Tetrahedron Letters,Vol.29,No.45,pp 5829-5832,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

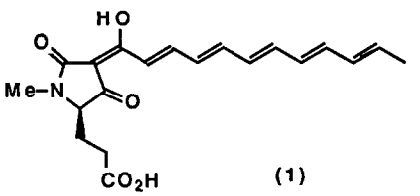
USE OF t-BUTYL 4-DIETHYLPHOSPHONO-3-OXOBUTANETHIOATE FOR TETRAMIC ACID SYNTHESIS: TOTAL SYNTHESIS OF THE PLASMODIAL PIGMENT FULIGORUBIN A

Steven V. Ley,* Stephen C. Smith and Peter R. Woodward

Department of Chemistry, Imperial College, London SW7 2AY, U.K.

Summary: *A short, efficient synthesis of the yellow slime mould pigment fuligorubin A (1) has been achieved using coupling of t-butyl 4-diethylphosphono-3-oxobutanethioate with deca-2,4,6,8-tetraenal and subsequent substitution with a glutamic acid derivative followed by Dieckmann cyclisation.*

The polyene acyltetramic acid fuligorubin A (1) is a naturally occurring pigment recently isolated from the yellow slime mould *Fuligo septica (L.)* Wiggers.[1] This compound is thought to be involved in photoreceptor and energy conversion processes during the life cycle of this interesting species.

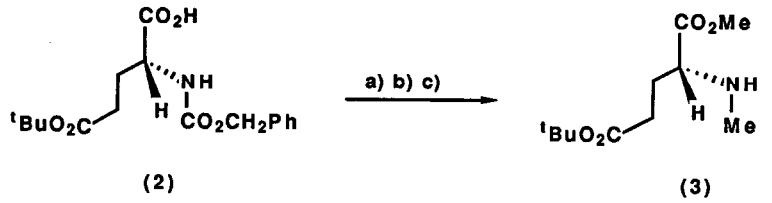


(1)

Here we report a concise and efficient synthesis which both confirms the absolute configuration of (1) and employs methodology developed in these laboratories for the preparation of unsaturated β-ketoamides.[2,3]

The amino acid fragment in (1) was readily prepared from the commercially available (R)-glutamic acid derivative (2) by a straightforward sequence of reactions involving N-methylation[4] and esterification using ethereal diazomethane followed by deprotection to give (3) in 36% overall yield (Scheme 1).

Scheme 1

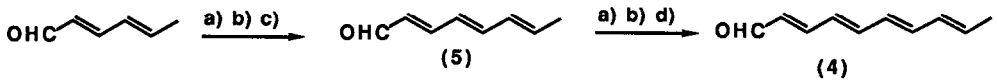


(2) (3)

a) NaH, MeI, THF at RT, 45%; b) CH_2N_2, Et_2O, 90%; c) H_2/Pd/C, EtOAc, 88%.

The polyene aldehyde (4) required for the fuligorubin A synthesis was known previously[5], although it was found that it could be obtained more efficiently by reaction of *trans*, *trans*-hexa-2,4-dienal with triethylphosphonoacetate, followed by treatment with DIBAL and MnO_2 oxidation of the allylic alcohol to give (5) in 82% overall yield. Iterative treatment of (5) with triethylphosphonoacetate, DIBAL reduction and oxidation with barium manganate gave geometrically pure polyene (4) (48%). (Scheme 2).

Scheme 2

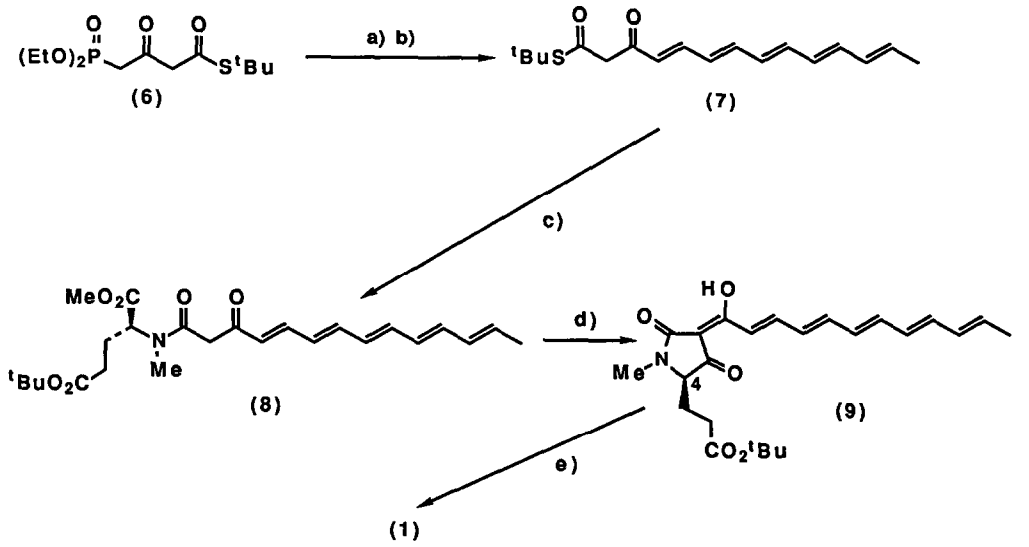


(5) (4)

a) $(EtO)_2P(O)CH_2CO_2Et$ 1.1eq, NaH 1.1eq, THF, 0°C 5min, b) DIBAL 3eq, toluene -78°C 15min, c) MnO_2 12eq, CH_2Cl_2, RT,90 min. d) $BaMnO_4$ 7.5 eq, CH_2Cl_2, RT,3h.

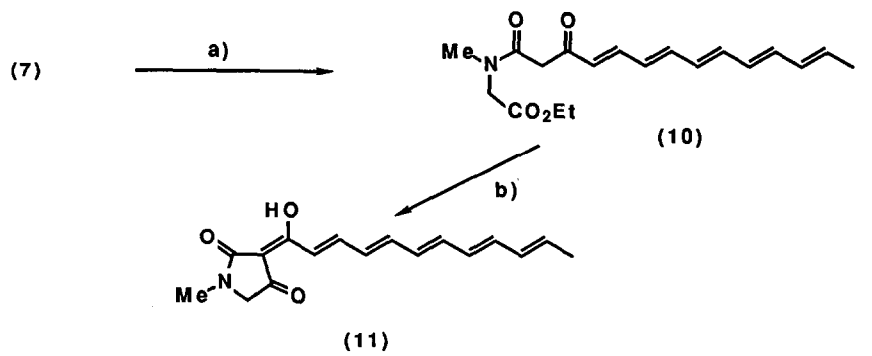
Final couplings of the above fragments for fuligorubin A synthesis were achieved using our previously established methods: thus, reaction of (4) with t-butyl 4-diethylphosphono-3-oxobutanethioate[2] (6) produced the polyene β-ketothioester (7) in 75% yield. Coupling of (7)[3] with the glutamic acid derivative (3) in the presence of silver(I) trifluoroacetate afforded the required β-ketoamide (8) (74%). This compound was smoothly converted to the acyltetramic acid derivative (9) in 62% yield by rapid treatment (30 min) with freshly sublimed potassium t-butoxide[6,7] in t-butanol at room temperature. Deprotection with formic acid gave fuligorubin A (1) (76%) (Scheme 3). The data for the synthetic material was identical in all respects to that reported for the natural product.[1,8] In order to confirm that no racemisation had occured at the chiral centre during these later stages of the synthesis, the sample was hydrogenated according to the procedure described by Steglich[1] to the decahydro derivative, which again was shown to be identical to the reported data in all respects including the optical rotation.

Scheme 3



a) NaH, 2.1eq, O°C, THF, 25 min ,b) (4) , O°C, THF, c) $AgOCOCF_3$ 1.5eq, Na_2HPO_4, (3) 2eq, THF, RT, 3h, d) ^tBuOK 2eq, ^tBuOH, RT,30min, e) HCOOH neat , RT, 1h.

Scheme 4



a) Sarcosine ethyl ester, $AgOCOCF_3$, Na_2HPO_4, THF, RT, 5h
b) KO^tBu, ^tBuOH, RT, 1h.

Finally, in related studies to probe the versatility of the above methods for polyene acyltetramic acid preparation, sarcosine ethyl ester was also coupled with the unsaturated β-ketothioester (7) (45%) to give the corresponding polyene (10). Cyclisation of this compound with potassium t-butoxide, as above, gave (11) as a bright red solid[9] (87%) (Scheme 4).

Acknowledgement We thank the SERC (Instant Award to PRW) and E.I. DuPont de Nemours and Co., Wilimington, USA and Pfizer Central Research Sandwich, UK for additional financial support.

References and Footnotes

1. I. Casser, B. Steffan and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 586.
2. S. V. Ley and P.R. Woodward, *Tetrahedron Lett.*, 1987, **28**, 345.
3. S. V. Ley and P.R. Woodward, *Tetrahedron Lett.*, 1987, **28**, 3019.
4. J.R. McDermott and N.L. Benoiton, *Can. J. Chem.*, 1973, **51**, 1915.
5. E.R. Blout, M. Fields, *J. Am. Chem. Soc.*, 1948, **70**, 189.
6. J. L. Bloomer and F.E. Kappler, *J. Chem. Soc., Perkin I.*, 1976, 1485.
7. Extended reaction with $^{t}BuO^{-}$ in these cyclisations (≥ 3h) caused appreciable racemisation. Details of these and related studies will be reported in full at a later date.
8. We thank Professor Steglich for spectra, and an authentic sample of (1) for comparison purposes.
9. Selected data: ν_{max} (film) 3600-2500 br, 1716, 1404, and 1223 cm^{-1}; δH (270 MHz, d_6 Acetone) 1.67 (3H, d, J = 7 Hz, H-12'), 3.04 (3H, 2s, N-Me tautomeric forms), 4.05, 4.10 (2H, 2s, H-5 minor and major tautomer respectively), 5.65-5.80 (1H, m, H-11'), 6.0-7.4 (9H, m, H-2' to H-10').

(Received in UK 1 September 1988)