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Synthetic Studies on the Molybdenum Cofactor. An Efficient Total Synthesis of (±)-Dephospho Form A

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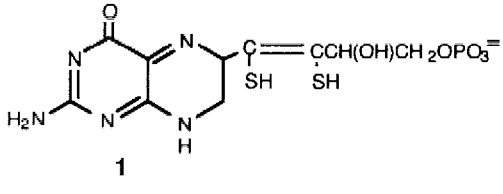
Abstract: (Dephospho) Form A (**4b**), obtained by oxidative degradation of the molybdenum cofactor, has been efficiently synthesized in racemic form for the first time. This material, as well as its protected derivative **11**, are now conveniently available as intermediates for a projected synthesis of the natural cofactor.

Our ongoing program directed at syntheses of molybdopterin (**1**) and the molybdenum cofactor (Moco) (**2**)[1,2] has led to an unequivocal total synthesis of urothione (**3**),[3] the urinary metabolite of Moco, as well as to



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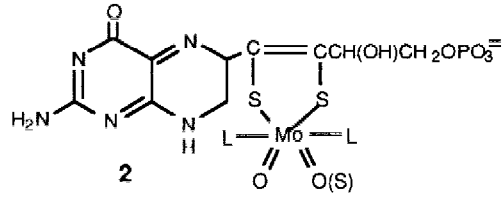

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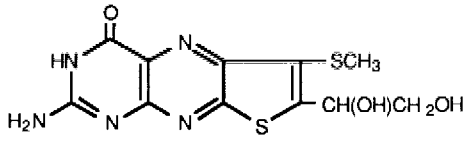
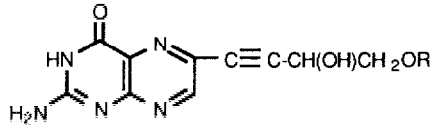


3

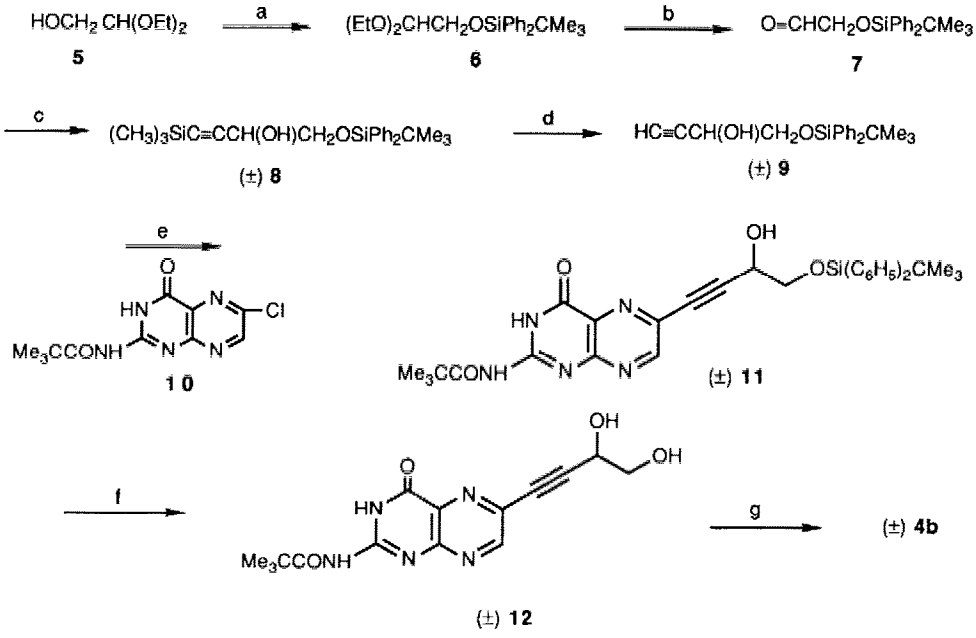
stereospecific syntheses of both enantiomers of dephospho Form A (**4b**).[4] A projected synthesis of molybdopterin (**1**) utilizes addition of $(Cp)_2MoS_4$ to the acetylenic bond of Form A which has been activated by



4a, R = $PO_3^{=}$
4b, R = H

oxidation of the propargylic secondary alcohol to the corresponding carbonyl group.[5] Since this (thus far) essential transformation destroys the only chiral center in Form A, we were obviously reluctant to utilize optically active material for this transformation, and we have thus devised an efficient synthesis of (±)-dephospho Form A for use as a synthetic intermediate to molybdopterin.

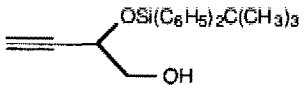
Scheme 1



a. $ClSiPh_2CMe_3$, DMF, Imidazole
b. p-Toluenesulfonic acid, acetone, rt, 24 h
c. $Li^+ {}^- C{\equiv}CSiCMe_3$, -78°→ 0°C, 0.5h, rt,1.5 h
d. K_2CO_3, abs. MeOH, rt, 12h
e. $Pd(Ph_3P)_4$, CuI, Et_3N, MeCN, 60°, 2h
f. $Bu_4N^+F^-$, THF, 18h, rt
g. 1N NaOH, 48h

Commercially available glycolaldehyde diethylacetal (**5**) was converted to its t-butyldiphenylsilyl (TBDPS) ether **6** (DMF, imidazole; 95%),[6-10] and the acetal grouping was then selectively hydrolyzed with p-toluenesulfonic acid/acetone/rt/24 h to give the protected glycolaldehyde derivative **7** (60%).[11] Although the TBDPS grouping was stable to p-toluenesulfonic acid/refluxing acetone for 5 hours,[12] the acetal cleavage reaction did not go to completion even under these conditions, and the overall yield of **7** was the same as that obtained at room temperature. Deprotection of the acetal functionality could also be carried out with lithium tetrafluoroborate in aqueous acetonitrile[13] or with titanium tetrachloride,[14] but yields of **7** were no better. Although the mixture of unreacted **6** and the aldehyde **7** could be readily separated either by chromatography over silica gel or by fractional distillation, the presence of some non-hydrolyzed **6** did not interfere with the conversion of **7** to **9** (*vide infra*), and all four steps leading from **5** to **9** could be carried out without purification

of intermediates. Condensation of **7** with lithium trimethylsilylacetylide[15] gave **8** (90%), which was then converted to **9** (95%) by selective hydrolysis of the trimethylsilyl grouping [in the presence of the t-butyldiphenylsilyl grouping[16]] by treatment with potassium carbonate in absolute methanol at room temperature for 12 hours. A very small amount (<5%) of the silyl-transferred[17, 18] isomer **13** was isolated by chromatography of the reaction mixture over silica gel.



13

Palladium-catalyzed coupling of **9** with 2-pivaloyl-6-chloropterin (**10**) readily afforded **11** (68%).[19] Desilylation of **11** with tetrabutylammonium fluoride in THF at room temperature to give **12**, followed by removal of the N-pivaloyl grouping with 1 N sodium hydroxide, then gave (±)-dephospho Form A of Moco (**4a**) in 75% yield as yellow flakes. This product was identical in all respects except optical activity with (dephospho) Form A isolated from naturally-occurring Moco.[20]

This route to (±)-dephospho Form A can be carried out on a large scale with reproducible yields as cited above. In contrast to our previously reported synthesis of chiral dephospho Form A,[4] all intermediates involved in the present route to racemic dephospho Form A are stable, high boiling liquids which, although readily purified by simple chromatography over silica gel, can be utilized without purification in the above series of synthetic transformations.

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2. Although these are the latest proposed structures for **1** and **2**, the state of oxidation (dihydro vs. tetrahydro) of the pterin moiety remains uncertain and may vary from species to species. Similarly, the additional ligands (L) on Mo are unspecified and may vary from enzyme to enzyme.

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