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STUDIES RELATED TO THE SYNTHESIS OF PEDERIN. PART 2. SYNTHESIS OF PEDEROL DIBENZOATE AND BENZOYLPEDAMIDE.

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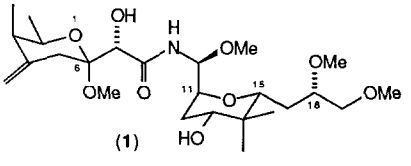
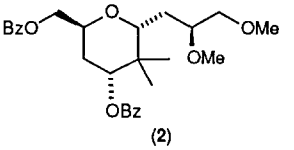
Abstract Syntheses of the ring B fragments (+)-pederol dibenzoate (**2**) and (±)-benzoylpedamide (**3**) of the insect toxin pederin (**1**) are described An intramolecular directed aldol condensation was used to construct the tetrahydropyran ring in (+)-pederol dibenzoate (**2**) Better stereocontrol in the synthesis of (±)-benzoylpedamide (**3**) was achieved in which the stereochemistry at C-11 was introduced by a conjugate addition of TMSCN to the dihydropyranone (**31**) The synthesis of (±)-pederin from (±)-(**3**) and the ring A fragment (±)-benzoylselenopederic acid (**38**) is described

In Part 1 of this series on the synthesis of the potent insect toxin pederin (**1**)[3], we decribed syntheses of the ring A fragments ethyl pederate and benzoylselenopederic acid In this paper, we now describe the completion of the synthesis of (**1**) and give details of syntheses of the ring B fragments pederol dibenzoate (**2**)[4] and (±)-benzoylpedamide (**3**)[5]



(**1**)



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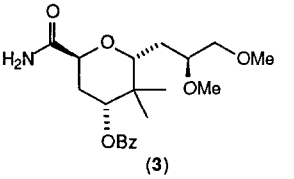
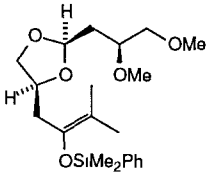


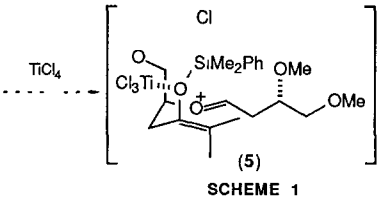
(**3**)

Synthesis of (+)-Pederol Dibenzoate (2)

Our first approach to the ring B fragment of pederin was conceived along the lines shown in Scheme 1 in which an intramolecular directed aldol reaction, in the variant developed by Mukaiyama and co-workers[6], was to play a crucial strategic role Success depended on the regioselective cleavage of the dioxolane (**4c**) giving a bridged (*E*)-oxonium ion intermediate (**5**) which would then suffer nucleophilic attack by a pendant enol silane from the Si face to generate the tetrahydropyranone (**6**) having the C-11 substituent (pederin numbering) in an axial position At the time these studies were launched (1981), there were very few examples of the intramolecular aldol condensation known[7] and thus no precedent for predicting the stereochemical course of the salient annulation reaction



(**4c**)



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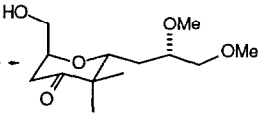
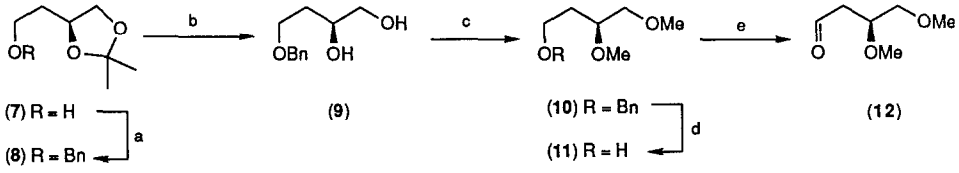


(**6**)

SCHEME 1

The dioxolane (**4**) was constructed from two chiral fragments diol (**9**) and aldehyde (**12**) These were synthesised efficiently on a substantial scale from the known (*S*)-butane-1,2,4-triol derivative (**7**)[8] as shown in Scheme 2 using standard functional group manipulations The only step in this sequence which caused concern was the Swern oxidation of the alcohol (**11**) to the aldehyde

(12) If triethylamine was used as prescribed in the usual recipe[9], the product aldehyde (12) underwent easy β-elimination of MeOH In order to circumvent this problem, the weaker base N-methylmorpholine was used in the decomposition of the intermediate sulphoxonium salt



SCHEME 2 YIELDS AND REAGENTS

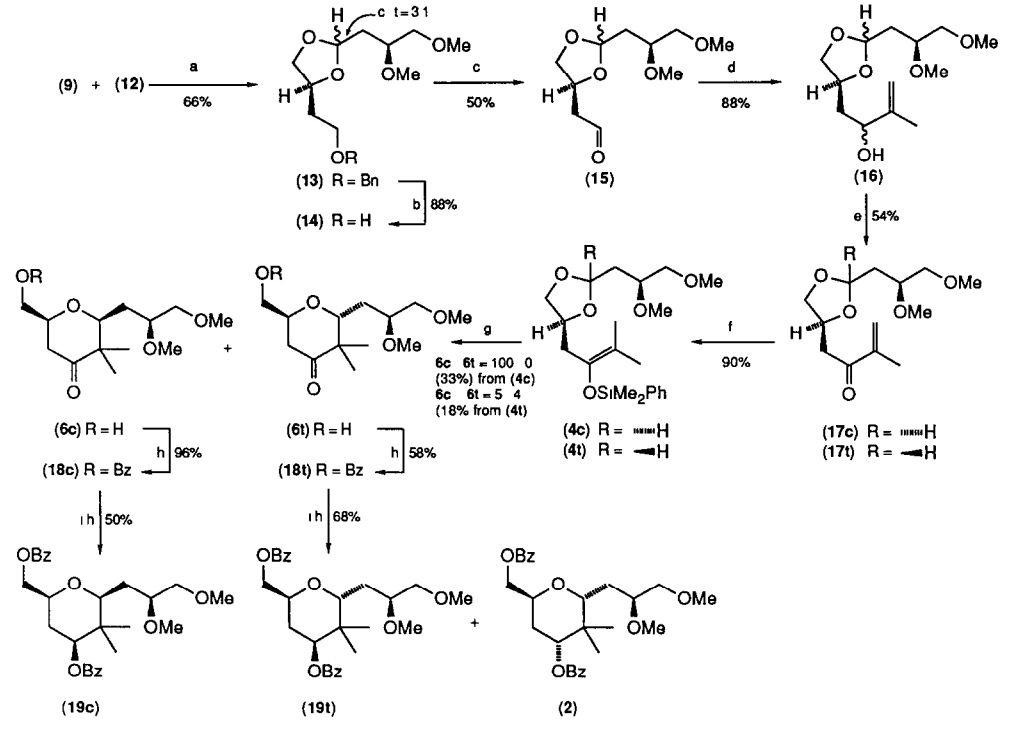
(a) 88% $PhCH_2Br$ NaH, NaI / THF, rt, 1 h, (d) 96% H_2, Pd-C / EtOH,
(b) 100% aq HCl, THF, reflux, 3 h, (e) 98% Swern oxidation
(c) 93% MeI, NaH / THF, rt, 12 h,

Condensation of aldehyde (12) with diol (9) (Scheme 3) gave an equilibrium mixture of the diastereomeric 1,3-dioxolanes (13) in only 66% yield That the *cis*-isomer was the major product (ca 75% of the mixture) was expected from Eliel's work[10] and verified by ^{13}C NMR spectroscopy[11] The *cis*-isomer gave a signal at δ 102 1 for the acetal carbon whereas the corresponding signal in the trans-isomer appeared at δ 101 4 Once again the easy elimination of methanol from aldehyde (12) dictated the conditions used to form the dioxolane Best results were obtained by treating a mixture of (12) and diol (9) in CH_2Cl_2 with TsOH at room temperature in the presence of anhydrous $MgSO_4$ as the dehydration agent Since the diastereomeric dioxolanes (13) were inseparable, the mixture was carried through the next four steps as outlined in Scheme 3 The base-sensitive enones (17c) and (17t) were then separated by tedious column chromatography and individually converted to the corresponding enol silanes (4c) and (4t) respectively using Rh(I)-catalysed hydrosilylation[12] This method was very mild and efficient (90% yield) and provided the desired enol silanes regiospecifically without competing β-elimination

With isomerically pure (4c) and (4t) in hand, we next investigated the key intramolecular directed aldol reaction in considerable detail The requisite 6-*endo*$_e$*endo*$_n$ annulation[13] was best achieved using 2 equivalents of $TiCl_4$ in CH_2Cl_2 at -78°C Two equivalents of Lewis acid were necessary because the methoxy groups in the side chain formed a very stable complex with the $TiCl_4$[14] which prevented the desired reaction from taking place The diastereoisomeric dioxolanes behaved differently in the cyclisation reaction The major *cis*-dioxolane (4c) gave the tetrahydropyranone (6c) as the sole identifiable annulation product in 33% yield whereas the minor *trans*-dioxolane (4t) gave a mixture of the tetrahydropyranones (6c)(10%) and (6t)(8%) In both cases several very minor products and polar material accounted for the balance of the mass The stereochemistry of the hydroxymethyl substituent in (6c) and (6t) was readily determined by ^1H NMR analysis (90 MHz) of the corresponding benzoates (18c) and (18t) The resonances for the C-12 axial proton (δ 2 71, dd, J_{gem} 13 Hz, J_{vic} 12 Hz) and the C-12 equatorial proton (δ 2 38, dd, J_{gem} 13 Hz, J_{vic} 3Hz) indicated a *trans*-diaxial coupling between C-12 and C-11 protons compatible with structure (18c) in which both the side chains occupy an equatorial position The corresponding signals in (18t) appeared as a broad multiplet centred at δ 2 67

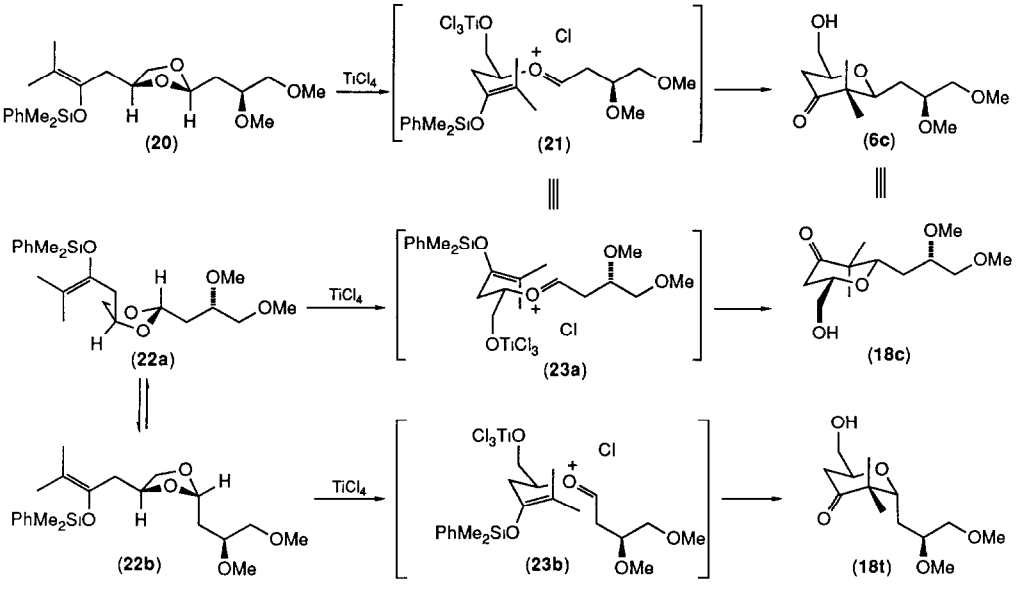
To complete the synthesis of (+)-pederol dibenzoate (2), the keto group in (18t) was reduced and the resultant alcohol benzoylated in the usual way to give a 68% yield of a 1 1 mixture of (19t) and (2) which required HPLC to effect separation The poor stereoselectivity in the reduction of (18t) probably reflects the steric hindrance to axial attack by hydride caused by the axial benzoyloxymethyl group since the isomeric tetrahydropyranone (18c) was reduced and benzoylated to give (19c) in which the expected axial delivery of hydride had occurred exclusively

Scheme 4 attempts to rationalise the stereochemical course of the reaction If we assume that the *cis*-dioxolane (4c) occupies a conformation (20) which undergoes cleavage of the dioxolane ring to form an (*E*)-oxonium ion, then cyclisation *via* the chair-shaped intermediate (21) would generate the major tetrahydropyranone (6c) Assuming the *trans*-dioxolane (4t) exists as an equilibrium mixture of the conformers (22a) and (22b) which undergoes cleavage of the dioxolane ring to (*E*)-oxonium ions, cyclisation *via* chair-shaped intermediates (23a) and (23b) would account for the formation of the two observed tetrahydropyranones (18c) and (18t)



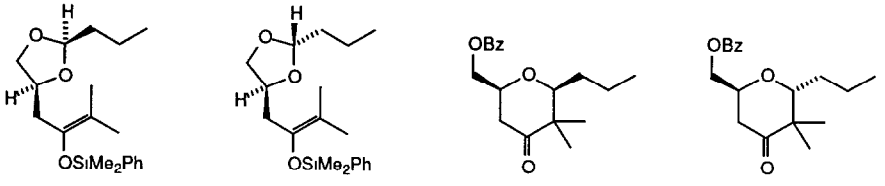
SCHEME 3 REAGENTS

(a) TsOH $MgSO_4$ / CH_2Cl_2 rt 48 h
(b) Na / NH_3(l) Et_2O 78°C
(c) PCC / CH_2Cl_2 rt 2 5 h
(d) CH_2=C(Me)MgBr / THF 0°C 10 min
(e) PCC / CH_2Cl_2 rt 3 5 h
(f) $PhMe_2SiH$ $[Ph_3P]_3RhCl$ 55°C 1 h
(g) $TiCl_4$ / CH_2Cl_2 78°C 1 h
(h) BzCl DMAP (cat) / pyridine rt
(i) $NaBH_4$ / EtOH rt, 2 h



SCHEME 4

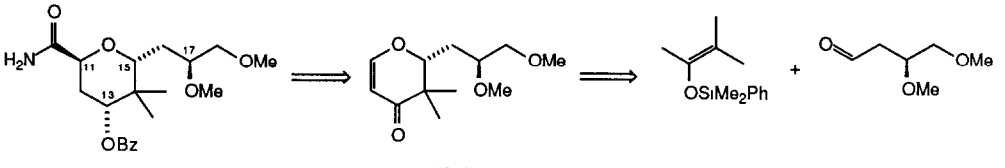
In an attempt to gain some insight into the causes of the inefficiency of the key annulation reaction and its unfortunate stereochemical course, the model dioxolanes (**24c**) and (**24t**) were prepared and their cyclisation studied using a variety of Lewis acid catalysts and conditions[13] Under the conditions used to effect cyclisation in the pederin series, the model *cis*-dioxolane (**24c**) gave the tetrahydropyranone (**25c**) exclusively in 65% yield whereas the *trans*-dioxolane (**24t**) gave a 1 1 mixture of the tetrahydropyranones (**25c**) and (**25t**) in 72% yield Thus, the stereochemical course of the cyclisation of the model compounds (**24c**) and (**24t**) paralleled that observed in the pederin series but the efficiency of the process was greatly improved This difference in efficiency may reflect problems associated with the chelation of the side chain methoxyl groups to $TiCl_4$ Our failure to produce significant quantities of tetrahydropyranone (**6t**) indicated that the central premise of our approach to diastereocontrolled annulation–coordination of the enol silane and dioxolane oxygens to an octahedral Ti(IV) complex–was wrong Consequently an alternative synthesis of the B-ring fragment (±)-benzoylpedamide (**3**) was devised



(**24c**) (**24t**) (**25c**) (**25t**)

(±)-Benzoylpedamide (3)

The overall strategy of our synthesis of (**3**) is outlined in Scheme 5 It has one feature in common with the synthesis of pederol dibenzoate (**2**) the stereogenic centre on the ring at C-15 was introduced by nucleophilic addition of an enol silane to an activated 3,4-dimethoxybutanal unit Then, in subsequent steps, the dihydropyranone ring (**31**) was forged and the axial carboxamide unit introduced by a stereoselective conjugate addition reaction However, once again the relative stereochemistry between C-17 and C-15 was to prove problematic



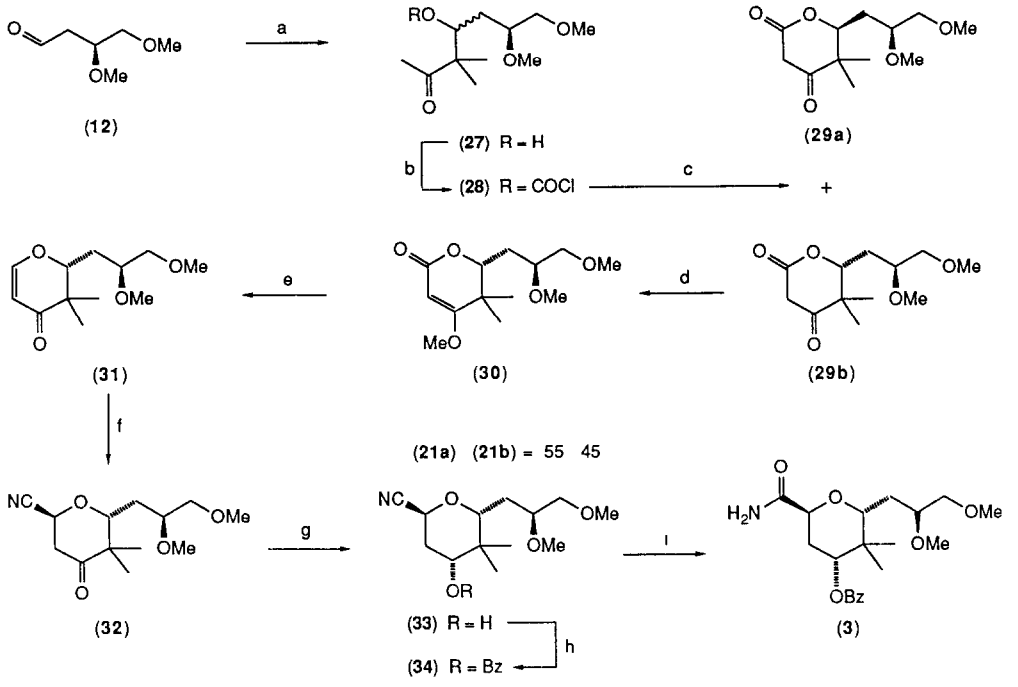
(**3**) (**31**) (**26**) (**12**)

SCHEME 5

Condensation of the enol silane (**26**) with (±)-3,4-dimethoxybutanal (**12**)[15] (Scheme 6) provided the delicate aldol product (**27**) as an inseparable mixture of diastereoisomers in high yield but with varying diastereoselectivity depending on the Lewis acid catalyst and the precise reaction conditions (*vide infra*) The mixture was efficiently cyclised to the β-ketolactones (**29a**) and (**29b**) *via* intramolecular acylation of the enolate derived from treatment of the chloroformate (**28**) with LDA This reaction gave several byproducts but these were readily removed by extraction of the β-ketolactones (**29a**) and (**29b**) into aqueous $NaHCO_3$ followed by acidification Upon cooling an ethereal solution of the mixture, the unwanted diastereoisomer (**29a**) crystallised out and concentration of the mother liquor gave the desired isomer (**29b**) as an oil of *ca* 90% diastereomeric purity Isomer (**29b**) was then transformed into the dihydropyranone (**31**) using standard transformations and the isomeric impurities finally removed by chromatography

Introduction of the axial carboxamide function at C-11 was launched by a highly efficient and diastereoselective conjugate addition of TMSCN to the dihydropyranone (**31**) to give the β-cyanoketone (**32**) in 95% yield after hydrolysis of the intermediate enol silane[16] Analysis of the crude product by NMR at 360 MHz gave no evidence of contamination by the corresponding equatorial nitrile The one remaining stereogenic centre at C-13 was then introduced by reduction of the β-cyanoketone (**32**) The stereoselectivity of this reaction depended on the conditions and the reducing agent Both $NaBH_4$ and $LiBH_4$ were essentially non-selective even at low temperatures Reduction with BH_3NH_3 complex[17] in THF at low temperature gave a 3 1 mixture of

diastereoisomeric alcohols in which the desired equatorial isomer (33) was the major product However, best results were obtained when β-cyanoketone (32) was reduced with $NaBH_4$ at -78°C in MeOH in the presence of $CeCl_3$ Under these conditions, the ratio of products was dramatically improved to 13 1 in favour of the desired isomer (33) and the yield was essentially quantitative To complete the synthesis, the alcohol function was benzoylated and the cyano function converted to the carboxamide giving (±)-benzoylpedamide in 9 steps from aldehyde (12) in an overall yield of *ca* 16%

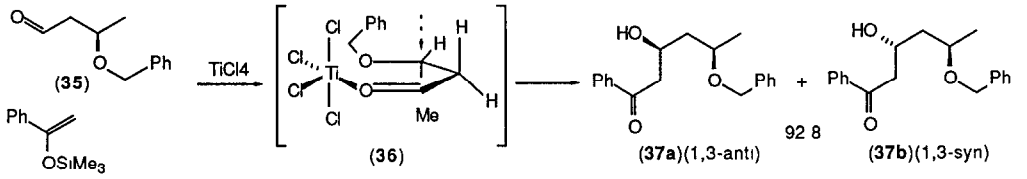


SCHEME 6 YIELDS AND REAGENTS

(a) 91% $Me_2C{=}C(Me)OSiMe_2Ph$ $TiCl_4$ / CH_2Cl_2 -70°C 1 h
(b) 93% $COCl_2$ / pyridine 0°C 1 h
(c) 80% LDA / THF -70°C 1 h
(d) 99% Me_2SO_4 K_2CO_3 / acetone reflux 2 h
(e) 70% DIBAL / toluene -70°C, 3 h
(f) 95% Me_3SiCN BF_3OEt_2 / CH_2Cl_2 0°C 1 5 h,
(g) 90% $NaBH_4$ $CeCl_3$ $7H_2O$ / MeOH, -78°C 0 5 h,
(h) 100% BzCl / pyridine r t 2 h
(i) 74% H_2O_2 K_2CO_3 / EtOH 70 min r t

Stereochemistry of the Directed Aldol Reaction At the time the synthesis of benzoylpedamide was undertaken, we were not aware of any systematic study of the stereochemistry of the Lewis acid catalysed addition of C-nucleophiles to β-alkoxy aldehydes to guide us in predicting the stereochemistry of the initial aldol condensation between aldehyde (12) and enol silane (26) That the reaction was essentially non-selective remains the prime blemish in an otherwise efficient and highly stereoselective synthesis of (±)-benzoylpedamide In fact, the formation of (27) as a roughly 1 1 mixture of diastereoisomers was a blessing in disguise since the more recent work from the Reetz[18] and Heathcock[19] laboratories would suggest that the desired diastereoisomer should have been formed in only very minor amounts We would now like to consider first the expected stereochemical course of an analogous aldol condensation between an enol silane and a β-alkoxy aldehyde, and then offer an explanation for the results we observed in the synthesis of aldol (27)

Scheme 7 shows the impressive diastereoselectivity obtained from the $TiCl_4$-catalysed addition of the enol silane derived from acetophenone to the β-benzyloxyaldehyde (35)[18a] The marked bias in favour of the 1,3-*anti*[20] addition product (37a) was interpreted in terms of a chelation-controlled addition to an intermediate (36) in which the enol silane approached from the less hindered side of the ring opposite the pseudo-axial methyl group[21] A substantial body of evidence now supports this view[22] The diastereoselectivity in this case is typical of a wide range of similar additions involving other C-nucleophiles



SCHEME 7

For the synthesis of benzoylpedamide, we required that the aldol condensation occur in a sense opposite to that outlined in Scheme 7, *i e* , we required that nucleophilic addition of enol silane (**26**) to aldehyde (**12**) provide the 1,3-*syn* addition product (**27b**) (see Table 1) This was achieved by a careful study of the various reaction parameters A slight bias in favour of the desired 1,3-*syn* adduct (**27b**) was best achieved by adding the aldehyde to 2 equivalents of $TiCl_4$ at low temperature followed by subsequent addition of the enol silane We propose that the chelation-controlled model outlined in Scheme 7 is disrupted by initial coordination of the first molecule of $TiCl_4$ to the more basic methoxy oxygen atoms whilst the second molecule of $TiCl_4$ is required to activate the aldehyde towards addition According to this model, the absence of annular chelation leads to diastereofacially indiscriminate addition There are several observations that support this postulate

(1) 1,2-Dimethoxyethane forms a stable yellow bidentate complex, m p 161°C, with $TiCl_4$[14] Aldehyde (**12**) similarly forms a yellow precipitate on addition of the first equivalent of $TiCl_4$

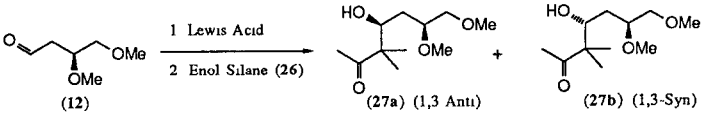
(2) The reaction of (**12**) and (**26**) is fast when 2 equivalents of $TiCl_4$ are used, but slow with just 1 equivalent (entries 1 and 2)

(3) The reaction is fast and gives the same product ratios independent of whether $TiCl_4$ or BF_3 etherate is the second molecule of Lewis acid (entries 1 and 3)

(4) With the mono-coordinate Lewis acid BF_3, aldehyde (**12**) underwent 1,3-*anti* addition with similar diastereoselectivities (entry 7) to those of other simple β-alkoxy aldehydes

These results suggest that care must be exercised in predicting the stereochemistry of chelation-controlled addition to β-alkoxy aldehydes when other potential coordination sites are proximate

Table 1 Effect of Reaction Conditions on Aldol Diastereoselectivity



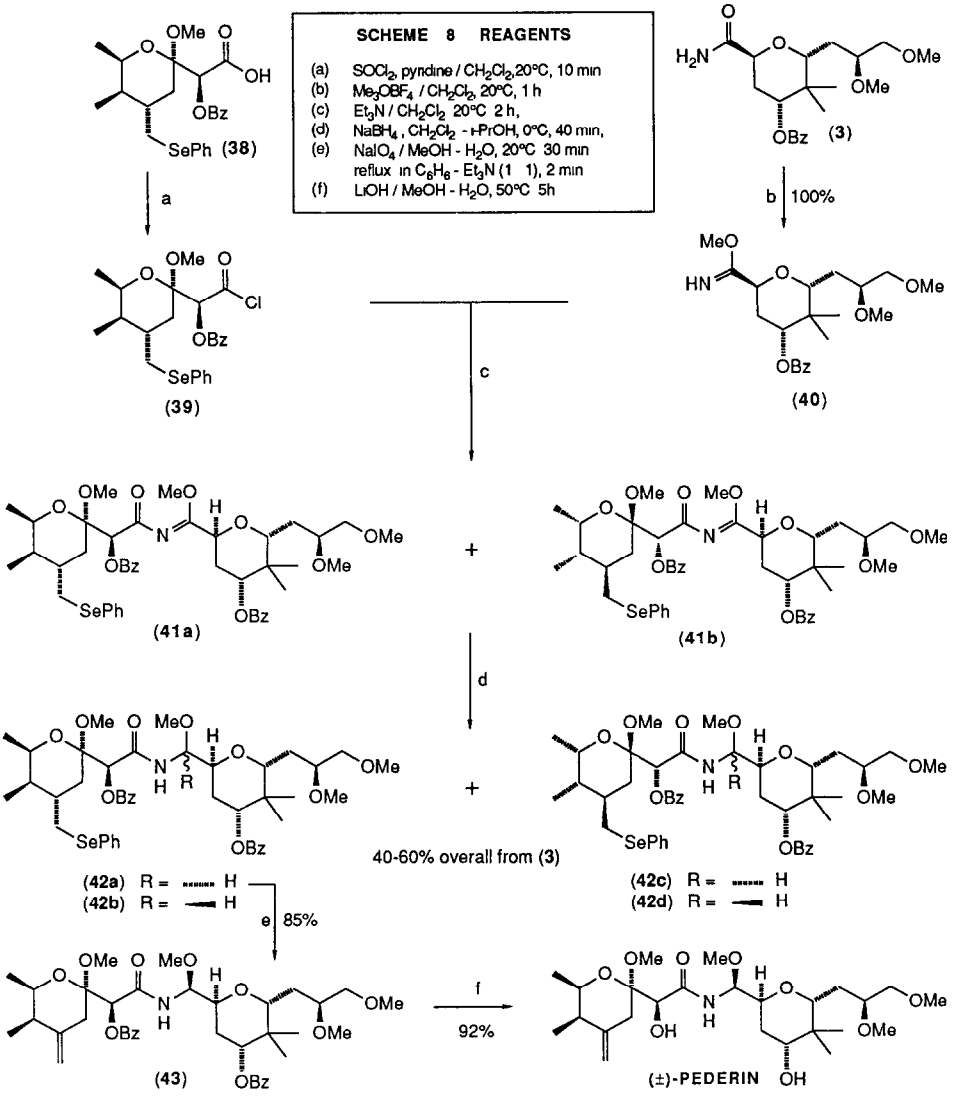
Entry	Lewis Acid (eq)	Method	Reaction Time (h)	27a : 27b
1	$TiCl_4$ (2)	A	1	54 46
2	$TiCl_4$ (1)	A	>8	56 44
3	$TiCl_4$ (1) / BF_3OEt_2 (1)	B	1	55 45
4	$TiCl_4$ (2)	C	1	36 64
5	$TiCl_4$ (1 1)	D	1	26 74
6	$Ti(i\text{-}PrO)_2Cl_2$ (2)	E	1	25 77
7	BF_3OEt_2 (2)	E	1	20 80

Method A The aldehyde was added to the Lewis acid at -70°C giving a thick precipitate After 15 min, the enol silane was added
Method B $TiCl_4$ was added to the aldehyde at 70°C giving a yellow precipitate After 10 min BF_3OEt_2 was added followed after 5 min by enol silane
Method C $TiCl_4$ was added dropwise to a mixture of aldehyde and enol silane at 70°C
Method D $TiCl_4$ was added to enol silane at 0°C After 5 min the temperature was reduced to 70°C and the aldehyde added
Method E Aldehyde was added to the Lewis acid at 70°C After 10 min, the enol silane was added

The aldol products (**27a**) and (**27b**) were characterised as their benzoate derivatives and the isomer ratio determined by HPLC analysis and verified by NMR integration

Synthesis of (±)-Pederin Finale

In order to construct the the N-(1-methoxyalkyl)amide bridge linking (±)-benzoylpedamide (3) with (±)-benzoylselenopederic acid (38) (Scheme 8), we adopted the protocol developed in Matsumoto's laboratory[23] as later modified by Nakata, Oishi, and co-workers[24] Accordingly, the acid function in (38) was activated by conversion to the acid chloride (39)[25] and the amide function in (3) was converted to the imidate ester (40) These were condensed in the presence of base and thionyl chloride to give the diastereoisomeric N-acyl imidates (41a) and (41b) which were then immediately reduced to a mixture of the four N-(1-methoxyalkyl)amides(42a)-(42d) in equimolar ratio After HPLC separation isomers (42a) and (42b) were identified as belonging to the pederin and 10-epi-pederin series (diastereomeric at the aza-acetal centre) by comparison of their high field NMR spectroscopic data with related compounds[24] Diastereoisomers (42c) and (42d) were derived from reduction of the N-acyl imidate (41b) which was an artifact of the coupling of the racemic ring A and ring B fragments Two final efficient steps-selenoxide elimination and ester hydrolysis-transformed (42a) into (±)-pederin which was identical by high field ^{1}H NMR, IR, TLC, and MS with an authentic sample of natural (+)-pederin



In conclusion, a few comments about the closing stages of the pederin synthesis are warranted The brevity of description belies the difficulty of execution A great deal of effort was dissipated before the synthesis was successfully concluded because benzoylpederic acid and its activated derivatives such as (**39**) were unstable with decomposition occurring within minutes of preparation Unfortunately, the coupling reaction with imidate (**40**) was very slow Hence, the reactions were messy and the products difficult to separate Attempts to vary the method of carboxyl activation and increase the rate of coupling merely multiplied the complications and real improvements proved elusive Taken together, these obstinate experimental facts created obstacles which could not be surmounted Obviously the separation problems would have been simplified if homochiral ring A and ring B fragments, which could be readily prepared by trivial modifications to our routes, had been used in the coupling step But the improvements were deemed to be too insignificant to warrant further consideration Instead, we turned to an investigation of alternative coupling procedures which are currently in progress

Acknowledgments We thank the Science and Engineering Research Council for CASE studentships (T M W and K I) and post-doctoral support (K J) We thank Professor D Ghiringhelli (University of Milan) for an authentic sample of natural (+)-pederin and Professor T Nakata (RIKEN) for providing valuable experimental details and spectroscopic data 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 shifts are reported in ppm relative to Me_4Si as an internal standard Coupling constants J are given in Hertz Unless otherwise stated, all distillations were performed using a kugelrohr apparatus $MgSO_4$ was used to dry all extracts Chromatography refers to column chromatography on silical 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

(*S*)-4-(2-Benzyloxyethyl)-2,2-dimethyl-1,3-dioxolane (8) - Alcohol (**7**)(36 24 g, 0 248 mol) in THF (100 ml) was added dropwise to a mechanically stirred suspension of NaH (10 9 g of a 60% dispersion in mineral oil freed of oil by suspension several times in petroleum ether, 0 262 mol) in THF (100 ml) After 10 min benzyl bromide (38 0 ml, 0 320 mol) and KI (50 mg) in THF (100 ml) was added slowly The suspension was stirred at 20°C for 1 h and then poured onto water Extraction with petrol (4 x 500 ml) followed by drying, concentration, and short path distillation gave (**8**) (51 6 g, 88%) as a colourless oil b p 106-108°C/ 0 2 mm Hg, $[\alpha]_D$ (20°C) -1 6° (c 1 156 in $CHCl_3$), ^1H NMR (90 MHz) δ 7 3 (5H, s), 4 45 (2H, s), 4 11 (1H, m), 4 01 (1H, dd, J 8, 8), 3 55 (3H, apparent t, J 8), 1 85 (2H, m), 1 36 and 1 31 (3H each, s), ^{13}C NMR (22 5 MHz) δ 138 4, 128 3, 127 4, 108 3, 73 8, 72 9, 69 6, 67 0, 33 9, 26 9, 25 7, (Found M^+ 236 14143 Calc for $C_{14}H_{20}O_3$ M, 236 14135)

(*S*)-4-Benzyloxybutan-1,2-diol (9) - To dioxolane (**8**) (88 7 g, 0 376 mol) in THF (200 ml) was added 2N HCl (5 ml) followed by saturation with water The mixture was refluxed for 3 h after which it was saturated with NaCl and the product extracted into CH_2Cl_2 After drying and concentration, the residue was distilled to give diol (**9**) (73 6 g, 100%) as a colourless oil b p 155-158°C/0 2 mm Hg, $[\alpha]_D$ -5 2° (c 18 in $CHCl_3$), ^1H NMR (60 MHz) δ 7 22 (5H, s), 4 42 (2H, s), 3 85-3 3 (5H, m), 1 7 (2H, apparent q, J 6)

(*S*)-4-Benzyloxy-1,2-dimethoxy-butane (10) - Diol (**9**) (73 6 g, 0 376 mol) in THF (160 ml) was added dropwise to a mechanically stirred suspension of petrol-washed NaH (60% dispersion in mineral oil, 35 g, 0 840 mol) in THF (250 ml) with ice bath cooling After 15 min MeI (52 ml, 0 840 mol) in THF (90 ml) was added and the mixture allowed to warm gradually to 20°C over 12 h The reaction mixture was quenched by the addition of water (500 ml) and the product extracted with petrol The combined extracts were dried, evaporated, and the residue distilled to give (**10**) (78 3 g, 93%) as a colourless oil b p 96-100°C/0 3 mm Hg, $[\alpha]_D$ -13 2° (c 20 in $CHCl_3$), ^1H NMR (60 MHz) δ 7 24 (5H, s), 4 44 (2H, s), 3 6-3 3 (5H, m), 3 35 and 3 30 (3H each, s), 2 78 (2H, apparent q, J 6), ^{13}C NMR (25 MHz) δ 138 6, 128 3, 127 5, 77 2, 74 6, 72 9, 66 6, 59 0, 57 5, 31 7, (Found M^+, 224 14106 Calc for $C_{13}H_{20}O_3$ M, 224 141235)

(*S*)-3,4-Dimethoxybutan-1-ol (11) - A mixture of (**10**) (36 1 g, 0 161 mol) and Pd/C (5%, 3 6 g) in EtOH (200 ml) was hydrogenated at atmospheric pressure in the usual way to give alcohol (**11**) (20 74 g, 96%) as a colourless oil b p 68-70°C/0 02 mm Hg, $[\alpha]_D$ -22 6° (c 6 5 in $CHCl_3$), ^1H NMR (90 MHz) δ 3 71 (2H, t, J 5 5), 3 53-3 30 (3H, m), 3 40 and 3 35 (3H each, s), 2 75 (1H, br s), 1 76 (2H, apparent q, J 6), ^{13}C NMR (22 5 MHz) δ 79 1, 74 3, 60 1, 59 3, 57 6, 34 2, (Found M^+, 135 10202 Calc for $C_6H_{15}O_3$ M, 135 102113

(*S*)-3,4-Dimethoxybutanal (12) - To a solution of oxalyl chloride (9 6 ml, 110 mmol) in CH_2Cl_2 (90 ml) was added dropwise at -70°C dry DMSO (15 6 ml, 220 mmol) in CH_2Cl_2 (50 ml) After 10 min, alcohol (**11**) (13 4 g, 100 mmol) in CH_2Cl_2 (50 ml) was added dropwise giving a copious white precipitate After 25 min, N-methylmorpholine (36 3 ml, 330 mmol) was added and the solution warmed to 0°C and stirred for 2 5 h After pouring into iced 2N HCl (111 ml) and saturating the mixture with NaCl, the organic layer was washed with $NaHCO_3$ and brine, dried, and evaporated The residue was purified by chromatography eluting with 30-50% EtOAc / petrol to give aldehyde (**12**) (13 1 g, 98%) as a colourless oil The product was unstable towards heat so only a small sample was further purified by distillation b p 110°C (bath) / 15 mm Hg, $[\alpha]_D$ -7 8° (c 9 2 in $CHCl_3$), IR (film) 1724

cm^{-1}, ^{1}H NMR (90 MHz) δ 9 62 (1H, t, J 2), 3 76 (1H, m), 3 36 (2H, t, J 6), 3 31 and 3 26 (3H each, s), 2 6 (2H, dd, J 6, 2), ^{13}C NMR (22 5 MHz) δ 200 6 d, 75 1 d, 73 4 t, 59 1 q, 57 4 q, 45 7 t, (Found M$^+$, 132 07435 Calc for $C_6H_{12}O_3$ M, 132 078638)

Dioxolane benzyl ether (13) - A mixture of aldehyde (**12**) (2 90 g, 22 0 mmol), diol (**9**) (4 29 g, 22 0 mmol), TsOH (0 2 g), and $MgSO_4$ (2 g) in CH_2Cl_2 (30 ml) was allowed to stir for at room temperature for 48 h and then filtered and concentrated The residue was purified by chromatography eluting with 15% EtOAc in petrol and short path distilled to give the dioxolane (**13**) (4 53 g, 66%) as an inseparable mixture of diastereoisomers (*cis trans* 3 1) b p 147-149°C/0 05 mm Hg, IR (film) 2920m, 2880m, 1450m 1370m, 1190w, 1100 br, 960m, 740m, and 700m cm^{-1}, ^{1}H NMR (90 MHz) δ 7 3 (5H, s), 5 05 (1H, two overlapping t), 4 5 (2H, s), 4 3-3 3 (8H, m), 3 35 and 3 38 (3H each, s), 1 85 (4H, m), ^{13}C NMR (22 5 MHz) (signals not specified as *cis* or *trans* are coincident) δ 138 4, 128 4, 127 5, 102 1 (*cis*), 101 5 (*trans*), 76 6, 74 7, 74 5 (*cis*), 73 5 (*trans*), 73 1, 70 7 (*trans*), 69 7 (*cis*), 67 0, 59 1, 57 4, 36 2, 34 0 (*cis*), 33 5 (*trans*), (Found M$^+$, 310 17786 Calc for $C_{17}H_{26}O_5$ M, 310 178012)

Dioxolane alcohol (14) - Benzyl ether (**13**) (2 46 g, 7 9 mmol) in dry ether (2 ml) was added to approximately 40 ml of liquid ammonia at -78°C and small pieces of sodium added until the blue colour persisted After 30 min MeOH was added until the blue colour disappeared The cooling bath was removed and the mixture allowed to stand until all the ammonia had evaporated Aqueous NH_4Cl was added and the mixture extracted with CH_2Cl_2 The extracts were dried and evaporated and the residue distilled to give dioxolane alcohol (**14**) (1 53 g, 88%) as a colourless oil b p 125°C (bath)/0 05 mm Hg, IR (film) 3460br, 2900s, 1190m, 1100s, 950m, 750w, and 700m cm^{-1}, ^{1}H NMR (90 MHz) δ 5 0 (1H, two overlapping t), 4 3-3 0 (8H, m), 3 38 and 3 34 (3H each, s), 1 9-1 8(4H, m), (Found M$^+$, 220 1263 Calc for $C_{10}H_{20}O_5$ M, 220 131064)

Dioxolane aldehyde (15) - Dioxolane alcohol (**14**) (8 8 g, 40 mmol) in CH_2Cl_2 (10 ml) was added in one portion to a stirred suspension of pyridinium chlorochromate (20 g, 93 mmol) and Celite in CH_2Cl_2 After 2 5 h at 20°C ether (100 ml) was added and the suspension filtered through a short column of Florisil The column was washed with a further portion of ether (250 ml) and the filtrates concentrated and chromatographed (EtOAc) to give the desired aldehyde (**15**) (4 36 g, 50%) as a colourless oil after kugelrohr distillation b p 130°C (bath)/0 05 mm Hg, IR (film) 1720s, 1380m, 1190m, 1100s, 1020m, and 905s cm^{-1}, ^{1}H NMR (90 MHz) δ 9 79 (1H, t, J 1), 5 0 (1H, two overlapping t), 4 45 (1H, tt, J 6, 6), 4 02 (1H, dd, J 8, 6), 3 7-3 3 (4H, m), 3 40 and 3 36 (3H each, s), 2 78 (2H, ddd, J 6, 6, 1), 1 85 (2H, m), (Found M$^+$, 218 11514 Calc for $C_{10}H_{18}O_5$ 218 115414)

Dixolane alcohol (16) - 2-Bromopropene (0 65 ml, 6 9 mmol) in THF (1 ml) was added dropwise to a stirred mixture of Mg turnings (220 mg, 9 2 g atom) and a crystal of iodine in THF (5 ml) at 0°C After 15 min the aldehyde (**15**) (1 0 g, 4 6 mmol) in THF (10 ml) was added dropwise After a further 10 min the mixture was poured into NH_4Cl solution and extracted with ether The extracts were dried and evaporated and the residue distilled to give alcohol (**16**) (1 08 g, 88%) as a colourless oil b p 130°C (bath) / 0 05 mm Hg), IR (film) 3400 br, 1640w, 1430m, 1190m, 1100 s, and 900m cm^{-1}, ^{1}H NMR (90MHz) δ 4 8-5 0 (3H, m), 4 3-3 2 (7H, m), 3 37 and 3 33 (3H each, s), 2 0-1 6 (4H, m), (Found M$^+$, 260 16182 Calc for $C_{13}H_{24}O_5$ M, 260 162362)

Dioxolane enones (17c) and (17t) - Alcohol (**16**) (1 00 g, 3 85 mmol) in CH_2Cl_2 (5 ml) was added in one portion to a stirred suspension of pyridinium chlorochromate (1 66 g, 7 7 mmol) and Celite in CH_2Cl_2 (100 ml) After 3 5 h of vigorous stirring, ether (20 ml) was added and the mixture passed through a short Florisil column washing with a further 100 ml of ether The combined filtrates were concentrated and the residue distilled *via* kugelrohr [140°C (bath)/0 05 mm Hg] to give the mixture of enones (**17c**) and (**17t**) (536 mg, 54%) as a colourless oil The mixture could be separated by careful chromatography using 200 g of silical gel 60 per gram of mixture eluting with 5% EtOAc in petroleum ether (**17c**) $[\alpha]_D$ +21 6° (c 8 04 in $CHCl_3$), IR (film) 1670s, 1630w, 1190s, and 1020m cm^{-1}, ^{1}H NMR (90 MHz) δ 5 85 and 6 00 (1H each, br s), 5 0 (1H, dd, J 6, 5), 4 4 (1H, m), 4 1 (1H, dd, J 6, 6), 3 6-3 3 (4H, m), 3 40 and 3 38 (3H each, s), 3 30 (1H, dd, J 18, 6), 2 82 (1H, dd, J 18, 8), 1 9 (7H, m), 1 9 (3H, s), ^{13}C NMR (22 5 MHz) δ 199 0, 144 4, 125 5, 102 0, 76 6, 74 6, 72 9, 69 9, 58 8, 57 3, 42 2, 36 4, 17 2, EIMS m/z 155 (37), 110 (13), 109 (100), 69 (29), (Found M$^+$, 258 14644 Calc for $C_{13}H_{22}O_5$ M, 258 146713) (**17t**) $[\alpha]_D$ +15 5° (c 1 4 in $CHCl_3$), IR (film) 1670s, 1625w, 1100s, and 1020m cm^{-1}, ^{1}H NMR δ 5 82 and 5 96 (1H each, br s), 5 13 (1H, dd, J 6, 6), 4 7-4 0 (2H, br m), 3 6-3 2 (5H, m), 3 41 and 3 39 (3H each, s), 2 81 (1H, dd, J 17, 8), 1 9 (2H, m), 1 9 (3H, s), ^{13}C NMR (22 5 MHz) δ 199 0, 144 4, 125 5, 101 5, 76 6, 74 6, 72 2, 70 7, 58 9, 57 3, 41 4, 36 4, 17 2, (Found M$^+$, 258 14644)

Dioxolane enol silanes (4c) and (4t) - Dioxolane enone (**17c**) (530 mg, 2 05 mmol), $PhMe_2SiH$ (0 32 ml, 2 05 mmol) and ca 2 mg of $[Ph_3P]_3RhCl$ were heated in an oil bath at 55°C for 1 h The product was then directly distilled from the reaction mixture using a kugelrohr apparatus to give dioxolane enol silane (**4c**) as a colourless oil b p 160°C (bath)/0 02 mm Hg, IR (film) 1675m, 1425s, 1250s, 1165s, 1120 br s, 960s, 825s, and 785s cm^{-1} The enol silane was used immediately in the next step Similar yields and IR data were obtained for (**4t**)

Cyclisation of dioxolane enol silane (4c) Keto benzoate (18c) - Dioxolane enol silane (**4c**) (453 mg, 1 15 mmol) in dry CH_2Cl_2 (4 ml) was added dropwise to a stirred solution of freshly distilled $TiCl_4$ (0 95 ml, 2 3 mmol) in CH_2Cl_2 (10 ml) at -78°C After 1 h at -78°C the reaction mixture was poured into rapidly stirring brine The organic layer was washed with $NaHCO_3$ and brine, dried, and concentrated The residue was purified by chromatography eluting with 25-75% EtOAc in petroleum ether to give the tetrahydropyranone (**6c**) (101 mg, 33%) as a viscous oil A sample of (**6c**) (157 mg, 0 604 mmol) was benzoylated in the usual way using BzCl in pyridine to give the keto benzoate ester (**18c**) (213 mg, 96%) as a viscous, colourless oil after filtration through a plug of silica gel to remove minor polar impurities $[\alpha]_D$ -57° (c 7 2 in $CHCl_3$), IR (film) 1720s, 1275s, 1110s, and 720s cm^{-1}, ^{1}H NMR (90 MHz) δ 8 0 (2H, m), 7 45 (3H, m), 4 4 (2H, dd, J 6, 1), 4 0 (1H, br m), 3 7-3 3 (4H, m), 3 3 (6H, s),

2 71 (1H, dd, J 13, 12), 2 38 (1H, dd, J 13, 3), 1 68 (2H, m), 1 03 and 1 13 (3H each, s), ^{13}C NMR (22 5 MHz) δ 209 7, 165 8, 133 1, 130 0, 129 6, 128 4, 128 3, 80 0, 76 5, 74 9, 74 7, 66 6, 59 0, 58 0, 49 0, 40 4, 32 0, 19 1, 18 7, (Found M$^+$, 364 18846 Calc for $C_{20}H_{28}O_6$ M, 364 188575)

Cyclisation of dioxolane enol silane (4t) Keto benzoate (18t) - Dioxolane enol silane (**4t**) (309 mg, 0 785 mmol) was treated with $TiCl_4$ as described for (**4c**) After chromatographic purification tetrahydropyranones (**6c**) (20 2 mg, 10%) and (**6t**) (18 4 mg, 8%) were obtained Benzoylation of (**6t**) (18 mg) as above gave keto benzoate (**18t**) (15 mg, 58%) as a viscous, colourless oil $[\alpha]_D$ +10° (c 3 2 in $CHCl_3$), IR (film) 1715s, 1270s, 1100 br s cm^{-1}, ^{1}H NMR (90 MHz) δ 8 05 (2H, m), 7 45 (3H, m), 4 41 (3H, s), 4 1-3 7 (2H, m), 3 5-3 2 (2H, m), 3 30 and 3 27 (3H each, s), 2 62 (2H, m), 1 75 (2H, m), 1 20 and 1 06 (3H each, s), ^{13}C NMR (22 5 MHz) δ 210 8, 166 0, 134 8, 130 2, 127 9, 126 1, 78 5, 77 5, 73 0, 69 9, 66 2, 59 2, 57 1, 49 5, 39 3, 29 6, 23 2, 19 1, (Found M$^+$, 364 18838 Calc for $C_{20}H_{28}O_6$ M, 364 188575)

Reduction of keto benzoate (18c) Dibenzoate (19c) - Sodium borohydride (564 mg, 14 9 mmol) was added in one portion to a stirred solution of the keto benzoate (**18c**) (543 mg, 1 49 mmol) in EtOH (5 ml) After 2 h the reaction was quenched with dil HCl and concentrated The residue was continuously extracted with dichloromethane for 12 h The extract was dried and concentrated and the residue benzoylated in the usual way using BzCl and a catalytic amount of 4-(dimethylamino)-pyridine (DMAP) in pyridine to give the dibenzoate (**19c**) as a crystalline solid Recrystallisation from from petroleum ether afforded a pure sample (350 mg, 50%) m p 116-118°C, $[\alpha]_D$ -1 7° (c 3 5 in $CHCl_3$), IR ($CHCl_3$) 1715s, 1450m, 1320m, 1270 br s, 1180m, 1110 br s, 1030m, 975m, and 710m cm^{-1}, ^{1}H NMR (400 MHz) δ 8 0 (4H, m), 7 4 (6H, m), 5 01 (1H, dd, J 12, 5, BzO-C**H**), 4 39 (1H, dd, J 12, 7, BzO-CHH'), 4 34 (1H, dd, J 12, 4, BzO-CHH'), 3 94 (1H, dddd, J 12, 7, 4, 2 5, BzO-CH_2-C**H**), 3 56 (1H, dddd, J 11, 4, 2, 2, MeO-C**H**), 3 49 (1H, dd, J 11, 4, MeO-CHH'), 3 45 (1H, dd, J 11, 2, O-C**H**-CMe_2), 3 36 (1H, dd, J 11, 4, MeO-CHH'), 3 32 and 3 36 (3H each, s, OMe), 2 05 (1H, ddd, J 12, 5, 2 5, BzO-CH-$CH_{ax}\mathbf{H}_{eq}$), 1 75 (1H, apparent q, J 12, BzO-CH-$\mathbf{CH}_{ax}H_{eq}$), 1 69 (1H, ddd, J 14, 11, 2, MeO-CH-CHH'), 1 52 (1H, ddd, J 14, 11, 3, MeO-CH-CH**H'**), 1 10 and 0 90 (3H each, s, CMe_2), (Found C 69 1, H, 7 55 Calc for $C_{27}H_{34}O_7$ C, 68 93, H, 7 23%)

Reduction of keto benzoate (18t) Dibenzoate (19t) and pederol dibenzoate (2) - Reduction of keto benzoate (**18t**) (48 mg, 0 13 mmol) as decribed above for (**18c**) gave a mixture of dibenzoates (**19t**) and (**2**) (46 mg, 74%) after purifiction by column chromatography The mixture was separated by HPLC on a Whatman Partisil Magnum 9 column (9 4 x 25 cm) eluting with 15% EtOAc in hexane to give dibenzoate (**19t**) (20 mg, 34%) as a colourless viscous oil $[\alpha]_D$ +26 1° (c 1 05 in $CHCl_3$), IR (film) 1715s, 1455m, 1320m, 1280s, 1180m, 1100br s, 1070m, 1030m, 970m, and 710m cm^{-1}, ^{1}H NMR (400 MHz) δ 8 05 (4H,m), 7 45 (6H, m), 5 27 (1H, dd, J 9, 4, BzO-C**H**), 4 55 (1H, dd, J 11, 7, BzO-CHH'), 4 30 (1H, dd, J 11, 4, BzO-CHH'), 4 26 (1H, m, BzO-CH_2-C**H**), 3 78 (1H, dd, J 12, 3, O-C**H**-CMe_2), 3 49 (3H, m, MeO-CH_2-C**H**), 3 35 and 3 34 (3H each, s, OMe), 2 15 (1H, dddd, J 13, 4, 4, 1, BzO-CH-$CH_{ax}H_{eq}$), 2 06 (1H, ddd, J 13, 9, 4, BzO-CH-$CH_{ax}\mathbf{H}_{eq}$), 1 82 (1H, ddd, J 12, 9, 9, MeO-CH-CHH'), 1 80 (1H, ddd, J 13, 9, 3, MeO-CH-CHH'), 1 20 and 1 00 (3H each, s, CMe_2) and pederol dibenzoate (**2**) (20 mg, 34%) as a white crystalline solid m p 79-80°C (hexane), $[\alpha]_D$ +65 3° (c 1 96 in $CHCl_3$), IR ($CHCl_3$) 1715s, 1455m, 1320m, 1280s, 1180m, 1100s, 1075m, 1030m, and 710m cm^{-1}, ^{1}H NMR (400 MHz) δ 8 05 (4H, m), 7 45 (6H, m), 5 13 (1H, dd, J 7, 6, BzO-C**H**), 4 64 (1H, dd, J 11, 7, BzO-CHH'), 4 63 (1H, dd, J 11, 4, BzO-CHH'), 4 4 (1H, m, BzO-CH_2-C**H**), 3 59 (1H, dd, J 11, 2, MeO-CH_2-C**H**), 3 45 (3H, m, MeO-CH_2-C**H**), 3 31 and 3 29 (3H each, s, OMe), 2 1 (4H, m), 1 84 (1H, ddd, J 13, 9, 2, MeO-CH-CHH'), 1 07 (6H, s, CMe_2), (Found C, 68 85, H, 7 5 Calc for $C_{27}H_{34}O_7$ C, 68 93, H, 7 23 %)

Aldols (27) - To a solution of $TiCl_4$ (29 4 ml, 0 264 mol) in CH_2Cl_2 (400 ml) at -70° C was added dropwise aldehyde (**12**) (17 4 g, 0 132 mmol) in CH_2Cl_2 (100 ml) , with mechanical stirring, forming a bright yellow precipitate After 10 min silyl ether (**26**)[26] (37 6 ml, 0 158 mmol) in CH_2Cl_2 (50 ml) was added dropwise The solution was stirred for 1 h and then poured into ice-cold NH_4Cl solution (700 ml) The product was extracted into CH_2Cl_2 and the combined organic extracts washed with $NaHCO_3$ solution and brine After drying and concentration the product was divided in half and chromatographed (10 to100 % ethyl acetate-petrol) to yield the aldols (**27**) (26 1 g, 91 %) as a colourless oil IR (film) 3700-3100m, 3000-2780s, 1690s, 1470m, 1415w, 1380w, 1350m, 1240w, 1190m, 1120s, 1085s, 965m, 915m, and 730s cm^{-1}, ^{1}H NMR (90MHz) δ 4 1-3 8 (1H, m), 3 45 (3H, s), 3 35 (3H, s) , 3 75 - 3 30 (3H, m), 3 10-3 0 (1H, br s) , 2 2 (3H, s), 2 11 (3H , s) , 1 70-1 45 (2H, m), 1 15 (6H, s), ^{13}C NMR (22 5 MHz) δ 214 9 s, 214 0 s, 80 6 d, 77 7 d, 75 3 d, 74 2 t, 73 8 t, 72 8 d, 59 3 q, 59 2 q, 57 9 q, 57 3 q, 51 9 q, 51 8 q, 33 9 s, 33 3 s, 26 5 q, 26 3 q, 21 5 q, 21 1 q, m/z 155(21%), 101(10), 89(20), 87(32), 86(44), 71(36), 59(37), 43(100), (Found M$^+$, 218 15225 Calc for $C_{11}H_{22}O_4$ M, 218 15180)

Chloroformates (28) - A 1l 3-neck flask fitted with a Hershberg stirrer and gas inlet tube was charged with aldols (**27**) (21 7 g, 100 mmol), toluene (95 ml), and pyridine (8 ml, 100 mmol) At 0°C, with vigorous stirring, phosgene (2M in toluene, 100 ml, 200 mmol) was added over 5 min and a thick white precipitate formed After 1 h at 0°C, nitrogen was bubbled through the reaction mixture and purged through saturated ammonia in methanol followed by 2N NaOH solution to remove the excess $COCl_2$ After 1 h the crude reaction mixture was taken up in ether (300 ml) and filtered through a plug of celite The filtrate was concentrated to yield the chloroformates (**28**) (26 0 g, 93 %) as a yellow oil IR (film) 3060-2780m,1780s, 1710s, 1470m, 1390m, 1360m, and1250w cm^{-1}, ^{1}H NMR (90 MHz) δ 5 40-5 25 (1H m), 3 50-3 10 (3H, m), 3 37 (3H, s), 3 32 (3H, s), 2 15 (3H, s), 1 85-1 50 (2H, m), 1 15 (6H, s) The crude chloroformates were used immediately in the next step without further purification

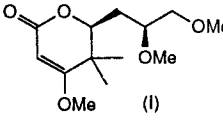
β-Ketolactones (29a) and (29b) - To *i*-Pr_2NH (20 3 ml, 0 144 mol) in THF (240 ml) at 0°C was added dropwise *n*-BuLi (1 4

M in hexane, 100 ml) After 5 min the solution was cooled to - 70°C and chloroformates (**28**) (20 2 g, 72 mmol) in THF (60 ml) was added dropwise After 1 h at - 70°C the solution was poured into ice-cold dil HCl (2N, 288 ml) and extracted with ether and $CHCl_3$ The combined organic extracts were washed with $NaHCO_3$ solution and the combined aqueous extracts re-acidified to pH = 2 by careful dropwise addition of conc HCl The acidic solution was then extracted with CH_2Cl_2 and the combined extracts dried Concentration gave the crude β-ketolactones (**29a**) and (**29b**) as a light yellow oil After storing an ethereal solution of the crude product overnight at 0°C, white crystals (2 crops) of isomer (**29a**) (6 7 g, 38%) were collected Recrystallisation of a sample from Et_2O gave m p 99-103°C (Found C, 58 75, H, 8 2 Calc for $C_{12}H_{20}O_5$ C, 59 0, H, 8 2%) UV (Et_2O) 233 nm (ε 2700), IR (CCl_4) 1765s, 1730s, 1545m, 1270m, 1250s, 1220m, 1130m, 1100m, 1030m, and 1000m cm^{-1}, ^{1}H NMR (270 MHz) 4 50 (1H, dd, J 10, 3), 3 41 (3H, s), 3 39 (3H, s), 3 66-3 22 (5H, m), 1 99 (1H, ddd, J 14, 10, 4), 1 90 (1H, ddd, J 14, 10, 4), 1 17 (3H, s), 1 10 (3H, s), ^{13}C NMR (67 5 MHz) 205 6 s, 167 3 s, 80 0 d, 76 8 d, 73 2 t, 59 5 q, 57 4 q, 47 0 s, 45 2 t, 30 7 t, 20 9 q, 17 8 q, m/z 212 (10%), 199 (42), 167 (31), 141 (29), 127 (8), 112 (9), 99 (100)

The residual oil was distilled by kugelrohr [b p 150-160°C (bath)/2 0 mm Hg] to give isomer (**29b**) as a colourless oil contaminated by 5-10% of isomer (**29a**) ^{1}H NMR (270 MHz) 4 66 (1H, dd, J 11, 2), 3 44 (3H, s), 3 39 (3H, s), 3 71-3 32 (5H, m), 1 87 (1H, ddd, J 14, 10, 2), 1 76 (1H, ddd, J 15, 11, 3), 1 16 (3H, s), 1 08 (3H, s), ^{13}C NMR (67 5 MHz) 205 8 s, 167 4 s, 79 4 d, 75 1 d, 73 0 t, 59 4 q, 57 6 q, 46 5 s, 45 3 t, 31 7 t, 20 4 q, 17 7 q (Found M$^+$, 244 13150 $C_{12}H_{20}O_5$ requires M, 244 13106)

Methylation of β-ketolactone (29b) Dihydropyranone (30) - K_2CO_3 (4 51 g, 27 8 mmol) was added to a solution of β-ketolactone (**29b**) (6 17 g, 25 3 mmol) and $(MeO)_2SO_2$ (2 42 ml, 25 3 mmol) in acetone (90 ml) The mixture was refluxed for 2 h, then stirred at room temperature for 1 h before filtering through a plug of celite and concentrating The residue was taken up in CH_2Cl_2 (50 ml) and washed with $NaHCO_3$ solution, dried and concentrated, and then distilled by kugelrohr (bath 110-125°C/0 3 mm Hg) to yield enol ether (**30**) (6 49 g, 99%) as a colourless oil which slowly crystallised on standing at -40°C An analytical sample gave m p 60 0-61 6°C (from EtOAc/hexane) (Found C, 60 3, H, 8 7 $C_{13}H_{22}O_5$ requires C, 60 5, H, 8 5%), UV (Et_2O) 234 nm (ε 6800), IR (CCl_4) 3040-2800m, 1720s, 1620s, 1470m, 1365m, 1275m, 1220s, 1200m, 1135m, 1105s, 1085m, 1060m, 1050m, and 995m cm^{-1}, ^{1}H NMR (90 MHz) δ 5 05 (1H, s), 4 25-4 05 (1H, m), 3 70 (3H, s) 3 6-3 35 (3H, m), 3 40 (3H, s), 3 35 (3H, s), 2 0-1 8 (2H, m), 1 10 (6H, s), ^{13}C NMR (67 5 MHz) δ 179 8 s, 166 6 s, 88 7 d, 80 3 d, 76 8 d, 72 5 t, 59 3 q, 57 0 q, 56 4 q, 38 6 s, 29 5 t, 20 5 q, 18 8 q, m/z 213 (18%), 169 (13), 155 (100), 137 (49), 111 (15), 89 (19)

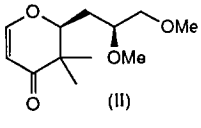
The diastereoisomeric dihydropyranone (**i**), prepared from β-ketolactone (**29a**) in the same way (100% yield), was a colourless oil which gave IR (film) 1710s and 1625s cm^{-1}, ^{1}H NMR (90 MHz) δ 5 06 (1H, s), 4 32 (1H, dd, J 10, 2 5), 3 71 (3H, s), 3 58 (1H, dd, J 10, 4), 3 42 and 3 38 (3H each, s), 3 78-3 32 (2H, m), 1 74 (2H, ddd, J 14, 13, 2), 1 11 and 1 08 (3H each, s), ^{13}C NMR (22 5 MHz) δ 180 0 s, 166 8 s, 88 7 d, 80 3 d, 75 4 d, 73 5 t, 59 3 q, 57 8 q, 56 3 q, 38 3 s, 31 6 t, 20 4 q, 19 0 q



(I)

Reduction of dihydropyranone (30) Dihydropyranone (31) - DIBAL-H (1 5 M in toluene, 25 1 ml) was added dropwise to a stirred solution of enol ether (**30**) (6 49 g, 25 1 mmol) in toluene (75 ml) keeping the temperature below -50°C After 3 h at -70°C, the reaction mixture was poured into dilute HCl (2N, 38 ml) and stirred at room temperature for 15 min The mixture was extracted with CH_2Cl_2 and the organic extracts washed with $NaHCO_3$ solution, and then dried and concentrated to a colourless oil Chromatography, 10 to 50% EtOAc/hexanes) gave the isomerically pure dihydropyranone (**31**) which was distilled by kugelrohr (bath 120-140°C/1 0 mm Hg) to yield 4 0 g (70%) of a colourless oil Found C, 63 25, H, 8 7 $C_{12}H_{20}O_4$ requires C, 63 15, H, 8 8%, UV (Et_2O) 216 and 249 nm (ε 2300 and 5500), IR (film) 2980-2830m, 1675s, 1605s, 1470m, 1405m, 1385m, 1370m, 1270s, 1230m, 1195m, 1160m, 1115 br s, 1040m, and 820m cm^{-1}, ^{1}H NMR (90 MHz) δ 7 28 (1H, d, J 5), 5 33 (1H, d, J 5), 4 12 (1H, dd, J 10, 2), 3 8-3 2 (3H, m), 3 40 (3H, s), 3 37 (3H, s), 2 1-1 7 (2H, m), 1 10 (3H, s), 1 03 (3H, s), ^{13}C NMR (67 5 MHz) 198 3 s, 161 4 d, 105 4 d, 83 4 d, 77 3 d, 73 4 t, 59 3 q, 57 2 q, 44 2 s, 29 6 t, 19 6 q, 17 8 q, m/z 213 (4%), 126 (46), 113 (13), 99 (22), 89 (95), 81 (100)

The diastereoisomeric dihydropyranone (**ii**), prepared from dihydropranone (**i**) in 80% yield as a colourless oil as described above gave IR (film) 2980s, 2960s, 2880s, 1670s, 1605s, 1465m, 1405m, 1375m, 960m, and 810s cm^{-1}, ^{1}H NMR (360 MHz) δ 7 31 (1H, d, J 6), 5 34 (1H, d, J 6), 4 31 (1H, dd, J 11, 2), 3 66-3 34 (3H, m), 3 343 and 3 399 (3H each, s), 1 94-1 66 (2H, m), 1 102 and 1 101 (3H each, s), ^{13}C NMR (90 MHz) δ 198 6, 161 5 d, 105 3 d, 82 8 d, 75 7 d, 74 0 t, 59 4 q, 58 1 q, 43 9 s, 31 4 t, 19 7 q, 18 0 q

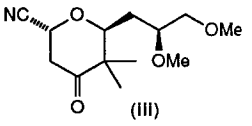


(II)

Cyanosilylation of dihydropyranone (31) β-Cyanoketone (32) - Freshly distilled BF_3OEt_2 (0 27 ml, 2 22 mmol) was added dropwise to a stirred solution of dihydropyranone (**31**) (5 07 g, 22 2 mmol) and Me_3SiCN (13 0 ml, 60 1 mmol) in CH_2Cl_2 (50 ml) at 0°C The reaction mixture was stirred at 0°C for 90 min, and then poured into NH_4Cl solution and extracted with CH_2Cl_2 The organic extracts were washed with $NaHCO_3$ solution, and brine, and then dried and concentrated The resulting enol silane [IR (film) 1660s, 1250s, 850s cm^{-1}] was taken up in THF (30 ml) and at 0°C dilute HCl (2N, 12 ml) was added The heterogeneous mixture was vigorously stirred at room temperature for 30 min and then extracted with Et_2O, and CH_2Cl_2 The organic extracts were washed with $NaHCO_3$ solution and brine, and then dried and concentrated Distillation by kugelrohr (bath 140-150°C/0 3 mm Hg) gave β-cyanoketone (**32**) (5 40 g, 95%) as a colourless oil which slowly crystallised in the distillation bulb An analyti-

cal sample gave m p 69 0-70 0°C (from hexane) (Found C, 61 1, H, 8 35, N, 5 35 $C_{13}H_{21}NO_4$ requires C, 61 2, H, 8 2, N, 5 5%), IR (CCl_4) 1720s, 1470m, 1390m, 1250m, 1195m, 1130s, 1095s, and 970m cm^{-1}, ^1H NMR (400 MHz) δ 5 173 (1H, dd, J 2, 8), 4 12 (1H, dd, J 10, 2), 3 57-3 45 (3H, m), 3 413 (3H, s), 3 388 (3H, s), 3 074 (1H, dd, J 8, 15 5), 2 560 (1H, dd, J 2, 15 5), 1 91-1 80 (2H, m), 1 159 (3H, s), 1 093 (3H, s), ^{13}C NMR (90 MHz) δ 206 3 s, 116 6 s, 79 1 d, 77 4 d, 72 6 t, 64 4 d, 59 3 q, 57 2 q, 50 0 s, 40 1 t, 30 2 t, 18 9 q, m/z 210 (32%), 178 (15), 152 (20), 123 (4), 103 (13), 89 (36), 81 (13), 71 (100)

The diastereoisomeric β-cyanoketone (iii), prepared from dihydropyranone (ii) in 91% yield as described above, gave white crystals from ether-hexane m p 58-59°C, IR ($CHCl_3$) 2980s, 2960s, 2880s, 1720s, 1055m, and 840s cm^{-1}, ^1H NMR (360 MHz) δ 5 159 (1H, dd, J 8, 1 5), 4 072 (1H, dd, J 8,4), 3 59-3 26 (3H, m), 3 437 and 3 361 (3H each, s), 3 047 (1H, dd, J 15, 8), 2 532 (1H, dd, J 15, 1 5), 1 664 and 1 631(1H each, t, J 4), 1 102 and 0 989 (3H each, s), ^{13}C NMR (90 MHz) δ 206 8 s, 116 8 s, 78 4 d, 76 1 d, 73 9 t, 64 4 d, 59 4 q, 58 4 q, 49 8 s, 40 1 t, 32 4 t, 19 0 q, 18 9 q

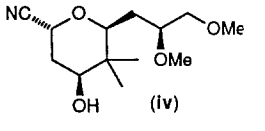


(iii)

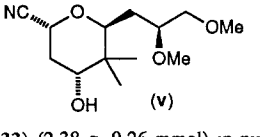
Reduction of β-cyanoketone (32) Cyanoalcohol (33) - To β-cyanoketone (32) (1 00 g, 3 9 mmol) and $CeCl_3$ heptahydrate (0 745 g, 2 mmol) in MeOH (10 ml) was added in one portion at -78°C $NaBH_4$ (0 148 g, 3 9 mmol) After 5 min the solution was poured in to dilute HCl (10 ml) and extracted into ether The ether extracts were washed with $NaHCO_3$ and brine, dried, and evaporated to give (33) (1 01 g, 100%) as a waxy white solid after kugelrohr distillation b p 125-135°C (bath)/0 02 mm Hg, (Found C, 60 8, H, 8 8, N, 5 5 Calc for $C_{13}H_{23}NO_4$ C, 60 7, H, 8 95, N, 5 45%) IR (film) 3480br m, 2970s, 2940s, 2880s, 2820m, 1470m, 1455m, 1390m, 1370m, 1290m, 1195m, 1160m, 1100s and 980w cm^{-1}, ^1H NMR (360 MHz) δ 4 870 (1H, d, J 5 5), 3 689 (1H, m), 3 55-3 30 (4H, m), 3 369 and 3 359 (3H each, s), 2 333 (1H, d, J 5 0 Hz), 2 075-1 55 (4H, m), 0 981 and 0 956 (3H each, s), ^{13}C NMR (90 MHz) δ 117 7 s, 78 6 d, 77 7 d, 72 8 t, 71 8 d, 64 0 d, 59 3 q, 57 1 q, 39 4 s, 32 8 t, 29 7 t, 22 2 q, 11 9 q (Found M^+ 257 16192 $C_{13}H_{23}NO_4$ requires M, 257 16270)

The 13-*epi*-diastereoisomer of (33) bearing an axial hydroxyl group gave m p 85 5-87 0°C (from hexane) (Found C, 61 0, H, 8 9, N, 5 55%) IR (CCl_4) 3480br m, 1470m, 1455m, 1385m, 1285m, 1190m, 1160m, 1100s, 1070s, and 1045m cm^{-1}, ^1H NMR (400 MHz) δ 4 787 (1H, dd, J 1 5, 7), 4 042 (1H, dd, J 2 5, 10), 3 635 (1H, t, J 3), 3 61-3 20 (3H, m), 3 411 and 3 401 (3H each, s), 2 320 (1H, ddd, J 3, 7, 15), 1 887 (1H, ddd, J 1 5, 3, 15), 1 80 (1H, br, OH), 1 753 (1H, ddd, J 2 5, 8 5, 14), 1 676 (1H, ddd, J 4, 10, 14), 0 981 and 0 949 (3H each, s)

Virtually identical yields and diastereoselectivities were obtained in the reduction of the β-cyanoketone (iii) to give the cyanoalcohols (iv) and (v) Isomer (iv) gave m p 64 0-65 5°C (from EtOAc-hexane) (Found C, 60 45, H, 8 95, N, 5 4%) ^1H NMR (400 MHz) δ 4 908 (1H, dd, J 1 7, 6), 3 765 (1H, dd, J 5, 12), 3 725 (1H, dd, J 1 5, 10 5), 3 55-3 30 (3H, m), 3 475 and 3 3880 (3H each, s), 2 007 (1H, ddd, J 6, 12, 14), 1 935 (1H, ddd, J 1 7, 5, 14), 1 92 (1H, br, OH), 1 678 (1H, ddd, J 1 5, 10, 14), 1 498 (1H, ddd, J 2 5, 10 5, 14) 1 000 and 0 845 (3H each, s), ^{13}C NMR (22 5 MHz) δ 117 8 s, 78 0 d, 76 5 d, 74 4 t, 71 8 d, 63 9 d, 59 3 q, 58 5 q, 39 1 s, 32 8 t, 32 0 t, 22 1 q, 12 0 q Isomer (v) was obtained as colourless oil ^1H NMR (90 MHz) δ 4 78 (1H, dd, J 1 5, 7), 4 27 (1H, dd, J 3, 9), 3 85 (1H, m), 3 50 and 3 38 (3H each, s), 3 7-3 0 3H, m), 2 33 (1H, ddd, J 3, 7, 15), 2 1-1 3 (4H, m), 1 00 and 0 92 (3H each, s)



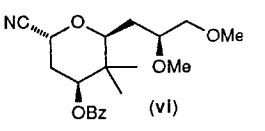
(iv)



(v)

Benzoylation of cyanoalcohol (33) Nitrile (34) - To a stirred solution of cyanoalcohol (33) (2 38 g, 9 26 mmol) in pyridine (37 ml) at 0°C was added benzoyl chloride (5 4 ml, 46 mmol) dropwise The reaction mixture was stirred at room temperature for 2 h, and then cooled to 0°C and quenched by the dropwise addition of 1-(N,N-dimethylamino)-3-propanamine (5 8 ml, 46 mmol) The red homogeneous solution was stirred at room temperature for 10 min, poured into ice-cold dilute HCl (2N, 280 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 to yield the benzoate (34) (3 34 g, 100%) as a white solid An analytical sample gave m p 85 0-86 5°C (from hexane) (Found C, 66 7, H, 7 45, N, 3 7 Calc for $C_{20}H_{27}NO_5$ C, 66 5, H, 7 5, N, 3 9%), IR (CCl_4) 2980w, 2940w, 2880w, 2815w, 1730s, 1540m, 1265s, 1110s, 1100s, 1000m, and 710s cm^{-1}, ^1H NMR (400 MHz) δ 8 06-8 02 (2H, m), 7 62-7 44 (3H, m), 5 183 (1H, dd, J 5, 11 5, H-13), 4 955 (1H, dd, J 1 5, 6, H-11), 3 692 (1H, dd, J 2, 10 5, H-15), 3 60-3 34 (3H, m), 3 412 (3H, s), 3 407 (3H, s), 2 219 (1H, ddd, J 1 5, 5, 13 5, H-12_{eq}), 2 145 (1H, ddd, J 6, 11 5, 13 5, H-12_{ax}), 1 884 (1H, ddd, J 2, 8 5, 14), 1 758 (1H, ddd, J 4, 10 5, 14), 1 113 (3H, s), 0 983 (3H, s), m/z 316 (22%), 258 (31), 194 (5), 136 (22), 105 (100)

Benzoylation of cyanoalcohol (iv) as described above gave nitrile (vi) in 97% yield as white crystals m p 115 8-117 8°C (Et_2O) (Found C, 66 55, H, 7 65, N, 3 9 Calc for $C_{20}H_{27}NO_5$ C, 66 5, H, 7 5, N, 3 9%) ^1H NMR (400 MHz) δ 8 05-8 02 (2H, m), 7 61-7 43 (3H, m), 5 207 (1H, dd, J 5, 11 5, H-13), 4 970 (1H, dd, J 1 5, 6, H-11), 3 926 (1H, dd, J 1 5, 10, H-15), 3 50-3 38 (3H, m), 3 498 and 3 392 (3 each, s), 2 248 (1H, ddd, 1 5, 5, 13, H-12_{eq}), 2 144 (1H, ddd, J 1 5, 9 5, 14, H-12_{ax}), 1 61 (1H, br), 1 563 (1H, ddd, J 1 5, 5, 13), 1 09 and 0 99 (3H each, s), ^{13}C NMR (22 5 Mz) δ 165 6 s, 133 3 d, 129 9 s, 129 6 d, 128 5 d, 117 2 s, 78 1 d, 76 7 d, 74 2 d, 74 2 t, 63 6 d, 59 4 q, 58 5 q, 38 3 s, 32 0 t, 30 0 t, 22 3 q, 13 6 q



(vi)

Hydrolysis of nitrile (33) Benzoylpedamide (3) - To a solution of nitrile (33) (1 16 g, 3 20 mmol) in EtOH (35 ml)

was added aqueous K_2CO_3 solution (30% w/v, 9 0 ml) followed by H_2O_2 (30% v/v, 11 0 ml) The heterogeneous mixture was vigorously stirred for 70 min at room temperature, and then solid Na_2SO_3 was added until the effervescence ceased The mixture was concentrated and the aqueous residue extracted with Et_2O and CH_2Cl_2 The organic extracts were washed with brine, and then dried and concentrated to give an off-white solid Recrystallisation from MeOH/Et_2O yielded benzoylpedamide (**3**) (0 90 g, 74%) as a white powder m p 150 5-152 5°C (Found C, 63 35, H, 7 65, N, 3 6 Calc for $C_{20}H_{29}NO_6$ C, 63 3, H, 7 65, N, 3 7%), IR ($CHCl_3$) 3520w, 3480m, 3400w, 3330m, 2970m, 2940m, 2890m, 1720s, 1690s, 1600w, 1450m, 1315m, 1270s, 1115s, 1095s, 1070m, and 1030m cm^{-1}, ^{1}H NMR (400 MHz) δ 8 07-8 02 (2H, m), 7 54 (1H, br, NH), 7 69-7 42 (3H, m), 5 63 (1H, br, NH), 4 985 (1H, dd, J 4 5, 11, H-13), 4 480 (1H, dd, J 3, 6 5, H-11), 3 615 (1H, dd, J 4 5, 5, H-19), 3 598 (1H, dd, J 1 5, 4, H-19), 3 555 (1H, dd, J 2 5, 9, H-15), 3 46-3 40 (1H, m, H-18), 3 424 (3H, s), 3 386 (3H, s), 2 583 (1H, ddd, J 3, 4 5, 13, H-12$_{eq}$), 2 030 (1H, ddd, J 6 5, 11, 13, H-12$_{ax}$), 1 888 (1H, ddd, J 2 5, 5 5, 14 5, H-17), 1 815 (1H, ddd, J 5 5, 9, 14 5, H-17), 1 080 (3H, s), 0 936 (3H, s), ^{13}C NMR (100 MHz) δ 173 8 s, 165 5 s, 132 9 d, 130 3 s, 129 6 d, 128 3 d, 78 9 d, 78 1 d, 74 9 t, 74 4 d, 72 4 d, 59 1 q, 56 6 q, 37 7 s, 30 2 t, 26 7 t, 23 2 q, 14 5 q, m/z 334 (10%), 276 (19), 213 (25), 154 (12), 126 (16), 105 (100)

18-epi-Benzoylpedamide (vii) - By the method above nitrile (**vi**) (2 14 g, 5 93 mmol) was transformed to (±)-18-epi-benzoylpedamide (**vii**) as an off-white solid Recrystallisation yielded 1 73 g (77%) of a white powder m p 138 5-140 0°C (from Et_2O) (Found C, 63 2, H, 7 9, N, 3 65 $C_{20}H_{29}NO_6$ requires C, 63 3, H, 7 65, N, 3 7%) IR (CCl_4) 3510vw, 3470w, 3390vw, 3300w, 2960m, 2930m, 2880m, 2820w, 1720s, 1690s, 1575m, 1440m, 1305m, 1265s, 1165m, 1150m, 1100s, 1085s, 1015m, and 955m cm^{-1}, ^{1}H NMR (400 MHz) 8 06-8 02 (2H, m), 7 59-7 42 (3H, m), 7 48 (1H, br, NH), 5 66 (1H, br, NH), 4 995 (1H, dd, J 4 5, 11, H-13), 4 460 (1H, dd, J 3, 6 5, H-11), 3 740 (1H, m, H-18), 3 650 (1H, dd, J 3, 10, H-15), 3 485 (2H, d, J 4 5, H-19), 3 420 (3H, s), 3 395 (3H, s), 2 585 (1H, ddd, J 3, 4 5, 13, H-12$_{eq}$), 2 035 (1H, ddd, J 6 5, 11, 13, H-12$_{ax}$), 1 875 (1H, ddd, J 4, 10, 14 5, H-17), 1 810 (1H, ddd, J 3, 7 5, 14, H-17), 1 080 (3H, s), 0 930 (3H, s), ^{13}C NMR (100 MHz) 173 9 s, 165 5 s, 132 9 d, 130 4 s, 129 6 d, 128 3 d, 76 3 d, 76 0 d, 74 4 d, 73 4 t, 72 3 d, 59 2 q, 55 9 q, 37 5 s, 29 6 t, 27 0 t, 23 2 q, 14 6 q, m/z 379 (M$^+$, 0 4%),276 (11), 213 (13), 154 (11), 126 (14), 105 (100)

Single crystal x-ray analysis of benzoylpedamide diastereoisomer (vii) - The structure and relative stereochemistry of (**vii**) and, by inference, the structure and stereochemistry of benzoylpedamide (**3**) was firmly established by X-ray analysis of a crystal of (**vii**) grown from a dilute EtOAc/hexane solution Crystal data - $C_{20}H_{29}NO_6$, M 379 5, monoclinic, space group $P2_1/c$, a = 14 208(2), b = 9 686(3), c = 15 323(2) Å, β = 105 00(2)°, U = 2036 9 Å^3, Z = 4, D_c = 1 24 gcm^{-3} Monochromated Mo-Kα radiation, λ = 0 71069 Å, μ = 0 9 cm^{-1}

A crystal ca 0 37 x 0 20 x 0 13 mm was mounted on an Enraf Nonius CAD4 diffractometer Intensities for unique data with 2 < θ < 25° were measured with an ω-2θ scan with a maximum scan time of 1 minute No correction was made for absorption Out of 3575 measured, 1732 reflections with $|F^2| > \sigma(F^2)$ were used in the refinement, where $\sigma(F^2) = [\sigma^2(I) + (0\ 04I)^2]^{1/2}/Lp$

The structure was solved by direct methods using MULTAN[27] and refined by full matrix least squares with anisotropic temperature factors Hydrogen atoms, except for those on C(20) (arbitrary numbering, see figure below), were located on a difference map and held fixed with B_{iso} = 4 0 Å^2 Refinement converged at R = 0 065, R' = 0 073, with a weighting scheme ω = $1/\sigma^2(F)$ All calculations were done on a PDP11/34 computer using the Enraf Nonius SDP-Plus program package Tables of fractional atomic coordinates, isotropic thermal parameters, torsion angles and bond lengths have been deposited in the Cambridge Crystallographic Data Centre In the ORTEP drawing, the structure is displayed as the mirror image of (**vii**)

Figure 1 ORTEP drawing of racemic benzoylpedamide diastereoisomer (vii)(arbitrary numbering)

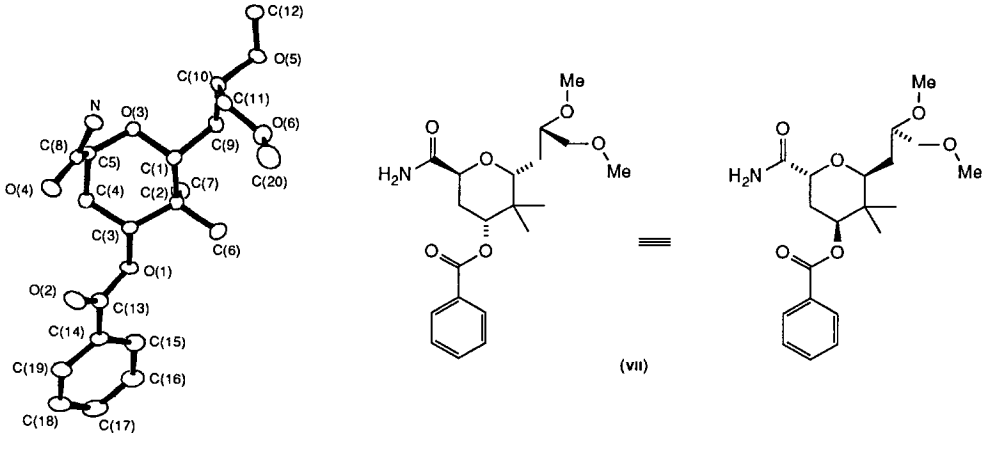


Table 2 Fractional Atomic Coordinates (x10^4) with Estimated Standard Deviations in Parentheses

	x	y	z
O(1)	3241(2)	2583(3)	3434(2)
O(2)	2071(2)	1146(4)	2707(3)
O(3)	2063(2)	6544(3)	3067(2)
O(4)	248(2)	4144(3)	2007(2)
O(5)	2256(2)	9352(3)	5150(2)
O(6)	1336(3)	6950(4)	5729(2)
N	88(3)	6251(4)	2570(3)
C(1)	2277(3)	5982(5)	3963(3)
C(2)	3013(3)	4780(5)	4094(3)
C(3)	2537(3)	3717(5)	3374(3)
C(4)	2286(3)	4281(5)	2429(3)
C(5)	1665(3)	5573(5)	2363(3)
C(6)	3162(4)	4159(6)	5015(3)
C(7)	3993(3)	5269(5)	3965(4)
C(8)	601(3)	5249(5)	2310(3)
C(9)	2609(3)	7201(5)	4582(3)
C(10)	1805(3)	8236(5)	4582(3)
C(11)	963(4)	7644(5)	4901(3)
C(12)	1731(5)	10597(6)	4981(4)
C(13)	2914(3)	1379(5)	3059(3)
C(14)	3706(3)	377(5)	3103(3)
C(15)	4631(3)	559(6)	3669(4)
C(16)	5346(4)	-408(6)	3675(4)
C(17)	5149(4)	-1535(6)	3109(4)
C(18)	4234(4)	-1721(6)	2537(4)
C(19)	3501(3)	-773(5)	2531(4)
C(20)	599(5)	6245(7)	6052(4)

Table 3 Hydrogen Atom Coordinates (x10^3)

	x	y	z
H(1)	166	555	416
H(N1)	-63	609	250
H(N2)	43	721	271
H(3)	188	332	354
H(4A)	188	359	188
H(4B)	291	471	229
H(5)	166	639	188
H(6A)	270	389	520
H(6B)	355	334	521
H(6C)	334	473	563
H(7B)	438	443	395
H(7A)	395	582	332
H(7C)	438	609	457
H(9A)	334	750	459
H(9B)	293	668	521
H(10)	146	859	375
H(11A)	63	693	438
H(11B)	63	861	500
H(12B)	146	1082	438
H(12C)	125	1057	541
H(12A)	207	1141	541
H(15)	480	139	418
H(16)	605	-29	418
H(17)	582	-223	313
H(18)	396	-279	209
H(19)	271	-84	209

Alkylation of Benzoylpedamide (3) - Imidate (40) To a solution of amide (**3**) (130 mg, 0 344 mmol) in CH_2Cl_2 (3 ml) was added Me_3OBF_4 (305 mg, 2 06 mmol) in one portion The cloudy solution was stirred at room temperature for 6 h to give a red/brown suspension which was poured into $NaHCO_3$ solution (10 ml) and extracted with CH_2Cl_2 The organic extracts were dried and concentrated to give the crude methylimidate (**40**) (135 mg, 100%) as a light yellow oil [contaminated in some cases with 5-10% of the starting amide (**3**)], which was used in the next step without further purification IR ($CHCl_3$) 3400w, 1725s, 1665m, 1280s, 1120s, 1105s, and 720s cm^{-1}, ^{1}H NMR (360 MHz) δ 8 07-8 02 (2H, m), 7 65-7 43 (4H, m), 5 309 (1H, s), 4 917 (1H, dd, J 4 2, 10 0), 4 478 (1H, dd, J 4 1, 5 8), 3 832 (3H, s), 3 55-3 40 (4H, m), 3 472 (3H, s), 3 397 (3H, s), 2 358 (1H, ddd, J 4 1, 4 2, 15 8), 2 081 (1H, ddd, J 5 8, 10 0, 15 8), 1 95-1 82 (2H, m), 1 087 (3H, s), 0 975 (3H, s)

Union of Benzoylpedamide (3) and Imidate (40) - To a solution of acid (**38**) (252 mg, 0 513 mmol) in CH_2Cl_2 (1 ml) was added purified $SOCl_2$[28] (52 4 µl, 0 718 mmol) dropwise and the resulting yellow solution stirred at room temperature for 10 min The methylimidate (40) (135 mg, 0 344 mmol) and Et_3N (136 µl, 0 975 mmol) in CH_2Cl_2 (3 ml) was added dropwise giving a slight exotherm The reaction mixture was stirred at room temperature for 2 h, and then concentrated to give a light yellow solid containing the N-acylimidates (**41a, 41b**) and unreacted starting materials

The residue was taken up in CH_2Cl_2 (4 5 ml) to give a yellow solution which was cooled to 0°C and $NaBH_4$ (180 mg, 4 76 mmol) added in one portion After 2 min, *i*-PrOH (8 4 ml) was added dropwise and the resulting yellow suspension stirred at 0°C for 40 min The reaction mixture was diluted with Et_2O (10 ml) and H_2O (10 ml) added cautiously to destroy the excess borohydride The resulting mixture was extracted with Et_2O The organic extracts were washed with $NaHCO_3$ solution, and brine, and then dried and concentrated to a yellow/brown oil Chromatography (25 to 50% Et_2O/hexane) yielded 187 mg of a colourless oil which contained the four diastereomeric products (**42a**)-(**42d**)

Separation of the isomers (42a)-(42d) - Semi-preparative hplc (Zorbax SIL, 9 4 mm x 25 cm, 50% MTBE/hexane, 6 ml/min, 254 nm) showed a 1 1 1 1 mixture of the four isomers Separation on this column yielded 19 2 mg [6 5%, based on (**40**)] of isomer (**42d**) as a white foam retention time 4 5 min, IR ($CHCl_3$) 3410s, 3350w, 2970m, 2940s, 1730sh, 1720s, 1700s, 1605w, 1455m, 1320m, 1275s, 1180m, 1120s, 1110s, 1070m, 1040m, 915m, and710m cm^{-1}, ^{1}H NMR (360 MHz) δ 8 15-8 0 (4H, m), 7 6-7 4 (10H, m), 7 3-7 2 (2H, m), 5 46 (1H, dd, J 5 5, 10 5), 5 30 (1H, s), 5 17 (1H, dd, J 3, 9 5), 4 02 (1H, dq, J 2, 6 5), 3 92 (1H, d, J 9 5), 3 88 (1H, dd, J 3, 7 5), 3 69 (1H, m), 3 6-3 2 (2H, m), 3 48 and 3 47 (3H each, s), 3 46 and 3 25 (3H each, s), 2 27 (1H, dd, J 6 5, 15), 2 1-1 6 (9H, m), 1 18 (3H, d, J 6 5), 1 09 and 0 93 (3H each, s), 0 87 (3H, d, J 7 Hz), m/z (FAB) 892 (MNa^+, 5%), 842 (5), 736 (2), 634 (10), 526 (8), 384 (9), 231 (12), 189 (100)

Next was collected 66 5 mg (22%) of a mixture of isomer (**42b**) and (**42c**) as a colourless oil retention time 5 0-5 5 min

Last was collected 30 1 mg (10%) of isomer (**42a**) as a while solid retention time 7 3 min, IR ($CHCl_3$) 3340w, 2940s, 1730s, 1720s, 1700s, 1605w, 1455m, 1320m, 1275s, 1115s, 1100s, 1070s, and 710m cm^{-1}, ^{1}H NMR (360 MHz) δ 8 15-8 05 (4H, m), 7 65-7 45 (9H, m), 7 3-7 2 (2H, m), 6 72 (1H, d, J 9 5, NH), 5 43 (1H, s), 5 33 (1H, dd, J 4, 9 5), 5 15 (1H, dd, J 4, 7 5), 3 99

(1H, dq, J 2, 6 5), 3 94 (1H, dd, J 5 5, 10), 3 64 (1H, d, J 9), 3 6-3 2 (3H, m), 3 45 (3H, s), 3 36 (3H, s), 3 34 (3H, s), 3 22 (3H, s), 2 2-1 7 (10H, m), 1 07 (3H, d, J 6 5), 1 01 (3H, s), 0 98 (3H, s), 0 90 (3H, d, J 7), m/z (FAB) 8 92 (MNa^+, 38%), 842 (10), 736 (10), 417 (85), 231 (20), 115 (100)

The isomers (**42b**) and (**42c**) were separated by gradient elution semi-preparative HPLC (Zorbax SIL, 9 4 mm x 25 cm, 25 + 40% MTBE/hexane, 6 ml/min, 254 nm) to yield first 13 8 mg of isomer (**42b**) as a white solid IR ($CHCl_3$) 3300w, 2940m, 1730sh, 1720s, 1700s, 1605w, 1455m, 1320m, 1275s, 1120s, 110s, 1075m, and 710m cm^{-1}, ^1H NMR (360 MHz) δ 8 1-8 0 (4H, m), 7 80 (1H, d, J 9 5, NH), 7 6-7 4 (9H, m), 7 3-7 2 (1H, m), 5 4-5 3 (1H, m), 5 35 (1H, s), 5 16 (1H, dd, J 3 5, 9 5), 4 04 (1H, dq, J 2, 6 5), 3 97 (1H, dd, J 3, 7), 3 80 (1H, dd, J 2, 11), 3 74 (1H, dd, J 5 5, 10), 3 68 (1H, m), 3 48 (3H, s), 3 46 (3H, s), 3 37 (3H, s), 3 33 (1H, m), 3 24 (3H, s), 2 47 (1H, dd, J 6, 14), 2 2-1 7 (9H, m), 1 15 (3H, d, J 6 5), 1 05 (3H, s), 1 04 (3H, s), 0 96 (3H, d, J 7), m/z (FAB) 892 (MNa^+, 40%), 842 (10), 736 (8), 634 (22), 526 (28), 384 (40), 231 (75), 189 (100)

Second to elute was 31 0 mg of isomer (**42c**) as a colourless oil IR ($CHCl_3$) 3370w, 2940s, 1730s, 1720s, 1700s, 1605w, 1510m, 1455m, 1320m, 1275s, 1115s, 1100s, 1075s, and 710m cm^{-1}, ^1H NMR (360 MHz) δ 8 2-8 0 (4H, m), 7 65-7 4 (10H, m), 7 3-7 2 (2H, m), 5 54 (1H, s), 5 17 (1H, dd, J 4 5, 9), 5 11 (1H, dd, J 4, 7), 4 10 (1H, dq, J 2, 6 5), 3 99 (1H, m), 3 7-3 2 (4H, m), 3 47 (3H, s), 3 44 (3H, s), 3 36 (3H, s), 3 21 (3H, s), 2 2-1 7 (10H, m), 1 21 (3H, d, J 6 5), 1 12 (3H, s), 1 04 (3H, s), 1 03 (3H, d, J 6 5), m/z (FAB) 892 (MNa^+, 50%), 842 (38), 736 (10), 417 (18), 231 (12), 115 (100)

Equilibration of isomer (42b) - AcCl vapour (0 5 ml) was passed through a solution of isomer (**42b**) (1 5 mg, 1 7 x 10^{-3} mmol) in MeOH (100 µl) After 6 h, analytical HPLC (Zorbax SIL, 4 6 mm x 25 cm, 50% MTBE/hexane, 1 5 ml/ min, 254 nm) showed a 1 1 mixture of the starting isomer (**42b**) (retention time 6 0 min) and the isomer (**42a**) (retention time 8 0 min)

Pederin Dibenzoate (43) - $NaIO_4$ (2 5 mg, 11 5 x 10^{-3} mmol) was added in one portion to a rapidly stirred solution of the selenide (**42a**) (6 0 mg, 6 90 x 10^{-3} mmol) in MeOH/H2O) (3 1, 1 0 ml) The solution immediately turned from colourless to light brown and a precipitate formed after 5 min After 30 min, the reaction mixture was diluted with Et_2O (10 ml), washed with H_2O, and then dried and concentrated to a red oil

The crude selenoxide was taken up in benzene (0 2 ml) and added dropwise to a refluxing solution of benzene (1 0 ml) and Et_3N (1 0 ml) After 2 min at reflux, the solution was poured into $NaHCO_3$ solution (10 ml) and extracted with Et_2O The organic extracts were dried and concentrated to an orange oil, which was filtered through kieselgel 60 (5 x 35 mm, Et_2O) to give 12 mg of a light yellow solid Purification by semi-preparative HPLC (Zorbax SIL, 9 4 mm x 25 cm, 50% MTBE/hexane, 6 ml/min, 254 nm) gave 5 2 mg (85%) of a 5 2 mixture of pederin dibenzoate (**43**) and the starting selenide (**42a**) respectively Partial separation was achieved by gradient elution semi-preparative hplc (Zorbax SIL, 9 4 x 25 mm, 20 - 25% EtOAc/hexane + 0 1% H_2O, 6 ml/ min, 254 nm) to yield 2 8 mg of mixed fractions and 2 4 mg of the pure pederin dibenzoate (**43**) as a colourless oil ^1H NMR (360 MHz) δ 8 15-8 05 (4H, m), 7 6-7 4 (6H, m), 6 80 (1H, d, J 9 5, NH), 5 52 (1H, s), 5 36 (1H, dd, J 4 5, 9 5), 5 15 (1H, dd, J 4, 7), 4 88 (1H, t, J 1), 4 81 (1H, t, J 1), 3 97 (2H, m), 3 65 (1H, dd, J 1 5, 10), 3 6-3 4 (4H, m), 3 47 (3H, s), 3 38 (3H, s), 3 37 (3H, s), 3 26 (3H, s), 2 77 (1H, d, J 4 5), 2 51 (1H, d J 4 5), 2 3-2 0 (3H, m), 1 9-1 75 (2H, m), 1 12 (3H, d, J 6 5), 1 02 (3H, s), 1 00 (3H, s), 0 98 (3H, d, J 8)

Hydrolysis of Pederin Dibenzoate Pederin (1) - To a solution of pederin dibenzoate (**43**) (2 0 mg, 2 81 x 10^{-3} mmol) in MeOH (1 0 ml) was added aqueous LiOH (1 M, 100 µl) The solution was warmed at 50°C for 5 h and then concentrated The residue was taken up in Et_2O (10 ml) and washed with H_2O, and brine, and then dried and concentrated Chromatography (6 x 32 mm, eluting first with Et_2O and then EtOAc) yielded 1 3 mg (92%) of Pederin (**1**) IR (CH_2Cl_2) 3620w, 3420m, 3370w, 3060w, 2980s, 2940s, 2840m, 1680s, 1660m, 1515s, 1455m, 1385m, 1125s, 1110s, 1090s, 1080s, 1050s, 1015m, 970w, and 910w cm^{-1}, ^1H NMR (360 MHz) δ 7 158 (1H, d, J 9 7, NH), 5 391 (1H, dd, J 8 0, 9 7, C10-H), 4 863 and 4 75 (1H each, t, J 1 9, $=CH_2$), 4 313 (1H, t, J 2 2, H-7), 4 013 (1H, dq, J 2 8, 6 6, H-2), 3 897 (1H, d, J 2 2, C7-**OH**), 3 806 (1H, ddd, J 2 5, 6 3, 8 0, H-11), 3 650 (1H, dd, J 4 6, 10 9, H-13), 3 5-3 3 (3H, m, H-18, 2H-19), 3 407 (3H, s, OCH3), 3 394 (3H, s, OCH3), 3 348 (3H, s, OCH3), 3 343 (3H, s, OCH3), 3 250 (1H, dd, J 2 0, 10 2, H-15), 2 454 (1H, d, J 14 2, H-5), 2 362 (1H, dt, J 1 9, 14 2, H-5),2 258 (1H, dq, J 2 8, 7 0, H-3), 2 052 (1H, ddd, J 2 5, 4 6, 13 4, H-12),1 761 (1H, ddd, J 6 2, 10 9, 13 4, H-12), 1 729 (1H, ddd, J 3 0, 10 2, 14 0, H-17), 1 609 (1H, ddd, J 2 0, 9 3, 14 0, H-17), 1 61 (1H, br, C13-**OH**), 1 202 (3H, d, J 6 6, C2-**Me**), 1 028 (3H, d, J 7 0, C3-**Me**), 0 951 (3H, s, C14-**Me**), 0 884 (3H, s, C14-**Me**), m/z (FAB) 526 (MNa^+, 2%), 504 (MH^+, 10), 440 (20), 89 (100), (EI) 454 (1%), 439 (3), 421 (9), 394 (6), 368 (5), 362 (7), 336 (11), 282 (9), 264 (8), 257 (9), 240 (32), 222 (18), 208 (40), 155 (71), 60 (100)

Synthetic Pederin was identical by IR, 1H NMR, EIMS and tlc mobility (double elution, Et_2O, EtOAc, or 10% MeOH/$CHCl_3$) to a sample of natural (+)-Pederin In addition, natural Pederin gave the following 13C NMR data (90 MHz) δ 171 9, 145 9, 110 7, 99 9, 79 7, 77 9, 76 0, 74 0, 73 1, 72 8, 72 1, 69 7, 59 2, 56 9, 56 4, 49 1, 41 5, 38 7, 34 3, 30 3, 29 7, 23 1, 18 0, 13 1, 12 2

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