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Dienophilicity of Imidazole in Inverse Electron Demand Diels−Alder Reactions. 4. Intermolecular Reactions with 1,2,4-Triazines

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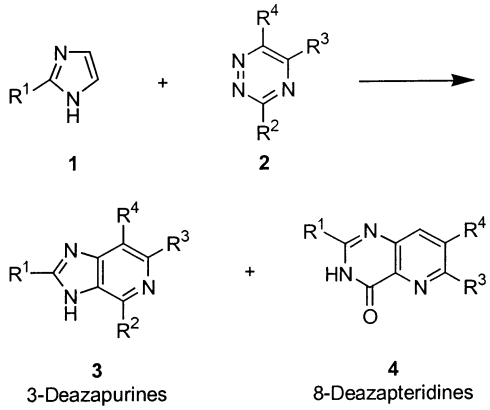
Intermolecular inverse electron demand cycloadditions of 2-substituted imidazoles with various 1,2,4-triazines produced both imidazo[4,5-*c*]pyridines (3-deazapurines) and pyrido[3,2-*d*]pyrimid-4-ones (8-deazapteridines). The product distribution was controlled by reactant substituents and influenced by reaction temperature. A regioselective method for the preparation of 6-unsubstituted 1,2,4-triazines was also developed. By using this route to 8-deazapteridines, a new 8-deazafolate analogue was prepared.

Introduction

The ability of electron-rich heterocycles with latent enamine functionalities to participate in inverse electron demand Diels−Alder reactions with electron-deficient dienes has been the focus of research for some time.[1] A prominent example is the chemistry of indole in reactions with electron-deficient heteroaromatic azadienes, which has been probed by several groups.[2] Recently we have become interested in utilizing imidazole as a dienophile in such reactions with 1,2,4-triazines as a means to prepare imidazo[4,5-*c*]pyridines (3-deazapurines, **3**, Scheme 1).[3] 3-Deazapurines have been of long-standing interest in drug development as purine analogues, and have been shown to be adenosine-deaminase inhibitors,[4] angiotensin II receptor antagonists,[5] antiosteoporotic agents,[6] anti-HIV 1 and antitumor agents.[7] The reactivity of imidazole in cycloaddition chemistry, however, has not been reported to a great extent in the literature. Seitz first reported successful inverse electron demand Diels−Alder reactions of imidazoles with 1,2,4,5-tetrazines in modest yields,[8] while Horne demonstrated the condensation of 2-aminoimidazole with aldehydes by a concerted cycloaddition route to give tetrahydropurine analogues.[9] Since then, Dang has described the concise syntheses of purine analogues through the [4 + 2] cycloaddition of in situ

SCHEME 1



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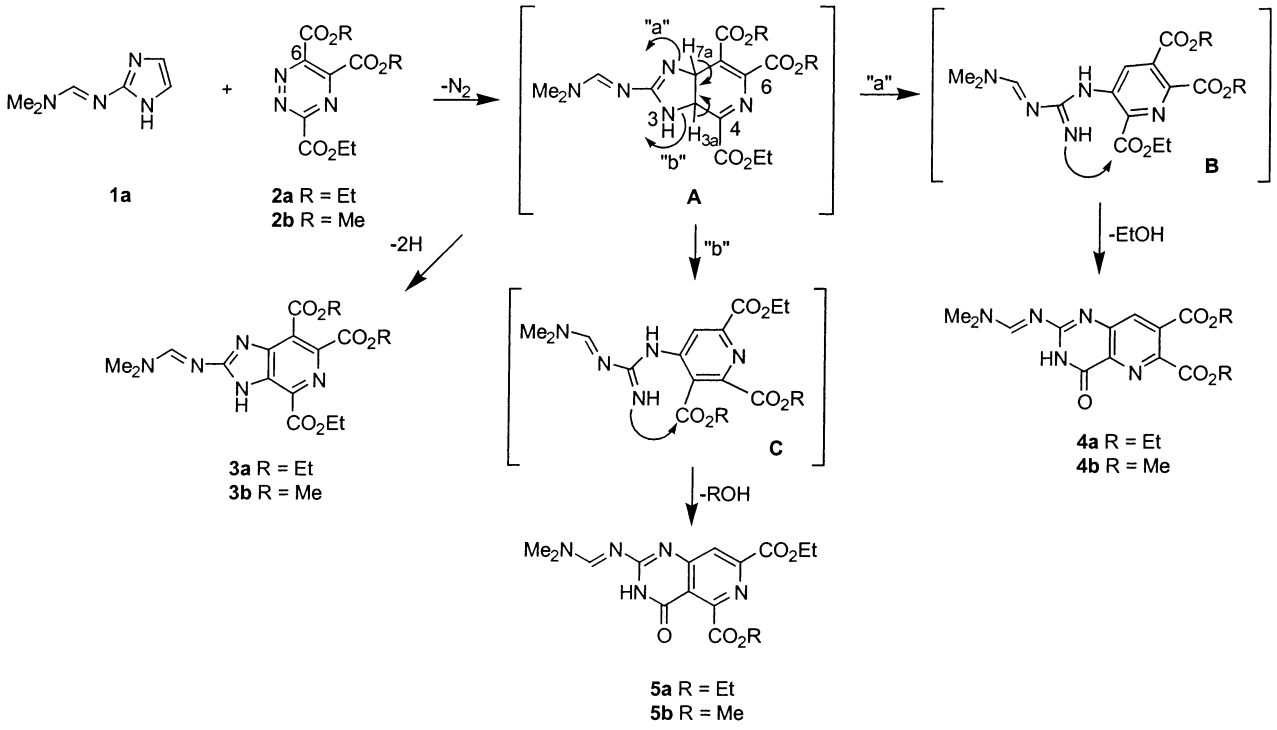
SCHEME 2



generated 4-aminoimidazoles with 1,3,5-triazines.[10] More recently, we have also used the inverse electron demand Diels−Alder reaction of imidazoles with 1,2,4,5-tetrazines to prepare the structure reported for the cytotoxic marine natural product zarzissine.[11]

In preliminary work with triazines, we examined the cycloadditions of imidazole and 2-substituted imidazoles with several 1,2,4-triazines **2** and found that only 2-aminoimidazole was sufficiently reactive to participate in the intermolecular cycloadditions (Scheme 1, R^1 = NP).[3a] Two distinct reaction pathways for protected 2-aminoimidazoles were uncovered leading to 3-deazapurines and pyrido[3,2-*d*]pyrimid-4-ones (8-deazapteridines).[3a] This latter product was especially prominent with triethyl 1,2,4-triazine-3,5,6-tricarboxylate[12] (**2a**, Scheme 2), giving a remarkable 77% yield of the deazapteridine. We now report full details of our earlier work and also expand the scope of this chemistry with other 1,2,4-triazines.

Results and Discussion

Beginning with triazine tricarboxylate **2a**, one of the most reactive 1,2,4-triazines in inverse electron demand Diels−Alder reactions, cycloadditions were attempted with imidazole, 2-phenylimidazole, and 2-aminoimidazole, but no cycloadducts were observed. While imidazole and 2-phenylimidazole proved too unreactive and returned only starting materials or decomposed under more forcing conditions, 2-aminoimidazole gave an intractable mixture, at or even below room temperature. Consequently, cycloadditions of 2-aminoimidazole, protected as the aminoimine **1a**,[13] were examined in THF (rt) with triazine **2a**, resulting in a mixture of the anticipated [4 + 2]-cycloadduct, imidazo[4,5-*c*]pyridine **3a** (32%), and rearranged pyridopyrimidones **4a** (55%) and **5a** (<1%) in excellent combined yield (Table 1, item 1). The latter two products arose from rearrangements of intermediate **A** formed from the initial cycloadduct following release of N_2 (Scheme 2).

Mechanistically, this rearrangement is similar to that observed previously with indole in cycloadditions with 1,2,4,5-tetrazines,[14] first noted by Acheson,[15] as well as with 1,2,4-triazines,[16] and with 1,2-diazines[16] albeit in very low yields. From intermediate **A**, aromatization leads to 3-deazapurine **3a** while deprotonation of H_{3a} or H_{7a} (pathway "a" or "b", respectively) followed by opening of the imidazole ring to intermediates **B** or **C** and subsequent closure to the respective proximal ester produces rearranged products **4a** and **5a**. The agent responsible for the dehydrogenation of **A**, leading to 3-deazapurine **3a**, is possibly the triazine **2a**. However, dihydro triazine byproducts, which would indicate the

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TABLE 1. Cycloadditions of Imidazoles (1) with 1,2,4-Triazines 2a and 2b (Schemes 1 and 2)

item	imidazole	R^1	triazine	conditions[b]	product code	yield (%)[a] 3	yield (%)[a] 4
1	**1a**	$(Me)_2NCH{=}N-$	**2a**	THF, rt, 60 h	**a**	32	55
2	**1a**	$(Me)_2NCH{=}N-$	**2a**	dioxane, rt, 60 h	**a**	43	47
3	**1a**	$(Me)_2NCH{=}N-$	**2a**	CH_2Cl_2, rt, 60 h	**a**	25	60
4	**1a**	$(Me)_2NCH{=}N-$	**2a**	THF, ↑↓, 10 h	**a**	17	72
5	**1a**	$(Me)_2NCH{=}N-$	**2a**	dioxane, ↑↓, 5 h	**a**	13	77
6	**1a**	$(Me)_2NCH{=}N-$	**2b**	65 °C, dioxane, 16 h	**b**	16	70
7	**1a**	$(Me)_2NCH{=}N-$	**2b**	dioxane, ↑↓, 5 h	**b**	11	74
8	**1b**	$(Me)_2NC(Me){=}N-$	**2a**	dioxane, rt, 12 h	**c**	11	58
9	**1b**	$(Me)_2NC(Me){=}N-$	**2a**	dioxane, ↑↓, 3 h	**c**	5	83
10	**1c**[c]	$(Me)_2N-$	**2a**	dioxane, rt, 24 h	**d**	T[d]	T[d]
11	**1c**[c]	$(Me)_2N-$	**2a**	dioxane, ↑↓, 2 h	**d**	11	60

[a] Isolated yields. [b] All reactions were run at 0.1−0.3 M. [c] Air sensitive, must be run under inert atmosphere. [d] Trace amount detected by ^{1}H NMR of the crude reaction mixture.

triazine is functioning as the aromatization agent, were not isolated. Such byproducts were detected in the corresponding reactions of indole with **2a**.[16a] Furthermore, running the reaction under ambient atmosphere rather than argon also had no impact on the outcome of the reaction. Thus, it is unlikely that adventitious oxygen is responsible for the dehydrogenation of intermediate **A** to **3a**.

To distinguish the regioisomeric rearrangement products **4a** and **5a**, as well as to offer evidence of this mechanistic pathway, 5,6-dimethyl-3-ethyl 1,2,4-triazine-3,5,6-tricarboxylate (**2b**)[17] was subjected to the same reaction with imidazole **1a** (Scheme 2, Table 1, item 7). The dominant rearrangement product (74%) contained no ethyl resonances in the ^{1}H NMR spectrum and was therefore assigned the structure **4b**; also produced were the aromatized product **3b** (11%) and a trace amount of **5b**.

The ratio of **3a**:**4a** was strikingly dependent on the reaction temperature, but only slightly dependent upon the solvent (Table 1, items 1−5). As the reaction temperature was raised, increasing amounts of pyrido[3,2-*d*]pyrimidones **4a** were produced at the expense of **3a** (compare Items 1 and 2 with 4 and 5, respectively). Thus, when triazine **2a** was heated with imidazole **1a** in refluxing dioxane (item 5), the yield of rearranged 8-deazapteridine **4a** reached a remarkable 77%, formed in a 6:1 ratio with 3-deazapurine **3a** (13%), while at room temperature in dioxane, **4a** and **3a** were produced in yields of 47% and 43%, respectively (item 2). A similar increase in **4a** was found in refluxing THF (72%, item 4) in comparison to the room temperature reaction, also in THF (55%, item 1). Only a minor solvent effect was observed, with increasing polarity (CH_2Cl_2−THF−dioxane) seemingly favoring **3a** very slightly (25%, 32%, and 43%, items 1−3). The concentration at which the reaction was run failed to have a significant effect on the product distribution.

Analogous rearrangements following inverse electron demand Diels−Alder cycloadditions have been noted in the reactions of indole with both 1,2,4,5-tetrazines[14−16] and 1,2,4-triazines,[16] but only as minor products. Pyrrole has also been reported to participate in inverse electron demand cycloadditions with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate through a similar pathway.[8a] Mechanistically, it seemed possible that the addition of a base would favor the rearrangement of cycloadduct **A** to produce **4** since this was speculated to result from a deprotonation/ring opening sequence (Scheme 2). However, the addition of 2,6-lutidine or triethylamine (1 equiv) to the reaction of **2a** with **1a** failed to alter the distribution of products in refluxing dioxane. Reacting **2a** with **1a** in refluxing triethylamine produced only trace amounts of reaction products **3a** and **4a** along with decomposed starting materials.

Given the success of the cycloadditions with **1a,** other electron-rich imidazoles were prepared and subjected to cycloadditions (Table 1, items 8−11). 2-(*N*′,*N*′-Dimethylacetamidino)imidazole (**1b**) not only reacted faster with triazine **2a** in comparison to the reaction of **1a** with **2a** (3 h vs 5 h), but also produced a slightly increased yield of the rearranged product, **4c** (83% vs 77%, items 9 and 5). 2-(Dimethylamino)imidazole (**1c**),[18] which was expected to be the most reactive of the imidazoles investigated due to the significant electron donation of the dimethylamino group, reacted completely with triazine **2a** within 2 h in refluxing dioxane producing **4d** (60%, item 11) along with aromatized **3d** (11%). At room temperature in dioxane, however, this reaction produced only trace amounts of cycloaddition products. The air and thermal sensitivity of imidazole **1c** was presumed to be the cause of these reduced yields of cycloadducts (items 10 and 11). As with imidazole **1a**, increasing the temperature of the reaction of **1b** with triazine **2a** also increased the amount of 8-deazapteridine **4c** at the expense of 3-deazapurine **3c** (items 8 and 9). The less electron-rich 2-(methylthio)imidazole (**1d**)[19] required extended reaction times as well as higher temperatures (156 °C, refluxing bromobenzene, 69 h) to react completely with triazine **2a** (Scheme 3). With **1d** and this increased reaction temperature, a significant amount (13%) of the minor rearranged pyrido[4,3-*d*]pyrimidone **5e** was also formed, though **4e** remained the dominant product in good yield (72%), while aromatized 3-deazapurine **3e** formed in only small amounts (7%). Thus in all cases examined, the rearranged pyrido[3,2-*d*]pyrimidin-4-ones **4 (**8-deazapteridines) were the main products, all produced efficiently in a single step in synthetically useful yields.

Since triazine **2a** reacted readily with imidazoles **1a**−**d** and indole,[16a] a competition experiment was performed

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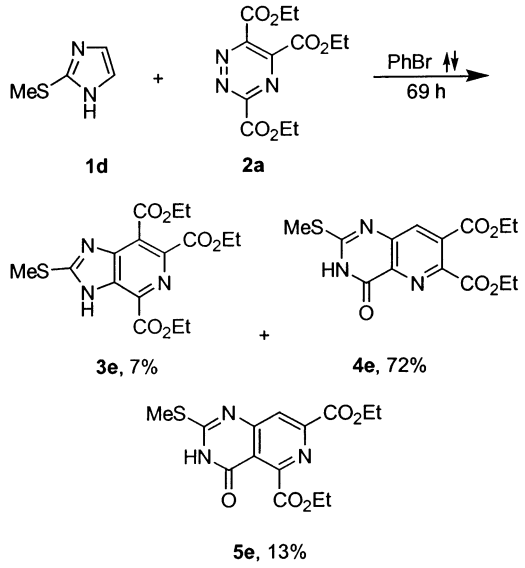
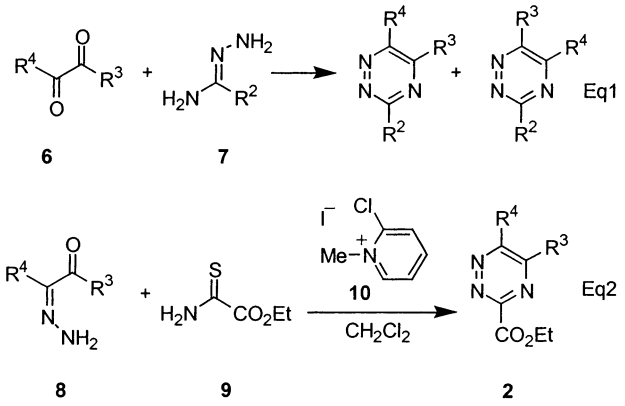
SCHEME 3



SCHEME 4



to determine the relative reactivity of indole and protected 2-aminoimidazole **1b**. When triazine **2a** (1 equiv) was refluxed in dioxane containing indole (1 equiv) and imidazole **1b** (1 equiv), the only cycloadducts detected by ^{1}H NMR were those of **1b** (**3c** and **4c**), indicating that **1b** is significantly more reactive than indole in inverse electron demand Diels−Alder reactions with heterocyclic azadienes.

Since indole also participated in cycloadditions with other 1,2,4-triazines, a variety of 1,2,4-triazine-3-carboxylates were prepared and examined in cycloadditions with 2-aminoimidazole derivatives to expand the scope of this chemistry. The most common method for preparing these 1,2,4-triazines was the condensation of 1,2-dicarbonyl compounds **6** with amidrazones **7** (Scheme 4, eq 1),[12] and this strategy was used to prepare known triazines **2a**, **2b**, and **2d**−**g** (structures given in Table 3 below). While fairly general, this procedure can result in a mixture of regioisomers when unsymmetric 1,2-dicarbonyl compounds are involved.[20]

Neunhoeffer[21] has reported the regioselective preparation of a variety of trialkyl-1,2,4-triazines, ethyl 1,2,4-triazine-6-carboxylates,[22] and ethyl 1,2,4-triazine-5-carboxylates[23] through linear methodologies. However, no procedure has been reported for the completely regioselective synthesis of 5,6-unsymmetrically substituted 1,2,4-triazine-3-carboxylates. Such triazines were desirable in this work since their cycloadditions with **1a** or **1b**, with subsequent rearrangement to the corresponding 8-deazapteridines, would provide ready access to 8-deazafolate libraries (vide supra). To prepare such new 1,2,4-triazines while avoiding the regioselectivity problems often encountered with amidrazone condensations, a procedure was developed from the basic protocol reported by Mukaiyama for the synthesis of esters.[24] In this procedure, a thioamide was condensed with an α-ketohydrazone through the intervention of the Mukaiyama coupling reagent 2-chloro-1-methylpyridinium iodide (**10**, Scheme 4, eq 2).[24c] Precedence for the use of **10** with thioamides had been demonstrated by Lipton in the guanylation of amines using thioureas.[25] Adapting this methodology, the previously unknown diethyl 1,2,4-triazine-3,5-dicarboxylate (**2c**) was prepared in 40% yield in one step by the coupling and concomitant cyclization (and aromatization) of hydrazone **8a**[23] and ethylthioamidooxalate (**9a**)[12] in the presence of **10** (Table 2, item 1). In the absence of the pyridinium salt, no product was formed. The outcome of this reaction was effected significantly by the stability and reactivity of the hydrazone. The sensitivity of hydrazone **8a** to base and heat limited the yield of triazine product **2c**. The more stable hydrazone **8b**[26] produced known triazine **2d**[16a] in 72% yield (item 2), while the less nucleophilic hydrazone **8c**[23] failed to give any conversion (item 3), even under harsher conditions (101 °C, dioxane) or in the presence of base ($NaHCO_3$, K_2CO_3, and Et_3N).

TABLE 2. Condensation of α-Ketohydrazones 8 with Thioamides To Produce 1,2,4-Triazines 2

item	**8**	R^3	R^4	product	yield (%)[a]
1	**a**	CO_2Et	H	**2c**	40
2	**b**	Ph	H	**2d**	72
3	**c**	Me	CO_2Et		0

[a] Isolated yields.

With the new triazine **2c** in hand, along with known 1,2,4-triazines **2d**,[16a] **2e**,[27] **2f**,[16a,28] and **2g**,[16a,29] cycloadditions with 2-aminoimidazoles were examined (Table 3).

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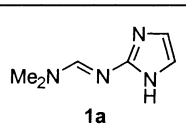
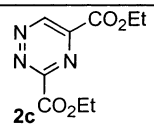
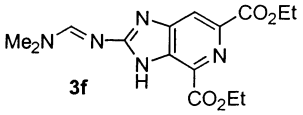
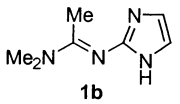
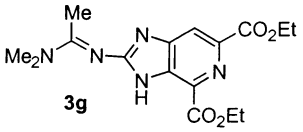
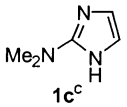
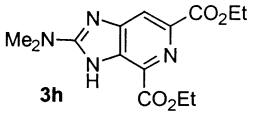
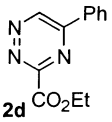
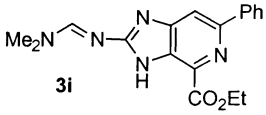
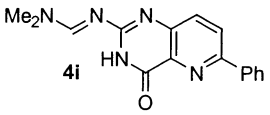
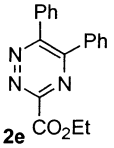
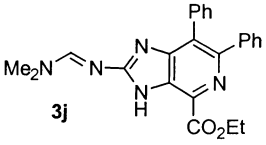
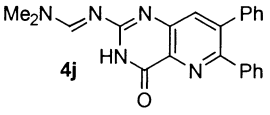
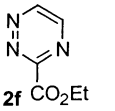
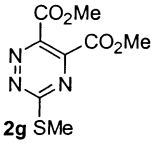
TABLE 3. [4 + 2] Cycloadditions of Various 1,2,4-Triazines with 2-Aminoimidazoles[a]

Item	Imidazole	Triazine	Conditions	3-Deazapurine	Yield (%)[b]	8-Deazapteridine	Yield (%)[b]
1	 **1a**	 **2c**	dioxane, ⇅, 4h	 **3f**	25	-	
2	 **1b**	**2c**	neat, 60°C, 2h	 **3g**	64	-	
3	 **1c**[c]	**2c**	THF, 0°C-rt, 16h	 **3h**	84	-	
4	**1a**	 **2d**	neat, 120-125°C	 **3i**	24	 **4i**	16
5	**1a**	 **2e**	neat, 120-125°C	 **3j**	13	 **4j**	31
6	**1a-1c**	 **2f**	neat, 120-125°C		No Reaction		
7	**1a-1c**	 **2g**	neat, 120-125°C		No Reaction		

[a] See Scheme 1. [b] Isolated yields. [c] Air sensitive, must be run under an inert atmosphere.

In reaction with **1a**, triazine **2c**, which lacks the C6 ester group of **2a**, yielded only aromatized cycloadduct **3f** (25%), and no rearrangement products (**4** or **5**) were detected (Table 3, item 1). This contrasted sharply with the reaction of **1a** with the more electron deficient **2a** that gave primarily rearranged **4a** under the same conditions (Table 1). The reactions of **2c** with imidazoles **1b** and **1c** produced 3-deazapurines **3g** and **3h** in good yields of 64% and 84% (items 2 and 3, respectively). Higher reaction temperatures failed to produce any detectable rearrangement products **4** or **5** and led only to lower yields of 3-deazapurines **3** and decomposition of triazine **2c**. The relatively poor thermal stability of **2c** to the reaction conditions presumably contributed to the lower yields in these cycloadditions, though the reaction of 2-dimethylaminoimidazole (**1c**) produced **3h** in excellent yield (84%, item 3), since the reaction temperature for this more reactive imidazole could be much lower (0 °C to rt). Replacement of the two electron-withdrawing ester groups in triazine **2a** at C5 and C6 with one or two phenyl groups (**2d** and **2e**, respectively) significantly reduced the reactivity of the triazine such that heating the reactants in the absence of solvent to 120−125 °C was required to achieve the chemistry (items 4 and 5), producing mixtures of 3-deazapurines **3** and 8-deazapteridines **4** in disappointing yields and poor selectivity. The 5,6-unsubstituted triazine **2f**, as well as triazine **2g** with an electron-donating C3 thiomethyl group, failed to give any reaction products at all with **1a**−**c**. In all aromatized products with a C4 ester group (**3a**−**j**), broadening of the ester resonances in the ^{1}H NMR spectra occurred, presumably due to intramolecular hydrogen bonding with the 3-NH (Figure 1).

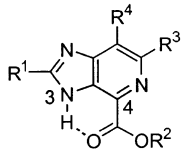


FIGURE 1. Intramolecular hydrogen bonding observed in ^{1}H NMR spectra.

While it was determined that higher temperatures favored the rearrangement of intermediate **A** to produce the 8-deazapteridine skeleton **4**, the results from Table 3 indicate the C6 ester group on triazine **2a** was important to the cycloaddition and to the subsequent rearrangement (Scheme 2) since **2c**, which lacks this ester, failed to produce any rearrangement products. The resonance stabilization of the developing negative charge

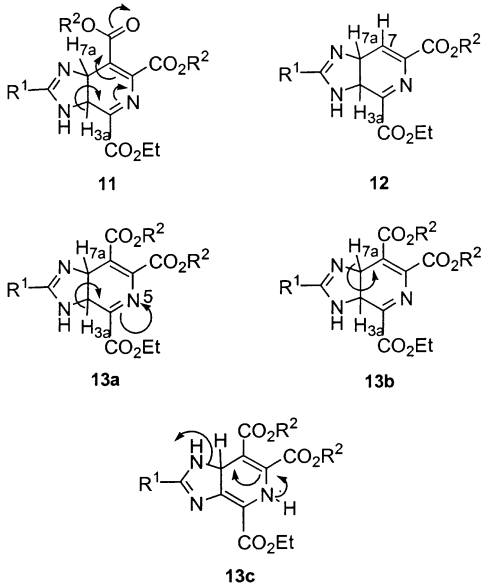


FIGURE 2. Resonance stabilization of intermediate **A**, and alternative intermediate **13c**.

formed by deprotonation of H_{3a} in intermediate **A** onto this ester (**11**, Figure 2) may therefore direct the chemistry to this rearrangement pathway to 8-deazapteridines **4**. In the absence of the C7 ester (**12**), the missing resonance stability may be the cause for the lack of rearrangement products **4** or **5**. With triazines **2a**, **2b**, **2d**, and **2e**, the dominance of rearrangement products **4** over **5** could be attributed to additional resonance stabilization of this anion onto N5 (**13a**) in the pathway leading to **4**, which cannot be attained via this mechanistic route (**13b**) leading to **5**. Alternatively, tautomerization of intermediate **A** to the 1,4-dihydro form **13c** would also favor the production of **4** over **5**, though in itself this tautomer cannot account for the lack of imidazole-ring opened product from **2c**, nor the appearance of **5e** in the cycloaddition of **1d** with **2a** as shown in Scheme 3.[30] Nevertheless, the intermediacy of **13c** in the pathway to **4** cannot be ruled out.

The unprecedented high yield (maximum 83% with **1b**, Table 1, item 9) of the rearrangement products **4** provides a novel, concise, and convergent route to the protected 8-deazapteridine skeleton. With the appropriate choice of nitrogen protecting group, this methodology reveals a high-yielding route to this heterocyclic core found in a variety of dihydrofolate reductase,[31] thymidylate synthase,[32] and tyrosine kinase[33] inhibitors.

By using this chemistry, a new analogue of 8-deazafolic acid was prepared in a four-step sequence (Scheme 5). Selective hydrolysis of the more reactive ester of **4a** adjacent to the pyridine ring nitrogen with LiOH (3 equiv) at 0 °C in THF/H_2O followed by acidification produced **14**. The use of <3 equiv of LiOH failed to give complete conversion of **4a**, which proved difficult to separate from compounds **17** and **18** in the forthcoming peptide coupling. The 8-deazafolic acid side chain (**16**)[34] was prepared, protected as the acid-labile *tert*-butyl esters, by peptide coupling of di-*tert*-butyl (*S*)-glutamate[35] with *p*-nitrobenzoic acid to give **15**, followed by reduction of the nitro group to the amine **16**. Amidation (EDC, HOBt) of carboxylic acid **14** with aniline **16** under carefully adjusted pH (3.5−4.0) yielded **18**; the regioselectivity of the original ester hydrolysis was then confirmed by a NOESY experiment. Thus, an NOE was observed between the methylene proton resonance of the ethyl ester with H8 of the deazapteridine core. It should be noted that under more basic (pH 5−6) or more acidic conditions (below pH 3) the amidation failed to produce the desired product **18**. Under more basic conditions, the major product was imide **17** while under more acidic conditions the poor solubility of carboxylic acid **14** in CH_2Cl_2/H_2O prevents the amidation from occurring. Sequential deprotection of the *tert*-butyl ester and aminoimine groups in **18** was achieved with TFA/Et_3SiH[36] to give the 8-deazafolic acid analogue **19**.

Conclusions

The inverse electron demand Diels−Alder reactions of imidazoles with 1,2,4-triazines produce imidazo[4,5-*c*]-pyridines (3-deazapteridines) and pyrido[3,2-*d*]pyrimid-4-ones (8-deazapteridines). Either can be the main product depending on the triazine substituents. The 8-deazapteridines can be produced in excellent yields (>76%), particularly at higher reaction temperatures. The cycloadditions require a strong electron-donating C2 substituent on the imidazole as well as strong electron-withdrawing substituents on the triazine. The formation of the 8-deazapteridine skeleton **4** in high yield provides a facile route to the syntheses of 8-deazafolate analogues such as **19**.

Experimental Section

General Procedure A: Cycloadditions of Imidazoles with 1,2,4-Triazines. Imidazole **1** and 1,2,4-triazine **2** were mixed in anhydrous solvent (CH_2Cl_2, THF, dioxane, or bromobenzene as indicated, Tables 1 and 3, Scheme 3) under argon. The reaction mixture was then stirred at room temperature or refluxed until the limiting reagent was gone as monitored by TLC. The solvent was removed in vacuo and the residue was purified by flash chromatography.

General Procedure B: Cycloadditions of Imidazoles with 1,2,4-trIazines. Imidazole **1** and 1,2,4-triazine **2** were mixed under argon and heated in an oil bath in the absence of solvent (Table 3). The residue was purified by flash chromatography.

2-(*N*′,*N*′-Dimethylformamidino)imidazole (1a). 2-Aminoimidazole sulfate (539 mg, 2.0 mmol) was stirred with

(30) We thank two reviewers for this suggestion.

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(35) Boger, D. L.; Haynes, N.-E.; Kitos, P. A.; Warren, M. S.; Ramacharan, J.; Marolewski, A. E.; Benkovic, S. J. *Bioorg. Med. Chem.* **1997**, *5*, 1817−1830.

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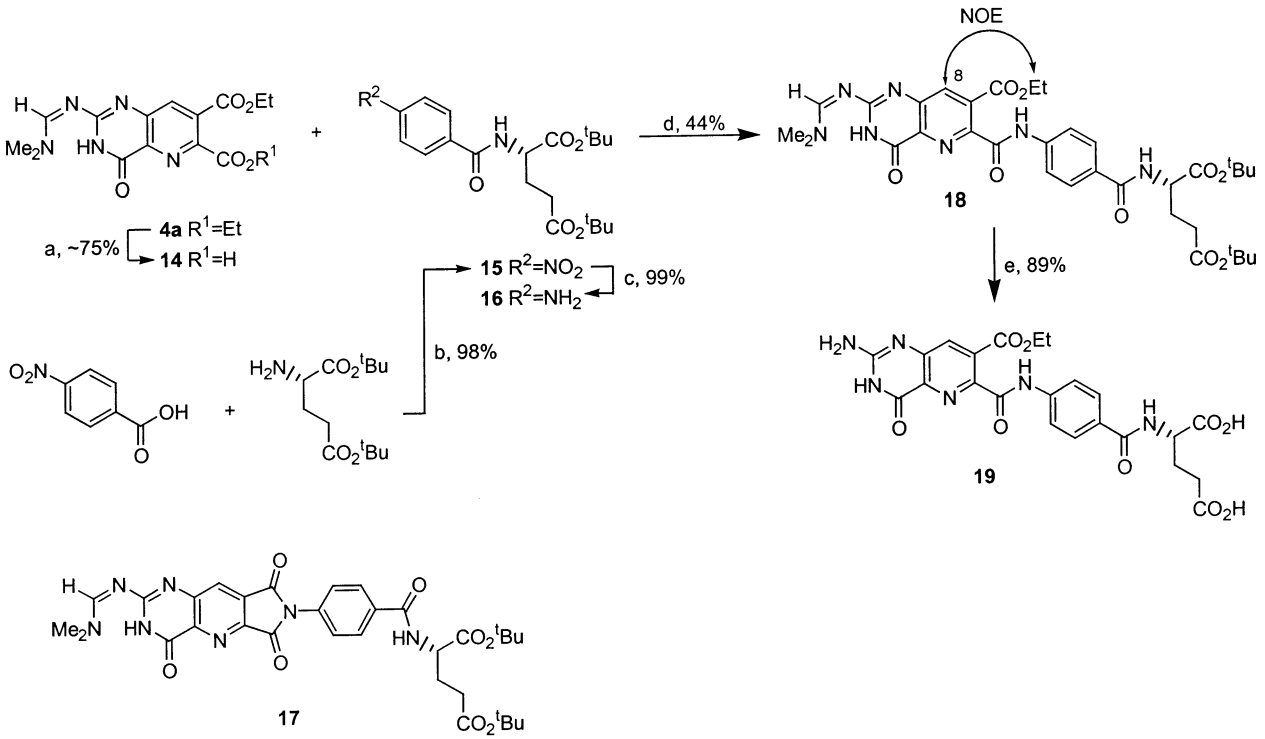
SCHEME 5[a]



[a] Key: (a) LiOH (3 equiv), THF/H_2O, 0 °C, 1 h; (b) EDC, HOBt, CH_2Cl_2/H_2O, 0 to 10 °C, 16 h; (c) H_2, Pd/C, MeOH, rt, 2 h; (d) EDC, HOBt, $NaHCO_3$, CH_2Cl_2/H_2O, 0 to 15 °C, 18 h; (e) TFA, Et_3SiH, rt, 16 h then CH_2Cl_2, H_2O, reflux, 1 h.

Na_2CO_3 (424 mg, 4.0 mmol) in water (4 mL) for 15 min, then the solvent was removed in vacuo and the residue triturated with anhydrous ethanol (30 mL). After filtration and evaporation of the ethanol, *N*,*N*-dimethylformamide dimethyl acetal (3 mL, 20.5 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The solvent was evaporated and the crude product purified by flash chromatography (CH_2Cl_2/Et_3N, 3:1) to give **1a** as a white solid (R_f 0.20, 524 mg, 95%). Mp 140−142 °C; IR (NaCl) ν_{max} 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (br s, ex, NH), 8.48 (s, 1H), 6.71 (s, 2H), 3.04 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7 (2C), 152.5, 118.9 (br), 40.4, 34.4; HRMS (EI, 70 eV) *m*/*z* 138.0916 ($[M]^+$) 100%) calcd for $C_6H_{10}N_4$ 138.0905.

2-(*N*′,*N*′-Dimethylacetamidino)imidazole (1b). 2-Aminoimidazole sulfate (550 mg, 2.03 mmol) was stirred with Na_2CO_3 (430 mg, 4.06 mmol) in water (4 mL) for 15 min, then the solvent was removed in vacuo and the residue triturated with anhydrous ethanol (30 mL). After filtration and evaporation of the ethanol, *N*,*N*-dimethylaminoacetamide dimethyl acetal (3 mL, 20.5 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The solvent was evaporated and the crude product was purified by flash chromatography (CH_2Cl_2/Et_3N, 3:1) to give **1b** as a white solid (R_f 0.20, 502 mg, 86%). Mp 125−126 °C; IR (NaCl) ν_{max} 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 2H), 3.05 (s, 6H), 2.32 (s, 3H), (NH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 152.0, 119.0 (2C), 38.2 (2C), 16.4; HRMS (CI, NH_3, 140 eV) *m*/*z* 153.1130 ($[M + H]^+$, 3%), calcd for $C_7H_{13}N_4$ 153.1140.

Diethyl 1,2,4-Triazine-3,5-dicarboxylate (2c). Hydrazone **8a**[23] (135 mg, 0.94 mmol) in CH_2Cl_2 (5 mL) was added dropwise (1 min) to a stirred suspension of ethyl thioamidooxalate (**9**,[12] 125 mg, 0.94 mmol) and 2-chloro-1-methylpyridinium iodide (**10**,[24c] 288 mg, 1.1 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was then allowed to warm slowly to room temperature over 4 h followed by refluxing for 0.5 h. After the mixture was cooled to room temperature, the yellow ppt was filtered and the filtrate was diluted with additional CH_2Cl_2 (10 mL), then washed with saturated aqueous NH_4Cl. The organic fraction was collected, dried ($MgSO_4$), and concentrated in vacuo, and the crude reaction product was purified by flash chromatography (hexanes/EtOAc, 2:1) to give **2c** as a yellow oil (R_f 0.40, 85 mg, 40%). IR (NaCl) ν_{max} 1740, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 4.60 (q, J = 7.2 Hz, 2H), 4.55 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 161.8, 157.5, 148.8, 147.2, 63.8, 63.6, 14.2, 14.1; HRMS (EI, 70 eV) *m*/*z* 225.0741 ($[M]^+$, 49%), calcd for $C_9H_{11}N_3O_4$ 225.0749.

Triethyl 2-(*N*′,*N*′-Dimethylformamidino)-3*H*-imidazo-[4,5-*c*]pyridine-4,6,7-tricarboxylate (3a) and Diethyl 2-(*N*′,*N*′-Dimethylformamidino)-3*H*-pyrido[3,2-*d*]pyrimid-4-one-6,7-dicarboxylate (4a). Prepared following general procedure A, optimized for **3a** with imidazole **1a** (402 mg, 2.90 mmol) and triazine **2a** (864 mg, 2.90 mmol) in dioxane (29 mL) at room temperature for 60 h; purified by flash chromatography (CH_2Cl_2/acetone, 3:1) to give **3a** as a tan solid (R_f 0.25, 507 mg, 43%) and **4a** as a light yellow solid (R_f 0.20, 493 mg, 47%). Also optimized for **4a** with imidazole **1a** (1.40 g, 10.1 mmol) and triazine **2a** (3.01 g, 10.1 mmol) by refluxing in dioxane (90 mL) for 5 h to give **3a** (532 mg, 13%) and **4a** (2.82 g, 77%). **3a**: mp 145−148 °C; IR (NaCl) ν_{max} 1732, 1631, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.86 (br s, ex, NH), 8.83 (s, 1H), 4.50 (q, J = 7.3 Hz, 2H), 4.49 (q, J = 7.3 Hz, 2H), 4.41 (q, J = 6.9 Hz, 2H), 3.19 (s, 3H), 3.12 (s, 3H), 1.45 (t, J = 7.3 Hz, 3H), 1.39 (t, J = 7.3 Hz, 3H), 1.38 (t, J = 6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 165.9, 165.3, 165.1, 163.6, 160.0, 150.0, 138.9, 135.5, 128.3, 121.7, 62.2, 62.01, 61.96, 41.3, 35.0, 14.2, 14.1, 14.0; HRMS (CI, NH_3, 140 eV) *m*/*z* 405.1667 ($[M]^+$, 2%), calcd for $C_{18}H_{24}N_5O_6$ 405.1648. **4a**: mp 187−188 °C; IR (NaCl) ν_{max} 1731, 1705, 1635, 1551, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (br s, ex, NH), 8.74 (s, 1H), 8.13 (s, 1H), 4.42 (q, J = 7.3 Hz, 2H), 4.39 (q, J = 7.3 Hz, 2H), 3.23 (s, 3H), 3.12 (s, 3H), 1.39 (t, J = 7.3 Hz, 3H), 1.36 (t, J = 7.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 165.6, 165.0, 160.5, 159.0, 156.5, 147.6, 146.0, 137.1, 135.6, 131.2, 62.25, 62.21, 41.7, 35.4, 14.0 (2C); HRMS (EI, 70 eV) *m*/*z* 361.1415 ($[M]^+$, 1%), calcd for $C_{16}H_{19}N_5O_5$ 361.1385.

4-Ethyl 6,7-Dimethyl 2-(*N*′,*N*′-Dimethylformamidino)-3*H*-imidazo[4,5-*c*]pyridine-4,6,7-tricarboxylate (9b) and Dimethyl 2-(*N*′,*N*′-Dimethylformamidino)-3*H*-pyrido[3,2-*d*]pyrimid-4-one-6,7-dicarboxylate (4b). Prepared following general procedure A with imidazole **1a** (62 mg, 0.45 mmol) and triazine **2b** (120 mg, 0.45 mmol) in refluxing dioxane (4 mL) for 5 h; purified by flash chromatography (CH_2Cl_2/acetone, 3:1) to give **3b** as a tan solid (R_f 0.36, 19 mg, 11%) and **4a** as a pale yellow solid (R_f 0.28, 111 mg, 74%). **3b**: mp 195−198 °C; IR (NaCl) ν_{max} 1736, 1631, 1590, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (br s, ex, NH), 8.82 (s, 1H), 4.52 (q, J = 7.3 Hz, 2H), 4.03 (br s, 3H), 3.96 (s, 3H), 3.19 (s, 3H), 3.13 (s, 3H), 1.48 (t, J = 7.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.5, 165.5, 165.0, 163.7, 160.0, 149.3, 137.7, 134.9, 128.3, 121.7, 62.3, 52.9, 52.8, 41.2, 35.0, 14.1; HRMS (EI, 70 eV) *m*/*z* 377.1317 ([M]$^+$, 56%), calcd for $C_{16}H_{19}N_5O_6$ 377.1335. **4b**: mp 241−244 °C; IR (NaCl) ν_{max} 1735, 1705, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (br s, ex, NH), 8.75 (s, 1H), 8.08 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.23 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 165.7, 160.6, 159.1, 156.6, 147.7, 144.7, 136.9, 135.2, 131.5, 53.10, 52.96, 41.8, 35.4; HRMS (EI, 70 eV) *m*/*z* 333.1090 ([M]$^+$, 21%), calcd for $C_{14}H_{15}N_5O_5$ 333.1073.

Triethyl 2-(*N*′,*N*′-Dimethylacetamidino)-3*H*-imidazo-[4,5-*c*]pyridine-4,6,7-tricarboxylate (3c) and Diethyl 2-(*N*′,*N*′-Dimethylacetamidino)-3*H*-pyrido[3,2-*d*]pyrimid-4-one-6,7-dicarboxylate (4c). Prepared following general procedure A, optimized for **3c** with imidazole **1b** (113 mg, 0.74 mmol) and triazine **2a** (221 mg, 0.74 mmol) in 1,4-dioxane (7 mL) at room temperature for 12 h; purified by flash chromatography (CH_2Cl_2/acetone, 3:1) to give **3c** as a yellow oil (R_f 0.33, 34 mg, 11%) and **4c** as a yellow oil that solidifies upon standing (R_f 0.25, 162 mg, 58%). Also optimized for **4c** with imidazole **1b** (102 mg, 0.67 mmol) and triazine **2a** (200 mg, 0.67 mmol) in refluxing 1,4-dioxane (6 mL) for 3h, to give **3c** (14 mg, 5%) and **4c** (210 mg, 83%). **3c**: IR (NaCl) ν_{max} 1731, 1703, 1548 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (br s, ex, NH), 4.52 (q, J = 7.1 Hz, 2H), 4.49 (q, J = 7.1 Hz, 2H), 4.43 (q, J = 7.1 Hz, 2H), 3.19 (s, 3H), 3.17 (s, 3H), 2.55 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 166.1, 165.5, 165.2, 161.8, 150.1, 138.1, 134.8, 127.7, 122.0, 62.3, 62.0, 61.8, 38.9, 38.4, 17.1, 14.2, 14.1 (2C); HRMS (CI, NH_3, 140 eV), *m*/*z* 420.1865 ([M + H]$^+$, 1%), calcd for $C_{19}H_{26}N_5O_6$ 420.1883. **4c**: mp 166−168 °C; IR (NaCl) ν_{max} 3200, 1731, 1705, 1547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (br s, ex, NH), 8.1 (s, 1H), 4.42 (q, J = 7.3 Hz, 2H), 4.39 (q, J = 7.3 Hz, 2H), 3.18 (s, 3H), 3.16 (s, 3H), 2.43 (s, 3H), 1.39 (t, J = 7.3 Hz, 3H), 1.36 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 165.6, 165.1, 161.0, 155.3, 147.9, 145.7, 136.2, 135.3, 131.2, 62.1, 62.0, 38.8, 38.6, 17.4, 13.98 (2C); HRMS (EI, 70 eV) *m*/*z* 375.1540 ([M]$^+$, 13%), calcd for $C_{17}H_{21}N_5O_5$ 375.1542.

Triethyl 2-(Dimethylamino)-3*H*-imidazo[4,5-*c*]pyridine-4,6,7-tricarboxylate (3d) and Diethyl 2-(Dimethylamino)-3*H*-pyrido[3,2-*d*]pyrimd-4-one-6,7-dicarboxylate.[4d] Prepared following general procedure A with imidazole **1c** (103 mg, 0.93 mmol) and triazine **2a** (110 mg, 0.37 mmol) in refluxing 1,4-dioxane (3 mL) for 2 h; purified by flash chromatography (CH_2Cl_2/acetone, 3:1) to give **3d** (R_f 0.31, 15 mg, 11%) and **4d** (R_f 0.26, 74 mg, 60%) as light yellow solids. **3d**: mp 156−158 °C; IR (NaCl) ν_{max} 3278, 1734, 1722, 1639, 1570 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (br s, ex, NH), 4.56 (q, J = 7.2 Hz, 2H), 4.51 (q, J = 7.2 Hz, 2H), 4.44 (q, J = 7.2 Hz, 2H), 3.34 (s, 6H), 1.49 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.2 Hz, 3H), 1.40 (t, J = 7.2 Hz, 3H); insufficient material for ^{13}C spectrum; HRMS (CI, NH_3, 140 eV), *m*/*z* 379.1601 ([M + H]$^+$, 3%), calcd for $C_{17}H_{23}N_4O_6$ 379.1618. **4d**: mp 192−194 °C; IR (NaCl) ν_{max} 3200, 3140, 1734, 1685, 1617 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (br s, ex, NH), 7.99 (s, 1H), 4.41 (q, J = 7.3 Hz, 2H), 4.38 (q, J = 7.3 Hz, 2H), 3.29 (s, 6H), 1.38 (t, J = 7.3 Hz, 3H), 1.36 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4 (2C), 162.0, 151.4, 148.4, 143.6, 134.1, 133.2, 132.3, 62.1, 62.0, 37.9 (2C), 14.0 (2C); HRMS (EI, 70 eV) *m*/*z* 334.1297 ([M]$^+$, 60%), calcd for $C_{15}H_{18}N_4O_5$ 334.1277.

Triethyl 2-(Methylthio)-3*H*-imidazo-[4,5-*c*]pyridine-4,6,7-tricarboxylate (3e), **Diethyl 2-(Methylthio)-3*H*-pyrido[3,2-*d*]pyrimid-4-one-6,7-dicarboxylate 4e, and Diethyl 2-(Methylthio)-3*H*-pyrido[4,3-*d*]pyrimid-4-one-5,7-dicarboxylate (5e).** Prepared following general procedure A with imidazole **1d** (87 mg, 0.76 mmol) and triazine **2a** (226 mg, 0.76 mmol) in refluxing bromobenzene (5 mL) for 69 h; purified by flash chromatography (CH_2Cl_2/EtOAc, 3:1) to give **5e** as a white solid (R_f 0.47, 33 mg, 13%), **3e** as an off-white solid (R_f 0.34, 20 mg, 7%), and **4e** as a tan solid (R_f 0.27, 182 mg, 72%). **3e**: mp 195−198 °C; IR (NaCl) ν_{max} 1731, 1695, 1618 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (br s, ex, NH), 4.54 (br q, J = 7.2 Hz, 2H), 4.53 (br q, J = 7.2 Hz, 2H), 4.45 (q, J = 7.2 Hz, 2H), 2.84 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H), 1.43 (t, J = 7.2 Hz, 3H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 165.1, 164.6, 161.1, 149.0, 138.4, 136.2, 129.5, 123.7, 62.8, 62.4, 62.3, 14.4, 14.1 (3C); HRMS (CI, NH_3, 140 eV) *m*/*z* 382.1110 ([M + H]$^+$, 22%) calcd for $C_{16}H_{20}N_3O_6S$ 382.1073. **4e**: mp 224−226 °C; IR (NaCl) ν_{max} 1734, 1695, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (br s, ex, NH), 8.35 (s, 1H), 4.44 (q, J = 7.2 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 2.67 (s, 3H), 1.39 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 164.4, 159.7, 159.6, 148.2, 146.0, 137.3, 136.5, 131.5, 62.6, 62.5, 14.00 (2C), 13.8; HRMS (EI, 70 eV) *m*/*z* 337.0734 ([M]$^+$, 6%), calcd for $C_{14}H_{15}N_3O_5S$ 337.0732. **5e**: mp 214−216 °C; IR (NaCl) ν_{max} 1772, 1740, 1646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (br s, ex, NH), 8.23 (s, 1H), 4.51 (q, J = 7.2 Hz, 2H), 4.49 (q, J = 7.2 Hz, 2H), 2.70 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 164.0, 163.1, 159.9, 155.6, 153.8, 151.4, 122.7, 114.1, 62.57 (2C), 14.3, 14.0, 13.7; HRMS (CI, NH_3, 140 eV) *m*/*z* 338.0810 ([M + H]$^+$, 27%), calcd for $C_{14}H_{16}N_3O_5S$ 338.0810.

Diethyl 2-(*N*′,*N*′-Dimethylformamidino)-3*H*-imidazo-[4,5-*c*]pyridine-4,6-dicarboxylate (3f). Prepared following general procedure A with imidazole **1a** (17 mg, 0.12 mmol) and triazine **2c** (68 mg, 0.30 mmol) in refluxing dioxane (2 mL) for 4 h; purified by flash chromatography (CH_2Cl_2/acetone, 3:1) to give **3f** as a light yellow solid (R_f 0.33, 10 mg, 25%); mp 149−151 °C; IR (NaCl) ν_{max} 1735, 1715, 1629, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (br s, ex, NH), 8.77 (s, 1H), 8.35 (s, 1H), 4.51 (q, J = 7.2 Hz, 2H), 4.46 (q, J = 7.2 Hz, 2H), 3.20 (s, 3H), 3.15 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 166.0, 161.9, 161.5, 142.6, 134.4, 130.4, 116.7, 112.3, 63.5, 63.1, 42.7, 36.3, 15.3 (2C); HRMS (EI, 70 eV) *m*/*z* 333.1455 ([M]$^+$, 8%), calcd for $C_{15}H_{19}N_5O_4$ 333.1437.

Diethyl 2-(*N*′,*N*′-Dimethylacetamidino)-3*H*-imidazo-[4,5-*c*]pyridine-4,6-dicarboxylate (3g). Prepared following general procedure A with imidazole **1b** (34 mg, 0.23 mmol) and triazine **2c** (51 mg, 0.23 mmol) in refluxing dioxane (2.5 mL) for 2 h; purified by flash chromatography (CH_2Cl_2/acetone, 3:1) to give **3g** as a yellow oil (R_f 0.35, 50 mg, 64%). IR (NaCl) ν_{max} 1734, 1632, 1520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (br s, ex, NH), 8.38 (s, 1H), 4.51 (q, J = 7.2 Hz, 2H), 4.45 (q, J = 7.2 Hz, 2H), 3.18 (s, 3H), 3.17 (s, 3H), 2.52 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 165.9, 165.3, 159.3, 149.4, 141.1, 134.0, 128.8, 116.2, 62.3, 61.8, 39.1, 38.7, 17.7, 14.3 (2C); HRMS (EI, 70 eV) *m*/*z* 347.1577 ([M]$^+$, 23%), calcd for $C_{16}H_{21}N_5O_4$ 347.1593.

Diethyl 2-(Dimethylamino)-3*H*-imidazo[4,5-*c*]pyridine-4,6-dicarboxylate (3h). Prepared following general procedure A with imidazole **1c** (72 mg, 0.64 mmol) and triazine **2c** (58 mg, 0.26 mmol) in THF (2.5 mL) at 0 °C with gradual warming (2 h) to room temperature; purified by flash chromatography (CH_2Cl_2/acetone, 3:1) to give **3h** as a tan solid (R_f 0.38, 66 mg, 84%). Mp 164−165 °C; IR (NaCl) ν_{max} 1733, 1700, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (br s, ex, NH), 8.26 (s, 1H), 4.50 (q, J = 7.1 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 3.27 (s, 6H), 1.50 (t, J = 7.1 Hz, 3H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 162.0, 151.5, 148.4, 143.6, 134.1, 133.3,

132.3, 62.1, 61.9, 37.9 (2C), 14.0 (2C); HRMS (EI, 70 eV) *m*/*z* 306.1358 ([M]$^+$, 3%), calcd for $C_{14}H_{18}N_4O_4$ 306.1328.

Ethyl 2-(*N*′,*N*′-Dimethylformamidino)-6-phenyl-3*H*-imidazo[4,5-*c*]pyridine-4-carboxylate (3i) and 2-(*N*′,*N*′-Dimethylformamidino)-6-phenyl-3*H*-pyrido[3,2-*d*]pyrimid-4-one (4i). Prepared following general procedure B with imidazole **1a** (31.3 mg, 0.227 mmol) and triazine **2d** (62.4 mg, 0.272 mmol) at 120−125 °C for 2 h; purified by flash chromatography (Et_3N/EtOAc, 3:100) to give **3i** as a tan solid (R_f 0.40, 18 mg, 24%) and **4i** as a light yellow solid (R_f 0.33, 11 mg, 16%). **3i**: mp 172−175 °C; IR (NaCl) ν_{max} 3400, 1734, 1700, 1627, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (br s, ex, NH), 8.77 (s, 1H), 8.03 (dd, J = 7.2, 1.2 Hz, 2H), 7.93 (s, 1H), 7.44 (dd, J = 7.3, 7.2 Hz, 2H), 7.33 (tt, J = 7.3, 1.2 Hz, 1H), 4.52 (q, J = 7.0 Hz, 2H), 3.17 (s, 3H), 3.13 (s, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 162.0, 159.0, 151.8, 150.4, 140.2, 132.4, 130.8, 128.6 (2C), 128.0, 127.0 (2C), 111.8, 61.7, 41.1, 34.9, 14.4; HRMS (CI, NH_3, 140 eV) *m*/*z* 338.1621 ([M + H]$^+$, 0.4%), calcd for $C_{18}H_{20}N_5O_2$ 338.1617. **4i**: mp 317−320 °C; IR (NaCl) ν_{max} 2928, 1554, 1539 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (br s, ex, NH), 8.72 (s, 1H), 8.12 (br d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.45 (br t, J = 8.0 Hz, 2H), 7.39 (br t, J = 8.0 Hz, 1H), 3.20 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 158.3, 154.8, 153.9, 146.0, 138.4, 136.2, 134.5, 129.1, 128.7 (2C), 127.2 (2C), 125.7, 41.5, 35.2; HRMS (EI, 70 eV) *m*/*z* 293.1289 ([M]$^+$, 18%), calcd for $C_{16}H_{15}N_5O$ 293.1276.

Ethyl 2-(*N*′,*N*′-Dimethylformamidino)-6,7-diphenyl-3*H*-imidazo[4,5-*c*]pyridine-4-carboxylate (3j) and 2-(*N*′,*N*′-Dimethylformamidino)-6,7-diphenyl-3*H*-pyrido[3,2-*d*]pyrimid-4-one (4j). Prepared following general procedure B with imidazole **1a** (56.6 mg, 0.41 mmol) and triazine **2e** (150 mg, 0.492 mmol) at 120−125 °C for 2 h; purified by flash chromatography (Et_3N/EtOAc, 3:100) to give **3j** as a tan solid (R_f 0.40, 21 mg, 13%) and **4j** as a light yellow solid (R_f 0.31, 48 mg, 31%). **3j**: mp 111−113 °C; IR (NaCl) ν_{max} 3350, 1733, 1699, 1627, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (br s, ex, NH), 8.71 (s, 1H), 7.37−7.34 (m, 3H), 7.29−7.23 (m, 4H), 7.18−7.15 (m, 3H), 4.53 (q, J = 7.3 Hz, 2H), 3.13 (s, 3H), 3.10 (s, 3H), 1.47 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 162.0, 159.3, 150.2, 149.9, 140.8, 135.9, 132.5, 131.1 (2C), 130.5 (2C), 127.8 (3C), 127.5 (3C), 127.1, 126.9, 61.7, 41.1, 34.9, 14.4; HRMS (EI, 70 eV) *m*/*z* 414.1933 ([M + H]$^+$, 4%), calcd for $C_{24}H_{24}N_5O_2$ 414.1930. **4j**: mp 272−275 °C; IR (NaCl) ν_{max} 3300, 1730, 1692, 1632, 1550 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (br s, ex, NH), 8.73 (s, 1H), 7.78 (s, 1H), 7.39−7.37 (m, 2H), 7.28−7.25 (m, 3H), 7.21−7.18 (m, 5H), 3.20 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 158.3, 155.3, 154.5, 145.9, 141.5, 139.4, 139.0, 135.4, 135.1, 130.1 (2C), 129.4 (2C), 128.2 (2C), 127.74, 127.66 (3C), 41.5, 35.2; HRMS (EI, 70 eV) *m*/*z* 369.1563 ([M]$^+$, 3%), calcd for $C_{22}H_{19}N_5O$ 369.1589.

2-(*N*,*N*′-Dimethylformamidino)-3*H*-pyrido[3,2-*d*]pyrimid-4-one-6,7-dicarboxylic Acid 7-Ethyl Ester (14). To a solution of **4a** (51 mg, 0.14 mmol) in THF (3 mL) and H_2O (1 mL) at 0 °C was added LiOH (18 mg, 0.42 mmol), and the reaction was stirred for 1 h and quenched with concentrated HCl (to pH 2−3) and the solvent evaporated at room temperature by directing a stream of air into the flask to give crude **14**, which was used without further purification. ^{1}H NMR (400 MHz, D_2O) indicates a 3:1 mixture of **14** (δ 8.67 (s, 1H), 8.32 (s,1H), 4.47 (q, J = 7.0 Hz, 2H), 3.41 (s, 3H), 3.29 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H)) and the corresponding dicarboxylic acid (δ 8.67* (s, 1H), 8.18 (s, 1H), 3.41* (s, 3H), 3.29* (s, 3H)) [the asterisk indicates peaks which overlap with those of **14**].

Di-*tert*-butyl (*S*)-*N*-(*p*-Nitrobenzoyl)-glutamate (15). To a solution of *p*-nitrobenzoic acid (629 mg, 2.43 mmol) in CH_2Cl_2 (24 mL) were added in order: H_2O (24 mL), di-*tert*-butyl (*S*)-glutamate[35] (405 mg, 2.43 mmol), and HOBt (370 mg, 2.43 mmol). The reaction mixture was cooled to 0 °C and 1,3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (EDC, 511 mg, 2.67 mmol) was added. The reaction was allowed to warm to 10 °C over 18 h then diluted with water and extracted with CH_2Cl_2, the combined organic fractions were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo and purified by flash chromatography (hexanes/EtOAc, 3:1) to give **15** as a colorless oil that solidified upon standing to a white solid (R_f 0.45, 976 mg, 98%): Mp 58−60 °C (lit.[34b] mp 52.5−54.5 °C); $[\alpha]_D$ +2.4 (*c* 1.9); IR (NaCl) ν_{max} 1731, 1672, 1530, 1347 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.7 Hz, 2H), 7.99 (d, J = 8.7 Hz, 2H), 7.42 (br d, J = 7.5 Hz, ex, NH), 4.61 (ddd, J = 7.5, 7.0, 4.5 Hz, 1H), 2.44 (ddd, J = 17.2, 7.1, 7.1 Hz, 1H), 2.34 (ddd, J = 17.2, 7.1, 7.1 Hz, 1H), 2.21 (dddd, J = 14.2, 7.1, 7.1, 4.5 Hz, 1H), 2.07 (dddd, J = 14.2, 7.1, 7.1, 7.0 Hz, 1H), 1.48 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 170.8, 164.9, 149.7, 139.5, 128.3 (2C), 123.6 (2C), 82.6, 81.1, 53.4, 31.6, 28.0 (6C), 26.9; HRMS (CI, NH_3, 140 eV) *m*/*z* 409.2001 ([M + H]$^+$, 2%), calcd for $C_{20}H_{29}N_2O_7$ 409.1975.

Di-*tert*-butyl (*S*)-*N*-(*p*-Aminobenzoyl)-glutamate (16). To **15** (976 mg, 2.39 mmol) in MeOH (20 mL) was added 10% Pd/C (146 mg, 15 wt %), and the flask was sealed with a septum and purged with H_2, then the mixture, was stirred at room temperature for 3 h under an H_2 atmosphere (balloon). The reaction mixture was filtered through Celite and the solvent removed in vacuo to give **16** as a white solid (895 mg, 99%): mp 138−139 °C (lit.[34b] mp 138−140 °C); $[\alpha]_D$ +7.7 (*c* 0.65); IR (NaCl) ν_{max} 1726, 1634, 1606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 7.7 Hz, ex, NH), 6.64 (d, J = 8.5 Hz, 2H), 4.64 (ddd, J = 7.8, 7.7, 5.3 Hz, 1H), 2.39 (ddd, J = 16.5, 8.3, 6.3 Hz, 1H), 2.27 (ddd, J = 16.5, 8.3, 6.3 Hz, 1H), 2.19 (dddd, J = 14.2, 7.8, 6.3, 6.3 Hz, 1H), 1.99 (dddd, J = 14.2, 8.3, 8.3, 5.3 Hz, 1H), 1.46 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 171.6, 166.8, 149.7, 128.9 (2C), 123.6, 114.1 (2C), 82.2, 80.7, 52.7, 31.7, 28.0 (6C), 27.8; HRMS (EI, 70 eV) *m*/*z* 378.2129 ([M]$^+$, 3%), calcd for $C_{20}H_{30}N_2O_5$ 378.2155.

(S)-2-{4-[7-(*N*,*N*′-Dimethylformamidino)-1,3,5-trioxo-1,3,5,6-tetrahydro-2,4,6,8-tetraaza-cyclopenta[*b*]naphthalen-2-yl]-benzoylamino}-pentanedioic Acid Di-*tert*-butylEster(17)and(S)-2-(4-{[2-(*N*,*N*′-Dimethylformamidino)-7-ethoxycarbonyl-4-oxo-3,4-dihydro-pyrido[3,2-*d*]pyrimidine-6-carbonyl]-amino}-benzoylamino)-pentanedioic Acid Di-*tert*-butyl Ester (18). A slurry of crude **14** (~0.14 mmol) in CH_2Cl_2 (3 mL) and H_2O (3 mL) was adjusted to pH 5−6 (optimized for **17**) or pH 3.5−4.0 (optimized for **18**) with $NaHCO_3$ and cooled to 0 °C, then the following were added in order: HOBt (19 mg, 0.14 mmol), **16** (53 mg, 0.14 mmol), and EDC (30 mg, 0.15 mmol). The reaction was gradually warmed to 15 °C over 18 h, diluted with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, then dried ($MgSO_4$). The solvent was removed in vacuo and the product was purified by flash chromatography (CH_2Cl_2/acetone/MeOH, 3:1:1%) to give **17** as a yellow solid (R_f 0.30, visible with long wave UV, 10 mg, 11%) or **18** as a white solid (R_f 0.20, visible with long wave UV, 42 mg, 44%). **17**: mp 237−239 °C; $[\alpha]_D$ +6.6 (*c* 0.50); IR (NaCl) ν_{max} 3511, 3386, 1727, 1680, 1638, 1556 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.25 (br s, ex, NH), 8.81 (s, 1H), 8.73 (d, J = 7.3 Hz, ex, NH), 8.07 (s, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 4.35 (m, 1H), 3.23 (s, 3H), 3.11 (s, 3H), 2.36 (dd, J = 7.4 Hz, 2H), 2.05 (m, 1H), 1.94 (m, 1H), 1.42 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.4, 170.7, 165.93, 165.90, 164.2, 164.1, 159.2, 157.6, 144.3, 139.7, 134.2, 133.6, 130.5, 128.2, 127.9 (3C), 126.7 (2C), 80.5, 79.6, 52.5, 40.9, 34.9, 31.3, 27.64 (3C), 27.57 (3C), 25.9; HRMS (ESI) *m*/*z* 648.2794 ([M + H]$^+$, 100%), calcd for $C_{32}H_{38}N_7O_8$ 648.2777. **18**: mp 118−120 °C; $[\alpha]_D$ +4.7 (*c* 0.55); IR (NaCl) ν_{max} 3583, 3451, 3326, 2977, 2931, 1733, 1684, 1632, 1557, 1530 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, ex, NH), 8.78 (s, 1H), 8.52 (d, J = 7.3 Hz, ex, NH), 8.02 (s, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.85 (d, J = 8.7 Hz, 2H), 4.31 (m, 1H), 4.28 (q, J = 7.0 Hz, 2H), 3.22 (s, 3H), 3.09 (s, 3H), 2.34 (dd, J = 7.4 Hz, 2H), 2.04 (m,1H), 1.92 (m, 1H), 1.41 (s, 9H), 1.38 (s, 9H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C

NMR (100 MHz, DMSO-d_6) δ 172.1, 171.7, 166.7, 165.9, 164.5, 161.1, 159.6, 158.2, 148.2, 146.7, 142.0, 136.3, 134.8, 132.0, 129.5, 128.9 (2C), 119.4 (2C), 81.1, 80.3, 62.2, 53.0, 41.5, 35.4, 31.9, 28.25 (3C), 28.20 (3C), 26.5, 14.2; HRMS (ESI) *m*/*z* 694.3195 ([M + H]$^+$, 55%), calcd for $C_{34}H_{44}N_7O_9$ 694.3195.

(S)-2-{4-[(2-Amino-7-ethoxycarbonyl-4-oxo-3,4-dihydropyrido[3,2-*d*]pyrimidine-6-carbonyl)-amino]-benzoylamino}-pentanedioic Acid (19). Trifluoroacetic acid (1 mL) was added to a mixture of Et_3SiH (10 μL, 0.063 mmol) and **18** (11 mg, 0.016 mmol) and stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (3 mL) and H_2O (0.1 mL) then was refluxed for 1 h and cooled to room temperature, then the solvent was evaporated by directing a stream of air into the flask to give **19** as an off-white solid (7.5 mg, 89%); **19** could be further purified by recrystallization from 1:1 MeOH/H_2O if necessary. Mp 266−269 °C; $[\alpha]_D$ +8.0 (H_2O, *c* 0.25); IR (NaCl) ν_{max} 3104, 2080, 1360; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (br s, ex, NH), 10.78 (s, ex, NH), 8.53 (d, J = 7.9 Hz, ex, NH), 7.89 (d, J = 8.7 Hz, 2H), 7.85 (d, J = 8.7 Hz, 2H), 7.81 (s, 1H), 6.94 (br s, ex, NH_2), 4.39 (m, 1H), 4.27 (q, J = 7.0 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.07 (m, 1H), 1.95 (m, 1H), 1.20 (t, J = 7.0 Hz, 3H) (2 CO_2H not observed); poor solubility of **19** in DMSO-d_6, D_2O, 1:1 DMSO-d_6/D_2O, CD_3CO_2H precluded obtaining adequate ^{13}C NMR spectra; HRMS (ESI) *m*/*z* 527.1527 ([M + H]$^+$, 100%), calcd for $C_{23}H_{23}N_6O_9$ 527.1521.

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Supporting Information Available: ^{1}H and ^{13}C spectra for previously unreported compounds and General Experimental Methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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