

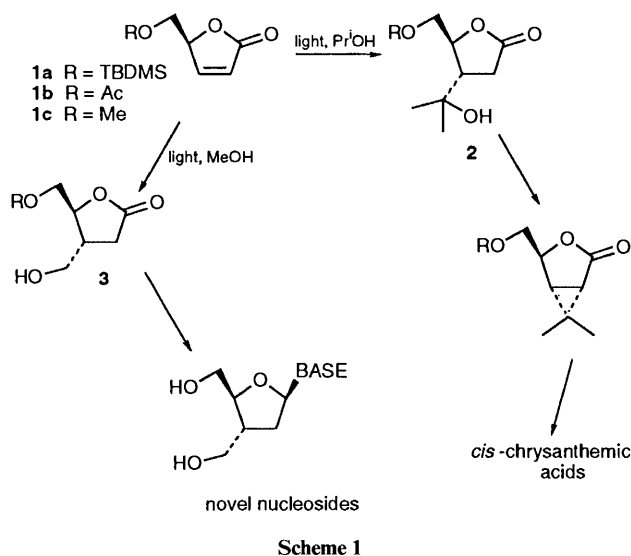
Photocatalysed Addition of Pyrrolidines to Butenolides: a Concise Synthesis of the Pyrrolizidine Alkaloid Ring System

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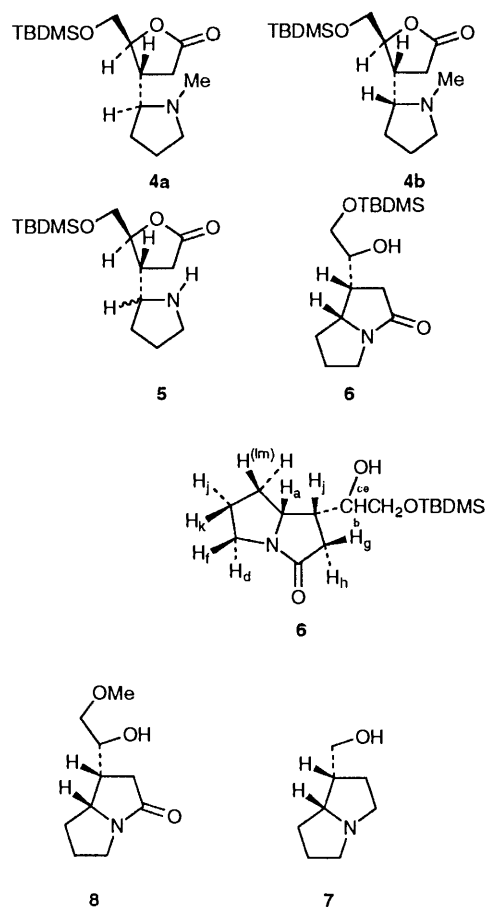
The regioselective and stereoselective photocatalysed addition of *N*-substituted pyrrolidines to 5(*S*)-substituted furan-2-(5*H*)-ones (butenolides), and subsequent conversion of the adduct from *N*-(trimethylsilyl)pyrrolidine into the 1-azabicyclo[3.3.0]octane ring system of the pyrrolizidine alkaloids are described.

We recently described^{1,2} the regioselective and (apparently) stereospecific addition of various alcohols to butenolides **1** under irradiation in the presence of benzophenone (Scheme 1).



The photoadducts **2** and **3** were then used for the construction of *cis*-chrysanthemic acids and novel nucleosides, respectively. In an attempt to widen the scope of this process, we have now examined the photocatalysed addition of *N*-substituted pyrrolidines to butenolides.

Irradiation (Pyrex, water-cooled immersion well, degassing with nitrogen, 350 nm) of 5-*O*-TBDMS-butenolide **1a** (ref. 3) with *N*-methylpyrrolidine in acetonitrile in the presence of benzophenone (1 mol equiv.) yielded the two photoadducts **4a** and **4b** in isolated yields of 40 and 20%, respectively. A small amount of benzopinacol was also obtained, but over 70% of benzophenone was recovered. The reaction was complete within 4 h and has been carried out routinely on the 5 g scale. Attempts to remove the *N*-methyl group using 1-chloroethyl chloroformate⁴ (even in the presence of an acid scavenger) led to loss of the *tert*-butyldimethylsilyl (TBDMS) group and complex product mixtures. In consequence, the photoreaction was repeated with *N*-(trimethylsilyl)pyrrolidine (Aldrich Chemical Company) in place of *N*-methylpyrrolidine. After irradiation for 1–2 h, the butenolide had been consumed, and treatment of the crude reaction mixture with potassium *tert*-butoxide in tetrahydrofuran (THF) effected the conversion of the presumed photoadduct **5** into the 4-substituted 1-azabicyclo[3.3.0]octane-2-one **6** which has the ring skeleton and stereochemistry of the pyrrolizidine alkaloid lindelofidine **7** (in particular 2D-COSY and NOE experiments showed that H_a



and H_i had the relative stereochemistry depicted). The overall yield of this compound from butenolide **1a** was around 15–20%. Use of the alternative butenolide **1c** allowed recovery of unchanged benzophenone through extraction of the crude adducts into aqueous HCl, with subsequent neutralisation and extraction into dichloromethane prior to treatment with potassium *tert*-butoxide. However, the overall yield of the corresponding azabicyclo compound **8** was still around 15–20%.

These transformations are reproducible, though the reactions remain to be optimised, and the rapid conversion achieved with the TMS-pyrrolidine suggests that a judicious change of solvent and photosensitiser may enhance even further what is almost certainly an electron transfer process.⁵ The other stereoisomer of butenolide **1** is readily available, thus extending the stereochemical possibilities of these reactions.

Experimental

3-(*N*-Methylpyrrolidin-2'-yl)-4-(*tert*-butyldimethylsiloxy-methyl)butan-4-olide **4a**.—A solution of (*S*)-5-(*tert*-butyldimethylsilyloxy)methylfuran-2(5*H*)-one **1a** (3.66 g, 0.016 mol), benzophenone (2.91 g, 0.016 mol) and *N*-methylpyrrolidine (4 cm³) in acetonitrile (70 cm³) was degassed with nitrogen for 1 h. The solution was then irradiated under a medium pressure mercury lamp (350 nm, 120 W) for 4 h in a Pyrex water-cooled immersion well. Removal of the solvent under reduced pressure followed by purification by flash chromatography (ethyl acetate) yielded a yellow oil (2.00 g, 40%); *R*_f 0.52 [diethyl ether-methanol (9:1, v/v)]; ν_{\max} (thin film)/cm⁻¹ 2953, 2856 (Si-CH₃), 2781 (NCH₂) and 1777 (C=O) (Found: M⁺, 313.2078. C₁₆H₃₁NO₃Si requires *M*, 313.2074); δ_{H} (400 MHz; CDCl₃; *J*/Hz) 0.04 and 0.05 (2 × s, 6 H, SiMe₂), 0.87 [s, 9 H, C(CH₃)₃], 1.46–1.53 (m, 1 H, 3'-H_a), 1.65–1.73 (m, 2 H, 4'-H), 1.77–1.86 (m, 1 H, 3'-H_b), 2.13–2.21 (m, 2 H, 5'-H_a, 2-H_b), 2.23–2.27 (m, 4 H, NMe, 2'-H), 2.70–2.78 (m, 2 H, 2-H_a, 3-H), 3.00–3.04 (m, 1 H, 5'-H_b), 3.57–3.60 (dd, 1 H, *J*_{gem} 11.3, *J*_{4,5b} 2.4, 5-H_b), 3.87–3.91 (dd, 1 H, *J*_{4,5a} 2.5, 5-H_a) and 4.48–4.50 (m, 1 H, 4-H); δ_{C} (100 MHz; CDCl₃) -5.8 (SiMe), -5.7 (SiMe), 18.1 [C(CH₃)₃], 22.2 (C-4'), 25.7 [C(CH₃)₃], 25.8 (C-3'), 32.7 (C-2), 36.2 (C-3), 40.4 (NMe), 57.2 (C-5'), 65.2 (C-5), 67.7 (C-2'), 81.0 (C-4) and 177.2 (C=O).

(4*R*,5*R*)-4(2'-*tert*-butyldimethylsiloxy-1'-hydroxyethyl)-1-azabicyclo[3.3.0]octan-2-one **6**.—A solution of (*S*)-5-(*tert*-butyldimethylsilyloxymethylfuran-2(5*H*)-one **1a** (2.0 g, 8.77 × 10⁻³ mol), benzophenone (1.60 g, 8.79 × 10⁻³ mol) and TMS-pyrrolidine (2.51 g, 3.06 cm³, 17.5 × 10⁻³ mol) in dried acetonitrile (70 cm³) was degassed for 1 h. The mixture was irradiated for 2 h (354 nm, 125 W) and all butenolide was consumed. The acetonitrile was evaporated and the crude oil was taken up in dried THF (200 cm³) and potassium *tert*-butoxide (0.98 g, 8.77 × 10⁻³ mol) in THF (50 cm³) was added.

The mixture became dark blue when the first drops of base were added going to dark red at the end of the reaction. The cyclo adduct **6** was purified by flash column chromatography (light petroleum-ethyl acetate 1:1, v/v and neat ethyl acetate) (0.39 g, 15%); *R*_f 0.26 (ethyl acetate); ν (solution in CH₂Cl₂)/cm⁻¹ 2957, 2932, 2859 (Si-CH) and 1681 (NC=O) (Found: MH⁺, 300.1995. C₁₅H₂₉NO₃Si requires, MH⁺, 300.1996); δ_{H} (400 MHz; CDCl₃; *J*/Hz) 0.06 (s, 6 H, 2 × Me), 0.88 (s, 9 H, Bu⁺), 1.68–1.74 (m, 2 H, H₁, H_m), 1.87–2.00 (m, 1 H, H_j), 2.08–2.17 (m, 1 H, H_k), 2.42–2.54 (m, 3 H, H_g, H_i, OH), 2.62–2.69 (dd, 1 H, *J*_{hi} 9.1, *J*_{hg} 16.8, H_h), 3.00–3.07 (m, 1 H, H_d), 3.40–3.45 (dd, 1 H, *J*_{bc} 7.8, *J*_{ce} 9.8, H_e), 3.51–3.56 (m, 1 H, H_f), 3.56–3.60 (dd, 1 H, *J*_{bc} 3.8, *J*_{ce} 9.8, H_c), 3.75–3.80 (m, 1 H, H_b) and 3.84–3.90 (m, 1 H, H_a); δ_{C} (100 MHz; CDCl₃) -5.6 (2 × Me), 18.1 [C(CH₃)₃], 25.5 (CH₂), 25.7 [C(CH₃)₃], 2.62 (CH₂), 34.5 (CH), 35.2 (O=CCH₂), 41.2 (NCH₂), 64.0 (OCH₂), 65.7 (NCH), 71.0 (OCH) and 175.8 (C=O).

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