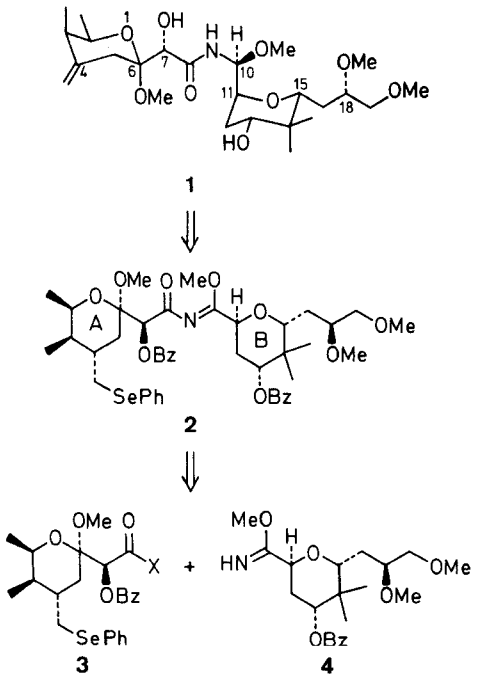
Pederin: The Metallated Dihydropyran Approach. Stereoselective Reduction of *N*-Acylimidates *via* Rhodium-Catalysed Hydroboration

Philip Kocieński,* Krzysztof Jarowicki, Stanislaw Marczak
Department of Chemistry, The University, Southampton, SO9 5NH, England

Dedicated to Professor H.J. Bestmann in recognition of seven years distinguished service as Executive Editor of Synthesis

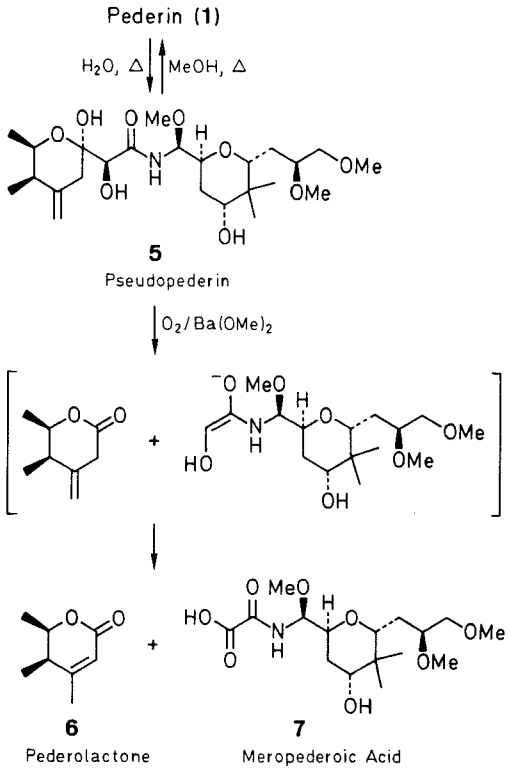
A synthesis of the insect toxin pederin (**1**) based upon the union of metallated dihydropyran **8** with the oxamate ester derivative **9** is described. Noteworthy features include (a) a new method for the construction of metallated dihydropyrans which tolerates heteroatom functionality and (b) a rhodium-catalyzed hydroboration reaction which enables stereocontrolled formation of the stereogenic centre at C10.

Pederin (**1**) is a vesicant isolated from the beetle *Paederus fuscipes*. It is one of a small class of potent, biologically active natural products whose novel structure and dense array of sensitive functionality poses a considerable synthetic challenge.[1] Pederin is not robust and the first three total syntheses were designed to avoid problems associated with the high acid lability of the homoallylic acetal array in ring A. The *N*-acyl aminal is sensitive too: it can be destroyed with acid or base though it is much less sensitive to acid than the acetal. The first total synthesis of pederin was accomplished by Matsumoto and co-workers[2] who pioneered viable protocols for achieving the difficult task of constructing both the highly hindered *N*-acyl aminal bridge and the homoallylic acetal. Their approach depended upon the union of the imidate ester **4** (Scheme **1**) with the ring-A acyl derivative **3** – a slow transformation that was complicated by the instability of **3**. The two subsequent syntheses by Nakata, Oishi, and co-workers[3] and the Southampton group[4] made use of the Matsumoto protocol for constructing the *N*-acyl aminal bridge and they fared no better. All three approaches were blighted by poor stereoselectivity in the reduction of the *N*-acyl imidate **2**.

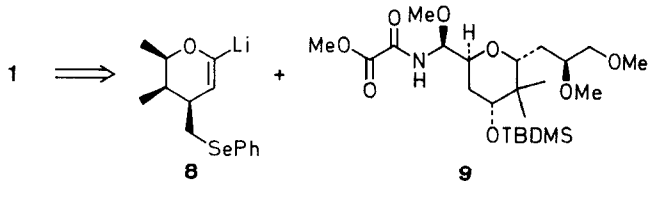


Scheme 1

We now report substantial improvements to a new strategy[5] which was inspired by some of the elegant degradation studies conducted by Quilico and co-workers[6] during their structure elucidation of pederin. Pseudopederin (**5**), the hydrolysis product of pederin, undergoes an easy retroaldol reaction on heating in base (Scheme **2**) in presence of air to give meropederoic acid (**7**) wherein the *N*-acyl aminal group is still intact. These transformations suggested an alternative disconnection which might circumvent the cascade of problems which beset the closing stages of our previous synthesis. The new strategy (Scheme **3**) required a metallated dihydropyran (e.g. **8**) functioning as an acyl anion equivalent in reaction with a suitably activated meropederoic acid derivative such as **9**. In the ensuing discussion we will describe first the synthesis of the A-ring fragment **8**, then the meropederoic acid derivative **9**, and finally their union in the key step *en route* to pederin.



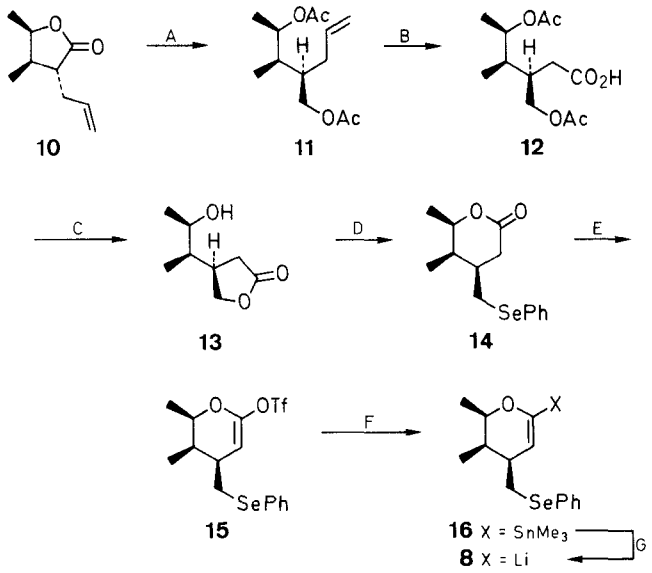
Scheme 2



Scheme 3

Synthesis of Metallated Dihydropyran 8

Previous investigators[2-4] had confirmed the wisdom of avoiding problems associated with the instability of the C4 methylene in ring A by delaying its introduction until very late in the synthesis;[7] therefore this troublesome functionality had to be integrated into a suitable ring-A fragment in latent form from the outset. We chose the aryl selenoether group because its easy elimination via the corresponding selenoxide was well precedented in the pederin series. A second boundary condition implied in our approach was the use of a metallated dihydropyran as an acyl anion equivalent. There was good precedent for the ready formation of metallated dihydropyrans[8] and their efficient participation in C–C bond formation reactions is well established[9] but no useful information was at hand which suggested ways of making a lithiated dihydropyran bearing the requisite arylselenyl group. The problem is not a trivial one because alkyllithiums which deprotonate dihydropyrans also attack aryl selenoethers with displacement of aryllithium.[10] Experience had shown that the problem could not be eluded by simply delaying the introduction of the arylselenyl group into ring A until after the construction of the bulk of the pederin skeleton and, in any event, to do so would deprive us of some of the benefits of convergence. We were therefore obliged to devise a new method for making metallated dihydropyrans which would tolerate the aryl selenoether group. Scheme **4** shows how this was done.



10 11 12 13 14 15

Yields, reagents, and conditions

A	96%	(i) $LiAlH_4/Et_2O$, reflux, 3 h; (ii) Ac_2O/DMAP/Py/CH_2Cl_2, r.t., 15 h.
B	–	(i) O_3/MeOH, −80 °C; (ii) Me_2S, −80 °C → r.t., 1.5 h then r.t., 10 h; (iii) H_2CrO_4/acetone/H_2O; r.t., 15 min.
C	75%	(i) KOH/H_2O/MeOH, r.t., 10 h; (ii) HCl.
D	77%	(i) PhSeNa/18-crown-6/THF, reflux, 20 h; (ii) aq 2 M HCl/Et_2O; r.t., 45 min.
E	–	(i) LHMDS/THF/HMPT, −80 °C, 2 h; (ii) $PhN(Tf)_2$, 0 °C, 1 h then r.t., 2 h.
F	61%	Me_6Sn_2/LiCl/$Pd[Ph_3P]_4$/THF, reflux, 15 h.
G	100%	BuLi/THF, −80 °C, 15 min.

Overall yield of **16** from **10** = 34% (11 steps).

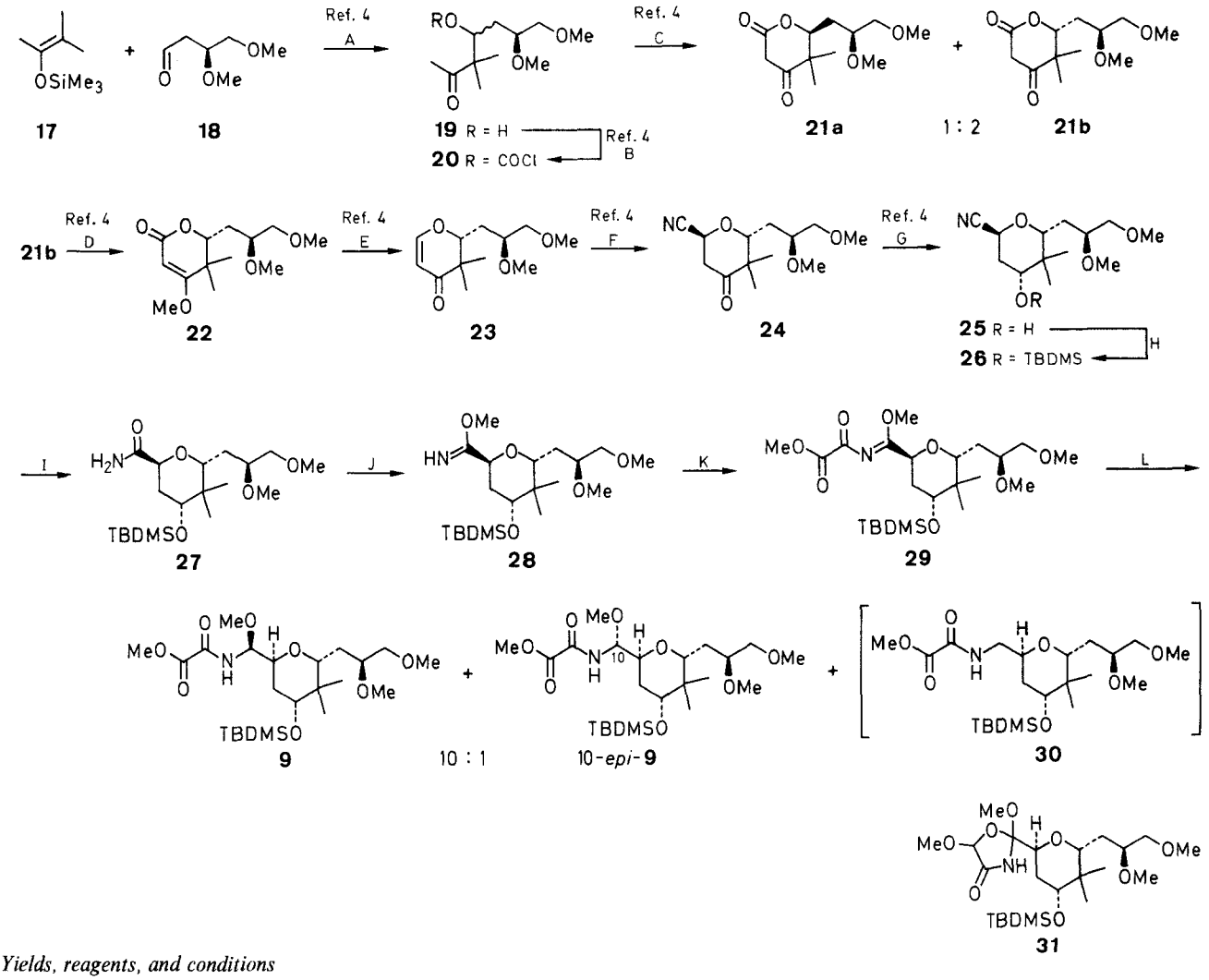
Scheme **4**

The readily available homochiral lactone **10** was prepared by the method of Meinwald[11] and transformed to a mixture of the crystalline butyrolactone **13** (72%) and the corresponding valerolactone (3%) which were separable by chromatography. Treatment of the mixture with sodium phenylselenide in the presence of 18-crown-6, conditions which interconvert the isomeric lactones, resulted in selective nucleophilic displacement of the carboxyl group of the butyrolactone to give, after workup, the aryl selenoether **14** in 77% yield.[12] The lactone **14** was then converted to the unstable enol triflate derivative **15**, and coupled under palladium catalysis with Me_6Sn_2 to give the desired enol stannane derivative **16** in 61% overall yield from the lactone. The enol stannane was sensitive to acid but it could be purified by rapid chromatography on basic alumina deactivated with water. The transmetallation of **16** to the corresponding lithium derivative **8** occurred with the speed and efficiency expected without interference from the aryl selenoether group.[13]

Synthesis of the Meropederoic Acid Derivative 9

The preparation of the homochiral meropederoic acid derivative **9** is summarised in Scheme **5**. Our previous synthesis[4] of the racemic cyano alcohol **25** was simply adapted for the present synthesis by starting the sequence with a directed aldol reaction between the enol silane **17** and (*S*)-(−)-3,4-dimethoxybutanal **(18)**. The delicate aldol product **19**, obtained as an inseparable mixture of diastereoisomers (ca. 1:2) was efficiently converted to the β-ketolactones **21a** and **21b** via intramolecular acylation of the enolate derived from treatment of the chloroformate **20** with lithium diisopropylamide. This reaction gave several byproducts but these were readily removed by extraction of the β-ketolactones into aqueous sodium hydrogen carbonate solution followed by acidification. Upon cooling an ethereal solution of the mixture, the unwanted diastereoisomer **21a** crystallised out and concentration of the mother liquor gave the desired isomer **21b** as an oil of ca. 90% diastereomeric purity. Isomer **21b** was then transformed to the dihydropyranone **23** using standard transformations and the isomeric impurities finally removed by chromatography. Thus the ease of separation at step C compensated for the low level of diastereocontrol in the directed aldol reaction – the step which remains the worst (in stereochemical terms) of our synthesis. Subsequent reactions leading to **25** enjoyed much better stereocontrol (step F, ≥ 30:1 and step G, 25:1).

To complete the synthesis of the ring-B meropederoic acid derivative **9**, the cyano alcohol **25** was converted to the *N*-acylimidate **29** in four steps using standard transformations. Both imidate ester intermediates **28** and **29** were prone to hydrolysis and best overall yields were



Yields, reagents, and conditions

A	91%	$TiCl_4/CH_2Cl_2$, −85°C, 1 h.	G	99%	$NaBH_4/CeCl_3$/MeOH, −80°C, 0.5 h.
B	93%	$COCl_2$/Py, 0°C, 1 h.	H	94%	TBDMSCl/imidazole/DMAP/DMF, reflux, 2 h.
C	80%	LDA/THF, −70°C, 1 h.	I	74%	H_2O_2/K_2CO_3/EtOH, r.t., 1.5 h.
D	99%	Me_2SO_4, K_2CO_3/acetone, reflux, 2 h.	J	–	Me_3OBF_4/CH_2Cl_2, r.t., 3 h.
E	70%	DIBAL-H/toluene, −70°C, 3 h.	K	–	MeO_2C–COCl/Py/CH_2Cl_2, 0°C, 15 min.
F	95%	$Me_3SiCN/BF_3 \cdot OEt_2/CH_2Cl_2$, 0°C, 1.5 h.	L	70%	catecholborane, $RhCl[PPh_3]_3$/PhMe, −70°C, 15 h.

Overall yield of **9** from **18** = 21% (12 steps).

Scheme **5**

Table 1. Metal Hydride Reduction **29**

Metal Hydride	**9** : 10-*epi*-**9**	Yield (%)
$BH_3 \cdot NH_3/CH_2Cl_2$, 0°C, 1 h	2 : 1	45
$BH_3 \cdot NH_3$/HMPT, r.t.	1 : 3	–
BH_3 · morpholine/HOAc, r.t., 1.5 h	1 : 3	55
9-BBN/THF, r.t., 2 h	3 : 1	15
$NaBH_3(CN)$/HOAc, r.t., 1.5 h	1 : 5	70
$NaBH_3(CN)$/*t*-amyl alcohol, r.t., 12 h	1 : 8	–
$NaBH(OAc)_3$/HOAc, r.t., 1.5 h	2 : 1	50
Bu_4NBH_4/CH_2Cl_2, 0°C	1 : 20	33
Bu_4NBH_4/HOAc	3 : 2	–

Table 2. Physical Constants for Intermediates in Scheme **5**

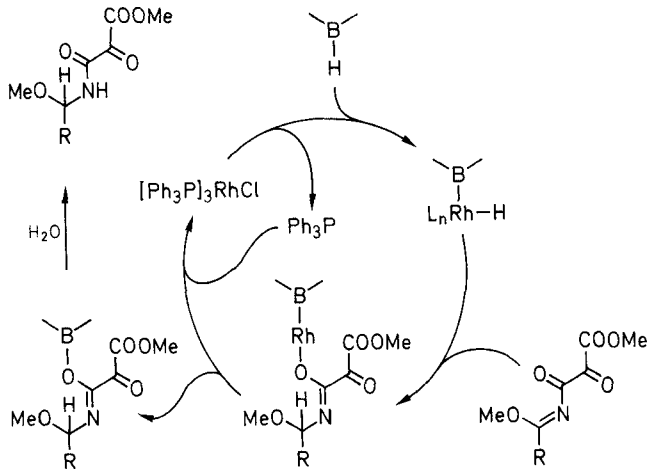
Compound	$[\alpha]_D$ (*c*, $CHCl_3$)	mp (°C) (solvent) or bp (°C/Torr)
18	−10.5 (3.4)	23–26/0.2
21a	−29.0 (1.0)	115–117 (Et_2O)
21b	−1.8 (6.0)	–
22	−12.0 (1.0)	–
23	+107.0 (1.0)	–
24	+104.1 (1.3)	61–62 (Et_2O/hexane)
25	+66.2 (1.3)	–
26	+57.0 (1.1)	46–48 (hexane)
27	+27.8 (1.2)	–
9	+41.9 (7.5)	–

obtained by working fast and with minimal purification. Acylation of imidate **28** was accompanied by small amounts of the nitrile **26** from elimination of MeOH.

Reduction of the *N*-acylimidate **29** (step L, Scheme **5**) proved the most difficult step of all and considerable experimentation was required before a satisfactory

conclusion was reached. A wide variety of reducing agents failed to generate the desired diastereoisomer **9** selectively: for example, no reaction occurred under the usual catalytic hydrogenation conditions (Pd-C) in aprotic solvents. Homogeneous hydrogenation using $[Ph_3P]_3RhCl$ was equally ineffective. Metal hydride reducing agents were more promising and Table 1 lists a small selection of the 50 reagents and conditions examined. In most cases stereoselectivity or yields were low. In the case of L-Selectride® ($LiBH(s\text{-}Bu)_3$), the only product observed was oxazolidine derivative **31**.

A stereoselective reduction of *N*-acylimidate **29** to the desired *N*-acyl aminal **9** was eventually achieved using an unprecedented reaction – reduction with catecholborane in the presence of a catalytic amount of $[Ph_3P]_3RhCl$.[14] Under these conditions a 70% yield of a mixture of diastereoisomeric *N*-acyl aminals was obtained in which the desired isomer **9** predominated (10:1) and this could be substantially enriched by column chromatography. Varying amounts of the over-reduction product **30** were also formed and occasionally this could be the major product if the *N*-acylimidate **29** was insufficiently pure. A mechanism for the reduction involving a rhodium-catalysed 1,4-hydroboration reaction is proposed in Scheme **6**.



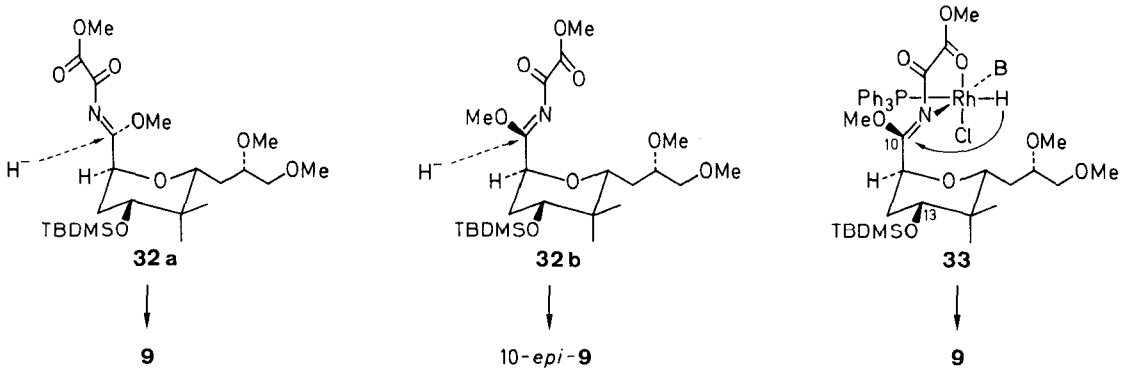
Scheme **6**

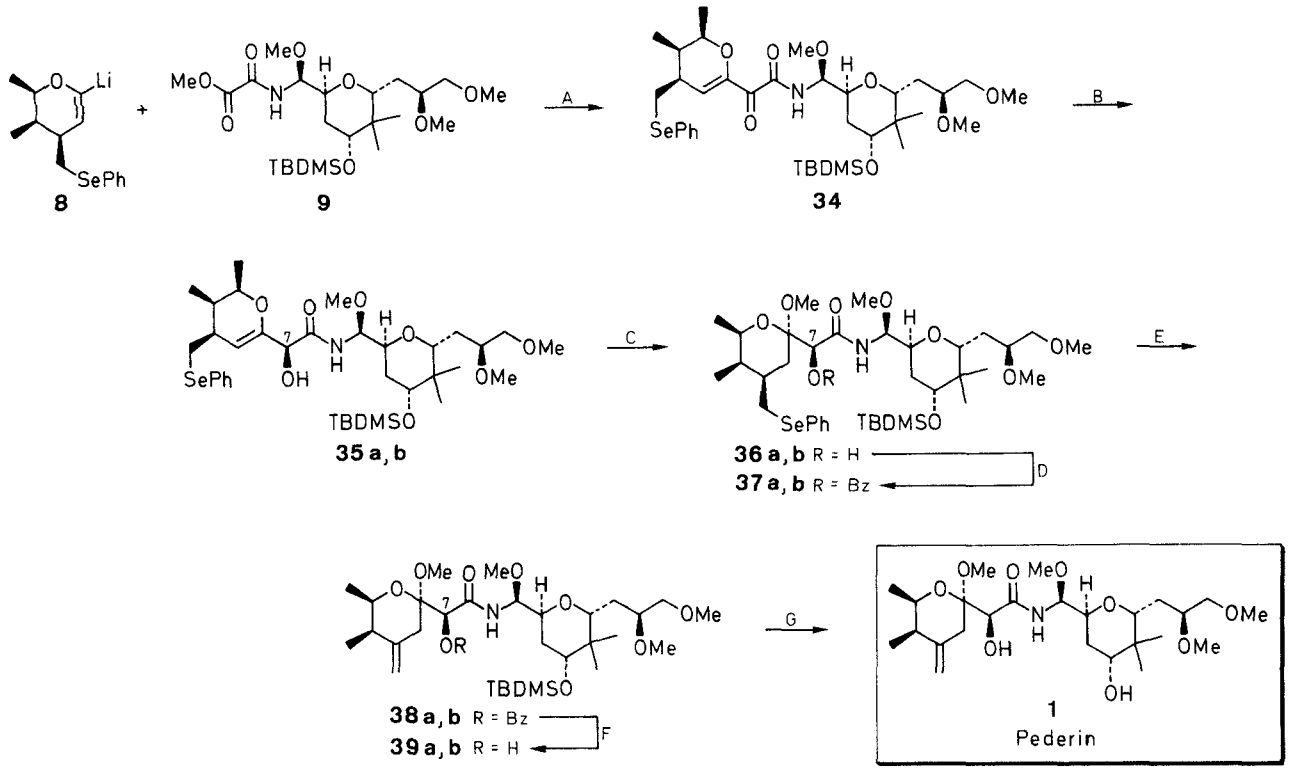
The welcome stereoselectivity of the catecholborane reduction deserves further comment. Previous experience and the results from the present study demonstrates that high levels of stereocontrol are achieved in the formation of the unwanted diastereoisomer 10-*epi*-**9** in accord with a preferential attack on rotamer **32b** from the least hindered face of the *N*-acylimidate function. Consequently, stereoselective reduction in the desired sense requires some means for enhancing the population of rotamer **32a** or, alternatively, a means for delivering hydride from the more hindered face of **32b**. The latter condition could be met by means of hydride delivery (intra- or intermolecularly) via complex **33** in which the *N*-acylimidate side chain serves as a bidentate ligand in the rhodium complex derived from oxidative addition of Rh(I) to the borane. In this complex, the triphenylphosphine ligand very effectively shields one face of the *N*-acylimidate thereby directing reduction in the desired sense. According to models, the corresponding complex from rotamer **32a** suffers from severe steric congestion with the *tert*-butyldimethylsilyl protecting group at C13. The crucial role of the protecting group in ensuring preferential formation of complex **33** was verified experimentally since reduction of the *N*-acylimidate bearing an *O*-benzoyl function at C13 was much less diastereoselective (3:2 vs 10:1).

Union of the Fragments

Construction of the *N*-acyl aminal bridge by acylation of a suitable metallated dihydropyran was simple enough in principle but considerable effort was required before it could be put into practice. Model studies in linking 6-lithio-3,4-dihydropyran with an anhydride derived from reaction of 13-*O*-benzoyl meropederoic acid with catecholborane were promising but all attempts to extend this method to pederin itself were fruitless despite extensive variation in the metal and the acyl activating group. The desired transformation was eventually accomplished by simply reacting lithiated dihydropyran **8** with the methyl ester **9** in the presence of tetramethylethylenediamine (TMEDA) at low temperature to give a 54% yield of the adduct **34** (Scheme **7**).

With the bulk of the pederin skeleton now constructed, completion of the synthesis merely required the introduction of the two adjacent stereogenic centres at C6 and C7 and a few functional group transformations. The





Yields, reagents, and conditions
[**a** series shown; **b** series = C7 epimer]

A	54%	TMEDA/THF, −80°, 30 min.
B	–	L-Selectride/THF, −80°, 15 min.
C	–	CSA/10% MeOH in CH_2Cl_2, r.t., 3.5 h.
D	70%	$BzCl/Et_3N/DMAP/CH_2Cl_2$, r.t., 12 h.
E	84%	(i) $NaIO_4/MeOH : H_2O$ (3:1), r.t., 30 min; (ii) Et_3N/benzene, reflux, 2 min.
F	86%	(i) LiOH/MeOH, r.t., 30 min; (ii) separate diastereoisomers.
G	69%	TBAF/MS 4A/THF, r.t., 15 h.

Overall yield of pederin from **9** = 19% (8 steps).

Scheme 7

stereogenic centre at C7 was introduced by metal hydride reduction of the enone function in **34** (step B, Scheme 7). The modest diasteroselectivity in this reduction (**35a:35b** = 3:1) required the bulky reducing agent $LiBH(s\text{-}Bu)_3$ since smaller reagents such as $NaBH_4$ in EtOH at 0°C produced the unwanted diastereoisomer **35b** as the major product but again with only modest stereoselectivity (**35a:35b** = 1:3). The diastereoisomers were chromatographically inseparable at this stage and purification was complicated by the instability of the products – a problem which was to persist in varying degrees for the next 4 steps. Much better overall yields were obtained when the crude product containing 10–15% conjugate reduction products was immediately subjected to the next reaction.

Addition of methanol to the dihydropyran occurred with excellent diastereoselectivity (≥ 20:1) in favour of the desired isomer **36a** as judged by NMR analysis of the corresponding benzoates **37a,b** (70% overall yield from **34**). The diastereoisomers were stable enough to withstand column chromatography but their polarity difference was such that only partial separation was practicable. Separation of the diastereoisomers at C7 was finally accomplished easily and completely by flash chromatography after selenoxide elimination (step E) followed by hydrolysis of the benzoates **38a,b** (step F). Unfortunately, attempts to avoid the benzoylation-hydrolysis steps D and F by conducting the selenoxide elimination on the alcohols **36a,b** led to extensive decomposition.

The inherent fragility of the pederin system made one final claim on our patience. Removal of the *tert*-butyldimethylsilyl protecting group proved unexpectedly resistant. Only by using a large excess of tetrabutylammonium fluoride (TBAF) in the presence of crushed and freshly activated 4A molecular sieves could the hydroxy group at C13 be freed of its protector and even then the reaction had to be stopped before completion in order to prevent extensive decomposition. After one recycling of recovered **39a** a 69% yield of pederin was obtained which was identical by IR and high field ^1H and ^{13}C NMR

Table 3. ^{1}H-NMR Data for Pederin and Derivatives

Compound **38a**[a,b]			Compound **39a**[a,c]			Pederin (**1**)[d,e]			Assignment
δ_H (integration)	multiplicity	J (Hz)	δ_H (integration)	multiplicity	J (Hz)	δ_H (integration)	multiplicity	J (Hz)	
6.90 (1H)	d	9.5	7.21 (1H)	d	9.7	7.169 (1H)	d	9.8	N–H
5.27 (1H)	dd	9.7, 5.4	5.37 (1H)	dd	9.7, 7.9	5.403 (1H)	dd	9.9, 8.0	C10-H
4.89 (1H)	br s		4.86 (1H)	br s		4.871 (1H)	t	1.9	C4=CH_a
4.81 (1H)	br s		4.75 (1H)	br s		4.757 (1H)	t	1.9	C4=CH_b
5.60 (1H)	s		4.32 (1H)	d	2.7	4.331 (1H)	d	2.9	C7-H
4.01 (1H)	dq	6.4, 2.5	4.00 (1H)	dq	6.6, 2.7	4.013 (1H)	dq	6.6, 2.7	C2-H
3.88 (1H)	q	5.2	3.77 (1H)	ddd	7.7, 5.6, 2.7	3.799 (1H)	ddd	8.3, 6.2, 2.3	C11-H
3.53 (1H)	dd	7.7, 3.6	3.56 (1H)	dd	10.6, 4.4	3.648 (1H)	dt	11.2, 4.9	C13-H
–	–		–	–		3.462 (1H)	dd	10.1, 2.3	C18-H
3.5–3.3 (3H)	m		3.5–3.3 (3H)	m		3.4–3.3 (2H)	m		C17-H, C18-H
3.40 (3H)	s		3.41 (3H)	s		3.404 (3H)	s		OMe
3.31 (3H)	s		3.39 (3H)	s		3.399 (3H)	s		OMe
3.31 (3H)	s		3.34 (3H)	s		3.350 (3H)	s		OMe
3.27 (3H)	s		3.33 (3H)	s		3.339 (3H)	s		OMe
3.3–3.2 (1H)	m		3.22 (1H)	dd	10.3, 1.5	3.239 (1H)	dd	10.4, 1.8	C15-H
2.52 (1H)	d	14.3	2.45 (1H)	d	14.3	2.448 (1H)	d	14.0	C5-H_{eq}
2.77 (1H)	br d	14.3	2.36 (1H)	br d	14.3	2.345 (1H)	dt	14.2, 2.0	C5-H_{ax}
2.26 (1H)	dq	7.0, 2.6	2.25 (1H)	dq	7.1, 2.7	2.264 (1H)	dq	7.0, 2.8	C3-H
–	–		1.92 (1H)	dt	13.5, 4.5	2.060 (1H)	ddd	13.5, 4.7, 2.3	C12-H_{eq}
2.1–1.4 (4H)	m		–	–		1.784 (1H)	ddd	13.3, 11.2, 6.2	C12-H_{ax}
–	–		1.8–1.6 (2H)	m		1.697 (1H)	ddd	14.0, 10.5, 3.1	C16-H_a
–	–		1.55 (1H)	m		1.598 (1H)	ddd	14.1, 9.9, 1.8	C16-H_b
1.18 (3H)	d	6.4	1.19 (3H)	d	6.6	1.203 (3H)	d	6.8	C2-Me
1.04 (3H)	d	7.1	1.02 (3H)	d	7.0	1.024 (3H)	d	7.0	C3-Me
0.82 (3H)	s		0.87 (3H)	s		0.947 (3H)	s		C14-Me_{eq}
0.81 (3H)	s		0.84 (3H)	s		0.880 (3H)	s		C14-Me_{ax}

[a] Recorded at 270 MHz ($CDCl_3$).
[b] Additional signals were observed at δ = 8.11 (2H, apparent d, J = 7 Hz), 7.60 (1H, apparent t, J = 7.3 Hz), 7.47 (2H, apparent t, J = 7.3 Hz), 0.89 (9H, s), 0.03 (6H, s).
[c] Additional signals were observed at δ = 3.93 (1H, d, J = 2.7 Hz, C7-OH), 0.90 (9H, s), 0.05 (6H, s).
[d] Recorded at 500 MHz ($CDCl_3$).
[e] Additional signals were observed at δ = 3.934 (1H, d, J = 2.9 Hz, C7-OH), 1.466 (1H, d, J = 5.2 Hz, C13-OH).

Table 4. ^{13}C-NMR Data for Pederin (**1**)[a]

δ_C	Assignment	δ_C	Assignment	δ_C	Assignment
171.9	C8	73.0	C11	41.5	C3
146.0	C4	72.9	C7	38.8	C14
110.8	C4=C	72.2	C13	34.3	C5
100.0	C6	69.7	C2	30.3	C16
79.6	C10	59.3	OMe[b]	29.8	C12
77.9	C17	57.0	OMe[c]	23.2	C14-Me_{eq}
76.0	C15	56.6	OMe[d]	18.1	C2-Me
74.0	C18	49.2	C6-OMe	13.1	C14-Me_{ax}
				12.2	C3-Me

[a] Recorded at 90 MHz in $CDCl_3$.
[b] Correlates with the signal at δ 3.399 in the ^{1}H-NMR spectrum.
[c] Correlates with the signal at δ 3.339 in the ^{1}H-NMR spectrum.
[d] Correlates with the signal at δ 3.404 in the ^{1}H-NMR spectrum.

spectroscopy, mass spectrometry, and TLC analysis with an authentic sample of natural pederin kindly provided by Professor Dario Ghiringhelli.

In conclusion we have acomplished a synthesis of pederin using a strategy based on *C*-acylation of a metallated dihydropyran which surmounts many of the obstacles encountered previously in the construction of the congested *N*-acyl aminal bridge. A prime asset of the synthesis is the Rh(I)-catalysed hydroboration of an *N*-acylimidate which, for the first time, permits stereoselective construction of the novel *N*-acyl aminal functionality. Other noteworthy features include an efficient conjugate silylcyanation of pyranones (step F, Scheme **5**) which could have important implications for chain extension in carbohydrates and a new protocol which enables the synthesis of metallated dihydropyrans incorporating heteroatomic functionality otherwise incompatible with conditions ordinarily used in metallation reactions (steps F and G, Scheme **4**).

Unless otherwise stated all ^{1}H-NMR spectra were recorded in $CDCl_3$ at 270 MHz using $CHCl_3$ as an internal standard (δ = 7.27) and ^{13}C-NMR spectra were recorded at 67.5 MHz using the central peak of the $CDCl_3$ signal as an internal standard (δ = 77.2). Numbers in parenthesis following the ^{13}C data refer to the number of protons attached to that carbon as revealed by DEPT techniques. Mass spectra were recorded using an ionising potential of 70 eV and an asterisk in the MS data refers to the highest peak of a complex isotope cluster. Optical rotations were measured on an Optical Activity AA-100 polarimeter using 5 or 50 mm cells. Unless otherwise stated all extracts were dried over $MgSO_4$ and solvent evaporation was accomplished at aspirator vacuum using rotary evaporation. Petroleum ether refers to the boiling fraction 40–60 °C.

(3*R*,4*R*,5*R*)-Dihydro-4,5-dimethyl-3-(2-propenyl)furan-2(3*H*)-one (10):

To a solution of LDA [prepared by addition of diisopropylamine (8.3 mL, 0.059 mol) to a solution of BuLi (23.6 mL, 0.059 mol, 2.5 M solution in hexane) in THF (120 mL) at 0 °C] at − 80 °C, was added dropwise a solution of (4*R*,5*R*)-dihydro-4,5-dimethylfuran-2(3*H*)-one[15] (6.13 g, 0.054 mol) in THF (60 mL). The mixture was stirred at − 80 °C for 1 h, before allyl bromide (7 mL, 0.81 mol) was added. After 2 h at − 30 °C the mixture was poured into aq NH_4Cl (150 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined extracts were dried, concentrated, and the residue (9.5 g) purified by chromatography on silica gel (400 mL) eluting with petroleum ether/Et_2O [10:1, 5:1] to give the title compound **10** (6.38 g, 78%) as a colourless oil; $[\alpha]_D$ + 46° (*c* = 2.58, $CHCl_3$). On a smaller scale (2 g) **10** was obtained in 94% yield.

IR (film): *v* = 3078 w, 2979 m, 1771 s, 1642 w, cm^{-1}.

^{1}H-NMR: *δ* = 5.90–5.70 (1 H, m), 5.20–5.05 (2 H, m), 4.64 (1 H, quintet, *J* = 7.0 Hz), 2.55–2.26 (4 H, m), 1.24 (3 H, d, *J* = 7.0 Hz), 1.05 (3 H, d, *J* = 7.0 Hz).

^{13}C-NMR: *δ* = 177.7 (0), 134.2 (1), 117.4 (2), 77.4 (1), 44.7 (1), 37.1 (1), 32.5 (2), 15.2 (3), 13.2 (3).

(2*R*,3*R*,4*S*)-2-Acetoxy-4-(acetoxymethyl)-3-methyl-6-heptene (11):

(2R,3R,4S)-4-Hydroxymethyl-3-methyl-6-hepten-2-ol:

To a suspension of $LiAlH_4$ (1.63 g, 0.043 mol) in Et_2O (200 mL), at r.t. was added a solution of lactone **10** (6.61 g, 0.43 mol) in Et_2O (50 mL) and the mixture was stirred under reflux for 3 h. Then MeOH (20 mL) was added to the mixture followed by water (50 mL) and finally 2 M HCl (50 mL). The resulting mixture was saturated with NaCl and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$, dried, and concentrated to give crude (2*R*,3*R*,4*S*)-4-(hydroxymethyl)-3-methyl-6-hept-en-2-ol (6.65 g), as a colourless oil, which was used in the next step without further purification.

(2R,3R,4S)-2-Acetoxy-4-acetoxymethyl-3-methyl-6-heptene (**11**):

A solution of the crude diol (6.65 g), Ac_2O (15 mL, 0.158 mol), pyridine (12.7 mL, 0.158 mol) and DMAP (0.25 g,4 mol%) in CH_2Cl_2 (250 mL) was stirred at r.t. for 15 h. Then MeOH (20 mL) was added and after 15 min the mixture was poured into 2 M HCl (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$, dried, and concentrated to give a colourless oil (10.0 g) which was distilled (Kugelrohr, bp 170 °C (bath)/0.1 Torr) to give the title compound **11** (9.89 g, 96%) as a colourless oil; $[\alpha]_D$ − 7.0° (*c* = 3.72, $CHCl_3$).

IR (film): *v* = 3077 w, 2979 s, 1737 s, 1640 m, 1444 m, 1371 m, 1241 s, cm^{-1}.

^{1}H-NMR: *δ* = 5.81–5.64 (1 H, m), 5.08–4.98 (2 H, m), 4.95 (1 H, dq, *J* = 5, 6 Hz), 4.02 (1 H, dd, *J* = 7, 11 Hz), 3.98 (1 H, dd, *J* = 6, 11 Hz), 2.28–2.11 (1 H, m), 2.03 (3 H, s), 2.02 (3 H, s), 2.09–.68 (3 H, m), 1.20 (3 H, d, *J* = 6 Hz), 0.92 (3 H, d, *J* = 7 Hz).

^{13}C-NMR: *δ* = 171.2 (0), 170.8 (0), 136.4 (1), 117.0 (2), 72.5 (1), 65.2 (2), 39.2 (1), 38.0 (1), 32.2 (2), 21.5 (3), 21.1 (3), 18.4 (3), 11.1 (3).

(4*R*)-Dihydro-4-[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]furan-2(3*H*)-one (13):

(3S,4R,5R)-5-Acetoxy-3-acetoxymethyl-4-methylhexanal:

A stream of ozone was passed through a solution of **11** (4 g, 0.0165 mol) in MeOH (200 mL) at − 80 °C until a permanent blue colour was observed whereupon N_2 was passed through the solution for 40 min to remove excess ozone. Then Me_2S (24 mL, 3.2 mol) was added at − 80 °C, and the mixture allowed to warm to r.t. over 1.5 h. After 10 h at r.t. concentration yielded crude aldehyde (4.1 g).

(3S,4R,5R)-5-Acetoxy-3-acetoxymethyl-4-methylhexanoic Acid (**12**):

Crude (3*S*,4*R*,5*R*)-5-acetoxy-3-acetoxymethyl-4-methylhexanal (4.1 g) was dissolved in acetone (100 mL) and a solution of Jones reagent (0.075 M in acetone/water 3:2, 230 mL) was added and the mixture stirred at r.t. for 15 min. Then *i*-PrOH was added until permanent green colour was observed. After 15 min the mixture was filtered, the filtrate was poured into brine (250 mL), and the product extracted into CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried and concentrated to give crude acid **12** (5.5 g) as a yellow oil.

(4R)-Dihydro-4-[1R,2S)-2-hydroxy-1-methylpropyl]furan-2(3H)-one (**13**):

Crude **12** (5.5 g) was dissolved in MeOH (500 mL) and a solution of KOH (35 g) in water (120 mL) was added and the resulting mixture stirred for 10 h. After acidification (conc. HCl; until pH 4), the mixture was concentrated to a volume of ca 250 mL, saturated with NaCl and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried and concentrated to give crude product (3.2 g) which was purified by chromatography on silica gel (250 mL) eluting with petroleum ether/AcOEt [5:1, 1:1, and AcOEt] to yield the title compound **13** (1.882 g, 72%) as a crystalline solid. An analytical sample crystallised from Et_2O/petroleum ether gave mp 62–63 °C; $[\alpha]_D$ + 25.7° (*c* = 2.04, $CHCl_3$). The same procedure on a smaller scale beginning with 1.5 g of diacetate **11** gave **13** in 86% overall yield.

IR (film): *v* = 3614 m, 3497 m, 3023 s, 2978 s, 2910 m, 1773 s, 1731 s, 1731 s, 1375 s, 1250 s, cm^{-1}

^{1}H-NMR: *δ* = 4.54 (1 H, dd, *J* = 8, 9 Hz), 4.06 (1 H, t, *J* = 9 Hz), 3.82 (1 H, dq, *J* = 3, 6 Hz), 2.76–2.51 (2 H, m), 2.35–2.18 (1 H, m), 1.68–1.54 (1 H, m), 1.6 (1 H, br s), 1.18 (3 H, d, *J* = 6 Hz), 0.93 (3 H, d, *J* = 7 Hz).

^{13}C-NMR: *δ* = 177.4 (0), 73.0 (2), 69.5 (1), 42.6 (1), 38.6 (1), 33.4 (2), 20.2 (3), 12.5 (3).

LRMS (CI mode, NH_3): *m/z* (%) = 159 (M^+ + H, 100), 141 (60), 129 (28), 114 (37), 68 (22), 55 (28), 45 (35).

(4*R*,5*R*,6*R*)-Tetrahydro-5,6-dimethyl-4-phenylselenylmethyl-2*H*-pyran-2-one (14):

PhSeH (1.88 mL, 17.7 mmol) was added dropwise to a stirred suspension of THF-washed NaH (50% in oil, 0.77 g, 16.1 mmol) in THF (8 mL). The mixture was stirred at r.t. for 10 min and then 18-crown-6 (0.21 g, 5 mol%) was added, followed, after 10 min, by a solution of lactone **13** (0.94 g, 5.9 mmol) in THF (3 mL). The mixture was refluxed for 20 h and then cooled to r.t. Water (10 mL) was added and the mixture poured into 2 M HCl (25 mL). Et_2O (20 mL) was then added and the mixture stirred vigorously for 45 min. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried and concentrated and the residue (3.77 g) purified by chromatography on silica gel (250 mL) eluting with petroleum ether/AcOEt [10:1, 5:1] to give the title compound **14** (1.35 g, 77%); $[\alpha]_D$ + 16.7° (*c* = 4.5, $CHCl_3$).

IR (film): *v* = 3055 w, 2976 m, 2927 m, 1728 s, 1578 m, 1478 m, 1240 s, cm^{-1}.

^{1}H-NMR: *δ* = 7.56–7.23 (5 H, m), 4.44 (1 H, dq, *J* = 2, 7 Hz), 2.94–2.66 (3 H, m), 2.32–2.00 (3 H, m), 1.33 (3 H, d, *J* = 7 Hz), 0.84 (3 H, d, *J* = 7 Hz).

^{13}C-NMR: *δ* = 170.6 (0), 133.1 (1), 129.3 (1), 129.2 (0), 127.5 (1), 80.3 (1), 37.1 (1), 34.3 (1), 32.3 (2), 31.0 (2), 18.5 (3), 4.3 (3).

LRMS (EI mode): *m/z* (%) = 298* (M; + H, 100), 171* (14), 158* (35), 97 (27), 95 (25), 69 (90), 55 (83), 41 (57).

(2*R*,3*R*,4*S*)-3,4-Dihydro-2,3-dimethyl-4-phenylselenylmethyl-6-trimethylstannyl-2*H*-pyran (16):

(2R,3R,4S)-3,4-Dihydro-2,3-dimethyl-4-phenylselenylmethyl-6-trifluoromethylsulfonyloxy-2H-pyran (**15**):

To a solution of lithium hexamethyldisilazide (LHMDS, 1.0 M solution in THF, 4.4 mL, 4.4 mmol) in THF (5 mL) at − 80 °C was added dropwise a solution of lactone **14** (1.0 g, 3.37 mmol) in THF (8 mL) followed hexamethylphosphoric triamide (HMPT, 0.8 mL). After 2 h at − 80 °C, a solution of $PhNTf_2$ (1.44 g, 4.02 mmol) in THF (5 mL) was added dropwise and the mixture stirred at 0 °C for 1 h and at r.t. for 2 h. The mixture was concentrated and the oily

residue was extracted with petroleum ether (3 × 20 mL). The combined extracts were concentrated to yield the crude enol triflate **15** (1.34 g)

(2R,3R,4S)-3,4-Dihydro-2,3-dimethyl-4-phenylselenylmethyl-6-trimethylstannyl-2H-pyran **(16)**:

Crude enol triflate **15** (.34 g) was dissolved in THF (10 mL) to which was added a solution of Me_6Sn_2 (1.11 g, 3.39 mmol) in THF (3 mL) followed by $Pd[Ph_3P]_4$ (0.12 g, 3 mol%) and LiCl (0.86 g, 20.5 mmol). The resulting mixture was stirred under reflux for 15 h before being poured into sat. aq $NaHCO_3$ (15 mL) and extracted with petroleum ether (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) concentrated and the residue purified by chromatography on alumina deactivated by 5% water (50 mL) eluting with 2% Et_3N in petroleum ether to give the title compound **16** (0.915 g, 61%) as a colourless oil.

IR (film): ν = 3057 w, 2974 s, 2921 m, 1645 w, 1598 s, 1579 s, cm^{-1}.

^{1}H-NMR: δ = 7.58–7.20 (5 H, m), 4.48 (1 H, t, J = 2 Hz), 3.95 (1 H, dq, J = 2, 6 Hz), 2.88–2.81 (2 H, m), 2.80–2.66 (1 H, m), 1.93–1.78 (1 H, m), 1.20 (3 H, d, J = 6 Hz), 0.77 (3 H, d, J = 7 Hz), 0.16 (9 H, s).

^{13}C-NMR: δ = 162.8 (0), 132.7 (1), 130.5 (0), 129.2 (1), 126.9 (1), 112.2 (1), 75.7 (1), 38.5 (1), 34.0 (1), 31.6 (2), 18.7 (3), 5.4 (3), −9.6 (3).

MS (EI mode): m/z (%) = 444* (M^+, 16), 429* (7), 305* (26), 289* (53), 275* (44), 165* (100), 125* (39).

(2S,4R)-4-*tert*-Butyldimethylsiloxy-6-[(*S*)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2*H*-pyran-2-carbonitrile (2b):

To a solution of alcohol **25** (2.38 g, 9.3 mmol) in DMF (50 mL), imidazole (2.0 g, 27.8 mmol), DMAP (0.25 g, 0.9 mmol) and TBDMSCI (4.2 g, 27.8 mmol) was added. The mixture was refluxed for 2 h (under *nitrogen*) before being poured into water (50 mL) and extracted with Et_2O (3 × 100 mL). The organic extracts were dried, concentrated, and purified by chromatography on silica gel, (100 mL) eluting with petroleum ether/Et_2O [50:1, 10:1] to give **26** (3.64 g, 94%). mp 46–48 °C (petroleum ether/Et_2O); $[\alpha]_D$ + 57.0° (c = 1.1, $CHCl_3$).

IR (CCl_4): ν = 2940 s, 2930 s, 2880 s, 2860 s, 1471 m, 1255 m, 1105 s, 905 m, 875 m, 835 m, cm^{-1}.

^{1}H-NMR: δ = 4.83 (1 H, dd, J = 1.4, 6.0 Hz), 3.65 (1 H, dd, J = 4.6, 11.4 Hz), 3.55–3.34 (4 H, m), 3.38 (3 H, s), 3.37 (3 H, s), 1.97 (1 H, ddd, J = 6.2, 11.7, 13.7 Hz), 1.85–1.60 (3 H, m), 0.89 (3 H, s), 0.88 (9 H, s), 0.84 (3 H, s), 0.07 (3 H, s), 0.06 (3 H, s).

^{13}C NMR: δ = 117.8 (0), 78.8 (1), 77.7 (1), 72.9 (2), 72.5 (1), 63.9 (1), 59.4 (3), 57.1 (3), 39.9 (0), 33.7 (2), 29.8 (2), 25.8 (3), 22.7 (3), 18.1 (0), 12.3 (3), −4.1 (3), −4.9 (3).

LRMS (EI mode): m/z (%) = 371 (M^+, 2), 345 (1.5), 340 (2.5), 326 (7), 314 (32), 287 (62), 214 (78), 210 (23), 156 (100).

HRMS (Found: M^+, 371.2475. $C_{19}H_{37}NO_4Si$ requires: 371.2491).

(2S,4R)-4-*tert*-Butyldimethylsiloxy-6-[(*S*)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2*H*-pyran-2-carboxamide (27):

To a solution of nitrile **26** (1.3 g, 3.5 mmol) in EtOH (30 mL), a solution of K_2CO_3 (10 g in 20 mL of water) was added followed by H_2O_2 (12 mL, 30%). The reaction mixture was stirred at r.t. for 1.5 h; then $Na_2S_2O_3 \cdot 7H_2O$ was added portionswise until effervescence ceased. The solvent was evaporated and the residue extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were dried, concentrated, and purified by chromatogrphy on silica gel (60 mL) eluting with petroleum ether/AcOEt (3:1, 1:1) to give amide **27** (1.2 g, 88%) as a colourless oil; $[\alpha]_D$ + 28.4° (c = 2.6, $CHCl_3$).

IR ($CHCl_3$): ν = 3500 w, 3360 w, 2980 s, 2950 s, 2900 s, 2860 s, 1690 s, 1600 w, 1470 m, 1460 m, 1400 m, 1360 m, 1255 m, 1100 s, 895 s, 850 s, cm^{-1}.

^{1}H-NMR: δ = 7.51 (1 H br s), 6.04 (1 H, br s), 4.34 81 H, dd, J = 2.1, 6.6 Hz), 3.62–3.50 (2 H, m), 3.45–3.25 (3 H, m), 3.37 (3 H, s), 3.35 (3 H, s), 2.31 (1 H, ddd, J = 2.3, 4.4, 13.1 Hz), 1.85–1.60 (3 H, m), 0.87 (9 H, s), 0.83 (3 H, s), 0.82 (3 H, s), 0.07 (3 H, s), 0.02 (3 H, s).

^{13}C-NMR: δ = 174.8 (0), 79.3 (1), 78.3 (1), 75.5 (2), 73.2 (72.9 (1), 59.3 (3), 56.6 (3), 38.9 (0), 30.4 (2), 30.0 (2), 26.0 (3), 23.4 (3), 18.2 (0), 13.1 (3), −4.0 (3), −4.9 (3).

LRMS (EI mode): m/z (%) = 389 (M^+, 2), 332 (63), 314 (139, 300 (8), 232 (19), 214 (41), 200 (20), 174 (100), 89 (31), 73 (48).

Methyl 13-*O*-(*tert*-Butyldimethylsilyl)meropederoate (9):

Methyl (2S,4R)-4-tert-Butyldimethylsiloxy-6-[(S)-2,3-dimethoxypropyl]-tetrahydro-5,5-dimethyl-2H-pyran-2-carboximidate **(28)**:

To a solution of pedamide **27** (650 mg, 1.67 mmol) in CH_2Cl_2 (35 mL) was added MeO_3BF_4 (794 mg, 5.4 mmol). After 3 h at r.t. the mixture was poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give methyl imidate **28** (675 mg, 100%) as a colourless oil.

Methyl (2S,4R)-4-tert-Butyldimethylsiloxy-6-[(S)-2,3-dimethoxypropyl]-tetrahydro-N-methoxalyl-5,5-dimethyl-2H-pyran-2-carboximidate **(29)**:

The crude methyl imidate **28** (675 mg) was taken up in CH_2Cl_2 (35 mL) and cooled to 0 °C whereupon pyridine (0.55 mL, 6.84 mmol) was added followed by methyl oxalyl chloride (251 mg, 2.05 mmol). After 15 min at 0 °C the mixture was poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give moisture-sensitive acyl imidate **29** (880 mg) which was ca. 85% pure by NMR spectroscopy the contaminants being pyridine, nitrile **26** and the ester derived from hydrolysis of the imidate esters **28** or **29**. This crude mixture was used immediately in the next step without further purification.

Methyl 13-O-(tert-Butyldimethylsilyl)meropederoate **(9)**:

To a solution of crude *N*-acylimidate **29** (880 mg) in toluene (*25 mL*) at r.t. was added $RhCl[Ph_3P]_3$ (77 mg, 5 mol%). The mixture was cooled to −70 °C and catecholborane (2.5 mL, 1.0 M solution in THF) was added. The resulting mixture was stirred at −70 °C for 15 h and then poured into sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried and concentrated to give a brown oil (1.2 g) which was purified by chromatography on silica gel (80 mL) eluting with petroleum ether/AcOEt [10:1, 5:1, 3:1, 1:1 and AcOEt] to give (in order of elution) 200 mg of mixed fractions consisting of the methyl ester derived from hydrolysis of acylimidate **29** (75%), nitrile **26** (13%) and catechol (12%) followed by a mixture of meropederoic acid ester **9** and 10-*epi*-**9** (575 mg, 1.17 mmol) (70% overall yield of **9** and 10-*epi*-**9**); $[\alpha]_D$ + 41.9° (c = 7.5, $CHCl_3$).

IR (film): ν = 3334 w, 2931 s, 2859 s, 1747 s, 1714 s, 1520 m, 1472 m, 1259 m, 1206 m, 1120 s, 837 m, 775 m, cm^{-1}.

^{1}H-NMR (**9**): δ = 7.53 (1 H, d, J = 9.5 Hz, N–H), 5.21 (1 H, dd, J = 7.1, 9.5 Hz), C10-H9, 3.95–3.8 (1 H, m, C11-H), 3.916 (3 H, s, OCH_3), 3.54 (1 H, dd, J = 3.8, 9.0 Hz, C15-H), 3.42–3.25 (3 H, m, C17-H, C18-H2), 3.398, 3.322, and 3.306 (3 H each, s, OMe), 3.14 (1 H, br d, J = 10.1 Hz, C13-H), 1.95–1.43 (4 H, m, C12-H2, C16-H2), 0.887 (9 H, s, Me_3Si), 0.876 and 0.841 (3 H each, s, C14-Me), 0.046 and 0.043 (3 H each, s, Me_3Si). Integration of the signals arising from C10-H revealed **9**/10-*epi*-**9** = 10:1. Signals coming from the minor isomer which could be distinguished include: 8.05 (1 H, d, J = 10 Hz), 5.12 (1 H, dd, J = 9.9, 3.5 Hz), 3.90, 3.382, 3.379, and 3.35 (3 H each, s, OMe).

^{13}C-NMR: δ = 160.73 (0), 157.46 (0), 80.58 (1), 77.95 (1), 76.73 (1), 74.54 (s), 72.69 (1), 70.48 (1) br, 59.16 (3), 57.03 (3), 56.96 (3), 53.85 (3), 38.57 (0), 30.71 (29, 29.54 (2), 25.90 (3), 24.43 (3), 18.12 (0), 16.44 (3) br, −4.24 (3), −4.80 (3).

Acylation of Lithiated Dihydropyran 8; Acyldihydropyran 34:

To a solution of dihydropyran **16** (290 mg, 0.654 mmol) in THF (4.5 mL), at −80 °C was added BuLi (0.41 mL, 0.656 mmol, 1.6 M solution in hexane) and the solution stirred at −80 °C for 15 min. Then TMEDA (0.098 mL, 0.65 mmol) was added and after 10 min at −80 °C, a solution of esters **9** and 10-*epi*-**9** (145 mg, 0.295 mmol) in THF (4 mL) was added. After a further 30 min at −80 °C, the mixture was treated with sat. aq. NH_4Cl (2 mL), and extracted with

Et_2O (2 × 10 mL). The combined extracts were dried and concentrated to give a yellow oil (420 mg) which was purified by chromatography on silica gel (30 mL), eluting with hexane/AcOEt [10:1, 5:1, 3:1, 1:1] to give recovered **9** and 10-*epi*-**9** (35 mg) and coupling product **34** (117 mg, 54%).

IR (CCl_4): ν = 3584 br, 3399 w, 2931 s, 2858 m, 1695 m, 1672 s, 1503 m, 1257 m, 1104 s, cm^{-1}.

^{1}H-NMR: δ = 7.65–7.45 (3 H, m), 7.35–7.20 (3 H, m), 7.10 (1 H, t, J = 2.0 Hz), 5.15 (1 H, dd, J = 6.0, 10.0 Hz), 4.10 (1 H, dq, J = 1.5, 6.6 Hz), 3.95 (1 H, dt, J = 5.0, 6.0 Hz), 3.56 (1 H, dd, J = 3.2, 7.4 Hz), 3.42–3.25 (4 H, m) 3.39, 3.33, and 3.32 (3 H each, s), 3.02–2.8 (3 H, m), 2.16–1.50 (5 H, m), 1.39 (3 H, d, J = 6.6 Hz), 0.94 (3 H, s), 0.91 (9 H, s), 0.86 (3 H, s), 0.83 (3 H, d, J = 7.0 Hz), 0.06 (6 H, s).

^{13}C-NMR: δ = 180.5 (0), 161.8 (0), 148.4 (0), 133.3 (1), 129.5 (1), 129.4 (0), 127.6 (2C, 1), 124.3 (2C, 1), 80.9 (1), 77.9 (1), 77.3 (1), 76.9 (1), 73.6 (2), 73.0 (1), 69.4 (1), 59.3 (3), 57.0 (3), 56.7 (3), 39.2 (1), 38.3 (0), 33.4 (19, 30.9 (2), 29.7 (2), 29.0 (2), 26.0 (3), 25.2 (3), 18.4 (3), 18.2 (0), 18.0 (br, 3), 6.1 (3), −4.3 (3), −4.8 (3).

Reduction of Adduct 34 and Addition of Methanol. Acetal Alcohols 36a,b:

To a solution of acyldihydropyran **34** (140 mg, 0.19 mmol) in THF (9 mL), at −80 °C was added LiBH(*s*-Bu)$_3$ (0.2 mL, 0.2 mmol, 1.0 M solution in THF). After 15 min at −80 °C the mixture was treated with sat. aq. NaCl (4 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried and concentrated to give the sensitive allylic alcohols **35a,b** (170 mg) which were dissolved in CH_2Cl_2 (8 mL) and MeOH (0.8 mL). Camhorsulphonic acid (16 mg) was added and the solution stirred at r.t. for 3 h. Then solid K_2CO_3 (100 mg) was added slowly during 1 h after which the mixture was poured into sat. aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried and concentrated to give the diastereoisomeric acetals **36a,b** (160 mg) as a colourless oil which was used immediately in the next step.

IR (CCl_4): ν = 3414 w, 2929 s, 1736 w, 1678 m, 1519 m, 1463 m, 1382 m, 1257 m, 1120 s, 1073 cm^{-1}.

^{1}H-NMR: δ = 7.5–7.4 (2 H, m), 7.3–7.2 (3 H, m), 7.18 (1 H, d, J = 9.0 Hz), 5.31 (1 H, dd, J = 8.0, 9.5 Hz), 4.28 (1 H, d, J = 3.0 Hz), 3.92 (1 H, dq, J = 2.8, 6.6 Hz), 3.87 (1 H, d, J = 3.0 Hz), 3.78 (1 H, m), 3.51 (1 H, m), 3.4–3.2 (3 H, m), 3.374, 3.349, 3.317 and, 3.276 (3 H each, s), 3.18 (1 H, br d, J = 6.1 Hz), 2.8 (2 H, m), 2.4–1.4 (8 H, m), 1.15 (3 H, d, J = 6.6 Hz), 0.872 (9 H, s), 0.841 (3 H, s), 0.820 (3 H, s), 0.716 (3 H, d, J = 7.0 Hz), 0.028 (6 H, s); NMR spectroscopy indicates that **36** is a mixture of two isomers at C7 (ratio 3:1, integration of C7-H signals); other signals coming from the minor isomer include: 7.40 (1 H, d, J = 10 Hz), 5.20 (1 H, dd, J = 9.7, 5.2 Hz), 4.15 (1 H, d, J = 3.0 Hz), 3.40, 3.36, 3.35 and, 3.32 (3 H each, s), 0.03 (6 H, s).

^{13}C-NMR: δ = 171.83, 132.52, 130.39, 129.11 (2C), 126.82 (2C), 99.07, 79.79, 77.81, 76.24, 74.12, 73.41, 72.51, 70.48, 65.90, 59.17, 56.80, 56.51, 48.76, 38.86, 34.97, 34.87, 32.06, 30.79, 30.54, 29.92, 25.84, 23.87, 18.40, 18.05, 14.20 (br), 4.33, −4.28, −4.89.

Benzoylation of 36a,b; Synthesis of Benzoates 37a,b:

Benzoyl chloride (34 mg) was added to a stirred solution of acetal alcohols **36a, b** (160 mg), Et_3N (0.05 mL) and DMAP (24 mg) in CH_2Cl_2 (10 mL) and the mixture was stirred at r.t. for 12 h. Then MeOH (2 mL) was added and after 15 min the mixture was poured into sat. ag,NaCl (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried and concentrated to give a pale yellow oil (165 mg) which was purified by chromtography on silica gel (30 mL) eluting with hexane/AcOEt [10:1, 5:1, 3:1] to give diastereomeric benzoates **37a,b** (colourless oil, 117 mg, 70% from **34**) as a mixture of two diastereoisomers at C6 in the ratio 3:1. Further chromatography gave enriched fractions of the major isomer (ca. 6:1) but complete separation was better achieved later.

IR ($CHCl_3$): ν = 3696 w, 3431 w, 2931 s, 1727 s, 1693 s, 1602 m, 1504 m, 1453 m, 1382 m, 1271 s, 1094 s, 836 m, cm^{-1}.

^{1}H-NMR: δ = 8.08 (2 H, apparent dd, J = 1.0, 8.1 Hz), 7.60 (1 H, apparent tt, J = 0.9, 7.5 Hz), 7.54–7.41 (4 H, m), 7.31–7.18 (3 H, m), 6.83 (1 H, d, J = 9.5 Hz), 5.53 (1 H, s), 5.22 (1 H, dd, J = 4.4, 9.7 Hz), 4.0–3.8 (2 H, m), 3.55 (1 H, dd, J = 3.6, 7.2 Hz), 3.5–3.2 84 H, m), 3.393, 3.336, 3.331, and 3.242 (3 H each, s), 2.85 (2 H, 8 lines, AB part of the ABX system), 2.4–1.4 (8 H, m), 1.17 (3 H, d, J = 6.6 Hz), 0.899 (9 H, s), 0.826 (3 H, s), 0.820 (3 H, s), 0.763 (3 H, d, J = 7.0 Hz), 0.036 (6 H, s). Signals arising from the minor diastereoisomer at C7 **(37b)** which could be distinguished from the mixture include 5.56 (1 H, s), 5.13 (1 H, dd, J = 9.0, 4.0 Hz), 3.43, 3.38, 3.34, and 3.29 (3 H each, s), 1.12 (3 H, d, J = 6.6 Hz).

^{13}C-NMR: δ = 167.75 (0), 165.36 (0), 133.66 (1), 132.71 (2C, 1), 130.14 (2C,1), 130.04 (0), 129.32 (0), 129.24 (2C, 1), 128.63 (2C, 1), 126.96 (1), 98.99 (0), 81.40 (1), 77.65 (2C, 1), 77.07 (1), 73.36 (2), 73.13 (1), 72.95 (1), 70.69 (1), 59.21 (3), 56.81 (3), 56.28 (3), 48.53 (3), 38.20 (0), 35.20 (1), 35.04 (1), 32.20 (2), 30.84 (2), 30.65 (2), 28.98 (2), 25.94 (3), 25.28 (3), 18.53 (3), 18.12 (0), 4.50 (3), −4.32 (3), −4.86 (3). One of the Me groups at C14 gives very weak signal under the pulse conditions used and as a consequence is submerged in the base line.

LRMS (EI mode): m/z (%) = 879* (M^+, 0.16), 847* (0.74), 845* (0.76), 815* (5.0), 770* (4.5), 648 (22.4), 380 (29.3), 321 (46.7), 257 (28.3), 191 (26.5), 155 (30.5), 105 (100).

HRMS (Found: M^+, 879.3843. $C_{44}H_{69}NO_{10}SiSe$ requires: 879.3856).

7-*O*-Benzoyl-13-*O*-(*tert*-butyldimethylsilyl)pederin (38a):

$NaIO_4$ (28 mg, 0.13 mmol) was added in one portion to a stirred solution of the selenides **37a,b** (ca. 6:1) (71 mg, 0.081 mmol) in MeOH/H_2O (3:1, 18 mL). After 30 min the mixture was diluted with Et_2O (50 mL) and washed with H_2O (2 × 20 mL), and then dried (Na_2SO_4) and concentrated to give selenoxide (69 mg) as a pale brown oil. The crude selenoxide was taken up in benzene (3 mL) and added dropwise to a refluxing solution of benzene (12 mL) and Et_3N (12 mL). After 2 min at reflux, the solution was poured into sat. aq $NaHCO_3$ (25 mL) and the mixture extracted with Et_2O (2 × 50 mL). The organic extracts were dried (Na_2SO_4) and concentrated to give a yellow oil (57 mg) which was purified by chromatography on silica gel (10 mL) eluting with hexane/AcOEt [10:1, 5:1, 3:1] to give **38a,b** as a colourless oil (49 mg, 84%):

IR ($CHCl_3$): ν = 3690 w, 3428 w, 2931 s, 1728 s, 1693 s, 1693 s, 1602 w, 1508 m, 1452 m, 1383 m, 1268 s, 1104 s, 1071 s, 837 m, cm^{-1}.

^{1}H-NMR analysis (270 MHz) (Table 3) of the chromatographically purified product revealed a mixture of diastereoisomers at C7 (ca. 6:1) by integration of the signals at 5.60 (major) and 5.57 (minor). Other signals coming from the minor isomer **38b** which could be distinguished include: 5.14 (1 H, dd, J = 10.0, 5.0 Hz), 3.46 (3 H, s), 3.38 (3 H, s), 3.36 (3 H, s), 3.30 (3 H, s), 1.13 (3 H, d, J = 6.6 Hz). See Table 3 for data on the major isomer **38a**.

^{13}C-NMR: δ = 167.69 (0), 165.40 (0), 145.98 (0), 133.69 (1), 130.19 (2C, 1), 129.32 (0), 128.62 (2C, 1), 1170.76 (2), 99.55 (0), 80.81 (1), 77.69 (1), 77.60 (1), 76.94 (1), 73.24 (2), 72.94 (1), 72.84 (1), 69.84 (1), 59.25 (39, 56.87 (3), 56.28 83), 48.91 (3), 41.46 (1), 38.38 (0), 34.52 (2), 30.79 (2), 29.18 (2), 25.94 (3), 25.02 (3), 18.14 (0), 18.10 (3), 17.2 (3) br, 12.16 (3), −4.31 (3), −4.86 (3).

LRMS (EI mode): m/z (%) = 721 (M^+, 0.21), 664 (12.4), 657 (17.1), 612 (24.3), 525 (16.4), 462 (16.8), 344 (37.6), 285 (53.5), 257 (28.9), 222 (31.2), 155 (47), 105 (100).

HRMS (Found: M^+, 721.4238. $C_{38}H_{63}NO_{10}Si$ requires: 721.4221).

13-*O*-(*tert*-Butyldimethylsilyl)pederin (39a):

To a solution of **38a,b** (45 mg, 0.062 mmol) in MeOH (20 mL) was added aq LiOH (1.0 M, 2 mL). After 30 min at r.t. the mixture was concentrated. The residue was taken up in Et_2O (25 mL) and washed with H_2O (2 × 5 mL), and brine (5 mL), and then dried (Na_2SO_4) and concentrated to give an oil (44 mg) which was purified by chromatography on silica gel (8 mL) eluting with hexane/AcOEt [5:1, 3:1, 1:1] to give diastereomerically pure **39a**

(25 mg) along with mixed fractions (8 mg) consisting of a mixture (ca. 1:1) of **39a** and **39b** (total yield 33 mg, 86%)

IR ($CHCl_3$): ν = 3418 w, 2932 s, 1674 m, 1635 m, 1606 m, 1503 s, 1472 m, 1389 m, 1257 m, 1202 m, 1093 s, 877 m, cm^{-1}.

For ^{1}H-NMR data on the pure diastereoisomer **39a** see Table 3. Signals coming from the minor isomer **39b** which could be distinguished in the mixture include: 7.40 (1 H, d, J = 10.0 Hz, N–H), 5.25 (1 H, dd, J = 6.0, 10.0 Hz, C10-H), 4.21 (1 H, d, J = 2.7 Hz, C7-H), 3.82 (1 H, d, J = 3.0 Hz, OH), 3.42, 3.38, 3.373 and 3.369 (3 H each, s, OME), 2.61 (1 H, br. d, J = 14.0 Hz, C5-H), 1.05 (3 H, d, J = 7.0 Hz, C3-Me), 0.92 (3 H, s, C14-Me), 0.91 (9 H, s, t-Bu), 0.06 (6 H, s, Me_2Si).

^{13}C-NMR: δ = 171.96 (0), 145.94 (0), 110.76 (2), 99.89 (0), 79.59 (1), 77.85 (1), 76.32 (1), 74.09 (2), 73.04 (1), 72.62 (1), 72.52 (1), 69.70 (1), 59.33 (3), 56.97 (3), 56.58 (3), 49.28 (3), 41.46 (1), 39.04 (0), 34.32 82), 30.58 (2), 30.06 (2), 25.94 (3), 23.90 (3), 18.18 (0), 18.08 (3), 14.10 br (3), 12.22 (3), −4.18 (3), −4.78 (3).

FAB MS: m/z (%) = 640 (M^+ + Na, 0.8), 610 (0.9), 580 (0.6), 554 (10), 422 (58), 155 (43), 89 (42), 73 (100).

Pederin (1):

To a solution of **39a** (25 mg, 0.041 mmol) in THF (5 mL) was added 4A molecular sieves (1.15 g, crushed and activated in vacuo at 180 °C) and TBAF (0.5 mL, 1.0 M solution in THF). After 15 h at r.t. the reaction mixture was diluted with Et_2O (25 mL) and washed with sat. aq $NaHCO_3$ (5 mL). The water layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers dried (Na_2SO_4) and concentrated to give an oil (100 mg) which was purified by chromatography on silica gel (10 mL) eluting with hexane/AcOEt [3:1, 1:1, AcOEt] to give: **39a** (9 mg, 36%) and **1** (11 mg, 53%). Recovered **39a** was recycled to give **39a** (2 mg, 22%) and **1** (2.8 mg, 38%).

IR ($CDCl_3$): ν = 3406 w, 2936 s, 1681 s, 1521 m, 1452 m, 1382 m, 1089 s, cm^{-1}.

For ^{1}H and ^{13}C NMR data see Tables 3 and 4 respectively.

FAB MS: m/z (%) = 504 (M^+ + H, 7), 472 (10), 440 (86), 422 (98), 240 (27), 125 (44), 95 (100).

FAB HRMS (Found: M^+ + H, 504.3174. $C_{25}H_{45}NO_9$ + H requires: 504.3172).

Our programme was generously supported by Pfizer Central Research, Glaxo Group Research, and the Science and Engineering Research Coucil. The authors wish to thank Anna Marczak for technical assistance; John Langley and Joan Street for expert spectroscopic analyses; and Dario Ghiringhelli for authentic samples of natural pederin and methyl meropederoate.

Received: 10 July 1991; revised: 1 August 1991

(1) For a detailed review of the history of pederin which includes an account of its isolation, structure proof, and biological activity, see: Frank, J.H.; Kanamitsu, K. *J. Med. Entomol.* **1987**, *24*, 155.

(2) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1988**, *44*, 7063 and references therein.

(3) Nakata, T.; Nagao, S.; Mori, N.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6461.
Nakata, T.; Nagao, S.; Oishi, T. *Ibid.* **1985**, *26*, 6465.

(4) Willson, T.M.; Kocieński, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Campbell, S.F.; Bordner, J. *Tetrahedron* **1990**, *46*, 1757.
Willson, T.M.; Kocieński, P.; Jarowicki, J.; Isaac, K.; Hitchcock, P.M.; Faller, A.; Campbell, S.F. *Tetrahedron* **1990**, *46*, 1767.

(5) Jarowicki, K.; Kocieński, P.; Marczak, S.; Willson, T. *Tetrahedron Lett.* **1990**, *31*, 3433.

(6) Cardani, C.; Ghiringhelli, D.; Mondelli, R.; Quilico, A. *Gazz. Chim. Ital.* **1966**, *96*, 3.

(7) Matsumoto and co-workers have described the synthesis of pederin using ring-A fragments bearing the sensitive alkene at C4 (see reference 2). A synthesis of mycalamides A and B (marine natural products related to pederin) has also been described recently in which an intact methylene at C4 was used: Hong, C.Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242. The modest yields in these cases reflect the problem of stability.

(8) Boeckman, R.K.; Bruza, K.J. *Tetrahedron* **1981**, *37*, 3997.

(9) Kocieński, P.; Yeates, C.; Street, S.D.A.; Campbell, S.F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2183 and references therein.
Kocieński, P.; Wadman, S.; Copper, K. *Tetrahedron Lett.* **1988**, *29*, 2357.
Kocieński, P.; Dixon, N.J.; Wadman, S. *Tetrahedron Lett.* **1988**, *29*, 2353.
Kocieński, P.; Wadman, S.; Cooper, K. *J. Org. Chem.* **1989**, *54*, 1215.
Kocieński, P.; Love, C.; Whitby, R.; Costello, G.; Roberts, D. *Tetrahedron* **1989**, *45*, 3839.
Takle, A.; Kocieński, P. *Tetrahedron* **1990**, *46*, 4503.
Smith, A.B.; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109* 1269.
Boeckman, R.K.; Charette, A.B.; Asberom, T.; Johnston, B.H. *J. Am. Chem. Soc.* **1987**, *109* 7553.

(10) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press, Oxford, 1986, p. 105.

(11) Meinwald, J. *Pure Appl. Chem.* **1977**, *49*, 1275.

(12) Liotta, D. *Acc. Chem. Res.* **1984**, *17*, 28.

(13) Barber, C.; Jarowicki, K.; Kocieński, P. *Synlett* **1991**, 197.

(14) After this work was completed a Rh(I)-catalysed conjugate reduction of α,β-unsaturated carbonyls was reported: Evans, D.A.; Fu, G.C. *J. Org. Chem.* **1990**, *55*, 5678.

(15) Bystrom, S.; Hogberg, H.E.; Norin, T. *Tetrahedron* **1981**, *37*, 2249.