8 potassium phosphate buffer was added 90 mg (0.18 mmol) of **2a** (or **2b**) under strict anaerobic conditions. The reaction mixture was then stirred for 10 min at room temperature. After this time, the reaction was opened to the air and made basic (pH ~10) with KOH. The brick-red potassium salt of **1d** crystallized from solution upon chilling, yield 50 mg (94%). The salt was dissolved in 2 mL of water containing 2 drops of concentrated HCl, chilling of this solution afforded **1d** as a yellow crystalline solid: mp >300 °C dec; TLC (1-butanol, acetic acid, water [5:2:3]) R_f = 0.29; ^{1}H NMR (Me_2SO-d_6) δ 3.87 (3 H, s, N(3)-methyl), 2.46 and 2.42 (6 H, 2 s, 2- and 6-methyls, no assignments made); IR (KBr) 3450, 3280, 2946, 2923, 1700, 1566, 1470, 1125, 1041 cm^{-1}.

Conversion of **1d** to the hydroquinone dihydrobromide **2d**·2HBr was carried out using the procedure for the preparation of **12**. Physical properties of **2d**·2HBr are as follows: mp 299–301 °C; ^{1}H NMR (Me_2SO-d_6) δ 4.12 (3 H, s, N(3)-methyl), 2.77 and 2.45 (6 H, 2 s, 2- and 6-methyls, no assignment made); mass spectrum (EI mode), m/z 260 (P^+). Anal. Calcd for $C_{12}H_{12}N_4O_3$·2HBr·0.5H_2O: C, 33.43; H, 3.51; N, 12.99. Found: C, 33.33; H, 3.41; N, 12.00.

Benzaldehyde Trappings Products of 3. To 60 mL of methanol-d_1, buffered with 4.3 × 10^{-2} M trisma (50:50, base and HCl salt) and containing 4.5 mL of benzaldehyde, was added 37 mg (0.074 mmol) of **2a** (or **2b**) under strict anaerobic conditions. The mixture was stirred at room temperature for 1 h and then opened to the air. Evaporation in vacuo to a solid residue was followed by extraction of the residue with 2 × 5 mL of chloroform. The chloroform extracts were evaporated to a small volume (~1 mL) and diluted with hexane, which resulted in precipitation of an orange solid. Mass spectral studies (EI mode) and ion intensity plots showed the solid to be **19** (m/z 348 (P^+ + 2)), with a trace amount of **18** (362 (P^+ + 2)). The P^+ + 2 peaks are the result of quinone to hydroquinone reduction by the solvent used to introduce the sample on the probe.

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Convergent and Efficient Palladium-Effected Synthesis of 5,10-Dideaza-5,6,7,8-tetrahydrofolic Acid (DDATHF)

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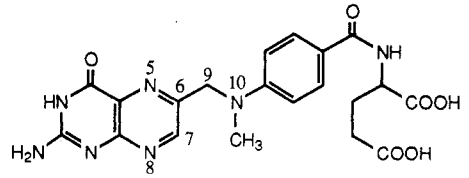
A new nine-step synthesis of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid, an extraordinarily active and selective antitumor agent now in preclinical trial, is described which utilizes two successive palladium-catalyzed carbon–carbon coupling reactions to form the C_6–C_7 and C_{10}–aryl bonds.

Methotrexate (1) has a long and distinguished history as an antineoplastic and immunosuppressive drug, but its extreme toxicity severely limits its clinical effectiveness. Methotrexate is an inhibitor of dihydrofolate reductase, which plays a critical role in many different phases of mammalian metabolism. Attempts to discern significant differences between dihydrofolate reductases derived from tumors, bacteria, and normal mammalian cells have not been rewarding, with the consequence that methotrexate, as well as all other dihydrofolate reductase inhibitors currently used clinically, are nonselective in their cytotoxicity.[1] Several years ago we reported the synthesis and preliminary biological evaluation of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, **2**), the lead compound of a new class of folate antagonists designed to be inhibitors of folate metabolism at sites other than dihydrofolate reductase.[2-4] For reasons which have been fully documented elsewhere,[5] our target was glycinamide ribonucleotide transformylase, which mediates the first formyl transfer step in the de novo purine biosynthetic pathway and which utilizes 10-formyl-5,6,7,8-tetrahydrofolic acid as its cofactor. In the event, DDATHF has been shown to possess extraordinary and selective antitumor activity; indeed, both its therapeutic index and its broad spectrum of activity against solid tumors are unrivaled among known antitumor agents.[3-10] Since DDATHF is not a DHFR inhibitor, it is fully active against tumors which have developed resistance to DHFR inhibitors such as methotrexate. DDATHF is now in preclinical trial.



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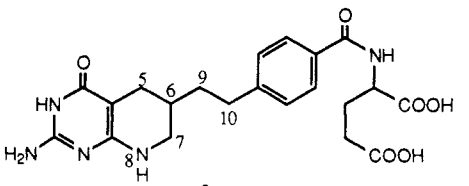

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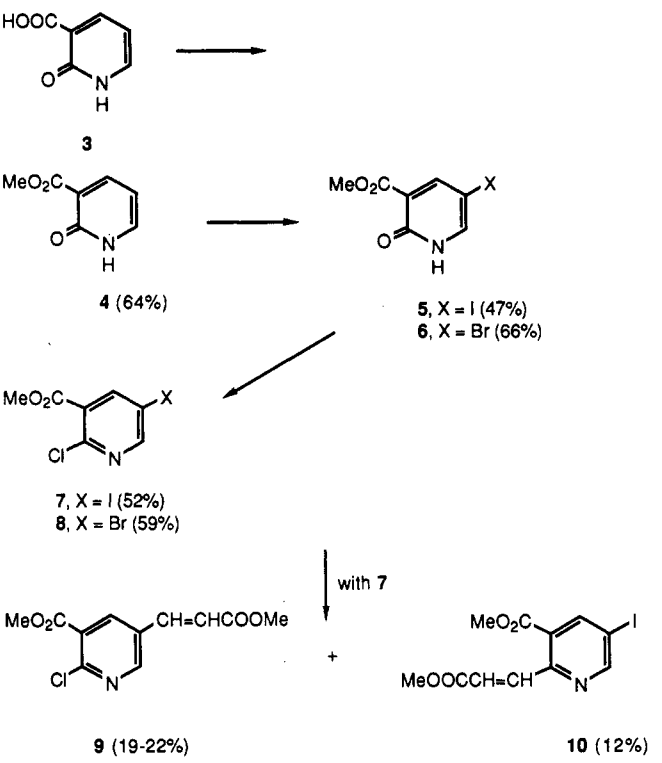
Our original synthesis of DDATHF was a nonconvergent one which commenced with cyanothioacetamide and progressed stepwise through construction of the pyridine ring, attachment of the benzoic acid moiety through a Wittig olefin synthesis, annulation of the pyrimidine ring, introduction of the peptide linkage, reduction to the tetrahydropyridine stage, adjustment of substituents, and final removal of protecting groups.[2] Considering its length (18 steps), this is a remarkably efficient synthesis, but at the same time it does not allow for convenient chemical modification of the basic DDATHF skeleton, and many of the individual steps are not amenable to scaleup. The extraordinary promise of DDATHF as a potential clinical antitumor agent clearly necessitated a new synthesis which at the same time should allow for the preparation of congeners and analogues.[11]

We report in this paper details of an efficient and convergent *nine-step* synthesis of DDATHF. The key feature of this new methodology is a double exploitation of a palladium-catalyzed carbon–carbon bond coupling reaction to form the C_6–C_9 and C_{10}–aryl bonds. The evolution of this new synthesis was as follows:

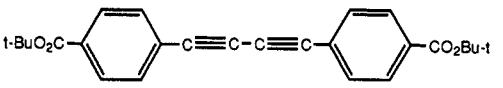
Methyl 2-chloro-5-iodo-3-pyridinecarboxylate (**7**)[12] appeared to be an attractive intermediate with which to explore the concept of attaching carbon chains at position 5 of a pyridine ring suitably functionalized for eventual annulation of the required pyrimidine ring. An improved synthesis of this material was first developed from commercially available 2-hydroxynicotinic acid (**3**) by esterification to **4** and subsequent iodination with *N*-iodosuccinimide in refluxing methylene chloride to give **5**. The 2-chloro derivative **7** was then prepared most effectively from **5** with a mixture of phosphorus oxychloride and DMF in methylene chloride at room temperature. Utilization of this sequence of reactions gave multigram quantities of **7** with an overall yield of 25–30%. The corresponding 5-bromo derivative **8** was prepared in analogous fashion. However, palladium-catalyzed C–C coupling reactions[13] with these substrates were disappointing. Treatment of **7** with an excess of methyl acrylate in DMF in the presence of catalytic amounts of bis(triphenylphosphine)–palladium acetate at 120–130 °C led to a mixture of products derived from competitive substitution of the iodine grouping at position 5 (giving compound **9**) and chlorine substitution at position 2 (giving compound **10**) (Scheme I).

Although exclusive formation of **9** could be achieved when the reaction was carried out at lower temperatures, the very low yields encouraged us to examine the utilization of acetylenes rather than olefins in this coupling reaction. Accordingly, **7** was treated with (trimethylsilyl)-acetylene in diethylamine as solvent, in the presence of bis(triphenylphosphine)–palladium chloride and cuprous iodide as catalyst, leading to the coupled product **11** (in

Scheme I



which, however, displacement of the 2-chloro substituent by diethylamine had taken place) in 68% yield (Scheme II). An analogous carbon–carbon bond coupling reaction could be achieved by using *tert*-butyl 4-ethynylbenzoate (itself prepared by palladium-catalyzed coupling of *tert*-butyl 4-bromobenzoate with (trimethylsilyl)acetylene) in refluxing triethylamine, leading to the coupled product **12** (no displacement of the 2-chloro group) in 45–65% yield. An attempt to carry out this coupling reaction with the bromo derivative **8**, however, led only to the acetylene dimer **13**.



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Compound **12** now contains all of the necessary functionality both for annulation of the pyrimidine ring and for formation of the requisite L-glutamic acid peptide bond. Cyclization of **12** with guanidine in refluxing *tert*-butyl alcohol gave the desired 5-deazapterin **14** in 44% yield, and the *tert*-butyl group was then removed with gaseous HCl in nitromethane to give **15**. The extraordinary insolubility of **15**, however, proved to be a major frustration. We were unable to obtain satisfactory microanalytical data for **14** and **15**, which were completely recalcitrant toward recrystallization or other means of purification. Attempted peptide coupling in *N*-methylpyrrolidone with phenyl *N*-phenylphosphoramidochloridate was unsuccessful. An attempt to solubilize **15** by conversion into its 2-pivaloyl derivative **16** by refluxing pivalic anhydride in the presence of 4-(dimethylamino)pyridine was also frustrated by its poor solubility. An attempt to reverse the above order of steps and pivaloylate the 2-amino group in **14** to give **17** was likewise unsuccessful; **14** was recovered unchanged upon attempted pivaloylation.

However, we successfully prepared the pivaloylated *tert*-butyl ester **17** by palladium-catalyzed coupling of *tert*-butyl 4-ethynylbenzoate with 2-pivaloyl-6-bromo-5-

(11) Two further syntheses of DDATHF have recently been described that constitute modifications of our originally described Wittig strategy; these involve condensation of 2-acetyl-6-formyl-5-deazapterin or of 6-formyl-2,4-diamino-5-deazapteridine with the Wittig reagents derived from diethyl [4-(bromomethyl)benzoyl]glutamate or methyl 4-(bromomethyl)benzoate, respectively (Boschelli, D. H.; Webber, S.; Whiteley, J. M.; Oronsky, A. L.; Kerwar, S. S. *Arch. Biochem. Biophys.* **1988**, *265*, 43. Piper, J. R.; McCaleb, G. S.; Montgomery, J. A.; Kisliuk, R. L.; Gaumont, Y.; Thorndike, J.; Sirotnak, F. M. *J. Med. Chem.* **1988**, *31*, 2164). We have also recently described a Diels–Alder route to DDATHF (Taylor, E. C.; Harrington, P. M.; Warner, J. C. *Heterocycles* **1988**, *27*, 1925).

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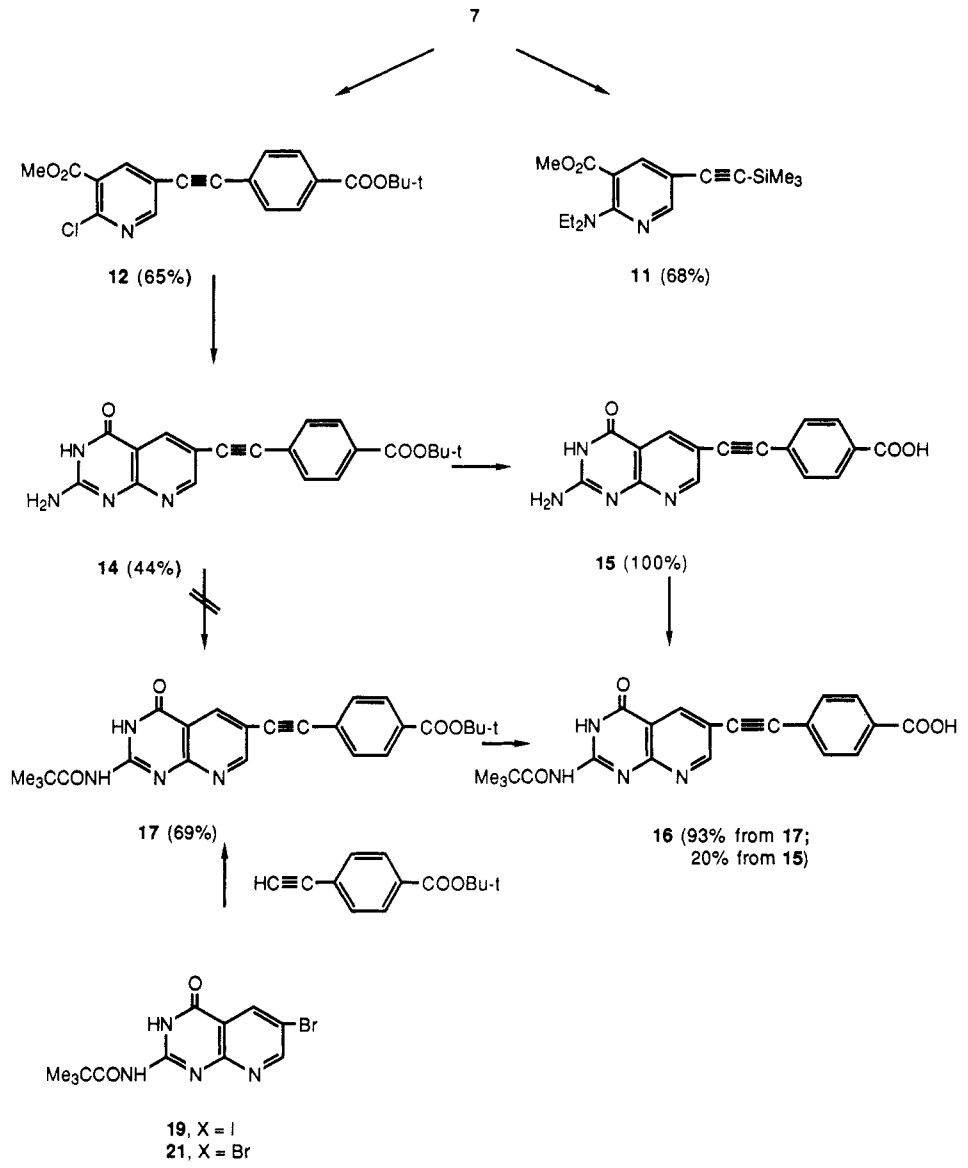
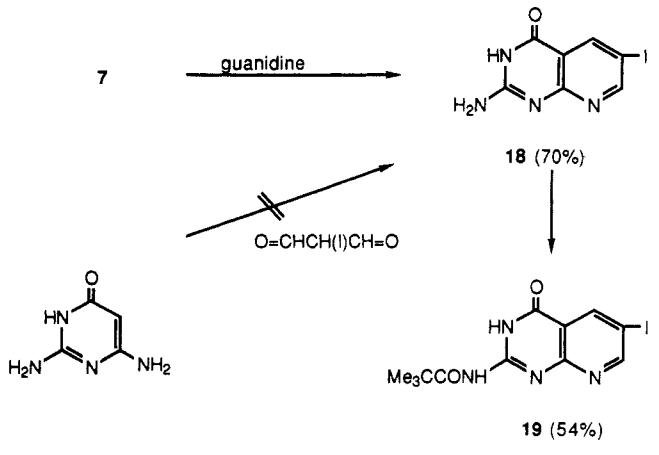
(13) For representative examples of palladium-catalyzed C–C coupling reactions of halo-substituted pyridines or condensed pyridines, see: (a) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312. (b) Sakamoto, T.; Kondo, Y.; Watanabe, R.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2719. (c) Taylor, E. C.; Yoon, C.-m. *Synth. Commun.* **1988**, *18*, 1187.

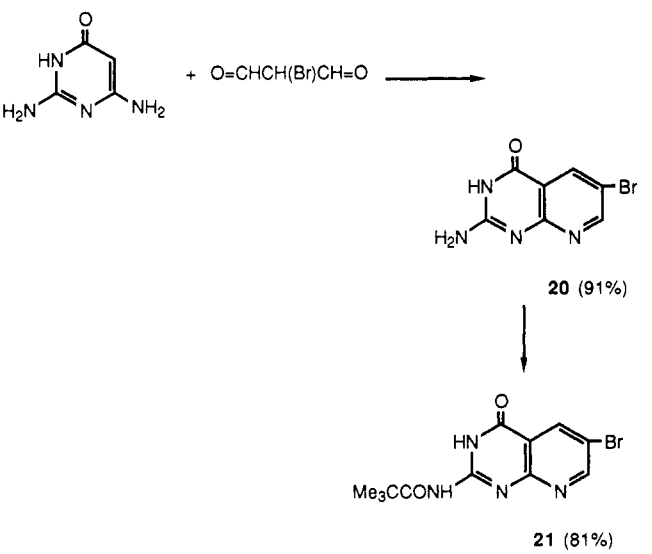
Scheme II



Scheme III



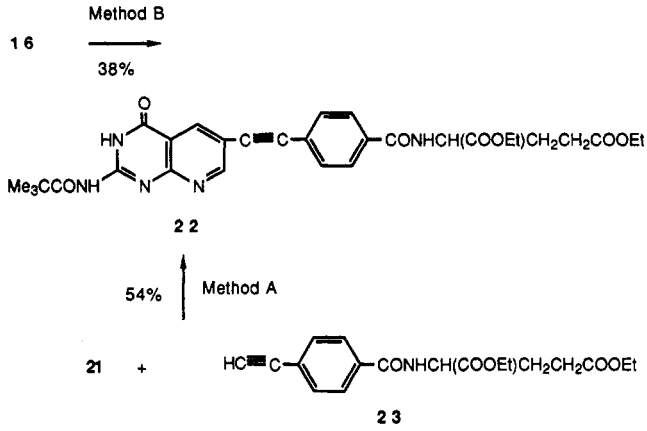
Scheme IV[a]



[a] See ref 13c.

deazapterin (**21**)[13c] or with the corresponding 6-iodo derivative **19**. The latter intermediate was readily prepared by guanidine cyclization of 2-chloro-3-carbomethoxy-5-iodopyridine (**7**) to give 6-iodo-5-deazapterin (**18**) followed by pivaloylation with pivalic anhydride/4-(dimethylamino)pyridine [the greater solubility of **18** compared with **14** or **15**, vide supra, is probably responsible for the success of this transformation]. An attempt to synthesize **18** directly from iodomalonaldehyde and 2,4-diamino-6-

Scheme V



hydroxypyrimidine was not successful. By contrast, condensation of 2,4-diamino-6-hydroxypyrimidine with bromomalonaldehyde proceeds smoothly to give **20**, which is readily pivaloylated under normal conditions to give **21** in excellent overall yield[13c] (Schemes III and IV). Our desired intermediate **16** for the peptide coupling step was finally prepared in good yield by removal of the *tert*-butyl ester grouping in **17** with gaseous hydrochloric acid in nitromethane.

As anticipated, compound **16**, in contrast to its nonpivaloylated precursor **15**, proved to be readily amenable to peptide coupling, which was accomplished in *N*-methylpyrrolidone as solvent with phenyl *N*-phenylphosphoramidochloridate as the coupling agent. Although DDATHF precursor **22** could thus be obtained in yields which varied from 26 to 38%, it could be obtained alternatively and in better yield by palladium-catalyzed coupling of **21** with diethyl 4-(ethynylbenzoyl)glutamate (**23**), which itself was prepared in two steps from *tert*-butyl 4-ethynylbenzoate (hydrolysis with trifluoroacetic acid followed by peptide coupling) (Scheme V).

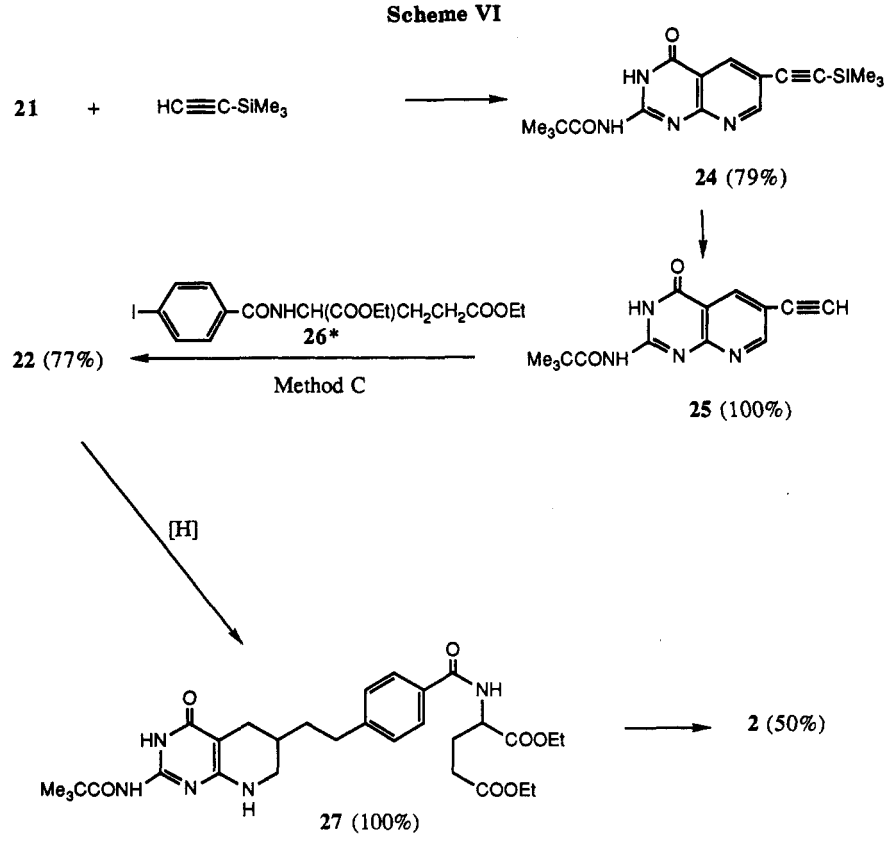
While the above synthetic reactions leading to intermediate **22** were under way, we were simultaneously investigating a reverse strategy for its preparation involving coupling of (trimethylsilyl)acetylene with 2-pivaloyl-6-bromo-5-deazapterin (**21**), followed by a second palladium-catalyzed coupling with diethyl [4-iodo(or bromo)benzoyl]glutamate. In the event, this "inverse" approach proved to be the synthetic method of choice. Thus, **21** was coupled with (trimethylsilyl)acetylene, and the coupled product **24** was desilylated with tetrabutylammonium fluoride to give 2-pivaloyl-6-ethynyl-5-deazapterin (**25**). A second palladium-catalyzed coupling with diethyl (4-iodobenzoyl)glutamate (**26**) then gave intermediate **22** in an improved yield of 77%. DDATHF was then readily prepared from **22** by catalytic reduction with palladium-on-carbon in TFA to give **27**, followed by careful hydrolysis of the 2-pivaloyl and glutamate ester groups (Scheme VI).

DDATHF was isolated as a 50:50 mixture of two diastereomers (as a consequence of the chiral center introduced at C-6 through reduction of the pyridine ring). We have described elsewhere the separation of these diastereomers (termed isomer A and isomer B) by means of their camphor-D-sulfonic acid salts and a comparison of their biochemical and pharmacological properties.[3,4] Studies are currently under way to determine their absolute configuration and to devise a chiral synthesis of isomer B, which has been selected for preclinical trial.

Experimental Section[14]

Methyl 2-Oxo-1,2-dihydro-3-pyridinecarboxylate (4). A

Scheme VI



*Prepared in 75% yield from diethyl glutamate hydrochloride and 4-iodobenzoyl chloride.

mixture containing 27.8 g (0.20 mol) of 1,2-dihydro-2-oxo-3-pyridinecarboxylic acid (2-hydroxynicotinic acid), 3.0 mL of concentrated H_2SO_4 in 500 mL of CH_3OH, and 300 mL of benzene was heated under reflux for 2.5 h. A Dean–Stark trap was then attached, and the azeotrope collected was removed periodically in 25-mL fractions over a period of 28 h. The remaining solvent was removed by evaporation under reduced pressure, and the solid residue was suspended in 500 mL of cold water. The suspension was filtered, and the filtrate was continuously extracted with methylene chloride. The extracts were concentrated under reduced pressure to yield 4 as a white solid, which, upon recrystallization from 1.4 L of benzene, yielded 19.5 g (64%) of methyl ester 4: mp 148–151 °C (lit.[15] mp 142–143 °C); NMR (DMSO-d_6, 80 MHz) δ 3.72 (s, 3 H), 6.25 (dd, 1 H, J = 7.1 Hz, J = 6.3 Hz), 7.64 (dd, 1 H, J = 6.3 Hz, J = 2.2 Hz), 8.03 (dd, 1 H, J = 7.1 Hz, J = 2.2 Hz).

Methyl 5-Iodo-2-oxo-1,2-dihydro-3-pyridinecarboxylate (5). A solution containing 19.5 g (0.13 mol) of **4** and 36.2 g (0.17 mol) of *N*-iodosuccinimide in 500 mL of anhydrous CH_2Cl_2 was heated at reflux under N_2 in the dark for 48 h. The reaction mixture was concentrated to 150 mL under reduced pressure, and the solid which formed was collected by filtration and washed with small portions of cold CH_2Cl_2 and benzene to give 16.6 g (47%) of **5** as a pale yellowish solid. This material was sufficiently pure for the next reaction; its properties upon recrystallization from ethyl acetate are as follows: mp 190 °C; IR (KBr) 2500–3050 (br), 1725, 1630, 1585, 1475, 1425, 1320, 1260, 1235, 1180, 1150, 1105, 1065, 965, 875, and 800 cm^{-1}; NMR (DMSO-d_6, 300 MHz) δ 3.71 (s, 3 H), 7.93 (d, 1 H, J = 2.26 Hz), 8.10 (d, 1 H, J = 2.26 Hz); MS (279, M^+) 247, 127, and 93. Anal. Calcd for $C_7H_6INO_3$: C, 30.13; H, 2.17; I, 45.48; N, 5.02. Found: C, 30.24; H, 2.22; I, 45.55; N, 4.87.

The filtrate was evaporated, and the residue was dissolved in 500 mL of CH_2Cl_2. The organic solution was extracted with 10% sodium thiosulfate solution, washed with a saturated NaCl solution, and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure, and the residue was triturated with ethyl acetate and filtered to yield an additional 5.49 g (15%) of **5**.

Methyl 5-Bromo-2-oxo-1,2-dihydro-3-pyridinecarboxylate (6). This compound was similarly prepared, as described above, from **4** and *N*-bromosuccinimide in 66% yield: mp 181–182 °C; IR (KBr) 2500–3200 (broad), 1735, 1700, 1665, 1595, 1545, 1480, 1440, 1370, 1190, 1160, 1120, 970, 900, and 800 cm^{-1}; NMR (DMSO-d_6, 300 MHz) δ 3.72 (s, 3 H), 7.97 (d, 1 H, J = 2.80 Hz), 8.05 (d, 1 H, J = 2.80 Hz).

Methyl 2-Chloro-5-iodo-3-pyridinecarboxylate (7). Procedure A. To a mixture containing 2.0 g (13 mmol) of **5**, 1.6 g of diethylaniline, 1.64 g of benzyltriethylammonium chloride, and 3.6 mL of distilled $POCl_3$ in 100 mL of dry CH_3CN was added 15 drops of water. The mixture was heated under reflux for 18 h. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure and the residue was taken up in CH_2Cl_2 and extracted with water. The organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The oily residue was flash chromatographed on a column of silica gel with CH_2Cl_2 as the eluent. Evaporation of the eluant gave 1.21 g of a pale yellowish solid, which was recrystallized from aqueous ethanol to give 1.1 g (52%) of **7** as a white solid: mp 73–73.5 °C (lit.[15] mp 75–76 °C); NMR (80 MHz, $CDCl_3$) δ 3.96 (s, 3 H), 8.43 (d, 1 H, J = 2.3 Hz), 8.71 (d, 1 H, J = 2.3 Hz).

Procedure B. To a solution containing 1.10 mL of dry DMF and 1.34 mL of distilled $POCl_3$ in 100 mL of anhydrous CH_2Cl_2 was added 2.0 g (13 mmol) of **5** in one portion. The mixture was stirred at room temperature under a N_2 atmosphere for 28 h. Workup as described in procedure A and recrystallization of the crude product from aqueous ethanol gave 1.41 g (66%) of **7**, mp 73–73.5 °C.

Methyl 5-Bromo-2-chloro-3-pyridinecarboxylate (8). This compound was prepared, as described in procedure B above, from **6**, $POCl_3$, and DMF in 59% yield: mp 49–50 °C; NMR ($CDCl_3$, 300 MHz) δ 3.99 (s, 3 H), 8.32 (d, 1 H, J = 2.86 Hz), 8.60 (d, 1 H, J = 2.86 Hz).

Methyl 2-Chloro-5-(2-carbomethoxyvinyl)-3-pyridinecarboxylate (9) and Methyl 2-(2-Carbomethoxyvinyl)-5-iodo-3-pyridinecarboxylate (10). A mixture containing 107 mg (0.36 mmol) of **7**, 16.1 mg (0.07 mmol) of palladium acetate, 43.8 mg (0.14 mmol) of tri-*o*-tolylphosphine, 74.6 mg of anhydrous K_2CO_3, and 0.2 mL of methyl acrylate in 20 mL of DMF was heated at 120–130 °C under N_2 for 15 h. After removal of solvent, the residue was chromatographed on silica gel with 50% ethyl acetate/hexanes as eluent. The first band separated consisted of a complex mixture of compounds and was discarded. Evaporation of the second fraction gave 17.9 mg (19%) of **9**, mp 131–132 °C; NMR ($CDCl_3$, 250 MHz) δ 3.82 (s, 3 H), 3.99 (s, 3 H), 6.74 (d, 1 H, J = 16 Hz), 7.64 (d, 1 H, J = 16 Hz), 8.28 (d, 1 H, J = 2.4 Hz), 8.59 (d, 1 H, J = 2.4 Hz). The assignment of structure **9** to this compound was further confirmed by an NOE experiment, where irradiation at δ 7.64 led to enhancement of the signals at δ 8.28 and 8.59.

The third chromatographic fraction contained 15 mg (12%) of **10**: NMR ($CDCl_3$, 80 Mz) δ 3.79 (s, 3 H), 3.90 (s, 3 H), 6.28 (d, 1 H, J = 16 Hz), 7.60 (d, 1 H, J = 16 Hz), 8.08 (d, 1 H, J = 2.4 Hz), 8.33 (d, 1 H, J = 2.4 Hz).

When the above reaction was carried out at 95–105 °C for 21.5 h, compound **9** was isolated in 22% yield as the only identifiable reaction product.

Methyl 2-(Diethylamino)-5-[(trimethylsilyl)ethynyl]-3-pyridinecarboxylate (11). A mixture consisting of 0.33 g (1.1 mmol) of pyridine ester **7**, 0.13 g (1.32 mmol) of (trimethylsilyl)acetylene, 0.04 g (0.22 mmol) of palladium chloride, 0.12 g (0.46 mmol) of triphenylphosphine, and a catalytic amount of cuprous iodide in 10 mL of diethylamine was stirred at room temperature under N_2. After 20 h, the solvent was removed under reduced pressure, and the residue was subjected to radial chromatography on silica gel with CH_2Cl_2 as the eluent. The major fraction isolated from the plate contained 0.40 g of a brown oil, which was distilled with a Kugelrohr apparatus (150 °C, 0.5 mmHg) to give 0.23 g (68%) of **11** as a colorless oil: IR (neat) 2950, 2150, 1720, 1595, 1490, 1430, 1350, 1295, 1245, 1205, 1155, and 840 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 0.23 (s, 9 H), 1.18 (t, 6 H, J = 7.04 Hz), 3.44 (q, 4 H, J = 7.04 Hz), 3.86 (s, 3 H), 7.90 (d, 1 H, J = 2.43 Hz), 8.29 (d, 1 H, J = 2.43 Hz). Anal. Calcd for $C_{16}H_{24}N_2O_2Si$: C, 63.12; H, 7.95; N, 9.20. Found: C, 62.92; H, 7.67; N, 8.92.

***tert*-Butyl 4-Bromobenzoate.** To a mixture of 5.5 g (0.074 mol) of dry *tert*-butyl alcohol and 7.08 g (0.09 mol) of dry pyridine was added a solution of 9.79 g (0.045 mol) of 4-bromobenzoyl chloride[16] in 20 mL of anhydrous CH_2Cl_2. The mixture was stirred under N_2 for 2 days. The reaction mixture was then diluted with CH_2Cl_2, and the organic solution was extracted with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual oil was distilled under reduced pressure to give 8.9 g (70%) of the title compound as a colorless oil: bp 91–92 °C (1.2 mm); IR (neat) 2970, 1710, 1585, 1475, 1390, 1290, 1160, 1110, 1070, 845, and 745 cm^{-1}; NMR ($CDCl_3$, 80 MHz) δ 1.59 (s, 9 H), 7.53 (d, 2 H, J = 8.7 Hz). Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.09; Br, 31.08. Found: C, 51.41; H, 5.36; Br, 30.38.

***tert*-Butyl 4-Ethynylbenzoate.** A mixture containing 1.31 g (6 mmol) of *tert*-butyl 4-bromobenzoate, 1.0 g (10 mmol) of (trimethylsilyl)acetylene, 10 mg (0.04 mmol) of palladium acetate, and 25.6 mg (0.06 mmol) of triphenylphosphine in 15 mL of anhydrous triethylamine was heated in a sealed container at 100 °C for 16 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and extracted with water. The organic solution was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The dark residue was flash chromatographed on a column of silica gel with a 10% ethyl acetate–hexanes mixture as the eluent to give *tert*-butyl 4-[(trimethylsilyl)ethynyl]benzoate as a dark oil: NMR ($CDCl_3$, 300 MHz) δ 0.26 (s, 9 H), 1.59 (s, 9 H), 7.49 (d, 2 H, J = 8.23 Hz), 7.91 (d, 2 H, J = 8.23 Hz). This material was dissolved in 20 mL

(14) The purity of all title compounds for which microanalyses could not be obtained was judged to be >95% by HPLC and/or ^1H NMR spectral determinations; full NMR data are given for all compounds prepared.

(15) Fibel, L. R.; Spoerri, P. E. *J. Am. Chem. Soc.* **1948**, *70*, 3908.

(16) Spencer, A. *J. Organomet. Chem.* **1984**, *265*, 323.

of CH_3OH containing 0.1 g of anhydrous K_2CO_3, and the mixture was allowed to stir at room temperature under nitrogen for 3 h, diluted with CH_2Cl_2, extracted with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was distilled under reduced pressure (60–70 °C/0.1 mm) to give 0.75 g (73% over two steps) of *tert*-butyl 4-ethynylbenzoate as a white solid: mp 71.5–72 °C; IR (KBr) 3240, 2970, 2100, 1700, 1600, 1450, 1365, 1300, 1250, 1160, 1115, 1015, 845, and 765 cm^{-1}; NMR ($CDCl_3$, 80 MHz) δ 1.62 (s, 9 H), 3.23 (s, 1 H), 7.55 (d, 2 H, J = 8.11 Hz), 7.96 (d, 2 H, J = 8.11 Hz); MS 202 (M^+), 187, 157, 146, 129, 101, 75, and 57. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.86; H, 6.79.

Methyl 5-[[4-(*tert*-Butoxycarbonyl)phenyl]ethynyl]-2-chloro-3-pyridinecarboxylate (12). To a solution containing 0.53 g (1.78 mmol) of **7** and 0.4 g (1.98 mmol) of *tert*-butyl 4-ethynylbenzoate in 30 mL of triethylamine was added 0.19 g (0.72 mmol) of triphenylphosphine, 0.06 g (0.34 mmol) of palladium chloride, and 0.03 g of cuprous iodide. The mixture was heated under reflux under a N_2 atmosphere for 4 h. The solvent was removed under reduced pressure, and the residue was subjected to radial chromatography on silica gel with CH_2Cl_2 as the eluent. The major fraction isolated from the plate contained 0.43 g (65%) of **12** as a pale yellowish oil, which crystallized on standing. A small portion of this material was recrystallized from hexanes: mp 123–124 °C; IR (KBr) 3050, 3000, 2970, 2210, 1730, 1700, 1600, 1530, 1420, 1360, 1325, 1285, 1255, 1220, 1160, 1060, 845, and 765 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.63 (s, 9 H), 4.00 (s, 3 H), 7.61 (d, 2 H, J = 8.15 Hz), 8.02 (d, 2 H, J = 8.15 Hz), 8.33 (d, 1 H, J = 2.16 Hz), 8.67 (d, 1 H, J = 2.16 Hz); LRMS 373 (M^+ + 2), 371 (M^+), 315, 298, 282, and 256. Anal. Calcd for $C_{20}H_{18}ClNO_4$: C, 64.60; H, 4.88; Cl, 9.53; N, 3.77. Found: C, 64.87; H, 4.88; Cl, 9.58; N, 3.77.

1,4-Bis[4-(*tert*-butoxycarbonyl)phenyl]-1,3-butadiyne (13). A mixture consisting of 0.1 g (0.42 mmol) of **8**, 0.09 g (0.45 mmol) of *tert*-butyl 4-ethynylbenzoate, 0.01 g (0.056 mmol) of palladium chloride, 0.03 g (0.11 mmol) of triphenylphosphine, and 0.01 g of cuprous iodide in 10 mL of triethylamine was heated under reflux under N_2 for 17 h. After removal of the solvent, the residual material was taken up in CH_2Cl_2 and extracted with a saturated NaCl solution, and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual material was passed through a pad of silica gel, eluting with CH_2Cl_2. The major fraction isolated contained 0.03 g (67%) of a compound, mp 166–167 °C, tentatively identified as **13** on the basis of its NMR spectrum: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.62 (s, 18 H), 7.59 (d, 4 H, J = 8.3 Hz), 7.99 (4 H, J = 8.3 Hz).

2-Amino-4-hydroxy-6-[[4-(*tert*-butoxycarbonyl)phenyl]ethynyl]pyrido[2,3-*d*]pyrimidine (14). To a solution containing 0.11 g (4.78 mmol) of Na in 30 mL of anhydrous *tert*-butyl alcohol was added 0.45 g (4.71 mmol) of guanidine hydrochloride. After the mixture was stirred at room temperature for 15 min, 0.35 g (0.94 mmol) of **12** was added in one portion. The mixture was heated under reflux under N_2 for 4 h, cooled, and diluted with ethanol, and the solvent was removed under reduced pressure. The residue was dissolved in water and filtered to remove a small amount of insoluble material, the filtrate was acidified with a 3 N HCl solution, and the precipitate that formed was collected by filtration, washed with water, and dried under reduced pressure to give 0.15 g (44%) of **14** as a pale yellowish solid: mp >260 °C; NMR (DMSO-d_6, 80 MHz) δ 1.55 (s, 9 H), 7.71 (d, 2 H, J = 8.6 Hz), 7.96 (d, 2 H, J = 8.6 Hz), 8.36 (d, 1 H, J = 2.5 Hz), 8.73 (d, 1 H, J = 2.5 Hz). A satisfactory microanalysis of this compound could not be obtained.

2-Amino-4-hydroxy-6-[(4-carboxyphenyl)ethynyl]pyrido[2,3-*d*]pyrimidine (15). Pyrimidine **14** (1.31 g, 3.92 mmol) was added to 15 mL of nitromethane, which had been saturated with HCl gas at 0 °C. The mixture was stirred for 1 h, anhydrous ether was added, and the solid was filtered to give 1.18 g (100%) of **15** as a pale yellowish solid: mp >260 °C; ^1H NMR (DMSO-d_6, 80 MHz) δ 7.71 (d, 2 H, J = 8.4 Hz), 8.00 (d, 2 H, J = 8.4 Hz), 8.40 (d, 1 H, J = 2.3 Hz), 8.75 (d, 1 H, J = 2.3 Hz). A satisfactory microanalysis of this compound could not be obtained.

2-Amino-4-hydroxy-6-iodopyrido[2,3-*d*]pyrimidine (18). To a solution containing 2.30 g (0.1 mol) of Na in 150 mL of anhydrous *tert*-butyl alcohol was added, under N_2, 9.54 g (0.1 mol) of guanidine hydrochloride, followed by 5.94 g (0.02 mol) of **7**. The resulting mixture was heated under reflux for 6 h and concentrated under reduced pressure, the residue was diluted with water and filtered, and the filtrate was acidified with concentrated HCl. The precipitate that separated was collected by filtration, washed well with water followed by acetone and ether, and dried in vacuo: yield 4.04 g (70%) of **18** as a light yellow solid; mp >280 °C; ^1H NMR (Me_2SO-d_6 + TFA-d_1, 80 MHz) δ 8.47 (d, 1 H, J = 2.2 Hz), 8.67 (d, 1 H, J = 2.2 Hz). A satisfactory microanalysis of this compound could not be obtained, so it was converted to its 2-pivaloyl derivative **19** as described for the preparation of **21**.[13c]

2-(Pivaloylamino)-4-hydroxy-6-iodopyrido[2,3-*d*]pyrimidine (19) was obtained in 54% yield as a colorless solid: mp 272–273 °C (from CH_3CN); IR (KBr) 3240, 3200, 3120, 2970, 1670, 1610, 1580, 1545, 1480, 1430, 1370, 1325, 1270, 1230, 1140, 1020, 950, 810, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 9 H), 8.29 (br s, 1 H), 8.83 (d, 1 H, J = 2.32 Hz), 9.06 (d, 1 H, J = 2.32 Hz); HRMS calcd for $C_{12}H_{13}N_4O_2I$ 372.0053, found 372.0069.

2-(Pivaloylamino)-4-hydroxy-6-[[4-(*tert*-butoxycarbonyl)phenyl]ethynyl]pyrido[2,3-*d*]pyrimidine (17). A mixture of 2.0 g (6.15 mmol) of **21**,[13c] 1.31 g (6.48 mmol) of *tert*-butyl 4-ethynylbenzoate, 0.32 g (1.22 mmol) of triphenylphosphine, 2.57 mL of triethylamine, 0.11 g (0.62 mmol) of palladium chloride, and 0.05 g of cuprous iodide in 250 mL of CH_3CN was heated at reflux under N_2 for 2.5 h. The reaction mixture was cooled; the solid was collected by filtration and washed with small portions of cold CH_3CN to yield 1.91 g (69%) of **17** as a pale yellowish powder which was sufficiently pure for the next reaction. A small sample of this solid was purified further by chromatography on silica gel with a 5% CH_3OH/CH_2Cl_2 mixture as the eluent: mp >250 °C; IR (KBr) 3200, 2980, 1710, 1670, 1600, 1545, 1440, 1375, 1290, 1140, and 770 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 9 H), 1.63 (s, 9 H), 7.61 (d, 2 H, J = 8.50 Hz), 8.02 (d, 2 H, J = 8.50 Hz), 8.42 (br s, 1 H), 8.66 (slightly br s, 1 H, 9.01). Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 67.25; H, 5.87; N, 12.55. Found: C, 67.07; H, 5.98; N, 12.36.

2-(Pivaloylamino)-4-hydroxy-6-[(carboxyphenyl)ethynyl]pyrido[2,3-*d*]pyrimidine (16). Method A. Compound **17** (1.0 g, 2.24 mmol) was added to 25 mL of nitromethane saturated with HCl gas at 0 °C. After being stirred at 0 °C, the reaction mixture was allowed to reach room temperature and stirred for an additional hour. The suspension was diluted with anhydrous ether and filtered, and the collected solid was washed with ether, methanol, and ether again and then dried under reduced pressure to give 0.81 g (93%) of **16** as a light yellowish powder: mp >250 °C; IR (KBr) 3420, 3000, 1725, 1680, 1425, 1405, 1360, 1250, 1130, 1020, and 800 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 9 H), 7.72 (d, 2 H, J = 8.02 Hz), 7.98 (d, 2 H, J = 8.02 Hz), 8.52 (d, 1 H, J = 2.01 Hz), 9.01 (d, 1 H, J = 2.01 Hz). No attempt was made to obtain a microanalysis of this intermediate.

Method B. Compound **15** was heated in refluxing pivalic anhydride[13c] to yield **16** in 20% yield.

Diethyl *N*-(4-Ethynylbenzoyl)-L-glutamate (23). To a solution of 0.55 g (3.76 mmol) of 4-ethynylbenzoic acid (obtained from *tert*-butyl 4-ethynylbenzoate in 84% yield by hydrolysis with trifluoroacetic acid) in 50 mL of anhydrous ether and 25 mL of anhydrous THF was added 1.58 mL of triethylamine, followed by 1.00 g (3.74 mmol) of phenyl *N*-phenylphosphoramidochloridate. After the reaction was stirred at room temperature under N_2 for 0.5 h, 0.90 g (3.76 mmol) of diethyl L-glutamate hydrochloride was added in one portion. The mixture was allowed to stir for another 8 h and evaporated, and the residue was subjected to column chromatography on silica gel, with a 1% CH_3OH/CH_2Cl_2 mixture as the eluent. The major fraction isolated from the column contained 0.68 g (54%) of **23** as an oil, which slowly solidified: IR (KBr) 3330, 3280, 2990, 1735, 1640, 1520, 1380, 1200, 1105, 1020, 855, and 770 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3 H, J = 6.9 Hz), 1.33 (t, 3 H, J = 6.9 Hz), 2.11–2.60 (m, 4 H), 3.23 (s, 1 H), 4.09 (q, 2 H, J = 6.9 Hz), 4.27 (q, 2 H, J = 6.9 Hz), 4.80 (m, 1 H), 7.12 (d, 1 H, J = 7.2 Hz), 7.59 (d, 2 H, J = 8.4 Hz), 7.81 (d, 2 H, J = 8.4 Hz); LRMS 331 (M^+), 286, 258, 202, 129, 112, 101; HRMS calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1403.

Diethyl *N*-[4-[[2-(Pivaloylamino)-4-hydroxypyrido[2,3-*d*]pyrimidin-6-yl]ethynyl]benzoyl]-L-glutamate (22). Method A. A mixture of 2.0 g (6.15 mmol) of **21**,[13c] 2.1 g (6.34 mmol) of **23**, 2.57 mL of triethylamine, 0.11 g (0.62 mmol) of palladium

chloride, 0.32 g (1.22 mmol) of triphenylphosphine, and 0.05 g of cuprous iodide in 150 mL of CH_3CN was heated at reflux under nitrogen for 2.5 h. The solid that formed upon cooling was collected by filtration and washed with cold CH_3CN to yield 1.91 g (54%) of **22**, which was purified by chromatography on silica gel (5% CH_3OH/CH_2Cl_2): mp >250 °C; IR (KBr) 3330, 3290, 2970, 1730, 1655, 1590, 1530, 1440, 1370, 1260, 1140, 1020, 965, 925, 850, 810, and 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3 H, J = 7.20 Hz), 1.33 (t, 3 H, J = 7.20 Hz), 1.36 (s, 9 H), 2.14–2.62 (m, 4 H), 4.14 (q, 2 H, J = 7.20 Hz), 4.27 (q, 2 H, J = 7.20 Hz), 4.79–4.86 (m, 1 H), 7.30 (d, 1 H, J = 8.40 Hz), 7.63 (d, 2 H, J = 8.25 Hz), 7.86 (d, 2 H, J = 8.25 Hz), 8.51 (br s, 1 H), 8.64 (d, 1 H, J = 2.40 Hz), 8.97 (d, 1 H, J = 2.40 Hz), 12.2 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 27.1, 27.2, 30.7, 40.6, 52.7, 61.1, 62.0, 87.61, 92.71, 115.1, 117.3, 125.9, 127.4, 127.5, 132.0, 133.9, 138.7, 149.6, 157.8, 158.6, 160.5, 166.4, 172.1, 173.5, 180.8 Anal. Calcd for $C_{30}H_{33}N_5O_7$: C, 62.60; H, 5.78; N, 12.17. Found: C, 62.84; H, 5.60; N, 12.35.

Method B. To a solution of 0.09 g (0.32 mmol) of **16** and 0.07 mL of *N*-methylmorpholine in 5 mL of dry *N*-methylpyrrolidone was added 0.09 g (0.34 mmol) of phenyl *N*-phenylphosphoramidochloridate. After the reaction mixture was stirred at room temperature under a N_2 atmosphere for 20 min, 0.08 g (0.33 mmol) of diethyl L-glutamate hydrochloride was added, and the mixture was stirred for another 24 h. The solvent was removed by distillation under reduced pressure, and the residue was partitioned between chloroform and water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to repeated chromatography on silica gel with a 2% CH_3OH/CH_2Cl_2 mixture as the eluent. The major fraction isolated contained 0.05 g (38%) of **22**, mp >250 °C, identical with the material prepared by method A as shown by comparison of NMR and IR spectra and by TLC.

2-(Pivaloylamino)-4-hydroxy-6-[(trimethylsilyl)ethynyl]pyrido[2,3-*d*]pyrimidine (24). A mixture containing 2.0 g (6.15 mmol) of **21**,[13c] 1.21 g (12.3 mmol) of (trimethylsilyl)acetylene, 0.11 g (0.62 mmol) of palladium chloride, 0.23 g (1.23 mmol) of triphenylphosphine, 0.06 g (0.3 mmol) of cuprous iodide, and 2.57 mL (18.5 mmol) of triethylamine in 100 mL of CH_3CN was heated in a sealed tube for 1.5 h at 50 °C and then at reflux for 3 h. The solvent was removed under reduced pressure, and the residue was triturated with 50% ethyl acetate/hexanes and filtered. The collected solid was dissolved in methylene chloride and passed through a pad of silica gel, eluting with 1% CH_3OH/CH_2Cl_2. The eluate was concentrated to give 1.67 g (79%) of **24**, mp >250 °C; IR (KBr) 3200, 2970, 2170, 1680, 1620, 1545, 1475, 1440, 1380, 1275, 1250, 1145, 930, and 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.29 (s, 9 H), 1.35 (s, 9 H), 8.36 (br s, 1 H), 8.57 (d, 1 H, J = 2.45 Hz), 8.92 (d, 1 H, J = 2.45 Hz). This material was used for the next reaction without further purification.

2-(Pivaloylamino)-4-hydroxy-6-ethynylpyrido[2,3-*d*]pyrimidine (25). To a solution of 1.47 g (4.29 mmol) of **24** in 100 mL of anhydrous THF was added, under N_2 and at 0 °C, 4.75 mL of 1 M tetrabutylammonium fluoride in THF. After 5 min, the reaction mixture was allowed to warm to room temperature and then was stirred for 2 h. The solvent was removed under reduced pressure, and the residue was passed through a small pad of silica gel, eluting with a 1% CH_3OH/CH_2Cl_2 solution. The filtrate was concentrated under reduced pressure, and the residue was purified further by radial chromatography on silica gel. The major fraction isolated from the plate contained 1.20 g (100%) of **25** and an off-white solid: mp 246–247 °C dec; IR (KBr) 3300, 3200, 2980, 1670, 1620, 1550, 1470, 1445, 1380, 1325, 1280, 1240, 1140, 1025, and 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 9 H), 3.31 (s, 1 H), 8.39 (br s, 1 H), 8.60 (d, 1 H, J = 1.99 Hz), 8.49 (d, 1 H, J = 1.99 Hz). Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.47; H, 5.48; N, 20.60.

Diethyl *N*-(4-Bromobenzoyl)-L-glutamate. To a mixture of 0.92 g (4.19 mmol) of 4-bromobenzoyl chloride and 1.0 g (4.19 mmol) of diethyl L-glutamate hydrochloride in 50 mL of dry CH_2Cl_2 was added 1.16 mL of triethylamine. The reaction mixture was stirred overnight under N_2 and then extracted with water, 0.5 N HCl, and finally a saturated solution of Na_2CO_3. The CH_2Cl_2 solution was concentrated under reduced pressure, and the residue was recrystallized from hexanes to give 0.68 g (46%) of the title compound as a white solid: mp 82.5–83.5 °C; IR (KBr) 3320, 2980, 1745, 1720, 1635, 1520, 1375, 1300, and 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, 3 H, J = 6.9 Hz), 1.33 (t, 3 H, J = 6.9 Hz), 2.11–2.60 (m, 4 H), 4.14 (q, 2 H, J = 6.9 Hz), 4.27 (q, 2 H, J = 6.9 Hz) 4.78 (m, 1 H), 7.14 (d, 1 H, J = 7.2 Hz), 7.61 (d, 2 H, J = 8.4 Hz), 7.73 (d, 2 H, J = 8.4 Hz). Anal. Calcd for $C_{16}H_{20}BrNO_5$: C, 49.75; H, 5.22; N, 3.63; Br, 20.69. Found: C, 49.70; H, 5.15; N, 3.65; Br, 20.90.

Diethyl *N*-(4-Iodobenzoyl)-L-glutamate (26) was prepared from 4-iodobenzoyl chloride and diethyl L-glutamate hydrochloride in 75% yield by the same method: mp 105–106 °C (from hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, 3 H, J = 7.2 Hz), 1.33 (t, 3 H, J = 7.2 Hz), 2.11–2.60 (m, 4 H), 4.14 (q, 2 H, J = 7.2 Hz), 4.78 (m, 1 H), 7.15 (d, 1 H, J = 7.2 Hz), 7.58 (d, 2 H, J = 8.4 Hz), 7.83 (d, 2 H, J = 8.4 Hz). Anal. Calcd for $C_{16}H_{20}INO_5$: C, 44.36; H, 4.65; N, 3.23. Found: C, 44.20; H, 4.55; N, 3.25.

Diethyl *N*-[4-[[2-(Pivaloylamino)-4-hydroxypyrido[2,3-*d*]pyrimidin-6-yl]ethynyl]benzoyl]-L-glutamate (22). Method C. A mixture of 0.68 g (2.52 mmol) of **24**, 1.20 g (2.77 mmol) of **26**, 0.35 mL of triethylamine, 0.04 g (0.23 mmol) of palladium chloride, 0.139 (0.46 mmol) of triphenylphosphine, and 0.02 g of cuprous iodide in 75 mL of CH_3CN was heated at reflux under N_2 for 3.5 h. The reaction mixture was cooled, and the solid was collected, triturated with ethyl acetate, and filtered. The collected solid was recrystallized from ethanol to yield 1.12 g of **22** (77%), identical with the material prepared by methods A and B as shown by comparison of NMR and IR spectra and by TLC.

Diethyl *N*-[4-[[2-(Pivaloylamino)-4-hydroxy-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl]ethyl]benzoyl]-L-glutamate (27). A mixture of 0.59 g (1.0 mmol) of **22** and 1.5 g of 5% palladium-on-charcoal in 30 mL of trifluoroacetic acid was hydrogenated at 53 psi at room temperature for 24.5 h. The reaction mixture was diluted with CH_2Cl_2 and filtered through Celite, the solvent was removed under reduced pressure, and the residue was redissolved in CH_2Cl_2, extracted with a saturated $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel with a 4% CH_3OH/CH_2Cl_2 mixture as the eluent. Evaporation of the eluate yielded 0.60 g (100%) of **27** as a white solid: mp >250 °C; IR (KBr) 3400, 3280, 2980, 1735, 1630, 1570, 1460, 1390, 1350, 1310, 1200, 1155, 1025, 930, and 800 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3 H, J = 7.20 Hz), 1.29 (s, 9 H), 1.30 (t, 3 H, J = 7.20 Hz), 1.61–3.35 (m, 13 H), 4.11 (q, 2 H, J = 7.20 Hz), 4.23 (q, 2 H, J = 7.20 Hz), 4.77–4.84 (m, 1 H), 5.15 (br s, 1 H), 7.17 (d, 1 H, J = 7.50 Hz), 7.23 (d, 2 H, J = 8.10 Hz), 8.56 (br s, 1 H). Anal. Calcd for $C_{30}H_{41}N_5O_7$: C, 61.73; H, 7.08; N, 12.00. Found: C, 61.49; H, 6.94; N, 12.04.

***N*-[4-[2-(2-Amino-4-hydroxy-5,6,7,8-tetrahydropyrido-[2,3-*d*]pyrimidin-6-yl)ethyl]benzoyl]-L-glutamic Acid (DDATHF) (2).** A suspension of 0.53 g (0.91 mmol) of **27** in 50 mL of 1% NaOH was stirred at room temperature for 70 h. The mixture was then acidified with acetic acid, and the solid that formed was collected by filtration, washed with CH_3OH, and dried under reduced pressure to give 0.20 g (50%) of **2** (DDATHF) as a 50:50 mixture of two diastereomers, identical in all respects (NMR, IR, HPLC) with material as prepared and described earlier.[3,4]

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Registry No. (6*R*)-**2**, 106400-81-1; (6*S*)-**2**, 106400-18-4; **3**, 609-71-2; **4**, 10128-91-3; **5**, 116387-40-7; **6**, 120034-05-1; **7**, 78686-83-6; **8**, 78686-79-0; **9**, 120034-06-2; **10**, 120034-07-3; **11**, 120034-08-4; **12**, 116387-41-8; **13**, 120034-09-5; **14**, 116387-33-8; **15**, 116387-38-3; **16**, 116387-35-0; **17**, 116387-37-2; **18**, 91997-12-5; **19**, 116387-30-5; **21**, 116387-22-5; **22**, 116387-24-7; **23**, 116387-23-6; **24**, 116387-32-7; **25**, 116387-25-8; **26**, 116387-21-4; (6*R*)-**27**, 120142-54-3; (6*S*)-**27**, 120142-55-4; H_2C=CHCOOMe, 96-33-3; HC≡$CSiMe_3$, 1066-54-2; 4-BrC_6H_4COCl, 586-75-4; 4-BrC_6H_4COOBu-*t*, 59247-47-1; 4-(HC≡C)C_6H_4COOBu-*t*, 111291-97-5; 4-(Me_3SiC≡C)C_6H_4COOBu-*t*, 111291-96-4; $(Me_3CCO)_2O$, 1538-75-6; 4-(HC≡C)C_6H_4COOH, 10602-00-3; H-Glu(OEt)-OEt·HCl, 1118-89-4; 4-BrC_6H_4CO-Glu(OEt)-OEt, 116387-26-9; 4-IC_6H_4COCl, 1711-02-0.