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Synthesis of 1,3-dithiol-2-ones as proligands related to molybdopterin

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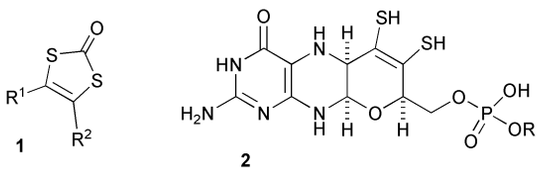
The reaction of suitably disubstituted alkynes with diisopropyl xanthogen disulfide gives differentially substituted 4,5-disubstituted-1,3-dithiol-2-ones as proligands for metal complexes related to the molybdenum cofactor.

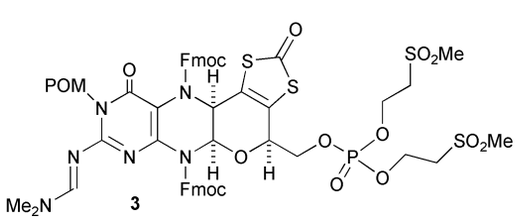
Introduction

We have described linear[1–4] and convergent[5,6] routes to differentially 4,5-disubstituted 1,3-dithiol-2-ones **1** (and -2-thione analogues) and shown how these can be used to form metal complexes[7–12] *via* hydrolytic release of the masked ene-1,2-dithiolate ligand from 1,3-dithiol-2-one. We have also demonstrated how appropriately substituted 1,3-dithiol-2-ones **1** can serve as key intermediates for the construction of tricyclic pyrano-quinoxalines, and complexes therefrom, which mimic[13,14] the structure of molybdopterin **2**, and we have constructed molybdopterin itself, in protected form and with the ene-dithiolate masked in this way, **3**.[15]



1

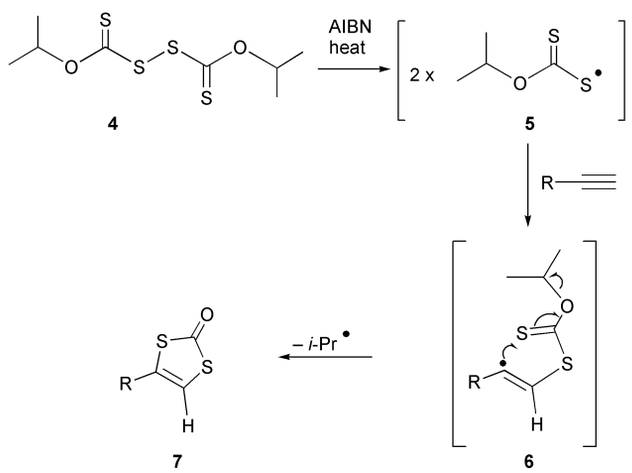
2
molybdopterin (MPT)



3

In the context of the synthesis of 1,3-dithiol-2-ones, key intermediates in our strategy for the construction of molybdopterin and its analogues, we were attracted to reports by Gareau[16,17] that the reaction of alkynes with diisopropyl xanthogen disulfide† **4** (and the corresponding dithiodiisopropyl xanthogen disulfide), in the presence of a radical initiator, leads directly to these five-membered heterocycles. Gareau proposed that homolytic cleavage of the S–S bond produces a radical **5** that adds to the alkyne, generating **6**, which cyclises with loss of an isopropyl radical (Scheme 1). At the time it seemed significant that *all* of the examples (12) given in the two papers involved terminal alkynes and thus led to mono-substituted 1,3-dithiol-2-ones **7**. Accordingly, we did not immediately investigate the method in the context of our molybdopterin research.

Later, Gareau reported[18] the successful application of his route to 1,3-dithiol-2-ones using *di*substituted alkynes, though yields were poorer, especially where the alkynes had carbonyl conjugation and/or bulky substituents.



4 **5** **6** **7**

Scheme 1

Based on Gareau's observations, there seemed to be two reasons why the process might not be suitable for our purposes: (1) the considerable size of alkyne substituents that would be required to generate relevant proligands, and (2) the presence of the imine unit of the quinoxaline/pteridine substituent that might act like a conjugated carbonyl group, and discourage reaction. Nevertheless, we have now examined five relevantly disubstituted alkynes, finding in each case a very useful, in some cases, high yielding, synthesis of 4,5-differentially disubstituted-1,3-dithiol-2-ones.

Taylor and co-workers were the first to describe the synthesis of 2-alkynylquinoxalines and 6-alkynylpteridines related to molybdopterin,[19] such as would be required for the application of the Gareau method for the assembly of proligands for molybdopterin and its analogues. In our previous studies we have also described the synthesis of various 2-alkynylquinoxalines[13,14,20,21] and 6-alkynylpteridines.[22,23]

Results and discussion

Synthesis of alkynes

The alkynes chosen for study were **8**–**10**,**11b**,**12b**. Full details of the synthesis of **8** by palladium(0)-catalysed coupling of 2-chloroquinoxaline with racemic but-3-yn-2-ol have been published.[14] We have previously described[4] a synthesis of the alkynyl-acetal **9** from 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline, but for the present work, it was made by coupling of 2-chloroquinoxaline with (4*R*)-4-ethynyl-2,2-dimethyl-1,3-dioxolane;[24] the analogous protected pteridine **10** was made in this way too, coupling to 6-chloro-2-(dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-one.[15]

† The IUPAC name for diisopropyl xanthogen disulfide is bis(isopropyloxythiocarbonyl) disulfide.

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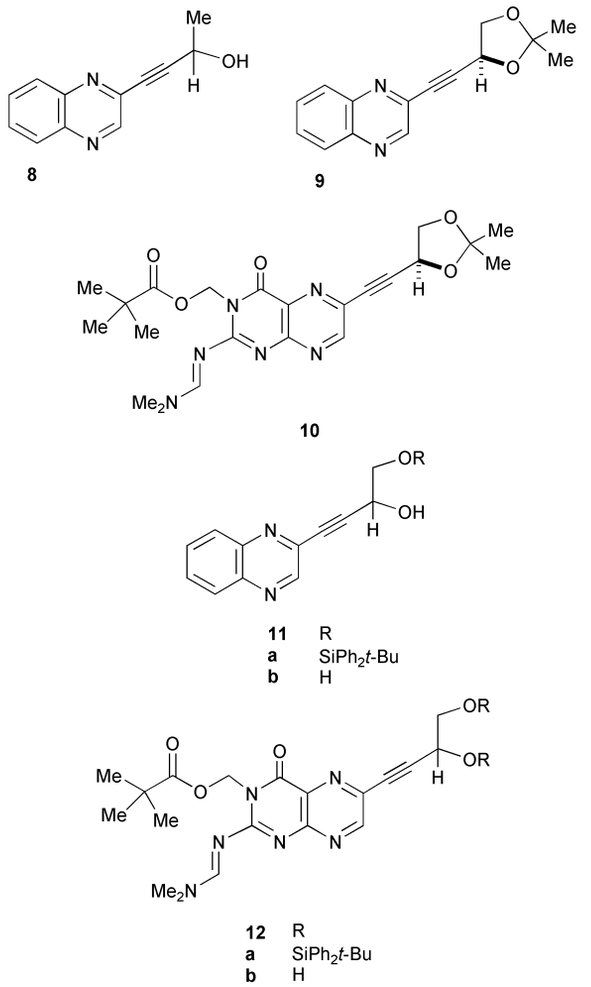
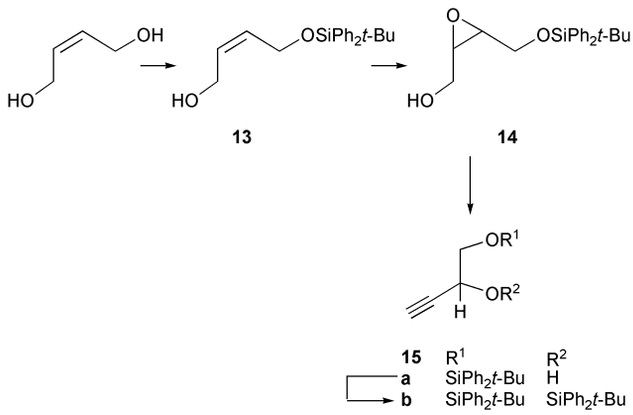
From other, previously unpublished work on an alternative route to such substances, the alkyne-diols **11b** and **12b** were available to us. Quinoxaline **11b** was made by coupling 2-chloroquinoxaline with 4-*tert*-butyldiphenylsiloxy-3-hydroxybut-1-yne, giving **11a**, followed by fluoride deprotection. Diol **12b** was prepared by coupling 6-chloro-2-(dimethylaminomethyleneamino-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-one [15] with 3,4-bis(*tert*-butyldiphenylsiloxy)but-1-yne, giving **12a**, followed by fluoride deprotection; in this much more polar pteridine series, the use of the doubly *O*-silylated C_4-alkyne-diol facilitated handling and isolation.



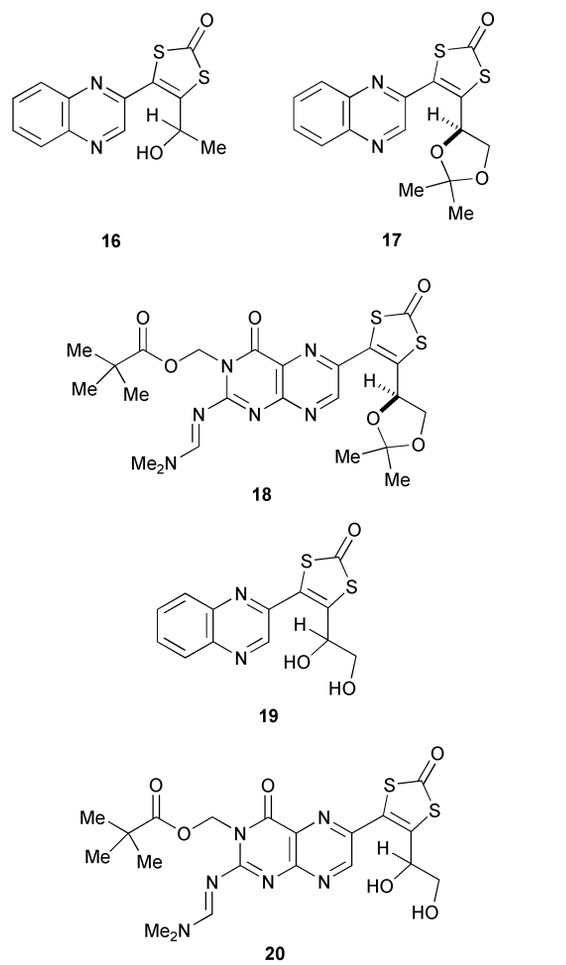
We found that the best route for the synthesis of the alkyne coupling partners started from commercially available (*Z*)-1,4-dihydroxybut-2-ene which was mono-protected by reaction with *tert*-butyldiphenylsilyl chloride giving **13**, the alkene was then epoxidised using *m*-chloroperbenzoic acid generating **14**, and then this was transformed [25] into the alkyne **15a** by treatment with *n*-butyllithium. Finally, the doubly silyl-protected alkyne **15b** was prepared by exposure again to *tert*-butyldiphenylsilyl chloride (Scheme 2).



Scheme 2

Synthesis of 1,3-dithiol-2-ones

Notwithstanding the reservations mentioned above, reaction of each of the alkynes **8**–**10**, **11b**, and **12b** with diisopropyl xanthogen disulfide **4**, initiated using AIBN, gave rise to 1,3-dithiol-2-ones, **16**–**20** respectively. The acetal protected substrates reacted in better yields (**17** (77%); **18** (61%)) than the alcohol **8** (41%) or the diols **11b** (30%) and **12b** (20%). We have previously shown [14,15] that it is easy to remove the acetal protection from **17** and **18**, revealing diols, **19** and **20**, and thus clearly the method of choice for the synthesis of these substances involves the formation of **17** and **18**, then acetal hydrolysis.



Given the relative efficiency of the alkyne coupling procedure and the directness of this approach (*e.g.* the synthesis of a 6-iodopterin, as was previously required,[15] is not necessary), this route now proves to be the strategy of choice to the key 1,3-dithiol-2-one intermediates **17** and **18** in our route to molybdopterin and pteridine and quinoxaline analogues thereof.

We shall be reporting on the use of this method for the synthesis of suitably modified analogues which will be designed to cast light on the mode of action of the cofactor of the oxomolybdoenzymes.

Experimental

General

Organic solutions were dried over anhydrous $MgSO_4$. Solid products were dried under reduced pressure using P_4O_{10} as a desiccant. Proton nuclear magnetic resonance (^{1}H NMR)

spectra were recorded on Inova-300 Athos (300 MHz) and Unity 500 (500 MHz) spectrometers. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on an Inova-300 Athos spectrometer running at 75 MHz. All chemical shifts (δ) are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). Signal splittings are reported as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), multiplet (m), and broad (br); J values are given in Hertz (Hz). UV spectra were recorded on a Hewlett Packard 8452A diode array spectrophotometer and are given in nm. IR spectra were recorded on an Ati Mattson Genesis Series FTIR spectrometer; only absorptions of importance to structure determination are listed. Mass spectra were recorded on a Fisons VG Trio 2000 (EI/CI{NH_3}/ES) (abundance relative to the base peak is given in parentheses as a percentage; only fragment ions of intensity >10% of the base peak are cited), and a Concept IS (MM/FAB) spectrometer for accurate mass determinations. Melting points were recorded on a Reichart heated stage microscope and are uncorrected. Flash column chromatography was carried out using Merck 9385 silica gel 60 (230–400 mesh). Acetonitrile, dichloromethane, and triethylamine were distilled from calcium hydride. Petroleum ether was the fraction bp 40–60 °C.

(*R*)-(+)-4-Ethynyl-2,2-dimethyl-1,3-dioxolane[24]

To a stirred solution of freshly prepared (+)-2,3-*O*-isopropylidene-D-glyceraldehyde[26] (5.0 g, 38.4 mmol) and the Bestmann–Ohira reagent (7.38 g, 38.4 mmol, prepared according to the modified method of Callant *et al.*[27] using *p*-acetamidobenzenesulfonyl azide[28] as the diazo transfer reagent) in methanol (250 ml) at 0 °C was added K_2CO_3 (7.1 g, 51.2 mmol) portionwise over 30 min. The resulting mixture was stirred for a further 18 h then a solution of saturated aqueous NH_4Cl (250 ml) was added and the aqueous layer was extracted with pentane (3 × 750 ml). The combined organic layers were dried ($MgSO_4$) and the solvent concentrated very carefully at reduced pressure (care!—product is quite volatile). Purification by flash chromatography (silica, 5⟶10% Et_2O in pentane) provided the alkyne (2.66 g, 55%) as a colourless oil with spectroscopic data consistent with the published data.[24]

1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(quinoxalin-2-yl)ethyne 9

To a degassed solution of 2-chloroquinoxaline (2.27 g, 13.7 mmol), (*R*)-(+)-4-ethynyl-2,2-dimethyl-1,3-dioxolane (1.81 g, 14.4 mmol) and Et_3N (15 ml) in MeCN (35 ml), was added $Pd(OAc)_2$ (155 mg, 0.69 mmol), Ph_3P (362 mg, 1.38 mmol) and CuI (263 mg, 1.38 mmol) and the resulting mixture stirred for 18 h then refluxed for 2 h. On cooling, the mixture was concentrated and the residue partitioned between water (50 ml) and CH_2Cl_2 (100 ml). The mixture was filtered through Celite to break the emulsion, the layers separated and the aqueous layer re-extracted with CH_2Cl_2 (2 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (silica, 10⟶20% EtOAc in petroleum ether) provided **9** (2.61 g, 75%) as a yellow oil, with physical and spectroscopic data identical to those reported previously.[14]

1-[2-(Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-4-oxopteridin-6-yl]-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyne 10

To a degassed solution of 6-chloro-2-(dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-pteridin-4-one[15] (2.17 g, 5.92 mmol), (4*R*)-(+)-4-ethynyl-2,2-dimethyl-1,3-dioxolane (1.12 g, 8.88 mmol) and Et_3N (15 ml) in MeCN (50 ml), was added $Pd(OAc)_2$ (60 mg, 0.30 mmol), Ph_3P (155 mg, 0.59 mmol) and CuI (113 mg, 0.59 mmol) and the resulting mixture stirred at rt for 18 h then refluxed for 2 h. On cooling, the mixture was concentrated and the residue partitioned between water (50 ml) and CH_2Cl_2 (150 ml). The mixture was filtered through Celite to break the emulsion, the layers separated and the aqueous layer re-extracted with CH_2Cl_2 (2 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (silica, 1⟶2% MeOH in CH_2Cl_2) provided **10** (1.76 g, 65%) as a yellow solid, mp 186 °C (dec.); ν_{max}(film)/cm^{-1} 2983, 2934, 2875, 1731, 1705, 1634, 1527, 1448, 1423, 1393, 1368, 1330, 1144, 1115, 1061; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (1H, s, H-7′), 8.78 (1H, s, C*H*NMe$_2$), 6.38 (2H, s, NCH_2OCO*t*-Bu), 4.98 (1H, t, J = 6.3 Hz, C*H*O), 4.25 (1H, dd, J = 6.6, 8.1, one of CH_2O), 4.08 (1H, dd, J = 6.3, 8.1, one of CH_2O), 3.25 (3H, s, NCH_3), 3.08 (3H, s, NCH_3), 1.55 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.08 (9H, s, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 161.2, 159.7, 157.8, 153.8, 153.1, 135.0, 130.2, 111.0, 90.8, 82.5, 69.9, 66.1, 66.0, 42.0, 39.0, 36.0, 27.2, 26.4, 26.1; *m*/*z* (CI) 457 (MH$^+$, 100%), 391 (40), 279 (20); found C, 57.65; H, 6.01, N, 18.54%; M + H$^+$ 456.2121. $C_{22}H_{28}N_6O_5$ requires C, 57.88; H, 6.18, N, 18.41%, M (+ H) 456.2121.

(*Z*)-4-*tert*-Butyldiphenylsiloxy-1-hydroxybut-2-ene 13

To a stirred solution of (*Z*)-1,4-dihydroxybut-2-ene (192 g, 2.18 mol), DMAP (1.33 g, 0.012 mol) and Et_3N (30 ml) in dry CH_2Cl_2 (300 ml) at 25 °C, was added *tert*-butyldiphenylsilyl chloride (30 g, 0.11 mol) over 30 min. After 6 h water (200 ml) was added and the organic layer separated, the aqueous layer was then extracted with CH_2Cl_2 (2 × 100 ml). The combined organic extracts were washed with 12% citric acid solution (100 ml), brine (100 ml), dried ($MgSO_4$) and the solvent was evaporated. Purification by flash chromatography (silica, 5⟶10% EtOAc in petroleum ether) provided **13** (35.6 g, 99%) as a colourless oil; λ_{max}($CHCl_3$)/nm 226, 266; ν_{max}(film)/cm^{-1} 3331, 3070, 3049, 3024, 2957, 2931, 2891, 2857, 1690, 1589, 1471, 1428, 1390, 1361, 1188, 1109, 1079, 823; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (4H, m, Ar*H*), 7.46 (6H, m, Ar*H*), 5.75 (2H, m, H-2 and H-3), 4.35 (2H, d, J = 5.5 Hz, H-4), 4.08 (2H, d, J = 6.9 Hz, H-1), 2.25 (1H, br s, O*H*), 1.15 (9H, s, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.9, 133.4, 130.7, 130.0, 129.8, 127.9, 127.7, 60.2, 58.5, 26.8, 19.1; *m*/*z* (CI) 327 (MH$^+$, 100%) 196 (40); found MH$^+$, 327.1784. $C_{20}H_{26}O_2Si$ requires M (+ H) 327.1780. The spectroscopic data were exactly comparable with those reported for this compound prepared previously from the diol using *n*-butyllithium in THF at −78 °C[29] or subsequently using sodium hydride in ether at room temperature.[30]

3-Hydroxymethyl-2-*tert*-butyldiphenylsilyloxymethyloxirane 14

To a stirred solution of *m*-chloroperbenzoic acid (52.5 g, 0.15 mol) in CH_2Cl_2 (250 ml) was added a solution of alkene **13** (35 g, 0.11 mol) in CH_2Cl_2 (100 ml) over 0.5 h. After 36 h the solution was cooled to 0 °C, precipitating *m*-chlorobenzoic acid, which was removed by filtration. Water was added, the organic layer separated and washed with aqueous Na_2SO_3 (2 × 350 ml), aqueous $NaHCO_3$ (3 × 350 ml), brine (300 ml), dried ($MgSO_4$) and the solvent evaporated. Purification by flash chromatography (silica, 10% EtOAc in petroleum ether) provided epoxide **14** (36.72 g, 100%) as a colourless oil; λ_{max}($CHCl_3$)/nm 214, 226, 266; ν_{max}(film)/cm^{-1} 3426, 3070, 3048, 3012, 2996, 2954, 2933, 2892, 2859, 1589, 1471, 1428, 1391, 1361, 1260, 1188, 1109, 1091, 1046, 975, 937; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (4H, m, Ar*H*), 7.45 (6H, m, Ar*H*), 4.0–3.75 (4H, m, H-2,3 and CH_2OH), 3.28 (2H, m, CH_2OSi), 1.92 (1H, br s, O*H*), 1.1 (9H, s, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 135.4, 132.9, 132.7, 129.9, 127.8, 62.2, 60.7, 56.3, 56.1, 26.7, 19.1; *m*/*z* (CI) 360 (MNH$^+$, 100%) 343 (MH$^+$, 50%); found MNH_4^+ 360.1991. $C_{20}H_{26}O_3Si$ + NH_4^+ requires 360.1995. The spectroscopic data were exactly comparable with those reported

previously[29] for this compound prepared in homochiral form using Sharpless' method.

3-Hydroxy-4-*tert*-butyldiphenylsiloxybut-1-yne 15a

To a stirred solution of **14** (12 g, 0.033 mol) in THF (150 ml) at −78 °C was added a solution of *n*-BuLi (62.5 ml, 0.10 mol) over 0.5 h. After 1 h the solution was warmed to room temperature and a solution of sat. aq. NH_4Cl (150 ml) was added. The organic layer was separated and the aqueous layer re-extracted with Et_2O (2 × 100 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$) and the solvent evaporated. Purification by flash chromatography (silica, 5⟶10% EtOAc in petroleum ether) provided alkyne **15a** (8.13 g, 76%) as a colourless oil; $\lambda_{max}(CH_2Cl_2)$/nm 266; ν_{max}(film)/cm^{-1} 3560, 3422, 3291, 3071, 3050, 2957, 2931, 2890, 2859, 1472, 1428, 1132, 1020, 938, 823; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (4H, m, Ar*H*), 7.34 (6H, m, Ar*H*), 4.4 (1H, m, H-3), 3.7 (2H, m, CH_2OSi), 2.58 (1H, d, *J* = 5.6 Hz, O*H*), 2.35 (1H, d, *J* = 2.19 Hz, H-1), 1.1 (9H, s, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 135.6, 135.5, 132.8, 132.7, 129.9, 127.8, 82.1 73.6, 67.3, 62.9, 26.9, 26.8, 19.3; *m*/*z* (CI) 342 (MNH_4^+, 100%), 325 (MH^+, 5%); found MNH_4^+ 342.1893. $C_{20}H_{24}O_2Si$ (+ NH_4) requires *M* 342.1889. The spectroscopic data were exactly comparable with those reported previously for this compound prepared by mono-silylation of the corresponding diol.[31]

3,4-Bis(*tert*-butyldiphenylsiloxy)but-1-yne 15b

To a stirred solution of alcohol **15a** (3 g, 9.26 mmol), DMAP (113 mg, 0.926 mol) and Et_3N (5 ml) at 25 °C in dry CH_2Cl_2 (20 ml), was added *tert*-butyldiphenylsilyl chloride (3.31 g, 12.0 mmol). After 24 h, water (20 ml) was added and the organic layer separated, the aqueous layer was then extracted with CH_2Cl_2 (2 × 20 ml). The combined organic extracts were washed with 12% citric acid solution (30 ml), brine (30 ml), dried ($MgSO_4$) and the solvent was evaporated. Purification by flash chromatography (silica, 2.5⟶5% EtOAc in petroleum ether) provided **15b** (5.15 g, 99%) as a white crystalline solid, mp 83–84 °C (previously prepared in 5% yield as a byproduct in a preparation of 3-hydroxy-4-*tert*-butyldiphenylsiloxybut-1-yne **15a** by silylation of the corresponding diol[31]); $\lambda_{max}(CHCl_3)$/nm 242, 262; ν_{max}(film)/cm^{-1} 3306, 3071, 3050, 2957, 2931, 2891, 2858, 1472, 1428,1112, 962, 823; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (8H, m, Ar*H*), 7.4 (12H, m, Ar*H*), 4.56 (1H, m, H-3), 3.8 (2H, m, H-4), 2.28 (1H, d, *J* = 2.1 Hz, H-1), 1.14 (9H, s, *t*-Bu), 1.07 (9H, s, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 135.8, 135.6, 135.5, 133.4, 133.3, 129.6, 127.6, 127.5, 127.4, 83.0, 73.4, 68.1, 65.0, 26.9, 26.7, 19.3, 19.2; *m*/*z* (CI) 580 (MNH_4^+, 30%), 485 (15), 267 (100); found C, 76.92; H, 7.76%; MNH_4^+ 580.3077. $C_{36}H_{42}O_2Si_2$ requires C, 76.82; H, 7.76%; *M* (+ NH_4) 580.3067.

1-(Quinoxalin-2-yl)-3-hydroxy-4-*tert*-butyldiphenylsiloxybut-1-yne 11a

To a degassed solution of 2-chloroquinoxaline (0.77 g, 4.66 mmol), alkyne **15a** (1.78 g, 4.23 mmol) and Et_3N (5 ml) in MeCN (10 ml), was added $Pd(OAc)_2$ (47 mg, 0.21 mmol), Ph_3P (111 mg, 0.423 mmol) and CuI (80 mg, 0.42 mmol). The resulting mixture was refluxed for 2 h, cooled to 25 °C and concentrated *in vacuo*. The residue was partitioned between water (50 ml) and EtOAc (50 ml), the layers separated and the aqueous layer extracted with EtOAc (2 × 50 ml). The combined organic extracts were washed with brine (75 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, 5⟶10% EtOAc in petroleum ether) provided **11a** (1.40 g, 73%) as a coloured oil; $\lambda_{max}(CHCl_3)$/nm 256, 334; ν_{max}(film)/cm^{-1} 3329, 2956, 2930, 2888, 2857, 1541, 1487, 1471, 1427, 1364, 1295, 1216, 1114, 824; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (1H, s, H-3′), 8.08 (2H, m, Ar*H*), 7.74 (6H, m, Ar*H*), 7.36 (6H, m, Ar*H*), 4.90 (1H, t, *J* = 5.4 Hz, H-3), 4.22 (1H, br s, O*H*), 4.05 (2H, m, H-4) 1.14 (9H, s, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 141.9, 140.8, 138.7, 135.6, 135.5, 132.8, 130.7, 130.6, 129.9, 129.0, 127.8, 92.9, 82.7, 77.6, 77.2, 76.8, 67.3, 63.6, 26.8, 19.3; *m*/*z* (CI) 453 (MH^+, 70%); found M^+ 452.1919. $C_{28}H_{28}N_2O_2Si$ requires *M* 452.1919.

1-(Quinoxalin-2-yl)-3,4-dihydroxybut-1-yne 11b

To a stirred solution of quinoxaline **11a** (0.5 g, 1.11 mmol) in THF (10 ml) at 0 °C was added HF–pyridine (7 : 3, 3 ml). The mixture was then allowed to warm to room temperature. After 2 h the solution was diluted with water (20 ml) and the resulting mixture neutralised by the addition of solid $NaHCO_3$. CH_2Cl_2 (50 ml) was added, the layers separated, and the aqueous layer re-extracted with CH_2Cl_2 (2 × 50 ml), the organic layer was washed with brine (30 ml), dried and concentrated. Purification by flash chromatography (silica, 0⟶2⟶5⟶8% MeOH in EtOAc) provided **11b** (152 mg, 64%) as a white solid, mp >230 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.95 (1H, s, H-3′), 8.1 (1H, m, Ar*H*), 8.04 (1H, m, Ar*H*), 7.88 (2H, m, Ar*H*), 4.7 (1H, dd, *J* = 5.5, 6.3 Hz, H-3), 3.82 (2H, m, H-4); *m*/*z* (CI) 215 (MH^+, 15%); found MH^+ 215.0822. $C_{12}H_{10}N_2O_2$ requires *M* + H 215.0820.

1-[2-(Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-4-oxopteridin-6-yl]-3,4-bis(*tert*-butyldiphenylsiloxy)but-1-yne 12a

To a degassed solution of 6-chloro-2-(dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)pteridin-4-one[15] (1.0 g, 2.73 mmol), alkyne **15b** (2.34 g, 4.10 mol) and Et_3N (7 ml) in MeCN (30 ml), was added $Pd(OAc)_2$ (31 mg, 0.14 mmol), Ph_3P (72 mg, 0.27 mmol) and CuI (52 mg, 0.27 mmol) and the resulting mixture refluxed for 2 h. On cooling, the mixture was concentrated and the residue partitioned between water (50 ml) and EtOAc (50 ml). The layers were separated and the aqueous layer re-extracted with EtOAc (2 × 25 ml). The combined organic fractions were washed with brine (25 ml), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (silica, 30⟶50⟶100% EtOAc in petroleum ether) provided **12a** (1.95 g, 80%) as a yellow foam; $\lambda_{max}(CHCl_3)$/nm 256, 332, 374; ν_{max}(film)/cm^{-1} 2960, 2932, 2859, 1732, 1705, 1634, 1525, 1424, 1365, 1332, 1113, 755; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (1H, s, H-7′), 8.12 (1H, s, C*H*NMe_2), 7.75 (8H, m, Ar*H*), 7.38 (12H, m, Ar*H*), 7.4 (8H, m, Ar*H*), 6.38 (2H, s, NCH_2OC*O*t-Bu), 4.84 (1H, m, H-3), 3.91 (2H, m, H-4), 3.25 (3H, s, NCH_3), 3.17 (3H, s, NCH_3), 1.17 (9H, s, *t*-Bu), 1.13 (9H, s, *t*-Bu), 1.08 (9H, s, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 160.8, 159.2, 157.3, 153.1, 152.8, 136.1, 135.8, 135.5, 135.2, 133.5, 133.1, 133.0, 129.7, 129.6, 127.6, 127.4, 92.6, 82.5, 68.0, 65.8, 65.6, 41.6, 38.8, 35.6, 27.0, 26.8, 26.7, 19.1, 19.2, 15.1; *m*/*z* (ES+) 892 (M^+, 100%).

1-[2-(Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-4-oxopteridin-6-yl]-3,4-dihydroxybut-1-yne 12b

To a stirred solution of pteridine **12a** (1.5 g, 1.68 mmol) in THF (30 ml) at 0 °C was added TBAF (0.97 ml of a 1.0 M solution of 5% H_2O in THF). The mixture was then allowed to warm to room temperature. After 5 h the solution was diluted with EtOAc (100 ml) and water (50 ml), the layers separated, the organic layer washed with brine (50 ml), dried and concentrated. Purification by flash chromatography (silica, 0⟶2⟶5⟶10% MeOH in EtOAc) provided **12b** (531 mg, 76%) as a yellow solid, mp >230 °C; $\lambda_{max}(CHCl_3)$/nm 256, 334, 376; ν_{max}(film)/cm^{-1} 3343, 2930, 1731, 1704, 1638, 1518, 1361, 1326, 1145, 1114; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (1H, s, H-7′), 8.72 (1H, s, C*H*NMe_2), 6.27 (2H, s, NCH_2OC*O*t-Bu), 4.73 (1H, t, *J* = 5.5 Hz, H-3), 3.83 (2H, m, H-4), 3.19 (3H, s, NCH_3), 3.10

(3H, s, NCH_3), 1.08 (9H, s, *t*-Bu); *m*/*z* (CI) 417 (MH^+, 80%); found MH^+ 417.1886. $C_{19}H_{24}N_6O_5$ requires *M* (+ H) 417.1886.

4-(1-Hydroxyethyl)-5-(quinoxalin-2-yl)-1,3-dithiol-2-one 16

Alcohol **8** (2.0 g, 0.01 mol), disulfide **4** (3.0 g, 11 mmol), and AIBN (0.75 g, 4.55 mmol) in toluene (1 ml) were heated to reflux for 6 h. The cooled mixture was purified directly by flash chromatography (silica, 0⟶5⟶10% EtOAc in CH_2Cl_2) giving the 1,3-dithiol-2-one **16** (320 mg, 41%) as a yellow crystalline solid, with physical and spectroscopic data identical to those reported previously.[14]

4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-5-(quinoxalin-2-yl)-1,3-dithiol-2-one 17

Protected diol **9** (331 mg, 1.30 mmol), disulfide **4** (267 mg, 1.63 mmol), and AIBN (702 mg, 2.6 mmol) in toluene (0.6 ml) were heated at reflux for 1.5 h then further portions of disulfide **4** (267 mg, 1.63 mmol), and AIBN (702 mg, 2.6 mmol) were added and the resulting mixture refluxed for a further 1.5 h. The cooled mixture was purified directly by flash chromatography (silica, 20% EtOAc in petroleum ether) giving **17** (347 mg, 77%) as a yellow crystalline solid, with physical and spectroscopic data identical to those reported previously.[4,14]

5-[2-(Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-4-oxopteridin-6-yl]-4-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-dithiol-2-one 18

To a solution of protected diol **10** (200 mg, 0.44 mmol) in chlorobenzene (0.25 ml) (NOTE—strong heating was necessary to achieve solution) was added disulfide **4** (474 mg, 1.75 mmol), and AIBN (180 mg, 1.11 mmol). The resulting mixture was heated at reflux for 2 h after which further portions of disulfide **4** (474 mg, 1.75 mmol), and AIBN (180 mg, 1.11 mmol) were added and the refluxing continued for a further 2 h. The cooled mixture was purified directly by flash chromatography (silica, 1⟶2% MeOH in CH_2Cl_2) giving **18** (146 mg, 61%) as a yellow solid, with physical and spectroscopic data identical to those reported previously.[15]

5-(Quinoxalin-2-yl)-4-(1,2-dihydroxyethyl)-1,3-dithiol-2-one 19

A mixture of diol **11b** (2.0 g, 0.01 mol), disulfide **4** (3.0 g, 0.011 mol), and AIBN (0.75 g, 4.55 mmol) in toluene (1 ml) was heated to reflux for 6 h. The cooled mixture was purified directly by flash chromatography (silica, 0⟶5⟶10% EtOAc in CH_2Cl_2) giving **19** (234 mg, 30%) as a yellow solid. All spectroscopic data were identical to those previously reported.[14]

5-[2-(Dimethylaminomethyleneamino)-3-(2,2-dimethylpropanoyloxymethyl)-4-oxopteridin-6-yl]-4-(1,2-dihydroxyethyl)-1,3-dithiol-2-one 20

Diol **12b** (30 mg, 0.072 mmol), disulfide **4** (21.4 mg, 0.079 mmol), AIBN (5.32 mg, 0.032 mmol) in toluene (0.1 ml) were heated to reflux for 6 h. The cooled mixture was purified directly by flash chromatography (silica, 0⟶2⟶5% EtOAc in CH_2Cl_2) giving **20** (7 mg, 20%) as a yellow crystalline solid with spectroscopic data identical to those reported previously.[15]

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References

1 D. J. Rowe, C. D. Garner and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1907.
2 L. Larsen, D. J. Rowe, C. D. Garner and J. A. Joule, *Tetrahedron Lett.*, 1988, **29**, 1453.
3 L. Larsen, C. D. Garner and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2311.
4 L. Larsen, D. J. Rowe, C. D. Garner and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2317.
5 A. Dinsmore, C. D. Garner and J. A. Joule, *Tetrahedron*, 1998, **54**, 3291.
6 A. Dinsmore, C. D. Garner and J. A. Joule, *Tetrahedron*, 1998, **54**, 9559.
7 S. Boyde, C. D. Garner, J. A. Joule and D. J. Rowe, *J. Chem. Soc., Chem. Commun.*, 1987, 800.
8 E. M. Armstrong, M. S. Austerberry, J. H. Birks, R. L. Beddoes, M. Helliwell, J. A. Joule and C. D. Garner, *Heterocycles*, 1993, **35**, 563.
9 R. L. Beddoes, A. Dinsmore, C. D. Garner and J. A. Joule, *Acta Crystallogr., Sect. C*, 1997, **53**, 213.
10 A. Dinsmore, J. H. Birks, C. D. Garner and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1997, 801.
11 E. S. Davies, R. L. Beddoes, D. Collison, A. Dinsmore, A. Docrat, J. A. Joule, C. R. Wilson and C. D. Garner, *J. Chem. Soc., Dalton Trans.*, 1997, 3985.
12 E. S. Davies, G. M. Aston, R. L. Beddoes, D. Collison, A. Dinsmore, A. Docrat, J. A. Joule, C. R. Wilson and C. D. Garner, *J. Chem. Soc., Dalton Trans.*, 1998, 3647.
13 B. Bradshaw, A. Dinsmore, C. D. Garner and J. A. Joule, *Chem. Commun.*, 1998, 417.
14 B. Bradshaw, A. Dinsmore, D. Collison, C. D. Garner and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3232.
15 B. Bradshaw, A. Dinsmore, D. Collison, C. D. Garner and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3239.
16 Y. Gareau, *J. Chem. Soc., Chem. Commun.*, 1995, 1429.
17 Y. Gareau and A. Beauchemin, *Phosphorus, Sulfur, Silicon*, 1997, **120&121**, 393.
18 Y. Gareau and A. Beauchemin, *Heterocycles*, 1998, **48**, 2003.
19 (*a*) E. C. Taylor, P. S. Roy, I. Darwish, J. L. Johnson and K. V. Rajagopalan, *J. Am. Chem. Soc.*, 1989, **111**, 285; (*b*) R. C. Pilato, K. A. Eriksen, M. A. Greaney, E. I. Stiefel, S. Goswami, L. Kilpatrick, T. G. Spiro, E. C. Taylor and A. L. Rheingold, *J. Am. Chem. Soc.*, 1991, **113**, 9372.
20 M. Armengol and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 2001, 154.
21 M. Armengol and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 2001, 978.
22 J. R. Russell, C. D. Garner and J. A. Joule, *Tetrahedron Lett.*, 1992, **33**, 3371.
23 J. R. Russell, C. D. Garner and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1245.
24 J. Pietruszka and A. Witt, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4293.
25 S. Takano, K. Samizu, T. Sugihara and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1989, 1344.
26 D. Y. Jackson, *Synth. Commun.*, 1988, **18**, 337.
27 P. Callant, L. D'Haenens and M. Vandewalle, *Synth. Commun.*, 1984, **14**, 155.
28 D. G. Brown, E. J. Velthuisen, J. R. Commerford, R. G. Brisbois and T. R. Hoye, *J. Org. Chem.*, 1996, **61**, 2540.
29 W. R. Roush, J. A. Straub and M. S. VanNieuwenhze, *J. Org. Chem.*, 1991, **56**, 1636.
30 D. Crich, M. A. de la Mora and R. Cuz, *Tetrahedron*, 2002, **58**, 35.
31 O. W. Gooding, C. C. Beard, D. Y. Jackson, D. L. Wren and G. F. Cooper, *J. Org. Chem.*, 1991, **56**, 1083.