

Synthetic Approaches to Pederin. A Synthesis of Pederol Dibenzoate

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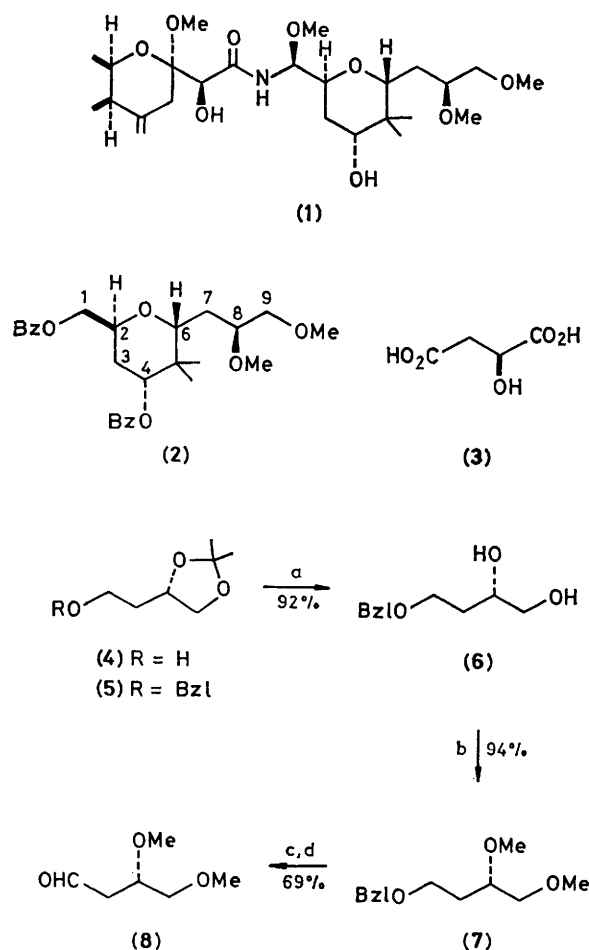
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A new synthesis of functionalized tetrahydropyran-4-ones based on an intramolecular directed aldol condensation has been applied to a key fragment of pederin.

Pederin (**1**) is the active vesicant agent in the defence secretion of the East African beetle *Paederus fuscipes*.^{1,2} It is a powerful inhibitor of protein biosynthesis and mitosis.³ We report a synthesis of pederol dibenzoate (**2**), a key intermediate in a

proposed synthesis of (**1**), in which the salient feature is a cyclization based on the Mukaiyama directed aldol condensation.⁴

Pederol dibenzoate incorporates two four-carbon fragments

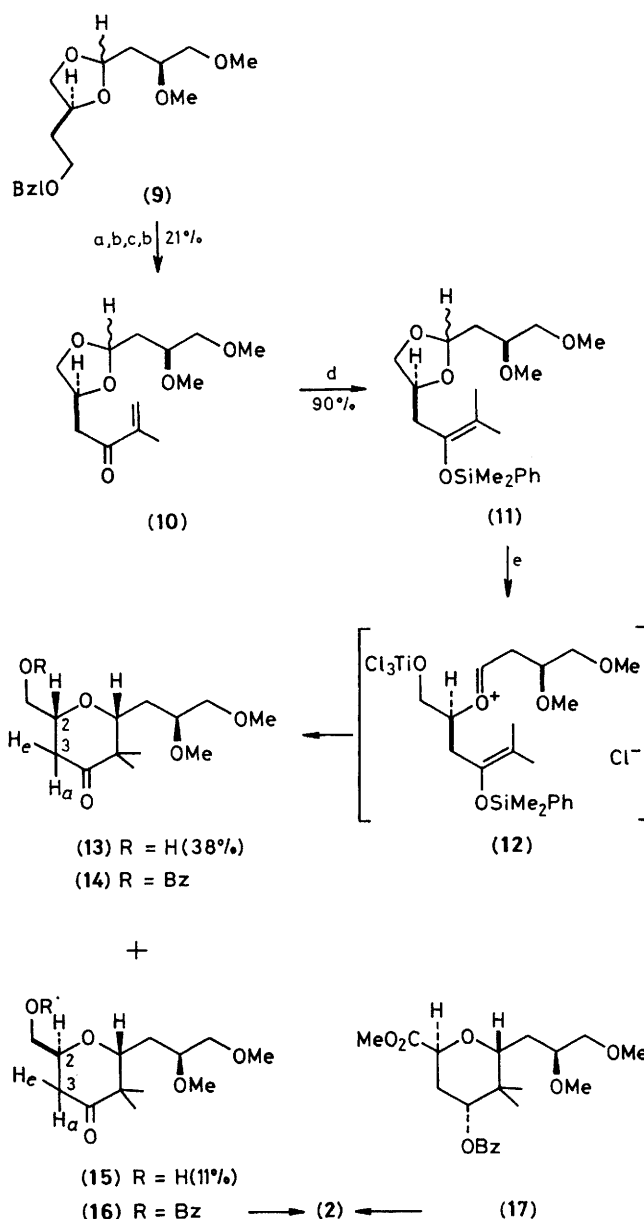


Bz = PhC(:O)-; Bzl = PhCH₂-; PCC = pyridinium chlorochromate; Ts = *p*-MeC₆H₄SO₂; THF = tetrahydrofuran; HMPA = hexamethylphosphoric triamide.

Scheme 1. a, TsOH-H₂O, THF, reflux, 3 h; b, NaI, MeI, THF-HMPA, 25 °C, 3 h; c, H₂-Pd/C in EtOH; d, PCC, CH₂Cl₂.

(C-1—C-4 and C-6—C-9) in which three of the four carbon atoms bear oxygen substituents. Furthermore, the chiral centres at C-2 and C-8 have the (*S*)-configuration. Taken together, these structural features suggested (*S*)-(-)-malic acid (3) as a suitable starting material. Thus (3) was converted by known procedures into the alcohol (4)⁵ from which the benzyl ether (5) was prepared (PhCH₂Br, NaH, HMPA-THF) in 95% yield. Routine transformations then served to convert (5) into the diol (6) and the aldehyde (8) (Scheme 1). These were condensed (TsOH, CH₂Cl₂) at room temperature in the presence of MgSO₄ to give a 66% yield of the isomeric dioxolans (9) as an inseparable mixture. That the *cis*-isomer was the major product (*ca.* 75% of the mixture) was expected from Eliel's work⁶ and verified by ¹³C n.m.r. spectroscopy:⁷ δ 102.1 and 101.5 p.p.m. for the *cis*- and *trans*-isomers respectively.

The benzyl ether (9) was transformed in four unexceptional steps into the sensitive enone (10) which underwent smooth rhodium(i)-catalysed hydrosilylation⁸ (Scheme 2) to give the enol silyl ether (11) in 90% yield. Compound (11) contains both the acetal and enol silyl ether components required for the pivotal directed aldol condensation. Thus, treatment of (11) with 2 equiv. of TiCl₄ in CH₂Cl₂ at -78 °C for 1 h gave several products among which were the tetrahydropyran-4-ones (13) (38%) and (15) (11%), which were separated by



Scheme 2. a, Na, liq. NH₃; b, PCC, CH₂Cl₂; c, CH₂=CMe-MgCl, THF; d, PhMe₂SiH, (Ph₃P)₃RhCl, 55 °C, 1 h; e, TiCl₄ (2 equiv.), CH₂Cl₂, -78 °C, 1 h.

chromatography. It was presumed that co-ordination of the Lewis acid to the less hindered dioxolan oxygen atom would lead to the same (*E*)-oxonium ion (12) from both the *cis*- and *trans*-dioxolan isomers.

That the desired product (15) was the minor isomer was evident from the 90 MHz ¹H n.m.r. spectra of the corresponding benzoates (14) and (16). The resonances for the C-3 axial proton H_a (δ 2.71, dd, *J*_{gem} 13 Hz, *J*_{vic} 12 Hz) and the C-3 equatorial proton H_e (δ 2.38, dd, *J*_{gem} 13 Hz, *J*_{vic} 3 Hz) indicated a *trans*-diaxial coupling of H_a with the axial proton on C-2, compatible with structure (14). The corresponding signals in (16) appeared as a multiplet centred at δ 2.67 (*W*₁ 10 Hz).

The synthesis was completed by reduction of the oxobenzoate (16) (NaBH₄) followed by benzylation to give pederol dibenzoate (2) as a gum. The 400 MHz ¹H n.m.r. spectrum of (2) was not first order and definitive assignment of the relative stereochemistry was not possible by spectral means

alone. Therefore, an independent synthesis of (2) was required. The known¹² diester (17) was reduced with Bu^1_2AlH and the product benzoylated to give a compound whose ^1H n.m.r. spectrum and h.p.l.c. mobility were identical with those of (2).

This new synthesis of a highly functionalized tetrahydropyran-4-one from acyclic precursors further extends the versatility of the Mukaiyama directed aldol condensation which has seldom been used in annelation reactions.^{9,10} Of critical importance in implementing this strategy was the successful application of the rhodium-catalysed hydrosilylation reaction to the regiospecific synthesis of an enol silyl ether in a highly oxygenated, base-sensitive substrate. Finally, by using readily available chiral precursors, the correct absolute stereochemistry of a key pederin fragment was obtained which hitherto has been prepared only in racemic form.^{11,12}

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