

## A NOVEL METHOD FOR INTRODUCTION OF CARBON SUBSTITUENTS INTO PTERIDINE

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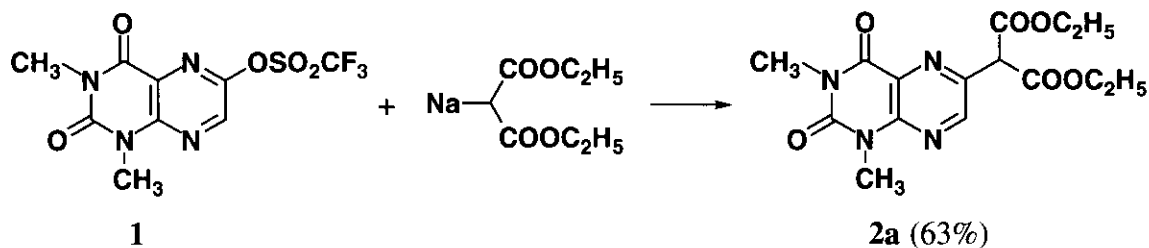
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**Abstract**—A reaction of 1,3-dimethyl-6-trifluoromethanesulfonyloxylumazine with an anion of a 1,3-dicarbonyl compound such as diethyl malonate and 1,3-cyclohexanedione gives the corresponding 6-substituted lumazine.

Pteridine is one of the most important naturally occurring nitrogen heterocycles in biochemistry and clinical chemistry. For example, tetrahydrobiopterin and tetrahydrofolic acid are cofactors in enzymatic redox and C<sub>1</sub> transfer processes in many different organisms. In addition, neopterin and oncopterin are good monitors for immune activity and are employed as indicators in the diagnosis of cancer and HIV infection.<sup>1–8</sup> Since almost all biologically active pteridines have substituents on the C(6) position, regioselective synthesis of 6-substituted pteridines is a very important subject in the chemistry of pteridine.<sup>9,10</sup> Recently, we reported that substitution of 6-trifluoromethanesulfonyloxypteridine by various heteroatom nucleophiles occurred selectively under mild conditions to give 6-substituted pteridines.<sup>11</sup> Described herein is an application of 6-trifluoromethanesulfonyloxypteridine for preparation of 6-alkylated pteridines.

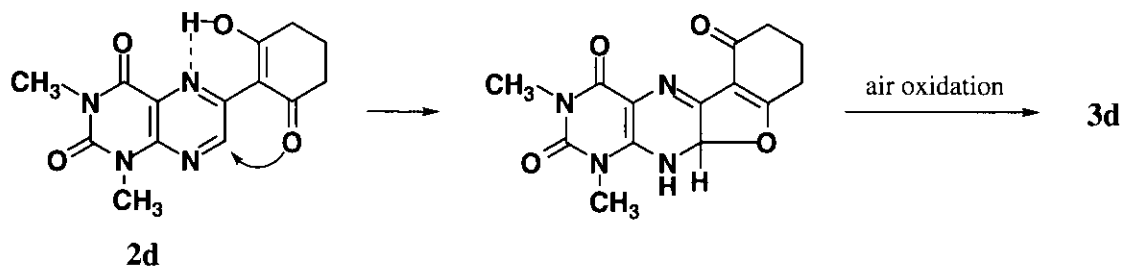
Reaction of 1,3-dimethyl-6-trifluoromethanesulfonyloxylumazine (**1**)<sup>12</sup> with the sodium enolate of diethyl malonate, which is generated by the action of sodium metal, in THF at 65 °C (reflux) for 2 h gave ethyl 2'-ethoxycarbonyl-1,3-dimethylumazine-6-acetate (**2a**). The yield was 63% after purification by silica gel column chromatography. Under the same conditions, monoanions prepared from diethyl methylmalonate and 2-ethoxycarbonylcyclopentanone reacted with **1** to give **2b** and **2c** in 51 and 45% yields, respectively. Similar reactions of **1** with 1,3-cyclohexanedione and its 5,5-dimethyl analog yielded **2d** and **2e** under enol forms together with furan derivatives (**3d** and **3e**), respectively. Ethyl acetoacetate afforded a mixture of **3f** and ethyl 1,3-dimethylumazine-6-acetate (**4f**)<sup>13</sup> but no similarly alkylated product (**2**). However, similar reactions of **1**, yielding **2** or related derivatives, did not proceed under the same conditions with monoanions of the following active methylene compounds: C<sub>2</sub>H<sub>5</sub>OCOCH<sub>2</sub>CN,<sup>14</sup> C<sub>2</sub>H<sub>5</sub>OCOCH<sub>2</sub>NO<sub>2</sub>, and (C<sub>2</sub>H<sub>5</sub>O)<sub>2</sub>P(O)CH<sub>2</sub>COOC<sub>2</sub>H<sub>5</sub>. Results are summarized in Table 1.



The reactions of **1** with the sodium enolate of ethyl malonate afforded **2a** in higher yield than reactions using other metal enolates. For example, under the same conditions, yields of **2a** were 6 and 38%, respectively, when Li and K were employed to the reaction. Since **1** is highly reactive with heteroatom nucleophiles,<sup>11,15</sup> formation of 6-ethoxy-1,3-dimethylumazine predominated over the desired product (**2**) when the reaction was carried out in the presence of ethanol or sodium ethoxide. Therefore, it is important in this reaction to keep the enolate anion free from any nucleophilic contaminants. This is the first example that regiospecific substitution on the pteridine ring by carbanions practically proceeds without cationic accelerators.<sup>16</sup>

Results of <sup>13</sup>C and <sup>1</sup>H NMR studies (in CDCl<sub>3</sub>) showed that **2a**, **2d**, and **2e** did not exist as tautomeric (keto/enol) mixtures but as the single structures illustrated in Table 1. Red shifts which were caused by elongation of the conjugate systems were recognized in UV spectra (in CH<sub>3</sub>OH) of enol-form products (**2d** and **2e**), whose λ<sub>max</sub> were 348 and 349 nm, respectively. The keto-form products (**2a**, **2b**, and **2c**) showed λ<sub>max</sub> at 334, 332, and 335 nm, respectively. In <sup>1</sup>H NMR spectra, chemical shifts of C(7)-H of **2d** and **2e** (δ 8.49 and 8.48 ppm, respectively) were about 0.5 ppm higher than those of **2a** – **2c**. In <sup>13</sup>C NMR spectra, **2a** – **2c** showed pair signals assignable to carbonyl carbons (keto and/or ester carbonyl) of the side chain, but **2d** and **2e** showed only one carbonyl carbon in the region of δ 210 – 170 ppm. In addition, **2d** and **2e** exhibited the β-carbons of the enol structures at 110.1 and 109.6 ppm, respectively.

The C(7)=N bond of pteridines are readily accessible to the attack of oxygen nucleophiles,<sup>17–19</sup> and, in **2d** and **2e**, the keto carbonyl group existed in the same plane of the pteridine ring because of intramolecular hydrogen bonding between OH and N=C(6) groups. Therefore, the intramolecular attack of the oxygen atom to C(7) easily occurred to give the tetracyclic dihydropteridine intermediate. Air oxidation of the intermediate afforded the furan derivative (**3**) with the fully conjugated pteridine ring. The significant stability of the coplanar structure of **2d** was confirmed by MO studies.



**Table 1. Reaction of 1 with 1,3-Dicarbonyl Compounds.**

1,3-dicarbonyl compound	products (No. yield <sup>a</sup> )	
		(2b 51%)
		(2c 45%)
		(2d 44%)
	(3d 17%)	
		(2e 7%)
	(3e 31%)	
		(3f 11%)
	(4f 9%)	

<sup>a</sup>Isolated yield after silica gel column chromatography.

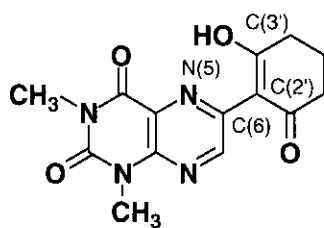
Energies of several conformers of **2d** (based on the rotation, every 30°, around the C(6)–C(2') bond) and the tautomers ( $\beta$ -diketone and enamine) were obtained by PM3 calculations.<sup>20</sup> Dihedral angles ( $\theta$ : N(5)=C(6)–C(2')=C(3')) and relative potentials ( $E$ ) are shown in Table 2. The most stable structure of **2d** ( $E = 0$ ) was the enol form with  $\theta = 2.10^\circ$ , in which the N(5)–HO distance was 1.783 Å. It is obvious that the coplanar structure with hydrogen bond ( $\theta = 0^\circ$ ) is more stable than that without hydrogen bond ( $180^\circ$ ). In the tautomeric  $\beta$ -diketone structure, the lowest energy conformer ( $E = 2.09$  kcal/mol) was the twist form ( $\theta = 66.2^\circ$ ). The energy of the enamine tautomer ( $\theta = 0.6^\circ$ ), in which hydrogen bond might be exist, was 3.16 kcal/mol higher.

**Table 2. Conformational Potentials of 2d.<sup>a</sup>**

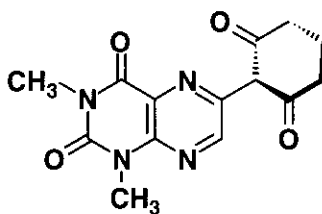
dihedral angle ( $\theta$ /deg)	potential $E$ /kcal/mol
-150.00	15.70
-120.00	7.38
-90.00	6.05
-30.00	4.23
0.00	0.03
2.10 <sup>b</sup>	0
30.00	3.96
60.00	5.01
90.00	5.85
120.00	6.89
150.00	14.45
180.00	31.74

<sup>a</sup>Obtained by PM3 running on HyperChem®.

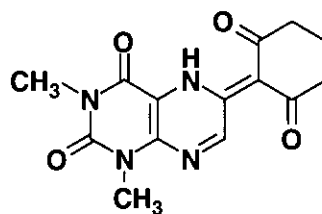
<sup>b</sup>The most stable structure.



**2d-enol**

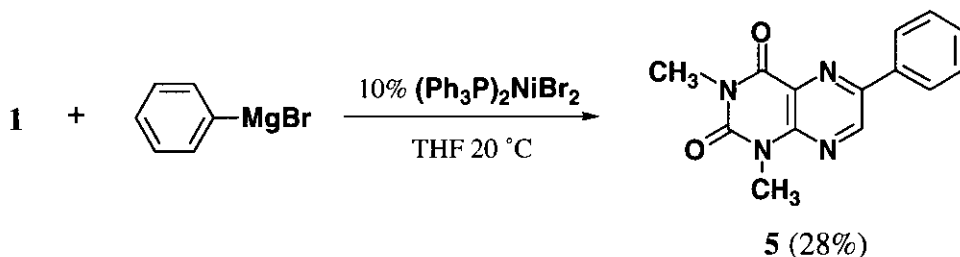


**2d- $\beta$ -diketone**  
( $E = 2.09$  kcal/mol)



**2d-enamine**  
( $E = 3.16$  kcal/mol)

Reactions of **1** with organometallics, such as Grignard reagents and organolithium compounds, did not proceed,<sup>21</sup> but some transition metal complexes ((R<sub>3</sub>P)<sub>2</sub>MX<sub>2</sub>: R<sub>3</sub>P = Ph<sub>3</sub>P, *n*-Bu<sub>3</sub>P, and diphosphines (dppe and dppp)<sup>22</sup>; M = Ni and Pd; X = Cl and Br) were able to catalyze the reaction of **1** with Grignard reagents. For example, 6-phenyl-1,3-dimethylumazine (**5**) was obtained in 28 and 17% isolated yields by the reaction of **1** with phenylmagnesiumbromide in THF at 20 °C for 1 h in the presence of 10% (Ph<sub>3</sub>P)<sub>2</sub>NiBr<sub>2</sub> and 10% (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, respectively.



## ACKNOWLEDGMENTS

We thank Mr. Y. Andoh in School of Informatics and Sciences of Nagoya University for technical supports to MO calculations. The author, S. M., thanks Fujisawa Pharmaceutical Co. Ltd., for elemental analyses of some products. This research was supported by Grants in Aids for Scientific Research, No. 09640722, Ministry of Education, Science, Sports and Culture (Japan).

## EXPERIMENTAL

**Reaction of 1 with diethyl malonate.** A typical example: A mixture of sodium (0.044 g, 1.9 mmol) and diethyl malonate (0.37 mL, 2.4 mmol) in THF (10 mL) was heated under reflux for 2 h. To this was added **1** (0.341 g, 0.10 mmol), and the mixture was heated for additional 2 h. Sat.  $\text{NH}_4\text{Cl}$  solution was added to the mixture, and the organic components were extracted by dichloromethane (15 mL x 3). Column chromatography on silica gel eluting with a 5:1 (v/v) mixture of toluene and ethyl acetate gave pure **2a** (0.220 g, 63%).

**Compound (2a):** colorless solid. mp 95–97 °C.<sup>23</sup> UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 334 (7900), 242 (19000). IR (KBr)  $\nu/\text{cm}^{-1}$  = 1723, 1680, 1553, 1501, 1460, 1314, 1182, 1032, 754.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$  = 8.95 (1H, s), 5.20 (1H, s), 4.27 (4H, m), 3.74 (3H, s), 3.55 (3H, s), 1.30 (6H, t,  $J$  = 7.1 Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$  = 166.6, 159.8, 150.5, 149.1, 147.5, 144.5, 126.1, 62.6, 58.3, 29.5, 29.1, 14.0. *Anal.* Calcd for  $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_6$ : C 51.43, H 5.18, N 15.99. Found: C 51.45, H 5.35, N 15.56.

**Compound (2b):** colorless oil. UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 332 (4500), 242 (10900). IR ( $\text{CDCl}_3$ )  $\nu/\text{cm}^{-1}$  = 3063, 2988, 1726, 1680, 1587, 1550, 1500.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$  = 8.84 (1H, s), 4.26 (4H, q,  $J$  = 7.0 Hz), 3.72 (3H, s), 3.52 (3H, s), 2.01 (3H, s), 1.29 (6H, t,  $J$  = 7.0 Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$  = 170.0, 159.7, 150.7, 148.9, 148.7, 147.0, 125.6, 62.4, 59.8, 29.5, 29.0, 20.4, 14.0. *Anal.* Calcd for  $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_6$ : C 52.74, H 5.53, N 15.38. Found: C 52.75, H 5.53, N 15.04.

**Compound (2c):** colorless oil. UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 335 (4600), 242 (10900). IR ( $\text{CDCl}_3$ )  $\nu/\text{cm}^{-1}$  = 3055, 2980, 1726, 1687, 1585, 1548.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$  = 8.94 (1H, s), 4.25 (2H, m), 3.73 (3H, s), 3.53 (3H, s), 3.42 (1H, m), 2.74 (1H, m), 2.59 (1H, m), 2.39 (1H, m), 2.19 (1H, m), 2.11 (1H, m), 1.29 (3H, t,  $J$  = 7.3 Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$  = 211.5, 170.0, 159.8, 150.6, 149.5, 147.2, 146.1, 125.6, 65.6, 62.5, 38.1, 32.3, 29.4, 28.9, 19.8, 14.0. *Anal.* Calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_5$ : C 55.48, H 5.24, N 16.18. Found: C 55.67, H 5.30, N 16.14.

**Compound (2d):** colorless solid. mp 223–226 °C.<sup>23</sup> UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 348 (7700), 249 (23000). IR (KBr)  $\nu/\text{cm}^{-1}$  = 3432, 2924, 1725, 1672, 15551, 1493, 1462, 1375, 1329, 1294, 1240, 1204, 1138.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$  = 8.49 (1H, s), 5.42 (1H, s), 3.74 (3H, s), 3.54 (3H, s), 2.73

(2H, t,  $J = 6.3$  Hz), 2.43 (2H, t,  $J = 6.3$  Hz), 2.13 (2H, quint,  $J = 6.3$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 199.0, 174.4, 159.0, 152.2, 150.3, 145.9, 141.4, 124.1, 110.1, 36.5, 29.9, 29.2, 28.0, 21.1$ . *Anal.* Calcd for  $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_4$ : C 55.63, H 4.67, N 18.53. Found: C 55.43, H 4.80, N 18.34.

**Compound (3d):** colorless solid. mp 294–296 °C.<sup>23</sup> UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 356 (12000), 296 (4900), 247 (13000), 219 (16000). IR (KBr)  $\nu/\text{cm}^{-1} = 2955, 1715, 1680, 1602, 1561, 1516, 1462, 1429, 1368, 1312, 1281, 1250, 1159, 1107, 1011, 995, 804, 750$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 3.85$  (3H, s), 3.57 (3H, s), 3.26 (2H, m), 2.73 (2H, m), 2.40 (2H, m).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 191.4, 179.9, 159.8, 151.5, 147.7, 140.0, 120.7, 115.4, 38.0, 30.3, 29.1, 24.8, 21.4$ . *Anal.* Calcd for  $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_4$ : C 56.00, H 4.03, N 18.66. Found: C 56.00, H 4.04, N 18.64.

**Compound (2e):** colorless solid. mp 139–142 °C.<sup>23</sup> UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 349 (6700), 253 (19000). IR (KBr)  $\nu/\text{cm}^{-1} = 3424, 2959, 1717, 1674, 1497, 1460, 1343, 1215, 1136, 980$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 8.48$  (1H, s), 5.48 (1H, s), 3.73 (3H, s), 3.54 (3H, s), 2.58 (2H, s), 2.30 (2H, s), 1.17 (6H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 198.9, 172.5, 159.0, 152.5, 150.3, 145.8, 141.3, 124.0, 109.6, 50.7, 41.8, 33.0, 29.8, 29.1, 28.3$ . *Anal.* Calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_4$ : C 58.17, H 5.49, N 16.96. Found: C 58.08, H 5.59, N 16.52.

**Compound (3e):** colorless solid. mp 265–267 °C.<sup>23</sup> UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 356 (14000), 297 (6100), 248 (16000), 218 (20000). IR (KBr)  $\nu/\text{cm}^{-1} = 2961, 1721, 1688, 1601, 1562, 1514, 1466, 1429, 1356, 1281, 1034, 748$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 3.86$  (3H, s), 3.57 (3H, s), 3.12 (2H, s), 2.61 (2H, s), 1.27 (6H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 191.1, 179.1, 159.8, 151.8, 150.5, 147.7, 139.9, 120.6, 114.4, 52.3, 38.6, 34.8, 30.3, 29.2, 28.5$ . *Anal.* Calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_4$ : C 58.53, H 4.91, N 17.06. Found: C 58.54, H 4.99, N 16.92.

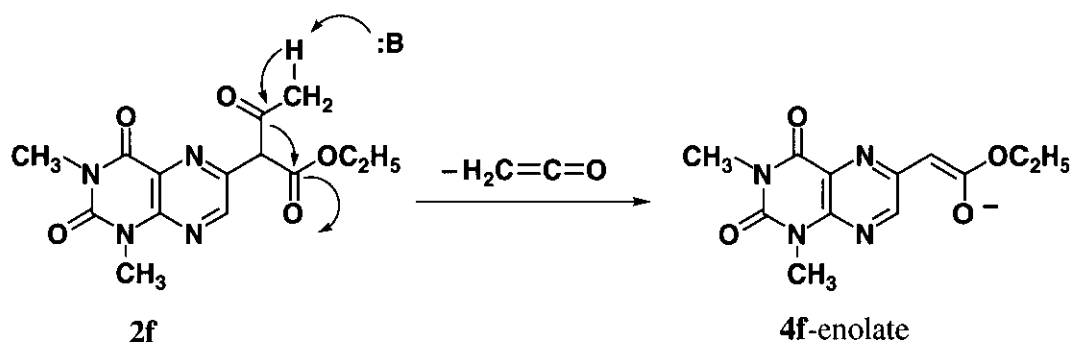
**Compound (3f):** yellow solid. mp 183–186 °C.<sup>23</sup> UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 356 (14000), 295 (6700), 216 (28000). IR (KBr)  $\nu/\text{cm}^{-1} = 2924, 2363, 1718, 1672, 1570, 1512, 1460, 1420, 1325, 1287, 1250, 1088, 806, 748$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 4.47$  (2H, q,  $J = 6.8$  Hz), 3.83 (3H, s), 3.57 (3H, s), 2.98 (3H, s), 1.48 (3H, t,  $J = 6.8$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 174.1, 161.7, 160.1, 150.8, 150.7, 147.3, 142.0, 109.8, 61.3, 33.0, 29.2, 15.9, 14.3, 13.6$ . *Anal.* Calcd for  $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_5$ : C 52.83, H 4.43, N 17.60. Found: C 53.03, H 4.70, N 17.30.

**Compound (4f):** pale yellow solid. mp 129–131 °C.<sup>23</sup> UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 335 (8500), 240 (20000). IR (KBr)  $\nu/\text{cm}^{-1} = 2965, 1732, 1672, 1594, 1503, 1333, 1262, 1194, 1100, 1030, 910, 802, 752$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 8.68$  (1H, s), 4.12 (2H, q,  $J = 7.3$  Hz), 4.05 (2H, 2), 3.73 (3H, s), 3.55 (3H, s), 1.20 (3H, t,  $J = 7.3$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 169.7, 160.0, 159.0, 148.6, 147.1, 145.9, 126.6, 61.6, 40.4, 29.5, 29.1, 14.2$ . *Anal.* Calcd for  $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_4$ : C 51.79, H 5.07, N 20.14. Found: C 51.65, H 5.10, N 19.71.

**Compound (5):** colorless needles. mp 258–259 °C (ethanol).<sup>24,25</sup> UV ( $\text{CH}_3\text{OH}$ )  $\lambda/\text{nm}$  ( $\epsilon$ ) = 359 (8900), 280 (21400).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 9.07$  (1H, s), 8.10 (2H, m), 7.52 (3H, m), 3.76 (3H, s), 3.57 (3H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm} = 160.1, 150.6, 148.7, 146.9, 144.9, 134.9, 130.2, 129.2, 127.0, 126.8, 29.5, 29.1$ .

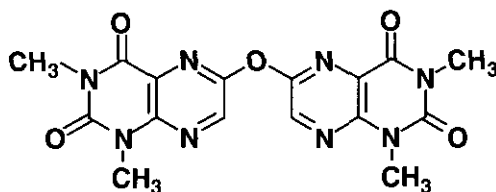
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12. 1,3-Dimethyl-2,4(1*H*,3*H*)-pteridinedione: 2,4(1*H*,3*H*)-Pteridinedione is abbreviated as lumazine. Compound **1** is prepared by the procedures described in ref. 11.
13. Although we do not have any evidences, we suppose that the formation of **4f** proceeded through the mechanism illustrated in the following scheme. Since lumazine and the ester group have strong electron withdrawing characters, **4f** could stabilize its carbanion (**4f**-enolate) very well. Base induced elimination of ketene from initially produced **2f** might be occurred to give **4f**-enolate. See: W. E. Hanford and J. C. Sauer, "Organic Reactions", Vol. 3, eds by R. Adams, W. E. Bachmann, J. R. Johnson, L. F. Fieser, and H. R. Snyder, Robert E. Krieger Publishing Co., Malabar Florida, 1975, Chap. 3.



14. Under the same conditions, a reaction of **1** with ethyl cyanoacetate afforded the dimeric bis(lumazine)ether (**6**). Hydrolysis of **1** gave 6-hydroxy-1,3-dimethylumazine, and condensation of the 6-hydroxylumazine with **1** afforded **6** in 50% yield. **Compound (6)**: colorless powder. mp 272–274 °C (ethanol), UV (CH<sub>3</sub>OH)  $\lambda/\text{nm}$  ( $\epsilon$ ) = 345 (18000), 249 (37000). IR (KBr)  $\nu/\text{cm}^{-1}$  = 2927, 1718, 1670, 1561, 1493, 1462, 1395, 1333, 1310, 1277, 1221, 1024, 985, 912, 831, 802,

750.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$  = 8.71 (2H, s), 3.74 (6H, s), 3.50 (6H, s).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta/\text{ppm}$  = 159.2, 153.4, 150.4, 145.8, 141.2, 123.7, 29.9, 29.1. *Anal.* Calcd for  $\text{C}_{16}\text{H}_{14}\text{N}_8\text{O}_5$ : C 48.24, H 3.52, N 28.13. Found: C 48.07, H 3.64, N 28.34.



6

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16. Reaction of 6-chloro-1,3-dimethylumazine with the sodium enolate of ethyl cyanoacetate was carried out in the presence of trimethyloxonium tetrafluoroborate. See: A. Heckel and W. Pfeleiderer, *Helv. Chim. Acta*, 1986, **69**, 704.
17. S. Murata, T. Sugimoto, S. Ogiwara, K. Mogi, and H. Wasada, *Synthesis*, 1992, 303.
18. S. Murata, K. Kiguchi, and T. Sugimoto, *Heterocycles*, 1993, **35**, 639.
19. K. Kiguchi, S. Murata, and T. Sugimoto, *Pteridines*, 1995, **6**, 160.
20. PM3 Calculations were carried out using a HyperChem<sup>®</sup> program running. Atomic coordinates of the optimized (most stable) structure of **2d** are cited in Table 3, where hydrogen atoms are omitted.
21. Those reactions afforded significant amounts of 6-hydroxy-1,3-dimethylumazine (ref. 16), which was produced by alkaline hydrolysis of **1** (ref. 11).
22. 1,2-Bis(triphenylphosphino)ethane (dppe) and 1,3-bis(triphenylphosphino)propane (dppp).
23. Pure solid (crystalline) products were obtained when solvents were removed *in vacuo* (13 Pa, room temperature) from fractions of  $\text{SiO}_2$  column chromatography.
24. T. Sugimoto, C. Seo, S. Murata, and W. Pfeleiderer, *Pteridines*, 1997, **8**, 188.
25. R. B. Angier, *J. Org. Chem.*, 1963, **28**, 1398.

**Table 3. Atomic Coordinates of the Optimized Structure of 2d-enol.**

atom numbering<sup>a</sup> (coordinates:  $x/\text{Å}$ ,  $y/\text{Å}$ ,  $z/\text{Å}$ )

N(1) (9.5636, 0.0599, -0.6353); C(2) (9.5279, -1.3777, -0.5328); N(3) (8.2857, -2.0673, -0.7500); C(4) (7.0273, -1.3755, -0.6567); C(4a) (7.1063, 0.1001, -0.5527); N(5) (5.9418, 0.8116, -0.4866); C(6) (5.9753, 2.1607, -0.3808); C(7) (7.2367, 2.8213, -0.3313); N(8) (8.3824, 2.1405, -0.3945); C(8a) (8.3406, 0.7677, -0.5121); C(N(1)) (10.8506, 0.7538, -0.3974); C(N(3)) (8.3011, -3.5506, -0.7440); O(C(2)) (10.5608, -2.0028, -0.3397); O(C(4)) (5.9988, -2.0266, -0.6856); C(1') (4.7265, 4.3621, -0.2447); C(2') (4.7061, 2.8832, -0.3188); C(3') (3.4962, 2.2232, -0.3224); C(4') (2.1702, 2.9278, -0.2630); C(5') (2.2954, 4.3074, 0.3535); C(6') (3.3975, 5.0868, -0.3327); O(C(1')) (5.7578, 5.0123, -0.13409); O(C(3')) (3.3335, 0.8978, -0.3910)

<sup>a</sup>Atom numberings follow the IUPAC rule. Numbers of carbon atoms of *N*-methyl groups and carbonyl oxygen atoms are shown with the number of the connecting atom. For example, C(N(1)) and O(C(2)) mean the carbon atom (CH<sub>3</sub>) on N(1) and the oxygen atom of carbonyl group at C(2), respectively.

Received, 11th May, 1998