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Synthesis of the Spore Photoproduct

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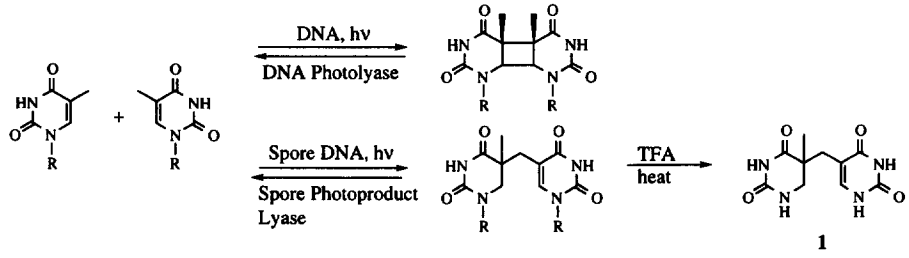
Abstract: *The spore photoproduct was synthesized in seven steps from dihydrothymine and 5-formyluracil using a mixed Aldol coupling as the key bond forming step.* © 1997, Elsevier Science Ltd. All rights reserved.

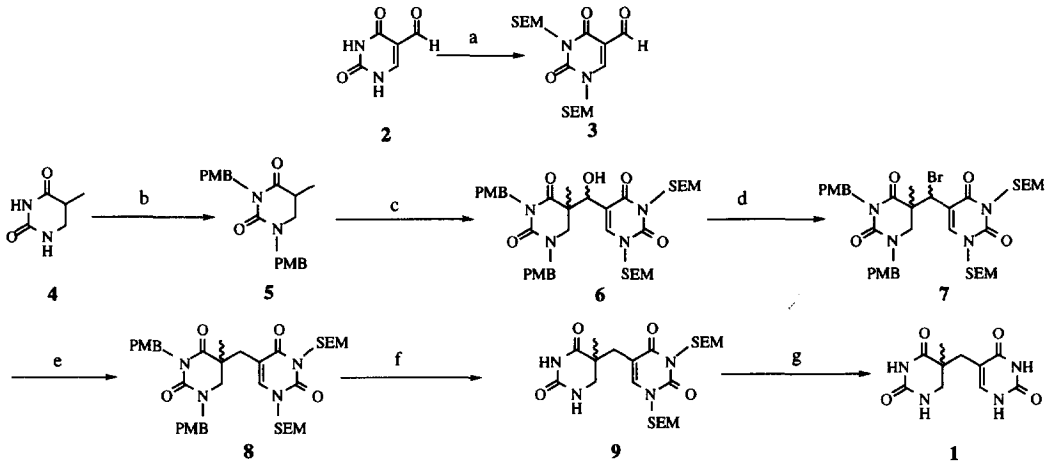
In contrast to the effects of UV light on cellular DNA, where the cyclobutane photodimer is the major photoproduct,[1] irradiation of DNA in bacterial spores results in the formation of 5,6-dihydro-5-(α-thyminyl) thymine **1**, the spore photoproduct.[2]

Scheme 1



The spore photoproduct has been synthesized by coupling 6-aminothymine with 5-hydroxymethyl uracil.[3] However, this synthesis does not work for N1 substituted pyrimidines and is not amenable to making derivatives. The synthesis of the spore photoproduct described here is based on our recently published route to the dinucleotide spore photoproduct.[4] This route has the flexibility to allow for the synthesis of derivatives (at N1, N3, or the methylene bridge) for use as mechanistic probes for spore photoproduct lyase, a recently cloned[5] and overexpressed[6] enzyme that catalyzes the repair of this UV lesion in spore DNA.

5-formyluracil **2** was protected with SEM-Cl to give **3**.[7] Dihydrothymine **4** was protected with p-methoxybenzyl chloride to give **5**.[8] The enolate of **5**, generated by reaction with LDA, was reacted with **3** to give alcohol **6**.[9] If the reaction mixture is not deoxygenated hydroxylation of **5** is the major reaction.[10] Conversion of **6** to bromide **7** was accomplished with PBr_3.[11] Dehalogenation gave spore photoproduct **8**.[12] Successive deprotection with ceric ammonium nitrate[13] and trifluoroacetic acid afforded the spore photoproduct **1**[3] as a white solid.



Scheme 2 a) NaH, SEMCl, DMF, rt, 18 hrs, 88% b) NaH, PMBCl, DMF, rt, 8 hrs, 63% c) -78°C, LDA, THF, 30 min, then **3**, 2 hrs, 37% d) PBr_3, THF, rt, 10 min e) Bu_3SnH, AIBN, toluene, reflux, 30 min, 58% (steps d and e) f) CAN, CH_3CN/H_2O (9:1), rt, 2hrs, 40% g) TFA, 60°C, 2 hrs, 70%

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9. Compound **6**: 400 MHz ^{1}H NMR ($CDCl_3$) ppm: 7.35-7.33 (2H, m), 7.27-7.25 (2H, m), 6.87-6.82 (5H, m), 5.41 (0.5H, s), 5.34 (2H, s), 5.16 (0.5H, s), 4.97 (1H, d, J=10Hz), 4.92-4.83 (2H, m), 4.70-4.65 (2H, m), 4.44-4.41 (1H, m), 3.79 (3H, s), 3.78 (3H, s), 3.70-3.53 (4H, m), 3.45 (1H, d, J=13 Hz), 2.99 (1H, d, J=13Hz), 1.08 (3H, s), 0.96-0.90 (4H, m), 0.01-0.02 (18H, m)
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11. Partial purification of **7** was accomplished by filtering through a short plug of silica using 5% ethyl acetate in methylene chloride as the eluent. Since **7** is unstable, it was used immediately following work up.
12. Compound **9**: 400 MHz ^{1}H NMR ($CDCl_3$) ppm: 7.32 (2H, d, J=8Hz), 7.22 (2H, d, J=8Hz), 7.00 (1H, s), 6.84 (2H, d, J=8Hz), 6.81 (2H, d, J=8Hz), 5.35 (2H, s), 5.03 (1H, d, J=10Hz), 4.87 (2H, dd, J=14Hz, 24Hz), 4.79 (1H, d, J=14Hz), 4.77 (1H, d, J=10Hz), 4.24 (1H, d, J=14Hz), 3.79 (3H, s), 3.78 (3H, s), 3.64 (2H, dd, J=8Hz, 8Hz), 3.56 (2H, dd, J=8Hz, 8Hz), 3.15 (1H, d, J=13 Hz), 3.03 (1H, d, J=13Hz), 2.61 (1H, d, J=14Hz), 2.54 (1H, d, J=14Hz), 1.03 (3H, s), 0.95-0.90 (4H, m), 0.00 (9H, 2s), -0.02 (9H, 2s).
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