Synthetic Approaches to Pederin. A Synthesis of (±)-Benzoylpedamide

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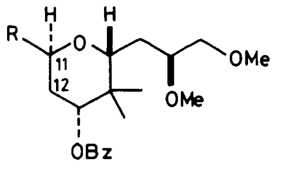
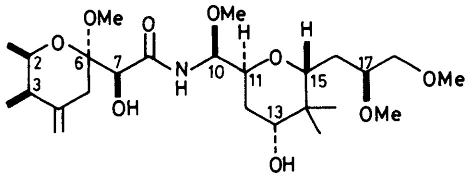
A Lewis acid-catalysed addition of Me_3SiCN to a 4-oxo-3,4-dihydro-2*H*-pyran is a key step in the synthesis of (±)-benzoylpedamide (**2**).

A disadvantage of recent syntheses of fragments (**1**)[1] and (**2**)[2] of the potent insect toxin pederin (**3**)[3] is the lack of stereocontrol at C(11). We now report a new synthesis of (±)-benzoylpedamide (**2**) in which the axial carboxamide function was introduced with high stereoselectivity *via* a Lewis acid-catalysed conjugate addition of Me_3SiCN to a vinylogous lactone.

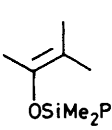
The bulk of the carbon skeleton of (**2**) was constructed from the enol silane (**4**) and (±)-3,4-dimethoxybutanal (**5**)[1] *via* a



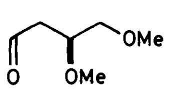
(**1**) R = CH_2OBz
(**2**) R = $CONH_2$



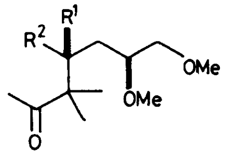
(**3**)



(**4**)

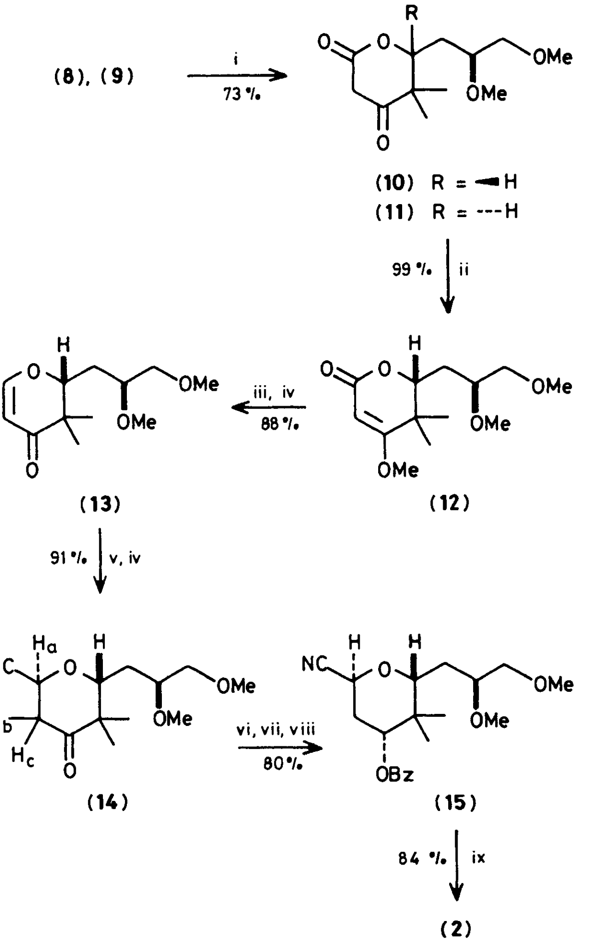


(**5**)



(**6**) R^1 = H, R^2 = OH
(**7**) R^1 = OH R^2 = H
(**8**) R^1 = H, R^2 = OCOCl
(**9**) R^1 = OCOCl, R^2 = H

Bz = Benzoyl



Scheme 1. *Reagents:* i, 2.2 equiv. Pr^i_2NLi–THF, −78 °C; ii, $MeOSO_2OMe$, K_2CO_3–acetone, reflux; iii, Bu^i_2AlH–toluene, −78 °C; iv, aqueous HCl–THF, 20 °C; v, 2 equiv. Me_3SiCN, 0.1 equiv. BF_3–Et_2O, CH_2Cl_2, −78 °C; vi, $NaBH_4$–EtOH; vii, chromatography on silica gel G (1:9 dioxane–benzene); viii, BzCl–pyridine; ix, H_2O_2, K_2CO_3–EtOH, 20 °C. THF = tetrahydrofuran.

Mukaiyama directed aldol condensation.[4] The stereochemistry of the reaction depended on the Lewis acid and the precise reaction conditions. At best, the desired aldol adduct (**6**) was obtained as the major diastereoisomer only when the enol silane (**4**) was added to the bright yellow complex derived by addition of 1—2 equivalents of $TiCl_4$ to the aldehyde (**5**) in CH_2Cl_2 at −78 °C. With 1 equivalent of $TiCl_4$ the reaction was complete in 7½ h whereas 2 equivalents effected the same transformation in 1 h. Under these conditions the mixture of diastereoisomers [(**6**) : (**7**) = 55 : 45] was obtained in 90% yield.

The stereorandom nature of the directed aldol condensation is surprising in the light of the impressive 1,3-asymmetric induction which has been observed[5,6] recently in the $TiCl_4$-catalysed addition of enol silanes and other carbon nucleophiles to β-alkoxyaldehydes.

The mixture (**6**), (**7**) was converted into the chloroformates (**8**), (**9**) in 88% yield in CH_2Cl_2 using 2 equivalents each of phosgene and pyridine. Cyclisation of (**8**), (**9**) was achieved in tetrahydrofuran at −78 °C with 2.2 equivalents of lithium di-isopropylamide to give a 73% yield of a mixture of β-keto lactones from which the desired diastereoisomer (**10**) was separated from the crystalline (**11**) by trituration in ether followed by filtration. The key intermediate (**13**) was then derived from (**10**) by standard transformations (Scheme 1).

Introduction of the axial substituent at C(11) was achieved by reaction of (**13**) with excess of Me_3SiCN in CH_2Cl_2 at −78 °C in the presence of BF_3–Et_2O (0.1 equiv.) to give an enol silane which was hydrolysed to give the ketonitrile (**14**) with dilute HCl. The ketonitrile (**14**) was obtained in 91% yield as a single isomer, the stereochemistry of which was assigned from its ^1H n.m.r. spectrum (400 MHz, $CDCl_3$): H_a (δ 5.175, dd, J_{ab} 8, J_{ac} 2 Hz); H_b (δ 3.070, dd, J_{bc} 15.5, J_{ba} 8 Hz); H_c (δ 2.560, dd, J_{cb} 15.5, J_{ca} 2 Hz). By using standard transformations (Scheme 1), (**14**) was converted in 3 steps into (±)-benzoylpedamide (**2**) (m.p. 150.5—152.5 °C).

The synthesis reported herein provides multigram quantities of (**2**) from cheap, readily available starting materials. Since the aldehyde (**5**) is available in chiral form from (*S*)-(−)-malic acid,[1] the route will also provide chiral (**2**).

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