Synthetic Approaches to Pederin. A Synthesis of Pederol Dibenzoate

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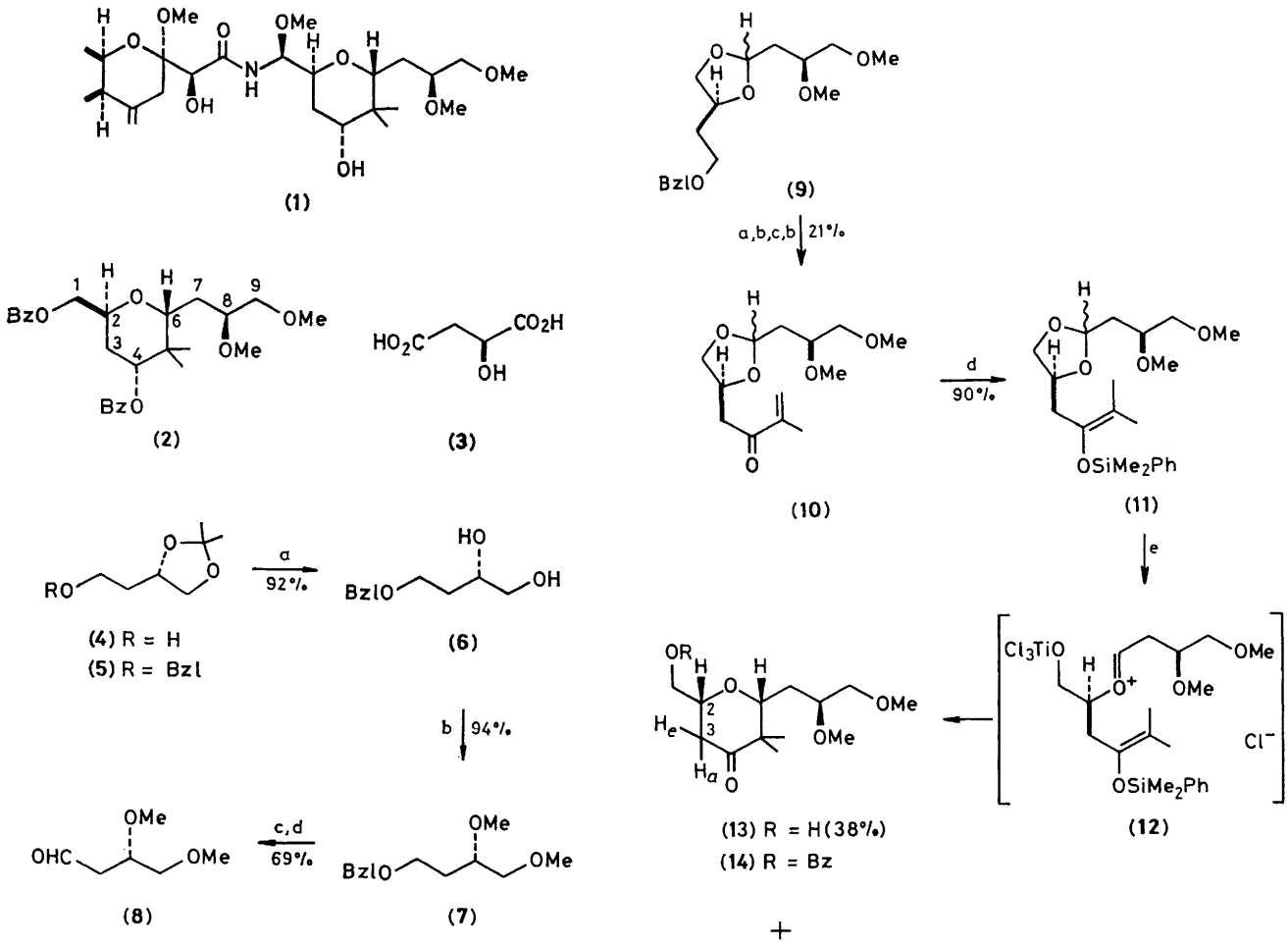
A new synthesis of functionalized tetrahydropyran-4-ones based on an intramolecular directed aldol condensation has been applied to a key fragment of pederin.

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 = $PhCH_2$–; PCC = pyridinium chlorochromate; Ts = *p*-$MeC_6H_4SO_2$; THF = tetrahydrofuran; HMPA = hexamethylphosphoric triamide.

Scheme 1. a, TsOH–H_2O, THF, reflux, 3 h; b, NaI, MeI, THF–HMPA, 25 °C, 3 h; c, H_2–Pd/C in EtOH; d, PCC, CH_2Cl_2.

(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 ($PhCH_2Br$, 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, CH_2Cl_2) at room temperature in the presence of $MgSO_4$ 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 work[6] and verified by ^{13}C 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 hydrosilylation[8] (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 $TiCl_4$ in CH_2Cl_2 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. NH_3; b, PCC, CH_2Cl_2; CH_2=CMe–MgCl, THF; d, $PhMe_2SiH$, $(Ph_3P)_3RhCl$, 55 °C, 1 h; e, $TiCl_4$ (2 equiv.), CH_2Cl_2, −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 ($W_{\frac{1}{2}}$ 10 Hz).

The synthesis was completed by reduction of the oxobenzoate (**16**) ($NaBH_4$) followed by benzoylation 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 known[12] diester (17) was reduced with $Bu^{i}_{2}AlH$ and the product benzoylated to give a compound whose ^{1}H 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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