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Unexpected And Facile Bridgehead Substitution In 5,6,7,8,9,10-Hexahydro-5,9-methano-pyrimido[4,5-b]azocin-4(3H)-ones‡

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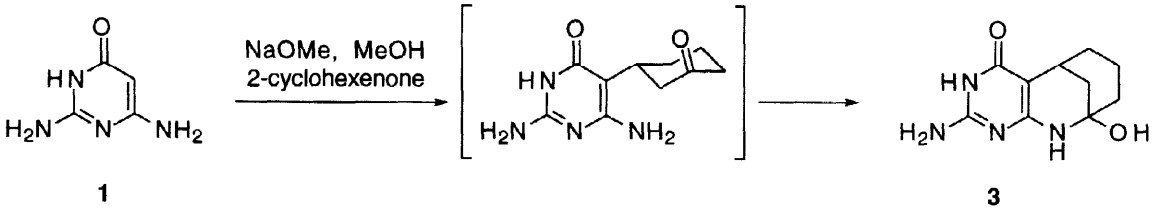
Abstract: Condensation of 2,6-diamino-4(3H)-pyrimidinone with 2-cyclohexen-1-one gives a tricyclic product resulting from Michael addition followed by intramolecular hemiaminal formation. A methodology has been developed for reductive removal of the bridgehead hydroxyl group.

When activated towards electrophilic substitution at the C-5 position by the presence of electron-releasing substituents, 4-aminopyrimidines react with α,β-unsaturated carbonyl compounds,[2] or their protected forms,[3] to afford pyrido[2,3-d]pyrimidines or their dihydro derivatives.[4] Ring annulations of this type are considered to commence with Michael addition by *C*-5 of the 4-aminopyrimidine, which is endowed with enamine-like character. Subsequent attack by the exocyclic amino group on the carbonyl group of the initial Michael adduct completes the cyclization.

As part of a study on the regiochemical outcome of alkylation of 2,6-diamino-4(3H)-pyrimidinone (**1**) with a variety of electrophiles, we sought to determine if, and to what extent, cyclic Michael acceptors, such as 2-cyclohexen-1-one (**2**), could participate.

Treatment of a suspension of **1** in methanol with sodium methoxide, followed by addition of **2** gave, in 65% yield, a material which was assigned the azabicyclo[3.3.1]nonane structure **3** (Equation 1).

Equation 1



1 **3**

The inability of the bicyclic framework to accommodate a stable carbon-nitrogen double bond at the bridgehead apparently preserves the hemiaminal linkage. Evidence for this assignment comes in part from the ^{13}C NMR spectrum which is devoid of the high field (220 ppm) signal indicative of a ketone carbonyl group yet whose signal at 80 ppm suggests the presence of a quaternary center bearing oxygen and nitrogen substituents.

Precedent for the formation of adducts of this type exists in the acid-catalyzed reaction of **2** and its derivatives with cyclic enaminones[5] and deoxyguanosine.[6]

‡Dedicated with all good wishes to a long-time friend and colleague, Prof. Alan R. Katritzky, on the occasion of his 70th birthday.

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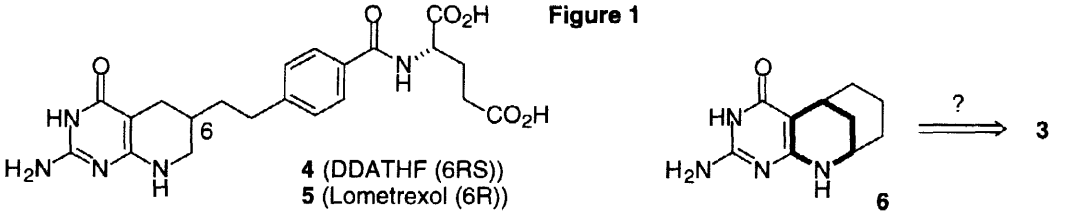
In addition to offering an impediment to dehydration, the bicyclic portion of **3**, in which the hemiaminal linkage defines a latent pyridine ring, can be regarded as a 5,7-propanopyrido[2,3-d]pyrimidine which is effectively confined to the tetrahydro oxidation state. Given our current interest in the development of tetrahydrofolate-based inhibitors of glycinamide ribonucleotide formyltransferase (GARFT) as potential cancer chemotherapeutic agents,[7] we discerned in **3** the features of conformationally-constrained analogs of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, **4**, Figure 1). The 6*R* diastereomer of DDATHF (lometrexol, **5**) is a potent and selective inhibitor of GARFT and is currently being evaluated in a phase II clinical study against a variety of solid tumors.[8]

Figure 1



Prior to applying this reaction to the synthesis of more extensively functionalized compounds of interest for our antifolate program, it was necessary to devise a suitable protocol for conversion of **3** to the requisite "deoxygenated" material (**6**). This paper describes the evolution of methodology developed to effect this seemingly straightforward transformation.

A significant feature of π-deficient heterocycles is the marked decrease in solubility that accompanies introduction of amino and hydroxy (lactam) groups. The presence of both in structures such as **3** increases insolubility by enabling the formation of strong intermolecular hydrogen-bonded networks which give rise to dense microcrystalline lattices into which water and other solvents can penetrate only with great difficulty.[9] In order to overcome operational difficulties associated with the extreme insolubility of **3**, conversion of the exocyclic amino group to its corresponding pivamide, a modification which has been used to great advantage in conferring improved solubility upon pyrimidine and deazapterin derivatives,[10] was attempted. However, treatment of **3** with pivalic anhydride or pivaloyl chloride in pyridine or DMF using DMAP as an acylation catalyst failed to produce the desired product (**7**); the starting material was recovered unchanged. Although heating the above reaction mixtures produced no improvement in the outcome, conversion to a new material was ultimately accomplished by resorting to harsher conditions, namely, suspending **3** in neat pivalic anhydride and heating the mixture at reflux for several hours. Recrystallization of the white solid which formed upon cooling of the resulting solution gave a material (**8**) whose spectral data clearly indicated the presence of both a pivamide and a pivaloyl ester. A single-crystal X-ray analysis[11] identified the new compound (Figure 2)

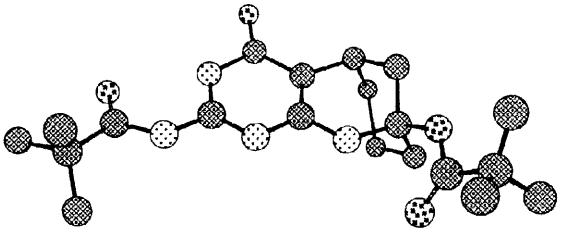
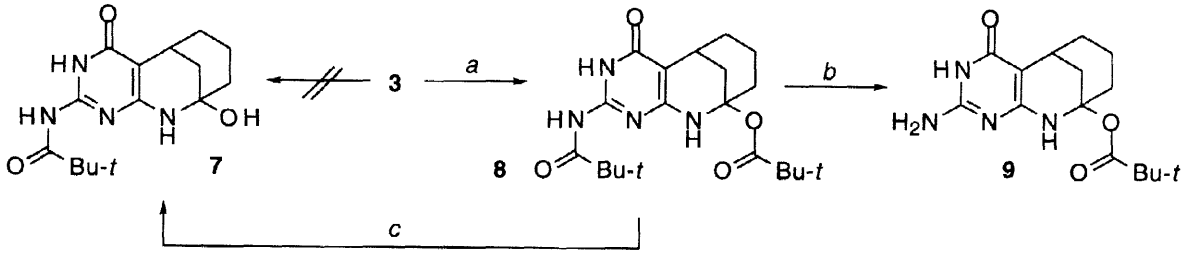


Figure 2: Depiction of the X-ray crystal structure of **8**. Hydrogen atoms have been omitted for clarity.

as one in which both the bridgehead hydroxyl (*O*-9) and the exocyclic amino group of the starting material had been acylated. Seeking to turn this unexpected result to our advantage, direct reductive cleavage of the pivaloyl ester using triphenylsilane and *t*-butyl hydroperoxide[12] was attempted but without success.

A strategy was then devised which relied on selective hydrolysis of the ester followed by derivatization of the bridgehead hydroxyl group with one of the commonly-employed thiocarbonyl reagents.[13] The resulting thiocarbonate or thiocarbamate could then be cleaved in a radical-induced process to afford the desired reduction product. The use of sodium borohydride in methanol or in a mixture of methanol and *t*-butanol, conditions reported to cleave esters chemoselectively,[14] readily removed the pivamide to give the undesired mono-pivaloylated regioisomer **9**, as evidenced by the presence of an absorption band at 1711 cm^{-1} in the infrared spectrum. Selective hydrolysis of the pivaloyl ester was ultimately accomplished with LiOH in a mixture of THF and water at 50 °C for 6 hours which afforded amide **7** in 60% yield (Equation 2).

Equation 2

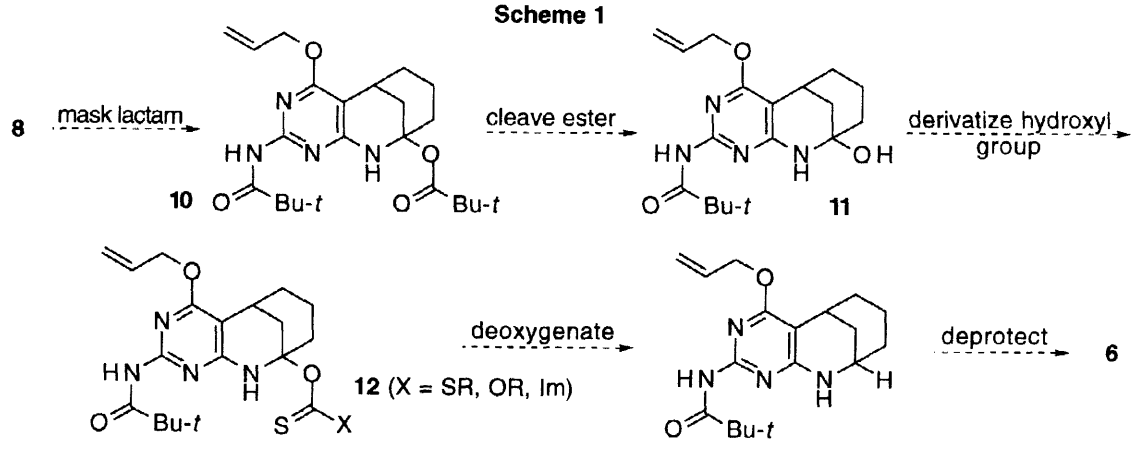


Reagents and Conditions: a. $(t\text{-BuCO})_2O$, 180 °C; b. $NaBH_4$, MeOH, CH_2Cl_2; c. LiOH, THF, H_2O.

With a method for liberating the bridgehead hydroxyl group in hand, we next endeavored to mask the lactam portion of **8** in anticipation of the potential for competitive generation of the regioisomeric *O*-9 and *O*-4 derivatives upon treatment with thiocarbonyl reagents. A recently-described method for the introduction of an *O*-allyl group into guanine and thymine residues in oligodeoxy ribonucleotides, which relies on trimethylamine-promoted displacement of the respective mesitylenesulfonate derivatives, seemed well suited for this purpose.[15]

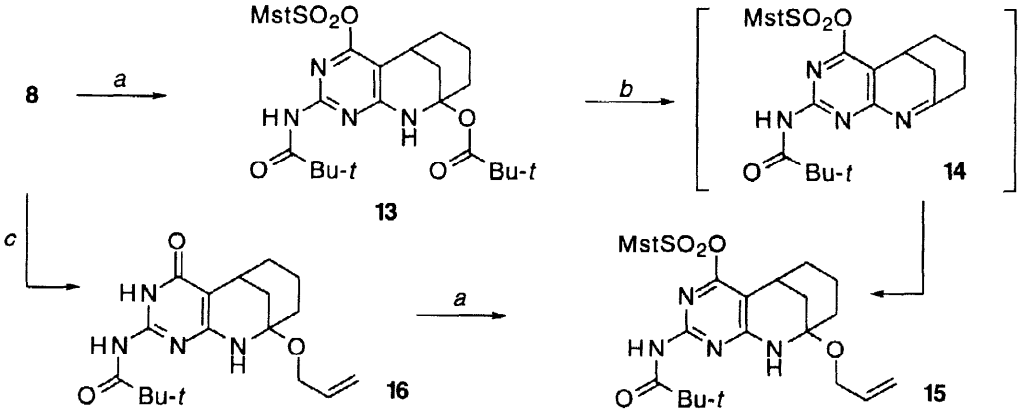
It was envisioned that selective cleavage of the pivaloyl ester from the allyloxy derivative **10** would afford a substrate (**11**) that could be converted to a thiocarbonate or xanthate derivative (**12**), deoxygenated and deprotected to afford our target (Scheme 1).

Scheme 1



In the event, treatment of **8** with mesitylenesulfonyl chloride and triethylamine in dichloromethane using a catalytic quantity of DMAP afforded sulfonate **13**. When the latter was subjected to the conditions described for the trimethylamine-promoted allyloxy group insertion, the product which formed was found to be one into which an *O*-allyl group had been incorporated yet which retained both the pivamide and mesitylene sulfonate moieties. This result suggested that trimethylamine, which was expected to displace the sulfonate group from the pyrimidine nucleus, was instead removing the proton from the vinylogous amide adjacent to the bridgehead. Subsequent elimination of pivaloate ion would then generate an intermediate bridgehead imine **14** which was trapped by allyl alcohol to give the observed product (**15**).

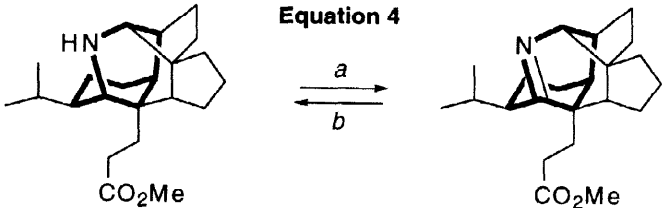
Equation 3



Reagents and Conditions: a. 2-mesitylenesulfonylchloride ($MstSO_2Cl$), Et_3N, DMAP, CH_2Cl_2; b. allyl alcohol, Me_3N, DBU, CH_2Cl_2; c. allyl alcohol, Na^o.

Although the anti-Bredt character of **14** likely confers upon it a high degree of reactivity, introduction of a site of unsaturation at the bridgehead in a ring system of this size is not unreasonable. There exists in the literature ample evidence to indicate that the stability of a bridgehead imine can parallel that of the corresponding olefin.[16] The proposed intermediate (**14**) can be regarded as a derivative of 2-azabicyclo[3.3.1]non-1-ene, albeit one which suffers from the increased strain which results from the presence of an unsaturated ring fusion. The equivalent all-carbon system, bicyclo[3.3.1]non-1-ene, is an isolable species which readily reacts under conditions which offer an avenue for release of its ring strain.[17] Further support for the viability of an intermediate such as **14** is offered by degradation studies carried out on methyl homosecodaphniphyllate. Treatment of the alkaloid with lead tetraacetate in anhydrous benzene afforded a stable product whose spectral features and chemical properties clearly identified it as a 2-azabicyclo[3.3.1]non-1-ene derivative (Equation 4).[18]

Equation 4

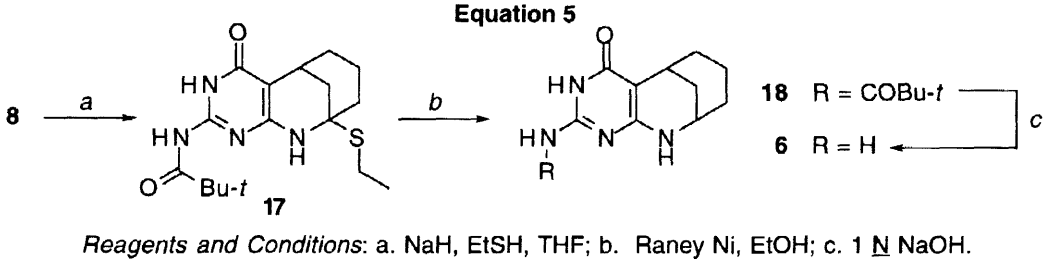


Reagents and Conditions: a. $Pb(OAc)_4$, benzene; b. PtO_2, H_2.

Since the mesitylenesulfonate moiety did not appear to be involved in the overall transformation of **13** to **15**, the unmasked pyrimidinone (**8**) was subjected to the same conditions for 5 days to give, in 26% yield, a material whose spectral data were consistent with the bridgehead-bearing *O*-allyl material **16**. When the latter reaction was repeated using 2.1 equivalents of NaH in place of trimethylamine and 1.25 equivalents of allyl alcohol in THF for 48 hours at room temperature, a 32% conversion to the desired material was achieved. Increasing the quantity of NaH to 4.1 equivalents and using 1.5 equivalents of allyl alcohol gave, after 72 hours, an improved yield of 52%. The most efficient conversion was achieved when sodium allyloxide was generated by the addition of metallic sodium to neat allyl alcohol followed by introduction of **8**; application of this protocol resulted in a 92% yield of **16**. Evidence for the regiochemical assignment of the allyl ether substituent was initially obtained from a HMBC/HMQC experiment which revealed a cross-peak corresponding to the interaction of the allylic methylene doublet at 3.94 ppm with the bridgehead carbon signal at 84.9 ppm. This conclusion was firmly confirmed by conversion of **16** to the corresponding mesitylenesulfonyl derivative; the spectra of the isolated product were identical to those of the previously-identified **15**.

Having arrived at a method, albeit a serendipitous one, to effect nucleophilic replacement at the bridgehead position of **8**, we introduced a substituent which in a subsequent step could be manipulated to give the desired deoxygenated material (**6**). Exposure of **8** to a suspension of NaH (4.1 eq) and ethyl mercaptan (1.2 eq) in THF for 2 hours followed by purification by radial chromatography gave, in 94% yield, the anticipated ethyl sulfide (**17**). Although desulfurizaton of **17** could be accomplished using tributyltin hydride and AIBN in refluxing toluene,[19] it was more convenient to obtain the desired reduction product (**18**) by treatment of **17** with freshly-prepared Raney nickel in ethanol.[20] Replacement of the ethylthio group by a hydrogen atom was confirmed by an APT experiment which gave an inverted signal at 47.53 ppm corresponding to the bridgehead methine carbon. Subsequent basic hydrolysis of the pivaloyl protecting group in **18** afforded the product of formal deoxygenation of **3**, the desired **6** (Equation 5).

Equation 5



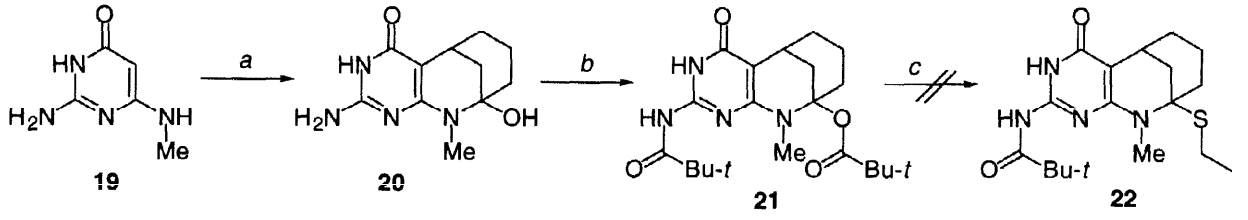
Reagents and Conditions: a. NaH, EtSH, THF; b. Raney Ni, EtOH; c. 1 N NaOH.

To probe the validity of the mechanism advanced to explain the observed bridgehead substitutions, a substrate was prepared which was expected to be incapable of forming the postulated bridgehead imine intermediate. The reaction of 2-amino-6-methylamino-4(3H)-pyrimidinone[21] (**19**) with NaOMe followed by **2** gave the *N*-methyl derivative **20** which was then converted, by treatment with pivalic anhydride, to the corresponding dipivaloylated material (**21**). The ^{1}H NMR spectrum of this material exhibited a well-resolved aliphatic region which allowed the assignment of each resonance and permitted a confirmation of the structure to be made by analogy with that of **8**. The broadened signal at δ 3.35 lacks the large geminal coupling common to its neighbors at lower field, a feature which suggests that the signal corresponds to the proton which occupies the equatorial position at the bridgehead carbon linking the six-membered ring to the *C*-5 position of the

pyrimidine ring. This assignment is further strengthened by the downfield shift of the signal, indicative of the proximity of the proton to the deshielding cone of the pyrimidinone carbonyl group. The 2D COSY spectrum of **21** contains cross peaks which indicate that the resonance at δ 3.35 arises from coupling with the equatorial proton at δ 2.45 and its axial counterpart, a doublet of doublets centered on δ 2.17. Based on the 2D COSY spectrum and chemical shift data the protons in the other methylene group which flanks the bridgehead hemiaminal linkage can be assigned as those which give rise to a broad doublet at δ 2.09 and a doublet of triplets at δ 1.97. The signals corresponding to the remaining pair of methylene groups can be readily identified based on the 2D COSY data.

Exposure of this substrate to a mixture of NaH and ethyl mercaptan in THF for an extended period resulted only in return of unchanged starting material; none of the ethyl sulfide (**22**) was detected (Equation 6). This result is in accord with the argument that removal of the proton from the annular nitrogen atom in **8** and **13** is required for pivaloate elimination.

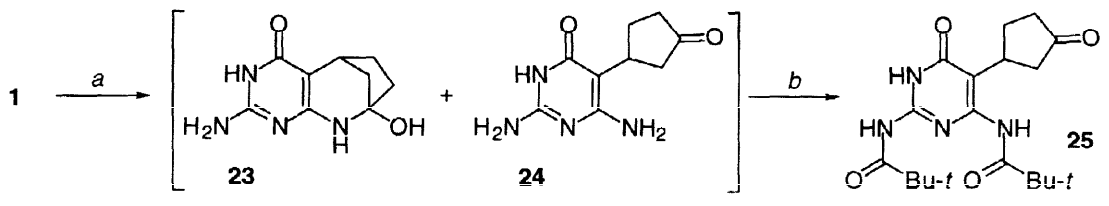
Equation 6



Reagents and Conditions: a. 2-cyclohexen-1-one, NaOMe; b. pivalic anhydride, 170 °C; c. EtSH, NaH, THF.

In a further experiment, **1** was treated with 2-cyclopenten-1-one in the presence of NaOMe. Although the product obtained during the preparation of **3** was generally quite pure, the ^{1}H and ^{13}C NMR spectra of the new material indicated the presence of two components which proved to be inseparable by chromatography or recrystallization. In the ^{1}H NMR spectra of **3**, **20** and their derivatives, the signal corresponding to the *C*-9 methine proton, which occurs in the range δ 2.9-3.9, is diagnostic for the presence of the tricyclic hemiaminal. The ^{1}H NMR spectrum of the new material exhibits such a signal at δ 2.95 which is flanked by additional signals at δ 2.91(t) and δ 3.18 (m) suggesting that the product consists of a mixture of the desired 5,9-methano-pyrimido[4,5-b]azepine (**23**) and the initial Michael adduct (**24**). Curiously, however, treatment of the crude material with pivalic anhydride gave exclusively, after chromatographic separation, the dipivaloylated derivative of the product of *C*-5 Michael addition (**25**). It seems likely that **23** undergoes slow reversion to its immediate precursor, a process which is accelerated under the acylation reaction conditions; opening of the hemiaminal linkage is then made irreversible by pivaloylation of the liberated amino group. This behavior suggests that the greater degree of ring strain in the kinetic product (**23**) leads to a thermodynamic preference for the initial Michael adduct (Equation 7).

Equation 7



Reagents and Conditions: a. NaOMe, 2-cyclopenten-1-one; b. pivalic anhydride, 140 °C.

The above four-step sequence of dipivaloylation, base-assisted bridgehead substitution, Raney nickel desulfurization and deprotection for conversion of **3** to **6** should now permit assembly of novel conformationally-constrained DDATHF analogues, an endeavor whose results will be reported in due course.

Experimental Section

General Methods. NMR spectra were recorded on a JEOL GSX 270 FT or a Varian Unity-INOVA 500 spectrometer. Proton and carbon chemical shifts are reported in parts per million (ppm) and are referenced to internal solvent. Multiplicites are abbreviated in the following manner: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broadened (br). High and low resolution mass spectra were obtained on a Kratos MS50 spectrometer. Analytical thin-layer chromatography (TLC) was conducted using silica gel IB-F precoated plates with a fluorescent indicator. Radial chromatography was performed with the aid of the Chromatotron, a product of Harrison Research Inc. All reactions were carried out under an argon atmosphere with dry, freshly-distilled solvents under anhydrous conditions unless otherwise noted. All reagents obtained from commercial suppliers were used without further purification unless otherwise stated.

2-Amino-9-hydroxy-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocin-4(3H)-one (3). To a solution of freshly-prepared sodium methoxide (0.92 g, 40 mmol of sodium metal) in 50 mL of anhydrous MeOH was added 2,6-diamino-4(3H)-pyrimidinone (**1**) (5.0 g, 40 mmol) in one portion. The resulting clear, pale yellow solution was warmed to 50 °C, held at this temperature for 0.5 h, and allowed to cool to rt over a period of 1 h. Neat 2-cyclohexene-1-one was added dropwise via syringe and the black solution was then stirred at rt for 20 h during which time a voluminous precipitate was deposited. After refrigerating the thick, light brown suspension for 1 h, the product was collected, washed with 10 mL of cold MeOH and dried to give 5.8 g (65%) of a white powder, mp 310-312 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.32 (d, 2 H, J = 9.1 Hz), 1.45 (m, 2 H), 1.56 (dd, 2 H, J = 4.6, 12.2 Hz), 1.69 (br d, 2 H, J = 12.2 Hz), 2.97 (br s, 1 H), 5.81 (s, 1 H), 6.12 (s, 2 H), 6.66 (s, 1 H), 9.77 (s,1 H); ^{13}C NMR (DMSO-d_6, 75.6 MHz) δ 20.0, 27.9, 31.0, 38.8, 41.5, 80.3, 86.7, 154.5, 160.8, 160.9; IR (KBr) 3410, 2932, 1645, 1615, 1550 cm^{-1}; MS m/e (relative intensity) 222 (24), 205 (8), 179 (100), 162 (8); HRMS calcd for $C_{10}H_{14}N_4O_2$: 222.1117. Found: 222.1116.

2-Pivaloylamino-9-pivaloyloxy-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocin-4(3H)-one (8). A suspension of **3** (500 mg, 2.20 mmol) in 8 mL of pivalic anhdyride was heated to 175 °C over a period of 1 h to give a clear amber solution which was allowed to remain at this temperature for 5 h. The solid which formed upon cooling of the reaction mixture to rt was suspended in ether, collected and recrystallized from MeOH to give 720 mg (84%) of fine, white needles, mp 258-260 °C. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.16 (s, 9 H), 1.27 (s, 9 H), 1.49-1.79 (m, 5 H), 1.95 (m, 2 H), 2.60 (d, 1 H, J = 12.2 Hz), 3.37 (br t, 1 H, J = 2.9 Hz), 6.50 (s, 1 H), 8.11 (br s, 1 H), 11.34 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 19.3, 26.6, 26.6, 27.0, 30.1, 35.6, 37.3, 38.9, 39.9, 88.1, 94.9, 148.8, 158.2, 159.3, 178.5, 179.6; IR (KBr) 3414, 1711, 1668, 1651, 1606, 1558 cm^{-1}; MS m/e (relative intensity) 390 (2), 290 (2), 289 (8), 260 (36); HRMS calcd for $C_{20}H_{30}N_4O_4$: 390.2267. Found: 390.2275; Anal. Calcd for $C_{20}H_{30}N_4O_4$: C, 61.52; H, 7.74; N, 14.35. Found: C, 61.82; H, 7.91; N, 14.58.

2-Amino-9-pivaloyloxy-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocin-4(3H)-one (9). To a stirred solution of **8** (390 mg, 1.0 mmol) in 10 mL of MeOH and 10 mL of CH_2Cl_2 was added sodium borohydride (380 mg, 10 mmol, 10 eq) in portions over 1 h. The resulting heterogeneous mixture was

stirred at rt for 12 h, partitioned between 20 mL of H_2O and 20 mL of CH_2Cl_2, and the organic phase was then dried over Na_2SO_4. Filtration and evaporation of the solvent *in vacuo* gave a solid residue which was purified by chromatography on silica using 10% MeOH in CH_2Cl_2 as eluent to afford 230 mg (75%) of a white solid, mp 179-181 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (s, 9 H), 1.45 (m, 5 H), 1.98 (dd, 2 H, J = 11.7, 17.6 Hz), 2.59 (d, 1 H, J = 11.4 Hz), 3.18 (s, 1 H), 5.82 (s, 2 H), 6.56 (s, 1 H), 11.45 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.3, 27.7, 28.0, 31.4, 37.1, 38.10, 39.9, 89.2, 90.1, 155.0, 161.7, 163.1, 179.3; IR (KBr); 1711, 1638, 1598, 1511 cm^{-1}; MS m/e (relative intensity) 306 (2), 204 (5), 189 (2), 176 (12), 163 (4); HRMS calcd for $C_{15}H_{22}N_4O_3$: 306.1691. Found: 306.1695.

2-Pivaloylamino-9-hydroxy-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocin-4(3H)-one (7). A stirred suspension of **8** (54 mg, 0.14 mmol) and LiOH (4 eq, 23 mg, 0.55 mmol) in 5 mL of THF/water (10:1) was heated at 55 °C for 6 h. The reaction mixture was allowed to cool to rt and evaporated *in vacuo* to give a solid residue. The crude material was dissolved in 2 mL of MeOH, filtered and purified by radial chromatography (1 mm plate) using 5% MeOH in CH_2Cl_2 as eluent to afford 25 mg (60%) of a white solid, mp 279-281 °C. ^1H NMR (DMSO-d_6, 500 MHz) δ 1.21 (s, 9 H), 1.34 (m, 2 H), 1.51 (d, 1 H, J = 11.6 Hz), 1.57 (m, 2 H), 1.63 (d, 1 H, J = 12.5 Hz), 1.73 (d, 1 H, J = 11.3 Hz), 1.79 (d, 1 H, J = 12.2 Hz), 3.04 (br s, 1 H), 5.75 (s, 1 H), 6.31, (s, 1 H), 10.60 (s, 1 H), 11.22 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 19.8, 27.2, 27.5, 30.8, 36.6, 37.6, 39.5, 88.7, 89.6, 154.5, 161.2, 162.6, 178.3; IR (KBr) 3414, 1638, 1598, 1558 cm^{-1}; MS m/e (relative intensity) 306 (84), 289 (41), 264 (45), 263 (100) 250 (14),205 (22),179 (80), 57 (99); HRMS calcd for $C_{15}H_{22}N_4O_3$: 306.1691. Found: 306.1691.

2-Pivaloylamino-9-pivaloyloxy-4-(2',4',6'-trimethylbenzenesulfonyloxy)-5,6,7,8,9,10-hexa-hydro-5,9-methanopyrimido[4,5-b]azocine (13). To a stirred solution of **8** (190 mg, 0.48 mmol), 2-mesitylenesulfonyl chloride (136 mg, 0.62 mmol, 1.3 eq) and triethylamine (73 mg, 0.72 mmol, 1.5 eq) in 8 mL of CH_2Cl_2 was added DMAP (10 mol %, 6 mg) and the resulting mixture was stirred at rt under nitrogen for 14 h. The reaction mixture was partitioned between water (10 mL) and CH_2Cl_2 (10 mL) and the organic phase was then washed with an aqueous NaCl solution (10 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated *in vacuo* to give a solid residue which was purified by radial chromatography (2 mm plate) using 25% EtOAc in hexanes as eluent to afford 233 mg (85%) of a white powder which sublimed between 100-110 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (s, 9 H), 1.20 (s, 9 H), 1.44 (m, 1 H), 1.62 (m, 1 H), 1.69 (m, 1 H), 1.76 (m, 1 H), 1.81 (d, 1 H, J = 14.1 Hz), 1.95 (d, 1 H, J = 12.9 Hz), 2.10 (dt, 1 H, J = 2.9, 12.1 Hz), 2.32 (s, 3 H), 2.58 (d, 1 H, J = 12.1 Hz), 2.66 (s, 6 H), 3.38 (br t, 1 H, J = 2.9 Hz), 6.98 (s, 2 H), 7.20 (s, 1 H), 7.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4, 21.3, 22.9, 27.1, 27.4, 27.8, 31.4, 35.2, 36.8, 39.4, 40.2, 88.0, 99.1, 131.7, 133.5, 140.0, 143.9, 154.9, 160.2, 163.7, 175.5, 178.2; IR (KBr) 3441, 3401, 1718, 1611, 1565 cm^{-1}; MS m/e (relative intensity) 572 (6), 509 (14), 508 (40), 471 (37), 470 (41), 423 (8), 408 (11), 407 (41), 406 (47), 405 (39), 391 (17), 390 (26), 389 (18); HRMS calcd for $C_{29}H_{40}N_4O_6S$: 572.2668. Found: 572.2674; Anal. Calcd for $C_{29}H_{40}N_4O_6S$-H_2O: C, 58.96; H, 7.17; N, 9.48. Found: C, 59.21; H, 6.88; N, 9.13.

2-Pivaloylamino-9-allyloxy-4-(2',4',6'-trimethylbenzenesulfonyloxy)-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocine (15). Method A. A solution of **8**, triethylamine (0.10 g, 1.0 mmol), 2-mesitylenesulfonyl chloride (62 mg, 1.1 eq) and DMAP (3 mg, 10 mol %) in 15 mL of CH_2Cl_2 was stirred at rt for 4 h. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and water (10

mL) and the organic phase was then washed sequentially with saturated aqueous $NaHCO_3$ solution (10 mL) and water (10 mL). The solution was dried over Na_2SO_4, filtered and evaporated *in vacuo* to give **13** as a solid residue. A solution of the crude material, allyl alcohol (14 eq, 210 mg, 3.6 mmol), trimethylamine (15 eq, 390 mg, 3.9 mmol) and DBU (40 mg, 1.0 eq) in 5 mL of CH_2Cl_2 in a screw-capped pressure tube was stirred at rt for 72 h. The precipitate which formed was removed by filtration and washed with 1 mL of CH_2Cl_2. The filtrate was partitioned between CH_2Cl_2 (25 mL) and brine (25 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a clear oil which was purified by chromatography on silica using 30% EtOAc in hexanes as eluent to afford 40 mg (29%) of a white powder, mp 104-106 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.21 (s, 9 H), 1.39 (m, 1 H), 1.58 (m, 2 H), 1.66 (d, 1 H, J = 14.0 Hz), 1.75 (m, 2 H), 1.86 (d, 1 H, J = 12.8 Hz), 2.01 (d, 1 H, J = 12.2 Hz), 2.32 (s, 3 H), 2.64 (s, 6 H), 3.42 (br s, 1 H), 4.03 (dd, 1 H, J = 5.8, 12.5 Hz), 4.09 (dd, 1 H, J = 5.2, 12.5 Hz), 5.14 (d, 1 H, J = 10.3 Hz), 5.26 (d, 1 H, J = 17.1 Hz), 5.85 (m, 1 H), 6.98 (s, 2 H), 7.34 (s, 1 H); IR (KBr) 3347, 2931, 1631, 1558, 1452 cm^{-1}; MS m/e (relative intensity) 528 (11), 485 (18), 464 (21), 421 (32), 305 (39),119 (81), 105 (29); HRMS calcd for $C_{27}H_{36}N_4SO_5$: 528.2406. Found: 528.2396. Anal. Calcd for $C_{27}H_{36}N_4SO_5$: C, 61.34; H, 6.87; N, 10.60. Found: C, 61.42; H, 6.65; N, 10.48.

2-Pivaloylamino-9-allyloxy-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocin-4(3H)-one (16). Sodium metal (100 mg, 4.0 mmol, 4.0 eq) was added in portions to 6 mL of neat allyl alcohol at rt and the resulting mixture was stirred for 1 h. In one portion, **8** (390 mg, 1.0 mmol) was added and the reaction was monitored by tlc (5% MeOH in CH_2Cl_2) until no starting material remained (1.5 h). The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and an aqueous NH_4Cl solution (10 mL) and the aqueous phase was reextracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with 15 mL of an aqueous NaCl solution, dried over Na_2SO_4, filtered and evaporated *in vacuo* to give a solid residue. Recrystallization from $CHCl_3$/hexanes afforded 328 mg (95%) of a white solid, mp 238-240 °C. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.10 (s, 9 H), 1.31-1.84 (m, 8 H), 3.20 (s, 1 H), 3.94 (m, 2 H), 5.05 (dd, 2 H, J = 10.3, 17.1 Hz), 5.28 (s, 1 H), 5.71 (m, 1 H), 8.15 (s, 1 H), 11.28 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 19.6, 26.4, 27.9, 30.6, 32.7, 40.2, 40.4, 62.6, 84.9, 93.5, 116.0, 135.2, 149.6, 160.1, 161.2, 181.2; IR (KBr) 3347, 3254, 1631, 1558 cm^{-1}; MS m/e (relative intensity) 346 (29), 305 (90), 289 (32), 221 (23), 85 (19) 78 (48); HRMS calcd for $C_{18}H_{26}N_4O_3$: 346.2004. Found: 346.1998; Anal. Calcd for $C_{18}H_{26}N_4O_3$: C, 62.41; H, 7.56; N, 16.17. Found: C, 62.21; H, 7.57; N, 16.13.

2-Pivaloylamino-9-allyloxy-4-(2',4',6'-trimethylbenzenesulfonyloxy)-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocine (15). Method B. To a stirred solution of **16** (173 mg, 0.50 mmol), 2-mesitylenesulfonyl chloride (130 mg, 0.60 mmol) and triethylamine (75 mg, 0.75 mmol) in 5 mL of CH_2Cl_2 was added DMAP (10 mol%, 6 mg) and the resulting mixture was allowed to stir at rt under nitrogen for 5 h. The reaction mixture was partitioned between CH_2Cl_2 (5 mL) and aqueous NaCl solution (5 mL) and the aqueous phase was extracted with 5 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a clear oil which was purified by radial chromatography (2 mm plate) using 20% EtOAc in hexanes as eluent. Evaporation of similar fractions gave 229 mg (87%) of a white solid whose spectral data were identical with those of the previously prepared material.

2-Pivaloylamino-9-ethylthio-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocin-4(3H)-one (17). To a stirred suspension of NaH (124 mg, 5.2 mmol, 4.2 eq) in 20 mL of dry THF at rt was added ethyl mercaptan (110 mL, 1.5 mmol, 1.1 eq) neat, via syringe, and the resulting mixture was stirred at rt under nitrogen for 1 h. In one portion, **8** (520 mg, 1.3 mmol) was added and the pale brown suspension was stirred at rt for 4 h. The reaction mixture was partitioned between EtOAc (20 mL) and aqueous NH_4Cl solution (20 mL) and the aqueous phase was extracted with an additional 20 mL of EtOAc. The combined organic phases were washed with 20 mL of an aqueous NaCl solution, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a solid white residue which was purified by radial chromatography (2 mm plate) using 5% MeOH in CH_2Cl_2 as eluent. Evaporation gave 440 mg (96%) of a white powder, mp 256-258 °C. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.21 (t, 3 H, J = 7.3 Hz), 1.28 (s, 9 H), 1.40 - 1.68 (m, 4 H), 1.74 - 1.93 (m, 4 H), 2.51- 2.66 (m, 2 H), 3.30 (br t, 1 H, J = 2.9 Hz), 4.91 (s, 1 H), 8.06 (s, 1 H), 11.27 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 16.0, 20.4, 22.4, 28.1, 28.2, 31.6, 36.8, 41.2, 42.7, 63.3, 94.9, 149.6, 160.4, 160.6, 180.5; IR (KBr) 3344, 3238, 2921, 1632, 1555 cm^{-1}; MS m/e (relative intensity) 350 (6), 321 (8), 307 (4), 289 (21), 261 (3); HRMS calcd for $C_{17}H_{26}N_4O_2S$: 350.1776. Found: 350.1760; Anal. Calcd for $C_{17}H_{26}N_4O_2S$: C, 58.26; H, 7.48; N, 15.99. Found: C, 57.96; H, 7.26; N, 15.86.

2-Pivaloylamino-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocin-4(3H)-one (18). A suspension of Raney nickel in ethanol was freshly prepared from 30 g of nickel aluminum alloy according to the method of Brown.[15] The entire quantity of metal was added as a slurry in EtOH to a solution of **17** (2.0 g, 0.10 mmol) in 100 mL of EtOH. After stirring at rt for 20 h the heavy suspension was filtered through a Soxhlet extraction thimble into a 500 ml round bottomed flask with 100 mL of EtOH to assist in the transfer. The filtrate thus obtained was concentrated *in vacuo* to approximately 250 mL and, with the aid of a Soxhlet apparatus, used to continuously extract the Raney nickel within the thimble over a 48 h period. The lime green solution was concentrated *in vacuo*, impregnated onto silica gel and the resulting powder was applied to the top of a silica gel column and eluted with 5% MeOH in CH_2Cl_2. Further purification of the similar fractions using radial chromatography (4 mm plate) with 5% MeOH in CH_2Cl_2 as eluent gave 1.0 g (60%) of the desulfurized material as a white powder, mp 320 °C (dec). ^1H NMR (DMSO-d_6, 500 MHz) δ 1.20 (s, 9 H), 1.40 (d, 2 H, J = 13.1 Hz), 1.49 (m, 2 H), 1.51 (m, 2 H), 1.66 (d, 1 H, J = 11.9 Hz), 1.74 (d, 1 H, J = 12.1 Hz), 2.96 (s, 1 H), 3.58 (s, 1 H), 6.73 (s, 1 H), 10.59 (s, 1 H), 11.16 (s, 1 H); ^{13}C NMR (F_3CCO_2D, 75.6 MHz) δ 15.7, 24.5, 24.6, 26.6, 29.4, 31.5, 40.2, 47.5, 95.8, 147.5, 154.8, 162.3, 184.2. IR (KBr) 3379, 3253, 2921, 1632, 1611 cm^{-1}; MS m/e (relative intensity) 290 (1), 247 (4), 170 (1), 163 (1); HRMS calcd for $C_{15}H_{22}N_4O_2$: 290.1742. Found: 290.1739; Anal. Calcd for: $C_{15}H_{22}N_4O_2$: C, 62.05; H 7.64; N, 19.30. Found: C, 62.26; H, 7.64; N, 19.21.

2-Amino-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocin-4(3H)-one (6). A supension of **18** (29 mg, 0.1 mmol) in 1 mL of 1 N NaOH was stirred vigorously at rt to give a clear, colorless solution. After 48 h, acidification with 6 M HCl gave a white precipitate which was collected, washed sequentially with water and ether (10 mL) and dried to afford a white, microcrystalline solid (18 mg, 87%) which darkened above 200 °C and did not melt below 320 °C. ^1H NMR (DMSO-d_6, 500 MHz) δ 1.32 (m, 1 H), 1.37 (m, 3 H), 1.45 (m, 2 H), 1.52 (d, 1 H, J = 11.9 Hz), 1.68 (d, 1 H, J = 11.9 Hz), 2.88 (br s, 1 H), 3.48 (br s, 1 H), 5.91 (s, 2 H), 6.50 (d, 1 H, J = 4.5 Hz), 9.62 (s, 1 H); MS m/e (relative intensity) 206 (16), 163 (100), 146 (19); HRMS calcd for $C_{10}H_{14}N_4O$: 206.1167. Found: 206.1171.

2-Amino-9-hydroxy-10-methyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-b]azocin-4(3H)-one (20). A solution of NaOMe in MeOH was prepared from sodium metal (94 mg, 4.1 mmol) and 10 mL of MeOH. To the stirred solution was added 2-amino-6-methylamino-4(3H)-pyrimidinone (**19**)[21] (520 mg, 3.71 mmol), and the resulting suspension was heated at 50 °C for 0.5 h. The resulting clear yellow solution was allowed to cool to rt and neat 2-cyclohexene-1-one (392 mg, 4.08 mmol) was injected via syringe. The solution, which gradually turned black, was stirred at rt for 24 h and quenched by the addition of HOAc. The reaction mixture was impregnated onto silica gel and purified by chromatography using 10% MeOH in CH_2Cl_2 as eluent to give 320 mg (36%) of a pale brown solid, mp 260-262 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (m, 1 H), 1.38 (m, 2 H), 1.43 (m, 2 H), 1.69 (d, 1 H, J = 11.6 Hz), 1.76 (dd, 1 H, J = 2.7, 11.9 Hz), 1.93 (d, 1 H, J = 12.2 Hz), 2.87 (s, 3 H), 2.97 (m, 1 H), 5.63 (s, 1 H), 6.08 (s, 2 H), 9.80 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 20.3, 27.7, 27.9, 31.7, 37.6, 40.1, 83.2, 88.9, 154.5, 161.2, 162.0; IR (KBr) 3330, 3231, 2921, 1647, 1597 cm^{-1}; MS m/e (relative intensity) 236 (10), 193 (100), 151 (17); HRMS calcd for $C_{11}H_{16}N_4O_2$: 236.1273. Found: 236.1268; Anal. Calcd for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71. Found: C, 55.62; H, 6.68; N, 23.43.

2-Pivaloylamino-9-pivaloyloxy-10-methyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido-[4,5-b]azocin-4(3H)-one (21). A suspension of **20** (0.10 g, 0.42 mmol) in 2 mL of pivalic anhydride was heated at 140 °C for 4 h. After cooling to rt the solvent was removed *in vacuo* with the aid of a short-path distillation apparatus and the resulting solid residue was purified by radial chromatography (2 mm plate) using 5% MeOH in CH_2Cl_2 as eluent. Recrystallization from $CHCl_3$/hexanes gave 144 mg (85%) of a fluffy white solid, mp 263-264 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.21 (s, 9 H), 1.31 (s, 9 H), 1.57 (ddd, 1 H, J = 13.2, 4.2, 3.8 Hz), 1.61 (d, 2 H, J = 13.9 Hz), 1.78 (d, 1 H, J = 12.7 Hz), 1.97 (dt, 1 H, J = 13.2, 4.6 Hz), 2.09 (d, 1 H, J = 12.7 Hz), 2.17 (dd, 1 H, J = 11.7, 2.9 Hz), 2.45 (d, 1 H, J = 11.7), 2.92 (s, 3 H), 3.35 (d, 1 H, J = 2.9), 8.04 (s, 1 H), 11.32 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.6, 27.2, 27.3, 28.1, 30.6, 33.1, 35.1, 39.8, 40.3, 91.5, 96.2, 148.2, 159.3, 159.4, 176.3, 179.7; IR (KBr) 3182, 2950, 1724, 1639, 1604, 1555 cm^{-1}; MS m/e (relative intensity) 404, 319, 303, 287, 277, 261, 203; HRMS calcd for $C_{21}H_{32}N_4O_4$: 404.2423. Found: 404.2418; Anal. Calcd for $C_{21}H_{32}N_4O_4$: C, 62.34, H 7.98, N, 13.86. Found: C, 61.59, H 7.65, N, 13.65.

2,6-Bis(pivaloylamino)-5-(3-oxocyclopentyl)-4(3H)-pyrimidinone (25). As described for the preparation of **3**, 2,6-diamino-4(3H)-pyrimidinone (**1**) (5.0 g, 40 mmol) was treated with NaOMe and 2-cyclopenten-1-one (5.0 g, 40 mmol). The solid which formed was collected and dried *in vacuo*. A portion of the crude material (ca. 1 g) was suspended in 2 mL of pivalic anhydride and heated at 140 °C for 4 h. After cooling to rt, the solvent was removed *in vacuo* and the resulting solid residue was then purified by radial chromatography, using 5% MeOH in CH_2Cl_2 as eluent, to afford 520 mg of a pale yellow powder, mp 150-152 °C . ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (s, 9 H), 1.30 (s, 9 H), 1.97 (br s, 1 H), 2.16 (br t, 1 H), 2.32 (m, 2 H), 2.50 (m, 2 H), 2.99 (m, 1 H), 7.22 (s, 1 H), 8.45 (s, 1 H), 11.88 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.6, 26.9, 27.5, 36.0, 38.9, 39.9, 40.5, 40.9, 114.7, 148.4, 152.4, 162.0, 177.4, 180.4, 220.4; IR (KBr) 2964, 1731, 1654, 1569 cm^{-1}; MS m/e (relative intensity) 376 (10), 348 (2), 320 (4), 319 (5), 291 (11), 275 (3); HRMS calcd for $C_{19}H_{28}N_4O_4$: 376.2110. Found: 376.2118. Anal. Calcd for $C_{19}H_{28}N_4O_4$: C, 60.60, H 7.50, N, 14.89. Found: C, 60.54, H 7.33, N, 14.81.

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