Synthesis of a Series of 4-(Arylethynyl)-6-chloro-4-cyclopropyl-3,4-dihydroquinazolin-2(1*H*)-ones as Novel Non-nucleoside HIV-1 Reverse Transcriptase Inhibitors

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As part of an ongoing effort to prepare novel non-nucleoside inhibitors of human immunodeficiency virus type-1 (HIV-1) reverse transcriptase (RT), a series of 4-(arylethynyl)-6-chloro-4-cyclopropyl-3,4-dihydroquinazolin-2(1*H*)-ones **4aa–l** has been prepared. Target compounds **4a–e** were synthesized via addition of various 1-lithio-2-(aryl)alkyne nucleophiles to a 1-protected-4-cyclopropylquinazolin-2(1*H*)-one (**7**), followed by deprotection. The 3-methyl compound **4aa** was prepared in an analogous manner, with the 3-alkylation performed prior to deprotection. Alternatively, the target compounds **4f–l** were prepared by addition of 1-lithio-2-(trimethylsilyl)acetylene to **7**, followed by deprotection and subsequent palladium-catalyzed coupling with various aryl halides. By incorporating an aryl group onto the end of the 4-acetylene functionality, the requirement for a metabolically labile 3-methyl group on the dihydroquinazolinone nucleus has been eliminated. A number of the target compounds were shown to be potent inhibitors of HIV-1 RT. Compound **4a**, which had exhibited the most favorable overall biological profile, was resolved via a four-step procedure to provide the enantiomers **13a** and **13b**. Compound **13a** having the (−)-4(*S*) configuration was shown to be the active enantiomer and was selected as a candidate for further investigation.

Introduction

The rapid global spread of acquired immune deficiency syndrome (AIDS) has prompted numerous efforts to develop therapeutic agents against the human immunodeficiency virus type-1 (HIV-1).[1] One such effort has focused on inhibition of the virally encoded reverse transcriptase (RT) enzyme, which is responsible for the conversion of retroviral RNA to proviral DNA. The nucleoside RT inhibitors 3′-azidothymidine (AZT) and dideoxyinosine (ddI) have proven to be clinically useful anti-HIV-1 agents.[2] Unfortunately, these compounds are flawed by their inherent toxicity, which may be a result of a lack of selectivity versus other DNA polymerases.[3] Some researchers have therefore shifted their focus toward the development of novel non-nucleoside RT inhibitors. A number of potent non-nucleoside HIV-1 RT inhibitors have been reported.[4–9] These inhibitors appear to act at an allosteric site unique to HIV-1 RT, which should help to provide selectivity versus other DNA polymerases.[9] Our efforts in this area have focused on modifications of the unstable screening lead 1 (Figure 1, L-608,788).[10] Several reports from our laboratories have described the evolution of the dihydroquinazolinone class of HIV-1 RT inhibitors (Figure 1). Initial efforts, which centered on preparing stable, nonthiourea analogs of **1**, resulted in the synthesis of **2**, the first potent non-thiourea in this class.[10] Further investigations led to the discovery of the 4,4-dialkyl compounds of generic structure **3a**[11] and the 4-cyclopropyl-4-ethynyl compound **3b**.[11]

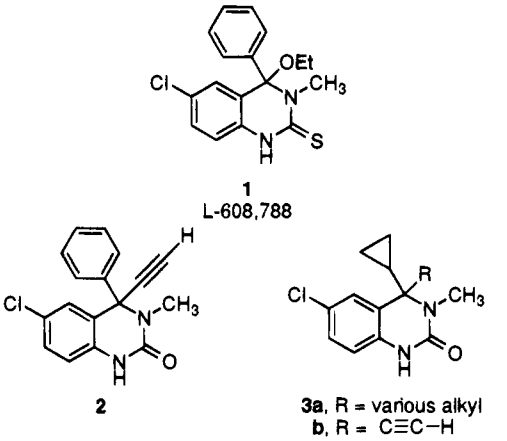

Figure 1.

Although compounds such as **2**, **3a**, and **3b** were shown to be potent inhibitors of HIV-1 RT, their potential therapeutic utility is hampered by metabolic liabilities. In all of these dihydroquinazolinone RT inhibitors, the 3-methyl group is susceptible to oxidative metabolism,[11b] which results in loss of the methyl group. The removal of this methyl group results in large losses in inhibitory potency and severely limits oral bioavailability. The 4-alkyl group of compounds like **3a** also proved to be susceptible to metabolism,[11b] again providing losses in inhibitory potency and oral bioavailability. In an attempt to develop potent compounds of this class which did not contain metabolically unstable alkyl groups in the 3- and 4-positions, we chose to use **3b** as a starting point for further investigation. We hoped to fuse various aryl groups onto the end of the acetylene functionality of **3b** to provide novel inhibitors of generic structure **4** (Figure 2). These compounds might provide a more metabolically stable group at the 4-position,

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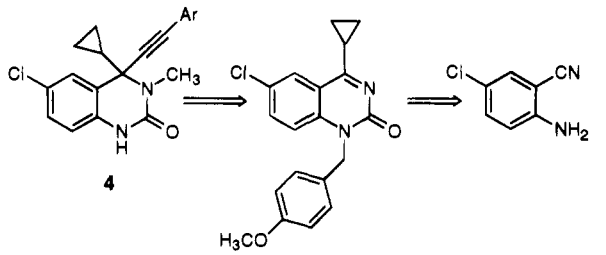


Figure 2.

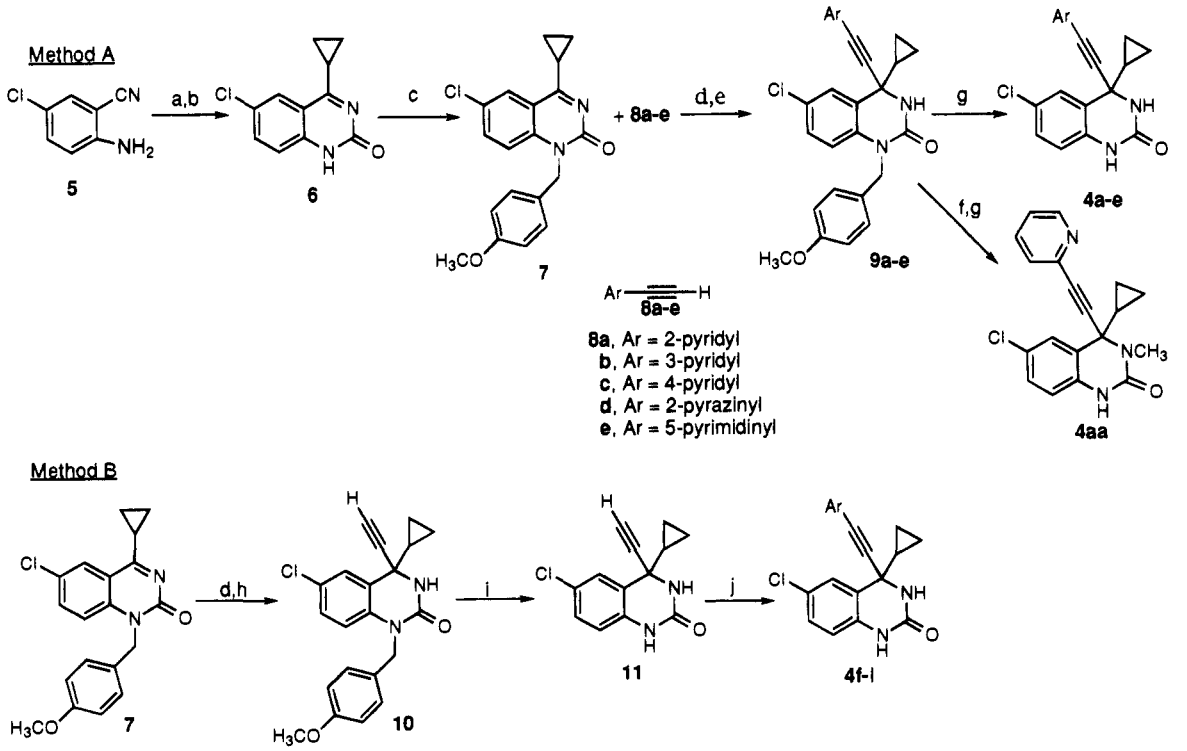
while having the potential to show enhanced potency due to additional binding interactions provided by the aryl group. Careful choice of the proper aryl group might also help to enhance the oral biovailability of these compounds. If the proper aryl group could be found which would enhance both potency and oral bioavailability, the need for an alkyl substituent at the 3-position could possibly be eliminated. This paper details our synthetic efforts toward achieving these goals. In this paper, we describe our approach to the synthesis of various 4-(arylethynyl)-6-chloro-4-cyclopropyl-3,4-dihydroquinazolin-2(1*H*)-ones and describe a methodology for the resolution of these compounds.

Results and Discussion

Retrosynthetic analysis of our target **4** indicated that these molecules should be accessible via addition of organometallic alkynyl nucleophiles to a 1-protected-4-cyclopropyl-6-chloroquinazolin-2(1*H*)-one (Figure 2). The intermediate quinazolinones could be readily obtained in several steps from the known compound 4-chloroanthranilonitrile[12] (Scheme 1, **5**).

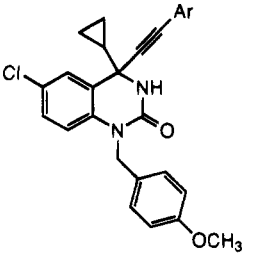
Addition of cyclopropylmagnesium bromide to **5**, followed by *in situ* trapping of the intermediate imine salt with dimethyl carbonate, proved to be an efficient procedure for the preparation of **6** (Scheme 1). Due to the ease of removal and lack of sensitivity to the addition conditions, the *p*-methoxybenzyl group was chosen for the protection of the 1-position of the quinazolinone nucleus. The protected quinazolinone **7** became the key synthetic intermediate for the preparation of our target compounds. We chose to probe the addition of lithioalkynyl nucleophilies to **10** using the commercially available 2-ethynylpyridine. In an attempt to surpress the formation of the undesired reduction product, the quinazolinone substrate was precomplexed with magnesium triflate prior to treatment with the lithioethyne nucleophile. Earlier work[10,11] in our laboratories had shown that precomplexation of a quinazolinone substrate with magnesium bromide etherate or magnesium triflate, followed by addition of an alkylorganomagnesium nucleophile gave smooth addition to the 4-position of the quinazolinone nucleus while surpressing formation of undesired reduction product. Treatment of a complex of **7** and magnesium triflate in ether at room temperature with a −78 °C solution of 1-lithio-2-(2-pyridyl)ethyne in THF gave smooth addition at the 4-position to provide **9a** in 78% yield. Alkylation of the 3-position of **9a** with NaH/CH_3I in DMF followed by removal of the protecting group with TFA provided **4aa**. Treatment of **9a** with TFA gave the 3-desmethyl analog **4a**. Comparison of the inhibitory potency of **4aa** and **4a** (Table 2) showed that removal of the 3-methyl group did not have the detrimental effect on potency that had been seen with previous dihydroquinazolinones.[10,11] Removal of the requirement for the metabolically labile 3-methyl group was a key accomplishment of this investigation. We therefore chose

Scheme 1[a]



[a] Reagents: (a) cyclopropylmagnesium bromide/THF, 50 °C; (b) dimethyl carbonate/THF, 55 °C; (c) $LiN(TMS)_2$, 4-$(OCH_3)C_6H_4CH_2Cl$/DMF, 60 °C; (d) $Mg(OTf)_2/Et_2O$, rt; (e) *n*-BuLi/THF, −78 °C; (f) NaH, CH_3I/DMF, rt; (g) TFA; (h) *n*-BuLi, TMS acetylene/Et_2O, −78 °C; (i) TFA/CH_2Cl_2; (j) $(Ph_3P)_2PdCl_2$ (5 mol %), ArX/TEA−CH_3CN (1:1), 80 °C sealed tube.

Table 1. Structure and Physical Data for 1-Protected-3,4-dihydroquinazolinones **9a–e**

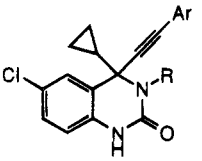


9a-e

no.	Ar	mp, °C	yield, %	HPLC purity,[a] % at 210 nm	FABHRMS (mmu) calcd	FABHRMS (mmu) obsd
9a	2-pyridyl	196–197.5	78	98.8	444.147 88	444.147 54
9b	3-pyridyl	179–181	47	98.2	444.147 88	444.147 83
9c	4-pyridyl	156–160 dec	50	99.3	444.147 88	444.147 00
9d	2-pyrazinyl	foam	70	97.0	*b*	*b*
9e	5-pyrimidinyl	165–167	32	97.5	445.143 13	445.143 95

[a] See the Experimental Section for HPLC conditions. [b] HRMS not available for this compound, characterization by NMR.

Table 2. Structural, Physical, and Enzyme Inhibition Data for 3,4-Dihydroquinazolinones **4aa–l**



4aa-l

no.	R	Ar[a]	method	yield, %	mp, °C	formula	anal.	IC_{50}, nM (rC-dG)
4aa	CH_3	2-pyridyl	A	54[b]	foam	$C_{19}H_{16}N_3OCl{\cdot}0.50H_2O{\cdot}0.50EtOAc$	C,H,N	19.6
4a	H	2-pyridyl	A	78	foam	$C_{18}H_{14}N_3ClO{\cdot}0.50H_2O$	C,H,N	23.2
4b	H	3-pyridyl	A	60	231–233	$C_{18}H_{14}N_3OCl{\cdot}0.40CHCl_3$	C,H,N	64.5
4c	H	4-pyridyl	A	63	131–133	$C_{18}H_{14}N_3OCl{\cdot}0.30H_2O{\cdot}0.20Et_2O$	C,H,N	450
4d	H	2-pyrazinyl	A	41	245 dec	$C_{17}H_{13}N_4OCl{\cdot}0.40H_2O{\cdot}0.10EtOAc$	C,H,N	270
4e	H	5-pyrimidinyl	A	54	255–256 dec	$C_{17}H_{13}N_4OCl{\cdot}0.30H_2O$	C,H,N	1500
4f	H	2-pyrimidinyl	B	66	259–261 dec	$C_{17}H_{13}N_4OCl{\cdot}0.85H_2O$	C,H,N	130
4g	H	4-NO_2-2-pyridyl	B	54	210–212 dec	$C_{18}H_{13}N_4OCl{\cdot}0.10CHCl_3{\cdot}0.10Et_2O$	C,H,N	>10000
4h	H	phenyl	B	55	193–195	$C_{19}H_{15}N_2OCl{\cdot}0.10H_2O$	C,H,N	17.7
4i	H	2-NO_2-phenyl	B	62	181–182 dec	$C_{19}H_{14}N_3O_3Cl{\cdot}0.15H_2O$	C,H,N	12.8
4j	H	2-CN-phenyl	B	42	123–125	$C_{20}H_{14}N_3OCl{\cdot}0.15H_2O$	C,H,N	10.8
4k	H	2-thiazolyl	B	37	227–228 dec	$C_{16}H_{12}N_3OClS$	C,H,N	10.9
4l	H	2-furanyl	B	15[c]	201 dec	$C_{17}H_{13}N_2O_2Cl{\cdot}0.15H_2O$	C,H,N	9.2

[a] Aryl bromides were used in all coupling reactions except the preparation of **4h**, where iodobenzene was used. [b] Yield is for two-step process. [c] Low yield due to poor stability of 2-bromofuran[15] under the coupling conditions.

to prepare only 3-desmethyl compounds in our further synthetic efforts in this series.

Treatment of **7** with various 1-lithio-2-arylalkynes **8b–e** using the above described addition conditions (method A, Scheme 1) provided **9b–e** in moderate yield (Table 1). **9b–e** were deprotected with TFA to give the target compounds **4b–e** (Table 2). During the preparation of arylalkynes **8b–e**, an inherent lack of stability of these compounds became apparent and is reflected in the yields obtained for **9b–e** (Table 1). The poor stability of **8b–e** as well as a desire to develop a more direct synthetic approach to preparing analogs of **4a** led us to pursue an alternate method. Rather than having to prepare a number of potentially unstable arylalkynes and use the two-step elaboration detailed previously, we sought a more concise route which would allow the rapid preparation of analogs of **4a** in one step. Using conditions essentially identical to those described earlier for the preparation of **9a–e**, a complex of magnesium triflate and **7** in ether was treated with a −78 °C solution of 1-lithio-2-(trimethylsilyl)acetylene in ether (method B, Scheme 1). The addition product was desilylated with KOH/MeOH to give **10** in good yield. **10** was deprotected with TFA to provide **11**. We hoped to be able to incorporate various aryl groups onto the end of the acetylene functionality of **11** via palladium-catalyzed coupling with the appropriate aryl halides. Previous work had shown that aryl halides undergo palladium-catalyzed coupling with terminal acetylenes in the presence of cuprous iodide and an alkylamine solvent.[13] All attempts at using this procedure to effect cross coupling of various aryl halides with **11** resulted in the recovery of dimerized acetylenic compound as the only product. Removing the cuprous iodide co-catalyst and performing the coupling in a mixed acetonitrile/triethylamine solvent system at 80 °C (sealed tube) provided a solution to the dimerization problem. A possible explanation for these observations is that the use of cuprous iodide as a co-catalyst activates the acetylenic functionality and causes self-coupling via a palladium(II)-based mechanism. Removal of the cuprous iodide may favor a palladium(0)-based mechanism which leads to the desired product. Coupling of **11** with 2-bromopyrimidine using bis(triphenylphosphine)pal-

Table 3. Antiviral Activity of Selected Compounds in Cultured MT-4 Cells

compound	IC_{50}, nM	CIC_{95}, nM (MT-4 cells)
4a	23.2	25
4h	17.7	100
4j	10.8	12
4k	10.9	12
TIBO	70	200
nevirapine	73	100
L-697,661	19	50

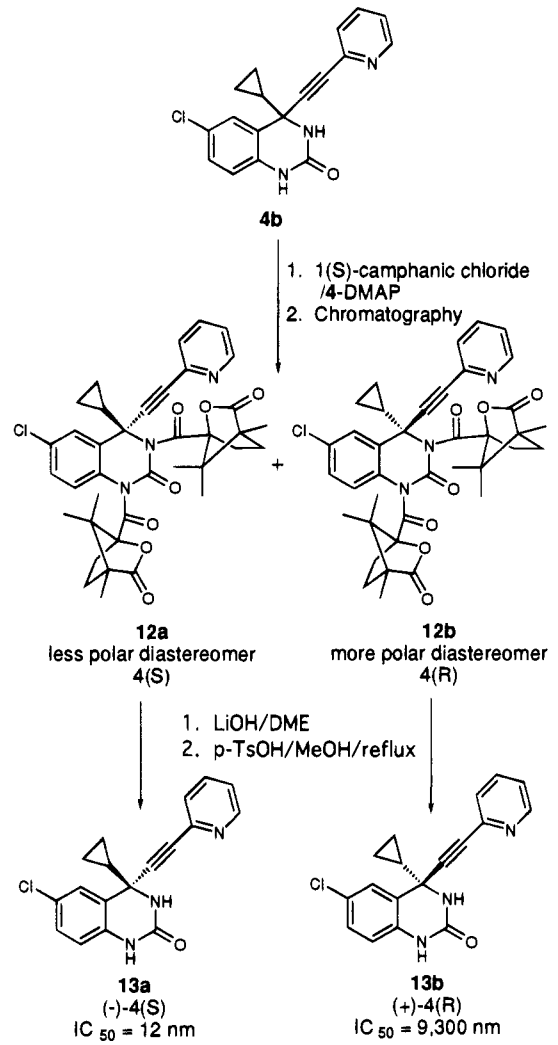
ladium dichloride as catalyst provided the desired product **4f** in moderate yield. This coupling was repeated with various aryl/heteroaryl halides and **11** to give moderate yields of target compounds **4f–l** (Table 2). Thus, by preparing **11** in quantity, it was possible to synthesize numerous analogs of **4a** via a rapid and efficient one-step procedure.

Compounds **4aa–l** were evaluated for their ability to inhibit HIV-1 RT using an rC-dG template/primer as previously described.[14] IC_{50} values for the compounds are presented in Table 2. In general, most of the 5- and 6-membered aryl groups were well-tolerated, providing potent inhibitors of HIV-1 RT. Use of more than one nitrogen atom in a six-membered ring or attempted substitution at the 4-position of a six-membered ring was the only change which produced substantial decreases in inhibitory potency. Stepwise movement of the pyridyl nitrogen atom around the ring resulted in a 3-fold loss of potency from the ortho (**4a**) to the meta (**4b**) position and a 20-fold loss from ortho to para (**4c**) positions (Table 2).

Selected compounds were also evaluated as antiviral agents in cultured MT-4 cells infected with HIV-IIIb. The CIC_{95} values are reported in Table 3. The CIC_{95} (95% cell inhibitory concentration) is defined as the concentration of compound which inhibited by greater than 95% the spread of infection as assessed by p24 core antigen ELISA.[16] In general, the compounds proved to be potent anti-HIV-1 agents in cell culture.

During the detailed evaluation of the biological properties of these compounds, **4a** was shown to posses an excellent overall profile of antiviral and pharmacokinetic properties.[17] In order to further characterize the biological activity of **4a**, we chose to resolve the compound (Scheme 2). Compound **4a** was treated with 1(*S*)-camphanic chloride and 4-(dimethylamino)pyridine to provide a mixture of the diastereomeric dicamphanic imides **12a,b**. Compounds **12a** and **12b** were separated by careful column chromatography, and crystallization of the more polar diastereomer **12b** yielded crystals suitable for X-ray crystallographic analysis. Single-crystal X-ray analysis of **12b**[18] indicated that this diastereomer possessed the (*R*)-configuration at the 4-position of the 3,4-dihydroquinazolinone nucleus. Diastereomers **12a** and **12b** were each treated with 1 M LiOH/DME (45 min), followed by *p*-toluenesulfonic acid in refluxing methanol (72 h) to give stepwise removal of the camphanates to provide the pure enantiomers **13a** and **13b**. The (−)-4(*S*) enantiomer **13a** was shown to be the active enantiomer (IC_{50} = 12nM), while the (+)-4(*R*) enantiomer **13b** was essentially inactive (IC_{50} = 9300 nM). Compound **13a** was a potent antiviral agent in cultured MT-4 cells infected with HIV-IIIb, posessing a CIC_{95} value of 25 nM (n > 10).[17] Oral administration of **13a** to rhesus monkeys at 10 mg/kg (n = 4) provided

Scheme 2



peak levels of 12 μM at 2–4 h, with levels of parent drug remaining above 4 μM after 24 h.[17] Therefore, **13a** was shown to possess an excellent overall profile of biological activity and was chosen as a candidate for further preclinical investigation. The potential for the development of resistant mutant strains of HIV-1 to various non-nucleoside HIV-1 RT inhibitors has been clearly demonstrated in a clinical setting. We are currently assessing the potential of **13a** to induce resistance, and are evaluating the activity of **13a** against a number of known HIV-1 RT mutants. A detailed description of the full biological profile of **13a** will be reported in a future publication.

In summary, we have developed an efficient synthesis of 6-chloro-4-cyclopropyl-3,4-dihydro-4-(arylethynyl)-quinazolin-2(1*H*)-ones. The key step involves the addition of various lithioethyne nucleophiles to the 4-position of the quinazolinone **7**. The resulting product is subsequently deprotected to provide target compounds **4a–e**. Alternatively, treatment of **7** with 1-lithio-2-(trimethylsilyl)acetylene, followed by removal of the protecting groups, provides **11**. Intermediate **11** is coupled with various aryl bromides or iodides via palladium catalysis to provide target compounds **4f–l**. A number of the target compounds were potent inhibitors of HIV-1 RT. Compound **4a**, which possessed the best overall biological profile of the series, was resolved via a four-step process to provide the pure enantiomers

13a and **13b**. The (−)-4(*S*) enantiomer **13a** was shown to be the more active enantiomer and retained the excellent overall biological profile of **4a**.[16] The incorporation of an aryl group onto the terminus of the 4-acetylene functionality has produced a potent series of novel non-nucleoside HIV-1 RT inhibitors, while eliminating the requirement for a metabolically labile 3-methyl group on the dihydroquinazolinone nucleus.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass spectra were taken on a VG Micromass MM7035 spectrometer. ^{1}H NMR spectra were obtained with a Varian VXR-400S spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. Column chromatography was performed on E. Merck silica gel 60 (230–400 mesh) unless otherwise noted. Thin-layer chromatography was performed on E. Merck 60F-254 (0.25 mm) precoated silica gel plates, with visualization by UV light and/or phosphomolybdic acid stain. Anhydrous diethyl ether was obtained from Mallincrodt in sealed cans which were opened immediately prior to use. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Analytical HPLC analysis was performed as follows: A = 0.1% H_3PO_4 in H_2O, B = CH_3CN; 95:5 to 5:95 A:B linear gradient over 20 min, flow = 1.5 mL/min; Waters μ Bondapak C^{18} 300 × 3.9 mm analytical column; detection at 210 and/or 254 nm. Chiral HPLC analysis was performed as follows: A = 20 mM monobasic sodium phosphate (pH = 3.0), B = CH_3CN; 90:10 to 10:90 A:B linear gradient over 20 min, flow = 1.5 mL/min; Chiral AGP analytical column, with detection at 254 nm.

6-Chloro-4-cyclopropylquinazolin-2(1*H*)-one (6). A three-necked round-bottom flask equipped with a thermometer, magnetic stirrer, addition funnel, and septum inlet was oven-dried and swept with argon. The flask was charged with a suspension of 5.50 g (0.226 mol) of magnesium turnings (Aldrich) in 150 mL of dry THF. A 3.00-mL portion of cyclopropyl bromide (Aldrich, distilled) was added to the suspension in one portion, and the mixture heated to 33 °C, at which time a gentle exotherm began. After the temperature had stabilized at 48 °C, the remaining 15.80 mL (0.235 mol total) of cyclopropyl bromide was added dropwise as a solution in 30 mL of dry THF while maintaining an internal temperature of 48–52 °C. After the addition, the solution was kept at 48–52 °C for 45 min using a heating mantle. A solution of 10.00 g (0.066 mmol) of 2-cyano-4-chloroaniline[12] in 50 mL of dry THF was added dropwise at a rate which maintained an internal temperature of 47–50 °C. This temperature was maintained for 30 min after the addition was complete using a heating mantle. A 17.40-mL (0.206-mol) quantity of dimethyl carbonate (Aldrich) was added dropwise at a rate which maintained the internal temperature at 48–55 °C. After completion of the addition, the reaction mixture was kept at this temperature for 30 min using a heating mantle. The reaction solution was cooled to 25 °C and poured into a rapidly stirred mixture of ice and 500 mL of 1 M citric acid. The mixture was extracted with two portions of $CHCl_3$, and the combined organic extracts were washed with 10% Na_2CO_3 solution. The extracts were dried (anhydrous $MgSO_4$) and concentrated to a volume of approximately 450 mL. The solution was stored in the refrigerator under argon overnight, which caused the product to crystallize. The crystals were filtered and washed with cold $CHCl_3$ to give 6.50 g (44%) of the title compound as a pale yellow solid. Chromatography of the mother liquors on 850 g of fine silica with 35:1 $CHCl_3$/CH_3OH provided an additional 5.20 g (35%) of product. A small sample of product was recrystallized from hot MeOH to provide an analytical sample as a white crystalline solid: mp 207–209 °C dec; ^{1}H NMR ($CDCl_3$) 1.27 (m, 2 H), 1.57 (m, 2 H), 2.55 (m, 1 H), 7.48 (d, J = 8 Hz, 1 H), 7.61 (dd, J = 2, 8 Hz, 1 H), 8.10 (d, J = 2 Hz, 1 H); FAB MS M + H = 221. Anal. ($C_{11}H_9N_2OCl$) C, H, N.

6-Chloro-4-cyclopropyl-1-(4-methoxybenzyl)-quinazolin-2(1*H*)-one (7). To a 0 °C solution of 9.00 g (0.041 mol) of **6** in 150 mL of dry DMF (Aldrich Sure-Seal) under argon was added dropwise 42.50 mL of a 1.0 M solution of lithium bis(trimethylsilyl)amide in hexanes. After completion of the addition, 8.14 mL (0.06 mol) of 4-methoxybenzyl chloride (Aldrich) was added in one portion, and the flask was immersed in an oil bath maintained at 55–60 °C. The reaction was heated for 12 h and then allowed to stand at room temperature overnight. The solvents were removed *in vacuo*, and the residue was partitioned between $CHCl_3$ and cold 1 M citric acid. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were washed with 10% Na_2CO_3 solution and dried (anhydrous Na_2SO_4). After concentration *in vacuo*, the residue was triturated with ether to give 10.50 g (75%) of the title compound as a light yellow solid. Recrystallization of a small sample from hot *n*-BuCl/EtOAc provided a pale yellow crystalline solid: mp 214–216 °C dec; ^{1}H NMR ($CDCl_3$) 1.25 (m, 2 H), 1.56 (m, 2 H), 2.52 (m, 1 H), 3.76 (s, 3 H), 5.40 (s, 2 H), 6.83 (d, J = 9 Hz, 2 H), 7.18 (d, J = 9 Hz, 2 H), 7.21 (d, J = 9 Hz, 1 H), 7.53 (dd, J = 2, 9 Hz, 1 H), 8.10 (d, J = 2 Hz, 1 H); FAB MS M + H = 341. Anal. ($C_{19}H_{17}N_2O_2Cl$) C, H, N.

Preparation of Arylacetylenes 8a–e. 8a was obtained commercially from Lancaster. **8b**[19] and **8c**[20] were prepared according to literature methods. **8d** and **8e** were prepared from the appropriate heteroaryl bromide and TMS–acetylene using the method of Yamanaka et al.[19] Due to their inherent instability and difficulty in storing these compounds, they were prepared as needed and used immediately as obtained from the reaction mixture. Products were characterized by NMR. **8d**: ^{1}H NMR ($CDCl_3$) 3.36 (s, 1 H), 8.55 (d, J = 2 Hz, 1 H), 8.57 (d, J = 2 Hz, 1 H), 8.73 (s, 1 H); yield 25%. **8e:** ^{1}H NMR ($CDCl_3$) 3.38 (s, 1 H), 8.82 (s, 2 H), 9.19 (s, 1 H); yield 30%.

General Procedure for the Addition of Arylacetylenes 8a–e to 7. 6-Chloro-4-cyclopropyl-3,4-dihydro-1-(4-methoxybenzyl)-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (9a). To a −78 °C solution of 10.89 g (105.63 mmol) of 2-ethynylpyridine (Lancaster) in 225 mL of anhydrous THF under a nitrogen atmosphere was added 42.25 mL (105.63 mmol) of 2.5 M *n*-BuLi in hexanes as a slow, steady stream. The reaction was stirred at −78 °C for 0.5 h and gradually became a pink-colored suspension. Separately, a suspension of 9.00 g (26.41 mmol) of **7** and 34.06 g (105.63 mmol) of magnesium triflate (Aldrich) in 225 mL of dry Et_2O was stirred vigorously at room temperature for 0.5 h. After 0.5 h, the cold anion suspension was added to the room temperature magnesium triflate/substrate complex as a steady stream via a jacketed addition funnel. The resulting suspension was stirred at ambient temperature until complete by TLC (1:1 hexanes/EtOAc). The reaction became more homogeneous over time and was essentially complete after 1 h. The crude reaction mixture was poured into 450 mL of 10% citric acid solution and the mixture diluted with 250 mL of Et_2O. The mixture was stirred vigorously at room temperature for 10 min, the layers were separated, and the aqueous layer was extracted with 2 × 250 mL of Et_2O. The combined Et_2O extracts were washed with 3 × 450 mL of H_2O and 400 mL of brine. The extracts were treated with anhydrous $MgSO_4$ and 7–8 scoops of Celite and were diluted with 250 mL of chloroform. The resulting suspension was stirred vigorously for 20 min and was filtered. The filtercake was washed with 300 mL of $CHCl_3$, and the combined filtrate was concentrated *in vacuo* to near dryness, at which point a precipitate began to form. The thick suspension was diluted with small portions of 4:1 Et_2O/hexanes and was filtered to give a dark tan solid. The solid was washed with small portions of Et_2O and hexanes and was dried *in vacuo* (crude wt 12–13 g). The solid was recrystallized by dissolving the crude product in 1300 mL of hot *n*-BuCl, and the hot solution was filtered and concentrated to ca. 400 mL. The slightly cloudy solution was covered and allowed to stand at ambient temperature for 18 h. The suspension was filtered to give title product as an off-white fluffy crystalline solid, mp 196.0–197.5 °C. A second crop of only slightly lower purity was obtained by concentration of the mother liquors to ca. 60 mL and allowing it to stand at room temperature. Overall yield of product was 9.10 g (78%): ^{1}H NMR ($CDCl_3$) 0.69 (m, 1 H), 0.80 (m, 1 H), 0.88 (m, 1 H), 1.02

(m, 1 H), 1.55 (m, 1 H), 3.74 (s, 3 H), 5.04 (d, J = 16 Hz, 1 H), 5.23 (d, J = 16 Hz, 1 H), 5.46 (s, 1 H), 6.89 (d, J = 4 Hz, 1 H), 6.80 (d, J = 5 Hz, 2 H), 7.14 (dd, J = 2, 8 Hz, 1 H), 7.22 (d, J = 8 Hz, 1 H), 7.27 (t, 1 H), 7.39 (d, J = 8 H, 1 H), 7.59 (d, J = 3 Hz, 1 H), 7.67 (t, 1 H), 8.59 (d, J = 3 Hz, 1 H); HRFABMS M + H calcd 444.147 879, obsd 444.147 537.

6-Chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (4aa). To a stirred suspension of 8.82 mg (0.22 mmol) of 60% sodium hydride in 2 mL of dry DMF under a nitrogen atmosphere was added a solution of 95.00 mg (0.21 mmol) of **9a** in 3 mL of dry DMF. After stirring at room temperature for 45 min, the reaction mixture was treated with 26.65 μL (0.43 mmol) of methyl iodide, and the solution was stirred at room temperature for 3 h. The reaction mixture was poured into 25 mL of cold 10% citric acid, and the mixture was stirred for 5 min. The mixture was extracted with 2 × 25 mL of EtOAc, and the combined extracts were washed with 2 × 25 mL of H_2O and 1 × 25 mL of brine. Drying (anhydrous $MgSO_4$) and concentration *in vacuo* provided 78 mg of a yellow oil. The oil was dissolved in a mixture of 1 mL of trifluoroacetic acid/1 mL of CH_2Cl_2, and the resulting solution was stirred at room temperature in an N_2 atmosphere overnight. The reaction was concentrated *in vacuo* at 30 °C, and the crude purple oil was placed on a vacuum pump for several hours. The oil was dissolved in 25 mL of $CHCl_3$, and the solution was washed with 2 × 15 mL of saturated $NaHCO_3$ solution and 1 × 15 mL of brine. Drying (anhydrous Na_2SO_4) and concentration *in vacuo* provided a dark oil. The oil was purified via flash chromatography over silica gel with 5% MeOH/$CHCl_3$ to give an off-white foam/glass. The foam was dissolved in 1 mL of Et_2O/EtOAc and was allowed to stand at room temperature. Crystallization occurred over ca. 1 h, and filtration of the suspension provided 39 mg (54%) of title compound as a white crystalline solid: mp 185.5-186.5 °C; ^{1}H NMR ($CDCl_3$) 0.36 (m, 1 H), 0.42 (m, 1 H), 0.76 (m, 1 H), 0.96 (m, 1 H), 1.47 (m, 1 H), 3.33 (s, 3 H), 6.70 (d, J = 9 Hz, 1 H), 7.20 (dd, J = 2, 9 Hz, 1 H), 7.32 (m, 1 H), 7.50 (d, J = 9 Hz, 1 H), 7.52 (s, 1 H), 7.72 (t, 1 H), 7.85 (s, 1 H), 8.64 (t, 1 H); HRFABMS M + H calcd 338.106015, found 338.104095. Anal. ($C_{19}H_{16}N_3OCl$·0.50H_2O·0.25 EtOAc) C, H, N.

Deprotection of 9a–e. 6-Chloro-4-cyclopyropyl-3,4-dihydro-4-[2-(2-pyridyl)ethyn-1-yl]quinazolin-2(1*H*)-one (4a). A solution of 70.00 mg (0.16 mmol) of **9a** in 3 mL of trifluoroacetic acid was stirred at room temperature in a nitrogen atmosphere for 96 h. The reaction was concentrated *in vacuo*, and the residue was placed on a vacuum pump for ca. 2 h. The resulting residue was dissolved in 20 mL of EtOAc, and the solution was washed with 2 × 10 mL of saturated $NaHCO_3$ solution and with 1 × 10 mL of brine. The EtOAc layer was dried (anhydrous $MgSO_4$) and concentrated *in vacuo* to give a clear oil. The oil was purified via flash chromatography over silica gel with 4% MeOH/$CHCl_3$ to provide the desired product as a clear glass. The glass was triturated with hexanes containing a little Et_2O and was filtered to provide 38 mg (73%) of product as a white amorphous solid which became a foam on heating: ^{1}H NMR ($CDCl_3$) 0.65 (m, 1 H), 0.81 (m, 1 H), 0.83 (m, 1 H), 0.97 (m, 1 H), 1.54 (m, 1 H), 5.85 (s, 1 H), 6.78 (d, J = 8 Hz, 1 H), 7.15 (dd, J = 2, 8 Hz, 1 H), 7.24 (m, 1 H), 7.39 (d, J = 8 Hz, 1 H), 7.52 (d, J = 2 Hz, 1 H), 7.63 (dd, J = 2, 8 Hz, 1 H), 8.58 (d, J = 4 Hz, 1 H), 9.13 (s, 1 H); HRFABMS M + H calcd 324.09036, obsd 324.09105. Anal. ($C_{18}H_{14}N_3ClO$·0.50H_2O) C, H, N.

6-Chloro-4-cyclopropyl-3,4-dihydro-4-ethynyl-1-(4-methoxybenzyl)quinazolin-2(1*H*)-one (10). A suspension of 5.00 g (14.67 mmol) of **7** and 14.19 g (44.01 mmol) of magnesium triflate (Aldrich) in 160 mL of dry Et_2O was stirred vigorously at room temperature in a nitrogen atmosphere for 30 min. Simultaneously, a solution of 4.32 g (44.01 mmol) of (trimethylsilyl)acetylene (Lancaster) in 130 mL of dry Et_2O was cooled to −78 °C and was treated dropwise with 17.60 mL (44.01 mmol) of 2.5 M *n*-BuLi in hexanes. The resulting solution was stirred at −78 °C for 30 min and was added dropwise to the previously prepared suspension (substrate/$Mg(OTf)_2$). The resulting suspension was stirred at room temperature for 18 h and was poured into 150 mL of cold 10% citric acid solution. The mixture was stirred vigorously for 20 min, and the layers separated. The aqueous layer was extracted with 2 × 150 mL of Et_2O, and the combined Et_2O extracts washed with 150 mL of H_2O and 150 mL of brine. Drying (anhydrous $MgSO_4$) and concentration *in vacuo* provided ca. 7 g of crude product as an oil. The oil was immediately dissolved in 200 mL of THF and was treated with 150 mL of 1 N KOH solution. The resulting mixture was stirred vigorously at room temperature for 30 min and was acidified to Ph ~3 with 3 N HCl. The mixture was extracted with 2 × 75 mL of Et_2O, and the combined Et_2O extracts were washed with 100 mL of H_2O and 100 mL of brine. Drying (anhydrous $MgSO_4$) and concentration *in vacuo* provided an oily yellow solid. The solid was triturated with Et_2O/hexane, and filtration provided an off-white solid. This solid was retrituated in a minimum of CH_3CN for 15–20 min. Filtration and drying gave 3.54 (66%) of title compound as a fluffy white solid: mp 170–172 °C; ^{1}H NMR ($CDCl_3$) 0.62 (m, 1 H), 0.66 (m, 1 H), 0.83 (m, 1 H), 0.86 (m, 1 H), 1.44 (m, 1 H), 2.52 (s, 1 H), 3.77 (s, 3 H), 5.05 (d, J = 16 Hz, 1 H), 5.17 (d, J = 16 Hz, 1 H), 5.34 (s, 1 H), 6.75 (d, J = 8 Hz, 2 H), 6.85 (d, J = 8 Hz, 2 H), 7.12 (dd, J = 2, 8 Hz, 1 H), 7.21 (d, J = 8 Hz, 2 H), 7.50 (s, 1 H). Anal. ($C_{21}H_{17}NO_2Cl$) C, H, N.

6-Chloro-4-cyclopropyl-3,4-dihydro-4-ethynylquinazolin-2(1*H*)-one (11). A solution of 1.40 g (4.11 mmol) of **10** in 5 mL of CH_2Cl_2 was treated with 10 mL of trifluoroacetic acid, and the resulting solution was stirred at room temperature in a nitrogen atmosphere overnight. The reaction was concentrated *in vacuo*, and the residue was dissolved in 50 mL of EtOAc. The EtOAc solution was washed with 20 mL of 5% aqueous $NaHCO_3$ solution, 20 mL of H_2O, and 20 mL of brine and was dried (anhydrous $MgSO_4$). Filtration and concentration *in vacuo* provided an oil. The oil was purified via flash chromatography over silica gel with 5% MeOH/$CHCl_3$ to give a white foam. The foam was dissolved in a minimum of Et_2O, and scratching provided 720 mg (80%) of the title compound as a white crystalline solid: mp 217–219 °C; ^{1}H NMR ($CDCl_3$) 0.61 (m, 1 H), 0.68 (m, 1 H), 0.76 (m, 1 H), 0.87 (m, 1 H), 1.43 (m, 1 H), 2.52 (s, 1 H), 5.56 (s, 1 H, 3-NH), 6.74 (d, J = 8 Hz, 1 H), 7.19 (dd, J = 1, 9 Hz, 1 H), 7.45 (s, 1 H), 8.59 (s, 1 H, 1-NH). Anal. ($C_{13}H_{11}N_2OCl$) C, H, N.

Palladium-Catalyzed Coupling of 11 with Aryl Halides. 6-Chloro-4-cyclopropyl-3,4-dihydro-4-[2-(2-pyrimidinyl)ethyn-1-yl]quinazolin-2(1*H*)-one (4f). A solution of 87.00 mg (0.35 mmol) of **11**, 111.00 mg (0.70 mmol) of 2-bromopyrimidine, and 13.00 mg (0.018 mmol; 5 mol %) of bis(triphenylphosphine)palladium dichloride in 0.75 mL of CH_3CN/0.75 mL of triethylamine was stirred at 80 °C in a sealed tube for 18 h. The solution was cooled and diluted with methanol, and the suspension was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give an oily orange solid. The crude product was purified via flash chromatography over silica gel with 5% MeOH/$CHCl_3$ to give a clear glassy solid. The solid was crystallized from Et_2O/$CHCl_3$ to give 75 mg (66%) of the product as a white crystalline solid: mp 259–261 °C dec; ^{1}H NMR ($CDCl_3$) 0.66 (m, 1 H), 0.81 (m, 2 H), 0.99 (m, 1 H), 1.53 (m, 1 H), 6.02 (s, 1 H, 3-NH), 6.88 (d, J = 8 Hz, 1 H), 7.17 (dd, J = 2, 8 Hz, 1 H), 7.33 (m, 1 H), 7.31 (s, 1 H), 8.75 (m, 2 H), 9.27 (s, 1 H, 1-NH); FABMS M + 1 = 325. Anal. ($C_{17}H_{13}N_4OCl$·0.85H_2O) C, H, N.

Resolution of 4a. To a stirred solution of 2.15 g (6.63 mmol) of **4a,** 4.31 g (19.90 mmol) of 1(*S*)-camphanic chloride (Aldrich), and 2.43 g (19.90 mmol) of 4-DMAP in 25 mL of CH_2Cl_2 in a nitrogen atmosphere was added 4.60 mL (33.10 mmol) of triethylamine. The resulting solution was stirred at room temperature for 24 h. The reaction was diluted with 400 mL of $CHCl_3$ and was washed with 150 mL of 1 M citric acid, 150 mL of H_2O, 150 mL of 10% Na_2CO_3 solution, and 150 mL of brine. Drying and concentration *in vacuo* provided a yellow foam. The foam was chromatographed on 500 g of silica gel with 2:1 hexanes/EtOAc. Two major products were recovered, each corresponding to a diastereomer of the dicamphanic imide. The less polar diastereomer fractions were combined and concentrated to provide 2.26 g (99%) of a white foam, **12a**. The more polar diastereomer fractions were combined and concentrated to provide 1.55 g (68%) of a white foam, **12b**. HPLC analysis of each diastereomer indicated that they were pure and free of any of the other diastereomer. A 100-mg

sample of **12b** was crystallized from methanol to give 80 mg of a white crystalline solid, mp 185–186 °C. Anal. ($C_{38}H_{38}N_3O_7Cl$) C, H, N. Single-crystal X-ray analysis of this material indicated that the configuration at C4 of the quinazolinone ring was *R*.[18]

The camphanates were removed stepwise in the following manner. A solution of 2.16 g (3.16 mmol) of **12a** in 20 mL of 1,2-dimethoxyethane was treated with 6.60 mL (6.60 mmol) of 1 M LiOH solution. The suspension was stirred at room temperature for 45 min and was concentrated *in vacuo* to remove solvent. The residue was extracted with 2 × 40 mL of EtOAc. The combined EtOAc extracts were washed with 30 mL of H_2O and 30 mL of brine, dried (anhydrous $MgSO_4$), and concentrated *in vacuo* to give 1.33 g of a white foam. The foam was dissolved in 15 mL of methanol and was treated with 376 mg (1.98 mmol) of *p*-toluenesulfonic acid. The resulting solution was stirred at reflux for 48 h, at which point HPLC indicated that ca. 7% of the starting material remained. The reaction was treated with an additional 95 mg (0.50 mmol) of *p*-toluenesulfonic acid, and the refluxing continued for an additional 24 h. The reaction was concentrated to dryness *in vacuo*, and the residue was partitioned between 100 mL of EtOAc and 80 mL of cold 10% Na_2CO_3 solution. The aqueous layer was reextracted with 50 mL of EtOAc, and the combined organic extracts were washed with 75 mL of 10% Na_2CO_3 solution and 75 mL of brine. Drying (anhydrous $MgSO_4$) and concentration *in vacuo* gave a dark oil which was chromatographed over silica gel with 96:4 EtOAc/2-PrOH to give 765 mg of a white foam. The foam was dissolved in 25 mL of hot EtOAc on a steam bath and was treated with three 25-mL portions of cyclohexane with heating applied after each addition. The solution was allowed to cool overnight with stirring. Filtration and drying provided 725 mg (75% based on dicamphanate) of the pure (−)-4(*S*) enantiomer (**13a**) as a white crystalline solid: mp 130–131 °C; $[\alpha]_D = -103°$ (c = 0.195 in $CHCl_3$); ^1H NMR ($CDCl_3$) 0.64 (m, 1 H), 0.81 (m, 1 H), 0.85 (m, 1 H), 0.99 (m, 1 H), 1.55 (m, 1 H), 5.61 (s, 1 H, 3-NH), 6.77 (d, *J* = 9 Hz, 1 H), 7.20 (dd, *J* = 2, 9 Hz, 1 H), 7.31 (m, 1 H), 7.43 (d, *J* = 9 Hz, 1 H), 7.55 (d, *J* = 2 Hz, 1 H), 7.74 (m, 1 H), 8.26 (d, *J* = 2 Hz, 1 H), 8.82 (s, 1 H, 1-NH); HPLC purity = 99.9% at 210 nm; Chiral HPLC purity = 99.7% at 254 nm. Anal. ($C_{18}H_{14}N_3ClO{\cdot}0.30H_2O{\cdot}0.30EtOAc$) C, H, N. The material can be converted to its monohydrate form by stirring in H_2O for 18 h, filtration, and drying *in vacuo*: mp (monohydrate) 112–113 °C dec. Anal. ($C_{18}H_{14}N_3OCl{\cdot}H_2O$) C, H, N.

An identical procedure performed on 204.00 mg (0.30 mmol) of the more polar dicamphanate diastereomer **12b** provided (after lyophilization from 1,4-dioxane) 25 mg (37%) of the (+)-4(*R*) enantiomer **13b** as an amorphous solid: $[\alpha]_D = +102°$ (*c* = 0.195 in $CHCl_3$); ^1H NMR ($CDCl_3$) 0.66 (m, 1 H), 0.84 (m, 2 H), 1.02 (m, 1 H), 1.56 (m, 1 H), 5.78 (s, 1 H, 3-NH), 6.79 (d, *J* = 9 Hz, 1 H), 7.28 (m, 2 H), 7.36 (dt, 1 H), 7.65 (dd, *J* = 2, 9 Hz, 1 H), 7.66 (s, 1 H), 8.26 (s, 1 H, 1-NH), 8.59 (m, 1 H); HPLC purity = 99% at 210/254 nm; Chiral HPLC purity = 99.8% at 254 nm; FABMS M + 1 = 324. Anal. ($C_{18}H_{14}N_3ClO{\cdot}0.30H_2O{\cdot}0.25$ dioxane) C, H, N.

X-ray Crystallography. Colorless crystals of **12b** were grown from ethanol by evaporation. The crystal chosen for data collection (approximate dimensions 0.18 × 0.11 × 0.32 mm) was mounted in a nonspecific orientation on a Rigaku AFC5 diffractometer supplied with a rotating anode generator. The crystal data and experimental conditions are as follows: formula = $C_{38}H_{38}ClN_3O_7$, M_r = 684.20, orthorhombic space group $P2_12_12_1$, a = 15.996(1) Å, b = 16.313(1) Å, c = 13.845(1) Å, V = 3612.8 Å^3, Z = 4, D_{calc} = 1.258 g cm^{-3}, μ(Cu Kα) = 1.35 mm^{-1}, $F(000)$ = 1440, T = 296 K. Data were collected with[21] Cu Kα monochromatized radiation (λ = 1.541 84 Å) to a 2θ limit of 142° yielding 3665 measured reflections. Scan type was $\omega-2\theta$ with a range of 1.15 + 0.14 tan (θ)° and a variable speed of 1 to 32 deg min^{-1}. The data set was corrected for Lorentz, polarization, and background effects. Monitoring standard reflections (3 every 400 reflections) showed no decay correction necessary. Of the 3665 reflections measured there are 1375 observed data at the $I \geq 3\sigma(I)$ level. The data were corrected for absorption effects using the DIFABS[22] procedure. Structure was solved using SHELXS-86[23] and refined[24] using full-matrix least-squares on F with a weighting scheme of $1/\sigma^2(F)$. The final agreement statistics for 262 variables, are R = 0.069, R_w = 0.061, S = 2.29, $(\Delta/\sigma)_{max}$ = 0.02. There is no structural significance to the maximum peak (0.28(6) e Å^{-3}) in a final difference Fourier.

Tables of crystallographic coordinates, thermal parameters, and geometrical quantities are included in the supplementary material.

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Supplementary Material Available: 400-MHz NMR spectrum of **9a**, tables of selected interatomic angles, selected interatomic distances, and positional and thermal parameters of **12b**, and an ORTEP diagram of **12b** (11 pages). Ordering information is given on any current masthead page.

References

(1) Mitsuya, H.; Yarchoan, R.; Broder, S. Molecular Targets for AIDS Therapy. *Science* **1990**, *249*, 1533–1544.
(2) (a) Fischl, M. A.; et al. The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex. *N. Engl. J. Med.* **1987**, *317*, 185–191. (b) Lambert, J. S.; Seidlin, M.; Reichman, R. C.; Plank, C. S.; Laverty, M.; Morse, G. D.; Knupp, C.; McLaren, C.; Pettinelli, C.; Valentine, F. T.; Dolin, R. 2′,3′-Dideoxyinosine (ddI) in Patients With the Acquired Immunodeficiency Syndrome or AIDS-Related Complex. *N. Engl. J. Med.* **1990**, *322*, 1333–1345.
(3) Richman, D. D.; Fischl, M. A.; Grieco, M. H.; Gattlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Hirsch, M. S.; Jackson, G. G.; Durack, D. T.; Nusinoff-Lehrman, S.; and the AZT Collaborative Working Group. The Toxicity of Azidothymidine (AZT) in the Treatment of Patients With AIDS and AIDS-related Complex. *N. Engl. J. Med.* **1987**, *317*, 192–197.
(4) Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M. J.; Bresdin, H. J.; Raemaekers, A.; Von Gelder, J.; Woestenborghs, R.; Heyrants, J.; Schellekens, K.; Janssen, M. A. C.; De Clerq, E.; Janssen, P. A. J. Potent and Selective Inhibition of HIV-1 Replication in Vitro by a Novel Series of TIBO Derivatives. *Nature* **1990**, *343*, 470–474.
(5) (a) Saari, W. S.; Hoffman, J. M.; Wai, J. S.; Fisher, T. E.; Rooney, C. S.; Smith, A. M.; Thomas, C. M.; Goldman, M. E.; O'Brien, J. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Stern, A. M.; Anderson, P. S. 2-Pyridone Derivatives: A New Class of Nonnucleoside, HIV-1 Specific Reverse Transcriptase Inhibitors. *J. Med. Chem.* **1991**, *34*, 2922–2925. (b) Wai, J. S.; Williams, T. A.; Bamberger, D. L.; Fisher, T. E.; Hoffman, J. M.; Hudcosky, R. J.; MacTough, S. C.; Rooney, C. S.; Saari, W. S.; Thomas, C. M.; Goldman, M. E.; O'Brien, J. A.; Emini, E. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Anderson, P. S. Synthesis and Evaluation of 2-Pyridone Derivatives as Specific HIV-1 Reverse Transcriptase Inhibitors. 3. Pyridyl and Phenyl analogs of 3-aminopyridin-2(1H)one. *J. Med. Chem.* **1993**, *36*, 249–255.
(6) Merluzzi, V. J.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shih, C.-K.; Eckner, K.; Hattox, S.; Adams, J.; Rosenthal, A. S.; Faanes, R.; Eckner, R. J.; Koup, R. A.; Sullivan, J. L. Inhibition of HIV-1 Replication by a Nonnucleoside Reverse Transcriptase Inhibitor. *Science* **1990**, *250*, 1411–1413.
(7) Tanaka, H.; Baba, M.; Saito, S.; Miyasaka, T.; Takashima, H.; Sekiya, K.; Ubasawa, M.; Nitta, I.; Walker, R. T.; Nakashima, H.; De Clercq, E. Specific Anti-HIV-1"Acyclonucleosides" Which Cannot be Phosphorylated: Synthesis of Some Deoxy Analogues of 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-thymine. *J. Med. Chem.* **1991**, *34*, 1508–1511.
(8) Romero, D. L.; Busso, M.; Tan, C.-K.; Reusser, F.; Palmer, J. R.; Poppe, S. M.; Aristoff, P. A.; Downey, K. M.; So, A. G.; Resnick, L.; Tarpley, W. G. Nonnucleoside Reverse Transcriptase Inhibitors That Potently and Specifically Block Human Immunodeficiency Virus Type 1 Replication. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8806–8810.
(9) Terrett, N. K.; Bojanic, D.; Merson, J. R.; Stephenson, P. T. Imidazo [2′,3′:6,5] Dipyrido [3,2-b:2′,3-e]-1,4-diazepines: Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors with Greater Enzyme Affinity than Nevirapine. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1745–1750.

(10) Britcher, S. F.; Goldman, M. E.; Huff, J. R.; Lumma, W. C.; Lyle, T. A.; Payne, L. S.; Quesada, M. L.; Sanders, W. M.; Sanderson, P. E.; Tucker, T. J.; Young, S. D. Eur. Pat. Appl. EP-A-0 530994, 1992.

(11) (a) Sanders, W. M.; Anderson, P. S.; Britcher, S. E.; Emini, E. A.; Goldman, M. E.; Huff, J. R.; Lumma, W. C.; Lyle, T. A.; O'Brien, J. A.; Olsen, D. B.; Payne, L. S.; Pettibone, D. J.; Quintero, J. C.; Sanderson, P. E. J.; Schleif, W. A.; Thomas, C. M.; Tran, L. P.; Tucker, T. J.; Wiscount, C. M.; Young, S. D. Development of Quinazolinones as HIV-1 Reverse Transcriptase Inhibitors. Presented at 27th American Chemical Society Middle Atlantic Regional Meeting, Hofstra University, Hempstead, NY, June 2–4, 1993. (b) Lyle, T. A.; Young, S. D.; Anderson, P. S.; Balani, S. K.; Britcher, S. F.; Emini, E. A.; Goldman, M. E.; Homnick, C. F.; Huff, J. R.; Lumma, W. C.; O'Brien, J. A.; Payne, L. S.; Pettibone, D. J.; Quintero, J. C.; Sanders, W. M.; Schleif, W. A.; Smith, S. J.; Theoharides, A. M.; Tran, L. O.; Tucker, T. J.; Wiscount, C. M. Structure-Activity Studies of Novel Inhibitors of HIV-1 Reverse Transcriptase. Presented at the 206th American Chemical Society National Meeting, Chicago, IL, August 1993.

(12) Nickson, T. E.; Roche-Dolson, C. A. A Convenient Procedure for the Chlorination of Deactivated Anilines. *Synthesis* **1985**, 669–670.

(13) Sonogashira, K.; Tohda, Y.; Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes, and Bromopyridines. *Tetrahedron Lett.* **1975**, 4467–4470.

(14) Goldman, M. E.; Salituro, G. S.; Bowen, J. A.; Williamson, J. M.; Zink, D. L.; Schleif, W. A.; Emini, E. A. Inhibition of Human Immunodeficiency Virus-1 Reverse Transcriptase Activity by Rubromycins: Competetive Interaction at the Template-Primer Site. *Mol. Pharmacol.* **1990**, *38*, 20–25.

(15) Verkruijsse, H. D.; Keegstra, M. A.; Brandsma, L. A High-Yield Preparative Scale Method for 2-Bromofuran. *Synth. Commun.* **1989**, *19*, 1047–1049.

(16) Goldman, M. E.; Nunberg, J. H.; O'Brien, J. A.; Quintero, J. C.; Schleif, W. A.; Freund, K. F.; Gaul, S. L.; Saari, W. S.; Wai, J. S.; Hoffman, J. M.; Anderson, P. A.; Hupe, D. J.; Emini, E. A. Pyridinone Derivatives: Specific HIV-1 RT inhibitors with Antiviral Activity. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 6863–6867.

(17) Details of the pharmacology of these compounds were presented at the Keystone Symposium on the Prevention and Treatment of AIDS, Hilton Head Island, SC, January 23–30, 1994.

(18) See Supplementary Material for Details of X-Ray Crystal Analysis of **12b**.

(19) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. A Facile Synthesis of Ethynyl-Substituted Six Membered *N*-heteroaromatic Compounds. *Synthesis* **1983**, 312–314.

(20) Suffert, J.; Ziessel, R. Towards Molecular Electronics: A New Family of Aromatic Polyimine Chelates Substituted with Alkyne Groups. *Tetrahedron Lett.* **1991**, *32*, 757–760.

(21) The diffractometer control programs are those supplied by Rigaku and Molecular Structure Corp. for operating the diffractometer.

(22) Walker, N.; Stuart, D. An Empirical Method for Correcting Diffractometer Data for Absorbtion Effects. *Acta Crystallogr.* **1983**, *A39*, 158–166.

(23) Sheldrick, G. M. SHELXS-86. In *Crystallograpic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press: Oxford, 1985; pp 175–189.

(24) *Structure Determination Package Version 3*; Enraf-Nonius: Delft, The Netherlands, 1985. Implemented on a Sun Microsystems workstation.