Synthetic Approaches to Pederin. A Synthesis of Ethyl Pederate

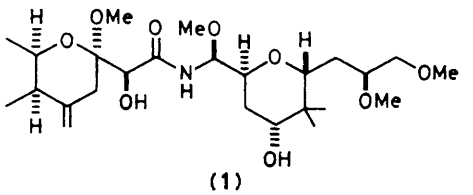
Kim Isaac,[a] Philip Kocienski,*[a] and Simon Campbell[b]

[a] *Department of Organic Chemistry, The University, Leeds LS2 9JT, U.K.*
[b] *Pfizer Central Research, Sandwich, CT13 9NJ, U.K.*

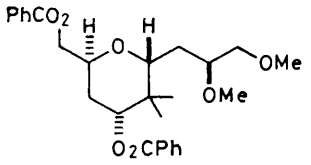
Treatment of the chloroformate (**7**) with $SnCl_4$ gives the unstable lactone (**8**) which is a key intermediate in a brief synthesis of ethyl pederate.

For a projected synthesis of the potent insect toxin pederin (**1**),[1] the major fragments pederol dibenzoate (**2**) and ethyl pederate (**3**) are required. We report a synthesis of ethyl pederate which, like our recent synthesis of pederol dibenzoate,[2] has as its cardinal step a silicon-mediated cyclisation.

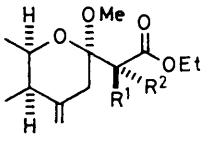
The reaction of the Grignard reagent prepared from the bromide (**5**)[3] with *trans*-2,3-epoxybutane in the presence of a catalytic amount of CuI gave the alcohol (**6**) in 47% yield. Thus, in one step, two of the four chiral centres present in the final product were established. The alcohol (**6**) reacted with phosgene in the presence of pyridine to give the chloroformate (**7**) which cyclized on treatment with $SnCl_4$ in CH_2Cl_2 at 0 °C for 3 h to give the unstable β,γ-unsaturated lactone (**8**) in 57% yield.[4] The lithium enolate prepared from the ethyl glycolate derivative (**10**)[5] (lithium di-isopropylamide, tetrahydrofuran, −78 °C) reacted with the lactone (**8**) to give a diastereoisomeric mixture of hemiacetals (**11**) from which the hydroxy protecting group was cleaved on treatment with aqueous acid. The resultant diol (**12**) reacted stereospecifically with acidic MeOH to give a 2:1 mixture of ethyl *epi*-pederate (**4**) and ethyl pederate (**3**) in *ca.* 20% overall yield from (**8**). The isomers (**3**) and (**4**) were easily separated by column chromatography on Kieselgel and identified by their highly characteristic[5,6] ^1H n.m.r. spectra: δ (**3**) 1.15 (3H, d, *J* 9 Hz), 0.95 (3H, d, *J* 9 Hz), 1.35 (3H, t, *J* 7 Hz), 2.2 (1H, dq, *J* 14, *J'* 3 Hz), 2.4 (2H, s), 3.32 (3H, s), 3.95 (1H, dq, *J* 14, *J'* 3 Hz), 4.31 (2H, q,



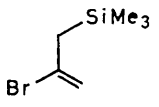
(1)



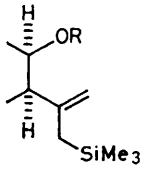
(2)



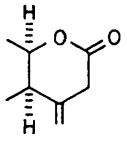
(3) R^1 = OH, R^2 = H
(4) R^1 = H, R^2 = OH



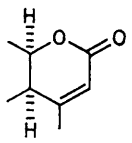
(5)



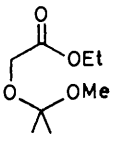
(6) R = H
(7) R = COCl



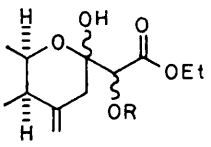
(8)



(9)



(10)



(11) R = C(Me)$_2$OMe
(12) R = H

J 7 Hz), 4.35 (1H, s), and 4.8 (2H, dt, *J* 11, *J'* 1 Hz); (**4**) 1.05 (3H, d, *J* 8 Hz), 1.2 (3H, d, *J* 8 Hz), 1.35 (3H, t, *J* 7 Hz), 1.98 and 2.84 (1H each, d, *J* 15 Hz), 2.25 (1H, dq, *J* 15, *J'* 3 Hz), 3.38 (3H, s), 3.95 (1H, dq, *J* 14, *J'* 3 Hz), 4.32 (2H, q, *J* 7 Hz), 4.42 (1H, s), and 4.8 (2H, dt, *J* 13, *J'* 2 Hz).

Previous syntheses of the pederic acid skeleton[5,6] used reagents and conditions which required that the unstable exocyclic methylene be introduced in the closing stages of the synthesis. The present approach has the advantage of being more direct and hence substantially shorter because the exocyclic methylene is incorporated early in the synthesis. There is economy in the reagents employed too, since the entire skeleton was constructed from the readily available reagents *trans*-but-2-ene, 1,2-dibromopropene, and glycolic acid. Finally the cyclisation of (**7**) is noteworthy for proceeding under conditions mild enough to permit the formation and isolation of the β,γ-lactone (**8**)—a compound which rearranges exclusively to the more stable isomer (**9**) under the slightest provocation.

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