SELECTIVE REDUCTION OF THE 7-OXO GROUP IN PYRIDO[2,3-*d*]PYRIMIDINE-4,7-DIONES: A NEW SYNTHETIC APPROACH TO 5,10-DIDEAZATETRAHYDROFOLIC ACID (DDATHF)

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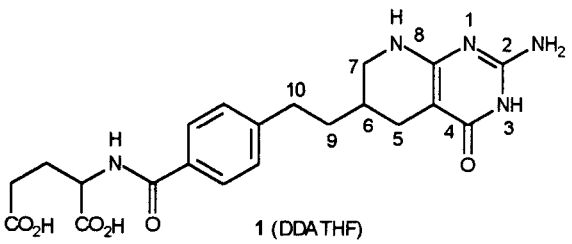
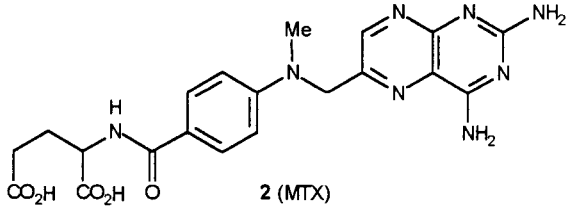
Abstract- A selective reduction of the carbonyl group at C7 with borane in THF is accomplished for 2,4-diamino-7-oxo and 2-amino-4,7-dioxo substituted pyridopyrimidines (**7a-c**) and (**13a-c**) respectively, the ester group remaining unaltered in both cases. The synthesis of **21c** allows a new synthetic approach to 5,10-dideazatetrahydrofolic acid (DDATHF, **1**) because it is a common intermediate in two procedures that afford the aforementioned antifolate.

5,10-Dideazatetrahydrofolic acid (DDATHF, **1**) is a member of the second generation of antifolate analogues that overcomes, entirely or partially, the drawbacks associated with the administration of Methotrexate (MTX, **2**) in the therapy of cancer. MTX presents, among others, a limited antitumoral spectrum and acquisition of drug resistance through four main mechanisms:[1,2] membrane impaired transport, impaired polyglutamation, dihydrofolate reductase (DHFR, EC 1.5.1.3) increase activity, and decrease in the enzyme affinity. In contrast, DDATHF has a different mode of action respect to MTX, which inhibits DHFR, acting on glycinamide ribonucleotide transformylase (GARTFase, EC 2.1.2.2),[3] responsible for the transformation of glycinamide ribonucleotide (GAR) into α-*N*-formylglycinamide ribonucleotide (FGAR), therefore inhibiting the biosynthesis of purines. To this respect DDATHF was the first antifolate clinically investigated with a locus of action different of DHFR and thymidilate synthase (TS, EC 2.1.1.45). The 6*R*-diastereomer of DDATHF (Lometrexol, LY264618),[4] topological analogue of natural 6*S*-H_4FA,[5] has recently finished Phase II clinical trials.[6-8]



1 (DDATHF)



2 (MTX)

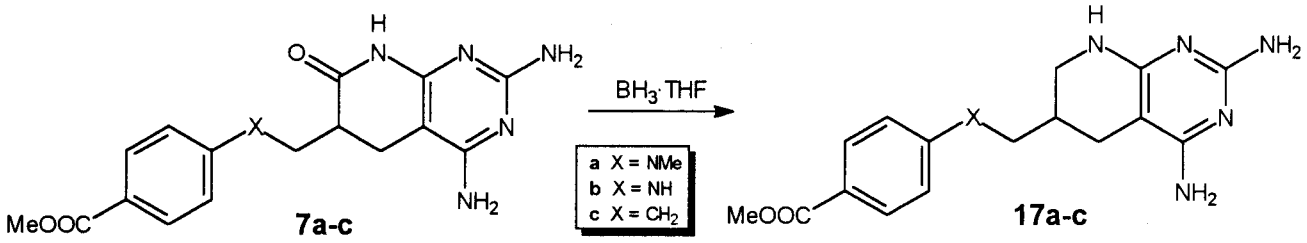
The first synthesis of DDATHF[9] was described by Taylor in 1985 within a program focused on the preparation of deaza analogues of MTX.[10] The synthetic pathway comprised fourteen steps and 0.94% global yield, employing extreme experimental conditions and reaction times. Since then Taylor *et al.* and other groups have described some new synthetic routes[7,10-18] including an asymmetric one.[19-21] The most efficient is a four-step convergent process with a 48% overall yield.

In this context, our group has synthesized a new family of 2,4-diamino-7-oxo and 2-amino-4,7-dioxo substituted tetrahydrofolic acid analogues of general structures (**10a-c**) and (**16a-c**), employing a novel strategy that implies the use of acyclic precursors (**12a-c**) and (**11a-c**) in contrast to the conventional use of preformed cyclic intermediates such as **6a-c** (Scheme 1).[22]

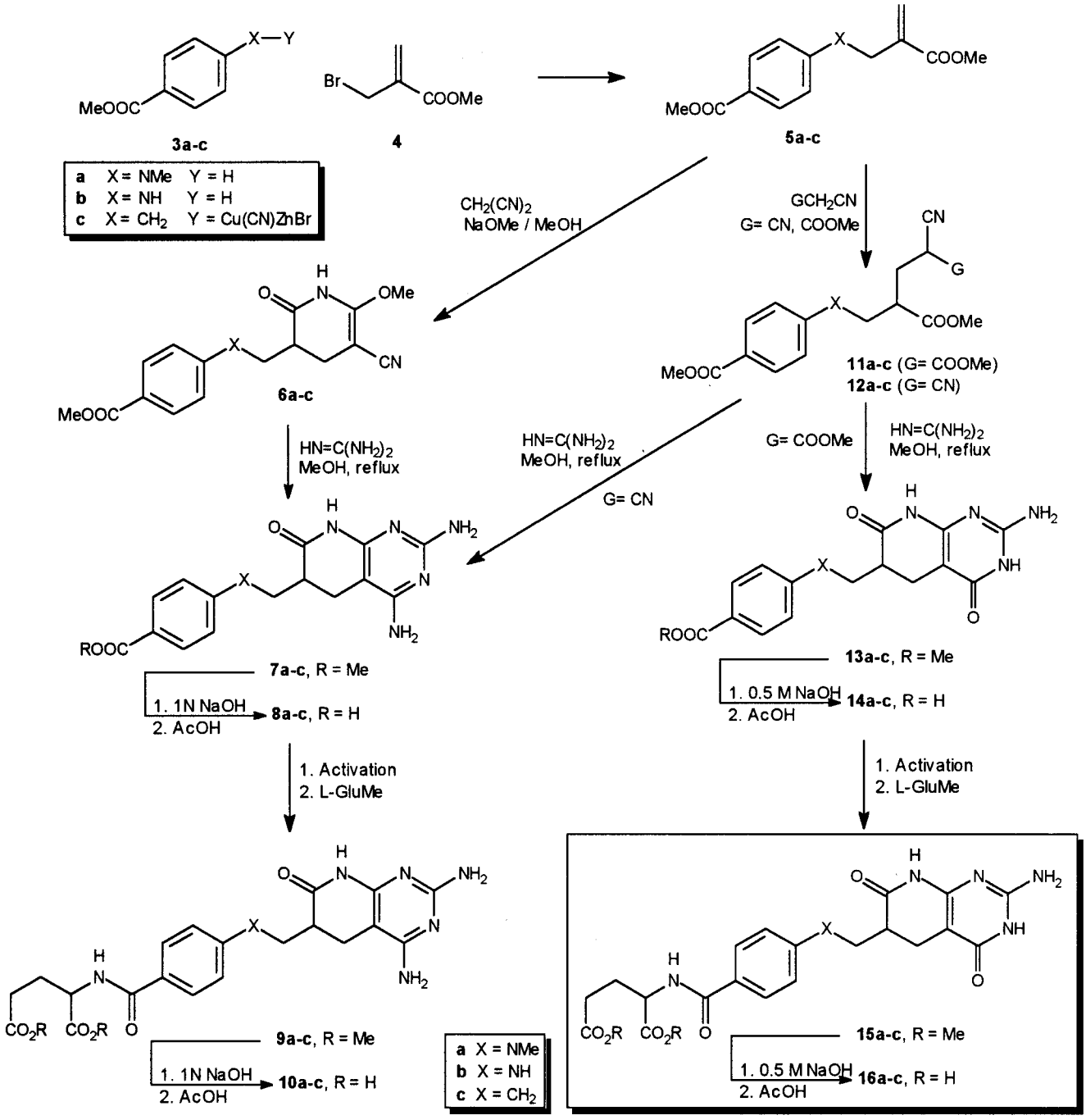
As it can be seen, the major difference between compounds (**16a-c**) and DDATHF is the presence of a carbonyl group at C-7 position. If reduction of this group would be possible, a new synthetic approach to DDATHF will be achieved.

RESULTS AND DISCUSSION

1 M Borane in tetrahydrofuran (Fluka part no. 15594) was chosen in order to assay the reduction of the extra carbonyl group at C7 due to its great selectivity for lactam groups with respect to other functional groups.[23-27] At first sight, reduction of the carbonyl group could be carried out on the final products (**16**) as well as at intermediates (**15**), but the amide carbonyl group present in the side chain could interfere in the reaction. Consequently, esters (**13a-c**) were selected as substrates to assay the reduction because carboxylic acid groups present in **14a-c** are incompatible with this reagent. Preliminarily, we successfully tested the reduction with BH_3·THF on the 2,4-diamino-7-oxo substituted esters (**7a-c**), at 50°C for 72 h, to afford **17a-c** in 79-94% yield, leaving unaltered the ester group.

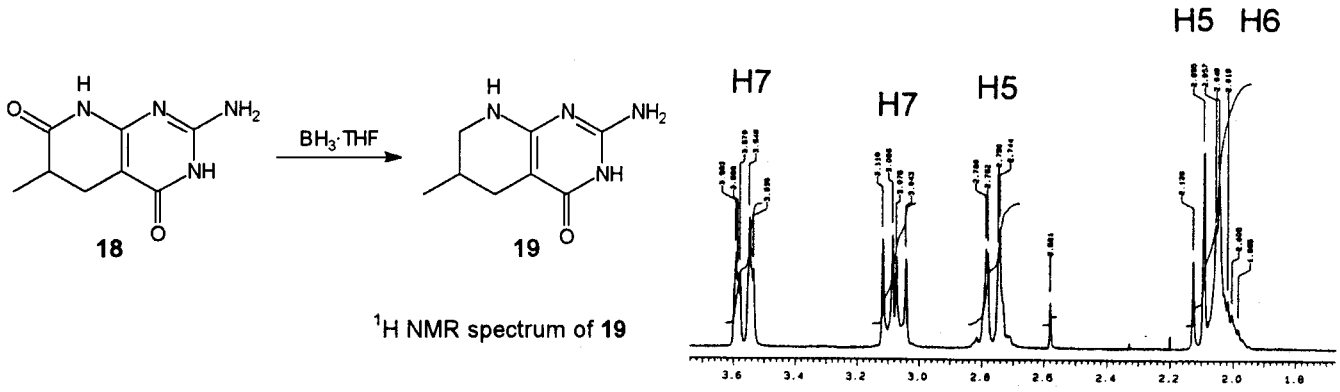


However, the reduction of **15a-c** had an added problem, the lactam carbonyl group at C-4, which also could be reduced with BH_3·THF. No examples were found in the literature that implied the reduction of a 2-amino-4,7-dioxopyrido[2,3-*d*]pyrimidine. Consequently, we chose **18** as a model compound to study the behavior of the two oxo groups during the reduction of the pyrido[2,3-*d*]pyrimidine skeleton.[28] Reaction was carried out employing 1 M BH_3·THF at reflux for 24 h, with a 1:4.66 molar ratio of **18**:borane, to afford compound (**19**) in 80% yield. The most important conclusion obtained was to confirm the selective reduction of the 7-oxo group, the 4-oxo group remaining unaltered. It has to be pointed out that the solubility of **19** in organic solvents was greatly improved in respect to **18**, supporting the idea that the great insolubility of 2-amino-7-oxo substituted pyrido[2,3-*d*]pyrimidines is a consequence of strong intermolecular H-bridge interactions[29] caused by the polar front present in them.

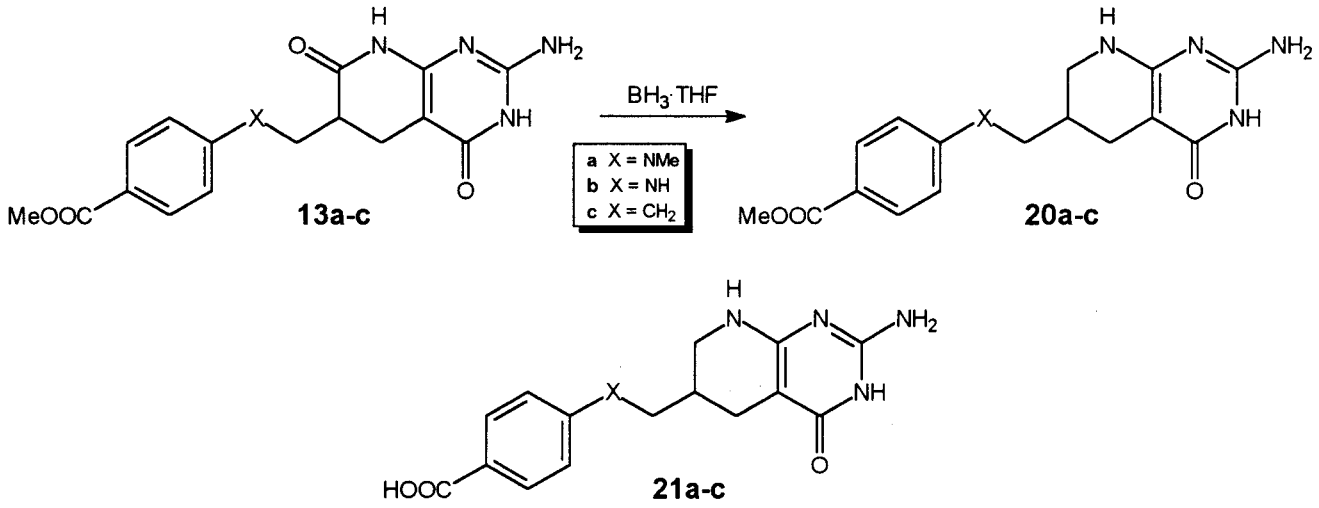


Scheme 1

Spectroscopic data were of major importance in the evaluation of the results obtained, NMR especially gave the most useful and interesting information. Thus, the ^{1}H-NMR spectrum showed two signals at 3.5 and 3.0 ppm corresponding to H-7 protons. The assignment of H-5 and H-7 was carried out by means of a H-C correlation spectrum. The ^{13}C-NMR and DEPT spectra of **19** showed the absence of the signal at 179.4 ppm corresponding to the 7-oxo group and the presence of a signal at 49.3 ppm due to the new methylene unit. It is interesting to note the minimum variation in the chemical shift of C-4 (from 162.9 in **18** to 161.7 ppm in **19**) and the shielding of C-4a (from 94.3 to 87.7 ppm) due to the greater donor effect of N-8. It is also noteworthy the shift to higher-field of C-6 (from 36.4 to 26.6 ppm) due to the absence of the deshielding effect of the 7-oxo group.



Taking this result into account, reduction was carried out on compounds (**13a-c**) in similar reaction conditions to afford 2-amino-4-oxopyrido[2,3-*d*]pyrimidines (**20a-c**) in 52-79% yields. If the destruction of the complex formed by borane and the reduced product with 6M HCl is prolonged more than the required time, carboxylic acids (**21a-c**) are obtained instead of **20a-c**.Table 1 shows the variation of the chemical shifts in the ^{13}C-NMR spectra of **13a-c** in respect to **20a-c**. Once again, C-7 and C-4a are shifted to higher-field.



^{13}C NMR	20a	13a	20b	13b	20c	13c
C4'	163.2	162.8	163.2	162.7	161.8	163.3
C4a'	85.2	93.2	84.9	93.3	87.1	93.9
C7'	45.1	175.5	44.8	175.8	47.4	178.3
C6'	28.9	36.4	29.2	37.0	31.0	40.5

Table1

To summarize, selective reduction of the carbonyl group at C7 with borane in THF is accomplished for 2,4-diamino-7-oxo and 2-amino-4,7-dioxo substituted pyridopyrimidines (**7a-c**) and (**13a-c**) respectively, the ester group remaining unaltered in both cases.

Moreover, the synthesis of **21c** allows a new synthetic approach to DDATHF because it is a common intermediate in two procedures that afford the aforementioned antifolate. The first one is an asymmetric

synthesis which needs 16 steps to reach (*R*)-**21c** in 3.3 % yield.[21] The second one, described by Taylor in 1996, consists in 7 steps with 38 % global yield in 6*R*-DDATHF.[14] In our case, DDATHF can be obtained in 6 steps as the diastereomeric mixture of 6*R*-DDATHF (Lometrexol) and 6*S*-DDATHF with a non-optimized yield of 18 %.

ACKNOWLEDGMENTS

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EXPERIMENTAL

Compounds (**7a-c**),[22a] (**13a-c**),[22b] and (**18**)[28] were prepared according to reported procedures. IR spectra were recorded on a Perkin-Elmer 683 and a Nicolet Magna 560 FTIR spectrophotometers. UV spectra were registered on a Hewlett-Packard 8450 spectrophotometer. NMR spectra were recorded on a Varian Gemini 300 spectrometer (300 and 75.5 MHz for ^{1}H and ^{13}C, respectively) using TSPNa as internal standard. MS spectra were obtained on a Hewlett-Packard 5995 A spectrometer. Elemental analyses were obtained on a Carlo-Erba CHNS-O/EA 1108 analyzer. Anhydrous THF was obtained by distillation over $LiAlH_4$ and kept over 4 Å molecular sieves.

General procedure for the reduction of 7-oxo group present in 2,4-diamino-7-oxo substituted pyridopyrimidines (7). Methyl 4-[(2,4-Diamino-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-ylmethyl)-methylamino]benzoate (17a). A suspension of 0.90 g (2.5 mmol) of **7a** in 30 mL of anhydrous THF was heated to 50ºC in an inert atmosphere. Then, 11.6 mL (11.6 mmol) of BH_3·THF (1 M) were added dropwise with a syringe. During addition, hydrogen was evolved and the solid dissolved. After 72 h solvent was removed *in vacuo*, 10 mL of 6 M HCl were added to the crude material and reflux was maintained for 30 min. After cooling, the mixture was basified with 6M NaOH until pH 7-8. The solid formed was filtered off, washed with THF and dried in vacuum over P_2O_5 to give 0.81 g (94 %) of **17a** as a white solid, mp 240-243 ºC (MeOH). IR ν: 3350-3190 (N-H), 1692 (C=O), 1655, 1607, 1561 and 1527 (N-H, C=C, C=N), 765 (C-H). ^{1}H NMR (TFA-d) δ: 2.36-2.42 (1H, m, H-5'), 2.44-2.66 (1H, m, H-6'), 2.68-2.80 (1H, m, H-5'), 3.45 (3H, s, N-Me), 3.32-3.50 (1H, m, H-7'), 3.54-3.70 (1H, m, H-7'), 3.82-3.94 (2H, m, N-CH_2-), 4.07 (3H, s, OMe), 7.86 (2H, m, H-3) and 8.36 (2H, m, H-2). ^{13}C NMR (TFA-d) δ: 170.0 (COOMe), 154.0 (C4'), 152.1 (C2'), 151.3 (C8a'), 145.0 (C4), 139.4 (C2), 134.7 (C1), 123.2 (C3), 80.3 (C4a'), 62.8 (N-CH_2), 55.2 (OMe), 49.3 (N-Me), 44.8 (C7'), 28.7 (C6') and 23.7 (C5'). MS, m/z (%): 342 (26) [M^+], 311 (15), 283 (11), 178 (74), 164 (25). UV (MeCN): λ_{max} (log ε): 314 (4.33). *Anal.* Calcd for $C_{17}H_{22}N_6O_2$: C, 59.63; H, 6.48; N, 24.54. Found: C, 59.42; H, 6.50; N, 24.43.

Methyl 4-[(2,4-Diamino-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-ylmethyl)amino]benzoate (17b). The same procedure as described above but using: 0.20 g (0.60 mmol) of **7b** and 3.6 mL (3.6 mmol) of BH_3·THF (1M) in 4 mL of THF to give 0.17 g (94%) of **17b** as a white solid, mp 176-178 ºC (MeOH). IR ν: 3350, 3200 (N-H), 1700 (C=O), 1660, 1610 and 1570 (N-H, C=C, C=N), 750 (C-H). ^{1}H NMR (TFA-d) δ: 2.56 (1H, b. s., H-5'), 2.83 (1H, b. s., H-5'), 2.91 (1H, b. s., H-6'), 3.57-3.85 (4H, m, H-6 and H-7'), 4.06 (3H, s, OMe), 7.40 (2H, m, H-3) and 8.30 (2H, m, H-2). ^{13}C NMR (TFA-d) δ: 170.3 (COOMe), 154.0

(C4'), 152.2 (C2'), 151.3 (C8a'), 139.9 (C4), 134.3 (C2), 134.1 (C1), 124.7 (C3), 80.4 (C4a'), 56.8 (C6), 55.1 (OMe), 44.7 (C7'), 29.2 (C6') and 23.7 (C5'). MS, m/z (%): 328 (41) [M^+], 177 (71), 164 (100). *Anal.* Calcd for $C_{16}H_{20}N_6O_2$: C, 58.52; H, 6.14; N, 25.59. Found: C, 58.30; H, 6.09; N, 25.29.

Methyl 4-[2-(2,4-Diamino-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)ethyl]benzoate (17c). The same procedure as described above but using: 1.0 g (2.9 mmol) of **7c** and 13.5 mL (13.5 mmol) of BH_3·THF (1 M) in 30 mL of THF to give 0.76 g (79%) of **17c** as a white solid, mp 252-254 °C (MeOH). IR ν: 3400-3150 (N-H), 1750 (C=O), 1650, 1605 and 1565 (N-H, C=C, C=N), 760 (C-H). ^{1}H NMR (TFA-d) δ: 1.70-1.89 (2H, m, Ar-CH_2-C$\underline{H}_2$), 1.90-2.10 (1H, m, H-6'), 2.16 (1H, dd, *J*=15 Hz and *J*=10 Hz, H-5'), 2.70 (1H, dd, *J*=15 Hz and *J*=5 Hz, H-5'), 2.75-2.91 (1H, m, Ar-CH_2), 3.19 (1H, dd, *J*=13 Hz and *J*=10 Hz, H-7'), 3.67 (1H, dd, *J*=13 Hz and *J*=3 Hz, H-7'), 3.99 (3H, s, OMe), 7.29 (2H, m, H-3) and 7.97 (2H, m, H-2). ^{13}C NMR (TFA-d) δ: 173.3 (C$\underline{O}$OMe), 153.0 (C4'), 152.2 (C2'), 151.1 (C8a'), 149.9 (C4), 132.0 (C2), 130.2 (C3), 128.8 (C1), 82.3 (C4a'), 54.5 (OMe), 47.4 (C7'), 35.3 (Ar-CH_2-$\underline{C}H_2$), 34.3 (Ar-CH_2-), 31.1 (C6') and 25.4 (C5'). MS, m/z (%): 327 (100) [M^+], 178 (13), 164 (33), 162 (23), 150 (50). UV (MeCN): λ_{max} (log ε): 284 (4.07). *Anal.* Calcd for $C_{17}H_{21}N_5O_2$: C, 62.37; H, 6.47; N, 21.39. Found: C, 62.39; H, 6.45; N, 21.40.

2-Amino-6-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidine (19). A suspension of 0.5 g (2.6 mmol) of 2-amino-6-methyl-4,7-dioxo-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidine (**18**) in 4 mL of anhydrous THF was heated at reflux in an inert atmosphere. Then, 12.1 mL (12.1 mmol) of 1 M BH_3·THF were added dropwise with a syringe. During addition hydrogen was evolved and the solid dissolved. After 24 h at reflux the mixture was allowed to cool, solvent was eliminated *in vacuo* and the solid residue was suspended in 5 mL of 6 M HCl and refluxed for 30 min. After cooling, the resulting mixture was basified at pH 7-8 with 6 M NaOH. The solid was collected, recrystallized from glacial acetic acid, filtered off, washed with water and dried over P_2O_5 to give 0.37 g (80% yield) of **19** as a white solid, mp 261-263 °C. IR ν: 3450-3000 (N-H), 1670 (C=O), 1635, 1600, 1570 and 1550 (N-H, C=C, C=N). ^{1}H NMR (TFA-d) δ: 1.11 ppm (3H, d, *J*=6 Hz, Me), 1.99-2.10 (1H, m, H-6), 2.10 (1H, dd, *J*= 11 Hz, *J*= 11 Hz, H-5), 2.77 (1H, dd, *J*=11 Hz, *J*=2 Hz, H-5) 3.08 (1H, dd, *J*=14 Hz, *J*=9 Hz, H-7) and 3.57 (1H, dd, *J*=14 Hz, *J*=4 Hz, H-7). ^{13}C NMR (TFA-d) δ: 161.7 (C4), 154.4 (C2), 151.7 (C8a), 87.7 (C4a), 49.3 (C7), 26.9 (C5), 26.6 (C6) and 18.0 (Me). MS, m/z (%): 180 (85) [M^+], 165 (100), 151 (15), 110 (21). UV (CH_3CN): λ_{max}(log ε): 283 (4.02), 224 (4.27). *Anal.* Calcd for $C_8H_{12}N_4O$·0.3H_2O: C, 51.77; H, 6.84; N, 30.18. Found: C, 52.18; H, 6.72; N, 29.85.

General procedure for the reduction of 7-oxo group in 2-amino-4,7-dioxo substituted pyrido[2,3-*d*]pyrimidines (13). Methyl 4-[(2-amino-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidin-6-ylmethyl)methylamino]benzoate (20a). A suspension of 0.5 g (1.4 mmol) of **13a** in 10 mL of anhydrous THF was heated at 50°C in an inert atmosphere. Then, 6.5 mL (6.5 mmol) of 1 M BH_3·THF were added dropwise with a syringe and the heating was maintained for 72 h. Solvent was eliminated *in vacuo* and the residue was heated at reflux with 10 mL of 6 M HCl for 30 min. After cooling, the mixture was basified to pH 7-8 with 6 M NaOH. The resulting solid was filtered off, washed with THF and recrystallized from hexane/ethanol to give 0.25 g (52% yield) of **20a** as a white solid, mp >250 °C. IR ν: 3400-3000 (N-H), 1680 (C=O), 1640, 1595 and 1510 (N-H, C=C, C=N), 750 (C-H). ^{1}H NMR (TFA-d) δ: 2.10-2.41 (1H, m, H-5'), 2.40-2.60 (1H, m, H-6'), 2.60-2.86 (1H, m, H-5'), 3.48 (3H, s, N-Me), 3.30-3.85 (4H, m, H-7' and N-CH_2), 4.07 (3H, s, OMe), 7.87 (2H, m, H-3) and 8.35 (2H, m, H-2). ^{13}C NMR (TFA-d) δ: 170.2 (C$\underline{O}$OMe), 163.2 (C4'), 152.8 (C2'), 152.1 (C8a'), 145.2 (C4), 135.0 (C2), 134.8 (C1), 123.4 (C3), 85.4 (C4a'), 63.4 (N-CH_2), 55.4 (OMe), 49.7 (N-Me), 45.1 (C7'), 28.9 (C6') and 23.7 (C5'). MS, m/z

(%): 328 (20), 327 (100), 312 (1), 284 (16), 179 (62), 178 (39), 165 (64). *Anal.* Calcd for $C_{17}H_{21}N_5O_3$: C, 59.46; H, 6.16; N, 20.39. Found: C, 59.17; H, 6.18; N, 20.35.

Methyl 4-[(2-amino-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidin-6-ylmethyl)amino]benzoate (20b). The procedure was the same as that stated above for **20a** but using 1.0 g (2.9 mmol) of **13b** in 30 mL of THF, 17.4 mL (17.4 mmol) of 1 M BH_3·THF and 20 mL of 6 M HCl to afford 0.71 g (74% yield) of **20b** as a white solid, mp >250 °C (hexane/ethanol). IR ν: 3330-3000 (N-H), 1692 and 1663 (C=O), 1632, 1606 and 1528 (N-H, C=C, C=N), 770 (C-H). ^{1}H NMR (TFA-d) δ: 2.54 (1H, dd, *J*=16 Hz, *J*=7 Hz, H-5'), 2.64-2.78 (1H, m, H-6'), 2.92 (1H, dd, *J*=16 Hz, *J*=4 Hz, H-5'), 3.46 (1H, dd, *J*=13 Hz, *J*=7 Hz, H-7'), 3.67-3.80 (3H, m, H-7' and N-CH_2), 4.06 (3H, s, OMe), 7.74 (2H, m, H-3) and 8.29 (2H, m, H-2). ^{13}C NMR (TFA-d) δ: 170.3 (COOMe), 163.2 (C4'), 152.8 (C2'), 152.0 (C8a'), 140.0 (C4), 134.2 (C2), 133.9 (C1), 124.6 (C3), 84.9 (C4a'), 56.9 (N-CH_2), 55.0 (OMe), 44.8 (C7'), 29.2 (C6') and 23.3 (C5'). MS, m/z (%): 329 (24) [M^+], 298 (10), 178 (59), 165 (100), 164 (37), 151 (21). *Anal.* Calcd for $C_{16}H_{19}N_5O_3$: C, 58.35; H, 5.81; N, 21.26. Found: C, 58.07; H, 5.72; N, 21.04.

Methyl 4-[2-(2-amino-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidin-6-yl)ethyl]benzoate (20c). The procedure was the same as that stated above for **20a** but using 1.0 g (2.9 mmol) of **13c** in 40 mL of THF, 13.5 mL (13.5 mmol) of 1 M BH_3·THF and 25 mL of 6 M HCl to afford 0.76 g (2.3 mmol, 79% yield) of **20c** as a white solid, mp >250 °C (hexane/ethanol). IR ν: 3300-3000 (N-H), 1690 and 1660 (C=O), 1640, 1610 and 1520 (N-H, C=C, C=N), 745 (C-H). ^{1}H NMR (TFA-d) δ: 1.66-1.82 (2H, m, Ar-CH_2-CH_2), 1.80-2.00 (1H, m, H-6'), 2.11-2.20 (1H, m, H-5'), 2.66-2.87 (3H, m, H-5' and Ar-CH_2), 3.10-3.20 (1H, m, H-7'), 3.63 (1H, d, *J*=14 Hz, H-7'), 3.99 (3H, s, OMe), 7.29 (2H, m, H-3) and 7.96 (2H, m, H-2). ^{13}C NMR (TFA-d) δ: 173.2 (COOMe), 161.8 (C4'), 154.0 (C2'), 151.4 (C8a'), 150.0 (C4), 131.8 (C2), 130.1 (C3), 128.5 (C1), 87.1 (C4a'), 54.3 (OMe), 47.4 (C7'), 35.1 (Ar-CH_2-CH_2), 34.2 (Ar-CH_2), 31.0 (C6') and 25.0 (C5'). *Anal.* Calcd for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 62.16; H, 6.16; N, 17.05.

4-[2-(2-Amino-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidin-6-yl)ethyl]benzoic acid (21c).[14,21] The same procedure as described above for **20c** but using: 0.50 g (1.5 mmol) of **13c**, 7.0 mL (7.0 mmol) of 1 M BH_3·THF in 20 mL of THF. Destruction of the complex was carried out with 10 mL of 6 M HCl during several hours to afford 0.31 g (65 %) of **21c**, mp >200 °C [(*R*)-**21c**, lit.[21] mp 312 °C]. IR ν: 3300-2700 (N-H, O-H), 1680 (C=O), 1635, 1605 and 1515 (N-H, C=C, C=N), 730 (C-H). ^{1}H NMR (TFA-d) δ: 1.70-1.86 (2H, m, Ar-CH_2-CH_2-), 1.86-2.02 (1H, m, H-6'), 2.18 (1H, dd, *J*=16 Hz, *J*=10 Hz, H-5'), 2.76-2.90 (3H, m, H-5' and Ar-CH_2-), 3.15 (1H, dd, *J*=13 Hz, *J*=9 Hz, H-7'), 3.66 (1H, dd, *J*=13 Hz, *J*=2 Hz, H-7'), 7.33 (2H, m, H-3) and 8.03 (2H, m, H-2). ^{13}C NMR (TFA-d) δ: 175.6 (COOH), 161.7 (C4'), 154.2 (C2'), 151.5 (C8a'), 151.0 (C4), 132.6 (C2), 130.3 (C3), 127.6 (C1), 87.3 (C4a'), 47.7 (C7'), 35.2 (Ar-CH_2-CH_2-), 34.4 (Ar-CH_2-), 31.1 (C6') and 25.1 (C5'). MS, m/z (%): 193 (2), 179 (3), 165 (3), 149 (4), 135 (4), 57 (29), 43 (52). UV (MeCN): λ_{max}(log ε): 282 (4.00), 225 (4.40).

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