Base/Solvent System C. CH_2Cl_2 (5 mL) and 25% aqueous NH_3 (5 mL) were stirred at −25 to −30 °C, and then salt **3a–d** was added. The mixture was stirred at −25 to −30 °C for 0.5 h (salt **3a**), for 0.75 h (salts **3b,c**), or for 1 h (salt **3d**) and diluted with water, and the phases were separated. The water phase was extracted with CH_2Cl_2 (three times), and the combined organic phases were washed with water and dried over $MgSO_4$. The solvent was evaporated, and the residue was analyzed by ^1H NMR (Table II).

5a. This product was used for the preparation of **7a**.

4b + 5b: ^1H NMR spectrum as described above (lack of the signals of **6b**). The ratio of **5b/4b** was calculated from the integration of the signals of the Ar CH_3 protons. This mixture was diluted with EtOH, the product **4b** was filtered, and the filtrate was used for the preparation of **7b**.

5c: ^1H NMR spectrum as described.

5d + 6d: ^1H NMR spectrum as described above. This mixture was used for the preparation of **7d** and **8d**.

Aldehydes 7 and 8. Crude products which resulted from the rearrangement of salt **3** (5 mmol) were dissolved in EtOH (20 mL; in some cases EtOH was already added in order to remove **4**), and $CuSO_4 \cdot 5H_2O$ (1.25 g, 5 mmol) dissolved in water (20 mL) was added. The mixture was gently refluxed until solid separated (ca. 5–10 min) and was then filtered; the filtrate was diluted with water and extracted with CH_2Cl_2 (three or four times). The organic extracts were washed with water, dried over $MgSO_4$, and concentrated to give crude aldehydes **7** and **8**, which were analyzed and purified (Table III).

7a + 8a. The ratio of **7a/8a** was determined by the integration of the signals of the CH_2CN protons in the ^1H NMR spectra. Pure **7a** was isolated from the reaction carried out under conditions A or C.

7a: bp (Kugelrohr) 100–130 °C (0.2 Torr); mp 50–52 °C.

8a. A sample of pure **8a** was isolated by preparative HPLC from the reaction carried out under conditions B.

Products **7a** and **8a** were deformylated,[4] affording 4-chlorophenylacetonitrile (**9a**) and 3-chlorophenylacetonitrile (**10a**), respectively, which were identified by comparison with authentic samples (GC, HPLC).

7b + 8b: ^1H NMR ($CDCl_3$) δ 2.41 (s, 3 H, Ar CH_3, **8b**), 2.47 (s, 3 H, Ar CH_3, **7b**), 3.70 (s, 2 H, CH_2CN, **8b**), 4.26 (s, 2 H, CH_2CN, **7b**), 7.44–7.67 (m, Ar H, **7b + 8b**), 9.94 (s, 1 H, CHO, **8b**), 10.06 (s, 1 H, CHO, **7b**). The ratio of **7b/8b** was calculated from the integration of the signals of the CH_2CN protons. GC/MS (one signal on GC): *m/e* (relative intensity) 159 (M^+, 32), 132 (100), 104 (47), 77 (33), 63 (12), 51 (17).

7b: isolated from the reaction carried out under conditions, B or C (Table III, entries 5 and 6); bp (Kugelrohr) 90–120 °C (0.02 Torr). Deformylation[4] of **7b** gave 2-methylphenylacetonitrile, identified by comparison with an authentic sample (GC).

7c: bp (Kugelrohr) 90–120 °C (0.02 Torr). Deformylation[4] of **7c** afforded 4-methylphenylacetonitrile, which was compared with an authentic sample (GC).

7d + 8d. The products decomposed during the attempted distillation: IR (film) 2250, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.14 (s, 2 H, CH_2CN, **8d**), 4.33 (s, 2 H, CH_2CN, **7d**), 7.38 (q, $^3J_{AB}$ = 5.32 Hz, 2 H, Ar H, **7d**), 7.54 (q, $^3J_{AB}$ = 4.73 Hz, 2 H, **8d**), 9.91 (s, 1 H, CHO, **8d**), 10.00 (s, 1 H, CHO, **7d**). The ratio of **7d/8d** was calculated from the integration of the signals of the CH_2CN or CHO protons. Attempted deformylation[4] of this mixture failed.

7e: bp 92–93 °C (0.2 Torr); mp 36.5–38.5 °C.

Acknowledgment. We gratefully acknowledge financial support from the Polish Academy of Sciences (Grant CPBP No. 01.13).

Registry No. **1a**, 104-88-1; **1b**, 529-20-4; **1c**, 104-87-0; **1d**, 98-03-3; **1e**, 100-52-7; **2a**, 135737-05-2; **2b**, 136262-88-9; **2c**, 136262-89-0; **2d**, 135737-06-3; **2e**, 135762-90-2; **3a**, 135737-02-9; **3b**, 136262-91-4; **3c**, 136262-93-6; **3d**, 135737-04-1; **3e**, 135737-00-7; **4a**, 135737-09-6; **4b**, 136262-94-7; **4e**, 135737-07-4; **5a**, 135737-10-9; **5b**, 136262-95-8; **5c**, 136262-97-0; **5d**, 135737-12-1; **5e**, 135737-08-5; **6a**, 135737-11-0; **6b**, 136262-96-9; **6d**, 135737-13-2; **7a**, 135737-15-4; **7b**, 136262-98-1; **7c**, 136263-00-8; **7d**, 135737-17-6; **7e**, 135737-14-3; **8a**, 135737-16-5; **8b**, 136262-99-2; **8d**, 135737-18-7; **9a**, 140-53-4; **10a**, 1529-41-5; (*N*-methylamino)acetonitrile hydrochloride, 5616-32-0; 4-methylphenylacetonitrile, 2947-61-7.

Supplementary Material Available: Reaction conditions for the preparation of **2** and **3** and their yields (Table I), rearrangements of **3a** under different conditions (Table IV), and characterization data (^1H NMR, IR, or MS spectra and elemental analyses) for compounds **2a–e**, **3a–e**, **4a,b,e**, **5a,c**, **7a–e**, and **8a,d** (5 pages). Ordering information is given on any current masthead page.

Synthesis of [4-(2-Guanin-8-ylethyl)benzoyl]glutamic Acid, a Guanine Analogue of DDATHF

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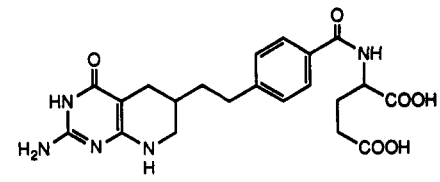
5,10-Dideaza-5,6,7,8-tetrahydrofolic acid (1, DDATHF)[1] is the first member of a new class of folate antimetabolites



1

whose site of action as a folate inhibitor, after intracellular polyglutamation by folylpolyglutamate synthetase,[1-3] has been shown to be glycinamide ribonucleotide formyltransferase (GARFT, E.C. 2.1.2.1) rather than dihydrofolate reductase (DHFR, E.C. 1.5.1.3). The remarkable potency and broad-spectrum antitumor activity of DDATHF, which is now in clinical trial, has stimulated an extensive structure–activity relationship study on this new agent for cancer chemotherapy.[4] One structural change which has not as yet been explored is contraction of the pyrazine "B" ring of the natural cofactor for GARFT,[5] and this paper describes the synthesis and biological evalutation of the novel guanine derivative **2**.

Application of the synthetic strategy developed for an efficient synthesis of DDATHF itself[6] to the guanine derivative **2** would involve a palladium-catalyzed coupling either of an 8-ethynylguanine derivative such as **3** with dimethyl (4-iodobenzoyl)glutamate (**4**) or of an 8-haloguanine derivative **5** with dimethyl (4-ethynylbenzoyl)-

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(2) Moran, R. G.; Baldwin, S. W.; Taylor, E. C.; Shih, C. *J. Biol. Chem.* **1989**, *264*, 21047.

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(5) Shrinkage of the B ring of 5-deazaaminopterins from a six- to a five-membered ring has led to pyrrolopyrimidine and dihydropyrrolopyrimidine MTX analogues exhibiting high in vitro cytotoxic activity: Miwa, T.; Hitaka, T.; Akimoto, H.; Nomura, H. *J. Med. Chem.* **1991**, *34*, 555.

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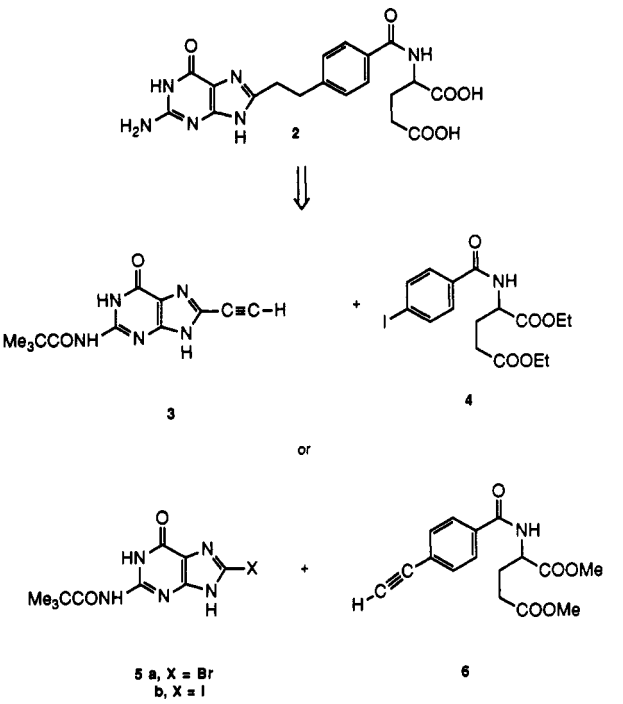
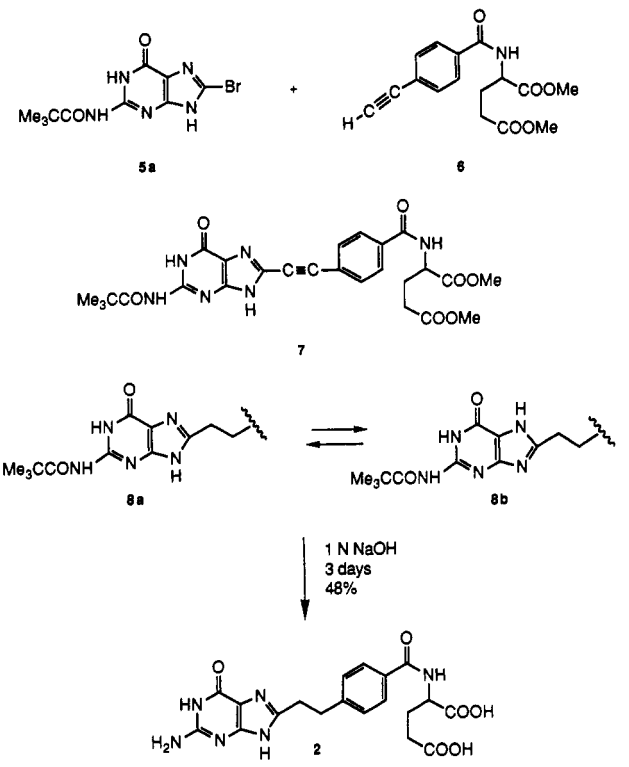
Scheme I



Scheme II



glutamate (6) (Scheme I). Attempts to iodinate guanine[7] or 2-pivaloylguanine[8] directly with iodine chloride or with *N*-iodosuccinimide failed. Iodination of guanosine followed by removal of the sugar with 1 N HCl gave 8-iodoguanine as previously reported,[9] but the insolubility of this latter compound negated all attempts at palladium-catalyzed coupling with 4 or 6, while pivaloylation of the 2-amino group in an attempt to prepare **5b** gave 2-pivaloylguanine with comcomitant loss of the 8-iodo substituent.

We therefore turned to an investigation of 2-pivaloyl-8-bromoguanine (**5a**), which was readily prepared by bromination of 2-pivaloylguanine with bromine in acetic acid. Initial coupling results, however, were not promising. The use of (trimethylsilyl)acetylene or (trimethylsilyl)-(tributylstannyl)acetylene gave only traces (<3%) of coupled products, while the usual coupling conditions (palladium chloride, cuprous iodide, triphenylphosphine, and triethylamine) with **6** led only to dimerization of the latter.[6] We finally found that the desired coupling product **7** was formed without competitive dimerization of the acetylene component **6** by the use of palladium acetate rather than the chloride, cuprous iodide, triphenylphosphine, and 1.9 equiv of the acetylene **6** (Scheme II). Hydrogenation of **7** gave the saturated ester **8** in 31% yield for an overall yield, based on 8-bromoguanine, of 15%. NMR studies revealed that, in DMSO-d_6, the ester **8** exists as a 2:1 ratio of the tautomers **8a** and **8b**. The two sets of signals for all of the NH and CH protons collapsed to singlets upon protonation with trifluoroacetic acid. It is also interesting to note that ester **8**, even after careful purification by repeated recrystallizations from ethyl acetate, showed an unusual melting point behavior; the compound softened at 145 °C but did not melt until 175–176 °C.[10]

Hydrolysis of the 2-pivaloyl and glutamate ester groupings in **8** was accomplished with 1 N NaOH under previously described conditions[6] to give the target DDATHF analogue **2**. Biological evaluation of this compound by in vitro cell culture experiments showed that it was essentially inactive in inhibiting cell growth.

Experimental Section

2-Pivaloylguanine. To a suspension of 20.5 g (0.135 mol) of guanine in 500 mL of pyridine was added 50 mL (0.406 mol) of pivaloyl chloride, and the suspension was refluxed for 3 h. The resulting clear brown solution was evaporated under reduced pressure, the residue was diluted with 500 mL of EtOH, and the solution was refluxed for 2 h. It was then cooled, and 180 mL of 5% NH_4OH was added. The resulting precipitate was collected by filtration, washed with water and dried over P_2O_5 in a vacuum oven at 120 °C to give 29.0 g (91%) of 2-pivaloylguanine. Purification of a small sample by vacuum sublimation gave a white solid, mp 315–318 °C dec: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.19 (s, 9 H), 8.02 (s, 1 H, 8-CH), 10.99 (s, 1 H), 12.14 (s, 1 H). Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 50.93; H, 5.46; N, 29.56. The crude product was used without further purification in the following bromination reaction.

8-Bromo-2-pivaloylguanine (5a). To a solution of 20 g (85 mmol) of 2-pivaloylguanine in 190 mL of acetic acid was added 9 mL of Br_2 and 20 g of NaOAc. The resulting orange suspension was heated at 65–75 °C for 36 h. Acetic acid was removed by evaporation under reduced pressure to give a residue which was diluted with 100 mL of EtOH and 200 mL of 2-propanol. The resulting suspension was heated for 3 h and evaporated under reduced pressure, and the resulting yellow suspension was diluted with 500 mL of water to precipitate the product. The precipitate was filtered, washed with water, and dried over KOH/P_2O_5 at 100 °C for 12 h to give 18.2 g (68%) of **5a** as a yellow solid. Purification of the product was achieved by passing it through a column of 100 g of silica gel using 1% MeOH in CH_2Cl_2 to afford 15.8 g of a yellowish white solid, mp 250 °C dec: ^{1}H NMR

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(10) Such tautomeric phenomena have previously been observed with guanine; see: Shapiro, R. *Progr. Nucl. Acid Res. Mol. Biol.* **1968**, *8*, 73.

(DMSO-d_6, 300 MHz) δ 1.20 (s, 9 H), 11.07 (s, 1 H), 12.19 (s, 1 H), 13.8 (br s, 1 H). Anal. Calcd for $C_{10}H_{12}BrN_5O_2$: C, 38.23; H, 3.85; N, 22.29; Br, 25.44. Found: C, 38.08; H, 4.04; N, 22.01; Br, 25.68.

Dimethyl [4-[(2-Pivaloylguanin-8-yl)ethynyl]benzoyl]glutamate (7). To a solution of 1.1 g (3.5 mmol) of **5a** in 20 mL of CH_3CN and 2 mL of Et_3N was added a mixture of 82 mg (0.36 mmol) of $Pd(OAc)_2$, 108 mg (0.57 mmol) of CuI, and 213 mg (0.81 mmol) of Ph_3P followed by a solution of 2.02 g (6.6 mmol) of dimethyl [4-ethynylbenzoyl]glutamate (**6**)[6] in 20 mL of CH_3CN. The resulting solution was heated at 70–80 °C for 6 h and then concentrated under reduced pressure, and the resulting solid was purified by flash chromatography with 145 g of silica gel, using 3% MeOH in CH_2Cl_2 as the eluting solvent, to give 0.91 g of a solid which (by NMR) consisted of 60% of 2-pivaloyl-8-bromoguanine **5a** and 40% of **7**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.22 (s, 9 H), 2.0 (m, 1 H), 2.1 (m, 1 H), 2.48 (t, 2 H, J = 7.3 Hz, CH_2CH_2CH), 3.57 (s, 3 H, CH_3), 3.64 (s, 3 H, CH_3), 4.45 (m, 1 H, $CHCH_2$), 7.74 (d, 2 H, J = 8.0 Hz, C_6H_4), 7.96 (d, 2 H, J = 8.0 Hz, C_6H_4), 8.92 (d, 1 H, J = 7.3 Hz, $NHCH$), 11.09 (s, 1 H), 12.21 (s, 1 H), 13.68 (br s, 1 H, 9-NH).

Dimethyl [4-[2-(2-Pivaloylguanin-8-yl)ethyl]benzoyl]glutamate (8). A suspension of 0.5 g of 3% palladium-on-charcoal and 0.7 g (1.30 mmol) of the above mixture of **5b** and **7** in 40 mL of MeOH was stirred at rt under 50 psi of hydrogen for 16 h. The catalyst was removed by filtration through a pad of Celite, which was washed with 25 mL of 5% MeOH in CH_2Cl_2. The filtrate was concentrated to give a solid which was dissolved in 5% MeOH in CH_2Cl_2. Filtration removed a small amount of a white solid (2-pivaloylguanine), and concentration of the filtrate then gave 0.58 g of an orange solid which was purified by flash chromatography (5% MeOH in CH_2Cl_2) through 86 g of silica gel, yield 0.22 g (31%) of **8** as a yellow solid. The analytical sample, mp 175–176 °C, was prepared by recrystallization from ethyl acetate: IR (KBr) 3140, 2940, 1735, 1660, 1400, 1155 cm^{-1}. For the major tautomer: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.22 (s, 9 H), 2.0 and 2.1 (2m, 2 H, CH_2CH), 2.42 (t, 2 H, J = 7.3 H, CH_2CH_2CH), 3.06 (m, 4 H, CH_2CH_2), 3.55 (s, 3 H, CH_3), 3.61 (s, 3 H, CH_3), 4.41 (m, 1 H, $CHNH$), 7.29 (d, 2 H, J = 8.0 Hz, C_6H_4), 7.75 (d, 2 H, J = 8.0 Hz, C_6H_4), 8.66 (d, 1 H, J = 7.3 Hz, $CHNH$), 11.02 (s, 1 H), 12.16 (s, 1 H), 13.08 (s, 1 H). For the minor tautomer, the upper field region (lower than 7 ppm) is the same as that of the major tautomer: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.31 (d, 2 H, J = 6.1 Hz, C_6H_4), 7.77 (d, 2 H, J = 6.1 Hz, C_6H_4), 8.67 (d, 2 H, J = 7.0 Hz, $CHNH$), 10.93 (s, 1 H), 12.03 (s, 1 H), 12.60 (s, 1 H). MS (FAB, m/e), 541 (MH^+), 366; exact mass (FAB) calcd for $C_{26}H_{33}N_6O_7$ (MH^+) 541.2410, found 541.24049. Anal. Calcd for $C_{26}H_{32}N_6O_7$: C, 57.77; H, 5.97; N, 15.55. Found: C, 57.56; H, 5.78; N, 15.32.

[4-(2-Guanin-8-ylethyl)benzoyl]glutamic Acid (2). A suspension of 0.14 g (0.26 mmol) of the ester **8** in 2.5 mL of 1 N NaOH was stirred at rt for 3 days. The resulting clear solution was neutralized with acetic acid until pH 6 and then diluted with 10 mL of water, and the resulting solid was collected by filtration, washed throughly with water, MeOH, and ether, and finally dried to give 50 mg (48%) of a yellow solid, mp 200–230 °C dec: IR (KBr) 3350 (br), 1690, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.95 and 2.05 (2m, 2 H, CH_2CH), 2.32 (s, 2 H, CH_2CH_2CH), 2.9 and 3.34 (2 br s, 4 H, CH_2CH_2), 4.37 (m, 1 H, $CHNH$), 6.23 (s, 2 H, NH_2), 7.29 (d, 2 H), 7.70 (d, 2 H), 8.51 (d, 1 H, $NHCH$), 10.5 (s, 1 H), 12.1 (s, 1 H), 12.5 (s, 2 H, 2 COOH); mass (FAB, m/e), 429.5 (MH^+) 282.4; exact mass (FAB) calcd for $C_{19}H_{21}N_6O_6$ (MH^+) 429.1522, found 429.15107. Anal. Calcd for $C_{19}H_{20}N_6O_6 \cdot {}^1/_2H_2O$: C, 52.17; H, 4.84; N, 19.21. Found: C, 52.44; H, 4.60; N, 18.98.

Acknowledgment. We are grateful to the National Institutes of Health (Grant No. CA42367) and to Eli Lilly & Company, Indianapolis, IN for support of this work, to Dr. G. B. Grindey, Eli Lilly & Company, for carrying out the preliminary biological screening for in vitro cytotoxic activity, and to the Alexander von Humboldt-Stiftung for a Feodor Lynen Postdoctoral Fellowship awarded to D.K.

Registry No. **2**, 136675-81-5; **5a**, 136675-83-7; **6**, 135352-72-6; **7**, 136675-84-8; **8**, 136675-85-9; guanine, 73-40-5; 2-pivaloylguanine, 136675-82-6.

Direct, Highly Efficient Synthesis from (*S*)-(+)-Phenylglycine of the Taxol and Taxotere Side Chains

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Received May 29, 1991

Taxol (**3a**, Chart I), a natural product obtainable in only low yield from yew bark,[1] and taxotere (**3b**), a semisynthetic analogue,[2] are very exciting antileukemic and tumor-inhibiting agents.[3] Each of these substances, fortunately, can now[4] be secured in good yield from the appropriate hydroxyl-protected side chain (**1a,b**)[5] and naturally abundant 10-desacetyl baccatin III (**2**, in protected form).[6]

The increasingly apparent cancer chemotherapeutic potential of these compounds has generated the need for a highly efficient enantioselective synthesis of the required side chains **1a,b**. In this note we wish to disclose a particularly effective approach to these side chains from inexpensive, enantiomerically pure (*S*)-(+)-phenylglycine.

The synthetic strategy was based on the assumption that the aldehydes derived from alcohols **5a,b** (Scheme I) would, under the proper conditions, undergo chelation-controlled carbonyl addition[7] and provide preferentially the desired threo amino alcohol derivatives **6a,b**. It was, of course, presupposed that the aldehydes would have the necessary configurational stability for this approach.[8]

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