Synthesis of salinomycin

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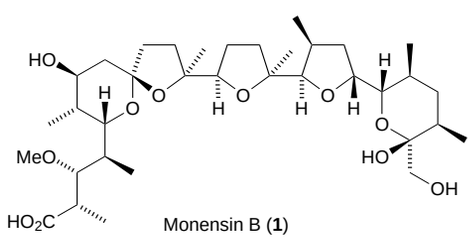
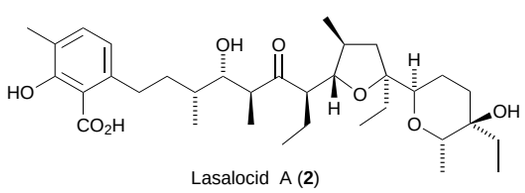
Salinomycin, a commercially significant coccidiostat isolated from *Streptomyces albus*, has been synthesised from three principal fragments. Key steps include (a) the use of η^3-allylmolybdenum cationic complexes 21a,b for the stereoselective construction of two contiguous stereogenic centres in fragment 5a; (b) the electrophilic cyclisation of 2-(prop-2-ynyl)-2-hydroxyoxanes to give molybdenum and chromium carbene complexes which are precursors to the furan fragment 7; (c) the diastereoselective oxidation of a 1,5-diene with potassium permanganate to generate four stereogenic centres in a single step leading to fragment 8; (d) the oxidative rearrangement of acylfuran 89 *en route* to the 1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene dispiroacetal core; and finally (e) the use of an allenol ether as an acyl anion equivalent together with the stereoselective hydrolysis of allenol ether intermediate 112 in an alternative synthesis of the dispiroacetal core.

Introduction

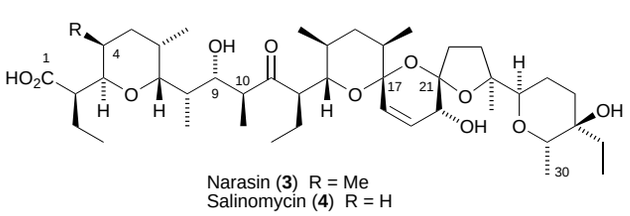
Coccidiosis is a gastrointestinal infection in birds and mammals caused by a protozoan parasite of the sporozoan subclass *Coccidia*. A significant event in the history of veterinary medicine occurred in 1968 when a group from the Eli Lilly company showed that monensin (**1**) was a potent orally active



Monensin B (**1**)



Lasalocid A (**2**)



Narasin (**3**) R = Me
Salinomycin (**4**) R = H

treatment for coccidiosis.[1] Because of the large potential market for coccidiostats in the poultry industry, a number of other laboratories began the search for polyether ionophores and by 1995 over 120 structures had been determined[2] including the commercial agents lasalocid (**2**), narasin (**3**) and salinomycin (**4**). Due to the high parenteral toxicity of the polyethers, they have no use as clinical antibacterial agents but low doses of ionophores are used as feed additives to improve feed utilisation in cattle, sheep and goats by controlling bacteria causing degradation of carbohydrate to pyruvic acid in the rumen.[3]

Salinomycin, one of the most complex of the commercial coccidiostats, was isolated[4] from the culture broth of *Streptomyces albus* and an X-ray crystallographic analysis of a *p*-iodophenacyl ester derivative[5] revealed the presence of a 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene motif which is rare in the polyether ionophores. A wealth of spectroscopic information is now available for salinomycin and its relatives including completely assigned ^{1}H and ^{13}C NMR spectra[6,7] as well as mass spectra.[8,9]

A lecture published in 1982 was the sole vehicle for disclosing the first total synthesis of salinomycin **4** and its 4-methyl analogue narasin **3** by Kishi *et al.*[10] Kishi's synthesis was noteworthy for two reasons: (a) it amplified and extended a general strategy for polyketide synthesis based on directed olefin epoxidation and regioselective oxirane cleavage and (b) it grappled for the first time with the thorny issue of spiroacetalisation stereochemistry in the complex dispiroacetal core. A 'chiral pool' strategy was used in the second synthesis of salinomycin by the Yonemitsu group[11–14] to construct the entire skeleton from three cheap precursors: D-glucose, D-mannitol and (*S*)-lactic acid. An enduring contribution of this group to organic synthesis was the development of the *p*-methoxybenzyl and 3,4-dimethoxybenzyl ether as protecting groups for hydroxy functions. Several laboratories have also reported approaches to the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system.[15–21] We now report details of our approach[22,23] to salinomycin which features: (a) the alkylation of an η^3-molybdenum cationic complex by an α-alkoxyalkyl cuprate to append a stereogenic centre to an oxane ring; (b) the use of a spirocyclic molybdenum carbene complex as a precursor to a furan; (c) the asymmetric oxidation of a 1,5-diene to create four stereogenic centres in a single step; and (d) two approaches to the 1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene ring system based on Achmatowicz's furan oxidation or the acylation-protonation of a metallated allenol ether intermediate.

Incunabula

Our synthetic plan (Scheme 1) involved the union of three fragments of roughly equal complexity which, taken together, constitute 40 of the 42 carbon atoms of salinomycin. In the ensuing discussion we will describe in sequence the construc-

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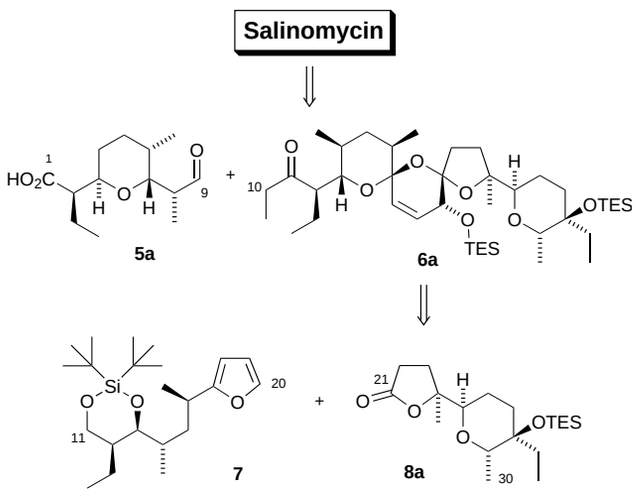
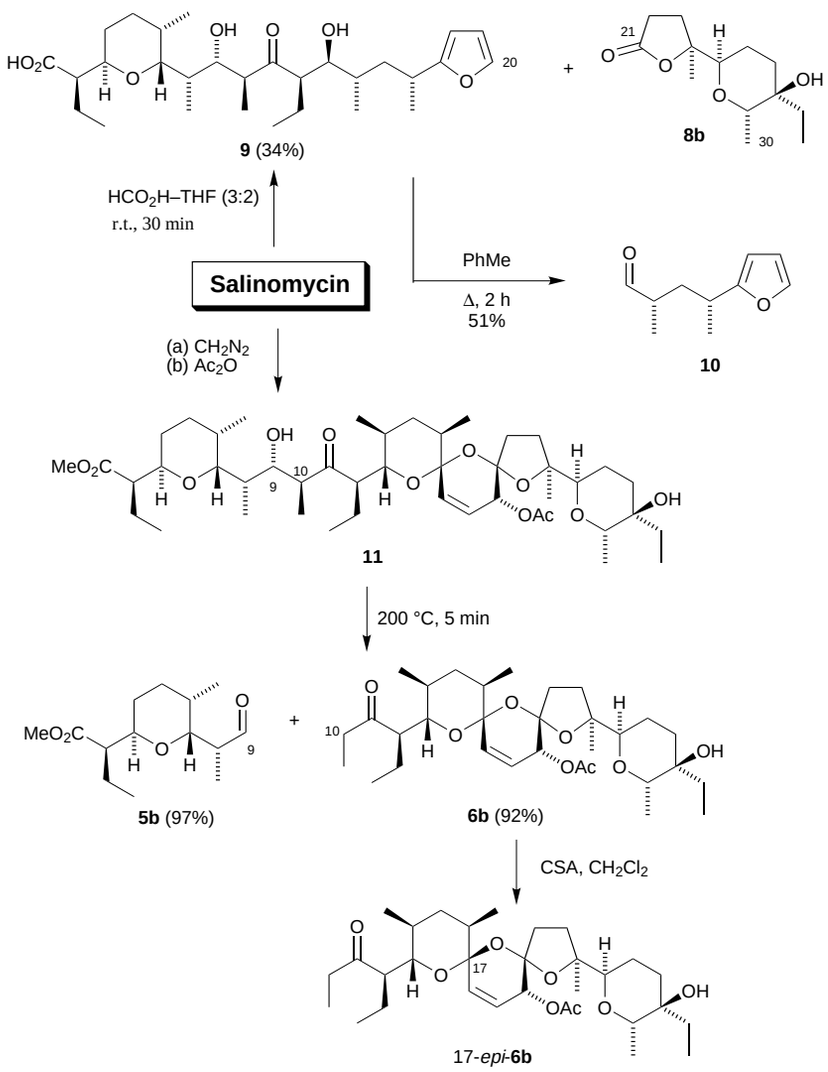
tion of C1–C9 fragment **5a**, C11–C20 fragment **7** and C21–C30 fragment **8a** (salinomycin numbering). We will then show how the furan can be used to conjoin fragments **7** and **8a** and serve as a latent enedione in the elaboration of the dispiroacetal moiety **6a**. Finally, we will connect fragments **5a** and **6a** using directed aldol chemistry along lines precedented in the work of Kishi. The significance of the four fragments depicted in Scheme 1 is best appreciated by considering some of the degradation chemistry of salinomycin (Scheme 2) which, run in reverse, served as inspiration for our synthetic plan. Thus, brief treatment of salinomycin with formic acid results in rupture of the central ring of the dispiroacetal core leading to the furan **9** and lactone **8b**.[24] Lactone **8b** can also be generated by treating salinomycin with NaOH.[6] Furan **9** underwent retroaldolisation in refluxing toluene to the smaller furan fragment **10** (51% yield) and other unidentified products but a far more efficient and cleaner retroaldolisation was observed on brief heating of 20-*O*-acetyl-salinomycin methyl ester **11** at 200 °C *in vacuo*. Aldehyde **5b** (97%) and ketone **6b** (92%) were isolated as crystalline products.[14]

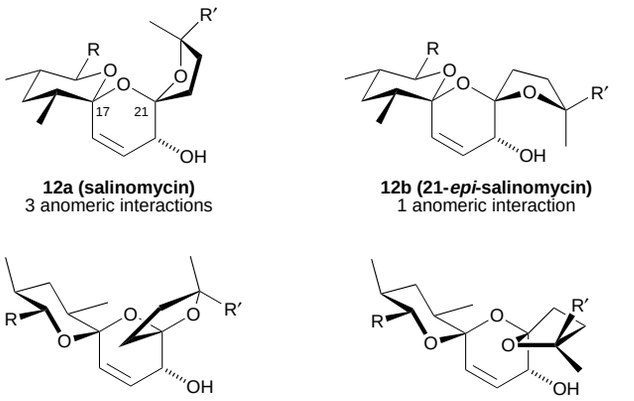


Scheme 1

One of the fundamental assumptions in our synthetic plan is that the spiroacetal system of salinomycin adopts the most stable configuration at both acetal centres consistent with a thermodynamically controlled cyclisation of a suitable acyclic diketo diol precursor. The assumption is not unreasonable: the vast majority of the natural spiroacetal systems are generated under thermodynamic control with the configuration of the spiroacetal centre being determined by a combination of anomeric effects and steric effects.[25–28] Hence, the one transformation depicted in Scheme 2 with ominous implications for the total synthesis of salinomycin is the acid-catalysed isomerisation of the dispiroacetal **6b** to 17-*epi*-**6b**—a transformation which indicates that the C17 epimer of the dispiroacetal system is more stable. A crude qualititative analysis of steric and anomeric effects in the four possible dispiroacetal diastereoisomers **12a**–**d** lends credence to the enhanced stability of the 17-*epi*-diastereoisomer. Consideration of anomeric effects alone suggests that 21-*epi*-diastereoisomer **12b** would be a fairly high



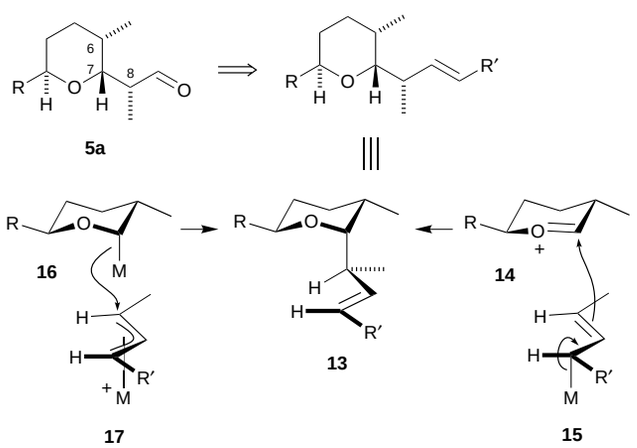
Scheme 2



energy structure as it only possesses one stabilising anomeric interaction whereas the others have three. Although the 17-*epi*-diastereoisomer **12c** suffers from a slightly larger 1,3-diaxial interaction between the C17 methylene and the C21 oxygen atom, it does not suffer from the unfavourable 1,3-dipole–dipole interaction exhibited by **12a** (corresponding to salinomycin) and the 17-*epi*-21-*epi*-diastereoisomer **12d**. Nevertheless, the fact that salinomycin was eventually prepared by an acid-catalysed isomerisation entails bizarre and fascinating factors whose elucidation must await the conclusion of this report.

Synthesis of C1–C9 fragment 5a

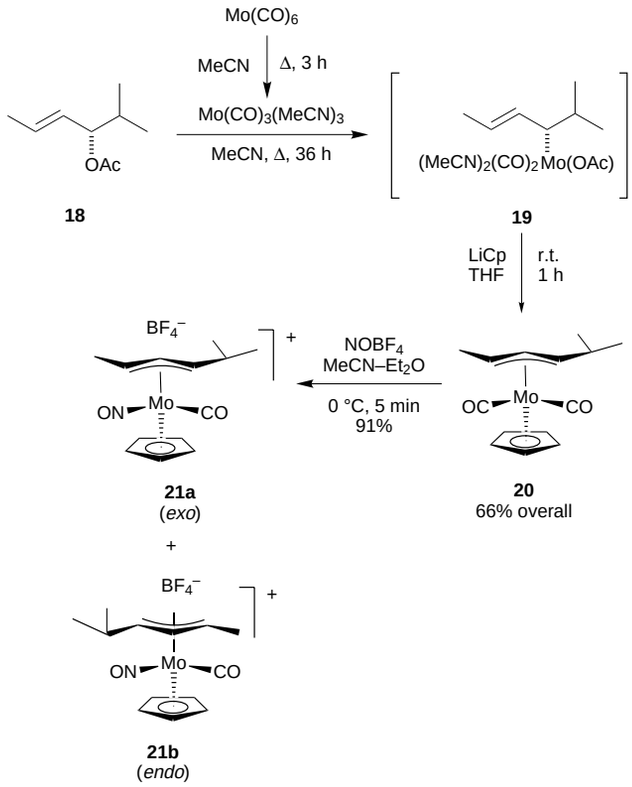
We considered two approaches to the C6–C8 stereotriad of fragment **5a** which converge at the alkene **13** (Scheme 3). In the



Scheme 3

first approach, a crotylmetal species **15** undergoes S_E2' attack by oxonium ion **14**. There is excellent precedent for axial stereoselectivity in such 'C-glycosidation' reactions[29] involving allylsilanes but the facial selectivity in the attack on **15** which controls the stereochemistry at C8 of the annectant chain was not easy to predict—especially when R′ = H (Note 1). By reversing the polarity of the S_E2' reaction, we expected better opportunities for stereocontrol in the union of the α-alkoxyalkylmetal species **16** and the η^3-allyl cationic complex **17**. However, success in the latter strategy would be crucially dependent on stereoselective routes to both reactants; *i.e.* a configurationally stable α-alkoxyalkylmetal **16** and an enantiomerically pure η^3-allyl cationic complex **17** with a substituent R′ large enough to impart adequate regioselectivity in the alkylation.

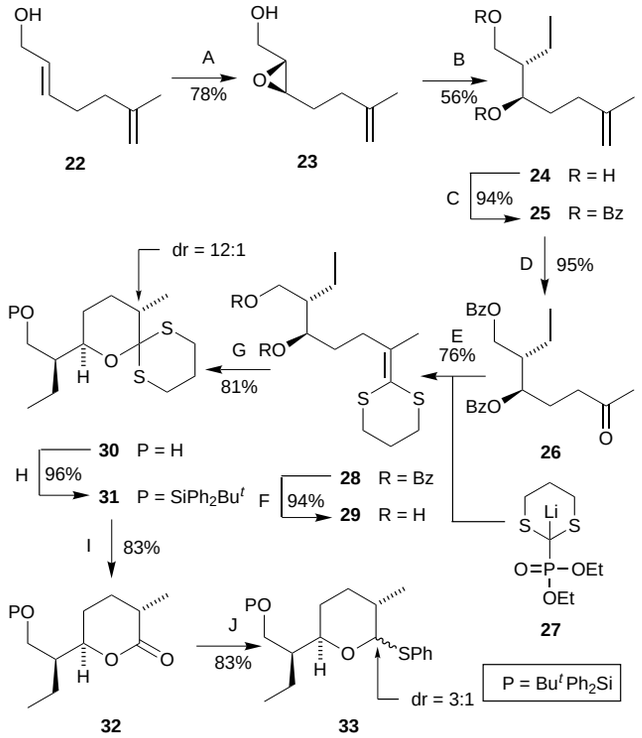
Faller's η^3-allyl cationic complex **21** was selected as the electrophilic partner in our chain appendage sequence because the cursory details available suggested that it should be readily accessible.[30] Scheme 4 outlines the route which began with the



Scheme 4

reaction of (*S*)-allylic acetate **18** (er 97:3) with $Mo(CO)_3(MeCN)_3$ generated *in situ* by thermolysis of $Mo(CO)_6$ in acetonitrile. The oxidative addition occurs with retention of configuration to give (π-allyl)molybdenum(II) complex **19** which was then treated immediately with lithium cyclopentadienide (LiCp) to produce the stable (−)-$CpMo(CO)_2$(5-methyl-2–4-η^3-hexenyl) complex **20** as an orange crystalline solid (Note 2). Replacement of one of the carbonyl ligands by a nitrosyl group occurred on treatment with nitrosonium tetrafluoroborate to give the desired cationic complex **21** as a mixture of isomers (Note 3). The route depicted in Scheme 4 has a number of practical advantages: (a) the starting allylic acetate is cheap and conveniently prepared in enantiomerically enriched form by a Sharpless kinetic resolution; (b) the entire sequence can be conducted on a substantial scale using ordinary laboratory glassware; (c) the yellow crystalline complex **21a**,**b** can be stored under an inert atmosphere in the cold; and (d) the complex is stable enough to be manipulated briefly in air.

A simple Sharpless catalytic asymmetric epoxidation primed the sequence which ultimately led to the axial oxanyllithium partner depicted figuratively in Scheme 3. Thus oxidation of the trivial allylic alcohol **22** (Scheme 5) produced the oxirane **23**[31] in 78% yield and enantiomeric ratio (er) 97:3 according to NMR spectroscopic analysis of the corresponding mandelate ester. Copper(I)-catalysed scission of the oxirane **23** by ethylmagnesium bromide gave a mixture of the desired 1,3-diol **24** together with its 1,2-diol regioisomer. The ratio of 1,3- to 1,2-diol was 10:1 on ≤10 mmol scale but decreased to 3:1 on a 25 mmol scale. Separation was best accomplished by selective destruction of the 1,2-diol with sodium periodate followed by chromatographic purification. After protection of the pure 1,3-diol as its dibenzoate **25**, the alkene was ozonolysed to ketone **26** which then condensed with the lithiated phosphonate derivative **27**[32] to give ketenedithioacetal **28**. Hydrolysis of the benzoate esters followed by acid-catalysed cyclisation of the resultant diol **29** returned the spirocyclic dithioorthoester **30** in



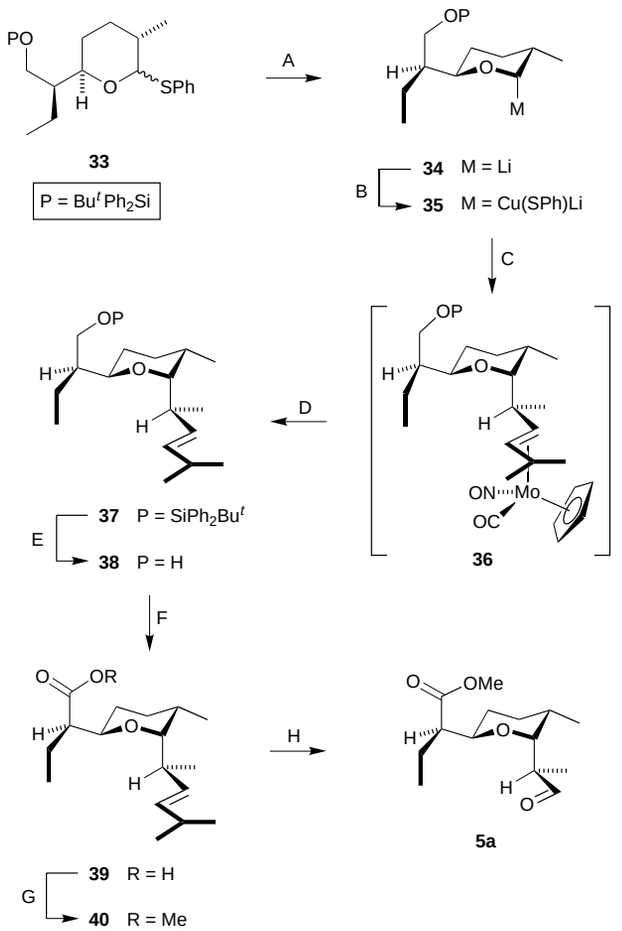
Scheme 5 *Reagents and conditions:*

A	78%	Bu^{t}OOH, (−)-DIPT, Ti(Pr^{i}O)$_4$, CH_2Cl_2, −25 °C, 6 h
B	56%	(a) EtMgBr, CuI, Et_2O, −40 °C, 3 h; (b) $NaIO_4$, acetone–H_2O, r.t., 14 h
C	94%	BzCl, DMAP, Pyr, $CHCl_3$, 50 °C, 16 h
D	95%	(a) O_3, MeOH–CH_2Cl_2 (1:1), −80 °C; (b) Me_2S, −80 °C ⟶ r.t., 16 h
E	76%	**27**, THF, −40 °C, 1 h
F	94%	KOH, MeOH, r.t., 2 h
G	81%	anhydrous HCl, CH_2Cl_2, 0 °C
H	96%	Bu^{t}Ph$_2$SiCl, imidazole, CH_2Cl_2, r.t., 2 h
I	83%	I_2, $NaHCO_3$, Et_2O–H_2O, *ca.* 40 °C, 30 min
J	79%	(a) DIBALH, PhMe, −80 °C, 45 min; (b) BF_3·OEt_2, PhSH, −80 ⟶ −50 °C

14% overall (11 steps)

81% yield [diastereomeric ratio (dr) 12:1].[33] The remaining hydroxy group was protected as its *tert*-butyldiphenylsilyl ether and the lactone **32** unveiled by iodine-mediated hydrolysis of the dithiane ring.[34] To complete the sequence, the lactone was reduced to a mixture of lactols whence the phenylthioacetal **33** was obtained as a 3:1 mixture of diastereoisomers on treatment with thiophenol under BF_3 catalysis.

Fortunately, the poor diastereoselectivity that attended the thioacetalisation reaction cited above was no obstacle because reductive lithiation of the mixture of phenylthioacetals **33** with lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB)[35] gave the desired axial oxanyllithium reagent **34** as a single diastereoisomer. Both the reductive lithiation and its stereochemical consequence were well-precedented in the work of Cohen and co-workers[36,37] who showed that such reactions proceed by two one-electron transfers involving radical intermediates. The preference for the axial lithium reflects the ease of radical inversion and the stabilisation available to the axial radical (radical anomeric effect[38–40]) generated in the first step of the reductive lithiation. Moreover, the configurational stability (at ⩽ −50 °C) of the axial anion was anticipated from the work of Sinaÿ and Fuchs.[41,42] Attempts to alkylate the oxanyllithium reagent **34** with the η^3-allyl cationic complex **21a**,**b** were not fruitful but the corresponding cuprate **35** alkylated with high regio- and facial-selectivity to provide the desired adduct **37** in 44% overall yield from **33** after oxidative destruction of the η^2-molybdenum intermediate **36**. Proof of the stereochemistry of



Scheme 6 *Reagents and conditions:*

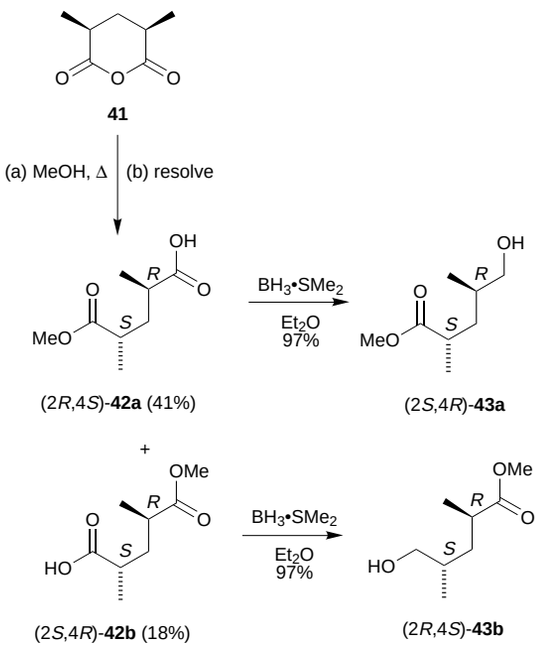
A	↓	LiDBB, THF, −80 °C, 15 min
B	↓	CuBr·SMe_2, −80 °C, 30 min
C	↓	complex **21a**,**b**, −80 °C, 14 h
D	44%	O_2, CH_2Cl_2, r.t., 26 h
E	91%	TBAF·$3H_2O$, THF, r.t., 16 h
F	↓	(a) Dess–Martin oxidation; (b) $NaClO_2$, H_2NSO_3H, CH_2Cl_2–H_2O, r.t., 2 h
G	64%	tetramethylguanidine, MeI, PhH, r.t., 4.5 h
H	94%	(a) O_3, CH_2Cl_2, −80 °C; (b) Ph_3P, −80 °C ⟶ r.t., 2 h

24% overall (9 steps)

the alkylation came from subsequent standard oxidative transformations which gave a crystalline sample of **5a** identical by mp, ^{1}H and ^{13}C NMR spectroscopic analysis and $[a]_D$ with material derived from degradation of natural salinomycin.[14]

Synthesis of the C11–C20 fragment 7

For reasons of convenience and economy we began our synthesis of the C11–C20 fragment **7** with the crystalline 2,4-dimethylpentanedioic anhydride **41** (Scheme 7) which can be prepared in three steps on a mole scale from cheap commercial reagents.[43,44] Methanolysis of the anhydride afforded the racemic mixture of 2,4-dimethylpentanedioic acid monomethyl esters **42a**,**b** whose classical resolution with (+)- and (−)-α-methylbenzylamine has been well described.[45–47] For our immediate purposes we required the (2*R*,4*S*)-enantiomer **42a** but as we shall see later, the (2*S*,4*R*)-enantiomer **42b** was to serve our ends as well. Owing to the low cost of (+)- and (−)-α-methylbenzylamine, the high crystallinity of their salts with **42a**,**b**, and the ease of recycling the resolving agent, this route was adopted in preference to alternatives such as the enzymatic hydrolysis of methyl 2,4-dimethylpentanedioate by *Gliocladium roseum*.[48] Selective reduction of the carboxy functions in **42a**,**b**

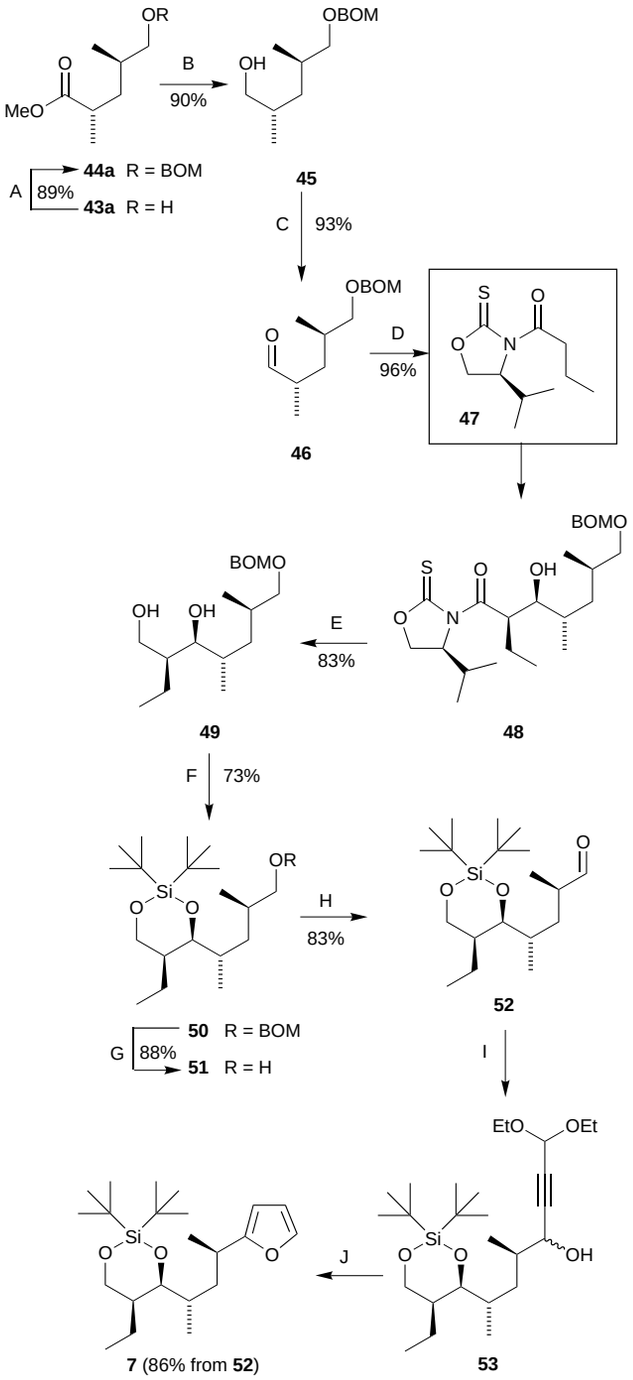


Scheme 7

with $BH_3{\cdot}SMe_2$[47] gave the corresponding alcohols **43a**,**b** in excellent yield.

O-Benzylation of the hydroxy function in **43a** with benzyl-trichloroacetimidate under acidic conditions was inefficient and capricious but formation of the benzyloxymethyl (BOM) ether under mildly basic conditions consistently accomplished the desired protection step in high yield with no evidence of competing lactonisation[49] (Scheme 8). The ester group was reduced with lithium aluminium hydride and the resultant primary alcohol **45** was oxidised by the method of Swern to aldehyde **46** in good overall yield.[50] Attempts to construct the C12–C13 bond using the popular titanium variant of the Evans asymmetric aldol protocol[51] gave only modest stereoselectivity in our hands and this, together with difficulties encountered in cleaving the oxazolidinone auxiliary, encouraged us to seek alternatives. By contrast the asymmetric aldol variant of Nagao and co-workers[52,53] accomplished the highly stereoselective construction of the C13–C14 bond using the *N*-butanoyl-oxazolidinethione **47** and aldehyde **46** promoted by tin(II) triflate (trifluoromethanesulfonate).

The 1,3-oxazolidine-2-thione auxiliary was readily removed from adduct **48** using sodium borohydride in wet THF;[52] however, the resulting diol **49** was difficult to separate from the auxiliary by chromatography. Fortunately, this problem was easily overcome by washing the ethereal mixture of diol **49** and the 1,3-oxazolidine-2-thione with 2 M NaOH whereupon the auxiliary was extracted into the aqueous layer as its sodium salt. The crude diol **49** was protected as its di-*tert*-butylsilylene derivative **50**[54] in good yield. Reductive cleavage of the benzyloxymethyl ether followed by oxidation of the resulting alcohol **51** provided the desired aldehyde **52** in 83% yield. With all four stereogenic centres now in place, all that remained to complete the construction of fragment **7** was appendage of the furan ring. Treatment of aldehyde **52** with the lithium derivative of lithioprop-1-yne 3,3-diethyl acetal gave a mixture of epimeric propynyl alcohols **53** which were hydrogenated over a poisoned catalyst[55] to provide a mixture of diastereoisomeric (*Z*)-alkenes. They too were not separated or purified; rather, treatment of the isomeric allylic alcohols **53** with catalytic pyridinium toluene-*p*-sulfonate (PPTS) resulted in cyclisation with loss of two molecules of ethanol to give the desired furan ring in 86% overall yield from the aldehyde **52**. Fortunately, the mild conditions required for the cyclisation–elimination sequence did not affect the silylene protector.



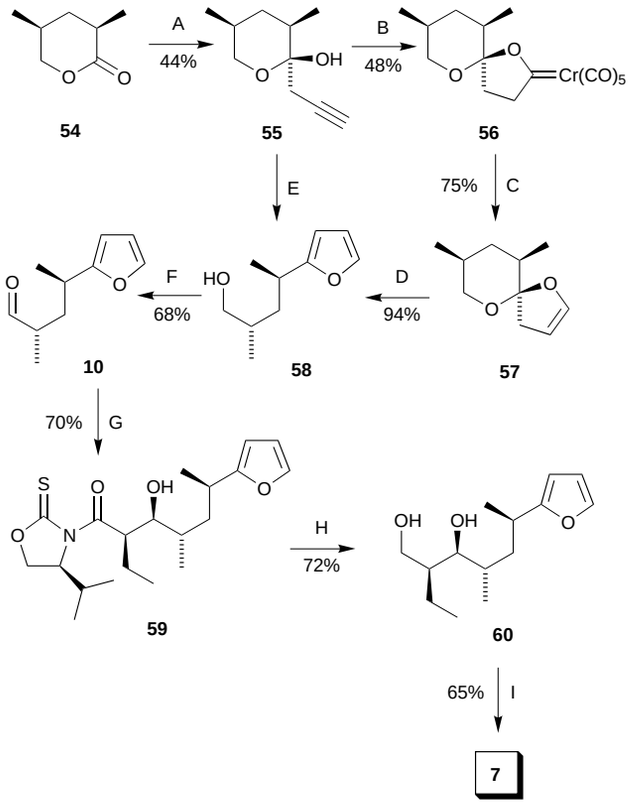
Scheme 8 *Reagents and conditions:*

A	89%	BOM–Cl, $(Pr^i)_2NEt$, Bu_4NI, THF, 10 °C ⟶ r.t., 12 h
B	90%	LAH, THF, 0 °C
C	93%	Swern oxidation
D	96%	(a) **47**, $Sn(OTf)_2$, *N*-Et-piperidine, CH_2Cl_2, −45 °C, 3 h; (b) aldehyde **46**
E	83%	$NaBH_4$, THF–H_2O, 0 °C ⟶ r.t., 100 min
F	73%	$(Bu^t)_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min
G	88%	W2 Ra–Ni, H_2 (1 atm.), EtOH, r.t., 100 h
H	83%	Dess–Martin oxidation
I	↓	(a) $(EtO)_2CH{-}C{\equiv}C{-}Li$, THF, −78 ⟶ 0 °C; (b) H_2, Pd–$BaSO_4$, quinoline;
J	86%	(c) PPTS, CH_2Cl_2

27% overall (11 steps)

Alternative synthesis of the C11–C20 fragment 7

A parallel research programme on the chemistry of oxacyclic carbene complexes[56] inspired an alternative approach to the C11–C20 fragment **7** depicted in Scheme 9. Addition of prop-1-



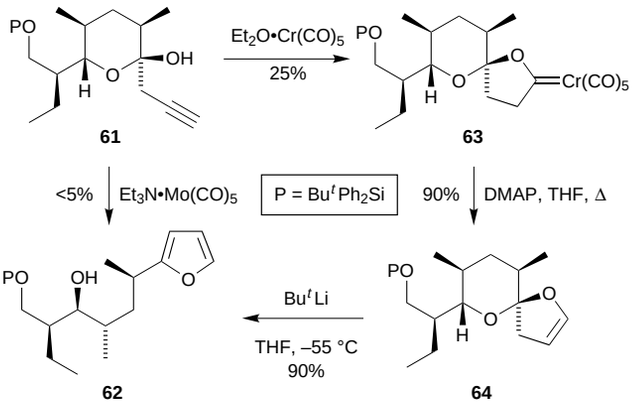
Scheme 9 *Reagents and conditions:*

A	44%	$HC{\equiv}CCH_2MgBr$, Et_2O, −60 °C, 2 h; r.t., 20 h
B	48%	(a) $Cr(CO)_6$, Et_2O, *hv*, −30 °C; (b) add **55**, r.t., 2 h
C	75%	DMAP, THF, Δ, 8 h
D	94%	Bu^{t}Li, THF, −55 °C, 4 h
E	43%	(a) $Mo(CO)_6$, Et_2O–NEt_3, *hv*, −30 °C, 3 h; (b) add **55**, r.t., 12 h
F	68%	Swern oxidation
G	70%	(a) **47**, $Sn(OTf)_2$, *N*-Et-piperidine, CH_2Cl_2, −45 °C, 3 h; (b) add **10**, −80 °C
H	72%	$NaBH_4$, THF–H_2O, 0 °C ⟶ r.t., 2 h
I	65%	$(Bu^t)_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 0 °C ⟶ r.t., 15 min

4% overall (6 steps *via* **55** ⟶ **58**)

ynylmagnesium bromide to the lactone **54**[47] at −80 °C gave the lactol **55** as a single diastereoisomer in 44% yield. Addition of the lactol to a solution of the yellow–orange complex $Et_2O{\cdot}Cr(CO)_5$, generated by UV irradiation of $Cr(CO)_6$ in Et_2O through a Pyrex filter at −30 °C according to the procedure of Dötz,[57] resulted in formation of the Fischer carbene complex **56** as a single diastereoisomer (48% yield) whose relative stereochemistry was established unambiguously by X-ray crystallography[56] (Note 4). On heating carbene complex **56** in THF with DMAP, a base-induced 1,2-hydrogen migration[58] occurred to give the spirocyclic dihydrofuran derivative **57** in 75% yield. Dihydrofuran derivative **57** was stable towards column chromatography on silica gel but it underwent base-induced elimination on treatment with Bu^{t}Li at −55 °C to give the furan **58** in 94% yield. The three-step transformation of lactol **55** to furan **58** was later abbreviated to a single step (43% yield) by treating **55** with $Et_3N{\cdot}Mo(CO)_5$ complex generated by irradiating $Mo(CO)_6$ in Et_2O containing Et_3N according to the procedure of McDonald.[59,60]

The modest yields attending both cyclisation steps B and E depicted in Scheme 9 diminished to the point of impractability when the lactol substrate was substituted at the 6-position. Thus, direct conversion of lactol **61** (Scheme 10) to the furan **62** with the $Et_3N{\cdot}Mo(CO)_5$ complex gave many products from which **62** could be obtained in impure form in less than 5% yield. The alternative stepwise route *via* the chromium carbene

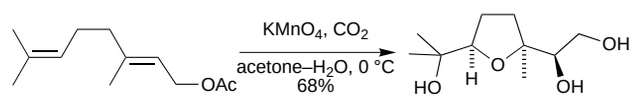


Scheme 10

complex **63** foundered on the low yield of the ring closure step (25% yield) though the base-induced 1,2-hydrogen migration to give dihydrofuran **64** was efficient (90%).

Synthesis of the C21–C30 lactone fragment 8a

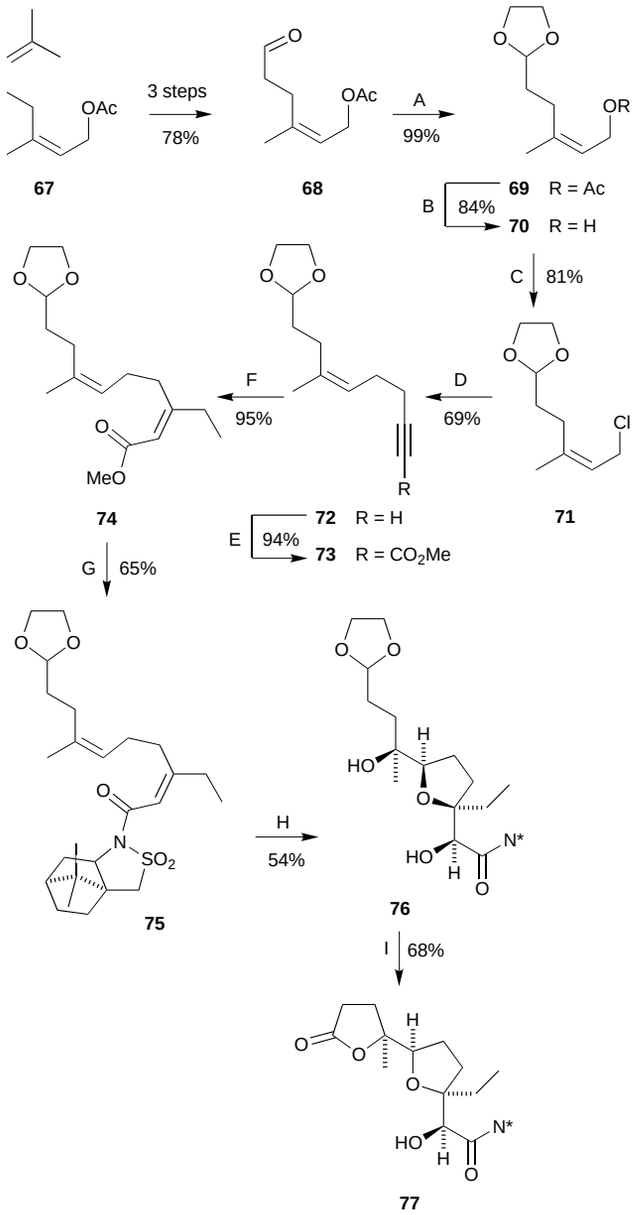
In 1965 Klein and Rojahn[61] showed that oxidation of geranyl acetate **65** with potassium permanganate (Scheme 11) gave the



Scheme 11

tetrahydrofuran triol **66**—a reaction which had been first reported in 1927 by Kötz and Steche.[62] Walba *et al.*[63] later reported an asymmetric variant of the permanganate promoted oxidative cyclisation in which four stereogenic centres are created in a single operation from a 1,5-diene precursor. Such spectacular stereochemical return from the meagre investment of two (*Z*)-trisubstituted alkenes was an asset we hoped to exploit in our synthesis of fragment **8a**.

The requisite 1,5-diene precursor was synthesised from neryl acetate **67** (Scheme 12), a cheap commercial reagent which harboured the first of the (*Z*)-alkene moieties we required. The terminal alkene was cleaved in a three step sequence on a large scale to give the known[64] aldehyde **68** in 78% overall yield (three steps). After protection of the aldehyde as its 1,3-dioxolane derivative **69**, the acetate was hydrolysed and the resultant alcohol **70** converted to the labile allylic chloride **71**. Substitution of the chloride with propynyldilithium[65,66] gave the terminal alkyne **72** which was converted to the ynoate ester **73** *via* methoxycarbonylation of the corresponding alkynyllithium with methyl chloroformate. The second (*Z*)-trisubstituted alkene was then generated with excellent stereoselectivity by carbocupration[67] to give the 1,5-diene derivative **74** in 96% yield. In order to achieve absolute stereocontrol in the subsequent oxidative cyclisation reaction, Oppolzer's (2*S*)-bornane-10,2-sultam[68] was appended. Attempts to introduce the sultam directly by reaction of its *N*-dimethylaluminium derivative with ester **74** failed completely. Condensation of the corresponding carboxylic acid with the sultam using DCC gave substantial amounts of the *N*-acyldicyclohexylurea. Competing urea formation could be suppressed by adding more than one equivalent of DMAP but significant isomerisation of the trisubstituted alkene (*ca.* 20%) was observed presumably due to addition–elimination of the DMAP to the enoyl system. Condensation was eventually achieved by acylation of the lithium derivative of the sultam with the acid chloride derived from ester **74**. Here, too, difficulties were encountered: the dioxolane group was partially removed in the formation of the acid chloride with oxalyl chloride despite strenuous efforts to exclude HCl formation.



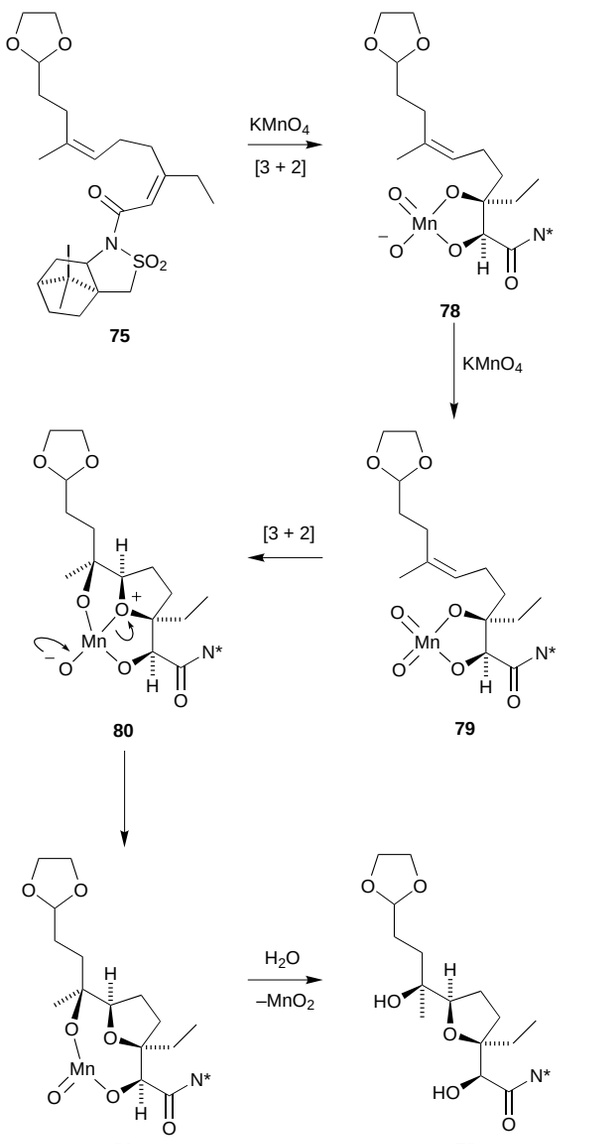
Scheme 12 *Reagents and conditions:*

A	99%	$HOCH_2CH_2OH$, PTSA, PhH, Δ ($-H_2O$), 3 h
B	84%	K_2CO_3, MeOH, r.t., 6.5 h
C	81%	MsCl, LiCl, 2,6-lutidine, DMF, 0–15 °C, 3.5 h
D	69%	$LiC{\equiv}CCH_2Li$, THF, −65 °C ⟶ −10 °C, 2.25 h
E	94%	(a) BuLi, THF, −78 °C; (b) $ClCO_2Me$, −90 ⟶ −10 °C, 3.5 h
F	95%	Et_2CuLi, THF, −85 °C, 3 h
G	65%	(a) NaOH, MeOH; (b) $(COCl)_2$; (c) (2*S*)-bornane-10,2-sultam, BuLi
H	54%	$KMnO_4$, pH 6 acetate buffer, acetone–HOAc–H_2O, −35 °C, 5 h
I	68%	(a) O_3, EtOAc, −80 °C, 70 min; (b) PTSA, CH_2Cl_2, r.t., 8 h

10% overall (13 steps from **68**)

Attempts to effect the key oxidative cyclisation reaction according to well established precedents were disappointing. Addition of excess potassium permanganate to a solution of the diene in aqueous acetone with continuous CO_2 ebullition (Note 5) gave complex mixtures. Assuming control of pH was at the root of the problem, we attempted the cyclisation in the presence of various buffers. Use of acetate buffer mixed with acetic acid at pH 5 gave complex mixtures but the same reaction conducted at pH 6 and at −35 °C was quite clean giving the desired oxidative cyclisation product **76** together with a diastereoisomer (dr 6:1) in 54% yield. If the reaction was run in the absence of added acetic acid, inferior results were obtained. The inseparable mixture of diastereoisomeric tetrahydrofuran diols predominating in **76** was treated with excess ozone[69] at −80 °C giving intermediate hydroxy esters which cyclised using PTSA to give two crystalline diastereoisomeric lactones (Note 6) which were separable by careful chromatography. X-Ray analysis showed that the major product **77** had the desired stereochemistry at all four nascent stereogenic centres (unpublished work).

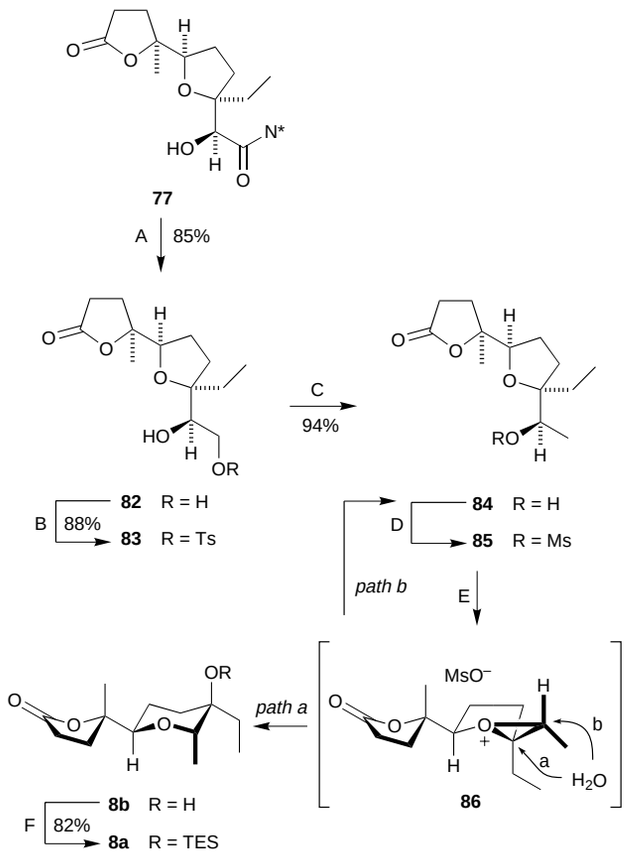
Scheme 13, adapted from the proposals of Baldwin *et al.*,[70]



Scheme 13

accounts for the stereochemistry observed in the oxidative cyclisation. The sequence begins with a diastereoselective [3 + 2] cycloaddition of permanganate to the electron-deficient enoyl double bond to form a cyclic Mn^V diester **78** which then undergoes rapid oxidation by permanganate to the Mn^{VI} diester **79**. A second intramolecular cycloaddition on the remaining trisubstituted alkene followed by hydrolysis of the Mn^{IV} diester **81** then generates the observed product. An alternative mechanism has been proposed by Walba *et al.*[71]

To complete the synthesis of lactone **8a**, the sultam was reductively removed by treatment of the α-hydroxy carboxylic acid derivative **77** with $NaBH_4$ and $BH_3{\cdot}SMe_2$[72] and the primary hydroxy group of diol **82** (Scheme 14) was selectively tosylated yielding hydroxy tosylate (toluene-*p*-sulfonate) **83**. It was easier to separate the diastereoisomers by chromatography



Scheme 14 *Reagents and conditions:*

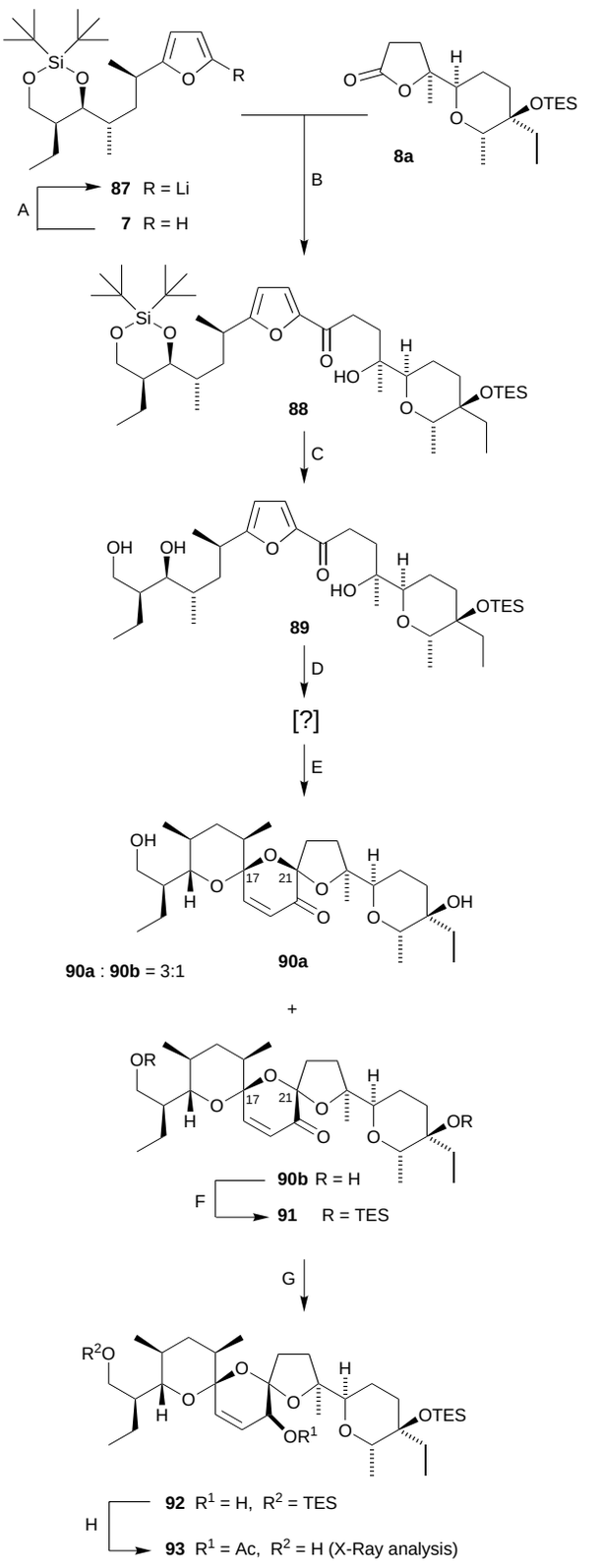
A	85%	BH_3·SMe_2, $NaBH_4$, THF, −10 °C, 2 h
B	92%	TsCl, Et_3N, CH_2Cl_2, r.t., 41 h
C	90%	NaI, Bu_3SnH, AIBN, DME, 80 °C, 7.5 h
D	↓	MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min
E	56%	Ag_2CO_3, acetone–H_2O, Δ, 27 h
F	82%	TESOTf, 2,6-lutidine, CH_2Cl_2, −50 ⟶ 0 °C, 3.25 h

32% overall (6 steps from **77**)

at this stage rather than two steps earlier. Reductive removal of the *O*-tosyl group was achieved by tributylstannane reduction of the corresponding iodide generated *in situ* providing the secondary alcohol **84** in 94% yield.[73] The corresponding methanesulfonate **85**, underwent silver carbonate promoted solvolytic ring expansion in which capture of the oxiranium ion intermediate **86** *via* path *a* gave the desired oxane derivative **8a** together with recovered starting material derived from path *b* (dr 5:1).[74,75] To avoid protracted reaction times we found that portionwise addition of one equivalent of the promoter at intervals of 3 to 9 hours was desirable. Unfortunately, isomeric alcohols **8a** and **84** were inseparable and since selective acylation of the secondary alcohol **84** was fruitless, separation was achieved by oxidation of the secondary alcohol to the less polar ketone. Finally, protection of the tertiary alcohol **8b** as its triethylsilyl ether **8a** completed the synthesis of the C21–C30 lactone fragment.

Construction of the dispiroacetal ring *via* furan oxidation

With adequate supplies of the C11–C20 furan fragment **7** and the C21–C30 lactone fragment **8a** now in hand, the time has come to meet the challenge of constructing the dispiroacetal ring system in fragment **6a** according to the plan outlined in Scheme 1. The union of fragments **7** and **8a** required the metallation of the furan ring in **7**—a transformation which was critically dependent on the diol protecting group (Scheme 15).



Scheme 15 *Reagents and conditions:*

A	↓	Bu^{t}Li (1.1 equiv.), THF, −60 ⟶ −5 °C over 2.3 h;
B	↓	add lactone **8a** (0.9 equiv.), −65 ⟶ 0 °C over 3 h; r.t., 20 min
C	51%	pyr·HF (4 equiv.), THF–pyr, r.t., 20 min
D	↓	NBS (1.5 equiv.), THF–H_2O (10:3), −10 °C, 30 min
E	59%	HF, MeCN–H_2O, r.t., 3 h
F	74%	TESOTf, 2,6-lutidine, CH_2Cl_2
G	93%	$NaBH_4$, $CeCl_3$·$7H_2O$, MeOH, −60 ⟶ 0 °C, 100 min
H	99%	(a) Ac_2O, DMAP, pyr, CH_2Cl_2, r.t., 12 h; (b) pyr·HF, THF–pyr, r.t., 1 h

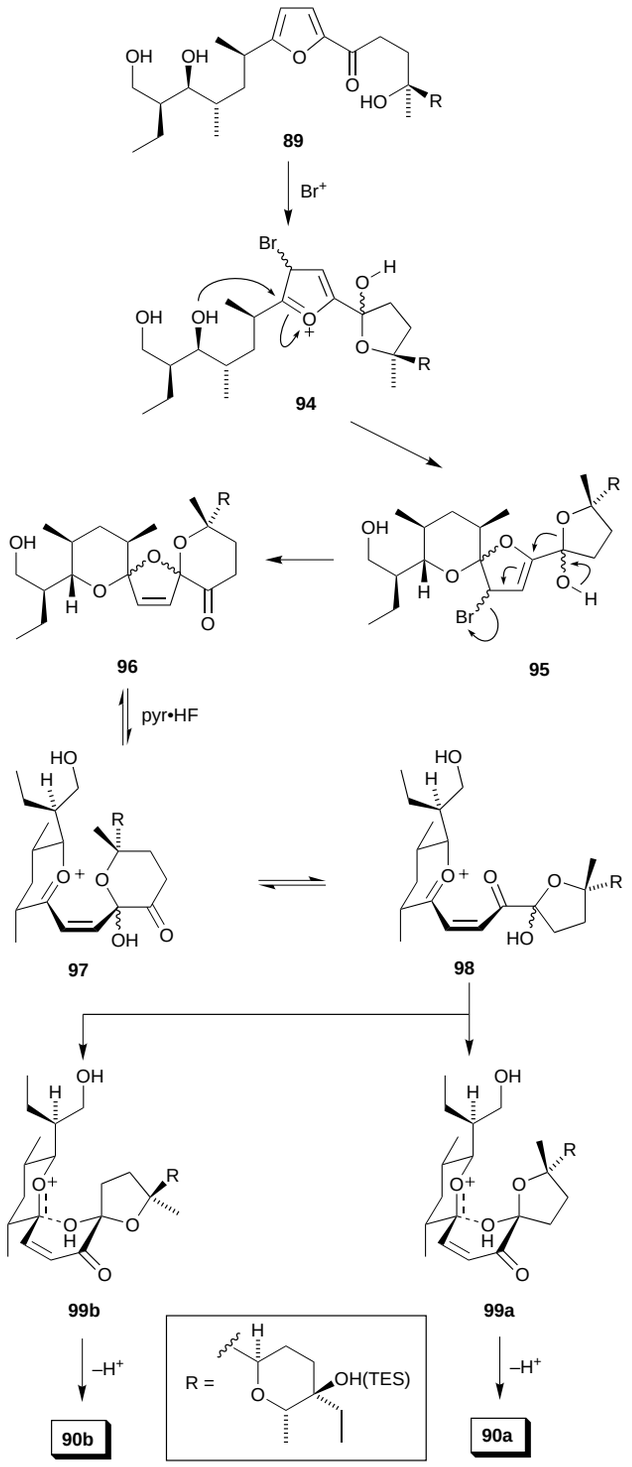
30% overall to **90a**,**b** from **8a** (5 steps)

Early attempts to metallate analogues of **7** bearing an isopropylidene protecting group could only be accomplished with >3 equiv. of Bu^{t}Li and the yield of lithiofuran was poor judging from deuteriation experiments. With *tert*-butyldimethylsilyl protecting groups on both hydroxys, metallation occurred preferentially on the methyl groups of the silane.[76] After much effort we found that di-*tert*-butylsilylene protection for the diol was optimal: it was easily put on, easily removed, and it was inert to the metallation conditions.[54,77] Best results were obtained by treating furan **7** with one equivalent of Bu^{t}Li in THF at −80°C followed by *slow* warming to 0 °C over 2 h. The lithiofuran was re-cooled to −65 °C whereupon lactone **8a** was added and the mixture allowed to warm slowly to 0 °C over 3 h. A mixture of the desired acylfuran **88** was obtained together with unreacted furan **7** and lactone **8a** (Note 7). The furan (30%) was easily recovered by chromatography; however, to facilitate separation of the lactone from the adduct, the di-*tert*-butylsilylene group was first removed with pyridine·HF complex in the presence of excess pyridine. In this way the desired pure acylfuran diol **89** was obtained in 51% yield.

Release of the latent enedione ensconced in the furan ring of **89** would give an enetrione intermediate whose cyclisation could, in principle, lead directly to the target ring system with its characteristic enone functionality in the central ring (*e.g.* **90a** in Scheme 15, Note 8). But, when acylfuran diol **89** was treated with *N*-bromosuccinimide in aqueous THF, a complex mixture of products was generated none of which contained the expected enone chromophore. Subsequent treatment of the mixture with HF in aqueous acetonitrile led to the formation of only two major UV-active products, together with polar impurities, which were easily separated by column chromatography. The major product (44% yield) was assigned structure **90a** based on extensive NOESY spectroscopy of a derivative (**119**, Scheme 18) and the minor product (15%) was assigned structure **90b** (see below). Thus, neither product corresponded to the desired stereochemistry at C17 and C21. Furthermore, neither **90a** nor **90b** interconverted under the reaction conditions and prolonged treatment with camphorsulfonic acid simply resulted in decomposition.

The relative stereochemistry of the minor isomer **90b** was determined as follows. Reduction of the enone in the bistriethylsilyl ether derivative **91** under the Luche conditions ($NaBH_4$–$CeCl_3$·$7H_2O$)[78] was highly stereoselective leading to a single allylic alcohol **92** in 93% yield albeit with the incorrect stereochemistry at C20. Unfortunately, all efforts to invert the stereochemistry of the allylic alcohol **92** using the Mitsunobu reaction[79] failed but acetylation of the alcohol function followed by selective removal of the primary triethylsilyl ether gave a crystalline compound **93** from which the relative configuration was determined by X-ray analysis (unpublished work).

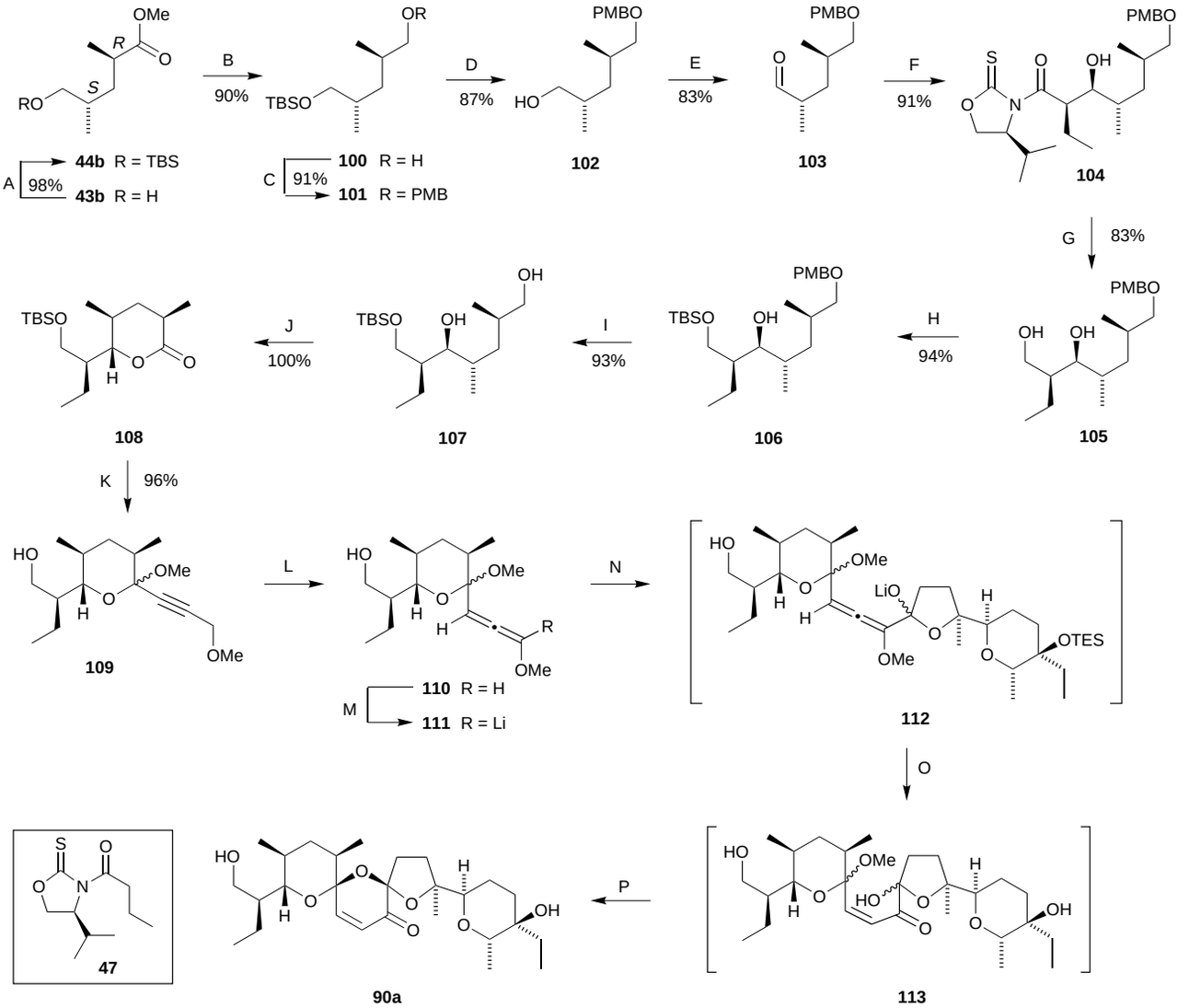
In an attempt to interpret the complex course of events leading to **90a**,**b**, we suggest that the initial products of the oxidative spirocyclisation are the diastereoisomeric 1,7,9-trioxadispiro-[5.1.5.2]pentadec-14-enes **96** generated by the sequence of reactions depicted in Scheme 16. The subsequent acid-catalysed rearrangement begins with scission of the central five-membered ring to give oxonium ion **97**. Ring contraction of the α-ketoacetal to the two diastereoisomeric α-ketoacetals **98** followed by preferential addition of the hemiacetal hydroxy groups to the axial face of the oxonium ion (see structures **99a** and **99b**) then leads to the observed products. We suggest that the failure of the two spiroacetals to interconvert reflects the destabilisation of the oxonium ion **98** by the electron deficient enone moiety. Furthermore, we suggest that the dispiroacetals are formed under kinetic control wherein the preponderance of **90a** reflects the lower energy of the transition state **99a** (1,3-diaxial O↔O interaction) *vs.* transition state **99b** (1,3-diaxial O↔CH_2 interaction).



Scheme 16

Alternative construction of the dispiroacetal 90a *via* allenol ether chemistry

In an attempt to secure a more favourable stereochemistry in the spirocyclisation reaction, we examined an alternative route to the dispiroacetal ring system which used fragments already in hand, namely lactone **8a** and the hydroxy ester **43b**. Hydroxy ester **43b**, the enantiomer of the hydroxy ester **43a** used in the synthesis of furan **7** (Scheme 8), was converted to lactone **108** using standard transformations (Scheme 17). Addition of the lithium derivative of 1-methoxyprop-2-yne to lactone **108** followed by treatment of the crude hemiacetal adduct with boron trifluoride–diethyl ether in methanol returned the alkyne **109** as a single diastereoisomer of unknown stereochemistry in 96%



Scheme 17 *Reagents and conditions:*

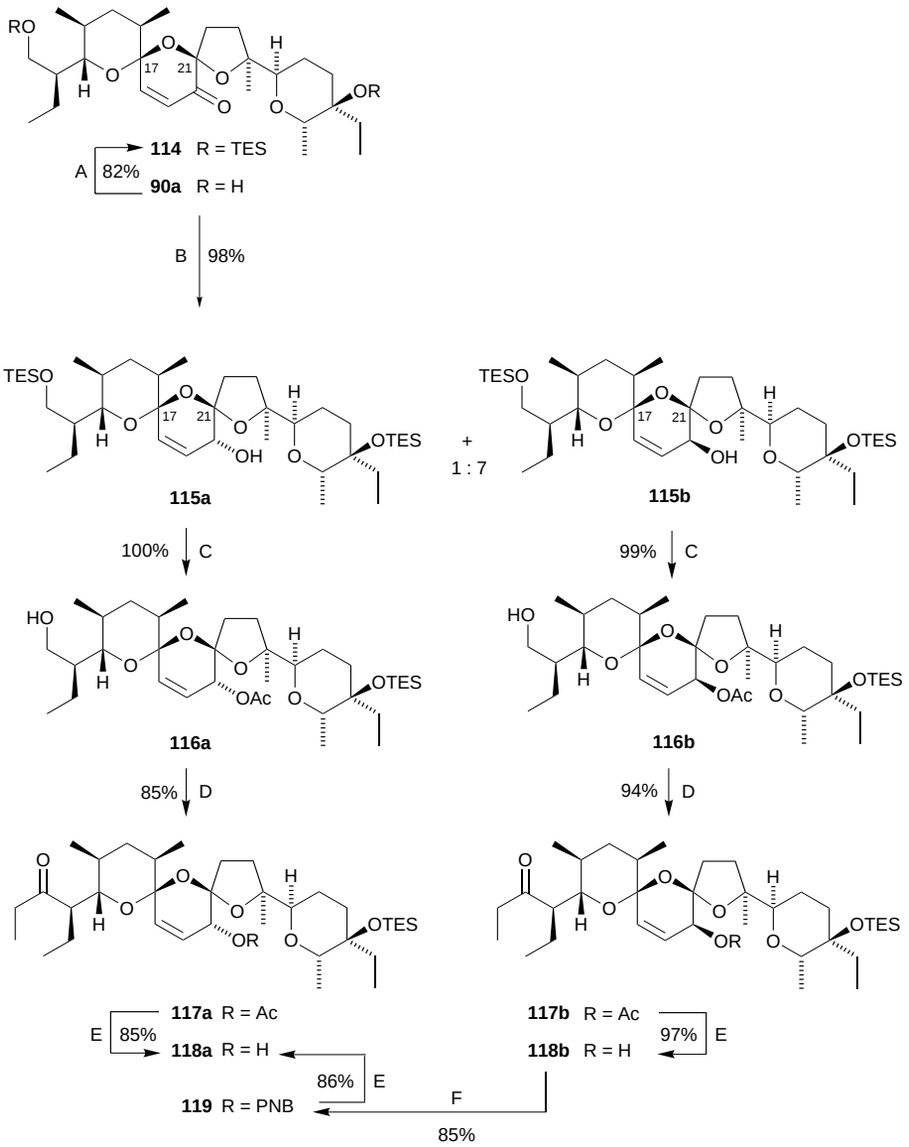
A	96%	TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C, 1 h
B	90%	LAH, Et_2O, 15 min, 0 °C
C	91%	PMBCl, NaH, DMF, r.t., 16 h
D	87%	TBAF, THF, r.t., 12 h
E	92%	Swern oxidation
F	91%	(a) **47**, $Sn(OTf)_2$, *N*-Et-piperidine, CH_2Cl_2, −50 °C, 3 h; (b) aldehyde **103**
G	82%	$NaBH_4$, THF–H_2O, 0 °C ⟶ r.t., 90 min
H	94%	TBSCl, imidazole, DMAP, CH_2Cl_2, r.t., 3 h
I	93%	5% Pd/C, H_2 (1 atm), EtOAc, r.t., 15 h
J	100%	$[Ph_3P]_3RuCl_2$, NMMO, acetone, r.t., 72 h
K	94%	(a) $MeOCH_2C{\equiv}C{-}Li$; (b) $BF_3{\cdot}OEt_2$, MeOH
L	↓	Bu′OK, 18-crown-6, pentane, r.t., 2.5 h
M	↓	BuLi, Et_2O, −80 ⟶ −30 °C
N	↓	add lactone **8a**
O	↓	H_2SO_4, THF–H_2O, r.t., 25 min
P	49%	HF, I_2, MeCN–H_2O, r.t., 48 h

19% overall from **7** (16 steps)

yield. Prototropic rearrangement of the alkyne occurred on treatment with potassium *tert*-butoxide in pentane in the presence of 18-crown-6 to give the allenol ether **110** in essentially quantitative yield. Metallation of the *unprotected* allenol ether (Note 9) with BuLi followed by addition of lactone **8a** gave an adduct **112** which hydrolysed stereoselectivity on *brief* treatment with 1 M H_2SO_4 in THF to the *cis*-enone **113** (Note 10). It was imperative at this stage to work the reaction up and treat the crude *cis*-enone **113** with HF in aqueous acetonitrile. After 48 h at room temperature, the dispiroacetal **90a** was isolated by column chromatography. The column was then washed with methanol, the solvent removed *in vacuo* and the residue again treated with HF as described above. After four cycles the total yield of the dispiroacetal **90a** was 49% and it is noteworthy that none of the isomeric dispiroacetal **90b** was obtained under these conditions. Thus the allenol ether route was comparable in overall length to the furan route but the allenol ether route is both more efficient, and more stereoselective.

From the smoke into the smother

In nature there are neither rewards nor punishments—there are consequences. The consequence of many months of effort was a dispiroacetal fragment **90a** with the wrong stereochemistry at C17 and C21. Worse was to come. Reduction of the bis(triethylsilyl)ether **114** with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$[78] (Scheme 18) gave a separable mixture of two allylic alcohols (79% yield) predominating in the diastereoisomer **115b** (**115a**:**115b** = 1:7) with the incorrect stereochemistry at *all three* positions in the central ring of the dispiroacetal core unit (C17, C20 and C21). Although the minor isomer could be efficiently elaborated to the complete carbon skeleton in **118a**, success would ultimately depend on inversion of the major allylic alcohol **115b**—a transformation which had been impossible in a diastereoisomeric system (**92**, Scheme 15). The sequence began with protection of the C20 hydroxy as the acetate and selective deprotection of the primary TES ether whereupon alcohol **116b** was converted in three steps to the ketone **117b**. Fortunately,



Scheme 18 *Reagents and conditions:*

A TESOTf, 2,6-lutidine, CH_2Cl_2
B $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, $-60 \longrightarrow 0$ °C
C (a) Ac_2O, pyr, DMAP, CH_2Cl_2, r.t.; (b) pyr·HF, pyr–THF, r.t.
D (a) Dess–Martin oxidation; (b) EtMgCl, THF; (c) Dess–Martin oxidation
E K_2CO_3, MeOH
F *p*-$O_2NC_6H_4CO_2H$, Ph_3P, DEAD, PhH

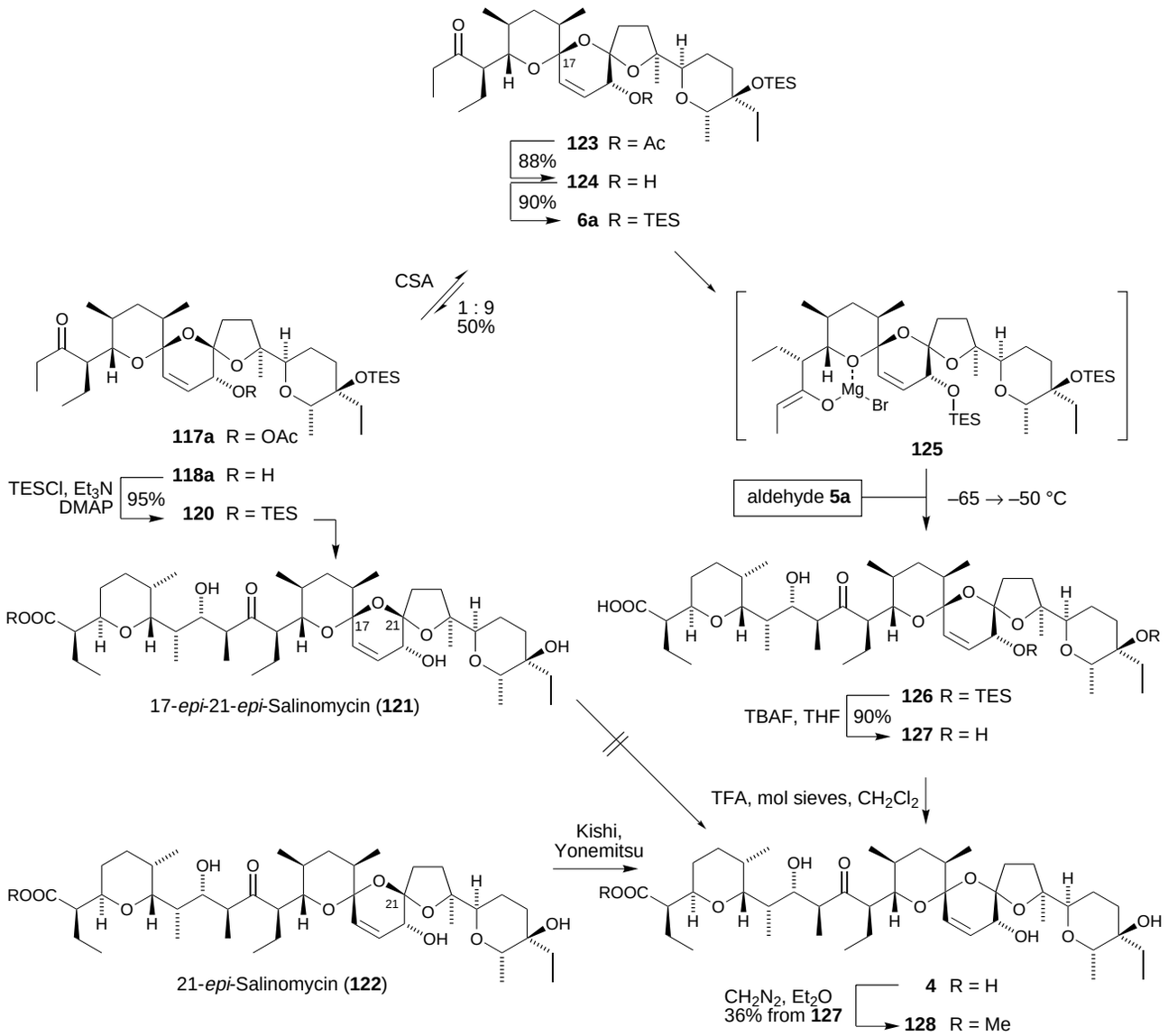
52% overall (8 steps; **b** series)

hydrolysis of the acetate in **117b** followed by Mitsunobu inversion at C20 with 20 equivalents of DEAD, Ph_3P, and *p*-nitrobenzoic acid gave the allylic alcohol **118a** after hydrolysis of the intermediate *p*-nitrobenzoate ester **119** (Note 11).

The total synthesis of salinomycin—finale

With all the requisite fragments now in hand, we had hoped that the synthesis could be brought to a swift conclusion by an acid-catalysed rearrangement of the 17-*epi*-21-*epi*-salinomycin **121** derived from anti-selective aldol reaction between the ketone **120** with the C1–C9 aldehyde **5a** (Scheme 19). Our expectations were endorsed by the precedent of both Kishi[10] and Yonemitsu[13] who had previously rearranged two of the three possible diastereoisomeric dispiroacetals (**122** and **127**) to salinomycin. However, all attempts to epimerise the errant stereogenic centres at C17 and C21 with acid returned only traces of salinomycin by TLC amidst a phantasmagorical display of spots. Since the 17-*epi*-21-*epi*-salinomycin appeared to decompose faster than it epimerised, we then attempted to adjust the stereochemistry of the dispiroacetal *before* the aldol reaction. Thus treatment of **117a** with camphorsulfonic acid caused epimerisation at C21 to give dispiroacetal **123** (**117a** : **123** = 1 : 9) now having only one incorrect stereogenic centre at C17 (Note 12).

Ketone **6a**, obtained on replacement of the acetate function in **123** with a TES group, was converted to its magnesium enolate **125** (Scheme 19) according to precedent[10,13] and condensed with aldehyde **5a** to give a single major anti-adduct **126** (Note 13) in 43% yield. In order to remove the two TES groups, the adduct **126** was dissolved in commercial 1.1 M TBAF. The 20-*O*-TES group was cleaved readily but the tertiary TES ether at C-28 required 34 h at room temperature to give 17-*epi*-salinomycin **127** in 90% yield. Attempted chromatographic purification of **126** was accompanied by serious decomposition; therefore, the crude product was immediately treated with tri-



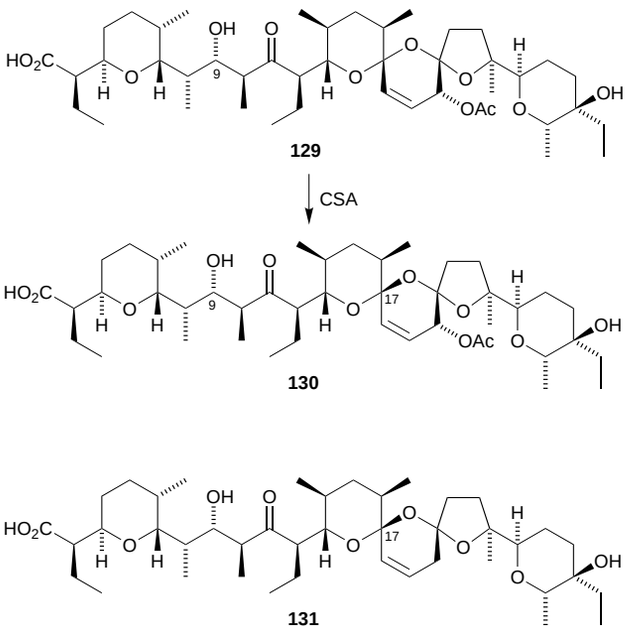
Scheme 19

fluoroacetic acid in dichloromethane at room temperature whereupon rapid rearrangement occurred to give salinomycin according to NMR spectroscopic analysis of the crude product. Since attempted chromatographic purification of the free acid was attended by decomposition, it was converted to salinomycin methyl ester **128** with diazomethane. The methyl ester, purified by column chromatography, was identical by high field ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectroscopy, TLC mobility, mass spectrometry and IR spectroscopy with an authentic sample of salinomycin methyl ester.

The stereochemistry of spirocyclisation was the cause of considerable vexation in our synthesis. At the outset we assumed that salinomycin, like most natural spiroacetals, exists in its most thermodynamically stable configuration (*vide supra*). We have already seen from the early degradation work (Scheme 2) that the dispiroacetal **6b** (corresponding to configuration **12a**) epimerises to 17-*epi*-**6b** (corresponding to configuration **12c**) when the salinomycin skeleton is shorn of the C1–C9 fragment. The driving force for the isomerisation may be relief of dipolar interactions of the two axially disposed oxygen atoms. We have also seen from our work and that of Kishi[10] and Yonemitsu[13] that restitution of the C1–C9 fragment enables isomerisation back to configuration **12a** (*cf*. **127**→**4**). These data lend support to Kishi's notion that the repulsive dipolar interaction in salinomycin is compensated by a hydrogen bond between the C9 and C20 hydroxy groups. Indeed, systems in which a remote hydrogen bond is precluded do not adopt the salinomycin configuration **12a** at equilibrium. Thus treatment of salinomycin-20-acetate **129** and ketone **6b** with acid results in complete isomerisation to the 17-*epi*-series (**130**, Scheme 20) whilst 20-deoxysalinomycin **131** (a natural product) is epimeric at C17.[80] It is noteworthy that X-ray data available for salinomycin derivatives reveal a folded conformation in which the C9 and C20 hydroxy groups are in close proximity.[5,81]

Conclusion

Salinomycin has been a fruitful scaffold on which to explore and extend new synthetic methodology. In particular we commend (a) the use of η^3-allylmolybdenum cationic complexes **21a**,**b** for the stereoselective construction of two contiguous stereogenic centres in fragment **5a** (Scheme 6); (b) the electrophilic cyclisation of 2-(prop-2-ynyl)-2-hydroxyoxanes to give molybdenum and chromium carbene complexes which are precursors to the furan fragment **7** (Schemes 9 and 10); (c) the diastereoselective oxidation of a 1,5-diene to generate four stereogenic centres in a single step leading to fragment **8** (Schemes 12–14); (d) the oxidative rearrangement of acylfuran **89** *en route* to the dispiroacetal core (Scheme 15); and finally (e) the use of an allenol ether as an acyl anion equivalent together with the stereoselective hydrolysis of allenol ether intermediate **112** in the synthesis of the dispiroacetal core (Scheme 17). Our

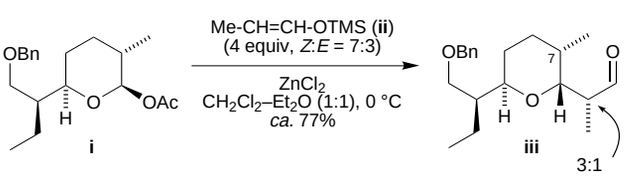


Scheme 20

strategy was robust enough to allow the construction of a dispiroacetal core rich in functional groups and stereochemical density but, by a stroke of ill fortune, our routes produced 17-*epi*-21-*epi*-salinomycin in which the stereochemistry at both spiroacetal centres was incorrect and all our attempts to rearrange it to salinomycin were thwarted by speedier decomposition—a predicament which could not have been anticipated from the results of our predecessors. Nevertheless, our eventual triumph illustrates the exquisite subtle effects of remote hydrogen bonds in fixing the stereochemistry of the polyether antibiotics.

Notes

1 Kishi and co-workers[82] reported that acetate **i** reacts with the enol silane **ii** (4 equiv.) derived from propanal ($Z:E = 7:4$) in the presence of excess $ZnCl_2$ to give the oxane derivative **iii** as a 3:1 mixture of diastereoisomers



with the major diastereoisomer having the correct stereochemistry at C8. Note the high stereoselectivity in the formation of the axial C–C bond at C7 consistent with exclusive axial attack of the enol silane on an oxonium ion intermediate.

2 The central proton of the allyl ligand in the neutral complex **20** gave characteristic signals in the ^1H NMR spectrum in $CDCl_3$: $\delta_{exo} = 3.96$ (t, J 9.7 Hz); $\delta_{endo} = 3.45$ (t, J 9.6 Hz); *exo*:*endo* = 85:15.

3 NMR spectroscopic analysis of the cationic complex **21** was hampered by its instability in the polar solvents (*e.g.* $[^2H]_6$acetone) needed for solubility. A ^1H NMR spectrum revealed two major components along with some minor impurities. We presume that the two major components correspond to the *exo* and *endo* isomers **21a** and **21b** (*exo*:*endo* = 55:45). For further details see the Experimental section.

4 The analogous tungsten complex was prepared in better yield (64%) but it was extremely unstable in solution.

5 The course of the oxidation is very pH dependent. The role of the CO_2 is to react with KOH formed during the reaction.[61,63]

6 The diastereoisomers were formed in the ratio 7:1. Preliminary evidence suggests that the minor diastereoisomer arises from isomerisation of the (*Z*)-enoate in **75** to the (*E*)-isomer under the conditions of the $KMnO_4$ oxidation.

7 Competing proton abstraction from lactone **8a** by the lithiated furan **87** is responsible for the recovery of furan **7** and lactone **8a**.

8 The formation of 1,7-dioxaspiro[5.5]undecane[83] and 1,6-dioxaspiro[4.5]decane systems[20,21] *via* the Achmatowicz oxidative rearrangement of furfurol derivatives[84] has been reported previously.

9 Metallation of the allenol ether was much less efficient when the hydroxy in fragment **110** was protected with a *tert*-butyldimethylsilyl group and failed completely under comparable conditions when a *tert*-butyldiphenylsilyl protecting group was used.

10 The stereoselective *cis*-protonation of allenol ethers first noted by Derguini and Linstrumelle[85] has been employed in spiroacetal synthesis.[86,87]

11 The allylic hydroxy function in **118b** is extremely hindered so the use of benzene as solvent and the large excess of DEAD, Ph_3P and *p*-nitrobenzoic acid were essential to the success of the Mitsunobu reaction.

12 The structure and stereochemistry of **123** was determined by correlation with a sample derived from degradation of salinomycin. Thus the thermolysis product **6b** (Scheme 2), prepared according to the Yonemitsu procedure,[14] was converted to its TES ether derivative (TESOTf, 2,6-lutidine) which then isomerised on treatment with camphorsulfonic acid in dichloromethane to give a 1:9 mixture of **117a** and **123** in 72% overall yield.

13 The anti-selectivity of the aldol reaction can be explained by assuming that the (*Z*)-enolate **125** condenses with aldehyde **5a** *via* an open transition state according to Cram's rule. An alternative explanation might be that the corresponding (*E*)-enolate reacts with aldehyde **5a** *via* a closed Zimmerman–Traxler transition state.[88]

Experimental

General

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus. Where appropriate, solvents and reagents were dried by standard methods, *i.e.* by distillation from the usual drying agent prior to use: tetrahydrofuran from sodium and benzophenone; pyridine, triethylamine, dichloromethane, dimethylformamide, dimethyl sulfoxide and hexamethylphosphoric triamide from calcium hydride. Chloroform was distilled from phosphorus pentoxide. Diethyl ether (ether), benzene and toluene were stored over sodium wire. Copper(I) bromide·dimethyl sulfide complex was purified by recrystallisation from anhydrous dimethyl sulfide and anhydrous pentane. The concentration of alkyllithium reagents was determined by titration against 1,3-diphenylacetone *p*-tosylhydrazone.[89] All reactions were magnetically stirred unless otherwise stated. Organic extracts were dried over $MgSO_4$ and concentrated at aspirator pressure using a Büchi rotary evaporator. All reactions were monitored by TLC with Macherey-Nagel Duren Alugram Sil G/UV_{254} pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised with UV light, followed by ceric sulfate–ethanolic sulfuric acid or phosphomolybdic acid. Column chromatography was performed on Sorbsil C60 (0.04–0.063 mm, 230–400 mesh). Column dimensions are expressed as height × width.

IR spectra were recorded as thin films on NaCl plates or as a solution in the solvent specified. Details are reported as ν_{max}/cm^{-1}, followed by a description using the following abbrevi-

ations: s = strong, m = medium, w = weak or br = broad. ^{1}H NMR spectra were recorded on Fourier Transform mode in $CDCl_3$ or $[^2H]_6$acetone solution and the chemical shift values are reported as values in ppm, relative to residual chloroform (δ 7.27) or acetone (δ 2.05) as internal standard unless otherwise stated. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, app. = apparent and br = broad. Coupling constants (J) are reported in Hz. ^{13}C NMR spectra were recorded in $CDCl_3$ solution and the chemical shift values are reported as values in ppm relative to residual chloroform (δ 77.2) as internal standard. The multiplicities refer to the signals in the off-resonance spectra and were elucidated using the distortionless enhancement by polarisation transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are described using the following abbreviations: 0 = singlet (due to quaternary carbon), 1 = doublet (methine), 2 = triplet (methylene), 3 = quartet (methyl). Ion mass (m/z) signals, are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%). Combustion analyses were performed by University College London. Optical rotations were recorded on an Optical Activity AA-100 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}.

Synthesis of C1–C9 fragment 5a

(η^5-Cyclopentadienyl)(5-methyl-2,3,4-η-hex-3-en-2-yl)(dicarbonyl)molybdenum 20

A suspension of molybdenum hexacarbonyl (5.0 g, 19.0 mmol) in degassed MeCN (140 cm^3) was refluxed under nitrogen for 3 h. After cooling, allylic acetate **18**[90] (2.97 g, 19.0 mmol) was added to the yellow solution in one portion, and the reaction mixture was refluxed for 36 h. A separate flask was charged with freshly prepared cyclopentadiene (1.26 g, 19.0 mmol) and THF (30 cm^3) under nitrogen, and cooled to 0 °C. BuLi (16.5 cm^3, 19.0 mmol of a 1.15 M solution in hexanes) was added dropwise over 5 min, and the reaction mixture stirred at 0 °C for 15 min. The resulting pale yellow solution was added to the original reaction vessel *via* syringe in one portion, and the resulting mixture stirred at room temperature (r.t.) for 1 h. The solvent was removed *in vacuo* to give a dark semi-solid. The products were triturated with Et_2O and filtered under an inert atmosphere through Celite and the solvent removed from the resulting filtrate. The resulting products were purified by column chromatography [deactivated alumina (5% water), degassed CH_2Cl_2 : hexanes = 1 : 4]. The resulting red oil crystallised in the freezer overnight, and the product was recrystallised from hexane (3.94 g, 12.5 mmol, 66%); mp 65–67 °C; $[\alpha]_D$ −150.0 (c 0.85, $CHCl_3$); ν_{max}(MeCN)/cm^{-1} 1929s, 1846s; δ_H(*exo*-isomer, 270 MHz, $CDCl_3$) 5.28 (5H, s, CpH), 3.95 (1H, t, J 9.7), 1.76 (3H, d, J 6.2), 1.72–1.57 (1H, m), 1.47–1.20 (2H, m), 1.25 (3H, d, J 6.6), 1.15 (3H, d, J 6.8); δ_C(*exo*-isomer, 75 MHz, $CDCl_3$) 206.8 (0), 205.3 (0), 92.5 (1, 5C), 71.7 (1), 70.9 (1), 59.2 (1), 36.0 (1), 28.1 (3), 24.8 (3), 21.1 (3); m/z (electrospray) 316.1 {[M(^{98}Mo)]$^+$, 68%}, 288.2 {[M(^{98}Mo) − CO]$^+$, 100%}, with associated isotope patterns.

(η^5-Cyclopentadienyl)(5-methyl-2,3,4-η-hex-3-en-2-yl)(carbonyl)(nitrosyl)molybdenum tetrafluoroborate 21a,b

To a solution of molybdenum complex **20** (1.40 g, 4.45 mmol) in MeCN (14 cm^3), under N_2, at 0 °C, was added nitrosonium tetrafluoroborate (521 mg, 4.46 mmol) in one portion. The red solution was stirred at 0 °C for 5 min, before transferring to Et_2O (140 cm^3) at 0 °C, to yield the product as a suspension. Filtration under an inert atmosphere gave the product as a yellow solid (1.64 g, 4.07 mmol, 91%); δ_H(270 MHz, $[^2H]_6$acetone, mixture of *endo* and *exo* isomers) 6.47 (5H, s, CpH), 6.44 (5H, s, CpH), 5.73 (1H, t, J 12.6, H-3), 5.61 (1H, t, J 13.1, H-3), 4.56 (1H, dq, J 6.8, 12.8), 4.17 (1H, dd, J 10.2, 12.9), 3.97 (1H, dd, J 4.6, 12.9), 3.68 (1H, dq, J 6.4, 12.2), 3.02–2.88 (2H, m, C5H), 2.62 (3H, d, J 6.8, C1H$_3$), 2.32 (3H, d, J 6.2, C1H$_3$), 1.56 (3H, d, J 6.6), 1.52 (3H, d, J 6.8), 1.37 (3H, d, J 6.6), 1.15 (3H, d, J 7.0); δ_C(75 MHz, $CDCl_3$) 206.8 (0, CO), 205.3 (0, CO), 92.5 (1, 5C), 71.7 (1, C2 or C4), 70.9 (1, C2 or C4), 59.2 (1, C3), 36.0 (1, C5), 28.1 (3), 24.8 (3), 21.1 (3); m/z (electrospray) 318.1 {[M(^{98}Mo) + H]$^+$, 65%}, 290.1.

(2*R*,3*R*)-2,3-Epoxy-6-methylhept-6-en-1-ol 23

To a solution of titanium isopropoxide (2.05 cm^3, 6.89 mmol) in CH_2Cl_2 (80 cm^3) at −35 °C under nitrogen were added successively (−)-diisopropyl L-tartrate (1.94 g, 8.27 mmol), and *tert*-butyl hydroperoxide (43.6 cm^3 of a 3.0 M solution in toluene, 130.9 mmol) whereupon the temperature rose to −30 °C. After stirring at −30 °C for 1 h, a solution of allyl alcohol **22** (16.4 g, 128.0 mmol) in CH_2Cl_2 (10 cm^3) was added dropwise over 20 min and the solution stirred between −25 and −18 °C for 6 h. 10% Aqueous NaOH saturated with NaCl (20 cm^3) was added to the reaction mixture, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (500 cm^3) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O : hexanes = 3 : 7) to give the epoxy alcohol **23** (14.2 g, 99.9 mmol, 78%) as a pale yellow oil; $[\alpha]_D$ +29.8 (c. 1.01, $CHCl_3$). The enantiomeric ratio was shown to be 97 : 3 by ^{1}H NMR spectroscopic analysis of the mandelic ester derivative. ν_{max}(film)/cm^{-1} 3419br, 2979s, 2935s, 2863m, 1650m, 1450s, 1376m, 1092m, 1028m, 886s; δ_H(300 MHz, $CDCl_3$) 4.77–4.74 (1H, br s), 4.72–4.69 (1H, br s), 3.90 (1H, ddd, J 12.6, 5.6, 2.3), 3.61 (1H, ddd, J 12.6, 6.6, 4.5), 3.01–2.92 (2H, m), 2.41 (1 H, t, J 6.3, OH), 2.15 (1H, app. dt, J 8.5, 2.5), 1.72 (3H, s), 1.75–1.66 (2H, m); δ_C(75 MHz, $CDCl_3$) 144.8 (0), 110.7 (2), 61.9 (2), 58.7 (1), 55.8 (1), 34.0 (2), 29.8 (2), 22.5 (3); m/z (electrospray) 127.1 [(M + H)$^+$, 7%], 108.1 (41), 95.1 (69), 93.1 (100).

(2*S*,3*R*)-2-Ethyl-6-methylhept-6-ene-1,3-diol 24

To a suspension of copper(I) iodide (4.93 g, 25.9 mmol) in THF (71 cm^3) and Et_2O (360 cm^3), at −10 °C, under argon, was added ethylmagnesium bromide (86.7 cm^3, 260.0 mmol of a 1.5 M solution in Et_2O) dropwise over 20 min. The dark reaction mixture was stirred at −10 °C for 15 min before cooling to −45 °C whereupon a solution of epoxy alcohol **23** (12.3 g, 86.5 mmol) in Et_2O (54 cm^3) was added slowly over 20 min. The reaction mixture was stirred at −40 °C for 3 h before adding aqueous ammonium chloride (100 cm^3) and aqueous ammonia (100 cm^3). The organic phase was separated, and the aqueous phase extracted with Et_2O (2 × 100 cm^3). The combined organic phases were combined, washed with brine (100 cm^3), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was dissolved in acetone (200 cm^3) and water (50 cm^3) before adding sodium periodate (9.03 g, 42.2 mmol), and the suspension stirred for 14 h at r.t. The reaction mixture was filtered, and the solvent removed *in vacuo* before adding water (200 cm^3) and ether (100 cm^3). The aqueous phase was extracted with Et_2O (4 × 100 cm^3), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O : hexanes = 5 : 1) to give alcohol **24** (8.34 g, 48.4 mmol, 56%) as a colourless oil [Found: (M + H)$^{+\bullet}$, 173.1542. $C_{10}H_{21}O_2$ requires M, 173.1554]; $[\alpha]_D$ +31.9 (c 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 3363br, 2964s, 2935s, 2878s, 1649m, 1447m, 1075m, 1032m, 1014m, 910m, 887m, 734s; δ_H(300 MHz, $CDCl_3$) 4.67 (2H, br s), 3.95 (1 H, dd, J 2.5, 10.8), 3.73–3.66 (2H, m), 2.90–2.99 (1H, m), 2.81 (1H, d, J 4.4), 2.19 (1H, dt, J 7.5, 14.5), 2.10 (1H, dt, J 7.5, 14.5), 1.75 (3H, s), 1.74–1.66 (2H, m), 1.54–1.38 (3H, m), 0.95 (3H, t, J 7.2); δ_C(75 MHz, $CDCl_3$) 146.1 (0), 110.5 (2), 75.6 (1), 63.9 (2), 46.2 (1), 34.4 (2), 33.6 (2), 22.6 (3), 21.6 (2), 11.9 (3).

(2*S*,3*R*)-2-Ethyl-6-methyl-1,3-bis(benzoyloxy)hept-6-ene 25
A solution of diol **24** (8.30 g, 48.2 mmol), DMAP (500 mg), pyridine (9.75 cm^3, 120.5 mmol) and benzoyl chloride (10.4 cm^3, 120.5 mmol) in $CHCl_3$ (250 cm^3) was warmed to 50 °C under nitrogen for 16 h. The solution was allowed to cool before adding 3-(*N*,*N*-dimethylamino)propylamine (6.0 cm^3, 48.2 mmol), and the yellow suspension stirred at r.t. for 30 min. The reaction mixture was partitioned between 1 M hydrochloric acid (200 cm^3) and CH_2Cl_2 (200 cm^3). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 cm^3). The combined organic phases were washed with 1 M hydrochloric acid (50 cm^3), brine (100 cm^3), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O : hexanes = 1 : 9) to give the bisbenzoate **25** (17.4 g, 45.7 mmol, 94%) as a colourless oil; $[\alpha]_D$ −20.3 (*c* 0.99, $CHCl_3$); ν_{max}(film)/cm^{-1} 2965s, 2936m, 2878m, 1715s, 1649m, 1602m, 1584m, 1451s, 1268s, 1176m, 1111s, 1069s, 1026s, 890m, 710s, 687s; δ_H(300 MHz, $CDCl_3$) 8.12–8.09 (4H, m), 7.60–7.52 (2H, m), 7.48–7.38 (4H, m), 5.45 (1H, dt, *J* 4.6, 9.3), 4.73 (1H, br s), 4.70 (1H, br s), 4.57 (1H, dd, *J* 5.4, 11.4), 4.43 (1H, dd, *J* 6.0, 11.4), 2.14 (2H, app. t, *J* 6.6), 2.09–1.94 (3H, m), 1.73 (3H, s), 1.59 (2H, app. quintet, *J* 7.5), 1.05 (3H, t, *J* 7.5); δ_C(75 MHz, $CDCl_3$) 166.8 (0), 166.3 (0), 144.9 (0), 133.1 (0), 133.1 (2C, 1), 130.4 (0), 130.3 (0), 129.8 (4C, 1), 128.6 (4C, 1), 110.5 (2), 74.5 (1), 64.3 (2), 43.1 (1), 33.9 (2), 30.0 (2), 22.7 (3), 21.5 (2), 12.0 (3); *m*/*z* (CI, NH_3) 398 [$(M + NH_4)^+$, 100%], 381 (22), 259 (41).

(5*R*,6*S*)-5-Benzoyloxy-6-(benzoyloxymethyl)octan-2-one 26
A solution of alkene **25** (17.0 g, 44.7 mmol) in methanol (200 cm^3) and CH_2Cl_2 (200 cm^3) was cooled to −80 °C before bubbling ozone through the solution until a blue colour was apparent. The blue solution was stirred at −80 °C for a further 10 min before bubbling argon through the solution until the colour discharged. Dimethyl sulfide (29.3 cm^3, 400 mmol) was added, and the cooling bath removed. After stirring the reaction mixture at r.t. for 16 h, the solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, Et_2O : hexanes = 3 : 7) to give ketone **26** (16.1 g, 42.1 mmol, 95%) as a colourless oil; $[\alpha]_D$ −14.2 (*c* 0.97, $CHCl_3$); ν_{max}(film)/cm^{-1} 2965m, 2931m, 1715s, 1062m, 1451m, 1359m, 1314m, 1269s, 1176m, 1111s, 1070m, 1026m, 710s; δ_H(300 MHz, $CDCl_3$) 8.09–8.00 (4H, m), 7.60–7.52 (2H, m), 7.48–7.38 (4H, m), 5.39 (1H, dt, *J* 4.4, 8.7), 4.52 (1H, dd, *J* 6.0, 11.6), 4.40 (1H, dd, *J* 5.2, 11.4), 2.60–2.48 (2H, m), 2.18–2.04 (3H, m), 2.1 (3H, s), 1.57 (2H, dq, *J* 2.7, 7.7), 1.04 (3H, t, *J* 7.5); δ_C(75 MHz, $CDCl_3$) 207.8 (0), 166.7 (0), 166.4 (0), 133.3 (1), 133.1 (1), 130.3 (0), 130.1 (0), 129.8 (2C, 1), 129.7 (2C, 1), 128.6 (2C, 1), 128.6 (2C, 1), 74.1 (1), 64.0 (2), 43.8 (1), 39.9 (2), 30.2 (3), 26.3 (2), 21.3 (2), 11.9 (3); *m*/*z* (CI, NH_3) 400 [$(M + NH_4)^+$, 100%].

(5*R*,6*S*)-5-Benzoyloxy-6-(benzoyloxymethyl)-2-(1,3-dithian-2-ylidene)octane 28
A solution of diisopropylamine (17.5 cm^3, 125.2 mmol) in THF (250 cm^3) was cooled to −30 °C, under nitrogen, before adding BuLi (52.2 cm^3, 125.2 mmol of a 1.4 M in hexane) dropwise over 20 min. The solution was cooled to −80 °C whereupon a solution of 1,3-dithiane (7.5 g, 62.6 mmol) in THF (100 cm^3) was added dropwise over 10 min. The colourless solution was stirred at −80 °C for 30 min and then a solution of diethyl chlorophosphate (9.0 cm^3, 62.6 mmol) in THF (100 cm^3) was added over 15 min during which the internal temperature rose to −45 °C. The yellow solution of lithiated phosphonate **27** was stirred at −45 °C for 1 h before adding a solution of ketone **26** (12.0 g, 31.3 mmol) in THF (100 cm^3) at a rate sufficient to maintain the temperature below −40 °C. The reaction mixture was stirred at −40 °C for 1 h, then allowed to warm to −20 °C over 15 min, before quenching with saturated aqueous ammonium chloride (200 cm^3). The organic phase was separated, and the aqueous phase extracted with Et_2O (2 × 100 cm^3). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O : hexanes = 1 : 5) to give ketene dithioacetal **28** (11.5 g, 23.7 mmol, 76%) as a colourless oil; $[\alpha]_D$ −9.3 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 2962m, 2932m, 1715s, 1061s, 1450s, 1314s, 1269s, 1176m, 1111s, 1070s, 1026s, 988m, 756s, 711s; δ_H(300 MHz, $CDCl_3$) 8.80–8.20 (4H, m), 7.60–7.52 (2H, m), 7.38–7.46 (4H, m), 5.38 (1H, dt, *J* 5.0, 9.7), 4.52 (1H, dd, *J* 7.1, 11.4), 4.41 (1H, dd, *J* 5.6, 11.4), 2.84–2.74 (5H, m), 2.47 (1H, t, *J* 8.1), 2.20–2.15 (1H, m), 2.05 (2H, app. quintet with fine splitting, *J* 5.8), 1.84 (3H, s), 2.00–1.83 (2H, m), 1.66–1.50 (2H, m), 1.05 (3H, t, *J* 7.5); δ_C(75 MHz, $CDCl_3$) 166.8 (0), 166.3 (0), 138.8 (0), 133.0 (1), 130.5 (0), 130.3 (0), 129.8 (4C, 1), 128.5 (2C, 1), 128.5 (2C, 1), 120.5 (0), 74.6 (1), 64.2 (2), 43.0 (1), 32.0 (2), 30.3 (2), 30.2 (2), 29.8 (2), 25.0 (2), 21.3 (2), 20.2 (3), 12.0 (3); *m*/*z* (EI) 484 [$(M)^{+\bullet}$, 70%], 159 (87), 105 (100).

(2*S*,3*R*)-6-(1,3-Dithian-2-ylidene)-2-ethylheptane-1,3-diol 29
A solution of diester **28** (11.3 g, 23.3 mmol) and potassium hydroxide (10.5 g, 186.4 mmol) in methanol (250 cm^3), CH_2Cl_2 (50 cm^3) and water (30 cm^3) was stirred at r.t. for 2 h. The solvent was removed *in vacuo*, before adding water (200 cm^3) and Et_2O (200 cm^3). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 100 cm^3). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O : hexanes = 1 : 1) to give diol **29** (6.05 g, 21.9 mmol, 94%) as a colourless oil (Found: $MH^{+\bullet}$, 277.1296. $C_{13}H_{25}O_2S_2$ requires *M*, 277.1302); $[\alpha]_D$ +11.0 (*c* 1.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 3357br, 2958s, 2930s, 1423m, 1372m, 1300m, 1275m, 1240m, 1073m, 1012m, 911m, 733s; δ_H(300 MHz, $CDCl_3$) 3.93 (1H, dd, *J* 2.5, 11.2), 3.74–3.60 (2H, m), 3.08 (2H, br s, 2 × OH), 2.88 (4H, dd, *J* 5.8, 6.0), 2.60 (1H, dt, *J* 8.1, 13.3), 2.34 (1H, ddd, *J* 6.0, 7.3, 13.3), 2.17–2.09 (2H, m), 1.92 (3H, s), 1.72–1.64 (2H, m), 1.52–1.36 (3H, m), 0.95 (3H, t, *J* 7.5); δ_C(75 MHz, $CDCl_3$) 140.0 (0), 119.7 (0), 75.0 (1), 64.1 (2), 46.1 (1), 33.4 (2), 32.0 (2), 30.5 (2), 30.3 (2), 25.0 (2), 21.8 (2), 20.3 (3), 11.9 (3); *m*/*z* (EI) 276 [$(M)^{+\bullet}$, 30%], 159 (100), 119 (87).

(8*R*,11*S*)-8-[(*S*)-1-Ethyl-2-hydroxyethyl]-11-methyl-7-oxa-1,5-dithiaspiro[5.5]undecane 30
A solution of diol **29** (5.85 g, 21.2 mmol) in CH_2Cl_2 (250 cm^3) was cooled to 0 °C under N_2. A saturated solution of anhydrous hydrogen chloride in CH_2Cl_2 (30 cm^3) was then added, and the solution stirred at 0 °C for 5 min. Triethylamine (5 cm^3) was added, and the mixture concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O : hexanes = 1 : 3) to give spirocycle **30** (4.74 g, 17.1 mmol, 81%) as a colourless oil; $[\alpha]_D$ −54.7 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 3456br s, 2959s, 2930s, 1455m, 1423m, 1413m, 1379m, 1277m, 1086m, 1049m, 1004s, 954m, 907m, 787s, 764m; δ_H(300 MHz, $CDCl_3$) 4.02 (1H, ddd, *J* 2.5, 5.4, 11.1), 3.94 (1H, ddd, *J* 2.0, 7.0, 11.4), 3.73 (1H, ddd, *J* 3.7, 5.1, 11.4), 3.38 (1H, ddd, *J* 2.9, 12.7, 13.9), 3.08 (1H, ddd, *J* 2.5, 10.4, 13.9), 2.76–2.56 (3H, m), 2.18–2.06 (1H, m), 2.00–1.82 (2H, m), 1.72–1.47 (6H, m), 1.12 (3H, d, *J* 6.8), 0.98 (3 H, t, *J* 7.0); δ_C(75 MHz, $CDCl_3$), 93.8 (0), 75.8 (1), 62.6 (2), 46.8 (1), 42.2 (1), 29.8 (2), 27.8 (2), 27.0 (2), 25.7 (2), 24.9 (2), 21.5 (2), 18.7 (3), 11.9 (3).

(8*R*,11*S*)-8-[(*S*)-1-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-11-methyl-7-oxa-1,5-dithiaspiro[5.5]undecane 31
To a solution of alcohol **30** (2.00 g, 7.24 mmol), imidazole (1.97 g, 28.96 mmol) and DMAP (20 mg) in CH_2Cl_2 (100 cm^3), under nitrogen, was added *tert*-butyldiphenylsilyl chloride (2.25 cm^3, 8.69 mmol) dropwise, and the reaction mixture was stirred at r.t. for 2 h. Saturated aqueous ammonium chloride (100 cm^3) and CH_2Cl_2 (50 cm^3) were added and the organic phase was separated, washed with brine (50 cm^3), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O : hexanes = 1 : 19) to give the silyl

ether **31** (3.57 g, 6.93 mmol, 96%) as a colourless oil; $[\alpha]_D$ −35.4 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 3070m, 3048m, 2958s, 2929s, 2857s, 1474m, 1461m, 1427s, 1412m, 1389m, 1380m, 1360m, 1276m, 1216m, 1111s, 1052s, 1002s, 970m, 933m, 907m, 823m, 800m, 758s, 702s; δ_H(270 MHz, $CDCl_3$) 7.70–7.65 (4H, m), 7.46–7.35 (6H, m), 3.99 (1H, ddd, *J* 2.1, 7.0, 13.5), 3.86 (1H, dd, *J* 5.2, 10.1), 3.82 (1H, dd, *J* 5.8, 10.1), 3.17 (1H, ddd, *J* 6.0, 9.5, 13.8), 2.79 (1H, ddd, *J* 6.2, 9.5, 13.9), 2.47 (1H, dtd, *J* 1.4, 4.5, 13.5), 2.36 (1H, dt with fine splitting, *J* 3.5, 13.7), 1.84–1.74 (2H, m), 1.80–1.40 (8H, m), 1.10 (3H, d, *J* 6.8), 1.08 (9H, s), 0.85 (3H, t, *J* 7.5); δ_C(75 MHz, $CDCl_3$) 136.0 (2C, 1), 135.9 (2C, 1), 134.2 (0), 134.0 (0), 129.7 (1), 129.7 (1), 127.8 (4C, 1), 93.6 (0), 72.1 (1), 62.8 (2), 47.5 (1), 42.3 (1), 28.7 (2), 28.1 (2), 26.7 (2), 25.8 (2), 25.1 (2), 27.2 (3C, 3), 19.7 (2), 19.5 (0), 18.6 (3), 11.6 (3).

(3*S*,6*R*)-6-[(*S*)-1-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-3-methyloxan-2-one 32

To a vigorously stirred two phase mixture containing orthoester derivative **31** (3.54 g, 6.87 mmol), sodium hydrogen carbonate (1.38 g, 16.49 mmol), water (50 cm^3) and Et_2O (100 cm^3) was added a solution of iodine (1.74 g, 6.87 mmol) in Et_2O (50 cm^3) over 15 min. The dark reaction mixture was gently warmed until the organic phase was refluxing and the mixture stirred at this temperature for 30 min. After cooling to r.t., saturated aqueous sodium thiosulfate (50 cm^3) was added and stirring continued until the dark colour disappeared. The organic phase was separated and the aqueous phase extracted with Et_2O (100 cm^3). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes = 1:4) to yield the lactone **32** (2.43 g, 5.72 mmol, 83%) as a colourless oil which solidified in the freezer. Recrystallisation from aqueous ethanol gave a white solid; mp 38–40 °C; $[\alpha]_D$ −2.0 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 2961s, 2932s, 2858m, 1731s, 1472m, 1461m, 1427m, 1373m, 1361m, 1240m, 1181m, 1111s, 1084m, 1058m, 1009m, 823m, 739m, 702s; δ_H(270 MHz, $CDCl_3$) 7.70–7.60 (4H, m), 7.50–7.30 (6H, m), 4.56 (1H, ddd, *J* 3.1, 5.0, 11.6), 3.81 (1H, dd, *J* 4.4, 10.6), 3.63 (1H, dd, *J* 7.0, 10.6), 2.47–2.35 (1H, m), 2.15–1.97 (1H, m), 1.90–1.40 (6H, m), 1.30 (3H, d, *J* 7.2), 1.07 (9H, s), 0.84 (3H, t, *J* 7.5); δ_C(75 MHz, $CDCl_3$) 174.8 (0), 135.8 (4C, 1), 133.7 (2C, 0), 133.6 (2C, 1), 127.9 (4C, 1), 82.6 (1), 62.3 (2), 47.2 (1), 36.5 (1), 28.9 (2), 25.7 (2), 27.1 (3C, 3), 19.4 (0), 19.2 (2), 17.6 (3), 12.0 (3); *m*/*z* (CI, NH_3) 442 [$(M + NH_4)^+$, 22%], 367 (33), 347 (100).

(2*RS*,3*S*,6*R*)-6-[(*S*)-1-(*tert*-Butyldiphenylsilyloxymethyl)-propyl]-3-methyl-2-(phenylthio)oxane 33

A solution of lactone **32** (2.30 g, 5.42 mmol) in toluene (100 cm^3), under N_2, was cooled to −80 °C before adding DIBALH (4.15 cm^3 of a 1.5 M solution in toluene, 6.22 mmol) dropwise. The reaction mixture was stirred at −80 °C for 45 min before adding $BF_3{\cdot}OEt_2$ (2.10 cm^3, 16.98 mmol) dropwise, followed by thiophenol (0.87 cm^3, 8.49 mmol). The yellow solution was stirred at −80 °C for 15 min before removing the cooling bath and allowing the reaction mixture to warm to −50 °C. The reaction was quenched with saturated aqueous ammonium chloride (20 cm^3), and the organic phase was separated. The aqueous phase was extracted with Et_2O (20 cm^3), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes→Et_2O:hexanes = 1:49) to give thioacetal **33** (2.32 g, 4.47 mmol, 82%) as a colourless oil; $[\alpha]_D$ −90.6 (*c* 1.00, $CHCl_3$). ^{1}H and ^{13}C NMR spectroscopic analysis revealed a 3:1 mixture of diastereoisomers. NMR data reported below refers to the major (2*S*)-diastereoisomer: ν_{max}(film)/cm^{-1} 3070m, 2958s, 2929s, 2858s, 1585m, 1472m, 1461m, 1438m, 1427m, 1390m, 1388m, 1360m, 1111s, 1088s, 1055s, 1026m, 1008m, 951m, 823m, 794m, 739s, 701s; δ_H(270 MHz, $CDCl_3$) 7.75–7.62 (4H, m), 7.60–7.52 (2H, m), 7.48–7.35 (6H, m), 7.20–7.10 (3H, m), 5.77 (1H, dd, *J* 1.5, 4.1), 4.29–4.21 (1H, m), 3.69 (1H, dd, *J* 6.2, 10.2), 3.57 (1H, dd, *J* 6.3, 10.4), 2.03–1.92 (1H, m), 1.68–1.28 (7H, m), 1.06 (9H, s), 0.99 (3H, d, *J* 6.8), 0.79 (3H, t, *J* 7.3); δ_C(75 MHz, $CDCl_3$) 135.8 (4C, 1), 134.3 (2C, 0), 132.1 (0), 130.8 (2C, 1), 129.6 (2C, 1), 128.8 (2C, 1), 127.7 (4C, 1), 126.2 (1), 92.3 (1), 69.3 (1), 63.5 (2), 47.4 (1), 36.5 (1), 28.3 (2), 28.2 (2), 27.0 (3C, 3), 20.1 (2), 19.4 (0), 19.0 (3), 11.6 (3); *m*/*z* (electrospray) 541.2 [$(M + Na)^+$, 58%], 102.1 (100).

(2*R*,3*S*,6*R*)-6-[(*S*)-1-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-3-methyl-2-[(*S*,*E*)-1,4-dimethylpent-2-enyl]oxane 37

A 0.4 M solution of lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) in THF was prepared according to the general procedure of Freeman and Hutchinson.[35] To a flame-dried two-necked RB flask, fitted with a glass-coated magnetic stirrer and argon inlet, was added 4,4′-di-*tert*-butylbiphenyl (850 mg, 3.2 mmol) under a steady flow of argon. THF (7 cm^3) was added to the reaction flask, and the colourless solution vigorously stirred at r.t. A piece of lithium wire (24 mg, 3.4 mmol, low sodium content) was cut and cleaned under oil and then cut into small pieces, which were washed with pentane, and added to the reaction flask under a flow of argon. The suspension was cooled to 0 °C using an ice bath, and the reaction mixture was stirred at 0 °C, under a static argon atmosphere for 5 h. The blue–green colour of the radical anion became apparent after *ca.* 10 min.

To a flame dried two-necked RB flask, fitted with a glass-coated stirring bar, under argon, was added LDBB (7.0 cm^3, 2.80 mmol, 0.4 M solution in THF) and THF (3 cm^3). The blue solution was cooled to −80 °C, before adding a degassed solution of (phenylthio)acetals **33** (608 mg, 1.17 mmol) in THF (2.0 cm^3) dropwise over 5 min. The orange solution was stirred at −80 °C for 15 min before rapidly adding a degassed solution of CuBr·DMS (261 mg, 1.27 mmol) in THF (0.8 cm^3) followed immediately by diisopropyl sulfide (0.7 cm^3). After the brown reaction mixture was stirred at −80 °C for 30 min, complex **21a**,**b** (960 mg, 2.38 mmol) was added as a solid, and the dark reaction mixture stirred at −80 °C for 1 h. A solution of saturated aqueous ammonium chloride (30 cm^3) and ammonia (20 cm^3) was added to the reaction, followed by Et_2O (70 cm^3), and the mixture stirred at r.t. until a blue solution was apparent. The organic phase was separated and the aqueous phase extracted with Et_2O (50 cm^3). The combined organic phases were washed with brine (30 cm^3), dried (Na_2SO_4), then filtered, and concentrated *in vacuo*. The residual brown solid was purified by column chromatography (SiO_2, Et_2O:hexanes, 1:99→5:95) allowed isolation of the products as a yellow oil. The products were dissolved in $CHCl_3$ (30 cm^3) and exposed to air for 26 h in which time a precipitate was observed. The products were pre-adsorbed onto silica, and column chromatography (SiO_2, Et_2O:hexanes = 1:49) gave the adduct **37** (260 mg, 0.51 mmol, 44%) as a colourless oil; $[\alpha]_D$ −32.2 (*c* 0.98, $CHCl_3$); ν_{max}(film)/cm^{-1} 2959m, 2930m, 2854m, 1460m, 1427m, 1381m, 1360m, 1112m, 1081m; δ_H(360 MHz, $CDCl_3$) 7.75–7.65 (4H, m), 7.45–7.35 (6H, m), 5.16 (1H, dd, *J* 6.7, 15.5), 4.95 (1H, ddd, *J* 1.1, 7.9, 15.4), 3.78 (1H, dd, *J* 4.4, 10.3), 3.78–3.52 (1H, m), 3.69 (1H, dd, *J* 7.9, 10.4), 3.07 (1H, dd, *J* 2.7, 9.3), 2.11–2.00 (2H, m), 1.75–1.35 (8H, m), 1.06 (9H, s), 0.95 (3H, d, *J* 7.0), 0.84 (3H, t, *J* 7.5), 0.78 (3H, d, *J* 6.8), 0.69 and 0.68 (3H each, d, *J* 6.8); δ_C(75 MHz, $CDCl_3$) 136.5 (1), 135.9 (2C, 1), 135.8 (2C, 1), 134.4 (0), 134.1 (0), 131.6 (1), 129.7 (1), 129.6 (1), 127.8 (4C, 1), 76.1 (1), 73.1 (1), 62.6 (2), 39.6 (1), 38.9 (1), 30.9 (1), 29.4 (1), 27.0 (3C, 3), 26.9 (2), 22.9 (3), 22.8 (3), 21.1 (2), 19.8 (2), 19.5 (0), 17.2 (3), 12.6 (3), 10.2 (3); *m*/*z* (electrospray) 507.4 [$(M + H)^+$, 100%].

(2*R*,3*S*,6*R*)-6-[(*S*)-1-(Hydroxymethyl)propyl]-3-methyl-2-[(*S*,*E*)-1,4-dimethylpent-2-enyl]oxane 38

To a solution of silyl ether **37** (325 mg, 0.64 mmol) in THF (10 cm^3) was added TBAF·3H_2O (261 mg, 0.83 mmol). The result-

ing solution was stirred at r.t. for 16 h, before adding saturated aqueous ammonium chloride (20 cm^3) and Et_2O (20 cm^3). The organic phase was separated, and the aqueous phase extracted with Et_2O (20 cm^3). The combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes = 1:4) to give alcohol **38** (155 mg, 0.58 mmol, 91%) as a colourless oil; $[\alpha]_D$ −39.4 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3451m, 2960s, 2931s, 2872m, 1461m, 1381m, 1260m, 1053m, 1010m; δ_H(270 MHz, $CDCl_3$) 5.44 (1H, dd, *J* 6.0, 15.5), 5.32 (1H, ddd, *J* 1.2, 8.3, 15.3), 3.80–3.70 (2H, m), 3.59 (1H, ddd, *J* 5.7, 6.0, 11.6), 3.38 (1H, dd, *J* 3.3, 9.3), 2.74 (1H, t, *J* 6.2, OH), 2.33–2.17 (2H, m), 1.95–1.65 (4H, m), 1.53–1.36 (2H, m), 1.34–1.20 (2H, m), 0.99 (3H, d, *J* 6.8), 0.98 (3H, d, *J* 6.8), 0.97 (3H, d, *J* 7.2), 0.92 (3H, d, *J* 8.1), 0.99 (3H, t, *J* 7.7); δ_C(75 MHz, $CDCl_3$) 137.9 (1), 130.8 (1), 77.9 (1), 76.3 (1), 63.6 (2), 41.4 (2), 39.1 (1), 31.0 (1), 29.9 (1), 26.9 (2), 22.7 (2), 21.5 (2), 22.5 (3), 22.5 (3), 17.8 (3), 13.3 (3), 11.7 (3); *m/z* (electrospray) 291.4 [$(M + Na)^+$, 100%], 269.4 [$(M + H)^+$, 20%].

(2*R*,3*S*,6*R*)-6-[(*R*)-1-(Methoxycarbonyl)propyl]-3-methyl-2-[(*S*,*E*)-1,4-dimethylpent-2-enyl]oxane 40

To a solution of alcohol **38** (98 mg, 0.37 mmol) in CH_2Cl_2 (5 cm^3) under N_2, was added Dess–Martin periodinane (132 mg, 0.55 mmol). After stirring for 2 h at r.t., saturated aqueous sodium thiosulfate (4 cm^3), saturated aqueous sodium hydrogen carbonate (4 cm^3), water (30 cm^3), and CH_2Cl_2 (30 cm^3) were added. The organic phase was separated, and the aqueous phase extracted with CH_2Cl_2 (20 cm^3). The combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residual crude aldehyde was dissolved in CH_2Cl_2 (5 cm^3) to which was added 1-methylcyclohex-1-ene (0.22 cm^3, 1.82 mmol), sulfamic acid (0.37 cm^3, 0.36 mmol of a 1 M aqueous solution) and water (1 cm^3). The two phase mixture was cooled to −5 °C, before adding sodium chlorite (1.10 cm^3, 1.10 mmol of a 1 M aqueous solution), and the reaction mixture stirred at −5 °C for 1 h before allowing to warm to r.t. Further portions of sulfamic acid (0.17 cm^3, 0.17 mmol of a 1 M aqueous solution) and sodium chlorite (0.55 cm^3, 0.55 mmol of a 1 M aqueous solution) were added and the reaction mixture stirred at r.t. for 2 h. Water (20 cm^3) and CH_2Cl_2 (20 cm^3) were added to the reaction mixture, and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (20 cm^3) and the combined organic phases washed with brine (20 cm^3), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residual carboxylic acid **39** was purified by column chromatography (SiO_2, Et_2O:hexanes = 1:4) and added to benzene (5 cm^3) containing tetramethylguanidine (0.94 cm^3, 0.75 mmol). After 90 min at r.t., methyl iodide (0.65 cm^3, 1.05 mmol) was added and stirring continued for a further 3 h. The reaction mixture was filtered through Celite, and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, Et_2O:hexanes = 1:19) to give the ester **40** (69 mg, 0.23 mmol, 62%) as a colourless oil; $[\alpha]_D$ −38.4 (*c* 1.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 2962s, 2931s, 2866m, 1741s, 1461m, 1381m, 1274m, 1239m, 1215m, 1161m, 1122m, 1091m, 1052m, 1025m; δ_H(270 MHz, $CDCl_3$) 5.32–5.30 (2H), 4.03 (1H, ddd, *J* 2.4, 5.6, 10.9), 3.70 (3H, s), 3.43 (1H, dd, *J* 2.8, 9.3), 2.94 (1H, ddd, *J* 5.3, 10.0, 10.7), 2.28–2.18 (1H, m), 2.15–2.07 (1H, m), 1.96–1.70 (3H, m), 1.51–1.34 (4H, m), 0.99 and 0.97 (3H each, d, *J* 6.8), 0.96 (3H, d, *J* 6.9), 0.90 (3H, t, *J* 7.5), 0.87 (3H, d, *J* 6.9); δ_C(75 MHz, $CDCl_3$) 174.5 (0), 136.5 (1), 131.8 (1), 76.7 (1), 74.7 (1), 51.5 (3), 48.6 (1), 39.1 (1), 31.5 (1), 29.2 (1), 26.4 (2), 22.9 (2), 20.8 (2), 23.0 (3), 22.9 (3), 17.6 (3), 12.1 (3), 12.0 (3); *m/z* (electrospray) 319.3 [$(M + Na)^+$, 100%], 297.3 [$(M + H)^+$, 13%].

(2*R*,3*S*,6*R*)-6-[(*R*)-1-(Methoxycarbonyl)propyl]-3-methyl-2-[(*R*)-1-methyl-2-oxoethyl]oxane 5a

Ozone was bubbled through a solution of alkene **40** (76 mg, 0.25 mmol) in CH_2Cl_2 (10 cm^3) at −80 °C until the blue colour persisted. Excess ozone was discharged in a stream of oxygen whereupon a solution of triphenylphosphine (131 mg, 0.50 mmol) in CH_2Cl_2 (2 cm^3) was added dropwise. The solution was allowed to warm to 0 °C over 2 h before pre-adsorbing the reaction mixture onto silica. Column chromatography (SiO_2, Et_2O:hexanes = 1:4) gave a crystalline solid which was recrystallised from pentane to give aldehyde **5a** (62 mg, 0.24 mmol, 94%) as white needles; mp 42.0–43.0 °C (lit.,[14] 44.0–45.5 °C); $[\alpha]_D$ −71.0 (*c* 1.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 2954s, 2919s, 2884m, 2848m, 1727s; δ_H(270 MHz, $CDCl_3$) 9.51 (1H, d, *J* 3.7), 4.10–3.94 (1H, m), 3.91 (1H, dd, *J* 2.5, 10.4), 3.64 (3H, s), 2.96 (1H, td, *J* 4.4, 10.6), 2.36 (1H, ddq, *J* 3.6, 7.0, 10.2), 2.02–1.76 (3H, m), 1.58–1.38 (4H, m), 0.98 (3H, d, *J* 7.1), 0.95 (3H, d, *J* 7.0), 0.90 (3H, t, *J* 7.3); δ_C(75 MHz, $CDCl_3$) 205.2 (0), 174.7 (0), 75.1 (1), 73.8 (1), 51.7 (3), 48.6 (1), 48.5 (1), 28.3 (1), 25.9 (2), 22.9 (2), 20.4 (2), 12.0 (3), 11.7 (3), 9.9 (3); *m/z* (electrospray) 279.2 [$(M + Na)^+$, 100%].

Synthesis of C11–C20 furan fragment 7

Methyl (2*S*,4*R*)-5-(Benzyloxymethoxy)-2,4-dimethylpentanoate 44a

To a magnetically stirred solution of the alcohol **43a** (9.20 g, 57.5 mmol) in THF (45 cm^3) at 10 °C was added chloromethyl benzyl ether (10.7 cm^3, 78 mmol) and ethyl diisopropylamine (16.7 cm^3, 37 mmol) in THF (18 cm^3). Tetrabutylammonium iodide (1.94 g, 5.24 mmol) was added and the mixture stirred overnight. After addition of methanol (0.7 cm^3) the mixture was stirred for an additional 2 h. Dilution with EtOAc followed by washing with saturated aqueous sodium hydrogen carbonate, pH 7 buffer and brine gave an orange solution which was dried ($MgSO_4$) and concentrated *in vacuo*. The residual dark orange oil (18.9 g) was purified by column chromatography (SiO_2, hexanes:Et_2O = 97:3→9:1) to give ester **44a** (14.3 g, 51.1 mmol, 89%) as a colourless oil [Found: $(M + NH_4)^{+\bullet}$, 298.2023. $C_{16}H_{24}O_4 + NH_4$ requires *M*, 298.2018]; $[\alpha]_D$ +12.7 (*c* 2.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 2952s, 2877s, 1738s, 1455s, 1380m, 1261m, 1195s, 1173s, 1112s, 1047s, 738s, 698m; δ_H(270 MHz, $CDCl_3$) 7.38–7.26 (5H, m), 4.75 (2H, s), 4.60 (2H, s), 3.67 (3H, s), 3.43 (1H, dd, *J* 9.5, 5.6), 3.38 (1H, dd, *J* 9.5, 6.0), 2.68–2.52 (1H, m), 1.91–1.65 (2H, m), 1.27–1.15 (1H, m), 1.18 (3H, d, *J* 7), 0.98 (3H, d, *J* 6.6); δ_C(67.5 MHz, $CDCl_3$) 177.38 (0), 138.09 (0), 128.57 (1), 128.04 (1), 127.82 (1), 94.87 (2), 73.38 (2), 69.44 (2), 51.67 (3), 38.24 (2), 37.30 (1), 31.63 (1), 18.17 (3), 17.23 (3); *m/z* (EI) 281 [$(M + 1)^{+\bullet}$, 3%], 263 (2), 174 (30), 142 (30), 120 (30), 91 (100), 83 (25), 69 (15).

(2*S*,4*R*)-5-(Benzyloxymethoxy)-2,4-dimethylpentan-1-ol 45

To a magnetically stirred suspension of LAH (1.52 g, 40 mmol) in dry THF (60 cm^3) was slowly added at 0 °C ester **44a** (8.00 g, 28.6 mmol) in THF (40 cm^3) maintaining the temperature below 3 °C. After a further 30 min at 0 °C, the reaction was quenched by careful dropwise addition of saturated aqueous sodium sulfate until a white precipitate appeared. The mixture was dried ($MgSO_4$), filtered, and concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, 7 × 5 cm, hexanes:Et_2O = 6:4) to give alcohol **45** (6.48 g, 25.7 mmol, 90%) as a colourless oil [Found: $(M + NH_4)^{+\bullet}$, 270.2073. $C_{15}H_{24}O_4 + NH_4$ requires *M*, 270.2069]; $[\alpha]_D$ −6.0 (*c* 1.37, $CHCl_3$); ν_{max}(film)/cm^{-1} 3671–3120br, 2954s, 2928s, 1497m, 1454s, 1173m, 1110s, 1045s, 735s, 698s; δ_H(270 MHz, $CDCl_3$) 7.4–7.2 (5H, m), 4.76 (2H, s), 4.61 (2H, s), 3.55–3.34 (4H, m), 1.95–1.65 (3H, m), 1.49 (1H, ddd, *J* 6.8, 6.8, 13.5), 1.05–0.93 (1H, m), 0.98 (3H, d, *J* 6.5), 0.96 (3H, d, *J* 6.4); δ_C(67.5 MHz, $CDCl_3$) 138.06 (0), 128.59 (1), 128.04 (1), 127.85 (1), 94.94 (2), 73.51 (2), 69.48 (2), 68.11 (2), 37.65 (2), 33.29 (1), 31.07 (1), 18.28 (3), 17.72 (3); *m/z* (CI, NH_3) 270 [$(M + NH_4)^+$, 100%], 253 [$(M + H)^+$, 7%], 150 (10).

(2*S*,4*R*)-5-(Benzyloxymethoxy)-2,4-dimethylpentanal 46

To a magnetically-stirred solution of oxalyl chloride (580 μl,

6.54 mmol) in CH_2Cl_2 (13 cm^3), cooled in an acetone–liquid nitrogen bath, was added DMSO (860 μl, 13.1 mmol) in CH_2Cl_2 (2 cm^3) at a rate sufficient to maintain the reaction temperature below −50 °C. The solution was stirred at −50 °C for 2 min whereupon alcohol **45** (1.47 g, 5.83 mmol) in CH_2Cl_2 (6 cm^3) was added dropwise at −55 °C, resulting in the formation of a white precipitate. The mixture was stirred at −55 to −50 °C for 20 min whereupon *N*-methylmorpholine (3.3 cm^3, 30 mmol) was added causing the solid to disappear then reappear. The mixture was allowed to warm to 5 °C over 2 h and then poured into ice-cooled 1 M HCl. The organic layer was separated, washed with aqueous sodium hydrogen carbonate, brine, dried ($MgSO_4$) and filtered. The yellow residue obtained on concentration *in vacuo* was purified by column chromatography (SiO_2, 4.5 × 4.5 cm, hexanes : EtOAc = 5 : 1) to yield aldehyde **46** as a colourless oil (1.35 g, 5.40 mmol, 93%); $[\alpha]_D$ +5.7 (*c* 2.85, $CHCl_3$); ν_{max}(film)/cm^{-1} 2931s, 1724s, 1454m, 1380m, 1110s, 1047s, 738m, 698m; δ_H(270 MHz, $CDCl_3$) 9.58 (1H, d, *J* 2.3), 7.5–7.2 (5H, m), 4.75 (2H, s), 4.61 (2H, s), 3.42 (2H, d, *J* 5.6), 2.54–2.38 (1H, m), 1.96–1.74 (2H, m), 1.28–1.14 (1H, m), 1.12 (3H, d, *J* 7.0), 0.98 (3H, d, *J* 6.8); δ_C(67.5 MHz, $CDCl_3$) 205.20 (1), 138.02 (0), 128.56 (1), 127.97 (1), 127.82 (1), 94.92 (2), 73.07 (2), 69.54 (2), 44.20 (1), 34.98 (2), 31.28 (1), 17.60 (3), 14.42 (3); *m*/*z* (CI, NH_3) 268 [$(M + NH_4)^+$, 95%], 219 (10), 130 (25), 113 (100).

(*S*)-*N*-Butanoyl-4-isopropyloxazolidine-2-thione 47

The title compound was prepared according to the procedure of Fujita and co-workers.[53]

(*S*)-*N*-[(2*R*,3*S*,4*S*,6*R*)-7-(Benzyloxymethoxy)-2-ethyl-3-hydroxy-4,6-dimethylheptanoyl]-4-isopropyl-1,3-oxazolidine-2-thione 48

To a magnetically stirred suspension of tin(II) triflate (9.14 g, 21.9 mmol) in dry CH_2Cl_2 (30 cm^3) under an atmosphere of argon, at −50 °C was added *N*-ethylpiperidine (3.5 cm^3, 26.7 mmol) dropwise. To the resulting lemon yellow suspension was added a solution of oxazolidine-2-thione **47** (3.92 g, 18.2 mmol) in CH_2Cl_2 (30 cm^3) at such a rate that the temperature did not exceed −45 °C. After stirring at −45 °C for 3 h, the cloudy solution was then cooled to −80 °C whereupon a solution of the aldehyde **46** (3.04 g, 12.2 mmol) in CH_2Cl_2 (30 cm^3) was added slowly. The cloudy solution was stirred for 20 min and then poured into pH 7 phosphate buffer. The mixture was filtered through Celite, washing with several portions of CH_2Cl_2. The organic layer was then separated, and the aqueous layer extracted with two portions of CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a brown oil (13 g) which was filtered through a short pad of silica (hexanes : EtOAc = 1 : 1). Removal of solvent gave the crude product as a pale yellow oil (7.1 g) which was purified by column chromatography (SiO_2, 6 × 8 cm, hexanes : EtOAc = 5 : 1) to give **48** (5.40 g, 11.6 mmol, 96%) as a viscous, pale yellow oil; $[\alpha]_D$ +74.5 (*c* 0.95, $CHCl_3$); ν_{max}(film)/cm^{-1} 3508br, 2964s, 2876s, 1694s, 1462s, 1372s, 1324s, 1291s, 1191s, 1155s, 1117s, 1045s, 958s, 788m, 736m, 698m; δ_H(270 MHz, $CDCl_3$) 7.40–7.28 (5H, m), 5.24 (1H, ddd, *J* 4, 4, 10), 4.78 (1H, ddd, *J* 4, 4, 8), 4.75 (2H, s), 4.61 (2H, s), 4.44–4.36 (2H, m), 3.66 (1H, dd, *J* 3, 8), 3.51 (1H, dd, *J* 5, 9), 3.35 (1H, dd, *J* 7, 9), 2.6–2.0 (1H, br), 2.42–2.26 (1H, m), 2.0–1.54 (5H, m), 1.08–0.95 (1H, m), 1.01 (3H, d, *J* 6), 0.98 (3H, d, *J* 7), 0.93 (3H, d, *J* 7), 0.91 (3H, t, *J* 7), 0.89 (3H, d, *J* 7); δ_C(67.5 MHz, $CDCl_3$) 186.1 (0), 177.7 (0), 138.1 (0), 128.5 (1), 128.0 (1), 127.8 (1), 94.9 (2), 76.2 (1), 73.0 (2), 69.4 (2), 67.5 (2), 63.4 (1), 46.2 (1), 38.2 (2), 35.1 (1), 31.4 (1), 29.2 (1), 19.4 (3), 18.6 (2), 18.4 (3), 16.6 (3), 15.1 (3), 12.0 (3); *m*/*z* (EI) 465 ($M^{+\bullet}$, 1%), 447 (7), 226 (70), 146 (90), 91 (100).

(2*S*,3*S*,4*S*,6*R*)-7-(Benzyloxymethoxy)-2-ethyl-4,6-dimethylheptane-1,3-diol 49

To a magnetically stirred solution of sodium borohydride (950 mg, 25 mmol) in THF (40 cm^3) and water (3 cm^3) was added at 0 °C a solution of the oxazolidine-2-thione **48** (3.87 g, 8.32 mmol) in THF (40 cm^3) dropwise. The cooling bath was removed and stirring continued for 100 min whereupon HCl (10%) was added until there was no further reaction. The mixture was then extracted with three portions of Et_2O. The organic layers were combined and washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil which was dissolved in Et_2O (100 cm^3), and washed with 1 M aqueous NaOH (3 × 50 cm^3) to remove the oxazolidinethione. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil (2.4 g) which was purified by column chromatography (SiO_2, 6 × 4.5 cm, hexanes : EtOAc = 2 : 1) to give diol **49** (2.23 g, 6.88 mmol, 83%) as a colourless oil; $[\alpha]_D$ −17.2 (*c* 1.34, $CHCl_3$); ν_{max}(film)/cm^{-1} 3400br, 2960s, 2930s, 2875s, 1456m, 1380m, 1110s, 1045s, 981s, 737m, 698s; δ_H(270 MHz, $CDCl_3$) 7.40–7.27 (5H, m), 4.76 (2H, s), 4.62 (2H, s), 3.88 (1H, dd, *J* 4,11), 3.76 (1H, dd, *J* 2, 11), 3.54–3.38 (3H, m), 2.52 (2H, br), 2.00–1.34 (6H, m), 1.02–0.89 (1H, m), 1.01 (3H, d, *J* 7), 1.01 (3H, t, *J* 7), 0.85 (3H, d, *J* 7); δ_C(67.5 MHz, $CDCl_3$) 138.0 (0), 128.6 (1), 128.0 (1), 127.9 (1), 94.9 (2), 81.2 (1), 73.0 (2), 69.5 (2), 64.8 (2), 42.9 (1), 38.2 (2), 34.5 (1), 31.6 (1), 19.4 (3), 17.1 (2), 15.7 (3), 12.3 (3); *m*/*z* (CI, NH_3) 342 [$(M + NH_4)^+$, 50%], 326 (25), 325 [$(M + H)^+$, 100%], 234 (60), 217 (85), 205 (20).

The oxazolidine-2-thione **47** (1 g) was recovered by acidifying the aqueous layer and extracting with CH_2Cl_2.

(4*S*,5*S*)-5-Ethyl-4-[(1*S*,3*R*)-4-(benzyloxymethoxy)-1,3-dimethylbutyl]-2,2-di-*tert*-butyl-1,3-dioxa-2-silacyclohexane 50

To an ice cooled magnetically stirred solution of the diol **49** (1.96 g, 6.05 mmol) (which had been azeotropically dried with two portions of toluene) in dry CH_2Cl_2 (40 cm^3) was added 2,6-lutidine (2.1 cm^3, 18.15 mmol) followed by di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (2.7 cm^3) at r.t. After 10 min the solution was diluted with Et_2O (60 cm^3) and poured into aqueous sodium hydrogen sulfate (40 cm^3, 0.3 M). The organic layer was separated, washing the aqueous layer with Et_2O (50 cm^3). The organic layers were combined, washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated *in vacuo* to give an oily solid. Purification by column chromatography (SiO_2, 8 × 4.5 cm, hexanes : EtOAc = 96 : 4) gave **50** (2.04 g, 4.40 mmol, 73%) as a colourless oil; $[\alpha]_D$ −21.9 (*c* 0.775, $CHCl_3$); ν_{max}(film)/cm^{-1} 2933s, 2859s, 1476m, 1384m, 1165m, 1108s, 1050s, 995m, 854m, 800m, 735m, 696m, 648s; δ_H(270 MHz, $CDCl_3$) 7.40–7.27 (5H, m), 4.77 (2H, s), 4.61 (2H, s), 4.24–4.12 (2H, m), 3.83 (1H, dd, *J* 2, 9), 3.55 (1H, dd, *J* 4, 9), 3.31 (1H, dd, *J* 7, 9), 2.04–1.30 (6H, m), 1.09 (9H, s), 1.02 (3H, d, *J* 7), 1.01 (9H, s), 1.00–0.90 (1H, m), 0.96 (3H, t, *J* 7), 0.78 (3H, d, *J* 7); δ_C(67.5 MHz, $CDCl_3$) 138.2 (0), 128.6 (1), 128.1 (1), 127.8 (1), 95.0 (2), 82.6 (1), 73.5 (2), 69.3 (2), 66.9 (2), 42.1 (2), 38.9 (2), 34.7 (1), 32.0 (1), 29.0 (3), 27.8 (3), 23.8 (0), 20.7 (0), 19.2 (3), 16.3 (3), 15.5 (2), 12.5 (3); *m*/*z* (CI, NH_3) 482 [$(M + NH_4)^+$, 100%], 465 [$(M + H)^+$, 50%], 377 (20), 357 (30), 151 (15), 108 (15), 91 (15).

The reaction by-products recovered from the column (hexanes : EtOAc = 1 : 1) as a waxy solid were diluted with THF (5 cm^3) and treated with TBAF (10 cm^3, 1.0 M, 10 mmol). The yellow solution was stirred at r.t. for 1 h. The solution was then diluted in Et_2O and washed with aqueous sodium hydrogen sulfate (0.3 M), aqueous sodium hydrogen carbonate, then dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a waxy white solid. Purification by column chromatography (SiO_2, 4 × 4 cm, hexanes : Et_2O = 1 : 1) gave recovered diol **49** (390 mg, 1.20 mmol, 20%).

(4*S*,5*S*)-5-Ethyl-4-[(1*S*,3*R*)-4-hydroxy-1,3-dimethylbutyl]-2,2-di-*tert*-butyl-1,3-dioxa-2-silacyclohexane 51

A mixture of the benzyloxymethyl ether **50** (2.83 g, 6.1 mmol) and W2 Raney nickel (10 cm^3) in ethanol (10 cm^3) was hydro-

genated at atmospheric pressure for 100 h. Celite was added and the solids were filtered off. The solvent was removed *in vacuo* to give a colourless oil which was purified by column chromatography (SiO_2, 4.5 × 4.5 cm, hexanes : Et_2O = 6 : 1) to give alcohol **51** (1.85 g, 5.38 mmol, 88%) as a colourless oil [Found: $(M + H)^+$, 345.3809. $C_{19}H_{41}O_3Si$ requires *M*, 345.2825]; $[\alpha]_D$ −20.0 (*c* 0.940, $CHCl_3$); ν_{max}(film)/cm^{-1} 3400br, 2963s, 2859s, 1474s, 1386m, 1164m, 1006s, 1027s, 1010s, 853s, 799m, 650s; δ_H(270 MHz, $CDCl_3$) 4.24–4.10 (2H, m), 3.87 (1H, dd, *J* 2, 10), 3.58 (1H, dd, *J* 5, 11), 3.48 (1H, dd, *J* 4, 11), 1.94–1.62 (7H, m), 1.50–1.30 (2H, m), 1.10 (9H, s), 1.03 (9H, s), 1.00–0.90 (1H, m), 0.96 (3H, d, *J* 6), 0.96 (3H, t, *J* 7), 0.80 (3H, d, *J* 7); δ_C(67.5 MHz, $CDCl_3$) 82.84 (1), 67.8 (2), 66.8 (2), 41.9 (1), 38.4 (2), 34.9 (1), 34.1 (1), 29.0 (3), 27.7 (3), 23.8 (0), 20.8 (0), 19.0 (3), 17.0 (3), 12.4 (0); *m*/*z* (CI, NH_3) 362 [$(M + NH_4)^+$, 2%], 345 [$(M + H)^+$, 100], 287 (6), 231 (5), 169 (5), 151 (25), 109 (5), 95 (5).

(4*S*,5*S*)-5-Ethyl-4-[(1*S*,3*R*)-1,3-dimethyl-4-oxobutyl]-2,2-di-*tert*-butyl-1,3-dioxa-2-silacyclohexane 52

To a magnetically stirred suspension of the Dess–Martin periodinane (1.18 g, 2.78 mmol) in dry CH_2Cl_2 (8 cm^3) was added a solution of the alcohol **51** (564 mg, 1.63 mmol) in dry CH_2Cl_2 (8 cm^3). The mixture was stirred for 100 min. The mixture was then poured into a solution of sodium thiosulfate (2.16 g) in saturated aqueous sodium hydrogen carbonate (50 cm^3), washing in with Et_2O (100 cm^3). The mixture was stirred until the layers became clear. The aqueous layer was removed and the organic layer was washed with brine, then dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil. Purification by column chromatography (SiO_2, 3 × 4 cm, hexanes : Et_2O = 3 : 2) gave the aldehyde **52** (557 mg, 1.63 mmol, 83%) as a colourless oil which was used immediately in the next step; δ_H(270 MHz, $CDCl_3$) 9.55 (1H, d, *J* 2.9), 4.24–4.10 (2H, m), 3.88 (1H, dd, *J* 1.9, 9.5), 2.66–2.50 (1H, m), 2.34–2.20 (1H, m), 1.90–1.60 (2H, m), 1.50–1.20 (3H, m), 1.12 (3H, d, *J* 7.0), 1.08 (9H, s), 1.01 (9H, s), 0.94 (3H, t, *J* 7.3), 0.78 (3H, d, *J* 6.8); δ_C(67.5 MHz, $CDCl_3$) 206.1 (0), 82.4 (1), 66.7 (2), 45.1 (1), 41.9 (1), 35.8 (2), 34.7 (1), 28.9 (3), 27.7 (3), 23.8 (2C, 0), 16.1 (3), 15.5 (2), 14.9 (3), 12.4 (3).

(4*S*,5*S*)-5-Ethyl-4-[(1*S*,3*R*)-3-(2-furyl)-1,3-dimethylpropyl]-2,2-di-*tert*-butyl-1,3-dioxa-2-silacyclohexane 7

To a magnetically stirred solution of 3,3-diethoxyprop-1-yne (2.4 cm^3, 15 mmol) in dry THF (100 cm^3) at −78 °C was added BuLi (4.6 cm^3, 2.4 M in hexanes, 11 mmol) dropwise. The yellow solution was stirred at −78 °C for 10 min, allowed to warm to 0 °C over 30 min, and then re-cooled to −78 °C before a solution of the aldehyde **52** (3.05 g, 8.9 mmol) in THF (30 cm^3) was added over 5 min. The solution was allowed to warm to 0 °C over 2 h. The reaction was quenched by pouring into aqueous sodium hydrogen carbonate and the product extracted into Et_2O (3 ×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the crude alkyne **53** (4.3 g) which was immediately dissolved in methanol (150 cm^3) to which was added Pd–$BaSO_4$ (820 mg, 5%) followed by quinoline (0.44 cm^3). After hydrogenation at atmospheric pressure for 12 h, the mixture was filtered through Celite and the solvent was removed *in vacuo* to give a yellow oil which was diluted in Et_2O and washed with 2 M HCl, aqueous sodium hydrogen carbonate then dried ($MgSO_4$), and the solvent was removed *in vacuo*. The resulting oil (4.0 g) was diluted in dry CH_2Cl_2 (150 cm^3) and PPTS (250 mg) was added. The solution was stirred at r.t. for 1 h, poured into aqueous sodium hydrogen carbonate, and the product extracted into three portions of Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a brown oil which was purified by column chromatography (SiO_2, 4 × 3 cm, hexanes : Et_2O = 99.5 : 0.5) to give furan **7** (2.9 g, 7.6 mmol, 85% from **52**) as a colourless oil that crystallised in the freezer. An analytical sample recrystallised from ethanol–water gave white microprisms; mp 38–39 °C [Found: $(M + 1)^{+\bullet}$, 381.2825. $C_{22}H_{40}O_3Si$ + H requires 381.2810] (Found: C, 69.1; H, 11.0%. $C_{22}H_{40}O_3Si$ requires C, 69.42; H, 10.59%); $[\alpha]_D$ −25.4 (*c* 0.62, $CHCl_3$); ν_{max}(film)/cm^{-1} 2967s, 2860s, 1475m, 1385m, 1363m, 1161m, 1104s, 1027s, 994s, 854m, 826m, 799m, 728m, 649s; δ_H(270 MHz, $CDCl_3$) 7.30 (1H, dd, *J* 1.9, 0.8), 6.27 (1H, dd, *J* 3.1, 1.9), 6.06 (1H, d, *J* 3.1), 4.18 (2H, m), 3.87 (1H, dd, *J* 9.7, 2.1), 3.04 (1H, m), 2.34 (1H, ddd, *J* 13.3, 10.1, 3.1), 1.88–1.55 (3H, m), 1.46–1.32 (2H, m), 1.26 (3H, d, *J* 7.0), 1.12 (9H, s), 1.04 (9H, s), 0.93 (3H, t, *J* 7.3), 0.75 (3H, d, *J* 6.8); δ_C(67.5 MHz, $CDCl_3$) 161.1 (0, C_{ipso}), 140.6 (1), 109.9 (1), 103.6 (1), 82.1 (1), 66.9 (2), 42.1 (1), 40.1 (2), 34.6 (1), 31.4 (1), 29.0 and 27.8 (3C each), 23.9 (0), 15.8 (3), 15.5 (2), 12.4 (3); *m*/*z* (CI, NH_3) 398 [$(M + NH_4)^+$, 10%], 382 (25), 381 [$(M + H)^+$, 100%], 323 (30), 205 (35), 95 (25), 80 (10).

Alternative synthesis of C11–C20 furan fragment 7

(2*S*,4*R*)-4-(2-Furyl)-2,4-dimethylbutan-1-ol 58

Alcohol **58** was prepared from (3*R*,5*S*)-3,5-dimethyloxan-2-one **54**[47] according to the procedure recently described for the racemic derivative.[56] The enantiomerically pure alcohol gave $[\alpha]_D$ −29.2 (*c* 0.5, $CHCl_3$). Alcohol **58** was also prepared from spirocyclic dihydrofuran derivative **57** as follows. To a solution of dihydrofuran **57** (85 mg, 0.50 mmol) in THF (20 cm^3) at −78 °C was added dropwise Bu^{t}Li in pentane (1.0 cm^3, 1.50 mmol) whereupon the solution was warmed to −55 °C and stirred at this temperature for 4 h. The mixture was then warmed to room temp. and diluted with Et_2O (30 cm^3), washed with brine (20 cm^3) and dried over $MgSO_4$. Concentration *in vacuo* gave **58** (80 mg, 94%) identical with the sample prepared directly from **55**[56] *via* cyclisation with $Et_3N{\cdot}Mo(CO)_5$ according to the procedure of McDonald.[59]

(2*S*,4*R*)-4-(2-Furyl)-2,4-dimethylbutanal 10

A solution of oxalyl chloride (1.50 cm^3, 17.1 mmol) in CH_2Cl_2 (15 cm^3) was cooled to −50 °C. Then DMSO (1.82 cm^3, 25.7 mmol) was added slowly. After 5 min a solution of the alcohol **58** (1.44 g, 8.6 mmol) in CH_2Cl_2 (12 cm^3) was added dropwise. Stirring at low temperature was continued for 15 min, followed by the addition of *N*-methylmorpholine (6.52 cm^3, 60.0 mmol). The mixture was stirred at 0 °C for 2 h. Then it was poured onto saturated aqueous NH_4Cl (40 cm^3), stirred for 10 min, the organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic layers were dried over $MgSO_4$ and the residue after evaporation of the solvent was purified by column chromatography (SiO_2, hexanes→ Et_2O : hexanes = 1 : 4) to give **10** (970 mg, 5.84 mmol, 68%) as a colourless oil; $[\alpha]_D$ −15.3 (*c* 0.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 2968s, 2933s, 2876s, 2814m, 2713m, 1725s, 1592m, 1508s, 1459s, 1377m, 1275m, 1177m, 1150s, 1078m, 1010s, 923m, 803m, 734s; δ_H(270 MHz, $CDCl_3$) 9.52 (1H, d, *J* 1.8), 7.32 (1H, dd, *J* 1.8, 0.7), 6.29 (1H, dd, *J* 3.3, 1.8), 6.02 (1H, d, *J* 3.3), 2.95 (1H, m), 2.30 (1H, m), 2.15 (1H, ddd, *J* 13.6, 9.2, 5.9), 1.47 (1H, ddd, *J* 13.6, 7.7, 5.5), 1.29 (3H, d, *J* 7.0), 1.10 (3H, d, *J* 7.0); δ_C(67.5 MHz, $CDCl_3$) 204.6 (1), 158.9 (0), 141.0 (1), 110.0 (1), 104.4 (1), 44.5 (1), 36.8 (2), 31.0 (1), 20.0 (3), 13.5 (3); *m*/*z* (EI) 166 ($M^{+\bullet}$, 20%), 109 (37), 108 (100), 95 (63), 81 (39), 67 (32), 41 (45).

(*S*)-[*N*-(2*R*,3*S*,4*S*,6*R*)-2-Ethyl-6-(2-furyl)-3-hydroxy-4,6-dimethylhexanoyl]-4-isopropyl-1,3-oxazolidine-2-thione 59

To a suspension of freshly prepared tin(II) triflate (4.70 g, 11.2 mmol) in CH_2Cl_2 (30 cm^3) was added *N*-ethylpiperidine (1.87 cm^3, 13.6 mmol) at −50 °C followed by a solution of the oxazolidine-2-thione **47** (2.15 g, 10 mmol) in CH_2Cl_2 (20 cm^3) at a rate sufficient to maintain the internal temperature below −45 °C. Stirring at this temperature was continued for 3 h. The yellow mixture was then cooled to −80 °C and a solution of the aldehyde **10** (1.03 g, 6.2 mmol) in CH_2Cl_2 (20 cm^3) added slowly.

After stirring for 40 min the mixture was poured into a pH 7 buffer solution (50 cm^3) with rapid stirring, filtered through Celite, the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. The crude mixture was purified by column chromatography (SiO_2, hexanes→Et_2O : hexanes = 1 : 3) to give unreacted aldehyde **10** (150 mg, 14%) and aldol adduct **59** (1.65 g, 4.33 mmol, 70%) as a pale yellow oil; $[\alpha]_D$ +75.5 (*c* 0.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3510m, 2966s, 2934m, 2876m, 1691s, 1369s, 1324s, 1291s, 1190s, 1151s, 1008s, 958m, 911m, 732; δ_H(270 MHz, $CDCl_3$) 7.29 (1H, dd, *J* 1.9, 0.8), 6.25 (1H, dd, *J* 3.1, 1.9), 6.02 (1H, dt, *J* 3.1, 0.8), 5.20 (1H, ddd, *J* 10.1, 3.9, 3.1), 4.76 (1H, ddd, *J* 7.3, 3.7, 3.7), 4.45–4.32 (2H, m), 3.68 (1H, dd, *J* 8.3, 3.1), 2.98 (1H, m), 2.30 (2H, m), 2.18 (1H, ddd, *J* 13.5, 10.8, 2.9), 1.78 (1H, m), 1.54 (1H, m), 1.24 (3H, d, *J* 6.8), 1.26 (1H, m), 0.98–0.82 (13H, m); δ_C(67.5 MHz, $CDCl_3$) 186.1 (0), 177.7 (0), 160.3 (0), 140.7 (1), 110.0 (1), 104.0 (1), 75.8 (1), 67.6 (2), 63.5 (1), 46.2 (1), 39.8 (2), 35.1, 31.1 (1), 29.3 (1), 21.3 (3), 18.6 (2), 18.4 (3), 16.1 (3), 15.1 (3), 11.9 (3); *m*/*z* (EI) 381 ($M^{+\bullet}$, 5%), 146 (100), 108 (18), 95 (15).

(2*S*,3*S*,4*S*,6*R*)-2-Ethyl-6-(2-furyl)-4,6-dimethylhexane-1,3-diol 60

A suspension of $NaBH_4$ (550 mg, 14.6 mmol) in THF (20 cm^3) and water (2 cm^3) was cooled to 0 °C and a solution of **59** (1.85 mg, 4.9 mmol) in THF (20 cm^3) was added dropwise. Stirring at r.t. was continued for 2 h. The reaction was quenched by slowly adding saturated aqueous NH_4Cl until gas evolution ceased. The mixture was extracted with Et_2O (3 × 30 cm^3), the combined organic extracts were dried over $MgSO_4$, the solvents removed *in vacuo* and the residue dissolved in ether (50 cm^3). The solution was washed with 1 M aqueous NaOH (3 × 20 cm^3), dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (SiO_2, hexanes→EtOAc : hexanes = 1 : 3) to give diol **60** (0.84 g, 3.5 mmol, 72%) as a colourless oil; $[\alpha]_D$ −71.4 (*c* 0.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3381s, 2964–2837s, 1647m, 1592m, 1507s, 1461s, 1380s, 1243m, 1149s, 1078s, 1009s, 978m, 917m, 884m, 798m; δ_H(270 MHz, $CDCl_3$) 7.31 (1H, dd, *J* 1.9, 0.9), 6.28 (1H, dd, *J* 3.3, 1.9), 6.02 (1H, dm, *J* 3.1), 3.81 (1H, dd, *J* 10.8, 4.6), 3.69 (1H, dd, *J* 10.8, 2.7), 2.97 (1H, m), 2.28 (2H, br s, OH), 2.09 (1H, ddd, *J* 13.3, 11.0, 2.7), 1.55–1.30 (4H, m), 1.27 (3H, d, *J* 7.0), 1.23 (1H, m), 0.93 (3H, t, *J* 7.1), 0.85 (3H, d, *J* 6.8); δ_C(67.5 MHz, $CDCl_3$) 160.2 (0), 140.8 (1), 110.1 (1), 104.1 (1), 80.0 (1), 64.5 (2), 43.2 (1), 39.6 (2), 34.4 (1), 31.3 (1), 21.4 (3), 16.5 (3), 16.1 (2), 12.1 (3); *m*/*z* (EI) 240 ($M^{+\bullet}$, 7%), 108 (100), 95 (28).

(4*S*,5*S*)-5-Ethyl-4-[(1*S*,3*R*)-3-(2-furyl)-1,3-dimethylpropyl]-2,2-di-*tert*-butyl-1,3-dioxa-2-silacyclohexane 7

A solution of diol **60** (0.65 mg, 2.7 mmol) in CH_2Cl_2 (40 cm^3) was cooled to 0 °C and 2,6-lutidine (0.94 cm^3, 8.1 mmol) added, followed by di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (1.18 cm^3, 3.2 mmol). The mixture was stirred at r.t. for 15 min, diluted with Et_2O and poured onto aqueous $NaHSO_4$ (40 cm^3, 0.3 M). The organic layer was separated, the aqueous layer washed with Et_2O (2 × 20 cm^3) and the combined organic extracts washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, evaporated and purified by column chromatography (SiO_2, hexanes) to give **7** (0.67 g, 1.76 mmol, 65%) as a colourless oil giving spectroscopic data identical to those reported above.

(2*S*,3*R*,5*S*,6*S*)-6-[(*S*)-1-(*tert*-Butyldiphenylsilyloxymethyl)-propyl]-2-hydroxy-3,5-dimethyl-2-(prop-2-ynyl)oxane 61

A solution of prop-2-ynylmagnesium bromide in Et_2O was prepared according to a literature procedure.[91] The titer of the solution was determined by reacting a sample of the solution with an excess of iodine in THF and titrating the unreacted iodine with aqueous sodium thiosulfate.

To a magnetically stirred solution of the Grignard reagent (2.3 cm^3, 0.94 M solution in Et_2O, 2.18 mmol) at −40 °C was added dropwise (3*R*,5*S*,6*S*)-6-[(*S*)-1-(*tert*-butyldiphenylsilyloxymethyl)propyl]-3,5-dimethyloxan-2-one[92] (0.80 g, 1.82 mmol) in Et_2O (5.0 cm^3). The mixture was slowly warmed to r.t. and stirred for 2 h. It was diluted with Et_2O (20 cm^3) and then poured onto ice–water (30 cm^3). Saturated aqueous NH_4Cl was added to dissolve the precipitate and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 20 cm^3) and the combined organic layers dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexanes : Et_2O = 9 : 1) to give lactol **61** (0.51 g, 1.07 mmol, 59%) together with recovered lactone (0.23 g, 0.525 mmol). The yield based on recovered starting lactone was 82%. Lactol **61** was isolated as a colourless oil after column chromatography [Found: $(M + NH_4)^+$, 496.3215. $C_{30}H_{46}O_3NSi$ requires *M*, 496.3247]; $[\alpha]_D$ +4.8 (*c* 1.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 3415s, 3311s, 2960m, 2931m, 1112; δ_H(270 MHz, $CDCl_3$) 7.69 (4H, ddm, *J* 11.4, 7.3), 7.41 (6H, m), 3.88 (1H, dd, *J* 10.5, 1.8), 3.75 (1H, app. t, *J* 9.4), 3.68 (1H, dd, *J* 9.6, 5.3), 2.52 (1H, dd, *J* 16.2, 2.7), 2.35 (1H, dd, *J* 16.2, 2.5), 2.12 (1H, d, *J* 1.7, OH), 1.88 (1H, t, *J* 2.6), 1.80–1.24 (7H, m), 1.07 (9H, s), 0.92 (3H, d, *J* 6.8), 0.83 (3H, d, *J* 6.6), 0.80 (3H, t, *J* 7.3); δ_C(67.5 MHz, $CDCl_3$) 135.8 (1), 134.4 (0), 129.7 (1), 127.8 (1), 96.6 (0), 80.0 (0), 74.1 (1), 71.1 (1), 63.9 (2), 43.4 (1), 37.6 (2), 37.3 (1), 31.8 (1), 31.1 (2), 27.1 (3), 19.5 (0), 17.8 (2), 17.5 (3), 16.6 (3), 13.1 (3); *m*/*z* (CI, NH_3) 479 [$(M + H)^+$, 5%], 462 (100), 362 (50).

{(5*R*,7*S*,8*S*,10*R*)-7-[(*S*)-1-(*tert*-Butyldiphenylsilyloxymethyl)-propyl]-8,10-dimethyl-1,6-dioxaspiro[4.5]decan-2-ylidene}-pentacarbonylchromium 63

Carbene complex **63** was prepared from lactol **61** according to the procedure previously described.[56] The complex was isolated as a yellow oil (25% yield) after column chromatography [Found: $(M + 1)^+$, 671.2110. $C_{35}H_{43}O_8SiCr$ requires *M*, 671.2132]; $[\alpha]_D$ −6.3 (*c* 0.7, C_6H_6); ν_{max}(film)/cm^{-1} 2063m, 1938s, 1463m, 1428m, 654m; δ_H(270 MHz, C_6D_6) 7.82–7.74 (4H, m), 7.31–7.20 (6H, m), 3.92 (1H, d, *J* 9.2), 3.77 (1H, dd, *J* 10.5, 7.0), 3.72 (1H, dd, *J* 10.5, 6.6), 3.09 (2H, dd, *J* 8.5, 7.4, CH_2CCr), 1.65 (1H, m), 1.50–1.05 (5H, m), 1.21 (9H, s), 1.08 (2H, t, *J* 7.9, CH_2CH_2Cr), 0.80 (1H, m), 0.79 (3H, t, *J* 7.7), 0.66 (3H, d, *J* 5.9), 0.46 (3H, d, *J* 6.3); δ_C(67.5 MHz, C_6D_6) 341.2 (0, C=Cr), 223.9 (0, *trans*-CO), 216.6 (0, *cis*-CO), 135.9 (1, Ph), 134.2 (0, Ph), 129.7 (1, Ph), 128.6 (0, O–C–O), 127.7 (1, Ph), 80.2 (1, CHO), 64.9 (2, CH_2O), 60.2 (2, CH_2C=Cr), 43.7 (1, CH–Et), 37.6 (2), 37.1 (1, CH–CH_3), 31.7 (1, CH–CH_3), 30.8 (2), 27.1 (3C, 3), 19.4 (0, Bu′), 18.3 (2), 17.8 (3), 15.8 (3), 13.0 (3); *m*/*z* (CI) 688 (M^+, 32%), 671 (100), 587 (35), 531 (42), 502 (45), 479 (47), 451 (55), 393 (27), 373 (17), 343 (18), 274 (25), 216 (42), 196 (32), 109 (26), 35 (40).

(5*S*,7*S*,8*S*,10*R*)-7-[(*S*)-1-(*tert*-Butyldiphenylsilyloxymethyl)-propyl]-8,10-dimethyl-1,6-dioxaspiro[4.5]dec-2-ene 64

Carbene complex **63** (0.955 g, 1.42 mmol) and DMAP (0.55 g, 4.5 mmol) in THF (15 cm^3) were refluxed for 8 h. The mixture was concentrated *in vacuo* and the residue extracted with hexanes (3 × 10 cm^3). The combined hexanes extracts were concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, hexanes→hexanes : Et_2O = 4 : 1) to give spirocyclic dihydrofuran derivative **64** (0.61 g, 1.28 mmol, 90%) as a colourless oil [Found: $(M + H)^+$, 479.2972. $C_{30}H_{43}O_3Si$ requires *M*, 479.2982]; $[\alpha]_D$ +62 (*c* 1.0, C_6H_6); ν_{max}(film)/cm^{-1} 2960s, 2930s, 2876s, 1622m, 1462m, 1428m, 1379m, 1290m, 1211m, 1112s, 1057s, 1038s, 826m, 740m, 702s; δ_H(270 MHz, C_6D_6) 7.90–7.80 (4H, m), 7.32–7.20 (6H, m), 6.24 (1H, q, *J* 2.4), 4.74 (1H, q, *J* 2.5), 4.29 (1H, dd, *J* 10.3, 2.0), 3.95 (1H, t, *J* 9.5), 3.76 (1H, dd, *J* 9.5, 4.8), 2.52 (2H, t, *J* 2.4), 1.84 (1H, m), 1.70–1.06 (6H, m), 1.22 (9H, s), 0.86 (3H, d, *J* 6.4), 0.81 (3H, d, *J* 6.4), 0.78 (3H, t, *J* 7.5); δ_C(67.5 MHz, C_6D_6) 144.8 (1), 136.2 (2C, 1), 136.1 (2C, 1), 134.6 (2C, 0), 129.8 (2C, 1), 129.7 (2C, 1), 128.0 (2C, 1), 111.1 (0), 98.9 (1), 75.6 (1), 63.9 (2), 43.8 (1), 40.1 (2), 38.7 (1), 38.1 (2), 31.9 (1), 27.1 (3C, 3), 19.6 (0), 18.2 (2),

17.7 (3), 16.3 (3), 13.2 (3); *m/z* (CI) 479 [(M + 1)$^+$, 100%], 421 (15), 205 (28), 95 (7).

Synthesis of C21–C30 lactone fragment 8a

2-[(*Z*)-5-Acetoxy-3-methylpent-3-enyl]-1,3-dioxolane 69

A mixture of the aldehyde **68** (23.6 g, 139 mmol), ethane-1,2-diol (16.7 g, 270 mmol), PTSA (230 mg, 1.2 mmol) and benzene (350 cm^3) was refluxed for 2 h with removal of water (*ca*. 3 cm^3) using a Dean–Stark trap. The cooled mixture was washed with saturated aqueous $NaHCO_3$ and the aqueous layers back-extracted with Et_2O (2 × 200 cm^3). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residual yellow oil (29.3 g, 137 mmol, 99%) was used in the next step without further purification; ν_{max}(film)/cm^{-1} 2965s, 2882s, 1738s, 1446m, 1381s, 1236s, 1140s, 1024s, 956s; δ_H(270 MHz, $CDCl_3$) 5.31 (1H, dt, *J* 1, 7), 4.79 (1H, t, *J* 5), 4.53 (2H, d, *J* 7), 3.98–3.76 (4H, m), 2.16 (2H, dd, *J* 8, 11), 2.00 (3H, s), 1.72 (3H, d, *J* 1), 1.72–1.64 (2H, m); δ_C(67.5 MHz, $CDCl_3$) 171.1 (0), 141.8 (0), 119.6 (1), 103.9 (10), 64.9 (2), 61.0 (2), 32.2 (2), 26.3 (2), 23.4 (3), 21.1 (3); *m/z* (CI, NH_3) 232 [(M + NH_4)$^+$, 25%], 213 (5), 172 (15), 155 (100), 93 (15), 73 (17).

2-[(*Z*)-5-Hydroxy-3-methylpent-3-enyl]-1,3-dioxolane 70

To a magnetically stirred solution of the crude acetate **69** (26.2 g, 122 mmol) in methanol (270 cm^3) was added potassium carbonate (850 mg). The mixture was stirred at r.t. for 6.5 h whereupon the solvent was removed *in vacuo* and the residue taken up in Et_2O (300 cm^3). The suspension was washed with water (100 cm^3) and brine (100 cm^3). After drying ($MgSO_4$), filtration and concentration *in vacuo*, the residual yellow oil (21.2 g) was purified by short-path distillation to give the alcohol **70** (17.8 g, 103 mmol, 84%) as a colourless oil, bp 92–100 °C/0.4 mmHg; ν_{max}(film)/cm^{-1} 3412br, 2963s, 2880s, 1668w, 1446w, 1410s, 1208m, 1140s, 1102m, 1017s, 894s; δ_H(270 MHz, $CDCl_3$) 5.44 (1H, dt, *J* 1, 7), 4.79 (1H, t, *J* 5), 4.05 (2H, d, *J* 7), 4.00–3.74 (4H, m), 2.35 (1H, s), 2.19 (2H, t, *J* 7), 1.77–1.67 (2H, m), 1.70 (3H, d, *J* 1); δ_C(67.5 MHz, $CDCl_3$) 138.8 (0), 125.1 (1), 103.9 (1), 64.9 (2C, 2), 58.5 (2), 31.8 (2), 26.1 (2), 23.2 (3).

2-[(*Z*)-5-Chloro-3-methylpent-3-enyl]-1,3-dioxolane 71

To a mechanically stirred suspension consisting of the allylic alcohol **70** (40 g, 0.23 mmol), LiCl (29 g, 0.70 mol), and 2,6-lutidine (108 cm^3, 0.93 mol) in DMF (300 cm^3) was added dropwise at 0 °C MsCl (54 cm^3, 0.70 mol) over 30 min. The mixture was stirred for 3.5 h during which time the temperature rose to 15 °C. The mixture was diluted with Et_2O (300 cm^3) and washed with water (3 × 100 cm^3). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to a brown oil (58 g) which was purified by column chromatography in two equal portions (SiO_2, hexanes : Et_2O = 19 : 1) to give the allylic chloride **71** (35.6 g, 0.19 mol, 81%) as a yellow oil which was used directly in the next reaction; ν_{max}(film)/cm^{-1} 2966s, 2883s, 1662m, 1443m, 1409m, 1379m, 1256m, 1140s, 1058s, 1033s; δ_H(270 MHz, $CDCl_3$) 5.44 (1H, t, *J* 8.1), 4.82 (1H, t, *J* 4.8), 4.08 (2H, d, *J* 8.1), 3.79–4.01 (4H, m), 2.21 (1H, dd, *J* 7.7, 10.2), 1.68–1.82 (3H, m), 1.75 (3H, s); δ_C(67.5 MHz, $CDCl_3$) 141.0 (0), 121.7 (1), 103.8 (1), 65.0 (2C, 2), 40.9 (2), 32.0 (2), 26.0 (2), 23.4 (3); *m/z* (EI) 189 [(M − 1)$^{+\bullet}$, 2%], 155 (25), 128 (7), 111 (3), 102 (3), 99 (15), 93 (25), 86 (45), 81 (8), 73 (100).

2-[(*Z*)-3-Methyloct-3-en-7-ynyl]-1,3-dioxolane 72

The preparation of terminal alkyne **72** was adapted from the method of Hooz *et al.*[93] To a solution of BuLi (2.5 M in hexanes, 120 cm^3, 0.3 mol) in THF (160 cm^3) was added *via* cannula propyne (6.8 cm^3, 0.12 mol) in THF (15 cm^3) at −30 °C. The cooling bath was removed and the mixture stirred for 1 h at r.t. The resultant orange suspension was cooled to −65 °C and allylic chloride **71** (12.8 g, 67 mmol) in THF (12 cm^3) added dropwise over 10 min. The mixture was allowed to warm slowly to −10 °C over 2.25 h and then poured into rapidly stirring aqueous NH_4Cl and the organic layer separated. The aqueous layer was extracted with Et_2O (2 × 200 cm^3) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting brown oil (14.3 g) was purified by column chromatography (SiO_2, 6 × 10 cm, hexanes : Et_2O = 95 : 5) to give the alkynes **72** (7.4 g, 38 mmol, 57%) as a colourless oil. When 3 equiv. of propyne was used, the yield was 69%. ν_{max}(film)/cm^{-1} 3293s, 2962s, 2880s, 2116w, 1433m, 1408m, 1138s, 1035s, 944m, 895m; δ_H(270 MHz, $CDCl_3$) 5.19 (1H, t, *J* 7), 4.82 (1H, t, *J* 5), 4.00–3.80 (4H, m), 2.30–2.09 (6H, m), 1.94 (1H, t, *J* 2), 1.80–1.68 (2H, m), 1.70 (3H, d, *J* 1); δ_C(67.5 MHz, $CDCl_3$) 136.2 (0), 123.8 (1), 104.3 (1), 84.6 (1), 68.4 (0), 65.0 (2), 32.3 (2), 27.0 (2), 26.4 (2), 23.4 (3), 19.1 (2); *m/z* (EI) 193 [(M − 1)$^{+\bullet}$, 5%], 179 (10), 155 (10), 132 (10), 99 (75), 93 (50), 86 (80), 73 (100), 55 (15), 45 (60).

Methyl (*Z*)-9-(1,3-dioxolan-2-yl)-7-methylnon-6-ene-2-ynoate 73

To a magnetically stirred solution of the acetylene **72** (17.7 g, 91 mmol) in dry THF (250 cm^3) was added BuLi (38 cm^3, 2.5 M solution in hexanes, 96 mmol) at −78 °C. The internal temperature rose briefly to −60 °C and after 10 min the cooling bath was replaced by an ice bath and the temperature allowed to rise to −5 °C. The mixture was re-cooled to −90 °C and methyl chloroformate (9.1 g, 118 mmol) added in one portion. The solution was allowed to warm to −10 °C over 3.5 h whereupon saturated aqueous NH_4Cl (100 cm^3) was then added. The organic layer was separated and the aqueous layer extracted with Et_2O (2 × 200 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a brown oil which was purified by rapid column chromatography (SiO_2, 3.5 × 9 cm, hexanes : Et_2O = 95 : 5) to give the alkynyl ester **73** (21.5 g, 85 mmol, 93%) as a colourless oil; ν_{max}(film)/cm^{-1} 2959s, 2233s, 1710s, 1444m, 1408m, 1365s, 1252s, 1139s, 1067s, 1034s, 943m, 894m, 752s; δ_H(270 MHz, $CDCl_3$) 5.22–5.10 (1H, m), 4.83 (1H, t, *J* 5), 4.02–3.80 (4H, m), 3.76 (3H, s), 2.39–2.23 (4H, m), 2.14 (2H, dd, *J* 5, 9), 1.76–1.62 (2H, m), 1.71 (3H, d, *J* 1); δ_C(67.5 MHz, $CDCl_3$) 154.2 (0), 136.9 (0), 122.9 (1), 104.1 (1), 89.6 (0), 72.9 (0), 64.9 (2), 52.6 (2), 32.1 (2), 26.2 (2), 26.0 (2), 23.2 (3), 19.3 (2).

Methyl (2*Z*,6*Z*)-3-ethyl-9-(1,3-dioxolan-2-yl)-7-methylnona-2,6-dienoate 74

To a magnetically stirred suspension of CuI (3.95 g, 22 mmol) in dry THF (200 cm^3) under an atmosphere of argon was added a solution of EtLi·LiBr (35 cm^3, 1.2 M in pentane, 42 mmol) dropwise at −80 °C. The flask was transferred to a bath at −30 °C and the mixture stirred for 20 min during which time the internal temperature rose to −23 °C. The black mixture was cooled to −85 °C and the alkynyl ester **73** (5.0 g, 19.8 mmol) in THF (20 cm^3) was added dropwise over 20 min and the resulting mixture stirred for 3 h at −85 °C whereupon methanol (20 cm^3) was added dropwise. After 10 min at −85 °C, the mixture was poured into rapidly stirring saturated aqueous NH_4Cl (500 cm^3). The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 200 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a pale yellow oil which was purified by column chromatography (SiO_2, hexanes : Et_2O = 9 : 1) giving the ester **74** (5.3 g, 19 mmol, 95%) as a colourless oil; ν_{max}(film)/cm^{-1} 2966s, 2881s, 1716s, 1644s, 1434m, 1214m, 1157s, 1034s, 869s; δ_H(270 MHz, $CDCl_3$) 5.60 (1H, s), 5.18 (1H, dt, *J* 1, 7), 4.81 (1H, t, *J* 4.8), 4.02–3.81 (4H, m), 3.64 (3H, s), 2.58 (2H, dd, *J* 6.8, 7), 2.20–2.00 (6H, m), 1.76–1.64 (2H, m), 1.65 (3H, d, *J* 1), 1.06 (3H, t, *J* 7); δ_C(67.5 MHz, $CDCl_3$) 166.8 (0), 165.3 (0), 135.0 (0), 125.2 (1), 114.6 (1), 104.5 (1), 64.0 (2C, 2), 51.0 (3), 32.7 (2), 32.4 (2), 31.5 (2), 27.1 (2), 26.3 (2), 23.4 (3), 12.2 (3).

(1*R*,2*S*)-*N*-[(2*Z*,6*Z*)-3-Ethyl-9-(1,3-dioxolan-2-yl)-7-methylnona-2,6-dienoyl]bornane-10,2-sultam 75

The sultam **75** was prepared by a four-step sequence in which

all of the intermediates were used immediately without purification. The sequence began with the hydrolysis of ester **74**. Thus, a magnetically stirred heterogeneous mixture of ester **74** (5.64 g, 20 mmol), NaOH (4.36 g, 109 mmol), $NaHCO_3$ (730 mg, 10 mmol) in methanol (23 cm^3) and water (80 cm^3) was refluxed for 2 h by which time the mixture became homogeneous. After cooling to 0 °C, Et_2O (100 cm^3) was added and the mixture acidified with 2 M HCl. The organic layer was separated and the aqueous layer extracted with Et_2O (2 × 200 cm^3). The combined extracts were dried ($MgSO_3$), filtered, and concentrated *in vacuo* to give the crude acid (5.0 g, 20 mmol) as a yellow oil.

The crude acid (5.0 g) in THF (30 cm^3) was cooled to −78 °C and BuLi (8 cm^3, 2.5 M in hexanes, 20 mmol) added dropwise with stirring. The cooling bath was removed and the mixture allowed to warm to r.t. whereupon the solvent was removed *in vacuo* to give the lithium salt of the carboxylic acid as an orange foam. The crude lithium salt was dissolved in toluene (25 cm^3) and cooled to 0 °C after which oxalyl chloride (2.4 cm^3, 28 mmol) was added dropwise. After further stirring for 10 min at 0 °C the cooling bath was removed and the mixture allowed to stir at ambient temperature for 70 min. The solvent was removed *in vacuo* to give the crude acid chloride.

To a magnetically stirred solution of the (2*S*)-bornane-10,2-sultam [94] (4.3 g, 20 mmol) in dry THF (50 cm^3) was added BuLi (8.0 cm^3 of 2.5 M, 20 mmol) at −70 °C. The grey solution was stirred in the cooling bath for 40 min during which the temperature rose to −50 °C. A solution of the crude acid chloride in THF (25 cm^3) was added maintaining the reaction temperature below −30 °C. The orange solution was stirred in the bath for 2 h during which time the temperature rose to 0 °C. The cooling bath was then removed and the solution was left at r.t. for 9 h. The orange solution was treated with aqueous $NaHCO_3$ and then extracted with Et_2O (2 × 100 cm^3). Purification by column chromatography (SiO_2, 7 × 7 cm, hexanes : EtOAc = 4 : 1) gave the title compound and the corresponding aldehyde derived from hydrolysis of the dioxolane in about a 5 : 1 ratio estimated from the ^1H NMR spectrum. This mixture (6.45 g) was dissolved in CH_2Cl_2 (20 cm^3), cooled to −40 °C, and the bistrimethylsilyl ether of ethane-1,2-diol (1 cm^3, *ca.* 4 mmol) and TMSOTf (70 μl) added. After 2 h at −40 °C, a standard aqueous workup using aqueous $NaHCO_3$ followed by purification of the product by column chromatography (SiO_2) gave the sultam **75** (6.0 g, 12.9 mmol, 65% overall from the ester **74**) as a viscous yellow oil; $[\alpha]_D$ +45.6 (*c* 0.90, $CHCl_3$); ν_{max}(film)/cm^{-1} 2964s, 2882s, 1681s, 1632s, 1455m, 1413m, 1330s, 1270s, 1240s, 1062s, 1039s, 997m; δ_H(270 MHz, $CDCl_3$) 6.30 (1H, s), 5.19 (1H, t, *J* 6.8), 4.84 (1H, t, *J* 4.8), 5.78–4.04 (5H, m), 3.48 (1H, d, *J* 13.7), 3.43 (1H, d, *J* 13.7), 2.64–2.52 (2H, m), 2.30–2.04 (8H, m), 1.94–1.82 (3H, m), 1.78–1.64 (2H, m), 1.68 (3H, d, *J* 1.2), 1.48–1.30 (2H, m), 1.18 (3H, s), 1.10 (3H, t, *J* 7.4), 0.98 (3H, s); δ_C(67.5 MHz, $CDCl_3$) 167.5 (0), 164.3 (0), 134.9 (0), 125.0 (1), 114.5 (1), 104.4 (1), 65.1 (1), 64.9 (2), 53.2 (2), 48.2 (0), 47.8 (0), 44.8 (1), 38.8 (2), 33.6 (2), 32.9 (2), 32.3 (2), 31.7 (2), 26.9 (2), 26.7 (2), 26.3 (2), 23.3 (3), 21.0 (3), 20.0 (3), 12.0 (3); *m/z* (EI) 465 ($M^{+\bullet}$, 10%), 403 (30), 298 (40), 161 (100), 135 (65), 93 (75), 73 (100).

(1*R*,2*S*)-*N*-((*S*)-2-Hydroxy-2-{(2*S*,5*R*)-5-[(2*S*)-5-oxo-2-methyloxolan-2-yl]-2-ethyloxolan-2-yl}ethanoyl)bornane-10,2-sultam 77

To a rapidly stirring mixture of the sultam **75** (2.5 g, 5.38 mmol), pH 6 acetate buffer solution (15 cm^3) and acetone (50 cm^3) cooled to −35 °C was added a solution of $KMnO_4$ (1.71 g, 10.8 mmol) and acetic acid (670 μl, 11.7 mmol) in water (25 cm^3) and acetone (100 cm^3) over 2 h. After a further 3 h the brown mixture was treated with a solution of sodium thiosulfate (95 g, 500 mmol) in water (200 cm^3) and Et_2O. After 15 min, the remaining solid was filtered off and the organic layer was separated, re-extracting the aqueous layer with three portions of Et_2O. The organic solutions were washed with saturated aqueous $NaHCO_3$ and then combined, dried ($MgSO_4$) and the solvent removed *in vacuo* leaving a yellow foam (2.7 g). Purification on SiO_2 which had been washed with a 1% solution of triethylamine prior to column chromatography (6 × 5 cm, hexanes–EtOAc, 2 : 1→1.5 : 1) gave the tetrahydrofuran diol **76** (1.50 g, 2.91 mmol, 54%) as an inseparable mixture of diastereoisomers (*ca.* 7 : 1 according to ^1H NMR analysis) which was used directly in the next reaction.

A solution of the diol **76** (1.50 g, 2.91 mmol) in EtOAc (30 cm^3) was ozonolysed at −80 °C for 70 min. After discharge of excess ozone in a stream of nitrogen, the solvent was evaporated and the residue treated with PTSA (3 mg) in CH_2Cl_2 (20 cm^3) for 8 h at r.t. The reaction mixture was washed with aqueous $NaHCO_3$ (20 cm^3), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue (1.5 g) was purified by column chromatography (SiO_2, 5 × 5 cm, hexanes–EtOAc, 2 : 1) to give pure lactone **77** (340 mg) along with a further 590 mg of a diastereoisomeric mixture in which **77** was the major component. The total yield of both diastereoisomers was 930 mg (1.98 mmol, 68%). A sample of lactone **77** recrystallised from ethanol gave mp 194–195 °C [Found: $(M + 1)^+$, 470.2193. $C_{23}H_{35}NO_7S$ + H requires *M*, 470.22125] (Found: C, 58.46; H, 7.29; N, 3.25%. $C_{23}H_{35}NO_7S$ requires C, 58.83; H, 7.51; N, 2.98%); $[\alpha]_D$ +51.5 (*c* 1.2, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3022s, 2966s, 2884m, 1760s, 1704s, 1332s, 1266s, 1235s, 1166s, 1134s, 1076s, 946s; δ_H(360 MHz, $CDCl_3$) 4.59 (1H, d, *J* 5.8), 3.94 (1H, dd, *J* 10.2, 5.6), 3.87 (1H, dd, *J* 7.7, 4.8), 3.54 (1H, d, *J* 13.9), 3.47 (1H, d, *J* 13.9), 3.32 (1H, d, *J* 5.8), 2.74–2.32 (4H, m), 2.17–2.08 (1H, m), 2.02 (1H, dd, *J* 15.8, 7.7), 1.97–1.52 (9H, m), 1.45–1.28 (2H, m), 1.33 (3H, s), 1.12 (3H, s), 0.97 (3H, s), 0.86 (3H, t, *J* 7.4); δ_C(67.5 MHz, $CDCl_3$) 177.3 (0), 169.1 (0), 87.8 (0), 86.7 (0), 83.0 (1), 73.9 (1), 65.0 (1), 53.0 (2), 49.0 (0), 47.9 (0), 44.5 (1), 38.0 (2), 32.7 (2), 31.1 (2), 29.8 (2), 28.4 (2), 26.4 (2), 23.9 (3), 20.8 (3), 19.9 (3), 7.9 (3); *m/z* (CI, NH_3) 487 [$(M + NH_3)^+$, 65%], 470 (50), 406 (25), 244 (95), 233 (100), 197 (45).

(*S*)-5-{(2*R*,5*S*)-5-Ethyl-5-[(*R*)-1,2-dihydroxyethyl]-5-methyloxolan-2-yl}oxolan-2-one 82

To a magnetically stirred solution of the sultam **77** (469 mg, 0.96 mmol) in THF (8 cm^3) was added at −10 °C $BH_3 \cdot SMe_2$ (720 μl, 2.0 M solution in THF, 1.44 mmol) followed by $NaBH_4$ (33 mg, 0.86 mmol). The effervescing mixture was stirred at −10 °C for 2 h whereupon 10% MeOH in CH_2Cl_2 (8 cm^3) was added. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, 2.5 × 5 cm, CH_2Cl_2–MeOH, 99 : 1, 95 : 5, 9 : 1) to give diol **82** (209 mg, 0.81 mmol, 84%) as a white solid; mp 125–126 °C (CH_2Cl_2–Et_2O) (Found: $MH^{+\bullet}$, 259.1559. $C_{13}H_{23}O_5$ requires *M*, 259.1564) (Found: C, 60.35; H, 8.26%. $C_{13}H_{22}O_5$ requires C, 60.44; H, 8.58%); $[\alpha]_D$ −16.3 (*c* 0.75, $CHCl_3$); ν_{max}($CHCl_3$)/cm^1 3541br, 2978s, 2882s, 1760s, 1463m, 1382s, 1235s, 1084s, 946s; δ_H(400 MHz, $CDCl_3$) 3.95 (1H, dd, *J* 9.1, 6.3), 3.78 (1H, ddd, *J* 8.1, 3.3, 3.3), 3.69 (1H, ddd, *J* 10.8, 7.4, 3.3), 3.52 (1H, ddd, *J* 10.8, 8.1, 2.4), 2.76 (1H, d, *J* 3.3), 2.63 (2H, t, *J* 8.6), 2.32 (1H, dd, *J* 7.4, 3.3), 2.23 (1H, ddd, *J* 13.1, 8.6, 8.6), 2.13–2.05 (1H, m), 2.0–1.9 (1H, m), 1.93 (1H, ddd, *J* 13.1, 8.6, 8.6), 1.80–1.40 (4H, m), 1.45 (3H, s), 0.93 (3H, t, *J* 7.4); δ_C(100 MHz, $CDCl_3$) 176.6 (0), 87.5 (0), 87.1 (0), 83.0 (1), 75.3 (1), 63.0 (2), 30.1 (2), 29.4 (2), 28.9 (2), 28.8 (2), 27.4 (2), 24.0 (3), 7.9 (3); *m/z* (EI) 259 ($MH^{+\bullet}$, 6%), 197 (100), 141 (20), 125 (30), 95 (25), 57 (35), 43 (43).

(*S*)-5-{(2*R*,5*S*)-5-Ethyl-5-[(1*R*)-1-hydroxy-2-(*p*-tosyloxy)ethyl]oxolan-2-yl}-5-methyloxolan-2-one 83

A solution of diol **82** (255 mg, 0.99 mmol) and TsCl (267 mg, 1.4 mmol) and Et_3N (280 μl) in CH_2Cl_2 was stirred at r.t. for 41 h. The mixture was diluted with Et_2O (75 cm^3) and washed with brine. After drying ($MgSO_4$), filtration and concentration

in vacuo, the residue was purified by column chromatography (SiO_2, 10 × 2.5 cm, hexanes : EtOAc, 2 : 1) to give the monotosylate **83** (373 mg, 0.91 mmol, 92%) as a waxy yellow solid; mp 94–96 °C (Found: C, 58.25; H, 6.71; S, 7.22%. $C_{20}H_{28}O_7S$ requires C, 58.24; H, 6.84; S, 7.77%); $[\alpha]_D$ +18.8 (*c* 1.68, $CHCl_3$); ν_{max}(film)/cm^{-1} 3359br, 2978s, 2887s, 1755s, 1598m, 1356s, 1177s, 1096s, 977s, 954s, 844s, 753s, 668s; δ_H(270 MHz, $CDCl_3$) 7.84–7.78 (2H, m), 7.40–7.34 (2H, m), 4.22 (1H, dd, *J* 10.4, 2.5), 4.04–3.92 (2H, m), 3.85 (1H, ddd, *J* 7.7, 3.5, 2.5), 2.57 (2H, t, *J* 8.1), 2.48 (1H, d, *J* 3.5), 2.46 (3H, s), 2.3–2.0 (8H, m), 1.59 (3H, s), 0.87 (3H, t, *J* 7.3); δ_C(67.5 MHz, $CDCl_3$) 177.2 (0), 145.3 (0), 132.8 (0), 130.2 (2C, 1), 128.1 (2C, 1), 87.5 (0), 86.9 (0), 84.1 (1), 73.9 (1), 72.0 (2), 30.8 (2), 29.4 (2), 28.9 (2), 28.1 (2), 27.4 (2), 24.0 (3), 21.9 (3), 8.0 (3).

(*S*)-5-{(2*R*,5*S*)-5-Ethyl-5-[(2*R*)-1-hydroxyethyl]oxolan-2-yl}-5-methyloxolan-2-one 84

To a solution of the monotosylate **83** (300 mg, 0.73 mmol) in dry DME (4 cm^3) was added NaI (210 mg, 1.4 mmol), Bu_3SnH (380 µl, 1.4 mmol) and AIBN (16 mg, 0.1 mmol). The mixture was heated at 80 °C for 4 h. Additional amounts of Bu_3SnH (300 µl, 1.1 mmol), and AIBN (8 mg, 0.05 mmol) were added and heating was resumed. After 3.5 h the solution was allowed to cool, and MeOH (0.5 cm^3) added. The solvent was removed *in vacuo* and the residue (900 mg) purified (SiO_2, 10 × 2.5 cm, hexanes : EtOAc = 2 : 1) to give the title alcohol **84** (160 mg, 0.66 mmol, 90%) as a colourless oil [Found: $(M + NH_4)^+$, 260.1849. $C_{13}H_{22}O_4 + NH_4$ requires *M*, 260.1862]; $[\alpha]_D$ +2.3 (*c* 1.08, $CHCl_3$); ν_{max}(film)/cm^{-1} 3477br, 2974s, 1770s, 1463m, 1380m, 1266m, 1162m, 1084s, 944s; δ_H(360 MHz, $CDCl_3$) 3.94 (1H, dd, *J* 9.3, 6.5), 3.83 (1H, dq, *J* 6.4, 2.7), 2.60 (1H, t, *J* 8.0), 2.60 (1H, dd, *J* 9.1, 8.6), 2.27 (1H, d, *J* 2.7), 2.22 (1H, ddd, *J* 13.0, 9.1, 8.0), 2.09 (1H, ddd, *J* 12.2, 9.8, 3.7), 1.97–1.87 (2H, m), 1.74–1.30 (4H, m), 1.42 (3H, s), 1.04 (3H, d, *J* 6.5), 0.88 (3H, t, *J* 7.5); δ_C(75 MHz, $CDCl_3$) 176.6 (0), 89.3 (0), 87.2 (0), 83.1 (1), 70.5 (1), 29.5 (2), 29.2 (2), 29.1 (2), 29.0 (2), 27.4 (2), 23.9 (3), 17.7 (3), 7.9 (3).

(*S*)-5-[(2*R*,5*R*,6*S*)-5-Ethyl-5-hydroxy-6-methyloxan-2-yl]-5-methyloxolan-2-one 8b

To an ice cooled, magnetically stirred solution of the secondary alcohol **84** (160 mg, 0.66 mmol) in dry CH_2Cl_2 (3 cm^3) was added Et_3N (280 µl, 2.0 mmol) and MsCl (80 µl, 1.0 mmol) after 30 min the reaction was quenched with MeOH. The solution was diluted with Et_2O and washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual crude mesylate **85** (220 mg), silver carbonate (180 mg, 0.66 mmol) and water (2 cm^3) was refluxed in acetone (8 cm^3). Additional portions of silver carbonate were added after 3.5 h, 15.5 h and 21 h and heating continued for an additional 6 h whereupon the reaction mixture was cooled to r.t., diluted with Et_2O and dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue (150 mg) was purified by column chromatography (SiO_2, 6 × 2 cm, hexanes : EtOAc = 2 : 1) to give an inseparable mixture of the desired tertiary alcohol **8b** and the starting secondary alcohol **84** (112 mg, 0.46 mmol, 70%) in a ratio of 5 : 1, estimated from the ^{1}H NMR spectrum. The mixture of alcohols **8b** and **84** was treated with the Dess–Martin periodinane and the ketone derived from oxidation of the secondary alcohol in **84** was separated from unreacted **8b** by column chromatography (SiO_2, hexanes : EtOAc = 2 : 1) to give pure **8b** (90 mg, 0.37 mmol, 56% from **84**); $[\alpha]_D$ −26.1 (*c* 2.43, $CHCl_3$). Lactone **8b** was identical by $[\alpha]_D$, ^{1}H and ^{13}C NMR spectroscopy with a sample prepared by degradation of natural salinomycin.[6] δ_H(360 MHz, $CDCl_3$) 3.80 (1H, q, *J* 6.9), 3.67–3.60 (1H, m), 2.67 (1H, ddd, *J* 18.0, 10.5, 7.8), 2.53 (1H, ddd, *J* 18.0, 10.4, 5.3), 2.37 (1H, ddd, *J* 13.0, 10.5, 5.5), 1.87 (1H, ddd, *J* 13.0, 10.4, 2.8), 1.8–1.1 (7H, m), 1.36 (3H, s), 1.23 (3H, d, *J* 6.9), 0.92 (3H, t, *J* 7.6); δ_C(90 MHz, $CDCl_3$) 177.2 (0), 87.3 (0), 77.3 (1), 73.2 (1), 71.1 (0), 30.7 (2), 29.7 (2), 29.5 (2), 29.1 (2), 23.0 (3), 21.4 (2), 14.4 (3), 6.5 (3).

(*S*)-5-[(2*R*,5*R*,6*S*)-5-Ethyl-5-(triethylsilyloxy)-5-methyloxan-2-yl]-5-methyloxolan-2-one 8a

To a solution of alcohol **8b** (483 mg, 2.00 mmol) and 2,6-lutidine (1.1 cm^3, 10 mmol) in CH_2Cl_2 (10 cm^3) was added TESOTf (530 µl, 2.40 mmol) at −50 °C. The mixture was allowed to warm gradually to 0 °C over 3.25 h. The mixture was diluted with Et_2O and washed with 2 M HCl, $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (540 mg) which was purified by column chromatography (SiO_2, 5 × 3.5 cm, hexanes : Et_2O = 4 : 1) to give TES ether **8a** (580 mg, 1.63 mmol, 82%) as a pale yellow oil; $[\alpha]_D$ −32.1 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2953s, 2876s, 1773s, 1459s, 1414m, 1379s, 1240s, 1103s, 1060s, 1010s, 944s, 737s; δ_H(300 MHz, $CDCl_3$) 3.77 (1H, q, *J* 6.8), 3.57 (1H, dd, *J* 11.1, 2.7), 2.76–2.36 (3H, m), 1.86–1.10 (7H, m), 1.32 (3H, s), 1.15 (3H, d, *J* 6.8), 0.95 (9H, t, *J* 7.9), 0.86 (3H, t, *J* 7.4), 0.61 (6H, q, *J* 8.0); δ_C(75 MHz, $CDCl_3$) 177.6 (0), 87.7 (0), 77.1 (1), 74.7 (0), 73.6 (1), 31.6 (2), 29.8 (2), 29.7 (2), 29.1 (2), 23.1 (3), 21.5 (2), 15.4 (3), 7.2 (3), 6.8 (3), 6.8 (2); *m*/*z* (CI, NH_3) 374 [$(M + NH_4)^+$, 5%], 357 [$(M + H)^+$, 10], 327 (5), 272 (5), 242 (20), 225 (100), 199 (5).

Synthesis of dispiroacetals 90a,b *via* furan oxidation

2-{(1*R*,3*S*)-3-[(4*S*,5*S*)-2,2-di-*tert*-Butyl-5-ethyl-1,3-dioxa-2-silacyclohexyan-4-yl]-1,3-dimethylpropyl}-5-{(*S*)-4-[(2*R*,5*R*,6*S*)-5-ethyl-5-(triethylsilyloxyl)-6-methyloxan-2-yl]-4-hydroxypentanoyl}furan 88

To a magnetically stirred solution of furan **7** (497 mg, 1.31 mmol) in THF (6.5 cm^3) at −60 °C was added dropwise Bu^{t}Li (0.92 cm^3 of a 1.56 M solution in pentane, 1.44 mmol). The yellow solution was allowed to warm to −5 °C over 2.3 h during which time the colour discharged. The solution was re-cooled to −65 °C whereupon a solution of the lactone **8a** (400 mg, 1.12 mmol) in THF (5 cm^3) was added. The solution was warmed to 0 °C over 3 h whereupon the bath was removed and stirring continued at ambient temperature for 20 min. The reaction mixture was diluted with Et_2O and then washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual yellow oil was purified by column chromatography (SiO_2, 5 × 4 cm, hexanes : Et_2O = 4 : 1) to give the acylfuran **88** (150 mg, 0.2 mmol) together with mixed fractions (410 mg) containing the desired acylfuran **88** and the lactone **8a**. Unreacted furan **7** (150 mg, 0.39 mmol, 30%) was also recovered (Found: $M^{+\bullet}$, 736.5115. $C_{41}H_{76}O_7Si_2$ requires *M*, 736.5130); ν_{max}(film)/cm^{-1} 3450br, 2965s, 2875s, 1674s, 1582s, 1513s, 1462s, 1381s, 1104s, 1028s, 825s, 739s, 648s; δ_H(360 MHz, C_6D_6) 7.26 (1H, d, *J* 3.4), 6.38 (1H, d, *J* 3.4), 4.31 (1H, dd, *J* 11.7, 1.9), 4.24 (1H, dd, *J* 11.4, 1.9), 4.04 (1H, q, *J* 6.9), 3.99 (1H, dd, *J* 9.6, 2.5), 3.51 (1H, dd, *J* 11.7, 2.1), 3.38 (1H, ddd, *J* 16.9, 9.4, 5.9), 3.33–3.22 (1H, m), 3.17 (1H, ddd, *J* 16.9, 9.3, 6.0), 2.8 (1H, br), 2.66 (1H, ddd, *J* 13.3, 9.7, 3.3), 2.47 (1H, ddd, *J* 14.8, 9.2, 5.5), 2.20–2.00 (3H, m), 1.93–1.77 (2H, m), 1.60–1.20 (7H, m), 1.45 (3H, d, *J* 6.9), 1.43 (3H, s), 1.41 (9H, s), 1.40 (9H, s), 1.31 (9H, t, *J* 7.9), 1.18 (3H, d, *J* 6.9), 1.07 (3H, t, *J* 7.2), 1.06 (3H, t, *J* 7.2), 1.00–0.90 (6H, m), 0.80 (3H, d, *J* 6.7); δ_C(90 MHz, C_6D_6) 189.5 (0), 166.2 (0), 153.0 (0), 118.3 (1), 107.6 (1), 83.0 (1), 78.1 (1), 76.0 (1), 75.9 (1), 67.3 (2), 42.9 (1), 40.9 (2), 35.5 (1), 33.7 (2), 32.9 (2), 32.8 (1), 32.2 (2), 31.0 (2), 29.7 (3C, 3), 28.6 (3C, 3), 24.6 (3), 24.5 (0), 23.8 (3), 21.9 (2), 21.6 (3), 21.5 (3), 16.4 (3), 16.3 (3), 13.0 (3), 8.3 (3), 7.9 (2), 7.8 (3); *m*/*z* (EI) 736 ($M^{+\bullet}$, 4%), 718 (55), 675 (100), 587 (18), 529 (20), 503 (15), 473 (19), 403 (13), 377 (40), 255 (25), 216 (65), 157 (30), 115 (40), 75 (45).

2-[(1*R*,3*S*,4*S*,5*S*)-5-Ethyl-4,6-dihydroxy-1,3-dimethylhexyl]-5-{(*S*)-4-[(2*R*,5*R*,6*S*)-5-ethyl-5-(triethylsilyloxy)-6-methyloxan-2-yl]-4-hydroxypentanoyl}furan 89

A solution of the pure acylfuran **88** (150 mg) and the mixture of **7** and lactone **8a** (410 mg, *vide supra*) in dry THF (2 cm^3) was treated with 1.5 cm^3 of 2 M HF in an excess of pyridine and

THF. After 20 min at r.t., Et_2O was added and the solution washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual yellow oil (650 mg) was purified by column chromatography (SiO_2, 13 × 2.5 cm, hexanes : EtOAc = 1 : 1) to give the diol **89** (340 mg, 0.57 mmol, 51% from **88**) and recovered lactone **8a** (160 mg, 0.44 mmol, 40%) [Found: $(M + Na)^+$, 619.3987. $C_{33}H_{60}O_7SiNa$ requires *M*, 619.4006]; ν_{max}(film)/cm^{-1} 3436br, 2960s, 2872s, 1657s, 1580s, 1511s, 1460s, 1380s, 1099s, 1058s, 722s; δ_C(75 MHz, C_6D_6) 189.8 (0), 165.7 (0), 152.1 (0), 118.6 (1), 107.9 (1), 79.2 (1), 77.6 (1), 75.3 (0), 75.2 (1), 73.3 (0), 63.9 (2), 43.8 (1), 39.5 (2), 34.4 (1), 33.0 (2), 32.3 (2), 32.1 (2), 32.0 (1), 30.5 (2), 23.0 (3), 21.4 (3), 21.3 (2), 17.0 (2), 16.8 (3), 15.8 (3), 12.4 (3), 7.7 (3), 7.3 (2), 7.2 (3).

Oxidative dispiroannulation of acylfuran 89

To a stirred solution of acylfuran **89** (293 mg, 0.492 mmol) in THF (10 cm^3) and H_2O (3 cm^3) at −10 °C was added portionwise over 9 min NBS (131 mg, 0.738 mmol). After addition was complete, the mixture was allowed to stir at −10 °C for a further 20 min whereupon saturated aqueous $Na_2S_2O_3$ (3 cm^3) and $NaHCO_3$ (3 cm^3) were added and the product extracted into Et_2O. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to a brown oil (230 mg) which was dissolved in MeCN (7 cm^3) and cooled to 0 °C whereupon 40% HF (1 cm^3) was added. The mixture was allowed to stir at ambient temperature for 3 h and then diluted with Et_2O and washed with H_2O followed by saturated aqueous $NaHCO_3$. The brown oil (230 mg) obtained after drying and concentration *in vacuo*, was purified by column chromatography (SiO_2, 5 × 2.5 cm, hexanes : EtOAc = 3 : 1→2.5 : 1) to give (in order of elution); **90a** (104 mg, 0.217 mmol, 44%) and **90b** (36 mg, 0.075 mmol, 15%).

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*)-9-[(*S*)-1-Ethyl-2-hydroxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-one 90a

(Found: $M^{+\bullet}$, 480.3075. $C_{27}H_{44}O_7$ requires *M*, 480.3087); $[\alpha]_D$ +1.4 (*c* 2.0, Et_2O); ν_{max}(film)/cm^{-1} 3496br, 2960s, 2878s, 1698s, 1637w, 1461s, 1378s, 1090s, 1050s, 985s, 877s; δ_H(360 MHz, C_6D_6) 6.42 (1H, d, *J* 10), 6.17 (1H, d, *J* 10), 4.85 (1H, br s), 4.56 (1H, dd, *J* 10.2, 2.2), 4.44 (1H, dd, *J* 6.8, 6.8), 4.23 (1H, q, *J* 7.0), 4.04 (1H, ddd, *J* 8.2, 8.2, 4.2), 3.94–3.86 (1H, m), 3.52 (1H, dd, *J* 12.0, 2.5), 2.44–2.26 (3H, m), 2.20–1.20 (13H, m), 1.75 (3H, s), 1.27 (3H, t, *J* 7.4), 1.23 (3H, d, *J* 7.0), 1.22 (3H, d, *J* 6.4), 1.00 (3H, t, *J* 7.5), 0.98 (3H, d, *J* 6.5), 0.87 (1H, br s); δ_C(90 MHz, C_6D_6) 194.8 (0), 150.9 (1), 128.2 (1), 106.3 (0), 96.4 (0), 91.2 (0), 77.8 (1), 75.6 (1), 74.3 (1), 70.8 (0), 62.3 (2), 43.3 (1), 40.1 (1), 39.7 (2), 36.8 (2), 33.8 (2), 32.6 (1), 32.4 (2), 30.9 (2), 25.4 (3), 22.3 (2), 18.4 (2), 18.2 (3), 16.9 (3), 15.1 (3), 13.4 (3), 7.5 (3); *m*/*z* (EI) 480 ($M^{+\bullet}$, 25%), 462 (30), 238 (80), 225 (50), 111 (100), 99 (35), 57 (50), 43 (45).

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*)-9-[(*S*)-1-Ethyl-2-hydroxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-one 90b

(Found: $M^{+\bullet}$, 480.3085. $C_{27}H_{44}O_7$ requires *M*, 480.3087); $[\alpha]_D$ −5.6 (*c* 2.15, Et_2O); ν_{max}(CCl_4)/cm^{-1} 3528br, 2965s, 2877s, 1706s, 1459s, 1380s, 1122s, 1073s, 982s; δ_H(360 MHz, C_6D_6) 6.13 (1H, d, *J* 10.4), 6.10 (1H, d, *J* 10.4), 4.10 (1H, d, *J* 9.5), 4.00 (1H, q, *J* 7.6), 3.95–3.82 (2H, m), 3.78 (1H, dd, *J* 10.5, 2.9), 2.85–2.77 (1H, m), 2.62–2.45 (2H, m), 2.36–2.27 (1H, m), 2.10–2.02 (1H, m), 1.85–1.10 (12H, m), 1.74 (3H, s), 1.23 (3H, d, *J* 6.9), 1.21 (3H, t, *J* 7.4), 1.16 (3H, t, *J* 7.4), 0.99 (3H, d, *J* 6.4), 0.92 (3H, d, *J* 6.5), 0.80 (2H, br); δ_C(90 MHz, C_6D_6) 191.8 (0), 147.5 (1), 127.4 (1), 106.4 (0), 97.4 (0), 87.6 (0), 78.6 (1), 77.5 (1), 72.0 (1), 70.7 (0), 63.4 (2), 42.8 (1), 39.7 (1), 37.4 (2), 35.6 (2), 35.0 (2), 31.9 (1), 30.8 (2), 29.4 (2), 22.7 (3), 21.0 (2), 17.7 (3), 17.3 (2), 16.2 (3), 14.2 (3), 12.8 (3), 6.6 (3); *m*/*z* (EI) 480 ($M^{+\bullet}$, 25%), 462 (10), 436 (5), 378 (5), 338 (35), 307 (20), 238 (40), 225 (20), 183 (40), 165 (25), 111 (100), 99 (40), 81 (30), 57 (55).

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*)-9-[(*S*)-1-Ethyl-2-triethylsilyloxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-(triethylsilyloxy)-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-one 91

TES ether **91** (100 mg, 0.141 mmol, 74%) was obtained as a colourless oil from alcohol **90b** (90 mg, 0.19 mmol) by the procedure described for the preparation of the diastereoisomer **114** (*vide infra*) (Found: $M^{+\bullet}$, 708.4824. $C_{39}H_{72}O_7Si_2$ requires *M*, 708.4817); $[\alpha]_D$ −13.8 (*c* 2.5, Et_2O); ν_{max}(film)/cm^{-1} 2956s, 2876s, 1704s, 1642w, 1460s, 1378s, 1237s, 1087s, 1017s, 986s, 739s; δ_H(270 MHz, C_6D_6) 6.28 (1H, d, *J* 10.2), 6.18 (1H, d, *J* 10.2), 4.24 (1H, dd, *J* 10.2, 1.4), 4.09 (1H, q, *J* 6.9), 3.98–3.82 (3H, m), 3.02–2.90 (1H, m), 2.76–2.38 (3H, m), 2.30–1.20 (16H, m), 1.94 (3H, s), 1.32 (3H, d, *J* 6.9), 1.30 (9H, t, *J* 7.9), 1.25 (9H, t, *J* 7.9), 1.09–1.02 (9H, m), 0.98–0.8 (12H, m); δ_C(67.5 MHz, C_6D_6) 192.5 (0), 148.3 (1), 127.4 (1), 106.9 (0), 97.4 (0), 88.4 (0), 77.2 (1), 75.6 (0), 75.6 (1), 73.4 (1), 63.0 (2), 44.9 (1), 40.1 (1), 37.6 (2), 36.0 (2), 35.6 (2), 32.2 (1), 31.7 (2), 30.6 (2), 23.4 (3), 21.7 (2), 18.6 (2), 18.3 (3), 16.5 (3), 15.8 (3), 13.7 (3), 7.7 (3), 7.3 (2C, 3), 7.2 (2), 5.0 (2); *m*/*z* (EI) 708 ($M^{+\bullet}$, 20%), 679 (45), 662 (40), 576 (5), 547 (15), 529 (5), 509 (15), 492 (5), 452 (60), 352 (45), 323 (35), 297 (20), 257 (35), 225 (65), 199 (100), 157 (65), 115 (95), 99 (35), 87 (95).

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,15*S*)-9-[(*S*)-1-Ethyl-2-triethylsilyloxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-ol 92

Allylic alcohol **92** (137 mg, 0.192 mmol, 93%) was obtained by reduction of enone **91** (146 mg, 0.206 mmol) by the procedure described for the preparation of the diastereoisomers **115a**,**b** (*vide infra*) (Found: $M^{+\bullet}$, 710.4980. $C_{39}H_{74}O_7Si_2$ requires *M*, 710.4973); $[\alpha]_D$ +50 (*c* 2.25, Et_2O); δ_H(300 MHz, C_6D_6) 6.27 (1H, dd, *J* 10.2, 1.0), 5.58 (1H, dd, *J* 10.2, 2.7), 4.83 (1H, dd, *J* 2.7, 1.0), 4.28 (1H, br), 4.26 (1H, d, *J* 9.6), 4.09–3.95 (3H, m), 3.80 (1H, dd, *J* 10.6, 1.8), 2.94 (1H, dd, *J* 9.5, 3.1), 2.92 (1H, d, *J* 9.5), 2.75 (1H, ddd, *J* 11.8, 7.5, 5.0), 2.41 (1H, dt, *J* 11.8, 9.2), 2.10–1.48 (16H, m), 1.70 (3H, s), 1.31 (9H, t, *J* 7.7), 1.29 (9H, t, *J* 7.6), 1.23 (3H, d, *J* 7.0), 1.14 (3H, d, *J* 6.4), 1.08 (3H, d, *J* 5.7), 1.00 (3H, t, *J* 7.2), 0.97–0.86 (12H, m); δ_C(75 MHz, C_6D_6) 131.6 (1), 129.3 (1), 110.6 (0), 100.2 (0), 87.2 (0), 77.6 (1), 75.8 (2C, 1), 75.1 (0), 69.7 (1), 64.2 (2), 45.0 (1), 39.9 (1), 36.2 (2), 32.3 (1), 32.0 (2), 31.4 (2), 30.9 (2), 30.1 (2), 27.2 (3), 22.9 (2), 18.9 (2), 18.4 (3), 16.4 (3), 15.9 (3), 13.8 (3), 7.7 (3), 7.3 (3), 7.3 (2), 7.2 (3), 5.7 (2); *m*/*z* (EI) 710 ($M^{+\bullet}$, 5%), 692 (25), 681 (25), 663 (10), 578 (10), 523 (10), 453 (20), 435 (20), 354 (100), 327 (20), 309 (20), 303 (30), 257 (20), 225 (30), 199 (80), 157 (50), 115 (80), 103 (60), 87 (80).

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,15*S*)-15-Acetoxy-9-[(*S*)-1-ethyl-2-hydroxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene 93

Primary alcohol **93** (40 mg, 0.063 mmol, 99%) was obtained by acetylation followed by deprotection of the secondary TES ether in **92** (48 mg, 0.0634 mmol) by the procedure described for the preparation of the diastereoisomers **116a**,**b** (*vide infra*): mp 121–123 °C (MeOH) (Found: $M^{+\bullet}$, 638.4203. $C_{35}H_{62}O_8Si$ requires *M*, 638.4214) (Found: C, 65.52; H, 9.72%. $C_{35}H_{62}O_8Si$ requires C, 65.79; H, 9.78%); $[\alpha]_D$ +52.5 (*c* 0.14, Et_2O); ν_{max}(film)/cm^{-1} 3334br, 2938s, 2876s, 1751s, 1458s, 1371s, 1236s, 1034s, 964s; δ_H(270 MHz, C_6D_6) 5.98 (1H, dd, *J* 2.5, 1.9), 5.84 (1H, dd, *J* 10.2, 1.9), 5.52 (1H, dd, *J* 10.2, 2.5), 4.20–3.98 (3H, m), 3.94 (1H, dd, *J* 10.9, 2.9), 3.64 (1H, dd, *J* 10.9, 2.5), 2.92–2.82 (1H, m), 2.70–2.20 (4H, m), 2.10 (3H, s), 2.10–1.20 (13H, m), 1.97 (3H, s), 1.32 (3H, d, *J* 7.0), 1.31 (9H, t, *J* 7.9), 1.15 (3H, t, *J* 6.5), 1.10 (3H, t, *J* 6.5), 1.07 (3H, d, *J* 6.4), 1.0–0.9 (9H, m); δ_C(75 MHz, C_6D_6) 169.1 (0), 131.0 (1), 128.7 (1), 108.0 (0), 99.7 (0), 87.1 (0), 80.3 (1), 77.1 (1), 75.4 (0), 73.6 (1), 69.1 (1), 64.3 (2), 42.7 (1), 39.8 (1), 35.6 (2), 34.2 (2), 32.1 (1), 31.7 (2), 31.2

(2), 30.7 (2), 24.3 (3), 21.8 (2), 20.8 (3), 17.9 (3), 17.2 (3), 16.2 (3), 15.7 (3), 12.8 (3), 7.7 (3), 7.4 (3), 7.3 (3); *m/z* (EI) 638 ($M^{+\bullet}$, 5%), 609 (45), 578 (43), 549 (18), 494 (10), 425 (14), 381 (18), 351 (19), 327 (21), 321 (100), 282 (79), 257 (33), 199 (58), 171 (22), 165 (25), 157 (36), 115 (30), 99 (30), 87 (35).

The structure of **93** was unambiguously established by X-ray crystallographic analysis.

Synthesis of dispiroacetal 90a *via* allenol ether chemistry

Methyl (2*R*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpentanoate 44b

Hydroxy ester **43b** (9.43 g, 59 mmol) was added to a suspension of *tert*-butyldimethylchlorosilane (12.4 g, 83 mmol) and imidazole (10.8 g, 15.9 mmol) in CH_2Cl_2 (50 cm^3) at 0 °C, followed by DMAP (0.77 g, 5.9 mmol). The mixture was stirred at 0 °C for 1 h before being quenched by addition of a mixture of water–hexanes (1 : 2, 30 cm^3). The aqueous phase was removed and the organic phase washed with brine (2 × 50 cm^3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, hexanes : Et_2O = 9 : 1) to give **44b** (15.45 g, 56.4 mmol, 96%) as a colourless oil; $[\alpha]_D$ +13.7 (*c* 1.62, $CHCl_3$); ν_{max}(film)/cm^{-1} 2954s, 2857s, 1741s, 1463s, 1388m, 1362m, 1257s, 1092s, 1039m, 837s, 776m; δ_H(270 MHz, $CDCl_3$) 3.63 (3H, s), 3.43 (1H, dd, *J* 9.8, 6.0), 3.35 (1H, dd, *J* 9.8, 6.4), 2.60 (1H, ddq, *J* 9.1, 6.9, 6.9), 1.78 (1H, ddd, *J* 13.5, 9.1, 5.2), 1.68–1.55 (1H, m), 1.15 (3H, d, *J* 6.0), 1.20–1.10 (1H, m), 0.89 (3H, d, *J* 6.0), 0.90 (9H, s), 0.05 (6H, s); δ_C(67.9 MHz, $CDCl_3$) 177.55 (0), 68.37 (2), 51.60 (3), 37.40 (1), 33.88 (2), 30.00 (1), 26.06 (3C, 3), 18.47 (0), 18.14 (3), 16.86 (3), −5.00 (2C, 3); *m/z* (CI, NH_3) 292 (5%), 275 (100), 259 (3), 243 (5), 217 (26), 185 (6), 143 (7), 106 (5).

(2*R*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol 100

To a suspension of lithium aluminium hydride (1.64 g, 43.0 mmol) in dry Et_2O (120 cm^3) at −10 °C was added ester **44** (15.45 g, 56.4 mmol) dropwise in order to maintain the internal temperature below 0 °C. The reaction mixture was stirred for a further 15 min before being quenched by addition of water (1.6 cm^3), 15% aqueous sodium hydroxide (1.6 cm^3) and water (5 cm^3). The stirring was continued at r.t. until a white precipitate formed. The solid was filtered, washed with Et_2O (3 × 20 cm^3), and the filtrate dried over $MgSO_4$, filtered again and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, hexanes : Et_2O = 3 : 1) to give **100** (12.5 g, 50.8 mmol, 90%) as a colourless oil; $[\alpha]_D$ +18.75 (*c* 2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3345br, 2955s, 2857s, 1463s, 1388m, 1361m, 1255s, 1095s, 1040m, 836s, 774m; δ_H(270 MHz, $CDCl_3$) 3.50 (1H, dd, *J* 10.6, 5.2), 3.47 (1H, dd, *J* 10.6, 5.2), 3.42 (1H, dd, *J* 9.5, 6.2), 3.36 (1H, dd, *J* 9.5, 6.2), 1.77 (1H, m), 1.84–1.64 (2H, m), 1.43 (1H, ddd, *J* 13.5, 6.8, 6.8), 1.00–0.90 (1H, m), 0.94 (3H, d, *J* 6.6), 0.88 (3H, d, *J* 6.8), 0.89 (9H, s), 0.2 (6H, s); δ_C(67.9 MHz, $CDCl_3$) 68.45 (2), 68.35 (2), 37.45 (2), 33.43 (1), 33.40 (1), 26.12 (3C, 3), 18.53 (0), 17.98 (3), 17.88 (3), −5.20 (2C, 3); *m/z* (CI, NH_3) 247 (MH^+, 100), 229 (1), 132 (2), 114 (3), 97 (9).

(2*R*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)-2,4-dimethylpentane 101

To an ice cooled magnetically stirred solution of the alcohol **100** (10.00 g, 40.60 mmol) in dry DMF (50 cm^3) was added sodium hydrogen carbonate (6.14 g, 73.08 mmol) followed by sodium hydride (2.44 g of a 60% dispersion in oil, 60.90 mmol). The effervescing suspension was stirred at r.t. for 30 min whereupon 4-methoxybenzyl chloride (8.26 cm^3, 60.90 mmol) was added. After stirring for 16 h at r.t., the mixture was poured into water (100 cm^3), extracted with Et_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residual yellow oil was purified by chromatography (SiO_2, hexanes : Et_2O = 49 : 1 to 5 : 1) to give PMB ether **101** (13.61 g, 37.12 mmol, 91%) as a colourless oil; $[\alpha]_D$ −4.1 (*c* 1.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 2955s, 2855s, 1613m, 1513s, 1463s, 1360m, 1302m, 1249s, 1095s, 1039m, 837s, 775m; δ_H(300 MHz, $CDCl_3$) 7.28–7.25 (2H, m), 6.90–6.87 (2H, m), 4.43 (2H, s), 3.81 (3H, s), 3.47 (1H, dd, *J* 9.7, 5.3), 3.33 (1H, dd, *J* 9.1, 5.2), 3.31 (1H, dd, *J* 9.7, 7.0), 3.16 (1H, dd, *J* 9.1, 7.1), 1.92–1.78 (1H, m), 1.76–1.60 (1H, m), 1.41 (1H, dt, *J* 13.7, 6.8), 0.95–0.88 (1H, m), 0.96 (3H, d, *J* 6.6), 0.91 (9H, s), 0.90 (3H, d, *J* 6.6), 0.04 (6H, s); δ_C(75 MHz, $CDCl_3$) 159.19 (0), 131.09 (0), 129.22 (2C, 1), 113.86 (2C, 1), 75.89 (2), 72.78 (2), 68.40 (2), 55.40 (3), 37.93 (2), 33.35 (1), 31.12 (1), 26.14 (3C, 3), 18.52 (0), 18.38 (3), 17.90 (3), −5.20 (2C, 3).

(2*R*,4*S*)-5-(4-Methoxybenzyloxy)-2,4-dimethylpentan-1-ol 102

To an ice cooled magnetically stirred solution of **101** (13.60 g, 37.10 mmol) in dry THF (100 cm^3) was added TBAF·$3H_2O$ (17.56 g, 55.64 mmol). The cold bath was removed and the reaction mixture stirred at r.t. for 12 h. Water (50 cm^3) was then added and the mixture was extracted with Et_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, hexanes : Et_2O = 1 : 1) to give the alcohol **102** (8.16 g, 32.38 mmol, 87%) as a colourless oil; $[\alpha]_D$ −5.45 (*c* 2.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 3695–3096br, 2955s, 2869s, 1612s, 1586m, 1513s, 1463s, 1362m, 1301m, 1247s, 1172m, 1090s, 1036s, 820s; δ_H(270 MHz, $CDCl_3$) 7.28–7.24 (2H, m), 6.90–6.87 (2H, m), 4.42 (2H, s), 3.80 (3H, s), 3.46 (1H, dd, *J* 5.2, 10.6), 3.40 (1H, dd, *J* 6.2, 10.6), 3.28 (1H, dd, *J* 6.0, 9.0), 3.24 (1H, dd, *J* 6.4, 8.9), 1.91 (1H, br), 1.92–1.80 (2H, m), 1.47 (1H, ddd, *J* 7.0, 7.0, 13.7), 1.02–0.88 (1H, m), 0.94 (3H, d, *J* 6.6), 0.93 (3H, d, *J* 6.6); δ_C(67.5 MHz, $CDCl_3$) 159.15 (0), 130.70 (0), 129.26 (1), 113.81 (1), 75.68 (2), 72.79 (2), 67.88 (2), 55.32 (3), 37.73 (2), 33.25 (1), 31.03 (1), 18.25 (3), 17.76 (3); *m/z* (EI) 252 (M^+, 10%), 234 (1), 137 (50), 121 (100).

(2*S*,4*R*)-5-(4-Methoxybenzyloxy)-2,4-dimethylpentanal 103

By the same procedure described above for the preparation of **46**, alcohol **102** (8.85 mmol) was oxidised to the aldehyde **103** (2.04 g, 8.16 mmol, 92%); $[\alpha]_D$ +7.7 (*c* 2.33, $CHCl_3$); ν_{max}(film)/cm^{-1} 2960s, 2852s, 1723s, 1613s, 1513s, 1462s, 1362m, 1301m, 1247s, 1172s, 1090s, 1035s, 820s; δ_H(270 MHz, $CDCl_3$) 9.56 (1H, d, *J* 2.5), 7.25 (2H, d, *J* 8.7), 6.88 (2H, d, *J* 8.7), 4.41 (2H, s), 3.80 (3H, s), 3.27 (2H, d, *J* 5.8), 2.54–2.38 (1H, m), 1.95–1.75 (2H, m), 1.22–1.05 (1H, m), 1.09 (3H, d, *J* 6.9), 0.95 (3H, d, *J* 6.8); δ_C(67.5 MHz, $CDCl_3$) 205.35 (1), 159.16 (0), 130.65 (0), 129.23 (1), 113.81 (1), 75.12 (2), 72.70 (2), 55.32 (3), 44.23 (1), 35.09 (2), 31.31 (1), 17.66 (3), 14.42 (3).

(*S*)-*N*-[(2*R*,3*S*,4*S*,6*R*)-7-(4-Methoxybenzyloxy)-4,6-dimethyl-3-hydroxy-2-ethylheptanoyl]-4-isopropyloxazolidine-2-thione 104

To a magnetically stirred suspension of tin(II) triflate (9.14 g, 21.9 mmol) in dry CH_2Cl_2 (30 cm^3) under an atmosphere of argon, at −50 °C was added *N*-ethylpiperidine (3.5 cm^3, 26.7 mmol) dropwise. To the resulting lemon yellow suspension was added a solution of (*S*)-*N*-butanoyl-4-isopropyloxazolidine-2-thione **47** (3.92 g, 18.2 mmol) in CH_2Cl_2 (30 cm^3) at such a rate that the temperature did not exceed −45 °C. After stirring at −45 °C for 3 h, the cloudy solution was then cooled to −80 °C whereupon a solution of the aldehyde **103** (3.05 g, 12.2 mmol) in CH_2Cl_2 (30 cm^3) was added slowly. The cloudy solution was stirred for 20 min and then poured into pH 7 phosphate buffer. The mixture was filtered through Celite, washing with several portions of CH_2Cl_2. The organic layer was then separated, and the aqueous layer extracted with two portions of CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a brown oil (13 g) which was filtered through a short pad of SiO_2 (hexanes–EtOAc, 1 : 1). Concentration *in vacuo* gave the crude product as a pale yellow oil (7.1 g) which was purified by chromatography (SiO_2, 6 × 8 cm, hexanes : EtOAc, 5 : 1) to give **104** (5.16 g, 11.1 mmol, 91%) as a viscous colourless oil; $[\alpha]_D$ +71.4 (*c* 2.0,

$CHCl_3$); ν_{max}(film)/cm^{-1} 3500br, 2964s, 2875s, 1693s, 1613s, 1513s, 1463s, 1472s, 1324s, 1248s, 1190s, 1091s, 958s, 832s; δ_H(270 MHz, C_6D_6 $CDCl_3$) 7.26 (2H, d, *J* 8.7), 6.88 (2H, d, *J* 8.7), 5.21 (1H, ddd, *J* 3.5, 3.5, 10.0), 4.79 (1H, ddd, *J* 4.1, 4.1, 6.8), 4.32–4.49 (4H, m), 3.81 (3H, s), 3.66 (1H, dd, *J* 3.1, 8.3), 3.37 (1H, dd, *J* 5.0, 9.0), 3.21 (1H, dd, *J* 6.7, 9.0), 2.25–2.38 (1H, m), 1.5–2.00 (6H, m), 0.80–0.95 (1H, m), 0.98 (3H, d, *J* 6.6), 0.97 (3H, d, *J* 6.8), 0.93 (3H, d, *J* 6.4), 0.92 (3H, t, *J* 7.5), 0.88 (3H, d, *J* 6.8); δ_C(67.5 MHz, C_6D_6) 185.9 (0), 177.4 (0), 159.0 (0), 130.8 (0), 129.2 (1), 113.7 (1), 76.2 (2), 75.3 (2), 72.7 (2), 67.4 (2), 63.3 (1), 55.3 (1), 46.3 (1), 38.4 (2), 35.2 (1), 31.4 (1), 29.1 (1), 19.3 (3), 18.4 (2), 18.3 (3), 16.4 (3), 14.9 (3), 11.9 (3); *m*/*z* (EI) 465 ($M^{+\bullet}$, 4%), 447 (4), 326 (7), 226 (15), 146 (25), 121 (100).

(2*S*,3*S*,4*S*,6*R*)-7-(4-Methoxybenzyloxy)-4,6-dimethyl-2-ethylheptane-1,3-diol 105

To an ice cooled, magnetically stirred solution of sodium borohydride (1.8 g, 47.4 mmol) in THF (40 cm^3) containing water (4 cm^3) was added dropwise a solution of the aldol **104** (7.4 g, 15.9 mmol) in THF (40 cm^3). When the addition was complete the cooling bath was removed. After 1.5 h the reaction mixture was quenched by pouring into 10% aqueous HCl. Most of the THF was removed *in vacuo*. The residue was dissolved in ether (200 cm^3), washed with 2 M NaOH (3 × 30 cm^3) and then dried ($MgSO_4$). The residual colourless oil obtained on concentration *in vacuo* was purified by chromatography (SiO_2, 7 × 7 cm, hexanes:ethyl acetate, 2.5:1→2:1) to give the diol **105** (4.2 g, 13.0 mmol, 82%) as a colourless oil (Found: $M^{+\bullet}$, 324.2310. $C_{19}H_{32}O_4$ requires *M*, 324.2301); $[\alpha]_D$ −12.6 (*c* 0.97, $CHCl_3$); ν_{max}(film)/cm^{-1} 3648–3037br, 2959s, 1612m, 1513s, 1463s, 1302m, 1247s, 1172m, 1085s, 1036s; δ_H(270 MHz, $CDCl_3$) 7.2 (2H, d, *J* 9), 6.8 (2H, d, *J* 9), 4.37 (1H, d, *J* 9.8), 4.34 (1H, d, *J* 9.8), 3.77 (1H, dd, *J* 4.0, 10.9), 3.73 (3H, s), 3.67 (1H, dd, *J* 2.0, 10.9), 3.40 (1H, dd, *J* 1.4, 8.7), 3.24 (1H, d, *J* 1.1), 3.22 (1H, d, *J* 1.0), 2.72–2.3 (2H, br), 1.88–1.76 (1H, m), 1.68–1.29 (5H, m), 0.95–0.8 (1H, m), 0.88 (3H, d, *J* 6.6), 0.87 (3H, t, *J* 7.3), 0.75 (3H, d, *J* 6.7); δ_C(67.5 MHz, $CDCl_3$) 159.15 (0), 131.01 (0), 129.25 (1), 113.83 (1), 81.07 (1), 75.44 (2), 72.78 (2), 65.31 (2), 55.39 (3), 38.32 (1), 38.32 (2), 33.27 (1), 31.25 (1), 19.48 (3), 15.65 (3), 14.88 (2), 11.99 (3); *m*/*z* (EI) 324 ($M^{+\bullet}$, 5%), 306 (1), 185 (7), 137 (30), 121 (100).

(2*S*,3*S*,4*S*,6*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-ethyl-7-(4-methoxybenzyloxy)-4,6-dimethylheptan-3-ol 106

To an ice cooled, magnetically stirred solution of the diol **105** (2.50 g, 7.71 mmol) in dry CH_2Cl_2 (50 cm^3), was added imidazole (1.26 g, 18.50 mmol) and DMAP (113 mg, 0.93 mmol). A solution of *tert*-butyldimethylchlorosilane (1.39 g, 9.26 mmol) in CH_2Cl_2 (15 cm^3) was then added dropwise. After 3 h at r.t., the reaction mixture was quenched by the addition of aqueous sodium hydrogen carbonate (15 cm^3) and the separated aqueous phase extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, hexanes:Et_2O = 9:1) to give **106** (3.19 g, 7.26 mmol, 94%) as a colourless oil (Found: $MH^{+\bullet}$, 439.3260. $C_{25}H_{46}O_4Si$ + H requires *M*, 439.3243); $[\alpha]_D$ −27.9 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3508br, 2956s, 2930s, 2857s, 1513m, 1463m, 1249s, 1089s, 1040m, 836; δ_H(300 MHz, $CDCl_3$) 7.24 (2H, br d, *J* 8.1), 6.87 (2H, dt, *J* 8.8, 2.2), 4.47 (1H, d, *J* 11.8), 4.40 (1H, d, *J* 11.8), 3.91 (1H, dd, *J* 10.3, 3.0), 3.81 (3H, s), 3.74 (1H, dd, *J* 10.3, 2.2), 3.46 (1H, dd, *J* 8.5, 4.0), 3.45 (1H, br t, *J* 8.8), 3.36 (1H, d, *J* 1.5), 3.16 (1H, dd, *J* 8.8, 7.4), 1.92 (1H, m), 1.77 (1H, m), 1.66 (1H, m), 1.57–1.38 (3H, m), 0.99 (3H, d, *J* 6.6), 0.95 (1H, m), 0.93 (3H, t, *J* 4.8), 0.90 (9H, s), 0.80 (3H, d, *J* 6.6), 0.084 (3H, s), 0.079 (3H, s); δ_C(75 MHz, $CDCl_3$) 159.13 (0), 131.13 (0), 129.24 (2C, 1), 113.81 (2C, 1), 80.80 (1), 75.57 (2), 72.77 (2), 65.71 (2), 55.37 (3), 43.06 (1), 38.30 (2), 33.94 (1), 31.27 (1), 26.02 (3C, 3), 19.67 (3), 18.29 (0), 16.43 (3), 15.76 (2), 12.34 (3), −5.49 (3), −5.56 (3).

(2*R*,4*S*,5*S*,6*S*)-7-(*tert*-Butyldimethylsilyloxy)-6-ethyl-2,4-dimethylheptane-1,5-diol 107

To a magnetically stirred solution of PMB ether **106** (2.47 g, 5.6 mmol) in EtOAc (100 cm^3) (washed with aq. Na_2CO_3 and distilled over CaH_2) was added 5% Pd/C (1 g, 0.47 mmol) under argon. The mixture was then placed under an atmosphere of hydrogen and stirred at r.t. for 15 h. The suspension was filtered through Celite, the solvent removed *in vacuo* and the residue purified by chromatography (SiO_2, hexanes:Et_2O = 1:1) to give diol **107** (1.65 g, 5.2 mmol, 93%) as a colourless oil [Found: $(M + H)^{+\bullet}$, 319.2661. $C_{17}H_{38}O_3Si$ + H requires *M*, 319.2668]; $[\alpha]_D$ −15.5 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3450–3340br, 2955s, 1463m, 1256s, 1086s, 1045m, 1026m, 836s; δ_H(300 MHz, $CDCl_3$) 3.94 (1H, dd, *J* 10.3, 2.9), 3.88 (1H, s), 3.75 (1H, dd, *J* 9.6, 2.2), 3.58 (1H, dd, *J* 11.0, 5.2), 3.49 (1H, m), 3.46 (1H, m), 2.96 (1H, br s), 1.80 (1H, m), 1.70 (1H, m), 1.61–1.36 (3H, m), 0.97–0.92 (2H, m), 0.95 (3H, d, *J* 6.6), 0.92 (3H, t, *J* 7.4), 0.89 (9H, s), 0.81 (3H, d, *J* 7.4), 0.084 (3H, s), 0.074 (3H, s); δ_C(75 MHz, $CDCl_3$) 81.71 (1), 67.02 (2), 66.04 (2), 42.62 (1), 37.99 (2), 34.02 (1), 33.93 (1), 25.97 (3C, 3), 19.13 (3), 18.26 (0), 17.46 (3), 15.16 (2), 12.24 (3), −5.55 (3), −5.63 (3).

(3*R*,5*S*,6*S*)-6-[(*S*)-1-(*tert*-Butyldimethylsilyloxymethyl)propyl]-3,5-dimethyloxan-2-one 108

To a magnetically stirred solution of the heptanediol **107** (1.64 g, 5.15 mmol) in dry acetone (150 cm^3) were added *N*-methylmorpholine *N*-oxide (1.8 g, 15.5 mmol) and $(Ph_3P)_3RuCl_2$ (100 mg). The gold solution was stirred at r.t. for 72 h (more reagents are added if necessary), after which time the reaction was black. After removal of solvent *in vacuo*, the black residue was purified by chromatography (SiO_2, hexanes:Et_2O = 4:1) to give the lactone **108** (1.61 g, 5.15 mmol, *ca.* 100%) as a colourless oil which crystallised at −20 °C (Found: $MH^{+\bullet}$, 315.2346. $C_{17}H_{34}O_3Si$ + H requires *M*, 315.2355); $[\alpha]_D$ +64.7 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 2929s, 1723s, 1463m, 1383m, 1256m, 1091s, 1006m, 835s, 774m; δ_H(300 MHz, $CDCl_3$) 4.26 (1H, d, *J* 11.8), 3.65 (2H, d, *J* 6.6), 2.47 (1H, ddq, *J* 13.2, 6.6, 6.6), 1.94 (1H, m), 1.90 (1H, m), 1.66 (1H, m), 1.50–1.36 (1H, m), 1.39 (1H, app. quintet, *J* 12.5), 1.27 (3H, d, *J* 7.4), 1.24–1.07 (1H, m), 0.96 (3H, d, *J* 5.9), 0.94 (3H, t, *J* 8.1), 0.88 (9H, s), 0.05 (6H, s); δ_C(75 MHz, $CDCl_3$) 174.77 (0), 85.78 (1), 62.10 (2), 44.65 (1), 37.92 (2), 36.39 (1), 30.78 (1), 26.04 (3C, 3), 18.37 (0), 17.85 (2), 17.63 (3), 17.48 (3), 12.97 (3), −5.20 (2C, 3).

(2*RS*,3*R*,5*S*,6*S*)-5-[(*S*)-1-Hydroxymethylpropyl]-3,5-dimethyl-2-methoxy-2-(3-methoxyprop-1-ynyl)oxane 109

To a magnetically stirred solution of 1-methoxyprop-2-yne (0.85 cm^3, 10 mmol) in Et_2O (50 cm^3) at −30 °C under argon, was added dropwise BuLi (2 M, 3.75 cm^3, 7.5 mmol). The resultant white suspension was stirred for 30 min whereupon a solution of lactone **108** (1.6 g, 5.1 mmol) in Et_2O (15 cm^3) was added causing the suspension to disappear. The mixture was then allowed to warm up slowly to 0 °C over 1 h, quenched by the addition of water (15 cm^3), extracted with Et_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude product was dissolved in MeOH (20 cm^3) at 0 °C and $BF_3{\cdot}Et_2O$ (0.1 cm^3, 0.8 mmol) was added dropwise. The solution was allowed to warm up slowly to r.t. over 2 h, whereupon 1 cm^3 of saturated aqueous $NaHCO_3$ was added. After removal of the solvent *in vacuo*, the residue was purified by chromatography (SiO_2, hexanes:Et_2O = 3:2) to give **109** (1.37 g, 4.8 mmol, 94%) as a colourless oil; $[\alpha]_D$ +92.9 (*c* 0.97, $CHCl_3$); ν_{max}(film)/cm^{-1} 3550–3400br, 2952s, 2932s, 1462m, 1231m, 1176m, 1105s, 1032s; δ_H(300 MHz, $CDCl_3$) 4.15 (2H, s), 3.86 (1H, ddd, *J* 11.0, 9.6,

4.8), 3.76 (1H, dt, *J* 11.0, 1.5), 3.53 (1H, dd, *J* 10.5, 2.0), 3.40 (3H, s), 3.38 (3H, s), 2.86 (1H, dd, *J* 9.6, 1.5), 1.94 (1H, ddt, *J* 13.6, 7.0, 4.0), 1.75 (1H, m), 1.65–1.55 (2H, m), 1.56–1.44 (2H, m), 1.33 (1H, app. quintet, *J* 12.5), 1.00 (3H, d, *J* 7.0), 0.99 (3H, t, *J* 7.4), 0.79 (3H, d, *J* 6.6); δ_C(75 MHz, $CDCl_3$) 98.12 (0), 83.85 (0), 80.59 (1), 80.15 (0), 64.74 (2), 59.79 (2), 57.69 (3), 50.53 (3), 41.47 (1), 40.54 (1), 35.76 (2), 31.54 (1), 17.29 (3), 16.69 (3), 15.83 (2), 12.39 (3).

(2*RS*,3*R*,5*S*,6*S*)-5-[(*S*)-1-Hydroxymethylpropyl]-3,5-dimethyl-2-methoxy-2-(3-methoxypropadienyl)oxane 110

To a magnetically stirred solution of **109** (880 mg, 3.09 mmol) in dry pentane (10 cm^3), was added Bu′OK (520 mg, 4.63 mmol) and 18-crown-6 (30 mg). The yellow suspension was stirred at r.t. for 2.5 h, then filtered through SiO_2 which had been washed with ether–pentane (1:1). The filtrate was concentrated *in vacuo*, dried 2 times by azeotropic distillation with benzene and the crude allenol ether **110** (897 mg) used immediately in the next step; ν_{max}(film)/cm^{-1} 3454br, 2960s, 2830s, 1961s, 1461s, 1405s, 1379m, 1207s, 1167s, 1041s, 911m.

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*)-9-[(*S*)-1-Ethyl-2-hydroxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-one 90a

To a magnetically stirred solution of the allene **110** (*ca*. 3.09 mmol) in Et_2O (8 cm^3) at −80 °C under argon, was added dropwise BuLi (2.5 M, 2.5 cm^3, 6.25 mmol). The light yellow solution was allowed to warm up slowly to −30 °C over 1.5 h, then re-cooled to −60 °C whereupon a solution of lactone **8a** (880 mg, 2.47 mmol) in Et_2O (3 cm^3) was added. The mixture was allowed to warm up slowly to r.t. over 5 h, quenched by the addition of water (5 cm^3), extracted with Et_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product thus obtained was dissolved in THF (15 cm^3) and H_2SO_4 (1 M, 4 cm^3) was added. The solution was stirred at r.t. for 25 min before being quenched by the slow addition of saturated aqueous $NaHCO_3$. The product was extracted with Et_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product thus obtained was dissolved in CH_3CN (25 cm^3) and HF 40% aq. (1 cm^3) and I_2 (20 mg) were added. The solution was then stirred at r.t. for 48 h before being quenched by the slow addition of saturated aqueous $NaHCO_3$. The resultant mixture was extracted with Et_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, hexanes:EtO_2 = 3:2) to give a first sample of dispiroacetal **90a**. The column was then washed with methanol, the solvent removed *in vacuo* and the residue again treated with HF as described above. After four cycles a total of 581 mg (1.21 mmol, 49%) of the dispiroacetal was obtained as a colourlesss oil.

The synthesis of salinomycin: finale

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*)-9-[(*S*)-1-Ethyl-2-triethylsilyloxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-one 114

Reaction of diol **90a** (180 mg, 0.38 mmol) with TESOTf (180 μl, 0.83 mmol) and 2,6-lutidine (340 μl, 3 mmol) in CH_2Cl_2 (5 cm^3) in the usual way gave the bis(triethylsilyl) ether **114** (216 mg, 0.31 mmol, 82%) as a colourless oil after purification by column chromatography (SiO_2, 4 × 2 cm, hexanes:Et_2O = 96:4) (Found: $M^{+\bullet}$, 708.4792. $C_{39}H_{72}O_7Si_2$ requires *M*, 708.4817); $[a]_D$ −46.6 (*c* 4.4, Et_2O); ν_{max}(film)/cm^{-1} 2954s, 2876s, 1701s, 1459s, 1375s, 1240s, 1059s, 1010s, 741s; δ_H(300 MHz, C_6D_6) 6.40 (1H, d, *J* 10.2), 6.16 (1H, d, *J* 10.2), 4.24–4.05 (4H, m), 3.94 (1H, dd, *J* 11.6, 2.0), 3.50–2.66 (2H, m), 2.32–1.84 (9H, m), 1.78 (1H, dd, *J* 13.4, 4.0), 1.70 (3H, s), 1.70–1.0 (5H, m), 1.43 (3H, t, *J* 7.7), 1.41 (3H, d, *J* 6.8), 1.39 (3H, d, *J* 6.8), 1.30 (18H, t, *J* 7.9), 1.13 (3H, d, *J* 6.4), 1.11 (3H, t, *J* 7.5), 1.00–0.85 (12H, m); δ_C(75 MHz, C_6D_6) 193 (0), 49.5 (1), 128.4 (1), 105.5 (0), 95.5 (0), 89.5 (0), 78.3 (1), 77.2 (1), 75.4 (0), 75.1 (1), 65.0 (2), 44.4 (1), 39.3 (1), 38.1 (2), 36.2 (2), 34.5 (2), 32.7 (1), 32.3 (2), 30.6 (2), 22.7 (2), 21.9 (3), 20.4 (2), 18.4 (3), 16.3 (3), 16.0 (3), 13.5 (3), 7.7 (3), 7.4 (3), 7.3 (3), 7.2 (2), 5.0 (2); *m*/*z* (EI) 708 ($M^{+\bullet}$, 7%), 679 (25), 451 (45), 353 (35), 257 (35), 225 (75), 199 (100), 157 (45), 115 (70), 87 (90).

Reduction of enone 114

To a solution of enone **114** (345 mg, 0.486 mmol) in MeOH (15 cm^3) was added $CeCl_3 \cdot 7H_2O$ (186 mg, 0.5 mmol) and the mixture cooled to −60 °C whereupon $NaBH_4$ (57 mg, 1.5 mmol) was added in one portion and the mixture allowed to warm to 0 °C over 100 min. The mixture was diluted with Et_2O and washed with brine, dried and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5 × 3 cm, hexanes:Et_2O = 19:1→9:1) to give **115b** (290 mg, 0.41 mmol, 84%) and **115a** (50 mg, 0.07 mmol, 14%).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*S*)-9-[(*S*)-1-Ethyl-2-triethylsilyloxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-ol 115b (Found: $M^{+\bullet}$, 710.5000. $C_{39}H_{74}O_7Si_2$ requires *M*, 710.4973); $[a]_D$ +21.9 (*c* 2.8, Et_2O); ν_{max}(film)/cm^{-1} 3454br, 2955s, 2876s, 1456s, 1372s, 1241m, 1076s, 1042s, 982s, 740s; δ_H(270 MHz, C_6D_6) 6.12 (1H, dd, *J* 10.0, 2.5), 5.75 (1H, dd, *J* 10.0, 1.9), 4.20 (1H, dd, *J* 10.2, 4.8), 4.16–4.05 (3H, m), 3.98 (1H, dd, *J* 11.4, 2.5), 3.93 (1H, dd, *J* 11.0, 2.5), 2.61 (1H, d, *J* 12.0), 1.74–1.44 (4H, m), 1.55 (3H, s), 1.48 (3H, d, *J* 6.7), 1.38 (3H, t, *J* 7.1), 1.36–1.26 (31H, m), 1.20 (3H, d, *J* 6.4), 1.15 (3H, t, *J* 7.5), 1.20–0.86 (15H, m); δ_C(67.5 MHz, C_6D_6) 131.5 (1), 131.0 (1), 107.1 (0), 96.7 (0), 87.4 (0), 79.2 (1), 77.1 (1), 76.7 (1), 75.6 (0), 66.4 (1), 62.6 (2), 47.2 (1), 40.0 (1), 36.8 (2), 36.7 (2), 35.8 (2), 33.4 (1), 32.3 (2), 30.9 (2), 22.1 (2), 21.9 (2), 20.5 (3), 19.3 (3), 16.35 (3), 16.0 (3), 13.7 (3), 7.7 (3), 7.4 (2), 7.3 (3), 5.1 (2); *m*/*z* (EI) 710 ($M^{+\bullet}$, 1%), 255 (10), 227 (20), 199 (70), 157 (65), 103 (100), 87 (55), 75 (98), 59 (30).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*R*)-9-[(*S*)-1-Ethyl-2-triethylsilyloxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-ol 115a (Found: $M^{+\bullet}$, 710.4979. $C_{39}H_{74}O_7Si_2$ requires *M*, 710.4973); $[a]_D$ −59.7 (*c* 2.7, Et_2O); ν_{max}(film)/cm^{-1} 3456br, 2967s, 2876s, 1459s, 1374s, 1238s, 1093s, 1010s, 966s, 724s; δ_H(270 MHz, C_6D_6) 6.27 (1H, dd, *J* 9.6, 2.1), 5.80 (1H, dd, *J* 9.6, 2.9), 5.02 (1H, br), 4.21–4.04 (5H, m), 2.68–2.50 (2H, m), 2.35–1.24 (31H, m), 1.59 (3H, s), 1.46 (3H, d, *J* 6.8), 1.36 (3H, t, *J* 7.8), 1.32 (3H, t, *J* 7.8), 1.13 (3H, t, *J* 7.2), 1.12 (3H, d, *J* 6.4), 1.02 (3H, d, *J* 6.2), 1.06–0.88 (12H, m); δ_C(75.0 MHz, C_6D_6) 133.6 (1), 131.9 (1), 112.9 (0), 98.0 (0), 86.0 (0), 77.4 (1), 77.1 (1), 75.7 (0), 75.2 (1), 67.9 (1), 65.9 (2), 44.9 (1), 39.4 (1), 37.5 (2), 36.1 (2), 32.6 (2), 32.4 (1), 31.3 (2), 31.2 (2), 22.3 (2), 20.8 (3), 19.9 (2), 18.3 (3), 16.4 (3), 16.2 (3), 13.7 (3), 7.7 (3), 7.4 (3), 7.4 (2), 7.3 (3), 5.1 (2); *m*/*z* (EI) 710 ($M^{+\bullet}$, 2%), 692 (50), 681 (40), 453 (40), 436 (45), 354 (100), 303 (40), 199 (100), 157 (65), 115 (80), 103 (65), 87 (80).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*S*)-15-Acetoxy-9-[(*S*)-1-ethyl-2-hydroxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene 116b

A solution of **115b** (56 mg, 0.079 mmol), Ac_2O (80 μl, 0.8 mmol), DMAP (5 mg) and pyridine (160 μl, 2.0 mmol) in CH_2Cl_2 (4 cm^3) was allowed to stand at r.t. for 12 h. A standard aqueous workup returned an oil which was dissolved in THF (4 cm^3). A solution of pyridine·HF [600 μl of a stock solution made by dissolving 660 μl of pyridine·HF in THF (20 cm^3) and pyridine (4 cm^3)] was added and the mixture allowed to stand at r.t. for 1 h. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated to a brown oil which was purified by column chromatography (SiO_2, 4 × 2 cm, hexanes:Et_2O = 5:1) to give **116b** (50 mg, 0.078 mmol, 99%) as a colourless oil

(Found: $M^{+\bullet}$, 638.4229. $C_{35}H_{62}O_8Si$ requires *M*, 638.4214); $[\alpha]_D$ +52.0 (*c* 2.5, Et_2O); ν_{max}(film)/cm^{-1} 3522br, 2960s, 2876s, 1746s, 1456s, 1372s, 1238s, 1101s, 1043s, 981s; δ_H(270 MHz, C_6D_6) 5.96 (1H, dd, *J* 10.1, 3.0), 5.72 (1H, dd, *J* 10.1, 1.7), 5.62 (1H, dd, *J* 3.0, 1.7), 4.23–4.12 (4H, m), 4.06 (1H, dd, *J* 10.6, 2.8), 3.40 (1H, br), 2.50–1.20 (17H, m), 2.08 (3H, s), 1.59 (3H, s), 1.30 (9H, t, *J* 7.5), 1.24 (3H, t, *J* 7.3), 1.11 (3H, t, *J* 7.3), 1.10–0.90 (15H, m); δ_C(75.0 MHz, C_6D_6) 170.2 (0), 132.4 (1), 127.6 (1), 105.3 (0), 96.9 (0), 88.3 (0), 80.3 (1), 77.3 (1), 76.4 (1), 75.7 (0), 68.2 (1), 64.6 (2), 42.5 (1), 40.0 (1), 36.8 (2), 35.9 (2), 35.7 (2), 32.6 (2), 32.0 (1), 30.6 (2), 22.1 (2), 20.7 (3), 20.6 (3), 17.8 (3), 17.0 (2), 16.3 (3), 12.7 (3), 7.7 (2C, 3), 7.4 (2), 7.3 (3); *m*/*z* (EI) 638 ($M^{+\bullet}$, 5%), 609 (15), 578 (35), 351 (20), 321 (100), 282 (40), 199 (40), 87 (40).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*R*)-15-Acetoxy-9-[(*S*)-1-ethyl-2-hydroxyethyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene 116a

By the same two-step procedure described above for the conversion **115b** to **116b**, the diastereoisomeric **116a** (45 mg, 0.070 mmol, *ca*. 100%) was prepared from **115a** (50 mg, 0.070 mmol) (Found: $M^{+\bullet}$, 638.4210. $C_{35}H_{62}O_8Si$ requires *M*, 638.4214); $[\alpha]_D$ −52.7 (*c* 2.25, Et_2O); ν_{max}(film)/cm^{-1} 3517br, 2960s, 1747s, 1456s, 1372s, 1230s, 1044s; δ_H(270 MHz, $CDCl_3$) 6.12 (1H, dd, *J* 10.0, 3.7), 5.97 (1H, dd, *J* 3.7, 1.8), 5.87 (1H, dd, *J* 10.0, 1.8), 4.34 (1H, dd, *J* 10.2, 2.1), 4.30–4.08 (3H, m), 4.06 (1H, dd, *J* 10.6, 3.3), 3.84 (1H, t, *J* 7.5), 2.60–2.40 (2H, m), 2.24–1.00 (15H, m), 1.93 (3H, m), 1.50 (3H, s), 1.48 (3H, t, *J* 7.7), 1.32 (9H, t, *J* 7.7), 1.16 (3H, t, *J* 7.7), 1.14–0.9 (15H, m); δ_C(75 MHz, C_6D_6) 169.3 (0), 134.0 (1), 128.0 (1), 108.4 (0), 97.5 (0), 88.0 (0), 77.4 (1), 77.3 (1), 75.6 (0), 75.0 (1), 69.3 (1), 63.4 (2), 43.0 (1), 39.1 (1), 36.9 (2), 35.1 (2), 34.2 (2), 32.5 (2), 32.1 (1), 30.6 (2), 22.2 (2), 20.9 (3), 20.5 (3), 17.8 (3), 17.3 (2), 16.6 (3), 16.2 (3), 12.9 (3), 7.8 (3), 7.4 (2), 7.3 (3); *m*/*z* (EI) 638 ($M^{+\bullet}$, 4%), 609 (10), 578 (20), 494 (15), 381 (15), 321 (100), 282 (45), 257 (35), 240 (30), 199 (50), 157 (48), 115 (40), 99 (50).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*S*)-15-Acetoxy-9-[(*R*)-1-ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyl-oxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene 117b

Ketone **117b** was prepared from the alcohol **116b** by a 3-step sequence involving oxidation, addition of EtMgBr, and oxidation without isolation of intermediates. Thus, alcohol **116b** (226 mg, 0.35 mmol) in dry CH_2Cl_2 (10 cm^3) was oxidised with the Dess–Martin periodinane (297 mg, 0.70 mmol) at r.t. for 40 min. Saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ (3 cm^3 each) were added with rapid stirring and the mixture diluted with Et_2O. The layers were separated and the aqueous layer extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was filtered through a plug of SiO_2 (7 × 3 cm) eluting with hexanes : Et_2O (9 : 1) to give the crude aldehyde (226 mg) as a colourless oil. The crude aldehyde in THF (10 cm^3) was cooled to −80 °C and EtMgBr (880 μl of a 1.7 M solution in THF) was added. The solution was allowed to warm to −47 °C over 1 h and quenched by the addition of saturated aqueous NH_4Cl and the product extracted into Et_2O. The Et_2O extract was dried ($MgSO_4$) and concentrated and the residue (240 mg) dissolved in CH_2Cl_2 (10 cm^3) and treated with the Dess–Martin periodinane (297 mg, 0.70 mmol) for 25 min at r.t. Extractive workup as described above gave **117b** (220 mg, 0.33 mmol, 94%) as a colourless oil after purification by column chromatography (SiO_2, 4 × 2 cm, hexanes : Et_2O = 19 : 1) (Found: $M^{+\bullet}$, 664.4377. $C_{37}H_{64}O_8Si$ requires *M*, 664.4370); $[\alpha]_D$ +5.6 (*c* 2.5, Et_2O); ν_{max}(film)/cm^{-1} 2959s, 2876s, 1745s, 1712s, 1456s, 1372s, 1239s, 1102s, 1044s, 984s; δ_H(270 MHz, C_6D_6) 5.94 (1H, dd, *J* 10.3, 1.7), 5.64 (1H, dd, *J* 10.3, 2.5), 5.59 (1H, dd, *J* 2.5, 1.7), 4.12 (1H, q, *J* 6.8), 4.02 (1H, dd, *J* 10.0, 4.0), 3.85 (1H, dd, *J* 11.2, 2.7), 3.01 (1H, ddd, *J* 13.1, 4.3, 3.2), 2.91 (1H, dq, *J* 18.1, 7.2), 2.46 (1H, dq, *J* 18.1, 7.3), 2.40–2.00 (7H, m), 2.0–1.2 (15H, m), 1.98 (3H, s), 1.59 (3H, s), 1.48 (3H, d, *J* 6.8), 1.31 (3H, t, *J* 7.2), 1.30 (3H, t, *J* 7.5), 1.13 (3H, t, *J* 7.2), 1.10 (3H, d, *J* 6.2), 1.09 (3H, t, *J* 7.2), 0.98–0.88 (9H, m); δ_C(67.5 MHz, C_6D_6) 212.7 (0), 170.6 (0), 131.1 (1), 128.2 (1), 105.5 (0), 97.5 (0), 88.3 (0), 79.5 (1), 77.7 (1), 77.3 (1), 76.1 (0), 69.2 (1), 59.9 (1), 40.2 (1), 39.8 (2), 37.2 (2), 36.9 (2), 36.0 (2), 34.7 (1), 33.0 (2), 31.2 (2), 24.2 (2), 22.6 (2), 21.4 (3), 20.8 (3), 19.6 (3), 16.6 (3), 16.5 (3), 14.4 (3), 8.6 (3), 8.3 (3), 7.9 (2), 7.8 (3); *m*/*z* (EI) 664 ($M^{+\bullet}$, 5%), 635 (15), 604 (30), 465 (45), 407 (90), 347 (80), 308 (35), 266 (45), 199 (50), 157 (45), 57 (100).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*R*)-15-Acetoxy-9-[(*R*)-1-ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyl-oxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene 117a

By the same 3-step procedure used to convert alcohol **116b** to ketone **117b**, the diastereoisomer ketone **117a** (40 mg, 0.060 mmol, 85%) was obtained from alcohol **116a** (45 mg, 0.071 mmol) as a colourless oil after column chromatography (Found: $M^{+\bullet}$, 664.4360. $C_{37}H_{64}O_8Si$ requires *M*, 664.4370); $[\alpha]_D$ −85.8 (*c* 2.0, Et_2O); ν_{max}(film)/cm^{-1} 2964s, 2877s, 1741s, 1712s, 1459s, 1372s, 1234s, 1043s, 987s, 722s; δ_H(270 MHz, C_6D_6) 6.20 (1H, dd, *J* 10.0, 4.3), 5.82 (1H, dd, *J* 10.0, 1.4), 5.68 (1H, dd, *J* 4.3, 1.4), 4.20 (1H, dd, *J* 9.7, 4.2), 4.13 (1H, q, *J* 7), 3.94 (1H, dd, *J* 11.4, 2.1), 3.02–2.85 (2H, m), 2.54 (1H, dq, *J* 18.4, 7.5), 2.46–1.00 (8H, m), 2.0–1.2 (8H, m), 1.92 (3H, s), 1.52 (3H, s), 1.48 (3H, d, *J* 6.9), 1.39 (3H, t, *J* 7.1), 1.32 (9H, t, *J* 7.6), 1.15 (3H, t, *J* 7.5), 1.12 (3H, d, *J* 6.2), 1.10 (3H, t, *J* 7.5), 1.01 (3H, d, *J* 6.2), 0.9–1.07 (6H, m); δ_C(67.5 MHz, C_6D_6) 212.2 (0), 169.9 (0), 134.2 (1), 128.9 (1), 127.4 (1), 108.3 (0), 97.7 (0), 87.9 (0), 78.0 (1), 76.8 (1), 76.2 (0), 69.3 (1), 59.0 (1), 39.7 (1), 38.2 (2), 37.7 (2), 36.7 (2), 34.9 (2), 34.9 (1), 33.1 (2), 31.2 (2), 22.6 (2), 22.5 (3), 21.1 (3), 20.9 (3), 19.4 (3), 17.1 (3), 16.6 (3), 14.1 (3), 8.6 (3), 8.3 (3), 7.9 (2), 7.8 (3); *m*/*z* (EI) 664 ($M^{+\bullet}$, 5%), 635 (30), 618 (45), 604 (28), 494 (15), 465 (35), 407 (100), 348 (95), 327 (60), 308 (45), 266 (45), 257 (58), 247 (44), 199 (55), 157 (44), 99 (46), 57 (85).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*S*)-9-[(*R*)-1-Ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-ol 118b

A solution of the acetate **117b** (220 mg, 0.331 mmol) and K_2CO_3 (46 mg, 0.33 mmol) in MeOH (10 cm^3) was allowed to stand at r.t. for 5 h whereupon the mixture was concentrated to one third its volume and then diluted with Et_2O. The resultant solution was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil which was purified by column chromatography (SiO_2, 4 × 2 cm, hexanes : Et_2O = 9 : 1) to give **118b** (200 mg, 0.322 mmol, 97%) as a colourless oil (Found: $M^{+\bullet}$, 622.4290. $C_{35}H_{62}O_7Si$ requires *M*, 622.4265); $[\alpha]_D$ +12.3 (*c* 2.0, Et_2O); ν_{max}(film)/cm^{-1} 3500br, 2960s, 2875s, 1711s, 1460s, 1372s, 1139s, 1098s, 1040s, 984s, 738s, 720s; δ_H(270 MHz, C_6D_6) 6.05 (1H, dd, *J* 10.3, 1.7), 5.58 (1H, dd, *J* 10.3, 2.3), 4.14–4.05 (2H, m), 4.00 (1H, dd, *J* 9.9, 4.3), 3.84 (1H, dd, *J* 11.1, 2.1), 2.97 (1H, ddd, *J* 11.6, 3.9, 3.2), 2.90 (1H, dq, *J* 18.0, 3.9), 2.60–1.12 (18H, m), 1.50 (3H, s), 1.48 (3H, d, *J* 6.8), 1.31 (3H, t, *J* 7.2), 1.30 (9H, t, *J* 7.9), 1.11 (6H, t, *J* 7.2), 1.09 (3H, d, *J* 6.4), 0.99–0.88 (6H, m), 0.85 (3H, d, *J* 6.0); δ_C(75 MHz, C_6D_6) 212.8 (0), 132.0 (1), 130.4 (1), 107.3 (0), 97.0 (0), 88.4 (0), 79.5 (1), 77.7 (1), 77.4 (1), 76.1 (0), 66.7 (1), 59.8 (1), 40.2 (1), 39.8 (2), 37.4 (2), 36.9 (2), 36.0 (2), 34.6 (1), 33.0 (2), 31.2 (2), 23.9 (2), 22.6 (2), 20.9 (3), 19.7 (3), 16.6 (3), 16.5 (3), 14.3 (3), 8.6 (3), 8.3 (3), 7.9 (2), 7.8 (3); *m*/*z* (EI) 622 ($M^{+\bullet}$, 10%), 604 (35), 576 (15), 472 (10), 423 (55), 365 (60), 348 (40), 309 (25), 266 (100), 249 (25), 199 (50), 157 (45).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*R*)-9-[(*R*)-1-Ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-15-(*p*-nitrobenzoyloxy)-1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene 119

To a solution of allylic alcohol **118b** (200 mg, 0.32 mmol), Ph_3P (1.68 g, 6.4 mmol), and *p*-nitrobenzoic acid (1.07 g, 6.4 mmol) in benzene (8 cm^3) at 0 °C was added dropwise DEAD (1.0 cm^3, 6.4 mmol). After 10 min, the ice bath was removed and the mixture stirred at ambient temperature for 16 h. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and evaporated to give a residue (3.8 g) which was purified by column chromatography (SiO_2, 5.5 × 3.5 cm, hexanes:Et_2O = 9:1). The inverted *p*-nitrobenzoate ester **119** (210 mg, 0.27 mmol, 85%) was obtained as colourless needles from EtOH; mp 104–106 °C (EtOH) [Found: (M − $Et^{+\bullet}$), 742.4016. $C_{40}H_{60}NO_{10}Si$ requires *M*, 742.3987] (Found: C, 64.99; H, 8.45; N, 1.90%. $C_{42}H_{65}NO_{10}Si$ requires C, 65.34; H, 8.49; N, 1.81%); $[\alpha]_D$ −125.9 (*c* 2.75, Et_2O); ν_{max}(film)/cm^{-1} 2960s, 2875s, 1725s, 1608m, 1530s, 1460s, 1270s, 1100s, 1058s, 990s, 710s; δ_H(500 MHz, C_6D_6) 8.06 (2H, d, *J* 2), 7.93 (2H, d, *J* 2), 6.24 (1H, dd, *J* 4.5, 10.0), 5.88 (1H, dd, *J* 1.0, 10.0), 5.82 (1H, dd, *J* 4.5, 1.0), 4.24 (1H, dd, *J* 4.5, 10.0), 4.14 (1H, q, *J* 7.0), 3.94 (1H, d, *J* 11.0), 2.88–3.00 (2H, m), 2.54 (1H, dq, *J* 7.5, 18.0), 2.30–2.49 (3H, m), 2.19–2.29 (2H, m), 2.04–2.14 (3H, m), 1.78–1.95 (3H, m), 1.73 (1H, q, *J* 12.0), 1.59–1.65 (2H, m), 1.43–1.56 (2H, m), 1.52 (3H, s), 1.51 (3H, d, *J* 7.0), 1.40 (3H, t, *J* 7.0), 1.31 (9H, t, *J* 8.0), 1.18 (3H, t, *J* 7.0), 1.13 (3H, d, *J* 6.5), 1.11 (3H, t, *J* 7.5), 1.06 (3H, d, *J* 6.5), 0.92–0.99 (6H, m); *m*/*z* (EI) 742 (M$^{+\bullet}$ − Et, 15%), 725 (20), 572 (25), 514 (50), 415 (50), 347 (70), 327 (40), 257 (100), 199 (95), 162 (85), 113 (60).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*R*)-9-[(*R*)-1-Ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-ol 118a

A suspension of PNB ester **119** (190 mg, 0.246 mmol) in MeOH (10 cm^3) containing K_2CO_3 (34 mg, 0.246 mmol) was allowed to stir at r.t. for 4 h by which time the solid had dissolved. Most of the MeOH was removed *in vacuo* and the residue was diluted with Et_2O and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, 5 × 2.5 cm, hexanes:Et_2O = 4:1) to give allylic alcohol **118a** (132 mg, 0.212 mmol, 86%) as a colourless viscous oil (Found: M$^{+\bullet}$, 622.4248. $C_{35}H_{62}O_7Si$ requires *M*, 622.4265); $[\alpha]_D$ −83.5 (*c* 2.0, Et_2O); ν_{max}(film)/cm^{-1} 3460br, 2954s, 1712s, 1455s, 1374s, 1240s, 1097s, 967s, 722s; δ_H(360 MHz, C_6D_6) 6.72 (1H, dd, *J* 9.8, 2.5), 6.23 (1H, dd, *J* 9.8, 2.6), 4.51 (1H, br), 4.29 (1H, dd, *J* 10.1, 3.5), 4.15 (1H, q, *J* 6.9), 4.06 (1H, dd, *J* 11.9, 1.9), 3.02 (1H, dq, *J* 18.1, 7.3), 2.76 (1H, dt, *J* 10.4, 3.2), 2.65–1.2 (18H, m), 1.54 (3H, s), 1.46 (3H, d, *J* 7.2), 1.38 (3H, t, *J* 7.2), 1.34 (9H, t, *J* 7.9), 1.17 (3H, t, *J* 7.4), 1.13 (3H, t, *J* 7.6), 1.07 (3H, d, *J* 6.4), 1.03–0.95 (9H, m); δ_C(67.5 MHz, C_6D_6) 210.7 (0), 134.1 (1), 131.0 (1), 112.5 (0), 98.0 (0), 86.5 (0), 77.5 (1), 76.3 (1), 75.7 (0), 75.2 (1), 67.5 (1), 56.5 (1), 39.3 (1), 37.4 (2), 35.9 (2, 2C), 33.6 (1), 32.6 (2), 31.9 (2), 31.0 (2), 22.2 (2), 20.8 (3), 18.9 (2), 18.4 (3), 16.4 (3), 16.2 (3), 13.5 (3), 8.3 (3), 7.8 (3), 7.4 (2), 7.4 (3); *m*/*z* (EI) 622 (M$^{+\bullet}$, 5%), 604 (15), 576 (20), 365 (30), 348 (40), 327 (15), 266 (100), 249 (25), 199 (35), 157 (40).

(2*S*,5*R*,7*S*,9*S*,10*S*,12*R*,15*R*)-15-Triethylsilyloxy-9-[(*R*)-1-ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene 120

A solution of allylic alcohol **118a** (132 mg, 0.212 mmol), TESCl (50 μl, 0.368 mmol), Et_3N (90 μl, 0.65 mmol) and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 was stirred at r.t. for 1.75 h. The mixture was diluted with Et_2O and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to an oil which was purified by column chromatography (SiO_2, 4 × 2.5 cm, hexanes:Et_2O = 98:2) to give the TES ether **120** (148 mg, 0.201 mmol, 95%) as a colourless oil (Found: M$^{+\bullet}$, 736.5117. $C_{41}H_{76}O_7Si_2$ requires *M*, 736.5130); $[\alpha]_D$ −78.1 (*c* 3.0, Et_2O); ν_{max}(film)/cm^{-1} 2956s, 2877s, 1719s, 1460s, 1415m, 1375s, 1240s, 1174s, 1104s, 1045s, 969s, 738s; δ_H(270 MHz, C_6D_6) 6.14 (1H, dd, *J* 9.9, 2.1), 5.80 (1H, dd, *J* 9.9, 2.9), 4.81 (1H, dd, *J* 2.9, 2.1), 4.27 (1H, dd, *J* 9.9, 3.3), 4.14 (1H, q, *J* 6.8), 4.07 (1H, dd, *J* 11.6, 1.9), 2.99 (1H, dq, *J* 17.6, 7.3), 2.74–2.44 (2H, m), 2.54 (1H, dq, *J* 17.6, 7.2), 2.42–1.2 (15H, m), 1.64 (3H, s), 1.47 (3H, d, *J* 6.8), 1.39 (3H, t, *J* 7.2), 1.32 (9H, t, *J* 8.1), 1.29 (9H, t, *J* 7.7), 1.14 (3H, t, *J* 7.4), 1.13 (3H, t, *J* 7.3), 1.06 (3H, d, *J* 6.0), 1.03 (3H, d, *J* 5.6), 1.02–0.88 (12H, m); δ_C(67.5 MHz, C_6D_6) 209.9 (0), 135.9 (1), 130.9 (1), 112.8 (0), 97.7 (0), 86.4 (0), 77.6 (1), 76.0 (1), 75.7 (0), 75.3 (1), 68.1 (1), 56.4 (1), 39.3 (1), 37.5 (2), 36.0 (2), 35.6 (2), 33.6 (1), 32.6 (2), 31.9 (2), 31.1 (2), 22.2 (2), 20.9 (3), 18.6 (2), 18.5 (3), 16.4 (3), 16.3 (3), 13.5 (3), 8.4 (3), 7.8 (3), 7.5 (2), 7.4 (3), 5.5 (2); *m*/*z* (EI) 736 (M$^{+\bullet}$, 5%), 707 (15), 637 (4), 604 (6), 566 (5), 537 (3), 479 (50), 380 (100), 327 (15), 199 (10), 157 (67), 115 (15), 87 (15), 57 (15).

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,15*R*)-15-Acetoxy-9-[(*R*)-1-ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene 123

The diastereoisomer **117a** (40 mg, 0.0602 mmol) and CSA (10 mg) in CH_2Cl_2 (7.5 cm^3) were stirred at r.t. for 1 h. Pyridine (5 drops) was added and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, 5 × 3 cm, hexanes:Et_2O = 8:1) to give recovered **117a** (2 mg) and **123** (20 mg) as a colourless viscous oil (Found: M$^{+\bullet}$, 664.4366. $C_{37}H_{64}O_8Si$ requires *M*, 664.43705); $[\alpha]_D$ −74.1 (*c* 0.7, Et_2O); ν_{max}(film)/cm^{-1} 2959s, 2877s, 1740s, 1707s, 1460s, 1392s, 1242s, 1031s, 737s; δ_H(270 MHz, C_6D_6) 6.05 (1H, dd, *J* 9.9, 6.0), 5.76 (1H, d, *J* 9.9), 5.46 (1H, d, *J* 6.0), 4.18 (1H, dd, *J* 9.9, 2.9), 4.08 (1H, q, *J* 6.7), 2.67 (1H, dd, *J* 11.7, 2.2), 2.80–2.33 (8H, m), 2.3–1.4 (10H, m), 2.02 (3H, s), 1.77 (3H, s), 1.4–1.2 (19H, m), 1.05 (3H, t, *J* 7.1), 1.05–0.98 (12H, m); δ_C(75 MHz, C_6D_6) 211.0 (0), 169.9 (0), 134.8 (1), 124.9 (1), 106.7 (0), 99.6 (0), 87.6 (0), 77.4 (1), 77.3 (1), 75.4 (0), 74.1 (1), 67.0 (1), 56.7 (1), 39.6 (1), 36.4 (2), 36.2 (2), 34.4 (2), 33.0 (2), 32.2 (2), 30.5 (2), 24.4 (3), 21.9 (2), 20.8 (3), 19.3 (2), 18.3 (3), 16.9 (3), 15.8 (3), 13.6 (3), 7.8 (3), 7.7 (3), 7.3 (3), 7.2 (3); *m*/*z* (EI) 664 (M$^{+\bullet}$, 6%), 618 (40), 407 (70), 348 (60), 308 (85), 766 (60), 199 (65), 157 (50), 87 (45), 57 (100).

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,15*R*)-9-[(*R*)-1-Ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-ol 124

Acetate **123** (620 mg, 0.934 mmol) in MeOH (30 cm^3) containing K_2CO_3 (129 mg, 0.934 mmol) was stirred at r.t. for 60 h. Half the solvent was removed *in vacuo* and the mixture partitioned between brine and Et_2O. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil which was purified by chromatography (SiO_2, 4.5 × 3.5 cm, hexanes:Et_2O = 5:1) to give pure alcohol **124** (511 mg, 0.822 mmol, 88%) as a colourless viscous oil; $[\alpha]_D$ −68.1 (*c* 5.1, Et_2O). A further 90 mg of a mixture consisting principally of **124** and the diastereoisomer **118a** (*ca.* 5:1) was isolated (Found: M$^{+\bullet}$, 622.4296. $C_{35}H_{62}O_7Si$ requires *M*, 622.4265); ν_{max}(film)/cm^{-1} 3416br, 2958s, 2875s, 1720s, 1460s, 1378s, 1096s, 1061s, 1008s, 987s, 915s, 737s; δ_H(270 MHz, C_6D_6) 6.38 (1H, dd, *J* 10.0, 2.9), 5.78 (1H, dd, *J* 10.0, 2.1), 4.52 (1H, dt, *J* 8.1, 4.7), 4.33 (1H, d, *J* 8.1), 4.23 (1H, dd, *J* 9.4, 2.9), 4.02 (1H, q, *J* 7.0), 3.65 (1H, dd, *J* 10.6, 3.1), 2.76–2.36 (6H, m), 2.28–2.08 (1H, m), 1.98–1.60 (8H, m), 1.53 (3H, s), 1.38–1.21 (10H, m), 1.27 (9H, t, *J* 7.5), 1.17

(3H, d, *J* 7.0), 1.08 (3H, t, *J* 7.4), 0.99 (3H, t, *J* 7.1), 1.00–0.84 (9H, m); δ_C(75 MHz, C_6D_6) 211.9 (0), 134.3 (1), 130.3 (1), 109.8 (0), 97.8 (0), 86.9 (0), 77.4 (1), 76.7 (1), 75.1 (0), 74.3 (1), 68.2 (1), 56.3 (1), 39.9 (1), 37.2 (2), 37.1 (2), 34.9 (2), 33.9 (1), 32.0 (2), 31.6 (2), 30.2 (2), 25.5 (3), 22.6 (2), 18.5 (2), 18.0 (3), 16.7 (3), 15.8 (3), 13.4 (3), 7.9 (3), 7.7 (3), 7.3 (2), 7.2 (3); *m/z* (EI) 622 ($M^{+\bullet}$, 2%), 604 (15), 348 (20), 266 (100), 199 (35), 157 (30), 99 (50), 57 (90).

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,15*R*)-15-Triethylsilyloxy-9-[(*R*)-1-ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-triethylsilyloxy-6-methyloxan-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene 6a

Allylic alcohol **124** (419 mg, 0.674 mmol) was converted to the TES ether **5a** (445 mg, 0.605 mmol, 90%) by the same procedure described above for the preparation of **91** (Found: $M^{+\bullet}$, 736.5103. $C_{41}H_{76}O_7Si$ requires *M*, 736.5130); $[a]_D$ −64 (*c* 2.0, Et_2O); ν_{max}(film)/cm^{-1} 2955s, 2875s, 1719s, 1459s, 1380s, 1237s, 1105s, 1008s, 971s, 918s, 741s; δ_H(270 MHz, C_6D_6) 6.14 (1H, dd, *J* 10.0, 4.0), 5.80 (1H, dd, *J* 10.0, 1.4), 4.35 (1H, dd, *J* 3.9, 1.4), 4.21 (1H, dd, *J* 6.5, 1.5), 4.08 (1H, q, *J* 7.0), 3.73 (1H, dd, *J* 9.4, 2.5), 2.80–1.20 (42H, m), 1.13–0.88 (28H, m); δ_C(75 MHz, C_6D_6) 210.4 (0), 132.3 (1), 131.1 (1), 109.6 (0), 98.5 (0), 87.1 (0), 77.1 (1), 76.6 (1), 75.5 (0), 73.8 (1), 67.8 (1), 56.3 (1), 40.0 (1), 37.1 (2), 36.1 (2), 35.4 (2), 34.8 (2), 33.8 (1), 32.1 (2), 30.6 (2), 23.9 (3), 22.0 (2), 18.5 (2), 18.1 (3), 17.0 (3), 15.9 (3), 13.5 (3), 8.0 (3), 7.7 (3), 7.3 (3), 7.3 (2), 5.6 (2); *m/z* (EI) 736 ($M^{+\bullet}$, 35%), 707 (45), 637 (30), 604 (40), 566 (25), 479 (40), 380 (100), 327 (15), 115 (25), 87 (35), 57 (30).

20,28-Bis-*O*-(triethylsilyl)-17-*epi*-salinomycin 126

To a magnetically stirred suspension of dicyclohexylmagnesium bromide (0.95 M in THF, 0.74 cm^3, 0.7 mmol) at −65 °C was added a solution of ketone **6a** (104 mg, 0.141 mmol) in THF (4 cm^3) dropwise. The mixture was allowed to warm to −50 °C over 35 min. The buff suspension was re-cooled to −65 °C whereupon a solution of aldehyde **5a** (31 mg, 0.141 mmol) in THF (2 cm^3) was added dropwise. Stirring was continued for 40 min during which time the temperature rose to −50 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted twice with Et_2O. The combined Et_2O extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The brown oily residue was purified by column chromatography (SiO_2, hexanes:EtOAc = 3:1) to give the desired adduct **126** (58 mg, 0.059 mmol, 42%); $[a]_D$ −64 (*c* 1.05, Et_2O). In addition, 50 mg of ketone **6a** (*ca*. 80% pure) was recovered (Found: $M^{+\bullet}$, 978.6675. $C_{54}H_{98}O_{11}Si_2$ requires *M*, 978.6648); ν_{max}(CCl_4)/cm^{-1} 3513m, 3100br, 2962s, 2876s, 1720s, 1459s, 1379s, 1326m, 1238s, 1181m, 1107s, 1072s, 1019s, 973s, 945s; δ_H(500 MHz, C_6D_6) 6.21 (1H, dd, *J* 10.2, 5.7), 5.95 (1H, d, *J* 10.2), 4.71 (1H, d, *J* 9.9), 4.46 (1H, d, *J* 10.0), 4.36 (1H, d, *J* 5.7), 4.34 (1H, dd, *J* 10.8, 5.7), 4.11 (1H, q, *J* 7.0), 3.90 (1H, dd, *J* 10.0, 1.0), 3.46 (1H, dq, *J* 9.9, 7.0), 3.34–3.26 (1H, m), 3.18 (1H, dd, *J* 10.0, 3.3), 3.13 (1H, dt, *J* 10.8, 3.3), 2.62 (1H, ddd, *J* 12.0, 9.2, 3.0), 2.54–2.46 (1H, m), 2.32–2.16 (3H, m), 2.07–1.80 (9H, m), 1.96 (3H, s), 1.78–1.50 (5 H, m), 1.50–1.27 (7H, m), 1.38 (3H, d, *J* 6.0), 1.35 (9H, t, *J* 8.4), 1.30 (9H, t, *J* 8.0), 1.29 (3H, d, *J* 7.0), 1.24 (3H, t, *J* 7.5), 1.20 (3H, t, *J* 7.5), 1.20 (3H, d, *J* 6.5), 1.16 (3H, d, *J* 7.0), 1.15 (3H, d, *J* 7.0), 1.12 (3H, d, *J* 7.0), 1.07 (3H, t, *J* 7.4), 1.02–0.90 (12H, m); δ_C(125 MHz, C_6D_6) 217.6 (0), 178.2 (0), 132.1 (1), 131.6 (1), 109.8 (0), 99.4 (0), 87.3 (0), 77.9 (1), 76.9 (1), 76.1 (0), 75.7 (1), 74.9 (1), 72.2 (1), 71.1 (1), 68.4 (1), 57.4 (1), 49.5 (1), 49.1 (1), 40.4 (1), 37.7 (1), 37.6 (2), 36.9 (2), 36.2 (2), 34.0 (1), 32.9 (2), 31.6 (2), 29.2 (1), 27.0 (2), 24.1 (3), 23.3 (2), 22.4 (2), 20.9 (2), 20.7 (2), 19.2 (3), 17.7 (3), 16.3 (3), 14.7 (3), 14.3 (3), 12.9 (3), 11.8 (3), 8.3 (3), 8.2 (3), 7.9 (2), 7.8 (3), 6.2 (2) [One Me signal overlaps]; *m/z* (EI) 979 ($M^{+\bullet}$, 10%), 960 (12), 932 (5), 891 (2), 846 (12), 765 (3), 721 (20), 622 (100), 589 (25), 479 (28), 380 (65), 327 (25), 225 (20), 199 (40), 157 (35), 115 (60), 87 (60).

Isomerisation of 127 to salinomycin methyl ester 128. To a solution of **126** (58 mg, 0.059 mmol) in dry THF (1 cm^3) was added a solution of TBAF (0.55 cm^3 of 1.1 M solution in THF, 0.61 mmol). The solution was stirred at r.t. for 12 h before an additional aliquot of TBAF (1.0 cm^3, 1.1 mmol) was added. After a further 22 h the reaction mixture was partitioned between Et_2O and 0.05 M HCl. The organic layer was separated, washed with brine (3 ×), dried ($MgSO_4$) and concentrated *in vacuo*. The crude 17-*epi*-salinomycin **127** (41 mg, 0.055 mmol, 93%) in dry CH_2Cl_2 (12 cm^3) containing 3 Å molecular sieves (*ca*. 40 mg, freshly activated) was added trifluoroacetic acid (10 μl). The resultant pink suspension was stirred at r.t. for 36 min whereupon triethylamine (3 drops) was added causing the colour to discharge. The mixture was diluted with Et_2O (20 cm^3) and washed with saturated aqueous sodium hydrogen carbonate, 0.1 M HCl, and then brine (2 ×). The residue (37 mg) obtained after drying over $MgSO_4$ followed by filtration and concentrated *in vacuo*, was treated with excess diazomethane to give the crude methyl ester which was purified by column chromatography (SiO_2, hexanes:Et_2O = 1:1→2:3). The synthetic salinomycin methyl ester **128** (15 mg, 0.020 mmol, 36%) gave IR, ^1H NMR, ^{13}C NMR, LRMS, and optical rotation data identical with a sample of the methyl ester obtained from natural salinomycin.

20,28-Bis-*O*-(triethylsilyl)-17-*epi*-21-*epi*-salinomycin 121. The aldol condensation of ketone **120** (120 mg, 0.163 mmol) with aldehyde **5a** (36 mg, 0.163 mmol) according to the general procedure described above gave three fractions after column chromatography: fraction A (23 mg, 0.024 mmol, 14%, *ca*. 80% pure), fraction B (22 mg, 0.022 mmol, 14%, >95% pure), fraction C (10 mg, 0.010 mmol, 6%, low purity). Analytical data were recorded on fraction B (Found: $M^{+\bullet}$, 978.6664. $C_{54}H_{98}O_{11}Si_2$ requires *M*, 978.6648); $[a]_D$ −87.4 (*c* 1.1, Et_2O); ν_{max}(CCl_4)/cm^{-1} 3501br, 3000br, 2935s, 2875s, 1703s, 1549m, 1459s, 1374s, 1242s, 1101s, 1046s, 1007s, 971s; δ_H(360 MHz, C_6D_6) 6.26 (1H, dd, *J* 9.9, 3.1), 6.05 (1H, dd, *J* 9.9, 1.9), 4.97 (1H, dd, *J* 3.1, 1.9), 4.72 (1H, d, *J* 10.5), 4.38–4.27 (2H, m), 4.16 (1H, q, *J* 6.6), 4.15–4.06 (1H, m), 3.98 (1H, dd, *J* 9.9, 1.9), 3.57 (1H, m), 3.38–3.32 (1H, m), 3.12 (1H, dt, *J* 11.1, 3.4), 2.73 (1H, ddd, *J* 11.7, 9.9, 7.9), 2.58 (1H, ddd, *J* 11.1, 10.8, 6.8), 2.45–1.72 (17H, m), 1.73 (3H, s), 1.72–1.36 (7H, m), 1.48 (3H, d, *J* 6.9), 1.34 (9H, t, *J* 8.1), 1.28 (9H, t, *J* 7.7), 1.35–1.10 (24H, m), 1.03–0.90 (12H, m); δ_C(90 MHz, C_6D_6) 218 (0), 178.7 (0), 133.9 (1), 132.1 (1), 112.3 (0), 98.1 (0), 87.6 (0), 78.2 (1), 78.0 (1), 76.3 (0), 76.1 (1), 75.9 (1), 72.3 (1), 70.8 (1), 68.6 (1), 58.6 (1), 50.3 (1), 49.7 (1), 39.6 (1), 38.0 (2), 37.8 (1), 36.5 (2), 33.8 (1), 33.3 (2), 33.1 (2), 31.5 (2), 31.2 (2), 29.9 (1), 27.2 (2), 23.5 (2), 22.7 (2), 22.6 (2), 21.5 (3), 20.7 (2), 19.4 (3), 17.2 (3), 16.8 (3), 14.9 (3), 14.4 (3), 13.0 (3), 11.7 (3), 8.3 (3), 8.1 (3), 8.0 (2), 7.9 (3); *m/z* (EI) 979 ($M^{+\bullet}$, 3%), 949 (2), 847 (2), 765 (2), 736 (10), 707 (6), 622 (45), 589 (5), 566 (5), 479 (40), 380 (100), 327 (15), 199 (25), 157 (15), 115 (30), 87 (35).

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