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Methods for the Synthesis of 5,6,7,8-Tetrahydro-1,8-naphthyridine Fragments for $\alpha_V\beta_3$ Integrin Antagonists

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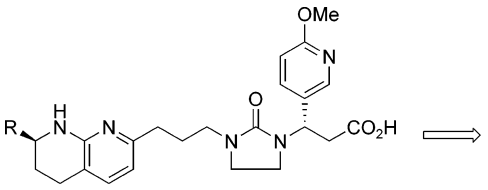
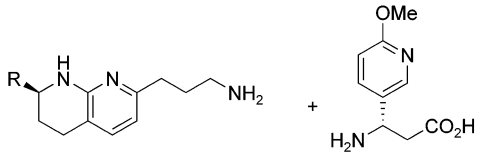
The preparation of 3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propan-1-amine **2a** and 3-[(7*R*)-7-methyl-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl]propan-1-amine **2b**, key intermediates in the synthesis of $\alpha_V\beta_3$ antagonists, is described. The syntheses rely on the efficient double Sonogashira reactions of 2,5-dibromopyridine **3** with acetylenic alcohols **4a/4b** and protected propargylamines **10a**−**e** followed by Chichibabin cyclizations of 3,3′-pyridine-2,5-diyldipropan-1-amines **9a/9b**.

The development of efficacious therapies for the treatment of osteoporosis remains an active field of research. In the US alone, 10 million individuals have already been diagnosed with the disease, and the estimated direct cost for hospital and nursing home care in 2001 was $17 billion. Osteoporosis results from an imbalance between the natural processes of bone resorption and bone formation. An initial step in bone resorption is the binding of osteoclast cells to bone surfaces, which is thought to be mediated by the cell surface glycoprotein, $\alpha_V\beta_3$ integrin. A novel approach to interrupting this mechanism is minimizing osteoclast activity by introducing $\alpha_v\beta_3$ integrin antagonists.[1] The binding of $\alpha_v\beta_3$ to the receptor occurs through recognition of the Arg-Gly-Asp ("RGD") peptide sequence. Accordingly, recent efforts to develop drug therapies have centered on small molecule (nonpeptide) mimetics of RGD.[2] Reports from these laboratories[3] and others[4] have described a series of novel compounds designed to bind to $\alpha_v\beta_3$ and thus act as antagonists. A common structural component of these compounds is the 5,6,7,8-tetrahydro-1,8-naphthyridine skeleton that functions as a guanidine mimic. Herein, we describe two synthetic methods for 3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propan-1-amine (**2a**) and 3-[(7*R*)-7-methyl-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl]propan-1-amine (**2b**), structural components of drug candidates in this class.



1a, R = H
1b, R = Me



2a, R = H
2b, R = Me

A practical synthesis of **1a**, in which tetrahydronaphthyridine **2a** serves as a key intermediate, was recently described.[5] Two methods for the preparation of **2a** via the Friedländer reaction were discussed. Although a scalable synthesis was developed, it required cryogenic conditions and an expensive Rh catalyst. A synthesis of **2a** via a double Suzuki−Miyaura reaction of 2,5-dibromopyridine **3** with the borane derived from 9-BBN addition to phthalimide-protected allylamine was previously reported by some of us in a communication.[6] The phthaloyl groups were subsequently removed by treat-

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(3) (a) Askew, B. C.; Coleman, P. J.; Duggan, M. E.; Halczenko, W.; Hutchinson, J. H.; Meissner, R. S.; Patane, M. A.; Wang, J. U.S. Patent 6017926, 2000. (b) Hutchinson, J. H.; Halczenko, W.; Brashear, K. M.; Breslin, M. J.; Coleman, P. J.; Duong, L. T.; Fernandez-Metzler, C.; Gentile, M. A.; Fisher, J. E.; Hartman, G. D.; Huff, J. R.; Kimmel, D. B.; Leu, C.-T.; Meissner, R. S.; Merkle, K.; Nagy, R.; Pennypacker, B.; Perkins, J. J.; Prueksaritanont, T.; Rodan, G. A.; Varga, S. L.; Wesolowski, G. A.; Zartman, A. E.; Rodan, S. B.; Duggan, M. E. *J. Med. Chem.* **2003**, *46*, 4790. (c) Breslin, M. J.; Duggan, M. E.; Halczenko, W.; Hartman, G. D.; Duong, L. T.; Fernandez-Metzler, C.; Gentile, M. A.; Kimmel, D. B.; Leu, C.-T.; Merkle, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4515.

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ment with hydrazine, and the resultant diamine was converted to **2a** with a Chichibabin cyclization. Though this synthesis of **2a** was shorter than those employing the Friedländer reaction, it still suffered from high catalyst loading for the double Suzuki−Miyaura reaction (10 mol %), the use of expensive (9-BBN) or hazardous (hydrazine) reagents, and low productivity because of the poor solubility of 9-BBN and large protecting groups. A double Sonogashira[7] reaction of **3** with propynyl and chiral butynyl derivatives could provide a solution to these problems. Indeed, the ability of **3** to undergo double Sonogashira reactions is known.[8] Presented in this paper are efficient syntheses of **2a** and **2b** and results from a study of the double Sonogashira reaction of 2,5-dibromopyridine with acetylenic alcohols and protected acetylenic amines.

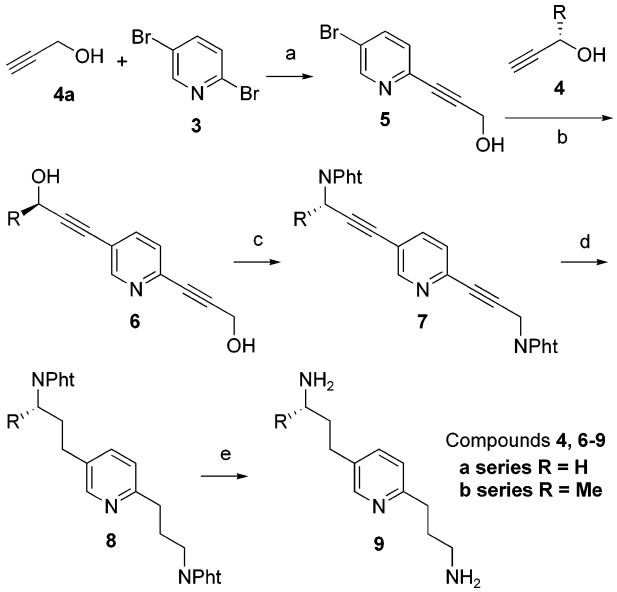
Results and Discussion

Sonogashira Coupling of 2,5-Dibromopyridine 3 with Acetylenic Alcohols. Initially, we investigated acetylenic alcohols as coupling partners in the Sonogashira reaction with **3**, as propargyl alcohol **4a** is commercially available and inexpensive, while (*S*)-3-butyn-2-ol (**4b**) is readily prepared by Noyori's Ru-catalyzed asymmetric transfer hydrogenation (ATH).[9] The reaction of 1.0 equiv of **4a** with **3** under standard Sonogashira conditions proceeded at room temperature in MeCN to give 3-(5-bromopyridin-2-yl)prop-2-yn-1-ol **5** in 75% yield with 98:2 mono/bis selectivity (Scheme 1). Under the same conditions, coupling at the 5-position with a second equivalent of **4a** proceeded slowly, but at 70 °C, conversion to disubstituted pyridine **6a** was rapid, and the product could be isolated in 80% yield. Coupling of monosubstituted pyridine **5** with (*S*)-3-butyn-2-ol at 65 °C for 20 h afforded mixed product **6b** in 89% assay yield.

Although a recent report indicated that the 2-(3-halopropyl) derivatives of both 1,8-naphthyridine and the 5,6,7,8-tetrahydro analogue are very prone to intramolecular cyclization to the cyclic ammonium derivatives,[5] under Mitsunobu conditions (PPh_3/DIAD) with phthalimide in THF the reactions of both bis-alkyndiols **6a** and **6b** gave bis-phthalimides **7a** and **7b** in 85% and 70% yield, respectively. The successful outcome of this reaction was likely due to the presence of the triple bonds, which structurally resisted intramolecular cyclization. Hydrogenation of **7a** and **7b** at 3 atm H_2 using 5% Pd/C in DMF at 45 °C gave the saturated derivatives **8a** and **8b** in 90% isolated yield. Interestingly, reversing the latter two steps whereby **6** was hydrogenated first followed by the Mitsunobu reaction gave **8** in poor yield. Finally, amine deprotection was achieved using hydrazine in EtOH at 60 °C for 2 h to provide **9b** in 85% yield.

Although the double Sonogashira approach with acetylenic alcohols was successful, it still suffered from some of the problems of the Suzuki−Miyaura route, as well as, poor atom economy associated with the Mitsunobu

SCHEME 1. Synthetic Route to 3,3′-Pyridine-2,5-diyldipropan-1-amines (9a/9b) Using Propargyl Alcohols[a]



[a] Reagents: (a) $PdCl_2(PPh_3)_2$, CuI, MeCN, rt, 75%; (b) $PdCl_2(PPh_3)_2$, CuI, MeCN, 70 °C, **6a** 80%, **6b** 89%; (c) phthalimide, DIAD, PPh_3, THF, **7a** 85%, **7b** 70%; (d) H_2, 5% Pd/C, DMF, 90%; (e) H_2NNH_2, EtOH, 85%.

reaction. To overcome these issues, we explored the Sonogashira coupling using acetylenic amine derivatives.

Selection of *N*-Protecting Group. Notwithstanding reports that 1,1-dimethyl-2-propynylamine[10] and propargylamine[11] are viable coupling partners in Sonogashira reactions, some difficulty was encountered during an initial investigation of this chemistry. Attempts to couple propargylamine with **3** afforded at best a 4:1 ratio of mono-Sonogashira product (substitution at the 2-position) to starting material.[6] However, communications of successful reactions with protected propargylamines, including *N*-tosylpropargylamine,[12] *N*-Boc-propargylamine **10d**,[13] *N*-methoxycarbonylpropargylamine,[14] and *N*-trifluoroacetylpropargylamine,[11] as well as a report on the Sonogashira reaction of **3**[8] suggested that this approach with the appropriate reagent should be achievable. Indeed, modification of propargylamine by protection of the amino functionality with acyl groups, including acetyl, Boc, and Cbz, afforded reagents that cross-coupled with **3** under Sonogashira conditions (vide infra) (Scheme 2).

Initially, the Cbz-protected propargylamine **10c** was selected for further study since the Cbz group could be removed from the product concurrently with the hydrogenation of the triple bonds. However, during the course of this work, we learned that propargylamine is unavailable in bulk quantities because of safety issues. It is also tedious to prepare.[15] Because the Cbz, acetyl, and Boc propargylamine derivatives are prepared from propar-

(6) Palucki, M.; Hughes, D. L.; Yasuda, N.; Yang, C.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6811.
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(9) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.
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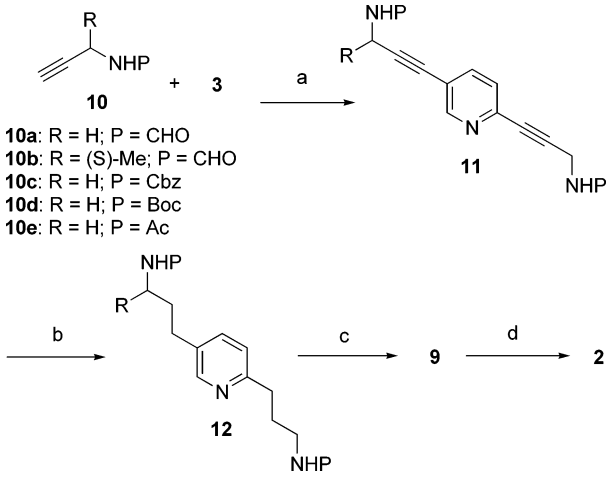
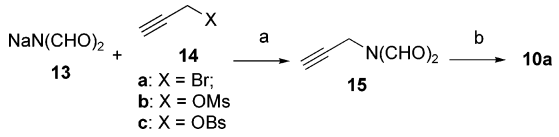
(14) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812.

SCHEME 2. Synthetic Route to 3,3′-Pyridine-2,5-diyldipropan-1-amines Using Protected Propargylamines[a]



[a] Reagents: (a) $PdCl_2(PPh_3)_2$, CuI, DIPA; (b) H_2, 5% Pd/Al_2O_3, MeOH; (c) 6 N HCl; (d) $NaNH_2$, toluene.

SCHEME 3. Synthesis of *N*-Formylpropargylamine[a]



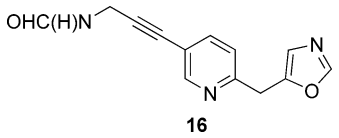
[a] Reagents: (a) reflux, CH_3CN; (b) K_2CO_3, MeOH (87%, two steps).

gylamine, the need arose for an alternative protecting group. The *N*-formyl protecting group could overcome this shortcoming. Although the literature preparation[16] of **10a** also begins with propargylamine, a more attractive route would involve amidation of activated propargyl derivatives with sodium diformylamide **13** (Scheme 3). Alkylations of **13** with a variety of electrophiles were reported, although propargyl derivatives were not studied.[17]

The literature procedure for preparing **13** was modified to include the use of a solvent, 1,2-dimethoxyethane, to facilitate mixing and isolation.[17] Propargylimide **15** was prepared by alkylation of **13** with propargyl mesylate **14b**[18] in refluxing MeCN. A Sonogashira reaction of **3** with **15** gave a complex mixture due to the instability of the imide toward loss of one formyl group. Alternatively, **15** was solvolyzed to **10a** using MeOH and K_2CO_3. The product **10a** could also be obtained by alkylation of **13** with propargyl bromide **14a** or propargyl benzenesulfonate **14c**, but high levels of bromoallene were observed when **14a** was used.[19]

Sonogashira Coupling of 2,5-Dibromopyridine 3 with *N*-Protected Propargylamines. The double Sonogashira reaction proceeded well when the standard Sonogashira catalysts, $PdCl_2(PPh_3)_2$ and CuI, were employed with amines containing α-protons as solvent. Several variables were explored with **10c** or **10e** using the relative amounts of bis- vs monosubstituted products as a guide for an optimized set of conditions (Table 1). The reaction proceeded in amine solvents such as diisopropylamine (DIPA), triethylamine (TEA), diisopropylethylamine (DIEA), and dibenzylamine, but no reaction was observed with collidine. DIPA was the solvent of choice as the product readily crystallized in high yield during the course of the reaction. The Sonogashira reaction proceeded stepwise. Substitution at the 2-position occurred at room temperature, while reaction at the 5-position required temperatures >50 °C.[20] At >50 °C the reaction was faster, but impurity levels also increased. The optimum balance between reaction rate and the generation of impurities was found between 65 and 70 °C. $PdCl_2(PPh_3)_2$, which is air stable and readily available, was employed in this reaction at an optimized level of 1 mol %. Coupling at the 2-position of **3** was independent of the CuI/Pd ratio and could be accomplished without CuI. The second coupling proceeded sluggishly at the usual ratio of >1 reported in the literature. Experiments revealed an optimum CuI/Pd ratio of 0.25. Several cocatalysts, including $Co(acac)_2$, $FeCl_3$, and $ZnCl_2$, were compared to the commonly employed CuI[21] in reactions with **10e**, and the latter produced the best results. Using these optimized conditions of 1 mol % $PdCl_2(PPh_3)_2$, 0.25 mol % CuI, at 65−70 °C in DIPA, a double Sonogashira reaction of **10c** was successfully demonstrated on a 1 kg scale.

The above conditions for the Sonogashira coupling were not further optimized for **10a**. The reaction proceeded to a 2-substituted intermediate in 1−2 h and to the product in 5−10 h. The disubstituted product **11a** was isolated in 79% yield. Several minor impurities were generated in the Sonogashira reaction, including oxazole **16** and the homocoupling product of **10a**. An independent experiment showed that **16** did not form from the product.



To further explore the reactivity of these protected propargylamine reagents with **3**, a series of cross-coupling reactions was performed using reported procedures that were successful with analogous substrates. For example, the reaction of 5-bromo-2-[2-(trimethylsilyl)-ethynyl]pyridine with 4-pentyn-2-ol with 1 mol % $PdCl_2(PPh_3)_2$ and CuI in a 3:1 mixture of triethylamine and dichloromethane at room temperature afforded the di-

(15) (a) Beil. *4*, **IV**, 1135. (b) Koziara, A.; Zwierzak, A. *Synthesis* **1992**, 1063.

(16) Dumont, J.-L.; Chodkiewicz, W.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1967**, 588.

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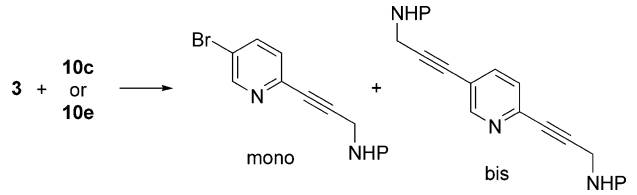
(18) Masuyama, Y.; Watabe, A.; Ito, A.; Kurusu, Y. *J. Chem. Soc., Chem. Commun.* **2000**, 2009.

(19) Neat *N*-formylpropargylamine (**10a**) is a crystalline solid. Although it was not stable when it was heated to >170 °C as neat, its solutions were safe. Thus, a nonisolation procedure was developed in which the reaction solvent, acetonitrile, was switched to DIPA, and the DIPA solution was used directly without further purification in the Sonogashira coupling. Thermal characterization of **10a** showed an exotherm of 5.3 cal/g that initiated at 170 °C followed immediately by a large decomposition exotherm of 311 cal/g that initiated at 215 °C. The heat release of the second exotherm was rapid and approached the shock sensitivity potential range.

(20) Chambers, R. D.; Hall, C. W.; Hutchinson, J.; Millar, R. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1705.

(21) Campbell, I. B. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; IRL Press: Oxford, 1994; pp 217−235.

TABLE 1. Effect of Conditions on Double Sonogashira Reaction of 3[a]



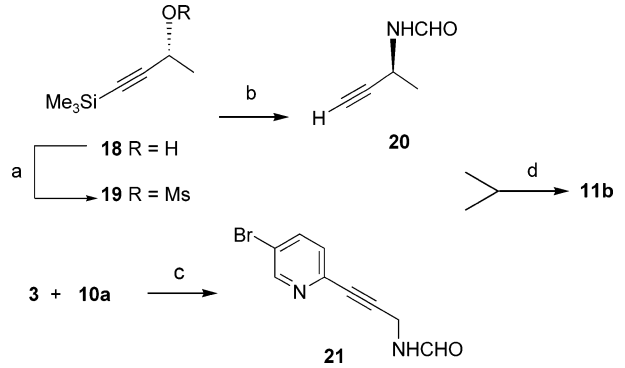
entry	substrate	solvent	cocatalyst	T (°C)	time, h	% mono	% bis
1	**10c**	collidine	CuI, 1 mol %	50	2.5	0	0
2	**10c**	dibenzylamine	CuI, 1 mol %	50	2.5	72	13
3	**10c**	DIEA	CuI, 1 mol %	50	2.5	63	31
4	**10c**	TEA	CuI, 1 mol %	50	2.5	63	29
5	**10c**	DIPA	CuI, 1 mol %	50	2.5	62	31
6	**10c**	DIPA	CuI, 1 mol %	21	2.5	58	2
7	**10c**	DIPA	CuI, 1 mol %	65	1.5	76	23
8	**10c**	DIPA	CuI, 1 mol %	85	2	4	85
9	**10c**	DIPA	none	65	1.5	35	1
10	**10c**	DIPA	CuI, 0.1%	65	1.5	66	34
12	**10c**	DIPA	CuI, 0.25%	65	1.5	61	39
13	**10c**	DIPA	CuI, 0.5%	65	1.5	58	38
16	**10e**	DIPA	CuI, 0.25%	85	3	4	96
17	**10e**	DIPA	$Co(acac)_2$, 2 mol %	85	3	22	63
18	**10e**	DIPA	$FeCl_3$, 1 mol %	85	3	56	15
19	**10e**	DIPA	$ZnCl_2$, 2 mol %	85	3	48	31
20	**10e**	DIPA	$Ni(acac)_2$, 1 mol %	85	3	18	66

[a] Percent mono and bis were determined by HPLC area percent.

substituted product.[8] However, under the same conditions, reaction of **3** with less reactive alkyne **10a** gave predominantly the 2-substituted product and only 5% of the desired disubstituted compound, even at 70 °C. The use of pyrrolidine and piperidine as solvents with $PdCl_2(PPh_3)_2$ or $PdCl_2(PhCN)_2$ as catalysts had been shown to greatly improve the reactivity of alkynes with iodobenzene and vinyl chloride substrates.[22] In contrast, reactions of **3** with **10a** in pyrrolidine using $PdCl_2(PPh_3)_2$ or in piperidine using $PdCl_2(PhCN)_2$ produced 2-pyrrolidinyl-5-bromopyridine and 2-piperidinyl-5-bromopyridine as the major products, respectively, and only traces of the desired 2-substituted acetylenic product.[23] Difficulty in coupling *N*-propargylalanine with 3-bromopyridine was overcome using Pd/C, PPh_3, CuI, and K_2CO_3 in DME/water.[24] A reaction of **10a** with **3** under the same conditions produced mainly the 2-substituted product, however. The same result was found using $PdCl_2(PhCN)_2$, P(*t*-Bu)$_3$, CuI, and DIPA in dioxane, although this procedure had been effective for the coupling of 4-bromoanisole with alkyl and aryl alkynes.[25] The results of these cross-coupling experiments suggested that the reactivity of these propargylamine reagents lay between the reactivity of most alkyl or aryl alkynes and the reactivity of alkynes that are conjugated to electron-withdrawing groups, which are poor coupling partners.[21]

Applying our methodology to the synthesis of **2b** began with the preparation of the alkyne piece. Thus, the product of the ATH reaction, (*S*)-4-trimethylsilyl-3-butyn-2-ol **18** (98% ee), was converted into the corresponding

SCHEME 4. Synthesis of Diyne 11b.



[a] Reagents/conditions: (a) MsCl/TEA/DCM/rt (94%); (b) (i) **13**/DMF, 65 °C; (ii) MeOH/cat K_2CO_3/rt (58%); (c) $PdCl_2(PPh_3)_2$/CuI/DIPA/MeCN 18h/rt (77%); (d) $PdCl_2(PPh_3)_2$/CuI/DIPA/DMF 60 °C/5 h (77%).

mesylate **19** under standard conditions (MsCl/TEA) in 94% yield. The crude product was reacted with **13** in DMF at 62 °C for 6 h, followed by MeOH/K_2CO_3, which solvolyzed one of the formyl groups to give **20** as a low melting solid in 58% overall yield. The requisite bromopyridine **21** was prepared by coupling **3** with **10a** in MeCN at room temperature (vida supra) to give **21** in 77% yield. The Sonogashira coupling of alkyne **20** with aryl bromide **21** proceeded under standard conditions to give diyne **11b** in 77% assay yield (Scheme 4). Chiral SFC assay indicated 98% ee.

Preparation of Diamines 9a/9b. Conversion of the Sonogashira product **11a** to diamine **9a** was accomplished by hydrogenation at 40 psi H_2 in MeOH using 5% Pd/Al_2O_3 to give **12a**, followed by hydrolysis of the formyl groups with 6 N HCl at 90 °C. Diamine **9a** was obtained as an oil in 88% yield over the two steps. Similarly, diyne

(22) (a) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403. (b) Alami, M.; Crousse, B.; Ferri, F. *J. Organomet. Chem.* **2001**, *624*, 114.
(23) DIPA did not react with **3** even in the absence of an alkyne.
(24) (a) Lopez-Deber, M. P.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 2823. (b) Bleicher, L.; Cosford, N. D. P. *Synlett* **1995**, 1115.
(25) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729.

11b was hydrogenated to **12b** in THF/MeOH (90% yield) and deprotected with $HONH_2$·HCl to give diamine **9b** in 94% yield.

Chichibabin Cyclization. The Chichibabin cyclization of diamines **9a/9b** to target compounds **2a/2b** was accomplished in 90%/69% assay yield, respectively, using 4−5 equiv of $NaNH_2$ in toluene at 90 °C, conditions that had been optimized for these substrates.[6] As published studies on the Chichibabin reaction in aprotic solvents were confined to intermolecular examples, we investigated whether the intramolecular cyclization could provide additional mechanistic details. There is extensive literature on the mechanism of the Chichibabin reaction, but only limited work has been done on heterogeneous systems because of the difficulty in studying the transformation.[26] The reaction is regarded to proceed by an addition−elimination pathway, but σ-adduct intermediates have not been observed.[27] We investigated the reaction using FT-IR and NMR, which revealed a clean transformation of **9a** to **2a** with no evidence for an intermediate. This observation suggested that oxidation (re-aromatization) occurred during the reaction, not after the quench, which corresponds to the intermolecular examples reported previously.

Summary. In summary, an efficient synthesis of 3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propan-1-amine **2a** and 3-[(7*R*)-7-methyl-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl]propan-1-amine **2b** was accomplished via a double Sonogashira coupling and a Chichibabin cyclization reaction. Conditions were discovered for the coupling of 2,5-dibromopyridine with *N*-protected propargylamines that provided the double-substituted product in significantly better yield compared to successful literature procedures for other reaction partners.[28]

Experimental Section

General Methods. All reactions were carried out under an atmosphere of N_2 (unless otherwise noted), and solvents and reagents were dried where appropriate over molecular sieves prior to use. Other solvents and reagents were used as received. ^{1}H and ^{13}C NMR spectra were collected at 400 and 101 MHz, respectively. Coupling constants (*J*) are reported in Hz. Melting points are uncorrected.

3-(5-Bromopyridin-2-yl)prop-2-yn-1-ol (5).[8] A mixture of **3** (94.8 g, 400 mmol), **4a** (22.4 g, 400 mmol), DIPA (115 mL), $PdCl_2(PPh_3)_2$ (2.8 g, 4.0 mmol), and CuI (0.8 g, 4.4 mmol) in CH_3CN (1 L) was prepared at 13−15 °C and allowed to warm slowly to rt and to stir overnight. Water (200 mL) was added, and the reaction mixture was concentrated at reduced pressure to ≤300 mL. The mixture was further diluted with water (300 mL) and aged for 1 h at rt. The crystallized solid was filtered, and the cake was washed with water. The solid was dried at reduced pressure at 40 °C. The brown solid was dissolved in THF (800 mL), and the solution was passed through a pad of silica gel (130 g). The silica pad was further washed with THF (800 mL). The solution was concentrated at reduced pressure to 300 mL, and toluene (300 mL) was slowly added. The mixture was concentrated by half at 50 °C at reduced pressure. The mixture was allowed to cool to rt and was stirred for 30 min. The crystallized product was filtered and washed with toluene and hexane. The product was dried at reduced pressure at 50 °C to afford 65.4 g (77%). Mp: 128.3−129.6 °C. ^{1}H NMR ($CDCl_3$): δ 8.62 (d, J = 2.0, 1H), 7.79 (dd, J = 8.3, 2.0, 1H), 7.31 (d, J = 8.3, 1H), 4.52 (d, J = 6.1, 2H), 3.43 (t, J = 6.1, 1H). ^{13}C NMR ($CDCl_3$): δ 150.9, 141.0, 139.0, 128.0, 120.3, 89.4, 83.4, 51.0.

3,3′-(2,5-Pyridinediyl)bis-2-propyn-1-ol (6a). A mixture of **3** (23.7 g, 100 mmol), **4a** (14.0 g, 250 mmol), $PdCl_2(PPh_3)_2$ (1.4 g, 2.0 mmol), and CuI (0.22 g, 1.2 mmol) in DIPA (300 mL) was heated at 70 °C overnight. The mixture was cooled to rt, and the solvent was removed at reduced pressure. The residue was dissolved in THF (300 mL), and the solution was filtered through a pad of silica gel (160 g). The silica gel pad was washed with THF. The solution was concentrated to 300 mL at reduced pressure, and the remaining THF was gradually removed while maintaining the volume with toluene. The mixture was stirred in toluene for 1 h at rt, and the precipitated product was filtered and washed with toluene. The crude product was suspended in EtOAc (50 mL), and the slurry was stirred overnight at rt. The slurry was cooled at 0 °C for 1 h and filtered. The product was washed with cold EtOAc. The product was dried at reduced pressure at 40 °C overnight to give 15.0 g (80%) of a tan solid. ^{1}H NMR (DMSO-d_6): δ 8.58 (d, J = 2.4, 1H), 7.83 (dd, J = 8.0, 2.4, 1H), 7.49 (d, J = 8.0, 1H), 5.44 (t, J = 6.0, 1H), 5.42 (t, J = 6.0, 1H), 4.34 (d, J = 6.4, 4H). ^{13}C NMR (DMSO-d_6): δ 151.8, 141.2, 138.8, 126.4, 118.7, 94.8, 91.3, 83.1, 80.2, 49.4, 49.3. HRMS (ESI): calcd for $C_{11}H_9NO_2$ 188.0712, found 188.0712.

(2*R*)-4-[6-(3-Hydroxyprop-1-yn-1-yl)pyridin-3-yl]but-3-yn-2-ol (6b). A solution of **5** (25.0 g, 118 mmol), powdered K_2CO_3 (32 g, 231 mmol), and MeCN (250 mL) was prepared. $PdCl_2(PPh_3)_2$ (1.2 g, 1.7 mmol) was added, the solution was aged at rt for 30 min, and **4b** (84 mL of 2.1 M solution in MeOH, 176 mmol) and CuI (224 mg, 1.2 mmol) were added. The reaction was warmed to 65 °C, aged for 17 h, and filtered through a neutral alumina plug (62 g). The alumina plug was washed with MeCN and THF. Assay of the combined filtrates indicated 18.2 g of **6b** was present (77% yield). A sample was removed, chromatographed over neutral alumina (eluting with THF), and recrystallized from IPAc−toluene to provide an analytically pure sample. Mp:. 102.7−103.8 °C. ^{1}H NMR (DMSO-d_6): δ 8.55 (J = 1.8, 1H), 7.80 (dd, J = 8.1, 1.8, 1H), 7.47 (d, J = 8.1, 1H), 5.54 (d, J = 5.4, 1H), 5.43 (t, J = 6.0, 1H), 4.62 (m, 1H), 4.33 (d, J = 6.0, 2H), 1.38 (d, J = 6.6, 3H). ^{13}C NMR (DMSO-d_6): δ 152.2, 141.5, 139.2, 126.9, 119.1, 98.7, 91.7, 83.5, 79.2, 57.1, 49.7, 24.7. HRMS (ESI): calcd for $C_{12}H_{11}NO_2$ 202.0868, found 202.0865. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.87. Found: C, 71.92; H, 5.47; N, 6.88.

2,2′-[Pyridine-2,5-diylbis(prop-1-yne-1,3-diyl)]bis(1*H*-isoindole-1,3(2*H*)-dione) (7a). DIAD (2.43 g, 12 mmol) was added slowly to a mixture of **6a** (0.94 g, 5 mmol), PPh_3 (3.3 g, 12.5 mmol), and phthalimide (1.84 g, 12.5 mmol) in THF (30 mL) while maintaining the temperature below 40 °C. The reaction was complete within 30 min. The volume was reduced by 66%, and MTBE (10 mL) was slowly added. The THF/MTBE mixture was filtered after 1 h, and the collected product was washed with THF/MTBE (1:2). The product was dried at reduced pressure at 40 °C to give 2.0 g (90% yield) of a beige solid. ^{1}H NMR (CF_3CO_2H-*d*): δ 8.73 (s, 1H), 8.52 (d, J = 8.4, 1H), 8.02 (d, J = 8.4, 1H), 8.01−7.95 (m, 4H), 7.92−7.85 (m, 4H), 4.94 (s, 2H), 4.87 (s, 2H). ^{13}C NMR (CF_3CO_2H-*d*): δ 172.4, 172.1, 151.5, 146.9 (2C), 138.2, 138.1, 136.1, 133.1, 133.0, 126.8, 126.7, 126.0, 100.6, 95.4, 77.4, 75.4, 29.8 (2C).

2-(3-{5-[(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-but-1-yn-1-yl]pyridin-2-yl}prop-2-yn-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (7b). The solution of diol **6b** from above (10.6 assay g, 52 mmol) was solvent switched into THF (200 mL) and was treated with PPh_3 (34.3 g, 131 mmol) and phthalimide (19.3 g, 131 mmol). The solution was stirred at rt for 30 min, and DIAD (24.7 mL, 126 mmol) was slowly added as a solution in THF (50 mL) at 22−48 °C. The reaction mixture was aged

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(27) Breuker, J.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 367.
(28) During the preparation of our manuscript, a paper describing a synthesis of Boc- and phthaloyl-protected aminopropargyl derivatives of similar bromopyridines was published: Russo, O.; Alami, M.; Brion, J.-D.; Sicsic, S.; Berque-Bestel, I. *Tetrahedron Lett.* **2004**, *45*, 7069.

for 3 h at rt, concentrated at reduced pressure, and solvent switched into MeCN (200 mL). The resulting slurry was stirred at rt for 2 h, and the solids were isolated by filtration to provide 13.2 g (55%) of **7b** after drying at reduced pressure at 40 °C. Mp: >230 °C dec. ^{1}H NMR ($CDCl_3$): δ 8.57 (d, J = 2.1, 1H), 7.92−7.83 (m, 4H), 7.78−7.71 (m, 4H), 7.74 (dd, J = 8.1, 2.1, 1H), 7.33 (d, J = 8.1, 1H), 5.43 (q, J = 7.2, 1H), 4.71 (s, 2H), 1.79 (d, J = 7.2, 3H). ^{13}C NMR ($CDCl_3$): δ 166.8, 166.8, 152.4, 141.2, 138.8, 134.1 (2C), 131.9, 131.8, 126.3, 123.5, 123.4, 119.0, 91.7, 84.4, 82.0, 79.4, 37.5, 27.6, 20.0. HRMS (ESI): calcd for $C_{28}H_{17}N_3O_4$:460.1297, found 460.1290. Anal. Calcd for $C_{28}H_{17}N_3O_4$: C, 73.20; H, 3.73; N, 9.15. Found: C, 72.93; H, 3.70; N, 9.08.

2,2′-[Pyridine-2,5-diylbis(propane-3,1-diyl)]bis(1*H*-isoindole-1,3(2*H*)-dione) (8a). Compound **7a** (256 mg, 0.58 mmol) was dissolved in a mixture of TFA (7 mL) and MeOH (3 mL) and hydrogenated at 40 psi with 5% Pd/C (25 mg) at rt for 18 h. The reaction mixture was filtered through a plug of Solka Floc, the filtrate was concentrated at reduced pressure, and the residue was neutralized with aq $KHCO_3$. The solution was extracted with EtOAc and dried over sodium sulfate. The filtrate was concentrated at reduced pressure to give an off-white solid (285 mg, 100% yield). Mp: 155−156 °C. ^{1}H NMR: ($CDCl_3$): δ 8.30 (d, J = 2.0, 1H), 7.82 (m, 4H), 7.70 (m, 4H), 7.41 (dd, J = 8.0, 0.4), 7.06 (d, J = 8.0, 1H), 3.74 (m, 4H), 2.78 (apparent t, 2H), 2.61 (apparent t, 2H), 2.10 (m, 2H), 1.98 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 168.2 (2C), 158.4, 149.1, 136.0, 133.8, 133.8, 133.5, 132.1, 131.9, 123.1, 123.0, 122.3, 37.6, 37.5, 35.0, 29.8, 29.5, 28.2.

2-(3-{5-[(3*S*)-3-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-butyl]pyridin-2-yl}propyl)-1*H*-isoindole-1,3(2*H*)-dione (8b). Compound **7b** (18.0 g, 39 mmol) was dissolved in DMF (375 mL) and hydrogenated at 40 psi with 5% Pd/C (1.3 g) at 40 °C for 18 h. The reaction mixture was filtered through a plug of Solka Floc, and the filtrate was concentrated at reduced pressure to an oil. The oil was dissolved in a mixture of IPAc (75 mL) and MTBE (100 mL), and the solution was washed with water. The organic layer was dried over sodium sulfate, and the volatiles were removed at reduced pressure to give 16.6 g of **8b** as an orange solid (91% yield). Mp: 117−119 °C. ^{1}H NMR ($CDCl_3$): δ 8.24 (s, 1H), 7.83−7.77 (m, 4H), 7.71−7.67 (m, 4H), 7.35 (dd, J = 8.0, 2, 1H), 7.01 (d, J = 8.0, 1H), 4.37 (m, 1H), 3.73 (m, 2H), 2.72 (apparent t, 2H), 2.61−2.40 (m, 3H), 2.04 (m, 2H), 1.95 (m, 1H), 1.48 (d, J = 6.9, 3H). ^{13}C NMR ($CDCl_3$): δ 168.3, 168.2, 158.2, 149.0, 136.0, 133.8, 133.7, 133.6, 132.0, 131.7, 123.0 (2C), 122.2, 47.1, 37.6, 35.0, 34.5, 29.9, 28.2, 18.8. HRMS (ESI): calcd for $C_{28}H_{25}N_3O_4$ 468.1923, found 468.1937. Anal. Calcd for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 71.67; H, 5.27; N, 5.85.

(2*S*)-4-[6-(3-Aminopropyl)pyridin-3-yl]butan-2-amine (9b) (from 8b). A mixture of **8b** (16.6 g, 35.5 mol), hydrazine hydrate (10.2 mL, 328 mmol), and ethanol (400 mL) was heated at 65 °C for 4 h. The mixture was filtered, and the cake was washed with toluene. The filtrate was concentrated, solvent switched into toluene, and azeotropically dried. A sample of **9b** was removed for purification/identification. ^{1}H NMR ($CDCl_3$): δ 8.34 (d, J = 2.3, 1H), 7.40 (dd, J = 8.0, 2.3, 1H), 7.06 (d, J = 8.0, 1H), 2.95−2.87 (m, 1H), 2.80−2.76 (m, 2H), 2.74−2.71 (m, 2H), 2.69−2.54 (m, 2H), 1.88−1.81 (m, 2H), 1.68−1.55 (m, 2 H), 1.34 (br s, 4H), 1.10 (d, J = 6.2, 3H). ^{13}C NMR ($CDCl_3$): δ 159.2, 149.1, 136.2, 134.6, 122.3, 46.4, 41.8, 41.5, 35.1, 33.9, 29.5, 24.1. HRMS (ESI): calcd for $C_{12}H_{21}N_3$ 208.1814, found 208.1813.

Representative Procedure of the Sonogashira Reaction. [Pyridine-2,5-diylbis(prop-1-yne-1,3-diyl)]diformamide (11a). A mixture of **3** (1.242 kg, 5.243 mol), $PdCl_2(PPh_3)_2$ (36.8 g, 52.4 mmol), CuI (2.49 g, 13.1 mmol), and DIPA (27 L) was stirred at ambient temperature for 1 h. A DIPA solution of **10a** (6.127 kg of solution containing 1.089 kg of **10a**, 13.11 mol) was added, and the mixture was heated at 70 °C for 5 h. The reaction was monitored by HPLC and was considered complete when the ratio of disubstituted product to monosubstituted intermediate was ≥96%. HPLC conditions: Zorbax SB-C8 4.6 × 250, 1 mL/min, 210 nm, 30 °C, gradient A = 0.1% H_3PO_4, B = CH_3CN, t = 0, B = 10%, t = 10, B = 85%, t = 15, B = 85%. Retention times of **11a**, the 2-substituted intermediate, and **3** were 6.3, 8.2, and 11.2 min, respectively. The mixture was cooled to 20−22 °C and filtered, and the cake was washed with DIPA and dried. The dried cake was slurried in water (32 L), and the mixture was cooled with an ice bath to 0−5 °C. The slurry was filtered, and the cake was washed with cold H_2O. The cake was dried to afford 1.187 kg of solid (84.3 wt % purity, 79.1% yield). The product was assayed by HPLC. HPLC conditions: Zorbax SB-C8 4.6 × 250, 1 mL/min, 210 nm, 30 °C, A = 0.1% H_3PO_4, B = CH_3CN, t = 0, B = 20%, t = 10, B = 20%, t = 15, B = 85%. Retention times for **11a** and the 2-substituted intermediate were 5.8 and 15 min, respectively. The product was recrystallized from 10% aq CH_3CN. Mp: 178.1−179.1 °C. The compound exists as a 92:8 mixture of rotamers; only the major is reported. ^{1}H NMR (DMSO-d_6): δ 8.56−8.58 (m, 3H), 8.10 (s, 2H), 7.82 (dd, J = 8.1, 2.1, 1H), 7.47 (d, J = 8.1, 1H), 4.19 (d, J = 5.6, 4H). ^{13}C NMR (DMSO-d_6): δ 161.0, 161.0, 152.0, 141.0, 139.0, 126.6, 118.6, 91.8, 88.3, 81.1, 78.3, 27.3, 27.1. Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.32; H, 4.51; N, 17.20.

Diphenyl [Pyridine-2,5-diylbis(prop-1-yne-1,3-diyl)]-biscarbamate (11c). Mp: 156−158 °C. ^{1}H NMR ($CDCl_3$): δ 8.65 (br s, 1H), 7.63 (d, J = 7.6, 1H), 7.32−7.37 (m, 11H), 5.16 (s, 2H), 5.15 (s, 2H), 5.09 (broad s, 2H), 4.24−4.28 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 156.1, 152.7, 141.7, 138.9, 136.40, 136.37, 128.69, 128.67, 128.5, 128.4, 126.5, 119.3, 90.5, 87.3, 82.6, 80.0, 67.32, 67.28, 31.8, 31.7. Anal. Calcd. for $C_{27}H_{23}N_3O_4$: C, 71.51; H, 5.11; N, 9.27. Found: C, 71.78; H, 5.23; N, 9.18.

Di-*tert*-butyl[Pyridine-2,5-diylbis(prop-1-yne-1,3-diyl)]-biscarbamate (11d). The preparation of **11d** followed the procedure described above for **11a**. At the end of the reaction, the mixture was diluted with EtOAc, and the precipitates were filtered and washed with EtOAc. The filtrate and washings were combined, concentrated under reduced pressure, and purified by silica gel column chromatography (hexanes/MTBE). The fractions containing **11d** were combined and concentrated under reduced pressure to give crystalline product. Mp: 123.0−124.5 °C. ^{1}H NMR ($CDCl_3$): δ 8.55 (d, J = 2.0, 1H), 7.61 (dd, J = 8.0, 2.0, 1H), 7.31 (d, J = 8.0, 1H), 4.96 (br s, 2H), 4.24−4.05 (m, 4H), 1.45 (s, 9H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 155.3, 152.4, 141.5, 138.7, 126.2, 119.1, 90.8, 87.6, 82.1, 80.1, 79.4, 31.0, 28.3. Anal. Calcd for $C_{21}H_{27}N_3O_4$: C, 65.44; H, 7.06; N, 10.90. Found: C, 65.37; H, 7.05; N, 10.77.

***N*,*N*′-[Pyridine-2,5-diylbis(prop-1-yne-1,3-diyl)]diacetamide (11e).** Mp: 188.8−189.8 °C. ^{1}H NMR (DMSO-d_6): δ 8.55 (dd, J = 2.4, 0.8, 1H), 8.44−8.36 (m, 2H), 7.82 (dd, J = 8.0, 2.4, 1H), 7.47 (dd, J = 8.0, 0.8, 1H), 4.131 (d, J = 5.6, 2H), 4.127 (d, J = 5.6, 2H), 1.85 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 169.0, 169.0, 152.0, 141.1, 139.0, 126.6, 118.6, 92.3, 88.9, 80.9, 78.1, 28.6, 28.4, 22.3. Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.77; H, 5.52; N, 15.38.

[Pyridine-2,5-diylbis(propane-3,1-diyl)]diformamide (12a). A stirred autoclave was charged with a slurry of **11a** (693 g, 2.87 mol) in MeOH (9 L), a slurry of 5% Pd/Al_2O_3 (21 g) in MeOH (1 L), and a final wash of MeOH (4 L). The mixture was cooled to 10 °C and hydrogenated at 40 psi of H_2. The temperature rose to 24 °C over 1 h and was maintained at that temperature for 17 h. The reaction was assayed by ^{1}H NMR (DMSO-d_6), which showed about 5% of an olefinic intermediate remaining (olefinic protons at 5.7 and 6.5 ppm). An additional charge of 5% Pd/Al_2O_3 (14 g) was made, and the hydrogenation was continued for 7 h. Analysis showed no olefinic intermediate. The reaction mixture was removed from the autoclave and filtered through a pad of Solka Floc. HPLC analysis of the filtrate showed a total of 638 g (89%). A sample was isolated by concentration at reduced pressure and was chromatographed on silica gel (EtOAc/MeOH) to afford crystals. Mp: 85.7−87.1 °C. HPLC conditions: Zorbax SB-C8 4.6

× 250, 1 mL/min, 210 nm, 30 °C, gradient A = 0.15% H_3PO_4, 5 mM heptanesulfonic acid, B = CH_3CN, t = 0, B = 10%, t = 10, B = 30%, t = 18, B = 30%, t = 18.1, B = 10%. The retention time of **12a** was 5.8 min, and that of **11a** was 7.7 min. ^{1}H NMR (DMSO-d_6): δ 8.32 (d, J = 2.0, 1H), 8.01−8.04 (m, 4H), 7.53 (dd, J = 8.0, 2.0, 1H), 7.17 (d, J = 8.0, 1H), 3.09 (quintet, J = 6.8, 4H), 2.69 (t, J = 7.6, 2H), 2.56 (t, J = 7.6, 2H), 1.78 (quintet, J = 7.2, 2H), 1.69 (quintet, J = 7.6, 2H). ^{13}C NMR (DMSO-d_6): δ 161.1, 161.0, 158.4, 148.8, 136.4, 134.2, 122.4, 48.6, 36.9, 36.6, 34.3, 30.5, 29.1. Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.60; H, 7.66; N, 16.85.

3,3′-Pyridine-2,5-diyldipropan-1-amine (9a). The MeOH solution of **12a** (638 g, 2.56 mol) was concentrated to wet solids, and 6 N HCl (5.15 L) was slowly added. The solution was heated to 90 °C for 1 h and cooled to 15 °C. The pH was adjusted to 12.7 with 50% NaOH (1.9 L) while maintaining the temperature at ≤31 °C. The solution was extracted with 2-BuOH, and the extracts were combined. The 2-BuOH solution was concentrated, toluene was added, and the mixture was concentrated again. This was repeated until the mole percent of 2-BuOH vs product was ≤1%. The progress of the solvent switch was monitored by ^{1}H NMR (DMSO-d_6). Signals for 2-BuOH at 0.83 and 1.05 ppm were integrated vs signals for the amine product at 1.63 and 1.70 ppm. The solvent switch was done at a temperature of about 70 °C. The final toluene solution was cooled to 20 °C, and Solka Floc was added. The mixture was stirred for 10 min and filtered, and the cake was washed with toluene. The weight of the final toluene solution was 8.02 kg, and it contained 489 g (98.8%) of **9a** by HPLC assay. HPLC conditions: Zorbax SB-C8 4.6 × 250, 1 mL/min, 210 nm, 30 °C, gradient A = 0.15% H_3PO_4, 5 mM heptanesulfonic acid, B = CH_3CN, t = 0, B = 10%, t = 10, B = 30%, t = 18, B = 30%, t = 18.1, B = 10%. The retention time of **12a** was 5.8 min and that of **9a** was 9.4 min. ^{1}H NMR (DMSO-d_6): δ 8.29 (d, J = 2.0, 1H), 7.49 (dd, J = 8.0, 2.0, 1H), 7.13 (d, J = 8.0, 1H), 2.68 (t, J = 7.6, 2H), 2.55 (t, J = 7.6, 2H), 2.52 (m, 4H), 1.69 (m, 2H), 1.60 (m, 2H), 1.3 (br s, 4H). ^{13}C NMR (DMSO-d_6): δ 159.0, 148.7, 136.0, 134.5, 122.0, 41.3, 41.0, 34.9, 34.5, 33.5, 29.1. HRMS (ESI): calcd for $C_{11}H_{19}N_3$ + 1 194.1657, found 194.1658.

Sodium Diformylamide (13).[17] To a solution of NaOMe in MeOH (25.4 wt %, 3.619 kg, 17.02 mol) were added formamide (1765 g, 39.18 mol) and 1,2-dimethoxyethane (DME) (2.0 L). The mixture was heated to begin distillation of volatiles. Approximately 2 L of volatiles was collected, and then additional DME (8.8 L) was added at a rate such that the volume of the mixture remained constant. A total of 13.6 L of distillate was collected by the end of the addition (6 h). The mixture was cooled to 20−25 °C and was filtered. The cake was washed with DME and dried to afford 1.595 kg (98.6%) of an off-white solid. ^{1}H NMR (DMSO-d_6): δ 8.96 (s). ^{13}C NMR (DMSO-d_6): δ 180.6.

Prop-2-yn-1-ylformamide (10a).[16] To a solution of **14b** (89.5 wt % in toluene, 15.00 g, 100.1 mmol) were added CH_3CN (73 mL) and **13** (11.42 g, 120.1 mmol), and the mixture was heated to reflux for 12 h. The mixture was cooled to 18−22 °C, MeOH (7.85 mL) and K_2CO_3 (2.70 g) were added, and the mixture was stirred for 4 h. The mixture was concentrated at reduced pressure to 47 mL. DIPA (50 mL) was added, and the mixture was reconcentrated a total of three times. The mixture was filtered, and the cake was washed with DIPA. The filtrate and washes were combined to give a light colored solution. The total weight was 37.72 g, which contained 7.25 g of *N*-formylpropargylamine (87.1% yield). The amount of *N*-formylpropargylamine in the solution was determined by concentrating an aliquot to an oil, seeding, and drying the resulting crystals. Thus, 6.56 g of solution gave 1.26 g of crystals. ^{1}H NMR ($CDCl_3$): major rotamer δ 8.13 (s, 1H), 6.94 (br, 1H), 4.02 (ddd, J = 5.6, 2.6, 0.8, 2H), 2.23 (t, J = 2.6, 1H); minor rotamer δ 8.09 (d, J = 12.1, 1H), 6.51 (br, 1H), 3.97 (dd, J = 6.0, 2.6, 2H), 2.34 (t, J = 2.6, 1H). ^{13}C NMR ($CDCl_3$): major rotamer δ 161.4, 78.9, 71.3, 27.4; minor rotamer δ 164.7, 78.7, 72.8, 31.2.

((3*R*)-3-{[Dihydroxy(methyl)-λ^4-sulfanyl]oxy}but-1-yn-1-yl)(trimethyl)silane (19). Compound **18** (5.73 g, 40 mmol) was dissolved in CH_2Cl_2 (50 mL) and triethylamine (6.7 mL, 48 mmol), and the solution was cooled to −10 °C. Methanesulfonyl chloride (3.5 mL, 45 mmol) was added slowly over 15 min, and the resulting solution was warmed to 22 °C and aged for 1 h. Water (25 mL) was added, followed by sufficient aq HCl to lower the pH to 3.0. The layers were separated, and the organic layer was dried over sodium sulfate. The volatiles were removed at reduced pressure to provide 8.35 g (94% yield) of **19** as an oil. ^{1}H NMR: δ 5.26 (q, J = 6.7, 1H), 3.12 (s, 3H), 1.64 (d, J = 6.7, 3H), 0.20 (s, 9H). ^{13}C NMR: δ 101.2, 93.6, 68.5, 57.9, 39.0, 22.4, −0.6.

[(1*S*)-1-Methylprop-2-yn-1-yl]formamide (20). To a solution of **19** (8.35 g, 37.6 mmol) in DMF (50 mL) was added **13** (4.1 g, 43.3 mmol). The solution was heated to 62 °C for 6 h and cooled to 22 °C. The reaction mixture was partitioned between EtOAc and water. The layers were separated, and the aqueous layer was back extracted with EtOAc. The combined organic layers were washed with water and dried over Na_2SO_4. The volatiles were removed at reduced pressure, and the residue was dissolved in MeOH (11 mL). K_2CO_3 (193 mg) was added, and the solution was stirred at 22 °C for 1 h. The solution was filtered, and the volatiles were removed at reduced pressure. The residue was dissolved in EtOAc/hexanes (4/1 v/v) and passed through a plug of neutral alumina eluting with the diluent. Evaporation of the filtrate provided **20** (2.1 g, 58%) as an orange solid. Mp: 59.3−60.7 °C. The compound exists as rotamers: 87:13 ratio. ^{1}H NMR: major rotamer ($CDCl_3$) δ 8.12 (s, 1H), 6.07 (br, 1H), 4.88 (m 1H), 1.50 (d, J = 7.0, 1H), 1.44 (d, J = 7.0). ^{13}C NMR: major rotamer δ 159.9, 83.5, 70.5, 35.5, 22.0. Anal. Calcd for C_5H_7NO: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.85; H, 7.50; N, 14.39.

[3-(5-Bromopyridin-2-yl)prop-2-yn-1-yl]formamide (21). To a mixture of **3** (8.3 g, 35 mmol) and MeCN (85 mL) were added DIPA (16 mL, 116 mmol), **10a** (3.1 g, 37 mmol), $PdCl_2(PPh_3)_2$ (245 mg, 0.35 mmol), and CuI (31 mg, 0.16 mmol), and the solution was stirred at 22 °C for 18 h. The solids were removed by filtration, and the volatiles were removed at reduced pressure. The residue was dissolved in EtOAc, and the solution was washed with water. The organic layer was dried over sodium sulfate, and the volatiles were removed at reduced pressure. The residue was combined with 75 mL of 95:5 MeCN/EtOAc. The slurry was heated to reflux and slowly cooled to 20 °C during which time the product crystallized. Isolation by filtration provided 6.5 g (77% yield) of **21**. Mp: 153.5−155 °C. The compound exists as rotamers: 91:9 ratio. ^{1}H NMR: δ 8.62 (d, J = 2.4, 1H), 8.23 (s, 1H), 7.79 (dd, J = 8.4, 2.4, 1H), 7.30 (d, J = 8.4, 1H), 6.23 (br s, 1H), 4.35 (dd, J = 5.6, 0.7, 2H). ^{13}C NMR: δ 160.5, 151.1, 140.7, 138.9, 128.0, 120.4, 85.7, 81.9, 28.3. HRMS: calcd for $C_9H_7BrN_2O$ + 1 238.9820, found 238.9821. Anal. Calcd for $C_9H_7BrN_2O$: C, 45.22; H, 2.95; N, 11.72. Found: C, 45.23; H, 2.75; N, 11.44.

(3-{5-[(3*S*)-3-(Formylamino)but-1-yn-1-yl]pyridin-2-yl}prop-2-yn-1-yl)formamide (11b). To a mixture of **21** (1.97 g, 8.2 mmol) and DMF (12 mL) at rt was added a 0.84 M DIPA solution of alkyne **20** (14.2 mL, 11.9 mmol), followed by $PdCl_2(PPh_3)_2$ (125 mg, 0.18 mmol). The mixture was stirred at 25 °C for 20 min, CuI (16 mg, 0.08 mmol) was added, and the mixture was heated to 60 °C. The solution was aged at 60 °C for 5 h and cooled to rt, and the DIPA was evaporated at reduced pressure. The residue was passed through a plug of neutral alumina eluting with 4:1 EtOAc/:MeOH. Assay of the filtrate revealed that 1.60 g of product was present (77% yield). The eluant was evaporated at reduced pressure (<35 °C), the DMF-rich residue was treated with toluene (20 mL), and the resulting slurry was aged at rt for 17 h. The solids were collected by filtration and washed with toluene. Drying at reduced pressure at 45 °C provided **11b** (850 mg, 41% isolated yield) as an off-white solid. A second crop provided an

additional 325 mg for a total of 1.175 g (57% isolated yield). Mp: 161−162 °C dec. ^{1}H NMR: δ 8.62 (1H), 8.23 (1H), 8.18 (1H), 7.65 (d, J = 8.1, 1H), 7.35 (d, J = 8.1, 1H), 6.41 (br, 1H), 6.30 (?), 5.15 (m, 1H), 4.36 (d, J = 5.3, 2H), 1.49 (d, J = 6.5, 3H). ^{13}C NMR ($CDCl_3$): δ 160.7, 159.9, 152.2, 141.2, 138.8, 126.3, 119.1, 94.1, 86.6, 82.3, 78.7, 36.2, 28.3, 22.0. HRMS (ESI): calcd for $C_{14}H_{13}N_3O_2$ + 1 256.1086, found 256.1083. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.56; H, 4.80; N, 16.37. Chiral SFC assay: Chiralpak AD-H, 250 mm × 4.6 mm, 4% MeOH/CO_2 for 4 min, 2%/min to 40% MeOH/CO_2, hold for 3 min, 1.5 mL/min, 200 bar, 35 °C, 215 nm. The retention time of **11b** was 19.2 min, and that of its enantiomer was 20.3 min.

(3-{5-[(3*S*)-3-(Formylamino)butyl]pyridin-2-yl}propyl)-formamide (12b). 11b (800 mg, 3.1 mmol) was dissolved in 1/1 THF/MeOH (20 mL) at 25 °C. The solution was combined with 5% Pd/Al_2O_3 (100 mg) and hydrogenated at 40 psi for 18 h. The catalyst was removed by filtration, and the filtrate was evaporated at reduced pressure to give an oil, which upon trituration with MTBE provided **12b** as an off-white solid (755 mg, 90%). Mp: 61−63.5 °C. ^{1}H NMR ($CDCl_3$): δ 8.34 (1H), 8.16 (2H), 7.48 (dd, J = 8.0, 2.3, 1H), 7.11 (d, J = 8.0, 1H), 6.49 (br, 1H), 5.74 (d, J = 5.5, 1H), 4.12 (dq, J = , 1H), 3.33 (m, 2H), 2.64 (m, 2H), 1.96 (m, 2H), 1.77 (m, 2H), 1.21 (d, J = 6.8, 3H). ^{13}C NMR ($CDCl_3$): major rotamer δ 161.4, 160.7, 158.4, 148.7, 136.8, 134.4, 122.7, 43.6, 38.7, 37.5, 34.7, 29.0, 28.8, 20.9. HRMS (ESI): calcd for $C_{14}H_{21}N_3O_2$ + 1 264.1712, found 264.1712.

(2*S*)-4-[6-(3-Aminopropyl)pyridin-3-yl]butan-2-amine (9b) (from 12b). Compound **12b** (87 mg, 0.33 mmol) was dissolved in a mixture of methanol (2.5 mL) and water (0.25 mL), and hydroxylamine hydrochloride (100 mg, 1.4 mmol) was added. The solution was heated at 70 °C for 20 h. Assay of the reaction mixture showed 64 mg of **9b** present (94% yield).

3-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)propan-1-amine (2a).[6] To a solution of **9a** (233 g, 1.21 mol) in toluene (4 L) was added $NaNH_2$ (255 g, 90 wt %, 5.88 mol), and the mixture was heated to 90 °C for 7 h. The reaction was monitored by HPLC and was considered complete when the ratio of **2a** to **9a** was >99:1. HPLC conditions were as described for **9a** above. The retention time of **2a** was 9.8 min. The mixture was cooled to 5 °C, and a 4.4 M aqueous solution of NaCl (1 L) was added at such a rate as to maintain the temperature ≤10 °C. When the addition was complete, the mixture was allowed to warm to 18−22 °C and was stirred for 18 h. The layers were separated, and the aqueous phase was extracted with toluene. Water was added to the aqueous phase, and it was further extracted with toluene. The toluene extracts were combined to give 6.1 kg of solution containing 207 g of **2a** (90% yield).

3-[(7*R*)-7-Methyl-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl]propan-1-amine (2b) (from 9b). The dry toluene solution of **9b** prepared from **8b** above (110 mL, 35.5 mmol) was treated with $NaNH_2$ (6.2 g, 110 mmol) and was heated to 90 °C for 17 h. The reaction mixture was cooled to 30 °C and treated with a solution of citric acid (8 g) in THF (100 mL). After being stirred for 10 min, the slurry was filtered, and the solids were washed with THF. The volatiles were evaporated at reduced pressure to give 5.0 g of crude **2b** (69% overall from **8b**) as a brown oil. **2b** free base: Mp: < 22 °C. ^{1}H NMR ($CDCl_3$): δ 7.03 (d, J = 7.2, 1 H), 6.32 (d, J = 7.2, 1H), 4.61 (br s, 1H), 3.48 (m, 1H), 2.73−2.61 (overlapping m, 4H), 2.54 (overlapping m, 2H), 1.87 (m, 1H), 1.76 (m, 2H), 1.49 (m, 1H), 1.19 (d, J = 6.4, 3H), 1.15 (v br s, 2H). ^{13}C NMR ($CDCl_3$): δ 157.9, 155.6, 136.3, 112.6, 111.2, 47.0, 41.8, 35.1, 33.9, 29.4, 25.5, 22.3. **2b** bis HCl salt: ^{13}C NMR (MeOH-d_4) δ 152.6, 147.4, 142.8, 121.2, 112.1, 49.0, 39.8, 30.4, 28.2, 27.6, 25.0, 21.5. HRMS (ESI): calcd for $C_{28}H_{25}N_3O_4$ 206.1657, found 206.1658. Anal. Calcd for $C_{12}H_{21}Cl_2N_3$ (bis HCl salt): C, 51.80; H, 7.61; N, 15.10. Found: C, 51.78; H, 7.54; N, 14.84.

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Supporting Information Available: Copies of ^{1}H NMR spectra of **6a**, **7a**, **8a**, **9a**, **12b**, and **19** and a copy of the ^{13}C NMR spectrum of **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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