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Model Studies Related to the Cofactor of the Oxomolybdoenzymes Part 5.[1] Synthesis of 6-Alkenyl- and 6-Alkynylpterins

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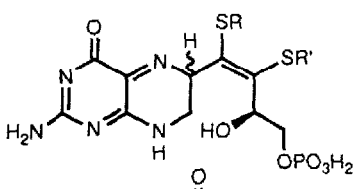
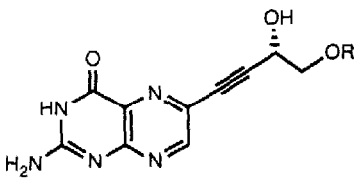
Key Words: Moco; molybdopterin; Wittig strategy; (Dephospho) Form A

Abstract: 6-Alkenylpterin (**6**) was prepared from pteridine (**3a**) and (*R*)-glyceraldehyde acetonide *via* a Wittig condensation. Treatment of **6** with bromine and then diazabicycloundecane (DBU) produced the corresponding alkyne (**8**).



Moco (**1a**) R,R' = Mo(=O)(=S/O)



Form A (**2a**) R = PO_3H_2

Molybdopterin (**1b**) R = R' = H

(Dephospho) Form A (**2b**) R = H

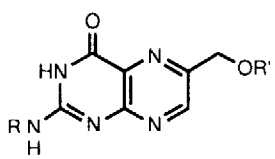
All the oxomolybdoenzymes except nitrogenase, including xanthine oxidase, aldehyde oxidase, sulphite oxidase, and nitrate reductase, contain a common, molybdenum-containing cofactor, known as Moco. Moco is extremely unstable, has not been isolated, so most of the evidence for its structure has come from identifications of fully aromatic pteridines, believed to be oxidative degradation products. Coupled with spectroscopic and other evidence it has been proposed that Moco comprises a reduced pterin linked to a side chain carrying sulphurs which coordinate molybdenum. There is evidence that in Moco itself the pyrazine ring of the pterin is in a reduced state, earlier views being that it is at a tetrahydro-level but the most recent work suggesting that molybdopterin is a dihydropterin, has a quinonoid tautomeric form, and that therefore partial structure (**1a**) represents Moco.[2]

In order to continue our synthetic studies[1] aimed ultimately at a synthesis of Moco, we required a preparation of 6-substituted pterins in which the substituent had the potential for transformation into the ene-1,2-dithiol-containing, reduced pterin moiety known as molybdopterin (**1b**). It seemed to us that an obvious

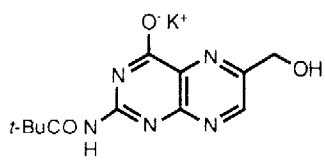
approach to dihydropterins of this type could utilise the readily accessible ester-amide (**3a**),[1] obtainable *via* degradation of folic acid. Selective *O*-deprotection was required to allow manipulation of the side chain, while at the same time retaining the pivalamide unit which Taylor showed to convey highly desirable solubilising properties.[3] The 6-substituent was to be extended into a but-1-enyl side chain *via* conversion into a phosphonium salt or phosphonate then Wittig reaction with (*R*)-glyceraldehyde acetonide as the key step. Our earlier quinoxaline studies[4] have shown that 6-alkenylquinoxalines can be used as precursors of 4-quinoxalinyl-1,3-dithiole-2-thiones and-1,3-dithiolane-2-thiones, which, in turn, we have used in the synthesis of ene-1,2-dithiolate-containing complexes such as cyclopentadienyl-1-(quinoxalin-2-yl)ethene-1,2-dithiolato-cobalt (III).[5] Since alkynyl-quinoxalines and -pterins have also been used by Taylor and Steifel[6] and by Burgmayer[7] as direct precursors of Mo(IV)ene-1,2-dithiolates of the type $(C_5H_5)_2MoS_2C_2[\{CO\}Me]R$ (where R = quinoxalin-2-yl or 2-pivaloylamino-4-oxo-3*H*-pteridin-6-yl) it was also relevant to examine the possibility of conversion of alkenyl-pteridines into alkynyl-pteridines.

In this Letter we report the synthesis of alkene (**6**) and its use in the preparation of the but-1-yne-3,4-diol (**2b**) which is the dephosphorylated version of the Moco degradation product Form A (**2a**). This report is prompted by Taylor's recent description of syntheses of (dephospho) Form A in racemic[8] and homochiral[9] forms *via* palladium catalysed coupling reactions of 6-chloropterin and butyne derivatives. We also show that alkene (**6**) can be transformed into alkyne (**8**).

Since 2-pivaloylpterins have been shown to undergo amide hydrolysis under acidic conditions,[10] and since it is generally observed that hydrolysis of esters, under basic conditions, is more rapid than that of amides, the required selective deprotection of the ester group in (**3a**) was addressed by examining basic hydrolytic conditions. Ester-amide (**3a**) reacted with NH_3/MeOH or Amberlyst® 15/MeOH to produce, to our surprise only ester (**3c**),[11] in 76 and 71% yields, respectively. However, methanolysis with K_2CO_3/MeOH did bring about selective ester cleavage to give the alcohol (**3b**), which was characterised[11] as its potassium salt (**4**) (42%); this in turn was readily converted into the mesylate (**3d**)[11] (72%) using Et_3N/MesCl/CH_2Cl_2/0°C.



3a R = *t*-BuCO, R' = CO-*t*-Bu
3b R = *t*-BuCO, R' = H
3c R = H, R' = CO-*t*-Bu
3d R = *t*-BuCO, R' = Mes



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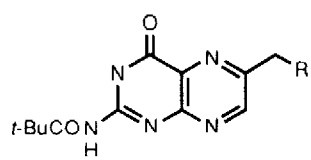
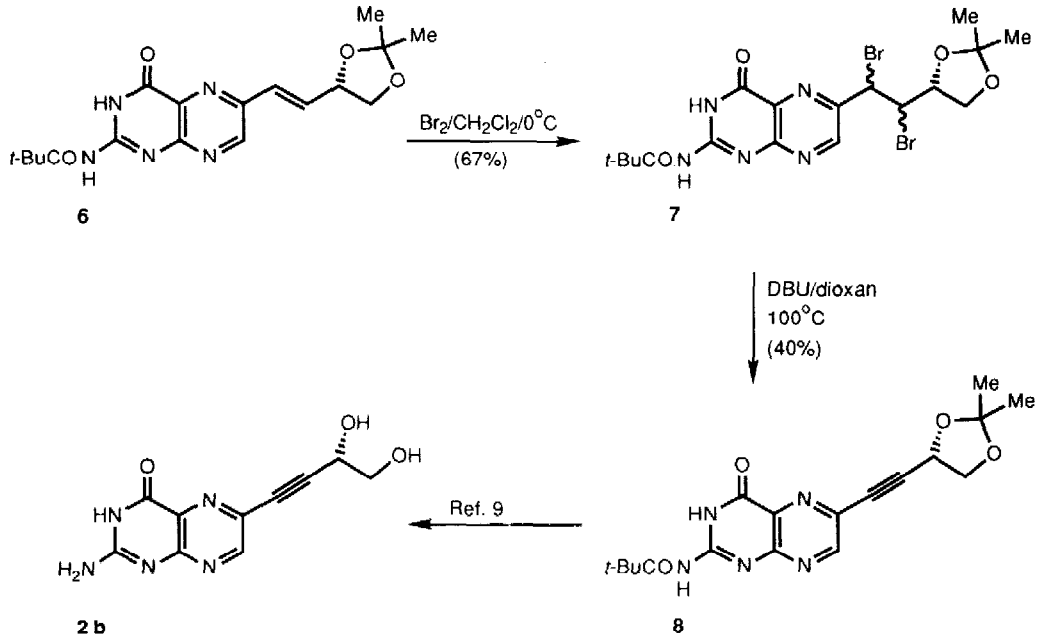


5a R = Br
5b R = $\overset{+}{P}Ph_3$ MesO$^-$
5c R = $\overset{+}{P}Bu_3$ MesO$^-$
5d R = $PO(OEt)_2$

Since an early report by Klamann and Weyerstahl[12] of the preparation of phosphonium methanesulphonates there have been no other examples of such salts being utilised as precursors for Wittig ylids. Despite this we envisaged the use of **3d** to prepare phosphoranes and/or phosphonates in order to investigate their potential in Wittig reactions. Formation of phosphonium salts, **5b**[11] (Ph_3P/MeCN/90°C) and **5c**[11] (Bu_3P/MeCN/90°C) from methanesulphonate (**3d**) was achieved in good yields (76% and 86%). Although the

synthesis of phosphonate (**5d**)[11] could not be achieved by heating **3d** in refluxing $(EtO)_3P$, it could be accessed *via* bromide (**5a**) ($LiBr/Me_2CO/80^oC$ (78%)) then $(EtO)_3P/MeCN/90^oC$ (70%).

Deprotonation of **5b**, **5c**, and **5d** with *n*-BuLi in THF at -78°C gave characteristic deep red ylids and an anion, each of which upon treatment with (*R*)-glyceraldehyde acetonide[13] produced alkene (**6**)[14] as a *cis/trans* mixture[15] [4:1 (72%), 1:1 (62%), and 1:7 (71%), respectively]. These *cis/trans* mixtures, like 2-alkenylquinoxalines,[4] were found to convert readily in solution, at room temperature within 48 h, to the pure *trans* isomer.



Bromine addition to alkene (**6**) afforded the vicinal dibromide (**7**) (67%) as a mixture of diastereoisomers, which without purification was reacted with DBU in refluxing dioxan generating alkynyl-pterin-acetal-amide (**8**)[16] in 40% yield. The deprotection of **8** using aqueous HCl in dioxan to give (dephospho) Form A (**2b**) has been previously reported.[9]

Synthetic endeavours towards molybdopterin and Moco utilising compounds (**6**) and (**8**) are continuing.

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11 All new compounds were characterised by a combination of IR, UV, ^{1}H-NMR, ^{13}C-NMR and low resolution mass spectroscopy, as well as combustion analysis and high resolution mass spectroscopy.

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14 *trans*-Alkene (**6**) had m.p. 115-116°C, $\nu_{max.}$ (film) 1681, 1623, 1562, 1480, 972 cm^{-1}; $\lambda_{max.}$ (EtOH) 246, 314, 360 nm; δ_H ($CDCl_3$, 300 MHz) 1.35 (9H, s, CMe_3), 1.44 and 1.49 (2x3H, 2xs, CMe_2), 3.74 (1H, t, J 7.5 Hz, 4'-H), 4.22 (1H, dd, J 6, 3 Hz, 4'H), 4.77 (1H, q, J 5, 5 Hz, 3'-H), 6.96 (2H, m, 2'-H, 1'-H), 8.85 (1H, s, 7-H), 8.90 (1H, br s, NH), 12.50 (1H, br s, NH); δ_C ($CDCl_3$, 50 MHz) 25.98 and 26.75 ((*CMe*$_2$), 26.99 (*CMe*$_3$), 40.77 (Me$_3$*C*), 69.35 (C-4'), 76.21 (C-3'), 110.17 (*C*Me$_2$), 127.30 (C-2'), 131.07, 136.27, 149.09, 149.18, 159.52, 180.98 (C:O); *m/z* (FAB) 374 (MH$^+$, 100%), 315 (14), 298 (11), 286 (11), 219 (24), (Found MH$^+$ 374.1833; C, 54.1; H, 6.3; N, 17.5 % $C_{18}H_{24}N_5O_4$ requires M+H, 374.1828; $C_{18}H_{24}N_5O_4.0.5H_2O$ requires C, 54.0; H, 6.5; N, 17.5 %)

15 *Cis/trans* ratios were determined by 200 MHz ^{1}H-NMR spectroscopy.

16 Alkyne (**8**) had m.p. 227-230 °C (lit[9] 240-241°C), $\nu_{max.}$ (KBr) 1680, 1620, 1559 cm^{-1}; $\lambda_{max.}$ (EtOH) 260, 308, 356 nm; δ_H ($CDCl_3$, 300 MHz) 1.36 (9H, s, CMe_3), 1.44 and 1.55 (2x3H, 2xs, CMe_2), 4.12 (1H, dd, J 8, 6 Hz, 4'-H), 4.28 (1H, dd, J 8, 6 Hz, 4'-H), 4.99 (1H, t, J 6 Hz, 3'-H), 8.65 (1H, br s, NH), 8.87 (1H, s, 7-H), 12.45 (1H, br s, NH); δ_C ($CDCl_3$, 50 MHz) 26.00 and 26.34 ((*CMe*$_2$), 27.04 (*CMe*$_3$), 40.74 (Me$_3$*C*), 65.76 (C-4'), 69.71 (C-3'), 81.88 (C-2'), 92.21 (C-1'), 111.10 (*C*Me$_2$), 131.54, 137.20, 149.72, 153.10, 157.90, 158.82, 180.84 (C:O); *m/z* (FAB) 372 (MH$^+$, 98%), 314 (15), 161 (22), 73 (100) (Found MH$^+$ 372.1680. $C_{18}H_{22}N_5O_4$ requires M+H, 372.1672).

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