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Novel Stereoselective Syntheses of the Fused Benzazepine Dopamine D_1 Antagonist (6a*S*,13*bR*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (Sch 39166): 2. L-Homophenylalanine-Based Syntheses

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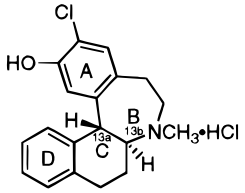
Abstract:

Two enantioselective syntheses of the fused benzazepine dopamine D_1 antagonist (6a*S*,13b*R*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (1) are described in which the starting material is (+)-L-homophenylalanine (6). In the first approach, methyl (2*S*)-(1,2,3,4-tetrahydro-1-oxo-2-naphthalenyl)carbamate (5) is prepared by intramolecular Friedel−Crafts cyclization of *N*-carbomethoxy (+)-L-homophenylalanine (9). Subsequent alkylation of 5 with (4-chloro-3-methoxyphenyl)magnesium bromide, deoxygenation with Et_3SiH, reduction, alkylation, and epimerization yields (+)-*trans*-(1*R*,2*S*)-1-(4-chloro-3-methoxyphenyl)-*N*-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthalenamine (2), a key intermediate in the previously described route to 1 (Draper, R. W.; Hou, D.; Iyer, R.; Lee, G. M.; Liang, J. T.; Mas, J. L.; Tormos, W.; Vater, E. J.; Günter, F.; Mergelsberg, I.; Scherer, D. *Org. Process Res. Dev.* 1998, *2,* XXXXX). A complementary route to 2 is also described in which arylation of an N-protected, carboxyl-activated (+)-L-homophenylalanine affords (2*S*)-1-(4-chloro-3-methoxyphenyl)-2-(methoxycarbamoyl)-4-phenyl-1-butanone (26). Reduction of the latter compound followed by an acid-catalyzed, diastereoselective cyclization affords (+)-(1*R*,2*S*)-[1-(4-chloro-3-methoxyphenyl)-1,2,3,4-tetrahydro-2-naphthalenyl]carbamate (16), which is reduced and alkylated as before to produce 2.

Introduction

In the preceding paper we described several enantioselective syntheses based on a chiral aziridinium salt approach to the novel, selective, dopamine D_1 receptor antagonist Sch 39166 (**1**), whose pharmacological profile makes it an important commercial synthetic target.[1] In this paper, we describe a number of alternative stereoselective syntheses of **1** starting from the readily available synthon (+)-L-homophenylalanine (**6**).[2]



Sch 39166 (1)

Two parallel retrosynthetic analyses of the key tricyclic compound **2**, a known precursor[1] of **1**, are illustrated in Scheme 1. Disconnection of the seven-membered ring and removal of the 2-carbon appendage leads to a synthon such as **3**, which might be assembled from an organometallic reagent derived from 5-bromo-2-chloroanisole and a suitably protected 2-amino-1-tetralone **5**. **5** in turn might be generated by an internal Friedel−Crafts cyclization of an appropriate (+)-L-homophenylalanine derivative.

An alternative retrosynthetic analysis juxtaposes the order of scission of the C ring and attachment of the A ring. Cleavage of the tetralin $C_{13a}-C_{13b}$ bond and elimination of the two-carbon chain suggests the amino alcohol intermediate **7**, which could be constructed by arylation of a suitable carboxyl group activated (+)-L-homophenylalanine derivative. We report herein the realization of the synthesis of **1** along both of these pathways.

Results and Discussion

Of the various blocking groups such as the trifluoroacetyl group,[3a] phenylsulfonyl group,[3b] and ethoxycarbonyl group,[3b] normally used for N-protection of amino acids during Friedel−Crafts reactions, McClure[4] reported that the carbomethoxy group is superior, as they found that *N*-methylcarbamate protected (+)-L-homophenylalanine undergoes a stereoselective Friedel−Crafts cyclization to give the N-protected aminotetralone ring system with high ee. This was fortuitous, since for our purposes the carbomethoxy group not only can serve to protect the nitrogen but also, upon reduction, can be transformed to the *N*-methyl group of **1**. Following McClure's procedure,[4] **6** was converted in three steps to **5** in 86% overall yield with excellent ee (>98%)

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(1) See preceding paper and references therein for an introduction to the pharmacology of **1** and a discussion on alternative synthetic approaches: Draper, R. W.; Hou, D.; Iyer, R.; Lee, G. M.; Liang, J. T.; Mas, J. L.; Tormos, W.; Vater, E. J.; Günter, F.; Mergelsberg, I.; Scherer, D. *Org. Process Res. Dev.* **1998**, *2*, 175.

(2) (+)-L-Homophenylalanine is available in bulk quantities from Tanabe U.S.A., Inc., and Aceto Corporation (U.S. Representative for Ajinomoto).

(3) (a) Norlander, E. J.; Payne, M. J.; Njoroge, F. G.; Vishwanath, V. M.; Han, G. R.; Laikos, G. D.; Balk, M. A. *J. Org. Chem.* **1985**, *50*, 3619. (b) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157.

(4) McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1983**, *48*, 2675.

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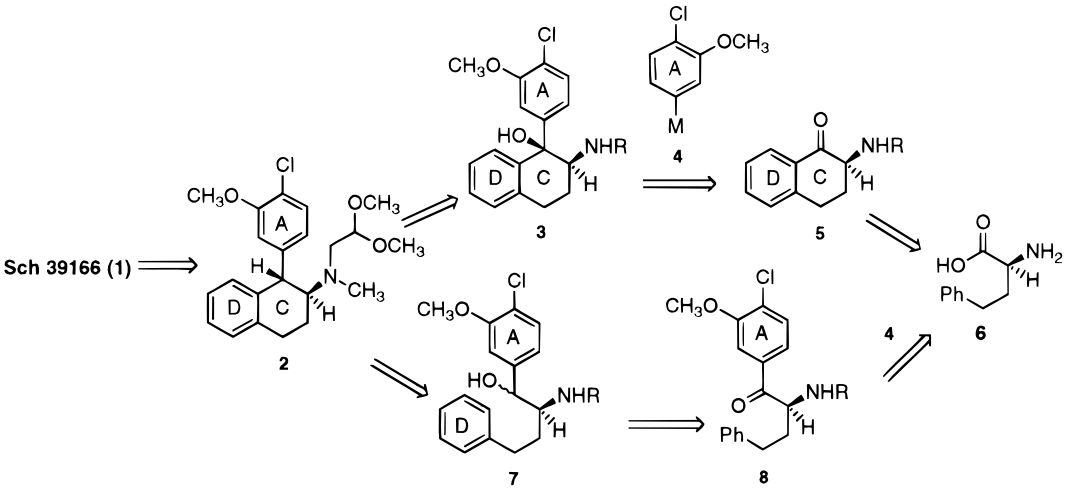
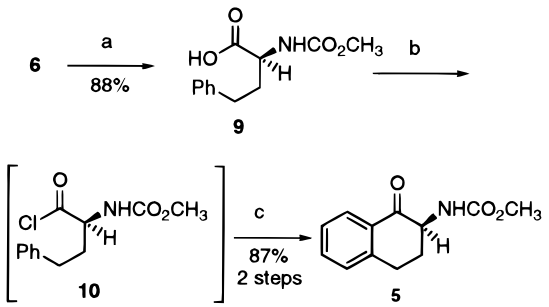
Scheme 1[a]



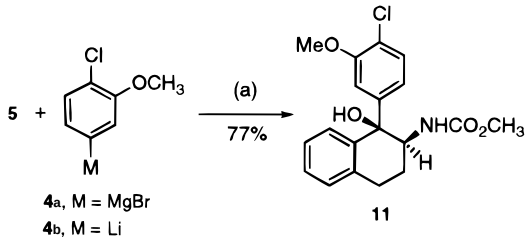
[a] R = CO_2CH_3; M = Li or MgBr.

Scheme 2[a]



[a] (a) $ClCO_2CH_3$, NaOH, $NaHCO_3$; (b) $SOCl_2$, CH_2Cl_2; (c) $AlCl_3$, CH_2Cl_2.

Scheme 3[a]



[a] (a) THF, −30 °C.

(Scheme 2). Carbamate **9** formation proceeds enantioselectively (>98% ee); however, it was found in the subsequent sequence of activation to acid chloride **10** (not isolated) and ensuing cyclization that careful control of the workup conditions was required to avoid racemization of **5**. Although McClure reported that quenching of the reaction mixture with ice cold HCl does not racemize the product, we found on occasion that various amounts of racemization (24−76% ee) had occurred. However, when ice in NH_4Cl solution was used, no racemization was observed.

With ketone **5** in hand, we next focused on the addition of the nucleophilic reagents **4a** or **4b** (readily prepared from 5-bromo-2-chloroanisole) (Scheme 3). Initial attempts to arylate **5** with Grignard reagent **4a** gave a 3:4 mixture of the desired product **11** and starting material. Addition of CuI[5] or conversion of **4a** to either the higher-order mixed cuprate with CuCN[6] or the organocerium reagent with $CeCl_3$[7] produced similar results. However, reaction of **5** with 3.5 equiv of **4b** gave a 77% yield of **11** and only 12% recovery of **5**. Lower yields were observed using 2 equiv of **4b**. The effect of solvent on the reaction was also examined, with the best results obtained using THF or Et_2O (lower yields were observed using other solvents such as diglyme and CH_2Cl_2). The addition occurs with high diastereoselectivity to afford the trans product (equatorial addition: steric approach control from the less hindered face of 5, i.e., anti to the *N*-carbomethoxy group), with no racemization occurring (98% ee). The configuration of **11** was confirmed by ^{1}H NMR NOE experiments.

The source of the recovered starting material presumably arises either from incomplete reaction of the starting material (presumably deprotonated at the carbamate nitrogen) or from deprotonation α to the carbonyl of **5** to give the enolate, since upon acidic quenching **5** is recovered racemized to some extent (from about 10% to complete racemization, depending on the reaction conditions). This is somewhat surprising since it was assumed that deprotonation of the more acidic amide proton would preclude this. Perhaps a facile equilibration between the two anions is occurring which is competing with the addition of **4a** or **4b** to the carbonyl moiety. We reasoned that N-alkylation might prevent this transformation from occurring, and a number of attempts to alkylate **5** were made using MeI or dimethyl sulfate, but only mixtures of the mono *C*- and *N*-methyl compounds **12** and **13**, as well as the O,N-dimethylated **14** were obtained (See Figure 1). These results confirm the facile equilibration between the various resonance forms (C-, N-, and O-anions).

Silane-mediated deoxygenation of **11** gave an ≈3:1 mixture of *cis* **15** and *trans* **16** (See Scheme 4). The *trans*/*cis* mixture indicates that the reaction proceeds, at least in part, through the intermediacy of the benzylic cation. Furthermore, under certain conditions racemization of the

(5) Martin, L. D.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 3630.

(6) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

(7) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.

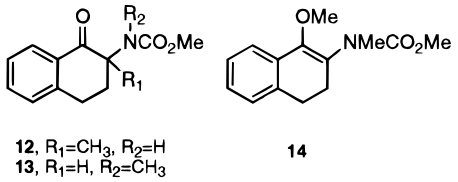
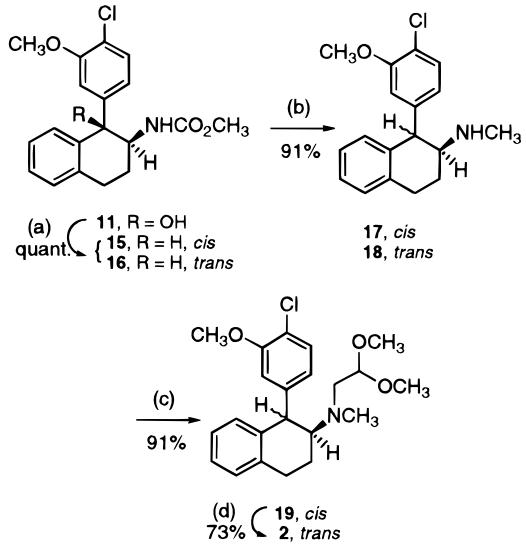


Figure 1.

Scheme 4 [a]



[a] (a) Et_3SiH (5 equiv), CF_3CO_2H (25 equiv), rt; (b) $LiAlH_4$, THF, reflux; (c) $BrCH_2CH(OCH_3)_2$, KF on Al_2O_3, CH_3CN, reflux; (d) *t*-BuOK, DMSO, DMF, rt.

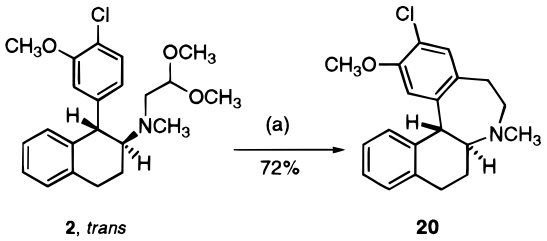
product carbamates **15** and **16** had also occurred (presumably via reduction of the enamide). However, racemization was avoided by using at least 2.5 equiv of Et_3SiH and 25 equiv of CF_3CO_2H. $LiAlH_4$ reduction then converted the methyl carbamate group of **15** and **16** to a 3.6:1 mixture of the *N*-methylamines *cis* **17** and *trans* **18**. N-Alkylation of the mixture of **17** and **18** with $BrCH_2CH(OMe)_2$ to give the tertiary amines *cis* **19** and *trans* **2** in an ≈3:1 ratio proceeded in 91% yield using KF on Al_2O_3[8] as the base. Other bases, such as K_2CO_3, although affording the desired product, were not as efficient. The ≈1:3 *trans*/*cis* mixture was improved to a >50:1 *trans*/*cis* **2**/**19** mixture in 73% yield by treating with KO-*t*-Bu in DMSO/DMF. This is in significant contrast to the results of a similar epimerization of the secondary substituted amine ($-NHCH_2CH(OCH_3)_2$) in which case only an 85:15 *trans*/*cis* mixture was obtained[1] and presumably is due to the increased bulk on the nitrogen.

This concludes a formal total synthesis of **1** since **2** has been previously converted to **1**.[1] However, to confirm the stereochemical integrity, **2** (prepared from **6**) was converted to *O*-methyl **20**, whose enantiomeric excess was shown to be 95% ee by chiral HPLC (see Scheme 5).

Our second approach to intermediate **2** contemplated the arylation of an optically active α-aminoaldehyde, itself derived from a protected (+)-L-homophenylalanine or, alternatively by direct arylation of the protected amino acid derivative (Scheme 1, lower route). Subsequent cyclization or reduction/cyclization, respectively, followed by alkylation,

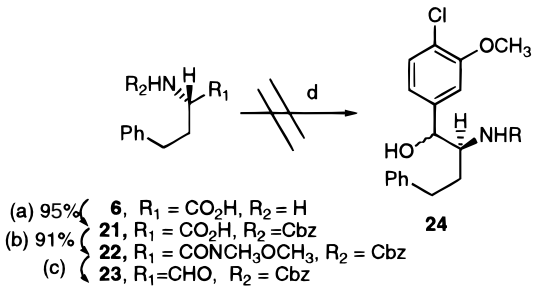
(8) Yamawaki, J.; Ando, T.; Hanafusa, T. *Chem. Lett.* **1981**, 1143.

Scheme 5 [a]



[a] (a) (i) CH_3SO_3H, CH_2Cl_2, 40 °C (ii) $NaBH_4$.

Scheme 6 [a]



[a] (a) CbzCl, Na_2CO_3, NaOH; (b) $NHCH_3OCH_3$·HCl, BOP, TEA, CH_2Cl_2; (c) LiAlH, THF; (d) 5-bromo-2-chloroanisole, Mg, THF, −15 °C → rt.

should afford intermediate **2**, which has been previously converted to **1**. Several recent publications have appeared describing the synthesis of optically active α-amino aldehydes from the corresponding α-amino acids[9] and the alkylation of α-amino acids.[10] In particular, Fehrentz and Castro[9a] have been able to form α-aminoaldehydes from the corresponding α-amino acids in high yield and optical purity by reduction of the corresponding Weinreb amide[11] with $LiAlH_4$. In light of this work, *N*-carbobenzyloxy-*N*-methyl amide **22** was prepared in >90% yield from **21** with *N*,*O*-dimethyl hydroxylamine·HCl in the presence of NEt_3 and benzotriazol-1-yloxytris[dimethylamino]phosphonium hexafluorophosphate (BOP) (Scheme 6). **21** was readily prepared by carbamate protection of **6** with benzylchloroformate and Na_2CO_3 in aqueous NaOH in 95% yield. However, the reduction of hydroxamate **22** with $LiAlH_4$ to crude aldehyde **23** and subsequent alkylation with **4a** (M = MgBr) produced a complex mixture of products and was abandoned.

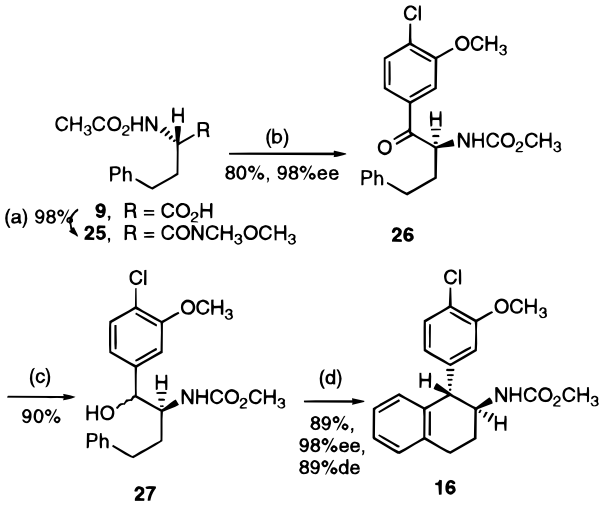
Alternatively, arylation of hydroxamate **25** with **4a** followed by reduction could also afford a similar amino alcohol **27** as in the previous sequence while being easier to handle. Indeed, arylation of hydroxamate **25** with 2.5 equiv of Grignard reagent **4a** at −15 °C followed by aqueous workup produced an 80% isolated yield of keto carbamate **26**, with 98% ee as determined by chiral HPLC (Scheme 7). As in the case of compound **22**, Weinreb amide **25** was readily prepared in excellent yield (98%) from **9** with *N*,*O*-dimethyl hydroxylamine·HCl in the presence of NEt_3 and BOP. To form the tetralin ring system, a reduction step is

(9) (a) Fehrentz, J.-A.; Castro, B.; Synthesis 1983, 676. (b) Ito, A.; Takahashik R.; Baba, Y. *Chem. Pharm. Bull.* **1969**, *17*, 1902. (c) Khatrik, H.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 79. (d) Tokita, S.; Umezawa, Y. *Tetrahedron Lett.* **1982**, *23*, 521.

(10) (a) Reetz, M. T.; Rolfing, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969. (b) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157.

(11) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Scheme 7 [a]



[a] (a) $NHCH_3OCH_3$·HCl, BOP, TEA, CH_2Cl_2; (b) 5-bromo-2-chloroanisole, Mg, THF, −15 °C → rt; (c) $NaBH_4$, EtOH; (d) CH_3SO_3H, CH_2Cl_2, 0 °C → rt.

needed, which was performed with $NaBH_4$ to afford the alcohol **27** as a pair of diastereomers in an approximately 3:1 ratio. The latter mixture was converted in a highly stereoselective ring closure ($MeSO_3H$, CH_2Cl_2, 0 °C → rt) to the trans-substituted tetralin (94:6 *trans*/*cis*) **16** in which no racemization of the chiral center was observed. Presumably the cyclization proceeds through a late transition state in which product development control favors the thermodynamically more stable trans isomer.[12] The conversion of intermediate **16** to Sch 39166 (**1**) has been described previously (*vide supra*).

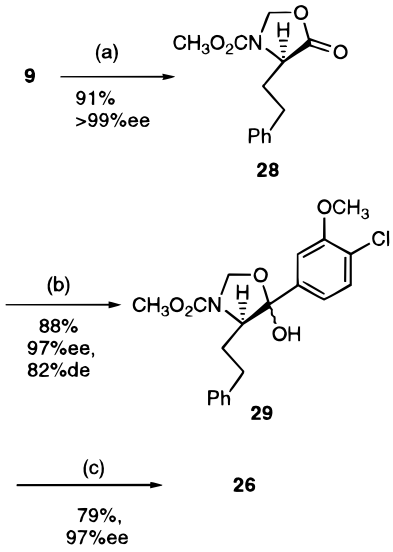
The sequence of activation of **9** with Weinreb's reagent followed by arylation produced the desired keto carbamate **26** in high yield with no significant racemization of the chiral center. It nevertheless concerned us that 2 equiv of Grignard reagent **4a** was consumed because of an unproductive acid/base reaction with the carbamate nitrogen proton, since the precursor 5-bromo-2-chloroanisole was, at the time, considered to represent a considerable portion of the material cost. To limit the use of **4a**, the arylation reaction was also carried out in the presence of 1.5 equiv of NaH or *t*-BuLi, which was added prior to the addition of 1.1 equiv of the Grignard reagent. In both instances, lower yields, 32% and 47%, of intermediate **26** were obtained along with considerable starting material.

The protection of the amino group of **6** as a secondary rather than tertiary amine precluded the use of less than 2 equiv of **4a**. Conversion of (+)-L-homophenylalanine to an oxazolidinone such as **28** can serve as carboxyl function activator and additionally can protect the nitrogen as a tertiary amino group (Scheme 8). Therefore, oxazolidinone **28** was prepared[13] from **9** using 2 equiv of paraformaldehyde and a catalytic amount of *p*-TsOH in benzene with azeotropic removal of water. Analysis of **28** by chiral HPLC demonstrated that the cyclization occurs without epimerization.

(12) For a related cyclization example, see: Ehrlich, P. P.; Ralston, J. W.; Michaelides, M. R. *J. Org. Chem.* **1997**, *62*, 2782.

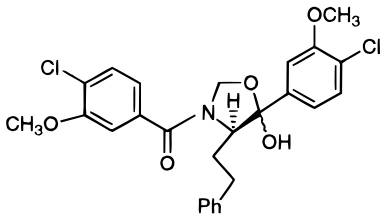
(13) (a) Ben-Ishai, D. *J. Am. Chem. Soc.* **1957**, *79*, 5736. (b) Itoh, M. *Chem. Pharm. Bull.* **1969**, *17*, 1679.

Scheme 8 [a]



[a] (a) Paraformaldehyde, *p*-TsOH, reflux; (b) 5-bromo-2-chloroanisole, Mg, THF, 0 °C → rt; (c) BF_3·Et_2O, Et_2O.

Addition of 1.3 equiv of Grignard reagent **4a** to a solution of **28** in THF at −15 °C and warming to 0 °C followed by an aqueous NH_4Cl quench led to a mixture (approximately 89:11 *cis*/*trans*) of oxazolidines **29** in 88% yield with an ee of 97%. Minor amounts of addition to the carbamate group were also observed to give compound **30**. Finally, Lewis acid catalyzed rearrangement of **29** using BF_3·Et_2O gave the desired keto carbamate **26** in 79% isolated yield and 97% ee. The conversion of intermediate **26** to Sch 39166 (**1**) has been described previously (*vide supra*).



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Conclusion

A number of enantio- and stereoselective syntheses of **1** has been developed starting from (+)-L-homophenylalanine (**6**). The first route proceeds through the key intermediate **5**, which is further elaborated to the *trans*-substituted 1-aryl-2-aminotetralin **2**, a known intermediate for the synthesis of **1**. The second route proceeds through amino ketone **26**, which is prepared from either the Weinreb amide **25** or oxazolidinone **28**. Further elaboration of **26** then gives the previously prepared **2**. The overall yields for these sequences proceeding via ketone **5**, Weinreb amide **25**, and oxazolidinone **28** are 19.5%, 22.3%, and 25.4%, respectively, and the stereochemical integrity of **6** is maintained throughout each synthetic sequence. Of the three routes developed, the one proceeding through oxazolidinone **28** is the preferred route, not only because of its higher overall yields but also because it minimizes the amount of 5-bromo-2-chloroanisole required.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR (400 and 300 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ or $(CD_3)_2SO$ solutions with Me_4Si as the internal standard, unless specified otherwise. IR spectra were obtained using a Matteson Galaxy 7000 IR spectrometer. Unless specified otherwise, all reagents and solvents were used as supplied by the manufacturer. TLC refers to thin-layer chromatography. All reactions were run under an inert atmosphere. Retention times for the chiral HPLC are provided in the Supporting Information. Flash chromatography refers to the procedure developed by Still et al.[14]

(2*S*)-α-[(Methoxycarbonyl)amino]benzenebutanoic Acid (9). A solution of **6** (100.14 g, 0.559 mol), NaOH (1.12 L, 1.12 mol, 1 N aqueous solution), and Na_2CO_3 (88.61 g, 0.836 mol) was cooled in a dry ice/acetone bath to about −78 °C. $ClCO_2CH_3$ (90 mL, 1.17 mol) was then added dropwise over 15 min, and the reaction mixture was stirred at rt for 3 h. The pH of the solution was adjusted to 2 using 5% HCl (≈500 mL) followed by 50% HCl (about 400 mL), and then 1 L of CH_2Cl_2 was added. The layers were separated, the aqueous layer was extracted with 3 × 150 mL of CH_2Cl_2, and the combined organic layers were washed with 1 × 250 mL of saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated using a Büchi rotavapor to give **9** in 96% yield (137.91 g, 0.539 mmol). Chiral HPLC (Chiralpak WH, 4.6 × 240 mm) indicates 98% ee.

^{1}H NMR ($CDCl_3$): δ 7.10−7.30 (m, 5H); 5.25 (br d, 1H); 4.42 (br s, 1H); 3.70 (s, 3H); 2.70 (m, 2H); 2.20 (m, 1H) 2.01 (m, 1H). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.79; H, 6.18; N, 5.60.

Methyl (2*S*)-(1,2,3,4-Tetrahydro-1-oxo-2-naphthalenyl)carbamate (5). A solution of **9** (5.014 g, 21.135 mmol), 40 mL of CH_2Cl_2, and SO_2Cl_2 (1.6 mL, 21.935 mmol) was heated to reflux for 2 h and then cooled to rt. The product, α-[(methoxycarbonyl)amino]benzenebutanoic acid chloride (**10**), was not isolated but used as is.

To a slurry of $AlCl_3$ (8.483 g, 63.616 mmol) and 40 mL of CH_2Cl_2 was added the solution of **10** (from above) over a 2 h period, and after further stirring for 1 h, the reaction mixture was gradually added to 300 mL of a saturated NH_4Cl solution and ice mixture (1:1 ratio). The reaction mixture was allowed to warm gradually to rt and was filtered through a pad of Celite, and the layers were separated. The aqueous layer was extracted with 2 × 20 mL of CH_2Cl_2, and the combined organic layers were dried over anhydrous $MgSO_4$ and then concentrated using a Büchi rotavapor to afford **5** in 88% yield (4.064 g, 18.538 mmol). Chiral HPLC (Chiralpak AS, 4.6 × 250 mm) indicated 99% ee.

^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H, J = 7.5 Hz); 7.62 (t, 1H, J = 7.5 Hz); 7.22−7.35 (m, 2H); 5.90 (br s, 1H); 4.40−4.50 (m, 1H); 3.72 (s, 3H); 3.25 (dt, 1H, J = 3.7, 11.2 Hz); 3.02 (m, 1H, J = 15 Hz); 2.78 (br m, 1H); 1.95 (dd, 1H, J = 3.7, 15 Hz). $[\alpha]_D^{20}$ = +69.5° (c 1.01, $CHCl_3$) (lit.[4] $[\alpha]_D^{20}$ = +67.0° (c 0.60, $CHCl_3$)). Mp 122−123 °C (lit.[4] mp 125−127 °C). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.72; H, 5.90; N, 6.34.

(−)-Methyl [1-(4-chloro-3-methoxyphenyl)-1,2,3,4-tetrahydro-1-hydroxy-2-naphthalenyl]carbamate (11). A solution of 5-bromo-2-chloroanisole (3.043 g, 13.740 mmol) and 10 mL of Et_2O was cooled to −15 °C (acetone/ice bath), and then *t*-BuLi (16.4 mL, 27.88 mmol, 1.7 M in pentane) was added dropwise via an addition funnel over a 1 h period. After stirring for 20 min at −15 °C, **5** (1.005 g, 4.582 mmol) was added portionwise over a 5 min period and the reaction mixture was stirred for 2 h at rt. Saturated NH_4Cl (50 mL) and 30 mL of EtOAc were then added, the layers were separated, and the aqueous layer was extracted with 3 × 20 mL of EtOAc. The combined organic layers were washed with 1 × 50 mL of saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated using a Büchi rotavapor. Flash chromatography of the crude mixture (20:80 hexane/Et_2O) afforded **11** in 77% yield (1.274 g, 3.521 mmol). Starting material **5** was recovered in 12% yield (0.117 g, 0.535 mmol). Chiral HPLC (Chiralpak AS, 4.6 × 250 mm) indicated 98% ee for **11**. $[\alpha]_D^{24}$ = −211.3° (c 4.08, EtOH). Mp: softens 155−157 °C, melts 167−168 °C. MS: m/z 361 (M^+ + 1); 344 (M^+ − 17, OH). Anal. Calcd for $C_{19}H_{20}NO_4Cl$: C, 63.07; H, 3.87; N, 3.87. Found: C, 62.93; H, 5.18; N, 3.46.

^{1}H NMR ($CDCl_3$): δ 7.05−7.35 (m, 6H); 6.40 (d, 1H, J = 9.4 Hz); 4.40 (d, 1H, J = 15 Hz); 4.32 (br s, 1H); 4.20 (m, 1H); 3.82 (s, 3H); 3.62 (s, 3H); 2.90−3.20 (m, 2H); 1.60−1.90 (m, 2H).

NOE experiments indicated the trans relationship between the aryl and carbamate groups. H-2 was determined to be pseudoaxial, J = 9 Hz, J_{H2H3} = 12 and 3 Hz. NOEs were observed between H-2 and H-3 (equatorial) and H-2 and H-4 (axial) as well as between H-2 and the ortho protons of the aryl ring. (See Supporting Information for details.)

Methylation of Methyl (2*S*)-(1,2,3,4-Tetrahydro-1-oxo-2-naphthalenyl)carbamate (5). A series of experiments were carried out in which **5** was treated with methyl iodide or dimethyl sulfate in the presence of base (NaH/THF; K_2CO_3/THF; K_2CO_3/DMF; KF/Al_2O_3 and 50% NaOH/CH_2Cl_2/Aliquat 336). Workup and flash chromatography (20−30% EtOAc/hexanes) afforded three products, which were identified as the following.

Methyl (1,2,3,4-Tetrahydro-2-methyl-1-oxo-2-naphthalenyl)carbamate (12). ^{1}H NMR ($CDCl_3$): δ 8.08 (dd, 1H, J = 1.2, 7.9 Hz); 7.55 (dt, 1H, J = 1.4, 7.5 Hz); 7.35 (t, 1H, J = 7.6 Hz); 7.28 (d, 1H, J = 4.8 Hz); 6.13 (br s, 1H); 3.68 (s, 3H); 3.00 (m, 3H); 2.32 (dt, 1H, J = 5.5, 13.1 Hz); 1.56 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 198.1; 155.8; 143.0; 134.1; 130.3; 129.0; 128.6; 127.0; 58.7; 51.6; 32.8; 25.9; 20.1. MS: m/z 234 (M^+ + 1); 202 (M^+ − 15, CH_3).

Methyl [(1,2,3,4-Tetrahydro-1-oxo-2-naphthalenyl)-methyl]carbamate (13) (Mixture of Rotamers). *Major Rotamer*. ^{1}H NMR ($CDCl_3$): δ 8.07 (d, 1H, J = 7.9 Hz); 7.55 (m, 1H); 7.35 (m, 2H); 5.02 (dd, 1H, J = 5.2, 13.6 Hz); 3.77 (s, 3H); 3.22 (m, 1H); 3.05 (m, 1H); 2.87 (s, 3H); 2.6 (m, 2H).

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Minor Rotamer. ^{1}H NMR ($CDCl_3$): δ 8.07 (d, 1H, J = 7.9 Hz); 7.55 (m, 1H); 7.35 (m, 2H); 4.82 (dd, 1H, J = 5.2, 13.6 Hz); 3.69 (s, 3H); 3.22 (m, 1H); 3.05 (m, 1H); 2.91 (s, 3H); 2.6 (m, 2H).

Methyl [(3,4-Dihydro-1-methoxy-2-naphthalenyl)-methyl]carbamate (14). ^{1}H NMR ($CDCl_3$): δ 7.44 (d, 1H, J = 7 Hz); 7.20 (m, 3H); 3.77 (s, 3H); 3.72 (s, 3H); 3.17 (s, 3H); 2.92 (t, 2H, J = 7.9 Hz); 2.51 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 147.7; 136.3; 131.9; 127.7; 127.4; 126.5; 122.2; 59.5; 52.7; 35.7; 29.5; 28.2; 26.5; 26.4. MS: m/z 248 ($M^+ + 1$); 232 ($M^+ - 15$, CH_3); 216 ($M^+ - 31$, OCH_3).

***cis*-(1*S*,2*S*)-Methyl [1-(4-Chloro-3-methoxyphenyl)-1,2,3,4-tetrahydro-2-naphthalenyl]carbamate (15) and *trans*-(1*R*,2*S*)-Methyl [1-(4-Chloro-3-methoxyphenyl)-1,2,3,4-tetrahydro-2-naphthalenyl]carbamate (16).** A solution of **11** (1.137 g, 3.142 mmol) and 10 mL of CH_2Cl_2 was cooled to 0 °C (ice water bath), and then Et_3SiH (1.30 mL, 0.946 g, 8.14 mmol) was added. The reaction mixture was stirred for 15 min at rt and cooled to 0 °C (ice water bath), and then CF_3CO_2H (6.10 mL, 79.2 mmol) was added. After stirring for 1 h at rt, 10 mL of saturated $NaHCO_3$ and 25 mL of CH_2Cl_2 were added and the layers were separated. The aqueous layer was extracted with 1 × 25 mL of CH_2Cl_2, and the combined organic layers were washed with 1 × 20 mL of saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated using a Büchi rotavapor to afford a mixture of cis and trans isomers **15** and **16** in quantitative yield. ^{1}H NMR indicated an ≈3:1 **15**:**16** ratio. The crude product was used as is in the next reaction. Analytical samples of **15** and **16** were prepared by flash chromatography (1:1 Et_2O/hexanes).

Cis **15**. ^{1}H NMR ($CDCl_3$): δ 7.05−7.25 (m, 4H); 6.94 (d, 1H, J = 7 Hz); 6.60 (s, 1H); 6.42 (d, 1H, J = 7 Hz); 4.20−4.50 (m, 3H); 3.80 (s, 3H); 3.67 (s, 3H); 3.02 (m, 2H); 1.70−1.85 (m, 2H).

Trans **16**. ^{1}H NMR ($CDCl_3$): δ 7.05−7.30 (m, 4H); 6.85 (d, 1H, J = 7.5 Hz); 6.71 (s, 1H); 6.55 (dd, 1H, J = 1.5, 7.5 Hz); 4.80 (br s, 1H); 4.08 (br s, 2H); 3.82 (s, 3H); 3.61 (s, 3H); 2.85−3.07 (m, 2H); 2.05−2.15 (m, 1H); 1.70−1.90 (m, 1H).

***cis*-(1*S*,2*S*)-1-(4-Chloro-3-methoxyphenyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthalenamine (17) and *trans*-(1*R*,2*S*)-1-(4-Chloro-3-methoxyphenyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthalenamine (18).** To a solution of *cis* and *trans* **15** and **16** (412.8 mg, 1.141 mmol) in 5 mL of THF was added $LiAlH_4$ (3.60 mL, 3.60 mmol, 1 M in Et_2O), and the reaction mixture was then heated to reflux for 1 h. After cooling to rt, 10 mL of saturated $NaHCO_3$ and 25 mL of CH_2Cl_2 were added and the layers were separated. The aqueous layer was extracted with 2 × 5 mL of CH_2Cl_2, and the combined organic layers were washed with 1 × 10 mL of saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated using a Büchi rotavapor to yield the product as a mixture of cis and trans **17** and **18** in 91% yield (313.3 mg, 1.038 mmol). ^{1}H NMR indicated an ≈3:1 **17**:**18** ratio. Analytical samples of **17** and **18** were prepared by flash chromatography (3:7 EtOAc/hexanes).

Cis **17**. ^{1}H NMR ($CDCl_3$): δ 6.52−7.35 (m, 7H); 4.35 (d, 1H, J = 5.6 Hz); 3.81 (d, 1H, J = 7.5 Hz); 2.85−3.10 (m, 3H); 2.50 (s, 3H); 1.30−1.99 (m, 3H).

Trans **18**. ^{1}H NMR ($CDCl_3$): δ 6.17−7.32 (m, 7H); 3.90 (d, 1H, J = 7.5 Hz); 3.85 (s, 3H); 2.80−3.0 (m, 3H); 2.40 (s, 3H); 2.20−2.30 (m, 1H); 1.30−1.80 (m, 2H).

***cis*-(1*S*,2*S*)-1-(4-Chloro-3-methoxyphenyl)-*N*-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthalenamine (19) and *trans*-(1*R*,2*S*)-1-(4-Chloro-3-methoxyphenyl)-*N*-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthalenamine (2).** A mixture of *cis* and *trans* amines **17** and **18** (2.01 gm, 6.660 mmol), K_2CO_3 (9.282 g, 66.7 mmol, milled), bromoacetaldehyde dimethyl acetal (4.00 mL, 33.8 mmol), and 20 mL of DMF was added to a 250 mL Teflon acid digestion bomb, sealed, placed in a stainless steel closed system reactor (bomb), and then heated with stirring for 3 days (oil bath temperature about 170 °C). After cooling to rt, 25 mL of saturated $NaHCO_3$, 25 mL of water, and 50 mL of *t*-BuOMe were added and the layers separated. The aqueous layer was extracted with 2 × 50 mL of *t*-BuOMe, and the combined organic layers were washed with 3 × 25 mL water and 1 × 10 mL saturated salt, dried over $MgSO_4$, and concentrated using a Büchi rotavapor. Flash chromatography (30−50% EtOAc/hexanes) then afforded the product as a mixture of *trans* **2** and *cis* **19** isomers (1:3 ratio) in 76% combined yield (1.98 g, 5.078 mmol).

Trans **2**. ^{1}H NMR ($CDCl_3$): δ 6.65−7.30 (m, 7H); 4.12 (t, 1H, J = 5.6 Hz); 4.09 (d, 1H, J = 11.3 Hz); 3.82 (s, 3H); 3.21 (s, 3H); 3.12 (s, 3H); 2.95 (m, 3H); 2.60 (dd, 2H, J = 5.6, 11.3 Hz); 2.31 (s, 3H); 2.08 (m, 1H); 1.70−1.80 (m, 1H).

Cis **19**. ^{1}H NMR ($CDCl_3$): δ 6.65−7.35 (m, 7H); 4.51 (t, 1H, J = 5.6 Hz); 4.09 (d, 1H, J = 11.3 Hz); 3.82 (s, 3H); 3.40 (2s, 6H); 2.40−2.90 (m, 3H); 2.32 (s, 3H); 2.25 (m, 1H); 2.08 (m, 1H); 1.51−1.81 (m, 1H).

(+)-*trans*-(1*R*,2*S*)-1-(4-Chloro-3-methoxyphenyl)-*N*-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthalenamine (2). To a solution of *trans* **2** and *cis* **19** (280.9 mg, 0.720 mmol) in 2 mL of freshly degassed DMSO and 1 mL of freshly degassed DMF cooled to 0 °C (ice/water bath) was added KO-*t*-Bu (172.8 mg, 1.540 mmol). After stirring for 1 h at rt, 15 mL of saturated $NaHCO_3$, 20 mL of *t*-BuOMe, and 5 mL of H_2O were added and the layers were separated. The aqueous layer was extracted with 3 × 15 mL of *t*-BuOMe, and the combined organic layers were washed with 4 × 5 mL of H_2O, dried over anhydrous $MgSO_4$, and concentrated using a Büchi rotavapor to yield a 51:1 ratio of the *trans*/*cis* isomers. Flash chromatography (30−50% EtOAc/hexanes) afforded **2** in 73% yield (214.2 mg, 0.549 mmol).

The ^{1}H NMR spectrum was identical to that previously described. $[\alpha]_D^{20} = +63.53°$ (*c* 1.49, EtOH).

***trans*-(−)-(6a*S*,13b*R*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (20).** A solution of CH_3SO_3H (16.3 g, 169.4 mmol) and 10 mL of CH_2Cl_2 was cooled to −15 °C (acetone/dry ice bath), and then a solution of *N*-methyl amine **2** (0.981 g, 2.512 mmol) in 5 mL of CH_2Cl_2 was added over a 5 min

period. After stirring at 20−25 °C for 24 h, *t*-$BuNH_2$·BH_3 (0.27 g, 3.057 mmol) was added, and then after 1 h, a solution of $NaHCO_3$ (11.389 g, 135.6 mmol) dissolved in 150 mL of H_2O was added. The layers were separated, and the aqueous layer was extracted with 2 × 50 mL of CH_2Cl_2, and the combined organic layers were washed with 2 × 30 mL of H_2O, dried over anhydrous $MgSO_4$, and concentrated using a Büchi rotavapor to give the crude product. Flash chromatography (2.5% MeOH/CH_2Cl_2) afforded (−)-**20** in 72% yield (0.593 g, 1.811 mmol). Chiral HPLC (Chiralcel OD, 4.6 × 250 mm) indicates 95% ee.

Note: Sulfuric acid can be used instead of methanesulfonic acid, with the same results.

^{1}H NMR ($CDCl_3$): δ 6.95−7.19 (m, 5H); 5.88 (s, 1H); 4.78 (d, 1H, J = 7.5 Hz); 3.5−3.62 (m, 1H); 3.49 (s, 3H); 3.2 (dd, 1H, J = 3.75, 11.3 Hz); 2.65−2.86 (m, 4H); 2.51 (s, 3H); 2.41 (dd, 1H, J = 5.6, 11.3 Hz); 1.98−2.18 (m, 1H); 1.6−1.8 (dq, 1H, J = 5.6, 11.3 Hz). $[\alpha]^{20}_D = -191.77°$ (*c* 0.90, EtOH).

(2*S*)-*N*-(Benzyloxycarbonyl)benzenebutanoic acid (21). A solution of **6** (3.509 g, 19.578 mmol) and NaOH (28 mL, 28 mmol, 1 N aqueous solution) was cooled in an ice bath (about 0 °C), then $ClCO_2CH_2Ph$ (4.780 g, 28.019 mmol) was added dropwise over a 3 min period, and the reaction mixture was stirred for 1 h at 0 °C and then for 3 h at rt. The pH was adjusted to 6.5 with concentrated HCl, the solution extracted with 50 mL *t*-BuOMe, the pH readjusted to 4.5 with concentrated HCl, and the precipitate that forms was collected. The solid was washed with 250 mL H_2O and then dissolved in 250 mL EtOAc. The remaining aqueous layer was adjusted to pH 1 with concd HCl and extracted with 150 mL of EtOAc, and the combined organic layers were dried over $MgSO_4$ and concentrated using a Büchi rotavapor to yield **21** in 99% yield (6.065 g, 19.354 mmol).

^{1}H NMR ($CDCl_3$): δ 8.01 (br s, 1H); 7.10−7.42 (m, 10H); 5.32 (d, 1H, J = 7 Hz); 5.12 (br s, 2H); 4.48 (m, 1H); 2.70 (t, 2H, J = 5 Hz); 2.23 (m, 1H); 2.06 (m, 1H).

Phenylmethyl (2*S*)-[1-[[(Methoxymethyl)amino]carbonyl]-3-phenylpropyl]carbamate (22). To a solution of **21** (0.71 g, 2.3 mmol) in 10 mL of CH_2Cl_2 was added NEt_3 (0.23 g, 2.3 mmol). Benzotriazol-1-yloxytris[dimethylamino]-phosphonium hexafluorophosphate (1.0 g, 2.3 mmol) in 5 mL of CH_2Cl_2 was added, and the reaction mixture was stirred for 10 min, followed by the addition of *N*,*O*-dimethylhydroxylamine hydrochloride (0.24 g, 2.5 mmol) and NEt_3 (0.23 g, 2.3 mmol). The reaction was monitored by TLC, and upon completion, 300 mL of CH_2Cl_2 was added and the mixture was extracted sequentially with 3 × 30 mL of 10% HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried with $MgSO_4$ and concentrated using a Büchi rotavapor, and the crude product was purified by flash chromatography (70:30 hexane/EtOAc) to give **22** as a clear oil in 91% yield (0.735 g, 2.06 mmol).

^{1}H NMR ($CDCl_3$): δ 7.5−7.2 (m, 10H); 5.6 (d, 1H); 5.17 (dd, 2H, J = 20.2, 12.2 Hz); 4.8 (m, 1H); 3.7 (s, 3H); 3.2 (s, 3H); 2.9−2.6 (m, 2H); 2.2−1.9 (m, 2H). IR (CH_2Cl_2): 3425, 3050, 1725, 1650, 1500, 1225, 1050 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O_4N_2$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.17; H, 6.63; N, 7.81.

Methyl (2*S*)-[1-[[(Methoxymethyl)amino]carbonyl]-3-phenylpropyl]carbamate (25). To a solution of **9** (2.97 g, 12.5 mmol) in 60 mL of CH_2Cl_2 was added NEt_3 (1.26 g, 12.5 mmol). Benzotriazol-1-yloxytris[dimethylamino]phosphonium hexafluorophosphate (5.53 g, 12.5 mmol) in 30 mL of CH_2Cl_2 was added, and the reaction mixture was stirred for 20 min, followed by the addition of *N*,*O*-dimethylhydroxylamine hydrochloride (1.34 g, 13.7 mmol) and NEt_3 (1.26 g, 12.5 mmol). The reaction was monitored by TLC, and additional NEt_3 (1.26 g, 12.5 mmol) was needed to ensure complete reaction. Upon completion, 300 mL of CH_2Cl_2 was added and the mixture was washed sequentially with 2 × 125 mL of 10% HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried with $MgSO_4$ and concentrated using a Büchi rotavapor, and the crude product was purified by flash chromatography (98.5:1.5 CH_2Cl_2/MeOH) to give **25** as a yellow oil in 98% yield (3.45 g, 12.3 mmol).

^{1}H NMR ($CDCl_3$): δ 7.3−7.2 (m, 5H); 5.53 (d, 1H, J = 9.0 Hz); 4.8−4.7 (m, 1H); 3.75 (s, 3H); 3.67 (s, 3H); 3.22 (s, 3H); 2.9−2.6 (m, 2H); 2.2−1.9 (m, 2H). IR (film): 3300, 3025, 2950, 1725, 1650, 1550, 1450, 1250, 1050 cm^{-1}.

(2*S*)-1-(4-Chloro-3-methoxyphenyl)-2-(methoxycarbamoyl)-4-phenyl-1-butanone (26). Dry THF was added to a mixture of 5-bromo-2-chloroanisole (0.96 g, 4.33 mmol) and magnesium (0.104 g, 4.28 mmol), and the reaction mixture was stirred until initiation commenced (indicated by a color change to yellow and heat evolution), at which time additional THF was added until a 1 M solution of **4a** was approximated. The temperature of the reaction mixture was not allowed to exceed 40 °C, and upon completion, a back-titration to a phenolphthalein endpoint established the Grignard concentration.

A solution of **25** (0.477 g, 1.70 mmol) in 6 mL of dry THF was cooled to 0 °C, and then 2.5 equiv of **4a** (solution in THF) was added dropwise. The reaction mixture was allowed to warm to rt (reaction monitored by TLC), and after complete disappearance of **25**, the reaction was quenched with 10 mL of EtOH and 10 mL of 5% HCl and the mixture was extracted with a solution of 1:1 CH_2Cl_2/Et_2O. The organic layer was dried with $MgSO_4$, concentrated using a Büchi rotavapor, and purified by flash chromatography (95:5 → 85:15, EtOAc/hexane) to give **26** in 80% yield (0.44 g, 1.3 mmol) as a clear oil.

^{1}H NMR ($CDCl_3$): δ 7.4−7.2 (m, 8H); 5.72 (d, 1H, J = 8 Hz); 5.33 (dt, 1H, J = 4, 8 Hz); 3.89 (s, 3H); 2.8−2.6 (m, 2H); 2.3−2.1 (m, 1H); 2.0−1.8 (m, 1H). IR (film): 3350, 2950, 1675, 1425, 1250, 1050 cm^{-1}.

(2*S*)-1-(4-Chloro-3-methoxyphenyl-2-amino-*N*-(methoxycarbonyl)-4-phenyl-1-butanol (27). A solution of **26** (0.45 g, 1.2 mmol) and 15 mL of EtOH was cooled to 0 °C, $NaBH_4$ (0.047 g, 1.2 mmol) was added, and the reaction mixture was stirred until completion. Upon complete reaction (monitored by TLC), the reaction was quenched with saturated aqueous $NaHCO_3$. The solvent was removed using a Büchi rotavapor, and the crude product was redissolved in

Et_2O, washed sequentially with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed using a Büchi rotavapor, and the crude was purified by flash chromatography (70:30 hexanes/EtOAc) to give **27** as a colorless oil in 90% yield (0.40 g, 1.1 mmol).

^{1}H NMR ($CDCl_3$): δ 7.4−7.1 (m, 6H); 67.0−6.8 (m, 3H); 5.1 (d, 1H); 4.9 (d, 3/4H); 4.7 (d, 1/4H); 3.90 (s, 3H); 3.8 (s, 9/4H); 3.7 (s, 3/4H); 2.9−2.5 (m, 3H); 2.0−1.6 (m, 2H).

(+)-(1*R*,2*S*)-[1-(4-Chloro-3-methoxyphenyl)-1,2,3,4-tetrahydro-2-naphthalenyl]carbamate (16) from 27. A solution of **27** (0.22 g, 0.60 mmol) and 5 mL of CH_2Cl_2 was cooled to 0 °C, and $MeSO_3H$ (0.74 g, 0.78 mmol) was then added. The reaction mixture was brought to rt and stirred overnight. Upon completion (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 and basified with 5 mL of saturated aqueous $NaHCO_3$ and the organic layer was separated. The organic layer was washed with 5 mL of brine and dried over $MgSO_4$, and the solvent was removed using a Büchi rotavapor, to give an oil, which was purified by flash chromatography (10:90 → 20:80, EtOAc/hexanes), providing **16** as a white solid in 89% yield (0.18 g, 0.70 mmol). Chiral HPLC (Chiralpak AS, 4.6 × 250 mm) indicated 98% ee.

The ^{1}H NMR spectrum was identical to that for **16** previously prepared from **11**. IR (film): 3250, 3040, 3000, 2920, 2840, 1650, 1580, 1270, 1240, 1050, 720 cm^{-1}. MS (CI): *m*/*z* 348 ($M^+ + 1$, ^{37}Cl), 346 ($M^+ + 1$, ^{35}Cl), 274 ($M^+ - 73$, ^{37}Cl, $NHCO_2CH_3 + H$), 272 ($M^+ - 73$, ^{35}Cl, $NHCO_2CH_3 + H$). Anal. Calcd for $C_{19}H_{20}O_3NCl$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.86; H, 5.80; N, 4.00.

(4*S*)-*N*-(Methoxycarbonyl)-4-(2-phenylethyl)-5-oxazolidinone (28). A solution of **9** (23.7 g, 100 mmol), paraformaldehyde (6.00 g, 200 mmol), *p*-toluenesulfonic acid (1.2 g, 6.00 mmol), and 800 mL of benzene was heated to reflux. Water was removed with the aid of a Dean−Stark trap, and heating was continued until no starting material remained as observed by TLC. The reaction mixture was cooled to rt, washed with 10 mL of 0.3 M Na_2CO_3 and 2 × 10 mL of brine, dried over $MgSO_4$, and concentrated using a Büchi rotavapor to give **28** as a yellow oil in 91% yield (24.2 g, 91.0 mmol). Upon standing, **28** solidified to an off-white solid.

^{1}H NMR ($CDCl_3$): δ 7.4−7.2 (m, 5H); 5.53 (br s, 1H); 5.21 (d, 1H, J = 4.3 Hz); 4.3 (m, 1H); 3.81 (s, 3H); 2.8−2.7 (m, 2H); 2.4−2.2 (m, 2H). IR (CH_2Cl_2): 3075, 3025, 2950, 2900, 1800, 1725, 1475, 1400, 1050 cm^{-1}. MS: *m*/*z* 250 (21), 204 (86), 169 (100). Anal. Calcd for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.34; H, 5.93; N, 5.64. Mp 62−65 °C.

(4*S*)-*N*-(Methoxycarbonyl)-5-(4-chloro-3-methoxyphenyl)-4-(2-phenylethyl)-5-hydroxyoxazolidine (29). Dry THF (8 mL) was added to a mixture of 5-bromo-2-chloroanisole (1.77 g, 8.00 mmol) and magnesium (0.19 g, 8.00 mmol), and the reaction mixture was stirred until initiation commenced (indicated by a color change to yellow and heat evolution), at which time additional THF was added until a 1 M solution of **4a** was approximated. The temperature of the reaction mixture was not allowed to exceed 40 °C, and upon completion, a back-titration to a phenolphthalein endpoint established the Grignard concentration.

A solution of **28** (1.0 g, 3.8 mmol) in 3.8 mL of dry THF was cooled to 0 °C, and 1.3 equiv of **4a** (solution in THF) was added dropwise. The reaction mixture was allowed to warm to rt (reaction monitored by TLC), and after complete disappearance of **28**, the reaction was quenched with 4 mL of 1 N HCl and the mixture extracted with Et_2O. EtOAc (250 mL) was added, and the layers were separated. The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed using a Büchi rotavapor. The reaction mixture was purified by flash chromatography (75:25 → 60:40 hexanes/EtOAc) to give **29** as a white solid in 88% yield (1.30 g, 3.4 mmol).

^{1}H NMR (mixture of diastereomers, $CDCl_3$): δ 7.5−7.0 (m, 8H); 5.7 (dd, 1H); 5.4−4.8 (m, 2H); 3.9−3.5 (m, 4H); 3.9 (s, 3H); 2.9−2.6 (m, 2H), 2.3−2.1 (m, 2H).

(4*S*)-*N*-(4-Chloro-3-methoxyphenyl)-5-(4-chloro-3-methoxyphenyl)-4-(2-phenylethyl)-5-hydroxyoxazolidine (30). Mixture of Diastereomers. ^{1}H NMR ($CDCl_3$): δ 7.5−7.2 (m, 6H); 7.0−6.9 (m, 4H); 6.85 (dd, 1H); 6.7 (dd, 1H); 5.1−4.9 (m, 1H); 4.9−4.8 (m, 1H); 4.6 (t, 1H); 3.9 (s, 3H); 3.8 (s, 3H); 3.3 (m, 1H); 2.5 (t, 2H); 1.85 (m, 2H). IR (film): 3400, 2920, 1740, 1480, 1450, 1395, 1250, 1015 cm^{-1}.

(2*S*)-1-(4-Chloro-3-methoxyphenyl)-2-(methoxycarbomyl)-4-phenyl-1-butanone (26) from 29. A solution of **29** (0.25 g, 0.63 mmol) in 1.3 mL of Et_2O was cooled to 0 °C, and then $BF_3 \cdot Et_2O$ (80 mL, 0.63 mol) was added. The reaction mixture was stirred until complete by TLC, the reaction was quenched with aqueous $NaHCO_3$, and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated using a Büchi rotavapor. The crude product was purified by preparative TLC (80:20 hexane/EtOAc) to give **26** as a clear oil in 79% yield (0.180 g, 0.50 mmol).

^{1}H NMR ($CDCl_3$): δ 7.4−7.2 (m, 8H); 5.72 (d, 1H, J = 8 Hz); 5.33 (dt, 1H, J = 4, 8 Hz); 3.89 (s, 3H); 2.8−2.6 (m, 2H); 2.3−2.1 (m, 1H); 2.0−1.8 (m, 1H). IR (film): 3350, 2950, 1675, 1425, 1250, 1050 cm^{-1}.

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Supporting Information Available

^{1}H NMR spectra for **2**, **5**, **9**, **11**−**21**, **25**−**30**, NOE experiment for **11**, ^{13}C NMR spectra for **12** and **14**, and chiral HPLC conditions for **2**, **5**, **9**, **11**, **19**, **20**, and **26**−**29** (27 pages). See any current masthead page for ordering and Internet access instructions.

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