Photocyclisation of enamides. Part 39.[1,2] General strategy for the synthesis of pseudodistomins: synthesis of triacetates of (±)-tetrahydropseudodistomin and proposed structures of pseudodistomins A and B

Takeaki Naito,* Yoko Yuumoto, Toshiko Kiguchi and Ichiya Ninomiya

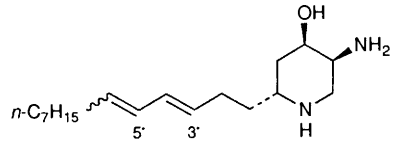
Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658, Japan

A synthetic strategy of pseudodistomin was developed by first synthesizing the (±)-(2α,4β,5β)-5-amino-2-(3-hydroxypropyl)piperidin-4-ol 14 as a key intermediate *via* a route involving the reductive photocyclisation of enamide 5 followed by the introduction of a three-carbon side-chain by application of an α-acylamino photo-induced radical allylation by allyltributyltin replacing a methylsulfanyl group. The key intermediate 14 was then converted into the piperidines 19 and 20, with a dienyl side-chain, which have the structures proposed for pseudodistomins A 1 and B 2. However, direct comparisons with the triacetates of the natural alkaloids have shown that a revision of the proposed structures is required.

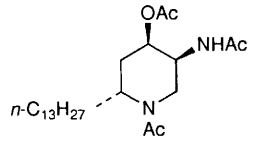
Introduction

Pseudodistomins A **1** and B **2**, potent antineoplastic piperidine alkaloids with calmodulin antagonistic activity, were isolated from the Okinawan tunicate *Pseudodistoma kanoko* as the first piperidine alkaloids from marine sources.[3] Their structures were proposed based only on UV, IR, ^{1}H and ^{13}C NMR and MS evidence.[3] In particular, ^{1}H and ^{13}C NMR spectra including decoupling experiments have established the relative configuration of the three substituents on the piperidine ring and the position and stereochemistry of the diene moiety in the side-chain. Absolute configuration was also deduced by applying the dibenzoate chirality method. Synthetic studies of pseudodistomins have so far been focused only on (±)-tetrahydropseudodistomin 'triacetate' **3**, by Natsume,[4] ourselves[2] and the Knapp group[5] who reported an asymmetric synthesis of (+)-tetrahydropseudodistomin[6] from D-serine that confirmed the absolute stereochemistry of the piperidine ring.[3]

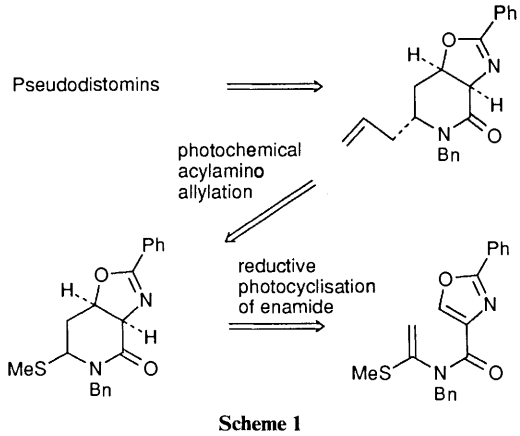
We now report in detail our investigations towards a general synthetic route for pseudodistomin and related compounds by preparing the 'triacetate' **3** of tetrahydropseudodistomin and then the proposed structures of natural alkaloids *via* a route involving two photochemical reactions; reductive photocyclisation of an enamide[7] for the construction of the piperidine ring, and acylamino photoallylation[8] for the introduction of a side-chain as shown in Scheme 1.



1 5'*Z*: Pseudodistomin A
2 5'*E*: Pseudodistomin B



3 Tetrahydropseudodistomin 'triacetate'

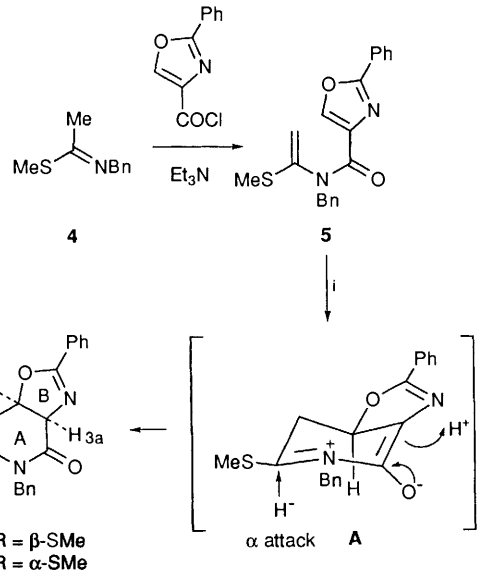


Scheme 1

Results and discussion

Preparation of 1-benzyl-5-benzylamino-2-(3-hydroxypropyl)-piperidin-4-ol *via* two steps of photochemical reaction

We chose 1-benzyl-5-benzylamino-2-(3-hydroxypropyl)-piperidin-4-ol **14** as a key synthetic intermediate which can be synthesized *via* a route involving two photochemical reactions. Acylation of the thioimidate **4**,[9] which was readily prepared from *N*-benzylacetamide, with 2-phenyloxazole-4-carbonyl chloride[10] in the presence of triethylamine gave the (methylsulfanyl)enamide **5** which was so unstable that, without purification, it was subjected to the following reductive photocyclisation. Irradiation of the enamide **5** in the presence of sodium boranuide in acetonitrile–methanol (85:15, v/v) at 0–5 °C by using a high-pressure mercury lamp (300 W) through a Pyrex filter afforded a mixture of two photocyclised lactams **6** and **7**, which were separated by medium-pressure column chromatography (MPLC) in 59 and 5% isolated yield, respectively, from the thioimidate **4** (Scheme 2). The structures of two products **6** and **7** were established from their spectral data. The two lactams **6** and **7** showed quasi-molecular ion peaks at *m/z* 353 and IR absorptions at 1656–1644 cm^{-1} (six-membered NCO), respectively. The ring junction of the lactams **6** and **7** as being A/B-*cis* juncture, that is, a *cis*-configuration of hydrogens at the 3a- and 7a-position, was deduced from a comparison of the coupling constant ($J_{3a,7a}$ 10 Hz) in ^{1}H NMR spectra with those (J 10–12 Hz) of the already known compounds[11] which were also prepared by reductive



Scheme 2 *Reagents and conditions:* i, $NaBH_4$, MeCN–MeOH, *hv*

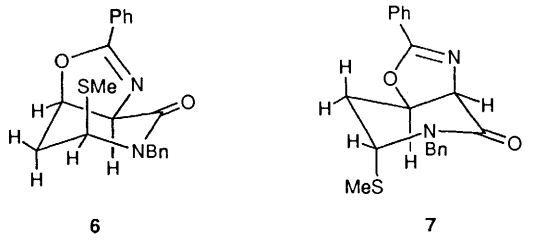


Fig. 1

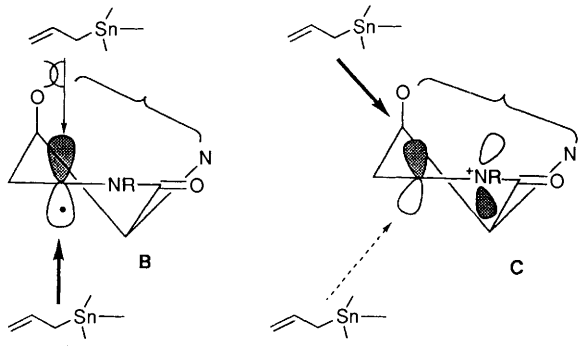


Fig. 2

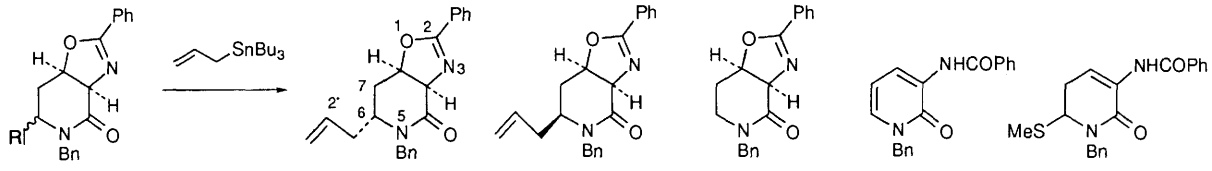
photocyclisation of enamides. Furthermore, a W-shaped long-range coupling signal between two hydrogens at the 6- and 7a-position in compound **6** and the signal of 7^{ax}-hydrogen at δ 1.93 (ddd, J 13.5, 10 and 3.5 Hz) in compound **7** clearly suggested the conformations of the lactams **6** and **7** as depicted in Fig. 1, which bear the methylsulfanyl group in an axial orientation. These two conformations would be reasonably explained by $A^{1,3}$-strain around the N-substituted lactam carbonyl group. Predominant formation of β-(methylsulfanyl)lactam **6** over α-isomer **7** would be explained in terms of hydride attack from the less hindered α-side in the cyclic intermediate **A**. Thus, we have succeeded in preparing the desired 2-substituted 4,5-*cis*-piperidines carrying protected amino and hydroxy groups in a *cis*-configuration.

Then, in order to introduce a C_3-unit into the adjacent position of nitrogen, we investigated the reaction of the (methylsulfanyl)lactams **6** and **7** with allyltributyltin under various conditions. According to the procedure reported by Fliri,[8a] we investigated the thermal radical reaction of the β-(methylsulfanyl)lactam **6** with allyltributyltin in the presence of azoisobutyronitrile (AIBN) which, however, did not give the desired product **9** but instead afforded the ring-opened products **12** and **13**. On the other hand, radical reaction [8] of the β-(methylsulfanyl)lactam **6** with allyltributyltin under photochemical conditions proceeded smoothly to give a mixture of three lactams **9**–**11** as follows. Irradiation of the β-(methylsulfanyl)lactam **6** with a high-pressure mercury lamp (100 W) through a Pyrex filter in the presence of allyltributyltin in acetonitrile–toluene (3:7) yielded the desired α-allyl lactam **9** with the formation of small amount of β-allyl isomer **10** and the hydrogenated lactam **11** in the yields shown in Table 1. Addition of a mixture of allyltributyltin (4–6 mol equiv.) and bis(tributyltin) (1 mol equiv.) followed by irradiation for 43 h gave a mixture of three products **9**–**11**. Photoallylation occurred slowly in the presence of only allyltributyltin and required 70 h of irradiation. However, the highest yield (40% yield) of the desired lactam **9** was obtained from the reaction in the absence of bis(tributyltin). In every case, a mixture of α- and β-allylated lactams **9** and **10** was obtained in the ratio ~2:1. Upon irradiation under the same reaction conditions as in entry 5, α-(methylsulfanyl)lactam **7** gave almost the same results, affording a mixture of three products **9**–**11** as in the case of β-(methylsulfanyl)lactam **6**. The structures of all products **9**–**11** were firmly established from their spectral data and by the chemical conversion of compound **9** into the final target compounds. The two allyl lactams **9** and **10** showed the same molecular ion peak at m/z 346, IR absorptions at 1644 cm^{-1} and ^1H NMR peaks at δ 5.71–4.99 due to three olefinic protons. Additionally, ^1H NMR peaks at δ 5.28 (td, J 10 and 6 Hz, 7a-H) and 1.76 (ddd, J 13.5, 10 and 4.5 Hz, 7-H^{ax}) in compound **9** and those at δ 5.17 (br dd, J 10.5 and 5 Hz, 7a-H) and 1.88 (dt, J 15.5 and 5 Hz, 7-H^{ax}) in compound **10** suggested the structures and configurations for these compounds as shown in Table 1.

As an alternative method for the introduction of the C_3-unit into the 2-position, we investigated the thermal ionic reaction of the sulfoxide of β-(methylsulfanyl)lactam **6** with allyltributyltin in the presence of Lewis acid. Oxidation of the lactam **6** with 3-chloroperbenzoic acid (MCPBA) gave the corresponding sulfoxide **8**. Treatment of the sulfoxide **8** with allyltributyltin in the presence of boron trifluoride–diethyl ether [8b] gave exclusively the β-allyl isomer **10**. Stereochemical difference between radical and ionic reactions would be explained as follows. In both cases, we propose two intermediates **B** and **C** which bear an oxygen function in the axial orientation based on conformational analysis of the hydrogenated lactam **11** (see Fig. 2). On the assumption that α-acylamino radical **B** would be planar (sp^2), we propose that the β-face would be sterically more hindered than its α-face, thus providing the α-allylated lactam **9** as major product. On the other hand, β-face-attack of allyltributyltin to *N*-acyliminium ion **C** would be stereoelectronically favourable, to give the β-allylated product **10**. Steric hindrance on the β-face would be negligible due to the direction of the lowest unoccupied molecular orbital (LUMO) which is not perpendicular to the carbon–nitrogen bond.[12]

Next, we investigated the conversion of the allyl lactam **9** into the piperidinepropanol **14** as the key intermediate in the pseudodistomin synthesis. Treatment of the lactam **9** with borane–tetrahydrofuran (THF) complex [13] followed by hydrogen peroxide and sodium hydroxide yielded the amino alcohol **14** as a result of oxidation of the allyl group to the propanol, reduction of the carbonyl group of the lactam to give the amine, and ring-opening of the oxazoline moiety to give the amino alcohol. The amino alcohol **14** showed the following spectra [m/z 354 (M^+); ν_{max} 3600–3200 cm^{-1} (OH and NH); δ 4.06 and 3.25 (2 H, ABq, J 13 Hz) and 3.67 and 3.60 (2 H, ABq, J 13 Hz) (NCH_2Ph), 3.92 (br q, J 4 Hz, 4-H) and 2.75 (br dt, J 9 and 4 Hz, 5-H)] which established the structure and configuration with 4β-axial hydroxy, 5β-equatorial amino and 2α-equatorial

Table 1 Allylation of the lactams **6**, **7** and **8**



6 R = β-SMe → **8** R = β-$\overset{\overset{O}{\|}}{S}$Me
7 R = α-SMe

Entry	Substrate	$SnBu_3$ (mol equiv.)	Conditions	Solvent	Temp. (T/°C)	Time (t/h)	Yield (%) **9**	**10**	**11**	**12**	**13**
1	**6**	2	AIBN	Toluene	80	8				20	23
2	**6**	4	$(Bu_3Sn)_2/h\nu$	MeCN–toluene (3:7)	20	43	29	15	23		
3	**6**	6	$(Bu_3Sn)_2/h\nu$	MeCN–toluene (3:7)	20	43	32	16	18		
4	**6**	6	$h\nu$	MeCN–toluene (3:7)	20	70	40	21	15		
5	**7**	6	$h\nu$	MeCN–toluene (3:7)	20	70	36	18	20		
6	**8**	2	$BF_3{\cdot}Et_2O$	CH_2Cl_2	20	8		33		18	

hydroxypropyl groups. Successive treatments involving selective protection of the primary hydroxy group of the diol **14** with a silyl group, double debenzylation by hydrogenolysis in the presence of Pearlman's catalyst,[14] acetylation and desilylation gave the desired triacetyl alcohol **17** in four steps in overall 50% yield. The structure of compound **17** was deduced from its ^1H NMR spectrum, which exhibited a complex signal pattern due to the presence of rotational isomers around the tertiary amide group. As also described in the following section, all the tertiary amides **16**–**21** were found to exist as a 5:1 mixture of rotational isomers which exhibited ^1H NMR signals of two separated chemical shifts due to the hydrogens of the 2-, 5- and 6-position and the secondary amide. Thus, we prepared the synthetic intermediate **17** which carries all the necessary functional groups for the conversion into the proposed structures of the pseudodistomins.

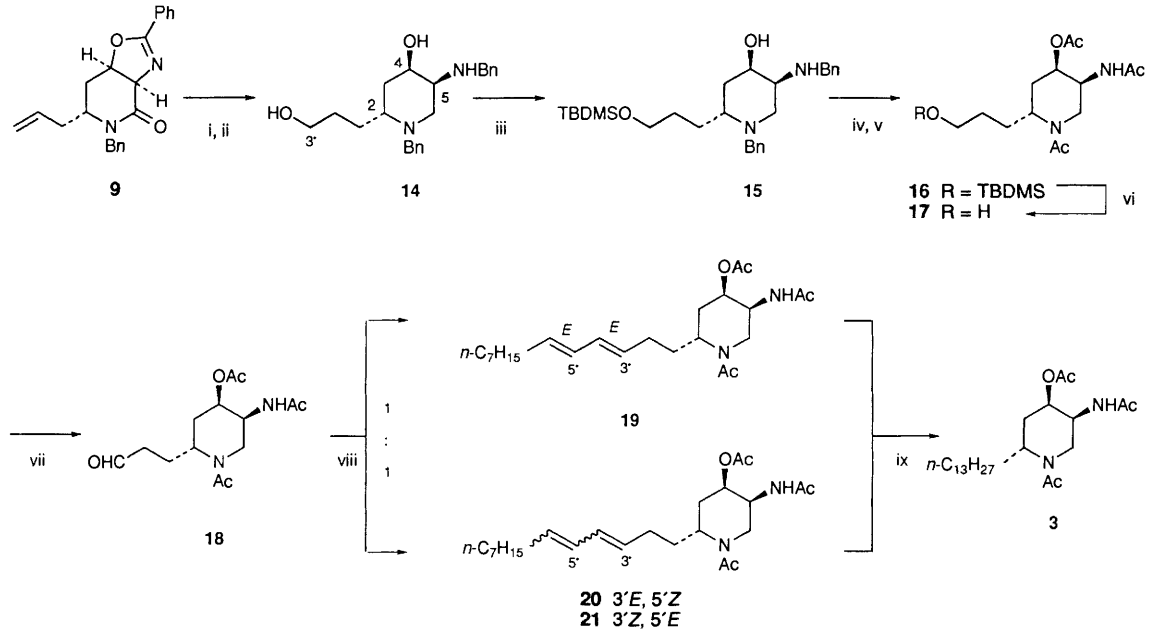
Synthesis of the proposed structures of pseudodistomins A and B

First, we investigated the total synthesis of pseudodistomin B which bears a stable *E*,*E*-diene moiety. Oxidation of the alcohol **17** with pyridinium chlorochromate (PCC) in the presence of sodium acetate gave the unstable aldehyde **18**, which was then condensed with the known (*E*)-(dec-2-enyl)triphenylphosphorane[15] under Wittig conditions to give a mixture of three dienes **19**–**21**. Upon catalytic hydrogenation in the presence of 10% palladium on carbon, the mixture of three dienes **19**–**21** yielded a homogeneous product **3** in quantitative yield (Scheme 3), which exhibited identical spectral data (^1H and ^{13}C NMR and IR) with those of an authentic specimen.[3] Thus, we have succeeded in the synthesis of tetrahydropseudodistomin 'triacetate', which has provided concrete evidence for the structures of natural pseudodistomins A and B except for the position and geometry of the diene in the alkenyl side-chain. Thorough separation and purification of a mixture of three dienes **19**–**21**, prepared by the above mentioned Wittig reaction, by reversed-phase HPLC (ODS) afforded pure diene **19** and an equal amount of an inseparable mixture of two dienes **20** and **21**. The structure of the diene **19**, particularly the position and geometry of the diene moiety, was firmly established by ^1H NMR spectra including ^1H–^1H 2D homonuclear chemical-shift correlation spectroscopy (COSY) which exhibited cross-peaks between 3′-H/2′-H_2 and 2′-H_2/1′-H_2. However, direct comparisons of ^1H and ^{13}C NMR spectra of both synthetic diene **19** and natural pseudodistomin B on their triacetyl derivatives have shown clear differences and were not superposable, particularly signals due to the diene moiety in the long alkenyl side-chain, though they were closely similar. Therefore it was concluded that the structure of pseudodistomin B would have to be revised with respect to the diene moiety. Two other dienes **20** and **21** were not completely separated by repeated HPLC but they appeared to be a mixture of 3′*E*,5′*Z*- and 3′*Z*,5′*E*-diene from their spectral data.

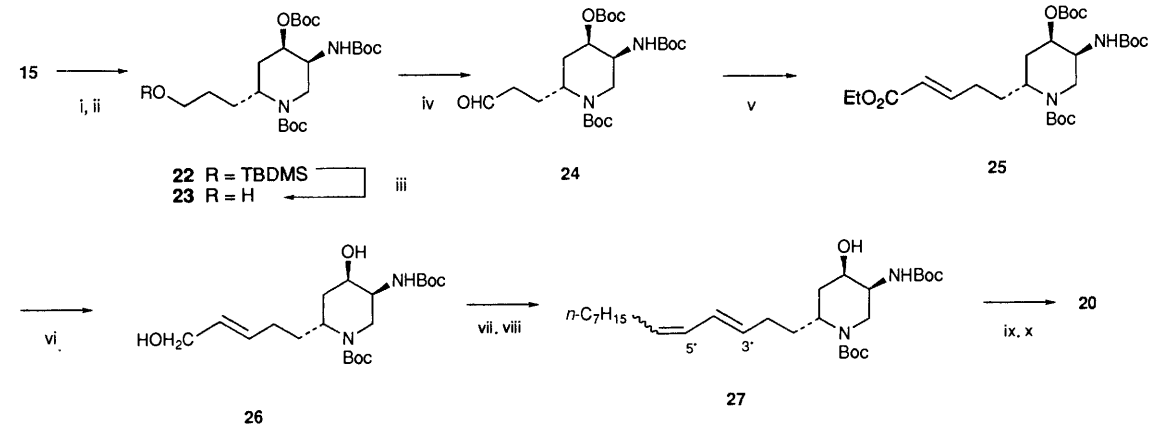
Then, in order to prepare 3′*E*,5′*Z*-diene **20** stereoselectively, we investigated a stepwise elongation reaction by using the less water-soluble tri(Boc)piperidine **23**.† According to the conventional methods, oxidation of the alcohol **23** with chromium trioxide–pyridine, Horner–Emmons reaction of the resulting aldehyde **24** with the requisite phosphate ester, and reduction of the unsaturated ester **25** with diisobutylaluminium hydride (DIBAH) gave the allyl alcohol **26** in 21% yield from the alcohol **23**. Wittig reaction of the corresponding aldehyde, which was readily prepared from the alcohol **26**, with octyltriphenylphosphorane in the presence of butyllithium proceeded smoothly to give a mixture of 3′*E*,5′*Z*- and 3′*E*,5′*E*-diene **27** in 31% combined yield in two steps from the alcohol **26**. Without separation, the mixture was subjected to deprotection by treatment with trifluoroacetic acid (TFA) followed by acetylation to give a 5:1 mixture of triacetyl derivatives **20** and **19** (Scheme 4). The mixture was carefully separated by HPLC to give the respective isomers **20** and **19**. The minor isomer **19** was identical with the sample **19** prepared by the above mentioned method upon direct comparisons of their spectral data. Comparison of the ^1H NMR spectra of the major isomer **20** and the mixture of the dienes **20** and **21** prepared from aldehyde **18** suggested that isomers **20** and **21** are a 3′*E*,5′*Z*- and 3′*Z*,5′*E*-diene, respectively. Unfortunately, direct comparisons of ^1H and ^{13}C NMR spectra of synthetic diene **20** with those of authentic pseudodistomin A 'triacetate'[3] have shown that their spectra are not superposable.

In conclusion, we have now succeeded in the syntheses of the proposed structures (3′*E*,5′*E*- and 3′*E*,5′*Z*-diene) for pseudodistomins B and A *via* a route involving two photochemical reactions. However, the synthetic samples were not identical with the authentic samples upon comparison of the spectra of their triacetyl derivatives, suggesting that the proposed structures have to be revised with respect to the dienyl structure in the side-chain. With accumulated data on the analogous derivatives, we now propose the structures of pseudodistomins A and B as having the 6′*E*,8′*E*- and 6′*E*,8′*Z*-dienyl moiety, respectively,[16] in their tridecyl side-chains. We are now extensively synthesizing all the possible analogues of pseudodistomins with respect to the dienyl structure.

† Boc = *tert*-butoxycarbonyl.



Scheme 3 *Reagents:* i, BH_3·THF, THF; ii, H_2O_2, NaOH; iii, TBDMSCl, imidazole, DMF; iv, H_2, 20% $Pd(OH)_2$–C, MeOH; v, Ac_2O, pyridine; vi, AcOH–THF–water (3 : 1 : 1); vii, PCC, CH_2Cl_2; viii, (*E*)-(dec-2-enyl)triphenylphosphonium bromide, NaH, THF; ix, H_2, 10% Pd–C, MeOH



Scheme 4 *Reagents:* i, H_2, 20% $Pd(OH)_2$–C, MeOH; ii, Boc_2O, Et_3N, DMAP, CH_2Cl_2; iii, TBAF, THF; iv, CrO_3, pyridine, CH_2Cl_2; v, $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; vi, DIBAH, hexane; vii, MnO_2, $CHCl_3$; viii, octyltriphenylphosphonium bromide, BuLi, THF; ix, TFA, CH_2Cl_2; x, Ac_2O, pyridine, DMAP

Experimental

^{1}H NMR spectra were measured using Varian XL-200 (200 MHz) and VXR-500 (500 MHz) instruments and ^{13}C NMR spectra were measured with VXR-500 (125 MHz) for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane was used as the internal reference); *J* values are given in Hz. IR spectra were measured with a Hitachi 270-30 machine, Perkin-Elmer 1600 FTIR and Shimadzu FTIR-4200 for solutions in chloroform unless otherwise stated. Mass spectra were taken with Hitachi M-80 and M-4100 instruments. HPLC was performed using a Waters Associates ALP/GPC 204 liquid chromatograph with a UV detector at 254 nm with a Develosil ODS-5 (10 × 250 mm). Mps were determined with Kofler-type hot-stage apparatus and are uncorrected. Photochemical reactions were carried out by irradiation with a high-pressure (100 or 300 W) mercury lamp through a Pyrex filter (Eikosha, Osaka, Japan, PIH-100 or PIH-300); during irradiation the solutions were stirred and bubbled with nitrogen. All other reactions were carried out under nitrogen and the extracts from the reaction mixtures were washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. TLC was performed on precoated silica gel 60F-254 (0.25 mm thick, Merck) and preparative TLC (PLC) on precoated silica-gel 60F-254 (0.5 mm thick, Merck), with UV detection at 254 and 300 nm. MPLC was undertaken on a 530-4-10V apparatus (Yamazen) with Lobar größe B (310-25, Lichroprep Si60, Merck) as column adsorbent. Ether refers to diethyl ether. All products described in this paper were found to be homogeneous by TLC, MPLC and ^{1}H NMR spectra.

N-Benzyl-*N*-[1-(methylsulfanyl)ethenyl]-2-phenyloxazole-4-carboxamide 5

A solution of 2-phenyloxazole-4-carbonyl chloride[10] (1.4 g, 6.7 mmol) in benzene (30 cm^3) was added to a stirred solution of the methylthioimidate **4**[9] (1.2 g, 6.7 mmol) and triethylamine (3 cm^3) in benzene (50 cm^3) at room temperature. The mixture was refluxed for 2 h, then cooled, and was filtered to remove triethylamine hydrochloride. The filtrate was evaporated to give the unstable enamide **5** (2.2 g) as a brown oil; ν_{max}/cm^{-1} 1648 (NCO); δ_H(200 MHz) 8.20 (1 H, s, 5-H), 8.14–8.00 (2 H, m, ArH), 7.60–7.18 (8 H, m, ArH), 4.98 and 4.82 (2 H, ABq, *J* 4, CH_2=C), 4.94 (2 H, s, CH_2Ph) and 2.30 (3 H, s, SMe). This enamide **5** was used for the following photocyclisation without further purification.

Reductive photocyclisation of the enamide 5

Sodium boranuide (1.8 g, 49.4 mmol) and methanol (150 cm^3) were added successively to a stirred solution of the enamide **5**

(2.16 g, 6.1 mmol) in acetonitrile (850 cm^3) at room temperature. When the added sodium boranuide had dissolved, the resulting solution was cooled and irradiated at 0–5 °C for 4 h. The mixture was concentrated to half its original volume, water was added, and the whole was extracted with methylene dichloride. The extract was washed, dried and evaporated to give a residue, which was purified by MPLC [ethyl acetate–hexane (2:1)] to give the lactams **6** (1.27 g, 59%) and **7** (110 mg, 5%).

(±)-(3aα,6β,7aα)-5-Benzyl-6-(methylsulfanyl)-2-phenyl-3a,4,5,6,7,7a-hexahydrooxazolo[4,5-*c*]pyridin-4-one 6. *Needles*; mp 166–167 °C (from ether–methanol); ν_{max}/cm^{-1} 1656 (NCO); δ_H(200 MHz) 8.10–8.00 (2 H, m, ArH), 7.60–7.24 (8 H, m, ArH), 5.63 and 4.02 (2 H, ABq, *J* 15, CH_2Ph), 5.23 (1 H, ddt, *J* 10, 4 and 2, 7a-H), 5.15 (1 H, d, *J* 10, 3a-H), 4.45 (1 H, br dd, *J* 4 and 2, 6-H), 2.67 (1 H, dt, *J* 12 and 2, 7-H^{eq}), 2.16 (1 H, dt, *J* 12 and 4, 7-H^{ax}) and 2.12 (3 H, s, SMe); *m/z* (CI, isobutane) 353 (QM^+) (Found: C, 68.0; H, 5.7; N, 7.8. $C_{20}H_{20}N_2O_2S$ requires C, 68.2; H, 5.7; N, 7.95%).

(±)-(3aα,6α,7aα)-5-Benzyl-6-(methylsulfanyl)-2-phenyl-3a,4,5,6,7,7a-hexahydrooxazolo[4,5-*c*]pyridin-4-one 7. *Oil*; ν_{max}/cm^{-1} 1644 (NCO); δ_H(200 MHz) 8.10–8.00 (2 H, m, ArH), 7.60–7.20 (8 H, m, ArH), 5.59 and 4.04 (2 H, ABq, *J* 14.5, CH_2Ph), 5.44 (1 H, td, *J* 10 and 6, 7a-H), 4.97 (1 H, d, *J* 10, 3a-H), 4.34 (1 H, t, *J* 3.5, 6-H), 2.60 (1 H, ddd, *J* 13.5, 6 and 3.5, 7-H^{eq}), 2.14 (3 H, s, SMe) and 1.93 (1 H, ddd, *J* 13.5, 10 and 3.5, 7-H^{ax}) [Found: QM^+ (CI, isobutane), 353.1319. $C_{20}H_{20}N_2O_2S$ + H requires QM, 353.1322].

Thermal allylation of the β-(methylsulfanyl)lactam 6 with allyltributyltin in the presence of AIBN

To a solution of the β-(methylsulfanyl)lactam **6** (70 mg, 0.2 mmol) in toluene (0.4 cm^3) were added allyltributyltin (0.12 cm^3, 0.4 mmol) and AIBN (1.6 mg, 0.04 mmol) and the mixture was heated at 80 °C for 8 h. Acetonitrile was added to the reaction mixture and the whole was extracted with hexane to remove allyltributyltin. The acetonitrile layer was separated, and evaporated to give a residue, which was purified by PLC [ethyl acetate–hexane (1:2)] to give the lactams **12** (14 mg, 20%), **13** (14 mg, 23%) and the starting lactam **6** (28 mg, 40% recovery).

***N*-(1-Benzyl-2-oxo-1,2-dihydropyridin-3-yl)benzamide 12.** *Needles*; mp 117–118 °C (from methanol); ν_{max}/cm^{-1} 1644 and 1598 (NHCO, NCO); δ_H(200 MHz) 9.29 (1 H, br s, NH), 8.56 (1 H, br d, *J* 7, 4- or 6-H), 8.10–7.88 (2 H, m, ArH), 7.64–7.20 (8 H, m, ArH), 7.08 (1 H, br d, *J* 7, 6- or 4-H), 6.32 (1 H, t, *J* 7, 5-H) and 5.26 (2 H, s, CH_2Ph) (Found: C, 75.0; H, 5.3; N, 9.1. $C_{19}H_{16}N_2O_2$ requires C, 75.0; H, 5.3; N, 9.2%).

(±)-*N*-[1-Benzyl-6-(methylsulfanyl)-2-oxo-1,2,5,6-tetrahydropyridin-3-yl]benzamide 13. *Oil*; ν_{max}/cm^{-1} 1656 and 1632 (NHCO, NCO); δ_H(200 MHz) 9.01 (1 H, br s, NH), 8.00–7.60 (2 H, m, ArH), 7.66–7.28 (9 H, m, ArH and 4-H), 5.55 and 4.16 (2 H, ABq, *J* 15, CH_2Ph), 4.50 (1 H, dt, *J* 7 and 2, 6-H), 3.12 (1 H, ddd, *J* 19, 7 and 3, 5-H^{eq}), 2.84 (1 H, ddd, *J* 19, 7 and 2, 5-H^{ax}) and 2.14 (3 H, s, SMe) (Found: M^+, 352.1229. $C_{20}H_{20}N_2O_2S$ requires M, 352.1244).

Photochemical allylation of the β-(methylsulfanyl)lactam 6 with allyltributyltin

(*a*) To a solution of the β-(methylsulfanyl)lactam **6** (704 mg, 2 mmol) in toluene–acetonitrile (7:3; 6 cm^3) were added allyltributyltin (2.48 cm^3, 8 mmol) and bis(tributyltin) (1.37 cm^3, 2 mmol) and the mixture was irradiated at 20 °C for 43 h. Acetonitrile was added to the reaction mixture and the whole was extracted with hexane to remove allyltributyltin. The acetonitrile layer was separated and evaporated to give a residue, which was purified by MPLC [ethyl acetate–hexane (2:1)] to give the α-allyl lactam **9** (200 mg, 29%), β-allyl lactam **10** (104 mg, 15%) and the lactam **12** (140 mg, 23%).

(±)-(3aα,6α,7aα)-5-Benzyl-2-phenyl-6-(prop-2′-enyl)-3a,4,5,6,7,7a-hexahydrooxazolo[4,5-*c*]pyridin-4-one 9. *Oil*; ν_{max}/cm^{-1} 1644 (NCO); δ_H(500 MHz) 8.09–8.07 (2 H, m, ArH), 7.53–7.22 (8 H, m, ArH), 5.71 (1 H, dddd, *J* 18, 10, 8 and 6, 2′-H), 5.44 and 4.00 (2 H, ABq, *J* 15, CH_2Ph), 5.28 (1 H, td, *J* 10 and 6, 7a-H), 5.20 (1 H, br d, *J* 18, 3′-H), 5.18 (1 H, br d, *J* 10, 3′-H), 5.03 (1 H, d, *J* 10, 3a-H), 3.42 (1 H, m, 6-H), 2.49 (1 H, ddd, *J* 14, 6 and 5, 1′-H), 2.36 (1 H, ddd, *J* 13.5, 6 and 4.5, 7-H^{eq}), 2.24 (1 H, ddd, *J* 14, 10 and 8, 1′-H) and 1.76 (1 H, ddd, *J* 13.5, 10 and 4.5, 7-H^{ax}) (Found: M^+, 346.1972. $C_{22}H_{22}N_2O_2$ requires M, 346.1679).

(±)-(3aα,6β,7aα)-5-Benzyl-2-phenyl-6-(propen-2′-yl)-3a,4,5,6,7,7a-hexahydrooxazolo[4,5-*c*]pyridin-4-one 10. *Needles*; mp 186–187 °C (from methanol); ν_{max}/cm^{-1} 1644 (NCO); δ_H(500 MHz) 8.04–8.03 (2 H, m, ArH), 7.53–7.24 (8 H, m, ArH), 5.67 (1 H, dddd, *J* 18, 10, 8 and 6, 2′-H), 5.47 and 3.92 (2 H, ABq, *J* 15, CH_2Ph), 5.17 (1 H, br dd, *J* 10.5 and 5, 7a-H), 5.08 (1 H, br d, *J* 10, 3′-H), 5.06 (1 H, d, *J* 10.5, 3a-H), 4.99 (1 H, br d, *J* 18, 3′-H), 3.38 (1 H, m, 6-H), 2.45 (1 H, dt, *J* 15.5 and 2, 7-H^{eq}), 2.40 (1 H, br dt, *J* 14 and 6, 1′-H), 2.17 (1 H, br ddd, *J* 14, 10 and 8, 1′-H) and 1.88 (1 H, dt, *J* 15.5 and 5, 7-H^{ax}); *m/z* 346 (M^+) (Found: C, 75.6; H, 6.3; N, 8.1. $C_{22}H_{22}N_2O_2 \cdot 1/5$ MeOH requires C, 75.6; H, 6.5; N, 7.9%).

(±)-*cis*-5-Benzyl-2-phenyl-3a,4,5,6,7,7a-hexahydrooxazolo-[4,5-*c*]pyridin-4-one 11. *Oil*; ν_{max}/cm^{-1} 1650 (NCO); δ_H(200 MHz) 8.10–7.97 (2 H, m, ArH), 7.60–7.18 (8 H, m, ArH), 5.19 (1 H, br dt, *J* 10 and 4, 7a-H), 4.98 (1 H, d, *J* 10, 3a-H), 4.84 and 4.44 (2 H, ABq, *J* 14.5, CH_2Ph), 3.36 (1 H, ddd, *J* 13.5, 11 and 4, 6-H^{ax}), 3.09 (1 H, dtd, *J* 13.5, 4 and 1, 6-H^{eq}), 2.14 (1 H, dq, *J* 14.5 and 4, 7-H^{eq}) and 1.98 (1 H, ddt, *J* 14.5, 11 and 4, 7-H^{ax}) (Found: M^+, 306.1343. $C_{19}H_{18}N_2O_2$ requires M, 306.1367).

(*b*) According to the procedure described above, a solution of the β-(methylsulfanyl)lactam **6** (704 mg, 2 mmol), allyltributyltin (3.72 cm^3, 12 mmol) and bis(tributyltin) (1.37 cm^3, 2 mmol) in toluene–acetonitrile (7:3; 6 cm^3) was irradiated at 20 °C for 43 h. Purification of the crude product by MPLC [same solvents as in (*a*)] gave two allyl lactams, **9** (221 mg, 32%) and **10** (111 mg, 16%) and the hydrogenated lactam **11** (110 mg, 18%), which were identical with the samples obtained in (*a*) based on comparison of their R_f-values, IR and NMR spectra, respectively.

(*c*) According to the procedure described above, a solution of the β-(methylsulfanyl)lactam **6** (2.84 g, 8 mmol) and allyltributyltin (14.9 cm^3, 48 mmol) in toluene–acetonitrile (7:3; 14 cm^3) was irradiated at 20 °C for 70 h. Purification of the crude product by MPLC [same solvents as in (*a*)] gave two allyl lactams **9** (1.1 g, 40%) and **10** (581 mg, 21%) and the hydrogenated lactam **11** (367 mg, 15%), which were identical with the samples obtained in (*a*) based on comparison of their R_f-values, IR and NMR spectra, respectively.

Photochemical allylation of the α-(methylsulfanyl)lactam 7 with allyltributyltin

According to the procedure described above, a solution of the α-(methylsulfanyl)lactam **7** (500 mg, 1.42 mmol) and allyltributyltin (2.6 cm^3, 8.5 mmol) in toluene–acetonitrile (7:3; 9 cm^3) was irradiated at 20 °C for 70 h. Purification of the crude product by MPLC [ethyl acetate–hexane (2:1)] gave two allyl lactams **9** (177 mg, 36%) and **10** (88 mg, 18%) and the hydrogenated lactam **11** (87 mg, 20%), which were identical with the samples obtained from β-(methylsulfanyl)lactam **6** based on comparison of their R_f-values, IR and NMR spectra, respectively.

Allylation of the sulfoxide 8 with allyltributyltin in the presence of boron trifluoride–ether

To a solution of the β-(methylsulfanyl)lactam **6** (70 mg, 0.2 mmol) in methylene dichloride (5 cm^3) was added MCPBA (49 mg, 0.2 mmol) at 0 °C, and the mixture was stirred at the same

temperature for 0.5 h. The reaction mixture was diluted with methylene dichloride and then washed with saturated aq. sodium hydrogen carbonate. The organic layer was washed, dried and evaporated to give the unstable sulfoxide **8** (74 mg). Allyltributyltin (0.124 cm^3, 0.4 mmol) and boron trifluoride–ether (0.0126 cm^3, 0.1 mmol) were added successively to a solution of the crude product **8** (74 mg) in methylene dichloride (1 cm^3) at 0 °C. The resulting mixture was stirred at room temperature for 8 h. Water was added to the reaction mixture. The aqueous layer was made alkaline with saturated aq. sodium hydrogen carbonate and extracted with methylene dichloride. The extract was washed, dried and evaporated to afford a residue, which was purified by MPLC [ethyl acetate–hexane (2:1)] to give the β-allyl lactam **10** (23 mg, 33%) and the lactam **12** (11 mg, 18%), which were identical with the samples obtained above based on comparison of their R_f-values, IR and NMR spectra.

(±)-(2α,4β,5β)-1-Benzyl-5-benzylamino-2-(3′-hydroxypropyl)-piperidin-4-ol 14

To a stirred solution of the α-allyl lactam **9** (922 mg, 2.7 mmol) in THF (11 cm^3) was added borane–tetrahydrofuran complex (1 mol dm^{-3} in THF) (16 cm^3, 16 mmol) dropwise at 0 °C, and the mixture was refluxed for 4 h. Then 3 mol dm^{-3} aq. sodium hydroxide (16 cm^3) and 30% hydrogen peroxide (18 cm^3) were added to the resulting mixture at 0 °C, and the whole was refluxed for 3 h. The mixture was concentrated to half its original volume and was then extracted with ethyl acetate. The extract was washed, dried and evaporated to give a residue, which was purified by MPLC [methanol–methylene dichloride (5:95)] to afford the *amino alcohol* **14** (604 mg, 64%) as an oil, ν_{max}/cm^{-1} 3600–3200 (NH, OH); δ_H(500 MHz; $CDCl_3$ + D_2O) 7.33–7.19 (10 H, m, ArH), 4.06 and 3.25 (2 H, ABq, *J* 13, CH_2Ph), 3.92 (1 H, br q, *J* 4, 4-H), 3.67 and 3.60 (2 H, ABq, *J* 13, CH_2Ph), 3.67 (2 H, m, 3′-H_2), 2.83 (1 H, m, 2-H), 2.75 (1 H, br dt, *J* 9 and 4, 5-H), 2.48 (1 H, dd, *J* 11.5 and 4, 6-H^{eq}), 2.25 (1 H, br dd, *J* 11.5 and 9, 6-H^{ax}) and 1.89–1.58 (6 H, m, 3-, 1′- and 2′-H_2) (Found: M^+, 354.2309. $C_{22}H_{30}N_2O_2$ requires M, 354.2306).

(±)-(2α,4β,5β)-1-Benzyl-5-benzylamino-2-{3′-[(1,1-dimethylethyl)dimethylsiloxy]propyl}piperidin-4-ol 15

To a solution of the amino alcohol **14** (354 mg, 1 mmol) and imidazole (204 mg, 3 mmol) in dimethylformamide (DMF) (5 cm^3) was added *tert*-butyldimethylsilyl chloride (226 mg, 1.5 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with 10% aq. potassium carbonate, dried and evaporated to give a residue, which was purified by MPLC [ethyl acetate–hexane (2:1)] to give *siloxy compound* **15** (374 mg, 80%) as an oil, ν_{max}/cm^{-1} 3600–3000 (NH, OH); δ_H(200 MHz) 7.38–7.13 (10 H, m, ArH), 3.85 and 3.32 (2 H, ABq, *J* 13, CH_2Ph), 3.85 (1 H, m, 4-H), 3.65–3.52 (4 H, m, CH_2Ph and 3′-H_2), 2.89–2.66 (2 H, m, 2- and 5-H), 2.60–2.24 (4 H, m, 6-H_2, OH and NH), 1.85–1.38 (6 H, m, 3-, 1′- and 2′-H_2), 0.85 (9 H, s, CMe × 3) and 0.00 (6 H, s, SiMe × 2) (Found: M^+, 468.3155. $C_{28}H_{44}N_2O_2Si$ requires M, 468.3169).

(±)-(2α,4β,5β)-5-Acetamido-4-acetoxy-1-acetyl-2-{3′-[(1,1-dimethylethyl)dimethylsiloxy]propyl}piperidine 16

A solution of compound **15** (374 mg, 0.80 mmol) in methanol (15 cm^3) was catalytically hydrogenated over 20% palladium hydroxide on carbon (250 mg) under hydrogen at atmospheric pressure and room temperature for 40 h. The catalyst was filtered off and the filtrate was evaporated to give a residue, which was acetylated with acetic anhydride (2 cm^3) in pyridine (1.5 cm^3) at room temperature for 24 h. The reaction mixture was concentrated to small volume, made alkaline with saturated aq. sodium hydrogen carbonate and extracted with methylene dichloride. The extract was washed, dried and evaporated to give a residue, which was purified by MPLC [methanol–methylene dichloride (5:95)] to give the *amide* **16** (209 mg, 63%) as needles, mp 147–148 °C (from ethyl acetate); ν_{max}/cm^{-1} 1738 (OCO) and 1670 and 1634 (NHCO, NCO); δ_H(200 MHz) 6.69 (4/5 H, br d, *J* 7, NH), *5.58 (1/5 H, br d, *J* 7, NH), 5.16 (1 H, dt, *J* 12 and 5, 4-H), 4.94 (4/5 H, br s, 2-H), *4.62 (1/5 H, br d, *J* 14, 6-H^{eq}), *4.55 (1/5 H, m, 5-H), 4.47 (4/5 H, br s, 5-H), *4.10 (1/5 H, m, 2-H), 3.88 (4/5 H, br d, *J* 14, 6-H^{eq}), 3.61 (2 H, t, *J* 6, 3′-H_2), 3.32 (4/5 H, br d, *J* 14, 6-H^{ax}), *2.94 (1/5 H, br d, *J* 14, 6-H^{ax}), 2.05, 2.03 and 2.01 (each 3 H, s, Ac × 3), 1.94–1.30 (6 H, m, 3-, 1′- and 2′-H_2), 0.89 (9 H, s, CMe × 3) and 0.00 (6 H, s, SiMe × 2). The asterisks show the signals due to the minor conformer (Found: C, 57.9; H, 9.4; N, 6.6. $C_{20}H_{38}N_2O_5Si$ requires C, 57.9; H, 9.2; N, 6.8%).

(±)-(2α,4β,5β)-5-Acetamido-4-acetoxy-1-acetylpiperidine-2-propanol 17

A solution of siloxy compound **16** (68 mg, 0.16 mmol) in acetic acid–THF–water (3:1:1; 6 cm^3) was stirred at room temperature for 1 h. The reaction mixture was concentrated to give a residue, which was crystallised from ether–hexane to afford the propanol **17** (47 mg, 98%) as pale yellow crystals, mp 161–162 °C; ν_{max}/cm^{-1} 1740 (OCO) and 1678 and 1628 (NHCO, NCO); δ_H(200 MHz) 6.85 (4/5 H, br d, *J* 7, NH), *6.15 (1/5 H, br d, *J* 7, NH), 5.20 (1 H, dt, *J* 12 and 4, 4-H), 4.99 (4/5 H, br s, 2-H), *4.68 (1/5 H, br d, *J* 14.5, 6-H^{eq}), *4.60 (1/5 H, br s, 5-H), 4.48 (4/5 H, br s, 5-H), *4.16 (1/5 H, br s, 2-H), 3.94 (4/5 H, br d, *J* 14.5, 6-H^{eq}), 3.69 (2 H, t, *J* 6, 3′-H_2), 3.40 (4/5 H, br d, *J* 14.5, 6-H^{ax}), *3.00 (1/5 H, br d, *J* 14.5, 6-H^{ax}), 2.10, 2.06 and 2.07 (each 3 H, s, Ac × 3) and 2.00–1.44 (6 H, m, 3-, 1′- and 2′-H_2). The asterisks show the signals due to the minor conformer (Found: M^+, 300.1709. $C_{14}H_{24}N_2O_5$ requires M, 300.1684).

(±)-(2α,4β,5β)-5-Acetamido-4-acetoxy-1-acetylpiperidine-2-propanal 18

To a suspension of the alcohol **17** (50 mg, 0.167 mmol) and sodium acetate (41 mg, 0.5 mmol) in methylene dichloride (6 cm^3) was added PCC (55 mg, 0.25 mmol) and the mixture was stirred at room temperature for 1 h. After filtration off of the insoluble compounds, the filtrate was concentrated to small volume and diluted with ether. After filtration of the resulting suspension with Celite, the filtrate was evaporated to give the unstable aldehyde **18** (43 mg) as an oil; δ_H(200 MHz) 9.90 (1 H, br s, CHO), 5.98 (1 H, br s, NH), 5.21 (1 H, m, 4-H), 5.02 (1 H, m, 2-H), 4.40 (1 H, br s, 5-H), 4.26 (2 H, m, 2′-H_2), 4.02 (1 H, br d, *J* 14.5, 6-H^{eq}), 3.38 (1 H, br d, *J* 14.5, 6-H^{ax}), 2.23–1.94 (9 H, br s, Ac × 3) and 1.90–1.20 (4 H, m, 1′- and 3-H_2). Though the existence of the minor conformer was recognized in the ^1H NMR spectrum, this aldehyde **18** was used for the following Wittig reaction without further purification.

Wittig reaction of the aldehyde 18

To a solution of (*E*)-(dec-2-enyl)triphenylphosphonium bromide (133 mg, 0.28 mmol) in THF (3 cm^3) was added sodium hydride (60% dispersion in mineral oil) (11 mg, 0.28 mmol) and the mixture was stirred at room temperature for 0.5 h. To the resulting reddish orange solution was added the aldehyde **18** (42 mg, 0.14 mmol) at room temperature and the mixture was refluxed for 5 h. Water was added to the mixture and the whole was extracted with methylene dichloride. The extract was washed, dried and evaporated to give a residue, which was purified by MPLC [methanol–methylene dichloride (5:95)] to give the diene mixture (27 mg, 46%). A solution of the diene mixture (21 mg, 0.05 mmol) in ethanol (2 cm^3) was catalytically hydrogenated over 10% Pd–C (27 mg) under hydrogen at atmospheric pressure and room temperature for 2 h. After filtration off of the catalyst, the filtrate was evaporated to give a

residue, which was crystallised from ether to afford (±)-(2α,4β,5β)-5-*acetamido*-4-*acetoxy*-1-*acetyl*-2-*tridecylpiperidine* (tetrahydropseudodistomin 'triacetate') **3** (20 mg, 92%) as crystals, mp 114–115 °C; δ_H(500 MHz) 6.29 (4/5 H, br d, *J* 7, NH), *5.76 (1/5 H, br d, *J* 7, NH), 5.15 (1 H, dt, *J* 11.5 and 4.5, 4-H), 4.90 (4/5, br q, *J* 4.5, 2-H), *4.61 (1/5 H, br d, *J* 14.5, 6-H^{eq}), *4.52 (1/5 H, br s, 5-H), 4.39 (4/5 H, br s, 5-H), *4.01 (1/5 H, br s, 2 H), 3.90 (4/5 H, br d, *J* 14.5, 6-H^{eq}), 3.30 (4/5 H, br d, *J* 14.5, 6-H^{ax}), *2.93 (1/5 H, br d, *J* 14.5, 6-H^{ax}), 2.18–1.96 (9 H, m, Ac × 3), 1.82–1.74 (2 H, m, 3-H_2), 1.63 and 1.52 (each 1 H, m, 1′-H_2), 1.32–1.10 (22 H, m, 2′–12′-H_2) and 0.88 (3 H, t, *J* 7, 12′-Me). The asterisks show the signals due to the minor conformer; δ_C(125 MHz): 170.8, 170.3 and 170.1 (each s, *C*OCH_3), 67.0 (d, C-4, 47.7 and 46.9 (each d, C-5 and -2), 44.0 (t, C-6), 31.9 (t, C-11′), 30.2 (t, C-1′), 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.4 and 28.3 (each t, C-3 and -3′–10′), 26.3 (t, C-2′), 23.2, 21.8 and 21.1 (each q, CO*C*H_3), 22.7 (t, C-12′) and 14.1 (q, C-13′). The IR and ^{1}H and ^{13}C NMR spectra of compound **3** were found to be identical with those of tetrahydropseudodistomin 'triacetate' obtained from natural pseudodistomins A and B 'triacetate'[3] (Found: M^+, 424.3287. Calc. for $C_{24}H_{44}N_2O_4$: M, 424.3298).

The diene mixture obtained by the Wittig reaction as above was separated by HPLC [methanol–water (88 : 12)] to give the 3′*E*,5′*E*-diene **19** and a mixture of the 3′*E*,5′*Z*-diene **20** and the 3′*Z*,5′*E*-diene **21** in the ratio 2 : 1 : 1.

(±)-[2α(3′*E*,5′*E*),4β,5β]-5-Acetamido-4-acetoxy-1-acetyl-2-(trideca-3′,5′-dienyl)piperidine 19. *Oil*; ν_{max}(neat)/cm^{-1} 1740 (OCO) and 1660 and 1630 (NHCO, NCO); δ_H(500 MHz) 6.04–5.94 (2 H, m, 4′- and 5′-H), 5.84 (4/5 H, br d, *J* 5, NH), *5.63 (1/5 H, m, NH), 5.60 and 5.52 (each 1 H, m, 3′- and 6′-H), 5.14 (4/5 H, m, 4-H), *5.12 (1/5 H, m, 4-H), 4.97 (4/5 H, br s, 2-H), *4.63 (1/5 H, br d, *J* 14.5, 6-H^{eq}), *4.51 (1/5 H, br s, 5-H), 4.36 (4/5 H, br s, 5-H), *4.03 (1/5 H, m, 2-H), 3.96 (4/5 H, br d, *J* 14.5, 6-H^{eq}), 3.29 (4/5 H, br d, *J* 14.5, 6-H^{ax}), *2.93 (1/5 H, br d, *J* 14.5, 6-H^{ax}), 2.16–1.96 (13 H, m, 2′- and 7′-H_2 and Ac × 3), 1.82–1.73 (3 H, m, 3-H_2 and 1′-H), 1.62 (1 H, m, 1′-H), 1.36 (2 H, m, 8′-H_2), 1.32–1.23 (8 H, m, 9′–12′-H_2) and 0.88 (3 H, t, *J* 7, 12′-Me). The asterisks show the signals due to the minor conformer; δ_C(125 MHz) 170.6, 170.5 and 169.9 (each s, *C*OCH_3), 130.0 and 129.9 (each d, C-4′ and -5′), 133.5 and 131.3 (each d, C-3′ and -6′), 66.8 (d, C-4), 47.3 and 47.0 (each d, C-5 and -2), 43.7 (t, C-6), 32.6 (t, C-7′), 31.8 (t, C-11′), 29.9, 29.3, 29.3, 29.2, 29.1 and 28.5 (each t, C-3, -1′, -2′ and -8′–10′), 23.3, 21.7 and 21.0 (each q, CO*C*H_3), 22.6 (t, C-12′) and 14.1 (q, C-13′) (Found: M^+, 420.2994. $C_{24}H_{40}N_2O_4$ requires M, 420.2986).

A mixture of (±)-[2α(3′*E*,5′*Z*),4β,5β]-5-acetamido-4-acetoxy-1-acetyl-2-(trideca-3′,5′-dienyl)piperidine 20 and (±)-[2α(3′*Z*,5′*E*),4β,5β]-5-acetamido-4-acetoxy-1-acetyl)-2-(trideca-3′,5′-dienyl)piperidine 21. *Oil*; δ_H(500 MHz) 6.36–5.18 (5 H, m, 3′–6′-H and NHAc), 5.15 (1 H, m, 4-H), 4.98 (4/5 H, br s, 2 H), *4.64 (1/5 H, br d, *J* 15, 6-H^{eq}), *4.51 (1/5 H, br s, 5-H), 4.34 (4/5 H, br s, 5-H), *4.03 (1/5 H, br s, 2-H), 3.97 (4/5 H, br d, *J* 15, 6-H^{eq}), 3.30 (4/5 H, br d, *J* 15, 6-H^{ax}), *2.94 (1/5 H, br d, *J* 15, 6-H^{ax}), 2.20–1.96 (13 H, m, 2′- and 7′-H_2 and Ac × 3), 1.90–1.50 (4 H, m, 3- and 1′-H_2), 1.41–1.20 (10 H, m, 8′–12′-H_2) and 0.88 (3 H, t, *J* 7, 12′-Me). The asterisks show the signals due to the minor conformer; *m*/*z* 420 (M^+).

1,1-Dimethylethyl (±)-(2α,4β,5β)-5-{[(1,1-dimethylethoxy)carbonyl]amino}-2-{3′-[(1,1-dimethylethyl)dimethylsiloxy]-propyl}-4-{[(1,1-dimethylethoxy)carbonyl]oxy}piperidine-1-carboxylate 22

A solution of compound **15** (60 mg, 0.13 mmol) in methanol (5 cm^3) was catalytically hydrogenated over 20% palladium hydroxide on carbon (40 mg) under hydrogen at atmospheric pressure and room temperature for 40 h. The catalyst was filtered off and the filtrate was evaporated to give a residue, which was dissolved in methylene dichloride (5 cm^3). To this solution were added triethylamine (66 mg, 0.65 mmol), a catalytic amount of 4-(dimethylamino)pyridine (DMAP) (1 mg), and di-*tert*-butyl dicarbonate (141 mg, 0.65 mmol) and the mixture was refluxed for 20 h. The reaction mixture was concentrated to give a residue, which was purified by MPLC [ethyl acetate–hexane (1 : 5)] to afford *title compound* **22** (45 mg, 59%) as an oil, ν_{max}/cm^{-1} 1740 (OCO_2) and 1711 and 1685 ($NHCO_2$, NCO_2); δ_H(200 MHz) 4.86–4.66 (2 H, m, 4-H, N*H*Boc), 4.33 (1 H, m, 2-H), 4.17 (1 H, m, 5-H), 4.13 (1 H, br d, *J* 14, 6-H^{eq}), 3.56 (2 H, t, *J* 6, 3′-H_2), 2.97 (1 H, br d, *J* 14, 6-H^{ax}), 1.98–1.10 (6 H, m, 3-, 1′- and 2′-H_2), 1.45, 1.42 and 1.41 (each 9 H, s, Bu^t × 3), 0.85 (9 H, s, Bu^t) and 0.00 (6 H, s, SiMe × 2) (Found: M^+, 588.3815. $C_{29}H_{56}N_2O_8Si$ requires M, 588.3803).

1,1-Dimethylethyl (±)-(2α,4β,5β)-5-{[(1,1-dimethylethoxy)carbonyl]amino}-4-{[(1,1-dimethylethoxy)carbonyl]oxy}-2-(3′-hydroxypropyl)piperidine-1-carboxylate 23

A solution of compound **22** (298 mg, 0.51 mmol) and tetrabutylammonium fluoride (TBAF) (1.0 mol dm^{-3} in THF) (0.61 cm^3, 0.61 mmol) in THF (8 cm^3) was stirred at room temperature for 3 h. The solvent was removed to give a residue, which was purified by MPLC [ethyl acetate–hexane (1 : 1)] to afford *title compound* **23** (203 mg, 84%) as an oil; ν_{max}/cm^{-1} 1740 (OCO_2), 1710 ($NHCO_2$) and 1685 (NCO_2); δ_H(200 MHz) 4.86–4.70 (2 H, m, 4-H, N*H*Boc), 4.43 (1 H, m, 2-H), 4.30–4.10 (2 H, m, 5-H and 6-H^{eq}), 3.67 (2 H, t, *J* 6, 3′-H_2), 3.01 (1 H, br d, *J* 13, 6-H^{ax}), 1.99–1.30 (6 H, m, 3-, 1′- and 2′-H_2) and 1.49, 1.46 and 1.45 (each 9 H, s, Bu^t × 3) (Found: M^+, 474.2921. $C_{23}H_{42}N_2O_4$ requires M, 474.2938).

1,1-Dimethylethyl (±)-(2α,4β,5β)-5-{[(1,1-dimethylethoxy)carbonyl]amino}-4-{[(1,1-dimethylethoxy)carbonyl]oxy}-2-(2′-formylethyl)piperidine-1-carboxylate 24

To a solution of pyridine (404 mg, 5.1 mmol) in methylene dichloride (8 cm^3) was added chromium(VI) trioxide (256 mg, 2.6 mmol) in small portions, and the mixture was stirred at room temperature for 15 min. To the solution was added dropwise a solution of the alcohol **23** (203 mg, 0.43 mmol) in methylene dichloride (8 cm^3) at room temperature and the mixture was stirred at room temperature for 1 h. The solvent was removed to give a residue, which was diluted with ether. After filtration of the resulting solution with Celite, the filtrate was evaporated to give the unstable aldehyde **24** (174 mg) as an oil; δ_H(200 MHz) 9.77 (1 H, t, *J* 2, CHO), 4.92–4.70 (2 H, m, 4-H and N*H*Boc), 4.43 (1 H, m, 2-H), 4.30–4.10 (2 H, m, 5-H and 6-H^{eq}), 3.00 (1 H, br d, *J* 13, 6-H^{ax}), 2.48 (2 H, td, *J* 6 and 2, 2′-H_2), 2.15–1.20 (4 H, m, 3- and 1′-H_2) and 1.49, 1.46 and 1.45 (each 9 H, s, Bu^t × 3). This aldehyde **24** was used for the following Horner–Emmons reaction without further purification.

1,1-Dimethylethyl (±)-[2α(*E*),4β,5β]-5-{[(1,1-dimethylethoxy)carbonyl]amino}-4-{[(1,1-dimethylethoxy)carbonyl]oxy}-2-(4′-ethoxycarbonylbut-3′-enyl)piperidine-1-carboxylate 25

To a solution of triethyl phosphonoacetate (83 mg, 0.37 mmol) and the crude aldehyde **24** (174 mg) in THF (1 cm^3) was added sodium hydride (60% dispersion in mineral oil) (9.8 mg, 0.41 mmol) and the mixture was stirred at room temperature for 1.5 h. Water was added to the mixture and the whole was extracted with ethyl acetate. The extract was washed, dried, and evaporated to give a residue, which was purified by MPLC [AcOEt–hexane (1 : 3)] to afford the *olefin* **25** (134 mg, 57%) as an oil, ν_{max}/cm^{-1} 1720–1680 (OCO, OCO_2, NCO_2, $NHCO_2$, δ_H(200 MHz) 6.93 (1 H, dt, *J* 16 and 6, 3′-H), 5.84 (1 H, br d, *J* 16, 4′-H), 4.90–4.70 (2 H, m, 4-H and N*H*Boc), 4.42 (1 H, m, 2-H), 4.30–4.12 (2 H, m, 5-H and 6-H^{eq}), 4.18 (2 H, q, *J* 6, $CO_2CH_2CH_3$), 2.98 (1 H, br d, *J* 13, 6-H^{ax}), 2.30–1.30 (6 H, m, 3-, 1′- and 2′-H_2), 1.49, 1.46 and 1.45 (each 9 H, s, Bu^t × 3) and 1.28 (3 H, t, *J* 6, $CO_2CH_2CH_3$) (Found: M^+, 542.3215. $C_{27}H_{46}N_2O_9$ requires M, 542.3201).

1,1-Dimethylethyl (±)-[2α(*E*),4β,5β]-5-{[(1,1-dimethylethoxy)-carbonyl]amino}-4-hydroxy-2-(5′-hydroxy-3′-pentenyl)-piperidine-1-carboxylate 26

A solution of the ester **25** (134 mg, 0.25 mmol) in hexane (5 cm^3) was treated dropwise with a solution of DIBAH (1.0 mol dm^{-3} in hexane) (2.2 cm^3, 2.2 mmol) at −78 °C and the mixture was stirred at room temperature for 2 h. A small amount of acetic acid was added, the mixture was filtered through Celite, and the filtrate was evaporated to give a residue, which was purified by MPLC (ethyl acetate) to give compound **26** (37 mg, 37%) as an oil, ν_{max}/cm^{-1} 1683 (NCO_2, $NHCO_2$); δ_H(200 MHz) 5.75–5.58 (2 H, m, 3′- and 4′-H), 4.93 (1 H, m, N*H*Boc), 4.32 (1 H, m, 2-H), 4.13 (1 H, br d, *J* 15, 6-H^{eq}), 4.12–4.02 (2 H, m, 5′-H_2), 4.05–3.88 (2 H, m, 4- and 5-H), 2.20–1.95 (2 H, m, 2′-H_2), 1.90–1.60 (4 H, m, 3- and 1′-H_2) and 1.47 and 1.45 (each 9 H, s, Bu^t × 2) (Found: M^+, 400.2581. $C_{20}H_{36}N_2O_6$ requires M, 400.2571).

1,1-Dimethylethyl (±)-(2α,4β,5β)-5-{[(1,1-dimethylethoxy)carbonyl]amino}-4-hydroxy-2-(trideca-3′,5′-dienyl)piperidine-1-carboxylate 27

A solution of the alcohol **26** (40 mg, 0.1 mmol) in chloroform (1.25 cm^3) containing manganese dioxide (800 mg) was stirred at room temperature for 1 h. The mixture was filtered through Celite, and the filtrate was evaporated to give the unstable aldehyde (27 mg) as an oil, δ_H(200 MHz) 9.42 (1 H, d, *J* 8, CHO), 6.75 (1 H, dt, *J* 16 and 7, 3′-H), 6.04 (1 H, br dd, *J* 16 and 8, 4′-H), 4.83 (1 H, m, N*H*Boc), 4.29 (1 H, m, 2-H), 4.10 (1 H, br d, *J* 14, 6-H^{eq}), 3.97–3.80 (2 H, m, 4- and 5-H), 2.90 (1 H, br dd, *J* 14 and 2, 6-H^{ax}), 2.40–1.40 (6 H, m, 3-, 1′- and 2′-H_2) and 1.39 and 1.37 (each 9 H, s, Bu^t × 2).

To a solution of octyltriphenylphosphonium bromide (150 mg, 0.33 mmol) in THF (0.7 cm^3), was added butyllithium (1.6 mol dm^{-3}, hexane) (0.21 cm^3, 0.33 mmol) at −30 °C and the mixture was stirred at 0 °C for 20 min. To the resulting orange solution was added the crude aldehyde (27 mg) at −10 °C and the mixture was stirred at 0 °C for 2 h. Water and 10% hydrochloric acid (0.05 cm^3) were added to the mixture and the whole was extracted with ethyl acetate. The extract was washed, dried, and evaporated to give a residue, which was purified by MPLC [ethyl acetate–hexane (1 : 1)] to give a 5 : 1 *mixture of the dienes* **27** (15.2 mg, 31%), as an oil, ν_{max}/cm^{-1} 1684 (NCO_2, $NHCO_2$); δ_H(200 MHz) (*inter alia*) 6.31 (4/5 H, br dd, *J* 15 and 11, 4′-H for 3′*E*,5′*Z*-isomer), 5.92 (4/5 H, br t, *J* 11, 3′-H for 3′*E*,5′*Z*-isomer), 6.10–5.90 (2/5 H, m, 4′- and 5′-H for 3′*E*,5′*E*-isomer), 5.65–5.45 (2/5 H, m, 3′- and 6′-H for 3′*E*,5′*E*-isomer), 5.62 (4/5 H, br dt, *J* 15 and 7, 3′-H for 3′*E*,5′*Z*-isomer), 5.32 (4/5 H, br dt, *J* 11 and 7, 6′-H for 3′*E*,5′*Z*-isomer), 4.92 (1 H, m, N*H*Boc), 4.32 (1 H, m, 2-H), 4.13 (1 H, br d, *J* 15, 6-H^{eq}), 4.06–3.88 (2 H, m, 4- and 5-H), 3.01 (1 H, br dd, *J* 15 and 2, 6-H^{ax}), 2.20–1.27 (6 H, m, 3-, 1′- and 2′-H_2), 1.47 and 1.45 (each 9 H, s, Bu^t × 2) and 0.88 (3 H, t, *J* 6, 12′-Me) (Found: M^+, 494.3724. $C_{28}H_{50}N_2O_5$ requires M, 494.3717).

(±)-[2α(3*E*,5*Z*),4β,5β]-5-Acetamido-4-acetoxy-1-acetyl-2-(trideca-3′,5′-dienyl)piperidine 20

To a solution of a mixture of the dienes **27** (15.2 mg, 0.031 mmol) in chloroform (0.9 cm^3) was added dropwise TFA (0.12 cm^3), and the mixture was stirred at room temperature for 3 h. The solvent was evaporated off to give a residue, which was acetylated with acetic anhydride (1 cm^3) and a catalytic amount of DMAP (0.2 mg) in pyridine (3 cm^3) at room temperature for 24 h. Ethanol (0.5 cm^3) was added to the reaction mixture, which was then stirred at room temperature for 30 min and concentrated to give a residue, which was purified by MPLC [methanol–methylene dichloride (5:95)] to afford a 5:1 mixture of the diene acetates **20** and **19** (7.2 mg, 47%). The dienyl mixture was separated by HPLC [methanol–water (88:12)] to give the 3′*E*,5′*Z*-diene **20** and 3′*E*,5′*E*-diene **19**. The 3′*E*,5′*E*-diene **19** was identical with the samples obtained from the aldehyde **18** based on comparisons of their R_f-values, IR and NMR spectra.

3′E,5′Z-*Diene* **20**. Oil; ν_{max}/cm^{-1} 1741 (OCO) and 1677 and 1635 (NHCO, NCO); δ_H(500 MHz) 6.31 (1 H, br dd, *J* 16 and 11, 4′-H), 5.92 (1 H, br t, *J* 11, 5′-H), 5.86 (1 H, m, NH), 5.61 (1 H, br dt, *J* 16 and 7.5, 3′-H), 5.34 (1 H, m, 6′-H), 5.16 (1 H, m, 4-H), 4.97 (4/5 H, br s, 2-H), *4.64 (1/5 H, br d, *J* 14.5, 6-H^{eq}), *4.51 (1/5 H, br s, 5-H), 4.34 (4/5 H, br s, 5-H), *4.03 (1/5 H, m, 2-H), 3.96 (4/5 H, br d, *J* 15, 6-H^{eq}), 3.30 (4/5 H, br d, *J* 15, 6-H^{ax}), *2.93 (1/5 H, br d, *J* 14.5, 6-H^{ax}), 2.18–1.96 (13 H, m, 2′- and 7′-H_2 and Ac × 3), 1.82–1.60 (4 H, m, 3- and 1′-H_2), 1.37 (2 H, m, 8′-H_2), 1.33–1.22 (8 H, m, 9′–12′-H_2) and 0.88 (3 H, t, *J* 7, 12′-Me). The asterisks show the signals due to the minor conformer; δ_C(125 MHz) 170.6, 170.2 and 169.2 (each s, $COCH_3$), 132.3 and 131.0 (each d, C-3′ and -4′), 128.1 and 126.5 (each d, C-5′ and -6′), 66.8 (d, C-4), 47.3 (d, C-2), 47.0 (d, C-5), 43.8 (t, C-6), 31.8 (t, C-11′), 29.7, 29.6, 29.2, 29.2, 29.2 (each t, C-1′, -2′ and -8′-10′), 28.4 (t, C-3), 27.7 (t, C-7′), 23.3, 21.8 and 21.0 (each q, $COCH_3$), 22.6 (t, C-12′) and 14.0 (q, C-13′) (Found: M^+, 420.2995. $C_{24}H_{40}N_2O_4$ requires M, 420.2986).

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