# AN INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION APPROACH TO 5,6,7,8-TETRAHYDRO-4-ETHOXY-6-HYDROXYMETHYL-2-PIVALOYLAMINO-5-DEAZAPTERIDIN-5(8*H*)-ONE, A POTENTIALLY USEFUL INTERMEDIATE TO 5-DEAZA- AND 5,10-DIDEAZA-5,6,7,8-TETRAHYDROFOLIC ACID ANALOGS

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Abstract: 2-Amino-4,6-dichloro-5-formylpyrimidine was converted to the title compound (**12**), a potentially useful intermediate for the synthesis of 5-deaza- and 5,10-dideaza-5,6,7,8-tetrahydrofolic acid analogs. The key steps in the sequence were an intramolecular 1,3-dipolar cycloaddition of an in situ generated nitrile oxide (**10b**) to give the isoxazolo[3',4':4,5]pyrido[2,3-d]pyrimidine (**11b**) followed by reductive cleavage of the isoxazoline N-O bond.

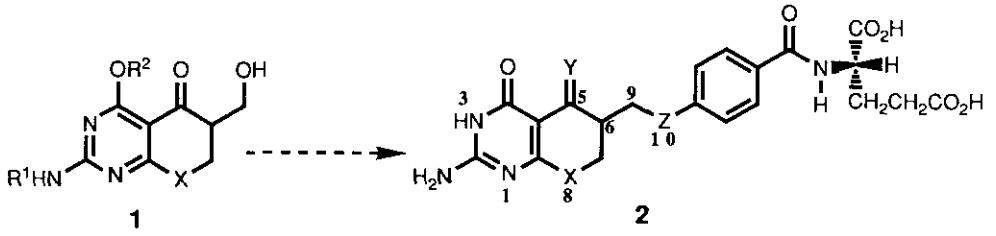
5,10-Dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF; **2**, X = NH, Y = $H_2$, Z = $CH_2$) is the first potent and selective inhibitor of the folate cofactor-requiring enzyme, glycinamide ribonucleotide transformyl-ase (GAR TFase), required for de novo purine biosynthesis.[1-9] DDATHF exhibits a broad spectrum of activity against a variety of murine solid tumors and human colon xenografts in mice, and the 6(R) diastereomer (LY264618) is currently in Phase I clinical trials as an antineoplastic

agent.

As part of our continuing efforts to establish a structure-activity profile for DDATHF,[9] we were interested in preparing analogs in which the 8-NH grouping was replaced by N-alkyl, O and S, as well as analogs bearing a carbonyl group at position 5. In addition, since 5-deaza-5,6,7,8-tetrahydrofolic acid (5-DATHF: **2**, X = Z = NH, Y = $H_2$)[10] has been shown to be a potent cytotoxic agent whose focus of action is also GAR TFase, we were particularly interested in developing a general synthetic method which would allow for the preparation of both 5-deaza and 5,10-dideazatetrahydrofolic acid analogs with the above specific structural modifications in mind.

6-Hydroxymethyl derivatives of type (**1**) (X = NH, NMe, O or S) could, in principle, lead both to 5-deaza- and to 5,10-dideazafolic acid analogs (**2**) (Scheme 1). Since β-hydroxy ketones of type **1** are readily available by reductive cleavage of isoxazolines, retrosynthetic analysis suggests the overall strategy outlined in Scheme 2. There are some precedents in pyrimidine chemistry for intramolecular 1,3-dipolar cycloaddition reactions of the type suggested in Scheme 2.[11-13] For example,

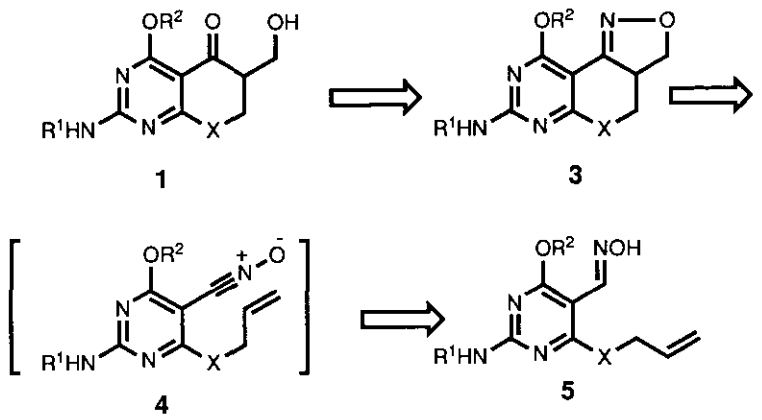
**Scheme 1**




X = NH, NMe, O or S
$R^1$ and $R^2$ = protecting groups

X = NH, NMe, O or S
Y = O or $H_2$
Z = NH or $CH_2$

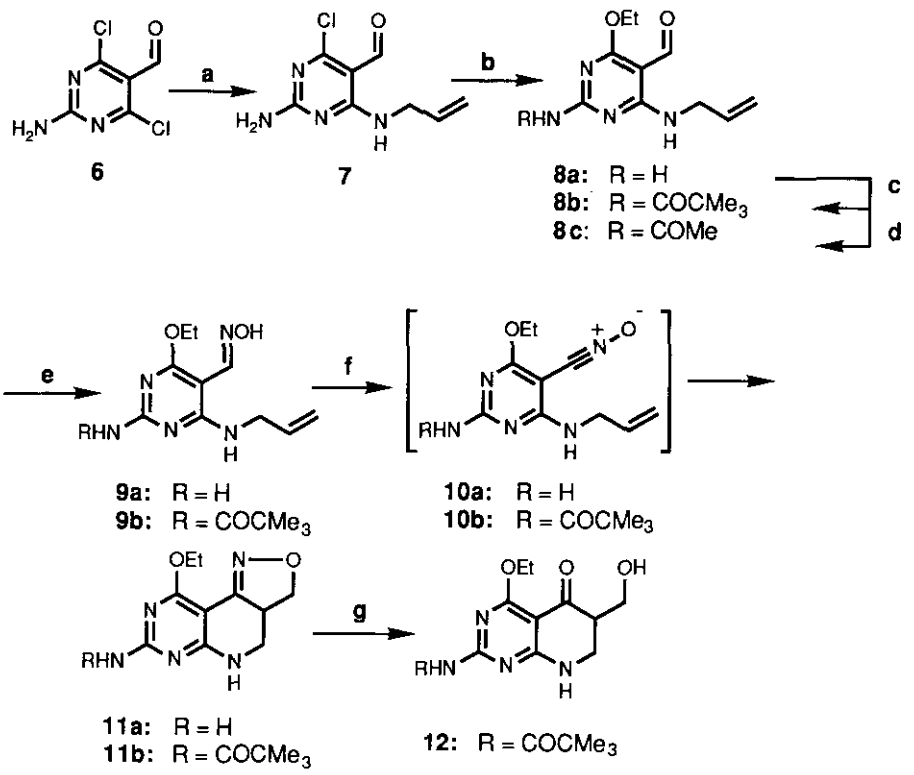
**Scheme 2**




1,3-dimethyl-5-oximinomethyl-6-allylaminouracil has been converted to the corresponding isoxazolo[3',4':4,5]pyrido[2,3-d]pyrimidine.[11] Similarly, the reaction of tosylhydrazones of 6-allylamino-5-formyluracils with lead tetraacetate has been reported to yield pyrazolo[3',4':4,5]pyrido[2,3-d]pyrimidines.[13] However, we are not aware of any reports of the formation by this strategy of isoxazolo[3',4':4,5]-pyrido[2,3-d]pyrimidines which do not contain the uracil moiety. Herein, we describe the results of our synthetic studies leading to the title compound (**12** )from 2-amino-4,6-dichloro-5-formylpyrimidine (**6**).

Formylation-chlorination of 2-amino-4,6-dihydroxypyrimidine using phosphorus oxychloride in DMF to give **6** in 51% yield has been reported by Bell et al.[14] Treatment of **6** with methanolic allylamine gave the 4-chloro-6-allylaminopyrimidine derivative (**7**) in 90% yield (Scheme 3).

**Scheme 3**



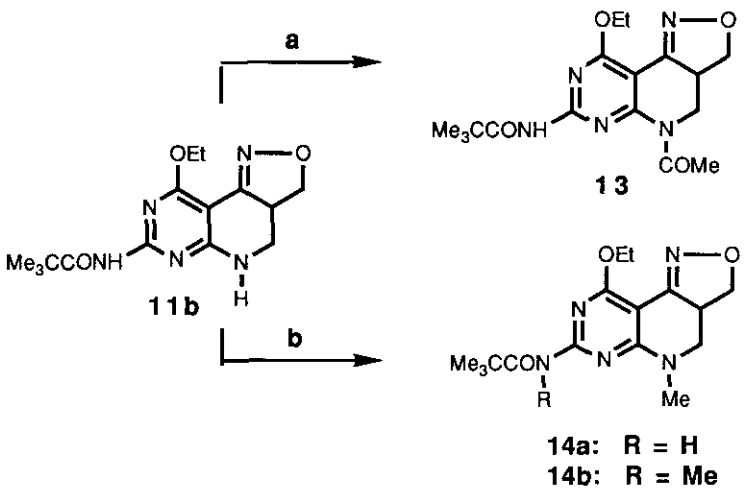

(a) $CH_2$=$CHCH_2NH_2$, $Et_3N$, MeOH, Δ; (b) NaOEt, EtOH, Δ; (c) $(Me_3CCO)_2O$, toluene, Δ; (d) $Ac_2O$, Δ; (e) $NH_2OH.HCl$, pyridine, EtOH, Δ; (f) $Me_3COCl$, $CH_2Cl_2$, 2 °C, followed by $Et_3N$; (g) Raney nickel, MeOH, AcOH, $H_2O$, $H_2$,room temperature, 1 atm

Reaction of **7** with sodium ethoxide in refluxing ethanol provided the 4-ethoxypyrimidine (**8a**) (85%), which then gave the oxime (**9a**) in 84% yield upon treatment with hydroxylamine. The nitrile oxide (**10a**), which was generated in situ by treatment of the oxime (**9a**) either with N-chlorosuccinimide, aqueous sodium hypochlorite or tert-butyl hypochlorite followed by triethylamine, underwent intramolecular cyclization to give the cycloadduct (**11a**). Yields, however, were routinely poor (5-10%),[15] and starting material (**9a**) was not recovered. In the anticipation that the 2-amino and/or the 6-allylamino group(s) were interfering with the cycloaddition reaction by reacting with the chlorinating agent and/or with the intermediate chlorooxime/nitrile oxide, **7** was acylated with pivalic anhydride in refluxing toluene to give the corresponding 2-pivaloylaminopyrimidine (**8b**) in 91%

yield. From a comparison of the nmr spectrum of the product (single 2-NH proton at δ 7.81; 6-allylamino NH at δ 9.29) with the spectrum of the starting material **7** (two $NH_2$ protons at δ 5.2; 6-allylamino NH at δ 9.31), it was clear that acylation had taken place at the 2-amino group of **7**. Analogous results were obtained upon treatment of **7** with a large excess of acetic anhydride at reflux; the 2-acetamidopyrimidine (**8c**) was obtained in 70% yield, with no observable acetylation at the 6-allylamino nitrogen. Reaction of the pivaloylated 5-formylpyrimidine (**8b**) with hydroxylamine gave the corresponding oximinomethylpyrimidine (**9b**) in 88% yield. Best results in the ensuing cycloaddition reaction leading to **11b** were obtained when freshly prepared tert-butyl hypochlorite was used as the chlorinating agent. Nevertheless, the highest yields obtained of the cycloadduct (**11b**) were in the range 40-45%, with recovery of some 40-45% of the starting material (**9b**). Although yields of the cycloadduct (**11b**) might be improved by the use of a suitable protecting group on the 6-allylamino nitrogen atom, such modifications were not explored.

Treatment of the cycloadduct (**11b**) with acetic anhydride at reflux gave the 8-N acetyl derivative (**13**) in 72% yield (Scheme 4). Also, reaction of **11b** with two equivalents of sodium hydride followed by addition of methyl iodide in refluxing tetrahydrofuran gave the 8-N methyl derivative (**14a**) in 51% yield. When a large excess of methyl iodide was used, the dimethylated compound (**14b**) (50%) was isolated (Scheme 4). Finally, reaction of **11b** with Raney nickel and hydrogen in aqueous methanol in the presence of acetic acid provided the desired intermediate (**12**) in 78% yield.

**Scheme 4**




(a) $Ac_2O$, Δ; (b) NaH (2 eq.), THF, MeI (excess), Δ

Thus, we have developed a method for the conversion of 2-amino-4,6-dichloro-5-formylpyrimidine (**6**) to 5,6,7,8-tetrahydro-(6-hydroxymethyl)-5-deazapteridin-5(8H)-one (**12**) in six steps. Analogous methodology could, in principle, be used to prepare intermediates of type **1** where X = NMe (starting from the reaction of **6** and N-methylallylamine), and X = O or S (from allyl alcohol or allyl mercaptan respectively). Further manipulation of the intermediate (**12**) to provide 5-deaza- and 5,10-dideaza-5,6,7,8-tetrahydrofolic acid analogs is currently under investigation.

## Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. The $^1H$ nmr data were recorded on a General Electric QE300 (300 MHz) instrument and chemical shifts are reported in ppm relative to residual nondeuterated solvent. Mass spectral data were obtained by Dr. Dorothy Little (Princeton University) on a Kratos MS50TC spectrometer. Elemental analyses were performed by Eli Lilly and Co., Indianapolis, IN. Column

chromatography was performed on Merck silica gel 60 (240-400) mesh. Tlc analyses were routinely carried out on Bakerflex IB2-F (silica gel) plates utilizing uv visualization.

6-Allylamino-2-amino-4-chloro-5-formylpyrimidine (**7**). A mixture of 2-amino-4,6-dichloro-5-formylpyrimidine[14] (20 g, 0.104 mol), allylamine (5.95 g, 0.104 mol), triethylamine (14.5 g, 0.104 mol) and methanol (500 ml) was heated at reflux for 2 h. The solvent was removed by evaporation under reduced pressure, the residue was suspended in water and the solid was collected by vacuum filtration and washed thoroughly with water. The filter cake was dried in vacuo over calcium chloride to give 21.2 g (90%) of a colorless solid ($R_f$ = 0.35; 5% methanol in methylene chloride). Recrystallization from ethanol gave the analytical sample, mp 147-148 °C; $^1$H nmr ($CDCl_3$) δ 4.14 (2H, m), 5.17-5.26 (2H, m), 5.5 (2H, br), 5.86-5.99 (1H, m), 9.33 (1H, br), 10.11 (1H, s). Anal. Calcd for $C_8H_9N_4OCl$;: C, 45.19; H, 4.27; N, 26.35; Cl, 16.67. Found: C, 44.99; H, 4.33; N, 26.22; Cl, 16.62. Hrms Calcd for $C_8H_9N_4OCl$ m/z 212.0465, found 212.0466.

6-Allylamino-2-amino-4-ethoxy-5-formylpyrimidine (**8a**). To a freshly prepared solution of sodium ethoxide (7.07 g, 0.094 mol) in absolute ethanol (500 ml) was added 6-allylamino-2-amino-4-chloro-5-formylpyrimidine (**7**) (20 g, 0.094 mol). The mixture was heated at reflux under nitrogen for 5 h, the precipitated sodium chloride was removed by filtration, and the filtrate was evaporated. The residual solid was partitioned between methylene chloride (300 ml) and water (100 ml), the organic layer was separated, dried (anhy $MgSO_4$) and the solvent was removed in vacuo to give 17.7 g (85%) of a pale yellow solid ($R_f$ = 0.4; 5% methanol in methylene chloride). Recrystallization from ethanol gave colorless microcrystals, mp 104-105 °C; $^1$H nmr ($CDCl_3$) δ 1.38 (3H, t, J = 7.1 Hz), 4.10 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 5.12-5.27 (4H, m with superimposed br peak,), 5.87-6.0 (1H, m), 9.31 (1H, br), 9.98 (1H, s). Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.05; H, 6.35; N, 25.21. Found: C, 54.10; H, 6.38; N, 25.17. Hrms calcd for $C_{10}H_{14}N_4O_2$ m/z 222.1117, found 222.1116.

6-Allylamino-4-ethoxy-5-formyl-2-pivaloylaminopyrimidine (**8b**).

A mixture of 6-allylamino-2-amino-4-ethoxy-5-formylpyrimidine (**7**) (3.82 g, 16.1 mmol), pivalic anhydride (3.5 ml, 17.25 mmol) and toluene (40 ml) was heated at reflux for 8 h. The solvent was removed in vacuo and the residue was triturated with pentane. A cream colored solid (4.5 g, 91%) was collected by vacuum filtration ($R_f$ = 0.75; 10% methanol in methylene chloride), mp 105-106 °C; $^1$H nmr ($CDCl_3$) δ 1.33 (9H, s), 1.41 (3H, t, J = 7.3 Hz), 4.2-4.25 (2H, m), 4.51 (2H, q, J = 7.3 Hz), 5.15-5.3 (2H, m), 5.9-6.0 (1H, m), 7.81 (1H, br), 9.29 (1H, br), 10.11 (1H, s). Anal. Calcd for $C_{15}H_{22}N_4O_3$: C, 58.81; H, 7.24; N, 18.29. Found: C, 58.74; H, 7.28; N, 18.26. Hrms calcd for $C_{15}H_{22}N_4O_3$ m/z 306.1692, found 306.1688.

2-Acetylamino-6-allylamino-4-ethoxy-5-formylpyrimidine (**8c**).

A mixture of 6-allylamino-2-amino-4-ethoxy-5-formylpyrimidine (**7**) (500 mg, 2.25 mmol) and acetic anhydride (5 ml) was heated at reflux for 3 h. The solvent was removed under reduced pressure, the residue was triturated with ether and the suspended solid was collected by filtration. Recrystallization from ethanol gave 420 mg (70%) of colorless needles, mp 110-111 °C; $^1$H nmr ($CDCl_3$) δ 1.41 (3H, t, J = 7.2 Hz), 2.61 (3H, s), 4.12-4.16 (2H, m), 4.46 (2H, q, J = 7.2 Hz), 5.16-5.26 (2H, m), 5.85-5.96 (1H, m), 7.7 (1H, br), 9.36 (1H, br), 10.10 (1H, s). Anal. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.10; N, 21.20. Found: C, 54.43; H, 6.33; N, 21.32. Hrms calcd for $C_{12}H_{16}N_4O_3$ m/z 264.1222, found m/z 264.1219.

6-Allylamino-2-amino-4-ethoxy-5-oximinomethylpyrimidine (**9a**).

A mixture of 6-allylamino-2-amino-4-ethoxy-5-formylpyrimidine (**8a**) (1.0 g, 4.5 mmol), hydroxylamine hydrochloride (315 mg, 4.5 mmol), pyridine (1.0 ml), and ethanol (20 ml) was heated at reflux for 6 h. The solvent and excess pyridine were revoved *in vacuo* and the residue was partitioned between methylene chloride (50 ml) and water (30 ml). The organic layer was separated, dried (anhy $MgSO_4$) and the solvent was removed under reduced pressure to give 0.9 g (84%) of a colorless

solid ($R_f$ = 0.6; 10% methanol in methylene chloride). Recrystallization from chloroform gave colorless microcrystals, mp 149-151 °C; $^1$H nmr ($CDCl_3$) δ 1.35 (1H, t, J = 7.1 Hz), 4.13-4.6 (2H, m), 4.32 (2H, q, J = 7.1 Hz), 4.81 (2H, br), 5.12-5.26 (2H, m), 5.92-6.01 (1H, m), 6.93 (1H, s), 7.93 (1H, br), 8.52 (1H, s). Anal. Calcd for $C_{10}H_{15}N_5O_2$: C, 50.63; H, 6.37; N, 29.52. Found: C, 50.54; H, 6.39; N, 29.44. Hrms calcd for $C_{10}H_{15}N_5O_2$ m/z 237.1225, found 237.1227.

6-Allylamino-4-ethoxy-5-oximinomethyl-2-pivaloylaminopyrimidine (**9b**). A mixture of 6-allylamino-4-ethoxy-5-formyl-2-pivaloylaminopyrimidine (**8b**) (4.1 g, 13.38 mmol), hydroxylamine hydrochloride (0.93 g, 13.38 mmol), pyridine (2 ml) and ethanol (50 ml) was heated at reflux for 0.5 h. The solvent and excess pyridine were removed by evaporation under reduced pressure. The residue was partitioned between methylene chloride (50 ml) and 0.1 N hydrochloric acid (30 ml), and the organic layer was separated, dried (anhy $MgSO_4$) and the solvent was removed under reduced pressure. Trituration of the residue with ether gave 3.78 g (88%) of a cream colored solid ($R_f$ = 0.65; 10% methanol in methylene chloride), mp 170-171 °C; $^1$H nmr ($CDCl_3$) δ 1.33 (9H, s), 1.37 (3H, t, J = 7.3 Hz), 4.22-4.26 (2H, m), 4.47 (2H, q, J = 7.3 Hz), 5.13-5.28 (2H, m), 5.93-6.02 (1H, m), 7.05 (1H, br), 7.77 (1H, br), 8.02 (1H, br), 8.54 (1H, s). Anal. Calcd for $C_{15}H_{23}N_5O_3$: C, 56.06; H, 7.21; N, 21.79. Found: C, 55.88; H,7.16; N, 21.89. Hrms calcd for $C_{15}H_{23}N_5O_3$ m/z 321.1801, found 321.1806.

4-Ethoxy-2-pivaloylaminoisoxazolo[3',4':4,5]-7,8-dihydropyrido[2,3-d]pyrimidine (**11b**). To a well stirred solution of 6-allylamino-4-ethoxy-5-oximinomethyl-2-pivaloylaminopyrimidine (**9b**) (1.0 g, 3.11 mmol) in anhydrous methylene chloride (20 ml) cooled to 2 °C was added dropwise a mixture of freshly prepared tert-butyl hypochlorite[16] (340 mg, 3.11 mmol) in methylene chloride (10 ml) over a 15 min period. The mixture was stirred at 2 °C for a further 15 min, and triethylamine (3.11 mmol) was then added dropwise over a 15 min period. The mixture was stirred for a further 1 h while allowing it to warm to 20 °C. The reaction mixture

was then washed with water, the organic layer was separated, and dried (anhy $MgSO_4$), and the solvent was removed under reduced pressure. The residual solid was chromatographed on silica gel eluting with 1% methanol in chloroform. The fractions containing the pure product ($R_f$ = 0.5; 10% methanol in methylene chloride) were combined and the solvent was removed under reduced pressure to give 440 mg (44%) of a microcrystalline powder, mp 263-264 °C (decomp.) (420 mg of the starting material(**9b**) was recovered from this reaction). $^1H$ nmr ($CDCl_3$) δ 1.32 (9H, s), 1.43 (3H, t, J = 7.2 Hz), 3.36-3.43 (1H, m), 3.73-3.81 (1H, m), 3.85-3.91 (2H, m), 4.52 (2H, q, J = 7.2 Hz), 4.58-4.63 (1H, m), 5.76 (1H, br), 7.74 (1H, br). Anal. Calcd for $C_{15}H_{21}N_5O_3$: C, 56.41; H, 6.63; N, 21.93. Found: C, 56.48; H, 6.73; N, 21.67. Hrms calcd for $C_{15}H_{21}N_5O_3$ m/z 319.1644, found m/z 319.1641.

8-Acetyl-4-ethoxy-2-pivaloylaminoisoxazolo[3',4':4,5]-7,8-dihydro-[2,3-d]pyrimidine (**13**). A mixture of **11b** (0.5 g, 1.565 mmol) and acetic anhydride (6 ml) was heated at reflux for 0.5 h. The solvent was removed in vacuo and the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution (20 ml). The organic layer was separated, dried (anhy $MgSO_4$) and the solvent was removed in vacuo. The residue was recrystallized from ethanol to give 410 mg (72%) of colorless needles ($R_f$ = 0.65; 10% methanol in methylene chloride), mp 190-191 °C; $^1H$ nmr ($CDCl_3$) δ 1.35 (9H, s), 1.48 (3H, t, J = 7 Hz), 2.82 (3H, s), 3.05-3.14 (1H, m), 3.7-3.79 (1H, m), 3.85-3.92 (1H, m), 4.57-4.7 (3H, m), 5.19-5.25 (1H, m), 7.89 (1H, br). Anal. Calcd for $C_{17}H_{23}N_5O_4$: C, 56.50; H, 6.42; N, 19.38. Found: C, 56.24; H, 6.49; N, 19.36. Hrms calcd for $C_{17}H_{23}N_5O_4$ m/z 361.1750, found 361.1753.

4-Ethoxy-8-methyl-2-pivaloylaminoisoxazolo[3',4':4,5]-7,8-dihydropyrido[2,3-d]pyrimidine (**14a**). To a stirred suspension of sodium hydride (80% dispersion in oil; 12 mg, 0.4 mmol), in anhydrous tetrahydrofuran (5 ml) under nitrogen was added the cycloadduct(**11b**) (65 mg, 0.2 mmol) in tetrahydrofuran (5 ml). The mixture was stirred at room temperature for 10 min and methyl iodide (0.013 ml,

0.2 mmol) was then added. Starting material was still present (by tlc) after the mixture was heated at reflux for 0.5 h. Another 0.065 ml (1 mmol) of methyl iodide was added and the mixture was heated at reflux for a further 0.5 h. The reaction mixture was cooled (ice-water), neutralized with ammonium chloride solution and extracted with ethyl acetate (20 ml). The organic layer was separated, dried (anhy $MgSO_4$), filtered and the solvent removed in vacuo. The residue was triturated with ether and the resulting colorless solid was collected by vacuum filtration to give 35 mg (51%) of **14a**, mp 214-215 °C; $^1H$ nmr ($CDCl_3$) δ 1.34 (9H, s), 1.43 (3H, t, J = 7.1 Hz), 3.24 (3H, s), 3.41-3.49 (1H, m), 3.62-3.68 (1H, m), 3.8-3.91 (2H, m), 4.54 (2H, q, J = 7.1 Hz), 4.61-4.63 (1H, m), 7.77 (1H, br). Anal. Calcd for $C_{16}H_{23}N_5O_3$: C, 57.65; H, 6.95; N, 21.01. Found: C, 57.35; H, 7.07; N, 20.74. Hrms calcd for $C_{16}H_{23}N_5O_3$ m/z 333.1801, found 333.1799.

4-Ethoxy-8-methyl-2-pivaloyl(N-methyl)aminoisoxazolo[3',4':4,5]-7,8-dihydropyrido[2,3-d]pyrimidine (**14b**). To a stirred suspension of sodium hydride (80% dispersion in oil; 480 mg, 16.0 mmol) in anhydrous tetrahydrofuran (25 ml) under nitrogen and cooled to 2 °C , was added dropwise a solution of the cycloadduct (**11b**) (2.55 g, 8.0 mmol) in anhydrous tetrahydrofuran (25 ml). The mixture was allowed to warm to room temperature and stirred for 0.5 h. Methyl iodide (2.5 ml, 40 mmol) was added and the mixture was heated at reflux for 1 h. Since starting material was still present (tlc), a further 2.5 ml of methyl iodide was added and the mixture was heated at reflux for an additional 3 h. The reaction mixture was cooled to 5 °C, quenched with water, neutralized with 1N hydrochloric acid and extracted with ethyl acetate (100 ml). The organic layer was dried (anhy $MgSO_4$), filtered and the solvent removed in vacuo. The residue was chromatographed on silica gel eluting with 1% methanol in chloroform. The fractions containing the pure product ($R_f$ = 0.65; 10% methanol in methylene chloride) were combined and the solvent removed in vacuo. The residue was triturated with diethyl ether and the resulting cream-colored solid was collected by vacuum filtration to give 1.4 g (50%), mp 117-118 °C; $^1H$ nmr ($CDCl_3$) δ 1.27 (9H,

s), 1.43 (3H, t, J = 7.1 Hz), 3.18 (3H, s), 3.32 (3H, s), 3.42-4.9 (1H, m), 3.62-3.68 (1H, m), 3.81-3.92 (2H, m), 4.55 (2H, q, J = 7.1 Hz), 4.61-4.65 (1H, m). Anal. Calcd for $C_{17}H_{25}N_5O_3$: C, 58.78; H, 7.25; N, 20.16. Found: C, 58.55; H, 7.40; N, 20.29. Hrms calcd for $C_{17}H_{25}N_5O_3$ m/z 347.1957, found 347.1955.

5,6,7,8-Tetrahydro-(4-ethoxy-6-hydroxymethyl-2-pivaloylamino)-5-deazapteridin-5(8H)-one (**12**). A mixture of W-2 Raney nickel (washed well with water and then with methanol; approx. 2 g), the cycloadduct **11b** (0.7 g, 2.192 mmol), methanol (30 ml), acetic acid (0.5 ml) and water (3 ml) was stirred vigorously at room temperature under a hydrogen-filled balloon for 18 h. The mixture was filtered through a pad of Celite which was then washed well with methanol. The combined filtrates were evaporated under reduced pressure and the residue was triturated with cold ethanol (5 ml) to give a colorless solid which was collected by filtration; yield 0.55 g (78%) ($R_f$ = 0.4; 10% methanol in methylene chloride), mp 250-251 °C (decomp.); $^1$H nmr ($CDCl_3$) δ 1.31 (9H, s), 1.45 (3H, t, J = 7.2 Hz), 2.82-2.87 (2H, m), 3.49-3.57 (2H, m), 3.83-3.89 (2H, m), 4.5 (2H, q, J = 7.2 Hz), 5.98 (1H, br), 7.76 (1H, br). Anal. Calcd for $C_{15}H_{22}N_4O_4$: C, 55.89; H, 6.88; N, 17.38. Found: C, 55.64; H, 6.91; N, 17.38. Hrms calcd for $C_{15}H_{22}N_4O_4$ m/z 322.1641, found, 322.1625.

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