Stereoselective total synthesis of (−)-pumiliotoxin C by an aqueous intramolecular acylnitroso Diels–Alder approach

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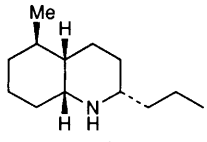
A chiral approach to (−)-pumiliotoxin C based on an aqueous intramolecular acylnitroso Diels–Alder reaction is described. Upon treatment of the (*S*)-1,3-diene hydroxamic acid 19, available from L-malic acid, with Pr_4NIO_4 under the aqueous conditions, the *in situ* generated acylnitroso compound 19 was subjected to intramolecular [4 + 2] cycloaddition to yield the *trans*-1,2-oxazino lactam 21 with significantly increased diastereoselectivity in comparison with the same cycloaddition conducted in a chloroform solution. Subsequent addition of the propyl side chain was achieved by means of a tandem Grignard reaction–$NaBH_3CN$ reduction in a completely stereocontrolled manner. The bicyclic 1,2-oxazine 26 thus obtained was converted into the all-*cis*-decahydroquinoline 34 by sequential reductive N–O bond cleavage, aldol condensation of the diketone 31 and hydrogenation of the octahydroquinolone 33. Clemmensen reduction of 34, followed by $LiAlH_4$ reduction, provided a *ca.* 2:1 epimeric mixture of α-methyl and β-methyl isomers 36 and 37, and subsequent debenzylation converted the major isomer 36 into 5-*epi*-pumiliotoxin C 2. On the other hand, 34 underwent $LiAlH_4$ reduction followed by Swern oxidation to afford a 1.2:1 epimeric mixture of the decahydroquinolones 39 and 41. Equilibrium control of this epimeric mixture by prolonged heating with $Zn(OTf)_2$ followed by treatment with ethane-1,2-dithiol resulted in the exclusive formation of the thermodynamically more stable β-methyl epimer 43 as a single isomer, which was converted into (−)-pumiliotoxin C 1 by desulfurization and debenzylation.

Introduction

Approximately 300 alkaloids with noxious or toxic effects on nerves and muscles have been isolated from, or detected in, amphibians. These alkaloids serve as a chemical defense against predators and/or microorganisms and exhibit marked biological activity.[1] Of these known amphibian alkaloids, most have been characterized from the neotropical poison frogs of the family Dendrobatidae and grouped into more than two dozen classes. One major class of dendrobatid alkaloids is the 2,5-disubstituted decahydroquinolines. The first member of this group named pumiliotoxin C **1**† was isolated from the skin secretions of a Panamanian population of *Dendrobates pumilio*[2,3] and *D. auratus*[4] and more recently found in skin extracts of a Madagascan genus of ranid frogs *Mentella*.[5] Although there had been some confusion in the literature, the absolute configuration of natural (−)-pumiliotoxin C was unambiguously established as shown in **1** by X-ray crystallographic analysis of the hydrochloride salt[2b,6] and its total synthesis.[7] The unusual chemical and neuromuscular characteristics[1,8] have prompted chemists to develop numerous approaches to nonchiral[9] and chiral[10] syntheses of pumiliotoxin C and to prepare diastereoisomers namely the 2-*epi*[9k] and the 5-*epi* analogues[11] with the *cis*-fused decahydroquinoline ring system, both in racemic form.

Recently we have reported that, in aqueous media, intramolecular hetero Diels–Alder cycloadditions of chiral acylnitroso compounds show a remarkable enhancement of the diastereoselectivity in comparison with the same reaction under conventional nonaqueous conditions.[12] An application of this reaction to an enantioselective synthesis of (−)-swainsonine was also described.[13] Although many studies on natural product synthesis utilizing intramolecular acylnitroso Diels–Alder reaction have been published,[14] in all cases, except for our synthesis of (−)-swainsonine, nonaqueous conditions have been employed for such cycloadditions. Our interest in this area led us to investigate a further application of the strategy utilizing aqueous acylnitroso Diels–Alder cycloaddition for the preparation of chiral natural products. In continuation of our studies on the development of enantioselective methods for the total syntheses of dendrobatid alkaloids,[14i,15] we now describe in detail the enantioselective synthesis of (−)-pumiliotoxin C **1** and its 5-epimeric analogue **2** based on an aqueous acylnitroso Diels–Alder approach in an intramolecular manner.[16]



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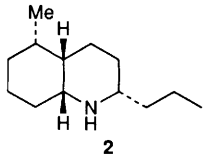

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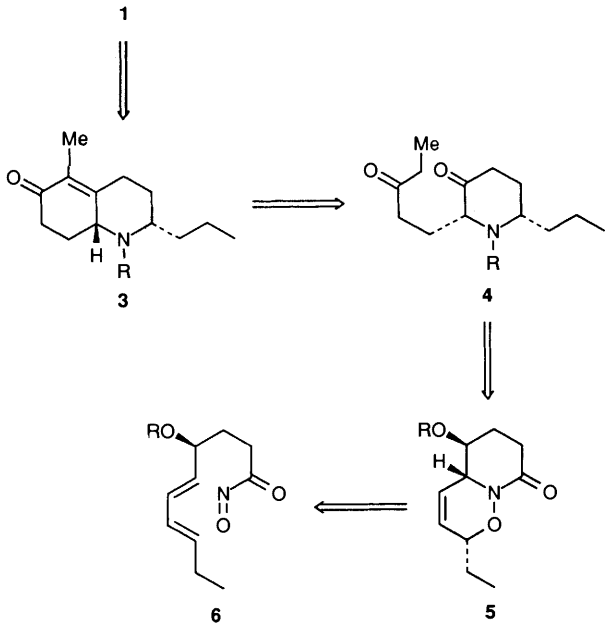
Results and discussion

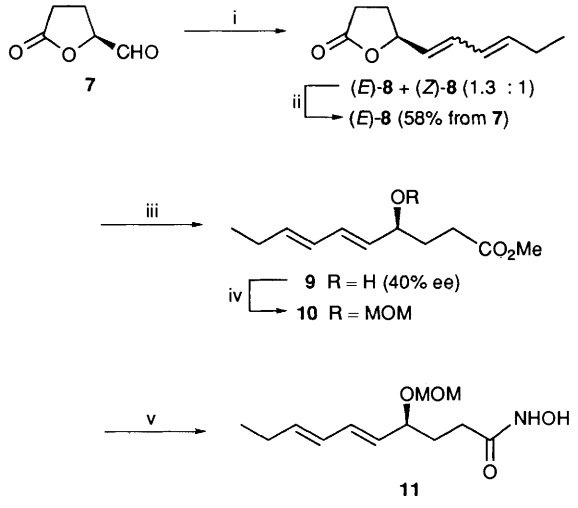
The strategy adopted in our approach to (−)-pumiliotoxin C **1** centred on the intramolecular acylnitroso Diels–Alder reaction (**6**→**5**) is outlined in Scheme 1. A crucial feature of this approach involves the stereoselective introduction of an α-orientated propyl side chain at C-2 (related to **1**). An additional benefit of this route is the stereoselective construction of the *cis*-decahydroquinoline ring system by aldol condensation of a diketone **4** followed by catalytic hydrogenation of the resulting 6-oxooctahydroquinoline **3**. Thus, our approach started with the preparation of the (*S*)-hydroxamic acid **11** needed for the Diels–Alder cycloaddition of the diene acylnitroso compound **6** (Scheme 1, R = MOM). To this end, (*S*)-5-oxooxolane-2-carbaldehyde **7** was prepared from L-glutamic acid in three steps according to the method of Doolittle.[17] Being labile, this compound was immediately subjected to Wittig reaction with *trans*-pent-2-enyl(triphenyl)phosphonium bromide and potassium *tert*-butoxide in tetrahydrofuran (THF) to give the 1,3-diene **8** as a 1.3:1 mixture (based on ^1H NMR analysis) of

† Pumiliotoxin C has relatively low toxicity and the nomenclature decahydroquinoline *cis*-195A for it has been recommended to avoid confusion with the more toxic pumiliotoxin A class of alkaloids; the structures of the two compounds are quite different (see ref. 1).



Scheme 1

E- and *Z*-isomers which are chromatographically separable. Without separation, subsequent photoisomerization of this mixture was carried out by UV irradiation in the presence of iodine, resulting in the single *E*-isomer of **8** in 58% overall yield from **7**. During the Wittig reaction, significant loss in the optical purity due to partial racemization at the C-2 chiral centre adjacent to the formyl group was envisioned.[18] However, it was difficult at this point to analyse, by chiral HPLC, the optical purity of this material, (*E*)-**8**, which had $[\alpha]_D$ +17.2 ($CHCl_3$). However, we could determine the optical purity of the hydroxy ester **9**, which was derived from (*E*)-**8** by alkaline hydrolysis followed by diazomethane esterification. Conversion of **9** into the corresponding (*S*)-MTPA ester[19] and subsequent HPLC analysis indicate that the optical purity of **9** was 40% ee and that for (*E*)-**8** the $[\alpha]_D$ value in chloroform had to be corrected to at least +43. Although **9** could easily be converted into the required hydroxamic acid **11** by protection with the methoxymethyl group followed by treatment with hydroxylamine under alkaline conditions as shown in Scheme 2, we abandoned this route because of the low optical purity.



Scheme 2 *Reagents:* i, (*E*)-EtCH=CHCH$_2$PPh$_3^+$Br$^-$, KOBu^t (95%); ii, *hv*, I_2, benzene; iii, 5% KOH–MeOH–THF, room temp., then CH_2N_2 (75%); iv, MOMCl, Pr$^i_2$NEt (91%); v, H_2NOH, KOH–MeOH (85%)

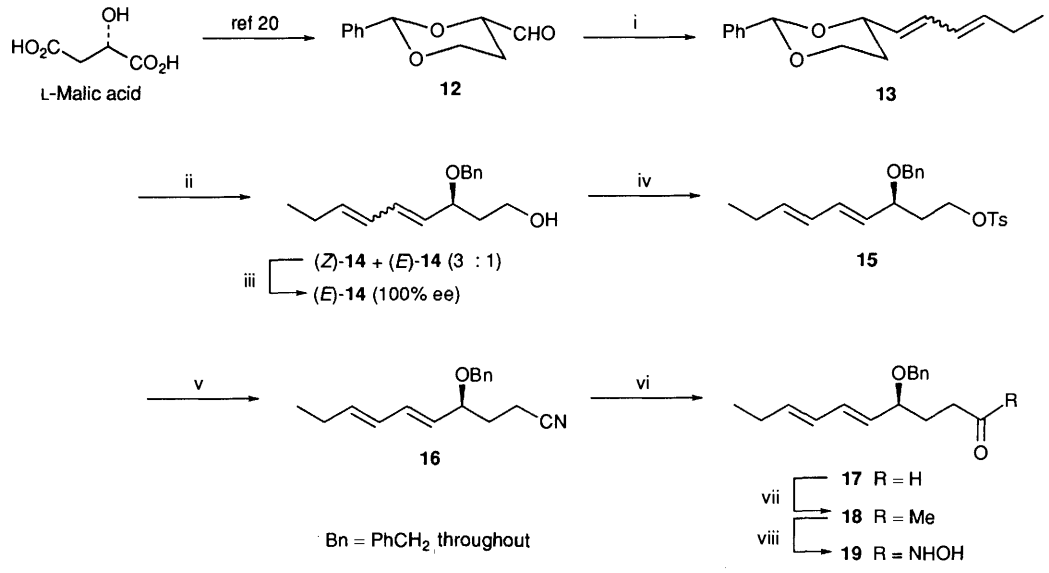
We considered that a solution to the decreased optical purity encountered in obtaining the 1,3-diene **9** would be to preclude racemization at the chiral centre adjacent to the formyl group as previously recognized in the enantioselective synthesis of (−)-swainsonine.[13] Accordingly, the Wittig reaction was carried out with (2*S*,4*S*)-2-phenyl-1,3-dioxane-4-carbaldehyde **12**, prepared from L-malic acid in three steps following described procedures.[20] Both the phenyl and the carbaldehyde groups are expected to be preserved in an energetically favoured equatorial conformation during the reaction without epimerizing to the axially orientated 1,3-dioxane-4-carbaldehyde with the undesirable *R* configuration (Scheme 3). The reaction was completed within 10 min to provide the 1,3-diene **13** as a 3:1 *Z*/*E* mixture (by NMR analysis) in 95% yield. Subsequently, the benzylidene acetal was treated with DIBALH, followed by UV irradiation (I_2, benzene) of the resulting **14** (*Z*:*E* = 3:1). In this way the geometrically pure (*E*)-1,3-dienol (*E*)-**14** was obtained and proved to be substantially enantiopure (>99.5% ee) by HPLC analysis after conversion into the corresponding (*S*)-MTPA ester.

As shown in Scheme 3, straightforward transformation of (*E*)-**14** to the (*S*)-1,3-diene ester **18** was sequentially achieved by tosylation, cyanide displacement of the tosyl group, alkaline hydrolysis, and then diazomethane esterification in 65% overall yield for 4 steps. Treatment of **18** with hydroxylamine under the alkaline conditions (KOH in methanol) produced the requisite (*S*)-1,3-diene hydroxamic acid **19** in 89% yield.

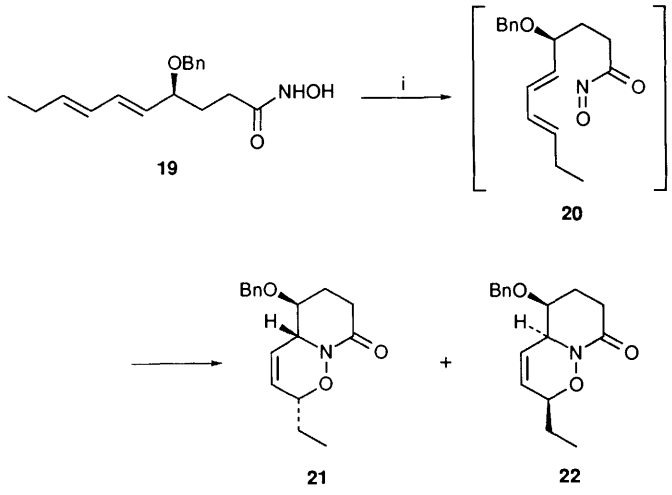
Our previous studies revealed[12] that the use of aqueous media rather than non-aqueous conditions for intramolecular Diels–Alder reactions of an *R* series of chiral 1,3-diene acylnitroso compounds, produces significant enhancement of the *trans* selectivity. Consistent with these observations, the (*S*)-hydroxamic acid **19** on treatment with Pr_4NIO_4 at 0 °C in water–DMSO (5:1) underwent cycloaddition *via* the *in situ* generated acylnitroso compound **20** to yield the *trans* (with respect to C-4a and C-5) cycloadduct **21** as a major isomer. The diastereoselectivity was significantly increased (4.1:1) compared with the reaction conducted in a chloroform solution which affords a 1.4:1 *trans*/*cis* ratio[12] (Scheme 4). In this case, addition of α-cyclodextrin (1 equiv.) was found to be effective for the improvement of the yield (75 to 84%) of the cycloaddition although no further increase of the *trans*/*cis* selectivity was observed. The best *trans* selectivity (5.0:1, **21**/**22**) was obtained when water–methanol (5:1) was used as a reaction medium.

After hydrogenation of the olefin moiety of the *trans* adduct **21**, we thought that we could achieve stereoselective introduction of the propyl side chain at C-8 of the pyridoxazine ring (C-2 of the target compound, pumiliotoxin C **1**) by the tandem Grignard reaction–reduction procedure developed earlier in these laboratories.[14d,f,g,i,j] Thus, **23** was allowed to react with propylmagnesium bromide to generate an unstable enamine **24** as a *ca.* 1:1 equilibrium mixture (by NMR analysis) of *endo*- and *exo*-cyclic olefins (Scheme 5). Upon subsequent reduction with $NaBH_3CN$ under acidic conditions, by analogy to the Stevens' principle,[21] stereoelectronically preferred axial attack by hydride preferably occurred from the β face of the iminium moiety of the conformer **25A**, which gave **26** as a *single* diastereoisomer having the desired 8*S* configuration in 96% overall yield from **23**. The alternative hydride approach from the α side of the iminium moiety of the conformer **25B**, leading to the 8*R* diastereoisomer **27**, should be precluded because of the strong interaction between the 2-ethyl group and the incoming hydride species (see Scheme 5).

In agreement with previous observations,[14d,g] on the NMR time-scale at ambient temperature there was slow conformational exchange between the *trans*- and *cis*-fused pyridoxazines of the product **26** which provided the ^{13}C NMR spectrum with pairs of resonances for each of the carbons in the molecule with an average ratio of 2:1. A set of 2-H signals, H_A in *trans*-**26**



Scheme 3 *Reagents:* i, (*E*)-EtCH=CHCH$_2$PPh$_3^+$Br$^-$, KOBu^t (95%); ii, DIBALH (86%); iii, *hν*, I_2, benzene (80%); iv, TsCl, Py (95%); v, NaCN, DMSO (93%); vi, 25% NaOH, MeOH, reflux (84%); CH_2N_2 (88%); vii, H_2NOH, KOH–MeOH (89%)



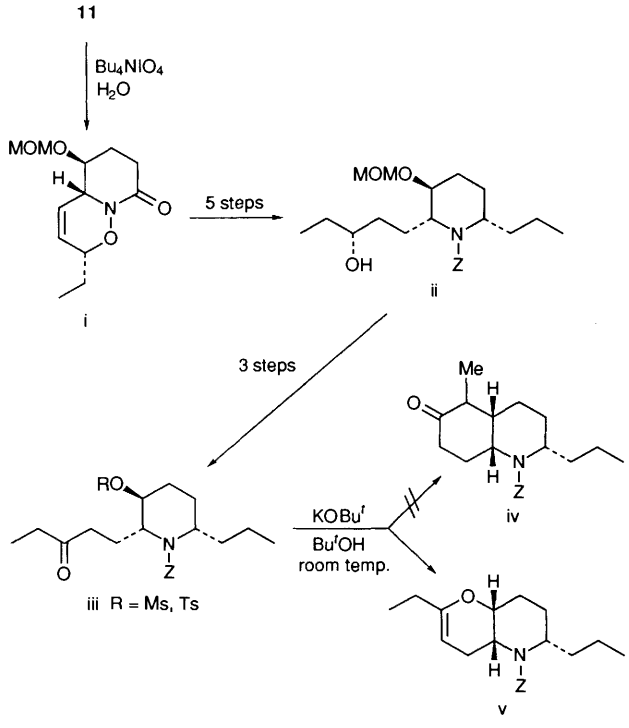
Scheme 4 *Reagent:* i, Pr_4NIO_4, 0 °C

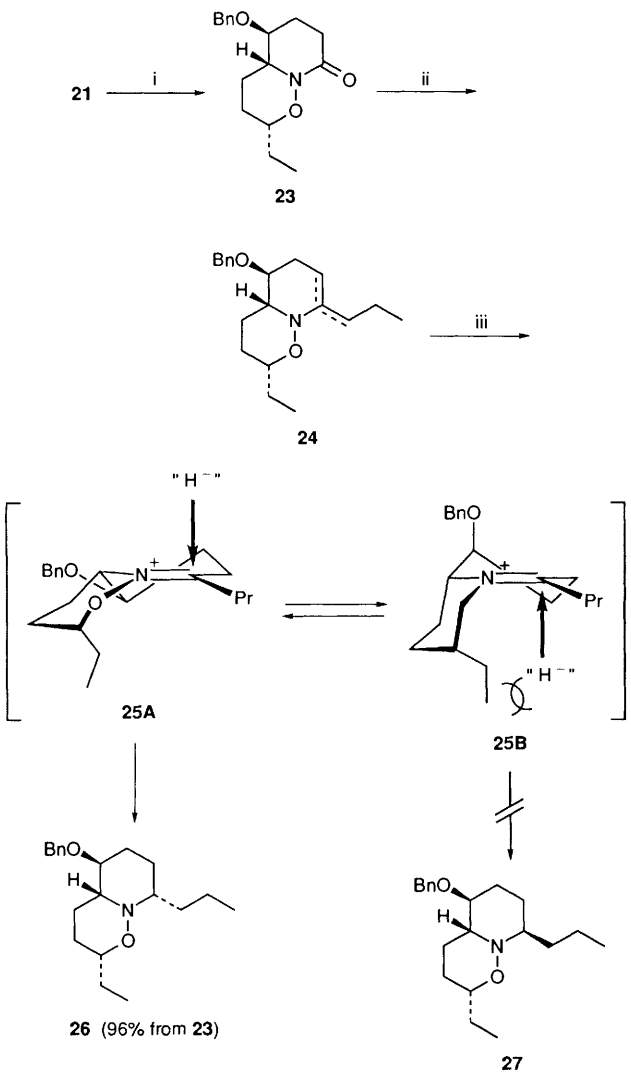
(δ 3.74, td, J 10.9 and 4.1 Hz) and H_B in *cis*-**26** (δ 3.56, m) appeared as a 1 : 2 ratio in the ^{1}H NMR spectrum (in a $CDCl_3$ solution) which converged to a single resonance at an elevated temperature (333 K in a [$^2H_5$]pyridine solution); this suggests that **26** exists as a *ca.* 2 : 1 ratio of two conformers, with the *cis*-fused pyridoxazine, *cis*-**26**, predominating.

Reductive N–O bond cleavage of compound **26** with zinc dust in 80% acetic acid formed the amino alcohol **28**, which was converted into the amide **29** (89% yield from **26**) in tandem by *N*,*O*-dibenzoylation (2.5 equiv. of PhCOCl, aqueous K_2CO_3, CH_2Cl_2) followed by saponification (5% aqueous KOH in MeOH–THF, room temp.) (Scheme 6). After catalytic hydrogenolysis of the benzyl ether of **29**, the resulting diol **30** was oxidized with pyridinium chlorochromate (PCC) to yield the diketone **31** (73% from **29**), which was subjected to aldol cyclization using ethanolic KOH followed by dehydration (aqueous $KHSO_4$) to form the octahydroquinolone **33**. Subsequent catalytic hydrogenation of **33** over palladium-on-carbon produced the all-*cis*-decahydroquinolone **34**‡ as a single isomer (71%), wherein hydrogen delivery to the C(4a)–C(5) double bond would occur exclusively from the convex β-face. Although this transformation established the correct chirality at C-2, C-4a and C-8a for (−)-pumiliotoxin C **1**, the α-methyl substitution at C-5 in **34** was not consistent with that in **1**, but related to the 5-*epi*-isomer of pumiliotoxin C **2**.

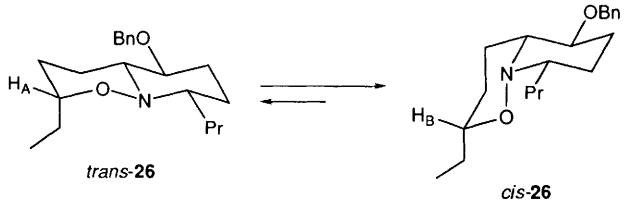
Thus, with **34** in hand, we addressed the chiral synthesis of 5-*epi*-pumiliotoxin C **2** which had earlier been prepared in racemic form by Stille and Paulvannan.[11] Clemmensen reduction of the *cis*-fused decahydroquinolone **34** (Zn, HCl, −5 °C) afforded **35** (57%) as a 2 : 1 epimeric mixture, which was then subjected to reduction with $LiAlH_4$ followed by chromatographic separation of the epimers to give **36** (54%) and **37** (28%) (Scheme 7). The major epimer **36**, with $[\alpha]_D^{25}$ +4.1 (*c* 0.97 in $CHCl_3$), upon hydrogenolysis over palladium-on-carbon in methanolic HCl

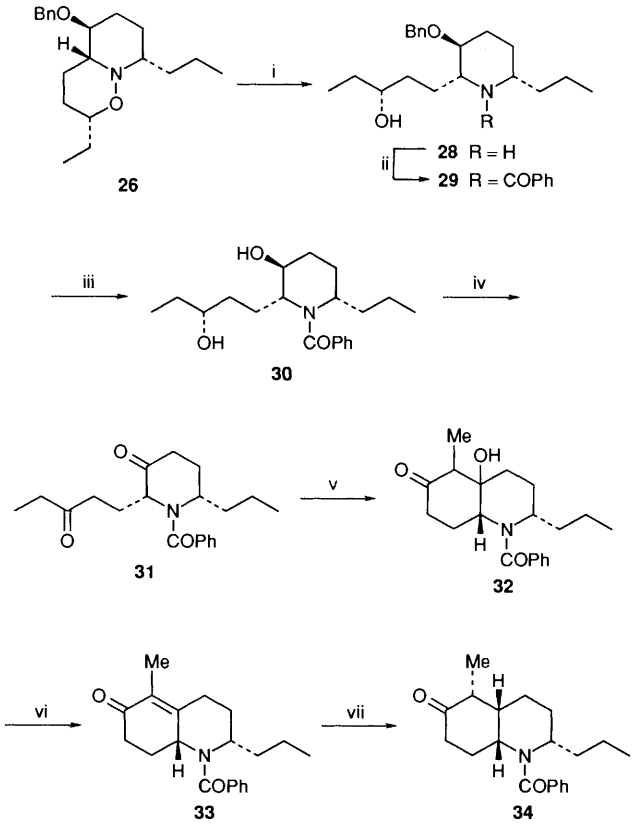
‡ In an attempt at alternative construction of the *cis*-fused decahydroquinolone ring system iv, the hydroxamic acid **11** was subjected to aqueous acylnitroso cycloaddition (*cf.* ref. 12) to give the *trans*-adduct i, which was converted into ii in 5 steps according to Schemes 5 (**21**→**26**) and 6 (**26**→**29**). Sequential Swern oxidation, de-*O*-protection, and *O*-sulfonylation provided the mesylate and tosylate iii, both of which were then treated with potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature; however, this resulted only in the formation of the *cis*-fused hexahydropyridopyrane v in 37% yield.



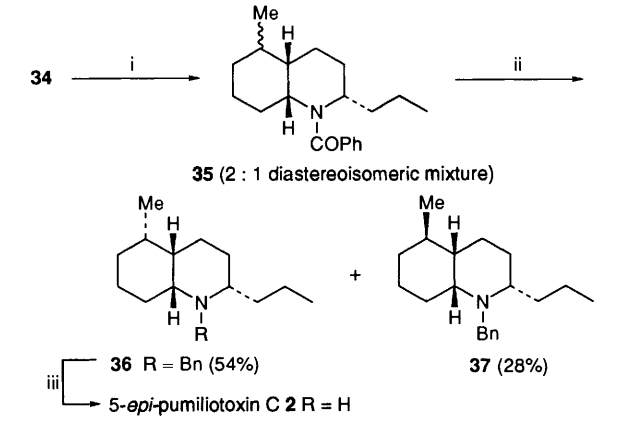


Scheme 5 *Reagents:* i, H_2, Pd–C, THF (100%); ii, PrMgBr, THF, 0 °C; iii, $NaBH_3CN$, AcOH, THF, 0 °C





Scheme 6 *Reagents:* i, Zn, AcOH (91%); ii, PhCOCl (2.5 equiv.), aq. K_2CO_3, then 5% KOH (89%); iii, H_2, Pd–C (99%); iv, PCC, CH_2Cl_2 (74%); v, KOH–EtOH, 0 °C (85%); vi, aq. $KHSO_4$, MeOH, room temp., 2 days (72%); vii, H_2, Pd–C, HCl–MeOH (71%)



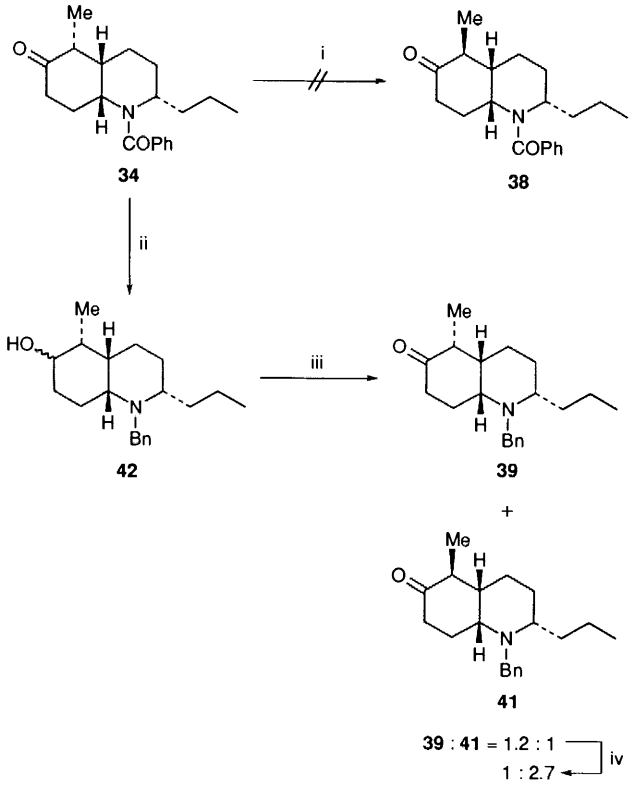
Scheme 7 *Reagents:* i, Zn, HCl, Et_2O, −5 °C (57%); ii, $LiAlH_4$, THF; iii, H_2, Pd–C, HCl–MeOH (91%)

lost its benzyl protecting group to provide the hydrochloride salt of 5-*epi*-pumiliotoxin C (**2**·HCl); this showed an optical rotation of 0.0 in methanol, despite being shown to be in enantiomerically pure form by chiral HPLC analysis.

In this manner, the desired β-methyl epimer **37** with the correct absolute stereochemistry for (−)-pumiliotoxin C **1** was obtained only as a minor product. In an attempt to effect epimerization at C-5 of the α-methyldecahydroquinolone **34** and thus obtain the β-methyl isomer **38**, we next employed forcing conditions; treatment of **34** with NaOMe (in MeOH, room temp. to 50 °C) or KOBu^t (THF–DMSO, room temp.), however, resulted only in recovery of **34** unchanged (Scheme 8).

Booth[22] reported that the conformationally mobile *cis*-decahydroquinoline itself [eqn. (1), R = H] has a strong preference for a type 2 conformation, whereas the *N*-acyl derivatives [eqn. (1), R = acyl] prefer type 1 in order to avoid $A^{1,3}$ type strain[23] between the *N*-substituent and the C-8 methylene group. This should hold even more so for the *N*-benzoyl-*cis*-decahydroquinolone **34**, which should exist preferentially in the type 1 conformation **34A** [eqn. (2)]. The alternative type 2 conformation **34B** is unlikely owing to the additional $A^{1,3}$ strain between the *N*-benzoyl group and the 2-propyl group. Therefore, the configuration of the 5-methyl group in **34** is presumably placed in the energetically favoured equatorial conformation, which may be preserved under the basic conditions, thus precluding the C-5 epimerization of **34** to produce **38** by enolate equilibration. In order to confirm unambiguously the structural and conformational outcome for **34**, a single-crystal X-ray diffraction study of **34** was undertaken. The crystal structure is shown in Fig. 1 which indicates that in agreement with the above discussion **34** takes the type 1 conformation **34A** in crystal form.

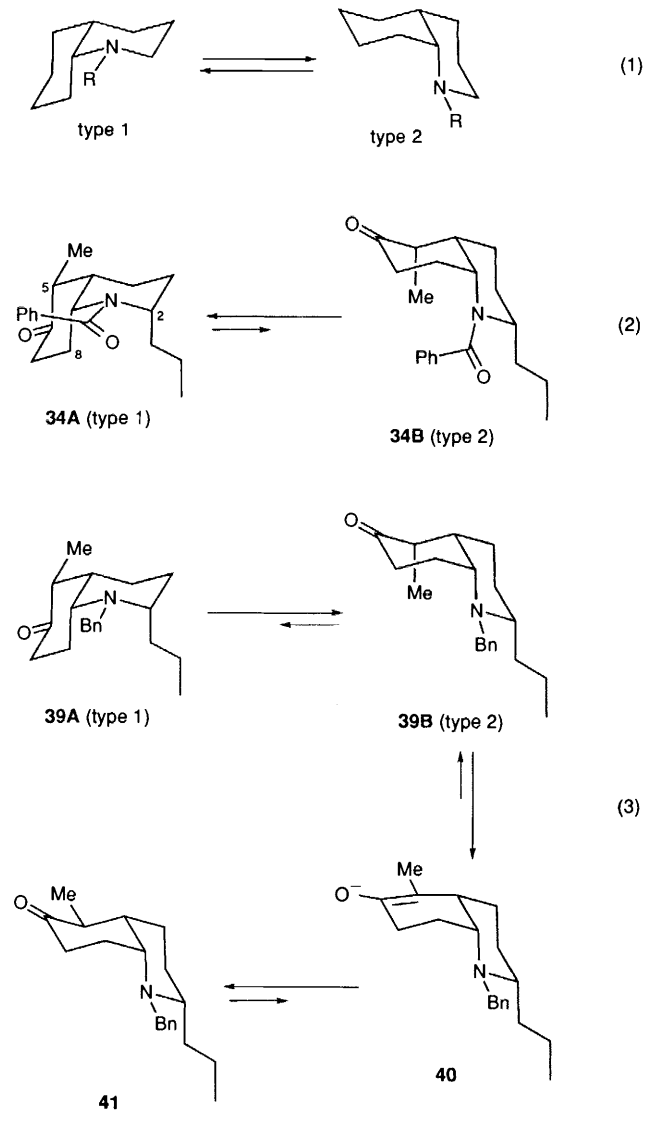
However, replacement of the *N*-benzoyl group by an *N*-benzyl group (see **39** in Scheme 8), should lead to disappearance of allylic strain with the type 2 conformation **39B** [eqn. (3)] then being preferred; in this the 2-propyl group is equatorial,



Scheme 8 *Reagents:* i, NaOMe or KOBu^t; ii, $LiAlH_4$, THF (87%); iii, Swern ox. (84%); iv, KOH–MeOH, reflux, 12 h

thus avoiding 1,3-diaxial interaction between the axial 2-propyl group and the C-8 ring methylene group. Hence, upon epimerization through the enolate **40**, **39B** possessing the axial C-5 methyl group would be converted into the thermodynamically more stable **41** with an equatorial 5-methyl group [eqn. (3)].

With these considerations in mind, our attention next focussed on an epimeric transformation using the *N*-benzyl derivative **39** wherein the $A^{1,3}$ strain caused by the *N*-benzoyl group is absent. Thus, the benzamide **34** was reduced with $LiAlH_4$ to **42** as a mixture of the alcohol epimers in 87% yield (Scheme 8). This mixture was oxidized under Swern conditions [24] to afford an epimeric mixture of the 5α- and 5β-methyl isomers **39** and **41** in a ratio of 1.2 : 1 (determined by ^1H NMR). The formation of the β-isomer **41** may result from the initially formed α-isomer **39** being in equilibrium with the enolate [**40** in eqn. (3)] under the reaction conditions. To influence the equilibrium in favour of **41**, this 1.2 : 1 α-/β-isomeric (**39**/**41**) mixture was heated with methanolic potassium hydroxide at reflux for 12 h; although this gave a ratio of the α-/β-isomers of 1 : 2.7, complete conversion into the β-isomer **41** could not be attained under these conditions. This problem was eventually solved by Lewis acid-promoted epimerization. Thus, the 1.2 : 1 mixture of the diastereoisomers **39** and **41** was refluxed with 1 equiv. of $Zn(OTf)_2$ in CH_2Cl_2 for 4 days and subsequently treated with ethane-1,2-dithiol. By this one-pot procedure, the dithioketal of the β-isomer **41**, *i.e.* **43**, was obtained in 66% yield as a single product. It is apparent that prolonged exposure to $Zn(OTf)_2$ led to exclusive conversion of the α-isomer **39** into the β-isomer **41**, *in situ* reaction of the latter with dithioglycol then resulting in the dithioketal **43** as a single product. The complete epimerization so obtained at C-5 of **39** is presumed to arise from equilibrium control. Thus, as a result of the strong non-bonded interaction between the 5-methyl group and the 3-methyne group in the chelated zinc complex **44** (see Fig. 2), the equilibrium will be entirely on the side of the thermodynamically more stable zinc complex **46** with its 5β-



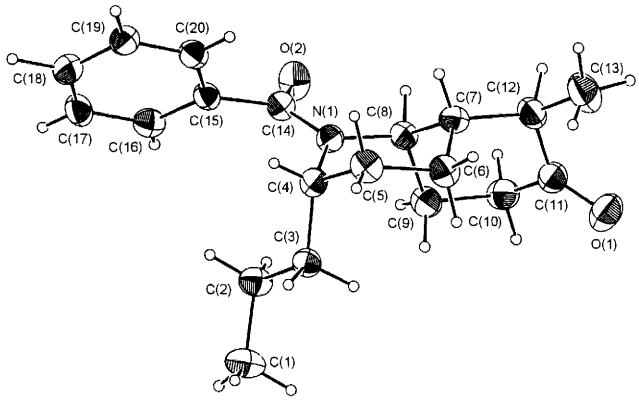


Fig. 1 X-Ray molecular structure of compound **34**

methyl, the zinc enolate **45** being an intermediate in this equilibration.

Having thus established all the correct chiral centres in **43**, we had only then to remove the 1,3-dithiane moiety and the benzyl protecting group to complete the natural alkaloid synthesis. Desulfurization of the dithioketal **43** with Raney Ni provided **37** in 68% yield, which was subjected to hydrogenolytic removal of the *N*-benzyl protecting group to yield (−)-pumiliotoxin C **1** (Scheme 9). The synthetic material of **1** exhibited ^1H and ^{13}C NMR spectra identical with those reported [3] for the natural alkaloid. Treatment of the synthetic sample of **1** with methanolic HCl and subsequent recrystallization from Pr^{i}OH–

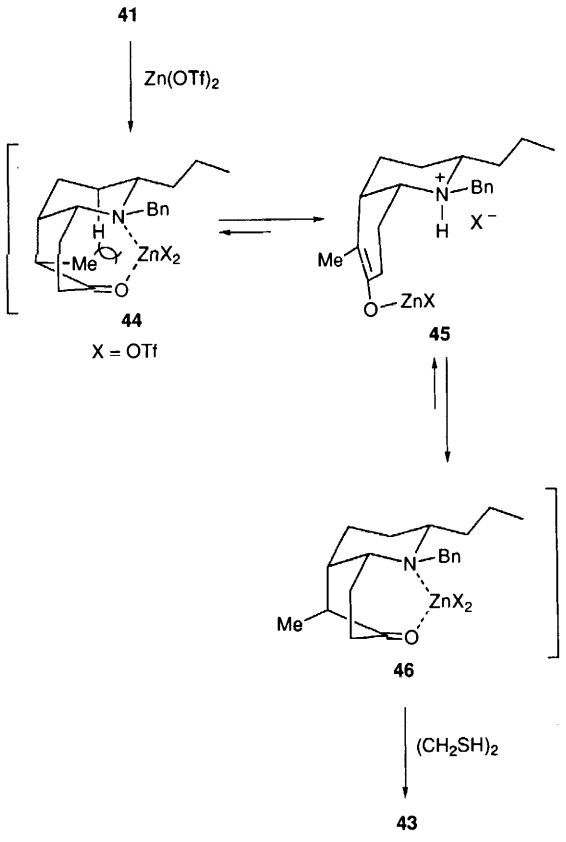


Fig. 2 Possible pathway for epimerization of the 5α-methyl isomer **41** by enolization and subsequent dithioketalization to the thermodynamically more stable 5β-methyl isomer **43**

Et_2O gave the hydrochloride salt of **1** as colourless needles, mp 284–288 °C (scaled capillary) [lit.,[10b] 286–288 °C (sealed capillary under Ar)]; $[\alpha]_D^{24}$ −15.2 (*c* 0.46 in MeOH) {lit.,[10b] $[\alpha]_D^{21}$ −16.2 (*c* 1.00 in MeOH)}.

Conclusions

We have described a stereoselective chiral synthesis of (−)-pumiliotoxin C **1** and 5-*epi*-pumiliotoxin C **2**. Our strategy is based on an aqueous intramolecular Diels–Alder reaction of the chiral acylnitroso compound **20** which leads to significantly enhanced *trans* selectivity in comparison with the same reaction performed under non-aqueous conditions. The alternative crucial feature of this approach is the elaboration of the propyl side-chain by means of the completely stereocontrolled tandem procedure involving a Grignard addition–reduction process. Preparation of the *cis*-decahydroquinoline with the β-methyl group at C-5 necessary for the synthesis of (−)-pumiliotoxin C **1** has been achieved efficiently in one pot by a tandem sequence involving Lewis acid-promoted epimerization using $Zn(OTf)_2$ followed by dithioketalization.

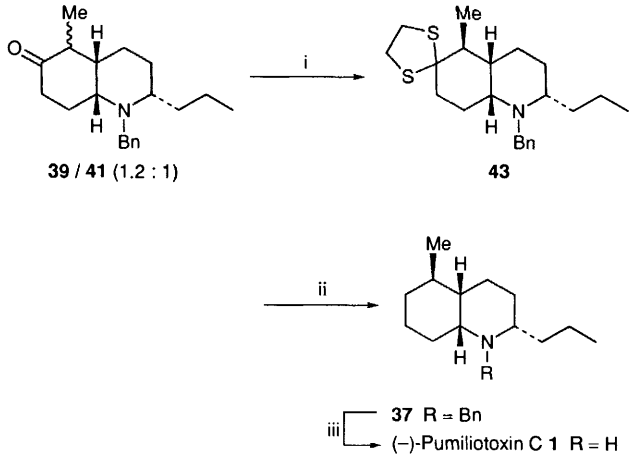
Experimental

Mps were determined by using a Yanaco MP-500D micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 digital polarimeter in a 1 dm cell and are recorded in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer. ^1H and ^{13}C NMR spectra were obtained for solutions in deuteriochloroform with a Varian Gemini-300, or a Bruker AM-400 or an AM-500 instrument. Mass spectra were measured on a Hitachi M-80 or a VG Auto Spec spectrometer at 70 eV. TLC was performed on pre-coated Merck silica gel 60 F_{254} plates, and Merck silica gel 60 (230–400 mesh) (Merck) was used for column chromatography. Microanalyses were carried out in the Microanalytical Laboratory of this University.

Table 1 Diastereoselective intramolecular hetero Diels–Alder reaction of *N*-acylnitoso compound **20**

Solvent	**21**:**22**	Yield (%)
$CHCl_3$[a]	1.4:1	87
H_2O–DMSO (5:1)	4.1:1	75
H_2O–DMSO (5:1) + α-cyclodextrin	4.1:1	84
H_2O–MeOH (5:1)	4.5:1	80

[a] Result previously obtained by using the (*R*)-enantiomer of **19** (ref. 12).



Scheme 9 *Reagents:* i, $Zn(OTf)_2$, CH_2Cl_2, reflux, 4 days, then $(CH_2SH)_2$, reflux, 24 h (66%); ii, Raney Ni (68%); iii, H_2, Pd–C (92%)

(5*E*,7*E*,*S*)-Deca-5,7-dien-4-olide (*E*)-8

A solution of KOBu^t (10.7 g, 95.0 mmol) in THF (180 cm^3) was added to a stirred suspension of pent-2-enyl(triphenyl)phosphonium bromide (41.8 mg, 102 mmol) and the mixture was stirred at room temperature for 30 min under Ar, during which time it turned deep red. To this was added dropwise a solution of (*S*)-5-oxooxolane-2-carbaldehyde **7**[17] (5.40 g, 47.5 mmol) in THF (70 cm^3) at room temperature over 5 min. After the mixture had been stirred for 7.5 h it was cooled to 0 °C, diluted with water (30 cm^3), stirred for 5 min, diluted with Et_2O (600 cm^3), washed with brine, dried ($MgSO_4$) and evaporated. Purification of the residue by chromatography on silica gel (hexane–Et_2O, 4:1) gave a colourless oil which was found to be a 1.3:1 mixture of 5*E*- and 5*Z*-**8** by ^1H NMR analysis. A solution of this mixture in benzene (100 cm^3) containing I_2 (10 mg) was irradiated through Pyrex with a 100 W high-pressure Hg lamp for 30 min and then washed with 10% aqueous $Na_2S_2O_3$ and water, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 1:1) gave (*E*)-**8** (3.17 g, 58%) as a colourless oil, bp 135–140 °C (2 mmHg); $[\alpha]_D^{25}$ +17.2 (*c* 1.55 in $CHCl_3$); δ_H 1.02 (3 H, t, *J* 7.5), 1.88–1.93 (1 H, m), 2.31–2.41 (1 H, q, *J* 7.1), 5.57 (1 H, dd, *J* 15.2 and 7.1), 5.83 (1 H, dt, *J* 15.2 and 6.5), 6.03 (1 H, ddd, *J* 15.2, 10.4 and 1.2) and 6.28 (1 H, dd, *J* 15.1 and 10.4); *m*/*z* (EI) 166 (M^+, 69%), 137 (94), 124 (16), 109 (44) and 93 (52) (Found: C, 72.3; H, 8.5. Calc. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49%). This material was estimated to have a 40% ee by conversion into the corresponding (*S*)-MTPA ester of **9** and HPLC analysis (see below).

Methyl (5*E*,7*E*,*S*)-4-hydroxydeca-5,7-dienoate 9

A solution of compound (*E*)-**8** (1.00 g, 6.02 mmol) in 5% aqueous KOH–MeOH–THF (1:9:10; 15 cm^3) was stirred at room temperature for 2.5 h, after which it was evaporated under reduced pressure, treated with 0.5 mol dm^{-3} phosphate

buffer (pH 6.2; 20 cm^3) and extracted with Et_2O (2 × 20 cm^3). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford a colourless oil (963 mg). This was dissolved in Et_2O (10 cm^3) and treated dropwise with a solution of diazomethane in Et_2O at 0 °C until a yellowish colour persisted. After being stirred at 0 °C for an additional 20 min and then at room temperature for 1 h, the mixture was washed with brine, dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (hexane–Et_2O, 4:1) gave the title compound **9** (868 mg, 75%) as a colourless oil; δ_H 1.00 (3 H, t, *J* 7.5), 1.85–1.90 (2 H, m), 2.08–2.12 (2 H, m), 2.42 (2 H, td, *J* 7.4 and 1.7), 3.66 (3 H, s), 4.17 (1 H, q, *J* 6.6), 5.56 (1 H, dd, *J* 15.2 and 6.6), 5.75 (1 H, dt, *J* 15.1, 6.6), 6.01 (1 H, ddt, *J* 15.1, 10.3 and 1.2) and 6.20 (1 H, dd, *J* 15.2 and 10.3); δ_C 13.4, 25.7, 30.1, 32.1, 51.7, 71.9, 128.4, 131.5, 132.6, 137.4 and 174.3 (Found: C, 66.3; H, 9.15. Calc. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%). This material was estimated to have a 40% ee by conversion into the (*S*)-MTPA ester by treatment with (*S*)-(−)-methoxy(trifluoromethyl)-phenylacetyl chloride,[20] followed by HPLC analysis using a Shimpack CLC-SIL column and elution with hexane–AcOEt (9:1).

Methyl (5*E*,7*E*,*S*)-4-(methoxymethoxy)deca-5,7-dienoate 10

A mixture of compound **9** (839 mg, 4.23 mmol), *N*,*N*-diisopropylethylamine (820 mg, 6.34 mmol), and chloromethyl methyl ether (510 mg, 6.33 mmol) in CH_2Cl_2 (20 cm^3) was heated at 60 °C for 10 h after which it was diluted with CH_2Cl_2 (40 cm^3), washed with 5% aqueous HCl and water, dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (hexane–Et_2O, 9:1) gave the title compound **10** (937 mg, 91%) as a colourless oil; δ_H 0.99 (3 H, t, *J* 7.0), 1.88 (2 H, quint, *J* 7.4), 2.08 (2 H, quint, *J* 7.4), 2.37–2.41 (2 H, m), 3.65 (3 H, s), 4.03 (1 H, q, *J* 7.4), 4.48 and 4.68 (2 H, AB q, *J* 6.7), 5.35 (1 H, dd, *J* 15.2 and 7.4), 5.73 (1 H, dt, *J* 15.2 and 7.4), 6.01 (1 H, dd, *J* 15.2 and 10.4) and 6.05 (1 H, dd, *J* 15.2 and 10.4); δ_C 13.4, 25.7, 30.1, 30.7, 51.5, 55.4, 75.5, 93.5, 128.2, 129.6, 133.8, 137.5 and 173.9 (Found: C, 64.6; H, 9.1. Calc. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15%).

(5*E*,7*E*,*S*)-*N*-Hydroxy-4-(methoxymethoxy)deca-5,7-dienamide 11

A solution of KOH (2.03 g, 31.0 mmol) in MeOH (6.6 cm^3) was added to a stirred solution of hydroxylamine hydrochloride (1.08 mg, 15.5 mmol) in MeOH (2 cm^3) at 0 °C and stirring was continued for 5 min. After this, a solution of compound **10** (927 mg, 3.87 mmol) in MeOH (4 cm^3) was added to the mixture which was then stirred for 30 min at 0 °C before being carefully neutralized with 5% aqueous HCl and extracted with CH_2Cl_2 (2 × 50 cm^3). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford a crude product, which was recrystallized from Et_2O–hexane to give the title compound **11** (802 mg, 85%) as colourless needles, mp 65–67 °C; δ_H 1.01 (3 H, t, *J* 7.0), 1.89 (2 H, q, *J* 7.0), 2.10 (2 H, quint, *J* 7.0), 2.28 (2 H, m), 3.37 (1 H, q, *J* 7.0), 4.03 (2 H, q, *J* 7.0), 4.54 and 4.66 (2 H, AB q, *J* 6.5), 5.37 (1 H, dd, *J* 15.2 and 7.0), 5.76 (1 H, dt, *J* 15.1 and 7.0), 6.01 (1 H, dd, *J* 15.1 and 10.4) and 6.16 (1 H, dd, *J* 15.2 and 10.4); δ_C 13.4, 25.7, 29.1, 31.1, 55.6, 76.3, 94.1, 128.2, 129.3, 133.8, 137.9 and 171.2; *m*/*z* (CI, isobutane) 242 ($M^+ - 1$).

(2*S*,4*S*)-4-(Hexa-1,3-dienyl)-2-phenyl-1,3-dioxane 13

To a stirred suspension of pent-2-enyl(triphenyl)phosphonium bromide (32.3 g, 78.5 mmol) in THF (100 cm^3) was added dropwise a solution of KOBu^t (8.24 g, 73.4 mmol) in THF (140 cm^3) at room temperature. Stirring was continued for 20 min under Ar, during which time a deep-red solution formed. To this was added a solution of compound **12**[20] (7.05 g, 36.7 mmol) in THF (70 cm^3) over 5 min and the resulting mixture was stirred at room temperature for 5 min. The reaction was quenched by addition of water (30 cm^3) at 0 °C to the mixture which was then diluted with Et_2O (400 cm^3), washed with brine (2 × 40 cm^3), dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 20:1) gave a 3:1 *Z*/*E* mixture (based on ^1H NMR) of the title compound **13** (8.56 g, 95%) as a colourless oil; δ_H 0.99–1.06 (3 H, m), 1.53–1.64 (2 H, m), 1.93–2.04 (1 H, m), 2.07–2.26 (1 H, m), 4.00–4.08 (1 H, m), 4.27–4.32 (1 H, m), 4.38–4.46 and 4.80–4.88 (total 1 H in 1:3 ratio, each m), 5.38–6.10 (4 H, m), 6.24–6.42 (1 H, m), 6.24–6.42 (1 H, m) and 7.30–7.54 (5 H, m) (Found: C, 78.5; H, 8.4. Calc. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25%).

(4*Z*,6*E*,3*S*)- and (4*E*,6*E*,3*S*)-3-Benzyloxynona-4,6-dienol (*Z*)-14 and (*E*)-14

To a stirred, cold (0 °C) solution of the above 3:1 *Z*/*E* mixture of **13** (8.31 g, 34.0 mmol) in CH_2Cl_2 (80 cm^3) was added dropwise DIBALH (0.93 mol dm^3 solution in hexane; 150 cm^3, 140 mmol) and the mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of 5% hydrochloric acid (1 cm^3) to the mixture at 0 °C, after which the resulting insoluble material was filtered off. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was chromatographed on silica gel (hexane–EtOAc, 9:1) to give a 3:1 *Z*/*E* mixture of the title compound **14** (7.20 g, 86%) as a colourless oil (Found: C, 78.0; H, 9.3. Calc. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%).

Data for (*Z*)-**14**: δ_C 14.1, 25.8, 38.0, 60.6, 73.8, 79.3, 127.87, 127.93 (2 carbons), 128.4 (2 carbons), 128.7, 130.9, 132.2, 136.4 and 139.2.

Data for (*E*)-**14**: see below.

Irradiation of the *Z*/*E* mixture of 14: preparation of pure (*E*)-14

A solution of the above 3:1 *Z*/*E* mixture of **14** (520 mg, 2.11 mmol) in benzene (500 cm^3) containing I_2 (3 mg) was irradiated through Pyrex with a 100 W high-pressure Hg lamp for 15 min. The mixture was washed with 5% aqueous $Na_2S_2O_3$ (100 cm^3) and water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 9:1) to give (*E*)-**14** (416 mg, 80%) as a colourless oil, $[\alpha]_D^{28}$ −62.2 (*c* 0.77 in $CHCl_3$); δ_H 1.04 (3 H, t, *J* 7.4), 1.76–1.94 (2 H, m), 2.14 (2 H, t, *J* 7.5), 3.73–3.81 (2 H, m), 4.04 (1 H, dt, *J* 8.1, 4.5), 4.35 and 4.61 (2 H, AB q, *J* 11.8), 5.53 (1 H, dd, *J* 15.3 and 8.2), 5.79 (1 H, dt, *J* 15.1 and 6.5), 6.08 (1 H, dd, *J* 15.3 and 10.3), 6.21 (1 H, dd, *J* 15.1 and 10.3) and 7.27–7.36 (5 H, m); δ_C 13.4, 25.7, 38.2, 60.7, 70.2, 79.4, 127.7, 127.8 (2 carbons), 128.3, 128.5 (2 carbons), 130.4, 133.4, 137.6 and 138.4; *m*/*z* (EI) 246 (M^+, 0.2%), 228 (0.8), 201 (6), 155 (23), 129 (2), 109 (9), 91 (100) and 73 (99) (Found: C, 78.0; H, 9.1. Calc. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%). The material obtained proved to be >99.5% ee by HPLC analysis of the corresponding (*S*)-MTPA ester.

(4*E*,6*E*,3*S*)-3-Benzyloxynona-4,6-dienyl toluene-*p*-sulfonate 15

To a cold (0 °C), stirred solution of **14** (102 mg, 0.414 mmol) in pyridine (0.6 cm^3) was added dropwise a solution of toluene-*p*-sulfonyl chloride (236 mg, 1.24 mmol) in pyridine (0.5 cm^3), and the mixture was stirred at 0 °C for 4 h. After this the mixture was poured into 10% aqueous hydrochloric acid (5 cm^3) and extracted with CH_2Cl_2 (2 × 10 cm^3). The combined extracts were washed with water (5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 19:1) provided the title compound **15** (157 mg, 95%) as a colourless oil, $[\alpha]_D^{30}$ −3.4 (*c* 0.10 in $CHCl_3$); δ_H 1.03 (3 H, t, *J* 7.5), 1.80–1.99 (2 H, m), 2.09–2.16 (2 H, m), 2.44 (3 H, s), 3.88 (1 H, td, *J* 8.2 and 5.0), 4.10 (1 H, dt, *J* 9.7 and 5.7), 4.19–4.25 (2 H, m with ½ AB q at δ 4.21, *J* 11.6), 4.51 (1 H, ½ AB q, *J* 11.6), 5.38

(1 H, dd, *J* 15.1 and 8.2), 5.76 (1 H, dt, *J* 14.9 and 6.6), 6.02 (1 H, ddt, *J* 14.9, 10.4 and 1.3), 6.13 (1 H, dd, *J* 15.1 and 10.4), 7.21–7.34 (8 H, m) and 7.76–7.79 (2 H, m); δ_C 13.4, 21.6, 25.6, 35.3, 67.4, 70.2, 76.0, 127.5, 127.7 (2 C), 128.0 (2 C), 128.2 (2 C), 128.7 (2 C), 129.8 (3 C), 134.0, 137.8, 138.5 and 144.6; *m/z* (EI) 400 (M^+, 0.5%), 309 (16), 227 (5), 201 (11), 156 (74), 137 (100) and 109 (33) (Found: M^+, 400.1699. Calc. for $C_{23}H_{28}SO_4$: *M*, 400.1708).

(4*E*,6*E*,4*S*)-4-Benzyloxydeca-5,7-dienenitrile 16

To a solution of compound **15** (96.4 mg, 0.241 mmol) in DMSO (1 cm^3) was added NaCN (15.3 mg, 0.313 mmol) and the mixture was stirred at 55 °C. After 1 h, the mixture was poured into ice–water (1 cm^3) and extracted with Et_2O (2 × 3 cm^3). The combined extracts were washed with water (2 × 2 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel (hexane–EtOAc, 10:1) gave the title compound **16** (57.1 mg, 93%) as a colourless oil, $[\alpha]_D^{27}$ −35.6 (*c* 1.00 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3027, 2933, 2872, 2246, 1658, 1497, 1455, 1095, 1067, 1028, 993, 738 and 699; δ_H 1.04 (3 H, t, *J* 7.5), 1.80–1.98 (2 H, m), 2.11–2.18 (2 H, m), 2.37–2.54 (2 H, m), 3.91 (1 H, dt, *J* 8.2, 5.0), 4.33 and 4.59 (2 H, AB q, *J* 11.6), 5.44 (1 H, dd, *J* 15.3 and 8.1), 5.82 (1 H, dt, *J* 15.2 and 6.5), 6.04–6.11 (1 H, m), 6.25 (1 H, dd, *J* 15.3 and 10.3) and 7.27–7.38 (5 H, m); δ_C 13.3, 13.5, 25.7, 31.5, 70.4, 77.7, 119.6, 127.7, 127.9 (2 C), 128.0, 128.5 (2 C), 129.1, 134.5, 138.2 and 138.3; *m/z* (EI) 255 (M^+ + 1, 0.6%), 226 (1), 201 (2), 183 (0.2), 164 (7), 150 (3), 107 (4), 91 (100), 77 (9) and 65 (9) (Found: C, 80.1; H, 8.3; N, 5.3. Calc. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49%).

(4*E*,6*E*,4*S*)-4-Benzyloxydeca-5,7-dienoic acid 17

To a solution of compound **16** (595 mg, 2.33 mmol) in MeOH (15 cm^3) was added 25% aqueous NaOH (12 cm^3) and the mixture was heated at reflux for 9 h. After the mixture had been allowed to cool to room temperature, it was acidified with 5% aqueous HCl (80 cm^3) and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined extracts were washed with brine (2 × 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 19:1) to give the title compound **17** (539 mg, 84%) as a colourless oil, $[\alpha]_D^{25}$ +38.4 (*c* 0.96 in $CHCl_3$); δ_H 1.03 (3 H, t, *J* 7.1), 1.83–2.00 (2 H, m), 2.13 (2 H, quint, *J* 7.1), 2.46 (2 H, t, *J* 7.6), 3.83 (1 H, td, *J* 7.9 and 5.5), 4.33 and 4.59 (2 H, AB q, *J* 11.8), 5.47 (1 H, dd, *J* 15.1 and 7.9), 5.78 (1 H, td, *J* 15.0 and 7.1), 6.06 (1 H, dd, *J* 15.0 and 10.4), 6.20 (1 H, dd, *J* 15.1 and 10.4) and 7.25–7.36 (5 H, m); δ_C 13.4, 25.7, 30.2, 30.7, 70.2, 78.7, 127.5, 127.8 (2 C), 128.4 (3 C), 130.4, 133.7, 137.5, 138.6 and 179.1; *m/z* (EI) 274 (M^+, 0.1%), 256 (0.4), 214 (0.1), 201 (2), 183 (13), 165 (7), 107 (5), 91 (100) and 65 (9) (Found: C, 74.3; H, 8.3. Calc. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08%).

Methyl (4*E*,6*E*,4*S*)-4-benzyloxydeca-5,7-dienoate 18

To a cold (0 °C), stirred solution of compound **17** (100 mg, 0.364 mmol) in Et_2O (2 cm^3) was added a solution of diazomethane in Et_2O until a yellowish colour persisted. After 15 min at 0 °C, the mixture was treated with AcOH until the yellowish colour disappeared when it was washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel (hexane–EtOAc, 19:1) to give the title compound **18** (92.4 mg, 88%) as a colourless oil, $[\alpha]_D^{24}$ −44.5 (*c* 1.12 in $CHCl_3$); δ_H 1.04 (3 H, t, *J* 7.3), 1.85–1.98 (2 H, m), 2.09–2.17 (2 H, m), 2.41 (2 H, td, *J* 7.4 and 1.7), 3.63 (3 H, s), 3.81 (1 H, td, *J* 7.7 and 5.7), 4.32 and 4.68 (2 H, AB q, *J* 11.9), 5.47 (1 H, dd, *J* 15.2 and 8.0), 5.78 (1 H, dt, *J* 15.0 and 7.0), 6.06 (1 H, ddt, *J* 15.0, 10.4 and 1.3), 6.19 (1 H, dd, *J* 15.2 and 10.4) and 7.24–7.36 (5 H, m); δ_C 13.4, 25.7, 30.2, 30.9, 51.5, 70.1, 78.8, 127.5, 127.9 (2 C), 128.3 (2 C), 128.2, 130.6, 133.5, 137.3, 138.6 and 174.0; *m/z* (EI) 288 (M^+, 0.1%), 271 (0.1), 257 (0.2), 239 (0.3), 211 (0.1), 197 (24), 165 (17), 115 (49), 91 (100) and 65 (7) (Found: C, 75.0; H, 8.6. Calc. for $C_{18}H_{24}O_3$: C, 74.86; H, 8.38%).

(4*E*,6*E*,4*S*)-4-Benzyloxy-*N*-hydroxyocta-5,7-dienamide 19

A solution of KOH (364 mg, 5.55 mmol) in MeOH (1 cm^3) was added to a solution of hydroxylamine hydrochloride (193 mg, 2.78 mmol) in MeOH (2 cm^3) at 0 °C and the mixture was stirred for 5 min. To this was added a solution of compound **18** (200 mg, 0.694 mmol) in MeOH (1 cm^3) at 0 °C and the resulting mixture was stirred at the same temperature for 30 min. The mixture was diluted with CH_2Cl_2 (15 cm^3) and neutralized with 5% aqueous HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 cm^3). The combined organic layers were washed with water (5 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 1:1) to give the title compound **19** (178 mg, 89%) as a colourless oil, $[\alpha]_D^{26}$ −42.1 (*c* 0.76 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3397, 3062, 2930, 1716, 1661, 1652, 1497, 1404, 1374, 1309, 1259, 1211, 1177, 1109, 1071, 1028, 741 and 700; δ_H 1.02 (3 H, t, *J* 7.4), 1.89 (2 H, q, *J* 7.0), 2.12 (2 H, quint, *J* 6.9), 2.17–2.25 (2 H, m), 3.79 (1 H, q, *J* 7.0), 4.29 and 4.57 (2 H, AB q, *J* 11.7), 5.44 (1 H, dd, *J* 15.2 and 7.0), 5.78 (1 H, dt, *J* 15.1 and 6.9), 6.05 (1 H, dd, *J* 15.1 and 10.4), 6.19 (1 H, dd, *J* 15.2 and 10.4) and 7.28–7.37 (5 H, m); δ_C 13.4, 25.7, 29.2, 31.1, 70.2, 78.8, 127.8, 128.0 (2 C), 128.3, 128.5 (2 C), 130.0, 133.8, 137.7, 138.3 and 171.2; *m/z* (CI, isobutane) 288 (M^+ − 1) (Found: C, 70.65; H, 8.13; N, 4.76. Calc. for $C_{17}H_{23}NO_3$: C, 70.6; H, 8.0; N, 4.8%).

Intramolecular acylnitroso Diels–Alder reaction of 19

(a) Cycloaddition in water–DMSO. To a stirred, cold (0 °C) suspension of compound **19** (36.1 mg, 0.125 mmol) in a 5:1 mixture (11 cm^3) of water and DMSO was added solid Pr_4NIO_4 (moistened with 10% water; 78.6 mg, 0.188 mmol) in one portion, and the mixture was vigorously stirred at 0 °C for 30 min. 10% Aqueous $Na_2S_2O_3$ (6 cm^3) was added to this mixture which was then briefly stirred to quench the periodate and extracted with $CHCl_3$ (2 × 20 cm^3). The combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure to give a crude oil, which was chromatographed on silica gel (hexane–EtOAc, 4:1) to afford a mixture of the cycloadducts **21** and **22** (combined yield: 26.9 mg, 75%) in a ratio of 4.1:1 (based on ^1H NMR) as a colourless oil. This mixture was separated by further chromatography on silica gel (CH_2Cl_2–acetone, 19:1), the first fractions affording (2R,4aR,5S)-5-*benzyloxy*-2-*ethyl*-2,4a,5,6,7,8-*hexahydropyrido*[1,2-b][1,2]*oxazin*-8-*one* **21** (21.1 mg, 59%) as a colourless oil, $[\alpha]_D^{22}$ −33.4 (*c* 1.57 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3035, 2835, 1674, 1455, 1403, 1359, 1309, 1108, 1058, 1029, 847 and 741; δ_H 1.07 (3 H, t, *J* 7.4), 1.49–1.59 (1 H, m), 1.65–1.84 (2 H, m), 2.16–2.22 (1 H, m), 2.38 (1 H, ddd, *J* 17.4, 12.4 and 5.9), 2.60 (1 H, ddd, *J* 17.4, 5.5 and 3.2), 3.43 (1 H, ddd, *J* 10.7, 8.8 and 3.5), 4.23–4.27 (2 H, m), 4.54 and 4.70 (2 H, AB q, *J* 11.5), 5.91–6.01 (2 H, m) and 7.30–7.39 (5 H, m); δ_C 10.6, 25.4, 27.1, 29.0, 60.5, 71.6, 76.7, 80.8, 123.6, 127.8 (2 C), 128.1, 128.6 (2 C), 128.8, 137.6 and 164.9; *m/z* 288 (CI, isobutane) (MH^+) (Found: M^+, 287.1544. Calc. for $C_{17}H_{21}NO_3$: *M* + H, 287.1521).

The second fractions afforded (2S,4aS,5S)-5-*benzyloxy*-2-*ethyl*-2,4a,5,6,7,8-*hexahydropyrido*[1,2-b][1,2]*oxazin*-8-*one* **22** (5.0 mg, 14%) as a colourless oil, which solidified on storage in a refrigerator. Recrystallization from benzene–hexane afforded colourless needles, mp 130–131 °C; $[\alpha]_D^{26}$ +121 (*c* 0.97 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2878, 1656, 1453, 1379, 1108, 961 and 735; δ_H 1.08 (3 H, t, *J* 7.4), 1.57–1.67 (1 H, m), 1.75–1.89 (2 H, m), 2.13–2.20 (1 H, m), 2.44 (1 H, ddd, *J* 17.0, 5.7 and 1.0), 2.73 (1 H, ddd, *J* 17.0, 13.4 and 6.1), 3.90 (1 H, br s), 4.27 (1 H, m), 4.45 (1 H, br s), 4.49 and 4.65 (2 H, AB q, *J* 12.1), 5.65 (1 H, d, *J* 10.3), 6.00 (1 H, ddd, *J* 10.3, 3.7 and 2.4) and 7.27–7.36 (5 H, m);

δ_C 0.6, 23.5, 27.0, 28.1, 60.9, 70.9, 73.2, 80.8, 123.0, 127.3 (2 C), 127.8, 128.4 (2 C), 129.1, 137.9 and 165.3; *m/z* (CI, isobutane) 288 (MH^+) (Found: C, 71.1; H, 7.3; N, 4.93. Calc. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.36; N, 4.87%).

(b) Cycloaddition in the presence of α-cyclodextrin. To a stirred suspension of compound **19** (30.0 mg, 0.115 mmol) in water–DMSO (5:1; 8.5 cm^3) was added α-cyclodextrin (112 mg, 0.115 mmol). After being stirred for 5 min the suspension was cooled to 0 °C and solid Pr_4NIO_4 (moistened with 10% water; 72.3 mg, 0.173 mmol) was added in one portion. The mixture was vigorously stirred for 10 min at 0 °C and then worked up according to the described above procedure, to afford a 4.5:1 mixture (by ^1H NMR) of the cycloadducts **21** and **22** (combined yield: 17.8 mg, 84%).

(c) Cycloaddition in water–methanol. To a stirred, cold (0 °C) suspension of compound **19** (24.5 mg, 0.0847 mmol) in water–MeOH (5:1; 8.5 cm^3) was added solid Pr_4NIO_4 (moistened with 10% water; 53.2 mg, 0.127 mmol) in one portion, and the mixture was vigorously stirred for 30 min at 0 °C. Work-up as described above afforded a 4.1:1 mixture (by ^1H NMR) of the cycloadducs **21** and **22** (combined yield: 25.0 mg, 84%).

(2*R*,4a*R*,5*S*)-5-Benzyloxy-2-ethyl-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazin-8-one 23

A mixture of compound **21** (1.30 g, 4.52 mmol) and 10% palladium-on-carbon (325 mg) in THF (91 cm^3) was stirred under H_2 at a balloon pressure for 30 min after which it was filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 2:1) afforded **23** (1.31 g, 100%) as a colourless oil, $[\alpha]_D^{24}$ +11.6 (*c* 0.27 in $CHCl_3$); δ_H 0.99 (3 H, t, *J* 7.5), 1.44–1.73 (3 H, m), 1.78–2.09 (5 H, m), 2.35 (1 H, ddd, *J* 17.1, 8.2 and 5.2), 2.64 (1 H, ddd, *J* 17.1, 7.9 and 5.1), 3.49 (1 H, ddd, *J* 7.8, 4.8 and 3.0), 3.72 (1 H, ddd, *J* 11.5, 4.8 and 3.3), 4.05 (1 H, q, *J* 6.4), 4.53 and 4.63 (2 H, AB q, *J* 11.8) and 7.29–7.38 (5 H, m); δ_C 10.8, 22.8, 23.6, 24.2, 26.4, 28.4, 62.8, 70.9, 77.2, 80.7, 127.6 (2 C), 127.9, 128.5 (2 C), 137.7 and 165.3; *m/z* (EI) 289 (M^+, 2%), 260 (1), 204 (20), 176 (12), 155 (5), 114 (36), 91 (100) and 64 (13) (Found: C, 70.4; H, 8.1; N, 4.8. Calc. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84%).

(2*R*,4a*R*,5*S*,8*S*)-5-Benzyloxy-2-ethyl-8-propyl-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazine 26

To a stirred THF solution (12 cm^3) of propylmagnesium bromide, prepared from 1-bromopropane (1.03 g, 8.37 mmol) and Mg (185 mg, 7.61 mmol), under Ar at 0 °C was added a solution of compound **23** (735 mg, 2.54 mmol) in THF (12 cm^3). The mixture was stirred at 0 °C for 1 h and then quenched by addition of 5% aqueous NaOH (10 cm^3). The mixture was filtered through a Celite pad and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 cm^3) and the combined organic layer and extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude enamine **24**, which was immediately dissolved in THF (12 cm^3) and acidified by addition of AcOH (0.5 cm^3). To this solution was added $NaBH_3CN$ (319 mg, 5.08 mmol) in small portions at 0 °C and the mixture was stirred for 30 min at 0 °C. After neutralization with 5% aqueous NaOH, the mixture was extracted with CH_2Cl_2 (2 × 40 cm^3), and the combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 19:1) afforded the title compound **26** (779 mg, 96%) as a colourless oil, $[\alpha]_D^{27}$ +69.4 (*c* 1.24 in $CHCl_3$); δ_H(conformers due to nitrogen inversion) 0.89 (3 H, t, *J* 7.1), 1.11–1.90 (14 H, m), 2.01–2.75 (2 H, m), 3.56 and 3.74 (total 1 H, in 2:1 ratio, m, and td, *J* 10.9 and 4.1, respectively), 3.08 and 3.91 (total 1 H in 1:2 ratio, td, *J* 10.5 and 4.9, each), 4.45 and 4.67 (2 H, AB q, *J* 11.7) and 7.25–7.35 (5 H, m); δ_C major conformer 10.0, 14.3, 19.9, 24.2, 25.5, 26.7, 28.2, 30.3, 35.3, 62.8, 63.1, 70.8, 71.2, 80.8, 127.6, 127.9 (2 C), 128.4 (2 C) and 138.8; sp^3 carbons of minor conformer 11.03, 14.51, 18.81, 23.25, 23.94, 26.52, 27.49, 29.14, 35.23, 64.17, 69.21, 71.26, 77.90 and 78.86; *m/z* (EI) 317 (M^+, 6%), 274 (47), 226 (27), 182 (4), 162 (6), 114 (61), 91 (100) and 69 (17) (Found: C, 75.61; H, 9.89; N, 4.47. Calc. for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41%).

(2*R*,3*S*,6*S*)-3-Benzyloxy-2-[(3*R*)-3-hydroxypentyl]-6-propylpiperidine 28

Zn dust (2.00 g, 31.0 mmol) was added in small portions at room temperature to a stirred solution of compound **26** (350 mg, 1.10 mmol) in 85% aqueous AcOH (3.5 cm^3) and the mixture was stirred at 60 °C for 1 h. After being allowed to cool to room temperature, the mixture was filtered through a Celite pad and the filtrate was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (2 × 10 cm^3). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$–10% methanolic NH_3, 50:1) to give the title compound **28** (319 mg, 91%) as a colourless oil, $[\alpha]_D^{28}$ +48.7 (*c* 1.31 in $CHCl_3$); δ_H 0.91 (3 H, t, *J* 7.2), 0.92 (3 H, t, *J* 7.4), 1.08–1.64 (11 H, m), 1.68–1.90 (4 H, m), 2.27 (1 H, dq, *J* 12.5 and 3.9), 2.54–2.59 (1 H, m), 2.68 (1 H, ddd, *J* 9.3, 6.8 and 2.7), 3.28 (1 H, td, *J* 10.5 and 4.1), 3.40–3.46 (1 H, m), 4.46 and 4.66 (2 H, AB q, *J* 11.5) and 7.25–7.35 (5 H, m); δ_C 10.4, 14.2, 19.3, 29.90, 29.92, 30.4, 31.1, 32.7, 38.7, 56.1, 60.3, 70.7, 73.0, 77.8, 127.6, 127.8 (2 C), 128.4 (2 C) and 138.8; *m/z* (CI, isobutane) 320 (MH^+) (Found: M^+, 319.2537. Calc. for $C_{20}H_{33}NO_2$: *M*, 319.2511).

(2*R*,3*S*,6*S*)-1-Benzoyl-3-benzyloxy-2-[(3*R*)-3-hydroxypentyl]-6-propylpiperidine 29

A solution of benzoyl chloride (285 mg, 1.67 mmol) in CH_2Cl_2 (1 cm^3) was added dropwise to a cold (0 °C), stirred solution of compound **28** (214 mg, 0.670 mmol) in CH_2Cl_2 (5 cm^3) including 10% aqueous K_2CO_3 (3 cm^3) and stirring was continued for 2 h at 0 °C. The mixture was extracted with CH_2Cl_2 (2 × 10 cm^3) and the combined extracts were washed with water (5 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. For saponification of the resulting *N,O*-dibenzoyl derivative, the product was treated with a mixture of 5% aqueous KOH (2.5 cm^3) and MeOH–THF (9:1, 2.5 cm^3) at room temperature. After being stirred for 1 h, the mixture was diluted with water (10 cm^3) and extracted with $CHCl_3$ (2 × 10 cm^3). The combined extracts were washed with water (5 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 2:1) gave the title compound **29** (277 mg, 98%) as a colourless oil, $[\alpha]_D^{28}$ −22.2 (*c* 1.05 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3423, 2932, 1718, 1598, 1428, 1113 and 739; δ_H(amide rotamers) 0.85 and 0.66 (total 3 H in 2:1 ratio, t, *J* 7.3, and t, *J* 7.4, respectively), 0.96–1.93 (17 H, m), 2.12–2.21 (1 H, m), 3.36–3.39 and 3.56 (total 1 H in 2:1 ratio, m and s, respectively), 3.73 and 3.82–3.89 (total 1 H in 1:2 ratio, m each), 4.36 and 4.54 (total 1 H in 1:2 ratio, ½ AB q, *J* 12.1, and ½ AB q, *J* 12.2, respectively), 4.54 and 4.64 (total 1 H in 1:2 ratio, ½ AB q, *J* 12.1, and ½ AB q, *J* 12.2, respectively), 4.71–4.79 and 4.87 (total 1 H in 1:2 ratio, m each) and 7.28–7.40 (10 H, m); *m/z* (EI) 423 (M^+, 3%), 380 (19), 336 (8), 258 (5), 216 (8), 105 (100), 91 (51) and 77 (23) (Found: C, 76.3; H, 8.8; N, 3.3. Calc. for $C_{27}H_{37}NO_3$: C, 76.56; H, 8.80; N, 3.31%).

(2*R*,3*S*,6*S*)-1-Benzoyl-2-[(3*R*)-3-hydroxypentyl]-6-propylpiperidine-3-ol 30

A suspension of 10% palladium-on-carbon (150 mg) in MeOH (6 cm^3) together with compound **29** (300 mg, 0.708 mmol) was stirred under H_2 at a balloon pressure for 30 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography

on silica gel (hexane–EtOAc, 2:1) afforded **30** (234 mg, 99%) as a colourless oil, $[\alpha]_D^{26}$ −9.8 (*c* 1.05 and $CHCl_3$); δ_H 0.66 (3 H, t, *J* 7.1), 0.85–1.07 (6 H, unresolved, containing 3 H, t, *J* 7.1 at δ 0.97), 1.20–1.80 (10 H, m), 1.89–1.96 (1 H, m), 2.11–2.16 (1 H, m), 3.24–3.35 (1 H, m), 3.71–3.81 (2 H, m), 4.68–4.76 (1 H, m) and 7.33–7.41 (5 H, br s); δ_C 9.7, 10.2, 20.2, 20.8, 21.5, 29.6, 30.6, 33.4, 37.1, 54.0, 56.2, 66.9, 67.3, 126.5 (2 C), 127.0 (2 C), 129.2, 137.1 and 173.8; *m/z* (EI) 333 (M^+, 1%), 315 (0.6), 290 (13), 246 (12), 168 (20), 122 (3), 105 (100) and 83 (37) (Found: M^+, 333.2305. Calc. for $C_{20}H_{31}NO_3$: *M*, 333.2304).

(2*R*,6*S*)-1-Benzoyl-2-(3-oxopentyl)-6-propylpiperidine-3-one 31

A solution of **30** (218 mg, 0.654 mmol) in CH_2Cl_2 (22 cm^3) was added to a stirred mixture of pyridinium chlorochromate (1.40 g, 6.49 mmol) and powdered 3 Å molecular sieves (1.1 g) in CH_2Cl_2 (70 cm^3), and the mixture was stirred at room temperature for 2 h; it was then diluted with Et_2O (350 cm^3). $MgSO_4$ (3.5 g) was added to this mixture and the suspension was stirred for 10 min before filtration through a Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane–EtOAc, 4:1) to give the title compound **31** (158 mg, 74%) as a colourless oil, $[\alpha]_D^{24}$ −38.7 (*c* 1.29 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2960, 1730, 1640, 1420, 1160, 1120 and 795; δ_H(amide rotamers) 0.72–1.25 (7 H, m), 1.31–1.69 (4 H, m), 1.85–1.99 (2 H, m), 2.16–2.85 (7 H, m), 3.96 (1 H, br s), 4.46 and 4.96 (total 1 H in 1:1 ratio, each br s) and 7.24–7.41 (5 H, m); *m/z* (EI) 329 (M^+, 10%), 244 (2), 224 (15), 208 (4), 168 (5), 136 (4), 105 (100) and 77 (39) (Found: C, 72.7; H, 8.4; N, 4.2. Calc. for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25%).

(2*S*,4a*RS*,5*RS*,8a*R*)-1-Benzoyl-4a-hydroxy-5-methyl-2-propyldecahydroquinolin-6-one 32

A solution of compound **31** (18.4 mg, 0.0559 mmol) in EtOH (0.1 cm^3) was added by syringe to a cold (0 °C), stirred 2 mol dm^{-3} ethanolic KOH (0.1 cm^3). After being stirred at 0 °C for 10 min the mixture was treated with 10% aqueous NH_4Cl (0.5 cm^3) and extracted with $CHCl_3$ (2 × 10 cm^3). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 4:1). The initial fractions contained recovered starting material **31** (2.3 mg, 13%) whilst later ones afforded the title compound **32** (13.7 mg, 74% or 85% based on starting material recovered) as a pale yellow oil, ν_{max}(neat)/cm^{-1} 3330, 2950, 1705, 1605, 1430, 1260, 1230, 1200 and 710; δ_H 0.67 (3 H, br s), 0.87–1.05 (5 H, m), 1.26–1.58 (5 H, m), 1.68–2.59 (6 H, m), 3.47–4.93 (3 H, m) and 7.34–7.55 (5 H, m); *m/z* (EI) 329 (M^+, 2%), 311 (3), 286 (16), 164 (5), 105 (100) and 77 (35) (Found: $M^+ - H_2O$, 311.1902. Calc. for $C_{20}H_{25}NO_2$: $M - H_2O$, 311.1885).

(2*S*,8a*R*)-1-Benzoyl-5-methyl-2-propyl-1,2,3,4,6,7,8,8a-octahydroquinolin-6-one 33

1 mol dm^{-3} Aqueous $KHSO_4$ (10 cm^3) was added to a solution of compound **32** (1.06 g, 3.22 mmol) in MeOH (20 cm^3) and the mixture was stirred at room temperature for 2 days. After this it was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$ (2 × 30 cm^3). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 4:1) with the initial fractions providing the title compound **33** (506 mg, 50% or 72% based on starting material recovered) as a colourless oil which solidified on storage in a refrigerator. A sample of this compound when recrystallized from Et_2O–hexane afforded colourless fine needles, mp 80–82 °C $[\alpha]_D^{26}$ −100.9 (*c* 0.43 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2955, 1714, 1418, 1378, 1325, 1167 and 739; δ_H 0.77 (3 H, t, *J* 7.0), 1.11–1.26 (2 H, m), 1.36 (1 H, sextet, *J* 7.0), 1.52–1.60 (3 H, m), 1.82 (3 H, s), 2.15–2.79 (6 H, m), 3.89 (1 H, br s), 5.24 (1 H, br s), 7.34–7.42 (5 H, m); δ_C 10.6, 13.4, 19.2, 24.3, 27.6, 30.1, 37.0, 38.3, 52.9, 53.9, 125.9 (2 C), 128.3 (2 C), 129.0, 130.5, 145.1, 154.6, 175.2 and 196.8; *m/z* (EI) 311 (M^+, 5%), 105 (100) and 77 (57) (Found: C, 77.0; H, 8.3; N, 4.5. Calc. for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50%).

Starting material **32** was recovered (317 mg, 30%) from later fractions.

(2*S*,4a*S*,5*R*,8a*R*)-1-Benzoyl-5-methyl-2-propyldecahydroquinolin-6-one 34

A suspension of 10% palladium-on-carbon (125 mg) in a mixture of MeOH (4.3 cm^3) and 1 mol dm^{-3} aqueous hydrochloric acid (0.8 cm^3) containing compound **33** (255 mg, 0.819 mmol) was stirred under H_2 at balloon pressure for 30 min. After removal of the catalyst by filtration, the methanolic solution was concentrated under reduced pressure and the residue was neutralized with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2 (2 × 10 cm^3). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 4:1) gave the title compound **34** (183 mg, 71%) as a colourless oil which was crystallized on storage. Recrystallization of this from Et_2O–hexane afforded colourless fine needles, $[\alpha]_D^{30}$ −32.8 (*c* 0.27 in $CHCl_3$); mp 95–101 °C; δ_H(amide rotamers) 0.65 and 0.78–1.00 (total 3 H in 2:1 ratio, t, *J* 7.2 and m, respectively), 1.02 (3 H, d, *J* 6.8), 1.22–1.49 (3 H, m), 1.53–1.74 (5 H, m), 1.78–1.93 (1 H, m), 2.04–2.39 (4 H, m), 2.54–2.63 and 2.83–2.89 (total 1 H in 2:1 ratio, m each), 3.73–3.82 and 4.14–4.19 (total 1 H in 2:1 ratio, m each), 4.76–4.78 and 5.22–5.27 (total 1 H in 1:2 ratio, m each) and 7.30–7.45 (5 H, m); *m/z* (EI) 313 (M^+, 5%), 301 (2), 270 (19), 258 (100), 242 (21), 149 (5), 105 (42) and 91 (49) (Found: C, 76.7; H, 8.9; N, 4.5. Calc. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47%).

(2*S*,4a*S*,5*RS*,8a*R*)-1-Benzoyl-5-methyl-2-propyldecahydroquinoline 35

Zn dust (88.9 mg, 1.36 mmol) was added to a cold (−20 °C), stirred solution of compound **34** (52.9 mg, 0.169 mmol) in a saturated ethereal solution (1.5 cm^3) of gaseous HCl after which the mixture was allowed to warm to 0 °C at which temperature it was stirred for 2 h. After this the mixture was slowly poured onto crushed ice. The organic layer was separated, and the aqueous layer was extracted with Et_2O (10 cm^3). The combined extracts were washed with brine (5 cm^3), dried, and concentrated and the resulting oil was chromatographed on silica gel (hexane–EtOAc, 9:1) to afford the title compound **35** (28.6 mg, 57%) as a colourless oil, which was found to be a 2:1 mixture of 5*R*- and 5*S*-isomers according to ^1H NMR analysis; δ_H 0.63–0.99 (6 H, m), 1.32–1.84 (16 H, m), 3.67–3.73 and 3.49–3.55 (total 1 H in 2:1 ratio, m each), 4.27–4.32 and 4.60–4.78 (total 1 H in 1:2 ratio, m each) and 7.31–7.37 (5 H, m).

$LiAlH_4$ Reduction of compound 35

$LiAlH_4$ (13.5 mg, 0.356 mmol) was added to an ice-cold, stirred solution of compound **35** (21.3 mg, 0.0711 mmol) in THF (2 cm^3) and the mixture was heated at reflux for 2 h. After being cooled to 0 °C, the mixture was quenched by the addition of saturated aqueous $NaHCO_3$. The resulting slurry was filtered through a Celite pad and the solid white residue was washed with THF (10 cm^3). The combined filtrates were dried (K_2CO_3) and concentrated under reduced pressure and the residue was chromatographed on silica gel (hexane–EtOAc, 50:1) to give a 2:1 (based on ^1H NMR) mixture of compounds **36** and **37** as a colourless oil (combined yield: 16.9 mg, 83%). This mixture was separated by further chromatography on silica gel (hexane–benzene, 2:1). The initial fractions afforded (2S,4aS,5R,8aR)-1-*benzyl*-5-*methyl*-2-*propyldecahydroquinoline* **37** (5.6 mg, 28%), $[\alpha]_D^{25}$ +14.2 (*c* 0.07 in $CHCl_3$); δ_H 0.83 (3 H, t, *J* 7.3), 0.86 (3 H, d, *J* 6.8), 0.97–1.06 (1 H, m), 1.10–1.52 (9 H, m), 1.56–1.66 (3 H, m), 1.80–1.91 (2 H, m), 1.94–2.03 (1 H, m), 2.32–2.37 (1 H, m),

2.60–2.63 (1 H, m), 3.69 and 3.77 (2 H, AB q, J 6.4) and 7.17–7.39 (5 H, m); δ_C 14.5, 19.6, 19.9, 21.2, 25.5, 27.3, 29.8, 30.3, 34.1, 36.9, 44.0, 56.6, 61.2, 61.5, 126.0 (2 C), 127.9 (2 C), 129.5 and 142.5; m/z (EI) 285.7 (M^+, 3%), 270.6 (3), 256.6 (1), 242.6 (100), 197.4 (0.1), 172.4 (0.4), 91.2 (54) and 55.1 (7) (Found: M^+, 285.2449. Calc. for $C_{20}H_{31}N$: M, 285.2457).

Later fractions afforded (2S,4aS,5S,8aR)-1-*benzyl*-5-*methyl*-2-*propyldecahydroquinoline* **36** (10.9 mg, 54%) as a colourless oil, $[\alpha]_D^{26}$ +4.1 (c 0.97 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2928, 1454, 1160, 736 and 698; δ_H 0.88 (3 H, t, J 7.6), 0.89 (3 H, d, J 6.9), 0.98–1.11 (2 H, m), 1.19–1.84 (14 H, m), 2.58–2.70 (2 H, m), 3.78 and 3.82 (2 H, AB q, J 14.3) and 7.18–7.41 (5 H, m); δ_C 14.2, 14.5, 19.4, 21.9, 25.4, 25.8, 28.3, 29.7, 33.5, 35.8, 41.9, 56.5, 56.8, 60.4, 126.5, 128.1 (2 C), 128.3 (2 C) and 129.1; m/z (EI) 285.2 (M^+, 5%), 268.2 (1), 256.1 (4), 242.2 (100) and 91 (60) (Found: C, 84.3; H, 11.0; N, 5.0. Calc. for $C_{20}H_{31}N$: C, 84.15; H, 10.95; N, 4.91%).

(2*S*,4a*S*,5*S*,8a*R*)-5-Methyl-2-propyldecahydroquinoline (5-*epi*-pumiliotoxin C) 2

10% Palladium-on-carbon (2.5 mg) was added to a solution of compound **36** (10.1 mg, 0.0354 mmol) in 5% methanolic gaseous HCl (1.2 cm^3) and the mixture was stirred under H_2 at balloon pressure for 12 h. Removal of the catalyst by filtration and evaporation of the filtrate left an oily product, which was thoroughly rinsed with Et_2O and dried *in vacuo* (0.1 mmHg) to afford the hydrochloride salt of **2** (7.5 mg, 91%) as a gummy product, $[\alpha]_D^{26}$ 0.0 (c 0.73 in MeOH); δ_H 0.85–1.06 (6 H, m), 1.19–2.28 (15 H, m) and 3.39–3.64 (2 H, m); δ_C 12.8, 13.9, 18.7, 20.9, 24.8, 25.4, 25.8, 28.3, 34.3, 34.7, 38.2, 52.2 and 55.6; m/z (EI) 242.2 (31), 194.2 (M^+, 19%), 180.2 (15), 166.1 (9), 152.1 (100), 135.1 (8) and 109.1 (38) (Found: M^+, 195.1994. Calc. for $C_{13}H_{25}N$: M, 195.1987).

(2*S*,4a*S*,5*R*,6*RS*,8a*R*)-1-Benzyl-5-methyl-2-propyldecahydroquinolin-6-ol 42

$LiAlH_4$ (42 mg, 1.1 mmol) was added to an ice-cold, stirred solution of compound **34** (68.9 mg, 0.220 mmol) in THF (7 cm^3) and the mixture was heated at reflux for 2 h. With ice-cooling, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$. The resulting slurry was filtered through a Celite pad and the solid residue was washed with THF (20 cm^3). The combined THF solutions were dried (K_2CO_3) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 9:1) to give the title compound **42** (57.6 mg, 87%) as a colourless oil, δ_H 0.80–1.13 (6 H, m), 1.16–1.95 (10 H, m), 2.12–2.20 (4 H, m), 2.59–2.69 (2 H, m), 3.58–3.86 and 3.34 (total 3 H in 8:1 ratio, m and td, J 10.6 and 4.2) and 7.16–7.38 (5 H, m).

Swern oxidation of compound 42

A solution of dimethyl sulfoxide (19.5 mg, 0.250 mmol) in CH_2Cl_2 (0.1 cm^3) was added by syringe to a solution of oxalyl chloride (15.9 mg, 0.125 mmol) in CH_2Cl_2 (0.2 cm^3) at −78 °C, and the mixture was stirred for 1 h at this temperature. To this mixture was added dropwise a solution of compound **42** (18.8 mg, 0.0624 mmol) in CH_2Cl_2 (0.2 cm^3) and stirring was continued at −78 °C for 2 h. After addition of triethylamine (37.8 mg, 0.374 mmol), the mixture was allowed to warm to room temperature and stirring was continued for a further 1 h. The mixture was then diluted with CH_2Cl_2 (5 cm^3), washed with water (2 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 9:1) provided a 1.2:1 mixture (based on ^{1}H NMR) of compounds **39** and **41** as a colourless oil (combined yield: 15.8 mg, 84%). This mixture was separated by further chromatography on silica gel (hexane–EtOAc, 9:1), the initial fractions affording (1S,4aS,5S,8aR)-1-*benzyl*-5-*methyl*-2-*propyldecahydroquinolin*-6-*one* **41** (7.1 mg, 38%) as a colourless oil, $[\alpha]_D^{24}$ +12.5 (c 0.47 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2930, 1714, 1455, 1261, 1028, 802, 738 and 700; δ_H 0.87 (3 H, t, J 7.3), 0.99 (3 H, d, J 6.7), 1.12–1.27 (3 H, m), 1.40–1.89 (7 H, m), 2.13–2.42 (3 H, m), 2.71 (1 H, q, J 3.1), 2.96–3.07 (1 H, dt, J 17.4 and 6.7), 3.28–3.32 (1 H, m), 3.66 and 3.92 (total 2 H, AB q, J 17.8) and 7.17–7.40 (5 H, m); δ_H 11.3, 14.5, 19.6, 25.9, 26.3, 30.3, 36.9, 37.6, 43.2, 45.5, 56.7, 61.4, 62.1, 126.4, 127.6 (2 C), 128.2 (2 C), 141.8 and 214.7; m/z (EI) 299 (M^+, 1%), 287 (0.6), 276 (4), 256 (100), 242 (22), 91 (73) and 41 (5) (Found: M^+, 299.2252. Calc. for $C_{20}H_{29}NO$: M, 299.2249).

Later fractions afforded (1S,4aS,5R,8aR)-1-*benzyl*-5-*methyl*-2-*propyldecahydroquinolin*-4-*one* **39** (8.5 mg, 45%) as a colourless oil, $[\alpha]_D^{24}$ −47.1 (c 0.51 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2931, 1714, 1454, 1160, 1071, 1028, 740 and 699; δ_H 0.84 (3 H, t, J 7.1), 0.97 (3 H, t, J 6.8), 1.05–1.29 (5 H, m), 1.40–1.92 (6 H, m), 2.14–2.33 (3 H, m), 2.61 (1 H, quint, J 6.4), 2.69 (1 H, s), 3.14–3.17 (1 H, m), 3.81 and 3.85 (2 H, AB q, J 14.2) and 7.23–7.39 (5 H, m); δ_C 11.3, 14.3, 16.1, 21.8, 26.2, 27.9, 33.7, 40.2, 44.9, 47.3, 56.6, 57.1, 58.1, 126.8 (2 C), 127.7, 128.2, 128.3 (2 C) and 213.1; m/z (EI) 299 (M^+, 1%), 256 (100), 242 (27), 91 (80), 55 (5) and 41 (6) (Found: C, 80.0; H, 9.7; N, 4.7. Calc. for $C_{20}H_{29}NO$: C, 79.95; H, 10.06; N, 4.66%).

(2*S*,4a*S*,5*S*,8a*R*)-1-Benzoyl-5-methyl-2-propylspiro-[decahydroquinoline-6-2′-1′,3′-dithiolane] 43

To a solution of the above 1.2:1 mixture of **39** and **41** (4.4 mg, 0.014 mmol) in CH_2Cl_2 (3 cm^3) was added a solution of $Zn(OTf)_2$ (5.4 mg, 0.015 mmol) in CH_2Cl_2 (0.4 cm^3) and the mixture was heated at reflux for 4 days. Ethanedithiol (1.7 mg, 0.018 mmol) added to the mixture which was then heated at reflux for additional 24 h. After the mixture had been diluted with CH_2Cl_2 (5 cm^3) it was washed with saturated aqueous $NaHCO_3$ (3 cm^3) and water (3 cm^3), dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel (hexane–EtOAc, 1:1) afforded the title compound **43** (3.72 mg, 66%) as a colourless oil, $[\alpha]_D^{25}$ −4.1 (c 0.47 in $CHCl_3$); δ_H 0.82 (3 H, t, J 7.2), 1.10 (3 H, d, J 6.6), 1.15–1.67 (9 H, m), 1.86–1.95 (2 H, m), 2.10–2.17 (2 H, m), 2.22–2.31 (1 H, m), 2.49–2.52 (1 H, m), 2.60 (1 H, dq, J 10.9 and 6.6), 3.08–3.24 (4 H, m), 3.61–3.79 (2 H, AB q, J 17.1) and 7.26–7.37 (5 H, m); δ_C 11.9, 14.5, 19.3, 26.7, 27.2, 30.3, 38.0, 38.6, 39.0, 39.1, 40.6, 43.6, 56.8, 62.3, 63.0, 76.5, 126.1, 127.7 (2 C), 128.8 (2 C) and 142.4; m/z (EI) 375 (M^+, 2%), 332 (100), 272 (14), 256 (5), 242 (11), 194 (6), 167 (17), 149 (48), 105 (16), 91 (67), 70 (20) and 57 (27) (Found: M^+, 374.2075. Calc. for $C_{22}H_{33}NS_2$: M, 375.2054).

Desulfurization of the dithioacetal 43

A dense Raney nickel (W-7) suspension in EtOH (0.15 cm^3) was added to a solution of compound **43** (3.5 mg, 9.3 mmol) in dioxane (1 cm^3) and the mixture was stirred and heated at reflux for 3 days. The mixture was then filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane–EtOAc, 9:1) to give compound **37** (1.8 mg, 68%) as a colourless oil. The data for this material agreed with those of the material derived from **35** by $LiAlH_4$ reduction as previously described.

(2*S*,4a*S*,5*R*,8a*R*)-5-Methyl-2-propyldecahydroquinoline-[(−)-pumiliotoxin C] 1

A mixture of compound **37** (15.7 mg, 0.055 mmol), 10% palladium-on-carbon (4.1 mg) and a 5% methanolic solution (1.6 cm^3) of gaseous HCl was stirred under an atmosphere of hydrogen at balloon pressure for 12 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give a colourless solid, which was recrystallized from EtOH–EtOAc to afford the hydrochloride salt of **1** (11.7 mg, 92%) as colourless needles, mp 284–288 °C (lit.,[10b] 286–288 °C); $[\alpha]_D^{26}$ −15.2 (c 0.46 in MeOH) {lit.,[10b] $[\alpha]_D^{21}$ −16.2 (c 1.00 in MeOH)}; ν_{max}(KBr)/cm^{-1} 3430, 2955, 2931, 2873, 2823, 2708, 1584, 1471, 1457 and 1443; δ_H 0.90 (3 H,

d, J 6.2), 0.93 (3 H, t, J 7.1), 1.23–2.52 (16 H, m), 2.92–3.04 (1 H, m) and 3.27–3.36 (1 H, m); δ_C 14.3, 19.6, 20.0, 21.3, 23.7, 25.3, 27.9, 29.9, 34.9, 35.4, 40.8, 58.9 and 60.7; m/z (FAB) 196 (MH^+) (Found: C, 67.2; H, 11.25; N, 6.0. Calc. for $C_{13}H_{25}N$·HCl: C, 67.36; H, 11.31; N, 6.04%).

Crystal data for and structure determination of compound 34

$C_{20}H_{27}NO_2$, M = 314.45, orthorhombic, space group $P2_12_12_1$, a = 7.998(3), b = 8.444(8), c = 26.589(2) Å, V = 1796(1) Å^3, Z = 4, D_c = 1.16 g cm^{-3}, $F(000)$ = 680, μ(Mo-Kα) = 0.664 cm^{-1}, crystal size 0.30 × 0.35 × 0.20 mm.

Intensity data were collected on a Mac Science DIP 2000 diffractometer with graphite-monochromated Mo-Kα X-radiation, λ = 0.707 13 Å. The data were corrected for Lorentz and polarization effects to yield 1211 results with $I > 3.0\sigma(I)$. The structure was solved by direct method using the SIR program.[25] Full-matrix least-squares refinement on F and all subsequent calculations were performed using Lsq program system.[26] The refinement converged with R = 0.0404 and R_w = 0.0467.

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