

915  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.70 (q, 2 H,  $J = 7.3$  Hz), 2.04 (q, 2 H,  $J = 7.3$  Hz), 2.66 (t, 2 H,  $J = 7.3$  Hz), 3.09 (t, 2 H,  $J = 6.0$  Hz), 3.32 (t, 2 H,  $J = 6.0$  Hz), 4.91-5.00 (m, 2 H), 5.65-5.78 (m, 1 H), 7.41 (t, 2 H,  $J = 7.3$  Hz), 7.49 (t, 1 H,  $J = 7.3$  Hz), and 7.93 (d, 2 H,  $J = 7.3$  Hz).

A solution containing 152 mg (0.51 mmol) of **39** in 7 mL of dry benzene was treated with 5 mg of rhodium(II) acetate for 1 h at 60 °C. The solution was filtered and concentrated under reduced pressure. The crude residue was examined by proton NMR spectroscopy and showed none of the expected internal cycloadduct or cyclopropanation product. All attempts to isolate any characterizable product failed. The rhodium(II) catalyzed decomposition was also carried out in the presence of DMAD. A solution containing 153 mg (0.51 mmol) of **39** and 130  $\mu\text{L}$  (1.03 mmol) of DMAD in 6 mL of dry benzene was treated with 5 mg of rhodium(II) acetate for 1 h at 60 °C. The solution was filtered and concentrated under reduced pressure. NMR analysis of the reaction mixture indicated the presence of a 46% yield of dimethyl 4-oxo-5-(1-oxo-5-hexenyl)-1-phenyl-8-oxabicyclo[3.2.1]oct-6-ene-

6,7-dicarboxylate (**40**). Unfortunately, a pure sample could not be isolated by chromatography due to its rapid decomposition:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.70 (quint, 2 H,  $J = 7.3$  Hz), 1.99 (q, 2 H,  $J = 7.3$  Hz), 2.46 (dt, 1 H,  $J = 18.0$  and 7.2 Hz), 2.58-2.77 (m, 3 H), 2.90-2.99 (m, 2 H), 3.56 (s, 3 H), 3.81 (s, 3 H), 4.87-4.97 (m, 2 H), 5.63-5.78 (m, 1 H), and 7.32-7.50 (m, 5 H).

**Acknowledgment.** We gratefully acknowledge support of this work by the National Institutes of Health (CA-26751). Use of the high-field NMR spectrometer used in these studies was made possible through equipment grants from the NIH and NSF.

**Supplementary Material Available:** NMR spectra of **8**, **9**, **11**, **13**, and **34** to indicate purity (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

## Notes

### Further Acyclic Analogues of 5,10-Dideaza-5,6,7,8-tetrahydrofolic Acid

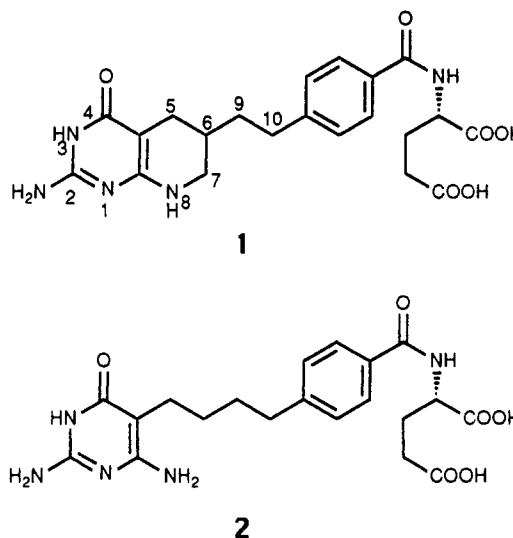
Edward C. Taylor\* and Paul Gillespie

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

Received February 21, 1992

5,10-Dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, lometrexol, **1**) is an antitumor agent with a novel site of action as an inhibitor of glycylamide ribonucleotide formyltransferase (EC 2.1.2.1) in the purine de novo biosynthetic pathway.<sup>1</sup> In vitro studies have shown that DDATHF inhibits the growth of a large number of cancer cell lines, and in vivo studies have shown it to be effective against a range of solid tumors, including lung, mammary, and colon tumors.<sup>2</sup> Early syntheses of DDATHF<sup>3</sup> relied on catalytic hydrogenation to reduce the pyridine ring and led to the formation of a mixture of diastereomers epimeric at C-6 which were then separated via recrystallization of camphor-D-sulfonic acid salts; a chiral synthesis of the drug has recently been developed.<sup>4</sup> We recently reported the preparation of 7-desmethylene-DDATHF (**2**),<sup>5</sup> an acyclic analogue of the parent compound which lacks the C-6 chiral center by virtue of deletion of the C-7 methylene group and which exhibited excellent in vitro cytotoxicity. An alternate strategy for removing the C-6 chiral center would be deletion of the C-5 methylene group, and we have

now prepared several representatives of this isomeric 5-desmethylene system. In this note we describe our synthetic route to these compounds and several problems and unexpected reactions which were encountered in the course of this work.



Our initial approach was to use a Wittig reaction between a suitably substituted 5-formylpyrimidine (**7**) and the phosphonium ylide generated from (3-(4-(methoxycarbonyl)phenyl)propyl)triphenylphosphonium iodide (**12**) (Scheme I). One of the chlorine substituents in 2-amino-4,6-dichloro-5-formylpyrimidine (**3**) was displaced by *N*-methylbenzylamine to give chloropyrimidine **4**, and the second was displaced using sodium methoxide to give compound **5**. It was planned to protect the remaining amino group as a 2,5-dimethylpyrrole so that the substrate for the Wittig reaction would have no remaining acidic hydrogens. When compound **5** was heated at 140 °C with hexane-2,5-dione in the presence of catalytic *p*-toluenesulfonic acid, two products were isolated in low yield. In addition to the desired product (**7**), the decarbonylated derivative **6** was obtained. Decarbonylation of formyl-

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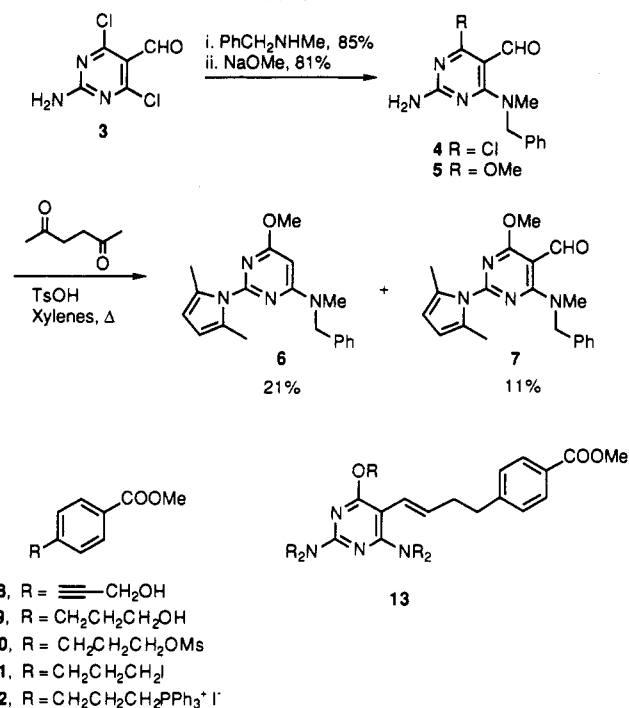
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## Scheme I

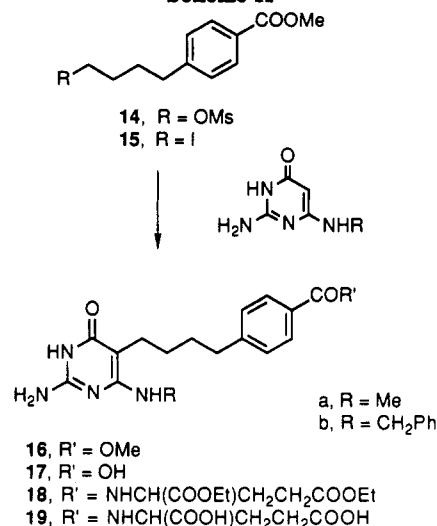


pyrimidines has been observed previously<sup>6</sup> but only in the presence of strong acids.

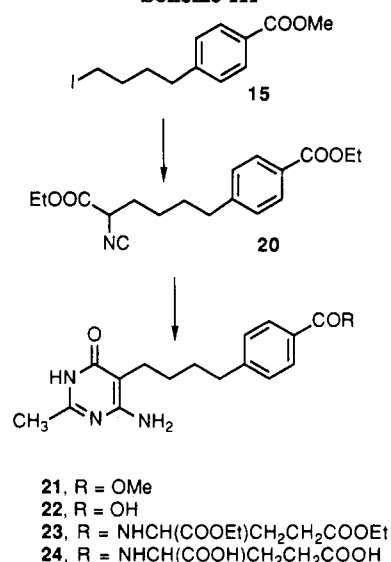
Iodide 11 was prepared as follows. Methyl 4-iodobenzoate underwent palladium-catalyzed coupling with propargyl alcohol to give compound 8. The triple bond was reduced to give alcohol 9 which we had earlier prepared by another route.<sup>7</sup> The alcohol was converted to the mesylate (10) which was heated in acetone with sodium iodide to give compound 11 in good yield. The iodide was then heated with triphenylphosphine in acetonitrile in a sealed tube to give phosphonium salt 12. Heating the phosphonium salt with formylpyrimidine 7 in refluxing methanolic sodium methoxide gave only recovered formylpyrimidine and none of the desired olefin (13). Discouraged by the poor yield of 7, coupled with its unreactivity in the Wittig reaction, we changed our approach and turned to a direct C-5 pyrimidine alkylation strategy which has recently been developed in our laboratory.<sup>8</sup>

Methyl 4-(4-(methanesulfonyloxy)butyl)benzoate (14)<sup>6</sup> reacted with sodium iodide in refluxing acetone to give iodide 15 in 88% yield (Scheme II). When 15 was reacted with 2-amino-6-(methylamino)-4(3*H*)-pyrimidone,<sup>9</sup> the desired C-alkylated product (16a) crystallized from the reaction mixture in 49% yield. In the case of 2-amino-6-(benzylamino)-4(3*H*)-pyrimidone,<sup>10</sup> the C-alkylated product (16b) did not crystallize from the reaction mixture but had to be isolated chromatographically. Hydrolysis in refluxing aqueous sodium hydroxide gave the corresponding carboxylic acids (17a,b), which were coupled with diethyl glutamate using the procedure of Kaminsky.<sup>11</sup> Hydrolysis of the glutamate esters was accomplished by stirring in 1 M sodium hydroxide solution at room temperature to give the desired "open-chain" DDATHF analogues (19a and 19b).

## Scheme II



## Scheme III



The synthesis of 2-methyl-2-desamino-7-desmethylene-DDATHF (24) is shown in Scheme III. Ethyl cyanoacetate was alkylated using iodide 15 and sodium ethoxide to give compound 20 (with transesterification), which was then cyclized with acetamide and sodium methoxide to give pyrimidine 21 (again with complete transesterification). The methyl ester was hydrolyzed in refluxing aqueous sodium hydroxide to give carboxylic acid 22, and this was coupled with diethyl glutamate to give diester 23. The ethyl esters were then hydrolyzed in aqueous sodium hydroxide at room temperature to give the desired glutamic acid derivative 24.

Preliminary *in vitro* biological evaluation of these new acyclic DDATHF analogues indicated that they were poor inhibitors of cell growth. Full details will be published independently.

## Experimental Section

**2-Amino-6-chloro-5-formyl-4-(*N*-methylbenzylamino)pyrimidine (4).** A solution of 2-amino-4,6-dichloro-5-formylpyrimidine (8.00 g, 41.66 mmol), methylbenzylamine (5.06 g, 41.76 mmol), and triethylamine (4.22 g, 41.70 mmol) in EtOH (150 mL) was heated under reflux for 3 h. The solution was allowed to cool, and the product was filtered off, washed with EtOH, and air dried: yield 9.82 g (35.49 mmol, 85%); mp 168–170 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.88 (s, 3 H, NCH<sub>3</sub>), 4.84 (s, 2 H, PhCH<sub>2</sub>), 5.57 (br s, 2 H, NH<sub>2</sub>), 7.20–7.37 (m, 5 H, Ph), 10.13 (s, 1 H, CHO); HRMS

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calcd for  $C_{13}H_{13}ClN_4O$  276.0778, found 276.0787. Anal. Calcd for  $C_{13}H_{13}ClN_4O$ : C, 56.42; H, 4.74; N, 20.25; Cl, 12.81. Found: C, 56.49; H, 4.73; N, 20.46; Cl, 13.08.

**2-Amino-5-formyl-6-methoxy-4-(*N*-methylbenzylamino)-pyrimidine (5).** Compound 4 (9.70 g, 35.05 mmol) was added to a solution of sodium methoxide prepared by the addition of sodium (1.03 g, 44.80 mmol) to MeOH (200 mL). The solution was heated at reflux for 3 h, and the solvent was evaporated under reduced pressure. The residue was taken up in  $CHCl_3$  (100 mL) and washed with  $H_2O$  ( $2 \times 100$  mL). After drying over anhydrous  $MgSO_4$ , the solvent was evaporated to give 9.03 g (33.16 mmol, 95%) of the product as a pale yellow oil. The analytical sample was obtained as white crystals after flash chromatography using EtOAc/hexanes (2:3) as eluent: mp 119–121 °C;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  2.90 (s, 3 H,  $NCH_3$ ), 3.94 (s, 3 H,  $OCH_3$ ), 4.80 (s, 2 H,  $PhCH_2$ ), 5.21 (br s, 2 H,  $NH_2$ ), 7.20–7.31 (m, 5 H, Ph), 9.96 (s, 1 H, CHO); HRMS calcd for  $C_{14}H_{16}N_4O_2$  272.1273, found 272.1282. Anal. Calcd for  $C_{14}H_{16}N_4O_2$ : C, 61.75; H, 5.92; N, 20.58. Found: C, 61.47; H, 5.76; N, 20.32.

**6-Methoxy-4-(*N*-methylbenzylamino)-2-(2,5-dimethylpyrrol-1-yl)pyrimidine (6) and 5-Formyl-6-methoxy-4-(*N*-methylbenzylamino)-2-(2,5-dimethylpyrrol-1-yl)pyrimidine (7).** A solution of 5 (10.10 g, 37.09 mmol), hexane-2,5-dione (5.50 g, 48.18 mmol), and *p*-toluenesulfonic acid (0.25 g) in xylenes (40 mL) was heated at an oil-bath temperature of 140 °C for 4 h. A further portion of hexane-2,5-dione (2.15 g, 18.84 mmol) was added, and the solution was heated at 140 °C for another 4 h. The solvent was evaporated in vacuo (70 °C at 0.25 mmHg at the end). The residue was chromatographed using EtOAc/hexanes (1:19) as eluent to give 2.48 g (7.69 mmol, 21%) of 6 and 1.30 g (3.71 mmol, 11%) of 7.

Compound 6: clear oil;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  2.37 (s, 6 H, pyrrole  $CH_3$ ), 3.02 (s, 3 H,  $NCH_3$ ), 3.92 (s, 3 H,  $OCH_3$ ), 4.81 (s, 2 H,  $PhCH_2$ ), 5.65 (s, 1 H, C-5 H), 5.83 (s, 2 H, pyrrole H), 7.16–7.33 (m, 5 H, Ph); HRMS calcd for  $C_{19}H_{22}N_4O$  322.1794, found 322.1787. Anal. Calcd for  $C_{19}H_{22}N_4O$ : C, 70.78; H, 6.88; N, 17.38. Found: C, 70.57; H, 6.80; N, 17.12.

Compound 7: clear oil;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  2.30 (s, 6 H, pyrrole  $CH_3$ ), 2.83 (s, 3 H,  $NCH_3$ ), 3.93 (s, 3 H,  $OCH_3$ ), 4.80 (s, 2 H,  $PhCH_2$ ), 5.73 (s, 2 H, pyrrole H), 7.06–7.21 (m, 5 H, Ph), 10.10 (s, 1 H, CHO); HRMS calcd for  $C_{20}H_{22}N_4O_2$  350.1743, found 350.1737. Anal. Calcd for  $C_{20}H_{22}N_4O_2$ : C, 68.55; H, 6.33; N, 15.99. Found: C, 68.40; H, 6.48; N, 15.69.

**Methyl 4-(3-Hydroxy-1-propynyl)benzoate (8).** A solution of methyl 4-iodobenzoate (6.09 g, 23.06 mmol), propargyl alcohol (2.59 g, 46.20 mmol),  $PdCl_2$  (75 mg, 0.42 mmol),  $CuI$  (151 mg, 0.79 mmol), and  $PPh_3$  (223 mg, 0.85 mmol) in  $Et_2NH$  (100 mL) was stirred at rt overnight. Tlc (EtOAc/hexanes, 2:3) indicated that the reaction was not complete, so further portions of propargyl alcohol (2.00 g, 35.67 mmol),  $PdCl_2$  (20 mg, 0.12 mmol),  $CuI$  (20 mg, 0.06 mmol), and  $PPh_3$  (58 mg, 0.24 mmol) were added and the solution was heated at reflux for 2 h. Ethyl acetate (70 mL) was added, and the solution was washed with  $H_2O$  ( $2 \times 70$  mL). The ethyl acetate solution was dried over anhydrous  $MgSO_4$  and chromatographed, using EtOAc/hexanes (2:3) as eluent, to give the product (3.48 g, 18.30 mmol, 79%) as a white solid: mp 79–81 °C;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  2.87 (br s, 1 H, OH), 3.91 (s, 3 H,  $COOCH_3$ ), 4.52 (s,  $CH_2O$ ), 7.45 and 7.95 (AA'BB', 4 H, aromatic protons); HRMS calcd for  $C_{11}H_{10}O_3$  190.0630, found 190.0644. Anal. Calcd for  $C_{11}H_{10}O_3$ : C, 69.46; H, 5.30. Found: C, 69.20; H, 5.12.

**Methyl 4-(3-Hydroxy-1-propyl)benzoate (9).** A suspension of 8 (5.00 g, 26.29 mmol) and 10% palladium on carbon (500 mg) in ethanol (100 mL) was shaken at 50 psi on a Parr shaker for 4 h. The solution was filtered through Celite, and the solvent was evaporated. The residue was purified by flash chromatography using EtOAc/hexanes (2:3) as eluent to give 9 (4.79 g, 24.66 mmol, 94%) as a pale yellow oil:  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  1.86–1.93 (m, 2 H,  $ArCH_2CH_2$ ), 2.52 (br s, 1 H, OH), 2.75 (t, 2 H,  $J = 7.5$  Hz,  $ArCH_2$ ), 3.62–3.68 (m, 2 H,  $CH_2O$ ), 3.89 (s, 3 H,  $COOCH_3$ ), 7.25 and 7.94 (AA'BB', 4 H, aromatic protons); HRMS calcd for  $C_{11}H_{14}O_3$  194.0939, found 194.0948. Anal. Calcd for  $C_{11}H_{14}O_3$ : C, 68.02; H, 7.27. Found: C, 67.98; H, 7.46.

**Methyl 4-(3-(Methanesulfonyloxy)-1-propyl)benzoate (10).** Methanesulfonyl chloride (6.50 g, 56.74 mmol) was added to an ice-cooled solution of alcohol 9 (5.50 g, 28.32 mmol) and tri-

ethylamine (5.75 g, 56.82 mmol) in  $CHCl_3$  (100 mL). The solution was allowed to stir at rt for 1.5 h, and it was then washed with water (100 mL) and brine (100 mL). After drying over anhydrous  $MgSO_4$  and evaporation of solvent, the residue was flash chromatographed, using EtOAc/hexanes (7:3) as eluent, to give 10 (7.40 g, 27.17 mmol, 96%) as a pale brown oil which crystallized on standing: mp 42–45 °C;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  2.03–2.13 (m, 2 H,  $ArCH_2CH_2$ ), 2.80 (t, 2 H,  $J = 7.4$  Hz,  $ArCH_2$ ), 3.00 (s, 3 H,  $OSO_2CH_3$ ), 3.89 (s, 3 H,  $COOCH_3$ ), 4.22 (t, 2 H,  $J = 6.2$  Hz,  $CH_2O$ ), 7.27 and 7.96 (AA'BB', 4 H, aromatic protons); HRMS calcd for  $C_{12}H_{16}O_5S$  272.0718, found 272.0721. Anal. Calcd for  $C_{12}H_{16}O_5S$ : C, 52.93; H, 5.92. Found: C, 52.74; H, 6.10.

**Methyl 4-(3-Iodo-1-propyl)benzoate (11).** A solution of mesylate 10 (7.40 g, 27.17 mmol) and sodium iodide (10.61 g, 70.78 mmol) in acetone (250 mL) was heated under reflux for 2 h. The solid was filtered from the cooled solution, and the solvent was evaporated from the filtrate. The residue was taken up in  $CHCl_3$  (100 mL) and the solution washed with water (100 mL), 10% aqueous  $K_2S_2O_8$  solution (100 mL), and brine (100 mL). After drying over anhydrous  $MgSO_4$ , the solvent was evaporated and the residue chromatographed, using EtOAc/hexanes (1:4) as eluent, to give 11 as a yellow liquid which crystallized on standing: yield 6.72 g (22.10 mmol, 81%); mp 37–38 °C;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  2.08–2.18 (m, 2 H,  $ArCH_2CH_2$ ), 2.78 (t, 2 H,  $J = 7.4$  Hz,  $ArCH_2$ ), 3.15 (t, 2 H,  $J = 6.7$  Hz,  $ICH_2$ ), 3.90 (s, 3 H,  $COOCH_3$ ), 7.26 and 7.96 (AA'BB', 4 H, aromatic protons); HRMS calcd for  $C_{11}H_{13}IO_2$  303.9959, found 303.9962. Anal. Calcd for  $C_{11}H_{13}IO_2$ : C, 43.44; H, 4.31; I, 41.73. Found: C, 43.30; H, 4.48; I, 41.62.

**(3-(4-(Methoxycarbonyl)phenyl)propyl)triphenylphosphonium Iodide (12).** A solution of iodide 11 (5.00 g, 16.44 mmol) and triphenylphosphine (43.12 g, 164.40 mmol) in acetonitrile (90 mL) was heated in a sealed tube at 95 °C (oil-bath temperature) for 20 h. The solvent was evaporated, and the excess triphenylphosphine was removed by Soxhlet extraction with hexane for 12 h. Compound 12 was isolated as a white powder (7.11 g, 12.55 mmol, 76%); mp 190–192 °C;  $^1H$  NMR ( $DMSO-d_6$ , 270 MHz)  $\delta$  1.81–1.90 (m, 2 H,  $ArCH_2CH_2$ ), 2.87 (t, 2 H,  $J = 7.3$  Hz,  $ArCH_2$ ), 3.57–3.68 (m, 2 H,  $PCH_2$ ), 3.81 (s, 3 H,  $COOCH_3$ ), 7.32 (d, 2 H,  $J = 8.2$  Hz), 7.71–7.92 (m, 17 H, aromatic protons). Anal. Calcd for  $C_{23}H_{23}IO_2P$ : C, 61.49; H, 4.98; I, 22.40. Found: C, 61.24; H, 4.80; I, 22.14.

**Methyl 4-(4-Iodo-1-butyl)benzoate (15).** A solution of mesylate 14 (5.75 g, 20.08 mmol) and sodium iodide (10.47 g, 69.85 mmol) in acetone (200 mL) was heated under reflux for 30 min. The solution was filtered and heated under reflux for another 30 min. The solution was filtered again and the solvent evaporated. The residue was taken up in  $CHCl_3$  (100 mL) and washed with water (100 mL), 10% aqueous  $K_2S_2O_8$  (100 mL), and brine (100 mL). After drying over anhydrous  $MgSO_4$ , the solvent was evaporated and the residue purified by flash chromatography, using EtOAc/hexanes (1:4) as eluent, to give 15 (5.62 g, 17.66 mmol, 88%) as a yellow liquid:  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  1.68–1.84 (m, 4 H,  $ArCH_2CH_2CH_2$ ), 2.64 (t, 2 H,  $J = 7.4$  Hz,  $ArCH_2$ ), 3.16 (t, 2 H,  $J = 6.6$  Hz,  $ICH_2$ ), 3.87 (s, 3 H,  $COOCH_3$ ), 7.21 and 7.95 (AA'BB', 4 H, aromatic protons); HRMS calcd for  $C_{12}H_{15}IO_2$  318.0117, found 318.0119. Anal. Calcd for  $C_{12}H_{15}IO_2$ : C, 45.30; H, 4.75; I, 39.89. Found: C, 45.52; H, 4.95; I, 39.78.

**Methyl 4-(4-(2-Amino-3,4-dihydro-6-(methylamino)-4-oxopyrimidin-5-yl)butyl)benzoate (16a).** A solution of 2-amino-6-(methylamino)-4(3*H*)-pyrimidone<sup>9</sup> (0.95 g, 6.78 mmol) in a solution of sodium methoxide (366 mg, 6.66 mmol) in MeOH (10 mL) was heated under reflux under  $N_2$  for 30 min. Compound 15 (2.16 g, 6.79 mmol) was added, and the solution was heated at reflux for 12 h. The solution was cooled in a refrigerator overnight, and the yellow solid was filtered off and washed with cold ethanol: yield 1.08 g (3.27 mmol, 49%); mp 255–257 °C;  $^1H$  NMR ( $DMSO-d_6$ , 300 MHz)  $\delta$  1.25–1.35 (m, 2 H), 1.46–1.53 (m, 2 H), 2.14 (t, 2 H,  $J = 7.0$  Hz), 2.59 (t, 2 H,  $J = 7.5$  Hz), 2.71 (d, 3 H,  $J = 4.1$  Hz,  $NHCH_3$ ), 3.79 (s, 3 H,  $COOCH_3$ ), 5.88–5.90 (m, 1 H), 6.05 (br s, 2 H,  $NH_2$ ), 7.27 and 7.81 (AA'BB', 4 H, aromatic protons), 9.78 (br s, 1 H, N-3 H); HRMS calcd for  $C_{17}H_{22}N_4O_3$  330.1692, found 330.1707. Anal. Calcd for  $C_{17}H_{22}N_4O_3$ : C, 61.80; H, 6.71; N, 16.96. Found: C, 61.56; H, 6.77; N, 16.70.

**Methyl 4-(4-(2-Amino-6-(benzylamino)-3,4-dihydro-4-oxopyrimidin-5-yl)butyl)benzoate (16b).** A solution of 2-amino-6-(benzylamino)-4(3*H*)-pyrimidone<sup>10</sup> (800 mg, 3.70 mmol)

in a solution of sodium methoxide (296 mg, 5.48 mmol) in MeOH (10 mL) was heated under reflux under N<sub>2</sub> for 30 min. Methyl 4-(4-iodobutyl)benzoate (15) (1.74 g, 5.48 mmol) was added, and the solution was heated at reflux for 12 h. The solvent was evaporated, and the residue was chromatographed, using 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent, to give 300 mg (0.74 mmol, 20%) of 16b: mp 142–144 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.42–1.50 (m, 2 H), 1.62–1.70 (m, 2 H), 2.29 (t, 2 H, *J* = 7.4 Hz, het-CH<sub>2</sub>), 2.64 (t, 2 H, *J* = 7.4 Hz, C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>), 3.88 (s, 3 H, COOCH<sub>3</sub>), 4.60 (s, 2 H, PhCH<sub>2</sub>N), 5.48 (br s, 1 H, NH), 7.15–7.37 (m, 7 H, aromatic protons), 7.92 (part of AA'BB' system, 2 H); HRMS calcd for C<sub>23</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub> 406.2005, found 406.2011. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub>: C, 67.96; H, 6.45; N, 13.78. Found: C, 67.84; H, 6.30; N, 13.57.

**4-(4-(2-Amino-3,4-dihydro-6-(methylamino)-4-oxopyrimidin-5-yl)butyl)benzoic Acid (17a).** A solution of ester 16a (400 mg, 1.21 mmol) in 3 M NaOH (10 mL) was heated under reflux for 30 min. On cooling, the pH was brought to 6 by the addition of 3 M HCl, and the white precipitate was filtered off, washed with water, and dried overnight in the vacuum oven: yield 336 mg (1.06 mmol, 88%); mp 263–265 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 1.23–1.30 (m, 2 H), 1.46–1.56 (m, 2 H), 2.15 (t, 2 H, *J* = 7.1 Hz, het-CH<sub>2</sub>), 2.59 (t, 2 H, *J* = 7.5 Hz, C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>), 2.70 (d, 3 H, *J* = 4.2 Hz, NHCH<sub>3</sub>), 5.88–5.90 (m, 1 H, NH), 6.12 (br s, 2 H), 7.25 and 7.80 (AA'BB', 4 H, aromatic protons), 9.95 (br s, 1 H, N-3 H), 12.50 (br s, 1 H, COOH); HRMS calcd for C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub> 316.1535, found 316.1566.

**4-(4-(2-Amino-6-(benzylamino)-3,4-dihydro-4-oxopyrimidin-5-yl)butyl)benzoic Acid (17b).** A solution of ester 16b (300 mg, 0.74 mmol) in 1 M NaOH (40 mL) was heated under reflux for 1 h. On cooling, the pH was brought to 5 by the addition of 3 M HCl, and the white precipitate was filtered off, washed with water, and dried overnight in the vacuum oven: yield 235 mg (0.60 mmol, 81%); mp 171–175 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 1.30–1.38 (m, 2 H), 1.50–1.55 (m, 2 H), 2.25 (t, 2 H, *J* = 6.8 Hz, het-CH<sub>2</sub>), 2.61 (t, 2 H, *J* = 7.3 Hz, C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>), 4.48 (d, 2 H, *J* = 5.6 Hz, PhCH<sub>2</sub>N), 6.08 (br s, 2 H), 6.48 (br t, 1 H, NHCH<sub>2</sub>), 7.11–7.27 (m, 7 H, aromatic protons), 7.80 (part of AA'BB' system, 2 H); HRMS calcd for C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub> 392.1848, found 392.1857.

**Diethyl N-(4-(4-(2-Amino-3,4-dihydro-6-(methylamino)-4-oxopyrimidin-5-yl)butyl)benzoyl)-L-glutamate (18a).** A solution of acid 17a (313 mg, 0.99 mmol), 4-methylmorpholine (200 mg, 1.98 mmol), and 2-chloro-4,6-dimethoxy-1,3,5-triazine (320 mg, 2.00 mmol) in DMF (20 mL) was stirred at rt under N<sub>2</sub> for 30 min. Diethyl L-glutamate hydrochloride (481 mg, 2.00 mmol) and 4-methylmorpholine (200 mg, 1.98 mmol) were added, and the solution was allowed to stir at rt under N<sub>2</sub> for 18 h. The solvent was removed in vacuo, and CHCl<sub>3</sub> (100 mL) was added to the residue. The solution was washed with water (100 mL) and brine (100 mL), and after drying over anhydrous MgSO<sub>4</sub>, the solvent was evaporated and the residue chromatographed using 7% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to give 220 mg (0.44 mmol, 44%) of 18a: mp 88–90 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.21 (t, 3 H, *J* = 7.2 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 1.29 (t, 3 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 1.34–1.41 (m, 2 H), 1.56–1.61 (m, 2 H), 2.09–2.16 (m, 1 H, glutamate C<sub>β</sub>-H), 2.23–2.33 (m, 3 H), 2.39–2.56 (m, 2 H), 2.55 (t, 2 H, *J* = 7.2 Hz, C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>), 2.89 (d, 3 H, *J* = 4.4 Hz, NHCH<sub>3</sub>), 4.09 (q, 2 H, *J* = 7.2 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 4.22 (q, 2 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 4.41–4.44 (m, 1 H), 4.74–4.80 (m, 1 H, glutamate C<sub>α</sub>-H), 5.65 (br s, 2 H, NH<sub>2</sub>), 7.12 (d, 1 H, *J* = 7.5 Hz, CONH), 7.19 and 7.70 (AA'BB', 4 H, aromatic protons); HRFABMS calcd for C<sub>25</sub>H<sub>36</sub>N<sub>5</sub>O<sub>6</sub> (MH<sup>+</sup>) 502.2665, found 502.2678. Anal. Calcd for C<sub>25</sub>H<sub>36</sub>N<sub>5</sub>O<sub>6</sub>: C, 59.87; H, 7.03; N, 13.96. Found: C, 60.01; H, 6.90; N, 13.91.

**Diethyl N-(4-(4-(2-Amino-6-(benzylamino)-3,4-dihydro-4-oxopyrimidin-5-yl)butyl)benzoyl)-L-glutamate (18b).** A solution of acid 17b (210 mg, 0.54 mmol), 4-methylmorpholine (85 mg, 0.84 mmol), and 2-chloro-4,6-dimethoxy-1,3,5-triazine (150 mg, 0.85 mmol) in DMF (10 mL) was stirred at rt under N<sub>2</sub> for 30 min. Diethyl L-glutamate hydrochloride (240 mg, 1.00 mmol) and 4-methylmorpholine (101 mg, 1.00 mmol) were added, and the solution was allowed to stir at rt under N<sub>2</sub> overnight. The solvent was removed in vacuo, and CHCl<sub>3</sub> (75 mL) was added to the residue. The solution was washed with water (100 mL) and brine (100 mL), and after drying over anhydrous MgSO<sub>4</sub>, the solvent was evaporated and the residue chromatographed using

7% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent to give 180 mg (0.31 mmol, 58%) of 18b: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.20 (t, 3 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 1.28 (t, 3 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 1.41–1.46 (m, 2 H), 1.58–1.65 (m, 2 H), 2.05–2.15 (m, 1 H, glutamate C<sub>β</sub>-H), 2.26–2.32 (m, 3 H, glutamate C<sub>γ</sub>-H and het-CH<sub>2</sub>), 2.35–2.45 (m, 2 H, glutamate C<sub>γ</sub>-H<sub>2</sub>), 2.61 (t, 2 H, *J* = 7.3 Hz, C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>), 4.09 (q, 2 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 4.21 (q, 2 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 4.60 (d, 2 H, *J* = 5.1 Hz, PhCH<sub>2</sub>N), 4.63–4.66 (m, 1 H, PhCH<sub>2</sub>NH), 4.75–4.79 (m, 1 H, glutamate C<sub>α</sub>-H), 5.58 (br s, 2 H, NH<sub>2</sub>), 7.05 (d, 1 H, *J* = 7.5 Hz, CONH), 7.16 and 7.69 (AA'BB', 4 H, aromatic protons), 7.23–7.33 (m, 5 H, Ph); HRMS calcd for C<sub>31</sub>H<sub>38</sub>N<sub>5</sub>O<sub>6</sub> 577.2900, found 577.2885. Anal. Calcd for C<sub>31</sub>H<sub>38</sub>N<sub>5</sub>O<sub>6</sub>: C, 64.44; H, 6.81; N, 12.13. Found: C, 64.18; H, 6.99; N, 11.90.

**N-(4-(4-(2-Amino-3,4-dihydro-6-(methylamino)-4-oxopyrimidin-5-yl)butyl)benzoyl)-L-glutamic Acid (19a).** A solution of diester 18a (180 mg, 0.36 mmol) in 1 M sodium hydroxide solution (20 mL) was stirred at rt for 96 h. The pH was brought to 5 by the addition of 1 M HCl, and the suspension was centrifuged. The water was decanted, and the residue was centrifuged with EtOH/Et<sub>2</sub>O (1:1) and then with Et<sub>2</sub>O. The solid was filtered off and dried overnight in the vacuum oven: yield 32 mg (0.07 mmol, 20%); mp >250 °C dec; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 1.22–1.27 (m, 2 H), 1.45–1.60 (m, 2 H), 1.87–2.05 (m, 2 H, glutamate C<sub>β</sub>-H<sub>2</sub>), 2.14 (t, 2 H, *J* = 7.2 Hz, glutamate C<sub>γ</sub>-H<sub>2</sub>), 2.28 (t, 2 H, *J* = 7.2 Hz, het-CH<sub>2</sub>), 2.58 (t, 2 H, *J* = 7.5 Hz, C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>), 2.70 (d, 3 H, *J* = 4.2 Hz, NHCH<sub>3</sub>), 4.26–4.33 (m, 1 H, glutamate C<sub>γ</sub>-H), 5.84 (br s, 1 H, NHCH<sub>3</sub>), 6.31 (br s, 2 H, NH<sub>2</sub>), 7.22 and 7.73 (AA'BB', 4 H, aromatic protons), 8.36 (d, 1 H, *J* = 7.1 Hz, CONH), 10.05 (br s, 1 H, N-3 H); HRFABMS calcd for C<sub>21</sub>H<sub>25</sub>N<sub>5</sub>O<sub>6</sub> (MH<sup>+</sup>) 446.2040, found 446.2039.

**N-(4-(4-(2-Amino-3,4-dihydro-6-(benzylamino)-4-oxopyrimidin-5-yl)butyl)benzoyl)-L-glutamic Acid (19b).** A solution of diester 18b (120 mg, 0.21 mmol) in 1 M sodium hydroxide solution (10 mL) was stirred at rt for 96 h. The pH was brought to 4.5 by the addition of 1 M HCl, and the suspension was centrifuged. The water was decanted and EtOH added. The solid dissolved so Et<sub>2</sub>O was added, and it came out of solution again. The solvents were allowed to evaporate, and the product was air-dried: yield 80 mg (0.15 mmol, 74%); mp 95–97 °C dec; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 1.30–1.35 (m, 2 H), 1.50–1.60 (m, 2 H), 1.86–2.10 (m, 2 H, glutamate C<sub>β</sub>-H<sub>2</sub>), 2.23 (t, 2 H, *J* = 7.1 Hz, glutamate C<sub>γ</sub>-H<sub>2</sub>), 2.32 (t, 2 H, *J* = 7.3 Hz, het-CH<sub>2</sub>), 2.60 (t, 2 H, *J* = 7.3 Hz, C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>), 4.26–4.33 (m, 1 H, glutamate C<sub>α</sub>-H), 4.47 (d, 2 H, *J* = 4.7 Hz, PhCH<sub>2</sub>NH), 6.05 (br s, 2 H, NH<sub>2</sub>), 6.45 (t, 1 H, *J* = 5, NHCH<sub>2</sub>Ph), 7.11–7.35 (m, 7 H, aromatic protons), 7.75 (part of AA'BB', 2 H, aromatic protons), 8.48 (d, 1 H, *J* = 7.6 Hz, CONH), 12.45 (br s, 2 H, COOH); HRFABMS calcd for C<sub>27</sub>H<sub>32</sub>N<sub>5</sub>O<sub>6</sub> (MH<sup>+</sup>) 522.2353, found 522.2365.

**Ethyl 4-(5-(Ethoxycarbonyl)-5-cyanopentyl)benzoate (20).** Ethyl cyanoacetate (11.31 g, 100 mmol) was added to a solution of sodium ethoxide prepared from 2.30 g (100 mmol) of sodium and 200 mL of ethanol. After 10 min, iodide 15 (8.10 g, 25.46 mmol) was added, and the solution was heated at reflux for 2 h. The solvent was evaporated on the rotary evaporator, and saturated aqueous NH<sub>4</sub>Cl was added (100 mL). The suspension was extracted with CHCl<sub>3</sub> (100 mL), and the organic layer was washed with water (100 mL) and brine (2 × 100 mL). After drying (MgSO<sub>4</sub>), the solvent was evaporated and the residue chromatographed using EtOAc/hexanes (1:4) as eluent. Excess ethyl cyanoacetate was removed by distillation in vacuo to give 20 as a clear liquid (6.51 g, 20.51 mmol, 81%). The analytical sample was prepared by vacuum distillation: bp 210 °C (0.25 mmHg); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.28 (t, 3 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 1.39 (t, 3 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 1.52–1.60 (m, 2 H), 1.66–1.73 (m, 2 H), 1.94–2.02 (m, 2 H), 2.70 (t, 2 H, *J* = 7.5 Hz, ArCH<sub>2</sub>), 3.48 (t, 1 H, *J* = 7.0 Hz, NCCCHCOOEt), 4.25 (q, 2 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 4.36 (q, 2 H, *J* = 7.1 Hz, COOCH<sub>2</sub>CH<sub>3</sub>), 7.23 and 7.96 (AA'BB', 4 H, aromatic protons); HRMS calcd for C<sub>18</sub>H<sub>23</sub>NO<sub>4</sub> 317.1627, found 317.1621. Anal. Calcd for C<sub>18</sub>H<sub>23</sub>NO<sub>4</sub>: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.34; H, 7.47; N, 4.47.

**Methyl 4-(4-(6-Amino-3,4-dihydro-2-methyl-4-oxopyrimidin-5-yl)butyl)benzoate (21).** A solution of 20 (2.00 g, 6.30 mmol), acetamide hydrochloride (600 mg, 6.35 mmol), and sodium methoxide (1.05 g, 19.08 mmol) in methanol (100 mL) was

heated under reflux under  $N_2$  for 12 h. The pH was brought to 5 by the addition of 3 M HCl, and the solution was placed in the refrigerator overnight. The solid was filtered off, washed with water, and dried in the vacuum oven: yield 0.95 g (3.01 mmol, 48%); mp 258–260 °C;  $^1H$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  1.29–1.36 (m, 2 H), 1.48–1.58 (m, 2 H), 2.05 (s, 3 H,  $CH_3$ ), 2.21 (t, 2 H,  $J$  = 7.1 Hz, Het- $CH_2$ ), 2.62 (t, 2 H,  $J$  = 7.5 Hz,  $ArCH_2$ ), 3.79 (s, 3 H,  $COOCH_3$ ), 6.00 (br s, 2 H,  $NH_2$ ), 7.29 and 7.82 (AA'BB', 4 H, aromatic protons), 11.32 (br s, 1 H, N-3 H); HRMS calcd for  $C_{17}H_{21}N_3O_3$  315.1583, found 315.1576. Anal. Calcd for  $C_{17}H_{21}N_3O_3$ : C, 64.74; H, 6.71; N, 13.32. Found: C, 64.71; H, 6.77; N, 13.16.

**4-(4-(6-Amino-3,4-dihydro-2-methyl-4-oxopyrimidin-5-yl)butyl)benzoic Acid (22).** A solution of ester 22 (750 mg, 2.38 mmol) in 1 M NaOH (30 mL) was heated under reflux for 2 h. After cooling, the pH was brought to 5 by the addition of 1 M HCl, and the precipitate was filtered off, washed with water, and dried to give 480 mg (1.59 mmol, 67%) of 22 as a white powder; mp 278–280 °C;  $^1H$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  1.30–1.37 (m, 2 H), 1.49–1.58 (m, 2 H), 2.05 (s, 3 H,  $CH_3$ ), 2.22 (t, 2 H,  $J$  = 7.2 Hz, het- $CH_2$ ), 2.61 (t, 2 H,  $J$  = 7.5 Hz,  $ArCH_2$ ), 6.00 (br s, 2 H,  $NH_2$ ), 7.26 and 7.80 (AA'BB', 4 H, aromatic protons), 11.40 (br s, 1 H, N-3 H), 12.75 (br s, 1 H, COOH); HRMS calcd for  $C_{16}H_{19}N_3O_3$  301.1426, found 301.1438. Anal. Calcd for  $C_{16}H_{19}N_3O_3$ : C, 63.77; H, 6.36; N, 13.94. Found: C, 63.89; H, 6.31; N, 13.71.

**Diethyl N-(4-(4-(6-Amino-3,4-dihydro-2-methyl-4-oxopyrimidin-5-yl)butyl)benzoyl)-L-glutamate (23).** A solution of acid 22 (450 mg, 1.49 mmol), 4-methylmorpholine (230 mg, 2.27 mmol), and 2-chloro-4,6-dimethoxy-1,3,5-triazine (320 mg, 2.00 mmol) in DMF (15 mL) was stirred at rt under  $N_2$  for 30 min. Diethyl L-glutamate hydrochloride (481 mg, 2.00 mmol) and 4-methylmorpholine (200 mg, 1.98 mmol) were added, and the solution was allowed to stir at rt under  $N_2$  for 2.5 h. The solvent was removed in vacuo, and  $CH_2Cl_2$  (100 mL) was added to the residue. The solution was washed with water (100 mL) and brine (100 mL), and after drying over anhydrous  $MgSO_4$ , the solvent was evaporated and the residue chromatographed using 7% MeOH/ $CH_2Cl_2$  as eluent to give 350 mg (0.72 mmol, 48%) of 23:  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  1.18 (t, 3 H,  $J$  = 7.1 Hz,  $COOCH_2CH_3$ ), 1.26 (t, 3 H,  $J$  = 7.1 Hz,  $COOCH_2CH_3$ ), 1.44–1.50 (m, 2 H), 1.59–1.69 (m, 2 H), 2.03–2.13 (m, 1 H, glutamate  $C_\beta$ -H), 2.16–2.26 (m, 1 H, glutamate  $C_\beta$ -H), 2.21 (s, 3 H,  $CH_3$ ), 2.31–2.50 (m, 4 H, het- $CH_2$  and glutamate  $C_\gamma$ -H $_2$ ), 2.64 (t, 2 H,  $J$  = 7.4 Hz,  $C_6H_4CH_2$ ), 4.07 (q, 2 H,  $J$  = 7.1 Hz,  $COOCH_2CH_3$ ), 4.19 (q, 2 H,  $J$  = 7.1 Hz,  $COOCH_2CH_3$ ), 4.72–4.77 (m, 1 H, glutamate  $C_\alpha$ -H), 4.85 (br s, 2 H,  $NH_2$ ), 7.16 and 7.68 (AA'BB', 4 H, aromatic protons), 7.22 (d, 1 H,  $J$  = 7.6 Hz, CONH); HRMS calcd for  $C_{25}H_{34}N_4O_8$  486.2478, found 486.2492. Anal. Calcd for  $C_{25}H_{34}N_4O_8$ : C, 61.71; H, 7.04; N, 11.51. Found: C, 61.50; H, 6.92; N, 11.46.

**N-(4-(4-(6-Amino-3,4-dihydro-2-methyl-4-oxopyrimidin-5-yl)butyl)benzoyl)-L-glutamic Acid (24).** A solution of diester 23 (250 mg, 0.51 mmol) in 1 M NaOH (15 mL) was stirred at rt for 24 h. The pH was brought to 5 by the addition of 1 M HCl, and the precipitate was allowed to stand for 15 min. The suspension was centrifuged and the water decanted off. The remaining solid was centrifuged twice with ethanol and once with ether before being filtered off and dried in the vacuum oven: yield 150 mg (0.35 mmol, 68%); mp 190–192 °C;  $^1H$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  1.29–1.35 (m, 2 H), 1.48–1.58 (m, 2 H), 1.87–2.01 (m, 2 H, glutamate  $C_\beta$ -H $_2$ ), 2.05 (s, 3 H,  $CH_3$ ), 2.21 (t, 2 H,  $J$  = 7.2, glutamate  $C_\gamma$ -H $_2$ ), 2.31 (t, 2 H,  $J$  = 7.3 Hz, het- $CH_2$ ), 2.60 (t, 2 H,  $J$  = 7.3 Hz,  $C_6H_4CH_2$ ), 4.31–4.38 (m, 1 H, glutamate  $C_\alpha$ -H), 6.04 (s, 2 H,  $NH_2$ ), 7.24 and 7.74 (AA'BB', 4 H, aromatic protons), 8.45 (d, 1 H,  $J$  = 7.6 Hz, CONH), 11.32 (br s, 1 H, N-3 H), 12.46 (br s, 2 H, COOH); FABMS calcd for  $C_{21}H_{27}N_4O_6$  (MH $^+$ ) 431.1931, found 431.1946.

**Acknowledgment.** This work was supported by a grant (CA42367) to Princeton University from the National Cancer Institute, NIH. We are indebted to Dr. G. B. Grindey of Eli Lilly & Co., Indianapolis, IN, for the biological evaluation studies.

**Registry No.** 3, 5604-46-6; 4, 142979-46-2; 5, 142979-47-3; 6, 142979-48-4; 7, 142979-49-5; 8, 61266-36-2; 9, 15403-22-2; 10,

141618-99-7; 11, 142979-50-8; 12, 142979-51-9; 14, 124656-56-0; 15, 142979-52-0; 16a, 142979-53-1; 16b, 142979-61-1; 17a, 142979-54-2; 17b, 142979-62-2; 18a, 142979-55-3; 18b, 142979-63-3; 19a, 142979-56-4; 19b, 142979-64-4; 20, 142979-57-5; 21, 142979-58-6; 22, 142979-59-7; 23, 142979-60-0; 24, 143006-13-7; PhCH $_2$ NHMe, 103-67-3; H $_3$ CCOCH $_2$ CH $_2$ COCH $_3$ , 110-13-4; 4-IC $_6$ H $_4$ COOMe, 619-44-3; HC=CCH $_2$ OH, 107-19-7; Ph $_3$ P, 603-35-0; H-Glu(OEt)-OEt-HCl, 1118-89-4; EtOCOCH $_2$ CN, 105-56-6; H $_3$ CC(NH $_2$ )=NH-HCl, 124-42-5.

**Supplementary Material Available:**  $^1H$  NMR spectra and  $^{13}C$  NMR, IR, and mass spectral data of the compounds reported in this paper (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

## Dehalogenation of $\alpha$ -Halo Aldehydes via $\alpha$ -Halo Aldimines and 2-Aza-1,3-dienes

Norbert De Kimpe,\*<sup>†</sup> Milan Nagy,<sup>‡</sup> Marc Boeykens, and Danny Van der Schueren

Laboratory of Organic Chemistry, Faculty of Agricultural Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium

Received April 8, 1992

### Introduction

The selective removal of halogens  $\alpha$  to a carbonyl moiety yielding the parent carbonyl compound has received considerable attention. An array of procedures for the reductive dehalogenation of  $\alpha$ -halo ketones has been developed, including the use of zinc in acetic acid,<sup>1</sup> metal carbonyls,<sup>2–4</sup> transition metals,<sup>5</sup> tributyltin hydride,<sup>6</sup> iodide ion,<sup>7,8</sup> nickel boride,<sup>9</sup> tellurium reagents,<sup>10,11</sup> samarium iodide,<sup>12</sup> lithium diisopropylamide,<sup>13</sup> iodophosphines,<sup>14</sup> the combination of phenylsilane and catalytic amounts of molybdenum hexacarbonyl and triphenylphosphine,<sup>15</sup> and many other reagents.<sup>15,16</sup> Few of these reagents are applicable for the dehalogenation of  $\alpha$ -halo aldehydes because of competitive reactions mainly centered at the reactive aldehyde carbon. However, 1,3-dimethyl-2-phenylbenzimidazole has been found recently to be a powerful and chemoselective reducing agent for the mild reductive dehalogenation of a variety of  $\alpha$ -halo carbonyl compounds, including  $\alpha$ -halo aldehydes.<sup>17</sup>

In the present paper a new method for the dehalogenation of  $\alpha$ -halo aldehydes employing very common chemicals is disclosed.

### Discussion of the Results

The dechlorination of  $\alpha$ -halo aldehydes consists of a sequence of reactions by which an  $\alpha$ -chloro aldehyde 1 is converted into a N-benzylic  $\alpha$ -chloro aldimine 3, which is subjected to base-induced 1,4-dehydrochlorination<sup>18</sup> and subsequent hydrolysis (Scheme I).  $\alpha$ -Chloro aldehydes 1 are cleanly converted into  $\alpha$ -chloro aldimines 3 by reaction with 1 molar equiv of benzylamine or *p*-chlorobenzylamine in  $CH_2Cl_2$  in the presence of  $MgSO_4$  as drying agent at room temperature for 2 h. These N-benzylic  $\alpha$ -chloro aldimines 3 are sufficiently pure for use in the next step. N-Benzylaldimines 3 contain an active methylene function at the benzylic position, allowing deprotonation by potassium *tert*-butoxide. The resulting me-

\* Research Director of the National Fund for Scientific Research.

<sup>†</sup> Comenius University, Bratislava, Czechoslovakia.