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Synthesis of 6-Methylpretetramid

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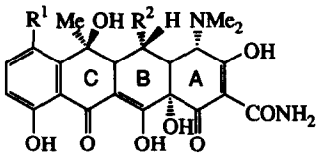
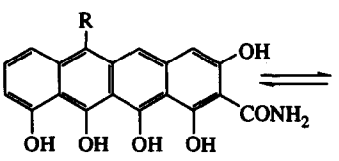
Abstract: An efficient and highly regioselective route to the tetracycline precursor 6-methylpretetramid (**5**) has been developed, based on Diels-Alder cycloaddition methodology.

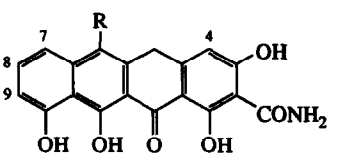
Since their isolation from certain species of *Streptomyces* almost fifty years ago, the tetracycline antibiotics, *e.g.* (**1**)-(**3**), have become one of the most widely prescribed categories of antimicrobials in clinical medicine. The initial chemical degradations that were aimed at elucidating their structure, led to formation of a number of aromatic naphthacenic amides[1,2,3a] including pretetramid (**4**) and its 6-methyl analogue (**5**). Feeding experiments[2] established that these pretetramids are also important intermediates in tetracycline biosynthesis. They are often represented as naphthacenols (**4a**) and (**5a**), however, pretetramid is known to exist chiefly as the tautomeric naphthacenone (**4b**)[3b] and 6-methylpretetramid has been identified in the present work as having the analogous structure (**5b**).



(1) R^1 = H, R^2 = H
(2) R^1 = H, R^2 = OH
(3) R^1 = Cl, R^2 = H



(4a) R = H
(5a) R = Me

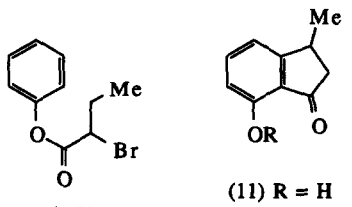


(4b) R = H
(5b) R = Me

This paper describes a simple, convergent synthesis of 6-methylpretetramid (**5**). Whilst there have been several successful syntheses reported for pretetramid itself (**4**),[3] the 6-methyl system (**5**) has been obtained only twice before,[4] by very different chemistry from that described here. The new approach anticipated Diels-Alder cycloaddition between a new 1,4-anthraquinonoid dienophile (**6**), having an appropriate C-methyl substituent already in place, and a 1,3-butadiene such as (**7**). Aromatisation of the stoichiometric addition product from such a reaction should lead to the tetracyclic nucleus of the pretetramids. Interception of analogous adducts prior to aromatisation might in the long term allow stereocontrolled formation of the A-ring of the tetracyclines themselves.

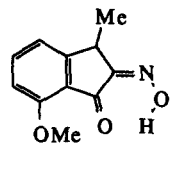
Formation of (**6**) necessitated further cycloaddition methodology, involving base-induced reaction[5] of an appropriate homophthalic anhydride (**8**) with the chlorinated benzoquinone (**9**). The synthesis of (**8**) was

achieved in 5 steps. Thus, phenol was treated with 2-bromobutanoyl bromide to give the ester (**10**) (92%).[6] This underwent a Fries rearrangement, followed by intramolecular cyclisation ($AlCl_3$/145°) to give the indanone (**11**) (59%).[7] Protection by methylation (Me_2SO_4/K_2CO_3) then afforded (**12**). Treatment of (**12**) with butyl nitrite in acidic methanol[8] gave the oxime (**13**) (55%). The tosylate of (**13**) readily underwent abnormal Beckmann rearrangement in boiling aqueous NaOH[8] to give the diacid (**14**) (88%) m.p. 177-79° (δ [$(CD_3)_2CO$] 1.42, d, CH<u>Me</u>; 3.88, q, C<u>H</u>Me, *J* 7 Hz). Dehydration of (**14**) (AcCl, followed by sublimation at 100°/0.05mm) then yielded the desired homophthalic anhydride (**8**)[9] (78%) m.p. 90-92° (ν_{max} 1787, 1743 cm^{-1}) (δ [$(CD_3)_2CO$] 1.66, d, CH<u>Me</u>; 4.21, q, C<u>H</u>Me, *J* 7 Hz). The lithiated species derived from (**8**) by treatment with BuLi (1.1 equivalents) at room temperature, was then slowly added to the benzoquinone (**9**). Acidic work-up induced aromatisation with concomitant extrusion of CO_2 and HCl[5] to give the dark purple (**6**) (78%) (δ [$CDCl_3$] 2.94, s, CMe; 4.08, s, OMe; 7.18, s, H3, 15.73, s, OH).

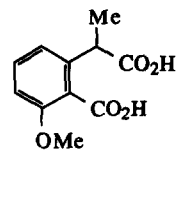


(10)

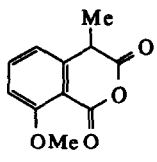
(11) R = H
(12) R = Me



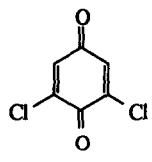
(13)



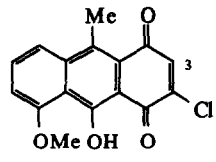
(14)



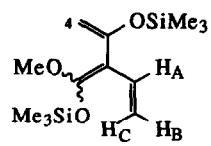
(8)



(9)

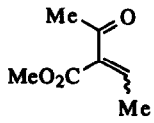


(6)

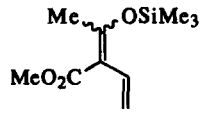


(7)

With the new dienophile (**6**) thus made available, attention was directed towards obtaining an appropriately functionalised 1,3-butadiene, to facilitate formation of the linear tetracyclic framework of (**5**) by cycloaddition. The most effective diene system proved to be the cross-conjugated triene (**7**). Attempts at obtaining an analogous system in which the ethenyl group (-CH_A=CH_BH_C) of (**7**) was replaced by a substituent at the same oxidation level as the amide group of (**5**) were unsuccessful. In earlier work here,[10] triene (**7**) was shown to undergo regioselective cycloaddition to standard quinonoid dienophiles. It was anticipated that after cycloaddition to (**6**), the resulting ethenyl substituent on the tetracyclic framework would be amenable to oxidation. Compound (**7**) was prepared in a 3-step process from methyl acetoacetate and acetaldehyde.[10] The initial condensation product (**15**)[11] was silylated under conditions similar to those described by Danishefsky and Kitahara[12] to give the diene (**16**). This underwent enolisation and silylation at -78° (LDA/Me_3SiCl) to afford (**7**) (90%) (δ [$CDCl_3$] 0.20, 0.26, s, s, 2 x $OSiMe_3$; 3.60, s, OMe; 4.21, 4.48, s, s, =C(4)H_XH_Y; 4.81, dd, *J* 11, 2 Hz, H_B; 5.05, dd, *J* 17, 2 Hz, H_C; 6.59, dd, *J* 17,11 Hz, H_A). Triene (**7**) proved to be thermally sensitive and was routinely made to react, without further purification, in a 4-fold excess.

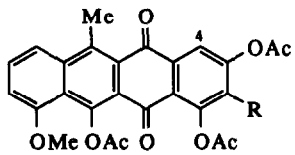


(15)

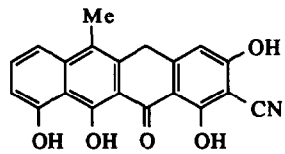


(16)

Cycloaddition between (7) and (6) proceeded smoothly (CH_2Cl_2, room temperature) to afford, after one-pot aromatisation and acetylation (Ac_2O/pyridine/100°), the vinyl-substituted tetracycle (17) (65%) m.p. >206° (dec.) (δ [$CDCl_3$] 3.05, s, CMe; 5.66, dd, *J* 12, 1.5 Hz, -CH_A=CH_BH_C *cis* to H_A; 5.86, dd, *J* 18, 1.5 Hz. -CH_A=CH_BH_C *trans* to H_A; 6.57, dd, *J* 18, 12 Hz, -CH_A=CH_BH_C; 7.78, s, H4). The confirmed presence of an ethenyl substituent indicated that cycloaddition of (7) had proceeded in the desired sense, where the reactive 1,3-butadiene was the one triply activated by the 3 oxy substituents electronically reinforcing one another. The alternative mode of cycloaddition, whereby the ethenyl substituent became part of a reactive diene doubly activated by 2 oxy substituents, was not detected.



(17) R = $CH=CH_2$
(18) R = CHO
(19) R = CN



(20)

With the carboxamido synthon successfully incorporated into the correct position of the tetracyclic system as an ethenyl group, its oxidation state was raised to the desired level in 2 stages. Ozonolysis (CH_2Cl_2, -78°) of (17) followed by treatment of the ozonide with Me_2S, gave the aldehyde (18) (90%) (δ 3.05, s, CMe; 7.83, s, H4; 10.28, s, CHO). Conversion of (18) to the corresponding nitrile (19) (ν_{max} 2242 cm^{-1}) (δ [$CDCl_3$] 3.05, s, CMe; 8.00, s, H4) was smoothly achieved, (70%) in a buffered (pH 4) reaction with hydroxylamine-*O*-sulfonic acid, followed by warming in aqueous $NaHCO_3$ and reacetylation.

The final stages, converting (19) to 6-methylpretetramid (5), required deprotection of the oxy substituents, hydration of the nitrile to form the amide and selective reduction of the carbonyl *peri* to the C-methyl group. There is analogy for the last stage, selective formation of anthrones from quinones, by treatment with HI.[10,13] The preceding stage,hydration of the *ortho-ortho* disubstituted nitrile group, was expected to require forcing conditions. These considerations led to exploring severe treatment of (19) with HI in the hope that all three transformations: deprotection, hydration and reduction, might be effected concurrently. From the severely acidic conditions able to be employed in the published degradation of the natural tetracyclines,[1a,14] it was appreciated that the hindered amide group of (5), once formed, would be very stable indeed to further attack by acid.

Thus, (19) was treated with 47% aqueous HI and CF_3CO_2H in boiling AcOH for 1.5 h. However the orange solid that crystallised on cooling corresponded to only two of the transfomations having occurred, leaving the nitrile group unaffected, and giving rise to (20) (ν_{max} 2240 cm^{-1}) (δ [$(CD_3)_2SO$] 2.44, s, Me;

4.42, s, CH_2) (*m/z* 347 [M, 96%]). Accordingly, the reduction conditions were made more vigorous by heating (**19**) in 47% aqueous HI/CF_3CO_2H/AcOH in a sealed tube at 125° for 52 h. Upon cooling, this mixture deposited 6-methylpretetramid (**5**) in 76% yield. The product was exceptionally insoluble in most organic solvents and underwent oxidation in the solvent system reported for analogous n.m.r. purposes;[3b] however freshly prepared solutions gave clear spectra, for the first time establishing tautomeric structure (**5b**) (δ [$(CD_3)_2SO$/1% $Mg(OAc)_2$] 2.29, s, Me; 4.01, s, CH_2; 5.93, s, H4; 6.43, d, *J* 8 Hz, H9; 7.06, d, *J* 8 Hz, H7; 7.28, apparent t, *J* 8 Hz, H8) (*m/z* 365 [M, 42%]). The regiochemistry of reduction was confirmed by the considerable associated shielding of the C-methyl resonance. The spectroscopic characteristics of the product were indistinguishable from those of an authentic sample of (**5**), prepared by chemical degradation of (**2**).[14]

6-Methylpretetramid (**5**) has thus been efficiently assembled in a new manner, in 11 steps from phenol.

All new compounds gave satisfactory analyses and spectroscopic data. We thank Dr P.G. Griffiths for useful discussion and acknowledge financial support from the Australian Research Council and an Australian Postgraduate Research Award (PJdB).

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