Synthesis of the Selective D_2 Receptor Agonist PNU-95666E from D-Phenylalanine Using a Sequential Oxidative Cyclization Strategy

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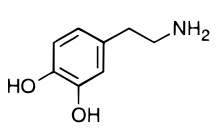
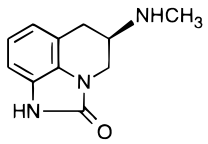
Compound **1** (PNU-95666E) is a selective and high-affinity agonist at the dopamine D_2 receptor subtype and is of interest as a potential agent for the treatment of Parkinson's disease. Requiring a synthetic route amenable to scale-up, a synthesis of this enantiomerically pure tricyclic compound was developed, starting from D-phenylalanine. Critical to the success of this synthesis were two oxidative nitrogen annulations to provide the tricyclic ring system. A highly efficient reduction with borane−methyl sulfide was used to reduce three different functional groups, a total of six hydrides transferred, with no concomitant racemization, contributing to the synthesis of **1** in eight steps with an overall yield of 26%. The utility of this synthetic route has been demonstrated by the completion this synthesis on multikilogram scale.

Introduction

Parkinson's disease, a neurodegenetive disease characterized by deteriorating motor function, is brought about by the loss of cells in the brain responsible for synthesizing the neurotransmitter dopamine. The standard treatment for this condition is L-DOPA, which is converted to dopamine *in situ* by L-DOPA decarboxylase. However, after a period of time L-DOPA loses its effectiveness, requiring adjunct therapy with dopamine agonists to attempt to re-establish the necessary level of dopamine receptor activation; adverse side effects such as psychiatric disorders are also common. Evidence suggests that it is the activation of D_2 receptors in the striatum, an area of the brain associated with motor function, that is responsible for drug efficacy.[1] However, currently available dopamine agonist drugs are not selective and possess high affinity for other dopamine receptor subtypes, possibly contributing to the etiology of drug-induced psychosis.[2] Compound **1** (PNU-95666E) is a potent and highly selective agonist at the dopamine D_2 receptor subtype and may possess potential as a treatment for Parkinson's disease with greatly diminished side-effect liability.[3] Such a drug may also have potential as a treatment for early stage Parkinson's disease in place of L-DOPA, possibly preventing the development of response fluctuations seen with long term L-DOPA therapy. This approach is not as feasible with currently available, nonselective dopamine agonists due to their undesirable side-effect profiles.



Dopamine



1
PNU-95666E

Requiring a synthetic route amenable to large-scale synthesis,[4] we sought an efficient procedure to synthesize **1**, characterized structurally by three mutually fused rings, as well as exhibiting (R)-chirality at the methylamine-substituted position. Retrosynthetic analysis (Figure 1) indicated that D-phenylalanine (**4**) could potentially provide a highly efficient starting material, already containing the requisite stereochemistry as well as all of the ring carbons except for the urea carbonyl group. To successfully take advantage of these features would require the attachment of a nitrogen onto the benzene ring at the *ortho*-position to ultimately obtain a tetrahydroquinoline ring (*e.g.*, **2**), followed by the further substitution of another adjacent nitrogen to provide the essential elements needed to generate the cyclic urea. These requirements were realized using a pair of electrophilic oxidative cyclizations to sequentially attach these two nitrogen atoms.

Discussion

Examination of the retrosynthetic analysis (Figure 1) indicated that the tetrahydroquinoline ring construction would be a key step in the synthesis of **1** from D-phenylalanine; we were therefore delighted to find that Kikugawa had previously performed this type of transformation (Scheme 1), where *N*-methoxyamide **5** was oxidized to the *N*-chloro adduct, subsequently treating this with a silver(I) salt in trifluoroacetic acid solvent to generate an electrophilic intermediate (**6**), which cyclized to afford **7**.[5] However, the necessity of working with insoluble silver chloride salts and large amounts of trifluoroacetic acid made this two-step procedure rela-

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(1) Seeman, P.; Niznik, H. B. Dopamine receptors and transporters in Parkinson's disease and schizophrenia. *FASEB J.* **1990**, 2737−2744.

(2) Coleman, R. J. Current drug therapy for Parkinson's disease. A review. *Drugs and Aging* **1992**, *2*, 112−1124. Collier, D. S.; Berg, M. J.; Fincham, R. W. Parkinsonism treatment: Part III-Update. *Ann. Pharmacother.* **1992**, *26*, 227−233.

(3) Compound **1** possesses a K_i of 9 nM for the D_2 receptor subtype, while the affinity of **1** for the D_1, D_3, D_4, and α_1 receptors is greater than 2300 nM and at the α_2 and cholinergic receptors is greater than 1100 nM. Heier, R. F.; Dolak, L. A.: Duncan, J. N.; Hyslop, D. K.; Lipton, M. F.; Martin, I. J.; Mauragis, M. A.; Piercey, M. F.; Nichols, N. F.; Schreur, P. J. K. D.; Smith, M. W.; and Moon, M. W. Synthesis and biological activities of (*R*)-5,6-dihydro-*N*,*N*-dimethyl-4*H*-imidazo[4,5,1-*ij*]quinolin-5-amine and its metabolites. *J. Med. Chem.* **1997**, *40*, 639−646.

(4) The original synthesis was 12 steps, including a tartaric acid resolution to obtain optically pure **1** (see ref 3). Also, the use of potentially hazardous reagents such as *p*-toluenesulfonyl azide made it not amenable to large scale use.

S0022-3263(97)00526-4 CCC: $14.00

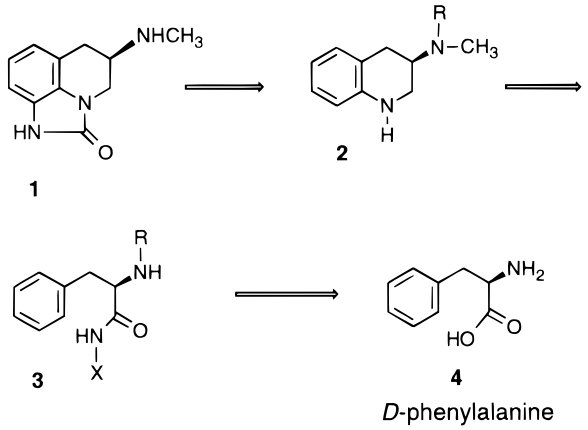
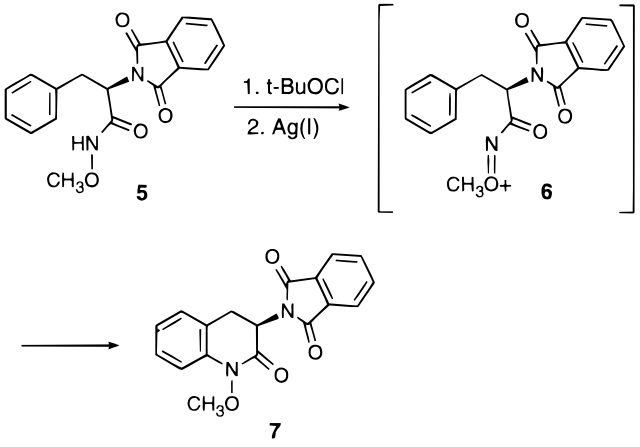


Figure 1. Retrosynthetic analysis of **1**.

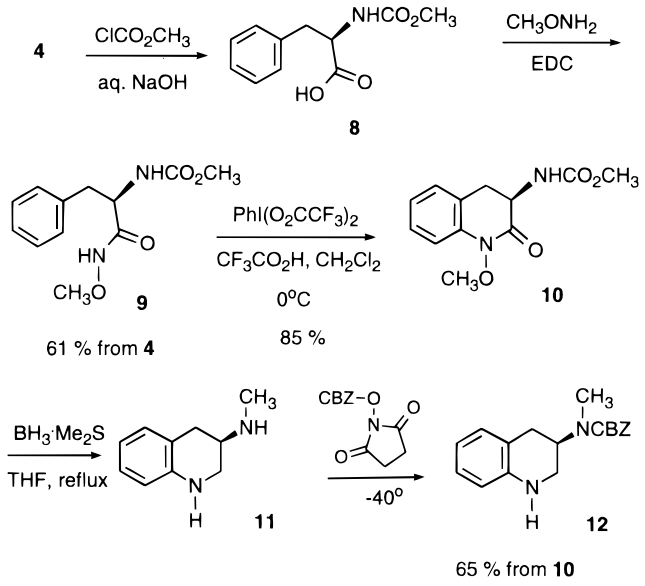
tively unattractive on a large scale. An alternative one-step approach was examined, using the powerful oxidant bis(trifluoroacetoxy)iodobenzene which was also reported to induce the oxidative *N*-methoxyamide substitution of aromatic rings.[6] It was found that treatment of **5** with this reagent in dichloromethane at 0 °C gave **7** in good yield without any detectible racemization.[7]

Scheme 1. Kikugawa's Oxidative Cyclization of 5 To Obtain the Tetrahydroquinoline Skeleton 7



Although encouraged by this result, for a chemoefficient synthesis it was desirable to avoid the use of the phthalimide protecting group due to its sizable molecular weight and deprotection step. As an alternative, it was envisioned that a simple carbamate group could serve to protect the nitrogen of D-phenylalanine, serving as a latent *N*-methyl group by eventual reduction after the oxidative cyclization. However, it was not clear whether a secondary carbamoyl nitrogen would tolerate exposure to bis(trifluoroacetoxy)iodobenzene, since structurally related primary amides undergo a Hoffmann-type rearrangement in the presence of this oxidant[8] and, as

Scheme 2. Preparation of the Optically Pure Tetrahydroquinoline Ring System from D-Phenylalanine (4)



described above, *N*-methoxyamides also react in the presence of this reagent.

To investigate this approach, the nitrogen of D-phenylalanine was protected under Schotten–Baumann conditions, affording the methyl carbamate as a thick liquid (**8**) which was carried on without purification (Scheme 2). The free carboxylic acid was converted to *N*-methoxyamide **9** by coupling with methoxylamine using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC).[9] The choice of EDC as the coupling agent was 2-fold, permitting water to be used as solvent and allowing for the removal of coupling reagents by aqueous extraction. The resulting *N*-methoxyamide was purified by crystallization from ethyl acetate, affording **9** in 61% overall yield from D-phenylalanine.[10]

When *N*-methoxyamide **9** was treated with bis(trifluoroacetoxy)iodobenzene in dichloromethane at 0 °C, it cyclized to lactam **10** in disappointingly low yield (40%). A survey of experimental conditions was undertaken in an attempt to improve the yield of **10**. While changing solvents (acetonitrile, toluene, acetone, chloroform) demonstrated that halogenated solvents afforded cleaner product; it did not improve the yield of **10**. Addition of sodium carbonate to scavenge trifluoroacetic acid only further reduced the yield. However, this result suggested that the presence of trifluoroacetic acid was beneficial; to examine this possibility the cyclization was run in the presence of 3 equiv of trifluoroacetic acid. This modification dramatically increased the yield of **10** to 85%. It is likely that the added trifluoroacetic acid serves to increase the electrophilicity of the *N*-methoxy-*N*-acylnitro-

(5) Kawase, M.; Kitamura, T.; Kikugawa, Y. Electrophilic aromatic substitution with *N*-methoxy-*N*-acylnitrenium ions generated from *N*-chloro-*N*-methoxyamides: synthesis of nitrogen heterocyclic compounds bearing a *N*-methoxyamide group. *J. Org. Chem.* **1989**, *54*, 3394–3403.

(6) Kikugawa, Y.; Kawase, M. An electrophilic aromatic substitution by *N*-methoxyamides *via* hypervalent iodine intermediates, *Chem. Lett.* **1990**, 581–582.

(7) Enantiomeric purity was determined by converting **1** to the BOC-amine and analyzing this with a chiral HPLC column, where the two enantiomers cleanly resolved, as determined by examination of racemic **1**. See Experimental Section for details. We thank Malcolm W. Moon for providing us with this procedure.

(8) (a) Louden, M. G.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. Conversion of aliphatic amides into amines with [*I*,*I*-bis(trifluoroacetoxy)iodo]benzene. 1. Scope of the reaction. *J. Org. Chem.* **1984**, *49*, 4272–4276. (b) Using bis(acetoxy)iodobenzene: Moriarty, R. M.; Chany, C. J., II; Vaid, R. K; Prakash, O.; Tuladhar, S. M. Preparation of methyl carbamates from primary alkyl- and arylcarboxamides using hypervalent iodine. *J. Org. Chem.* **1993**, *58*, 2478–2482.

(9) The coupling reagent EDC is a water soluble form of dicyclohexylcarbodimide (DCC): Sheehan, J. C.; Preston, J.; Cruickshank, P. A. A rapid synthesis of oligopeptide derivatives without isolation of intermediates. *J. Am. Chem. Soc.* **1965**, *87*, 2492–2493.

(10) The ethyl carbamate version of **9** was not crystalline and required silica gel chromatography for purification.

nium ion intermediate, or possibly increases the reactivity of the bis(trifluoroacetoxy)iodobenzene reagent itself. Interestingly, it was also found that *N*-methoxyamide **9** cyclized in good yield using the less powerful oxidant bis(acetoxy)iodobenzene in the presence of 10 equiv of trifluoroacetic acid, whereas only a small amount of product is observed in the absence of trifluoroacetic acid.[11]

With a good synthesis of lactam **10** in hand, we were now ready to attempt an exhaustive reduction to obtain diamine **11**. This was achieved with surprising ease using an excess of borane−methyl sulfide complex in refluxing tetrahydrofuran, representing a total of six hydrides transferred to multiple reaction sites, including the reduction of a nitrogen−oxygen bond. The liquid diamine was of sufficient purity to be carried on to the next step without purification; if desired, air sensitive **11** could be crystallized to purity as the maleic acid salt (71% yield). Substituting lithium aluminum hydride for borane−methyl sulfide gave much less satisfactory results.

Before we could attempt to synthesize the benzo-fused urea (2-benzimidazolinone) portion of the molecule, it was necessary to selectively protect the aliphatic methyl-substituted amine of **11**. The carbobenzyloxy (CBZ) group was chosen for this protection because of the ability to remove it by hydrogenolysis, the significance of which will become apparent later (*vide infra*). Treatment of **11** with 1 equiv of benzyl chloroformate (CBZ-Cl) afforded **12** significantly contaminated with material where the CBZ group was substituted on the arylamine, as well as diprotected product.[12] Decreasing the reaction temperature from 0 to −30 °C during the CBZ-Cl addition substantially decreased the amounts of these side products. Based upon this result, it was anticipated that selectivity could be further improved by substituting the less reactive CBZ transfer reagent *N*-(benzyloxycarbonyloxy)succinimide (BCS). Indeed, when **11** was treated with BCS at −40 °C excellent selectivity was demonstrated for the aliphatic amine, with only a trace amount of other CBZ-substituted products, by GLC analysis.[13] Purification by silica gel chromatography gave **12** in 65% overall yield from **10** (borane reduction and CBZ protection steps).

At this point there remained the critical introduction of the second aryl nitrogen onto **12** for incorporation into the benzo-fused urea. An examination of the mechanism of the oxidative cyclization of *N*-methoxyamides (see Scheme **1**) suggested that this reaction may be general to other types of *N*-methoxyacyl groups and that acyclic *N*-methoxyurea **17** could potentially serve as a substrate; substantiating this were two reports describing procedures for the oxidative cyclization of **13** to obtain **14**. These employed (1) lead tetraacetate under dilute conditions to aid in recovering **14** from the intractable lead residue,[14] making this procedure unappealing for large scale synthesis, or (2) the chlorination of **13** to give an unstable *N*-chloro-*N*-methoxyurea species which was induced to cyclize to **14** by treatment with strong base to generate an anionic intermediate (Figure 2).[15] Obviously this latter procedure which requires hydrogen substitution on the aryl nitrogen of the urea (*i.e.*, **13**) would not be compatible with our substrate (**17**).[16]

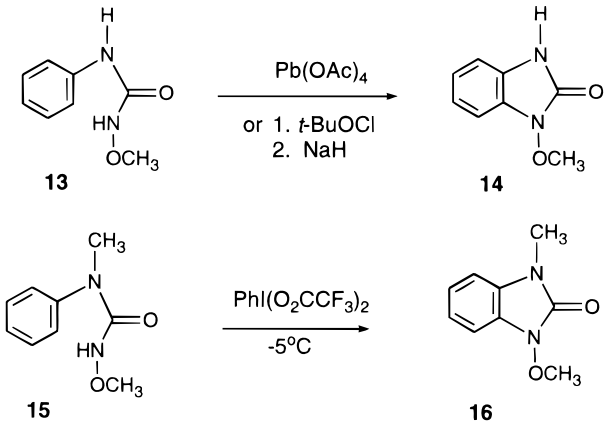


Figure 2. Model systems for synthesizing benzo-fused ureas (2-benzimidazolinones) by oxidative cyclization of *N*-methoxyureas (see text).

Requiring an alternative oxidant to activate the *N*-methoxyurea group for intramolecular cyclization, we quickly considered the possibility of once again using bis(trifluoroacetoxy)iodobenzene. The demonstrated ability of this reagent to activate *N*-methoxyamide groups for electrophilic aryl substitution suggested that it might provide a superior method to induce oxidative cyclization on the analogous *N*-methoxyurea groups. However, we were disappointed to find that when model system **13** was treated with this reagent a mixture of unidentifiable products was obtained (Figure 2). While at first puzzled by this result, we speculated that the aryl-substituted nitrogen could be serving as an alternative site for oxidation by the bis(trifluoroacetoxy)iodobenzene reagent. To examine this question, the *N*-methyl-substituted model system **15**, which more accurately represents the aryl *N*-substitution of our actual substrate (**17**), was treated with the oxidant and found to afford **16** in 79% yield. Indeed, examination of this bis(trifluoroacetoxy)-iodobenzene-mediated annulation procedure with other *N*-methoxyurea substrates indicated that carbon substitution at the aryl *N*-position of the *N*-methoxyurea was critical,[17] constituting a procedure complimentary to the chlorination/sodium hydride method. However, our optimism for the application of the bis(trifluoroacetoxy)-iodobenzene procedure to **17** was attenuated by the consideration that an attempt to cyclize *N*-methoxy-3*N*-benzyl-3*N*-methylurea (benzyl substituted for the phenyl

(11) For another example of *in situ* generation of the more reactive bis(trifluoroacetoxy)iodobenzene reagent, see ref 6 in the following: Radhakrishna, A. S.; Parham, M. E.; Riggs, R. M.; Louden, G. M. New method for direct conversion of amides to amines. *J. Org. Chem.* **1979**, *44*, 1746−1747.

(12) Not surprisingly, selective protection with the more reactive trifluoroacetic anhydride totally failed, giving a statistical mixture of products.

(13) This selectivity, the relative stability of this crystalline reagent to storage, and its non-lachrymator properties also made it more desirable than CBZ-Cl for the multikilo-scale reaction.

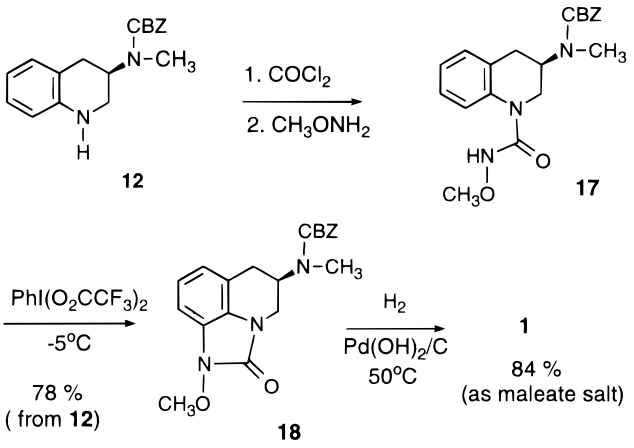
(14) Cooley, J. H.; and Jacobs, P. T. Oxidative ring closure of 1-benzyloxy-3-arylureas to 1-benzyloxybenzimidazolones. *J. Org. Chem.* **1975**, *40*, 552−557.

(15) Perronnet, J.; and Demoute, J.-P. Approach to the 1-methoxy-2-benzimidazolinones. *Gazz. Chim. Ital.* **1982**, *112*, 507−511.

(16) The *N*-chlorination/sodium hydride procedure requires a substrate containing a hydrogen on the aryl-substituted nitrogen; an attempt to perform the cyclization without such substitution failed, demonstrating the need to enhance the reactivity of the aryl ring by converting the aryl nitrogen into its anionic form. See ref 15.

(17) The absence of a substituent on the aryl-substituted nitrogen of the *N*-methoxyurea apparently open up other avenues for bis(trifluoroacetoxy)iodobenzene oxidation, leading to decomposition. This does not appear to be a problem when this nitrogen is substituted. For further discussion, see: Romero, A. G.; Darlington, W. H.; Jacobsen, E. J.; Mickelson, J. W. Oxidative cyclization of acyclic ureas with bis(triflyoroacetoxy)iodobenzene to generate *N*-substituted 2-benzimidazolinones. *Tetrahedron Lett.* **1996**, *37*, 2361−2364.

Scheme 3. Introduction of the Benzo-Fused Urea *via* Oxidative Cyclization



in **15**) resulted in decomposition, presumably by oxidation of the activated benzylic methylene. Consequently we maintained a concern about the stability of the benzylic methylene portion of **17**'s CBZ protecting group to oxidation by bis(trifluoroacetoxy)iodobenzene.[18]

Having thus determined with the aid of these model compounds the manner in which we were going to attempt to carry out the urea annulation on the authentic substrate (**17**), we turned to the actual preparation of this compound (Scheme 3), easily accomplished by the addition of aryl amine **12** to a THF solution of phosgene, subsequently adding methoxylamine to the carbamoyl chloride adduct to afford **17**.[19] In the critical step, treatment of *N*-methoxyurea **17** with bis(trifluoroacetoxy)iodobenzene proved our concerns regarding the stability of the CBZ group to be unfounded; the reaction smoothly afforded the desired tricyclic *N*-methoxyurea **18** in 78% overall yield from **12**.

All that remained to complete the synthesis of **1** was to concurrently remove the CBZ protecting group and cleave the nitrogen−oxygen bond of *N*-methoxyurea **18** by means of hydrogenation over palladium hydroxide on carbon (Pearlman's catalyst). While the CBZ group came off quickly, cleavage of the nitrogen−oxygen bond was quite sluggish, requiring 2−3 days at 25 °C with 50 psi of hydrogen pressure. To increase the rate of this conversion, the ethanol slurry was heated to 50 °C, causing the nitrogen−oxygen bond reduction to proceed to completion in several hours. Verification of the enantiomeric purity of **1** by chiral HPLC demonstrated that it was greater than 99% optically pure.[7] Since **1** was very water soluble, it was isolated directly as the maleic acid salt (84% yield of pure, crystalline material), after first removing the hydrogenation catalyst by filtration.

Conclusion

The utility of oxidative cyclization of *N*-methoxyacyl groups, both amides and ureas, has been demonstrated to be a powerful tool for the organic chemist to synthesize heterocyclic rings in complex molecules. In part this is because few procedures exist to directly attach a nitrogen atom onto a benzene ring; traditional approaches frequently focus on nitration chemistry, a hazard on large scale and not always amenable to *ortho* substitution. This sequence of tandem oxidative cyclizations was instrumental in providing an eight-step synthesis of optically pure **1** (PNU-95666E) from D-phenylalanine in 26% overall yield and has been performed successfully on a multikilo scale.[20]

Experimental Section

General. Methoxyamine hydrochloride, D-phenylalanine, diacetoxyiodobenzene, and Pearlman's catalyst were obtained from Aldrich; phosgene in toluene was obtained from Fluka; and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC) was obtained from Sigma. Both commercial bis(trifluoroacetoxy)iodobenzene and reagent prepared from diacetoxyiodobenzene as described by Loudon[21] was used. All reactions were run under a nitrogen atmosphere. Proton NMR were run on a Bruker Model AM-300 spectrometer at 300 MHz field strength and are reported in ppm relative to TMS. *J* vaues are in hertz. Mass spectrometry was performed at 70 eV ionization energy with ions reported as *m/e*. Melting points are uncorrected. GLC conditions are as follows: Hewlett-Packard Model 5890A capillary gas chromatograph, J & W Scientific Inc., DB-5.5% phenylmethyl silicone column (15 m × 0.53 mm × 1.5 μm film thickness), helium carrier gas (100 mL/min.), hydrogen flame ionization detector. Programmed: 100 °C, 1 min; increasing 20 °C/min to 250 °C; 250 °C, 10 min. HPLC conditions are as follows: Zorbax Rx-C8 column (4.6 mm × 25 cm), solvent A, 10% CH_3CN and 90% H_2O (pH 3 phosphate buffer), solvent B, 85% CH_3CN and 15% H_2O (pH 3 phosphate buffer), programmed gradient, 90% A/10% B to 5% A/95% B over 12 min, maintain at 5% A/95% B for 4 to 10 min; λ = 215 nm, flow = 2 mL/min.

(*R*)-2-((Methoxycarbonyl)amino)-3-phenylpropanoic Acid (8). A solution of D-phenylalanine (25.00 g, 0.151 mol) and sodium hydroxide (6.05 g, 0.151 mol) in water (170 mL) and tetrahydrofuran (225 mL) was cooled to −15 °C, and a solution of methyl chloroformate (18.6 g, 0.197 mol) in tetrahydrofuran (50 mL) was added dropwise. When the one-half of the methyl chloroformate had been added, a solution of sodium hydroxide (9.10 g, 0.227 mol) in water (20 mL) was added. When the addition was complete, the solution was stirred at 25 °C for an additional 2 h and acidified with 10% hydrochloric acid to pH 2. The solution was extracted twice with diethyl ether, and the extracts were washed with brine and dried ($MgSO_4$). The solvent was removed under vacuum to leave a clear oil (34 g): ^{1}H NMR ($CDCl_3$) δ 3.09 (dd, 1H, *J* = 6.4, 14.0), 3.19 (dd, 1H, *J* = 5.6, 13.8), 3.65 (s, 3H), 4.66 (two d, 1H, *J* = 6), 5.25 (d, 1H, *J* = 8.2), 7.15−7.31 (m, 5H), 8.22 (br s, 1 H); IR (thin film) 1726, 1498, 1455, 1448, 1377 cm^{-1}; exact mass calcd for $C_{11}H_{13}NO_4$ 224.0923, found 224.0921.

(*R*)-*N*-Methoxy-2-((methoxycarbonyl)amino)-3-phenylpropanamide (9). A solution of sodium carbonate (10.20 g, 96.2 mmol) in water (170 mL) was added to a solution of **8** (~0.148 mol crude) in methylene chloride. Methoxyamine hydrochloride (14.2 g, 0.170 mol) and 1-(3-(dimethylamino-)propyl)-3-ethylcarbodiimide hydrochloride (EDC) (31.21 g, 0.163 mol) were added, and the mixture was stirred at room temperature for 22 h. The mixture was diluted with tetrahydrofuran (to dissolve the precipitate), and the layers were separated. The aqueous layer was extracted with 1:1 tetrahydrofuran/diethyl ether, and the combined organic extracts were washed with 10% hydrochloric acid and a saturated sodium bicarbonate solution. The solution was dried ($MgSO_4$) and filtered, and the solvent was removed under vacuum to leave a white solid (34.2 g). Crystallization from ethyl acetate gave 22.6 g of colorless crystals as a single crop, mp 154−155 °C

(18) For example, treatment of the *N*-methoxyurea obtained from *N*-benzyl-*N*-methylamine with bis(trifluoroacetoxy)iodobenzene led to decomposition. We postulate that this is due to the enhanced sensitivity of the benzylic methylene group to oxidation.

(19) Phosgene was replaced with triphosgene, affording a similar yield when the reaction was scaled-up. While also effective, substitution of carbonyldiimidazole (CDI) was less satisfactory.

(20) This synthesis was presented at the Technical Achievement Symposium at the 210th National Meeting of the American Chemical Society, Chicago, IL, August 20−24, 1995.

(21) For a preparation of bis(trifluoroacetoxy)iodobenzene, see ref 8a.

(61% overall from D-phenylalanine): ^{1}H NMR ($CDCl_3$) δ 3.05 (d, 2H, J = 7.4), 3.58 (s, 3H), 3.61 (s, 3H), 4.34 (q, 1H, J = 7.9), 5.66 (br d, 1H, J = 8.2), 7.15−7.31 (m, 5H), 9.44 (s, 1H); IR (mineral oil) 1694, 1668 cm^{-1}; $[\alpha]^{25}_D$ = +5.2° (CH_3OH, c = 1.045). Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.39; H, 6.41; N, 11.09.

Methyl (*R*)-*N*-(1,2,3,4-Tetrahydro-1-methoxy-2-oxo-3-quinolinyl)carbamate (10). A suspension of (*R*)-*N*-methoxy-2-((methoxycarbonyl)amino)-3-phenylpropanamide (**9**) (11.25 g, 44.6 mmol) in dichloromethane (170 mL) was cooled in an ice bath, and trifluoroacetic acid (9.25 mL, 13.7 g, 0.120 mol) was added. Bis(trifluoroacetoxy)iodobenzene (19.78 g, 0.046 mol) was added portion wise over 10 min at 0 °C, and the mixture was stirred at this temperature for 1 h. The mixture was washed with a 10% sodium carbonate solution and dried ($MgSO_4$). The solvent was removed under vacuum to leave an amber oil (19.58 g). Purification by flash chromatography (230−400 mesh silica gel, 40−50% ethyl acetate/hexane) gave the desired product as an amber oil which solidified (9.45 g, 85% yield). An analytical sample (1.5 g) was crystallized from ethyl acetate/hexane to give white crystals (1.36 g, mp 117−119 °C): ^{1}H NMR ($CDCl_3$) δ 2.85 (t, 1H, J = 14.7), 3.44 (dd, 1H, J = 15.0, 5.8), 3.72 (s, 3H), 3.93 (s, 3H), 4.42 (dt, 1H, J = 14.2, 5.6), 5.82 (br s, 1H), 7.09 (dt, 1H, J = 7.4, 1.2), 7.33 (t, 1H, J = 7.7), 7.22 (d, 2H, J = 7.6); IR (mineral oil) 1722, 1703 cm^{-1}; $[\alpha]^{25}_D$ = +34.2° (CH_3OH, c = 0.927). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.55; H, 5.64. N, 11.32.

(*R*)-3-(Methylamino)-1,2,3,4-tetrahydroquinoline Maleate Salt (11). A solution of (*R*)-*N*-(1,2,3,4-tetrahydro-1-methoxy-2-oxo-3-quinolinyl)carbamate (**10**) (29.1 g, 116.4 mmol) in dry tetrahydrofuran (400 mL) was cooled to 0 °C, and borane−methyl sulfide (10.0 M solution, 70 mL, 6.0 equiv) was slowly added. The solution was allowed to warm to 25 °C and stirred for 2.5 h. The solution was then refluxed on a steam bath for 30 h and then cooled to 0 °C, quenching dropwise (careful hydrogen evolution) with 10% hydrochloric acid (160 mL). This solution was refluxed on the steam bath for 1.5 h, cooled in ice, and made basic with 12 N aqueous sodium hydroxide. The mixture was extracted twice with diethyl ether, and the combined extracts were washed with brine and dried ($MgSO_4$). The solvent was removed under vacuum to leave a clear oil (19.6 g, approximately 100% crude yield) which was carried on without further purification. Examination of crude diamine **11** by GLC shows peaks at 5.15 min (2%), 5.46 min (**11**, 85%), 5.83 min (3%), and 7.39 min (10%). To obtain an analytical sample, an aliquot of crude **11** was crystallized as its maleate salt in methanol/ether (71% yield); mp 175 °C; ^{1}H NMR of the maleic acid salt ($CDCl_3$) δ 2.64 (s, 3H), 2.80 (dd, 1H, J = 17.0, 5.3), 3.11 (dd, 1H, J = 16.9, 4.9), 3.20−3.52 (m, 3H), 3.55 (m, 1H), 5.92 (s, 1H), 6.03 (s, 2H, maleic acid CH=CH), 6.53−6.58 (m, 2H), 6.927−6.97 (m, 2H), 8.48 (br s, 1H); $[\alpha]^{25}_D$ = +19.0° (CH_3OH, c = 1.01); IR (thin film) 1638, 1608 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2 \cdot C_4H_4O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.51; H, 6.53; N, 10.06.

(*R*)-Methyl(1,2,3,4-tetrahydro-3-quinolinyl)carbamic Acid, Phenylmethyl Ester (12). A solution of (*R*)-1,2,3,4-tetrahydro-*N*-methyl-3-quinolinamine (**11**) (15.0 g of crude material prepared above, approximately 84.4 mmol) in toluene (50 mL) was stirred at −40 °C while *N*-(benzyloxycarbonyloxy)succinimide (24.2 g, 97.1 mmol) in toluene (150 mL) was added over 1 h. After 30 min at −40 °C, GLC analysis indicated that all of **11** had been consumed. The solution was quenched by the addition of sodium bicarbonate (300 mL of a 10% aqueous solution) and warmed to 0 °C, followed by the addition of methanol (100 mL). This was stirred overnight and then extracted with ethyl acetate. Drying over $MgSO_4$ and solvent removal afforded a liquid which was purified by flash chromatography (230−400 mesh silica gel; 4:1 hexane/ethyl acetate) to give a liquid (17.2 g, 65% overall yield from **10**) which crystallized from ethyl acetate/hexane to afford white crystals (mp 80 °C): ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 3H,), 2.80−3.04 (m, 2H), 3.30 (d, 2H, J = 6.9), 3.83 (s, 1H), 4.57 (m, 1H), 5.16 (s, 2H), 6.51 (d, 1H, J = 7.9), 6.64 (t, 1H, J = 7.4), 6.96−7.02 (m, 2H), 7.35 (m, 5H); $[\alpha]^{25}_D$ = −50.1° (CH_3OH, c = 0.816); IR (mineral oil) 1680, 1606 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.87; H, 6.84; N, 9.32.

(*R*)-Methyl[1,2,3,4-tetrahydro-1-[(methoxyamino)carbonyl]-3-quinolinyl]carbamic Acid, Phenylmethyl Ester (17). A solution of (*R*)-methyl(1,2,3,4-tetrahydro-3-quinolinyl)carbamic acid, phenylmethyl ester (**12**) (3.81 g, 12.86 mmol) and triethylamine (3.9 g, 39 mmol) in dry tetrahydrofuran (50 mL) was added with stirring to a solution of phosgene (7.1 mL of a 1.93 M toluene solution) in tetrahydrofuran (100 mL) at 0 °C. After 1 h, methoxyamine hydrochloride (2.15 g, 25.7 mmol) and triethylamine (3.9 g, 39 mmol) were added, and the mixture was stirred at room temperature for 2 days. The solution was diluted with diethyl ether and washed with water and brine. The organic layer was dried ($MgSO_4$), and the solvent was removed under vacuum to leave an oil (5.13 g, >100% crude yield) which was sufficiently pure for the next step. An analytical sample was purified via flash chromatography (230−400 mesh silica gel; 50% ethyl acetate/hexane) to give the title compound as an oil: ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 3H), 2.77−2.97 (m, 2H), 3.75 (s, 3H), 3.52−4.08 (m, 2H), 4.54 (m, 1H), 5.13 (s, 2H), 7.10−7.27 (m, 4H), 7.35 (br s, 5H), 7.76 (br s, 1H); IR (thin film) 1734, 1697, 1605 cm^{-1}; $[\alpha]^{25}_D$ = +38° (CH_3OH, c = 0.980); exact mass calcd for $C_{20}H_{23}N_3O_4$ 369.1688, found 369.1682.

(*R*)-Methyl(1,2,5,6-tetrahydro-1-methoxy-2-oxo-4*H*-imidazo[4,5,1-*ij*]quinolin-5-yl)carbamic Acid, Phenylmethyl Ester (18). A solution of (*R*)-methyl[1,2,3,4-tetrahydro-1-[(methoxyamino)carbonyl]-3-quinolinyl]carbamic acid, phenylmethyl ester (**17**) (7.26 g, 19.7 mmol) in chloroform (150 mL) was cooled to −5 °C in an ice−salt bath. Bis(trifluoroacetoxy)iodobenzene (10.14 g, 23.6 mmol) was added, and the mixture was stirred at −5 to 0 °C for 4 h and then at 25 °C for 2 h more at which time the reaction was complete by TLC. The reaction mixture was washed with 10% aqueous sodium carbonate, back-extracting the aqueous fractions with diethyl ether. The combined organic layers were dried ($MgSO_4$), and the solvent was removed under vacuum to leave a brown oil (10.7 g). Purification by flash chromatography (230−400 mesh silica gel, 50% ethyl acetate/hexane) gave an amber oil which slowly solidified (5.67 g, 78% yield). HPLC analysis indicated two peaks, 10.79 (97.4%) and 11.95 min (2.6%). An analytical sample (0.54 g) was crystallized from ethyl acetate/hexane to give off-white crystals (0.41 g, mp 105−106.5 °C): ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 3H), 2.90−3.30 (m, 1H), 3.14 (dd, 1H, J = 15.5, 11.0), 3.68 (m, 1H), 4.07 (s, 3H), 4.11 (dd, 1H, J = 11.9, 4.8 Hz), 4.65 (m, 1H), 5.16 (m, 2H), 6.88 (d, 1H, J = 7.5), 6.96 (d, 1H, J = 7.5), 7.04 (t, 1H, J = 7.7), 7.36 (m, 5H); IR (mineral oil) 1725, 1717, 1694 cm^{-1}; $[\alpha]^{25}_D$ = +46.8° (CH_3OH, c = 0.731). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.41; H, 5.77; N, 11.42.

(*R*)-5,6-Dihydro-5-(methylamino)-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one Maleate Salt (1; PNU-95666E). A mixture of methyl(1,2,5,6-tetrahydro-1-methoxy-2-oxo-4*H*-imidazo[4,5,1-*ij*]quinolin-5-yl)carbamic acid, phenylmethyl ester (**18**) (3.87 g, 10.5 mmol) and 20% palladium hydroxide on carbon (1.0 g) in absolute ethanol (100 mL) was shaken in a Parr apparatus with an initial hydrogen pressure of 50 psi for 19 h. The mixture was filtered through diatomaceous earth, and the catalyst was washed with ethanol, and the solvent was removed under vacuum to leave a thick oil (2.2 g). This was dissolved in methanol (25 mL) and added to a solution of maleic acid (1.20 g, 10.3 mmol) in methanol (25 mL). Crystallization gave an off-white solid (2.55 g, mp 211 °C). A second crop was obtained by adding diethyl ether (0.29 g) obtaining a total of 2.84 g of analytically pure material (84% yield). HPLC analysis of this salt indicated it to be greater than 99% pure: ^{1}H NMR of the maleic acid salt (DMSO) δ 2.68 (s, 3H), 3.05 (dd, 1H, J = 16.6, 5.7), 3.22 (dd, 1H, J = 3.3, 16.3), 3.90−4.06 (m, 3H), 6.05 (s, 2H, maleic acid CH=CH), 6.85−6.97 (m, 3H), 8.74 (br s, 1H), 10.83 (s,1H); IR (mineral oil) 1696, 1638 cm^{-1}; $[\alpha]^{25}_D$ = −26.3° (H_2O, c = 0.836). Anal. Calcd for $C_{11}H_{13}N_3O \cdot C_4H_4O_4$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.45; H, 5.17; N, 13.13.

Preparation of BOC-Protected 1. Sodium hydroxide (2.0 N, 78 μL, 0.16 mmol) was added to a mixture of **1** (32.7 mg,

0.136 mmol) and di-*tert*-butyl dicarbonate (0.034 g, 0.155 mmol) in dry tetrahydrofuran (1.0 mL) at room temperature-,and the mixture was heated at reflux for 20 min. The mixture was diluted with diethyl ether, washed with brine, and dried ($MgSO_4$). The solvent was removed under vacuum to leave an oil. Purification by flash chromatography (230−400 mesh silica gel, 50% ethyl acetate in hexane to pure ethyl acetate) gave BOC-protected **1**: ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.88 (s, 3H), 2.93 (m, 1H), 3.13 (dd, 1H, J = 15.9, 11.1), 3.68 (t, 1H, J = 11.2), 4.12 (dd, 1H, J = 11.8, 4.8), 4.58 (m, 1H), 6.87 (d, 1H, J = 6.9), 6.94−7.02 (m, 2H). Analysis with a chiral HPLC column (Regis (R,R)-WHELK-O 1 column; 25 cm × 4.6 mm i.d.; 5 μm; 50% 2-propanol in hexane; flow 1 mL/min; λ 215 nm) showed a single peak at 12.7 min (>99.5%). Previously prepared racemic BOC-protected **1** displayed peaks at 8.0 and 12.7 min, corresponding to the two enantiomers.

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