synthesis of racemic CP-99,994, see: (a) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831−5834. (b) Rosen, T.; Seeger, T. F.; Mclean, S.; Desai, M. C.; Guarino, K. J.; Bryce, D.; Pratt, K.; Heym, J. *J. Med. Chem.* **1993**, *36*, 3197−3201 (tritiated derivative).

(9) For the synthesis of CP-122,721, see: Rosen, T. J.; Coffman, K. J.; McLean, S.; Crawford, R. T.; Bryce, D. K.; Gohda, Y.; Tsuchiya, M.; Nagahisa, A.; Nakane, M.; Lowe, J. A., III. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 281−284.

(10) Grochowski, E.; Jurezak, J. *Synthesis* **1976**, 682−684.

(11) When these condensations with **8** were run without the addition of TsOH, the same results were obtained, although prolonged reaction time (2−4 h) was necessary.

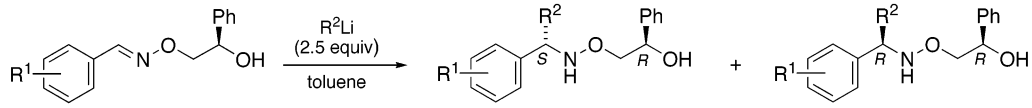
TABLE 1. Diastereoselective Addition of Organolithium Reagents to (*S*)-Hydroxy Oxime Ethers 9a–f[a]



entry	hydroxy oxime ether	R^1	R^2	solvent	temp, °C	products	*R,S*/*S,S* ratio[b]	yield, %[c]
1	**9a**	H	Me	THF	0	(*R,S*)/(*S,S*)-**14**		0
2	**9a**	H	Me	Et_2O	0	(*R,S*)/(*S,S*)-**14**	9.8:1	64
3	**9a**	H	Me	toluene	0	(*R,S*)/(*S,S*)-**14**	9.8:1	80
4	**9a**	H	Me	toluene	−20	(*R,S*)/(*S,S*)-**14**	14.0:1	78(10)
5	**9b**	2-OMe	Me	toluene	−20	(*R,S*)/(*S,S*)-**15**	7.6:1	81(10)
6	**9d**	3-OMe	Me	toluene	−20	(*R,S*)/(*S,S*)-**16**	8.1:1	79(12)
7	**9e**	3-SMe	Me	toluene	−20	(*R,S*)/(*S,S*)-**17**	7.1:1	77(10)
8	**9f**	4-Me	Me	toluene	−20	(*R,S*)/(*S,S*)-**18**	11.6:1	76(11)
9	**9c**	2-OMOM	$CH{=}CH_2$	toluene	0	(*R,S*)/(*S,S*)-**19**	8.1:1	75
10	**9c**	2-OMOM	Ph	toluene	0	(*R,S*)/(*S,S*)-**20**	5.0:1	81

[a] All reactions were carried out in a 0.1 M solution of hydroxy oxime ether. [b] Determined by ^{1}H NMR spectra. [c] Combined yield of diastereomers is presented with the recovery of starting material shown in parentheses where appropriate.

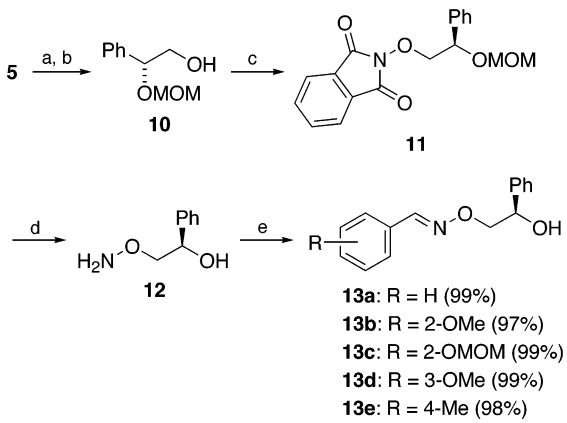
TABLE 2. Diastereoselective Addition of Organolithium Reagents to (*R*)-Hydroxy Oxime Ethers 13a–e[a]



entry	hydroxy oxime ether	R^1	R^2	temp, °C	products	*S,R*/*S,R* ratio[b]	yield, %[c]
1	**13a**	H	Me	−20	(*S,R*)/(*R,R*)-**21**	1.5:1	73(12)
2	**13b**	2-OMe	Me	−20	(*S,R*)/(*R,R*)-**22**	2.2:1	83(8)
3	**13d**	3-OMe	Me	−20	(*S,R*)/(*R,R*)-**23**	2.8:1	82(8)
4	**13e**	4-Me	Me	−20	(*S,R*)/(*R,R*)-**24**	1.8:1	70(9)
5	**13a**	H	Bu	0	(*S,R*)/(*R,R*)-**25**	5.2:1	78
6	**13a**	H	*t*-Bu	0	(*S,R*)/(*R,R*)-**26**	3.0:1	78
7	**13c**	2-OMOM	*t*-Bu	−20	(*S,R*)/(*R,R*)-**27**	6.5:1	65
8	**13a**	H	$CH{=}CH_2$	0	(*S,R*)/(*R,R*)-**28**	3.5:1	72
9	**13c**	2-OMOM	Ph	−20	(*S,R*)/(*R,R*)-**29**	3.5:1	80

[a] All reactions were carried out in a 0.1 M solution of hydroxy oxime ether. [b] Determined by ^{1}H NMR spectra. [c] Combined yield of diastereomers is presented with the recovery of starting material shown in parentheses where appropriate.

SCHEME 2[a]



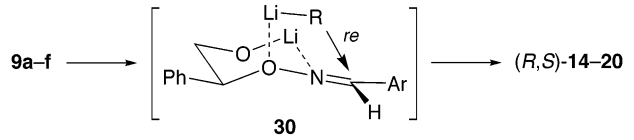
[a] Reagents and conditions: (a) MOMCl, iPr$_2$EtN; (b) $LiAlH_4$, THF, 90% over two steps; (c) *N*-hydroxyphthalimide, Ph_3P, DEAD, 84%; (d) HCl−MeOH, then $(NH_2)_2{\cdot}H_2O$, EtOH, 84%; (e) ArCHO, toluene, TsOH, reflux.

the starting material. In the latter case, changing the solvent from diethyl ether to a very weakly polar toluene led to an improved total yield of 80% with the same diastereoselectivity (entry 3). When the addition to **9a** in toluene was performed at lower temperature (−20 °C), the diastereomeric ratio increased significantly to 14.0:1 (entry 4). Application of these reaction conditions to other hydroxyoxime ethers **9b**,**d**−**f** resulted in diastereoselective methyl addition, affording (*R,S*)-**15**−**18** (entries 5−8). Similar treatment of **9c** with vinyllithium and phenyllithium at 0 °C led to the diastereoselective formation of the corresponding adducts (*R,S*)-**19** and (*R,S*)-**20** (entries 9 and 10). The (1′*R*)-configuration of these adducts was assigned by conversion into the corresponding 1-(aryl)ethylamines via N−O bond cleavage (vide infra).

The addition of MeLi to the 2-phenyl hydroxyoxime ethers **13a**,**b**,**d**,**e** was next examined under the optimal conditions used in the addition to the 1-phenyl hydroxyoxime ethers **9a**,**b**,**d**−**f** in the above experiments (Table 1, entries 4−8), involving the use of 2.5 equiv of MeLi in toluene at −20 °C. It was notable that in all cases the reaction led to the opposite sense of chiral induction, albeit in relatively low selectivity, giving rise to the methyl adducts (*S,R*)-**21**−**24** (Table 2, entries 1−4), in sharp contrast to the chiral induction of the methyl group observed with the 1-phenyl hydroxyoxime ethers **9a**,**b**,**d**−**f**. Additions of the 1-phenyl hydroxyoxime ethers **13a** with BuLi, *t*-BuLi, and vinyllithium led to the diastereoselective formation of the corresponding adducts (*S,R*)-**25**, **26**, and **28** (entries 5, 6, and 8). Similarly, diastereo-

selective addition of *t*-BuLi and phenyllithium to **13c** yielded (*S*,*R*)-**27** and (*S*,*R*)-**29**, respectively (entries 7 and 9).

The (*R*)-selectivity observed for the addition of the organolithium reagents to the 1-phenyl hydroxyoxime ethers **9a**−**f** can be rationalized by a chairlike conformation of the six-membered chelate **30**. In this structure, one molecule of MeLi would be consumed for the initial formation of the lithium alkoxide followed by coordination of the lithium atom to the nitrogen atom of the oxime ether,[12] which is activated toward nucleophilic attack. A second molecule of MeLi coordinated to the oxygen atom might occupy an axial position to avoid 1,3-allylic strain,[13] and a subsequent internal alkoxy-mediated delivery of the methyl group would occur to the *re* face of the imino group, leading to the (*R*)-adducts (*R*,*S*)-**14**−**20**. The use of a noncoordinating solvent such as toluene favors an intramolecular chelation phenomenon associated with the oxime activation, providing improved yield of the methyl adducts.



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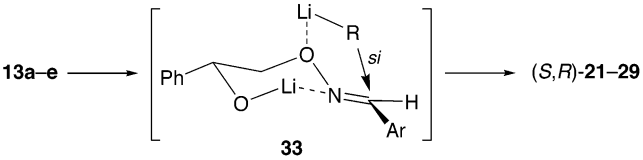
This mechanism was supported by the observation that the methyl addition to the (*S*)-methoxy oxime ether **31**, prepared by O-methylation (MeI, NaH) of the 1-phenyl hydroxyoxime ether **9d**, in toluene at 0 °C led to the (*R*)-adduct (*R*,*S*)-**32** in only poor yield (28%) and low diastereoselectivity (3.0:1), suggesting that the formation of the lithium salt of the primary alcohol is important in promoting the diastereoselective methyl addition to the oxime ethers.

On the other hand, the (*S*)-selectivity observed in the addition of the organolithium reagents to the 2-phenyl hydroxyoxime ethers **13a**−**e** can also be explained by invoking a six-membered chairlike chelated intermediate **33**, which facilitates the internal delivery of the methyl group from the *si* face via activation of the imino group by the lithium alkoxide coordination to the nitrogen atom, thus predominantly leading to (*S*,*R*)-**21**−**29**.



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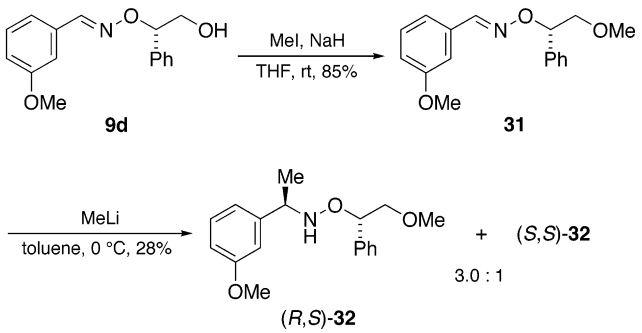
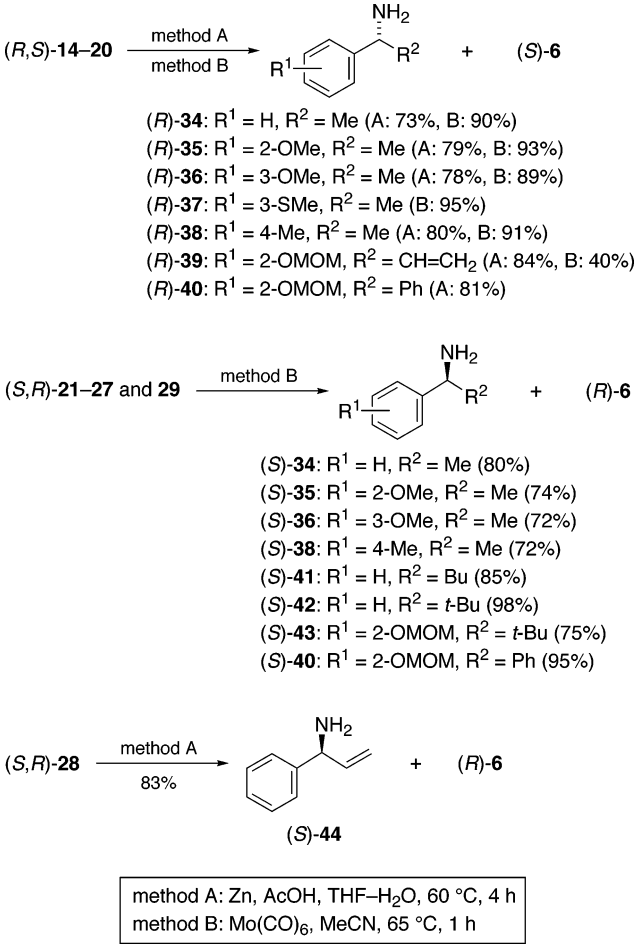
Removal of the chiral auxiliary group was carried out with the *O*-alkyl oximes (*R*,*S*)-**14**−**20** by reductive N−O bond cleavage. Thus, on treatment of (*R*,*S*)-**14**−**16** and (*R*,*S*)-**18**−**20** with Zn−AcOH in THF−H_2O at 60 °C (method A), the corresponding (*R*)-1-(aryl)ethylamines

SCHEME 3



SCHEME 4



(*R*)-**34**−**36** and (*R*)-**38**−**40** were obtained in 73−84% yield with recovery of the antipodal auxiliary (*S*)-**6**, which can be utilized for the preparation of the (*R*)-1-phenyl hydroxyoxime ethers *ent*-**9a**−**f** (Scheme 4). The use of molybdenum hexacarbonyl[14] in acetonitrile at 65 °C (method B) for the reductive N−O bond cleavage was effective for (*R*,*S*)-**14**−**19**, and in each case except the case of (*R*,*S*)-**19** the yield of corresponding (*R*)-**34**−**38** was noticeably improved to 89−95%. The low yield (40%) observed in the molybdenum-based N−O bond cleavage of (*R*,*S*)-**19** may be due to complexation of the olefin moiety with molybdenum, leading to the accompanying formation of undesired complex products. Thus, the

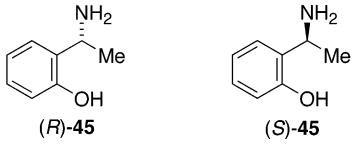
(12) For diastereoselective Grignard addition to imine compounds involving chelation of metal alkoxides with the imine nitrogen, see: (a) Takahashi, H.; Tomita, K.; Noguchi, H. *Chem. Pharm. Bull.* **1981**, *29*, 3387−3391. (b) Takahashi, H.; Inagaki, H. *Chem. Pharm. Bull.* **1982**, *30*, 922−926. (c) Takahashi, H.; Hsieh, B. C.; Higashiyama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2429−2434. (d) Veith, U.; Leurs, S.; Jäger, V. *Chem. Commun.* **1996**, 329−330.

(13) For reviews, see: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(14) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354.

O-alkyl oximes (*S*,*R*)-**21**−**27** and (*S*,*R*)-**29** were subjected to molybdenum-based reductive cleavage (method B) and to the vinyl adduct (*S*,*R*)-**28** zinc-based reductive cleavage (method A), providing the (*S*)-1-(aryl)ethylamines (*S*)-**34**−**36**, **38**, and **40**−**43** in 72−95% yield and (*S*)-**44** in 83% yield, respectively, along with the recovered auxiliary (*R*)-**6** in each case.

Enantiodivergent Preparation of 1-(2-Hydroxyphenyl)ethylamine. Recently, we have shown that 1-(2-hydroxyphenyl)ethylamine (**45**) is a notably effective chiral auxiliary for the enantioselective *N*,*O*-acetal-based allylation and demonstrated the potential utility of this methodology for the asymmetric synthesis of natural alkaloids.[15] Having established a convenient general method for the enantioselective preparation of the primary 1-(aryl)ethylamines based on the hydroxyoxime ethers, we sought to use this method for the synthesis of both enantiomers (*R*)-**45** and (*S*)-**45** of 1-(2-hydroxyphenyl)ethylamine since there has been no efficient preparation of chiral **45** prior to the present study.[16]

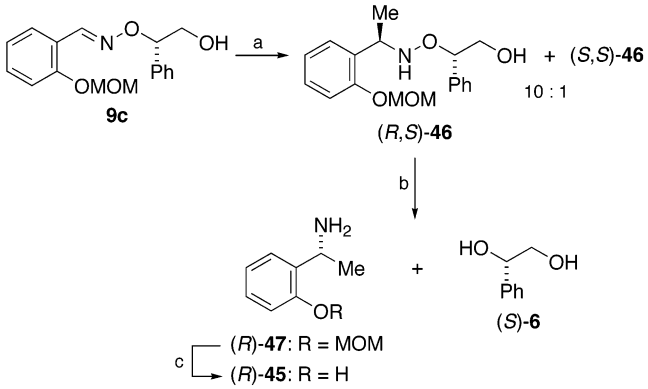


The above-described 1-phenyl hydroxyoxime ether **9c** was subjected to addition of MeLi (2.5 equiv) in toluene at −20 °C to preferentially afford the (1′*R*)-diastereomer (*R*,*S*)-**46** in a ratio of 10:1 with 74% combined yield. Subsequent molybdenum-based reductive cleavage of the N−O bond yielded the (*R*)-primary amine (*R*)-**47** with recovery of the chiral auxiliary (*S*)-**6**. Removal of the MOM group (HCl, MeOH, reflux) provided (*R*)-1-(2-hydroxyphenyl)ethylamine [(*R*)-**45**] in 45% overall yield starting from methyl (*R*)-mandelate (**5**).

On the other hand, when the (*R*)-1-phenyl hydroxyoxime ether **13c** underwent the addition reaction with MeLi under the same conditions as above, the (1′*S*)-diastereomer (*S*,*R*)-**48** was obtained as the major product in a diastereomer ratio of 3.3:1. Molybdenum-based N−O bond cleavage of (*S*,*R*)-**48** gave the (*S*)-primary amine (*S*)-**47** along with the auxiliary (*R*)-**6**, and deprotection of (*S*)-**47** afforded (*S*)-**45** in 36% overall yield from methyl (*R*)-mandelate (**5**).

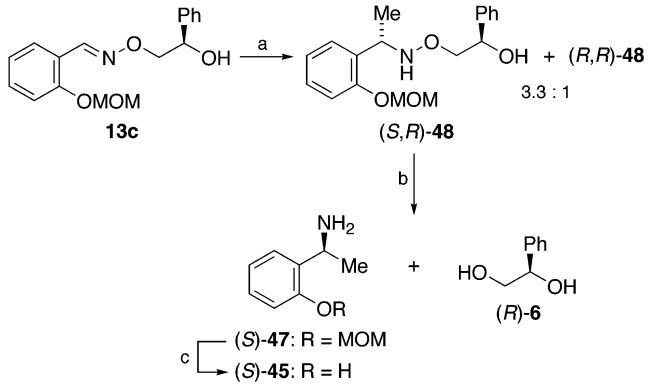
Enantioselective Synthesis of Calcium Receptor Agonists, (*R*)-NPS R-568 and Its Thio Analogue. With the chiral 1-(aryl)ethylamines (*R*)-**36** and (*R*)-**37** prepared above, we next envisaged the use of these compounds for the enantioselective synthesis of (*R*)-NPS R-568 (**1**) and its thio analogue (**2**). The former compound,

SCHEME 5[a]



[a] Reagents and conditions: (a) MeLi (2.5 equiv), toluene, −20 °C, 74%; (b) $Mo(CO)_6$, MeCN−H_2O (15:1), 97% for (*R*)-**47**, 83% for (*S*)-**6**; (c) HCl−MeOH, reflux, 88%.

SCHEME 6[a]



[a] Reagents and conditions: (a) MeLi (2.5 equiv), toluene, −20 °C, 78%; (b) $Mo(CO)_6$, MeCN−H_2O (15:1), 91% for (*S*)-**47**, 74% for (*R*)-**6**; (c) HCl−MeOH, reflux, 88%.

which represents a new class of calcium receptor agonist (calcimimetics) with potent and selective activity, has been developed into drug candidates for the treatment of primary and secondary hyperparathyroidism.[17] The (*R*)-enantiomer of **1** has been reported to be 10- to 100-fold more potent than the (*S*)-enantiomer.[17] The latter compound, **2**, recently synthesized as a racemate, has been proposed to be a potent calcium-receptor-modulating agent.[6]

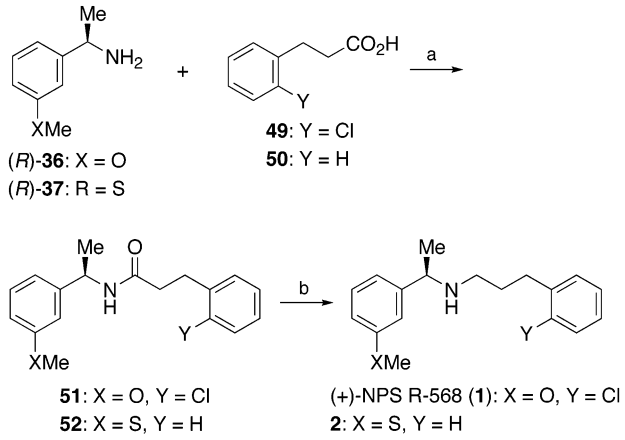
Coupling of (*R*)-**36** and 3-(2-chlorophenyl)propionic acid (**49**) was effected with DCC-DMAP (CH_2Cl_2, rt) to give the amide **51** in 95% yield. The DIBALH reduction of **51** yielded (+)-(*R*)-NPS R-568 (**1**), $[\alpha]^{20}_D$ +41.9 (*c* 1.1, $CHCl_3$) [lit.[5b] $[\alpha]_D$ +38.6 (*c* 1.1, $CHCl_3$)]. In a similar sequence, coupling of (*R*)-**37** with phenylpropionic acid (**50**) afforded the amide **52**, which underwent DIBALH reduction to provide the thio analogue of **1**, (*R*)-(+)-*N*-{1-[3-(methylsulfanyl)phenyl]ethyl}-3-phenyl-1-propanamine (**2**), $[\alpha]^{20}_D$ +44.4 (*c* 0.3, $CHCl_3$) (Scheme 7).

(15) (a) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett.* **1999**, *40*, 739−742. (b) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 465−467. (c) Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett.* **2001**, *3*, 193−196. (d) Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469−2472.

(16) Published procedure on the enantioselective synthesis of (+)-1-(2-hydroxyphenyl)ethylamine [(*S*)-**45**] relied on asymmetric reduction of 2-benzyloxyacetophenone *O*-methyloxime, prepared in 77% yield from 2-hydroxyacetophenone, using an optically active amino-borane reagent. This led to (+)-1-(2-benzyloxyphenyl)ethylamine with 67% ee in 53% yield, which was debenzylated by hydrogenolysis to produce (*S*)-**45**. Yoneyoshi, Y.; Suzukamo, G.; Sakito, Y. Eur. Pat. Appl. EP 311,385, 1989; *Chem. Abstr.* **1990**, *112*, 35431z.

(17) (a) Steffey, M. E.; Fox. J.; Van Wagenen, B. C.; Balandrin, M. F.; Nemeth, E. F. *J. Bone Miner. Res.* **1993**, *8*, S175. (b) Silverberg, S. J.; Bone, H. G., III; Marriott, T. B.; Locker, F. G.; Thys-Jacobs, S.; Dziem, G.; Kaatz, E. L.; Sanguinetti, E. L.; Bilezikian, J. P. *New Engl. J. Med.* **1997**, *337*, 1506−1510. (c) Nemeth, E. F.; Steffey, M. E.; Hammerland, L. G.; Hung, B. C. P.; Van Wagenen, B. C.; DelMar, E. G.; Balandrin, M. F. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4040−4045.

SCHEME 7[a]

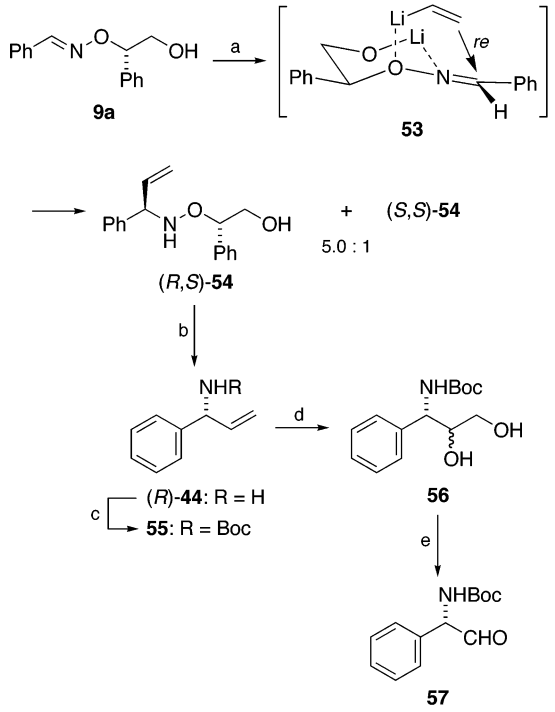


[a] Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 95% for **51**, 92% for **52**; (b) DIBAL-H, CH_2Cl_2, rt, 71% for **1**, 81% for **2**.

Enantioselective Synthesis of NK-1 Receptor Antagonists, (+)-CP-99,994 and (+)-CP-122,721. The neuropeptide substance P (SP) is involved in a variety of biological actions, including pain transmission, vasodilatation, smooth muscle contraction, and neurogenic inflammation.[18] It binds preferentially to the NK-1 receptor. Although the physiological role of the NK-1 receptor remains to be more clearly defined, selective SP receptor antagonists might be of potential therapeutic value. Recently, the search for nonpeptide antagonists of the NK-1 receptor led to the discovery of CP-99,994 (**3**), which has been shown to bind with high affinity to the human and rodent NK-1 receptors and to possess potent antiemetic activity.[19] Since the discovery of **3**, numerous 3-amino- or 3-alkoxy-2-phenylpiperidines have been tested, and it has been established that the cis relationship between the two substituents on the piperidine ring and (2*S*,3*S*)-configuration are required for high-affinity binding to the human NK-1 receptor.[20] More recently, the trifluoromethoxy analogue, CP-122,721 (**4**), was developed as a second-generation NK-1 receptor antagonist, which shows a significant increase in efficacy for in vivo blockade of NK-1 receptor-mediated responses, together with its potent antiemetic activity.[21] These nonpeptide ligands **3** and **4** were indicated to be much more potent NK-1 receptor antagonists than the enantiomerical antipodes designated as CP-100,263 (*ent*-**3**) and CP-132,687 (*ent*-**4**), respectively.[19,21]

With efficient hydroxyoxime ether-based nucleophilic addition leading to the enantioselective preparation of 1-(aryl)ethylamines thus established, our next objective was to extend this methodology to the enantioselective total synthesis of the NK-1 antagonists, CP-99,994 (**3**) and CP-122,721 (**4**). Toward this end, the 1-phenyl hydroxyoxime ether **9a** prepared above was subjected to treatment with vinyllithium (5 equiv) in toluene at 0 °C, resulting in a 5.0:1 selectivity favoring the desired (1′*R*)-epimer (*R*,*S*)-**54** (Scheme 8). The *re* face selectivity observed in this reaction can be accounted for in terms of a six-membered lithium-coordinated transition state **53** consistent with the results previously described above in nucleophilic addition of MeLi to the chiral hydroxy oxime ethers.

SCHEME 8[a]



[a] Reagents and conditions: (a) CH_2=CHLi (5 equiv), toluene−cyclohexane, 0 °C, 79%; (b) Zn, AcOH, THF−H_2O (3:1), 88%; (c) $(Boc)_2O$, NaOH, dioxane−H_2O, 99%; (d) OsO_4, NMO, MeCN−H_2O (2:1), 99%; (e) $NaIO_4$, Et_2O−H_2O, 99%.

The vinyl adduct (*R*,*S*)-**54** underwent N−O bond cleavage using Zn−AcOH to give the primary amine (*R*)-**44**, allowing us to confirm the absolute configuration of the newly formed stereocenter to be the desired *R* on the basis of comparison of optical rotation of synthetic (*R*)-**44**, $[\alpha]^{25}_D$ +10.2 (*c* 1, $CHCl_3$), with the published value,[22] $[\alpha]^{25}_D$ +10.3 (*c* 4, $CHCl_3$). After protection of (*R*)-**44** as its *N*-Boc derivative **55**, the olefinic double bond was cleaved by a two-step sequence via OsO_4-catalyzed dihydroxylation followed by oxidation with $NaIO_4$ to afford the aldehyde **57** in an almost quantitative yield.

Allylation of **57** with allylmagnesium bromide (Et_2O, −80 °C) (Scheme 9) provided the secondary alcohol **58** as a diastereomeric mixture (α-OH/β-OH = 1.2:1), which was protected as the TBDMS ether to give **59** as a diastereomeric mixture. Hydroboration of **59** using siamylborane followed by a hydrogen peroxide basic workup yielded the primary alcohol **60**. The mesylate **61** derived from **60** underwent *t*-BuOK-mediated cyclization

(18) (a) von Euler, V. S.; Gaddum, J. H. *J. Physiol.* **1931**, *72*, 577−583. (b) Chang, M. M.; Leeman, S. E. *J. Biol. Chem.* **1970**, *245*, 4784−4790. (c) Pernow, B. *Pharmacol. Rev.* **1983**, *35*, 85−141. (d) Nakanishi, S. *Physiol. Rev.* **1987**, *67*, 1117−1142. (e) Vaught, J. *Life Sci.* **1988**, *43*, 1419−1431.

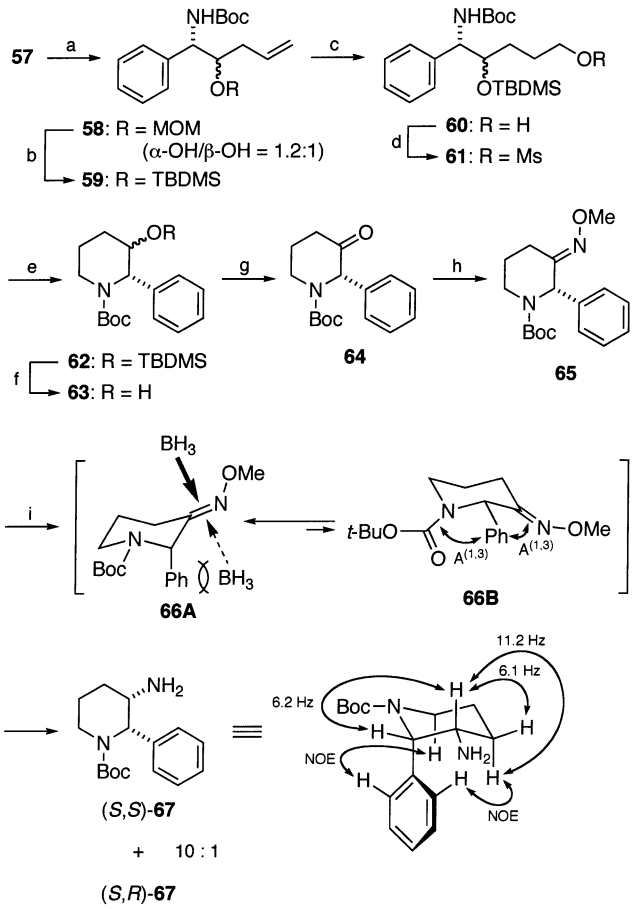
(19) (a) Watson, J. W.; Gonsalves, S. F.; Fossa, A. A.; McLea, S.; Seeger, T.; Obach, S.; Andrews, P. L. R. *Br. J. Pharmacol.* **1995**, *115*, 84−94. (b) Zaman, S.; Woods, A. J.; Watson, J. W.; Reynolds, D. J. M.; Andrews, P. L. R. *Neuropharmacology* **2000**, *39*, 316−323.

(20) Boks, G. J.; Tollenaere, J. P.; Kroon, J. *Bioorg. Med. Chem.* **1997**, *5*, 535−547.

(21) McLean, S.; Ganong, A.; Seymour, P. A.; Bryce, D. K.; Crawford, R. T.; Morrone, J.; Reynolds, L. S.; Schmidt, A. W.; Zorn, S.; Watson, J.; Fossa, A.; DePasquale, M.; Rosen, T.; Nagahisa, A.; Tsuchiya, M.; Heym, J. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 900−908.

(22) Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **2000**, *11*, 4017−4025.

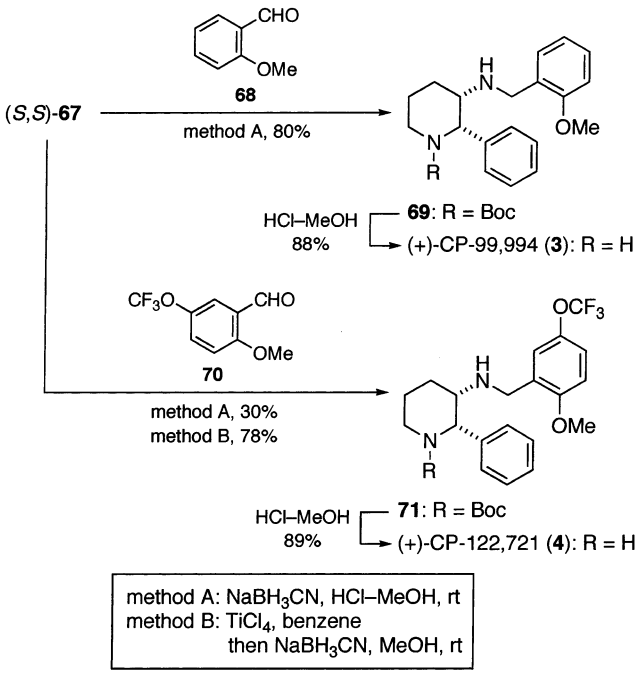
SCHEME 9[a]



[a] Reagents and conditions: (a) CH_2=$CHCH_2MgBr$, Et_2O, −80 °C, 99%; (b) TBDMSCl, imidazole, DMF, 94%; (c) $(Sia)_2BH$, Et_2O, then NaOH, H_2O_2, 94%; (d) MsCl, Et_3N, CH_2Cl_2; (e) *t*-BuOK, THF, rt 96% over two steps; (f) TBAF, THF, 99%; (g) Dess−Martin periodinate, 88%; (h) NH_2OMe·HCl, pyridine, rt 96%; (i) BH_3·THF, 45 °C, 70%.

at room temperature to provide the piperidine derivative **62** in 96% overall yield. After deprotection of the TBDMS group with TBAF, a 1.2:1 mixture of cis/trans isomers of the hydroxypiperidine **63** was subjected to Dess−Martin oxidation[23] to form the ketone **64**.[24] Treatment of **64** with methyloxyamine hydrochloride and pyridine at room temperature yielded (*E*)-oxime ether **65** as a single geometrical isomer. Upon treatment of **65** with borane−THF complex in THF at 45 °C, stereoselective reduction of the imine moiety proceeded along with reductive cleavage of the N−O bond, affording the 2,3-cis-disubstituted piperidine derivative (*S*,*S*)-**67** as a major diastereomer in a 10:1 ratio and 70% combined yield. The configuration and conformation of (*S*,*S*)-**67** were determined by the coupling constants and NOE difference data. The stereoselectivity observed in the reduction of **65** can be rationalized by invoking a chairlike conformation **66A** with an axially disposed phenyl group, which minimizes the unfavorable 1,3-allylic interactions existing in the alternative conformation **66B**. The bottom face

SCHEME 10



of the C=N bond of the conformation **66A** is sterically hindered by the axial phenyl group, so that the approach of borane can take place preferentially from the less hindered top face.

The 3-aminopiperidine derivative (*S*,*S*)-**67** thus obtained was converted to **69** via reductive amination with 2-methoxybenzaldehyde (**68**) under the conditions using sodium cyanoborohydride in HCl−MeOH at room temperature (method A). Deprotection of the *N*-Boc group with HCl−MeOH provided CP-99,994 dihydrochloride (**3**·2HCl), mp 254.5 °C (EtOH) [lit.[7a] mp 255 °C (EtOH)]; $[\alpha]^{25}_D$ +75.5 (*c* 1.1, MeOH) [lit.[7a] $[\alpha]^{25}_D$ +77 (*c* 1.0, MeOH)], in 88% yield. The ^{1}H NMR data for the free base **3** was identical with those reported[7a] for racemic **3** in the literature.

The same protocol was applied to the preparation of CP-122,721 (**4**) (Scheme 10). Thus, 3-aminopiperidine (*S*,*S*)-**67** was subjected to reductive amination using 5-trifluoromethyl-2-methoxybenzaldehyde (**70**) via method A to give **71** with an unsatisfactory yield (30%). The low yield of this reaction most likely results from the presence of the electron-withdrawing 5-trifluoromethyl group in **70**, which decreases the electrophilicity of the intermediacy imine. The electrophilicity of the imine can be enhanced by complexation with a Lewis acid to form a reactive iminium salt.[25] Therefore, (*S*,*S*)-**67** was treated with **70** and sodium cyanoborohydride in the presence of $TiCl_4$ in MeOH−benzene at room temperature (method B). In this manner, the yield of the reductive amination product **71** was significantly improved up to 78%. Deprotection of the *N*-Boc group in HCl−MeOH furnished, in 89% yield, CP-122,721 (**4**) as the dihydrochloride salt (**4**·2HCl), mp 275−276 °C (EtOH−Et_2O) (lit.[9] mp 277−278 °C); $[\alpha]^{26}_D$ +75.6 (*c* 1.0, MeOH) [lit.[9] $[\alpha]^{20}_D$ +71.2 (*c* 1.0, MeOH)].

(23) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J.; Smith, A. B., III. *Org. Synth.* **1999**, *77*, 141−152.

(24) Compound **64** has been prepared from (2*S*,3*S*)-**63** by Swern oxidation; see: Kulagowski, J. J.; Curtis, N. R.; Swain, C. J.; Williams, B. J. *Org. Lett.* **2001**, *3*, 667−670

(25) (a) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883−5889. (b) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Am. Chem. Soc.* **2000**, *122*, 2122−2123.

Conclusion

In conclusion, we have developed an efficient method for the enantioselective preparation of (*R*)- and (*S*)-1-(aryl)ethylamines via diastereoselective addition of organolithium reagents to the (*E*)-arylaldehyde oxime ethers bearing a (1*S*)-2-hydroxy-1-phenylethyl or (2*R*)-1-hydroxy-2-phenylethyl group as a chiral auxiliary, both derived from a single precursor, methyl (*R*)-mandelate. This synthetic protocol involving hydroxyoxime ether-based methylation was applied in an enantiodivergent fashion to the preparation of both enantiomers of 1-(2-hydroxyphenyl)ethylamine, which has been previously used as an efficient chiral auxiliary for the synthesis of natural products in this laboratory. The synthetic utility of this methodology was demonstrated by further application to the enantioselective synthesis of a new type of calcium receptor agonist (calcimimetics), (*R*)-(+)-NPS R-568 and its thio analogue. We also presented diastereoselective vinylation accomplished by the application of the hydroxy oxime ether-based protocol using vinyllithium, which allowed the development of the enantioselective synthesis of the NK-1 receptor antagonists (+)-CP-99,994 and (+)-CP-122,721.

Experimental Section

(2*S*)-2-[({(1*R*)-1-[2-(Methoxymethoxy)phenyl]ethyl}amino)oxy]-2-phenylethanol [(*R*,*S*)-46] and (2*S*)-2-[({(1*S*)-1-[2-(Methoxymethoxy)phenyl]ethyl}amino)oxy]-2-phenylethanol [(*S*,*S*)-46]. To a stirred ice-cold solution of **9c** (110 mg, 0.369 mmol) in toluene (3.7 mL) was added a 1.14 M solution of methyllithium in Et_2O (0.323 mL, 0.369 mmol) under N_2 atmosphere. After 5 min, the mixture was cooled to −20 °C and a 1.14 M solution of methyllithium in Et_2O (0.485 mL, 0.553 mmol) was again added, and then stirring was continued for another 25 min at −20 °C. The reaction was quenched with water (10 mL) under cooling, the organic layer separated, and the aqueous layer extracted with ether (3 × 25 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (hexanes−EtOAc, 4:1) to give as the first fraction (*R*,*S*)-**46** (78 mg, 67%) as a colorless oil: $[\alpha]^{25}_D$ +56.5 (*c* 1.6, $CHCl_3$); IR (neat) 3408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (3H, d, J = 6.8 Hz), 3.47 (3H, s), 3.65−3.69 (1H, A part of ABX, J = 12.1, 2.9 Hz), 3.81−3.62 (1H, B part of ABX, J = 12.1, 8.8 Hz), 4.62 (1H, q, J = 6.8 Hz), 4.84 (1H, dd, J = 8.8, 2.7 Hz), 5.19 (1H, 1/2 ABq, J = 6.8 Hz), 5.21 (1H, 1/2 ABq, J = 6.8 Hz), 7.00 (1H, td, J = 7.5, 1.0 Hz), 7.10 (1H, dd, J = 8.3, 1.0 Hz), 7.22−7.32 (6H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.3 (CH_3), 55.1 (CH), 56.3 (CH_3), 68.0 (CH_2), 85.4 (CH), 94.7 (CH_2), 114.5 (CH), 122.2 (CH), 126.8 (CH, 2 carbons), 127.9 (CH), 128.0 (CH), 128.5 (CH, 2 carbons), 128.7 (CH), 130.7 (C), 138.7 (C), 155.0 (C); EIMS *m*/*z* (relative intensity) 319 (M^+ + 2, 21), 318 (M^+ + 1, 100), 197 (28), 182 (5), 165 (12), 150 (5), 121 (83), 102 (86), 90 (51), 77 (37). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.04; H, 7.21; N, 4.25.

The second fraction gave (*S*,*S*)-**46** (8.6 mg, 7%) as a colorless oil: $[\alpha]^{20}_D$ +29.2 (*c* 0.2, $CHCl_3$); IR (neat) 3407 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, d, J = 6.8 Hz), 3.48 (3H, s), 3.59 (1H, A part of ABX, J = 12.1, 2.7 Hz), 3.74 (1H, B part of ABX, J = 12.1, 8.7 Hz), 4.66 (1H, q, J = 6.8 Hz), 4.78 (1H, dd, J = 8.7, 2.7 Hz), 5.22 (2H, s), 7.04 (1H, t, J = 7.4 Hz), 7.10 (1H, d, J = 8.2 Hz), 7.22−7.42 (7H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4 (CH_3), 54.7 (CH), 56.4 (CH_3), 67.8 (CH_2), 85.7 (CH), 94.8 (CH_2), 114.5 (CH), 122.2 (CH), 126.8 (CH, 2 carbons), 127.8 (CH), 128.1 (CH), 128.5 (CH, 3 carbons), 131.2 (C), 138.8 (C), 155.0 (C); ESI *m*/*z* $[M + H]^+$ 318; HRMS (ESI) calcd for $C_{18}H_{24}NO_4$ $[M + H]^+$ 318.1705, found 318.1727.

(1*R*)-1-[2-(Methoxymethoxy)phenyl]ethanamine [(*R*)-47]. To a solution of (*R*,*S*)-**46** (416 mg, 1.31 mmol) in a mixture of MeCN−water (15:1) (13 mL) was added $Mo(CO)_6$ (692 mg, 2.62 mmol) at room temperature, and the mixture was stirred at 85 °C. After 1 h, concentrated NH_4OH (10 mL) was added and the resultant mixture was stirred for 1 h at room temperature and extracted with $CHCl_3$ (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give the crude product, which was subjected to chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 200:9:1) to give as the first fraction (*S*)-phenylethanediol [(*S*)-**6**] (156 mg, 83%). The second fraction gave (*R*)-**47** (230 mg, 97%) as a pale yellow oil: $[\alpha]^{25}_D$ +14.3 (*c* 0.6, $CHCl_3$); IR (neat) 3365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, d, J = 6.7 Hz), 3.49 (3H, s), 4.40 (1H, q, J = 6.7 Hz), 5.23 (2H, s), 6.69 (1H, td, J = 7.5, 1.1 Hz), 7.07 (1H, dd, J = 8.2, 1.0 Hz), 7.16−7.18 (1H, m), 7.35 (1H, dd, J = 7.6, 1.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.2 (CH_3), 45.9 (CH), 56.1 (CH_3), 94.3 (CH_2), 113.9 (CH), 121.8 (CH), 125.8 (CH), 127.6 (CH), 136.0 (C), 154.3 (C); EIMS *m*/*z* (relative intensity) 182 (M^+ + 1, 6), 180 (M^+ − 1, 34), 179 (5), 167 (9), 166 (100), 164 (9), 150 (77), 148 (16). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.28; H, 8.32; N, 7.55.

2-[(1*R*)-1-Aminoethyl]phenol [(*R*)-45]. To a solution of (*R*)-**47** (230 mg, 1.26 mmol) in MeOH (13 mL) was added concentrated HCl (1 mL), and the mixture was stirred at room temperature for 30 min. After addition of saturated aqueous K_2CO_3 (10 mL), the mixture was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$). Evaporation of the solvent followed by chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 200:9:1) of the residue gave (*R*)-**45** (153 mg, 88%) as yellow cubics: mp 91−92 °C; $[\alpha]^{25}_D$ −5.75 (*c* 0.2, $CHCl_3$) [lit.[25] $[\alpha]^{25}_D$ −5.17 (*c* 0.6, $CHCl_3$)]. Spectroscopic data coincided with those of reported material.[25] Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.10; H, 7.92; N, 9.82.

(1*R*)-2-[({(1*S*)-1-[2-(Methyloxymethoxy)phenyl]ethyl}amino)oxy]-1-phenylethanol [(*S*,*R*)-48] and (1*R*)-2-[({(1*R*)-1-[2-(Methyloxymethoxy)phenyl]ethyl}amino)oxy]-1-phenylethanol [(*R*,*R*)-48]. In the same manner described above for the methylation of the hydroxyoxime ethers **9c**, **13c** was subjected to methylation. Workup and chromatography (hexanes−EtOAc, 4:1) gave as the first fraction (*S*,*R*)-**48** (253 mg, 60%) as a colorless oil: $[\alpha]^{20}_D$ −21.7 (*c* 1.0, $CHCl_3$); IR (neat) 3420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, d, J = 6.8 Hz), 3.50 (3H, s), 3.72 (1H, A part of ABX, J = 12.1, 8.1 Hz), 3.79 (1H, B part of ABX, J = 12.1, 1.4 Hz), 4.60 (1H, q, J = 6.8 Hz), 5.02 (1H, dd, J = 8.1, 1.4 Hz), 5.24 (1H, 1/2 ABq, J = 6.7 Hz), 5.25 (1H, 1/2ABq, J = 6.7 Hz), 7.01−7.37 (9H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.1 (CH_3), 55.1 (CH_3), 74.5 (CH), 78.6 (CH_2), 94.6 (CH_2), 114.4 (CH), 126.1 (CH, 2 carbons), 127.6 (CH, 2 carbons), 127.8 (CH), 128.3 (CH, 2 carbons), 128.6 (CH), 130.3 (C), 140.7 (C), 154.9 (C); EIMS *m*/*z* (relative intensity) 318 (M^+ + l, 11), 317 (M^+, 100). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.10; H, 7.29; N, 4.45.

The second fraction gave [(*R*,*R*)-**48**] (77 mg, 18%) as a colorless oil: $[\alpha]^{20}_D$ −23.0 (*c* 0.5, $CHCl_3$); IR (neat) 3407 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, d, J = 6.8 Hz), 3.50 (3H, s), 3.78 (1H, A part of ABX, J = 12.1, 8.4 Hz), 3.81 (1H, B part of ABX, J = 12.1, 2.4 Hz), 4.60 (1H, q, J = 6.8 Hz), 5.01 (1H, dd, J = 8.4, 2.4 Hz), 5.24 (1H, 1/2 ABq, J = 6.7 Hz), 5.25 (1H, 1/2 ABq, J = 6.7 Hz), 6.00 (1H, br s), 7.02−7.36 (9H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.2 (CH_3), 55.2 (CH_3), 56.4 (CH), 74.8 (CH), 78.6 (CH_2), 94.7 (CH_2), 114.5 (CH), 122.1 (CH), 126.2 (CH, 2 carbons), 127.6 (CH), 128.0 (CH), 128.4 (CH, 2 carbons), 128.8 (CH), 130.4 (C), 140.7 (C), 155.0 (C); ESI *m*/*z* $[M + H]^+$ 318; HRMS (ESI) calcd for $C_{18}H_{24}NO_4$ $[M + H]^+$ 318.1708, found 318.1728.

(1*S*)-1-[2-(Methoxymethoxy)phenyl]ethanamine [(*S*)-47]. In the same manner described above for the preparation of the phenylethanamines (*R*)-**47**, (*S*,*R*)-**48** (253 mg, 0.798

mmol) was subjected to N−O bond cleavage. Workup and chromatography ($CHCl_3$−MeOH−35% NH_4OH, 200:9:1) gave as the first fraction (*R*)-phenylethanediol [(*R*)-**6**] (82 mg, 74%). The second fraction gave (*S*)-**47** (132 mg, 91%) as a pale yellow oil: $[\alpha]^{23}_D$ −14.4 (*c* 1.5, $CHCl_3$)

2-[(1*S*)-1-Aminoethyl]phenol [(*S*)-45]. In the same manner described above for the preparation of (*R*)-**45**, (*S*)-**47** (131 mg, 0.726 mmol) was hydrolyzed. Workup and chromatography ($CHCl_3$−MeOH−35% NH_4OH, 200:9:1) gave (*S*)-**45** (88 mg, 88%) as yellow cubics: $[\alpha]^{20}_D$ +5.3 (*c* 0.2, $CHCl_3$).

3-(2-Chlorophenyl)-*N*-[(*R*)-1-(3-methoxyphenyl)ethyl]-propanamide (51). To a stirred solution of **49** (30.0 mg, 0.163 mmol) in CH_2Cl_2 (0.65 mL) were added dicyclohexylcarbodiimide (37.0 mg, 0.179 mmol) and *N*,*N*-(dimethylamino)pyridine (2.0 mg, 0.016 mmol). Stirring was continued for 30 min at room temperature until a white precipitate deposited; (*R*)-**38** (24 mg, 0.163 mmol) was added, and the mixture was stirred for an additional 10 min at the same temperature. The white precipitate was removed by filtration through a Celite pad, the filtrate concentrated in vacuo, and the residue purified by chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 1600:9:1) to give **51** (49.2 mg, 95%) as colorless needles: mp 92−92.5 °C ($CHCl_3$−hexane); $[\alpha]^{20}_D$ +45.6 (*c* 1.0, $CHCl_3$); IR (KBr) 3286, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, d, J = 6.9 Hz), 2.49 (2H, td, J = 7.4, 0.9 Hz), 3.08 (2H, t, J = 7.6 Hz), 3.79 (3H, s), 5.07 (1H, quint, J = 7.1 Hz), 5.56 (1H, br d, J = 7.1 Hz), 6.78−6.81 (3H, m), 7.13−7.34 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.7 (CH_3), 29.7 (CH_2), 36.5 (CH_2), 48.8 (CH_3), 53.3 (CH), 112.3 (CH), 112.6 (CH), 118.5 (CH), 127.0 (CH), 127.9 (CH), 129.6 (CH), 129.8 (CH), 130.9 (CH), 133.8 (C), 138.4 (C), 144.8 (C), 159.9 (C), 170.8 (C); EIMS *m*/*z* (relative intensity) 319 (M^+[^{37}Cl], 3), 317 (M^+[^{35}Cl], 9), 282 (16), 167 (21), 150 (21), 107 (74), 91 (41). Anal. Calcd for $C_{18}H_{20}ClNO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.72; H, 6.33; N, 4.25.

***N*-{(1*R*)-1-[3-(Methylsulfanyl)phenyl]ethyl}-3-phenyl-1-propanamide (52).** In the same manner described above for the preparation of **51**, (*R*)-**39** (30 mg, 0.179 mmol) was allowed to react with **50** (27.0 mg, 0.179 mmol). Workup and chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 1600:9:1) furnished **52** (49.8 mg, 93%) as colorless needles ($CHCl_3$−hexane): mp 86−87.5 °C; $[\alpha]^{19}_D$ +66.9 (*c* 0.1, $CHCl_3$); IR (neat) 3285, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, d, J = 7.0 Hz), 2.45 (3H, s), 2.46 (2H, t, J = 7.3 Hz), 2.95 (2H, t, J = 7.6 Hz), 5.04 (1H, quint, J = 7.0 Hz), 5.59 (1H, br d, J = 7.1 Hz), 6.95 (1H, br d, J = 7.7 Hz), 7.71−7.26 (8H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.9 (CH_3), 21.7 (CH_3), 31.8 (CH_2), 38.6 (CH_2), 48.6 (CH), 123.0 (CH), 124.5 (CH), 125.4 (CH), 126.3 (CH), 128.4 (CH, 2 carbons), 128.6 (CH, 2 carbons), 129.2 (CH), 138.9 (C), 140.8 (C), 143.9 (C), 171.2 (C); EIMS *m*/*z* (relative intensity) 301 (M^+ + 2, 17), 300 (M^+ + 1, 26), 299 (M^+, 100), 284 (3), 208 (7), 166 (10), 151 (18), 136 (5), 105 (8), 91 (12), 76 (5). Anal. Calcd for $C_{18}H_{21}NOS$: C, 72.20; H, 7.07; N, 4.68. Found: C, 72.50; H, 7.41; N, 4.58.

3-(2-Chlorophenyl)-*N*-[(*R*)-1-(3-methoxyphenyl)ethyl]-1-propanamine (NPS R-568) (1). To a stirred solution of **51** (32.7 mg, 0.18 mmol) in CH_2Cl_2 (1.1 mL) was added a 0.95 M solution of diisobutylaluminum hydride in toluene (0.22 mL, 0.21 mmol) at room temperature. After being stirred for 3 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL). The mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 1000:9:1) gave **1** (22.2 mg, 71%) as a pale yellow oil: $[\alpha]^{20}_D$ +41.9 (*c* 1.1, $CHCl_3$) [lit.[5b] $[\alpha]^{20}_D$ +38.6 (*c* 1.1, $CHCl_3$)]; IR (neat) 3058, 2957, 2927, 2857, 2833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, d, J = 6.6 Hz), 1.76−1.81 (2H, m), 2.50−2.59 (2H, m), 2.70−2.77 (2H, m), 3.74 (1H, q, J = 6.5 Hz), 3.82 (3H, s), 6.79 (1H, ddd, J = 8.3, 2.4, 0.9 Hz), 6.89−6.90 (2H, m), 7.11−7.33 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.4 (CH_3), 29.8 (CH_2), 30.3 (CH_2), 31.4 (CH_2), 47.4 (CH_3), 55.3 (CH), 58.4 (CH), 112.2 (CH), 112.3 (CH), 119.1 (CH), 126.8 (CH), 127.3 (CH), 129.4 (CH), 129.5 (CH), 130.4 (CH), 134.0 (C), 139.9 (C), 147.7 (C), 159.9 (C); EIMS *m*/*z* (relative intensity) 306 (M^+[^{37}Cl], 8), 304 (M^+[^{35}Cl], 24), 290 (100), 288 (44), 163 (65), 134 (64), 135 (55). **1**·HCl: mp 190.5−191.5 °C (EtOH). Anal. Calcd for $C_{18}H_{24}Cl_2NO$: C, 63.53; H, 6.81; N, 4.12. Found: C, 63.56; H, 6.94; N, 4.01.

***N*-{(1*R*)-1-[3-(Methylsulfanyl)phenyl]ethyl}-3-phenyl-1-propanamine (2).** In the same manner described above for the preparation of **1**, **52** (20.0 mg, 0.067 mmol) was reduced to give **2** (15.3 mg, 80%) as a pale yellow oil: $[\alpha]^{19}_D$ +44.4 (*c* 0.6, $CHCl_3$); IR (neat) 3346 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 6.6 Hz), 1.76−1.81 (2H, m), 2.45−2.66 (4H, m), 3.71 (1H, q, J = 6.6 Hz), 7.06−7.28 (9H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.9 (CH_3), 24.4 (CH_3), 32.0 (CH_2), 33.7 (CH_2), 47.4 (CH_2), 59.4 (CH), 123.5 (CH), 124.9 (CH), 125.1 (CH), 125.8 (CH), 128.4 (CH), 128.4 (CH), 129.0 (CH), 138.5 (C), 142.3 (C), 146.7 (C); EIMS *m*/*z* (relative intensity) 286 (M^+ + 1, 10), 285 (M^+, 46), 271 (17), 270 (88), 180 (16), 166 (11), 152 (86), 136 (33), 117 (19), 104 (36), 91 (100), 77 (30).

(2*S*)-2-Phenyl-2-({[(1*R*)-1-phenyl-2-propenyl]amino}-oxy)ethanol [(*R*,*S*)-54] and (2*S*)-2-Phenyl-2-({[(1*S*)-1-phenyl-2-propenyl]amino}oxy)ethanol [(*S*,*S*)-54]. To a stirred solution of tetravinyltin (3.22 g, 14.2 mmol) was added a 1.06 M solution of phenyllithium in cyclohexane (41 mL, 42.6 mmol) under a N_2 atmosphere at 0 °C, and the stirring was continued for 30 min to give a 0.71 M solution of vinyllithium. A portion of prepared vinyllithium (16.4 mL, 17.0 mmol) was transferred via cannula into a stirring solution of **9a** (1.71 g, 7.09 mmol) in toluene (71 mL) at 0 °C. After the mixture was stirred for 5 min, another vinyllithium (24.6 mL, 25.5 mmol) was added to the mixture at 0 °C and stirring was continued for an additional 25 min. After addition of water (100 mL), the organic phase was separated, and the aqueous phase was extracted with ether (3 × 200 mL). The organic phases were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by chromatography (hexanes−EtOAc, 3.5:1) gave as the first fraction (*S*,*S*)-**54** (252 mg, 13%) as a colorless oil: $[\alpha]^{21}_D$ +69.7 (*c* 0.2, $CHCl_3$); IR (neat) 3408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.50 (1H, m), 3.63 (1H, dd, J = 11.8, 8.8 Hz), 4.65 (1H, d, J = 7.6 Hz), 4.70 (1H, dd, J = 8.8, 3.0 Hz), 5.22 (2H, dd, J = 17.6, 10.3 Hz), 5.96 (1H, ddd, J = 17.6, 10.3, 7.6 Hz), 7.25−7.40 (10H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 66.9 (CH_2), 68.7 (CH), 86.2 (CH), 118.0 (CH_2), 126.8 (CH, 2 carbons), 127.8 (CH), 127.85 (CH), 127.9 (CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 138.6 (C), 140.2 (C); ESI *m*/*z* [M + H]$^+$ 270; HRMS (ESI) calcd for $C_{17}H_{20}NO_4$ [M + H]$^+$ 270.1494, found 270.1496. The second fraction afforded (*R*,*S*)-**54** (1.26 g, 66%) as a colorless oil: $[\alpha]^{27}_D$ +34.3 (*c* 1.1, $CHCl_3$); IR (neat) 3419 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.91 (1H, br s), 3.59−3.62 (1H, A part of ABX, J = 12.1, 2.7 Hz), 3.74−3.79 (1H, B part of ABX, J = 12.0, 8.8 Hz), 4.59 (1H, d, J = 7.5 Hz), 4.75 (1H, dd, J = 8.8, 3.0 Hz), 5.23 (1H, d, J = 10.4 Hz), 5.30 (1H, d, J = 17.2 Hz), 6.10 (1H, ddd, J = 17.2, 10.4, 7.5 Hz), 7.19−7.30 (10H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 67.1 (CH_2), 68.6 (CH), 86.1 (CH), 117.7 (CH), 126.8 (CH), 127.9 (CH, 2 carbons), 128.0 (CH), 128.1 (CH), 128.5 (CH, 2 carbons), 128.7 (CH, 2 carbons), 138.3 (CH), 138.5 (C), 139.2 (C); EIMS *m*/*z* (relative intensity) 271 (M^+ + 2, 6), 270 (M^+ + 1, 46), 149 (13), 132 (2), 103 (10), 91 (6), 77 (5). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.77; H, 7.21; N, 5.07.

(1*R*)-1-Phenyl-2-propen-1-amine [(*R*)-44]. To a stirred solution of (*R*,*S*)-**54** (1.40 g, 5.18 mmol) in a mixture of AcOH−THF−water (3:1:1) (37 mL) was added zinc powder (8.10 g, 124 mmol) in several portions at room temperature, and stirring was continued for 4 h at 60 °C. After addition of concentrated NH_4OH (20 mL), the mixture was stirred at room temperature for 1 h and then inorganic material was removed by filtration through a Celite pad. The filtrate was extracted with $CHCl_3$ (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 500:9:1) to give as the first

fraction (*S*)-phenylethanediol [(*S*)-**6**] (615 mg, 86%). The second fraction provided (*R*)-**44** (607 mg, 88%) as a pale yellow oil: $[\alpha]^{25}_D$ +10.2 (*c* 1, $CHCl_3$); IR (neat) 3366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (2H, br s), 4.52 (1H, td, J = 6.1, 1.1 Hz), 5.10 (1H, dt, J = 10.3, 1.4 Hz), 5.24 (1H, dt, J = 17.2, 1.4 Hz), 6.03 (1H, ddd, J = 16.9, 10.2, 6.1 Hz), 7.25−7.36 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 58.5 (CH), 113.8 (CH_2), 126.7 (CH, 2 carbons), 127.2 (CH), 128.6 (CH, 2 carbons), 142.4 (CH), 14.5 (C); EIMS *m*/*z* (relative intensity) 133 (M^+, 5), 132 (M^+ − H, 40), 131 (100), 116 (24), 105 (57), 91 (6), 77 (18); HRMS (ESI) calcd for $C_9H_{12}N$ $[M + H]^+$ 134.0970, found 134.0993.

***tert*-Butyl (1*R*)-1-Phenyl-2-propenylcarbamate (55).** To a stirred solution of (*R*)-**43** (494 mg, 3.71 mmol) in dioxane (8 mL) containing a 2.5 M aqueous solution of NaOH (8 mL) was added $(Boc)_2O$ (810 mg, 3.71 mmol), and the mixture was stirred at room temperature for 30 min. After addition of water (10 mL), the mixture was extracted with ether (4 × 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (hexanes−EtOAc, 8:1) to give **55** (866 mg, 99%) as white needles: mp 67−68 °C (hexane−$CHCl_3$); $[\alpha]^{19}_D$ +65.9 (*c* 0.3, $CHCl_3$); IR (KBr) 3333, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, br s), 4.84 and 5.28 (total 1H, br s, respectively, in ca. 1.2:1.0 due to the carbamate rotamers), 5.19−5.24 (2H, m), 5.99 (1H, ddd, J = 17.3, 10.2, 5.4 Hz), 7.23−7.36 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.5 (CH_3, 3 carbons), 79.8 (C), 115.5 (CH_2), 127.1 (2 carbons) (CH), 127.3 (CH), 127.4 (CH), 127.6 (CH), 128.7 (CH), 128.8 (CH, 2 carbons), 138.1 (CH), 141.1 and 142.2 (total 1 carbon) (C), 155.1 (C); EIMS *m*/*z* (relative intensity) 233 (M^+, 1), 176 (M^+ − *t*Bu, 100), 131 (39), 116 (41), 103 (14), 91 (10), 77 (12), 56 (70); HRMS (EI) calcd for $C_{10}H_{10}NO_2$ (M^+ − *t*Bu) 176.07115, found 176.0697.

***tert*-Butyl (1*S*,2*R*)- and (1*S*,2*S*)-2,3-Dihydroxy-1-phenylpropylcarbamate (56).** To a stirred solution of **55** (574 mg, 0.246 mmol) in a mixture of MeCN−water (2:1) (24 mL) was added *N*-methylmorpholine-*N*-oxide (549 mg, 4.68 mmol) followed by a 4% aqueous solution of OsO_4 (1.53 mL, 0,24 mmol) at room temperature. After 12 h of stirring at room temperature, the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (10 mL) and the mixture was extracted with $CHCl_3$ (5 × 50 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo followed by chromatography (hexanes−EtOAc, 1:1) afforded **56** (625 mg, 95%) as a colorless oil: IR (neat) 3363, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, br s), 2.39 and 3.82−3.86 (total 1H, m, respectively, in ca. 1:1), 2.61 and 3.69 (total 1H, m, respectively, in ca. 1:1 due to the carbamate rotamers), 2.98 and 3.56 (total 1H, m and t, J = 6.0 Hz, respectively, in ca. 1:1 due to the carbamate rotamers), 3.69 and 3.96 (total 1H, m, respectively, in ca. 1:1 due to the carbamate rotamers), 4.68 and 5.17 (total 1H, t, J = 7.9 Hz and m, respectively, in ca. 1:1 due to the carbamate rotamers), 4.83 and 5.28 (total 1H, m and br d, J = 7.3 Hz, respectively, in ca. 1:1 due to the carbamate rotamers), 7.21−7.40 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 56.3 and 57.1 (total 1 carbon in 1:1), 63.5 and 64.1 (total 1 carbon respectively, in ca. 1:1 due to the carbamate rotamers) (CH_2), 74.5 and 75.5 (total 1 carbon respectively, in ca. 1:1 due to the carbamate rotamers), 127.2 (CH, total 2 carbons), 127.8 (CH), 128.1 and 128.4 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 128.9 and 128.9 (CH, total 2 carbons), 139.1 (C), 156.4 and 156.8 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers); EIMS *m*/*z* (relative intensity) 268 (M^+ + H, 1), 211 (5), 205 (23), 193 (5), 149 (95), 105 (92), 91 (21), 77 (18), 56 (100). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.90; N, 5.24. Found: C, 62.97; H, 7.90; N, 5.18.

***tert*-Butyl (1*S*)-2-Oxo-1-phenylethylcarbamate (57).** To a stirred solution of **56** (260 mg, 0.973 mmol) in a mixture of Et_2O−H_2O (2:1) (10 mL) was added $NaIO_4$ (416 mg, 1.95 mmol), and the resulting mixture was stirred for 1 h at room temperature. After the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (10 mL), the organic layer was separated and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude aldehyde **57** (227 mg, 99%). This product was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (9H, s), 5.32 (1H, br d, J = 1.5 Hz), 5.76 (1H, m), 7.26−7.45 (5H, m), 9.53 (1H, s).

***tert*-Butyl (1*S*,2*R*)- and (1*S*,2*S*)-2-Hydroxy-1-phenyl-4-pentenylcarbamate (58).** To a stirred solution of **57** (272 mg, 0.975 mmol) in ether (10 mL) was added a 1.14 M solution of allylmagnesium bromide (1.23 mL, 1.40 mmol) in ether at −80 °C under a N_2 atmosphere. After the mixture was stirred for 30 min at −80 °C, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), the organic phase separated, and the aqueous phase extracted with ether (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (hexanes−EtOAc, 6:1) to give **58** (270 mg, 99%) as colorless needles: mp 97−98 °C ($CHCl_3$−hexane); IR (KBr) 3422, 1691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 and 2.05 (total 3H in 1.2:1.0 ratio, each br s), 1.91−1.95 and 2.20−2.34 (total 2H in 1.5:0.5 ratio, each m), 3.87−3.96 (1H, m), 4.67 (1H, br s), 5.05−5.17 (2H, m), 5.38−5.42 (1H, m), 5.80−5.84 (1H, m), 7.24−7.37 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.4 (3 carbons), 38.7 and 38.8 (CH_2, total 1 carbon), 79.8 (C), 118.4 and 118.6 (CH_2, total 1 carbon, respectively, in ca. 1:1), 126.7 (CH, 2 carbons), 127.6 and 128.8 (CH, total 1 carbon, respectively, in ca. 1:1), 128.0 (CH, 2 carbons), 128.5 and 128.8 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 134.1 and 134.3 (CH, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers), 155.5 and 156.0 (C, total 1 carbon, respectively, in ca. 1:1 due to the carbamate rotamers); EIMS *m*/*z* (relative intensity) 277 (M^+, 4), 221 (6), 205 (25), 149 (100), 105 (44). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.09; H, 8.19; N, 5.02.

***tert*-Butyl (1*S*,2*R*)- and (1*S*,2*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-phenyl-4-pentenylcarbamate (59).** To a stirred solution of **58** (270 mg, 0.111 mmol) in DMF (10 mL) were added *tert*-butylchlorodimethylsilane (294 mg, 1.95 mmol) and imidazole (199 mg, 2.92 mmol), and the mixture was stirred at room temperature for 36 h. After the reaction was quenched with saturated aqueous NH_4Cl (10 mL), the organic phase was separated and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 15:1) to give **59** (358 mg, 94%) as a colorless oil: IR (neat) 1691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.48 and 0.06 (total 3H, respectively, in ca. 1:2.4, each s), −0.12 and 0.13 (total 3H in 2.4:1.0 ratio, each s), 0.83 and 0.90 (total 9H, respectively, in ca. 2.4:1 due to the carbamate rotamers, each s), 1.45 and 1.50 (total 9H, respectively, in ca. 1:2.4 due to the carbamate rotamers, each br s), 2.01 and 2.34 (total 1H, respectively, in ca. 1:2.4 due to the carbamate rotamers, each ddd, J = 14.4, 7.4, 7.3 Hz), 2.15 and 2.47 (total 1H, respectively, in ca. 1:2.4 due to the carbamate rotamers, each m), 3.86 and 4.10 (total 1H, respectively, in ca. 2.4:1 due to the carbamate rotamers, each br s), 4.69 and 4.82 (total 1H, respectively, in ca. 1:2.4 due to the carbamate rotamers, each m), 5.05 and 5.17 (total 2H, respectively, in ca. 1:2.4 due to the carbamate rotamers, each dd, J = 17.3, 13.2 and 16.0, 4.8 Hz), 5.40 (1H, br m), 5.81 and 5.91 (total 1H, respectively, in ca. 1:2.4 due to the carbamate rotamers, each m), 7.22−7.39 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.6, −5.1, −4.3 and −2.9 (CH_3, total 6 carbons), 18.0 and 18.2 (C, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 24.7 (CH_3, 3 carbons), 37.6 and 38.9 (CH_2, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 55.0 and 57.0 (CH, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 73.3 (CH), 79.4 (C), 116.6 and 117.2 (CH_2, total 1 carbon, respectively, in ca. 2.4:1 due to the

carbamate rotamers), 125.4 (CH, 2 carbons), 125.5 and 125.7 (CH, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 128.2 and 128.5 (CH, 2 carbons), 133.9 and 134.3 (CH, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 142.0 (C), 155.6 (C); EIMS *m*/*z* (relative intensity) 278 ($M^+ - 2 \times t$-Bu, 46), 250 (4), 185 (100), 149 (34). Anal. Calcd for $C_{23}H_{37}NO_3Si$: C, 67.47; H, 9.52; N, 3.58. Found: C, 97.20; H, 9.51; N, 3.34.

***tert*-Butyl (1*S*,2*R*)- and (1*S*,2*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-hydroxy-1-phenylpentenylcarbamate (60).** To a 0.9 M solution of BH_3-Me_2S complex (0.178 mL, 1.88 mmol) in CH_2Cl_2 was added 2-methyl-2-butene (0.479 mL, 4.52 mmol) with stirring at −10 °C under a N_2 atmosphere. After being stirred for 1.5 h at −10 °C, the mixture was diluted with ether (4 mL) yielding a solution of disiamylborane. The ethereal solution of disiamylborane thus prepared was added to a solution of **59** (295 mg, 0.753 mmol) in ether (7.5 mL) at 0 °C under a N_2 atmosphere, and stirring was continued for 4 h at 0 °C. To the reaction mixture was added a 3 M aqueous solution of NaOH (7.5 mL) followed by 31% H_2O_2 (7.5 mL), and then stirring was continued for 1 h at room temperature. The organic layer was separated, and the aqueous phase was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 2:1) to give **60** (290 mg, 94%) as a colorless oil: IR (neat) 3446, 1691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.54 and 0.05 (total 3H, respectively, in ca. 2.5:1, each s), −0.17 and 0.07 (total 3H, respectively, in ca. 2.5:1 due to the carbamate rotamers, each s), 0.78 and 0.90 (total 9H, respectively, in ca. 2.5:1 due to the carbamate rotamers, each s), 1.31 and 1.73 (total 3H m), 3.55 and 3.68 (total 2H, respectively, in ca. 1:2.5 due to the carbamate rotamers, each br s), 3.86 and 3.99 (total 1H, respectively, in ca. 1:2.5 due to the carbamate rotamers, each br s), 3.86 and 3.99 (total 1H, respectively, in ca. 2.5:1 due to the carbamate rotamers, each br s), 4.66 and 5.36 (total 1H, respectively, in ca. 2.5:1 due to the carbamate rotamers, each br s), 4.79 and 5.12 (total 1H, respectively, in ca. 2.5:1 due to the carbamate rotamers, each br s), 7.17−7.32 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.5 and −4.6 (CH_3, total 6 carbons), 18.1 and 18.2 (C, total 1 carbon, respectively, in ca. 2.5:1 due to the carbamate rotamers), 25.92 and 25.98 (CH_3, 3 carbons), 28.4 (CH_2, total 3 carbons), 29.0 (CH_2), 31.6 (CH_2), 56.4 (CH), 62.9 (CH_2), 74.7 (CH_2), 79.6 (C), 126.6 (CH), 127.0 (CH), 128.1 and 128.3 (CH, 2 carbons), 155.4 and 156.0 (C, total 1 carbon, respectively, in ca. 2.5:1 due to the carbamate rotamers); EIMS *m*/*z* (relative intensity) 410 ($M^+ + H$, 100), 354 (25), 309 (32); HRMS (ESI) calcd for $C_{22}H_{40}NO_4Si$ $[M + H]^+$ 410.2727, found 410.2728.

***tert*-Butyl (2*S*,3*R*)- and (2*S*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-phenyl-1-piperidinecarbamate (62).** To a stirred ice-cooled solution of **60** (245 mg, 0.598 mmol) in CH_2Cl_2 (6 mL) including triethylamine (67 mg, 0.717 mmol) was added methanesulfonyl chloride (82 mg, 0.717 mmol), and stirring was continued for 30 min. After addition of water (10 mL), the organic phase was separated and the aqueous phase was extracted with $CHCl_3$ (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo to yield the crude mesylate **61** (diastereomeric mixture of α-OTBDMS/β-OTBDMS = 1.2;1) as a colorless oil. For α-OTBDMS: ^1H NMR (300 MHz, $CDCl_3$) δ −0.15 and 0.07 (total 6H, 2.2:1, due to rotamer, s), 0.60 and 0.88 (total 9H, 2.2:1, due to rotamer), 1.56−1.92 (4H, m), 1.98 (9H, s), 3.00 (3H, s), 3.86 and 3.98 (total 1H, 2.2:1, due to rotamer), 4.11 and 4.25 (total 2H,1:2.2, due to rotamer, t, J = 6.8 Hz each), 4.64 and 4.74 (total 1H, br d, J = 8.6 Hz), 5.07 and 5.33 (total 1H br d, J = 8.6 Hz), 7.18−7.35 (5H, m). For β-OTBDMS: ^1H NMR (300 MHz, $CDCl_3$) δ −0.54 and 0.05 (total 6H, 2.2:1, due to rotamer, s each), 0.60 and 0.88 (total 9H, 2.2:1, due to rotamer, s each), 1.38 (9H, s), 1.56−1.92 (4H, m), 3.13 (3H, s), 3.86 and 3.98 (total 1H, 2.2:1, due to rotamer, m), 4.11 and 4.25 (total 2H, 1:2.2, due to rotamer, t, J = 6.8 Hz each), 4.64 and 4.74 (total 1H, br d, J = 8.6 Hz), 5.07 and 5.33 (total 1H, br d, J = 8.6 Hz), 7.18−7.35 (5H, m).

The crude mesylate **61** so obtained was, without purification, immediately dissolved in THF (6 mL). To this solution was added *t*-BuOK (201 mg, 1.79 mmol) at 0 °C, and the mixture was stirred at room temperature. After 1 h, water (10 mL) was added, and the mixture was extracted with ether (3 × 30 mL); the combined extracts were dried ($MgSO_4$). The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (hexanes−EtOAc, 15:1) to give **62** (222 mg, 94%) as a pale yellow oil: IR (neat) 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 and 0.09 (total 3H in a 1.0:1.0 ratio, each s), 0.11 and 0.13 (total 3H in a 1.0:1.0 ratio, each s), 0.87 and 0.93 (total 9H, respectively, in ca. 2.4:1, each s), 1.43 (9H, br s), 1.71−1.75 and 1.87−1.90 (total 1.5H, in a 1.0:1.0 ratio, each m), 2.15−2.47 (0.5H, m), 2.65−2.73 (0.5H, s), 2.82 (0.5H, td, J = 11.7, 3.3 Hz), 5.05 and 5.17 (total 2H, respectively, in ca. 2.4:1 due to the carbamate rotamers, each dd, J = 17.3, 13.2 and 16.0, 4.8 Hz), 3.91 (0.5H, br d, J = 13.2 Hz), 4.04 (0.5H, ddd, J = 9.2, 5.2, 4.0 Hz), 4.1 (0.5H, br d, J = 14.1 Hz), 4.4 (0.5H, dd, J = 5.7, 2.7 Hz), 5.25 (0.5H, br s), 5.35 (0.5H, br d, J = 4.3 Hz), 7.18−7.40 (5H, m) 7.58−7.61 (0.5H, d, J = 12.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.0 and −2.0 (CH_3, total 6 carbons), 19.3 and 24.4 (C, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 27.4 and 29.0 (CH_2, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 26.2 (CH_3, 3 carbons), 28.8 (CH_3, 3 carbons), 60.8 (CH), 68.3 and 72.3 (CH, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 79.4 and 79.8 (C, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 126.5 and 126.6 (CH_2, total 2 carbons), 128.0 (C, 2 carbons), 128.6 and 128.7 (CH, total 2 carbons), 138.9 and 139.2 (C, total 1 carbon, respectively, in ca. 2.4:1 due to the carbamate rotamers), 155.4 (C); EIMS *m*/*z* (relative intensity) 392 ($M^+ + H$, 100), 292 (13), 277 (27), 259 (12), 233 (16), 186 (20), 160 (16), 142 (12), 129 (10), 91 (4), 73 (6). Anal. Calcd for $C_{22}H_{37}NO_3Si$: C, 67.47; H, 9.52; N, 3.58. Found: C, 67.42; H, 9.38; N, 3.54.

***tert*-Butyl (2*S*,3*R*)- and (2*S*,3*S*)-3-Hydroxy-2-phenyl-1-piperidinecarboxylate (63).** To a stirred solution of **62** (177 mg, 0.453 mmol) in THF (4.5 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (1.36 mL, 1.36 mmol) in a mixture of THF−H_2O (9:1). After the mixture was stirred for 24 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo to give **63** (99%) as a colorless oil. Obtained material was used without further purification for the next step. To confirm the structure and characterize compounds, a sample of the product was subjected to column chromatography (hexanes−EtOAc, 4:1). The first fraction containing the more mobile component afforded (2*S*,3*S*)-**63**, which was identical in all respects with that reported in the literature.[24]

The second fraction containing the less mobile component afforded (2*S*,3*R*)-**63** as a colorless oil: $[\alpha]^{22}_D$ +65.9 (*c* 0.3, $CHCl_3$); IR (neat) 3433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38−1.43 (1H, m), 1.45 (9H, br s), 1.64 (1H, m), 1.74−1.78 (1H, m), 1.92 (1H, ddt, J = 17.3, 13.3, 4.6 Hz), 2.06 (1H, br s), 2.87 (1H, td, J = 13.3, 3.4 Hz), 4.07−4.11 (1H, m), 4.51 (1H, br s), 5.37 (1H, br s), 7.18−7.26 (3H, m), 7.33−7.40 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.9 (CH_2), 26.0 (CH_2), 28.8 (CH_3, 3 carbons), 40.0 (CH_2), 60.4 (CH, 2 carbons), 67.6 (CH), 80.2 (C), 126.7 (CH, 2 carbons), 127.3 (CH), 129.1 (CH, 2 carbons), 138.3 (C), 156.8 (C); EIMS *m*/*z* (relative intensity) 277 (M^+, 100), 221 (39), 203 (64), 176 (100), 158 (67), 142 (51), 127 (56), 116 (77), 102 (39), 91 (72); HRMS (EI) calcd for $C_{16}H_{22}NO_2$ ($M^+ - OH$) 259.1572, found 259.1586.

***tert*-Butyl (2*S*)-3-Oxo-2-phenyl-1-piperidinecarboxylate (64).** To a solution of the 1.2:1 diastereomeric mixture (56 mg, 0.216 mmol) of (2*S*,3*S*)-**63** and (2*S*,3*R*)-**63** in CH_2Cl_2 (2.2 mL) was added Dess−Martin periodinane (413 mg, 0.973

mmol), and the mixture was stirred at room temperature for 30 min. After the reaction was quenched with aqueous $NaHCO_3$ (10 mL), the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). All the organic layers were combined, washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (hexanes−EtOAc, 8:1) to give **64** (52.3 mg, 88%) as a colorless oil, which was identical in all respects with that reported in the literature.[24]

***tert*-Butyl (2*S*,3*S*)-3-Amino-2-phenyl-1-piperidinecarboxylate [(*S*,*S*)-67] and *tert*-Butyl (2*S*,3*R*)-3-Amino-2-phenyl-1-piperidinecarboxylate [(*S*,*R*)-67].** To a stirred solution of **64** (245 mg, 0.598 mmol) in pyridine (6 mL) was added *O*-methylhydroxylamine hydrochloride (82 mg, 0.717 mmol) at room temperature, and the stirring was continued for 30 min. To the reaction mixture was added saturated aqueous NH_4Cl (10 mL), and the resulting mixture was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in THF (6 mL), and to this was added a 0.9 M solution of BH_3−THF complex in THF (0.834 mL, 0.75 mmol) under a N_2 atmosphere at 45 °C. After the mixture was stirred for 1 h, an additional 0.9 M solution of BH_3−THF complex in THF (0.834 mL, 0.75 mmol) was added, and stirring was further continued for an additional 3 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product mixture was found to consist of a 10:1 ratio of the diastereomers (*S*,*S*)-**67** and (*S*,*R*)-**67** as determined by ^{1}H NMR integration of the clearly separated signals due to the C2-benzylic protons at δ 5.19 and 5.45 (d, J = 5.8 Hz), respectively. This product was then subjected to column chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 1000:9:1) to give as the first fraction (*S*,*R*)-**67** (2.8 mg, 7%) as a colorless oil: $[\alpha]^{20}_D$ +17.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (9H, s), 1.74 (2H, m), 2.01 (2H, m), 2.22 (2H, m), 3.24 (2H, m), 4.07 (1H, m), 5.45 (1H, d, J = 5.8 Hz), 7.37−7.45 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.4 (CH_2), 24.4 (CH_2), 28.2 (CH_3, 3 carbons), 39.8 (CH_2), 56.8 (CH), 56.9 (CH), 80.5 (C), 128.7 (CH), 129.2 (CH, 4 carbons), 133.0 (C); ESI *m*/*z* $[M + H]^+$ 277; HRMS (ESI) calcd for $C_{16}H_{25}N_2O_2$ $[M + H]^+$ 277.1916, found 277.1912. The second fraction afforded (*S*,*S*)-**67** (27.8 mg, two steps 67%) as a pale yellow oil: $[\alpha]^{20}_D$ +65.3 (*c* 0.1, $CHCl_3$); chiral HPLC (Chiralpak AD, hexanes−EtOH−Et_2NH (97.5:2.5:0.5, v/v), 0.5 mL/min, 254 nm, t_R (*S*,*S*) = 13.4 min, t_R (*R*,*R*) = 14.5 min) >99% ee; IR (neat) 3365, 1689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (9H, br s), 1.65−1.73 (2H, m), 1.77 (1H, m), 1.86 (1H, m), 3.13−3.22 (2H, m), 4.00 (1H, br m), 5.19 (1H, d, J = 6.2 Hz), 7.21−7.33 (3H, m), 7.43 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.7 (CH_2), 28.7 (CH_3, 3 carbons), 40.1 (CH_2), 51.4 (CH), 60.6 (CH), 79.8 (C), 127.3 (CH), 128.3 (CH, 2 carbons), 129.5 (CH, 2 carbons), 139.2 (CH), 155.4 (C); EIMS *m*/*z* (relative intensity) 277 (M^+ + H, 23), 276 (M^+, 27), 220 (11), 220 (11), 164 (20), 120 (67), 106 (27), 69 (100); HRMS (EI) calcd for $C_{16}H_{24}N_2O_2$ (M^+) 276.1838, found 276.1850.

Preparation of *tert*-Butyl (2*S*,3*S*)-3-({[2-(Methyloxy)-phenyl]methyl}amino)-2-phenylpiperidine-1-carboxylate (69) by Reductive Amination. To a solution of (*S*,*S*)-**67** (26.5 mg, 0.096 mmol) in MeOH (1 mL) containing a small amount of bromocresol green (ca. 1.0 mg) was added a 1 M solution of HCl in MeOH until the color changed to yellow (pH 5). To this was added *o*-anisaldehyde (16 mg, 0.115 mmol) followed by $NaBH_3CN$ (12 mg, 0.191 mmol). After the mixture was stirred for 16 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was basified with NH_4OH (10 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$−MeOH−35% NH_4OH, 200:9:1) to give **69** as a colorless oil (38 mg, 83%): $[\alpha]^{20}_D$ +27.5 (*c* 0.3, $CHCl_3$); IR (neat) 3375, 2929, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, s), 1.60 (2H, m), 1.79 (2H, m), 2.96 (1H, td, J = 13.4, 3.1 Hz), 3.05 (1H, m), 3.71 (3H, s), 3.81 (1H, 1/2ABq, J = 13.5 Hz), 3.86 (1H, 1/2 ABq, J = 13.5 Hz), 3.94 (1H, m), 5.46 (1H, br s), 6.81 (1H, d, J = 8.4 Hz), 6.90 (1H, t, J = 7.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.4 (CH_2), 26.9 (CH_2), 28.5 (CH_3, 3 carbons), 39.6 (CH_2), 46.6 (CH_2), 55.1 (CH), 57.3 (CH), 79.7 (C), 110.2 (CH), 120.5 (CH), 127.0 (CH), 128.1 (CH, 2 carbons), 128.6 (C), 129.3 (CH), 129.6 (CH), 139.3 (C), 155.4 (C), 157.7 (C); ESI *m*/*z* $[M + H]^+$ 397; HRMS (ESI) calcd for $C_{24}H_{33}N_2O_3$ $[M + H]^+$ 397.2491, found 397.2476. Anal. Calcd for $C_{24}H_{32}N_2O_3$: C, 72.70; H, 8.13; N, 7.06. Found: C, 72.80; H, 8.21; N, 6.88.

(2*S*,3*S*)-*N*-(2-Methoxybenzyl)-2-phenyl-3-piperidinamine (CP-99,994) (3). A solution of **69** (38 g, 0.096 mmol) in a mixture of concentrated HCl−MeOH (1:1, 1 mL) was stirred for 4 h. The reaction mixture was concentrated in vacuo. To the residue was added saturated $NaHCO_3$ (10 mL), and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$−MeOH−35% NH_4OH, 200:9:1) to give CP-99,994 (**3**) (27.8 mg, 88%) as a pale yellow oil: $[\alpha]^{20}_D$ +67.2 (*c* 1.0, $CHCl_3$); IR (neat) 3322 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33−1.45 (1H br d, J = 12.5 Hz), 1.53−1.70 (1H, dt, J = 13.4, 3.5 Hz), 1.84−2.01 (1H, dt, J = 13.0, 4.0 Hz), 2.09−2.19 (1H br d, J = 13.7 Hz), 2.72−2.86 (2H, m), 3.22−3.31 (1H, bd, J = 12.2 Hz), 3.31 (1H, A part of 1/2Abq, J = 13.9 Hz), 3.64 (1H, B part of 1/2Abq, J = 13.9 Hz), 6.66 (1H, d, J = 8.2 Hz), 6.97 (1H, dd, J = 7.4, 1.7 Hz), 7.10−7.36 (6H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.4 (CH_2), 28.2 (CH_2), 46.8 (CH_2), 47.8 (CH_2), 54.8 (CH), 54.9 (CH_3), 64.1 (CH), 109.9 (CH), 120.1 (CH), 126.4 (CH), 126.6 (CH), 127.9 (CH), 128.2 (CH), 129.7 (CH), 142.5 (CH), 157.7 (C); EIMS *m*/*z* (relative intensity) 297 (M^+ + H, 83), 296 (M^+, 37), 295 (83), 177 (40), 159 (100) 120 (36) 90 (27); HRMS (EI) Calcd for $C_{19}H_{24}N_2O$ (M^+) 296.1889, found 296.1894. An aliquot was treated with 1 M HCl−MeOH and then recrystallized (EtOH) to give CP-99,994 hydrochloride (**3**·2HCl): mp 254−255 °C (lit.[7a] mp 255); $[\alpha]^{25}_D$ +75.5 (*c* 1.1, MeOH) [lit.[7a] $[\alpha]^{25}_D$ +77 (*c* 1.0, MeOH)].

Preparation of *tert*-Butyl (2*S*,3*S*)-3-{[2-Methoxy-5-(trifluoromethoxy)benzyl]amino}-2-phenyl-1-piperidinecarboxylate (71). Method A. In the same manner described above for the preparation of **69**, (*S*,*S*)-**67** (30 mg, 0.109 mmol) was subjected to reductive amination with **70**. Workup followed by purification by column chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 1500:9:1) afforded **71** (20 mg, 38%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (9H, br s), 1.54−1.88 (4H m), 2.95−3.05 (2H m), 3.72 (3H, s), 3.80 (1H, A part of 1/2ABq, J = 14.3 Hz), 3.82 (1H, B part of 1/2ABq, J = 14.3 Hz), 3.96 (1H, dd, J = 13.4, 3.0 Hz), 5.44 (1H br s), 6.76 (1H, d, J = 8.9), 7.04 (1H, dd, J = 8.8, 2.5 Hz), 7.14 (1H, br d, J = 2.4 Hz), 7.25−7.34 (3H, m), 7.55 (1H, br d, J = 7.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.4 (CH_2), 26.8 (CH_2), 28.5 (CH_3, 3 carbons), 39.6 (CH_2), 45.7 (CH_2), 55.5 (CH_3), 57.3 (CH_3), 79.8 (C), 110.6 (CH), 120.3 (CH), 122.3 (CH), 127.1 (CH), 128.2 (CH, 3 carbons), 129.3 (CH, 2 carbons), 130.5 (C), 139.3 (C), 142.6 (C), 155.4 (C), 155.9 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ 4.53 (CF_3, s); EIMS *m*/*z* (relative intensity) 481 (M^+ + H, 90), 480 (M^+, 32), 423 (15), 407 (10), 379 (7), 273 (66), 260 (100), 220 (19), 204 (70), 160 (16); HRMS (EI) calcd for $C_{25}H_{31}F_3N_2O_4$ (M^+) 480.2236, found 480.2257.

Method B. To a stirred solution of (*S*,*S*)-**67** (18 mg, 0.065 mmol) and **70** (19 mg, 0.065 mmol) in benzene (1 mL) was added $TiCl_4$ (28 mL, 0.249 mmol) at 0 °C. After 1 h of stirring at 0 °C, a solution of $NaBH_3CN$ (11 mg, 0.166 mmol) in MeOH (0.5 mL) was added to the mixture and the stirring was continued for 4 h at room temperature. The reaction was quenched with concentrated NH_4OH (2 mL), and the mixture was extracted with $CHCl_3$ (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column

chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 1500:9:1) to give **71** (24.4 mg, 78%) as a pale yellow oil.

(2*S*,3*S*)-*N*-[2-Methoxy-5-(trifluoromethoxy)benzyl]-2-phenyl-3-piperidinamine (CP-122,721) (4). A solution of **71** (45 mg, 0.094 mmol) in a 1:1 mixture of concentrated HCl−MeOH (1 mL) was stirred for 4 h at room temperature. The mixture was basified with concentrated NH_4OH (5 mL), extracted with $CHCl_3$ (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$−MeOH−concentrated NH_4OH, 200:9:1) to give **4** (30 mg, 89%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58−1.71 (1H br m), 1.82−2.15 (1H, m), 2.25−2.37 (1H, m), 2.81 (2H td, J = 12.1, 3.0 Hz), 3.29 (1H, br m), 3.38 (1H, A part of 1/2ABq, J = 14.5 Hz), 3.63 (1H, B part of 1/2ABq, J = 14.5 Hz), 3.51 (3H, s), 3.90 (1H, d, J = 2.2 Hz), 6.62 (1H, d, J = 8.9 Hz), 6.85 (1H, br d, J = 2.6 Hz), 6.98 (1H, dd, J = 8.7, 2.5 Hz), 7.21−7.35 (5H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.3, 22.8, 28.4, 29.4, 32.0, 46.0, 47.7, 55.1, 55.4, 64.2, 110.3, 120.2, 122.5, 126.4 (2 carbons), 126.9, 128.3 (2 carbons), 130.3, 132.6, 142.3, 156.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ 4.52 (CF_3, s); EIMS *m*/*z* (relative intensity) 381 (M^+ + H, 23), 380 (M^+, 40), 273 (73), 261 (55), 204 (19) 166 (51) 148 (100); HRMS (EI) calcd for $C_{20}H_{23}F_3N_2O_2$ (M^+) 380.1712, found 380.1714. An aliquot was treated with methanolic HCl and then concentrated in vacuo to give a solid product, which was crystallized from EtOH to provide **4**·2HCl as colorless needles: mp 275−276 °C (lit.[9] mp 277−278 °C); $[\alpha]^{26}_D$ +75.6 (*c* 1.0, MeOH) [lit.[9] $[\alpha]^{20}_D$ +71.2 (*c* 1.0, MeOH)].

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

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