A Practical and Efficient Synthesis of the Selective Neuronal Acetylcholine-Gated Ion Channel Agonist (*S*)-(−)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine Maleate (SIB-1508Y)

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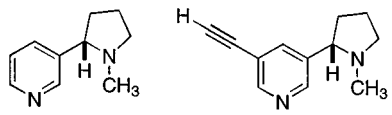
An efficient, high-yielding synthetic procedure for the preparation of the novel neuronal acetylcholine-gated ion channel agonist (*S*)-(−)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine maleate [(*S*)-**2**, SIB-1508Y] is described. The key steps in the process include the lithium bis(trimethylsilyl)amide-mediated acylation of *N*-vinylpyrrolidinone with ethyl 5-bromonicotinate, a high-yielding sodium borohydride reduction of imine **5**, and a new heteroaryl−alkyne cross-coupling protocol for the introduction of the ethyne moiety in (*S*)-**2**. The preparation of enantiomerically pure (*S*)-**2** was accomplished via a combination of enantioselective reduction of imine **5** and crystallization of enantiomerically enriched 5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (**7**) as the dibenzoyl-L-tartaric acid salt.

Introduction

The therapeutic potential of drug molecules acting at neuronal nicotinic acetylcholine receptors (neuronal NAChRs) is now well established.[1,2] Several studies have demonstrated that the naturally occurring alkaloid nicotine (**1**) and other NAChR agonists may have beneficial effects in the treatment of Parkinson's disease (PD),[3] Alzheimer's disease (AD),[3−5] attention deficit hyperactivity disorder (ADHD),[6] Tourette's syndrome,[7] and schizophrenia.[8,9] Recently a number of drug candidates, such as ABT-418,[4,10,11] ABT-089,[12] DMXB (GTS-21),[5,13] and RJR-2403[14,15] have been disclosed as a result of ongoing research aimed at the rational design of neuronal NAChR modulatory compounds. In our own laboratories the investigation of the therapeutic properties of the novel NAChR agonist 5-ethynyl-3-(1-methyl-2-pyrrolidinyl)-pyridine fumarate (**2**, SIB-1765F)[16−18] and the enantiomerically pure (*S*)-(−)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine maleate [(*S*)-**2**, SIB-1508Y][19] led to the selection of (*S*)-**2** for clinical development to treat Parkinson's disease. Consequently, large quantities of **2** and (*S*)-**2** were required for biological characterization. Herein are described our efforts toward the development of an efficient large scale synthesis of **2** and an enantioselective synthesis of (*S*)-**2**.



1 (*S*)-**2**

Results and Discussion

The synthetic method used initially to produce research quantities of racemic **2** is shown in Scheme 1. The first

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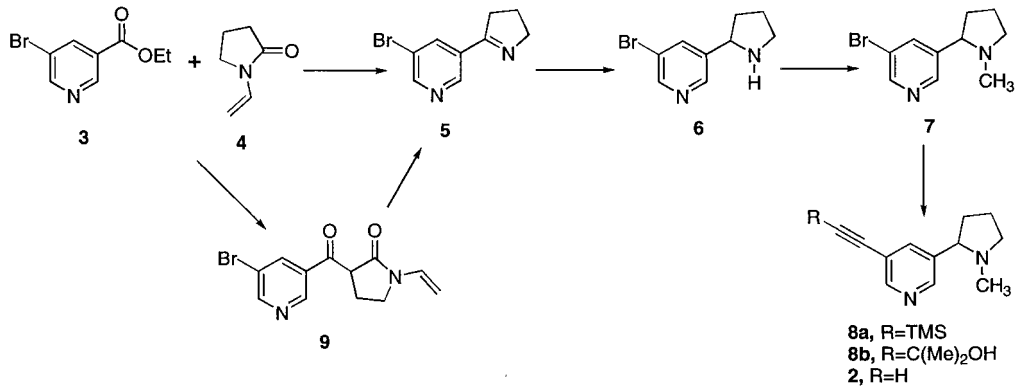
Scheme 1



step, based on a published method,[20] involved the condensation of ester **3** with the sodium enolate of *N*-vinylpyrrolidinone (**4**). The crude reaction mixture containing intermediate **9** was acidified with 6 M HCl and the solvent removed in vacuo. The resulting aqueous mixture was heated for 3 h at reflux to effect hydrolysis and decarboxylation, providing imine **5** upon treatment with base. Reduction of **5** with sodium borohydride at −40 °C in MeOH−acetic acid (4:1) provided the secondary amine **6** which was converted to **7** via reductive amination using formaldehyde and sodium cyanoborohydride with a catalytic amount of glacial acetic acid in acetonitrile. Cross-coupling of **7** with (trimethylsilyl)acetylene (TMSA) in the presence of a catalytic amount of palladium tetrakis(triphenylphosphine) [$Pd(PPh_3)_4$] and copper(I) iodide (Sonogashira reaction)[21] gave the coupled product **8a**. Deprotection with cesium carbonate in MeOH provided racemic **2** in an overall yield of 20% from **3**.

Unfortunately this procedure suffered from a number of drawbacks. Several of the reaction steps employed reagents that were considered either too hazardous, too unstable, or too expensive to be employed on a large scale. Also problematic were the five chromatographic purifications performed during the synthesis. Furthermore, the process provided racemic material rather than the desired active single enantiomer. Thus several modifications were necessary to produce an efficient, inexpensive, and scaleable synthesis of **2** and subsequently (*S*)-**2**. To improve the yield of this process and simplify purification of the intermediates, each step in the synthesis was carefully investigated and optimized.

The conditions reported by Jacob[20] for the first step (conversion of **3** to **5**) resulted in the generation of tarry material which necessitated the chromatograpic purification of **5**. Furthermore, the reaction had an induction period, was highly exothermic, and evolved hydrogen gas. The first modification, therefore, was to replace NaH with LiHMDS in the formation of the enolate. This allowed the enolate acylation reaction to proceed at ambient temperature and eliminated the induction period, the evolution of hydrogen gas, and the exotherm. Thus, **4** was treated with LiHMDS (2 equiv) in THF at −22 °C, a solution of ester **3** in *t*BuOMe was added, and the mixture was then stirred at ambient temperature for 18 h. Dilution of the reaction mixture with water caused the intermediate ketoamide **9** to precipitate out of solution, and this material was collected by vacuum filtration to provide **9** as a solid in 94 to 99% yield. Rinsing solid **9** removed the impurities which led to the formation of the tarry byproducts produced by the original method. Heating **9** in 6 M HCl at reflux (12 h) effected the removal of the *N*-vinyl group, amide bond hydrolysis, and decarboxylation. Subsequent basic workup produced the crude imine **5** with no observable byproducts. While **5** prepared in this way was of sufficient purity to proceed, material of higher purity could be obtained by the addition of activated charcoal and simple filtration through a silica gel pad. The yield of imine **5** from ester **3** ranged from 65 to 75% over the two steps.

The sodium borohydride reduction of **5** to racemic **6** was investigated next. It was found that reducing the amount of HOAc employed from 8 to 5 equiv did not affect the reaction adversely, but greatly simplified the workup. Sodium borohydride was still employed, but the excess used in the original procedure was found to be unnecessary. By maintaining the reaction temperature at −40 °C during the addition of the solid $NaBH_4$, complete conversion could be effected with only 0.5 equiv of reducing agent, giving a 90% yield of amine **6**. If the reaction was allowed to warm to 0 °C as the $NaBH_4$ dissolved, more than 2 equiv of the reducing agent was required to drive the reaction to completion, resulting in the formation of byproducts. While the precise nature of the active reductant in this reaction is not known, it is noteworthy that the reaction of **5** with 2 equiv $NaBH(OAc)_3$ in THF was slow and resulted in incomplete reduction of the imine. These observations would appear to preclude in situ formation of sodium triacetoxyborohydride as the active reductant in the formation of **6**.

The introduction of the pyrrolidine *N*-methyl functionality was the next step to be studied. To eliminate the need for $NaBH_3CN$ on a large scale, *N*-methylation using an Eschweiler−Clarke reductive amination procedure was investigated.[11] It was found that heating **6** at 80 °C with formaldehyde (37%, aqueous) in the presence of formic acid as the reducing agent greatly simplified the isolation of the product, avoided the generation of HCN, and allowed the preparation of **7** in 92% yield with minimal purification.

The palladium catalyzed cross-coupling to introduce the ethyne moiety and provide **8** suffered from several problems. The reaction of **7** with TMSA catalyzed by $Pd(PPh_3)_4$ and copper(I) iodide did not go to completion and afforded the product **8a** as an oil which was difficult to separate from unreacted starting material. The homogeneous catalyst $Pd(PPh_3)_4$, is not only expensive,

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(21) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−4470.

but also air and temperature sensitive and difficult to remove from the crude product. Furthermore, the method required an excess of TMSA, a comparatively expensive reagent. It was clear, therefore, that this critical step in the process required considerable refinement. Sonogashira aryl−alkyne cross coupling reactions typically employ a homogeneous source of Pd(0), a catalytic amount of a copper(I) salt, and an organic amine base as the solvent or cosolvent.[22] Our strategy for optimizing the transformation of **7** to **8** consequently focused on the modification of three components of the reaction conditions: the catalyst system, the alkyne coupling partner, and the solvent/base combination.

A number of recent studies pointed to the utility of heterogeneous palladium on carbon (Pd/C) as an alternative to the standard homogeneous catalysts for carbon−carbon bond formation. Of particular interest to us was an article reporting the use of a catalytic amount of Pd/C in the presence of PPh_3 and CuI to promote coupling of aryl bromides and phenylacetylene in anhydrous triethylamine−acetonitrile,[23] and another disclosing a Pd/C-catalyzed Suzuki cross-coupling reaction.[24] Thus we envisioned that a catalytic system consisting of Pd/C in combination with PPh_3 might replace $Pd(PPh_3)_4$ in the coupling reaction.

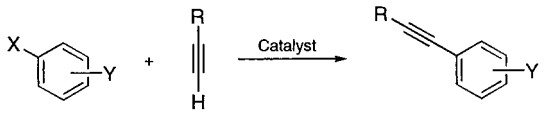
A survey of the literature revealed a potentially viable replacement for TMSA as the ethyne equivalent in the reaction. 2-Methyl-3-butyn-2-ol (mebynol) has been employed previously as a protected ethynyl moiety, although reports of its use are less common than the analogous reactions with TMSA.[25,26] This is quite surprising considering the low cost of mebynol and the generally crystalline nature of the resulting coupled products.

The beneficial effect of water in some palladium-mediated processes has also been noted recently.[27−30] In light of these observations it seemed likely that a mixture of 1,2-dimethoxyethane (DME) and water would be a viable solvent system. While organic amine bases are commonly employed in Sonogashira coupling protocols, there was concern that the presence of triethylamine in a reaction mixture which also contained **8b**, a tertiary amine, would complicate the workup and purification. Since similar problems were envisioned with the use of a phase transfer catalyst,[31] we elected to use an inorganic base without additives. K_2CO_3 was selected as the reagent of choice for its high water solubility and mildness compared with NaOH which has been reported to induce the in situ deprotection of mebynol-coupled products.[31]

When **7** was heated with mebynol in the presence of catalytic amounts of 10% Pd/C, PPh_3 and CuI (in a molar ratio of 1:4:2), and K_2CO_3 (2.5 equiv) in a DME−water mixture (1:1) cross-coupling proceeded to afford **8b** in high yield. The product was isolated as a solid which was readily recrystallized from cyclohexane or heptane in purified yields ranging from 92 to 98%. Deprotection to afford **2** was accomplished by simply heating **8b** in toluene in the presence of a catalytic quantity of NaH (10 mol %) at a high enough temperature to distill a portion of the solvent.[32] Racemic **2**, an oil at ambient temperature, was converted to the monofumaric acid salt (SIB-1765F) for biological evaluation.

To define the scope and limitations of the new cross-coupling conditions, experiments were performed on a variety of readily available substrates. The results of these experiments are presented in Tables 1 and 2 and were the subject of a recent communication from this laboratory.[33] The coupling partners were selected to

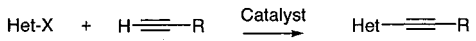
Table 1. Cross Coupling of Substituted Aryl Halides with Substituted Alkynes[a]

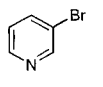
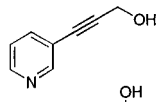
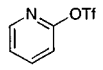
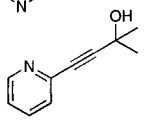
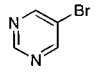
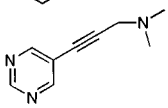
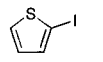
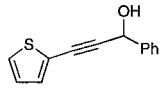
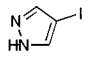
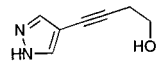


entry	compound	X	Y	R	% isolated yield
1	**10**	Br	*m*-CHO	$C(CH_3)_2OH$	98[b]
2	**11**	Br	*p*-NO_2	$C(CH_3)_2OH$	92[b]
3	**12**	I	*m*-NH_2	$C(CH_3)_2OH$	78[b]
4	**13**	Br	*o*-CN	$C(CH_3)_2OH$	89[b]
5	**14**	Br	*o*-CN	$CH_2N(CH_3)_2$	92[c]
6	**15**	I	*p*-OH	1-cyclohexenyl	50[d]
7	**16**	I	*p*-CO_2H	1-cyclohexenyl	80[d,e]

[a] Reactions performed using a 1:4:2 ratio of 10% Pd/C:PPh_3:CuI, 2.5 equiv of K_2CO_3, and 2.5 equiv of alkyne in DME:water 1:1 at 80 °C. a: 2 mol % Pd/C. b: 2.5 mol % Pd/C. c: 3.3 mol % Pd/C. d: Reaction performed in DME with 5 equivalents water.

Table 2. Coupling of Heterocyclic Halides with Substituted Alkynes



Entry	Heterocycle	R	Product	Compound	Isolated Yield[10]
1		CH_2OH		17	90%[a]
2		$C(CH_3)_2OH$		18	95%[a]
3		$CH_2N(CH_3)_2$		19	50%[b]
4		$CH(OH)C_6H_5$		20	95%[b]
5		CH_2CH_2OH		21	85%[b]

Reactions performed using a 1:4:2 ratio of 10% Pd/C:PPh_3:CuI, 2.5 equiv of K_2CO_3, and 2.5 equiv of alkyne in DME:water 1:1 at 80 °C. [a] 2 mol % Pd/C. [b] 3.3 mol % Pd/C.

(22) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, 129−160.
(23) De la Rosa, M.; Velarde, E.; Guzman, A. *Synth. Commun.* **1990**, *20*, 2059−2064.
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(29) Genet, J. P.; Linquist, A.; Blart, E.; Mouries, V.; Savignac, M. *Tetrahedron Lett.* **1995**, *36*, 1443−1446.
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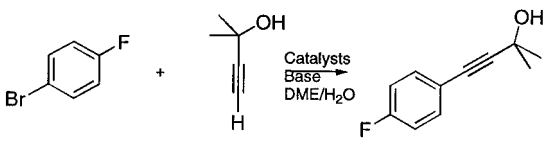
(32) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763−1764.

Table 3. Required Reagent Study



entry	Pd/C	PPh_3	CuI	K_2CO_3	% yield[b]
1	0.05[a]	0.2	0.0	2.5	2.5
2	0.05	0.0	0.1	2.5	0
3	0.0	0.2	0.1	2.5	0
4	0.05	0.2	0.1	0.0	3
5	0.05	0.2	0.1	2.5	80

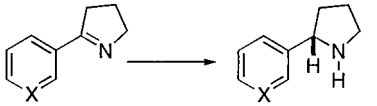
[a] Amounts are equivalents relative to 1-bromo-4-fluorobenzene, using 2.5 equiv of mebynol in all cases. [b] Yields determined by GC/MS.

assess the applicability of the reaction conditions to a wide range of unprotected functional groups. In addition to the observations noted in the earlier publication, an interesting aspect of the cross-coupling of aniline derivatives has been noted. While iodoanilines cross-couple in high yield at both the *meta* (Table 1, entry 3) and *ortho* positions,[34] the corresponding bromoanilines are completely unreactive. The likely reason for this is that the increased reactivity of the iodo- versus bromoaryl substrates offsets the deactivating effect of the arylamine functional group.[35]

To determine the necessity of each component of the catalyst−base system for successful coupling, a series of experiments, each lacking one of the components, was performed (Table 3). Thus, when cross-coupling of 1-bromo-4-fluorobenzene with mebynol was attempted in the absence of either Pd/C or PPh_3 from the reaction mixture, no coupled product was observed. In the absence of CuI or K_2CO_3, only traces of product could be detected by GC/MS. These results clearly indicate that cycling of the catalyst for this reaction requires all four of the components. Furthermore, while it has been reported that alkynes couple with aryl iodides in the absence of a copper(I) source, our results are in accordance with others who have demonstrated the beneficial effect of copper(I) salts in this[22] and other palladium-catalyzed coupling reactions.[36] Indeed, prolonged reaction times in the absence of CuI resulted in byproducts evidently derived from the coupling of mebynol with product, forming the corresponding enyne, a result which has been utilized synthetically by Trost.[37] Another observation concerns the degassing of the reaction mixture solvents. In many cases where the reaction conditions failed to give cross-coupled product, prior degassing of the reaction mixture allowed cross-coupling to proceed.

Having optimized the preparation of large amounts of racemic **2**, we next considered the synthesis of the individual enantiomers (*S*)-**2** and (*R*)-**2**. Nicotine (**1**) exhibits stereoselectivity in biological assays, the natural (*S*)-(−)-isomer being a more potent agonist than the (*R*)-(+)-isomer.[38] It appeared likely, therefore, that the (*S*)-enantiomer of **2** would possess the desired biological properties. At the outset, two basic approaches to the preparation of (*S*)-**2** were available: classical resolution of **2** or one of its precursors (**6**, **7**, or **8b**) or enantioselective synthesis.

The classical resolution of **6** has been reported by Jacob.[20] After several unsuccessful attempts using inexpensive resolving agents, such as (+)-tartaric acid, Jacob found that resolution with the appropriate enantiomer of Mosher's acid provided either (*S*)- or (*R*)-**6**. To date, the resolution of racemic **7** has not been reported,[39] while **8b** and **2** were hitherto unknown compounds. It was envisioned that an alternative approach to the problem via the enantioselective reduction of imine **5** might be effective. While there are numerous procedures in the literature for the enantioselective reduction of ketones, there are comparatively few methods for the analogous transformation of imines.[40] Among those reported are the asymmetric hydrogenation protocols developed separately by Noyori,[41] Buchwald,[42] and Burk.[43] While these methods provide a variety of amines in high enantiomeric excess a number of limitations have been noted. For example, Buchwald reported that while 2-phenyl-1-pyrroline (**22**) underwent enantioselective hydrogenation at very high pressure to give **23** in >99% ee, the corresponding pyridyl imine **24** failed to reduce under these conditions.[42]



22, X = CH
24, X = N

23, X = CH

We were intrigued, however, by a report which described the enantioselective reduction of imines employing a reagent formed from the reaction of sodium borohydride (1 equiv) with CBZ-L-proline **25** (3 equiv).[44] While the reported enantioselectivities were not spectacular (up to 86% ee) the simplicity of the procedure and the ready availability of the reagents made this methodology attractive. Furthermore the authors reported successful reduction of a cyclic imine **27** to give the enantiomerically enriched amine **28**.

In the event, application of this methodology to our substrate proved to be fruitful. Stirring a solution of the preformed chiral (acyloxy)borohydride reagent **26** with imine **5** provided secondary amine **6**, after workup and purification, in 98% yield and 30% ee. The ee of **6** was determined by recording the ^1H NMR spectrum of the enantiomerically enriched material in the presence of Mosher's acid as a chiral shift reagent. The resonance due to the methine proton at C-2′, an apparent triplet, appears as two signals and the ratio of the integrated peaks provided an estimate of the ee (Figure 1). Predict-

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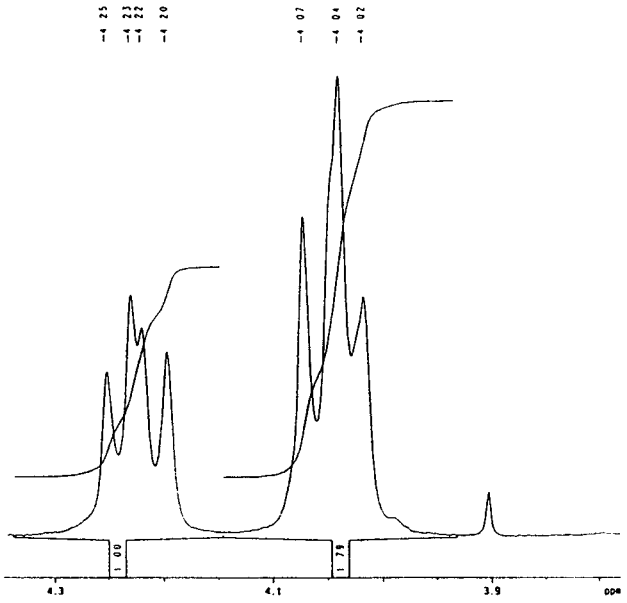
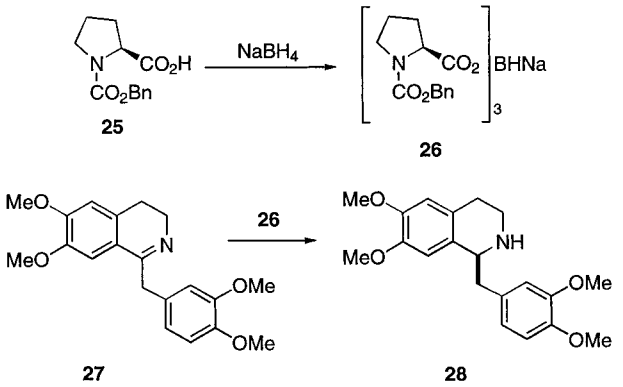
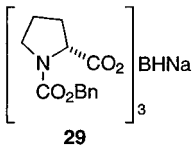


Figure 1. Resonances (^{1}H NMR) due to the C-2′ proton of **6** (30% ee) in the presence of Mosher's acid.



ably, reduction of **5** with the (acyloxy)borohydride reagent **29** derived from CBZ-D-proline gave **6** enriched in the other enantiomer with a 30% ee (Scheme 2).



Racemic nicotine has been resolved by sequential crystallizations with *d*-tartaric acid and di-*p*-toluoyl-L-tartaric acid.[38] This approach appeared more attractive than using the expensive Mosher's acid to resolve 5-bromonornicotine (**6**), as in Jacob's method, and it was therefore decided to *N*-methylate the enantiomerically enriched **6** and complete the resolution with nicotine analogue **7**. After some experimentation, it was found that crystallization of the salt formed from enantiomerically enriched **7** (30% ee) with the correct stoichiomeric quantity of dibenzoyl-L-tartaric acid in a mixture of EtOH and EtOAc provided (*S*)-**7** with >99% ee over two crystallizations (Scheme 2).

The determination of ee for **7** and **2** was accomplished using a chiral capillary GC column. Interestingly, while baseline separation was achieved for the key intermediate **7** and final product **2**, neither **8b** nor nicotine (**1**) could be resolved using this GC method. Determination of the ee of **2** showed that the asymmetric center was not sensitive to the conditions of the *N*-methylation, palladium-catalyzed aryl−alkyne cross coupling, or the NaH-catalyzed deprotection, as no loss of stereochemical integrity could be detected. Finally, conversion of (*S*)-**2**, an oil at ambient temperature, to its mono maleic acid salt gave the desired product SIB-1508Y, in 93% yield.

The absolute stereochemistry of the enantiomers of **7**, and by analogy **2**, was established by hydrogenation of (*S*)-**7** to afford a compound which was identical in all respects to (*S*)-(−)-nicotine. It was thus proven that reduction with the (acyloxy)boroborohydride reagent (**29**) derived from CBZ-D-proline ultimately provided (*S*)-**2**, the more active enantiomer, while using CBZ-L-proline resulted in the formation of (*R*)-**7** and ultimately (*R*)-**2**. Fortunately, extraction of the acidic aqueous phase with *i*-PrOAc during workup following the reduction of **5** allowed recovery of the CBZ-D-proline which could be purified by chromatography and reused, offsetting the expense of using the reagent derived from the unnatural amino acid.

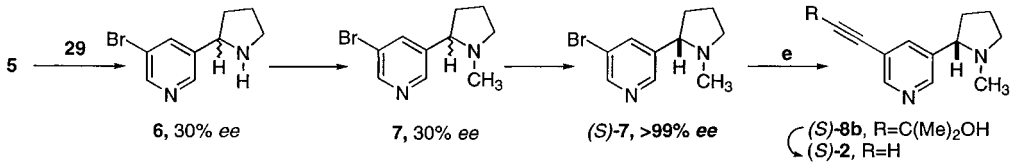
Conclusion

Practical and efficient syntheses of **2** and (*S*)-**2** have been described. Each step in the process was examined individually, optimized and incorporated into the final synthetic scheme. Novel palladium chemistry was developed for the transformation of **7** to **8b**, and this methodology was shown to be general. The yield of the conversion of **3** to **2** was improved by a factor of 2 (from 20 to 40% overall), while concurrently improving the scaleability, economy, and safety of each step. The preparation of enantiopure (*S*)-**2** was accomplished using a combination of enantioselective reduction, providing material with 30% ee, coupled with resolution via crystallization of a diastereomeric salt with >99% ee. Finally, these improvements and the development of an enantioselective route to (*S*)-**2** have contributed to the efficient production of multikilogram quantities of (*S*)-**2** required for the preclinical and clinical study of its therapeutic properties.

Experimental Section

General. All reactions, unless otherwise noted, were conducted under an inert atmosphere. Purchased reagents and solvents were used as received. Solvents designated as anhydrous were purchased in an anhydrous state (pre-packaged under nitrogen) and stored over activated 3 Å molecular sieves. Analytical thin-layer chromatography was carried out on precoated silica gel plates (0.25 mm, 60 F_{254}) with detection by UV, phosphomolybdic acid solution, or iodine vapor. Column chromatography was performed on silica gel (35−70 μm). Melting points were obtained in unsealed capillaries and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in the indicated solvents, and the chemical shifts are reported in ppm downfield from tetramethylsilane. Solvent ($CDCl_3$ $\delta_C = 77.00$, $\delta_H = 7.25$; DMSO-d_6 $\delta_C = 39.43$, $\delta_H = 2.5$; CD_3OD $\delta_C = 49.05$, $\delta_H = 3.30$) or added tetramethylsilane served as internal references. Infrared spectra are reported in wavenumbers and were measured as KBr pellets. Low resolution mass spectra were recorded in EI mode at 70 EV with a quadrupole instrument. Optical rotations were obtained at 589 nm (sodium D line) using a 1.9 dm cell at 20 °C. Chiral gas chromatographic separations were conducted on a 20 m × 0.25 mm capillary column coated with permethylated hydroxypropyl β-cyclodextrin phase at the

Scheme 2



indicated temperatures under isothermal conditions with a flow rate of 3.0 mL/min, using flame ionization detection.

3-(5-Bromo-3-pyridoyl)-*N*-vinylpyrrolidinone (9). A 5 L reaction vessel equipped for overhead stirring and fitted with a temperature probe was charged with lithium bis(trimethylsilyl)amide (1600 mL of a 1 M solution in THF, 1.6 mol, 2 equiv) and was cooled to an internal temperature of −22 °C ($CaCl_2/H_2O$ cooling bath). *N*-Vinylpyrrolidinone (103 mL, 0.96 mol, 1.2 equiv) was added in one portion, and the solution was stirred for 0.5 h at −22 °C. Ethyl 5-bromo-3-pyridinecarboxylate (184 g, 0.8 mol) was added to the mixture via cannula as a solution in *tert*-butyl methyl ether (800 mL), and the reaction mixture was allowed to warm to 25 °C. After stirring for 18 h at 25 °C, the reaction was quenched with water (400 mL) and stirring was continued. After 5−10 min a yellow precipitate appeared which was collected by filtration, rinsed with CH_2Cl_2, and dried under vacuum at 65 °C to afford 3-(5-bromo-3-pyridoyl)-*N*-vinylpyrrolidinone (**9**) (235 g, 99%). ^{1}H NMR (DMSO-d_6) apparent rotamers; major: δ_H 8.68 (d, J = 2 Hz, 1 H), 8.63 (d, J = 3 Hz, 1 H), 8.05 (m, 1 H), 7.06 (dd, J = 16, 9 Hz, 1 H), 4.11 (m, 2 H), 3.33 (t, J = 8 Hz, 2 H), 2.18 (t, J = 8 Hz, 2 H); minor: δ_H 8.53 (m, 1 H), 8.45 (m, 1 H), 7.94 (m, 1 H), 6.94 (dd, J = 16, 9 Hz, 1 H), 3.87 (m, 2 H), 3.23 (t, J = 7 Hz, 2 H), 2.68 (t, J = 8 Hz, 2 H). IR (KBr) 3418, 2923, 2869, 1651, 1629, 1525, 1422, 1281, 1020 cm^{-1}; LRMS (EI) *m/e* 297 ($C_{12}H_{11}N_2$81Br + H^+), 296 ($C_{12}H_{11}N_2$81Br), 295 ($C_{12}H_{11}N_2$79Br + H^+), 294 ($C_{12}H_{11}N_2$79Br); HRMS calcd for $C_{12}H_{11}$79BrN_2O_2 + Li^+ 301.0164 found 301.0155.

5-Bromo-3-(2-pyrrolin-1-yl)pyridine (5). 3-(5-Bromo-3-pyridoyl)-*N*-vinylpyrrolidinone (**9**) (230 g, 0.78 mol) was dissolved in a mixture of water (1.25 L), 12 M HCl (1.25 L), and charcoal (125 mL) in a 5 L reaction vessel equipped for overhead stirring and fitted with an internal temperature probe and a reflux condenser. The mixture was gradually heated to 98 °C over 2 h and then held at this temperature for 2 h. The reaction flask was allowed to cool to 25 °C overnight (HPLC analysis indicated completion). The reaction mixture was filtered through Celite and the pad thoroughly washed with CH_2Cl_2 (3 × 300 mL). The aqueous solution was basified with solid NaOH to pH 11, the layers were separated, and the aqueous was extracted with CH_2Cl_2 (5 × 500 mL). The combined organic extracts were stirred with $MgSO_4$ and charcoal prior to filtration through a pad consisting of layers of silica gel, Florisil, and Celite. This was flushed through with more CH_2Cl_2 (4 L) followed by EtOAc (4 L). The combined eluants were concentrated in vacuo to afford 5-bromo-3-(2-pyrrolin-1-yl)pyridine (**5**) (124.8 g, 71%) as a solid. Mp 98−99 °C (EtOAc) (lit.[19] mp 97.5−98.5 °C); ^{1}H NMR ($CDCl_3$) δ_H 8.88 (d, J = 2 Hz, 1 H), 8.71 (d, J = 2 Hz, 1 H), 8.36 (app t, J = 2 Hz, 1 H), 4.10 (app tt, J = 8, 2 Hz, 2 H), 2.94 (app tt, J = 8, 2 Hz, 1 H), 2.09 (app quintet, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ_C 169.8, 152.1, 147.0, 137.2, 131.6, 120.9, 61.7, 34.8, 22.5.

5-Bromo-3-(1-*H*-2-pyrrolidinyl)pyridine (6). A three-necked, 2L, round-bottomed flask equipped for overhead stirring and fitted with an internal temperature probe was charged with 5-bromo-3-(2-pyrrolin-1-yl)pyridine (**5**) (67.5 g, 0.3 mol) and dissolved in a mixture of MeOH (560 mL) and glacial acetic acid (140 mL). The solution was cooled to −42 °C ($CaCl_2/H_2O$ cooling bath), causing the imine to precipitate, and solid sodium borohydride (1.96 g, 0.052 mol) was slowly added in portions over 1 h, maintaining the internal temperature below −40 °C. The reaction was stirred at −40 °C for 3 h and then at 0 °C for 18 h, the course of the reaction being monitored by TLC. Water (200 mL) was added, and the mixture was concentrated to a volume of about 200 mL. The resulting solution was further diluted with water (200 mL) to provide a solution of pH 4. Concentrated HCl (30 mL) was added to afford a solution of pH 3 and this was then extracted with CH_2Cl_2 (3 × 100 mL). The aqueous phase was basified with solid NaOH and extracted with CH_2Cl_2 (3 × 200 mL). The combined basic organic extracts were washed with brine (100 mL) and stirred with $MgSO_4$ and charcoal for 18 h. Filtration through Celite and concentration in vacuo gave **6** as an oil (44.8 g, crop 1). The acidic organic extracts, shown by TLC to contain product, were extracted with 1 M HCl (2 × 200 mL). The combined extracts were washed with CH_2Cl_2 (2 × 50 mL) and then basified with solid NaOH to pH 12. The basic aqueous layer was then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase was washed with brine (50 mL) and then stirred with $MgSO_4$ and charcoal for 18 h. Filtration through Celite and concentration in vacuo gave **6** as an oil (6 g, crop 2). The basic aqueous fractions were combined and concentrated in vacuo (2-propanol azeotrope) giving a reduced volume which was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were stirred with $MgSO_4$ and charcoal for 18 h. Filtration through Celite and concentration in vacuo gave **6** as an oil (10.5 g, crop 3). Total yield of product 61.3 g, 90%. LRMS (EI) *m/e* 228 ($C_9H_{11}N_2$-81Br), 227 ($C_9H_{11}N_2$81Br − H^+), 226 ($C_9H_{11}N_2$79Br), 225 ($C_9H_{11}N_2$79Br − H^+); HRMS calcd for C_9H_{11}79BrN_2 + H^+ 227.0184 found 227.0193; ^{1}H NMR ($CDCl_3$) δ_H 8.53 (d, J = 2 Hz, 1 H), 8.49 (d, J = 2 Hz, 1 H), 7.91 (t, J = 2 Hz, 1 H), 4.17 (t, J = 7.5 Hz, 1 H), 3.18 (m, 1 H), 3.06 (m, 1 H), 2.30 (s, 1 H), 2.24 (m, 1 H), 1.80−2.00 (m, 2 H), 1.63 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ_C 149.0, 146.6, 142.6, 136.6, 120.7, 59.1, 46.9, 34.5, 25.4.

5-Bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (7). A three-necked 2L round-bottomed flask equipped for overhead stirring and fitted with an internal temperature probe and a reflux condenser was charged with 5-bromo-3-(1-*H*-2-pyrrolidinyl)pyridine (**6**) (50 g, 0.22 mol), 98% formic acid (400 mL), and 37% aqueous formaldehyde solution (200 mL). The mixture was heated for 18 h at 80 °C. After cooling to 25 °C, the mixture was concentrated in vacuo to a volume of approximately 200 mL and water (200 mL), and concentrated HCl (10 mL) were added giving a solution of pH 3. CH_2Cl_2 (100 mL) was added and the mixture filtered through a pad of Celite to destroy the emulsion. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The aqueous phase was basified with solid NaOH to pH 12, and the mixture was again filtered through Celite. The basic aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL), and the combined basic organic extracts were stirred with $MgSO_4$ and charcoal for 1 h. The mixture was filtered through Celite and concentrated in vacuo to afford **7** as an oil (44 g, crop 1). The basic aqueous fractions were combined and concentrated in vacuo (2-propanol azeotrope) giving a reduced volume which was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were stirred with $MgSO_4$ and charcoal for 18 h. Filtration through Celite and concentration in vacuo gave **7** as an oil (4.7 g, crop 2). Total yield 48.7 g, 92%. LRMS (EI) *m/e* 242 ($C_{10}H_{13}N_2$81Br), 241 ($C_{10}H_{13}N_2$81Br − H^+), 240 ($C_{10}H_{13}N_2$79Br), 239 ($C_{10}H_{13}N_2$79Br − H^+); ^{1}H NMR ($CDCl_3$) δ_H 8.56 (d, J = 2.5 Hz, 1 H), 8.47 (d, J = 2.5 Hz, 1 H), 7.90 (t, J = 2.5 Hz, 1 H), 3.22 (bt, J = 8.5 Hz, 1 H), 3.10 (t, J = 8.0 Hz, 1 H), 2.30 (app dd, J = 8.5, 8.5 Hz, 1 H), 2.20 (m, 1 H), 2.17 (s, 3 H), 1.93 (m, 1 H), 1.80 (m, 1 H), 1.68 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ_C 149.0, 146.9, 140.6, 136.7, 120.4, 67.4, 56.2, 39.8, 34.8, 22.1.

A portion of this material was converted to the dihydrobromide salt and characterized as follows. Mp 225−226 °C (EtOH−Et_2O); IR (KBr) 3429, 2934, 2635, 2559, 2499, 1537, 1439, 1319, 1254, 851, 672 cm^{-1}; ^1H NMR (CD_3OD): δ_H 9.23 (d, J = 2 Hz, 1 H), 9.21 (d, J = 2 Hz, 1 H), 9.11 (app t, J = 2 Hz, 1 H), 4.85 (app dd, J = 10, 8 Hz, 1 H), 3.97 (m, 1 H), 3.43 (m, 1 H), 2.92 (s, 3 H), 2.65−2.77 (m, 1 H), 2.31−2.53 (m, 3 H); ^{13}C NMR (CD_3OD) δ_C 148.8, 148.0, 144.8, 134.8, 123.9, 69.8, 57.6, 39.5, 32.5, 22.9. Anal. Calcd for $C_{10}H_{15}Br_3N_2$: C, 29.78; H, 3.72; N, 6.95%. Found: C, 30.03; H, 3.70; N, 6.82%.

5-(2-Hydroxy-2-methylbut-3-ynyl)-3-(1-methyl-2-pyrrolidinyl)pyridine (8b). A 1 L three-necked flask fitted with an overhead stirrer and reflux condenser was charged with 5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (**7**) (44.0 g, 182 mmol), K_2CO_3 (52.4 g, 455 mmol), copper(I) iodide (3.47 g, 18.2 mmol), 10% palladium on carbon (4.86 g, 4.56 mmol Pd), and triphenylphosphine (4.78 g, 18.2 mmol) in DME (220 mL) and water (220 mL). This mixture was stirred at 25 °C for 0.5 h before 2-methyl-3-butyn-2-ol (37.8 g, 450 mmol) was added. The mixture was heated under reflux for 16 h, allowed to cool to 25 °C, filtered through a pad of Celite, and concentrated *in vacuo*. The aqueous residue (approximately 250 mL) was slowly added to 2 M HCl (400 mL) and extracted with toluene (600 mL). The aqueous layer was basified to pH 11 with solid K_2CO_3 and extracted with EtOAc (3 × 500 mL). The organic layers were washed with saturated Na_2CO_3 (300 mL) and brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford **8b** as a light brown oil. This material was crystallized from hot cyclohexane (400 mL). The colorless solid (**8b**) which precipitated was collected (32.4 g, 72%). The mother liquors were concentrated to approximately 200 mL, allowing the precipitation of a second crop of **8b** (4.2 g, 9%). The remaining mother liquors were concentrated in vacuo and purified by flash column chromatography on silica gel, eluting with hexane:EtOAc (1:1) followed by CH_2Cl_2:MeOH (95:5), to give a further 4.5 g of **8b** (10%). The total yield of **8b** was 41.0 g, 92%. Mp 79−81 °C (cyclohexane); IR (KBr) 3233, 2972, 2787, 1450, 1417, 1373, 1313, 1215, 1178, 1150, 900, 704 cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 8.65 (d, J = 2 Hz, 1 H), 8.41 (d, J = 2 Hz, 1 H), 7.80 (t, J = 2 Hz, 1 H), 4.71 (bs, 1 H), 3.24 (app dt, J = 7, 2 Hz, 1 H), 3.07 (app t, J = 8.5 Hz, 1 H), 2.31 (app dd, J = 8.5, 8.5 Hz, 1 H), 2.19 (m, 1 H), 2.16 (s, 3 H), 1.90−2.10 (m, 1 H), 1.77−1.90 (m, 1 H), 1.65−1.77 (m, 1 H), 1.62 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ_C 150.6, 147.8, 138.6, 137.8, 120.1, 98.2, 78.3, 68.3, 64.7, 56.9, 40.3, 35.1, 31.3, 31.0, 22.5. Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.77; H, 8.20; N, 11.48%. Found: C, 73.86; H, 8.21; N, 11.47%.

5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine (2). 5-(2-Hydroxy-2-methylbut-3-ynyl)-3-(1-methyl-2-pyrrolidinyl)pyridine (**8b**) (40.8 g, 0.167 mol) and NaH as a 60% dispersion in mineral oil (680 mg, 17.0 mmol) were dissolved in dry toluene (700 mL) in a 1 L round-bottom flask. The mixture was heated to an internal temperature of 111 °C, and a portion of the toluene/acetone mixture (approximately 250 mL) was removed by distillation. The mixture was allowed to cool to 25 °C and then washed with 1 M K_2CO_3 (100 mL), water (100 mL), and brine (100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford **2** (30.4 g, 97%) as a light brown oil. LRMS (EI) *m/e* 187 ($M^+ + H$), 186 (M^+), 185 ($M^+ - H$); ^1H NMR ($CDCl_3$): δ_H 8.58 (d, J = 2 Hz, 1 H), 8.48 (d, J = 2 Hz, 1 H), 7.80 (app t, J = 2 Hz, 1 H), 3.23 (bt, J = 8 Hz, 1 H), 3.18 (s, 1 H), 3.08 (app t, J = 8.5 Hz, 1 H), 2.32 (app dd, J = 9, 9 Hz, 1 H), 2.21 (m, 1 H), 2.16 (s, 3 H), 1.65−2.00 (m, 3 H).

5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine Fumarate. 5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine (**2**) (31.2 g, 0.167 mol) was dissolved in MeOH (150 mL), and solid fumaric acid (19.4 g, 0.167 mol) was added. After 0.5 h the solids had dissolved completely. Charcoal was added, and the mixture was stirred for 18 h at 25 °C, filtered through Celite, and concentrated in vacuo to afford a solid. Crystallization was accomplished using the minimum of hot absolute EtOH to dissolve the fumarate; the product crystallized at 25 °C to afford a first crop (17.3 g). The mother liquors were concentrated and recrystallized from EtOH as before to provide a second crop (14.2 g). The total yield of racemic **2** fumarate was 31.5 g, 62%. Mp 149−150 °C (EtOH); IR (KBr) 3438, 3194, 2939, 2658, 2510, 2103, 1680, 1614, 1454, 984, 643 cm^{-1}; ^1H NMR (DMSO-d_6): δ_H 8.57 (d, J = 2 Hz, 1 H), 8.54 (d, J = 2 Hz, 1 H), 7.83 (app t, J = 2 Hz, 1 H), 6.61 (s, 2 H), 4.44 (s, 1 H), 3.25 (app dd, J = 16, 8 Hz, 1 H), 3.19 (dd, J = 8, 3 Hz, 1 H), 2.33 (app dd, J = 16, 8 Hz, 1 H), 2.20 (m, 1 H), 2.12 (s, 3 H), 1.6−1.9 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ_C 166.4, 151.1, 148.9, 137.8, 137.0, 134.2, 118.6, 84.1, 80.3, 67.4, 56.0, 39.5, 34.0, 22.1. Anal. Calcd for $C_{12}H_{14}N_2 \cdot C_4H_4O_4$: C, 63.58; H, 5.96; N, 9.27%. Found: C, 63.47; H, 6.03; N, 9.17%.

Enantiomerically Enriched 5-Bromo-3-(1*H*-2-pyrrolidinyl)pyridine (6). A single neck 500 mL round-bottomed flask was charged with CBZ-D-proline (42.9 g, 172 mmol) and DME (120 mL). The stirred solution was cooled to −10 °C and sodium borohydride (2.08 g, 55 mmol) was added in portions as a solid. After the addition, the cooling bath was removed and the stirring continued at 25 °C for 2 h. The colorless solution was concentrated *in vacuo* to afford a syrup which was dissolved in CH_2Cl_2 (50 mL). 5-Bromo-3-(2-pyrrolin-1-yl)pyridine (**5**) (8.00 g, 35.6 mmol) in CH_2Cl_2 (50 mL) was added to the solution of CBZ-D-Pro/$NaBH_4$ and the mixture stirred at 25 °C for 48 h. The solvents were removed in vacuo, and 6 M HCl (240 mL) and *i*-PrOAc (240 mL) were added. The aqueous phase was extracted with *i*-PrOAc (2 × 240 mL), and the combined *i*-PrOAc extracts were concentrated in vacuo to afford CBZ-D-proline (essentially quantitative recovery). The aqueous phase was made basic (pH 13) with solid NaOH and extracted with CH_2Cl_2 (3 × 150 mL). The combined CH_2Cl_2 extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford enantiomerically enriched **6** as an oil (7.95 g, 98%). LRMS (EI) *m/e* 228 ($C_9H_{11}N_2{}^{81}Br$), 227 ($C_9H_{11}N_2{}^{81}Br - H^+$), 226 ($C_9H_{11}N_2{}^{79}Br$), 225 ($C_9H_{11}N_2{}^{79}Br - H^+$); ^1H NMR ($CDCl_3$) δ_H 8.53 (d, J = 2 Hz, 1 H), 8.49 (d, J = 2 Hz, 1 H), 7.91 (t, J = 2 Hz, 1 H), 4.17 (t, J = 7.5 Hz, 1 H), 3.18 (m, 1 H), 3.06 (m, 1 H), 2.30 (s, 1 H), 2.24 (m, 1 H), 1.80−2.00 (m, 2 H), 1.63 (m, 1 H). This product was carried on to the next step without further purification. The enantiomeric purity of this material was determined in the following manner. An NMR tube was charged with enantiomerically enriched **6** and the ^1H NMR was recorded in $CDCl_3$. Into the same NMR tube was added (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (*S*-Mosher's acid) (1.5−2 equiv). The ^1H NMR was again recorded and the integral ratio of the pair of ^1H resonances at δ_H 4.12 and 4.32 (app t or dd) corresponding to the C2′-H signal of each stereoisomer was measured. This analysis showed the ee of **6** produced in this manner to be 30%.

Enantiomerically Enriched 5-Bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (7). Enantiomerically enriched **6** (7.95 g, 35 mmol) was dissolved in a mixture of 98% formic acid (74 mL) and 37% aqueous formaldehyde (37 mL). The solution was heated with stirring for 3 h at 80 °C. After being cooled to 25 °C, the mixture was concentrated in vacuo and water (30 mL) added. The mixture was basified with solid NaOH to pH 12 and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was chromatographed on silica gel with EtOAc:hexane (1:3 to 1:1) as the eluant to afford enantiomerically enriched **7** as an oil (6.0 g, 71%). LRMS (EI) *m/e* 242 ($C_{10}H_{13}N_2{}^{81}Br$), 241 ($C_{10}H_{13}N_2{}^{81}Br - H^+$), 240 ($C_{10}H_{13}N_2{}^{79}Br$), 239 ($C_{10}H_{13}N_2{}^{79}Br - H^+$); ^1H NMR ($CDCl_3$) δ_H 8.56 (d, J = 2.5 Hz, 1 H), 8.47 (d, J = 2.5 Hz, 1 H), 7.90 (t, J = 2.5 Hz, 1 H), 3.22 (bt, J = 8.5 Hz, 1 H), 3.10 (t, J = 8.0 Hz, 1 H), 2.30 (app dd, J = 8.5, 8.5 Hz, 1 H), 2.20 (m, 1 H), 2.17 (s, 3 H), 1.93 (m, 1 H), 1.80 (m, 1 H), 1.68 (m, 1 H).

(*S*)-(−)-5-Bromo-3-(1-methyl-2-pyrrolidinyl)pyridine [(*S*)-7]. A flask was charged with enantiomerically enriched (30% ee) 5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (**7**) (6.0 g, 24.9 mmol) and dibenzoyl-L-tartaric acid (5.9 g, 16.4 mmol). Absolute EtOH (80 mL) and EtOAc (540 mL) were added, and the mixture was warmed to afford a solution. Heating was continued until the solvent distilled. After removal of part of the solvent the solution started to become cloudy, and the

heating was stopped. The mixture was allowed to stand at 25 °C and the product crystallized as a colorless solid. After 18 h the crystals were collected and dried in vacuo to give (*S*)-(−)-5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine, dibenzoyl-L-tartaric acid salt [(*S*)-**7**] (9.15 g, 93% based on dibenzoyl-L-tartaric acid used). The enantiomeric enrichment of this material was 87% as determined by chiral GC (oven temperature 120 °C, retention time 11.5 min major peak, 12.0 min minor peak). A second crystallization provided (*S*)-**7** with >99% ee as determined by chiral GC under the same conditions. Mp 160−161 °C (EtOH−EtOAc); IR (KBr) 3429, 2967, 2929, 1721, 1607, 1449, 1264, 1112, 715 cm^{-1}; ^1H NMR (DMSO-d_6): δ_H 8.68 (d, J = 2 Hz, 1 H), 8.59 (d, J = 2 Hz, 1 H), 8.14 (app t, J = 2 Hz, 1 H), 8.00 (d, J = 7 Hz, 4 H), 7.69 (app t, J = 7 Hz, 2 H), 7.56 (app t, J = 7 Hz, 4 H), 5.79 (s, 2 H), 3.75 (m, 1 H), 3.41 (m, 1 H), 2.65 (app t, J = 9 Hz, 1 H), 2.31 (s, 3 H), 2.23 (m, 1 H), 1.73−1.94 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ_C 167.8, 164.9, 150.2, 148.2, 138.1, 136.5, 133.9, 129.4, 129.0, 128.5, 120.5, 72.1, 67.3, 55.6, 38.8, 32.8, 21.7. Anal. Calcd for $C_{10}H_{13}BrN_2 \cdot C_{18}H_{14}O_8$: C, 56.09; H, 4.51; N, 4.67%. Found: C, 56.02; H, 4.55; N, 4.63%. A portion of this material was converted to the free amine by treatment with base, providing (***S***)-**7** with $[\alpha]_D$ −124° (c = 14.5, EtOH).

(*S*)-(−)- 5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine Maleate. Free base (***S***)-**2** (5.25 g, 28.2 mmol) was dissolved in MeOH (150 mL), and solid maleic acid (3.3 g, 28.2 mmol) was added. After 0.5 h the solids had dissolved completely. The mixture was stirred for 1 h at 25 °C and concentrated in vacuo to afford a light yellow powder. Crystallization was accomplished using the minimum of hot absolute EtOH to dissolve the (*S*)-**2** maleate; the product crystallized at 8 °C to afford (*S*)-**2** maleate, 7.95 g, 93% as an off-white solid. This product possessed a >99% ee as determined by chiral GC (oven temperature 125 °C, retention time 10.0 min major peak, peak due to other enantiomer not detected). Mp 152.5−153.5 °C (EtOH); IR (KBr) 3433, 3219, 2918, 2652, 2510, 2102, 1586, 1500, 1382, 1367, 1199, 1005, 877, 867, 709 cm^{-1}; ^1H NMR (DMSO-d_6): δ_H 8.74 (d, J = 2 Hz, 1 H), 8.70 (d, J = 2 Hz, 1 H), 8.11 (app t, J = 2 Hz, 1 H), 6.07 (s, 2 H), 4.56 (s, 1 H), 4.34 (bt, J = 8 Hz, 1 H), 3.68 (dd, J = 8, 3 Hz, 1 H), 3.14 (app dd, J = 16, 8 Hz, 1 H), 2.63 (s, 3 H), 2.45−2.35 (m, 1 H), 2.25−2.05 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ_C 167.2, 152.8, 149.8, 138.9, 135.4, 130.1, 118.9, 85.0, 79.9, 68.0, 55.6, 39.5, 30.8, 21.5. Anal. Calcd for $C_{12}H_{14}N_2 \cdot C_4H_4O_4$: C, 63.58; H, 5.96; N, 9.27%. Found: C, 63.61; H, 5.95; N, 9.17%. A portion of this material was converted to the free amine by treatment with base, providing [(***S***)-**2**] with $[\alpha]_D$ −164° (c = 5, EtOH).

Enantiomerically Enriched 5-Bromo-3-(1*H*-2-pyrrolidinyl)pyridine (6). (Carbobenzyloxy)-L-proline (37.4 g, 150 mmol) was dissolved in DME (100 mL) and cooled to 0 °C with stirring. Sodium borohydride (1.89 g, 50 mmol) was added in portions (gas evolution), and the resulting mixture was stirred for 2 h at 25 °C to afford a colorless solution. The solvents were removed in vacuo, and the resulting gum was dissolved in CH_2Cl_2 (50 mL). To this solution was added a mixture of 5-bromo-3-(2-pyrrolin-1-yl)pyridine (5.63 g, 25 mmol) and (carbobenzyloxy)-L-proline (6.23 g, 25 mmol) in CH_2Cl_2 (50 mL). The resulting solution was stirred at 25 °C for 36 h. The solvent was removed in vacuo, and 6 M HCl (200 mL) was added to the residue. The resulting solution was extracted with *i*-PrOAc (200 mL), and the phases were separated. The acidic aqueous phase was basified with solid NaOH to pH 14 and then extracted with CH_2Cl_2 (3 × 200 mL). The combined CH_2Cl_2 extracts were washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel with EtOAc and then MeOH:EtOAc (1:19 to 1:9) as eluants to afford 5-bromo-3-(1*H*-2-pyrrolidinyl)pyridine (**6**) (4.1 g, 72%) as a pale yellow oil. LRMS (EI) *m/e* 228 ($C_9H_{11}N_281Br$), 227 ($C_9H_{11}N_281Br - H^+$), 226 ($C_9H_{11}N_279Br$), 225 ($C_9H_{11}N_279Br - H^+$); ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.53 (d, J = 2 Hz, 1 H), 8.49 (d, J = 2 Hz, 1 H), 7.91 (t, J = 2 Hz, 1 H), 4.17 (t, J = 7.5 Hz, 1 H), 3.18 (m, 1 H), 3.06 (m, 1 H), 2.30 (s, 1 H), 2.24 (m, 1 H), 1.80−2.00 (m, 2 H), 1.63 (m, 1 H). The enantiomeric purity of this material was determined in the following manner. An NMR tube was charged with (5−10 mg) enantiomerically enriched 5-bromo-3-(1*H*-2-pyrrolidinyl)pyridine, and the ^1H NMR was recorded in $CDCl_3$. Into the same NMR tube was added (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (*R*-Mosher's acid), 1.5−2 times the molar quantity of the amine. The ^1H NMR was again recorded and the integral ratio of the pair of ^1H resonances at δ_H 4.04 and 4.23 (app t or dd) corresponding to the C2′-H signal of each stereoisomer was measured. This analysis showed the ee of **6** produced in this manner to be 30%.

Enantiomerically Enriched 5-Bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (7). Enantiomerically enriched 5-bromo-3-(1*H*-2-pyrrolidinyl)pyridine (**6**) (1.82 g, 8 mmol) was dissolved in a mixture of 98% formic acid (16 mL) and 37% aqueous formaldehyde (8 mL). The solution was heated with stirring for 3 h at 80 °C. After being cooled to 25 °C the mixture was concentrated in vacuo and water (30 mL) added. The mixture was basified with solid NaOH to pH 12 and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was chromatographed on silica gel with EtOAc:hexane (1:3) as eluant to afford enantiomerically enriched **7** as an oil (1.63 g, 84%). LRMS (EI) *m/e* 242 ($C_{10}H_{13}N_281Br$), 241 ($C_{10}H_{13}N_281Br - H^+$), 240 ($C_{10}H_{13}N_279Br$), 239 ($C_{10}H_{13}N_279Br - H^+$); ^1H NMR ($CDCl_3$) δ_H 8.56 (d, J = 2.5 Hz, 1 H), 8.47 (d, J = 2.5 Hz, 1 H), 7.90 (t, J = 2.5 Hz, 1 H), 3.22 (bt, J = 8.5 Hz, 1 H), 3.10 (t, J = 8.0 Hz, 1 H), 2.30 (app dd, J = 8.5, 8.5 Hz, 1 H), 2.20 (m, 1 H), 2.17 (s, 3 H), 1.93 (m, 1 H), 1.80 (m, 1 H), 1.68 (m, 1 H).

(*R*)-5-Bromo-3-(1-methyl-2-pyrrolidinyl)pyridine [(*R*)-7]. Enantiomerically enriched 5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (482 mg, 2.00 mmol) was treated with di-*p*-toluoyl-D-tartaric acid monohydrate (534 mg, 1.32 mmol) and recrystallized from EtOH−EtOAc (1:4) to afford (*R*)-5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine di-*p*-toluoyl-D-tartrate [(***R***)-**7**] (659 mg, 80%). This material had an 88% ee as determined by chiral GC (oven temperature 120 °C, retention time 11.9 min major peak, 11.4 min minor peak). A second crystallization provided material with 95% ee as determined by chiral GC under the same conditions. Mp 161−162 °C (EtOH−EtOAc); IR (KBr) 3429, 2956, 1721, 1612, 1270, 1178, 1112, 1025, 753 cm^{-1}; ^1H NMR (DMSO-d_6): δ_H 8.66 (d, J = 2 Hz, 1 H), 8.57 (d, J = 2 Hz, 1 H), 8.08 (bt, J = 2 Hz, 1 H), 7.88 (d, J = 8 Hz, 4 H), 7.38 (d, J = 8 Hz, 4 H), 5.76 (s, 2 H), 3.6 (bm, 1 H), 3.34 (bm, 1 H), 2.58 (dd, J = 9, 9 Hz, 1 H), 2.39 (s, 6 H), 2.27 (s, 3 H), 2.24 (m, 1 H), 1.70−1.95 (m, 3 H). Anal. Calcd for $C_{10}H_{13}BrN_2 \cdot C_{20}H_{18}O_8$: C, 57.42; H, 4.94; N, 4.47%. Found: C, 57.46; H, 5.01; N, 4.39%.

(*R*)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine Di-*p*-toluoyl-D-tartrate. Enantiomerically enriched 5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine [(***R***)-**2**] (248 mg, 1.3 mmol) was treated with di-*p*-toluoyl-D-tartaric acid monohydrate (485 mg, 1.2 mmol) and recrystallized from EtOH to afford (*R*)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine di-*p*-toluoyl-D-tartrate [(***R***)-**2**] (452 mg, 66%). This product possessed a 97% ee as determined by chiral GC (oven temperature 130 °C, retention time 8.07 min major peak, 7.8 min minor peak). Mp 163−164 °C (EtOH); IR (KBr) 3434, 2929, 2363, 2341, 1727, 1618, 1270, 1180, 1106, 758 cm^{-1}; ^1H NMR (DMSO-d_6): δ_H 8.64 (d, J = 2 Hz, 1 H), 8.61 (d, J = 2 Hz, 1 H), 7.95 (t, J = 2 Hz, 1 H), 7.88 (d, J = 8 Hz, 4 H), 7.37 (d, J = 8 Hz, 4 H), 5.75 (s, 2 H), 4.49 (s, 1 H), 3.6 (bm, 1 H), 3.37 (bm, 1 H), 2.62 (app t, J = 9 Hz, 1 H), 2.39 (s, 6 H), 2.29 (s, 3 H), 2.24 (m, 1 H), 1.75−1.95 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ_C 168.2, 165.1, 152.3, 149.6, 144.3, 138.8, 132.7, 129.6, 126.6, 119.0, 84.7, 80.2, 72.4, 67.7, 55.5, 38.4, 32.1, 21.5, 21.4. Anal. Calcd for $C_{12}H_{14}N_2 \cdot C_{20}H_{18}O_8$: C, 67.13; H, 5.59; N, 4.90%. Found: C, 67.22; H, 5.64; N, 4.86%.

Establishment of Absolute Stereochemistry. (−)-5-Bromo-3-(1-methyl-2-pyrrolidinyl)pyridine [(*S*)-**7**] (2.0 g, 8.3 mmol) as the free amine was dissolved in absolute EtOH (20 mL), and 10% palladium on carbon (107 mg, 0.1 mmol Pd) was added. This was hydrogenated at 40 psi in a Parr hydrogenation apparatus for 3 h. The slurry was then filtered through Celite and concentrated *in vacuo*. This material was chro-

matographed on silica gel with CH_2Cl_2:MeOH (95:5) as eluant to afford a light yellow oil. Spectral data indicated that the isolated material was nicotine hydrobromide. This was taken up in CH_2Cl_2 and washed with aqueous K_2CO_3. The organic phase was dried over Na_2SO_4 and concentrated to afford (*S*)-(−)-nicotine (850 mg, 63%) as an oil. $[\alpha]_D$ −154° (*c* = 4, EtOH); lit.[3] −169° (neat); LRMS (EI) *m/e* 163 ($M^+ + H$), 162 (M^+), 161 ($M^+ - H$); ^1H NMR ($CDCl_3$): δ_H 8.56 (app t, *J* = 2 Hz, 1 H), 8.53 (d, *J* = 2 Hz, 1 H), 7.88 (dt, *J* = 8, 2 Hz, 1 H), 7.31 (dd, *J* = 8, 5 Hz, 1 H), 3.41 (bt, *J* = 8 Hz, 1 H), 3.29 (app t, *J* = 8 Hz, 1 H), 2.46 (app t, *J* = 8 Hz, 1 H), 2.28 (m, 1 H), 2.26 (s, 3 H), 2.07 (m, 1 H), 1.80−2.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ_C 149.5, 149.1, 136.7, 135.3, 123.9, 69.1, 56.8, 39.9, 34.5, 22.3.

3-(2-Hydroxy-2-methylbut-3-ynyl)benzaldehyde (10). 3-Bromobenzaldehyde (0.35 mL, 3.0 mmol), K_2CO_3 (1.03 g, 7.5 mmol), CuI (23 mg, 0.12 mmol), PPh_3 (64 mg, 0.24 mmol), and 10% Pd/C (63 mg, 0.06 mmol Pd) were mixed in DME (5 mL) and H_2O (5 mL) at 20 °C. This was stirred for 30 min, and 2-methyl-3-butyn-2-ol (0.73 mL, 7.5 mmol) was added. The mixture was heated at 80 °C for 16 h, cooled to room temperature, and filtered through Celite, and the filtrate was extracted with EtOAc (35 mL). The organic layer was washed with H_2O (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. This material was purified by flash column chromatography eluting with 3:2 hexane:EtOAc to yield 550 mg of **10** as a colorless oil 97%. ^1H NMR ($CDCl_3$) δ_H 9.98 (s, 1 H), 7.91 (m, 1 H), 7.82 (d, *J* = 8 Hz, 1 H), 7.65 (d, *J* = 8 Hz, 1 H), 7.47 (t, *J* = 8 Hz, 1 H), 2.52 (br s exch, 1 H); 1.64 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ_C 191.7, 137.2, 136.3, 133.0, 129.0, 124.0, 95.4, 80.6, 65.5, 31.3. Anal. Calcd for $C_{12}H_{12}O$: C, 76.57; H, 6.43%. Found: C, 76.34; H, 6.48%.

4-(2-Hydroxy-2-methylbut-3-ynyl)nitrobenzene (11). The procedure described for **10** was employed using 4-bromonitrobenzene (606 mg, 3.0 mmol), K_2CO_3 (1.03 g, 7.5 mmol), CuI (23 mg, 0.12 mmol), PPh_3 (62 mg, 0.24 mmol), 10% Pd/C (63 mg, 0.06 mmol Pd), and 2-methyl-3-butyn-2-ol (0.73 mL, 7.5 mmol). Yield 92% (570 mg) as a colorless oil; ^1H NMR ($CDCl_3$) δ_H 8.18 (d, *J* = 9 Hz, 2 H), 7.56 (d, *J* = 9 Hz, 1 H), 2.28 (s exch, 1 H), 1.64 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ_C 147.0, 132.4, 129.7, 123.5, 99.0, 80.4, 65.6, 60.5, 31.2. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83%. Found: C, 64.45; H, 5.42; N, 6.82%.

3-(2-Hydroxy-2-methylbut-3-ynyl)aniline (12). The procedure described for **18** was employed using 3-bromoaniline (657 mg, 3.0 mmol), K_2CO_3 (1.03 g, 7.5 mmol), CuI (23 mg, 0.12 mmol), PPh_3 (62 mg, 0.24 mmol), 10% Pd/C (63 mg, 0.06 mmol Pd), and 2-methyl-3-butyn-2-ol (0.73 mL, 7.5 mmol). Yield 78% as a off white solid. Mp 119−20 °C; ^1H NMR (DMSO-d_6) δ_H 6.97 (t, *J* = 8 Hz, 1 H), 6.57 (m, 1 H), 6.50 (m, 2 H), 5.42 (s, 1 H), 5.17 (s, 2 H), 1.43 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ_C 148.7, 129.0, 122.8, 118.5, 116.2, 114.0, 94.5, 81.1, 63.5, 31.6. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.47; N, 8.00%. Found: C, 75.50; H, 7.61; N, 7.78%.

2-(2-Hydroxy-2-methylbut-3-ynyl)benzonitrile (13). The procedure described for **10** was employed using 2-bromobenzonitrile (5.0 g, 27.5 mmol), K_2CO_3 (9.5 g, 68.7 mmol), CuI (209 mg, 1.1 mmol), PPh_3 (576 mg, 2.2 mmol), 10% Pd/C (587 mg, 0.55 mmol Pd), and 2-methyl-3-butyn-2-ol (6.7 mL, 68.7 mmol). Yield 89% as a clear oil; ^1H NMR ($CDCl_3$) δ_H 7.62 (d, *J* = 8 Hz, 1 H), 7.51 (m, 2 H), 3.48 (s, 1 H), 1.67 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ_C 132.4, 132.1, 128.3, 127.8, 117.6, 115.2, 100.8, 78.3, 65.4, 31.1. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.98; N, 7.56%. Found: C, 77.57; H, 6.00; N, 7.52%.

2-[1-(*N*,*N*-Dimethylamino)prop-2-ynyl]benzonitrile Fumarate (14). The procedure described for **18** was employed using 2-bromobenzonitrile (910 mg, 5.0 mmol), K_2CO_3 (1.725 g, 12.5 mmol), CuI (48 mg, 0.25 mmol), PPh_3 (126 mg, 0.48 mmol), 10% Pd/C (134 mg, 0.12 mmol Pd), and *N*,*N*-dimethylpropargylamine (1.35 mL, 12.5 mmol). Yield 850 mg, 92%. ^1H NMR ($CDCl_3$) δ_H 7.65 (d, *J* = 8 Hz, 1 H), 7.54 (m, 2 H), 7.40 (m, 1 H), 3.58 (s, 2 H), 2.42 (s, 6 H). 2-[1-(*N*,*N*-Dimethylamino)prop-2-ynyl]benzonitrile (250 mg, 1.35 mmol) was dissolved in MeOH (100 mL), and fumaric acid (160 mg, 1.35 mmol) was added. This mixture was concentrated in vacuo, triturated with Et_2O, and recrystallized from EtOAc to yield 330 mg of a white powder 81%. Mp 117−118 °C; ^1H NMR ($CDCl_3$) δ_H 7.31 (d, *J* = 9 Hz, 2 H), 6.76 (d, *J* = 9 Hz, 2 H), 6.17 (m, 1 H), 5.22 (br s exch, 1 H), 2.19 (m, 2 H), 2.12 (m, 2 H), 1.64 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ_C 155.2, 134.6, 133.0, 120.7, 116.0, 115.4, 89.8, 86.5, 29.3, 25.7, 22.3, 21.5. Anal. Calcd for $C_{14}H_{14}N_2 \cdot C_4H_4O_4$: C, 63.99; H, 5.37; N, 9.33%. Found: C, 63.89; H, 5.38; N, 9.33%.

4-[2-(Cyclohex-1-enyl)ethynyl]phenol (15). The procedure described for **10** was employed using 4-iodophenol (660 mg, 3.0 mmol), K_2CO_3 (1.03 g, 7.5 mmol), CuI (38 mg, 0.20 mmol), PPh_3 (106 mg, 0.40 mmol), 10% Pd/C (107 mg, 0.10 mmol Pd), and cyclohex-1-enylacetylene (0.88 mL, 7.5 mmol). Yield 290 mg, 49%, as an off-white solid. Mp 95−97 °C; ^1H NMR ($CDCl_3$) δ_H 7.31 (d, *J* = 9 Hz, 2 H), 6.76 (d, *J* = 9 Hz, 2 H), 6.17 (m, 1 H), 5.22 (br exch, 1 H), 2.19 (m, 2 H), 2.12 (m, 2 H), 1.64 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ_C 155.2, 134.6, 133.0, 120.7, 116.0, 115.4, 89.8, 86.5, 29.27, 25.7, 22.3, 21.5. Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12%. Found: C, 84.56; H, 7.11%.

4-[2-(Cyclohex-1-enyl)ethynyl]benzoic Acid (16). The procedure described for **10** was employed using 4-iodobenzoic acid (744 mg, 3.0 mmol), K_2CO_3 (1.03 g, 7.5 mmol), CuI (38 mg, 0.20 mmol), PPh_3 (106 mg, 0.40 mmol), 10% Pd/C (107 mg, 0.10 mmol Pd), and cyclohex-1-enylacetylene (0.88 mL, 7.5 mmol) in 10 mL of DME and 0.5 mL of H_2O. Purification was accomplished by trituration with a mixture of toluene:EtOAc:acetic acid (1:1:0.06), and recrystallization from EtOAc:MeOH 97:3. Yield 81% as translucent yellow flakes. Mp 228−230 °C; ^1H NMR ($CDCl_3$) δ_H 7.90 (d, *J* = 8 Hz, 2 H), 7.51 (d, *J* = 8 Hz, 2 H), 6.24 (m, 1 H), 2.13 (m, 4 H), 1.58 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ_C 136.9, 131.5, 129.8, 127.5, 120.0, 94.4, 86.5, 28.9, 25.5, 22.0, 21.2. Anal. Calcd for $C_{15}H_{14}O_2 \cdot 0.5\ H_2O$: C, 76.58; H, 6.43%. Found: C, 76.57; H, 6.13%.

3-(1-Hydroxy-prop-2-ynyl)pyridine (17). The procedure described for **18** was employed using 3-bromopyridine (1.91 mL, 20.0 mmol), K_2CO_3 (6.90 g, 50.0 mmol), CuI (342 mg, 1.8 mmol), PPh_3 (628 mg, 2.4 mmol), 10% Pd/C (640 mg, 0.60 mmol Pd), and propargyl alcohol (2.92 mL, 50.0 mmol). Purification was effected by flash column chromatography on silica eluting with CH_2Cl_2:MeOH 95:5. Yield 2.40 g 90% as a white solid. Mp 99−100 °C. ^1H NMR ($CDCl_3$) δ_H 8.80 (d, *J* = 2 Hz, 1 H), 8.51 (dd, *J* = 2, 5, 1 H), 7.74 (dt, *J* = 8, 2 Hz, 1 H), 7.28 (m, 1 H), 4.72 (m, 1 H), 4.52 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ_C 151.9, 148.1, 139.1, 123.4, 120.3, 92.4, 81.3, 50.8. Anal. Calcd for C_8H_7NO: C, 72.21; H, 5.29; N, 10.41%. Found: C, 72.22; H, 5.29; N, 10.41%.

2-(2-Hydroxy-2-methylbut-3-ynyl)pyridine (18). 2-Pyridyl trifluoromethanesulfonate (0.46 mL, 3.0 mmol), K_2CO_3 (1.03 g, 7.5 mmol), CuI (23 mg, 0.12 mmol), PPh_3 (64 mg, 0.24 mmol), and 10% Pd/C (64 mg, 0.06 mmol Pd) were mixed in DME (5 mL) and H_2O (5 mL) at 20 °C. This solution was stirred for 30 min and 2-methyl-3-butyn-2-ol (0.73 mL, 7.5 mmol) was added. The mixture was heated at 80 °C for 16 h, cooled to room temperature, filtered through Celite, and acidified with 1 M HCl. The organic solvents were removed in vacuo, and the solution was extracted with toluene, and the aqueous phase basified with K_2CO_3. The aqueous layer was then extracted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel eluting with 1:1 hexane:EtOAc. Yield 95% (458 mg) as an off white solid. Mp 82−84 °C; ^1H NMR ($CDCl_3$) δ_H 8.57 (d, *J* = 4 Hz, 2 H), 7.67 (t, *J* = 8 Hz, 1 H), 7.40 (d, *J* = 8 Hz, 1 H), 7.22 (m, 1 H), 1.65 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ_C 149.7, 142.9, 136.3, 132.0, 127.1, 122.9, 94.4, 81.2, 65.1, 60.4. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.88; N 8.69%. Found: C, 74.45; H, 6.92; N, 8.61%.

5-[1-(*N*,*N*-Dimethylamino)prop-2-ynyl]pyrimidine Fumarate (19). The procedure described for **18** was employed using 5-bromopyrimidine (477 mg, 3.0 mmol), K_2CO_3 (1.03 g, 7.5 mmol), CuI (48 mg, 0.25 mmol), PPh_3 (105 mg, 0.40 mmol), 10% Pd/C (107 mg, 0.10 mmol Pd), and *N*,*N*-dimethylpropargylamine (0.81 mL, 7.5 mmol). The crude material was purified by flash column chromatography on silica eluting with 95:5 EtOAc:MeOH. Yield 50% as a pale yellow oil. ^1H NMR

($CDCl_3$) δ_H 9.13 (s, 1 H), 8.78 (s, 2 H), 3.52 (s, 2 H), 2.38 (s, 6 H). 5-[1-(*N*,*N*-Dimethylamino)prop-2-ynyl]pyrimidine (141 mg, 0.9 mmol) was mixed with fumaric acid (101 mg, 0.9 mmol) and dissolved in 30 mL of MeOH. This mixture was concentrated to give a light yellow solid which was triturated with Et_2O and recrystallized from hot EtOAc to give, **19** 158 mg, 42%, as a hemifumarate, white needles. Mp 155−156 °C (dec); ^{1}H NMR (DMSO-d_6) δ_H 9.17 (s, 1 H), 8.92 (s, 2 H), 6.61 (s, 4 H), 3.61 (s, 1 H), 2.31 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ_C 166.2, 158.9, 156.8, 134.1, 118.7, 91.4, 79.2, 47.3, 43.3. Anal. Calcd for $C_9H_{11}N_3 \cdot C_8H_8O_8$: C, 51.90; H, 4.87; N 10.68%. Found: C, 52.00; H, 4.89; N, 10.74%.

2-(1-Hydroxy-1-phenylprop-2-ynyl)thiophene (20). The procedure described for **10** was employed using 2-iodothiophene (0.38 mL, 3.0 mmol), K_2CO_3 (1.03 g, 7.5 mmol), CuI (38 mg, 0.2 mmol), PPh_3 (106 mg, 0.4 mmol), 10% Pd/C (107 mg, 0.10 mmol Pd), and 1-phenyl-2-propyn-1-ol (990 mg, 7.5 mmol). Purification was effected by flash column chromatography on silica eluting with 9:1 CH_2Cl_2:MeOH. Yield 95% as a dark brown oil. ^{1}H NMR ($CDCl_3$) δ_H 7.59 (d, J = 7 Hz, 2 H), 7.38 (m, 3 H), 7.25 (m, 2 H), 6.98 (m, 1 H), 5.69 (d, J = 6 Hz, 1 H), 2.39 (d, J = 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ_C 140.2, 132.5, 128.7, 128.5, 127.6, 127.0, 126.7, 122.2, 92.4, 80.0, 65.2. Anal. Calcd for C_8H_7NO: C, 72.87; H, 4.70; S, 14.96%. Found: C, 72.98; H, 4.68; S, 14.84%.

4-(1-Hydroxy-but-3-ynyl)pyrazole (21). The procedure described for **18** was employed using 4-iodopyrazole (582 mg, 3.0 mmol), K_2CO_3 (1.03 g, 7.5 mmol), CuI (38 mg, 0.20 mmol), PPh_3 (105 mg, 0.40 mmol), 10% Pd/C (107 mg, 0.10 mmol Pd), and 3-butynol (0.57 mL, 7.5 mmol). Purification was effected by flash column chromatography on silica eluting with EtOAc. Yield 85% (348 mg) as an off white solid. Mp 102−104 °C; ^{1}H NMR (DMSO-d_6) δ_H 12.99 (br s, 1H), 7.89 (br s, 1 H), 7.58 (br s, 1 H), 4.89 (t, J = 5 Hz, 1 H), 3.54 (m, 2 H), 2.50 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ_C 143.5, 133.6, 104.3, 90.3, 78.7, 75.6, 62.4, 25.9. Anal. Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N 20.58%. Found: C, 61.86; H, 5.98; N, 20.37%.

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