Specific inhibitors in vitamin biosynthesis. Part 11. Syntheses of pterins with extended side chains at C-6

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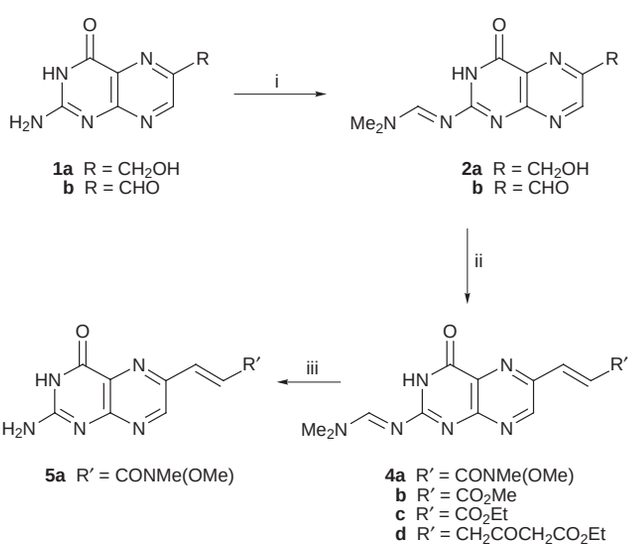
In order to provide access to highly functionalised pterins as potential inhibitors of enzymes in the folate biosynthesis pathway, the Wittig reaction has been applied to 6-formylpterin (**1b**) and 6-formyl-7,7-dihydro-7,7-dimethylpterin (**6**). Dimethylaminomethylene and pivaloyl moieties were found to be suitable protecting groups for the 2-amino group of the pterins compatible with reactions of phosphoranes with a variety of substituents including esters, ethers and amides. In contrast, attempts to prepare extended side chains at C-6 using aldol and Claisen chemistry were unsuccessful.

Enzyme cofactors comprising the pteridine ring system have immense importance in biosynthesis, being involved in both one carbon transfer and in redox reactions.[1] Many established drugs interact with enzymes in the biosynthetic pathway or with enzymes that use and transform pteridine cofactors, especially folates.[2] A range of herbicides also act by the inhibition of folate biosynthesis.[3] The problems of increasing bacterial resistance to drugs[4] and the demands for more selective agrochemicals (herbicides, insecticides and fungicides) have renewed interest in pterins and their relatives as templates for the discovery of biologically active compounds. Supporting this approach is the fact that mammals lack the ability to synthesise pteridine cofactors *de novo* and hence the inhibition of the relevant biosynthetic enzymes is likely to be selective to the infective agent, weed or insect. Two enzymes that have received limited attention are dihydropterin diphosphokinase and dihydropteroate synthase.[5] The former enzyme catalyses the phosphorylation of 6-hydroxymethylpterin (**1a**) and is known to be inhibited by 7,7-dialkyl-7,7-dihydropterins including **6**.[6] The latter catalyses the coupling with 4-aminobenzoic acid.[2] Both enzymes require magnesium cations for activity and it is believed that they coordinate with the diphosphate groups in either ATP or the pterin substrates. A rational, mechanism-based approach to the discovery of new biologically active lead compounds directed at these targets is therefore to include metal-coordinating sites as substituents in pterins. In this paper, we report the synthesis of a new range of polyfunctional pterins with extended side-chains at C-6.[7]

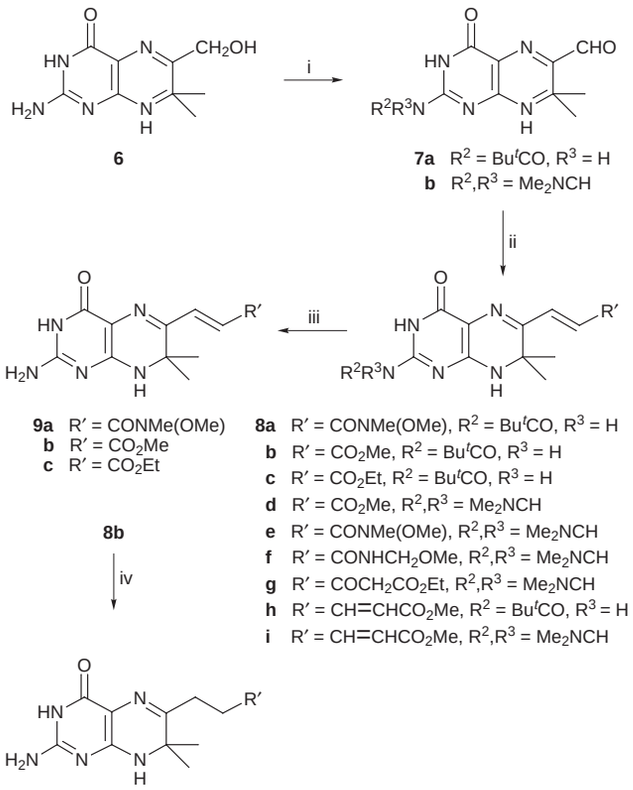
The elaboration of side chains at C-6 in pterins and their close relatives has been largely restricted to N-alkylation of 4-aminobenzoate analogues using 6-bromomethylpterins,[8] to palladium-mediated couplings of 6-iodo analogues with alkynes,[9] and to their inclusion directly by ring synthesis.[10] Undoubtedly a deterrent to the development of more complex derivatives has been the well-known poor solubility of pterins in both organic and aqueous media. We initially investigated the selective protection of the 2-amino group in 6-hydroxymethylpterin (**1a**), for example using O-silylation and pivaloylation. In the latter case, following Joule,[11] the 2,6-dipivaloyl derivative was obtained in good yield, but in our hands the selective deprotection of the 6-pivalate ester gave poor yields of the 2-pivaloyl amide, which was in any case inadequately soluble. The most promising protecting group was dimethylaminomethylene, introduced using DMF dimethyl acetal;[12] derivatives both of 6-hydroxymethyl- and 6-formyl-pterin (**2a** and **2b**) had satisfactory solubility and were obtained in good yield. Since a brief investigation of the activation of the 6-hydroxymethyl group to direct nucleophilic substitution was unsuccessful, attention focused on the Wittig reaction to elaborate polyfunctional side chains at C-6 (Scheme 1).



Scheme 1 *Reagents*: i, $Me_2NCH(OMe)_2$, DMF, 50 °C; ii, Ph_3PCHR' [**(3a)** R′ = CONMe(OMe), **(b)** CO_2Me, **(c)** CO_2Et, **(d)** $CH_2COCH_2CO_2Et$]; iii, NH_3/MeOH.

A range of representative phosphoranes was reacted with the protected 6-formylpterin **2b** in boiling dimethylacetamide to afford the 6-substituted alkenes **4a**–**c** in satisfactory to good yield (67–92%). Contamination of products with triphenylphosphine oxide was a problem in purification and characterisation of the products. Cleavage of the 2-dimethylaminomethylene protecting group was readily accomplished using methanolic ammonia giving the novel pterin **5a**. To extend the applicability of this chemistry, 6-hydroxymethyl-7,7-dihydro-7,7-dimethylpterin **6** was used as a substrate. Many years ago, we showed that this compound undergoes autoxidation in mildly acidic media to afford the 6-formyl derivative in good yield.[13] The direct application of these conditions to the preparation of the required C-2 protected derivatives **7** and using related conditions with stronger acids failed. However we

found that the oxidation of **6** in DMF solution in the presence of a hindered base (proton sponge) together with the protecting reagent (DMF dimethyl acetal or pivalic anhydride) afforded good yields of the 2-protected pterins with concomitant oxidation of the 6-hydroxymethyl group to formyl (Scheme 2).



Scheme 2 *Reagents*: i, $(Bu^tCO)_2O$, proton sponge, DMF, 80 °C; ii, $Ph_3P{=}CHR'$ [R′ = (**a**, **e**) CONMe(OMe)], (**b**, **d**) CO_2Me, (**c**) CO_2Et, (**f**) $CONHCH_2OMe$, (**g**) $COCH_2CO_2Et$, (**h**, **i**) $CH{=}CHCO_2Me$]; iii, NH_3/MeOH; iv, Bu_3SnH, AIBN, MeOH, reflux.

Using the 2-pivalamides, a range of Wittig reactions was successfully carried out using toluene or tetrahydrofuran as solvents, but yields of alkenes (**8a**–**c**, **h**) were low to moderate (7–50%). In most cases, for 2-pivalamides, phosphoranes were used but in one case (**8h**) a phosphonate gave a successful reaction. Purification problems were again evident. The dimethylaminomethylene derivatives were better substrates for these reactions, using toluene or ethanol as solvents, giving **8d**, **e** and **g** in moderate to good yields (20–85%) except for the case of the methoxymethylacetamide derivative (**8f**). In this case, the required ylide is known to be unstable.[14] In the majority of cases, the NMR spectra of the products indicated clearly that the *E*-isomer of the alkenes had formed, as shown by coupling constants for the alkene protons in the range 12 to 15 Hz. Cleavage of both protecting groups in these series was also easy using methanolic ammonia, as exemplified by the deprotection of **4a** to give **5a** and of **8a**–**c** to give **9a**–**c**.

The further exploitation of the alkenes described above requires the ability to modify the alkene either by reduction or by addition. Such reactions cannot be expected to be simple because, in all cases, the alkenes are conjugated to the heterocyclic rings that are themselves susceptible to reduction and, in the case of the dihydropterins, to addition also. Indeed catalytic reduction of the pivaloyl-protected dihydropterin **8b** led to a mixture of products in which reduction of the pyrazine ring was evident. Selective reduction of **8b** was, however, possible under radical conditions using tri-*n*-butyltin hydride and AIBN in methanol to afford **10**.[15] Unfortunately these conditions also led to cleavage of the dimethylaminomethylene protecting group, thereby limiting the scope of this reduction.

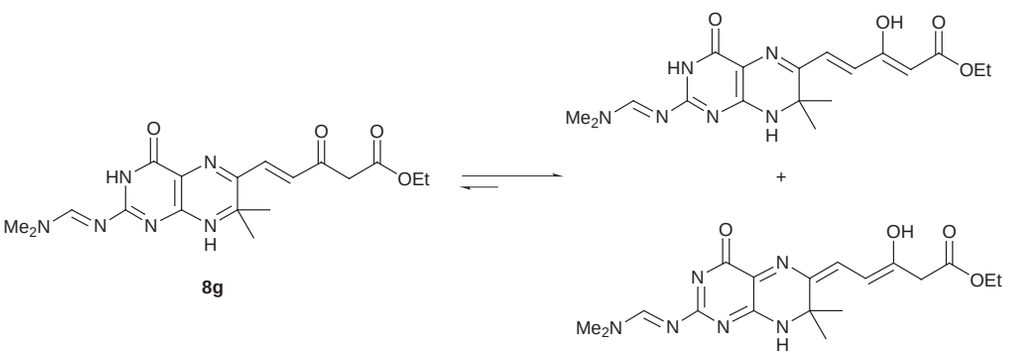
Although some of the examples prepared in the reactions described above contain metal coordinating sites (for example the methoxy amides), an alternative appropriate functionality is a 1,3-dicarbonyl or hydroxycarbonyl derivative. With the encouragement of the success of the Wittig chemistry we also investigated aldol condensations for the elaboration of polyfunctional C-6 side chains. However the pivaloyl-protected formyl pterin **7a** failed to react with methyl acetoacetate dianion even under forcing conditions. β-Dicarbonyl functionality was nevertheless introduced by Wittig reactions in both series of pterins using ethyl 3-oxo-4-triphenylphosphoranylidenebutyrate with lithium ethoxide in ethanol.[16] In the 7,7-dimethyl pterin series, the product **8g** was seen to exist in two tautomeric forms, both of which were enolic (Scheme 3). One tautomer was the simple side chain enol and the second showed enolisation through loss of the 3-proton of the pyrimidine ring, leading to a quinonoid pterin. The same reaction in the 7-unsubstituted series (using **2b**) led to a complex mixture of products from which two fractions were separable. One contained the anticipated alkenes together with other compounds whilst the second contained a highly blue fluorescent compound for which the structure **11** was proposed on the basis of NMR spectroscopy: the absence of a resonance corresponding to a 7-proton, the smaller coupling constant (9.7 Hz) and somewhat lower chemical shifts of the AB pattern. Presumably this compound arose from intramolecular nucleophilic addition of the enol(ate) derived from **4d** in the *Z*-configuration followed by autoxidation (Scheme 4). Additions to C-7 of pteridines are well-known and occur, for example, in the biosynthesis of the important pyranopterin group of cofactors.

Experimental

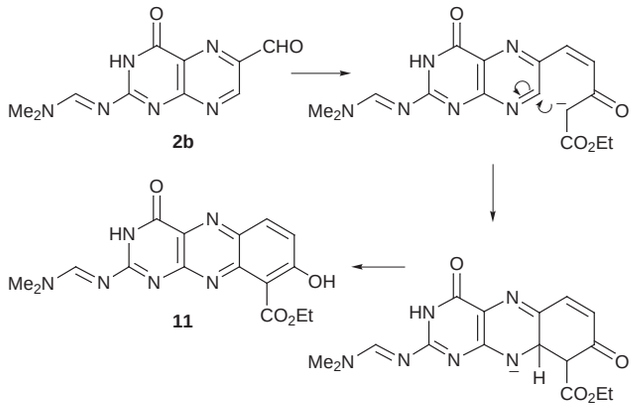
^1H NMR spectra were recorded at 250 MHz except where stated. ^{13}C NMR spectra were recorded at 63 MHz except where stated; when no multiplicity is stated, the resonance refers to that observed in the off-resonance decoupled spectrum. *J* Values are given in Hz.

Protection reactions

2-(*N*,*N*-Dimethylaminomethyleneamino)-6-hydroxymethylpteridin-4(3*H*)-one (2a). 6-Hydroxymethylpterin[17] (**1a**) (57.0



Scheme 3



Scheme 4

mg, 0.3 mmol) was suspended in dry *N*,*N*-dimethylformamide (5 ml). *N*,*N*-Dimethylformamide dimethyl acetal (41.0 mg, 0.03 ml, 0.3 mmol) was added to this suspension. The mixture was stirred and warmed to 50 °C for 2 h. The homogeneous red solution was diluted 1 : 2 with methanol and washed through a 5 cm plug of silica gel to remove the red baseline material (100% MeOH). *N*,*N*-Dimethylformamide and methanol were removed from the filtrate under reduced pressure (cold finger apparatus, 0.1 mmHg). The crude product was dissolved in absolute alcohol (1 ml) and triturated with diethyl ether to afford the required protected *pterin*, which was dried at reduced pressure and stored under nitrogen (69.5 mg, 0.28 mmol, 94%), mp >300 °C (decomp.), ν_{max}(KBr)/cm^{-1} 3405, 3310, 2779, 1695, 1680, 1625, 1613, 1533, 1467, 1280, 1235, 1155, 1120, 1063, 1045; δ_H[$(CD_3)_2SO$] 3.07, 3.20 (2 × 3H, 2 × s, CH_3), 4.65 (2H, s, CH_2), 8.78 (1H, s H-7), 8.79 (1H, s, H-9); δ_C[$(CD_3)_2SO$] 34.62 and 40.89 (C-10 and C-11), 62.55 (C-12), 129.18 (C-6), 148.15 (C-9), 151.94 (C-4a), 155.32 (C-8a), 159.02 (C-7), 159.15 (C-2), 163.53 (C-4); HRMS (FAB, thioglycerol matrix): found 249.1157, $C_{10}H_{13}N_6O_2$ (M + 1) requires 249.1100; λ_{max}(MeOH)/nm 345, 315, 275, 234, 219.

2-(*N*,*N*-Dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (2b). A suspension of 6-formylpterin[18] (**1b**) (300.0 mg, 1.6 mmol) in *N*,*N*-dimethylformamide (20 ml) was treated with a stoichiometric quantity of *N*,*N*-dimethylformamide dimethyl acetal (187.0 mg, 0.21 ml, 1.6 mmol). This reaction mixture was heated to 50 °C under a nitrogen atmosphere. After 30 min, the mixture was completely homogeneous and red in colour. Any unreacted starting material was removed by gravity filtration and the filtrate concentrated under reduced pressure (cold finger apparatus, 0.1 mmHg). The resultant orange solid was triturated with diethyl ether, filtered by suction and dried at reduced pressure to give the required protected *pterin* (310.0 mg, 1.3 mmol, 79%), mp 190–198 °C (decomp.), ν_{max}(KBr)/cm^{-1} 3452, 2804, 1700, 1634, 1545, 1455, 1425, 1350, 1285, 1250; δ_H[$(CD_3)_2SO$] 3.14, 3.27 (2 × 3H, 2 × s, CH_3), 8.89 (1H, s, H-9), 9.11 (1H, s, H-7), 10.00 (1H, s, H-12); δ_C[$(CD_3)_2SO$] 35.25 and 41.32 (C-10 and C-11), 130.74 (C-6), 141.76 (C-9), 148.10 (C-4a), 159.97 (C-8a), 160.14 (C-7), 161.29 (C-2), 162.30 (C-4), 191.32 (C-12); HRMS (FAB; 3-nitrobenzyl alcohol matrix): found 247.1022, $C_{10}H_{11}N_6O_2$ (M + 1) requires 247.0943, λ_{max}($CHCl_3$)/nm 365, 334, 277.

Wittig reactions

2-(*N*,*N*-Dimethylaminomethyleneamino)-6-[2-(*N*-methoxy-*N*-methylcarbamoyl)vinyl]pteridin-4(3*H*)-one (4a). A mixture of pterin (**2b**) (80.0 mg, 0.3 mmol) and *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (109.0 mg, 0.3 mmol) in *N*,*N*-dimethylacetamide (25 ml) was prepared. This was brought to reflux over a period of 3 d, under nitrogen. The *N*,*N*-dimethylacetamide was then removed under reduced pressure (cold finger apparatus, 0.1 mmHg) (azeotrope MeOH–toluene; 3 times) leaving an orange powder. Unreacted starting material was removed by dissolving this powder in chloroform and filtering by suction. The filtrate was concentrated at reduced pressure and the residue triturated with a minimum of diethyl ether to afford the required *pterin* which was dried to constant weight at reduced pressure (91 mg, 0.27 mmol, 92%), mp 200–203 °C (decomp.), ν_{max}(KBr)/cm^{-1} 3452, 2924, 1709, 1640, 1552, 1476, 1421, 1357, 1117; δ_H($CDCl_3$) 3.19, 3.26 (2 × 3H, 2 × s, CH_3N), 3.34 (3H, s, CH_3N), 3.80 (3H, s, CH_3O), 7.64 (1H, d, CH=, *J* 15.7), 7.86 (1H, d, CH=, *J* 15.7), 8.87 (1H, s, CH=N), 9.00 (1H, s, H-7); δ_C($CDCl_3$) 32.47 (CH_3N), 35.55 and 41.76 (CH_3N), 62.14 (CH_3O), 121.78 (CH=), 131.90 (C-6), 137.81 (CH=), 145.44 (N–C=N), 150.30 (C-4a), 156.35 (C-8a), 157.66 (C-7), 159.86 (C-2), 161.62 (C-4), 166.02 (C=O); HRMS (FAB; 3-nitrobenzyl alcohol matrix): found 332.1408, $C_{14}H_{18}N_7O_3$ (M + 1) requires 332.1471; λ_{max}($CHCl_3$)/nm 387, 329, 260.

2-(*N*,*N*-Dimethylaminomethyleneamino)-6-(2-methylcarbonylvinyl)pteridin-4(3*H*)-one (4b). Methoxycarbonylmethylenetriphenylphosphorane (109.0 mg, 0.3 mmol) was added in one portion to a solution of 2-(*N*,*N*-dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (**2b**) (80.0 mg, 0.3 mmol) in *N*,*N*-dimethylacetamide (25 ml), under a nitrogen atmosphere. These reagents were then heated to reflux for 3 d. The *N*,*N*-dimethylacetamide was removed at reduced pressure (cold finger apparatus, 0.1 mmHg) (azeotrope MeOH–toluene; 3 times) and the crude residue triturated with toluene. The title compound was filtered by suction and washed on the filter with cold toluene (20 ml) and then diethyl ether (20 ml). This solid was then dried under reduced pressure to a constant weight to give the required *pterin* (88.2 mg, 0.29 mmol, 97%), mp 180–186 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3446, 1709, 1640, 1545, 1430, 1345, 1117; δ_H($CDCl_3$) 3.19, 3.26 (2 × 3H, 2 × s, CH_3N), 3.81 (3H, s, CH_3O), 7.03 (1H, d, CH=, *J* 15.9), 7.81 (1H, d, CH=, *J* 15.9), 8.87 (1H, s, N=CH), 8.99 (1H, s, H-7), 10.00 (1H, br s, NH); δ_C($CDCl_3$) 35.83 and 42.07 (CH_3N), 52.18 (CH_3O), 123.57 (CH=), 131.35 (C-6), 139.59 (CH=), 144.74 (N=C–N), 149.91 (C-4a), 156.71 (C-8a), 158.17 (C-7), 160.16 (C-2), 161.94 (C-4), 166.87 (C=O); HRMS (FAB; 3-nitrobenzyl alcohol matrix): found 303.1226, $C_{13}H_{15}N_6O_3$ (M + 1) requires 303.1205; λ_{max}($CHCl_3$)/nm 380, 336, 259.

2-(*N*,*N*-Dimethylaminomethyleneamino)-6-(2-ethoxycarbonylvinyl)pteridin-4(3*H*)-one (4c). Ethoxycarbonylmethylenetriphenylphosphorane (113.0 mg, 0.3 mmol) and 2-(*N*,*N*-dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (80.0 mg, 0.3 mmol) were combined in *N*,*N*-dimethylacetamide (25 ml). These reagents were then heated to reflux, under nitrogen gas, for 4 d. The *N*,*N*-dimethylacetamide was then evaporated at reduced pressure (cold finger apparatus, 0.1 mmHg) (azeotrope MeOH–toluene; 3 times) and the residue triturated with toluene. The resultant powder was filtered by suction and washed with toluene and then diethyl ether to afford the required *pterin* which was dried under reduced pressure (68.9 mg, 0.2 mmol, 67%), mp 174–180 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3419, 2928, 1706, 1638, 1549, 1424, 1349, 1255, 1119; δ_H($CDCl_3$) 1.31 (3H, t, CH_3C, *J* 7.2), 3.19, 3.25 (2 × 3H, 2 × s, CH_3N), 4.26 (2H, q, CH_2O, *J* 7.2), 6.99 (1H, d, CH=, *J* 16.0), 7.80 (1H, d, CH=, *J* 16.0), 8.87 (1H, s, CH=N), 8.98 (1H, s, H-7), 10.18 (1H, br s, NH); δ_C($CDCl_3$) 14.38 (CH_3C), 35.82 and 42.08 (CH_3N), 61.01 (CH_2O), 124.02 (CH=), 131.30 (C-6), 139.40 (CH=), 144.84 (N–CH=N), 149.76 (C-4a), 156.63 (C-8a), 158.17 (C-7), 160.16 (C-2), 162.01 (C-4), 166.35 (C=O); HRMS (FAB; 3-nitrobenzyl alcohol matrix): found 317.1390, $C_{14}H_{17}N_6O_3$ (M + 1) requires 317.1362; λ_{max}($CHCl_3$)/nm 380, 336, 259.

Attempted preparation of 2-(*N*,*N*-dimethylaminomethyleneamino)-6-(5-ethoxycarbonyl-4-oxopent-1-enyl)pteridin-4(3*H*)-one (4d): isolation of 2-(*N*,*N*-dimethylaminomethyleneamino)-9-ethoxycarbonyl-8-hydroxybenzo[*g*]pteridin-4(3*H*)-one (11). To dry methanol (10 ml) was added lithium hydride (2.6 mg, 0.33 mmol). After the lithium hydride had dissolved, ethyl 3-oxo-4-(triphenylphosphoranylidene)butyrate (127 mg, 0.326 mmol) and then 7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (50.0 mg, 0.20 mmol) were added. The mixture was stirred at room temperature for 2 h, then evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of methanol, and the solution was neutralized with glacial acetic acid. The mixture was subjected to thin layer chromatography (5 sheets) developing with chloroform–methanol (9 : 1). The yellow band with blue fluorescence (R_f value was *ca*. 0.5) and yellow band with only absorbance (R_f value was *ca*. 0.4) were scraped off. Each of the silica gel bands was extracted with methanol, and the extracts were evaporated to dryness. The purification was repeated. To the residue was added a small amount of ethanol and then diethyl ether. The non-fluorescent precipitate was filtered off to afford a complex mixture (6.3 mg) as shown by ^{1}H NMR spectroscopy. The fluorescent product (**11**) (2 mg); δ_H[$(CD_3)_2SO$] 1.24 (3H, t, *J* 7.0, CH_2CH_3), 3.07 (3H, s, NCH_3), 3.20 (3H, s, NCH_3), 4.15 (2H, q, *J* 7.0, CH_2), 6.71 (1H, d, *J* 9.7, CH=), 7.43 (1H, d, *J* 9.7, CH=), 8.79 (1H, s, N=CH), 11.22 (1H, br s, H-3). These data are consistent with 2-(*N*,*N*-dimethylaminomethyleneamino)-9-ethoxycarbonyl-8-hydroxybenzo[*g*]pteridin-4(3*H*)-one (**11**).

Deprotection

6-[2-(*N*-Methoxy-*N*-methylcarbamoyl)vinyl]pterin (5a). A solution of 2-(*N*,*N*-dimethylaminomethyleneamino)-6-[2-(*N*-methoxy-*N*-methylcarbamoyl)vinyl]pteridin-4(3*H*)-one (**4b**) (26 mg, 7.9×10^{-5} mol) and saturated methanolic ammonia (20 ml) was stirred continuously at room temperature for 24 h in a sealed flask. Concentration of the residue under reduced pressure left a solid residue which was triturated with cold dichloromethane to afford the required *pterin* as an orange powder (15.3 mg, 5.5×10^{-5} mol, 70%), mp 220–223 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3435, 2930, 1684, 1646, 1621, 1460, 1111; δ_H[$(CD_3)_2SO$] 3.24 (3H, CH_3N), 3.77 (3H, s, CH_3O), 7.41 (1H, d, CH=, *J* 15.5), 7.66 (1H, d, CH=, *J* 15.5), 8.92 (1H, d, H-7); δ_C[$(CD_3)_2SO$] 32.22 (CH_3N), 61.90 (CH_3O), 118.66 (CH=), 129.10 (C-6), 138.45 (CH=), 141.76 (C-4a), 150.15 (C-8a), 156.74 (C-7), 157.67 (C-2), 163.52 (C-4), 165.39 (CO); HRMS [FAB; $(CH_3)_2SO$/TFA/3-nitrobenzyl alcohol matrix]: found 277.10433, $C_{11}H_{13}N_6O_3$ (M + 1) requires 277.10491; λ_{max}(MeOH)/nm 379, 313.

Protection reactions

7,8-Dihydro-7,7-dimethyl-6-formyl-2-pivaloylaminopteridin-4(3*H*)-one (7a). 7,8-Dihydro-7,7-dimethyl-6-hydroxymethylpterin (**6**) (500.0 mg, 2.3 mmol) and proton sponge [1,8-bis(dimethylamino)naphthalene] (514.0 mg, 2.3 mmol) were combined in *N*,*N*-dimethylformamide (15 ml). This mixture was heated to 50 °C for 15 min. Pivalic anhydride (trimethylacetic anhydride) (410.0 mg, 0.5 ml, 2.3 mmol) was then added and this mixture was left to stir at 50 °C, under a nitrogen atmosphere, for 48 h. Solvent and trimethylacetic acid were removed at reduced pressure (cold finger apparatus, 0.1 mmHg). The residue was then dissolved in ethyl acetate and filtered through a plug of Kieselguhr clay to remove any unreacted starting material. The filtrate was concentrated under reduced pressure and the dry residue triturated with diethyl ether to give the protected *pterin* (175.6 mg, 0.6 mmol, 25%), mp 197–199 °C (decomp.); ν_{max}(CH_3Cl)/cm^{-1} 3240, 2950, 2810, 1654, 1608, 1585, 1551, 1531, 1458, 1386; δ_H($CDCl_3$) 1.00 (9H, s, $3 \times CH_3$), 1.23 (6H, s, $2 \times CH_3$), 9.03 (1H, s, H-12); δ_C($CDCl_3$) 26.92 (Bu^t), 28.05 ($2 \times$ 7-CH_3), 40.68 (C-10), 54.48 (C-7), 107.13 (C-4a), 150.89 (C-6), 152.04 (C-2), 153.42 (C-8a), 157.16 (C-4), 181.27 (CON), 191.80 (CHO); HRMS (FAB; thioglycerol matrix): found 306.1573, $C_{14}H_{20}N_5O_3$ (M + 1) requires 306.1566; λ_{max}($CHCl_3$)/nm 425, 321.

7,8-Dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (7b). 7,8-Dihydro-7,7-dimethyl-6-hydroxymethylpteridin-4(3*H*)-one (**6**) (100.0 mg, 0.4 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (48.0 mg, 0.05 ml, 0.4 mmol) were combined in *N*,*N*-dimethylformamide (5 ml), under an atmosphere of nitrogen gas. This mixture was stirred and warmed to 50 °C for 3 d. The solvent was removed under reduced pressure (cold finger apparatus, 0.1 mmHg) and the residue dissolved in 10% methanol in ethyl acetate. Unreacted **6** was removed by filtering this solution through a silica gel plug. The fluorescent green filtrate was then concentrated under reduced pressure and the resultant residue triturated with diethyl ether to afford the required *pterin* (88.4 mg, 0.3 mmol, 80%); ν_{max}(Nujol)/cm^{-1} 3200, 1682, 1630, 1570, 1502, 1463, 1418, 1378; δ_H(CD_3OD) 1.68 (6H, s, $2 \times CH_3C$), 3.25, 3.35 ($2 \times$ 3H, $2 \times$ s, CH_3N), 8.90 (1H, s, H-9), 9.50 (1H, s, H-12); δ_C(CD_3OD) 28.27 ($2 \times CH_3C$), 35.55 and 41.79 ($2 \times CH_3N$), 55.03 (C-7), 107.51 (C-4a), 150.66 (C-6), 154.49 (C-8a), 155.53 (C-2), 159.78 (N–CH=N), 192.70 (CHO); HRMS (CI): found 277.1500, $C_{12}H_{17}N_6O_2$ (M + 1) requires 277.1410; λ_{max}($CHCl_3$)/nm 274.

Wittig reactions

7,8-Dihydro-7,7-dimethyl-2-pivaloylamino-6-[2-(*N*-methoxy-*N*-methylcarbamoyl)vinyl]pteridin-4(3*H*)-one (8a). *N*-Methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (238.0 mg, 0.7 mmol) and pterin (**7a**) (200.0 mg, 0.7 mmol) were combined in dry tetrahydrofuran (20 ml) under a nitrogen atmosphere. This mixture was stirred at room temperature for 24 h. Evaporation under reduced pressure of the solution gave the crude reaction product which was purified by silica gel column chromatography (10% MeOH in EtOAc). The combined fractions were then concentrated at reduced pressure and the residue triturated with diethyl ether to afford the required *dihydropterin* (85.6 mg, 0.2 mmol, 34%), mp 182–184 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3558, 3485, 3413, 3242, 2980, 2935, 1646, 1625, 1564, 1461, 1389, 1224, 1162; δ_H($CDCl_3$) 1.29 (9H, s, Bu^t), 1.42 (6H, s, $2 \times CH_3$), 3.27 (3H, s, CH_3N), 3.74 (3H, s, CH_3O), 6.08 (1H, s, NH-8), 7.27 (1H, d, CH=, *J* 15.1), 7.49 (1H, d, CH=, *J* 15.1), 9.23 (1H, br s, NH), 11.63 (1H br s, NH); δ_C($CDCl_3$) 26.99 [$(CH_3)_3C$], 28.02 ($2 \times CCH_3$), 40.61 (CH_3N), 54.31 (C-7), 62.55 (CH_3O), 107.37 (C-4a), 123.00 (CH=), 136.13 (CH=), 149.96 (C-2), 151.71 (C-8a), 152.88 (C-6), 157.51 (C-4), 165.30 (N–CH=N), 180.82 (CON); HRMS (FAB; 3-nitrobenzyl alcohol matrix): found 391.2145, $C_{18}H_{27}N_6O_4$ (M + 1) requires 391.2094; λ_{max}($CHCl_3$)/nm 418, 255.

7,8-Dihydro-7,7-dimethyl-2-pivaloylamino-6-(2-methoxycarbonylvinyl)pteridin-4(3*H*)-one (8b). Methoxycarbonylmethylenetriphenylphosphorane (435.0 mg, 1.3 mmol) was added to 7,8-dihydro-7,7-dimethyl-6-formyl-2-pivaloylaminopteridin-4(3*H*)-one (**7a**) (400.0 mg, 1.3 mmol) in dry toluene (20 ml). This mixture was refluxed, under an inert atmosphere of nitrogen gas, for 24 h. The reaction mixture was then evaporated and the oily, orange residue purified by silica gel column chromatography (100% EtOAc). The combined fractions were concentrated under reduced pressure to give the required *dihydropterin* as an orange solid (252.8 mg, 0.7 mmol, 54%), mp 174–180 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3452, 3377, 3264, 1722, 1652, 1555, 1530, 1457, 1388, 1306, 1250, 1160; δ_H($CDCl_3$) 1.28 (9H, s, Bu^t), 1.42 (6H, s, $2 \times CH_3$), 3.73 (3H, s, CH_3O), 6.82 (1H, d, CH=, *J* 15.0), 7.23 (1H, d, CH=, *J* 15.0); δ_C($CDCl_3$) 26.96 [$(CH_3)_3$], 28.10 ($2 \times CH_3$), 40.60 (CH_3N), 52.01 (CH_3O), 54.26

(C-7), 107.04 (C-4a), 124.55 (CH=), 137.65 (CH=), 150.25 (C-2), 150.84 (C-8a), 153.12 (C-6), 157.66 (C-4), 167.25 (=CHCON), 181.13 (CON); HRMS (FAB; 3-nitrobenzyl alcohol matrix): found 362.1865, $C_{17}H_{24}N_5O_4$ (M + 1) requires 362.1829; λ_{max}(CHCl$_3$)/nm 420, 256.

7,8-Dihydro-7,7-dimethyl-2-pivaloylamino-6-(2-ethoxycarbonylvinyl)pteridin-4(3*H*)-one (8c). Ethoxycarbonylmethylenetriphenylphosphorane (341.0 mg, 1.0 mmol) and 7,8-dihydro-7,7-dimethyl-6-formyl-2-pivaloylaminopteridin-4(3*H*)-one (**7a**) (300.0 mg, 1.0 mmol) were heated to reflux in toluene (150 ml) under nitrogen gas. After 24 h, the toluene was removed under reduced pressure and the product purified by column chromatography with neutralised alumina (5–10% MeOH gradient in EtOAc). The combined fractions were evaporated at reduced pressure and the residue triturated with diethyl ether and filtered by suction to afford the required *dihydropterin*, which was then dried to constant weight at reduced pressure (82.2 mg, 0.2 mmol, 20%), mp 168–170 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3446, 3232, 2974, 2924, 2855, 1650, 1552, 1457, 1388, 1375, 1300, 1250, 1162; δ_H(CDCl$_3$) 1.21 (3H, t, CH$_3$, *J* 7.3), 1.30 (9H, s, 3 × CH$_3$), 1.45 (6H, s, 2 × CH$_3$), 4.20 (2H, q, CH$_2$, *J* 7.3), 6.79 (1H, d, CH=, *J* 15.4), 7.21 (1H, d, CH=, *J* 15.4); δ_C(CDCl$_3$) 14.25 (CMe$_3$), 26.83 [(*C*H$_3$)$_3$C], 28.00 (2 × CH$_3$), 40.47 (CH$_3$N), 54.27 (CH$_3$O), 60.75 (C-7), 106.86 (C-4a), 124.96 (CH=), 137.37 (CH=), 150.04 (C-2), 151.28 (C-8a), 152.99 (C-6), 157.75 (C-4), 166.61 (=CH*C*ON), 180.97 (CON); HRMS (FAB; 3-nitrobenzyl alcohol matrix): found 376.2001, $C_{18}H_{26}N_5O_4$ (M + 1) requires 376.1984; λ_{max}(CHCl$_3$)/nm 419, 255.

7,8-Dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-(2-methoxycarbonylvinyl)pteridin-4(3*H*)-one (8d). To a suspension of the 7,8-dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (**7b**) (40.0 mg, 0.145 mmol) in toluene (5 ml) was added methoxycarbonylmethylenetriphenylphosporane (54.0 mg, 0.150 mmol). The mixture was refluxed overnight. The precipitate was filtered off (45.0 mg), and then the solid was dissolved in 10% methanol in ethyl acetate (10 ml). The insoluble material was removed by filtration. The filtrate was evaporated, then addition of diethyl ether afforded the required *pterin alkene* (34.1 mg, 74%), mp 194 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3434, 2955, 2917, 2855, 1625, 1552, 1501, 1426, 1350, 1174, 1130; δ_H(CDCl$_3$) 1.42 (6H, s 2 × CH$_3$), 3.09, 3.16 (2 × 3H, 2 × s, CH$_3$N), 3.75 (3H, s, CH$_3$O), 5.41 (1H, s, NH-8), 6.90 (1H, d, CH=, *J* 15.4), 7.26 (1H, d, CH=, *J* 15.4), 8.53 (1H, s, N–CH=N), 10.25 (1H, br s, NH-3); δ_C(CDCl$_3$) 27.21 (2 × CH$_3$), 36.14 and 42.32 (CH$_3$N), 52.47 (CH$_3$O), 54.72 (C-7), 107.46 (C-4a), 124.33 (CH=), 138.43 (CH=), 149.78 (C-6), 153.84 (C-8a), 155.54 (C-2), 158.73 (N–CH=C), 159.51 (C-4), 168.09 (CO); HRMS (FAB; 3-nitrobenzyl alcohol matrix): found 333.1723, $C_{15}H_{21}N_6O_3$ (M + 1) requires 333.1675; λ_{max}(CHCl$_3$)/nm 429, 258.

7,8-Dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-[2-(*N*-methoxy-*N*-methylcarbamoyl)vinyl]pteridin-4(3*H*)-one (8e). To a solution of 7,8-dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (**7b**) (55.2 mg, 0.20 mmol) in ethanol (10 ml) was added *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)-acetamide (54.5 mg, 0.150 mmol). The mixture was stirred at room temperature for 20 h, then evaporated to a small volume. Toluene was added and the mixture was evaporated again. This procedure was repeated a few times to remove ethanol. The precipitate was suspended in toluene (5 ml), filtered off, washed with toluene and then diethyl ether to afford the yellow *pterin* (68.3 mg, 88%); mp darkened at 240 °C, 290 °C (decomp.); ν_{max}/cm^{-1} 3435, 3236 (NH), 2927 (CH), 1665, 1627 (C=O), 1605, 1544, 1496, 1415, 1341, 1122; δ_H[(CD$_3$)$_2$SO] 1.31 (6H, s, C-CH$_3$), 3.02 (3H, s, NCH$_3$), 3.12 (3H, s, NCH$_3$), 3.19 (3H, s, CONCH$_3$), 3.73 (3H, s, OCH$_3$), 7.13 (1H, d, CH=, *J* 15.7), 7.19 (1H, d, CH=, *J* 15.7), 7.37 (1H, s, NH-8), 8.51 (1H, s, N=CH–N), 10.75 (1H, br s, NH-3); δ_C[(CD$_3$)$_2$SO] 27.47 (2 × CH$_3$), 32.56 (CH$_3$N), 35.04 (CH$_3$NCO), 41.15 (CH$_3$N), 53.27 (C-7), 62.12 (CH$_3$O), 106.00 (C-4a), 119.82 (CH=), 137.02 (CH=), 147.53 (C-6), 153.59 (C-8a), 158.77 (C-2), 159.43 (C-4), 166.01 (CON); HRMS (FAB): found 362.1901. $C_{16}H_{23}N_7O_3$ (M + 1) requires 362.1940; λ_{max}(MeOH)/nm 281, 436.

[*N*-(Methoxymethyl)carbamoylmethyl]triphenylphosphonium chloride.[14] To a solution of 2-chloro-*N*-(hydroxymethyl)acetamide (3.80 g, 0.0308 mol) in methanol (20 ml) was added conc. HCl (1.3 ml). The mixture was stirred at room temperature for 16 h, then neutralised with sodium hydrogen carbonate. The mixture was evaporated to dryness. The residue was extracted a few times with acetone. The extracts were evaporated, then the residue, distilled at 125 °C (0.1 mmHg), gave the product (4.03 g, 95%); δ_H(CDCl$_3$) 3.36 (3H, s, CH$_3$), 4.11 (2H, s, ClCH$_2$CO), 4.75 (2H, d, *J* 6.5, NHC*H*$_2$O), 7.34 (1H, br s, NH). To a solution of 2-chloro-*N*-(methoxymethyl)acetamide prepared as described above (0.225 g, 2.0 mmol) in dry acetonitrile (10 ml) was added triphenylphosphine (0.524 g, 2.0 mmol). The mixture was refluxed for 20 h, then the solvent was removed under reduced pressure to give the product. Since this phosphonium salt decomposes during purification, it was used without purification for further reaction.

7,8-Dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-[2-(*N*-methoxymethylcarbamoyl)vinyl]pteridin-4(3*H*)-one (8f). To a solution of [*N*-(methoxymethyl)carbamoylmethyl]triphenylphosphonium chloride, which was prepared from 2-chloro-*N*-(methoxymethyl)acetamide (0.225 g), in methanol (10 ml), was added 7,8-dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (**7b**) (49.8 mg, 0.18 mmol). After the pterin dissolved, to the solution was added 0.2 M KOH–MeOH (1 ml). The mixture was stirred at room temperature for 2 h, then another portion of 0.2 M KOH–MeOH (1 ml) was added. After 2 h, the mixture was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel (2 × 6 cm column) packed with chloroform and eluted with 10% methanol–chloroform. The orange band was collected. This fraction was further purified by column chromatography packed in ethyl acetate and eluted with 20% methanol–ethyl acetate. The yellow band was collected, the solution concentrated, ethyl acetate added, and evaporated again to remove methanol. After further concentration, diethyl ether was added and the precipitate was filtered off to give the required *pterin methoxyamide* (14.1 mg, 23%); δ_H[(CD$_3$)$_2$SO] 1.34 (6H, s, CCH$_3$), 3.07 (3H, s, NCH$_3$), 3.11 (3H, s, NCH$_3$), 3.20 (3H, s, OCH$_3$), 4.55 (2H, d, *J* 6.4, CH$_2$), 8.93 (1H, t, *J* 6.4, CONH), 6.81 (1H, d, *J* 14.1, CH=), 7.06 (1H, d, *J* 14.1, CH=), 7.34 (1H, s, NH-8), 8.51 (1H, s, N=CH–N), 10.8 (1H, br s, NH-3); λ_{max}(MeOH)/nm 281, 436.

7,8-Dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-(4-ethoxycarbonyl-3-oxobut-1-enyl)pteridin-4(3*H*)-one (8g in two enolic forms). To dry ethanol (10 ml) was added lithium hydride (6.4 mg, 0.80 mmol). After the lithium hydride had dissolved, ethyl 3-oxo-4-(triphenylphosphoranylidene)-butyrate (312 mg, 0.80 mmol) and then 7,8-dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (**7b**) (110 mg, 0.40 mmol) were added. The solution was stirred at room temperature for 20 h. The solution was neutralised with glacial acetic acid, then evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel (3 × 6 cm column) eluting with chloroform, followed by 10% methanol in chloroform. The fraction of 10% methanol in chloroform was collected and evaporated to dryness. The residue was further purified by repeating the chromatography eluting with methanol in chloroform (1–8% v/v). The purified material was dissolved in a mixture of

methanol and ethyl acetate and concentrated. To the mixture was added diethyl ether, which was then triturated to afford the required *pterin β-keto ester* (90.2 mg, 58%) as a mixture of two tautomers (A and B) in solution; mp 145 °C (decomp.); ν_{max}/cm^{-1} 3421, 3233 (NH), 2974, 2932 (CH), 1632 (C=O), 1547, 1508, 1421, 1342, 1219, 1144, 1120; δ_H[$(CD_3)_2SO$] 1.35 (3H, m, CH_2CH_3 of A and B), 1.44 (6H, s, 7-CH_3 of A and B), 3.12 (3H, s, NCH_3 of A and B), 3.19 (3H, s, NCH_3 of A and B), 3.63 (2H, s, =COHCH_2CO_2Et of B), 4.21 (2H, m, CH_2CH_3 of A and B), 5.09 (1H, br s, OH of A and B), 5.21 (1H, s, COH=$CH$$CO_2$Et of A), 6.98 (1H, d, *J* 14.9, CH= of A), 7.11 (1H, d, *J* 14.9, CH= of A), 7.20 (1H, d, *J* 15.4, CH= of B), 7.28 (1H, d, *J* 15.4, CH= of B), 7.37, 8.59 (1H, s, N=CH–N), 9.53 (1H, br s, H-8 of A and B), 11.85 (1H, br s, H-3 of A and B); δ_C[$(CD_3)_2SO$] 14.36, 14.47, 28.36, 28.51, 35.57, 35.62, 41.74, 41.80, 48.81, 54.26, 54.35, 60.54, 61.57, 94.06, 107.08, 128.66, 128.99, 129.00, 129.60, 137.04, 152.76, 158.79, 158.98, 159.98, 167.52, 168.41, 173.00, 192.19; HRMS (FAB): found 389.1949, $C_{18}H_{24}N_6O_4$ (M + 1) requires 389.1937; λ_{max}(MeOH)/nm 251, 286, 449.

7,8-Dihydro-7,7-dimethyl-6-(4-methoxycarbonylbuta-1,3-dienyl)-2-pivaloylaminopteridin-4(3*H*)-one (8h). Hexamethyldisilazane (158.0 mg, 0.21 ml, 1.0 mmol) in dry tetrahydrofuran (7 ml) was cooled to −78 °C under a nitrogen atmosphere. After 10 min, *n*-butyllithium (2.5 M solution in hexanes) (0.32 ml, 0.8 mmol) was added and the lithiated amine left to stir at −78 °C for a further 15 min. Trimethyl 4-phosphonocrotonate (162.0 mg, 0.16 ml, 0.8 mmol) was then added to the reaction mixture. The resultant ylide was stirred at −78 °C for 15 min. On addition of the 7,8-dihydro-7,7-dimethyl-6-formyl-2-pivaloylaminopteridin-4(3*H*)-one (**7a**) (200.0 mg, 0.7 mmol), the solution instantly turned blood red in colour. After completion of the reaction [3 d (TLC analysis)] the tetrahydrofuran was removed under reduced pressure and the red residue triturated with diethyl ether and filtered by suction. The crude material was then purified by silica gel column chromatography (MeOH–*n*-hexane–EtOAc 1:5:14). The combined fractions were then evaporated. The residue was triturated with diethyl ether to afford the required *dihydropterin*, which was dried under reduced pressure to constant weight (41.2 mg, 0.1 mmol, 16%), mp 158–162 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3558, 3485, 3422, 3242, 2962, 2926, 2862, 1646, 1625, 1553, 1461, 1378, 1265, 1152; δ_H($CDCl_3$) 1.31 (9H, s, Bu^t), 1.43 (3H, s, CH_3), 1.68 (3H, s, CH_3), 3.75 (3H, s CH_3O), 5.01 (1H, br, NH-8), 6.10 (1H, d, CH=, *J* 15.0), 6.49 (1H, d, CH=, *J* 14.6), 7.36 (1H, dd, CH=, *J* 15.0 and 11.8), 7.55 (1H, dd, CH=, *J* 14.6 and 11.8), 8.21 (1H, br s, NH), 11.54 (1H, s, NH); δ_C($CDCl_3$) 27.02 [$(CH_3)_3C$], 28.07 (2 × CH_3), 40.57 [$C(CH_3)_3$], 51.82 (C-7), 54.08 (CH_3O), 107.71 (C-4a), 123.74 (CH=), 132.74, 133.67 (CH=), 143.71 (CH=), 149.61 (C-2), 152.20 (C-8a), 157.49 (C-4), 167.48 ($COCH_2$), 180.55 (CO); HRMS (FAB; 3-nitrobenzyl alcohol matrix): found 388.1927, $C_{19}H_{26}N_5O_4$ (M + 1) requires 388.1985; λ_{max}($CHCl_3$)/nm 438, 274, 257.

7,8-Dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-(4-methoxycarbonylbuta-1,3-dienyl)pteridin-4(3*H*)-one (8i). To a solution of 7,8-dihydro-7,7-dimethyl-2-(*N*,*N*-dimethylaminomethyleneamino)-6-formylpteridin-4(3*H*)-one (**7b**) (40.0 mg, 0.145 mmol) in methanol (5 ml) was added trimethyl 4-phosphonocrotonate (36.2 mg, 0.174 mmol) and potassium carbonate (24.0 mg, 0.174 mmol). The mixture was stirred at room temperature for 3 d. After neutralisation with glacial acetic acid, the mixture was evaporated to dryness. The residue was chromatographed on silica gel (2 × 6 cm column) eluting with chloroform, followed by 1, 2 and 6% methanol in chloroform. Fractions of 2% methanol in chloroform (fraction A) and 6% (fraction B) were separately collected. Fraction A was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of methanol–ethyl acetate. The solution was concentrated and then diethyl ether was added. The precipitate was triturated and filtered to afford the required *pterin* (8.0 mg). Fraction B was treated similarly, and afforded the same product (5.2 mg); mp 170 °C (decomp.); ν_{max}/cm^{-1} 3412, 3229 (NH), 2925 (CH), 1702, 1627 (CO), 1541, 1501, 1423, 1343, 1266, 1139, 1117, 999; δ_H[$(CD_3)_2SO$] 1.42 (6H, s, CH_3-7), 3.07 (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 3.76 (3H, s, CO_2CH_3), 4.96 (1H, br s, H-8), 6.06 (1H, d, *J* 15.0, CH=), 6.55 (1H, d, *J* 14.7, CH=), 7.36 (1H, dd, J_1 15.0, J_2 12.0, CH=CH–CH=CH), 7.49 (1H, dd, J_1 14.7, J_2 12.0, CH=CH–CH=CH), 8.67 (1H, s, N–CH=N), 9.35 (1H, br s, 3-H); δ_C[$(CD_3)_2SO$] 28.34 (2 × CH_3), 35.54 and 41.70 (CH_3N–C=NCH_3), 51.77 (OCH_3), 54.06 (C-7), 107.24 (C-4a), 123.18 (CH=), 132.98 (CH=), 133.15 (CH=), 144.01 (N–CH=C), 150.75 (C-6), 152.90 (C-8a), 157.69 (C-8), 158.75 (C-2), 160.10 (C-4), 167.63 (CO); HRMS (FAB): found 359.1919, $C_{17}H_{23}N_6O_3$ (M + 1) requires 359.1831; λ_{max}(MeOH)/nm 253, 284, 448.

Fraction B: δ_H[$(CD_3)_2SO$] 1.42 (6H, s, CH_3-7), 3.10 (3H, s, NCH_3), 3.13 (3H, s, NCH_3), 3.74 (3H, s, CO_2CH_3), 4.85 (1H, br s, H-8), 6.07 (1H, d, *J* 15.0, CH=), 6.49 (1H, d, *J* 14.7, CH=), 7.36 (1H, dd, J_1 15.0, J_2 12.0, CH=CH–CH=CH), 7.50 (1H, dd, J_1 14.7, J_2 12.0, CH=CH–CH=CH), 8.54 (1H, s, N–CH=N), 9.40 (1H, br s, H-3).

Deprotection

2-Amino-7,8-dihydro-7,7-dimethyl-6-[2-(*N*-methoxy-*N*-methylcarbamoyl)vinyl]pterin (9a). As for compound **5a** above from **8a** (13.9 mg, 4.5×10^{-5} mol, 89%), mp 195–205 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3427, 2965, 2936, 1655, 1558, 1457, 1388, 1199, 1174; δ_H(CD_3OD) 1.41 (6H, s, 2 × CH_3), 3.31 (3H, s, CH_3N), 3.80 (3H, s, CH_3O), 7.27 (1H, CH=, *J* 15.1), 7.55 (1H, d, CH=, *J* 15.1); δ_C(CD_3OD) 28.32 (CH_2 and 2 × CH_3), 55.21 (C-7), 57.13 (CH_3O), 104.23 (C-4a), 122.22 (CH=), 137.96 (CH=), 150.30 (C-2), 156.27 (C-8a), 156.49 (C-6), 161.63 (C-4), 168.75 (CO); HRMS (FAB; MeCN–thioglycerol matrix): found 307.15117, $C_{13}H_{19}N_6O_3$ (M + 1) requires 307.15186; λ_{max}(MeOH)/nm 423, 260, 217.

7,8-Dihydro-7,7-dimethyl-6-(2-methoxycarbonylvinyl)pterin (9b). As for the preceding compound from **8b** (8.5 mg, 3.1×10^{-5} mol, 56%), mp 185–190 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3340, 3213, 2962, 1651, 1558, 1460, 1438, 1394, 1300, 1174; δ_H(CD_3OD) 1.41 (6H, s, 2 × CH_3), 3.76 (3H, s, CH_3O), 6.88 (1H, d, CH=, *J* 15.4), 7.30 (1H, d, CH=, *J* 15.4); δ_C(CD_3OD) 28.28 (2 × CH_3), 52.34 (CH_3O), 55.12 (C-7), 104.40 (C-4a), 123.68 (CH=), 139.65 (CH=), 149.64 (C-2), 156.37 and 156.48 (C-6 and C-8a), 161.65 (C-4), 169.16 (C-11); HRMS (FAB; MeCN–thioglycerol matrix): found 278.12445, $C_{12}H_{16}N_5O_3$ (M + 1) requires 278.12531; λ_{max}(MeOH)/nm 422, 262.

7,8-Dihydro-7,7-dimethyl-6-(2-ethoxycarbonylvinyl)pterin (9c). As described for the previous compound from **8c** (5.0 mg, 1.7×10^{-5} mol, 32%), mp 190–195 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3434, 1650, 1558, 1460, 1306, 1174; δ_H(CD_3OD) 1.30 (3H, t, CH_3, *J* 7.1), 1.41 (6H, s, 2 × CH_3), 4.22 (2H, q, CH_2, *J* 7.1), 6.89 (1H, d, CH=, *J* 15.4), 7.30 (1H, d, CH=, *J* 15.4); δ_C(CD_3OD) 14.71 (CH_2CH_3), 28.27 (2 × CH_3), 52.34 (CH_2O), 55.12 (C-7), 104.41 (C-4a), 123.68 (CH=), 139.65 (CH=), 149.63 (C-2), 156.37 and 156.48 (C-6 and C-8a), 161.65 (C-4), 169.17 (CO); HRMS (FAB; MeCN–thioglycerol matrix): found 292.14269, $C_{13}H_{18}N_5O_3$ (M + 1) requires 292.14069; λ_{max}(MeOH)/nm 421, 255, 216.

Reduction reaction

7,8-Dihydro-7,7-dimethyl-2-pivaloylamino-6-(2-methoxycarbonylethyl)pteridin-4(3*H*)-one (10). The α,β-unsaturated pterin ester (**8b**) (0.3 g, 0.84 mmol) was dissolved in dry methanol (50 ml) and stirred under a nitrogen gas atmosphere. A catalytic quantity of azobisisobutyronitrile was then added. Tri-*n*-butyltin hydride (247.3 mg, 0.27 ml, 0.84 mmol) was transferred

to the reaction mixture by syringe. The solution was then gently refluxed for 24 h. The methanol was removed at reduced pressure and the tin residues washed out of the reaction mixture by elution down a narrow silica gel column (3 cm depth) (100% *n*-hexane). The reduced product was eluted with 10% methanol in ethyl acetate. After evaporation of the filtrate and trituration of the residue with cold diethyl ether, the required *pterin* was obtained as an orange powder (54.9 mg, 0.15 mmol, 18%), mp 136–140 °C (decomp.); ν_{max}(Nujol)/cm^{-1} 3351, 3243, 1736, 1651, 1550, 1458, 1387; δ_H($CDCl_3$) 1.30 [9H, s, $(CH_3)_3C$], 1.45 (6H, s, 2 × CH_3), 2.64 (2H, t, CH_2, *J* 8.1), 2.86 (2H, t, CH_2, *J* 8.1), 3.68 (3H, s, CH_3O), 8.03 (1H, br s, NH); δ_C($CDCl_3$) 26.42 (2 × CH_3), 26.87 [$(CH_3)_3C$], 27.85 (CH_2), 29.94 (CH_2), 40.22 [$(CH_3)_3C$], 51.65 (CH_2O), 54.10 (C-7), 106.74 (C-4a), 148.72 (C-2), 151.93 (C-8a), 157.14 (C-4), 158.28 (C-6), 174.26 (CON), 179.86 (CO_2); HRMS (FAB; MeCN–thioglycerol matrix): found 364.1549, $C_{17}H_{26}N_5O_4$ (M + 1) requires 364.1979; λ_{max}($CHCl_3$)/nm 410, 332, 279.

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