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STUDIES RELATED TO THE SYNTHESIS OF (±)-PEDERIN. PART 1. SYNTHESIS OF ETHYL PEDERATE AND BENZOYLSELENOPEDERIC ACID

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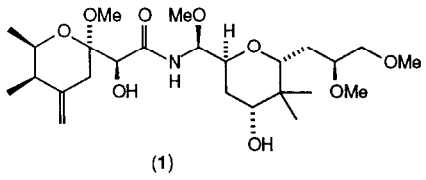
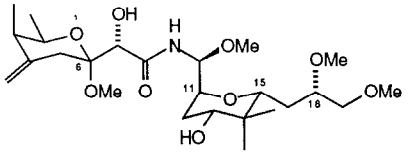
Abstract The first in a series of 2 papers on the synthesis of the insect toxin pederin (**1**) begins with a discussion of syntheses of the ring A fragments (±)-ethyl pederate (**2**) and (±)-benzoylselenopederic acid (**4**) A silicon-mediated intramolecular cyclisation of a chloroformate onto an allyl silane (**11**) was used to introduce the ring A methylene group at C-4 in ethyl pederate Conjugate addition of phenylselenomethyl-lithium to the α,β-unsaturated lactone (**19**) was a key step in the construction of (**4**)

The presence of a nasty vesicant in the Staphylinid beetle *Paederus fuscipes* has long been appreciated by its victims However, potential benefits to human ailments were also noted over 1000 years ago In a Chinese pharmacopoeia of 739 A D , Ch'en states that a *Paederus* preparation 'will take the skin off one's face and remove tattoo marks completely It is used as a caustic for toxic boils, nasal polypi and ringworm' The toxic effects of *Paederus fuscipes* first became known to Western science in 1901 through a report by Vorderman of the severe dermatitis inflicted on personnel at the Anjet-Kidoel lighthouse in Java, Indonesia by small winged insects called locally *semoet-kalong*[3] However, it was not until 1952 that the pure toxic component was isolated by Pavan and Bo[4] and in 1968 the correct structure of that component, named pederin (**1**), was finally announced In the interim 16 years Italian and Japanese groups had established the bulk of the structure by means of extensive chemical investigation aided by low field ^{1}H NMR spectroscopy[5,6] However, the finishing touches, including absolute stereochemistry, were finally supplied by x-ray crystallographic analysis of a derivative[7,8]

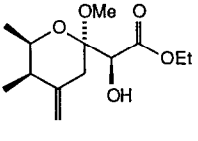
Pederin



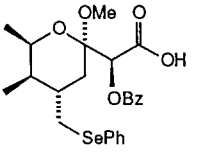
(**1**)



Ring A Fragments

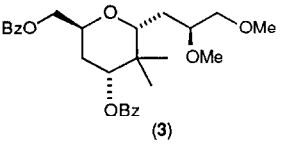


(**2**)

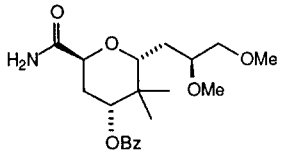


(**4**)

Ring B Fragments

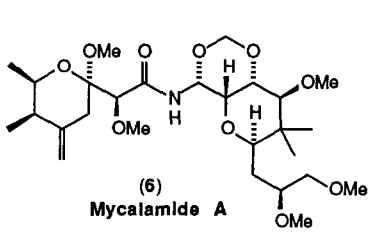


(**3**)

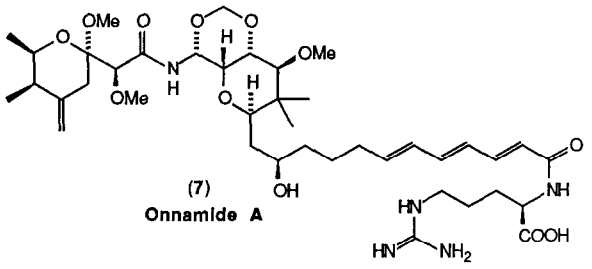


(**5**)

For many years, pederin was considered to be structurally unique in the realm of natural products However, the recent isolation of Mycalamide A (**6**)[9] and Onnamide A (**7**)[10] from marine sources indicates that structures bearing two tetrahydropyran rings bridged by an N-acyl aminal are rather more common than hitherto supposed The presence of (**6**) and (**7**) in marine organisms also casts further doubt on the defensive role previously assigned to pederin It is significant that all three structures have potent biological activity pederin is reputed to promote skin growth, inhibit mitosis, induce cell fusion in human skin fibroblasts, and block protein and DNA biosynthesis[3], (**6**) and (**7**) have antiviral activity *in vivo*



(6)
Mycalamide A

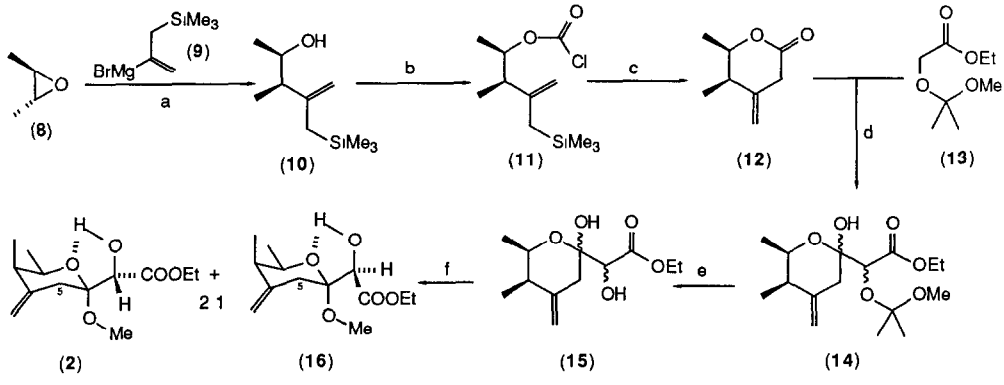


(7)
Onnamide A

The novel architecture of pederin and its dense array of sensitive functionality poses a considerable synthetic challenge All three total syntheses of pederin reported to date were designed to avoid problems associated with the high acid-lability of the homoallylic acetal array in ring A and the N-acyl aminal The elegant pioneering work by Matsumoto and co-workers[11] has provided the only viable protocols for achieving the very difficult task of constructing the highly hindered N-acyl aminal bridge The two subsequent syntheses by Nakata, Oishi, and co-workers[12] and the Southampton group[13] depend to a large extent on these Matsumoto protocols In addition to the total syntheses, sundry approaches to various fragments have also been reported[11] We now give details of the Southampton synthesis of pederin In this paper (Part 1) we record our early efforts on the synthesis of (±)-ethyl pederate (2)[14] and focus on the stereoselective construction of the key ring A tetrahydropyran fragment (±)-benzoylselenopederic acid (4) In Part 2 (see accompanying paper) we give details of syntheses of the ring B fragments pederol dibenzoate (3) and (±)-benzoylpedamide (5) and the union of the latter with (4) to give (±)-pederin

Synthesis of (±)-Ethyl Pederate (2)

In the early stages of our approach to pederin, we had intended to unite a ring A fragment bearing an intact C-4 methylene group to a suitable ring B fragment To that end we devised the short synthesis of (±)-ethyl pederate (2) shown in Scheme 1 Nucleophilic scission of (±)-*trans*-2,3-epoxybutane (8) by the Grignard reagent (9) in the presence of CuI gave the homoallylic alcohol (10) in 47% yield The corresponding chloroformate (11) cyclised on treatment with $SnCl_4$ to give the unstable β,γ-unsaturated lactone (12) Considerable care had to be exercised in the purification and storage of (12) because it rearranged under the slightest provocation to the more stable α,β-unsaturated isomer The conjugated lactone could be converted back to the β,γ-unsaturated lactone by conversion to the enolate with lithium di-isopropylamide followed by kinetic protonation with HOAc but the recovery was poor and mixtures of (12) and its conjugated isomer inevitably resulted



SCHEME 1 YIELDS AND REAGENTS

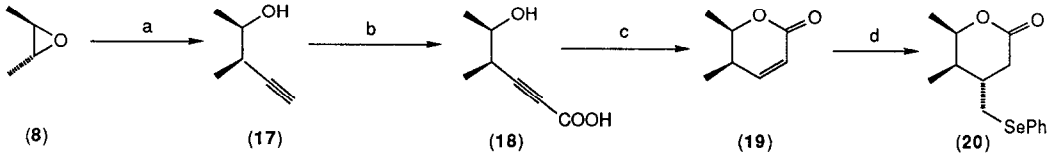
(a)	47%	THF, -30 to 0°C, 3h	(d)	37%	(13) + LDA / THF, -78°C then add (12) at -78°C, 2h
(b)	88%	phosgene / toluene-pyridine 0°C 1h	(e)	------	conc HCl / THF rt, 30 min,
(c)	56%	1 eq $SnCl_4$ / CH_2Cl_2 0°C 3h	(f)	45%	TsOH / MeOH rt 4h

The lactone (**12**) reacted with the lithium enolate prepared from the the known ethyl glycolate derivative (**13**)[15] to give a mixture of hemiacetals (**14**) from which the hydroxyl protecting group was removed with acid The resultant mixture of diastereomeric diols (**15**) was then treated with acidic methanol to give a 1 2 mixture of ethyl *epi*-pederate (**16**) and ethyl pederate (**2**) in 20% overall yield from (**12**) The isomers were easily separated by column chromatography and their stereochemistry ascertained by ^{1}H NMR spectroscopy Thus the C-5 methylene protons in ethyl *epi*-pederate (**16**) gave characteristic doublets at δ1 98 and 2 84 (J = 14 Hz) whereas the same protons in ethyl pederate appeared as a 2H singlet at δ2 4 This distinction may result from an anisotropic effect of the ester carbonyl on the C-5 protons in the *epi*-series assuming that the the hydroxyl group is hydrogen bonded to the tetrahydropyran ring oxygen A similar conformation in ethyl pederate holds the carbonyl remote from the C-5 methylene group

All attempts to effect base-catalysed hydrolysis of ethyl pederate resulted in decomposition Ethyl pederate was also very susceptible to acid-catalysed decomposition The methyl ester proved no less tractable Our experience with this synthesis suggested that any attempt to utilise a ring A fragment with an intact C-4 methylene was likely to prove troublesome Since the homoallylic relation between the C-4 methylene and the methoxy group at C-6 was judged to be the root of the problem, we amended our strategy by constructing a ring A fragment in which provision was made for the late introduction of the C-4 methylene under very mild conditions–a strategy also adopted by Matsumoto and co-workers[11] In addition, a milder method for unmasking the carboxyl group was devised which overcame the problems of ester hydrolysis

Synthesis of (±)-Benzoylselenopederic Acid (4)

Our synthesis of (±)-benzoylselenopederic acid (**4**) required two principal fragments the selenolactone (**20**)(Scheme 2) and the glycolic acid derivative (**25**)(Scheme 3) Selenolactone (**20**) was prepared as a single diastereoisomer in one step by conjugate addition of phenylselenomethyl-lithium[16] to the known α,β-unsaturated lactone (**19**)[15] for which a substantially more efficient synthesis was developed (see Experimental) Though the successful conjugate addition was gratifying in this particular case, the reaction was not general since attempts to achieve similar additions to other α,β-unsaturated lactones lacking the branching substituent at C-3(pederin numbering) failed to give useful yields of the desired selenolactones

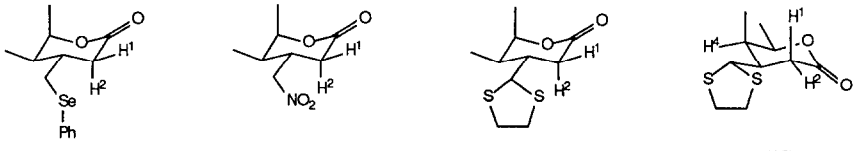


SCHEME 2 YIELDS AND REAGENTS

(a) 82% lithium acetylide (3 6 eq) / HMPT, 20°C, 6 days, (c) 85% H_2 Pd/$BaSO_4$ quinoline followed by distillation,
(b) 96% n-BuLi followed by CO_2, -70°C 20 min, (d) 89% $PhSeCH_2Li$ / THF - HMPA (1 1) -86°C, 1h

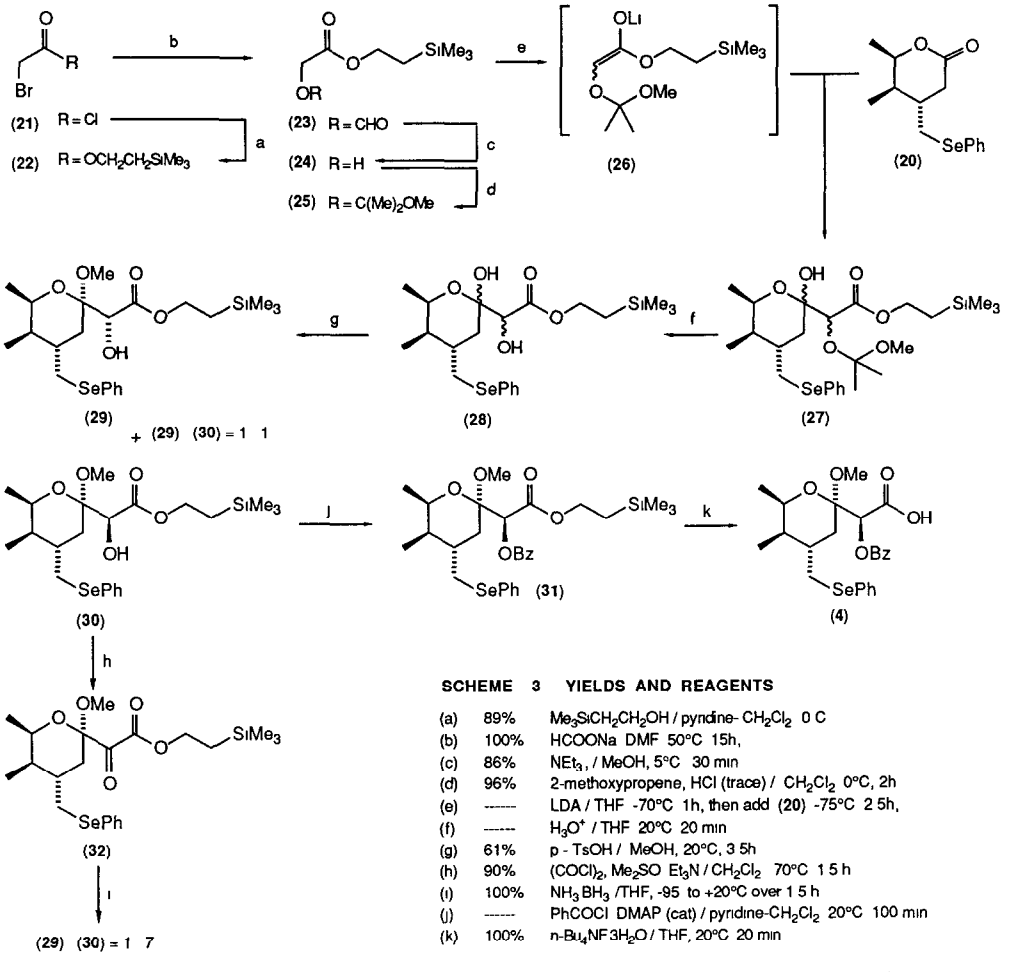
Comparison of the 400 MHz ^{1}H NMR spectral data for the protons at C-5 of the 4-phenylselenomethyl lactone (**20**) with the available data for the known compounds (**33**)-(**35**)[12 15] (Table 1) indicated that C-4 had the (S*) configuration Note that compound (**35**), which has the (R*)-configuration at C-4 shows an additional long range W-coupling between H-1 and H-4 of 1 2 Hz which is absent in the other compounds with the C-4 (S*)-configuration Final proof of the relative stereochemistry in (**20**) was obtained later by a single crystal x-ray analysis of a subsequent derivative (*vide infra*)

Table 1 Stereochemistry of 4-substituted 2,3-dimethyltetrahydropyran-5-ones



	(20)	(33)	(34)	(35)
H^1/δ	2 37	2 42	2 57	2 90
J / Hz	9 6 16 4	10 0 16 0	10 8, 15 9	1 2 5 6, 18 1
H^2/δ	2 67	2 71	2 73	2 26
J / Hz	6 3, 16 4	6 4 16 0	6 4 15 9	12 0 18 1

The next stage of the synthesis required the appendage of the glycolate side chain onto the ring (**20**)(Scheme 3) The lithium enolate (**26**) of ester (**25**) condensed with the lactone (**20**) though varying amounts of (**20**) were recovered owing to proton abstraction by the glycolate enolate competing with the desired nucleophilic addition After two further steps, the alcohols (**29**) and (**30**) were isolated as a 1 1 mixture of isomers which were separable with difficulty by chromatography However, it was more convenient to oxidise the mixture to the corresponding α-keto ester (**32**) followed by reduction *in situ* to give the diastereoisomers (**29**) and (**30**) in the more favourable ratio of 1 7 The ratio of diastereoisomers was stongly dependent on the reducing agent. In our hands, reduction of the α-keto ester with BH_3-NH_3[17] complex in THF at low temperature gave the best results After removal of the undesired minor diastereoisomer by column chromatography, the relative stereochemistry of (**30**) was firmly established by a single crystal x-ray analysis (see Experimental) The alcohol function in (**30**) was then converted to the crystalline benzoate derivative (**31**)

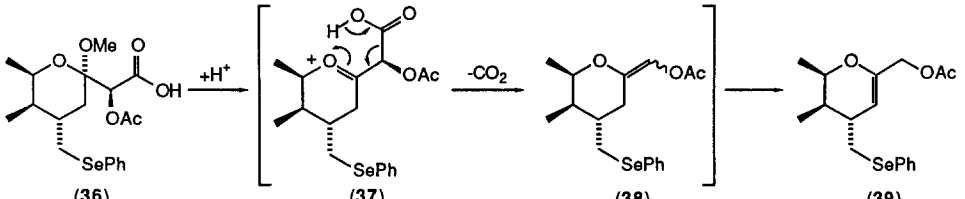


SCHEME 3 YIELDS AND REAGENTS

(a)	89%	$Me_3SiCH_2CH_2OH$ / pyridine- CH_2Cl_2 0 C
(b)	100%	HCOONa DMF 50°C 15h,
(c)	86%	NEt_3 / MeOH, 5°C 30 min
(d)	96%	2-methoxypropene, HCl (trace) / CH_2Cl_2 0°C, 2h
(e)	------	LDA / THF -70°C 1h, then add (**20**) -75°C 2 5h,
(f)	------	H_3O^+ / THF 20°C 20 min
(g)	61%	p - TsOH / MeOH, 20°C, 3 5h
(h)	90%	$(COCl)_2$, Me_2SO Et_3N / CH_2Cl_2 70°C 1 5 h
(i)	100%	NH_3BH_3 /THF, -95 to +20°C over 1 5 h
(j)	------	PhCOCl DMAP (cat) / pyridine-CH_2Cl_2 20°C 100 min
(k)	100%	n-Bu_4NF3H_2O / THF, 20°C 20 min

To complete the synthesis of benzoylselenopederic acid the carboxylic acid was unmasked by fluoride-induced fragmentation of the 2-(trimethylsilyl)ethyl ester (**31**)[18] using tetra-*n*-butylammonium fluoride Initial attempts to recover the desired acid (**4**) by acidification of the resultant tetra-*n*-butylammonium salt were complicated by problems with decomposition However, the free acid was fortuitously generated by partitioning the tetra-*n*-butylammonium salt between ether and water Evaporation of the ether layer then gave the desired acid cleanly and efficiently with minimal contamination by decomposition products This deprotection and isolation procedure was crucial to the successful isolation and purification of the labile acid (**4**) Although the decomposition products derived from (**4**) were not characterised, the analogous acetate (**36**) underwent easy acid-catalysed loss of CO_2 and MeOH to give the

dihydropyran (39)(Scheme 4) The successful union of (±)-benzoylselenopederic acid with a suitable ring B fragment will be described in the accompanying report



(36) (37) (38) (39)

SCHEME 4

Acknowledgments We thank the Science and Engineering Research Council for CASE Studentships (T M W and K I) and post-doctoral support (K J) This is a contribution from the Southampton University Institute of Biomolecular Science

EXPERIMENTAL

General ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ Chemical shift are reported in ppm relative to TMS as an internal standard Coupling constants J are given in Hertz Unless otherwise stated, all distillations were performed using a kugelrohr apparatus Chromatography refers to column chromatography on silica gel 60 (230-400 mesh) High resolution mass spectra were obtained for compounds ascertained to be at least 95% pure by tlc, and high field ^1H and ^{13}C NMR analysis Extracts were dried over $MgSO_4$ and evaporated at aspirator vacuum using rotary evaporation

(2R*, 3R*)-4-(Trimethylsilylmethyl)-3-methylpent-4-en-2-ol (10) – 2-Bromo-3-(trimethylsilyl)prop-2-ene[19](41 4 g, 0 215 mol) in THF (100 ml) was added dropwise over 3 h to a stirred mixture of Mg turnings (5 2 g, 0 215 g atom) in THF (50 ml) whilst maintaining the internal temperature at 5°C The solution of the Grignard reagent (**9**) was transferred *via* cannula to a dropping funnel and added dropwise to a rapidly stirred suspension of CuI (4 g, 21 5 mmol) in THF (30 ml) at -40°C To the resultant yellow suspension was added dropwise a solution of (±)-*trans*-2,3-epoxybutane (**8**)[20](17 g, 0 236 mol) in THF (50 ml) and the mixture stirred at -30°C for 1 h and then allowed to warm to room temperature over 2 h The mixture was poured into aqueous ammonium chloride and the product extracted several times with ether The combined extracts were washed with water, dried, and concentrated The residue was purified by chromatography eluting with ether-petroleum ether (5 95) Distillation of the residue gave (**10**)(16 35 g, 47%) as a colourless oil b p 150°C (bath)/0 05 mm Hg, IR (neat) 3380 br, 1630s, 1245s, and 850 cm^{-1}, ^1H NMR (90 MHz) δ 4 68 (2H, s), 3 8 (1H, m), 1 9 (1H, m), 1 65 (1H, br s, OH), 1 56 (2H, d, J 7), 1 2 and 1 05 (3H each, d, J 7), 0 02 (9H, s), ^{13}C NMR (22 5 MHz) 150 6, 107 4, 68 1, 47 5, 27 4, 20 6, 12 8, -1 35, (Found M^+, 186 14362 Calc for $C_{10}H_{22}OSi$ M, 186 143985)

(2R*, 3R*)-4-(Trimethylsilylmethyl)-3-methyl-2-chloroformyloxypent-4-ene (11) – Alcohol (**10**) (16 36 g, 87 mmol) and dry pyridine (8 2 ml, 100 mmol) in toluene (100 ml) were added dropwise to a stirred solution of phosgene (0 2 mol) in toluene (200 ml) at 0°C After 1h, the system was purged with N_2 for 1 h and the effluent gases bubbled through Dresher bottles charged with 2M NaOH followed by aniline Pentane (100 ml) was added and the mixture filtered The solvent was then removed *in vacuo* and the residue again taken up into pentane (100 ml) and filtered The filtrate was concentrated and placed under high vacuum for 15 min to give the crude chloroformate (**11**) which was used directly in the next step IR (neat) 1780s, 1170s, 850s cm^{-1}, ^1H NMR (90MHz) δ 4 92 (1H, dq, J 7, 7), 4 66 (2H, s), 2 12 (1H, dq, J 7, 7), 1 49 (2H, d, J 5), 1 28 and 1 05 (3H each, d, J 7), 0 01 (9H, s)

(5R*, 6R*)-4-Methylene-5,6-dimethyltetrahydropyran-2-one (12) – To a stirred solution of the chloroformate (**11**) (19 4 g, 78 mmol) in dry CH_2Cl_2 (750 ml) was added dropwise at 0°C $SnCl_4$ (9 1 ml, 78 mmol) After 3h the solution was poured into a mixture of saturated brine, water, and saturated aqueous $NaHCO_3$ (1 1 1) with rapid stirring The organic layer was separated, washed with $NaHCO_3$ and brine, dried, and evaporated The residue was chromatographed with ether-petroleum ether (15 85) to give (**12**) (6 12 g, 56%) IR (neat) 1730s, 1650m, 1380s, 1280s, 1240s, and 1000s cm^{-1}, UV (EtOH) 223 nm (ε 445), ^1H NMR (90 MHz) δ 4 95 (2H, s), 4 55 (1H, dq, J 3, 7), 3 3 (1H, t, J 1), 2 6 (2H, br m), 1 26 and 1 09 (3H each, d, J 7), ^{13}C NMR (22 5 MHz) δ 170 1, 141 7, 110 35, 77 5, 38 5, 37 1, 16 7, 12 9, (Found M^+, 140 08309 Calc for $C_8H_{12}O_2$ M, 140 083724)

(±)-Ethyl Pederate (2) and (±)-Ethyl *epi*-Pederate (16) – n-BuLi (1 5M in hexanes, 35 ml, 52 mmol) was added dropwise to a stirred solution of di-isopropylamine (8 4 ml, 60 mmol) in THF (20 ml) at 0°C After 30 min the solution was cooled to -78°C

and a solution of ethyl O-(2-methoxy-2-propyl)glycolate[15] (**13**)(10 65 g, 60 mmol) in THF (20 ml) was added dropwise After 1 h at -78°C, the lactone (**12**) (5 60 g, 40 mmol) in THF (20 ml) was added dropwise After a further 2 h at -78°C the mixture was quenched by the addition of ethanol (10 ml) Ether (100 ml) was added and the mixture extracted with brine (40 ml) The extract was dried, evaporated, and chromatographed with ether-petroleum ether (3 7) to give a mixture of diastereomeric hemiacetals (**14**) (4 73 g, 37%) and the α,β-unsaturated lactone 4,5,6-trimethyl-5,6-dihydropyran-2-one (3 34 g, 60% after kugelrohr distillation) b p 130°C (bath)/ 15 mm Hg, m p 50 3-52 4°C from hexane, IR (CCl4) 1730s, 1690m, 1645w, 1380s, 1280s, 1015s and 860s cm-1, UV (EtOH) 220 nm (ε 9333), ^{1}H NMR (90 MHz) δ 5 7 (2H, m), 4 51 (1H, dq, J 3,7), 2 11 (1H, dq, J 3,7), 2 0 (3H, s), 1 33 and 1 03 (3H each, d, J 7), ^{13}C NMR (22 5 MHz) δ 165 2, 164 2, 115 1, 75 9, 38 0, 21 3, 17 1, 10 35, (Anal calc for $C_8H_{12}O_2$ C, 68 57, H, 8 57 Found C, 68 6, H, 8 75%)

The hemiacetals (**14**) (4 09 g, 12 9 mmol) were dissolved in THF (40 ml) and 3 drops of conc HCl added After 30 min the solution was poured into a mixture of brine and aqueous $NaHCO_3$ (1 1) The aqueous layer was extracted with ether and the combined extracts dried and evaporated. The resultant mixture of crude diols (**15**) (2 54 g) were immediately dissolved in dry MeOH (30 ml) and a trace of *p*-toluenesulphonic acid added After 4 h at 20°C, the solution was diluted with ether and poured into aqueous $NaHCO_3$ with rapid stirring The ether layer was separated and the aqueous layer extracted with a further portion of ether The combined extracts were dried and evaporated, and the residue chromatographed with ether-petroleum ether (1 4) to give first ethyl *epi*-pederate (**16**) (417 mg, 15%) m p 65 5-68 5°C (from hexane), IR (CCl_4) 3520br, 1755m, 1730s, 1655m, 1280s, 1210s, 1165s, 1110,s, 1070s, 1040s, 1010s, and 895s cm^{-1}, ^{1}H NMR (see reference 14) ^{13}C NMR (25 MHz) δ 170 8, 146 6, 109 9, 100 1, 72 3, 69 3, 61 6, 49 0, 41 3, 32 45, 17 8, 14 1, 11 7, (Anal calc for $C_{13}H_{22}O_5$ C, 60 46, H, 8 53 Found C, 60 55, H, 8 5%) followed by ethyl pederate (**2**) (0 801 g, 30%) b p 150°C (bath)/0 1 mm Hg, IR (CCl_4) 3520br, 1725s, 1655m, 1450s, 1380s, 1280s, 1220s, 1075s, 1050s, 1015s, 895s, and 880s cm^{-1}, ^{1}H NMR (see reference 14), ^{13}C NMR (22 5 MHz) δ 172 5, 146 3, 110 0, 99 8, 72 2, 69 3, 61 8, 48 6, 41 4, 33 2, 17 7, 14 2, 11 7, (Found M$^+$, 258 14696 Calc for $C_{13}H_{22}O_5$ M, 258 146713)

(2R*,3R*)-3-Methyl-4-pentyne-2-ol (17) - To lithium acetylide ethylenediamine complex (90%, 50 g, 0 543 mol) in HMPA (50 ml) at 0°C was added in one portion epoxide (**8**) (10 8 g , 0 15 mol) and the flask immediately sealed The reaction was warmed to 20°C and stirred for 6 days, then cautiously poured into dil HCl (300 ml) Extraction with Et_2O (6 x 150 ml) gave crude (**17**) Purification by distillation (69 - 73°C, 22 mm Hg) gave (**17**) as a colourless oil (12 06 g, 82 %) IR (film) 3700 - 3040br, 3310s, 2165m cm^{-1}, ^{1}H NMR (60 MHz) δ 3 65 (1H, m), 2 28 (1H, s), 2 8 - 2 35 (1H, m), 2 08 (1H, d, J 1 5), 1 25 (3H, d, J 6), 1 15 (3H, d, J 6)

(4R*,5R*)-4-Methyl-5-hydroxy-2-hexynoic acid (18) - To a mechanically stirred solution of alcohol (**17**) (18 54 g, 189 mmol) in THF (350 ml) at - 70°C was added dropwise *n*-BuLi (2 5 M, 178 ml) The solution was stirred for 45 min then a solution of *i*-Pr_2NH (10 9 ml, 78 mmol) in THF (35 ml) was added dropwise After 15 min dry CO_2(g) was bubbled through the solution for 20 min forming a thick jelly This was very carefully poured into ice/dil HCl (450 ml) and extracted with Et_2O After saturation with NaCl the aqueous residue was further extracted with $CHCl_3$ (3 x 200 ml) and the combined aqueous extracts dried and concentrated, yielding a pale orange solid Washing with petrol yielded (**18**) as a yellow solid (25 9 g, 96 %) m p 95 - 96°C (from Et_2O/hexanes)The product was used in the next step without further purification, IR ($CHCl_3$) 3600 - 2400br, 2980m, 2250s, 1705s, 1360m cm^{-1}, ^{1}H NMR (270 MHz) 7 20 (2H, br s), 3 90 (1H, dq, J 5, 6), 2 79 (1H, dq, J 5, 7), 1 29 (3H, d, J 6), 1 22 (3H, d, J 7)

(±)-*cis*-5,6-Dimethyl-5,6-dihydro-2H-pyran-2-one (19) - To a solution of acid (**18**) (2 25 g, 16 mmol) in EtOH (40 ml) was added Pd/$BaSO_4$ (5%, 0 337 g) and quinoline (0 169 g) This was semi-hydrogenated for 1 h then filtered through Celite Concentration yielded crude (**19**) and its hydroxy acid form Kugelrohr distillation (130 - 140°C, 0 2 mmHg) yielded pure (**19**) (1 705 g, 85%) as a colourless oil IR (film) 2980s, 1730s, 1710s cm^{-1}, ^{1}H NMR (270 MHz) 6 93 (1H, dd, J 10, 6), 5 96 (1H, dd, J 10, 1), 4 62 (1H, dq, J 7, 4), 2 43-2 30 (1H, m), 1 36 (3H, d, J 7), 1 05 (3H, d, J 7)

(4S*,5R*,6R*)-5,6-Dimethyl-4-phenylselenomethyltetrahydro-2H-pyran-2-one (20) - To a solution of $(PhSe)_2CH_2$ (1 8 g, 5 6 mmol) in THF (3 ml) at -78°C was added dropwise *n*-BuLi (1 7 ml, 2 5N) followed by THF/HMPA (2/3 ml) The resulting brown solution was cooled to -85°C and a solution of lactone (**19**) (0 50 g, 4 mmol) in THF/HMPA (2/1 5 ml) added dropwise giving a yellow solution which was stirred for 30 min The solution was poured into dil HCl (2M, 20 ml) and extracted with ether The combined extracts were washed with $NaHCO_3$, H_2O, and brine, dried and concentrated to a yellow oil Purification by chromatography (20-80% ether/hexanes) gave product (**20**) (0 99 g, 89%) as a yellow oil IR (film) 3090-3040w, 2980m, 2930w, 1740s, 1580m, 1480m, 1455m, 1385m, 1335w, 1280m, 1255s, 1220m, 1210m, 1125m, 1095m, 1075m, 1025m, 1005m, 965m, 740s, 695m cm^{-1}, ^{1}H NMR (400MHz) δ 7 55-7 46 (2H, m), 7 32-7 23 (3H, m), 4 50 (1H, dq, J 3, 7), 3 03 (1H, dd, J 6, 12), 2 96

(1H, dd, J 7, 12), 2 67 (1H, dd, J 6, 16), 2 37 (1H, dd, J 10, 16), 1 93 (1H, m), 1 89 (1H, m), 1 29 (3H, d, J 7), 0 948 (3H, d, J 7), m/z 300 (7%), 299 (61), 298 (M^+, ^{80}Se, 40), 297 (3), 296 (M^+, ^{78}Se, 21), 295 (7), 194 (8), 158 (29), 141 (23), 123 (22), 95 (40), 77 (30), 69 (98), 55 (100), (Found M^+, 298 04758 Calc for $C_{14}H_{18}O_2{}^{80}Se$ M, 298 04714)

2-Trimethylsilylethyl 2-bromoethanoate (22) - At 0°C, bromoacetyl chloride (47 25 g, 24 7 ml, 0 3 mol) in CH_2Cl_2 (50 ml) was added dropwise to a mechanically stirred solution of 2-trimethylsilylethanol (35 5 g, 43 0 ml, 0 3 mol) in CH_2Cl_2 (250 ml) over 25 min After 20 min at 0°C, the thick white suspension was poured into brine (300 ml), and extracted with CH_2Cl_2 The organic extracts were concentrated , and the residue taken up in Et_2O (400 ml) and washed with brine (2 x 100 ml), and then dried and concentrated Distillation through a short Vigreaux column gave bromoester (**22**) (62 g, 89%) as a colourless oil b p 61 - 66°C/0 7 mm Hg, IR (film) 2960s, 2900m, 1740s, 1280s, 1250s, 1170m, 860s cm^{-1}, ^{1}H NMR (90 MHz, CCl_4) δ 4 05 (2H, t, J 8), 3 55 (2H, s), 0 85 (2H, t, J 8), 0 05 (9H, s)

2-Trimethylsilylethyl 2-formyloxyethanoate (23) - Bromoester (**22**) (62 2 g, 0 26 mol) was added to a mechanically stirred suspension of sodium formate (35 4 g, 0 52 mol) in DMF (500 ml) and the resulting mixture stirred at 50°C for 15 h After cooling to room temp diluting with Et_2O (750 ml) and washing with water (5 x 400 ml), the organic layer was dried and concentrated Distillation through a short Vigreaux column gave formyloxyester (**23**) (53 3 g, 100%) as a colourless oil b p 76-77°C/0 9 mm Hg, IR (film) 2960s, 2900w, 1765s, 1250s, 1160s, 1170m, 860s 840s cm^{-1}, ^{1}H NMR (90 MHz, CCl_4) δ 8 2 (1H, s), 4 65 (1H, s), 4 3 (2H, t, J 8), 1 05 (2H, t, J 8), 0 05 (9H s), m/z 177(2%), 161 (10), 133(19), 117 (3), 103 (17), 87 (3), 73 (100)

2-Hydroxy-O-(2-trimethylsilylethyl)ethanoate (24) - To a stirred solution of formyloxyester (**24**) (53 3 g, 0 26 mol) in MeOH (500 ml) at 0°C was added Et_3N (180 ml, 1 3 mol) in MeOH (200 ml) over 15 min The solution was stirred at 5°C for 30 min, concentrated and then distilled through a short Vigreaux column, to yield the α-hydroxyester (**24**) (39 1 g, 86%) as a colourless oil which solidified on storage at 2°C b p 96-98°C/18 mm Hg, m p 20-25°C, IR (film) 3450br m, 2960s, 2900m, 1745s, 1250s, 1100s, 860s, 840s cm^{-1}, ^{1}H NMR (90 MHz, CCl_4) δ 4 2 (2H, t, J 8), 3 95 (2H, s), 2 4 (1H, br), 1 0 (2H, t, J 8), 0 05 (9H, s), m/z 133 (18), 101 (5), 85 (3), 77 (20), 75 (65), 73 (100) (Found M^+, 176 08690 Calc for $C_7H_{16}O_3Si$ M, 176 08687

2-Trimethylsilylethyl 2-(2-methyl-2-methoxyethoxy)ethanoate (25) - 2-Methoxypropene (14 1 ml, 0 15 mol) was added dropwise to a stirred solution of α-hydroxyester (**24**) (8 8 g, 50 mmol) in CH_2Cl_2 (50 ml) keeping the temperature below 0°C Acetyl chloride vapour (30 ml) was bubbled through the solution before it was stirred at room temperature for 2 h Powdered potassium carbonate (4 6 g, 33 mol) was added and the suspention vigorously stirred at room temperature for 1 h The reaction mixture was diluted with Et_2O (250 ml) and filtered through a plug of Celite and then concentrated Distillation *via* short path gave the ester (**25**) (11 9 g, 96%) as a colourless oil b p 70-80°C/0 1 mm Hg, IR (film) 3000m, 2960s, 2900m, 2740w,1760s, 1740m,1380s, 1250s, 1220s, 1185s, 1155m, 1110s, 1065s, 860s, 840s,700m cm^{-1}, ^{1}H NMR (90 MHz, CCl_4) δ 4 1 (2H, dd, J 8, 10), 3 8 (2H, s), 3 05 (3H, s), 1 2 (6H, s), 0 9 (2H, dd, J 8, 10), 0 05 (9H, s), m/z 249 (M^++1, 10%), 223 (8), 205 (12), 173 (20), 149 (18), 75 (100)

Adduct (27) *via* alkylation of tetrahydropyranone (20) - *n*-BuLi (5 48 ml, 2 5 M in hexane, 13 7 mmol) was added dropwise to a stirred solution of diisopropyloamine (1 92 ml, 13 7 mmol) in THF (50 ml) at 0°C After 10 min, the temperature was lowered to -70°C and ester (**25**) (3 40 g, 13 7 mmol) in THF (30 ml) was added dropwise The solution was stirred at -75°C for 1 h, and then tetrahydropyranone (**20**) (2 70 g, 9 1 mmol) in THF (20 ml) was added dropwise keeping the temperature below -70°C The reaction mixture was stirred at -75°C for 2 5 h and then poured into water (200 ml) and extracted with Et_2O The organic extracts were washed with water, and brine, and then dried and concentrated Chromatography (20 to 50% EtOAc/hexanes) gave first the alkylated product (**27**) contaminated with about 10% of starting ester (**25**), 4 4 g IR (film) 3700-3100m, 2960s, 1755sh, 1740m, 1380m, 1250s, 1210m, 1180m, 1100s, 1060s, 860s, 840s cm^{-1}, ^{1}H NMR (360 MHz) δ 7 6-7 2 (5H, m), 4 28 (2H, dd, J 4, 7) 4 17 (0 5 H, s), 4 05 (0 5 H, s), 3 40 (1H, m) 3 26 (1 5H, s), 3 23 (1 5 H, s), 2 1-1 2 (7H, m), 1 43 (6H, s), 1 1-0 9 (8H, m), 0 10 (9H, s), m/z 548 (0 1%), 547 (0 2), 546 ($M^+{}^{80}Se$, 0 6), 545 (0 1), 544 ($M^+{}^{78}Se$, 0 3), 543 (0 1), 542 (0 1), 299 (7), 171 (6), 141 (10), 95 (6), 73 (100) (Found M^+, 544 19469 Calc for $C_{25}H_{42}O_6{}^{78}SeSi$ M, 544 19244, Found M^+, 546 19110 Calc for $C_{25}H_{42}O_6{}^{80}SeSi$ M, 546 19152) Second to elute was 0 76 g (28%) of the starting tetrahydropyranone (**20**) as a colourless oil

Deprotection of (27) to give alcohols (29) and (30) -The alkylated product (**27**) (4 4 g) was dissolved in saturated aqueous THF (20 ml) and one drop of conc HCl was added The homogeneous solution was stirred at room temperature for 20 min and then poured into sodium bicarbonate solution and extracted with Et_2O The organic extracts were washed with water, and brine, and then dried and concentrated to give the crude deprotected product (**28**), 3 5 g IR (film) 3700-3100m, 2960s, 2900w, 1735s, 1580w, 1250s, 1100m, 1065s, 860s, 840s cm^{-1}, which was dissolved in MeOH (35 ml) A catalytic amount of *p*-TsOH was added and the solution was stirred at room temperature for 3 5 h, and then poured into sodium bicarbonate solution (50 ml) and extracted with Et_2O The organic extracts were washed with water and brine and then dried and concentrated The 1 1 mixture of alcohols was purified by

chromatography (20% EtOAc/hexanes) to yield 2 83 g of (**29**) and (**30**) [61% from (**20**)] and achieved a partial separation First to elute was 1 06 g of the (2*R*)-isomer (**29**) as a colourless oil which slowly crystallised on standing at 2°C An analytical sample gave m p 47 0-48 5°C (from EtOAc/hexane) IR (CCl_4) 3600-3450w, 2960s, 2900m, 1725s, 1480m, 1440m, 1380m, 1275s, 1250s, 1200s, 1180s, 1110s, 1085s, 1075s, 1040s, 860s, 840s, 690m cm^{-1}, ^{1}H NMR (400 MHz) δ 7 5-7 2 (5H, m), 4 35-4 20 (3H, m), 3 96 (1H, ddd, J 3, 7, 9), 3 31 (3H, s), 3 25 - 3 21 (2H, m), 2 73 (1H, d, J 5), 2 14 (1H, dd, J 7, 15) 1 82 (1H, m), 1 70 (1H, m), 1 38 (1H, dd, J 2, 14), 1 13 (3H, d, J 7), 1 07 (2H, t, J 9), 0 95 (3H, d, J 7), 0 06 (9H, s), m/z 456(3%), 454 (2), 299 (33), 285 (12), 281 (2), 239 (2), 234 (2), 155 (11), 101 (16), 73 (100) (Found M^+, 488 14998 Calc for $C_{22}H_{36}O_5{}^{80}SeSi$ M, 488 14966

Next eluted 0 97 g of mixed fractions followed by 0 80 g of the pure (2*S*)-isomer (**30**) as a colourless oil which slowly crystallised on standing at 2°C An analytical sample gave m p 80 5-81 0°C (from EtOAc/hexane) (Found C, 54 05, H, 7 4 Calc for $C_{22}H_{36}O_5SeSi$ C, 54 15, H, 7 45%), IR (CCl_4) 3650-3450w, 2960s, 2900m, 1725s, 1480m, 1455m, 1440m, 1380m, 1280s, 1250s, 1230s, 1210s, 1180s, 1150s, 1095s, 1065m, 1045s, 1025s, 1000m, 970m, 935m, 860s, 840s, 695s cm^{-1}, ^{1}H NMR (400 MHz) δ 7 5-7 2 (5H, m), 4 35-4 20 (3H, m), 3 95 (1H, ddd, J 3, 7, 9), 3 27 (3H, s), 3 25 - 3 22 (2H, m), 2 91 (1H, d, J 6), 2 40 (1H, t, J 6), 1 77-1 67 (3H, m), 1 12 (3H, d, J 7), 1 08-1 00 (2H m), 0 86 (3H, d, J 7), 0 05 (9H, s), m/z 488 (M^+ ^{80}Se, 2%), 486 (M^+^{78}Se, 1), 456(2), 454 (1), 429 (0 5), 427 (0 3), 372 (2), 370 (1), 313 (15), 311 (8), 299 (9), 285 (3), 281 (2), 279 (1), 171 (11), 155 (65), 123 (25), 101 (8), 95 (23), 81 (13), 73 (100), (Found M^+, 488 14943 Calc for $C_{22}H_{36}O_5{}^{80}SeSi$ M, 488 14966)

Transformation of alcohol (29) into alcohol (30) - DMSO (0 078 ml, 1 1 mmol) in CH_2Cl_2 (0 5 ml) was added dropwise to a stirred solution of oxalyl chloride (0 047 ml, 0 55 mmol) in CH_2Cl_2 (3 ml) at -75°C After 10 min at -75°C a 1 1 mixture of alcohols (**29**) and (**30**) (244 mg, 0 5 mmol) in CH_2Cl_2 (1 5 ml) was added dropwise to give a yellow solution After 20 min at -70°C, Et_3N (0 209 ml, 1 5 mmol) was added dropwise to give a colourless solution which was allowed to warm to 0°C over 90 min The resulting cloudy yellow solution was re-cooled to -95°C and NH_3BH_3 (1 M in THF, 2 3 ml) added dropwise The reaction mixture was allowed to warm to -60°C over 1 h, and then stirred at room temperature for 30 min The resulting light yellow suspension was poured into dilute HCl (2N, 25 ml) and extracted with $CHCl_3$ The organic extracts wrer dried and concentrated to yield 244 mg (100%) of a light yellow semi-solid HPLC analysis (Zorbax SIL, 9 4 mm x 25 cm, 15% EtOAc/hexane, 5 0 ml/min, 254 nm) showed this mixture to be 7 1 (2*S*) (2*R*) Chromatography (15% EtOAc/hexane) gave first 100 mg of mixed fractions, and then 129 mg of the pure (2*S*)-isomer (**30**) as a white powder spectral data as above

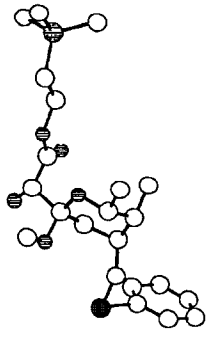
Benzoate (31) - To a solution of alcohol (**30**) (250 mg, 0 513 mmol), pyridine (0 208 ml, 2 57 mmol) and DMAP (2 mg) in CH_2Cl_2 (1 5 ml) was added benzoyl chloride (0 179 ml, 1 54 mmol) dropwise The reaction mixture was stirred at room temperature for 100 min, then cooled to 0°C and quenched by the dropwise addition of 1-(N,N-dimethylamino)-3-propanamine (0 194 ml, 1 54 mmol) After 5 min at 0°C, the red solution was poured into diluted HCl (2N, 10 ml) and extracted with Et_2O, and CH_2Cl_2 The organic extracts were washed with dilute HCl (2N), $NaHCO_3$ solution and brine, and then dried and concentrated Chromatography (10% Et_2O/hexane) yielded the benzoate (**31**) (304 mg, 100%) as a colourless oil IR ($CHCl_3$) 3050-2850m, 1740sh, 1730s, 1455m, 1385m, 1295m, 1275m, 1260m, 1220s, 1125m, 1045m, 715s cm^{-1}, ^{1}H NMR (360 MHz) δ 8 10-8 05 (2H, m), 7 60-7 20 (8H, m), 5 31 (1H, s), 4 27 (2H, t, J 7), 3 97 (1H, dq, J 2, 7), 3 30 (2H, d, J 8), 3 25 (3H, s), 2 33 (1H, dd, J 5, 13), 1 95-1 70 (3H, m), 1 13 (3H, d, J 7), 1 06 (2H, t, J 7), 0 90 (3H, d, J 7), 0 048 (9H, s), m/z 592 (M^+, 1%), 560 (2), 476 (1), 313 (5), 253 (9), 155 (51), 105 (100) (Found M^+, 592 1793 Calc for $C_{29}H_{40}O_6{}^{80}SeSi$ M, 592 1759

Acid (4) - To a solution of the silylether ester (**31**) (304 mg, 0 513 mmol) in THF (4 ml) was added *n*-Bu_4NF $3H_2O$ (486 mg, 1 54 mmol) in one portion The resulting yellow/green solution was stirred at room temperature for 20 min and slow gas evolution was observed Et_2O (5ml) and water (5ml) were added and the heterogenous mixture was vigorously stirred for 10 min The layers were separated and the aqueous layer re-extracted with Et_2O The combined organic extracts were washed with water, and brine, and then dried and concentrated to give the acid (**4**) (252 mg, 100%) as a white foam that was not further purified IR (CCl_4) 3500-2500m, 2900m, 2940m, 1730s, 1290m, 1270m, 1245m, 1120m, 1100m, 910m cm^{-1}, ^{1}H NMR (360 MHz) δ 11 H, br), 8 20 (2H, m), 7 65-7 20 (8H, m), 5 59 (1H, s), 4 11 (1H, m), 3 35-3 20 (2H, m), 3 24 (3H, s), 2 15-1 80 (4H, m), 1 22 (3H, d, J 7), 0 97 (3H, d, J 7), m/z 416 (M^+, 1%), 259 (15), 245 (14), 137 (9), 123 (23), 105 (100), 91 (12), (Found M^+-Ph, 416 0641 Calc for $C_{18}H_{24}O_6{}^{80}Se$ M, 416 0738

Crystal data for compound (30) Crystallisation solvent dilute MeOH-H_2O Space group P1, a = 8 222 (2), b = 12 241 (3), c = 13 560 (3) Å, α = 8 29 (2), β = 78 33 (2), γ = 73 37 (2)°, U = 1280 2 (7) Å^3, D_m = 1 25, Z =2, D_X = 1 26, μ = 28 70 cm^{-1} A crystal ca 0 07 x 0 09 x 0 10 mm was surveyed and a 1A data set (maximum sin θ/λ = 0 5) was collected on a Nicolet R3m/μ diffractometer Atomic scattering factors were taken from the International Tables for X-ray Crystallography All crystallographic calculations were facilitated by the SHELXTL system All diffractometer data was collected at room temperature

Structure analysis and refinement Number of reflections = 2604, non-zero reflections = 2321, R-index = $\Sigma||Fo|-|Fc||/\Sigma|Fo| = 0\ 040$, GOF = $[\Sigma w(Fo^2-Fc^2)^2/(m-s)]^{1/2} = 1\ 54$, scale factor = 1 455 (3), secondary extinction coefficient = 40 (6) x 10^{-4}

A trial structure was obtained by direct methods and refined routinely Hydrogen positions were calculated wherever possible The methyl and hydroxyl groups were located by difference Fourier techniques The hydrogen parameters were added to the structure factor calculations but were not refined The shifts calculated in the final cycle of least squares refinement were all less than 0 1 of their corresponding standard deviations The final R-index was 0 040 A final difference Fourier revealed no missing or misplaced electron density Tables of atomic coordinates, isotropic thermal parameters, bond lengths and bond angles have been deposited in the Cambridge Crystallographic Data Base



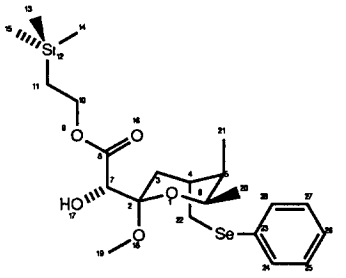


Table 2 Atomic Coordinates (x 10^4) for Pederic Acid Derivative (30)

Atom	x	y	z	Atom	x	y	z
Se	7776(1)	-2432(1)	4977(1)	H(6)	4726	928	6547
O(1)	6570(3)	1180(2)	7234(2)	H(7)	9420	1622	6627
C(2)	8042(5)	492(3)	6631(3)	H(10A)	7997	1526	9841
C(3)	8245(5)	-781(3)	6797(3)	H(10B)	9914	1589	9646
C(4)	6574(5)	-1134(3)	6893(3)	H(11A)	8899	3539	9285
C(5)	5061(5)	-289(4)	7572(3)	H(11B)	7014	3431	9640
C(6)	4965(5)	920(4)	7212(3)	H(13A)	6821	5394	10586
C(7)	9569(5)	853(3)	6871(3)	H(13B)	8199	5430	11223
C(8)	9551(5)	796(4)	7996(3)	H(13C)	6410	5261	11761
O(9)	8905(4)	1837(2)	8391(2)	H(14A)	7696	1960	11978
C(10)	8794(7)	1919(4)	9479(3)	H(14B)	5926	2874	11945
C(11)	8186(7)	3153(4)	9740(4)	H(14C)	7106	3038	12666
Si(12)	8201(2)	3524(1)	11036(1)	H(15A)	10664	3200	11833
C(13)	7302(10)	5091(5)	11168(5)	H(15B)	11163	3609	10723
C(14)	7099(10)	2759(5)	12022(5)	H(15C)	11128	2342	10942
C(15)	10587(9)	3119(6)	11146(5)	H(17)	11074	-96	5757
O(16)	10058(4)	-43(3)	8468(2)	H(19A)	7430	1933	4576
O(17)	11180(3)	155(2)	6391(2)	H(19B)	8241	2269	5422
O(18)	7986(3)	705(2)	5581(2)	H(19C)	6309	2234	5656
C(19)	7448(5)	1883(3)	5284(3)	H(20A)	2451	1739	7816
C(20)	3558(6)	1853(4)	7819(4)	H(20B)	3592	2584	7527
C(21)	5207(7)	-470(4)	8681(3)	H(20C)	3735	1825	8500
C(22)	6102(5)	-1268(3)	5878(3)	H(21A)	5385	-1264	8851
C(23)	7697(7)	-3764(4)	5779(4)	H(21B)	4163	-31	9096
C(24)	6305(8)	-4217(4)	5832(4)	H(21C)	6169	-230	8792
C(25)	6206(10)	-5202(5)	6387(5)	H(22A)	5023	-1457	6013
C(26)	7562(11)	-5676(5)	6859(4)	H(22B)	5962	-547	5531
C(27)	8946(12)	-5327(6)	6851(5)	H(24)	5396	-3846	5475
C(28)	9009(10)	-4296(5)	6251(4)	H(25)	5267	-5537	6442
H(3A)	9062	-1181	6237	H(26)	7519	-6353	7251
H(3B)	8690	-1005	7404	H(27)	9847	-5717	7207
H(4)	6793	-1877	7203	H(28)	9977	-3989	6191
H(5)	3990	-428	7519				

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