The Synthesis of (+)-Allopumiliotoxin 323B′

Choon-Hong Tan[a, b] and Andrew B. Holmes*[a]

Abstract: This paper describes the synthesis of (+)-allopumiliotoxin 323B′ (**1**) using the intramolecular [3 + 2]-cycloaddition reaction of the (*Z*)-*N*-alkenylnitrone **4**. This synthesis began with (*R*)-*tert*-butyl-3-hydroxy-pent-4-enoate [(***R***)**-13**] which was obtained by enzymatic resolution with Amano PS lipase. A series of manipulations gave intermediate **17** and in situ coupling with 4-benzoyloxybutanal lead to the (*Z*)-*N*-alkenylnitrone **4** which underwent an intramolecular [3 + 2]-cycloaddition reaction to give the isoxazolidine **3** as the major cycloadduct. Isoxazolidine **3** provided the piperidinone **24** which upon diastereofacial selective addition of MeMgBr gave the required tertiary alcohol **25**. Formation of the indolizidine core **2** was achieved by an intramolecular S_N2 reaction. The side chain was assembled from a Wittig reaction between the phosphorane **8** and the enantiomerically pure aldehyde **9**. Further modifications afforded the aldehyde **7** which underwent an aldol condensation with the potassium enolate of the indolizidone core **2**. Dehydration gave the enone **37** which was converted into the *anti*-diol **38** by intramolecular hydride reduction. Finally, deprotection of the BOM protecting group gave (+)-allopumiliotoxin 323B′ (**1**).

Keywords: allopumiliotoxin · alkenylnitrone · cycloaddition · natural products · total synthesis

Introduction

The neotropical poison arrow frogs contain a remarkable diversity of alkaloids including histrionicotoxins, epibatidines, gephyrotoxins and the steroidal batrachotoxins. Such alkaloids, released onto the skin surface from the cutaneous granular glands, serve as a passive "chemical defense" against predators. The pumiliotoxin A class of alkaloids was first isolated from the skin extracts of one of these species, *Dendrobates pumilio*.[1] This class has been subdivided into three subclasses, the pumiliotoxins, the allopumiliotoxins and the homopumiliotoxins. The pumiliotoxins and allopumiliotoxins are indolizidines with an alkylidene side chain. The allopumiliotoxins differ by having an additional C-7 hydroxy group on the indolizidine ring and the homopumiliotoxins by having a quinolizidine core instead of an indolizidine. Individual alkaloids within each subclass differ from one another by the nature of the side chain attached to C-11 of the alkylidene moiety. The allopumiliotoxins are mildly toxic and exhibit cardiotonic and myotonic activities. Being the most complex members of this series of alkaloids, the allopumiliotoxins have been the subject of many attempted syntheses. To date, several successful total syntheses of allopumiliotoxins have been reported.[2–8] However, the only previous synthesis of allopumiliotoxin 323B′ (**1**) (Figure 1) was accomplished by

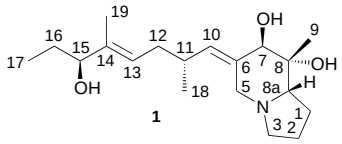

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Figure 1. (+)-Allopumiliotoxin 323B′ **1**.

Overman using iodide-promoted iminium ion – alkyne cyclisation chemistry.

So far, all the syntheses of the allopumiliotoxins have used L-proline or its analogues as the starting material, providing the five-membered ring of the indolizidine core and one stereocentre. Herein we report a different approach to the asymmetric synthesis based on the proposal that the indolizidone core **2** can be synthesized from the isoxazolidine cycloadduct **3**, which in turn can be derived from an intramolecular [3 + 2]-cycloaddition reaction of the (*Z*)-*N*-alkenylnitrone **4** (Figure 2).

We have previously shown that the preferred folding of *N*-pentenylnitrones bearing an internal allylic alkoxy substituent follows a chair like transition state in which the substituent prefers to be axial.[9] Subsequent investigation into the effects

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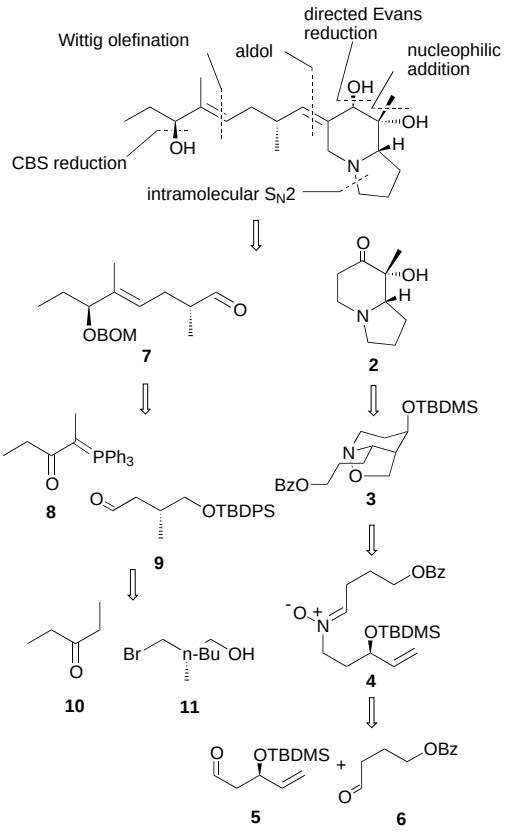
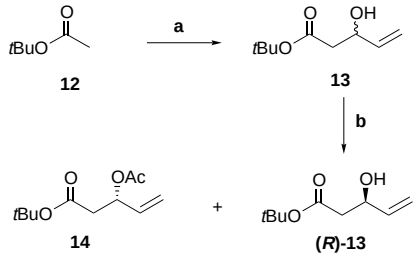


Figure 2. Retrosynthetic analysis of (+)-allopumiliotoxin 323B′ **1**.

of various alkenyl substituents was also carried out.[10] The choice of (*Z*)-*N*-alkenylnitrone **4** which had the correct allylic ether would deliver the correct enantiomer of the indolizidone core **2** as well as the relative stereochemistry of the required substituents in isoxazolidine **3**. After the allylic ether had fulfilled its initial stereodirecting role, it was lost by oxidation in the formation of the indolizidone core **2**. We have described in a preliminary report, this approach to the indolizidone **2**[11] and herein we report a full account of the relevant details relating to the synthesis of (+)-allopumiliotoxin 323B′ (**1**).

Results and Discussion

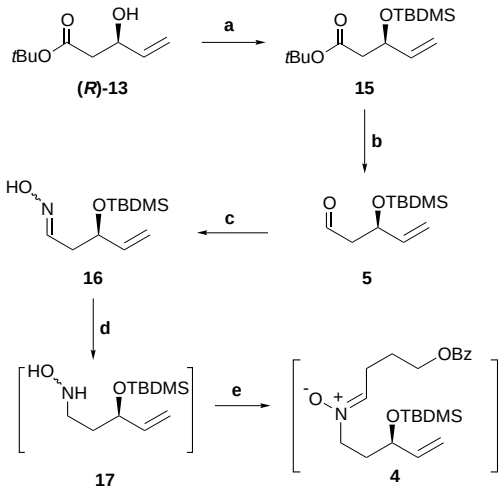
Synthesis of the indolizidone core: The synthesis began with reactions designed to obtain the β-hydroxy-ester **(*R*)-13**. The aldol reaction of the lithium enolate of *tert*-butyl acetate with acrolein afforded the racemic β-hydroxy-ester **13**.[12, 13] Enzymatic resolution of **13** was achieved by incubating a solution of the ester in pentane with Amano PS lipase at 30 °C (Scheme 1). The progress of the reaction was monitored by gas chromatography (GC) and the reaction was stopped after 3 h, when 50 % conversion was reached. In the absence of molecular sieves, the rate of reaction slowed considerably. The enantiomeric excess was determinded to be 92 % using the (*S*)-Mosher ester of **(*R*)-13**. An even higher enantiomeric excess (> 99 % *ee*) was obtained if the yield was sacrificed by stopping the reaction at 55 % conversion. The absolute



Scheme 1. Enzymatic resolution of β-hydroxyester **13**. a) LDA, THF then acrolein (46 %); b) PS Amano lipase, pentane, 30 °C, 4 Å MS, vinyl acetate [**(*R*)-13**, 47 %, 92 % *ee*; **14**, 49 %].

configuration of the resolved alcohol **(*R*)-13** was assigned using the model presented in the literature.[14–16]

The next few steps of the synthesis were designed to obtain the (*Z*)-*N*-alkenylnitrone **4** and subsequently to subject it to the cycloaddition conditions. The (*R*)-β-hydroxyl ester **(*R*)-13** was protected to provide the silyl ether **15** (Scheme 2) and



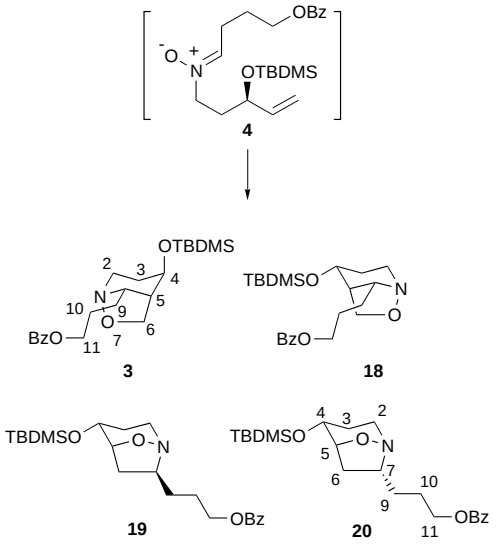
Scheme 2. Synthesis of (*Z*)-*N*-alkenylnitrone **4**. a) TBDMSCl, imidazole, CH_2Cl_2 (98 %); b) DIBAL, toluene, – 78 °C (79 %); c) $H_2NOH \cdot HCl$, H_2O/EtOH, NaOAc (98 %); d) $NaBH_3CN$, MeOH/HCl, MeOH; e) **6**, CH_2Cl_2.

reduction with diisobutylaluminium hydride at low temperature gave the aldehyde **5**. On a larger scale (≈25 g) reaction, 5 – 10 % overreduction occurred owing to localised warming. This could not be avoided even with a low concentration of substrate, slow addition of diisobutylaluminium hydride (DIBAL) using a dropping funnel and vigorous mechanical stirring. However, the alcohol could be separated easily by flash chromatography and was converted into the aldehyde using pyridinium chlorochromate. Treatment of the aldehyde **5** with hydroxylamine gave the oxime **16** in high yield. ^{1}H NMR analysis revealed that the oxime consisted of a mixture (1.1:1) of geometrical isomers. The oxime was subsequently subjected to a two-step reduction – condensation procedure[17] to give the (*Z*)-*N*-alkenylnitrone **4**. The reduction of the oxime with sodium cyanoborohydride was carried out in MeOH/HCl at a pH 3. This was carefully controlled since, at a higher pH, it was expected that a dialkylhydroxylamine would be formed.[18] After the reduction was completed, as shown by the disappearance of the

0947-6539/01/0709-1846 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 9

starting material, the reaction mixture was made strongly alkaline at −50 °C and the intermediate hydroxylamine **17** was extracted into pre-cooled CH_2Cl_2 in the presence of salt/ice-water mixture. The hydroxylamine was treated immediately with 4-benzoyloxybutanal (**6**), prepared in two steps from 1,4-butanediol,[9] to form the (*Z*)-*N*-alkenylnitrone **4** [$\delta = 6.67$ (t, $J = 6.0$ Hz, 1H, $^+$N=CH)]. Only a single isomer was observed, and this was assumed to be the thermodynamically favoured (*Z*)-isomer. Although it was possible to isolate the (*Z*)-*N*-alkenylnitrone for analytical purposes, purification generally resulted in a poor yield when the reaction was executed on a larger scale.

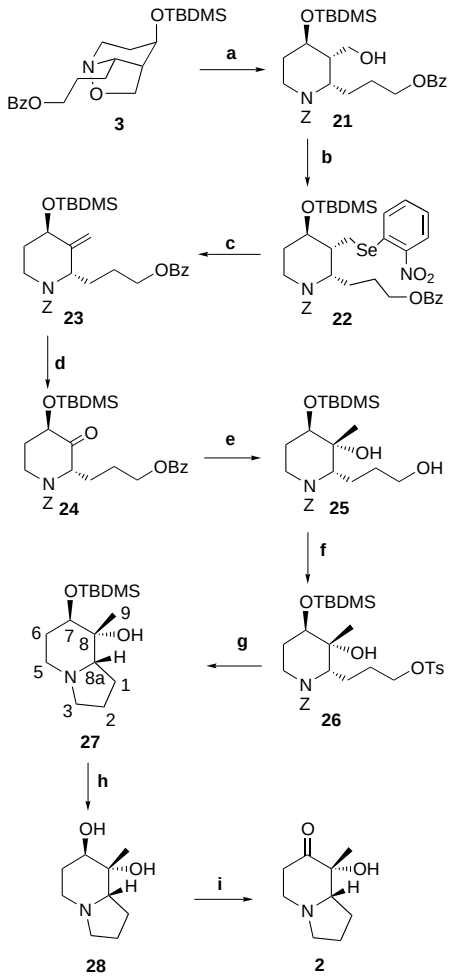
The intramolecular [3 + 2]-cycloaddition reaction was carried out by heating a dilute solution of the unpurified nitrone **4** in toluene for 18 h at 70 °C to give four isoxazolidine cycloadducts **3**, **18**, **19** and **20** (32:5:8:8) in a combined yield of 53 % from the oxime **16** (Scheme 3). The major product **3** was



Scheme 3. Intramolecular [3 + 2]-cycloaddition reaction of (*Z*)-*N*-alkenylnitrone **4**. Toluene, 70 °C (**5**, 32 %; **18**, 5 %; **19**, 8 %; **20**, 8 % from **16**).

identify by ^{1}H NMR, NOE studies and X-ray crystallographic analysis[10] and this also supported the assignment of the configuration of the (*Z*)-*N*-alkenylnitrone **4**. The isoxazolidines **19** and **20** were separated by flash chromatography from **3**. The equatorial isomer **18** could not be isolated in a pure form. The origin of the four products can be explained using a chair-like transition state.[17] i) The major product **3** [$\delta = 4.00$ (br s, 1H, H-4)] arose from the regiochemical preference for incorporation of the newly formed C–C bond in a six-membered ring which places the *O-tert*-butyldimethylsilyl (OTBDMS) group in an axial orientation.[9] ii) The minor product **18** [$\delta = 4.17$ (d, $J = 7.1$ Hz, 1H, H-4)] arose from the alternate folding in a chair-like transition state with the OTBDMS group equatorial. iii) The minor cycloadduct **19** [$\delta = 3.83$ (ddd, $J = 4.2, 5.8, 10.0$ Hz, 1H, H-4)] also folded with an equatorial OTBDMS but with an alternative regiocontrol in which the new C–C bond resided in a seven-membered ring. iv) The cycloadduct **20** [$\delta = 3.89$ (ddd, $J = 4.2, 5.9, 9.8$ Hz, 1H, H-4)] arose from a similar regiocontrol as cycloadduct **19** but with the corresponding (*E*)-*N*-alkenylnitrone which was apparently formed by nitrone isomerisation[19, 20] during the reaction.

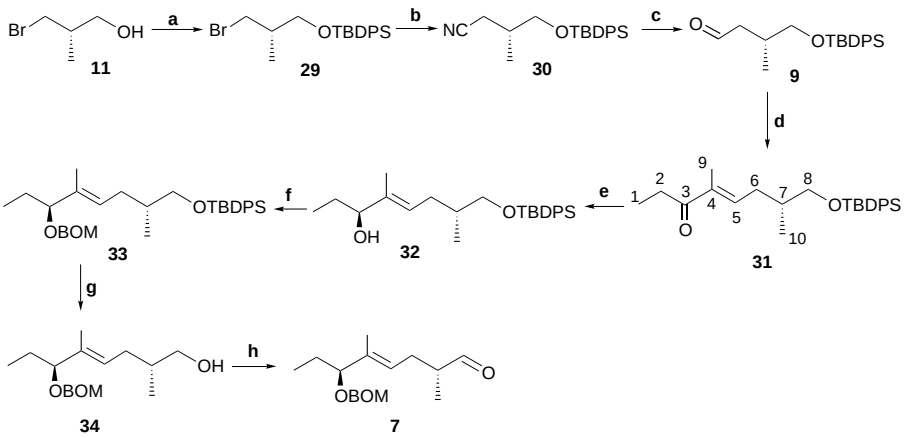
Elaboration of the isoxazolidine **3** into the indolizidone core **2** was conducted through a series of reactions described below. Hydrogenolysis of the isoxazolidine **3** and protection of the resulting free amino group with benzyl chloroformate (abbreviated as Z) gave the hydroxymethyl Z-protected piperidine **21** (Scheme 4). At this stage, the cleavage product



Scheme 4. Synthesis of the indolizidone core **2**. a) H_2, 10 % Pd/C, MeOH then Z-Cl, Et_2O, aq. $NaHCO_3$ (90 %, two steps); b) nBu$_3$P, pNO$_2$PhSeCN, THF (75 %); c) mCPBA, CH_2Cl_2 (85 %); d) O_3, CH_2Cl_2 then Ph_3P (88 %); e) MeMgBr, THF (90 %); f) TsCl, DMAP, Et_3N, CH_2Cl_2 (97 %); g) 10 % Pd/C, $NH_4^+HCO_2^-$, MeOH, 40 °C (96 %); h) TBAF, THF (83 %); i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N (60 %).

of the isomer **18** could be removed by flash chromatography. In order to produce the tertiary alcohol, it was necessary to functionalise the piperidine **21**. Our preference was to eliminate the primary alcohol, epoxidize the resulting alkene and reductively open the epoxide. Unfortunately, the epoxidation occurred on the opposite face of the alkene and subsequent ring opening of the epoxide afforded the tertiary alcohol with the methyl group *trans* to the silyl ether at C-7.[11] It was therefore expected that the preferred approach of a methyl Grignard reagent to the ketone **24** would be from the

same face as the peracid during epoxidation. The dehydration of the primary alcohol to form the exocyclic alkene **23** was carried out by formation of the selenide **22** using *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphine[21] followed by oxidation with one equivalent of *m*-chloroperoxybenzoic acid (*m*CPBA). The rapid oxidation of the selenide gave the selenoxide intermediate which at ambient temperature eliminates slowly to give the alkene **23**. Thus all the *m*CPBA was used up before the alkene **23** was liberated. Ozonolysis of the alkene **23** yielded the ketone **24**. Diastereofacial selective nucleophilic addition with an excess of MeMgBr afforded the ketone **25** in which the exclusive attack from the top face had occurred with concomitant removal of the benzoyl group. Selective tosylation of the primary alcohol of the piperidine **25** gave the tosylate **26**. Catalytic transfer hydrogenolysis removed the benxyloxycarbonyl protecting group and the resulting secondary amine underwent intramolecular ring closure to form the indolizidine **27**. Desilylation and oxidation of the resulting secondary alcohol **28** gave the indolizidone core **2** {$[\alpha]_D^{25} = -51.6$ ($c = 0.06$, $CHCl_3$); lit.:[3] $[\alpha]_D^{25} = -44.2$ ($c = 4.7$, $CHCl_3$)}, which was identical in all respects with the data reported by Overman.



Scheme 5. Synthesis of the side chain, aldehyde **7**. a) TBDPSCl, DMF, imidazole (96%); b) DMSO, NaCN, 120°C (90%); c) DIBAL, toluene, 0°C (80%); d) **8**, toluene, 90°C (85%); e) (*R*)-CBS catalyst, CH_2Cl_2, −40°C, catecholborane (73%); f) BOMCl, toluene, *i*Pr_2EtN, Bu_4NI, reflux (97%); g) TBAF, THF (90%); h) TPAP, NMO, CH_2Cl_2 (94%).

Selectivity of methyl Grignard addition on the ketone 24: The stereochemical control in the formation of tertiary alcohol **25** was remarkably high. The ketone may adopt the chair conformations **24A** and **24B** (Figure 3) in which the OTBDMS group is axial or equatorial respectively. The *N*-benzyloxycarbonyl group imposes $A_{1,3}$-strain[22, 23] on piperidine derivatives leading to a general preference for the α-substituents to occupy a pseudoaxial position (i.e., **24B**). Attack of MeMgBr from the less hindered upper face in conformation **24B** would give the observed product **25**. A further enhancement of the selectivity would arised from the Cieplak hypothesis.[24] A stereoelectronic factor favouring the axial attack on the preferred conformation **24B** is that the developing σ* of the transition state (TS) is stabilised by the antiperiplanar donor σ_{C-H} and σ_{C-C} (TS **24B′**). No such stabilisation is possible for an axial attack on the conformation **24A** as a result of the poor donating power of σ_{C-O} antiperiplanar to the incoming nucleophile (TS **24A′**). Thus conformation **24B** may be the most populated and also the more reactive conformation.

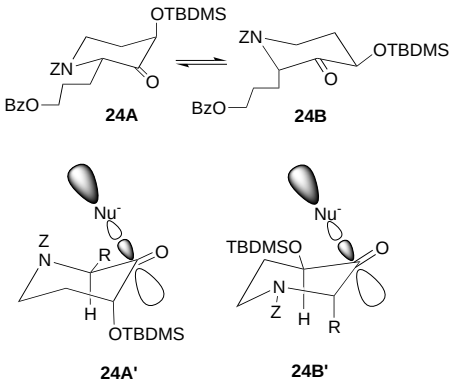
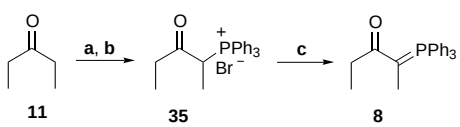


Figure 3. Conformation **24A** and **24B** of piperidinone **24** and transition states **24A′** and **24B′** arising from attack by a nucleophile at the carbonyl group.

Synthesis of the side chain: With the indolizidone core **2** in hand, the stage was set for the synthesis of the side chain and the completion of (+)-allopumiliotoxin 323B′ (**1**). The side chain can be assembled from a Wittig olefination of two fragments, the aldehyde **9** and the phosphorane **8**. The synthesis of the aldehyde **9** began with the commercially available (*S*)-bromoalcohol **11** (Scheme 5).

Silylation of the alcohol gave the *tert*-butyldiphenylsilyl (TBDPS) ether **29** and subsequent displacement of the bromide with sodium cyanide provided the nitrile **30**. This was reduced by DIBAL to the aldehyde **9**.[25] The phosphorane **8** was synthesised from 3-pentanone **10** through monobromination with molecular bromine and acetic acid[26, 27] and treatment of the resulting bromoketone with triphenylphosphine in benzene to give the phosphonium salt **35** which was converted to the phosphorane **8** using 20% NaOH solution (Scheme 6). A one pot procedure in which the phosphorane **8** was generated in situ from the phosphonium salt **35** with various bases such as lithium diisopropylamide (LDA) and



Scheme 6. Synthesis of the phosphorane **8**. a) AcOH, H_2O, Br_2, 65°C (42%); b) Ph_3P, benzene (47%); c) 20% NaOH (83%).

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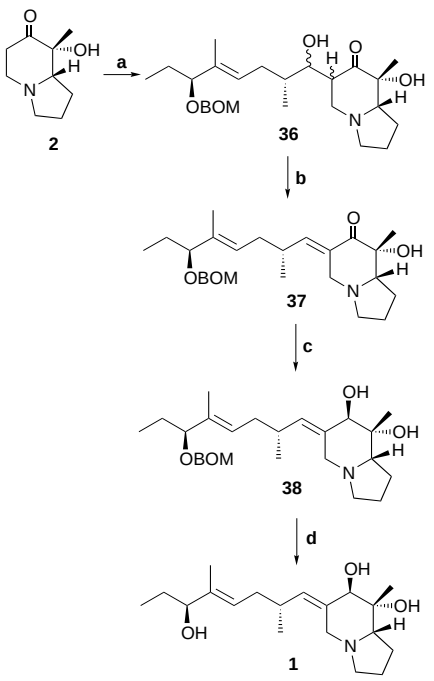
potassium bis(trimethylsilyl)amide gave poor yields in the succeeding Wittig reaction. This may be due to the presence of other acidic α-keto protons in the salt. Heating the vacuum dried phosphorane **8** with the aldehyde **9** at 90 °C in toluene for 14 h gave the *trans*-octene **31** as the only product. The geometry of **31** was confirmed by NOE studies on the octenol **32** (7% gradient NOE between H-3 and H-5), which was obtained by catalytic asymmetric reduction using the (*R*)-CBS oxazaborolidine catalyst and catecholborane.[28, 29] The stereochemistry was assigned according to Corey's model. The diastereometric ratio was determined to be 9:1 based on ^{13}C NMR of the alcohol **32**. The absolute stereochemistry was confirmed by ozonolysis of the alkene **32** and measurement of the optical rotation of the resulting (*S*)-3-hydroxypent-2-one {$[\alpha]_D^{25} = +48$ ($c = 0.05$, $CHCl_3$); lit.:[30] $[\alpha] = +52$ ($c = 7$, $CHCl_3$)}. Benzylation of the allylic alcohol **32** with NaH/THF was capricious and often did not proceed to completion even after extended reaction time. The yield could not be improved even when an aprotic solvent such as DMF was used. At elevated temperatures or when NaH was replaced by KH, side products began to appear with no improvement of yield. The benzyloxymethoxy (BOM) protecting group provided a better alternative as it was easier to introduce.[31] The BOM protection reaction proceeded with an excellent yield and with the additional advantage that the diastereoisomers were separable using column chromatography. Finally, the BOM ether **33** was treated with tetra-*n*-butyl ammonium fluoride (TBAF) to remove the silyl protecting group and the resulting alcohol was oxidized with tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide (TPAP/NMO)[32] to give the octenal **7**.

This efficient synthesis (eight steps, 30% from bromoalcohol **11**) provided a ready supply of the side chain, aldehyde **7** for the aldol condensation with the indolizidone core **2**.

Synthesis of (+)-allopumiliotoxin 323B′: With both the indolizidone core **2** and the side chain, aldehyde **7** synthesized, conditions to bring these two fragments together were investigated. Initial attempts at the aldol condensation of indolizidine core **2** with the aldehyde **7** were carried out with trityllithium that was prepared from triphenylmethane and *n*BuLi.[33] However, this base proved to be capricious and with much experimentation, potassium bis(trimethylsilyl)amide (Scheme 7) and the use of a mixed solvent hexamethylphosphoric triamide/tetrahydrofuran (HMPA/THF) was found to be the condition of choice. Owing to the possibility of racemisation of the α-methyl aldehyde **7** with an excess of base, a very small amount of fluorene was added to the reaction to enhance the end point of the enolisation of the ketone. A pink colouration was observed at the end point. The crude products of the aldol reaction were passed through a plug of silica to remove baseline materials as well as the nonpolar compounds such as fluorene. The diastereisomers were used without further purification.

The dehydration of these diastereoisomers **36** to the enone **37** proceeded smoothly with trifluoroacetic anhydride (TFAA) buffered with diazabicycloundecane (DBU). The elimination proceeded through an E1cb mechanism and gave the more thermodynamically favourable S-*cis* conformation



Scheme 7. Synthesis of (+)-allopumiliotoxin 323B′ **1**. a) KHMDS, THF/HMPA, 0 °C then **7**; b) DBU, TFAA, DMAP, −50 °C, CH_2Cl_2 (42%, two steps); c) $Me_4NBH(OAc)_3$, acetone, AcOH (89%); d) LiDBB, THF, −78 °C (88%).

leading to the exclusive formation of the (*E*)-enone. The *anti*-diol **38** was prepared by the hydroxyl-assisted intramolecular hydride reduction of α-hydroxy ketone **37**. The use of tetramethyammonium triacetoxyborohydride and a catalytic amount of acetic acid in acetone[34] took six days for completion, and gave the *anti*-diol **38** as the only observable product. A more reactive reagent, sodium triacetoxyborohydride, shortened the reaction time to three days but a selectivity of 3:1 (*anti*:*syn*) was unsatisfactory. In order to complete the synthesis of (+)-allopumiliotoxin (**1**), a mild condition was required to remove the BOM protecting group from its ether **38** without affecting its highly functionalised core and double bonds. Initially, hydrogenolysis with $Pd(OH)_2$ as the catalyst was used in an attempt to remove the protecting group; however, contrary to expectation[35, 36] the trisubstituted double bonds did not survive this condition. Finally, the synthesis of (+)-allopumiliotoxin 323B′ (**1**) was completed with the removal of the BOM protecting group under reductive conditions using lithium di-*tert*-butylbiphenyl (LiDBB).[37, 38] Synthetic (+)-allopumiliotoxin 323B′ (**1**) {$[\alpha]_D^{25} = +24.9$ ($c = 0.55$, MeOH); lit.: $[\alpha]_D^{25} = +22.3$ ($c = 1.0$, MeOH)} had characteristics in accordance with the data published by Daly[39, 40] and spectra provided by Overman.[41]

Conclusion

The synthesis of allopumiliotoxin was achieved in 20 steps from the β-hydroxyester **(*R*)-13** with an overall yield of 1.7%. The key step of the synthesis was the intramolecular [3+2]-cycloaddition reaction of the (*Z*)-*N*-alkenylnitrone **4**. The choice of the correct allylic silyl ether and the alkenyl

substituents in the (*Z*)-*N*-alkenylnitrone **4** proved to be crucial. This controlling stereocentre created the correct enantiomer of the indolizidone core **2** and the stereochemistry of its substituents by directing the folding of the chair-like transition state in the intramolecular [3+2]-cycloaddition reaction. This synthesis was also significantly different from other previous syntheses by using starting material other than L-proline or its derivative, providing an alternative route to functionalised enantiomerically pure indolizidines. This synthesis also demonstrated the viability of this strategy in the construction of enantiomerically pure piperidines and more importantly, an enantiomerically pure azabicyclic system of which indolizidine is one example. One area which will be explored will be the quinolizidine family which include a number of interesting and biologically active natural products.

Experimental Section

General techniques: ^{1}H NMR spectra were recorded on the Bruker DPX-250 (250 MHz), Bruker AM-400 (400 MHz) and Bruker DRX-500 (500 MHz) instruments using deuterochloroform as reference and internal deuterium lock. The multiplicity of the signal is indicated as: s - singlet, d - doublet, t - triplet, q - quartet, qn - quintet, m - multiplet, dd - doublet of doublets, dt - doublet of triplets, etc. Broad peaks are denoted as: br s - broad singlet, etc. Aromatic protons are indicated with arom. Coupling constants (*J*) are given in Hz. ^{13}C NMR spectra were recorded on the Bruker DPX-250 (62.5 MHz) and Bruker WM-400 (100 MHz) instruments in the solvent indicated. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. The sample were prepared as a thin film or as a solution in the solvent indicated. Mass spectra are recorded either by Mass Spectrometry Services of the University of Swansea or the University of Cambridge. Microanalyses were carried out by the staff of the Cambridge University Chemical Laboratories Microanalytical Department. Optical rotations were measured using a Perkin–Elmer 241 polarimeter, in a cell of 1 dm path length. *c* is expressed as g 100 cm^{-3}and $[\alpha]_D^{25}$ are quoted in implied units of 10^{-1} deg cm^2 g^{-1}. All solvents used were freshly distilled. $Et_2O(s)NH_3$ refers to diethyl ether saturated with ammonia. PE: petroleum ether, b.p. 60–80 °C. All reactions were performed under an inert atmosphere of nitrogen with dried glassware unless otherwise indicated.

(*R*)-*tert*-Butyl-3-hydroxy-pent-4-enoate [(*R*)-13], (*S*)-*tert*-butyl-3-acetoxy-pent-4-enoate (14): Vinyl acetate (83.72 mL, 0.546 mol) was added to a solution of **13** (31.33 g, 0.182 mol) in pentane (600 mL). Amano PS-D lipase (20 g) and 4 ÅMS (30 g) were added and the suspension was stirred at 30 °C. The reaction was monitored by GC and after 25 h, 52% conversion was achieved. The lipase and sieves were filtered and were washed with Et_2O. The solvent was removed and the crude product was purified by FC (PE/EtOAc 7:3) to give both **(*R*)-13** (15.3 g, 47%) and **14** (18.48 g, 49%) as colourless oils: **(*R*)-13**, $[\alpha]_D^{25} = +7.7$ ($c = 3.58$, $CHCl_3$); IR ($CDCl_3$): $\tilde{\nu}$ = 3503, 2982, 1715, 1646 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.84$ (ddd, $J = 5.4$, 10.5, 17.2 Hz, 1H, C*H*=CH$_a$H$_b$), 5.24 (dd, $J = 1.0$, 17.2 Hz, 1H, CH=CH$_a$*H*$_b$), 5.10 (dt, $J = 1.0$, 10.5 Hz, 1H, CH=CH$_a$*H*$_b$), 4.50–4.41 (m, 1H, C*H*OH), 3.20 (d, $J = 4.3$ Hz, 1H, OH), 2.52–2.34 (m, 2H, *t*BuCO$_2$C*H*$_2$), 1.43 (s, 9H, *tBu*O); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 171.6$ (s), 139.0 (d), 115.1 (t), 81.3 (s), 69.0 (d), 42.2 (t), 28.1 (s); CIMS: *m*/*z* (%): 190 (50) $[M+NH_4]^+$, 173 (20) $[M+H]^+$, 134 (100); HRMS: calcd for $C_9H_{17}O_3$: 173.1178; found: 173.1178 $[M+H]^+$; elemental analysis calcd (%) for $C_9H_{16}O_3$ (172.2): C 62.8, H 9.4; found: C 63.1, H 9.6. **14**: $[\alpha]_D^{25} = -5.6$ (c = 3.88, $CHCl_3$); IR (250 MHz, $CDCl_3$): $\tilde{\nu}$ = 2982, 1735, 1647, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 5.81$ (ddd, $J = 6.2$, 10.5, 17.2 Hz, 1H, C*H*=CH$_a$H$_b$), 5.52 (m, 1H, C*H*OAc), 5.21 (dd, $J = 1.0$, 17.2 Hz, 1H, CH=CH$_a$*H*$_b$), 5.11 (dd, $J = 1.0$, 10.5 Hz, 1H, CH=CH$_a$*H*$_b$), 2.57–2.39 (m, 2H, *t*BuCO$_2$C*H*$_2$), 2.00 (s, 3H, C*H*$_3$O$_2$), 1.35 (s, 9H, *tBu*O); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 169.5 (s), 168.8 (s), 135.2 (d), 117.1 (t), 80.8 (s), 70.9 (d), 40.6 (t), 27.9 (q), 20.9 (q); EIMS: *m*/*z* (%): 237 (70) $[M+Na]^+$, 181 (30); HRMS: calcd for $C_{11}H_{18}O_4Na$: 237.1103; found: 237.1099 $[M+Na]^+$; elemental analysis calcd (%) for $C_{11}H_{18}O_4$ (214.3): C 61.7, H 8.5; found: C 61.7, H 8.3.

(*R*)-*tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-pent-4-enoate (15): A solution of **(*R*)-13** (15.3 g, 88.3 mmol) in CH_2Cl_2 (250 mL) was stirred for 4 h with imidazole (18.14 g, 0.27 mol) and *tert*-butyldimethylsilylchloride (16.07 g, 0.11 mol). The reaction was quenched with sat. aq NH_4Cl (125 mL) and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and were evaporated to give a crude product which was purified by FC (PE/CH_2Cl_2 6:4) to yield **15** (25.03 g, 98%) as a colourless oil: $[\alpha]_D^{25} = +3.5$ ($c = 1.94$, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2930, 1722, 1472, 1368, 1255 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.81$ (ddd, $J = 6.2$, 10.5, 17.2 Hz, 1H, C*H*=CH$_a$H$_b$), 5.18 (dt, $J = 17.2$, 1.4 Hz, 1H, CH=CH$_a$*H*$_b$), 5.02 (dt, $J = 10.5$, 1.4 Hz, 1H, CH=CH$_a$*H*$_b$), 4.51 (m, 1H, C*H*OSi), 2.43 (dd, $J = 7.3$, 14.7 Hz, 1H, *t*BuCO$_2$CH$_a$*H*$_b$), 2.30 (dd, $J = 5.8$, 14.7 Hz, 1H, *t*BuCO$_2$C*H*$_a$H$_b$), 1.41 (s, 9H, O*tBu*), 0.85 (s, 9H, *tBu*Me$_2$SiO), 0.04, 0.02 (2s, 2×3H, *t*Bu*Me*$_2$SiO); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.2 (s), 140.5 (d), 114.3 (t), 80.3 (s), 70.8 (d), 44.7 (t), 28.1 (q), 25.8 (q), 25.6 (q), 18.1 (s); CIMS: *m*/*z* (%): 287 (20) $[M+H]^+$, 248 (100), 231 (50); HRMS: calcd for $C_{15}H_{31}O_3Si$: 287.2042; found: 287.2042 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{30}O_3Si$ (286.5): C 62.9, H 10.6 ; found: C 63.1, H 10.6.

(*R*)-3-*tert*-Butyldimethylsilyloxy-pent-4-enal (5): A solution of DIBAL (105 mL, 1.0 M in hexane, 105 mmol) was added dropwise to a solution of **15** (25.03 g, 87.4 mmol) in toluene (500 mL) at −78 °C. Following the addition, the reaction was stirred for 30 min. The reaction was quenched by dropwise addition of a sat. NH_4Cl (50 mL). After allowing the reaction mixture to reach RT, a saturated solution of Rochelle salt (200 mL) was added. The mixture was poured into brine (250 mL) and more Rochelle solution was added (150 mL) before it was extracted with EtOAc. The combined organic phases were dried and evaporated to a crude product, which was purified by FC (PE/Et_2O 9:1) to yield **5** (14.84 g, 79%) as a colourless oil: $[\alpha]_D^{25}$ = +3.0 ($c = 2.58$, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2990, 1728, 1472, 1254 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 9.74$ (t, $J = 2.3$ Hz, 1H, C*H*O), 5.84 (ddd, $J = 5.7$, 10.5, 17.0 Hz, 1H, C*H*=CH$_a$H$_b$), 5.23 (dt, $J = 1.0$, 17.0 Hz, 1H, CH=CH$_a$*H*$_b$), 5.08 (dt, $J = 1.0$, 10.5 Hz, 1H, CH=CH$_a$*H*$_b$), 4.62 (m, 1H, C*H*OSi), 2.60 (ddd, $J = 2.5$, 6.5, 15.5 Hz, 1H, CH$_a$H$_b$CHO), 2.50 (ddd, $J = 2.0$, 5.0, 15.5 Hz, 1H, CH$_a$H$_b$CHO), 0.85 (s, 9H, *tBu*Me$_2$SiO), 0.04, 0.02 (2s, 2×3H, *t*Bu*Me*$_2$SiO); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 201.5$ (s), 139.9 (d), 114.8 (t), 69.3 (d), 51.2 (t), 25.7 (q), 18.0 (s), −4.4 (q), −5.1 (q); elemental analysis calcd (%) for $C_{11}H_{22}O_2Si$ (214.4): C 61.6, H 10.3; found: C 61.4, H 10.3.

(*Z*/*E*)-(*R*)-3-(*tert*-Butyldimethylsilyloxy)-pent-4-enal oxime (16): Sodium acetate (1.95 g, 23.7 mmol) and hydroxylamine hydrochloride (1.65 g, 23.7 mmol) were added to a solution of **5** (1.70 g, 7.9 mmol) in EtOH (16 mL) and H_2O (16 mL). The reaction mixture was stirred for 14 h at RT. The solvent was evaporated and the aqueous phase was saturated with brine. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated to yield the crude oxime which was purified by flash chromatography (CH_2Cl_2/EtOAc 9:1) to give the oxime **16** (1.78 g, 98%) as a colourless oil: IR (neat): $\tilde{\nu}$ = 3250, 3095, 1645, 1254 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), 2 geometrical isomers in approximately 1.1:1 ratio: major isomer, $\delta = 9.99$ (br s, 1H, OH), 6.82 (t, $J = 5.0$ Hz, 1H, N*H*OH), 5.80 (ddd, $J = 5.7$, 10.5, 17.1 Hz, 1H, C*H*=CH$_a$H$_b$), 5.19 (ddt, $J = 1.5$, 5.7, 17.1 Hz, 1H, CH=CH$_a$*H*$_b$), 5.06 (br s, $J = 10.4$ Hz, 1H, CH=CH$_a$*H*$_b$), 4.37 (m, 1H, C*H*OSi), 2.58 (t, $J = 6.0$ Hz, 2H, NHCC*H*$_2$), 0.88 (s, 9H, *tBu*Me$_2$SiO), 0.06, 0.04 (2s, 2×3H, *t*Bu*Me*$_2$SiO); minor isomer, $\delta = 9.68$ (br s, 1H, OH), 7.42 (t, $J = 6.5$ Hz, 1H, N*H*OH), 5.80 (ddd, $J = 5.7$, 10.5, 17.1 Hz, 1H, C*H*=CH$_a$H$_b$), 5.19 (ddt, $J = 1.5$, 5.7, 17.1 Hz, 1H, CH=CH$_a$*H*$_b$), 5.06 (br s, $J = 10.4$ Hz, 1H, CH=CH$_a$*H*$_b$), 4.29 (m, 1H C*H*OSi), 2.39 (t, $J = 6.0$ Hz, 2H, NHCC*H*$_2$), 0.88 (s, 9H, *tBu*Me$_2$SiO), 0.02, 0.05 (2s, 2×3H, *t*Bu*Me*$_2$SiO); ^{13}C NMR (100 MHz, $CDCl_3$): major isomer: δ = 148.9 (s), 140.3 (s), 114.6 (d), 70.5 (t), 33.3 (t), 25.7 (q), 18.1 (s), −4.6 (q), −5.0 (q); minor isomer: δ = 149.3 (s) 140.2 (s), 114.7 (d), 71.8 (t), 37.8 (t), 25.7 (q), 18.1 (s), −4.6 (q), −5.0 (q); CIMS: *m*/*z* (%): 230 (30) $[M+H]^+$, 214 (100), 171 (60), 132 (20), 82 (75); HRMS: calcd for $C_{11}H_{24}NO_2Si$: 230.1576; found: 230.1576 $[M+H]^+$; elemental analysis calcd (%) for $C_{11}H_{23}NO_2Si$ (229.4): C 57.6, H 10.1, N 6.1; found: C 57.9, H 10.1, N 6.0.

(4*R*,5*R*,8*S*)-8-(3-Benzoyloxy-propyl)-4-(*tert*-butyldimethylsilyloxy)-7-oxa-1-aza-bicyclo[3.2.1]octane (3): Sodium cyanoborohydride (1.64 g, 26.2 mmol) was added to a solution of **16** (4.0 g, 17.4 mmol), five drops of methyl orange solution and ten drops of HCl (50% in MeOH) in MeOH

0947-6539/01/0709-1850 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 9

(40 mL) at −10 °C. The colour of the reaction was kept pink (acidic) by the addition of more HCl. After the pink colour persisted, the reaction was stirred for 30 min and the reaction mixture was cooled to −50 °C before being made strongly alkaline by the addition of 20% NaOH. The reaction mixture was subsequently poured into iced brine in a separating funnel. The aqueous phase was extracted with pre-cooled CH_2Cl_2 and the combined organic extracts were added to a solution of benzoyloxybutanal **6** (3.35 g, 17.4 mmol). The reaction mixture was stirred for 1 h at 0 °C with $MgSO_4$. The crude product was obtained after filtration and the evaporation of the solvent. $MgSO_4$ (5.0 g) was added to a solution of crude **4** in toluene (500 mL) and the resulting mixture was heated at 70 °C for 24 h. The solvent was removed and the product was purified by flash chromatography (PE/EtOAc 7:3) to give a mixture of cycloadducts (3.7 g, 53% for three steps from **16**) containing **3** (2.25 g, 32% from **16**), **18** (0.35 g, 5%), **19** (0.56 g, 8%) and **20** (0.55 g, 8%) as colourless oils. The cycloadduct **3** could be crystallised from EtOAc. **3**: M.p. 44.5–46.0 °C; $[\alpha]_D^{25} = -1.93$ ($c = 0.88$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2930$, 1720, 1602, 1452, 1275, 1107 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.03$ (d, $J = 7.5$ Hz, 2H, arom.), 7.54 (t, $J = 7.5$ Hz, 1H, arom.), 7.42 (t, $J = 7.5$ Hz, 2H, arom.), 4.35 (t, $J = 6.6$ Hz, 2H, H-11), 4.00 (brs, 1H, H-4), 3.82 (d, $J = 7.4$ Hz, 1H, H-6), 3.76 (t, $J = 6.3$ Hz, 1H, H-6), 3.64 (t, $J = 7.2$ Hz, 1H, H-8), 3.23 (dd, $J = 6.5$, 14.0 Hz, 1H, H-2a), 3.01 (ddd, $J = 5.0$, 13.0, 14.0 Hz, 1H, H-2b), 2.44 (t, $J = 4.50$ Hz, 1H, H-5), 2.02–1.90 (m, 2H, H-3b, H-10b), 1.88–1.77 (m, 1H, H-10a), 1.62–1.52 (m, 1H, H-9b), 1.38–1.36 (m, 2H, H-3a, H-9a), 0.89 (s, 9H, *t*BuMe$_2$SiO), 0.05 (s, 6H, *t*Bu*Me*$_2$SiO); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta =$ 166.6 (s), 132.8 (d), 130.4 (s), 129.5 (d), 128.3 (d), 69.9 (t), 68.6 (t), 64.7 (d), 53.7 (t), 49.8 (d), 28.1 (t), 26.9 (t), 25.9 (t), 25.7 (q), 63.3 (d), 18.0 (s), −4.8 (q); CIMS: *m*/*z* (%): 406 (100) $[M+H]^+$; HRMS: calcd for $C_{22}H_{36}NO_4Si$: 406.2414 $[M+H]^+$; found: 406.2414; elemental analysis calcd (%) for $C_{22}H_{35}NO_4Si$ (405.6): C 65.2, H 8.7, N 3.5; found: C 64.9, H 8.6, N 3.6.

(4*S*,5*S*,7*R*)-7-(3-Benzoyloxy-propyl)-4-(*tert*-butyldimethylsilyloxy)-8-oxa-1-aza-bicyclo[3.2.1]octane (19): $[\alpha]_D^{25} = -5.6$ ($c = 0.64$, $CHCl_3$); IR ($CDCl_3$): $\tilde{\nu} = 2931$, 1714, 1602, 1452, 1278 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 4.31$ (dt, $J = 6.3$, 0.9 Hz, 1H, H-11), 4.17 (dd, $J = 4.2$, 6.8 Hz, 1H, H-5), 3.83 (ddd, $J = 4.2$, 5.8, 10.0 Hz, 1H, H-4), 3.26 (ddd, $J = 4.5$, 11.4, 14.3 Hz, 1H, H-2), 3.02 (ddd, $J = 5.2$, 8.3, 12.4 Hz, 1H, H-7), 2.80 (dd, $J = 5.8$, 14.4 Hz, 1H, H-2), 2.49 (dd, $J = 8.4$, 12.5 Hz, 1H, H-6a), 1.99–1.44 (m, 6H, H-10, H-9, H-3), 0.84 (s, 9H, *t*BuMe_2SiO), 0.03 (s, 6H, *t*Bu*Me*$_2$SiO); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 166.6$ (s), 132.8 (d), 130.4 (s), 129.5 (d), 128.3 (d), 79.7 (d), 66.5 (d), 64.8 (t), 63.6 (d), 54.2 (t), 35.4 (t), 33.7 (t), 26.7 (t), 26.4 (t), 25.7 (q), 17.9 (d), −4.6 (q), −4.5 (q); CIMS: *m*/*z* (%): 406 (100) $[M+H]^+$, 284 (30), 152 (50); HRMS: calcd for $C_{22}H_{36}NO_4Si$: 406.2414; found: 406.2420 $[M+H]^+$.

(4*S*,5*S*,7*S*)-7-(3-Benzoyloxy-propyl)-4-(*tert*-butyldimethylsilyloxy)-8-oxa-1-aza-bicyclo[3.2.1]octane (20): $[\alpha]_D^{25} = +6.3$ ($c = 0.78$, $CHCl_3$); $\tilde{\nu} = 2931$, 1716, 1602, 1452, 1277 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 8.00–7.35$ (m, 5H, arom.), 4.32 (t, $J = 6.0$ Hz, 2H, H-11), 4.17 (dd, $J = 3.7$, 7.0 Hz, 2H, H-5), 3.89 (ddd, $J = 4.2$, 5.9, 9.8 Hz, 1H, H-4), 3.43 (qn, $J = 7.9$ Hz, 1H, H-7), 3.23 (ddd, $J = 4.9$, 11.6, 14.9 Hz, 1H, H-2), 2.98 (dd, $J = 6.1$, 15.0 Hz, 1H, H-2), 2.21 (ddd, $J = 7.0$, 8.1, 12.2 Hz, 1H, H-6b), 1.98–1.60 (m, 6H, H-3, H-6a, H-9, H-10), 1.40 (m, 1H, H-3), 0.83 (s, 9H, *t*BuMe_2SiO), 0.01 (s, 6H, *t*Bu*Me*$_2$SiO); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 166.5$ (s) 132.9 (d), 130.2 (s), 129.5 (d), 128.3 (d), 79.0 (d), 66.7 (d), 64.5 (t), 64.2 (d), 48.3 (t), 34.0 (t), 27.7 (t), 27.4 (t), 25.7 (q), 25.4 (t), 17.9 (s), −4.6 (q), −4.5 (q); *m*/*z* (%): 406 (100) $[M+H]^+$, 286 (90), 210 (60), 152 (30); HRMS: calcd for $C_{22}H_{36}NO_4Si$: 406.2414; found: 406.2414 $[M+H]^+$.

(4*R*,5*R*,8*S*)-*N*-Benzyloxycarbonyl-2-(3-benzoyloxy-propyl)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxymethyl-piperidine (21): A solution of **3** (3.0 g, 7.4 mmol) in MeOH (150 mL) and Pd/C (1.5 g, 20 mol%) was stirred under an atmosphere of H_2 for 48 h and was filtered through Celite with ample washes of MeOH. After evaporation, the crude product was taken up in Et_2O (120 mL) and $NaHCO_3$ (60 mL). The reaction mixture was cooled to 0 °C before benzyl chloroformate (6.3 g, 37 mmol) was added. After stirring for 20 h, the reaction mixture was added to brine and the aq. phase was extracted with Et_2O. The organic phases were dried over $MgSO_4$ and after evaporation, the crude product was purified by FC (PE/EtOAc 7:3) to give the product **21** (2.88 g, 90%) as a colourless oil: $[\alpha]_D^{25} = -16.7$ ($c = 0.71$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3478$, 2955, 1694, 1429, 1276 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, broadening due to a mixture of rotamers): $\delta = 8.02–7.23$ (m, 10H, arom.), 5.13 (m, 1H), 4.60 (m, 1H), 4.26 (brs, 3H), 3.84 (m, 2H), 3.50 (brs, 1H), 2.82 (m 1H), 2.63 (d, $J = 6.1$ Hz, 1H), 1.87 (m, 2H), 1.59 (m, 4H), 0.87 (s, 9H, *t*BuMe_2Si), 0.07 (s, 6H, *t*Bu*Me*$_2$Si); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 166.6$ 155.4, 136.7, 132.9, 130.3, 129.5, 128.5, 128.4, 128.0, 127.4, 126.9, 70.1, 67.3, 65.0, 64.4, 63.4, 52.7, 49.3, 37.3, 35.4, 25.7, 25.2, 22.2, 17.9, −3.8, −4.8; CIMS: *m*/*z* (%): 542 (15) $[M+H]^+$, 408 (40), 228 (80), 108 (100); HRMS: calcd for $C_{30}H_{44}O_6NSi$: 542.2938; found: 542.2938 $[M+H]^+$; elemental analysis calcd (%) for $C_{30}H_{43}O_6NSi$ (541.8): C 66.5, H 8.0, N 2.6; found: C 66.5, H 8.2, N 2.6.

(4*R*,5*R*,8*S*)-*N*-Benzyloxycarbonyl-2-(3-benzoyloxy-propyl)-4-(*tert*-butyldiphenylsilyloxy)-2-(*o*-nitrophenylselanylmethyl)piperidine (22): *o*-Nitro phenylselenocyanate (0.49 g, 2.15 mmol) followed by tri-*n*-butylphosphine (0.45 mL, 1.82 mmol) was added to a solution of **21** (0.75 g, 1.11 mmol) in THF (20 mL). The reaction mixture was stirred for 2 h and after evaporation of solvent, the crude product was purified by FC (PE/EtOAc 9:1) to give of the product **22** (50.9 mg, 72%) as a yellow oil: $[\alpha]_D^{25} = -25.1$ ($c = 0.85$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3019$, 1794, 1690, 1215 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, broadening due to a mixture of rotamers): $\delta = 8.38–7.26$ (m, 24H, arom.), 5.10 (s, 2H), 4.73 (brs, 1H), 4.22 (brs, 2H), 3.99 (brs, 1H), 3.84 (dt, $J = 4.6$, 10.4 Hz, 1H), 3.70 (dd, $J = 2.8$, 12.1 Hz, 1H), 2.58 (brt, 1H), 2.33 (brt, 1H), 2.17 (brs, 1H), 1.65–1.32 (m, 6H), 1.09 (s, 9H, *t*BuPh_2Si); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 166.5$, 155.2, 146.9, 136.5, 135.9, 135.8, 133.9, 133.6, 133.3, 132.9, 130.2, 130.1, 129.9, 129.5, 129.0, 128.5, 128.3, 128.0, 127.9, 127.7, 125.6, 125.4, 71.4, 67.3, 64.2, 60.4, 53.2, 37.4, 35.3, 27.1, 25.4, 24.9, 19.4, 14.2; FAB: *m*/*z* (%): 851 (90) $[M+H]^+$, 794 (60), 453 (60), 258 (60), 197 (100); HRMS: calcd for $C_{46}H_{51}N_2O_7SiSe$: 851.2630; found: 851.2600 $[M+H]^+$.

(2*S*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-2-(3-benzoyloxy-propyl)-4-(*tert*-butyldimethylsilyloxy)-3-methylene-piperidine (23): A solution of **22** (0.12 g, 0.16 mmol) in CH_2Cl_2 (10 mL) and *m*CPBA (0.06 g, 0.34 mmol) was stirred for 5 min and was quenched by the addition of aq. Na_2SO_3. The reaction mixture was stirred for another 1 h. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with sat. $NaHCO_3$ until benzoic acid was no longer detected by TLC. The extracts were dried with Na_2SO_4 and the solvent was removed to give the crude product which was purified by FC (PE/EtOAc 7:3) to afford the product **23** (0.075 g, 85%) as a colourless oil: $[\alpha]_D^{25} = +5.8$ ($c = 0.48$, $CHCl_3$); IR ($CDCl_3$): $\tilde{\nu} = 2956$, 1690, 1427, 1277 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, broadening due to a mixture of rotamers): $\delta = 8.04–7.33$ (m, 10H, arom.), 5.00 (m, 5H), 4.19 (m, 4H), 3.09 (brq, $J = 11.2$ Hz, 1H), 1.74 (brs, 6H), 0.91 (s, 9H, *t*BuMe_2Si), 0.07 (s, 6H, *t*Bu*Me*$_2$Si); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 166.5$, 155.1, 147.1, 132.9, 129.5, 128.5, 128.3, 128.0, 127.8, 109.4, 68.5, 67.2, 136.7, 64.5, 59.2, 38.7, 36.6, 29.7, 27.7, 25.8, 18.3, −4.9, −5.0; FAB: *m*/*z* (%): 546 (90) $[M+Na]^+$, 524 (100) $[M+H]^+$, 466 (40), 348 (90), 316(80); HRMS: calcd for $C_{30}H_{42}O_5NSi$: 524.2816; found: 524.2832 $[M+H]^+$; elemental analysis calcd (%) for $C_{30}H_{41}O_5NSi$ (647.9): C 68.8, H 7.9, N 2.7; found: C 68.6, H 7.8, N 2.6.

(2*S*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-2-(3-benzoyloxy-propyl)-4-(*tert*-butyldimethylsilyloxy)-piperidin-3-one (24): Ozone was bubbled into a solution of **23** (0.98 g, 1.87 mmol) in CH_2Cl_2 (150 mL) until the solution became blue. The excess ozone was removed by purging the solution with N_2. Triphenylphosphine (0.98 g, 3.74 mmol) was added and the reaction mixture was stirred for 2 h at RT. The solvent was removed and the crude product was purified by FC (PE/EtOAc 7:3) to give the product **24** (7.9 mg, 88%) as a colourless oil: $[\alpha]_D^{25} = +20.1$ ($c = 0.91$, $CHCl_3$); IR (neat): $\tilde{\nu} =$ 2954, 1715, 1424, 1275 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, broadening due to a mixture of rotamers): $\delta = 8.03–7.32$ (m, 10H, arom), 5.14 (m, 1H), 4.75 (brs, 1H), 4.30 (m, 4H), 3.25 (brt, $J = 12.5$ Hz, 1H), 2.17 (m, 1H), 2.00 (td, $J = 4.8$, 12.7 Hz, 1H), 1.81 (brs, 4H), 0.89 (s, 9H, *t*BuMe_2Si), 0.13, 0.03 (2s, 2×3H, *t*Bu*Me*$_2$Si); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 205.1$, 166.4, 155.0, 133.0, 130.2, 129.6, 128.6, 128.4, 128.2, 128.0, 73.1, 67.8, 63.9, 63.4, 38.0, 35.0, 27.2, 25.7, 25.2, 18.4, −4.6, −5.5; FAB: *m*/*z* (%): 526 (100) $[M+H]^+$, 482 (50), 424 (50), 307 (30), 272 (30); HRMS: calcd for $C_{29}H_{40}O_6NSi$: 526.2625; found: 526.2625 $[M+H]^+$; elemental analysis calcd (%) for $C_{23}H_{39}O_5NSi$ (650.0): C 66.3, H 7.5, N 2.7; found: C 66.2, H 7.5, N, 2.7.

(2*S*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-2-(3-hydroxypropyl)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-methylpiperidine (25): Methylmagnesium bromide (2.37 mL, 3.0 M in Et_2O) was added dropwise into a solution of **24** (0.89 g, 1.69 mmol) in THF (30 mL) maintained at 0 °C. The reaction mixture was stirred for 2 h and was quenched with sat. NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc and the combined organic extracts was dried with $MgSO_4$. The solvent was removed and the crude product was purified by FC (PE/EtOAc 7:3) to give the product **25** (0.67 g,

90%) as a colourless oil: $[\alpha]_D^{25} = +2.6$ ($c = 0.46$, $CHCl_3$); IR (neat): $\tilde{\nu} =$ 3436, 2954, 1682, 1434, 1111 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, broadening due to a mixture of rotamers): $\delta = 7.34$ (m, 5H, arom.), 5.12 (s, 2H), 4.18 (br s, 2H), 3.84 (dd, $J = 5.4$, 11.5 Hz, 1H), 3.61 (br s, 2H), 2.90 (br t, $J =$ 11.9 Hz, 1H), 2.05 (s, 1H), 1.92 (br s, 1H), 1.65–1.44 (m, 6H), 1.81 (s, 3H, Me), 0.89 (s, 9H, *t*BuMe$_2$Si), 0.09, 0.07 (2s, 2 × 3H, *t*Bu*Me*$_2$Si); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 156.0$, 136.7, 128.5, 128.0, 72.4, 67.3, 60.3, 37.4, 31.8, 29.4, 25.7, 21.1, 20.7, 18.0, −73.7, 4.2, 62.5, −4.8; CIMS: *m*/*z* (%): 438 (60) $[M+H]^+$, 304 (30), 132 (30), 108 (100); HRMS: calcd for $C_{23}H_{40}O_5NSi$: 438.2675; found: 438.2676 $[M+H]^+$; elemental analysis calcd (%) for $C_{23}H_{39}O_5NSi$ (437.7): C 63.1, H 9.0, N 3.2; found: C 62.9, H 8.9, N 3.1.

(2*S*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-2-(3-tosyloxypropyl)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-methyl-piperidine (26): Triethylamine (1.84 mL, 13 mmol) and DMAP (1.59 g, 13 mmol) were added to a solution of the diol **25** (0.57 g, 1.3 mmol) dissolved in CH_2Cl_2 (30 mL). This was followed by TsCl (0.37 g, 19 mol) and the reaction mixture was stirred for 3 h. The solvent was removed and the crude product was purified by FC (PE/EtOAc 1:1) to give the product **26** (0.75 g, 97%) as a colourless oil: $[\alpha]_D^{25} = +5.3$ ($c = 0.43$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3538$, 2955, 1694, 1428, 1360 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, broadening due to a mixture of rotamers): $\delta = 7.78$–7.31 (m, 9H, arom.), 4.10 (m, 2H), 3.99 (br s, 2H), 3.77 (dd, $J = 5.3$, 11.5 Hz, 5.09 (s, 2H), 1H), 2.81 (br s, 1H), 2.44 (s, 3H), 1.96 (s, 1H), 1.87 (br d, $J = 4.6$ Hz, 1H), 1.13 (s, 3H, Me), 0.89 (s, 9H, *t*BuMe_2Si), 1.67–1.42 (m, 5H), 0.09, 0.07 (2s, 2 × 3H, *t*Bu*Me*$_2$Si); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 155.8$, 144.6, 133.2, 129.8, 128.5, 128.1, 127.9, 73.5, 72.3, 70.3, 67.4, 60.0, 37.3, 31.7, 25.8, 25.7, 21.6, 20.7, 18.0, −4.1, −4.8; FAB: *m*/*z* (%): 614 (10) $[M+Na]^+$, 592 (50) $[M+H]^+$, 534 (20), 458 (40), 307 (100); HRMS: calcd for $C_{30}H_{46}O_7NSiS$: 592.2764; found: 592.2749 $[M+H]^+$.

(8*R*,8*aS*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-8-hydroxy-8-methyl-octahydroindolizidine (27): Piperidine **26** (0.75 g, 1.26 mmol) was dissolved in MeOH (30 mL) containing ammonium formate (0.4 g, 6.3 mmol). 10% Pd/C (1.48 g) was added and the reaction mixture was heated at 40 °C for 30 min. The reaction mixture was filtered through Celite and washed with MeOH/Et_2O/NH_3 1:1:0.1. The solvent was removed and the crude product was purified by FC (hexanes/Et_2O/NH_3 3.9:6:0.1) to give the product **27** (0.35 g, 96%) as a colourless oil: $[\alpha]_D^{25} = -29.4$ ($c = 0.97$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3476$, 2954, 1462, 1256 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.14$ (br s, 1H, OH), 3.56 (t, $J = 2.4$ Hz, 1H, H-7), 3.00 (dd, $J = 5.3$, 8.2 Hz, 1H, H-3eq), 2.74 (ddd, $J = 1.6$, 5.0, 10.6 Hz, 1H, H-5eq), 2.32 (ddd, $J = 2.7$, 7.7, 12.9 Hz, 2H, H-8ax, H-5eq), 2.20 (dd, 1H, $J = 8.9$, 17.1 Hz, H-3ax), 2.05 (tdd, $J = 13.1$, 5.1, 2.7 Hz, 1H, H-6ax), 1.73–1.64 (m, 4H, H-1, H-2), 1.48 (dd, $J = 14.1$, 2.2 Hz, 1H, H-6eq), 1.09 (s, 3H, H-9), 0.09 (s, 9H, *t*BuMe_2Si), 0.05 (s, 6H, *t*Bu*Me*$_2$Si); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 73.1$ (d), 70.9 (s), 65.1 (d), 54.6 (t), 47.1 (t), 29.7 (t), 25.8 (q), 23.0 (t), 21.5 (q), 20.8 (t), 17.9 (s), −5.0 (q), −4.4 (q); FAB: *m*/*z* (%): 286 (100) $[M+H]^+$; HRMS: calcd for $C_{15}H_{32}O_2NSi$: 286.2202; found: 286.2195 $[M+H]^+$.

(8*R*,8*aS*,7*R*)-7,8-Dihydroxy-8-methyl-octahydroindolizidine (28): A solution of **27** (20 mg, 79 μmol) in THF (1 mL) and TBAF (0.7 mL, 0.7 mmol, 1M in THF) was stirred for 3 d. The solvent was removed and water (0.5 mL) was added. The aqueous layer was extracted with ether and the solvent was removed. The crude mixture was purified by FC (EtOAc/MeOH/NH_3 9.0:0.8:0.2) to give the product **28** (10.1 mg, 83%) as a colourless oil: $[\alpha]_D^{25} = -7.2$ ($c = 0.36$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3691$, 3624, 3460, 2950, 1669, 1602 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.62$ (t, $J =$ 2.7 Hz, 1H, H-7), 3.16 (br s, 1H, OH), 3.04 (m, 1H, H-3eq), 2.83 (ddd, $J =$ 1.4, 4.0, 10.3 Hz, 1H, H-5eq), 2.35–2.30 (m, 2H, H-8ax, H-5ax), 2.22 (dd, $J = 9.0$, 17.2 Hz, 1H, H-3ax), 2.15 (tdd, $J = 3.2$, 5.1, 14.5 Hz, 1H, H-6ax), 1.78–1.66 (m, 3H, H-1, H-2), 1.61 (dd, $J = 1.6$, 14.4 Hz, 2H, H-6eq), 1.47 (br s, 1H, OH), 1.18 (s, 3H, H-9); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 72.8$ (d), 70.4 (s), 65.1 (d), 54.6 (t), 47.0 (t), 29.4 (t), 22.9 (t), 21.0 (q), 20.8 (t); CIMS: *m*/*z* (%): 172 (80) $[M+H]^+$, 154 (30), 70 (90), 44 (100); HRMS: calcd for $C_9H_{17}O_2N$: 171.1259; found: 171.1248 $[M]^+$.

(8*R*,8*aS*)-8-Hydroxy-8-methyl-7-octahydroindolizidone (2):[3] A solution of $(COCl)_2$ (81 μL, 0.93 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −50 °C. DMSO (99 μL, 1.4 mmol) was added dropwise and the reaction mixture was stirred for 20 min. The diol **28** (80.0 mg, 0.47 mmol) was added dropwise as a solution in CH_2Cl_2 (0.3 mL) and the reaction mixture was stirred for a further 20 min. Triethylamine (0.65 mL, 4.67 mmol) was added and the reaction mixture was stirred at RT. for a further 30 min. EtOAc was added and CH_2Cl_2 was removed before the reaction mixture was filtered. The crude mixture was purified by column chromatography (Et_2O/NH_3 9.8:0.2) to give **2** (47.4 mg, 60%) as a colourless oil: $[\alpha]_D^{25} = -51.6$ ($c = 0.06$, $CHCl_3$); lit.: $[\alpha]_D^{25} = -44.2$ ($c = 4.7$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3430$, 2936, 2799, 1722, 1124 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.77$ (br s, 1H, OH), 3.26 (dd, $J = 7.7$, 9.6 Hz, H-3eq), 3.16 (t, $J = 7.5$ Hz, 1H, H-5eq), 3.06 (ddd, $J =$ 7.5, 12.5, 14.4 Hz, 1H, H-6ax), 2.30 (m, 2H, H-8, H-3ax), 2.23 (dd, $J = 2.7$, 14.6 Hz, 1H, H-6eq), 2.16 (t, $J = 8.1$ Hz, 1H, H-5ax), 1.84–1.75 (m, 4H, H-1, H-2), 1.18 (s, 3H, H-9); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 209.5$ (s), 75.4 (s), 72.3 (d), 54.0 (t), 50.1 (t), 36.4 (t), 23.5 (t), 22.8 (t), 16.8 (q); CIMS: *m*/*z* (%): 170 (50) $[M+H]^+$, 154 (30), 98 (20), 70 (100); HRMS: calcd for $C_9H_{16}O_2N$: 170.1181; found: 170.1186$[M+H]^+$.

(2*R*,4*E*)-1-(*tert*-Butyldiphenylsiloxy)-2,5-dimethyl-4-octen-6-one (31): Aldehyde **9**[25] (7.18 g, 21 mmol) was added to a solution of triphenyl(1-propionylethylidene)phosphorane (**8**, 8.17 g, 23.6 mmol) in toluene (150 mL) and was heated at 90 °C for 6 h. The solvent was removed and crude mixture was purified by FC (EtOAc/PE 2:8) to give the product **31** (6.3 g, 85%) as a colourless oil: $[\alpha]_D^{25} = +9.6$ ($c = 3.6$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2932$, 1673, 1428, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.66$–7.37 (10H, arom.), 6.60 (t, $J = 7.2$ Hz, 3H, H-5), 3.55, 3.50 (dd, $J = 5.6$, 9.9 Hz, 1H, H-8), 2.61 (q, $J = 7.3$ Hz, 2H, H-2), 2.43 (m, 1H, H-6), 2.11 (m, 1H, H-6), 1.87 (m, 1H, H-7), 1.77 (s, 3H, H-9), 1.07 (s, 12H, H-1, *t*BuPh_2Si), 0.95 (d, $J = 6.7$ Hz, 3H, H-10); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 202.4$ (s), 140.6 (d), 137.7 (s), 135.6 (d), 133.8 (s), 129.6 (d), 127.6 (d), 68.3 (t), 36.1 (d), 32.6 (t), 30.3 (t), 26.9 (q), 19.3 (s), 16.8 (q), 11.5 (q), 8.9 (q); FAB: *m*/*z* (%): 431 (50) $[M+Na]^+$, 407 (25), 351 (80), 331 (80); HRMS: calcd for $C_{26}H_{36}O_2$-SiNa: 431.2382; found: 431.2378 $[M+Na]^+$; elemental analysis calcd (%) for $C_{26}H_{36}O_2Si$ (408.7): C 76.4, H 8.9; found: C 76.3, H 8.8.

(2*R*,6*S*,4*E*)-1-(*tert*-Butyldiphenylsiloxy)-2,5-dimethyl-4-octen-6-ol (32): Ketone **31** (1.09 g, 2.66 mmol) and (*R*)-CBS catalyst (1.0M in toluene, 0.4 mL, 15 mol%) was azeotroped twice with toluene before CH_2Cl_2 (16 mL) was added. The reaction mixture was cooled to cooled to −40 °C before catecholborane (0.64 g, 5.33 mmol) in CH_2Cl_2 (4.0 mL) was added dropwise. The reaction mixture was quenched with MeOH (1.0 mL) after 24 h and was allowed to be warmed to RT. The solvent was removed and crude mixture was purified by FC (EtOAc/PE 2:8) to give the product **32** (0.8 g, 73%) as a colourless oil: $[\alpha]_D^{25} = +9.0$ ($c = 0.82$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3384$, 2960, 1428, 1112 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.78$–7.41 (10H, arom.), 5.39 (t, $J = 7.3$ Hz, 1H, H-5), 3.91 (t, $J = 6.7$ Hz, 3H, H-3), 3.54 (dd, $J = 1.0$, 5.9 Hz, 2H, H-8), 2.22 (m, 1H, H-6), 1.96 (m, 1H, H-6), 1.79 (m, 1H, H-7), 1.60 (s, 3H, H-9), 1.57–1.50 (m, 2H, H-2), 1.06 (s, 9H, *t*BuPh_2Si), 0.95 (d, $J = 6.6$ Hz, 3H, H-10), 0.82 (t, $J = 7.1$ Hz, 3H, H-1); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 137.9$ (s), 135.7 (d), 134.1 (s), 129.6 (d), 127.6 (d), 125.3 (d), 79.6 (d), 68.5 (t), 36.5 (d), 31.2 (t), 27.6 (t), 26.9 (q), 19.4 (s), 16.7 (q), 11.2 (q), 10.2 (q); FAB: *m*/*z* (%): 433 (100) $[M+Na]^+$, 393 (35), 353 (20), 199 (100); HRMS: calcd for $C_{26}H_{38}O_2SiNa$: 433.2539; found: 433.2566 $[M+Na]^+$; elemental analysis calcd (%) for $C_{26}H_{36}O_2Si$ (410.7): C 76.0, H 9.3; found: C 76.2, H 9.3.

(2*R*,6*S*,4*E*)-6-Benzyloxymethyloxy-1-(*tert*-butyldiphenylsiloxy)-2,5-dimethyl-4-octene (33): Hünigs base (13.5 mL, 78 mmol), followed by BOMCl (2.17 mL, 15.6 mmol) were added to a solution of **32** (3.2 g, 7.8 mmol) in toluene (100 mL) containing a catalytic amount of Bu_4NI (100 mg). The reaction mixture was heated at reflux for 14 h. The solvent was removed and the crude mixture was purified by FC (Et_2O/PE 1:9) to give **33** (4.03 g, 97%) as a colourless oil: $[\alpha]_D^{25} = -53.7$ ($c = 0.3$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2931$, 1454, 1428, 1112, 1027 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.79$–7.42 (15H, arom.), 5.47 (t, $J = 7.0$ Hz, 1H, H-5), 4.85–4.55 (m, 4H, O*CH*$_2$O*CH*$_2$Ph), 3.99 (t, $J = 7.0$ Hz, 1H, H-3), 3.59 (dd, $J = 2.7$, 5.9 Hz, 2H, H-8), 2.31 (m, 1H, H-6), 2.04 (m, 1H, H-6), 1.87–1.63 (m, 3H, H-2, H-7), 1.62 (s, 3H, H-9), 1.17 (s, 9H, *t*BuPh_2Si), 0.99 (m, 6H, H-1, H-10); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 138.3$ (s), 135.7 (d), 134.5 (s), 134.1 (s), 129.6 (d), 128.6 (d), 128.5 (d), 128.2 (d), 128.0 (d), 127.8 (d), 127.7 (d), 91.3 (t), 83.6 (d), 69.5 (t), 68.6 (t), 36.5 (d), 31.3 (t), 27.0 (q), 26.5 (t), 19.4 (s), 16.7 (q), 10.9 (q), 10.6 (q); EIMS: *m*/*z* (%): 553 (20) $[M+Na]^+$, 453 (30), 413 (35), 381 (40); HRMS: calcd for $C_{34}H_{46}O_3SiNa$: 553.3114; found: 553.3107 $[M+Na]^+$; elemental analysis calcd (%) for $C_{34}H_{46}O_3Si$ (530.8): C 76.9, H 8.7; found: C 77.1, H 8.6.

(2*R*,6*S*,4*E*)-6-Benzyloxymethyloxy-2,5-dimethyl-4-octen-1-ol (34): Tetrabutylammonium fluoride (1.0M in THF, 14 mL) was added to a solution of **33** (4.03 g, 7.6 mmol) in THF (20 mL). The reaction mixture was stirred for 2 h and the solvent was removed. The crude mixture was purified by FC (Et_2O/PE 1:1) to give the product **34** (1.98 g, 90%) as a colourless oil: $[\alpha]_D^{25} = -92.3$ ($c = 0.9$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3380$, 2961, 1454, 1380,

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1036 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.34$ (5H, arom.), 5.41 (t, $J =$ 6.7 Hz, 1H, H-5), 4.73–4.50 (m, 4H, OCH_2OCH_2Ph), 3.90 (t, $J = 7.0$ Hz, 1H, H-3), 3.46 (dd, $J = 6.0$, 10.6 Hz, 2H, H-8), 2.13 (m, 1H, H-6), 1.96 (m, 1H, H-6), 1.72–1.56 (m, 3H, H-2, H-7), 1.55 (s, 3H, H-9), 0.91 (m, 6H, H-1, H-10); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 138.1$ (s), 134.8 (s), 128.4 (d), 127.9 (d), 127.6 (d), 83.6 (d), 69.5 (t), 68.0 (t), 36.3 (d), 31.3 (t), 26.3 (t), 91.4 (t), 16.5 (q), 10.9 (q), 10.4 (q); CIMS: m/z (%): 310 (10) $[M+NH_4]^+$, 172 (100), 155 (20), 106 (55); HRMS: calcd for $C_{18}H_{32}NO_3$: 310.2382; found: 310.2377 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{18}H_{28}O_3$ (292.4): C 73.9, H 9.7; found: C 74.0, H 9.5.

(2*R*,6*S*,4*E*)-6-Benzyloxymethyloxy-2,5-dimethyl-4-octen-1-al (7): A solution of **34** (43.5 mg, 0.14 mmol) in CH_2Cl_2 (4.0 mL) was stirred with NMO (48 mg, 0.41 mmol) and TPAP (1.6 mg, 10 mol%) for 30 min. EtOAc was added and CH_2Cl_2 was removed before the reaction mixture was filtered. The solvent was removed in vacuo and the crude mixture was purified by FC (Et_2O/PE 1:1) to give **7** (40.8 mg, 94%) as a colourless oil: $[\alpha]_D^{25} = -101.93$ ($c = 0.83$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2964$, 1728, 1454, 1100, 1038 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.65$ (d, $J = 0.8$ Hz, 1H, C*H*O), 7.35 (m, 5H, arom.), 5.37 (t, $J = 6.3$ Hz, 1H, H-5), 4.71 (d, $J = 11.8$ Hz, 2H, OCH_2O), 4.66 (m, 2H, OCH_2Ph), 4.52 (d, $J = 11.8$ Hz, 2H, OCH_2O), 3.91 (t, $J = 7.0$ Hz, 1H, H-3), 2.42 (m, 2H, H-7, H-6), 2.18 (m, 1H, H-6), 1.56 (s, 3H, H-9), 1.52 (m, 1H, H-2), 1.09 (d, $J = 7.0$ Hz, 1.63 (m, 1H, H-2), 3H, H-10), 0.88 (t, $J = 7.4$ Hz, 3H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 204.5$ (s) 138.1 (s), 136.3 (s), 127.9 (d), 127.8 (d), 127.6 (d), 125.4 (d), 91.4 (t), 83.2 (d), 69.5 (t), 46.5 (d), 28.6 (t), 26.3 (t), 13.1 (q), 11.0 (q), 10.4 (q); CIMS: m/z (%): 308 (10) $[M+NH_4]^+$, 125 (30), 106 (100), 91 (35), 61 (35); HRMS: calcd for $C_{18}H_{30}NO_3$: 308.2226; found: 308.2225 $[M+NH_4]^+$.

(8*R*,8*αS*,6*E*)-8-Hydroxy-8-methyl-6-[(2*R*,4*E*,6*S*)-2,5-dimethyl-6-benzyloxymethyloxy-4-octenylidene]octahydroindolizin-7-done (36): A solution of **2** (52.4 mg, 0.31 mmol) in 10% HMPA/THF (5.0 mL) with fluorene (1.0 mg) was cooled to 0 °C before KHMDS (1.36 mL, 0.5 M in toluene) was added dropwise. The reaction mixture was stirred for 15 min and **7** (99 mg, 0.30 mmol) was added as a solution of THF (1.0 mL). The reaction was quenched with sat. NH_4Cl after stirring for a further 15 min and was adjusted to pH 11 with conc. NH_3 solution. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried with K_2CO_3. The solvent was removed in vacuo and a plug of silica gel was used to remove fluorene and base line impurities. The crude products (119 mg, 83%) and DMAP (0.158 g, 1.3 mmol) were then dissolved in CH_2Cl_2 (8.0 mL) and were cooled to −50 °C before DBU (0.19 mL, 1.3 mmol), followed by TFAA (0.109 mL, 0.77 mmol) were added. The reaction mixture was maintained at this temperature for 1 h and was allowed to stir for a further 0.5 h at 0 °C. The solvent was removed and the crude products were purified by FC (Et_2O) to give the product **36** (57 mg, 50%, 42% over two steps): $[\alpha]_D^{25} = -74.4$ ($c = 0.32$, $CHCl_3$); IR (neat): $\tilde{\nu} =$ 3690, 2966, 1710, 1602, 1455, 1364 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.33 (5H, arom.), 6.50 (d, $J = 10.5$ Hz, 1H, H-10), 5.28 (t, $J = 7.0$ Hz, 1H, H-13), 4.70 (d, $J = 11.7$ Hz, 1H, OCH_2O), 4.58 (s, 2H, OCH_2Ph), 4.45 (d, $J = 11.7$ Hz, 1H, OCH_2O), 3.97 (d, $J = 14.0$ Hz, 1H, H-5eq), 3.88 (t, $J =$ 7.0 Hz, 1H, H-15), 3.64 (br s, 1H, OH), 3.17 (t, $J = 6.7$ Hz, 1H, H-3), 2.97 (dd, $J = 2.5$, 14.0 Hz, 1H, H-5ax), 2.45 (m, 1H, H-11), 2.36 (t, $J = 8.1$ Hz, 1H, H-8α), 2.26 (q, $J = 9.2$ Hz, 1H, H-3), 2.11 (t, $J = 7.1$ Hz, 2H, H-12), 1.90 (m, 1H, H-1), 1.78 (m, 4H, H-16, H-2, H-1), 1.62 (m, 1H, H-16), 1.51 (s, 3H, H-19), 1.21 (s, 3H, H-9), 1.04 (d, $J = 6.6$ Hz, 3H, H-18), 0.88 (t, $J = 7.4$ Hz, 3H, H-17); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 196.9$ (s), 146.8 (d), 138.1 (s), 135.1 (s), 129.8 (s), 128.4 (d), 128.3 (d), 128.0 (d), 127.9 (d), 127.6 (d), 127.0 (d), 91.0 (t), 83.0 (d), 73.0 (s), 69.4 (t), 68.8 (d), 55.1 (t), 51.9 (t), 34.5 (t), 33.3 (d), 26.3 (t), 23.5 (t), 22.7 (t), 19.6 (q), 17.7 (q), 10.8 (q), 10.5 (q); EIMS: m/z (%): 464 (100) $[M+Na]^+$, 442 (35) $[M+H]^+$, 413 (10); HRMS: calcd for $C_{27}H_{39}O_4NNa$: 464.2777; found: 464.2798 $[M+Na]^+$.

(7*S*,8*R*,8*αS*,6*E*)-7,8-Dihydroxy-8-methyl-6-[(2*R*,4*E*,6*S*)-2,5-dimethyl-6-benzyloxymethyloxy-4-octenylidene]octahydroindolizine (37): Acetone (4.0 mL) and acetic acid (0.1 mL, 1.87 mmol) were added to $Me_4NBH(OAc)_3$ (0.25 g, 0.935 mmol) and stirred as a suspension for 20 min at RT. Enone **36** (41.3 mg, 0.094 mmol) was added as a solution in acetone (1.0 mL). The reaction mixture was stirred for 6 d before it was quenched with sat. NH_4Cl (0.5 mL). Most of the acetone was removed by blowing a gentle stream of nitrogen over the surface. Water (0.5 mL) was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$ and were dried with K_2CO_3. The solvent was removed under vacuo and the residue was purified by FC (Et_2O(s)NH_3) to give the product **37** (37.3 mg, 89%) as a colourless oil: $[\alpha]_D^{25} = +10.4$ ($c =$ 0.51, $CHCl_3$); IR (neat): $\tilde{\nu} = 3462$, 2961, 1594, 1454, 1312 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.36-7.29$ (5H, arom.) 5.22 (d, $J = 9.9$ Hz, 1H, H-10), 5.18 (t, $J = 6.9$ Hz, 1H, H-13), 4.66 (d, $J = 6.8$ Hz, 1H, OCH_2Ph), 4.65 (d, $J = 6.8$ Hz, 1H, OCH_2Ph), 4.65 (d, $J = 11.4$ Hz, 1H, OCH_2O), 4.51 (d, $J = 11.4$ Hz, 1H, OCH_2O), 3.82 (t, $J = 7.1$ Hz, H-15), 3.56 (s, 1H, H-7), 3.55 (d, $J = 11.8$ Hz, 1H, H-5eq), 2.98 (br s, 1H, H-3), 2.81 (br s, 1H, OH), 2.60 (d, $J = 12.0$ Hz, 1H, H-5ax), 2.53 (m, 1H, H-11), 2.33 (s, 2H, H-8α, OH), 2.15 (q, $J = 8.3$ Hz, 1H, H-3), 2.07–2.00 (m, 2H, H-12), 1.70–1.62 (m, 6H, H-16, H-1, H-2), 1.50 (s, 3H, H-19), 1.16 (s, 3H, H-9), 1.01 (d, $J =$ 6.6 Hz, 3H, H-18), 0.86 (t, $J = 7.4$ Hz, 3H, H-17); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 137.6$ (s), 137.4 (d), 133.5 (s), 129.3 (d), 128.5 (d), 128.4 (d), 127.8 (d), 91.0 (t), 84.1 (d), 80.5 (d), 70.4 (t), 69.5 (t), 65.1 (d), 54.1 (t), 48.9 (t), 35.3 (t), 32.4 (d), 26.1 (t), 22.6 (t), 21.2 (q), 21.1 (t), 20.6 (q), 10.6 (q), 10.4 (q); EIMS: m/z (%): 444 (100) $[M+H]^+$, 349 (20), 305 (10); HRMS: calcd for $C_{27}H_{42}O_4N$: 444.3114; found: 444.3111 $[M+H]^+$.

(7*S*,8*R*,8*αS*,6*E*)-7,8-Dihydroxy-8-methyl-6-[(2*R*,4*E*,6*S*)-2,5-dimethyl-6-hydroxy-4-octenylidene]octahydroindolizine, allopumiliotoxin 323B′ (1): [39–41] A stock solution of LiDBB was made from 4,4′-di-*tert*-butylbiphenyl (1.0 g, 3.7 mmol) and Li (52 mg, 7.4 mmol). The mixture was sonicated at 0 °C in a solution of THF (4.0 mL) for 2 h. LiDBB was added dropwise to **37** (1.7 mg, 3.8 μmol) in a THF solution at −78 °C until a green colouration persisted for 5 min. The reaction was quenched with sat. NH_4Cl (0.5 mL) and was allowed to warm to RT before $NaHCO_3$ (1.0 mL) was added. The aqueous layer was extracted with $CHCl_3$ and the combined organic layers were dried with K_2CO_3 before being removed in vacuo. The crude products were purified by FC ($CHCl_3$/MeOH/NH_3 9.6:0.2:0.2) to give (+)-allopumiliotoxin 323B′ (**1**, 1.1 mg, 88%) as a colourless oil: $[\alpha]_D^{25} = +24.9$ ($c =$ 0.55, MeOH); lit. $[\alpha]_D^{25} = +22.3$ ($c = 1.0$, MeOH); IR (neat): $\tilde{\nu} = 3396$, 2960, 1312, 1018 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.28$ (d, $J = 10.0$ Hz, 1H, H-10), 5.24 (t, $J = 7.5$ Hz, 1H, H-13), 3.87 (t, $J = 6.9$ Hz, 1H, H-15), 3.69 (s, 1H, H-7), 3.57 (d, $J = 12.2$ Hz, 1H, H-5eq), 3.03 (m, 1H, H-3), 2.87 (s, 1H, OH), 2.69 (d, $J = 12.2$ Hz, 1H, H-5ax), 2.54–2.49 (m, 2H, H-11, H-8α), 2.27 (q, $J = 7.9$ Hz, 1H, H-3), 2.07–1.94 (m, 3H, H-12, OH), 1.67–1.77 (m, 6H, H-16, H-1, H-2), 1.55 (s, 3H, H-19), 1.19 s, 3H, H-9), 1.04 (d, $J = 6.5$ Hz, H-18), 0.83 (t, $J = 7.4$ Hz, H-17); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 137.5$ (d), 137.2 (d), 133.7 (s), 125.8 (d), 80.9 (d), 80.2 (d), 70.3 (s), 65.2 (d), 54.3 (t), 49.3 (t), 35.3 (t), 32.6 (d), 27.7 (t), 22.6 (t), 21.2 (t), 20.9 (q), 20.5 (q), 10.9 (q), 10.1 (q); EIMS: m/z (%): 346 (25) $[M+Na]^+$, 324 (100) $[M+H]^+$, 306 (15), 186 (5); HRMS: calcd for $C_{19}H_{34}ON_3$: 324.2533; found: 324.2519 $[M+H]^+$.

Acknowledgements

We thank the ESPRC for financial support and provision of the Swansea Mass Spectrometry Service, and the Cambridge Commonwealth Trust, Trinity College, the CVCP (scholarship to C.-H.T) and Zeneca for generous financial support. A gift of Lipase PS "Amano" from Amano Europe Ltd is gratefully acknowledged. We are indebted to Professor L. E. Overman for providing us with the NMR spectra of **1** and **2**.

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Received: December 13, 1999
Revised version: November 22, 2000 [F2186]

  0947-6539/01/0709-1854 $ 17.50+.50/0