The Total Synthesis of (±)-Pederin†

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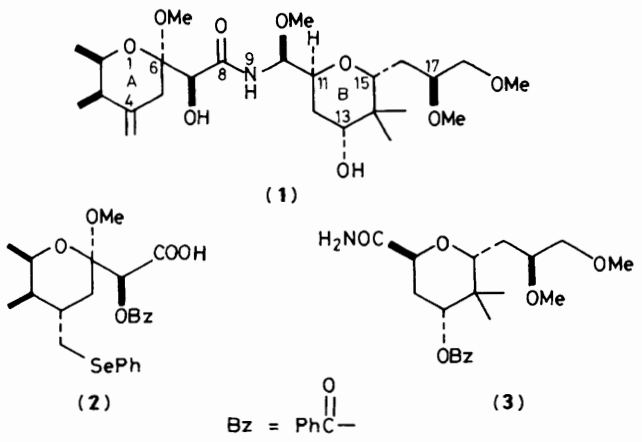
The conjugate addition of phenylselenomethyl-lithium to the α,β-unsaturated lactone (**4**) was a key step in a short synthesis of (±)-benzoylselenopederic acid (**2**); union of (**2**) and (±)-benzoylpedamide (**3**) by a modification of known procedures gave (±)-pederin (**1**).

Pederin (**1**) is a defence component of the blister beetle *Paederus fuscipes*. Pederin's unique structure is associated with several dramatic biological activities: it is a powerful vesicant; it induces cell fusion in human skin fibroblasts; it inhibits mitosis in intact HeLa cells; and it blocks protein biosynthesis at very low concentrations.[1] Two total syntheses of pederin have been reported[2,3] as have syntheses of various fragments.[4—8] We now report an alternative synthesis[3] of the ring A fragment benzoylselenopederic acid (**2**) and its union with the ring B fragment benzoylpedamide (**3**)[8] to give pederin (**1**).

For the synthesis of benzoylselenopederic acid (**2**) we required the selenolactone (**5**) and the protected glycolate ester (**10**) (Scheme 1). The selenolactone (**5**) was obtained stereoselectively by the conjugate addition of phenylselenomethyl-lithium[9] to the known[5] lactone (**4**) in 59% yield. The protected glycolate ester (**10**) was prepared in 4 steps in 73% overall yield from bromoacetyl chloride (**6**) as shown in Scheme 1. The lithium enolate of (**10**) reacted with selenolactone (**5**) to give a mixture of diastereoisomeric adducts (**11**) which, without purification, was hydrolysed to the diol (**12**); methanolysis then gave a chromatographically separable 1 : 1 mixture of (**13**) and (**14**) differing only in the stereochemistry at C-7 (pederin numbering). The relative stereochemistry of (**13**) was established by a single crystal *X*-ray analysis.[10] The

† All compounds reported are racemic.

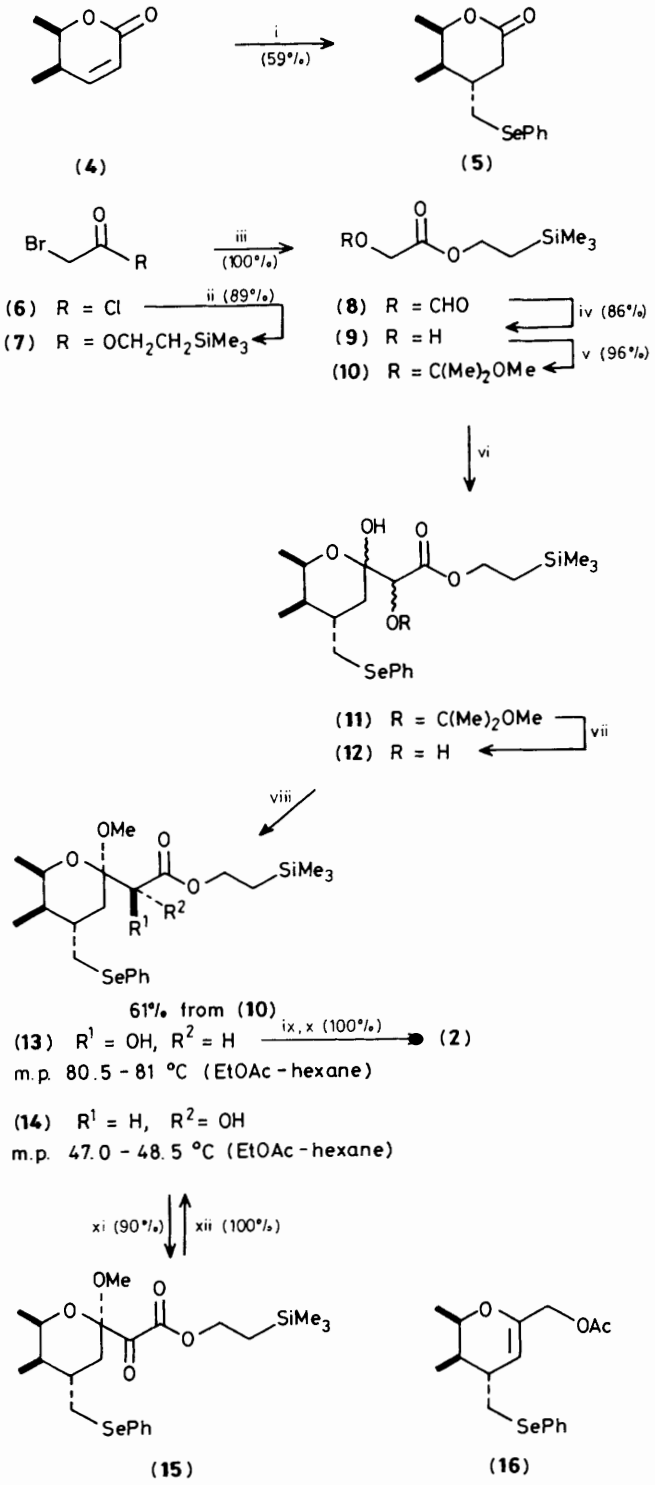


undesired isomer (**14**) could be oxidised to the α-ketoester (**15**) which was reduced stereoselectively with $NH_3{\cdot}BH_3$ complex to give a 7 : 1 mixture of (**13**) and (**14**) respectively. Two further steps were used to convert (**13**) into benzoylselenopederic acid (**2**).

The acid (**2**) was rather labile and was best generated and used immediately in the next step without further purification. For example, (**2**) (acetate instead of benzoate) decomposed on attempted chromatographic purification with loss of CO_2 and MeOH to give the dihydropyran (**16**). In practice, the acid (**2**) was isolated by partitioning the tetra-n-butylammonium salt, derived from fragmentation of the silylester (**13**), between ether and water. Under these conditions, *without the addition of any acid*, the desired carboxylic acid (**2**) extracted into the ether layer from which it could be recovered after drying and evaporation.

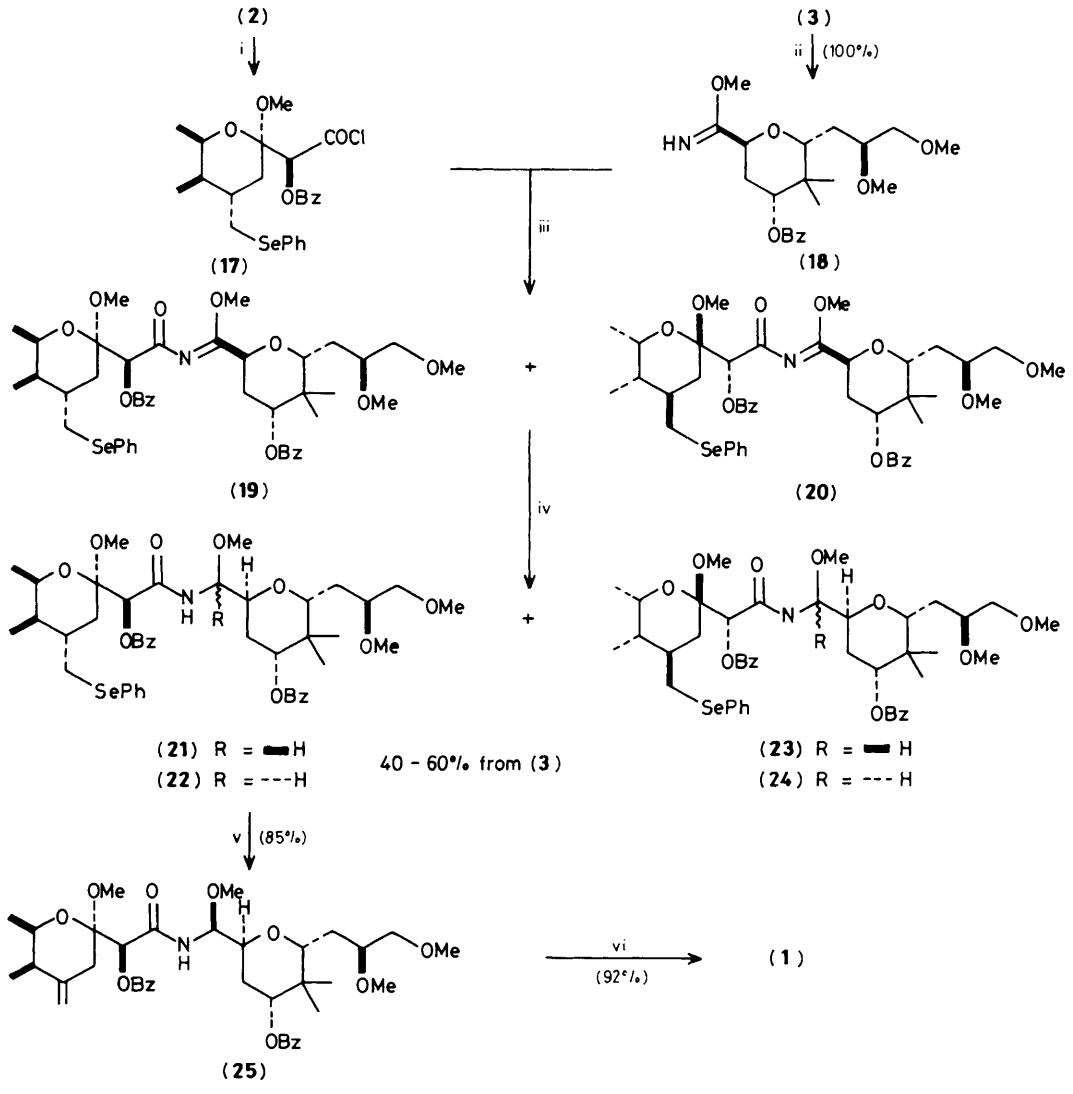
Union of the A- and B-ring fragments (**2**) and (**3**) and construction of the crucial *N*-acylaminal bridge was achieved by the Matsumoto–Nakata–Oishi procedure[2,3] as shown in Scheme 2. Thus, acid chloride (**17**)[11] (1.5 equiv.) and imidate ester (**18**) (1 equiv.) condensed in the presence of NEt_3 to form a 1 : 1 mixture of diastereoisomeric *N*-acylimidates (**19**) and (**20**) which, without separation or purification, was reduced to a 1 : 1 : 1 : 1 mixture of the diastereoisomeric *N*-acylaminals (**21**)—(**24**) in 40—60% overall yield from (**3**). The desired diastereoisomer (**22**) was separated with difficulty by gradient-elution high performance liquid chromatography (Zorbax SIL, 9.5 mm × 25 cm, 25 → 40% methyl t-butyl ether–hexane, 6 cm³/min), and converted into pederin dibenzoate (**25**) by selenoxide elimination. Hydrolysis of (**25**) then gave (±)-pederin which was identical by 360 MHz ^{1}H n.m.r. spectroscopy, mass spectrometry, and t.l.c. mobility with an authentic sample of natural (+)-pederin provided by Professor Ghiringhelli: δ_H (360 MHz, $CDCl_3$) 7.158 (1H, d, *J* 9.7 Hz, NH), 5.391 (1H, dd, *J* 8.0, 9.7 Hz, 10-H), 4.863 [1H, t, *J* 1.9 Hz, C(4)=CH], 4.751 [1H, t, *J* 1.9 Hz, C(4)=CH], 4.313 (1H, t, *J* 2.2 Hz, 7-H), 4.013 (1H, dq, *J* 2.8, 6.6 Hz, 2-H), 3.897 (1H, d, *J* 2.2 Hz, 7-OH), 3.806 (1H, ddd, *J* 2.5, 6.3, 8.0 Hz, 11-H), 3.650 (1H, dd, *J* 4.6, 10.9 Hz, 13-H), 3.5—3.3 (3H, m, 17-H, 18-H_2); 3.407, 3.394, 3.348, and 3.343 (each 3H, s, OMe); 3.250 (1H, dd, *J* 2.0, 10.2 Hz, 15-H), 2.454 (1H, d, *J* 14.2 Hz, 5-H), 2.362 (1H, dt, *J* 1.9, 14.2 Hz, 5-H), 2.258 (1H, dq, *J* 2.8, 7.0 Hz, 3-H), 2.052 (1H, ddd, *J* 2.5, 4.6, 13.4 Hz, 12-H), 1.761 (1H, ddd, *J* 6.2, 10.9, 13.4 Hz, 12-H), 1.729 (1H, ddd, *J* 3.0, 10.2, 14.0 Hz, 16-H), 1.609 (1H, ddd, *J* 2.0, 9.3, 14.0 Hz, 16-H), 1.61 (1H, br., 13-OH), 1.202 (3H, d, *J* 6.6 Hz, 2-Me), 1.028 (3H, d, *J* 7.0 Hz, 3-Me), 0.951 (3H, s, 14-Me), and 0.884 (3H, s, 14-Me); δ_C (90 MHz, $CDCl_3$)‡ 171.9, 145.9,

‡ Recorded on a sample of naturally-derived (+)-pederin.



Scheme 1. *Reagents:* i, $PhSeCH_2Li$, THF–HMPA (1 : 1), −85 °C, 1 h; ii, $Me_3SiCH_2CH_2OH$, pyridine, CH_2Cl_2, 0 °C; iii, HCO_2Na, DMF, 50 °C, 15 h; iv, NEt_3, MeOH, 5 °C, 30 min; v, 2-methoxypropene, HCl (trace), CH_2Cl_2, 0 °C, 2 h; vi, Pr^i_2NLi, THF, −70 °C, 1 h followed by dropwise addition of (**5**) in THF, −75 °C, 2.5 h; vii, H_3O^+–THF, 20 °C, 20 min; viii, *p*-TsOH, MeOH, 20 °C, 3.5 h; ix, PhCOCl, catalytic amount of DMAP, pyridine, CH_2Cl_2, 20 °C, 100 min; x, $Bu^n_4NF{\cdot}3H_2O$, THF, 20 °C, 20 min; xi, $Me_2\overset{+}{S}Cl\ \bar{C}l$, NEt_3, CH_2Cl_2, −70 °C, 1.5 h; xii, $NH_3{\cdot}BH_3$, THF, −95 → + 20 °C over 1.5 h.

Abbreviations: THF = tetrahydrofuran; HMPA = hexamethylphosphoric triamide; DMF = dimethylformamide; *p*-TsOH = *p*-$MeC_6H_4SO_3H$; DMAP = 4-*N*,*N*-dimethylaminopyridine.



Scheme 2. *Reagents*: i, $SOCl_2$, pyridine CH_2Cl_2, 20 °C, 10 min; ii, Me_3OBF_4, CH_2Cl_2, 20 °C, 1 h; iii, NEt_3, CH_2Cl_2, 20 °C, 2 h; iv, $NaBH_4$, CH_2Cl_2–Pr^iOH, 0 °C, 40 min; v, $NaIO_4$, MeOH–H_2O, 20 °C, 30 min followed by refluxing in benzene–NEt_3 (1 : 1), 2 min; vi, LiOH, MeOH–H_2O, 50 °C, 5 h.

110.7, 99.9, 79.7, 77.9, 76.0, 74.0, 73.1, 72.8, 72.1, 69.7, 59.2, 56.9, 56.4, 49.1, 41.5, 38.7, 34.3, 30.3, 29.7, 23.1, 18.0, 13.1, and 12.2; *m/z* (fast atom bombardment) 526 (MNa$^+$, 2%), 504 (MH$^+$, 10), 472 (5), 440 (20), and 89 (100); (electron impact) 454 (0.5%), 439 (3), 421 (9), 394 (6), 368 (5), 362 (7), 336 (4), 282 (9), 240 (32), and 60 (100).

We thank the S.E.R.C., Pfizer Central Research, and the Royal Society of Chemistry (Hickinbottom Fellowship to P. K.) for financial support. We also thank Pfizer Central Research for a CASE studentship (T. W.) and for recording the mass spectra of pederin (Dr. David Bowen). We gratefully acknowledge the assistance of Professor D. Ghiringhelli (Institute of Chemistry, Polytechnic of Milan) for a generous sample of natural (+)-pederin and Professor T. Nakata (RIKEN) for providing crucial experimental details and spectral data.

Received, 25th September 1986; Com. 1369

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10 The *X*-ray analysis was performed by Dr. J. Bordner, Pfizer Central Research, Groton, Connnecticut, U.S.A. Details will be published elsewhere.
11 The coupling of fragments (**2**) and (**3**) probably does not proceed exclusively *via* acid chloride (**17**). Matsumoto and co-workers have suggested a competing pathway involving *N,N'*-sulphinyl-diacylimidates: F. Matsuda, M. Yanagiya, and T. Matsumoto, *Tetrahedron Lett.*, 1982, **23**, 4043.