A synthesis of 18-*O*-methyl mycalamide B

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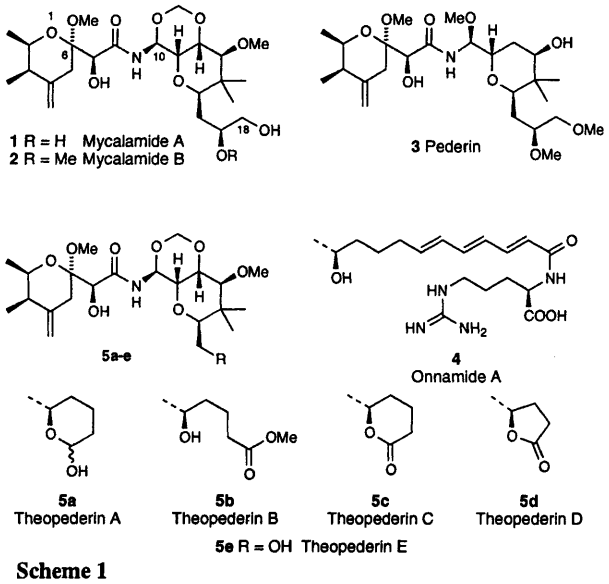
Metallated dihydropyran 9 and the dihydropyranone 10 previously used in a synthesis of the insect toxin pederin were adapted to the synthesis of 18-*O*-methyl mycalamide B, the most potent derivative of the anti-tumour agents isolated from a sponge. Key steps in the synthesis include the oxidation of enol silane 11 from the more hindered face using dimethyldioxirane to introduce the hydroxy group at C-12 and the acylation of 6-lithio-3,4-dihydro-2*H*-pyran 9 with oxalamide 8 to forge the *N*-(1-alkoxy-1-alkyl)amide bridge. Biological tests in human tumour cell lines confirm the potent anti-proliferative effect of 18-*O*-methyl mycalamide B in pM concentrations.

Introduction

Mycalamides A **1** and B **2** were isolated in 1988 from a sponge of the genus *Mycale* collected from the Otago Harbour in New Zealand.[1] Extensive mass spectrometry and NMR experiments[2] revealed a close structural resemblance to the insect toxin pederin **3**[3,4] isolated from the blister beetle *Paederus fuscipes*. The unusual trioxabicyclo[4.4.0]decane ring system is formally derived from oxidative cyclisation involving the methoxy and hydroxy groups of pederin. Their kinship was further underscored when synthetic studies established that pederin and the mycalamides share the same absolute configuration.[5] Recently, the pederin family has expanded with the discovery of onnamide A **4**[6,7] and the theopederins **5a–e**[8]



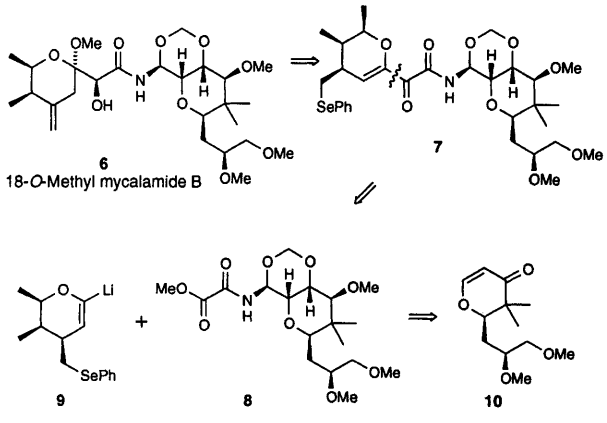
Scheme 1

(Scheme 1) from sponges of the genus *Theonella*. The significance of the mycalamides, onnamides and theopederins in sponge physiology is unclear although it has been suggested that the occurrence of closely related compounds in such taxonomically remote animals as sponges and terrestrial beetles may indicate connection by a common producer, possibly a symbiotic micro-organism.[9]

The mycalamides reveal potent *in vitro* cytotoxicity and *in vivo* antitumour efficacy against several leukemia and solid tumour model systems as well as antiviral activity.[1] In addition, 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.[10] Structure–activity data have been gleaned from simple alkyl, acyl and silyl derivatives prepared[11–14] from the naturally occurring mycalamides. For example, when the amidic NH and the 7-OH were methylated, the activity was reduced by a factor of 10^3 whereas methylation of the 17-OH and 18-OH, the side-chain constitution found in pederin, increased activity by 10^3. It appears that the *N*-(1-alkoxy-1-alkyl)amide bridge plays a crucial role in the biological activity of the mycalamides, possibly by eliminative cleavage of the C–O bond at C-10 resulting in the formation of an acylimine which could subsequently act as an alkylating agent.

Mode of action studies[11] confirm that the mycalamides, like pederin, are protein synthesis inhibitors. Mycalamide A also disrupted DNA metabolism but did not intercalate into DNA itself. A correlation between their relative ability to inhibit protein synthesis, cytotoxicity and their *in vivo* efficacy suggests that inhibition of protein synthesis may be a major determinant of their anti-tumour activity.[11]

Total syntheses of onnamide A[15] and mycalamides A and B[5] have been reported as well as syntheses of various fragments.[16–19] We now report a synthesis of 18-*O*-methyl mycalamide B **6** based on the retrosynthetic analysis shown in Scheme 2. The key step in the sequence is the acylation of



Scheme 2

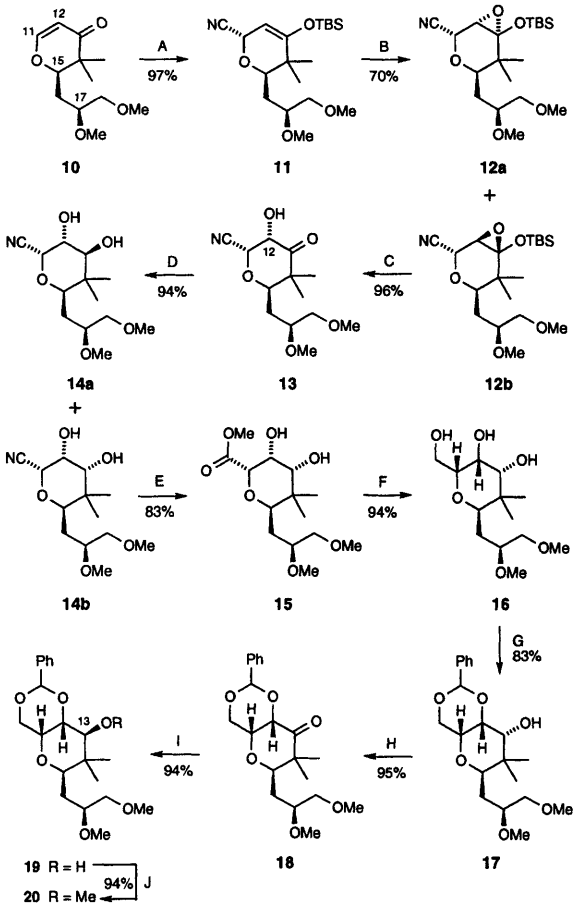
lithiated dihydro-2*H*-pyran **9** by the ester group in **8** to forge the *N*-(1-alkoxy-1-alkyl)amide bridge in intermediate **7**. In turn, the trioxabicyclo[4.4.0]decane **8** is constructed from the

dihydropyranone **10**. Our choice of the key step and intermediates **9** and **10** is significant: together they were the foundation of our synthesis of pederin[20] and since the second side of the bread takes less time to toast, we hoped that our pederin synthesis could be quickly adapted to the the synthesis of 18-*O*-methyl mycalamide B **6**—the derivative with the highest anti-tumour potency identified to date.[12]

Results and discussion

Introduction of stereogenic centres at C-11, C-12 and C-13

Dihydropyranone **10** was prepared on a large scale from (*S*)-(−)-malic acid as described previously.[20,21] In order to fuse a 1,3-dioxane ring onto dihydropyranone **10** we had to create three contiguous stereogenic centres on its upper periphery. First, a single carbon at C-11 (mycalamide numbering) had to be introduced followed by a hydroxy function onto the same face at the adjacent carbon (C-12). The single carbon was appended with very high 1,3-asymmetric induction by conjugate addition of *tert*-butyldimethylsilyl cyanide (TBSCN) to the dihydropyranone catalysed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) to give enol silane **11** in 97% yield (Scheme 3). A large number of conditions were



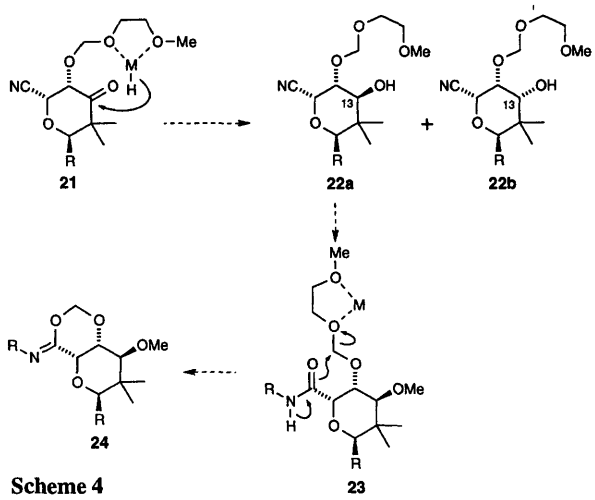
Scheme 3 *Reagents and Conditions*:

A	97%	TBSCN, TBSOTf, CH_2Cl_2, 0°C, 3 h.
B	70%	Oxone, 18-crown-6, acetone, $NaHCO_3$, PhH–H_2O, 3–5°C.
C	96%	HF, MeCN, rt, 7 h.
D	94%	BH_3•SMe_2, THF, rt, 20 min.
E	83%	$HClO_4$, MeOH–H_2O, Δ, 30 h.
F	94%	LAH, THF, 0°C, 10 min; Δ, 25 min.
G	83%	$PhCH(OMe)_2$, PTSA, CH_2Cl_2, rt, 2 h;
H	95%	Swern oxidation.
I	94%	$NaBH(OAc)_3$, $CeCl_3$•$7H_2O$, MeOH, 0°C, 30 min;
J	94%	Me_2SO_4, Bu_4NHSO_4, 50% NaOH, PhMe, rt, 2 h.

9 steps, 33% overall

investigated for the critical oxidation of enol silane **11**. Various epoxidising agents [peracids,[22,23] peroxybenzimidic acid,[24] 2-benzenesulfonyl-3-(4-nitrophenyl)oxaziridine[25]] and dihydroxylating agents (OsO_4) invariably returned a mixture of α-hydroxyketones with the major product having the undesired stereochemistry at C-12. However, oxidation of the enol silane with dimethyldioxirane,[26,27] generated *in situ* under phase transfer conditions,[28] gave the diastereoisomeric oxiranes in a ratio of 3.5:1 in favour of the desired isomer **12a** (70% yield).† The oxiranes **12a,b** were easily separated by column chromatography and the desired crystalline isomer **12a** could be stored for months in the cold without decomposition. Hydrolysis of **12a** with HF then gave α-hydroxyketone **13** in 96% yield.

Introduction of the third stereogenic centre at C-13 by reduction of the ketone in **13** was not easy. In our original plan (Scheme 4) we intended to use the coordinating properties



Scheme 4

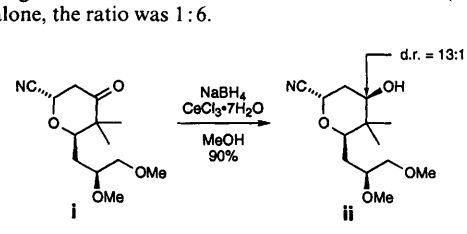
of the (2-methoxyethoxy)methyl group[29–33] to first direct the stereochemistry of reduction and then later serve as a means for triggering 1,3-dioxane ring formation under Lewis acid catalysis. Unfortunately, a wide range of metal hydride reducing agents [*e.g.* $ZnBH_4$, $NaBH_4$, $NaBH_4$–$CeCl_3$, LiBH(*sec*-Bu)$_3$, $LiBHEt_3$, $NaBH(OAc)_3$] all returned the incorrect isomer **14b** as the exclusive product.‡ Attempts to use single-electron reducing conditions (Mg–MeOH, SmI_2, Ca–NH_3) gave messy reactions. The only reducing agents which gave appreciable amounts of the desired isomer were $NaBH_3CN$ in MeOH at room temp. (**14a**:**14b** = 1:3, 70% yield) and methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide)–*tert*-BuMgCl in toluene[34,35] at 0 °C (**14a**:**14b** = 2:3, 38%). When equally dismal results were later obtained in the attempt to cyclise **23** to **24** (Scheme 4), the route was abandoned in favour of the extended detour depicted in Scheme 3.

Reduction of the α-hydroxyketone **13** with BH_3•SMe_2 gave an inseparable mixture of diastereoisomeric alcohols (**14a**:**14b** = 1:13, 94% yield).§ On treatment of the mixture

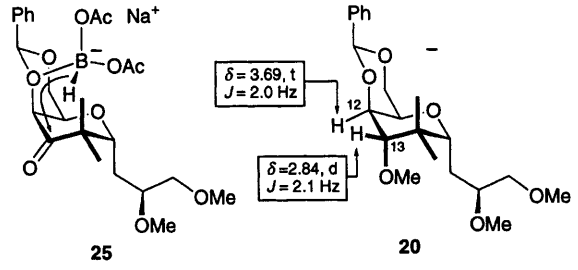
† Previous workers have noted dramatic changes in facial selectivity of epoxidation using peroxybenzimidic acid in place of peracids[39,40] but we are unaware of similar observations with dimethyldioxirane.

‡ Attempts to invert the stereochemistry of the highly hindered alcohol in **14a** by a Mitsunobu reaction failed.

§ In our synthesis of pederin,[20] the ketone **i** was reduced with $NaBH_4$ in the presence of $CeCl_3$ to give the desired equatorially oriented alcohol **ii** as the major product. However, with compound **13**, the same conditions gave an unfavourable ratio of **14a**:**14b** = 1:9 (95%). With $NaBH_4$ alone, the ratio was 1:6.



with perchloric acid in aqueous MeOH, the nitrile function in isomer **14b** was selectively transformed to the ester **15** leaving its diastereoisomer **14a** untouched whereupon chromatographic separation was easily achieved.¶ After reduction of the ester function, triol **16** was converted into its benzylidene acetal derivative **17**‖ and the remaining secondary alcohol function oxidised to the corresponding crystalline ketone **18**. Now reduction of the ketone with $NaBH(OAc)_3$ in the presence of $CeCl_3$ was highly stereoselective (25:1) leading to the desired stereochemistry at C-13 in alcohol **19**. The stereochemistry of the reduction can be rationalised in terms of intramolecular delivery of hydride** in the conformer **25** (Scheme 5). Removal

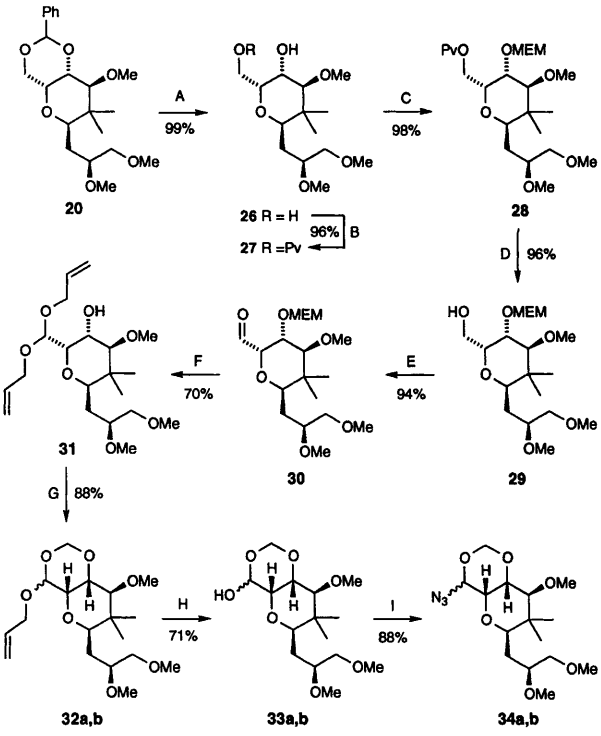


Scheme 5

of minor impurities by crystallisation followed by *O*-methylation gave the crystalline methyl ether **20** whose relative configuration and conformation were assigned on the basis of the vicinal coupling constants for 12-H and 13-H (*J* 2.1 and 2.0 Hz respectively) which accord with equatorial disposition of all three protons at C-11, C-12 and C-13.

Construction of the 2,4,7-trioxabicyclo[4.4.0]decane ring

In the next phase of our synthesis, the benzylidene acetal was hydrolysed (Scheme 6, step A) and the C-13 secondary hydroxy function protected as its (2-methoxyethoxy)methyl (MEM) ether **28** by a standard three-step sequence. Dess–Martin oxidation followed by immediate acid-catalysed acetalisation with allyl alcohol was accompanied by partial destruction of the MEM ether. In order to complete the removal of the MEM group, $ZnCl_2$ was added and the mixture heated for a further 5 h whereupon the diallyl acetal **31** was obtained in 70% yield for



Scheme 6 *Reagents and Conditions:*

A	99%	PTSA, MeOH, Δ, 6 h.
B	96%	PvCl, Pyr, CH_2Cl_2, rt, 4 h.
C	98%	MEMCl, Bu_4NI, DMAP, $(i\text{-}Pr)_2NEt$, PhMe, 75–80°C, 15 h.
D	96%	LAH, Et_2O, 0°C, 25 min.
E	94%	Dess–Martin periodinane, CH_2Cl_2, rt, 1 h.
F	70%	$H_2C{=}CH{-}CH_2OH$, PTSA, CH_2Cl_2, Δ, 22 h; then add $ZnCl_2$, Δ, 5 h.
G	88%	$(HCHO)_n$, HCl(g), CH_2Cl_2, rt, 85 min.
H	71%	$RhCl[PPh_3]_3$, DABCO, EtOH–H_2O, Δ, 1.75 h; $Hg(OAc)_2$, THF–H_2O.
I	88%	MsCl, DMAP, NEt_3, CH_2Cl_2; TASF, $TMSN_3$, CH_2Cl_2, −70→0°C, 8.5 h.

12 steps, 32% overall

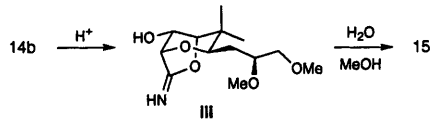
the two steps. The desired 1,3-dioxane ring was then introduced in a single step on treatment of **31** with paraformaldehyde in the presence of HCl to give the allyl acetals **32a,b** in 88% yield as a separable mixture of diastereoisomers (1:4) along with a further 7% yield of the hemiacetals **33a,b** (2:1 mixture of diastereoisomers). Since deliberate attempts to secure **33a,b** by acid-cataysed hydrolysis of **32a,b** led to messy reactions, a milder two-step procedure was adopted which was reproducible and efficient. The allyl ether was first isomerised with Wilkinson's catalyst and the resultant enol ether hydrolysed with the aid of mercuric acetate[36] to give the hemiacetals **33a,b** in 71% yield, again as a 2:1 mixture of diastereoisomers.

The last hurdle in the sequence was displacement of the hydroxy group in **33a,b** by an azido group. Attempts to use a Mitsunobu reaction failed to give the desired azides in a single step[37] and so various two-step procedures were examined involving prior activation of the hydroxy group. The best of the established procedures examined had been used by Hong and Kishi—displacement of a mesylate by Bu_4NN_3—but in our hands the yields ranged from 20% (typically) to 72% (rarely) and we were unable to identify the cause of the caprice. We therefore developed a new method which, to our knowledge, is novel: the crude mesylate derived from the mixture of hemiacetals **33a,b** was treated with trimethylsilyl azide ($TMSN_3$) in the presence of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[38] to give the azides **34a,b** as a mixture of diastereoisomers in the ratio 1:1 to 1:2 depending on the reaction conditions. The isomers could be separated for purposes of characterisation but in practice it was best to carry the mixture of azides forward to the next stage of the synthesis.

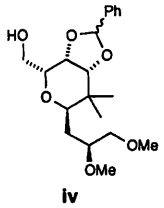
Construction of the *N*-(1-alkoxy-1-alkyl)amide bridge

Catalytic reduction of the azides **34a,b** gave a sensitive mixture

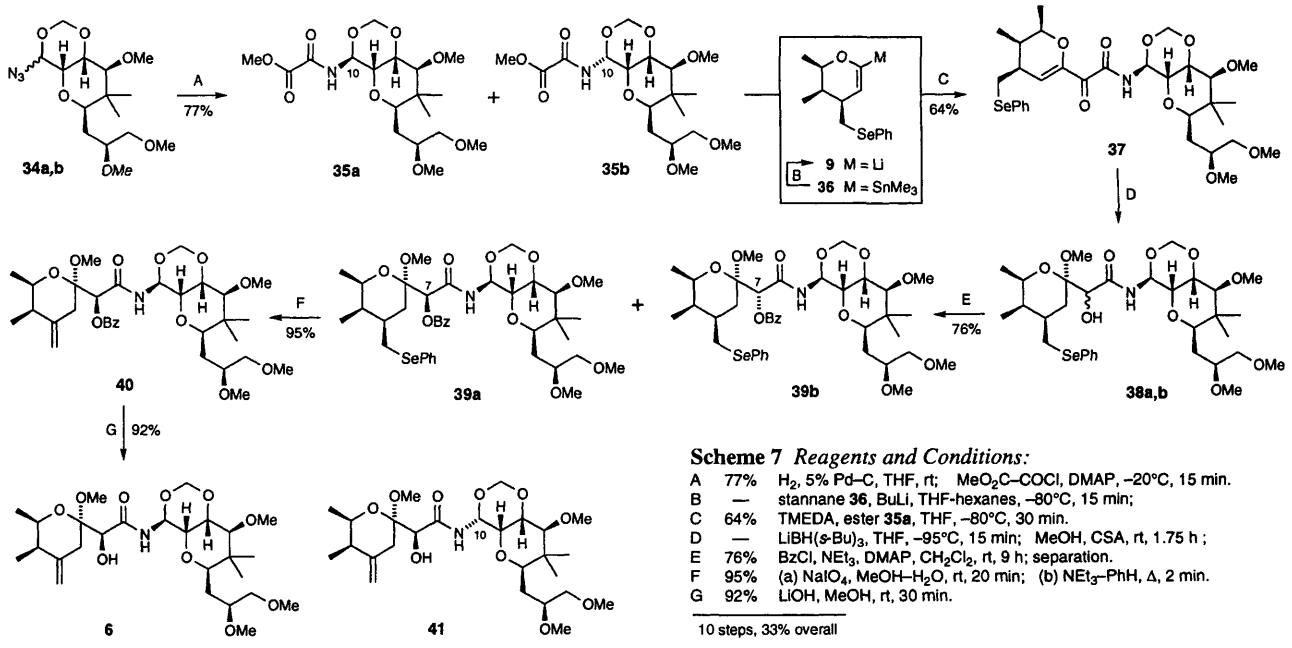
¶ The faster rate of methanolysis of diastereoisomer **14b** presumably reflects intramolecular addition of the C-13 hydroxy function to the cyano function to form the imino lactone **iii** which then undergoes hydrolysis and transesterification to the ester **15**.



‖ Benzylidenation of triol **16** was accompanied by formation of up to 15% of the dioxolane derivative **iv**. Separation of **iv** from the desired 1,3-dioxane derivative **17** could only be achieved by selective tritylation of the primary alcohol in **iv** followed by column chromatography (see Experimental section) or **iv** was selectively destroyed during the succeeding oxidation (step H, Scheme 3).



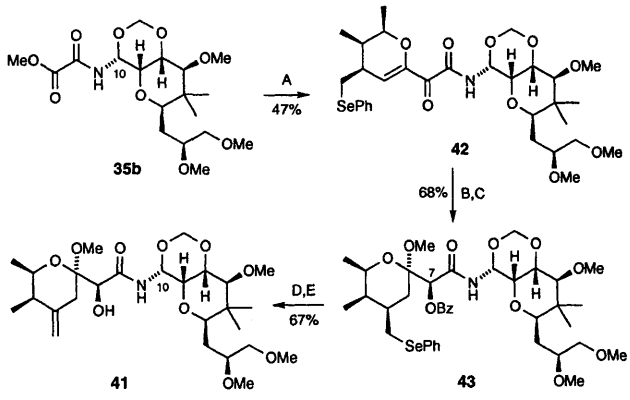
** Similar observations were made by Hong and Kishi for an analogous reduction performed in their synthesis of onnamide.[15]



Scheme 7 *Reagents and Conditions:*

A	77%	H_2, 5% Pd–C, THF, rt; MeO_2C–COCl, DMAP, –20°C, 15 min.
B	—	stannane **36**, BuLi, THF-hexanes, –80°C, 15 min;
C	64%	TMEDA, ester **35a**, THF, –80°C, 30 min.
D	—	LiBH(*s*-Bu)$_3$, THF, –95°C, 15 min; MeOH, CSA, rt, 1.75 h ;
E	76%	BzCl, NEt_3, DMAP, CH_2Cl_2, rt, 9 h; separation.
F	95%	(a) $NaIO_4$, MeOH–H_2O, rt, 20 min; (b) NEt_3–PhH, Δ, 2 min.
G	92%	LiOH, MeOH, rt, 30 min.

10 steps, 33% overall



Scheme 8 *Reagents and Conditions:*

A	47%	lithium reagent **9**, TMEDA, THF, –80°C, 30 min.
B	—	LiBH(*s*-Bu)$_3$, THF, –95°C, 15 min; MeOH, CSA, rt, 1.75 h ;
C	68%	BzCl, NEt_3, DMAP, CH_2Cl_2, rt, 9 h; separation.
D	—	(a) $NaIO_4$, MeOH–H_2O, rt, 20 min; (b) NEt_3–PhH, Δ, 2 min.
E	67%	LiOH, MeOH, rt, 45 min.

7 steps, 21% overall

of aminals (Scheme 7) which were acylated with methyl oxalyl chloride in the presence of 4-dimethylaminopyridine (DMAP) to afford the diastereoisomeric methyl oxalamides **35a,b** (1:2) in 77% yield. The diastereoisomers were separated by column chromatography and the minor crystalline diastereoisomer **35a** having the correct stereochemistry at C-10 was added to a solution of the dihydro-2*H*-pyranyllithium reagent **9** in the presence of excess *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to give the acylated dihydro-2*H*-pyran derivative **37** in 64% yield. Reduction of the keto function with LiBH(*sec*-Bu)$_3$ at −95 °C followed by acid-catalysed addition of MeOH to the dihydropyran gave a mixture of four diastereoisomeric hydroxy acetals which were separated by preparative thin layer chromatography after benzoylation. The two major diastereoisomers **39a** (64%) and **39b** (28%) were assigned the (6*R*,7*S*) and (6*R*,7*R*) stereochemistry, respectively, based on comparison of the chemical shifts of their 7-H signals with those previously observed in our synthesis of pederin.[20] To complete the synthesis of 18-*O*-methyl mycalamide B, the selenoxide derived from oxidation of **39a** was heated briefly to generate the C-4 methylene and the benzoate hydrolysed—both steps taking place in excellent yield. The product gave identical ^{1}H and ^{13}C NMR data to those reported for 18-*O*-methyl mycalamide B by Perry and co-workers.[12] By the identical procedure, 10-*epi*-18-*O*-methyl mycalamide B **41** was prepared from the methyl oxalamide diastereoisomer **35b** (Scheme 8) (see Experimental section).

Biological evaluation of 18-*O*-methyl mycalamide B

In standard mitogenesis assays using quiescent murine fibroblasts transfected with the human epidermal growth factor (EGF) receptor, 18-*O*-methyl mycalamide B **6** inhibited DNA synthesis in response to 40 pM EGF with an IC_{50} of 0.4 ng ml^{-1} (range 0.3–0.5). The compound showed similar potency when tested in anchorage-dependent growth assays using an epidermoid (A431), a colon (HT-29) or a mammary (MCF-7) carcinoma cell line. After four days growth with continuous exposure to the compound, IC_{50} values (mean, ng ml^{-1}) were A431: 0.14 (range 0.09–0.19); HT-29: 0.14 (range 0.13–0.15); MCF-7: 0.11. Thus, the cytotoxicity of 18-*O*-methyl mycalamide B was similar to that previously reported for mycalamides A and B.[1,2] The latter inhibit the *in vitro* replication of murine lymphoma P388 cells (IC_{50} 3.0 ± 1.3 and 0.7 ± 0.3 ng ml^{-1} respectively) and human HL-60, HT-29 and A549 cells (IC_{50} < 5 nM).[11] In contrast, we found that 10-*epi*-18-*O*-methyl mycalamide B **41** was over three orders of magnitude less potent than its diastereoisomer. In mitogenesis assays, it had a mean IC_{50} value (ng ml^{-1}) of 1350 (range 1200–1500) and in proliferation assays mean IC_{50} values were A431: 575 (range 480–670); HT-29: 450 (range 380–520); MCF-7: 355 (range 290–420). Full details of the biological activity of 18-*O*-methyl mycalamide B and its 10-*epi* diastereoisomer will be published elsewhere.

Experimental

IR spectra were recorded using a Perkin-Elmer 1600 series FT-IR spectrophotometer using a thin film supported on NaCl plates or KBr discs where stated. Details are reported as ν_{max} in cm^{-1}, followed by an intensity descriptor: s = strong, m = medium, w = weak or br = broad. ^{1}H and ^{13}C NMR spectra were recorded in Fourier Transform mode at the field strength specified. All spectra were obtained in $CDCl_3$ 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 or δ_C = 77.2) as the internal standard. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Coupling con-

stants (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°. Mycalamide numbering was used throughout in assigning NMR signals. Low (LRMS) and high (HRMS) resolution mass spectra were run on a VG 70-250-SE 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 ^1H and ^{13}C NMR spectroscopy unless otherwise stated.

(2*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-cyano-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-5,6-dihydro-2*H*-oxine 11

A solution of enone **10** (5.28 g, 23.13 mmol) and *tert*-butyldimethylsilyl cyanide (3.54 g, 24.63 mmol) in CH_2Cl_2 (60 cm^3) was stirred at 0 °C under N_2. *tert*-Butyldimethylsilyl triflate (0.16 cm^3, 0.7 mmol, 0.03 equiv.) was added. The reaction mixture was stirred for 3 h and then triethylamine (0.63 cm^3, 4.53 mmol) was added. The mixture was poured onto sat. aqueous $NaHCO_3$ (50 cm^3). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (80 g, hexanes: EtOAc 5–10%) to give the silyl enol ether **11** (8.29 g, 97%) as a colourless oil, $[\alpha]_D$ −34.1 (*c* 2.23 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1658 (s); δ_H(270 MHz, $CDCl_3$) 5.02 (1 H, d, *J* 4.1, 11-H), 4.60 (1 H, d, *J* 4.1, 12-H), 3.67 (1 H, dd, *J* 10.0 and 2.0, 15-H), 3.64–3.48 (3 H, m, 17-H, 18-H_2), 3.42 (3 H, s, OMe), 3.40 (3 H, s, OMe), 1.91–1.60 (2 H, m, 16-H_2), 1.01 (6 H, s, 14-Me), 0.95 (9 H, s, *tert*-BuSi), 0.21 and 0.18 (3 H each, s, Me_2Si); δ_C(67.5 MHz, $CDCl_3$) 159.9 (0), 118.4 (0), 94.1 (1), 78.4 (1), 77.8 (1), 72.9 (2), 63.3 (1), 59.4 (3), 57.2 (3), 39.3 (0), 30.3 (2), 25.7 (3), 20.8 (3), 19.3 (3), 18.3 (0), −4.9 (3), −4.2 (3); m/z (CI, NH_3) 387 [(M + NH_4)$^+$, 26%], 370 [(M + H)$^+$, 5], 343 (100) (EI, Found: M$^{+\cdot}$, 369.2333. $C_{19}H_{35}NO_4Si$ requires *M*, 386.2335).

(2*R*,3*S*,4*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-cyano-3,4-epoxy-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyloxane 12a

Oxone® was added in 7 portions (7 × 26 g, 296 mmol) in 30 min intervals to a vigorously stirred mixture of enol ether **11** (8.25 g, 22.3 mmol), 18-crown-6 (850 mg, 3.2 mmol, 0.15 equiv.), $NaHCO_3$ (85 g), acetone (105 cm^3), benzene (400 cm^3) and water (530 cm^3) at 5 °C. The reaction mixture was stirred at 3–5 °C for 14 h and allowed to warm up to 14 °C over 6 h. Then the mixture was treated with water (750 cm^3) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 300 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on SiO_2 (150 g, hexanes: ether 5–80% with 0.1% Et_3N) to give the epoxide **12a** as a colourless oil. Crystallisation from pentane gave the diastereoisomerically pure epoxide **12a** (6.00 g, 70%) as white crystals, mp 64–66 °C (pentane); $[\alpha]_D$ −1.9 (*c* 1.79 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3020 (s), 2400 (w), 1217 (s), 758 (s); δ_H(270 MHz, $CDCl_3$) 4.97 (1 H, d, *J* 3.9, 11-H), 3.56–3.35 (4 H, m), 3.43 (1 H, d, *J* 3.9, 12-H), 3.39 (3 H, s, OMe), 3.38 (3 H, s, OMe), 1.75 (1 H, ddd, *J* 1.7, 8.7 and 14.5, 16-H), 1.56 (1 H, ddd, *J* 4.6, 10.4 and 14.5, 16-H), 1.07 (3 H, s, 14-Me), 1.02 (3 H, s, 14-Me), 0.90 (9 H, s, *tert*-BuSi), 0.09 and 0.18 (3 H each, s, Me_2Si); δ_C(67.5 MHz, $CDCl_3$) 115.4 (0), 86.1 (0), 77.8 (1), 75.4 (1), 72.8 (2), 63.2 (1), 59.3 (3), 58.3 (1), 57.1 (3), 39.0 (0), 30.2 (2), 25.7 (3), 18.6 (3), 17.9 (0), 16.6 (3), −3.4 (3), −3.5 (3); m/z (CI, NH_3) 403 [(M + NH_4)$^+$, 100%], 386 [(M + H)$^+$, 54] [Found: (M + H)$^+$, 386.2376. $C_{19}H_{36}NO_5Si$ requires *M*, 386.2363].

(2*R*,3*S*,6*R*)-2-Cyano-3-hydroxy-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyloxan-4-one 13

A solution of HF (40%, 5 cm^3) in MeCN (20 cm^3) was added to a stirred solution of epoxide **12a** (5.84 g, 15.15 mmol) in MeCN (30 cm^3). The reaction mixture was stirred for 7 h at room temp., then poured into sat. aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 150 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on SiO_2 (100 g, hexanes: EtOAc 10–50%) to give the hydroxy ketone **13** (3.95 g, 96%) as a colourless oil which solidified on refrigeration (mp 38–42 °C); $[\alpha]_D$ +102.2 (*c* 1.0 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3478 (br s), 3016–2829 (s), 1721 (s), 1467 (s), 1393 (s), 1340 (m), 1291 (m), 1248 (m), 1220 (s), 1093 (s); δ_H(270 MHz, $CDCl_3$) 5.27 (1 H, d, *J* 7.9, 11-H), 4.64 (1 H, dd, *J* 4.8 and 7.9, 12-H), 3.91 (1 H, d, *J* 4.8, OH), 3.83 (1 H, dd, *J* 9.7 and 2.4, 15-H), 3.58–3.34 (3 H, m, partially concealed, 17-H, 18-H_2), 3.41 (3 H, s, OMe), 3.38 (3 H, s, OMe), 1.94 (1 H, m, 16-H), 1.84 (1 H, ddd, *J* 14.8, 8.1 and 2.4, 16-H), 1.24 (3 H, s, Me), 1.14 (3 H, s, Me); δ_C(67.5 MHz, $CDCl_3$) 208.2 (0), 114.3 (0), 80.3 (1), 77.3 (1), 72.6 (1), 71.3 (1), 69.1 (1), 59.3 (3), 57.3 (3), 49.7 (0), 30.2 (2), 19.1 (3), 18.9 (3); m/z (CI, NH_3) 289 [(M + NH_4)$^+$, 100%] (Found: C, 57.52; H, 7.77; N, 5.28. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.80; N, 5.16%).

Reduction of ketone 13

To a stirred solution of ketone **13** (1.88 g, 6.93 mmol) in THF (40 cm^3) at room temp. under N_2 was added BH_3·SMe_2 (0.9 cm^3, 9.18 mmol) over 30 s. The temperature of the reaction mixture rose to 35 °C. The solution was stirred for 20 min, poured into sat. aqueous $NaHCO_3$ (60 cm^3) and then extracted with CH_2Cl_2 (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was filtered through a pad of SiO_2 (2 g) to give the diols **14a,b** (1:13 mixture of C-4 epimers, 1.78 g, 94%) as a white solid. For analysis both isomers were separated by chromatography on SiO_2 (CH_2Cl_2: MeOH, 1–5%).

(2*R*,3*R*,4*R*,6*R*)-2-Cyano-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyloxane-3,4-diol 14b. Mp 110–112 °C (AcOEt–hexanes); $[\alpha]_D$ +86.3 (*c* 0.5 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3440 (br s), 3016–2830 (s), 1475 (s), 1464 (s), 1394 (s), 1371 (s), 1292 (s), 1260 (s), 1229 (s), 1073 (s); δ_H(270 MHz, $CDCl_3$) 4.80 (1 H, d, *J* 6.75, 11-H), 4.03 (1 H, m, 12-H), 3.94 (1 H, dd, *J* 2.4 and 10.3, 15-H), 3.65–3.37 (4 H, m, 13-H, 17-H, 18-H_2), 3.42 (3 H, s, OMe), 3.40 (3 H, s, OMe), 3.07 (1 H, d, *J* 9.2, OH, D_2O exchange), 2.58 (1 H, dd, *J* 2.0 and 3.7, OH, D_2O exchange), 1.80–1.60 (2 H, m, 16-H_2), 1.02 (3 H, s, OMe), 0.96 (3 H, s, OMe); δ_C(67.5 MHz, $CDCl_3$) 118.0 (0), 77.9 (1), 75.9 (1), 72.8 (2), 72.5 (1), 66.2 (1), 63.9 (1), 59.4 (3), 57.2 (3), 38.4 (0), 29.2 (2), 23.2 (3), 18.8 (3); m/z (CI, NH_3) 291 [(M + NH_4)$^+$, 100%], 274 [(M + H)$^+$, 10%] (Found: C, 56.70; H, 8.54; N, 4.97. $C_{13}H_{23}NO_5$ requires C, 57.13; H, 8.48; N, 5.12%).

(2*R*,3*R*,4*S*,6*R*)-2-Cyano-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyloxane-3,4-diol 14a. $[\alpha]_D$ +106.2 (*c* 1.9 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3424 (br s); δ_H(270 MHz, $CDCl_3$) 4.89 (1 H, d, *J* 6.2, 11-H), 4.47 (1 H, br, OH), 3.89 (1 H, br, OH), 3.72 (1 H, dd, *J* 6.0 and 9.5, 12-H), 3.58–3.36 (5 H, m), 3.37 (3 H, s, OMe), 3.36 (3 H, s, OMe), 1.80 (1 H, ddd, *J* 1.8, 7.9 and 14.1, 16-H), 1.68 (1 H, ddd, *J* 3.9, 10.0 and 14.3, 16-H), 0.86 and 0.96 (3 H each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 116.4 (0), 78.9 (1), 77.8 (1), 77.1 (1), 72.8 (2), 69.0 (1), 66.9 (1), 59.3 (3), 57.1 (3), 40.1 (0), 29.5 (2), 22.5 (3), 13.2 (3); m/z (CI, NH_3) 291 [(M + NH_4)$^+$, 100%], 274 [(M + H)$^+$, 45].

(2*R*,3*R*,4*R*,6*R*)-6-[(2*S*)-2,3-Dimethoxypropyl]-5,5-dimethyl-2-methoxycarbonyloxane-3,4-diol 15

A solution of perchloric acid (2 cm^3, 60%) in MeOH (30 cm^3) was added to a stirred solution of a mixture of nitriles **14a,b** (2.71 g, 9.9 mol, 13:1 mixture of isomers) in MeOH (40 cm^3). The reaction mixture was heated at reflux for 30 h, cooled to room temp., diluted with CH_2Cl_2 (200 cm^3) and washed with sat. aqueous $NaHCO_3$ (150 cm^3). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated.

The residue was chromatographed on SiO_2 (75 g, CH_2Cl_2–MeOH, 1–5%) to give the ester **15** (2.53 g, 83%) as a colourless oil along with recovered starting material **14a,b** (340 mg, 13%), $[\alpha]_D$ +70.8 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3442 (br s), 3012–2828 (s), 1751 (s), 1708 (s), 1475 (m), 1439 (m), 1392 (m), 1371 (m), 1341 (m), 1290 (s), 1231 (s), 1202 (s), 1121 (s), 1088 (s), 1046 (s), 922 (m); δ_H(270 MHz, $CDCl_3$) 4.44 (1 H, d, *J* 6.2, 11-H), 4.23–4.15 (2 H, m, 12-H + OH, appeared as 1 H, dd, *J* 6.75 and 2.4, after treatment with D_2O), 3.67–3.35 (4 H, m, overlapping), 3.82 (3 H, s, OMe), 3.41 (6 H, s, 2 overlapping OMe), 2.31 (1 H, dd, *J* 4.1 and 1.5, OH, D_2O exchange), 1.63 (2 H, m, 16-H_2), 0.98 (3 H, s, Me), 0.96 (3 H, s, Me); δ_C(67.5 MHz, $CDCl_3$) 173.8 (0), 78.1 (1), 77.3 (1), 73.6 (2), 71.6 (1), 71.5 (1), 67.5 (1), 59.4 (3), 57.2 (3), 52.4 (3), 38.5 (0), 29.8 (2), 23.6 (3), 19.4 (3); *m/z* (CI, NH_3) 324 [$(M + NH_4)^+$, 100%], 307 [$(M + H)^+$, 83], 292 (15) [Found: $(M + H)^+$, 307.1747. $C_{14}H_{27}O_7$ requires *M*, 307.1758].

(2*R*,3*R*,4*R*,6*R*)-2-(Hydroxymethyl)-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyloxane-3,4-diol 16

Lithium aluminium hydride (LAH) (440 mg, 10.6 mmol) was added to a stirred solution of ester **15** (2.1 g, 6.85 mmol) in THF (62 cm^3) at 0 °C. After 10 min the reaction mixture was heated under reflux for 25 min, cooled to 0 °C and carefully quenched with a mixture of water (4 cm^3) and THF (10 cm^3). The mixture was stirred for 2 h whereupon the white milky suspension was concentrated *in vacuo*. The residue was treated with MeOH (250 cm^3) and filtered through a pad of Celite. The filtrate was concentrated and the residue chromatographed on SiO_2 (14 g, CH_2Cl_2:MeOH 2–20%) to give the triol **16** (1.8 g, 94%) as a white solid, mp 124–125 °C (ethyl acetate–hexanes); $[\alpha]_D$ +78.8 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3624–3425 (br s), 3011–2829 (s), 1464 (m), 1390 (m), 1368 (m), 1337 (m), 1214 (s), 1091 (s), 1060 (s), 1034 (s), 968 (m), 925 (m); δ_H(270 MHz, $CDCl_3$) 4.20–4.10 (2 H, m, overlapping), 4.06–3.96 (1 H, m), 3.82 (1 H, dd, *J* 10.1 and 3.4), 3.73 (1 H, m, on treatment with D_2O to dd, *J* 13.8 and 4.0, 10-H), 3.63–3.35 (3 H, m, overlapping), 3.42 (3 H, s, OMe), 3.39 (3 H, s, OMe), 2.92 (1 H, d, *J* 4.2, D_2O exchange, OH), 2.72 (1 H, d, *J* 7.0, D_2O exchange), 1.67 (2 H, m, 16-H_2), 0.99 (3 H, s, Me), 0.97 (3 H, s, Me); δ_C(67.5 MHz, $CDCl_3$) 78.4 (1), 76.3 (1), 75.6 (1), 74.9 (2), 69.1 (1), 66.8 (1), 59.9 (2), 59.3 (3), 57.3 (3), 38.4 (0), 30.5 (2), 23.3 (3), 19.8 (3); *m/z* (CI, NH_3) 296 [$(M + NH_4)^+$, 60%], 279 [$(M + H)^+$, 100] (Found: C, 55.48; H, 9.10. $C_{13}H_{26}O_6$ requires C, 56.10; H, 9.42%).

(1*R*,6*R*,8*R*,10*R*)-9,9-Dimethyl-8-[(2*S*)-2,3-dimethoxypropyl]-3-phenyl-2,4,7-trioxabicyclo[4.4.0]decan-10-ol 17

A solution of triol **16** (1.8 g, 6.47 mmol), benzaldehyde dimethyl acetal (1.7 cm^3, 11.3 mmol, 1.7 equiv.) and toluene-*p*-sulfonic acid (PTSA) (43 mg, 0.23 mmol, 0.035 equiv.) in CH_2Cl_2 (62 cm^3) was stirred at room temp. for 2 h. Solid $NaHCO_3$ (3 g) was added and then the mixture was treated with solid $MgSO_4$ and filtered through a pad of Celite. The filtrate was concentrated and the crude mixture of isomeric 6- and 5-membered ring benzylidene acetals (5.2:1) was dissolved in CH_2Cl_2 (5 cm^3) and treated with pyridine (0.25 cm^3, 3.09 mmol) and Ph_3CCl (0.4 g, 1.43 mmol, 0.22 equiv.). The reaction mixture was stirred at room temp. overnight, poured into sat. aqueous $NaHCO_3$ (20 cm^3) and extracted with CH_2Cl_2 (3 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (60 g, hexanes:AcOEt 20–80%) to give the major 6-membered benzylidene acetal **17** (1.96 g, 83%) as a colourless oil, $[\alpha]_D$ +55.8 (*c* 1.27 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3473 (s), 1454 (s), 1401 (s), 1367 (s), 1104 (s); δ_H(270 MHz, $CDCl_3$) 7.45–7.55 (2 H, m), 7.30–7.45 (3 H, m), 5.47 (1 H, s, Ph-C*H*), 4.25 (1 H, dd, *J* 1.4 and 12.6, 10-H), 4.15 (1 H, dd, *J* 1.7 and 4.1, 12-H), 4.08 (1 H, dd, *J* 2.1 and 12.6, 10-H), 3.81 (1 H, dd, *J* 3.7 and 12.4, 15-H), 3.69 (1 H, m, 11-H), 3.68 (1 H, dd, *J* 4.1 and 10.7, 13-H), 3.55 (1 H, dd, *J* 3.5 and 10.2, 18-H), 3.49 (1 H, dd, *J* 4.4 and 10.2, 18-H), 3.41 (3 H, s, OMe), 3.39 (3 H, s, OMe), 3.31–3.43 (1 H, m, 17-H), 2.39 (1 H, d, *J* 10.2, OH), 1.97 (1 H, ddd, *J* 5.2, 12.4 and 14.7, 16-H), 1.75 (1 H, ddd, *J* 3.9, 7.0 and 14.7, 16-H), 0.97 and 1.27 (3 H each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 139.2 (0), 129.2 (1), 128.5 (1), 127.0 (1), 101.7 (1), 80.7 (1), 78.9 (1), 75.3 (1), 73.9 (2), 71.9 (1), 70.3 (2), 63.6 (1), 58.9 (3), 57.4 (3), 37.8 (0), 27.7 (2), 24.6 (3), 22.8 (3); *m/z* (CI, NH_3) 384 [$(M + NH_4)^+$, 10%], 367 [$(M + H)^+$, 100] [Found: $(M + H)^+$, 367.2130. $C_{20}H_{31}O_6$ requires *M*, 367.2121].

The following signals attributed to the dioxolane isomer **iv** were gleaned from the mixture: δ_H(270 MHz, C_6D_6) 5.58 (1 H, s, PhC*H*), 3.18 (3 H, s, OMe), 3.07 (3 H, s, OMe), 0.95 (3 H, s, Me), 0.72 (3 H, s, Me); δ_C(67.5 MHz, $CDCl_3$) 129.4 (1), 128.5 (1), 127.2 (1), 102.6 (1), 82.2 (1), 78.6 (1), 74.5 (2), 73.3 (1), 71.6 (1), 71.2 (1), 62.2 (2), 58.9 (3), 57.0 (3), 36.0 (0), 31.1 (2), 23.7 (3), 20.6 (3).

(1*R*,6*R*,8*R*)-9,9-Dimethyl-8-[(2*S*)-2,3-dimethoxypropyl]-3-phenyl-2,4,7-trioxabicyclo[4.4.0]decan-10-one 18

To a stirred solution of oxalyl chloride (0.55 cm^3, 6.33 mmol) in CH_2Cl_2 (32 cm^3) at −55 °C under N_2 was added dropwise a solution of DMSO (1 cm^3, 14 mmol) in CH_2Cl_2 (8 cm^3) over 5 min. The reaction mixture was cooled to −65 °C and stirred for 5 min whereupon a solution of alcohol **17** (2.03 g, 5.53 mmol) in CH_2Cl_2 (12 cm^3) was added dropwise over 5 min. The resulting white suspension was stirred for 5 min, cooled to −78 °C and treated with Et_3N (4 cm^3, 28.7 mmol, 5.2 equiv.). The reaction mixture was allowed to warm up to −10 °C over 2.5 h and poured into ice-cooled sat. aqueous $NaHCO_3$ (100 cm^3). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (30 g, hexanes:AcOEt 20–40%) to give the ketone **18** (1.92 g, 95%) as a white solid, mp 55–56 °C (hexanes); $[\alpha]_D$ −14.2 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3013–2831 (s), 1725 (s), 1458 (m), 1390 (m), 1307 (m), 1240 (m), 1163 (m), 1096 (s), 995 (m); δ_H(270 MHz, $CDCl_3$) 7.56 (2 H, m, Ph), 7.40–7.32 (3 H, m, Ph), 5.56 (1 H, s, PhC*H*), 4.60 (1 H, dd, *J* 9.8 and 4.2, 15-H), 4.37 (1 H, dd, *J* 12.9 and 1.4, 10-H), 4.35 (1 H, d, *J* 2.6, 12-H), 4.13 (1 H, dd, *J* 12.8 and 2.1, 10-H), 3.89 (1 H, ddd, *J* 2.3, 2.3 and 1.8, 11-H), 3.56–3.51 (3 H, m, 17-H, 18-H_2), 3.42 (3 H, s, OMe), 3.31 (3 H, s, OMe), 1.78–1.70 (2 H, m, 16-H_2), 1.35 (3 H, s, Me), 1.08 (3 H, s, Me); δ_C(67.5 MHz, $CDCl_3$) 207.4 (0), 137.7 (0), 129.4 (1), 128.4 (1), 126.4 (1), 100.8 (1), 79.2 (1), 79.0 (1), 78.1 (1), 72.8 (2), 71.2 (2), 65.5 (1), 59.3 (3), 57.3 (3), 48.9 (0), 29.7 (2), 24.3 (3), 19.4 (3); *m/z* (CI, NH_3) 382 [$(M + NH_4)^+$, 90%], 365 [$(M + H)^+$, 100], 229 (42) (Found: C, 65.91; H, 7.88. $C_{20}H_{28}O_6$ requires C, 65.92; H, 7.74%).

(1*R*,6*R*,8*R*,10*S*)-8-[(2*S*)-2,3-Dimethoxypropyl]-9,9-dimethyl-3-phenyl-2,4,7-trioxabicyclo[4.4.0]decan-10-ol 19

Solid $CeCl_3 \cdot 7H_2O$ (1.14 g, 3.05 mmol) was added to a stirred solution of ketone **18** (973 mg, 2.67 mmol) in MeOH (35 cm^3) at 0 °C. The solution was stirred for 20 min and solid $NaBH(OAc)_3$ (1.87 g, 8.84 mmol) was added. The reaction mixture was stirred for 30 min and treated with sat. aqueous $NaHCO_3$ (100 cm^3). Methanol was removed *in vacuo* and the residue was extracted with CH_2Cl_2 (4 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude alcohol **19** as a 25:1 mixture of C-10 epimers (NMR). Purification by chromatography on SiO_2 eluting with ethyl acetate/hexanes (3:7) gave the diastereoisomerically pure alcohol **19** as a colourless oil (919 mg, 2.51 mmol, 94%) which crystallised from ethyl acetate–hexanes as white needles, mp 107–108 °C; $[\alpha]_D$ +13 (*c* 1.0 in CCl_4); $\nu_{max}(CCl_4)/cm^{-1}$ 3637 (m), 3462 (br m), 2778–2829 (s), 1477 (m), 1455 (m), 1398 (m), 1381 (m), 1310 (m), 1213 (m), 1191 (m), 1115 (s), 1099 (s), 1003 (s); δ_H(C_6D_6, referenced to 7.13 ppm) 7.72–7.63 (2 H, m Ph),

7.05–7.23 (3 H, m, Ph, coincident with C_6H_6 reference signal), 5.29 (1 H, s, PhC*H*), 4.19 (1 H, dd, *J* 13.2 and 2.3, 10-H), 3.75 (1 H, dd, *J* 8.4 and 3.2), 3.66 (1 H, m), 3.64 (1 H, dd, *J* 13.3 and 2.1, partially concealed), 3.54 (1 H, t, *J* 2.1), 3.50 (1 H, t, *J* 3.5), 3.43 (1 H, dd, *J* 15.4 and 5.6), 3.48–3.36 (1 H, m, concealed), 3.32 (1 H, t, *J* 3.2, after treatment with D_2O the signal appeared as: 1 H, d, *J* 2.8), 3.28 (3 H, s, OMe), 3.14 (3 H, s, OMe), 2.54 (1 H, ddd, *J* 15.8, 9.4 and 4.3, 16-H), 1.80 (1 H, ddd, *J* 14.8, 7.1 and 3.2, 16-H), 1.30 (3 H, s, Me), 1.50 (1 H, br m, OH, D_2O exchange), 0.79 (3 H, s, Me); δ_C(67.5 MHz, C_6D_6, referenced to 128.4 ppm) 139.9 (0), 129.4 (1), 128.8 (1), 127.3 (1), 101.7 (1), 79.8 (1), 79.5 (1), 77.8 (1), 75.2 (1), 74.5 (2), 71.0 (2), 60.3 (1), 59.3 (3), 57.7 (3), 36.4 (0), 29.8 (2), 28.2 (3), 23.2 (3); *m*/*z* (CI) 384 [$(M + NH_4)^{+\bullet}$, 100%], 367 [$(M + H)^+$, 84] (Found: C, 65.47; H, 8.17. $C_{20}H_{30}O_6$ requires C, 65.55; H, 8.25%).

(1*R*,6*R*,8*R*,10*S*)-10-Methoxy-9,9-dimethyl-8-[(2*S*)-2,3-dimethoxypropyl]-3-phenyl-2,4,7-trioxabicyclo[4.4.0]decane 20

To a mixture of alcohol **19** (919 mg, 2.51 mmol) in toluene (9 cm^3) and 50% NaOH (4.5 cm^3), was added tetrabutylammonium hydrogen sulfate (187 mg, 0.55 mmol) and dimethyl sulfate (1.3 cm^3, 13.7 mmol). The reaction mixture was vigorously stirred at room temp. for 2 h. Then MeOH (1.3 cm^3) was added dropwise. The reaction mixture was stirred for 15 min, diluted with water (25 cm^3) and extracted with CH_2Cl_2 (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on SiO_2 (30 g, hexanes: AcOEt 20–30%) to give the pure methyl ether **20** (895 mg, 2.35 mmol, 94%) as a white solid, mp 91–92 °C (AcOEt–hexanes); $[\alpha]_D$ +7.2 (*c* 1.0 in CCl_4); ν_{max}($CHCl_3$)/cm^{-1} 2879–2823 (s), 1477 (s), 1457 (s), 1400 (s), 1310 (m), 1190 (s), 1146 (s), 1099 (s), 1023 (s); δ_H(270 MHz, C_6D_6, referenced to 7.13 ppm) 7.69–7.64 (2 H, m, Ph), 7.21–7.07 (3 H, m, Ph, coincident with C_6D_6 reference signal), 5.31 (1 H, s, PhC*H*), 4.20 (1 H, dd, *J* 12.8 and 1.4, 10-H), 3.75 (1 H, dd, *J* 12.2 and 3.1, 10-H), 3.69 (1 H, t, *J* 2.0, 12-H), 3.64 (1 H, dd, *J* 10.2 and 2.0), 3.61 (1 H, m, 11-H), 3.57–3.36 (4 H, m, 18-H_2, 17-H, 15-H), 3.30 (3 H, s, OMe), 3.14 (3 H, s, OMe), 3.01 (3 H, s, OMe), 2.84 (1 H, d, *J* 2.1, 13-H), 2.52 (1 H, ddd, *J* 15.1, 11.9 and 4.6, 16-H), 1.82 (1 H, ddd, *J* 14.7, 6.9 and 3.2, 16-H), 1.36 (1 H, s, Me), 0.89 (1 H, s, Me); δ_C(67.5 MHz, C_6D_6, referenced to 128.4 ppm) 140.0 (0), 129.3 (1), 128.7 (1), 127.3 (1), 101.8 (1), 85.6 (1), 79.7 (1), 79.4 (1), 74.8 (2), 73.8 (1), 71.1 (2), 60.6 (1), concealed signal at 60.6 (3), 59.3 (3), 57.7 (3), 36.7 (0), 29.8 (2), 28.4 (3), 22.9 (3); *m*/*z* (CI, NH_3) 398 [$(M + NH_4)^+$, 70%], 381 [$(M + H)^+$, 100] (Found: C, 66.21; H, 8.42. $C_{21}H_{32}O$ requires C, 66.29; H, 8.48%).

(2*R*,3*R*,4*S*,6*R*)-2-Hydroxymethyl-4-methoxy-6-[(2*S*)-dimethoxypropyl]-5,5-dimethyloxan-3-ol 26

A solution of acetal **20** (2.63 g, 6.91 mmol) and PTSA (130 mg, 0.74 mmol) in MeOH (120 cm^3) was heated at reflux for 6 h. The reaction mixture was cooled and treated with solid $NaHCO_3$ (1.5 g). The mixture was concentrated *in vacuo* to remove the methanol. The residue was dissolved in CH_2Cl_2 (50 cm^3), filtered through a pad of Celite, concentrated and chromatographed on SiO_2 (32 g, hexanes: AcOEt 50–100%) to give the diol **26** (2.0 g, 99%) as a colourless oil, $[\alpha]_D$ +89.4 (*c* 1.0 in $CHCl_3$); ν_{max}(CCl_4)/cm^{-1} 3620 (m), 3462 (br s), 2976–2824 (s), 1469 (m), 1385 (m), 1305 (m), 1193 (m), 1101 (s), 1047 (s), 969 (m); δ_H(270 MHz, $CDCl_3$) 4.14 (1 H, ddd, *J* 9.7, 6.7 and 4.9, 11-H), 4.00–3.87 [1 H, m, on treatment with D_2O resolved as: 3.94 (1 H, dd, *J* 13.5 and 9.7, 12-H)], 4.00–3.87 [1 H, m, on treatment with D_2O resolved as: 3.92 (1 H, dd, *J* 13.5 and 9.7, 10-H)], 3.76 (1 H, ddd, *J* 13.5, 10.8 and 4.9, on treatment with D_2O appeared as 1 H, dd, *J* 13.5 and 4.9, 10-H), 3.65–3.26 (4 H, m, concealed, 15-H, 17-H, 18-H_2), 3.59 (3 H, s, OMe), 3.41 (3 H, s, OMe), 3.38 (3 H, s, OMe), 2.89 (1 H, d, *J* 9.6, 13-H), 2.38 (1 H, d, *J* 3.3, D_2O exchange, OH), 1.70 (2 H, dd, *J* 6.8 and 5.7, 16-H_2), 0.96 (3 H, s, Me), 0.88 (3 H, s, Me); δ_C(67.5 MHz, $CDCl_3$) 87.1 (1), 78.0 (1), 75.4 (1), 75.0 (2), 72.7 (1), 69.6 (1), 62.3 (3), 58.9 (3), 57.6 (2), 57.0 (3), 40.8 (0), 30.6 (2), 23.2 (3), 13.6 (3); *m*/*z* (CI, NH_3) 310 [$(M + NH_4)^+$, 55%], 293 [$(M + H)^+$, 100].

(2*R*,3*R*,4*S*,6*R*)-2-[(*tert*-Butylcarbonyloxy)methyl]-4-methoxy-6-[(2*S*)-dimethoxypropyl]-5,5-dimethyloxan-3-ol 27

To a stirred solution of diol **26** (3.12 g, 10.67 mmol), pyridine (2.7 cm^3, 33.4 mmol) in CH_2Cl_2 (15 cm^3) was added pivaloyl chloride (PvCl) (2.7 cm^3, 21.9 mmol) at 0 °C. The reaction mixture was stirred at room temp. for 4 h, then poured into sat. aqueous $NaHCO_3$ and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 cm^3). The combined extracts were washed with HCl (2 mol dm^{-3}), brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on SiO_2 (75 g, hexanes: AcOEt 5–40%) to give the ester **27** (3.86 g, 96%) as a colourless oil, $[\alpha]_D$ +86.7 (*c* 2.27 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3444 (s), 1728 (s); δ_H(270 MHz, $CDCl_3$) 4.53 (1 H, dd, *J* 9.3 and 12.5, 10-H), 4.23–4.35 (2 H, m, 11-H and 10-H), 3.93 (1 H, ddd, *J* 3.5, 6.6 and 10.0, 12-H), 3.58 (3 H, s, OMe), 3.49–3.36 (3 H, m), 3.36 (6 H, s, OMe), 2.87 (1 H, d, *J* 9.9, 13-H), 2.34 (1 H, d, *J* 3.5, OH), 1.56–1.78 (2 H, m, 16-H_2), 1.23 (9 H, s, Bu^t), 0.88 and 0.96 (3 H each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 178.7 (0), 87.6 (1), 77.9 (1), 74.2 (1), 74.0 (1), 73.4 (1), 69.1 (2), 62.7 (3), 60.1 (2), 59.3 (3), 56.9 (3), 41.2 (0), 38.9 (0), 29.8 (2), 27.4 (3), 23.6 (3), 14.1 (3); *m*/*z* (MNOBA matrix) 377 [$(M + H)^+$, 42%], 273 (45), 57 (100).

(2*R*,3*R*,4*S*,6*R*)-2-[(*tert*-Butylcarbonyloxy)methyl]-4-methoxy-3-[(2-methoxyethoxy)methoxy]-6-[(2*S*)-dimethoxypropyl]-5,5-dimethyloxane 28

A mixture of alcohol **27** (1.03 g, 2.74 mmol), $EtN(Pr^i)_2$ (1.9 cm^3, 10.9 mmol), tetrabutylammonium iodide (43 mg, 0.12 mmol), DMAP (25 mg, 0.2 mmol), MEM chloride (0.93 cm^3, 8.14 mmol) and toluene (17 cm^3) was stirred at 75–80 °C for 15 h. The reaction mixture was cooled, diluted with Et_2O (200 cm^3), and washed successively with water (50 cm^3), HCl (2 mol dm^{-3}) and sat. aqueous $NaHCO_3$. The extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed on SiO_2 (20 g, hexanes: AcOEt 5–40%) to give the MEM ether **28** (1.25 g, 98%) as a colourless oil, $[\alpha]_D$ +48.7 (*c* 1.33 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1729 (s); δ_H(270 MHz, $CDCl_3$) 4.84 (1 H, d, *J* 6.9, OCH_AH_BO), 4.77 (1 H, d, *J* 6.9, OCH_AH_BO), 4.48 (1 H, dd, *J* 9.5 and 12.5, 10-H), 4.32–4.24 (2 H, m, 11-H and 10-H), 3.88 (1 H, dd, *J* 6.4 and 9.8, 12-H), 3.78 (1 H, ddd, *J* 4.1, 5.0 and 10.8, $OCH_AH_BCH_2O$), 3.67 (1 H, ddd, *J* 4.1, 5.4 and 10.6, $OCH_AH_BCH_2O$), 3.57–3.53 (2 H, m, OCH_2CH_2OMe), 3.50 (3 H, s, OMe), 3.39 (3 H, s, OMe), 3.36–3.50 (3 H, m), 3.36 (6 H, s, OMe), 2.89 (1 H, d, *J* 9.8, 13-H), 1.61–1.73 (2 H, m, 16-H), 1.23 (9 H, s, Bu^t), 0.88 and 0.94 (3 H each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 178.5 (0), 96.1 (2), 85.7 (1), 77.9 (1), 75.1 (1), 73.8 (1), 73.5 (2), 71.9 (2), 67.4 (2), 62.0 (3), 60.6 (2), 59.3 (3), 59.1 (3), 56.9 (3), 41.2 (0), 38.8 (0), 29.8 (2), 27.3 (3), 23.3 (3), 14.2 (3); *m*/*z* (CI, NH_3) 482 [$(M + NH_4)^+$, 47%], 465 [$(M + H)^+$, 100] [Found: $(M + H)^+$, 465.3079. $C_{23}H_{45}O_9$ requires *M*, 465.3064].

(2*R*,3*R*,4*S*,6*R*)-2-Hydroxymethyl-4-methoxy-3-[(2-methoxyethoxy)methoxy]-6-[(2*S*)-dimethoxypropyl]-5,5-dimethyloxane 29

To a stirred solution of ester **28** (1.25 g, 2.69 mmol) in Et_2O (18 cm^3) was added LAH (225 mg, 5.77 mmol) at 0 °C. The reaction mixture was stirred for 25 min, diluted with ether (25 cm^3), treated with sat. aqueous Na_2SO_4 (0.5 cm^3). After 1 h at room temp. solid Na_2SO_4 was added and the mixture filtered through Celite and concentrated. The residue was chromatographed on SiO_2 (10 g, CH_2Cl_2: Et_2O) to give the alcohol **29** (984 mg, 96%) as a colourless oil, $[\alpha]_D$ +18.5 (*c* 2.08 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3425 (s); δ_H(270 MHz, $CDCl_3$) 4.82 (1 H, d, *J*

6.8, OCH_AH_BO), 4.75 (1 H, d, *J* 6.8, OCH_AH_BO), 4.15 (1 H, ddd, *J* 4.2, 6.6 and 10.6, 11-H), 3.95 (1 H, dd, *J* 10.6 and 12.3, 10-H), 3.90 (1 H, dd, *J* 6.8 and 9.8, 12-H), 3.76 (1 H, dt, *J* 4.2 and 10.4), 3.50 (3 H, s, OMe), 3.41 (3 H, s, OMe), 3.39 (3 H, s, OMe), 3.37 (3 H, s, OMe), 3.3–3.7 (7 H, m), 2.87 (1 H, d, *J* 9.8, 13-H), 1.68 (2 H, t, *J* 6.1, 16-H), 0.87 and 0.92 (3 H each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 95.9 (2), 85.7 (1), 78.2 (1), 75.7 (1), 75.4 (2), 74.9 (1), 72.2 (1), 71.7 (2), 67.1 (2), 59.0 (3), 58.9 (3), 57.2 (2), 57.1 (3), 41.2 (0), 30.8 (2), 22.9 (3), 13.6 (3); *m*/*z* (CI, NH_3) 398 [$(M + NH_4)^+$, 8%], 381 [$(M + H)^+$, 100], 305 (44) [Found: $(M + H)^+$, 381.2491. $C_{18}H_{37}O_8$ requires *M*, 381.2488].

(2*R*,3*R*,4*S*,6*R*)-2-Formyl-4-methoxy-3-[(2-methoxyethoxy)-methoxy]-6-[(2*S*)-dimethoxypropyl]-5,5-dimethyloxane 30

Dess–Martin periodinane (502 mg) was added in one portion to a stirred solution of alcohol **29** (103 mg, 0.271 mmol) in CH_2Cl_2 (4 cm^3). After 1 h at room temp. the reaction mixture was treated with sat. aqueous $Na_2S_2O_3$ (10 cm^3) and sat. aqueous $NaHCO_3$ (10 cm^3). After stirring for 10 min the reaction mixture was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated to give the crude aldehyde **30** (105 mg). Chromatography on SiO_2 (3 g, hexanes:AcOEt 20–50%) gave the pure aldehyde **30** (96 mg, 94%) as a colourless oil, $[\alpha]_D$ +139 (*c* 1.37 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1733 (s); δ_H(270 MHz, $CDCl_3$) 9.97 (1 H, s, CHO), 4.88 (1 H, d, *J* 6.8, OCH_AH_BO), 4.82 (1 H, d, *J* 6.8, OCH_AH_BO), 4.54 (1 H, d, *J* 7.1, 11-H), 4.05 (1 H, dd, *J* 7.1 and 9.8, 12-H), 3.81 (1 H, ddd, *J* 3.7, 5.2 and 10.6, OCH_2CH_2O), 3.70 (1 H, dd, *J* 3.7 and 5.2, OCH_2CH_2O), 3.69–3.58 (1 H, m), 3.61 (1 H, br s), 3.56 (1 H, ddd, *J* 1.5, 3.7 and 5.2, OCH_2CH_2O), 3.50 (3 H, s, OMe), 3.46 (1 H, dd, *J* 3.1 and 9.1, 15-H), 3.44–3.25 (1 H, m), 3.40 (3 H, s, OMe), 3.38 (3 H, s, OMe), 3.37 (3 H, s, OMe), 2.76 (1 H, d, *J* 10.0, 13-H), 1.76–1.54 (2 H, m, 16-H_2), 0.85 and 0.88 (3 H each, s, 14-Me); δ_C(62.5 MHz, $CDCl_3$) 202.2 (0), 96.7 (2), 86.7 (1), 79.1 (1), 77.8 (1), 76.8 (1), 76.4 (1), 72.8 (2), 71.6 (2), 67.4 (2), 61.8 (3), 58.9 (3), 56.7 (3), 41.3 (0), 29.6 (2), 22.7 (3), 13.6 (3); *m*/*z* (CI, NH_3) 396 [$(M + NH_4)^+$, 50%], 379 [$(M + H)^+$, 100], 317 (50). Owing to the instability of aldehyde **30**, it was better to use it immediately without purification as described in the following procedure.

(2*R*,3*R*,4*S*,6*R*)-4-Methoxy-6-[(2*S*)-dimethoxypropyl]-5,5-dimethyl-2-{di[(prop-2-enyl)oxy]methyl}oxan-3-ol 31

Dess–Martin periodinane (3 g) was added in one portion to a stirred solution of alcohol **29** (628 mg, 1.65 mmol) in CH_2Cl_2 (25 cm^3) at room temp. After 80 min the reaction mixture was treated with sat. aqueous $Na_2S_2O_3$ (25 cm^3) and sat. aqueous $NaHCO_3$ (50 cm^3). After stirring for 30 min the reaction mixture was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated to give the crude aldehyde **30** which was added to a mixture of allyl alcohol (13 cm^3) and PTSA (50 mg, 0.26 mmol, 0.16 equiv.) in CH_2Cl_2 (13 cm^3) and the mixture heated at reflux for 22 h (oil bath at 65 °C). Traces of water from a condenser were removed at 2 h intervals. The reaction mixture was stirred at room temp. overnight (TLC showed *ca.* 1:1 mixture of MEM ether and alcohol). Anhydrous $ZnCl_2$ (500 mg, 3.65 mmol) was added and the reaction mixture was refluxed for a further 5 h. After cooling to room temp. the mixture was poured onto sat. aqueous $NaHCO_3$. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 30 cm^3). The combined extracts were dried ($MgSO_4$), concentrated, and the residue was chromatographed on SiO_2 (50 g, hexanes:AcOEt 10–30%) to give the hydroxy acetal **31** (447 mg, 70%) as a colourless oil, $[\alpha]_D$ +46.6 (*c* 1.0 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3488 (br s), 3011–2826 (s), 1648 (w), 1467 (m), 1424 (m), 1388 (m), 1366 (m), 1216 (m), 1210 (m), 1102 (s), 1054 (s), 993 (m), 934 (m); δ_H(270 MHz, $CDCl_3$) 5.93 (2 H, 2 × overlapping dddd, *J* 17.1, 10.3, 6.2 and 5.3, 2 × H_2C=C*H*–), 5.33 (1 H, dq, *J* 17.2 and 1.6, H_2C=CH–), 5.31 (1 H, dq, *J* 17.2 and 1.6, H_2C=CH–), 5.23 (1 H, dq, *J* 10.3 and 1.5, H_2C=CH–), 5.19 (1 H, dq, *J* 10.3 and 1.5, H_2C=CH–), 4.97 (1 H, d, *J* 5.8, 10-H), 4.26 (1 H, ddt, *J* 12.7, 5.3 and 1.5, H_2C=CH–CH_2–O), 4.18 (2 H, apparent dq, *J* 5.5 and 1.6, H_2C=CH–CH_2–O), 4.11 (1 H, ddt, *J* 12.7, 5.9 and 1.4, H_2C=CH–CH_2–O), 4.03 (1 H, t, *J* 5.7, 11-H), 3.95 (1 H, ddd, *J* 8.2, 5.9 and 4.7, 12-H, appeared as dd, *J* 8.2 and 5.9 after D_2O exchange), 3.56–3.36 (4 H, m, concealed, 15-H, 17-H, 18-H_2), 3.56 (3 H, s, OMe), 3.36 (6 H, s, 2 × overlapping OMe), 2.99 (1 H, d, *J* 5.0, OH), 2.99 (1 H, d, *J* 8.2, 13-H), 1.73 (1 H, m, 16-H), 1.65 (1 H, m, 16-H), 0.99 (3 H, s, Me), 0.87 (3 H, s, Me); δ_C(67.5 MHz, $CDCl_3$) 134.3 (1), 133.8 (1), 118.0 (2), 116.9 (2), 100.3 (1), 87.1 (1), 78.0 (1), 76.7 (1), 73.1 (2), 72.1 (1), 69.5 (1), 68.9 (2), 66.3 (2), 61.9 (3), 59.4 (3), 56.9 (3), 40.1 (0), 29.5 (2), 24.5 (3), 15.7 (3); *m*/*z* (CI, NH_3) 406 [$(M + NH_4)^+$, 15%], 389 [$(M + H)^+$, 33], 348 (56), 331 (100), 299 (51), 290 (50), 127 (93) [Found: $(M + H)^+$, 389.2521. $C_{20}H_{37}O_7$ requires *M*, 389.2539].

Formation of trioxabicyclo[4.4.0]decanes 32a,b

HCl gas was passed through a stirred mixture of hydroxy acetal **31** (236 mg, 0.61 mmol), paraformaldehyde (206 mg, 6.8 mmol) and CH_2Cl_2 (25 cm^3) at 0 °C for 35 min. The white suspension of paraformaldehyde disappeared to give a colourless solution. Then a stream of N_2 was passed through the mixture for 50 min. The solution was poured onto sat. aqueous $NaHCO_3$ and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated to give a solid residue. The residue was treated with Et_2O and filtered. The filtrate was concentrated and chromatographed on SiO_2 (12 g, hexanes:AcOEt 10–60%) to give the acetal **35** as a mixture of C-5 epimers (**32a**:**32b** = 1:4, 177 mg, 81%) and the hemiacetals **33a,b** (13.5 mg, 7%, a 2:1 mixture of C-5 epimers). The epimeric acetals were separated on SiO_2 (hexanes:AcOEt).

(1*R*,5*S*,6*R*,8*R*,10*S*)-10-Methoxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-5-[(prop-2-enyl)oxy]-2,4,7-trioxabicyclo-[4.4.0]decane 32a. $[\alpha]_D$ +9.5 (*c* 0.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1648 (w), 1469 (s), 1181 (s), 1107 (s), 994 (s); δ_H(270 MHz, $CDCl_3$) 5.97 (1 H, dddd, *J* 5.0, 5.8, 10.6 and 17.2, =C*H*CH_2O), 5.32 (1 H, dq, *J* 1.7 and 17.4, =CH_2 *trans*), 5.25 (1 H, dq, *J* 1.5 and 10.4, =CH_2 *cis*), 5.21 (1 H, d, *J* 6.6, OCH_AH_BO), 4.94 (1 H, br d, *J* 3.5, 10-H), 4.62 (1 H, d, *J* 6.4, OCH_AH_BO), 4.36 (1 H, ddt, *J* 1.7, 5.0 and 13.0, =$CHCH_2O$), 4.15–3.90 (2 H, m), 4.06 (1 H, ddt, *J* 1.5, 6.0 and 13.0, =$CHCH_2O$), 3.53 (3 H, s, OMe), 3.46 (1 H, d, *J* 9.9, 13-H), 3.38 (3 H, s, OMe), 3.37 (3 H, s, OMe), 3.35–3.55 (4 H, m), 1.50–1.80 (2 H, m, 16-H), 0.86 and 1.02 (3 H each, s, 14-Me); δ_H(270 MHz, C_6D_6, referenced to 7.20 ppm) 5.90 (1 H, dddd, *J* 5.0, 5.8, 10.4 and 17.2, =C*H*CH_2O), 5.27 (1 H, dq, *J* 1.7 and 17.4, =CH_2 *trans*), 5.17 (1 H, d, *J* 6.2, OCH_ACH_BO), 5.10 (1 H, dq, *J* 1.5 and 10.4, =CH_2 *cis*), 4.84 (1 H, d, *J* 4.6, 10-H), 4.50 (1 H, d, *J* 6.2, OCH_ACH_BO), 4.20–4.32 (2 H, m, 12-H, 11-H), 4.16 (1 H, dd, *J* 3.9 and 7.0, 15-H), 4.14 (1 H, ddt, *J* 1.7, 5.0 and 12.9, =$CHCH_2O$), 3.82 (1 H, ddt, *J* 1.5, 5.8 and 13.1, =$CHCH_2O$), 3.70 (1 H, m, 17-H), 3.63 (1 H, d, *J* 9.9, 13-H), 3.56 (2 H, d, *J* 4.4, 18-H_2), 3.45 (3 H, s, OMe), 3.37 (3 H, s, OMe), 3.29 (3 H, s, OMe), 1.67–1.83 (2 H, m, 16-H_2), 0.97 and 1.04 (3 H each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 133.4 (1), 116.8 (2), 98.3 (1), 81.1 (1), 76.3 (1), 76.1 (1), 73.3 (2), 72.9 (1), 68.7 (2), 66.6 (1), 60.8 (3), 58.8 (3), 56.6 (3), 39.6 (0), 29.4 (2), 23.9 (3), 14.6 (3); δ_C(62.5 MHz, C_6D_6, referenced to 128.4 ppm) 134.6 (1), 117.3 (2), 99.3 (1), 81.8 (1), 81.2 (2), 79.2 (1), 76.8 (1), 75.1 (2), 74.2 (1), 69.5 (2), 68.3 (1), 61.5 (3), 59.4 (3), 57.4 (3), 40.9 (0), 31.2 (2), 24.6 (3), 14.7 (3); *m*/*z* (CI, NH_3) 378 [$(M + NH_4)^+$, 23%], 361 [$(M + H)^+$, 100].

(1*R*,5*R*,6*R*,8*R*,10*S*)-10-Methoxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-5-[(prop-2-enyl)oxy]-2,4,7-trioxabicyclo-[4.4.0]decane 32b. $[\alpha]_D$ +86.8 (*c* 1.5 in $CHCl_3$); ν_{max}(CCl_4)/cm^{-1} 1648 (w), 1459 (m), 1179 (s), 1132 (s), 1102 (s), 1042 (s),

984 (s); δ_H(270 MHz, $CDCl_3$) 5.93 (1 H, dddd, *J* 5.2, 6.2, 10.4 and 17.0, =C*H*CH_2O), 5.32 (1 H, dq, *J* 1.5 and 17.2, =CH_2 *trans*), 5.22 (1 H, dq, *J* 1.3 and 10.4, =CH_2 *cis*), 5.08 (1 H, d, *J* 6.0, OCH_AH_BO), 4.818 (1 H, s, 10-H), 4.816 (1 H, d, *J* 5.6, OCH_AH_BO), 4.27 (1 H, ddt, *J* 1.5, 5.2 and 13.0, =$CHCH_AH_BO$), 4.07 (1 H, ddt, *J* 1.2, 6.4 and 13.0, =$CHCH_AH_BO$), 3.93 (1 H, t, *J* 2.9, 12-H), 3.68 (1 H, t, *J* 2.0, 11-H), 3.57 (1 H, dd, *J* 3.1 and 12.0, 15-H), 3.50 (1 H, dd, *J* 3.7 and 9.6, 18-H_AH_B), 3.46 (1 H, dd, *J* 2.1 and 9.6, 18-H_AH_B), 3.39 (3 H, s, OMe), 3.38 (3 H, s, OMe), 3.37 (3 H, s, OMe), 3.35–3.40 (1 H, m), 2.89 (1 H, d, *J* 3.3, 13-H), 2.27 (1 H, ddd, *J* 4.2, 12.0 and 15.1, 16-H_AH_B), 1.60 (1 H, ddd, *J* 3.3, 7.9 and 15.1, 16-H_AH_B), 0.91 and 1.21 (3 H each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 133.8 (1), 117.7 (2), 96.7 (1), 85.2 (2), 83.7 (1), 78.5 (1), 78.4 (1), 73.5 (2), 70.2 (1), 68.2 (2), 63.4 (1), 59.5 (3), 59.2 (3), 57.2 (3), 37.2 (0), 28.5 (2), 27.2 (3), 21.4 (3); *m*/*z* (CI, NH_3) 378 [$(M + NH_4)^+$, 7%], 361 [$(M + H)^+$, 100] [Found: $(M + H)^+$, 361.2228. $C_{18}H_{33}O_7$ requires *M*, 361.2226].

(1*R*,5*RS*,6*R*,8*R*,10*S*)-10-Methoxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decan-5-ol 33a,b

A solution of allyl acetals **32a,b** (1:4 mixture of epimers, 353 mg, 0.98 mmol), 1,4-diazabicyclo[2.2.2]octane (DABCO) (24 mg, 0.21 mmol) in aqueous EtOH (EtOH:H_2O = 9:1, 11 cm^3) was stirred under argon. Wilkinson's catalyst (63 mg, 0.068 mmol, 97% from Fluka) was added and the red suspension heated at reflux for 1.75 h. After cooling to room temp. the yellow suspension was filtered through a Celite pad with CH_2Cl_2 (*ca.* 120 cm^3). The filtrate was concentrated to give a yellow oil which was chromatographed on SiO_2 (5 g, hexanes:AcOEt:Et_3N 80:20:0.1) to give a mixture of prop-1-enyl acetals and propyl acetals (330 mg). This mixture was treated with THF (10 cm^3) and a solution of $Hg(OAc)_2$ (412 mg) in water (7 cm^3) and stirred at room temp. After 5 min the solution was extracted with CH_2Cl_2 (3 × 30 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated and the residue chromatographed on SiO_2 (13 g, hexanes:AcOEt 20–60%) to give a 2:1 mixture of C-5 epimers of the hemiacetals **33a,b** as a colourless oil (222 mg, 71%) and a 4:1 mixture of C-5 epimers of the propyl acetals (66 mg, 18%). The following data were recorded on a mixture of the hemiacetals.

ν_{max}/cm^{-1} ($CHCl_3$) 3596–3409 (br m), 3025–2826 (s), 1478 (s), 1463 (s), 1423 (m), 1396 (m), 1367 (m), 1232 (m), 1198 (m), 1179 (m), 1129 (s), 1101 (s), 1031 (s), 979 (m), 960 (m), 909 (m).

In the ^1H NMR spectrum of the diastereoisomeric mixture (3:1 ratio at C-10) those signals readily ascribed to the minor component by their relative integration are listed separately. Overlapping and concealed signals are included within the data listed for the major isomer. δ_H(270 MHz, $CDCl_3$, major isomer) 5.20 (1 H, t, *J* 3.8, partially overlapping, 10-H), 5.17 (1 H, d, *J* 6.7, OCH_2O), 4.89 (1 H, d, *J* 6.7, OCH_2O), 4.03 (1 H, dd, *J* 5.4 and 3.2), 3.70 (1 H, t, *J* 3.6), 3.44 (3 H, s, OMe), 3.39 (3 H, s, OMe), 3.38 (3 H, s, OMe), 3.62–3.36 (4 H, overlapping m), 3.02 (1 H, d, *J* 5.1), 2.34–2.09 (1 H, m, 16-H), 1.71–1.56 (1 H, m, 16-H), 1.17 (3 H, s, Me), 0.92 (3 H, s, Me). δ_H(minor isomer) 5.12 (1 H, d, *J* 6.7, OCH_2O), 4.88 (1 H, dd, *J* 11.3 and 2.1, partially overlapping, 10-H), 4.74 (1 H, d, *J* 6.7, OCH_2O), 4.23 (1 H, d, *J* 11.3, D_2O exchange, OH), 3.79 (1 H, t, *J* 2.2), 3.74 (1 H, dd, *J* 2.2 and 3.0), 3.41 (3 H, s, OMe), 3.39 (3 H, s, OMe), 2.98 (1 H, d, *J* 3.0, 13-H), 1.20 (3 H, s, Me), 0.95 (3 H, s, Me).

When the ^{13}C NMR spectrum of the diastereoisomeric mixture (3:1 at C-10) of **33a,b** was accumulated over 10 h, we observed interconversion of the two isomers to give a mixture (1:1.4 ratio at C-10) favouring the previously minor component. Assignment of the signals to individual isomers in the resulting spectrum was unclear and therefore the visible signals in the ^{13}C NMR spectrum are listed together, δ_C(67.5 MHz, $CDCl_3$) 94.1 (1), 92.2 (1), 89.9 (2), 85.3 (2), 83.7 (1), 82.9 (1), 79.2 (1), 78.5 (1), 78.4 (1), 73.8 (2), 73.3 (2), 73.0 (1), 71.0 (1), 62.7 (1), 60.2 (3), 59.7 (3), 59.4 (3), 57.3 (3), 37.4 (0), 29.1 (2), 28.8 (2), 27.4 (3), 26.4 (3), 21.9 (3), 20.0 (3). Two CH signals and a quaternary carbon were not discernible in the spectrum. *m*/*z* (CI, NH_3) 321 [$(M + H)^+$, 91%], 303 (25), 271 (54), 217 (18), 187 (41).

Formation of azides 34a,b

A solution of hemiacetal **33a,b** (94 mg, 0.29 mmol) and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 was stirred at −70 °C under nitrogen. Et_3N (0.125 cm^3, 0.9 mmol) and MsCl (1.3 mol dm^{-3}) in CH_2Cl_2 (0.5 cm^3) were added. The reaction mixture was allowed to warm to −10 °C over 1 h and cooled to −70 °C. Then $TMSN_3$ (0.33 cm^3, 2.5 mmol) and a solution of TASF (530 mg, 1.9 mmol) in CH_2Cl_2 (6 cm^3) were added. The reaction mixture was allowed to warm to 0 °C over 8.5 h and then poured into sat. aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (2 g, hexanes:AcOEt 5–30%) to give a mixture of the azides **34a,b** (**a**:**b** = 1:1.2, 89 mg, 88%) as a colourless oil. For analysis both epimers of the azide were separated on SiO_2 (hexanes:AcOEt).

(1*R*,5*S*,6*R*,8*R*,10*S*)-5-Azido-10- methoxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane 34a. ν_{max}/cm^{-1} (film) 2114 (s); δ_H(270 MHz, $CDCl_3$) 5.28 (1 H, d, *J* 2.9, 10-H), 5.11 (1 H, d, *J* 6.4, OCH_AH_BO), 4.47 (1 H, d, *J* 6.2, OCH_AH_BO), 3.89 (1 H, dd, *J* 2.8 and 3.8, 12-H), 3.57 (1 H, t, *J* 2.7, 11-H), 3.57 (1 H, dd, *J* 3.1 and 12.4, 15-H), 3.50 (1 H, dd, *J* 4.0 and 10.2, 18-H_AH_B), 3.46 (1 H, dd, *J* 4.4 and 10.2, 18-H_AH_B), 3.41 (3 H, s, OMe), 3.40–3.35 (1 H, m, 17-H), 3.39 (3 H, s, OMe), 3.38 (3 H, s, OMe), 2.96 (1 H, d, *J* 4.1, 13-H), 2.17 (1 H, ddd, *J* 4.2, 11.8 and 14.7, 16-H_AH_B), 1.63 (1 H, ddd, *J* 3.1, 7.5 and 14.9, 16-H_AH_B), 0.91 and 1.18 (3 H, each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 87.4 (1), 86.7 (2), 83.2 (1), 78.7 (1), 78.6 (1), 73.6 (2), 70.3 (1), 63.7 (1), 59.9 (3), 59.4 (3), 57.3 (3), 37.6 (0), 28.9 (2), 26.8 (3), 20.6 (3); *m*/*z* (CI, NH_3) 363 [$(M + NH_4)^+$, 33%], 346 [$(M + H)^+$, 100], 303 (16).

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-Azido-10-methoxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane 35b. Mp 67–67.5 °C (pentane); $[\alpha]_D$ −51.5 (*c* 0.635 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2119 (s); δ_H(270 MHz, $CDCl_3$) 5.21 (1 H, d, *J* 6.6, OCH_AH_BO), 4.78 (1 H, d, *J* 6.6, OCH_AH_BO), 4.63 (1 H, d, *J* 2.3, 10-H), 3.86 (1 H, t, *J* 2.1, 11-H), 3.70 (1 H, dd, *J* 1.9 and 3.5, 12-H), 3.69 (1 H, dd, *J* 3.1 and 12.6, 15-H), 3.64–3.45 (3 H, m, 17-H, 18-H_2), 3.41 (3 H, s, OMe), 3.40 (3 H, s, OMe), 3.39 (3 H, s, OMe), 2.99 (1 H, d, *J* 3.5, 13-H), 2.27 (1 H, ddd, *J* 3.9, 12.2 and 14.9, 16-H_AH_B), 1.66 (1 H, ddd, *J* 3.1, 9.3 and 14.7, 16-H_AH_B), 0.93 and 1.19 (3 H, each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 90.9 (2), 87.3 (1), 83.6 (1), 78.4 (1), 78.0 (1), 73.3 (1), 72.5 (2), 63.9 (1), 59.8 (3), 59.4 (3), 57.1 (3), 37.1 (0), 28.4 (2), 27.2 (3), 21.2 (3); *m*/*z* (CI, NH_3) 363 [$(M + NH_4)^+$, 17%], 346 [$(M + H)^+$, 100], 303 (32) [Found: $(M + H)^+$, 346.1969. $C_{15}H_{28}N_3O_6$ requires *M*, 346.1978].

Formation of oxalamides 35a,b

A solution of 1:2 mixture of C-5 diastereoisomeric azides **34a,b** (45 mg, 0.13 mmol) in THF (5.5 cm^3) was stirred under argon at room temp. 5% Pd on C (97 mg) was added and the argon atmosphere was replaced by hydrogen. The reaction mixture was stirred for 15 min, cooled to −20 °C and hydrogen was replaced by argon. A solution of DMAP (54 mg, 0.44 mmol, 3.4 equiv.) in THF (1 cm^3) and methyl oxalyl chloride (40 μl, 0.43 mmol, 3.3 equiv.) were added. The reaction mixture was stirred for 15 min at −20 °C, diluted with CH_2Cl_2 (30 cm^3), and filtered through a pad of Celite. The filtrate was washed with water and sat. aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. The residue (1:2 mixture of C-5 diastereoisomers **35a** and **35b**) was chromatographed on SiO_2 (5.5 g, hexanes:AcOEt 30–100%) to give the amides **35a,b** (41 mg,

77%) as a colourless oil. The isomers **35a** [R_f 0.29 ($CHCl_3$:MeOH = 39:1)] and **35b** [R_f 0.49 ($CHCl_3$:MeOH = 39:1)] were separated by chromatography on SiO_2 (hexanes:AcOEt).

(1*R*,5*S*,6*R*,8*R*,10*S*)-10-Methoxy-5-(methoxydioxoethanamido)-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane 35a. Mp 99.5–100 °C (ether:hexane); $[\alpha]_D$ +88.2 (*c* 0.73 in $CHCl_3$); $\nu_{max}(CCl_4)/cm^{-1}$ 3409 (m), 1727 (s), 1520 (m), 1110 (s); δ_H(270 MHz, $CDCl_3$) 7.58 (1 H, br d, *J* 9.1, NH), 5.71 (1 H, t, *J* 9.8, 10-H), 5.17 (1 H, d, *J* 7.0, OCH_AH_BO), 4.80 (1 H, d, *J* 7.0, OCH_AH_BO), 4.25 (1 H, dd, *J* 6.8, 10.4, 12-H), 3.94 (3 H, s, CO_2Me), 3.94 (1 H, dd, *J* 6.8 and 9.8, 11-H), 3.58 (3 H, s, OMe), 3.46 (1 H, d, *J* 10.4, 13-H), 3.40–3.20 (4 H, m), 3.31 (3 H, s, OMe), 3.30 (3 H, s, OMe), 1.56–1.75 (2 H, m, 16-H_2), 0.89 and 0.98 (3 H each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 160.4 (0), 156.8 (0), 86.8 (2), 79.6 (1), 78.0 (1), 76.0 (1), 74.9 (1), 74.2 (1), 74.0 (2), 70.4 (1), 62.0 (1), 59.3 (3), 57.1 (3), 54.0 (3), 41.9 (0), 30.0 (2), 23.3 (3), 13.5 (3); *m*/*z* (CI, NH_3) 423 [$(M + NH_4)^+$, 67%], 406 [$(M + H)^+$, 100] [Found: $(M + H)^+$, 406.2062. $C_{18}H_{32}NO_9$ requires *M*, 406.2077].

(1*R*,5*R*,6*R*,8*R*,10*S*)-10-Methoxy-5-(methoxydioxoethanamido)-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decane 35b. $[\alpha]_D$ +19.7 (*c* 0.745 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3417 (m), 1768 (m), 1724 (s), 1516 (s), 1289 (s), 1195 (s), 1110 (s); δ_H(270 MHz, $CDCl_3$) 8.19 (1 H, br d, *J* 9.5, NH), 5.44 (1 H, dd, *J* 1.7 and 9.3, 10-H), 5.11 (1 H, d, *J* 6.8, OCH_AH_BO), 4.84 (1 H, d, *J* 6.8, OCH_AH_BO), 3.90 (3 H, s, CO_2Me), 3.75 (2 H, m, 12-H, 11-H), 3.69 (1 H, dd, *J* 3.1 and 12.2, 15-H), 3.55 (1 H, dd, *J* 3.1 and 10.4, 18-H_AH_B), 3.50 (1 H, dd, *J* 4.4 and 10.4, 18-H_AH_B), 3.42–3.25 (1 H, m), 3.39 (3 H, s, OMe), 3.385 (3 H, s, OMe), 3.33 (3 H, s, OMe), 2.95 (1 H, d, *J* 1.7, 13-H), 2.32 (1 H, ddd, *J* 4.6, 12.2 and 14.9, 16-H_AH_B), 1.68 (1 H, ddd, *J* 3.1, 8.1 and 14.9, 16-H_AH_B), 0.95 and 1.23 (3 H each, s, 14-Me); δ_C(67.5 MHz, $CDCl_3$) 164.4 (0), 156.0 (0), 91.8 (2), 83.9 (1), 79.4 (1), 78.5 (1), 77.5 (1), 72.9 (1), 72.8 (2), 61.5 (1), 59.5 (3), 59.4 (3), 57.1 (3), 36.8 (0), 28.5 (2), 27.6 (3), 22.4 (3); *m*/*z* (CI, NH_3) 423 [$(M + NH_4)^+$, 77%], 406 [$(M + H)^+$, 100] [Found: $(M + H)^+$, 406.2070. $C_{18}H_{32}NO_9$ requires *M*, 406.2077].

Coupling product 37

A flame-dried 10 cm^3 tube was charged with stannane **36** (34 mg, 0.0766 mmol) and THF (0.4 cm^3). BuLi (50 μl, 1.52 mol dm^{-3} in hexane, 0.076 mmol) was added at −80 °C under argon. The solution was stirred for 15 min at −80 °C. Then TMEDA (15 μl) was added and after 10 min a cold (−80 °C) solution of ester **35a** (9.5 mg) in THF (2 × 0.25 cm^3) was added *via* cannula. The reaction mixture was stirred at −80 °C for 30 min, treated with sat. aqueous NH_4Cl (1 cm^3), and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (0.83 g, hexanes:AcOEt 5–40%) to give the adduct **37** [9.8 mg, 64%, R_f 0.34 (benzene:AcOEt = 7:3)] as a pale yellow oil, $[\alpha]_D$ −6.4 (*c* 0.55 in $CHCl_3$); $\nu_{max}(CCl_4)/cm^{-1}$ 3400 (m), 1703 (m), 1673 (s), 1613 (w), 1510 (m), 1109 (s), 1027 (s); δ_H(270 MHz, $CDCl_3$) 7.58 (1 H, br d, *J* 9.3, NH), 7.55–7.48 (2 H, m), 7.32–7.26 (3 H, m), 7.16 (1 H, dd, *J* 1.6 and 2.1, 5-H), 5.69 (1 H, t, *J* 9.5, 10-H), 5.17 (1 H, d, *J* 7.0, OCH_AH_BO), 4.89 (1 H, d, *J* 6.8, OCH_AH_BO), 4.24 (1 H, dd, *J* 6.8 and 10.4, 12-H), 4.10 (1 H, dq, *J* 1.5 and 6.6, 2-H), 3.95 (1 H, dd, *J* 6.6 and 9.9, 11-H), 3.58 (3 H, s, OMe), 3.45 (1 H, d, *J* 10.4, 13-H), 3.40–3.20 (4 H, m), 3.284 (3 H, s, OMe), 3.279 (3 H, s, OMe), 3.02–2.90 (2 H, m, CH_2SePh), 2.86 (1 H, m, 4-H), 2.03 (1 H, m, 3-H), 1.8–1.5 (2 H, m, 16-H_2), 1.39 (3 H, d, *J* 6.6, 2-Me), 1.00 (3 H, s, 14-Me_{eq}), 0.89 (3 H, s, 14-Me_{ax}), 0.82 (3 H, d, *J* 7.0, 3-Me); δ_H(270 MHz, C_6D_6 referenced to 7.20 ppm) 7.54 (1 H, br d, *J* 9.1, NH), 7.50–7.42 (2 H, m), 7.27 (1 H, dd, *J* 1.7 and 2.3, 5-H), 7.10–7.00 (3 H, m), 5.84 (1 H, t, *J* 9.7, 10-H), 4.73 (1 H, d, *J* 7.0, OCH_AH_BO), 4.65 (1 H, d, *J* 6.8, OCH_AH_BO), 4.27 (1 H, dd, *J* 7.0 and 10.4, 12-H), 3.60–3.45 (4 H, m), 3.35–3.40 (1 H, m), 3.35 (3 H, s, OMe), 3.32–3.26 (1 H, m), 3.30 (3 H, s, OMe), 3.28 (3 H, s, OMe), 3.04 (1 H, d, *J* 10.4, 13-H), 2.78 (1 H, dd, *J* 7.9 and 11.8, CH_AH_BSePh), 2.73 (1 H, dd, *J* 8.7 and 11.8, CH_AH_BSePh), 2.60 (1 H, m, 4-H), 1.8–1.5 (2 H, m), 1.35 (1 H, m), 1.06 (3 H, d, *J* 6.4, 2-Me), 0.92 (3 H, s, 14-Me_{eq}), 0.85 (3 H, s, 14-Me_{ax}), 0.67 (3 H, d, *J* 7.0, 3-Me); δ_C(67.5 MHz, C_6D_6 referenced to 128.4 ppm) 181.0 (0), 162.0 (0), 149.0 (0), 133.7 (1), 130.6 (0), 129.8 (1), 127.7 (1), 123.9 (1), 86.7 (2), 79.6 (1), 78.8 (1), 76.8 (1), 75.8 (1), 75.4 (1), 75.1 (2), 74.2 (1), 70.8 (1), 61.7 (3), 59.5 (3), 57.3 (3), 42.0 (0), 39.6 (1), 33.7 (1), 31.1 (2), 30.0 (2), 23.3 (3), 18.4 (3), 13.7 (3), 6.1 (3); *m*/*z* (CI, NH_3) 673 [$(M + NH_4)^+$, 23%], 656 [$(M + H)^+$, 36], 515 [$(M + NH_4 - PhSeH)^+$, 42], 498 [$(M + H - PhSeH)^+$, 100] (EI, Found: $M^{+\bullet}$, 655.2223. $C_{31}H_{45}NO_9Se$ requires *M*, 655.2260).

Benzoates 39a,b

L-Selectride® (50 μl, 0.05 mmol, 1 mol dm^{-3} in THF) was added to a stirred solution of the ketone **37** (16 mg, 0.0245 mmol) in THF (0.5 cm^3) at −95 °C. The reaction mixture was stirred for 15 min at −95 °C whereupon brine was added and the mixture extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated. The residual crude alcohols **38a,b** (22 mg, *ca.* 2.5:1 mixture by NMR of the crude product) were treated with camphorsulfonic acid (CSA) (1.8 mg) in a mixture of CH_2Cl_2 (1 cm^3) and MeOH (0.1 cm^3). The reaction mixture was stirred at room temp. for 1.75 h. K_2CO_3 (10 mg) was added and after 30 min the reaction mixture was poured into sat. aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue (20 mg) was treated with CH_2Cl_2 (1 cm^3), DMAP (6 mg, 0.05 mmol), Et_3N (40 μl, 0.29 mmol) and finally a solution of benzoyl chloride (BzCl) (1 mol dm^{-3}) in CH_2Cl_2 (73 μl, 0.073 mmol). After 9 h stirring at room temp. MeOH (0.1 cm^3) was added and the reaction mixture was stirred for 10 min and then poured into brine and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (1.5 g, hexanes:AcOEt 5–40%) to give a mixture of four diastereoisomers of the benzoate **39a–d** as a colourless oil (14.7 mg, 76%). The four diastereoisomers had the following R_f values in (hexanes:Et_2O = 1:2): **39d** (0.38), **39a** (0.31), **39b** (0.26), **39c** (0.20). The relative ratio of the four diastereoisomers could be easily distinguished by ^1H NMR analysis ($CDCl_3$) of the sharp singlets arising from the 7-H: **39a** (δ 5.90, 65%), **39b** (δ 5.44, 28%), **39c** (δ 5.64, 5%), **39d** (δ 5.51, 2%). The diastereoisomers were separated by preparative TLC (Merck, silica gel 60 F_{254}, 20 × 20 cm, 0.25 mm thick, hexanes:Et_2O = 1:2) and data collected for **39a** and **39b**. Insufficient quantities of isomers **39c** and **39d** precluded their full characterisation.

Diastereoisomer **39a** (R_f 0.31), $[\alpha]_D$ +87.2 (*c* 0.43 in $CHCl_3$); $\nu_{max}(CCl_4)/cm^{-1}$ 3360 (m), 1736 (s), 1708 (s), 1603 (w), 1518 (m), 1263 (s), 1110 (s), 1038 (s); δ_H(360 MHz, C_6D_6 referenced to 7.16 ppm) 8.29 (2 H, dd, *J* 1.4 and 8.1), 7.47 (2 H, dd, *J* 1.5 and 8.1), 7.42 (1 H, br d, *J* 9.7, NH), 7.10–6.90 (6 H, m), 5.97 (1 H, s, 7-H), 5.93 (1 H, t, *J* 9.7, 10-H), 4.59 (1 H, d, *J* 7.0, OCH_AH_BO), 4.58 (1 H, d, *J* 7.0, OCH_AH_BO), 4.29 (1 H, dd, *J* 6.7 and 10.3, 12-H), 3.78 (1 H, dd, *J* 6.7 and 9.7, 11-H), 3.65–3.53 (4 H, m), 3.43 (1 H, dd, *J* 2.4 and 9.5, 15-H), 3.39 (3 H, s, OMe), 3.31 (3 H, s, OMe), 3.26 (3 H, s, OMe), 3.05 (1 H, d, *J* 10.3, 13-H), 2.93 (1 H, dd, *J* 11.9 and 12.8, CH_AH_BSePh), 2.92 (3 H, s, OMe), 2.90 (1 H, dd, *J* 7.0 and 11.9, CH_AH_BSePh), 2.44 (1 H, m with 10 lines, 4-H), 2.30 (1 H, dd, *J* 3.3 and 13.3, 5-H_AH_B), 1.84 (1 H, t, *J* 12.9, 5-H_AH_B), 1.84 (1 H, ddd, *J* 2.7, 8.8 and 14.5, 16-H_AH_B), 1.73 (1 H, ddd, *J* 4.4, 9.5 and 14.3, 16-H_AH_B), 1.58 (1 H, m, 3-H), 0.89 (3 H, s, 14-Me_{eq}), 0.877 (3 H, d, *J* 6.8, 2-Me), 0.868 (3 H, s, 14-Me_{ax}), 0.868 (3 H, d, *J* 7.1, 3-Me); δ_C(90 MHz, C_6D_6 referenced to 128.4 ppm) 167.3 (0), 165.7 (0), 133.6 (1), 133.3 (1), 131.5 (0), 130.7 (0), 130.6 (1), 129.7 (1), 129.0 (1), 127.3 (1), 99.7 (0), 86.8 (2), 79.6 (1), 78.4 (1), 76.6 (1), 75.4 (1), 74.6 (1), 73.8 (2), 73.2 (1),

72.0 (1), 71.1 (1), 61.6 (3), 59.4 (3), 57.2 (3), 48.4 (3), 42.1 (0), 36.0 (1), 35.6 (1), 32.6 (2), 31.8 (2), 31.7 (2), 23.5 (3), 18.5 (3), 14.0 (3), 5.2 (3); *m/z* (CI, NH_3) 811 [$(M + NH_4)^+$, 4%], 793 [$(M + H)^+$, 3], 779 [$(M + NH_4 - MeOH)^+$, 52], 762 [$(M + H - MeOH)^+$, 100], 621 (35), 604 (80) (EI, Found: $M^{+\bullet}$, 793.2946. $C_{39}H_{55}NO_{11}Se$ requires *M*, 793.2940).

Diastereoisomer **39b** (R_f 0.26), ν_{max}/cm^{-1} (CCl_4) 3356 (w), 3073 (w), 1736 (s), 1712 (s), 1603 (w), 1520 (m), 1261 (s), 1129 (s), 1110 (s), 1034 (s); δ_H(360 MHz, C_6D_6 referenced to 7.16 ppm) 8.33 (2 H, dd, *J* 1.5 and 7.8), 7.44 (2 H, dd, *J* 1.6 and 7.9), 7.40 (1 H, br d, *J* 9.3, NH), 7.10–6.90 (6 H, m), 5.97 (1 H, t, *J* 9.7, 10-H), 5.85 (1 H, s, 7-H), 4.68 (1 H, d, *J* 6.9, OCH_AH_BO), 4.63 (1 H, d, *J* 6.9, OCH_AH_BO), 4.31 (1 H, dd, *J* 7.0 and 10.5, 12-H), 3.86–3.68 (4 H, m), 3.54 (1 H, dq, *J* 2.3 and 6.6, 2-H), 3.50 (3 H, s, OMe), 3.43 (1 H, dd, *J* 1.7 and 10.0, 15-H), 3.41 (3 H, s, OMe), 3.29 (3 H, s, OMe), 3.25 (3 H, s, OMe), 3.03 (1 H, d, *J* 10.5, 13-H), 2.56 (1 H, dd, *J* 6.9 and 12.0, CH_AH_BSePh), 2.53 (1 H, dd, *J* 9.0 and 12.0, CH_AH_BSePh), 2.44 (1 H, m, 4-H), 2.08 (1 H, dd, *J* 3.8 and 13.2, 5-H_AH_B), 2.00 (1 H, ddd, *J* 1.5, 9.6 and 13.7, 16-H_AH_B), 1.81 (1 H, ddd, *J* 3.3, 10.3 and 13.6, 16-H_AH_B), 1.60 (1 H, t, *J* 13.2, 5-H_AH_B), 1.49 (1 H, m, 3-H), 0.94 (3 H, s, 14-Me_{eq}), 0.89 (3 H, s, 14-Me_{ax}), 0.85 (3 H, d, *J* 6.5, 2-Me), 0.58 (3 H, d, *J* 7.0, 3-Me); δ_C(90 MHz, C_6D_6 referenced to 128.4 ppm) 167.6 (0), 166.0 (0), 133.6 (1), 133.4 (1), 131.4 (0), 130.8 (0), 130.6 (1), 129.7 (1), 129.0 (1), 127.4 (1), 100.0 (0), 86.7 (2), 79.6 (1), 78.7 (1), 76.3 (1), 75.7 (1), 74.3 (1), 74.0 (1), 73.4 (2), 72.0 (1), 71.1 (1), 61.7 (3), 59.7 (3), 57.2 (3), 49.3 (3), 42.2 (0), 35.8 (1), 35.3 (1), 32.4 (2), 32.1 (2), 31.2 (2), 23.3 (3), 18.4 (3), 13.7 (3), 4.6 (3); *m/z* (CI, NH_3) 811 [$(M + NH_4)^+$, 8%], 793 [$(M + H)^+$, 4], 779 [$(M + NH_4 - MeOH)^+$, 81], 762 [$(M + H - MeOH)^+$, 100], 604 (52) (EI, Found: $M^{+\bullet}$, 793.2932. $C_{39}H_{55}NO_{11}Se$ requires *M*, 793.2940).

7-*O*-Benzoyl-18-*O*-methyl mycalamide B 40

The diastereoisomerically pure selenide **39a** (8.5 mg, 0.0107 mmol) was dissolved in MeOH (0.6 cm^3) and then water (0.2 cm^3) was added to give a white suspension. $NaIO_4$ (15 mg, 0.07 mmol) was added in one portion. After 20 min at room temp. the reaction mixture was diluted with CH_2Cl_2 (30 cm^3) and washed with water (2 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude selenoxide which was dissolved in a mixture of benzene (0.5 cm^3) and Et_3N (0.5 cm^3) and heated at reflux for 2 min. After cooling to room temp., the reaction mixture was poured into sat. aqueous $NaHCO_3$ and extracted with Et_2O (2 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (0.5 g, hexanes: AcOEt 5–40%) to give the olefin **40** (6.5 mg, 95%) as a colourless oil: $[\alpha]_D$ + 116.0 (*c* 0.325 in benzene), $\nu_{max}(CCl_4)/cm^{-1}$ 3363 (m), 3069 (w), 1737 (s), 1709 (s), 1655 (w), 1603 (w), 1521 (m), 1264 (s), 1126 (s), 1109 (s), 1038 (s); δ_H(360 MHz, C_6D_6 referenced to 7.16 ppm) 8.31 (2 H, dd, *J* 1.6 and 8.4), 7.49 (1 H, br d, *J* 9.5, NH), 7.10–7.00 (3 H, m), 5.98 (1 H, s, 7-H), 5.96 (1 H, t, *J* 9.8, 10-H), 4.82 (1 H, t, *J* 1.8, =CH_2), 4.81 (1 H, t, *J* 1.8, =CH_2), 4.60 (1 H, d, *J* 6.9, OCH_AH_BO), 4.58 (1 H, d, *J* 6.9, OCH_AH_BO), 4.32 (1 H, dd, *J* 6.7 and 10.4, 12-H), 3.82 (1 H, dq, *J* 2.8 and 6.6, 2-H), 3.82 (1 H, dd, *J* 6.7 and 10.1, 11-H), 3.66 (2 H, d, *J* 3.8, 18-H_2), 3.57 (1 H, ddt, *J* 3.8, 3.8 and 10.0, 17-H), 3.44 (1 H, dd, *J* 1.6 and 9.7, 15-H), 3.41 (3 H, s, OMe), 3.34 (3 H, s, OMe), 3.26 (3 H, s, OMe), 3.05 (1 H, d, *J* 10.4, 13-H), 2.93 (3 H, s, OMe), 2.91 (1 H, dt, *J* 1.9 and 14.0, 5-H_AH_B), 2.82 (1 H, d, *J* 14.0, 5-H_AH_B), 1.96 (1 H, dq, *J* 2.8 and 7.2, 3-H), 1.87 (1 H, ddd, *J* 1.8, 10.0 and 14.0, 16-H_AH_B), 1.74 (1 H, ddd, *J* 3.8, 9.8 and 13.8, 16-H_AH_B), 1.14 (3 H, d, *J* 7.2, 2-Me), 0.93 (3 H, s, 14-Me), 0.93 (3 H, d, *J* 6.6, 3-Me), 0.87 (3 H, s, 14-Me); δ_C(90 MHz, C_6D_6 referenced to 128.4 ppm) 167.2 (0), 165.8 (0), 146.0 (0), 133.7 (1), 130.7 (1), 129.0 (1), 111.5 (2), 100.3 (0), 86.9 (2), 79.4 (1), 78.5 (1), 76.6 (1), 75.5 (1), 74.5 (1), 73.8 (2), 73.1 (1), 72.3 (1), 70.3 (1), 61.7 (3), 59.5 (3), 57.5 (3), 48.6 (3), 42.0 (2C, 1), 35.7 (2), 35.3 (1), 31.8 (2), 23.5 (3), 18.1 (3), 13.8 (3), 12.8 (3); *m/z* (CI, NH_3) 653 [$(M + NH_4)^+$, 3%], 621 [$(M + NH_4 - MeOH)^+$, 26], 604 [$(M + H - MeOH)^+$, 100] (EI, Found: $M^{+\bullet}$, 635.3328. $C_{33}H_{49}NO_{11}$ requires *M*, 635.3306).

18-*O*-Methyl mycalamide B 6

LiOH (0.2 cm^3, 1 mol dm^{-3} in H_2O) was added to a solution of the ester **40** (4.9 mg, 0.008 mmol) in MeOH (1 cm^3). The reaction mixture was stirred at room temp. for 30 min, diluted with benzene (20 cm^3), washed successively with water (2 × 5 cm^3) and brine (5 cm^3), dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (0.15 g, benzene: AcOEt 0–50%) to give 18-*O*-methyl mycalamide B **6** [3.8 mg, 92%, R_f 0.19 (benzene: EtOAc = 1:1)] as a colourless oil, $\nu_{max}(CCl_4)/cm^{-1}$ 3451 (w), 3418 (w), 3354 (m), 3081 (w), 1687 (s), 1531 (m), 1128 (s), 1110 (s), 1038 (s); δ_H(360 MHz, C_6D_6 referenced to 7.16 ppm) 7.70 (1 H, br d, *J* 9.4, NH), 5.97 (1 H, t, *J* 9.8, 10-H), 4.79 (1 H, t, *J* 2.0, =CH_2), 4.74 (1 H, t, *J* 2.0, =CH_2), 4.64 (1 H, d, *J* 6.9, OCH_AH_BO), 4.60 (1 H, d, *J* 6.9, OCH_AH_BO, 4.30 (1 H, dd, *J* 6.9 and 10.6, 12-H), 4.23 (2 H, m, 7-H and OH), 3.89 (1 H, dq, *J* 2.7 and 6.5, 2-H), 3.81 (1 H, dd, *J* 6.9 and 9.9, 11-H), 3.60 (1 H, dd, *J* 5.4 and 10.5, 18-H_AH_B), 3.58 (1 H, dd, *J* 2.5 and 10.5, 18-H_AH_B), 3.50 (1 H, m, 17-H), 3.41 (1 H, dd, *J* 2.0 and 9.7, 15-H), 3.36 (3 H, s, OMe), 3.33 (3 H, s, OMe), 3.27 (3 H, s, OMe), 3.11 (3 H, s, OMe), 3.05 (1 H, d, *J* 10.5, 13-H), 2.70 (1 H, d, *J* 14.0, 5-H_AH_B), 2.48 (1 H, dt, *J* 2.0 and 14.1, 5-H_AH_B), 1.94 (1 H, dq, *J* 2.9 and 7.1, 3-H), 1.78 (1 H, ddd, *J* 2.0, 9.7 and 14.1, 16-H_AH_B), 1.69 (1 H, ddd, *J* 3.9, 9.8 and 13.8, 16-H_AH_B), 1.00 (3 H, d, *J* 7.1, 2-Me), 0.87 (3 H, s, 14-Me), 0.862 (3 H, d, *J* 6.4, 3-Me), 0.858 (3 H, s, 14-Me); δ_C(90 MHz, C_6D_6 referenced to 128.4 ppm) 172.8 (0), 146.3 (0), 111.3 (2), 101.0 (0), 86.8 (2), 79.4 (1), 78.6 (1), 76.5 (1), 75.5 (1), 74.6 (1), 74.1 (2), 72.5 (1), 72.1 (1), 69.7 (1), 61.7 (3), 59.5 (3), 57.5 (3), 48.6 (3), 42.1 (1), 42.0 (0), 34.6 (2), 31.6 (2), 23.4 (3), 18.2 (3), 14.9 (3), 12.9 (3); *m/z* (CI, NH_3) 549 [$(M + NH_4)^+$, 0.5%], 532 [$(M + H)^+$, 0.5], 517 [$(M + NH_4 - MeOH)^+$, 5], 500 [$(M + H - MeOH)^+$, 100] (EI, Found: $M^{+\bullet}$, 531.3022. $C_{26}H_{45}NO_{10}$ requires *M*, 531.3043).

10-*epi*-18-*O*-Methyl mycalamide B **41** was prepared from ester **35b** and the dihydro-2*H*-pyranyllithium **9** as summarised in Scheme 8.

Coupling product 42

By the same procedure as described above stannane **36** (42 mg, 0.0946 mmol) and ester **35b** (12.5 mg) gave the adduct **42** [9.4 mg, 47%, R_f 0.47 (benzene: AcOEt = 7:3)] as a pale yellow oil; $\nu_{max}(CCl_4)/cm^{-1}$ 3410 (m), 1702 (m), 1673 (s), 1614 (w), 1506 (s), 1108 (s), 1038 (s); δ_H(270 MHz, $CDCl_3$) 8.07 (1 H, br d, *J* 9.3, NH), 7.55–7.48 (2 H, m), 7.35–7.25 (3 H, m), 6.93 (1 H, t, *J* 1.7, 5-H), 5.42 (1 H, dd, *J* 1.6 and 19.1, 10-H), 5.14 (1 H, d, *J* 6.6, OCH_AH_BO), 4.87 (1 H, d, *J* 6.6, OCH_AH_BO), 4.09 (1 H, dq, *J* 1.4 and 6.6, 2-H), 3.77 (2 H, d, *J* 1.4, 11-H, 12-H), 3.69 (1 H, dd, *J* 2.7 and 12.9, 15-H), 3.64 (1 H, dd, *J* 3.5 and 10.6, 18-H_AH_B), 3.52 (1 H, dd, *J* 2.9 and 10.6, 18-H_AH_B), 3.40–3.25 (1 H, m), 3.40 (3 H, s, OMe), 3.38 (3 H, s, OMe), 3.33 (3 H, s, OMe), 3.00–2.80 (4 H, m), 2.35 (1 H, ddd, *J* 4.5, 12.4 and 14.9, 16-H_AH_B), 2.03 (1 H, m, 3-H), 1.73 (1 H, ddd, *J* 3.3, 8.9 and 14.9, 16-H_AH_B), 1.38 (3 H, d, *J* 6.4, 2-Me), 1.24 (3 H, s, 14-Me_{eq}), 0.96 (3 H, s, 14-Me_{ax}), 0.78 (3 H, d, *J* 7.0, 3-Me); δ_C(67.5 MHz, C_6D_6 referenced to 128.4 ppm), 181.7 (0), 161.4 (0), 149.2 (0), 133.7 (1), 130.7 (0), 129.8 (1), 127.6 (1), 123.4 (1), 91.9 (2), 84.7 (1), 79.6 (1), 79.2 (1), 77.8 (1), 76.7 (1), 73.5 (2), 73.3 (1), 62.1 (1), 59.4 (3), 59.2 (3), 57.5 (3), 39.5 (1), 37.2 (0), 33.7 (1), 29.82 (2), 29.79 (2), 28.2 (3), 22.7 (3), 18.4 (3), 6.1 (3); *m/z* (CI, NH_3) 673 [$(M + NH_4)^+$, 28%], 656 [$(M + H)^+$, 60], 515 [$(M + NH_4 - PhSeH)^+$, 37], 498 [$(M + H - PhSeH)^+$, 100] (EI, Found: $M^{+\bullet}$, 655.2247. $C_{31}H_{45}NO_9Se$ requires *M*, 655.2260).

Benzoate 43

By the same procedure as described above ketone **42** (17 mg, 0.026 mmol) was reduced by L-Selectride®, and the product

treated with CSA and MeOH followed by BzCl to give a 20:1 mixture of two discernible diastereoisomers (14 mg, 68%) as a colourless oil. The 7-H signal appeared at δ 5.49 for the major diastereoisomer **43** and at δ 5.43 for the minor. The data given below collected on the mixture refer to the major isomer, δ_H(270 MHz, $CDCl_3$) 8.10 (2 H, dd), 8.08 (1 H, br d, *J* 9.5, NH), 7.65–7.40 (5 H, m), 5.49 (1 H, s, 7-H), 7.20–7.35 (3 H, m), 5.37 (1 H, dd, *J* 2.3 and 9.5, 10-H), 5.02 (1 H, d, *J* 6.6, OCH_AH_BO), 4.76 (1 H, d, *J* 6.6, OCH_AH_BO), 4.02 (1 H, dq, *J* 2.5 and 6.6, 2-H), 3.80–3.65 (2 H, m, 11-H, 12-H), 3.58 (1 H, dd, *J* 2.7 and 11.8, 15-H), 3.45–3.55 (2 H, m), 3.44 (3 H, s, OMe), 3.42 (3 H, s, OMe), 3.40–3.30 (1 H, m), 3.38 (3 H, s, OMe), 3.18 (3 H, s, 6-OMe), 2.91 (1 H, dd, *J* 6.5 and 12.2, CH_AH_BSePh), 2.91 (1 H, d, *J* 2.5, 13-H), 2.84 (1 H, dd, *J* 9.5 and 12.2, CH_AH_BSePh), 2.45–2.25 (1 H, m), 2.37 (1 H, ddd, *J* 4.6, 12.0 and 15.6, 16-H_AH_B), 1.95 (1 H, dd, *J* 3.5 and 13.5, 5-H_AH_B), 1.84 (1 H, m, 3-H), 1.67 (1 H, ddd, *J* 3.3, 7.0 and 15.3, 16-H_AH_B), 1.53 (1 H, t, *J* 13.5, 5-H_AH_B), 1.28 (3 H, d, *J* 6.6, 2-Me), 1.23 (3 H, s, 14-Me_{eq}), 0.96 (3 H, s, 14-Me_{ax}), 0.87 (3 H, d, *J* 7.1, 3-Me).

10-*epi*-18-*O*-Methyl mycalamide 41

To a mixture of selenide **43** (14.5 mg, 0.018 mmol) in MeOH and water (3:1, 2 cm^3) was added $NaIO_4$ (15 mg, 0.07 mmol) in one portion. The reaction mixture was stirred at room temp. for 20 min and then diluted with Et_2O (50 cm^3). The organic layer was washed with water (2 × 10 cm^3) and brine, dried (Na_2SO_4) and concentrated to give the crude selenoxide as a pale brown oil. The selenoxide (14 mg) in benzene (2.5 cm^3) and Et_3N (1 cm^3) was heated at reflux for 2 min, cooled to room temp., poured into sat. aqueous $NaHCO_3$ and extracted with Et_2O (2 × 30 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude olefin (14 mg) which was treated with MeOH (2.5 cm^3) and LiOH (1 mol dm^{-3}) in H_2O (0.5 cm^3). The reaction mixture was stirred at room temp. for 45 min and concentrated. The residue was taken up in Et_2O (25 cm^3) and washed with water (2 × 10 cm^3) and brine. The extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (1 g, hexanes:AcOEt 30–100%) to give the 10-*epi*-18-*O*-methyl mycalamide **41** [6.3 mg, 67%, R_f 0.25 (benzene:AcOEt = 1:1)] as a colourless oil, $\nu_{max}(CCl_4)$/cm^{-1} 3430 (m), 3099 (w), 1692 (m), 1604 (w), 1520 (m), 1263 (m), 1104 (s), 1038 (s); δ_H(270 MHz, C_6D_6, referenced to 7.20 ppm) 8.54 (1 H, br d, *J* 9.3, NH), 5.37 (1 H, dd, *J* 2.2 and 9.7, 10-H), 4.88 (1 H, t, *J* 1.9, $=CH_2$), 4.84 (1 H, d, *J* 6.4, OCH_AH_BO), 4.80 (1 H, t, *J* 1.9, $=CH_2$), 4.48 (2 H, br s), 4.35 (1 H, d, *J* 6.6, OCH_AH_BO), 4.08 (1 H, dq, *J* 2.9 and 6.6, 2-H), 3.69 (1 H, dd, *J* 3.0 and 11.8, 15-H), 3.59 (1 H, br s), 3.55–3.40 (2 H, m), 3.40–3.20 (2 H, m), 3.35 (3 H, s, OMe), 3.29 (3 H, s, OMe), 3.20 (3 H, s, OMe), 2.95 (3 H, s, 6-OMe), 2.74 (1 H, d, *J* 2.1, 13-H), 2.66 (1 H, d, *J* 13.9, 5-H_{eq}), 2.53 (1 H, dt, *J* 1.8 and 13.9, 5-H_{ax}), 2.43 (1 H, ddd, *J* 4.6, 11.8 and 16.0, 16-H_AH_B), 2.12 (1 H, dq, *J* 2.9 and 7.3, 3-H), 1.84 (1 H, ddd, *J* 3.2, 4.8 and 15.5, 16-H_AH_B), 1.42 (3 H, s, 14-Me_{eq}), 1.39 (3 H, d, *J* 7.3, 3-Me), 1.28 (3 H, d, *J* 6.6, 2-Me), 0.97 (3 H, s, 14-Me_{ax}); δ_C(62.5 MHz, C_6D_6 referenced to 128.4 ppm) 173.1 (0), 146.9 (0), 110.9 (2), 101.0 (0), 91.6 (2), 84.5 (1), 80.4 (1), 79.7 (1), 78.2 (1), 75.4 (2), 72.8 (1), 71.3 (1), 70.1 (1), 61.5 (1), 59.3 (3), 59.2 (3), 57.9 (3), 48.3 (3), 42.6 (1), 37.1 (0), 33.7 (2), 30.0 (2), 28.0 (3), 23.5 (3), 18.5 (3), 12.7 (3); *m/z* (CI, NH_3) 549 [$(M + NH_4)^+$, 0.5%], 532 [$(M + H)^+$, 0.5], 517 [$(M + NH_4 - MeOH)^+$, 10], 500 [$(M + H - MeOH)^+$, 100] [Found: $(M + NH_4)^+$, 549.3409. $C_{26}H_{49}N_2O_{10}$ requires *M*, 549.3387].

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