PERKIN 1

Synthetic studies on the pederin family of antitumour agents. Syntheses of mycalamide B, theopederin D and pederin

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A general modular approach to the members of the pederin family of antitumour agents is exemplified by syntheses of mycalamide B and theopederin D as well as a formal synthesis of pederin. All three compounds are prepared from 6-lithio-2,3-dimethyl-4-phenylselenomethyl-3,4-dihydro-2*H*-pyran and 2-(3-chloropropyl)-3,3-dimethyl-3,4-dihydro-2*H*-pyran-4-one.

Introduction

The chemical history of the pederin family began in 1919 when Netolitzky isolated the active vesicant principle from the dermestid beetle *Paederus fuscipes* in crystalline form.[1,2] An interval of 33 years elapsed before Pavan and Bo[3] isolated the toxic agent afresh from 25 million specimens (*ca.* 100 kg), determined its mp and gave it the name pederin by which it is known to this day. Structural investigations were soon launched independently by the Matsumoto group in Japan[4] and the Quilico group in Italy.[5] The correct molecular formula ($C_{25}H_{45}O_9N$) established by Quilico and co-workers[5] in 1961 led to a detailed study of the chemical constitution of pederin and a structure, devoid of stereochemical definition, was proposed in 1965.[6] With one minor exception all the conclusions drawn from the degradation and ^{1}H NMR studies of Quilico[7] and Matsumoto[8] were later confirmed by an X-ray crystallographic analysis of pederin bis(*p*-bromobenzoate) which also established the absolute and relative stereochemistry.[9,10] Pederin (**1**) remained unique in the realm of natural products until 1988 when routine screening for antiviral agents identified two marine natural products which bore a close structural resemblance to pederin. Mycalamide A (**2**) was isolated from a sponge of the genus *Mycale* found in the Otago harbour off New Zealand[11] whilst onnamide A (**4**) was isolated from a sponge of the genus *Theonella* found in Okinawan waters.[12] The pederin family grew to 22 members by 1993 with the isolation of mycalamide B (**3**),[13] a further 11 onnamides[14,15] and theopederins A–E.[16]

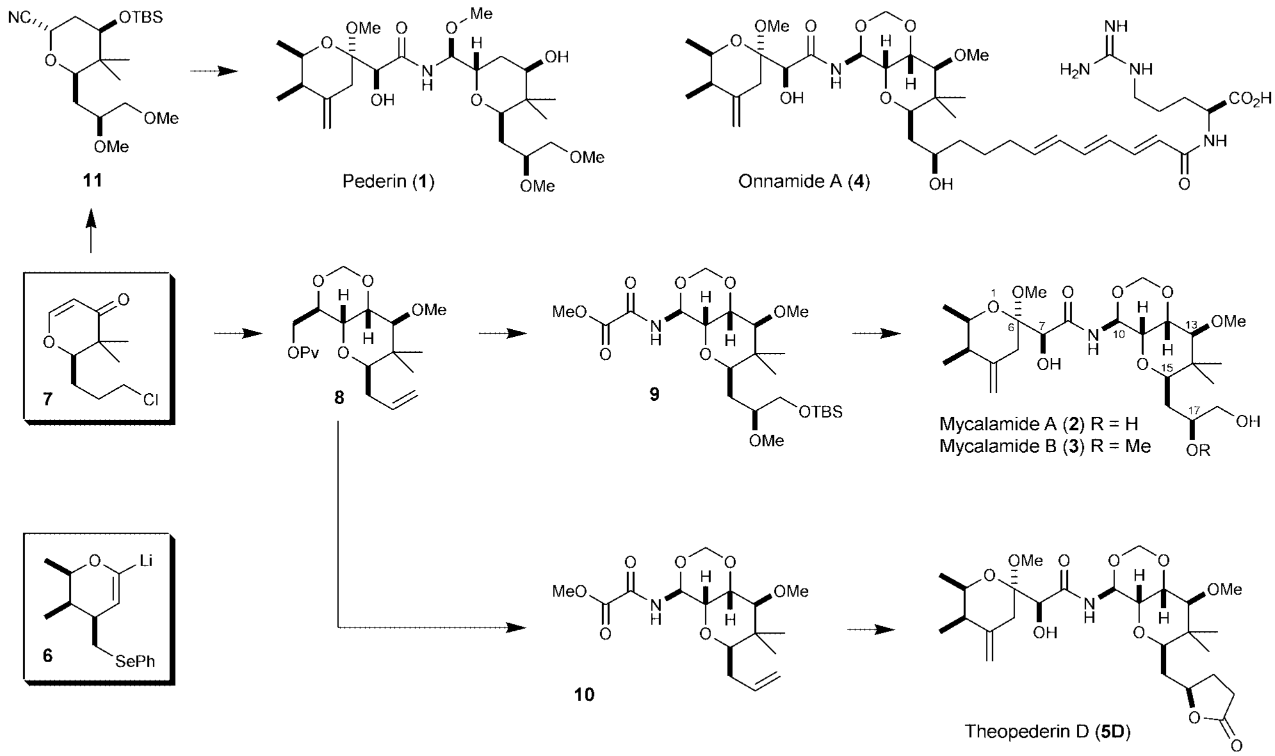
All members of the pederin family are rare, difficult to isolate, and comparatively frail; many of them have potent and potentially useful activity as antiviral and antitumour agents. Moreover, mycalamide A blocks T-cell activation in mice and is 10-fold more potent than FK-506 and 1000-fold more potent than cyclosporin A in this model.[17] Total syntheses of pederin,[18–26] mycalamide A,[27–31] mycalamide B[27,32,33] and onnamide A[34] have been reported, as have significant syntheses of various fragments.[35–44] Previous publications from our laboratory have traced the evolution of a general approach to the pederin family including pederin itself,[26] mycalamide B,[32] 18-*O*-methylmycalamide B[32] and theopederin D (**5D**).[45] Our aim was to devise a synthesis which was robust enough to secure sufficient quantities of most members of the family for biological evaluation together with their analogues. We now give full details of our syntheses of mycalamide B and theopederin D together with substantial tactical improvements to our previous synthesis of pederin. In the basic strategy outlined in Scheme 1, all three targets are constructed from two basic building blocks, the lithiated dihydropyran **6** and the dihydropyranone **7**. Furthermore, there are two common features to all three syntheses. First, the high acid-lability of the homoallylic acetal resulting from the exocyclic methylene at C4 was circumvented by introduction of this troublesome functionality in latent form—a tactic which had been devised by Matsumoto in his pioneering syntheses of pederin.[21] Secondly, the highly hindered and acid- and base-labile *N*-acyl aminal bridge linking the two heterocyclic systems was constructed by acylation of the lithiated dihydropyran **6** by oxalamide derivatives (*e.g.* **9** or **10**) which can be prepared from a common intermediate **8**.

Results and discussion

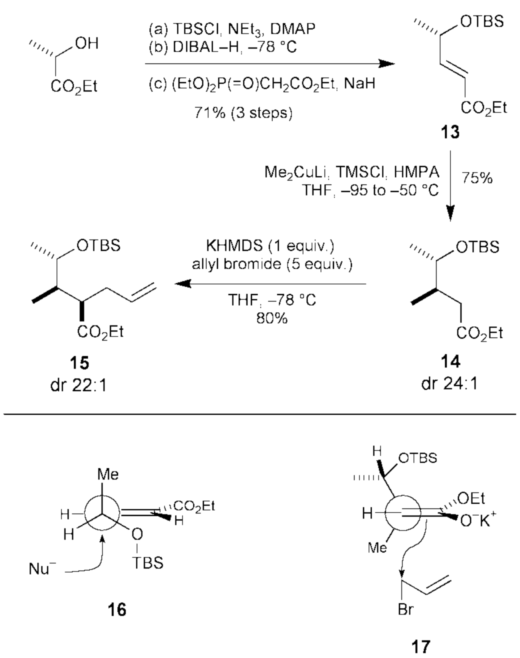
Synthesis of mycalamide B

We began with the construction of the stannane which serves as the precursor to the key lithiated dihydropyran **6**. Ethyl (*S*)-lactate was transformed in three simple steps to the α,β-unsaturated ester **13** in 71% overall yield on a 0.26 mol scale (Scheme 2).[46] A diastereoselective conjugate addition of lithium dimethylcuprate to the ester **13** in the presence of HMPA and TMSCl at −95 °C[47,48] afforded adduct **14** in 75% yield (dr 24 : 1). The final C–C bond forming reaction in the sequence was also highly diastereoselective. Alkylation of the potassium enolate of the ester **14** with allyl bromide gave the third contiguous stereogenic centre in **15** in 80% yield (dr 22 : 1).

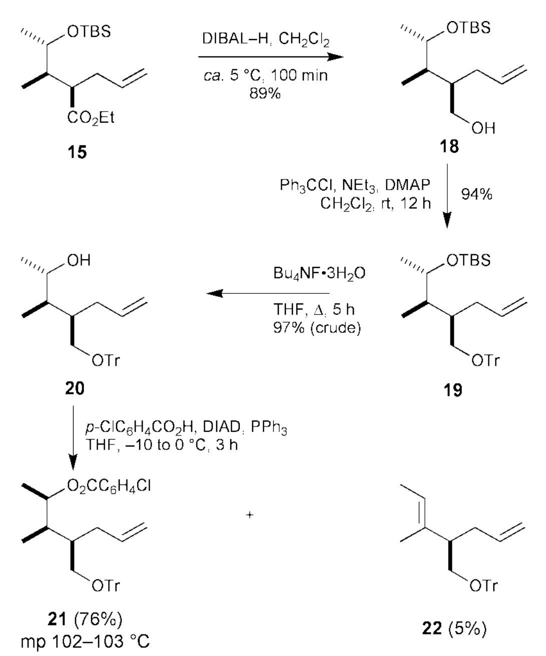
Ground state conformational models have been proposed to explain the stereoselectivity of the foregoing reactions. Yamamoto's model for the diastereoselective conjugate addition of various organocopper reagents to γ-alkoxy-α,β-unsaturated carbonyl derivatives places the best electron donating group perpendicular to the plane of the π-system and the OTBS group in the more sterically demanding "inside position".[48] The clear steric discrimination between the diastereotopic faces as indicated in structure **16** accounts for the *anti* attack of the nucleophile giving the *anti*-adduct **14**. Houk's "electrophilic rule" rationalises the diastereoselective alkylation of enolates with adjacent stereogenic centres.[49] Thus the eclipsed conformation **17** placing the hydrogen of the stereogenic centre in the plane of the π-system again causes steric discrimination between the two diastereotopic faces of the enolate leading to alkylation as shown in structure **15**. Corroborating evidence for the Houk model has been presented.[50–52]



Scheme 1



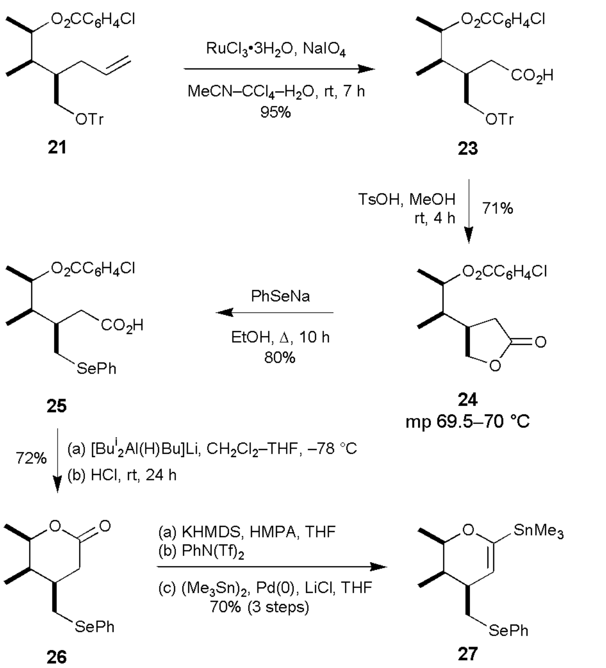
Scheme 2



Scheme 3

Routine transformations accomplished the conversion of **15** to the alcohol **20** (Scheme 3) but the Mitsunobu reaction used to invert the configuration at C-2 (mycalamide numbering) in alcohol **20** was plagued by a competing elimination to give alkene **22**. A number of variations in carboxylic acid and azodicarboxylate ester eventually established that the combination of trityl as the protecting group, *p*-chlorobenzoic acid as the nucleophile, and diisopropyl azodicarboxylate as the activator returned the ester **21** in 76% yield together with only 5% of the elimination product **22** which was easily separated by column chromatography—the first in the sequence. Any minor diastereoisomers were easily separated by crystallisation of the *p*-chlorobenzoate **21**. We have since found that *p*-chlorobenzoic acid is frequently superior as the nucleophilic partner in Mitsunobu inversions in a wide range of applications and it is now our reagent of choice.

Oxidative cleavage of the alkene **21** (Scheme 4) followed by acid treatment achieved simultaneous trityl deprotection and lactonisation to give the second crystalline compound of the series, the lactone **24**. The phenylseleno group in **25** was introduced by nucleophilic substitution of the butyrolactone **24**.[53] Saponification of the *p*-chlorobenzoate ester in the usual way using hot 2 M NaOH was accompanied by an unexpected side reaction: epimerisation at C-2. Although the extent of epimerisation was small (*ca.* 5%), we chose to suppress it altogether by performing the cleavage with an "ate" complex derived from addition of BuLi to DIBAL-H.[54] The resultant hydroxy acid lactonised to give **26** in 72% yield. Conversion of lactone **26** to

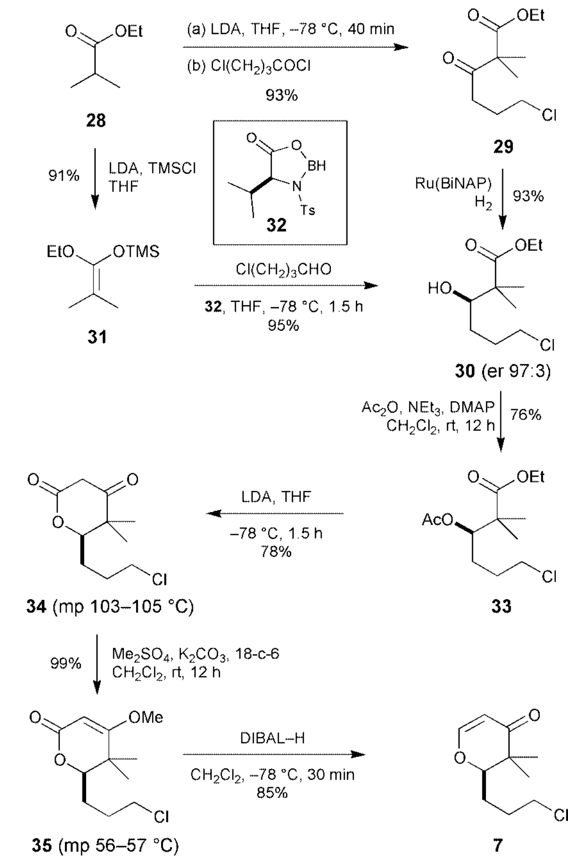


Scheme 4

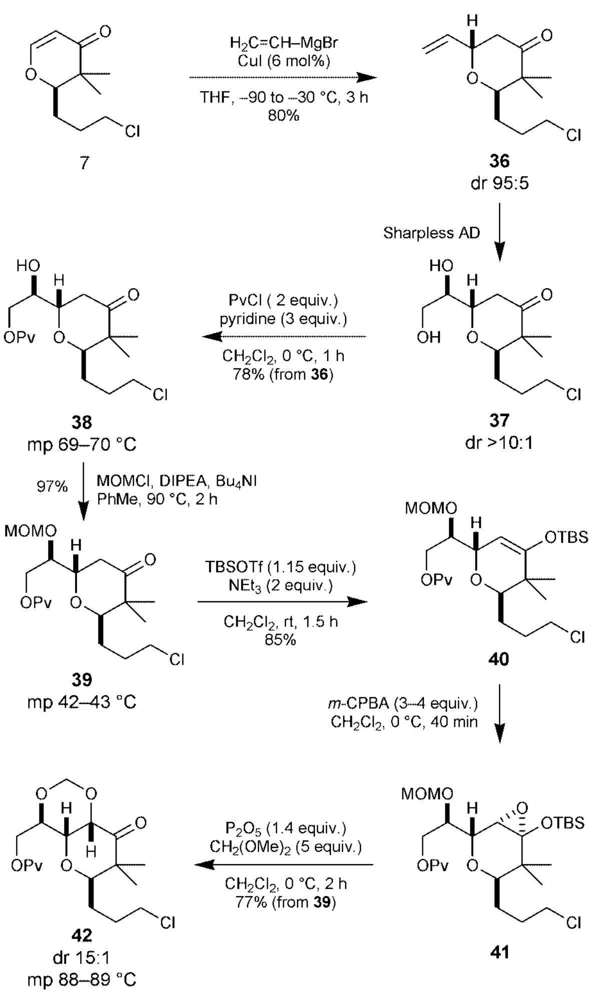
the stannane **27** was accomplished by a three-step sequence previously described in our synthesis of pederin.[26]

Dihydropyranone **7** is a critical intermediate in our synthetic strategy because it could, in principle, be converted to the simple monocyclic system of pederin as well as the more complex trioxadecalin ring system of the mycalamides, onnamides and theopederins. The 3-chloropropyl side chain in **7** also satisfied the need for an inert latent alkene which could be fashioned into any of the side chain variations of the pederin family. Dihydropyranone **7** harbours a single stereogenic centre at C-15 (mycalamide numbering) which was constructed efficiently by two different routes. In the first route, the lithium enolate prepared from ethyl isobutyrate was condensed with 4-chlorobutanoyl chloride to give the β-keto ester **29** in 93% yield (Scheme 5). Noyori catalytic asymmetric hydrogenation of the β-keto ester **29** using [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride[55–58] installed the requisite (*R*)-configured stereogenic centre in good yield and high enantiomeric ratio (97:3). The reaction worked well on a 50 mmol scale but on scaleup to 150 mmol, the reaction time was variable and occasionally it failed to go to completion. Moreover, the ruthenium catalyst was expensive and commercial supplies gave variable activity. Economy, scale, cost and reliability led us to an alternative synthesis of β-hydroxy ester **30** using an asymmetric directed aldol reaction mediated by the scalemic borane **32** according to the method of Kiyooka.[59,60] Although the Kiyooka method requires stoichiometric amounts of the borane **32**, it was easily prepared from cheap crystalline *N*-tosyl valine which was recovered in pure form after one recrystallisation in 90% yield. The directed aldol approach gave comparable yields and enantioselectivity and its ease of execution won our favour. To complete the synthesis, the ring was constructed by Dieckmann cyclisation of the acetate **33** to give the highly crystalline β-keto lactone **34** which could be easily obtained enantiopure by crystallisation. Simple *O*-methylation under phase transfer catalysed conditions afforded the crystalline enol ether **35**. Reduction of the remaining carbonyl with DIBAL-H returned the desired dihydropyranone **7** in 50–52% overall yield from ethyl isobutyrate. Note that none of the steps depicted in Scheme 5 required column chromatography.

Construction of the 1,3-dioxane ring (Scheme 6) required a three-stage sequence of 7 steps comprising appendage of a two-carbon unit to the dihydropyranone; two oxidations at C10 and



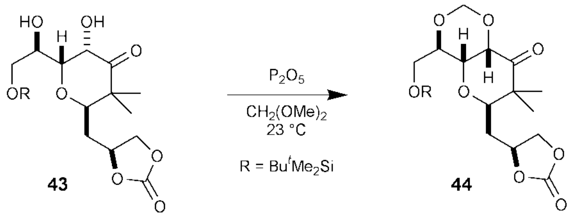
Scheme 5



Scheme 6

C12; and finally ring closure. The first stage was accomplished in high yield (80%) and high diastereoselectivity (dr 95:5) by Cu(I)-catalysed conjugate addition of vinylmagnesium bromide to dihydropyranone **7**. Attempts to launch the second stage by substrate controlled dihydroxylation gave poor diastereocontrol [10(*R*):10(*S*) 2:3] so the task was accomplished using the Sharpless asymmetric dihydroxylation.[61] Using 20 mg of substrate, several ligand systems were screened but the diastereoselectivity was modest at best: AD-mix-α [10(*S*):10(*R*) 1:2], AD-mix-β (2:1), $(DHQ)_2PYR$[62] (1:3.5), $(DHQD)_2PYR$ (2.6:1), DHQD–PYDZ[63] (1.3:1) and DHQ 4-methyl-2-quinolyl ether[64] (1:7.5). Best results were obtained with DHQ 9-phenanthryl ether[64] which gave a 75% yield of diols with dr > 10:1 in favour of the desired 10(*R*) derivative **37**. The diols were inseparable but the corresponding monopivalates were separable by simple crystallisation from ether–hexanes to afford pure **38** in 78% yield. The remaining hydroxy group was converted to its crystalline MOM ether **39** which not only served as a protecting group, but also as an essential participant in the final ring construction.

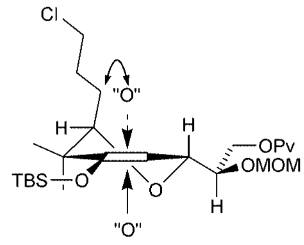
The second oxidation was accomplished by simple epoxidation of the enol silane derivative **40** prepared from ketone **39** and TBSOTf. Two aspects of the conversion **40** to **41** are noteworthy. First, the epoxidation was highly diastereoselective giving virtually a single diastereoisomer with the desired stereochemistry at C12 (see below). Secondly, the oxirane **41** was surprisingly stable—*e.g.*, it could be purified by silica gel chromatography without detriment, though in practice, the crude product was generally used in the next step. During a synthesis of the trioxadecalin nucleus of mycalamide A, Roush[65] had prepared the methylene acetal in **44** (Scheme 7) by



Scheme 7

adding phosphorus pentoxide to a solution of diol **43** in dimethoxymethane according to literature precedent. We found that the methylene acetal could be constructed directly by adding the oxirane **41** to a solution of phosphorus pentoxide in dichloromethane containing a large excess of dimethoxymethane at 0 °C. An overall yield of 77% was obtained for the three steps from ketone **39** to methylene acetal **42** with a diastereoselectivity of 15:1. However, both a lower yield (70%) and lower diastereoselectivity (*ca.* 8:1) was obtained when the phosphorus pentoxide was added to a solution of the oxirane in a mixture of dimethoxymethane in dichloromethane. The methylene acetal could be obtained as a single diastereoisomer by simple crystallisation from ether–hexanes.

The very favourable stereochemistry of the epoxidation of enol silane **40** deserves comment. We had originally expected difficulty with this step because it would appear that epoxidation was required from the same face of the ring as the bulky and branched side chain at C11. However, the C11 side chain can occupy a pseudo-equatorial position in the half chair conformation as shown in Scheme 8 in which it offers comparatively little steric impediment to the approach of the oxidant compared with the pseudo-axial 3-chloropropyl side chain at C15. Indeed, an MM2 calculation (Chem3D) predicts that the 3-chloropropyl side chain protrudes over the ring somewhat, thereby exacerbating its steric effect, hence forcing the epoxidation to take place as shown. The favourable stereochemistry could be ascribed to tethered delivery of the *m*-chloroperbenzoic acid *via* a hydrogen-bonded intermediate but the same



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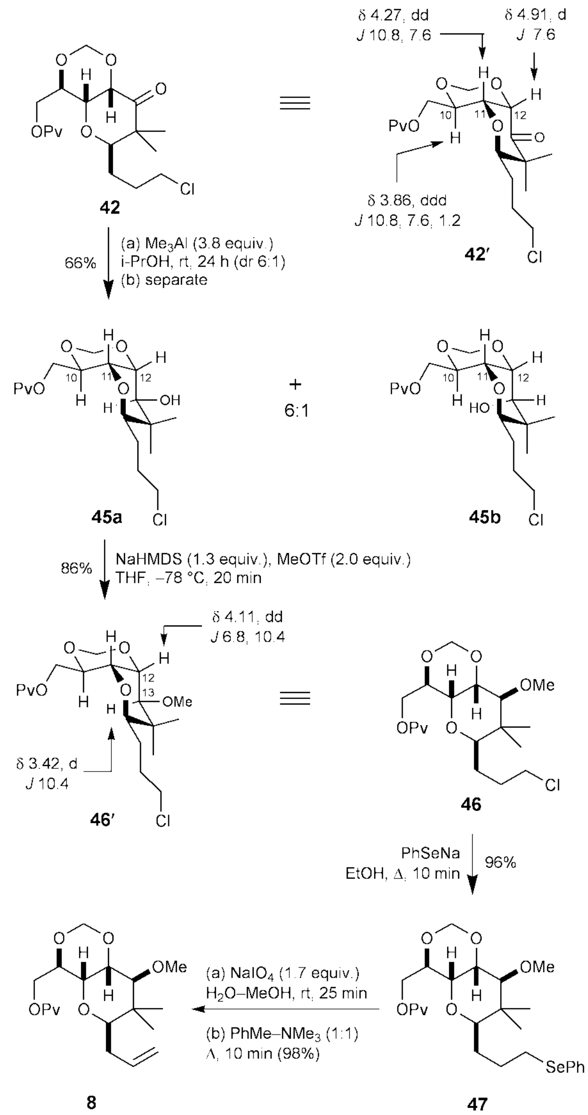
Scheme 8

favourable stereochemistry was also obtained with dimethyldioxirane in which hydrogen bonding is precluded.

The reduction of the C13 carbonyl which introduced the single remaining stereogenic centre on the ring was thwarted by poor stereoselectivity (Scheme 9). The most favourable ratio of

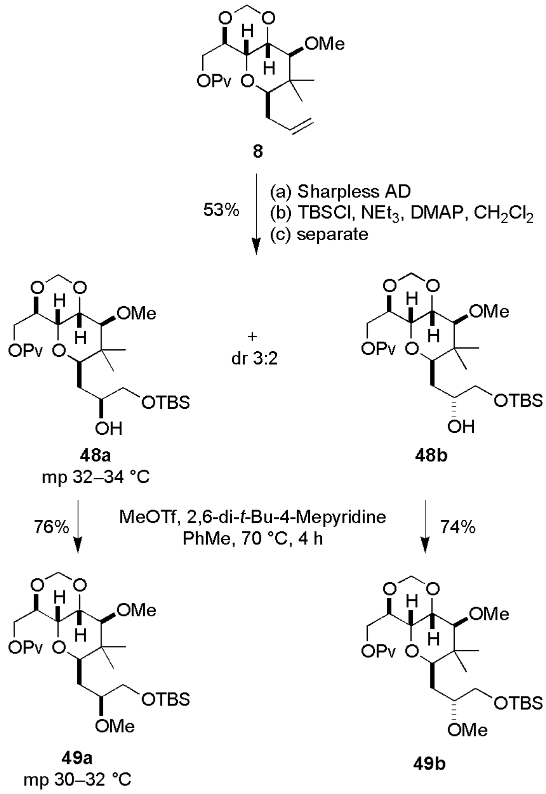


Scheme 9

45a:**45b** (1:2) was obtained with KBH_4 and $CeCl_3 \cdot 7H_2O$ in MeOH at −90 to −20 °C; all other variants gave mixtures rich in **45b**. $BH_3 \cdot THF$ and $LiBH(s\text{-}Bu)_3$ gave exclusively **45b**; Rhodium-catalysed hydrosilylation gave predominantly **45b**. Dissolving metal reduction (Na, SmI_2) gave decomposition but Mg in MeOH gave a 1:1 mixture with competing reduction of the chloride. Fortunately, the diastereoisomeric alcohols are easily separable, thereby allowing a recycling process. A reason for the poor stereoselectivity can be gleaned from the ground state conformation of the ketone **42**: formation of the desired stereoisomer **45a** requires delivery of hydride from the more hindered concavity of the *cis*-fused trioxadecalin system. This recalcitrant reduction was the greatest obstacle to progress until a simple, convenient and effective solution to the problem was found in the form of a modified Meerwein–Ponndorf–Verley reduction. Thus treatment of ketone **42** at room temperature with a reagent prepared by reaction of isopropanol with trimethylaluminium (3.8 equiv.) gave a mixture of **45a** and **45b** in 66% yield with a dr of 6 : 1 in favour of **45a**. Starting ketone **42** was also recovered (28%) making the yield based on recovered starting material 92%. The reversible nature of the Meerwein–Ponndorf–Verley reduction is well known to afford the thermodynamic alcohol.[66] Evidence that **45a** is the thermodynamic product comes from two observations. First, the dr of the reaction was a function of time with the mol fraction of **45a** increasing with time. Secondly, subjection of the pure axial alcohol **45b** to the reaction conditions led to isomerisation. Attempts to drive the reduction to completion by removing the acetone at elevated temperature led to diminished dr. *O*-Methylation of **45a** gave a methyl ether **46** whose stereochemistry was assigned based on the large coupling constant $J_{12,13}$ 10.4 Hz for C13H consistent with a *trans*-diaxial disposition of the vicinal hydrogens as indicated in structure **46′**.

The C15 side chain is the principal seat of structural variation in the pederin family and our route was designed to access as many members of the pederin family and their analogues as possible. The chloropropyl side chain was introduced at the outset because it offered opportunities for nucleophilic substitution or elimination and thence a rich vein of transformations. For the synthesis of mycalamide B, we required an elimination reaction. However, neither the chloride nor iodide would eliminate without severe decomposition. Therefore, we were forced to adopt a regrettable three-step sequence involving substitution by phenyl selenide anion to give phenylseleno ether **47** (Scheme 9) whence thermolysis of the corresponding selenoxide[67] afforded the desired alkene **8** in excellent overall yield (94%) for the three-step sequence from **46**.

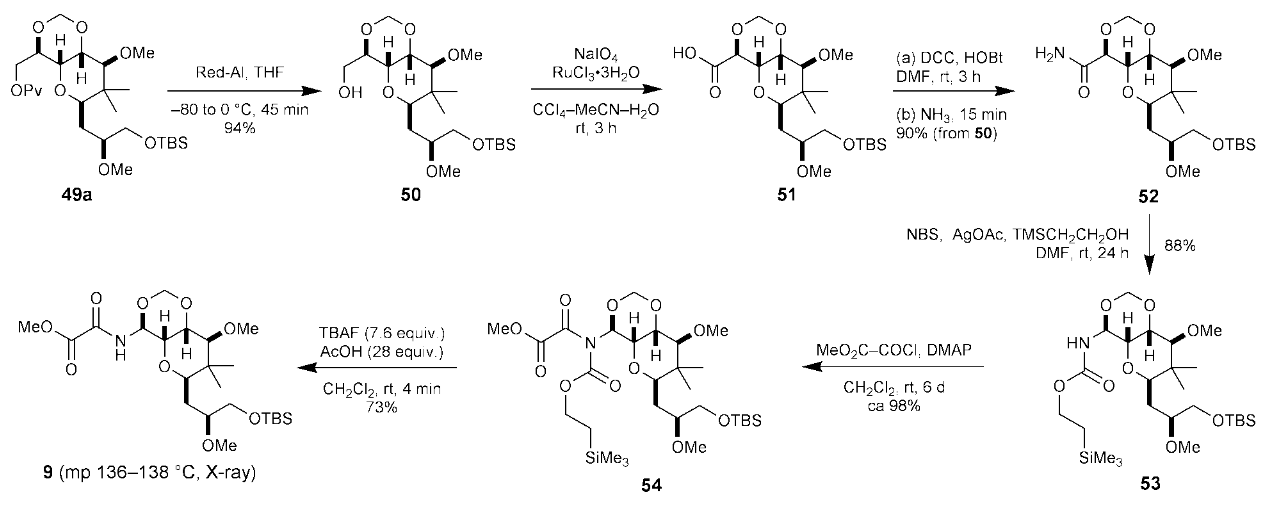
To complete the elaboration of the C15 side chain (Scheme 10) we performed a Sharpless asymmetric dihydroxylation as Hong and Kishi[27] had done before us. The diastereoselectivity was poor giving a mixture of diols (dr 3 : 2) which was difficult to separate, but the corresponding mono-TBS ethers were separable by chromatography and gave the desired alcohol **48a** as a crystalline solid together with its C17 epimer **48b**. Both compounds were converted to their respective methyl ethers **49a** and **49b**. As before the whole gamut of standard ligands used for the Sharpless asymmetric dihydroxylation was surveyed in the search for improved diastereoselectivity, but to no avail. Once



Scheme 10

again DHQ 9-phenanthryl ether[64] maximised the desired diastereoisomer but the highest diastereoselectivity (9 : 1) was obtained with $(DHQD)_2PYR$[62] with the major isomer being the unwanted C17 epimer **49b**. The stereochemistry of the desired alcohol **49a** was established by X-ray analysis of a subsequent advanced intermediate (see below).

The last remaining task in the synthesis of the trioxadecalin fragment entailed the introduction of the *N*-acyl aminal function. The acid- and base-lability of the *N*-acyl aminal together with the threat of isomerisation under basic conditions demanded a mild, and reliable route. Our optimised solution is depicted in Scheme 11. Reductive cleavage of the pivalate ester **49a** followed by oxidation of the primary alcohol **50** using the Sharpless protocol[68] gave the carboxylic acid **51** which was converted to the corresponding primary amide **52** using standard procedures. A classical Hofmann rearrangement using Ag(I)-assisted rearrangement[69] of the *N*-bromoamide derivative occurred at room temperature with clean retention of configuration to give an isocyanate intermediate which was trapped by



Scheme 11

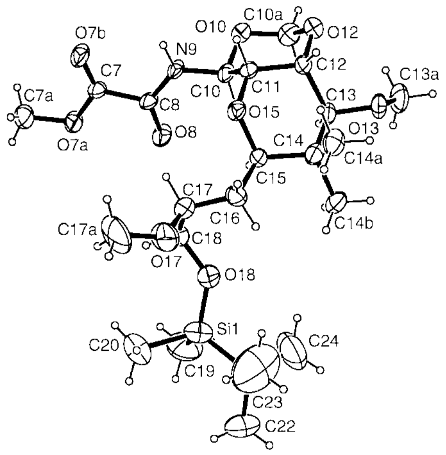
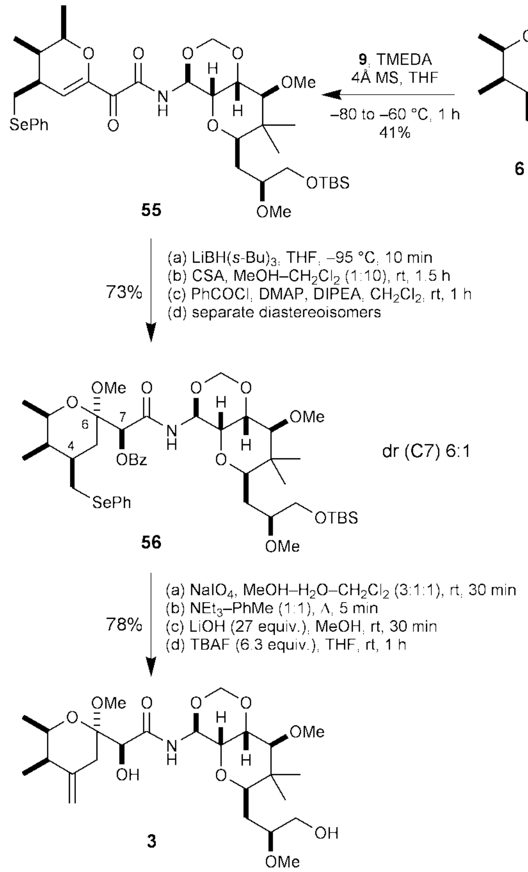


Fig. 1 X-Ray crystal structure of compound **9** showing the atom numbering and 20% probability ellipsoids for non-hydrogen atoms.

2-(trimethylsilyl)ethanol to give the carbamate **53** in 79% overall yield from the alcohol **50**. Alternatively, the Hofmann rearrangement could be induced by reaction of amide **52** with 1,1-bis(trifluoroacetoxy)iodobenzene[70,71] but the yield was slightly lower (73%). The Curtius rearrangement of an acyl azide derived from acid **51** is a well-precedented route to the carbamate **53** (see below) which we also evaluated. However, the elevated temperatures (70 °C) required for the rearrangement resulted in decomposition with an overall reduction in yield to 56% at best with typical yields being more like 40%. Attempts to reduce the temperature by employing the photochemical variant of the Curtius rearrangement were rewarded with a multiplicity of products and so the route was abandoned in favour of the Hofmann rearrangement.

The remaining two-carbon fragment was installed by reaction of carbamate **53** with methyl oxalyl chloride in the presence of DMAP[41] to yield the imide derivative **54**. Although the reaction required six days to go to completion, the yield of the imide was excellent (98%). To complete the sequence, the urethane function was expunged using TBAF buffered with acetic acid to give the crystalline trioxadecalin fragment **9** in 73% yield. In the absence of acetic acid, the primary TBS group was also partially cleaved. The structure and relative stereochemistry of **9** was firmly established by X-ray crystallography (Fig. 1).

The principal task required to complete the synthesis of mycalamide B was the construction of the *N*-acyl aminal bridge linking the two ring systems. The *N*-acyl aminal bridge is responsible for the protein synthesis inhibitory activity in the pederin family[72] and its potency depends on precise definition of the stereochemistry at C6, C7 and C10. We had already invested a substantial effort to achieve a method for the construction of the *N*-acyl aminal bridge of pederin which reconciled the problems of steric hindrance and acid- and base-lability and we now hoped to reap a further dividend by deploying the same linkage strategy in our synthesis of mycalamide B. Thus addition of the trioxadecalin fragment **9** (Scheme 12) to a mixture of the lithiated dihydropyran **6** (2.7 equiv.) and *N*,*N*,*N′N′*-tetramethylethylenediamine (TMEDA) at low temperature gave the adduct **55** in 41% yield. Two aspects of the acylation require further comment. First, the method as used here is inherently wasteful since one equivalent of lithiated dihydropyran **6** was squandered in abstracting the amide proton. Attempts to improve the stoichiometry by using a sacrificial lithium reagent (BuLi) in model systems were foiled by rapid competing addition of the butyllithium to the oxalamide. Secondly, the yield of the coupling was variable. Whilst the 41% yield quoted here is typical, >70% was obtained in related systems such as theopederin which will be discussed below.



Scheme 12

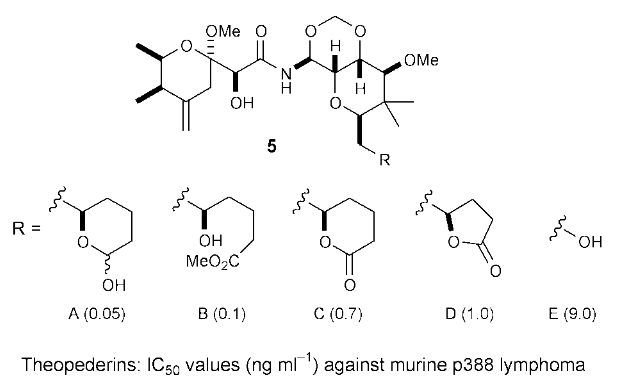
The acyldihydropyran adduct **55** harboured the entire skeleton of mycalamide B and completion of the synthesis now only required some functional group manipulations which began with reduction of the keto group with LiBH(*s*-Bu)$_3$. The crude product underwent acid-catalysed addition of MeOH to the dihydropyran and the remaining hydroxy function was acylated with benzoyl chloride. ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed two diastereoisomeric benzoates (dr 6 : 1) which were separated by chromatography to give the pure benzoate **56** in 73% overall yield from **55**. Two stereogenic centres at C6 and C7 were created in the foregoing transformations but the detection of only two isomers at C7 indicates that addition of MeOH had occurred with very high diastereoselectivity. Brief thermolysis of the selenoxide derived from oxidation of phenylseleno ether **56** installed the hypersensitive methylene function at C4. Finally, hydrolysis of the benzoate ester with lithium hydroxide followed by cleavage of the primary TBS ether with TBAF produced mycalamide B in 78% overall yield from **56**. By using identical procedures, 17-*epi*-mycalamide B was prepared from **49b** with comparable overall efficiency. The ^{1}H and ^{13}C NMR spectroscopic data recorded on natural and synthetic mycalamide B together with the data for the 17-*epi* diastereoisomer are summarised in Table 1. Data for the synthetic material are also given in C_6D_6 owing to the slow deterioration of the synthetic material in $CDCl_3$.

Theopederin D

Theopederins A–E are a family of five closely related metabolites isolated from a sponge of the genus *Theonella* collected off Hachijo-jima island 300 km south-east of Tokyo (Scheme 13).[16] Their structures were elucidated by a combination of mass spectrometry, infra-red spectroscopy, and NMR spectroscopy. Their spectroscopic features were reminiscent of mycalamides A and B and detailed COSY, HMQC and HMBC experiments revealed that all five theopederins shared a common skeleton

Table 1 ^{1}H and ^{13}C NMR data for natural and synthetic mycalamide B derivatives

Position	Mycalamide B natural ($CDCl_3$) δ_H (*J*/Hz)	δ_C	Mycalamide B synthetic ($CDCl_3$) δ_H (*J*/Hz)	Mycalamide B synthetic (C_6D_6) δ_H (*J*/Hz)	δ_C	17-*epi*-Mycalamide B synthetic (C_6D_6) δ_H (*J*/Hz)	δ_C
2	4.02, dq (2.8, 6.6)	69.64	4.04, dq (2.8, 6.5)	3.80, dq (1.8, 6.6)	68.1	3.82, dq (2.6, 6.6)	68.0
2-Me	1.20, d (6.6)	17.93	1.21, d (6.6)	0.81, d (6.6)	16.5	0.81, d (6.6)	16.5
3	2.24, dq (2.4, 6.9)	41.27	2.28, dq (2.8, 7.1)	1.86, dq (1.7, 7.0)	40.4	1.88, dq (2.6, 7.1)	40.3
3-Me	1.01, d (7.1)	12.13	1.02, d (7.2)	0.92, d (7.0)	11	0.90, d (7.1)	12.1
4	—	145.10	—	—	144.6	—	145.0
4=CH_2	4.85, dd (2.0, 2.0)	111.02	4.86, br s	4.71, dd (1.8, 1.8)	109.6	4.75–4.70, m	109.4
	4.72, dd (1.9, 1.9)		4.73, br s	4.66, dd (1.9, 1.9)		4.75–4.70, m	
5	2.22, ddd (2.0, 2.0, 13.5)	36.43	2.24, dm (13.9)	2.40, dd (1.8, 14.0)	32.9	2.42, br d (13.9)	33.0
	2.36, d (13.9)		2.37, d (14.0)	2.60, d (14.0)		2.60, d (13.9)	
6	—	99.95	—	—	99.2	—	99.1
6-OMe	3.29, s	48.57	3.3, s	3.15, s	47	3.21, s	47.1
7	4.29, s	71.73	4.29, d (2.0)	4.16, s	70.7 or 70.9	4.17, s	71.1
7-OH	—	—	3.88, d (2.1)	4.07 (br s)	—	4.17, s	—
8	—	171.88	—	—	171.1	—	171.1
NH	7.54, br d (10.0)	—	7.52, d (9.6)	7.58, d (9.8)	—	7.48, d (9.9)	—
10	5.79, dd (9.7, 9.7)	73.90	5.81, dd (9.6, 9.6)	5.83, d (9.9)	72.9	5.94, d (9.9)	72.8
10-O-CH_2	5.12, d (7.0)	86.49	5.12, d (7.0)	4.56, d (7.0)	85.1	4.57, d (6.9)	85.0
	4.84, d (6.9)		4.86, d (6.7)	4.53, d (6.9)		4.54, d (6.9)	
11	3.79, dd (6.7, 9.7)	70.94 (br)	3.79, dd (6.8, 9.6)	3.69, dd (7.0, 10.0)	70.7 or 70.9	3.65, dd (7.1, 9.7)	70.1
12	4.21, dd (6.7, 10.4)	74.44	4.22, dd (6.8, 10.2)	4.24, dd (7.0, 10.6)	73.9	4.23, dd (6.9, 10.2)	73.8
13	3.44, d (10.5)	79.27	3.44, d (10.4)	2.94, d (10.5)	77.5 or 77.7	2.96, d (10.4)	77.8
13-OMe	3.55, s	61.78	3.56, s	3.22, s	60	3.32, s	60.0
14	—	41.47	—	—	40.3	—	40.1
14-Me_{eq}	0.97, s	23.13	0.99, s	0.80, s	21.5	0.83, s	21.7
14-Me_{ax}	0.85, s	13.32 (br)	0.87, s	0.76, s	11.9	0.77, s	12.1
15	3.41, d (3.3, 8.3)	75.46	3.46–3.40, m	3.40, dd (5.6, 6.1)	74.4	3.51, d (9.3)	75.9
16	1.55, m	29.63	1.58–1.52, m	1.59–1.55, m	29.3	1.65, dd (8.2, 14.8)	31.5
	1.55, m		1.58–1.52, m	1.59–1.55, m		1.27, ddd (2.8, 10.0, 14.6)	
17	3.2, m	78.84	3.23–3.16, m	3.33–3.28, m	77.5 or 77.7	3.27–3.18, m	78.3
17-OMe	3.24, s	56.64	3.25, s	3.03, s	55.2	3.06, s	55.6
18	3.65, dd (3.3, 11.9)	63.48	3.70–3.63, m	3.85–3.77, m	62.6	3.61–3.55, m	62.6
	3.47, dd (5.7, 11.9)		3.52–3.46, m	3.74–3.68, m		3.61–3.55, m	
18-OH	—	—	—	2.33, br s	—	1.50, br s	—



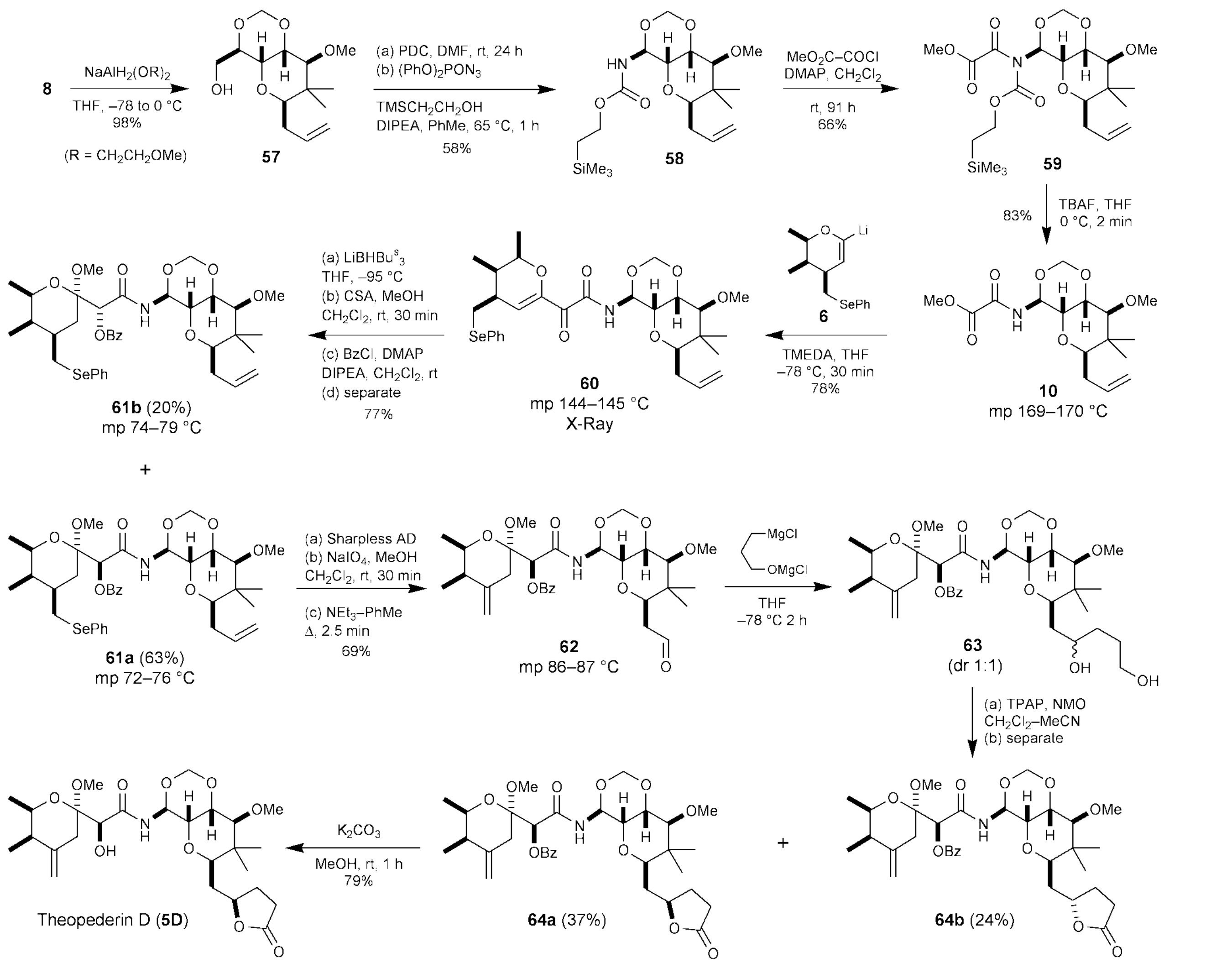
Scheme 13

from O1 to C15 with the variable domain being the side chain appended to C15. The theopederins were isolated in minute quantities and hence only very limited biological data have been gleaned. All five theopederins are cytotoxic towards murine P388 leukaemia cells with IC_{50}'s (see Scheme 13) in the region of those reported for mycalamide A (0.7 ± 0.3 ng ml^{-1}) and B (3.0 ± 1.3 ng ml^{-1}) in the same animal model.[13]

Progress towards the synthesis of the theopederins has been disclosed by Fukumoto and co-workers[38,73] but only one total synthesis has been reported.[45] We now give full details of our synthesis of theopederin D (**5D**) and its C17 epimer in which we simply divert the course of the mycalamide synthesis described above at intermediate **8**. As before, our principal concerns were first, the creation of the *N*-acyl aminal at C10, and then elaboration of the butyrolactone side chain at C15. Introduction of the aminal centre at C10, was performed using a Curtius rearrangement as described by Roush,[39,65] Hoffmann[43] and Nakata[28] in order to secure the stereochemistry at the aminal centre unambiguously. The requisite acyl azide was prepared by cleavage of the pivalate ester in **8** (Scheme 14) using Red-Al™ followed by oxidation of the primary alcohol with pyridinium dichromate to give a carboxylic acid. The acyl azide prepared by reaction of the carboxylic acid with diphenylphosphoryl azide using the conditions of Shioiri *et al.*,[74] followed by thermolysis in the presence of 2-(trimethylsilyl)ethanol, gave the 2-(trimethylsilyl)ethyl carbamate **58** in 57% overall yield from **8** for the four-step sequence.[65] No epimerisation of the aminal centre was observed. The yield of the 2-(trimethylsilyl)ethyl carbamate **58** would probably improve with deployment of the Hofmann rearrangement as described above for mycalamide B but the opportunity to revisit the synthesis of theopederin D was impossible.

The six-step sequence by which carbamate **9** was converted to the bridged adducts **61a**,**b** was achieved by methods already described in our mycalamide synthesis and warrants no further comment here except that the structure of crystalline intermediate **60** was secured by X-ray crystallography (Fig. 2).

Elaboration of the side chain at C15 began with Sharpless asymmetric dihydroxylation of alkene **61a** using dihydroquinine-9-phenanthryl ether[64] as the ligand. A 1 : 1 mixture of diastereoisomeric diols—one of which corresponds to mycalamide A—was obtained without complications from the selenium atom. The lack of stereoselectivity in the dihydroxylation was of no consequence since the diol was cleaved to an aldehyde function with concomitant oxidation of the selenium to the selenoxide in a single operation using sodium periodate. Brief thermolysis of the selenoxide in refluxing toluene installed the exocyclic methylene to give aldehyde **62** in 69% overall yield from **61a**. The acid sensitivity of the homoallylic acetal imposed significant constraints on the subsequent chemistry.



Scheme 14

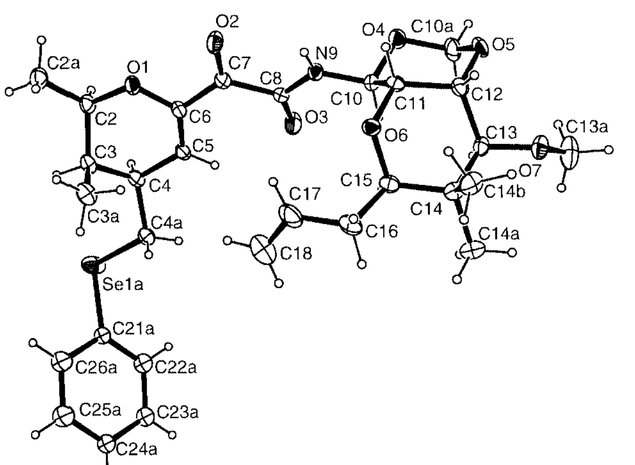


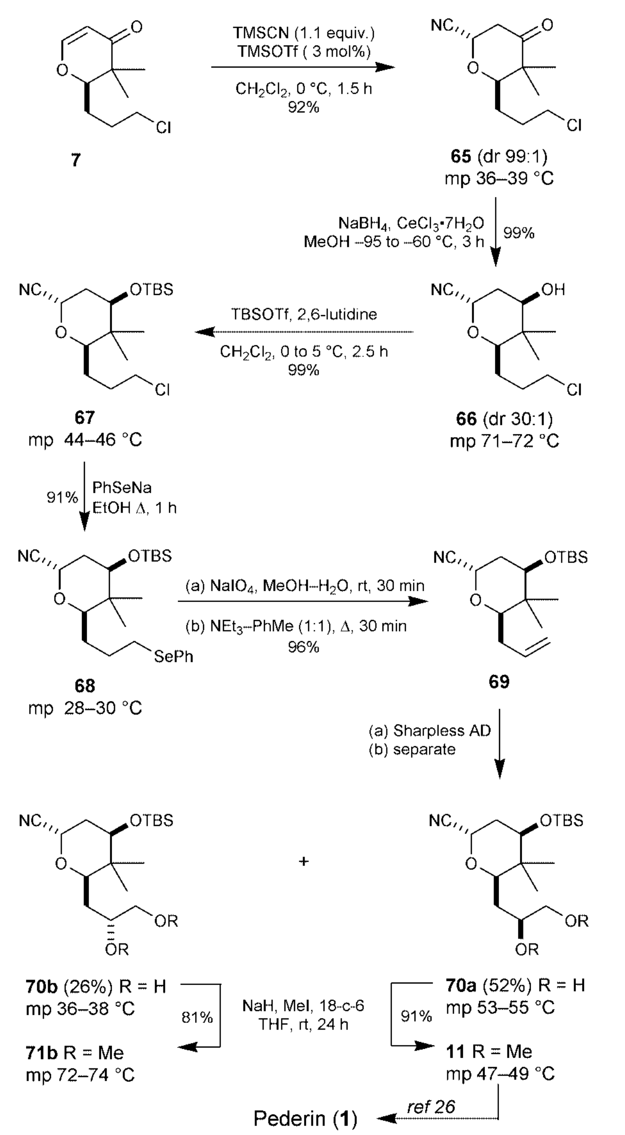
Fig. 2 X-Ray crystal structure of compound **60** showing the atom numbering and 20% probability ellipsoids for non-hydrogen atoms.

Attempts to introduce a propionate fragment directly by addition of 2-ethoxycarbonylethylzinc or samarium reagents gave complex mixtures. However, the Grignard reagent derived from *unprotected* 3-chloropropan-1-ol[75] underwent clean but stereorandom addition to give a 1:1 mixture of diastereoisomeric adducts **63** at C17. Oxidation of the mixture of 1,4-diols with TPAP[76] then gave a mixture of butyrolactones from which the desired diastereoisomer **64a** was isolated by preparative TLC. Finally, methanolysis of the benzoate ester using potassium carbonate gave theopederin D (**5D**) by comparison of the ^{1}H and ^{13}C NMR spectra (400 and 100 MHz respectively) with published data for the natural product.[16] 17-*epi*-Theopederin D prepared by the same method from **64b** was clearly distinguishable by ^{1}H NMR spectroscopy.

A formal synthesis of pederin

The first meaningful SAR study of the mycalamides and their derivatives conducted by Thompson and co-workers[77–80] established that 18-*O*-methylmycalamide B prepared from natural mycalamide A is the most potent antitumour agent in the mycalamide series against a range of human tumour models. Their work together with our own based on synthetic 18-*O*-methylmycalamide B also established that 18-*O*-methylmycalamide B and pederin are nearly equipotent[81] and therefore pederin represents a simpler and more readily accessible candidate for development. We have already described a synthesis of pederin from the metallated dihydropyran **6** and the nitrile **11** which was expensive and impractical.[26] The ready accessibility of dihydropyranone **7** on a large scale stimulated a fresh approach to the synthesis of nitrile **11** which is far more practical. Below we summarise the conversion of dihydropyranone **7** to nitrile **11** which, together with our much improved synthesis of metallated dihydropyran **6** reported herein, represents a new formal total synthesis of pederin.

Conjugate addition of trimethylsilyl cyanide to dihydropyranone **3** (Scheme 15) catalysed by TMSOTf gave the nitrile **65** as a single isomer in 92% yield. Luche reduction[82] of the carbonyl group was diastereoselective affording a quantitative



Scheme 15

yield of diastereoisomeric alcohols (dr 30:1) from which the pure desired isomer **66** could be obtained by crystallisation. After protection of the hydroxy as its TBS ether and displacement of chloride with sodium phenyl selenide, the alkene was generated by thermolysis of a selenoxide intermediate giving terminal alkene **69**. Sharpless asymmetric dihydroxylation gave a 3:2 mixture of diastereoisomeric diols **70a**,**b** which were separable by column chromatography. The desired (17*S*)-diol **70a** was then methylated to give the crystalline nitrile **11** which was converted to pederin as described previously.[26]

Conclusions

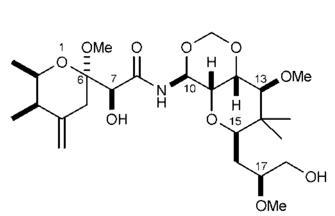
Our syntheses of mycalamide B, theopederin D and pederin from two common intermediates (**6** and **7**) testify to the flexibility of our strategy. Acylation of metallated dihydropyran **6** with oxalamides first disclosed in 1990[83] remains one of the few viable and general routes for accomplishing the difficult construction of the *N*-acyl aminal bridge though the modest yield remains a problem. Noteworthy tactical features include (a) the construction of the methylene acetal **42** by a series of reactions on the oxirane **41** triggered by a methoxymethyl carbenium ion or its equivalent (Scheme 6); (b) the modified Meerwein–Ponndorf–Verley reduction used to reduce ketone **42** (Scheme 9); and (c) the Hofmann rearrangement by which the *N*-acyl aminal is introduced under mild conditions (Scheme 11). The fortuitous interspersion of crystalline intermediates and the infrequent need for chromatographic separation at the earlier stages of the synthesis, together with the ready availability of the key intermediates **6** and **7** from cheap starting materials, make the current approach much more efficient and practical than routes we have described previously. Good to excellent stereoselectivity was obtained for most diastereoselective reactions but the poor diastereocontrol obtained in the Sharpless asymmetric dihydroxylation of the terminal alkenes **8**, **61a** and **69** remains a general problem awaiting a general solution. However, even this blemish is unlikely to affect future developments since analogues with C15 side chains devoid of stereochemical definition are likely to be as active as the natural congeners.

Experimental

General aspects

^{1}H and ^{13}C NMR spectra were recorded in Fourier Transform mode at the field strength specified. All spectra were obtained in $CDCl_3$ or C_6D_6 solution in 5 mm diameter tubes, and the chemical shift in ppm is quoted relative to the residual signals of chloroform (δ_H 7.27, δ_C 77.0) or C_6H_6 (δ_H 7.10, δ_C 126.7) as the internal standard unless otherwise specified. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet and br = broad. Coupling constants (*J*) are reported in Hz. Numbers in parentheses following the chemical shift in the ^{13}C NMR spectra refer to the number of protons attached to that carbon as revealed by the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Signal assignments were based on COSY, HMQC and HMBC correlations. Mycalamide numbering was used throughout in assigning NMR signals. Low and high resolution mass spectra were run on a JEOL MStation JMS-700 spectrometer. Ion mass/charge (*m*/*z*) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%). Mass spectra were recorded on samples judged to be ≥95% pure by ^{1}H and ^{13}C NMR spectroscopy unless otherwise stated.

Numbering of all intermediates uses the mycalamide system as shown.



1. Mycalamide B and 17-*epi*-mycalamide B

Ethyl (*S*)-*O*-(*tert*-butyldimethylsilyl)lactate (12)

The title compound **12** prepared in 99% yield (0.54 mol scale) from ethyl (*S*)-lactate by the procedure of Smith, Kocienski and Street gave $[\alpha]_D^{22}$ −30.0 (*c* 2.5, $CHCl_3$); lit. $[\alpha]_D$ −30.5 (*c* 2.1, $CHCl_3$).[84]

Ethyl (*S*)-4-(*tert*-butyldimethylsilyloxy)pent-2-enoate (13)

The title enoate ester **13** was prepared in 72% yield (0.175 mol scale) by the method of Annunziata *et al.*[46]

Ethyl (3*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate (14)

The title ester **14** was prepared in 75% yield (71 mmol scale) by the method of Yamamoto *et al.*[48]

Ethyl (2*R*,3*R*,4*S*)-2-allyl-4-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate (15)

Ester **14** (24.0 g, 91.6 mmol) was added dropwise *via* syringe to a stirred solution of potassium bis(trimethylsilyl)amide (23.3 g, 80%, 93.0 mmol) in THF (350 ml) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and then allyl bromide (40 ml, 456 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h, quenched with saturated aqueous NH_4Cl and extracted with hexanes (2 × 100 ml). The combined organic extracts were washed with brine (100 ml), dried (Na_2SO_4) and concentrated. The residue was purified by short path distillation to give ester **15** (22.2 g, 73.4 mmol, 80%) as a colourless oil: bp 84–88 °C at 0.5 mmHg as a 22:1 mixture of diastereoisomers according to integration of the doublets at δ 0.06 (minor) and 0.04 (major) as revealed in the ^1H NMR spectrum ($CDCl_3$): $[a]_D^{22} = -2.9$ (*c* 1.5, $CHCl_3$); ν_{max} film/cm^{-1} 2926, 1740, 1261, 838; δ_H (360 MHz, $CDCl_3$): 5.74 (1H, ddt, *J* 17.0, 10.1, 7.0, =CH), 5.05 (1H, ddt, *J* 17.1, 3.3, 1.5, =CH_AH_B), 4.99 (1H, dddd, *J* 10.2, 3.0, 2.2, 1.1, =CH_AH_B), 4.12 (2H, m, OCH_2), 3.68 (1H, dq, *J* 6.2, 5.4, C2H), 2.47 (1H, ddd, *J* 8.8, 7.6, 3.7, C4H), 2.29 (2H, m, $C5H_2$), 1.89 (1H, partially resolved m, *J* 7.0, 5.3, C3H), 1.25 (3H, t, *J* 7.1, OCH_2CH_3), 1.07 (3H, d, *J* 6.2, C2Me), 0.89 (3H, d, *J* 7.0, C3Me), 0.886 (9H, s, Bu^t), 0.043 (3H, s, SiMe), 0.355 (3H, s, SiMe); δ_C (90 MHz, $CDCl_3$): 175.5 (0), 136.2 (1), 116.5 (2), 69.8 (1), 60.2 (2), 47.5 (1), 42.5 (1), 32.9 (2), 26.0 (3, 3C), 19.2 (3), 18.2 (0), 14.5 (3), 11.1 (3), −4.2 (3), −4.7 (3); *m*/*z* (CI, NH_3) 315 [(M + H)$^+$, 6%], 332 [(M + NH_4)$^+$, 1], 275 (1.5), 202 (1.2), 110 (1.2). Found: (M + H)$^+$, 315.2354. $C_{17}H_{35}O_3Si$ requires *M*, 315.2355.

(2*R*,3*R*,4*S*)-2-Allyl-4-(*tert*-butyldimethylsilyloxy)-3-methylpentanol (18)

A solution of DIBAL-H (neat, 28 ml, 156 mmol) was added dropwise to a stirred solution of ester **15** (21.0 g, 66.9 mmol) in CH_2Cl_2 (30 ml) between 5 and 10 °C over 40 min. The reaction mixture was stirred at −5 °C for 1 h. A mixture of water (4 ml) and acetone (40 ml) was added dropwise over 45 min keeping the temperature of the reaction mixture below 20 °C. The clear solution became a white solid. Aqueous HCl (2 M, 230 ml) was then added over 15 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated. Kugelrohr distillation afforded alcohol **18** (16.2 g, 59.6 mmol, 89%) as a colourless oil: bp 140–145 °C (bath) at 0.02 mmHg; $[a]_D^{22}$ 1.1 (*c* 1.6, $CHCl_3$); ν_{max} film/cm^{-1} 3374, 1261, 838; δ_H (360 MHz, $CDCl_3$): 5.84 (1H, dddd, *J* 17.1, 10.1, 7.8, 5.8, =CH), 5.06 (1H, dm, *J* 17.1, =CH_AH_B), 5.01 (1H, dm, *J* 10.0, =CH_AH_B), 3.78 (1H, quint., *J* 6.2, C2H), 3.68 (1H, dd, *J* 11.0, 4.4, CH_AH_BOH), 3.49 (1H, dd, *J* 11.0, 6.3, CH_AH_BOH), 2.30–2.10 (1H, m), 1.95–1.50 (4H, m), 1.16 (3H, d, *J* 6.2, C2Me), 0.90 (9H, s, Bu^t), 0.85 (3H, d, *J* 7.0, C3Me), 0.08 (3H, s, SiMe), 0.06 (3H, s, SiMe); δ_C (90 MHz, $CDCl_3$): 138.3 (1), 116.1 (2), 71.0 (1), 64.1 (2), 41.1 (1), 40.8 (1), 32.6 (2), 26.1 (3, 3C), 21.5 (3), 18.2 (0), 12.5 (3), −4.0 (3), −4.7 (3); *m*/*z* (CI, NH_3) 273 [(M + H)$^+$, 100%], 290 [(M + NH_4)$^+$, 50]. Found: (M + H)$^+$, 273.2247. $C_{15}H_{33}O_2Si$ requires *M*, 273.2250.

(2*R*,3*R*,4*S*)-2-Allyl-4-(*tert*-butyldimethylsilyloxy)-3-methyl-1-triphenylmethyloxypentane (19)

A solution of alcohol **18** (15.0 g, 55.0 mmol), trityl chloride (17.3 g, 62.0 mmol), triethylamine (22 ml, 157 mmol) and DMAP (610 mg, 5.0 mmol) in CH_2Cl_2 (50 ml) was stirred at rt for 12 h, poured onto aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 100 ml) and concentrated. The oily residue was dissolved in Et_2O (100 ml) treated with hexanes (200 ml) and washed with water (500 ml). The organic layer was dried (Na_2SO_4) and concentrated. The residue was filtered through a pad of silica gel (5% Et_2O in hexanes) to give trityl ether **19** (26.6 g, 51.7 mmol, 94%) as a colourless oil, $[a]_D^{22}$ 9.8 (*c* 1.0, $CHCl_3$); ν_{max} film/cm^{-1} 2935, 1452, 829; δ_H (360 MHz, $CDCl_3$): 7.50–7.15 (15H, m), 5.65 (1H, dddd, *J* 17.1, 10.1, 7.8, 5.8, =CH), 4.88 (2H, m, =CH_2), 3.73 (1H, quint., *J* 6.2, C2H), 3.10 (1H, dd, *J* 9.2, 4.8, CH_AH_BO), 2.90 (1H, dd, *J* 9.0, 7.6, CH_AH_BO), 2.25 (1H, m), 2.06 (1H, m), 1.82 (2H, m), 1.09 (3H, d, *J* 6.1, C2Me), 0.91 (9H, s, Bu^t), 0.72 (3H, d, *J* 7.1, C3Me), 0.04 (3H, s, SiMe), 0.02 (3H, s, SiMe); δ_C (90 MHz, $CDCl_3$): 144.7 (0, 2C), 144.7 (0), 137.9 (1), 129.0 (1, 3C), 128.8 (1, 2C), 127.9 (1, 3C), 127.8 (1, 2C), 127.0 (1, 3C), 126.9 (1, 2C), 115.6 (2), 86.6 (0), 70.6 (1), 64.6 (2), 41.0 (1), 38.8 (1), 31.8 (2), 26.1 (3, 3C), 21.0 (3), 18.2 (0), 11.2 (3), −3.8 (3), −4.7 (3); *m*/*z* (CI, NH_3) 532 [(M + NH_4)$^+$, 7%], 243 (100). Found: (M + NH_4)$^+$, 532.3610. $C_{34}H_{50}O_2NSi$ requires *M*, 532.3611.

(2*R*,3*R*,4*S*)-2-Allyl-3-methyl-1-triphenylmethyloxypentan-4-ol (20)

A solution of TBS ether **19** (53.6 g, 104.0 mmol) and TBAF trihydrate (53.0 g, 168.0 mmol) in THF (200 ml) was stirred at reflux for 5 h. After cooling to rt, the mixture was poured onto water (1 l) and extracted with Et_2O (3 × 150 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude alcohol **20** (40.4 g, 100.9 mmol, 97%) as a colourless oil which was immediately used in the next step. Data were obtained by purification of a small sample by column chromatography (SiO_2, 5–10% Et_2O in hexanes); $[a]_D^{22}$ +12.3 (*c* 1.6, $CHCl_3$); ν_{max} film/cm^{-1} 3409, 1449, 706; δ_H (360 MHz, $CDCl_3$): 7.50–7.15 (15H, m), 5.71 (1H, ddt, *J* 17.1, 10.1, 7.2, =CH), 4.96 (1H, dm, *J* 17.2, =CH_AH_B), 4.91 (1H, dm, *J* 10.1, =CH_AH_B), 3.61 (1H, quintet, *J* 6.7, C2H), 3.15 (1H, dd, *J* 9.3, 4.8, CH_AH_BO), 3.00 (1H, dd, *J* 9.3, 7.1, CH_AH_BO), 2.30–2.28 (1H, m), 2.10–1.87 (2H, m), 1.78 (1H, dquint., *J* 7.1, 4.1, C3H), 1.68 (1H, br, OH), 1.11 (3H, d, *J* 6.2, C2 Me), 0.67 (3H, d, *J* 7.0, C3Me); δ_C (90 MHz, $CDCl_3$): 144.4 (0, 3C), 137.9 (1), 128.8 (1, 4C), 127.8 (1, 8C), 126.9 (1, 3C), 115.8 (2), 86.7 (0), 69.6 (1), 64.3 (2), 41.1 (1), 39.4 (1), 32.0 (2), 21.0 (3), 11.6 (3); *m*/*z* (CI, NH_3) 418 [(M + NH_4)$^+$, 0.4%], 243 (32). Found: C, 84.07; H, 8.00%. $C_{28}H_{32}O_2$ requires C, 84.00; H, 8.00.

(2*R*,3*R*,4*R*)-2-Allyl-4-(4-chlorobenzoyloxy)-3-methyl-1-triphenylmethyloxypentane (21)

A solution of diisopropyl azodicarboxylate (16.05 ml, 81.5 mmol) in THF (10 ml) was added dropwise to a stirred solution of alcohol **20** (18.5 g, 46.3 mmol), triphenylphosphine (21.4 g, 81.6 mmol) and *p*-chlorobenzoic acid (12.8 g, 81.7 mmol) in THF (150 ml). The temperature of the reaction mixture was maintained between −10 °C and 0 °C. The reaction mixture was stirred for 3 h between −10 °C and 0 °C. Water (1 ml) was added and the mixture was stirred at rt for 15 min before concentration. The residual oil was dissolved in Et_2O (50 ml) and hexanes (100 ml) were added dropwise to cause formation of white crystals. The crystals (triphenylphosphine oxide) were filtered off and washed with hexanes (3 × 50 ml). The filtrate was extracted with 2 M aqueous NaOH (2 × 30 ml), water (50 ml) and brine (50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 0–4% Et_2O in hexanes) to give the *p*-chlorobenzoate **21** as a colourless oil that crystallised on standing (19 g, 35 mmol, 76%) and its C2 epimer (0.6 g, 1.1 mmol, 2.4%) and elimination product **22** (0.9 g, 2.35 mmol, 5.1%). A sample recrystallised from MeOH–H_2O gave mp 102–103 °C; $[a]_D^{22}$ −25.7 (*c* 1.25, $CHCl_3$); ν_{max} film/cm^{-1} 2972, 1719, 1273, 762; δ_H (360 MHz, $CDCl_3$): 7.91 (2H, dm, *J* 8.6), 7.50–7.35 (7H, m), 7.30–7.15 (10H, m), 5.63 (1H, ddt, *J* 17.1, 10.1, 7.0, =CH), 5.09 (1H, quint., *J* 6.3, C2H), 4.92 (1H, dm, *J* 17.1, =CH_AH_B), 4.90 (1H, dm, *J* 10.1, =CH_AH_B), 3.11 (1H, 4 lines of ABX system, *J* 9.4, 7.2, CH_AH_BO), 3.08 (1H, 4 lines of ABX system, *J* 9.4, 5.7, CH_AH_BO), 2.25–2.12 (1H, m), 2.10–1.95 (2H, m), 1.90–1.80 (1H, m), 1.32 (3H, d, *J* 6.3, C2Me), 0.92 (3H, d, *J* 7.0, C3Me);

δ_C (90 MHz, $CDCl_3$): 165.2 (0), 144.4 (0, 3C), 139.3 (0), 137.1 (1), 131.1 (1, 2C), 129.9 (0, 3C), 128.9 (1, 3C), 128.8 (1, 3C), 127.9 (1, 6C), 127.0 (1, 3C), 116.3 (2), 86.7 (0), 73.8 (1), 63.6 (2), 41.0 (1), 38.1 (1), 32.2 (2), 18.7 (3), 11.1 (3); *m/z* (CI, NH_3) 556 $[(M + NH_4)^+$, 0.24%], 539 $[(M + H)^+$, 0.01%], 316 (4), 263 (2), 243 (100). Found: C, 77.92; H, 6.60%. $C_{35}H_{35}ClO_3$ requires C, 77.99; H, 6.49.

(3*R*,4*R*,5*R*)-5-(4-Chlorobenzoyloxy)-4-methyl-3-(triphenylmethoxymethyl)hexanoic acid (23)

Oxidative cleavage of the olefin was accomplished by the procedure of Sharpless *et al.*[68] $NaIO_4$ (18.3 g, 85.7 mmol) was added to a stirred mixture of olefin **21** (11.0 g, 20.4 mmol), CCl_4 (41 ml), acetonitrile (41 ml) and water (62 ml). After 15 min $RuCl_3 \cdot 3H_2O$ (270 mg, 1.0 mmol) was added and the reaction mixture stirred vigorously for 7 h. The mixture was poured onto water (600 ml), the organic layer removed and the aqueous phase extracted with CH_2Cl_2 (3 × 150 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 200 g, 5% EtOAc in hexanes) to give acid **23** (10.8 g, 19.4 mmol, 95%) as a stable white foam, mp 55–57 °C; $[a]_D^{22}$ −44.4 (*c* 0.85, $CHCl_3$); ν_{max} KBr/cm^{-1} 2977, 1715, 1594, 1488, 1448, 1273, 1091, 1014, 760, 707; δ_H (360 MHz, $CDCl_3$): 7.87 (2H, dm, *J* 7.2), 7.48–7.38 (7H, m), 7.32–7.15 (10H, m), 5.09 (1H, dq, *J* 6.0, 0.9, C2H), 3.24 (1H, dm, *J* 4.4), 3.12–3.06 (1H, dm, *J* 6.2), 2.48–2.35 (3H, m), 2.10–1.90 (1H, m), 1.33 (3H, d, *J* 6.3, C2Me), 0.94 (3H, d, *J* 7.0, C3Me); δ_C (90 MHz, $CDCl_3$): 179.5 (0), 165.1 (0), 144.1 (0, 3C), 139.4 (0), 131.1 (1, 3C), 129.2 (0), 128.8 (1, 3C), 128.8 (1, 3C), 128.8 (1, 3C), 127.9 (1, 5C), 127.1 (1, 2C), 86.9 (0), 73.2 (1), 64.3 (2), 38.4 (1), 37.9 (1), 33.8 (2), 18.4 (3), 11.3 (3); *m/z* (EI) 556 $[(M + H)^{+\bullet}$, 0.03%], 479 (0.15), 400 (3), 324 (7), 243 (100), 165 (46), 139 (70). Found: $(M + Na)^+$, 579.1913. $C_{34}H_{33}O_5ClNa$ requires *M* 579.1914.

(*R*)-4-[(1*R*,2*R*)-2-(4-Chlorobenzoyloxy)-1-methylpropyl]-dihydrofuran-2(3*H*)-one (24)

A solution of acid **23** (10.8 g, 19.3 mmol) and toluene-*p*-sulfonic acid (490 mg, 2.6 mmol) in MeOH (180 ml) was stirred at rt for 4 h before concentration *in vacuo*. The residue was purified by column chromatography (SiO_2 120 g, 10–50% Et_2O in hexanes) to give lactone **24** (4.0 g, 13.5 mmol, 71%) as a white solid. The lactone **24** was further purified by recrystallisation from hexanes–Et_2O to remove the minor diastereoisomers: mp 69.5–70 °C (hexanes–Et_2O); $[a]_D^{22}$ −0.37 (*c* 1.9, $CHCl_3$); ν_{max} film/cm^{-1} 1785, 1716, 1595, 1275; δ_H (360 MHz, $CDCl_3$): 7.93 (2H, dd, *J* 6.7, 2.0), 7.43 (2H, dd, *J* 6.8, 2.0), 5.17 (1H, dq *J* 6.5, 2.7, C2H), 4.55 (1H, dd, *J* 9.0, 8.1, $CH_A H_B O$), 4.03 (1H, t, *J* 9.1, $CH_A H_B O$), 2.67–2.52 (2H, m), 2.33–2.21 (1H, m), 1.90–1.80 (1H, m), 1.34 (3H, d, *J* 6.5, C2Me), 1.10 (3H, d, *J* 6.9, C3Me); δ_C (90 MHz, $CDCl_3$): 176.4 (0), 165.0 (0), 139.7 (0), 130.9 (1, 2C), 128.9 (1, 2C), 128.6 (0), 72.6 (1), 72.4 (2), 41.0 (1), 38.5 (1), 33.0 (2), 16.7 (3), 13.0 (3); *m/z* (CI, isobutane) 297 $[(M + H)^+$, 5%], 265 (1.7), 139 (100), 111 (20), 82 (12). Found: C, 60.84; H, 5.74%. $C_{15}H_{17}ClO_4$ requires C, 60.71; H, 5.73.

(3*S*,4*R*,5*R*)-5-(4-Chlorobenzoyloxy)-4-methyl-3-(phenylselanylmethyl)hexanoic acid (25)

The lactone cleavage was accomplished using sodium phenyl selenide as described in the literature.[53] Sodium borohydride (350 mg, 9.25 mmol) was added portionwise to a stirred yellow suspension of diphenyl diselenide (1.6 g, 5.15 mmol) in EtOH (5.8 ml) causing exothermic reaction and gas evolution. Lactone **24** (1.0 g, 3.37 mmol) was added to the colourless solution of sodium phenyl selenide. The resulting mixture was stirred at reflux for 10 h. After cooling to rt, the reaction mixture was diluted with Et_2O (8 ml) and treated with aqueous HCl (2 M, 5 ml). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 ml). The combined organic extracts were washed with aqueous $NaHCO_3$ (2 × 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 20 g, 10–40% Et_2O in hexanes) to give acid **25** as a yellow oil (1.05 g, 2.72 mmol, 80%); $[a]_D^{22}$ −3.5 (*c* 1.5, $CHCl_3$); ν_{max} film/cm^{-1} 1719, 1595, 1281, 1100; δ_H (360 MHz, $CDCl_3$): 7.97–7.90 (2H, dm, *J* 8.5), 7.50–7.45 (2H, m), 7.44–7.38 (2H, dm, *J* 8.5), 7.23–7.16 (3H, m), 5.18 (1H, quintet, *J* 6.2), 3.06 (1H, dd, *J* 5.8, 3.0, $C5H_A H_B$), 3.02 (1H, dd, *J* 5.6, 3.0, $C5H_A H_B$), 2.61 (1H, dd, *J* 11.5, 4.9, $CH_A H_B$-Se), 2.48 (1H, dd, *J* 16.4, 8.0, $CH_A H_B Se$), 2.40–2.30 (1H, m, C4H), 2.25–2.15 (1H, m, C3H), 1.28 (3H, d, *J* 6.3, C2 Me), 1.01 (3H, d, *J* 7.0, C3Me); δ_C (90 MHz, $CDCl_3$): 179.2 (0), 165.3 (0), 139.5 (0), 133.0 (1), 131.1 (1, 2C), 129.8 (0), 129.2 (1, 2C), 129.0 (0), 128.8 (1, 2C), 127.2 (1, 2C), 73.2 (1), 40.0 (1), 37.2 (1), 35.5 (2), 31.5 (2), 18.5 (3), 10.8 (3); *m/z* (EI) 454 $[(M + H)^{+\bullet}$, 8%], 298 (24), 156 (45), 139 (100), 111 (29). Found: C, 55.53; H, 5.23%. $C_{21}H_{23}ClO_4Se$ requires C, 55.56; H, 5.07.

(4*R*,5*R*,6*R*)-5,6-Dimethyl-4-(phenylselanylmethyl)tetrahydro-2*H*-pyran-2-one (26)

Reductive cleavage of the *p*-chlorobenzoate ester was accomplished according to the procedure of Trost *et al.*[85] *n*-BuLi (3.75 ml, 2.32 M in hexanes, 8.7 mmol) was added dropwise to a solution of DIBAL-H (neat, 8.7 mmol, 1.55 ml) in CH_2Cl_2 (16 ml) at −5 °C. THF (32 ml) was then added, the mixture was cooled to −78 °C and a solution of the ester **25** (1.31 g, 2.9 mmol) in THF (32 ml) was added *via* cannula. The mixture was allowed to warm to −20 °C over 5 min and stirred at −20 °C for 3 h. The mixture was then treated with aqueous HCl (2 M, 35 ml, 70 mmol), and Et_2O (30 ml) and stirred vigorously for 24 h. The organic layer was removed and the aqueous phase extracted with Et_2O (2 × 40 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 40 g, 10–30% Et_2O in hexanes) to give **26** as a clear colourless oil (619 mg, 2.08 mmol, 72%). ^1H NMR and ^{13}C NMR spectroscopic data agree with the literature.[81]

(2*R*,3*R*,4*R*)-2,3-Dimethyl-4-(phenylselanylmethyl)-6-trimethylstannyl-3,4-dihydro-2*H*-pyran (27)

The conversion of lactone **26** (150 mg, 0.50 mmol) to **27** (156 mg, 0.35 mmol) was accomplished in 70% yield according to a reported procedure.[26]

Ethyl 6-chloro-2,2-dimethyl-3-oxohexanoate (29)

n-BuLi (2.5 M in hexanes, 120 ml, 0.3 mol) was added dropwise to a solution of diisopropylamine (42 ml, 0.3 mol) in THF (100 ml) at 0 °C over 15 min. After 1 h at 0 °C, the mixture was cooled to −78 °C whereupon a solution of ethyl isobutyrate (40.1 ml, 0.3 mol) in THF (100 ml) was added over 30 min at a rate sufficient to maintain the internal temperature below −70 °C. After 1 h, a solution of 4-chlorobutanoyl chloride (Aldrich, 33.6 ml, 0.3 mol) in THF (50 ml) was added over 20 min at a rate sufficient to maintain the internal temperature below −68 °C. After 1 h at −78 °C, the reaction was quenched by addition of saturated aqueous ammonium chloride (200 ml). The organic phase was separated and washed successively with H_2O (3 × 200 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$, concentrated *in vacuo*, and the residue purified by short path distillation to give the title β-keto ester **29** (61.6 g, 0.28 mol, 93%) as a colourless oil: ν_{max} film/cm^{-1} 1714; δ_H (300 MHz, $CDCl_3$): 4.19 (2H, q, *J* 7, CH_2O), 3.56 (2H, t, *J* 6.0, CH_2Cl), 2.66 (2H, t, *J* 6.8, $CH_2C{=}O$), 2.06 (2H, dt, *J* 6.6, 6.8, $CH_2CH_2CH_2$), 1.37 (6H, s, CMe_2), 1.26 (3H, t, *J* 7.1, CH_3CH_2); δ_C (75 MHz, $CDCl_3$): 207.3 (0), 173.7 (0), 62.6 (2), 55.7 (0), 44.4 (2), 34.8 (2), 26.7 (2), 22.20 (3), 14.2 (3). Found: $(M + H)^+$, 221.0946. $C_{10}H_{18}ClO_3$ requires *M*, 221.0944.

Ethyl (*R*)-6-chloro-3-hydroxy-2,2-dimethylhexanoate (30)

A. By asymmetric hydrogenation. A Parr high pressure hydrogenator was charged with a solution of the β-keto ester **29** (11.0 g, 50.0 mmol) in methanol (100 ml). Methanolic HCl (2 M, 0.1 ml) was added followed by the addition of the [(*R*)-BINAP][*p*-cymene]$RuCl_2$ catalyst (Aldrich, 0.2 mol%, 93 mg). The apparatus was evacuated and filled with hydrogen three times and the mixture allowed to stir for three days under an atmosphere of hydrogen at 120 psi and 40 °C, after which time the mixture was concentrated *in vacuo* and purified by filtering the dark orange oil through a pad of silica (30 g) eluting with hexanes–Et_2O (5:1). The hydroxy ester **30** (10.4 g, 46.7 mmol, 93%) was obtained as a pale yellow oil. The enantiomeric ratio (97:3) was determined as described below.

B. By directed aldol condensation. A solution of BH_3·THF complex (313 ml, 1 M in THF, 313 mmol) was added dropwise to a stirred suspension of (*S*)-*N*-tosylvaline[86] (105.3 g, 388 mmol) in CH_2Cl_2 (1.85 l) under nitrogen at rt over 30 min. After 30 min, the clear solution was cooled to −70 °C and a solution of 4-chlorobutanal[87] (41.4 g, 388 mmol) in CH_2Cl_2 (35 ml) was added over 10 min. Silyl ketene acetal **31**[88] (78.9 g, 419 mmol) was then added over 30 min maintaining the reaction temperature below −65 °C. After 2 h at −70 °C a solution of NaOH (24.5 g, 612 mmol) in 300 ml of water was added and the reaction mixture was allowed to warm to rt. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 100 ml) and the combined organic extracts were washed with water (500 ml) and concentrated *in vacuo*. The residue was treated with water (500 ml) and extracted with Et_2O (4 × 200 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the hydroxy ester **30** (97.7 g, 370 mmol, 95%) as a yellow oil: $[a]_D^{27}$ 18.7 (*c* 0.9, $CHCl_3$); ν_{max} film/cm^{-1} 3490, 1718; δ_H (270 MHz, $CDCl_3$): 4.17 (2H, q, *J* 7.1, CH_2O), 3.70–3.54 (3H, m, C15H and C18H_2), 2.69 (1H, br d, *J* 6.4, OH), 2.20–2.00 (1H, m, C17H), 1.85 (1H, ddq, *J* 14.5, 9.2, 6.2, C17H), 1.69 (1H, dddd, *J* 13.5, 9.3, 6.0, 1.9, C16H_AH_B), 1.39 (1H, dddd, *J* 13.9, 10.8, 9.3, 4.8, C16H_AH_B), 1.28 (3H, t, *J* 7.1, CH_3CH_2O), 1.22 (3H, s, C14Me), 1.18 (3H, s, C14Me); δ_C (67.5 MHz, $CDCl_3$): 177.8 (0), 76.1 (1), 60.9 (2), 47.1 (0), 45.2 (2), 29.8 (2), 28.9 (2), 22.5 (3), 20.5 (3), 14.3 (3); *m*/*z* (CI, NH_3) 223 [(M + H)$^+$, 100%], 205 (25), 187 (45), 116 (20). Found: C, 53.67; H, 8.29%. $C_{10}H_{19}O_3Cl$ requires C, 53.93; H, 8.54.

The enantiomeric ratio (97:3) was determined by integration of the ^{1}H NMR signals at δ 1.16 (major) and δ 1.11 (minor) of the (*R*)-MTPA esters prepared from **30** in the usual way (270 MHz, C_6D_6, referenced to 7.16 ppm).

Ethyl (*R*)-3-acetoxy-6-chloro-2,2-dimethylhexanoate (33)

To a solution of the crude hydroxy ester **30** (97.7 g, 370 mmol), triethylamine (76 ml, 550 mmol), and DMAP (233 mg, 1.9 mmol) in CH_2Cl_2 (300 ml) was added acetic anhydride (49 ml, 517 mmol) dropwise. The solution was stirred overnight at rt and then diluted with hexanes (1 l), washed with water (3 × 200 ml), and brine (100 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was filtered through a pad of silica gel (15 g, 10% Et_2O in hexanes), concentrated *in vacuo* and the residue distilled (bp 88–96 °C/0.01 mmHg) to give acetate **33** (78.2 g, 0.295 mol, 76%) as a colourless oil; $[a]_D^{22}$ +9.4 (*c* 1.6, $CHCl_3$); ν_{max} film/cm^{-1} 1718, 1236; δ_H (270 MHz, $CDCl_3$): 5.24 (1H, dd, *J* 9.3, 3.9, C15H), 4.14 (2H, q, *J* 7.1, CH_2O), 3.63–3.49 (2H, m, C18H_2), 2.06 (3H, s, OAc), 1.83–1.57 (4H, m, C16H_2 and C17H_2), 1.26 (3H, t, *J* 7.1, CH_3CH_2O), 1.18 (6H, s, C14Me); δ_C (67.5 MHz, $CDCl_3$): 175.4 (0), 170.5 (0), 76.1 (1), 60.8 (2), 46.5 (0), 44.4 (2), 29.2 (2), 27.6 (2), 21.8 (3), 20.8 (3), 20.3 (3), 14.1 (3); *m*/*z* (CI, NH_3): 223 [(M + H)$^+$, 100%], 205 (25), 187 (45), 116 (20). Found: C, 54.67; H, 7.96%. $C_{12}H_{21}ClO_4$ requires C, 54.44; H, 7.93.

(*R*)-6-(3-Chloropropyl)-5,5-dimethyltetrahydro-2*H*-pyran-2,4-dione (34)

n-BuLi (293 ml, 2.32 M in hexane, 610 mmol) was added to a stirred solution of diisopropylamine (90 ml, 637 mmol) in THF (875 ml) at 0 °C over 15 min. After stirring at 0 °C for 20 min, the solution was cooled to −74 °C and a solution of the ester acetate **33** (78.2 g, 292 mmol) in THF (125 ml) was added dropwise over 15 min keeping the temperature of the reaction mixture below −68 °C. The yellow solution was stirred at −74 °C for 1.5 h before adding aqueous HCl (2 M, 750 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 240 ml). The combined organic extracts were washed with brine (200 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was recrystallised twice from hexanes–Et_2O to give the β-ketolactone **34** (50 g, 228 mmol, 78%) as a white solid: mp 103–105 °C; $[a]_D^{20}$ +10.8 (*c* 1.0, $CHCl_3$); ν_{max} film/cm^{-1} 1679, 1605, 1464; δ_H (400 MHz, $CDCl_3$): 4.35 (1H, dd, *J* 10.9, 1.8, C15H), 3.69 (1H, ddd, *J* 11.1, 7.1, 4.8, C18H_AH_B), 3.61 (1H, ddd, *J* 11.1, 7.1, 5.1, C18H_AH_B), 3.61 (1H, d, *J* 19.0, C12H_AH_B), 3.44 (1H, d, *J* 19.0, C12H_AH_B), 2.28–2.19 (1H, m, C17H_AH_B), 1.97–1.87 (2H, m, C16H_AH_B and C17H_AH_B), 1.83–1.72 (1H, m, C16H_AH_B), 1.21 (3H, s, C14Me), 1.12 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 205.4 (0, C11), 167.3 (0, C13), 82.5 (1, C15), 46.9 (0, C14), 45.0 (2, C12), 44.5 (2, C18), 28.8 (2, C17), 26.1 (2, C16), 20.5 (3, C14Me), 17.6 (3, C14Me); *m*/*z* (CI, NH_3) 236 [(M + NH_4)$^+$, 30%], 219 [(M + H)$^+$, 25%], 112 (70), 70 (100). Found: C, 54.93; H, 6.71%. $C_{10}H_{15}ClO_3$ requires C, 54.92; H, 6.86.

(*R*)-6-(3-Chloropropyl)-5,6-dihydro-4-methoxy-5,5-dimethyl-2*H*-pyran-2-one (35)

Potassium carbonate (4.74 g, 34.4 mmol) was added to a solution of β-ketolactone **34** (5.00 g, 22.9 mmol), 18-crown-6 (60 mg, 0.25 mmol) and dimethyl sulfate (2.6 ml, 27.5 mmol) in CH_2Cl_2 (50 ml). The reaction mixture was vigorously stirred at rt for 20 h, filtered through a pad of Celite and concentrated *in vacuo*. Kugelrohr distillation (bp 245–250 °C (oven)/0.05 mmHg) gave enol ether **35** (5.28 g, 22.7 mmol, 99%) as a colourless oil which formed a white solid on cooling: mp 56–57 °C; $[a]_D^{22}$ −68.8 (*c* 1.7, $CHCl_3$); ν_{max} film/cm^{-1} 1673, 1603; δ_H (400 MHz, $CDCl_3$): 5.06 (1H, s, C12H), 4.03 (1H, dd, *J* 11.0, 2.2, C15H), 3.72 (3H, s, OMe), 3.70–3.53 (2H, m, C18H_2), 2.30–2.11 (1H, m), 1.97–1.62 (3H, m), 1.13 (3H, s, C14Me), 1.10 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 179.9 (0, C11), 166.7 (0, C13), 88.7 (1, C12), 82.9 (1, C15), 56.4 (3, OMe), 44.8 (2, C18), 38.7 (0, C14), 29.7 (2, C17), 25.8 (2, C16), 20.6 (3, C14Me), 19.0 (3, C14Me); *m*/*z* (CI, NH_3) 233 [(M + H)$^+$, 100%], 126 (85), 112 (45), 70 (70). Found: C, 56.74; H, 7.45%. $C_{11}H_{17}ClO_3$ requires C, 56.77; H, 7.31.

(*R*)-6-(3-Chloropropyl)-5,6-dihydro-5,5-dimethyl-4*H*-pyran-4-one (7)

DIBAL-H (neat, 8.7 ml, 48.6 mmol) was added dropwise to a stirred solution of lactone **35** (10.3 g, 44.2 mmol) in CH_2Cl_2 (80 ml) maintaining the temperature of the reaction mixture below −70 °C. The reaction mixture was stirred at −70 °C for 40 min and then poured onto aqueous HCl (2 M, 250 ml) and vigorously stirred at rt for 15 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled to give enone **7** (7.6 g, 37.4 mmol, 85%) as a colourless oil: bp 110–112 °C/0.8 mmHg; $[a]_D^{22}$ +135.1 (*c* 2.2, $CHCl_3$); ν_{max} film/cm^{-1} 1674, 1603; δ_H (400 MHz, $CDCl_3$): 7.29 (1H, d, *J* 5.8, C11H), 5.36 (1H, d, *J* 5.8, C12H), 4.02 (1H, dd, *J* 10.2, 2.5, C15H), 3.67–3.55 (2H, m, C18H_2), 2.20–2.05 (1H, m, C17H_AH_B), 1.96–1.75 (3H, m, C16H_2 and C17H_AH_B), 1.13 (3H, s, C14Me), 1.04 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 198.3

(0, C13), 161.4 (1, C11), 105.2 (1, C12), 85.7 (1, C15), 44.6 (2, C18), 44.3 (0, C14), 28.9 (2, C17), 25.4 (2, C16), 19.6 (3, C14Me), 17.8 (3, C14Me); *m*/*z* (CI, NH_3) 203 [$(M + H)^+$, 100%], 167 (8), 112 (45), 132 (8), 98 (7), 69 (6), 41 (4). Found: $(M + H)^+$, 203.0840. $C_{10}H_{15}ClO_2$ requires *M*, 203.0839.

HPLC analysis on Chiracel OD 2 (4.6 × 50 mm) using 2% isopropanol in cyclohexane separated the two enantiomers of **7** (major enantiomer 13.24 min; minor enantiomer 14.63 min) and established their ratio as >99 : 1.

(2*S*,6*R*)-6-(3-Chloropropyl)tetrahydro-5,5-dimethyl-2-vinyl-2*H*-pyran-4-one (36)

To a stirred solution of enone **7** (17.6 g, 86.8 mmol) and copper(I) iodide (1.0 g, 5.35 mmol) in THF (170 ml) at −95 °C was added a solution of vinylmagnesium chloride (1.7 M in THF, 90 ml, 153 mmol) over 30 min. The reaction mixture was stirred for 1.5 h at −90 °C and then allowed to warm up to −30 °C over 1.5 h. Saturated aqueous NH_4Cl (300 ml) was added followed by concentrated ammonia solution (60 ml). The resulting mixture was stirred for 30 min at rt before being extracted with Et_2O (3 × 80 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation to give vinyl ketone **36** (16.0 g, 63.3 mmol, 80%) as a colourless oil: bp 160–180 °C (bath) at 0.07 mmHg. The diastereoisomeric ratio was 95 : 5 according to integration of the ^1H NMR spectrum signals (400 MHz, $CDCl_3$) at δ 2.85 and 2.81 ppm (minor) and 2.67 and 2.55 ppm (major) corresponding to $C12H_2$. The following data were recorded on the mixture: $[\alpha]_D^{20}$ +46.5 (*c* 1.1, $CHCl_3$); ν_{max} film/cm^{-1} 1712, 1128; δ_H (400 MHz, $CDCl_3$): 5.85 (1H, ddd, *J* 17.2, 11.2, 4.8, C10H), 5.25 (1H, t, *J* 1.2, $C9H_AH_B$), 5.21 (1H, dt, *J* 8.8, 1.2, $C9H_AH_B$), 4.56 (1H, qt, *J* 4.8, 1.6, C11H), 3.61 (1H, dd, *J* 10.0, 3.6, C15H), 3.55 (2H, t, *J* 6.4, $C18H_2$), 2.67 (1H, dd, *J* 14.4, 6.0, $C12H_AH_B$), 2.55 (1H, dd, *J* 14.4, 6.0, $C12H_AH_B$), 2.02–1.92 (1H, m, $C17H_AH_B$), 1.81–1.70 (1H, m, $C17H_AH_B$), 1.70–1.50 (2H, m, $C16H_2$), 1.11 (3H, s, C14Me), 1.06 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 211.5 (0, C13), 137.3 (1, C10), 117.9 (2, C9), 79.3 (1, C15), 72.6 (1, C11), 49.8 (0, C14), 45.0 (2, C18), 41.5 (2, C12), 29.3 (2, C17), 25.9 (2, C16), 22.0 (3, C14Me), 19.4 (3, C14Me); *m*/*z* (CI) 248 [$(M + NH_4)^+$, 100%]. Found: $(M + H)^+$, 230.1071. $C_{12}H_{19}ClO_2$ requires *M*, 230.1074. Found: C, 62.48; H, 8.18%. $C_{12}H_{19}ClO_2$ requires C, 62.47; H, 8.24.

(2*S*,6*R*)-6-(3-Chloropropyl)-2-[(*R*)-1,2-dihydroxyethyl]tetrahydro-5,5-dimethyl-2*H*-pyran-4-one (37)

The procedure of Sharpless *et al.* was used.[64] Olefin **36** (10.0 g, 43.5 mmol) and hydroquinine 9-phenanthryl ether (Aldrich, 439 mg, 0.9 mmol) were stirred in ^{t}BuOH (260 ml) until the ligand dissolved completely. After cooling to rt, water (260 ml), $K_3Fe(CN)_6$ (43.3 g, 131.3 mmol) and K_2CO_3 (18.3 g, 132.6 mmol) were added and the mixture was cooled to 0 °C before addition of potassium osmate dihydrate (267 mg, 0.72 mmol). The reaction mixture was stirred for 3 h at 0 °C, then treated with saturated aqueous Na_2SO_3 (400 ml) and water (100 ml). After stirring at ambient temperature for 30 min the mixture was extracted with CH_2Cl_2 (400 ml + 2 × 200 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude diol. Filtration through silica gel (100 g, 10–40% EtOAc in Et_2O) afforded diol **37** (8.63 g, 32.7 mmol, 75%) as a 13 : 1 mixture of diastereoisomers according to integration of ^1H NMR signals (360 MHz, $CDCl_3$) derived from the *gem*-dimethyl groups [δ 1.26 ppm (major) and 1.28 ppm (minor)]: $[\alpha]_D^{19}$ −8.0 (*c* 1.1, $CHCl_3$); ν_{max} film/cm^{-1} 3412, 1712; δ_H (400 MHz, $CDCl_3$): 3.94 (1H, dt, *J* 9.7, 4.6, C11-H), 3.81 (1H, ddd, *J* 9.8, 6.2, 3.7, C10H), 3.77 (1H, dd, *J* 11.9, 3.5, C15H), 3.73 (1H, dd, *J* 11.4, 3.6, $C9H_AH_B$), 3.65 (1H, dd, *J* 11.3, 6.4, $C9H_AH_B$), 3.58 (2H, t, *J* 6.0, $C18H_2$), 2.80 (1H, dd, *J* 14.6, 9.7, $C12H_AH_B$), 2.38 (1H, dd, *J* 14.6, 4.3, $C12H_AH_B$), 2.00–1.74 (2H, br, OH), 2.00–1.89 (1H, m, $C17H_AH_B$), 1.83–1.74 (1H, m, $C17H_AH_B$), 1.73–1.63 (1H, m, $C16H_AH_B$), 1.61–1.50 (1H, m, $C16H_AH_B$), 1.27 (3H, s, C14Me), 1.01 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 212.9 (0, C13), 81.6 (1, C15), 73.6 (1, C10), 71.7 (1, C11), 63.2 (2, C9), 49.6 (0, C14), 44.5 (2, C18), 38.8 (2, C12), 28.7 (2, C17), 25.3 (2, C16), 24.2 (3, C14Me), 19.3 (3, C14Me); *m*/*z* (CI) 248 [$(M + NH_4)^+$, 100%]. Found: C, 54.50; H, 7.74; Cl, 13.72%. $C_{12}H_{21}ClO_4$ requires C, 54.44; H, 7.94; Cl, 13.42.

(2*S*,6*R*)-2-[(*R*)-2-(*tert*-Butylcarbonyloxy)-1-hydroxyethyl]-6-(3-chloropropyl)tetrahydro-5,5-dimethyl-2*H*-pyran-4-one (38)

To a solution of diols **37** (dr 13 : 1, 4.8 g, 18.2 mmol) and pyridine (4.45 ml, 55.0 mmol) in CH_2Cl_2 (35 ml) at 0 °C was added pivaloyl chloride (4.6 ml, 37.5 mmol). The reaction mixture was stirred at 0 °C for 1 h, treated with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 70 ml). The combined extracts were washed with aqueous HCl (2 M, 50 ml), brine (70 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered through a pad of silica (50 g, 20–50% Et_2O in hexanes) and concentrated *in vacuo*. Diastereoisomerically pure monopivalate ester **38** (11.6 g, 33.5 mmol, 78%) was obtained as colourless needles by recrystallisation from hexanes–Et_2O: mp 69–70 °C; $[\alpha]_D^{19}$ −2.0 (*c* 1.0, $CHCl_3$); ν_{max} CCl_4/cm^{-1} 3599, 1716; δ_H (400 MHz, $CDCl_3$): 4.27 (1H, dd, *J* 11.6, 3.6, $C9H_AH_B$), 4.12 (1H, dd, *J* 11.6, 6.4, $C9H_AH_B$), 3.96 (1H, dddd, *J* 14.8, 6.4, 5.6, 4.0, C10H), 3.92 (1H, dt, *J* 9.8, 5.3, C11H), 3.80 (1H, dd, *J* 12.0, 3.2, C15H), 3.58 (1H, ddd, *J* 10.9, 6.2, 1.1, $C18H_AH_B$), 3.55 (1H, ddd, *J* 10.9, 6.6, 1.6, $C18H_AH_B$), 2.82 (1H, dd, *J* 14.8, 9.6, $C12H_AH_B$), 2.70–2.20 (1H, d, *J* 4.4, OH), 2.42 (1H, dd, *J* 14.8, 4.0, $C12H_AH_B$), 2.00–1.85 (1H, m, $C17H_AH_B$), 1.83–1.73 (1H, m, $C17H_AH_B$), 1.73–1.61 (1H, m, $C16H_AH_B$), 1.60–1.50 (1H, m, $C16H_AH_B$), 1.29 (3H, s, C14Me), 1.22 (9H, s, ^{t}Bu), 1.03 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 211.9 (0, C13), 179.1 (0, ester C=O), 82.1 (1, C15), 72.3 (1, C10), 71.2 (1, C11), 64.9 (2, C9), 49.7 (0, C14), 44.8 (2, C18), 39.1 (0, *C*Me$_3$), 38.6 (2, C12), 28.8 (2, C17), 27.4 (3, 3C, C*Me*$_3$), 25.4 (2, C16), 24.8 (3, C14Me), 19.5 (3, C14Me); *m*/*z* (CI) 349 [$(M + H)^+$, 20%]. Found: C, 58.71; H, 8.02; Cl, 10.37%. $C_{17}H_{29}ClO_5$ requires C, 58.54; H, 8.32; Cl, 10.19.

(2*S*,6*R*)-2-[(*R*)-2-(*tert*-Butylcarbonyloxy)-1-(methoxymethoxy)-ethyl]-6-(3-chloropropyl)tetrahydro-5,5-dimethyl-2*H*-pyran-4-one (39)

A mixture of alcohol **38** (7.1 g, 20.0 mmol), *N*-ethyldiisopropylamine (10.8 ml, 62.0 mmol), tetabutylammonium iodide (355 mg, 0.92 mmol), chloromethyl methyl ether (4.7 ml, 62.0 mmol) and anhydrous toluene (55 ml) were stirred at 90 °C for 2 h. The reaction mixture was cooled to rt and treated with saturated aqueous $NaHCO_3$ (30 ml). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 30 ml). The combined organic extracts were washed with brine (30 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 50 g, 10–40% Et_2O in hexanes) to give the desired MOM ether **39** (2.63 g, 6.7 mmol, 97%) as a white solid: mp 42–43 °C (hexanes–Et_2O); $[\alpha]_D^{21}$ +3.4 (*c* 1.4, $CHCl_3$); ν_{max} CCl_4/cm^{-1} 1732, 1716, 1154; δ_H (400 MHz, $CDCl_3$): 4.69 (1H, d, *J* 6.9, OCH_AH_BO), 4.61 (1H, d, *J* 6.9, OCH_AH_BO), 4.29 (1H, dd, *J* 11.8, 4.3, $C9H_AH_B$), 3.99 (1H, dd, *J* 11.8, 4.9, $C9H_AH_B$), 3.92 (1H, dt, *J* 9.9, 4.6, C11H), 3.78 (1H, q, *J* 5.0, C10H), 3.68 (1H, dd, *J* 11.7, 3.2, C15H), 3.47 (2H, t, *J* 5.5, $C18H_2$), 3.30 (3H, s, OMe), 2.71 (1H, dd, *J* 14.8, 10.0, $C12H_AH_B$), 2.34 (1H, dd, *J* 14.7, 4.3, $C12H_AH_B$), 1.90–1.80 (1H, m, $C17H_AH_B$), 1.74–1.62 (1H, m, $C17H_AH_B$), 1.62–1.51 (1H, m, $C16H_AH_B$), 1.50–1.40 (1H, m, $C16H_AH_B$), 1.19 (3H, s, C14Me), 1.11 (9H, s, ^{t}Bu), 0.93 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 211.3 (0, C13), 177.8 (0, ester C=O), 96.2 (2, O–CH_2–O), 81.5 (1, C15), 76.5 (1, C10), 70.3 (1, C11), 62.4 (2, C9), 55.8 (3, OMe), 49.3 (0, C14), 44.4 (2, C18), 38.7 (2, C12), 38.6 (0, *C*Me$_3$), 28.4 (2, C17), 26.9 (3, 3C, C*Me*$_3$), 24.9 (2, C16), 24.3 (3, C14Me), 19.1 (3, C14Me); *m/z* (CI) 393 [(M + H)$^+$, 7%]. Found: C, 58.36; H, 8.12; Cl, 8.94%. $C_{19}H_{33}ClO_6$ requires C, 58.09; H, 8.41; Cl, 9.04.

(2*S*,6*R*)-2-[(*R*)-2-(*tert*-Butylcarbonyloxy)-1-(methoxymethoxy)-ethyl]-4-[(*tert*-butyldimethylsilyl)oxy]-6-(3-chloropropyl)-5,6-dihydro-5,5-dimethyl-2*H*-pyran (40)

To a mixture of ketone **39** (17.5 g, 44.5 mmol) and triethylamine (12.1 ml, 86.6 mmol) in CH_2Cl_2 (70 ml) at 0 °C was added TBSOTf (12.1 ml, 51.5 mmol) in a dropwise fashion over 5 min. After the addition was complete the cooling bath was removed and the reaction mixture stirred for 1.5 h at rt. Saturated aqueous $NaHCO_3$ (200 ml) was added and the mixture extracted with hexanes (3 × 50 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give crude silyl enol ether **56**. TBSOH was removed under vacuum at 50 °C/1 mmHg overnight to give the desired silyl enol ether **40** (19.2 g, 37.8 mmol, 85%) as a clear colourless oil: $[a]_D^{17}$ +10.3 (*c* 1.1, $CHCl_3$); ν_{max} film/cm^{-1} 1732, 1664, 1154; δ_H (400 MHz, $CDCl_3$): 4.74 (1H, d, *J* 3.0, C12H), 4.72 (1H, d, *J* 6.8, OCH_AH$_B$O), 4.66 (1H, d, *J* 6.8, OCH$_A$$H_B$O), 4.46 (1H, dd, *J* 11.9, 2.5, C9H_AH$_B$), 4.20 (1H, dd, *J* 7.8, 3.0, C11H), 4.08 (1H, dd, *J* 12.0, 5.7, C9H$_A$$H_B$), 3.71 (1H, ddd, *J* 7.9, 5.7, 2.5, C10H), 3.65–3.53 (2H, m, C18H$_2$), 3.40 (1H, dd, *J* 10.6, 2.1, C15H), 3.37 (3H, s, OMe), 2.10–2.00 (1H, m, C17H_AH$_B$), 1.83–1.70 (1H, m, C17H$_A$$H_B$), 1.70–1.59 (1H, m, C16$H_AH_B$), 1.59–1.49 (1H, m, C16H$_A$$H_B$), 1.19 (9H, s, ^{t}Bu), 1.01 (3H, s, C14Me), 0.93 (3H, s, C14Me), 0.92 (9H, s, ^{t}BuSi), 0.16 (3H, s, MeSi), 0.15 (3H, s, MeSi); δ_C (100 MHz, $CDCl_3$): 178.2 (0, ester C=O), 156.0 (0, C13), 98.2 (1, C12), 96.4 (2, OCH$_2$O), 79.0 (1, C15), 77.3 (1, C10), 70.0 (1, C11), 64.2 (2, C9), 55.8 (3, OMe), 45.2 (2, C18), 38.7 (0, *C*Me$_3$ or C14), 38.4 (0, C14 or *C*Me$_3$), 29.6 (2, C17), 27.1 (3, 3C, ^{t}BuC=O), 26.2 (2, C16), 25.6 (3, 3C, ^{t}BuSi), 23.0 (3, C14Me), 19.7 (3, C14Me), 18.1 (0, CSi), −4.5 (3, MeSi), −4.8 (3, MeSi); *m/z* (CI, NH$_3$) 524 [(M + NH$_4$)$^+$, 40%]. Found: (M + H)$^+$, 507.2910. $C_{25}H_{48}ClO_6Si$ requires *M*, 507.2909. Found: C, 59.31; H, 9.01%. $C_{25}H_{47}ClO_6Si$ requires C, 59.35; H, 9.23.

(2*R*,3*S*,4*S*,6*R*)-2-[(*R*)-2-(*tert*-Butylcarbonyloxy)-1-(methoxymethoxy)ethyl]-4-[(*tert*-butyldimethylsilyl)oxy]-6-(3-chloropropyl)-3,4-epoxytetrahydro-5,5-dimethyl-2*H*-pyran (41)

A solution of *m*-chloroperbenzoic acid (15.2 g, 57–80%) in CH_2Cl_2 (150 ml) was dried over Na_2SO_4, filtered and stirred with sodium hydrogen orthophosphate (11.2 g, 78.7 mmol) at rt for 30 min. The mixture was then cooled to 0 °C and a solution of enol ether **40** (8.58 g, 17.0 mmol) in CH_2Cl_2 (56 ml) was added dropwise over 20 min. The reaction mixture was stirred for 40 min, treated with saturated aqueous Na_2SO_3 and hexanes (500 ml). The phases were separated and the organic layer was extracted with aqueous NaOH (2 M, 2 × 70 ml), washed with water (70 ml), brine (70 ml), dried (Na_2SO_4) and concentrated *in vacuo* to afford crude oxirane **41** (9.58 g, 18.4 mmol, *ca.* 100%, single diastereoisomer) as a clear colourless oil: $[a]_D^{20}$ +10.0 (*c* 2.0, $CHCl_3$); ν_{max} film/cm^{-1} 1732, 1152; δ_H (360 MHz, $CDCl_3$): 4.78 (1H, d, *J* 6.7, OCH$_A$$H_B$O), 4.74 (1H, d, *J* 6.7, OCH_AH$_B$O), 4.54 (1H, dd, *J* 12.0, 1.8, C9H$_A$$H_B$), 4.05 (1H, dd, *J* 9.9, 3.2, C11H), 4.01 (1H, dd, *J* 12.0, 4.3, C9H_AH$_B$), 3.94 (1H, ddd, *J* 9.9, 4.1, 1.6, C10H), 3.57–3.47 (2H, m, C18H$_2$), 3.51 (1H, d, *J* 3.2, C12H), 3.43 (3H, s, OMe), 3.27 (1H, dd, *J* 10.3, 1.4, C15H), 2.00–1.85 (1H, m), 1.70–1.50 (2H, m), 1.40–1.30 (1H, m), 1.22 (9H, s, ^{t}BuC=O), 1.05 (3H, s, C14Me), 0.98 (3H, s, C14Me), 0.91 (9H, s, ^{t}BuSi), 0.14 (3H, s, SiMe), 0.06 (3H, s, SiMe); δ_C (90 MHz, $CDCl_3$): 178.5 (0), 96.3 (2), 86.6 (0), 76.0 (1), 71.7 (1), 68.9 (1), 63.6 (2), 60.4 (1), 56.2 (3), 45.3 (2), 39.1 (0), 38.9 (0), 30.1 (2), 27.4 (3, 3C), 26.9 (2), 25.8 (3, 3C), 18.7 (3), 18.0 (0), 16.8 (3), −3.1 (3), −3.4 (3); *m/z* (CI, NH$_3$) 540 [(M + NH$_4$)$^+$, 100%]. Found: (M + H)$^{+\bullet}$, 522.2781. $C_{25}H_{47}ClO_7Si$ requires *M*, 522.2780.

(1*S*,5*R*,6*R*,8*R*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decan-10-one (42)

A mixture of crude oxirane **41** (3.5 g, *ca.* 92% pure, 6.17 mmol) in CH_2Cl_2 (15 ml) was added *via* cannula to a solution of dimethoxymethane (30 ml) and P_2O_5 (2.5 g, 8.8 mmol) in CH_2Cl_2 (15 ml) at 0 °C over 5 min. The cool bath was removed and the reaction mixture was stirred at rt for 2 h whereupon the reaction mixture was poured onto saturated aqueous $NaHCO_3$ (50 ml). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 ml). The combined extracts were washed with brine (100 ml), dried (Na_2SO_4) and concentrated *in vacuo*. A ^{1}H NMR spectrum of the crude product showed a 15 : 1 ratio of diastereoisomers by integration of the ^{1}H NMR signals (360 MHz, $CDCl_3$) derived from *gem*-dimethyl groups at δ 1.06 ppm (major) and 1.32 ppm (minor)]. The crude product was purified by column chromatography (SiO_2 45 g, 10–40% Et_2O in hexanes) to give ketone **42** (1.79 g, 4.75 mmol, 77%) as a white solid: mp 88–89 °C (hexanes–Et_2O); $[a]_D^{20}$ +166.6 (*c* 1.4, $CHCl_3$); ν_{max} KBr/cm^{-1} 1724, 1282, 1164, 1150; δ_H (400 MHz, $CDCl_3$): 4.94 (1H, d, *J* 7.8, C12H), 4.87 (1H, d, *J* 6.5, OCH_AH$_B$O), 4.83 (1H, d, *J* 6.5, OCH$_A$$H_B$O), 4.50 (1H, dd, *J* 12.2, 1.6, C9H_AH$_B$), 4.30 (1H, dd, *J* 10.9, 7.8, C11H), 4.03 (1H, dd, *J* 12.2, 6.9, C9H$_A$$H_B$), 3.88 (1H, ddd, *J* 10.8, 6.9, 1.6, C10H), 3.60 (2H, dt, *J* 6.8, 5.1, C18H$_2$), 3.56 (1H, dd, *J* 12.4, 4.0, C15H), 2.12–2.02 (1H, m, C17H_AH$_B$), 1.90–1.70 (1H, m, C17H_AH$_B$), 1.70–1.61 (2H, m, C16H$_2$), 1.22 (12H, s, ^{t}BuC=O and C14Me), 1.08 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 208.2 (0, C13), 178.3 (0, ester C=O), 89.8 (2, OCH$_2$O), 78.6 (1, C15), 73.3 (1, C12), 72.6 (1, C10), 70.0 (1, C11), 62.8 (2, C9), 51.0 (0, C14 or *C*Me$_3$), 45.0 (2, C18), 38.7 (0, *C*Me$_3$ or C14), 29.4 (2, C17), 27.0 (3, 3C, ^{t}BuC=O), 26.7 (2, C16), 19.0 (3, C14Me), 18.9 (3, C14Me); *m/z* (CI, NH$_3$) 394 [(M + NH$_4$)$^+$, 100%]. Found: (M + H)$^+$, 376.1652. $C_{18}H_{30}ClO_6$ requires *M*, 376.1653. Found: C, 57.37; H, 7.64; Cl, 9.46%. $C_{18}H_{29}ClO_6$ requires C, 57.37; H, 7.70; Cl, 9.43.

Reduction of ketone 42

Two procedures were used, the more selective being a modified Meerwein–Ponndorf–Verley reduction. Thus, trimethylaluminium (2.5 ml, 2.0 M in hexane, 5 mmol) was added to isopropanol (50 ml). The solution was stirred for 30 min at rt before solid ketone **42** (500 mg, 1.325 mmol) was added. The reaction mixture was stirred for 24 h at rt, then concentrated *in vacuo*. The residue was diluted with EtOAc (50 ml) and treated with HCl (0.5 M, 25 ml). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture of the ketone **42**, the alcohol **45a**, and the undesired alcohol **45b** as a colourless oil. Separation by column chromatography (SiO_2 10 g, 30–50% Et_2O in hexanes) gave ketone **42** (140 mg, 0.371 mmol, 28%), and a mixture of alcohols **45a** and **45b** (332 mg, 0.878 mmol, 66%, or 92% based on recovered starting material) in the ratio 6 : 1 (major product is the desired one). The alcohols were then separated by a second column chromatography (SiO_2 10 g, 10–50% Et_2O in hexanes) to give alcohols **45a** and **45b** as colourless oils.

(1*S*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decan-10-ol (45a). $[a]_D^{20}$ +87.0 (*c* 2.0, $CHCl_3$); ν_{max} film/cm^{-1} 3486, 1740, 1728; δ_H (400 MHz, $CDCl_3$): 4.94 (1H, d, *J* 6.4, OCH$_A$$H_B$O), 4.80 (1H, d, *J* 6.8, OCH_AH$_B$O), 4.49 (1H, dd, *J* 12.0, 2.0, C9H$_A$$H_B$), 4.16 (1H, ddd, *J* 10.4, 6.8, 1.6, C10H), 4.06 (1H, dd, *J* 10.4, 6.4, C11H), 4.03–3.94 (3H, m), 3.65–3.50 (2H, m, C18H$_2$), 3.26 (1H, dd, *J* 10.4, 1.6, C15H), 2.24 (1H, br, OH), 2.10–1.90 (1H, m), 1.80–1.60 (2H, m), 1.50–1.37 (1H, m), 1.23 (9H, s, ^{t}BuCOO), 1.04 (3H, s, C14Me), 0.93 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 178.6 (0), 86.7 (2), 78.1 (1), 72.8 (1), 71.4 (1), 69.4 (1), 67.4 (1), 63.8 (2), 45.4 (2), 40.8 (0), 39.0 (0), 29.7 (2), 27.3 (3, 3C), 26.3 (2), 23.1 (3), 12.6 (3); *m/z* (CI) 379 [(M + H)$^+$, 100%]. Found: C, 57.11; H, 8.10%. $C_{18}H_{31}ClO_6$ requires C, 57.07; H, 8.19.

(1*S*,5*R*,6*R*,8*R*,10*R*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decan-10-ol (45b). $[\alpha]_D^{22}$ +66.3 (*c* 0.3, $CHCl_3$); ν_{max} film/cm^{-1} 3496, 1734; δ_H (360 MHz, $CDCl_3$): 5.15 (1H, d, *J* 5.8, OCH_AH_BO), 4.89 (1H, d, *J* 5.8, OCH_AH_BO), 4.30 (2H, apparent d, *J* 5.7, C9H_2), 4.21 (1H, dt, *J* 10.4, 5.2, C10H), 4.06 (1H, t, *J* 3.8), 3.75–3.62 (3H, m), 3.59 (2H, t, *J* 5.5, C18H_2), 2.32 (1H, d, *J* 8.1, OH), 2.00–1.58 (4H, m), 1.21 (9H, s, ^{t}BuC=O), 1.13 (3H, s, C14Me), 0.96 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 178.3 (0), 89.1 (2), 78.0 (1, broad signal), 74.3 (1, broad signal), 73.1 (1), 70.2 (1), 65.4 (1), 62.3 (2), 45.1 (2), 38.9 (0), 38.5 (0), 29.3 (2), 27.2 (3, 3C), 24.0 (2), 22.6 (3), 22.2 (3, broad signal); δ_C (90 MHz, $CDCl_3$, 333 K): 178.1 (0), 89.1 (2), 78.0 (1), 74.3 (1), 73.1 (1), 70.3 (1), 65.7 (1), 62.6 (2), 44.9 (2), 38.9 (0), 38.4 (0), 29.5 (2), 27.2 (3, 3C), 24.1 (2), 22.7 (3), 22.1 (3); *m/z* (CI) 379 [(M + H)$^+$, 100%]. Found: C, 57.05; H, 8.05%. $C_{18}H_{31}ClO_6$ requires C, 57.07; H, 8.19.

Alcohols **45a** and **45b** were also generated by reduction of ketone **42** with KBH_4 in the presence of $CeCl_3\cdot7H_2O$. A solution of ketone **42** (1.80 g, 4.8 mmol) and $CeCl_3\cdot7H_2O$ (2.6 g, 7.1 mmol) in anhydrous methanol (90 ml) was stirred at rt for 15 min and then cooled to 0 °C. Solid KBH_4 (740 mg, 14.1 mmol) was added (gas evolution!). After 1.5 h acetone (1 ml) was added to the reaction mixture followed by saturated aqueous $NaHCO_3$ (50 ml). The methanol was removed *in vacuo* and the aqueous phase extracted with CH_2Cl_2 (3 × 50 ml). The combined extracts were washed with brine (50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. ^{1}H NMR spectrum of the crude product showed a 1 : 2 ratio of diastereoisomers by integration of ^{1}H NMR signals (360 MHz, $CDCl_3$) derived from the *gem*-dimethyl groups at δ 1.14 ppm (major) and 1.05 ppm (minor). The undesired alcohol **45b** was the major product. The crude product was purified by column chromatography (SiO_2 50 g, 30–50% Et_2O in hexanes) to give a mixture of alcohols **45a**,**b** (1.72 g, 4.56 mmol, 95%) as a colourless oil. The diastereoisomers were separated by column chromatography (SiO_2 150 g, hexanes–Et_2O 20–40%).

The undesired alcohol **45b** was converted back to ketone **42** by Dess–Martin oxidation.[89] Dess–Martin periodinane (2.7 g, 6.35 mmol) was added in one portion to a stirred solution of alcohol **45b** (1.6 g, 4.3 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was stirred at rt for 25 min and treated with saturated aqueous $Na_2S_2O_3$ (25 ml) and saturated aqueous $NaHCO_3$ (20 ml). After 1 h the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 10 g, 10–30% Et_2O in hexanes) to give ketone **42** (1.61 g, 4.3 mmol, 100%).

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo-[4.4.0]decane (46)

A solution of alcohol **45a** (4.2 g, 11.0 mmol) in THF (25 ml) was added dropwise to a stirred solution of sodium bis(trimethylsilyl)amide (2 M in THF, 7.3 ml, 14.5 mmol) in THF (5 ml) at −78 °C. After 5 min methyl trifluoromethanesulfonate (2.5 ml, 22.4 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 20 min, treated with saturated aqueous $NaHCO_3$ (50 ml) and extracted with Et_2O (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5–20% Et_2O in hexanes) to give methyl ether **46** (3.7 g, 9.41 mmol, 86%) as a colourless oil: $[\alpha]_D^{21}$ +54.7 (*c* 1.1, $CHCl_3$); ν_{max} film/cm^{-1} 1732, 1162, 1112, 1040; δ_H (400 MHz, $CDCl_3$): 4.98 (1H, d, *J* 6.6, OCH_AH_BO), 4.84 (1H, d, *J* 6.6, OCH_AH_BO), 4.48 (1H, dd, *J* 12.0, 1.6, C9H_AH_B), 4.19–4.13 (2H, m, C10H, C12H), 4.00 (1H, dd, *J* 12.0, 7.0, C9H_AH_B), 3.92 (1H, dd, *J* 10.6, 6.8, C11H), 3.63–3.50 (2H, m, C18H_2), 3.55 (3H, s, OMe), 3.42 (1H, d, *J* 10.3, C13H), 3.24 (1H, d, *J* 9.7, C15H), 2.02–1.94 (1H, m, C17H_AH_B), 1.80–1.68 (1H, m, C17H_AH_B), 1.68–1.60 (1H, m, C16H_AH_B), 1.46–1.35 (1H, m, C16H_AH_B), 1.22 (9H, s, ^{t}BuC=O), 1.00 (3H, s, C14Me), 0.86 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 178.4 (0, ester C=O), 86.9 (2, OCH_2O), 79.2 (1, C13), 78.0 (1, C15), 73.3 (1, C10 or C12), 71.2 (1, C12 or C10), 67.3 (1, C11), 63.7 (2, C9), 61.7 (3, OMe), 45.2 (2, C18), 41.6 (0, C14), 38.8 (0, *C*Me$_3$), 29.5 (2, C17), 27.1 (3, 3C, ^{t}Bu), 26.1 (2, C16), 23.1 (3, C14Me), 13.4 (3, C14Me); *m/z* (CI) 393 [(M + H)$^+$, 100%]. Found: (M + H)$^+$, 393.2040. $C_{19}H_{34}ClO_6$ requires *M*, 393.2044. Found: C, 58.19; H, 8.41%. $C_{19}H_{33}ClO_6$ requires C, 58.09; H, 8.41.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-10-methoxy-9,9-dimethyl-8-(3-phenylselanylpropyl)-2,4,7-trioxabicyclo[4.4.0]decane (47)

Solid $NaBH_4$ (610 mg, 16.1 mmol) was added in several batches to a stirred suspension of diphenyl diselenide (2.5 g, 8.26 mmol) in anhydrous ethanol (30 ml) to cause exothermic reaction. The reaction mixture was stirred at rt until a clear yellow solution was obtained. A solution of chloride **46** (4.2 g, 10.7 mmol) in ethanol (30 ml) was then added *via* cannula and the resulting mixture was heated at reflux for 10 min. The reaction mixture was cooled to rt, poured onto saturated aqueous $NaHCO_3$ (200 ml) and extracted with Et_2O (3 × 200 ml). The combined organic extracts were washed with aqueous NaOH (2 M, 100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 10–40% Et_2O in hexanes) to give selenide **47** (5.25 g, 10.2 mmol, 96%) as a colourless oil: $[\alpha]_D^{20}$ +71.3 (*c* 1.6, $CHCl_3$); ν_{max} film/cm^{-1} 1732, 1580, 1186, 1162, 1112, 1040; δ_H (400 MHz, $CDCl_3$): 7.54–7.51 (2H, m), 7.31–7.23 (3H, m), 4.99 (1H, d, *J* 6.6, OCH_AH_BO), 4.88 (1H, d, *J* 6.6, OCH_AH_BO), 4.47 (1H, dd, *J* 12.0, 1.6, C9H_AH_B), 4.20–4.16 (1H, m, C10H collapsed by C12H), 4.18 (1H, dd, *J* 10.3, 6.8, C12H), 4.02 (1H, dd, *J* 12.1, 6.9, C9H_AH_B), 3.97 (1H, dd, *J* 10.6, 6.8, C11H), 3.59 (3H, s, OMe), 3.42 (1H, d, *J* 10.3, C13H), 3.23 (1H, dd, *J* 10.2, 1.4, C15H), 2.96 (2H, t, *J* 7.0, C18H_2), 2.00–1.90 (1H, m, C17H_AH_B), 1.75–1.65 (1H, m, C17H_AH_B), 1.65–1.57 (1H, m, C16H_AH_B), 1.47–1.40 (1H, m, C16H_AH_B), 1.25 (9H, s, ^{t}BuC=O), 1.00 (3H, s, C14Me), 0.87 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 178.3 (0, ester C=O), 132.7 (1, 2C), 130.3 (0), 129.0 (1, 2C), 126.7 (1), 86.9 (2, OCH_2O), 79.2 (1, C13), 78.1 (1, C15), 73.4 (1, C10 or C12), 71.2 (1, C12 or C10), 67.3 (1, C11), 63.6 (2, C9), 61.7 (3, OMe), 41.6 (0, C14 or *C*Me$_3$), 38.9 (0, *C*Me$_3$ or C14), 28.6 (2, C18), 27.9 (2, C17 or C16), 27.1 (3, 3C, ^{t}Bu), 27.1 (2, C16 or C17), 23.2 (3, C14Me), 13.4 (3, C14Me); *m/z* (EI) 514 [(M + H)$^{+\bullet}$, 33%], 357 (15), 243 (15), 193 (20), 113 (25), 71 (100). Found: (M + H)$^{+\bullet}$, 514.1830. $C_{25}H_{38}O_6Se$ requires *M*, 514.1835. Found: C, 58.47; H, 7.48%. $C_{25}H_{38}O_6Se$ requires C, 58.48; H, 7.41.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-10-methoxy-9,9-dimethyl-8-(prop-2-enyl)-2,4,7-trioxabicyclo-[4.4.0]decane (8)

Sodium metaperiodate (3.5 g, 16.8 mmol) was added in one portion to a stirred mixture of selenide **47** (5.20 g, 10.1 mmol), water (60 ml) and MeOH (150 ml) at rt. The reaction mixture was stirred for 25 min then diluted with water (50 ml) and extracted with CH_2Cl_2 (3 × 50 ml). To the combined organic extracts was added 5 ml of triethylamine and the extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in toluene (110 ml) and triethylamine (110 ml) and heated at reflux for 10 min. The yellow reaction mixture was allowed to cool to rt, poured onto saturated aqueous $NaHCO_3$

(200 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated at rt *in vacuo*. The residue was dissolved in toluene (7 ml) and purified by column chromatography (SiO_2, hexanes until the yellow band eluted and then Et_2O–hexanes) (5–50%) to give olefin **8** (3.55 g, 9.96 mmol, 98%) as a colourless oil: $[\alpha]_D^{22}$ +25.9 (*c* 1.4, $CHCl_3$); ν_{max} film/cm^{-1} 1732, 1480, 1284; δ_H (400 MHz, $CDCl_3$): 5.84 (1H, ddt, *J* 18.0, 11.4, 6.8, C17H), 5.08 (1H, ddm, *J* 5.6, 1.2, C18H_A*H_B*), 5.04 (1H, dm, *J* 1.2, C18*H_A*H_B), 4.99 (1H, d, *J* 6.6, OC*H_A*H_BO), 4.86 (1H, d, *J* 6.6, OCH_A*H_B*O), 4.47 (1H, dd, *J* 12.0, 1.9, C9*H_A*H_B), 4.20–4.15 (1H, m, C10H collapsed by C12H), 4.18 (1H, dd, *J* 10.2, 6.8, C12H), 4.06 (1H, dd, *J* 12.0, 6.6, C9H_A*H_B*), 3.99 (1H, dd, *J* 10.6, 6.8, C11H), 3.57 (3H, s, OMe), 3.44 (1H, d, *J* 10.2, C13H), 3.30 (1H, dd, *J* 10.1, 2.3, C15H), 2.19 (1H, dddt, *J* 14.4, 10.2, 7.1, 1.2, C16*H_A*H_B), 2.12–2.03 (1H, m, C16H_A*H_B*), 1.23 (9H, s, ^{t}BuC=O), 1.02 (3H, s, C14Me), 0.89 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 178.6 (0, ester C=O), 135.8 (1, C17), 116.7 (2, C18), 87.2 (2, OCH_2O), 79.3 (1, C13), 78.5 (1, C15), 73.5 (1, C12), 71.3 (1, C10), 67.3 (1, C11), 63.5 (2, C9), 61.8 (3, OMe), 41.6 (0, C14), 38.9 (0, *C*Me_3), 33.4 (2, C16), 27.2 (3, 3C, ^{t}Bu), 23.2 (3, C14Me), 13.4 (3, C14Me); *m/z* (CI) 357 [(M + H)$^+$, 100%]. Found: (M + H)$^+$, 357.2277. $C_{19}H_{33}O_6$ requires *M*, 357.2276. Found: C, 64.04; H, 9.19%. $C_{19}H_{32}O_6$ requires C, 64.04; H, 9.00.

Sharpless asymmetric dihydroxylation of alkene 8

Alkene **8** (2 g, 5.61 mmol) and dihydroquinine 9-phenanthryl ether[64] (86 mg, 0.170 mmol) were stirred in ^{t}BuOH (40 ml) until the crystals of ligand dissolved completely. After cooling to rt, water (40 ml), $K_3Fe(CN)_6$ (5.6 g, 17.1 mmol) and K_2CO_3 (2.3 g, 16.7 mmol) were added and the mixture was cooled to 0 °C. Potassium osmate dihydrate (60 mg, 0.16 mmol) was added and the reaction mixture was stirred for 3 h at 0 °C, then treated with saturated aqueous Na_2SO_3 (70 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude diols as an inseparable mixture (1.5 : 1) of diastereoisomers which were used immediately in the next step. The isomeric ratio was ascertained by integration of the crude mixture which revealed signals derived from one of the C9 protons at δ 4.82 (dd, *J* 12.2, 1.2, minor) and 4.60 ppm (dd, *J* 12.1, 1.2, minor)] in the ^{1}H NMR spectrum (360 MHz, $CDCl_3$).

tert-Butyldimethylsilyl chloride (1.72 g, 11.45 mmol) was added in one portion to a stirred solution of crude mixture of diols, triethylamine (1.6 ml, 11.0 mmol) and DMAP (70 mg, 0.58 mmol) in CH_2Cl_2 (25 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at rt for 2 h. Saturated aqueous $NaHCO_3$ (40 ml) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by column chromatography (SiO_2, 30–40% Et_2O in hexanes) to give a mixture of **48a** and **48b** (2.7 g, 5.3 mmol, 95% from the alkene). Separation by chromatography on silica gel (0–50% Et_2O in hexanes) gave the desired monoprotected diol **48a** (1.5 g, 3.0 mmol, 53%) which crystallised on standing and the undesired monoprotected diol **48b** (1.0 g, 2.0 mmol, 36%) as a colourless oil. TLC monitoring conditions: 50% Et_2O in hexanes (phosphomolybdic acid); R_f (**8**) 0.00 (black); R_f (**48a**) 0.43 (black), (**48b**) 0.31 (black).

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-{(2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxypropyl}-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (48a). Mp 32–34 °C (hexanes–Et_2O); $[\alpha]_D^{23}$ +58.0 (*c* 0.42, $CHCl_3$); ν_{max} film/cm^{-1} 3542, 2958, 1186, 1732, 1472, 1040; δ_H (400 MHz, $CDCl_3$): 5.00 (1H, d, *J* 6.6, OC*H_A*H_BO), 4.86 (1H, d, *J* 6.6, OCH_A*H_B*O), 4.54 (1H, dd, *J* 12.0, 1.7, C9*H_A*H_B), 4.22 (1H, ddd, *J* 10.5, 6.4, 1.7, C10H), 4.17 (1H, dd, *J* 12.0, 6.8, C9H_A*H_B*), 4.14 (1H, dd, *J* 12.4, 6.4, C12H), 4.00 (1H, dd, *J* 10.6, 6.8, C11H), 3.79 (1H, m, C17H), 3.62 (1H, dd, *J* 10.0, 5.2, C18*H_A*H_B), 3.57 (3H, s, OMe), 3.52–3.43 (3H, m, C13H, C15H and C18H_A*H_B*), 3.12 (1H, br d, *J* 1.6, OH), 1.82 (1H, ddd, *J* 14.5, 3.6, 2.0, C16*H_A*H_B), 1.44 (1H, ddd, *J* 14.5, 10.0, 8.0, C16H_A*H_B*), 1.23 (9H, s, ^{t}BuC=O), 1.00 (3H, s, C14Me), 0.90 (3H, s, C14Me), 0.89 (9H, s, ^{t}BuSi), 0.07 (6H, s, Me_2Si); δ_C (100 MHz, $CDCl_3$): 178.3 (0, ester C=O), 86.9 (2, OCH_2O), 78.92 (1, C13 or C15), 78.87 (1, C15 or C13), 73.1 (1, C12), 71.7 (1, C17), 71.2 (1, C10), 67.4 (1, C11), 66.4 (2, C18), 63.4 (2, C9), 61.7 (3, OMe), 41.7 (0, C14 or *C*Me_3), 38.8 (0, *C*Me_3 or C14), 32.2 (2, C16), 27.1 (3, 3C, ^{t}Bu), 25.8 (3, 3C, ^{t}BuSi), 23.1 (3, C14Me), 18.2 (0, CSi), 13.4 (3, C14Me), −5.4 (3, 2C, $SiMe_2$); *m/z* (CI, isobutane) 505 [(M + H)$^+$, 100%]. Found: (M + H)$^+$, 505.3193. $C_{25}H_{49}O_8Si$ requires *M*, 505.3197. Found: C, 59.29; H, 9.53%. $C_{25}H_{48}O_8Si$ requires C, 59.49; H, 9.59.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-{(2*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxypropyl}-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (48b). $[\alpha]_D^{23}$ +75.3 (*c* 0.3, $CHCl_3$); ν_{max} film/cm^{-1} 3568, 2958, 1186, 1732, 1472, 1040; δ_H (400 MHz, $CDCl_3$): 5.00 (1H, d, *J* 6.6, OC*H_A*H_BO), 4.86 (1H, d, *J* 6.6, OCH_A*H_B*O), 4.66 (1H, dd, *J* 12.1, 1.3, C9*H_A*H_B), 4.22–4.15 (1H, m, C10H collapsed by C12H), 4.19 (1H, dd, *J* 10.3, 7.1, C12H), 4.03 (1H, dd, *J* 12.1, 6.9, C9H_A*H_B*), 3.95 (1H, dd, *J* 11.0, 7.0, C11H), 3.85–3.75 (1H, m, C17H), 3.62 (1H, dd, *J* 9.8, 2.4, C15H), 3.57 (3H, s, OMe), 3.57 (1H, dd, *J* 9.9, 4.4, C18*H_A*H_B) 3.47 (1H, d, *J* 10.5, C13H), 3.47 (1H, dd, *J* 10.0, 3.3, C18H_A*H_B*), 3.13 (1H, br d, *J* 4.0, OH), 1.45–1.33 (2H, m, C16H_2), 1.23 (9H, s, ^{t}BuC=O), 0.99 (3H, s, C14Me), 0.90 (9H, s, ^{t}BuSi), 0.86 (3H, s, C14Me), 0.07 (6H, s, Me_2Si); δ_C (100 MHz, $CDCl_3$): 178.8 (0, COO), 86.9 (2, OCH_2O), 79.4 (1, C13), 74.0 (1, C15), 73.6 (1, C10 or C12), 71.7 (1, C12 or C10), 67.9 (1, C17), 67.8 (2, C18), 67.3 (1, C11), 64.0 (2, C9), 61.8 (3, OMe), 41.3 (0, C14 or *C*Me_3), 38.9 (0, *C*Me_3 or C14), 32.0 (2, C16), 27.1 (3, 3C, ^{t}Bu), 25.9 (3, 3C, ^{t}BuSi), 22.9 (3, C14Me), 18.3 (0, CSi), 13.2 (3, C14Me), −5.3 (3, 2C, $SiMe_2$); *m/z* (CI, isobutane) 505 [(M + H)$^+$, 100%], 487 (8), 447 (10). Found: (M + H)$^+$, 505.3193. $C_{25}H_{49}O_8Si$ requires *M*, 505.3197. Found: C, 59.58; H, 9.40%. $C_{25}H_{48}O_8Si$ requires C, 59.49; H, 9.59.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-{(2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methoxypropyl}-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (49a)

A solution of alcohol **48a** (525 mg, 1.04 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (700 mg, 3.36 mmol) and methyl trifluoromethanesulfonate (350 µl, 3.05 mmol) in toluene (3 ml) was stirred at 70 °C (oil bath temperature) for 4 h and overnight at 40 °C. The reaction mixture was cooled to rt and treated with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 20 ml). The combined organic extracts were washed with aqueous HCl (2 M) and brine, then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5–25% Et_2O in hexanes) to give methyl ether **49a** (412 mg, 0.794 mmol, 76%) as a colourless oil which solidified on standing: mp 30–32 °C (hexanes–Et_2O); $[\alpha]_D^{21}$ +91.4 (*c* 0.3, $CHCl_3$); ν_{max} KBr/cm^{-1} 2958, 1732, 1472, 1108; δ_H (400 MHz, $CDCl_3$): 5.01 (1H, d, *J* 6.6, OC*H_A*H_BO), 4.86 (1H, d, *J* 6.6, OCH_A*H_B*O), 4.46 (1H, dd, *J* 10.1, 5.5, C9*H_A*H_B), 4.20–4.11 (3H, m, C9H_A*H_B*, C10H, C12H), 4.00 (1H, dd, *J* 10.2, 6.8, C11H), 3.67 (2H, d, *J* 4.3, C18H_2), 3.57 (3H, s, OMe), 3.43 (1H, d, *J* 10.3, C13H), 3.36 (3H, s, OMe), 3.35 (1H, dd, *J* 9.8, 1.6, C15H), 3.29 (1H, dq, *J* 8.1, 4.3, C17H), 1.81 (1H, ddd, *J* 14.2, 8.1, 1.6, C16*H_A*H_B), 1.52 (1H, ddd, *J* 14.2, 10.1, 4.3, C16H_A*H_B*), 1.23 (9H, s, ^{t}BuC=O), 1.00 (3H, s, C14Me), 0.90 (9H, s, ^{t}BuSi), 0.89 (3H, s, C14Me), 0.07 (6H, s, Me_2Si); δ_C (100 MHz, $CDCl_3$): 178.4 (0, ester C=O), 87.0 (2, OCH_2O), 79.8 (1, C17), 79.5 (1, C13), 76.2 (1, C15), 73.4 (1, C10 or C12), 71.4 (1, C12 or C10), 67.3 (1, C11), 63.8 (2, C18 or C9), 63.6 (2, C9 or C18), 61.8 (3, OMe), 57.2 (3, OMe), 41.7 (0, C14 or *C*Me_3), 39.0

(0, CMe_3 or C14), 30.5 (2, C16), 27.3 (3, 3C, ^tBu), 26.1 (3, 3C, ^tBuSi), 23.4 (3, C14Me), 18.4 (0, CSi), 13.5 (3, C14Me), −5.2 (3, 2C, Me_2Si); *m/z* (CI, isobutane) 519 [$(M + H)^+$, 100%], 461 (8), 387 (10). Found: $(M + H)^+$, 519.3350. $C_{26}H_{51}O_8Si$ requires *M*, 519.3353. Found: C, 60.31; H, 9.63%. $C_{26}H_{51}O_8Si$ requires C, 60.20; H, 9.71.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-{(2*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methoxypropyl}-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (49b)

Methylation of **48b** (530 mg, 1.05 mmol) by the same procedure gave methyl ether **49b** (403 mg, 0.78 mmol, 74%) as a colourless oil: $[a]_D^{19}$ +82.5 (*c* 0.8, $CHCl_3$); ν_{max} KBr/cm^{-1} 2957, 1732, 1473, 1111; δ_H (400 MHz, $CDCl_3$): 5.02 (1H, d, *J* 6.6, OCH_AH_BO), 4.85 (1H, d, *J* 6.6, OCH_AH_BO), 4.36–4.30 (1H, m, $C9H_AH_B$), 4.23 (1H, dd, *J* 10.4, 7.0, $C9H_AH_B$), 4.23–4.18 (1H, m collapsed by signals at 4.23 and 4.21 ppm, C10H), 4.16 (1H, dd, *J* 10.2, 6.9, C12H), 3.98 (1H, dd, *J* 10.4, 6.9, C11H), 3.63 (1H, dd, *J* 10.8, 4.6, $C18H_AH_B$), 3.60–3.54 (1H, m, $C18H_AH_B$), 3.56 (3H, s, OMe), 3.51 (1H, dd, *J* 10.1, 1.0, C15H), 3.47 (1H, d, *J* 10.3, C13H), 3.37 (3H, s, OMe), 3.38–3.31 (1H, m, C17H), 1.52 (1H, ddd, *J* 14.3, 10.4, 1.4, $C16H_AH_B$), 1.40 (1H, ddd, *J* 14.4, 10.4, 2.3, $C16H_AH_B$), 1.21 (9H, s, $^tBuC{=}O$), 0.97 (3H, s, C14Me), 0.88 (9H, s, ^tBuSi), 0.85 (3H, s, C14Me), 0.04 (6H, s, Me_2Si); δ_C (100 MHz, $CDCl_3$): 178.2 (0, ester C=O), 86.8 (2, OCH_2O), 79.4 (1, C13), 77.6 (1, C17), 74.0 (1, C15), 73.5 (1, C12), 71.3 (1, C10), 67.0 (1, C11), 64.5 (2, C18), 63.6 (2, C9), 61.7 (3, OMe), 57.4 (3, OMe), 41.2 (0, C14 or CMe_3), 38.8 (0, CMe_3 or C14), 31.5 (2, C16), 27.1 (3, 3C, ^tBu), 25.8 (3, 3C, ^tBuSi), 23.1 (3, C14Me), 18.2 (0, CSi), 13.3 (3, C14Me), −5.4 (3, 2C, Me_2Si); *m/z* (CI, isobutane) 519 [$(M + H)^+$, 80%], 487 (60), 461 (10), 387 (10), 355 (100), 315 (15). Found: $(M + H)^+$, 519.3352. $C_{26}H_{51}O_8Si$ requires *M*, 519.3353. Found: C, 60.28; H, 9.59%. $C_{26}H_{50}O_8Si$ requires C, 60.20; H, 9.71.

(1*R*,5*R*,6*R*,8*R*,10*S*)-8-{(2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxypropyl}-5-hydroxymethyl-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (50)

To a solution of ester **49a** (415 mg, 0.800 mmol) in THF (5 ml) at −80 °C was added Red-Al™ (400 µl, 1.1 M in THF, 0.44 mmol) dropwise over 5 min. The cooling bath was removed and the clear colourless reaction mixture allowed to warm to 0 °C over 30 min whereupon acetone (40 µl) was added and the mixture then poured onto ice cold aqueous NaOH (1 M, 1.9 ml). Dichloromethane (2 ml) and H_2O (2 ml) were added and the clear colourless phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 40% Et_2O in hexanes) to give alcohol **50** (327 mg, 0.75 mmol, 94%) as a clear colourless oil: $[a]_D^{21}$ +67.4 (*c* 1.6, $CHCl_3$); ν_{max} film/cm^{-1} 3466, 2932, 1472; δ_H (400 MHz, $CDCl_3$): 5.02 (1H, d, *J* 6.5, OCH_AH_BO), 4.85 (1H, d, *J* 6.5, OCH_AH_BO), 4.14 (1H, dd, *J* 10.3, 6.0, C11H), 4.20–3.80 (2H, m, C10H, C12H), 3.85 (1H, br d, *J* 11.7, $C9H_AH_B$), 3.73–3.66 (1H, m, $C9H_AH_B$), 3.65 (1H, dd, *J* 10.8, 4.7, $C18H_AH_B$), 3.59 (1H, dd, *J* 10.8, 4.5, $C18H_AH_B$), 3.56 (3H, s, OMe), 3.42 (1H, d, *J* 10.4, C13H), 3.36 (3H, s, OMe), 3.37–3.33 (1H, m, C15H), 3.28 (1H, dq, *J* 7.6, 4.4, C17H), 2.48 (1H, br s, OH), 1.76 (1H, ddd, *J* 14.4, 7.6, 1.6, $C16H_AH_B$), 1.49 (1H, ddd, *J* 14.4, 9.6, 4.8, $C16H_AH_B$), 0.97 (3H, s, C14Me), 0.89 (9H, s, ^tBuSi), 0.86 (3H, s, C14Me), 0.06 (6H, s, Me_2Si); δ_C (100 MHz, $CDCl_3$): 86.7 (2, OCH_2O), 79.9 (1, C17), 79.2 (1, C13), 76.0 (1, C15), 73.3 (1, C10 or C11 or C12), 73.2 (1, C10 or C11 or C12), 68.0 (1, C10 or C12), 63.9 (2, C18), 63.4 (2, C9), 61.7 (3, OMe), 57.0 (3, OMe), 41.7 (0, C14), 30.5 (2, C16), 25.8 (3, 3C, ^tBuSi), 23.2 (3, C14Me), 18.2 (0, CSi), 13.1 (3, C14Me), −5.4 (3, 2C, Me_2Si); *m/z* (CI, isobutane) 435 [$(M + H)^+$, 100%], 403 (12), 377 (15), 345 (4), 303 (23). Found: $(M + H)^+$, 435.2779. $C_{21}H_{43}O_7Si$ requires *M*, 435.2778. Found: C, 58.08; H, 9.73%. $C_{21}H_{42}O_7Si$ requires C, 58.03; H, 9.74.

17-*epi*-50

Reductive cleavage of pivalate ester **49b** (320 mg, 0.62 mmol) by the same procedure afforded alcohol **17-*epi*-50** (264 mg, 0.61 mmol, 98%) as a clear colourless oil: $[a]_D^{22}$ +92.0 (*c* 1.5, $CHCl_3$); ν_{max} film/cm^{-1} 3466, 2930, 1470; δ_H (400 MHz, $CDCl_3$): 5.02 (1H, d, *J* 6.5, OCH_AH_BO), 4.83 (1H, d, *J* 6.5, OCH_AH_BO), 4.13 (1H, dd, *J* 10.3, 6.8, C12H), 4.05 (1H, ddd, *J* 10.6, 5.5, 2.5, C10H), 3.96 (1H, dd, *J* 10.6, 6.9, C11H), 3.89–3.81 (1H, m, $C9H_AH_B$), 3.71–3.64 (1H, m, $C9H_AH_B$), 3.62–3.55 (2H, m, $C18H_2$), 3.53 (3H, s, OMe), 3.49 (1H, d, *J* 10.3, C13H), 3.43 (1H, d, *J* 10.4, C15H), 3.39 (3H, s, OMe), 3.37–3.30 (1H, m, C17H), 2.54 (1H, br s, OH), 1.53–1.45 (1H, m, $C16H_AH_B$), 1.40–1.30 (1H, m, $C16H_AH_B$), 0.93 (3H, s, C14Me), 0.86 (9H, s, ^tBuSi), 0.82 (3H, s, C14Me), 0.02 (6H, s, Me_2Si); δ_C (100 MHz, $CDCl_3$): 86.6 (2, OCH_2O), 79.4 (1, C15), 77.8 (1, C17), 73.9 (1, C13), 73.5 (1, C10 or C12), 73.4 (1, C10 or C12), 67.4 (1, C11), 64.7 (2, C18), 62.8 (2, C9), 61.6 (3, OMe), 57.5 (3, OMe), 41.2 (0, C14), 31.2 (2, C16), 25.8 (3, 3C, ^tBuSi), 23.0 (3, C14Me), 18.2 (0, CSi), 13.1 (3, C14Me), −5.5 (3, 2C, Me_2Si); *m/z* (CI, isobutane) 435 [$(M + H)^+$, 100%], 403 (12), 377 (10), 345 (4), 303 (23). Found: $(M + H)^+$, 435.2777. $C_{26}H_{43}O_7Si$ requires *M*, 435.2778. Found: C, 58.12; H, 9.68%. $C_{21}H_{42}O_7Si$ requires C, 58.03; H, 9.74.

(1*R*,5*S*,6*S*,8*R*,10*S*)-8-{(2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxypropyl}-10-methoxy-9,9-dimethyl-5-{*N*-[(2-trimethylsilyl)ethoxycarbonyl]amino}-2,4,7-trioxabicyclo[4.4.0]decane (53) *via* Curtius rearrangement

Sodium periodate (750 mg, 3.5 mmol) was added to a stirred mixture of alcohol **50** (280 mg, 0.65 mmol), carbon tetrachloride (5 ml), acetonitrile (5 ml) and water (7.5 ml) followed by ruthenium chloride trihydrate (11.3 mg, 0.043 mmol). The reaction mixture was stirred at rt for 3 h and extracted with CH_2Cl_2 (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude black-green residue was dissolved in anhydrous toluene (2 ml) and concentrated *in vacuo* three times and then immediately used in the next step.

The crude acid **51** was dissolved in anhydrous toluene (3 ml) to which freshly activated 4 Å molecular sieves (80 mg) and anhydrous *N*-ethyldiisopropylamine (0.180 ml, 1.03 mmol) were added. 2-Trimethylsilylethanol (0.73 ml, 5.1 mmol), dried by the addition of freshly activated 4 Å molecular sieves (80 mg), and diphenylphosphoryl azide (0.18 ml, 0.83 mmol) were then added. The mixture was plunged into an oil bath at 65 °C and evolution of N_2 gas was observed. After heating at 65 °C for 3 h the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (15 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5–25% Et_2O in hexane) to give carbamate **53** (205 mg, 0.364 mmol, 56%) as a pale yellow oil: $[a]_D^{18}$ +56.6 (*c* 0.73, $CHCl_3$); ν_{max} ($CDCl_3$)/cm^{-1} 3437, 2959, 1729, 1514, 1212; δ_H (400 MHz, $CDCl_3$): 5.51 (1H, br t, *J* 9.3, C10H), 5.32 (1H, d, *J* 9.3, NH), 5.14 (1H, d, *J* 6.7, OCH_AH_BO), 4.85 (1H, d, *J* 7.0, OCH_AH_BO), 4.25–4.15 (3H, m, C12H and OCH_2CH_2TMS), 3.80 (1H, dd, *J* 9.5, 6.9, C11H), 3.63 (1H, dd, *J* 11.1, 3.5, $C18H_AH_B$), 3.56 (1H, dd, *J* 10.8, 4.0, $C18H_AH_B$), 3.56 (3H, s, OMe), 3.43 (1H, d, *J* 10.3, C13H), 3.32 (3H, s, OMe), 3.29 (1H, d, *J* 9.5, C15H), 3.18 (1H, dq, *J* 7.8, 4.0, C17H), 1.84 (1H, dd, *J* 13.2, 8.0, $C16H_AH_B$), 1.47 (1H, m, $C16H_AH_B$), 1.05–0.95 (2H, m, CH_2TMS), 0.99 (3H, s, C14Me), 0.89 (9H, s, ^tBuSi), 0.88 (3H, s, C14Me), 0.06 (6H, s, Me_2Si), 0.05 (9H, s, Me_3Si); δ_C (90 MHz, $CDCl_3$): 155.8 (0, O–C(O)–NH), 86.3 (2, OCH_2O), 79.7 (1, C17), 79.6 (1, C13), 76.5 (1, C10 or C15), 76.3 (1, C10 or C15), 74.4 (1, C12), 70.3 (1, C11), 63.9

(2, OCH_2CH$_2$TMS), 62.1 (2, C18), 61.8 (3, OMe), 56.9 (3, OMe), 41.7 (0, C14), 29.7 (2, C16), 25.9 (3, 3C, ^{t}BuSi), 23.3 (3, C14Me), 18.3 (0, CSi), 17.7 (2, CH_2Si), 13.4 (3, C14Me), −1.5 (3, 3C, Me_3Si), −5.4 (3, 2C, Me_2Si); *m*/*z* (CI, isobutane) 564 [(M + H)$^+$, 20%], 536 (100), 488 (25), 372 (25). Found: (M + H)$^+$, 564.3385. $C_{26}H_{54}NO_8Si_2$ requires *M*, 564.3388.

(1*R*,5*S*,6*S*,8*R*,10*S*)-8-{(2*R*-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxypropyl}-10-methoxy-9,9-dimethyl-5-{*N*-[(2-trimethylsilyl)ethoxycarbonyl]amino}-2,4,7-trioxabicyclo[4.4.0]decane (17-*epi*-53)

Alcohol **17-*epi*-50** (258 mg, 0.59 mmol) was converted to carbamate **17-*epi*-53** (192 mg, 0.340 mmol, 57%) by the same procedure: $[\alpha]_D^{19}$ +65.0 (*c* 0.4, $CHCl_3$); ν_{max} ($CDCl_3$)/cm^{-1} 3322, 2953, 1729; δ_H (400 MHz, $CDCl_3$): 5.52 (1H, br t, *J* 8.5, C10H), 5.36 (1H, d, *J* 8.3, NH), 5.14 (1H, d, *J* 6.7, OCH_AH$_B$O), 4.85 (1H, d, *J* 7.0, OCH$_A$$H_B$O), 4.24–4.17 (2H, m, C12H and OCH_AH$_B$-CH$_2$TMS), 4.17–4.05 (1H, m, OCH$_A$$H_BCH_2$TMS), 3.80 (1H, br t, *J* 8.5, C11H), 3.61–3.53 (2H, m, C18H_2), 3.56 (3H, s, OMe), 3.51–3.40 (2H, m, C13H and C15H), 3.49 (3H, s, OMe), 3.31–3.25 (1H, m, C17H), 1.48–1.35 (2H, m, C16H_2), 0.98 (3H, s, C14Me), 0.98–0.93 (2H, m, CH_2TMS), 0.89 (9H, s, ^{t}BuSi), 0.84 (3H, s, C14Me), 0.045 and 0.032 (15H, 2 × s, Me_2Si and Me_3Si); δ_C (100 MHz, $CDCl_3$): 155.9 (0, N–C=O), 86.1 (2, OCH_2O), 79.6 (1, C13 or C15), 78.3 (1, C17), 76.3 (1, C10), 74.9 (1, C13 or C15), 74.4 (1, C12), 70.2 (1, C11), 65.2 (2, OCH_2–CH$_2$TMS), 63.8 (2, C18), 61.8 (3, OMe), 58.1 (3, OMe), 41.3 (0, C14), 31.9 (2, C16), 25.9 (3, 3C, ^{t}BuSi), 23.1 (3, C14-Me), 18.3 (0, CSi), 17.7 (2, CH_2TMS), 13.4 (3, C14Me), −1.6 (3, 3C, $SiMe_3$), −5.4 (3, 2C, $SiMe_2$); *m*/*z* (FAB mode, PEG) 564 [(M + H)$^+$]. Found: (M + H)$^+$, 564.3384. $C_{26}H_{54}NO_8Si_2$ requires *M*, 564.3388.

(1*R*,5*S*,6*S*,8*R*,10*S*)-5-Aminocarbonyl-8-{(2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methoxypropyl}-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane (52)

Sodium periodate (50 mg, 0.24 mmol) was added to a stirred mixture of alcohol **50** (21 mg, 0.048 mmol), carbon tetrachloride (0.3 ml), acetonitrile (0.3 ml) and a solution of ruthenium chloride trihydrate in water (6.7 mM, 0.45 ml, 0.003 mmol). The reaction mixture was stirred at rt for 5 h and extracted with CH_2Cl_2 (3 × 3 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude black-green residue (24 mg) was immediately used in the next step.

To crude acid **51** in CH_2Cl_2 (0.5 ml) was added 1-hydroxybenzotriazole monohydrate (6.5 mg, 0.048 mmol) followed by a solution of 1,3-dicyclohexylcarbodiimide in CH_2Cl_2 (96 mM, 0.5 ml, 0.048 mmol) at rt. The reaction mixture was stirred for 1 h and ammonia (gas) was bubbled into the reaction mixture for 15 min to yield a white precipitate. The solution was filtered and the solid was washed with CH_2Cl_2 (4 ml). The combined filtrate was washed with saturated aqueous $NaHCO_3$ (3 ml), ice cooled HCl (0.1 M, 3 ml), aqueous $NaHCO_3$ (3 ml), brine (3 ml), and then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 5g, 70–100% Et_2O in hexanes and then 0–50% EtOAc in Et_2O) to give the desired amide **52** (19.3 mg, 0.043 mmol, 90%) as an oil: $[\alpha]_D^{24}$ +35.9 (*c* 0.85, $CHCl_3$); ν_{max} ($CDCl_3$)/cm^{-1} 3332, 2929, 1697; δ_H (400 MHz, $CDCl_3$): 6.65 (1H, s, NH_AH$_B$), 5.45 (1H, s, NH$_A$$H_B$), 5.06 (1H, d, *J* 6.5, OCH_AH$_B$O), 4.91 (1H, d, *J* 6.5, OCH$_A$$H_B$O), 4.39 (1H, d, *J* 8.0, C10H), 4.24 (1H, dd, *J* 7.8, 5.4, C11H), 4.05 (1H, dd, *J* 7.7, 5.2, C12H), 3.78 (1H, dd, *J* 11.1, 4.2, C18H_AH$_B$), 3.69 (1H, dd, *J* 11.1, 4.1, C18H$_A$$H_B$), 3.51 (3H, s, OMe), 3.51–3.46 (1H, m, C15H), 3.41–3.36 (1H, m, C17H), 3.37 (3H, s, OMe), 3.26 (1H, d, *J* 7.9, C13H), 1.85 (1H, ddd, *J* 14.5, 7.7, 2.4, C16H_AH$_B$), 1.79–1.64 (1H, m, C16H$_A$$H_B$), 1.08 (3H, s, C14Me), 0.91 (3H, s, C14Me), 0.90 (9H, s, ^{t}BuSi), 0.07 (6H, s, Me_2Si); δ_C (100 MHz, $CDCl_3$): 170.7 (0, H_2N–C=O), 87.4 (2, OCH_2O), 80.5 (1, C13), 79.7 (1, C17), 77.2 (1, C15), 73.4 (1, C10), 72.7 (1, C12), 67.0 (1, br, C11), 63.1 (2, C18), 61.6 (3, OMe), 57.1 (3, OMe), 49.1 (0, C14), 29.9 (2, C16), 24.9 (3, 3C, ^{t}BuSi), 24.5 (3, C14Me), 18.3 (0, CSi), 16.5 (3, br, C14Me), −5.317 (3, MeSi), −5.373 (3, MeSi); *m*/*z* (CI, isobutane) 448 [(M + H)$^+$, 30%], 279 (20), 225 (100). Found: (M + H)$^+$, 448.2729. $C_{21}H_{42}NO_7Si$ requires *M*, 448.2731. Found: C, 56.40; H, 9.16; N, 3.12%. $C_{21}H_{41}O_7Si$ requires C, 56.35; H, 9.23; N, 3.13.

(1*R*,5*S*,6*S*,8*R*,10*S*)-8-{(2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxypropyl}-10-methoxy-9,9-dimethyl-5-{*N*-[(2-trimethylsilyl)ethoxycarbonyl]amino}-2,4,7-trioxabicyclo[4.4.0]decane (53) *via* Hofmann rearrangement

Procedure A. Trimethylsilylethanol (0.05 ml, 0.35 mmol), silver acetate (4.1 mg, 0.025 mmol) followed by *N*-bromosuccinimide (4.5 mg, 0.025 mmol) were added to a solution of amide **52** (8.1 mg, 18.1 µmol) in *N*,*N*-dimethylformamide (1 ml) at rt. The reaction mixture was stirred at rt for 24 h, treated with saturated aqueous $NaHCO_3$ (1 ml) and extracted with hexanes–Et_2O (1 : 1) (3 × 3 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, 0–30% Et_2O in hexanes) to give carbamate **53** (8.9 mg, 15.9 µmol, 88%) as a pale yellow oil.

Procedure B. Trimethylsilylethanol (0.05 ml, 0.35 mmol), pyridine (2 µl, 24.5 µmol) followed by *I*,*I*-bis(trifluoroacetoxy)iodobenzene (Aldrich, 10.5 mg, 24.5 µmol) were added to a solution of amide **52** (8.5 mg, 19.0 µmol) in acetonitrile (0.1 ml) at rt. The reaction mixture was stirred at rt for 24 h, treated with saturated aqueous $NaHCO_3$ (2 ml) and extracted with CH_2Cl_2 (3 × 3 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, 0–30% Et_2O in hexanes) to give carbamate **53** (8.6 mg, 15.3 µmol, 81%) as a pale yellow oil.

(1*R*,5*S*,6*S*,8*R*,10*S*)-8-{(2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxypropyl}-10-methoxy-9,9-dimethyl-5-[*N*-(methoxalyl)-amino]-2,4,7-trioxabicyclo[4.4.0]decane (9)

To a solution of DMAP (233 mg, 1.68 mmol) and methyl oxalyl chloride (140 µl, 1.53 mmol) in CH_2Cl_2 (2 ml) was added carbamate **53** (178 mg, 0.316 mmol) and the reaction mixture was stirred at rt for 6 d. The solution was then diluted with Et_2O (5 ml) and quickly washed with ice-cooled ammonia solution (0.1 M, 10 ml) and then washed quickly with ice-cooled aqueous HCl solution (0.1 M, 10 ml) and finally washed with saturated aqueous $NaHCO_3$ (10 ml). The organic phase was then dried (Na_2SO_4) and concentrated *in vacuo* to give the fairly pure *N*-Teoc amide **54** as a pale yellow oil (201 mg, 0.309 mmol, 98%) which was used crude in the next reaction. *N*-Teoc amide **54** was unstable towards column chromatography but a sample isolated in low yield (34%) gave the following spectroscopic data: $[\alpha]_D^{20}$ +30.9 (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2955, 2919, 2856, 1748, 1715, 1253; δ_H (400 MHz, $CDCl_3$): 6.12 (1H, d, *J* 10.4, C10H), 5.13 (1H, d, *J* 6.7, OCH_AH$_B$O), 4.97 (1H, d, *J* 6.7, OCH$_A$$H_B$O), 4.88 (1H, dd, *J* 10.4, 7.2, C11H), 4.39–4.36 (2H, m, OCH_2CH$_2$TMS), 4.32 (1H, dd, *J* 10.6, 7.2, C12H), 3.90 (3H, s, OMe), 3.66 (1H, dd, *J* 11.3, 3.3, C18H_AH$_B$), 3.59 (3H, s, OMe), 3.49 (1H, dd, *J* 11.3, 3.3, C18H$_A$$H_B$), 3.47 (1H, d, *J* 10.3, C13H), 3.31 (3H, s, OMe), 3.23 (1H, d, *J* 9.9, C15H), 3.14 (1H, dq, *J* 9.0, 3.0, C17H), 1.90 (1H, dd, *J* 14.0, 10.0, C16H_AH$_B$), 1.41 (1H, ddd, *J* 14.0, 10.2, 3.1, C16H$_A$$H_B$), 1.16–1.10 (2H, m, C$H_2$TMS), 0.97 (3H, s, C14Me), 0.90 (9H, s, ^{t}BuSi), 0.89 (3H, s, C14Me), 0.074 (6H, s, Me_2Si), 0.070 (9H, s, Me_3Si); δ_C (90 MHz, $CDCl_3$): 163.0 (0), 161.1 (0), 152.3 (0), 87.5 (2, OCH_2O), 79.2 (1, C13), 78.7 (1, C17), 76.9 (1, C10), 76.3 (1, C15), 74.8 (1, C12), 67.3 (2, CH_2CH$_2$TMS), 66.7 (1, C11), 61.4 (2, C18), 61.2 (3, OMe), 56.5 (3, OMe), 52.9 (3, OMe), 41.7 (0, C14), 30.0 (2, C16), 25.9 (3, 3C, ^{t}BuSi), 23.1 (3, C14Me), 18.3 (0, CSi), 17.3 (2, CH_2TMS), 13.1 (3, C14Me), −1.7 (3, 3C, Me_3Si), −5.40 (3, MeSi), −5.46 (3, MeSi); *m*/*z* (CI, isobutane) 650 [(M + H)$^+$, 100%], 578 (70), 506 (50), 490 (50), 403 (70). Found: (M + H)$^+$, 650.3393. $C_{29}H_{56}NO_{11}Si_2$ requires *M*, 650.3392. Found: C, 55.38; H, 9.52; N, 2.24%. $C_{29}H_{55}O_{11}Si_2$ requires C, 55.38; H, 9.47; N, 2.48.

A solution of TBAF (0.76 g, 2.4 mmol) and acetic acid (0.5 ml, 8.8 mmol) in CH_2Cl_2 (9.5 ml) was added to the *N*-Teoc amide **54** and immediate gas evolution was observed. The reaction mixture was stirred for 4 min and then immediately diluted with CH_2Cl_2 (10 ml), and washed with water (3 × 10 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, 50–70% Et_2O in hexanes) to give **9** (116 mg, 0.230 mmol, 73%) as a white solid: mp 136–138 °C (hexanes–ether); $[\alpha]_D^{20}$ +56.2 (*c* 0.8, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3401, 3019, 2956, 2884, 1720; δ_H (360 MHz, $CDCl_3$): 7.53 (1H, d, *J* 9.2, NH), 5.71 (1H, t, *J* 9.5, C10H), 5.16 (1H, d, *J* 7.0, OCH_AH$_B$O), 4.88 (1H, d, *J* 7.0, OCH$_A$$H_B$O), 4.23 (1H, dd, *J* 10.1, 6.6, C12H), 3.93 (1H, dd, *J* 9.5, 6.7, C11H), 3.93 (3H, s, OMe), 3.57 (1H, dd, *J* 10.8, 4.4, C18H_AH$_B$), 3.57 (3H, s, OMe), 3.52 (1H, dd, *J* 11.0, 4.1, C18H$_A$$H_B$), 3.43 (1H, d, *J* 10.2, C13H), 3.30 (1H, dd, *J* 9.6, 0.9, C15H), 3.27 (3H, s, OMe), 3.12 (1H, dq, *J* 8.2, 4.1, C17H), 1.82 (1H, ddd, *J* 14.3, 7.5, 1.4, C16H_AH$_B$), 1.47 (1H, ddd, *J* 14.5, 9.9, 4.2, C16H$_A$$H_B$), 1.00 (3H, s, C14Me), 0.88 (12H, s, ^{t}BuSi and C14Me), 0.05 (6H, s, Me_2Si); δ_C (90 MHz, $CDCl_3$): 160.2 (0, C(O)), 156.4 (0, C(O)), 86.4 (2, OCH_2O), 79.7 (1, C17), 79.4 (1, C13), 76.7 (1, C15), 74.2 (1, C12), 74.0 (1, C10), 69.9 (1, C11), 62.7 (2, C18), 61.7 (3, OMe), 56.8 (3, OMe), 53.9 (3, OMe), 41.6 (0, C14), 29.7 (2, C16), 25.8 (3, 3C, ^{t}BuSi), 23.3 (3, C14Me), 18.2 (0, CSi), 13.5 (3, C14Me), −5.5 (3, 2C, Me_2Si); *m*/*z* (CI, isobutane) 506 [(M + H)$^+$, 100%], 474 (25), 448 (20), 444 (10), 374 (15). Found: (M + H)$^+$, 506.2782. $C_{23}H_{44}NO_9Si$ requires *M*, 506.2785. Found: C, 54.09; H, 8.29; N, 2.69%. $C_{23}H_{43}NO_9Si$ requires C, 54.63; H, 8.57; N, 2.77.

The structure and relative stereochemistry of **9** were confirmed by X-ray crystallography with Mo X-rays on a CAD4 diffractometer.[90,91] Crystal data (**9**): $C_{23}H_{43}NO_9Si$, $M = 505.67$, orthorhombic, $a = 9.824(2)$, $b = 12.368(2)$, $c = 22.340(6)$ Å, $U = 2934(1)$ Å^3, $T = 293$ K, space group $P2_12_12_1$, $Z = 4$, μ(Mo-Kα) 0.13 mm^{-1}, 10536 reflections measured, 3588 unique ($R_{int} = 0.052$) used in refinement. R_1[2369 with $I > 2\sigma(I)$] = 0.083, wR_2(all data) = 0.27. The absolute structure could not be determined from the X-ray data. The results for **9** reflect the poor quality of the crystals. The atoms of the C15 side-chain show large U_{eq} values and some atypical bond lengths which suggest positional disorder.†

17-*epi*-9

Acylation of carbamate **17-*epi*-53** (190 mg, 0.337 mmol) by the same procedure described above gave the *N*-Teoc amide **17-*epi*-54** in 50% yield: $[\alpha]_D^{24}$ +74.2 (*c* 1.1, $CHCl_3$); ν_{max} ($CDCl_3$)/cm^{-1} 2954, 2922, 2857, 1749, 1715, 1252, 1109, 1026, 837, 775; δ_H (400 MHz, $CDCl_3$): 6.13 (1H, d, *J* 10.4, C10H), 5.13 (1H, d, *J* 6.7, OCH_AH$_B$O), 4.96 (1H, d, *J* 6.7, OCH$_A$$H_B$O), 4.89 (1H, dd, *J* 10.4, 7.3, C11H), 4.40–4.35 (2H, m, OCH_2CH$_2$TMS), 4.32 (1H, dd, *J* 10.6, 7.3, C12H), 3.89 (3H, s, OMe), 3.62 (1H, dd, *J* 10.8, 4.5, C18H_AH$_B$), 3.59 (3H, s, OMe), 3.55 (1H, dd, *J* 10.8, 4.4, C18H$_A$$H_B$), 3.53–3.50 (2H, m, *J* 10.3, C13H and C15H), 3.34 (3H, s, OMe), 3.23–3.18 (1H, m, C17H), 1.52 (1H, dd, *J* 14.5, 9.4, C16H_AH$_B$), 1.41 (1H, ddd, *J* 14.6, 9.4, 2.3, C16H$_A$-H_B), 1.15–1.10 (2H, m, CH_2TMS), 1.00 (3H, s, C14Me), 0.89 (9H, s, ^{t}BuSi), 0.85 (3H, s, C14Me), 0.073 (9H, s, Me_3Si), 0.044 (6H, s, Me_2Si); δ_C (90 MHz, $CDCl_3$): 162.9 (0), 161.1 (0), 152.6 (0), 87.5 (2, OCH_2O), 79.1 (1, C13 or C15), 77.8 (1, C17), 77.2 (1, C10), 75.6 (1, C15 or C13), 74.8 (1, C12), 67.6 (2, CH_2CH_2-TMS), 66.3 (1, C11), 64.5 (2, C18), 61.8 (3, OMe), 57.2 (3, OMe), 52.9 (3, OMe), 41.5 (0, C14), 32.3 (2, C16), 25.9 (3, 3C, ^{t}BuSi), 23.1 (3, C14Me), 18.3 (0, CSi), 17.3 (2, CH_2TMS), 13.2 (3, C14Me), −1.6 (3, 3C, Me_3Si), −5.38 (3, MeSi), −5.40 (3, MeSi); *m*/*z* (CI, isobutane) 650 [(M + H)$^+$, 55%], 622 (70), 578 (60), 506 (35), 474 (45), 458 (25), 403 (70), 371 (45). Found: (M + H)$^+$, 650.3387. $C_{29}H_{56}NO_{11}Si_2$ requires *M*, 650.3392.

Cleavage of *N*-Teoc amide **17-*epi*-54** by the same procedure described above gave recovered carbamate **17-*epi*-53** (29 mg, 0.052 mmol, 15%) and **17-*epi*-9** (106 mg, 0.230 mmol, 63%) as an oil: $[\alpha]_D^{23}$ +70.6 (*c* 1.5, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3330, 2954, 2930, 2857, 1717, 1529, 1111, 1026, 836, 777; δ_H (360 MHz, $CDCl_3$): 7.56 (1H, d, *J* 9.1, NH), 5.73 (1H, t, *J* 9.4, C10H), 5.18 (1H, d, *J* 7.0, OCH_AH$_B$O), 4.87 (1H, d, *J* 7.0, OCH$_A$$H_B$O), 4.25 (1H, dd, *J* 10.3, 6.8, C12H), 3.96–3.90 (1H, m, C11H), 3.92 (3H, s, OMe), 3.60–3.52 (2H, m, C18H_2), 3.58 (3H, s, OMe), 3.52–3.46 (2H, m, C13H and C15H), 3.27 (3H, s, OMe), 3.22–3.17 (1H, m, C17H), 1.51–1.38 (2H, m, C16H_2), 1.00 (3H, s, C14Me), 0.88 (9H, s, ^{t}BuSi), 0.87 (3H, s, C14Me), 0.04 (6H, s, Me_2Si); δ_C (90 MHz, $CDCl_3$): 160.3 (0, C(O)), 156.4 (0, C(O)), 86.3 (2, OCH_2O), 79.5 (1, C13 or C15), 78.0 (1, C17), 75.2 (1, C13 or C15), 74.4 (1, C12), 74.1 (1, C10), 70.0 (1, C11), 64.8 (2, C18), 61.8 (3, OMe), 57.7 (3, OMe), 53.9 (3, OMe), 41.3 (0, C14), 31.7 (2, C16), 25.9 (3, 3C, ^{t}BuSi), 23.2 (3, C14Me), 18.2 (0, C-Si), 13.5 (3, C14Me), −5.5 (3, 2C, Me_2-Si); *m*/*z* (CI, isobutane) 506 [(M + H)$^+$, 100%], 476 (15), 474 (10), 448 (10), 391 (7). Found: (M + H)$^+$, 506.2785. $C_{23}H_{44}NO_9Si$ requires *M*, 506.2785.

Formation of adduct 55

To a solution of stannane **27** (170 mg, 0.383 mmol) and 4 Å MS in THF (2.5 ml) at −80 °C was added *n*-BuLi (265 µl, 1.43 M solution in hexane, 0.370 mmol) and the bright yellow solution stirred at −80 °C for 15 min. TMEDA (57 µl, 0.378 mmol) was added and after 10 min at −80 °C, a solution of ester **9** (73 mg, 0.144 mmol) and 4 Å MS in THF (2.25 ml) was quickly added. After stirring for 1 h maintaining the temperature below −60 °C, the mixture was poured into brine (3 ml), and extracted with CH_2Cl_2 (2 × 5 ml). The combined extracts were dried (Na_2SO_4) and concentrated to give a yellow oil which was purified by column chromatography (SiO_2, PhMe–hexanes–EtOAc, 100:0:0, 0:95:5, 0:75:25, 0:50:50) to give (2*R*,3*R*,64*R*)-2,3-dimethyl-4-phenylselanylmethyl-3,4-dihydro-2*H*-pyran (77 mg, 0.274 mmol, 74%) and the coupling product **55** (44 mg, 0.058 mmol, 41% based on the fragment **9**) as a colourless oil: $[\alpha]_D^{24}$ +29.0 (*c* 0.9, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3054, 2974, 2933, 2878, 1640, 1578, 1477, 1454, 1437, 1382, 1237, 1091, 736, 690; δ_H (400 MHz, $CDCl_3$): 7.43–7.40 (2H, m), 7.20–7.10 (3H, m), 6.21 (1H, dd, *J* 2.4, 6.2, C6H), 4.40 (1H, dt, *J* 1.7, 6.2, C5H), 3.92 (1H, dq, *J* 1.7, 6.6, C2H), 2.78 (1H, dd, *J* 9.1, 11.8, CH_AH$_B$), 2.73 (1H, dd, *J* 7.2, 11.8, CH$_A$$H_B$), 2.65–2.57 (1H, m, C4H), 1.83–1.75 (1H, m, C3H), 1.14 (3H, d, *J* 6.6, C2 Me), 0.72 (3H, d, 7.0, C3Me); δ_C (100 MHz, $CDCl_3$): 143.8 (1, C6), 132.6 (1, 2C), 130.0 (0), 129.0 (1, 2C), 126.8 (1), 101.9 (1, C5), 75.3 (1, C2), 37.0 (1, C4), 34.0 (1, C3), 31.0 (2, CH_2Se), 18.2 (3, C2Me), 5.1 (3, C3Me). Found: (M + H)$^+$, 282.0522. $C_{14}H_{18}OSe$ requires *M*, 282.0523.

Acyl dihydropyran **55**: $[\alpha]_D^{20}$ −21.2 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3319, 2928, 1671, 1106, 1023, 826; δ_H (400 MHz, $CDCl_3$): 7.56 (1H, d, *J* 9.5, NH), 7.55–7.51 (2H, m), 7.31–7.28 (3H, m), 7.14 (1H, t, *J* 1.8, C5H), 5.68 (1H, t, *J* 9.3, C10H), 5.16 (1H, d, *J* 6.9, OCH_AH$_B$O), 4.88 (1H, d, *J* 6.9, OCH$_A$$H_B$O), 4.23 (1H, dd, *J* 6.4, 9.9, C12H), 4.09 (1H, dq, *J* 1.2, 6.5, C2H), 3.95 (1H, dd, *J* 6.5, 9.3, C11H), 3.57 (3H, s, OMe), 3.57 (1H, dd, *J* 4.1, 10.9, C18H_AH$_B$), 3.50 (1H, dd, *J* 3.8, 11.0, C18H$_A$$H_B$), 3.42 (1H, d, *J* 10.0, C13H), 3.31 (1H, br d, *J* 9.3, C15H), 3.26 (3H, s, OMe), 3.10–3.16 (1H, m, C17H), 2.98–2.94 (2H, m, CH_2Se),

† CCDC reference number 207/406. See http://www.rsc.org/suppdata/p1/a9/a909898d/ for crystallographic files in .cif format.

2.85 (1H, dddd, *J* 2.5, 5.7, 8.1, 10.6, C4H), 2.07–1.99 (1H, m, C3H), 1.83 (1H, ddd, *J* 1.4, 8.0, 14.1, C16H_AH_B), 1.57–1.47 (1H, m, C16H_AH_B), 1.39 (3H, d, *J* 6.5, C2Me), 1.01 (3H, s, C14Me), 0.90 (3H, s, C14Me), 0.88 (9H, s, ${}^tBuSi$), 0.82 (3H, d, *J* 7.0, C3Me), 0.04 (6H, s, Me_2Si); δ_C (100 MHz, $CDCl_3$): 179.6 (0), 160.7 (0), 148.0 (0), 133.2 (1, 2C), 129.3 (1, 2C), 129.1 (0), 127.4 (1), 125.0 (1, C5), 86.4 (2, OCH_2O), 79.7 (1, C13 or C17), 79.4 (1, C17 or C13), 77.2 (1, C2 or C15), 76.8 (1, C15 or C2), 74.1 (1, C12), 73.8 (1, C10), 69.6 (1, C11), 62.3 (2, C18), 61.7 (3, OMe), 56.9 (3, OMe), 41.4 (0, C14), 39.0 (1, C4), 33.1 (1, C3), 29.5 (2, C16 or CH_2Se), 29.4 (2, CH_2Se or C16), 25.9 (3, 3C, ${}^tBuSi$), 23.5 (3, C14Me), 18.3 (0, CSi), 18.2 (3, C2 Me), 13.9 (3, C14Me), 5.9 (3, C3Me), −5.30 (3, MeSi), −5.33 (3, MeSi); *m*/*z* (CI, isobutane) 756 [(M + H)$^+$, 30%], 698 (20), 598 (100), 540 (60). Found: (M + H)$^+$, 756.3047. $C_{36}H_{58}NO_9SeSi$ requires *M*, 756.3045.

Formation of adduct 17-*epi*-55

Acylation of dihydropyran **6** (135 mg, 0.304 mmol) by the procedure described above gave (2*R*,3*R*,4*R*)-3,4-dihydro-2,3-dimethyl-4-phenylselanylmethyl-2*H*-pyran (66 mg, 0.235 mmol, 77%) and the coupling product **17-*epi*-55** (36 mg, 0.048 mmol, 39% based on the right half fragment **17-*epi*-9**) as a colourless oil: $[\alpha]_D^{23}$ +16.0 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3366, 2928, 2855, 1727, 1670, 1104, 1024, 836; δ_H (400 MHz, $CDCl_3$): 7.63 (1H, d, *J* 8.7, NH), 7.52–7.45 (2H, m), 7.30–7.20 (3H, m), 7.15 (1H, t, *J* 1.8, C5H), 5.67 (1H, t, *J* 9.2, C10H), 5.14 (1H, d, *J* 7.0, OCH_AH_BO), 4.85 (1H, d, *J* 6.9, OCH_AH_BO), 4.21 (1H, dd, *J* 6.5, 10.2, C12H), 4.06 (1H, dq, *J* 1.3, 6.5, C2H), 3.93 (1H, dd, *J* 6.6, 9.5, C11H), 3.54 (3H, s, OMe), 3.52–3.43 (4H, m, C18H_2, C15H, C13H), 3.23–3.14 (1H, m, C17H), 3.19 (3H, s, OMe), 2.90–2.84 (2H, m, CH_2Se), 2.84–2.77 (1H, m, C4H), 2.10–1.92 (1H, m, C3H), 1.50–1.40 (1H, m, C16H_AH_B), 1.30–1.18 (1H, m, C16H_AH_B), 1.34 (3H, d, *J* 6.5, C2Me), 0.97 (3H, s, C14Me), 0.84 (9H, s, ${}^tBuSi$), 0.83 (3H, s, C14Me), 0.73 (3H, d, *J* 7.0, C3Me), 0.00 (6H, s, Me_2Si); δ_H (400 MHz, C_6D_6): 7.49 (1H, d, *J* 9.0, NH), 7.35–7.32 (2H, m), 7.16 (1H, t, *J* 1.9, C5H), 6.97–6.91 (3H, m), 5.81 (1H, t, *J* 9.5, C10H), 4.68 (1H, d, *J* 6.9, OCH_AH_BO), 4.57 (1H, d, *J* 6.9, OCH_AH_BO), 4.19 (1H, dd, *J* 6.9, 10.4, C12H), 3.53–3.40 (5H, m), 3.38 (3H, s, OMe), 3.38–3.36 (1H, m), 3.19 (3H, s, OMe), 2.98 (1H, *J* 10.4, C13H), 2.59–2.51 (2H, m), 2.50–2.44 (1H, m), 1.61–1.53 (1H, m, C16H_AH_B), 1.48–1.40 (2H, m, C3H and C16H_AH_B), 0.95 (3H, d, *J* 6.7, C2Me), 0.91 (9H, s, ${}^tBuSi$), 0.85 (3H, s, C14Me), 0.82 (3H, s, C14Me), 0.55 (3H, d, *J* 7.0, C3Me), 0.004 (3H, s, MeSi), −0.003 (3H, s, MeSi); δ_C (100 MHz, C_6D_6): 179.4 (0), 160.5 (0), 147.2 (0), 131.9 (1, 2C), 128.1 (1, 2C), 126.6 (0), 126.0 (1), 122.4 (1, C5), 84.9 (2, OCH_2O), 77.9 (1, C13), 77.0 (1), 75.0 (1), 73.8 (1), 73.7 (1, C12), 72.7 (1, C10), 68.9 (1), 63.5 (2, C18), 60.0 (3, OMe), 56.6 (3, OMe), 40.1 (0, C14), 37.7 (1), 32.0 (1), 31.0 (2, C16), 28.2 (2, CH_2Se), 24.8 (3, 3C, ${}^tBuSi$), 21.6 (3, C14Me), 17.2 (0, CSi), 16.7 (3, C2Me), 12.2 (3, C14Me), 4.5 (3, C3Me), −6.47 (3, MeSi), −6.52 (3, MeSi); *m*/*z* (CI, isobutane) 756 [(M + H)$^+$, 20%], 598 (100), 540 (20). Found: (M + H)$^+$, 756.3049. $C_{36}H_{58}NO_9SeSi$ requires *M*, 756.3045.

Synthesis of benzoate 56

To a solution of acyldihydropyran **55** (30.0 mg, 39.7 μmol) in THF (2.5 ml) at −95 °C was added dropwise LiBH(*s*-Bu)$_3$ (0.1 ml, 1.0 M solution in THF, 0.1 mmol). After 10 min at −95 °C the mixture was treated with brine (1 ml) and extracted with CH_2Cl_2 (2 × 4 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was immediately dissolved in CH_2Cl_2 (2 ml) and MeOH (0.2 ml). Camphorsulfonic acid (3.0 mg, 0.012 mmol) was added and the solution stirred at rt for 1.5 h. Solid K_2CO_3 (25 mg, 0.18 mmol) was added slowly during 10 min after which the mixture was poured into saturated aqueous $NaHCO_3$ (2 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*, to give the crude diastereoisomeric acetals as a colourless oil which were used immediately in the next step.

A yellow solution of benzoyl chloride (15 μl, 0.129 mmol), DMAP (10 mg, 0.082 mmol) and *N*,*N*-diisopropylethylamine (80 μl, 0.459 mmol) in CH_2Cl_2 (0.5 ml) and 4 Å MS was added to a stirred solution of the crude acetals in CH_2Cl_2 (1.5 ml). The reaction mixture was stirred for 1 h at rt before MeOH (0.5 ml) was added. After 10 min the mixture was poured into brine (3 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (5 g) eluting with 50% hexanes–Et_2O in hexanes to give 26 mg (29.1 μmol, 73% over 3 steps) of a mixture of the two diastereoisomers at C7 in the ratio 6 : 1 (determined by integration of signals derived from C12H [^1H NMR (400 MHz, C_6D_6): δ 4.24 (dd, major) and 4.17 (dd, minor)]. The mixture was purified by column chromatography on silica gel (5 g) eluting with 10–20% Et_2O in CH_2Cl_2 to give diastereoisomer **56** (16 mg, 17.9 μmol, 45%) along with an impure mixture of **56** and its C7-epimer (8 mg, 8.95 μmol, 23%). Data for benzoate **56**: $[\alpha]_D^{20}$ +50.0 (*c* 0.55, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3358, 2929, 2856, 1732, 1706, 1524, 1471, 1263, 1123, 1032, 836; δ_H (400 MHz, C_6D_6): 8.23 (2H, ddm, *J* 1.6, 8.3), 7.41 (2H, ddm, *J* 1.6, 8.1), 7.31 (1H, d, *J* 9.6, NH), 7.10–6.97 and 6.95–6.85 (6H, 2 m), 5.87 (1H, s, C7H), 5.86 (1H, t, *J* 9.7, C10H), 4.50 (1H, d, *J* 7.0, OCH_AH_BO), 4.44 (1H, d, *J* 7.0, OCH_AH_BO), 4.24 (1H, dd, *J* 6.6, 10.2, C12H), 3.95 (1H, dd, *J* 2.6, 11.7, C18H_AH_B), 3.86 (1H, dd, *J* 2.4, 11.7, C18H_AH_B), 3.71 (1H, dd, *J* 6.7, 9.5, C11H), 3.49 (1H, dq, *J* 2.3, 6.7, C2H), 3.46 (1H, br d, *J* 8.8, C15H), 3.42–3.38 (1H, m, C17H), 3.32 (3H, s, OMe), 3.21 (3H, s, OMe), 3.05 (1H, d, *J* 10.1, C13H), 2.85 (3H, s, OMe), 2.78 (2H, dd, *J* 7.9, $SeCH_2$), 2.41–2.31 (1H, m, C4H), 2.20 (1H, dd, *J* 3.5, 8.1, C5H_AH_B), 2.09 (1H, ddd, *J* 0.8, 5.6, 10.6, C16H_AH_B), 1.69 (1H, t, *J* 13.0, C5H_AH_B), 1.66–1.57 (1H, m, C16H_AH_B), 1.52–1.48 (1H, m, C3H), 0.99 (3H, s, C14Me), 0.96 (9H, s, ${}^tBuSi$), 0.89 (3H, s, C14Me), 0.80 (3H, d, *J* 6.6, C2Me), 0.77 (3H, d, *J* 7.1, C3Me), 0.101 (3H, s, MeSi), 0.091 (3H, s, MeSi); δ_C (100 MHz, C_6D_6): 165.3 (0), 164.0 (0), 132.0 (1), 131.5 (1), 129.7 (0), 129.0 (0), 128.9 (1, 2C), 128.0 (1, 2C), 127.4 (1, 2C), 125.6 (1, 2C), 98.0 (0, C6), 85.2 (2, OCH_2O), 78.0 (1, C13 or C17), 77.9 (1, C17 or C13), 75.1 (1, C15), 73.7 (1, C12), 72.9 (1, C7 or C10), 71.4 (1, C10 or C7), 70.3 (1, C11), 69.4 (1, C2), 61.0 (2, C18), 59.9 (3, OMe), 55.1 (3, OMe), 46.7 (3, OMe), 40.4 (0, C14), 34.2 (1, C3), 33.8 (1, C4), 30.8 (2, CH_2Se), 30.0 (2, C5), 28.5 (2, C16), 24.9 (3, 3C, ${}^tBuSi$), 22.2 (3, C14Me), 17.3 (0, CSi), 16.8 (3, C2 Me), 12.5 (3, C14Me), 3.4 (3, C3Me), −6.39 (3, MeSi), −6.49 (3, MeSi); *m*/*z* (FAB mode) 916 [(M + Na)$^+$, 4%], 914 (2), 758 (1), 628 (1), 479 (4). Found: (M + Na)$^+$, 916.3547. $C_{44}H_{67}NO_{11}SeSiNa$ requires *M*, 916.3547.

17-*epi*-56

Acyldihydropyran **17-*epi*-55** (30.0 mg, 39.7 μmol) was converted to **17-*epi*-56** (14 mg, 15.7 μmol, 40%) by the procedure described above: $[\alpha]_D^{20}$ +61.4 (*c* 0.7, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3359, 2929, 2856, 1732, 1706, 1523, 1471, 1263, 1124, 1030, 836; δ_H (400 MHz, C_6D_6): 8.21 (2H, ddm, *J* 1.5, 8.0), 7.45 (2H, ddm, *J* 1.5, 8.0), 7.36 (1H, d, *J* 9.6, NH), 7.05–6.88 (6H, m), 5.96 (1H, t, *J* 9.7, C10H), 5.91 (1H, s, C7H), 4.54 (1H, d, *J* 7.3, OCH_AH_BO), 4.52 (1H, d, *J* 7.5, OCH_AH_BO), 4.27 (1H, dd, *J* 6.9, 10.2, C12H), 3.73 (1H, dd, *J* 7.0, 9.6, C11H), 3.70 (1H, dd, *J* 9.4, 10.0, C15H), 3.67 (1H, dd, *J* 4.6, 9.9, C18H_AH_B), 3.62–3.57 (1H, m, C18H_AH_B) 3.58 (3H, s, OMe), 3.51 (1H, dq, *J* 2.3, 6.6, C2H), 3.51–3.43 (1H, m, C17H), 3.20 (3H, s, OMe), 3.01 (1H, *J* 10.3, C13H), 2.86 (1H, dd, *J* 7.1, 12.0, $SeCH_AH_B$), 2.86 (3H, s, OMe), 2.79 (1H, dd, *J* 8.6, 12.1, $SeCH_AH_B$), 2.44–2.35 (1H, m, C4H), 2.26 (1H, dd, *J* 3.5, 13.1, C5H_AH_B), 1.77 (1H, t, *J* 13.0, C5H_AH_B), 1.65 (1H, dd, *J* 10.2, 14.2, C16H_AH_B), 1.67–1.50 (1H, m, C3H), 1.46 (1H, br dd, *J* 9.3, 13.8, C16H_AH_B), 0.95

(9H, s, ^{t}BuSi), 0.92 (3H, s, C14Me), 0.88 (3H, s, C14Me), 0.81 (3H, d, *J* 6.4, C2 Me), 0.80 (3H, d, *J* 7.1, C3Me), 0.063 (3H, s, MeSi), 0.061 (3H, s, MeSi); δ_C (100 MHz, C_6D_6): 165.4 (0), 146 (0), 132.0 (1), 131.7 (1, 2C), 129.4 (0), 128.9 (1, 2C), 128.1 (1, 2C), 127.3 (1, 2C), 125.8 (1), 124.5 (1), 98.0 (0, C6), 84.9 (2, OCH_2O), 77.8 (1, C13), 76.8 (1, C17), 74.6 (1, C15), 73.8 (1, C12), 72.9 (1, C10), 71.4 (1, C7), 70.4 (1, C11), 69.5 (1, C2), 63.9 (2, C18), 60.0 (3, OMe), 56.8 (3, OMe), 46.7 (3, OMe), 40.1 (0, C14), 34.1 (1, C4), 33.8 (1, C3), 32.2 (2, C16), 30.9 (2, CH_2Se), 30.3 (2, C5), 24.9 (3, 3C, ^{t}BuSi), 21.9 (3, C14Me), 17.3 (0, CSi), 16.8 (3, C2 Me), 12.4 (3, C14Me), 3.3 (3, C3Me), −6.3 (3, MeSi), −6.4 (3, MeSi); *m*/*z* (FAB mode) 916 [(M + Na)$^+$, 28%], 914 (16), 758 (6), 329 (24). Found: (M + Na)$^+$, 916.3548. $C_{44}H_{67}NO_{11}SeSiNa$ requires *M*, 916.3547.

Mycalamide B (3)

Sodium periodate (30 mg, 0.14 mmol) was added in one portion to a solution of the diastereoisomerically pure selenide **56** (10 mg, 11.2 µmol) in MeOH–H_2O–CH_2Cl_2 (3 : 1 : 1, 3.5 ml). After 30 min the mixture was diluted with Et_2O (10 ml) and Et_3N (0.5 ml) and washed with H_2O (2 × 5 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the selenoxide as a colourless oil which was dissolved in toluene (2 ml) whereupon Et_3N (2 ml, 14.3 µmol) was added. After refluxing for 5 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (5 ml) and extracted with Et_2O (2 × 10 ml). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil which was dissolved in MeOH (3 ml) to which was added aqueous LiOH (0.3 ml, 1.0 M, 0.3 mmol). After 30 min at rt the mixture was concentrated, the residue was dissolved in Et_2O (5 ml), washed with H_2O (2 × 2 ml) and brine (2 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 18-*O*-TBS mycalamide B as a yellow oil which was used immediately in the next step.

TBAF (22 mg, 70 µmol) was added to a solution of 18-*O*-TBS mycalamide B in THF (1 ml) and after 1 h at rt the reaction mixture was diluted with Et_2O (5 ml) and washed with saturated aqueous $NaHCO_3$ (2 ml). The aqueous phase was extracted with CH_2Cl_2 (2 × 5 ml) and the combined organic layers dried (Na_2SO_4) and concentrated *in vacuo* to give an oil which was purified by column chromatography on silica gel (1 g) eluting with hexanes–EtOAc–NEt_3 (100 : 0 : 1, 75 : 25 : 1, 50 : 50 : 1, 25 : 75 : 1, 0 : 100 : 1) to give mycalamide B (**3**) (4.5 mg, 8.69 µmol, 78% over 4 steps): ν_{max} ($CHCl_3$)/cm^{-1} 3359, 2971, 2933, 1686, 1522, 1468, 1382, 1193, 1109, 1075, 1032, 959, 879, 789; δ_H (400 MHz, $CDCl_3$): 7.54 (1H, d, *J* 9.6, NH), 5.83 (1H, t, *J* 9.6, C10H), 5.14 (1H, d, *J* 7.0, OCH_AH_BO), 4.88 (1H, d, *J* 6.7, OCH_AH_BO), 4.88 (1H, br s, $=CH_AH_B$), 4.75 (1H, br s, $=CH_AH_B$), 4.31 (1H, d, *J* 2.0, C7H), 4.24 (1H, dd, *J* 6.8, 10.2, C12H), 4.06 (1H, dq, *J* 2.8, 6.5, C2H), 3.90 (1H, d, *J* 2.1, C7OH), 3.81 (1H, dd, *J* 6.8, 9.6, C11H), 3.72–3.65 (1H, m, $C18H_AH_B$), 3.58 (3H, s, OMe), 3.54–3.48 (1H, m, $C18H_AH_B$), 3.46 (1H, d, *J* 10.4, C13H), 3.48–3.42 (1H, m hidden, C15H), 3.32 (3H, s, OMe), 3.27 (3H, s, OMe), 3.25–3.18 (1H, m, C17H), 2.39 (1H, d, *J* 14.0, $C5H_AH_B$), 2.30 (1H, dq, *J* 2.8, 7.1, C3H), 2.26 (1H, dm, *J* 13.9, $C5H_AH_B$), 1.60–1.54 (2H, m, $C16H_2$), 1.23 (3H, d, *J* 6.6, C2Me), 1.04 (3H, d, *J* 7.2, C3Me), 1.01 (3H, s, C14Me), 0.89 (3H, s, C14Me); δ_H (400 MHz, C_6D_6): 7.58 (1H, d, *J* 9.8, NH), 5.83 (1H, t, *J* 9.9, C10H), 4.71 (1H, t, *J* 1.8, $=CH_AH_B$), 4.66 (1H, t, *J* 1.9, $=CH_AH_B$), 4.56 (1H, d, *J* 7.0, OCH_AH_BO), 4.53 (1H, d, *J* 6.9, OCH_AH_BO), 4.24 (1H, dd, *J* 7.0, 10.6, C12H), 4.16 (1H, s, C7H), 4.07 (1H, br s, C7OH), 3.85–3.77 (1H, m, $C18H_AH_B$), 3.80 (1H, dq, *J* 1.8, 6.6, C2H), 3.74–3.68 (1H, m, $C18H_AH_B$), 3.69 (1H, dd, *J* 7.0, 10.0, C11H), 3.40 (1H, dd, *J* 5.6, 6.1, C15H), 3.33–3.28 (1H, m, C17H), 3.22 (3H, s, C13OMe), 3.15 (3H, s, C6OMe), 3.03 (3H, s, C17OMe), 2.94 (1H, d, *J* 10.5, C13-H), 2.60 (1H, d, *J* 14.0, C5-H_AH_B), 2.40 (1H, dt, *J* 1.8, 14.0, $C5H_AH_B$), 2.33 (1H, br s, C18OH), 1.86 (1H, dq, *J* 1.7, 7.0, C3H), 1.59–1.55 (2H, m, $C16H_2$), 0.92 (3H, d, *J* 7.0, C3Me), 0.81 (3H, d collapsed by C14Me, *J* 6.6, C2Me), 0.80 (3H, s, C14Me), 0.76 (3H, s, C14Me); δ_C (100 MHz, C_6D_6): 171.1 (0, C8), 144.6 (0, C4), 109.6 (2, $=CH_2$), 99.2 (0, C6), 85.1 (2, OCH_2O), 77.7 (1, C13 or C17), 77.5 (1, C17 or C13), 74.4 (1, C15), 73.9 (1, C12), 72.9 (1, C10), 70.9 (1, C7 or C11), 70.7 (1, C11 or C7), 68.1 (1, C2), 62.6 (2, C18), 60.0 (3, C13OMe), 55.2 (3, C17OMe), 47.0 (3, C6OMe), 40.4 (1, C3), 40.3 (0, C14), 32.9 (1, C5), 29.3 (2, C16), 21.5 (3, $C14Me_{eq}$), 16.5 (3, $C2Me_{ax}$), 11.9 (3, C14Me), 11.0 (3, C3Me); *m*/*z* (FAB mode) 540 [(M + Na)$^+$, 100%], 507 (20), 486 (25), 176 (32). Found: (M + Na)$^+$, 540.2790. $C_{25}H_{43}NO_{10}Na$ requires *M*, 540.2785.

17-*epi*-Mycalamide B

Selenide **17-*epi*-56** (14 mg, 15.7 µmol) gave 17-*epi*-mycalamide B (**17-*epi*-3**) (6.3 mg, 12.2 µmol, 78% over 4 steps) by the procedure described above: ν_{max} ($CHCl_3$)/cm^{-1} 3356, 2971, 2933, 1686, 1524, 1468, 1382, 1194, 1109, 1074, 1033, 959, 878, 790; δ_H (400 MHz, C_6D_6): 7.48 (1H, d, *J* 9.9, NH), 5.94 (1H, t, *J* 9.9, C10H), 4.75–4.70 (2H, m, $=CH_2$), 4.57 (1H, d, *J* 6.9, OCH_AH_BO), 4.54 (1H, d, *J* 6.9, OCH_AH_BO), 4.23 (1H, dd, *J* 6.9, 10.2, C12H), 4.17 (2H, s, C7H and C7OH), 3.82 (1H, dq, *J* 2.6, 6.6, C2H), 3.65 (1H, dd, *J* 7.1, 9.7, C11H), 3.61–3.55 (2H, m, $C18H_2$), 3.51 (1H, d, *J* 9.3, C15H), 3.32 (3H, s, C13OMe), 3.27–3.18 (1H, m, C17H), 3.21 (3H, s, C6OMe), 3.06 (3H, s, C17OMe), 2.96 (1H, d, *J* 10.4, C13H), 2.60 (1H, d, *J* 13.9, $C5H_AH_B$), 2.42 (1H, br d, *J* 13.9, $C5H_AH_B$), 1.88 (1H, dq, *J* 2.6, 7.1, C3H), 1.65 (1H, dd, *J* 8.2, 14.8, $C16H_AH_B$), 1.50 (1H, br s, C18OH), 1.27 (1H, ddd, *J* 2.8, 10.0, 14.3, $C16H_AH_B$), 0.90 (3H, d, *J* 7.1, C3Me), 0.83 (3H, s, C14Me), 0.81 (3H, d, *J* 6.6, C2Me), 0.77 (3H, s, C14Me); δ_C (100 MHz, C_6D_6): 171.1 (0, C8), 145.0 (0, C4), 109.4 (2, $=CH_2$), 99.1 (0, C6), 85.0 (2, OCH_2O), 78.3 (1, C17), 77.8 (1, C13), 75.9 (1, C15), 73.8 (1, C12), 72.8 (1, C10), 71.1 (1, C7), 70.1 (1, C11), 68.0 (1, C2), 62.6 (2, C18), 60.0 (3, C13OMe), 55.6 (3, C17OMe), 47.1 (3, C6OMe), 40.3 (1, C3), 40.1 (0, C14), 33.0 (1, C5), 31.5 (2, C16), 21.7 (3, C14Me), 16.5 (3, C2 Me), 12.1 (3, C14Me), 11.1 (3, C3Me); *m*/*z* (FAB mode) 540 [(M + Na)$^+$, 100%], 508 (20), 486 (25). Found: (M + Na)$^+$, 540.2789. $C_{25}H_{43}NO_{10}Na$ requires *M*, 540.2785.

2. Theopederin D

(1*S*,5*R*,6*R*,8*R*,10*S*)-5-Hydroxymethyl-10-methoxy-9,9-dimethyl-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4,4,0]decane (57)

To a solution of ester **8** (814 mg, 2.29 mmol) in THF (10 ml) at −70 °C was added Red-Al™ (Aldrich, 1.55 M in PhMe and THF, 3 ml) dropwise over 5 min. The cooling bath was removed and the clear colourless reaction mixture was allowed to warm up to 0 °C over 30 min. After such time acetone (0.4 ml) was added. The mixture was then poured onto ice cold NaOH (2 M, 10 ml). CH_2Cl_2 (20 ml) and H_2O (20 ml) were then added. The clear colourless phases were then separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 ml), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, 50–60% Et_2O in hexanes) gave the alcohol **57** (608 mg, 2.24 mmol, 98%) as a clear colourless oil: $[a]_D^{23}$ +102.3 (*c* 1.2, $CHCl_3$); ν_{max} film/cm^{-1} 3465, 1640, 1468, 1177, 1110; δ_H (400 MHz, $CDCl_3$): 5.77 (1H, ddt, *J* 17.0, 10.4, 6.8, C17H), 5.07 (1H, dm, *J* 5.2, $C18H_AH_B$), 5.03 (1H, m, $C18H_AH_B$), 5.01 (1H, d, *J* 6.4, OCH_AH_BO), 4.82 (1H, d, *J* 6.4, OCH_AH_BO), 4.15 (1H, dd, *J* 10.4, 6.4, C12H), 4.01 (2H, m, C11H, C10H), 3.83 (1H, ddd, *J* 12.0, 6.8, 2.8 collapses to dd, *J* 12.0, 2.8 after D_2O shake, CH_AH_BOH), 3.66 (1H, ddm, *J* 11.6, 5.6 collapses to dd, *J* 11.6, 5.2 after D_2O shake, CH_AH_BOH), 3.56 (3H, s, OMe), 3.43 (1H, d, *J* 10.4, C13H), 3.26 (1H, dd, *J* 10.4, 2.0, C15H), 2.27 (1H, t, *J* 6.4, OH), 2.16 (1H, dddt, *J* 11.3, 7.4, 2.0, 1.2, $C16H_AH_B$), 2.03 (1H, dddt, *J* 14.2, 10.3, 6.8, 0.8, $C16H_AH_B$), 1.00 (3H, s, C14Me), 0.87 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 135.9 (1), 117.0 (2), 87.0 (2), 79.3 (1), 78.5 (1), 73.5 (1), 73.2 (1), 68.0 (1), 63.0 (2), 61.9 (3), 41.7 (0), 33.5 (2), 23.2 (3), 13.2 (3); *m*/*z* (CI, isobutane) 373 [(M + H)$^+$, 50%], 231 (100). Found: (M + H)$^+$, 273.1704. $C_{14}H_{25}O_5$ requires *M*, 273.1702.

(1*S*,5*R*,6*R*,8*R*,10*S*)-10-Methoxy-9,9-dimethyl-8-(prop-2-enyl)-5-{*N*-[(2-trimethylsilyl)ethoxycarbonyl]amino}-2,4,7-trioxabicyclo[4,4,0]decane (58)

Pyridinium dichromate (3.0 g, 7.97 mmol) was added to a mixture of alcohol **57** (200 mg, 0.735 mmol) in anhydrous DMF (4 ml) and stirred at rt. After 8 h a further portion of pyridinium dichromate (1.0 g, 2.66 mmol) was added and the mixture stirred for a further 15 h. After such time H_2O (60 ml) was added and the mixture extracted with EtOAc (5 × 25 ml). The combined organic extracts were washed with brine (20 ml), dried (Na_2SO_4) and concentrated. The residue was taken up in toluene (2 × 5 ml) and concentrated twice to give crude acid (290 mg) as a brown oil which was dissolved in anhydrous toluene (2 ml) to which freshly activated 4 Å molecular sieves and anhydrous *N*-ethyldiisopropylamine (0.2 ml, 148 mg, 1.15 mmol) were added. 2-Trimethylsilylethanol (0.8 ml, 660 mg, 5.58 mmol), dried by the addition of freshly activated 4 Å molecular sieves, and diphenylphosphoryl azide (0.2 ml, 255 mg, 0.93 mmol) were then added at the same time. The mixture was plunged into an oil bath at 65 °C and the evolution of N_2 gas was observed over a period of 8 min. After heating at 65 °C for 1 h the green reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (18 ml) and extracted with CH_2Cl_2 (3 × 25 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, 10–25% Et_2O in hexanes) to give carbamate **58** (171 mg, 4.26 mmol, 58%) as a pale yellow oil: $[a]_D^{23}$ +46.7 (*c* 0.09, $CHCl_3$); ν_{max} film/cm^{-1} 1720, 1542, 1109, 1032; δ_H (400 MHz, $CDCl_3$): 5.72 (1H, ddt, *J* 16.8, 10.0, 6.8, C17H), 5.53 (1H, t, *J* 9.2, C10H), 5.30 (1H, d, *J* 9.2, NH), 5.14 (1H, d, *J* 7.2, OCH_AH_BO), 5.03 (1H, dq, *J* 17.2, 1.6, C18H_AH_B), 4.95 (1H, dm, *J* 7.2, C18H_AH_B), 4.86 (1H, d, *J* 7.2, OCH_AH_BO), 4.21 (3H, m, $OCH_2CH_2SiMe_3$ and C11H), 3.80 (1H, dd, *J* 10.0, 6.8, C12H), 3.57 (3H, s, OMe), 3.45 (1H, d, *J* 10.4, C13H), 3.31 (1H, d, *J* 9.2, C15H), 2.18 (1H, ddm, *J* 6.8, 2.0, C16H_AH_B), 2.10–2.00 (1H, m, C16H_AH_B), 1.01 (2H, m, CH_2SiMe_3), 1.01 (3H, s, C14Me), 0.88 (3H, s, C14Me), 0.05 (9H, s, $SiMe_3$); δ_C (90 MHz, $CDCl_3$): 156.1 (0), 135.9 (1), 116.3 (2), 86.7 (2), 79.6 (1), 78.6 (1), 76.5 (1), 74.9 (1), 70.8 (1), 64.1 (2), 62.0 (3), 41.9 (0), 33.6 (2), 23.3 (3), 17.8 (2), 13.5 (3), −1.3 (3, 3C); *m*/*z* (CI, isobutane) 402 [(M + H)$^+$, 70%], 374 (100). Found: (M + H)$^+$, 402.2315. $C_{19}H_{36}O_6NSi$ requires *M*, 402.2312.

(1*S*,5*R*,6*R*,8*R*,10*S*)-10-Methoxy-9,9-dimethyl-8-(prop-2-enyl)-5-{*N*-(methoxalyl)-*N*-[(2-trimethylsilyl)ethoxycarbonyl]amino}-2,4,7-trioxabicyclo[4,4,0]decane (59)

To a solution of carbamate **58** (68 mg, 0.17 mmol) in CH_2Cl_2 was added DMAP (124 mg, 1.0 mmol, recrystallised from CH_2Cl_2–Et_2O–hexanes) and methyl oxalyl chloride (90 µl, 0.98 mmol). The mixture was stirred for 91 h and concentrated. The residue was purified by column chromatography (SiO_2, 5% Et_2O in hexanes) to give the imide **59** (55 mg, 0.11 mmol, 66%) as a clear colourless oil and starting carbamate **58** (6 mg, 0.15 mmol, 9%) as a clear colourless oil: $[a]_D^{22}$ +63.8 (*c* 0.8, $CHCl_3$); ν_{max} film/cm^{-1} 1776, 1689, 1644, 1470; δ_H (360 MHz, $CDCl_3$): 6.13 (1H, d, *J* 10.5, C10H), 5.68 (1H, ddt, *J* 17.0, 10.1, 6.8, C17H), 5.11 (1H, d, *J* 6.7, OCH_AH_BO), 4.98 (1H, d, *J* 6.8, OCH_AH_BO), 5.07 (2H, m, C18H_2), 4.86 (1H, dd, *J* 10.4, 7.3, C11H), 4.35 (2H, ddd, *J* 8.5, 6.3, 3.7, $OCH_2CH_2SiMe_3$), 4.33 (1H, dd, *J* 10.5, 7.3, C12H), 3.90 (3H, s, C(O)OMe), 3.59 (3H, s, OMe), 3.47 (1H, d, *J* 10.5, C13H), 3.29 (1H, dd, *J* 9.9, 2.1, C15H), 2.15 (1H, dddt, *J* 13.0, 7.2, 2.2, 1.5, C16H_AH_B), 2.03 (1H, dddt, *J* 14.4, 10.0, 6.9, 1.2, C16H_AH_B), 1.12 (2H, ddd, *J* 8.4, 6.2, 3.7, CH_2SiMe_3), 1.02 (3H, s, C14Me), 0.88 (3H, s, C14Me), 0.07 (9H, s, $SiMe_3$); δ_C (90 MHz, $CDCl_3$): 162.9 (0), 161.3 (0), 152.5 (0), 135.7 (1), 116.6 (2), 87.8 (2), 79.5 (1), 78.9 (1), 77.2 (1), 75.2 (1), 67.7 (2), 67.0 (1), 62.0 (3), 53.1 (3), 41.8 (0), 33.7 (2), 23.1 (3), 17.5 (2), 13.3 (3), −1.5 (3, 3C); *m*/*z* (EI) 487 [M$^{+•}$, 1%], 446 (7), 449 (8), 374 (14), 362 (35). Found: M$^{+•}$, 487.2219. $C_{22}H_{37}O_9NSi$ requires *M*, 487.2238.

(1*S*,5*R*,6*R*,8*R*,10*S*)-9,9-Dimethyl-10-methoxy-5-[*N*-(methoxalyl)amino]-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4,4,0]decane (10)

TBAF·3H_2O (*ca.* 95%, 400 mg) was added to a solution of carbamate **59** (155 mg, 0.318 mmol) in THF (6 ml) at 0 °C in one portion. After 2 min the mixture was diluted with CH_2Cl_2 (40 ml) and washed with H_2O (60 ml). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 ml) and the combined organic extracts dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, 50% Et_2O in hexanes) to give the desired amide **10** (90 mg, 0.262 mmol, 83%) as a white solid: mp 169–170 °C; $[a]_D^{23}$ +76.2 (*c* 0.6, $CHCl_3$); ν_{max} KBr/cm^{-1} 1737, 1701, 1036; δ_H (360 MHz, $CDCl_3$): 7.53 (1H, d, *J* 9.2, NH), 5.73 (1H, t, *J* 9.7, C10H), 5.62 (1H, ddt, *J* 17.0, 10.1, 6.9, C17H), 5.15 (1H, d, *J* 7.0, OCH_AH_BO), 4.97 (1H, dm, *J* 17.1, C18H_AH_B), 4.88 (1H, m, C18H_AH_B), 4.88 (1H, d, *J* 7.3, OCH_AH_BO), 4.25 (1H, dd, *J* 10.3, 6.8, C12H), 3.93 (3H, s, C(O)OCH_3), 3.90 (1H, dd, *J* 9.8, 6.8, C11H), 3.57 (3H, s, OMe), 3.45 (1H, d, *J* 10.3, C13H), 3.28 (1H, dd, *J* 9.9, 1.4, C15H), 2.16 (1H, ddm, *J* 14.0, 5.5, C16H_AH_B), 2.0 (1H, ddd, *J* 17.0, 5.6, 5.5, C16H_AH_B), 1.01 (3H, s, C14Me), 0.88 (3H, s, C14Me); δ_C (90 MHz, $CDCl_3$): 160.3 (0), 156.5 (0), 135.7 (1), 116.5 (2), 86.9 (2), 79.5 (1), 78.9 (1), 74.8 (1), 74.3 (1), 70.6 (1), 62.0 (3), 54.0 (3), 41.9 (0), 33.4 (2), 23.2 (3), 13.6 (3); *m*/*z* (CI, isobutane) 344 [(M + H)$^+$, 100%]. Found: (M + H)$^+$, 344.1708. $C_{16}H_{26}O_7N$ requires *M*, 344.1709. Found: C, 56.08; H, 7.14; N, 4.04%. $C_{16}H_{25}NO_7$ requires C, 55.98; H, 7.29; N, 4.08.

(1*S*,5*S*,6*S*,8*S*,10*R*)-5{[(2*R*,3*R*,4*R*)-2,3-Dimethyl-4-phenylselanylmethyl-3,4-dihydro-2*H*-pyran-6-yl]oxoethanamido}-9,9-dimethyl-10-methoxy-8-(prop-2-enyl)-2,4,7-trioxabicyclo-[4.4.0]decane (60)

A flame dried 25 ml Schlenk flask was charged with stannane **27** (230 mg, 0.52 mmol) in THF (3 ml) and cooled to −78 °C. *n*-BuLi (0.61 M in hexanes, 0.84 ml, 0.52 mmol) was added dropwise over 10 min keeping the reaction mixture at −78 °C. After 15 min TMEDA (0.35 ml, 0.44 g, 3.80 mmol) was added dropwise to the yellow solution over 1 min. The mixture was stirred for a further 15 min at −78 °C before a cold solution of ester **10** (60 mg, 0.174 mmol) in THF (2 + 2 ml) was added *via* cannula. The clear colourless reaction mixture was stirred for 2 h at −78 °C before being quenched by the addition of saturated aqueous NH_4Cl (6 ml) and stirred vigorously for 15 min. The mixture was then extracted with CH_2Cl_2 (3 × 20 ml) and the combined organic extracts dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, 10–40% Et_2O in hexanes) to give the desired product **60** (80 mg, 0.135 mmol, 78%) as a white solid: mp 144–145 °C (hexanes–Et_2O); $[a]_D^{21}$ −32.0 (*c* 0.5, $CHCl_3$); ν_{max} KBr/cm^{-1} 1670, 1124, 1024; δ_H (400 MHz, $CDCl_3$): 7.56–7.48 (3H, m), 7.31–7.25 (3H, m), 7.09 (1H, dd, *J* 2.0, 1.6, C5H), 5.72 (1H, t, *J* 9.6), 5.62 (1H, ddt, *J* 17.0, 10.2, 6.8, C17H), 5.16 (1H, d, *J* 6.9, OCH_AH_BO), 5.55 (1H, ddm, *J* 17.2, 2.0, C18H_AH_B), 4.90 (1H, d, *J* 6.9, OCH_AH_BO), 4.84 (1H, ddm, *J* 10.2, 1.6, C18H_AH_B), 4.25 (1H, dd, *J* 10.3, 6.7, C12H), 4.10 (1H, dq, *J* 1.2, 6.4, C2H), 3.92 (1H, dd, *J* 9.8, 6.7, C11H), 3.58 (3H, s, C13OMe), 3.46 (1H, d, *J* 10.3, C13H), 3.29 (1H, dd, *J* 10.0, 2.0, C15H), 2.95 (2H, m, CH_2SePh), 2.86 (1H, m, C4H), 2.15 (1H, ddm, *J* 13.6, 5.5, C16H_AH_B), 2.08–1.98 (2H, m, C16H_AH_B and C3H), 1.39 (3H, d, *J* 6.5, C2Me), 1.03 (3H, s, C14Me), 0.89 (3H, s, C14Me), 0.82 (3H, d, *J* 7.0, C3Me); δ_C (90 MHz, $CDCl_3$): 179.7 (0), 160.7 (0), 148.7 (0), 135.8 (1), 133.4 (1, 2C), 129.4 (1, 2C), 129.3 (0), 127.6 (1), 124.8 (1), 116.6 (2), 86.9 (2), 79.6 (1), 78.9 (1), 76.8 (1), 74.8 (1), 74.0 (1), 70.4 (1), 62.0 (3), 41.8 (0), 39.1 (1), 33.4 (1, 2, 2C), 29.6 (2), 23.3 (3), 18.3 (3), 13.7 (3), 6.1 (3); *m*/*z* (EI) 593 $[(M + H)^+$, 3%], 435 (10), 223 (50), 151 (52), 87 (100). Found: C, 58.67; H, 6.58; N, 2.25%. $C_{29}H_{39}NO_7Se$ requires C, 58.78; H, 6.59; N, 2.36.

The structure and absolute stereochemistry of **60** was confirmed by X-ray crystallography with Mo X-rays on a CAD4 diffractometer.[90,91] Crystal data (**60**): $C_{29}H_{39}NO_7Se$, $M = 592.57$, monoclinic, $a = 8.5035(5)$, $b = 10.0704(9)$, $c = 17.6777(6)$, $\beta = 103.768(3)°$, $U = 1470.3(2)$ Å^3, $T = 293$ K, space group $P2_1$, $Z = 2$, μ(Mo-Kα) 1.321 mm^{-1}, 4104 reflections measured, 3402 unique ($R_{int} = 0.023$) used in refinement. $R_1[2097$ with $I > 2\sigma(I)] = 0.036$, wR_2(all data) = 0.077. Flack absolute structure parameter $x = -0.010(11)$.†

Benzoates 61a,b

L-Selectride (1 M in THF, 0.27 ml, 0.27 mmol) was added dropwise to a solution of ketone **60** (85 mg, 0.144 mmol) in THF (2.7 ml) at −95 °C over 15 min. After stirring at −95 °C for 15 min the reaction was quenched by the addition of brine (5 ml) and CH_2Cl_2 (5 ml). The mixture was stirred vigorously for a further 15 min and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated to give a clear colourless oil (102 mg). The residue (102 mg) was dissolved in CH_2Cl_2 (4.5 ml) and MeOH (0.4 ml) to which CSA (4 mg) was added at rt. The mixture was stirred at rt for 40 min before K_2CO_3 (16 mg) was added. The mixture was then stirred for 30 min and poured onto saturated aqueous $NaHCO_3$ (6 ml). The mixture was extracted with CH_2Cl_2 (3 × 20 ml), dried (Na_2SO_4) and concentrated to give a clear yellow oil (114 mg). The residue (114 mg) was dissolved in CH_2Cl_2 (4.5 ml) to which DMAP (34 mg, 0.29 mmol), *N*-ethyldiisopropylamine (0.25 ml, 186 mg, 1.44 mmol) and benzoyl chloride (47 µl, 0.41 mmol) were added at rt. The mixture was stirred at rt for 1 h before MeOH (0.4 ml) was added. After stirring for 10 min, brine (6 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated to give a yellow solid. Column chromatography (SiO_2, 50% Et_2O in hexanes) afforded the desired benzoates **61a**,**b** (96 mg, 0.132 mmol, 91%) as a white solid. ^{1}H NMR spectroscopic analysis (C_6D_6, referenced to 7.16 ppm) of the mixture revealed doublets at δ 4.53 (major) and 4.71 (minor) attributed to the OCH_AH_BO proton corresponding to a 5 : 1 mixture of diastereoisomeric benzoates. The diastereoisomers were separated by column chromatography (SiO_2, 5% Et_2O in CH_2Cl_2) to give the desired diastereoisomer **61a** (66 mg, 0.090 mmol, 63%) as a white foam and the undesired diastereoisomer **61b** (10 mg, 0.0137 mmol, 10%) as a white foam and a mixture of diastereoisomers **61a**,**b** (20 mg, 0.027 mmol, 20%) as a white solid.

61a. Mp 72–76 °C; $[\alpha]_D^{23}$ +103.8 (*c* 0.8, $CHCl_3$); ν_{max} KBr/cm^{-1} 1732, 1704, 1272, 1033; δ_H (360 MHz, C_6D_6 referenced to 7.16 ppm): 8.32 (2H, dd, *J* 8.2, 1.6), 7.47 (2H, dd, *J* 7.8, 1.5), 7.42 (1H, d, *J* 9.6, NH), 7.10–6.92 (6H, m), 6.06 (1H, ddt, *J* 16.5, 10.3, 6.9, C17H), 5.95 (1H, s, C7H), 5.94 (1H, t, *J* 9.8, C10H), 5.14 (1H, ddm, *J* 10.1, 0.9, $C18H_AH_B$), 5.06 (1H, ddm, *J* 17.1, 1.2, $C18H_AH_B$), 4.59 (1H, d, *J* 6.9, OCH_AH_BO), 4.53 (1H, d, *J* 6.9, OCH_AH_BO), 4.32 (1H, dd, *J* 10.3, 6.8, C12H), 3.79 (1H, dd, *J* 9.7, 6.8, C11H), 3.56 (2H, m, C15H and C2H), 3.27 (3H, s, OMe), 3.07 (1H, d, *J* 10.4, C13H), 2.89 (3H, s, OMe), 2.85 (1H, m, CH_AH_BSePh), 2.83 (1H, dd, *J* 14.4, 11.9, CH_AH_BSePh), 2.43 (1H, m with 10 lines, C4H), 2.29 (1H, dd, *J* 13.5, 3.6, C5H), 2.09 (1H, m, $C16H_AH_B$), 2.03 (1H, dd, *J* 14.4, 7.6, $C16H_AH_B$), 1.86 (1H, t, *J* 13.0, C5H), 1.55 (1H, m, C3H), 0.87 (3H, s, C14Me), 0.85 (3H, d, *J* 6.7, C2Me), 0.80 (3H, d, *J* 6.8, C3Me), 0.79 (3H, s, C14Me); δ_C (90 MHz, C_6D_6 referenced to 128.4 ppm): 166.7 (0), 166.0 (0), 137.7 (1), 133.6 (1), 133.2 (1, 2C), 131.4 (0), 130.8 (0), 130.7 (1, 2C), 129.7 (1, 2C), 129.0 (1, 2C), 127.3 (1), 116.3 (2), 99.8 (0), 87.1 (2), 79.4 (1), 78.9 (1), 75.7 (1), 74.9 (1), 72.9 (1), 72.5 (1), 71.0 (1), 61.7 (3), 48.3 (3), 42.0 (0), 35.9 (1), 35.5 (1), 34.4 (2), 32.5 (2), 31.6 (2), 23.5 (3), 18.5 (3), 14.1 (3), 5.0 (3). Found: $M^{+\bullet}$, 731.2575. $C_{37}H_{49}NO_9Se$ requires *M*, 731.2576.

61b. Mp 74–79 °C; $[\alpha]_D^{23}$ +17.5 (*c* 0.4, $CHCl_3$); ν_{max} KBr/cm^{-1} 1733, 1708, 1264, 1128, 1107, 1026; δ_H (360 MHz, C_6D_6 referenced to 7.16 ppm): 8.32 (2H, dd, *J* 8.2, 1.5), 7.49–7.38 (3H, m), 7.11–6.92 (6H, m), 6.19 (1H, ddt, *J* 16.9, 10.2, 6.5, C17H), 6.02 (1H, t, *J* 9.8, C10H), 5.92 (1H, s, C7H), 5.55 (1H, dm, *J* 10.2, $C18H_AH_B$), 5.22 (1H, ddm, *J* 17.0, 2.1, $C18H_AH_B$), 4.71 (1H, d, *J* 6.9, OCH_AH_BO), 4.64 (1H, d, *J* 6.9, OCH_AH_BO), 4.33 (1H, dd, *J* 10.4, 6.8, C12H), 3.74 (1H, dd, *J* 10.1, 6.8, C11H), 3.52 (1H, dq, *J* 2.1, 6.5, C2H), 3.31 (1H, t, *J* 6.0, C15H), 3.27 (6H, s, C6OMe and C13OMe), 3.05 (1H, d, *J* 10.4, C13H), 2.54 (2H, m, CH_2SePh), 2.25 (1H, m with 10 lines, C4H), 2.07 (3H, m), 1.64 (1H, t, *J* 13.2, C5H), 1.50 (1H, m, C3H), 0.89 (3H, s, C14Me), 0.84 (3H, d, *J* 6.5, C2Me), 0.73 (3H, s, C14Me), 0.59 (3H, s, d, *J* 7.0, C3Me); δ_C (90 MHz, C_6D_6 referenced to 128.4 ppm): 167.3 (0), 166.0 (0), 137.1 (1), 133.6 (1), 133.3 (1, 2C), 131.4 (0), 130.8 (0), 130.7 (1, 2C), 129.7 (1, 2C), 129.0 (1, 2C), 127.3 (1), 117.0 (2), 99.9 (0), 87.1 (2), 79.6 (1), 78.9 (1), 76.0 (1), 74.5 (1), 72.7 (1), 72.1 (1), 70.9 (1), 61.7 (3), 49.3 (3), 42.1 (0), 35.7 (1), 35.3 (1), 34.1 (2), 32.4 (2), 32.0 (2), 23.1 (3), 18.4 (3), 13.8 (3), 4.6 (3). Found: $M^{+\bullet}$, 731.2581. $C_{37}H_{49}NO_9Se$ requires *M*, 731.2576.

Aldehyde 62

Olefin **61a** (50 mg, 0.0685 mmol) and hydroquinine 9-phenanthryl ether[64] (2 mg, 0.004 mmol) were dissolved in *t*-BuOH (1 ml) to which water (1 ml) was added followed by K_3FeCN_6 (45 mg, 0.14 mmol), K_2CO_3 (20 mg, 0.14 mmol) and potassium osmate dihydrate (1 mg, 0.003 mmol). After stirring at rt for 8 h saturated aqueous Na_2SO_4 (2 ml) was added. The mixture was extracted with EtOAc (3 × 15 ml) and the combined organic extracts were dried (Na_2SO_4) and concentrated to give a clear yellow oil which was dissolved in MeOH (2 ml) to which water (0.65 ml) and $NaIO_4$ (100 mg, 0.047 mmol) were added. The mixture was stirred at rt for 1 h then diluted with CH_2Cl_2 (30 ml) and washed with water (2 × 15 ml). The organic phase was dried (Na_2SO_4) to which Et_3N (2ml) was added before the mixture was concentrated *in vacuo* (12 mmHg, 18 °C) to give a yellow oil. The yellow oil was dissolved in toluene (1 ml) and Et_3N (1 ml) and heated at reflux for 2 min. The mixture was allowed to cool to rt before saturated aqueous $NaHCO_3$ (8 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 20 ml), the combined organic layers dried (Na_2SO_4) and concentrated *in vacuo*. The yellow oil was purified by column chromatography (SiO_2, 50% Et_2O in hexanes containing 1% Et_3N) to give the desired aldehyde **62** (27 mg, 0.0470 mmol, 69%) as a white powder: mp 86–87 °C; $[\alpha]_D^{23}$ +110.3 (*c* 0.3, CH_2Cl_2); ν_{max} KBr/cm^{-1} 1730, 1701, 1654, 1647, 1270, 1126, 1106, 1037; δ_H (400 MHz, C_6D_6 referenced to 7.16 ppm): 9.72 (1H, d, *J* 4.5, C17H), 8.38 (2H, dd, *J* 8.0, 1.6), 7.47 (1H, d, *J* 9.2, NH), 7.11–7.00 (3H, m), 5.93 (1H, s, C7H), 5.91 (1H, t, *J* 9.6, C10H), 4.94 (1H, d, *J* 1.6, $=CH_AH_B$), 4.85 (1H, *J* 1.6, $=CH_AH_B$), 4.59 (1H, d, *J* 6.8, OCH_AH_BO), 4.50 (1H, d, *J* 6.8, OCH_AH_BO), 4.26 (1H, dd, *J* 10.4, 6.8, C12H), 4.02 (1H, dd, *J* 10.4, 2.4, C15H), 3.81 (1H, dq, *J* 6.4, 2.8, C2H), 3.77 (1H, dd, *J* 9.6, 6.8, C11H), 3.27 (3H, s, C13OMe), 3.09 (1H, d, *J* 10.4, C13H), 2.91 (1H, d, *J* 14.4, $C5H_AH_B$), 2.90 (3H, s, C6OMe), 2.81 (1H, d, *J* 14.4, $C5H_AH_B$), 2.08 (1H, ddd, *J* 15.6, 10.4, 4.4, $C16H_AH_B$), 1.93 (1H, dq, *J* 7.2, 2.8, C3H), 1.82 (1H, dd, *J* 16.0, 2.4, $C16H_AH_B$), 0.99 (3H, d, *J* 7.2, C3Me), 0.86 (3H, d, *J* 6.8, C2 Me), 0.70 (3H, s, C14Me), 0.64 (3H, s, C14Me); δ_C (100 MHz, C_6D_6 referenced to 128.4 ppm): 200.9 (1), 167.3 (0), 166.1 (0), 145.6 (0), 133.7 (1), 130.8 (1, 2C), 130.7 (0), 129.1 (1, 2C), 111.6 (2), 100.4 (0), 87.3 (2), 79.0 (1), 75.5 (1), 75.0 (1), 75.0 (1), 73.0 (1), 72.7 (1), 70.3 (1), 61.7 (3), 48.4 (3), 44.1 (2), 42.0 (1), 41.5 (0), 35.3 (2), 23.3 (3), 18.0 (3), 13.8 (3), 12.7 (3). Found: M^+, 575.2734. $C_{30}H_{41}NO_{10}$ requires *M*, 575.2730.

7-*O*-Benzoyltheopederin D (65a) and 17-*epi*-7-*O*-benzoyltheopederin D (64b)

Chloromagnesium 3-chloromagesio-1-propoxide was prepared by the method of Normant *et al.*[75] 3-Chloropropan-1-ol (0.9 ml, 8.42 ml) in THF (8.0 ml) was cooled to −20 °C to which MeMgCl (3.1 M in THF, 2.72 ml, 8.42 mmol) was added dropwise over 3 min. After stirring at rt for 20 min Mg (314 mg, 14 mmol) and 1,2-dibromoethane (0.016 ml, 0.19 mmol) were added. The mixture was refluxed for 1 h before another portion of 1,2-dibromoethane (0.016 ml, 0.19 mmol) was added. After refluxing for a further 2 h, a homogeneous solution was formed. The mixture was allowed to cool to rt and the concentration was found to be 0.30 M in THF by titration.[92]

To a solution of aldehyde **62** (15 mg, 0.026 mmol) in THF (0.5 ml) at −78 °C was added the Grignard reagent prepared above (0.30 M in THF, 0.17 ml, 0.052 mmol). After stirring at −78 °C for 2 h the reaction was quenched at −78 °C by the addition of saturated aqueous $NaHCO_3$ (2 ml) and EtOAc (1 ml). The mixture was stirred and allowed to warm up to rt during a 15 min period. The mixture was extracted with EtOAc (3 × 4 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 30% Et_2O in hexanes, neat Et_2O and 50% Et_2O in EtOAc) afforded a diastereoisomeric mixture of diols **63** (20 mg) as a white solid. The diols **63** (20 mg) were dissolved in CH_2Cl_2 (0.9 ml) and MeCN (0.1 ml) to which 4-methylmorpholine *N*-oxide (6 mg, 0.048 mmol), 4 Å molecular sieves (16 mg) and TPAP (6 mg, 0.018 mmol) were added at rt. After stirring for 0.5 h, Et_2O (2 ml) was added and the mixture was concentrated *in vacuo*. The residue was purified by filtration through a pad of SiO_2 (50% EtOAc in CH_2Cl_2) to give a diastereoisomeric mixture of lactones **64a**,**b** (14 mg, 0.022 mmol, 85%) as a clear colourless oil. ^{1}H NMR spectroscopic analysis (C_6D_6, referenced to 7.16 ppm) of the mixture revealed singlets at δ 5.94 and 5.84 ppm attributed to the C7 proton corresponding to a 1 : 1 mixture of diastereoisomeric lactones **64a**,**b**. The diastereoisomers were separated by preparative TLC. The mixture was divided into six portions and each portion separated on a 5 × 20 cm silica gel 60 F-254 plate eluting with 50% EtOAc in hexanes containing 1% Et_3N. Two elutions were required for full separation. The top band gave 7-*O*-benzoyltheopederin D **64a** (6 mg, 0.0095 mmol, 37%) as a clear colourless oil and the lower band gave 17-*epi*-7-*O*-benzoyltheopederin D **64b** (4 mg, 0.0063 mmol, 24%) also as a clear colourless oil.

7-*O*-Benzoyltheopederin D (64a). $[a]_D^{23}$ +54.0 (*c* 0.5, EtOAc); δ_H (400 MHz, C_6D_6 referenced to 7.16 ppm): 8.25 (2H, dd, *J* 8.4, 1.6), 7.27 (1H, d, *J* 9.6, NH), 7.11–7.00 (3H, m), 5.84 (1H, s, C7H), 5.76 (1H, t, *J* 9.6, C10H), 4.80 (2H, m, =CH_2), 4.57 (1H, d, *J* 7.2, OCH_AH_BO), 4.60–4.50 (1H, m, C17H), 4.50 (1H, d, *J* 7.2, OCH_AH_BO), 4.23 (1H, dd, *J* 10.4, 6.8, C12H), 3.81 (1H, dq, *J* 6.4, 2.4, C2H), 3.66 (1H, dd, *J* 9.6, 6.8, C11H), 3.26 (3H, s, C13OMe), 3.15 (1H, d, *J* 10.4, C15H), 2.93 (1H, d, *J* 12.4, C13H), 2.92 (3H, s, C6OMe), 2.78 (1H, bd, *J* 13.6, $C5H_AH_B$), 2.72 (1H, d, *J* 14.0, $C5H_AH_B$), 2.50–2.35 (1H, m), 2.36 (1H, dt, *J* 17.2, 9.6, $C19H_AH_B$), 2.18–2.08 (1H, m, $C16H_AH_B$), 1.90 (1H, dq, *J* 2.8, 7.2, C3H), 1.92–1.82 (1H, m, $C16H_AH_B$), 1.13–1.15 (2H, m, $C18H_2$), 1.03 (3H, d, *J* 6.8, C3Me), 0.90 (3H, d, *J* 6.4, C2Me), 0.75 (3H, s, C14Me), 0.68 (3H, s, C14Me); δ_C (100 MHz, C_6D_6 referenced to 128.4 ppm): 176.4 (0), 167.4 (0), 165.8 (0), 145.3 (0), 134.0 (1), 130.5 (1, 2C), 130.2 (0), 129.3 (1, 2C), 111.9 (2), 100.1 (0), 86.9 (2), 79.1 (1), 78.4 (1), 75.5 (1), 75.3 (1), 74.5 (1), 73.4 (1), 72.4 (1), 70.3 (1), 61.7 (3), 48.8 (3), 41.8 (1), 41.6 (0), 36.0 (2), 35.0 (2), 29.2 (2), 28.6 (2), 23.2 (3), 18.0 (3), 14.7 (3), 12.6 (3); *m*/*z* (CI, isobutane) 649 [$(M + NH_4)^+$, 20%], 617 [$(M + NH_4 - OCH_3)^+$, 75%], 600 [$(M - OCH_3)^+$, 10%]. Found: $(M + NH_4)^+$, 649.3339. $C_{33}H_{49}N_2O_{11}$ requires *M*, 649.3336.

17-*epi*-7-*O*-Benzoyltheopederin D (64b). $[a]_D^{21}$ +71.3 (*c* 0.3, EtOAc); δ_H (400 MHz, C_6D_6 referenced to 7.16 ppm): 8.25 (2H, m), 7.12 (1H, d, *J* 9.2, NH), 7.09–7.02 (3H, m), 5.94 (1H, s, C7H), 5.77 (1H, t, *J* 9.2, C10H), 4.80 (2H, dm, *J* 9.7, =CH_2), 4.64 (2H, s, OCH_2O), 4.55 (1H, ddd, *J* 15.2, 9.2, 3.2, C17H), 4.24 (1H, dd, *J* 10.0, 6.8, C12H), 3.90 (1H, dd, *J* 9.6, 6.8, C11H), 3.83 (1H, dq, *J* 6.4, 2.8, C2H), 3.51 (1H, dd, *J* 8.8, 0.8, C15H), 3.28 (3H, s, OMe),3.04 (3H, s, OMe), 2.99 (1H, d, *J* 10.0, C13H), 2.85 (1H, bd, *J* 14.4, $C5H_AH_B$), 2.78 (1H, d, *J* 14.0, $C5H_AH_B$), 2.27 (1H, dt, *J* 17.6, 9.6, $C19H_AH_B$), 2.04 (1H, ddd, *J* 17.2, 9.2, 3.2, $C19H_AH_B$), 1.95 (1H, dq, *J* 7.2, 2.8, C3H), 1.74 (1H, dddd, *J* 12.8, 10.0, 6.4, 3.6, $C18H_AH_B$), 1.42 (1H, ddd, *J* 14.4, 8.8, 1.6, $C16H_AH_B$), 1.30–1.10 (2H, m, $C16H_AH_B$) and $C18H_AH_B$), 1.02 (3H, d, *J* 7.2, C3Me), 0.92 (3H, d, *J* 6.8, C2Me), 0.79 (3H, s, C14Me), 0.78 (3H, s, C14Me); δ_C (100 MHz, C_6D_6 referenced to 128.4 ppm): 176.0 (0), 167.1 (0), 166.1 (0), 146.5 (0), 133.8 (1), 130.6 (1, 2C), 130.4 (0), 129.2 (1, 2C), 111.2 (2), 100.1 (0), 87.1 (2), 79.4 (1), 78.0 (1), 76.2 (1), 75.4 (1), 75.2 (1), 73.7 (1), 71.4 (1), 70.1 (1), 61.7 (3), 48.9 (3), 42.0 (1), 41.5 (0), 36.3 (2), 35.3 (2), 29.3 (2), 29.1 (2), 23.4 (3), 18.1 (3), 14.7 (3), 12.8 (3); *m*/*z* (EI) 600 [$(M - OCH_3)^{+\bullet}$, 10%]. Found: $(M + NH_4)^+$, 649.3331. $C_{33}H_{49}N_2O_{11}$ requires *M*, 649.3336.

Theopederin D (5D)

Potassium carbonate (1 mg, 0.007 mmol) was added to a solution of 7-*O*-benzoyltheopederin D **64a** (3 mg, 0.0048 mmol) in anhydrous MeOH (0.3 ml) at rt. The mixture was stirred for 1 h before the addition of H_2O (3 ml). The mixture was then extracted with EtOAc (3 × 6 ml), the combined organic extracts washed with brine (2 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by filtration through a pad of SiO_2 (50% EtOAc in hexanes) to give theopederin D **5D** (2 mg, 0.0038 mmol, 79%) as a white solid, mp 87–88 °C: δ_H (400 MHz, $CDCl_3$ referenced to 7.24 ppm) 7.51 (1H, d, *J* 10.3, NH), 5.80 (1H, dd, *J* 9.5, 9.5, C10H), 5.11 (1H, d, *J* 7.0, OCH_AH_BO), 4.86 (1H, d, *J* 7.0, OCH_AH_BO), 4.84 (1H, app t, *J* 1.7, =CH_AH_B), 4.73 (1H, app t, *J* 1.7, =CH_AH_B), 4.42 (1H, ddd, *J* 14.1, 8.2, 5.9, C17H), 4.25 (1H, d, *J* 3.2, C7H), 4.19 (1H, dd, *J* 9.7, 6.4, C12H), 4.11 (1H, d, *J* 3.2, OH), 4.01 (1H, dq, *J* 2.8, 6.6, C2H), 3.80 (1H, dd, *J* 9.2, 6.4, C11H), 3.54 (3H, s, C13OMe), 3.42 (1H, d, *J* 9.5, C13H), 3.40 (1H, d, *J* 9.0, C15H), 3.28 (3H, s, C6OMe), 2.55–2.48 (1H, m, $C19H_AH_B$), 2.46 (1H, dd, *J* 18.0, 10.3, $C19H_AH_B$), 2.41–2.35 (1H, m, $C18H_AH_B$), 2.33 (1H, d, *J* 13.9, $C5H_AH_B$), 2.24 (1H, dq, *J* 7.1, 2.6, C3H), 2.18 (1H, d, *J* 14.1, $C5H_AH_B$), 1.97–1.87 (1H, m, $C16H_AH_B$), 1.80–1.68 (1H, m, $C18H_AH_B$), 1.58 (1H, ddd, *J* 14.3, 8.3, 1.3, $C16H_AH_B$), 1.18 (3H, d, *J* 6.6, C2Me), 1.00 (3H, s, C14Me), 0.98 (3H, d, *J* 7.1, C3Me), 0.86 (3H, s, C14Me); δ_C(100 MHz, $CDCl_3$ referenced to 77.0 ppm) 177.5 (0, C20), 172.3 (0, C8), 145.0 (0, C4), 111.0 (2, =CH_2), 99.8 (0, C6), 86.5 (2, OCH_2O), 79.5 (1, C13), 79.2 (1, C17), 76.0 (1, C15), 74.0 (1, C12), 73.6 (1, C10), 71.6 (1, C7), 69.5 (1, C11), 69.5 (1, C2), 61.7 (3, C13OMe), 48.5 (3, C6OMe), 41.3 (1, C3), 41.1 (0, C14), 35.0 (2, C16), 33.3 (2, C5), 28.7 (2, C19), 28.0 (2, C18), 22.6 (3, $C14Me_{eq}$), 18.0 (3, C2 Me), 14.1 (3, $C14Me_{ax}$), 12.0 (3, C3Me).

17-*epi*-Theopederin D

Potassium carbonate (1 mg, 0.007 mmol) was added to a solution of 17-*epi*-7-*O*-benzoyltheopederin D **64b** (2 mg, 0.0032 mmol) in anhydrous MeOH (0.3 ml) at rt. The mixture was stirred for 1 h before the addition of H_2O (3 ml). The mixture was then extracted with EtOAc (3 × 6 ml), the combined organic extracts washed with brine (2 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by filtration through a pad of SiO_2 (50% EtOAc in hexanes) to give 17-*epi*-

theopederin D (1 mg, 0.0019 mmol, 59%) as a white solid mp 80–82 °C; δ_H (400 MHz, $CDCl_3$ referenced to 7.24 ppm): 7.41 (1H, d, *J* 9.4, NH), 5.83 (1H, t, *J* 9.2, C10H), 5.12 (1H, d, *J* 7.0, OCH_AH_BO), 4.87 (1H, d, *J* 6.8, OCH_AH_BO), 4.87 (1H, t, *J* 2.0, $=CH_AH_B$), 4.75 (1H, t, *J* 1.7, $=CH_AH_B$), 4.48 (1H, ddd, *J* 12.1, 9.1, 6.4, C17H), 4.26 (1H, d, *J* 2.4, C7H), 4.19 (1H, dd, *J* 9.7, 6.5, C12H), 4.05 (1H, dq, *J* 6.6, 2.8, C2H), 3.83 (1H, d, *J* 2.5, C7OH), 3.82 (1H, dd, *J* 9.0, 6.5, C11H), 3.65 (1H, dd, *J* 9.8, 1.5, C15H), 3.54 (3H, s, OMe), 3.44 (1H, d, *J* 9.7, C13H), 3.30 (3H, s, OMe), 2.49 (2H, m, $C19H_2$), 2.36 (1H, d, *J* 13.9, C5H), 2.28 (1H, dq, *J* 2.7, 7.1, C3H), 2.20 (1H, m, $C18H_AH_B$), 2.16 (1H, bd, *J* 14.1, C5H), 1.83–1.70 (2H, m, $C16H_AH_B$ and $C18H_AH_B$), 1.60 (1H, dd, *J* 9.7, 3.0, $C16H_AH_B$), 1.19 (3H, d, *J* 6.6, C2Me), 1.02 (3H, s, C14Me), 0.99 (3H, d, *J* 7.1, C3Me), 0.84 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$ referenced to 77.0 ppm): 176.5 (0), 171.5 (0), 145.4 (0), 111.1 (2), 99.8 (0), 86.5 (2), 79.5 (1), 78.1 (1), 77.2 (1), 76.0 (1), 74.2 (1), 74.05 (1), 71.5 (1), 69.4 (1), 61.7 (3), 48.7 (3), 41.2 (1), 40.9 (0), 35.4 (2), 33.3 (2), 29.0 (2), 28.7 (2), 22.7 (3), 18.0 (3), 14.1 (3), 12.5 (3); *m/z* (CI, isobutane) 496 [$(M - OCH_3)^+$, 100%]. Found: $(M - OCH_3)^+$, 496.2516. $C_{25}H_{38}NO$ requires *M*, 496.2546.

3. Pederin

(2*S*,6*R*)-6-(3-Chloropropyl)-2-cyanotetrahydro-5,5-dimethyl-2*H*-pyran-4-one (65)

Trimethylsilyl trifluoromethanesulfonate (110 µl, 0.6 mmol) was added to a stirred solution of dihydropyranone **7** (4.0 g, 19.7 mmol) and trimethylsilyl cyanide (2.7 ml, 21.7 mmol) in CH_2Cl_2 (40 ml) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and poured onto saturated aqueous $NaHCO_3$ (10 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was treated with THF (10 ml) and aqueous HCl (2 M, 2 ml) and then stirred at rt for 30 min. The reaction mixture was extracted with CH_2Cl_2 (3 × 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Kugelrohr distillation [bp 250 °C (oven)/0.05 mmHg] gave a colourless oil which crystallised upon cooling in the refrigerator. Recrystallisation from hexanes–Et_2O gave cyano ketone **65** (4.15 g, 18.1 mmol, 92%) as a white solid: mp 36–38 °C; $[a]_D^{20}$ +120.0 (*c* 1.0, $CHCl_3$); ν_{max} film/cm^{-1} 1715; δ_H (400 MHz, $CDCl_3$): 5.18 (1H, dd, *J* 8.1, 1.5, C11H), 3.79 (1H, dd, *J* 8.8, 3.7, C15H), 3.62 (2H, t, *J* 6.6, $C18H_2$), 3.10 (1H, dd, *J* 15.5, 8.1, $C12H_AH_B$), 2.57 (1H, dd, *J* 15.5, 2.2, $C12H_AH_B$), 2.12–2.01 (1H, m, $C17H_AH_B$), 1.93–1.82 (1H, m, $C17H_AH_B$), 1.77–1.70 (2H, m, $C16H_2$), 1.16 (3H, s, C14Me), 1.12 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 206.4 (0, C13), 116.7 (0, C10), 81.4 (1, C15), 64.5 (1, C11), 50.1 (0, C14), 44.7 (2, C18), 40.1 (2, C12), 29.2 (2, C17), 26.0 (2, C16), 18.9 (3, 2C, C14Me); *m/z* (EI): 231 (10), 229 ($M^{+\bullet}$, 30), 123 (87), 70 (100%). Found: (M^+), 229.0867. $C_{11}H_{16}O_2NCl$ requires *M*, 229.0870. Found: C, 57.32; H, 6.95; N, 5.96%. $C_{11}H_{16}ClNO_2$ requires C, 57.52; H, 7.02; N, 6.10.

(2*S*,4*R*,6*R*)-6-(3-Chloropropyl)-2-cyanotetrahydro-5,5-dimethyl-2*H*-pyran-4-ol (66)

To a solution of ketone **65** (13 g, 56.6 mmol) and $CeCl_3 \cdot 7H_2O$ (10.4 g, 28.0 mmol) in MeOH (130 ml) at −95 °C was added in one portion sodium borohydride (6.5 g, 169.7 mmol). The reaction mixture was stirred for 1 h below −85 °C and was then allowed to warm to −60 °C over 1 h with stirring before pouring onto aqueous HCl (2 M, 150 ml) at 0 °C. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (35 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered through a pad of SiO_2 to give a 30:1 mixture of alcohols (13.0 g, >99%) as a white solid. Purification by column chromatography (SiO_2, 10% Et_2O in CH_2Cl_2) gave pure undesired alcohol ***epi*-66** (110 mg, 0.48 mmol, 0.8%) and 12.8 g of a mixture of **66** and ***epi*-66** which was recrystallised from hexanes–Et_2O to give pure alcohol **66** (10.1 g, 43.6 mmol, 77%) as white crystals: mp 71–72 °C; $[a]_D^{27}$ +83.0 (*c* 1.0, $CHCl_3$); ν_{max} (CCl_4)/cm^{-1} 3630, 3540; δ_H (400 MHz, $CDCl_3$): 4.91 (1H, dd, *J* 5.9, 1.5, C11H), 3.75 (1H, dd, *J* 11.0, 5.1, C13H), 3.67–3.53 (2H, m, $C18H_2$), 3.42 (1H, dd, *J* 10.3, 1.5, C15H), 2.01 (1H, ddd, *J* 13.5, 11.7, 6.0, $C12H_AH_B$), 1.94 (1H, ddd, *J* 13.5, 4.9, 1.5, $C12H_AH_B$), 2.05–1.90 (1H, m, $C17H_AH_B$), 1.73–1.87 (2H, m, $C16H_AH_B$ and $C17H_AH_B$), 1.67 (1H, br s, C13OH), 1.60–1.48 (1H, m, $C16H_AH_B$), 1.02 (3H, s, C14Me), 0.88 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 117.8 (0, C10), 81.1 (1, C15), 71.9 (1, C13), 64.0 (1, C11), 44.9 (2, C18), 39.4 (0, C14), 32.7 (2, C12), 29.4 (2, C17), 25.7 (2, C16), 22.2 (3, C14Me), 12.0 (3, C14Me); *m/z* (CI, NH_3) 249 [$(M + NH_4)^+$, 100%]. Found: C, 56.87; H, 7.70; N, 6.03; Cl, 15.35%. $C_{11}H_{18}ClNO_2$ requires C, 56.97; H, 7.76; N, 6.04; Cl, 15.32.

The minor isomer (2*S*,4*S*,6*R*)-6-(3-chloropropyl)-2-cyanotetrahydro-5,5-dimethyl-2*H*-pyran-4-ol (***epi*-66**) was isolated as a colourless oil: $[a]_D^{20}$ +84.2 (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3491, 2964; δ_H (400 MHz, $CDCl_3$): 4.77 (1H, d, *J* 6.7, C11H), 3.95 (1H, dd, *J* 10.7, 1.2, C15H), 3.61–3.54 (3H, m, C13H and $C18H_2$), 2.32–2.25 (2H, m, OH and $C12H_AH_B$), 2.04–1.94 (1H, m, $C17H_AH_B$), 1.89–1.78 (2H, m, C17–H_AH_B), 1.70–1.61 (1H, m, $C16H_AH_B$), 1.50–1.39 (1H, m, $C16H_AH_B$), 0.98 (3H, s, C14Me), 0.90 (3H, s, C14Me); δ_C (100 MHz, $CDCl_3$): 119.4 (0, C10), 75.1 (1, C15), 72.2 (1, C13), 60.7 (1, C11), 45.0 (2, C18), 36.9 (0, C14), 31.5 (2, C12), 29.2 (2, C17), 25.6 (2, C16), 22.7 (3, C14Me), 19.0 (3, C14Me); *m/z* (CI, NH_3) 249 [$(M + NH_4)^+$, 100%]. Found: $(M + NH_4)^+$, 249.1368. $C_{11}H_{22}O_2N_2Cl$ requires *M*, 249.1370. Found: C, 56.96; H, 7.74; N, 6.01%. $C_{11}H_{18}ClNO_2$ requires C, 56.97; H, 7.76; N, 6.04.

The isomers are easily separable on TLC (CH_2Cl_2–Et_2O 9:1) R_f (major isomer) 0.39: R_f (minor isomer) 0.47.

(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(3-chloropropyl)-2-cyanotetrahydro-5,5-dimethyl-2*H*-pyran (67)

tert-Butyldimethylsilyl trifluoromethanesulfonate (3.85 ml, 16.6 mmol) was added dropwise to a stirred solution of alcohol **66** (3.5 g, 15.1 mmol) and 2,6-lutidine (3.67 ml, 18.2 mmol) in dry CH_2Cl_2 (25 ml) at 0 °C. The reaction mixture was stirred at 0–5 °C for 2.5 h, then poured into saturated aqueous $NaHCO_3$ (10 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 ml). The combined organic extracts were washed with aqueous HCl (2 M, 70 ml) followed by water (90 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 10% Et_2O in hexanes) to give silyl ether **67** as a white solid (5.20 g, 15.0 mmol, >99%): mp 44–46 °C (hexanes–Et_2O); $[a]_D^{20}$ +60.7 (*c* 1.84, $CHCl_3$); ν_{max} (CCl_4)/cm^{-1} 2958, 2932, 2858, 1472, 1258, 1084, 876, 838; δ_H (400 MHz, $CDCl_3$): 4.87 (1H, dd, *J* 5.9, 1.5, C11H), 3.67 (1H, dd, *J* 11.8, 5.2, C13H), 3.65–3.53 (2H, m, $C18H_2$), 3.43 (1H, dd, *J* 10.3, 1.5, C15H), 2.08–1.91 (2H, m), 1.89–1.69 (3H, m), 1.60–1.44 (1H, m), 0.93 (3H, s, C14Me), 0.90 (9H, s, ^{t}BuSi), 0.85 (3H, s, C14Me), 0.09 (3H s, SiMe), 0.08 (3H, s, SiMe); δ_C (100 MHz, $CDCl_3$): 117.9 (0, C10), 81.2 (1, C15), 72.5 (1, C13), 63.9 (1, C11), 44.9 (2, C18), 40.0 (0, C14), 33.7 (2, C12), 29.5 (2, C17), 26.0 (2, C16), 25.9 (3, 3C, ^{t}BuSi), 22.8 (3, C14Me), 18.1 (0, CSi), 12.4 (3, C14Me), −4.0 (3, MeSi), −4.8 (3, MeSi); *m/z* (CI, NH_3) 363 [$(M + NH_4)^+$, 100%]. Found: C, 58.97; H, 9.24; N, 3.99; Cl, 10.26%. $C_{17}H_{32}ClNO_2Si$ requires C, 58.97; H, 9.26; N, 4.04; Cl, 10.26.

(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-(3-phenylselanylpropyl)-5,5-dimethyltetrahydro-2*H*-pyran (68)

Sodium borohydride (720 mg, 18.7 mmol) was added portionwise to a stirred suspension of diphenyl diselenide (2.65 g, 8.46 mmol) in dry ethanol (25 ml). The exothermic reaction resulted in a pale yellow solution to which was added chloride **67** (4.5 g, 13 mmol). The resulting mixture was refluxed for 1 h, cooled to rt and treated with aqueous NaOH (2 M, 40 ml) and extracted with hexanes (3 × 20 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 eluting with toluene–hexanes (1 : 1) until the yellow band passed and then hexanes–Et_2O (85 : 15) to give selenide **68** (5.5 g, 91%) as a colourless oil that crystallised on standing: mp 28–30 °C (hexanes–Et_2O); $[a]_D^{20}$ +36.9 (*c* 1.89, $CHCl_3$); v_{max} (CCl_4)/cm^{-1} 2958, 2932, 2858, 1595, 1472, 1258, 1084, 876, 838; δ_H (360 MHz, $CDCl_3$): 7.57–7.50 (2H, m), 7.35–7.20 (3H, m), 4.85 (1H, dd, *J* 6.0, 1.3, C11H), 3.67 (1H, dd, *J* 11.5, 4.6, C13H), 3.42 (1H, dd, *J* 10.3, 1.4, C15H), 3.02–2.90 (2H, m, C18H_2), 1.99 (1H, ddd, *J* 13.6, 11.6, 6.1, C12H_AH_B), 2.00–1.88 (1H, m), 1.85–1.64 (3H, m), 1.56–1.43 (1H, m), 0.93 (9H, s, ^{t}BuSi), 0.91 (3H, s, C14Me), 0.84 (3H, s, C14Me), 0.11 and 0.10 (3H each, s, Me_2Si); δ_C (90 MHz, $CDCl_3$): 132.4 (1, 2C), 130.4 (0), 129.0 (1, 2C), 126.6 (1), 117.8 (0), 81.1 (1), 72.4 (1), 63.7 (1), 39.8 (0), 33.6 (2), 28.5 (2), 27.5 (2), 27.0 (2), 25.8 (3, 3C), 22.6 (3), 17.9 (0), 12.3 (3), −4.2 (3), −4.9 (3); *m*/*z* (CI, NH_3) 485 [(M + NH_4)$^+$, 100%], 483 (50). Found: C, 59.29; H, 8.03; N, 2.92%. $C_{23}H_{37}NO_2SeSi$ requires C, 59.15; H, 7.92; N, 3.00.

(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyanotetrahydro-5,5-dimethyl-6-(prop-2-enyl)-2*H*-pyran (69)

Sodium metaperiodate (2.15 g, 10 mmol) was added in one portion to a stirred solution of selenide **68** (3.15 g, 6.75 mmol) in water (100 ml) and methanol (200 ml). The reaction mixture was stirred for 30 min, extracted with CH_2Cl_2 (3 × 50 ml). The combined organic phases were dried (Na_2SO_4), triethylamine (0.5 ml, 7.1 mmol) was added to the solution and the mixture then concentrated under high vacuum at rt. Toluene (25 ml) was added to the residue followed by the addition of triethylamine (10.5 ml, 75 mmol). The reaction mixture was then refluxed for 30 min. Solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, 10% toluene in hexanes) followed by Kugelrohr distillation [bp 200 °C (oven)/0.05 mmHg] to give the olefin **69** (2.0 g, 6.46 mmol, 96%) as a colourless oil: $[a]_D^{20}$ +48.6 (*c* 1.35, $CHCl_3$); v_{max} film/cm^{-1} 1644, 1472, 1258, 1162, 1104, 1082, 880, 838, 776; δ_H (400 MHz, $CDCl_3$): 5.84 (1H, ddt, *J* 16.8, 10.2, 6.8, C17H), 5.10 (1H, dq, *J* 16.8, 1.5, C18H_AH_B), 5.07 (1H, dq, *J* 10.2, 1.5, C18H_AH_B), 4.87 (1H, dd, *J* 6.0, 1.5, C11H), 3.68 (1H, dd, *J* 11.4, 4.6, C13H), 3.54 (1H, dd, *J* 10.0, 2.5, C15H), 2.33 (1H, dddt, *J* 15.0, 6.2, 2.5, 1.5, C16H_AH_B), 2.17 (1H, dddt, *J* 15.0, 9.8, 6.8, 1.3, C16H_AH_B), 2.00 (1H, ddd, *J* 13.7, 11.6, 6.0, C12H_AH_B), 1.78 (1H, ddd, *J* 13.7, 4.6, 1.6, C12H_AH_B), 0.94 (3H, s, C14Me), 0.90 (9H, s, ^{t}BuSi), 0.86 (3H, s, C14Me), 0.09 and 0.08 (3H each, s, Me_2Si); δ_C (90 MHz, $CDCl_3$): 135.7 (1, C17), 117.9 (0, C10), 116.6 (2, C18), 81.6 (1, C15), 72.5 (1, C13), 64.0 (1, C11), 40.0 (0, C14), 33.8 (2, C12), 33.5 (2, C16), 25.9 (3, 3C, ^{t}BuSi), 22.9 (3, C14Me), 18.1 (0, CSi), 12.6 (3, C14Me), −4.0 (3, MeSi), −4.8 (3, MeSi); *m*/*z* (CI, NH_3) 327 [(M + NH_4)$^+$, 100%]. Found: C, 66.15; H, 10.09; N, 4.62%. $C_{17}H_{31}NO_2Si$ requires C, 66.02; H, 10.03; N, 4.53.

Asymmetric dihydroxylation of alkene 69

Alkene **69** (1.4 g, 4.5 mmol) and dihydroquinine 9-phenanthryl ether[64] (113 mg, 0.225 mmol) were stirred in warm *t*-BuOH (28 ml) until the crystals of ligand dissolved completely. After cooling to rt, water (28 ml), $K_3Fe(CN)_6$ (4.5 g, 13.5 mmol) and K_2CO_3 (1.90 g, 13.5 mmol) were added and the mixture was cooled to 0 °C before addition of potassium osmate dihydrate (89 mg, 0.225 mmol). The reaction mixture was stirred for 3 h at 0 °C, then treated with saturated aqueous Na_2SO_3 (40 ml) and extracted with CH_2Cl_2 (80 + 2 × 40 ml). The combined organic extracts were washed with brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude diols **70a**,**b** as a 1.5 : 1 mixture of diastereoisomers. The residue was purified by column chromatography on SiO_2 (70 g, 0–1.4% MeOH in CH_2Cl_2) to give pure diol **70a** (806 mg, 2.34 mmol, 52%) and pure diol **70b** (402 mg, 1.2 mmol, 26%).

(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-[(2*S*)-2,3-dihydroxypropyl]tetrahydro-5,5-dimethyl-2*H*-pyran (70a).

Mp 53–55 °C (hexanes–Et_2O); $[a]_D^{25}$ +50.0 (*c* 2.0, $CHCl_3$); v_{max} film/cm^{-1} 3442, 1472, 1258, 1100, 1082, 878; δ_H (400 MHz, $CDCl_3$): 4.90 (1H, dd, *J* 6.0, 0.9, C11H), 3.96–3.90 (1H, m, C17H), 3.73–3.63 (3H, m (10 lines), C13H + C15H + C18H_AH_B), 3.51(1H, dd, *J* 11.1, 6.0, C18H_AH_B), 2.00 (1H, ddd, *J* 13.7, 11.6, 6.1, C12H_AH_B), 1.81 (1H, ddd, *J* 13.7, 4.6, 1.3, C12H_AH_B), 1.78–1.64 (2H, m, C16H_2), 1.64–1.40 (2H, br s, C17OH and C18OH), 0.91 (3H, s, C14Me), 0.89 (9H, s, ^{t}Bu), 0.86 (3H, s, C14Me), 0.08 (3H, s, SiMe), 0.07 (3H, s, SiMe); δ_C (100 MHz, $CDCl_3$): 117.6 (0, C10), 81.0 (1, C13 or C15 or C17), 72.2 (1, C13 or C15 or C17), 71.1 (1, C13 or C15 or C17), 65.8 (2, C18), 63.8 (1, C11), 39.8 (0, C14), 33.4 (2, C16 or C12), 32.1 (2, C12 or C16), 25.7 (3, 3C, ^{t}BuSi), 22.6 (3, C14Me), 17.9 (0, CSi), 12.3 (3, C14Me), −4.2 (3, MeSi), −5.0 (3, MeSi); *m*/*z* (CI, NH_3): 361 [(M + NH_4)$^+$, 100%], 343 [(M + H)$^+$, 8], 329 (12), 96 (12). Found: (M + H)$^+$, 344.2258. $C_{17}H_{34}O_4NSi$ requires *M*, 344.2257.

(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-[(2*R*)-2,3-dihydroxypropyl]tetrahydro-5,5-dimethyl-2*H*-pyran (70b).

Mp 36–38 °C ($CHCl_3$); $[a]_D^{25}$ +58.5 (*c* 1.0, $CHCl_3$); v_{max} KBr/cm^{-1} 3426, 1471, 1257, 1103, 1083, 881; δ_H (400 MHz, $CDCl_3$): 4.86 (1H, dd, *J* 6.0, 0.9, C11H), 3.92–3.85 (1H, m, C17H), 3.74 (1H, dd, *J* 10.3, 1.3, C15H), 3.70 (1H, dd, *J* 11.6, 4.7, C13H), 3.65 (1H, dd, *J* 11.1, 3.3, C18H_AH_B), 3.51(1H, dd, *J* 10.8, 7.2, C18H_AH_B), 2.00 (1H, ddd, *J* 13.6, 11.6, 6.1, C12H_AH_B), 1.79 (1H, ddd, *J* 13.6, 4.6, 1.4, C12H_AH_B), 1.67 (1H, ddd, *J* 14.4, 8.9, 1.6, C16H_AH_B), 1.67 (1H, ddd, *J* 14.4, 10.3, 3.6, C16H_AH_B), 1.60–1.40 (2H, br s, C17OH and C18OH), 0.92 (3H, s, C14Me), 0.90 (9H, s, ^{t}Bu), 0.84 (3H, s, C14Me), 0.09 (3H, s, SiMe), 0.08 (3H, s, SiMe); δ_C (100 MHz, $CDCl_3$): 117.7 (0, C10), 78.1 (1, C13 or C15), 72.3 (1, C15 or C13), 69.2 (1, C17), 66.8 (2, C18), 66.8 (1, C11), 39.6 (0, C14), 33.5 (2, C16 or C12), 32.2 (2, C12 or C16), 25.7 (3, 3C, ^{t}BuSi), 22.5 (3C, 14Me), 17.9 (0, CSi), 12.3 (3, C14Me), −4.2 (3, MeSi), −5.0 (3, MeSi); *m*/*z* (CI, NH_3) 361 [(M + NH_4)$^+$, 100%], 343 [(M + H)$^+$, 15], 329 (25), 96 (62). Found: (M + H)$^+$, 344.2258. $C_{17}H_{34}O_4NSi$ requires *M*, 344.2257.

Neither **70a** nor **70b** gave satisfactory microanalytical data.

(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-[(2*S*)-2,3-dimethoxypropyl]tetrahydro-5,5-dimethyl-2*H*-pyran (11)

NaH (310 mg, 7.7 mmol, 60% in oil) was added in one portion to diol **71a** (870 mg, 2.53 mmol), MeI (0.79 ml, 12.6 mmol) and 18-crown-6 (80 mg, 0.30 mmol) in THF (24 ml) at 0 °C. The ice bath was removed and the reaction mixture was sealed and stirred at rt for 24 h. The reaction mixture was then poured onto saturated aqueous NH_4Cl (5 ml), extracted with CH_2Cl_2 (3 × 25 ml) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 50 g, 20% Et_2O in hexanes) to give the title compound **11** (860 mg, 2.31 mmol, 91%) as a white solid: mp 47–49 °C (hexanes–Et_2O); lit. mp 46–48 °C.[25]

(2*S*,4*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-cyano-6-[(2*R*)-2,3-dimethoxypropyl]tetrahydro-5,5-dimethyl-2*H*-pyran (71b)

By the same procedure described above, diol **70b** (390 mg, 1.13 mmol), MeI (0.35 ml, 5.6 mmol) gave the dimethyl ether **71b** (341 mg, 0.91 mmol, 81%) as a white solid: mp 72–74 °C (hexanes–Et_2O); $[a]_D^{21}$ +51.0 (*c* 1.0, $CHCl_3$); v_{max} KBr/cm^{-1} 2953, 2931, 1857, 1473, 1252, 1104, 881, 839; δ_H (360 MHz, $CDCl_3$): 4.86 (1H, dd, *J* 6.1, 1.0, C11H), 3.73 (1H, dd, *J* 1.4, 10.0, C15H), 3.70 (1H, dd, *J* 11.6, 4.7, C13H), 3.48–3.37 (3H, m, C17H, $C18H_2$), 3.48 (3H, s, OMe), 3.38 (3H, s, OMe), 1.99 (1H, ddd, *J* 13.5, 11.6, 6.1, $C12H_AH_B$), 1.78 (1H, ddd, *J* 13.6, 4.7, 1.3, $C12H_AH_B$), 1.67 (1H, ddd, *J* 14.4, 9.3, 1.4, $C16H_AH_B$), 1.49 (1H, ddd, *J* 14.5, 10.3, 2.2, $C16H_AH_B$), 0.91 (3H, s, C14Me), 0.90 (9H, s, ^{t}Bu), 0.83 (3H, s, C14Me), 0.09 (3H, s, SiMe), 0.07 (3H, s, SiMe); δ_C (90 MHz, $CDCl_3$): 117.8 (0, C10), 78.1.0 (1, C15), 76.4 (1, C17), 74.3 (2, C18), 72.4 (1, C13), 63.7 (1, C11), 59.3 (1, OMe), 58.5 (1, OMe), 39.4 (0, C14), 33.6 (2, C12), 32.2 (2, C16), 25.7 (3, 3C, ^{t}BuSi), 22.5 (3, C14Me), 17.9 (0, CSi), 12.3 (3, C14Me), −4.2 (3, Me–Si), −5.0 (3, MeSi); *m*/*z* (CI, isobutane) 372 [$(M + H)^+$, 100%], 340 (5), 314 (5), 287 (5), 240 (5), 213 (20). Found: $(M + H)^+$, 372.2573. $C_{19}H_{38}O_4NSi$ requires *M*, 372.2570. Found: C, 61.56; H, 10.02; N, 3.72%. $C_{19}H_{37}NO_4Si$ requires C, 61.41; H, 10.04; N, 3.77.

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