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4-(2,2-Dimethyldioxalan-4-yl)-5-(pterin-6-yl)-1,3-dithiol-2-ones Proligands Relating to the Cofactor of the Oxomolybdoenzymes

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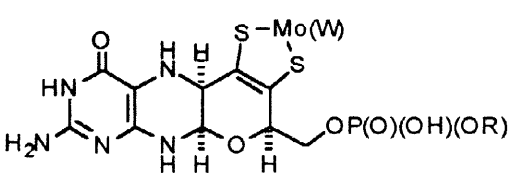
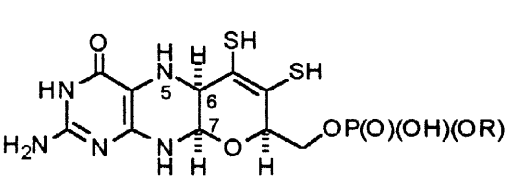
Abstract: The coupling of the 6-iodopterins **11e** and **12d** to 4-(2,2-dimethyl-1,3-dioxolan-4-yl)-5-(tributylstannyl)-1,3-dithiol-2-one **8** gave 4-(2-(N,N-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-on-6-yl)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one **6** and 4-(2-(2,2-dimethylpropanoylamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-on-6-yl)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one **7**, respectively.

This paper is dedicated to Alan Katritzky in acknowledgement of his pioneering contributions to heterocyclic chemistry and with best wishes for his 70th birthday

Degradative and spectroscopic work on the structure of the cofactors of the oxomolybdoenzymes, especially by Rajagopalan *et al.*,[1] concluded that each has a reduced pterin (molybdopterin **2**) carrying at C-6 a four-carbon side-chain involving two sulfur atoms which ligate a molybdenum atom. Further clarification of the nature of molybdopterin was obtained from X-ray crystallographic determinations of some of these enzymes. Thus the structures of aldehyde oxidase from *Desulfovibrio gigas*,[2] DMSO reductase from *Rhodobacter sphaeroides* and *R. capsulatus*[3] and formate dehydrogenase from *Escherichia coli*[4] and the hyperthermophilic tungsten enzyme, ferredoxin aldehyde oxidoreductase from *Pyrococcus furiosus*,[5] showed the cofactor to involve **1** as a common denominator.



1
(R = H or nucleoside)
(other ligands on metal not shown)



2
molybdopterin

The metal is chelated by the dithiolene moiety which is linked to C-6 of a reduced pteridine ring, as originally proposed by Rajagopalan.[1] However, unsuspected from the earlier investigations, each of the crystallographic studies has revealed the presence of a tetrahydropyran ring which can be viewed as resulting from cyclisation of a side-chain hydroxyl group to C-7 of a 5,6-dihydropteridine.

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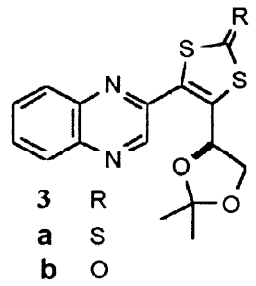
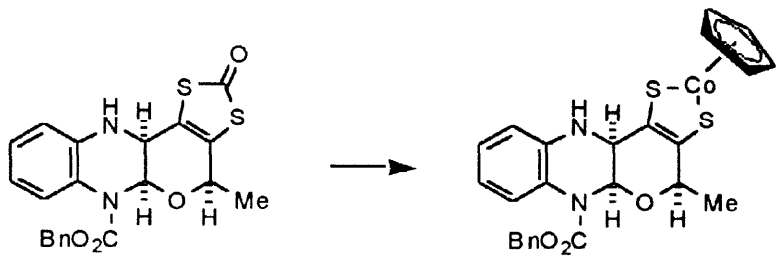
The reversal of such a ring-closing N–C–O bond formation, which could be readily initiated by *O*-protonation, would lead to the introduction of a double bond into the pyrazine ring and thus allow electronic communication (*i.e.* conjugation) between the metallocycle and the pteridine unit, and we have speculated on the possible involvement of such interactions in the biological mode of action of these cofactors.[6]

Arising from our interest in the structure and mode of action of the oxomolybdoenzymes,[7] we have previously described[8] syntheses of simple quinoxalin-2-yl and pteridin-6-yl dithiolene proligands and their conversion into cobalt and molybdenum complexes. These studies culminated in syntheses[8c,f] of quinoxaline-based proligands **3a** and **3b** each of which has a four-carbon side-chain, a dithiolene masked as a 1,3-dithiole-2-thione or -2-one, and two hydroxyl groups located on the distal two carbons of the side-chain, as are the oxygens on the side-chain of the cofactor, and masked as an acetal.

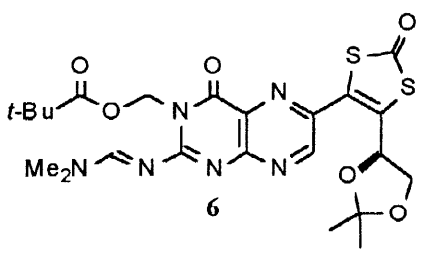


3 R
a S
b O

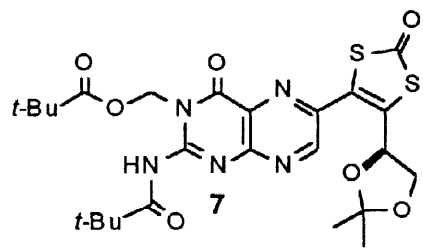


4 **5**

Also, we have demonstrated the construction of a tricyclic 1,2,3,4-tetrahydroquinoxaline-based heterocycle **4** incorporating both a tetrahydropyran and a tetrahydropyrazine, and with the natural relative stereochemistry at the chiral centres, and its conversion into cobalt complex **5**.[9] It is relevant to note that the reduced system was produced from a precursor which had an aromatic pyrazine ring, as do the pteridines described in this paper. We anticipate being able to apply the lessons learnt in the synthesis of **5** to pteridines. In this paper we describe the application of the convergent strategy developed for the synthesis of **3b** to the synthesis of pteridine-containing proligands **6** and **7**.

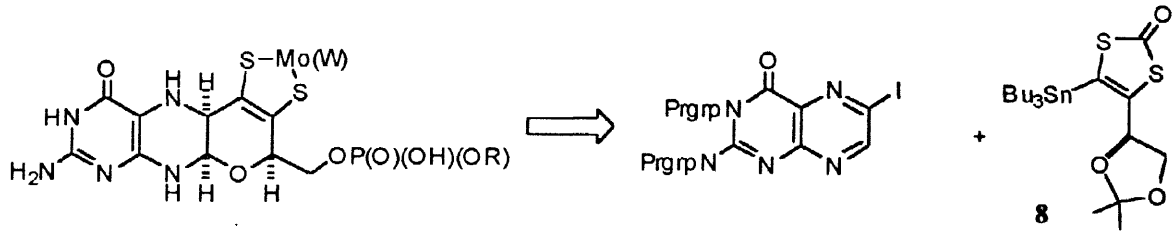


6



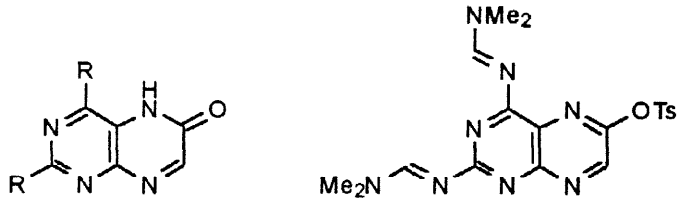
7

The key step in the approach used to make **3b**, was a coupling between a 2-iodoquinoxaline and a stannylated derivative of the 'right-hand' portion of the cofactor, in protected form.[8f] The use of copper thiophene-2-carboxylate (CuTC) was the only protocol[10] which allowed us to effect this coupling. Compound **8**, which we were able to produce in both racemic and the natural[11] homochiral forms, has the alcohol groups masked as an acetal and the dithiolene as a 1,3-dithiol-2-one. The strategy which ultimately proved successful is summarised in **Scheme 1** (Prgrp = protecting group), though we were not sure at the outset of the extent of protection which would be necessary in the pyrimidine ring nor that the 'left-hand' coupling partner would be a 6-*iodo*pterin. The removal of *N*–hydrogen(s) in the pyridimine serves a practically important secondary function, namely to increase the solubility and thus ease of handling of the pterins in organic solvents; it has been long known that without this, pterins are very reluctantly soluble.[12]



Scheme 1

We began our quest for a suitably protected 6-substituted-pterin coupling partner by examining 2,4-diaminopteridin-6-one **9a**.[13] It is known[14] that a 2,4-diaminopteridine can be selectively hydrolysed to a 2-aminopteridin-4-one, and thus **9a** can be viewed as a selectively "protected" pteridine-4,6-dione in which there is a differentiation between the two carbonyl groups. Treatment of **9a** with Bredereck's reagent, *t*-BuO(Me$_2$N)$_2$CH, in DMF gave the doubly protected derivative **9b**, in which both primary amino groups had been masked. Treatment of **9b** with TsCl and Et$_3$N gave the 6-tosyloxypterin **10** in 72% yield, allowing for the ready preparation of gram quantities of this substance.



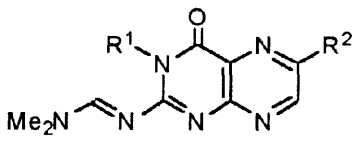
9 R
a NH_2
b $N{=}CHNMe_2$

10

Unfortunately, although we were able to show that the tosyloxypterin *could* be coupled with partners such as 1-tri-*n*-butylstannyl-1-ethoxyethene (see Experimental section) no coupling was observed when it was treated with CuTC and the stannane **8** under the conditions which were successful for the synthesis of **3b**. Since there was such a strong indication from Liebskind's work[10] and our own quinoxaline studies[8f] that iodides are required in CuTC-promoted couplings we decided to put the production of a 6-iodopterin as a priority. Attempted exchange of tosylate for iodide in **10** with NaI in the presence of acid or Ni(cod)$_2$,[15] or the direct conversion of **9b** into a 6-iodopterin using POCl$_3$/NaI or Ph$_3$P/I$_2$ were unsuccessful. We turned to the prospect

of carrying out a Curtius degradation of a 6-acid to 6-amine and then conversion of 6-amine to 6-iodide. 6-Formylpterin, readily available from the degradation[16] of folic acid, was the starting point.

With the aim of increasing solubility properties, which were expected to be acute in the prospective 6-carboxy- and 6-amino-pterin intermediates, the amidine-protected 6-formylpterin **11a**[8e] was reacted with chloromethyl pivaloate and DBU in dichloromethane to give the doubly protected pterin **11b**.[17] A second, minor product was isolated following purification by chromatography, the microanalytical, mass and ^{1}H NMR



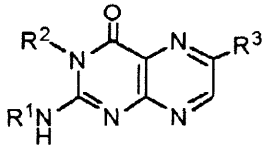
11	R^1	R^2
a	H	CHO
b	*t*-BuCOOCH$_2$	CHO
c	*t*-BuCOOCH$_2$	CO_2H
d	*t*-BuCOOCH$_2$	NH_2
e	*t*-BuCOOCH$_2$	I

spectroscopic data of which were consistent with its being a regioisomer of the *N*-3 alkylated major product, with the pivaloyloxymethyl substituent presumably on O-4 or at N-1. That the major product is the *N*-3-alkylated material is based on analogy with several comparable alkylations using DBU, in which the regiochemistry was rigorously established by both UV spectroscopic and X-ray crystal structure data.[8e] Reaction with chloromethyl pivaloate using K_2CO_3 in DMF gave the desired doubly protected product **11b** along with ~20% of the minor isomer. The mixture of isomers was utilised in subsequent steps.

Oxidation of **11b** with tetra-*n*-butyl permanganate[18] in DMF afforded the acid **11c** which was then subjected to a Curtius procedure. Treatment with di-(4-nitrophenyl)phosphoazidate,[19] then thermal rearrangement and *in situ* hydrolysis gave the required amine, **11d** albeit in poor yield. Various attempts at improving the overall yield, for example by attempted isolation of the intermediate acyl azide, or by varying the conditions, for instance heating the acyl azide for longer times, generally led to no improvement and more often to a product which contained by products which could not be effectively separated from the desired amine. The amine was converted into the desired iodide **11e** by diazotisation at 80 °C with *n*-pentyl nitrite in CH_2I_2 as the iodine source.[20]

It was extremely rewarding to find that the iodide **11e** coupled with stannane **8** using CuTC, producing the proligand **6** in 30% yield.

The limiting step in the sequence leading to **6** is unquestionably the synthesis of a suitable precursor for the 6-iodopterin coupling partner. Since we had already demonstrated[8f] that 2-chloroquinoxaline can be converted into the corresponding iodide and given that 6-chloro-2-pivaloylaminopteridin-4-one **12b** had been similarly transformed,[21] we turned to the synthesis of **12c** as a coupling partner.



12	R^1	R^2	R^3
a	H	H	Cl
b	*t*-BuC(O)	H	Cl
c	*t*-BuC(O)	H	I
d	*t*-BuC(O)	*t*-BuCOOCH$_2$	I

6-Chloropterin **12a** was prepared by literature procedures involving *N*-8-oxidation of pterin[22] then reaction of the 8-oxide with MeCOCl and CF_3CO_2H.[23] The pivalamide[24] **12b** was prepared by treatment with

hot pivalic anhydride. The conversion of 6-chloro- to 6-iodopterin **12c** required prolonged heating at reflux in MeCN saturated with NaI in the presence of a catalytic quantity of camphorsulfonic acid; the reaction was very variable however, and only poor yields of iodide **12c** were obtained. No coupling of the iodopterin **12c** and stannane **8** occurred under the usual reaction conditions possibly because of an interaction between the N-3–H and the copper salt. Accordingly the *N*-3–hydrogen was substituted, as before by reaction with chloromethyl pivaloate and K_2CO_3 in DMF giving the *N*-3–alkylated pterin **12d** in 45% yield. Treatment of **12d** with the stannane **8** and CuTC in NMP gave the coupled pterin **7**, in 34% yield, together with some destannylated material and some unreacted iodopterin.

We shall utilise proligands **6** and **7** in our further research to develop chemical analogues of the catalytic centres of the oxomolybdoenzymes.

EXPERIMENTAL

General: Organic extracts were dried with anhydrous $MgSO_4$ then filtered before evaporation. Chromatography refers to 'flash' chromatography on silica gel.

2,4-Di(*N,N*-dimethylaminomethyleneamino)pteridin-6-one 9b: 2,4-Diaminopteridin-6-one[13] **9a** (4.09 g, 23 mmol) was suspended in dry DMF (40 ml) and under nitrogen. To this was added *t*-BuO$(Me_2N)_2CH$, Bredereck's reagent (14.2 ml, 69 mmol), and the mixture was heated at 60 °C with efficient stirring for 90 min. The mixture was cooled to ice-bath temperature and the precipitated solid removed by filtration, washed with a little cold DMF, then Et_2O, air dried then dried in a dessicator over P_2O_5 to give *2,4-di(N,N-dimethylaminomethyleneamino)pteridin-6-one* **9b** as a pale yellow solid (5.76 g, 87%); δ_H (200 MHz, d_6-DMSO) 8.64 (2H, overlapping singlets, 2xMe_2NCH), 8.50 (1H, s, pteridin-7-yl-*H*), 7.60 (1H, bs, N*H*), 3.13 (3H, s, NCH_3), 3.11 (3H, s, NCH_3), 3.08, (3H, s, NCH_3), 2.95 (3H, s, NCH_3); *m/z* (EI) 288 (M^+, 100%), 273 (40), 244 (20) 232 (50); found M^+ 288.1443; C, 50.63; H, 6.70; N, 38.82%; $C_{12}H_{10}N_8O$ requires *M* 288.1447; C, 49.99; H, 5.89; N, 38.86%.

2,4-Di(*N,N*-dimethylaminomethyleneamino)-6-tosyloxypteridine 10: 2,4-Di(*N,N*-dimethylaminomethyleneamino)pteridin-6-one **9b** (3.57 g, 12.4 mmol), toluene-*para*-sulphonyl chloride (4.72 g, 25 mmol) and 4-dimethylaminopyridine (DMAP) (150 mg, 1.2 mmol) were mixed together in CH_2Cl_2 (30 ml). The solution was cooled to ice-bath temperature and Et_3N (4.31 ml, 31 mmol) was added. After stirring for 1 h the mixture was washed with sat. aq. $NaHCO_3$ (20 ml), the separated aq. phase was re-extracted with CH_2Cl_2 (2x15 ml) and the combined organic phases washed with brine, dried and evaporated *in vacuo* to give a brown oil. Trituration with EtOAc yielded a solid which was filtered and washed with EtOAc and Et_2O to give *2,4-di(N,N-dimethylaminomethyleneamino)-6-tosyloxypteridine* **10** as a mustard coloured solid (4.09 g, 75%), mp >280 °C, δ_H (200 MHz, $CDCl_3$) 8.96 (2H, 2 overlapping singlets, 2xMe_2NCH), 8.64 (1H, s, pteridin-7-yl-*H*), 8.12 (2H, m, Ar*H*), 7.33 (2H, m, Ar*H*), 3.31 (3H, s, CH_3), 3.26 (3H, s, CH_3), 3.22 (3H, s, CH_3), 3.18 (3H, s, CH_3), 2.43 (3H, s, $ArCH_3$); *m/z* (CI) 443 (MH^+, 25%), 289 (100); found M^+ 442.1540; C, 51.05; H, 4.88; N, 24.53; S, 7.13%; $C_{19}H_{22}N_8O_3S$ requires *M* 442.15355; C, 51.57; H, 5.01; N, 25.32; S, 7.24%.

4-Amino-2-(*N,N*-dimethylaminomethyleneamino)-6-(1-ethoxyethen-1-yl)pteridine: 2,4-Di(*N,N*-dimethylaminomethyleneamino)-6-tosyloxypteridine **10** (1.03 g, 2.33 mmol), 1-ethoxy-1-tri-*n*-butylstannyl)ethene (1.58 ml, 4.66 mmol), LiCl (490 mg, 11.7 mmol) and $Pd(OAc)_2$ were dissolved in degassed NMP (7 ml) under argon

and the mixture heated at 80 °C with efficient stirring for 1 h. A further quantity (0.5 ml, 1.48 mmol) of 1-ethoxy-1-tri-*n*-butylstannyl)ethene was added and heating continued for 30 min. After cooling to rt, the mixture was filtered through celite, the solvent evaporated *in vacuo* and the residue purified by chromatography eluting initially with CH_2Cl_2:MeOH, 95:5 and then 91:9 to give a solid yellow component contaminated with tin residues. Crystallisation from MeCN/Et_2O gave *4-amino-2-(N,N-dimethylaminomethyleneamino)-6-(1-ethoxy-ethen-1-yl)pteridine* as a yellow powder (100 mg), chromatography of the mother liquor over Al_2O_3, eluting with CH_2Cl_2:MeOH, 97:3 producing more material (160 mg in all, 24%), mp >280 °C, δ_H (200 MHz, $CDCl_3$) 9.22 (1H, s, pteridin-7-yl-*H*), 9.00 (1H, s, Me_2NCH), 6.75 (1H, bs, N*H*), 5.85 (1H, bs, N*H*), 5.37 (1H, d, J 2.3, one of $C{=}CH_2$), 4.43 (1H, d, J 2.3, one of $C{=}CH_2$), 4.02 (2H, q, J 7, CH_2CH_3), 3.20 (3H, s, one of $CHN(CH_3)_2$), 3.18 (3H, s, one of $CHN(CH_3)_2$), 1.48 (3H, t, J 7, CH_2CH_3); *m/z* (+ve FAB, 3-nba) 597 (M_2Na^+, 5%), 310 (MNa^+, 10), 288 (MH^+, 100), 260 (10); found MH^+, 288.1567; C, 54,85; H, 6.45; N, 34.27%; $C_{13}H_{17}N_7O$ requires *MH* 288.1573; C, 54.34; H, 5.96; N, 34.12%.

2-(*N,N*-Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-6-formylpteridin-4-one 11b: 2-(*N,N*-Dimethylaminomethyleneamino)-6-formylpteridin-4-one **11a**[8e] finely ground and dried (2.03 g, 8.3 mmol), K_2CO_3 (2.303 g, 16.7 mmol) and chloromethyl pivaloate (2.4 ml, 16.7 mmol) were suspended/dissolved in dry DMF (20 ml) under nitrogen, and heated at 62 °C for 2.5 h, with efficient stirring. The solvent was evaporated *in vacuo*, the resultant oily red solid partitioned between water (20 ml) and CH_2Cl_2 (20 ml), the aq. phase was separated and extracted twice with CH_2Cl_2 (10 ml). The combined organic phases were washed with aq. citric acid (12%, 10 ml), brine (10 ml), dried and evaporated *in vacuo* to give a red solid which was recrystallised from EtOAc. The first crop of *2-(N,N-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-6-formylpteridin-4-one* **11b** (1.25 g, 42%) had mp 218-223 °C, δ_H (200 MHz, $CDCl_3$) 10.22 (1H, s, C*H*O), 9.31 (1H, s, pterindin-7-yl-*H*), 9.03 (1H, s, Me_2NCH), 6.39 (2H, s, CH_2), 3.30 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 1.17 (9H, s, $C(CH_3)_3$); *m/z* (CI) 378 (MNH_4^+, 55%), 361 (MH^+, 100); found C, 53.31; H, 5.63; N, 23.34%; $C_{16}H_{20}N_6O_4$ requires C, 53.33; H, 5.59; N, 23.32%; a second crop (0.72 g, 66% combined yield) consisted of a mixture of **11b** contaminated with an isomer (ratio 6:4 as judged by ^1H NMR integration). Though mixtures of the two isomers were employed in later transformations, we found that the minor isomer (more polar by TLC analysis) could be obtained pure, in reduced yield, by chromatography eluting with CH_2Cl_2:MeOH, 96.5:3.5; this is probably the *N*-1-alkylated isomer *2-(N,N-dimethylaminomethyleneamino)-1-(2,2-dimethylpropanoyloxymethyl)-6-formylpteridin-4-one*, mp >280 °C (MeCN); δ_H (200 MHz, $CDCl_3$) 10.30 (1H, s, C*H*O), 9.20 (1H, s, pteridin-7-yl-*H*), 9.07 (1H, s, Me_2NCH), 6.63 (2H, s, CH_2), 3.30 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 1.17 (9H, s, $C(CH_3)_3$); *m/z* (CI) 361 (MH^+, 50%), 247 (30); found C, 53.28; H, 5.62; N, 23.54%; $C_{16}H_{20}N_6O_4$ requires C, 53.33; H, 5.59; N, 23.32%.

2-(*N,N*-Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-on-6-ylcarboxylic acid 11c: To 2-(*N,N*-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-6-formylpteridin-4-one **11b** (1.97 g, 5.47 mmol) in DMF (23 ml) was added *n*-Bu_4NMnO_4 (2.17 g, 8.3 mmol) with efficient stirring and initial cooling to maintain rt. After 140 min the reaction mixture was filtered through celite, the DMF was evaporated *in vacuo* and the resultant brown solid triturated and then stirred well with aq. citric acid (6% with 10 % (w/v) NaCl) until all the brown colouration had been quenched, leaving a mustard solid which was collected by filtration and washed with water (4x10 ml) then dried to give *2-(N,N-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-on-6-ylcarboxylic acid* **11c** (1.38 g, 67%) as a mustard coloured solid. An analytical sample was produced by recrystallisation from DMF,

mp >280 °C; δ_H (200 MHz, d_6-DMSO) 9.27 (1H, bs, pteridin-7-yl-*H*), 8.94 (1H, s, C*H*), 7.97 (1H, s, Me_2NCHO), 6.22 (2H, s, CH_2), 3.32 (coincident with water peak, *ca.* 3H, s, NCH_3), 3.14 (3H, s, NCH_3), 2.91 (3H, s, one of $(H_3C)_2NCHO$), 2.75 (3H, s, (one of $(H_3C)_2NCHO$), 1.14 (9H, s, $C(CH_3)_3$); *m/z* (+ve FAB, 3-nba) 399 (MNa^+, 80%), 377 (MH^+, 100), 275 (90); found C, 50.79; H, 6.01; N, 21.78%; $C_{10}H_{20}N_6O_5$.DMF requires C, 50.77; H, 6.05; N, 21.81%.

6-Amino-2-(*N,N*-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-pteridin-4-one 11d: To 2-(*N,N*-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-on-6-ylcarboxylic acid **11c** (60 mg, 0.16 mmol) was suspended in dry CH_2Cl_2 (3 ml) then triethylamine (23 ml, 0.165 mmol) was added, causing the suspended solid to dissolve. The solution was cooled to ice-bath temperature and di-(*para*-nitrophenyl)phosphorazidate[19] (56 mg, 0.165 mmol) was added. After 50 min, further di-(*para*-nitrophenyl)phosphorazidate (32 mg, 0.1 mmol) was added and stirring resumed for a further 50 min. The solvent was evaporated *in vacuo* and replaced with dioxane:water; 6:1 (6 ml) and the mixture heated at 90 °C for 20 min. The solvents were evaporated *in vacuo* and the resultant oil purified by chromatography, eluting initially with CH_2Cl_2:MeOH; 97:3, then 95:5. An early fraction contained material which appeared to be the methyl ester of the precursor acid **11c** as judged by mass spectroscopic analysis, presumably arising by displacement of azide from unrearranged acyl azide by MeOH. Later fractions contained *6-amino-2-(N,N-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-one* **11d** (18 mg, 33%), mp (DMF) >280 °C, δ_H (200 MHz, d_6-DMSO) 8.69 (1H, s, pteridin-7-yl-*H*), 8.23 (1H, s, C*H*), 6.85 (2H, bs, NH_2), 6.18 (2H, s, CH_2), 3.22 (3H, s, NCH_3), 3.05 (3H, s, NCH_3), 1.13 (9H, s, $C(CH_3)_3$); *m/z* (CI) 348 (MH^+, 100%), 248 (15), 102 (40); found C, 51.47; H, 6.14; N, 27.92%; $C_{15}H_{21}N_7O_3$ requires C, 51.86; H, 6.09; N, 28.22%.

2-(N,N-Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-6-iodopteridin-4-one 11e: 6-Amino-2-(*N,N*-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-one **11d** (74 mg, 0.21 mmol), CH_2I_2 (2ml) and *n*-pentyl nitrite (freshly distilled) (0.25 ml, *ca.* 2.1 mmol) were purged with argon for 10 min then heated at 82 °C for 17 min with efficient stirring (during this time the suspended solid dissolved and a dark brown solution resulted). After cooling, volatile components were evaporated *in vacuo* and the remainder was applied directly to a silica gel coloumn. Elution, first with CH_2Cl_2, then with CH_2Cl_2:MeOH, 98:2 gave *2-(N,N-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-6-iodopteridin-4-one* **11e** (38 mg, 39%); mp (95% EtOH) 150-165 °C; δ_H (200 MHz, $CDCl_3$) 8.92 (2H, overlapping singlets, 2xC*H*), 6.35 (2H, s, CH_2), 3.26 (3H, s, NCH_3), 3.17 (3H, s, NCH_3), 1.16 (9H, s, $C(CH_3)_3$); *m/z* (CI) 459 (MH^+, 50%), 333 (45), 233 (15); found M^+ 458.0572; $C_{15}H_{19}N_6O_3I$ requires *M* 458.05651.

4-(2-(*N,N*-Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-on-6-yl)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one 6: 2-(*N,N*-Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-6-iodopteridin-4-one **11e** (32 mg, 0.07 mmol) and 4-(4*R*-2,2-dimethyl-1,3-dioxolan-4-yl)-5-tributylstannyl-1,3-dithiol-2-one **8** (36 mg, 0.07 mmol) were dissolved together in NMP (1.1 ml) with stirring and under argon. The mixture was cooled to ice-bath temperature and copper thiophene-2-carboxylate (CuTC) (20 mg, 0.105 mmol) was added. After 40 min of vigorous stirring further **8** (40 mg) and CuTC (36 mg) were added and stirring continued for 55 min. The reaction mixture was filtered through celite, followed by CH_2Cl_2 and combined filtrate and washings were concentrated *in vacuo* to give a brown oil which was purified by chromatography twice, eluting initially with CH_2Cl_2:MeOH, 97.5:2.5, then 94.5:5.5 to give a

fraction (16 mg) which contained a *ca.* 3:7 mixture (as judged by integration in the ^{1}H NMR spectrum) of unreacted iodide **11e** and *4-(2-(N,N-dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-pteridin-4-on-6-yl)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one* **6** (yield *ca.* 29%); δ_H (200 MHz, $CDCl_3$) (signals from residual starting material not given) 8.96 (1H, s, Me_2NCH), 8.69 (1H, s, pteridin-7-yl-*H*), 6.36 (2H, s, CH_2), 5.71 (1H, dd, J 5.6, 7, C*H*), 5.04 (1H, dd, J 7.1, 9.1, CH_2), 4.06 (1H, dd, J 5.4, 9.1, CH_2), 3.26 (3H, s, CH_3), 3.17 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.18 (9H, s, $C(CH_3)_3$); *m/z* (CI) 549 (MH^+, 60%), 491 (30), 459 (50), 367 (80), 333 (50), 187 (45), 100 (100); found M^+ 549.1596; $C_{23}H_{29}N_6O_6S_2$ requires *M* 549.1590.

2-(2,2-Dimethylpropanoylamino)-6-iodopteridin-4-one 12c: 6-Chloro-2-(2,2-dimethylpropanoylamino)-pteridin-4-one **12b** (0.61 g, 2.2 mmol), NaI (flame dried under vacuum immediately before use) (2.8 g) and camphorsulfonic acid (100 mg, 0.43 mmol) were suspended/dissolved in dry MeCN (20 ml) and the mixture heated at reflux under nitrogen with efficient stirring for 42 h. The solvent was evaporated *in vacuo* and the residue partitioned between sat. aq. NH_4Cl (20 ml) and CH_2Cl_2 (20 ml). The biphasic mixture was twice filtered through celite, the layers separated and the aq. phase twice re-extracted with CH_2Cl_2 (2x15 ml) the combined organic phases were washed with brine, dried and evaporated to give a solid which was further purified by chromatography, eluting with CH_2Cl_2:MeOH, 98:2, to give *2-(2,2-dimethylpropanoylamino)-6-iodopteridin-4-one* **12c** (193 mg, 24%), mp (95% EtOH) >280 °C; δ_H (200 MHz, $CDCl_3$) 12.42 (1H, bs, N-3–*H*), 8.99 (1H, s, pteridin-7-yl–H), 8.49 (1H, bs, N*H*), 1.37 (9H, s, $C(CH_3)_3$); *m/z* (CI) 374 (MH^+, 50%), 248 (35), 57 (100); found M^+ 373.0043; C, 36.52; H, 3.50; N, 18.68%; $C_{11}H_{12}N_5O_2I$ requires *M* 373.00375; C, 35.40; H, 3.24; N, 18.77%.

2-(2,2-Dimethylpropanoylamino)-3-(2,2-dimethylpropanoyloxymethyl)-6-iodopteridin-4-one 12d: 2-(2,2-Dimethylpropanoylamino)-6-iodopteridin-4-one **12c** (190 mg, 0.52 mmol), chloromethyl pivaloate (150 ml, 1.04 mmol) and K_2CO_3 (143 mg, 1.03 mmol) were stirred in dry DMF (2 ml) under nitrogen for 19 h, after which further chloromethyl pivaloate (80 ml, 0.55 mmol) was added and stirring continued for 24 h. The solvent was evaporated *in vacuo* and the resultant solid partitioned between CH_2Cl_2 (15 ml) and H_2O (15 ml). The aq. phase was separated, re-extracted with CH_2Cl_2, the organic phases were then washed with brine (10 ml), dried and evaporated *in vacuo* to give a solid, was further purified by chromatography, eluting with CH_2Cl_2:EtOAc, 98:2, to give *2-(2,2-dimethylpropanoylamino)-3-(2,2-dimethylpropanoyloxy-methyl)-6-iodopteridin-4-one* **12d** as a cream solid (71 mg, 29%), mp (EtOH) 205-212 °C; δ_H (200 MHz, $CDCl_3$) 8.99 (1H, s, pteridin-7-yl–H), 6.47 (2H, s, CH_2), 1.22 (9H, s, $C(CH_3)_3$), 1.19 (9H, s, $C(CH_3)_3$); minor peaks (~ 30% by integration) were evident at d_H 8.88 (1H, s, pteridin-7-yl–*H*), 6.26 (2H, s, CH_2) which we have assumed to be due to a regioisomerically alkylated derivative; *m/z* (CI) 488 (MH^+, 100%), 362 (25); found MH^+ 488.0807; C, 42.26; H, 4.63; N, 14.52%; $C_{17}H_{22}N_5O_4I$ requires *MH* 488.0797; C, 41.90; H, 4.55; N 14.37%.

4-(2-(2,2-Dimethylpropanoylamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-on-6-yl)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one 7: 2-(2,2-Dimethylpropanoylamino)-3-(2,2-dimethylpropanoyloxy-methyl)-6-iodopteridin-4-one **12d** (65 mg, 0.133 mmol) and 4-(4*R*-2,2-dimethyl-1,3-dioxolan-4-yl)-5-tributylstannyl-1,3-dithiol-2-one **8** (75 mg, 0.147 mmol) were dissolved together in NMP (2 ml) under argon, and the solution cooled to ice-bath temperature. CuTC (42 mg, 0.22 mmol) was added under a positive pressure of argon and the mixture vigorously stirred for 35 min, allowed to warm to rt and stirring maintained for a further 45 min. The mixture was diluted with CH_2Cl_2, filtered through alumina, the solvents removed *in vacuo* and the resultant oil purified by chromatography eluting with CH_2Cl_2:EtOAc, 98:2, to give some

4-(4*R*-2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one, unreacted **12d** (25 mg) and *4-(2-(2,2-dimethylpropanoylamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-on-6-yl)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dithiol-2-one* **7** (20 mg, 26%; 42% on the basis of recovered **12d**) as a brown solid, δ_H (200 MHz, $CDCl_3$) 8.64 (1H, s, pteridin-7-yl-*H*), 6.51 (2H, s, C*H*$_2$), 5.67 (1H, dd, J 5.3, 7.1, C*H*), 4.98 (1H, dd, J 7.1, 9.1, one of C*H*$_2$), 4.03 (1H, dd, J 5.3, 9.1, one of C*H*$_2$), 1.25 (9H, s, C(C*H*$_3$)$_3$), 1.19 (9H, s, C(C*H*$_3$)$_3$); ***m/z*** (CI) 578 (MH^+, 100%), 520 (30), 488 (35), 362 (15); found MH^+ 578.1735; $C_{25}H_{31}N_5O_7S_2$ requires *MH* 578.1743.

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