A Ring-Transformation/Ring-Annulation Strategy for the Synthesis of the DHFR Inhibitor, TNP-351: A Correction

Edward C. Taylor* and Zhenmin Mao

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

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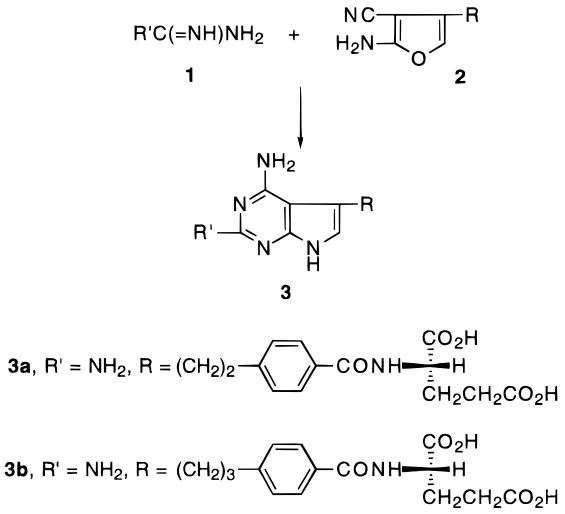
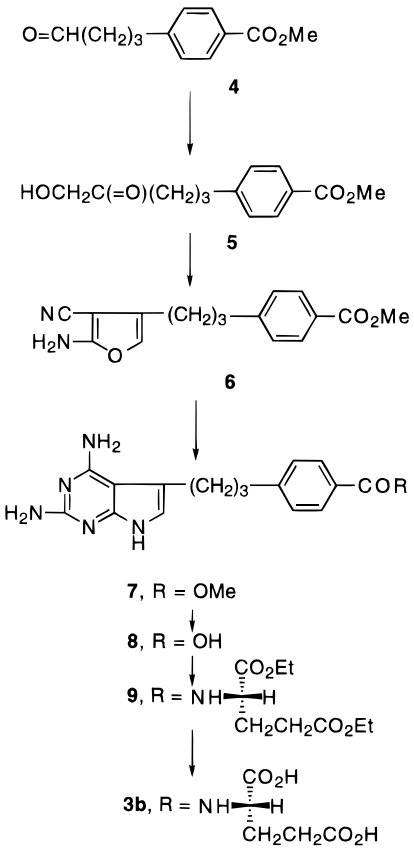
In a recent paper,[1] we described a versatile synthesis of 2-substituted 4-aminopyrrolo[2,3-*d*]pyrimidines (**3**) by the reaction of a variety of 2-amino-3-cyanofurans (**2**) with amidines (**1**). The reaction proceeds by a ring-opening, ring-recyclization sequence of reactions through which the starting furan 2-amino nitrogen becomes the pyrrole nitrogen of the final product, and one of the amidine nitrogens becomes N-1 of the fused pyrimidine ring. Among the compounds prepared by this strategy was the 2,4-diaminopyrrolo[2,3-*d*]pyrimidine **3a**, which we had incorrectly identified as the DHFR inhibitor TNP-351[2] (Scheme 1). The latter, however, has a *three*-carbon (propyl) bridge between the pyrrole and benzene rings (i.e., **3b**) rather than the *two*-carbon (ethyl) bridge found in its lower homologue **3a**.[3] We report in this paper a successful total synthesis of TNP-351 by the ring-opening, ring-recyclization strategy (Scheme 2).

Thus, 4-(4′-carbomethoxyphenyl)butyraldehyde (**4**)[4] was converted to the α-hydroxy ketone **5** by a mixed benzoin condensation with paraformaldehyde, catalyzed by *N*-ethylbenzothiazolium bromide in the presence of triethylamine.[5] Base-catalyzed condensation of **5** with malononitrile then provided methyl 4-[3-(2-amino-3-cyanofur-4-yl)propyl]benzoate (**6**), which was condensed with guanidine to give the pyrrolo[2,3-*d*]pyrimidine **7**. Hydrolysis of **7** to the corresponding benzoic acid **8**, peptide coupling with diethyl L-glutamate to give **9**, and final saponification as previously described[2] then provided TNP-351 (**3b**) in an overall yield of 10% from **4**, compared with the original 11-step, 16% yield of TNP-351 by Miwa.[2]

Scheme 1



Scheme 2



Experimental Section

Methyl 4-(5-Hydroxy-4-oxopentyl)benzoate (5). A ethanol solution (10 mL) of aldehyde **4**[4] (4.12 g, 20 mmol), paraformaldehyde (600 mg, 20 mmol), *N*-ethylbenzothiazolium bromide (878 mg, 3.6 mmol), and triethylamine (364 mg, 3.6 mmol) was heated at 65 °C for 20 h. The solvent was removed under reduced pressure, and the residue was chromatographed with hexane/EtOAc (7/3). Fractions containing the product were combined and evaporated under reduced pressure to give **5** (2.5 g, 53%) as a colorless oil which solidified upon standing: ^{1}H NMR ($CDCl_3$) δ 2.01 (m, 2H), 2.42 (t, 2H, J = 7.3 Hz), 2.71 (t, 2H, J = 7 Hz), 3.05 (s, 1H, br), 3.91 (s, 3H), 4.22 (s, 2H), 7.23 (d, 2H, J = 8 Hz), 7.96 (d, 2H, J = 8 Hz). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.17; H, 6.94.

Methyl 4-[3-(2-Amino-3-cyanofur-4-yl)propyl]benzoate (6). A mixture of malononitrile (603 mg, 9.13 mmol) and triethylamine (922 mg, 9.13 mmol) in MeOH (10 mL) was added to a solution of the α-hydroxy ketone **5** (1.96 g, 8.3 mmol) in MeOH (30 mL), and the resulting solution was stirred at rt for 15 h. Solvent was removed under reduced pressure, the residue was dissolved in EtOAc (300 mL), and the resulting solution was passed through a short silica gel column. Evaporation of the eluate under reduced pressure gave **6** (2.23 g, 94%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.94 (m, 2H), 2.42 (t, 2H, J = 7.6 Hz), 2.72 (t, 2H, J = 7.6 Hz), 3.91 (s, 3H), 4.62 (s, 2H, br), 6.56 (s, 1H), 7.24 (d, 2H, J = 7.9 Hz), 7.95 (d, 2H, J = 7.9 Hz). Anal. Calcd for $C_{16}H_{16}N_2O_3 \cdot 0.1H_2O$: C, 67.17; H, 5.71; N, 9.79. Found: C, 66.80; H, 5.62; N, 10.16.

Methyl 4-[3-(2,4-Diamino-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl]benzoate (7). To a solution of guanidine-free base (1.5 mmol, from 143 mg of guanidine hydrochloride and 81 mg of sodium methoxide) in anhydrous MeOH (30 mL) was added aminonitrile **6** (284 mg, 1 mmol), and the mixture was refluxed for 30 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel with 5% MeOH/CH_2Cl_2. The fractions containing the product were combined

(1) Taylor, E. C.; Patel, H. H.; Jun, J.-G. *J. Org. Chem.* **1995**, *60*, 6684.
(2) Miwa, T.; Hitaka, T.; Akimoto, H.; Nomura, H. *J. Med. Chem.* **1991**, *34*, 555.
(3) For the first reported synthesis of **3a**, see: Shih, C.; Gossett, L. S. *Heterocycles* **1993**, *35*, 825.
(4) Taylor, E. C.; Harrington, P. M. *J. Org. Chem.* **1990**, *55*, 3222.
(5) Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* **1985**, *50*, 603.

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and evaporated under reduced pressure to give **7** (150 mg, 42%) as a light brown solid: ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 2H), 2.66 (t, 2H, J = 7.6 Hz), 2.75 (t, 2H, J = 7.6 Hz), 3.91 (s, 3H), 4.58 (s, 2H, br), 4.84 (s, 2H, br), 6.50 (s, 1H), 7.24 (d, 2H, J = 7.9 Hz), 7.96 (d, 2H, J = 7.9 Hz), 8.19 (s, 1H, br). Anal. Calcd for $C_{17}H_{19}N_5O_2 \cdot 0.4CH_2Cl_2$: C, 58.16; H, 5.55; N, 19.49. Found: C, 58.13; H, 5.89; N, 19.24.

4-[3-(2,4-Diamino-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl]benzoic Acid (8). A solution of the ester **7** (108 mg, 0.30 mmol) in a mixture of MeOH (6 mL) and 0.5 N NaOH (1 mL) was heated under reflux for 15 h, cooled, and acidified with glacial HOAc. The resulting precipitate was collected by filtration, washed with water, and dried *in vacuo* to give **8** (90 mg, 87%) as an off-white solid: ^{1}H NMR (DMSO-d_6) δ 1.84 (m, 2H), 2.69 (m, 2H), 5.37 (s, 2H, br), 5.94 (s, 2H, br), 6.42 (s, 1H), 7.29 (d, 2H, J = 8 Hz), 7.82 (d, 2H, J = 8 Hz), 10.38 (s, 1H, br). Anal. Calcd for $C_{16}H_{17}N_5O_2 \cdot H_2O \cdot 0.25$HOAc: C, 57.55; H, 5.85; N, 20.34. Found: C, 57.70; H, 5.35; N, 19.92.

Diethyl *N*-[4-[3-(2,4-Diamino-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl]benzoyl]-L-glutamate (9). To a suspension of acid **8** (155 mg, 0.45 mmol) in DMF (10 mL) was added *N*-methylmorpholine (NMM, 62 μL, 0.57 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (100 mg, 0.57 mmol). The resulting solution was stirred at rt for 2 h, NMM (62 μL, 0.57 mmol) and diethyl L-glutamate hydrochloride (140 mg, 0.59 mmol) were added, and the mixture was stirred at rt for 4 h. Solvent was then removed under reduced pressure, and the residue was chromatographed on silica gel with CH_2Cl_2/MeOH (10/1). Fractions containing the product were combined and evaporated to give **9** as a gummy solid (145 mg, 62%). Recrystallization from aqueous MeOH gave a white solid: mp 134 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.16 (t, 3H, J = 7 Hz), 1.21 (t, 3H, J = 7 Hz), 1.79−2.14 (m, 4H), 2.41 (t, 2H, J = 7 Hz), 2.65 (t, 2H, J = 7.2 Hz), 2.70 (t, 2H, J = 7 Hz), 4.05 (q, 2H, J = 7 Hz), 4.11 (q, 2H, J = 7Hz), 4.24 (m, 1H), 5.35 (s, 2H), 5.92 (s, 2H), 6.42 (s, 1H), 7.29 (d, 2H, J = 8 Hz), 7.81 (d, 2H, J = 8 Hz), 8.66 (d, 1H, J = 7.3 Hz), 10.38 (s, 1H, br). Anal. Calcd for $C_{25}H_{32}N_6O_5 \cdot H_2O$: C, 58.35; H, 6.66; N, 16.33. Found: C, 58.71; H, 6.42; N, 16.53.

***N*-[4-[3-(2,4-Diamino-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-propyl]benzoyl]-L-glutamic Acid (3b, TNP-351).** To a solution of **9** (80 mg, 0.155 mmol) in THF (2 mL) and H_2O (1 mL) was added 1 mL of 1 N NaOH. The mixture was stirred at rt for 3 h. The THF was evaporated under reduced pressure, and the residual solution was acidified with HOAc. The resulting white precipitate was collected by filtration, washed successively with water, MeOH, and ether, and dried under reduced pressure (P_2O_5) to give 70 mg (88%) of **3b** (TNP-351): mp 190 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.73−2.13 (m, 4H), 2.34 (t, 2H, J = 7 Hz), 2.67 (m, 4H), 4.34 (m, 1H), 5.54 (s, 2H, br), 6.24 (s, 2H), 6.46 (s, 1H), 7.29 (d, 2H, J = 8 Hz), 7.78 (d, 2H, J = 8 Hz), 8.47 (d, 1H, J = 7.3 Hz), 10.54 (s, 1H). Anal. Calcd for $C_{21}H_{24}N_6O_5 \cdot 1.25$HOAc: C, 54.75; H, 5.67; N, 16.30. Found: C, 54.54; H, 5.83; N, 16.51.

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